

EAU Guidelines on Sexual and Reproductive Health

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1. INTRODUCTION

1.1 Aims and Objectives

The European Association of Urology (EAU) Sexual and Reproductive Health Guidelines aim to provide a comprehensive overview of the medical aspects relating to sexual and reproductive health in adult men. These Guidelines cover the former EAU Guidelines on Male Sexual Dysfunction, Male Infertility and Male Hypogonadism.

It must be emphasised that guidelines present the best evidence available to the experts. However following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - while taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Sexual and Reproductive Health Guidelines Panel consists of an international multi-disciplinary group of urologists, endocrinologists and a psychologist. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website:

<http://www.uroweb.org/guideline/sexualandreproductivehealth/>.

1.3 Available Publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available in print and as an app for iOS and android devices. These are abridged versions that may require consultation together with the full text version. All documents can be viewed through the EAU website: <http://www.uroweb.org/guideline/sexualandreproductivehealth/>.

1.4 Publication History

This document is a further update of the 2020 Guidelines which already included a comprehensive update of the 2018 versions of Male Sexual Dysfunction, Male Infertility and Male Hypogonadism guidelines, along with several new topics. Additional sections will be added in the coming years to address male contraception, vasectomy, and penile cosmetic surgery, which have not been previously addressed.

1.5 Changes in the Guideline for 2021

The results of ongoing and new systematic reviews have been included in the 2021 update of the Sexual and Reproductive Health Guidelines. Systematic reviews undertaken in 2020 were:

- What is the effectiveness of non-surgical therapies in the treatment of ischaemic priapism in patients with sickle cell disease?
- What is the effectiveness of non-surgical therapies in the management of priapism in patients without sickle cell disease?
- What is the effectiveness of surgical therapies in the treatment of priapism?

2. METHODOLOGY

2.1 Methods

For the 2021 Sexual and Reproductive Health Guidelines, further new evidence has been identified, collated and appraised through a structured assessment of the literature.

For each recommendation within the Guidelines there is an accompanying online strength rating form; the basis of which is a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [1, 2]. Each strength rating form addresses several key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis that panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the term 'strong' or 'weak' [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. Additional information can be found in the general Methodology section of this print, and online at the European Association of Urology (EAU) website: <http://www.uroweb.org/guideline/>. A list of associations endorsing the EAU Guidelines can also be viewed online at this address.

2.2 Review

The existing sections of the Sexual and Reproductive Health Guidelines were peer reviewed prior to publication in 2020. The new section for priapism was reviewed prior to publication in 2021.

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2022 update of the Sexual and Reproductive Health Guidelines. Systematic reviews planned for 2021 are:

- Penile cosmetic surgery;
- Vasectomy.

3. MALE HYPOGONADISM

3.1 Epidemiology and prevalence of male hypogonadism

Male hypogonadism is associated with decreased testicular function, with decreased production of androgens and/or impaired sperm production [5]. This is caused by poor testicular function or as a result of inadequate stimulation of the testes by the hypothalamic-pituitary axis. Several congenital or acquired disorders causing impaired action of androgens are also described [5]. Hypogonadism may adversely affect multiple organ functions and quality of life (QoL) [6]. Late-onset hypogonadism (LOH) is a clinical condition in ageing men, which, by definition, must comprise both persistent specific symptoms and biochemical evidence of testosterone deficiency [5, 7]. Late-onset hypogonadism is frequently diagnosed in the absence of an identifiable classical cause of hypogonadism, which becomes more prevalent with age, usually occurring, but not exclusively, in men aged > 40 years.

Male hypogonadism has also been called *Testosterone Deficiency*. The Panel has agreed to use the term *Male Hypogonadism*, which may better reflect and explain the underlying pathophysiology. Likewise, the Panel has further agreed to continue with the term *testosterone therapy*. The present Guidelines specifically address the management of adult male hypogonadism also called LOH. Some insights related to congenital or pre-pubertal hypogonadism are also provided and summarised.

The prevalence of hypogonadism increases with age and the major causes are central obesity, co-morbidity (e.g., diabetes) and overall poor health [8]. In healthy ageing men, there is only a small gradual decline in testosterone; up to the age of 80 years, age accounts for a low percentage of hypogonadism [8]. In men aged 40-79 years, the incidence of symptomatic hypogonadism varies between 2.1-5.7% [9-11]. The incidence of hypogonadism has been reported to be 12.3 and 11.7 cases per 1,000 people per year [9, 12].

There is a high prevalence of hypogonadism within specific populations, including patients with type 2 diabetes (T2DM), metabolic syndrome (MetS), obesity, cardiovascular disease (CVD), chronic obstructive pulmonary disease, renal disease and cancer [11]. Low testosterone levels are common in men with T2DM [13] and a high prevalence of hypogonadism (42%) has been reported in T2DM patients [14].

Klinefelter syndrome, a trisomy associated with a 47,XXY karyotype, is the most prevalent genetic cause of primary hypogonadism (hypergonadotropic hypogonadism), with a global prevalence of 1/500-1,000 live male births [15-17]. However, < 50% of individuals with Klinefelter syndrome are diagnosed in their lifetime [18].

3.1.1 Body Composition and Metabolic Profile

Low testosterone levels are common in men with obesity. Male hypogonadism is associated with a greater percentage of fat mass and a lesser lean mass compared to men with adequate testosterone levels [19]. There is much evidence that low testosterone level is strongly associated with increased visceral adiposity, but it also leads to lipid deposition in the liver and muscle and is associated with atherosclerosis [19]. *In vitro* studies have suggested that hypogonadism impairs glucose and triglyceride uptake into subcutaneous fat depots [19]. This enhances the uptake of glucose and triglycerides into ectopic fat depots.

Testosterone therapy has been associated with a reduced percentage of body fat and increase of lean body mass [20]. Data from a registry study have suggested that over a period of 8 years, testosterone therapy with long-acting intramuscular testosterone undecanoate was associated with a substantial but gradual loss of weight along with a reduction in waist circumference [21]. Testosterone also reduces liver fat content and muscle fat storage [19].

3.1.2 **Metabolic Syndrome/Type 2 Diabetes**

Metabolic Syndrome (MetS) is characterised by several specific components, including increased waist circumference, dyslipidaemia, hypertension, and impaired glucose tolerance. Hypogonadism is associated with central obesity, hyperglycaemia, insulin resistance and dyslipidaemia [low high-density lipoprotein (HDL) cholesterol, raised total and low-density lipoprotein (LDL) cholesterol and triglycerides], hypertension and predisposition to T2DM, which are all components of MetS [22].

Several randomised controlled trials (RCTs) have shown that testosterone therapy might improve insulin resistance and hyperglycaemia and lower cholesterol and LDL-cholesterol [23-27]. Testosterone therapy in hypogonadal T2DM improved glycaemic control in some RCTs and registry trials; however, there is no conclusive evidence from RCTs and meta-analyses [24, 28, 29]. A recent large placebo-controlled RCT, including 1,007 patients with impaired glucose tolerance or newly-diagnosed T2DM and total testosterone < 14 nmol/L, showed that testosterone therapy for 2 years reduced the proportion of patients with T2DM regardless of a lifestyle programme [30]. Similarly, a previously published registry study reported that testosterone therapy was associated in time with remission of T2DM [28]. HDL-cholesterol may decrease, remain unchanged or increase with testosterone therapy. Testosterone therapy in men with MetS and low testosterone has been shown to reduce mortality compared to that in untreated men [31, 32], although no conclusive evidence is available.

Erectile dysfunction (ED) is common in men with MetS and T2DM (up to 70% of patients). The causes of ED are multi-factorial and 30% of men with ED have co-existing testosterone-deficiency hypogonadism. Some evidence has suggested that for patients with T2DM this is only found in men with clearly reduced testosterone levels (< 8 nmol/L or 2.31 ng/mL) [33]. From a pathophysiological point of view, it has been reported that this is because ED is predominantly caused by vascular and neuropathic disease, and therefore not likely in men who do not have established vascular disease. Therefore, men presenting with ED should be screened for MetS. Likewise, patients with ED and diabetes may be offered testosterone measurement.

Placebo-controlled RCTs of testosterone therapy in T2DM have demonstrated improved sexual desire and satisfaction, but not erectile function [24, 33]. The presence of multiple comorbidity in this group of patients may confound the response to testosterone therapy alone. In a long-term registry study in men with T2DM, parenteral testosterone undecanoate therapy led to one third of patients entering remission from diabetes during 11 years' follow-up [34]. A large 2-year RCT of testosterone undecanoate vs. placebo showed that testosterone therapy significantly decreased progression of 999 men with low testosterone (< 14 nmol/L) from pre-diabetes to overt T2DM [30].

3.2 **Physiology of testosterone production**

The pituitary gland regulates testicular activity through secretion of luteinising hormone (LH), which regulates testosterone production in Leydig cells and follicle-stimulating hormone (FSH), which mainly controls sperm production in seminiferous tubules [35, 36]. The production and secretion of gonadotropins is stimulated by hypothalamic gonadotropin releasing hormone (GnRH) and inhibited by negative feedback mediated by the central action of sex steroids and inhibin B (Figure 1) [35, 36]. Gonadotropin releasing hormone is secreted in a pulsatile manner and negatively controlled by the activity of hypothalamic neurons, including corticotrophin-releasing hormone (CRH) and β endorphin neurons [35, 36]. Conversely, kisspeptin-1 (Kiss-1) neurons, neurokinin-B and tachykinin-3 are involved in GnRH stimulation. Leptin is involved in activation of Kiss-1 signalling [37]. About 25 mg of testosterone is present in the normal testes, and, on average, 5-10 mg of testosterone are secreted daily [35, 36]. The testes also produce lesser amounts of other androgens, such as androstenedione and dihydrotestosterone (DHT). A small amount of extra-gonadal testosterone is derived from circulating weak adrenal androgen precursor dehydroepiandrosterone (DHEA), although its specific contribution to daily testosterone production is limited in men [38, 39]. In physiological terms, DHT formation accounts for 6-8% of testosterone metabolism, and the ratio of plasma testosterone/DHT is approximately 1:20 [35, 36]. Finally, testosterone and its precursor, Δ 4 androstenedione, can be aromatised through P450 aromatase to other bioactive metabolites, such as oestrone (E1) and 17- β -oestradiol (E2), with a daily production of ~45 μ g [35, 36]. Leydig cells, can also directly produce and release into the bloodstream small amounts of oestrogens, with a daily production rate of 5-10 μ g (up to 20% of circulating oestrogens) [40].

Table 1: Main factors associated with an increase or reduction of SHBG circulating levels

SHBG increase	<ul style="list-style-type: none"> • Drugs: anticonvulsants, oestrogens, thyroid hormone • Hyperthyroidism • Hepatic disease • Ageing • Smoking • AIDS/HIV
SHBG decrease	<ul style="list-style-type: none"> • Drugs: growth hormone (GH), glucocorticoids, testosterone, anabolic androgenic steroids • Hypothyroidism • Obesity • Acromegaly [42] • Cushing's disease • Insulin resistance (MetS/T2DM) • Non-alcoholic fatty liver disease (NAFLD), • Nephrotic syndrome

3.2.2 **Androgen receptor**

Testosterone and DHT exert their biological action through activation of a specific nuclear receptor. The androgen receptor (AR) gene is localised on the X chromosome (Xq11–12), encoded in eight exons [43]. Exon 1 includes two polymorphic trinucleotide repeat segments encoding polyglutamine (CAG) and polyglycine (GGN) tracts in the N-terminal transactivation domain of its protein. Activity of the AR is inversely associated with the length of the CAG repeat chains [43]. However, the specific role of AR CAG repeat number in relation to hypogonadal symptoms or to clinical management of testosterone deficiency remains unclear [44, 45]. A RCT has shown that a higher CAG repeat number is positively associated with a change in fasting insulin, triglyceride and diastolic blood pressure, demonstrating the more sensitive the receptor, the greater the benefit [46].

3.3 **Role of testosterone in male sexual and reproductive health**

3.3.1 **Sexual development and maturation**

Testosterone production in the foetal testis starts between the eighth and ninth week of gestation after the expression of the SRY gene, which regulates organisation of the undifferentiated gonadal ridge into the testis [47]. During the first trimester, the testes drive the virilisation of internal and external genitalia through placental human chorionic gonadotropin (hCG)-stimulated androgen secretion by Leydig cells. During foetal life, testosterone mainly controls the differentiation of internal genitalia and testicular descent (regression of gubernaculum testis), whereas DHT is mainly involved in the development of the external male genitalia [48]. During puberty, reactivation of the hypothalamus–pituitary–gonadal (HPG) axis allows the development of secondary sexual characteristics, spermatogenesis maturation and, along with the contribution of other hormonal axes, completion of the adolescent growth spurt [5, 49]. Clinical models of aromatase deficiency and oestrogen receptor insensitivity have demonstrated that testosterone conversion to oestradiol is essential for epiphyseal closure and growth arrest [50].

3.3.2 **Sexual function**

Testosterone is involved in the regulation of all steps of the male sexual response. Sexual thoughts and motivations are universally accepted as the most testosterone-dependent aspects of male sexual behaviour [20]. The European Male Aging Study (EMAS), a population-based survey including 3,369 subjects aged 40–79 years from eight European countries, showed that sexual symptoms, particularly impairment of sexual desire, ED and decreased frequency of morning erections, were the most specific symptoms associated with age-dependent decline of testosterone [10]. Similar findings were reported in patients consulting for sexual dysfunctions [51]. Accordingly, several brain areas, including the amygdala, medial preoptic area, paraventricular nucleus of the hypothalamus, and peri-aqueductal grey matter express androgen receptors [51, 52]. Experimental and clinical studies have both documented that testosterone plays a crucial role in regulating penile function. In particular, testosterone controls the structural integrity necessary for penile erection, as well as several enzymatic activities within the corpus cavernosum, including a positive action on nitric oxide (NO) formation and a negative influence on the activity of the Ras homolog gene family member A/Rho-associated kinase (RhoA/ROCK) pathways [51, 53]. Testosterone is also involved in penile adrenergic response and cavernous smooth muscle cell turnover [51, 53]. Although some authors have suggested a positive role for testosterone in regulating penile phosphodiesterase 5 (PDE5) expression and activity, others have shown an inhibitory role of oestrogens on this pathway [51, 54].

More limited evidence has indicated a possible role of testosterone in regulating ejaculation, acting either at the central or peripheral level. Androgen receptors are expressed in several central spinal and super-spinal areas involved in the control of the ejaculatory reflex [55]. Additionally, the male genital tract expresses NO-PDE5 and RhoA/ROCK pathways, which are modulated by testosterone [55].

3.4 Classification and causes of male hypogonadism

Male hypogonadism can be classified according to the origin of the underlying problem into primary, if a consequence of testicular dysfunction, or secondary, if due to a pituitary or hypothalamic dysfunction (Table 2).

Primary hypogonadism is also called hypergonadotropic hypogonadism, since the pituitary tries to compensate for testicular dysfunction by increasing central stimulation. Conversely, in secondary hypogonadism the testes are inadequately stimulated by gonadotropins, usually with inappropriately normal or reduced gonadotropin levels [5, 36]. A compensated or subclinical form of hypogonadism, characterised by normal testosterone serum levels and elevated LH production, has also been reported [56]; the clinical significance of the latter condition is unclear [56-58]. Finally, hypogonadism can also result from several conditions leading to reduced sensitivity/insensitivity to testosterone and its metabolites [5, 36] (Table 2). This classification, based on the aetiology of hypogonadism, allows clinicians to adequately select appropriate treatment. In patients with secondary hypogonadism, both fertility and testosterone normalisation can be theoretically achieved with adequate treatment whereas in primary hypogonadism only testosterone therapy can be considered, which impairs fertility due to suppression of the HGP axis [5, 36] (Table 2). However, it should also be recognised that symptoms and signs of hypogonadism can be similarly independent of the site of origin of the disease. Conversely, the age of onset of hypogonadism can influence the clinical phenotype [37]. Accordingly, when the problem starts early, such as during foetal life, clinical phenotype can span from an almost complete female phenotype (e.g., complete androgen insensitivity or enzymatic defects blocking androgen synthesis) to various defects in virilisation. In the case of a pre- or peri-pubertal appearance of hypogonadism due to a milder central (isolated hypergonadotropic hypogonadism) or a peripheral defect (such as in Klinefelter's syndrome), there might be delayed puberty with an overall eunochoic phenotype. Finally, when hypogonadism develops after puberty and *especially* with ageing (i.e., LOH; see below), symptoms can be mild, and often confused with the ageing process *per se* [5, 37].

In 2017, Grossmann and Matsumoto suggested a new classification of adult male hypogonadism, distinguishing functional versus organic hypogonadism [59]. Accordingly, organic hypogonadism is characterised by any proven pathology affecting the HPG axis and should be treated with conventional medication (i.e., gonadotropins or testosterone therapy). Conversely, functional hypogonadism is based on the absence of any recognised organic alterations in the HPG axis and should be treated first by resolving or improving the associated comorbidity. These Guidelines refer to the validated international classification of adult male hypogonadism.

Table 2: Classification of male hypogonadism

PRIMARY HYPOGONADISM (hypergonadotropic hypogonadism)	
Congenital or developmental disorders	
<i>Common causes</i>	<i>Uncommon causes</i>
Klinefelter syndrome	<ul style="list-style-type: none"> - Rare chromosomal abnormalities - XX male syndrome - 47 XYY syndrome - 48 XXYY syndrome - 21 Trisomy (Down syndrome) - Noonan syndrome - Autosomal translocations¹ - Defects of testosterone biosynthesis - CAH (testicular adrenal rest tumours) - Disorders of sex development (gonadal dysgenesis) - LHR gene mutations - Myotonic dystrophy (including type I and II) - Uncorrected cryptorchidism (including INSL3 and LGR8 mutations) - Bilateral congenital anorchia - Sickle cell disease - Adreno-leukodystrophy

Acquired disorders	
<i>Drug-induced</i>	<i>Localised problems</i>
<ul style="list-style-type: none"> - Chemotherapy agents <ul style="list-style-type: none"> Alkylating agents Methotrexate - Testosterone synthesis inhibitors <ul style="list-style-type: none"> • Ketoconazole • Aminoglutethimide • Mitotane • Metyrapon 	<ul style="list-style-type: none"> - Bilateral surgical castration or trauma - Testicular irradiation - Orchitis (including mumps orchitis) - Autoimmune testicular failure - Testicular Torsion - Alcohol/Cirrhosis - Environmental Toxins
Systemic diseases/conditions with hypothalamus/pituitary impact	
<ul style="list-style-type: none"> - Chronic systemic diseases* - Chronic organ failure* - Glucocorticoid excess (Cushing syndrome)* - Aging* - HIV 	<ul style="list-style-type: none"> - Malignancies <ul style="list-style-type: none"> - Lymphoma - Testis cancer - Spinal cord injury - Vasculitis - Infiltrative diseases (amyloidosis; leukaemia)
SECONDARY HYPOGONADISM (hypogonadotropic hypogonadism)	
Congenital or developmental disorders	
<i>Common causes</i>	<i>Uncommon causes</i>
<ul style="list-style-type: none"> - Haemochromatosis* 	<ul style="list-style-type: none"> - Combined hormone pituitary deficiency - Idiopathic hypogonadotropic hypogonadism - (IHH) with variants: <ul style="list-style-type: none"> - Normosmic IHH - Kallmann syndrome - Isolated LH β gene mutations - Prader-Willi Syndrome
Acquired disorders	
<i>Drug-induced</i>	<i>Localised problems</i>
<ul style="list-style-type: none"> - Oestrogens - Testosterone or androgenic anabolic steroids - Progestogens (including cyproterone acetate) - Hyperprolactinaemia-induced drugs - Opiates <ul style="list-style-type: none"> - GnRH agonist or antagonist - Glucocorticoids 	<ul style="list-style-type: none"> - Traumatic brain injury - Pituitary neoplasm (micro/macro-adenomas) - Hypothalamus tumours - Pituitary stalk diseases - Iatrogenic <ul style="list-style-type: none"> - Surgical hypophisectomy - Pituitary or cranial irradiation - Inflammatory and infectious diseases <ul style="list-style-type: none"> - Lymphocytic hypophysitis - Pituitary infections - Granulomatous lesions - Sarcoidosis - Wegener's granulomatosis - Other granulomatosis - Encephalitis - Langerhans' histiocytosis - Hyperprolactinaemia as a consequence of localised problems (hypothalamus-pituitary mass)
Systemic diseases/conditions impacting the hypothalamus/pituitary	
<ul style="list-style-type: none"> - Chronic systemic diseases* <ul style="list-style-type: none"> - Metabolic diseases - HIV infection - Chronic organ failure - Chronic Inflammatory Arthritis - Glucocorticoid excess (Cushing syndrome)* - Eating disorders* - Endurance exercise - Acute and critical illness - Ageing* 	<ul style="list-style-type: none"> - Spinal cord injury - Transfusion-related iron overload (β-thalassemia)

ANDROGEN RESISTANCE/DECREASED TESTOSTERONE BIOACTIVITY	
Congenital or developmental disorders	
<ul style="list-style-type: none"> - Aromatase deficiency - Kennedy diseases (spinal and bulbar muscular atrophy) and other extensions of CAG repeats - Partial or complete androgen insensitivity - 5α reductase type II (5αR) deficiency 	
Acquired disorders	
<i>Drug-induced</i>	<i>Localised problems</i>
<ul style="list-style-type: none"> - Drug-induced AR blockage <ul style="list-style-type: none"> - Steroidal antiandrogen <ul style="list-style-type: none"> - Cyproterone acetate - Spironolactone - Non-steroidal antiandrogen <ul style="list-style-type: none"> - Flutamide - Bicalutamide - Nilutamide - Drug-induced 5α reductase (5αR) activity blockade <ul style="list-style-type: none"> - Finasteride - Dutasteride - Drug-induced ER blockade <ul style="list-style-type: none"> - Clomiphene - Tamoxifen - Raloxifene - Drug-induced aromatase activity blockade <ul style="list-style-type: none"> - Letrozole - Anastrozole - Exemestane - Increased SHBG 	<ul style="list-style-type: none"> - Coeliac disease

* Conditions acting and central and peripheral levels resulting in either primary and secondary hypogonadism.

¹ Different autosomal translocations can cause rare cases of hypogonadism and infertility.

3.5 Late-onset hypogonadism

Testosterone production declines with ageing. The EMAS study reported a 0.4% per annum (log hormone-age) decrease in total testosterone and a 1.3% per annum decline in free testosterone (fT) [8]. Late onset hypogonadism is the term frequently used to describe this phenomenon and the detection of hypogonadism in adulthood, in particular. Evidence has documented that several associated diseases and chronic co-morbidity can interfere with the HPG axis leading to development of primary hypogonadism or, more frequently, secondary hypogonadism in adulthood, thus significantly influencing the physiological age-dependent decline of testosterone. By combining the data from three different waves of the Massachusetts Male Aging Study (MMAS), a population-based, observational study including 1,709 men aged 40–70 years, showed that associated comorbidity and obesity significantly decreased, whereas smoking tended to increase total, free and bio-available testosterone concentrations [60]. Similarly, data derived from the EMAS study confirm these findings [8, 57]. Based upon these data and other evidence, the concept of *functional and organic hypogonadism* has been recently introduced [59]. The diagnosis of functional hypogonadism is based on the exclusion of a classical (organic) aetiology. The main causes of functional hypogonadism are obesity, co-morbidity and ageing with the first two accounting for most cases. Inflammatory cytokines released in chronic inflammation, and adipocytokines and oestradiol in obesity, can suppress the HPG axis. The role of ageing up to age 80 years seems relatively small [59]. Considering that suppression of HPG axis activity is functional, and potentially reversible by empiric measures, such as weight loss, the need for testosterone therapy has been questioned [59].

3.5.1 Diagnostic evaluation

The phenotype of the hypogonadal patient appears independent of the aetiology causing the problem, but is more often affected by the age of onset of hypogonadism. When androgen deficiency is complete and develops during foetal life, symptoms can be dramatic, spanning from an almost complete female phenotype (complete androgen insensitivity or enzymatic defects blocking androgen synthesis) to various defects in virilisation and ambiguous genitalia (micropenis, hypospadias and cryptorchidism) [5, 36]. Delay in puberty

with an overall eunuchoidal phenotype (scant body hair, high-pitched voice and small testes, penis and prostate) is typical of defects manifesting over the pre- or peri-pubertal period due to milder central (isolated HH) or peripheral defects (such as in Klinefelter syndrome) [5, 36]. When hypogonadism occurs in adulthood, especially functional hypogonadism, symptoms can often be mild, difficult to recognise and frequently confused with the ageing process [5, 36] or with chronic comorbidity. Several non-specific clinical features, such as fatigue, weakness, and decreased energy, as well as sexual impairment may be clinical manifestations. The EMAS study showed that a triad of sexual symptoms, including low libido, reduced spontaneous erections and ED, are typically associated with a decrease in serum testosterone levels [10]. Conversely, psychological and physical symptoms were less informative [10].

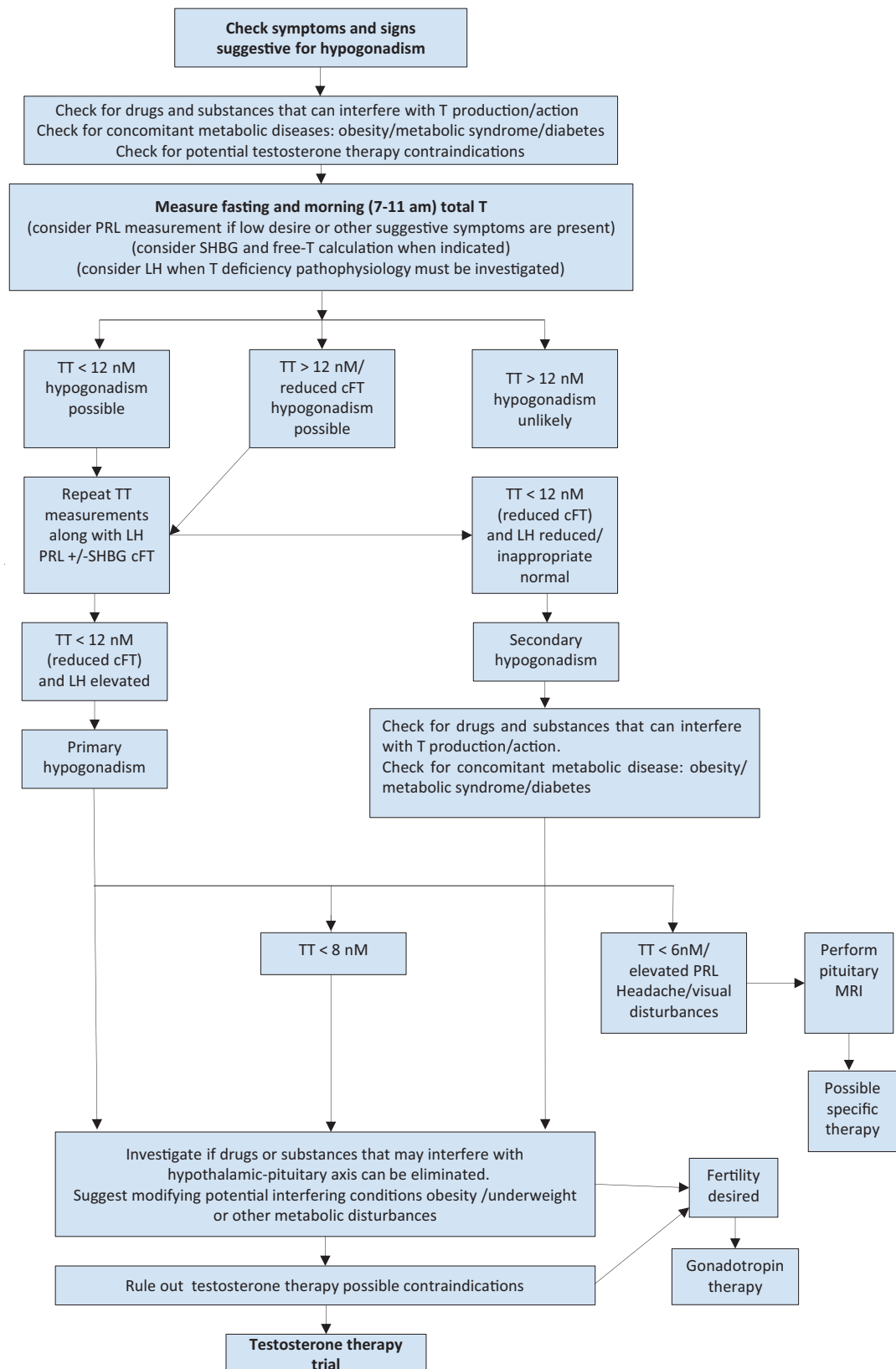
The mainstay of LOH diagnosis includes signs and symptoms consistent with hypogonadism, coupled with biochemical evidence of low morning serum total testosterone levels on two or more occasions, measured with a reliable assay. Testosterone levels show a circadian variation, which persist in ageing men [61, 62]. Likewise, testosterone levels are potentially influenced by food intake [63]; hence, serum total testosterone should be measured in fasting conditions and in the morning (between 07.00 and 11.00 hours). A confirmatory measurement should always be undertaken in the case of a primary pathological value, and certainly before starting any testosterone therapy.

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) represents the gold standard and most accurate method for sex steroid evaluation; however, standardised automated platform immuno-assays for total testosterone assessment demonstrate a good correlation with LC-MS/MS [64]. Conversely, available immuno-assays are not able to provide an accurate estimation of fT; therefore, direct fT evaluation with these methods is not recommended and should be avoided [41]. Liquid chromatography-tandem mass spectrometry remains the standard method for fT determination. Alternatively, fT can be derived from specific mathematical calculations taking into account serum SHBG and albumin levels [65] (<http://www.issam.ch/freetesto.htm>).

Data from available meta-analyses have documented that testosterone therapy is ineffective when baseline levels are > 12 nmol/L (3.5 ng/mL). Positive outcomes are documented when testosterone levels are < 12 nmol/L, being higher in symptomatic patients with more severe forms of hypogonadism (< 8 nmol/L). Hence, 12 nmol/L should be considered as a possible threshold for starting testosterone therapy in the presence of hypogonadal symptoms [21, 66]. As reported above, clinical conditions that may interfere with SHBG levels, evaluation of fT should be considered to better estimate actual androgen levels (Figure 2). Unfortunately, despite its potential clinical value [67], no validated thresholds for fT are available from clinical studies and this represents an area of uncertainty; however, some data indicate that fT levels < 225 pmol/L (6.5 ng/dL) are associated with hypogonadal symptoms [10, 51, 68, 69].

The determination of LH must be performed along with prolactin (PRL) when pathological total testosterone levels are detected, in order to correctly define the underlying conditions and exclude possible organic causes (Figure 2). Due to its negative influence on libido, PRL can also be considered as first-line screening in patients with reduced sexual desire. In addition, pituitary magnetic resonance imaging (MRI) scanning, as well as other pituitary hormone evaluations, is required in the presence of specific symptoms such as visual disturbances, headache [70, 71] or when hyperprolactinemia is confirmed. Limited evidence suggests performing pituitary MRI also in the case of severe hypogonadism (< 6 nmol/L, 1.75 ng/mL) with inadequate gonadotropin levels (Figure 2) [70, 71].

Figure 2: Diagnostic evaluation of Late-Onset Hypogonadism



TT = total testosterone; cFT = calculated free testosterone; PRL = prolactin; SHBG = sex hormone-binding globulin; LH = luteinising hormone; MRI = Magnetic resonance imaging.

3.5.2 History taking

Specific symptoms associated with LOH are shown in Table 3. History of surgical intervention for cryptorchidism or hypospadias must be taken into account as possible signs of congenital defects. Likewise, chronic and systemic comorbidity must be comprehensively investigated in every patient. Use of drugs that potentially interfere with the HPG axis should be ruled out (Table 2). Acute diseases are associated with development of functional hypogonadism and determination of serum total testosterone levels should be avoided in these conditions. However, recent data derived from SARS-CoV-2 infected patients showing worse outcomes in hypogonadal subjects suggest that the role of testosterone in the case of acute illness should be clarified [72, 73]. Several self-reported questionnaires or structural interviews have been developed for screening of hypogonadism. Although these case-history tools have demonstrated clinical utility in supporting the biochemical diagnosis of hypogonadism, or in the assessment of testosterone therapy outcomes, their specificity remains poor and they should not be used for a systematic screening of hypogonadal men [74].

Table 3: Specific symptoms associated with LOH

	Sexual symptoms	Physical symptoms	Psychological symptoms
More specific	<ul style="list-style-type: none"> - Reduced libido - Erectile dysfunction - Decreased spontaneous/ morning erections 	<ul style="list-style-type: none"> - Decreased vigorous activity - Difficulty walking >1 km - Decreased bending 	<ul style="list-style-type: none"> - Low mood/mood deflection - Decreased motivation - Fatigue
Less specific	<ul style="list-style-type: none"> - Reduced frequency of sexual intercourse - Reduced frequency of masturbation - Delayed ejaculation 	<ul style="list-style-type: none"> - Hot flushes - Decreased energy - Decreased physical strength/function/activity 	<ul style="list-style-type: none"> - Concentration or mnemonic difficulties - Sleep disturbances

3.5.3 Physical examination

Since obesity is frequently associated with hypogonadism (mostly functional), the determination of body mass index (BMI) and the measurement of waist circumference are strongly recommended in all individuals. Testicular and penile size, as well the presence of sexual secondary characteristics can provide useful information regarding overall androgen status. In addition, upper segment/lower segment ratio (n.v. > 0.92) and arm-span to height ratio (n.v. < 1.0) can be useful to identify a eunochoid body shape, especially in subjects with pre-pubertal hypogonadism or delayed puberty. Finally, digital rectal examination (DRE) should be performed in all subjects to exclude prostate abnormalities before testosterone therapy (any type) or to support suspicion of hypogonadism [75].

3.5.4 Summary of evidence and recommendations for the diagnostic evaluation of LOH

Summary of evidence
Sexual symptoms are the most specific symptoms associated with LOH.
Diagnosis of LOH should be based on specific signs and symptoms of androgen deficiency, together with consistently low serum testosterone levels.
Functional hypogonadism is a consequence of comorbidity/concomitant drugs, which can impair testosterone production in adulthood. The diagnosis of functional hypogonadism is a diagnosis of exclusion, after ruling out organic causes of hypogonadism.

Recommendations	Strength rating
Check for concomitant diseases, drugs and substances that can interfere with testosterone production/action.	Strong
Total testosterone must be measured in the morning (07.00 and 11.00 hours) and in the fasting state, with a reliable method.	Strong
Repeat total testosterone on at least two separate occasions when < 12 nmol/L and before starting testosterone therapy.	Strong
12 nmol/L total testosterone (3.5 ng/mL) represents a reliable threshold to diagnose late onset hypogonadism (LOH).	Strong
Consider sex hormone-binding globulin and free-testosterone calculation when indicated.	Strong
Calculated free-testosterone < 225 pmol/L has been suggested as a possible cut-off to diagnose LOH.	Weak
Analyse luteinising hormone (LH) and follicle-stimulating hormone (FSH) serum levels to differentiate between primary and secondary hypogonadism.	Strong
Consider prolactin (PRL) measurement if low sexual desire (or other suggestive signs/symptoms) and low or low-normal testosterone is present.	Strong
Perform pituitary magnetic resonance imaging (MRI) in secondary hypogonadism, with elevated PRL or specific symptoms of a pituitary mass and/or presence of other anterior pituitary hormone deficiencies.	Strong
Perform pituitary MRI in secondary severe hypogonadism (total testosterone < 6 nmol/L).	Weak

3.5.5 Recommendations for screening men with LOH

Recommendations	Strength rating
Screen for late onset hypogonadism (LOH) (including in T2DM) only in symptomatic men.	Strong
Do not use structured interviews and self-reported questionnaires for systematic screening for LOH as they have low specificity.	Strong

3.6 Treatment of LOH

3.6.1 Indications and contraindications for treatment of LOH

Patients with symptomatic hypogonadism (total testosterone < 12 nmol/L) without specific contraindications are suitable candidates to receive testosterone therapy (Table 4).

Absolute contraindications are untreated breast cancer and prostate cancer (PCa). Acute cardiovascular events as well as uncontrolled or poorly controlled congestive heart failure and severe lower urinary tract symptoms (LUTS) [International Prostate Symptom Score (IPSS) score > 19] represent other contraindications, as there is insufficient information on the long-term effects of testosterone therapy in these patients [66]. A positive family history for venous thromboembolism requires further analysis to exclude a condition of undiagnosed thrombophilia-hypofibrinolysis [76]. These patients need to be carefully counselled prior to testosterone therapy initiation. A haematocrit (HCT) > 54% should require testosterone therapy withdrawal, reduction in dose, change of formulation and venesection depending on the clinical situation to avoid any potential cardiovascular complications. Lower baseline HCT (48-50%) should be carefully evaluated before testosterone therapy initiation, to avoid pathological increases during treatment, especially in high-risk men such as those with chronic obstructive pulmonary disease (COPD) or Obstructive Sleep Apnoea Syndrome (OSAS). Accordingly, the Framingham Heart Study showed that HCT > 48% represented a condition associated with increased risk of coronary artery disease (CAD) and mortality and was associated with cardiovascular disorders [77]. Finally, testosterone therapy suppresses gonadotropin and endogenous testosterone secretion as well as spermatogenesis. Hence, testosterone therapy is contraindicated in individuals who desire fertility [78]. Secondary hypogonadism is characterised by low or inappropriately normal gonadotropin levels; therefore, the rationale is to substitute the gonadotropin deficiency with FSH and LH analogues, if fertility is desired [79].

Table 4: Main contraindications of testosterone therapy

Absolute contraindications	Locally advanced or metastatic prostate cancer (PCa) Male breast cancer Men with an active desire to have children Haematocrit \geq 54% Uncontrolled or poorly controlled congestive heart failure
Relative contraindication	IPSS score > 19 Baseline haematocrit 48-50% Familial history of venous thromboembolism

3.6.2 **Testosterone therapy outcomes**

3.6.2.1 *Sexual dysfunction*

Sexual concerns are the main symptoms of hypogonadal patient [5, 10, 80, 81]. A consistent body of evidence shows that testosterone therapy in hypogonadal men (total testosterone < 12 nmol/L) may have a beneficial effect on several aspects of sexual life; in contrast, there is no evidence of benefits in using testosterone therapy for treating sexual dysfunction in eugonadal men [53, 66, 82, 83]. The beneficial effect on sexual function seems to be more related to testosterone level normalisation than the specific testosterone formulations used [83, 84].

A recent meta-analysis of only placebo-controlled RCTs using the International Index of Erectile Function (IIEF) [85] as a possible tool for outcome evaluation, showed that testosterone therapy significantly improves erectile function (as measured by IIEF-Erectile Function domain score) and that patients with more severe hypogonadism (i.e., total testosterone < 8 nmol/L) are more likely to achieve better improvement than patients with milder hypogonadism (i.e., total testosterone < 12 nmol/L). Similar results were observed for sexual desire; however, the presence of metabolic comorbidity (such as diabetes and obesity) decreased the magnitude of these improvements. In particular, testosterone therapy alone resulted in a clinically effective outcome only in patients with milder ED [66]. Other sexual function parameters, such as intercourse, orgasm and overall satisfaction, were all improved compared with placebo [66]. Men with comorbidity such as diabetes usually show modest improvements in terms of sexual function after testosterone therapy and may potentially require concomitant phosphodiesterase type 5 inhibitors (PDE5Is) to improve effectiveness [5, 83]. However, the specific beneficial effect derived from the combined use of testosterone therapy and PDE5Is is not completely clear [53]. Similarly, information related to the combined use of testosterone therapy with other ED drug therapies is lacking [5, 83].

The Sexual Function Trial of the Testosterone Trials (TTrials) (one of the largest placebo-controlled trials on testosterone therapy) documented consistent improvements in 10 of 12 measures of sexual activities in older (\geq 65 years) hypogonadal men, particularly in frequency of intercourse, masturbation and nocturnal erections (as measured by PDQ-Q4) [86]. The magnitude in improvement was shown to be proportional to the increase in serum total testosterone, fT and oestradiol levels, it was not possible to demonstrate a threshold level [87]. A study of 220 men with MetS with or without T2DM also found that sexual function improved in men who reported sexual problems with improvement in IIEF scores with specific increases in libido and sexual satisfaction [24].

3.6.2.2 *Body composition and metabolic profile*

Late onset hypogonadism is associated with a greater percentage fat mass and a lesser lean mass compared to testosterone-replete men [88]. The major effect of low testosterone is to increase visceral adiposity but also leads to deposition of lipids in the liver and muscle and is associated with atherosclerosis [19]. Some published data have suggested that testosterone therapy reduces percentage body fat and increases lean mass [89]. Testosterone therapy has also been found to decrease waist circumference, body weight and BMI, with these effects more predominant after 12 months of treatment [89-91]. However, it should be recognised that these results are mainly derived from registry and observational trials, which have important limitations due to the risk of selection bias for the non-random assignment of testosterone exposure. Accordingly, data derived from RCTs showed only an improvement of fat mass and lean mass of the same amount without any modifications in body weight [21].

3.6.2.3 *Mood and cognition*

Several observational studies have documented a relationship between depressive symptoms, reduced QoL and hypogonadism [92, 93]. However, the specific relationship between hypogonadism and the incidence of depression is still unclear [93]. Only a few placebo-controlled RCTs have investigated the role of testosterone

therapy in improving depressive symptoms. Data derived from TTrialS showed that testosterone therapy improved mood, and depressive symptoms as continuous measures using several instruments [86]. However, the final effect was small in magnitude. In line with these data, the largest meta-analysis of available studies, including 1,890 hypogonadal men (baseline total testosterone < 12 nmol/L or fT < 225 pmol/L) men from 27 RCTs, documented that the positive effect of testosterone therapy was particularly evident in patients with milder symptoms [94]. The BLAST study of testosterone therapy in T2DM reported that those men with depression were less likely to respond with regard to symptoms of sexual dysfunction compared to men without depression [29].

Robust data on the effect of testosterone therapy on QoL are limited. Although recent meta-analyses suggest a significant effect of testosterone therapy over placebo, the magnitude is low and the heterogeneity high, therefore reducing the scientific value of the effect [84, 95].

The role of testosterone therapy in patients with cognitive impairment is even more uncertain. The TTrialS evaluated the effect of testosterone therapy in 493 individuals with age-associated memory impairment in order to assess possible improvement of several aspects of cognitive function. However, the final results failed to demonstrate any beneficial effect of testosterone therapy in improving cognitive function [86].

3.6.2.4 Bone

Evidence suggests that bone mineralisation requires circulating sex steroids within the normal range [96]. The possible association between mild hypogonadism and osteopenia/osteoporosis is weak, whereas severe hypogonadism (total testosterone < 3.5 nM) is frequently associated with bone loss and osteoporosis, independent of patient age [96]. Two independent meta-analyses showed a positive effect of testosterone therapy on bone mineral density (BMD), with the highest effect at the lumbar level [97, 98]. Similarly, data derived from TTrialS confirmed that testosterone therapy increased BMD in hypogonadal ageing men, particularly at the lumbar level [86]. However, available data are insufficient to determine the effect of testosterone therapy alone on the risk of fractures [96]. The use of testosterone therapy as an adjunct to anti-resorptive treatment in hypogonadal patients at high risk of fractures has not been established. Therefore, anti-resorptive therapy must be the first-choice treatment in hypogonadal men at high risk for bone fractures. The combination of anti-resorptive treatment and testosterone therapy should be offered only in conjunction with hypogonadism-related symptoms.

3.6.2.5 Vitality and physical strength

The role of testosterone in stimulating muscle growth and strength is well established. Accordingly, androgenic-anabolic steroids (AAS) have been used as performance-enhancing agents to increase physical performance in competitive sport [99]. In this regard, testosterone therapy in hypogonadal men has been shown to increase muscle mass and reduce fat mass, with limited effects on final weight [21]. Despite this evidence, the role of testosterone therapy in older men with mobility limitations remains unclear. The National Health and Nutrition Examination Survey 1999-2004 [100] was unable to detect any association between overall circulating testosterone levels and the amount of physical activity. However, among non-obese men, those in the highest physical activity tertile were significantly less likely to have low or low-normal testosterone than those in the lowest tertile. Data from TTrialS indicated that testosterone therapy did not substantially increase the fraction of men whose 6-minute walking distance increased > 50 m or the absolute increase in the distance walked by those enrolled in the physical function trial [86]. However, when the whole population of the TTrialS was considered, a significant, although modest, positive effect on these two parameters was reported [86]. Similar data were derived from the Vitality Trial [86].

3.6.2.6 Summary of evidence and recommendations for testosterone therapy outcome

Summary of evidence
Testosterone therapy can improve milder forms of ED and libido in hypogonadal men.
Testosterone therapy can improve other sexual symptoms, including intercourse frequency, orgasm and overall satisfaction.
Testosterone therapy can similarly increase lean mass, reduce fat mass, and improves insulin resistance.
Testosterone therapy can improve weight, waist circumference and lipid profile, but findings are not unique.
Testosterone therapy can improve milder depressive symptoms in hypogonadal men.
Testosterone therapy can improve bone mineral density, but information related to fracture risk is lacking.

Recommendations	Strength rating
The use of testosterone therapy in eugonadal men is not indicated.	Strong
Use testosterone therapy as first-line treatment in patients with symptomatic hypogonadism and mild erectile dysfunction (ED).	Strong
Use combination of phosphodiesterase type 5 inhibitors and testosterone therapy in more severe forms of ED as it may result in better outcomes.	Weak
Use conventional medical therapies for severe depressive symptoms and osteoporosis.	Strong
Do not use testosterone therapy to improve body composition, reduce weight and benefit cardio-metabolic profile.	Weak
Do not use testosterone therapy to improve cognition vitality and physical strength in ageing men.	Strong

3.6.3 **Choice of treatment**

3.6.3.1 *Lifestyle factors*

As reported above, functional hypogonadism is frequently associated with obesity and metabolic disorders [101]. Therefore, weight loss and lifestyle changes should be the first approach for all overweight and obese men with hypogonadism. A previous meta-analysis documented that a low-calorie diet is able to revert obesity-associated secondary hypogonadism by increasing total testosterone and fT, reducing oestrogens and restoring normal gonadotropin circulating levels [102]. This was confirmed in a recent updated meta-analysis showing that the increase in testosterone is significantly associated with weight reduction [103]. Similar results can be obtained through physical activity, which is associated with the duration of scheduled exercise and weight loss obtained [103]. However, it should be recognised that the increase in testosterone levels observed after a low-calorie diet and physical activity is small (1-2 nmol) [102, 103]. It should also be recognised that 60-86% of weight lost is regained after 3 years and 75-121% after 5 years [104]. A greater testosterone increase can be achieved through bariatric surgery, which results in an average increase of about 10 nmol/L depending on the degree of weight loss [103]. Lifestyle changes represent an essential part of the management of obesity; however, some evidence suggests that when compared to lifestyle modifications alone, testosterone therapy-treated obese men benefit most from relief of their symptoms associated with testosterone deficiency, whereas those not treated did not benefit [79]. There is limited evidence to suggest that combination of lifestyle interventions and testosterone therapy in symptomatic hypogonadal men might result in better outcomes [88]. There is a large, on-going placebo-controlled RCT that aims to determine whether lifestyle intervention alone or in combination with testosterone therapy reduces T2DM incidence and improves glucose tolerance [105].

3.6.3.2 *Medical preparations*

Several testosterone formulations are available (Table 5). Direct comparisons among different testosterone products are still lacking. Candidates for testosterone therapy should be adequately informed about the possible risks and benefits of all available testosterone preparations. The final choice should be based on the clinical situation, testosterone formulation availability, and patient needs and expectations [106].

3.6.3.2.1 Oral formulations

The esterification of testosterone with a long-chain fatty acid (testosterone undecanoate; TU) enables testosterone to be absorbed by the intestine through the lymphatic system, by-passing liver metabolism. This formulation has been available in oleic acid since the 1970s, and it has been recently reformulated in a mixture of castor oil and propylene glycol laureate (TU caps), to allow the drug to be maintained at room temperature without degradation [107]. The main limitation is related to the poor bioavailability, which is strongly dependent on dietary fat content [107]. Recently, the US Food and Drug Administration (FDA) approved a new formulation of oral TU incorporating a liquid-filled hard capsule drug delivery system and a higher amount (225 mg) of the compound, which improves oral availability (<https://www.fda.gov/media/110187/download>). In an open label study of approximately 4 months' duration (NCT02722278), 145 (87%) of 166 hypogonadal men enrolled who received the TU caps formulation had mean total testosterone concentration within the normal eugonadal range at the end of treatment (<https://www.fda.gov/media/110187/download>). However, the TU caps compound is not available in Europe.

Mesterolone is a 5 α -DHT derivate available for oral administration. Along with DHT, mesterolone cannot be converted to oestrogens and can only be used for a limited period and specific indications, such as the presence of painful gynaecomastia. However, the lack of a full spectrum of testosterone bioactivity strongly limits its long-term use [107].

3.6.3.2.2 Parenteral formulations

Injectable testosterone preparations can be classified according to their half-lives (Table 5). Testosterone propionate is a short-term ester formulation requiring multiple fractionated doses (usually 50 mg, every 2-3 days), thus representing a major limitation for its use [107]. Cypionate and enanthate-T esters are short-term formulations, requiring administration every 2-4 weeks. A formulation containing mixed testosterone esters (TU, isocaproate, phenyl propionate, propionate - Sustanon®) which allows some benefit of a smoother release of testosterone into the circulation is available in some countries. The use of these older formulations is associated with wide fluctuations in plasma testosterone concentrations and is often reported as unpleasant by patients and potentially resulting in adverse effects, such as polycythaemia [107, 108]. A longer-lasting TU injectable formulation is widely available [107]; which has a good safety/benefit profile allowing the maintenance of normal stable testosterone levels at a dose of 1,000 mg initially every 12 weeks, following a 6-week loading dose, but can be adjusted to a frequency of 10-14 weeks dependent on the trough (pre-injection level) after 3-5 injections to maintain levels in the therapeutic range (usually > 12 and < 18 nmol/L) [107, 109].

3.6.3.2.3 Transdermal testosterone preparations

Among the available transdermal formulations, testosterone gels represent the most frequently used preparations. The gel is quickly absorbed by the stratum corneum, creating a reservoir within the subcutaneous tissues from where testosterone is continuously delivered for 24 hours, after a single daily application. These formulations have been shown to normalise serum testosterone levels with an excellent safety profile [107]. The introduction of specific devices and skin enhancers has resulted in better skin penetration of the drugs, thus reducing potential adverse effects. Local skin adverse effects are limited when compared to those with traditional testosterone patches, but they potentially allow transference of testosterone during close contact with the skin surface. The risk can be reduced by wearing clothing or by applying the gel on skin surfaces not usually touched (e.g., the inner thigh surface) [107]. To reduce the total amount of gel applied and residual quantities remaining on the skin, new formulations of testosterone gel have been introduced with a testosterone concentration of 1.62-2% [107]. Another transdermal testosterone formulation includes a topical, alcohol-based testosterone (2%) solution, which must be applied to the underarm once daily, using a metered dose applicator [107]. This testosterone formulation is not available in Europe. Testosterone levels should be monitored to optimise the testosterone dose. Blood collection is best taken at 2-4 hours after gel application to use the peak level of testosterone absorbed as a reference for adequate therapeutic levels. Levels of testosterone after application can vary and a repeat measurement may be indicated especially as sometimes, inadvertently, the skin over the vene-puncture site can be contaminated by the gel, leading to falsely elevated results.

In some European countries, DHT is available as a hydroalcoholic 2.5% gel. It is rapidly absorbed, reaching a steady state in 2-3 days. Similar to that reported for mesterolone, DHT is not aromatised but can be useful for treating particular conditions, such as gynaecomastia and microphallus [107].

3.6.3.2.4 Transmucosal formulations

3.6.3.2.4.1 Transbuccal Testosterone preparations

A testosterone buccal system is still available in several countries. It consists on a sustained-release muco-adhesive buccal-testosterone-tablet requiring twice-daily application to the upper gums. The tablet does not dissolve completely in the mouth and must be removed after 12 hours. This formulation has been proven to restore testosterone levels within the physiological range with minimal or transient local problems, including gum oedema, blistering and gingivitis [107].

3.6.3.2.4.2 Transnasal testosterone preparations

A gel for intranasal administration is available in some countries, including the USA and Canada. It requires administration two or three times daily using a specific metered-dose pump. The application is rapid, non-invasive, convenient, and avoids secondary transference observed with other topical products [107].

3.6.3.2.5 Subdermal depots

The implantation of testosterone pellets, available in the USA, UK and Australia, represents the longest available testosterone formulation lasting from 4-7 months. However, the procedure is invasive and may be unattractive to patients [107].

3.6.3.2.6 Anti-oestrogens

Anti-oestrogens, including selective oestrogen receptor (ER) modulators (SERMs) and aromatase inhibitors (AI) have been suggested as off-label treatments to restore testosterone levels and fertility in men with functional secondary hypogonadism or idiopathic infertility. They work by preventing down-regulation of the HPG axis by oestrogens and, for this reason are particularly useful in men with obesity and metabolic disorders [103]. In

the latter case, the hypothesis is that the excess of adipose tissue leads to increased aromatase activity and oestrogens levels resulting in impairment of the HPG [101]. Due to their putative mechanism of action, they require an intact HPG axis and cannot work in primary hypogonadism or secondary hypogonadism due to organic damage of the HPG axis. Both types of SERMs, which bind ERs with an agonist or antagonist effect depending upon the target tissue, and AIs, which prevent androgens from being converted into oestrogens by aromatase, have been used in clinical practice [107]. The evidence published so far is poor; all these products are off-label treatments and SERMs, due to their agonistic effect on venous vessels, could predispose men to the development of venous thromboembolism [107]. In this context patients should be warned of the potential increased risk of venous thromboembolism, although data are lacking. Long-term use of these agents can lead to reduced bone density and development of osteoporosis, potentially increasing fracture risk.

3.6.3.2.7 Gonadotropins

Considering the aforementioned limitations regarding the use of anti-oestrogens, gonadotropin therapy should be considered the standard in men with secondary hypogonadism who desire paternity (Table 5) [107]. The treatment is based on the use of human chorionic gonadotropin (hCG), purified from the urine of pregnant women. The most expensive recombinant hCG (rhCG) and LH (rLH) formulations do not offer clinical advantages [107]. According to a meta-analysis of the available evidence, hCG should be administered with FSH as combined therapy results in better outcomes. Similar to recombinant hCG, recombinant FSH (rFSH) does not seem to offer any advantages compared to urinary-derived preparations [110]. More details on the use of gonadotropins are provided in Section 10.

Table 5: Available preparations for hypogonadism treatment

Formulation	Chemical structure	t 1/2	Standard dosage	Advantages	Disadvantages
GONADOTROPINS					
Human chorionic gonadotrophin (HCG)					
Extractive	HCG purified from the urine of pregnant women	NA	1,000-2,000 IU 3 times/week	Low cost	Multiple weekly administration
Recombinant	Human recombinant HCG	NA	No data in men	NA	
Luteotropic hormone (LH)					
Recombinant	Human recombinant LH	NA	No data in men	NA	
Follicle-stimulating hormone (FSH)					
Extractive	FSH purified from urine of pregnant women	NA	75-150 IU 3 times/week	Low cost	Multiple weekly administration
Recombinant	Human recombinant FSH	NA	75-150 IU 3 times/week		Multiple weekly administration
TESTOSTERONE PREPARATIONS					
Oral					
Testosterone undecanoate	17- α -hydroxylester	4 hours	120-240 mg 2-3 times daily	- Reduction of liver involvement - Oral convenience - Modifiable dosage	- Unpredictable absorption depending on dietary fat content - Must be taken with meals
Mesterolone	1 α -methyl-4, 5 α -dihydro-testosterone	12 hours	50-100 mg 2-3 times daily	- Oral convenience - Modifiable dosage - Useful in gynaecomastia	- Not aromatisable

Parental					
Testosterone enanthate	17- α -hydroxylester	4-5 days	250 mg every 2-3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of adverse effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone cypionate	17- α -hydroxylester	8 days	200 mg every 2-3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of adverse effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone propionate	17- α -hydroxylester	20 hours	100 mg every 2 days	- Low cost - Very short-acting preparation allowing drug withdrawal in case of adverse effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone ester mixture Propionate (30mg) Phenylpropionate (60 mg) Isocaproate (60 mg) Decanoate (100 mg)	4-androsten-3-one-17 beta-hydroxy-androst-4-en-3-one	4-5 days	250 mg every 3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of adverse effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone undecanoate in castor oil	17- α -hydroxylester	34 days	1,000 mg every 10-14 weeks *750 mg every 10 weeks	- Steady-state testosterone level without fluctuation - Long-lasting - Less frequent administration	- Pain at injection site - Long-acting preparation not allowing rapid drug withdrawal in case of adverse effects
Surgical implants	Native testosterone	--	4-6 200 mg implants lasting up to 6 months	- Long duration and constant serum testosterone level	- Placement is invasive - Risk of extrusion and site infections
TRANSDERMAL					
Testosterone patches	Native testosterone	10 hours	50-100 mg/day	Steady-state testosterone level without fluctuation	- Skin irritation - Daily administration
Testosterone gel 1-2%	Native testosterone	6 hours	50-100 mg/day	Steady-state testosterone level without fluctuation	- Possible transfer during intimate contact - Daily administration
Underarm testosterone (testosterone solution 2%)	Native testosterone	NA	60-120 mg/day	Steady-state testosterone level without fluctuation	- Possible transfer during intimate contact - Daily administration
Dihydro-testosterone gel 2.5%	Native dihydro-testosterone	NA	34-70 mg/day	- Steady-state testosterone level without fluctuation - Useful in gynaecomastia	- Possible transfer during intimate contact - Daily administration - Not aromatisable

TRANSMUCOSAL					
Testosterone buccal system	Native testosterone	12 hours	60 mg 3 times daily	Steady-state testosterone level without fluctuation	- Possible oral irritation - Twice-daily dosing - Unpleasant taste
Testosterone nasal	Native testosterone	6 hours	33 mg 3 times daily	Steady-state testosterone level without fluctuation	- Nasal irritation - Multiple daily administration

NA = not applicable.

3.6.3.3 Summary of evidence and recommendations for choice of treatment for LOH

Summary of evidence
Weight loss obtained through a low-calorie diet and regular physical activity result in a small improvement in testosterone levels.
Testosterone gels and long-acting injectable TU represent T preparations with the best safety profile.
Gonadotropins treatment can be used to restore fertility in men with secondary hypogonadism.

Recommendations	Strength rating
Treat, when indicated, organic causes of hypogonadism (e.g., pituitary masses, hyperprolactinemia, etc).	Strong
Improve lifestyle and reduce weight (e.g., obesity); withdraw, when possible, concomitant drugs that can impair testosterone production; treat co-morbidity before starting testosterone therapy.	Weak
Fully inform patients about expected benefits and adverse effects of any treatment option. Select the testosterone preparation in a joint decision process, only with fully informed patients.	Strong
The aim of testosterone therapy is to restore serum testosterone concentration to the average normal range for young men.	Weak
Use testosterone gels rather than long-acting depot administration when starting initial treatment, so that therapy can be adjusted or stopped in the case of treatment-related adverse effects.	Weak

3.7 Safety and follow-up in hypogonadism management

3.7.1 Hypogonadism and fertility issues

The aim of pharmacological management of hypogonadism is to increase testosterone levels. The first choice is to administer exogenous testosterone. However, while exogenous testosterone has a beneficial effect on the clinical symptoms of hypogonadism, it also inhibits gonadotropin secretion by the pituitary gland, resulting in impaired spermatogenesis and sperm cell maturation [111]. Therefore testosterone therapy is contraindicated in hypogonadal men seeking fertility treatment [78]. When secondary hypogonadism is present, gonadotropin therapy can maintain normal testosterone levels and restore sperm production [5].

3.7.2 Male breast cancer

In vitro and *in vivo* studies have clearly documented that breast cancer growth is significantly influenced by testosterone and/or by its conversion to E2 through different mechanisms and pathways [112]. Accordingly, the use of SERMs still represents an important therapeutic option in the management of this cancer [112]. No information is available on the role of testosterone therapy in patients successfully treated for male breast cancer; therefore, treated and active male breast cancer should be recognised as absolute contraindications for testosterone therapy.

3.7.3 Lower urinary tract symptoms/benign prostatic hyperplasia

Based on the assumption that prostate growth is dependent on the presence of androgens, historically testosterone therapy historically has raised some concerns regarding the possibility of aggravating LUTS in patients affected by benign prostatic hyperplasia (BPH) associated with prostate enlargement [75, 113]. However, pre-clinical and clinical data have indicated that low rather than high androgen levels may decrease bladder capacity, alter tissue histology and decrease the ratio of smooth muscle to connective tissue, thus impairing urinary dynamics [75, 113].

A trial of 60 patients undergoing testosterone therapy for 6 months showed no significant differences in post-voidal residual urine and prostate volume, while storage symptoms as measured by IPSS significantly improved, despite an increase in prostate-specific antigen (PSA) level. A larger pre-treatment prostate volume was a predictive factor of improvement in LUTS [114]. A long-term study of 428 men undergoing testosterone therapy for 8 years demonstrated significant improvements in IPSS, no changes max flow rate (Q_{max}) and residual urine volume, but also a significant increase in prostate volume [115]. Similar data from the Registry of Hypogonadism in Men (RHYME), including 999 patients with a follow-up of 3 years, did not document any difference in PSA levels or total IPSS in men undergoing testosterone therapy, compared to untreated patients [116]. Similar results were reported in an Italian registry (SIAMO-NOI), collecting data from 432 hypogonadal men from 15 centres [117]. Meta-analyses have not found significant changes in LUTS between patients treated with testosterone or placebo [118-124]. According to the most recent literature, there are no grounds to discourage testosterone therapy in hypogonadal patients with BPH/LUTS and there is evidence of limited benefit from androgen administration. The only concern is related to patients with severe LUTS (IPSS > 19), as they are usually excluded from RCTs, therefore limiting the long-term safety data of testosterone therapy in this specific setting [75].

3.7.4 **Prostate cancer (PCa)**

A considerable number of observational studies have failed to demonstrate any association between circulating higher testosterone levels and PCa [125]. In contrast, studies investigating the relationship between low levels of testosterone and risk of PCa have found that men with very low levels of fT have a reduced risk of developing low-to-intermediate-grade PCa, but have a non-significantly increased chance of developing high-grade PCa [125]. This peculiar pattern was also reported in trials such as the Health Professionals Follow-up Study, the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE), with varying magnitudes of significance [126].

The most recent meta-analysis, including 27 placebo-controlled, RCTs, found no evidence of increased PSA levels following testosterone therapy for one year. When considering 11 studies reporting on the occurrence of PCa, the meta-analysis found no evidence of increased risk of PCa. However, a 1-year follow-up may be considered too short to draw conclusions on PCa occurrence. Furthermore, the analysis was restricted to studies with > 1-year follow-up, but no significant changes in PSA levels nor increased risk of PCa were found [119]. After 5-years' median follow-up in three independent registry studies with > 1,000 patients undergoing testosterone therapy, PCa occurrence remained at all times below the reported incidence rate in the general population [127]. Similar results were reported by a more recent large observational study including 10,311 men treated with testosterone therapy and 28,029 controls with a median follow-up of 5.3 years [128]. The same study, also showed that the risk of PCa was decreased for men in the highest tertile of testosterone therapy cumulative dose exposure as compared with controls [128].

With regards to PCa survivors, safety in terms of the risk of recurrence and progression has not yet been established. Limited data are available in the literature, with most case series not providing sufficient data to draw definitive conclusions (e.g., insufficient follow-up, small samples, lack of control arms, heterogeneity in study population and treatment regimen, etc.) [129]. More recently, a meta-analysis derived from 13 studies including 608 patients, of whom 109 had a history of high-risk PCa, with follow-up of 1-189.3 months [130], suggested that testosterone therapy did not increase the risk of biochemical recurrence, but the available evidence is poor, limiting data interpretation [130]. Similar considerations can be derived from another, larger meta-analysis of 21 studies [131]. It is important to recognise that most of the studies analysed included low-risk patients with Gleason score < 8 [130].

In conclusion, recent literature does not support an increased risk of PCa in hypogonadal men undergoing testosterone therapy. Although it is necessary to avoid testosterone administration in men with advanced PCa, insufficient long-term prospective data on the safety of androgen administration in PCa survivors [131], without recurrence should prompt caution in choosing to treat symptomatic hypogonadal men in this setting. Specifically, patients should be fully counselled that the long-term effects of testosterone therapy in this setting are still unknown and requires further investigation. If an occult PCa is not detected before initiation of testosterone therapy, treatment may unmask the cancer detected by an early rise in PSA over 6-9 months of therapy. Due to the lack of strong evidence-based data on safety, the possible use of testosterone therapy in symptomatic hypogonadal men previously treated for PCa should be adequately discussed with the patients and limited to low-risk individuals.

3.7.5 **Cardiovascular Disease**

Evidence suggests that hypogonadal men have an increased risk of CVD [132, 133]. Whether or not LOH is a cause or a consequence of atherosclerosis has not been clearly determined. Late-onset hypogonadism is associated with CV risk factors, including central obesity, insulin resistance and hyperglycaemia, dyslipidaemia (elevated total cholesterol, LDL-cholesterol, triglycerides and low HDL-cholesterol), pro-thrombotic tendency

and chronic inflammatory state [133]. Atherosclerosis is a chronic inflammatory disease, that releases pro-inflammatory cytokines into the circulation, which are known to suppress testosterone release from the HPG axis. Evidence from RCTs of testosterone therapy in men with MetS and/or T2DM demonstrates some benefit in CV risk, including reduced central adiposity, insulin resistance, total cholesterol and LDL-cholesterol and suppression of circulating cytokines [14, 23-25, 29, 133]. However, due to the equivocal nature of these studies, testosterone therapy cannot be recommended for indications outside the specific symptoms.

Published data show that LOH is associated with an increase in all-cause and CVD-related mortality [12, 134-137]. These studies are supported by a meta-analysis that concluded that hypogonadism is a risk factor for cardiovascular morbidity [123] and mortality [138]. Importantly, men with low testosterone when compared to eugonadal men with angiographically proven coronary disease have twice the risk of earlier death [133]. Longitudinal population studies have reported that men with testosterone in the upper quartile of the normal range have a reduced number of CV events compared to men with testosterone in the lower three quartiles [134]. Androgen deprivation therapy for PCa is linked to an increased risk of CVD and sudden death [139]. Conversely, two long-term epidemiological studies have reported reduced CV events in men with high normal serum testosterone levels [140, 141]. Erectile dysfunction is independently associated with CVD and may be the first clinical presentation in men with atherosclerosis.

The knowledge that men with hypogonadism and/or ED may have underlying CVD should prompt individual assessment of their CV risk profile. Individual risk factors (e.g., lifestyle, diet, exercise, smoking, hypertension, diabetes and dyslipidaemia) should be assessed and treated in men with pre-existing CVD and in patients receiving androgen deprivation therapy. Cardiovascular risk reduction can be managed by primary care clinicians, but patients should be appropriately counselled by clinicians active in prescribing testosterone therapy [80]. If appropriate, they could be referred to cardiologists for risk stratification and treatment of co-morbidity.

No RCTs have provided a clear answer on whether testosterone therapy affects CV outcomes. The TTRial (n=790) in older men [142], the TIMES2 (n=220) [24] and the BLAST studies in men with MetS and T2DM and the pre-frail and frail study in elderly men - all of 1-year duration - did not reveal any increase in Major Adverse Cardiovascular Events (MACE) [24, 27, 142, 143]. In this context, MACE is defined as the composite of CV death, non-fatal acute myocardial infarction, acute coronary syndromes, stroke and cardiac failure. Randomised controlled trials between 3 and 12 months in men with known heart disease treated with testosterone have not found an increase in MACE, but have reported improvement in cardiac ischaemia, angina and functional exercise capacity [144-146]. The European Medicines Agency has stated that 'The Co-ordination Group for Mutual recognition and Decentralisation Procedures-Human (CMDh), a regulatory body representing EU Member States, has agreed by consensus that there is no consistent evidence of an increased risk of heart problems with testosterone in men who lack the hormone (a condition known as hypogonadism). However, the product information is to be updated in line with the most current available evidence on safety, and with warnings that the lack of testosterone should be confirmed by signs and symptoms and laboratory tests before treating men with these drugs [147].

As a whole, as for MACE, current available data from interventional studies suggest that there is no increased risk with up to 3 years of testosterone therapy [148-151]. The weight of the currently published evidence has reported that testosterone therapy in men with diagnosed hypogonadism has neutral or beneficial actions on MACE in patients with normalised testosterone levels. The findings could be considered sufficiently reliable for a 3-year course of testosterone therapy, after which no available study can exclude further or long-term CV events [152, 153].

3.7.5.1 *Cardiac Failure*

Testosterone treatment is contraindicated in men with severe chronic cardiac failure because fluid retention may lead to exacerbation of the condition. Some studies including one of 12 months' duration have shown that men with moderate chronic cardiac failure may benefit from low doses of testosterone, which achieve mid-normal range testosterone levels [145, 154, 155]. If a decision is made to treat hypogonadism in men with chronic cardiac failure, it is essential that the patient is followed up carefully with clinical assessment and both testosterone and haematocrit measurements on a regular basis. An interesting observation is that untreated hypogonadism increased the re-admission and mortality rate in men with heart failure [156].

3.7.6 *Erythrocytosis*

An elevated haematocrit is the most common adverse effect of testosterone therapy. Stimulation of erythropoiesis is a normal biological action that enhances delivery of oxygen to testosterone-sensitive tissues

(e.g., striated, smooth and cardiac muscle). Any elevation above the normal range for haematocrit usually becomes evident between 3 and 12 months after testosterone therapy initiation. However, polycythaemia can also occur after any subsequent increase in testosterone dose, switching from topical to parenteral administration and, development of co-morbidity, which can be linked to an increase in haematocrit (e.g., respiratory or haematological diseases).

There is no evidence that an increase of haematocrit up to and including 54% causes any adverse effects. If the haematocrit exceeds 54% there is a testosterone independent, but weak associated rise in CV events and mortality [77, 157-159]. Any relationship is complex as these studies were based on patients with any cause of secondary polycythaemia, which included smoking and respiratory diseases. There have been no specific studies in men with only testosterone-induced erythrocytosis.

Three large studies have not shown any evidence that testosterone therapy is associated with an increased risk of venous thromboembolism [160, 161]. However, one study showed that an increased risk peaked at 6 months after initiation of testosterone therapy, then declined over the subsequent period [162]. No study reported whether there was monitoring of haematocrit, testosterone and/or E2 levels. High endogenous testosterone or E2 levels are not associated with a greater risk of venous thromboembolism [163]. In one study venous thromboembolism was reported in 42 cases and 40 of these had diagnosis of an underlying thrombophilia (including factor V Leiden deficiency, prothrombin mutations and homocysteinuria) [164]. In a RCT of testosterone therapy in men with chronic stable angina there were no adverse effects on coagulation, by assessment of tissue plasminogen activator or plasminogen activator inhibitor-1 enzyme activity or fibrinogen levels [165]. A meta-analysis of RCTs of testosterone therapy reported that venous thromboembolism was frequently related to underlying undiagnosed thrombophilia-hypofibrinolysis disorders [76].

With testosterone therapy an elevated haematocrit is more likely to occur if the baseline level is toward the upper limit of normal prior to initiation. Added risks for raised haematocrit on testosterone therapy include smoking or respiratory conditions at baseline. Higher haematocrit is more common with parenteral rather than topical formulations. In men with pre-existing CVD extra caution is advised with a definitive diagnosis of hypogonadism before initiating testosterone therapy and monitoring of testosterone as well as haematocrit during treatment.

Elevated haematocrit in the absence of co-morbidity or acute CV or venous thromboembolism can be managed by a reduction in testosterone dose, change in formulation or if the elevated haematocrit is very high by venesection (500 mL), even repeated if necessary, with usually no need to stop the testosterone therapy.

3.7.7 **Obstructive Sleep Apnoea**

There is also no evidence that testosterone therapy can result in onset or worsening of sleep apnoea. Combined therapy with Continuous Positive Airway Pressure (CPAP) and testosterone gel was more effective than CPAP alone in the treatment of obstructive sleep apnoea [166]. In one RCT, testosterone therapy in men with severe sleep apnoea reported a reduction in oxygen saturation index and nocturnal hypoxaemia after 7 weeks of therapy compared to placebo, but this change was not evident after 18 weeks' treatment and there was no association with baseline testosterone levels [167].

3.7.8 **Follow up**

Testosterone therapy alleviates symptoms and signs of hypogonadism in men in a specific time-dependent manner. The TTrial clearly showed that testosterone therapy improved sexual symptoms as early as 3 months after initiation [86]. Similar results have been derived from meta-analyses [53, 76]. Hence, the first evaluation should be planned after 3 months of treatment. Further evaluation may be scheduled at 6 months or 12 months, according to patient characteristics, as well as results of biochemical testing (see below). Table 6 summarises the clinical and biochemical parameters that should be monitored during testosterone therapy.

Trials were designed to maintain the serum testosterone concentration within the normal range for young men (280–873 ng/dL or 9.6–30 nmol/L) [86]. This approach resulted in a good benefit/risk ratio. A similar approach could be considered during follow-up. The correct timing for evaluation of testosterone levels varies according to the type of preparation used (Table 5). Testosterone is involved in the regulation of erythropoiesis [108] and prostate growth [75], hence evaluation of PSA and haematocrit should be mandatory before and during testosterone therapy. However, it is important to recognise that the risk of PCa in men aged < 40 years is low. Similarly, the mortality risk for PCa in men aged > 70 years is not been considered high enough to warrant monitoring in the general population [168]. Hence, any screening for PCa through determination of PSA and DRE in men aged < 40 or > 70 years during testosterone therapy should be discussed with the patients.

Baseline and, at least, annually glyco-metabolic profile evaluation may be a reasonable

consideration, particularly in the management of functional hypogonadism. Testosterone therapy may be beneficial for hypogonadal men with low or moderate fracture risk [96]; therefore, dual energy X-ray absorptiometry (DEXA) bone scan may also be considered at baseline and 18-24 months following testosterone therapy, particularly in patients with more severe hypogonadism [96].

Digital rectal examination may detect prostate abnormalities that can be present even in men with normal PSA values. Hence, DRE is mandatory in all men at baseline and during testosterone therapy.

The decision to stop testosterone therapy or to perform prostate biopsy due to PSA increase or prostate abnormalities should be based on local PCa guidelines. There is a large consensus that any increase of haematocrit > 54% during testosterone therapy requires therapy withdrawal and phlebotomy to avoid potential adverse effects including venous-thromboembolism and CVD, especially in high-risk individuals. In patients with lower risk of relevant clinical sequelae, the situation can be alternatively managed by reducing testosterone dose and switching formulation along with venesection. A positive family history of venous-thromboembolism should be carefully investigated and the patient counselled with regard to testosterone therapy to avoid/prevent thrombophilia-hypofibrinolysis [76]. Finally, caution should be exercised in men with pre-existing CVD or at higher risk of CVD.

Table 6: Clinical and biochemical parameters to be checked during testosterone therapy

Parameters	Year 1 of treatment			After year 1 of treatment	
	Baseline	3 months	6/12 months	Annually	18-24 months
Clinical					
Symptoms	X	X	X	X	
Body Mass Index					
Waist circumference	X	X	X	X	
Digital rectal examination	X	X	X	X	
Blood pressure	X	X	X	X	
Biochemistry					
PSA (ng/mL)	X	X	X	X	
Haematocrit (%)	X	X	X	X	
Testosterone	X	X	X	X	
Lipid and glycaemic profile	X		X	X	
Instrumental					
DEXA	X				X

3.7.9 Summary of evidence and recommendations on risk factors in testosterone treatment

Summary of evidence
Testosterone therapy is contraindicated in men with secondary hypogonadism who desire fertility.
Testosterone therapy is contraindicated in men with active prostate cancer or breast cancer.
Testosterone therapy does not increase the risk of prostate cancer, but long-term prospective follow-up data are required to validate this statement.
The effect of testosterone therapy in men with severe lower-urinary tract symptoms is limited, as these patients are usually excluded from RCTs.
There is no substantive evidence that testosterone therapy, when replaced to normal levels, results in the development of major adverse cardiovascular events.
There is no evidence of a relationship between testosterone therapy and mild, moderate or CPAP-treated severe sleep apnoea.

Recommendations	Strength rating
Fully counsel symptomatic hypogonadal men who have been surgically treated for localised prostate cancer (PCa) and who are currently without evidence of active disease considering testosterone therapy, emphasising the benefits and lack of sufficient safety data on long-term follow-up.	Weak
Restrict treatment to patients with a low risk for recurrent PCa (i.e., pre-operative PSA < 10 ng/mL; Gleason score < 7 (International Society for Urological Pathology grade 1); cT1-2a)* and treatment should start after at least 1 year follow-up with PSA level < 0.01 ng/mL.	Weak
Safety data on the use of testosterone therapy in men treated for breast cancer are unknown.	Strong

Assess for cardiovascular risk factors before commencing testosterone therapy.	Strong
Assess men with known cardiovascular disease (CVD) for cardiovascular symptoms before testosterone therapy and with close clinical assessment and evaluation during treatment.	Strong
Treat men with hypogonadism and pre-existing CVD, venous-thromboembolism or chronic cardiac failure, who require testosterone therapy with caution, by careful clinical monitoring and regular measurement of haematocrit (not exceeding 54%) and testosterone levels.	Weak
Exclude a family history of venous-thromboembolism before starting testosterone therapy.	Strong
Monitor testosterone, haematocrit at 3, 6 and 12 months after testosterone therapy initiation, and thereafter annually. A haematocrit > 54% should require testosterone therapy withdrawal and phlebotomy. Re-introduce testosterone therapy at a lower dose once the haematocrit has normalised and consider switching to topical testosterone preparations.	Strong

*As for EAU risk groups for biochemical recurrence of localised or locally advanced prostate cancer (see EAU guidelines 2021 on prostate cancer)

4. EPIDEMIOLOGY AND PREVALENCE OF SEXUAL DYSFUNCTION AND DISORDERS OF MALE REPRODUCTIVE HEALTH

4.1 Erectile dysfunction

Epidemiological data have shown a high prevalence and incidence of ED worldwide [169]. Among others, the Massachusetts Male Aging Study (MMAS) [170] reported an overall prevalence of 52% ED in non-institutionalised men aged 40-70 years in the Boston area; specific prevalence for minimal, moderate, and complete ED was 17.2%, 25.2%, and 9.6%, respectively. In the Cologne study of men aged 30-80 years, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% [171]. The incidence rate of ED (new cases per 1,000 men annually) was 26 in the long-term data from the MMAS study [172] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [173]. In a cross-sectional real-life study among men seeking first medical help for new-onset ED, one in four patients was younger than 40 years, with almost 50% of the young men complaining of severe ED [174]. Differences among these studies can be explained by differences in methodology, ages, and socio-economic and cultural status of the populations studied. The prevalence rates of ED studies are reported in Table 7.

4.2 Premature ejaculation

As evidenced by the highly discrepant prevalence rates reported in Table 8 [175], the method of recruitment for study participation, method of data collection and operational criteria can all greatly affect reported prevalence rates of premature ejaculation (PE). The major problem in assessing the prevalence of PE was the lack of a universally recognised definition at the time the surveys were conducted [176]. Vague definitions without specific operational criteria, different manners of sampling, and non-standardised data acquisition have led to heterogeneity in estimated prevalence [176-180]. The highest prevalence rate of 31% (men aged 18-59 years) was found by the National Health and Social Life Survey (NHSLs), which determines adult sexual behaviour in the USA [181]. Prevalence rates were 30% (18-29 years), 32% (30-39 years), 28% (40-49 years) and 55% (50-59 years). It is, however, unlikely that the PE prevalence is as high as 20-30% based on the relatively low number of men who seek medical help for PE. These high prevalence rates may be a result of the dichotomous scale (yes/no) in a single question asking if ejaculation occurred too early, as the prevalence rates in European studies have been significantly lower [182]. Two separate observational, cross-sectional surveys from different continents found that overall prevalence of PE was 19.8 and 25.80%, respectively [183, 184]. Further stratifying these complaints into the classifications defined by Waldinger *et al.* [185], rates of lifelong PE were 2.3 and 3.18%, acquired PE 3.9 and 4.48%, variable PE 8.5 and 11.38% and subjective PE 5.1 and 6.4% [183, 184]. Both studies showed that men with acquired PE were more likely to seek treatment compared to men with lifelong PE. Treatment-seeking behaviour may have contributed to errors in the previously reported rates of PE, as it is possible that men with lifelong PE came to terms with their problem and did not seek treatment. The additional psychological burden of a new change in ejaculatory latency in acquired PE may have prompted more frequent treatment seeking [186]. Thus, it is likely that there is disparity between the incidence of the various PE sub-types in the general community and in men actively seeking treatment for PE [187, 188]. This disparity could be a further barrier to understanding the true incidence of each sub-type of PE. An approximately 5% prevalence of acquired PE and lifelong PE in the general population is consistent with epidemiological data indicating that around 5% of the population have an ejaculation latency of < 2 minutes [189].

4.3 Other ejaculatory disorders

4.3.1 *Delayed ejaculation*

Due to its rarity and uncertain definitions, the epidemiology of delayed ejaculation (DE) is not clear [190]. However, several well-designed epidemiological studies have revealed that its prevalence is around 3% among sexually active men [181, 191]. According to data from the NHSLs, 7.78% of a national probability sample of 1,246 men aged 18-59 years reported inability achieving climax or ejaculation [181]. In a similar stratified national probability sample survey completed over 6 months among 11,161 men and women aged 16-44 years in Britain, 0.7% of men reported inability to reach orgasm [192]. In an international survey of sexual problems among 13,618 men aged 40-80 years from 29 countries, 1.1-2.8% of men reported that they frequently experience inability to reach orgasm [193]. Another study conducted in the United States, in a national probability sample of 1,455 men aged 57-85 years, 20% of men reported inability to climax and 73% reported that they were bothered by this problem. [194]. Considering the findings of these epidemiological studies and their clinical experiences, some urologists and sex therapists have postulated that the prevalence of DE may be higher among older men [195-197]. Similar to the general population, the prevalence of men with DE is low among patients who seek treatment for their sexual problems. An Indian study that evaluated the data on 1,000 consecutive patients with sexual disorders who attended a psychosexual clinic demonstrated that the prevalence of DE was 0.6% and it was more frequent in elderly people with diabetes [198]. Nazareth *et al.* [199] evaluated the prevalence of International Classification of Diseases 10th edition (ICD-10) diagnosed sexual dysfunctions among 447 men attending 13 general practices in London, UK and found that 2.5% of the men reported inhibited orgasm during intercourse. Similar to PE, there are distinctions among lifelong, acquired and situational DE [200]. Although the evidence is limited, the prevalence of lifelong and acquired DE is estimated at 1 and 4%, respectively [201].

4.3.2 *Anejaculation and Anorgasmia*

Establishing the exact prevalence of anejaculation and anorgasmia is difficult since many men cannot distinguish between ejaculation and orgasm. The rarity of these clinical conditions further hampers the attempts to conduct epidemiological studies. In a report from the USA, 8% of men reported unsuccessfully achieving orgasm during the past year [181].

According to Kinsey *et al.* [202], 0.14% of the general population have anejaculation. The most common causes of anejaculation were spinal cord injury, diabetes mellitus and multiple sclerosis. Especially in most cases of spinal cord injury, medical assistance is the only way to ejaculate. While masturbation leads to the lowest rates of ejaculation, higher response rates can be obtained with penile vibratory stimulation or acetylcholine esterase inhibitors followed by masturbation in patients with spinal cord injury [203].

4.3.3 *Retrograde ejaculation*

Similar to anejaculation, it is difficult to estimate the true incidence of retrograde ejaculation (RE). Although RE is generally reported in 0.3-2% of patients attending fertility clinics [204], diabetes may increase these rates by leading to autonomic neuropathy. Autonomic neuropathy results in ED and ejaculatory dysfunctions ranging from DE to RE and anejaculation, depending on the degree of sympathetic autonomic neuropathy involved [205]. In 54 diabetic patients with sexual dysfunction, RE was observed with a 6% incidence [206]. In a controlled trial, RE was observed in 34.6% of diabetic men [207]. A more recent trial reported the rate of RE among 57 type-1-diabetes mellitus patients (aged 18-50 years) was at least 8.8% [208]. Retrograde ejaculation was also reported in studies of patients who had undergone transurethral resection of prostate (TURP) or open prostatectomy due to disrupted bladder neck integrity. A study of the effect of prostatectomy on QoL in 5,276 men after TURP, found that 68% reported post-surgical RE [209]. However, with the development of less invasive techniques, the incidence of RE decreases following the surgical treatment of LUTS [210-214].

4.3.4 *Painful ejaculation*

Painful ejaculation is a common but poorly understood clinical phenomenon, which is associated with sexual dysfunction. Several studies demonstrated its prevalence to range between 1 and 10% in the general population [215-217]; however, it may increase to 30-75% among men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [218-222]. It should be noted that the design of most of these studies was not scientifically sound and the condition was probably under-reported due to the lack of an evidence-based definition and well-defined prognostic criteria.

4.3.5 *Haemospermia*

The exact incidence and prevalence of haemospermia are difficult to elucidate due to a number of factors including its covert presentation, usually self-limiting nature and patient embarrassment. The symptom represents 1-1.5% of all urological referrals and occurs in all age groups, with a mean age of 37 years [223, 224]. In a PCa screening study of 26,126 men, aged \geq 50 years or older than 40 with a history of PCa or of black ethnicity, haemospermia was found in 0.5% on entry to the trial [225].

4.4 Low sexual desire

The global prevalence of low sexual desire in men is 3-28% [193, 226, 227]. Low solitary and dyadic sexual desires, have been reported in 68% and 14% of men, respectively [228]. Also, low sexual desire has been observed as a common complaint in gay men, with a prevalence of 19-57% [229, 230]. Despite its relationship with age, low sexual desire has been reported among young men (18-29 years), with prevalence of 6-19% [181, 231, 232].

Table 7: Prevalence rates of erectile dysfunction [169]

Date	Authors	Population	Response rate	Age (years)	Measurement technique	Principal findings	Correlates
1993	Solstad <i>et al.</i> [233, 234]	439 men; random population sample (Denmark)	81%	51	Interview and self-administered questionnaire	Overall, 4% of men had ED as assessed by questionnaire, interviews identified a higher frequency of ED (40%)	Not reported
1994	Feldman <i>et al.</i> [170] *MMAS	1,290 men; random population sample (United States)	40%	40-70	Self-administered questionnaire	Overall, 52% of men had ED 17.2% of men had minimal ED 25.2% of men had moderate ED 9.6% of men had complete ED	Age
1995	Panser <i>et al.</i> [235]	2,155 men; random population sample (United States)	55%	40-79	Self-administered questionnaire	1% ED in men aged 40-49 years 6% ED in men aged 50-59 years 22% ED in men aged 60-69 years 44% ED in men aged 70-79 years	
1996	Helgason <i>et al.</i> [236]	319 men; random population sample (Sweden)	73%	50-80	Self-administered questionnaire	3% ED in men aged 50-59 years 24% ED in men aged 60-69 years 49% ED in men aged 70-80 years	Age, Prostate cancer, Diabetes, Myocardial infarction, Diuretic use, Warfarin use, H2 receptor blocker use
1996	MacFarlane <i>et al.</i> [237]	1,734 men; random population sample (France)	86%	50-80	Self-administered questionnaire	20% ED in men aged 50-59 years 33% ED in men aged 60-69 years 38% ED in men aged 70-80 years	Age
1996	Fugl-Meyer [226]	1,288 men; random population sample men (Sweden)	52%	18-74	Structured interview	Overall, 5% of men had ED 3% ED in men aged 18-24 years 2% ED in men aged 25-34 years 2% ED in men aged 35-49 years 7% ED in men aged 50-65 years 24% ED in men aged 66-74 years	Age

1999	Laumann <i>et al.</i> [181] *NHSLS	1,244 men; random population sample (United States)	70%	18-59	Structured interview	Overall, 10% of men had ED (moderate plus severe) 7% ED in men aged 18–29 years 9% ED in men aged 30–39 years 11% ED in men aged 40–49 years 18% ED in men aged 50–59 years	Age, Race, Emotional stress, Urinary symptoms, Poor health, Low income
1999	Pinnock <i>et al.</i> [238]	427 men; random population sample (Australia)	69.8%	> 40	Self-administered questionnaire	6% ED in men aged 40–49 years 12% ED in men aged 50–59 years 41% ED in men aged 60–69 years 63% ED in men aged 70–79 years 81% ED in men aged 80+ years	Age, Hypercholesterolemia,
2000	Braun <i>et al.</i> [171] (COLOGNE Study)	8,000 men	56%	30-80	Self-administered questionnaire by mail (Cologne ED Questionnaire)	Prevalence of ED was 19.2%	Age, Hypertension, Diabetes, Pelvic surgery, LUTS
2001	Moreira <i>et al.</i> [239]	1,170 men; attending public places (heavy bias toward younger men) (Brazil)	91%	>18	Self-administered questionnaire	Overall, 14.7% of men had ED (moderate plus severe); 9.4% ED in men aged 18–39 years 15.5% ED in men aged 40–49 years 22.1% ED in men aged 50–59 years 37% ED in men aged 60–69 years 39.6% ED in men aged >70 years	Age, Education, Racial origin, Diabetes, Hypertension, Depression
2001	Meuleman <i>et al.</i> [240]	1,233 men; random population sample (the Netherlands)	70%	40-79	Self-administered questionnaire	Overall, 13% of men had ED 6% ED in men aged 40–49 years 9% ED in men aged 50–59 years 22% ED in men aged 60–69 years 38% ED in men aged 70–79 years	Age
2001	Blanker <i>et al.</i> [216, 241]	1,688 men; random population sample (the Netherlands)	50%	50-75	Self-administered questionnaire	3% ED in men aged 50–54 years 5% ED in men aged 55–59 years 11% ED in men aged 60–64 years 19% ED in men aged 65–69 years 26% ED in men aged 70–78 years	Age, Smoking, Obesity, LUTS, COPD, Treatment for CV disease

2001	Martin-Morales <i>et al.</i> [242]	2,476 men; random population sample (Spain)	75%	25-70	Self-administered questionnaire and single question	Overall, 12.1% of men had ED (single question) and 18.9% for questionnaire According to single question: 3.9% ED in men aged 25–39 years 6.3% ED in men aged 40–49 years 15.9% ED in men aged 50–59 years 32.2% ED in men aged 60–70 years IIEF identified milder ED, and single question identified more moderate and severe ED	Age, Hypertension, Diabetes, Cardiac disease, Pulmonary disease, Circulatory disease, Rheumatic disease, High cholesterol, Prostatic disease, Allergy, Medication “for nerves”, Sleeping tablets, Heavy smoking, Alcohol abuse
2002	Moreira <i>et al.</i> [243]	602 men; random population sample (Brazil)	92%	40-70	Interview	Overall, 14.4% of men had ED (moderate or severe) 9.9% ED in men aged 40–49 years 11.8% ED in men aged 50–59 years 31.7% ED in men aged 60–69 years	Age, Marital status, Diabetes, Depression, IPSS, Decreased physical activity
2002	Moreira <i>et al.</i> [244]	342 men; random population sample (Brazil)	47.6%	40-70	Self-administered questionnaire	Overall, 12.0% of men had ED (moderate or severe) 3.5% ED in men aged 40–49 years 16.7% ED in men aged 50–59 years 39.6% ED in men aged 60–69 years	Age, Diabetes, Hypertension, Heavy smoking
2002	Morillo <i>et al.</i> [245]	1,963 men; random population sample (Columbia, Venezuela and Ecuador)	82%	> 40	Standardised questionnaire	Overall, 19.8% of men had ED (moderate or severe)	Age, Diabetes, Hypertension, BPH
2003	Richters <i>et al.</i> [246]	8,517 men; random population sample (Australia)	69.4%	16-59	Computer-assisted telephone interview	Overall, 9.5% of men had ED 4.3% ED in men aged 16–19 years 4.5% ED in men aged 20–29 years 5.1% ED in men aged 30–39 years 12.5% ED in men aged 40–49 years 19.2% ED in men aged 50–59 years	Age

2003	Rosen <i>et al.</i> [247]	12,815 men; random population sample (multinational: United States, United Kingdom, France, Germany, the Netherlands, Italy, Spain)	36.8%	50-80	Self-administered questionnaire (IIEF and DAN-PSS)	According to DAN-PSS: Overall, 48.9% of men had ED 30.8% ED in men aged 50-59 years 55.1% ED in men aged 60-69 years 76% ED in men aged 70-80 years	Age, LUTS, Diabetes, Hypertension, Cardiac disease, Hyperlipidemia, Tobacco use
2004	Rosen <i>et al.</i> [248] *MALES	27,839 men random population sample (multinational: United States, United Kingdom, Germany, France, Italy, Spain, Mexico, and Brazil)	US: 45%; UK: 48%; Germany: 45%; France: 48%; Italy: 53%; Spain: 50%; Mexico: 55% and Brazil: 51%.	20-75	Random digit dialing and interviewed via computer-assisted telephone interviewing. A standardised questionnaire	Overall prevalence of ED in the MALES sample was 16%	Age, Hypertension, Heart trouble or angina, High cholesterol, Diabetes, Depression or anxiety
2004	Shiri <i>et al.</i> [249]	2,198 men; stratified birth cohort (Finland)	70%	50,60, and 70 at first survey 55, 65, and 75 at second survey	Self-administered questionnaire at two separate time points, 5 years apart	48% of men had minimal ED 15.2% of men had moderate ED 13.2% of men had complete ED	Age, Diabetes, Hypertension, Heart disease, Cerebrovascular disease, Smoking
2005	Laumann <i>et al.</i> [193] *GSSAB	13,750 men; random population sample (world)	19%	40-80	Telephone survey (random dialed digit)	Overall: In Northern Europe, 13.3% had ED In Southern Europe, 12.9% had ED In non-European West, 20.6% had ED In Central/South America, 13.7% had ED In Middle East, 14.1% had ED In East Asia, 13.3% had ED In Southeast Asia, 28.1% had ED	Age
2005	Moreira <i>et al.</i> [250]	750 men; random population sample (Spain)	23%	40-80	Telephone survey (random digit dialing)	Overall, 12.7% had ED	Age
2005	Moreira <i>et al.</i> [251]	750 men; random population sample (Germany)	17.4%	40-80	Telephone survey (random digit dialing)	Overall, 7.9% had ED	Age

2005	Moreira Junior <i>et al.</i> [252]	471 men; random population sample (Brazil)	18%	40-80	Telephone survey (random digit dialing)	Overall, 13.1% of men had ED	Age, Depression
2006	Brock <i>et al.</i> [253]	500 men; random population sample (Canada)	9.7%	40-80	Telephone survey (random digit dialing)	Overall, 16% of men had ED	Age, Depression, Diabetes
2007	De Almeida Claro <i>et al.</i> [254]	2,000 men; random population study (Brazil)	Not reported	>20	Standardised interview with self-reported questionnaire (IIEF)	Overall, 1.7% of men had ED 0.2% ED in men aged 20-30 years 0.22% ED in men aged 31-40 years 1.0% ED in men aged 41-50 years 2.8% ED in men aged 51-60 years 7.0% ED in men aged > 61 years	Age
2007	Ahn <i>et al.</i> [255]	1,570 men; geographically stratified random population study	Not reported	40-79	Self-administered questionnaire (IIEF-5)	Overall, 13.4% had self-reported ED prevalence as defined by IIEF-5 score less than 17 was 32.4% According to single question: 4.2% ED in men aged 40-49 years 13.0% ED in men aged 50-59 years 30.1% ED in men aged 60-69 years 41.1% ED in men aged 70-79 years	Age, Single status, Low income, Diabetes, Hypertension, Hyperlipidemia, Heart disease, Musculoskeletal disorders, Alcohol, Depression, Coffee intake
2008	Moreira <i>et al.</i> [256]	750 men; random population sample (Australia)	16.9%	40-80	Telephone survey (random digit dialing)	Overall, 32% of men had ED	Age
2008	Chew <i>et al.</i> [257]	1,580 men; random population sample (Australia)	37.3%	>20	Postal survey Self-administered questionnaire (IIEF-5)	15.7% ED in men aged 20-29 years 8.7% ED in men aged 30-39 years 12.9% ED in men aged 40-49 years 31.6% ED in men aged 50-59 years 52.4% ED in men aged 60-69 years 69.4% ED in men aged 70-79 years 68.2% ED in men aged > 80 years	Age, Marital status

2008	Teles <i>et al.</i> [258]	3,067 men; random population sample (Portugal)	81.3%	40-69	Self-administered questionnaire, including IIEF	Overall, 48.1% of men had ED 29% ED in men aged 40-49 years 50% ED in men aged 50-59 years 74% ED in men aged 60-69 years	Age, Diabetes, Cardiac insufficiency, Psychiatric illness
2008	Moreira <i>et al.</i> [259]	750 men; random population sample (United Kingdom)	17%	40-80	Telephone survey (random digit dialing)	Overall, 17.8% of men had ED	Age
2009	Laumann <i>et al.</i> [260]	742 men; random population sample (United States)	9%	40-80	Telephone survey (random digit dialing)	Overall, 22.5% of men had ED	Age, Depression
2009	Buvat <i>et al.</i> [261]	750 men; random population sample (France)	23.8%	40-80	Telephone survey (random digit dialing)	Overall, 15% of men had ED	Age
2010	Corona <i>et al.</i> [262]	3,369 men; random population study (Europe: Italy, Belgium, United Kingdom, Spain, Poland, Hungary, Estonia)	40%	40-80	Self-administered questionnaire	Overall, 30% of men had ED 6% ED in men aged 40-49 years 19% ED in men aged 50-59 years 38% ED in men aged 60-69 years 64% ED in men 70 and over	Age, Depression, LUTS, Cardiovascular disease, Diabetes, Obesity
2016	Oyelade <i>et al.</i> [263]	241 men; random sampling cross-sectional population based survey (Nigeria)	99%	30-80	Self-administered questionnaire (IIEF-5)	General prevalence of ED was 58.9%	Age, Hypertension, Use of anti-hypertensive drugs, Diabetes mellitus, Heart disease
2017	Cayan <i>et al.</i> [264]	2,760 men; random population study (Turkey)	Non-reported	≥ 40	Self-administered questionnaire (IIEF-5)	Prevalence of ED was calculated as 33% among all men aged ≥ 40 years. ED prevalence rates were 17% for 40-49 years, 35.5% for 50-59 years, 68.8% for 60-69 years, and 82.9% for ≥ 70 years	Age, Diabetes, Hypertension, Atherosclerosis, Dyslipidaemia, LUTS, Educational status, Monthly income
2017	Quilter <i>et al.</i> [265]	Randomly selected age-stratified population-based sample of 2,000 men (New Zealand)	30%	40-70	Self-reported erectile function (IIEF-5) and a single-question self-assessment tool.	Prevalence of ED was 42% (22% mild, 10% mild to moderate, 6% moderate, and 4% severe)	Age, Anxiety or depression

2020	Calzo <i>et al.</i> [266]	2,660 sexually active men (USA)		18-31	Self-administered questionnaire (IIEF-5)	Prevalence of mild ED was 11.3% and moderate-to-severe ED was 2.9%	Demographic (age; marital status) Metabolic (body mass index; waist circumference; history of diabetes, hypertension, hypercholesterolaemia) Mental health (depression, anxiety, antidepressant, tranquiliser use)
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Four baseline studies estimating the prevalence of Erectile Dysfunction:

MMAS = the Massachusetts Male Aging Study; NHLS = the National Health of Social Life Survey;

MALES = the multi-national men's attitudes to life events and sexuality; GSSAB = Global Study of Sexual Attitudes and Behaviours.

BPH = Benign Prostate Hyperplasia; COPD = Chronic Obstructive Pulmonary Disease; ED = Erectile Dysfunction; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LUTS = Lower urinary tract symptoms.

Table 8: The prevalence rates of premature ejaculation [175]

Date	Authors	Method of Data Collection	Method of Recruitment	Operational Criteria	Prevalence Rate	Number of Men
1998	Dunn <i>et al.</i> [267]	Mail	General practice registers - random stratification	Having difficulty with ejaculating prematurely	14% (past 3 mo)	617
					31% (lifetime)	618
1999	Laumann <i>et al.</i> (NHLS) [181]	Interview	NA	Climaxing/ ejaculating too rapidly during the past 12 months	31%	1,410
2002	Fugl-Meyer and Fugl-Meyer [268]	Interview	Population register	NA	9%	1,475
2004	Rowland <i>et al.</i> [269]	Mailed questionnaire	Internet panel	DSM IV	16.3%	1,158
2004	Nolazco <i>et al.</i> [270]	Interview	Invitation to outpatient clinic	Ejaculating fast or prematurely	28.3%	2,456
2005	Laumann <i>et al.</i> [193]	Telephone-personal interview/mailed questionnaires	Random (systematic) sampling	Reaching climax too quickly during the past 12 months	23.75% (4.26% frequently)	13,618
2005	Basile Fasolo <i>et al.</i> [271]	Clinician-based	Invitation to outpatient clinic	DSM IV	21.2%	12,558
2005	Stulhofer <i>et al.</i> [272]	Interview	Stratified sampling	Often ejaculating in less than < 2 minutes	9.5%	601
2007	Porst <i>et al.</i> (PEPA) [182]	Web-based survey Self-report	Internet panel	Control over ejaculation, distress	22.7%	12,133
2008	Shindel <i>et al.</i> [273]	Questionnaire	Male partners of infertile couples under evaluation	Self-report premature ejaculation	50%	73
2009	Brock <i>et al.</i> [274]	telephone interview	Web-based survey	DSM III	16%	3,816
				Control	26%	
				Distress	27%	
2010	Traeen and Stigum [232]	Mailed questionnaire + internet	Web interview + Randomisation		27%	11,746 + 1,671

2010	Son <i>et al.</i> [275]	Questionnaire	Internet panel (age < 60 years)	DSM IV	18.3%	600
2010	Amidu <i>et al.</i> [276]	Questionnaire	NA	NA	64.7%	255
2010	Liang <i>et al.</i> [277]	NA	NA	ISSM	15.3%	1,127
2010	Park <i>et al.</i> [278]	Mailed questionnaire	Stratified sampling	Suffering from PE	27.5%	2,037
2010	Vakalopoulos <i>et al.</i> [279]	One-on-one survey	Population-based cohort	EED	58.43%	522
				ISSM lifelong PE	17.7%	
2010	Hirshfeld <i>et al.</i> [229]	Web-based survey	Online advertisement in the United States and Canada	Climaxing/ ejaculating too rapidly during the past 12 months	34%	7,001
2011	Christensen <i>et al.</i> [280]	Interview + questionnaire	Population register (random)	NA	7%	5,552
2011	Serefoglu <i>et al.</i> [183]	Interview	Stratified sampling	Complaining about ejaculating prematurely	20.0%	2,593
2011	Son <i>et al.</i> [281]	Questionnaire	Internet panel	Estimated IELT \leq 5 mins, inability to control ejaculation, distress	10.5%	334
2011	Tang and Khoo [282]	Interview	Primary care setting	PEDT \geq 9	40.6%	207
2012	Mialon <i>et al.</i> [283]	Mailed questionnaire	Convenience sampling (age 18-25 years)	Control over ejaculation Distress	11.4%	2,507
2012	Shaeer and Shaeer [284]	Web-based survey	Online advertisement in Arabic countries	Ejaculate before the person wishes to ejaculate at least sometimes	83.7%	804
2012	Shindel <i>et al.</i> [285]	Web-based survey	Online advertisement targeted to MSM + distribution of invitation to organisations catering to MSM	PEDT \geq 9	8-12%	1,769
2012	McMahon <i>et al.</i> [286]	Computer assisted interviewing, online, or in-person self-completed	NA	PEDT \geq 11	16%	4,997
				Self-Reported (always/nearly-always)	13%	
2012	Lotti <i>et al.</i> [287]	Interview	Men seeking medical care for infertility	PEDT \geq 9	15.6%	244
2013	Zhang <i>et al.</i> [288]	Interview	Random stratified sample of married men aged 30-60	Self-reported premature ejaculation	4.7%	728
2013	Lee <i>et al.</i> [289]	Interview	Stratified random sampling	PEDT \geq 11	11.3%	2,081
				Self-Reported	19.5%	
				IELT < 1 min	3%	1,035
2013	Gao <i>et al.</i> [184]	Interview	Random stratified sample of monogamous heterosexual men in China	Self-reported premature ejaculation	25.8%	3,016
2013	Hwang <i>et al.</i> [290]	Survey of married couples	Married heterosexual couples in Korea	Estimated IELT < 2 minutes	21.7%	290
				PEDT > 11	12.1%	

2013	Vansintejan <i>et al.</i> [291]	Web Based survey	Online and flyer advertisements to Belgian men who have sex with men (Only HIV+ men in this study)	IPE score \leq 50% of total possible	4%	72
2013	Shaeer <i>et al.</i> [292]	Web Based survey	Targeting English-speaking men aged > 18 years, living most of their lives in the USA, regardless of personal interests and web browsing preferences	ISSM definition [179]	6.3%	1133
				PEDT	49.6%	
				Unfiltered self-reported	77.6%	
				Filtered self-reported	14.4%	
2016	Karabakan [293]	Interview (heavy bias toward younger men)	Targeting police academy students aged 24-30 years who applied for routine urological examination	PEDT > 10	9.2%	1000
2017	Gao <i>et al.</i> [294]	Field survey with face-to-face interviews	Comprising men aged 20-68 years in five cities in the Anhui province	Self-estimated IELT	Lifelong PE 10.98%	1239
					Acquired PE 21.39%	

DMS = Diagnostic and Statistical Manual of Mental Disorders; NA = not applicable; ISSM = International Society for Sexual Medicine; PEDT = Premature Ejaculation Diagnostic Tool; IELT = intravaginal ejaculatory latency time; IPE = Index of Premature Ejaculation; mo = months.

5. MANAGEMENT OF ERECTILE DYSFUNCTION

5.1 Definition and classification

Penile erection is a complex physiological process that involves integration of both neural and vascular events, along with an adequate endocrine milieu. It involves arterial dilation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism [295]. Erectile dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [296]. Erectile dysfunction may affect psychosocial health and have a significant impact on the QoL of patients and their partner's [170, 297-299].

There is established evidence that the presence of ED increases the risk of future CV events including myocardial infarction, cerebrovascular events, and all-cause mortality, with a trend towards an increased risk of cardiovascular mortality [300]. Therefore, ED can be an early manifestation of coronary artery and peripheral vascular disease and should not be regarded only as a QoL issue, but also as a potential warning sign of CVD [301-304]. A cost analysis showed that screening men presenting with ED for CVD represents a cost-effective intervention for secondary prevention of both CVD and ED, resulting in substantial cost savings relative to identification of CVD at the time of presentation [305].

Erectile dysfunction is commonly classified into three groups based on aetiology: organic, psychogenic and mixed ED. However, this classification should be used, with caution as most cases are actually of mixed aetiology. It has therefore been suggested to use the terms "primary organic" or "primary psychogenic".

5.2 Risk factors

Erectile dysfunction is associated with unmodifiable and modifiable common risk factors including age, diabetes mellitus, dyslipidaemia, hypertension, CVD, BMI/obesity/waist circumference, MetS, hyperhomocysteinemia, lack of exercise, and smoking (a positive dose-response association between quantity and duration of smoking has been demonstrated) [298, 302, 306-313]. Furthermore, an association between ED status and pharmaco-therapeutic agents for CVD (e.g., thiazide diuretics and β -blockers, except nebivolol), exert detrimental effects on erectile function, whereas newer drugs (i.e., angiotensin-converting enzyme-inhibitors, angiotensin-receptor-blockers and calcium-channel-blockers) have neutral or even beneficial effects

[302, 314, 315]. Atrial fibrillation [316], hyperthyroidism [20], vitamin D deficiency [317, 318], hyperuricemia [319], depression [320], chronic kidney disease [313], rheumatic disease [321] and chronic obstructive pulmonary disease [322] have also been reported as risks factors. Available data do not confirm a clear association between ED and hypothyroidism and hyperprolactinaemia [20].

Further epidemiological data have also highlighted other potential risk factors associated with ED including sleep disorders [323], obstructive sleep apnoea [324], psoriasis [325-327], gouty arthritis [328] and ankylosing spondylitis [329], non-alcoholic fatty liver disease [330], other chronic liver disorders [331], chronic periodontitis [332], open-angle glaucoma [333], inflammatory bowel disease [334], chronic fatigue syndrome [335] and allergic rhinitis [336]. Insufficient data are currently available to correlate primarily organic or primarily psychogenic ED with SARS-CoV-2 infection associated disease (COVID-19) [337, 338].

Erectile dysfunction is also frequently associated with other urological conditions and procedures (Table 9). Epidemiological studies have demonstrated consistent evidence for an association between LUTS/BPH and sexual dysfunction, regardless of age, other co-morbidity and lifestyle factors [339]. The Multinational Survey on the Aging Male study, performed in the USA, France, Germany, Italy, Netherlands, Spain, and the UK, systematically investigated the relationship between LUTS and sexual dysfunction in > 12,000 men aged 50-80 years. In the 83% of men who were reported to be sexually active, the overall prevalence of LUTS was 90%, with an overall 49% prevalence of ED and a reported complete absence of erections in 10% of patients. The overall prevalence of ejaculatory disorders was 46% [247]. Regardless of the technique used, surgery for BPH-LUTS had no significant impact on erectile function. A post-operative improvement of erectile function was even found depending on the degree of LUTS improvement [340, 341]. An association has been confirmed between ED and CP/CPSP [342], and bladder pain syndrome/interstitial cystitis (BPS/IC), mostly in younger men [343]. An association between ED and PE has also been demonstrated (see Section 6.2) [344]. An increased risk of ED is reported following transrectal ultrasound (TRUS)-guided prostate biopsy [345] and after open urethroplasty, especially for correction of posterior strictures [346], with recent findings emphasising the importance of patient-reported outcome measures (PROMs) in urethral reconstructive surgery to better report actual sexual function outcomes [347, 348].

Table 9: Urological conditions associated with ED

Urological Condition	Association with ED
LUTS/BPH [339]	Depending on the severity of LUTS and patients' age/population characteristics: Odds ratio (OR) of ED among men with LUTS/BPH ranges from 1.52 to 28.7 and prevalence ranges from 58% to 80%
Surgery for BPH/LUTS (TURP, laser, open, laparoscopic, etc.) [340]	Overall, absence of significant variations in terms of erectile function scores after surgery
Chronic Prostatitis/Chronic Pelvic Pain Syndrome [342]	Prevalence of ED among patients with CP/CPSP 29% [24%-33%, 95%CI], Range: 11% - 56% among studies
Bladder Pain Syndrome/Interstitial Cystitis [343]	OR of BPS/IC among patients with ED. Overall: OR (adjusted) = 1.75 [1.12 – 2.71, 95%CI] Age ≥ 60: OR (adjusted) = 1.07 [0.41 – 2.81, 95%CI] Age 40-59: OR (adjusted) = 1.44 [1.02 – 2.12, 95%CI] Age 18-39: OR (adjusted) = 10.40 [2.93 – 36.94, 95%CI]
Premature Ejaculation [345]	OR of ED among patients with PE = 3.68 [2.61 – 5.68, 95%CI]
Urethroplasty surgery for posterior urethral strictures [346]	OR of ED after posterior urethroplasty = 2.51 [1.82 – 3.45, 95%CI]

CI = confidence interval; OR = odds ratio; TURP = transurethral resection of the prostate; ED = erectile dysfunction; BPS/IC = bladder pain syndrome/interstitial cystitis; LUTS = lower urinary tract symptoms.

5.3 Pathophysiology

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 10) [295]. In most cases, numerous pathophysiological pathways can co-exist and may all negatively impact on erectile function.

The proposed ED etiological and pathophysiological division should not be considered prescriptive. In most cases, ED is associated with more than one pathophysiological factor and very often, if not always, will have a psychological component. Likewise, organic components can negatively affect erectile function with different pathophysiological effects. Therefore, Table 10 must be considered for diagnostic classifications only (along with associated risk factors for each subcategory).

Table 10: Pathophysiology of ED

Vasculogenic
Recreational habits (i.e., cigarette smoking)
Lack of regular physical exercise
Obesity
Cardiovascular diseases (e.g., hypertension, coronary artery disease, peripheral vasculopathy)
Type 1 and 2 diabetes mellitus; hyperlipidaemia; metabolic syndrome; hyperhomocysteinemia
Major pelvic surgery (e.g., radical prostatectomy) or radiotherapy (pelvis or retroperitoneum)
Neurogenic
Central causes
Degenerative disorders (e.g., multiple sclerosis, Parkinson's disease, multiple atrophy, etc.)
Spinal cord trauma or diseases
Stroke
Central nervous system tumours
Peripheral causes
Type 1 and 2 diabetes mellitus
Chronic renal failure, chronic liver failure
Polyneuropathy
Surgery (major surgery of pelvis/retroperitoneum) or radiotherapy (pelvis or retroperitoneum)
Surgery of the urethra (urethral stricture, open urethroplasty, etc.)
Anatomical or structural
Hypospadias, epispadias; micropenis
Phimosis
Peyronie's disease
Penile cancer (other tumours of the external genitalia)
Hormonal
Diabetes mellitus; Metabolic Syndrome;
Hypogonadism (any type)
Hyperthyroidism
Hyper- and hypocortisolism (Cushing's disease, etc.)
Panhypopituitarism and multiple endocrine disorders
Mixed pathophysiological pathways
Chronic systemic diseases (e.g., diabetes mellitus, hypertension, metabolic syndrome, chronic kidney disease, chronic liver disorders, hyperhomocysteinemia, hyperuricemia, chronic obstructive pulmonary disease, rheumatic disease)
Psoriasis, gouty arthritis, ankylosing spondylitis, non-alcoholic fatty liver disease, chronic periodontitis, open-angle glaucoma, inflammatory bowel disease, chronic fatigue syndrome, allergic rhinitis, obstructive sleep apnoea, depression
Iatrogenic causes (e.g. TRUS-guided prostate biopsy)
Drug-induced
Antihypertensives (i.e., thiazidediuretics, beta-blockers)*
Antidepressants (e.g., selective serotonin reuptake inhibitors, tricyclics)
Antipsychotics
Antiandrogens (GnRH analogues and antagonists; 5-ARIs)
Recreational drugs (e.g., heroin, cocaine, marijuana, methadone, synthetic drugs, anabolic steroids, excessive alcohol intake)
Psychogenic
Generalised type (e.g., lack of arousability and disorders of sexual intimacy)
Situational type (e.g., partner-related, performance-related issues or due to distress)
Trauma
Penile fracture
Pelvic fractures

GnRH = gonadotropin-releasing hormone; 5-ARIs = 5 α -reductase inhibitors.

*A symmetry analysis showed that cardiovascular drugs do not strongly affect the risk of subsequently being prescribed as anti-erectogenic drug. The analysis only assessed the short-term risk [356].

5.3.1 **Pelvic surgery and prostate cancer treatment**

Pelvic surgery, especially for oncological disease (e.g., radical prostatectomy (RP) [357] or radical cystectomy [358] and colorectal surgery [359]), may have a negative impact on erectile function and overall sexual health. The most relevant causal factor is a lesion occurring in the neurovascular bundles that control the complex mechanism of the cavernous erectile response, whose preservation (either partial or complete) during surgery eventually configures the so-called nerve-sparing (NS) approach [360]. Therefore, surgery resulting in damage of the neurovascular bundles, results in ED, although NS approaches have been adopted over the last few decades. This approach is applicable to all types of surgery that are potentially harmful to erectile function, although to date, only the surgical treatment of PCa has enough scientific evidence supporting its potential pathophysiological association with ED [361-363]. However, even non-surgical treatments of PCa (i.e., radiotherapy, or brachytherapy) can be associated with ED [364, 365]. The concept of active surveillance for the treatment of PCa was developed to avoid over-treatment of non-significant localised low-risk diseases, while limiting potential functional adverse effects (including ED). However, it is interesting that data suggest that even active surveillance has a detrimental impact on erectile function (and sexual well-being as a whole) [366-368].

To date, some of the most robust data on PROMs including erectile function, comparing treatments for clinically localised PCa come from the Prostate Testing for Cancer and Treatment (ProtecT) trial, in which 1,643 patients were randomised to active treatment (either RP or RT) and active monitoring and were followed-up for 6 years [369]. Sexual function, including erectile function, and the effect of sexual function on QoL were assessed with the Expanded Prostate Cancer Index Composite with 26 items (EPIC-26) instrument [370, 371]. At baseline, 67% of men reported erections firm enough for sexual intercourse but this fell to 52% in the active monitoring group, 22% in the RT group, and 12% in the RP group, at 6-months' assessment. The worst trend over time was recorded in the RP group (with 21% erections firm enough for intercourse after 3 years vs. 17% after 6 years). In the RT group, the percentage of men reporting erections firm enough for intercourse increased between 6 and 12 months, with a subsequent decrease to 27% at 6-years assessment. The percentage declined over time on a yearly basis in the active monitoring group, with 41% of men reporting erections firm enough for intercourse at 3 years and 30% at 6 year evaluations [369].

Radical prostatectomy (open, laparoscopic or robot-assisted) is a widely performed procedure with a curative intent for patients presenting with clinically localised intermediate- or high-risk PCa and a life expectancy of > 10 years based on health status and co-morbidity [372, 373]. This procedure may lead to treatment-specific sequelae affecting health-related QoL. Men undergoing RP (any technique) should be adequately informed before the operation that there is a significant risk of sexual changes other than ED, including decreased libido, changes in orgasm, anejaculation, Peyronie's-like disease, and changes in penile length [363, 365]. These outcomes have become increasingly important with the more frequent diagnosis of PCa in both younger and older men [374-376]. Research has shown that 25-75% of men experience post-RP ED [377], even though these findings had methodological flaws; in particular, the heterogeneity of reporting and assessment of ED among the studies [361, 378]. Conversely, the rate of unassisted post-operative erectile function recovery ranged between 20 and 25% in most studies. These rates have not substantially improved or changed over the past 17 years, despite growing attention to post-surgical rehabilitation protocols and refinement of surgical techniques [378-380].

Overall, patient age, baseline erectile function and surgical volume, with the consequent ability to preserve the neurovascular bundles, seem to be the main factors in promoting the highest rates of post-operative potency [362, 375, 377, 381]. Patients being considered for nerve-sparing RP (NSRP) should ideally be potent pre-operatively [374, 375]. The recovery time following surgery is of clinical importance in terms of post-operative recovery of erectile function. Available data confirm that post-operative erectile function recovery can occur up to 48 months after RP [382]. Likewise, it has been suggested that post-operative therapy (any type) should be commenced as soon as possible after the surgical procedure [374, 377], although evidence suggests that the number of patients reporting return of spontaneous erectile function has not increased.

In terms of the effects of surgical interventions (e.g., robot-assisted RP [RARP] vs. other types of surgery), data are still conflicting. An early systematic review showed a significant advantage in favour of RARP in comparison with open retropubic RP in terms of 12-month potency rates [383], without significant differences between laparoscopic RP and RARP. Some recent reports confirm that the probability of erectile function recovery is about twice as high for RARP compared with open RP [384]. More recently, a prospective, controlled, non-randomised trial of patients undergoing RP in 14 Swedish centres comparing RARP versus open retropubic RP, showed a small improvement in erectile function after RARP [385]. Conversely, a randomised controlled phase 3 study of men assigned to open RP or RARP showed that the two techniques yielded similar functional outcomes at 12 weeks [386]. More controlled prospective well-designed studies, with longer follow-up, are

necessary to determine if RARP is superior to open RP in terms of post-operative ED rates [387]. To overcome the problem of heterogeneity in the assessment of erectile function, for which there is variability in terms of the PROMs used (e.g., International Index of Erectile Function [IIEF], IIEF-5, Expanded Prostate Cancer Index Composite with 26 items [EPIC 26], Sexual Health Inventory for Men, etc.) to measure potency or erectile function, the criteria used to define restoration of erectile function should be re-evaluated utilising objective and validated thresholds (e.g., normalisation of scores or return to baseline erectile function) [361].

Erectile dysfunction is also a common problem after both external beam radiation therapy (EBRT) and brachytherapy for PCa. A systematic review and meta-analysis including men treated with EBRT (65%), brachytherapy (31%) or both (4%) showed that the post-treatment prevalence of ED was 34% at 1 year and 57% at 5.5 years [388, 389]. Similar findings have been reported for stereotactic radiotherapy with 26-55% of previously sexually functioning patients reporting ED at 5 years [390].

Recently other modalities have emerged as potential therapeutic options in patients with clinically-localised PCa, including whole gland and focal (lesion-targeted) treatments, to ablate tumours selectively while limiting sexual toxicity by sparing the neurovascular bundles. These include high-intensity focused US (HIFU), cryo-therapeutic ablation of the prostate (cryotherapy), focal padeliporfin-based vascular-targeted photodynamic therapy and focal radiation therapy (RT) by brachytherapy or CyberKnife®. All these approaches have a less-negative impact on erectile function, although they all lack robust mid- and long-term oncological outcomes, and prospective randomised controlled studies are needed to compare their functional and oncological outcomes [391, 392].

5.3.2 **Summary of evidence on the epidemiology/aetiology/pathophysiology of ED**

Summary of evidence	LE
Erectile dysfunction is common worldwide.	2b
Erectile dysfunction shares common risk factors with cardiovascular disease.	2b
Lifestyle modification (regular exercise and decrease in BMI) can improve erectile function.	1b
Erectile dysfunction is a symptom, not a disease. Some patients may not be properly evaluated or receive treatment for an underlying disease or condition that may be causing ED.	4
Erectile dysfunction is common after RP, irrespective of the surgical technique used.	2b
Erectile dysfunction is common after external radiotherapy and brachytherapy.	2b
Erectile dysfunction is less common after cryotherapy and high-intensity focused US.	2b

5.4 **Diagnostic evaluation (basic work-up)**

5.4.1 **Medical and sexual history**

The first step in evaluating ED is always a detailed medical and sexual history of patients and, when available, their partners [393]. It is important to establish a relaxed atmosphere during history-taking. This will make it easier to ask questions about erectile function and other aspects of the patient's sexual history; and to explain the diagnosis and therapeutic approach to the patient and their partner. Figure 3 lists the minimal diagnostic evaluation (basic work-up) in patients with ED.

The sexual history must include information about previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, and previous consultations and treatments. The sexual health status of the partner(s) (when available) can also be useful. A detailed description should be made of the rigidity and duration of both sexually-stimulated and morning erections and of problems with sexual desire, arousal, ejaculation, and orgasm [394, 395]. Validated psychometric questionnaires, such as the IIEF [85] or its short version (i.e., Sexual Health Inventory for Men; SHIM) [85], help to assess the different sexual function domains (i.e. sexual desire, erectile function, orgasmic function, intercourse satisfaction, and overall satisfaction), as well as the potential impact of a specific treatment modality. Similarly, structured interviews allow the identification and quantification of the different underlying factors affecting erectile function [396].

Psychometric analyses also support the use of the Erectile Hardness Score (EHS) for the assessment of penile rigidity in practice and in clinical trials research [397]. In cases of depressive mood, clinicians may use the Beck Depressive Inventory [398], which is one of the most recognised self-reported measures in the field, takes approximately 10 minutes to complete, and assigns the patient to a specific level of depression (varying from "normal mood" to "extreme depression").

Patients should always be screened for symptoms of possible hypogonadism (testosterone deficiency), including decreased energy and libido, and fatigue; potential cognitive impairment may be also observed in association with hypogonadism (see Sections 3.5 and 3.6), as well as for LUTS. In this regard,

although LUTS/BPH in themselves do not represent contraindications to treatment for LOH, screening for LUTS severity is clinically relevant [7].

5.4.2 **Physical examination**

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular and neurological systems [399, 400]. A physical examination may reveal unsuspected diagnoses, such as Peyronie's disease, pre-malignant or malignant genital lesions, prostatic enlargement or irregularity/nodularity, or signs and symptoms suggestive of hypogonadism (e.g., small testes or alterations in secondary sexual characteristics).

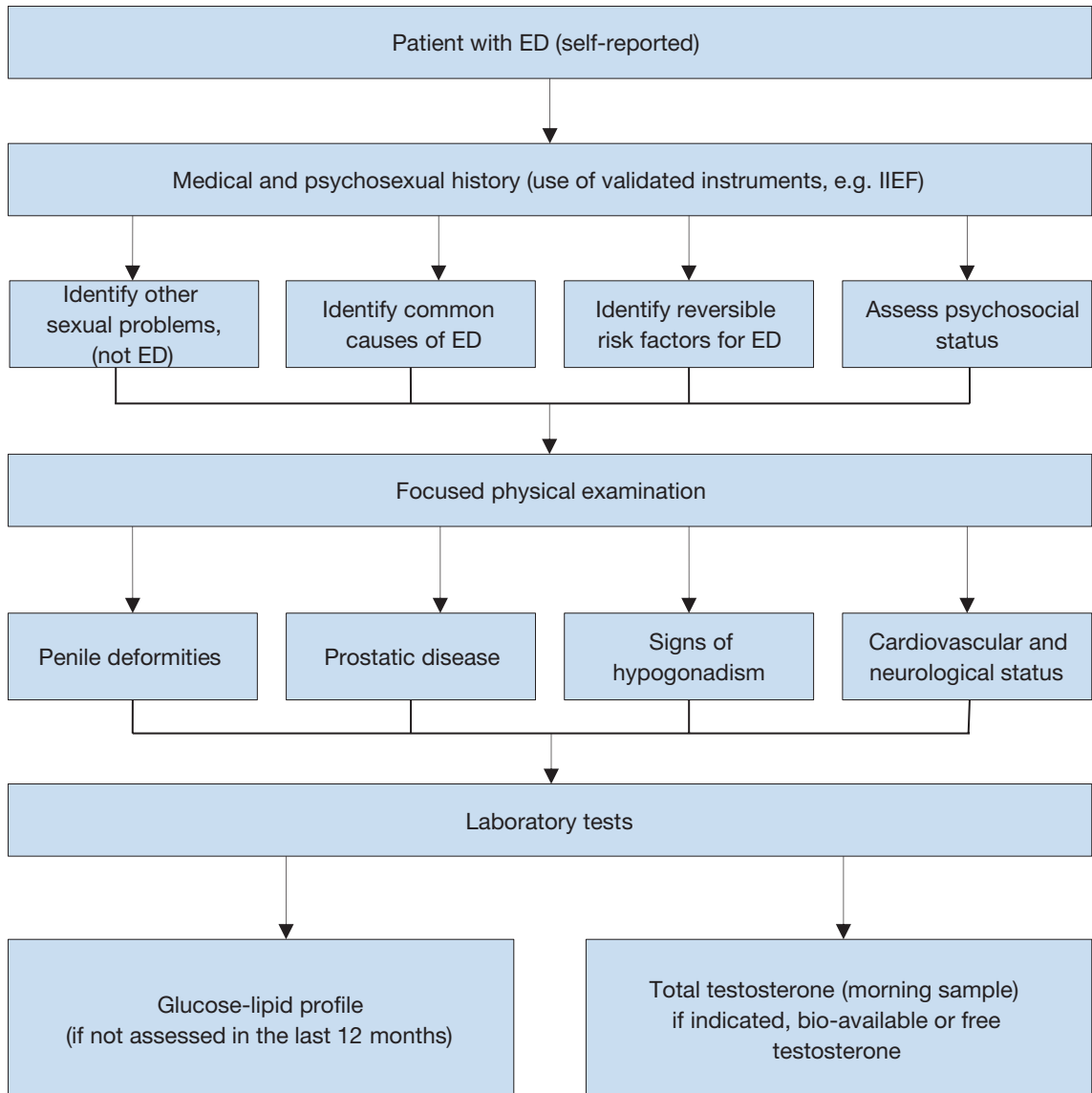
Assessment of previous or concomitant penile abnormalities (e.g., hypospadias, congenital curvature, or Peyronie's disease with preserved rigidity) during the medical history and the physical examination is mandatory.

Blood pressure and heart rate should be measured if they have not been assessed in the previous 3-6 months. Likewise either BMI calculation or waist circumference measurement should be undertaken to assess patients for comorbid conditions (e.g., MetS).

5.4.3 **Laboratory testing**

Laboratory testing must be tailored to the patient's complaints and risk factors. Patients should undergo a fasting blood glucose or haemoglobin A1c and lipid profile measurement if they have not been assessed in the previous 12 months. Hormonal tests should include early morning total testosterone in a fasting state. The bio-available or calculated-free testosterone values may sometimes be needed to corroborate total testosterone measurements. However, the threshold of testosterone required to maintain an erection is low and ED is usually a symptom of more severe cases of hypogonadism (see Sections 3.5 and 3.6) [20, 53, 401-403]. Additional laboratory tests may be considered in selected patients with specific signs and associated symptoms (e.g., PSA) [404], prolactin and luteinising hormone [405]). Although physical examination and laboratory evaluation of most men with ED may not reveal the exact diagnosis, clinical and biochemical evaluation presents an opportunity to identify comorbid conditions [400].

Figure 3: Minimal diagnostic evaluation (basic work-up) in patients with ED



ED = erectile dysfunction; IIEF = International Index of Erectile Function.

5.4.4 **Cardiovascular system and sexual activity: the patient at risk**

Patients who seek treatment for sexual dysfunction have a high prevalence of CVDs. Epidemiological surveys have emphasised the association between cardiovascular/metabolic risk factors and sexual dysfunction in both men and women [406]. Overall, ED can improve the sensitivity of screening for asymptomatic CVD in men with diabetes [407, 408]. Erectile dysfunction significantly increases the risk of CVD, coronary heart disease and stroke. Furthermore, the results of a recent prospective cohort study showed that ED is an independent predictor for incident atrial fibrillation [409]. All of these cause mortality and the increase is probably independent of conventional cardiovascular risk factors [301, 302, 410, 411]. Longitudinal data from an observational population-based study of 965 men without CVD showed that younger men (especially those < 50 years) with transient and persistent ED have an increased Framingham CVD risk [412].

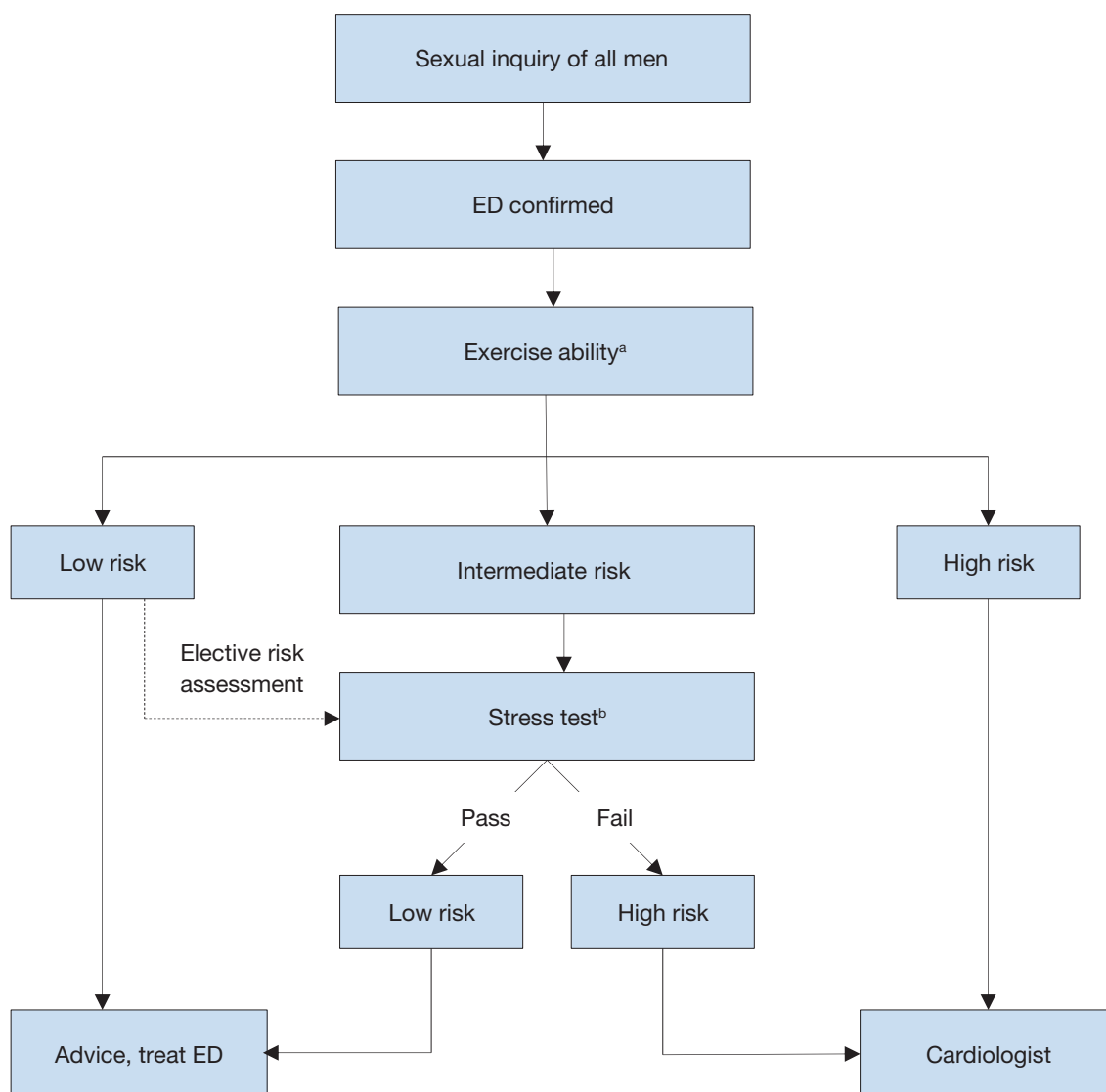
The EAU Guidelines for diagnosing and treating men with ED have been adapted from previously published recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk [413]. The Princeton Consensus (Expert Panel) Conference is dedicated to optimising sexual function and preserving cardiovascular health [413-415]. Accordingly, patients with ED can be stratified into three cardiovascular risk categories (Table 11), which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 3). It is also possible for the clinician to estimate the risk of sexual activity in most patients from their level of exercise tolerance, which can be determined when taking the patient's history [353].

Table 11: Cardiac risk stratification (based on 2nd and 3rd Princeton Consensus) [413, 415]

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding sex)	≥ 3 risk factors for CAD (excluding sex)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I or II)	LVD/CHF (NYHA class III)	LVD/CHF (NYHA class IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.

Figure 4: Treatment algorithm for determining level of sexual activity according to cardiac risk in ED (based on 3rd Princeton Consensus) [413]



^a Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing two flights of stairs in 10 seconds.

^b Sexual activity is equivalent to 4 minutes of the Bruce treadmill protocol.

5.4.4.1 *Low-risk category*

The low-risk category includes patients who do not have any significant cardiac risk associated with sexual activity. Low-risk is typically implied by the ability to perform exercise of modest intensity, which is defined as, ≥ 6 metabolic equivalents of energy expenditure in the resting state, without symptoms. According to current knowledge of the exercise demand or emotional stress associated with sexual activity, low-risk patients do not need cardiac testing or evaluation before initiation or resumption of sexual activity or therapy for sexual dysfunction.

5.4.4.2 *Intermediate- or indeterminate-risk category*

The intermediate- or indeterminate-risk category consists of patients with an uncertain cardiac condition or patients whose risk profile requires testing or evaluation before the resumption of sexual activity. Based upon the results of testing, these patients may be moved to either the high- or low-risk group. A cardiology consultation may be needed in some patients to help the primary physician determine the safety of sexual activity.

5.4.4.3 *High-risk category*

High-risk patients have a cardiac condition that is sufficiently severe and/or unstable for sexual activity to carry a significant risk. Most high-risk patients have moderate-to-severe symptomatic heart disease. High-risk individuals should be referred for cardiac assessment and treatment. Sexual activity should be stopped until the patient's cardiac condition has been stabilised by treatment, or a decision made by the cardiologist and/or internist that it is safe to resume sexual activity.

5.5 **Diagnostic Evaluation (advanced work-up)**

Most patients with ED can be managed based on the basis of medical and sexual history; conversely, some patients may need specific diagnostic tests (Tables 12 and 13).

5.5.1 **Nocturnal penile tumescence and rigidity test**

The nocturnal penile tumescence and rigidity (NPTR) test applies nocturnal monitoring devices that measure the number of erectile episodes, tumescence (circumference change by strain gauges), maximal penile rigidity, and duration of nocturnal erections. The NPTR assessment should be performed on at least two separate nights. A functional erectile mechanism is indicated by an erectile event of at least 60% rigidity recorded on the tip of the penis that lasts for ≥ 10 minutes [416]. Nocturnal penile tumescence and rigidity monitoring is an attractive approach for objectively differentiating between organic and psychogenic ED (patients with psychogenic ED usually have normal findings in the NPTR test). However, many potential confounding factors (e.g., situational) may limit its routine use for diagnostic purposes [417].

5.5.2 **Intracavernous injection test**

The intracavernous injection test gives limited information about vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within 10 minutes after the intracavernous injection and lasts for 30 minutes [418]. Overall, the test is inconclusive as a diagnostic procedure and a duplex Doppler study of the penis should be requested, if clinically warranted.

5.5.3 **Dynamic duplex ultrasound of the penis**

Dynamic duplex ultrasound (US) of the penis is a second-level diagnostic test that specifically studies the haemodynamic pathophysiology of erectile function. Therefore, in clinical practice, it is usually applied in those conditions in which a potential vasculogenic aetiology of ED (e.g., diabetes mellitus, renal transplantation, multiple concomitant CV risk factors and/or overt peripheral vascular disease, and poor responders to oral therapy) is suspected. Peak systolic blood flow > 30 cm/s, end-diastolic velocity < 3 cm/s and resistance index > 0.8 are considered normal [419, 420]. Recent data suggest that duplex scanning as a haemodynamic study may be better at tailoring therapy for ED, such as for low-intensity shock wave treatment (LI-SWT) and for diagnosing vasculogenic ED [421]. Further vascular investigation is unnecessary if a duplex US examination is normal.

5.5.4 **Arteriography and dynamic infusion cavernosometry or cavernosography**

Pudendal arteriography should be performed only in patients who are being considered for penile revascularisation [422]. Recent studies have advocated the use of computed tomography (CT) angiography as a diagnostic procedure prior to penile artery angioplasty for patients with ED and isolated penile artery stenosis [423]. Nowadays, dynamic infusion cavernosometry or cavernosography are infrequently used tools for diagnosing venogenic ED.

5.5.5 Psychiatric and psychosocial assessment

Whenever clinically indicated, patients with psychiatric disorders should be referred to a psychiatrist. In younger patients (< 40 years) with long-term primary ED [174], psychiatric assessment may be helpful before any clinical assessment is carried out.

Mental health issues are frequently comorbid with ED. This is most evident for depression and anxiety related disorders, but may also include transitory states of altered mood (i.e., dysfunctional affective states resulting from a specific life stressor) [320, 424]. Relationship factors, including lack of satisfaction with the partner, poor sexual relationships, length of the relationship, or feeling emotionally disconnected from the partner during sex, have been related to erectile difficulties and dysfunction [424-426]. In contrast, feeling emotionally supported, and motivated toward intimacy are protective factors in men with ED [427]. Additionally, the cognitive factors underpinning organic and non-organic ED must also be assessed. Cognitive factors include male dysfunctional thinking styles and expectations about sexuality and sexual performance. These expectations result from the sexuality norms and stereotypes, shared by a given culture. Expectations emphasising high sexual performance in men, result in anxiety, which acts as a maintenance factor for ED [428]. Unrealistic expectations about male sexual performance may further align with internal causal attributions regarding the loss of erection (i.e., men attribute the loss of erection to themselves [sense of personal inadequacy]), thereby worsening ED [429]. Likewise, poor self-esteem and cognitive distraction from erotic cues, are expected to negatively affect ED [430, 431].

Psychosexual assessment in ED cases include a clinical interview considering all the previous topics. Clinicians are expected to collect information on the individual's psychopathological symptoms, life stressors, relationship dynamics, cognitive style, and cognitive distraction sources [430]. Also, self-reported measures are frequently used within the psychological context. These may include measurement scales such as the Brief Symptom Inventory [432] for measuring psychopathology symptoms, the Sexual Dysfunctional Beliefs Questionnaire [433] or the Sexual Modes Questionnaire [434] for measuring dysfunctional cognitive styles in men.

Figure 5: Psychiatric and psychosocial assessment

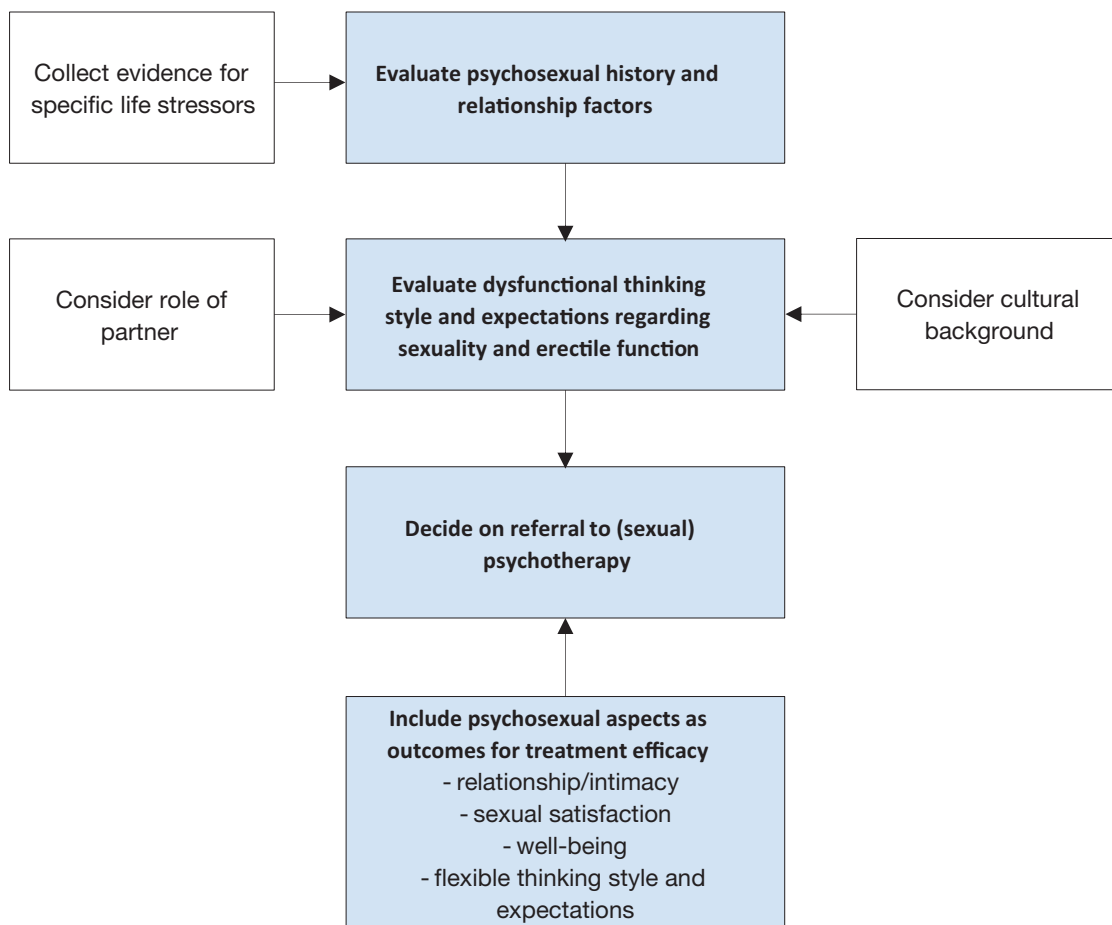


Table 12: Indications for specific diagnostic tests for ED

Primary ED (not caused by acquired organic disease or psychogenic disorder).
Young patients with a history of pelvic or perineal trauma, who could benefit from potentially curative revascularisation surgery or angioplasty.
Patients with penile deformities that might require surgical correction (e.g., Peyronie's disease and congenital penile curvature).
Patients with complex psychiatric or psychosexual disorders.
Patients with complex endocrine disorders.
Specific tests may be indicated at the request of the patient or their partner.
Medico-legal reasons (e.g., implantation of penile prosthesis to document end-stage ED, and sexual abuse).

Table 13: Specific diagnostic tests for ED

Nocturnal Penile Tumescence and Rigidity (NTPR) using Rigiscan®
Vascular studies <ul style="list-style-type: none"> - Intracavernous vasoactive drug injection - Penile dynamic duplex ultrasonography - Penile dynamic infusion cavernosometry and cavernosography - Internal pudendal arteriography
Specialised endocrinological studies
Specialised psycho-diagnostic evaluation

5.5.6 **Recommendations for diagnostic evaluation of ED**

Recommendations	Strength rating
Take a comprehensive medical and sexual history in every patient presenting with erectile dysfunction (ED). Consider psychosexual development, including life stressors, cultural aspects, and cognitive/thinking style of the patient regarding their sexual performance.	Strong
Use a validated questionnaire related to ED to assess all sexual function domains (e.g., International Index of Erectile Function) and the effect of a specific treatment modality.	Strong
Include a focused physical examination in the initial assessment of men with ED to identify underlying medical conditions and comorbid genital disorders that may be associated with ED.	Strong
Assess routine laboratory tests, including glucose and lipid profile and total testosterone, to identify and treat any reversible risk factors and lifestyle factors that can be modified.	Strong
Include specific diagnostic tests in the initial evaluation of ED in the presence of the conditions presented in Table 11.	Strong

5.6 **Treatment of erectile dysfunction**

5.6.1 **Patient education - consultation and referrals**

Educational intervention is often the first approach to sexual complaints, and consists of informing patients about the psychological and physiological processes involved in the individual's sexual response, in ways the patient can understand. This first level approach has been shown to favour sexual satisfaction in men with ED [435]. Accordingly, consultation with the patient should include a discussion of the expectations and needs of the patient's and their sexual partner. It should also review the patient's and partner's understanding of ED and the results of diagnostic tests, and provide a rationale for treatment selection [436]. Patient and partner education is an essential part of ED management [436, 437], and may prevent misleading information that can be at the core of dysfunctional psychological processes underpinning ED.

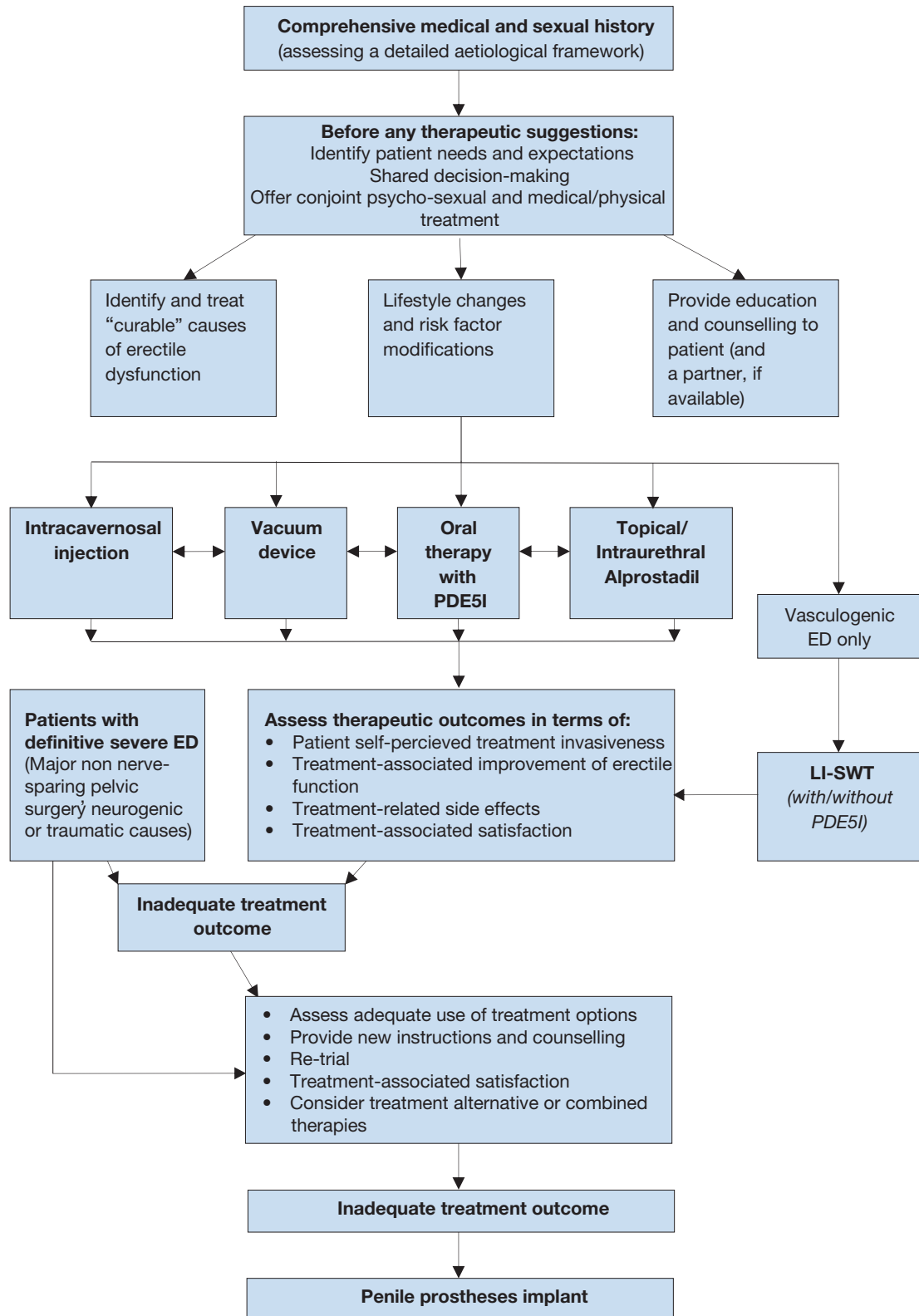
5.6.2 **Treatment options**

Based on the currently available evidence and the consensus of the Panel, a novel comprehensive therapeutic and decision-making algorithm (Figure 6) for treating ED, which takes into account the level of invasiveness of each therapy and its efficacy, has been presented. This newly-developed treatment algorithm was extensively discussed within the guidelines panel as an alternative to the traditional three-level concept, to better tailor a personalised therapy to individual patients, according to invasiveness, tolerability and effectiveness of the different therapeutic options and patients' expectations. In this context, patients should be fully counselled with respect to all available treatment modalities.

Erectile dysfunction may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors [349]. These factors may be modified either before, or at the same time as, specific therapies are used. Likewise, ED may be associated with concomitant and underlying conditions (e.g., endocrine disorders and metabolic disorders such as diabetes, and some cardiovascular problems such as hypertension) which should always be well-controlled as the first step of any ED treatment [438]. Major clinical potential benefits of lifestyle changes may be achieved in men with specific co-morbid CV or metabolic disorders, such as diabetes or hypertension [349, 439].

As a rule, ED can be treated successfully with current treatment options, but it cannot be cured. The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients, and hormonal causes (e.g., hypogonadism) [53, 405], which potentially can be cured with specific treatments. Most men with ED are not treated with cause-specific therapeutic options. This results in a tailored treatment strategy that depends on invasiveness, efficacy, safety and cost, as well as patient preference [436]. In this context, physician-patient (partner, if available) dialogue is essential throughout the management of ED. Interesting insights come from a recent systematic review that showed a consistent discontinuation rate for all available treatment options (4.4.-76% for PDE5Is; 18.6-79.9% for intracavernous injections; 32-69.2% for urethral suppositories; and 30% for penile prostheses). Therapeutic ineffectiveness, adverse effects, quality of men's intimate relationships and treatment costs are the most prevalent barriers to treatment utilisation [440].

Figure 6: Management algorithm for erectile dysfunction



ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors; LI-SWT = low-intensity shockwave therapy.

5.6.2.1 Oral pharmacotherapy

Four potent selective PDE5Is have been approved by the European Medicines Agency (EMA) for treatment of ED [441]. Phosphodiesterase type 5 catalyses the hydrolysis of the second messenger cyclic guanosine monophosphate (cGMP) in the cavernous tissue; cGMP is involved in intra-cellular signalling pathways of cavernous smooth muscle. Accumulation of cGMP sets in motion a cascade of events at the intracellular level,

which induces a loss of contractile tone of the penile vessels by lowering cytosolic Ca²⁺. Nitric oxide (NO) has an essential role in promoting the formation of cGMP and other pathways leading to corporeal smooth muscle relaxation and erection of the penis [438, 442]. This is associated with increased arterial blood flow, eventually leading to compression of the sub-tunical venous plexus followed by erection [443]. Since they are not initiators of erection, PDE5Is require sexual stimulation to facilitate an erection. Efficacy is defined as an erection, with rigidity, sufficient for satisfactory intercourse [438].

Sildenafil

Sildenafil was launched in 1998 and was the first PDE5I available on the market [444]. It is administered in doses of 25, 50 and 100 mg. The recommended starting dose is 50 mg and should be adapted according to the patient's response and adverse effects [444]. Sildenafil is effective 30-60 minutes after administration [444]. Its efficacy is reduced after a heavy, fatty meal due to delayed absorption. Efficacy may be maintained for up to 12 hours [445]. The pharmacokinetic profile for sildenafil is presented in Table 14. Adverse events (Table 15) are generally mild in nature and self-limited [446, 447]. After 24 weeks in a dose-response study, improved erections were reported by 56%, 77% and 84% in a general ED population taking 25, 50 and 100 mg sildenafil, respectively, compared to 25% of men taking placebo [448]. Sildenafil significantly improved patient scores for IIEF, sexual encounter profile question 2 (SEP2), SEP question 3 (SEP3) and General Assessment Questionnaire (GAQ) and treatment satisfaction. The efficacy of sildenafil in almost every subgroup of patients with ED has been successfully established, irrespective of age [449]. Recently, an orally disintegrating tablet (ODT) of sildenafil citrate at a dose of 50 mg has been developed, mainly for patients who have difficulty swallowing solid dosage forms.

Tadalafil

Tadalafil was licensed for treatment of ED in February 2003 and is effective from 30 minutes after administration, with peak efficacy after about 2 hours [450]. Efficacy is maintained for up to 36 hours [450] and is not affected by food [451]. Usually, tadalafil is administered in on-demand doses of 10 and 20 mg or a daily dose of 5 mg. The recommended on-demand starting dose is 10 mg and should be adapted according to the patient's response and adverse effects [450, 452]. Pharmacokinetic data for tadalafil are presented in Table 14. Adverse effects (Table 15) are generally mild in nature and self-limited by continuous use. In pre-marketing studies, after 12 weeks of treatment in a dose-response study, improved erections were reported by 67% and 81% of men with ED taking 10 and 20 mg tadalafil, respectively, compared to 35% of men in the placebo control group [450]. Tadalafil significantly improves patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction [450].

Efficacy of tadalafil has been confirmed in post-marketing studies [441, 453] and in almost every subgroup of patients with ED, including difficult-to-treat subgroups (e.g., diabetes mellitus) [454]. Tadalafil has also been shown to have a net clinical benefit in the short-term on ejaculatory and orgasmic functions in ED patients [455]. Daily tadalafil has been licensed for treatment of LUTS secondary to BPH. Therefore, it is useful in patients with concomitant ED and LUTS [456]. Recent data have confirmed that 40% of men aged > 45 years were combined responders for ED and LUTS/BPH to treatment with tadalafil 5 mg once daily, with symptom improvement after 12 weeks [457].

Vardenafil

Vardenafil became commercially available in March 2003 and is effective from 30 minutes after administration [458], with one of three patients achieving satisfactory erections within 15 minutes of ingestion [459]. Its effect is reduced by a heavy, fatty meal. Doses of 5, 10 and 20 mg have been approved for on-demand treatment of ED. The recommended starting dose is 10 mg and should be adapted according to the patient's response and adverse effects [460]. Pharmacokinetic data for vardenafil are presented in Table 14. Adverse events (Table 15) are generally mild in nature and self-limited by continuous use [460]. After 12 weeks in a dose-response study, improved erections were reported by 66%, 76% and 80% of men with ED taking 5, 10 and 20 mg vardenafil, respectively, compared with 30% of men taking placebo [460, 461]. Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction.

Efficacy has been confirmed in post-marketing studies [460, 461]. The efficacy of vardenafil in almost every subgroup of patients with ED, including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established. An orodispersible tablet (ODT) formulation of vardenafil has been released [461]. Orodispersible tablet formulations offer improved convenience over film-coated formulations and may be preferred by patients. Absorption is unrelated to food intake and they exhibit better bio-availability compared to film-coated tablets [462]. The efficacy of vardenafil ODT has been demonstrated in several RCTs and did not seem to differ from the regular formulation [462-464].

Avanafil

Avanafil is a highly-selective PDE5I that became commercially available in 2013 [465]. Avanafil has a high ratio of inhibiting PDE5 as compared with other PDE subtypes, ideally allowing for the drug to be used for ED while minimising adverse effects (although head-to-head comparisons are not yet available) [466]. Doses of 50, 100 and 200 mg have been approved for on-demand treatment of ED [465]. The recommended starting dose is 100 mg taken as needed 15-30 minutes before sexual activity and the dose may be adapted according to efficacy and tolerability [465, 467, 468]. In the general population with ED, the mean percentage of attempts resulting in successful intercourse was approximately 47%, 58% and 59% for the 50, 100 and 200 mg groups, respectively, as compared with ~28% for placebo [465, 467]. Data from sexual attempts made within 15 minutes of treatment showed successful attempts in 64%, 67% and 71% of cases treated with avanafil 50, 100 and 200 mg, respectively. Dose adjustments are not warranted based on renal function, hepatic function, age or sex [467]. Pharmacokinetic data for avanafil are presented in Table 14 [465, 467]. Adverse effects are generally mild in nature (Table 15) [465, 467]. Pairwise meta-analytic data from available studies have suggested that avanafil significantly improved patient scores for IIEF, SEP2, SEP3 and GAQ, with an evident dose-response relationship [465, 469]. Administration with food may delay the onset of effect compared with administration in a fasting state but avanafil can be taken with or without food [470]. The efficacy of avanafil in many groups of patients with ED, including difficult-to-treat subgroups (e.g., diabetes mellitus), has been successfully established. As for dosing, 36.4% (28 of 77) of sexual attempts (SEP3) at ≤ 15 minutes were successful with avanafil vs. 4.5% (2 of 44) after placebo ($P < 0.01$) [471]. A recent meta-analysis confirmed that avanafil had comparable efficacy with sildenafil, vardenafil and tadalafil [470].

Choice or preference among the different PDE5Is

To date, no data are available from double- or triple-blind multicentre studies comparing the efficacy and/or patient preference for the most-widely available PDE5Is (i.e., sildenafil, tadalafil, vardenafil, and avanafil). Choice of drug depends on frequency of intercourse (occasional use or regular therapy, 3-4 times weekly) and the patient's personal experience. Patients need to know whether a drug is short- or long-acting, its possible disadvantages, and how to use it. A meta-analysis demonstrated that ED patients who prioritise high efficacy must use sildenafil 50 mg whereas those who optimise tolerability should initially use tadalafil 10 mg and switch to udenafil 100 mg if the treatment is not sufficient (however, udenafil 100 mg is not EMA or US Food and Drug Administration approved and is not available in Europe) [453]. The results of another clinical trial have revealed that tadalafil 5 mg once daily may improve erectile function among men who have a partial response to on-demand PDE5I therapy [472].

Continuous use of PDE5Is

Animal studies have shown that chronic use of PDE5Is significantly improves or prevents the intracavernous structural alterations caused by age, diabetes or surgical damage [473-477]. No data exist in humans. In humans, it has been clinically demonstrated that treatment with tadalafil 5 mg once daily in men complaining of ED of various severities is well-tolerated and effective [478]. In 2007, tadalafil 2.5 and 5 mg/day were approved by the EMA for treatment of ED. According to the EMA, a once-daily regimen with tadalafil 2.5 or 5 mg might be considered suitable, based on patients' choice and physicians' judgement. In these patients, the recommended dose is 5 mg, taken once daily at approximately the same time. Overall, tadalafil, 5 mg once daily, provides an alternative to on-demand tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be linked. The appropriateness of the continuous use of a daily regimen should be re-assessed periodically [478, 479]. A recent integrated analysis has shown that no clinical populations of patients with ED seem to benefit overwhelmingly from tadalafil once daily over on-demand regimens and vice versa [480]. A recent RCT has shown that there is no clinically beneficial effect on endothelial dysfunction measured by flow-mediated dilation deriving from daily tadalafil when compared to placebo [481]. Although some authors have reported improved erectile function when long-term tadalafil 5 mg once daily is combined with sildenafil as needed [482], more safety analyses are required to give a formal recommendation on such a therapy.

Table 14: Summary of the key pharmacokinetic data for the four PDE5Is currently EMA-approved to treat ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil, 200mg
C _{max}	0.8-1 hours	2 hours	0.9 hours	0.5-0.75 hours
T _{max} (median)	2.6-3.7 hours	17.5 hours	3.9 hours	6-17 hours
T1/2	1,685 µg.h/L	8,066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
AUC	96%	94%	94%	99%
Protein binding	41%	NA	15%	8-10%
Bioavailability	41%	NA	15%	8-10%

* Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics. C_{max} = maximal concentration; T_{max} = time-to-maximum plasma concentration; T1/2 = plasma elimination half-time; AUC = area under curve or serum concentration time curve.

Table 15: Common adverse events of the four PDE5Is currently EMA-approved to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil, 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	None
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

* Adapted from EMA statements on product characteristics.

Safety issues for PDE5Is

(i) Cardiovascular safety

Clinical trial results for the four PDE5Is and post-marketing data of sildenafil, tadalafil, and vardenafil have demonstrated no increase in myocardial infarction rates in patients receiving PDE5Is, as part of either RCTs or open-label studies, or compared to expected rates in age-matched male populations. None of the PDE5Is has an adverse effect on total exercise time or time-to-ischæmia during exercise testing in men with stable angina [441, 483]. Chronic or on-demand use is well-tolerated with a similar safety profile. The prescription of all PDE5Is in patients with CVD or in those with high CV risk should be based on the recommendations of the 3rd Princeton Consensus Panel [413].

(ii) Contraindication for the concomitant use of organic nitrates

An absolute contraindication to PDE5Is is use of any form of organic nitrate (e.g., nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate) or NO donors (e.g., other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate such as “poppers” that are used for recreation). They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5Is depends upon the PDE5I and nitrate used. If a PDE5I is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 hours if sildenafil (and probably also vardenafil) is used (half-life, 4 hours), or at least 48 hours if tadalafil is used (half-life, 17.5 hours), and for no less than 12 hours if avanafil is used (half-life, 6-17 hours) [484-487].

(iii) Use caution with antihypertensive drugs

Co-administration of PDE5Is with antihypertensive agents (e.g., angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, β-blockers, and diuretics) may result in small additive decreases in blood pressure, which are usually minor [413]. In general, the adverse event profile of a PDE5I is not worsened by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents [488].

(iv) Interaction with Nicorandil

In vitro studies in animals suggest that the potassium channel opener nicorandil may potentiate the vasorelaxation induced by isoproterenol in isolated rat aorta by increasing cyclic GMP levels [489]. This may be due to the nitric oxide donating properties of nicorandil. Therefore, concurrent use of nicorandil and PDE5Is is also contraindicated.

α -Blocker interactions

All PDE5Is show some interaction with α -blockers. A recent meta-analysis concluded that a concomitant treatment with α -blockers and PDE5Is may produce changes in haemodynamic parameters, but it does not increase the rate of adverse events due to hypotension [490]. In everyday clinical practice, a patient presenting for ED should be stable on one medication before starting a PDE5Is, and the use of uroselective α -blockers is strongly preferred.

Available historical data suggest that:

- Sildenafil labelling advises that 50 or 100 mg sildenafil should be used with caution in patients taking an α -blocker (especially doxazosin). Hypotension is more likely to occur within 4 hours following treatment with an α -blocker. A starting dose of 25 mg is recommended [446].
- Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on their α -blocker therapy. Co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension [458, 460, 461].
- Tadalafil is not recommended in patients taking doxazosin, but this is not the case for tamsulosin [450, 491].
- Avanafil labelling currently reports that patients should be stable on α -blocker therapy prior to initiating avanafil. In these patients, avanafil should be initiated at the lowest dose of 50 mg. Conversely, in those patients already taking an optimised dose of avanafil, α -blocker therapy should be initiated at the lowest dose.

Dosage adjustment

Drugs that inhibit the CYP3A4 pathway inhibit the metabolic breakdown of PDE5Is, thus increasing PDE5Is blood levels (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin). Therefore, lower doses of PDE5Is are necessary. However, other agents, such as rifampin, phenobarbital, phenytoin and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5Is, so that higher doses of PDE5Is are required. Severe kidney or hepatic dysfunction may require dose adjustments or warnings.

Management of non-responders to PDE5Is

The two main reasons why patients fail to respond to a PDE5I are either incorrect drug use or lack of efficacy. Data suggest that an adequate trial involves at least six attempts with a particular drug [492]. The management of non-responders depends upon identifying the underlying cause [493].

Check that the medication has been properly prescribed and correctly used. The main reason why patients fail to use their medication correctly is inadequate counselling from their physician. The most common causes of incorrect drug use are: i) failure to use adequate sexual stimulation; ii) failure to use an adequate dose; and, iii) failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.

Check that the patient has been using a licensed medication. There is a large counterfeit market in PDE5Is. The amount of active drug in these medications varies enormously and it is important to check how and from which source the patient has obtained his medication.

PDE5I action is dependent on the release of NO by the parasympathetic nerve endings in the erectile tissue of the penis. The usual stimulus for NO release is sexual stimulation, and without adequate sexual stimulation (and NO release), the medication is ineffective. Furthermore, the reduced production of NO that occurs in diabetic patients due to peripheral neuropathy, is thought to be the justification for the higher failure rate of PDE5Is in this category of patients. Oral PDE5Is take different times to reach maximal plasma concentrations (C_{max}) [445, 447, 462, 469, 494-496]. Although pharmacological activity is achieved at plasma levels below the maximal plasma concentration, there will be a period of time following oral ingestion of the medication during which the drug is ineffective. Even though all four drugs have an onset of action in some patients within 15-30 minutes of oral ingestion [447, 462, 494-496], most patients require a longer delay between taking the medication [460, 469, 497, 498]. Absorption of both sildenafil and vardenafil can be delayed by a heavy, fatty meal [499]. Absorption of tadalafil is less affected, and food has negligible effects on its bioavailability [494]. When avanafil is taken with a high-fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 1.25 hours and a mean reduction in C_{max} of 39% (200 mg). There is no effect on the extent of exposure (area under the curve). The small changes in avanafil C_{max} are considered to be of minimal clinical significance [465, 466, 469].

It is possible to wait too long after taking the medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is ~4 hours, suggesting that the normal window of efficacy is 6-8 hours following drug ingestion, although responses following this time period are recognised. The half-life of avanafil is 6-17 hours. Tadalafil has a longer half-life of ~17.5 hours, so the window of efficacy is longer at ~36 hours. Data

from uncontrolled studies suggest patient education can help salvage an apparent non-responder to a PDE5I [493, 500-503]. After emphasising the importance of dose, timing, and sexual stimulation to the patient, erectile function can be effectively restored following re-administration of the relevant PDE5I [493, 500, 501].

A systematic review has addressed the association between genetic polymorphism, especially those encoding endothelial nitric oxide synthase, and the variability in response to PDE5Is [504]. Similar recent data have suggested that response to sildenafil treatment is also dependent on polymorphism in the PDE5A gene, which encodes the principal cGMP-catalysing enzyme in the penis, regulating cGMP clearance, and it is the primary target of sildenafil [505-507].

Clinical strategies in patients correctly using a PDE5Is

Overall, treatment goals should be individualised to restore sexual satisfaction for patients and/or couples, and improve QoL based on patients' expressed needs and desires [508]. In this context, data suggests that almost half of patients abandon first-generation PDE5Is within 1 year, with no single specific factor playing a major role in dropout rates [509].

Uncontrolled trials have demonstrated that hypogonadal patients not responding to PDE5Is may improve their response to PDE5Is after initiating testosterone therapy [53, 438, 510]. Therefore, in the real-life setting most patients with ED will first be prescribed a PDE5I, which is usually effective; however, if diagnostic criteria suggestive for testosterone deficiency are present, testosterone therapy may be more appropriate even in ED patients [5, 53].

Modification of other risk factors may also be beneficial, as previously discussed. Limited data suggest that some patients might respond better to one PDE5I than to another [511], and although these differences might be explained by variations in drug pharmacokinetics, they do raise the possibility that, despite an identical mode of action, switching to a different PDE5I might be helpful. However it is important to emphasise that the few randomised studies have shown any difference in clinical outcomes with different drugs and intake patterns in patients with classic ED [512] and in special populations such as people with diabetics [513].

In patients with severe ED, it has been suggested to combine tadalafil daily treatment with a short-acting PDE5I (such as sildenafil), without any significant increase in adverse effects [482]. Robust prospective data from RCTs to support combination treatments with any oral preparations are still lacking and should therefore be used with caution. If drug treatment fails, then patients can be offered an alternative therapy such as intracavernous injection therapy or use of a vacuum erection device (VED). Likewise, limited data suggest combination of a PDE5I with as intracavernous, intraurethral or topical alprostadil in patients who have previously failed therapy with either drug [514]. Review findings have indicated that, with all three formulations, combination therapy results in improved outcome compared with any of the drugs as monotherapy, even for patients with post-prostatectomy ED. Treatment-emergent adverse events of the combined treatment do not result in treatment discontinuation [514].

5.6.2.2 Topical/Intraurethral alprostadil

The vasoactive agent alprostadil can be administered intraurethrally with two different formulations. The first delivery method is topical, using a cream that includes a permeation enhancer to facilitate absorption of alprostadil (200 and 300 µg) via the urethral meatus [515, 516]. Clinical data are still limited. Significant improvement compared to placebo was recorded for IIEF-EF domain score, SEP2 and SEP3 in a broad range of patients with mild-to-severe ED [517]. Adverse effects include penile erythema, penile burning, and pain that usually resolve within 2 hours of application. Systemic adverse effects are rare. Topical alprostadil (VITAROS™) at a dose of 300 µg is available in some European countries. Recently, a randomised cross-over clinical trial has shown that, compared to the standard administration route, direct delivery within the urethral meatus can increase efficacy and confidence among patients, without increasing adverse effects [518].

The second delivery method is by intra-urethral insertion of a specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) [229]. Erections sufficient for intercourse are achieved in 30-65.9% of patients. In clinical practice, it is recommended that intra-urethral alprostadil is initiated at a dose of 500 µg, as it has a higher efficacy than the 250 µg dose, with minimal differences with regard to adverse events. In case of unsatisfactory clinical response, the dose can be increased to 1000 µg [519-521]. The application of a constriction ring at the root of the penis may improve efficacy [520, 521].

Overall, the most common adverse events are local pain (29-41%) and dizziness with possible hypotension (1.9-14%). Penile fibrosis and priapism are rare (< 1%). Urethral bleeding (5%) and urinary tract infections (0.2%) are adverse events related to the mode of administration. Efficacy rates are significantly lower than for intracavernous pharmacotherapy [522], with ~30% adherence to long-term therapy. Intraurethral pharmacotherapy provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-efficacious treatment.

5.6.2.3 *Shockwave therapy*

The use of LI-SWT has been increasingly proposed as a treatment for vasculogenic ED over the last decade, being the only currently marketed treatment that might offer a cure, which is the most desired outcome for most men suffering from ED [421, 523-530].

Overall, several single-arm trials have shown a beneficial effect of LI-SWT on patient-reported erectile function, but data from prospective randomised trials are conflicting, and many questions remain to be answered especially because of the heterogeneity among shockwave generators (i.e., electrohydraulic, electromagnetic, piezoelectric and electropneumatic); type of shockwaves delivered (i.e., focused, linear, semi-focused and unfocused); set-up parameters (e.g., energy flux density and number of pulses per session) and treatment protocols (i.e., duration of treatment, number of sessions per week, total number of shockwave pulses delivered and penile sites of application) [531]. Most of the studies have suggested that LI-SWT can significantly increase the IIEF and EHS in patients with mild vasculogenic ED, although this improvement appears modest. Few studies have shown an improvement in penile haemodynamic parameters after LI-SWT, but the clinical meaning of this improvement remains unclear [531, 532]. Likewise, data suggest that LI-SWT could ameliorate erection quality even in patients with severe ED who are either PDE5Is non-responders [528, 533, 534] or inadequate responders [535], thus reducing the immediate need for more invasive treatments. However, larger prospective RCTs and longer-term follow-up data are necessary to provide clinicians with more confidence regarding the use and effectiveness of LI-SWT for ED. Further clarity is also needed in defining treatment protocols that can result in greater clinical benefits [536, 537].

As a whole, according to the available data and the novel treatment decision algorithm, LI-SWT may be offered to patients with vasculogenic ED, although they should be fully counselled before treatment.

5.6.2.4 *Psychosexual counselling and therapy*

For patients with a recognised psychological problem [538], psychosexual therapy may be given either alone or with another therapeutic approach to improve couples' sexual satisfaction and partners' sexual function [539]. Psychosexual therapy requires ongoing follow-up and has had variable results [540]. Despite this psychological treatment including different modalities (e.g., sexual skills training, marital therapy and psychosexual education) [435], Cognitive and Behavioural Therapy (CBT), including group or couple format, is recommended [430]. Cognitive and behaviour therapy is aimed at altering dysfunctional cognitive and behavioural patterns influencing ED, and increasing adjustment during the course of the disorder. Some of its techniques include identifying triggers preceding erectile difficulties, cognitive restructuring of dysfunctional thinking styles, learning coping skills aimed at dealing with erectile difficulties and emotional symptoms, and relapse prevention. The CBT approach combined with medical treatment for ED has received empirical support and is considered an optimal procedure [430]. Moreover, there is preliminary evidence supporting the role of mindfulness-based therapy for ED and associated outcomes such as sexual satisfaction [541].

5.6.2.5 *Hormonal treatment*

The advice of an endocrinologist should be sought for managing patients with certain hormonal abnormalities or endocrinopathies [405]. Testosterone deficiency is either a result of primary testicular failure or secondary to pituitary/hypothalamic causes (e.g., a functional pituitary tumour resulting in hyperprolactinaemia) [405, 542]. When clinically indicated [543], testosterone therapy (intramuscular, transdermal, or oral) can be considered for men with low or low-normal testosterone levels and concomitant problems with their sexual desire, erectile function and dissatisfaction derived from intercourse and overall sex life (see Section 3.6 for a comprehensive discussion of testosterone therapy).

5.6.2.6 *Vacuum erection devices*

Vacuum erection devices (VED) provide passive engorgement of the corpus cavernosum, together with a constrictor ring placed at the base of the penis to retain blood within the corpus. Published data report that efficacy, in terms of erections satisfactory for intercourse, is as high as 90%, regardless of the cause of ED and satisfaction rates range between 27% and 94% [544, 545]. Most men who discontinue use of VEDs do so within 3 months. Long-term use of VEDs decreases to 50-64% after 2 years [546]. The most common adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness [545]. Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 minutes. Vacuum erection devices are contraindicated in patients with bleeding disorders or on anticoagulant therapy [547, 548]. Vacuum erection devices may be the treatment of choice in well-informed older patients with infrequent sexual intercourse and co-morbidity requiring non-invasive, drug-free management of ED [544, 545, 549].

5.6.2.7 *Intracavernous injections therapy*

Intracavernous administration of vasoactive drugs was the first medical treatment introduced for ED [503, 550]. According to invasiveness, tolerability, effectiveness and patients' expectations (Figure 6), patients may be offered intracavernous injections. The success rate is high (85%) [522, 551].

5.6.2.7.1 Alprostadil

Alprostadil (Caverject™, Edex/Viridal™) was the first and only drug approved for intracavernous treatment of ED [503, 552]. Intracavernous alprostadil is most efficacious as a monotherapy at a dose of 5-40 µg (40 µg may be offered off label in some European countries). The erection appears after 5-15 minutes and lasts according to the dose injected, but with significant heterogeneity among patients. An office-training programme is required for patients to learn the injection technique. In men with limited manual dexterity, the technique may be taught to their partners. The use of an automatic pen that avoids a view of the needle may be useful to resolve fear of penile puncture and simplifies the technique.

Efficacy rates for intracavernous alprostadil of > 70% have been found in the general ED population, as well as in patient subgroups (e.g., men with diabetes or CVD), with reported satisfaction rates of 87-93.5% in patients and 86-90.3% in partners after the injections [503, 550]. Complications of intracavernous alprostadil include penile pain (50% of patients reported pain only after 11% of total injections), excessively-prolonged undesired erections (5%), priapism (1%), and fibrosis (2%) [503, 550, 553]. Pain is usually self-limited after prolonged use and it can be alleviated with the addition of sodium bicarbonate or local anaesthesia [503, 550, 554]. Cavernosal fibrosis (from a small haematoma) usually clears within a few months after temporary discontinuation of the injection programme. However, tunical fibrosis suggests early onset of Peyronie's disease and may indicate stopping intracavernous injections indefinitely. Systemic adverse effects are uncommon. The most common is mild hypotension, especially when using higher doses. Contraindications include men with a history of hypersensitivity to alprostadil, men at risk of priapism, and men with bleeding disorders. Despite these favourable data, drop-out rates of 41-68% have been reported for intracavernous pharmacotherapy [503, 550, 555, 556], with most drop-outs occurring within the first 2-3 three months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rate (27.5%) compared to overall drug combinations (37.6%), with an attrition rate after the first few months of therapy of 10% per year [557]. Reasons for discontinuation included desire for a permanent mode of therapy (29%), lack of a suitable partner (26%), poor response (23%) (especially among early drop-out patients), fear of needles (23%), fear of complications (22%), and lack of spontaneity (21%). Careful counselling of patients during the office-training phase as well as close follow-up are important in addressing patient withdrawal from an intracavernous injection programme [558-560].

5.6.2.8 Combination therapy

Table 16 details the available intracavernous injection therapies (compounds and characteristics). Combination therapy enables a patient to take advantage of the different modes of action of the drugs being used, as well as alleviating adverse effects by using lower doses of each drug.

- Papaverine (20-80 mg) was the first oral drug used for intracavernous injections. It is most commonly used in combination therapy because of its high incidence of adverse effects as monotherapy. Papaverine is currently not licensed for treatment of ED.
- Phentolamine has been used in combination therapy to increase efficacy. As monotherapy, it produces a poor erectile response.
- Sparse data in the literature support the use of other drugs, such as vasoactive intestinal peptide (VIP), NO donors (linsidomine), forskolin, potassium channel openers, moxislyte or calcitonin gene-related peptide, usually combined with the main drugs [561, 562]. Most combinations are not standardised and some drugs have limited availability worldwide.
- Bimix, Trimix: papaverine (7.5-45 mg) plus phentolamine (0.25-1.5 mg) (also known as Bimix), and papaverine (8-16 mg) plus phentolamine (0.2-0.4 mg) plus alprostadil (10-20 µg) (also known as Trimix), have been widely used with improved efficacy rates, although they have never been licensed for ED [563, 564]. Trimix has the highest efficacy rates, reaching 92%; this combination has similar adverse effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis is more common (5-10%) when papaverine is used (depending on total dose).
- Invicorp™: Vasoactive intestinal peptide (25 µg) plus phentolamine mesylate (1-2 mg Invicorp), currently licensed in Scandinavia, is a combination of two active components with complementary modes of action. Clinical studies have shown that the combination is effective for intracavernous injections in > 80% of men with ED, including those who have failed to respond to other therapies and, unlike existing intracavernous therapies, is associated with a low incidence of penile pain and a virtually negligible risk of priapism [565].

Despite high efficacy rates, 5-10% of patients do not respond to combination intracavernous injections. The combination of sildenafil with intracavernous injection of the triple combination regimen may salvage as many as 31% of patients who do not respond to the triple combination alone [566]. However, combination therapy is associated with an increased incidence of adverse effects in 33% of patients, including dizziness in 20% of patients. This strategy can be considered in carefully selected patients before proceeding to a penile implant.

Table 16: Intracavernous injection therapy - compounds and characteristics

Name	Substance	Dosage	Efficacy	Adverse Events	Comment
Caverject™ or Edex/Viridal™	Alprostadil	5-40 µg/mL	~ 70%	Penile pain, priapism, fibrosis	Easily available
Papaverine	Papaverine	20 - 80 mg	< 55%	Elevation of liver enzymes, priapism, fibrosis	Abandoned as monotherapy
Phentolamine	Phentolamine	0.5 mg/mL	Poor efficacy as monotherapy	Systemic hypotension, reflex tachycardia, nasal congestion, and gastrointestinal upset	Abandoned as monotherapy
Bimix	Papaverine + Phentolamine	30 mg/mL + 0.5 mg/mL	~ 90%	Similar to Alprostadil (less pain)	Not licensed for the treatment of ED
Trimix	Papaverine + Phentolamine + Alprostadil	30 mg/mL + 1 mg/mL + 10 µg/mL	~ 92%	Similar as Alprostadil (less pain)	Not licensed for the treatment of ED
Invicorp™	Vasoactive intestinal peptide (VIP) + Phentolamine	25 µg + 1-2 mg	~ 80%	Similar as Alprostadil without pain	Easily available

There are currently several potential novel treatment modalities for ED, from innovative vasoactive agents and trophic factors to stem cell therapy and gene therapy. Most of these therapeutic approaches require further investigation in large-scale, blinded, placebo-controlled randomised studies to achieve adequate evidence-based and clinically-reliable recommendation grades [567-572]. A recent systematic review has concluded that five completed human clinical trials have shown promise for stem cell therapy as a restorative treatment for ED [573].

5.6.2.8.1 Erectile dysfunction after radical prostatectomy

Use of pro-erectile drugs following RP is important in achieving post-operative erectile function and to allow patients to resume sexual activity. There is also some evidence in animal studies that this may avoid cavernous fibrosis and maintain penile length. Several trials have shown improvements in erectile function after RP in patients receiving drugs (any therapeutic or prophylactic) for ED. Early compared with delayed erectile function treatment affects the natural recovery time for potency [574], although there is a lack of data to support any specific regimen, which is either optimal for penile rehabilitation or may result in the achievement of spontaneous, non-pharmacologically assisted erections [363, 575, 576]. In prospective studies, there has been no evidence that penile rehabilitation itself increases the chances of spontaneous recovery of erectile function in men following nerve-sparing RP (NSRP) [576]. The currently available therapeutic armamentarium follows the treatment algorithm for ED, which is shown in Figure 4.

Management of post-RP ED has been revolutionised by the advent of PDE5Is, with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. In this context, it must be emphasised that post-RP, ED patients are poor responders to PDE5Is. Since their launch on the market, PDE5Is have been considered as the first-line therapy in patients who have undergone NS surgery, regardless of the surgical technique used [363, 374, 375]. Several clinical parameters have been identified as potential predictors of PDE5Is outcomes in men undergoing RP. Patient age, baseline erectile function, and quality of NS technique are key factors in preserving post-RP erectile function [374, 375, 383, 577].

The response rate to sildenafil treatment for ED after RP in different trials has ranged from 35% to 75% among those who underwent NSRP and from 0% to 15% among those who underwent non-NSRP [374, 578]. Early use of high-dose sildenafil after RP is associated with preservation of smooth muscle within the corpus cavernosum [579]. A single study demonstrated that daily sildenafil also results in a greater return of spontaneous normal erectile function after RP compared to placebo following bilateral NSRP in patients who were fully potent before surgery [580]. Conversely, a more recent prospective, randomised, placebo-controlled study, which assessed the effects of nightly sildenafil citrate therapy during penile rehabilitation using nocturnal

penile rigidity score in addition to the IIEF-EF domain showed no therapeutic benefit for nightly sildenafil when compared to on-demand dosing in recovery of erectile function post-prostatectomy [581].

A large multicentre trial in Europe and the USA investigated the effects of tadalafil in patients with ED following bilateral NSRP. Erectile function was improved in 71% of patients treated with 20 mg tadalafil versus 24% of those treated with placebo, while the rate of successful intercourse attempts was 52% with 20 mg tadalafil versus 26% with placebo [582]. Moreover, a randomised, double-blind, double-placebo trial in men < 68 years of age and with normal pre-operative erectile function who underwent NSRP at 50 centres from nine European countries and Canada, compared tadalafil once daily with placebo [576]. Tadalafil was most effective for drug-assisted erectile function in men with ED following NSRP and data suggested a potential role for tadalafil once daily (provided early after surgery) in contributing to the recovery of post-operative erectile function and maintaining penile length [576]. Conversely, unassisted or spontaneous recovery of erectile function was not improved after cessation of active therapy for 9 months [576]. However, tadalafil once daily improved QoL post-operatively, both at double-blind and open label treatment periods [583].

Similarly, vardenafil has been tested in patients with ED following NSRP in a randomised, multicentre, prospective, placebo-controlled study [584]. Following bilateral NSRP, erectile function improved by 71% and 60% with 10 and 20 mg vardenafil, respectively. An extended analysis of the same cohort of patients showed the benefit of vardenafil compared to placebo in terms of intercourse satisfaction, hardness of erection, orgasmic function, and overall satisfaction with sexual experience [585]. A randomised, double-blind, double-dummy, multicentre, parallel-group study in 87 centres across Europe, Canada, South Africa and the USA, compared on-demand and nightly dosing of vardenafil in men with ED following bilateral NSRP [575]. In patients whose pre-operative erectile function domain score was > 26, vardenafil was efficacious when used on demand [575].

A double-blind, placebo-controlled, parallel-group study in 298 patients with ED after bilateral NSRP randomised to 100 or 200 mg avanafil or placebo (30 minutes before sexual activity) for 12 weeks showed significantly greater increases in SEP2 and SEP3 as well as in mean change of IIEF erectile function domain score with 100 and 200 mg avanafil versus placebo ($P < 0.01$) [415].

A recent Cochrane database systematic review analysed data from eight RCTs [586]. It showed that scheduled PDE5I may have little or no effect on short-term (up to 12 months) self-reported potency when compared to placebo or no treatment. In this study, daily PDE5I made little to no difference in short- and long-term erectile function. The authors conclude that penile rehabilitation strategies using PDE5I following RP do not increase self-reported potency and erectile function compared to on-demand use. Therefore, daily PDE5Is result in little to no difference in both short- and long-term (> 12 months) self-reported potency when compared to scheduled use. Finally, at short-term follow-up, daily PDE5I may result in little or no effect on self-reported potency when compared to scheduled intra-urethral application of prostaglandin E1.

Historically, the treatment options for post-RP ED have included intracavernous injections [587], urethral micro-suppository [374, 588], VED [363, 374, 589, 590], and penile implants [374, 591, 592]. Intracavernous injections and penile implants had been suggested as second- and third-line treatments, respectively, when oral PDE5Is are not adequately effective or not suitable for post-operative patients [362, 363, 593]. A recent meta-analysis has shown that the early use of VED has an excellent therapeutic effect on post-RP patients and no serious adverse effects, therefore it should be considered as a therapeutic alternative to discuss with the patient [594].

A recent systematic review has suggested that pelvic floor muscle training combined with bio-feedback is a promising alternative to pharmacological treatments, although there is a need for future well-powered, rigorously designed RCTs to draw strong conclusions [595].

5.6.2.9 *Vascular surgery*

5.6.2.9.1 *Surgery for post-traumatic arteriogenic ED*

In young patients with pelvic or perineal trauma, surgical penile revascularisation has a 60-70% long-term success rate [548, 596]. The stenosis must be confirmed by penile pharmaco-arteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularisation and must be excluded by dynamic infusion cavernosometry or cavernosography.

5.6.2.9.2 *Venous ligation surgery*

Venous ligation surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results [596].

5.6.2.9.3 Penile prostheses

The surgical implantation of a penile prosthesis may be considered in patients who (i) are not suitable for different pharmacotherapies or prefer a definitive therapy; and, (ii) do not respond to pharmacological therapies (Figure 6) [597]. A systematic review addressing cause and duration of symptoms before implantation has shown that most men receiving a penile prosthesis have an organic cause of ED, with vascular disease, diabetes, and previous pelvic surgery/trauma being the most common [598]. Similar findings have been reported by a prospective registry of penile prostheses with > a 3-year collection period in the UK; the three commonest aetiological factors for ED were diabetes, prostate surgery and Peyronie's disease [599]. The mean duration of ED symptoms before surgical intervention ranges from 3-6 six years [598].

The two currently available classes of penile implants include inflatable (two- and three-piece) and semi-rigid devices (malleable, mechanical and soft flexible) [374, 591, 600-602]. Patients may prefer the three-piece inflatable devices due to the more "natural" erections obtained, although no prospective RCTs have compared satisfaction rates with both types of implants. The two-piece inflatable prosthesis can be a viable option among patients who are deemed at high-risk of complications with reservoir placements (e.g., previous abdominal surgery). Semi-rigid prostheses result in a firm penis, which may be manually placed in an erect or flaccid state and offer the advantage of a simple implant technique, as well as easy use for the patient [374, 591, 600, 601]. Conversely, they can have the disadvantage of unnatural persistent erection and reduced concealability [601, 603]. They may also be an option in men with limited manual dexterity.

There are two main surgical approaches for penile prosthesis implantation: peno-scrotal and infrapubic [600, 601, 603, 604]. The peno-scrotal approach has been suggested to provide an excellent exposure; afford proximal crural exposure, avoid dorsal nerve injury, and permit direct visualisation of pump placement. However, with this approach, the reservoir is either placed blindly into the retropubic space, which can result in visceral injury in patients with a history of major pelvic surgery (mainly radical cystectomy) or a separate incision in the abdomen is placed under direct vision. A recent systematic review comparing the satisfaction and complication rates of the different surgical approaches has shown that there is no specific advantage between the two, but rather it is recommended that surgeons have knowledge of both techniques and are capable of tailoring the incision strategy for complex cases [605]. Revision surgery is associated with poorer outcomes and may be more challenging. Regardless of the indication, prosthesis implantation has one of the highest satisfaction rates (92-100% in patients and 91-95% in partners) among the treatment options for ED with appropriate counselling [374, 591, 600, 606-614]. In patients with favourable oncological prognosis after RP for PCa, a contemporary surgery to treat both ED, with the implant of a penile prosthesis, and stress urinary incontinence (male sling or artificial urinary sphincter) is effective and durable and has an established and definitive role to address both problems [374, 591, 615-617]. Structured psychosexual counselling may improve sexuality and sexual well-being in both patients and their partners after penile implant surgery [618].

5.6.2.9.4 Penile prostheses implantation: complications

Historically, the two main complications of penile prosthesis implantation are mechanical failure and infection. Several technical modifications of the most commonly used three-piece prostheses (e.g., AMS 700CX/CXR™ and Titan Zero degree™) resulted in mechanical failure rates of < 5% after 5 years of follow-up [591, 619, 620]. Careful surgical techniques with appropriate antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduced infection rates to 2-3% with primary implantation in low-risk patients and in high-volume centres, although the definition of a high-volume centre still needs clarification [621-624]. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) [591, 621, 625-628]. Methods that decrease infections include using coated prostheses and strictly adhering to surgical techniques that avoid prolonged wound exposure and skin contact minimisation (i.e., no-touch technique).

Techniques that might prevent penile prostheses infection but lack definitive evidence include the use of prolonged post-operative antibiotics (> 24 hours), shaving with clippers, and preparation with chlorhexidine-alcohol [629, 630]. Identification and pre-treatment of patients who are colonised with nasal *Staphylococcus aureus* with mupirocin and chlorhexidine prior to surgery has been shown to reduce the incidence of post-operative surgical site infection from 4.4% to 0.9% in a placebo-controlled randomised trial [631]. On the whole, growing evidence suggests that the risk of penile prosthesis infection has reduced over the last few decades with device improvement and surgical expertise [632].

Higher-risk populations include patients undergoing revision surgery, those with impaired host defences (immunosuppression, diabetes mellitus, or spinal cord injury) or those with penile corporal fibrosis [591, 600, 622, 633-635]. A recent large database-study has shown that diabetes mellitus is a risk factor for penile

prostheses infection, highlighting the need for optimal patient selection other than raising the question of whether lowering this risk by optimising glycaemic control before surgery [636]. Unfortunately, there are no RCTs determining the ideal and/or correct threshold of glycated haemoglobin that is acceptable prior to implant surgery in diabetic patients [637]. Recently, a large-cohort, multicentre, retrospective analysis in men with diabetes who received a Coloplast Titan™ implant demonstrated that vancomycin + gentamicin was the most efficacious combination of antibiotics used for implants dipping in terms of preventing postoperative infection and subsequent explantation and revision [638, 639].

Infection requires removal of the prosthesis and antibiotic administration. Alternatively, removal of the infected device with immediate replacement with a new prosthesis has been described using a wash-out protocol with successful salvages achieved in > 80% of cases [622, 634, 640, 641]. A final recommendation on how to proceed after removal in this setting cannot be given. The majority of revisions are secondary to mechanical failure and combined erosion or infection [627, 629]. Ninety-three percent of cases are successfully revised, providing functioning penile prosthesis [621, 622, 640, 642, 643].

Besides infection and mechanical failure, impending erosion involving the distal lateral corpora, urethra, glans or other structures can occur in 1-6% of cases after surgery [644]. Similarly glans ischaemia and necrosis have been reported in about 1.5% of patients [644, 645]. Risk factors for these serious complications are higher in those patients with significant vascular impairment, such as patients with diabetes, or who have undergone concomitant lengthening procedures.

5.6.2.9.4.1 Conclusions about penile prostheses implantation

Penile implants are an effective solution, usually for patients who do not respond to more conservative therapies. There is sufficient evidence to recommend this approach in patients not responding to less-invasive treatments due to its high efficacy, safety and satisfaction rate [646]. There are also currently no head to head studies comparing the different manufacturers' implants, demonstrating superiority of one implant type over another [647].

Table 17: Penile prostheses models available on the market

Semi-rigid prostheses	Inflatable prostheses	
	Two-piece	Three-piece
AMS Tactra™ [Boston Scientific]	AMS Ambicor™ [Boston Scientific]	Titan™ [Coloplast]
Genesis™ [Coloplast]		Titan OTR NB™ (Narrow base) [Coloplast]
		Titan Zero Degree™
Tube™ [Promedon]		AMS 700 CX™ [Boston Scientific]
ZSI 100™ [Zephyr]		AMS 700 LGX™ [Boston Scientific]
Virilis II™ [Subrini]		AMS 700 CXR™ [Boston Scientific]
		ZSI 475™ [Zephyr]

5.6.3 Recommendations for treatment of ED

Recommendations	Strength rating
Assess all patients for inadequate/incorrect information about the mechanism of action and the ways in which drugs should be taken, as they are the main causes of a lack of response to phosphodiesterase type 5 inhibitors (PDE5Is).	Weak
Use Cognitive Behaviour Therapy as a psychological approach (include the partner) combined with medical treatment to maximise treatment outcomes.	Strong
Discuss with patients undergoing radical prostatectomy (any technique) about the risk of sexual changes other than erectile dysfunction (ED), including libido reduction, changes in orgasm, anejaculation, Peyronie's like disease and penile size changes.	Strong
Initiate lifestyle changes and risk factor modification prior to, or at the same time, as initiating ED treatments.	Strong
Treat a curable cause of ED first, when found.	Weak
Use PDE5Is as first-line therapeutic option.	Strong
Use topical/intraurethral alprostadil as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy.	Weak

Use topical/intraurethral alprostadil as an alternative first-line therapy, in well-informed patients, who do not wish to have intracavernous injections or in patients who prefer a less-invasive therapy.	Weak
Use low intensity shockwave treatment (LI-SWT) in patients with mild vasculogenic ED or as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy or desire a curable option. Use LI-SWT in vasculogenic ED patients who are poor responders to PDE5Is.	Weak
Use vacuum erection devices (VEDs) as first-line therapy in well-informed patients with infrequent sexual intercourse and co-morbidity requiring non-invasive, drug-free management of ED.	Weak
Use intracavernous injections as an alternative first-line therapy in well-informed patients or as second-line therapy.	Strong
Use implantation of a penile prosthesis if other treatments fail or based upon patient preference.	Strong
Data is inadequate to support the use of any specific regimen for penile rehabilitation after radical prostatectomy.	Strong
Pro-erectile treatments should start at the earliest opportunity after radical prostatectomy/ pelvic surgery and other curative treatments for prostate cancer.	Weak

5.6.4 **Follow-up**

Follow-up is important in order to assess efficacy and safety of the treatment provided. It is also essential to assess patient satisfaction since successful treatment for ED goes beyond efficacy and safety. Physicians must be aware that there is no single treatment that fits all patients or all situations as described in detail in the previous section.

6. DISORDERS OF EJACULATION

6.1 Introduction

Ejaculation is a complex physiological process that comprises emission and expulsion processes and is mediated by interwoven neurological and hormonal pathways [648]. Any interference with those pathways may cause a wide range of ejaculatory disorders (Table 18).

Table 18: Spectrum of ejaculation disorders

Premature ejaculation
Retarded or delayed ejaculation
Anejaculation
Painful ejaculation
Retrograde ejaculation
Anorgasmia
Haemospermia

6.2 Premature ejaculation

6.2.1 **Epidemiology**

Historically, the main problem in assessing the prevalence of PE has been the lack of a universally recognised definition at the time that surveys were conducted [176]. See Section 4.2 for a comprehensive discussion about epidemiology of PE.

6.2.2 **Pathophysiology and risk factors**

The aetiology of PE is unknown, with few data to support suggested biological and psychological hypotheses, including anxiety [649-653], penile hypersensitivity [654-660] and 5-hydroxytryptamine (HT) receptor dysfunction [661-666]. The classification of PE into four subtypes [185] has contributed to a better delineation of lifelong, acquired, variable and subjective PE [667-669]. It has been hypothesised that the pathophysiology of lifelong PE is mediated by a complex interplay of central and peripheral serotonergic, dopaminergic, oxytocinergic, endocrinological, genetic and epigenetic factors [670]. Acquired PE may occur due to psychological problems - such as sexual performance anxiety, and psychological or relationship problems - and/or co-morbidity, including ED, prostatitis and hyperthyroidism [671-673].

A significant proportion of men with ED also experience PE [193, 345]. High levels of performance anxiety related to ED may worsen PE, with a risk of misdiagnosing PE instead of the underlying ED. According to the National Health and Social Life Survey (NHSLs), the prevalence of PE is not affected by age [181], unlike ED, which increases with age. Conversely, other data depicted an increased prevalence with ageing [653]; for instance, Verze *et al.* reported that PE prevalence based on the Premature Ejaculation Diagnostic Tool (PEDT) score (≥ 11) [674] proportionally increased with age [675]. Similarly, in a recent systematic review, PE was found to be more common in older age, with peak prevalence in men aged 60-69 years [676]. Premature ejaculation is not affected by marital or income status [181, 675]. However, PE is more common in Black men, Hispanic men, and men from regions where an Islamic background is common [180, 677] and prevalence may be higher in men with a lower educational level [181, 193]. Other risk factors include genetic predisposition [666, 678-681], poor overall health status and obesity [181], prostate inflammation [331, 682-685], hyperthyroidism [671], low prolactin levels [686], high testosterone levels [687], vitamin D and B12 deficiency [688, 689], diabetes [690, 691], MetS [692, 693], lack of physical activity [694], emotional problems and stress [181, 695, 696], depressive symptoms [696], and traumatic sexual experiences [181, 193]. In the only published study on risk modification/prevention strategies [697], successful eradication of causative organisms in patients with chronic prostatitis and PE produced marked improvements in intravaginal ejaculatory latency time (IELT) and ejaculatory control compared to untreated patients.

6.2.3 **Impact of PE on quality of life**

Men with PE are more likely to report low satisfaction with their sexual relationship, low satisfaction with sexual intercourse, difficulty relaxing during intercourse, and less-frequent intercourse [269, 698, 699]. However, the negative impact of PE extends beyond sexual dysfunction. Premature ejaculation can have a detrimental effect on self-confidence and the relationship with the partner, and may sometimes cause mental distress, anxiety, embarrassment and depression [269, 700, 701]. Moreover, PE may also affect the partner's sexual functioning and their satisfaction with the sexual relationship decreases with increasing severity of the patient's condition [702-704]. Despite the possible serious psychological and QoL consequences of PE, few men seek treatment. In the Global Study of Sexual Attitudes and Behaviors survey, 78% of men who self-reported a sexual dysfunction sought no professional help or advice for their sexual problems [193], with men more likely to seek treatment for ED than for PE [193]. In the Premature Ejaculation Prevalence and Attitudes (PEPA) survey, only 9% of men with self-reported PE consulted a physician [182]. The main reasons for not discussing PE with their physician are embarrassment and a belief that there is no treatment. Physicians are often uncomfortable discussing sexuality with their patients usually because of embarrassment and a lack of training or expertise in treating PE [705, 706]. Physicians need to encourage their patients to talk about PE.

6.2.4 **Classification**

There is still little consensus about the definition and classification of PE [707]. It is now universally accepted that "premature ejaculation" is a broad term that includes several concepts belonging to the common category of PE. The most recent definition comes from the International Classification of Diseases 11th Revision, where PE was renamed as Early Ejaculation [708]: *"Male early ejaculation is characterized by ejaculation that occurs prior to or within a very short duration of the initiation of vaginal penetration or other relevant sexual stimulation, with no or little perceived control over ejaculation. The pattern of early ejaculation has occurred episodically or persistently over a period of at least several months and is associated with clinically significant distress."*

This definition includes four categories: male early ejaculation, lifelong generalised and situational, acquired generalised and situational, unspecified.

In the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V), PE is defined as a sexual disorder with:

- consistent ejaculation within 1 minute or less of vaginal penetration;
- over a period of at least 6 months;
- experienced 75–100% of the time;
- the condition results in clinically significant distress, sexual frustration, dissatisfaction, or tension between partners;
- this condition is not better accounted for by another non-sexual mental disorder, medication or illicit substance use, or medical condition [200].

The EAU Guidelines have adopted the definition of PE that was developed by the International Society for Sexual Medicine as the first evidence-based definition [709]. According to this definition, PE (lifelong and acquired) is a male sexual dysfunction characterised by the following:

- ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE);

- inability to delay ejaculation on all or nearly all vaginal penetrations;
- negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.

Two more PE syndromes have been proposed [668]:

- ‘Variable PE’ is characterised by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance.
- ‘Subjective PE’ is characterised by subjective perception of consistent or inconsistent rapid ejaculation during intercourse, while ejaculation latency time is in the normal range or can even last longer. It should not be regarded as a symptom or manifestation of true medical pathology.

The addition of these new syndrome types may help in overcoming the limitations of each individual definition and it may support a more flexible view of PE for patient stratification, diagnosis and treatment [710].

6.2.5 Diagnostic evaluation

Diagnosis of PE is based on the patient’s medical and sexual history [189, 711, 712]. History should classify PE as lifelong or acquired and determine whether PE is situational (under specific circumstances or with a specific partner) or consistent. Special attention should be given to the duration time of ejaculation, degree of sexual stimulus, impact on sexual activity and QoL, and drug use or abuse. It is also important to distinguish PE from ED. Many patients with ED develop secondary PE caused by the anxiety associated with difficulty in attaining and maintaining an erection [345, 713]. Furthermore, some patients are not aware that loss of erection after ejaculation is normal and may erroneously complain of ED, while the actual problem is PE [714]. There are several overlapping definitions of PE, with four shared factors (Table 19), resulting in a multi-dimensional diagnosis [715].

Table 19: Common factors in different definitions of PE

Time to ejaculation assessed by IELT
Perceived control
Distress, bother, frustration, interpersonal difficulty related to the ejaculatory dysfunction

6.2.5.1 Intravaginal ejaculatory latency time (IELT)

Although it has been suggested as an objective diagnostic criterion and treatment outcome measure [716, 717], the use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE [718, 719]. Moreover, some men may experience PE in their non-coital sexual activities (e.g., during masturbation, oral sex or anal intercourse) thus measuring IELT will not be suitable for their assessment. Intravaginal ejaculatory latency time has a significant direct effect on perceived control over ejaculation, but not a significant direct effect on ejaculation-related personal distress or satisfaction with sexual intercourse [698]. In addition, perceived control over ejaculation has a significant direct effect on both ejaculation-related personal distress and satisfaction with sexual intercourse (each showing direct effects on interpersonal difficulty related to ejaculation) [720]. In everyday clinical practice, self-estimated IELT is sufficient [177]. Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity [721]. Specificity can be improved further to 96% by combining IELT with a single-item patient-reported outcome (PRO) scale on control over ejaculation and satisfaction with sexual intercourse (0 = very poor, to 4 = very good) and on personal distress and interpersonal difficulty (0 = not at all, to 4 = extremely). However, self-estimated IELT may be over-estimated by ~1 minute and therefore it must be carefully substituted with stopwatch-measured IELT while identifying men with the complaint of lifelong PE in a clinical setting [722].

Measurement of IELT with a calibrated stopwatch is mandatory in clinical trials. For any drug treatment study of PE, Waldinger *et al.* suggested using geometric mean instead of arithmetic mean IELT because the distributed IELT data are skewed. Otherwise, any treatment-related ejaculation delay may be overestimated if the arithmetic mean IELT is used instead of the geometric mean IELT [723].

6.2.5.2 Premature ejaculation assessment questionnaires

The need to assess PE objectively has led to the development of several questionnaires based on the use of PROs. Only two questionnaires can discriminate between patients who have PE and those who do not:

- Premature Ejaculation Diagnostic Tool (PEDT): A five-item questionnaire based on focus groups and interviews from the USA, Germany, and Spain assesses control, frequency, minimal stimulation, distress and interpersonal difficulty [724]. A total score > 11 suggests a diagnosis of PE, 9 or 10 suggests a probable diagnosis of PE, and < 8 indicates a low likelihood of PE.

- Arabic Index of Premature Ejaculation (AIPE): A seven-item questionnaire developed in Saudi Arabia assesses sexual desire, hard erections for sufficient intercourse, time to ejaculation, control, satisfaction of the patient and partner, anxiety or depression [725]. A cut-off score of 30 (range 7-35) discriminates PE diagnosis best. Severity of PE is classified as severe (score: 7-13), moderate (score: 14-19), mild-to-moderate (score: 20-25) and mild (score: 26-30).

Although it is widely used, some studies have reported a low correlation between a diagnosis provided by PEDT and a self-reported diagnosis. Only 40% of men with PEDT-diagnosed PE and 19% of men with probable PE self-reported the condition [286]. On the contrary, a recent study has shown that PEDT is valid in screening the presence of evidence-based-defined lifelong PE and acquired PE [62]. Questionnaires are a significant step in simplifying the methodology of PE drug studies, although further cross-cultural validation is needed [721].

Other questionnaires used to characterise PE and determine treatment effects include the Premature Ejaculation Profile (PEP) [719], Index of Premature Ejaculation (IPE) [726] and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [727]. Currently, their role is optional in everyday clinical practice.

6.2.5.3 Physical examination and investigations

Physical examination may be part of the initial assessment of men with PE. It may include a focused examination of the urological, endocrine and neurological systems to identify underlying medical conditions associated with PE or other sexual dysfunctions, such as endocrinopathy, Peyronie's disease, urethritis or prostatitis. Laboratory or physiological testing should be directed by specific findings from history or physical examination and is not routinely recommended [711].

6.2.5.4 Recommendations for the diagnostic evaluation of PE

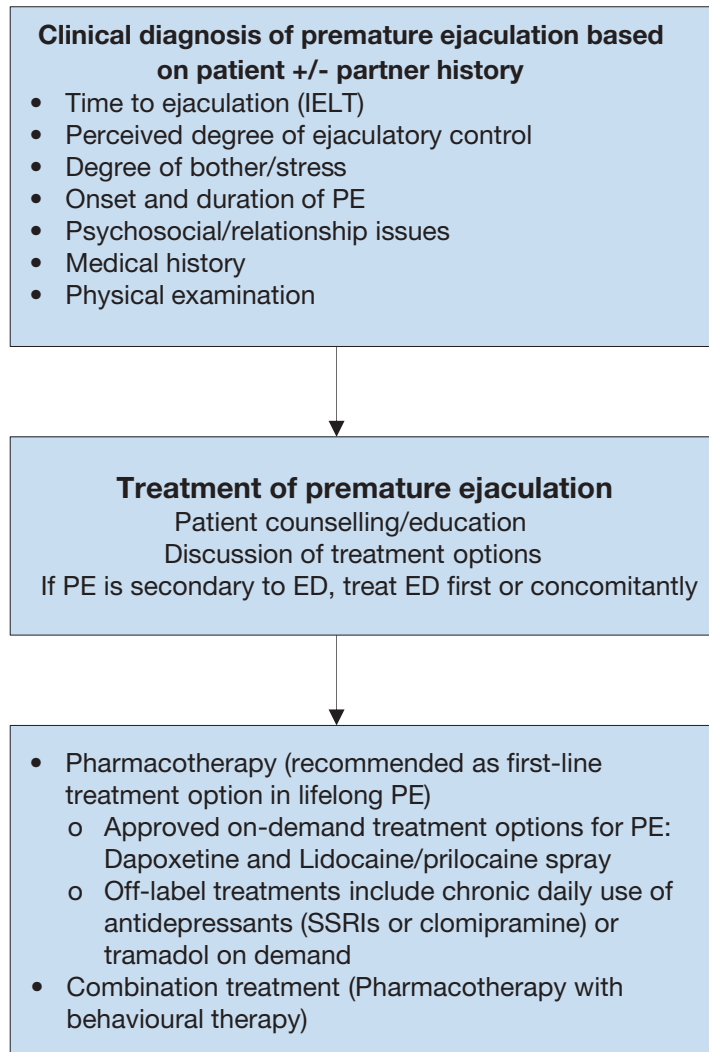
Recommendations	Strength rating
Perform the diagnosis and classification of premature ejaculation (PE) based on medical and sexual history, which should include assessment of intravaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	Strong
Use of stopwatch-measured IELT is not compulsory in clinical practice.	Weak
Use patient-reported outcomes in daily clinical practice.	Weak
Include physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly erectile dysfunction.	Strong
Do not perform routine laboratory or neuro-physiological tests. They should only be directed by specific findings from history or physical examination.	Strong

6.2.6 Disease management

Before commencing any treatment, it is essential to define the subtype of PE and discuss patient's expectations thoroughly. Pharmacotherapy must be considered as the first-line treatment for patients with lifelong PE, whereas treating the underlying cause (e.g., ED, prostatitis, LUTS, anxiety and hyperthyroidism) must be the initial goal for patients with acquired PE [189]. Various behavioural techniques may be beneficial in treating variable and subjective PE [728]. Psychotherapy can also be considered for PE patients who are uncomfortable with pharmacological therapy or in combination with pharmacological therapy [729, 730]. However, there is weak and inconsistent evidence regarding the effectiveness of these psychosexual interventions and their long-term outcomes in PE are unknown [731].

In lifelong PE, behavioural techniques are not recommended alone, and pharmacotherapy must be considered as the basis of treatment [189]. Dapoxetine (30 and 60 mg) is the first on-demand oral pharmacological agent approved for lifelong and acquired PE in many countries, except for the USA [732]. The metered-dose aerosol spray of lidocaine (150 mg/mL) and prilocaine (50 mg/mL) combination is the first topical formulation to be officially approved for on-demand treatment of lifelong PE by the EMA in the European Union [733]. All other medications used in PE are off-label indications [734]. Daily or on-demand use of selective serotonin re-uptake inhibitors (SSRIs) and clomipramine, and on-demand topical anaesthetic agents have consistently shown efficacy in PE [735-738]. Long-term outcomes of pharmacological treatments are unknown. An evidence-based analysis of all current treatment modalities was performed. Levels of evidence and grades of recommendation are provided, and a treatment algorithm is presented (Figure 7).

Figure 7: Management of premature ejaculation*



* Adapted from Lue *et al.* 2004 [739].

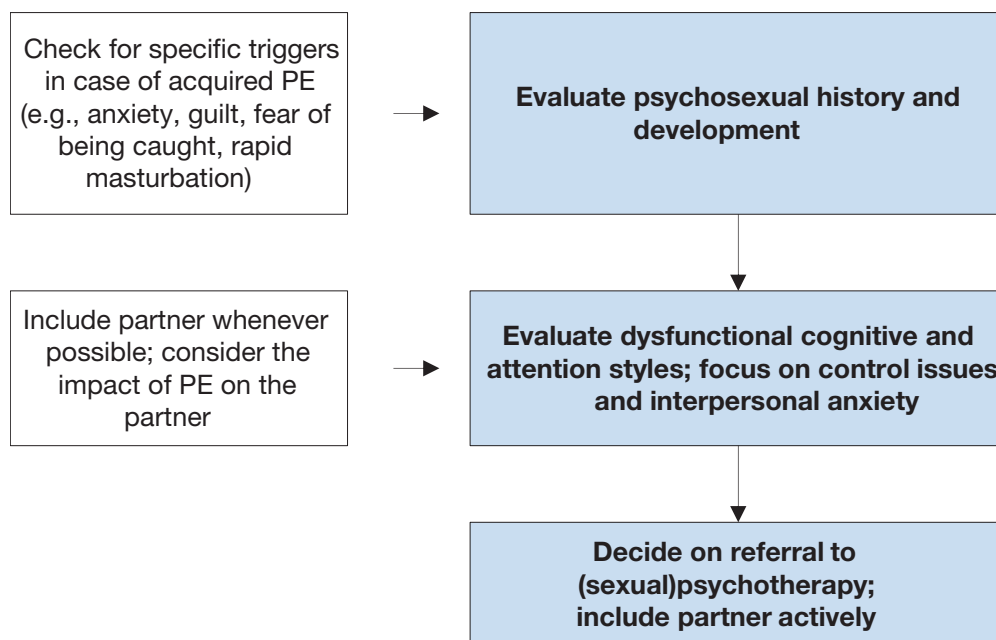
ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

6.2.6.1 Psychological aspects and intervention

Only a few studies have addressed the psychological factors underpinning PE. Men with PE have been shown to present dysfunctional responsibility attribution patterns regarding their sexual experience. These men blame themselves for their dysfunctional sexual response, even when the negative sexual outcome is unrelated to early ejaculation; additionally, they take less credit for any positive sexual experience they might have [740, 741]. In addition to this style of internalised blame, men with PE focus on bodily sensations and their partners' reactions during sex, to monitor potential signs of threat to their sexual performance. This monitoring process denotes a dysfunctional cognitive and attention style that contributes to the maintenance of PE [431]. Premature ejaculation is further related to increased levels of anxiety, including social anxiety [431, 720]. Yet, it is not known whether anxiety is a precursor or a consequence of PE [650]. The negative impact of PE on couples has been consistently mentioned. Female partners of men with PE present with an increased likelihood of sexual dysfunction [742, 743]; the intimate sphere, as well as the overall relationship quality, is compromised by PE [731]. An important trigger for seeking help in PE is partner dissatisfaction and the negative impact of PE on the general QoL of the couple [744]. Accordingly, psychosexual interventions, whether these are behavioural, cognitive, or focused on the couple, are aimed at teaching techniques to control/delay ejaculation, gaining confidence in sexual performance, reducing anxiety, and promoting communication and problem solving within the couple [728]. It is worth noting, however, that psychosexual interventions alone regarding PE lack empirical support. Recent evidence suggests that start-stop exercises, combined with psycho-education and mindfulness techniques improve PE symptoms, as well as PE-associated distress, anxiety and depression [745]. The potential benefits of mindfulness have been reported [746]. Behavioural therapy

may be most effective when used to ‘add value’ to medical interventions. Combination of dapoxetine and behavioural treatment was more effective than dapoxetine alone in patients with lifelong PE in a prospective, randomised trial [729]. Smartphone-delivered psychological intervention, aimed at improving behavioural skills for ejaculatory delay and sexual self-confidence, has positive effects, supporting E-health in the context of PE [747]. Validated assessment instruments need to be used as end-points. Longer follow-up periods are necessary to confirm these findings.

Figure 8: Key aspects for psychosexual evaluation



6.2.6.1.1 Recommendation for the assessment and treatment (psychosexual approach) of PE

Recommendations for assessment	Strength rating
Consider sexual history and psychosexual development.	Strong
Consider anxiety, interpersonal anxiety; focus on control issues.	Strong
Include partner if available; check for the impact of PE on the partner.	Strong
Recommendation for treatment (psychosexual approach)	
Use behavioural, cognitive and/or couple therapy approaches. Consider mindfulness exercises.	Weak

6.2.6.2 Pharmacotherapy

6.2.6.2.1 Dapoxetine

Dapoxetine hydrochloride is a short-acting SSRI, with a pharmacokinetic profile suitable for on-demand treatment for PE [734]. It has a rapid T_{max} (1.3 hours) and a short half-life (95% clearance rate after 24 hours) [748, 749]. It is approved for on-demand treatment of PE in European countries and elsewhere, but not in the USA. Both available doses of dapoxetine (30 mg and 60 mg) have shown 2.5- and 3.0-fold increases, respectively, in IELT overall, rising to 3.4- and 4.3-fold in patients with a baseline average IELT < 30 seconds [732, 750, 751].

In RCTs, dapoxetine, 30 mg or 60 mg 1-2 hours before intercourse, was effective at improving IELT and increasing ejaculatory control, decreasing distress, and increasing satisfaction [752]. Dapoxetine has shown a similar efficacy profile in men with lifelong and acquired PE [732, 753, 754]. Treatment-related adverse effects were dose-dependent and included nausea, diarrhoea, headache and dizziness. Treatment-emergent adverse events (TEAEs) were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects [177]. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [750, 755]. Dapoxetine is safer compared with formal anti-depressant compounds that are used for treatment of PE [756].

A low rate (0.1%) of vasovagal syncope was reported in phase 3 studies [757]. According to the summary of product characteristics, orthostatic vital signs (blood pressure and heart rate) must be measured prior to

starting dapoxetine and dose-titration must be considered [758]. The EMA assessment report for dapoxetine concluded that the potentially increased risk for syncope has been proven manageable with adequate risk minimisation measures [759]. No cases of syncope were observed in a post-marketing observational study, which had identified patients at risk for orthostatic reaction using the patient's medical history and orthostatic testing [760].

Many patients and physicians may prefer using dapoxetine in combination with a PDE5I to extend the time until ejaculation and minimise the risk of ED due to dapoxetine treatment. Phase 1 studies of dapoxetine have confirmed that it does not have any pharmacokinetic interactions with PDE5Is (i.e., tadalafil 20 mg and sildenafil 100 mg) [761]. When dapoxetine is co-administered with PDE5Is, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone [762]. A recent RCT including PE patients without ED, demonstrated that combination of dapoxetine with sildenafil can significantly improve IELT values and PROs compared with dapoxetine alone or sildenafil alone, with tolerable adverse events [763]. Efficacy and safety of dapoxetine/sildenafil combination tablets for the treatment of PE have also been reported [764].

Although dapoxetine is the only EMA approved oral drug for treatment of PE, discontinuation rates seem moderate-to-high. The cumulative discontinuation rates increase over time, reaching 90% at 2 years after initiation of therapy. The reasons for the high discontinuation rate are cost (29.9%), disappointment that PE was not curable and the on-demand nature of the drug (25%), adverse effects (11.6%), perceived poor efficacy (9.8%), a search for other treatment options (5.5%), and unknown (18.3%) [765]. Similarly, it was confirmed that a considerable number of patients who were on dapoxetine treatment spontaneously discontinue treatment, while this rate was reported 50% for other SSRIs and 28.8% for paroxetine [766]. In a Chinese cohort study, 13.6% of the patients discontinued dapoxetine due to lack of efficacy (62%), adverse effects (24%), and low frequency of sexual intercourse (14%) [767].

6.2.6.2.2 Off-label use of antidepressants: selective serotonin reuptake inhibitors and clomipramine

Ejaculation is commanded by a spinal ejaculation generator [768, 769] under excitatory or inhibitory influences from the brain and the periphery [690]. 5-hydroxytryptamine (5-HT or serotonin) is involved in ejaculatory control, with its ejaculation-retarding effects likely to be attributable to activation of 5-HT_{1B} and 5-HT_{2C} receptors, both spinally and supraspinally. By contrast, stimulation of 5-HT_{1A} receptors precipitates ejaculation [770].

Selective serotonin re-uptake inhibitors are used to treat mood disorders but can delay ejaculation and therefore have been widely used 'off-label' for PE since the 1990s [771]. For depression, SSRIs must be given for 1-2 weeks to be effective for PE [770]. Administration of chronic SSRIs causes prolonged increases in synaptic cleft serotonin, which desensitises the 5-HT_{1A} and 5-HT_{1B} receptors [772]. Commonly used SSRIs include continuous intake of citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, all of which have a similar efficacy, whereas paroxetine exerts the strongest ejaculation delay [716, 773, 774].

Clomipramine, the most serotonergic tricyclic antidepressant, was first reported in 1977 as an effective PE treatment [775, 776]. In a recent RCT, on-demand use of clomipramine 15 mg, 2-6 hours before sexual intercourse was found to be associated with IELT fold change and significant improvements in PRO measures in the treatment group as compared to the placebo group (4.66 ± 5.64 vs. 2.80 ± 2.19 , $P < 0.05$). [777, 778]. The most commonly reported TEAEs were nausea in 15.7% and dizziness in 4.9% of men, respectively [777, 778].

Several systematic reviews and meta-analyses of drug treatment have reported that, despite methodological problems in most studies, there remain several, well-designed, double-blind, placebo-controlled trials supporting the therapeutic effect of daily SSRIs on PE [716, 735-738]. Based on these meta-analyses, SSRIs may increase the geometric mean IELT by 2.6-13.2-fold. Paroxetine is superior to fluoxetine, clomipramine and sertraline. Sertraline is superior to fluoxetine, whereas the efficacy of clomipramine is not significantly different from that of fluoxetine and sertraline. Paroxetine was evaluated in doses of 20-40 mg, sertraline 25-200 mg, fluoxetine 10-60 mg and clomipramine 25-50 mg. There was no significant relationship between dose and response among the various drugs. There is limited evidence that citalopram may be less efficacious compared to other SSRIs, while fluvoxamine may not be effective [779, 780].

Ejaculation delay may start a few days after drug intake, but it is more evident after 1-2 weeks as receptor desensitisation requires time to occur. Although efficacy may be maintained for several years, tachyphylaxis (decreasing response to a drug following chronic administration) may occur after 6-12 months [775]. Common TEAEs of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea and perspiration;

TEAEs are usually mild and gradually improve after 2-3 weeks of treatment [750, 775]. Decreased libido, anorgasmia, anejaculation and ED have also been reported.

Because of the risk of suicidal ideation or suicide attempts, caution is suggested in prescribing SSRIs to young adolescents aged ≤ 18 years with PE, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation. Patients should be advised to avoid sudden cessation or rapid dose reduction of daily-dosed SSRIs, which may be associated with a SSRI withdrawal syndrome [177]. Moreover, PE patients who are trying to conceive should avoid using these medications because of their detrimental effects on sperm cells [781-784].

6.2.6.2.3 Topical anaesthetic agents

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE [785]. Several trials [657, 786, 787] support the hypothesis that topical desensitising agents reduce the sensitivity of the glans penis thereby delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation. Meta-analyses have confirmed the efficacy and safety of these agents for the treatment of PE [788, 789]. In a recent meta-analysis, the efficacy of local anaesthetics was best among the other treatment options including SSRIs, dapoxetine 30 and 60 mg, PDE5Is and tramadol for < 8 weeks of therapy [790].

6.2.6.2.3.1 Lidocaine/prilocaine cream

In a randomised, double-blind, placebo-controlled trial, lidocaine/prilocaine cream increased IELT from one minute in the placebo group to 6.7 minutes in the treatment group [791]. In another randomised, double blind, placebo-controlled trial, lidocaine/prilocaine cream significantly increased the stopwatch-measured IELT from 1.49 to 8.45 minutes, while no difference was recorded in the placebo group (1.67 to 1.95 minutes) [792]. Although no significant TEAEs have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any ingredient in the product. These anaesthetic creams/gels may be transferred to the partner and result in vaginal numbness. Therefore, patients are advised to use a condom after applying the cream to their penis. Alternatively, the penis can be washed to clean off any residual active compound prior to sexual intercourse. Since these chemicals may be associated with cytotoxic effects on fresh human sperm cells, couples seeking parenthood should not use topical lidocaine/prilocaine-containing substances [793].

6.2.6.2.3.2 Lidocaine/prilocaine spray

The eutectic lidocaine/prilocaine spray is a metered-dose aerosol spray containing purely base forms of lidocaine (150 mg/mL) and prilocaine (50 mg/mL), which has been officially approved by the EMA for the treatment of lifelong PE [794]. Compared to topical creams, the metered-dose spray delivery system has been proved to deposit the drug in a dose-controlled, concentrated film covering the glans penis, maximising neural blockage and minimising the onset of numbness [795], without absorption through the penile shaft skin [796].

To date, one phase 2 proof-of-concept [796] and two phase 3 RCTs [797, 798] have demonstrated the efficacy of lidocaine/prilocaine spray in improving both IELT and the Index of Ejaculatory Control of patients with primary PE, along with an improvement in scores assessing treatment satisfaction (IPE) [797, 798]. Based on these data, according to the patient information leaflet [799], the recommended dose of lidocaine/prilocaine spray is one dose (namely three sprays) to be applied on the glans penis at least 5 minutes before sexual intercourse [800]. Published data showed that lidocaine/prilocaine spray increases IELT over time up to 6.3-fold over 3 months, with a month-by-month improvement through the course of the treatment in long-term studies [801]. A low incidence of local TEAEs in both patients and partners has been reported, including genital hypoesthesia (4.5% and 1.0% in men and females partners, respectively) and ED (4.4%), and vulvovaginal burning sensation (3.9%), but is unlikely to be associated with systemic TEAEs [799, 802].

Lidocaine-only sprays are also effective in the treatment of PE. In a recent RCT, PE patients were randomly allocated to receive either dapoxetine 60 mg or topical lidocaine 10% spray. The geometric mean IELTs were significantly better in the lidocaine compared with dapoxetine group (179.43 vs. 63.44, respectively). However, both groups showed significant improvement compared with baseline IELTs value (63.44 and 179.4 vs. 21.87, $P < .05$) [803]. In another RCT lidocaine 5% spray was compared with alcohol spray (placebo) in the treatment of lifelong PE for 8 weeks; the mean values of the AIPE scores, IELT, and sexual intercourse frequency in the lidocaine 5% spray group were significantly increased compared with the placebo group [804].

6.2.6.2.4 Tramadol

Tramadol is a centrally-acting analgesic agent that combines opioid receptor activation and re-uptake inhibition of serotonin and noradrenaline. Tramadol is a mild-opioid receptor agonist, but it also displays antagonistic properties on transporters of noradrenaline and 5-HT [805]. This mechanism of action distinguishes tramadol

from other opioids, including morphine. Tramadol is readily absorbed after oral administration and has an elimination half-life of 5-7 hours.

A large, randomised, double-blind, placebo-controlled, multicentre 12-week study was carried out to evaluate the efficacy and safety of two doses of tramadol (62 and 89 mg) by ODT in the treatment of PE [806].

A bioequivalence study has demonstrated equivalence between tramadol ODT and tramadol HCl. In patients with a history of lifelong PE and an IELT < 2 minutes, increases in the median IELT of 0.6 minutes (1.6-fold), 1.2 minutes (2.4-fold) and 1.5 minutes (2.5-fold) were reported for placebo, 62 mg of tramadol ODT, and 89 mg of tramadol ODT, respectively. It should be noted that there was no dose-response effect with tramadol. Adverse effects were reported at doses used for analgesic purposes (\leq 400 mg daily) and included constipation, sedation and dry mouth. However, in May 2009, the US FDA released a warning letter about tramadol's potential to cause addiction and difficulty in breathing [807]. The tolerability during the 12-week study period in men with PE was acceptable. Several other studies have also reported that tramadol exhibits a significant dose-related efficacy and adverse effects during treatment of PE [808]. The efficacy and safety of tramadol have been confirmed in systematic reviews and meta-analyses [809-811].

6.2.6.2.5 Phosphodiesterase type 5 inhibitors

One well-designed, randomised, double-blind, placebo-controlled study compared sildenafil to placebo in men with PE [812]. Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety and the refractory time to achieve a second erection after ejaculation. Another RCT demonstrated that once-daily 5 mg tadalafil for 6 weeks was effective in improving PROs and was well tolerated by patients with PE [813]. Several open-label studies have shown that combination of PDE5Is and SSRIs is superior to SSRI monotherapy, which has also been recently confirmed by a Bayesian network meta-analysis [790]:

- Sildenafil combined with paroxetine improved IELT significantly and satisfaction vs. paroxetine alone [814];
- Sildenafil combined with sertraline improved IELT and satisfaction significantly vs. sertraline alone [815];
- Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed [816];
- Sildenafil combined with dapoxetine (30 mg.) improved IELT, satisfaction scores and PEDT vs. dapoxetine, paroxetine or sildenafil monotherapy [763];
- Tadalafil combined with paroxetine significantly improved IELT and satisfaction vs. paroxetine and tadalafil alone [817];
- Sildenafil combined with behavioural therapy significantly improved IELT and satisfaction vs. behavioural therapy alone [818].

Overall, there are limited data on the efficacy of other PDE5Is (tadalafil and vardenafil) [819, 820]. In a recent meta-analysis, PDE5Is were found to be significantly more effective than placebo in the treatment of patients with PE and without ED [821]. Some meta-analyses have demonstrated that the combined use of SSRIs and PDE5Is may be more effective than SSRI or PDE5I monotherapy [737, 822-826]. In a recent Bayesian meta-analysis, combined therapy of SSRI and PDE5I was found to be superior to other treatment modalities (including topical creams, tramadol, paroxetine or fluoxetine monotherapy, PDE5I monotherapy, dapoxetine 30 and 60 mg, clomipramine, citalopram, and placebo) lasting > 8 weeks [790].

6.2.6.2.6 Other drugs

In addition to the aforementioned drugs, there is continuous research into other treatment options. Considering the abundant α 1a-adrenergic receptors in seminal vesicles and the prostate, and the role of the sympathetic system in ejaculation physiology, the efficacy of selective α -blockers in the treatment of PE has been assessed [827-829]. A recent study demonstrated that wake-promoting agent modafinil may be effective in delaying ejaculation and improving PROMs [830]. The efficacy of acupuncture was compared to dapoxetine for the treatment of PE and although acupuncture showed a significant ejaculation-delaying effect, this was less effective as compared with that of dapoxetine [831].

Decreasing penile sensitivity with glans penis augmentation using hyaluronic acid for the treatment of PE was initially proposed by Korean researchers in 2004 [832], and since then has gained popularity mainly in Asian countries [833, 834]. In a randomised controlled cross-over study, hyaluronic acid glans injections were safe with a modest but significant increase in IELT [835]. However, these procedures may result in serious complications and more safety studies must be conducted before recommending this treatment to PE patients [836].

Considering the importance of central oxytocin receptors in ejaculation reflex, several researchers have

assessed the efficacy and safety of oxytocin receptor antagonists in the treatment of PE [837]. Epelsiban [838] and cligosiban [839-841] have been found to be safe and mildly effective in delaying ejaculation, but further controlled trials are needed [841].

The role of other proposed treatment modalities for the treatment of PE such as penis-root masturbation [842], vibrator-assisted start-stop exercises [745], transcutaneous functional electric stimulation [843], transcutaneous posterior tibial nerve stimulation [844], and practicing yoga [845] need more evidence to be considered in the clinical setting.

6.2.7 **Summary of evidence on the epidemiology/aetiology/pathophysiology of PE**

Summary of evidence	LE
Pharmacotherapy includes either dapoxetine on-demand (an oral short-acting SSRI) and eutectic lidocaine/prilocaine spray (a topical desensitising agent) which are the only approved treatments for PE, or other off-label antidepressants (daily/on-demand SSRIs and clomipramine).	1a

6.2.8 **Recommendations for the treatment of PE**

Recommendations	Strength rating
Treat erectile dysfunction (ED), other sexual dysfunction or genitourinary infection (e.g., prostatitis) first.	Strong
Use either dapoxetine or the lidocaine/prilocaine spray as first-line treatments for lifelong premature ejaculation (PE).	Strong
Use off-label topical anaesthetic agents as a viable alternative to oral treatment with selective serotonin re-uptake inhibitor (SSRIs).	Strong
Use tramadol on-demand as a weak alternative to SSRIs.	Weak
Use PDE5Is alone or in combination with other therapies in patients with PE (without ED).	Strong
Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired PE.	Weak

6.3 **Delayed Ejaculation**

6.3.1 **Definition and classification**

The American Psychiatric Association defines delayed ejaculation (DE) as requiring one of two symptoms as follows: marked delay, infrequency, or absence of ejaculation on 75-100% of occasions, that persists for at least 6 months, and which causes personal distress [200]. However, in a recent study, while ejaculatory latency and control were significant criteria to differentiate men with DE from those without ejaculatory disorders, bother/distress did not emerge as a significant factor [846]. Similar to PE, there are distinctions among lifelong, acquired and situational DE [200]. Although the evidence is limited, the prevalence of lifelong DE and acquired DE is estimated around 1% and 4%, respectively [201].

6.3.2 **Pathophysiology and risk factors**

The aetiology of DE can be psychological, organic (e.g., incomplete spinal cord lesion or iatrogenic penile nerve damage), or pharmacological (e.g., SSRIs, antihypertensive drugs, or antipsychotics) [847, 848] (Table 20). Other factors that may play a role in the aetiology of DE include tactile sensitivity and tissue atrophy [849]. Although low testosterone level has been considered a risk factor in the past [55, 687], more contemporary studies have not confirmed any association between ejaculation times and serum testosterone levels [850, 851]. Idiosyncratic masturbation and lack of desire for stimuli are also proposed risk factors for DE [195-197].

Table 20: Etiological Causes of Delayed Ejaculation and Anejaculation [852]

Ageing Men	Degeneration of penile afferent nerves inhibited ejaculation
Congenital	Mullerian duct cyst Wolfian duct abnormalities Prune Belly Syndrome Imperforate Anus Genetic abnormalities
Anatomic causes	Transurethral resection of prostate Bladder neck incision Circumcision Ejaculatory duct obstruction (can be congenital or acquired)
Neurogenic causes	Diabetic autonomic neuropathy Multiple sclerosis Spinal cord injury Radical prostatectomy Proctocolectomy Bilateral sympathectomy Abdominal aortic aneurysmectomy Para-aortic lymphadenectomy
Infective/Inflammation	Urethritis Genitourinary tuberculosis Schistosomiasis Prostatitis Orchitis
Endocrine	Hypogonadism Hypothyroidism Prolactin disorders
Medication	Antihypertensives; thiazide diuretics Alpha-adrenergic blockers Antipsychotics and antidepressants Alcohol Antiandrogens Ganglion blockers Selective serotonin reuptake Inhibitors
Psychological	Acute psychological distress Relationship distress Psychosexual skill deficit Disconnect between arousal and sexual situations Masturbation style

6.3.3 **Investigation and treatment**

Patients should have a full medical and sexual history performed along with a detailed physical examination when evaluating for DE. It is not uncommon for clinicians to feel uncomfortable with the level of sexual information that is warranted in obtaining a full sexual history. Understanding the details of the ejaculatory response, sensation, frequency, and sexual activity/techniques; cultural context and history of the disorder; quality of the sexual response cycle (desire, arousal, ejaculation, orgasm, and refractory period); partner's assessment of the disorder and if the partner suffers from any sexual dysfunction her/himself; and the overall satisfaction of the sexual relationship are all important to garner during history-taking [853]. Investigation by a sex therapist is often required to help obtain a complete psychological evaluation. It is incumbent on the clinician to diagnose medical pathologies that cause or contribute to DE, such as assessing the hormonal milieu, anatomy, and overall medical condition. Good communication between the sex therapist and medical practitioner is vital to successful diagnosis and treatment of DE.

6.3.3.1 *Psychological aspects and intervention*

There is scarce literature on the psychological aspects relating to DE, as well as on empirical evidence regarding psychological treatment efficacy. Studies on psychological aspects have revealed that men with DE show a strong need to control their sexual experiences. Delayed ejaculation is associated with difficulties surrendering to sexual pleasure during sex - i.e., the sense of *letting go* [854] - which denotes a psychological

underlying mechanism influencing the reaching of orgasm [855]. As for psychological treatments, these may include, but are not limited to: increased genital-specific stimulation; sexual education; role-playing on his own and in front of his partner; retraining masturbatory practices; anxiety reduction on ejaculation and performance; and, re-calibrating the mismatch of sexual fantasies with arousal (such as with pornography use and fantasy stimulation compared to reality) [853]. A basic understanding of the sexual cycle for their respective partners can assist men and women in managing expectations and in evaluating their own sexual practices. Masturbation techniques that are either solo or partnered can be considered practice for the “real performance” which can eventually result in greater psychosexual arousal and orgasm for both parties [197]. Although masturbation with fantasy can be harmful when not associated with appropriate sexual arousal and context, fantasy can be supportive if it allows blockage of critical thoughts that may be preventing orgasm and ejaculation. Techniques geared towards reduction of anxiety are important skills that can help overcome performance anxiety, as this can often interrupt the natural erectile function through orgasmic progression. Referral to a sexual therapist, psychologist or psychiatrist is appropriate and often warranted.

6.3.3.2 *Pharmacotherapy*

Several pharmacological agents, including cabergoline, bupropion, alpha-1-adrenergic agonists (pseudoephedrine, midodrine, imipramine and ephedrine), buspirone, oxytocin, testosterone, bethanechol, yohimbine, amantadine, cyproheptadine and apomorphine have been used to treat DE with varied success [849]. Unfortunately, there is no FDA or EMA approved medications to treat DE, as most of the cited research is based on case-cohort studies that were not randomised, blinded, or placebo-controlled. Many drugs have been used as both primary treatments and/or as antidotes to other medications that can cause DE. A recent survey of sexual health providers demonstrated an overall treatment success of 40% with most providers commonly using cabergoline, bupropion or oxytocin [856]. However, this survey measured the anecdotal results of practitioners and there was no proven efficacy or superiority of any drug due to a lack of placebo-controlled, randomised, blinded, comparative trials [852]. In addition to pharmacotherapy, penile vibratory stimulation (PVS) is also used as an adjunct therapy for DE [857]. Another study that used combined therapy of midodrine and PVS to increase autonomic stimulation in 158 men with spinal cord injury led to ejaculation in almost 65% of the patients [858].

6.4 **Anejaculation**

6.4.1 **Definition and classification**

Anejaculation involves the complete absence of antegrade or retrograde ejaculation. It is caused by failure of semen emission from the seminal vesicles, prostate, and ejaculatory ducts into the urethra [859]. True anejaculation is usually associated with a normal orgasmic sensation and is always associated with central or peripheral nervous system dysfunction or with drugs [860].

6.4.2 **Pathophysiology and risk factors**

Generally, anejaculation shares similar aetiological factors with DE and retrograde ejaculation (Table 20).

6.4.3 **Investigation and treatment**

Drug treatment for anejaculation caused by lymphadenectomy and neuropathy, or psychosexual therapy for anorgasmia, is not effective. In all these cases, and in men who have a spinal cord injury, PVS (i.e., application of a vibrator to the penis) is the first-line therapy. In anejaculation, PVS evokes the ejaculation reflex [861], which requires an intact lumbosacral spinal cord segment. If the quality of semen is poor, or ejaculation is retrograde, the couple may enter an *in vitro* fertilisation program whenever fathering is desired. If PVS has failed, electro-ejaculation can be the therapy of choice [862]. When electro-ejaculation fails or cannot be carried out, other sperm-retrieval techniques may be used [863]. Anejaculation following either retroperitoneal surgery for testicular cancer or total mesorectal excision can be prevented using unilateral lymphadenectomy or autonomic nerve preservation [864], respectively.

6.5 **Painful Ejaculation**

6.5.1 **Definition and classification**

Painful ejaculation is a condition in which a patient feels mild discomfort to severe pain during or after ejaculation. The pain can involve the penis, scrotum, and perineum [865].

6.5.2 **Pathophysiology and risk factors**

Many medical conditions can result in painful ejaculations, but it can also be an idiopathic problem. Initial reports demonstrated possible associations of painful ejaculation with calculi in the seminal vesicles [866], sexual neurasthenia [867], sexually transmitted diseases [865, 868], inflammation of the prostate [221, 869], PCA [870, 871], BPH [219], prostate surgery [872, 873], pelvic radiation [874], herniorrhaphy [875] and antidepressants

[876-878]. Further case reports have suggested that mercury toxicity or Ciguatera toxin fish poisoning may also result in painful ejaculation [879, 880]. Psychological issues may also be the cause of painful ejaculation, especially if the patient does not experience this problem during masturbation [881].

6.5.3 Investigation and treatment

Treatment of painful ejaculation must be tailored according to the underlying cause, if detected. Psychotherapy or relationship counselling, withdrawal of suspected agents (drugs, toxins, or radiation) [876, 877, 882] or the prescription of appropriate medical treatment (antibiotics, α -blockers or anti-inflammatory agents) may ameliorate painful ejaculation. Behavioural therapy, muscle relaxants, antidepressant treatment, anticonvulsant drugs and/or opioids, pelvic floor exercises, may be implemented if no underlying cause can be identified [883, 884].

6.5.3.1 Surgical intervention

If medical treatments fail, surgical operations such as TURP, transurethral resection of the ejaculatory duct and neurolysis of the pudendal nerve have been suggested [885, 886]. However, there is no strong evidence supporting that surgical therapy improves painful ejaculation and therefore it must be used with caution.

6.6 Retrograde ejaculation

6.6.1 Definition and classification

Retrograde ejaculation is the total, or sometimes partial, absence of antegrade ejaculation, as a result of semen passing backwards through the bladder neck into the bladder. Patients may experience a normal, or decreased, orgasmic sensation. The causes of retrograde ejaculation can be divided into neurogenic, pharmacological, urethral, or bladder neck incompetence [865].

6.6.2 Pathophysiology and risk factors

The process of ejaculation requires complex co-ordination and interplay between the epididymis, vas deferens, prostate, seminal vesicles, bladder neck and bulbourethral glands [887]. Upon ejaculation, sperm are rapidly conveyed along the vas deferens and into the urethra via the ejaculatory ducts. From there, the semen progresses in an antegrade fashion, in part maintained by coaptation of the bladder neck and rhythmic contractions of the periurethral muscles, co-ordinated by a centrally mediated reflex [887]. Closure of the bladder neck and seminal emission are initiated via the sympathetic nervous system from the lumbar sympathetic ganglia and subsequently hypogastric nerve. Prostatic and seminal vesicle secretion, as well as contraction of the bulbo-cavernosal, ischio-cavernosal and pelvic floor muscles are initiated by the S 2-4 parasympathetic nervous system via the pelvic nerve [887].

Any factor, that disrupts this reflex and inhibits contraction of the bladder neck (internal vesical sphincter) may lead to retrograde passage of semen into the bladder. These can be broadly categorised as pharmacological, neurogenic, anatomic and endocrinal causes of retrograde ejaculation (Table 21).

Table 21: Aetiology of retrograde ejaculation [847]

Neurogenic	Spinal cord injury Cauda equina lesions Multiple sclerosis Autonomic neuropathy Retroperitoneal lymphadenectomy Sympathectomy or aortoiliac surgery Prostate, colorectal and anal surgery Parkinson's disease Diabetes mellitus Psychological/behavioural
Urethral	Ectopic ureterocele Urethral stricture Urethral valves or verumontanum hyperplasia Congenital dopamine β -hydroxylase deficiency
Pharmacological	Antihypertensives, thiazide diuretics α -1-Adrenoceptor antagonists Antipsychotics and antidepressants

Endocrine	Hypothyroidism Hypogonadism Hyperprolactinaemia
Bladder neck incompetence	Congenital defects/dysfunction of hemitrigone Bladder neck resection (transurethral resection of the prostate) Prostatectomy

6.6.3 **Disease management**

Medical and surgical strategies exist for the treatment of retrograde ejaculation. In recent years the reliance on medical treatment as first-line management has become common practice.

6.6.3.1 *Pharmacological*

Sympathomimetics stimulate the release of noradrenaline as well as activating α - and β -adrenergic receptors, resulting in closure of the internal urethral sphincter, restoring the antegrade flow of semen. The most common sympathomimetics are synephrine, pseudoephedrine hydrochloride, ephedrine, phenylpropanolamine and midodrine [888]. Unfortunately, as time progresses their effect diminishes [889]. Many of the studies published about the efficacy of sympathomimetics in the treatment of retrograde ejaculation suffer from small sample size, with some represented by case reports.

A double-blind controlled study randomised patients to one of four α -adrenergic agents (dextroamphetamine, ephedrine, phenylpropanolamine and pseudoephedrine) with or without histamine. The patients suffered from failure of ejaculation following retroperitoneal lymphadenectomy. They found that 4 days of treatment prior to ejaculation was most effective and that all the adrenergic agonists restored antegrade ejaculation [888]. In a systematic review, the efficacy of this group of medications was found to be 28% [204]. The adverse effects of sympathomimetics include dryness of mucous membranes and hypertension.

The use of antimuscarinics has been described, including brompheniramine maleate and imipramine, as well as in combination with sympathomimetics. The calculated efficacy of antimuscarinics alone or in combination with sympathomimetics is 22% and 39%, respectively [204]. Combination therapy appears to be more effective although statistical analysis is not yet possible due to the small sample sizes.

6.6.3.2 *Management of infertility*

Infertility has been the major concern of patients with retrograde ejaculation. Beyond the use of standard sperm-retrieval techniques, such as testicular sperm extraction (TESE), three different methods of sperm acquisition have been identified for the management of infertility in patients with retrograde ejaculation. These include; i) centrifugation and resuspension of post-ejaculatory urine specimens; ii) the Hotchkiss (or modified Hotchkiss) technique; and, iii) ejaculation on a full bladder.

1. *Centrifugation and resuspension.* In order to improve the ambient conditions for the sperm, the patient is asked to increase their fluid intake or take sodium bicarbonate to dilute or alkalisate the urine, respectively. Afterwards, a post-orgasmic urine sample is collected by introducing a catheter or spontaneous voiding. This sample is then centrifuged and suspended in a medium. The types of suspension fluids are heterogeneous and can include bovine serum albumin, human serum albumin, Earle's/Hank's balanced salt solution and the patient's urine. The resultant modified sperm mixture can then be used in assisted reproductive techniques. A systematic review of studies in couples in which male partner had retrograde ejaculation found a 15% pregnancy rate per cycle (0-100%) [204].

2. *Hotchkiss method.* The Hotchkiss method involves emptying the bladder prior to ejaculation, using a catheter, and then washing out and instilling a small quantity of Lactated Ringers to improve the ambient condition of the bladder. The patient then ejaculates, and semen is retrieved by catheterisation or voiding [890]. Modified Hotchkiss methods involve variance in the instillation medium. Pregnancy rates were 24% per cycle (0-100%) [204].

3. *Ejaculation on a full bladder.* Few papers have described results using this technique [891, 892]. The patient is encouraged to ejaculate on a full bladder and semen is suspended in Baker's Buffer. The pregnancy rate in the two studies, which included only five patients in total, was 60% [204].

6.7 **Anorgasmia**

6.7.1 *Definition and classification*

Anorgasmia is the perceived absence of orgasm and can give rise to anejaculation. Regardless of the presence of ejaculation, anorgasmia can be a lifelong (primary) or acquired (secondary) disorder [201].

6.7.2 **Pathophysiology and risk factors**

Primary anorgasmia is defined as starting from a man's first sexual intercourse and lasts throughout his life, while for secondary anorgasmia patients should have a normal period before the problem starts [893]. Substance abuse, obesity and some non-specific psychological aspects, such as anxiety and fear, are considered risk factors for anorgasmia. Only a few studies have described anorgasmia alone and generally it has been considered as a symptom linked to ejaculatory disorders especially with DE, and therefore, they are believed to share the same risk factors. However, psychological factors are considered to be responsible for 90% of anorgasmia problems [894]. Causes of delayed orgasm and anorgasmia are shown in Table 22 [893].

Table 22: Causes of delayed orgasm and anorgasmia [893]

Endocrine	Testosterone deficiency Hypothyroidism
Medications	Antidepressants Antipsychotics Opioids
Psychosexual causes	
Hyperstimulation	
Penile sensation loss	

6.7.3 **Disease management**

The psychological/behavioural strategies for anorgasmia are similar to those for DE. The patient and his partner should be examined physically and psychosexually in detail, including determining the onset of anorgasmia, medication and disease history, penile sensitivity and psychological issues. Adjunctive laboratory tests can also be used to rule out organic causes, such as testosterone, prolactin and TSH levels. Patients who have loss of penile sensitivity require further investigations [893].

6.7.3.1 *Psychological/behavioural strategies*

Lifestyle changes can be recommended to affected individuals including: changing masturbation style; taking steps to improve intimacy, and decreasing alcohol consumption. Several psychotherapy techniques or their combinations have been offered, including alterations in arousal methods, reduction of sexual anxiety, role-playing an exaggerated orgasm and increased genital stimulation [855, 895]. However, it is difficult to determine the success rates from the literature.

6.7.3.2 *Pharmacotherapy*

Several drugs have been reported to reverse anorgasmia, including cyproheptadine, yohimbine, buspirone, amantadine and oxytocin [896-901]. However, these reports are generally from case-cohort studies and drugs have limited efficacy and significant adverse effect profiles. Therefore, current evidence is not strong enough to recommend drugs to treat anorgasmia.

6.7.3.3 *Management of infertility*

If patients fail the treatment methods mentioned above, penile vibratory stimulation, electro-ejaculation or TESE are the choice of options for sperm retrieval in anorgasmia cases [893].

6.8 Haemospermia

6.8.1 **Definition and classification**

Haemospermia is defined as the appearance of blood in the ejaculate. Although it is often regarded as a symptom of minor significance, blood in the ejaculate causes anxiety in many men and may be indicative of underlying pathology [224].

6.8.2 **Pathophysiology and risk factors**

Several causes of haemospermia have been acknowledged and can be classified into the following sub-categories; idiopathic, congenital malformations, inflammatory conditions, obstruction, malignancies, vascular abnormalities, iatrogenic/trauma and systemic causes (Table 23) [902].

Table 23: Pathology associated with haemospermia [902]

Category	Causes
Congenital	Seminal vesicle (SV) or ejaculatory duct cysts
Inflammatory	Urethritis, prostatitis, epididymitis, tuberculosis, CMV, HIV, Schistosomiasis, hydatid, condyloma of urethra and meatus, urinary tract infections
Obstruction	Prostatic, SV and ejaculatory duct calculi, post-inflammatory, seminal vesicle diverticula/cyst, urethral stricture, utricule cyst, BPH
Tumours	Prostate, bladder, SV, urethra, testis, epididymis, melanoma
Vascular	Prostatic varices, prostatic telangiectasia, haemangioma, posterior urethral veins, excessive sex or masturbation
Trauma/iatrogenic	Perineum, testis, instrumentation, post-haemorrhoid injection, prostate biopsy, vaso-venous fistula
Systemic	Hypertension, haemophilia, purpura, scurvy, bleeding disorders, chronic liver disease, renovascular disease, leukaemia, lymphoma, cirrhosis, amyloidosis
Idiopathic	-

The risk of any malignancy in patients presenting with haemospermia is approximately 3.5% (0-13.1%) [903]. In an observational study of 300 consecutive patients over a 30-month period, 81% had no identified cause of haemospermia. In those patients for whom a cause was identified, the diagnosis varied dependent upon the age of presentation. When the patients were divided into those under and those over 40 years of age, UTIs were more common among younger compared to older patients (15% vs. 10.3%). In the older group (> 40 years), stones (2.2% vs. 1.4%) and malignancy (6.2% vs. 1.4%) were more common when compared with the younger cohort. In the > 40 years group, 13 patients had PCa and one had low-grade urethral carcinoma. In the < 40 years group, one patient had testicular cancer [223]. In a recent study in which 342 patients with haemospermia were included, the most relevant aetiology for haemospermia was inflammation/infection (49.4%) while genitourinary cancers (i.e., prostate and testis) only accounted for 3.2% of the cases [904].

6.8.3 Investigations

As with other clinical conditions, a systematic clinical history and assessment to help identify the cause of haemospermia is undertaken. Although the differential diagnosis is extensive, most cases are caused by infections or other inflammatory processes [224].

The basic examination of haemospermia should start with a thorough symptom-specific and systemic clinical history. The first step is to understand if the patient has true haemospermia. Pseudo-haemospermia may occur as a consequence of haematuria or even suction of a partner's blood into the urethra during copulation [865, 905, 906]. A sexual history should be taken to identify those whose haemospermia may be a consequence of a sexually transmitted disease. Recent foreign travel to areas affected by schistosomiasis or tuberculosis should also be considered. The possibility of co-existing systemic disease such as hypertension, liver disease and coagulopathy should be investigated along with systemic features of malignancy such as weight loss, loss of appetite or bone pain. Examination of the patient should also include measurement of blood pressure, as there have been several case reports suggesting an association between uncontrolled hypertension and haemospermia [907, 908].

Most authors who propose an investigative baseline agree on the initial diagnostic tests, but there is no consensus in this regard [902, 903, 905]. Urinalysis should be performed along with sending the urine for culture and sensitivity testing, as well as microscopy. If tuberculosis or schistosomiasis is the suspected cause, the semen or prostatic secretions should be sent for analysis. A full sexually-transmitted disease screen including first-void urine as well as serum and genitourinary samples should be tested for *Chlamydia*, *Ureaplasma* and *Herpes Simplex* virus. Using this strategy, it may be possible to find an infectious agent among cases that would have been labelled as idiopathic haemospermia [909].

Serum PSA should be taken in men aged > 40 years who have been appropriately counselled [225]. Blood work including a full blood count, liver function tests, and a clotting screen should be taken to identify systemic diseases. The question of whether further investigation is warranted depends on clinician judgment, patient age and an assessment of risk factors [902]. Digital rectal examination (DRE) should also be performed and

the meatus re-examined after DRE for bloody discharge [910]. Detection of a palpable nodule in the prostate is important because an association between haemospermia and PCa has been postulated although not completely proven.

Magnetic resonance imaging is being increasingly used as a definitive means to investigate haemospermia. The multiplanar ability of MRI to accurately represent structural changes in the prostate, seminal vesicles, ampulla of vas deferens, and ejaculatory ducts has enabled the technique to be particularly useful in determining the origin of midline or paramedian prostatic cysts and in determining optimal surgical management [911]. The addition of an endorectal coil can improve the diagnostic accuracy for identifying the site and possible causes of haemorrhage [912].

Cystoscopy has been included in most suggested investigative protocols in patients with high-risk features (patients who are refractory to conservative treatment and who have persistent haemospermia). It can provide invaluable information as it allows direct visualisation of the main structures in the urinary tract that can be attributed to causes of haemospermia, such as: polyps, urethritis, prostatic cysts, foreign bodies, calcifications and vascular abnormalities [913, 914].

With the advancement of optics, the ability to create ureteroscopes of diameters small enough to allow insertion into the ejaculatory duct and seminal vesicles has been made possible [915]. In a prospective study, 106 patients with prolonged haemospermia underwent transrectal US and seminal vesiculoscopy. With both methods combined, diagnosis was made in 87.7% of patients. When compared head-to-head, the diagnostic yield for TRUS vs. seminal vesiculoscopy was 45.3% and 74.5%, respectively ($P < 0.001$) [916].

Melanospermia is a consequence of malignant melanoma involving the genitourinary tract and is a rare condition that has been described in two case reports [917, 918]. Chromatography of the semen sample can be used to distinguish the two by identifying the presence of melanin if needed.

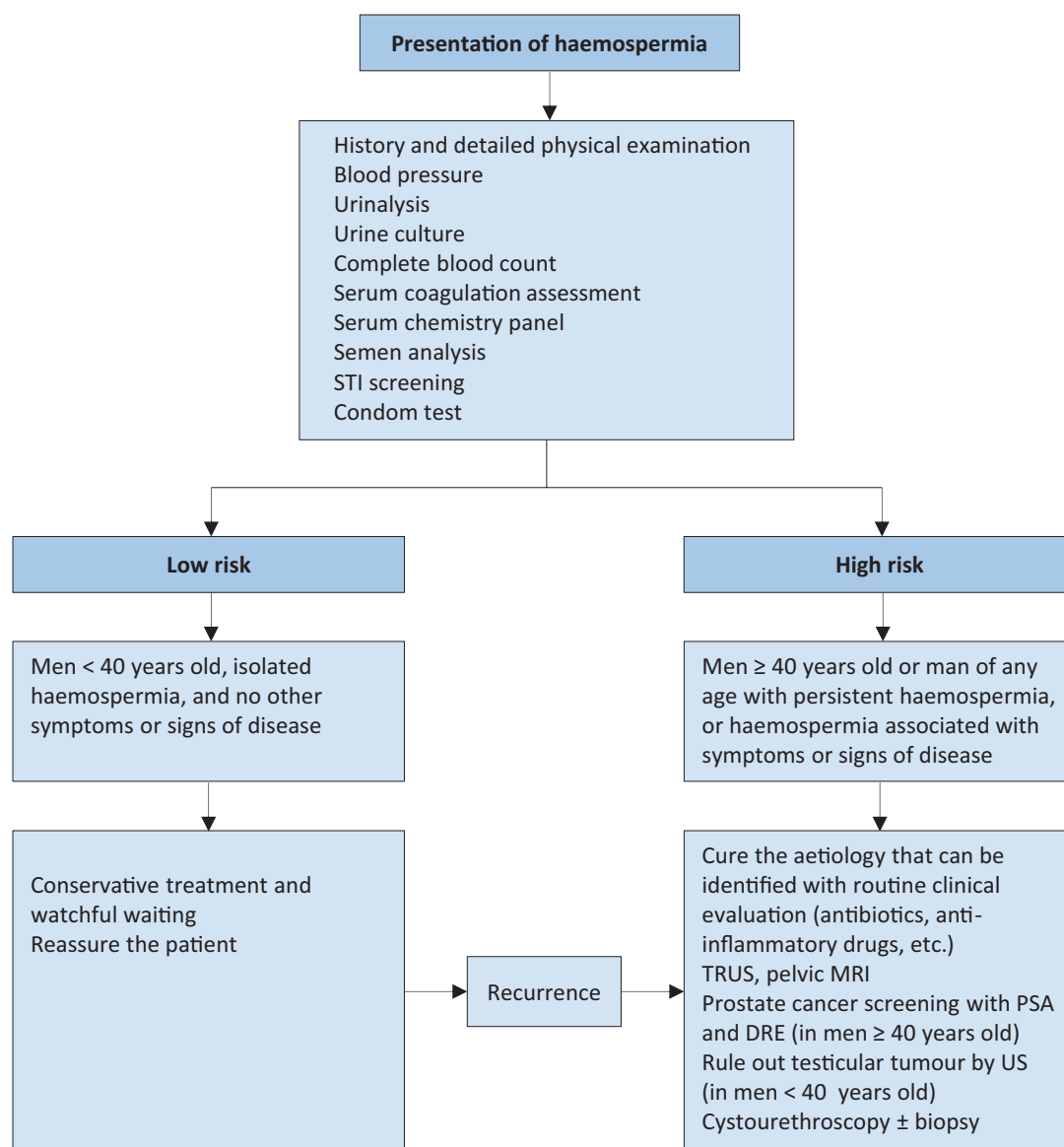
6.8.4 **Disease management**

Conservative management is generally the primary treatment option when the patients are aged < 40 years and have a single episode of haemospermia. The primary goal of treatment is to exclude malignant conditions like prostate and bladder cancer and treat any other underlying cause. If no pathology is found, then the patient can be reassured [224, 902].

Patients with recurrent haemospermia and who are middle-aged, warrant more aggressive intervention. Appropriate antibiotic therapy should be given to patients who have urogenital infections or STIs. Urethral or prostatic varices or angiodysplastic vessels can be fulgurated, whereas cysts, either of the seminal vesicles or prostatic urethra, can be aspirated transrectally [224]. Ejaculatory duct obstruction is managed by transurethral incision at the duct opening [919, 920]. Systemic conditions should be treated appropriately [903, 906, 921, 922].

Defining a management algorithm for haemospermia is based on the patient age and degree of haemospermia. Patients often find blood in the ejaculate alarming, and investigations should be aimed at excluding a serious, despite infrequent, underlying cause (e.g., cancer), while at the same time preventing over-investigation and alleviating patient anxiety. The literature describes a multitude of causes for haemospermia, although many of these are not commonly found after investigation. However, men may be stratified into higher-risk groups according to several factors including: age > 40 years, recurrent or persistent haemospermia, actual risk for PCa (e.g., positive family history), and concurrent haematuria. Based upon the literature, a management algorithm is proposed (Figure 9) [903, 906, 921, 922].

Figure 9: Management algorithm for haemospermia [903, 906, 921, 922]



STI = Sexually transmitted infections; PSA = Prostate specific antigen; DRE = Digital rectal examination; US = Ultrasonography; TRUS = Transrectal ultrasonography; MRI = Magnetic resonance imaging.

6.9 Recommendations for the management of recurrent haemospermia

Recommendations	Strength rating
Perform a full medical and sexual history with detailed physical examination.	Strong
Men aged ≥ 40 years with persistent haemospermia should be screened for prostate cancer.	Weak
Consider non-invasive imaging modalities (TRUS and MRI) in men aged ≥ 40 years or men of any age with persistent or refractory haemospermia.	Weak
Consider invasive methods such as cystoscopy and vesiculoscopy when the non-invasive methods are inconclusive.	Weak

7. LOW SEXUAL DESIRE AND MALE HYPOACTIVE SEXUAL DESIRE DISORDER

7.1 Definition, classification and epidemiology

It has always been a challenge to define sexual desire properly because it has a complicated nature and it can be conceptualised in many different ways. According to the International Classification of Diseases 10th edition (ICD-10), lack or loss of sexual desire should be the principal problem and no other sexual problems accompanying it such as ED [923]. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), male hypoactive sexual desire disorder (HSDD) is defined as “the persistent or recurrent deficiency (or absence) of sexual or erotic thoughts or fantasies and desire for sexual activity”. The judgment of deficiency is made by the clinician, taking into account factors that affect sexual functioning, such as age and general and socio-cultural contexts of the individual’s life [200]. According to the fourth International Consultation on Sexual Medicine (ICSM), the definition of male HSDD was proposed as a “persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity (clinical principle)” [924]. Although the exact prevalence of low sexual desire (LSD) is unknown, a prevalence of 4.7% was reported in a survey of a population-based sample of middle-aged German men (n = 12,646) [925].

7.2 Pathophysiology and risk factors

Several aetiological factors are considered to contribute to the pathophysiology of LSD. Levine proposed three components of sexual desire as drive (biological), motivation (psychological) and wish (cultural) [926]. However, it is believed that both in the surveys and clinical practice those three components are usually found interwoven [927].

7.2.1 Psychological aspects

The endorsement of negative thoughts during sexual intercourse (i.e., concerns about erection, lack of erotic thoughts, and restrictive attitudes toward sexuality) predicts LSD in men [928]. Furthermore, feeling shame during sexual intercourse, because of negative sexual thoughts (e.g., concern about achieving erection), characterises men with LSD as opposed to women with the same condition [929]. Psychological models testing the interplay role between biopsychosocial factors reveal that reduced male sexual desire is best predicted by negative thoughts and emotions during sex, more than general psychopathological symptoms or age [930-932]. Similarly, low confidence achieving erection, no attraction towards their partner, living in long-term relationships, and stress resulting from work are predictors of LSD in men [933]. In contrast, relationship factors such as marital satisfaction, cohesion or display of affection receive little support [928, 933]. Even so, it is worth noting that, despite LSD being less common in men than in women [924], it is the most frequent complaint in couples’ therapy [934]. Therefore, the role of relationship factors cannot be completely ruled out. In addition, anxiety proneness has been associated with LSD in men and is expected to shift men’s attention from erotic cues to worrying thoughts, thereby decreasing sexual desire [935].

7.2.2 Biological aspects

Testosterone seems to be essential for a man’s sexual desire; however, sexual desire does not directly relate to the circulating level of testosterone, especially in older men [936]. The biological and psychological components that take place in the pathophysiology of LSD are shown in Table 24 [927, 937]. In addition to these factors, there is some speculation about the role of thyroid and oxytocin hormones [671, 938].

Table 24: Common causes of low sexual desire in men [927, 937]

Androgen deficiency
Hyperprolactinaemia
Anger and anxiety
Depression
Relationship conflict
Stroke
Antidepressant therapy
Epilepsy
Post-traumatic stress syndrome
Renal failure

Coronary disease and heart failure
Ageing
HIV infection
Body-building and eating disorders
Erectile dysfunction
Prostatitis/chronic pelvic pain syndrome

7.2.3 **Risk factors**

In an international survey aimed at estimating the prevalence and correlates of sexual problems in 13,882 women and 13,618 men from 29 countries (Global Study of Sexual Attitudes and Behaviours), risk factors for male LSD were age 60-69 and 70-80 years, poor overall health, vascular diseases, being a current smoker, belief that ageing reduces sex, divorce in the past 3 years, financial problems in the last 3 years, major depression, being worried about the future of a relationship and less than one sexual relation in a week [193]. In a recent study that determined the factors associated with LSD in a large sample of middle-aged German men, PE, ED, and lower urinary tract symptoms were associated with LSD [925]. In contrast, men having more than two children, higher frequency of solo-masturbation, perceived importance of sexuality, and higher sexual self-esteem were less likely to have LSD [925].

7.3 **Diagnostic work-up**

7.3.1 **Assessment questionnaires**

Sexual Desire Inventory (SDI) evaluates different components influencing the development and expression of sexual desire [939]. This self-administered questionnaire consists of 14 questions that weigh the strength, frequency, and significance of an individual's desire for sexual activity with others and by themselves. The SDI suggests that desire can be split into two categories: dyadic and solitary desire. While dyadic desire refers to "interest in or a wish to engage in sexual activity with another person and desire for sharing and intimacy with another", solitary desire refers to "an interest in engaging in sexual behaviour by oneself, and may involve a wish to refrain from intimacy and sharing with others" [939].

7.3.2 **Physical examination and investigations**

Similar to other forms of sexual dysfunctions, a thorough medical and sexual history must be obtained from men who complain of LSD. The depressive symptoms of the patients must be assessed [940] and relationship problems (e.g., conflict with the sexual partner) must be questioned. In the presence of accompanying symptoms suggestive of endocrinological problems, circulating total testosterone [941], prolactin [942] and thyroid hormones [671] levels can be evaluated.

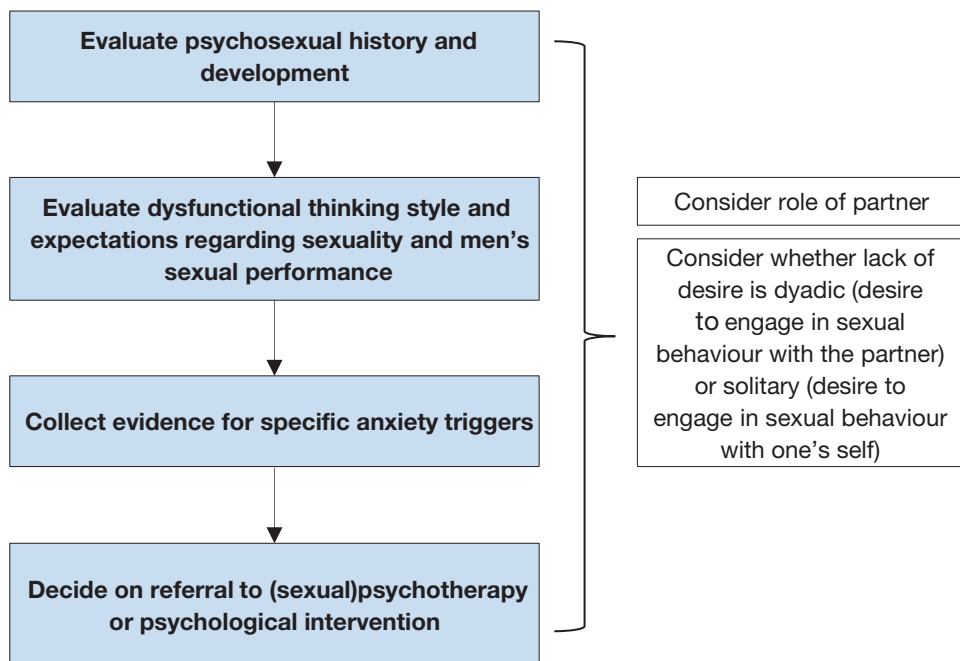
7.4 **Disease management**

Treatment of LSD should be tailored according to the underlying aetiology.

7.4.1 **Psychological intervention**

Data on efficacy of psychological interventions for LSD are scarce. Accordingly, recommendations must be interpreted with caution. Psychological interventions with a focus on cognitive and behavioural strategies may be beneficial for LSD in men [430, 943] (Figure 10). Since both members of a couple may experience age-related changes concurrently and interdependently, it could be helpful to address the sexual health needs of the ageing couple (including LSD) as a whole rather than treating the individual patient [944].

Figure 10: Flow-diagram of psychological evaluation of patients with low sexual desire



7.4.2 Pharmacotherapy

Low sexual desire secondary to low testosterone levels can be treated with different formulations of testosterone. The favourable effect of testosterone therapy on sexual motivation and the presence of sexual thoughts was shown in a meta-analysis [941]. The aim of treatment should be to reach the physiological range of testosterone (see Section 3.5).

Hyperprolactinaemia can also cause LSD and one of the most relevant aetiological factors is prolactin-secreting pituitary adenomas. These adenomas can be easily diagnosed with MRI of the pituitary gland and can be treated with dopamine agonist agents [945]. The other accompanying endocrine disorders, such as hypothyroidism, hyperthyroidism and diabetes, should be treated accordingly.

Pharmacotherapy can also be used to treat major depression; however, it should be remembered that antidepressants may negatively affect sexual functioning; therefore, antidepressant compounds with less effect on sexual function should be chosen. Psychotherapy can increase the efficacy of pharmacotherapy, especially for patients whose LSD is due to depression [946].

7.5 Recommendations for the treatment of low sexual desire

Recommendations	Strength rating
Perform the diagnosis and classification of low sexual desire (LSD) based on medical and sexual history, which could include validated questionnaires.	Weak
Include physical examination in the initial assessment of LSD to identify anatomical abnormalities that may be associated with LSD or other sexual dysfunctions, particularly erectile dysfunction.	Weak
Perform laboratory tests to rule out endocrine disorders.	Strong
Modulate chronic therapies which can negatively impact toward sexual desire.	Weak
Provide testosterone therapy if LSD is associated with signs and symptoms of testosterone deficiency.	Strong

8. PENILE CURVATURE

8.1 Congenital penile curvature

8.1.1 *Epidemiology/aetiology/pathophysiology*

Congenital penile curvature (CPC) is a rare condition, with a reported incidence of < 1% [947], although some studies have reported higher prevalence rates of 4-10%, in the absence of hypospadias [948]. Congenital penile curvature results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In most cases, the curvature is ventral, but it can also be lateral and, more rarely, dorsal [949].

8.1.2 *Diagnostic evaluation*

Taking a medical and sexual history is usually sufficient to establish a diagnosis of CPC. Patients usually present after reaching puberty as the curvature becomes more apparent with erections, and more severe curvatures can make intercourse difficult or impossible. Physical examination during erection (alternatively photographic or preferably after intracavernous injection [ICI] of vasoactive drugs) is important to document the curvature and exclude other pathologies [949].

8.1.3 *Disease management*

The definitive treatment for this disorder remains surgical and can be deferred until after puberty, although a survey has suggested that men with probable untreated ventral penile curvature report more dissatisfaction with penile appearance, increased difficulty with intercourse, and psychological problems; therefore, supporting surgical correction of CPC in childhood [950]. Surgical treatments for CPC generally share the same principles as in Peyronie's disease. Plication techniques (Nesbit, 16-dot, Yachia, Essed-Schröder, and others) with or without neurovascular bundle elevation (medial/lateral) and with or without complete penile degloving, have been described [951-960]. Other approaches are based on corporal body de-rotation proposed by Shaeer with different technical refinements that enable correction of a ventral curvature, with reported minimal narrowing and shortening [961-964]. There are no direct comparative studies therefore no single technique can be advocated as superior in terms of surgical correction.

8.1.4 *Summary of evidence for congenital penile curvature*

Summary of evidence	LE
Medical and sexual history are usually sufficient to establish a diagnosis of CPC. Physical examination after intracavernosal injection or a photograph during erection is mandatory for documentation of the curvature and exclusion of other pathologies.	3
There is no role for medical management of CPC. Surgery is the only treatment option, which can be deferred until after puberty and can be performed at any time in adult life in individuals with significant functional impairment during intercourse.	3

8.1.5 *Recommendation for the treatment congenital penile curvature*

Recommendation	Strength rating
Use plication techniques with or without neurovascular bundle dissection (medial/lateral) for satisfactory curvature correction, although there is currently no optimum surgical technique.	Strong

8.2 Peyronie's Disease

8.2.1 *Epidemiology/aetiology/pathophysiology*

8.2.1.1 *Epidemiology*

Epidemiological data on Peyronie's disease (PD) are limited. Prevalence rates of 0.4-20.3% have been published, with a higher prevalence in patients with ED and diabetes [965-975]. A recent survey has indicated that the prevalence of definitive and probable cases of PD in the USA is 0.7% and 11%, respectively, suggesting that PD is an under-diagnosed condition [976]. Peyronie's disease often occurs in older men with a typical age of onset of 50-60 years. However, PD also occurs in younger men (< 40 years), but at a lesser prevalence than in older men (1.5-16.9%) [969, 977, 978].

8.2.1.2 *Aetiology*

The aetiology of PD is unknown. However, repetitive microvascular injury or trauma to the tunica albuginea

is still the most widely accepted hypothesis to explain the aetiology [979]. Abnormal wound healing leads to the remodelling of connective tissue into a fibrotic plaque [979-981]. Penile plaque formation can result in a curvature, which, if severe, may impair penetrative sexual intercourse. The genetic underpinnings of fibrotic diatheses, including PD and Dupuytren's disease, are beginning to be understood, although much of the data are contradictory and we do not yet have the basis for predicting who will develop the disease or disease severity (Table 25) [982, 983].

Table 25: Genes with involvement in Peyronie's and Dupuytren's diseases (adapted from Herati *et al.* [982])

Gene	Gene Symbol	Chromosomal Location	Gene Function
Matrix metalloproteinase 2	MMP 2	16q12.2	Breakdown of extracellular matrix
Matrix metalloproteinase 9	MMP 9	20q13.12	Breakdown of extracellular matrix
Thymosin beta-10	TMSB-10	2p11.2	Prevents spontaneous globular actin monomer polymerisation
Thymosin beta-4	TMSB-4	Xq21.3-q22	Actin sequestering protein
Cortactin; amplexin	CTTN	11q13	Organises cytoskeleton and cell adhesion structures
Transforming protein RhoA H12	RHOA	3p21.3	Regulates cytoskeletal dynamics
RhoGDP dissociation inhibitor	ARHGDI1	17q25.3	Regulates Rho GTPase signaling
Pleiotrophin precursors; osteoblast specific factor 1	PTN/OSF-1	7q33	Stimulates mitogenic growth of fibroblasts and osteoblasts
Amyloid A4 protein precursor; nexin II	PN-II	21q21.3	Cell surface receptor
Defender against cell death 1	DAD1	14q11.2	Prevents apoptosis
Heat Shock 27-kDa protein (HSP27)	HSP27	7q11.23	Actin organisation and translocation from cytoplasm to nucleus upon
Macrophage-specific stimulating factor	MCSF/CSF1	1p13.3	Controls the production, differentiation and function of macrophages
Transcription factor AP-1	AP1	1p32-p31	Key mediator of macrophage education and point of recruitment for immunosuppressive regulatory T cells
Human Early growth response protein 1	hEGR1	5q31.1	Promotes mitosis
Monocyte chemotactic protein 1	MCP1	17q11.2-q12	Chemotactic cytokine for monocytes and basophils
Bone Proteoglycan II precursor; Decorin	DCN	12q21.33	Matrix proteoglycan
T-Cell specific rantes protein precursor	RANTES	17q12	Chemoattractant for monocytes, memory T cells and eosinophils
Integrin Beta-1	ITGB1	10p11.2	Membrane receptor involved in cell adhesion and recognition in a variety of processes including immune response, tissue repair and haemostasis
Osteonectin	SPARC	5q31.3-q32	Matrix protein that facilitates collagen ossification
Ubiquitin	RBX1	6q25.2-q27	Targets substrate proteins for proteasomal degradation
Transcription factor ATF-4	ATF4	22q13.1	Transcriptional regulation of osteoblasts and down-regulates apelin to promote apoptosis
Elastase IIB	ELA2B	1p36.21	Serine protease that hydrolyses matrix protein

c-myc	MYC	8q24.21	Transcription factor that regulates cell cycle progression, apoptosis, and cellular transformations
60 S ribosomal protein L13A	RPL13A	19q13.3	Repression of inflammatory genes
Prothymosin alpha	PTMA	2q37.1	Influences chromatin remodeling, anti-apoptotic factor
Fibroblast tropomyosin	TPM1	15q22.1	Actin-binding protein involved in contractile system of striated and smooth muscle
Myosin light chain	MYL2	12q24.11	Regulatory light chain associated with myosin Beta heavy chain
Filamin	FLN	Xq28	Actin-binding protein that crosslinks actin filaments and links actin to membrane glycoproteins. Interacts with integrins
Calcineurin A subunit alpha	PPP3CA	4q24	Promotes cell migration and invasion and inhibits apoptosis
DNA binding protein inhibitor Id-2	ID2	2p25	Transcriptional regulator that inhibits the function of basic helix-loop-helix transcription factors by preventing their heterodimerisation, negatively regulates cell differentiation
Smooth muscle gamma actin	ACTA2	10q23.3	Plays a role in cell motility, structure and integrity
Desmin	DES	2q35	Forms intra-cytoplasmic filamentous network connecting myofibrils
Cadherin FIB2	PCDHGB4	5q31	Cell adhesion proteins expressed in fibroblasts and playing a role in wound healing
Cadherin FIB1	DCHS1	11p15.4	Cell adhesion proteins expressed in fibroblasts and playing a role in wound healing
SMAD family member 7	SMAD7	18q21.1	Interacts with and promotes degradation of TGFBR1
Insulin-like growth factor binding protein 6	IGFBP6	12q13	Negative regulator of cellular senescence in human fibroblasts
Collagen 1 alpha	COL1A1	17q21.33	Encodes pro-alpha 1 chains of type 1 collagen
Transforming growth factor, beta 1	TGFB1	19q13.1	Cytokine that regulates proliferation, differentiation, adhesion and cell migration

8.2.1.3 Risk factors

The most commonly reported associated co-morbidity and risk factors are diabetes, hypertension, dyslipidaemias, ischaemic cardiopathy, autoimmune diseases [984], ED, smoking, excessive alcohol consumption, low testosterone levels and pelvic surgery (e.g., radical prostatectomy) [363, 969, 973, 985-987]. Dupuytren's contracture is more common in patients with PD affecting 8.3-39% of patients [970, 988-990], while 4-26% of patients with Dupuytren's contracture report PD [989, 991, 992].

8.2.1.4 Pathophysiology

Two phases of the disease can be distinguished [993]. The first is the active inflammatory phase (acute phase), which may be associated with painful erections and a palpable nodule or plaque in the tunica of the penis; typically, but not invariably, a penile curvature begins to develop. The second is the fibrotic phase (chronic phase) with the formation of hard, palpable plaques that can calcify, with stabilisation of the disease and of the penile deformity. With time, the penile curvature is expected to worsen in 21-48% of patients or stabilise in 36-67% of patients, while spontaneous improvement has been reported in only 3-13% of patients [985, 994-996]. Overall, penile deformity is the most common first symptom of PD (52-94%). Pain is the second most common presenting symptom of PD, which presents in 20-70% of patients during the early stages of the disease [997]. Pain tends to resolve with time in 90% of men, usually during the first 12 months after the onset

of the disease [994, 995]. Palpable plaques have been reported as an initial symptom in 39% of the patients and mostly situated dorsally [50, 997].

In addition to functional effects on sexual intercourse, men may also suffer from significant psychological distress. Validated mental health questionnaires have shown that 48% of men with PD have moderate or severe depression, sufficient to warrant medical evaluation [998].

8.2.1.5 Summary of evidence on epidemiology/aetiology/pathophysiology of Peyronie's disease

Summary of evidence	LE
Peyronie's disease (PD) is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which may lead to penile deformity.	2b
The contribution of associated co-morbidity or risk factors (e.g., diabetes, hypertension, lipid abnormalities and Dupuytren's contracture) to the pathophysiology of PD is still unclear.	3
Two phases of the disease can be distinguished. The first phase is the active inflammatory phase (acute phase - painful erections, nodule/plaque), and the second phase is the fibrotic/calcifying phase (chronic or stable phase) with formation of hard palpable plaques (disease stabilisation).	2b
Spontaneous resolution is uncommon (3-13%) and most patients experience disease progression (21-48%) or stabilisation (36-67%). Pain is usually present during the early stages of the disease, but tends to resolve with time in 90% of men within 12 months of onset.	2a

8.2.2 Diagnostic evaluation

The aim of the initial evaluation is to obtain information on the presenting symptoms and their duration (e.g., pain on erection, palpable nodules, deformity, length and girth and erectile function). It is important to obtain information on the distress caused by the symptoms and the potential risk factors for ED and PD. A disease-specific questionnaire (Peyronie's disease questionnaire [PDQ]) has been developed for use in clinical practice and trials. Peyronie's disease questionnaire measures three domains, including psychological and physical symptoms, penile pain and symptom bother [999].

Clinicians should take a focused history to distinguish between active and stable disease, as this will influence medical treatment or the timing of surgery. Patients who are still likely to have active disease are those with a shorter symptom duration, pain on erection, or a recent change in penile deformity. Resolution of pain and stability of the curvature for at least 3 months are well-accepted criteria of disease stabilisation and patients' referral for specific medical therapy [1000, 1001] or surgical intervention when indicated [1002].

The examination should start with a focused genital assessment that is extended to the hands and feet for detecting possible Dupuytren's contracture or Ledderhosen scarring of the plantar fascia [995]. Penile examination is performed to assess the presence of a palpable nodule or plaque. There is no correlation between plaque size and degree of curvature [1003]. Measurement of the stretched or erect penile length is important because it may have an impact on the subsequent treatment decisions and potential medico-legal implications [1004-1006].

An objective assessment of penile curvature with an erection is mandatory. According to current literature, this can be obtained by several approaches, including home (self) photography of a natural erection (preferably), using a vacuum-assisted erection test or an ICI using vasoactive agents. However, it has been suggested that the ICI method is superior, as it is able to induce an erection similar to or better than that which the patient would experience when sexually aroused [1007-1009]. Computed tomography and MRI have a limited role in the diagnosis of the curvature and are not recommended on a routine basis. Erectile function can be assessed using validated instruments such as the IIEF although this has not been validated in PD patients [1010]. Erectile dysfunction is common in patients with PD (30-70.6%) [1011, 1012]. It is mainly an arterial or cavernosal (veno-occlusive) dysfunction in origin [985, 1003, 1013]. The presence of ED and psychological factors may also have a profound impact on the treatment strategy [1012].

Ultrasound measurement of plaque size is inaccurate but it could be helpful to assess the presence of the plaque and its calcification and location [1014, 1015]. Doppler US may be used for the assessment of penile haemodynamics and ED aetiology [1012].

8.2.2.1 Summary of evidence for diagnosis of Peyronie's disease

Summary of evidence	LE
Ultrasound (US) measurement of plaque size is inaccurate and operator dependent.	3
Doppler US may be required to assess penile haemodynamic and vascular anatomy.	2a
Intracavernous injection method is superior to other methods to provide an objective assessment of penile curvature with an erection.	4

8.2.2.2 Recommendations for diagnosis of Peyronie's disease

Recommendations	Strength rating
Take a medical and sexual history of patients with Peyronie's disease (PD), include duration of the disease, pain on erection, penile deformity, difficulty in vaginal/anal intromission due to disabling deformity and erectile dysfunction (ED).	Strong
Take a physical examination, including assessment of palpable plaques, stretched or erect penile length, degree of curvature (self-photography, vacuum-assisted erection test or pharmacological-induced erection) and any other related diseases (e.g., Dupuytren's contracture, Ledderhose disease) in patients with PD.	Strong
Use the intracavernous injection (IC) method in the diagnostic work-up of PD to provide an objective assessment of penile curvature with an erection.	Weak
Use the PD specific questionnaire especially in clinical trials, but mainstream usage in daily clinical practice is not mandatory.	Weak
Do not use ultrasound (US), computed tomography or magnetic resonance imaging to assess plaque size and deformity in everyday clinical practice.	Weak
Use penile Doppler US in the case of diagnostic evaluation of ED, to evaluate penile haemodynamic and vascular anatomy, and to assess location and calcification of plaques, especially prior to surgery.	Weak

8.2.3 Disease management

8.2.3.1 Conservative treatment

Conservative treatment of PD is primarily focused on patients in the early stage of the disease as an adjunct treatment to relieve pain and prevent disease progression or if the patient declines other treatment options during the active phase [995, 1002]. Several options have been suggested, including oral pharmacotherapy, intralesional injection therapy, shockwave therapy (SWT) and other topical treatments (Table 26).

The results of the studies on conservative treatment for PD are often contradictory, making it difficult to provide recommendations in everyday, real-life settings [1016]. The Panel does not support the use of oral treatments for PD including pentoxifylline, vitamin E, tamoxifen, procarbazine, potassium para-aminobenzoate (potaba), omega-3 fatty acids or combination of vitamin E and L-carnitine because of their lack of efficacy (tamoxifen, colchicine, vitamin E and procarbazine) or evidence (potaba, L-carnitine and pentoxifylline) [1002, 1017-1019]. This statement is based on several methodological flaws in the available studies. These include their uncontrolled nature, the limited number of patients treated, the short-term follow-up and the different outcome measures used [1020, 1021]. Even in the absence of adverse events, treatment with these agents may delay the use of other efficacious treatments.

Table 26: Conservative treatments for PD

Oral treatments
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Phosphodiesterase type 5 inhibitors (PDE5Is)
Intralesional treatments
Verapamil
Nicardipine
Clostridium collagenase
Interferon α 2B
Hyaluronic acid
Botulinum toxin
Topical treatments
H-100 gel
Extracorporeal shockwave treatment
Other
Traction devices
Multimodal treatment

8.2.3.1.1 Oral treatment

Phosphodiesterase type 5 inhibitors

Phosphodiesterase type 5 inhibitors were first suggested as a treatment for PD in 2003 to reduce collagen deposition and increase apoptosis through the inhibition of transforming growth factor (TGF)- β 1 [1022-1024]. A retrospective study of 65 men suggested the use of PDE5Is as an alternative for the treatment of PD. The results indicated that treatment with tadalafil was helpful in decreasing curvature and remodelling septal scars when compared to controls [1025]. Another recent study concluded that sildenafil was able to improve erectile function and pain in PD patients. Thirty-nine patients with PD were divided into two groups receiving vitamin E (400 IU) or sildenafil 50 mg for 12 weeks and significantly better outcomes in pain and IIEF score were seen in the sildenafil group [1026].

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) may be offered to patients in active-phase PD in order to manage penile pain, which is usually present in this phase. Pain levels should be periodically reassessed in monitoring treatment efficacy.

8.2.3.1.2 Intralesional treatment

Injection of pharmacologically active agents directly into penile plaques represents another treatment option. It allows a localised delivery of a particular agent that provides higher concentrations of the drug inside the plaque. However, delivery of the compound to the target area is difficult to ensure, particularly when a dense or calcified plaque is present.

Calcium channel antagonists: verapamil and nicardipine

The rationale for intralesional use of channel antagonists in patients with PD is based on *in vitro* research [1027, 1028]. Due to the use of different dosing schedules and the contradictory results obtained in published studies, the evidence is not strong enough to support the clinical use of injected channel blockers verapamil and nicardipine and the results do not demonstrate a meaningful improvement in penile curvature compared to placebo [1029-1034]. In fact, most of the studies did not perform direct statistical comparison between groups.

Collagenase of *Clostridium histolyticum*

Collagenase of *Clostridium histolyticum* (CCH) is a chromatographically purified bacterial enzyme that selectively attacks collagen, which is known to be the primary component of the PD plaque [1035-1038]. Intralesional injection of CCH has been used in the treatment of PD since 1985. In 2014 the EMA approved CCH for the nonsurgical treatment of the stable phase of PD in men with palpable dorsal plaques in whom abnormal curvature of 30-90° and non-ventrally located plaques are present. It should be administered by a healthcare professional who is experienced and properly trained in the administration of CCH treatment for PD [1039, 1040].

The original treatment protocol in all studies consists of two injections of 0.58 mg of CCH 24-72 hours apart every 6 weeks for up to four cycles. Data from IMPRESS (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) I and II studies [976], as well as post approval trials [1041], which demonstrated the efficacy and safety of this treatment, are summarised in Table 27.

Table 27: Clinical evidence supporting CCH treatment

Author/Year	Study type	Special considerations	Number of patients	Number of injections	Decrease in PC in CCH group
Gelbard <i>et al.</i> (2013) [1042]	Phase 3 randomised double-blinded controlled trial	Pilot study	551	8 (in 78.8% of patients)	34% (17.0 ± 14.8 degrees)
Levine <i>et al.</i> (2015) [1043]	Phase 3 open-label	IMPRESS based	347	≤ 8	34.4% (18.3 ± 14.02 degrees)
Ziegelmann <i>et al.</i> (2016) [1044]	Prospective, double-blinded trial	IMPRESS based	69	Mean = 6	38% (22.6 ± 16.2 degrees)
Yang and Bennett (2016) [1045]	Prospective study	Included patients in acute phase	37 in SP 12 in AP	Median in SP = 6 Median in AP = 2.5	32.4% (15.4 degrees) AP = 20 degrees
Nguyen <i>et al.</i> (2017) [1010]	Retrospective study	Included patients in acute phase	126 in SP 36 in AP	Mean = 3.2	SP = 27,4% (15.2 ± 11.7 degrees) AP = 27,6% (18.5 ± 16.2 degrees) N/S differences in final change in curvature between group 1 (16.7°) and group 2 (15.6°) p = 0.654
Anaïssie <i>et al.</i> (2017) [1046]	Retrospective study	Included patients in acute phase	77	Mean = 6.6	29.6% (15.3 ± 12.9 degrees)
Abdel Raheem <i>et al.</i> (2017) [1047]	Prospective study	Shortened protocol	53	Mean = 3	31.4% (17.6 degrees)
Capece <i>et al.</i> (2018) [1048]	Prospective multicentric study	Shortened protocol	135	Mean = 3	42.9% (19.1 degrees)

SP = Stable phase; AP = Acute phase; N/S = Non-significant.

The average improvement in curvature was 34% compared to 18.2% in the placebo group. Three adverse events of corporeal rupture were surgically repaired. The greatest chance of curvature improvement is for curvatures between 30° and 60°, longer duration of disease, IIEF > 17, and no calcification [1001]. An 18.2% improvement from baseline in the placebo arm was also observed. These findings raise questions regarding the alleged role of plaque injection and penile modelling, regardless of the medication, in improving outcomes in men with PD as the placebo or modelling arm resulted in high curvature reduction compared to treatment.

The conclusion of the IMPRESS I and II studies is that that CCH improves PD both physically and psychologically [1042]. A *post hoc* meta-analysis of the IMPRESS studies demonstrated better results in patients with < 60° of curvature, > 2 years evolution, no calcification in the plaque and good erectile function [1041].

Thereafter, a modified short protocol consisting of administration of a single (0.9 mg, one vial) injection per cycle distributed along three lines around the point of maximum curvature up to three cycles, separated by 4-weekly intervals, has been proposed, and replaces the physician modelling with a multi-modal approach through penile stretching, modelling and VED at home [1047]. The results from this modified protocol were comparable to the results of the IMPRESS trials and appeared to decrease the cost and duration of treatment, although these represent non-randomised study protocols. These results were further explored in a prospective non-randomised multi-centre study [982]. In another large single-arm multi-centre clinical study using the

shortened protocol, longer PD duration, greater baseline PC and basal and dorsal plaque location were identified as clinically significant predictors of treatment success [1049]. Accordingly, a nomogram developed to predict treatment success after CCH for PD showed that patients with longer PD duration, greater baseline penile curvature and basal plaque location had a greater chance of treatment success [1049]; however, these findings need to be externally validated.

Regarding safety concerns, most PD patients treated with CCH experienced at least one mild or moderate adverse reaction localised to the penis (penile haematoma (50.2%), penile pain (33.5%), penile swelling (28.9%) and injection site pain (24.1%), which resolved spontaneously within 14 days of injection [1050]. The adverse reaction profile was similar after each injection, regardless of the number of injections administered. Serious treatment-emergent adverse events (TEAEs) (0.9%) include penile haematoma and corporeal rupture that require surgical treatment. According to IMPRESS data and the shortened protocol, to prevent serious TEAEs men should be advised to avoid sexual intercourse in the 4 weeks following injection. Recent preliminary data suggest that treatment in the acute phase of the disease can be effective and safe [1010, 1044, 1045, 1051-1053].

In conclusion, CCH is a safe and established treatment for stable-phase disease. More recent evidence suggests that CCH also has a role in affecting the progression of active-phase disease, thus supporting the idea that the indications for CCH use could be expanded, although there is the possibility of a high placebo effect. It should also be noted that there is a large effect of traction or modelling in controlled studies, while studies reporting on modified protocols have small numbers of patients and are largely uncontrolled. Therefore, patients should be counselled fully on the efficacy of collagenase and the high cost of treatment.

It has been suggested that those patients with severe curvature may also benefit from CCH injections because of a potential downgrading of the penile curvature: a decrease in curvature may allow for a penile plication procedure instead of a plaque incision and grafting procedure, therefore avoiding the more negative impact on erectile function. However, further investigation is needed to validate these initial findings [1010, 1045].

The Panel has agreed to keep the whole set of information and recommendations regarding the use of CCH in men with PD despite the recent official withdrawal of the product from the European market by the company.

Interferon α -2b

Interferon α -2b (IFN- α 2b) has been shown to decrease fibroblast proliferation, extracellular matrix production and collagen production by fibroblasts and improve the wound healing process from PD plaques *in vitro* [1054]. Intralesional injections (5x10⁶ units of IFN- α 2b in 10 mL saline every 2 weeks over 12 weeks for a total of six injections) significantly improved penile curvature, plaque size and density, and pain compared to placebo. Additionally, penile blood flow parameters are benefited by IFN- α 2b [1040, 1055, 1056]. Regardless of plaque location, IFN- α 2b is an effective treatment option. Treatment with IFN- α 2b provides a > 20% reduction in curvature in most men with PD, independent of plaque location [1057]. Given the mild adverse effects, which include sinusitis and flu-like symptoms, which can be effectively treated with NSAIDs before IFN- α 2b injection, and the moderate strength of data available, IFN- α 2b is currently recommended for treatment of stable-phase PD.

Steroids, hyaluronic acid and botulinum toxin (botox)

In the only single-blind, placebo-controlled study with intralesional administration of betamethasone, no statistically significant changes in penile deformity, penile plaque size, and penile pain during erection were reported [1058]. Adverse effects include tissue atrophy, thinning of the skin and immunosuppression [1059]. Only a case-controlled single site study and a prospective non-controlled study supported the use of hyaluronic acid injections in PD, with conflicting results related to penile curvature or penile pain [1060, 1061]. As only a single study evaluated intralesional botox injections in men with PD, the Panel conclude that there is no robust evidence to support these treatments [1062].

8.2.3.1.3 Topical treatments

Topical verapamil and H-100 Gel

There is no sufficient and unequivocal evidence that topical treatments (verapamil, H-100 Gel [a compound with nifedipine, superoxide dismutase and emu oil] or steroids) applied to the penile shaft, with or without the use of iontophoresis (now known as transdermal electromotive drug administration), result in adequate levels of the active compound within the tunica albuginea [1063-1066]. Therefore, the Panel does not support the use of topical treatments for PD applied to the penile shaft.

Extracorporeal shockwave treatment

The mechanical shear stress provoked by low-intensity extracorporeal shock wave treatment (LI-ESWT) on the treated tissue was deemed to induce neovascularisation and to enhance local blood flow [1016]. The mechanism of action involved in ESWT for PD is still unclear, but there are two hypotheses: (i) SWT works by directly damaging and remodelling the penile plaque; and (ii) SWT increases the vascularity of the area by generating thermodynamic changes resulting in an inflammatory reaction, with increased macrophage activity causing plaque lysis and eventually leading to plaque resorption [1067, 1068].

Four RCTs and one meta-analysis [1069-1073] assessed the efficacy of ESWT for PD. Three were sham-controlled trials while one compared ESWT with the combination of ESWT and PDE5i (tadalafil) [1067].

All trials showed positive findings in terms of pain relief, but no effect on penile curvature and plaque size. Inclusion criteria varied widely among studies and further investigation is needed. The results are summarised in Table 28.

Table 28: Efficacy of ESWT in the treatment of PD

Author/Year [Ref]	No. of cases/controls	Inclusion criteria	Comparator	Follow-up	Treatment protocol	Results	Adverse effects
Palmieri <i>et al.</i> 2009 [1069]	50 / 50	PD < 12 mo. No previous treatment	Sham therapy	6 month	1 session/week x 4 weeks 2000 sw, 0.25 mJ/mm ² , 4 Hz	Change in IIEF (+5.4 points) Pain reduction (-5.1 points) Change in curvature (-1.4°) Plaque size (-0.6 in)	None
Chitale <i>et al.</i> 2010 [1070]	16 / 20	Stable PD > 6 mo. No previous treatment	Sham therapy	6 month	1 session/week x 6 weeks. No other parameters mentioned.	Change in IIEF Significant in both groups Pain reduction Significant in both groups Change in curvature N/S Plaque size N/S	None
Palmieri <i>et al.</i> 2011 [1071]	50 / 50	PD < 12 mo. Painful erections Presence of ED	ESWT + tadalafil 5 mg OD	6 month	1 session/week x 4 weeks 2000 sw, 0.25 mJ/mm ² , 4 Hz	Change in IIEF Significant in both groups Pain reduction Significant in both groups Change in curvature N/S Plaque size N/S	None
Hatzichristodoulou <i>et al.</i> 2013 [1072]	51 / 51	Stable PD > 3 mo. Previous unsuccessful oral treatment	Sham therapy	1 month	1 session/week x 6 weeks 2000 sw, 0.29 mJ/mm ²	Change in IIEF N/A Pain reduction (-2.5 points) Change in curvature N/S Plaque size N/S	Ecchymosis 4,9%

N/A = no assessed; N/S = no significant; IIEF = International index of erectile function; VAS = Visual Analogic Scale; ED = Erectile dysfunction.

Penile traction therapy

In men with PD, potential mechanisms for disease modification with penile traction therapy (PTT) have been described, including collagen remodelling via decreased myofibroblast activity and matrix metalloproteinase up-regulation [1074, 1075].

The stated clinical goals of PTT are to non-surgically reduce curvature, enhance girth, and recover lost length, which are attractive to patients with PD. However, clinical evidence is limited due to the small number of patients included (267 in total), the heterogeneity in the study designs, and the non-standardised inclusion and exclusion criteria which make it impossible to draw any definitive conclusions about this therapy [1076-1080].

Most of the included patients will need further treatment to ameliorate their curvature for satisfactory sexual intercourse. Moreover, the effect of PTT in patients with calcified plaques, hourglass or hinge deformities which are, theoretically, less likely to respond to PTT has not been systematically studied. In addition, the treatment can result in discomfort and be inconvenient due to use of the device for an extended period (2-8 hours daily), but has been shown to be tolerated by highly motivated patients. There were no serious adverse effects, including skin changes, ulcerations, hypo-aesthesia or diminished rigidity [1078, 1081].

In conclusion, PTT seems to be effective and safe for patients with PD, but there is still lack of evidence to give any definitive recommendation in terms of monotherapy for PD.

Table 29: Summary of clinical evidence of PTT as monotherapy

Author/year	Study type	Device	No. of patients	Hours of use	Result
Levine <i>et al.</i> (2008)	Pilot Prospective, uncontrolled	Fast Size®	10	2-8h 6 months	Mean reduction in PC 33% (51°-34°) SPL: + 0.5-2 cm EG: + 0.5-1 cm IIEF: + 5.3
Gontero <i>et al.</i> (2009)	Phase II Prospective Uncontrolled	Andropenis®	15	> 5h 6 months	Mean reduction in PC: N/S SPL: + 0.8 cm (6 mo) + 1.0 cm (12 mo)
Martinez-Salamanca <i>et al.</i> (2014)	Prospective, controlled, open label Men in AP	Andropenis®	96 55 (PD) 41 (NIG)	6-9h (4.6 h/d) 6 months	Mean reduction in PC: 20° (33°-15°) p < 0.05. SPL: + 1.5 cm (6 mo) EG: + 0.9 cm (6 mo)
Moncada <i>et al.</i> (2018)	Controlled multicenter trial Men in CP	Penimaster®PRO	80 41 (PTT) 39 (NIG)	3-8h 3 months	Mean reduction in PC: 31° (50°-15°). SPL: + 1.8 cm (3 mo) EG: + 0.9 cm (6 mo) IIEF: + 2.5
Ziegelmann <i>et al.</i> (2019) [1080]	Randomised, prospective, controlled, single blind study Men in CP and controls 3:1	Restorex®	110	30-90 min/day 3 months	Mean reduction in PC (3 mo): 13.3° (PTT) + 1.3° (control) p < 0.001 SPL: + 1.5 cm (PTT) + 0 cm (control) p < 0.001 IIEF: + 4.3 (PTT) -0.7 (control) p = 0.01

NIG = non-intervention group; IIEF = International Index of Erectile Function; N/S = Not significant;
PD = Peyronie's Disease; AP = Acute phase; CP = Chronic phase; SPL - Stretched penile length; EG = Erect girth.

Vacuum erection device

Vacuum erection device (VED) therapy results in dilation of cavernous sinuses, decreased retrograde venous blood flow and increased arterial inflow [1082]. Intracorporeal molecular markers are affected by VED application, including decreases in hypoxia-inducible factor-1 α , TGF- β 1, collagenase, and apoptosis, and

increases endothelial nitric oxide synthase (eNOS) and α -smooth muscle actin, given their role in the pathogenesis of PD [1083]. Only one clinical study assessed the efficacy of VED therapy in mechanically straightening the penile curvature of PD as monotherapy and further investigation is needed [1084].

8.2.3.1.4 Multimodal treatment

There are some data suggesting that a combination of different oral drugs can be used for treatment of the acute phase of PD. However, there does not seem to be a consensus on which drugs to combine or the optimum drug dosage; nor has there been a comparison of different drug combinations.

A long-term study assessing the role of multimodal medical therapy (injectable verapamil associated with antioxidants and local diclofenac) demonstrated that it is efficacious to treat PD patients. The authors concluded that combination therapy reduced pain more effectively than verapamil alone, making this specific combination treatment more effective compared to monotherapy [1083]. Furthermore, combination protocols including injectable therapies, such as CCH, have been studied in controlled trials. The addition of adjunctive PTT and VED has been described; however, limited data are available regarding its use [1085].

Penile traction therapy has been evaluated as an adjunct therapy to intralesional injections with interferon, verapamil, or CCH [1030, 1086, 1087]. These studies have failed to demonstrate significant improvements in penile length or curvature, with the exception of one subset analysis identifying a 0.4 cm length increase among men using the devices for > 3 hours/day [1087]. A meta-analysis demonstrated that men who used PTT as an adjunct to surgery or injection therapy for PD had, on average, an increase in stretched penile length (SPL) of 1 cm compared to men who did not use adjunctive PTT. There was no significant change in curvature between the two groups [1088].

Data available on the combined treatment of CCH and the use of VED between injection intervals have shown significant mean improvements in curvature (-17°) and penile length (+0.4 cm) after treatment. However, it is not possible to determine the isolated effect of VED because of a lack of control groups [1047, 1088].

Recent data have suggested that combination of PDE5I (sildenafil 25 mg twice daily) after CCH treatment (shortened protocol combined with VED) is superior to CCH alone for improving penile curvature and erectile function. Further studies are necessary to externally validate those findings.

8.2.3.1.5 Summary of evidence for conservative treatment of Peyronie's disease

Summary of evidence	LE
Conservative treatment for PD is primarily aimed at treating patients in the early stage of the disease in order to relieve symptoms and prevent progression.	3c
There is no convincing evidence supporting oral treatment with acetyl esters of carnitine, vitamin E, potassium para-aminobenzoate (potaba) and pentoxifylline.	3c
Due to adverse effects, treatment with oral tamoxifen is no longer recommended.	3c
Nonsteroidal anti-inflammatory drugs can be used to treat pain in the acute phase.	5
Intralesional treatment with calcium channel antagonists: verapamil and nifedipine are no longer recommended due to contradictory results.	1b
Intralesional treatment with collagenase of <i>clostridium histolyticum</i> showed significant decreases in penile curvature, plaque diameter	1b
Intralesional treatment with interferon may improve penile curvature, plaque size and density, and pain.	2b
Intralesional treatment with steroids are no longer recommended due to adverse effects, including tissue atrophy, thinning of the skin and immunosuppression.	3c
No robust evidence is available to support treatment with intralesional hyaluronic acid or botulinum toxin.	3c
There is no evidence that topical treatments applied to the penile shaft result in adequate levels of the active compound within the tunica albuginea.	3c
The use of iontophoresis is not recommended due to the absence of efficacy data.	3c
Extracorporeal shockwave treatment may be offered to treat penile pain, but it does not improve penile curvature and plaque size.	2b
Treatment with penile traction therapy alone or in combination with injectable therapy as part of a multimodal approach may reduce penile curvature and increase penile length, although studies have limitations.	3c

8.2.3.1.6 Recommendations for non-operative treatment of Peyronie's disease

Recommendations	Strength rating
Offer conservative treatment to patients not fit for surgery or when surgery is not acceptable to the patient.	Strong
Discuss with patients all the available treatment options and expected results before starting any treatment.	Strong
Do not offer oral treatment with vitamin E, potassium para-aminobenzoate (potaba), tamoxifen, pentoxifylline, colchicine and acetyl esters of carnitine to treat Peyronie's disease (PD).	Strong
Nonsteroidal anti-inflammatory drugs can be used to treat penile pain in the acute phase of PD.	Strong
Extracorporeal shockwave treatment (ESWT) can be used to treat penile pain in the acute phase of PD.	Weak
Phosphodiesterase type 5 inhibitors can be used to treat concomitant erectile dysfunction or if the deformity results in difficulty in penetrative intercourse in order to optimise penetration .	Weak
Intralesional therapy with interferon alpha-2b may be offered in patients with stable curvature dorsal or lateral > 30° seeking a minimal invasive procedure.	Strong
Intralesional therapy with collagenase <i>clostridium histolyticum</i> CCH may be offered in patients with stable PD and dorsal or lateral curvature > 30°, who request non-surgical treatment, although the placebo effects are high.	Strong
Do not offer intralesional treatment with steroids to reduce penile curvature, plaque size or pain.	Strong
Do not offer ESWT to improve penile curvature and reduce plaque size.	Strong
Penile traction devices and vacuum devices may be offered to reduce penile deformity or as part of a multimodal therapy approach, although outcome data is limited.	Weak

8.2.3.2 Surgical treatment

Although conservative treatment for PD may resolve painful erections in most men, only a small percentage experience significant straightening of the penis. The aim of surgery is to correct curvature and allow penetrative intercourse. Surgery is indicated in patients with significant penile deformity and difficulty with intercourse associated with sexual bother. Patients must have a stable disease for 3-6 months (or more than 9-12 months after onset of PD) [993, 1002, 1089]. In addition to this requirement, there are other situations that may precipitate an indication for surgery, such as failed conservative or medical therapies, extensive penile plaques, or patient preference, when the disease is stable [1090, 1091].

Before considering reconstructive surgery, it is recommended to document the size and location of penile plaques, the degree of curvature, complex deformities (hinge or hourglass), the penile length and the presence or absence of ED. The potential aims and risks of surgery should be fully discussed with the patient so that he can make an informed decision [1089]. Specific issues that should be mentioned during this discussion are: risk of penile shortening; ED, penile numbness; and delayed orgasm, the risk of recurrent curvature, potential for palpation of knots and stitches underneath the skin, potential need for circumcision at the time of surgery, residual curvature and the risk of further penile wasting with shortening procedures [1002, 1092]. Selection of the most appropriate surgical intervention is based on penile length assessment, curvature severity and erectile function status, including response to pharmacotherapy in cases of ED [1002]. Patient expectations from surgery must also be included in the pre-operative assessment. The main objective of surgery is to achieve a "functionally straight" penis, and this must be fully understood by the patient to achieve the best possible satisfaction outcomes after surgery [1089, 1093].

Three major types of reconstruction may be considered for PD: (i) tunical shortening procedures; (ii) tunical lengthening procedures; and, (iii) penile prosthesis implantation, with or without adjunct straightening techniques in the presence of concomitant ED and residual curvature [1094, 1095].

Tunica shortening procedures achieve straightening of the penis by shortening the longer, convex side of the penis to make it even with the contralateral side. Tunical lengthening procedures are performed on the concave side of the penis after making an incision or partial excision of the plaque, with coverage of the defect with a graft. Although tunical lengthening procedures rarely lead to long-term penile length gain, they aim to minimise penile shortening caused by plication of the tunica albuginea, and correct complex deformities. In practice, tunical lengthening procedures are often combined with penile plication or shortening procedures to correct

residual curvature [1096]. In patients with PD and ED not responding to medical treatments, penile prosthesis implantation can be considered with correction of the curvature including adjunct techniques (modelling, plication or incision/excision with grafting).

Penile degloving with associated circumcision (as a means of preventing post-operative phimosis) should be considered the standard approach for all types of procedures, although modifications have been described. Only one study has suggested that circumcision is not always necessary (e.g., in cases where the foreskin is normal pre-operatively) [1097]. Non-degloving techniques have been described that have been shown to prevent ischaemia and lymphatic complications after subcoronal circumcision [1098, 1099].

There are no standardised questionnaires for the evaluation of surgical outcomes. Data from well-designed prospective studies are scarce, with low levels of evidence. Data are mainly based on retrospective single-centre studies, typically non-comparative and non-randomised, or on expert opinion [1002, 1100]. Therefore, surgical outcomes must be treated with caution.

8.2.3.2.1 Tunical shortening procedures

For men with good erectile function, adequate penile length, without complex deformities, such as an hourglass or hinge type narrowing abnormality, and non-severe curvature, a tunical shortening procedure can be considered an appropriate surgical approach. Numerous different techniques have been described, although they can be classified as excisional, incisional and plication techniques.

In 1965, Nesbit was the first to describe the removal of tunical ellipses opposite to the point of maximum curvature with a non-elastic corporal segment to treat CPC [1101]. Thereafter, this technique became a successful treatment option for PD-associated penile curvature [1102]. This operation is based on a 5-10 mm transverse elliptical excision of the tunica albuginea or ~1 mm for each 10° of curvature. The overall short- and long-term results of the Nesbit operation are excellent [1103-1107]. Some modifications of the Nesbit procedure have been described (partial thickness shaving instead of conventional excision; underlapped U incision) with similar results, although these are in non-randomised studies [1108-1112].

The Yachia technique is based on a completely different concept, as it utilises the Heineke-Mikowitz principle for which a longitudinal tunical incision is closed transversely to shorten the convex side of the penis. This technique, initially described by Lemberger in 1984, was popularised by Yachia in 1990, when he reported a series of 10 cases [1113-1118].

Pure plication techniques are simpler to perform. They are based on single or multiple plications performed without making excisions or incisions, to limit the potential damage to the veno-occlusive mechanism [1004, 1119-1135]. Another modification has been described as the '16-dot' technique that consists of application of two pairs of parallel Essed-Schroeder plications tensioned more or less depending on the degree of curvature [1112, 1136-1138]. The use of non-absorbable sutures or longer-lasting absorbable sutures may reduce recurrence of the curvature (Panel expert opinion). Results and satisfaction rates are both similar to the incision/excision procedures.

In general, using these tunical shortening techniques, complete penile straightening is achieved in > 85% of patients. Recurrence of the curvature and penile hypo-aesthesia is uncommon (~10%) and the risk of post-operative ED is low. Penile shortening is the most commonly reported outcome of these procedures. Shortening of 1-1.5 cm has been reported for 22-69% of patients, which is rarely the cause of post-operative sexual dysfunction and patients may perceive the loss of length as greater than it actually is. It is therefore strongly advisable to measure and document the penile length peri-operatively, both before and after the straightening procedure, whatever the technique used (Table 30).

As mentioned above, there are multiple techniques with small modifications and all of them have been reported in retrospective studies, most of them without comparison between techniques and therefore the level of evidence is not sufficient to recommend one method over another.

Table 30: Results of tunical shortening procedures for PD (data from different, non-comparable studies)
[1004, 1108-1135]

	Tunica shortening procedures				
	Nesbit	Modified Nesbit	Yachia	16-dot / mod16-dot	Simple plication
No. of patients/studies	652 / 4	387 / 5	150 / 6	285 / 5	1068 / 18
Significant penile shortening (%) ^{*†}	8.7% (5-39)	3.2% (0-13)	3.5% (0-10)	5.9% (0-6)	8.9% (0-55)
Any penile shortening (%) [*]	21.8% (9-39)	58.0% (23-74)	69% (47-97)	44.6% (40-52)	33.4% (0-90)
Penile straightening (%) [*]	88.5% (86-100)	97.6% (92-100)	95.5% (93-100)	96.9% (95-100)	94.7% (85-100)
Post-operative <i>de novo</i> ED (%) [*]	6.9% (0-17)	3% (0-13)	9.6% (0-13)	3.8% (0-13)	8.1% (0-38)
Penile hypoesthesia (%) [*]	11.8% (2-60)	5.6% (0-31)	1% (0-3)	8.2% (6-13)	9% (0-47)
Overall satisfaction (%) [*]	83.5% (76-88)	95.4% (87-100)	86.8% (78-100)	94% (86-100)	86.4% (52-100)
Follow-up (months) [*]	(69-84)	(19-42)	(10-24)	(18-71)	(12-141)

^{*}Data are expressed as weighted average. [†] Defined as > 30 degrees of curvature. Ranges are in parentheses. ED = Erectile dysfunction.

8.2.3.2.2 Tunical lengthening procedures

Tunica lengthening surgery is preferable in patients with significant penile shortening, severe curvature and/or complex deformities (hourglass or hinge) but without underlying ED. The definition of severe curvature has been proposed to be > 60°, although no studies have validated this threshold. However, it may be used as an informative guide for patients and clinicians in surgical counselling and planning, although there is no unanimous consensus based on the literature that such a threshold can predict surgical outcomes (Panel expert consensus opinion). On the concave side of the penis, at the point of maximum curvature, which usually coincides with the location of the plaque, an incision is made, creating a defect in the albuginea that is covered with a graft. Complete plaque removal or plaque excision may be associated with higher rates of post-operative ED due to venous leak, but partial excision in cases of florid calcification may be permissible [1139, 1140]. Patients who do not have pre-operative ED should be informed of the significant risk of post-operative ED of up to 50% [1092].

Since 1974, when the first study using dermal grafting to treat PD was published [1141], a large number of different grafts have been used. The ideal graft should be resistant to traction, easy to suture and manipulate, flexible (not too much, to avoid aneurysmal dilations), readily available, cost-effective, and morbidity should be minimal, especially when using autografts. No graft material meets all of these requirements. Moreover, the studies performed did not compare different types of grafts and biomaterials and were often single-centre retrospective studies so there is not a single graft that can be recommended for surgeons [1142]. Grafting procedures are associated with long-term ED rates as high as 50%. The presence of pre-operative ED, the use of larger grafts, age > 60 years, and ventral curvature are considered poor prognostic factors for good functional outcomes after grafting surgery [1095]. Although the risk for penile shortening appears to be less than that compared to the Nesbit, Yachia or plication procedures, it is still an issue and patients must be informed accordingly [1094]. Higher rates (3-52%) of penile hypo-aesthesia have also been described after these operations, as damage of the neurovascular bundle with dorsal curves (in the majority) is inevitable. A recent prospective study showed that 21% of patients had some degree of sensation loss at 1 week, 21% at 1 month, 8% at 6 months, and 3% at 1 year [1143]. The use of geometric principles introduced by Egydio may help to determine the exact site of the incision, and the shape and size of the defect to be grafted [1144].

Grafts for PD surgery can be classified into four types (Table 31) [994]:

- Autografts: taken from the individual himself, they include the dermis, vein, temporalis fascia, fascia lata, tunica vaginalis, tunica albuginea and buccal mucosa.
- Allografts: also of human origin but from a deceased donor, including the pericardium, fascia lata and dura mater.
- Xenografts: extracted from different animal species and tissues, including bovine pericardium, porcine small intestinal submucosa, bovine and porcine dermis, and TachoSil® (matrix of equine collagen).
- Synthetic grafts: these include Dacron® and Gore-Tex®.

All the autologous grafts have the inconvenience of possible graft harvesting complications. Dermal grafts are commonly associated with veno-occlusive ED (20%) due to lack of adaptability, so they have not been used in contemporary series [1141, 1142, 1145-1155]. Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. The saphenous vein has been the most commonly used vein graft [1156-1171]. For some extensive albuginea defects, more than one incision may be needed. Tunica albuginea grafts have perfect histological properties but have some limitations: the size that can be harvested, the risk of weakening penile support and making future procedures (penile prosthesis implantation) more complicated [1172-1174]. Tunica vaginalis is easy to harvest and has little tendency to contract due to its low metabolic requirements, although better results can be obtained if a vascular flap is used [1175-1179]. Under the pretext that by placing the submucosal layer on the corpus cavernosum the graft feeds on it and adheres more quickly, the buccal mucosal graft has recently been used with good short-term results [1180-1186].

Cadaveric dura mater is no longer used due to concerns about the possibility of infection [1187, 1188]. Cadaveric pericardium (Tutoplast®) offers good results by coupling excellent tensile strength and multidirectional elasticity/expansion by 30% [1077, 1140, 1151, 1189, 1190]. Cadaveric or autologous fascia lata or temporalis fascia offers biological stability and mechanical resistance [1191-1193].

Xenografts have become more popular in recent years. Small intestinal submucosa (SIS), a type I collagen-based xenogenic graft derived from the submucosal layer of the porcine small intestine, has been shown to promote tissue-specific regeneration and angiogenesis, and supports host cell migration, differentiation and growth of endothelial cells, resulting in tissue structurally and functionally similar to the original [1194-1203]. As mentioned above, pericardium (bovine, in this case) has good traction resistance and adaptability, and good host tolerance [1171, 1204-1207]. Grafting by collagen fleece (TachoSil®) in PD has some major advantages such as decreased operating times, easy application and an additional haemostatic effect [1208-1213].

It is generally recommended that synthetic grafts, including polyester (Dacron®) and polytetrafluoroethylene (Gore-Tex®) are avoided, due to increased risks of infection, secondary graft inflammation causing tissue fibrosis, graft contractures, and possibility of allergic reactions [1116, 1214-1217].

Some authors recommend post-operative penile rehabilitation to improve surgical outcomes. Some studies have described using VED and PTT to prevent penile length loss of up to 1.5 cm [1218]. Daily nocturnal administration of PDE5i enhances nocturnal erections, encourages perfusion of the graft, and may minimise post-operative ED [1219]. Massages and stretching of the penis have also been recommended once wound healing is complete.

Table 31: Results of tunical lengthening procedures for PD (data from different, non-comparable studies) [1077, 1116, 1140, 1141, 1145-1213, 1220, 1221]

	Year of publication	No. of patients / studies	Success (%)*	Penile shortening (%)*	De novo ED (%)*	Follow-up (mo)*
Autologous grafts						
Dermis	1974-2019	718 / 12	81.2% (60-100)	59.9% (40-75)	20.5% (7-67)	(6-180)
Vein grafts	1995-2019	690 / 17	85.6% (67-100)	32.7% (0-100)	14.8% (0-37)	(12-120)
Tunica albuginea	2000-2012	56 / 3	85.2% (75-90)	16.3% (13-18)	17.8% (0-24)	(6-41)
Tunica vaginalis	1980-2016	76 / 5	86.2% (66-100)	32.2% (0-83)	9.6% (0-41)	(12-60)
Temporalis fascia / Fascia lata	1991-2004	24 / 2	100%	0%	0%	(3-10)
Buccal mucosa	2005-2016	137 / 7	94.1% (88-100)	15.2% (0-80)	5.3% (0-10)	(12-45)
Allografts (cadaveric)						
Pericardium	2001-2011	190 / 5	93.1% (56-100)	23.1% (0-33)	37.8% (30-63)	(6-58)
Fascia lata	2006	14 / 1	78.6%	28.6%	7.1%	31
Dura matter	1988-2002	57 / 2	87.5%	30%	17.4% (15-23)	(42-66)
Xenografts						
Porcine SIS	2007-2018	429 / 10	83.9% (54-91)	19.6% (0-66)	21.9% (7-54)	(9-75)
Bovine pericardium	2002-2020	318 / 6	87.4% (76.5-100)	20.1% (0-79.4)	26.5% (0-50)	(14-67)
Bovine dermis	2016	28 / 1	93%	0%	25%	32
Porcine dermis	2020	19 / 1	73.7%	78.9%	63%	85
TachoSil®	2002-2020	529 / 7	92.6% (83.3-97.5)	13.4% (0-93)	13% (0-21)	(0-63)

*Data are expressed as weighted average. Ranges are in parentheses.

ED = Erectile dysfunction; SIS = Small intestinal submucosa.

The results of tunical shortening and lengthening approaches are presented in Tables 30 and 31. It must be emphasised that there have been no RCTs comparing surgical outcomes in PD. The risk of ED seems to be greater for penile lengthening procedures [1002]. Recurrent curvature is likely to be the result of failure to wait until the disease has stabilised, re-activation of the condition following the development of stable disease, or the use of early re-absorbable sutures (e.g., Vicryl) that lose their strength before fibrosis has resulted in acceptable strength of the repair. Accordingly, it is recommended that only non-absorbable sutures or slowly re-absorbed absorbable sutures (e.g., polydioxanone) should be used. With non-absorbable sutures, the knot should be buried to avoid troublesome irritation of the penile skin, but this issue may be alleviated by the use of slowly re-absorbable sutures (e.g., polydioxanone) [1103]. Penile numbness is a potential risk of any surgical procedure, involving mobilisation of the dorsal neurovascular bundle. This is usually a temporary neuropraxia, due to bruising of the dorsal sensory nerves. Given that the usual deformity is a dorsal deformity, the procedure most likely to induce this complication is a lengthening (grafting) procedure, or the association with (albeit rare) ventral curvatures [1094].

8.2.3.2.3 Penile prosthesis

Penile prosthesis (PP) implantation is typically reserved for the treatment of PD in patients with concomitant ED not responding to conventional medical therapy (PDE5I or intracavernous injections of vasoactive agents) [1002]. Although inflatable prostheses (IPPs) have been considered more effective in the general population with ED, some studies support the use of malleable prostheses in these patients with similar satisfaction rates [1002, 1222, 1223]. The evidence suggests that there is no real difference between the available IPPs [1224]. Surgeons can and should advise on which type of prosthesis best suits the patient but it is the patient who should ultimately choose the prosthesis to be implanted [1225].

Most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion [1169, 1226]. If the curvature after placement of the prosthesis is $< 30^\circ$ no further action is indicated, since the prosthesis itself will act as an internal tissue expander to correct the curvature during the subsequent 6-9 months. If, the curvature is $> 30^\circ$, the first-line treatment would be modelling with the prosthesis maximally inflated (manually bent on the opposite side of the curvature for 90 seconds, often accompanied by an audible crack) [1227, 1228]. If, after performing this manoeuvre, a deviation $> 30^\circ$ persists, subsequent steps would be incision with collagen fleece coverage or without (if the defect is small, it can be left uncovered) or plaque incision and grafting [1229-1234]. However, the defect may be covered if it is larger, and this can be accomplished using grafts commonly used in grafting surgery (described above) which prevent herniation and recurrent deformity due to the scarring of the defect [1235]. The risk of complications (infection, malformation, etc.) is not increased compared to that in the general population. However, a small risk of urethral perforation (3%) has been reported in patients with ‘modelling’ over the inflated prosthesis [1227].

In selected cases of end-stage PD with ED and significant penile shortening, a lengthening procedure, which involves simultaneous PP implantation and penile length restoration, such as the “sliding” technique has been considered [1236]. Although the “sliding” technique is not recommended due to reported cases of glans necrosis because of the concomitant release of the neurovascular bundle and urethra, new approaches for these patients have been recently described, such as the MoST (Modified Sliding Technique), MUST (Multiple-Slit Technique) or MIT (Multiple-Incision Technique) techniques, but these should only be used by experienced high-volume surgeons and after full patient counselling [1237-1240].

While patient satisfaction after IPP placement in the general population is high, satisfaction rates have been found to be significantly lower in those with PD. Despite this, depression rates decreased after surgery in PD patients (from 19.3% to 10.9%) [1241]. The main cause of dissatisfaction after PPI in the general population is a shortened penile length. Therefore, patients with PD undergoing PP surgery must be counselled that the prostheses are not designed to restore the previous penile length [1241, 1242].

8.2.3.2.4 Summary of evidence for surgical treatment of Peyronie’s disease

Summary of evidence	LE
Surgery for PD should only be offered in patients with stable disease with functional impairment.	2b
In patients with concomitant PD and ED without response to medical treatment, penile prosthesis implantation with or without additional straightening manoeuvres is the technique of choice.	2a
In other cases, factors such as penile length, rigidity of erection, degree of curvature, presence of complex deformities and patient choice must be taken into account to decide on a tunical shortening or lengthening technique.	3

8.2.3.2.5 Recommendations for surgical treatment of penile curvature

Recommendations	Strength rating
Perform surgery only when Peyronie's disease (PD) has been stable for at least 3 months (without pain or deformity deterioration), which is usually the case after 12 months from the onset of symptoms, and intercourse is compromised due to deformity.	Strong
Prior to surgery, assess penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction [ED]) and patient expectations.	Strong
Use tunical shortening procedures as the first treatment option for congenital penile curvature and for PD with adequate penile length and rigidity, non-severe curvature and absence of complex deformities (hourglass or hinge). The type of procedure used is dependent on surgeon and patient preference, as no procedure has proven superior to its counterparts.	Weak
Use tunical lengthening procedures for patients with PD and normal erectile function, without adequate penile length, severe curvature or presence of complex deformities (hourglass or hinge). The type of graft used is dependent on the surgeon and patient factors, as no graft has proven superior to its counterparts.	Weak
Use the sliding techniques with caution, as there is a significant risk of life changing complications (e.g., glans necrosis).	Strong
Do not use synthetic grafts in PD reconstructive surgery.	Strong
Use penile prosthesis implantation, with or without any additional procedure (modelling, plication, incision or excision with or without grafting), in PD patients with ED not responding to pharmacotherapy.	Strong

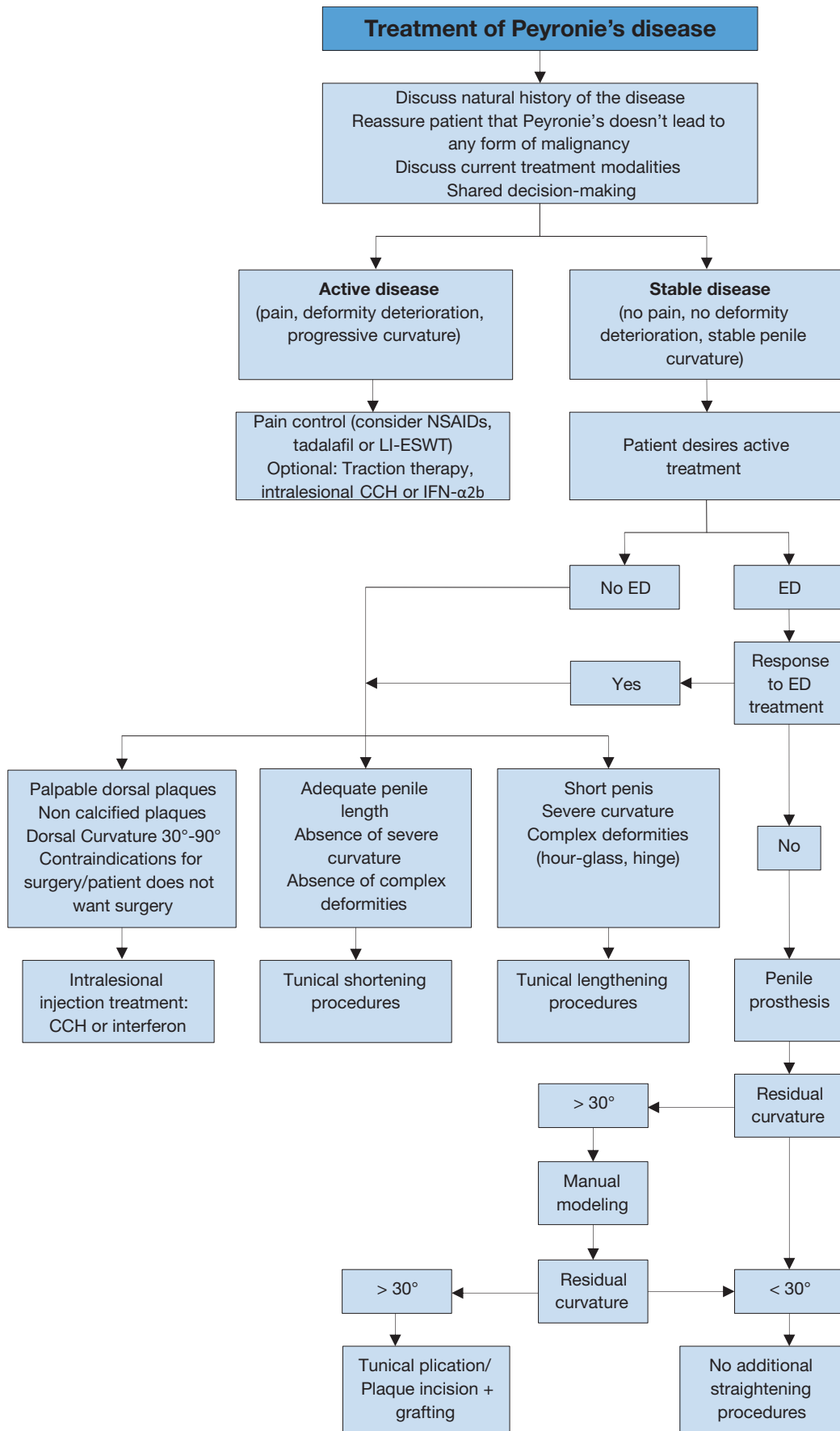
8.2.3.3 Treatment algorithm

As mentioned above, in the active phase of the disease, most therapies are experimental or with low evidence. In cases of pain, LI-ESWT, tadalafil and NSAIDs can be offered. In cases of curvature or penile shortening, traction therapy has demonstrated good responses.

When the disease has stabilised, intralesional treatments (mainly CCH) or surgery may be used. Intralesional treatments may reduce the indications for surgery or change the technique to be performed but only after full patient counselling, which should also include a cost-benefit discussion with the patient.

The decision on the most appropriate surgical procedure to correct penile curvature is based on pre-operative assessment of penile length, the degree of curvature and erectile function status. In non-complex and non-severe deformities, tunical shortening procedures are acceptable and are usually the method of choice. This is typically the case for CPC. If severe curvature or complex deformation is present (hourglass or hinge), or if the penis is significantly shortened in patients with good erectile function (preferably without pharmacological treatment), then tunical lengthening is feasible, using any of the grafts previously mentioned. If there is concomitant ED, which is not responsive to pharmacological treatment, the best option is the implantation of a penile prosthesis, with or without a straightening procedure over the penis (modelling, plication, incision or excision with or without grafting). The treatment algorithm is presented in Figure 11.

Figure 11: Treatment algorithm for Peyronie's disease



ED = erectile dysfunction; LI-ESWT = Low-intensity extracorporeal shockwave treatment.

9. PRIAPISM

Evidence Acquisition and limitations

The Panel conducted systematic reviews on the medical and surgical management of ischaemic and non-ischaemic priapism and a dedicated systematic review on the overall management of priapism related to sickle cell disease. The results of these systematic reviews are presented below in the guidelines and the limitations of the studies that were assessed are highlighted.

Most studies had the same limitations and methodological bias: lack of published protocols, retrospective and usually single-arm design, lack of randomisation and blinding, incomplete outcome data, and selective reporting. Additionally, most studies included small numbers of patients, reported non-standardised patient characteristics, and had short (or even unreported) follow-up times and, in general, they reflected single-unit practices.

The definitions of priapism and outcomes (such as success and related complications) were inconsistent across the literature and few of the trials met the clear definitions that were set by the Panel for use in the systematic reviews. Hence, any attempt to draw clinically meaningful conclusions and offer evidence-based guidance based on systematic assessment of the literature was a challenging task. These limitations highlight the urgent need for clear and commonly accepted definitions of conditions and outcomes that should be used by researchers in the future so that robust evidence can be developed to support relevant guidelines and clinical practice recommendations.

The Panel acknowledged the evidence-related limitations, and in accordance with the GRADE approach endorsed by the European Association of Urology Guidelines Office, also took into consideration the benefits/harms balance and the patient ideals, views and preferences prior to finalising the relevant recommendations (for/against, weak/strong).

Priapism is a persistent or prolonged erection in the absence of sexual stimulation that fails to subside. It can be divided into ischaemic, non-ischaemic and stuttering priapism.

9.1 Ischaemic (Low-Flow or Veno-Occlusive) Priapism

9.1.1 *Epidemiology, aetiology, pathophysiology and Diagnosis*

Ischaemic priapism is a persistent erection marked by rigidity of the corpora cavernosa and by little or no cavernous arterial inflow [1243]. Ischaemic priapism is the most common subtype of priapism, accounting for > 95% of all episodes [1243, 1244]. It presents as a painful rigid erection that is characterised clinically by absent or reduced intracavernous arterial inflow, although proximally there is a compensated high velocity picture with little flow distally [1245]. In ischaemic priapism, there are time-dependent metabolic alterations within the corpus cavernosum progressively leading to hypoxia, hypercapnia, glucopenia and acidosis [1246, 1247].

Ischaemic priapism that lasts beyond 4 hours is similar to a compartment syndrome, and characterised by the development of ischaemia within the closed space of the corpora cavernosa, which severely compromises the cavernosal circulation. Emergency medical intervention is required to minimise irreversible consequences, such as smooth muscle necrosis, corporal fibrosis and the development of permanent erectile dysfunction (ED) [1248, 1249]. The duration of ischaemic priapism represents the most significant predictor for the development of ED. In this context, interventions beyond 48-72 hours of onset may help to relieve the erection and pain, but have little clinical benefit in preventing long-term ED [1250].

Histological analysis of corporal smooth muscle biopsies shows that at 12 hours, there are features of interstitial oedema, progressing to destruction of the sinusoidal endothelium, exposure of the basement membrane and thrombocyte adherence by 24 hours. At 48 hours, thrombi in the sinusoidal spaces and smooth muscle necrosis with fibroblast-like cell transformation are evident [1251]. This implies that by 48 hours there appears to be smooth muscle necrosis and irreversibility of these ischaemic changes. A case-control study comparing corporal biopsies from patients with priapism lasting 48-72 hours with control penile tissues retrieved from autopsies demonstrated a significantly lower percentage of smooth muscle fibres, with an increase in elastic fibres and collagen [1248, 1252].

No specific pathophysiological causes of ischaemic priapism can be identified in most cases [1243, 1253], although the common aetiological factors include sickle cell disease (SCD), haematological dyscrasias, neoplastic syndromes, and several pharmacological agents (e.g., intracavernosal PGE1 therapy) (Table 32). Ischaemic priapism may occur (0.4-35%) after intracavernosal injection of erectogenic agents [551, 1243,

1248, 1254, 1255]. The risk is higher with papaverine-based combinations [1256], while the risk of priapism is < 1% following prostaglandin E1 injection [1257].

Second-generation antipsychotics (33.8%), other medications (11.3%), and alpha-adrenergic antagonists (8.8%) accounted for the greatest percentage of published drug-induced priapism cases [1258]. Isolated cases of priapism have been described in men who have taken Phosphodiesterase Type 5 Inhibitors (PDE5Is) [1243]. A recent study from the U.S. Food and Drug Administration (FDA) Adverse Reporting System Public Dashboard showed that PDE5Is-induced priapism accounted for only 2.9% of drug-induced priapism. However, most of these men also had other risk factors for priapism, and it is unclear whether PDE5Is *per se* can cause ischaemic priapism [1243]. Since most men who experience priapism following PDE5I treatment have additional risk factors for ischaemic priapism, PDE5Is use is usually not regarded as a risk factor in itself. In terms of haemoglobinopathies, SCD is the most common cause of priapism in childhood, accounting for 63% of cases. It is the primary aetiology in 23% of adult cases [1257], and men with SCD have a lifetime probability of 29-42% of developing ischaemic priapism [1257, 1259, 1260] (LE: 4).

Mechanisms of SCD-associated priapism may involve derangements of several signalling pathways in the penis, resulting in disinhibited vasorelaxation of the cavernous smooth muscle by nitric oxide synthase (NOS) and Rho-associated protein kinase (ROCK) signalling, and increased oxidative stress associated with nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-mediated signalling. Excessive adenosine and up-regulation of opiorphins in response to hypoxia reduce PDE5 gene expression and activity and impair NO bioavailability in the penis. Excessive oxidative/nitrosative stress and decreased activity of the RhoA/Rho-kinase contractile pathway further promotes priapism. Contrary to traditional belief, maintenance of physiological testosterone levels does not cause priapism, but rather preserves penile homeostasis and promotes normal erectile function [1261, 1262]. Testosterone deficiency is considered a controversial risk factor: it is prevalent in patients with SCD, but recent evidence indicates that it is not a risk factor *per se* for priapism [1263].

Priapism resulting from metastatic or regional infiltration by tumour is rare and usually reflects an infiltrative process, more often involving the bladder and prostate as the primary cancer sites [1264]. In a recent large retrospective study including 412 men with ischaemic priapism, eleven (3.5%) had malignant priapism, of which seven cases were a consequence of local invasion while the others were secondary to haematological malignancy [1265]. The conventional therapeutic recommendations for pharmacological treatment are unlikely to be effective and all of these men should have magnetic resonance imaging (MRI) of the penis and be offered supportive care and medical intervention for their primary cancer. In selected cases where palliative treatment options fail to control penile pain, a palliative penectomy can be considered.

Partial priapism, or idiopathic partial segmental thrombosis of the corpus cavernosum, is a rare condition. It is often classified as a subtype of priapism limited to a single crura without ischaemia, but rather a thrombus is present within the corpus cavernosum. Its aetiology is unknown, but bicycle riding, trauma, drug use, sexual intercourse, haematological diseases and α -blockers intake have all been associated with partial segmental thrombosis [1266]. The presence of a congenital web within the corpora is also a risk factor [1267].

Table 32: Aetiological factors for the development of priapism

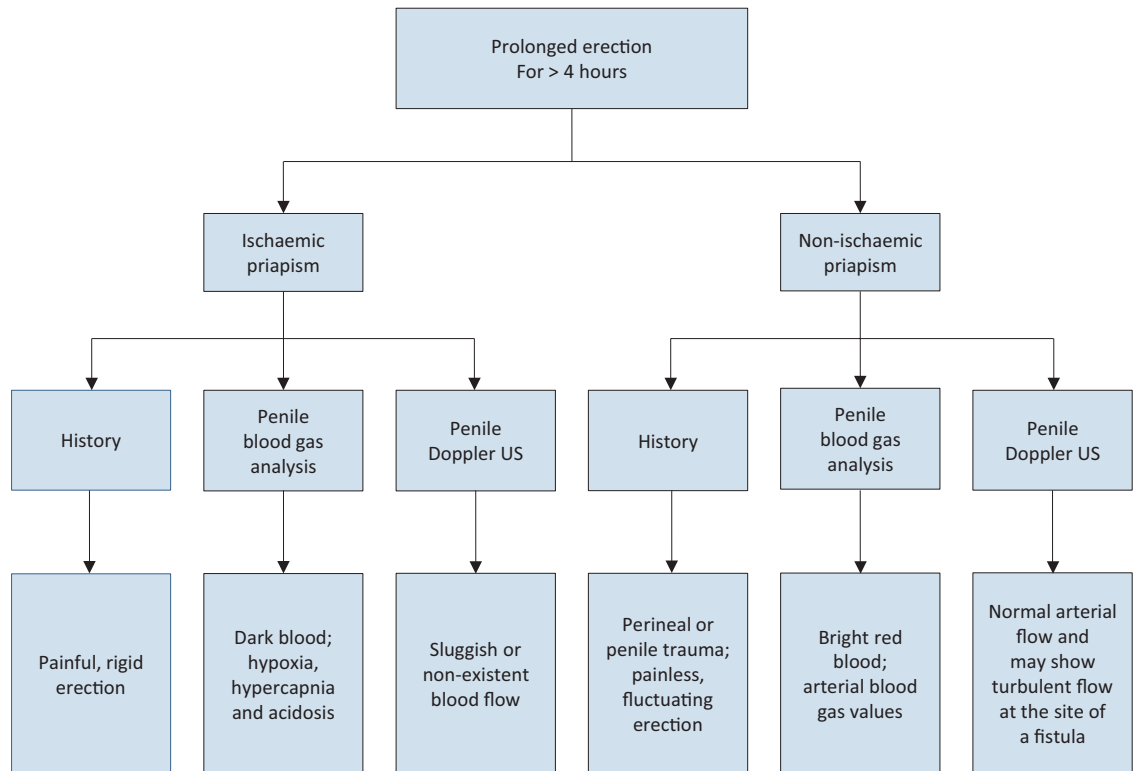
Idiopathic	Haematological dyscrasias Vascular and other disorders	Infections (toxin-mediated)	Metabolic disorders	Neurogenic disorders	Neoplasms (metastatic or regional infiltration)	Medications
	<ul style="list-style-type: none"> - SCD, - thalassemia, - leukaemia; - multiple myeloma, - haemoglobin Olmsted variant, - fat emboli during hyperalimentation, - haemodialysis, - glucose-6-phosphate dehydrogenase deficiency, - factor V Leiden mutation - vessel vasculitis (e.g., Henoch-Schönlein purpura; Behçet's disease; anti-phospholipid antibodies syndrome) 	<ul style="list-style-type: none"> - scorpion sting, - spider bite, - rabies, - malaria 	<ul style="list-style-type: none"> - amyloidosis, - Fabry's disease, - gout 	<ul style="list-style-type: none"> - syphilis, - spinal cord injury, - cauda equina syndrome, - autonomic neuropathy, - lumbar disc herniation, - spinal stenosis, - cerebrovascular accident, - brain tumour, - spinal anaesthesia 	<ul style="list-style-type: none"> - prostate, - urethra, - testis, - bladder, - rectal, - lung, - kidney 	<ul style="list-style-type: none"> - Vasoactive erectile agents (i.e., papaverine, phentolamine, prostaglandin E1/ alprostadil, combination of intracavernous therapies) - α-adrenergic receptor antagonists (i.e., prazosin, terazosin, doxazosin and tamsulosin) - Anti-anxiety agents (hydroxyzine) - Anticoagulants (heparin and warfarin) - Antidepressants and antipsychotics (i.e., trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thiorizadine, phenothiazines and methylphenidate) - Antihypertensives (i.e., hydralazine, guanethidine and propranolol) - Hormones (i.e., gonadotropin-releasing hormone and testosterone) - Recreational drugs (i.e., alcohol, marijuana, cocaine [intranasal and topical], and crack, cocaine)

9.1.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of ischaemic priapism

Summary of evidence	LE
Ischaemic priapism is the most common type, accounting for more than 95% of all cases.	1b
Ischaemic priapism is identified as idiopathic in most patients, while sickle cell disease is the most common cause in childhood.	1b
Ischaemic priapism occurs relatively often (about 5%) after intracavernous injections of papaverine-based combinations, while it is rare (< 1%) after prostaglandin E1 monotherapy.	2a
Priapism is rare in men who have taken Phosphodiesterase Type 5 Inhibitors, with only sporadic cases reported.	4

9.1.2 Diagnostic evaluation

Figure 12: Differential diagnosis of priapism



9.1.2.1 History

Taking a comprehensive history is critical in priapism diagnosis and treatment [1243, 1268]. The medical history must specifically enquire about SCD or any other haematological abnormality [1269, 1270] and a history of pelvic, genital or perineal trauma. The sexual history must include the duration of the erection, the presence and degree of pain, prior drug treatment, history of priapism and erectile function prior to the last priapism episode (Table 33). The history can help to determine the underlying priapism subtype (Table 34). Ischaemic priapism is classically associated with progressive penile pain and the erection is rigid. However, non-ischaemic priapism is often painless and the erections often fluctuate in rigidity.

Table 33: Key points in the history for a priapism patient (adapted from Broderick *et al.* [1243])

Duration of erection
Presence and severity of pain
Previous episodes of priapism and methods of treatment
Current erectile function, especially the use of any erectogenic therapies prescription or nutritional supplements
Medications and recreational drug use
Sickle cell disease, haemoglobinopathies, hypercoagulable states, vessel vasculitis
Trauma to the pelvis, perineum or penis

9.1.2.2 Physical examination

In ischaemic priapism, the corpora are fully rigid and tender, but the glans penis is soft. The patient complains of severe pain. Pelvic examination may reveal an underlying pelvic or genitourinary malignancy [1265].

9.1.2.3 Laboratory testing

Laboratory testing should include a complete blood count, white blood cell count with blood cell differential, platelet count and coagulation profile to assess anaemia and detect haematological abnormalities [1243, 1268].

A genome-wide association study on Brazilian patients identified four single nucleotide polymorphisms in LINC02537 and NAALADL2 significantly associated with priapism, although testing is not routinely recommended in clinical practice [1271].

Aspiration of blood from the corpora cavernosa usually reveals dark ischaemic blood (Table 33) (LE: 2b). Blood gas analysis is essential to differentiate between ischaemic and non-ischaemic priapism (Table 34). Further laboratory testing should be directed by the history, clinical examination and laboratory findings. These may include specific tests (e.g., haemoglobin electrophoresis) for diagnosis of SCD or other haemoglobinopathies.

9.1.2.4 Penile imaging

Colour Doppler US of the penis and perineum is recommended after clinical diagnosis and can differentiate ischaemic from non-ischaemic priapism as an alternative or adjunct to blood gas analysis [1245, 1272-1274] (LE: 2b). Colour Doppler US can identify the presence of the fistula as a blush with 100% sensitivity and 73% specificity [1274].

Ultrasound scanning of the penis should be performed before corporal blood aspiration in ischaemic priapism to prevent aberrant blood flow which can mimic a non-ischaemic picture or reperfusion picture after intervention for low-flow priapism [1275].

Following Colour Doppler US there will be an absence of blood flow in the cavernosal arteries in ischaemic priapism. Return of the cavernous artery waveform indicates successful detumescence [1243, 1274, 1276]. After aspiration, reactive hyperaemia may develop with a high arterial flow proximally that may be misleading and result in the diagnosis of non-ischaemic priapism.

Penile MRI can be used in the diagnostic evaluation of priapism and may be helpful in selected cases of ischaemic priapism to assess the viability of the corpora cavernosa and the presence of penile fibrosis. In particular, in cases of refractory priapism or delayed presentation (> 48 hours), smooth muscle viability can be indirectly assessed. In a prospective study of 38 patients with ischaemic priapism, the sensitivity of MRI in predicting non-viable smooth muscle was 100%, when correlated with corpus cavernosum biopsies [1275]. In this study, all patients with viable smooth muscle on MRI maintained erectile function on clinical follow-up with the non-viable group being offered an early prosthesis.

Table 34: Key findings in priapism (adapted from Broderick *et al.* [1243])

	Ischaemic priapism	Non-ischaemic priapism
Corpora cavernosa fully rigid	Typically	Seldom
Penile pain	Typically	Seldom
Abnormal penile blood gas	Typically	Seldom
Haematological abnormalities	Sometimes	Seldom
Recent intracavernosal injection	Sometimes	Sometimes
Perineal trauma	Seldom	Typically

Table 35: Typical blood gas values (adapted from Broderick *et al.* [1243])

Source	pO ₂ (mmHg)	pCO ₂ (mmHg)	pH
Normal arterial blood (room air) (similar values are found in arterial priapism)	> 90	< 40	7.40
Normal mixed venous blood (room air)	40	50	7.35
Ischaemic priapism (first corporal aspirate)	< 30	> 60	< 7.25

9.1.2.5 Recommendations for the diagnosis of ischaemic priapism

Recommendations	Strength rating
Take a comprehensive history to establish the diagnosis which can help to determine the priapism subtype.	Strong
Include a physical examination of the genitalia, perineum and abdomen in the diagnostic evaluation.	Strong
For laboratory testing, include complete blood count, white blood cell count with blood cell differential, platelet count and coagulation profile. Direct further laboratory testing should be performed depending upon history and clinical and laboratory findings. In children with priapism, perform a complete evaluation of all possible causes.	Strong

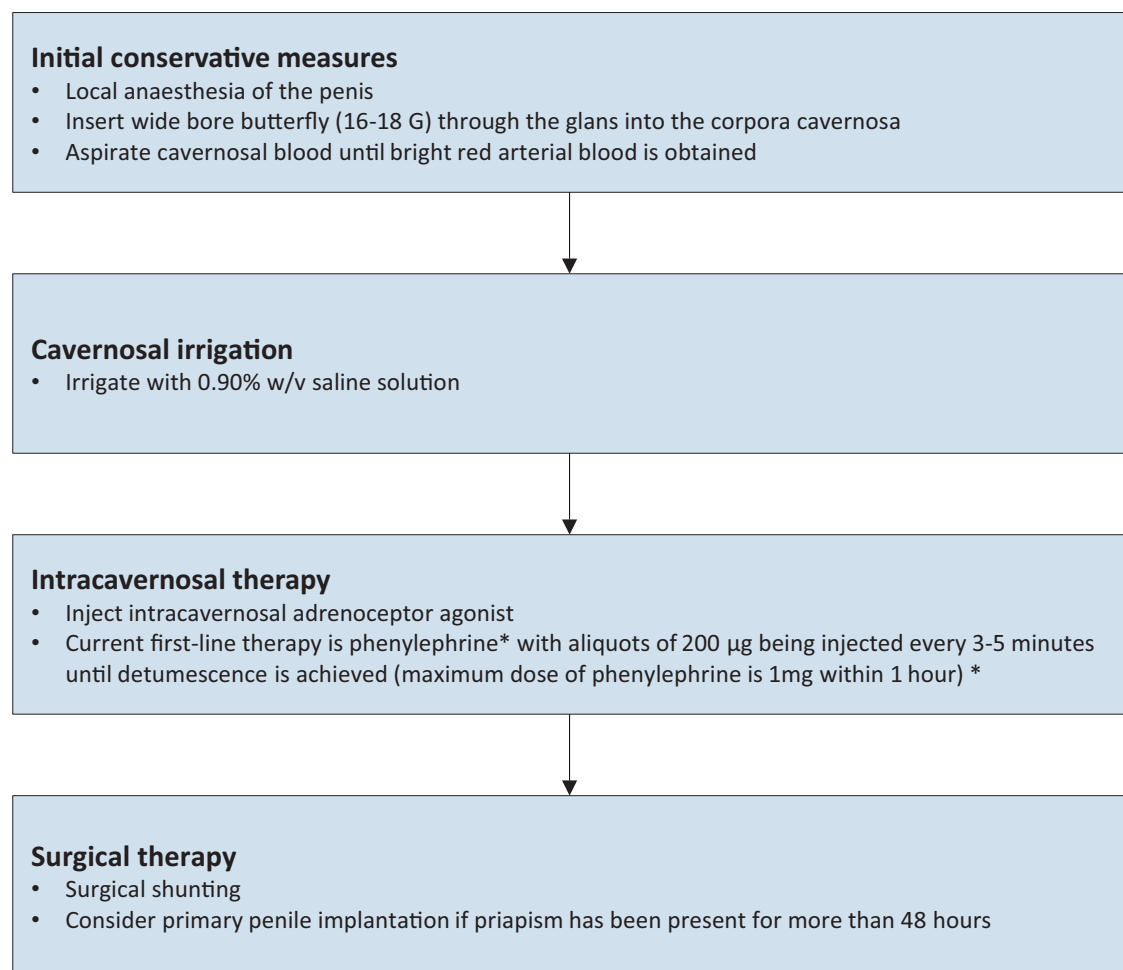
Analyse the blood gas parameters from blood aspirated from the penis to differentiate between ischaemic and non-ischaemic priapism.	Strong
Perform colour duplex ultrasound of the penis and perineum before aspiration to differentiate between ischaemic and non-ischaemic priapism.	Strong
In cases of prolonged ischaemic priapism or refractory priapism, magnetic resonance imaging of the penis may be used as an adjunct to predict smooth muscle viability.	Weak
Perform selected pudendal arteriogram when embolisation is planned for the management of non-ischaemic priapism.	Strong

9.1.3 Disease management

Acute ischaemic priapism is a medical emergency. Urgent intervention is mandatory and should follow a stepwise approach. The aim of any treatment is to restore penile detumescence, without pain, in order to prevent corporal smooth muscle fibrosis and subsequent ED.

Figure 13: Medical and surgical management of ischaemic priapism

The treatment is sequential and physicians should move on to the next stage if treatment fails.



(*) Dose of phenylephrine should be reduced in children. It can result in significant hypertension and should be used with caution in men with cardiovascular disease. Monitoring of pulse and blood pressure is advisable in all patients during administration and for 1 hour afterwards. Its use is contraindicated in men with a history of cerebro-vascular disease and significant hypertension.

9.1.3.1 Medical Management

Evidence Acquisition

The studies that were identified after abstract screening and used for this literature review pertaining to medical management are reported in the table in Appendix 1. Most of these studies were retrospective case series without an available protocol. Additionally, several limitations were encountered during their assessment, including small study samples, unclear definitions of conditions, interventions and outcomes,

short or no reported follow-up and selective reporting of outcomes. As such, providing clinicians with clear recommendations based on robust evidence was not possible. Based on the studies included in the Panel's systematic review, medical management of priapism demonstrates a wide range of effectiveness, although it seems that sexual dysfunction and complication rates in medical management responders were not too high, when reported. It should be emphasised that most patients included in the surgical management studies that are discussed below represent medical non-responders. The selection bias that by definition existed in the surgical management in these single-arm studies makes the estimation of true effectiveness of medical intervention difficult to quantify.

9.1.3.1.1 First-line treatments

First-line medical treatments of ischaemic priapism of more than 4 hours duration are strongly recommended before any surgical treatment (LE: 4). Conversely, first-line treatments initiated beyond 48 hours, while relieving priapism, have little documented benefit in terms of long-term potency preservation (LE: 4). This is likely to be the consequence of irreversible smooth muscle damage that begins to be established by approximately 48 hours of tissue hypoxia [1248-1250]. An *in-vitro* model of priapism has shown that there is window of opportunity for therapeutic intervention beyond which the recovery of functional erectile tissue is unlikely due to irreversible smooth muscle cell dysfunction [1246]. In line with this finding it has been shown in a series of 50 patients with low-flow priapism who were successfully treated and followed-up for a mean 66 months, those with priapism lasting for more than 48 hours had a significant risk of ED [1248].

Historically, several first-line treatments have been described including exercise, ejaculation, ice packs, cold baths, and cold water enemas [1243]. However, there is limited evidence for the benefit of such measures and they may even exacerbate crisis in SCD patients. Success rates of these conservative measures alone have been rarely reported. In a small series, for instance, cold water enemas have been reported to induce detumescence in 6 out of 10 cases [1277]. In another study 24.5% of 122 patients achieved detumescence following priapic episodes lasting for more than 6 hours by cooling of the penis and perineum, and walking upstairs [1259]. In SCD patients with priapism, it is recommended that the urology team works closely with the haematology team to optimise patient management.

Partial priapism usually resolves spontaneously with analgesic treatment while surgical intervention is rarely needed [1278].

9.1.3.1.2 Penile anaesthesia/analgesia

It is possible to perform blood aspiration and intracavernous injection of a sympathomimetic agent without any anaesthesia. However, anaesthesia may be necessary when there is severe penile pain. While it is recognised that the anaesthesia may not alleviate the ischaemic pain, cutaneous anaesthesia facilitates subsequent therapies. The treatment options for penile anaesthesia/systemic analgesia include:

- dorsal nerve block;
- circumferential penile block;
- subcutaneous local penile shaft block;
- oral conscious sedation (for paediatric patients).

9.1.3.1.3 Aspiration ± irrigation with 0.9% w/v saline solution

The first intervention for an episode of priapism lasting more than 4 hours consists of corporal blood aspiration (LE: 4) to drain the stagnant blood from the corporal bodies, making it possible to relieve the compartment-syndrome-like condition within the corpus cavernosum. Blood aspiration may be performed with intracorporeal access either through the glans or via percutaneous needle access to the lateral aspect of the proximal penile shaft, using a 16 or 18 G angio-catheter or butterfly needle. The needle must penetrate the skin, the subcutaneous tissue and the tunica albuginea to drain blood from the corpus cavernosum (LE: 4).

Some clinicians advocate using two angiocatheters or butterfly needles at the same time to accelerate drainage, as well as aspirating and irrigating simultaneously with a saline solution [1259] (LE: 4). Aspiration should be continued until bright red, oxygenated blood is aspirated (LE: 4).

Several case series have reported the outcomes from first-line treatments, although in most cases, aspiration and irrigation were combined with intracavernosal injection of sympathomimetic agents, thus making it difficult to draw conclusions about the success rate of aspiration + irrigation alone. In a RCT, 70 patients with ischaemic priapism secondary to intracavernosal injection and lasting more than 6 hours were treated with aspiration plus saline irrigation at different temperatures [1259]. The authors reported an 85% success rate with the optimum results achieved using a 10°C saline infusion after blood aspiration.

This approach has up to a 30% chance of resolving the priapism. There are insufficient data to determine whether aspiration followed by saline intracorporeal irrigation is more effective than aspiration alone (LE: 4).

9.1.3.1.4 Aspiration ± irrigation with 0.9% w/v saline solution in combination with intracavernous injection of pharmacological agents.

This combination is currently considered the standard of care for treatment of ischaemic priapism [1243, 1279, 1280] (LE: 4). Pharmacological agents include sympathomimetic drugs or α -adrenergic agonists. Intracavernous sympathomimetic agents include phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine and metaraminol with a resolution rate of up to 80% [1243, 1279, 1281-1288] (LE: 2b). The use of intracavernous adrenaline injection alone has also been sporadically reported [1289]. A literature review from the AUA reported that the use of a sympathomimetic agent combined with prior intracavernosal aspiration or irrigation had a resolution rate of 77% as compared with 58% in those who had a sympathomimetic injection alone [1280].

Phenylephrine

Adrenergic agonists act on the post-synaptic α -1-adrenergic receptors to stimulate cavernosal smooth muscle and arteriolar vasoconstriction, with a reduction in arteriolar inflow to the corporal bodies and smooth muscle contraction [1290]. Moreover, this class of drug also increases venous outflow through β 2-adrenergic receptor activity [1287].

Phenylephrine is a selective α -1-adrenergic receptor agonist that has been observed in small case series to be effective at producing detumescence in priapism, when given as an intracavernosal injection, with few adverse effects [1287, 1291]. Therefore, phenylephrine is the recommended adrenergic agonist drug of choice due to its high selectivity for the α -1-adrenergic receptor, without concomitant β -mediated inotropic and chronotropic cardiac effects [1281, 1285, 1286] (LE: 4).

Phenylephrine is diluted in normal saline to a concentration of 100-500 μ g/mL. Usually, 200 μ g are given every three to five minutes directly into the corpus cavernosum. The maximum dosage is 1 mg within 1 hour (LE: 4). A lower concentration or volume is applicable for children and patients with severe cardiovascular diseases (LE: 4).

Higher doses of phenylephrine have been used in small retrospective case series [1286, 1292-1294] without any adverse events, but further trials are needed to substantiate the efficacy of higher doses. There are *in-vitro* data suggesting that higher doses of phenylephrine are unlikely to be beneficial when conventional doses have failed because there is already significant apoptosis of the cavernosal smooth muscle [1295].

Phenylephrine has potential cardiovascular adverse effects [1243, 1279, 1281, 1282, 1285, 1286] and it is recommended that blood pressure and pulse are monitored every fifteen minutes for 1 hour after injection. This is particularly important in older men with pre-existing cardiovascular diseases. After injection, the puncture site should be compressed and the corpus cavernosum massaged to facilitate drug distribution.

The potential treatment-related adverse effects of intracavernous phenylephrine (and other sympathomimetic agents) include headache, dizziness, hypertension, reflex bradycardia, tachycardia and palpitations and sporadic subarachnoid haemorrhage [352]. Monitoring of blood pressure and pulse should be performed during intracavernous administration of sympathomimetic agents.

Given that intracavernous sympathomimetic agents can cause hypertension, the Panel is of the opinion that these agents are contraindicated in patients with malignant or poorly controlled hypertension, as there are case reports of significant cardiovascular and neurological complications following the use of these pharmacological agents for priapism [1282, 1296, 1297]. Similarly, there are data suggesting that sympathomimetic agents cause a hypertensive crisis when given with monoamine oxidase inhibitors, hence these medications should not be used together [1298] (LE: 4).

Etilephrine

Etilephrine is also an adrenergic agonist but directly stimulates both α and β adrenergic receptors [1280]. Most of the literature describing the use of etilephrine for treatment of priapism is related to men with SCD but there are small retrospective case series that have reported its benefits for priapism secondary to iatrogenic causes [1299, 1300]. Etilephrine is the second most widely used sympathomimetic agent, administered by intracavernous injection at a concentration of 2.5 mg in 1-2 mL normal saline [1282] (LE: 3).

Methylene blue

Methylene blue is a guanylate cyclase inhibitor, that may be a potential inhibitor of endothelial-mediated cavernous smooth muscle relaxation. Small retrospective case series have reported its successful use for treating short-term pharmacologically-induced priapism [1301, 1302] (LE: 3). Methylene blue, 50-100 mg [1301], should be injected intracavernously and left for five minutes. It is then aspirated and the penis compressed for an additional five minutes [1302]. Treatment-related adverse effects include a transient burning sensation and blue discolouration of the penis.

Adrenaline

Adrenaline produces both α -adrenergic receptor agonist and β -adrenergic receptor activity. Intracavernosal adrenaline (2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period [1289]) has been used in patients with ischaemic priapism due to an intracavernous injection of vasoactive agents. The limited literature [1289, 1303] suggests that adrenaline can achieve detumescence in short-term priapism, with one small case series reporting a success rate of over 50% after a single injection, with an overall success rate of 95% with repeated injections [1289, 1303] (LE: 3).

β -2-agonists

Oral terbutaline is a β -2-agonist with minor β -1 effects and some α -agonist activity. A dose of 5 mg has been suggested to treat prolonged erections lasting more than 2.5 hours, after intracavernous injection of vasoactive agents, although the mechanism of action is not yet fully understood [1304-1306] (LE: 1b). The main use of terbutaline is for prevention of recurrent episodes of prolonged erection. Terbutaline should be given cautiously in patients with coronary artery disease, increased intravascular fluid volume, oedema or hypokalaemia [1306]. In a single multi-centre prospective study, another β -2-agonist, salbutamol, has been reported to induce detumescence in 34% of cases of prolonged erection (more than 3 hours) after intracavernous injection of erectogenic agents [1307]. However, more robust data are needed to recommend oral salbutamol for the treatment of ischaemic priapism.

Antithrombotic agents

Ramstein *et al.* reported retrospective data pertaining to the use of antithrombotic therapy (a single dose of subcutaneous heparin or aspirin 325 mg) in patients who had undergone corporeal aspiration with and without phenylephrine. Antithrombotic therapy was associated with a significant reduction in further episodes of priapism following aspiration and successful T-shunt insertions in those who failed aspiration. However, these findings were based on a small cohort size ($n = 18$), doses and types of antithrombotic therapy were heterogeneous, and exact timing of the priapism episodes was not measured precisely. In this setting, further prospective randomised trials are needed prior to the recommendation of antithrombotic agents for treatment or adjunctive therapy in the management of ischaemic priapism [1308].

Table 36: Medical treatment of ischaemic priapism

Drug	Dose/Instructions for use
Phenylephrine	<ul style="list-style-type: none">• Intracavernous injection of 200 μg every 3-5 minutes.• Maximum dosage is 1 mg within 1 hour.• Lower doses are recommended in children and patients with severe cardiovascular diseases.
Etilephrine	<ul style="list-style-type: none">• Intracavernosal injection at a concentration of 2.5 mg in 1-2 mL normal saline.
Methylene blue	<ul style="list-style-type: none">• Intracavernous injection of 50-100 mg, left for 5 minutes. It is then aspirated and the penis compressed for an additional 5 minutes.
Adrenaline	<ul style="list-style-type: none">• Intracavernous injection of 2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period.
Terbutaline	<ul style="list-style-type: none">• Oral administration of 5 mg for priapism lasting more than 2.5 hours, after intracavernous injection of vasoactive agents.

Management of priapism related to sickle cell disease

The Panel conducted a systematic review on the overall management of priapism related to sickle cell disease. Unfortunately, few studies were conducted exclusively on patients with SCD and studies on mixed populations usually did not report separate data on SCD patients. Clear and systematic reporting of patient characteristics, interventions and outcomes was lacking, and the length of follow-up, if reported, varied significantly among the studies. Overall, the quality of studies was deemed poor for high-quality, evidence-based recommendations.

Urgent intervention is essential (LE: 4) and the general approach is similar to that described for other cases of ischaemic priapism and should be co-ordinated with a haematologist [1295, 1309, 1310] (LE: 4).

However, as with other haematological disorders, other therapeutic interventions may also need to be implemented [1309-1311]. Specific measures for SCD-related priapism include intravenous hydration and narcotic analgesia while preparing the patient for aspiration and irrigation. Additionally, supplemental oxygen administration and alkalinisation with bicarbonate can be helpful [1260, 1295].

Haemoglobin S (HbS) percentage should be measured in all SCD patients with acute priapism. Exchange blood transfusion has also been proposed, with the aim of increasing tissue delivery of oxygen [1312]. The transfused blood should be sickle cell haemoglobin negative and Rh and Kell antigen matched [1313]. However, the evidence is inconclusive as to whether exchange transfusion itself helps to resolve priapism. A systematic review reported that the mean time to detumescence was eleven days with exchange transfusions compared to eight days with conventional treatment. Moreover, there were 9 cases of ASPEN syndrome (association of sickle cell disease, priapism, exchange transfusion and neurological events) as a consequence of blood transfusion [1314].

Consensus recommendation: exchange transfusion should not be used as a primary treatment for ischaemic priapism in patients with SCD.

Several reports suggest that exchange transfusion may result in serious neurological sequelae [1314], although a series of 10 patients with SCD-related priapism showed that it was safe to perform exchange transfusion [1312]. Because of these considerations, routine use of exchange transfusion is not recommended as a primary treatment intervention in this group unless there is a risk of SCD-related symptoms (LE: 4). However, in patients who fail medical management, transfusion may be required to enable general anaesthesia to be safely administered prior to definitive surgery [1315].

9.1.3.2 Surgical management

Evidence acquisition

The majority of the identified studies for surgical management were retrospective and non-randomised. A significant proportion of the reports were case series reporting on one or two particular types of surgical procedures, often with low patient numbers (< 20) (Appendix 2). The studies showed a wide variation in data, including the proportion of patients who had prior conservative management, reporting of initial success, and duration of follow-up. Surgical complications were also not consistently reported. The systematic review captured specific end points of priapism resolution, sexual function and surgical adverse events when reported. However, due to the heterogeneity of the data, direct comparisons of success rates and long-term outcomes should be treated with caution.

9.1.3.2.1 Second-line treatments

Second-line intervention typically refers to surgical intervention in the form of penile shunt surgery and penile implant insertion for refractory or delayed ischaemic priapism, and should only be considered when other conservative management options fail (LE: 4). There is no evidence detailing the time frames before moving on to surgery after first-line treatment, although a period of at least 1 hour of first-line treatment without detumescence can be considered prior to moving to surgical intervention (LE: 4).

A number of clinical indicators suggest failure of first-line treatment including continuing corporal rigidity, cavernosal acidosis, anoxia, severe glucopenia, absence of cavernosal artery inflow by penile colour duplex US, and elevated intracorporal pressure [1316]. Colour duplex US of the penis in the ischaemic state may be helpful but it should be noted that blood flow may persist in the tumescent phase of erection [1317] (LE: 4).

9.1.3.2.1.1 Penile shunt surgery

Penile shunt surgery aims to produce an outflow for ischaemic blood from the corpus cavernosum thereby allowing restoration of normal circulation within these structures. Accordingly, a shunt creates an opening in the tunica albuginea, with either the glans, corpus spongiosum, or a vein for blood drainage (Table 37) [1243, 1279, 1318].

The type of shunt procedure is chosen according to the surgeon's preference and familiarity with the procedure. It is conventional for distal shunt procedures to be tried before considering proximal shunting (LE: 4). Gadolinium-enhanced penile MRI [1275] and cavernosal smooth muscle biopsy have been used to diagnose smooth muscle necrosis (which, if present, would suggest that shunting is likely to fail) and may help in decision-making and patient counselling in cases of refractory or delayed presentation (> 48 hours) that may be considered for immediate penile prosthesis insertion (see below).

It is important to assess the success of surgery by direct observation of penile rigidity or by repeated testing (e.g., cavernous blood gas testing) (LE: 4) [1243, 1279, 1319, 1320]. The use of penile colour US may not give appropriate information because of the hyperaemic (reperfusion) period that follows decompression after the ischaemic state [1317].

The recovery rates of erectile function in men undergoing shunt surgery following prolonged episodes of priapism are low and are directly related to the duration of priapism, pre-operative erectile status and age [1319-1321]. The exact duration of priapism for shunt surgery to preserve erectile function is not based on studies with high levels of evidence. If ischaemic priapism resolves within 24 hours of onset, it has been reported that 78- 100% of patients regain spontaneous functional erections (with or without PDE5Is use). In contrast, other studies have shown that priapism for more than 36-48 hours appears to result in both structural and functional effects on corporal smooth muscle, with poorer outcomes (ED > 90%) [1319, 1322]. In general, shunt procedures undertaken after this time period (36-48 hours) may only serve to limit pain without any beneficial effects on erectile function and early prosthesis insertion can be considered [1250, 1323].

Four categories of shunt procedures have been reported [1243, 1280, 1318, 1323]. The limited available data preclude any overall recommendation for one procedure over another based upon outcomes, but distal shunts are less invasive and associated with lower rates of post-operative ED and therefore are recommended as the first surgical intervention of choice (Table 37) (LE: 4).

Percutaneous distal (corpora-glanular) shunts

Winter's procedure uses a Trucut biopsy needle to create a fistula between the glans penis and each corpus cavernosum [1243, 1257, 1280, 1317, 1324] (LE: 3). Post-operative sequelae are uncommon [1325]. Winter's shunt is easy to perform, but has been reported as the least successful operation to create a distal shunt [1320]. This is because the diameter of the Trucut needle is only 1.6 mm (14-18 g) and therefore cannot accommodate the increased blood flow from post-ischaemic hyperaemia, resulting in poor drainage, increased intracavernous pressure and consequent premature closure of the shunt [1317].

Ebbehoj's technique involves making multiple tunical incision windows between the glans and each tip of the corpus cavernosum by means of a size 11 blade scalpel passed several times percutaneously [1243, 1280, 1317, 1326, 1327] (LE: 3).

T-Shunt involves performing a bilateral procedure using a scalpel with a size 10 blade inserted through the glans just lateral to the urethral meatus until it enters the tip of the corpus cavernosum. The blade is then rotated 90° away (to the lateral side) from the urethral meatus and withdrawn [1243, 1280, 1317, 1328] (LE: 3). If unsuccessful, the procedure is repeated on the opposite side. The T-shunt can be followed by a tunnelling procedure using a size 8/10 Hegar dilator inserted through the glans and into the corpus cavernosum, which can also be performed using US guidance, mainly to avoid urethral injury [1328]. The entry sites in the glans are sutured following detumescence. Tunnelling with a 7 mm metal sound or 7/8 Hegar dilator is necessary in patients with priapism duration > 48 hours. Tunnelling is a potentially attractive procedure as it combines the features of distal and proximal shunts with proximal drainage of the corpus cavernosum and may ameliorate the profibrotic effect of sludged blood retained in the corpus cavernosum [1321, 1323, 1328].

Open distal (corpora-glanular) shunts

Al-Ghorab's procedure consists of an open bilateral excision of circular cone segments of the distal tunica albuginea via the glans penis, along with subsequent glans closure by running suture with absorbable material. A transverse incision on the glans may compromise arterial blood flow because distal deep dorsal arteries run longitudinally in the glans [1243, 1280, 1317, 1329-1331] (LE: 3).

Burnett's technique (Snake manoeuvre) is a modification of the Al-Ghorab corpora-glanular shunt. It involves retrograde insertion of a 7/8 Hegar dilator into the distal end of each corpus cavernosum through the original Al-Ghorab glanular excision. After removal of the dilator from the corpus cavernosum, blood evacuation is facilitated by manual compression of the penis sequentially from a proximal to distal direction. After detumescence, the glans penis is closed as in the Al-Ghorab procedure [1243, 1280, 1317, 1332, 1333] (LE: 3). Reported complications include wound infection, penile skin necrosis and urethrocutaneous fistulae [1333].

Table 37: Distal shunt procedures in ischaemic priapism

Study	N: (shunt/shunt + tunnelling)	Duration of priapism (shunt/shunt + tunnelling)	Type of surgery	Detumescence rate (shunt/shunt + tunnelling)	Post-operative ED rate (shunt/shunt + tunnelling)
Ercole <i>et al.</i> [1329]	7 (7/0)	2.6 d / NA	Al-Ghorab	100% / NA	57% / NA
Macaluso <i>et al.</i> [1325]	12 (12/0)	58 h / NA	Winter	100% / NA	17% / NA
Nixon <i>et al.</i> [1320]	14 (14/0)	42 h / NA	Winter	14% / NA	90% / NA
Lund <i>et al.</i> [1327]	18 (18/0)	20 h to 8 months/NA	Ebbehoj	61% / NA	39% / NA
Brant <i>et al.</i> [1328]	13 (6/7)	50 h / 80 h	T-shunt/T-shunt + tunnelling	46% / 92%	16% / 57%
Segal <i>et al.</i> [1333]	10 (0/10)	NA / 60 h	Al-Ghorab + tunnelling	NA / 80%	NA / 40%
Zacharakis <i>et al.</i> [1323]	45 (0/45)	NA / 96 h	T-shunt + tunnelling	NA / 64%	NA / 93%
Ortaç <i>et al.</i> [1321]	19 (6/13)	48h / 70h	T-shunt/T-shunt + tunnelling	31% / 94%	83% / 85%
Summary	138 (63/75)	52h / 76h		60% / 82%	50% / 68%

ED = erectile dysfunction; h = hours; d = days.

Open proximal (corpora-spongiosal) shunts

Quackles's technique uses a trans-scrotal or perineal approach; a proximal open shunt technique creates a communication between the corpus cavernosum and the corpus spongiosum. The most frequent complications include an unwanted urethro-cavernous fistula and urethral stricture or cavernositis [1243, 1280, 1318, 1334]. The risk of urethral injury is less with a perineal approach to the bulb of the corpus spongiosum (LE: 3). Proximal shunts are more invasive and ED rates are documented to be higher [1316].

Peno-scrotal decompression

More recently a proximal decompression technique with the aim to spare the glans with high success rates has been described. The technique is based upon opening of the proximal corpus cavernosum combined with proximal and distal tunnelling using a suction tip [1335]. In a cohort of 25 patients, 12 had undergone previous corporoglanular shunt surgery. Recurrence was observed in two of 25 patients with unilateral peno-scrotal decompression. In the 15 patients who had follow-up data, 40% had ED.

Anti-thrombotic agents

Procedures for shunting require incision through the tunica albuginea and expose collagen to coagulation factors in the penile blood and thus activate the blood-clotting cascade. Peri-operative anti-coagulation is advocated to facilitate resolution of the priapism. There was an 84% decrease in priapism recurrence in the shunt group that received peri-procedural anti-thrombotic treatment (325 mg acetylsalicylic acid pre-operatively, and 5000 IU intraoperative heparin, post-operatively for 5 days (81 mg acetylsalicylic acid and 75 mg clopidogrel) compared with the group that did not receive peri-procedural anti-thrombotic treatment after failed aspiration [1308].

Vein anastomoses/shunts

Grayhack's procedure mobilises the saphenous vein below the junction of the femoral vein and anastomoses the vein end-to-side onto the corpus cavernosum. Venous shunts may be complicated by saphenofemoral thrombus formation and by pulmonary embolism [1243, 1280, 1336-1338] (LE: 3).

Immediate penile prosthesis implantation

The literature pertaining to penile implantation surgery is shown in Appendix 3. The studies identified here were principally retrospective non-randomised case series. In all but one study, patients had prior non-surgical management. All of the studies described priapism resolution rate, sexual function and surgical adverse events although the follow-up period was variable.

Refractory, therapy-resistant, acute ischaemic priapism or episodes lasting more than 48 hours usually result in complete ED, possibly along with significant penile deformity in the long-term. In these cases, immediate penile prosthesis surgery is advocated [1339-1342] (LE: 3).

The immediate insertion of a malleable penile prosthesis is recommended to avoid the difficulty and complications of delayed prosthetic surgery in the presence of corporal fibrosis. Potential complications that could compromise immediate penile prosthesis implantation include distal erosion and infection [1339, 1341], along with a small rate of revision surgery [1339]. Early surgery also offers the opportunity to maintain penile length and girth and prevent penile curvature due to cavernosal fibrosis. The prosthesis can be exchanged for an inflatable prosthesis at a later date, which may allow upsizing of the implant cylinders [1343].

Currently, there are no clear indications for immediately implanting a penile prosthesis in men with acute ischaemic priapism [1279].

Consensus recommendation [1243] (LE: 4):

Relative indications include:

- Ischaemia that has been present for more than 48 hours;
- Failure of aspiration and sympathomimetic intracavernous injections in delayed priapism (> 48 hours);
- Magnetic resonance imaging or corporal biopsy evidence of corporal smooth muscle necrosis [1243, 1339] (LE: 4);
- Failure of a shunting procedure (although in delayed cases (> 48 hours), implantation might be considered ahead of shunt surgery);
- Refractory priapism in patients who have undergone shunting procedures.

The optimal time for implantation is within first three weeks from the priapism episode [1250, 1316, 1344]. If shunt surgery has been performed, penile prosthesis implantation can be further delayed in order to allow reduction of oedema, wound healing and risk of prosthetic infection. A vacuum device to avoid fibrosis and penile shortening may be used during this waiting period [1345].

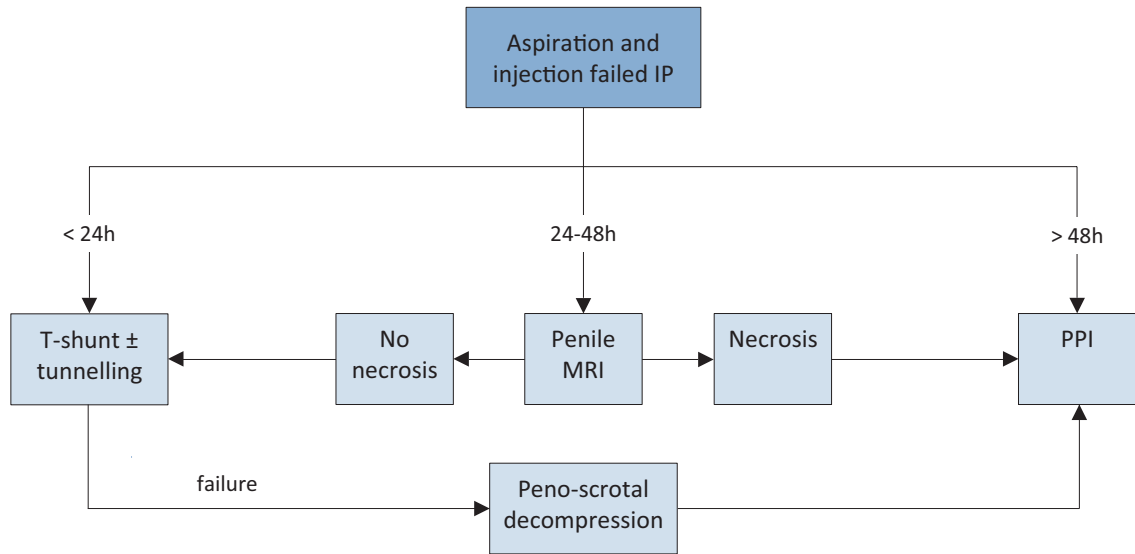
The decision on which type of implant to insert is dependent on patient suitability, surgeons' experience, and availability and cost of the equipment. There are no randomised trials comparing the efficacy and complication rate of malleable and inflatable penile prostheses. Despite the higher infection rate in priapism patients compared to those with virgin prosthesis, in patients who are well-motivated and counselled prior to the procedure, immediate inflatable penile prosthesis implantation may be undertaken, although in most cases a semi-rigid implant is more suitable as it is easier to implant and reduces operative time and hence the risk of prosthetic infection. A further issue with immediate insertion of an inflatable penile prosthesis is that the patient must begin cycling the device immediately to avoid a fibrous capsule forming and contracting. Early cycling of an inflatable penile prosthesis prevents penile curvature and shortening [1250].

Surgery for non-acute sequelae after ischaemic priapism

Structural changes may occur after ischaemic priapism including cavernosal tissue necrosis and fibrosis with consequent penile scarring, megalophallic deformities, penile shortening, and occasional penile loss [1318, 1339, 1346, 1347]. Erectile dysfunction is also often observed [1243, 1348]. Unfortunately, these outcomes can still occur despite apparently successful first-line or second-line treatment in detumescence of the penis.

Penile prosthesis implantation is occasionally indicated in SCD patients with severe ED because other therapeutic options, such as PDE5Is and intracavernous injections are avoided as they may provoke a further priapism event [1243, 1279]. In severe corporal fibrosis, narrow-based prosthetic devices are preferable because they are easier to insert and need less dilatation [1339] (LE: 3). After severe priapism that has resulted in penile destruction with complicated deformities or even loss of penile tissue, it may be necessary to make changes to the surgical technique. Multiple corporotomies, corporal excavation, optical corporotomy-Shaeer technique, dilatation with Carrion-Rosello cavernotome, Uramix or Mooreville cavernotome, excision of scar tissue, and use of small-diameter prosthesis, or penile reconstruction using grafts can be utilised, if concomitant prosthesis implantation is considered [1322, 1349] (LE: 3). Early implantation of a penile prosthesis is associated with lower infection rates (6-7% vs. 19-30%), penile shortening (3 vs. 40%) and revision rates (9 vs. 27%) compared to late insertion. General satisfaction rate for early implantation is higher (96%) than for late implantation (60%) [1250] (Appendix 4).

Figure 14: Algorithm on surgical management of priapism



MRI - Magnetic resonance imaging; PPI = penile prosthesis implantation.

9.1.4 Summary of evidence for treatment of ischaemic priapism

Summary of evidence	LE
Emergency intervention for ischaemic priapism is mandatory.	2b
The aim of treatment is to facilitate painless penile detumescence, to prevent chronic fibrosis of the corpus cavernosum.	3
Erectile function preservation is directly related to the duration of ischaemic priapism, age and pre-operative erectile status.	2b
Phenylephrine is the recommended drug due to its favourable safety profile in the cardiovascular system compared to other drugs. Phenylephrine is usually diluted in normal saline with a concentration of 100-500 µg/mL and given in 200 µg doses every three to five minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within one hour. Patients at high cardiovascular risk should be given lower doses. Patient monitoring is highly recommended.	2b
Gadolinium-enhanced MRI may be useful to diagnose smooth muscle necrosis in cases of delayed or refractory priapism.	3
Shunt procedures are effective to resolve priapism and provide pain relief. No clear recommendation of the superiority of one type of shunt over another can be given. Distal shunts are less invasive and associated with lower rate of erectile dysfunction.	2b
Peri- and post-operative anticoagulant prophylaxis (325 mg acetylsalicylic acid pre-operatively, 5,000 IU heparin intra-operatively and 81 mg acetylsalicylic acid and 75 mg clopidogrel five days post-operatively) may prevent priapism recurrence.	3
Erectile dysfunction is almost inevitable in prolonged cases or ischaemic priapism. Early implantation of penile prosthesis is associated with lower infection rates and complications compared to late implantation.	2b

9.1.5 Recommendations for the treatment of ischaemic priapism

Recommendations	Strength rating
Start management of ischaemic priapism as early as possible (within 4 to 6 hours) and follow a stepwise approach.	Strong
First, decompress the corpus cavernosum by penile aspiration and washout until fresh red blood is obtained.	Strong
In priapism secondary to intracavernous injections of vasoactive agents, replace blood aspiration with intracavernous injection of a sympathomimetic drug as the first step.	Strong
In priapism that persists despite aspiration, proceed to the next step, which is intracavernous injection of a sympathomimetic drug.	Strong

In cases that persist despite aspiration and intracavernous injection of a sympathomimetic drug, repeat these steps before considering surgical intervention.	Strong
Treat ischaemic priapism associated with sickle cell disease in the same fashion as idiopathic ischaemic priapism. Provide other supportive measures (intravenous hydration, oxygen administration with alkalinisation with bicarbonate, blood exchange transfusions), but do not delay initial treatment to the penis.	Strong
Proceed to surgical treatment only when blood aspiration and intracavernous injection of sympathomimetic drugs have failed.	Strong
Perform distal shunt surgical procedures first and combine them with tunnelling if necessary.	Weak
Proximal procedures may be used in cases of distal shunt failure (< 48 hours) or in patients who do not wish to proceed with immediate penile implant insertion.	Weak
Peri- and post-operative anticoagulation may decrease priapism recurrence.	Weak
A penile prosthesis may be preferred over proximal shunting particularly in delayed (> 48 hours) or refractory priapism.	Weak
Implantation of a prosthesis may be considered in delayed presentation (> 48 hours) and in those cases refractory to injection therapy and distal shunting.	Weak
If a shunt has been performed, then implantation of a penile prosthesis should be delayed to minimise the risk of infection and erosion of the implant.	Strong
The decision on which type of implant to insert is dependent on patient suitability, surgeons' experience and availability and cost of the equipment. If malleable penile prosthesis is implanted it can be later exchanged to an inflatable penile implant.	Strong
Patients must be fully counselled regarding the risks and benefits of implant insertion in every case of delayed presentation of refractory priapism.	Weak

9.2 Priapism in Special Situations

9.2.1 **Stuttering (recurrent or intermittent) priapism**

9.2.1.1 *Epidemiology/aetiology/pathophysiology*

Robust epidemiological studies of stuttering priapism are lacking [1350, 1351]. However, recurrent priapism episodes are common in men with SCD (42-64%) [1352, 1353] while in adolescents and young men the incidence of priapism is 35%, of whom 72% have a history of stuttering priapism [1350].

The aetiology of stuttering priapism is similar to that of ischaemic priapism. Whilst SCD is the most common cause, idiopathic cases and cases due to a neurological disorder have been reported. Men who have acute ischaemic priapism, especially which has been prolonged (for more than 4 hours) are at risk of developing stuttering priapism [1348].

Several studies have proposed alternative mechanisms for stuttering priapism including inflammation, cellular adhesion, NO metabolism, vascular reactivity and coagulation [1243, 1261, 1295, 1354, 1355]. Specifically, a deficiency in endothelial NO causes downregulation in a cyclic guanosine monophosphate (cGMP)-dependent protein kinase and PDE5, resulting in dysregulation in the corporal smooth muscle tone [1356]. Furthermore, decreased NO availability decreases RhoA (Ras homolog gene family) and Rho-kinase, which are important factors for penile detumescence, and disrupts adenosine signalling [1357]. The lack of mechanisms to regulate cGMP, along with reduced vasoconstriction, reduce cavernosal smooth muscle tone, leading to an increased and disproportionate response to stimuli. Adenosine, like NO, is a potent vasodilator and regulator of penile tumescence. It is increased in conditions of stress, hypoxia and ischaemia, suggesting an important role in the pathogenesis of the priapic state [1358]. Finally, although debated, androgens have also been observed to have an association with priapism [1359]. Androgens play an important role in the mediation of erections both centrally and peripherally. They are known to contribute toward the regulatory basis of both NO synthase and PDE5 expression and activity in various structures of the local erectile apparatus [1360]. Therefore, one of the options for the treatment of stuttering priapism is to reduce serum testosterone levels to hypogonadal levels, which then suppresses androgen-associated mechanisms believed to be involved in triggering recurrent priapism.

9.2.1.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of stuttering priapism

Summary of evidence	LE
Stuttering priapism is similar to ischaemic priapism in that it is low-flow and ischaemic and, if left untreated, can result in significant penile fibrosis, with SCD being the most common cause.	3

9.2.1.2 Classification

Stuttering priapism, also termed intermittent or recurrent priapism, is a distinct condition that is characterised by repetitive and painful episodes of prolonged erections. Erections are self-limiting with intervening periods of detumescence [1295, 1354]. These are analogous to repeated episodes of ischaemic priapism. In stuttering priapism the duration of the erections is generally shorter than in ischaemic priapism [1280]. The frequency and/or duration of these episodes is variable and a single episode can sometimes progress into prolonged ischaemic priapism.

9.2.1.3 Diagnostic evaluation

9.2.1.3.1 History

A comprehensive history is mandatory and follows the same principles as described in Table 33. There is a history of recurrent episodes of prolonged erections. These episodes can occur from several daily to isolated incidents every few months, continuously or followed by incident-free periods, of unknown duration, even months and years [1361]. The onset of the priapic episodes usually occurs during sleep and detumescence does not occur upon waking. These episodes can be painful and may be the reason that the patient first seeks medical attention. Priapism can cause significant impairment of mental health with patients experiencing sadness, embarrassment, fear, and exhaustion [1362].

9.2.1.3.2 Physical examination

Erections are painful and the penis is rigid as in ischaemic priapism, but the duration of events is usually shorter. Between erections the penis is usually normal, but in some cases signs of fibrosis can be found. Rarely, the penis may become enlarged, a condition known as megalophallus.

9.2.1.3.3 Laboratory testing

Laboratory testing follows the same principles as in the two other types of priapism. It is recommended to identify possible causes and should be directed by the history and clinical and laboratory findings.

9.2.1.3.4 Penile imaging

There are no specific findings on imaging for stuttering priapism. Colour duplex US of the penis and perineum and MRI are recommended and can differentiate non-ischaemic from ischaemic forms of priapism.

9.2.1.3.5 Recommendations for diagnosis of stuttering priapism

The same recommendations as described in Section 9.1.2.5 apply. Stuttering priapism is a recurrent or intermittent type of ischaemic priapism.

9.2.1.4 Disease management

The primary goal in the management of patients with stuttering priapism is the prevention of further episodes and limiting the chances of developing a prolonged ischaemic priapism that is refractory to conventional treatment options. In most cases, stuttering priapism can be managed by pharmacological treatment, the aim of which is to reduce the frequency and severity of stuttering episodes. The management of each acute episode is similar to that for ischaemic priapism; aspiration/irrigation in combination with intracavernous injections of α -adrenergic agonists. Unfortunately, the efficacy and safety of the various treatment modalities suggested over the medical literature are poorly reported. Specifically, most reports are from small case series and the Panel is not aware of any published, well-designed, controlled studies on the efficacy and safety of these treatments [1260, 1295, 1354, 1361].

9.2.1.4.1 α -Adrenergic agonists

Studies of oral α -adrenergic agonists have suggested some prophylactic benefit for daily treatment with these agents [1363]. Adverse effects include tachycardia and palpitations. Pseudoephedrine is widely used as an oral decongestant and can be a first-line treatment option for stuttering priapism [1305]. However, its effect on corporal smooth muscle is not fully understood. Etilephrine has been used successfully to prevent stuttering priapism caused by SCD. It is usually taken orally at doses of 5-10 mg daily, with response rates of up to 72% [1364-1366]. In one randomised, placebo-controlled clinical study comparing medical prophylaxis with etilephrine and ephedrine, there was no difference in efficacy between the two drugs.

9.2.1.4.2 Hormonal manipulations of circulating testosterone

The aim of hormonal manipulation is to down-regulate circulating testosterone levels to suppress the action of androgens on penile erection [1260, 1295, 1367]. This can be achieved by GnRH agonists or antagonists, antiandrogens or oestrogens [1368, 1369] (LE: 4). Potential adverse effects may include hot flushes, gynaecomastia, ED, loss of libido, and asthenia. All approaches have a similar efficacy profile (LE: 4) while the

potential cardiovascular toxicity of oestrogens limits their clinical use. Alternative endocrine approaches that have been used with some success include 5- α -reductase inhibitors [1370, 1371] (LE: 3) and ketoconazole; an anti-fungal agent that reduces adrenal and testicular androgen production [1367, 1372] (LE: 4).

The duration of hormonal treatment for effective suppression of recurrent priapism is problematic. It is not possible to draw any conclusions on the dose, duration of treatment and the efficacy. Caution is strongly advised when prescribing hormonal treatments to pre-pubertal boys and adolescents, and specialist advice from paediatric endocrinologists should be sought. Likewise, hormonal agents have a contraceptive effect and interfere with normal sexual maturation and spermatogenesis and affect fertility. Therefore men who are trying with their partner to conceive should be comprehensively counselled before using hormonal treatment. Moreover, sperm cryopreservation may be considered to mitigate any potential effects of anti-androgen therapy on fertility.

9.2.1.4.3 Digoxin

Digoxin is a cardiac glycoside and positive inotrope that is used to treat congestive heart failure. Digoxin regulates smooth muscle tone through several different pathways leading to penile detumescence [1260, 1295, 1373]. The use of maintenance digoxin doses (0.25-0.5 mg/daily) in idiopathic stuttering priapism reduces the number of hospital visits and improves quality of life [1295]. In a small, clinical, double-blind, placebo-controlled study, digoxin decreased sexual desire and excitement with a concomitant reduction in penile rigidity, regardless of any significant change in plasma levels of testosterone, oestrogens and LH [1373] (LE: 2b). Adverse effects include decreased libido, anorexia, nausea, vomiting, confusion, blurred vision, headache, gynaecomastia, rash and arrhythmia.

9.2.1.4.4 Terbutaline

Terbutaline is a β -agonist that causes vasodilation, resulting in vascular smooth muscle relaxation [1260, 1295] and has been used to prevent stuttering priapism with detumescence rates of 36% in patients with alprostadil-induced priapism [1305] (LE: 3). The only randomised, placebo-controlled study (n = 68) in patients with pharmacologically-induced priapism, demonstrated detumescence in 42% of the terbutaline-treated group compared to only 15% in the placebo-treated group [1306] (LE: 1b). Adverse effects include nervousness, shakiness, drowsiness, palpitations, headache, dizziness, hot flushes, nausea and weakness.

9.2.1.4.5 Gabapentin

Gabapentin has anticonvulsant, antinociceptive and anxiolytic properties and is widely used as an analgesic and anti-epileptic agent. Its proposed mechanism of action is to inhibit voltage-gated calcium channels, which attenuates synaptic transmission [1367], and reduces testosterone and FSH levels [1374]. It is given at a dose of 400 mg, four times daily, up to 2,400 mg daily, until complete penile detumescence occurs, with subsequent maintenance administration of 300 mg/daily [1375] (LE: 4). Adverse effects include anorgasmia and impaired erectile function.

9.2.1.4.6 Baclofen

Baclofen is a gamma-aminobutyric acid (GABA) derivative that acts as a muscle relaxant and anti-muscle spasm agent. It can inhibit penile erection and ejaculation through GABA activity and prevents recurrent reflexogenic erections or prolonged erections from neurological diseases [1260]. Oral baclofen has little efficacy and it is not usually used in stuttering priapism but intrathecal administration is more effective [1295, 1376-1378] (LE: 4). Adverse effects include drowsiness, confusion, dizziness, weakness, fatigue, headache, hypotension and nausea.

9.2.1.4.7 Hydroxyurea

Hydroxyurea blocks the synthesis of deoxyribonucleic acid (DNA) by inhibiting ribonucleotide reductase, which has the effect of arresting cells in the S-phase [1367, 1379]. Hydroxyurea is an established treatment for ameliorating SCD and improving life expectancy [1309, 1380]. For patients with recurrent priapism, there is limited evidence to suggest a prophylactic role of hydroxyurea (LE: 3), [1367, 1379, 1381]. Adverse effects include oligo-zoospermia and leg ulcers.

9.2.1.4.8 Phosphodiesterase type 5 inhibitors

Low doses of PDE5Is have a paradoxical effect in alleviating and preventing stuttering priapism; mainly in patients with idiopathic and SCD-associated priapism [1260, 1295, 1356, 1382-1386] (LE: 3). It is important to remember that therapy should be started when the penis is in its flaccid state and not during an acute episode. There is a delay of one week before treatment is effective. There are no reported impairments in male sexual function (LE: 3). Phosphodiesterase type 5 inhibitors treatment of stuttering priapism is possibly mediated by an increase in the concentration of cGMP in the smooth muscle in an NO dysfunctional state. This can occur

in priapism and may result in a change in the NO pathway, with down-regulation of cavernosal PDE5 thereby preventing the complete degradation of cGMP in the corpus cavernosum [1260, 1295, 1356, 1382].

9.2.1.4.9 Intracavernosal injections

Some patients with stuttering priapism, who have been started on systemic treatment to prevent recurrence of unwanted erections, may not see therapeutic benefits immediately and temporarily require intracavernous self-injections at home with sympathomimetic agents [1260, 1295]. The most commonly used drugs are phenylephrine and etilephrine (as described in the treatment of ischaemic priapism) [1243, 1280, 1351, 1365] (LE: 3). Adverse effects include hypertension, coronary ischaemia and cardiac arrhythmias.

Tissue plasminogen activator (TPA) is a secreted serine protease that converts the pro-enzyme plasminogen to plasmin, which acts as a fibrinolytic enzyme. Limited clinical data have suggested that a single intracavernous injection of TPA can successfully treat patients with recalcitrant priapism [1367, 1387] (LE: 3). Mild bleeding is the most commonly observed adverse effect.

9.2.1.4.10 Penile prosthesis

Patients with medically refractory stuttering priapism require frequent visits to the emergency department and are always at risk of a major ischaemic episode, which can be mitigated with insertion of a penile prosthesis [1342, 1388, 1389]. Nevertheless, penile prosthesis for preventing stuttering priapism should not be offered before medical treatment and a penile prosthesis should be performed only in carefully selected patients as a last resort [1389]. In patients with permanent ED due to stuttering priapism, medical treatments for ED (PDE5Is or intracavernosal injection) should be used cautiously because of the risk of inducing an ischaemic episode and a penile prosthesis can be considered [1389, 1390].

9.2.1.5 Summary of evidence for treatment of stuttering priapism

Summary of evidence	LE
The primary goal in the management of patients with stuttering priapism is prevention of future episodes, which can generally be achieved pharmacologically.	2b
Phosphodiesterase type 5 inhibitors have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease-associated priapism.	3
The evidence with other systemic drugs (digoxin, α -adrenergic agonists, baclofen, gabapentin and terbutaline, hydroxyurea) is limited.	3

9.2.1.6 Recommendations for treatment of stuttering priapism

Recommendations	Strength rating
Manage each acute episode similar to that for ischaemic priapism.	Strong
Use hormonal therapies (mainly gonadotropin-receptor hormone agonists or antagonists) and/or antiandrogens for the prevention of future episodes in patients with frequent relapses. Do not use them before sexual maturation is reached.	Weak
Initiate treatment with phosphodiesterase type 5 inhibitors only when the penis is in its flaccid state.	Weak
Use digoxin, α -adrenergic agonists, baclofen, gabapentin or terbutaline only in patients with frequent and uncontrolled relapses.	Weak
Use intracavernous self-injections of sympathomimetic drugs at home for treatment of acute episodes on an interim basis until ischaemic priapism has been alleviated.	Weak

9.2.1.7 Follow-up

Follow-up for stuttering priapism includes history and clinical examination to assess the efficacy of treatment in preventing or alleviating erectile events as well as assessing erectile function and penile fibrosis.

9.2.2 Priapism in children

The classification of priapism in children is similar to that in adults. In addition to ischaemic, stuttering and non-ischaemic priapism, a fourth type, neonatal priapism is also described [1243]. Priapism in children is considered rare as no data on its prevalence exist. Sickle cell disease is the major cause of priapism in children, followed by leukaemia (10%), trauma (10%), idiopathic causes (19%) and drugs (5%) [1391]. One study showed that 25% of children experienced SCD-related priapism in a pre-pubertal period [1392]. Another

study revealed that 90% of men with SCD had their first priapism episode before age 20 years [1353]. Priapism in children should be evaluated and treated in a timely manner, as untreated ischaemic priapism may lead to ED and psychosexual disorders in adulthood [1393]. A multi-disciplinary team approach should be utilised with specialist input from haematologists and paediatric endocrinologists.

9.3 Non-ischaemic (high-flow or arterial) priapism

Most of the identified studies were small retrospective case series reporting principally on the role of embolisation in post-traumatic non-ischaemic priapism (Appendix 5). This may reflect the uncommon nature of the condition. Success rates and erectile function were well documented across all reports. Some studies attempted to stratify outcomes based on the agent used for embolisation (e.g., microcoil or autologous clot), although care should be taken when interpreting case series with small patient numbers.

9.3.1 Epidemiology/aetiology/pathophysiology

Epidemiological data on non-ischaemic priapism are almost exclusively derived from small case series [1243, 1274, 1276, 1394, 1395]. Non-ischaemic priapism is significantly less common than the ischaemic type, comprising only 5% of all priapism cases [1243]. The most frequent cause of non-ischaemic priapism is blunt perineal or penile trauma [1396]. The injury results in a laceration in the cavernosal artery or branches, leading to a fistula between the artery and the lacunar spaces of the sinusoidal space [1395]. The resultant increased blood flow results in a persistent and prolonged erection [1397].

There is often a delay between the trauma and the development of the priapism that may be up to two to three weeks [1398]. This is suggested to reflect either spasm or ischaemic necrosis of the injured artery, with the fistula only developing as the spasm resolves or when the ischaemic segment “blows up”. The priapism typically occurs after a nocturnal erection or an erection related to sexual activity, resulting in the sudden increase of blood flow and pressure in the cavernous arteries [1399]. The patient typically reports an erection that is not fully rigid and is not associated with pain because the venous drainage is not compromised and the penile tissue does not become ischaemic [1400].

Non-ischaemic priapism can occur after acute spinal cord injury, presumably due to loss of sympathetic input, leading to predominant parasympathetic input and increased arterial flow [1401]. It has also been reported to occur following internal urethrotomy [1402], Nesbit procedure [1403], circumcision [1404], transrectal prostate biopsy [1405], and brachytherapy for prostate cancer [1406]. Some cases have also been described following shunting procedures performed for ischaemic priapism due to a lacerated cavernosal artery (conversion of low-flow to high-flow priapism) [1407-1409]. Although SCD is usually associated with ischaemic priapism, occasional cases of high-flow priapism have been reported; however, the pathophysiological mechanism remains unclear [1410]. Finally, metastatic malignancy to the penis can also rarely cause non-ischaemic priapism [1411, 1412] (Table 38).

Table 38: Causes of arterial priapism

Perineal or penile trauma
Spinal cord injury
Iatrogenic causes (e.g., shunting procedure for ischaemic priapism)
Sickle cell disease
Metastatic malignancy to the penis
Idiopathic

9.3.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of arterial priapism

Summary of evidence	LE
Non-ischaemic priapism is significantly less common than ischaemic priapism.	2b
Non-ischaemic priapism usually occurs after blunt perineal or penile trauma.	2
Non-ischaemic priapism if not treated may cause erectile dysfunction with time.	3

9.3.2 Classification

Non-ischaemic priapism is a persistent erection caused by unregulated cavernous arterial inflow [1243]. According to aetiology, non-ischaemic priapism can be categorised into four types: traumatic, neurogenic, iatrogenic and idiopathic in origin.

9.3.3 **Diagnostic evaluation**

9.3.3.1 *History*

A comprehensive history is mandatory in non-ischaemic priapism diagnosis and follows the same principles as described in Table 33. Arterial priapism should be suspected when the patient reports a history of pelvic, perineal, or genital trauma; no penile pain (discomfort is possible); and a persistent, not fully rigid erection (Table 34). The corpus cavernosum can become fully rigid with sexual stimulation, so the sexual intercourse is usually not compromised. The onset of post-traumatic non-ischaemic priapism can be delayed by several hours to weeks following the initial injury [1243].

9.3.3.2 *Physical examination*

In non-ischaemic priapism, the corpora are tumescent but not fully rigid. Abdominal, penile and perineal examination may reveal evidence of trauma (Table 34) [1243]. Neurological examination is indicated if a neurogenic aetiology is suspected.

9.3.3.3 *Laboratory testing*

Laboratory testing should include a blood count with white blood cell differential and a coagulation profile to assess for anaemia and other haematological abnormalities. Blood aspiration from the corpus cavernosum shows bright red arterial blood in arterial priapism, while blood is dark in ischaemic priapism (Table 34) (LE: 2b). Blood gas analysis is essential to differentiate between non-ischaemic and ischaemic priapism. Blood gas values in high-flow priapism show normal arterial blood [1243] (Table 35).

9.3.3.4 *Penile imaging*

Colour duplex US of the penis and perineum is recommended and can differentiate non-ischaemic from ischaemic priapism [1272-1274]. Ultrasound must be performed without intracavernosal vasoactive drug injection [1413]. In non-ischaemic priapism, US helps to localise the fistula site and appears as a characteristic colour blush and turbulent high-velocity flow on Doppler analysis [1414]. Patients with non-ischaemic priapism have normal to high blood velocities in the cavernous arteries [1245, 1415].

Selective pudendal arteriography can reveal a characteristic blush at the site of injury in arterial priapism [1416, 1417]. However, due to its invasiveness, it should be reserved for the management of non-ischaemic priapism when embolisation is being considered [1243, 1268].

The role of MRI in the diagnostic evaluation of priapism is controversial. Its role in non-ischaemic priapism is limited because the small penile vessels and fistulae cannot be easily demonstrated [1418].

9.3.3.5 *Recommendations for the diagnosis of non-ischaemic priapism*

Recommendations	Strength rating
Take a comprehensive history to establish the diagnosis, which can help to determine the priapism subtype.	Strong
Include a physical examination of the genitalia, perineum and abdomen in the diagnostic evaluation.	Strong
Include a neurological examination if neurogenic non-ischaemic priapism is suspected.	Strong
For laboratory testing, include complete blood count, with white blood cell differential, and coagulation profile.	Strong
Analyse the blood gas parameters from blood aspirated from the penis to differentiate between ischaemic and non-ischaemic priapism.	Strong
Perform colour duplex ultrasound of the penis and perineum for differentiation between ischaemic and non-ischaemic priapism.	Strong
Perform selected pudendal arteriography when embolisation is planned for non-ischaemic priapism.	Strong

9.3.4 **Disease management**

Although the conventional belief is that the management of non-ischaemic priapism is not an emergency because the corpus cavernosum does not contain ischaemic blood, recent data indicate that the duration of non-ischaemic priapism can also effect erectile function. High-flow priapism was reproduced in an *in vitro* model using pre-contracted strips of rabbit corpus cavernosum superfused at high pO₂ levels. This showed that the smooth muscle tone reduced by 43% after super-fusion for twelve hours, indicating irreversible smooth muscle dysfunction [1419]. In a case series consisting of six patients with high-flow priapism after

median follow-up of 4.5 (2-12) weeks, all patients reported development of ED or distal penile flaccidity [1420]. The goal of treatment is closure of the fistula. Non-ischaemic priapism can be managed conservatively or by direct perineal compression. Failure of conservative treatment requires selective arterial embolisation [1421]. The optimal time interval between conservative treatment and arterial embolisation is still under debate. Definitive management can be performed at the discretion of the treating physician and should be discussed with the patients so that they can understand the risks of treatment [1243, 1268].

9.3.4.1 Conservative management

Conservative management may include applying ice to the perineum or perineal compression, which is typically US-guided. The fistula occasionally closes spontaneously. Even in those cases where the fistula remains patent, intercourse is still possible [1274, 1394, 1422, 1423]. Androgen deprivation therapy (e.g., leuprolide injections, bicalutamide and ketoconazole) has been reported in case series to enable closure of the fistula reducing spontaneous and sleep-related erections [1424]. However, sexual dysfunction due to these treatments must be considered. Patients may develop ED or distal penile flaccidity while undergoing conservative treatment [1420].

Blood aspiration is not helpful for the treatment of arterial priapism and the use of α -adrenergic antagonists is not recommended because of potential severe adverse effects (e.g., such as transfer of the drug into the systemic circulation).

9.3.4.2 Selective arterial embolisation

Selective arterial embolisation can be performed using temporary substances, such as autologous blood clot [1425-1427] and gel foam [1426, 1428], or permanent substances such as microcoils [1426, 1428-1430], ethylene-vinyl alcohol copolymer (PVA), and N-butyl-cyanoacrylate (NBCA) [1431]. It is assumed that temporary embolisation provides a decreased risk of ED, with the disadvantage of higher failure/recurrence rates; this would be the consequence of artery recanalisation using temporary materials. However, there is insufficient evidence to support this hypothesis. A recent non-systematic review of the literature reported success rates ranging between 61.7 and 83.3%, and ED rates from 0 to 33.3% after the first arterial embolisation, showing that failure/recurrence may not be significantly higher with temporary embolisation materials, and preservation of erectile function may not be that different between the two modalities either [1399]. Other potential complications of arterial embolisation include penile gangrene, gluteal ischaemia, cavernositis, and perineal abscess [1243, 1432]. Repeated embolisation is a reasonable option for treating non-ischaemic priapism, both in terms of efficacy and safety [1399].

9.3.4.3 Surgical management

Surgical ligation of the fistula is possible through a transcorporeal or inguinoscrotal approach, using intra-operative Doppler US. Surgery is technically challenging and associated with significant risks, particularly of ED [1433]. Surgery is rarely performed and should only be considered when there are contraindications for selective embolisation, if embolisation is unavailable, or repeated embolisations have failed. If the patient desires more definitive treatment and is not sexually active or has pre-existing ED, surgical intervention can be an appropriate option [1399]. Erectile dysfunction rates ranging from 0 to 50% are reported following non-ischaemic priapism and its treatment, with surgical ligation having the highest reported rates [1399]. Patients can require penile prosthesis implantation for ED in the long-term [1322].

9.3.4.4 Summary of evidence for the treatment of arterial priapism

Summary of evidence	LE
Non-ischaemic priapism can cause erectile dysfunction over time and early definitive management should be undertaken.	3
Conservative management applying ice to the perineum or site-specific perineal compression is an option in all cases. The use of androgen deprivation therapy may enable closure of the fistula reducing spontaneous and sleep-related erections.	3
Selective artery embolisation, using temporary or permanent substances, has high success rates. No definitive statement can be made on the best substance for embolisation in terms of sexual function preservation and success rate.	3
Repeated embolisation is a reasonable option for the treatment of non-ischaemic priapism.	2b
Selective surgical ligation of the fistula should be reserved as the last treatment option when multiple embolisations have failed.	3

9.3.4.5 Recommendations for the treatment of arterial priapism

Recommendations	Strength rating
Because non-ischaemic priapism is not an emergency, perform definitive management at the discretion of the treating physician.	Weak
Manage conservatively with the use of site-specific perineal compression as the first step. Consider androgen deprivation therapy only in adults.	Weak
Perform selective arterial embolisation when conservative management has failed.	Strong
Perform first selective arterial embolisation using temporary material.	Weak
Repeat the procedure with temporary or permanent material for recurrent non ischaemic priapism following selective arterial embolisation.	Weak
Reserve selective surgical ligation of a fistula as a final treatment option when repeated arterial embolisations have failed.	Weak

9.3.4.6 High-flow priapism in children

Non-ischaemic priapism is a rare condition, especially in children. The embarrassment that children may have in speaking about it to their parents can lead to misdiagnosis and underestimating the prevalence of this condition [1434]. The aetiology, clinical presentation and diagnostic and therapeutic principles are comparable with those of arterial priapism in adults. However, some differentiating features should be noted.

Idiopathic non-ischaemic priapism can be found in a significant percentage of children [1435]. Perineal compression with the thumb may be a useful manoeuvre to distinguish ischaemic and non-ischaemic priapism, particularly in children, where it may result in immediate detumescence, followed by the return of the erection with the removal of compression [1399]. Conservative management using ice applied to the perineum or site-specific perineal compression may be successful, particularly in children [1436, 1437]. Although reportedly successful, embolisation in children is technically challenging and requires treatment within a specialist paediatric vascular radiology department [1284, 1438].

9.3.4.7 Follow-up

During conservative management of non-ischaemic priapism, physical examination and colour duplex US can be useful tools to assess treatment efficacy. Close follow-up using colour duplex US and MRI can help detect distal penile fibrosis and be beneficial in clinical decision-making to intervene with embolisation earlier [1420]. Follow-up after selective arterial embolisation should include clinical examination, colour duplex US, and erectile function assessment. If in doubt, repeat arteriography is required. The goals are to determine if the treatment was successful, identify signs of recurrence, and verify any anatomical and functional sequelae [1413].

9.4 Controversies and future areas of focus in the management of priapism

Low-flow priapism should be considered as a surgical emergency. Although the treatment of high-flow priapism can be delayed, there is some evidence to suggest that a delay in intervention may result in long-term fibrosis of the corpus cavernosum.

The evidence in the literature mainly consists of retrospective single centre cohort studies and therefore is of low quality, and prospective multicentre studies are needed to develop high levels of evidence to support contemporary guidelines.

There are a number of controversial areas including the prophylaxis of stuttering priapism, with no real evidence suggesting the superiority of a single pharmaceutical agent over another. In particular understanding of the time point at which irreversible corporal smooth muscle necrosis occurs due to low-flow priapism is limited; therefore, definitive management of delayed or refractory priapism remains controversial (i.e., immediate prosthesis implantation vs. penoscrotal decompression vs. shunting). Therefore, it is strongly recommended that multi-centre collaborative studies are performed to better understand this rare but devastating condition.

10. MALE INFERTILITY

10.1 Definition and classification

Infertility is defined by the inability of a sexually active, non-contraceptive couple to achieve spontaneous pregnancy within 1 year [1439]. Primary infertility refers to couples that have never had a child and cannot achieve pregnancy after at least 12 consecutive months having sex without using birth control methods. Secondary infertility refers to infertile couples who have been able to achieve pregnancy at least once before (with the same or different sexual partner). Recurrent pregnancy loss is distinct from infertility and is defined as two or more failed pregnancies [1440, 1441].

10.2 Epidemiology/aetiology/pathophysiology/risk factors

10.2.1 Introduction

About 15% of couples do not achieve pregnancy within 1 year and seek medical treatment for infertility. One in eight couples encounter problems when attempting to conceive a first child and one in six when attempting to conceive a subsequent child [1442]. In 50% of involuntarily childless couples, a male-infertility-associated factor is found, usually together with abnormal semen parameters [1439]. For this reason, all male patients belonging to infertile couples should undergo medical evaluation by a urologist trained in male reproduction.

Male fertility can be impaired as a result of [1439]:

- congenital or acquired urogenital abnormalities;
- gonadotoxic exposure (e.g., radiotherapy or chemotherapy);
- malignancies;
- urogenital tract infections;
- increased scrotal temperature (e.g., as a consequence of varicocele);
- endocrine disturbances;
- genetic abnormalities;
- immunological factors.

In 30-40% of cases, no male-associated factor is found to explain impairment of sperm parameters and historically was referred to as idiopathic male infertility. These men present with no previous history of diseases affecting fertility and have normal findings on physical examination and endocrine, genetic and biochemical laboratory testing, although semen analysis may reveal pathological findings (see Section 10.3.2). Unexplained male infertility is defined as infertility of unknown origin with normal sperm parameters and partner evaluation. Between 20 and 30% of couples will have unexplained infertility. It is now believed that idiopathic male infertility may be associated with several previously unidentified pathological factors, which include but are not limited to endocrine disruption as a result of environmental pollution, generation of reactive oxygen species (ROS)/sperm DNA damage, or genetic and epigenetic abnormalities [1443].

Advanced paternal age has emerged as one of the main risk factors associated with the progressive increase in the prevalence of male factor infertility [1444-1451]. Likewise, advanced maternal age must be considered over the management of every infertile couple, and the consequent decisions in the diagnostic and therapeutic strategy of the male partner [1452, 1453]. Therefore, this should include the age and ovarian reserve of the female partner, since these parameters might determine decision-making in terms of timing and therapeutic strategies (e.g., assisted reproductive technology [ART] versus surgical intervention) [1444-1447]. Table 39 summarises the main male-infertility-associated factors.

Table 39: Male infertility causes and associated factors and percentage of distribution in 10,469 patients
[1454]

Diagnosis	Unselected patients (n = 12,945)	Azoospermic patients (n = 1,446)
All	100%	11.2%
Infertility of known (possible) cause	42.6%	42.6%
Maldescended testes	8.4	17.2
Varicocele	14.8	10.9
Sperm auto-antibodies	3.9	-
Testicular tumour	1.2	2.8
Others	5.0	1.2
Idiopathic infertility	30.0	13.3

<i>Hypogonadism</i>	10.1	16.4
Klinefelter syndrome (47, XXY)	2.6	13.7
XX male	0.1	0.6
Primary hypogonadism of unknown cause	2.3	0.8
Secondary (hypogonadotropic) hypogonadism	1.6	1.9
Kallmann syndrome	0.3	0.5
Idiopathic hypogonadotropic hypogonadism	0.4	0.4
Residual after pituitary surgery	< 0.1	0.3
Late-onset hypogonadism	2.2	-
Constitutional delay of puberty	1.4	-
Others	0.8	0.8
<i>General/systemic disease</i>	2.2	0.5
<i>Cryopreservation due to malignant disease</i>	7.8	12.5
Testicular tumour	5.0	4.3
Lymphoma	1.5	4.6
Leukaemia	0.7	2.2
Sarcoma	0.6	0.9
<i>Disturbance of erection/ejaculation</i>	2.4	-
Obstruction	2.2	10.3
Vasectomy	0.9	5.3
Cystic fibrosis (congenital bilateral absence of vas deferens)	0.5	3.0
Others	0.8	1.9

CBAVD = Congenital bilateral absence of the vas deferens.

10.2.2 Recommendations on epidemiology and aetiology

Recommendations	Strength rating
Investigate both partners simultaneously to categorise the cause of infertility.	Strong
Infertility should be evaluated after 6 months of attempted conception when the female partner is aged > 35 years.	Weak
Examine all men seeking medical help for fertility problems, including men with abnormal semen parameters for urogenital abnormalities.	Strong

10.3 Diagnostic work-up

Focused evaluation of male patients must always be undertaken and should include: a medical and reproductive history; physical examination; semen analysis – with strict adherence to World Health Organization (WHO) reference values for human semen characteristics [1455], and hormonal evaluation. Other investigations (e.g., genetic analysis and imaging) may be required depending on the clinical features and semen parameters.

10.3.1 Medical/reproductive history and physical examination

10.3.1.1 Medical and reproductive history

Medical history should evaluate any risk factors and behavioural patterns that could affect the male partner's fertility, such as lifestyle, family history (including, testicular cancer), comorbidity (including systemic diseases; e.g., hypertension, diabetes mellitus, obesity, MetS, testicular cancer, etc.), genito-urinary infections (including sexually transmitted infections), history of testicular surgery and excluding any potential known gonadotoxins [1456].

Typical findings from the history of a patient with infertility include:

- cryptorchidism (uni- or bilateral);
- testicular torsion and trauma;
- genitourinary infections;
- exposure to environmental toxins;
- gonadotoxic medications (anabolic drugs, chemotherapeutic agents, etc.);
- exposure to radiation or cytotoxic agents.

10.3.1.2 Physical examination

Focused physical examination is compulsory in the evaluation of every infertile male, including presence of secondary sexual characteristics. The size, texture and consistency of the testes must be evaluated. In clinical practice, testicular volume is assessed by Prader's orchidometer [1457]; orchidometry may overestimate testicular volume when compared with US assessment [1458]. There are no uniform reference values in terms of Prader's orchidometer-derived testicular volume, due to differences in the populations studied (e.g., geographic area, nourishment, ethnicity and environmental factors) [1457-1459]. The mean Prader's orchidometer-derived testis volume reported in the European general population is 20.0 ± 5.0 mL [1457], whereas in infertile patients it is 18.0 ± 5.0 mL [1457, 1460, 1461]. The presence of the vas deferens, fullness of epididymis and presence of a varicocele should be always determined. Likewise, palpable abnormalities of the testis, epididymis, and vas deferens should be evaluated. Other physical alterations, such as abnormalities of the penis (e.g., phimosis, short frenulum, fibrotic nodules, epispadias, hypospadias, etc.), abnormal body hair distribution and gynecomastia, should also be evaluated.

Typical findings from the physical examination of a patient with characteristics suggestive for testicular deficiency include:

- abnormal secondary sexual characteristics;
- abnormal testicular volume and/or consistency;
- testicular masses (potentially suggestive of cancer);
- absence of testes (uni-bilaterally);
- gynecomastia;
- varicocele.

10.3.2 Semen analysis

A comprehensive andrological examination is always indicated in every infertile couple. Important treatment decisions are based on the results of semen analysis and most studies evaluate semen parameters as a surrogate outcome for male fertility. However, semen analysis cannot precisely distinguish fertile from infertile men [1462]; therefore, it is essential that the complete laboratory work-up is standardised according to reference values (Table 40). Ejaculate analysis has been standardised by the WHO and disseminated by publication of the most updated version of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn) [1463]. There is consensus that modern semen analysis must follow these guidelines. However, it has also become clear from studies that more complex testing than semen analysis may be required, particularly in men belonging to couples with recurrent pregnancy loss from natural conception or ART and men with unexplained male infertility. Although definitive conclusions cannot be drawn, also given the heterogeneity of the studies, in these patients there is evidence that sperm DNA may be damaged, thus resulting in pregnancy failure [1443, 1464, 1465] (see below).

Table 40: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10^6 /ejaculate)	39 (33-46)
Sperm concentration (10^6 /mL)	15 (12-16)
Total motility (PR + NP)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (10^6 /mL)	< 1.0
Optional investigations	
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc (μ mol/ejaculate)	≥ 2.4
Seminal fructose (μ mol/ejaculate)	≥ 13
Seminal neutral glucosidase (mU/ejaculate)	≤ 20

CIs = confidence intervals; MAR = mixed antiglobulin reaction; NP = non-progressive; PR = progressive (a+b motility).

If semen analysis is normal according to WHO criteria, a single test is sufficient. If the results are abnormal on at least two tests, further andrological investigation is indicated. It is important to differentiate between the following [1463]:

- oligozoospermia: < 15 million spermatozoa/mL;
- asthenozoospermia: < 32% progressive motile spermatozoa;
- teratozoospermia: < 4% normal forms.
- None of the individual sperm parameters (e.g., concentration, morphology and motility), are diagnostic *per se* of infertility.

Often, all three anomalies occur simultaneously, which is defined as oligo-astheno-terato-zoospermia (OAT) syndrome. As in azoospermia (namely, the complete absence of spermatozoa in semen), in severe cases of oligozoospermia (spermatozoa < 5 million/mL) [1466], there is an increased incidence of obstruction of the male genital tract and genetic abnormalities. In those cases, a more comprehensive assessment of the hormonal profile may be helpful to further and more accurately differentially diagnose among pathological conditions.

In azoospermia, the semen analysis may present with normal ejaculate volume and azoospermia after centrifugation. A recommended method is semen centrifugation at 3,000 g for 15 minutes and a thorough microscopic examination by phase contrast optics at $\times 200$ magnification of the pellet. All samples can be stained and re-examined microscopically [1463]. This is to ensure that small quantities of sperm are detected, which may be potentially used for intra-cytoplasmic sperm injection (ICSI) and obviate the need for surgical intervention.

10.3.3 **Measurement of sperm DNA Fragmentation Index (DFI)**

Semen analysis is a descriptive evaluation, and may be unable to discriminate between the sperm of fertile and infertile men. Therefore, it is now apparent that sperm DNA damage may occur in men with infertility. DNA fragmentation, or the accumulation of single- and double-strand DNA breaks, is a common property of sperm, and an increase in the level of sperm DNA fragmentation has been shown to reduce the chances of natural conception. Although no studies have unequivocally and directly tested the impact of sperm DNA damage on clinical management of infertile couples, sperm DNA damage is more common in infertile men and has been identified as a major contributor to male infertility, as well as poorer outcomes following ART [1467, 1468], including impaired embryo development [1467], miscarriage, recurrent pregnancy loss [1464, 1465, 1469], and birth defects [1467]. Sperm DNA damage can be increased by several factors including hormonal anomalies, varicocele, chronic infection and lifestyle factors (e.g., smoking) [1468].

Several assays have been described to measure sperm DNA damage. It has been suggested that current methods for assessing sperm DNA integrity still do not reliably predict treatment outcomes from ART and there is controversy whether to recommend them routinely for clinical use [1468, 1470]. Of those, terminal deoxynucleotidyl transferase mediated deoxyuridine triphosphate nick end labelling (TUNEL) and the alkaline comet test (COMET) directly measure DNA damage. Conversely, sperm chromatin structure assay (SCSA) and sperm chromatic dispersion test (SCD) are indirect tools for DNA fragmentation assessment. Sperm chromatin structure assay is still the most widely studied and one of the most commonly used techniques to detect DNA damage [1471, 1472]. In SCSA, the number of cells with DNA damage is indicated by the DNA fragmentation index (DFI) [1473], whereas the proportion of immature sperm with defects in the histone-to-protamine transition is indicated by high DNA stainability [1474]. It is suggested that a threshold DFI of 30% as measured with SCSA, is associated with reduced pregnancy rates via natural conception or Intra-uterine insemination (IUI) [1472]. Furthermore, DFI values > 50% on SCSA are associated with poorer outcomes from *in vitro* fertilisation (IVF). More recently, the mean COMET score and scores for proportions of sperm with high or low DNA damage have been shown to be of value in diagnosing male infertility and providing additional discriminatory information for the prediction of both IVF and ICSI live births [1468].

Testicular sperm is reported to have lower levels of sperm DFI when compared to ejaculated sperm [1475]. Couples with elevated DNA fragmentation may benefit from combination of testicular sperm extraction (TESE) and ICSI, an approach called TESE-ICSI, which may not overcome infertility when applied to an unselected population of infertile men with untested DFI values [1472, 1475]. However, further evidence is needed to support this practice in the routine clinical setting [1475].

10.3.4 **Hormonal determinations**

In men with testicular deficiency, hypergonadotropic hypogonadism (also called primary hypogonadism) is usually present, with high levels of FSH and LH, with or without low levels of testosterone. Generally, the levels of FSH negatively correlate with the number of spermatogonia [1476]. When spermatogonia are absent or markedly diminished, FSH level is usually elevated; when the number of spermatogonia is normal,

but maturation arrest exists at the spermatocyte or spermatid level, FSH level is usually within the normal range [1476]. However, for patients undergoing TESE, FSH levels do not accurately predict the presence of spermatogenesis, as men with maturation arrest on histology can have both normal FSH and testicular volume [1477, 1478]. Furthermore men with non-obstructive azoospermia (NOA) and high levels of FSH may still harbour focal areas of spermatogenesis at the time of TESE or microdissection TESE (mTESE) [1478, 1479].

10.3.5 Genetic testing

All urologists working in andrology must have an understanding of the genetic abnormalities most commonly associated with infertility, so that they can provide correct advice to couples seeking fertility treatment. Men with low sperm counts can still be offered a reasonable chance of paternity, using IVF, ICSI and sperm extraction from the testes in cases of azoospermia. However, the spermatozoa of infertile men show an increased rate of aneuploidy, structural chromosomal abnormalities, and DNA damage, carrying the risk of passing genetic abnormalities to the next generation. Current routine clinical practice is based on the screening of genomic DNA from peripheral blood samples. However, screening of chromosomal anomalies in spermatozoa (sperm aneuploidy) is also feasible and can be performed in selected cases (e.g., recurrent miscarriage) [1480-1482].

10.3.5.1 Chromosomal abnormalities

Chromosomal abnormalities can be numerical (e.g., trisomy) or structural (e.g., inversions or translocations). In a survey of pooled data from 11 publications, including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8% [1483]. Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. In comparison, the incidence of abnormalities was 0.38% in pooled data from three series, with a total of 94,465 new-born male infants, of whom 131 (0.14%) had sex chromosomal abnormalities and 232 (0.25%) autosomal abnormalities [1483]. The frequency of chromosomal abnormalities increases as testicular deficiency becomes more severe. Patients with sperm count < 5 million/mL already show a 10-fold higher incidence (4%) of mainly autosomal structural abnormalities compared with the general population [1484, 1485]. Men with NOA are at highest risk, especially for sex chromosomal anomalies (e.g., Klinefelter syndrome) [1486, 1487].

Based on the frequencies of chromosomal aberrations in patients with different sperm concentration, karyotype analysis is currently indicated in men with azoospermia or oligozoospermia (spermatozoa < 10 million/mL) [1485]. This broad selection criterion has been recently externally validated, with the finding that the suggested threshold has a low sensitivity, specificity, and discrimination (80%, 37%, and 59%, respectively) [1488]. In this context, a novel nomogram, with a 2% probability cut-off, which allows for a more careful detection of karyotype alterations has been developed [1488]. Notwithstanding, the clinical value of spermatozoa < 10 million/mL remains a valid threshold until further studies, evaluating the cost-effectiveness, in which costs of adverse events due to chromosomal abnormalities (e.g., miscarriages and children with congenital anomalies) are performed [1489]. If there is a family history of recurrent spontaneous abortions, malformations or mental retardation, karyotype analysis should be requested, regardless of the sperm concentration.

10.3.5.1.1 Sex chromosome abnormalities (Klinefelter syndrome and variants [47,XXY; 46,XY/47,XX mosaicism])

Klinefelter syndrome is the most common sex chromosomal abnormality [1490]. Adult men with Klinefelter syndrome usually have small firm testes along with features of primary hypogonadism. The phenotype is the final result of a combination between genetic, hormonal and age-related factors [15]. The phenotype varies from that of a normally virilised male to one with the stigmata of androgen deficiency. In most cases infertility and reduced testicular volume are the only clinical features that can be detected. Leydig cell function is also commonly impaired in men with Klinefelter syndrome and thus testosterone deficiency is more frequently observed than in the general population [1491], although rarely observed during the peri-pubertal period, which usually occurs in a normal manner [15, 1492]. Rarely, more pronounced signs and symptoms of hypogonadism can be present, along with congenital abnormalities including heart and renal problems [1493].

The presence of germ cells and sperm production are variable in men with Klinefelter syndrome and are more frequently observed in mosaicism, 46,XY/47,XXY. Based on sperm fluorescence *in situ* hybridisation (FISH) studies showing an increased frequency of sex chromosomal abnormalities and increased incidence of autosomal aneuploidy (disomy for chromosomes 13, 18 and 21), concerns have been raised about the chromosomal normality of the embryos generated through ICSI [1494]. The production of 24,XY sperm has been reported in 0.9% and 7.0% of men with Klinefelter mosaicism [1495, 1496] and in 1.36-25% of men with somatic karyotype 47,XXY [1497-1500]. In patients with azoospermia, TESE or mTESE are therapeutic options as spermatozoa can be recovered in up to 50% of cases [1501, 1502]. Although the data are not unique

[1502], there is growing evidence that TESE or mTESE yields higher sperm recovery rates when performed at a younger age [1486, 1503].

Numerous healthy children have been born using ICSI without pre-implantation genetic diagnosis (PGD) although the conception of one 47,XXY foetus has been reported [1490]. Although data published so far have not reported any difference in the prevalence of aneuploidy in children conceived using ICSI in Klinefelter syndrome compared to the general population, men with Klinefelter syndrome undergoing fertility treatments should be counselled regarding the potential genetic abnormalities in their offspring.

Regular medical follow-up of men with Klinefelter syndrome is recommended as testosterone therapy may be considered if testosterone levels are in the hypogonadal range when fertility issues have been addressed [1504]. Since this syndrome is associated with several general health problems, appropriate medical follow-up is therefore advised [16, 1505, 1506]. In particular, men with Klinefelter syndrome are at higher risk of metabolic and cardiovascular diseases (CVD), including venous thromboembolism (VTE). Therefore, men with Klinefelter syndrome should be made aware of this risk, particularly when starting testosterone therapy [1507]. In addition, a higher risk of haematological malignancies has been reported in men with Klinefelter syndrome [16].

Testicular sperm extraction in peri-pubertal or pre-pubertal boys with Klinefelter syndrome aiming at cryopreservation of testicular spermatogonial stem cells is still considered experimental and should only be performed within a research setting [1508]. The same applies to sperm retrieval in older boys who have not considered their fertility potential [1509].

10.3.5.1.2 Autosomal abnormalities

Genetic counselling should be offered to all couples seeking fertility treatment (including IVF/ICSI) when the male partner has an autosomal karyotype abnormality. The most common autosomal karyotype abnormalities are Robertsonian translocations, reciprocal translocations, paracentric inversions, and marker chromosomes. It is important to look for these structural chromosomal anomalies because there is an increased associated risk of aneuploidy or unbalanced chromosomal complements in the foetus. As with Klinefelter syndrome, sperm FISH analysis provides a more accurate risk estimation of affected offspring. However, the use of this genetic test is largely limited by the availability of laboratories able to perform this analysis [1510]. When IVF/ICSI is carried out for men with translocations, PGD or amniocentesis should be performed [1511, 1512].

10.3.5.2 Cystic fibrosis gene mutations

Cystic fibrosis (CF) is an autosomal-recessive disorder [1513]. It is the most common genetic disease of Caucasians; 4% are carriers of gene mutations involving the CF transmembrane conductance regulator (CFTR) gene located on chromosome 7p. It encodes a membrane protein that functions as an ion channel and influences the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two-thirds of the epididymis. Approximately 2,000 CFTR mutations have been identified and any CFTR alteration may lead to congenital bilateral absence of the vas deferens (CBAVD). However, only those with homozygous mutations exhibit CF disease [1514]. Congenital bilateral absence of the vas deferens is a rare reason of male factor infertility, which is found 1% of infertile men and in up to 6% of men with obstructive azoospermia [1515]. Clinical diagnosis of absent vasa is easy to miss and all men with azoospermia should be carefully examined to exclude CBAVD, particularly those with a semen volume < 1.0 mL and acidic pH < 7.0 [1516-1518]. In patients with CBAVD-only or CF, testicular sperm aspiration (TESA), microsurgical epididymal sperm aspiration (MESA) or TESE with ICSI can be used to achieve pregnancy. However, higher sperm quality, easier sperm retrieval and better ICSI outcomes are associated with CBAVD-only patients compared with CF patients [1514].

The most frequently found mutations are F508, R117H and W1282X, but their frequency and the presence of other mutations largely depend on the ethnicity of the patient [1519, 1520]. Given the functional relevance of a DNA variant (the 5T allele) in a non-coding region of CFTR [1521], it is now considered a mild CFTR mutation rather than a polymorphism and it should be analysed in each CBAVD patient. As more mutations are defined and tested for, almost all men with CBAVD will probably be found to have mutations. It is not practical to test for all known mutations, because many have a low prevalence in a particular population. Routine testing is usually restricted to the most common mutations in a particular community through the analysis of a mutation panel. Men with CBAVD often have mild clinical stigmata of CF (e.g., history of chest infections). When a man has CBAVD, it is important to test also his partner for CF mutations. If the female partner is found to be a carrier of CFTR mutations, the couple must consider carefully whether to proceed with ICSI using the man's sperm, as the risk of having a child with CF or CBAVD will be 50%, depending on the type of mutations carried by the parents. If the female partner is negative for known mutations, the risk of being a carrier of unknown mutations is ~0.4% [1522].

10.3.5.2.1 Unilateral or bilateral absence/abnormality of the vas and renal anomalies

Congenital unilateral absence of the vas deferens (CUAVD) is usually associated with ipsilateral absence of the kidney and probably has a different genetic causation [1523]. Consequently, in these subjects CFTR mutation screening is not indicated. Men with CUAVD are usually fertile, and the condition is most commonly encountered as an incidental finding in the vasectomy clinic. Cystic fibrosis transmembrane conductance regulator gene mutation screening is indicated in men with unilateral absence of the vas deferens with normal kidneys. The prevalence of renal anomalies is rare for patients who have CBAVD and CFTR mutations [1524]. Abdominal US should be undertaken both in unilateral and bilateral absence of vas deferens without CFTR mutations. Findings may range from CUAVD with ipsilateral absence of the kidney, to bilateral vessel and renal abnormalities, such as pelvic kidney [1525].

10.3.5.3 Y microdeletions - partial and complete

Microdeletions on the Y-chromosome are termed AZFa, AZFb and AZFc deletions [1526]. Clinically relevant deletions remove partially, or in most cases completely, one or more of the AZF regions, and are the most frequent molecular genetic cause of severe oligozoospermia and azoospermia [1527]. In each AZF region, there are several spermatogenesis candidate genes [1528]. Deletions occur *en bloc* (i.e., removing more than one gene), it is not possible to determine the role of a single AZF gene from the AZF deletion phenotype and it is unclear if they all participate in spermatogenesis. Gene-specific deletions, which remove a single gene, have been reported only in the AZFa region and concern the USP9Y gene. These studies have suggested that USP9Y is most likely to be a “fine tuner” of sperm production, and its specific screening is not advised [1529]. It has been observed that a number of commercial laboratories can use a limited number of primer sets over the AZF a, b and c regions in their Y chromosome microdeletion assay. This can eventually miss smaller microdeletions and clinicians should be aware over the managing work-up of patients scheduled for testicular surgery [1530, 1531].

10.3.5.3.1 Clinical implications of Y microdeletions

The clinical significance of Yq microdeletions can be summarised as follows:

- They are not found in normozoospermic men, proving there is a clear cut cause-and-effect relationship between Y-deletions and spermatogenic failure [1532].
- The highest frequency of Y-deletions is found in azoospermic men (8-12%), followed by oligozoospermic (3-7%) men [1533, 1534].
- Deletions are extremely rare with a sperm concentration > 5 million/mL (~0.7%) [1535].
- AZFc deletions are most common (65-70%), followed by Y-deletions of the AZFb and AZFb+c or AZFa+b+c regions (25-30%). AZFa region deletions are rare (5%) [1536].
- Complete deletion of the AZFa region is associated with severe testicular phenotype (Sertoli cell only syndrome), while complete deletions of the AZFb region is associated with spermatogenic arrest. Complete deletions that include the AZFa and AZFb regions are of poor prognostic significance for retrieving sperm at the time of TESE and sperm is not found in these patients. Therefore, TESE should not be attempted in these patients [1537, 1538].
- Deletions of the AZFc region causes a variable phenotype ranging from azoospermia to oligozoospermia.
- Sperm can be found in 50-75% of men with AZFc microdeletions [1537-1539].
- Men with AZFc microdeletions who are oligo-zoospermic or in whom sperm is found at the time of TESE must be counselled that any male offspring will inherit the deletion.
- Classical (complete) AZF deletions do not confer a risk for cryptorchidism or testicular cancer [1535, 1540].

The specificity and genotype/phenotype correlation reported above means that Y-deletion analysis has both a diagnostic and prognostic value for testicular sperm retrieval [1540].

10.3.5.3.1.1 Testing for Y microdeletions

Historically, indications for AZF deletion screening are based on sperm count and include azoospermia and severe oligozoospermia (spermatozoa count < 5 million/mL). A recent single meta-analysis assessing the prevalence of microdeletions on the Y chromosome in oligo-zoospermic men in 37 European and North American studies (n=12,492 oligo-zoospermic men) showed that the majority of microdeletions occurred in men with sperm concentrations ≤ 1 million sperm/mL, with < 1% identified in men with > 1 million sperm/mL [1535]. In this context, while an absolute threshold for clinical testing cannot be universally given, patients may be offered testing if sperm counts are < 5 million sperm/mL, but must be tested if ≤ 1 million sperm/mL.

With the efforts of the European Academy of Andrology (EAA) guidelines and the European Molecular Genetics Quality Network external quality control programme (<http://www.emqn.org/emqn/>), Yq testing has become

more reliable in different routine genetic laboratories. The EAA guidelines provide a set of primers capable of detecting > 95% of clinically relevant deletions [1541].

10.3.5.3.1.2 Genetic counselling for AZF deletions

After conception, any Y-deletions are transmitted to the male offspring, and genetic counselling is therefore mandatory. In most cases, father and son will have the same microdeletion [1541], but occasionally the son may have a more extensive deletion [1542]. The extent of spermatogenic failure (still in the range of azoo-/oligo-zoospermia) cannot be predicted entirely in the son, due to the different genetic background and the presence or absence of environmental factors with potential toxicity on reproductive function. A significant proportion of spermatozoa from men with complete AZFc deletion are nullisomic for sex chromosomes [1543, 1544], indicating a potential risk for any offspring to develop 45,X0 Turner's syndrome and other phenotypic anomalies associated with sex chromosome mosaicism, including ambiguous genitalia [1545]. Despite this theoretical risk, babies born from fathers affected by Yq microdeletions are phenotypically normal [1540, 1541]. This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortion of embryos bearing a 45,X0 karyotype.

10.3.5.3.1.3 Y-chromosome: 'gr/gr' deletion

A new type of Yq deletion, known as the gr/gr deletion, has been described in the AZFc region [1546]. This deletion removes half of the gene content of the AZFc region, affecting the dosage of multicopy genes mapping inside this region. This type of deletion confers a 2.5-8 fold increased risk for oligozoospermia [1541, 1547-1549]. The frequency of gr/gr deletion in oligozoospermic patients is ~5% [1550].

According to four meta-analyses, gr/gr deletion is a significant risk factor for impaired sperm production [1548-1550]. It is worth noting that both the frequency of gr/gr deletion and its phenotypic expression vary among different ethnic groups, depending on the Y-chromosome background. For example, in some Y haplo-groups, the deletion is fixed and appears to have no negative effect on spermatogenesis. Consequently, the routine screening for gr/gr deletion is still a debated issue, especially in those laboratories serving diverse ethnic and geographic populations. A large multi-centre study has shown that gr/gr deletion is a potential risk factor for testicular germ cell tumours [1521]. However, these data need confirmation in an ethnically and geographically matched case-control study setting. For genetic counselling it is worth noting that partial AZFc deletions, gr/gr and b2/b3, may predispose to complete AZFc deletion in the next generation [1551].

10.3.5.3.1.4 Autosomal defects with severe phenotypic abnormalities and infertility

Several inherited disorders are associated with severe or considerable generalised abnormalities and infertility (e.g., Prader-Willi syndrome [1552], Bardet-Biedl syndrome [1553], Noonan's syndrome, Myotonic dystrophy, dominant polycystic kidney disease [1554, 1555], and 5 α -reductase deficiency [1556-1559], etc.). Pre-implantation genetic screening may be necessary in order to improve the ART outcomes among men with autosomal chromosomal defects [1560, 1561].

10.3.5.4 Sperm chromosomal abnormalities

Sperm can be examined for their chromosomal constitution using FISH both in men with normal karyotype and with anomalies. Aneuploidy in sperm, particularly sex chromosome aneuploidy, is associated with severe damage to spermatogenesis [1483, 1562-1564] and with translocations and may lead to recurrent pregnancy loss (RPL) or recurrent implantation failure [1565]. In a large retrospective series, couples with normal sperm FISH had similar outcomes from IVF and ICSI on pre-implantation genetic screening (PGS). However, couples with abnormal FISH had better clinical outcomes after PGS, suggesting a potential contribution of sperm to aneuploidic abnormalities in the embryo [1566]. In men with sperm aneuploidy, PGS combined with IVF and ICSI can increase chances of live births [1482].

10.3.5.5 Measurement of Oxidative Stress

Oxidative stress is considered to be central in male infertility by affecting sperm quality, function, as well as the integrity of sperm [1567]. Oxidative stress may lead to sperm DNA damage and poorer DNA integrity, which are associated with poor embryo development, miscarriage and infertility [1568, 1569]. Spermatozoa are vulnerable to oxidative stress and have limited capacity to repair damaged DNA. Oxidative stress is generally associated with poor lifestyle (e.g., smoking) and environmental exposure, and therefore antioxidant regimens and lifestyle interventions may reduce the risk of DNA fragmentation and improve sperm quality [1570]. However, these data have not been supported by RCTs. Furthermore, there are no standardised testing methods for ROS and the duration of antioxidant treatments. Although ROS can be measured by various assays (e.g., chemiluminescence), routine measurement of ROS testing should remain experimental until these tests are validated in RCTs [1571].

10.3.5.6 *Outcomes from assisted reproductive technology and long-term health implications to the male and offspring*

It is estimated that > 4 million babies have been born with ART since the first baby was conceived by IVF in 1978 [1572]. As the number of couples undergoing ART has increased [1573, 1574], safety concerns related to ART have been raised. Assisted reproductive technology-conceived offspring have poorer prenatal outcomes, such as lower birth weight, lower gestational age, premature delivery, and higher hospital admissions compared with naturally conceived offspring [1575, 1576]. However, the exact mechanisms resulting in these complications remain obscure. Birth defects have also been associated with children conceived via ART [1577-1579]. Meta-analyses have shown a 30-40% increase in major malformations linked with ART [1580-1582]. However, debate continues as to whether the increased risk of birth defects are related to parental age, ART or the intrinsic defects in spermatogenesis in infertile men [1583-1588].

As for the long-term outcomes, post-natal growth patterns are mostly not associated with ART [1577, 1589, 1590]. However, a number of studies have shown that ART children are taller [1591, 1592]. This may be important as there is evidence showing that rapid weight gain during early childhood is linked with higher blood pressure levels in children conceived via ART [1593]. It is also suggested that ART-conceived children have similar childhood illnesses and hospital services rates as compared with naturally conceived children [1594-1596]. Some studies have shown an increased risk of retinoblastoma [1597] and hepatoblastoma in children after ART. However, these studies have been challenged with other studies that have not supported these findings [1598]. The current evidence for cancer risk in children conceived with ART is inadequate and further studies are warranted [1599, 1600]. Finally, several epigenetic alterations seem to be caused by ART, which might be the molecular basis to some complex traits and diseases [1601].

10.3.6 *Imaging in the infertile men*

In addition to physical examination, a scrotal US may be helpful in: (i) measuring testicular volume; (ii) assessing testicular anatomy and structure in terms of US patterns, thus detecting signs of testicular dysgenesis often related to impaired spermatogenesis (e.g., non-homogeneous testicular architecture and microcalcifications) and testicular tumours; and, (iii) finding indirect signs of obstruction (e.g., dilatation of rete testis, enlarged epididymis with cystic lesions, or absent vas deferens) [1458]. In clinical practice, Prader's orchidometer-derived testicular volume is considered a reliable surrogate of US-measured testicular volume, easier to perform and cost-effective [1457]. Nevertheless, scrotal US has a relevant role in testicular volume assessment when Prader's orchidometer is unreliable (e.g., large hydrocele, inguinal testis, epididymal enlargement/fibrosis, thickened scrotal skin; small testis, where the epididymis is large in comparison to the total testicular volume [1457, 1458]). Ultrasound-patterns of testicular inhomogeneity [1602, 1603] is usually associated with ageing, although it has also been reported in association with testicular atrophy and fibrosis [1458]. At present, a diagnostic testicular biopsy is not recommended when testicular inhomogeneity is detected [1602, 1603].

10.3.6.1 *Scrotal US*

Scrotal US is widely used in everyday clinical practice in patients with oligo-zoospermia or azoospermia, as infertility has been found to be an additional risk factor for testicular cancer [1604, 1605]. It can be used in the diagnosis of several diseases causing infertility including testicular neoplasms and varicocele.

10.3.6.1.1 *Testicular neoplasms*

In one study, men with infertility had an increased risk of testicular cancer (hazard ratio [HR] 3.3). When infertility was refined according to individual semen parameters, oligo-zoospermic men had an increased risk of cancer compared with fertile control subjects (HR 11.9) [1606]. In a recent systematic review infertile men with testicular microcalcification (TM) were found to have an ~18-fold higher prevalence of testicular cancer [1607]. However, the utility of US as a routine screening tool in men with infertility to detect testicular cancer remains a matter of debate [1604, 1605].

One issue in undertaking routine screening for testicular neoplasms in this cohort of patients is the risk of overdiagnosis and the increased detection of indeterminate lesions of the testis. These testicular lesions are often detected during the diagnostic work-up of infertile men and are difficult to characterise as benign or malignant based only upon US criteria, including size, vascularity and echogenicity.

A dichotomous cut-off of certainty in terms of lesion size that may definitely distinguish benign from malignant testicular masses is currently not available. However, in a study with 81 patients with a lesion size < 10 mm, on histology showed that 56 (69%) were benign lesions, although one-third were malignant. All lesions < 5 mm in diameter were benign [1608]. Available data suggest that the smaller the nodule, the less likely that it is malignant [1609], and lesions < 5 mm could be monitored, as they have a low probability of malignancy.

Small hypoechoic/hyperechoic areas may be diagnosed as intra-testicular cysts, focal Leydig cell hyperplasia, fibrosis and focal testicular inhomogeneity after previous pathological conditions. Hence, they require careful periodic US assessment and follow-up, especially if additional risk factors for malignancy are present (i.e., infertility, bilateral TM, history of cryptorchidism, testicular atrophy, inhomogeneous parenchyma, history of testicular tumour, history of/contralateral tumour) [1458].

In the case of interval growth of a lesion and/or the presence of additional risk factors for malignancy, testicular biopsy/surgery may be considered, although the evidence for adopting such a management policy is limited. In 145 men referred for azoospermia who underwent US before testicular biopsy, 49 (34%) had a focal sonographic abnormality; a hypoechoic lesion was found in 20 patients (14%), hyperechoic lesions were seen in 10 patients (7%); and, a heterogeneous appearance of the testicular parenchyma was seen in 19 patients (13%). Of 18 evaluable patients, 11 had lesions < 5 mm; all of which were confirmed to be benign. All other patients with hyperechoic or heterogeneous areas on US with subsequent tissue diagnoses were found to have benign lesions. The authors concluded that men with severe infertility who have incidental testicular lesions, negative tumour markers and lesions < 5 mm may be observed with serial scrotal US examinations and enlarging lesions or those of greater dimension can be considered for histological biopsy [1610].

Other studies have suggested that if a testicular lesion is hyperechoic and non-vascular on colour Doppler US and associated with negative tumour markers, the likelihood of malignancy is low and consideration can be given to regular testicular surveillance, as an alternative to radical surgery. In contrast, hypoechoic and vascular lesions are more likely to be malignant [1611-1615]. However, most lesions cannot be characterised by US (indeterminate), and histology remains the only certain diagnostic tool. A multidisciplinary team discussion (MDT), including invasive diagnostic modalities, should therefore be considered in these patients.

The role of US-guided intra-operative frozen section analysis in the diagnosis of testicular cancer in indeterminate lesions remains controversial, although several authors have proposed its value in the intra-operative diagnosis of indeterminate testicular lesions [1616]. Although the default treatment after patient counselling and MDT discussion may be radical orchidectomy, an US-guided biopsy with intra-operative frozen section analysis may be offered as an alternative to radical orchidectomy and potentially obviate the need for removal of the testis in a patient seeking fertility treatment. In men who have severe abnormalities in semen parameters (e.g., azoospermia), a concurrent mTESE can also be performed at the time of diagnostic biopsy (Panel recommendations).

In summary, if an indeterminate lesion is detected incidentally on US in an infertile man, MDT discussion is highly recommended. Based upon the current literature, lesions < 5mm in size are likely to be benign and serial US and self-examination can be performed. However, men with larger sized lesions (> 5mm), which are hypoechoic or demonstrate vascularity, may be considered for open US-guided testicular biopsy, testis sparing surgery with tumour enucleation for frozen section examination or radical orchidectomy. Therefore, in making a definitive treatment decision for surveillance vs. intervention, consideration should be given to the size of the lesion, echogenicity, vascularity and previous history (e.g., cryptorchidism, previous history of germ cell tumour [GCT]). If intervention is to be undertaken in men with severe hypospermatogenesis (e.g., azoospermia), then a simultaneous TESE can be undertaken, along with sperm banking.

10.3.6.1.2 Varicocele

At present, the clinical management of varicocele is still mainly based on physical examination; nevertheless, scrotal colour Doppler US is useful in assessing venous reflux and diameter, when palpation is unreliable and/or in detecting recurrence/persistence after surgery [1458]. Definitive evidence of reflux and venous diameter may be utilised in the decision to treat (Refer to Section 10.4.3.1 and 10.4.3.2).

10.3.6.1.3 Other

Scrotal US is able to detect changes in the proximal part of the seminal tract led due to obstruction. Especially for CBAVD patients, scrotal US is a favourable option to detect the abnormal appearance of the epididymis. Given that, three types of epididymal findings are described in CBAVD patients: tubular ectasia (honeycomb appearance), meshwork pattern, and complete or partial absence of the epididymis [1617, 1618].

10.3.6.2 Transrectal US

For patients with a low seminal volume, acidic pH and severe oligozoospermia or azoospermia, in whom obstruction is suspected, scrotal and transrectal US are of clinical value in detecting CBAVD and presence or absence of the epididymis and/or seminal vesicles (SV) (e.g., abnormalities/agenesis). Likewise, transrectal US (TRUS) has an important role in assessing obstructive azoospermia (OA) secondary to CBAVD or anomalies

related to the obstruction of the ejaculatory ducts, such as ejaculatory duct cysts, seminal vesicular dilatation or hypoplasia/atrophy, although retrograde ejaculation should be excluded as a differential diagnosis [1458, 1619].

10.3.7 Recommendations for the diagnostic work-up of male infertility

Recommendations	Strength rating
Include a parallel assessment of the fertility status, including ovarian reserve, of the female partner during the diagnosis and management of the infertile male, since this might determine decision making in terms of timing and therapeutic strategies (e.g., assisted reproductive technology (ART) versus surgical intervention).	Strong
A complete medical history, physical examination and semen analysis are the essential components of male infertility evaluation.	Strong
Prader's orchidometer-derived testicular volume is a reliable surrogate of ultrasound (US)-measured testicular volume in everyday clinical practice.	Weak
Perform semen analyses according to the WHO Laboratory Manual for the Examination and Processing of Human Semen (5 th edn.) indications and reference criteria.	Strong
Perform a full andrological assessment in all men with couple infertility, particularly when semen analysis is abnormal in at least two consecutive tests.	Strong
Include counselling for infertile men or men with abnormal semen parameters of the associated health risks.	Weak
In cases of oligozoospermia and azoospermia, a hormonal evaluation should be performed, including a serum total testosterone and Follicle Stimulating Hormone /Luteinising Hormone.	Weak
Offer standard karyotype analysis and genetic counselling to all men with azoospermia and oligozoospermia (spermatozoa < 10 million/mL) for diagnostic purposes.	Strong
Do not test for Y-chromosome microdeletions in men with pure obstructive azoospermia as spermatogenesis will be normal.	Strong
Y-chromosome microdeletion testing may be offered in men with sperm concentrations of < 5 million sperm/mL, but must be mandatory in men with sperm concentrations of ≤ 1 million sperm/mL.	Strong
Inform men with Yq microdeletion and their partners who wish to proceed with intracytoplasmic sperm injection (ICSI) that microdeletions will be passed to sons, but not to their daughters.	Strong
Testicular sperm extraction (any type) should not be attempted in patients with complete deletions that include the aZFa and aZFb regions, since they are a poor prognostic indicator for retrieving sperm at surgery.	Strong
In men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal agenesis), test the man and his partner for cystic fibrosis transmembrane conductance regulator gene mutations, which should include common point mutations and the 5T allele.	Strong
Provide genetic counselling in all couples with a genetic abnormality found on clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	Strong
For men with Klinefelter syndrome, offer long-term endocrine follow-up and appropriate medical treatment.	Strong
Do not routinely use reactive oxygen species testing in the diagnosis and management of the male partner of an infertile couple.	Weak
Sperm DNA fragmentation testing should be performed in the assessment of couples with recurrent pregnancy loss from natural conception and ART or men with unexplained infertility.	Strong
Perform scrotal ultrasound in patients with infertility, as there is a higher risk of testis cancer.	Weak
A multidisciplinary team discussion concerning invasive diagnostic modalities (e.g., US-guided testicular biopsy with frozen section versus radical orchidectomy versus surveillance) should be considered in infertile men with US-detected indeterminate testicular lesions, especially if additional risk factors for malignancy are present.	Weak
Perform transrectal ultrasound if a partial or complete distal obstruction is suspected.	Strong
Consider imaging for renal abnormalities in men with structural abnormalities of the vas deferens and no evidence of cystic fibrosis transmembrane conductance regulator abnormalities.	Strong

10.4 Special Conditions and Relevant Clinical Entities

10.4.1 Cryptorchidism

Cryptorchidism is the most common congenital abnormality of the male genitalia; at 1 year of age nearly 1% of all full-term male infants have cryptorchidism [1620]. Approximately 30% of undescended testes are non-palpable and may be located within the abdominal cavity. These guidelines will only deal with management of cryptorchidism in adults.

10.4.1.1 Classification

The classification of cryptorchidism is based on the duration of the condition and the anatomical position of the testes. If the undescended testis has been identified from birth then it is termed congenital while diagnosis of acquired cryptorchidism refers to men that have been previously noted to have testes situated within the scrotum. Cryptorchidism is categorised on whether it is bilateral or unilateral and the location of the testes (inguinal, intra-abdominal or ectopic).

Studies have shown that treatment of congenital and acquired cryptorchidism results in similar hormonal profiles, semen analysis and testicular volumes [1621, 1622]. However, testicular volume and hormonal function are reduced in adults treated for congenital bilateral cryptorchidism compared to unilateral cryptorchidism [1623].

10.4.1.1.1 Aetiology and pathophysiology

It has been postulated that cryptorchidism may be a part of the so-called testicular dysgenesis syndrome (TDS), which is a developmental disorder of the gonads caused by environmental and/or genetic influences early in pregnancy, including exposure to endocrine disrupting chemicals. Besides cryptorchidism, TDS includes hypospadias, reduced fertility, increased risk of malignancy, and Leydig/Sertoli cell dysfunction [1624]. Cryptorchidism has also been linked with maternal gestational smoking [1625] and premature birth [1626].

10.4.1.1.2 Pathophysiological effects in maldescended testes

10.4.1.1.2.1 Degeneration of germ cells

The degeneration of germ cells in maldescended testes is apparent even after the first year of life and varies, depending on the position of the testes [1627]. During the second year, the number of germ cells declines. Early treatment is therefore recommended (surgery should be performed within the subsequent year) to conserve spermatogenesis and hormone production, as well as to decrease the risk for tumours [1628]. Surgical treatment is the most effective. Meta-analyses on the use of medical treatment with GnRH and hCG have demonstrated poor success rates [1629, 1630]. It has been reported that hCG treatment may be harmful to future spermatogenesis; therefore, the Nordic Consensus Statement on treatment of undescended testes does not recommend its use on a routine basis [1631]. See also the EAU Guidelines on Paediatric Urology [1632].

There is increasing evidence to suggest that in unilateral undescended testis, the contralateral normal descended testis may also have structural abnormalities, including smaller volume, softer consistency and reduced markers of future fertility potential (spermatogonia/tubule ratio and dark spermatogonia) [1621, 1633]. This implies that unilateral cryptorchidism may affect the contralateral testis and patients and parents should be counselled appropriately.

10.4.1.1.2.2 Relationship with fertility

Semen parameters are often impaired in men with a history of cryptorchidism [1634]. Early surgical treatment may have a positive effect on subsequent fertility [1635]. In men with a history of unilateral cryptorchidism, paternity is almost equal (89.7%) to that in men without cryptorchidism (93.7%). In men with bilateral cryptorchidism, oligozoospermia can be found in 31% and azoospermia in 42%. In cases of bilateral cryptorchidism, the rate of paternity falls to 35-53% [1636]. It is also important to screen for hypogonadism, as this is a potential long-term sequelae of cryptorchidism and could contribute to impaired fertility and potential problems such as testosterone deficiency and MetS [1637].

10.4.1.1.2.3 Germ cell tumours

As a component of the TDS, cryptorchidism is a risk factor for testicular cancer and is associated with testicular microcalcifications and intratubular germ cell neoplasia *in situ* (GCNIS), formerly known as carcinoma *in situ* (CIS) of the testes. In 5-10% of testicular cancers, there is a history of cryptorchidism [1638]. The risk of a germ cell tumour is 3.6-7.4 times higher than in the general population and 2-6% of men with a history of cryptorchidism will develop a testicular tumour [1620]. Orchidopexy performed before the onset of puberty has been reported to decrease the risk of testicular cancer [1639]. However, there is evidence to suggest that even men who undergo early orchidopexy still harbour a higher risk of testicular cancer than men without cryptorchidism [1640]. Therefore all men with a history of cryptorchidism should be warned that they are at

increased risk of developing testicular cancer and should perform regular testicular self-examination [1641]. There is also observational study data suggesting that cryptorchidism may be a risk factor for worsening clinical stage of seminoma but this needs to be substantiated with future prospective studies [1642].

10.4.1.2 Disease management

10.4.1.2.1 Hormonal treatment

Human chorionic gonadotropin or GnRH is not recommended for the treatment of cryptorchidism in adulthood. Although some studies have recommended the use of hormonal stimulation as an adjunct to orchidopexy to improve fertility preservation, there is a lack of long-term data and concerns regarding impairment to spermatogenesis with the use of these drugs [1643].

10.4.1.2.2 Surgical treatment

In adolescence, removal of an intra-abdominal testis (with a normal contralateral testis) can be recommended, because of the risk of malignancy [1644]. In adults, with a palpable undescended testis and a normal functioning contralateral testis (i.e., biochemically eugonadal), an orchidectomy may be offered as there is evidence that the undescended testis confers a higher risk of GCNIS and future development of GCT [1645] and regular testicular self-examination is not an option in these patients. In patients with unilateral undescended testis (UDT) and impaired testicular function on the contralateral testis as demonstrated by biochemical hypogonadism and/or impaired sperm production (infertility), an orchidopexy may be offered to preserve androgen production and fertility. However, multiple biopsies of the UDT are recommended at the time of orchidopexy to exclude intra-testicular GCNIS as a prognostic indicator of future development of GCT (Panel consensus opinion). As indicated above, the correction of bilateral cryptorchidism, even in adulthood, can lead to sperm production in previously azoospermic men and therefore may be considered in these patients or in patients who place a high value on fertility preservation [1646]. Vascular damage is the most severe complication of orchidopexy and can cause testicular atrophy in 1-2% of cases. In men with non-palpable testes, the post-operative atrophy rate was 12% in cases with long vascular pedicles that enabled scrotal positioning. Post-operative atrophy in staged orchidopexy has been reported in up to 40% of patients [1647]. At the time of orchidectomy in the treatment of GCT, biopsy of the contralateral testis should be offered to patients at high risk for GCNIS (i.e., history of cryptorchidism, < 12 mL testicular volume, poor spermatogenesis [1648]).

10.4.1.3 Summary of evidence recommendations for cryptorchidism

Summary of evidence	LE
Cryptorchidism is multifactorial in origin and can be caused by genetic factors and endocrine disruption early in pregnancy.	2a
Cryptorchidism is often associated with testicular dysgenesis and is a risk factor for infertility and GCTs and patients should be counselled appropriately.	2b
Paternity in men with unilateral cryptorchidism is almost equal to men without cryptorchidism.	1B
Bilateral cryptorchidism significantly reduces the likelihood of paternity and patients should be counselled appropriately.	1B

Recommendations	Strength rating
Do not use hormonal treatment for cryptorchidism in post-pubertal men.	Strong
If undescended testes are corrected in adulthood, perform simultaneous testicular biopsy, for the detection of intratubular germ cell neoplasia <i>in situ</i> (formerly carcinoma <i>in situ</i>).	Strong
Men with unilateral undescended testis and normal hormonal function/spermatogenesis should be offered orchidectomy.	Strong
Men with unilateral or bilateral undescended testis with biochemical hypogonadism and or spermatogenic failure (i.e., infertility) may be offered unilateral or bilateral orchidopexy, if technically feasible.	Weak

10.4.2 Germ cell malignancy and male infertility

Testicular germ cell tumour (TGCT) is the most common malignancy in Caucasian men aged 15-40 years, and affects approximately 1% of sub-fertile men [1649]. The lifetime risk of TGCT varies among ethnic groups and countries. The highest annual incidence of TGCT occurs in Caucasians, and varies from 10/100,000 (e.g., in Denmark and Norway) to 2/100,000 (e.g., in Finland and the Baltic countries). Generally, seminomas and non-seminomas are preceded by GCNIS, and untreated GCNIS eventually progresses to invasive cancer [1650-1652]. There has been a general decline in male reproductive health and an increase in testicular cancer in

western countries [1653, 1654]. In almost all countries with reliable cancer registries, the incidence of testicular cancer has increased [1540, 1655]. This has been postulated to be related to TDS, which is a developmental disorder of the testes caused by environmental and/or genetic influences in pregnancy. As detailed above, the adverse sequelae of TDS include cryptorchidism hypospadias, infertility and an increased risk of testicular cancer [1624]. Endocrine disrupting chemicals have also been associated with sexual dysfunction [1656] and abnormal semen parameters [1657]. These cancers arise from premalignant gonocytes or GCNIS [1658]. Testicular microcalcification, seen on US, can be associated with TGCT and GCNIS of the testes [1607, 1659, 1660].

10.4.2.1 *Testicular germ cell cancer and reproductive function*

Sperm cryopreservation is considered standard practice in patients with cancer overall, and not only in those with testicular cancer [1661, 1662]. As such, it is important to stress that all men with cancer must be offered sperm cryopreservation prior to the therapeutic use of gonadotoxic agents or ablative surgery that may impair spermatogenesis or ejaculation (i.e., chemotherapy; radiotherapy or retroperitoneal surgery).

Men with TGCT have decreased semen quality, even before cancer treatment. Azoospermia has been observed in 5–8% of men with TGCT [1663] and oligospermia in 50% [1664]. Given that the average 10-year survival rate for testicular cancer is 98% and it is the most common cancer in men of reproductive potential, it is mandatory to include counselling regarding fertility preservation prior to any gonadotoxic treatment [1664, 1665]. Semen analysis and cryopreservation was therefore recommended prior to any gonadotoxic cancer treatment and all patients should be offered cryopreservation of ejaculated sperm or sperm extracted surgically (e.g., c/mTESE) if shown to be azoospermic or severely oligozoospermic. Given that a significant number of men with testicular cancer at the time of first presentation have severe semen abnormalities (i.e., severe oligozoospermia/azoospermia) even prior to (any) treatment [1658], it is recommended that men should undergo sperm cryopreservation prior to orchidectomy. As mentioned above, in those who are either azoospermic or severely oligo-zoospermic this will allow an opportunity to perform TESE prior to further potential gonadotoxic/ablative surgery [1664]. The use of cryopreservation has been demonstrated to be the most cost effective strategy for fertility preservation in patients undergoing potential gonadotoxic treatments [1666, 1667]. In cases of azoospermia, testicular sperm may be recovered to safeguard patient's fertility (onco-TESE) potential. The surgical principles in onco-TESE do not differ from the technique of mTESE for men with infertility (e.g., NOA) [1668, 1669]. In this context, referral to a urologist adept in microsurgery is desirable with facilities for sperm cryopreservation.

Rates of under-utilisation of semen analysis and sperm cryopreservation have been reported to be high; resulting in the failure to identify azoospermic or severely oligozoospermic patients at diagnosis who may eventually benefit from fertility-preserving procedures (e.g., onco-mTESE at the time of orchidectomy). Therefore, counselling about fertility preservation is a priority and needs to be broached earlier in men with testicular cancer [1664]. There are controversial arguments that performing cryopreservation prior to orchidectomy may delay subsequent treatment and have an adverse impact on survival. In this context, orchidectomy should not be unduly delayed if there are no facilities for cryopreservation or there is a potential delay in treatment.

Treatment of TGCT can result in additional impairment of semen quality [1670] and increased sperm aneuploidy up to two years following gonadotoxic therapy [1671]. Chemotherapy is also associated with DNA damage and an increased DNA fragmentation rate [1672]. However, sperm aneuploidy levels often decline to pre-treatment levels 18-24 months after treatment [1671]. Several studies reviewing the offspring of cancer survivors have not shown a significant increased risk of genetic abnormalities in the context of chemotherapy and radiotherapy [1673].

In addition to spermatogenic failure, patients with TGCT have Leydig cell dysfunction, even in the contralateral testis [1674]. The risk of hypogonadism may therefore be increased in men treated for TGCT. The measurement of pre-treatment levels of testosterone, SHBG, LH and oestradiol may help to stratify those patients at increased risk of hypogonadism and provide a baseline for post-treatment hypogonadism. Men who have had TGCT and have low normal androgen levels should be advised that they may be at increased risk of developing hypogonadism, as a result of an age-related decrease in testosterone production and could potentially develop MetS; there are no current long-term data supporting this. The risk of hypogonadism is increased in the survivors of testicular cancer and serum testosterone levels should be evaluated during the management of these patients [1675]. However, this risk is greatest at 6-12 months post-treatment and suggests that there may be some improvement in Leydig cell function after treatment. Therefore it is reasonable to delay initiation of testosterone therapy, until the patient shows continuous signs or symptoms of testosterone deficiency

[1650]. The risk of low libido and ED is also increased in TGCT patients [1676]. Patients treated for TGCT are also at increased risk of CVD [1672]. Therefore, patients may require a multi-disciplinary therapy approach and, in this context, survivorship programmes incorporating a holistic view of patients considering psychological, medical and social needs could be beneficial. In patients who place a high value on fertility potential, the use of testosterone therapy in men with symptoms suggestive for TDS needs to be balanced with worsening spermatogenesis. In these patients consideration can be given to the use of selective oestrogen receptor modulators (SERMs; e.g., clomiphene) or gonadotrophin analogues (e.g., hCG), although these are off-label treatments in this particular clinical setting.

10.4.2.2 Testicular microcalcification (TM)

Microcalcification inside the testicular parenchyma can be found in 0.6-9% of men referred for testicular US [1677, 1678]. Although the true incidence of TM in the general population is unknown, it is most probably rare. Ultrasound findings of TM have been seen in men with TGCT, cryptorchidism, infertility, testicular torsion and atrophy, Klinefelter syndrome, hypogonadism, male pseudohermaphroditism and varicocele [1625]. The incidence reported seems to be higher with high-frequency US machines [1679]. The relationship between TM and infertility is unclear, but may relate to testicular dysgenesis, with degenerate cells being sloughed inside an obstructed seminiferous tubule and failure of the Sertoli cells to phagocytose the debris. Subsequently, calcification with hydroxyapatite occurs. Testicular microcalcification is found in testes at risk of malignant development, with a reported incidence of TM in men with TGCT of 6-46% [1680-1682]. A recent systematic review and meta-analysis of case-control studies indicated that the presence of TM is associated with a ~18-fold higher odds ratio for testicular cancer in infertile men (pooled OR: 18.11, 95% CI: 8.09, 40.55; $P < 0.0001$) [1607].

Testicular microcalcification should therefore be considered pre-malignant in this setting and patients counselled accordingly. Testicular biopsies from men with TM have found a higher prevalence of GCNIS, especially in those with bilateral microcalcifications [1683]. However, TM can also occur in benign testicular conditions and the microcalcification itself is not malignant. Therefore, the association of TM and TGCT is controversial and the challenge is to identify those men at risk of harbouring GCNIS and future risk of TGCT. Further investigation of the association between TM and GCNIS requires testicular biopsies in large series of men without signs of TGCT with or without risk factors for TGCT. However, clinicians and patients should be reassured that testicular cancer does not develop in most men with asymptomatic TM [1660]. Available data indicate that only men in whom TM is found by US, and who have an increased risk of TGCT, should be offered testicular biopsy to exclude GCNIS. Men potentially at high-risk of harbouring or developing GCNIS include those with infertility, atrophic testes, undescended testes, history of TGCT, and contralateral TM and it has been suggested that men with these risk factors could be offered testicular biopsy [1654, 1659]. The normal mean testicular volume is estimated to be 12-30 mL and < 12 mL is considered small [1677]. Patients with a history of TGCT and TM in the contralateral testis and sub-fertile patients have been demonstrated to have an increased risk of GCNIS [1660], while there are only a few studies showing a further increase in GCNIS with TM in the context of cryptorchidism [1654, 1678, 1684]. A useful algorithm has been proposed [1654] to stratifying those patients at increased risk of GCNIS who may benefit from testicular biopsy. However, when undertaking a biopsy in this setting, the full risks and complications of adopting this strategy must be explained to the patient. With the lack of availability of large cohort studies, these recommendations must be treated with caution given the risk of overtreatment (i.e., biopsy) in these patients.

Decastro *et al.* [1685] suggested that testicular cancer would not develop in most men with TM (98.4%) during a 5-year follow-up. As such, an extensive screening programme would only benefit men at significant risk. In this context it would be prudent to advise patients with TM and risk factors for testicular cancer to at least undergo regular testicular examination. It has been suggested that these patients could also be offered annual physical examination by a urologist and US follow-up, although follow-up protocols may be difficult to implement in this invariably young cohort of patients [1625]. As testicular atrophy and infertility have an association with testicular cancer, some authors recommend biopsy or follow-up US if TM is seen [1654]. However, most patients who are azoospermic will be undergoing therapeutic biopsy (i.e., with the specific purpose of sperm retrieval) and therefore a definitive diagnosis can be made and there is a lack of evidence demonstrating a higher prevalence of testicular cancer in patients with both TM and testicular atrophy. In patients with incidental TM, the risk of GCNIS is low and a logical approach is to instruct patients to perform regular testicular self-examination.

10.4.2.3 Recommendations for germ cell malignancy and testicular microcalcification

Recommendations	Strength rating
Men with testicular microcalcification (TM) should learn to perform self-examination even without additional risk factors, as this may result in early detection of testicular germ cell tumour (TGCT).	Weak
Do not perform testicular biopsy, follow-up scrotal US, measure biochemical tumour markers, or abdominal or pelvic computed tomography, in men with isolated TM without associated risk factors (e.g., infertility, cryptorchidism, testicular cancer, and atrophic testis).	Strong
Testicular biopsy may be offered in infertile men with TM, who belong to one of the following higher risk groups: spermatogenic failure (infertility), bilateral TM, atrophic testes (< 12 mL), history of undescended testes and TGCT.	Weak
If there are suspicious findings on physical examination or US in patients with TM with associated lesions, perform inguinal surgical exploration with testicular biopsy or offer orchidectomy after multidisciplinary meeting and discussion with the patient.	Strong
Men treated for TGCT are at increased risk of developing hypogonadism, sexual dysfunction and cardiovascular (CV) risk. Men should be managed in a multi-disciplinary team setting with a dedicated late-effects clinic.	Weak
Sperm cryopreservation should be performed prior to planned orchidectomy, since men with testis cancer may have significant semen abnormalities (including azoospermia).	Weak
Men with testicular cancer and azoospermia or severe abnormalities in their semen parameters may be offered onco-testicular sperm extraction (onco-TESE) at the time of radical orchidectomy.	Weak

10.4.3 Varicocele

Varicocele is a common congenital abnormality, that may be associated with the following andrological conditions:

- male sub-fertility;
- failure of ipsilateral testicular growth and development;
- symptoms of pain and discomfort;
- hypogonadism.

10.4.3.1 Classification

The following classification of varicocele [1439] is useful in clinical practice:

- Subclinical: not palpable or visible at rest or during Valsalva manoeuvre, but can be shown by special tests (Doppler US).
- Grade 1: palpable during Valsalva manoeuvre.
- Grade 2: palpable at rest.
- Grade 3: visible and palpable at rest.

Overall, the prevalence of varicocele in one study was 48%. Of 224 patients, 104 had unilateral and 120 had bilateral varicocele; 62 (13.30%) were grade 3, 99 (21.10%) were grade 2, and 63 (13.60%) were grade 1 [1686]. Worsening semen parameters are associated with a higher grade of varicocele and age [1687, 1688].

10.4.3.2 Diagnostic evaluation

The diagnosis of varicocele is made by physical examination and Scrotal Doppler US is indicated if physical examination is inconclusive or semen analysis remains unsatisfactory after varicocele repair to identify persistent and recurrent varicocele [1439, 1689]. A maximum venous diameter of > 3 mm in the upright position and during the Valsalva manoeuvre and venous reflux with a duration > 2 seconds correlate with the presence of a clinically significant varicocele [1690, 1691]. To calculate testicular volume Lambert's formula ($V=L \times W \times H \times 0.71$) should be used, as it correlates well with testicular function in patients with infertility and/or varicocele [1692]. Patients with isolated, clinical right varicocele should be examined further for abdominal, retroperitoneal and congenital pathology and anomalies.

10.4.3.3 Basic considerations

10.4.3.3.1 Varicocele and fertility

Varicocele is present in almost 15% of the normal male population, in 25% of men with abnormal semen analysis and in 35-40% of men presenting with infertility [1439, 1687, 1693, 1694]. The incidence of varicocele among men with primary infertility is estimated at 35-44%, whereas the incidence in men with secondary infertility is 45-81% [1439, 1694].

The exact association between reduced male fertility and varicocele is unknown. Increased scrotal temperature, hypoxia and reflux of toxic metabolites can cause testicular dysfunction and infertility due to increased overall survival and DNA damage [1694].

A meta-analysis showed that improvements in semen parameters are usually observed after surgical correction in men with abnormal parameters [1695]. Varicocelectomy can also reverse sperm DNA damage and improve OS levels [1694, 1696].

10.4.3.3.2 Varicocelectomy

Varicocele repair has been a subject of debate for several decades. A meta-analysis of RCTs and observational studies in men with only clinical varicoceles has shown that surgical varicocelectomy significantly improves semen parameters in men with abnormal semen parameters, including men with NOA with hypospermatogenesis or late maturation (spermatid) arrest on testicular pathology [1693, 1697-1700]. Pain resolution after varicocelectomy occurs in 48-90% of patients [1701]. A recent systematic review has shown greater improvement in higher-grade varicoceles and this should be taken into account during patient counselling [1702].

In RCTs, varicocele repair in men with a subclinical varicocele was ineffective at increasing the chances of spontaneous pregnancy [1703]. Also, in randomised studies that included mainly men with normal semen parameters no benefit was found to favour treatment over observation. A Cochrane review from 2012 concluded that there is evidence to suggest that treatment of a varicocele in men from couples with otherwise unexplained subfertility may improve a couple's chance of spontaneous pregnancy [1704]. Two recent meta-analyses of RCTs comparing treatment to observation in men with a clinical varicocele, oligozoospermia and otherwise unexplained infertility, favoured treatment, with a combined OR of 2.39-4.15 (95% CI: 1.56-3.66) (95% CI: 2.31-7.45) [1700, 1704]. Average time to improvement in semen parameters is up to two spermatogenic cycles [1705, 1706] and spontaneous pregnancy between 6 and 12 months after varicocelectomy [1707, 1708]. A further meta-analysis has reported that varicocelectomy may improve outcomes following ART in oligozoospermic men with an OR of 1.69 (95% CI: 0.95-3.02) [1709].

10.4.3.3.3 Prophylactic varicocelectomy

In adolescents with a varicocele, there is a significant risk of over-treatment because most adolescents with a varicocele have no problem achieving pregnancy later in life [1710]. Prophylactic treatment is only advised in case of documented testicular growth deterioration confirmed by serial clinical or Doppler US examinations and/or abnormal semen analysis [1711, 1712].

More novel considerations for varicocelectomy in patients with NOA, hypogonadism and DNA damage are described below:

Varicocelectomy and NOA

Several studies have suggested that varicocelectomy may lead to sperm appearing in the ejaculate in men with azoospermia. In one such study, microsurgical varicocelectomy in men with NOA led to sperm in the ejaculate post-operatively with an increase in ensuing natural or assisted pregnancies [1713]. There were further beneficial effects on sperm retrieval rates (SRRs) and ICSI outcomes. Meta-analyses have further corroborated these findings; 468 patients diagnosed with NOA and varicocele underwent surgical varicocele repair or percutaneous embolisation. In patients who underwent varicocelectomy, SRRs increased compared to those without varicocele repair (OR: 2.65; 95% CI: 1.69-4.14; $P < 0.001$). In 43.9% of the patients (range: 20.8%-55.0%), sperm were found in post-operative ejaculate. These findings indicate that varicocelectomy in patients with NOA and clinical varicocele is associated with improved SRR, and overall, 44% of the treated men have sperm in the ejaculate and may avoid sperm retrieval. However, the quality of evidence available is low and the risks and benefits of varicocele repair must be discussed fully with the patient with NOA and a clinically significant varicocele prior to embarking upon treatment intervention [1698]. This must necessarily take into consideration the infertile couple together, especially considering the time needed for a possible SRR and the baseline characteristics of the female partner (i.e., age, medical history, anti-Müllerian hormone (AMH) levels = good ovarian reserve, etc.).

Varicocelectomy and hypogonadism

Evidence also suggests that men with clinical varicoceles who are hypogonadal may benefit from varicocele intervention. One meta-analysis studied the efficacy of varicocele intervention by comparing the pre-operative and post-operative serum testosterone of 712 men. The combined analysis of seven studies demonstrated that the mean post-operative serum testosterone improved by 34.3 ng/dL (95% CI: 22.57-46.04, $P < 0.00001$,

$I^2 = 0\%$) compared with their pre-operative levels. An analysis of surgery vs. untreated control results showed that mean testosterone among hypogonadic patients increased by 105.65 ng/dL (95% CI: 77.99-133.32 ng/dL), favouring varicocelectomy [1714]. However, results must be treated with caution and adequate cost-benefit analysis must be undertaken to determine the risks and benefits of surgical intervention over testosterone therapy in this setting. Although, varicocelectomy may be offered to hypogonadal men with clinically significant varicoceles, patients must be advised that the full benefits of treatment in this setting must be further evaluated with prospective RCTs.

10.4.3.3.4 Varicocelectomy for assisted reproductive technology and raised DNA fragmentation

Varicocelectomy can improve sperm DNA integrity, with a mean difference of -3.37% (95% CI: -2.65% to -4.09%) [1710]. There is now increasing evidence that varicocele treatment may improve DNA fragmentation and outcomes from ART [1709, 1710]. As a consequence, more recently it has been suggested that the indications for varicocele intervention should be expanded to include men with raised DNA fragmentation. If a patient has failed ART (e.g., failure of implantation, embryogenesis or recurrent pregnancy loss) there is an argument that if DNA damage is raised, consideration could be given to varicocele intervention after extensive counselling [1715], and exclusion of other causes of raised DNA fragmentation [1710, 1716]. The dilemma is whether varicocele treatment is indicated in men with raised DNA fragmentation and normal semen parameters.

In a meta-analysis of non-azoospermic infertile men with clinical varicocele by Estevez *et al.*, four retrospective studies were included of men undergoing ICSI, and included 870 cycles (438 subjected to ICSI with prior varicocelectomy, and 432 without prior varicocelectomy). There was a significant increase in the clinical pregnancy rates (OR = 1.59, 95% CI: 1.19-2.12, $I^2 = 25\%$) and live birth rates (OR = 2.17, 95% CI: 1.55-3.06, $I^2 = 0\%$) in the varicocelectomy group compared to the group subjected to ICSI without previous varicocelectomy. A further study evaluated the effects of varicocele repair and its impact on pregnancy and live birth rates in infertile couples undergoing ART in male partners with oligo-azoospermia or azoospermia and a varicocele [1709]. In 1,241 patients, a meta-analysis demonstrated that varicocelectomy improved live birth rates for the oligospermic (OR = 1.699) men and combined oligo-azoospermic/azoospermic groups (OR = 1.761). Pregnancy rates were higher in the azoospermic group (OR = 2.336) and combined oligo-azoospermic/azoospermic groups (OR = 1.760). Live birth rates were higher for patients undergoing IUI after intervention (OR = 8.360).

10.4.3.4 Disease management

Several treatments are available for varicocele (Table 41). Current evidence indicates that microsurgical varicocelectomy is the most effective among the different varicocelectomy techniques [1710, 1717]. Unfortunately, there are no large prospective RCTs comparing the efficacy of the various interventions for varicocele. However, microsurgical repair results in fewer complications and lower recurrence rates compared to the other techniques based upon case series [1718]. This procedure, however, requires microsurgical training. The various other techniques are still considered viable options, although recurrences and hydrocele formation appear to be higher [1719].

Radiological techniques (sclerotherapy and embolisation) are minimally invasive widely used approaches, although higher recurrence rates compared to microscopic varicocelectomy have been reported (4-27%) [1694]. Robot-assisted varicocelectomy has a similar success rate compared to the microscopic varicocelectomy technique, although larger prospective randomised studies are needed to establish the most effective method [1720-1722].

Table 41: Recurrence and complication rates associated with treatments for varicocele

Treatment	Refs.	Recurrence/ Persistence %	Overall complications	Specific Complications
Antegrade sclerotherapy	[1723, 1724]	5-9	Hydrocele (5.5%), haematoma, infection, scrotal pain, testicular atrophy, epididymitis	Technical failure 1-9%, left-flank erythema
Retrograde sclerotherapy	[1725, 1726]	6-9.8	Hydrocele (3.3%) wound infection, scrotal pain	Technical failure 6-7.5%, adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, venous perforation
Retrograde embolisation	[1725, 1727]	3-11	Hydrocele (10%) haematoma, wound infection	Technical failure 7-27%, pain due to thrombophlebitis, radiological complications (e.g., reaction to contrast media), misplacement or migration of coils (to femoral vein or right atrium), retroperitoneal haemorrhage, fibrosis, ureteric obstruction, venous perforation
<i>Open operation</i>				
Scrotal operation		-	Testicular atrophy, arterial damage with risk of devascularisation and testicular gangrene, scrotal haematoma, post-operative hydrocele	
Inguinal approach	[1728, 1729]	2.6-13	Hydrocele (7.3%), testicular atrophy, epididymo-orchitis, wound complications	Post-operative pain due to incision of external oblique fascia, genitofemoral nerve damage
Open retroperitoneal high ligation	[1717, 1730]	15-29	Hydrocele (5-10%), testicular atrophy, scrotal edema	External spermatic vein ligation failure
Microsurgical inguinal or subinguinal	[1718, 1728, 1731, 1732]	0.4	Hydrocele (0.44%), scrotal haematoma	
Laparoscopy	[1688, 1717, 1718, 1733, 1734]	3-6	Hydrocele (7-43%) epididymitis, wound infection, testicular atrophy due to injury of testicular artery, bleeding	External spermatic vein ligation failure, intestinal, vascular and nerve damage; pulmonary embolism; pneumo-scrotum; peritonitis; post-operative pain in right shoulder (due to diaphragmatic stretching during pneumo-peritoneum)

10.4.3.5 Summary of evidence and recommendations for varicocele

Summary of evidence	LE
The presence of varicocele in some men is associated with progressive testicular damage from adolescence onwards and a consequent reduction in fertility.	2a
Although the treatment of varicocele in adolescents may be effective, there is a significant risk of over-treatment: the majority of boys with a varicocele will have no fertility problems later in life.	3
Varicocele repair may be effective in men with abnormal semen parameters, a clinical varicocele and otherwise unexplained male factor infertility.	1a
Although there are no prospective randomised studies evaluating this, meta-analyses have suggested that varicocele repair leads to sperm appearing in the ejaculate in men with non-obstructive azoospermia	2
Microscopic approach (inguinal/subinguinal) may have lower recurrence and complications rates than non-microscopic approaches (retroperitoneal and laparoscopic), although no RCTs are available yet.	2a
Varicocele is associated with raised DNA fragmentation and intervention has been shown to reduce DNA fragmentation.	2a

Recommendations	Strength rating
Treat varicocele in adolescents with ipsilateral reduction in testicular volume and evidence of progressive testicular dysfunction.	Weak
Do not treat varicocele in infertile men who have normal semen analysis and in men with a sub-clinical varicocele.	Weak
Treat infertile men with a clinical varicocele, abnormal semen parameters and otherwise unexplained infertility in a couple where the female partner has good ovarian reserve to improve fertility rates.	Strong
Varicocelectomy may be considered in men with raised DNA fragmentation with otherwise unexplained infertility or who have suffered from failed of assisted reproductive techniques, including recurrent pregnancy loss, failure of embryogenesis and implantation.	Weak

10.4.4 Male accessory gland infections and infertility

10.4.4.1 Introduction

Infection of the male urogenital tract is a potentially curable cause of male infertility [1735-1737]. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs) [1735]. The effect of symptomatic or asymptomatic infections on sperm quality is contradictory [1738]. A systematic review of the relationship between sexually transmitted infections, such as those caused by *Chlamydia trachomatis*, genital mycoplasmas, *Neisseria gonorrhoeae*, *Trichomonas vaginalis* and viruses, and infertility was unable to draw a strong association between sexually transmitted infections and male infertility due to the limited quality of reported data [1739].

10.4.4.2 Diagnostic evaluation

10.4.4.2.1 Semen analysis

Semen analysis (see Section 10.3.2) clarifies whether the prostate is involved as part of a generalised MAGI and provides information regarding sperm quality. Leukocyte analysis allows differentiation between inflammatory and non-inflammatory chronic pelvic pain syndrome (CP/CPPS) (NIH IIa versus NIH 3b National Institutes of Health classification for CP/CPPS).

10.4.4.2.2 Microbiological findings

After exclusion of UTI (including urethritis), $> 10^6$ peroxidase-positive white blood-cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. In these cases, a semen culture or polymerase chain reaction (PCR) analysis should be performed for common urinary tract pathogens. A concentration of $> 10^3$ CFU/mL urinary tract pathogens in the ejaculate is indicative of significant bacteriospermia [1740]. The sampling should be delivered the same day to the laboratory because the sampling time can influence the rate of positive micro-organisms in semen and the frequency of isolation of different strains [1741]. The ideal diagnostic test for isolating *C. trachomatis* in semen has not yet been established [1742], but the most accurate method is PCR [1743-1745].

Historical data show that *Ureaplasma urealyticum* is pathogenic only in high concentrations ($> 10^3$ CFU/mL ejaculate). Fewer than 10% of samples analysed for *Ureaplasma* exceeded this concentration [1746]. Normal

colonisation of the urethra hampers the significance of mycoplasma-associated urogenital infections, using samples such as the ejaculate [1747].

A meta-analysis indicated that *Ureaplasma parvum* and *Mycoplasma genitalium* were not associated with male infertility, but a significant relationship existed between *U. urealyticum* (OR: 3.03 95% CI: 1.02–8.99) and *Mycoplasma hominis* (OR: 2.8; 95% CI: 0.93– 3.64) [1748].

The prevalence of human papilloma virus (HPV) in the semen ranges from 2 to 31% in the general population and is higher in men with unexplained infertility (10-35,7%) [1749, 1750]. Recent systematic reviews have reported an association between male infertility, poorer pregnancy outcomes and semen HPV positivity [1751-1753]. However, data still needs to be prospectively validated to clearly define the clinical impact of HPV infection in semen. Additionally, seminal presence of Herpes Simplex virus (HSV)-2 in infertile men may be associated with lower sperm quality compared to that in HSV-negative infertile men [1738]. However, it is unclear if anti-viral therapy improves fertility rates in these men.

10.4.4.2.3 White blood cells

The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial [1754]. Although leukocytospermia is a sign of inflammation, it is not necessarily associated with bacterial or viral infections, and therefore cannot be considered a reliable indicator [1755]. According to the WHO classification, leukocytospermia is defined as $> 10^6$ WBCs/mL. Only two studies have analysed alterations of WBCs in the ejaculate of patients with proven prostatitis [1756, 1757]. Both studies found more leukocytes in men with prostatitis compared to those without inflammation (CPPS, type NIH 3b). Furthermore, leukocytospermia should be further confirmed by performing a peroxidase test on the semen. There is currently no evidence that treatment of leukocytospermia alone without evidence of infective organisms improves conception rates [1758].

10.4.4.2.4 Sperm quality

The deleterious effects of chronic prostatitis (CP/CPPS) on sperm density, motility and morphology has been demonstrated in a recent systematic review based on case-controlled studies [1759]. Both *C. trachomatis* and *Ureoplasma spp.* can cause decreased sperm density, motility, altered morphology and increased DNA damage. Data from a recent retrospective cross-sectional study showed that *U. urealyticum* was the most frequent single pathogen in semen of asymptomatic infertile men; a positive semen culture was both univariably ($P < .001$) and multi-variably ($P = .04$) associated with lower sperm concentration [1760]. Human papilloma virus can also induce changes in sperm density, motility and DNA damage [1749, 1750]. *Mycoplasma spp.* can cause decreased motility and development of antisperm antibodies [1738].

10.4.4.2.5 Seminal plasma alterations

Seminal plasma elastase is a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate [1737, 1761, 1762]. Various cytokines are involved in inflammation and can influence sperm function. Several studies have investigated the association between interleukin (IL) concentration, leukocytes, and sperm function through different pathways, but no correlations have been found [1763-1765].

The prostate is the main site of origin of IL-6 and IL-8 in the seminal plasma. Cytokines, especially IL-6, play an important role in the male accessory gland inflammatory process [1766]. However, elevated cytokine levels do not depend on the number of leukocytes in expressed prostatic secretion [1767].

10.4.4.2.6 Glandular secretory dysfunction

The secretory function of the prostate gland can be evaluated by measuring seminal plasma pH, citric acid, or γ -glutamine transpeptidase levels; the seminal plasma concentrations of these factors are usually altered during infection and inflammation. However, they are not recommended as diagnostic markers for MAGIs [1768].

10.4.4.2.7 Reactive oxygen species

Reactive oxygen species may be increased in infertile patients with asymptomatic *C. trachomatis* and *M. hominis* infection, with subsequent decrease in ROS upon antibiotic treatment. However, the levels of ROS in infertile patients with asymptomatic *C. trachomatis* and *M. hominis* in the semen are low, making it difficult to draw any firm conclusions [1769]. Chronic urogenital infections are also associated with increased leukocyte numbers [1770]. However, their biological significance in prostatitis remains unclear [1737].

10.4.4.2.8 Disease management

Treatment of CP/CPPS is usually targeted at relieving symptoms [1771, 1772]. The indications and aims of therapy are:

- reduction or eradication of micro-organisms in prostatic secretions and semen;
- normalisation of inflammatory (e.g., leukocytes) and secretory parameters;
- improvement of sperm parameters associated with fertility impairment [1773].

Only antibiotic therapy of chronic bacterial prostatitis (NIH II according to the classification) has provided symptomatic relief, eradication of micro-organisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions. Although antibiotics might improve sperm quality [1773], there is no evidence that treatment of CP/CPPS increases the probability of natural conception [1737, 1774].

Asymptomatic presence of *C. trachomatis* and *M. hominis* in the semen can be correlated with impaired sperm quality, which recovers after antibiotic treatment. However further research is required to confirm these findings [1769].

10.4.4.3 Epididymitis

Inflammation of the epididymis causes unilateral pain and swelling, usually with acute onset. Among sexually active men aged < 35 years, epididymitis is most often caused by *C. trachomatis* or *N. gonorrhoea* [1775, 1776]. Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with UTIs and occurs more often in men aged > 35 years [1777].

10.4.4.3.1 Diagnostic evaluation

10.4.4.3.1.1 Ejaculate analysis

Ejaculate analysis according to WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn) criteria, may indicate persistent inflammatory activity. Transient reductions in sperm counts and progressive motility can be observed [1775, 1778, 1779]. Semen culture might help to identify pathogenic micro-organisms. Development of stenosis of the epididymal ducts, reduction of sperm count, and azoospermia are more important potential sequelae to consider in the follow-up of bilateral epididymitis (see Section 10.3.2).

10.4.4.3.1.2 Disease management

Treatment of epididymitis results in:

- microbiological cure of infection;
- improvement of clinical signs and symptoms;
- prevention of potential testicular damage;
- prevention of transmission;
- decrease of potential complications (e.g., infertility or chronic pain).

Patients with epididymitis known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* must be told to also refer their sexual partners for evaluation and treatment [1780].

10.4.4.4 Summary of evidence and recommendation for male accessory gland infections

Summary of evidence	LE
Male accessory gland infections are not clearly associated with impaired natural conception.	3
Antibiotic treatment often only eradicates micro-organisms; it has no positive effect on inflammatory alterations and cannot reverse functional deficits and anatomical abnormalities.	2a
Although antibiotic treatment for MAGIs may result in improvement in sperm quality, it does not enhance the probability of conception.	2a

Recommendations	Strength rating
Treating male accessory gland infections may improve sperm quality, although it does not necessarily improve the probability of increasing conception.	Weak
Data are insufficient to conclude whether antibiotics and antioxidants for the treatment of infertile men with leukocytospermia improve fertility outcomes.	Weak
Refer sexual partners of patients with accessory sex gland infections that are known or suspected to be caused by sexually transmitted diseases for evaluation and treatment.	Strong

10.5 Non-Invasive Male Infertility Management

10.5.1 Idiopathic male infertility and oligo-astheno-terato-zoospermia

Oligo-astheno-teratozoospermia (OAT) is a clinical condition with a reduced number of spermatozoa in the ejaculate, which is also characterised by reduced sperm motility and morphology; often referred to as OAT syndrome (OATS). Several conditions can cause OATS, although the aetiology may be unknown in a significant number of cases [78, 1605].

10.5.2 Empirical treatments

10.5.2.1 Life-style

Studies suggest that environmental and lifestyle factors may contribute to idiopathic infertility acting additively on a susceptible genetic background [78, 1605]. Hence, lifestyle improvement can have a positive effect on sperm parameters (see below).

10.5.2.1.1 Weight loss

Few authors have investigated the role of weight loss on male fertility outcomes. Non-controlled studies have suggested that weight loss can result in improved sperm parameters [78, 1781, 1782]. However, data derived from RCTs are more conflicting. A meta-analysis of 28 cohort studies and 1,022 patients, documented that bariatric surgery did not improve sperm quality and function in morbidly obese men [1783]. Data on ART outcomes are lacking. However, it is important to recognise that weight loss can improve obesity-related secondary hypogonadism, which may result in better outcomes in couples seeking medical care for infertility, and is important for the general health of the male partner [1781, 1783].

10.5.2.1.2 Physical activity

Regular physical activity is recommended by the WHO in order to prevent and reduced the risk of several long-term chronic diseases [1784]. A recent meta-analysis has documented that moderate-intensity (20–40 metabolic equivalents (METs)/week) or even high-intensity (40–80 METs-h/week) recreational physical activity can result in better semen parameters [1785]. In addition, similar to what is observed from weight loss, improvements in hormonal profile have also been reported [1781].

10.5.2.1.3 Smoking

Epidemiological data indicates that about one in three men of reproductive age smokes, with the highest prevalence observed in Europe among all the WHO regions [1786]. Data derived from a large meta-analysis of 20 studies with 5,865 participants clearly show a negative association between smoking and sperm parameters [1786]. Experimental studies performed in rats have shown that nicotine has a dose-dependent deleterious effect on sperm, which can be improved by nicotine cessation [1787]. Data in men are lacking and only one case report has indicated an improvement of sperm parameters after 3 months of a smoking cessation programme [1788]. Similar data have been reported in a recent non-controlled study, which showed a possible benefit on ART after the male partner stopped smoking [1789].

10.5.2.1.4 Alcohol consumption

Data derived from a recent meta-analysis including 15 cross-sectional studies and 16,395 men suggested that moderate alcohol does not adversely affect semen parameters, whereas high alcohol intake can have a detrimental effect on male fertility [1790]. Similar to what has been reported for weight loss, however, heavy chronic ethanol consumption (defined as > 2 drinks/day [1791]) can reduce testosterone levels, which can be restored by alcohol cessation [1792].

10.5.2.2 Antioxidant treatment

Inflammation is a positive reaction of the human body to overcome potential noxious stimuli. However, chronic inflammation can induce several negative biochemical and metabolic effects that contribute to the development of several medical conditions. Oxidative stress is considered to be of the most important contributing factors in the pathogenesis of idiopathic infertility. ROS, the final products of OS, can impair sperm function acting at several levels, including plasma membrane lipid peroxidation, which can affect sperm motility, the acrosome reaction and chromatin maturation leading to increased DNA fragmentation [1793]. Accordingly, seminal levels of ROS have been negatively associated with ART outcomes [1794]. Despite this, evidence for the role of antioxidant therapy in male infertility is still conflicting. A Cochrane systematic review and meta-analysis including 34 RCTs and 2,876 couples using various antioxidant compounds, it was concluded that antioxidant therapy had a positive impact on live-birth and pregnancy rates in sub-fertile couples undergoing ART cycles [1795]. Similar results were also reported in the most recent meta-analysis including 61 studies with 6,264 infertile men, aged 18–65 years [1796]. More recently, the Males, Antioxidants, and Infertility (MOXI) trial found that antioxidants did not improve semen parameters or DNA integrity compared

to placebo among infertile men with male factor infertility. Moreover, cumulative live-birth rate did not differ at 6 months between the antioxidant and placebo groups (15% vs. 24%) [1797]. However, all the aforementioned studies also recognised important limitations: data were derived from low-quality RCTs with serious risk of bias due to poor methods of reporting randomisation; failure to report on the clinical outcomes including live-birth and clinical pregnancy rates; high attrition rates; and imprecision due to often low event rates and small overall sample sizes [1796]. No clear conclusions were possible regarding the specific antioxidants to use or and/or therapeutic regimes for improving sperm parameters and pregnancy rate [1796].

10.5.2.3 Selective oestrogen receptor modulators

Selective oestrogen receptor modulators (SERMs) have been advocated as a possible empirical treatment in male idiopathic infertility. The proposed mechanism of action is based on the activity of these compounds to block oestrogen receptors at the level of the hypothalamus, which results in stimulation of GnRH secretion leading to an increase in pituitary gonadotropin release. The latter effect, by stimulating spermatogenesis, represents the rational basis for SERM administration to patients with reduced sperm count [1798]. In an initial meta-analysis including 11 RCTs, in which only 5 were placebo-controlled, it was concluded that SERMs were not associated with an increased pregnancy rate in the 459 patients analysed [1799]. In a subsequent Cochrane review published 1 year later, these findings were confirmed in a larger number of studies (n = 10 and 738 men), although positive effects on hormonal parameters were documented. More recently, Chua *et al.* meta-analysed data derived from 11 RCTs and showed that SERMs were associated with a significantly increased pregnancy rate [1800]. Additionally, a significant improvement in sperm and hormonal parameters was detected. Similar results were confirmed in the latest updated meta-analysis of 16 studies [1798]. However, it should be recognised that the quality of the papers included was low and only a few studies were placebo-controlled. In conclusion, although some positive results relating to the use of SERMs in men with idiopathic infertility have been reported, no conclusive recommendations can be drawn due to poor quality of the available evidence. Furthermore, complications from the use of SERMs were under-reported.

10.5.2.4 Aromatase inhibitors

Aromatase, a cytochrome p450 enzyme, is present in the testes, prostate, brain, bone, and adipose tissue of men; it converts testosterone and androstenedione to oestradiol and oestrone, respectively. Oestradiol negatively feeds back on the hypothalamus and pituitary to reduce gonadotropic secretions, ultimately affecting spermatogenesis. In this context, aromatase inhibitors (AIs) may decrease oestrogen production by reversibly inhibiting cytochrome p450 isoenzymes 2A6 and 2C19 of the aromatase enzyme complex inhibiting the negative feedback of oestrogen on the hypothalamus resulting in stronger GnRH pulses that stimulate the pituitary to increase production of FSH [1801-1804]. Aromatase activity has been associated with male infertility characterised by testicular dysfunction with low serum testosterone and/or testosterone to oestradiol ratio. In this context, AIs have been reported to increase endogenous testosterone production and improve spermatogenesis in the setting of infertility as an off-label option for treatment [1805]. Either steroidal (testolactone) and non-steroidal (anastrozole and letrozole) AIs significantly improve hormonal and semen parameters in infertile men, with a safe tolerability profile, although prospective RCTs are necessary to better define the efficacy of these medications in this clinical setting [1803, 1805].

Recommendations	Strength rating
In men with idiopathic oligo-astheno-teratozoospermia, life-style changes including weight loss and increased physical activity, smoking cessation and alcohol intake reduction can improve sperm quality and the chances of conception.	Weak
No clear recommendation can be made for treatment of patients with idiopathic infertility using antioxidants, although anti-oxidant use may improve semen parameters.	Weak
No conclusive recommendations on the use of selective oestrogen receptor modulators in men with idiopathic infertility can be drawn.	Weak
No conclusive recommendations on the use of either steroidal (testolactone) or nonsteroidal (anastrozole and letrozole) aromatase inhibitors in men with idiopathic infertility can be drawn, even before testis surgery.	Weak

10.5.3 Hormonal therapy

10.5.3.1 Gonadotrophins

Follicle Stimulating Hormone is primarily involved in the initiation of spermatogenesis and testicular growth during puberty. The role of FSH post puberty has not been clearly defined. Luteinising hormone stimulates testosterone production in the testes, but due to its short half-life, it is not suitable for clinical use. Human Chorionic Gonadotrophin acts in a similar manner to LH and can be used pharmacologically to stimulate

testosterone release in men with failure of their hypothalamic-pituitary-gonadal axis. Human Chorionic Gonadotrophin can adequately stimulate spermatogenesis in men whom have developed hypopituitarism after normal puberty. Therefore, the treatment of men with secondary hypogonadism depends on whether or not they developed hypothalamic-pituitary failure before or after puberty [5].

10.5.3.2 Secondary hypogonadism

10.5.3.2.1 Pre-Pubertal-Onset

Congenital causes resulting in low gonadotropin production are associated with testicular size < 4 mL and/or cryptorchidism. Testes size of < 4 mL occurs when they have not been exposed to any gonadotropins at all. These conditions require combination therapy with both hCG and FSH with subcutaneous administration or GnRH by pulsed delivery using a subcutaneous pump [1806]. However, GnRH treatment requires a pulsatile secretion using specific devices for either intravenous or subcutaneous administration, which may limit patient compliance. Moreover, GnRH therapy should be limited to subjects with a residual pituitary gonadotropic activity [5].

As for the type of gonadotropin treatment, it is usual to commence hCG first and titrate the dose to achieve testosterone levels within the normal physiological range. However, FSH can be given first or in combination with hCG [110]. Human Chorionic Gonadotrophin is given twice weekly and in patients with congenital secondary hypogonadism in high dose, commencing at 1,000 IU twice weekly. Testosterone levels can be assayed every 2 weeks with dose increases until ideally mid-range testosterone is achieved. Dose increases can be to 2,000, 3,000, 4,000 and 5,000 IU two or three times a week, until normal testosterone levels are achieved [1807-1810]. Failure to achieve normal testosterone status at the high dose would indicate that primary testicular failure is present; probably as a result of cryptorchidism or failure of testicular development. Human Chorionic Gonadotrophin is also used to stimulate testicular descent into the scrotum in individuals with cryptorchidism. Once the hCG dose giving a normal level testosterone is established with the implication that intra-testicular testosterone has occurred, FSH 75-150 IU three times per week subcutaneously should be commenced. Usually the higher 150 IU dose three times weekly is needed to be successful in men with testicular volume < 4mL. The trophic response of the testes to FSH is variable in these patients and it may range from no effect to achieving testicular sizes of 12-15 mL [1811]. A trophic response is usually an indication of an increase in spermatogenesis. The production of new spermatogenesis may be evident after 3 months of FSH therapy, but could occur even after 18 months of treatment [1809-1811]. A low baseline sperm concentration does not indicate a poor response to gonadotropin therapy [1812]. Semen analysis can be assessed at 3-monthly intervals. These patients can be fertile with low sperm counts < 20 million/mL as there is a high proportion of motile sperm. Follicle-stimulating hormone therapy prior to GnRH is also effective in stimulating testicular growth and fertility in men with congenital hypogonadotropic hypogonadism (HH) [1813]. A larger initial testicular volume is the best prognostic factor for induction of successful spermatogenesis [1814].

10.5.3.2.2 Post-Pubertal Onset Secondary

If secondary hypogonadism develops after puberty, hCG alone is usually required first to stimulate spermatogenesis. Doses of subcutaneous hCG required may be lower than those used in individuals with pre-pubertal onset; therefore, a starting dose of 250 IU twice weekly is suggested, and if normal testosterone levels are reached, hCG doses may be increased up to 2,000 IU twice weekly as for pre-pubertal onset. Again, semen analysis should be performed every 3 months to assess response, unless conception has taken place. If there is a failure of stimulation of spermatogenesis, then FSH can be added (75 IU three times per week, increasing to 150 IU three times per week if indicated). Similarly, combination therapy with FSH and hCG can be administered from the beginning of treatment, promoting better outcomes in men with HH [110]. No difference in outcomes were observed when urinary-derived, highly purified FSH was compared to recombinant FSH [110].

Greater baseline testicular volume is a good prognostic indicator for response to gonadotropin treatment [1814]. Data had suggested that previous testosterone therapy can have a negative impact on gonadotropin treatment outcomes in men with HH [1814]. However, this observation has been subsequently refuted by a meta-analysis that did not confirm a real negative role of testosterone therapy in terms of future fertility in this specific setting [110].

In the presence of hyperprolactinaemia, causing suppression of gonadotrophins resulting in sub-fertility the treatment independent of aetiology (including a pituitary adenoma) is dopamine agonist therapy or withdrawal of the drug that causes the condition. Dopamine agonists used include bromocriptine, cabergoline and quinagolide.

10.5.3.3 Primary Hypogonadism

There is no substantial evidence that gonadotrophin therapy has any beneficial effect in the presence of classical testicular failure. Likewise, there are no data to support the use of other hormonal treatments (including SERMs or AIs) in the case of primary hypogonadism to improve spermatogenesis [79, 1815].

10.5.3.4 Idiopathic Male Factor Infertility

There is some evidence that FSH treatment increases sperm parameters in idiopathic oligozoospermic men with FSH levels within the normal range (generally 1.5 – 8 mIU/mL) [1816]. It has also been reported that FSH may improve sperm DNA fragmentation rates as well as ameliorating AMH and inhibin levels [1817-1820]. High-dose FSH therapy is more effective in achieving a testicular response than lower doses are [1821]. A Cochrane systematic review including six RCTs with 456 participants, different treatment protocols and follow-up periods concluded that FSH treatment resulted in higher live-birth and pregnancy rates compared with placebo or no treatment. However, no significant difference among groups was observed when ICSI or IUI were considered [1822]. In a more recent meta-analysis including 15 trials with > 1,200 patients, similar findings after FSH treatment were observed in terms of both spontaneous pregnancies and pregnancies after ART [1823]. A further study showed that in azoospermic men undergoing TESE-ICSI there were improved SRRs and higher pregnancy and fertilisation rates in men treated with FSH compared to untreated men [1824]. In men with NOA, combination hCG/FSH therapy was shown to increase SRR in only one study [1825]. Human Chorionic Gonadotrophin alone prior to TESE in NOA has not been found to have any benefit on SRRs [1826].

10.5.3.5 Anabolic Steroid Abuse

Oligospermia or azospermia as a result of anabolic abuse should be treated initially by withdrawal of the anabolic steroid. There is no common indication for treating this disorder; the management is based on case reports and clinical experience. Usually, adequate sperm numbers and quality will improve over a six to twelve month period. If after this interval the condition persists, then hCG without or in combination with FSH as an alternative to clomiphene can be used to try and stimulate spermatogenesis [1827].

10.5.3.6 Recommendations for treatment of male infertility with hormonal therapy

Recommendations	Strength rating
Hypogonadotropic hypogonadism (secondary hypogonadism), including congenital causes, should be treated with combined human chorionic gonadotropin (hCG) and follicle-stimulating hormone (FSH) (recombinant FSH; highly purified FSH) or pulsed Gonadotropin-releasing hormone (GnRH) via pump therapy to stimulate spermatogenesis.	Strong
In men with hypogonadotropic hypogonadism, induce spermatogenesis by an effective drug therapy (hCG; human menopausal gonadotropins; recombinant FSH; highly purified FSH).	Strong
The use of GnRH therapy is more expensive and does not offer any advantages when compared to gonadotropins for the treatment of hypogonadotropic hypogonadism.	Strong
In men with idiopathic oligozoospermia and FSH values within the normal range, FSH treatment may ameliorate spermatogenesis outcomes.	Weak
No conclusive recommendations can be given on the use of high-dose FSH in men with idiopathic infertility and prior (m)TESE and therefore cannot be routinely advocated.	Weak
Do not use testosterone therapy for the treatment of male infertility.	Strong
Provide testosterone therapy for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood.	Strong
In the presence of hyperprolactinaemia, dopamine agonist therapy may improve spermatogenesis.	Weak

10.6 Invasive Male Infertility Management

10.6.1 Obstructive azoospermia

Obstructive azoospermia is the absence of spermatozoa in the sediment of a centrifuged sample of ejaculate due to obstruction [1828]. Obstructive azoospermia is less common than NOA and occurs in 20-40% of men with azoospermia [1829, 1830]. Men with OA usually have normal FSH, testes of normal size and epididymal enlargement [1831]. Of clinical relevance, men with late maturation arrest may present with normal gonadotropins and testicular size and may be only distinguished from those with OA at the time of surgical exploration. The vas deferens may be absent bilaterally (CBAVD) or unilaterally (CUAVD). Obstruction in primary infertile men is more frequently present at the epididymal level.

10.6.1.1 Classification of obstructive azoospermia

10.6.1.1.1 Intratesticular obstruction

Intratesticular obstruction occurs in 15% of men with OA [1832]. Congenital forms are less common than acquired forms (post-inflammatory or post-traumatic) (Table 42).

10.6.1.1.2 Epididymal obstruction

Epididymal obstruction is the most common cause of OA, affecting 30-67% of azoospermic men [1832-1835]. Congenital epididymal obstruction usually manifests as CBAVD, which is associated with at least one mutation of the CF gene in 82% of cases [1835]. Other congenital forms of epididymal obstruction include chronic sinu-pulmonary infections (Young's syndrome) [1836]. Acquired forms secondary to acute (e.g., gonococcal) and subclinical (e.g., *Chlamydia*) epididymitis are most commonly due to infections [1837, 1838]. Other causes may be trauma or surgical intervention [1839, 1840] (Table 42).

10.6.1.1.3 Vas deferens obstruction

Vas deferens obstruction is the most common cause of acquired obstruction following vasectomy [1837] (Table 42). Approximately 2-6 % of these men request vasectomy reversal (see 2019 EAU Guidelines on Male Infertility). Vasal obstruction may also occur after hernia repair [1841, 1842]. The most common congenital vasal obstruction is CBAVD, often accompanied by CF. Unilateral agenesis or a partial defect is associated with contralateral seminal duct anomalies or renal agenesis in 80% and 26% of cases, respectively [1524].

10.6.1.1.4 Ejaculatory duct obstruction

Ejaculatory duct obstruction is found in 1-5% of cases of OA and is classified as cystic or post-inflammatory or calculi of one or both ejaculatory ducts [1664, 1843] (Table 42). Cystic obstructions are usually congenital (i.e., Mullerian duct cyst or urogenital sinus/ejaculatory duct cysts) and are typically midline. In urogenital sinus abnormalities, one or both ejaculatory ducts empty into the cyst [1844], while in Mullerian duct anomalies, the ejaculatory ducts are laterally displaced and compressed by the cyst [1845]. Paramedian or lateral intraprostatic cysts are rare [1846]. Post-inflammatory obstructions of the ejaculatory duct are usually secondary to urethra-prostatitis [1847]. Congenital or acquired complete obstructions of the ejaculatory ducts are commonly associated with low seminal volume, decreased or absent seminal fructose, and acidic pH. The seminal vesicles (anterior-posterior diameter > 15 mm) and ejaculatory duct (> 2.3 mm in width) are usually dilated [1843, 1847-1849].

10.6.1.1.4.1 Functional obstruction of the distal seminal ducts

Functional obstruction of the distal seminal ducts might be attributed to local neurogenic dysfunction [1850]. This abnormality is often associated with urodynamic dysfunction. Impaired sperm transport can be observed as idiopathic or due to spinal cord injury, multiple sclerosis, retroperitoneal lymph node dissection, pelvic surgery, SSRIs, α -blockers and typical antipsychotic medications [1851].

Table 42: Causes of obstruction of the genitourinary system

Epydidimis
Infection (acute/chronic epididymitis)
Trauma
Post-surgical iatrogenic obstruction (i.e., MESA; hydrocelectomy or other scrotal surgery)
Congenital epididymal obstruction (usually manifests as congenital bilateral absence of the vas deferens [CBAVD])
Other congenital forms of epididymal obstruction (Young's syndrome)
Vas deferens
Vasectomy
Vasotomy/vasography (with improper technique)
Post-surgical iatrogenic obstruction (i.e., scrotal surgery or herniorrhaphy)
Congenital unilateral (CUAVD) or bilateral absence of the vas deferens (CBAVD)
Ejaculatory ducts
Cysts (Mullerian utricular, prostatic or seminal vesicular)
Infection (acute/chronic epididymitis)
Traumatic
Post-surgical iatrogenic obstruction
Functional obstruction
Idiopathic/acquired local neurogenic dysfunction

10.6.1.2 Diagnostic evaluation

10.6.1.2.1 Clinical history

Clinical history-taking should follow the investigation and diagnostic evaluation of infertile men (See Section 10.3). Risk factors for obstruction include prior surgery, iatrogenic injury during inguinal herniorrhaphy, orchidopexy or hydrocelectomy.

10.6.1.2.2 Clinical examination

Clinical examination should follow the guidelines for the diagnostic evaluation of infertile men. Obstructive azoospermia is indicated by at least one testis with a volume > 15 mL, although a smaller volume may be found in some patients with:

- obstructive azoospermia and concomitant partial testicular failure;
- enlarged and dilated epididymis;
- nodules in the epididymis or vas deferens;
- absence or partial atresia of the vas deferens.

10.6.1.2.3 Semen analysis

Azoospermia means the inability to detect spermatozoa after centrifugation at $\times 400$ magnification. At least two semen analyses must be carried out [1828, 1852] (see Section 10.3). When semen volume is low, a search must be made for spermatozoa in urine after ejaculation. Absence of spermatozoa and immature germ cells in the semen pellet suggest complete seminal duct obstruction.

10.6.1.2.4 Hormone levels

Hormones including FSH and inhibin-B should be normal, but do not exclude other causes of testicular azoospermia (e.g., NOA). Although inhibin-B concentration is a good index of Sertoli cell integrity reflecting closely the state of spermatogenesis, its diagnostic value is no better than that of FSH and its use in clinical practice has not been widely advocated [1853].

10.6.1.2.5 Genetic Testing

Inability to palpate one or both sides of the vas deferens should raise concern for a CFTR mutation. Any patient with unilateral or bilateral absence of the vas deferens or seminal vesicle agenesis should be offered CFTR testing [1854].

10.6.1.2.6 Testicular biopsy

Testicular biopsy must be combined with TESE for cryopreservation. Although studies suggest that a diagnostic or isolated testicular biopsy [1855] is the most important prognostic predictor of spermatogenesis and sperm retrieval, the Panel recommends not to perform testis biopsies (including fine needle aspiration [FNA]) without performing simultaneously a therapeutic sperm retrieval, as this will require a further invasive procedure after biopsy. Furthermore, even patients with extremes of spermatogenic failure (e.g., Sertoli Cell Only syndrome [SCOS]) may harbour focal areas of spermatogenesis [1856, 1857].

10.6.1.3 Disease management

Sperm retrieval

10.6.1.3.1 Intratesticular obstruction

Only TESE allows sperm retrieval in these patients and is therefore recommended.

10.6.1.3.2 Epididymal obstruction

Microsurgical epididymal sperm aspiration (MESA) or percutaneous epididymal sperm aspiration (PESA) [1858] is indicated in men with CBAVD. Testicular sperm extraction and percutaneous techniques, such as testicular sperm aspiration (TESA), are also options [1859]. The source of sperm used for ICSI in cases of OA and the aetiology of the obstruction do not affect the outcome in terms of fertilisation, pregnancy, or miscarriage rates [1860]. Usually, one MESA procedure provides sufficient material for several ICSI cycles [1861] and it produces high pregnancy and fertilisation rates [1862]. In patients with OA due to acquired epididymal obstruction and with a female partner with good ovarian reserve, microsurgical epididymovasostomy (EV) is recommended [1863]. Epididymovasostomy can be performed with different techniques such as end-to-site and intussusception [1864].

Anatomical recanalisation following surgery may require 3-18 months. A recent systematic review indicated that the time to patency in EV varies between 2.8 to 6.6 months. Reports of late failure are heterogeneous and vary between 1 and 50% [1865]. Before microsurgery, and in all cases in which recanalisation is impossible, epididymal spermatozoa should be aspirated intra-operatively by MESA and cryopreserved to be used for

subsequent ICSI procedures [1847]. Patency rates range between 65% and 85% and cumulative pregnancy rates between 21% and 44% [1840, 1866]. Recanalisation success rates may be adversely affected by pre-operative and intra-operative findings. Robot-assisted EV has similar success rates and larger studies are needed [1720].

10.6.1.3.3 Vas deferens obstruction after vasectomy

Vas deferens obstruction after vasectomy requires microsurgical vasectomy reversal. The mean post-procedural patency and pregnancy rates weighted by sample size were 90-97% and 52-73%, respectively [1840, 1866]. The average time to patency is 1.7-4.3 months and late failures are uncommon (0-12%) [1865]. Robot-assisted vasovasostomy has similar success rates, and larger studies, including cost-benefit analysis, are needed to establish its benefits over standard microsurgical procedures [1720].

The absence of spermatozoa in the intra-operative vas deferens fluid suggests the presence of a secondary epididymal obstruction, especially if the seminal fluid of the proximal vas deferens has a thick “toothpaste” appearance; in this case microsurgical EV may be indicated [1867-1869]. Simultaneous sperm retrieval may be performed for future cryopreservation and use for ICSI; likewise, patients should be counselled appropriately.

10.6.1.3.4 Vas deferens obstruction at the inguinal level

It is usually impossible to correct large bilateral vas deferens defects, resulting from involuntary excision of the vasa deferentia during hernia surgery in early childhood or previous orchidopexy. In these cases, TESE/MESA/PESA or proximal vas deferens sperm aspiration [1870] can be used for cryopreservation for future ICSI. Prostate cancer patients who express an interest in future fertility should be counselled for cryopreservation [1871, 1872].

10.6.1.3.5 Ejaculatory duct obstruction

The treatment of ejaculatory duct obstruction (EDO) depends on its aetiology. Transurethral resection of the ejaculatory ducts (TURED) can be used in post-inflammatory obstruction and cystic obstruction [1843, 1847]. Resection may remove part of the verumontanum. In cases of obstruction due to a midline intraprostatic cyst, incision, unroofing or aspiration of the cyst is required [1843, 1847].

Intra-operative TRUS makes this procedure safer. If distal seminal tract evaluation is carried out at the time of the procedure, installation of methylene blue dye into the seminal vesicles (chromotubation) can help to confirm intra-operative opening of the ducts. Pregnancy rates after TURED are 20-25% [1664, 1843, 1873]. Complications following TURED include epididymitis, UTI, gross haematuria, haematospermia, azoospermia (in cases with partial distal ejaculatory duct obstruction) and urine reflux into the ejaculatory ducts and seminal vesicles [1843].

Alternative therapies for EDO include, seminal vesiculoscopy to remove debris or calculi and balloon dilation and laser incision for calcification on TRUS [1874]. The alternatives to TURED are MESA, PESA, TESE, proximal vas deferens sperm aspiration and seminal vesicle-ultrasonically guided aspiration.

10.6.1.4 Summary of evidence and recommendations for obstructive azoospermia

Summary of evidence	LE
Obstructive lesions of the seminal tract are frequent in azoospermic or severely oligozoospermic patients, usually with normal-sized testes and normal reproductive hormones.	3

Recommendations	Strength rating
Perform microsurgical vasovasostomy or epididymovasostomy for azoospermia caused by epididymal or vasal obstruction in men with female partners of good ovarian reserve.	Strong
Use sperm retrieval techniques, such as microsurgical epididymal sperm aspiration (MESA), testicular sperm extraction (TESE) and percutaneous techniques (PESA and TESA) either as an adjunct to reconstructive surgery, or if the condition is not amenable to surgical repair, or when the ovarian reserve of the partner is limited or patient preference is not to undertake a surgical reconstruction and the couple prefer to proceed to ICSI treatment directly.	Strong

10.6.2 **Non-obstructive azoospermia**

Non-obstructive azoospermia (NOA) is defined as the absence of sperm at the semen analysis after centrifugation, with usually a normal ejaculate volume. This finding should be confirmed at least at two consecutive semen analyses [1875]. The severe deficit in spermatogenesis observed in NOA patients is often a consequence of primary testicular dysfunction or may be related to a dysfunction of the hypothalamus-pituitary-gonadal (HPG) axis.

10.6.2.1 *Investigation of non-obstructive azoospermia*

The diagnosis of NOA is based on the evidence of two consecutive semen analyses confirming azoospermia. Causes of OA should be ruled out. Patients with NOA should undergo a comprehensive assessment to identify genetically transmissible conditions, potential treatable causes of azoospermia, and potential health-relevant co-morbidity (e.g., testicular cancer and hypogonadism [of any type]). A detailed medical history (e.g., history of cryptorchidism, previous gonadotoxic treatments for cancer, etc.) and socio-demographic characteristics [1876], along with a comprehensive physical examination should be performed in every patient to detect conditions potentially leading to azoospermia, while ruling out co-morbidity frequently associated with azoospermia. Indeed, NOA could be the first sign of pituitary or germ cell tumours of the testis [1877-1879]. Patients with NOA have been shown to be at increased risk of being diagnosed with cancer [1880]. Moreover, other systemic conditions such as MetS, T2DM, osteoporosis and CVDs have been more frequently observed in patients with NOA compared to normozoospermic men [1881-1883]. Azoospermic men are at higher risk of mortality [1884, 1885]. Therefore, investigation of infertile men provides an opportunity for long-term risk stratification for other co-morbid conditions [1886].

Genetic tests should be performed in patients with NOA to detect genetic abnormalities. As discussed (see Section 10.3), patients should undergo karyotype analysis [1484, 1485], along with a screening of Y-chromosome micro-deletions [1535, 1887] and of the gene coding for CFTR in order to exclude concomitant mutations, and to rule out CBAVD [1519, 1520]. Genetic counselling for eventual transmissible and health-relevant genetic conditions should be provided to couples.

As detailed, all patients should undergo a complete hormonal investigation to exclude concomitant hypogonadism, which has been found in about 30% of patients with NOA [361, 1888, 1889]. A correct definition of the type of the associated hypogonadism (i.e., hypogonadotropic hypogonadism vs. hypergonadotropic vs. compensated hypogonadism) is relevant to differentiate diagnostic and therapeutic approaches to the patient [1890].

Scrotal US may show signs of testicular dysgenesis (e.g., non-homogeneous testicular architecture and/or microcalcifications) and testicular tumours. Testicular volume may be a predictor of spermatogenic function [1458] and is usually, but not invariably, low in patients with NOA. Some authors have advocated that testicular perfusion detected at US Doppler assessment can predict surgical sperm retrieval at TESE and guide testicular biopsies [1891]; however, to date, data are inconsistent to suggest a routine role of testicular Doppler evaluation before TESE. In a recent multicentre study including 806 men submitted to mTESE, the size of seminiferous tubules assessed with pre-operative US was significantly associated with sperm retrieval outcomes, with a sensitivity and specificity of 76.7% and 80.7% for a cut-off point of 250 μm , respectively [1892].

10.6.2.2 *Surgery for non-obstructive azoospermia*

Surgical treatment for NOA is mostly aimed at retrieval of vital sperm directly from the testes (either uni- or bilaterally). This treatment is normally part of ART protocols, including IVF cycles via ICSI. Techniques and indications for surgical sperm retrieval in patients with NOA are discussed below. Any surgical approach aimed at sperm retrieval must be considered not a routine and simple biopsy; in this context, performing a diagnostic biopsy before surgery (any type) unless dedicated to ART protocols is currently considered inappropriate.

10.6.2.3 *Indications and techniques of sperm retrieval*

Spermatogenesis within the testes may be focal, which means that spermatozoa can usually be found in small and isolated foci. With a wide variability among cohorts and techniques, positive SRRs have been reported in up to 50% of patients with NOA [1893, 1894]. Numerous predictive factors for positive sperm retrieval have been investigated, although no definitive factors have been demonstrated to predict sperm retrieval [1894].

Historically, there is a good correlation between the histology found at testicular biopsy and the likelihood of finding mature sperm cells during testicular sperm retrieval [1855, 1895, 1896]. The presence of hypospermatogenesis at testicular biopsy showed good accuracy in predicting positive sperm retrieval after either single or multiple conventional TESE or mTESE compared with maturation arrest pattern or SCOS

[1855, 1895, 1896]. However, formal diagnostic biopsy is not recommended in this clinical setting for the reasons outlined above.

Hormonal levels, including FSH, LH, inhibin B and AMH have been variably correlated with sperm retrieval outcomes at surgery, and data from retrospective series are still controversial [1897-1903]. Similarly, conflicting results have been published regarding testicular volume as a predictor of positive sperm retrieval [1855, 1900, 1901]. Therefore, no clinical variable may be currently considered as a reliable predictor for positive sperm retrieval throughout ART patient work-up [1894].

In case of complete AZFa and AZFb microdeletions, the likelihood of sperm retrieval is zero and therefore TESE procedures are contraindicated [1540]. Conversely, patients with Klinefelter syndrome [1502] and a history of undescended testes have been shown to have higher chance of finding sperm at surgery [1900].

Historically, surgical techniques for retrieving sperm in men with NOA include testicular sperm aspiration (TESA), single or multiple conventional TESE (cTESE) and mTESE.

• Fine needle aspiration

Fine needle aspiration (FNA) mapping technique has been proposed as a prognostic procedure aimed to select patients with NOA for TESE and ICSI [1904]. The procedure is performed under local anaesthesia in the office and percutaneous aspiration is performed with 23G needle in multiple sites, ranging from 4 to 18 [1904]. The retrieved tissue is sent for cytological and histological evaluation to provide information on the presence of mature sperm and on testicular histological pattern. Given that focal spermatogenesis may occur within the testes of patients with NOA, FNA mapping may provide information on the sites with the higher probability of retrieving sperm, thus serving as a guide for further sperm retrieval surgery in the context of ART procedures (e.g., ICSI). Turek *et al.* have shown that a higher number of aspiration sites may increase the chance of finding sperm [1905, 1906]. The extent and type of subsequent sperm retrieval procedure can be tailored according to the FNA mapping results: TESA or TESE could be suggested in case of multiple positive sites for sperm, while a more precise and potentially more-invasive technique, such as mTESE, could be considered for patients with few positive sites at FNA [1904]. However, no RCTs have compared the diagnostic yield from FNA and mTESE. A positive FNA requires a secondary therapeutic surgical approach, which may increase the risk of testicular damage, and without appropriate cost-benefit analysis, is not justifiable. No studies have evaluated the salvage rate of mTESE in men who have undergone FNA mapping. Therefore, FNA mapping cannot be recommended as a primary therapeutic intervention in men with NOA until further RCTs are undertaken.

• Testicular sperm aspiration

Testicular sperm aspiration (TESA) is a minimally invasive, office-based, procedure in which testicular tissue is retrieved with a biopsy needle under local anaesthesia. Reported SRRs with TESA range from 11 to 60% according to patient profile and surgical techniques [1907-1910]. Data have shown that using larger needles (18-21G) with multiple passes could yield a higher chance of positive sperm retrieval [1910]. Complications after TESA are uncommon and mainly include minor bleeding with scrotal haematoma and post-operative pain [1910].

As a less-invasive and less-costly procedure TESA has been proposed as a possible first-line approach before sending patients for a more-invasive procedure [1910]. To date no RCTs have compared SRRs from TESA, cTESE and mTESE. A meta-analysis including data from case-control studies, reported that TESE was two times (95% CI: 1.8-2.2) more likely to result in successful sperm retrieval as compared with TESA [1894]. Given the low success rates compared with TESE, TESA is no longer recommended in men with NOA.

• Conventional TESE

Conventional TESE (cTESE) requires a scrotal incision and open biopsy of the testes. Reported SRRs in single-arm studies are about 50% [1893]. Observational studies have demonstrated that multiple biopsies yield a higher chance of sperm retrieval [1893, 1911]. However, pooled data analysis of case-control studies comparing cTESE with mTESE showed a lower unadjusted SRR of 35% (95% CI: 30-40) for cTESE [1894]. A more recent meta-analysis showed that cTESE/mTESE in patients with NOA resulted in SRRs of up to 50%, with no differences when cTESE was compared to mTESE [1912].

The probability of finding vital sperm at TESE varies also according to testicular histology: data from non-randomised studies comparing cTESE with mTESE have shown a higher chance of sperm retrieval with mTESE only for patients with a histological diagnosis of SCOS [1913]. In such cases, results ranged from 22.5 to 41% and from 6.3 to 29% for mTESE versus cTESE, respectively [1913]. Conversely, no difference between the two

techniques has been found when comparing patients with a histology suggestive of maturation arrest [1913]. A single study showed a small advantage of mTESE when hypospermatogenesis was found [1914]. In light of these findings, some authors have advocated that cTESE could be the technique of choice in patients with a histological finding of maturation arrest or hypo-spermatogenesis [1894, 1913].

Conventional TESE has been associated with a higher rate of complications compared with other techniques [1893]. A total of 51.7% of patients have been found with intratesticular haematoma at scrotal US 3 months after surgery, with testicular fibrosis observed in up to 30% of patients at 6-months' assessment [1915].

A recent meta-analysis investigated the risk of hypogonadism after TESE due to testicular atrophy [1916]; patients with NOA experienced a mean 2.7 nmol/L decrease in total testosterone 6 months after cTESE, which recovered to baseline within 18-26 months.

• **Microdissection TESE)**

Microdissection TESE is aimed at identifying sites of focal spermatogenesis within the testes by performing focal biopsies in areas where larger dilated (and opaque) tubules are present by using optical magnification (20-25x) [1917]. The rationale of this technique is to increase the probability of retrieving sperm with a lower amount of sampled tissue and a consequent lower risk of complications.

Unadjusted SRR after mTESE was 52% (95% CI: 47-58%) in a pooled data analysis of studies comparing cTESE with mTESE [1894]. Specifically, mTESE resulted in a 1.5 higher chance of retrieving sperm compared with the conventional technique [1894]. In a study assessing the role of salvage mTESE after a previously failed cTESE or TESA, sperm were successfully retrieved in 46.5% of cases [1857]. Lower rates of complications have been observed with mTESE compared to cTESE, both in terms of haematoma and fibrosis [1913]. Both procedures have shown a recovery of baseline testosterone levels after long-term follow-up [1914].

As reported above, a recent meta-analysis of the currently available studies comparing cTESE and mTESE in patients with NOA showed a mean SRR of 47% (95% CI: 45;49%). No differences were observed when mTESE was compared with cTESE (46 [range 43;49] % for cTESE vs. 46 [range 42;49] % for mTESE, respectively). Meta-regression analysis demonstrated that SRR per cycle was independent of age and hormonal parameters at enrolment. However, the SRR increased as a function of testicular volume. Retrieved sperms resulted in a live-birth rate of up to 28% per ICSI cycle [1912].

Although no difference between cTESE/mTESE techniques in patients with NOA was found, to conclusively clarify if one technique is superior to the other, there is a need for sufficiently powered and well-designed RCTs to compare mTESE with cTESE. Therefore, a clear recommendation regarding the technique of choice cannot be given. Several variables should be considered before counselling patients for one specific technique, including surgical skills, testicular histology, cost of the procedure and risk of complications, thus including a lower amount of sampled tissue.

• **Follow-up after TESE**

When compared with cTESE, mTESE has been reported to have fewer post-operative complications and negative effects on testicular function. In a recent meta-analysis analysing the complications of TESE, men with Klinefelter syndrome and NOA had the largest decrease in total testosterone levels 6 months after TESE (mean decrease of 4.1 and 2.7 nmol/L, respectively), which recovered to baseline levels 26 and 18 months after TESE, respectively [1916]. Therefore, it would be reasonable to provide long-term endocrinological follow-up after TESE (any type) to detect hypogonadism, particularly for patients with Klinefelter syndrome. Testosterone measurement could be offered in asymptomatic men at 18 months post-TESE or in those men who become symptomatic for hypogonadism after surgery [1918].

• **Hormonal therapy prior to surgical sperm retrieval approaches**

Stimulating spermatogenesis by optimising intratesticular testosterone (ITT) has been proposed to increase the chance of sperm retrieval at the time of surgery in men with NOA. Similarly, increasing FSH serum levels could stimulate spermatogenesis. There is evidence that treatment with hCG can lead to an increase in ITT [1819] and Leydig cells within the testes [1919]. It has been shown in azoospermic patients with elevated gonadotropins levels that administration of hCG and/or FSH can lead to a so-called "gonadotropins reset", with a reduction in FSH plasma concentrations and improvement in Sertoli cells function [1920]. Similarly, clomiphene citrate may increase pituitary secretion by blocking feedback inhibition of oestradiol, thus inducing an increase in FSH and LH in patients with NOA [1921]. While azoospermic patients with secondary hypogonadism should be treated accordingly to stimulate sperm production [361], no RCT has shown a

benefit of hormonal treatment to enhance the chances of sperm retrieval among patients with idiopathic NOA [1922]. In a large multicentre case-control study, 496 patients with idiopathic NOA treated with a combination of clomiphene, hCG and human menopausal gonadotropin according to hormonal profile, were compared with 116 controls subjected to mTESE without receiving any pre-operative treatment [1825]. A total of 11% of treated patients had sperm in the ejaculate at the end of treatment; of the remaining patients, 57% had positive sperm retrieval at mTESE as compared with 33% in the control group. Likewise, in a small case-control study including 50 men with idiopathic NOA, of whom 25 were treated with recombinant FSH before mTESE, there was observed a 24% SRR compared with 12% in the control group [1824]. Conversely, Gul *et al.* [1923] failed to find any advantage of pre-operative treatment with hCG compared with no treatment, in 34 idiopathic NOA patients candidates for mTESE.

Hormonal therapy has been proposed to increase the chance of sperm retrieval at salvage surgery after previously failed cTESE or mTESE. Retrospective data have shown that treatment with hCG and recombinant FSH could lead to a 10-15% SRR at salvage mTESE [1819, 1924]. In a small case-control study 28 NOA patients were treated with hCG with or without FSH for 4-5 months before salvage mTESE and compared with 20 controls subjected to salvage surgery [1925]. Sperm retrieval rate was 21% in the treated group compared with 0% in the control group. The histological finding of hypo-spermatogenesis emerged as a predictor of sperm retrieval at salvage surgery after hormonal treatment [1925]. Further prospective trials are needed to elucidate the effect of hormonal treatment before salvage surgery in NOA patients, with a previously failed cTESE or mTESE. However, patients should be counselled that the evidence for the role of hormone stimulation prior to sperm retrieval surgery in men with idiopathic NOA is limited [1926]. Currently, it is not recommended in routine practice.

10.6.2.4 Recommendations for Non-Obstructive Azoospermia

Recommendations	Strength rating
Patients with non-obstructive azoospermia (NOA) should undergo a comprehensive assessment, including detailed medical history, hormonal profile and genetic tests to investigate the underlying aetiology and associated co-morbidity. Genetic counselling is mandatory in couples with genetic abnormalities prior to any assisted reproductive technology protocols.	Strong
Surgery for sperm retrieval can be performed in men who are candidates for assisted reproductive technology (i.e., ICSI). In patients with complete AZFa and AZFb microdeletions, surgery is contraindicated since the chance of sperm retrieval is zero.	Strong
Fine needle aspiration (FNA) and testicular sperm aspiration (TESA) should not be considered the treatments of choice in patients with NOA, given the lower probability of positive sperm retrieval compared to cTESE and mTESE .	Weak
Fine needle aspiration as a prognostic procedure prior to definitive testicular sperm extraction (any type) in patients with NOA is not recommended for use in routine clinical practice.	Weak
Conventional TESE (cTESE) and microdissection TESE (mTESE) are the techniques of choice for retrieving sperm in patients with NOA.	Weak
No pre-operative biochemical and clinical variables may be considered sufficient and reliable predictors of positive sperm retrieval at surgery in patients with NOA.	Weak
No conclusive recommendations on the routine use of medical therapy (e.g., recombinant follicle-stimulating hormone (FSH); highly purified FSH; human chorionic gonadotrophin (hCG); aromatase inhibitors or selective oestrogen receptor modulators [SERMs]) in patients with NOA can be drawn and are not therefore currently recommended routinely before TESE.	Weak

10.7 Assisted Reproductive Technologies

10.7.1 Types of assisted reproductive technology

Assisted reproductive technology consists of procedures that involve the in vitro handling of both human oocytes and sperm, or of embryos, with the objective of establishing pregnancy [1927, 1928].

Once couples have been prepared for treatment, the following are the steps that make up an ART cycle:

1. Pharmacological stimulation of growth of multiple ovarian follicles, while at the same time other medications is given to suppress the natural menstrual cycle and down-regulate the pituitary gland.
2. Careful monitoring at intervals to assess the growth of the follicles.
3. Ovulation triggering: when the follicles have reached an appropriate size, a drug is administered to bring about final maturation of the eggs.
4. Egg collection (usually with a trans-vaginal US probe to guide the pickup) and, in some cases of male infertility, sperm retrieval.
5. Fertilisation process, which is usually completed by IVF or ICSI.
6. Laboratory procedures follow for embryo culture: culture media, oxygen concentration, co-culture, assisted hatching etc.
7. The embryos are placed into the uterus. Issues of importance here include endometrial preparation, the best timing for embryo transfer, how many embryos to transfer, what type of catheter to use, the use of US guidance, need for bed rest etc.
8. Luteal phase support, for which several hormonal options are available.

Fertility treatments are complex and each cycle consists of several steps. If one of the steps is incorrectly applied, conception may not occur [1927].

Several ART techniques are available:

10.7.1.1 Intra-uterine insemination (IUI)

Intra-uterine insemination is an infertility treatment that involves the placement of the prepared sperm into the uterine cavity timed around ovulation. This can be done in combination with ovarian stimulation or in a natural cycle. The aim of the stimulation cycle is to increase the number of follicles available for fertilisation and to enhance the accurate timing of insemination in comparison to the natural cycle IUI [1929-1931].

Intra-uterine insemination is generally, though not exclusively, used when there is at least one patent fallopian tube with normal sperm parameters and regular ovulatory cycles (unstimulated cycles) and when the female partner is aged < 40 years.

The global pregnancy rate (PR) and delivery rate (DR) for each IUI cycle with the partner's sperm are 12.0% and 8.0%, respectively. Using donor sperm, the resultant PR and DR per cycle are 17.0% and 12.3%, respectively [1932]. The rates of successful treatment cycles for patients decrease with increase in age, and the birth rates across all age groups have remained broadly stable over time. The highest birth rates have been reported in patients younger than 38 years (14% in patients aged < 35 years and 12% in those aged 35-37 years). The rates of successful treatment are low for patients older than 42 years. The multiple pregnancy rate (MPR) for IUI is ~8% [1930]. IUI is not recommended in couples with unexplained infertility, male factor infertility and mild endometriosis, unless the couples have religious, cultural or social objections to proceed with IVF [1933].

Intra-uterine insemination with ovarian stimulation is a safer, cheaper, more patient-friendly and non-inferior alternative to IVF in the management of couples with unexplained and mild male factor infertility [1929, 1930]. A recent RCT showed lower multiple pregnancy rates and comparable live-birth rates in patients treated with IUI with hormonal stimulation when compared to women undergoing IVF with single embryo transfer [1934]. Additionally, IUI is a more cost-effective treatment than IVF for couples with unexplained or mild male subfertility [1935].

10.7.1.2 In vitro fertilisation (IVF)

involves using controlled ovarian hyperstimulation to recruit multiple oocytes during each cycle from the female partner. Follicular development is monitored ultrasonically, and ova are harvested before ovulation with the use of US-guided needle aspiration. The recovered oocytes are mixed with processed semen to perform IVF. The developing embryos are incubated for 2-3 days in culture and then placed trans-cervically into the uterus.

The rapid refinement of embryo cryopreservation methods has resulted in better perinatal outcomes of frozen-thawed embryo transfer (FET) and makes it a viable alternative to fresh embryo transfer (ET) [1936, 1937]. Frozen-thawed embryo transfer seems to be associated with lower risk of gestational complications than fresh ET is. Individual approaches remain appropriate to balance the options of FET or fresh ET at present [1938].

Generally, only 20%-30% of transferred embryos result in clinical pregnancies. The global PR and DR per aspiration for non-donor IVF is 24.0% and 17.6%, respectively [1932].

According to the NICE guidelines, IVF treatment is appropriate in cases of unexplained infertility for women who have not conceived after 2 years of regular unprotected sexual intercourse [1939].

10.7.1.3 Intracytoplasmic sperm injection

Intracytoplasmic sperm injection is a procedure through which a single sperm is injected directly into an egg using a glass micropipette.

The difference between ICSI and IVF is the method used to achieve fertilisation. In conventional IVF, oocytes are incubated with sperm in a Petri dish, and the male gamete fertilises the oocyte naturally. In ICSI, the cumulus–oocyte complexes go through a denudation process in which the cumulus oophorus and corona radiata cells are removed mechanically or by an enzymatic process. This step is essential to enable microscopic evaluation of the oocyte regarding its maturity stage, as ICSI is performed only in metaphase II oocytes [1940]. A thin and delicate glass micropipette (injection needle) is used to immobilise and pick up morphologically normal sperm selected for injection. A single spermatozoon is aspirated by its tail into the injection needle, which is inserted through the zona pellucida into the oocyte cytoplasm. The spermatozoon is released at a cytoplasmic site sufficiently distant from the first polar body. During this process, the oocyte is held still by a glass micropipette [1940].

With this technique the oocyte can be fertilised independently of the morphology and/or motility of the spermatozoon injected.

Intracytoplasmic sperm injection is currently the most commonly used assisted reproductive technology, accounting for 70–80% of the cycles performed [1941].

The procedure was first used in cases of fertilisation failure after standard IVF or when an inadequate number of sperm cells was available. The consistency of fertilisation independent of the functional quality of the spermatozoa has extended the application of ICSI to immature spermatozoa retrieved surgically from the epididymis and testis [1942]. Intracytoplasmic sperm injection is the natural treatment for couples with severe male factor infertility and is also used for a number of non-male factor indications (Table 43) [1943].

The need to denude the oocyte allows assessment of the nuclear maturity of the oocyte. Intracytoplasmic sperm injection is also preferred in conjunction with pre-implantation genetic diagnosis and has recently been used to treat HIV discordant couples, in whom there is a pressing need to minimise exposure of the oocyte to a large number of spermatozoa [1942].

The global PR and DR per aspiration for ICSI is 26.2% and 19.0%, respectively [1932]. For all ages and with all the different sperm types used, fertilisation after ICSI is at approximately 70%-80% and it ensures a clinical pregnancy rate of up to 45% [1941, 1942].

Existing evidence does not support ICSI in preference over IVF in the general non-male factor ART population; however, in couples with unexplained infertility, ICSI is associated with lower fertilisation failure rates than IVF is [1943].

Overall, pregnancy outcomes from ICSI are comparable between epididymal and testicular sperm and also between fresh and frozen–thawed epididymal sperm in men with OA [1944]. However, these results are from studies of low evidence [1943].

Sperm injection outcomes with fresh or frozen–thawed testicular sperm have been compared in men with NOA. In a meta-analysis of 11 studies and 574 ICSI cycles, no significant difference was observed between fresh and frozen–thawed testicular sperm with regards to fertilisation rate (RR: 0.97, 95% CI: 0.92–1.02) and clinical pregnancy rates (RR: 1.00, 95% CI: 0.75–1.33) [1945]. However, no meta-analysis was performed on data regarding implantation, miscarriage, and low-birth rates.

10.7.1.4 Testicular sperm in men with raised DNA fragmentation in ejaculated sperm

The use of testicular sperm for ICSI is associated with possibly improved outcomes compared with ejaculated sperm in men with high sperm DNA fragmentation [1475, 1943]. Men with unexplained infertility with raised DNA fragmentation may be considered for TESE after failure of ART, although they should be counselled that live-birth rates are under reported in the literature and patients must weigh up the risks of performing an invasive procedure in a potentially normozoospermic or unexplained condition. The advantages of the use of testicular sperm in men with cryptozoospermia have not yet been confirmed in large scale randomised studies [1946].

In terms of a practical approach, urologists may offer the use of testicular sperm in patients with high DNA fragmentation. However, patients should be counselled regarding the low levels of evidence for this (i.e., non-randomised studies). Furthermore, testicular sperm should only be used in this setting once the common causes of oxidative stress have been excluded including varicoceles, dietary/lifestyle factors and accessory gland infections.

Table 43: Fertilisation methods for male-factor and non-male factor infertility (adapted from [1943])

	Fertilisation method
Male Factor Infertility	
Sperm derived from men with azoospermia	ICSI mandatory
Severe OAT	ICSI highly recommended
Moderate OAT	IVF and ICSI equally effective
Isolated teratozoospermia	IVF and ICSI equally effective
Absolute asthenozoospermia	ICSI mandatory
Globozoospermia	ICSI mandatory
Anti-sperm antibodies	IVF and ICSI equally effective
Sperm DNA fragmentation	ICSI recommended
Non-male factor infertility	
Unexplained infertility	Equally effective. Couples should be informed that ICSI improves fertilisation rates compared to IVF alone, but once fertilisation is achieved the pregnancy rate is no better than with IVF. It should be noted for clarification that in the absence of male factors, ICSI should not be offered in the first treatment cycle [1947].
General non-male factor population	Equally effective, slightly in favour of IVF
Poor quality oocytes and advanced maternal age	Equally effective, slightly in favour of IVF
Pre-implantation genetic testing	ICSI highly recommended
Poor responders	Equally effective, slightly in favour of IVF
Tubal ligation	IVF preferable
Sero-discordant couples	Equally effective

ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilisation; OAT = oligo-asthenoter-atozoospermia

Intracytoplasmic sperm injection is carried out using viable sperm populations. Several semen processing techniques have been developed to select the optimal sperm fraction for ICSI. Density gradient centrifugation (DGC) and the swim-up procedures have been used as standards for semen preparation for ICSI for more than two decades [1948]. However, these traditional sperm selection techniques are unable to select sperm fractions with optimal DNA integrity and functional characteristics. Advanced sperm selection techniques have been introduced to optimise the selection of high-quality sperm for ICSI [1949]. These selection methods are based on sperm surface charge (electrophoresis and zeta potential), apoptosis (magnetic-activated sperm cell sorting (MACS) and glass wool), membrane maturity (hyaluronic acid binding), or ultra-morphological sperm assessment [1950].

10.7.1.5 Intra-cytoplasmic morphologically selected sperm injection

Intra-cytoplasmic morphologically selected sperm injection (IMSI) was first introduced in 2002 as a modification of the ICSI technique [1951]. This technique increases the magnification of sperm to > 6,000 times; the purpose of which is to perform the motile sperm organelle morphology examination (MSOME), a method used to select spermatozoa that have the choicest morphology in couples with the most severe male factor. Bartoov *et al.*

showed that, for patients with a history of ICSI failure, addition of IMSI resulted in a 60% pregnancy rate, compared with a 30% rate for patients not using IMSI [1952]. The pregnancy rate following IVF-IMSI was significantly higher and the miscarriage rate significantly lower, than for the routine IVF-ICSI procedure (60.0% vs. 25.0%, and 14% vs. 40%, respectively) [1953]. However, the most recently updated Cochrane review of RCTs neither supported nor refuted the clinical use of IMSI [1954].

10.7.1.6 *Physiological ICSI (PICSI) technique: a selection based on membrane maturity of sperm*

The Human oocytes are surrounded by hyaluronic acid (HA), which acts as a natural selector. Only mature sperm that express receptors specific to HA can reach the oocytes and fertilise them. Those sperm have normal shapes, low DNA fragmentation rates, and low frequency of chromosomal aneuploidy [1955]. Several studies have attempted to verify whether sperm selection based on HA binding affects IVF outcomes. A meta-analysis included six prospective randomised studies and one retrospective study, all of which used a PICSI sperm-selection dish (a plastic culture dish with microdots of HA hydro gel on its inner surface) or the Sperm Slow method (a viscous medium containing HA). No improvements in fertilisation and pregnancy rates were recorded, although embryo quality was superior in PICSI compared with conventional ICSI [1955]. A recent large-sample multicentre randomised trial provided conclusive evidence against the use of PICSI in ART (PICSI live-birth rate vs. ICSI: OR: 1.12, 95% CI: 0.95–1.34) [1956]. A time-lapse study found no difference in embryo development dynamics in oocytes fertilised via HA-ICSI vs. conventional ICSI [1957].

10.7.1.7 *Magnetic-activated cell sorting*

Magnetic-activated cell sorting (MACS) is an advanced sperm-selection technique used to isolate sperm that do not show signs of apoptosis and, therefore, are presumed to have a lower rate of DNA damage [1949]. Use of MACS after density gradient centrifugation (DGC) has been found to improve sperm morphology and decrease DNA fragmentation and apoptotic markers, but it reduces motility of the selected sperm [1949, 1950]. Magnetic-activated cell sorting failed to improve ICSI outcomes compared with DGC or swim-up, although a slightly higher pregnancy rate (RR: 1.5, 95% CI: 1.14–1.98) was observed in MACS patients relative to the control group [1958]. No difference in implantation or miscarriage rate was noted (RR: 1.03, 95% CI: 0.8–1.31 and RR: 2, 95% CI: 0.19–20.9, respectively).

Finally, another RCT performed on infants conceived via ovum-donation IVF cycles did not report any differences in terms of obstetrical and perinatal outcomes between pregnancies or babies conceived with sperm selected via MACS or swim-up [1959].

10.7.2 **Safety**

The most significant risk of pre-implantation ART treatment is the ovarian hyperstimulation syndrome, a potentially life-threatening condition resulting from excessive ovarian stimulation during ART techniques, ranging from 0.6% to 5% in ART cycles [1960].

Other problems include the risk of multiple pregnancies due to the transfer of more than one embryo and the associated risks to mother and baby, including multiple and preterm birth. The most prevalent maternal complications include pre-eclampsia, gestational diabetes, placenta previa, placental abruption, postpartum haemorrhage, and preterm labour and delivery [1898, 1961, 1962]. The risks of foetal demise during the third trimester, perinatal mortality, preterm birth, and low birth weight increase with the number of foetuses in the pregnancy. The foetal consequences of preterm birth (cerebral palsy, retinopathy, and broncho-pulmonary dysplasia) and foetal growth restriction (polycythaemia, hypoglycaemia, and necrotising enterocolitis) are significant [1963].

The average number of embryos transferred in fresh non-donor IVF and ICSI cycles in 2011 was 1.91, compared with 2.09 in 2008, 2.00 in 2009, and 1.95 in 2010, reflecting a continuing decrease from previous years. The average number of embryos transferred in frozen ET cycles decreased from 1.72 in 2008 to 1.65 in 2009 to 1.60 in 2010 and to 1.59 in 2011 [1964].

The global multiple birth rate for fresh cycle transfer has decreased from 21.5% in 2010 to 20.5% in 2011 and for frozen ET cycles from 12.0% to 11.5% [1932].

In 2011, the rate of early pregnancy loss was 20.1% after fresh ET, compared with 25.4% after frozen ET. Both rates showed wide regional variation [1932]. The multiple birth rates after fresh non-donor ET was 19.6% (twins) and 0.9% (triplets and higher-order births); for frozen ET non-donor cycles, twin and triplet and higher-order birth rates were 11.1% and 0.4%, respectively [1932].

Rates of premature delivery and perinatal mortality were lower for frozen ETs than for fresh ETs. The global preterm DR after non-donor fresh ET was 19.1%, and after frozen ET was 13.1%. The perinatal mortality rate per 1,000 births after non-donor fresh ET was 16.3 and after frozen ET was 8.6.

In terms of potential adverse effect, ICSI-conceived offspring has a greater neonatal morbidity, obstetric complications and congenital malformations, compared with spontaneous conception [1965-1967]. Additionally, epigenetic disorders and impaired neurodevelopment have been observed in infants born using ICSI compared with naturally conceived children [1943]. Among singleton infants born at 37 weeks of gestation or later, those following IVF had a risk of low birth weight that was 2.6 times (95% CI: 2.4–2.7) greater than in the general population (absolute risk of low birth weight with spontaneous vs. resulting from IVF was 2.5% versus 6.5%) [1576]. Singleton infants after IVF were 39% more likely (adjusted RR: 1.39, 95% CI: 1.21–1.59) to have a non-chromosomal birth defect (particularly gastrointestinal and musculoskeletal) compared with all other singleton births. No single ART procedure (e.g., ICSI, fresh, or frozen ETs) was found to substantially increase the risk of birth defects.

Analyses from the Massachusetts Outcome Study of ART reported a 50% increase (adjusted prevalence ratio of 1.5, 95% CI: 1.3–1.6) in birth defects in infants after IVF vs. spontaneous pregnancy, and a 30% increase (adjusted prevalence ratio of 1.3, 95% CI: 1.1–1.5) in birth defects in infants after subfertility vs. spontaneous pregnancy [1968-1970]. No difference in risk of cancer was found between ART-conceived children and those spontaneously conceived [1971].

Health differences between ICSI and IVF conceptions have not been comprehensively assessed and results are contradictory. Some authors found a significantly reduced risk of birth defects in IVF compared to ICSI conceived infants [1579], while two meta-analyses demonstrated no difference in risk of congenital malformations between IVF and ICSI conception [1582, 1972]. Data about ICSI- and IVF-conceived adolescents or young adults are scarce but it seems that there is no difference in outcomes between the two techniques. Further research into health outcomes in adolescence and adulthood is required before conclusions can be drawn about the long-term safety of ICSI compared to IVF [1973].

11. LATE EFFECTS, SURVIVORSHIP AND MEN'S HEALTH

The EAU Guidelines Panel of Sexual and Reproductive Health have extensively reviewed the literature to provide guidance on: (i) late effects of urological diseases (both occurring during childhood and adulthood) on male sexual and reproductive health; (ii) late and long-term effects of cancers on male sexual and reproductive health; and, (iii) future directions to support personalised medicine strategies for promotion and raising the awareness of overall male sexual and reproductive health.

A systematic literature search for original English-language publications and review articles published up to December 2019 and a further search up to December 2020 were performed using both Pubmed and Google, yielding only a limited number of papers addressing the role of health care professionals in supporting male patients who have suffered from cancers in terms of sexual and reproductive health, or the concept of Men's Health programmes.

Despite considerable public health initiatives over the past few decades, the Panel has observed that there is still a significant gender gap between male and female in life expectancy [1974, 1975]. The main contributors to male mortality in Europe are non-communicable diseases (namely CVDs), cancer, diabetes and respiratory disease) and injuries [1679], as highlighted in a recent WHO report disproving the prevailing misconception that the higher rate of premature mortality among men is a natural phenomenon [1975, 1976]. The recent pandemic situation linked with SARS-CoV-2 infection associated disease (COVID-19) further demonstrates how the development of strategies dedicated to male health is of fundamental importance [1977].

The WHO report also addresses male sexual and reproductive health which is considered under-reported, linking in particular male infertility, as a proxy for overall health, to serious diseases in men [1876, 1881, 1882, 1979-1982]. These data suggest that health care policies should redirect their focus to preventive strategies and in particular pay attention to follow-up of men with sexual and reproductive complaints [1884, 1983].

[1983]. Considering that infertile men seem to be at greater risk of death, simply because of their inability to become fathers, is unacceptable [1885]. The Panel aims to develop a concept of a more streamlined and holistic approach to men's health.

For these guidelines, the Panel aimed to challenge clinicians to look beyond the pathology of disorders alone and consider the potential associations with other health disorders. Men with varicoceles have a higher incidence of heart disease and higher risk of diabetes and hyperlipidaemia following diagnosis [1983]. A diagnosis of infertility may have a profound psychological impact on men (and their partners), potentially resulting in anxiety, enduring sadness, anger, and a sense of personal inadequacy and "unmet masculinity" [1984]. A combination of factors, personality, sociocultural background, and specific treatments/professional support, will determine how men cope with this diagnosis [1985].

The most common cancer among European men (excluding non-melanoma skin cancer) is PCa [373]. Due to new therapeutic approaches, survival rates have improved significantly [1986] and as men live longer, health-related quality of life and related sexual well-being will become increasingly important [361]. Regardless of the type of treatment used [1692], sexual dysfunction and distress are common post-treatment complications [362, 363, 1988-1990].

Furthermore, little is known about the relevance of fertility and fertility-preservation strategies in cancer survivors [1872, 1991-1994]. In PCa, it has been documented that the psychological consequences persist, even after complete remission or cure and erectile function is restored [1995]. Therefore urologists dealing with sexual and reproductive health are primed to act as a vanguard for cancer survivorship programmes.

Finally, the relationship between ED and heart disease has been firmly established for well over two decades [300, 301, 303, 1996-1999]. Cardiovascular disease is the leading cause of both male mortality and premature mortality [2000-2003]. Studies indicate that all major risk factors for CVD, including hypertension, smoking and elevated cholesterol are more prevalent in men than women [2004-2010]. Given that ED is an established early sign of atherosclerotic disease and predicts cardiovascular events as an independent factor [303], it provides urologists with the unique opportunity for CVD screening and health modification and optimise CVD risk factors, while treating men's primary complaint (e.g., ED). Currently, both the EAU and AUA guidelines recommend screening for CVD risk factors in men with ED and late onset hypogonadism [2011-2013] (see Sections 3.7.3 and 5.2).

There is clearly a need to prospectively collect data addressing all aspects of male health, including CVD screening protocols and assess the impact of primary and secondary preventive strategies. The EAU Sexual and Reproductive Health Guidelines Panel aims to promote and develop a long-term strategy to raise men's health at a global level.

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13. CONFLICT OF INTEREST

All members of the EAU Sexual and Reproductive Health Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of conflict of interest. This information is publicly accessible through the European Association of Urology website <http://www.uroweb.org/guidelines/>. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

14. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:

EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2021. ISBN 978-94-92671-13-4.

If a publisher and/or location is required, include:

EAU Guidelines Office, Arnhem, The Netherlands. <http://uroweb.org/guidelines/compilations-of-all-guidelines/>

References to individual guidelines should be structured in the following way:

Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

Appendix 1

Table on medical management of ischaemic priapism

Author	Intervention Types (N, %)	Resolution of Priapism	Requirement for surgical management of refractory priapism	Sexual dysfunction	Side effects/ complications	Comments
Ateyah	122= Conservative Methods (122, 100%) Corporeal aspiration (92, 75.4%), Corporeal irrigation (70, 57.4%), Intracavernosal Sympathomimetics (10, 8.2%)	Conservative Methods (30, 24.6%), Corporeal aspiration (22, 23.9%), Corporeal irrigation (55, 78.57%), Intracavernosal Sympathomimetics (10, 100%)	NR	NR	NR	
Baker	9= Corporeal Aspiration (7,77.7%), Antiandrogens (9, 100%)	Immediate 5 (55.5%), total 8 (88.8%)	1 (11.1%)	NR	3 (33.3%)	
Bansal	9= Corporeal irrigation (9, 100%)	6 (66.6%)	NR	NR	NR	
Bardin	10= Corporeal Aspiration (10, 100%), Corporeal Irrigation (10, 100%), Intracavernosal Sympathomimetics (4, 40%)	7 (70%)	3 (30%)	NR	4 (40%)	
Deholl	9= Corporeal Aspiration (9, 100%), Corporeal Irrigation (9, 100%), Intracavernosal Sympathomimetics (6, 66.6%)	6 (66.6%)	3 (33.3%)	NR	NR	
Dittrich	36 Intracavernosal sympathomimetics (100%)	36 (100%)	1 (2.7%)	NR	NR	
El-Bahnasawy	50 Corporeal Aspiration (100%), Intracavernosal Sympathomimetics (100%)	Immediate 9 (18%), total 29 (58%)	NR	NR	NR	
Farrer 1961	14 Conservative Methods (11, 78.4%), Corporeal Aspiration (14, 100%), Corporeal Irrigation (14, 100%)	1 (7.1%)	NR	8 (57.1%)	Corporeal fibrosis 1 (7.1%), time point NR	
Forsberg 1981	9- Corporeal Aspiration (9,100%), oestrogens, sedatives, anticoagulants and anticholinergics (9, 100%) - epidural block (1, 11.1%)	NR	NR	6 (66.6%)	NR	
Gordon 2005	6= Conservative Methods (4, 66.7%), Intracavernosal sympathomimetics (2, 33.3%)	6 (100%)	0	1 (16.7%)	NR	

Govier 1994	24= Terbutaline 5mg, (8, 33.3%), Terbutaline 2.5mg, (7, 29.2%), Placebo (9, 37.5%)	13 (54.2%)	Terbutaline 6mg 3 (37.5%) vs Placebo: 5 (55.6%), Terb 2.5mg 3 (42.9%), p>0.05	NR	NR	
Grace 1968	17- Conservative Methods (17, 100%), Corporeal Aspiration (5, 29.4%), Pharmacological interventions: anticoagulants 3, stibestrol 3 (6, 35.3%)	non-systematic reporting - immediate resolution is <5%	NR	NR	wound infection,	
Habous 2016	53= Conservative Methods (53, 100%), Corporeal Irrigation (14, 26.4%), Intracavernosal Sympathomimetics (3, 5.7%), Pharmacological Interventions: salbutamol (32, 60.4%)	Exercise: 21 (39.6%), salbutamol 18 (34%), aspiration + irrigation saline 11 (20.75%), 3 phenylephrine (5.7%)	0%	NR	0%	
Hubler 2003	5= Intracavernosal sympathomimetics (Methylene Blue, 5, 100%)	Immediate 3 (60%), total 5 (100%) in 24 hours	0%	all had ED pre-intervention	haematoma 5, burning sensation 5 (100%)	
Jiang 2014	44= Intracavernosal sympathomimetics: Phenylephrine (44, 100%)	44 (100%)	0%	Unclear but 18/44 had ED pre-procedure	throbbing sensation but unclear whether this was from phenylephrine or alprostadil	
Kadioglu 1995	9= Intracavernosal sympathomimetics (Methylene Blue, 9, 100%)	9 (100%)	0%	3 (33.3%) reported ED at 3 weeks; at 6 weeks, 1/3 had ED	pain 9 (100%)	
Keskin 2000	19= Intracavernosal Sympathomimetics (adrenaline, 19, 100%)	Immediate 10 (53%), total 18 (94.7%)	0%	0%	0%	
Khurana 2002	9- conservative Methods (cold enema, 9, 100%), Corporeal Irrigation (1/9, 11.1%)	enema 5 (55.5%) , aspiration 1 (11.1%)	NR (3 pts referred to urological center for further management)	NR	NR	
Kulmala 1996	53= Conservative Methods (16, 30.2%), Corporeal Aspiration (8, 15.1%), Corporeal Irrigation (17, 32.1%), Intracavernosal Sympathomimetics (12, 22.6%)	NR	NR	Conservative 5 (31%), Incision + Aspiration 3 (38%), Puncture + Lavation 12 (71%), Puncture +Alpha sympathomimetics 11 (92%)	NR	

Kumar 2019	71 (no separate results on 69 non-SCD pt): Corporeal Aspiration (71, 100%), some of the pts had phenylephrine but number unclear	15 (21%) no separate results on non-SCD pts	NR	NR	NR	
Larocque 1974	23= Conservative Methods (16, 69.6%), Corporeal Aspiration (7, 31.3%)	Conservative (5, 31.2%, includes various ways of management such as sedation, analgesics, exercise, ice packs, stilbestrol, enema, oxygen, proteolytic enzymes, epidural anaesthesia, sodium bicarbonate, low molecular weight dextran), aspiration (2, 28.6%)	NR	NR	NR	
Lowe 1993	75= Pharmacological Interventions: (25 oral terbutaline, 25 oral pseudoephedrine, 50 placebo)	Terbutaline 9 (36%), Pseudoephedrine 7 (28%), Pbo 3 (12%), Terbutaline sig >Pbo	0%	NR	NR	All non-responders were offered aspiration and irrigation (successful in all)
Martinez Portillo 2001	12= Corporeal Aspiration (12, 100%), Corporeal Irrigation (12, 100%), Intracavernosal Sympathomimetics (2, 17%), Pharmacological Intervention (1, 8%)	Total 10 (83.3%), all with corporeal injection	NR	no change in baseline ED function in patients with priapism due to corporeal injections. Leukaemia patient regained potency. Idiopathic patient impotent.	Temporary side effects: Burning sensation in 6/12, blue discolorisation in 4/12	
Molina 1989	12= Corporeal Aspiration (12, 100%), Corporeal Irrigation (12, 100%), Intracavernosal Sympathomimetics (12, 100%)	Irrigation and epinephrine, 10 (83.3%)	NR	Not specified individual data, "all patients who were spontaneously potent before continued to be potent"? 11/16	NR	
Moloney 1975	5= Conservative management, Corporeal Irrigation, Pharmacological Intervention (5, 100%, exact numbers not specified)	Unclear, but likely 5, 100%	NR	2(40%)	NR	

Muruve 1996	9= Intracavernosal Sympathomimetics (9, 100%)	Total 9, 100%; Sympathomimetics 8 (88.9%). Sympathomimetics followed by corporeal aspiration: 1 (11.1%)	0(0%)	NR	minor haematoma in 1 patient	
Pal 2016	19= Corporeal Aspiration (2, 11%), Intracavernosal Sympathomimetics (17, 89%)	Aspirin and ICI: 3 (15.8%)	16(84%)	Unclear; 2/3 patients treated with aspiration and ICI had preserved erectile function	NR	
Pantaleo-Gandais 1984	35= Conservative Methods (35, 100%)	Conservative management 4 (11.4%)	31(88.57%)	Good sexual function in only 1/4 responders	NR	Mixed SCD and non-SCD population
Passavanti 2009	17= Corporeal Aspiration (17, 100%), Corporeal Irrigation (17, 100%), Intracavernosal Sympathomimetics (7, 41%; adrenaline 5, and adrenaline + ethylephrine 2), Intracorporeal Sympathomimetics (Methylene Blue)	Total 12, (70.6%, 10 purely from methylene blue and aspiration and irrigation; 2 required additional ICI adrenaline)	4(24%)	NR	NR	
Priyadarshi 2004	68= Pharmacological Interventions (34 Terbutaline, 34 Placebo, 100%)	42% terbutaline group vs 15% placebo gp (p<0.05).	NR	NR	Tachycardia 34(30%)	
Ridyard 2016	50 (mixed SCD and non-SCD pts): Intracavernosal Sympathomimetics: (38, 65%; phenylephrine alone), Intracavernosal Sympathomimetics and Corporeal Irrigation: (12, 21%; phenylephrine and irrigation)	42 (84%)	overall 8(14%) [ICI (0%), idiopathic (14%), scd (0%), psychiatric medicines (37%), cocaine(05), PDE5inhibitors (0%), other (100%)	NR	0(0%)	
Zhao	136 episodes= Conservative Methods (25, 14.8%), Corporeal Aspiration/Irrigation (4, 2.4%), Intracavernosal Sympathomimetics (19, 11.4%), Combination of Corporeal Aspiration/ Irrigation and Sympathomimetics (119, 70.4%)	141 (84.6%)	26 (15.4%)	NR	NR	
Watters	17= Intracavernosal Sympathomimetics (17, 100%)	16 (94%)	1(6%)	NR	NR	

Vorobets	10= Intracavernosal Sympathomimetics (10, 100%)	0 (0%)	10 (100%)	NR	NR	
Van Driel	8= Corporeal Aspiration (8, 100%), Intracavernosal Sympathomimetics (8, 100%)	6 (75%)	2(25%)	NR	NR	
Ugwumba	7= Corporeal Aspiration (7, 100%), Corporeal Irrigation (7, 100%), Intracavernosal Sympathomimetics (1, 14%)	0	7(100%)	NR	NR	
Torok	72= Corporeal Aspiration (72, 100%), Intracavernosal Sympathomimetics (72, 100%)	72 (100%)	0(0%)	NR	NR	
Stief	29= Corporeal Aspiration (3, 10.3%), Intracavernosal Sympathomimetics (26, 89.7%)	29 (100%)	NR	NR	NR	
Sonmez	46= Corporeal Aspiration (46, 100%), Corporeal Irrigation (46, 100%), Intracavernosal Sympathomimetics (4, 8.7%)	39 (84.7%)	7(15.3%)	NR	NR	
Soler	14= Conservative Methods (14, 100%), Corporeal Aspiration (2, 14%), Pharmacological Interventions (14, 100%)	14 (100%)	0(0%)	NR	piloerection	
Serrate	23= Intracavernosal Sympathomimetics (23, 100%)	23 (100%)	NR	NR	NR	
Saffoncuartas	31= Conservative Methods (31, 100%), Corporeal Aspiration (1, 3.2%), Corporeal Irrigation (1, 3.2%), Intracavernosal Sympathomimetics (19, 61.3%), Pharmacological Interventions (1, 3.2%)	31 (100%)	NR	NR	NR	

Appendix 2

Table on Surgical shunts in ischaemic priapism

Study	n	Non-Surgical Intervention (%)	Surgical Intervention (n/ %)	Resolution of priapism (%)	Sexual function	Surgical adverse event
Kumar <i>et al.</i> 2019	71	Penile aspiration +/- alpha adrenergic agonist irrigation n=24 (33%)	Distal shunt n=38(53%) [Winter shunt (n=30), Ebbehøj (n=6), Al-Ghorab (n=2)] Proximal shunt n=9(12%) [Quackle(n=6,) Grayhack (n=3)]	Distal shunt 42.01% Proximal shunt 55.55% Penile aspiration 21.12%	21 (29.57%) patients followed up at 6 months n=15 (71.4%) reported moderate to severe ED	Complication following shunts (n=20, 42.5%) [Wound infection n=5, Shunt site bleeding n=14, skin necrosis n=1]
Lian <i>et al.</i> 2010	12	-	Corporospongiosal shunt with intracorporeal tunnelling (n=12)	100%	Average FU 21.6+/-10.1 months IIEF5 score 11.7+/-6.3 post treatment (vs 23.7+/- 1.1 prior to priapism)	No severe complications noted
Macaluso <i>et al.</i> 1985	34	n=29 (85.2%) had initial conservative treatment	12/29 patients (41.3%) required surgery with Winter's shunt	100% with Winter's shunt	-	Overall complications from surgery 5/12 (41.6%) [Urethral injury (n=1), Penoscrotal haematoma (n=3), Epididymitis (n=1)]
Moloney <i>et al.</i> 1975	11	-	Saphenocavernous bypass (n=12)	100%	70% 'good' if functional outcome' and 30% 'fair functional outcome'	-
Muneer <i>et al.</i> 2008	60 (stuttering)	100% initial non-surgical treatment	Surgical procedures in n=12 [Penile prosthesis n=3, embolisation n=5, Winter shunt n=1, El-Ebbehøj n=1, Cavernosal ligation n=1)	Success rate 100% for Penile prosthesis, 20% for embolisation and 0% for other surgical therapies	-	-
Nelson <i>et al.</i> 1976	48	-	Winter's shunt (n=8) Saphenocavernous bypass (n=3)	Shunt success 10/11 (failed in single case when done in priapism due to sickle cell disease)	50% potency rate in patients treated by aspiration followed by shunting	-
Nixon <i>et al.</i> 2003	28	-	Winter's shunt (n=14) Al Ghorab Shunt(n=13) Quackle shunt (n=1)	Winters shunt 14.2% (n=12 required reoperation) Al Ghorab 92% (n=1 required reoperation) Quackle 100% success	2/20 available patients for FU (10%) had preserved erectile function following shunt surgery	-

Pantaleo-Gandais <i>et al.</i> 1984	35	100% had initial conservative management	Surgery required in 31 cases (88.57%) [corporocavernosal incision n=8, cavernous spongiosum shunt n=9, cavernous-saphenous shunts n=4, Ebbehoj n=9, Winters n=1]	Overall 85.7% success across all shunts	100% preservation of sexual function if priapism <3 days duration (n=17) 11.1% preservation of sexual function if priapism >3days	-
Ugwumba <i>et al.</i> 2015	15	13/15 (86.6%) had initial conservative treatment prior to shunting	Glanulo-cavernous (Al-Ghorab) shunt n=15 (100%)	Immediate detumescence (n=14, 93.3%) Delayed detumescence (n=1, 6.7%)	46.7% ED ED increased if presentation was >24h	
Lawani <i>et al.</i> 1999	66	100% had initial conservative treatment	Surgical procedures in 53/66 (80.3%) [bilateral cavernotomies n=23, cavernoglandular shunt n=11, cavernospongiosal shunt n=18, cavernosaphenous shunt n=1]	100% immediate detumescence post-surgery	50% ED rate in 12 patients who had follow-up	-
Pal <i>et al.</i> 2016	19	100% had aspiration prior to surgery	16/19 (84%) had surgery [Winter's shunt (n=16) Al Ghorab shunt (n=6) Quackle shunt (n=5)]	18.7% Winter's shunt 66.7% Al Ghorab shunt 62.5% Corporal snake 60% Quackle's shunt	Preservation of erectile function 66.7% for aspiration only 18.1% for proximal shunts 20% for distal shunts	N=3 (15.7%) had complications [urethral injury n=1, cavernositis n=1, skin necrosis n=1]
Wendel <i>et al.</i> 1981	8	-	Corporo cavernosa – glans penis shunt (n=8)	87.5% success rate	-	-
Kihl <i>et al.</i> 1980	31	-	Saphenocavernous shunting (n=26)	76.9% initial success 23.1% required further shunting	7/26 (26.9%) potent at months – 10 yrs	N=5 (19.2%) complication rate [Urethrocutaneous fistula n=1, haematoma n=2, thrombophlebitis n=1, altered sensation n=1]
Kilinc <i>et al.</i> 2009	15		Cavernosal-cephalic vein shunt (n=15)	86.6% success (n=2 required further saphenocavernosal shunt)	3/13 (23) reported ED at 12 months	No major complications reported
Klufio <i>et al.</i> 1991	20		Al Ghorab shunt (n=20)	All had immediate detumescence (100%)	39% potency rate	10% complication rate (post-operative bleeding n=2)
Adeyato <i>et al.</i> 2009	54	N=19 (35%)	N= 35 (65%) Ebbhoj's shunt	2/35 (5.7%) had recurrence in the immediate postop period	Potency rate 47.37% conservative vs 70.37% for shunt	-

Aghagi <i>et al.</i> 2000	35	All had prior conservative treatment	N=35 had surgery [Perineal cavernospongiosal shunt (n=14), modified corporospongiosal shunt (n=21)]	100% detumescence postop	8/35 (22.8%) had absent erections post-surgery	-
Brant <i>et al.</i> 2009	13	All had prior conservative treatment	T shunt (n=13)	12/13 (92%) had resolution (n=1 required further T shunt)	84.6% erectile function	No major surgical complications
Canguven <i>et al.</i> 2013	15	-	Transient distal penile shunt	10/15 (66% success rate)	-	-
Carter <i>et al.</i> 1976	12	-	Corporosaphenous shunt (n=2) Cavernospongiosum shunt (n=10)	Not clear	100%ED in corporosaphenous shunt 4/7 (57.1%) potency rate following cavernospongiosus shunt	
Chary <i>et al.</i> 1981	8	-	Caverno-glandular shunt (n=8)	100% success	50% potency rate	(n=1 cavernositis, 12.5%)
Klein <i>et al.</i> 1972	9	-	Corpus saphenous shunt (n=9)	22.2% (n=2) had partial response immediately	11.1% potency rate	

Appendix 3

Table on penile prosthesis insertion for ischaemic priapism

Study	n	Non-Surgical Intervention (%)	Surgical Intervention (n/ %)	Resolution of priapism (%)	Sexual function	Surgical adverse event
Rees <i>et al.</i> 2002	8	All had prior conservative treatment	Penile prosthesis n=8 (4 had prior shunt)	All implants successful (mean duration of priapism at presentation 91h)	7/8 (87.5%) sexually active 100% satisfaction in those sexually active	N=1 penile deformity for revision due to fibrosis around cylinder
Zacharakis <i>et al.</i> 2014	95	All had prior conservative treatment	N=68 penile implants (early median 7 days) vs n=27 delayed implants (median of 5 months)	100%	25/95 (26.3%) able to have intercourse Satisfaction 96% for immediate implant vs. 60% for delayed group	13/95 (13.6%) required revision surgery due to complications
Salem <i>et al.</i> 2010	12	All had prior conservative treatment	12 acute	100%	100% achieved intercourse	No revision surgery required No postoperative complications noted
Sedigh <i>et al.</i> 2011	20	N=6 non-surgical treatment	N=10 shunts (n=5 of those had early penile prosthesis)	100%	100% satisfaction with prosthesis 100% of penile prosthesis group sexually active	No complications from prosthesis insertion
Zacharakis <i>et al.</i> 2015	10	-	N=10, malleable penile prosthesis	100%	80% satisfaction as per IIEF at 3 months	No erosion or urethral injury noted

Appendix 4

Table on series of early and delayed penile prosthesis implantation secondary to priapism

Study	n: early/ delayed	n: priapism/ total	n: malleable/ inflatable	Technique	Mean follow-up (months)	Complications	Outcomes
Small [2014]	0/4	4/4	3/0	Sharp dissection	38	inability (1)	Success (3)
Bertram <i>et al.</i> [2015]	0/6	6/6	4/1	Sharp dissection	N/A	inability (1)	Success (5)
Kelami [2016]	0/12	12/12	12/0	N/A	N/A	N/A	N/A
Mireku-Boateng [2017]	2/0	2/2	2/0	N/A	36	-	Success (2)
Douglas <i>et al.</i> [2018]	0/5	5/5	5/0	Excavation	48	Urethral erosion (2), revision (1)	Success (4)
Kabalin [2019]	0/1	1/1	1/0	corporotomy	N/A	Inability to insert inflatable prosthesis	Success (1)
Knoll <i>et al.</i> [2020]	0/20	2/20	0/20	Downsized device	20	Infection (1), mechanical failure (1), hypoesthesia (2)	Success (19)
Herschorn <i>et al.</i> [2021]	0/11	2/11	2/9	PTFE graft	46	Revision (3)	Success (8)
George <i>et al.</i> [2022]	0/12	2/12	7/5	Scar excision (12), PTFE graft (1)	22	Perforation (1), malfunction (1)	Success (11)
Sundaram [2023]	1/0	1/1	0/1	N/A	8	-	Success (1)
Upadhyay <i>et al.</i> [1342]	1/0	1/1	1/0	N/A	6	-	Success (1)
Rajpurkar <i>et al.</i> [2024]	0/34	4/34	11/23	Multiple incisions+ scar excision	23.7	Perforation (1), malfunction (1)	Success (34)
Mooreville <i>et al.</i> [2025]	0/16	3/16	0/16	Cavernotom+ Downsized (14)	N/A	Perforation (6), crossover (3)	Success (16)
Ghanem <i>et al.</i> [2026]	0/17	5/17	10/7	Corporal counter incision	N/A	Perforation (1)	Success (17)
Park <i>et al.</i> [2027]	0/1	1/1	0/1	Narrow base, evaporisation	12	-	Success (1)
Montague <i>et al.</i> [2028]	0/9	4/9	0/9	Excavation, downsized (7)	44	Malfunction (1)	Success (9)
Shaeer [2029]	0/12	4/12	8/4	Shaeer excavation	N/A	-	Success (12)
Durazi <i>et al.</i> [2030]	0/17	17/17	11/6	Corporotomy + partial excavation	22.7	Urethral injury (2)	Success (17)
Lopes <i>et al.</i> [2031]	0/8	3/8	8/0	Bovine pericardium graft	32	-	Success (5)
Ralph <i>et al.</i> [1339]	50/0	50/50	50/0	Hegar dilator	16	Infection (3), revision for erosion (3), cylinders too short (2), autoinflation (1), penile curvature (1)	Success (48)
Salem <i>et al.</i> [1340]	12/0	12/12	12/0	N/A	15	Significant penile shortening	Success (12)
Stember <i>et al.</i> [2032]	0/1	1/1	0/1	Narrow base, sharp corporal excision	3	Urethral injury (1)	
Sedigh <i>et al.</i> [1341]	5/0	5/5	1 /4	N/A	N/A	Urethral injury (1)	Success (5)

Bella <i>et al.</i> [1344]	0/5	5/5	0/5	Rosello dilator	N/A	Urethral injury (1)	Success (5)
Egydio <i>et al.</i> [2033]	0/69	24/69	57/12	Double-windsocks	22.5	Urethral injury (4)	Success (42), Somewhat satisfaction (19)
Razzaghi <i>et al.</i> [2034]	14/0	14/14	14/0	N/A	14	-	Success (14)
Zacharakis <i>et al.</i> [1250]	68/27	95/95	76/19	Downsized (15 in delayed group)	17	Infection (5), penile curvature (1)	96% success in early group / 60% success in delayed group
Tausch <i>et al.</i> [2035]	14/0	14/14	14/0	N/A	N/A	Infection (1), distal extrusion (1) Urethral injury (1)	Success (14)
Faddan <i>et al.</i> [2036]	1/0	1/1	1/0	N/A	N/A		Success (1)
Bozkurt <i>et al.</i> [2037]	0/2	1/2	1/1	Use of microdebrider for excavation	12	-	Success (2)
Tsambarlis <i>et al.</i> [1345]	0/13	2/13	0/13	use vacuum device preoperatively	N/A	Infection (1), revision (1)	Success (12)
Hebert <i>et al.</i> [2038]	30/42	14/72	0/72	Rosello dilator, downsized (63)	12	urethral injury (2), corporal perforation (15), cross-over (5), inability to dilate (1), infection (3), urethral erosion (2), glans erosion (7)	87% success in early group / 67% success in delayed group
Summary	198/344	317/542	311/229	Excavation, Shaeer technique, Rosello cavernotome, excision of scar, downsized prosthesis with grafting	22.4	Infection: early 1-10% / delayed 3-20% Perforation, crossover or erosion: early 11% / delayed 13% Urethral injury: early 1% / delayed 3%	Success rate: early 87-100% / delayed 60-100%

Appendix 5

Table on embolisation for non-ischaeamic priapism

Study	n	Non-Surgical Intervention (%)	Surgical Intervention (n/ %)	Resolution of priapism (%)	Sexual function	Surgical adverse event
Bastuba <i>et al.</i> 1994	7	-	Embolisation (n=7) post traumatic	100% resolution between 4 – 126 days	Full erectile function return at 2weeks-5months	-
Bartsch <i>et al.</i> 2004	9	-	Embolisation (n=9) post trauma	8/9 (88.8%) success; once case required repeat embolisation	100% potency at 4 weeks	Coil displacement in1 case requiring repeat procedure
Baba <i>et al.</i> 2007	6	-	Embolisation (n=9) with gelatine sponge or microcoil	Detumescence achieved in 83.3% at 1 months and 100% within 'few months'	100% normal erectile function at 5 years	-
Liu <i>et al.</i> 2008	8	-	Embolisation with gelatine (n=2, 25%) Embolisation with microcoil(n=6, 75%)	100% redo embolisation in gelatine group at 1 week 100% success rate from microcoil embolisation	Mean IIEF 22.2 at 6 months post embolisation	-
Miller <i>et al.</i> 1995	5	-	Embolisation with gelatine (n=4) Embolisation with autologous clot (n=1)	100%	-	-
Numan <i>et al.</i> 2008	11	-	Embolisation with autologous clot (n=11)	100% initial success Repeat embolisation required in 27.2% (n=3)	100% erectile function restoration at 6 weeks	-
Kim <i>et al.</i> 2007	27	-	Embolisation (autologous clot n=12, gelatine sponge n=12, microcoil and Sponge n=1, polyvinyl n=1, Nbutylcyanoacrylate n=1)	89% following first embolisation 7% required repeat embolization 4% subsequent shunt surgery	No change in premorbid erectile function (78%)	-
Cantademir <i>et al.</i> 2010	7	-	Embolisation (n=7)	6/7 (85.7%) complete detumescence (n=1 required redo embolisation)	No signs of ED detected at mean FU of 6 years	-
Chick <i>et al.</i> 2018	20	-	Embolisation using autologous clot, micocoil, polyvinyl or combination (n=20)	18/20 (90%) success	Mean IIEF score post embolisation 25.8	-
Ciampalini <i>et al.</i> 2002	10	-	Embolisation (n=9, 90%) Artery ligation (n=1, 10%)	44% recurrence rate following first embolisation	Sexual function preserved in 80%	-
DeMagistris <i>et al.</i> 2020	9	-	Embolisation with microcoils, microparticles or spingostran (n=11)	100% immediate detumescence 2/9 (22% required retreatment at 1-2 weeks)	Erectile function preserved compared to premorbid state	No major complications
Gorich <i>et al.</i> 2002	6	-	Embolisation with gelatine (n=3) and microcoil (n=3)	100% success	100% potency	-

