

# Oral contraceptives and cardiovascular disease: emerging evidence on potential associations with angina, myocardial infarction and stroke

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Associations between combined estrogen/progestin oral contraceptives (OCs) and cardiovascular disease (CVD) have long been the focus of considerable concern. Initial, epidemiologic studies demonstrated increased risks of potential complications including deep venous thrombosis/pulmonary embolism, myocardial infarction and stroke. While the studies regarding venous thromboembolism consistently demonstrate at least some degree of risk associated with OC use, recent studies of both current and past OC users indicate that the association with arterial disease is dynamic, changing rapidly as OC formulations and OC-user populations change. As physicians increase selection, screening and monitoring of OC users, a healthier OC-user population is developing. Thus, many newer studies are demonstrating rates of angina and myocardial infarction that are either lower or the same as that of non-users, unless pre-existing risk factors are present leading to potential increases in risk of CVD. The evidence with regards to strokes is more complicated and controversial. While further study is necessary, current evidence suggests that OC use provides significant contraceptive benefits with minimal potential adverse effects in healthy users. The potential for CVD reduction in selected OC users merits the highest priority for further investigation.

Arterial cardiovascular disease (CVD), herein defined as angina, myocardial infarction (MI), cerebrovascular accident and peripheral arterial disease, causes a distressing degree of morbidity and mortality in modern society. It is responsible for millions of deaths each year. In Europe, approximately four million deaths per year are attributed to CVD, accounting for almost half of all yearly deaths [101]. In the USA, nearly one million people died of cardiovascular-related diseases in 2002, resulting in 1 out of every 2.6 deaths being attributed to CVD [102]. Amongst women, CVD is the most common cause of death in developed nations. CVD-related morbidity and mortality are pre-eminent concerns in both basic science and clinical branches of medicine and represent a central focus of many public health programs.

The significance of CVD bears considerable import in all aspects of women's health, leading to heightened focus on any potential contributing factors. Common risk factors for adverse cardiovascular outcomes include obesity, hypercholesterolemia, smoking, diabetes and hypertension. With the exception of smoking, the prevalence of these risk factors is much higher in women over 35 years of age. Thus, the majority of cardiovascular morbidity and mortality occurs in peri-menopausal and postmenopausal

women, whose age and long-term exposure to risk factors substantially increase incidence rates.

Amongst premenopausal women, one factor that has been the source of significant scrutiny and controversy is the combined estrogen/progestin oral contraceptive pill (OC) – the focus of this review. Made widely available in the early 1960s, their immediate popularity spurred considerable concerns based on early studies that demonstrated an increased CVD risk in users of high-dose (> 50 µg ethinyl estradiol, and either norethynodrel, norethisterone or norethindrone) containing pills [1,2]. Cited concerns included increased risks of MI, fatal MI and stroke. As a result, OC formulations with lower doses of estradiol and newer progestins were marketed. Subsequently, many epidemiological studies have presented either conflicting results, or have demonstrated increased risks only in users of early generation OCs and/or those with risk factors at the time of prescription. The purpose of this article is to review the body of evidence in regards to the association of OCs and arterial CVD, with a specific focus on emerging evidence on differential risks for healthy versus at-risk OC users.

## Lessons from history

Early formulations of OCs, made available in the 1950s, contained relatively high doses of ethinyl

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estradiol ranging from 50 to 150 ug/day. The first report of an adverse vascular event associated with OC use appeared in 1961, when a nurse using a 100 ug (mestranol) estrogen formulation experienced a pulmonary embolism [3]. Subsequent case reports and epidemiological studies reported increased risks of adverse CVD outcomes in high-dose OC users [4–9]. Although these findings were not universal [10], the spectre of potential complications resulted in the development of low-dose (< 50 ug estrogen) formulations in an attempt to mitigate the adverse events associated with exposure to contraceptive steroids. These newer OC pills generally contained 30–35 ug of estrogen and also incorporated newer progestins [11]. Most recently, manufacturers have developed new formulations with even lower doses (i.e., 20 ug ethinyl estradiol) and newer, less androgenic progestins (e.g., desogestrel, norgestimate). Novel delivery systems have also been developed, including contraceptive steroid-bearing vaginal rings (Nuvaring®, Organon, USA) and transdermal patches (Ortho Evra®, Ortho-McNeil, USA). Since these systems eliminate the first-pass effect through the liver, their effect on CVD may be different than conventional delivery systems and at present remains largely unknown.

These changes are critical in terms of the pathophysiological mechanisms involved in the potential genesis of CVD as a result of OC use. Early formulations were known to have adverse effects on lipid profiles and thrombotic tendencies [12]. However, more recent studies have demonstrated variable changes in lipid profiles depending on OC composition and dose [13]. In particular, formulations containing newer or low-dose progestins have favorable changes on lipid profiles, including an increase in high-density lipoprotein levels [14], lower low-density lipoprotein (LDL) levels [15], and improved postprandial chylomicron levels [16], an important factor in reducing adverse CVD outcomes. Although some studies have demonstrated no related benefit in CVD outcomes [17], others claim population studies are inadequate to assess the impact of OC-induced lipid changes on CVD [18]. Adverse effects on blood pressure are also reduced or eliminated in low-dose formulations [19], a critical factor in light of evidence that shall be reviewed below regarding the importance of CVD risk factors in OC users.

OCs likely contribute to adverse changes in hemostatic variables. There is substantial biomolecular and epidemiologic data to support an increase in risk of occlusive venous disease with

virtually every OC formulation available [20], although not all authors agree that the association is causal [21]. In general, OC use increases the risk of deep venous thrombosis (DVT) and pulmonary embolus, three to six times above the baseline level [22]. Thus, it has been suggested that women at risk for venous thromboembolic disease based on personal history of inherited or acquired thrombophilias, family history of coagulopathy or other related risk factors, should avoid OC use, if possible, and in those with a personal history of DVT it is absolutely contraindicated [20]. With the existence of other reversible contraceptive methods with little or no risk of venous thromboembolism (i.e., intrauterine device), there is no mandate to prescribe OCs for this specific subpopulation of patients.

Although similarities exist between arterial and venous occlusion, substantial differences are also present. For example, while stasis is a significant risk factor for venous thrombosis, it plays a minimal role in arterial occlusions, where endothelial injury or dysfunction is the critical pathological step necessary for occlusion [23]. The role of prothrombotic genetic alteration in arterial disease is also not well understood, but is believed to only minimally increase arterial thrombosis [18]. Interestingly, potential OC-associated adverse cardiovascular events are thought to be caused by atypical vascular changes or thrombi. Angiographic studies of CVD events in OC users have revealed a greater preponderance of short-term, focal, smooth irregularities, associated with intimal cell hyperplasia or hypertrophy, rather than the irregular abnormalities observed in the angiograms of patients with coronary atherosclerosis [24]. These and other studies have led to the belief that potential CVD events associated with OC use are generally thrombotic in origin [25]. However, extensive pathologic data in women using newer OCs is lacking, and previous reports have included patients with pre-existing CVD risk factors.

Thus, while initial investigations revealed a positive association between OC use and CVD, many of these reports focused on patients exposed to high-dose pills, with different pathophysiologic-effect profiles from the currently marketed OCs [26]. As stated, newer contraceptive regimens have improved lipid profiles, with many demonstrating beneficial increases in high-density lipoprotein (HDL) levels. Angiographic studies of cardiovascular events in OC users have not been sufficiently powered to demonstrate differences in OC gen-

**Table 1. Common risk factors for cardiovascular disease.**

Risk factor	Threshold level
Hypertension	BP > 140 mmHg systolic or > 90 mmHg diastolic
Hypercholesterolemia	Total cholesterol > 200 mg/dL
Diabetes	Fasting BS > 126 mg/dL or 2 h OGTT > 200 mg/dL
Age	Postmenopausal (mean age 51 years)
Smoking	Any (risks higher when > 15 cigarettes/day)
Migraine	NA
Obesity	BMI > 30 kg/m <sup>2</sup>

BMI: Body mass index; BP: Blood pressure; BS: Blood sugar; NA: Not applicable; OGTT: Oral glucose challenge test.

erations, thus providing us with no evidence of the pathophysiologic impact of these agents, as currently prescribed and used, on CVD outcomes. Furthermore, patient selection and screening practices were not as widespread as currently practiced, resulting in some patients being prescribed OCs despite the presence of significant risk factors such as smoking and/or hypertension. Prescription practices and OC user characteristics have changed over time to reflect a healthier OC-user population [27]. These dramatic changes have reduced the applicability and relevance of previous studies, which analyzed patients with predominantly different risks and exposures than seen in current OC populations in developed countries [28]. In 1998, one author reported that when searching for reports of risk in healthy, non-smoking patients without obvious CVD risk factors, only one study of MI and one study of ischemic stroke were identified [29]. Thus, some older studies must be re-examined and more recent studies, from developed countries, need to be analyzed to elucidate the impact of OCs in terms of their current spectrum of usage.

#### Current evidence

The association between OC use and CVD has been extensively reviewed [17,25,30–32]. The majority of authors, including those who initially published results demonstrating increased risks, now believe that there is little or no risk associated with the current use of newer generation OCs in healthy, low-risk women [17,25,26,28–32]. Women with established risk factors (Table 1) such as, smoking, hypertension, diabetes, hyperlipidemia, obesity and migraine (for stroke) [35,36] who are questionable candidates for OC use, may experience a modest to highly significant increase in risk of CVD. Smoking, in particular, plays a critical role in the pathogenesis of all CVD in all

reproductive-age women and steroid contraceptives potentiate its effects [31].

A review of the evidence is important to understanding these associations. Few studies have focused on overall CVD risks, thus we will present outcomes in relation to some individual factors for which data exist, namely angina, MI, cerebrovascular accident (ischemic/thrombotic and hemorrhagic stroke), and peripheral arterial disease.

#### Angina

At least one study has specifically examined the relationship between OC use and angina pectoris (Table 2) [37]. Mant and colleagues analyzed the results in both current and past users of OCs in the Oxford Family Planning Association Study (OFPAS). In their final report on the results of this long-term study, the authors found 104 patients with angina pectoris. They demonstrated that amongst current OC users (defined as either current or within the last year), risks for angina pectoris were generally lower than in never-users, with odds ratios (ORs) ranging from 0.3 to 0.9 depending on the duration of OC use and time since last usage, although not all results were statistically significant. In current and recent (within 12 months) users, there was a nominally statistically significant 70% reduction in angina risk and in women who had used OCs for longer than 8 years, there was a statistically significant 40% reduction in angina incidence. Unexpectedly, these results were not significant after limiting the analysis to patients without any known risk factors. Past users of OCs demonstrated trends towards decreased risks, even 8 years or more since last usage, but these results were not significant. Although the authors did not rule out the possible influence of confounding biases, these results support a potential cardiovascular benefit in current OC users. Since angina is often the result of atherosclerotic changes, a reduction in angina incidence is potentially mediated by reducing the incidence or severity of atherosclerosis, an intriguing possibility in light of the aforementioned angiographic findings in reproductive-age patients with MI and the biological effects of estrogen and progestins on atherogenic processes [24,38]. The reduced risk of angina may suggest that OC-mediated pathophysiological adaptations result in a reduction or prevention of atherosclerotic changes. Results of one study, however, are difficult to apply to a general population of patients and so these findings must be verified by further investigation.

**Table 2. Association between oral contraceptives and angina pectoris.**

Time since last OC use (years)	Adjusted for CVD risk factors			Patients without CVD risk factors		
	OR	95% CI		OR	95% CI	
Current-1	0.3§	0.1	1.0	0.5	0.1	1.4
1-8	0.8	0.5	1.3	1.0	0.6	1.9
> 8	0.7	0.4	1.0	0.7	0.4	1.3

Results are referenced against never users of oral contraceptives. Adjusted results were controlled for age, parity, social class, smoking and quetelet index. Patients without risk factors excluded women with hypertension, hyperlipidemia, or diabetes. Adapted from [37].

§ $p < 0.05$ ; CI: Confidence interval; CVD: Cardiovascular disease; OC: Oral contraceptive; OR: Odds ratio.

#### MI in current OC users

Many studies have investigated the relationship between OC use and MI. Table 3 demonstrates that the majority of recent studies have reported either no increase in risk or an increase in risk only in OC users who have predisposing risk factors (Table 1) or who were not properly screened (Table 5), a finding that is supported by many, but not all, of the studies.

Several of these studies merit special consideration. The Royal College of Family Practitioners' study found a non-significant increase of 80% in the overall analysis (OR = 1.8, 95% CI 0.9–3.6), but a non-significant 10% reduction in OC users who never smoked (OR = 0.9, 0.3–2.7) [39]. The aforementioned OFPAS study examined the risk of MI in 17,032 women [37]. The study was conducted as a pro-

spective cohort, with recruitment between 1968 and 1974 and annual follow-up until patients achieved 45 years of age. Overall, there were 85 cases of MI over more than 310,000 woman-years of OC exposure. When controlled for conventional risk factors including age, parity, social class, smoking, and Quetelet index, there were no statistically significant increases of MI in current OC users as compared to never-users. Interestingly, in women with less than 8 years duration of OC use and no history of hypertension, hyperlipidemia or diabetes, there was a nominally significant increase in risk of MI (OR = 1.9, 95% CI 1.0–3.5,  $p < 0.05$ ). However, subanalysis of this group demonstrated that risks were elevated only in patients smoking 15 or more cigarettes per day (OR = 4.9, 95% CI 1.2–23.6).

**Table 3. Association between current oral contraceptive use and myocardial infarction.**

Author	Year	Adjusted for CVD risk factors			Patients without CVD risk factors			Ref.
		OR	95% CI		OR	95% CI		
Croft	1989	1.8	0.9	3.6	0.9	0.3	2.7	[41]
Mant	1998	1.2	0.5	2.7	0.6 <sup>†</sup>	0.1	2.3	[39]
WHO (Europe)	1997	5.01	2.54	9.90	1.10 <sup>*</sup>	0.12	9.69	[42]
Dunn	1999	1.40	0.78	2.52	NR			[43]
Tanis	2001	2.1	1.4	3.1	2.0 <sup>‡</sup>	1.0	4.1	[44]
Rosenberg	2001	1.3	0.8	2.2	1.3 <sup>§</sup>	0.6	3.0	[35]
Stampfer	1988	2.5	1.3	4.9	NR			[45]
Sidney	1998	0.94	0.44	2.20	NR			[46]
Lewis	1997	2.35	1.42	3.89	NR			[47]

\*Result from analysis of patients without hypertension, hyperlipidemia, diabetes or smoking.

†Results from analysis of low-risk patients with blood pressure screening prior to current OC use.

‡Results from analysis of nonsmoking OC users, adjusted for age, area of residence, and calendar year.

§Results from analysis of nonsmoking current OC users.

CI: Confidence interval; CVD: Cardiovascular disease; OR: Odds ratio; NR: Not reported; WHO: World Health Organization.

**Table 4. Association between past oral contraceptive use and myocardial infarction.**

Author	Year	OR	95% CI		Ref.
WHO (Europe)	1997	1.23	0.67	2.26	[43]
Rosenberg	2001	1.0	0.8	1.2	[35]
Mant	1998	1.2*	0.6	2.3	[39]
Stampfer	1988	0.80	0.64	0.99	[45]
Stampfer	1990	1.05	0.94	1.17	[49]

\*Results of analysis of patients with OC discontinuation between 1–8 years prior to MI. CI: Confidence interval; OC: Oral contraceptive; OR: Odds ratio; WHO: World Health Organization.

The World Health Organization (WHO) study represents one of the most significant studies regarding OC and CVD associations [40]. Conducted as a case–control study of patients from both European and developing nations, it included 21 centers in 17 different countries, comparing 368 patients with well documented MI to 941 control patients. The overall OR for acute MI in current European OC users was 5.01 (95% CI 2.54–9.90) and 4.78 (95% CI 2.52–9.07) in developing countries. However, these figures reflect all patients regardless of risk status. In Europe alone, 87% of patients had one or more risk factors for CVD compared to only 48% of controls. In all, only 11 of 62 OC users with MI had no identifiable risk factors. Only two of these had undergone appropriate blood pressure screening. Thus, amongst European women with no risk factors and appropriate blood pressure screening, there was no significant increase in risk of MI (OR = 1.10, 95% CI 0.12–9.69). Results were nearly identical in the developing countries. Critically, subanalysis of patients from the UK, where blood pressure screening is routine and patient screening is more selective than in many of the other centers, resulted in no significant association with MI in OC users (OR = 2.10, 95% CI 0.63–7.07).

It is thus not surprising that in the UK-led MICA study, Dunn and colleagues found no significant association between current OC use and MI compared to age and practice-matched patients without MI, when controlled for confounding risk factors [41]. Although no findings were statistically significant, OC formulations with second-generation progestins had ORs less than one, while third-generation progestin users had ORs approximating a twofold increase. The authors summarized their findings by stating that they found no difference between second- and third-generation OCs and no increase in risk of MI in current OC users. Furthermore, of

women under 45 years with MI, 87% were not OC users and 88% had one or more CVD risk factors.

In contrast, a Dutch case–control study authored by Tanis and colleagues included 248 women 18–49 years of age with a first MI and compared these to 925 randomly selected, telephone- and questionnaire-interviewed, age- and region-matched control patients [42]. Overall, the risk for MI was increased in OC users (OR = 2.1, 95% CI 1.4–3.1), even after control for putative risk factors, but when restricted to non-smokers or those with no conventional risk factors, CIs included the value of one, indicating statistical non-significance. Importantly, the patient number from this restricted analysis is not shown, but at a maximum included only 15 patients who were nonsmoking OC users. The cases had a two- to sixfold increase in the prevalence of CVD risk factors, including an 84% current smoking prevalence, 8% former smoking prevalence, and a 65% prevalence of having a family history of CVD. Despite the well-characterized association between age and CVD risk, the OR of 1.7 (95% CI 0.8–3.3) for MI risk in 45–49 year old OC users, the oldest age group and those likely to have the lowest levels of circulating estrogen, was not significant. Since this older age group would have a higher risk of age-related atherosclerotic changes, it is tempting to speculate on biological mechanisms related to the absence of risk in this group, including the aforementioned possibility that OC use is related to decreased atherosclerosis.

Three North American studies also contribute valuable information. Rosenberg and colleagues conducted a case–control study of women with incident MI [33]. This study showed no significant association of MI with current OC use (OR = 1.3, 95% CI 0.8–2.2) when compared with patients hospitalized for reasons other than CVD or DVT. However, OC users who concurrently smoked 1–24 cigarettes per day had an increased risk (OR = 3.4, 95% CI 1.4–8.0) and this number was dramatically elevated in OC users smoking more than 25 cigarettes per day (OR = 32, 95% CI 12–81), indicating significant evidence for interaction between OC use and smoking on the incidence of MI. The authors concluded that current OC use has little or no influence on the risk of a nonfatal first MI among women who do not smoke or who smoke fewer than 25 cigarettes a day. Similar to the findings we have cited above, these authors also demonstrated a non-significant OR of 0.5 for risk of MI in older



**Table 5. Screening for cardiovascular disease risk factors.**

Factor	Personal history	Family history
Hypertension	+	-
Hyperlipidemia	+	+/-
Myocardial infarction	+	+
Stroke	+	+
Diabetes	+	+/-
Obesity	+/-	-
Migraine*	+	-
DVT/PE	+	+
Thrombophilia(s)	+	+

*Appropriate screening prior to administration of oral contraceptives should include at least examination of blood pressure to rule out hypertension and history related to the factors cited above.*

*+: likely related to increased CVD risks.*

*+/-: factor may or may not be related to increased CVD risks.*

*-: unlikely to substantially contribute to increased risk of CVD in OC users.*

*\* Migraine has been associated with risk of stroke. Its relationship with other CVD factors is unknown.*

OC users, although these results were not statistically significant (95% CI 0.1–1.5). The Nurses Health Study (NHS) was a prospective cohort study including 7074 current OC users [43]. Results showed a 2.5-fold increase in the incidence of MI in current users (OR = 2.5, 95% CI 1.3–4.9), but of the ten patients with major coronary vascular disease, seven were smokers, supporting the increased risk of MI in smoking OC users, but reducing the applicability of this finding to the evolving population of healthier, better selected contemporary OC users. Sidney and colleagues conducted a pooled analysis of two case-control studies including 271 cases and 993 controls, from California and Washington State [44]. These authors demonstrated no association with MI risk in current OC users compared to non-users (OR = 0.94, 95% CI 0.44–2.20), and a non-significant OR of 0.56 (95% CI 0.21–1.49), when comparing OC users to never-users. There were no significant differences in incidence of hypertension, diabetes, hypercholesterolemia, or in educational level between never, past and current OC users in this study. Some may argue, however, that the finding of ORs less than one must be interpreted in light of the potential impact of selection, healthy user and prescription biases, as these factors may result in OC users being healthier, in general, than non-users.

Lewis and colleagues demonstrated a significantly increased risk with second-generation OC use (OR = 2.96, 95% CI 1.54–5.66) compared with a community and hospitalized, age- and participating center-matched control group, but a non-significant OR less than one (OR = 0.82, 95% CI 0.29–2.31) for risk of MI in users of third-generation OCs in a transnational, European study [45]. These authors also demonstrated a clear gradient of decreased risk of MI from first- to third-generation OCs, reducing the risk of MI by 72% when comparing third- to second-generation OC use.

Based on these recent studies the association of OCs and CVD has become much more refined from initial studies in the 1970s and early 1980s. Many previous and recent studies have demonstrated substantial increases in risk of MI in at-risk patients, suggesting a likely potentiation of MI risk with OC use in patients predisposed to such outcomes, a critical caveat for both clinicians and patients, alike. Thus, thresholds for MIs are likely lowered in patients with pre-existing thrombotic tendencies and/or acute or chronic endothelial injury (e.g., smoking and hypertension), necessitating full disclosure of risks to such patients [23]. Amongst such risks, smoking plays a pre-eminent role as the most significant contributor to adverse outcomes. Interestingly, more recent research suggests that such risks may be reduced in magnitude or eliminated entirely by the use of some third-generation OCs [41,44,46].

In the contemporary population of OC users in developed nations, where appropriate screening and selection prior to OC prescription are routine, leading to a population where heavy smokers and other high-risk patients are either excluded or closely monitored, studies suggest a trend towards reduced risks of CVD in OC users, particularly those using third-generation products [37,39,45,46]. Analysis of low-risk patients from previous, current and future studies are important in light of the evolving OC user patient population. Further studies to validate these findings are imperative, as some authors would argue that healthy user bias, lack of power from subgroup analysis, and other sources of bias, account for the discrepancies between previous studies demonstrating increased risks and more recent studies demonstrating little or even reduced risks amidst low-risk patients [17].

#### *MI in past OC users*

To date, the overwhelming majority of studies have demonstrated no significant association

between past OC use and risk of MI (Table 4). The WHO's European data demonstrated a non-significant OR of 1.23 (95% CI 0.67–2.26), although data for nonsmokers or those without risk factors was not published [40]. Rosenberg and colleagues demonstrated no overall risk of MI in past OC users (OR = 1.0, 95% CI 0.8–1.2) regardless of smoking status (data not shown), with a trend towards decreased risk in nonsmokers (OR = 0.8, 95% CI 0.6–1.3) [33]. The OFPAS study demonstrated no significant risk when women ceased OC use 1–8 years prior to the incident MI (OR = 1.2, 95% CI 0.6–2.3) [37]. Past or current OC users who were either non-smokers or smoking between 1–14 cigarettes per day had non-significant ORs of 0.6 (95% CI 0.1–2.3) and 0.9 (95% CI 0.4–2.2), respectively. Similar results were demonstrated for past users. The negative impact of smoking is again evident, however, in heavy smokers ( $\geq 15$  cigarettes/day) who were previous OC users (OR = 4.0, 95% CI 1.3–16.2).

The NHS evaluated 415,488 woman-years amongst 49,296 past OC users [43]. Overall, using a multivariate model controlling for CVD risk factors, this study demonstrated a statistically significant, 20% reduced risk of major coronary disease (OR = 0.80, 95% CI 0.64–0.99). A follow-up meta-analysis including 12 other studies, overall failed to validate the reduced risk with an OR of 1.05 (95% CI 0.94–1.7) [47]. When restricted to cohort studies, however, the trend was toward a reduction in risk, with a non-significant OR of 0.85 (95% CI 0.69–1.05).

Subsequently, Sidney and colleagues also demonstrated a statistically significant, 46% reduction in odds of MI in past OC users (OR = 0.54, 95% CI 0.31–0.95) [44]. These authors also demonstrated a trend towards a dose–response effect with a statistically significant benefit achieved after more than 10 years of use (OR = 0.51, 95% CI 0.29–0.91). The authors postulated that the observed benefit may be due to OC-mediated lipid effects, while other authors have explained similar findings based on the beneficial effects of newer generation OCs on lipids and/or coagulation and reductions in vascular atherogenesis in patients without CVD risk factors [38,46,48].

Thus, there is overwhelming evidence against any positive association between past OC use and MI. Some studies have demonstrated a potential for decreased risk, but only two have been able to show statistical significance [43,44]. The possibility of a dose–response effect is

intriguing and, if validated, would provide further biological plausibility for the protective effects of OC use. Taken as a whole, the results suggest that prior OC use does not increase risk of MI and may provide a long-term reduction in MI risk in properly screened and selected patients without existing risk factors, via a potential reduced risk of atherogenesis and its attendant risk factors [38]. As expected, heavy smoking may cause residual risk in past OC users.

#### *Stroke in current OC users*

The relationship between stroke and OC use is complicated (Table 6). As with other CVD outcomes, data from randomized controlled trials is lacking. Interpretation of the existing literature is hampered by differing case definitions and OC user classifications, evaluations of different types of stroke (e.g., venous thrombosis vs ischemic stroke vs hemorrhagic stroke vs subarachnoid hemorrhage) and significant sources of bias within each study. Furthermore, study designs have revealed significant differences. A recent pooled analysis of 20 studies demonstrated a stark contrast between cohort and case–control designs [49]. Data from the cohort studies revealed a non-significant OR less than one in overall risk of all types of stroke (OR = 0.95, 0.5–1.78), while case–control studies revealed a substantially increased ischemic/thrombotic stroke risk (OR = 2.13, 95% CI 1.59–2.86). Indeed, the vast majority of studies to date have employed case–control methodologies and have generally demonstrated varying estimates of increased risk for thrombotic stroke. However, the authors were not able to demonstrate any association between OC use and either hemorrhagic stroke or stroke-related mortality. Moreover, the authors assert that various sources of bias likely play a critical role in any previously demonstrated associations. They conclude that there is no credible evidence to support a causal association between OC use and stroke. Some may argue, however, that inclusion of hemorrhagic and thrombotic strokes in the same analysis is inappropriate because of the different etiological mechanisms involved in each outcome.

In contrast, a previous meta-analysis by Gilum and colleagues demonstrated an increased risk of ischemic stroke in all OC users regardless of OC generation [50]. There was an almost threefold increase in risk of ischemic stroke based on analysis of data from 16 studies, some of which were included in the meta-analysis by Chen and colleagues. While acknowledging that

**Table 6. Association between current oral contraceptive use and stroke.**

Author	Year	Type	OR	95% CI		Ref.
Chen	2004	All	0.95*	0.5	1.78	[51]
		All	2.13 <sup>†</sup>	1.59	2.86	
Gillum	2000	Thrombotic	2.75 <sup>§</sup>	2.24	3.38	[52]
Stampfer	1988	All	0.96	0.74	1.25	[45]
Mant	1998	Thrombotic	2.4 <sup>‡</sup>	1.1	5.1	[39]
Hirvonen	1990	Hemorrhagic	0.36 <sup>β</sup>	0.18	0.70	[53]
Schwartz	1998	Thrombotic	0.66	0.29	1.47	[55]
		Hemorrhagic	0.95	0.46	1.93	
Siritho	2003	Thrombotic	1.62	0.69	3.83	[56]
Heinemann	1998	Thrombotic	3.64	2.42	5.47	[57]
Lidegaard	2002	Thrombotic	1.8**	1.0	3.3	[58]
		Thrombotic	0.6 <sup>††</sup>	0.4	0.9	
Kemmeren	2000	Thrombotic	2.3	1.6	3.3	[59]

*Thrombotic: Cerebral arterial thrombosis; Hemorrhagic: intracerebral hemorrhage; All: all types of stroke combined. CI: Confidence interval; CVD: Cardiovascular disease; OR: Odds ratio; NR: Not reported; WHO: World Health Organization.*

*\*Results of meta-analysis of cohort studies.*

*†Results of meta-analysis of case-control studies.*

*§Results of meta-analysis of 16 studies with varying study methodologies.*

*‡Results not significant when examined for nonsmokers and light smokers.*

*βResults of fatal hemorrhagic stroke in a cohort of women from Finland.*

*\*\*Results of controlled and corrected analyses for use of first generation OCs, using second-generation OC as the referent group.*

*††Results of controlled and corrected analyses for use of third generation OCs, using second-generation OC as the referent group.*

their study demonstrated a specific CVD risk associated with OC use, the authors felt that these risks needed to be considered within the context of potential complications related to non-use of OCs. Thus, they concluded by stating that 'based on estimates of unintended pregnancies, abortions and pregnancy-related mortality, worldwide discontinuation of OC use would almost certainly result in an increase in strokes and deaths'.

Closer examination of the cohort studies demonstrates important findings. The OFPAS demonstrated no association of OC use and subarachnoid hemorrhage or transient ischemic attack, but an increased risk of ischemic stroke in current OC users of 2.4-fold (95% CI 1.1–5.1) [37]. However, these increases were not significant in nonsmokers (OR = 3.1, 95% CI 0.8–12.7), ex-smokers (OR = 1.5, 95% CI 0.1–13.4), or even in moderate smokers (OR = 1.5, 95% CI 0.1–20.5). Only heavy smokers (> 15 cigarettes/day) demonstrated a statistically significant increase in risk (OR = 6.5, 95% CI 1.1–68.3). Hirvonen and colleagues' study of women from Finland represents one of the largest pro-

spective cohort studies, with 935,000 patients followed during a 10-year study period [51]. Amongst OC users, the risk of fatal hemorrhagic stroke was dramatically reduced, with a relative risk of 0.36 compared with non-users (95% CI 0.18–0.70). Only one cohort study demonstrated an increased risk, but this was based on only one case [52]. Thus, the cohort studies overwhelmingly support the assertion that there is no increased stroke-risk associated with current OC use in properly selected low-risk patients.

Similarly, a pooled analysis of the data from two US case-control studies, including 175 ischemic stroke cases, 198 hemorrhagic stroke cases and 1191 control patients (randomly selected age- and year of event-matched patients without evidence of major coronary and/or cerebrovascular disease) aged 18–44 years, demonstrated non-significant, minimal increases in ischemic stroke risk (OR = 1.09, 95% CI 0.54–2.21) or hemorrhagic stroke risk (OR = 1.11, 95% CI 0.61–2.01) among current OC users when compared to non-current users. A statistically non-significant OR of 0.66 was shown when



comparing current users to never-users for ischemic strokes [53], unless patients had other risk factors such as migraines. The lack of association was also supported by a recent Australian case-control study, which compared current OC users with age-matched community controls who were either non-current users (past users and never-users combined) (OR = 1.76, 95% CI 0.86–3.61) or never-users (OR = 1.62, 95% CI 0.69–3.83), in multivariate analyses controlled for smoking, alcohol consumption, exercise, cholesterol, MI, hypertension, transient ischemic attack(s), and diabetes [54].

Heinemann and colleagues demonstrated a significantly increased risk of thromboembolic stroke in young women from the Transnational European study in OC users compared with non-current OC users, controlled for confounding risk factors and adjusted for age, center, smoking status, hypertension, hypercholesterolemia, parity, alcohol use, body mass index, family history of stroke, duration of use of current OC, and diabetes mellitus, with an OR of 3.64 (95% CI 2.42–5.47) [55]. However, these authors demonstrated non-significant increases in risk when restricting analysis to patients without hypertension (OR = 3.07, 95% CI 0.85–11.05), or those smoking less than 10 cigarettes per day (OR = 3.92, 95% CI 0.43–4.67), while those smoking more than ten cigarettes per day were at a substantially increased risk (OR = 8.57, 95% CI 3.7–19.86).

Interestingly, Lidegaard and colleagues recently demonstrated that there was a difference in ischemic stroke-risk associated with the generation of progestin used in the OC [56]. This study demonstrated that when controlled for confounding risk factors, estrogen dose and duration of use, there was a non-significant increase in risk of thrombotic stroke and/or transient ischemic attack with use of first-generation OCs (OR = 1.8, 95% CI 1.0–3.3), and a statistically significant 40% reduction in stroke amongst users of third-generation OCs (OR = 0.6, 95% CI 0.4–0.9).

In contrast, the recent case-control study by Kemmeren and colleagues evaluated 203 women with an ischemic stroke in comparison to 925 age- and region-matched control patients with no history of coronary, cerebrovascular or peripheral arterial disease [57]. Overall there was a substantial increase in stroke risk in current OC users (OR = 2.3, 95%

CI 1.6–3.3). Unexpectedly, the risk of ischemic stroke was lower (and non-significant) in users of first-generation OCs (OR = 1.7, 95% CI 0.7–4.4) compared to second- and third-generation OCs which approximated a twofold risk increase (OR = 2.4, 95% CI 1.6–3.7 and OR = 2.0, 95% CI 1.2–3.5, respectively), although the study was underpowered to evaluate the impact of first-generation OCs. Apparent risks were even greater when restricted to patients without risk factors. However, results were only significant for patients over 29 years of age. Excepting statistical power differences, the authors did not offer any explanation for the observed differences from studies demonstrating decreased risks with third-generation OCs.

How can all these disparate results be reconciled? It is possible that significant bias has influenced results of case-control studies. The meta-analysis by Gillum and colleagues demonstrated a significant reduction in ORs associated with more recent study publications [50]. Many studies have lacked sufficient power to demonstrate significant differences amongst healthy OC users or those with appropriate screening and selection. Study design differences may include varying estrogen doses in the same or differing populations, a range of progestogens, varying and occasionally questionable use of 'current-user' definitions, different reference groups and stroke types, and the presence of significant risk factors for stroke, including hypertension and/or smoking, which are potentiated when such patients use OCs. The presence of these factors is highlighted by studies such as the WHO study of stroke, where risk was elevated exclusively with high-dose OCs and with the use of all OC formulations in developing countries [58]. There are also significant concerns with regard to all epidemiologic studies of OCs and CVD because of the considerable potential of various biases including recall, selection, survivor, attrition and other factors [21,28]. These sources of bias do not invalidate study results but they may cause overestimation or underestimation of risks.

Unequivocally, these results suggest that further study is required to clearly delineate the risk of stroke in relation to the current practice of OC prescription and use. Patients with significant pre-existing risk factors are surely at higher risk, and need to be counselled carefully regarding the risks and benefits of

OC use. In the meantime, attributable risks are estimated to be 4.1 per 100,000 woman-years of use [50]. For OC users less than 35 years of age this risk decreases to 1 per 100,000 woman-years [36]. By comparison, maternal mortality figures are quoted as being 9 per 100,000 pregnancies and although useful for placing risks in context, all such figures fail to reflect the beneficial social and psychological impact of other OC-related effects including reductions in menstrual blood loss, dysmenorrhea, pelvic pain, and unwanted pregnancy, amongst others.

#### *Stroke in past OC users*

Most studies demonstrate no increase in risk of stroke in past OC users. Non-significant findings were demonstrated by the OFPAS cohort in patients who had stopped OC use 1 year or more prior to their stroke event [37]. In Schwartz's pooled analysis of two US studies, there was no significant increase in risk of ischemic stroke (OR = 1.09, 95% CI 0.54–2.21) [53]. Taken individually, the California portion of the study (from Kaiser Permanente patients) demonstrated a significant ischemic stroke reduction in past OC users, a result similar to that of the Transnational study [59]. In contrast, follow-up data of the Royal College of Family Practitioners' study demonstrated an increased risk of stroke-related death in recent OC users, but not in patients who had ceased OC use more than 10 years previous to the incident [60]. The meta-analysis by Gillum and colleagues also demonstrated no significant increase in risk, and a trend toward a lowered risk with an OR of 0.86 (95% CI 0.69–1.08), with no heterogeneity amongst the study results [50]. Interestingly, Heinemann demonstrated a significantly decreased risk of stroke in past users when compared to never-users (OR = 0.6, 95% CI 0.3–0.9), and Lidegaard demonstrated a non-significant OR of 0.7 (95% CI 0.6–1.0) for past users when compared to never-users.

These results suggest that, overall, there is likely little or no association between past OC use and ischemic or hemorrhagic stroke in patients without risk factors. Future studies should focus on factors predictive of stroke in past OC users.

#### *Peripheral arterial disease*

Only one study of peripheral arterial disease (PAD) and OCs has been conducted, to date

[61]. This study was part of the three CVD studies from The Netherlands, reporting on MI [42], stroke [57], and PAD. The results demonstrated significant increases in risk of PAD in OC users, with an OR of 3.8 (95% CI 2.4–5.8). However, as with the other two studies, the relevance of this study is hampered by an extremely high prevalence of smoking in the case population, since it is already clear that OC use potentiates smoking-related arterial atherogenesis and thromboembolism [38]. Of the 152 patients aged 18–49 years, with angiographically demonstrable PAD, 92% were current smokers, and 2% were previous smokers. This resulted in only nine patients without smoking as a risk factor, only seven of whom were OC users. Although the authors attempted individual analyses excluding patients with a smoking history, they did not demonstrate results for patients without any risk factors. Thus, the finding of increased risk in this high-risk population is consistent with previous findings of OC use in high-risk patients as described above, but does not offer any information on risks for healthy users – the current OC user population that may derive CVD benefits from OC use, in contrast to those who have risk factors [18,23,38].

#### *Summary*

The most recent evidence suggests that OCs are safe with regards to current and past use for MI and angina in appropriately selected patients, while risks for those with pre-existing risk factors are generally increased in current OC users, based on both biomolecular and epidemiologic studies. Data for stroke risk in current OC users is still unclear, and more definitive evidence is necessary before drawing appropriate conclusions. Even if a twofold risk increase is assumed, attributable risks are minimal, since the incidence of stroke in women of reproductive age is relatively low and lack of contraception can potentially carry significant morbidity worldwide. Overall, when restricting analyses to patients without any known risk factors, few studies have been able to demonstrate any significant increase in CVD risks, while many studies have demonstrated increased risks of all CVD outcomes in patients with risk factors. Thus, many epidemiologic studies have demonstrated increased overall risks despite controlling for confounding risk factors, because the overwhelming majority of adverse CVD events have occurred

in patients with pre-existing risk factors. All results must be considered within the context of the influences of bias and a lack of statistical power in both primary and sub-analyses.

As practitioners in developed countries implement greater diligence in screening, selecting and monitoring OC users, a healthy population of low-risk OC users are evolving who may actually derive short- and long-term benefit from OC use. There is evolving biological and clinical evidence to support a dichotomous effect of OCs in relation to CVD: it may lead to potential risk reductions in atherosclerosis development in both current and previous OC users who are healthy, but increased risks of adverse CVD outcomes in OC users with risk factors [62]. Although some new studies show minimal or no OC and CVD associations overall, most studies suggest that in patients with CVD risk factors, OC use can potentiate risks. Therefore, OC use must always be carefully considered by both the clinician and the patient.

The impact of risk factors on OC use decisions has been reviewed by both the American College of Obstetricians and Gynecologists and the WHO, and an excellent summary has previously been published [32]. Patients with risk factors, and especially those who are current heavy smokers, should be counselled extensively regarding potential complications of OC use, which include increased risks of MI, stroke and PAD, and that alternative contraceptive methods may be preferable. Patients should be screened for historical risk factors (Table 5), and blood pressure should be

evaluated prior to and during OC use to minimize risks [55]. Although not all risk factors necessarily contraindicate OC usage, clinicians should carefully document all risks and use the knowledge to counsel and follow patients appropriately. Routine evaluation of serum lipids and diabetic status are not currently considered cost-effective or clinically practicable globally, but should be considered when indicated by a personal or family history of CVD or associated risk factors, such as diabetes and obesity.

#### Future perspective

All findings of an association between OC use and CVD must be considered within the context of the low absolute CVD risks in women of reproductive age and the extensive contraceptive and noncontraceptive benefits of OC use [32]. Ideally, properly designed, long-term, randomized controlled trials would yield further information to clearly define risks, but ethical and technical quandaries limit the ability to conduct such studies. Thus, further research should be directed towards well-conducted, long-term cohort studies to assess OC and CVD associations, with an emphasis on confirming potential cardiovascular protective effects demonstrated by recent studies. It is possible that with greater physician and patient knowledge on at-risk groups, improved screening and follow-up management, future studies will demonstrate that both current and past OC use will result in decreased long-term morbidity and mortality.

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