NHS Quality Improvement Scotland

Health Technology Assessment Report 4

The organisation of troponin testing services in acute coronary syndromes

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With significant contributions from the Topic Specific Group and Peer Reviewers (see Appendix 1)

NHS Quality Improvement Scotland was set up to improve the quality of health care in Scotland. Its role is to set standards and monitor performance and provide NHSScotland with advice, guidance and support on effective clinical practice and service improvements.

NHSScotland is expected to take account of advice and evidence from NHS Quality Improvement Scotland and to ensure that recommended drugs or treatments are made available to meet clinical need.

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1 Executive summary

Acute coronary syndromes is the new but universally accepted collective term for the spectrum of acute coronary disease resulting from a rapid reduction in blood flow in the coronary circulation. The clinical presentations recognised within this definition include unstable angina and myocardial infarction with or without ST segment elevation on the electrocardiogram.

Troponin testing identifies the presence and extent of heart muscle cell death and, therefore, in association with clinical and electrocardiogram findings, is helpful in assessing the short- and long-term risk of adverse cardiac outcomes (such as death or non-fatal myocardial infarction) in patients with symptoms suggestive of acute coronary syndromes.

Objectives of the Health Technology Assessment

The Health Technology Assessment set out with two principal objectives, as agreed by the Board[1]:

- to determine whether troponin testing is clinically and cost effective for the management of patients presenting with acute coronary syndromes
- if troponin testing is found to be clinically and cost effective, to consider how such a service could be optimally organised for Scotland.

This Health Technology Assessment focuses on the use of troponins in patients with acute coronary syndromes, although it is recognised that raised cardiac troponins may be associated with conditions other than acute coronary syndromes such as myocarditis, cardiac trauma (e.g. road traffic accident, stabbing) or multiple organ disease (e.g. polymyositis).

Methods

This Health Technology Assessment takes account of four components: clinical effectiveness, cost effectiveness, patient issues and organisational issues.

Scientific literature was systematically searched to identify evidence. Experts, professional groups, patient interest groups, manufacturers and other interested parties were invited to submit evidence. All evidence was critically appraised. Cost-consequence analyses were performed and an economic model constructed to inform the organisation of a cost-effective troponin testing service. Patients' needs and preferences were considered by focus group work.

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[1] The Health Technology Assessment topic was approved by the Health Technology Board for Scotland Board. In January 2003, the Health Technology Board for Scotland became part of NHS Quality Improvement Scotland who completed this Health Technology Assessment.

Results and conclusions

Surveys undertaken by NHS Quality Improvement Scotland showed that troponin testing is currently available to clinicians working in most district general hospitals and tertiary centres across Scotland. A high proportion of cardiologists (96%) have local access to troponin. However, access to troponin testing is variable in community hospitals and in general practice. There is also evidence of considerable variation in the way in which troponin is used in clinical practice throughout Scotland, therefore this Health Technology Assessment aims to underpin evidence-based practice of the use of troponin.

Clinical effectiveness of troponin testing

Troponins T and I have near absolute myocardial tissue specificity as well as high sensitivity for myocardial necrosis and are therefore superior to both creatine kinase and its MB isoenzyme (and hence, are superior to aspartate aminotransferase and lactate dehydrogenase). However, creatine kinase is valuable in assessing early re-infarction i.e. within 96 hours of original infarct.

Biochemical considerations and clinical results suggest that cardiac troponins are maximally sensitive for the period of 12–72 hours after the onset of symptoms. Therefore, measuring cardiac troponin to *rule out* myocardial damage is only effective at least 12 hours after the onset of symptoms. There is some evidence that troponin testing on admission to hospital in patients with suspected acute coronary syndromes identifies approximately 50% of patients who will subsequently have a positive troponin result 12 hours later.

Clinical evidence has shown that raised troponin is predictive of adverse cardiac outcomes in the short and long term in both ST elevation and non-ST elevation acute coronary syndromes. Raised troponin levels on admission are also predictive of an increased risk of mortality in patients with ST elevation myocardial infarction.

There is evidence that other risk markers such as electrocardiogram, chest pain, age and cardiac risk factors are predictive of outcome, independently of troponin. Therefore, troponin is most effectively used in conjunction with clinical features and electrocardiogram findings to inform diagnostic decisions and to assess risk and aid therapy selection.

In patients with symptoms of acute coronary syndromes and with electrocardiograms with confounders (such as left bundle branch block, ST elevation from prior aneurysm or Q waves from prior infarction), the presence of troponin provides reassurance with respect to the diagnosis, therapy and prognosis.

For certain patients in whom there are no clear risk markers for coronary heart disease, the presence of troponin provides information to clinicians on likely diagnosis and prognosis.

Risk stratification in non-ST elevation acute coronary syndromes differentiates low-risk patients from high-risk patients, either using a formal protocol or a scoring system (such as the Thrombolysis in Myocardial Infarction [TIMI] score).

Low-risk patients may be safely discharged before[2] or after a cardiac stress test (which is usually an exercise tolerance test). The importance of rapid assessment methods that use multiple-marker testing such as creatine kinase, myoglobin and troponin to allow early safe discharge of low-risk patients remains uncertain, as there is no clear evidence from randomised controlled trials.

High-risk patients may be candidates for urgent invasive interventions or expensive pharmaceutical therapy. The current evidence base for troponin testing *alone* in selecting patients with acute coronary syndromes but with non-ST elevation for invasive or medical therapies is weak because it is drawn from retrospective subgroup analyses. However, there is some evidence that high-risk patients with non-ST elevation acute coronary syndromes, as predicted by the TIMI score or by individual components of this score (such as ST segment depression, raised biochemical markers or diabetes), appear to derive greater benefit from early invasive therapy, glycoprotein IIb/IIIa inhibition and low molecular weight heparin than low-risk patients.

There is no evidence that either troponin T or I is superior for risk assessment, prognosis and therapy selection in patients with acute coronary syndromes. However, raised troponin T is more frequently detected than troponin I in patients with chronic renal failure, possibly because it is less readily cleared by haemodialysis. Rises in either form of troponin appear to be equally predictive of mortality in such patients.

There is also substantial variability between current troponin I assay results for a single troponin sample because there is little standardisation of troponin I analysers. The problem of standardisation of troponin I analysers is being addressed by the International Federation of Clinical Chemistry. Standardised assays will reduce the potential for confusion.

Cost effectiveness of troponin testing

The evidence suggests that troponin testing is cost effective, with major savings arising from reduced length of inpatient stay, fewer admissions and avoiding over-prescribing of drugs in low-risk patients and appropriate expeditious treatment in high-risk patients.

Two cost-consequence analyses were performed. The first analysis determined the economic benefit of a troponin test 12 hours after admission in patients

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[2] provided a discharge management plan is in place to ensure a prompt outpatient review (which will include a stress test)

considered to have ST elevation myocardial infarction. This analysis compared the cost of undertaking an additional troponin test with the savings following a negative troponin test result. Patients with a negative troponin test do not require secondary prevention measures (such as the cost of rehabilitation, counselling on risk factor modification and prophylactic medication) and as such, these costs would be saved. If the level of misdiagnosis of ST elevation myocardial infarction exceeds 2.2%, then given the high cost of secondary prevention measures, the costs of undertaking a troponin test 12 hours after admission in patients considered to have had ST elevation myocardial infarction would be recovered within one year.

A second economic analysis was undertaken to compare the additional costs of a two-test strategy (measuring troponin on admission and 12 hours later, if the first test is negative) using point-of-care testing with a single-test strategy (measuring troponin 12 hours after admission) using laboratory testing in patients with symptoms suggestive of acute coronary syndromes but a normal or non-diagnostic electrocardiogram and no high-risk markers. This showed that if the variable costs of the point-of-care tests are less than £8.40 per test, it would be cost effective to measure troponin on admission in this subgroup of patients. The benefits measured are limited to placing high-risk patients in the appropriate ward. Other unquantified benefits for high-risk patients include earlier certainty with regards to diagnosis and possibly expeditious treatment.

An optimal troponin testing service

The second objective of this Health Technology Assessment focused on how to organise an optimal troponin testing service. An optimal service should not only use a test that is sensitive, specific and precise but it must also deliver a result in an appropriate timescale.

A timeous troponin result is important for clinical decision making in patients whose disease is rapidly evolving. Therefore test results should be available to inform clinicians at key clinical decision-making points e.g. at time of placement decisions. There is evidence that short turnaround times (i.e. the time from taking the blood sample to receipt of the result by a decision maker) allow safe and early discharge of low-risk patients and early appropriate treatment in high-risk patients.

An economic model was constructed to investigate the relative cost savings achieved by reducing turnaround time in either a laboratory or point-of-care troponin testing service. Results from the economic model concluded that savings could be achieved if the turnaround time is compatible with clinical need. The combination of continuously available decision making and troponin testing is the most cost-effective scenario of those analysed. For sites that only provide a weekday service, a batch service at weekends should be implemented as a minimum, provided clinicians are able to act on the result in a timely manner. However, a batched service is less cost effective than continuous weekend working.

The savings from short turnaround times could be realised through service re-design with primary, secondary and tertiary care providers organising Managed Clinical Networks and patient pathways to facilitate both timely treatment of high-risk patients in hospitals with revascularisation facilities and the timely transfer of high-risk patients between referring hospitals and hospitals with revascularisation facilities, and safe and expeditious discharge of low-risk patients.

Point-of-care analysers may reduce turnaround times and increase the availability of troponin testing outside normal working hours. Therefore, this Health Technology Assessment considered the accuracy and usability of point-of-care analysers for troponin testing.

Currently there is evidence that two of the quantitative point-of-care analysers (Stratus® CS and TROPT *Quantitative*®), but none of the qualitative readers, are sensitive and accurate enough (i.e. close to 10% coefficient of variation in the 99th percentile of the troponin distribution in the normal population) and have shown suitable discrimination when used to risk stratify patients. These two point-of-care analysers also meet the important criteria of preserving comparability with central laboratory analysers at levels above 0.05 μg/L. However, it is important to note that a positive result from any analyser (including qualitative readers) is adequate to indicate myocardial damage.

Both laboratory and point-of-care troponin testing services present organisational challenges. The following issues should be taken into account when deciding on the type of service that is adopted:

- experience suggests that operating point-of-care testing successfully requires rigorously defined and managed clinical and laboratory protocols, with one person who is clearly responsible for overseeing compliance
- a point-of-care service must produce troponin test results that are comparable with those produced by a laboratory service and must be supported by laboratory staff
- implementing quality control and quality assurance procedures for point-of-care testing may require more training than laboratory-based testing, as these procedures may be less familiar to non-laboratory staff
- the ability of laboratory services to respond to clinical need may be limited by the layout of the hospital, other demands on laboratory staff and transport limitations.

Any laboratory responsible for performing troponin testing should attain Clinical Pathology Accreditation. All users of point-of-care testing should adhere to Medicines and Healthcare products Regulatory Agency guidance. External quality assurance schemes, such as UK National External Quality Assurance Scheme–Cardiac Markers, are important in maintaining consistent quality of both laboratory and point-of-care testing, and all sites that undertake troponin testing (include point-of-care testing) should be members of such a scheme.

The decision on the type of troponin testing service a hospital adopts will depend on local circumstances (e.g. clinical decision-making protocol, the layout of the hospital, patient throughput and laboratory working practices).

Setting up a troponin testing service in community hospitals is estimated to cost £0.17 million, with annual operating costs estimated at £0.12 million. Estimated annual costs of between £0.28 and £0.35 million would enable all district general hospitals and tertiary centres to offer a troponin testing service that meets clinical need for patients with acute coronary syndromes. Introducing a two-stage troponin testing strategy (i.e. measuring troponin on admission and 12 hours later, if the initial test is negative) would increase annual costs to between £0.47 and £0.84 million, depending on whether troponin T or I assays are used.

An optimal troponin testing service should meet the needs and preferences of patients. Troponin testing can provide patients with a more rapid and certain diagnosis of heart damage, which may facilitate earlier targeted treatment. Patient and carer information needs will vary, but health professionals should offer to explain the purpose of the tests, how the diagnosis was made, treatment options, what may happen next, recovery and what to do if symptoms recur. This information will help patients and carers to understand the diagnosis, may enable them to make decisions about further treatment and may alleviate anxiety at discharge. Patient information leaflets should be available to support the content of oral communication between patients and carers and health professionals.

Health professionals should check that patients understand the information they have received and address any misconceptions patients may have about their diagnosis. Health professionals should provide clear messages to patients about their risk status – in particular that low-risk status does not imply that a patient is free of heart disease – and should encourage appropriate lifestyle changes. Patients are less likely to remember information when it is provided at times when they are anxious. Patient understanding and recall may be improved by health professionals using shorter words and sentences, giving the information in categories, repeating information and giving precise rather than general advice statements.

Finally, the diagnostic confusion caused by the re-definition of myocardial infarction may result in patient confusion if health professionals in the same hospital, and across primary care after patient discharge, use different criteria and terminology for a diagnosis of myocardial infarction. This underlines the importance of a universal working definition of myocardial infarction across the United Kingdom and the importance of using the same terms for a diagnosis throughout a patient's journey of care. Following agreement on a working definition of myocardial infarction, it is important that clear guidance on its implementation is provided to health professionals, in particular to general physicians.

HTA recommendations

1. Troponin testing should be complementary to clinical and ECG risk markers to inform diagnostic decisions and to assess risk in patients with suspected ACS. However, troponin must not be a substitute for these risk markers.

2. Troponin should replace existing cardiac enzyme tests tests – including creatine kinase (CK) and its MB isoenzyme (CK-MB) and 'older' biochemical markers such as aspartate aminotransferase and lactate dehydrogenase – for any diagnostic, prognostic or management decisions in all patients with symptoms suggestive of ACS (although CK retains a role in assessing early re-infarction).

3. Troponin testing in combination with the clinical and ECG risk markers should be part of a formal risk assessment system to assess prognosis and suitability for medical or invasive treatment and to guide the management strategy for patients with symptoms suggestive of ACS but without ST elevation.

4. In low-risk patients with symptoms suggestive of ACS, a troponin test in combination with clinical and ECG risk markers should be used to inform a decision on whether or not to discharge. Where low-risk status can be confirmed, a cardiac stress test should be scheduled without delay to facilitate discharge and to identify if other investigations need to be undertaken.

5. In patients with symptoms suggestive of an acute myocardial infarction who would benefit from urgent reperfusion therapy[3] but in whom there is diagnostic uncertainty on ECG, a troponin test with a short turnaround time may provide additional diagnostic information and should be considered as part of therapeutic decision making.

6. Troponin testing should be part of routine clinical assessment in patients who have received urgent reperfusion therapy for an acute myocardial infarction.

7. Troponin should be measured 12 hours after the onset of well-defined symptoms (when this can be reliably ascertained) in all patients with suspected or clinically diagnosed non-ST elevation ACS. If onset of symptoms is difficult to establish, an appropriate surrogate for the timing of this measurement is 12 hours after admission.

   In patients with clear high-risk markers (for example, those with recurrent symptomatic ischaemia or unequivocal ECG evidence of ischaemia such as

[3] Patients who are candidates for urgent reperfusion therapy present with symptoms suggestive of a myocardial infarction and in most cases with ST segment elevation on ECG, but some may present with confounding ECG changes e.g. left bundle branch block.

ST depression) who will clearly benefit from early pharmacological or interventional therapy, there is no clinical need for a troponin test prior to starting treatment.

8. Troponin may be measured on admission in patients with suspected ACS in whom there is clinical diagnostic uncertainty due to the absence of high-risk clinical or ECG risk markers (for example, no ST depression, no history of diabetes, renal failure or previous myocardial infarction). If this test is negative, a further troponin measurement should be taken as indicated in Recommendation 7[4].

   This recommendation is only advocated if hospitals have the resources available to change patient management when a troponin result is positive.

   If this testing regimen is adopted, clear protocols that recognise the two-step troponin assessment should be introduced, adherence to their use monitored and deviations addressed.

9. Troponin should be measured on admission in patients with symptoms suggestive of acute myocardial infarction who are being considered for urgent reperfusion therapy but in whom there is diagnostic uncertainty on ECG due to possible pre-existing confounding ECG changes (such as left bundle branch block).

   This recommendation is only advocated in hospitals where a troponin testing service, either a laboratory or point-of-care service, can provide a test result with a short turnaround time and is compatible with clinical decision making.

10. Troponin should be measured 12 hours after admission in patients who have received urgent reperfusion therapy for an acute myocardial infarction.

11. All analysers new to the market should meet the European Society of Cardiology criteria on sensitivity and reproducibility (i.e. ≤10% coefficient of variation at the 99th percentile of the normal population distribution of troponin).

    For all existing analysers, laboratories should work collaboratively with manufacturers to establish upper limits of troponin in patients without cardiac damage to form a cut-off limit that is appropriate for their patient group to assist in diagnosing acute myocardial infarction and in risk stratifying patients with non-ST elevation ACS.

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[4] Note that if the first troponin measurement is 12 hours after the onset of symptoms, the second measurement can be omitted.

12. Qualitative troponin readers should not be used to exclude myocardial damage in patients with symptoms suggestive of ACS.

13. A troponin testing service can be laboratory based or provided at the point of care[5]. The type of troponin testing service offered should be decided locally by laboratory, clinical and managerial staff working collaboratively to define the local requirements of a hospital.

14. If a combination of laboratory and point-of-care assays is used to measure troponin, the testing methods must provide results on the same scale. If this is not possible, one type of service should be used exclusively to avoid clinical confusion about cut-off levels.

15. A troponin testing service should deliver a result in an appropriate timescale that meets the needs of the clinical decision maker.

16. Where troponin testing is only available on weekdays, implementing a weekend batch run service is recommended as a minimum service, provided that clinicians are available to act on the results.

17. All laboratories responsible for troponin testing should attain Clinical Pathology Accreditation.

18. All sites that undertake troponin testing (including point-of-care testing) should participate in an external quality assurance scheme.

19. All users of point-of-care troponin testing should adhere to guidance by the Medicines and Healthcare products Regulatory Agency.

20. All point-of-care troponin-testing sites require the identification of a coordinator who is given responsibility for the service.

21. All point-of-care testing services must be supported by laboratory staff.

22. Only trained competent staff should perform troponin testing. Training and support from Managed Clinical Networks with regard to use of equipment and interpretation of the results should be offered on an ongoing basis for existing users and be provided for new users, especially for those in community hospitals where troponin testing may not be currently in use.

23. Appropriate protocols should be developed and used by clinicians, laboratory staff and management staff to make optimal use of the information provided by the troponin test result. This should include a protocol on equitable access to catheterisation facilities using evidence-based and transparent eligibility criteria.

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[5] Note that most point-of-care analysers do not currently meet the sensitivity requirements to rule out myocardial damage or to be used in risk assessment.

24. Health professionals should explain to patients and their carers what their diagnosis is, how it was made, the available treatment options and what to do and who to contact if symptoms return after discharge. Health professionals should use consistent terms for the diagnosis and check to ensure that patients understand the information given to them.

25. Health professionals need to provide a clear message to patients who are discharged as low 'short-term' risk that this status does not imply that they are free of heart disease and encourage them to make appropriate lifestyle changes.

26. All hospitals should have written information for patients who present with chest pain. Written information should be provided to reinforce the content of oral communication between patients and carers and health professionals. Patient information leaflets on heart disease should be written in simple easy-to-understand language, include an explanation of the troponin test and be updated to include the term ACS. Alternative formats such as video, audio, large print or illustrations should also be available and the use of other languages should be considered.

27. Audit data should be routinely collected from all patients with suspected or diagnosed ACS to allow thorough evaluation of the clinical and economic value of troponin. Data should include the number, timing and results of the troponin tests and the number of low-risk patients who were discharged within 24 hours of admission.

28. The only prospective study on the interaction between troponin level and treatment with glycoprotein IIb/IIIa inhibitors was performed using abciximab, which is not licensed currently in the UK for use in the medical management of patients with non-ST elevation ACS. This study showed no treatment effect. A similar study using small molecule glycoprotein inhibitors, such as eptifibatide and tirofiban which are licensed for this indication in the UK, should be performed. The study should estimate the effectiveness of using a troponin test to select patients for glycoprotein IIb/IIIa inhibition.

29. In existing scoring systems, the term 'biochemical marker' does not specifically refer to troponin but instead to any one of CK, CK-MB or troponin. As troponin is more specific and sensitive than CK or CK-MB, a study to investigate the effect of replacing 'any biochemical marker' by troponin is desirable.

30. The combination of multimarker testing (including troponin) and rapid[6] methods of chest pain assessment to reduce the rate of admissions or to achieve early discharge of low-risk patients may appear attractive but the

[6] The definition of 'rapid' varied among the studies but the time for assessment ranged from 90 minutes to nine hours after presentation to hospital.

evidence base for their long-term safety is weak. A randomised controlled trial comparing rapid troponin-based chest pain assessment methods with existing assessment protocols should be undertaken. The trial should assess long-term safety and use rigorous follow-up methods.

2 Introduction and objectives

2.1 Introduction

NHS Quality Improvement Scotland uses the internationally recognised definition of Health Technology Assessment (HTA) as a multidisciplinary field of policy analysis which studies the medical, social, ethical and economic implications of development, diffusion and use of health technology (INAHTA, 2000).

This form of HTA takes account of four components: clinical effectiveness, cost effectiveness, patient issues and organisational issues. National and international evidence is critically appraised, taking account of Scottish circumstances, so that clear and practicable recommendations can be made to the National Health Service in Scotland (NHSScotland). The aim is to influence decision making based on critically appraised evidence and shared best practice.

This HTA follows the process published by the Health Technology Board for Scotland (HTBS) in June 2002 (Health Technology Board for Scotland, 2002b) which involves the submission and collection of evidence from a wide variety of sources, robust analyses undertaken by expert staff, use of a multidisciplinary Topic Specific Group (TSG) (see Appendix 1 for TSG details) to critique evidence and analyses, expert review and wide-ranging open consultation. Figure 2-1 illustrates the development of an HTA report.

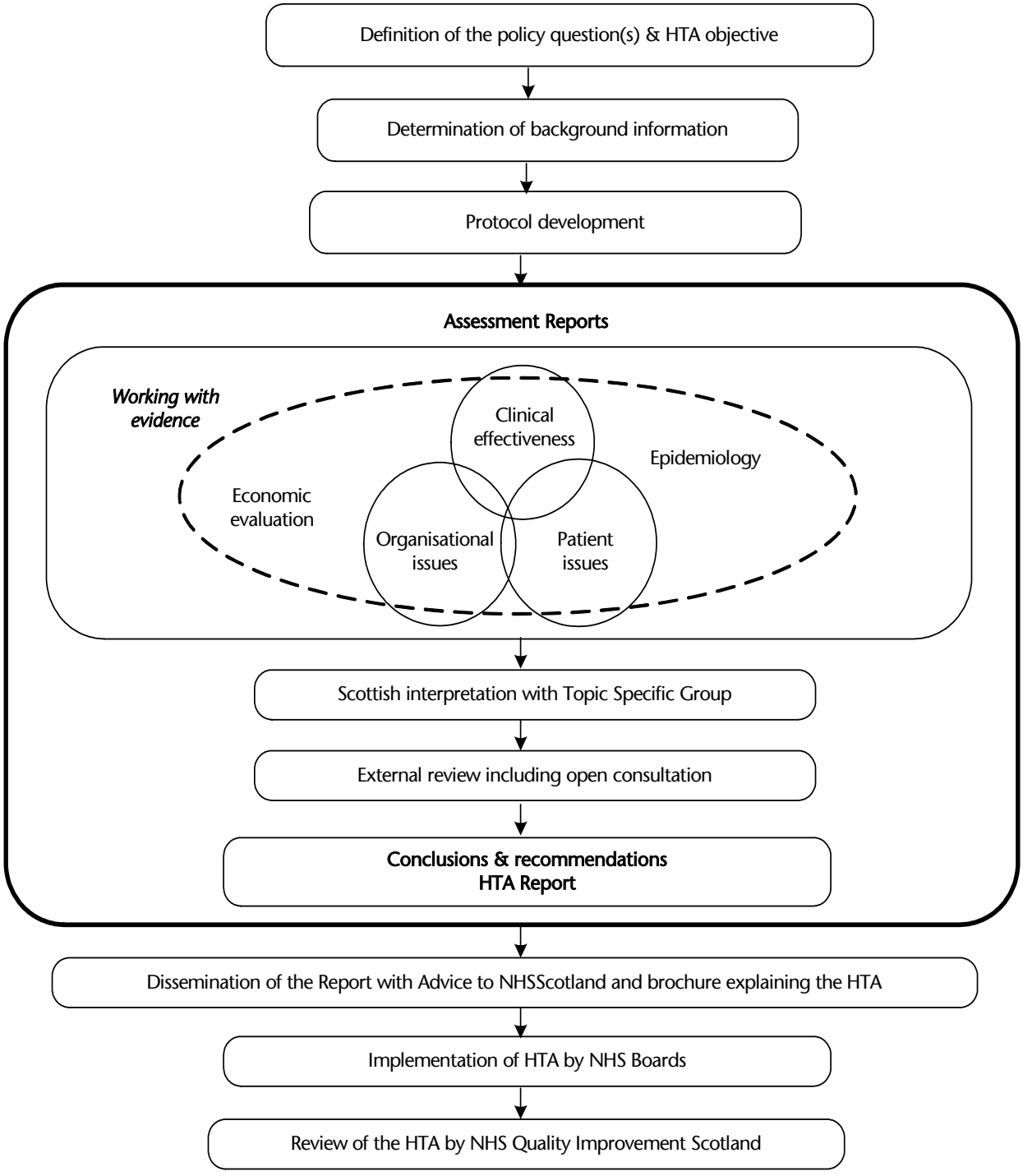
2.2 Objectives of the HTA

This HTA set out with two principal objectives:

1. to determine whether troponin testing is clinically and cost effective for the management of patients presenting with acute coronary syndromes (ACS)

2. if troponin testing is found to be clinically and cost effective, to consider how such a service could be optimally organised for Scotland.

Figure 2-1 Development of the HTA report



2.3 Aim and structure of the document

2.3.1 Rationale for undertaking the HTA

The HTA topic was proposed by a biochemist, supported by laboratory clinicians, cardiologists and policy makers and chosen according to the HTBS topic selection process (Health Technology Board for Scotland, 2001). The HTA topic was approved by the HTBS Board. In January 2003, HTBS became part of NHS Quality Improvement Scotland who continued this HTA.

The HTA topic fulfilled three of the initial criteria for HTBS topic selection.

Firstly, there is uncertainty about the organisation of a cost-effective troponin testing service i.e. central laboratory service or point-of-care service.

Secondly, the way in which a troponin testing service is organised will have a major impact on NHS resources. This is not simply due to the cost of the test itself, but because of implications of troponin testing for further cardiology investigation and intervention. For example, using troponin testing may allow more patients to be identified as candidates for invasive interventions. On the other hand, negative troponin results may also reduce inappropriate admissions. There is also evidence that troponin may be useful in identifying appropriate groups of patients for specific therapies. These issues will be addressed in this HTA.

Thirdly, there is evidence of considerable variation in the use of troponin testing throughout Scotland. To explore this, NHS Quality Improvement Scotland has undertaken surveys of laboratory services and cardiac services provided by cardiology departments, community hospitals and general practitioners (GPs).

2.3.2 Structure of the document

The HTA Report presents a critical appraisal and detailed presentation of the analysis of evidence gathered to inform the four components of the HTA: clinical effectiveness (Chapter 4); cost effectiveness (Chapter 5); patient issues (Chapter 6); organisational issues (Chapter 7) and a final discussion and recommendations (Chapter 8) bring together the key aspects from each chapter.

2.4 The HTA Report

This HTA Report was produced by a multidisciplinary team of staff in the HTA division of NHS Quality Improvement Scotland, and guided by the TSG, external consultants and peer reviewers.

The evidence used to compile this HTA Report was obtained from systematic literature searching, submissions from interested parties, patient interest groups, manufacturers and professional organisations, and by the collection of primary data. Details of the literature searching carried out are presented in

the relevant sections of this HTA Report. A list of evidence submissions is provided in Appendix 2.

Wide public consultation was also used to ensure that all views were taken into consideration. A six-week consultation was held between 06 June 2003 and 17 July 2003. During the consultation period, a public meeting with workshops was held on 10 June 2003 to present evidence on the clinical and cost effectiveness of troponin testing and to address organisational and patient issues, and to discuss key issues arising from the Consultation Report.

Twenty-eight consultation comments (and six late submissions) were received on the Consultation Report and draft recommendations. All consultation comments were considered in the production of the HTA Report.

This HTA Report is accompanied by *Health Technology Assessment Advice 4* outlining the HTA recommendations issued to NHSScotland and an *Understanding Our Advice* document which is suitable for, among others, the general public, patients and carers.

It is intended that the HTA Report should be used by those involved in the planning and management of cardiac services in NHSScotland and will inform decision making and policy.

3 Background

Sections 3.1 and 3.2 provide background to ACS and describe the impact of coronary heart disease (CHD) respectively. Recent policy initiatives to reduce the impact of CHD on the Scottish population and the organisation of cardiac services in Scotland are described in Sections 3.3 and 3.4 respectively. Finally, Section 3.5 describes the biochemistry of the troponin complex, troponin assay development, the different types of assays that are currently available and alternative cardiac markers.

3.1 Description of health issue in Scotland

3.1.1 Clinical description of ACS

CHD describes a range of diseases affecting the cardiovascular system. Damage to the heart may be caused by systemic disease e.g. hypertension, by diseases of the heart conduction or by diseases affecting the blood supply to the heart itself. Those conditions associated with the possible or actual death of heart tissue because of impaired blood supply are termed ACS and are listed in the order of increasing severity:

- unstable angina (UA)
- non-ST elevation myocardial infarction (NSTEMI)
- ST elevation MI (STEMI) (Wu, 1998).

STEMI is characterised by ongoing chest pain and in the majority of cases, the development of Q waves on the electrocardiogram (ECG) (Braunwald *et al.*, 2002). Q-wave development usually signifies an infarct affecting the full thickness of myocardium and is a rough guide of the extent of ventricular damage. ST segment elevation on ECG is typically generated by complete occlusion of coronary arteries which leads to necrosis of heart cells.

Patients presenting with symptoms suggestive of a myocardial infarction (MI) should be considered for urgent reperfusion therapy. Most of these patients will present with ST segment elevation but some may present with ECGs with confounders (e.g. left bundle branch block).

Patients without ST segment elevation have an uncertain diagnosis that may include UA or NSTEMI. These patients are described as non-ST elevation ACS. The distinction between UA and NSTEMI is the presence or absence of biochemical markers of necrosis in the blood (Braunwald *et al.*, 2002). NSTEMI is an acute process of myocardial ischaemia with sufficient severity and duration to result in myocardial necrosis.

3.1.2 Pathology of ACS

In the majority of patients, ACS have a common patho-physiological cause, that being thrombus formation on top of a ruptured atherosclerotic plaque in one or more coronary vessel resulting in reduction of blood supply to heart

tissue (Wu, 1998). Other causes of ACS, such as coronary artery spasm (Printzmetal angina) or coronary embolism, are rare.

The underlying processes of the disease occur over a long period of time, with the build up of atherosclerotic plaques (atherosclerosis) in the wall of the coronary arteries (Bertrand *et al.*, 2002). ACS are triggered by the rupture of the surface of a plaque (Wu, 1998), to which the body responds by forming a clot or thrombus. This causes a partial or total blockage of the artery, thereby reducing or obstructing blood flow to the cardiac muscle that it supplies.

There will be varying degrees of damage to the heart tissue and this will depend on the resultant obstruction, the duration of the compromised flow and the oxygen demand of the tissue in jeopardy (Wu, 1998). If the coronary obstruction is severe and/or long in duration, myocardial necrosis may occur and serum cardiac markers are released into the peripheral circulation (Braunwald *et al.*, 2002).

Cardiac biomarkers for myocardial damage include myoglobin, creatine kinase (CK), its MB isoenzyme (CK-MB) and cardiac troponins T and I. Cardiac troponins are both sensitive and specific markers of myocardial necrosis and have therefore been recommended by several international guidelines as the markers of choice in the evaluation of patients with suspected ACS (Bertrand *et al.*, 2002; Braunwald *et al.*, 2002). While it is recognised that raised cardiac troponins can also be associated with a range of conditions other than ACS (Collinson & Stubbs, 2002), this HTA focuses on the value of elevated troponins in the setting of ischaemic myocardial injury.

3.1.3 Prevalence and incidence of heart disease

Scotland has one of the highest CHD-related mortality rates in western Europe. In 2002, 11 692 deaths related to CHD were recorded (http://www.show.scot.nhs.uk/isd/). Mortality rates from CHD have improved over the past decade. The age-standardised mortality rate decreased from 249 per 100 000 in 1993 to 155 per 100 000 in 2002, albeit more slowly than countries such as the United States (US) and most European countries (http://www.show.scot.nhs.uk/isd/).

While data are available on the incidence and prevalence of CHD, the epidemiology of ACS is not well documented in Scotland. However, data indicate that approximately 10 000 patients with persistent ST segment elevation and raised cardiac enzyme levels and 12 000 patients without persistent ST segment elevation present to hospital each year (Scottish Executive Health Department, 2001).

The impact of heart disease on hospital services has increased, because of a demographic shift in the population and the rising numbers of recommended investigations and treatment. For example, the number of hospital discharges of patients with angina increased from 6989 to 14 595 between 1990 and 1999 respectively (Scottish Executive Health Department, 2001). In the year

ending 31 March 2003, Scottish NHS hospitals recorded 52 035 discharges for CHD, of which 17 427 were for acute myocardial infarction (AMI). Approximately 4.6% of hospital discharges were CHD-related. In the same period, 2737 coronary artery bypass grafts (CABG), 3783 angioplasties and 11 803 angiographies were performed on Scottish patients (http://www.isdscotland/org/isd).

3.1.4 Risk factors for CHD

Scotland's high incidence and prevalence of CHD is likely to be associated with poor cardiovascular risk factor profiles and unhealthy lifestyles of the population. Risk factors for CHD can be divided into modifiable and non-modifiable factors (Grubb & Newby, 2000). Non-modifiable risk factors include age, family history of premature CHD and gender (with increased risk in males and post-menopausal females). Modifiable risk factors include hypertension, diabetes, high levels of lipids, low levels of high-density lipoprotein cholesterol, high levels of low-density lipoprotein cholesterol, obesity and lifestyle factors such as smoking, high alcohol consumption, poor diet and lack of physical activity. Managing modifiable risk factors has been shown to reduce morbidity and mortality and offers significant benefits in CHD prevention.

CHD is unevenly distributed across Scotland, with the highest CHD mortality rates reported in the west of Scotland (http://www.isdscotland.org/isd).

Scottish data show a clear socio-economic group gradient, with the more socially disadvantaged having an increased risk of disease. For example, mortality from AMI is two to three times higher among men younger than 65 years in the most deprived areas compared with those in affluent areas (Scottish Executive Health Department, 2001). These inequalities can be partly explained by differences in risk factor prevalence among other reasons. Certain ethnic groups residing in the UK are also at increased risk of premature death from CHD (http://www.heartstats.org).

3.1.5 Management of patients with ACS

Several bodies such as the American College of Cardiology (ACC) and the American Heart Association (AHA), the European Society of Cardiology (ESC) and the British Cardiac Society (BCS) have published guidelines on managing patients with ACS (Braunwald *et al.*, 2002; Bertrand *et al.*, 2002) (http://www.bcs.com/). These three sets of guidelines are reasonably similar and advocate the use of cardiac troponin in the diagnosis of ACS.

In August 2002, the ESC guidelines on the management of ACS in patients presenting without persistent ST segment elevation were revised following the review of the ACC/AHA guidelines in March 2002. The ESC recommended strategy for ACS based on these guidelines is illustrated and described in Section 4.1.1.

The Scottish Intercollegiate Guidelines Network (SIGN) have published a series of national clinical guidelines on CHD (http://www.sign.ac.uk). A joint review of these existing guidelines is underway and will include early management of ACS. This HTA will contribute to this guideline review.

3.2 Impact of health issue

3.2.1 Economic implications of CHD

The financial implications of CHD are extensive. The burden of CHD to the United Kingdom (UK) economy is estimated to be approximately £7.1 billion per year (based on 1999 data) (Liu *et al.*, 2002). The cost of CHD is higher than that of any other disease considered in this cost-analysis comparison. A breakdown of the total cost of CHD in the UK is shown in Table 3-1.

Table 3-1 Total cost of CHD in UK

	Cost (£ in millions)	**% of total cost**
Direct health care costs	1730.10	25
Productivity loss due to mortality	701.20	10
Productivity loss due to morbidity	2207.51	31
Informal care costs	2416.51	34
Total	**7055.32**	**100**

Reproduced with the permission from BHF Coronary heart disease statistics at www.heartstats.org (Source: Liu *et al.* (2002))

Of the £1.73 billion directly attributed to the national health care system, the cost of hospital care (day cases and inpatient care) accounted for 53% of these costs and medication for approximately 34%. Other direct health care costs were attributed to primary prevention and primary care (4%), rehabilitation and community (6%), and accident and emergency (A&E) and outpatient care (3%).

No separate estimates of ACS costs are available.

3.2.2 Re-definition of MI

The World Health Organisation (WHO) definition of MI was established in 1971, featuring CK or CK-MB as the recommended diagnostic cardiac enzymes (Thygesen & Alpert, 2002). However, MI has recently been re-defined in collaborative documents by the ACC, AHA and ESC by changing the diagnostic criteria to include cardiac troponin as the preferred cardiac biomarker (Alpert, 2000).

A comparison of the two definitions of MI is shown in Table 3-2.

Table 3-2 Definition of MI

Old: definite AMI 1. Definite ECG or 2. Symptoms typical or atypical or inadequately described, together with probable ECG or abnormal enzymes, or 3. Symptoms typical with abnormal enzymes with ischaemic or non-codable ECG or ECG not available, or 4. Fatal case, whether sudden or not, with naked eye appearance of fresh MI and/or recent coronary occlusion found at necropsy.
New: either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI: 1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: (a) ischaemic symptoms; (b) development of pathological Q waves on the ECG; (c) ECG changes indicative of ischaemia (ST segment elevation or depression); or (d) coronary artery intervention (eg, coronary angioplasty). 2. Pathological findings of an acute MI.

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Under the ACC/ESC consensus definition (Alpert *et al*., 2001), troponin, in conjunction with other available clinical markers, is important in the diagnosis of MI and for clinical decision making. Under the ACC/ESC guidelines, any amount of myocardial necrosis, as shown by a rise in troponin, is classified as an infarct. Therefore, a patient with a previous diagnosis of stable or unstable angina may now undergo a troponin test which is sensitive enough to pick up a new lower level of myocardial necrosis and be diagnosed as having had an MI. Thus, the reported incidence of MI will increase under the revised definition.

The increase in the number of diagnoses of MI which would formerly have been UA has been calculated at between 30% and 60% (Thygesen & Alpert, 2002). Based on data from a Scottish district general hospital (DGH), the new criteria predict increases in MI admissions of 58% (Pell *et al*., 2003). This increase in MI reporting was also supported by a study from Lothian (Ferguson *et al*., 2002).

However, Richards *et al*. (2001) and Tunstall-Pedoe (2001) argue that the new definition will both fail to capture some patients with an MI under the WHO definition and disadvantage some patients with minor myocardial damage, labelling them as having had an MI.

The impact of changing the definition of MI is likely to have implications for the patient, treatment, clinical outcome, epidemiology, economics and society (Dargie, 2002).

For patients, the re-definition of MI may have consequences for their employment, particularly where driving is involved (http://www.dvla.gov.uk/at_a_glance/ch2_cardiovascular.html) or work is physically demanding and/or involves stressful situations. There is also likely to be an adverse psychological impact on the patient, and possible implications for their health and life insurance status (Dargie, 2002).

A diagnosis of MI will depend on whether clinicians use the WHO or ACC/ESC definition. In addition, there may also be the risk that the re-definition causes therapeutic confusion and results in inappropriate use of thrombolysis (Tormey *et al.*, 2001).

Furthermore, there appears to be no consistency in coding practice in Scotland (Section 7.2.2.2). Such confusion about the diagnosis of patients will limit trend and comparability analysis. Therefore, there is an urgent need for standardised data collection in order to monitor disease patterns and resource usage accurately.

There is also a societal impact of re-defining MI. For example, mortality statistics, sick leave and disability applications and clinical guideline preparation may all be affected (Alpert, 2000).

The joint ACC/ESC recommendations are not compulsory as neither organisation can enforce the new definition. However these bodies are influential, and their recommendations have already been considered and affected current clinical practice (Dargie, 2002).

For example, the new definition for MI has been also introduced without any clear guidance for or education of health professionals delivering patient care. Diagnostic confusion has resulted, particularly in relation to the patient group with non-ST segment elevation. As a result of the clinical confusion, inconsistencies have arisen regarding the information given to patients about their diagnosis.

There is unanimous agreement among health professionals regarding the importance of an agreed definition of MI across the UK. A working diagnosis needs to be formulated and implemented without delay. An agreed definition of MI requires support from national societies, clinicians, health care providers and epidemiologists and incorporates guidance on troponin cut-offs across the UK. The BCS has established a working group to advise on revised nomenclature for ACS and to obtain some consensus on a minimum concentration of troponin for the definition of MI. It is anticipated that the report will be published in the near future (Professor K Fox, Professor of Cardiology, Royal Infirmary of Edinburgh, personal communication, August 2003). Independent of this, a European working group is being set up to have a second attempt at the definition of MI (Professor K Fox, personal communication, August 2003).

3.3 Recent policy initiatives

In recent years, CHD has been the focus of several important policy documents addressing primary and secondary prevention of CHD and recommending improvements in the delivery of cardiac services in Scotland.

3.3.1 Scottish Executive

The 1999 White Paper *Towards a healthier Scotland* (Scottish Office, 1999) set a national target of reducing CHD-related premature mortality by 50% in people under the age of 75 years between 1995 and 2010.

A Task Force commissioned by the Scottish Executive was set up to identify ways to improve cardiac and stroke services in Scotland. In 2001, the Task Force published the *Coronary heart disease/stroke task force* report that consulted on 45 recommendations on issues such as equity of access, Managed Clinical Networks (MCNs), primary prevention, pre-hospital treatment, revascularisation and national databases (Scottish Executive Health Department, 2001).

The *Coronary heart disease and stroke strategy for Scotland* (Scottish Executive Health Department, 2002) recommended strategies to implement some of the recommendations of the Task Force report. The recommendations included:

- setting up MCNs to coordinate cardiac services by April 2004 in each NHS Board
- the development of a national network, the Scottish Cardiac Intervention Network (SCIN), to take responsibility for the delivery of all cardiac services
- improved workforce planning and recruitment of specialists
- the development of a national CHD database
- strategies to meet current and new waiting time targets.

In October 2003, the creation of a National Advisory Committee on CHD was announced and it will take forward the CHD Strategy, to include the work of SCIN.

3.3.2 Standards for NHSScotland

In October 2001, the Clinical Standards Board for Scotland (now part of NHS Quality Improvement Scotland) published the National Overview of CHD (Clinical Standards Board for Scotland, 2001a), which outlines the key findings of its assessment review of 37 hospitals managing patients with MI. Troponin testing was not covered by the CHD Standards and thus its use was not addressed in the report, but when the CHD Standards are reviewed they will take account of this HTA.

3.4 Organisation of health care in Scotland

3.4.1 Organisation of NHSScotland

Appendix 3 describes the organisation of NHSScotland.

3.4.2 Structure of cardiac services in Scotland

Primary care provides a broad range of cardiac services to manage patients with CHD in the community. It tackles prevention, oversees day-to-day management of heart disease and is involved in cardiac rehabilitation programmes. Primary care also plays an important role in delivering cardiac services to patients in rural and remote areas in Scotland, including community hospital settings.

Access routes to secondary care include GP referral, self-referral, through A&E or ambulance (Scottish Executive Health Department, 2001). Patients are triaged in A&E or designated specialist areas, such as medical assessment units and chest pain units and if admitted, transferred to medical wards or coronary care units (CCU). Settings and triage protocols vary between hospitals.

Tertiary care provides specialist services such as surgical interventions and elective investigation under the direction of cardiologists.

This approach to the delivery of cardiac services may not always provide optimal use of resources (Scottish Executive Health Department, 2001). The development of MCNs is underway and the purpose of these Networks is to 'encourage innovative ways of working across the traditional primary/secondary care interface and between different health care professionals' (Scottish Executive Health Department, 2002). A series of local MCNs should link to a national strategy that aims to integrate the full spectrum of cardiac services from primary prevention to cardiac rehabilitation. MCNs should also improve patient access and delivery of service in remote and island areas of Scotland (RARARI, 2002).

A key issue for NHSScotland is waiting times for non-emergency, hospital-based diagnosis and treatment. Any developments that promote earlier discharge of patients (and thus freeing up beds and other hospital resources) are important to help achieve national targets.

3.4.3 Current provision of troponin testing

NHS Quality Improvement Scotland conducted surveys to assess the availability and use of troponin testing in primary, secondary and tertiary care and in laboratories that serve each of these. The surveys showed variability in access to troponin testing, with the vast majority of DGHs and tertiary centres (96% of respondents) having local access to troponin. By comparison, the provision of troponin testing in community hospitals and general practice appeared to be limited, with only a minority having access. Overall, the surveys indicated that troponin testing tends to be laboratory based rather than provided at the point of care.

In different settings, troponin testing has specific purposes but fundamentally it can help to exclude a diagnosis of myocardial damage. Generally, there was

consensus among cardiologists on the use of troponin and this related to risk stratification of patients with UA and NSTEMI and changing patient management. In addition to these reasons, community hospitals noted that a troponin test result assists in a decision to transfer a patient to a DGH or tertiary centre. GPs also supported this rationale and noted the importance of its use in differentiating those patients who required admission to hospital.

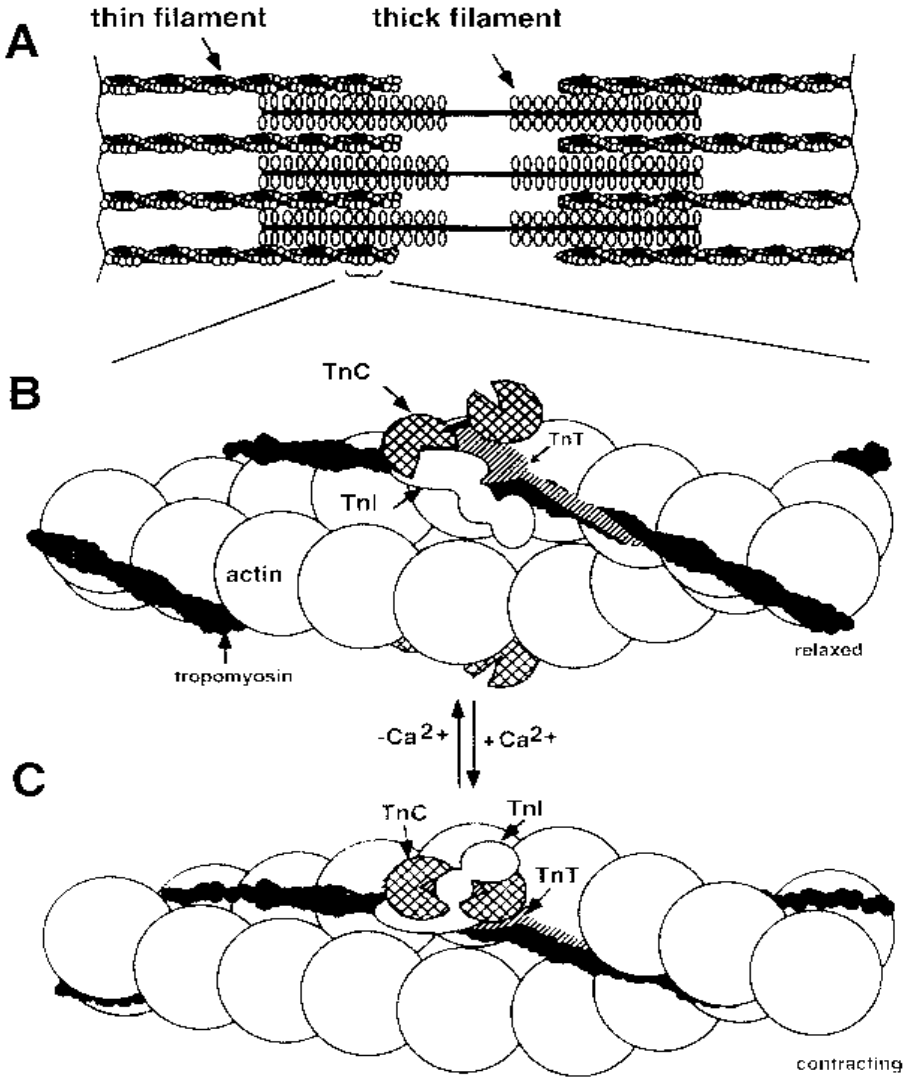
The timeliness of a troponin result is important as it affects its usefulness in clinical decision making. The time from receipt of a blood sample to reporting the troponin result differed among laboratories and ranged from 30 minutes to four hours. The surveys also highlighted that a large number of health professionals still use biomarkers other than troponin, particularly in community hospitals. Other areas of variation included the timing of troponin measurements, analyser equipment, out-of-hours working, use of protocols involving troponin (either for the management of patients with chest pain or the interpretation of results) and means for quality assurance. The results of the surveys are described in more detail in Section 7.2.2.

3.5 Description of technology (written by Dr Paul Collinson)

3.5.1 Biochemistry of the troponin complex

The troponins form part of the regulatory system of the contractile mechanism in muscle. Work to delineate the structure and function of the individual components has identified unique cardiac specific isoforms of troponin T and I: the cardiac troponins, cardiac troponin I and cardiac troponin T (see Figure 3-1).

Figure 3-1 Structure of troponin-tropomyosin complex



Reproduced with permission from the Association of Clinical Biochemists (Collinson *et al.*, 2001a).

3.5.2 Troponin assays

The prospect of a truly specific test for MI led to the development of immunoassays for the cardiac troponins. The first radioimmunoassay for troponin I using polyclonal antibodies was described in 1987 (Cummins *et al.*, 1987a; Cummins *et al.*, 1987b). Subsequently, an enzyme-linked immunoabsorbent assay (ELISA) for troponin T was developed and described by Katus *et al.* (1989) jointly with Boehringer Mannheim (subsequently Roche Diagnostics). The troponin T automated immunoassay is patented, so only one company produces reagents and equipment for the troponin T immunoassay. This was followed by the development of an ELISA for troponin I (Bodor *et al.*, 1992), then commercialised by Baxter Healthcare (subsequently Dade Behring). As the generic concept of an immunoassay for troponin I was not patented, several manufacturers have produced troponin I

assays on a number of platforms and these individual assays are patented. This has led to two types of problems with troponin I assays.

Firstly, marketing claims of superiority of one troponin I assay over another and claims that troponin I is better than troponin T (and vice-versa) have generated confusion. This has not been confirmed by clinical studies (see Chapter 4).

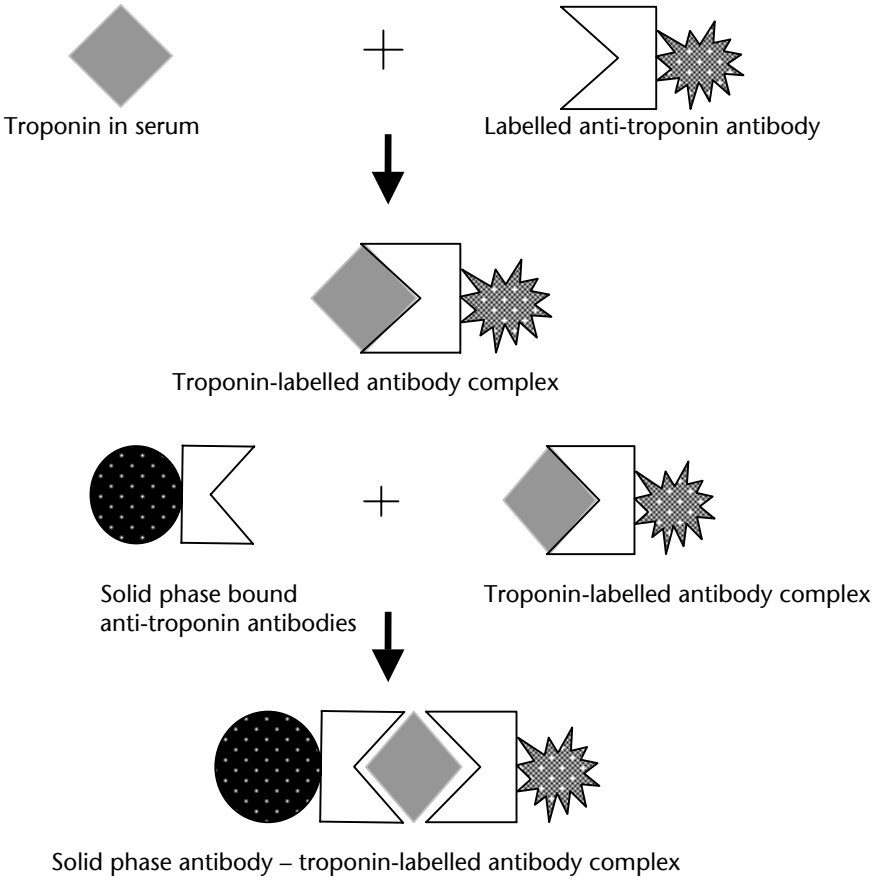
There are different development pathways for troponin T and troponin I. There is transient expression of a foetal cardiac isoform of troponin T in developing skeletal muscle but no expression of cardiac troponin I. This led to the suggestion that troponin T might be released from skeletal muscle in renal failure. This has proved to be erroneous with recent studies confirming that the troponin T elevations of renal failure are cardiac specific and prognostic (Fredericks *et al.*, 2001; Apple *et al.*, 2002b; Hamm *et al.*, 2002).

The second problem with troponin I assays is one of assay standardisation. Different manufacturers have produced assays that target different portions of the troponin I molecule and use different calibrators. Therefore, assays may give up to a 30-fold difference on measuring the same sample. This issue remains to be resolved but there is increasing convergence of assays. It has been shown that standardisation of different assays to give comparable results is possible and an active programme is underway (see Section 4.2.3.3.5.1).

3.5.3 Analytical technology and assay platforms for cardiac troponin measurement

The current methods for measuring cardiac troponin are based on a double-antibody methodology, using either a pair of monoclonal antibodies or a polyclonal antibody combined with a monoclonal antibody. One antibody is used to capture the troponin molecule. Other proteins are then washed away and a detection antibody is added. The detection antibody binds to the captured troponin. Excess is then washed away and the signal generation system is added (see Figure 3-2). The lifecycle of current assays is typically five years. Assay reconfiguration may occur more rapidly if a particular problem is highlighted.

Figure 3-2 Assay methodology



Adapted and reproduced with permission from Bayer plc.

3.5.4 Historical development

The progressive development of the commercially available cardiac troponin assays has addressed four major factors. These include:

- assay specificity
- selection of appropriate epitopes
- sensitivity
- standardisation.

3.5.4.1 Assay specificity

The use of a non-cardiac specific detection antibody may cause cross-reactivity. For example, skeletal troponin is a sticky molecule and significant adsorption to the assay tube can produce an apparent signal if there is any significant cross-reaction with the signal antibody. This was seen in the first generation troponin T assay (Collinson *et al.*, 1995b). The assay was reformulated and is currently based on two antibodies (the capture antibody and the detection antibody) recognising cardiac specific sequences of the troponin T molecule. This has removed problems of apparent cross-reaction.

3.5.4.2 Selection of appropriate epitopes

Post-release degradation of cardiac troponins T and I occurs. Therefore, it is important that assays have epitopes that are close together and not affected by *in vivo* degradation. The troponin T assay has epitopes that are six residues apart in the centre of the molecule. Degradation of troponin I is most marked at the C-terminal end and then at the N-terminal end. Stable epitopes in the troponin I molecule are located in the region 30–110. The reformulation of one commercial assay was required due to selection of epitopes in the unstable region.

Additional factors that induce variability between assays are biochemical changes such as oxidation and reduction and phosphorylation that occur on troponin I and which may alter the conformation of the molecule, thereby masking or exposing epitopes. Drugs and anticoagulants may also affect assay performance, either by binding to cardiac troponin and blocking epitopes or by inducing conformational change by calcium sequestration. A discussion of the physico-chemical factors affecting the analytical performance of the available assays is outlined in Collinson *et al.* (2001a).

3.5.4.3 Sensitivity

There have been continuous efforts to improve assay sensitivity, with most assay systems now on their second or third generation. Assay sensitivity has a direct impact on two aspects of assay performance:

- ability to detect a positive result (signal-to-noise ratio)
- assay imprecision.

The current background level for troponin in the normal individual appears to be zero so enhanced assay sensitivity allows accurate detection of minor degrees of cardiac damage. This has prognostic significance (see Chapter 4). Improved sensitivity allows a lower minimum detection limit of the assay, hence improved precision at the low end of the assay range.

An improvement in assay sensitivity may be achieved by a number of options. For example, selection of an entirely new antibody pair with higher binding constants may improve the absolute sensitivity of the assay. An example of this is the reformulated Beckman Access® assay (which also addressed the stability issue). There may be reformulation of the incubation procedures for the assay itself which optimises performance. Finally, there may be a shift in assay measurement technology that enhances sensitivity. An example is the adoption of electrochemical luminescent technology in the Roche Elecsys® system.

3.5.4.4 Standardisation

Assay reformulation to improve linearity of calibration and to achieve standardisation is desirable in any assay. Improved linearity occurred when

the troponin T assay was recalibrated using a recombinant human cardiac troponin T calibrator. Assay recalibration, which alters assay linearity, does have problems. Results with the new assay may not be equivalent, so clinical studies performed with the original assay may need to be re-interpreted. In the troponin T assay, this did not apply as there was no change in values in the critical clinical range for risk stratification. This is a potential problem for standardisation of troponin I assays. The majority of studies performed to date have used the Dade Stratus® system. Most manufacturers have attempted to achieve assay agreement with this system so there has been a degree of *de facto* standardisation or harmonisation but this level of agreement is not perfect. Any re-standardisation will have to take into account the potential impact on clinical studies performed to date.

3.5.5 Difficulties with assay use

The major advantages of cardiac troponin assays are their absolute cardiac specificity and sensitivity. As discussed in Sections 3.5.3 and 3.5.4, the use of two antibodies targeted at appropriate cardiac isoform specific sequences in the stable region has produced the current generation assays. These are cardiac-troponin specific and recognise epitopes that are not blocked or degraded. The resultant immunoassays are prone to the same problems as other immunoassay systems, such as interference from heterophile antibodies, rheumatoid factor and microparticle aggregates (Bjerner *et al.*, 2002; Marks, 2002). Microparticle aggregate interference arises either from fibrin microclots or from microaggregates of lipid. Centrifuging the sample or repeating the analysis can usually eliminate this problem.

The development and evolution of troponin assays has resulted in two problems. Firstly, the initial assays were less sensitive than current systems. In order to produce a clear distinction between the background value for cardiac troponin in the reference (disease-free) population and the detection limit of the assay (zero signal), relatively high cut-offs were used. Cardiac troponin is undetectable in the blood of normal individuals using current assays, therefore reference values produced had high cut-offs as a clear 97.5th or 99th percentile of the normal population could not be defined.

The second problem arose from the initial validation of troponin assays. This process used a diagnosis of MI based on WHO criteria and utilised CK-MB isoenzyme mass measurement as the diagnostic 'gold standard'. The measurement of cardiac troponin is intrinsically a more sensitive test. There was no problem in demonstrating diagnostic equivalence between CK-MB and troponin but in order to achieve comparable sensitivity and specificity with CK-MB mass, a high cut-off for troponin was proposed. This cut-off was significantly higher than the proposed upper reference limit of normal in a healthy population.

The current inability to define a true upper reference limit for cardiac troponin has led to the proposal that a functional sensitivity limit (defined as the lowest concentration yielding a 10% coefficient of variation [CV]) should be

adopted. This problem is addressed further in Section 4.2.3.3.5.1 but will not be adequately solved until a true upper reference limit can be defined.

The definition of a level of cardiac troponin that does not indicate significant excess risk over predicted population mortality in the general chest pain population has not been established and requires further investigation.

3.5.6 Future development

The future evolution of troponin assays is likely to address two issues. The first issue is to improve existing assay sensitivity to allow more accurate measurement of low levels of troponin. The second is the possibility that there may be intracellular degradation and release of troponin fragments. Therefore, fragment-specific assays are being developed with the assumption that they may be useful to diagnose ischaemia, producing either intracellular troponin degradation or release of reversible membrane ischaemia.

3.5.7 Technologies

There are three groups of analytical technologies for measuring cardiac troponins. These include:

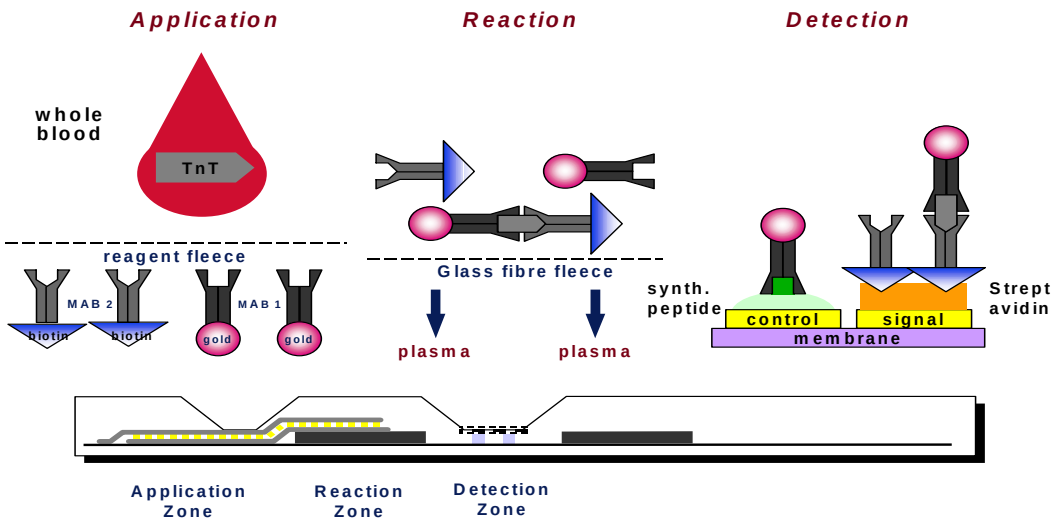
- dry chemistry immunochromatographic devices (also called 'stick tests')
- low throughput whole blood analytical systems
- conventional laboratory instruments.

Details of laboratory and point-of-care analysers are given in Appendix 4. The comparability of troponin results using laboratory and point-of-care analysers is examined in Section 4.3.3.3.4.

3.5.7.1 Dry chemistry immunochromatographic devices (used as qualitative point-of-care readers)

Dry chemistry immunochromatographic tests are based on the gold-labelled optical read immunoassay (GLORIA), as illustrated in Figure 3-3. Plasma is separated from red blood cells and it dissolves the detection and signal antibodies. The plasma proceeds along the reagent strip by capillary action and the complex binds to the detection line while excess reagent binds to the control line. Hence the system has in-built quality control. These devices are small, typically 10 cm x 2.5 cm x 0.5 cm.

Figure 3-3 Schematic of GLORIA format



Reprinted with permission from the Association of Clinical Biochemists (Collinson *et al.*, 2001a) and Roche Diagnostics Ltd.

One advantage of these systems is that they can be used at the point of care (i.e. in the patient's immediate vicinity). They are also rapid, utilise anticoagulated whole blood and have a total turnaround time of 15–20 minutes. Since staff involved in patient care perform the testing, the results are acted upon immediately.

There are two problems with this type of system. The results from original systems were intended to be visually read as either positive or negative. The sensitivity of the system is determined by the absolute detection limit of the system and by operator ability. This type of system has been found to be accurate in routine clinical use but do not offer quite the same sensitivity as laboratory-based results. This led to the development of devices that optically read the strips to improve sensitivity and reduce operator error. Some systems using the same type of technology do not allow visual inspection but require the device to be loaded into a strip reader. However, analytical sensitivity is still not as good as laboratory-based analysis. In addition, point-of-care testing is two to three times more expensive than laboratory-based testing.

These systems are complete with the test strip stored in a sealed foil package containing desiccant. They may or may not require refrigerated storage and are stable with a shelf life of 6–12 months.

3.5.7.2 Low throughput whole blood analytical systems (used as quantitative point-of-care analysers)

Low throughput whole blood systems are designed for point-of-care testing or for the emergency laboratory. They are not restricted to measuring troponin alone but may offer a range of tests. They are quantitative laboratory instruments, so methods are sensitive and precise and they can use whole

blood or plasma. This means there is no sample preparation time which improves turnaround time for analysis. A disadvantage of these systems is that when one sample is loaded, the analyser is committed until analysis is complete. These systems, like the strip tests, tend to utilise an all-in-one reagent pack with individual tests stored in a dry cartridge. Unlike the 'stick tests', there is usually an additional buffer solution which may also be used to dissolve the reagents. The reagent shelf life is typically 6–12 months.

3.5.7.3 Conventional laboratory analysers

Conventional laboratory analysers that measure troponin vary in size, speed and complexity. An advantage of these systems is that measuring troponin is only part of the test repertoire, hence there is economy of scale and the analytical performance is superior to that of point-of-care testing.

A disadvantage of these systems is that they have an increased turnaround time, which arises from three factors. The systems usually use serum, so there is a sample preparation step. The immunoassay is usually run as a continuous process, so samples will be queued with other tests. This can be overcome by using a 'stat' analysis position that schedules the troponin analysis into the first available analytical slot. Finally, a troponin measurement is often only one of a number of urgent tests required. This can be overcome either by appropriate scheduling, by incorporation of an immunochemistry and chemistry analytical system within one machine or automation with linked immunochemistry and chemistry modules. These systems are conventional immunoassays with a test-specific immunoassay reagent, wash solution, a detection reagent common to the analytical system, calibrators and controls. The typical shelf life for reagents is 6–12 months.

3.5.8 Alternatives to troponin

The diagnosis of MI is based on the combination of clinical features, an ECG and the measurement of cardiac biomarkers. As clinical features may not always be reliable, especially in high-risk patients (e.g. in people with diabetes where a painless MI may occur) and the ECG is unreliable in 25% of cases (McQueen *et al.*, 1983; Zarling *et al.*, 2003), the measurement of cardiac biomarkers is a significant component of the diagnostic assessment of ACS.

Cardiac biomarkers may be soluble proteins in the cell cytoplasm or structural proteins. 'Ideal' biomarkers of cardiac damage should possess certain characteristics, for example, they should have a high tissue concentration but low plasma concentration and the marker should have a high concentration in the heart relative to other organs. Biomarker release following tissue damage should be rapid. The marker should also be easy to measure, stable and the time course of release and disappearance should be known.

Biomarkers currently in use are CK, CK-MB, myoglobin and the cardiac troponins. The relative advantages of each are shown in Table 3-3 and the kinetics of release in Figure 3-4.

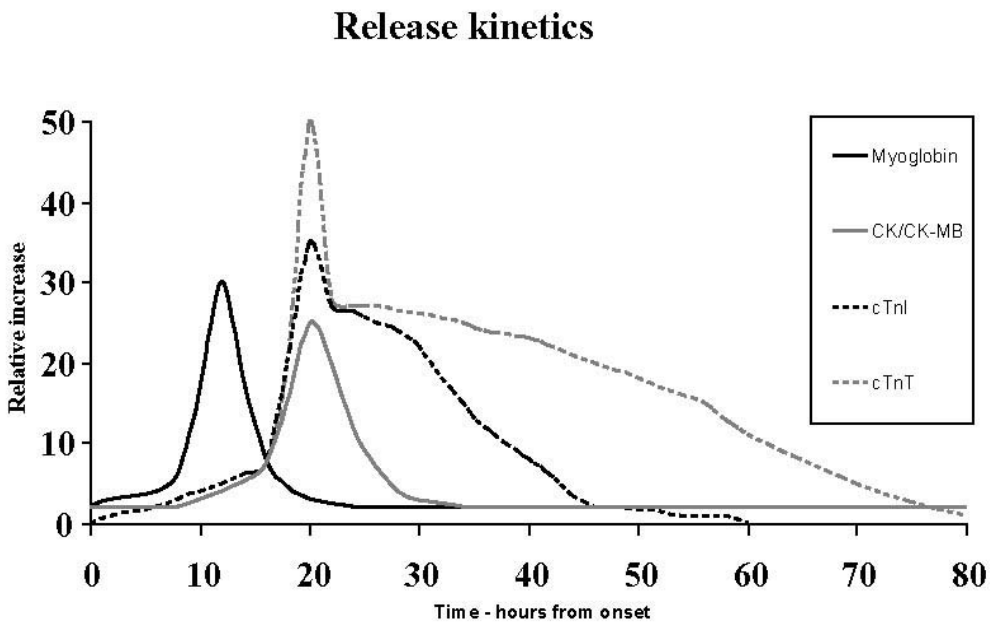
Table 3-3 Properties of cardiac markers

Marker	Tissue concent-ration	Plasma concent-ration	Organ specificity	Stability	Ease of measurement	Time to maximum concentration (hours)[a,b]	Comment
CK: cytosolic	High	Relatively low	Cardiac and skeletal muscle	Good	All current laboratory systems	24	Convenient and low cost but cannot be used if there is skeletal muscle injury (e.g. surgery, road traffic accident [RTA]).
CK-MB: cytosolic	High	Low	Skeletal muscle contains 3–10% CK-MB; cardiac muscle 25–45% CK-MB.	Good	Recommended measurement is of CK-MB mass by immunoassay, available on all laboratory immunoassay platforms.	21	More sensitive and cardiac specific than CK.
Myo-globin: cytosolic	High	Low	Cardiac and skeletal muscle	Good	Measured by immunoassay, available on most laboratory immunoassay platforms.	12	Cannot be used if there is skeletal muscle injury (e.g. surgery, RTA).
Cardiac troponins: structural	Very high	Undet-ectable	Cardiac muscle only	Good	Measured by immunoassay, available on most laboratory immunoassay platforms.	Troponin T: 24 Troponin I: 24 (Troponin peaks occur only when reperfusion, spontaneous or induced occurs, otherwise values reach a maximum at 24 hours and then plateau for the next 24 hours)	The most sensitive test, absolutely specific for cardiac damage. Elevations occur in any form of cardiac injury.

Note: [a] All cytosolic markers peak earlier following successful reperfusion.
[b] Values shown represent typical values and may vary on a patient-by-patient basis depending on the size of infarct and duration of symptoms.

Table by Dr P Collinson.

Figure 3-4 Idealised release kinetics of biochemical markers



Note: This is an idealised figure of the typical release pattern of biochemical markers in a patient with STEMI.
cTnT = cardiac troponin T; cTnI = cardiac troponin I

Figure by Dr P Collinson.

Troponins T and I are both elevated at the same time as CK/CK-MB, with troponin T remaining elevated for up to 7–10 days and troponin I for 4–5 days. The duration of troponin elevation depends on the extent of cardiac damage, with longer duration associated with greater damage. There is an early peak of troponin T (and to a lesser extent troponin I) only seen following successful coronary artery reperfusion (spontaneous or medically induced).

3.6 Focus of the HTA

Troponins may be valuable in assessing peri-procedural cardiac damage in cardiac or other surgery and are raised as a result of non-ischaemic injury such as myocarditis, cytotoxic chemotherapy, cardiac trauma (e.g. RTA, stabbing) or in multiple organ disease (e.g. polymyositis) (Collinson & Stubbs, 2002). However, this HTA focuses on the value of elevated troponins in the setting of ischaemic myocardial injury.

The Clinical Effectiveness Chapter (Chapter 4) firstly evaluates the role of raised cardiac troponins in predicting prognosis in patients with and without ST elevation. Since treatment selection in patients with non-ST elevation ACS is driven by assessed risk rather than diagnostic label, this HTA focuses on the

use of troponin testing in assessing that risk as part of a formal procedure and in guiding the selection of therapy.

Troponin testing is currently widely available in Scotland but in many hospitals, the test results are not available in an appropriate timescale to influence therapeutic decisions. Reduced turnaround times may allow early discharge of or early therapy selection for patients with ACS. Therefore, this HTA examines whether reduced turnaround times and increased 'on-demand' availability of troponin testing may provide benefits to patients and/or economic benefits.

Cardiac troponins are measured by a central laboratory service or at the point of care. A variety of analysers are available to accommodate these settings. This HTA assesses the effectiveness of point-of-care testing compared with laboratory-based testing and to identify those point-of-care analysers that meet with the ESC sensitivity criteria. It compares the accuracy of laboratory analysers with point-of-care analysers, and investigates the impact on patient management and outcomes of the reduced turnaround times and extended availability which may be available from point-of-care analysers.

The Economic Evaluation and Modelling Chapter (Chapter 5) establishes whether troponin testing is cost effective. It then considers the cost consequences of introducing additional troponin tests to testing regimens in certain subgroups of patients with ACS and describes an economic model which was undertaken to inform the organisation of a cost-effective troponin testing service using different scenarios. The scenarios differed in terms of the type of troponin service offered, the availability of troponin tests, the availability of clinical decision making and the turnaround times offered.

The Patient Issues Chapter (Chapter 6) focuses on the needs and preferences of patients with heart disease and their carers in relation to troponin testing. Specifically, it considers the impact of a rapid diagnosis on the patient (facilitated by the use of troponin) and its implications, and the need to communicate the effect a troponin test result will have on risk status and patient management.

The Organisational Issues Chapter (Chapter 7) describes the current provision of troponin testing in Scotland as evaluated by surveys undertaken by NHS Quality Improvement Scotalnd, addresses changes to the service that may need to be made to adopt point-of-care testing and considers the financial and resource implications of the main HTA recommendations.

Overall, this HTA will inform NHSScotland about the organisation of troponin testing to provide an equitable and high-quality service for all patients with ACS in Scotland.

4 Clinical effectiveness

Summary

- A systematic review of the literature was undertaken to assess whether the level of troponin is predictive of outcome in patients with or without ST elevation, whether troponin is superior to CK or CK-MB and whether it can identify patients with non-ST elevation ACS who are most likely to benefit from aggressive medical or interventional therapy. A second systematic review was performed to assess the use of troponin point-of-care testing. A literature review was undertaken to assess different methods of chest pain assessment.

- In patients with chest pain, raised troponin can be associated with a number of conditions other than ACS.

- Troponin levels are maximally sensitive for myocardial damage for the period of 12 to 72 hours after the onset of symptoms.

- Troponin is superior to CK and CK-MB for the sensitive and specific detection of myocardial damage (and hence is superior to aspartate aminotransferase and lactate dehydrogenase). However, CK is the preferred marker for detecting early re-infarction i.e. within 96 hours of original infarct.

- Raised troponin is predictive of short- and long-term risk of adverse cardiac outcomes in both ST elevation and non-ST elevation ACS.

- Raised troponin on admission is predictive of an increased risk of mortality in patients with STEMI.

- There is evidence that clinical and ECG-based risk markers are predictive of outcome independently of troponin.

- The evidence that troponin level alone is effective in determining therapy selection in patients with non-ST elevation ACS is weak, as it is drawn from retrospective subgroup analyses.

- Currently, published risk stratification schemes are based on the use of generic biochemical markers rather than specifically on troponin.

- Point-of-care analysers may reduce the turnaround time for troponin results. However, there are no published randomised controlled trials (RCTs) demonstrating that point-of-care testing of troponin alone improves clinical outcomes compared with laboratory-based testing. The majority of published work on risk stratification has used troponin results from central laboratories.

- Currently only two of the quantitative point-of-care analysers, and none of the qualitative point-of-care readers, are sufficiently sensitive and precise

to be used to rule out myocardial necrosis. These two analysers provide results that are comparable with laboratory analysers from the same manufacturers.

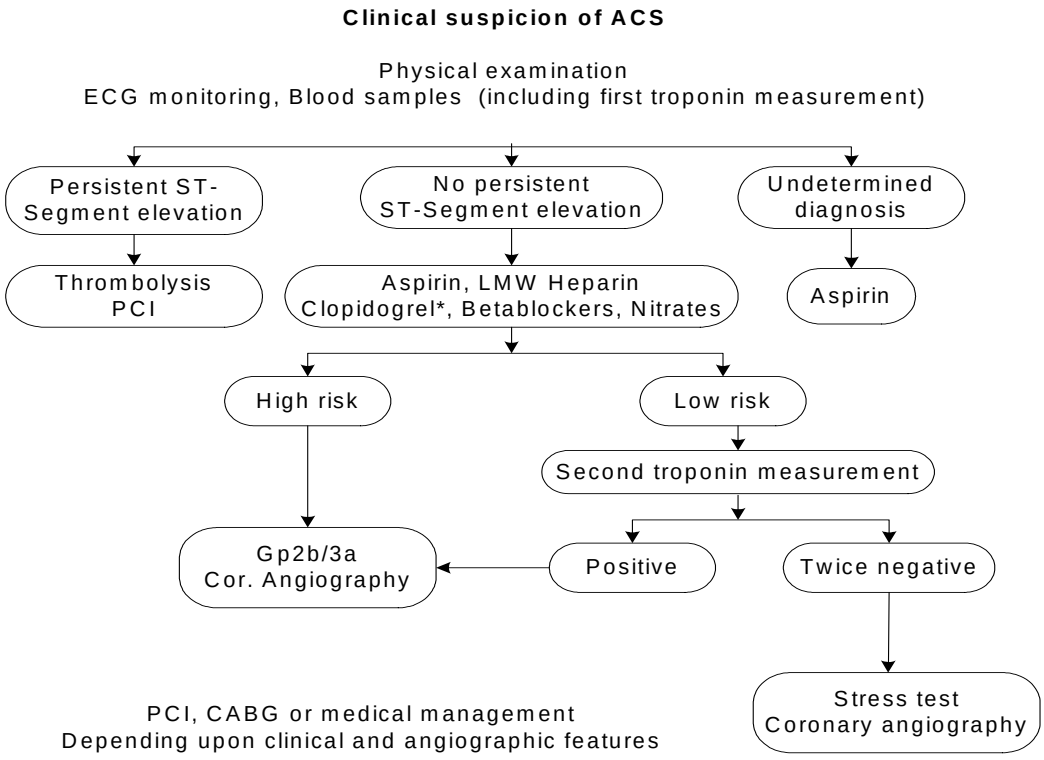
4.1 Introduction – clinical effectiveness

Section 4.1.1 of this chapter provides an example of a patient pathway for the management of patients with non-ST elevation ACS. Section 4.2 discusses the evidence for the effectiveness of troponin testing for prognosis and therapy selection, Section 4.3 compares point-of-care testing with laboratory testing, Section 4.4 examines different methods of chest pain assessment using troponin and Section 4.5 discusses the safety of troponin testing in clinical practice.

4.1.1 An example of a patient pathway for non-ST elevation ACS

In 2002, the ESC published guidelines on the management of ACS in patients presenting without persistent ST segment elevation (Bertrand *et al.*, 2002). Figure 4-1 illustrates the ESC recommended strategy for ACS based on these guidelines. The following subsections describe the role played by troponin in the diagnosis of ACS and risk assessment, and outline the management strategies based on these ESC guidelines.

Figure 4-1 ESC recommended strategy for ACS



*Omit clopidogrel if the patient is likely to go to CABG within 5 days

Reprinted from European Heart Journal, 23, Bertrand ME *et al.* Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, 1809–1840 ©2002, with permission from the European Society of Cardiology.

Note: The ESC guidelines state that only low-risk patients experiencing significant ischaemia during the stress test (particularly at a low workload on a bicycle or treadmill) should be considered for coronary angiography (Bertrand *et al.*, 2002).

The TSG agreed to adopt the ESC recommended strategy for non-ST elevation ACS for this HTA, as it was not possible to devise a Scottish patient pathway that captured all variations in clinical practice. However, it is recognised that not all components in the ESC recommended strategy for ACS are embraced in the Scottish setting. In particular, the schematic pathway for patients with suspected ACS of indeterminate diagnosis as shown in Figure 4-1 is not representative of clinical practice in Scotland. In addition, two areas where Scottish clinical practice differs are the timing and number of troponin measurements and the choice of therapy, in particular clopidogrel and glycoprotein IIb/IIIa inhibitors. These will be examined in Section 4.2.

In Scottish hospitals, local variations of these ESC guidelines have been implemented. Appendix 5 contains two examples of pathways for the management of patients with suspected ACS.

4.1.1.1 Diagnosis of ACS

The initial evaluation to assess whether or not a patient has chest pain of cardiac origin uses medical history and a precise description of symptoms, a physical examination, an ECG and cardiac biomarkers.

The ESC guidelines note that the 12-lead ECG is a critical risk stratification tool in the initial evaluation of heart disease and central to the decision pathway for managing patients with ACS. It identifies symptoms that qualify as ACS and shows changes such as ST segment shifts (ST segment elevation or depression) which help to guide the appropriate course of management. The ECG may also provide evidence of an alternative diagnosis such as pericarditis, pulmonary embolism or cardiomyopathy (Bertrand *et al.*, 2002). A completely normal ECG during an episode of pain does not exclude the possibility of ACS but is suggestive of other causes.

Biochemical markers provide diagnostic and prognostic information to help evaluate patients with suspect ACS. The ACC/AHA and ESC guidelines state a preference for troponin tests because they have near absolute myocardial tissue specificity as well as high sensitivity of myocardial necrosis, although CK-MB is an acceptable alternative despite its lack of specificity and presence in healthy people (Braunwald *et al.*, 2002; Bertrand *et al.*, 2002).

The ESC guidelines on the management of ACS in patients presenting without persistent ST segment elevation recommend that troponin is measured initially on presentation to hospital and then 6–12 hours later (Bertrand *et al.*, 2002) if the initial test was negative. If a second sample is taken, the clinician should ensure that this is taken at least 12 hours after the onset of pain to avoid the danger of a false-negative result.

The presence of troponin usually signifies myocardial cell death has occurred. According to the ESC/ACC consensus definition (Alpert *et al.*, 2001), raised troponin in the setting of myocardial ischaemia (chest pain and ST segment

changes) is suggestive of MI. However, raised troponin also occurs in patients with chest pain and without ischaemic injury and is associated with diagnoses such as pulmonary embolism, myocarditis and heart failure (Bertrand *et al.*, 2002; Collinson & Stubbs, 2002).

Raised cardiac troponin in patients predicts poorer outcomes and a higher rate of death than in patients without raised troponin. However, patients with a negative troponin result may still be at risk of adverse cardiac outcomes.

4.1.1.2 Risk assessment

ACS brings together a diverse group of patients with different clinical presentations, who have varying degrees of atherosclerosis and differing risks for subsequent cardiac events (Bertrand *et al.*, 2002). The medical history, clinical presentation, ECG and measurement of cardiac markers are all used to estimate the risk of death and non-fatal cardiac events in patients with suspected ACS at presentation (Braunwald *et al.*, 2002).

Initially, risk assessment takes place at the time of initial diagnosis or on presentation to hospital. Risk assessment identifies low- and high-risk patient groups and can be used to select patients for appropriate therapy. The risk should be re-assessed regularly throughout the observational period, during which additional information from multi-lead ECG, monitoring of clinical symptoms and biochemical marker or other test results may be available. If necessary, the course of therapy is changed (Bertrand *et al.*, 2002).

4.1.1.3 Management strategies

In clinical practice, there are two main approaches to managing ACS. These are:

- conservative management, which usually involves bed rest and pharmacological agents
- invasive management, which comprises revascularisation by percutaneous coronary intervention (PCI) or CABG.

Treatment of patients with ACS may involve both of these approaches. Secondary prevention of coronary events is also essential in both approaches. Therapy options and the ESC recommended management strategies for low- and high-risk patients with non-ST segment elevation ACS are described in Appendix 6. In the ESC guidelines, a particular point of interest is the role of a cardiac stress test (which is usually an exercise tolerance test [ETT]) in low-risk patients. A stress test is recommended to help confirm a diagnosis of heart disease and to establish prognosis. The results of the stress test, in combination with other factors, may determine whether early angiography is required.

4.2 Effectiveness of troponin testing for prognosis and therapy selection

4.2.1 Introduction

Figure 4-1 demonstrates how clinical factors, ECG monitoring and troponin testing may be integrated into an appropriate pathway for patients presenting with suspicious chest pain.

Two important points should be noted. Firstly, as described in the Chapter 3, elevations in cardiac troponin are diagnostic of damage to heart muscle cells but are not specific to ischaemia. Such cell damage may be caused by a variety of mechanisms, and the particular diagnosis of ischaemic disease and hence of MI, must be made using a combination of factors such as clinical symptoms, medical history and ECG. Secondly, non-elevated levels of troponin do not necessarily equate to low-risk status. For example, Cannon *et al*. (2001a) showed that among patients without raised troponin, a version of the Thrombolysis In Myocardial Infarction (TIMI) risk score calculated without biochemical markers allowed further stratification by risk level. The TIMI score is explained in Appendix 7.

This section reviews and summarises the available evidence relating to the use of troponin testing in patients with symptoms suggestive of ACS. The clinical evidence will be reviewed under the following headings:

- evidence on whether the level of troponin is predictive of outcome in patients without persistent ST elevation (Sections 4.2.3.2 and 4.2.3.3.1)
- evidence on whether the level of troponin is predictive of outcome in patients with ST elevation (Section 4.2.3.3.2)
- evidence on whether troponin is superior to CK or CK-MB for outcome prediction (Section 4.2.3.3.3)
- evidence on whether troponin test results can identify effectively patients who are most likely to benefit from medical or interventional therapy for patients with non-ST elevation ACS (Section 4.2.3.3.4).

Differences between troponin T and troponin I will be discussed throughout this section. Other aspects of troponin testing will be discussed in Section 4.2.3.3.5.

4.2.2 Methodology

4.2.2.1 Evidence sources

Evidence to support this chapter of the HTA was obtained from a wide variety of sources. These include published literature, grey literature, information submitted by interested parties and TSG members, data obtained from Information and Statistics Division (ISD) and survey results.

4.2.2.1.1 Literature search

A scoping search was carried out to establish the quantity and quality of the existing literature relevant to this topic, with particular attention being paid to finding studies by other HTA organisations, systematic reviews and research in progress. The results of this search led to the undertaking of two systematic literature searches for the clinical effectiveness aspects of this topic, as well as a number of smaller searches looking for very specific information.

The aim of the first systematic search was to look for RCTs on the use of troponin in ACS. Using the papers identified by this search, various separate systematic reviews were carried out. The strategy used to search the MEDLINE database is given in Appendix 8. This was modified, as appropriate, to search the other databases also listed in Appendix 8. No time or language restrictions were applied to the search. A flow chart showing the number of studies identified and then selected for inclusion in the systematic reviews is also given in Appendix 8.

The other two searches are described under appropriate headings of this chapter (Sections 4.3.2 and 4.4.2).

Following the main search in July 2002, additional searches were carried out to retrieve papers related to:

- NSTEMI and thrombolysis from 1996 onwards
- the proportion of patients with or without positive troponin on presentation to hospital
- the proportion of unsolicited patients with ST elevation or non-ST elevation presenting to chest pain clinics.

Literature was also identified from current awareness alerts, from scanning of the bibliographies of retrieved studies and by updating some of the searches used in retrieved studies.

4.2.2.2 Exclusion criteria

The following exclusion criteria were applied:

- descriptive review papers
- studies in populations not directly relevant to Scotland
- studies which were already included in Heidenreich *et al.* (2001) or Fleming & Daly (2001) papers, and only addressed the prognostic value of troponin alone
- studies in patients other than ACS patients (such as studies of peri-procedural damage)
- therapy selection studies not using troponin as one of the selection criteria.

4.2.2.3 Methodology for the evaluation of clinical effectiveness

As no further use would be made within the HTA of numerical results, no meta-analyses or other modelling work were undertaken.

4.2.3 Results of the effectiveness of troponin testing for prognosis and therapy selection – critical appraisal of literature

4.2.3.1 Previous HTAs

There are no HTAs published to date on the effectiveness of troponin in prognosis and therapy selection.

4.2.3.2 Systematic reviews and meta-analyses

Two published meta-analyses of patients with NSTEMI were found. These provide evidence that troponin levels are predictive of adverse cardiac outcomes (i.e. death and non-fatal MI) in patients with chest pain (Heidenreich *et al.*, 2002; Fleming & Daly, 2001). Both meta-analyses appear to be methodologically sound. However, they are limited in the scope of questions they address because of the manner in which data have been reported in the primary sources. The primary sources are not reviewed here.

As described in Section 3.5, although there is evidence (Antman *et al.*, 1996; Kaul *et al.*, 2003) that risk increases with increasing troponin level, because of the substantial variability in current assays it is usual to define a cut-off clearly separating patients with non-elevated troponin from those with increased circulating troponin. Patients with levels above the cut-off are described as 'troponin positive', 'having a raised troponin level' or 'having a positive troponin test result'.

The definition of raised troponin varied among the studies reviewed both by Heidenreich *et al.* (2001) and Fleming & Daly (2001). In these meta-analyses, 'raised troponin' equates to 'raised troponin as defined in the original study'.

Heidenreich *et al.* (2001) showed that patients with NSTEMI and a raised troponin (T or I) level had an increased risk of mortality during a median 12-week follow up (5.2% versus 1.6%, odds ratio [OR] 3.1, 95% CI 2.3, 4.1) and an increased risk of death or MI (13.5% versus 5.9%, OR 2.5, 95% CI 2.0, 3.1) compared with those without a raised troponin level. These risks were not adjusted. They also showed that the OR for death and MI during follow up was higher for both troponin T (OR 5.1, 95% CI 3.2, 8.4) and I (OR 8.5, 95% CI 3.5, 21.1) in cohort studies than in RCTs (troponin T: OR 3.0, 95% CI 1.6, 5.5; troponin I: OR 2.6, 95% CI 1.8, 3.6). The OR was also larger for cohort studies with follow up less than 12 weeks (11.4, 95% CI 4.5, 28.9) than for those with longer follow up (3.2, 95% CI 1.8, 5.5).

Fleming & Daly (2001) analysed the effects of raised troponin T and I separately on the adverse cardiac outcome of 30-day combined death and MI rate. They showed that:

- for troponin I, the event rate for NSTEMI patients without raised troponin was 5.9% and that for patients with raised troponin was 30.8% (OR 4.9, 95% CI 3.9, 6.2) based on a total sample of 5739 patients, of whom 31% had raised troponin levels
- for troponin T, the event rates were 10.9% and 30.2% for patients without raised troponin and patients with raised troponin respectively (OR 4.6, 95% CI 3.8, 5.5) based on a total sample of 5483 patients, of whom 30% had raised troponin
- both troponin T and I were more strongly predictive of outcome in studies where samples were timed to be measured at least six hours after the reported onset of pain. For troponin T, the OR was 8.8 (95% CI 5.9, 13.3) for 'timed' samples, and 3.2 (95% CI 2.3, 4.4) for 'non-timed' samples. For troponin I, the OR was 8.0 (95% CI 5.5, 11.8) for 'timed' samples and 3.5 (95% CI 2.5, 4.8) for other samples.
- troponins were more strongly predictive of outcome in unselected patients than in those selected on the basis of ECG changes or other evidence.

The two meta-analyses addressed different questions and hence are not directly comparable. Heidenreich *et al.* examined the effect of troponin elevation on long-term outcomes (i.e. median 12 weeks), whereas Fleming & Daly focused only on short-term outcomes (i.e. 30 days).

4.2.3.3 Other studies or reviews

4.2.3.3.1 Patients without persistent ST segment elevation[7]

Tables A1, A2 and A3 (Appendix 9) respectively display studies:

- dealing with the prognostic significance of troponin which were published after the meta-analyses reported in Section 4.2.3.2
- presenting results on the prognostic value of troponin in combination with one or more risk factors
- presenting results on the prognostic value of troponin I illustrating the variability in cut-off values used.

Taken together, the studies reported here demonstrate that:

- there is consistent evidence that cardiac troponin is predictive of adverse cardiac outcomes (i.e. death or non-fatal AMI) in the short (e.g. 30 days) and long term (e.g. 12 months) in patients presenting with non-ST elevation ACS
- cardiac troponin levels continue to be predictive after adjustment for other known risk factors

[7] The ESC guidelines describe ACS without persistent ST segment elevation as the following ECG changes: ST segment depression, negative T waves, pseudonormalisation of T waves or normal ECG (Bertrand *et al.*, 2002).

- because of the lack of standardisation, a comparison of results obtained using different troponin I assays is difficult.

The studies reported here have all examined the predictive value of troponin levels in patients diagnosed with non-ST elevation ACS. Such patients are likely to be likely to be at higher risk of adverse cardiac outcomes than patients presenting to hospital with chest pain.

4.2.3.3.2 Patients with ST segment elevation

Prognosis

Matetzky (2000) studied 110 patients with STEMI who underwent primary percutaneous transluminal coronary angioplasty (PTCA). In 54 of these patients, troponin I (Dade Behring) was raised ($\geq$ 0.4 μg/L) on admission. There was no evidence of significant correlation between troponin level on admission and time from onset of symptoms. Patients with raised troponin I had a significantly higher incidence of the combined endpoint (congestive heart failure, shock and death) during the hospital stay (30% versus 9%, $p<0.01$) and a significantly higher rate of death (11% versus 0%, $p=0.012$) on long-term follow up (median = 425 days) than patients without raised troponin I.

Ohman *et al.* (1999) studied patients from 550 of the 807 centres involved in the GUSTO III study of thrombolysis in STEMI. Of the 15 059 patients enrolled, 12 666 were included in the Ohman *et al.* study, of which 1127 (8.9%) were positive for troponin T at time of admission using a qualitative strip test with a sensitivity of 0.2 μg/L. These patients had a significantly higher mortality at 30 days than patients testing negative for troponin at time of admission (15.7% versus 6.2%, $p<0.001$). The OR for troponin status after adjustment for age, Killip class, systolic blood pressure, heart rate, infarct location and time from symptom onset to treatment was 2.05 (95% CI 1.68, 2.51).

The prognostic value of troponin in these patients is important because of the following results. Berger *et al.* (2000) showed that the presence of left bundle branch block is the strongest predictor of delayed thrombolysis (>30 minutes after admission) in a cohort of 17 379 elderly patients (mean age of 73.5 years), presumably because of uncertainty in the diagnosis. In this cohort, patients who received delayed thrombolysis experienced poorer survival than those patients receiving thrombolysis within 30 minutes, after adjustment for 'patient and institutional risk factors'. This suggests the possibility that any method that reduces the uncertainty associated with left bundle branch block, and hence allows earlier treatment, may improve survival.

There is also some evidence that elevated troponin T after thrombolysis may be associated with a left ventricular ejection fraction (LVEF) of less than 40%, and hence with an increased long-term risk of heart failure (Ryan *et al.*, 1999).

Studies of the relationship between troponin and LVEF are summarised in Table A4 (Appendix 9). However, this evidence is drawn from three case series, one of which was retrospective and only one examined the comparative predictive power of CK and troponin. The time window for troponin measurement also differed between the three studies. Therefore, although these findings are suggestive, clear conclusions on this topic must await further large-scale, prospective studies with clearly defined measurement times and objectives.

Standards issued by the Clinical Standards Board for Scotland (now a part of NHS Quality Improvement Scotland) advise that all patients recovering from STEMI should have their cardiovascular status assessed and be offered prophylactic medication, unless there are contraindications. Echocardiography should be routinely conducted for all patients. Therefore, the finding that troponin rises may predict LVEF is unlikely to have a practical application within NHSScotland because echocardiography is a superior predictor of LVEF.

Confirmation of diagnosis

Canepa-Anson *et al.* (1998) showed that 3% of patients admitted with chest pain received an inappropriate diagnosis of AMI based on clinical features, daily CK testing and ECG. These patients showed no rise in troponin 12–24 hours after admission and therefore were unlikely to have had an MI. In such patients, further treatment with antithrombotic therapy, angiotensin-converting enzyme (ACE) inhibitors and post-MI rehabilitation is inappropriate and other causes for chest pain should be sought and patients treated appropriately (Dr B Lindahl, Head of CCU, Department of Cardiology, Uppsala University Hospital, personal communication, 2003).

4.2.3.3.3 Evidence that troponin testing is superior to CK or CK-MB testing

The best commonly available alternatives to cardiac troponins as tests of myocardial necrosis are CK and CK-MB. These enzymes are also released by damaged cardiac muscle. However, unlike CK and CK-MB, the cardiac forms of both troponin I and troponin T are distinct from those found in skeletal muscle (Wu, 1998) which indicates that cardiac troponin may be a specific marker for cardiac muscle damage.

Clinically, this view is reinforced by evidence that both troponin T and I remain undetectable after arduous exercise in highly trained athletes and Marine commandos while CK and CK-MB levels are elevated (Collinson *et al.*, 1995a; Bremner *et al.*, 2000; Lavoinne *et al.*, 2000). Note, however, that raised levels of troponin I were reported using the Abbott Diagnostics AxSYM® assay in this instance (Collinson *et al.*, 1995a) but not with other assays such as the Bayer ACS:180® (Collinson *et al.*, 2001c).

The studies described in Table A5 (Appendix 9) provide evidence of the utility of cardiac troponins in patients with ACS who have normal CK and CK-MB.

Overall, the biochemical and clinical findings indicate that cardiac troponins are superior to CK-MB for risk assessment and the diagnosis of MI (as CK has superseded markers such as aspartate aminotransferase and lactate dehydrogenase, and therefore it may be inferred that troponins I and T are superior to these markers).

Furthermore, a study by Rao *et al.* (2003b) demonstrated that baseline troponin elevation, regardless of CK-MB result, is predictive of short- and long-term adverse cardiac outcomes across a range of patients with high- and low-risk clinical features. This study concluded that troponin is a superior marker of risk compared with CK-MB.

However, CK remains valuable in assessing early re-infarction, since troponin levels may remain elevated for up to 96 hours post infarction (Collinson *et al.*, 2001a).

4.2.3.3.4 Evidence that troponin testing may be effective in selecting therapy for patients with non-ST elevation ACS

Considerable evidence has accumulated from subgroup analyses of clinical trials to suggest that biochemical markers such as troponin, in combination with other risk markers, can be used to identify groups of patients with ACS that are more likely to benefit from aggressive medical or interventional therapy (including glycoprotein IIb/IIIa inhibitors, low molecular weight heparin [LMWH] and early surgical intervention). These therapies are examined in the following subsections.

4.2.3.3.4.1 Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa inhibition has been investigated in clinical trials for two distinct indications:

- in patients undergoing PCI
- in ACS patients not scheduled to undergo PCI.

These will be discussed in the following subsections.

4.2.3.3.4.1.1 Glycoprotein IIb/IIIa inhibition in patients undergoing PCI

The effect of using glycoprotein IIb/IIIa inhibitors in patients undergoing PCI was examined in four studies (Topol *et al.*, 1994; The CAPTURE investigators, 1997; The EPILOG Investigators, 1997; The EPISTENT Investigators, 1998) and was found to be clinically effective for this group of patients.

The Chimeric c7E3 AntiPlatelet Therapy in Unstable angina Refractory to standard treatment (CAPTURE) trial investigators published a retrospective analysis of the interaction between troponin T level measured at study entry and the effect of abciximab in reducing death or non-fatal MI (Hamm *et al.*, 1999). This suggested that the benefit of abciximab may be greater in patients with raised troponin T (0.1 μg/L) than in other patients. The analysis was undertaken on 890 of the 1265 patients randomised in the original trial,

and the effect of troponin was examined by subgroup analysis. The rates for death/MI at 30 days were 5.2% for placebo versus 4.9% for abciximab in patients with troponin T level ≤0.1 μg/L and 19.6% for placebo versus 5.8% for abciximab in patients with troponin level >0.1 μg/L. The authors also performed an exploratory analysis looking at the relationship between the effect of abciximab and the level of troponin. In this analysis, troponin was categorised into one of five groups (≤0.01 μg/L, 0.02–0.04 μg/L, 0.05–0.12 μg/L, 0.13–0.32 μg/L and >0.32 μg/L). The analysis suggested that the effect of abciximab was greatest in the two groups with the highest level of troponin.

It is not clear from the paper whether the authors decided to dichotomise the troponin level on the basis of the results from the exploratory analysis. To date, similar analyses have not been published from other studies in this indication and the results have not been confirmed by prospective studies, so the results of this retrospective subgroup analysis must be treated with caution.

4.2.3.3.4.1.2 Glycoprotein IIb/IIIa inhibition in the medical management of ACS

Two recently published meta-analyses (Boersma *et al.*, 2002; Roffi *et al.*, 2002) combined data from the six published RCTs on the use of glycoprotein IIb/IIIa inhibitors in the medical management of ACS and focused on the outcome variable 'death or non-fatal MI within 30 days'. However, Boersma *et al.* (2002) analysed individual patient data, whereas Roffi *et al.*(2002) combined summary measures from the six studies. Both analyses suggested that the overall effect of glycoprotein IIb/IIIa inhibitors on the outcome was significant (p=0.05). However, the subgroup analyses suggested that any beneficial effect of glycoprotein IIb/IIIa inhibitors may be largely confined to patients who undergo PCI.

Boersma *et al.* presented an analysis suggesting that troponin-positive patients receive greater benefit from glycoprotein IIb/IIIa inhibition than troponin-negative patients. However, only 35% of the patients could be included in this analysis and it is necessary to look at the individual trial results.

Boersma *et al.* analysed data from six RCTs. In four of the RCTs, troponin was measured in some or all of the patients. For each of these RCTs, individual study level analyses of the interaction between troponin and treatment with glycoprotein IIb/IIIa inhibitors have been published: the Platelet Receptor Inhibition in ischemic Syndrome Management (PRISM) trial (Heeschen *et al.*, 1999b); the Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in Global Organization Network B (PARAGON–B) trial (Newby *et al.*, 2001a); the Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms (PRISM–PLUS) trial (Januzzi *et al.*, 2001) and the Global Utilization of Strategies To open Occluded arteries trial IV (GUSTO IV) trial (Simoons & GUSTO IV ACS Investigators, 2001). These studies are described below:

Heeschen *et al.* (1999b)

This was a retrospective exploratory analysis of data from the PRISM study. Troponin results were available for 2222 of the 3232 patients. Following exploratory analysis, in which a variety of possible cut-offs were examined, the authors chose to dichotomise troponin T at 0.1 μg/L and troponin I at 1 μg/L. They found a significant interaction between each of these variables separately and the effect of treatment, in that patients with baseline troponin T >0.1 μg/L or troponin I >1 μg/L appeared to receive greater benefit from tirofiban than those with lower or undetectable troponin levels. For both markers, the p-value was <0.001 for an interaction test between the effect of treatment and baseline troponin level. Subgroup results for 30-day death or non-fatal MI are as follows: the ORs (tirofiban relative to heparin) were 0.29 (95% CI 0.15, 0.56) for troponin I-positive patients; 1.17 (95% CI 0.76, 1.83) for troponin I-negative patients; 0.23 (95% CI 0.12, 0.45) for troponin T-positive patients and 1.35 (95% CI 0.86, 2.1) for troponin T-negative patients.

Newby *et al.* (2001a)

This was a prospective study of 1160 patients from 4065 randomised in the original study (PARAGON–B). A pre-specified cut-off of 0.1 μg/L was used to define raised troponin T. Although there was a trend towards a greater effect of lamifiban in troponin-positive patients, the interaction between troponin status and treatment was not significant. The 30-day death or MI rates in troponin-positive patients were 11.0% for patients treated with lamifiban and 19.0% for those treated with placebo. The corresponding rates in troponin-negative patients were 9.6% for lamifiban and 10.4% for placebo.

Januzzi *et al.* (2001)

This was a very small substudy (110 of 1915 patients enrolled in the PRISM–PLUS study). Troponin I-positive patients (troponin I >0.5 μg/L) appeared to receive greater benefit from treatment with tirofiban than troponin I-negative patients, but the interaction between troponin elevation and treatment was not significant.

Simoons *et al.* (2001)

As part of a large study of abciximab in 7800 patients with non-ST elevation ACS (GUSTO IV), the interaction between treatment and positive troponin T was investigated and evaluated in all patients. No overall effect of the treatment was found, and there was no evidence of an interaction between treatment and troponin level.

Summary

Although three of the four studies (Heeschen *et al.*, 1999b; Januzzi *et al.*, 2001; Newby *et al.*, 2001a) published to date suggest that the effect of glycoprotein IIb/IIIa inhibition may be greater in patients with raised troponin before treatment, the evidence is inconclusive, especially given the results from the GUSTO IV trial (Simoons & GUSTO IV ACS Investigators, 2001).

The National Institute for Clinical Excellence (NICE) has issued guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of ACS (National Institute for Clinical Excellence, 2002). The guidance notes that troponin is useful in diagnosing ACS and in risk stratification. It recommends that in patients who are considered to be at high risk, treatment with small molecule glycoprotein IIb/IIIa should be initiated as soon as the high-risk status is determined, even though this may be before the result of the troponin test is known.

4.2.3.3.4.2 LMWHs

Lindahl *et al.* (1997b) analysed a subset of the Fragmin and fast Revascularisation during Instability in Coronary artery disease (FRISC) study (a comparison of dalteparin with placebo, in addition to aspirin, in patients with non-ST elevation ACS). In 971 of the 1506 patients enrolled, troponin T was measured on inclusion. The authors performed an exploratory analysis in which troponin values were categorised into tertiles (<0.1 μg/L, 0.1–0.64 μg/L, ≥0.64 μg/L). They noted that the treatment contrasts appeared very similar in the two higher groups and accordingly examined the treatment by troponin interaction for troponin values dichotomised at 0.1 μg/L. They found a significant interaction ($p<0.01$ interaction test in logistic regression) between treatment and troponin level, with the effect of dalteparin being significant in the high-troponin group but not in the low-troponin group.

Morrow *et al.* (2000a) examined a small subset of the TIMI 11B study comprising patients with normal CK-MB levels, in whom troponin was measured on inclusion. The original study compared enoxaparin with unfractionated heparin in patients with high-risk non-ST elevation ACS. The patients in the subgroup examined in Morrow *et al.* had troponin measured. The subgroup consisted of 190 patients randomised to unfractionated heparin and 169 to enoxaparin. Within this limited group, the benefit of enoxaparin was greater in patients with elevated troponin (interaction p-value of 0.03 for 30-day death/MI/recurrent angina).

These studies are detailed in Table A6 (Appendix 9). Although both studies found evidence that the effect of LMWH appeared greater in patients with raised troponin than in those without raised troponin, the evidence is not adequate for a definite conclusion because they were retrospective substudies.

In the original study reporting the development of the TIMI score, Antman *et al.* (2000) showed in a retrospective analysis that the benefit of enoxaparin over unfractionated heparin appeared to be greater in patients with TIMI risk scores of greater than four.

4.2.3.3.4.3 Clopidogrel

The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial investigators (Yusuf *et al.*, 2001) did not specifically examine the existence of an interaction between troponin level and the effect of clopidogrel. They did not show any evidence of an interaction between treatment and the presence of an elevated cardiac enzyme (defined as troponin, CK or CK-MB).

Budaj *et al.* (2002) re-analysed the CURE data and showed that there is no evidence of any interaction between risk (as measured by the TIMI score) and the treatment effect of clopidogrel. Specifically, the relative risks (RRs) (clopidogrel versus placebo) of the primary outcome (death, non-fatal MI or stroke occurring at any time in the 12 months of follow up) were 0.71 (95% CI 0.52, 0.97) in the low-risk group (TIMI score 0–2), 0.85 (95% CI 0.74, 0.98) in the intermediate-risk group (TIMI score 3 or 4) and 0.73 (95% CI 0.60, 0.90) in the high-risk group (TIMI score 5–7). The absolute differences by TIMI score are outlined in Table 4-1.

Table 4-1 Absolute difference in primary outcome, tabulated by TIMI score

TIMI score	Difference between placebo and clopidogrel (%)
0–1	0.1
2	2.1
3	1.9
4	1.4
5	4.2
6–7	7.9

The numbers of patients needed to be treated to avoid one primary outcome were 63 in the low-risk and intermediate-risk groups and 21 in the high-risk group.

Budaj *et al.* also showed that the incidence of major bleeding complications increased with TIMI score and that the relative risk of these complications was constant. Therefore, both the absolute benefit of clopidogrel and the complication rate increase with underlying risk.

4.2.3.3.4.4 Invasive therapy within 72 hours

Published studies examining the existence of a possible interaction between troponin level and the effect of early invasive therapy (i.e. angiography within 72 hours of presentation, followed by PCI or CABG if appropriate) in patients with non-ST elevation ACS are displayed in Table A7 (Appendix 9).

Diderholm *et al.* (2002) showed that the benefit of early invasive therapy appeared to be largely confined to patients with both raised troponin and ST depression at randomisation. Specifically, they performed a subgroup analysis

of the FRISC II study based on four groups: troponin T <0.03 μg/L and no ST depression; troponin T ≥0.03 μg/L and no ST depression; troponin T <0.03 μg/L and ST depression; and troponin T ≥0.03 μg/L and ST depression. The cut-off of 0.03 μg/L was chosen as the functional sensitivity of the assay (i.e. the measured value at which the CV is 20%). The primary endpoint of 30-day death or MI was only significantly reduced by the invasive strategy in the group with both elevated troponin and ST depression (p=0.05).

In a prospective analysis, Morrow *et al.* (2001) showed that there was a significant interaction between a treatment strategy of invasive therapy within 4–48 hours after randomisation and troponin level for either troponin I or troponin T using cut-offs previously established in the TIMI 11B study (Morrow *et al.*, 2000b). They did not examine the joint effect of troponin elevation and ST depression. However, univariate analyses presented in the original report of the Treat angina with Aggrastat and determine the Cost of Therapy with Invasive or Conservative Strategy (TACTICS) TIMI 18 study (Cannon *et al.*, 2001b) showed that the effect of an invasive strategy appeared to be confined to patients with ST depression. No interaction was found between treatment and troponin levels. They also showed that the effect of an invasive strategy was most marked in patients with a TIMI score of five or greater.

One recently published study (Randomised Intervention Trial of unstable Angina [RITA] trial III) comparing early invasive therapy with conservative management did not examine the effect of troponin (Fox *et al.*, 2002) because troponin testing was not available in many of the participating centres when the study opened (Professor K Fox, personal communication, 2002).

4.2.3.3.4.5 Invasive therapy within 24 hours

This section considers the evidence on whether patient outcomes are improved by very early invasive therapy (i.e. angiography within 24 hours of presentation, followed by PCI or CABG if appropriate). If the evidence suggests invasive therapy within 24 hours improves patient outcomes, then the benefit of measuring troponin on admission is enhanced.

Although the results from FRISC II and TACTICS TIMI 18 suggest that early revascularisation may be more effective than medical therapy in some high-risk non-ST elevation ACS patients, it is not clear from these studies whether very urgent revascularisation is needed or whether a 'cool-down' period of medical management may be effective.

Additionally, the RITA III study (Fox *et al.*, 2002) showed no difference in major event rates (death or non-fatal MI) between the two early invasive and early conservative groups, but only demonstrated a difference in subsequent hospital admissions for recurrent chest pain. The data from this study suggested that for many patients without recurrent or continuing pain, PCI may be delayed until recovery (Professor Henry Dargie, Professor of

Cardiovascular Medicine, North Glasgow University Hospitals Trust personal communication, July 2003).

However, two observational studies and one small clinical trial have suggested that very urgent intervention may be used more broadly rather than being restricted to patients with continuing or recurrent pain.

Bhatt *et al.* (1998) showed that the absolute risk reduction (30-day death or MI rate) for eptifibatide versus placebo appeared to fall from 2.8% for patients first treated between zero and six hours post-symptom onset to 1.7% for those treated between 12 and 24 hours post-symptom onset, and to zero for those first treated after 24 hours. However, this result was obtained from an 'accidental experiment' (i.e. patients were not assigned to different delay times) and as such, the result may be affected by bias of unknown size and direction.

Ronner *et al.* (2002) performed a retrospective analysis of the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) study (Ronner *et al.*, 1998) in which the 2419 patients (26% of the original sample) who underwent PCI within 30 days of enrolment were divided into four groups on the basis of time to intervention. The four time periods were: within 24 hours; 25–72 hours; 73–168 hours and 169–720 hours. The group receiving treatment with eptifibatide and early PCI within 24 hours had the lowest 30-day death and MI rate of all groups. Clearly this result may have occurred because of patient selection bias or differences between institutions. The authors recommended that a trial of very early revascularisation versus medical stabilisation followed by PCI be conducted.

More recently, Neumann (2003) reported the results of the Intracoronary Stenting with Antithrombotic Regimen Cooling-off (ISAR-COOL) trial of early versus delayed invasive therapy, in which 410 patients were randomised between early angiography (delay of less than eight hours) and PCI, and delayed angiography (delay of >72 hours) and PCI. In both groups, patients received aspirin, LMWH, clopidogrel and tirofiban before intervention. The risk of 30-day major adverse cardiac outcomes was significantly lower in the early intervention group compared with the delayed intervention group (5.9% versus 11.6%, $p<0.05$).

It should be noted that although both death and non-fatal Q-wave MI rates were higher in the 'cooling-off' group than the early intervention group (1.5% versus 0% for death and 3.4% versus 2.0% for non-fatal Q-wave MI respectively), the significant differences were driven by the rates of less severe non-Q-wave MIs (i.e. those not leading to Q-wave changes) (Neumann, 2002).

Clearly, a larger randomised trial with adequate power to detect differences in the rates of death or Q-wave MIs would resolve whether very urgent revascularisation is needed or whether a 'cool-down' period of medical

management may be more effective and also allow assessment of whether any benefit is seen more generally across a variety of centres. Until such a trial has been performed the evidence that very urgent invasive therapy (i.e. within 24 hours) is needed, except where clearly indicated on clinical grounds, is inconclusive. Based on the results available to date, there is no reason to conclude that very rapid invasive therapy will provide additional clinical benefit to patients. If further trials demonstrate that early invasive therapy does provide additional clinical benefits, then the benefits of an early troponin test will increase.

4.2.3.3.4.6 Summary of troponin and risk assessment for therapy selection

Results from both the FRISC II and TACTICS TIMI 18 studies suggest that the relative benefit of early invasive therapy within 72 hours is greatest in high-risk patients as defined either by the TIMI score (Antman *et al.*, 2000) or by a combination of ST segment depression and elevated troponin. Of course, even if *relative* benefit were unchanged, high-risk patients would in any case experience greater *absolute* benefit.

The results of individual trials and meta-analyses suggest that glycoprotein IIb/IIIa inhibition, in conjunction with PCI, is effective in high-risk patients. There is less evidence that glycoprotein IIb/IIIa inhibition is effective in medically managed patients with ACS, in particular in those with elevated troponin. Abciximab, in particular, has been shown to be ineffective in medically managed patients, even in the subset of troponin-positive patients (Simoons & GUSTO IV ACS Investigators, 2001). Results from an analysis of the impact of TIMI scores in PRISM-PLUS (Morrow *et al.*, 2002) suggested that any benefit of tirofiban and heparin over heparin alone is confined to patients with TIMI score of four or greater, although it is not clear from this report what proportion of the patients with high TIMI scores underwent early surgical intervention.

Similarly, although two reports suggested that the benefit of LMWH is greater in patients with elevated troponin than those without, in both cases the conclusions were derived from retrospective exploratory analyses of subsets of the original trial population and must therefore be regarded as tentative and requiring confirmation.

In addition to the use of troponin tests, ECG results and other risk factors in isolation or in pairwise combination, a number of authors have examined the prognostic value of combinations of risk factors (Antman *et al.*, 2000; Granger *et al.*, 2003) (Dr B Lindahl, personal communication, 2003). The scores differ in intention and construction. In particular, Granger *et al.* (2003) based their score on an unselected registry of patients with ACS with or without ST segment elevation, and suggested that their score may be applicable across the full range of clinical practice. However, all scores suggest that risk stratification should be based on a combination of biochemical markers, ECG changes, age, evidence of previous MI or ischaemic heart disease (IHD) and major risk factors such as diabetes and renal impairment.

As noted in Section 4.2.3.3.4.4, the TIMI score has been shown to be effective in selecting high-risk patients for early invasive therapy within 72 hours. Patients with higher TIMI scores also experience significantly more benefit (decreased OR) from LMWH and glycoprotein IIb/IIIa inhibitors than patients with lower TIMI scores. Although the score based on the Global Registry of Acute Coronary Event (GRACE) data (Granger *et al.*, 2003) has not yet been shown to be effective for this purpose, it is plausible that this score will be similarly effective for selecting patients for early invasive therapy and may be preferred because of its wider applicability.

The evidence suggests that appropriate risk stratification allows expensive and potentially hazardous surgical interventions, glycoprotein IIb/IIIa inhibitors and LMWH to be directed to those patients most at risk and is therefore effective and important. However, the current evidence base for troponin testing *alone* in selecting patients for surgical intervention or medical therapies is weaker than that for troponin in combination with other risk factors. Specifically, the evidence that troponin alone in selecting patients for surgical intervention or medical therapies is derived from largely retrospective subgroup analyses of clinical trials, frequently performed on subsets of the original trial population.

It should be noted that in both TIMI and GRACE scores, the term 'biochemical marker' refers to one of CK, CK-MB or troponin rather than specifically to troponin. Since troponin is both more specific and more sensitive than CK and CK-MB, it is plausible that the use of troponin results rather than a generic biochemical marker might result in a more powerfully predictive model. However, this remains to be proven.

4.2.3.3.5 Other aspects of troponin testing

4.2.3.3.5.1 Selection of cut-off levels for troponin testing

Recommendations from the International Federation of Clinical Chemistry (IFCC) (Panteghini *et al.*, 1999a) suggest that a single cut-off for troponin should be established at the 99th percentile of the distribution in normal volunteers (i.e. blood donors or non-cardiac patients) or at the lowest value where the CV is ≤10%. For all currently available assays, this point is higher than the 99th percentile of the normal population and in most cases, this is considerably so. The recommendation is also at variance with the common practice of defining a 'functional sensitivity' as the point at which the CV is 20% (Tate *et al.*, 2002; Spencer, 2003).

However, there is evidence for both troponin I (Morrow *et al.*, 2001; Venge *et al.*, 2002) and troponin T (Cannon *et al.*, 2001a; Lindahl *et al.*, 2001) that in patients with clinically diagnosed ACS, any rise in troponin including those below the 10% CV point of current assays is associated with an increased risk of adverse cardiac outcomes.

Since the evidence presented in this chapter indicates that troponin levels should be interpreted in conjunction with other cardiac risk markers, the

possible false-positive results which may occur due to assay variability are likely to be of less concern than genuine troponin rises missed by adopting the much higher 10% CV point as the cut-off.

If raised troponin is used alone to diagnose AMI, there may, as argued by Collinson *et al.* (2003), be a case for using a higher cut-off since the personal and economic costs of false-positive diagnoses are considerable. A complete assessment of this case requires quantification of these costs and their use in a formal decision analysis.

4.2.3.3.5.2 Early testing for troponin

Although cardiac troponins are valuable predictors of mortality and may predict treatment response (Chu *et al.*, 2002), alone they are not sufficient to identify all patients with chest pain at high risk of mortality or other coronary events (Kontos *et al.*, 2000; Lau *et al.*, 2001). Troponins should be interpreted in conjunction with clinical and ECG findings in risk assessment (Bertrand *et al.*, 2002).

Similarly, cardiac troponins are not generally useful for ruling out myocardial damage in the early period of onset of symptoms (i.e. less than six hours). Biochemical considerations (Collinson *et al.*, 2001a) and clinical results (Panteghini *et al.*, 1999b; Fleming & Daly, 2001) suggest that troponins are maximally sensitive for the period of 12 to 72 hours after the onset of symptoms.

However, if troponin testing is used as part of a risk stratification procedure to select patients to receive LMWHs or to undergo early invasive therapy, it may be appropriate to perform an earlier test (i.e. at admission) to aid in the identification of high-risk patients. Such early measurement should, of course, be confined to patients whose risk status is not clearly determined by their clinical presentation and history.

For example, data from the Royal Alexandra Hospital (RAH) Paisley (T Gaffney, Chest Pain Nurse Specialist, RAH, Paisley, personal communication, 2003) showed that approximately 50% of 306 patients who ever showed raised levels of troponin did so at presentation. These patients presented with symptoms suggestive of ACS but with normal or non-diagnostic ECG and no other high-risk clinical or ECG markers. Christenson *et al.* (2001) also reported that troponin testing at presentation to hospital identified a similar proportion of patients with non-ST elevation ACS who had a positive troponin at 12 hours.

4.2.3.3.5.3 Troponin testing in patients with chronic renal failure

Patients with chronic renal failure have an increased risk of developing cardiovascular disease (Joki *et al.*, 1997; Wolfe *et al.*, 1998) as well as a high risk of 'silent' presentation of disease (i.e. no clinical symptoms) (Aronow *et al.*, 2000). There is evidence (Ooi *et al.*, 2001) that a high proportion of patients with chronic renal failure have raised cardiac troponin T (0.05 μg/L) (124 of 244 patients), even with highly specific second generation assays.

Troponin I is also raised but less commonly detected (Wu *et al.*, 1997) – it may be, for example, that troponin I is more readily cleared by renal dialysis (Freda *et al.*, 2002). These results have led to the suggestion that troponin I may be more cardiac specific in patients with chronic renal failure (Martin *et al.*, 1998). However, three relatively small studies in patients with chronic renal failure (Ooi *et al.*, 2001; Stolear *et al.*, 1999; Dierkes *et al.*, 2000) suggested that troponin T levels are predictive of both cardiac and all-cause mortality. If confirmed by larger prospective studies, these results would imply that troponin T might be a valuable test in the assessment of patients with chronic renal failure.

Results from the GUSTO-IV trial (Aviles *et al.,* 2002a) also showed that troponin T rises are predictive of adverse cardiac outcomes in patients with ACS, independent of renal insufficiency.

Because many previous RCTs have excluded patients with renal insufficiency, there is limited evidence that glycoprotein IIb/IIIa inhibitors are effective or safe in such patients. A Januzzi *et al.* study (2002) showed that tirofiban is safe and effective in ACS patients with moderate renal insufficiency (serum creatinine <2.5 mg/dL). Generally, risk stratification using troponin T remains appropriate for ACS patients with chronic renal failure but therapy decisions must be individualised (Freda *et al.*, 2002).

4.2.4 Effectiveness of troponin testing for prognosis and therapy selection results – meta-analyses

A meta-analysis was not undertaken by NHS Quality Improvement Scotland for the effectiveness of troponin in prognosis prediction and therapy selection. This decision was taken because the outcome of such a meta-analysis would not inform this section or be used in the economic modelling.

4.2.5 Effectiveness of troponin testing for prognosis and therapy selection – conclusions

- Cardiac troponins have greater cardiac specificity and sensitivity for the detection of myocardial injury than CK or CK-MB but CK remains useful for detecting early re-infarction (i.e. within 96 hours of original infarct).
- Troponin levels are maximally sensitive 12–72 hours after the onset of symptoms. Therefore troponin testing at or shortly after admission is not able to rule out myocardial damage unless this is 12 hours after symptoms started.
- There is insufficient evidence to demonstrate differences in the effectiveness of troponin I and T for risk stratifying patients with ACS, although the substantial variability between current troponin I assays complicates comparisons between studies.
- Troponin testing is complementary to, and should not replace, clinical and ECG-based risk markers.
- Raised cardiac troponin levels are predictive of adverse cardiac outcomes in the short and long term in patients with non-ST elevation ACS.

- There is evidence that patients with non-ST elevation ACS who are at higher risk of adverse cardiac outcomes, as predicted by the TIMI score, appear to derive greater benefit from early invasive therapy, glycoprotein IIb/IIIa inhibitors and LMWH than patients at lower risk. The evidence that individual components of the scoring system, particularly troponin alone, can be used to select patients for therapy is less conclusive.
- Troponin is predictive of short- and long-term risk of adverse cardiac outcomes in patients with ST elevation ACS.
- Raised cardiac troponin levels on admission are predictive of an increased risk of mortality in patients with STEMI.
- Troponin testing should form part of routine risk assessment in patients who have received treatment for MI to confirm diagnosis.
- Raised troponin T and I appear to be predictive of mortality in patients with chronic renal failure, although raised troponin T is more likely to be detected in these patients. The significance of raised troponin T in these patients should be confirmed by further prospective studies. Both troponin T and I can be used to risk stratify patients with renal insufficiency and clinically diagnosed non-ST elevation ACS.

4.3 Point-of-care testing

4.3.1 Introduction

The ESC guidelines recommend using point-of-care troponin testing unless a central laboratory is able to achieve a turnaround time of less than one hour (Bertrand *et al.*, 2002) (although this particular time period was based on consensus opinion of experts (Wu *et al.*, 1999)). This recommendation appears to be based on the possible importance of short turnaround time in two areas. Firstly, short turnaround times may allow early discharge of patients who appear to be at low short-term risk of AMI or mortality and secondly, they may allow therapy to begin as early as possible in patients whose risk status is questionable until confirmed by a troponin result.

Unless appropriate early discharge or risk reduction from appropriate early therapy (which may include reperfusion therapy) is apparent and actually achievable, the case for the use of point-of-care troponin testing becomes less convincing. Section 4.3.3.3.1 therefore presents the evidence that such benefits may accrue. Section 4.3.3.3.2 outlines other reasons for using point-of-care testing.

Although point-of-care testing may lead to valuable decreases in both the mean turnaround time and the variability of turnaround time, it is important to ensure that these reductions are not obtained at the expense of reduced accuracy or usability of the analytical results (Collinson, 1999). Section 4.3.3.3.3 summarises the general criteria used for evaluating troponin point-of-care testing analysers.

Two types of point-of-care assays are available for troponin (see Section 3.5.7). The first are qualitative test strips which simply provide a ‘positive’ or

'negative' reading. The second are quantitative analysers which provide a numerical value and are similar to the central laboratory machines (but with lower throughput and possibly restricted ranges). Section 4.3.3.3.4 outlines the point-of-care analysers available and summarises the evidence on accuracy, variability and comparison with laboratory-based analysers from published literature and the data available on clinical outcomes, in particular on length of stay and risk stratification. Section 4.3.3.3.5 describes data from external quality assurance (EQA) schemes such as the United Kingdom National External Quality Assurance Scheme-Cardiac Markers (UKNEQAS-Cardiac Markers, formerly the Scottish External Quality Assurance Scheme-Cardiac Troponin [SEQAS-CT]) and the Welsh External Quality Assurance Scheme (WEQAS). Finally, Section 4.3.4 describes the meta-analyses undertaken to provide inputs for the economic evaluation for this HTA.

It is important to note that, in general, the claims made by manufacturers for point-of-care troponin tests relate to their usefulness in diagnosing AMI but the Stratus® CS has a recommendation from the Food and Drug Administration (FDA) for risk stratification. Troponin testing is most valuable in risk stratification (Bertrand *et al.*, 2002), and the review presented here will concentrate on this use.

4.3.2 Methodology

4.3.2.1 Evidence sources

4.3.2.1.1 Literature search

Section 4.2.2.1.1 describes general information about the literature searching carried out for the Clinical Effectiveness Chapter of this report.

A second systematic search was undertaken in October 2002 to retrieve studies covering the use of point-of-care testing for troponins. The search strategy ensured that all information relating to equipment currently in use in Scotland would be captured. Additional small scale, internet searches were also carried out to retrieve additional background data on specific pieces of equipment.

The strategy used to search the MEDLINE database is given in Appendix 8. This was modified appropriately to search the other databases also listed in Appendix 8. No time or language restrictions were applied to any of the searches. A flow chart showing the number of studies identified and then selected for inclusion is contained in Appendix 8.

4.3.2.2 Exclusion criteria

The following exclusion criteria were applied:

- descriptive review papers
- studies in populations not directly relevant to Scotland

- studies in patients other than ACS patients (such as studies of peri-procedural damage)
- studies using discontinued point-of-care technology (Alpha DX™).

4.3.2.3 Methodology for the evaluation of clinical effectiveness

Details of the methods for pooled fixed-effects meta-analysis for Section 4.3.4.1 are described in Appendix 10.

4.3.3 Point-of-care testing results – critical appraisal of literature

4.3.3.1 Previous HTAs

No published HTAs relating to point-of-care troponin testing have been found.

4.3.3.2 Systematic reviews and meta-analyses

There are no systematic reviews or meta-analyses currently available on point-of-care troponin testing.

4.3.3.3 Other studies or reviews

4.3.3.3.1 Evidence for use of point-of-care testing for early discharge and early therapy selection

Early discharge

Collinson (1999) reported an RCT of point-of-care testing in a CCU comparing point-of-care testing for troponin and CK-MB with laboratory-based testing. In this trial, the total in-hospital length of stay was reduced from 209 hours (central laboratory) to 150 hours (point-of-care testing) ($p<0.05$, one of three primary variables examined in the study), although the author emphasised that this was largely achievable because of a very clear data-driven protocol for discharge and further treatment.

Other studies have shown similar reductions in length of stay after implementing point-of-care testing, although generally these studies have used CK (Collinson *et al.*, 1993), CK-MB (Gibler *et al.*, 2000; Hedges, 1995) or a combination of CK-MB, myoglobin and troponin (Newby *et al.*, 2000b; Ng *et al.*, 2001). Although these results are important, it is not clear that the benefit of reduced length of stay obtained in these studies could also be realised when troponin is used alone since the time to maximal sensitivity of troponin testing is longer than that for myoglobin or delta-CK-MB. Furthermore, studies (Zarich *et al.*, 2001; Anderson *et al.*, 1998) have shown that the use of laboratory-based troponin testing can reduce length of stay by comparison with assessment regimens based on measurement of CK-MB over a three-day period. However, no studies have compared the use of point-of-care testing with central laboratory testing for decision rules based on cardiac troponin as a single marker.

In summary, there is no published evidence that the introduction of point-of-care troponin testing alone is associated with reduced overall length of stay when compared with laboratory-based troponin testing. However, there is one RCT (Collinson, 1999) in which the group randomised to point-of-care testing benefited from a reduced length of stay when troponin was measured 12 hours post presentation in combination with CK-MB.

Early therapy selection

As discussed in Section 4.2.3.3.4, there is evidence that early medical therapy such as glycoprotein IIb/IIIa inhibitors is likely to be effective in high-risk patients with ACS and that troponin test results, in combination with other clinical factors, are effective in identifying such patients (Antman *et al.*, 2000; Morrow *et al.*, 2002). There is therefore a clear role for troponin testing in therapy selection for ACS patients, which may determine whether point-of-care testing is in fact needed. For example, although minor reductions in turnaround time may be of little importance, the unavailability of central laboratory testing results outside office hours may be of major concern to clinicians who have to manage patients in the absence of troponin results. There is some evidence (Dr Garg, Cardiologist, Dr Gray's Hospital, Elgin, personal communication, 2003) that in these circumstances, clinicians will treat all patients as high risk until the marker results become available.

For point-of-care testing to be clinically effective, either as a replacement for or in addition to central laboratory testing in this situation, the following two conditions must be met. Firstly, there must be evidence that treatment delay is associated with poorer clinical outcomes. Evidence for this possibility is outlined in Section 4.2.3.3.4.5. Although some evidence (Neumann, 2003) for the claim exists, there is as yet insufficient evidence to make a definitive conclusion that very early invasive therapy is generally effective. In some patients, urgent revascularisation is required on clinical grounds, though it is unlikely that such a decision would be influenced by troponin measurements. Secondly, the necessary decision making and treatment systems must be in place to benefit from timely access to troponin results without needing to wait, for example, until the next consultant ward round.

4.3.3.3.2 Other arguments for point-of-care testing

Both Stubbs & Collinson (2001) and Cummings (2002) argue that patient management can be carried out more effectively if the timing of test results is consistent and predictable, regardless of the day of week and time of day. Certainly authors working in other applications of point-of-care testing technology support this view (Hull *et al.*, 1997; Despotis *et al.*, 1995).

Finally, Eggers *et al.* (2003) argue that a clinician would not expect to wait longer than 30 minutes for an ECG result. Therefore a similar time frame should be anticipated for a key biochemical result.

4.3.3.3.3 Criteria for evaluation of point-of-care testing assays

Collinson *et al.* (2002) suggested that for point-of-care testing to be effective, it must be simple to use, rapid, provide documented results for quality assurance purposes and have similar sensitivity and precision to laboratory analysers. They also emphasised that for troponin I, it was especially important that point-of-care testing and central laboratory testing delivered troponin measurements with equivalent cut-off values for detection of damage. For example, Apple *et al.* (2002c) showed that if the lowest troponin concentration corresponding to a 10% CV was used as a cut-off, the concentrations ranged from 0.06 μg/L for the Tosoh AIA, Stratus® CS and Access® AccuTnI to 0.8 μg/L for the AxSYM®. Additionally, since a major advantage of cardiac troponins is their value in risk stratification, it is desirable that evidence showing that point-of-care testing analysers are able to fulfil this role exists. The published evidence on this point is summarised in Section 4.3.3.3.4.

4.3.3.3.4 Point-of-care testing assays

4.3.3.3.4.1 Qualitative readers

Two qualitative point-of-care readers are available:

- TROPT®, a troponin T reader manufactured by Roche
- Cardiac STATus™, a troponin I reader manufactured by Spectral Diagnostics.

4.3.3.3.4.1.1 Accuracy results of qualitative readers

TROPT® (Roche)

The TROPT® (Roche) provides a qualitative measure of troponin T using the GLORIA technology (Collinson *et al.*, 2001b). Three generations of this device have been produced. The initial version marketed in 1994 had a reliable detection limit of 0.3 μg/L. A second version was marketed more widely as TROPT® with enhanced sensitivity (0.2 μg/L) in 1995 but was superseded in 1996 by a third generation system, TROPT *Sensitive*®. This version uses the same antibodies as the current laboratory-based troponin T assays and has a claimed detection limit of 0.05 μg/L with 100% sensitivity to detect a level of 0.1 μg/L (Muller-Bardorff *et al.*, 1999). Six reports assessing the accuracy of TROPT *Sensitive*® by comparison with the laboratory-based test are presented in Table A8 (Appendix 9).

The overall false-positive and false-negative rates for the condition 'troponin T (ELISA) ≥0.1 μg/L' were calculated from these reports as 5% and 4% respectively (see Section 4.3.4.1.1). It should be noted however that this probably represents 'best case' accuracy since the test strips were generally read by laboratory technicians, laboratory clinicians or 'trained readers' rather than being read as part of the daily routine by nurses or junior doctors. In a study using TROPT® rather than TROPT *Sensitive*®, van Domburg *et al.* (2000a)

noted that lighting conditions, operator experience and operator fatigue may all be important sources of variation in reading the test strips. This is particularly important for troponin levels close to the decision limit, as strips exposed to 'just positive' troponin levels will produce very faint coloured lines.

No data on turnaround time were presented in any of these studies but since the development time required for TROPT *Sensitive*® is 15 minutes (Hirschl *et al.*, 1996), it is reasonable to assume that the total turnaround time will be considerably less than one hour.

Cardiac STATus™ (Spectral Diagnostics)

The Cardiac STATus™ is a similar device to the TROPT® but it measures troponin I rather than troponin T. A comparison with a quantitative analyser constructed using the same antibodies as the Cardiac STATus™ suggested that the cut-off was 0.14 μg/L and gave 98.9% concordance at this level (Heeschen *et al.*, 1998). The authors also noted that there was considerable between-reader variability in reading strips exposed to troponin I levels between 0.06 and 0.14 μg/L and that this was influenced by the observer's experience as well as environmental conditions such as light levels.

Five studies assessing concordance of the Cardiac STATus™ with quantitative analysers are shown in Table A9 (Appendix 9). The interpretation of these results is complicated by the substantial variation in troponin I readings between quantitative analysers (Collinson *et al.*, 2001a; Christenson, 2001). Hohnadel *et al.* (2002) reported that the Cardiac STATus™ was not adopted by their institution because of the false-negative rate (7 out of 16 patients), which they regarded as unacceptably high.

In the RCT reported by Stubbs & Collinson (2001), the median turnaround time for point-of-care testing using both the Cardiac STATus™ and TROPT® was 20 minutes (width of the interquartile range [IQR] = 2) compared with 79 minutes (width of the IQR = 57.5) for central laboratory testing.

4.3.3.3.4.1.2 Use of qualitative point-of-care testing readers for risk stratification

TROPT *Sensitive*® and TROPT® have been used successfully to stratify patients for risk of adverse cardiac outcomes at 30 days or longer in some studies. The studies reported in Table A10 (Appendix 9) in ACS patients have used TROPT® (cut-off 0.2 μg/L) or TROPT *Sensitive*® (cut-off 0.1 μg/L). Additionally, the GUSTO III study of 12 666 patients with STEMI showed that the risk of mortality in patients with a positive TROPT® at entry was 15.7% compared with 6.2% in patients with a negative test (Ohman *et al.*, 1999).

No papers were found which reported the use of Cardiac STATus™ for risk stratification.

4.3.3.3.4.1.3 Drawbacks of qualitative point-of-care testing

Despite the apparent accuracy and predictive ability of TROPT *Sensitive*®, qualitative point-of-care testing readers have several disadvantages which

make them less likely to be effective compared with quantitative analysers. These are illustrated by:

- evidence of variability in the reading of qualitative point-of-care testing readers, with decisions close to the cut-off points potentially affected by lighting, operator experience and operator fatigue
- data from the GUSTO IV-ACS study (James *et al.*, 2001b), reproduced in Table A11 (Appendix 9), showing that a negative troponin test strip reading (95% of results were troponin I test strips, the remainder were troponin T; a troponin T laboratory analyser was used to provide the quantitative results) is not a reliable indicator of good short-term prognosis
- evidence from two studies comparing troponin I assay systems (Morrow *et al.*, 2000b; Venge *et al.*, 2002) that more sensitive assays identify larger groups of at-risk patients which suggests that the simple application of one universal cut-off point may not be appropriate.

Since quantitative analysers overcome these limitations, they may be more effective. These analysers are discussed and literature describing their performance summarised in Section 4.3.3.3.4.2.

4.3.3.3.4.2 Quantitative analysers

4.3.3.3.4.2.1 Accuracy results of quantitative analysers

The studies summarised in this section address one or more of the following issues:

- the precision of the analyser, as measured by the CV at one or more troponin concentrations. The ESC/ACC guidelines recommend that, if possible, the CV should be no more than 10% at the 99th percentile of the normal population troponin distribution. The guidelines also recommend that the 'functional sensitivity' point at which the CV is <10% be used as a cut-off point.
- the accuracy of the analyser relative to presumed 'gold standard' laboratory analysers, as measured by regression relationships between the numerical results from both analysers
- the accuracy of the analyser, as measured by concordance between a point-of-care testing analyser and a laboratory analyser when the data are categorised on the basis of one or more cut-off points.

Again, the interpretation of comparisons between laboratory and point-of-care testing analysers is complicated for troponin I because of the lack of standardisation between manufacturers (Christenson, 2001; Collinson *et al.*, 2001a).

TROPT *Quantitative*® (Roche)

The TROPT *Quantitative*® analyser is a rapid assay for quantitative point-of-care testing of troponin T. It consists of a charge-coupled device camera that

records the reflectance from a test strip. This test strip is essentially identical to the TROPT *Sensitive*®. The analyser has a quantitative measurement range from 0.1 to 2.0 μg/L. Values less than 0.05 μg/L are shown as 'negative', those between 0.05 and 0.1 μg/L as 'low' and those greater than 2 μg/L as 'high' (Collinson *et al.*, 2001b).

Table A12 (Appendix 9) shows five published studies comparing TROPT *Quantitative*® with laboratory-based ELISA systems. Table A13 (Appendix 9) shows the concordance between the Elecsys® and the TROPT *Quantitative*® using data from Collinson *et al.* (2001b). Additionally, Table A14 (Appendix 9) shows the concordance between TROPT *Quantitative*® results and Elecsys® 2010 results obtained from 306 patients with chest pain studied over a three-month period in early 2001 at Paisley RAH. The point-of-care testing analyser was read by a trained cardiac pain nurse in the emergency department, and the point-of-care testing results were compared with laboratory results for these patients (S Russell, Principal Biochemist, RAH, Paisley, personal communication, 2002). The results from these two studies suggest that the false-positive and false-negative rates obtained using the TROPT *Quantitative*® are very similar to those obtained from the qualitative TROPT *Sensitive*® (see Section 4.3.4.1.2).

Agewall (2003) studied 187 patients presenting with chest pain whose 12-hour troponin T measurement was negative (<0.05 μg/L) by TROPT *Quantitative*® and showed that 15 (8%) of them had 12-hour troponin T levels between 0.05 and 0.16 μg/L as measured by Elecsys® 2010.

Stratus® CS (Dade Behring)

The Stratus® CS is a rapid desktop scale assay system designed to provide a similar performance to Dade Behring's laboratory-based analysers for a restricted range of analytes. It is intended for use either in a satellite short turnaround time laboratory or point-of-care testing environment, and the turnaround time is 15 minutes. Table A15 (Appendix 9) shows 10 published studies assessing the accuracy and variability of this analyser.

In summary, the available data appear to show that the Stratus® CS comes close to meeting the ESC guidelines, with CV values between 10 and 20%, at or close to the 99th percentile point of the normal population. Although there is apparently considerable discrepancy between troponin I values measured by the Stratus® CS and those measured by laboratory analysers, this is likely to be a reflection of the broader difficulties of comparability between troponin I assays (Collinson *et al.*, 2001a). Kim *et al.* (2002) reported that the most recent revision of the Dimension® RxL troponin I assay shows very close agreement with the Stratus® CS assay, with slope values ranging from 0.96 to 1.05 and intercept from 0.02 to 0.24 μg/L across five test sites.

Heeschen *et al.* (1999a) and Ferguson *et al.* (2002) illustrated the difference in risk stratification using the Stratus® CS as compared with the Bayer Immuno 1®. Results from these studies are shown in Table A16 (Appendix 9). All of the

authors reported that the Stratus® CS is a sensitive and rapid assay, and that it appears to be superior to other troponin I comparators for risk stratification.

Biosite Triage®

The Biosite Triage® analyser uses disposable test strips which are optically read to provide quantitative measurements of troponin I, myoglobin and CK-MB. The three studies describing the accuracy of this analyser are summarised in Table A17 (Appendix 9). These studies suggest that the Biosite Triage® is adequately accurate for the diagnosis of AMI but no evidence has been published to show that its precision and low-level sensitivity meet ESC guidelines, and no evidence has been reported of its use in risk stratification. According to the manufacturer's literature, the 99th percentile of a normal population lies at or below 0.l9 μg/L, whereas the 10% CV point is at 0.5 μg/L (Apple *et al.*, 2002c).

Alpha DX™

A further quantitative point-of-care testing analyser, the Sigma Diagnostics/First Medical Alpha DX™, has recently been discontinued and is not considered further in this assessment.

4.3.3.3.4.2.2 Summary of literature on quantitative analysers

Troponin T

Only one quantitative point-of-care testing analyser is available for testing troponin T, the TROPT *Quantitative*®. Although the analyser has a higher than desirable variation at low levels of troponin T (CV at 0.1 μg/L ranges from 10 to 20%; this compares with CV estimates of 10% or below for the laboratory-based Elecsys® system), it shows reasonable agreement with the results produced by laboratory-based analysers (both false-positive and false-negative rates below 5%). It also has a short turnaround time of 20 minutes.

However, the lower detection limit (0.05 μg/L), recommended by manufacturers and used in literature reviewed here, is above the cut-off of 0.01 μg/L that is recommended for identifying patients with ACS who are at low risk of subsequent mortality (James *et al.*, 2003). James *et al.* recommended a higher cut-off level of 0.03 to 0.05 μg/L for the diagnosis of MI. A cut-off of 0.05 μg/L is also suggested by Collinson *et al.* (2003).

The James *et al.* analysis was based on patients diagnosed with unstable coronary artery disease (defined as either having a raised troponin T result or diagnostic ECG changes) who are thus at higher risk than undiagnosed patients in an unselected population. The clinical significance of using a low detection level in an unselected group of patients with chest pain is thus uncertain.

Troponin I

Two quantitative analysers, potentially suitable for point-of-care testing use, are available for testing troponin I. These include:

- the Biosite Triage®, an analyser similar to TROPT *Quantitative*®
- the Stratus® CS, a larger point-of-care instrument designed to give laboratory-equivalent results outside a laboratory environment.

Both systems can measure levels of myoglobin and CK-MB, in addition to troponin I.

The Biosite Triage® has been used effectively in accelerated protocols (90 minutes) to diagnose AMI (Mccord *et al.*, 2000) by using a combination of the three markers. However, there is no published evidence for the use of troponin I measured by Biosite Triage® in risk stratification, nor any published precision data to demonstrate that it meets the ACC/ESC criteria (the reported CV is >20% at 0.26 μg/L).

The Stratus® CS has a reported cut-off (upper 99% point of the distribution in normal people) of between 0.04 (Christenson *et al.*, 2002) and 0.1 μg/L (Heeschen *et al.*, 1999a). The manufacturer recommends that a cut-off point of 0.1 μg/L should be used for the detection of myocardial damage (Dade Behring product information sheet for cardiac troponin I tests).

The reported CV in the region of 0.1 μg/L ranges from 10% at 0.06 μg/L (Christenson *et al.*, 2002) to 19% at 0.07 μg/L (Altinier *et al.*, 1999). These results suggest that the Stratus® CS comes close to meeting the ESC guidelines. It has also been used to risk stratify patients in one published study (Heeschen *et al.*, 1999a) and one study in press (Eggers *et al.*, 2003). It has been shown to be more sensitive than the Bayer Immuno 1® assay (Ferguson *et al.*, 2002) and the Abbott AxSYM® (Chapelle *et al.*, 2000) for the detection of minor myocardial damage and to show close agreement with the modified Dimension® RxL assay (Kim *et al.*, 2002).

Unfortunately, no published studies have performed 'head-to-head' comparisons of the effectiveness of various point-of-care testing analysers on presentation for risk stratification.

4.3.3.3.5 Data from EQA schemes

There are two UK-based EQA schemes – UKNEQAS-Cardiac Markers and WEQAS. Both schemes distribute three samples per month of human serum spiked with troponin T, troponin I and CK-MB (also myoglobin for UKNEQAS-Cardiac Markers). The samples are distributed lyophilised by UKNEQAS-Cardiac Markers and frozen by WEQAS.

Between-laboratory CV estimates are produced by both schemes for a variety of analysers. The results from UKNEQAS-Cardiac Markers are shown in Table A18 (Appendix 9).

Note in particular that none of the analysers in Table A18 (Appendix 9) meet the suggested criterion of a 10% CV at the 99th percentile of the normal population. For example, the 99th percentile figure provided by the manufacturer for the Bayer Centaur® is 0.1 μg/L (Apple *et al.*, 2002c), at which level the CV exceeds 15%. The precision within a single laboratory should, of course, be somewhat lower than the between-laboratory precisions achieved here.

The WEQAS results for troponin T suggest a similar precision for laboratory-based Roche systems with 12% CV at 0.12 μg/L and 10% CV at 0.25 μg/L but a somewhat lower precision for the TROPT *Quantitative*® with 22% CV at 0.15 μg/L and 15% CV at 0.5 μg/L. WEQAS do not present precision data for individual troponin I systems, but produce a combined CV after (unspecified) method correction of >30% at 2 μg/L.

4.3.4 Point-of-care testing results – meta-analyses

Unfortunately for the majority of variables considered here, the studies available are sufficiently dissimilar that formal meta-analyses are impractical. For example, the range of CV measurement points for the Stratus® CS is shown in Table 4-2.

Table 4-2 Concentrations at which CV is measured for Stratus® CS

Study	Level (μg/L)	Number of replicates
Altinier *et al.* (1999)	0.07	Unspecified
Altinier *et al.* (2001)	0.63	12
Beneteau-Burnat *et al.* (2001b)	0.71	20
Heeschen *et al.* (1999a)	0.1	60
Moore *et al.* (1998)	0.6	20

The key variables for which any combination of study data may be feasible are the misclassification rates of point-of-care testing analysers relative to central laboratory testing equipment and estimated AMI, death and combined event rates for point-of-care testing positive and negative patients during follow up.

The first of these variables is complicated for troponin I analysers by the substantial variability between assays and the corresponding difficulty of attempting to define a 'gold standard' troponin I analyser. Since the Stratus® CS comes as near to meeting the ESC definition as any currently available analyser (Ferguson *et al.*, 2002), it may not be reasonable to speak of 'misclassification rates' for this analyser.

4.3.4.1 Misclassification rates

4.3.4.1.1 TROPT Sensitive®

Five studies (Christenson *et al.,* 1997a; Azzazy & Christenson, 2002; deFilippi & Parmar, 1997; Hirschel *et al.,* 2000) (the last reporting two substudies, one using laboratory technicians, the other cardiac nurses) reported false-negative and false-positive rates for the TROPT *Sensitive®* relative to laboratory-based analysers. For these data, pooled false-negative and false-positive rates were 4% (95% CI 0.04, 0.06) and 5% (95% CI 0.04, 0.06) respectively, using methods described in Appendix 10.

4.3.4.1.2 TROPT Quantitative®

Two studies reported false-negative and false-positive rates for this analyser relative to the Elecsys® 2010. These are shown in Tables A13 and A14 (Appendix 9). They have been dichotomised using a cut-off of 0.1 μg/L for this analysis. For these data, pooled false-negative and false-positive rates were 3% (95% CI 0.01, 0.05) and 4% (95% CI 0.02, 0.07) respectively.

4.3.4.1.3 Cardiac STATus™

Discordance rates for studies of this reader were not pooled because of differences between comparator analysers.

4.3.4.1.4 Biosite Triage®

No studies reported discordance rates.

4.3.4.2 Event rates on follow up

4.3.4.2.1 TROPT Sensitive®

Two studies reported follow-up event rates. deFilippi & Parmar (1997) reported event rates at a median follow up of 361 days, whereas van Domburg *et al.* (2000b) reported event rates at 30 days. The two studies therefore could not be pooled.

4.3.4.2.2 TROPT Quantitative®

No studies reported follow-up event rates.

4.3.4.2.3 Cardiac STATus™

No studies reported follow-up event rates.

4.3.4.2.4 Biosite Triage®

No studies reported follow-up event rates.

4.3.4.2.5 Stratus® CS

One published study reported 30-day event rates. Heeschen *et al.* (1999a) reported rates among patients with diagnosed UA or NSTEMI.

4.3.5 Point-of-care testing – conclusions

No compelling evidence has been found to suggest that central laboratory testing for troponin must be replaced by point-of-care testing in general. However, this conclusion may be affected if further well-designed studies confirm the observations of Bhatt & Topol (2002), Califf *et al.* (1998) and Neumann (2003) suggesting that treatment of patients with non-ST elevation ACS should begin as early as possible on the grounds of clinical effectiveness.

The issue of whether a central laboratory service which is only available during a restricted period, such as between 09:00 and 17:00 hours Monday to Friday, should be supplemented by an 'out-of-hours' point-of-care testing service will be examined in the Economic Evaluation Chapter of this HTA (see Chapter 5). Any such combined service (i.e. point of care and central laboratory) must adopt the same cut-off values to avoid clinical confusion.

The qualitative point-of-care testing readers are unlikely to have sufficient clinical effectiveness, for the reasons described in Section 4.3.3.3.4.1. Specifically, they rely on experienced readers to avoid variability, particularly near the detection limit and they remove the possibility of adopting a different, possibly more appropriate, threshold than that chosen by the manufacturer (James *et al.*, 2001b; Azzazy & Christenson, 2002).

Among the quantitative point-of-care analysers, only the TROPT *Quantitative*® (troponin T) and the Stratus® CS (troponin I) appear able to meet the important criterion of preserving comparability with central laboratory analysers (but currently this comparability has only been demonstrated for the Dimension® 'X' family of analysers in the latter case) and of acceptable low-end precision. The TROPT *Quantitative*® is not clearly superior to laboratory-based troponin T analysers but the Stratus® CS, on the other hand, is superior to many currently available troponin I laboratory analysers and appears comparable with the remainder. Other point-of-care analysers may be useful in selecting high-risk patients for early therapy but since negative results from these analysers would need to be confirmed by more sensitive laboratory-based tests, their use would be unlikely to result in major cost reductions from early discharge.

Although a variety of point-of-care testing analysers are available, all analysers are capable of delivering a turnaround time of ≤20 minutes. However, it should be noted that few, if any, of the currently available laboratory troponin assays meet the ESC criterion of 10% CV at the 99% point of the troponin distribution in the normal population (Apple *et al.*, 2002a; Bertrand *et al.*, 2002) and that the relative merits of different approaches to providing a troponin testing service may change as the technology improves.

The TROPT *Quantitative*® has lower precision than the corresponding laboratory-based troponin T systems and has false-positive and false-negative rates relative to those analysers of between 3 and 4%. As such, it would not in its current form be suitable for risk stratification at the low troponin T levels (0.01 μg/L) suggested by, for example James *et al.* (2003), but would be suitable if a cut-off of 0.05 μg/L is used. It is therefore important to supplement the troponin T point-of-care test with a cardiac stress test. The stress test identifies patients who, although classified as low risk by a point-of-care test, may have an elevated risk of adverse cardiac outcomes. A more accurate laboratory analyser may also identify these patients. The results also suggest the most accurate laboratory analysers should be used whenever there is less time pressure.

The Stratus® CS, although providing acceptable or nearly acceptable precision, (Christenson *et al*., 2002; Altinier *et al*., 1999) is different from other point-of-care analysers such as the TROPT *Qualitative*® or devices such as point-of-care glucose testers. It can be interfaced to laboratory or hospital systems.

A paper by Beneteau-Burnat *et al.* (2001a) describing their experience using the Stratus® CS reported a non-trivial rate of technical failures (approximately 5%). However in a poster presented at a recent meeting, a biochemist from the same hospital (Desplanques, 2003) presented a breakdown of these failures and suggested that at least 90% of them were caused by 'misuse' of the analyser. In particular, the majority of failures were caused by use of the analyser by staff who had not been trained in accordance with the appropriate standard operating procedures (SOPs).

Both the Stratus® CS and TROPT *Quantitative*® suffer from the problem that, unlike laboratory analysers, once the machine has been 'committed' there is an unavoidable delay of ≤20 minutes before the next sample can be analysed.

4.3.6 Protocols incorporating point-of-care testing

Troponin point-of-care testing forms a key part of the nurse-led protocol which is in operation at the RAH, Paisley (see Appendix 5). This standardised method of chest pain assessment is used to assess patients with suspected ACS.

Raigmore Hospital, Inverness, also use troponin point-of-care testing in the triage area of their medical receiving unit and as an integral part of their 'possible ischaemic chest pain discharge protocol' (http://www.show.scot.nhs.uk/haht/raigmore/clinical/gpprosp/medical/cardiology/cmg/query.htm). A project report reviewed the use of the protocol in the six-month period following its launch in May 1999, and noted that staff rapidly implemented the new system but that troponin testing was also used frequently outside the protocol. The importance of adherence to the protocol, particularly with respect to performing a repeat troponin test four hours after

a negative result (and at least eight hours after the onset of pain) was highlighted (Exton, 2000).

4.4 Assessment of chest pain methods and settings

4.4.1 Introduction

A variety of methods for assessing chest pain are currently in use in hospitals and other settings throughout the world (see Section 4.3.6 for two examples). These protocols are carried out on patients who have presented to an emergency setting and are assessed in a medical receiving unit. Such units are not specific to patients with chest pain, but are equipped for ongoing monitoring and observation. Specialist chest pain units (sometimes called evaluation or observation units) have been established within several A&E departments in parts of the UK (e.g. Sheffield, Belfast, Edinburgh) and in other countries (e.g. Italy, US). These units have clinically supported beds for patients previously seen in A&E but who require further assessment to confirm whether or not discharge or admission to hospital is appropriate. These units may be available 24 hours a day or for a restricted period.

Chest pain units should not be confused with chest pain clinics. Chest pain clinics have been established in more than 90% of Acute Trusts in England (Department of Health, 2003) and deal with a different patient group. GPs refer patients to a chest pain clinic who have new symptoms of exertional chest pain (i.e. within the previous two to four weeks) but have not been seen at the hospital and who are not thought to have had an AMI (Department of Health, 2000). A chest pain clinic may run, for example between 12:00 and 14:00 hours within a hospital cardiology department. High-risk patients are therefore not referred to chest pain clinics but to A&E or cardiology departments as appropriate.

This section comprises a review of published evidence on different methods for assessing chest pain using troponin in patients with suspected ACS. It focuses on evidence obtained from hospital departments or units in which patients were assessed for admission.

4.4.2 Methodology

4.4.2.1 Evidence sources

4.4.2.1.1 Literature search

Section 4.2.2.1.1 provides general information about the literature searching carried out for the clinical effectiveness aspects of this report.

A search of primary literature identified papers on the prognosis of patients presenting with chest pain who were subject to an initial assessment that included troponin testing. These assessments were carried out in a hospital and settings such as A&E or chest pain units.

The strategy used to search the MEDLINE database is given in Appendix 8. This was modified as appropriate to search the other databases also listed in Appendix 8. No time or language restrictions were applied to any of the searches. A flow chart showing the number of studies identified and then cited is also given in Appendix 8.

4.4.2.2 Exclusion criteria

The following inclusion/exclusion criteria were applied to the citations.

The inclusion criteria included:

- patient group comprising those presenting with chest pain or with symptoms of ACS or AMI to an emergency setting (including A&E and chest pain units)
- studies of any type (e.g. RCT, observational, prognostic)
- studies including details on admission/'rule out MI' protocols or other explicit methods of chest pain assessment
- studies including data on long-term outcomes of patients (at least 30 days), preferably by their troponin and/or ECG status during the admission assessment
- studies which identified or excluded patients with ST segment elevation, but the group should be otherwise unselected.

The exclusion criteria included:

- editorials, commentaries, letters, reviews, abstracts
- studies involving monitoring of patients post surgery or with non-ACS conditions
- studies focusing on sensitivity and specificity or performance of one particular diagnostic test only
- studies where outcome only extended to patients' in-hospital or short-term mortality and other adverse events
- paediatric or selected patient groups e.g. renal disease, during pregnancy
- studies undertaken in a post-admission setting (e.g. hospital ward, CCU).

Relevant outcomes were assumed to be the subsequent rate of adverse cardiac outcomes (e.g. cardiac death or AMI) and any change to patient's length of stay (or hospital admission rate).

4.4.2.3 Methodology for evaluation of clinical effectiveness

The heterogeneity of the studies and varying quality in follow up and presentation of patient outcomes meant that no quantitative data analysis was performed. Therefore, a qualitative review of the selected studies is presented here.

4.4.3 Assessment of chest pain results – critical appraisal of literature

4.4.3.1 Previous HTAs

A primary literature search was carried out for this section, and no HTAs were identified.

4.4.3.2 Systematic reviews and meta-analyses

No systematic reviews or meta-analyses were identified.

4.4.3.3 Other studies or reviews

Two RCTs that met the inclusion criteria are described in Section 4.4.3.3.1 and summarised in Table A19 (Appendix 9). However, controlled studies appear to be rare in this field of medical research. The vast majority of published papers retrieved by this search comprised observational cohort studies which inevitably used a variety of inclusion and exclusion criteria for their patient group (these studies are presented in Table A20 [Appendix 9]). They often did not specify outcomes over a long-term follow-up period or used a follow-up method that was not rigorous, for example checking hospital records for re-admission in the interim period. These factors make it impossible to draw robust conclusions on the relative merits of the selected methods of chest pain assessment.

4.4.3.3.1 Randomised controlled trials

Dagnone *et al.* (2000) declared a lack of improvement in the clinical management of patients or their outcomes when using additional markers (including troponin) in their standard assessment method. Although the proportions of patients for whom length of stay exceeded six hours and who were admitted were reduced, this was not significantly different. Zarich *et al.* (2001) demonstrated a reduced length of stay and lower hospital admission rate by adding troponin to their assessment method. These reductions were significantly different between the standard and troponin protocol groups only in patients with a diagnosis of ACS. Unfortunately, there was a poor follow-up rate (69%) of adverse cardiac outcomes at 30 days in this study.

4.4.3.3.2 Observational/diagnostic cohort studies

Herren *et al.* (2001) reported that their six-hour protocol for chest pain assessment reduced hospital admissions without affecting patient outcomes within the four-week follow up. No deaths or MIs were reported, but one patient was discharged with a false-negative troponin result. Goodacre *et al.* (2002) evaluated a chest pain observation unit in Sheffield. This chest pain assessment protocol allowed 86.3% of patients to be discharged with no clear cost difference in routine care. They noted that an assessment with negative troponin was effective in ruling out short-term adverse cardiac outcomes, but not longer-term morbidity or mortality. The publication of a RCT within this unit is anticipated in the near future.

Numerous papers describing chest pain units outside the UK have been published, although their applicability to the UK setting is not straightforward. The economic incentive to reduce length of stay within one type of health care setting is not likely to be directly relevant to the structure of the NHS. For example, Mutrie noted a clear cost benefit from their improved chest pain assessment method in a Canadian emergency department (Mutrie, 1999). However, few details were provided on patient outcomes or their follow-up methods. Newby *et al.* (2000a) tested serial CK-MB and troponin T in patients within a chest pain unit for risk stratification and found that all patients who would ever become positive for troponin or CK-MB were identified as such by eight hours after presentation. Conti *et al.* (2002) reported that their chest pain assessment unit within the emergency department reduced admission rates, with 60% of low-risk patients discharged within six hours.

Rapid/accelerated protocols for assessing patients with suspected ACS

The duration of chest pain assessment protocols varies greatly and a few 'accelerated' or 'rapid' types have been described. Table A21 (Appendix 9) presents studies in which rapid assessment or multimarker protocols were used. Caragher *et al.* reported a reduction in length of stay by 38% using their 'accelerated' nine-hour protocol for assessing patients with chest pain and an associated cost reduction (Caragher *et al.*, 2000). However, the rate of adverse cardiac outcomes and false negatives or positives was difficult to assess, with scarce detail on the extent of follow up of each patient group. Ng *et al.* (2001) described an assessment protocol that allowed patient discharge (or referral/further investigation) within 90 minutes of presentation. The follow up at 30 days involved a review of patient records to check if the patient had been re-admitted or suffered complications. This follow-up method clearly has the potential to miss adverse cardiac outcomes.

The comparison of a single marker laboratory-based testing strategy with two multimarker strategies carried out by point-of-care testing was described in the multicentre Chest pain Evaluation by Creatine Kinase-MB, Myoglobin and Troponin I (CHECKMATE) study (Newby *et al.*, 2001b). Results were not available for all patients for all markers, but authors reported that a minority of patients (40%), for whom all three markers, was available were positive on more than one of them. The follow up (of 95% of patients) revealed correlations between the status of all three strategies and 30-day MI or death and MI combined. The only strategy for which the serial result correlated with 30-day death rate was the three-marker strategy, however as the study did not separate use of troponin as a single marker, conclusions cannot be drawn on the efficacy of troponin-only assessment.

4.4.4 Assessment of chest pain – conclusions

Conclusions on the relative efficacy of different methods of chest pain assessment in the emergency setting have proved difficult to ascertain from this literature review. Published work comprises a heterogeneous array of

primarily observational cohort studies. These clearly confirm the prognostic ability of troponin testing, but do not provide clear evidence of the relative efficacy of troponin-based assessment methods for possible high-risk ACS patients.

The significance of rapid assessment protocols that allow discharge within six hours remains unclear. These protocols tend to involve multiple marker testing (e.g. serial myoglobin and/or CK-MB) in order to detect muscle damage prior to the rise of troponin. However the poor sensitivity and specificity of these markers for cardiac damage is well established. The ESC guidelines clearly state that in patients with suspected ACS, troponin should be measured on presentation to hospital and at 6–12 hours later (Bertrand *et al.*, 2000). Without better evidence of good outcomes in patients who have undergone rapid protocols for assessment of chest pain, their long-term safety remains unproven.

A recently published survey of A&E departments in the UK reported wide variety in approaches to the assessment of chest pain patients (Goodacre *et al.*, 2003). Of the 175 respondents, 74 indicated that they had formal guidelines for the management of chest pain, 14 of which involved troponin testing (at between 6 and 12 hours). The variability was demonstrated by the range in proportions of chest pain patients admitted to hospital, with 20 A&E departments reporting less than 20% admissions and 24 departments estimating over 80%.

Therefore, further high-quality comparative, preferably randomised, trials comparing different troponin-based chest pain assessment methods using well-defined protocols are required to provide objective data on their relative safety and efficacy. It is vital that patient outcomes in such trials are monitored closely following discharge to ensure that robust conclusions can be drawn. Where effective chest pain assessment methods are identified, clear protocols should be shared. If such chest pain assessment protocols are then implemented, adherence should be strongly encouraged to achieve the benefits identified in trials.

4.5 Assessment of safety in clinical practice

Troponin testing is carried out on blood samples obtained by routine venepuncture. There are no serious safety issues surrounding this procedure. The only safety concern for troponin testing is the misinterpretation of the test results leading to a sub-optimal treatment.

5 Economic evaluation and modelling

Summary

- A review of the literature established that using a single troponin test is cost effective and supports the clinical finding that all patients with symptoms suggestive of ACS should undergo a troponin test. The main benefits noted in the literature were savings from shorter hospital stays and fewer admissions, and avoidance of over-prescribing of drugs in low-risk patients and appropriate and expeditious treatment of high-risk patients.

- This chapter:

    - provides an analysis showing that if the level of misdiagnosis from other tests (primarily an ECG) exceeds 2.2%, the costs incurred testing troponin 12 hours after admission to confirm diagnosis in patients considered to have a diagnosis of STEMI would be fully recovered within one year

    - sets out an analysis showing that if the variable costs of the point-of-care tests are less than £8.40 per test, it would be cost effective to measure troponin on admission and 12 hours later (if the first test is negative) using point-of-care testing compared with a single troponin test measured 12 hours after admission using laboratory testing in patients with symptoms suggestive of ACS but with a normal or non-diagnostic ECG and no high-risk features. Benefits measured are limited to placing high-risk patients in the appropriate ward. Other unquantified benefits for high-risk patients include earlier treatment and earlier clinical certainty with respect to diagnosis and therapy, and hence avoidance of inappropriate therapies and reductions in length of stays. The base case assumed neither LMWH nor clopidogrel would be given until patients are stratified as high risk. If either drug is prescribed to all patients during risk stratification and is ceased on a negative troponin result with a single-test strategy but only prescribed to troponin-positive patients under the two-test strategy, then the cost effectiveness of the two-test strategy would improve.

    - develops an economic model that assumed only accurate point-of-care and laboratory analysers would be used. It concludes that:
        i. troponin test results should be available to inform clinical decision making. Combining continuously available decision making and troponin testing is the most cost-effective approach of the scenarios analysed.
        ii. for hospitals with seven-day clinical decision making, if laboratories cannot provide a service with turnaround times of within two hours, then hospitals would reduce the cost per patient by using point-of-care tests

iii. as laboratory turnaround times or costs rise, point-of-care testing would become increasingly cost effective compared with laboratory testing
iv. the greatest benefits for a hospital where troponin testing is available on a weekday-only basis would be by implementing *any* weekend service provided clinicians are available to act on the test results. Thereafter, further cost savings could arise from moving from a batch run at the weekend to having a full seven-day service.

5.1 Introduction

This chapter first evaluates the cost effectiveness of troponin testing by reviewing available literature (see Section 5.2). Having determined that the use of troponin tests is cost effective, further analyses, specific to the Scottish setting:

- consider the cost consequences of troponin testing at 12 hours after admission in patients considered to have a diagnosis of STEMI using other diagnostic tools such as an ECG reading (see Section 5.3.1)
- consider the cost consequences of a two-test strategy in which troponin is measured on admission and 12 hours later (if the initial test is negative) by point-of-care testing versus a single troponin test measured at 12 hours from admission by laboratory testing in all patients with symptoms suggestive of ACS but in whom there is diagnostic uncertainty (see Section 5.3.2)
- inform decisions on the organisation of an efficient troponin testing service using an economic model to rank different organisational scenarios in terms of their efficiency (see Section 5.4). The economic model compares the cost consequences of using point-of-care testing with laboratory testing, assuming various turnaround times for the laboratory troponin tests.

In principle, an economic evaluation should comprehensively assess the changes in health states and the associated cost changes that arise from the adoption of a technology, ideally adopting a full societal perspective (Health Technology Board for Scotland, 2002a; Drummond & McGuire, 2001). These economic analyses compare costs and outcomes over a very short timeframe, that being the initial assessment period for patients presenting with chest pain at hospital. No material short-run marginal societal costs are judged to occur in this timeframe and therefore the analysis adopts an NHSScotland perspective.

5.2 Review of economic literature

5.2.1 Methodology

5.2.1.1 Evidence sources

Evidence to support this chapter of the HTA has been obtained from a wide variety of sources including a systematic literature search, submissions from manufacturers and other interested parties, and evidence from TSG members.

5.2.1.1.1 Literature search

The literature search was undertaken to identify literature on the cost effectiveness of troponin testing. No relevant data were identified from the literature search for the subsequent economic analyses.

The results of the scoping search, which are detailed in Section 4.2.2.1.1, were taken into account when deciding how to proceed with retrieving information for this part of the assessment. A systematic search was undertaken to identify existing economic evaluations, suitable models, and costs and other inputs for the economic model. The sources searched included the NHS Economic Evaluation Database (NHS EED), the Health Economic Evaluation Database (HEED) and the websites of major economic organisations. Both the available subject headings (e.g. MeSH, EMTREE) and free-text terms were used. Members of the TSG provided assistance in identifying conditions and their synonyms. No language restrictions were applied.

The sources searched and the strategy used to search the MEDLINE database are given in Appendix 11. This strategy was adapted to search the other databases.

Additional studies were identified by scanning the bibliographies of retrieved items, through the use of alert services, by members of the TSG and within the submissions process.

5.2.1.2 Exclusion criteria

The exclusion criteria applied when reviewing the literature search results were:

- review articles not containing data on costs, outcomes or models
- studies not carried out in a population that is broadly relevant to Scotland
- studies where it is not possible to disaggregate results of troponin tests from other biochemical markers.

5.2.2 Results – review of economic literature

Appendix 12 summarises two business cases, one economic evaluation and seven retrospective studies on the introduction of troponin tests. The studies are heterogeneous with different outcome measures and are of variable quality. However, the results are consistent and applicable to the Scottish setting. The studies suggest that the introduction of a single troponin test to assist in the diagnosis of patients with symptoms suggestive of ACS is cost effective, with the main benefits being:

- savings in bed-days from fewer admissions and shorter hospital stays for low-risk patients
- avoidance of misprescribing or over-prescribing of drugs in low-risk patients
- appropriate and expeditious treatment of high-risk patients.

Other benefits noted in the literature include:

- protecting elective surgery by the increased availability of medical beds

- reduced mortality in the community as fewer 'high-risk' patients are discharged inappropriately
- improved identification of patients for revascularisation and thus fewer inappropriate transfers
- potentially lower laboratory costs if troponin tests are limited to one test per episode of pain and replace all other cardiac biochemical markers.

The last two studies summarised in Appendix 12 are an economic evaluation (Collinson, 1999) and a retrospective trial (Mutrie, 1999) on the use of point-of-care troponin tests. These show that the introduction of such tests can be cost effective if clinicians act on the shorter turnaround times offered by the point-of-care tests to reduce admission rates and time to discharge and thus bed-days.

The literature also supports an earlier conclusion from Chapter 4 that troponin tests, in conjunction with clinical and ECG risk markers, are effective in diagnosing and risk stratifying patients with ACS and therefore no other biochemical markers are required for this patient group (except CK for re-infarction).

A further point emerging from the literature is that any appraisal of the use of troponins should look at changes in the cost of a patient episode of care, not just the impact of a change in policy on individual departmental cash budgets.

5.3 Cost-consequence analyses

Two cost-consequence analyses were performed. Section 5.3.1 evaluates the cost consequences of measuring troponin at 12 hours after admission in patients initially diagnosed with STEMI. Section 5.3.2 considers the cost consequences of measuring troponin on admission in addition to a 12 hour test (if the initial test is negative) by point-of-care testing compared with measuring troponin 12 hours after admission by laboratory testing in patients with symptoms suggestive of ACS but in whom there is diagnostic uncertainty. The second analysis is highly dependent on data from one site and thus it may not be generalised to the rest of Scotland. As more sites develop point-of-care testing services, this analysis should be updated.

5.3.1 Cost consequences of measuring troponin 12 hours after admission in patients diagnosed with STEMI

5.3.1.1 Background

The ESC guidelines (Bertrand *et al.*, 2002) explain that patients who have persistent ST segment elevation or new onset left bundle branch block have coronary occlusion. Such patients should receive reperfusion therapy to limit infarct size and prevent infarct extension as soon as possible unless there are contraindications. The ESC guidelines recommend that biochemical tests be

undertaken and note the preferred marker is troponin (I or T) but that clinicians should not wait for the test results to initiate reperfusion therapy.

In patients considered to have a diagnosis of STEMI, the Standards on CHD recommend that eligible patients should be given thrombolysis within 30 minutes of presentation to hospital (Clinical Standards Board for Scotland, 2001a). Therefore, the time of treatment and admission to hospitals are relatively comparable. Although troponin testing 12 hours after treatment may be a biologically meaningful timepoint in this patient subgroup, measuring troponin 12 hours after admission is an appropriate surrogate as it is a timepoint that is reliable and is recorded consistently in patient records, and may facilitate comparisons of troponin results across hospitals.

Wang *et al.* (2003) explain that there are several causes of ST segment elevation other than AMI. Of patients with chest pain and ST segment elevation, 171 of 202 (85%) in one study and 63 of 123 (51%) in a second study had diagnoses other than MI. Some of these conditions can be misdiagnosed as AMI and result in unwarranted thrombolytic therapy or emergency angiography.

The ESC guidelines further recommend that patients diagnosed with AMI receive rehabilitation, counselling on risk factor modification and prophylactic medication.

Currently, there are no Scottish guidelines or Standards on the use of troponin test results to confirm a diagnosis of an AMI. This section considers whether introducing a troponin test in this patient subgroup is cost effective.

5.3.1.2 Methodology and assumptions

The costs of undertaking a troponin test 12 hours after admission in patients considered to have a diagnosis of STEMI were compared with the costs avoided by reducing the incidence of inappropriate diagnoses of AMI. The cost savings assumed in the base case would be from avoiding rehabilitation, counselling on risk stratification modification and prophylactic medication only. Other savings may also be made. For example, the patient could cease receiving LMWH in hospital if a diagnosis of AMI is not confirmed. However, in such an event, the clinicians could refer the patient for further assessment thereby incurring costs so no net saving may result.

The base case assumed that no other costs would arise from misdiagnosing such patients or from prescribing unnecessary drugs. These are conservative assumptions and thus the base case analysis understates the potential benefits.

5.3.1.3 Data inputs

Number of patients with STEMI and incidence rate of misdiagnosis

The base case assumed that 10 000 patients are diagnosed as having had STEMI each year in Scotland (Section 3.1.3). Topol *et al.* (1987) estimated that an ECG has 94.6% accuracy rate in identifying patients with AMI. A second study using data from the Mayday hospital indicated that 3% of patients considered to have had STEMI receive an inappropriate diagnosis of AMI using conventional markers (i.e. ECG, CK, presentation and history) (Canepa-Anson *et al.*, 1998). This value is the lowest estimate of misdiagnosis found in the literature and is used in the base case. Other estimates include a misdiagnosis rate of up to 10% (Dr B Lindahl, personal communication, June 2003).

Cost of misdiagnosis

High and low costs for each cost component are given in Table 5-1. Appendix 13 explains the derivation of each value.

Table 5-1 Cost of rehabilitation, counselling on risk factor modification and prophylactic medication per patient

Item	Unit costs (£)		Prescribing rate (%)	High cost (£)	Low cost (£)
	High cost	Low cost			
Counselling and rehabilitation	248	160	100/60[a]	200	112
Aspirin costs per annum	40 (150 mg)	12 (75 mg)	80	32	10
β-blocker costs per annum	87	13	80	70	10
ACE inhibitor costs per annum	273[b]	14[c]	80	218	12
Statin costs per annum	387 (20–80 mg)	210 (10 mg)	60	232	126
Total				752	270

[a] This assumed a 100% uptake rate for counselling and 60% uptake rate for an exercise rehabilitation programme (Dr I Findlay, personal communication, November 2003).

[b] Note there is a branded ACE inhibitor that costs £400 but this is considerably more expensive than similar drugs and has been excluded from the analysis.

[c] Assumes the drug is prescribed for six weeks only; in subsequent years, a low drug cost of £79 is used.

The assumed base case savings from avoiding the cost of counselling on risk factor modification, rehabilitation and prophylactic medication per patient would be £270 per patient (the low cost value) as shown in Table 5-1. There are other potentially important costs that will be avoided by using a troponin test to confirm diagnosis. These include the cost of failing to diagnose the patient appropriately and the cost of adverse events arising because the patient is given unnecessary drugs and interventions. These were excluded from the base case analysis.

Total cost of troponin tests

Appendix 13 also explains that the cost of troponin tests comprises three components:

- the manufacturers' charges
- additional annual variable costs for laboratory tests of £1 per test
- additional annual fixed costs for point-of-care tests.

It notes that the manufacturers' prices quoted to an individual site will be sensitive to the manufacturers' discount structure which normally includes volume of tests as a variable. The total inclusive unit costs per troponin test (combining the three types of costs) for different numbers of test are set out in Table 5-2.

Table 5-2 Total cost per troponin test for different number of tests performed annually

	Volume of tests		
	Low	**Middle**	**High**
Point-of-care tests	500	1000	2000
Laboratory tests	3000	5000	9000
	Costs (£) of tests		
Volume of tests	**Low**	**Middle**	**High**
Troponin I point-of-care test	31	19	11
Troponin T point-of-care test	20	13	9
Troponin I laboratory test	5	4	3
Troponin T laboratory test	5	4	3

The base case assumed a cost per laboratory test to be £4 per test (the middle value for laboratory tests). The base case assumed that laboratory tests, rather than point-of-care tests, would be used because the purpose of the test is to confirm a diagnosis and this decision is not judged to be time critical. In addition to these costs, an allowance of £1.83 per test is made for five minutes of a nurse's time to administer the test.

5.3.1.4 Results

Table 5-3 summarises the additional costs and savings assuming that troponin tests are performed on 10 000 patients diagnosed with STEMI and a misdiagnosis rate of 3%.

Table 5-3 Costs and savings from a laboratory troponin test for 10 000 patients with STEMI: misdiagnosis rate of 3%

	Costs (£)	**Savings (£)**	**Net cash flow (£)**
Year 0	58 258	81 086	22 828
Subsequent years		48 533	48 533

Further calculations showed that if the misdiagnosis rate is 2.2%, then the savings in the first year would be £1205, rising to almost £35 600 in the next year. Thus at this misdiagnosis rate, the savings in the first year would exceed the costs incurred by undertaking an extra 10 000 troponin tests. If the cost per test is £5 and there is a 3% misdiagnosis rate, savings of £228 per person misdiagnosed (70% of the low value) would be sufficient to recover the costs

of these additional tests within the first year. If the misdiagnosis rate is 5%, then the level of savings in the first year (after deducting the cost of tests) would be approximately £76 900.

5.3.1.5 Conclusion

If a troponin test at 12 hours after admission is used to confirm whether or not an MI is a correct diagnosis and the misdiagnosis rate from diagnostic tests on admission (primarily an ECG) is 2.2% or higher, then the costs of the additional laboratory troponin tests would likely to be exceeded by the savings available in the first year by avoiding secondary prevention measures (such as cost of rehabilitation, counselling on risk factor modification and prophylactic medication) for the patients who would otherwise be misdiagnosed.

Other benefits include avoiding the risk of exposing patients to unnecessary drugs and interventions, and the opportunity it affords to determine an appropriate diagnosis.

Moreover, Section 4.2.3.3.2 outlines that studies demonstrated that troponin is effective in predicting a LVEF of less than 40%, which is a predictor of adverse outcome. Thus the troponin test result is likely to assist in further risk stratification and patient management.

If data on the 12-hour post-admission troponin test results in STEMI patients were available nationally, it would facilitate the comparison of outcomes across hospitals for these patients. The data would also facilitate research into outcomes, for example, research into the clinical effectiveness of the secondary prevention drugs for different subgroups, stratified by troponin level.

5.3.2 Cost comparison of a two-test strategy with a single-test strategy

5.3.2.1 Background

Figure 3-4 illustrates the time course of the release and disappearance of troponins. Because there is a delay between myocardial cell necrosis and detectable cardiac troponins in peripheral blood, the ESC guidelines explain that a single troponin test on admission is not sufficient and recommend that troponin be measured 'on admission and if normal, repeated 6 to 12 hours later', with a proviso that the second test can be omitted if the initial test was more than 12 hours from the patient's last episode of pain (Bertrand *et al.*, 2002).

NHS Quality Improvement Scotland was advised that the majority of Scottish protocols mandate a troponin test at 12 hours from admission. Appendix 5 contains two protocols for the management of ACS. The North Glasgow University Hospitals Trust requires a troponin measurement be taken between 12 and 24 hours after admission, although there are plans to change the timing of the troponin measurement to 12 hours after the onset of pain. By

contrast, the Paisley RAH protocol adopts troponin point-of-care testing on admission for those patients who cannot be diagnosed from the ECG as having an AMI and, if normal, the troponin test is repeated at six hours. Section 4.2.3.3.5.2 outlines available evidence for early troponin testing.

Section 4.2.3.3.4.6 sets out evidence that treatment such as glycoprotein IIb/IIIa inhibitors are likely to be effective in high-risk patients with ACS, as predicted by the TIMI score or individual components of this score, and that troponin tests, in combination with other clinical factors are effective in selecting such patients. A recent study by Rao *et al.* (2003b) concluded that patients with raised troponin but normal CK-MB were at increased risk of adverse cardiac outcomes in the short term and recommended that these patients be admitted to hospital and monitored in either an intensive care or step-down unit. These studies suggest that there may be clinical benefit from identifying, monitoring and treating patients with raised troponin expeditiously. This view is also supported strongly by Dr Lindhal (Dr B Lindahl, personal communication, 2003).

5.3.2.2 Methodology and assumptions

The cost-consequence analysis compared the additional cost of a two-test strategy (i.e. measuring troponin on admission and 12 hours later) using point-of-care testing with a single-test strategy (i.e. measuring troponin 12 hours after admission) using laboratory testing.

As explained in Chapter 4, no clinical trial has been undertaken to test the clinical effect of reducing the risk stratification period by 12 hours in patients with non-ST elevation ACS. Anticipated benefits include shorter length of stay and avoidance of inappropriate therapies. Indeed, the patient benefit will vary depending on the availability of resources to facilitate the initiation of earlier treatment. A key assumption in this analysis was that there would be no additional clinical and patient benefits from diagnosing a patient at admission rather than 12 hours later. This is a conservative assumption and as supported by evidence from Rao *et al.* (2003b), understates the clinical and patient benefits.

5.3.2.3 Data inputs

Epidemiology

For a cohort of patients, the proportion of patients with symptoms suggestive of ACS, a normal ECG, no high-risk features but who have raised troponin at the time of admission to hospital was required to inform the economic analysis. These data were not available from the literature. Data from the RAH Paisley for the period from January 2003 to September 2003 showed that of 860 tests conducted on patients with normal ECGs and no other high-risk features, 139 (16.2%) showed raised troponin. Of these 139 tests, 71 (51%) were raised for troponin on admission, equivalent to 8.25% of all tests (Dr I Findlay, personal communication, October 2003).

The analysis used these values for the base case.

Savings

Savings would arise from admitting patients with raised troponin but equivocal ECG readings directly to the appropriate ward rather than to a medical receiving ward for 12 hours and then transferring them to a specialist ward.

Data in 'Scottish Health Service Costs' (Common Services Agency (CSA) Information and Statistics Division (ISD), 2000) showed that in 2001/02, the cost of a bed for 12 hours in a medical receiving unit, excluding pharmacy, was £119. This is equivalent to £125 in 2003 prices.

Figure 4-1 shows that the ESC guidelines recommend that patients receive various pharmacological agents, such as aspirin, clopidogrel and LMWH, prior to a second troponin measurement. If patients in the two-test strategy are only administered these drugs when they have a positive troponin test[8] in comparison with all patients receiving the drugs under the single-test strategy, then the estimated savings per patient would be:

- £6.31 for clopidogrel, assuming 300 mg is administered immediately and 75 mg the next day
- £5.81 for LMWH for a 12-hour period, assuming a dose of 1 mg/kg of enoxaprin and an average patient weight of 80 kg.

Costs are taken from the British National Formulary 45 (British Medical Association (BMA) & Royal Pharmaceutical Society of Great Britain (RPSGB), 2003).

Few hospitals in Scotland administer LMWH to all patients with suspected ACS during the initial risk assessment period. More hospitals prescribe clopidogrel to patients with symptoms suggestive of ACS and cease this treatment when a firm 'rule-out' diagnosis is made. This decision may follow a stress test and is thus independent of the troponin test. Nonetheless, sensitivity tests were conducted comparing the cost consequences of a two-test strategy with clopidogrel and LMWH administered to only high-risk patients (on receipt of positive troponin result) with a single-test strategy whereby all patients receive each drug during the 12-hour risk stratification period, ceasing when patients are identified as low risk (on receipt of negative troponin result).

[8] This analyses assumed all patients identified as high-risk using risk markers other than biochemical tests would be immediately treated as high risk and would receive the appropriate drugs.

Costs

The base-case estimated costs of the troponin tests for a cohort of 100 patients are set out in Table 5-2. For this cohort of 100 patients, the base case assumed eight patients have raised troponin on entry to medical care (that is, when placement decisions are taken and treatment commences).

If point-of-care tests are used, then the additional costs of the two-test strategy would be the cost of conducting 100 point-of-care troponin tests on admission plus a further 92 tests 12 hours later, less the cost of conducting 100 laboratory tests. These additional costs were estimated to be £1493.

If laboratory tests are used, the additional costs comprise a further 92 tests at a cost of £4 per test plus nursing costs of £1.83 per test, equal to £534.

5.3.2.4 Results

Table 5-4 shows the cost consequences (changes in costs and savings) of undertaking an additional troponin test on admission in patients with suspected ACS but in whom there is diagnostic uncertainty.

Table 5-4 Cost consequences of an additional troponin test on admission for a cohort of 100 patients

Test type	Cost (£) of extra tests	Savings (£) from correct bed placement	Savings (£) from clopidogrel (sensitivity test)	Savings (£) from LMWH (sensitivity test)	Net savings (£) (Bed savings only)	% to detect for break-even (Bed savings only)
Laboratory (£4)	534	1032	578	533	498	4.5
Point-of-care troponin T test (£9)	1493	1032	578	533	–461	11.7
Point-of-care troponin I or T test (£8.40)	1028	1032	578	533	4	8.25

It was assumed for this analysis that point-of-care testing would be used. Therefore if the troponin tests on admission and 12 hours later are to all performed by laboratories, then the two-test strategy would be highly cost effective, assuming the only savings are bed savings. However, the additional cost of the point-of-care testing option of £1493 (assuming a cost per test of £9 and additional nurse costs per test of £1.83) is £461 greater than the savings resulting from correct ward placement decisions alone.

If the pathway allows LMWH to be administered to all patients with suspected ACS during the 12-hour risk stratification period, then changing practice to using a two-test strategy and prescribing LMWH only to high-risk patients provides additional savings of £533 by not administering LMWH to 92 patients per cohort of 100. Similarly, under the two-test strategy, there are estimated savings of £578 from reduced prescribing of clopidogrel if all patients are currently prescribed this drug with the single-test strategy. Under

either sensitivity test, the point-of-care testing option at a cost of £9 per test is cost effective.

Table 5-4 also shows the percentage of additional patients who need to be detected as troponin positive by the test on admission in order to achieve financial break-even (excluding any savings from LMWH). The rate varies with the cost per test. If a laboratory test is used at a cost of £4, then about 4.5% additional patients need to be detected as high risk from the initial troponin test for financial break-even. If the point-of-care test costs £9, the detection rate needs to rise to 11.7%. These values compare with the observed detection rate of 8.25% at the Paisley RAH.

If the total cost per test including quality assurance and other variable costs is not more than £8.40 per test, the two-test strategy using point-of-care tests would be cost effective. This assumed that there would be no savings from LMWH or clopidogrel. Manufacturers have indicated that such costs are feasible in contracts for high volumes of tests, thereby attracting significant discounts.

As a further sensitivity test, cost savings in bed placement of £65 and £180 per patient (compared with the base case that assumed savings of £125 per patient) are sufficient to give financial break-even, assuming laboratory and point-of-care costs per test of £4 and £9 respectively and the base-case epidemiology assumptions.

5.3.2.5 Conclusions

The key driver of the cost effectiveness of adopting the two-test strategy, as recommended in the ESC guidelines, is the additional number of high-risk patients identified by the troponin test on admission. Assuming resources are available in cardiology wards, these high-risk patients could be admitted directly to cardiology wards and commence treatment. The alternative approach is to admit patients to a medical receiving ward where they are risk stratified, using a single troponin test result delivered some 12 hours later in conjunction with other diagnostic tools, and then to transfer high-risk patients to the relevant cardiology ward.

The more cost-effective approach depends on three key variables:

- the percentage of high-risk patients identified by the admission test
- the level of bed and/or drug savings
- the cost of the troponin tests.

Individual hospitals should be able to model these variables, possibly using a pilot study, in order to establish the cost effectiveness of a two-stage testing strategy for troponin for their own sites.

The economic analysis attributed no value to clinicians and patients having the troponin measurement available at admission. The value of such measures is explored in the economic model (Section 5.4).

5.4 Economic model

5.4.1 Objectives

The objective of the model was to produce recommendations concerning the most efficient (that is least cost) approach of using point-of-care and laboratory tests for various scenarios. The scenarios differed in terms of:

- the availability of laboratory tests, particularly at weekends
- the availability of clinical decision makers to act on the troponin test results
- the turnaround time (that is, the time between drawing blood and the decision maker receiving the test results).

The net cost of each scenario was measured, taking into account both the costs associated with introducing each scenario and the savings achieved.

5.4.2 Methodology

5.4.2.1 Evidence sources

5.4.2.1.1 Literature search

Section 5.2.1.1.1 provides a description of the literature searching for the economic aspects of this HTA. No relevant data from the literature search were found for the economic model.

5.4.2.1.2 Other sources of evidence

Other sources of evidence used for the economic model included:

- the clinical effectiveness literature search described in Section 4.2.2.1.1 which provided the epidemiological information
- manufacturers' submissions which were used to inform the costs of the troponin tests
- TSG members who defined the operational savings that would arise from facilitating quicker turnaround times for troponin test results, advised on arrival patterns and helped in determining the additional fixed and variable costs associated with introducing troponin tests (both laboratory and point-of-care tests).

5.4.2.2 Exclusion criteria

Exclusion criteria were not applicable as no literature was used to inform the economic model.

5.4.2.3 Description of model and data inputs

This section summarises:

- the assumptions underpinning the economic model
- the scenarios tested by the model
- the economic, epidemiological and other variables used in the model.

5.4.2.3.1 Model structure

5.4.2.3.1.1 Assumptions

The economic model compares a point-of-care troponin testing service with a laboratory-based service to risk stratify patients presenting with chest pain but without ST elevation as shown by an ECG. The model was based on the following assumptions:

- troponin testing at 12 hours after admission would be used as part of a risk stratification process to decide between discharge of low-risk patients and continued inpatient treatment, including early angiography and possible PCI, for the other patients
- there would be no clinical advantage in treating patients with angiography, PCI or glycoprotein inhibitors within 24 hours of presentation rather than within 48 hours of presentation. As yet, there is no convincing evidence that this is untrue (see Section 4.2.3.3.4). If such evidence emerges, then advantages of shorter turnaround times would increase and the results and conclusions would change to favour such scenarios.
- troponin testing would be only 'time critical' for patients without clear high-risk features and with a normal ECG. In fact, the group would be smaller than this because an abnormal ECG is not the only indicator of high-risk status. Other high-risk clinical features would present, such as continuing pain at rest.
- a patient would be continually observed until a troponin result is received. If the result is normal, further clinician-led tests for cardiac damage would cease and intensive nursing support would reduce, thereby releasing nursing and clinical resources. Discharge was assumed to be in accordance with normal procedure.
- the decision to 'stop nursing and further therapy' would only be affected by cardiac risk and there would be no serious co-morbidities requiring continued nursing[9]
- the analysers used provide accurate troponin readings with no false-positive or false-negative results

[9] Note two TSG members advised that some 80% of troponin-negative patients can be discharged into the community; of the remaining 20%, some would not be discharged because of social circumstances but such patients would not require intensive nursing (T Gaffney, Chest Pain Nurse Specialist, RAH, Paisley, personal communication, March 2003; C Mondoa, Cardiology Specialist Nurse, Stirling Royal Infirmary, personal communication, March 2003).

- decision-making time would be independent of the turnaround time of troponin tests, and would effectively be zero provided the 'decision maker' is available. It is argued by some authors (Collinson, 1999; Azzazy & Christenson, 2002) that a shorter, predictable turnaround time may be associated with a shorter subsequent decision-making period. This also accords with clinical experience using a nurse-led protocol (Dr I Findlay, personal communication, May 2003). However, there is no published data to support such an assumption.
- all analysers have no 'downtime' for maintenance or breakdown.

5.4.2.3.1.2 Scenarios

Eight scenarios were developed, each with a different combination of clinical decision making and laboratory or point-of-care testing availability. The scenarios included the possibility of continuous decision making including decisions made by prior instruction e.g. if a troponin test result is negative, then risk stratification for ACS would be discontinued.

The costs of operating the following scenarios for troponin I and T assays were compared. The scenarios are set out in Table 5-5.

Table 5-5 Eight scenarios for troponin testing

	Troponin testing available			**Batch available**			**Clinical decision making**						**Service**	
	09:00–17:00 Mon–Fri	**09:00–17:00 Mon–Sun**	**24/7**	**Daily Sat–Sun**	**Daily Mon–Fri**	**Daily Mon–Sun**	**09:00–20:00 Mon–Sun**	**09:00–20:00 Mon–Fri**	**09:00–17:00 Mon–Sun**	**09:00–17:00 Sat–Sun**	**9:00–17:00 Mon–Fri**	**24/7**	**Central laboratory**	**30 minutes TAT by point of care**
S 1	✔							✔					✔	
S 2		✔					✔						✔	
S 3		✔						✔					✔	✔
S 4		✔					✔						✔	✔
S 5			✔				✔					✔		✔
S 6	✔			✔				✔		✔			✔	
S 7						✔			✔				✔	
S 8					✔						✔		✔	

Note: S = Scenario
24/7 = 24 hours per day, seven days per week
TAT = turnaround time

These scenarios were created to capture the variability in current Scottish practice and were informed by responses to the laboratory survey (see Appendix 23) and discussions with TSG members (T Gaffney and C Mondoa, personal communication, March 2003). Three scenarios incorporate two alternative options. Scenarios 3 and 4 include point-of-care versus laboratory testing, and Scenario 5 includes 24 hours per day, seven days per week

clinical decision making versus 09:00 to 20:00 hours, seven days per week clinical decision making.

5.4.2.3.1.3 Distribution of turnaround times

The distribution of times from receipt of sample at the laboratory to reporting of the result was obtained from responses to the laboratory survey (see Appendix 23). These times are not directly applicable to the economic model, which is concerned with turnaround times from taking the blood sample to the decision maker receiving the results. However, using the data obtained from the laboratory survey and adding some time for transporting samples to the laboratory suggested it would be appropriate to run each scenario four times, using mean turnaround times of one, two, three and four hours.

5.4.2.3.2 Identification and measurement of model inputs

5.4.2.3.2.1 Epidemiology

The economic analysis required certain epidemiological inputs, specifically:

- the proportion of patients for whom troponin testing is a time-critical component of risk stratification
- the proportion of these patients who are troponin positive at 12 hours after admission
- the diurnal variations in arrival patterns at the unit.

A recent paper by Kontos *et al.* (2002) presented sufficiently full results on an unselected emergency department admission cohort of patients to be useful as the basis for the epidemiology inputs.

Specifically, the base-case model used the Kontos *et al.* (2002) findings:

- 5.6% of admissions with chest pain present with ST segment elevation
- 10.8% of admissions without ST elevation are classified as high risk on the basis of initial ECG findings
- 12.7% of patients not initially classified as high risk will have raised troponin at 12 hours.

Patients in the first two categories (16.4%) would not receive a troponin test. The remainder would have a troponin test. This underestimates the proportion of patients who may be identified as high risk without a 12-hour troponin measurement, since patients with a normal ECG but other risk factors, including continuing chest pain, would also be considered as high risk (Bertrand *et al.*, 2002). This approach would therefore overestimate the number of time-critical troponin tests required.

TSG members advised these proportions are applicable to a Scottish setting (T Gaffney, C Mondoa, personal communication, March 2003).

5.4.2.3.2.2 Arrival patterns

The only data found on arrival patterns were from RAH Paisley over the course of January 2003 (T Gaffney, personal communication, 2003) and from Ninewells Hospital Dundee over the same period (Dr M Johnson, Consultant in A&E medicine, Ninewells Hospital, Dundee, personal communication, 2003). The base case applied the arrival patterns from the RAH, Paisley. A sensitivity test adopted the arrival patterns from Ninewells Hospital, Dundee.

5.4.2.3.2.3 Outcomes

A major outcome from the model is the level of cost savings facilitated by providing clinicians with the results of a troponin test. As stated in Section 5.4.2.3.1.1, the model assumed that clinicians would decide that a patient is low risk when informed of a negative troponin test result. Thus, the patient would be mobilised and would no longer require intensive nursing care. Further clinical investigations, other than a stress test or an echocardiogram, would cease.

Savings from early identification of low-risk patients

Reducing the turnaround times for a troponin test would permit cardiac clinical staff to be available to manage patients at higher risk who might benefit more from their attention than those at lower risk and enable unwell patients, without ACS, to be transferred elsewhere for further diagnostic tests. Where LMWH is started before a troponin test result is available, faster turnaround times should reduce unnecessary expenditure on the drug and reduce the risk to patients taking LMWH.

The resource savings used in the base case are set out in Table 5-6. These are the avoidable clinical costs incurred while caring for patients during the risk-assessment period before a troponin result is available. The savings assumed a patient would be managed in a general medical receiving ward. These savings emerged from discussions with two TSG members (T Gaffney and C Mondoa, personal communication, March 2003) and were refined following debate with all TSG members on 28 March 2003.

Table 5-6 Avoided clinical costs

Clinical resource	Use during risk-stratification period	Cost per period
Nurse	One hour of contact time every four hours	£22.00
Specialist registrar and consultant	20 minutes of specialist registrar time and 10 minutes of consultant time every eight hours	£26.25
Subtotal for base case		**£48.25**
LMWH	One dose	£5.81

The value of each staff saving was taken from the unit costs set out in Health and Social Care 2001 (Netten *et al.*, 2002). The cost of LMWH was obtained from the British National Formulary 45 (British Medical Association (BMA) & Royal Pharmaceutical Society of Great Britain (RPSGB), 2003).

The model assumed all non-high risk patients would be tested at 12 hours from admission. All costs incurred before this 12-hour point were assumed to

be common across all scenarios and were not included in the analysis. Savings would thus only be available by reducing test turnaround times and clinical decision-making times after this initial 12-hour period.

For example, a patient whose risk stratification was completed three hours after the 12-hour point would incur a cost of £22 + £26.25 = £48.25 (£54.06 including LMWH), whereas a patient whose risk stratification was completed 10 hours after the 12-hour point would incur a cost of (£22 x 3) + (£26.25 x 2) = £118.50 (£130.12 including LMWH).

A sensitivity test assumed that earlier risk stratification would avoid further monitoring on an ECG machine, saving £20 per four hours. This assumed that patients would be monitored on an ECG machine and that this would be stopped for low-risk patients once the troponin status is known.

Note the analysis did not assume that low-risk patients would be discharged on receipt of the troponin test result, only that intensive cardiac nursing and clinical assessment would cease. It was indicated during consultation that the model was inappropriate for some settings because patients are not discharged after 20:00 hours, for example. However, no savings in bed costs were assumed for the reasons explained in the following subsection.

Other potential savings: improved bed utilisation and bed planning

Other potential savings were identified but were not included in the model or the sensitivity analyses. The modelling thus adopted a conservative valuation of potential savings. It attributed no further savings beyond the medical, nursing and pharmacy costs described in Table 5-6.

For a medical ward, medical, nursing, pharmacy and laboratory costs comprise about 90% of the total direct costs per case (Common Services Agency (CSA) Information and Statistics Division (ISD), 2000). The direct savings identified in Table 5-6 and the cost of the troponin test (see Appendix 13) thus captured 90% of the anticipated changes in cost categories from facilitating shorter turnaround times for troponin tests. The composition of the remaining 10% of costs includes costs for 'professions allied to medicine' and 'other direct costs' and it is not clear that improving turnaround times for troponin testing will impact at all on these cost categories.

Shorter turnaround times for troponin test results, combined with a protocol that facilitates safe but rapid discharge of low-risk patients, will reduce the length of stay of low-risk patients. This is supported by the literature (Section 5.2.2), reported from experience of using such a protocol at the RAH in Paisley (Appendix 5) and reinforced by several responses to the Consultation Report. Assuming there are patients waiting to occupy beds, then reducing length of stay could increase the throughput of patients using existing resources, thereby delaying the requirement to build new capacity, a significant if unquantified saving.

An indicative value of the higher bed utilisation was obtained by calculating the reduced direct and indirect costs per patient episode for an eight-hour period, assuming 10% more patients could be treated using the existing bed capacity. The baseline costs and utilisation were obtained from Scottish Health Service Costs 2002. The resultant savings would be £8 per case per eight-hour period.

However, the improvement in patient throughput arising from the use of troponins is likely to vary considerably across Scotland depending on a variety of factors including present bed occupancies and staffing levels. Thus, no average savings level was thus used in the model. Sensitivity analyses showed that increasing the assumed level of savings in the model did not alter the ranking of scenarios, instead it reinforced the benefits from short turnaround times.

The second source of possible cost savings arises from the potential to improve bed planning, in particular in hospitals also undertaking surgical procedures. For example, having troponin test results available at 21:00 hours, rather than waiting for a laboratory result the following day, should inform ward and hospital bed managers which beds will be vacated early next morning. At times of pressure on beds, particularly when medical patients are using beds in surgical wards, such information may prevent the cancellation of elective surgical procedures. It has been noted that using troponin tests has indeed reduced the incidence of cancelled elective surgery. The cost savings from avoiding the cancellation of a procedure in England and Wales are £520 per procedure (NHS reference costs [Available from: http://www.doh.gov.uk/nhsexec/refcosts.htm], £511 at 2000/01 prices). No equivalent figure is available for Scotland at this time.

It was not possible to quantify the number of cancelled procedures that could be prevented by reducing the turnaround times when troponin testing is organised as part of a rapid discharge protocol. Therefore, no sensitivity test to quantify the effect of this variable was undertaken.

Improving bed utilisation on medical wards may have other benefits such as:

- reducing the number of medical patients occupying non-medical beds ('boarding-out'), with a concomitant improvement in quality of care and reducing the length of ward rounds for consultants and other staff
- reducing delays, primarily in A&E, for admission to a CCU or medical receiving ward and thereby improving quality of care (and reducing adverse publicity i.e. with fewer patients with MIs on waiting trolleys).

All these intangible benefits lend weight to the case for shortening troponin test turnaround times, thereby releasing clinical resources to attend high-risk patients and to facilitate the safe but earlier discharge of low-risk patients.

Potential benefits to high-risk patients

No savings or cost benefits were assumed for high-risk patients. This is a conservative assumption given that, under certain scenarios, the clinicians managing such patients would receive test results earlier and could thus start appropriate treatment earlier, including transfer to a catheterisation facility assuming space is available in the intervention hospital. Indeed, consultation responses noted that such services are 'underdeveloped' in Scotland and thus patients identified earlier will 'end up in another queue or displace elective patients awaiting angiography'.

Such comments reflect the fact that currently the demand for revascularisation procedures exceeds supply (Scottish Executive Health Department, 2002), with resultant waiting lists for urgent and elective procedures. In such circumstances, it is difficult to realise the full potential of the clinical benefits and improved patient outcomes associated with using troponin tests.

Potential benefits to low-risk patients

In addition to the tangible benefits of not taking LMWH unnecessarily and reduced length of stay in hospital, a quicker risk stratification process is likely to generate substantial benefits for low-risk patients, in particular by reducing anxiety levels as uncertainty surrounding diagnosis and prognosis is resolved sooner. The economic tool to capture such improvement is a quality-of-life measure, usually expressed as a quality-adjusted life year. However, a quality-adjusted life year measure is not sufficiently sensitive to measure changes over such a short period. However, these patient benefits are highly relevant to this HTA and are explored in the Chapter 6.

5.4.2.3.3 Costs

The estimated costs of the troponin tests are set out in Table 5-2 and are explained in Appendix 13.

5.4.3 Analysis and results

5.4.3.1 Base case

The results of running the model for a cohort of 25 patients with chest pain each week (1300 patients per annum) for each of the scenarios outlined in Section 5.4.2.3.1.2, using the base-case assumptions for epidemiology costs, savings as set out in Section 5.4.2.3.2.3 and turnaround times of one, two, three and four hours are tabulated in Appendix 14 for troponin I and T tests. The base-case results are summarised in Table 5-7, assuming a two-hour turnaround time.

Table 5-7 Base-case results

Middle case/ TAT of two hours	Base case Troponin I		Middle case/ TAT of two hours	Base case Troponin T	
	Cost (£)	Cost saving (£)		Cost (£)	Cost saving (£)
Scenario 5 (24/7)	23 318		Scenario 5 (24/7)	15 955	
Scenario 2	32 195	8 877	Scenario 2	32 195	16 240
Scenario 5	39 684	16 366	Scenario 5	32 321	16 366
Scenario 4	39 825	16 507	Scenario 4	33 272	17 317
Scenario 6	45 271	21 953	Scenario 6	45 271	29 316
Scenario 7	79 673	56 355	Scenario 7	79 673	63 718
Scenario 1	115 747	92 429	Scenario 3	114 582	98 627
Scenario 3	121 135	97 817	Scenario 1	115 747	99 792
Scenario 8	164 918	141 600	Scenario 8	164 918	148 963

Note: TAT = turnaround time
24/7 = 24 hours per day, seven days per week

The results of the base case for both troponin I and troponin T tests clearly showed that the scenarios with highest costs are:

- Scenario 8 (batch run at 14:00 hours Monday to Friday, laboratory service)
- Scenario 1 (available 09:00 to 17:00 hours Monday to Friday, laboratory service)
- Scenario 3 (available 09:00 to 17:00 hours Monday to Sunday, point-of-care service, 30 minutes turnaround time).

Assuming a turnaround time of two hours, these scenarios would incur additional annual costs of £92 430 to almost £149 000 in comparison with the most cost-effective scenario.

Scenarios 6 and 7, which include a batch run at the weekend, are less cost effective than the remaining scenarios which have a full Monday-to-Sunday service available. Therefore, a batch service at weekends is better than no service but is less cost effective than continuous weekend working.

The most cost-effective (i.e. the least cost) scenarios are a 24 hours per day, seven days per week point-of-care testing service (Scenario 5) and a seven days per week laboratory service from 09:00 to 17:00 hours, with a turnaround time of less than two hours (Scenario 2).

These rankings are consistent for troponin T and I.

These rankings all assume that clinicians are available to act on the test results and that there are no marginal costs per troponin test of providing these services.

5.4.3.2 Sensitivity tests

Appendix 14 contains sensitivity analyses assuming:

- high and low costs per test. The relevant patient numbers and costs for these options are set out in Table 5-2.
- the avoided clinical costs (that is the savings from earlier risk stratification) set out in Table 5-6 would be extended to include LMWH at £5.81 per patient and also to include £20 for one fewer ECG per patient episode
- the avoided clinical costs would halve from £48 to £24 per patient (see Table 5-6).

The ranking of scenarios altered materially under any of these sensitive analyses.

With a low patient volume and resultant high cost per test (because of the structure of manufacturers' discounts), the most cost-effective approaches are a laboratory-based service operating seven days per week from 09:00 to 17:00 hours or a 24 hours per day, seven days per week point-of-care testing service. The least cost effective approach is a Monday-to-Friday only service. This broad ranking also applies to the high patient volume, low-cost option.

Adopting a higher saving from either reducing the use of LMWH or avoiding an ECG served to reinforce the benefits of moving to shorter turnaround times and earlier discharge (assuming timely clinical decision making), and did not alter the ranking.

The model is most sensitive to reductions in the assumed savings arising from early discharge. For example, in a hospital assessing 25 patients with chest pain each week, if savings were to fall from £48 to £24 for a patient, then with a two-hour turnaround time, the potential savings from moving from a Monday-to-Friday batch service to a 24 hours per day, seven days per week service would fall from £141 600 to £66 350 per annum.

With savings of £24 per patient (being 50% lower than the base case), the difference in cost between a 24 hours per day, seven days per week point-of-care testing service and a seven days per week laboratory service from 09:00 to 17:00 hours is minimal. The higher costs of the point-of-care service are equal to the additional savings arising from discharging more patients earlier. As turnaround times for a laboratory service lengthen to four hours, the additional number of patients who can be discharged earlier using a continuous troponin service produces savings that exceed the higher costs of using point-of-care testing. The model also indicated that even with savings of £27 per patient, if the turnaround time is three hours or above, then a 24 hours per day, seven days per week point-of-care testing service would be the most cost-effective scenario.

5.4.4 Conclusions of economic modelling

The model concludes that:

- hospitals assessing patients with non-ST elevation ACS should use point-of-care tests if their laboratories cannot offer a service consistent with clinical decision-making timescales
- if clinical decision making can occur at any time during the working day, then costs would be minimised by reducing turnaround time. The combination of continuously available decision making and point-of-care troponin testing is the most cost-effective approach of the scenarios analysed. It was assumed for this scenario that the troponin testing has a turnaround time of 30 minutes (which is an estimated turnaround time of point-of-care analysers and is supported by the literature).
- as laboratory turnaround times or costs rise, point-of-care testing would become increasingly cost effective compared with the laboratory testing scenarios
- the largest benefits for a hospital in which troponin testing is available on a weekday-only basis would come from implementing *any* weekend service, provided earlier discharge of patients is achieved and clinicians are available to act on the results. Thereafter, further cost savings could be made from moving from a batch run at the weekend to having a full Monday-to-Sunday service available.

The overall conclusion is that the potential savings from having an optimal troponin service could be realised if clinicians adopt protocols that facilitate early but safe discharge of low-risk patients. In such hospitals, a Monday-to-Sunday laboratory service operating a turnaround time of two hours or less would be similar in terms of its cost effectiveness to a continuously available point-of-care service. If laboratories cannot provide seven days per week service with turnaround times of within two hours, then hospitals would reduce the cost per patient by using point-of-care troponin tests.

6 Patient issues

Summary

- The needs and preferences of people with CHD and their carers were sought by a review of qualitative literature and conducting focus groups with people who had had a troponin test.

- Gender and socio-economic status may influence the time people take to seek medical advice and how they respond to information about CHD, especially their diagnosis.

- Protocols for the use of troponin testing need to recognise that some people with CHD – particularly those in lower socio-economic groups, women and those with a history of heart disease – delay seeking medical assistance.

- To help patients understand their diagnosis, it is useful for health professionals to find out about the beliefs that patients have about themselves and cardiac risk generally, and clarify any misunderstandings about heart disease.

- Patient and carer information needs will vary, but health professionals should offer to explain the purpose of tests, how the diagnosis was made, treatment options, what may happen next, recovery and what to do if symptoms recur. Health professionals should check that patients understand this information and are assured that it was appropriate to seek to medical advice.

- Patients are less likely to remember information when it was given at times when they were anxious. Patient understanding and recall may be improved by health professionals using shorter words and sentences, giving information in categories, repeating information and giving precise rather than general advice statements.

- Patients identified various times throughout their journey of care when they would have valued information, for example, when the troponin test was being done, in the hours between tests if their initial symptoms had subsided, when they were told that they were being discharged and at a follow-up visit to their GP.

- Early discharge of patients with high levels of anxiety may result in increased re-admissions and outpatient contact after discharge. As there is less time for consolidation and detailed discussion of diagnosis when patients are discharged early, health professionals should check to ensure patients and carers understand the information and feel equipped to return home.

- Low-risk patients should be informed that their status does not imply that they are risk free and be reminded that appropriate lifestyle changes may be needed and secondary prevention measures instituted.

- Diagnostic confusion may result in patient confusion if health professionals in the same hospital, and across primary care after patient discharge, use different criteria and terminology for a diagnosis of MI. This underlines the importance of a universal working definition of MI across the UK and the importance of using the same terms for a diagnosis throughout a patient's journey of care.

6.1 Introduction

This chapter describes the needs and preferences of patients, and their carers, in relation to troponin testing. While a patient's physical experience of troponin testing may not differ from that of a simple blood test, troponin testing increases the likelihood of an accurate diagnosis where myocardial damage has occurred. The ways in which patients and carers respond, both psychologically and behaviourally, to a diagnosis are important, as they will influence patient outcomes and compliance with treatment and lifestyle changes. Therefore, this chapter considers the psychological and social implications of a diagnosis of ACS for patients and carers and the implications of early discharge for patients at low risk.

Prior to this HTA, no research has been conducted on patients' or carers' experiences of troponin testing. Therefore, this review considers a wide range of qualitative studies that explored patients' perceptions and experiences of CHD. Additionally, focus groups with patients were undertaken to gain an understanding of any specific needs and preferences in relation to the use of troponin testing for ACS within NHSScotland.

6.2 Methodology

6.2.1 Evidence sources

Evidence was obtained from a variety of sources including published literature, grey literature and the Patient Issues Subgroup of the TSG (see Appendix 1 for TSG members). It was expanded by commissioning focus groups research.

6.2.1.1 Literature search

6.2.1.1.1 Patients' needs and preferences

Searches (see Appendix 15 for details) were undertaken in MEDLINE, Embase, Cinahl, PreMEDLINE, PsychINFO and the Social Sciences Citation Index. The strategy used to search the first five databases listed is given in Appendix 15. This strategy was adapted to search the Social Sciences Citation Index. These searches yielded 569 references. After reading the electronic abstracts, papers were excluded if they did not use qualitative methods, did not focus on the experiences of patients with some form of CHD or would take a substantial amount of time to retrieve (i.e. three dissertations from overseas). Ninety-nine papers appeared relevant and were retrieved and reviewed in full. An additional 10 papers were later identified from key references in the bibliographies of other papers and from the HTA authors' knowledge of the literature, making a total of 109 papers.

After more detailed examination, 35 papers were excluded from these 109 papers for the following reasons: one was a duplicate; 20 did not focus on CHD patients; one was a brief meeting abstract; two were carried out in populations which did not appear to be relevant to Scotland (Jordan and

South Africa); six did not use qualitative methods and five did not analyse qualitative data appropriately. Therefore, 74 papers were considered to meet inclusion criteria for the literature review (26 from the US, 23 from the UK, eight from Scandinavia, nine from Canada, seven from Australia and one from New Zealand). Appendix 16 summarises the design of studies conducted in the UK.

6.2.1.1.2 Carers' needs and preferences

In order to review this literature, searches were undertaken in MEDLINE, Embase, Cinahl, PreMEDLINE, PsychINFO, EBM Reviews, the Social Sciences Citation Index, ASSIA and the British Nursing Index (see Appendix 17 for search strategy details). The search was limited to recent literature (defined as 1997 to the present) on the families and partners of CHD patients. These searches yielded 74 references. After reading the electronic abstracts, papers were excluded if they did not use qualitative methods, did not focus on the informal carers of patients with some form of CHD or would take a substantial amount of time to retrieve (e.g. theses from overseas universities, papers not available from the British Library).

Twelve papers appeared relevant and were retrieved and reviewed in full. Another six papers were found in the bibliographies of other articles and an additional six papers were identified from the main search on CHD patients. This made a total of 24 papers. After more detailed examination, six papers were excluded from this total (five were not qualitative papers and one was not relevant to the topic). Therefore, 18 papers met the inclusion criteria (five from the US, four from Sweden, four from the UK, three from Australia and two from Canada). Four of these papers reviewed the literature, while 14 were empirical studies. These studies are summarised in Appendix 18.

6.2.1.2 Other sources of evidence

Information about the social implications of being diagnosed with ACS was gathered from relevant authorities such as the Driver and Vehicle Licensing Agency (DVLA).

Focus groups were conducted to supplement the literature and to identify some of the needs and preferences of people in Scotland in relation to the use of troponin testing for ACS. Participants had experience of troponin testing. Focus groups, or structured discussion groups, are commonly used in health research to study both *what* participants think, and *why* they think as they do (Barbour, 1995). The interaction between participants ensures that priority is given to their language, concepts and frameworks for understanding the world. The aim of focus groups is to cover different 'categories' of individual through group work (Reid & Armstrong, [No date]). Therefore, the aim was to bring together the following people:

- people from ethnic minority groups
- people from a variety of economic backgrounds

- men and women
- people from rural or urban areas
- people 45 years of age and under
- people over 45 years of age
- people who have been discharged 'early' as low risk.

Participants were recruited through health professionals on the Patient Issues Subgroup of the TSG. This included inviting participants from cardiac rehabilitation groups across Scotland and projects such as 'Healthy Hearts Club'. Once potential participants were identified, they were contacted by phone and then sent a letter giving them information about the study. They were further contacted by phone to confirm their participation. If they agreed to take part in a focus group, their GPs were informed, in case participants had further questions about issues raised at the focus group.

Focus groups lasted no more than one and a half hours, and took place at venues local to the Trusts that identified participants. The facilitator was guided by a list of topics, but there was also time to discuss topics raised by participants. Topics included:

- participants' understandings of different diagnoses (e.g. angina, MI)
- their experiences following their diagnosis
- their experiences and expectations of care and treatment
- views about earlier discharge
- their information needs after diagnosis
- the needs and perceptions of carers, partners or family members following diagnosis.

Information was sought about positive and negative aspects of their journey of care, particularly in relation to communication and information needs during their hospital stay and at discharge. The focus groups explored patients' understanding of CHD and their experiences of care. They sought information about patients' perceptions of different diagnoses of CHD (e.g. MI and angina), given that previous work has suggested that some diagnoses are recognised as more serious than others (Emslie *et al.*, 2001a). In addition, the diagnosis that people are given has important repercussions for patients' understandings of their illnesses and practical consequences such as entitlement to insurance and eligibility to drive.

Difficulties in recruitment limited the research to three focus groups with three to eight participants in each.

6.2.2 Methods of analysis

6.2.2.1 Literature

The analysis of the literature followed the principles outlined by Britten *et al.* (2002). The scope of the review was limited to qualitative studies i.e. those that use methods such as in-depth semi-structured interviews and focus

groups with a limited number of participants. Qualitative studies are much more suited to eliciting patients' detailed understandings and perceptions of illness than quantitative studies which often ask participants to indicate their preference from a limited range of answers. Each paper was read carefully in order to identify the main concepts of the study, details of the study setting and the participants. These were entered into a table (see Appendices 16 and 18). The papers were then compared for common and recurring concepts to establish similarities and differences in scope and findings across the studies.

6.2.2.2 Focus groups

With the consent of the participants, each group discussion was tape recorded and then transcribed. Transcripts were analysed according to the constant comparative method with due attention given to deviant cases (those which do not fit in with the overall theory) and features of group dynamics (Kitzinger, 1995). Throughout fieldwork, transcripts were studied repeatedly to identify common themes and explore the underlying reasoning of participants. This process of formulating hypotheses, going back to the data and revising hypotheses is dynamic and cyclical rather than linear.

6.3 Results – review of literature

6.3.1 Patients' needs and preferences

Only one published review of the qualitative literature on patients was found (Clark *et al.*, 1998). This review identified six qualitative studies which explored patients' experiences of cardiac conditions. Two studies were based in the UK and the remaining four in North America. Clark *et al.* reported that these studies were limited by their narrow focus on MI (rather than other experiences of CHD), married respondents and men. In addition, the roles of country, culture and ethnicity were neglected in the six studies identified by Clark *et al*. While there has been a large increase in the number of qualitative studies over the past five years, some of these criticisms remain relevant to more recent studies. Where studies focus on a particular manifestation of CHD, it still tends to be MI rather than chest pain, angina or heart failure. There is little information about the beliefs and experiences of patients from ethnic minority backgrounds. Many authors do not report the country in which the study took place, leaving the reader to extrapolate this information from the authors' institutional affiliation. However, recent studies are much less likely to focus on either married respondents or men than those conducted previously. The belated recognition in the 1990s that women have been excluded from much CHD research (Healy, 1991; Khaw, 1993) has resulted in a large increase in studies using female-only samples, particularly in North America.

The key themes, addressed by the literature, were:

- the 'career' of the cardiac patient
- reasons why patients delay presenting symptoms to health professionals

- gender and social class differences in experiences
- perceptions of health professionals and services.

6.3.1.1 'Career' of the cardiac patient

Cowie (1976) described the 'careers' of 27 heart attack patients, from their first perception of symptoms through to their decision to call for medical assistance and to their experiences in hospital. He argued that a heart attack is often not immediately recognisable to those experiencing it. Initial symptoms (e.g. chest pains, heartburn, sweating) were often 'normalised' by attributing them to indigestion or exertion. Patients (or sometimes their spouses) only sought medical assistance when the severity of pains in the chest increased so much that non-serious complaints were ruled out. After hospitalisation, most patients expected a full recovery and to return to normal life. Patients reviewed their history in an attempt to 'explain' their heart attack. These explanations included physically and/or mentally hard work, strenuous activity, past health problems, warnings such as earlier chest pain, ageing, smoking, stress and the idea that the heart attack 'built up' through strain over a long period. Cowie's account is valuable as he first raised many of the issues taken up by later researchers. However, some of the criticisms raised by Clark *et al.* (1998) also apply to Cowie's study. For example, he focused solely on heart attacks rather than other manifestations of CHD, he only interviewed married respondents and although women were included in the study, he does not give details of the gender mix and refers to the participants as male (e.g. 'his heart attack').

6.3.1.2 Delay in presentation

Given that receiving treatment quickly is vital for survival among those experiencing an AMI, it is not surprising that many researchers have concentrated on patients' first perception of symptoms and the reasons they delay presenting symptoms to health professionals. Subsequent research supports Cowie's (1976) argument that patients interpret their initial symptoms in a variety of different ways, attributing them to old age, tiredness, other illnesses or to less threatening causes such as heartburn or mild food poisoning rather than to CHD (White & Johnson, 2000; Clark, 2001). Other authors have interpreted these reactions as denial or an attempt to minimise the significance of the illness (Pattenden *et al.*, 2002; Foster & Mallik, 1998; Holliday *et al.*, 2000). Some patients worried about 'bothering' the doctor or calling the emergency services unnecessarily in case it was a false alarm (Pattenden *et al.*, 2002). Partners or spouses often encouraged patients to seek help, removing the responsibility from the patient for taking immediate action (Foster & Mallik, 1998). Many cardiac patients (Pattenden *et al.*, 2002; Wiles, 1998; Ruston *et al.*, 1998; Zuzelo, 2002) as well as those in the general population (Emslie *et al.*, 2001a) have an image of the 'typical' heart attack as involving dramatic, crushing pain and sudden collapse. As many patients do not experience these severe symptoms, they may be unsure about the nature of their illness. Wiles (Wiles & Kinmonth, 2001; Wiles, 1998) found that respondents believed a heart attack resulted in sudden death or

permanent disability. Patients subsequently tried to reconcile their earlier perceptions with their CHD event by viewing their heart attack as 'mild' rather than 'severe'. Research conducted with the general population also found that some diagnoses are perceived to be more serious than others. For example, Emslie *et al.* (2001a) found that respondents recognised a range of severity of heart attacks (from 'mild' and 'wee' to 'massive') and that 'heart disease' or a 'heart attack' were perceived to be more serious than a 'heart condition'.

People who had experienced a previous heart problem often delayed because they believed their changed lifestyle, cardiac rehabilitation or surgery would protect them from subsequent cardiac events (Pattenden *et al.*, 2002).

Quantitative studies have indicated that women, older people, those in lower socio-economic groups and those with a history of CHD are more likely to delay seeking medical assistance than other groups. However, qualitative research is necessary to identify *why* some groups delay longer than others (Clark, 2001).

6.3.1.3 Gender and social class

Gender and social class influence patients' perceptions of heart disease and subsequent care. Research on lay perceptions has identified the stereotypical 'coronary candidate' as a fat, red-faced, overweight, inactive smoker with a fatty diet (Davison *et al.*, 1991) and male (Emslie *et al.*, 2001b; Ruston *et al.*, 1998). Therefore, people were puzzled and sometimes indignant as they tried to align this image with their very different self-image and past behaviour (Clark, 2001). They expressed shock and disbelief at their diagnosis. The strong perception among people with cardiac conditions (Richards *et al.*, 2002b; Ruston & Clayton, 2002) and the general population (Emslie *et al.*, 2001b) that heart disease is a 'man's problem' may result in women finding it more difficult to attribute their symptoms to CHD (Foster & Mallik, 1998). Even women, who believe they may be at risk, feel they are safe until after menopause (Lacharity, 1999). Some researchers found that women are less likely to report the 'classic' symptoms of CHD than men and so find it harder to interpret these signs appropriately (Schoenberg *et al.*, 2003).

Women seem more likely than men to consider their own health a low priority compared with the health of other family members (Richards *et al.*, 2002b) and to prioritise meeting their role obligations (i.e. taking care of their husbands, children and homes) over seeking medical care (Zuzelo, 2002). Richards *et al.* (2002b) found that they did not want to worry their husbands so did not ask them for advice, while other studies found that women seek advice from relatives, but that this consultation can lead to increased delay (Foster & Mallik, 1998; Zuzelo, 2002). Women are also more likely than men to distance themselves from the risk of heart disease (Ruston & Clayton, 2002), fear being viewed by their physician as a worrier or hypochondriac (Schoenberg *et al.*, 2003), worry about wasting their GP's time and prioritise household responsibilities (which were viewed as essential) over CHD

symptoms because things 'fell apart' if they were not at home (Schoenberg *et al.*, 2003). They also believed that their problems would be attributed to 'nerves'.

Stereotypical views of coronary candidates may also result in delays in men presenting. For example, there is a perception among some men that they are 'too young' for heart problems (Finnegan, Jr. *et al.*, 2000). However, unlike women, men appear more likely to consult their wives (who often call for medical assistance on behalf of their husband) when experiencing cardiac symptoms (Richards *et al.*, 2002b).

Men's experiences may also be influenced by their traditional roles in society (e.g. as 'breadwinners'). Some men may have felt tension between experiencing severe pain (and the feeling that they were really ill) and soon afterwards, feeling symptom free (and feeling like 'a fraud' for being in hospital). The lack of visibility of their symptoms also added to their difficulty of feeling 'ill' and accepting the limitations imposed by health professionals and relatives (e.g. accepting that their spouse should do 'their' chores). Some men did not want to discuss health problems for fear of appearing a 'wimp' or 'unmanly' (White & Johnson, 2000; White, 1999). White & Johnson (2000) concluded that their respondents believed that men should be fit and productive at all times in order to carry out the roles expected of them. Finally, King (2002) found that while most respondents in rural Australia attributed their MI to 'stress', men tended to focus on work as the main area of stress in their lives, while women talked about it in terms of personal relationships and their own personality.

As outlined in Section 6.3.1.2, among men and women, being in a lower socio-economic group is associated with a higher risk of MI and a lower probability of reaching hospital alive after a cardiac event (Morrison *et al.*, 1997). Richards *et al.* (2002a) found that deprived patients with chest pain were more negative about their health than affluent patients and had low expectations about their likely lifespan. Often, they did not present their symptoms to medical professionals because they normalised their symptoms (e.g. related symptoms to working long hours), could not distinguish them from the other conditions they suffered from and did not want to overuse medical services. They had a more negative experience of health care than affluent patients and felt they were likely to be blamed by health professionals (e.g. for smoking) rather than be assisted.

6.3.1.4 Perceptions of health professionals and services

A number of studies have focused on patients' relationship with health professionals and their perceptions of health services. For example, Gardner & Chapple (1999) conducted a study in deprived areas of Liverpool. They found a 'cultural gap' between doctors and patients where patients were wary of hospitals and tests, perceived angina as a chronic condition to be managed or denied, and perceived that ill health was a natural part of older age. There was diagnostic confusion about angina and people did not want to bother

doctors whom they perceived as very busy. These issues prevented patients from being referred for possible revascularisation. Similarly Tod *et al.* (2001) found that barriers to the uptake of CHD health services included structural factors (e.g. poor transport, long waiting lists and inconvenient surgery times), personal factors (e.g. fear and denial), cultural factors (e.g. strength and stoicism in the south Yorkshire mining culture), past experiences of health services and professionals, and lack of awareness of the high incidence of heart disease.

Clark (2001) stressed the need for health professionals to find out the beliefs that patients have about themselves and about cardiac risk generally, in order to encourage them to see themselves at risk of CHD. However, Wiles & Kinmonth (2001) warned of the tension between reassuring patients and providing realistic information about the uncertainty of outcome (which could lead to anxiety or depression among patients). Others have identified barriers to effective communication between doctors and patients. For example, Rogers *et al.* (2000) found that some respondents felt that doctors did not want to give them too much information about their heart condition and had little information about their likely prognosis, Thompson *et al.* (1995) found that their respondents wanted more detailed information from physicians about their recovery, and Kennelly & Bowling (2001) found that older patients were not involved in medical decision making about their treatment, as most preferred their doctor to make the decision and were deferential towards the medical profession.

6.3.2 Carers' needs and preferences

For most cardiac patients the social context in which illness occurs, is experienced and is resolved, is the family. It has been argued that it is 'virtually impossible to separate the needs of family members from those of the patient' (Dougherty, 1997, p55). Social context can best be understood by using qualitative methods which explore the world from the respondent's perspective (James, 1999). As there has not been any research conducted on the reactions of family members to troponin testing, the review concentrates more generally on adjustment processes within the family following a cardiac event (James, 1999). This section contains a short summary of the literature review. A full literature review is included in Appendix 19.

Four key themes emerged from the literature:

- problems experienced by relatives
- sources of conflict between relatives and patients
- problems with the health care system
- need for support.

6.3.2.1 Problems experienced by relatives

Relatives reported a number of adverse effects after the patient's cardiac event. They experienced a variety of distressing emotions including guilt, self-

blame, anguish, frustration, resentment, powerlessness and fear (Daly *et al.*, 1998; Svedlund *et al.*, 1999; Theobald, 1997). Additionally, Daly *et al.* (1998) found that women's health suffered after their husband's MI and that they experienced problems trying to combine their normal roles with the new responsibilities of caring for the patient. Women also reported difficulties in dealing with the mood changes of their husband after an MI (Stewart *et al.*, 2000). Some partners had difficulties with eating, sleeping and concentrating (Theobald, 1997). Others worried about household finances (Stewart *et al.*, 2000).

6.3.2.2 Sources of conflict between relatives and patients

Studies identified a number of potential areas of conflict between patients and relatives. Firstly, the need for behavioural change by the patient could be stressful for the family as a whole, for example, wives reported not knowing what foods would be sufficiently healthy for the patient and some husbands reported finding life monotonous as their partner's illness imposed limitations on daily life (Svedlund & Axelsson, 2000).

Secondly, the role of the spouse as 'monitor' or 'enforcer' was highlighted. Wives felt they needed to check that their husbands were continuing to eat healthily, and this could lead to conflict, especially in a social situation (Daly *et al.*, 1998; Stewart *et al.*, 2000). Spouses also talked about how they spent endless hours observing the patient and how they felt the pressure of constant responsibility (Dickerson, 1998; Mahoney, 2001; Stewart *et al.*, 2000). The balance between supporting patients and letting them lead independent lives was difficult to achieve (Eckert & Jones, 2002).

Thirdly, lack of communication could be an issue. Both spouses and survivors engaged in processes of protective buffering, where they tried to protect the other person from stressful information and hide concerns (Svedlund & Axelsson, 2000; Tapp, 1993). There was also evidence that some patients and some partners distanced themselves from the disease and denied what was happening (Stewart *et al.*, 2000; Svedlund *et al.*, 2001).

Finally, conflict occurred when illness meant that patients could not perform the tasks traditionally associated with their gender. For example, men with CHD found it hard that their spouse had taken over what they perceived as traditional male tasks (e.g. shovelling snow) (Stewart *et al.*, 2000). Similarly, it has been suggested that men with internal cardioverter defibrillators, who are banned from driving, experience this and find it a threat to their self-image (James *et al.*, 2001a). The lack of research on the family relationships of female CHD patients makes it difficult to explore this in relation to women. However, quantitative research suggests that the situation for female CHD patients may be different. For example, Lemos *et al.* (2003) found that men who reported more cardiac symptoms than others tended not to engage in male-stereotyped activities such as repairs and paid employment, but that women who experienced more symptoms continued with their domestic activities.

6.3.2.3 Problems with the health care system

Relatives reported a number of problems when dealing with the health care system. They needed most help when the patient was discharged from hospital (Dickerson, 1998). However, discharge sometimes occurred suddenly without adequate preparation (Stewart *et al.*, 2000). This was very stressful as responsibility suddenly shifted from health professionals to the family, who felt very inexperienced in caring for the patient and felt unprepared to handle the side effects of medications at home (Dickerson, 1998; Dougherty, 1997; Murray *et al.*, 2002). Some relatives felt that they were not considered to be an important part of the patient's recovery by health professionals and were not given the information they required (Murray *et al.*, 2002). This lack of information heightened their anxiety. They also wanted health care staff to help resolve problems when patients and family members had different perspectives or opinions about care and recovery (Dougherty, 1997).

6.3.2.4 Need for support

Relatives expressed a need for support groups, but some felt guilty for asking for help for themselves. Martensson *et al.* (2001) found that elderly female spouses were particularly reluctant to complain or ask for help.

6.4 Results – other sources of evidence

The DVLA has indicated that ACS diagnosed by persistent or recurrent cardiac pain, positive cardiac troponin and ECG changes has implications for driving and vehicle licensing (http://www.dvla.gov.uk/at_a_glance/ch2_cardiovascular.htm). For a Group 1 licence (i.e. ordinary car licence), driving must cease for at least four weeks. Driving may recommence thereafter provided there is no other disqualifying condition. The DVLA need not be notified. For a Group 2 licence (i.e. a large goods vehicle and passenger carrying vehicles), drivers are disqualified from driving for at least six weeks. Re-licensing may be permitted thereafter provided the exercise test requirements can be met and there is no other disqualifying condition.

6.5 Results – views of service users

6.5.1 Focus group participants

The respondents who took part in the three focus groups had all had recent experience – within the past year, and some within the previous few weeks – of attending a major Scottish hospital with acute coronary symptoms. Most had been admitted to hospital via A&E. With prior ethical approval, all of the participants were invited to take part in the focus group discussions by health professionals who had had contact with them during their coronary episode. All were known to have had troponin testing.

The sample included men and women:

- from a range of socio-economic backgrounds
- with a range of severity of heart problems (from those who were discharged from hospital within a short time to those who were referred on to other specialist coronary centres for more extensive treatment e.g. triple bypass surgery)
- from a range of ages (from early 40s to early 70s)
- with a range of experience of cardiac problems both personally (some presenting for the first time, some with experience of attending with episodes of cardiac pain over many years) and among people's close family and friends (some had no indirect experience, others had parents and siblings who had died of heart disease, some had attended emergency care supporting a spouse with cardiac problems).

Difficulties in recruitment resulted in people from ethnic minority backgrounds not being represented in the focus groups.

6.5.2 People's experience of inpatient investigation of ACS

The major themes from the focus groups related to delay in presentation, feelings of guilt, anxiety, communication and information. Section 6.5.3 describes participants' experience and understanding of troponin testing, including information requirements. While it includes some criticisms of care, such as the lack of information given, it is important to contextualise this within people's wider comments which often praised the efforts made by individual hospital staff and described the treatment as 'second to none'. Some had no criticisms. Where people did express criticisms they sometimes also mentioned that they appreciated the pressures – including time stress, bed shortage, patient overload, difficult patients (e.g. drug users) – under which many staff were required to work in the busy cardiac and emergency department where they were seen.

In support of earlier research, many of the participants expressed a strong reluctance to consult health professionals about cardiac symptoms and guilt about using health care resources, saying such things as:

'*To me, it's just like I didn't want to go in an ambulance. I just was like really I don't feel bad enough that I'm taken in an ambulance and there's probably somebody that needs it*'

or:

'*You always think this is going to go away, or I'm going to feel better soon*'.

Feelings of guilt sometimes became more pronounced after patients arrived at the hospital, particularly if their immediate symptoms had been alleviated. Their sense of guilt might also extend to their families, with considerable anxiety experienced while they were undergoing tests and waiting for their results and anxiety about the worry and strain that they were placing on their family members, particularly if other family members had experienced fatal

coronary events. They were also concerned about the implications of the various diagnoses that they might receive.

Those who felt their families had been kept well informed throughout the admission to hospital and subsequent investigations expressed gratitude that staff had taken the time to give information to relatives. For those who did not know whether their relatives were being kept up-to date, the stress about the impact on relatives added to the patients' own anxieties. As one woman said:

'*I was very anxious and [it was] very stressful. People were walking past all the time, but nobody is stopping to tell you "It won't be long" . . . I kept on trying to catch somebody, like "Would you go up and tell me husband and my children I'm all right, I'm still breathing, I'm still here". Because they didn't know, they had just got the phone call at their work . . . nobody was telling them. My husband [who also had a heart condition] was up at the window a few times, and of course I was anxious about him because you know he would go into his problem, you know, and although my children are grown up they were very very anxious about it and I just felt that there could've been a bit more communication between them. They [the staff] weren't to know. They didn't know the family circumstances, you know that things have happened so quickly to us, as you know the kind of sudden death thing and I just felt as if they could have been kept more informed*'.

Medical and nursing staff may underestimate the extent to which patients will castigate themselves for being ill and going to hospital, as illustrated by one man who described his guilt about possibly wasting staff's time, colleagues at work covering for him while he was away and the stress and worry experienced by his family. Others agreed, for example:

'I don't think you've been made to feel that [you're wasting people's time] *from the hospital staff. Yes, they didn't make you feel as if you were wasting anyone's time. It's <u>you</u> personally feels that and it's because other people are putting the stress on you to make that decision to go in and do something about it, but I think if it happens to me again, I wouldn't be going down to the doctor, I wouldn't be, I would really wait a lot longer'*.

In their accounts, many participants expressed the anxiety and shock they had felt at different stages:

- during the often rushed and chaotic move to hospital
- during the administration of tests
- during the period when they were awaiting test results, which they often experienced as long and rather lonely.

One woman's statement that '*I felt that there were great big long gaps of time, you never saw anybody*' was greeted with general agreement from others in her group.

6.5.3 Awareness and understanding of troponin testing

All of the participants were aware of having blood tests, and most mentioned this as something that happened soon after their arrival in hospital. For example, during his description of his presentation to hospital one man said:

'*They took a blood sample, that was at 8.30 in the morning, and then they come back at about 11.00, put me on the monitoring machine and they says, "you've had a slight heart attack, it looks, but we've maybe took the blood sample too early". So he said, 'what we'll do is we'll take another blood sample now and come back about 6 o'clock and let you know what's happening". They came back at 6 o'clock, "you are getting kept in", so up to Ward X* [cardiac ward]'.

However, very few participants were aware that the blood tests they had had, included troponin testing or, except in the broadest terms, what the results of their blood tests were. For example, in one group, when the facilitator asked people about their experience of troponin testing, her question was met with blank looks and universal head-shaking. Most participants were not clear about the purpose of their blood tests, but had made some attempt to work out what it might be:

'You get blood tests done every day at 8 o'clock in the morning. A phlebotomist comes round, takes your blood. Now they are also looking, apart from telling them that you've got heart problems, or a heart attack will show up. They look to see if you've got too much potassium or things in your body that might, you know, if there is an imbalance'.

'I was told you know when my husband's been in a number of times, I had been told that each time he goes in, they are looking for an enzyme that's released. Is that it? Is that it? . . . When they take <u>him</u> in . . . I'm always, 'what you doing now? . . . I put two and two together because of my experiences over the last 20 years with him, you know.' (Female)

'*It was just generalised as in "blood tests were done", so I presumed like the cholesterol . . . so you were thinking, well what are they doing this for? I think if there was more information then we would do more ourselves*'.

Most people stressed that they would have liked more information about the tests, perhaps as they actually were being undertaken, although some acknowledged that it might be difficult to ask questions or to take in information during the immediate crisis of their admission to hospital with chest pain. While participants were unaware of troponin tests, many indicated that they were simply called blood tests, but that they would have liked to know the purpose of the blood tests:

Male 1: '*They didn't mention anything about say, troponin tests . . .*'

Female 1: '*They just call it the blood test . . .*'

Male 2: '*Well fair enough, because it probably wouldnae at that time mean, I mean they took the sheets, but it wouldn't mean anything to me, you know . . .*'

Female 1: '*You know, they <u>could</u> say, "I'm testing you for this, this and this", but then you would probably ask more questions*'.

When the facilitator asked more about troponin later in the interview, it seemed that, while some were still very vague, one man who had insisted he had not had a troponin test in fact recalled the purpose of a troponin test being explained to him:

'*They did say, I think they said if I remember right, they tested for an enzyme or something like that would tell if the heart muscles had been damaged. But they didn't name it, they didn't tell me what the name was . . . but they told me <u>why</u> they were taking the blood, things like that*'.

The other members of the group reported similar confusion.

Lack of feedback on the results and the purposes of specific tests led to confusion, particularly among those who did not have further treatment. Some of the participants reported that their experience of being discharged was abrupt, and they left unsure of their diagnosis. One man described how he was given a letter for his doctor at discharge rather than a diagnosis and indicated that no one had explained the tests to him. People's sense of frustration about not knowing what they had 'had' was compounded if there was delay in communication of results from the hospital to their GP.

Participants' comments demonstrate the acute emotional backdrop to being admitted to hospital with a suspected heart attack. People might be fearful, in shock, worried about whether they might die, worried about the immediate consequences for family, friends and colleagues. Uncertainty about the final diagnosis, what tests they have had and whether they should have sought care in the first place all add to the emotional impact and the need for explicit reassurance that they had legitimate reasons to consult a doctor.

Patients identified several points at which they thought it would have been helpful to get more information. These were:

- when the test was being done
- in the hours between tests when they felt very anxious about waiting for information on what they had, and often guilty about taking up bed space or other hospital resources if their initial symptoms had subsided
- when they were told that they were being discharged
- at a follow-up visit to their general practitioner.

Some also suggested that it would have helped to have a written leaflet or summary to take away with them following discharge.

6.6 Results – communication with patients and carers

6.6.1 Addressing misconceptions

The review of literature highlighted a range of perceptions among patients and their carers in response to a diagnosis of heart disease. These differing perceptions (e.g. guilt or denial) may influence the way in which patients and carers understand and respond to information. The following popular, but incorrect, beliefs need to be considered and addressed when communicating with patients:

- heart attacks are caused by stress
- heart attacks always involve severe symptoms
- some heart attacks are 'mild' and a heart condition is less serious
- only stereotypical 'coronary candidates' have heart attacks.

Additionally, patients may react differently, both emotionally and physically, to diagnosis of UA or MI and their responses may often be based on misconceptions. A diagnosis of MI is considered to be a more threatening and dangerous diagnosis than UA, with long-term implications for patients' lifestyle.

A diagnosis of UA can be perceived as a less dangerous than an MI or a benign condition, and as a result, the gravity of the diagnosis can be underestimated. Alternatively, it can be seen as 'a near miss or warning' and can lead to heightened anxiety, thereby triggering avoidance of the activity that initiated the condition or potentially even precipitating an MI. There is also a misconception that each episode of angina is a mini-heart attack and this can reinforce avoidance behaviour. Patients with a diagnosis of UA are also less likely to be offered rehabilitation although aspects of the condition can be debilitating (Lewin *et al.*, 1995; Lewin *et al.*, 2002).

Discussions with patients and carers may benefit from greater public awareness of the causes and symptoms of heart disease, for example through the information provided by NHS Health Scotland.

6.6.2 Consistent messages about diagnosis

Troponin testing provides clinicians with increased certainty about the diagnosis of myocardial damage which in turn may help them to communicate the diagnosis more clearly and give patients greater certainty.

However, there is the potential for patients to become confused and concerned by changes in their diagnosis during their hospital stay. This can be caused by changes in clinical presentation or information that emerges during the observational period, or encountering different health professionals between different wards during their patient journey i.e. from A&E to discharge. It would be beneficial if health professionals use the same

clinical terminology for a diagnosis to achieve consistency of messages received by patients.

Additionally, as identified in Section 3.2.2, clinical confusion has arisen from the redefinition of MI. This has serious implications for the consistency of messages received by patients regarding their diagnosis if health professionals within the same hospital, and across primary care after patient discharge, use different terminology for a diagnosis of MI. This exemplifies the importance of a universal working diagnosis of MI across the UK so that clinical diagnostic confusion does not translate into patient confusion. To facilitate the transition of patient care, a hospital discharge letter should include the patient's troponin status.

There may also be variation in the knowledge and current practice of health professionals with regards to troponin testing. Therefore, health professionals, in particular those in primary care who may not encounter troponin testing frequently, may benefit from training to help them to understand more about troponin testing and to address misconceptions in order to improve the consistency of messages provided to patients.

6.6.3 Content of communication

Regardless of diagnosis, patients and their carers need information. Patients with a positive troponin test need to be equipped to make decisions about further treatment and those with a negative result need information to alleviate unnecessary fears at discharge. Some patients may also be carers, and these patients may need extra support and have additional information needs. Spouses or carers need information to assist them in supporting the patient with ACS, to enable them to feel supported and equipped in their role and to reduce their anxieties when a patient is discharged. Carers may need specific information about dietary requirements and sources of support and information.

Within this context, information about the following should be communicated to the patient and carers:

- what has happened
- diagnosis, including how it has been made and what terms mean
- treatment options
- what could or will happen next
- why earlier identified options are no longer being offered
- what are the chances of further problems
- what to do and who to contact if pain returns after discharge
- side effects
- sources of support and further information.

This information may not only help people to participate in decision making, it may also help them to understand why their care differed from others. For example, their understanding of the time required to diagnose heart disease

may be based on the experiences of a friend or family member who received treatment prior to the introduction of troponin testing. As a result, the more rapid diagnosis could wrongly be perceived as less thorough.

The *National Overview of Coronary Heart Disease* (Clinical Standards Board for Scotland, 2001a) highlights potential areas of interest to patients and carers in its list of questions for patients to ask health professionals. These are:

- Did I have clot-busting drugs?
- Am I getting aspirin?
- What are the reasons for my not receiving it?
- Who is going to give me advice about my lifestyle?
- Do I need an exercise test?
- Do I need an ECG?
- How will you decide when I am able to go home?
- Are there any restrictions on what I can do when I get home?
- What treatment will I be getting?
- Who will be supervising my treatment?
- Will I receive a note of the treatment I have been given?
- Will my GP be informed?
- Do I need to come back to see you again?

Other questions patients may need information on are:

- Does my diagnosis affect my work, driving and normal day-to-day activities?
- How do secondary prevention measures help to prevent further heart damage?
- Why should I follow secondary prevention measures if I have not had a diagnosis of MI?

Health professionals should be prepared to provide answers to questions discussed in this section.

6.6.4 Oral communication

Health professionals should check that patients understand the information given to them. There is evidence that patients fail to understand and remember much of the information and advice provided to them particularly if they are anxious (Ley, 1979; Ley, 1989). This may be correlated with patient non-concordance and dissatisfaction with the information they have received. However, several methods for increasing patient understanding and recall have been shown to be effective (Ley, 1979). These are:

- using shorter words and sentences
- giving the information in categories, listing the category names to the patient and then repeating the appropriate category name before presenting the information. For example, a health professional might say:

' I am going to tell you what is wrong with you, what tests were carried out, and what treatment you will need'.
- repeating information
- using precise, rather than general, advice statements i.e. 'lose 10 kg in weight' rather than simply 'lose weight'.

There is evidence that these techniques have enhanced oral communication, resulting in increased patient satisfaction and faster recovery from illness. Patient recall may also be improved by frequent and prolonged contact with a health professional (Ley, 1982).

6.6.5 Written communication

Written information should be provided to reinforce oral communication between health professionals and patients and carers. The content of the written information should address the themes listed in Section 6.6.3. Patient information leaflets should be written in simple, easy-to-understand language and more detailed information should be available to the patient, if and when required. Information in other formats, such as video, audio, pictographic representation or large print, should be made available to people with difficulties with learning or literacy.

Patient information on heart disease needs to be updated to include an explanation of troponin and the term ACS. The British Heart Foundation publishes patient information which acknowledges the emotional needs of patients, their families and carers. It publishes a guide to tests used in diagnosing heart disease including what happens, possible outcomes and risks, and a guide about heart attack and rehabilitation which includes information about treatments, what happens in hospital, coming to terms with a heart attack and patient-held record cards (http://www.bhf.org.uk/publications/).

While it is unlikely that a patient or carer will have an interest in participating in a shared decision about having a troponin test to diagnose ACS, this information will help to equip them in shared decision making about their future treatment.

6.6.6 Requirements for low-risk patients

Low-risk patients, and their carers, have specific information needs because of potential misconceptions surrounding their risk status and limited opportunity for communication with a health professional due to their shorter hospital stay.

Due to potentially early discharge of low-risk patients, patients may misinterpret their health risk. Health professionals need to provide a clear message to patients who are discharged as low risk that this status does not imply that they are free of heart disease. Patients should be informed that a negative troponin result does not exclude the presence of underlying heart

disease and does not rule out future cardiac problems. Health professionals should remind patients that appropriate lifestyle changes may be needed and secondary prevention measures instituted.

As there is less time for consolidation and detailed discussion about the results of the investigations at early discharge than there is otherwise, health professionals should check to ensure that patients and carers understand the information.

While patients diagnosed as low risk may benefit from earlier discharge, as well as returning to work quickly and avoiding unnecessary medicines, some low-risk patients and their carers may not welcome early discharge. They may prefer the security and reassurance of a longer hospital stay. This may be a greater concern in certain subgroups of patients, in particular the elderly, those patients who are carers and those who live alone. Early discharge may also cause anxiety or distress if there is uncertainty about a diagnosis. This may be further heightened if there is a delay in receiving appropriate outpatient investigations to provide a definite diagnosis. There is also evidence that early discharge patients with high levels of anxiety have increased rates of re-admission and outpatient contact after discharge (Allison *et al.*, 1995; Frasure-Smith *et al.*, 2000).

After discharge, health professionals in the primary care sector take on the responsibility for the follow-up care of low-risk patients, although there is the potential for a patient to give more credence to the specialists' view rather than that of their GP. In order to assist with potential difficulties, it may be beneficial to provide GPs with guidance, perhaps in the discharge summaries.

7 Organisational issues

Summary

- The recommendations on the optimal provision of laboratory and point-of-care troponin testing services across Scotland have been informed by literature, manufacturers' evidence, patients' preferences, expert knowledge, surveys and existing policies relevant to troponin testing.

- The surveys undertaken by NHS Quality Improvement Scotland revealed that 96% of cardiologists who responded to the survey use troponins, mainly to risk stratify patients with UA or NSTEMI and to change patient management. However, there is variation in the availability of troponin testing across Scotland, with use in community hospitals and general practice showing greatest variation.

- The benefits from using troponin tests will be optimised through a service re-design with primary, secondary and tertiary care providers organising MCNs and patient pathways to facilitate the implementation of the HTA recommendations.

- Any laboratory performing troponin testing should be accredited, with appropriate internal and external quality assurance, SOPs and training in place. There should also be a 'liaison group' to oversee testing and resolve issues arising between laboratory and clinical staff. Given the importance of turnaround times, well-designed information technology (IT) and transport systems are also needed.

- Hospitals adopting point-of-care troponin testing should organise risk management and infrastructure for quality assurance, SOPs and training. These may be more demanding than for laboratory-based systems. Additional factors relevant to point-of-care testing include the need to have results comparable with those produced by the laboratory. If this is not possible, only one type of service should be offered to avoid clinical confusion on cut-off levels.

- Realising the advantages of the rapid turnaround times, facilitated by point-of-care testing, requires: a person coordinating the service to ensure the patient journey is completed according to the agreed protocols; available clinical decision makers to act on test results; appropriately trained operators in place; quality assurance and audit. A multidisciplinary point-of-care testing committee, which may include primary care representatives if the service extends to the community, is also required to oversee all point-of-care testing.

- The costs for 45 community hospitals to set up a troponin testing service are estimated to be £0.17 million, with the annual operating costs estimated at £0.12 million. Annual costs of between £0.28 and £0.35 million would enable all DGH and tertiary centres to perform

quality-assured troponin testing with a maximum turnaround time of two hours in both patients with non-ST elevation ACS and patients with STEMI within approved protocols and to provide patient information leaflets. Substantial discounts could be achieved if sites contract with manufacturers on a Health Board, regional or national level.

7.1 Introduction

This chapter describes the current provision of troponin testing in Scotland (Section 7.2) as evaluated by surveys and highlights issues for certain subgroups of patients (Section 7.3). It outlines the requirements of laboratory and point-of-care troponin testing services (Section 7.4) and considers the main recommendations for effective service delivery and their financial consequences (Section 7.5).

The recommendations regarding the organisation of troponin testing services have taken account of a review of the available literature, manufacturers' evidence, the clinical- and cost-effectiveness evidence base on troponin testing and recommendations, patients' needs and preferences, expert knowledge, surveys undertaken by NHS Quality Improvement Scotland and existing policies and procedures relevant to troponin testing.

The chapter aims to assist NHS Boards in organising their troponin testing services in the most effective and efficient manner.

7.2 Current provision of troponin testing services in Scotland

7.2.1 Evaluation of troponin testing services

To assess the current availability and use of troponin testing in Scotland, four surveys were undertaken. Surveys of hospital laboratories, cardiologists and community hospitals were conducted by NHS Quality Improvement Scotland (Appendices 20 to 22 respectively). Postal surveys were sent to named individuals in these settings for completion, and attempts were made to follow up non-responders by telephone or mailed reminders. An informal survey on the use of troponin testing in general practice was undertaken by Dr Susan Vincent, a member of the TSG representing the Scottish General Practitioners Committee. Responses to the short survey were emailed and collated by Dr Vincent.

7.2.2 Results of surveys

The following subsections contain summaries of the main findings of each survey. Appendices 23 to 26 contain full details of the survey results.

7.2.2.1 Survey of laboratories

Eighteen of 22 laboratories responded to a survey assessing the availability of troponin testing and all 18 laboratories reported that they provide troponin testing. Ten laboratories measure troponin T and seven measure troponin I. One laboratory only measures troponin T by point-of-care testing. Three laboratories provide troponin T point-of-care testing in addition to laboratory testing. All four laboratories with point-of-care testing are involved in the maintenance of the analyser and provide quality assurance and quality control. Seventeen laboratories have a protocol for troponin testing. Only one

laboratory reported that troponin has superseded other biochemical markers. Seventeen still offer one or more other conventional biochemical markers.

There is variation in the type of troponin testing service laboratories provide (e.g. an on-demand service during the week and batched service on weekends, a batch service during the week with an on-demand service for specific patients) but the majority of laboratories offer a weekend service and this tends to be a batched service. Five laboratories indicated that they provide a 24 hours per day, seven days per week service. Fourteen laboratories provide a troponin testing service to primary care or remote and rural sites.

Seventeen laboratories provide guidance on the timing of troponin tests. There is variation in the guidance: six laboratories recommend blood samples taken between 6 and 12 hours after admission; nine laboratories between 12 and 24 hours after admission or the onset of symptoms, one laboratory advises samples to be taken less than six hours after the onset of pain and another laboratory that samples be taken less than 10 hours after admission. One respondent indicated that they have different testing regimens for different subgroups of patients i.e. low-risk patients undergo a point-of-care troponin test at zero and six hours in contrast to the <12-hour test for other patients. Thirteen laboratories responded to the question about the time from receipt of the specimen in the laboratory to reporting the result and the responses ranged from 30 minutes to four hours.

Appendix 23 contains full details of the laboratory survey results.

7.2.2.2 Survey of cardiologists

Forty eight of 71 Scottish cardiologists responded to a survey assessing the use of troponin testing. Forty six of the 48 cardiologists have access to troponin testing (96%). Most cardiologists have access to laboratory-based troponin (16 use troponin T, 27 use troponin I). Only three have access to troponin T point-of-care testing. Sixteen cardiologists also use CK-MB. Thirty-six cardiologists reported that a protocol for the management of patients with chest pain involving troponin testing is in place.

Forty-five cardiologists indicated that troponin is used to risk stratify patients with NSTEMI or UA, 36 to change patient management and 23 to confirm or audit clinical decisions. A troponin test enabled earlier discharge of troponin-negative patients with chest pain (33 respondents), reduction in the use of other biochemical markers (27 respondents) and better risk stratification (43 respondents). Other impacts of troponin testing reported were: an increase in workload; increased rehabilitation; possible increases to patients' length of stay due to inadequate catheterisation capacity; inappropriate discharge due to misinterpretation of result and a more accurate diagnosis of ACS. One respondent noted that the failure 'to agree what exactly a raised troponin means' creates difficulties for cardiologists.

Full details of the cardiologist survey results are located in Appendix 24.

7.2.2.3 Survey of community hospitals

Of 70 surveys sent to community hospitals, 37 of the 54 returned were usable i.e. they treat CHD patients. A follow up of the 16 non-responders asked only one question (whether they have access to troponin) and nine follow-up questionnaires were returned, one of which was marked not applicable. In total, 18 community hospitals (14 to the full survey, 4 to follow-up survey) indicated that they can request troponin.

The following results refer only to those 37 community hospitals that returned the full survey. Of the 14 community hospital that can request troponin testing, the average number of troponin tests requested per month ranges from one to three and with turnaround times of the order of 24 hours. Four community hospitals have a protocol available for interpreting the results. Point-of-care troponin testing is offered by four community hospitals and is performed mainly by nurses. The average number of point-of-care tests requested per month ranges from one to 25. Of the 10 respondents to the question regarding the availability of a weekend laboratory service, only three reported that this is available.

In addition to the reasons for using troponin outlined in Section 7.2.2.2, a troponin test result in the community hospital setting informs the decision to transfer a patient to a DGH or tertiary centre.

Twenty three of 37 community hospitals cannot request troponin and 19 have no plans to introduce it. Reasons for this included: clinicians not wishing to use it; lack of finance; lack of laboratory or clinician willingness; distance to the laboratory and inappropriate to setting or patient. In these community hospitals, 19 have at least one other biochemical test available.

Full details of the community hospital survey results are located in Appendix 25.

7.2.2.4 Survey of GPs

Fifteen of 36 GPs responded to a survey assessing the availability of troponin in general practice. Of these 15 GPs, seven have access to troponin testing. Concerns were voiced about the delay in receiving a result. Those GPs without access commented that troponin might be helpful in situations where admission to hospital may not be clinically necessary (see Appendix 26 for further details).

7.2.3 Summary of service provision

The surveys of hospital laboratories, cardiologists, community hospitals and GPs demonstrated the variability in access to and equipment used for troponin testing across Scotland. There are differences in the interpretation of troponin results. There is also variability in the reported time from receipt of

sample to reporting of results by laboratories that affects how useful the results are for therapeutic decision making. While all hospitals receiving patients with ACS should have access to a troponin testing service to meet clinical needs, the issue of troponin testing in primary care and community hospitals, particularly in remote and rural areas, remains open to discussion. This is underlined by the fact that two laboratories noted that primary care and remote and rural sites rarely use the troponin testing service they offer. Only 18 of the responding community hospitals stated that they have access to troponin testing which raises issues about variation in access to this test for patients in Scotland. Some of the variation may be due to lack of local protocols for patients with ACS. This is an important issue for CHD MCNs to review. Furthermore, 19 out of 23 community hospitals without troponin testing have no plans to introduce it. Using troponin testing in primary care would help to exclude a diagnosis of myocardial damage but the benefits may vary depending on local facilities and distance from a hospital that treats patients with ACS.

The development of troponin testing contributes to the *Coronary heart disease and stroke strategy for Scotland* and will be facilitated by CHD MCNs (Scottish Executive Health Department, 2002) and the National Advisory Committee for CHD.

Troponin testing is only useful if it helps patients. A troponin result is only one aspect of defining high-risk patients and ensuring they receive appropriate treatment. In the survey undertaken by NHS Quality Improvement Scotland, 12 cardiologists said they do not have a formal protocol for troponin testing. Evidence-based protocols incorporating troponin testing (including nurse-led protocols for patients with chest pain of suspected cardiac origin) would ensure a consistent approach to managing patients with ACS in Scotland. This includes equitable access to revascularisation facilities, using evidence-based and transparent 'eligibility criteria' applied to all patients requiring invasive intervention in Scotland and adequate transport, beds and catheterisation laboratory capacity to facilitate compliance with the protocols.

7.3 Other issues

This section considers issues for remote and rural areas in relation to troponin testing and for the management of high-risk patients.

7.3.1 Issues for remote and rural areas

There is a small amount of literature dealing with troponin testing in remote and rural areas. Mutrie (2002) noted the potential of troponin testing in 'pre-hospital' settings such as 'urgent care' centres, ships and prison medical facilities (i.e. all communities confined in some way). The paper described the use of troponin testing in a prison to determine those prisoners who needed to be transferred to a hospital and those who could be dealt with safely in the prison medical facility. Worrall *et al.* (2001) described troponin testing in a rural emergency department in Newfoundland, Canada. In contrast to the

positive conclusions of Mutrie, they concluded that although a negative troponin I test excluded MI in one patient with a questionable ECG and in 45 patients who had other diagnoses, it 'did not provide additional diagnostic information over and above clinical examination and the ECG'.

The benefits of using troponin testing in remote and rural settings may vary depending on local facilities such as a community hospital and on the distance a primary care practitioner is from a hospital that treats patients with ACS. Therefore by excluding an MI using a clinical examination, an ECG and a troponin test result (possibly by point-of-care testing), the inappropriate use of emergency transport (i.e. ambulance by air or road) may be avoided. Conversely, earlier identification of high-risk patients would allow more prompt organisation and appropriate use of ambulances.

To identify the issues faced by GPs working in community hospitals, expert advice was sought from Dr Hamish Greig, Chair of the Scottish Association of Community Hospitals (personal communication, July 2003).

Currently, there are 81 community hospitals throughout Scotland with approximately 2250 beds, potentially serving a population of 1.5 million. Community hospitals play a significant role in diagnosing patients with suspected ACS. Therefore, the number of responses to the community hospital survey indicating that troponin testing was inappropriate for their setting or type of patients is surprising. GPs operating in community hospitals should have access to troponin testing. The only other marker required in community hospitals, in addition to troponin, should be CK for re-infarction.

The two main reasons for variation in access to troponin, as identified in the community hospital survey, are lack of funding and robust transport arrangements to ensure that results can be turned around in a timescale to provide clinical benefit. Community hospitals are also disadvantaged by the deficiency of an IT system to collect data. This is a significant barrier to prospective audits of troponin testing being undertaken in these settings.

In community hospitals, one of the main uses of troponin testing is to assist GPs in diagnosing patients who do not present with classic symptoms of MI i.e. where patients are asymptomatic and/or elderly. Troponin would only be used for borderline cases or for patients who present late and a decision on hospitalisation is unclear, with all other patients being diagnosed from ECG. Early diagnosis will enable prompt treatment and inform a decision to transfer a patient to an appropriate setting. Distance from a tertiary centre also increases the importance of early decision making. While greater availability of troponin testing may or may not result in increased transfer of patients to DGHs and tertiary centres, failure to place the patient in an appropriate setting for treatment may be expensive and potentially dangerous, and also has repercussions for the patient i.e. the uncertainty is stressful and creates confusion. Quantitative troponin tests are more appropriate than qualitative tests in the community hospital setting because values of troponin are needed to inform decisions on patient transfer to tertiary centres (see Section

4.2.3.3.4). Dr Greig concurred with the community hospital survey results of an average of one to three troponin tests per month (approximately one test per week).

Dr Greig agreed that lengthy turnaround times reduced the clinical utility of tests and therefore fully supported point-of-care troponin testing. He recommended that troponin tests should be performed at the point of care unless laboratories were able to turnaround the results in about two hours. Point-of-care testing enables GPs to undertake the tests in an appropriate setting, for example in the patient's home. GPs are often first on site after an emergency call in remote and rural areas and troponin enables GPs to advise on appropriate transfer of the patient. However, there may be quality assurance issues surrounding point-of-care testing, such as manufacturers requiring daily quality control for a service used three times per month. Problems with different cut-off limits between different hospitals also need to be resolved. However, these barriers need to be overcome in order for troponin to be implemented.

Protocols that include troponin testing are necessary in community hospitals to inform risk assessment and should be established in collaboration with local cardiologists. Good communication across MCNs is essential, in particular in relation to cut-off values for troponin. It was suggested that the current absence of protocols in community hospitals is symptomatic of a larger problem concerning education and communication. GPs, other health professionals and community hospital teams dealing with troponin need support and training in their use and the interpretation of results.

7.3.2 Issues for the treatment of high-risk patients

An underlying assumption informing the ESC guidelines and associated patient pathway is that facilities exist to enable interventions to be instituted immediately, if indicated. Indeed, unless patients are treated appropriately and expeditiously, including discharge of low-risk patients, the greatest benefits from reduction in turnaround times for troponin test results will not be realised. Hence, there is a need to ensure that high-risk patients with ACS have equitable access to catheterisation facilities. As data in Section 8.3 indicate, this may not be currently happening in Scotland, with notable variations in treatment in hospitals with and without on-site angiography facilities. Changing the present access arrangements so that more patients are referred to tertiary centres for revascularisation procedures will increase demands on related resources, such as ambulance journeys and beds in the receiving hospitals.

To assess the present variability in eligibility criteria, each tertiary centre was asked to provide information on the criteria adopted for urgent angiographies, PCIs and CABGs and to note whether the criteria differed between patients within the centre and patients from referral centres. Responses were received from eight centres. The main points identified are outlined here:

- the majority of cardiologists adhere to the BCS, ESC and AHA/ACC guidelines to identify high-risk patients who need urgent investigation and intervention but there is no single Scotland-wide accepted protocol in use
- proximity to a catheterisation laboratory is one of the strongest determinants of angiography being performed. This is confirmed by data from the GRACE registry.
- within each network served by a catheterisation laboratory, an agreed policy for the urgent transfer of patients and for elective angiography is required and is supported by audit to ensure adherence to the principles
- the use of a TIMI score to capture demographics, clinical parameters, ECG changes and biochemical results is a good starting point for discussion within CHD MCNs
- clinicians should avoid using protocols mechanistically and thus protocols, while helpful, should be supplemented by individual assessment of each patient, to include the patient's preferences and risk factors
- capacity limitations impact mostly on high-risk patients requiring urgent investigations (for example, older patients with raised troponins, dynamic ST change and recurrent pain). Emergency patients, for example with cardiogenic shock and major MI or needing rescue angioplasty, are usually accommodated in the tertiary centre. One cardiologist noted that patients requiring urgent treatment often wait up to a week for transfer. During this period, the patients are 'stabilised' enough to go home and be investigated on the elective list, although the evidence is to investigate within 48 hours.
- DGH cardiologists feel catheterisation laboratory capacity is insufficient. This is supported by data from the GRACE registry which confirms the relatively low level of angioplasty performed in Scotland, despite the high level of CHD in Scotland.
- primary care clinicians do not refer many patients with symptomatic coronary disease because of the inadequate availability of cardiologists.

Such concerns have led the Scottish Executive to set up SCIN (Scottish Executive Health Department, 2002). The National Advisory Committee on CHD will take SCIN's work forward.

7.4 The organisation of an optimum troponin testing service

7.4.1 Requirements of a troponin testing service

As discussed previously in this HTA, a troponin testing service can be based in a central laboratory or be provided at the point of care. There are certain requirements of a troponin testing service that are mandatory, such as compliance with health and safety and European legislations and certifying quality assurance. Quality assurance is a vital component of a troponin testing service and it must be applied rigorously. It guarantees that all measures have been taken to ensure that investigations are reliable from correct patient identification and obtaining a satisfactory sample to analysing, recording and

interpreting results accurately and taking appropriate action. Quality assurance also ensures that all procedures have been documented. Quality assurance in a troponin testing service includes accreditation, participating in external quality assurance schemes and training.

Requirements common to both laboratory and point-of-care troponin testing services are outlined in Sections 7.4.1.1 to 7.4.1.4. The organisational aspects that are specific to each type of service are discussed in Sections 7.4.1.5 and 7.4.1.6 respectively.

7.4.1.1 Accreditation

Clinical Pathology Accreditation (CPA) UK has identified a defined standard of practice for medical laboratories. Accreditation involves an external audit of all laboratory processes. Gaining accreditation provides a guarantee of a high-quality service for its users. The method used to analyse samples for troponin must be robust and all laboratories that perform troponin testing (including point-of-care testing) must meet the standards specified by CPA UK (Clinical Pathology Accreditation, 2001).

One of the CPA (UK) standards is that all medical laboratories have a quality manager, defined as 'the individual who ensures, on behalf of laboratory management, that the quality management system functions correctly' (Clinical Pathology Accreditation, 2001). The quality manager must monitor quality control results and test performance closely, and report to the 'liaison group' as part of regular patient management pathway review (Section 7.4.1.5). The standards also cover various aspects of quality management, including having a policy on borderline tests or outliers.

7.4.1.2 UKNEQAS-Cardiac Markers

CPA requires that laboratories are members of an EQA scheme. Most laboratories in Scotland use the CPA-accredited UKNEQAS-Cardiac Markers. Currently UKNEQAS-Cardiac Markers has 220 participating laboratories in the troponin scheme, 36 in the CK-MB scheme and 21 in the myoglobin scheme. There are 40 participants in the point-of-care schemes which cover troponin T, troponin I, CK-MB and myoglobin.

As mentioned in Section 4.3.3.3.5, UKNEQAS-Cardiac Markers issues three samples per month for testing at each participating centre, and the samples are returned for analysis. Statistical tests measuring cumulative bias, variability, cumulative variability, method bias and CV are performed by UKNEQAS-Cardiac Markers and the outcome is reported back to the participating centre. A traffic light, colour-coding system is used to assist participants in assessing their performance.

Currently there is a discrepancy between the number of sites offering troponin point-of-care testing services and those that are following strict EQA practices. Laboratories taking responsibility for monitoring troponin point-of-

care testing are able to ensure these analysers are tested alongside laboratory-based EQA testing. Other sites without laboratories can participate directly in the UKNEQAS-Cardiac Markers scheme, and commercial internal quality control material and EQA material are also available.

7.4.1.3 UK professional requirements and training of staff

7.4.1.3.1 Laboratory staff

Laboratory analysers are operated by degree-qualified biomedical scientists (BMSs). A laboratory already operating an immunoassay analyser should require no additional skills from its staff to offer laboratory-based troponin testing, as cardiac troponin testing is usually performed on one of the standard immunoassay analytical platforms currently in use. Such instruments are capable of performing a multitude of tests on a given patient sample. The overall factors governing their operation and maintenance are specific to each of these machine types and vary only in small detail, if at all, between individual analytes.

No universally applicable, formal training courses or models exist to train staff in the operation of point-of-care testing analysers. Point-of-care analysers will usually be operated by a nurse who has been trained in their use, and not a specifically trained laboratory officer. However senior BMSs (Grade 2 or higher) would usually conduct training for nurses and other point-of-care testing users. Training of staff in the use of point-of-care analysers could be improved by:

- having common procedures for training such as which staff should be trained, who undertakes the training and to what level
- ensuring a training manual is made available by the trainer (manufacturer/supporting laboratory) with local needs and circumstances incorporated
- assessing and documenting the competence of staff at the end of training
- continuing refresher programmes to be developed, maintained and documented for trained users
- monitoring of the service provided. It should be part of a quality management programme of the supporting laboratory or local body responsible for the point-of-care testing service.

7.4.1.3.2 Clinical biochemists

The level of training provided to clinical biochemists and medical staff on the interpretation of troponin test results is an integral part of their training and continuing professional development. Clinical biochemists undergo a well-defined training path, operated by the Royal College of Pathologists.

7.4.1.4 European Union directives and health and safety (UK)

Troponin testing must conform to all relevant European Union (EU) directives and health and safety legislation. The Medicines and Healthcare products Regulatory Agency (MHRA) is the designated competent authority for medical devices in the UK for all EU directives and is responsible for ensuring that manufacturers and others follow the directives' provisions. The EU directive relevant to troponin testing is the Directive 98/79/EC – *In vitro* diagnostic medical devices (Anon, 1998).

The application of health and safety standards to prevent injuries and cross infections is essential to protect patients and operators. All user protocols should thus be in line with The Health & Safety at Work Act (Great Britain, 1974) and guidance issued by the Department of Health, the Health and Safety Executive and the British Medical Association on the safe handling and disposal of hazardous materials, sharps and clinical waste.

7.4.1.5 Laboratory-based troponin testing

The Medical Devices Agency (MDA) publications (Medical Devices Agency, 2002a; Medical Devices Agency, 2002b) highlight that clear SOPs and systems must be in place for a point-of-care testing service to function effectively. This principle also applies to laboratory systems. To ensure this takes place, it is recommended that a 'liaison group' be set up at each centre, with representation from all stakeholders.

The group could have responsibility for protocols that cover the whole patient pathway, and not solely the laboratory aspects. Areas that should be considered are patient issues, instructions for sampling (e.g. blood tube type), transportation of samples, result reporting, result interpretation and ready access to information e.g. by ensuring adherence to protocols at appropriate locations such as in A&E departments and through specific telephone contact points.

A system must be in place to ensure that troponin samples are transported to the laboratory as quickly as possible in a safe manner manually or to the particular hospital site by vacuum shuttle or a similar system, if this is appropriate. A procedure for reporting transport-related incidents and implementing necessary remedial action should also be in place.

The laboratory must have a method of identifying troponin requests and samples arriving at specimen reception and acting on them according to the local protocol. A follow-up procedure (e.g. contact requesting clinical staff urgently) must be built into any sample rejection rules.

IT issues should also be addressed including the development of systems that facilitate single entry of data, that allow electronic information to be transferred between wards and laboratories, and that are compatible with the laboratory and patient-based information systems.

Protocols should also be developed and their use monitored. Failure to adhere to protocols can cause knock-on effects downstream. For example, failure to provide the appropriate blood sample type causes delay as repeat samples need to be requested (Dr A Stott, Consultant in Biochemistry, Department of Clinical Chemistry, University of Liverpool, personal communication).

In conclusion, a laboratory-based service may provide better quality control and reproducibility of testing compared with a point-of-care testing service, reduce the risks to the equipment by multiple non-specialist users, improve interpretation of the results by involvement of clinical biochemists and may accommodate changes/developments in the technology more easily.

7.4.1.6 Point-of-care troponin testing

Some of the potential advantages and disadvantages of point-of-care testing are outlined Table 7-1. These do not apply to all analysers and thus potential purchases should evaluate any point-of-care service against such criteria.

Table 7-1 Advantages and disadvantages of point-of-care testing

Advantages	Disadvantages
• Convenience to clinician • Shorter turnaround times • Convenience to patient • Attractive for remote areas • Wider economic benefits e.g. reduced patient length of stay, fewer hospital admissions • Increased flexibility if out-of-hours working is precluded[a]	• Generally more expensive • Potential to over-investigate • Initial and continued training of staff • Infrequent use of analysers leading to inaccuracy • Failure of maintenance • Difficulty in interpretation of results • Increased risks from biohazards • Testing before the condition (i.e. MI) has fully evolved • Incompatibility with laboratory results

References: Scottish Office (1996), MDA (2002a), [a]Dr F Dunn, Clinical Director, Cardiology, Stobhill Hospital, personal communication, 2003.

7.4.1.6.1 Introduction of a point-of-care testing service

A point-of-care testing service can be offered as an alternative to a central laboratory service or to supplement a central laboratory service (in the absence of an all-hours laboratory service with suitable turnaround times) to meet the needs of clinical decision making for patients with ACS.

However if point-of-care testing supplements a central laboratory service, the cut-off points of the two types of services must be the same. Otherwise, such a combination should be avoided and only a point-of-care or laboratory service be provided (see Section 4.3.3.3.4.2).

The potential sites of troponin point-of-care testing include in A&E departments, medical receiving units and community hospitals.

If a point-of-care testing service is to be developed, each site should develop a business case. Some of the issues, as outlined in the MDA publication, that should be considered and addressed are:

- which group of patients is this service is for
- how will point-of-care testing enable more rapid, effective diagnosis or treatment
- the location and management of equipment and consumables
- expected workload, number of operators and training needs
- required changes to protocols in laboratories and at point-of-care testing sites
- the need to ensure that clinicians have a troponin testing resource that provides consistent results
- capital and variable costs, to include ongoing training, laboratory support and quality assurance and quality control
- quantification of anticipated benefits from reduced length of stay, fewer admissions and less over-prescribing of drugs.

The business case should also address how point-of-care testing services will link with laboratory information systems and meet the requirements in Section 7.4.1.5.

7.4.1.6.2 Management and organisation of a point-of-care testing service

As with a laboratory-based service, a successful point-of-care testing service requires effective management and organisation of multidisciplinary staff. A point-of-care testing service should follow the MHRA guidance (Medical Devices Agency, 2002a). This section describes these stringent requirements.

The MHRA recommends that the local hospital laboratory should be involved in the selection of point-of-care testing analysers and management of point-of-care testing. Point-of-care testing must meet MHRA requirements on lines of accountability and responsibility. The MHRA strongly recommends the identification of an appropriate senior professional who is given the authority and responsibility for the point-of-care testing service (Medical Devices Agency, 2002a). A 'point-of-care testing coordinator' would be responsible for the correct use of the instruments as well as the results generated. Managers of point-of-care testing are also likely to have responsibility for clinical governance and the medico-legal implications of an erroneous result. The MHRA also advise that lines of accountability must be clear and should be written into local policies and procedures.

Experience of introducing a chest pain service using point-of-care testing at the RAH Paisley has highlighted the need to have a person responsible and accountable for coordinating the service and ensuring protocols are adhered to (M Morgan, Business Manager, RAH, Paisley, personal communication, 2003). In addition, the person is likely to have a major educational role, ensuring that all staff are aware of changes in practice required to deliver the benefits of the service.

The MHRA also recommends that a multidisciplinary point-of-care testing committee oversees point-of-care testing within the hospital. The aim of the committee is:

- to ensure audit and assessment systems are in place
- to determine if the clinical benefits justify use of point-of-care testing
- to ensure training and certification of staff using point-of-care testing
- to ensure that SOPs are in place
- to ensure compliance with maintenance procedures
- to maintain systems of accurate record keeping (including patient records)
- to ensure internal quality control and external quality assurance schemes are engaged.

The point-of-care testing committee could also be responsible for clinical governance issues. The committee should represent all stakeholders, including representatives from primary care if the service extends to the community.

Finally, the experience described by Desplanques (2003) illustrates the problems that can be caused by failure to adhere to these stringent guidelines. She noted that approximately 90% of the failures experienced with a Stratus CS® analyser were caused by failure to adhere to the local hospital policy, and that more rigorous enforcement of this policy markedly improves the apparent reliability of this analyser. This improvement in performance against guidelines was also facilitated by interfacing the Stratus® CS analyser with the laboratory information system.

7.4.2 Initiating and developing a troponin testing service

Both types of troponin testing services have distinct advantages but the decision about the type of service offered requires laboratory, clinical and managerial staff to work collaboratively in defining local needs and requirements. The optimum organisation of a troponin testing service must be decided locally but should be informed by the economic model. There are likely to be differing needs within a hospital and these should be recognised. For example, an A&E department may require turnaround times of less than one hour to identify low- and high-risk patients. In these circumstances, a laboratory-based service may be able to provide a test result within this timeframe. If this is not feasible, a point-of-care testing service should perhaps be considered.

Developing a laboratory-based service with extended or flexible working hours will require human resource (and funding) issues to be addressed. Innovative ways of working should be explored, such as laboratories carrying out early morning troponin testing (i.e. at 07:00 hours) on samples taken during the night in order to provide results for decision making at the morning ward round. One advantage of this system is better communication and organisation of the patient journey and possible reduction in length of hospital stay. The provision of a troponin testing service at the weekend is

also essential and is supported by conclusions from the economic model (see Section 5.4.4) which recommends implementing a weekend batch run service as a minimum provided there is clinical decision making available.

A troponin testing service should also develop locally agreed protocols on the use and interpretation of troponin. GPs or nursing staff, who require troponin to diagnose patients with suspected ACS either within or outside community hospitals, should have access to troponin testing but only in the context of locally agreed protocols with cardiologists and laboratory staff in DGHs and/or tertiary care centres. This is reinforced by consultation responses and by the experience of the use of troponin testing by GPs in the Luton and Dunstaple area. A major concern is that patients with a positive troponin test cannot always be contacted immediately (Dr D Housley, Principal Biochemist, Department of Chemical Pathology, Luton & Dunstable Hospital NHS Trust, personal communication, June 2003). The alternative of referring patients with suspected ACS to hospital eliminates this risk.

One of the challenges of initiating and developing a troponin service is persuading decision makers to look at costs across the patient pathway and not just within departmental budgets (Dr S Pringle, Consultant Cardiologist, Ninewells Hospital, Dundee, personal communication, October 2003). One conclusion from the literature review of the cost effectiveness of troponin testing (Section 5.2.2) is that any appraisal of the use of troponins should look at changes in the cost of a patient episode of care, not just the impact of a change in policy on individual departmental cash budgets. As Owen (2001) explained, the economic benefit from using troponin tests is partly from savings in the laboratory from reducing the use of other cardiac enzymes, but the biggest saving is in bed days due to earlier discharge. No real cash savings accrue because beds are occupied by new admissions but the cost per patient episode is materially reduced and higher demands on the service are accommodated without building new capacity. Considering cost per patient episode, and not simply departmental budgetary costs, should improve decision making and facilitate greater transparency of cost drivers.

7.5 Resource implications for NHSScotland

This HTA makes several recommendations for effective service delivery (see Section 8.5). Facilitating these recommendations is likely to require additional funding within NHSScotland.

The implementation of the HTA recommendations will give rise to additional costs in community hospitals (Section 7.5.1) and DGHs and tertiary centres (Section 7.5.2). This section outlines the underlying assumptions and estimates the additional costs of the recommendations that are appropriate to each setting.

Other additional costs for hospitals could arise following the introduction of evidence-based eligibility criteria to inform decisions on the use of angiography and revascularisation procedures, such as transferring more

high-risk patients to tertiary centres and treating them there. The scope of the HTA excluded any estimation of the downstream effects of introducing such criteria (see Section 8.1.4).

7.5.1 Additional costs for community hospitals to implement the HTA recommendations

Section 7.3.1 outlines that in community hospitals, troponin testing would only be used for borderline cases or for patients who present late and a decision on hospitalisation is unclear, with all other patients being diagnosed from ECG. Therefore, it is recommended that troponin testing should be available in community hospitals receiving patients with symptoms suggestive of ACS and be performed in accordance with agreed protocols.

Patients with a negative troponin test result and no clinical or ECG risk markers and who have no further chest pain should receive a stress test to complete the assessment and allow discharge.

The main costs to implement this recommendation are:

- providing and operating a quality-assured troponin testing service
- training the test operators (probably practice nurses) and clinicians
- developing, implementing and monitoring relevant protocols
- changing discharge procedures to include a stress test.

7.5.1.1 Assumptions

Responses to the community hospital survey (Section 7.2.2.3) were used to estimate the number of community hospitals in Scotland that manage patients with ACS and would require a troponin testing service. The responses showed that just over a third of these hospitals do not treat patients with ACS. Therefore, of the 81 community hospitals in Scotland, it was assumed that 50 community hospitals would manage patients with ACS. The survey responses also showed that in Autumn 2002, four community hospitals operated a point-of-care troponin testing service and one site had a turnaround time of one hour. So of the 50 sites, five sites have an adequate service (that is, it was assumed to have a turnaround time of less than two hours). Therefore, the budgetary analysis assumed 45 additional community hospitals would require a troponin testing service.

To verify the robustness of this estimate, data on the number of admissions for diagnoses of AMI and angina for each community hospital in Scotland from April 2001 to March 2003 was provided by ISD. The data indicate that the number of community hospitals requiring a troponin testing service is not likely to exceed 45. The budget assessment has adopted this figure, recognising that it is a conservative estimate.

The survey responses also showed that the average number of tests requested ranges from zero to three per month in 14 community hospitals for which

such data were available. The budgetary analysis assumed the number of patients receiving a troponin test would rise to three per week (Dr Greig, personal communication, July 2003). This would equate to 156 patients being tested for troponin annually at each hospital. A troponin test would also be performed for quality assurance purposes after 10 tests, so 172 troponin point-of-care tests would be conducted annually at each community hospital.

The rationale for costing a point-of-care service rather than a laboratory service was based on the assumption that these hospitals would not have on-site laboratories or access to laboratories that can process samples and deliver test results in accordance with clinical need. Clinical need was assumed to require troponin test results within a two-hour turnaround time.

Costings were prepared for a troponin T point-of-care service only using the TROPT *Quantitative*® analyser, based on the conclusions of Section 4.3. The choice of a troponin T analyser rather than troponin I analyser reflects the relative suitability of the assays for use at sites with a low number of tests (see Table 5-2). However, the decision on which troponin assay to use should also consider aspects such as consistency with assays used in the troponin testing service in a receiving DGH or tertiary centre and possible requirements for other tests from a point-of-care analyser. Moreover, any costings are for guidance only. Manufacturers have indicated that discounts are available for multiple placements of analysers.

The point-of-care equipment costs and cost per test were obtained from the manufacturer's price list (for this analysis, it was a Roche price list) and assumed each site would contract separately with the manufacturer. If group purchasing can be arranged, then the capital and operating costs would be lower than indicated. For example, the manufacturer has a policy that if a customer commits to purchasing 300 troponin tests per year, the equipment (costing £1798) would be placed free on loan.

Estimates of training needs, staff time to develop protocols and to conduct tests were made following discussions with a cardiac nurse and the Chair of the Association of Community Hospitals (T Gaffney, personal communication February 2003 and Dr Greig, personal communication, July 2003 respectively).

The £25 cost of stress test comprises £22 for two staff for 30 minutes (each at a cost of £22 per hour (Netten *et al.*, 2002)), a further £1 for maintenance and equipment costs and £2 for administration costs.

Sensitivity analyses assumed 25 community hospitals would manage patients with suspected ACS and thus would require a troponin testing service and that only one patient would be tested per week.

7.5.1.2 Estimated additional costs

The estimated additional costs to implement troponin testing in community hospitals are presented in Table 7-2.

Table 7-2 Additional costs for community hospitals

Description of service	Unit cost and source	Total cost per site (£)	Total cost for 45 sites (£)
Set-up costs			
Equipment (TROPT *Quantitative®*)	£1798 including VAT from the Roche price list	1798	80 899
Training for 4 GPs and 4 practice nurses for 3.5 hours	14 GP hours at £60.74 per hour + 14 nurse hours at £15.78 per hour + £250 for room, travel and sustenance, and trainer (source of hourly rate: PSSRU)	1324	59 602
Develop protocols	For first protocol: 2 clinicians for 20 hours each @ £60.74 per hour + 20% (of 40 hours) for peer review + £85 for administration: 16 other Health Boards revise for local needs at 50% of cost	1588	27 000
Total set-up costs		**4710**	**167 501**
Steady-state costs			
Equipment (TROPT *Quantitative®*)	Annual capital charge at 3.5% cost of capital (includes depreciation)	385	17 325
172 tests per annum (includes quality-assured tests)	Cost per box of 10 is £107 from the Roche price list	1836	82 625
Sample collection, conduct tests, record results and refresher training	10 minutes per test for practice nurse at £15.78 per hour + £50 per annum	500	22 514
Steady-state annual operating costs	**Annuity + troponin testing + nurse costs**	**2721**	**122 464**

Note: Equipment costs are rounded to the nearest pound for presentational purposes.

In summary, the initial set-up costs of buying the equipment, training staff and developing protocols were estimated to be £4710 per hospital, which is equivalent to £167 501 for 45 hospitals. Annual operating costs per hospital, to include an annualised cost of capital, were estimated to be £2721 for the troponin service, equivalent to a cost per patient of £17.44.

At present, few community hospitals operate discharge protocols that require a patient to undertake a stress test as part of the discharge procedure. Implementing this recommendation is estimated to increase costs by £25 per patient discharged under the revised protocol.

Not all of these costs are new monies. For example, if taking the troponin test displaces other nursing activities, then no additional costs for nursing will be incurred in hospitals. New cash costs per site could be limited to the initial cost of buying the equipment (£1798) and the cost of the tests (£1836).

The DGH or tertiary centres may make savings by not conducting further troponin tests on patients who have already tested positive for troponin, thereby reducing the costs to NHSScotland. Other savings for community hospitals may be obtained from stopping the use of other biochemical

markers (except CK for early re-infarction). The survey identified that the most widely available and used biochemical markers in community hospitals are CK, aspartate aminotransferase and lactate dehydrogenase. These tests cost 10 pence each, with CK-MB costing 90 pence per test (Dr U Kulkarni, Specialist Registrar, Grampian University Hospitals, personal communication, September 2003). Thus, the annual savings for many community hospitals from replacing these biomarkers with troponin would be estimated at £15 per site. To reduce complexity, these savings were excluded from the analysis.

The benefits of troponin testing arise from reducing inappropriate patient transfers to DGHs or tertiary centres and enabling safe but earlier discharge of low-risk patients. ISD advised that, in the year ending 31 March 2001, the cost per inpatient stay for a patient diagnosed with UA was £1360, which is equivalent to £1450 in 2003 prices. Each patient had an average length of stay of 5.3 days, giving a cost of £275 per inpatient day. This excludes the average cost of transfer by ambulance which is a further £25 per patient. (ISD, personal communication, October 2002). If using troponin testing would enable clinicians in each community hospital to diagnose and discharge safely only four patients each year, who would otherwise be transferred to a receiving DGH or tertiary centre for an average length of stay of three days, then the service would be cost effective.

7.5.1.3 Sensitivity tests

A key variable for sensitivity testing is the number of community hospitals likely to risk stratify patients with symptoms suggestive of ACS but in whom there is diagnostic uncertainty. Assuming only 25 rather than 45 additional sites were to adopt troponin tests, then the additional annual operating costs (including nurse time) would fall from £122 464 to £68 036, with the associated set-up costs being £116 854.

Another variable for sensitivity testing is the number of troponin tests performed per week. If the number of point-of-care tests was to fall from three to one per week, the annual costs of the troponin testing service to the community hospitals would fall by £1225 for the troponin tests and by £300 for staff time to perform the additional tests.

7.5.2 Additional costs for DGHs and tertiary centres

Currently, there are 32 DGHs and tertiary centres managing patients with AMI. All DGHs and tertiary centres have access to a troponin testing service but there is considerable variation in groups of patients receiving a troponin test, the timing of testing and turnaround times. Implementing the HTA recommendations could impose additional costs on some of these hospitals, with the main cost drivers being:

1. troponin measured 12 hours after admission in patients considered to have a diagnosis of STEMI

2. a) troponin measured on admission and 12 hours later (if the first test is negative) in patients with suspected ACS in whom there is clinical diagnostic uncertainty due to the absence of high-risk risk markers

   b) troponin measured 12 hours after onset of symptoms in patients with suspected ACS, with turnaround times in accordance with clinical need

3. revising local protocols and guidelines, and updating information used in MCNs.

There may also be additional costs for some hospitals arising from bringing forward the timing of stress tests from outpatient clinics to the discharge process.

It was assumed that some hospitals would already provide a troponin testing service that already fulfils many of these recommendations. The budget impact assessment adopted a conservative approach and assumed that all of the above recommendations would require funding. This provides the upper limit of additional costs estimated to be incurred as a result of implementing the recommendations.

This section estimates the potential costs of implementing each change.

7.5.2.1 Troponin testing 12 hours after admission in patients with STEMI

7.5.2.1.1 Assumptions

The costs of the troponin tests in patients with STEMI were calculated using the Scottish Executive Health Department (SEHD) estimate of 10 000 patients presenting with persistent ST elevation and raised cardiac enzymes to Scottish hospitals each year (see Section 3.1.3) and a cost per laboratory troponin I or T test of £4 plus VAT at 17.5% (see Table 5-2). This cost includes £1 per test for additional laboratory staff and time for transportation (see Appendix 13). Additional nursing time to administer the test would be required and this was assumed to be five minutes per test at an average cost of £21.91 per hour.

This analysis was based on laboratory troponin testing rather than point-of-care testing because the troponin test result and the subsequent decision regarding patient management are not time critical.

In addition, each site should update its protocols for this test. This was assumed to cost £500 per site.

7.5.2.2 Estimated additional costs

The estimated costs of undertaking troponin tests to confirm the diagnosis of AMI for all such patients in Scotland are presented in Table 7-3.

Table 7-3 Annual costs of measuring troponin 12 hours after admission in patients with STEMI

Description of service	Unit cost and source	Total cost (£)
Additional troponin test for STEMIs	10 000 patients with STEMI; test cost £4 plus VAT	47 000
Additional nurse time	5 minutes per test at £21.91per hour	18 260
Subtotal		**65 260**

In summary, the cost of performing a troponin test 12 hours after admission in all patients with STEMI was estimated to be £65 260 per annum. As noted in Section 7.5.1.2, not all of this sum is necessarily a new cash requirement. For example, £1 of the £4 cost of the test, equivalent to £11 750, is an allowance for the additional cost of transporting and processing the extra tests. Some sites may be able to accommodate the higher volume of tests at no additional cost.

In addition, if all sites are required to update their protocols, there would be one-off set-up costs of £16 000.

7.5.2.3 Sensitivity tests

If the cost of a laboratory test was to decrease or increase by £1 per test from the base-line cost of £4 per test (£3 and £5 respectively), then the cost of conducting troponin tests in STEMI patients would alter by £11 750, to £53 510 and £77 010 respectively.

If the number of tests required was to decrease or increase by 5%, the costs would alter by £3260 (18%), to £62 000 and £68 520 respectively.

7.5.2.4 Troponin testing on admission and 12 hours later in patients with symptoms suggestive of ACS but in whom there is diagnostic uncertainty

7.5.2.4.1 Assumptions

The budgetary estimate for this recommendation assumed that troponin would be measured by point-of-care testing and all settings would find that it is cost effective to adopt troponin point-of-care tests on admission and 12 hours later (a two-test strategy). The rationale for adopting point-of-care testing is set out in Section 4.3.1. Short turnaround times may allow therapy to commence as soon as possible in high-risk patients. The resultant cost estimate would thus be a maximum value. Hospitals with access to a laboratory troponin testing service that provides adequate turnaround times for test results should be able to provide a cheaper troponin testing service than the one costed in this analysis.

The additional number of troponin point-of-care tests performed under the two-test strategy was estimated using a forecast of 1146 for the annual number of tests conducted at the RAH Paisley which uses such a protocol (T Gaffney, personal communication, September 2003). This baseline was increased by the ratio of number of MIs in Scotland and divided by the number of MIs at the RAH (Clinical Standards Board for Scotland, 2001a).

This calculation suggested an additional 25 600 tests would be conducted each year in DGHs and tertiary centres across Scotland.

Separate costs are provided for troponin T and I point-of-care assays using the manufacturers' price lists including VAT, and applying the appropriate volume discount for each site. It was assumed that hospitals would use a reagent rental purchase option rather than a capital purchase option. As highlighted in Section 7.5.1.1, manufacturers have indicated that discounts are available for multiple placements of analysers.

Additional nurse costs of 10 minutes per point-of-care test were assumed. An allowance of £5000 per site per annum was made to cover functions such as to set up and to administer the point-of-care service, to develop and monitor relevant protocols (including protocols for transfer between hospitals) and to quality assure the test results.

It was also assumed that in the absence of adopting a point-of-care test protocol, each patient would otherwise receive a laboratory test. The point-of-care test option thus saves the cost of one test per patient at £4 and the cost of administration which was assumed to be 5 minutes of a nurse's time. This sought to capture current practice, with most hospitals in Scotland performing a troponin test on patients with ACS. Where hospitals do not currently provide such a test, then introducing a two-test strategy would be more cost effective than indicated here.

The analysis also assumed that no additional MIs would be detected as a result of implementing this recommendation. This assumed that the introduction of a troponin test on admission would bring forward the diagnostic timescale but not alter the existing diagnosis.

7.5.2.4.2 Estimated costs

The estimated additional costs of measuring troponin on admission and 12 hours later by a point-of-care testing service in patients with suspected ACS in whom there is diagnostic uncertainty at all DGHs and tertiary centres are presented in Table 7-4.

Table 7-4 Annual costs of implementing a troponin test on admission and 12 hours later by point-of-care testing in patients with suspected ACS but in whom there is diagnostic uncertainty

Description of service	Unit cost and source	Total cost (£)
Troponin point-of-care tests on admission and at 12 hours	25 600 troponin I tests	671 590
	25 600 troponin T tests	305 146
Additional nurse time	10 minutes per test at £21.91 per hour	93 473
Other variable costs	£5000 per site for 31 sites per annum	155 000
Savings from avoiding laboratory test	25 600/2 tests at £4 +VAT & nurse time	–83 523
Subtotal: Net troponin I additional costs		**836 540**
Subtotal: Net troponin T additional cost		**470 097**

The additional net costs of measuring troponin using a two-stage testing strategy by point-of-care testing were estimated to range from £0.47 to £0.84 million, depending on the type of troponin assay used. Assuming the savings were from correct placement decisions such that high-risk patients (identified by the troponin test) are moved directly to the appropriate ward rather than being managed for 12 hours in a general ward, then each correct placement decision was estimated to save £125 (Section 5.4.2.3.2). For a two-stage troponin testing strategy by a point-of-care service to be cost effective at a national level, then the number of 'saved 12 hours' necessary would range from 3760 to 6692 days (being £0.47 million and £0.84 million divided by £125). The latter is less than 2% of the inpatient days incurred by patients with UA, AMI and chronic IHD unspecified during the year ended 31 March 2001 (ISD, personal communication, October 2002).

7.5.2.4.3 Sensitivity analyses

If the number of point-of-care tests was to rise by 20% to 30 720 from the baseline of 25 600, then the net additional costs would rise and range from £0.53 to £0.97 million compared with the base case range of £0.47 to £0.84 million. If the number of tests was to fall by 20% to 20 840, then the cost range would be £0.41 to £0.70 million. Changes of 20% in the cost of tests would give similar high- and low-cost ranges.

7.5.2.5 Troponin testing with turnaround times in accordance with clinical need

Section 7.5.2.4 estimated the cost of providing troponin testing by two-test strategy using point-of-care testing, assuming it is cost effective to do so. If a troponin test is performed by a point-of-care testing service, the turnaround time is assumed to meet clinical need. However not all sites may find it clinically and cost effective to provide a point-of-care testing service. For such sites, it is recommended that troponin is measured 12 hours after the onset of symptoms in patients with suspected ACS and that the turnaround time for delivery of results should meet clinical need. This section estimates the cost of providing point-of-care troponin testing services in Scotland with turnaround times that meet clinical need.

7.5.2.5.1 Assumptions

The starting point of this analysis was to estimate the number of sites where current turnaround times are longer than those that meet clinical need. A key assumption in this section was that clinical need would require a seven days per week troponin testing service, with a turnaround time of within two hours. This is informed by the conclusions of economic modelling (Section 5.4.4).

This key assumption is also consistent with clinical practice, whereby troponin results are used, in conjunction with clinical and ECG risk markers, to inform admission and discharge decisions.

Responses to the laboratory survey and to a separate telephone follow up were used to identify the sites where turnaround times exceeded two hours. These data, combined with data on the number of MIs per hospital (Clinical Standards Board for Scotland, 2001b), indicate that 50% of patients with MIs in DGH or tertiary centres are managed in hospitals that operate a Monday-to-Friday troponin testing service with a batch service available at weekends. About 40% have access to a seven days per week service operating at least 09:00 to 16:00 hours daily, while the remaining 10% have a Monday-to-Friday only service. Thus, 40% of patients are managed in hospitals with a troponin service that was assumed to meet clinical need and 60% would benefit from an enhanced service.

The methodology adopted to cost the changes in troponin testing services by providing a two-hour turnaround time assumed the service would be delivered by point-of-care testing. It was assumed that all laboratories would currently offer a troponin testing service that provides test results in shortest turnaround times possible, given available resources. Some laboratories may be able to improve turnaround times by a cheaper solution than introducing point-of-care testing. This assumption is thus likely to over-estimate the additional costs of improving the service.

Moreover, it is not possible to provide informative costs based on extending the operating hours for laboratories from a Monday-to-Friday service to a seven-day service. This is because such a major change in working practices would not be initiated to improve access solely to troponin but it would rather be a strategic decision to provide improved laboratory access to all tests.

As Section 7.4.2 concluded, the decision on the appropriate service depends on hospital specific factors such as hospital layout and laboratory working practices. Since each hospital has its own unique factors, a more generic approach was used. This estimated the marginal costs of improving the service by adding the marginal cost per troponin test of adopting point-of-care testing rather than laboratory testing, to the additional nursing timing in administering the same, and multiplying the total by the relevant number of patients.

The additional costs of purchasing point-of-care tests rather than laboratory tests were assumed to be £6 for troponin I tests and £4 for troponin T tests. These costs are based on information from the manufacturers and include relevant discounts. The additional nursing costs for performing point-of-care troponin tests rather than drawing blood, sending a sample to a laboratory and entering the results on to the patient record were assumed to be five minutes per test.

The relevant patient base was calculated assuming 20%, 25% and 30% of all medical admissions are patients with cardiac-related symptoms and that all patients would receive a troponin test. The ranges were proposed by TSG members. The number of medical admissions to hospitals (excluding

maternity and community hospitals) was 226 640 in the year ended 31 March 2002 (Common Services Agency (CSA) Information and Statistics Division (ISD), 2000). Assuming 60% of these cardiac patients do not receive troponin results within two hours, then the additional number of point-of-care tests required would range from 27 200 to 40 800.

In addition, some sites may need to update their protocols at an assumed cost of £500 per site.

7.5.2.5.2 Estimated additional costs

Table 7-5 summarises the additional costs of measuring troponin 12 hours after the onset of symptoms in the estimated 60% of patients with suspected ACS for whom clinicians do not currently receive troponin test results within a two-hour turnaround time.

Table 7-5 Annual additional marginal cost of adopting point-of-care tests for sites where turnaround times exceed two hours

Percentage (%) of medical admissions of cardiac origin	Number of medical admissions[a] of cardiac origin	Additional point-of-care tests (60%) required	Marginal cost (£) of point-of-care tests (test + nurse time): Troponin I	Marginal cost (£) of point-of-care tests (test + nurse time): Troponin T
20	45 330	27 200	212 840	158 450
25	56 660	34 000	266 050	198 060
30	67 990	40 800	319 260	237 670

[a] The number of medical admissions to hospitals (excluding maternity and community hospitals) in the year ended 31 March 2002 = 226 640

In summary, if the number of medical admissions with undiagnosed chest pain is 56 660 (assuming the base case of 25%), of whom 34 000 currently wait more than two hours for a troponin test result, then introducing point-of-care testing to reduce turnaround times would increase costs by between £0.20 and £0.27 million, depending on the troponin assay chosen.

In addition, updating protocols at 60% of the hospitals would incur a one-of-set-up cost of £9500.

7.5.2.5.3 Sensitivity tests

If the number of cardiac-related medical admissions was 20% or 30% rather than the base case rate of 25%, then the cost of reducing turnaround times would range from £0.16 to £0.21 million and £0.24 to £0.32 million respectively, depending on troponin assay purchased. No other sensitivity tests were conducted for this variable.

7.5.2.6 Cost to undertake additional stress tests in low-risk patients

One of the HTA recommendations is that a stress test should be undertaken in low-risk patients with symptoms suggestive of ACS in order to complete the assessment and to inform a decision on whether or not to discharge. Hospital discharge protocols vary, with some Scottish hospitals (e.g. Lothian University

Hospitals Trusts and RAH) requiring a stress test prior to discharge or on the next working day in low-risk patients with negative troponin result and other hospitals (e.g. North Glasgow University Hospitals NHS Trust) requiring a stress test after discharge at an outpatient follow-up review. Therefore, providing a stress test at discharge is normal practice in some hospitals so costs will not change. Elsewhere the number of stress tests may not increase but the timing of the tests will be brought forward from an outpatient clinic to the discharge process. There are no data on the number of low-risk patients attending as cardiology outpatients each year, or the likely costs involved in providing tests at the discharge process rather than later. Therefore, it is not possible to cost this recommendation.

7.5.2.7 Patient information leaflets

Assuming that 25% of medical admissions are of cardiac origin (see Table 7-5), that each patient and their carer are provided with relevant patient information leaflets (see Section 6.6.5) and that this patient group can be easily targeted, then 120 000 patients leaflets would be required. Allowing for some interest outside this tightly defined audience indicated there could be demand for 200 000 leaflets a year at a cost of 10 pence each, giving a total cost of £20 000.

7.5.2.8 Summary of budget impact assessment

Table 7-6 summarises the additional annual costs of implementing the HTA recommendations.

Table 7-6 Additional annual costs to NHSScotland of implementing the HTA recommendations

	Costs (£)	
Community hospitals[a,b] (for 45 sites)		
Set-up costs	167 501	
Steady-state annual operating costs	122 464	
Total cost	**289 965**	
DGH and tertiary centres (for 31 sites)		
Option 1[c]	65 260	
Option 2a[d]		
If all use troponin I	836 540	
If all use troponin T	470 097	
Option 2b[e]		
If all use troponin I	266 050	
If all use troponin T	198 060	
Patient information leaflets[f]	20 000	
Total cost:	**If adopt option 2a**	**If adopt option 2b**
Troponin I option	**921 800**	**351 310**
Troponin T option	**555 357**	**283 320**

[a] Note costs exclude stress test assuming this test is conducted at DGH prior to discharge.
[b] Troponin testing measured by point-of-care testing (troponin T) in patients with symptoms suggestive of ACS but in whom there is diagnostic uncertainty
[c] Troponin measured 12 hours after admission by laboratory testing in patients considered to have a diagnosis of STEMI
[d] Troponin measured on admission and 12 hours later by point-of-care testing in patients with suspected ACS but in whom there is clinical diagnostic uncertainty due to the absence of high-risk markers
[e] Troponin measured 12 hours after onset of symptoms by point-of-care testing in patients with suspected ACS, with turnaround times to meet clinical need (i.e. less than two hours)
[f] Received by patients attending DGH and tertiary centres only

In summary, the costs enabling 45 community hospitals to set up a troponin testing service (which includes purchasing equipment, training staff and developing protocols) are estimated to be £0.17 million, with the annual operating costs estimated at £0.12 million. The estimate of community hospitals requiring a troponin testing is not likely to exceed 45 and this figure is thus likely to over-estimate the set-up and operating costs associated with this recommendation.

Annual costs of between £0.28 and £0.35 million would enable all DGH and tertiary centres to perform quality-assured troponin testing with a maximum turnaround time of two hours in both patients with non-ST elevation ACS and patients with STEMI within approved protocols and to provide patient information leaflets.

In addition, DGHs and tertiary centres may incur one-off set-up costs of £16 000 to alter existing protocols to include testing for troponin in STEMI patients and some may incur a further £9500 to alter protocols for managing patients with suspected ACS.

Adapting the service to measure troponin by a two-stage testing strategy (i.e. on admission and 12 hours later) by point-of-care testing in patients with suspected ACS but in whom there is diagnostic uncertainty would increase the annual costs to between £0.47 and £0.84 million, depending on whether sites have troponin I or troponin T assays.

Substantial reductions in these costs could be expected if sites undertaking troponin testing are able to contract with manufacturers on a Health Board, regional or national level, in order to increase the level of discounts available.

These costs assumed that tests would only be performed where there is clinical need and repeat testing would not be carried out other than with the test on admission. Unnecessary testing would add to these costs and it is essential that test use be monitored.

8 Discussion and conclusions

8.1 Discussion of principal findings

8.1.1 Scope of HTA

This HTA evaluates the issues of clinical effectiveness, cost effectiveness, patients' needs and preferences, and organisational issues that pertain to the organisation of an effective and efficient troponin testing service. The focus of this HTA is outlined in Section 3.6.

8.1.2 Discussion of four HTA components

8.1.2.1 Clinical effectiveness

Troponins have near absolute myocardial tissue specificity as well as high sensitivity for myocardial necrosis and are therefore superior to both CK and CK-MB. As CK has superseded aspartate aminotransferase and lactate dehydrogenase, troponins are therefore superior to these markers. However, CK remains necessary for assessing early re-infarction because it has a short half-life, unlike troponin whose levels remain elevated for at least 96 hours after the original infarct.

Clinical evidence suggests that cardiac troponins are maximally sensitive for the period of 12 to 72 hours after the onset of symptoms. Therefore, measuring cardiac troponin to rule out myocardial damage is only effective at least 12 hours after the onset of symptoms.

Therefore, this HTA recommends that troponin should be measured 12 hours after onset of symptoms in patients with suspected and diagnosed in patients with non-ST elevation ACS. However, it is often difficult to establish when symptoms started, therefore an alternative and appropriate reference point for the timing of a troponin measurement is on admission to hospital. Admission is an appropriate surrogate because of its administrative convenience (that is, it is timepoint that is reliable and is recorded consistently in patient records). This was the consensus of the Topic Specific Group.

Troponin is predictive of the short- and long-term risk of adverse cardiac outcomes (i.e. death or non-fatal MI) in both ST elevation and non-ST elevation ACS. Raised troponin levels on admission are also predictive of an increased risk of mortality in patients with STEMI and patients who present clinically with MI and new left bundle branch block. However, there is no evidence to suggest that any additional therapy is able to reduce this increased risk of mortality in such patients.

A patient with non-elevated troponin levels is not necessarily at low-immediate risk of adverse coronary outcomes. Additionally, since rises in troponin are specific for myocyte damage rather than for ischaemia, raised troponin can occur in other conditions such as heart failure, myocarditis and traumatic injury.

Risk markers such as ECG changes, recurrent chest pain, age and pre-existing cardiac risk factors are predictive of outcome independently of troponin. Therefore, troponin testing is most effectively used in conjunction with clinical and ECG risk markers to provide information for the assessment and management of patients with ACS.

There is some evidence to suggest that troponin testing on admission to hospital identifies approximately 50% of patients who will have a positive troponin result 12 hours later (RAH data, (Christenson, 2001)). A positive troponin test at admission in patients with symptoms suggestive of ACS but who have no high-risk clinical or ECG markers can provide valuable information as part of the continuing risk-assessment process and may alter the management strategy. Clinical opinion is that an early decision regarding the high-risk status of a patient may improve their prognosis by allowing them to be treated and maintained in an appropriate ward, and potentially allowing early 'queuing' for catheterisation facilities and transport. The size of any benefits will depend on the ability of hospitals to manage patients appropriately.

Troponin testing on admission provides additional diagnostic information in patients with symptoms suggestive of AMI who would benefit from reperfusion therapy but in whom there is diagnostic uncertainty because of an indeterminate ECG. There is evidence that the presence of confounding ECG changes, such as left bundle branch block, is a strong predictor of delayed thrombolysis, mainly due to diagnostic uncertainty (Berger *et al.*, 2000), which may result in poor survival. Based on this evidence, clinicians are of the opinion that the availability of a troponin test with a short turnaround time on admission may reduce the uncertainty associated with left bundle branch block sufficiently to allow earlier treatment of patients who may benefit from thrombolysis.

Finally, there is evidence to suggest that a small proportion (3%) of patients receive an inappropriate diagnosis of an AMI as a result of inaccuracy in diagnostic tools (Canepa-Anson *et al.*, 1998). Therefore, troponin testing can contribute to the confirmation of a diagnosis of MI in patients who have received urgent reperfusion therapy (i.e. patients with STEMI, patients presenting with symptoms suggestive of MI and with confounding ECGs such as left bundle branch block). The time of treatment in this subgroup of patients should be within 30 minutes of arrival at hospital. Therefore, admission is an appropriate reference point for measuring troponin as it is suitable on the grounds of administrative convenience and to facilitate comparisons of troponin results across hospitals.

Troponin levels are used in combination with clinical and ECG risk markers to differentiate risk status, and thereby guide therapy selection. This may be done using a formal protocol (Bertrand *et al.*, 2002) or through the use of a scoring system. One form of score system is the TIMI risk score, which has been shown to estimate prognosis (Antman *et al.*, 2000) and to identify patients who will most benefit from treatment with tirofiban (Morrow *et al.*,

2002) or with LMWH (Antman, 1996). It incorporates multiple predictors (including troponin or other biochemical marker), has been validated in several clinical trials and is simple to apply at the patient's bedside.

There is evidence that patients with non-ST elevation ACS who are at higher risk of adverse cardiac events – as predicted by the TIMI score – appear to derive greater benefit from early invasive therapy, glycoprotein IIb/IIIa inhibitors and LMWH than patients at lower risk. The evidence that individual components of the scoring system, particularly troponin alone, can be used to select patients for therapy is less conclusive. Some studies have reported that raised troponin alone may predict the benefit of early invasive therapy or glycoprotein IIb/IIIa inhibitors, but these findings have not been demonstrated in prospective studies and should be interpreted cautiously. In fact, one study (Simoons & GUSTO IV ACS Investigators, 2001) showed that troponin is not effective in predicting benefit from abciximab in the medical management of patients with non-ST elevation ACS. Furthermore, no studies have compared the predictive value of troponin level with that of combined risk scores such as the TIMI score.

Dargie (personal communication, 2003) has suggested that the TIMI scoring system could form the basis of a common Scotland-wide protocol to determine access to cardiac angiography and invasive therapy. However, any such protocol should allow scope for clinical judgement and recognise the challenges posed by the remoteness of some referring hospitals in Scotland (Wiseth *et al.*, 2002). One advantage of using a scoring system (in addition to clinical judgement) is that it facilitates audit, to assess whether equity of treatment is being achieved.

The TIMI score was developed in clinical trials, and thus it may not be optimal for the general population presenting at hospital. A scoring system based on the general population (i.e. GRACE registry data) has been published (Granger *et al.*, 2003). It is anticipated that such a scoring system may be as effective as the TIMI score in predicting the benefit of invasive therapy and glycoprotein IIb/IIIa inhibition and this system may provide a more appropriate basis for a protocol.

Any scoring system should be implemented on personal digital assistants (PDAs) or in the hospital information management system for ease of use.

Since troponin results are important for decision making in patients whose disease may be rapidly evolving, there is considerable interest in reducing turnaround times (possibly by using point-of-care analysers) and ensuring that troponin results are available to meet clinical need, which may be outside normal laboratory working hours in some settings.

It is likely that reduced turnaround times allow earlier treatment of high-risk patients. Anecdotal reports and retrospective subgroup analyses of therapy trials suggest that invasive therapy within 24 hours and glycoprotein IIb/IIIa inhibition are associated with a reduction in the incidence of recurrent angina

and non-Q wave MI. The results of a recently published abstract from an RCT (Neumann, 2003) provide some support for this, but further large studies and longer term follow up are needed to establish the impact of very urgent therapy upon morbidity and mortality.

There is evidence from one RCT (Collinson, 1999) and from observational studies (Newby *et al.*, 2001b) that early discharge may be facilitated by the use of point-of-care testing. However, no study has compared point-of-care testing with laboratory testing in a setting where troponin is used solely as the laboratory marker.

Assays are marketed for two types of cardiac specific troponin, troponin T and troponin I. There is no evidence that either is superior for the assessment of ACS, however, troponin T is more likely to be detected than troponin I in patients with chronic renal failure, possibly because it is less readily cleared by haemodialysis. Rises in either form of troponin appear to be equally predictive of mortality in such patients.

Since troponin I analysers are marketed by many manufacturers, there is substantial variability between assay results for a single troponin sample. This variability may cause clinical confusion as clinicians move between hospitals. It would be highly desirable to remove this variability by further standardisation of the assays (Christenson *et al.*, 2001). The IFCC is currently undertaking work in this area.

The ESC has stringent criteria for the precision of analysers and they recommend that, if possible, the CV should be no more than 10% at the 99th percentile of the normal population troponin distribution (Bertrand *et al.*, 2002). This is currently not the case for any of the existing analysers but should apply to all new analysers to the market. For all existing analysers, laboratories should work collaboratively with manufacturers to establish upper limits of troponin in patients without cardiac damage to form a cut-off limit that is appropriate for their patient group to assist in diagnosing acute myocardial infarction and in risk stratifying patients with non-ST elevation ACS.

Two broad types of point-of-care troponin test analyser are marketed: qualitative ('stick') readers that provide a simple raised/not raised result and quantitative analysers that provide a numerical value. None of the qualitative readers, and only two of the quantitative analysers (Stratus® CS and TROPT *Quantitative*®) are currently sensitive and accurate enough for a negative result (in association with other risk markers) to indicate low-risk status. A positive result from any of the analysers is adequate to indicate myocardial damage. Generally, laboratory analysers are more precise, more sensitive and allow a higher throughput of tests than point-of-care analysers.

A review of primary literature on different approaches to chest pain assessment in emergency settings has shown that there is no clear evidence from RCTs of a reduction in length of stay or admission rate for low-risk

patients using rapid assessment methods which incorporate tests for multiple markers.

8.1.2.2 Economic evaluation and modelling

The main conclusions from a review of economic studies are that introducing a single troponin test into an effective protocol to manage patients with ACS can improve therapy for high-risk patients, be beneficial to low-risk patients through avoidance of over-prescribing and be cost effective by facilitating the earlier discharge of low-risk patients.

These economic studies are primarily retrospective observational studies with different methodologies, study characteristics and outcomes. Therefore, they have a risk of bias and are not the higher quality of evidence provided by an RCT. However, the body of evidence shows consistent results and is directly applicable to the Scottish population such that recommendations can be made from it.

The economic benefit of a troponin test 12 hours after admission for patients considered to have a diagnosis of STEMI depends on the rate of misdiagnosis at each site. If the misdiagnosis rate is greater than 2.2%, then given the high cost of secondary prevention measures (such as cost of rehabilitation, counselling on risk factor modification and prophylactic medication), a troponin test to confirm diagnosis would be cost effective. The availability of such a test for all STEMI patients would also provide data that could be collected and used for comparisons of outcomes across hospitals. Such data could be standardised for risk and may be useful to evaluate the effectiveness of specific drugs for patient subgroups.

The cost-consequence analysis of a single troponin test measured 12 hours after admission by laboratory testing compared with a two-test strategy (measuring troponin on admission and 12 hours later, if the first test is negative) by point-of-care testing in patients with suspected ACS but in whom there is diagnostic uncertainty shows the two-test strategy has lower net costs than the single-test strategy, if the total variable costs of each point-of-care test is less than £8.40. However, only one source was found for the percentage of additional high-risk patients who were detected with raised troponin by a troponin test on admission. This limitation means it is inappropriate to generalise the conclusion to all Scottish settings. Moreover, the result cannot be applied to all hospitals because the availability of specialist beds to directly admit high-risk patients to will vary at each hospital and hospitals adopt different practices with regard to giving drugs to patients during the initial risk-assessment period. Nonetheless, the analysis provides values for the key variables that can be used in local settings to establish whether or not a two-test strategy by point-of-care testing would be cost effective.

Alternatives to this strategy include using point-of-care testing for the troponin test on admission and laboratory testing for the second troponin

test. This option would enhance the cost effectiveness of a two-test strategy and may have the additional benefit of improving the analytical accuracy of the results.[10]

The economic model is intended to be representative of epidemiology, outcomes and costs for different scenarios that reflect Scottish practice to help inform decisions on organising an efficient troponin service. The data and causal linkages between the variables have been obtained from various sources of expert opinion, primarily TSG members and manufacturers, but not from evidence emerging from systematic reviews or RCTs. Moreover, there are no probability distributions for any of the variables. These factors could be viewed as a weakness of the modelling approach. To overcome this, sensitivity analyses were conducted to measure the effect of uncertainty about the variables on the results. These clearly show that the conclusions are conditional on the level of savings facilitated by early discharge.

The economic model did also not address the potential benefits from reducing the risk of misdiagnosis as a result of implementing the HTA recommendations. This benefit could possibly be measured by observing changes in the rate of mortality for patients who attended hospital with chest pain and who were discharged as low risk in the community. However, no analysis of this endpoint is available.

None of these analyses quantify benefits from improved clinical outcomes arising from the earlier diagnosis of ACS, afforded by a troponin test on admission and shorter turnaround times. The focus has been on financial benefits only. This is primarily because no data has been found to demonstrate such benefit unequivocally. If such clinical data does emerge, then the case for a troponin test on admission and shorter turnaround times would be enhanced. The benefit from a troponin test on admission would also increase if more angiography and angioplasty facilities were available in Scotland to treat high-risk patients more effectively. Nonetheless, the earlier availability of troponin results should improve bed management.

The modelling and budget impact assessment assumed that protocols would be followed, with tests carried out only on patients with symptoms suggestive of ACS and no unnecessary tests performed. The conclusion that using troponins is cost effectiveness is thus predicated on the assumption that the test is only performed where there is clinical need and that repeat testing after a 12-hour test is not undertaken. Experience with introducing troponin at various sites, to include North Glasgow University Hospitals NHS Trust and RAH Paisley, has shown that it is essential to oversee the introduction of a new service and to monitor the use of troponin testing to avoid unnecessary testing.

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[10] Note the Roche quantitative point-of-care analyser (TROPT *Quantitative*®) has a lower precision than the corresponding laboratory troponin T system (see Section 4.3.5)

A key assumption in the analyses is that point-of-care tests have similar accuracy to laboratory tests. Section 4.3 highlights some concerns about the accuracy of many of these devices and this must be considered at the product selection stage.

8.1.2.3 Patient issues

A literature review of the needs and preferences of patients with CHD identified five key themes:

- the 'career' of the cardiac patient
- reasons for delays in presentation to health professionals
- gender and social class differences
- perceptions of health professionals and services
- the role of spouses or partners.

These themes were explored by focus group work with people who had had a troponin test. Focus group work helped to clarify the type of information patients sought on troponin testing and the need for clarity in communicating a diagnosis.

Troponin testing offers patients a more rapid and certain diagnosis of myocardial damage and possibly earlier targeted treatment or early discharge. However, the resultant changes in patient management may cause concern or anxiety among patients and carers because the care they receive differs from their expectations, which may be based on the experiences of a friend or family member who received treatment before the introduction of troponin testing. For example, some patients and carers may equate a longer stay in hospital with higher quality of care. Other patients who are considered at low risk and who may benefit from early discharge may feel concerned about leaving medical supervision and anxiety if there is still uncertainty about their diagnosis. Clear information about their diagnosis, including how it was made and follow-up care, may help to reduce anxieties and should be provided to patients and carers. As there is less time for consolidation when patients are discharged early, health professionals should check that patients and carers understand the information and feel equipped to return home.

The focus groups demonstrated the need for better and clearer communication with patients about the purpose of troponin testing and the implications of the troponin test result. Generally, people did not recall the troponin test being explained during their diagnostic assessment and were unaware of the additional certainty of heart damage that a troponin result could provide. This is despite their detailed memories of the dates and timings of the onset and development of symptoms, their movements around different parts of the hospital, the times that they received various tests and the timing of being informed that they were going to be discharged. This does not necessarily mean that they were not told that they were having a troponin test or what the results of the test were, but it highlights that information needs to be reiterated to patients. This is particularly important

because several patients felt reluctant to disturb staff (who they could see were very busy) by asking questions, despite their expressed desire for more information.

Many participants in the focus groups appeared to be confused about their ultimate diagnosis, except those who had undergone cardiac surgery. As a result, some participants were worried about their health and others were unaware of the impact that rehabilitative measures could improve their health. While some participants left hospital after their coronary episode with a clear understanding that they should return without delay if they experienced further symptoms, there were a few participants who indicated that they would in fact delay longer before seeking help if they were to experience chest pain in the future.

Diagnostic confusion may result in patient confusion if health professionals in the same hospital, and across primary care after patient discharge, use different terminology for a diagnosis of MI. This underlines the importance of a universal working definition of MI across the UK.

Troponin testing can also provide clinicians with increased certainty about a patient's diagnosis. This may assist in effective communication with patients and carers and help to address issues such as denial. Risk status should also be clearly communicated to patients. Health professionals need to provide a clear message to patients who are discharged as low risk that this status does not imply that they are free of heart disease and that they may need to make appropriate lifestyle changes.

Patients' and carers' information needs may vary but written information should be provided to reinforce the content of oral communication.

Finally, protocols for the use of troponin testing need to recognise that some people with CHD – particularly women, those in lower socio-economic groups and those with a history of heart disease – delay seeking medical assistance.

8.1.2.4 Organisational issues

Surveys of hospital laboratories, cardiologists, community hospitals and GPs undertaken by NHS Quality Improvement Scotland or TSG members highlighted the variability in access to troponin testing across Scotland. Ninety-six per cent of cardiologists who responded to the survey indicated that they have local access to troponin testing, with the majority using troponin test results for risk stratification and to alter patient management. The greatest variability in access to troponin testing was among community hospitals and in general practice, with only a minority having access. The survey results also highlighted differences in the interpretation of troponin results and variability in the reported time from receipt of a sample to reporting of results by laboratories. The variability in turnaround times affect

how useful the results are for admission and placement decisions, and for therapeutic decision making.

Both laboratory and point-of-care troponin testing present organisational challenges. The following issues should be taken into account when deciding on the type of service that is adopted:

- experience suggests that operating point-of-care testing successfully requires rigorously defined and managed clinical and laboratory protocols, with one person who is clearly responsible for overseeing compliance
- a point-of-care testing service needs to have troponin test results that are comparable with those produced by a laboratory service and be supported by laboratory staff
- implementing quality control and quality assurance procedures for point-of-care testing may require more training than laboratory-based testing, as these procedures may be less familiar to non-laboratory staff
- the ability of laboratory services to respond to clinical need may be limited by the layout of the hospital, other demands on laboratory staff and transport limitations.

Any laboratory responsible for performing troponin testing (including point-of-care testing) should attain Clinical Pathology Accreditation. All users of point-of-care testing should follow MHRA guidance. EQA schemes, such as UKNEQAS-Cardiac Markers, are important in maintaining consistent quality of both laboratory and point-of-care testing, and all sites that undertake troponin testing (including point-of-care testing) are required to join such a scheme.

The decision on the type of troponin testing service a hospital adopts will depend on local circumstances.

The benefits from using troponin tests could be optimised through a service re-design. Realising the full benefits of shorter turnaround times is likely to require the adoption of clinical protocols (possibly nurse led) that facilitate continuous decision making. It could also require the increased availability of catheterisation facilities and staff to perform necessary invasive interventions urgently.

To ensure equitable access to angiography and subsequent revascularisation procedures, it is important to have evidence-based and transparent 'eligibility criteria' for patients with ACS who are stratified as high risk. Section 8.1.2.1 discussed the possibility of adopting the TIMI scoring system for this purpose, recognising that further judgement may be needed because of extended travel times from some referral hospitals. Treating patients in accordance with such criteria may require additional resources as more patients are referred to tertiary centres. This is also likely to increase demands on related resources, such as ambulance journeys and beds in the receiving hospitals.

8.1.3 Assumptions

The assumptions used in the economic analyses are detailed in Sections 5.3.1.2, 5.3.2.2 and 5.4.2.3.1.1. A key assumption of the economic analyses is that there is no clinical advantage in treating patients with angiography, PCI or glycoprotein inhibitors within 24 hours rather than 48 hours of presentation to hospital. Moreover, it assumed delays in diagnosing patients would not affect length of stay in hospital, and that data-driven protocols would be in place and be followed. The analyses may thus understate the potential benefits of shorter turnaround times if these reduce delays in treatment and improve patient outcomes.

The cost-consequences analysis of measuring troponin 12 hours after admission in all patients diagnosed with STEMI assumed that there would be no costs from adverse events arising from giving prophylactic drugs to patients who have been misdiagnosed with AMI and that the misdiagnosis would not adversely affect patient outcomes. These assumptions are likely to be incorrect, thus the analysis may underestimate the benefits from undertaking a troponin test 12 hours after admission in patients with STEMI.

The economic model assumed that the results provided by point-of-care analysers would be essentially equivalent, for clinical purposes, to the results provided by laboratory analysers. This is a major assumption given the accuracy data presented in Section 4.3 and is important for service providers. Clinical equivalence between troponin T and I was also assumed (providing the troponin I assay has been standardised), with evidence to support this assumption in Section 4.2.

The model assumed that clinical decision-making time would be independent of turnaround time. This assumption could be relaxed. For example, if laboratory results are not acted upon for one hour after receiving the results because no decision maker is available, then in modelling terms, it would be equivalent to increasing the turnaround time by one hour.

Additionally, it was assumed that no monetary value would be placed on protecting day-care elective treatment or on the deleterious effects of having medical patients in surgical wards because of pressure on beds in medical wards.

Forecasting the costs of implementing the HTA recommendations inevitably depends on a number of assumptions. These were obtained from discussion with experts and estimates from published literature or data from clinical practice and are outlined in Section 7.5.

8.1.4 Limitations

There are deficiencies in the published clinical evidence base. No trial has directly compared treatment selection or outcome with and without

troponin. There is considerable reliance on subgroup analyses and substantial heterogeneity in the study designs and groups studied.

Additionally, some of the studies that would resolve important uncertainties have not yet been performed. For example, the only prospective investigation of the ability of troponin rises to predict the benefit of glycoprotein IIb/IIIa inhibitors used abciximab, which is not licensed in the UK for medical management in patients with non-ST elevation ACS (Simoons & GUSTO IV ACS Investigators, 2001).

However, since most of the studies of troponin testing reviewed in this HTA have involved patients with clinically confirmed ACS, there is limited direct evidence of the prognostic significance of small rises (0.03–0.05 μg/L) in troponin T in unselected chest pain patients. In peer-reviewed literature, the sensitivity limit of the point-of-care troponin T analyser is 0.05 μg/L. This problem is apparent for the troponin T point-of-care analyser because the laboratory analysers are very sensitive. Since troponin I analysers have not attained this level of sensitivity consistently, a similar problem has not yet been encountered but will occur as the sensitivity improves.

Section 4.2.3.3.5.1 explains there is evidence that any rise in troponin, including those below the 10% CV point, indicates an increased risk of adverse cardiac outcomes. However, it is not clear that the cut-offs derived from clinical trials can be used without modification in unselected chest pain patients, for example to select patients for transfer to cardiology units. Decisions on the relevant cut-off used in each hospital will also depend on the availability of staff and beds given the baseline risk of the local population. For decision making to be based on a locally derived cut-off, it requires a patient population to be reasonably homogeneous.

In contrast to laboratory analysers, there is also little published evidence on the reliability and usability of point-of-care analysers in practical health care settings.

Future generations of point-of-care analysers, especially for troponin I, may match or improve existing performance at reduced cost which would affect the model conclusions.

The HTA has not explored in detail the implications of troponin testing in a remote setting where costs of transfer to a DGH may be much higher for patients and the service (e.g. airlift may be needed for high-risk patients and therefore, accurate stratification is very important). The organisational issues relating to the appropriate setting for a troponin test on admission have also not been considered.

The model has not captured the costs or benefits of moving from an 09:00 to 17:00 hours, Monday-to-Friday service to a 24 hours per day, seven days per week or weekend laboratory service. There will undoubtedly be additional costs of extending laboratory hours (these are likely to be material in absolute

terms and give rise to human resource issues) but also benefits for many other laboratory services since such a service would not be introduced solely for troponin.

The benefit of introducing troponin tests in community hospitals has not been modelled explicitly because of a lack of data on events in these hospitals and how these may change with the introduction of troponin.

The HTA has not sought to undertake an evaluation of the impact of its recommendations on the demand for inter-hospital transfers and revascularisation procedures. This was not within the scope of the HTA.

Finally, the conclusions about the needs and preferences of patients and carers are limited to those subgroups of patients and carers who have participated in research. As a result, the specific needs of those diagnosed as low risk, carers other than spouses (e.g. significant friends or family members), carers with CHD or other conditions and those from ethnic minority groups are not known and need to be considered and investigated.

8.1.5 Uncertainties

The effects of uncertainties related to tests, costs and savings from early discharge have been explored by univariate sensitivity analyses.

The other major uncertainties relate to the clinical and patient benefits of earlier treatment. No data are currently available to resolve these issues.

8.2 Need for further research

It is recommended that audit data be routinely collected from all patients with suspected or diagnosed ACS to allow thorough evaluation of the clinical and economic value of troponin. Data should include the number, timing and results of the troponin tests and the number of low-risk patients who were discharged within 24 hours of admission. A national cardiac dataset has recently been approved by NHS Quality Improvement Scotland, and ISD is developing implementation plans. This dataset will include relevant data fields for troponin test results (Dr M Denvir, Consultant Cardiologist, Western General Hospital, personal communication, July 2003). The analysis of this dataset and other registry-based data on unselected chest pain patients may also resolve the uncertainty surrounding the prognostic impact of small troponin rises in these patients and should be pursued urgently.

The dataset may also identify organisational settings that have reduced admissions and length of stay through using troponin tests. If the dataset does not facilitate this analysis, then a separate review should be undertaken.

When the issue of standardisation of troponin I analysers has been addressed, the collection of troponin results will be invaluable to the audit process and enable comparison of troponin results across hospitals.

Updating the data collected from the surveys completed by laboratories, cardiologists and physicians in community hospitals for this HTA will enable NHS Quality Improvement Scotland to monitor compliance with the recommendations of this HTA. Analysis of this data will help to identify where changes in clinical and laboratory working practices have occurred, such as reduced turnaround times or the introduction of early morning troponin testing services.

As noted in Section 8.1.4, appraisal of published clinical evidence on troponin identified several areas where further clinical research is needed. Areas of recommended research are discussed in the following text.

Section 8.1.4 highlighted that the only prospective study on the interaction between troponin level and treatment with glycoprotein inhibitors was performed using abciximab which does not have a UK licence for use in the medical management of patients with non-ST elevation ACS. It is therefore recommended that a study using a small molecule glycoprotein inhibitor, such as tirofiban or eptifibatide which are licensed for this indication in the UK, is performed. The study should estimate the effectiveness of using a troponin test to select patients for glycoprotein IIb/IIIa inhibition.

In existing scoring systems, such as the TIMI and GRACE scores, the term 'biochemical marker' does not specifically refer to troponin but instead to any one of CK, CK-MB or troponin. As troponin is more specific and sensitive than CK or CK-MB, a study to investigate the effect of replacing 'any biochemical marker' by troponin is desirable.

There is evidence to suggest that a delay of 72 hours in PCI is associated with a worse patient outcome in patients with ACS compared with a delay of eight hours (Neumann, 2003). Currently delays in treatment of at least 72 hours are common in Scotland (ISD, 1999–2001). Together these results imply that reductions in the time from presentation to hospital to treatment are desirable. One component of the delay in treatment is the time from presentation to risk stratification (which includes a troponin test).

However, the Neumann study (2003) was a relatively small and significant differences were only seen in the relatively minor endpoint of non-Q wave MI. It is therefore desirable both to confirm this finding in a larger population and to investigate whether similar results are found in a more clinically relevant setting. An RCT should be performed to compare a protocol in which continuous clinical decision making using troponin is available with standard practice. Standard practice in some hospitals in Scotland is to monitor a patient following a coronary event for signs of deterioration in their condition and to perform urgent PCI in only those patients with clear signs of continuing ischaemia (i.e. continuing pain or breathlessness, possibly substantial ST changes). An alternative comparator for this trial would be to use a threshold for PCI, which would be based on a scoring system that included troponin. The primary outcome measurements of this trial should be the incidence of adverse cardiac events. This RCT could demonstrate whether

or not the continuous availability of troponin testing and clinical decision making allows early but safe discharge of low-risk patients and earlier interventions for high-risk patients lead to improved outcomes.

The combination of multimarker testing (including troponin) and rapid[11] methods of chest pain assessment to reduce the rate of admissions or to achieve early discharge of low-risk patients may appear attractive but the evidence base for their long-term safety is weak. An RCT comparing rapid troponin-based chest pain assessment methods using well-defined protocols with existing assessment protocols should be undertaken. The trial should assess long-term safety and use rigorous follow-up methods.

Finally, further research on registry data of unselected populations is desirable to determine the absolute risk associated with troponin rises in low-risk patients, since it may be that a higher cut-off is needed to select patients with substantial risks.

8.3 Challenges for implementation

The greatest benefit from reductions in turnaround time will accrue if patients can be treated appropriately and expeditiously. There is some evidence that access to treatment may not be uniform across Scotland. Table 8-1 summarises 1999–2001 ISD data (see Appendix 27) showing the access of emergency admissions (that is, patients with a diagnosis of angina, AMI and chronic IHD) to angiography in hospitals with and without on-site angiography facilities.

Table 8-1 Access of emergency admissions to angiography in hospitals with and without on-site facilities for angiography

	Total angina/AMI patients[a]	% of total patients undergoing angiography	Median delay from admission to angiography (days)	% of total patients undergoing PCI/CABG
Hospitals with on-site angiography facilities (n=11)	16 940			
Total		10.5	3	7.8
Range		3.2–21.8	1–8	1.6–15.9
Hospitals without on-site angiography facilities (n=33)	20 518[b]			
Total		4.6	7	4.0
Range		0.6–10.2	3–20	0.6–12.9

Source: ISD, 1999–2001 data

[a] Number of emergency admissions using ICD-10 codes (I20, I21, I24.8, I24.9 & I25.5). Emergency admissions were based on the admission type of the first episode within the continuous inpatient stay.

[b] n=35

[11] The definition of 'rapid' varied among the studies but the time for assessment ranged from 90 minutes to 9 hours after presentation to hospital.

The data show that 10.5% of patients who were emergency admissions to hospitals with on-site angiography facilities received angiography compared with 4.6% of those admitted to hospitals that were not equipped to perform angiography. Among hospitals with on-site angiography facilities, there is considerable variation in the percentage of patients undergoing angiography as indicated by the wide range of results, with two hospitals each performing more than 19% of angiographies in the total number of patients with a diagnosis of angina, AMI or chronic IHD.

The group of patients urgently admitted to hospitals with on-site angiography facilities experienced a median delay of three days, whereas the group admitted to hospitals without on-site angiography facilities experienced a median delay of seven days. The shortest delay was one day, which is recorded by two hospitals equipped with on-site angiography facilities while the longest delay reached 20 days in a hospital without on-site angiography facilities.

Moreover, patients at hospitals equipped with on-site angiography facilities were twice as likely to undergo PCI or CABG than patients at hospitals without on-site angiography facilities.

These data suggest that the treatment paradigm of early intervention for all high-risk patients, as set out in the ESC guidelines (Bertrand *et al.*, 2000), is not achieved in Scotland and that equity of access to angiography and catheterisation facilities is not uniform across Scotland. Clinical opinion also indicates that angiography facilities in Scotland are 'underdeveloped'. One of the core aims of improving a patient's journey in the NHS as set out in *Our National Health: A plan for action, a plan for change* was to 'achieve better, fairer access to services' (Scottish Executive Health Department, 2000). To maximise the potential of the HTA recommendations, barriers to implementation such the inequity of access to angiography, as outlined in Table 8-1, need to be addressed.

This problem could be addressed by the consistent use of one evidence-based protocol for risk assessment and treatment across the network of hospitals referring to one centre (for example, Bertrand *et al.* (2002)). The use of such a protocol, especially if implemented through MCNs across the primary, secondary and tertiary centres in Scotland, could contribute substantially to improving the equity and transparency of the treatment process for patients with ACS.

The consistent early angiography of all high-risk patients would increase demand for beds in hospitals equipped to perform catheterisation, require more space on catheterisation lists to be preserved for urgent cases and thus increase waiting times for elective angiography (unless there is more out-of-hours and weekend working).

Increasing the number of revascularisation procedures would increase the need for inter-hospital transfers given the current configuration of services

and may have implications for rehabilitation services. Inter-hospital transfers would need to take place efficiently i.e. rapidly and cost effectively.

To assist compliance with the protocols, a review of facilities – such as transport associated with inter-hospital transfers, beds in tertiary centres and catheterisation laboratory capacity – should be undertaken by NHS Boards and SEHD to identify where resources are insufficient.

Facilitating early discharge may require some service redesign e.g. to discharge patients and recall them for a cardiac stress test the following day if awaiting this test is the only reason for being in hospital.

Introducing troponin testing in all community hospitals that manage patients with chest pain will require training of health professionals and support through MCNs.

The evidence indicates that a consensus definition of MI is urgently required. Once a working diagnosis of MI has been established, it should be implemented without delay across the UK. Its implementation will require considerable effort to inform the necessary health professionals and provide appropriate guidance on the changeover.

8.4 Summary and conclusions

Troponin testing has been demonstrated to be clinically and cost effective when used as part of the risk stratification procedure for non-ST elevation ACS and for routine clinical assessment for ST elevation ACS (which includes patients with symptoms suggestive of MI presenting with confounding ECG changes). Troponin testing should be available in all hospitals receiving such patients. In addition to its role in the assessment of prognosis, elevated troponin – together with other risk factors such as ECG changes – plays an important role in the selection of patients for urgent invasive or pharmaceutical interventions.

Both the economic modelling and clinical evidence show that substantial advantages to patients and hospitals may accrue from ensuring that the troponin testing result is available at the earliest possible time at which a clinical decision can be made. These advantages include early treatment of high-risk patients, early discharge of low-risk patients and consequent reductions in expense.

Such a troponin testing service may be achieved by a 24 hours per day, seven days per week laboratory or point-of-care service and must comply with the relevant quality assurance requirements and MHRA guidelines. However, the decision on the type of service will depend on hospital specific factors (e.g. clinical decision-making protocol, the layout of the hospital, patient throughput and laboratory working practices).

It is important to note that troponin testing is only one component of the patient care process and that unless other aspects of the process are well

constructed, the potential advantages of increased availability of troponin testing and reduced turnaround time will not be delivered. For example, early treatment of high-risk patients requires that adequate angiography facilities are available, and that there is a clear protocol for access to them based on clinical and biochemical risk markers. Similarly, services may need to be re-organised to permit, for example, low-risk patients to be discharged before a stress test (usually an ETT) and then return as outpatients rather than waiting in hospital.

It is likely that reductions in time to discharge for low-risk patients and increased consistency and transparency of criteria for access to further treatment for high-risk patients will be beneficial to patients by improving clinical outcomes, reducing the number of inappropriate transfers between hospitals, reducing uncertainty for patients and shortening stressful waiting times. It will also be important to ensure that patients receive clear information and have a clear understanding about the impact of a troponin test result.

Increasing the availability of troponin testing and reducing turnaround times should provide valuable benefits to patients in Scotland, provided these changes are supported by appropriate clinical protocols and the necessary investment in treatment facilities.

Finally, troponin testing is a relatively new biochemical test, and the HTA conclusions are based on the clinical evidence available. Future research on very early invasive therapy, the use of multiple markers in rapid methods of chest pain assessment and the determination of appropriate cut-offs in low-risk unselected chest pain patients, in addition to further developments in analytical technology such as improved sensitivity and specificity of point-of-care analysers, may alter or strengthen the conclusions of this HTA, which should be reviewed in the light of any such developments.

8.5 HTA recommendations

1. Troponin testing should be complementary to clinical and ECG risk markers to inform diagnostic decisions and to assess risk in patients with suspected ACS. However, troponin must not be a substitute for these risk markers.

2. Troponin should replace existing cardiac enzyme tests tests – including creatine kinase (CK) and its MB isoenzyme (CK-MB) and 'older' biochemical markers such as aspartate aminotransferase and lactate dehydrogenase – for any diagnostic, prognostic or management decisions in all patients with symptoms suggestive of ACS (although CK retains a role in assessing early re-infarction).

3. Troponin testing in combination with the clinical and ECG risk markers should be part of a formal risk assessment system to assess prognosis and suitability for medical or invasive treatment and to guide the management

strategy for patients with symptoms suggestive of ACS but without ST elevation.

4. In low-risk patients with symptoms suggestive of ACS, a troponin test in combination with clinical and ECG risk markers should be used to inform a decision on whether or not to discharge. Where low-risk status can be confirmed, a cardiac stress test should be scheduled without delay to facilitate discharge and to identify if other investigations need to be undertaken.

5. In patients with symptoms suggestive of an acute myocardial infarction who would benefit from urgent reperfusion therapy[12] but in whom there is diagnostic uncertainty on ECG, a troponin test with a short turnaround time may provide additional diagnostic information and should be considered as part of therapeutic decision making.

6. Troponin testing should be part of routine clinical assessment in patients who have received urgent reperfusion therapy for an acute myocardial infarction.

7. Troponin should be measured 12 hours after the onset of well-defined symptoms (when this can be reliably ascertained) in all patients with suspected or clinically diagnosed non-ST elevation ACS. If onset of symptoms is difficult to establish, an appropriate surrogate for the timing of this measurement is 12 hours after admission.

   In patients with clear high-risk markers (for example, those with recurrent symptomatic ischaemia or unequivocal ECG evidence of ischaemia such as ST depression) who will clearly benefit from early pharmacological or interventional therapy, there is no clinical need for a troponin test prior to starting treatment.

8. Troponin may be measured on admission in patients with suspected ACS in whom there is clinical diagnostic uncertainty due to the absence of high-risk clinical or ECG risk markers (for example, no ST depression, no history of diabetes, renal failure or previous myocardial infarction). If this test is negative, a further troponin measurement should be taken as indicated in Recommendation 7[13].

   This recommendation is only advocated if hospitals have the resources available to change patient management when a troponin result is positive.

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[12] Patients who are candidates for urgent reperfusion therapy present with symptoms suggestive of a myocardial infarction and in most cases with ST segment elevation on ECG, but some may present with confounding ECG changes e.g. left bundle branch block.

[13] Note that if the first troponin measurement is 12 hours after the onset of symptoms, the second measurement can be omitted.

If this testing regimen is adopted, clear protocols that recognise the two-step troponin assessment should be introduced, adherence to their use monitored and deviations addressed.

9. Troponin should be measured on admission in patients with symptoms suggestive of acute myocardial infarction who are being considered for urgent reperfusion therapy but in whom there is diagnostic uncertainty on ECG due to possible pre-existing confounding ECG changes (such as left bundle branch block).

   This recommendation is only advocated in hospitals where a troponin testing service, either a laboratory or point-of-care service, can provide a test result with a short turnaround time and is compatible with clinical decision making.

10. Troponin should be measured 12 hours after admission in patients who have received urgent reperfusion therapy for an acute myocardial infarction.

11. All analysers new to the market should meet the European Society of Cardiology criteria on sensitivity and reproducibility (i.e. ≤10% coefficient of variation at the 99th percentile of the normal population distribution of troponin).

    For all existing analysers, laboratories should work collaboratively with manufacturers to establish upper limits of troponin in patients without cardiac damage to form a cut-off limit that is appropriate for their patient group to assist in diagnosing acute myocardial infarction and in risk stratifying patients with non-ST elevation ACS.

12. Qualitative troponin readers should not be used to exclude myocardial damage in patients with symptoms suggestive of ACS.

13. A troponin testing service can be laboratory based or provided at the point of care[14]. The type of troponin testing service offered should be decided locally by laboratory, clinical and managerial staff working collaboratively to define the local requirements of a hospital.

14. If a combination of laboratory and point-of-care assays is used to measure troponin, the testing methods must provide results on the same scale. If this is not possible, one type of service should be used exclusively to avoid clinical confusion about cut-off levels.

15. A troponin testing service should deliver a result in an appropriate timescale that meets the needs of the clinical decision maker.

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[14] Note that most point-of-care analysers do not currently meet the sensitivity requirements to rule out myocardial damage or to be used in risk assessment.

16. Where troponin testing is only available on weekdays, implementing a weekend batch run service is recommended as a minimum service, provided that clinicians are available to act on the results.

17. All laboratories responsible for troponin testing should attain Clinical Pathology Accreditation.

18. All sites that undertake troponin testing (including point-of-care testing) should participate in an external quality assurance scheme.

19. All users of point-of-care troponin testing should adhere to guidance by the Medicines and Healthcare products Regulatory Agency.

20. All point-of-care troponin-testing sites require the identification of a coordinator who is given responsibility for the service.

21. All point-of-care testing services must be supported by laboratory staff.

22. Only trained competent staff should perform troponin testing. Training and support from Managed Clinical Networks with regard to use of equipment and interpretation of the results should be offered on an ongoing basis for existing users and be provided for new users, especially for those in community hospitals where troponin testing may not be currently in use.

23. Appropriate protocols should be developed and used by clinicians, laboratory staff and management staff to make optimal use of the information provided by the troponin test result. This should include a protocol on equitable access to catheterisation facilities using evidence-based and transparent eligibility criteria.

24. Health professionals should explain to patients and their carers what their diagnosis is, how it was made, the available treatment options and what to do and who to contact if symptoms return after discharge. Health professionals should use consistent terms for the diagnosis and check to ensure that patients understand the information given to them.

25. Health professionals need to provide a clear message to patients who are discharged as low 'short-term' risk that this status does not imply that they are free of heart disease and encourage them to make appropriate lifestyle changes.

26. All hospitals should have written information for patients who present with chest pain. Written information should be provided to reinforce the content of oral communication between patients and carers and health professionals. Patient information leaflets on heart disease should be written in simple easy-to-understand language, include an explanation of the troponin test and be updated to include the term ACS. Alternative formats such as video, audio, large print or illustrations should also be available and the use of other languages should be considered.

27. Audit data should be routinely collected from all patients with suspected or diagnosed ACS to allow thorough evaluation of the clinical and economic value of troponin. Data should include the number, timing and results of the troponin tests and the number of low-risk patients who were discharged within 24 hours of admission.

28. The only prospective study on the interaction between troponin level and treatment with glycoprotein IIb/IIIa inhibitors was performed using abciximab, which is not licensed currently in the UK for use in the medical management of patients with non-ST elevation ACS. This study showed no treatment effect. A similar study using small molecule glycoprotein inhibitors, such as eptifibatide and tirofiban which are licensed for this indication in the UK, should be performed. The study should estimate the effectiveness of using a troponin test to select patients for glycoprotein IIb/IIIa inhibition.

29. In existing scoring systems, the term 'biochemical marker' does not specifically refer to troponin but instead to any one of CK, CK-MB or troponin. As troponin is more specific and sensitive than CK or CK-MB, a study to investigate the effect of replacing 'any biochemical marker' by troponin is desirable.

30. The combination of multimarker testing (including troponin) and rapid[15] methods of chest pain assessment to reduce the rate of admissions or to achieve early discharge of low-risk patients may appear attractive but the evidence base for their long-term safety is weak. A randomised controlled trial comparing rapid troponin-based chest pain assessment methods with existing assessment protocols should be undertaken. The trial should assess long-term safety and use rigorous follow-up methods.

8.6 Implications of HTA recommendations for service provision

This section considers the implications of the HTA recommendations for each of the three main hospitals groups (community hospitals, DGHs and tertiary centres) that manage patients with suspected ACS and the laboratories serving these hospitals.

Troponin should replace CK, CK-MB, aspartate aminotransferase and lactate dehydrogenase (except CK for early re-infarction). All local protocols and guidelines should be changed accordingly. Education and training for clinicians and other relevant health professionals must be provided to support the changes.

All NHSScotland hospitals managing patients with suspected or clinically diagnosed ACS should review current management protocols to ensure all

[15] The definition of 'rapid' varied among the studies but the time for assessment ranged from 90 minutes to nine hours after presentation to hospital.

such patients receive a troponin test at 12 hours after onset of pain but no later than 12 hours after admission.

All NHSScotland hospitals managing patients with symptoms suggestive of ACS but of uncertain diagnosis should determine whether it is cost effective in their setting to measure troponin in such patients on admission. The test will help identify additional high-risk patients who should be admitted directly to the appropriate ward for further monitoring. Patients with a negative troponin result on admission should receive a second test 12 hours later and if the result is negative and the patient has no further chest pain, then the patient should be considered for discharge and receive a stress test. If such change is cost effective, then appropriate changes should be made to existing management protocols and compliance with the revised protocols monitored.

All NHSScotland hospitals managing patients who have received urgent reperfusion therapy for an AMI should determine the level of misdiagnosis on ECG in such patients (using a troponin test) and the associated costs of misdiagnosis. If the misdiagnosis rate is clinically important, then the hospital should review current management protocols to ensure all such patients receive a troponin test 12 hours after admission to confirm diagnosis.

All NHSScotland hospitals managing patients with symptoms suggestive of a MI who would benefit from urgent reperfusion therapy (for example, thrombolysis) but in whom there is diagnostic uncertainty on ECG should consider measuring troponin on admission if the troponin testing service can provide a result with a short turnaround time and is compatible with clinical decision making. If this recommendation is adopted, appropriate changes should be made to existing management protocols.

All NHSScotland hospitals should review current discharge procedures to ensure that these enable a stress test to be scheduled, either before discharge if this can be arranged or at a follow-up review. The test completes the assessment and may confirm low-risk status allowing discharge, and with a view to identifying if other investigations are needed.

All NHSScotland hospitals that transfer patients to tertiary centres for revascularisation procedures should agree transparent, evidence-based criteria to enable transfer of patients with ACS to the relevant centre. The basis for such decisions should include a troponin value. These processes should be embraced by the relevant MCN. Implementation should follow on from SCIN's work (now incorporated into the National Advisory Committee on CHD) in developing protocols on eligibility for intervention.

All NHSScotland community hospitals should agree referral criteria for transferring patients with ACS to DGHs and tertiary centres. One of the referral criteria should include a troponin level. These processes should be covered by the relevant MCN.

Where there is a perceived need for a point-of-care testing service – for example, where transport arrangements between hospitals and the nearest laboratory service preclude the receipt of troponin results in a timescale to meet clinical need – then clinical and laboratory management teams should jointly develop a business case. The laboratory should oversee the selection of the point-of-care analysers and its maintenance and quality assurance. Point-of-care test users should adopt the guidance set out by the MHRA.

All laboratories providing NHSScotland hospitals with troponin results with average turnaround times of more than two hours should review current practices and identify ways to reduce turnaround times. A liaison group comprising representatives from the clinical, managerial and laboratory disciplines should consider these changes for implementation. If a reduction in turnaround time is not possible, then the group should consider moving to a point-of-care testing service (which should fulfil the recommendations outlined in Section 7.4.1) to supplement or replace the existing service.

All NHSScotland hospitals managing patients with symptoms suggestive of ACS should take into account the guidance about communication with patients and ensure that written information explaining the various clinical terms and tests is available for patients and carers.

Once a consensus definition of MI is achieved, health professionals including general physicians and GPs must be advised of the change and its importance explained.

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11 Appendices

Appendix 1

TOPIC SPECIFIC GROUP AND PEER REVIEWER DETAILS WITH REGISTER OF INTERESTS

TOPIC SPECIFIC GROUP DETAILS

Dr Iain Findlay (Chair)	Consultant Cardiologist	Royal Alexandra Hospital, Paisley
Dr Marion Barlow	Associate Specialist	Western Infirmary, Glasgow
Dr Alan Begg	General Practitioner	Montrose
Mr B Graham Bell	Patient Representative	Penicuik
Dr Paul Collinson	Consultant Chemical Pathologist	St Georges Hospital, London
Dr Michael Cornbleet	Senior Medical Officer	Scottish Executive Health Department
Dr Bernie Croal	Clinical Senior Lecturer	Department of Clinical Biochemistry, Grampian University Hospitals Trust
Professor Keith Fox	Professor of Cardiology	Royal Infirmary of Edinburgh
Mr Thomas Gaffney	Chest Pain Nurse Specialist	Royal Alexandra Hospital, Paisley
Dr Michael Johnston	Consultant in A&E Medicine	Ninewells Hospital, Dundee
Dr Utkarsh Kulkarni	Specialist Registrar	Department of Clinical Biochemistry, Grampian University Hospitals NHS Trust
Mr Stephen McGlynn	Principal Pharmacist	Clinical Pharmacy Research & Development, Western Infirmary, Glasgow
Ms Catherine Mondoa	Cardiology Specialist Nurse	Stirling Royal Infirmary
Dr Norman Peden	Consultant Physician	Falkirk and District Royal Infirmary
Dr Jill Pell	Consultant in Public Health Medicine and Honorary Clinical Senior Lecturer in Cardiology	Greater Glasgow NHS Board
Dr Andrew Rankin	Consultant Cardiologist and Senior Lecturer	Department of Medical Cardiology, Glasgow Royal Infirmary
Mr Alan Reid	Biochemist	Clinical Biochemistry Department, Victoria Infirmary, Glasgow
Dr Janet Tillman	Biochemist	Biochemistry Department, Hairmyres Hospital, East Kilbride
Dr D Susan Vincent	General Practitioner and Representative of the Scottish General Practitioners Committee	Dundee

PEER REVIEWERS

Dr Adam Bryson	Medical Director	CSA
Professor John Davies	Professor of Psychology and Director of the Centre for Applied Social Psychology	Strathclyde University, Glasgow
Dr Stephen Engleman	Honorary Fellow	Department of Community Health Sciences, University of Edinburgh
Professor Elizabeth Russell (Consultant)	Emeritus Professor of Social Medicine	University of Aberdeen
Ms Sharon Russell	Principal Biochemist	Royal Alexandra Hospital, Paisley
Dr Sara Twaddle	Director	SIGN

REGISTER OF INTERESTS

Dr Paul Collinson	Member, Scientific Advisory Board of Ischemia Technologies, Denver, USA
Professor John Davies	Director and shareholder, Human Factors Analysts Ltd Non-Executive Director, Glasgow Council on Alcohol
Professor Elizabeth Russell	Honorary Consultant in Public Health Medicine Shares in GlaxoSmithKline

Appendix 2

SUBMISSIONS OF EVIDENCE

- Beckman Coulter UK Ltd. 2002. The use of troponin testing in acute coronary syndromes and cardiac markers.
- Boehringer Ingelheim. 2002. Drugs for early thrombolysis in the treatment of acute myocardial infarction.
- British Heart Foundation. 1999. Heart attack and rehabilitation – information for people who have had a heart attack, and for their family and friends.
- British Heart Foundation. 2000. Confidential information on a range of issues relating to heart disease.
- British Heart Foundation. 2001. Tests for heart conditions – information about the tests which can help to diagnose heart disease, or assess the condition of your heart.
- Dade Behring. 2002. Submission of evidence relating to clinical and cost effectiveness in health technology assessments. Clarification of research and scope: issues for manufacturers.
- Fisher C, Findlay I and Morgan M. 2002. Business case for the management of chest pain. Royal Alexandra Hospital.
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- Medical Devices Agency. 2002. Management and use of *in vitro* diagnostic point-of-care test devices. London: Medical Devices Agency.
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- National Academy of Clinical Biochemistry. 1999. Recommendations for the use of cardiac markers in coronary artery diseases.
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- Roche. 2002. HTBS troponin, Roche submission.
- Vedalab. 2002. Evaluation of the Vedalab qualitative troponin (TnIc) test on plasma.

Appendix 3

ORGANISATION OF HEALTH CARE IN SCOTLAND

NHSScotland, like the NHS in other parts of the UK, provides comprehensive health care for its citizens, and is free at the point of use. It is funded mainly by direct taxation in the form of income tax and national insurance contributions, with a small proportion of funding coming from patient charges, such as for dental care and prescriptions. A key feature of the UK's funding system is its concept of fairness, providing maximum separation between an individual's financial contributions and their use of health care. After social security payments, health is the biggest single component of public expenditure (Wanless, 2001).

Mortality and morbidity rates are higher in Scotland than in England, reflecting differences in their populations and environmental and socio-economic factors. However, alongside these greater health needs, Scotland has more health care resources. Funding per head, the number of hospital beds and professional health care staff are all above the levels in England (Wanless, 2001). NHSScotland has core aims of improving the health of the population and reducing inequalities in health. There are currently five priority topics: CHD/stroke; cancer; mental health; children and young people and older people (Scottish Executive Health Department, 2000).

In 1998, the UK health expenditure per capita was £1510 or 6.8% of the gross domestic product (5.7% publicly funded and 1.1% privately funded). The EU weighted average figures were £1824 and 8.4% of the gross domestic product (6.4% publicly funded and 2.1% privately funded) (Wanless, 2001). Scotland has higher public health service expenditure per capita than the UK average (Wanless, 2001).

NHSScotland has around 132 000 staff, including more than 63 000 nurses, midwives and health visitors and over 8500 doctors. There are also more than 7000 GPs, including doctors, dentists, opticians and community pharmacists, who are independent contractors providing a range of services within the NHS in return for various fees and allowances (www.show.scot.nhs.uk/public/publicindex.htm).

SEHD leads the central management of NHSScotland. It oversees the work of 15 NHS Boards responsible for planning health services for people in their area.

A number of special Health Boards also exist which have Scotland-wide remits for specific functions. For example, NHS Education Scotland commissions education and training for some NHS staff, and NHS Quality Improvement Scotland sets standards and monitors performance, and provides NHSScotland with advice, guidance and support on effective clinical practice and service improvements.

More information about the health service in Scotland can be obtained from http://www.show.scot.nhs.uk and
http://www.show.scot.nhs.uk/publicationsindex.htm

Appendix 4

LABORATORY AND POINT-OF-CARE ANALYSERS

	Quantitative laboratory analysers			
Manufacturer	Abbott Diagnostics	Bayer Diagnostics	Bayer Diagnostics	Bayer Diagnostics
Instrument or device	AxSYM	ACS180	Advia Centaur	Immuno 1
Assay type	MEIA	2-site chemiluminescent immunoassay	2-site chemiluminescent immunoassay	Heterogeneous sandwich magnetic separation assay
Antibody selection	Mouse monoclonal anti-TnI coated microparticles: goat anti-TnI conjugated with ALP	Goat anti-cTnI labelled with acridinium esters; solid phase mouse MAb anti-cTnI	Goat anti-cTnI labelled with acridinium esters; solid phase mouse MAb anti-cTnI	Mouse MAb anti-cTnI conjugate; goat polyclonal anti-cTnI ALP conjugate
Sample type	Serum, plasma (Li/Na heparin). Serial samples should be of the same type.	Serum, heparinised plasma	Serum, heparinised plasma	Serum, plasma (Li heparin)
Reagent storage and handling/ preparation	cTnI reagent pack stored at 2–8°C until expiry. Reagent stable on board for 336 hours. MUP (solution 1) stored at 2–8°C, and stable for 14 days on system.	cTnI lite reagent stored at 2–8°C until expiry or for 120 cumulative hours at room temperature. cTnI solid phase stored at 2–8°C until expiry or for 120 cumulative hours at room temperature.	Primary reagent pack and solid phase stored at 2–8°C until expiry. On-board stability for 28 days.	Reagents are light sensitive. Unopened reagents, stored at 2–8°C until expiry. After initial use, reagent on-board stability may last for 60 days.
Calibrator storage and handling/ preparation	Calibrators shipped on dry ice. Stored at 2–8°C. Vortex prior to use.	Lyophylised calibrators stored at 2–8˚C until expiry. Reconstituted stability 1 day at 2–8°C, 60 days at -20°C or 4 hours onboard.	Lyophylised calibrators stored at 2–8˚C until expiry. Reconstituted stability 1 day at 2–8°C, 60 days at -20°C or 4 hours onboard.	Calibrators in liquid-ready format. Stored unopened at 2–8°C until expiry. After initial use, calibrators are stable at 2–8°C for 30 days.
Sample volume	220 µL including dead volume	100 µL	100 µL	50 µL
Serum/plasma differences	Not quoted	Heparinised plasma 16% lower than matched serum.	Heparinised plasma 11% lower than matched serum.	Heparinised plasma 10% lower than matched serum.
Sample storage	72 hours @ 2–8°C 14 days @ -10°C	4 hours @ room temperature, 4 hours @ 2–8°C, freeze if not assayed within 24 hours.	4 hours @ room temperature, 4 hours @ 2–8°C, freeze if not assayed within 24 hours.	1 week @ 2–8°C 1 month @ -20°C
Imprecision (CV) (control material)	Intra-assay: 3.2–6.4% Inter-assay: 3.9–5.2%	Intra-assay: 2.8–3.9% Inter-assay: 4.2–5.5%	Intra-assay: 1.4–4.3% Inter-assay: 3.0–6.4%	Intra-assay: 0.8–2.3% Inter-assay: 2.0–3.3%
Sensitivity (µg/L)	0.3	0.15	0.03	0.1
Linear range (µg/L)	50	50	50	200
Calibration	6-point	Master curve	Master curve	6-point
Reference values (95th centile) (µg/L)	<0.4	0.07	0.07	0–0.1
AMI cut-off (µg/L)	2	1.5	1.5	0.9
Assay time (min)	13	15	15	18
Correlation to other methods	AxSYM = 3.42 Stratus – 1.09			Immuno 1 = 0.81 Stratus – 0.41

	Quantitative laboratory analysers		
Manufacturer	Beckman Coulter	Dade Behring	Dade Behring
Instrument or device	Access, Access 2, LXi 725, DxI 800	Dimension RxL HM Dimension RxL HM MAX Dimension Xpand HM	[1]OPUS™ OPUS™ Plus
Assay type	1-step paramagnetic particle chemiluminescent assay	1-step EIA based on the 'sandwich' principle	
Antibody selection	MAb anti-cTnI conjugated to ALP: paramagnetic particles coated with MAb anti-cTnI antibody	Chromium dioxide particles coated with MAb specific for cTnI molecule and a conjugate reagent (ALP) labelled MAb specific for cTnI	
Sample type	Lithium heparin plasma, serum, EDTA plasma conversion factor applies.	Serum or heparinised plasma	
Reagent storage and handling/ preparation	Refrigerated cTnI reagent cartridges 2–10°C until expiry date. Reagents stable for 56 days at 2–10°C after initial use. Substrate stored at 4°C, required to warm to room temperature 24 hours prior to using on analyser.	CTNI Flex™ reagent cartridge stored at 2–8°C until expiry. Sealed/unhydrated Flex™ cartridges stable on-board for 30 days. Hydrated/working reagent stable for 3 days.	Refrigerated cTnI reagent cartridges (4°C) until expiry date.
Calibrator storage and handling/ preparation	Frozen liquid calibrators. Stored at 4°C for 5 days once thawed and opened.	Frozen liquid calibrators. Unopened vials – (1) when frozen, are stable until expiry date (2) when thawed, are stable at 2–8°C for 24 hours. Opened vials – stable for 24 hours at 2–8°C.	Liquid calibrators stored frozen. Stable for 24 hours at 2–8°C once opened.
Sample volume	40 µL	50 µL	
Serum/plasma differences	Conversion factor of 0.86 should be applied to AMI cut-off for EDTA plasma. Heparin plasma results the same as serum.	No difference	
Sample storage	Assay fresh samples within 2 hours if stored at room temperature. 2–4 hours, separate and store at 4°C. >24 hours, freeze at -20°C. Stable for up to 6 months.	14 days @ 2–8°C 8 weeks @ -20°C	
Imprecision (CV) (control material)	Intra-assay: 3.06–4.42% Inter-assay: 2.71–6.07%	Level (µg/L) : Intra-assay (%) : Inter-assay (%) 0.35 : 2.7 : 7.7 5.28 : 1.0 : 4.2 14.52 : 1.0 : 4.9	
Sensitivity (µg/L)	0.01	0.04	
Linear range (µg/L)	100	0.04–40.0	
Calibration	6-point calibration. Cals 0 & 1 measured in quadruplicate. Cals 2–5 measured in duplicate.	5-point calibration. Cals 1 & 2 in quadruplicate. Cal 3 in triplicate. Cals 4 & 5 in duplicate.	
Reference values (95th centile) (µg/L)	0.3 (0.4 µg/L, 99th centile)	0–0.05	
AMI cut-off (µg/L)	0.5	A cut-off of 0.6–1.5 µg/L is suggested as being consistent with the WHO criteria for AMI. Risk stratification cut-off 0.1 µg/L.	
Assay time (min)	12	10	
Correlation to other methods	Dade RxL	Dimension = 1.04 Stratus CS – 0.11; r=0.99	

[1] Note that the OPUS™ systems are no longer available from the end of December 2003.

	Quantitative laboratory analysers		
Manufacturer	Euro/DPC Ltd	Euro/DPC Ltd	Euro/DPC Ltd
Instrument or device	Immulite	Immulite Turbo assay	Immulite 2000
Assay type	Solid phase, 2-site chemiluminescence enzyme immunoassay	Solid phase, 2-site chemiluminescence enzyme immunoassay	Solid phase, 2-site chemiluminescence enzyme immunoassay
Antibody selection	Mouse anti-cTnI coated bead; ALP labelled goat anti-cTnI	Mouse anti-cTnI coated bead; ALP labelled goat anti-cTnI	Mouse anti-cTnI coated bead; ALP labelled goat anti-cTnI
Sample type	Serum, plasma (EDTA, heparin)	Serum, plasma (EDTA, heparin)	Serum, plasma (EDTA, heparin)
Reagent storage and handling/ preparation	Test modules and reagent wedges stored at 2–8°C until expiry. Test modules sensitive to humidity. Allowed to warm to room temperature for 15 minutes prior to use. Reagent wedge stable at 2–8°C until expiry. Once opened, recommended stability is 30 days.	Test modules and reagent wedges stored at 2–8°C until expiry. Test modules sensitive to humidity. Allowed to warm to room temperature for 15 minutes prior to use. Reagent wedge stable at 2–8°C until expiry. Once opened, recommended stability is 30 days.	Test beads and reagent wedges stored at 2–8°C until expiry. Test beads sensitive to humidity. Allowed to warm to room temperature for 15 minutes prior to use.
Calibrator storage and handling/ preparation	Lyophylised adjustors (calibrators). Reconstitute with distilled water. Aliquots stable at -20°C for 2 months.	Lyophylised adjustors (calibrators). Reconstitute with distilled water. Aliquots stable at -20°C for 2 months.	Lyophylised adjustors (calibrators). Reconstitute with distilled water. Aliquots stable at -20°C for 2 months.
Sample volume	50 µL	50 µL	100 µL
Serum/plasma differences	EDTA plasma gives lower results than serum.	EDTA plasma gives lower results than serum.	EDTA plasma gives lower results than serum.
Sample storage	5 days @ 2–8°C 1 month @ -20°C	5 days @ 2–8°C 1 month @ -20°C	5 days @ 2–8°C 1 month @ -20°C
Imprecision (CV) (control material)	Intra-assay: 2.7–5.8% Inter-assay: 6.1–8.4%	Intra-assay: 3.0–4.4% Inter-assay: 3.7–7.9%	
Sensitivity (µg/L)	0.1	0.15	0.2
Linear range (µg/L)	180	180	180
Calibration	Master curve	Master curve	Master curve
Reference values (95th centile) (µg/L)	<1.0 (98%)	<1.0 (98%)	<1.0 (98%)
AMI cut-off (µg/L)	Not quoted		
Assay time (min)	40	20	35
Correlation to other methods			

	Quantitative laboratory analysers		
Manufacturer	Ortho-Clinical Diagnostics	Roche Diagnostics	Tosoh Bioscience
Instrument or device	VITROS™ Immunoassay System	Elecsys 2010/1010/E170	AIA-Pack (AIA 600 II, AIA 21, AIA 1800)
Assay type	Immunometric, enhanced chemiluminescence	ECLIA	2-site EIA sandwich
Antibody selection	Biotinylated mouse MAb anti-cTnI; HRP-goat polyclonal anti-cTnI conjugate	3rd generation assay mouse MAb biotinylated anti-TnT; mouse MAb anti-cTnT labelled with Ruthenium	Enzyme labelled MAb bound to magnetic bead. Fluorogenic substrate 4-methylubelliferyl phosphate (4MUP).
Sample type	Heparin plasma	Serum or EDTA plasma Heparin is not recommended.	Serum or heparinised plasma
Reagent storage and handling/ preparation	Store unopened at 2–8°C until expiry. Open reagent packs stable for 12 weeks.	Reagent pack stored at 2–8°C until expiry date. After opening, store at 2–8°C for 8 weeks on 2010, E170 or 8 weeks at ambient temperature (maximum 20 hours) on 1010.	Reagent test cups stored at 2–8°C or onboard in sorter draw (AIA 21, 1800) for 24 hours at 18–25°C. Lyophylised substrate reconstituted with diluent stored at 2–8°C for 7 days or at room temperature on analyser for 3 days. Working diluent and wash solution are stable at room temperature for 30 days.
Calibrator storage and handling/ preparation		Lyophylised calibrators reconstituted with distilled water. Aliquots can be frozen at -20°C for 3 months or 2 weeks stored at 2–8°C.	Lyophylised calibrators reconstituted with distilled water, mixed and brought to room temperature before use. Aliquots can be stored at 2–8°C unopened until expiry. After opening, calibrators should be used within 1 day.
Sample volume	50 µL	15 µL	50 µL
Serum/plasma differences	Plasma claim only		
Sample storage	3 days @ 2–8°C >3 days @ -20°C	24 hours @ 2–8°C 12 months @ -20°C	24 hours @ 2–8°C 60 days @ -20°C
Imprecision (CV) (control material)	Intra-assay: 0.9–2.8% Inter-assay: 2.8–9.8%	Intra-assay: 3.0–4.2% Inter-assay: 6.0–9.3%	Inter-assay: 1.24–3.32% Intra-assay: 1.88–2.86%
Sensitivity (µg/L)	0.038	0.01	0.02%
Linear range (µg/L)	100	25	120
Calibration	Master curve	Master curve	6-point
Reference values (95th centile) (µg/L)	0.04 (97.5th) plasma	0.0–0.037 (99th centile)	0.01–0.31
AMI cut-off (µg/L)	0.4 (plasma)	0.1	0.64
Assay time (min)	16	9 or 18	
Correlation to other methods	Vitros = 0.728 Dade RxL – 0.093 (µg/L)	Not quoted	Not quoted

Manufacturer	Quantitative point-of-care devices		
	Biosite	Dade Behring	Roche Diagnostics
Instrument or device	Triage	Stratus CS	CARDIACT Quantitative measured on Cardiac Reader
Assay type	Fluorescence immunoassay	2-site (sandwich) assay based upon solid radial partition immunoassay	GLORIA 3rd generation
Antibody selection	Mouse MAb and goat polyclonal anti-cTnI labelled with fluorescent dye and immobilised on the solid phase	Anti-cardiac TnI mouse MAb conjugated to ALP. Dendrimer linked mouse MAb anti-cTnI.	Gold-labelled mouse MAb anti-cTnT; mouse MAb biotinylated anti-cTnT
Sample type	EDTA-anticoagulated whole blood or plasma	Lithium or sodium heparin whole blood samples and/or plasma samples	Heparinised whole blood
Reagent storage and handling/ preparation	Test strips stored at 2–8°C. Stable at room temperature for 14 days. Warm to room temperature for 15 minutes within foil pouch prior to use.	Reagent test pack stored at 2–8°C until expiry. Reagents used from fridge.	cTnT test strips stored at 2–8°C until expiry. Reagents used from fridge.
Calibrator storage and handling/ preparation	Lot code chip stored with reagent or at room temperature.	Single cTnI CalPak is stored frozen. Thaw to room temperature for at least 30 minutes before use for calibration.	Lot code chip stored with reagent or at room temperature.
Sample volume	Whole blood or plasma, 250 μL with transfer pipette provided.	Whole blood 2 mL – (internal centrifugation) 90 μL for plasma testing. Plasma sampling direct – 90 μL	150 μL
Serum/plasma differences	cTnI plasma = 0.9883 whole blood + 0.4203		
Sample storage	4 hours or plasma @ -20°C until tested	Whole blood – 2 hours. Plasma – 14 days @ 2–8°C, 8 weeks @ -20°C.	8 hours @ room temperature. Do not refrigerate or freeze.
Imprecision (CV) (control material)	Intra-assay: not given Inter-assay: 11.2–12%	Level (μg/L): Intra-assay (%): Inter-assay (%) 0.64 : 4.3 : 5.1 3.29 : 2.7 : 3.5 6.48 : 3.4 : 3.4	Not given
Sensitivity (μg/L)	0.05	0.03	0.1
Linear range (μg/L)	50	0.04–50	2.0
Calibration	Lot-specific master curve	6-level master curve. 1 level in triplicate to update C1 co-efficient.	Lot specific master curve on lot code chip
Reference values (95th centile) (μg/L)	0–0.05	0–0.06	Not quoted
AMI cut-off (μg/L)	0.4	A cut-off of 0.6–1.5 μg/L is suggested as being consistent with the WHO criteria for AMI.	0.1
Assay time (min)	15	13	14
Correlation to other methods	Triage cTnI = 0.42 RxL cTnI – 0.08	Stratus CS = 0.90 Stratus II + 0.12; r=0.988	Not quoted

	Quantitative point-of-care devices	Qualitative point-of-care devices	
Manufacturer	Response Biomedical Corporation	Roche Diagnostics	Spectral Diagnostics Inc
Instrument or device	RAMP	CARDIACT Qualitative	Cardiac STATus
Assay type	Immunochromatographic	GLORIA 3rd generation	Solid phase chromatographic immunoassay
Antibody selection	Fluorescent-dyed latex particles coated with anti-cTnI antibodies	Gold labelled mouse MAb anti-cTnT; mouse MAb biotinylated anti-cTnT	Anti-cTnI dye conjugate; polyclonal biotinylated anti-cTnT
Sample type	EDTA whole blood	Heparinised whole blood	Lithium heparin whole blood or plasma, serum
Reagent storage and handling/ preparation	Reagent test strip and diluent stored at 2–8°C. Remove diluent and test strip to room temperature for 15 minutes prior to use.	cTnT test strips stored at 2–8°C until expiry. Reagents used from fridge.	Test strips stored at 4°C. Warm to room temperature for 15 minutes prior to use.
Calibrator storage and handling/ preparation	Lot code chip stored with reagent or at room temperature	Lot code chip stored with reagent or at room temperature	Not applicable
Sample volume	70 μL		200 μL
Serum/plasma differences	Not applicable		Not quoted
Sample storage	2 hours from phlebotomy or store at 2–8°C for up to 5 days.		Whole blood within 4 hours. Plasma 24 hours @ 2–8°C, >24 hours @ -20°C
Imprecision (CV) (control material)	Intra-assay: 6.9–7.5% Inter-assay: 6.9–8.1%		Qualitative results
Sensitivity (μg/L)	0.03		1.5
Linear range (μg/L)	32		Not quoted
Calibration	Lot specific master curve on lot card		Not applicable
Reference values (95th centile) (μg/L)	<0.2		<1.5
AMI cut-off (μg/L)	0.2		>1.5
Assay time (min)	19		15
Correlation to other methods	RxL = 0.958		

ALP = alkaline phosphatase; HRP = horseradish peroxidase; MAb = monoclonal antibody; Ab = antibody; MEIA = microparticle enzyme immunoassay; EIA = enzyme immunoassay; GLORIA = gold-labelled optically read immunoassay; ECLIA = electrochemiluminescence immunoassay; EDTA = ethylenediaminetetraacetic acid.

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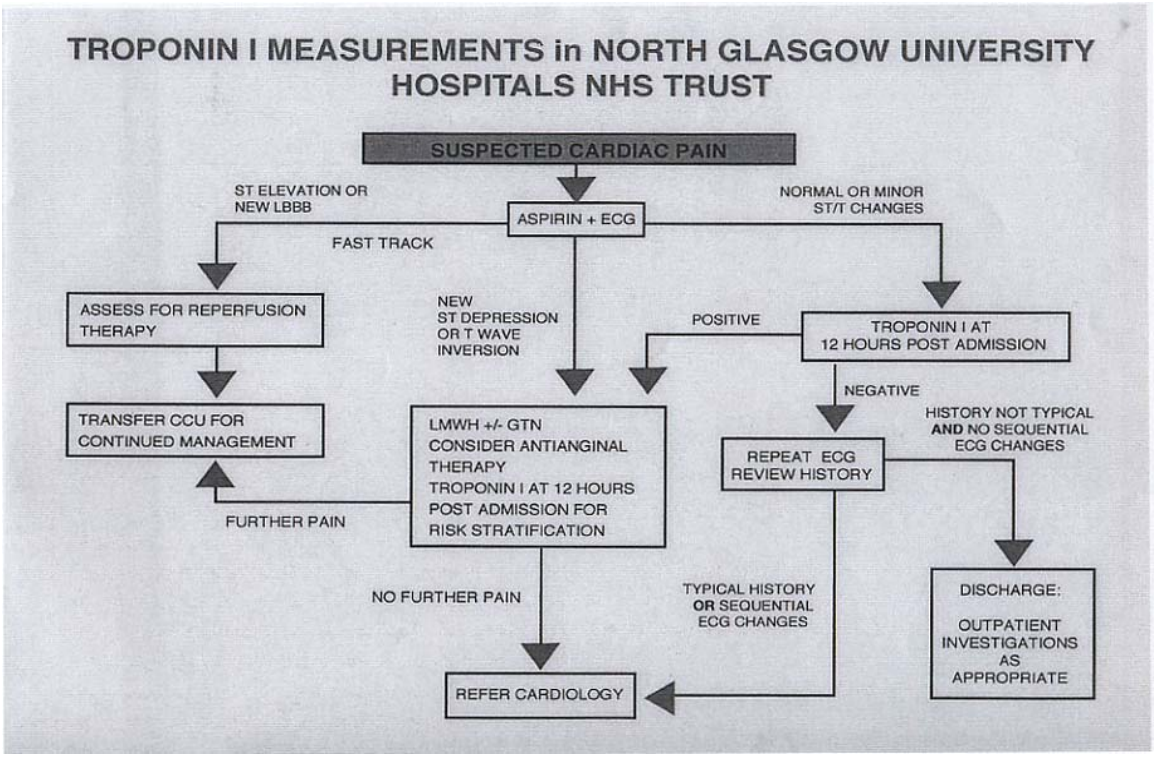
Note: Data is only available for most assays at the 95th centile, although guidelines recommend higher values.

Appendix 5

PROTOCOLS FOR ACS MANAGEMENT



- SerumTroponin I measurements will be undertaken in all patients across North Glasgow University NHS Trust presenting with suspected cardiac ischaemic pain with the exception of those eligible for Thrombolysis.
- CKMB will be available only on Consultant request. Standard cardiac enzymes will only be undertaken in those patients being considered for thrombolysis and Troponin will only be measured in these patients if the standard enzymes are normal .The adjoining algorithm displays our recommended approach in patients presenting with suspected cardiac pain.
- The sample for Troponin will be taken between 12 and 24 hours after admission. Morning samples need to be in the Biochemistry Department at GRI and Stobhill by 9.00am and by 8.30am at the Western. This includes weekends and will facilitate availability of results by 10am. During the week there will also be a continuous Tropinin service throughout the working day for samples delivered up to 4pm for patients who reach the 12 hour time window during this period.
- Repeat Troponin measurements should be taken only if there is further pain with ECG changes and the first Troponin was negative. If the first Troponin was positive then it is likely to remain positive for at least one week and repeat measurement would not be of value. Refer to Cardiology in this situation.
- The implications of a negative Troponin will allow reduction in inappropriate use of low molecular weight Heparin and Glycoprotein IIb IIIa receptor inhibitors. Similarly a positive Troponin requires referral to the cardiology services for further management. Thus intensive therapy and invasive investigations will be targeted to those most likely to benefit.
- Unnecessary standard cardiac enzymes, and repeat Troponin measurements will jeopardise the economic strength of this Troponin programme. Therefore requests for cardiac enzymes or Troponins outwith these guidelines will be refused unless there are exceptional circumstances.
- Interpretation of Troponin levels:

  Troponin I of ≥ 0.2 ng/L indicates myocardial damage ie a positive result

  Troponin I of < 0.2 ng/L is a negative result (below the level of detection of the assay)

Note: There is a planned change to the algorithm. The time of troponin I sampling is to be moved from 12 hours post admission to 12 hours post onset of pain.

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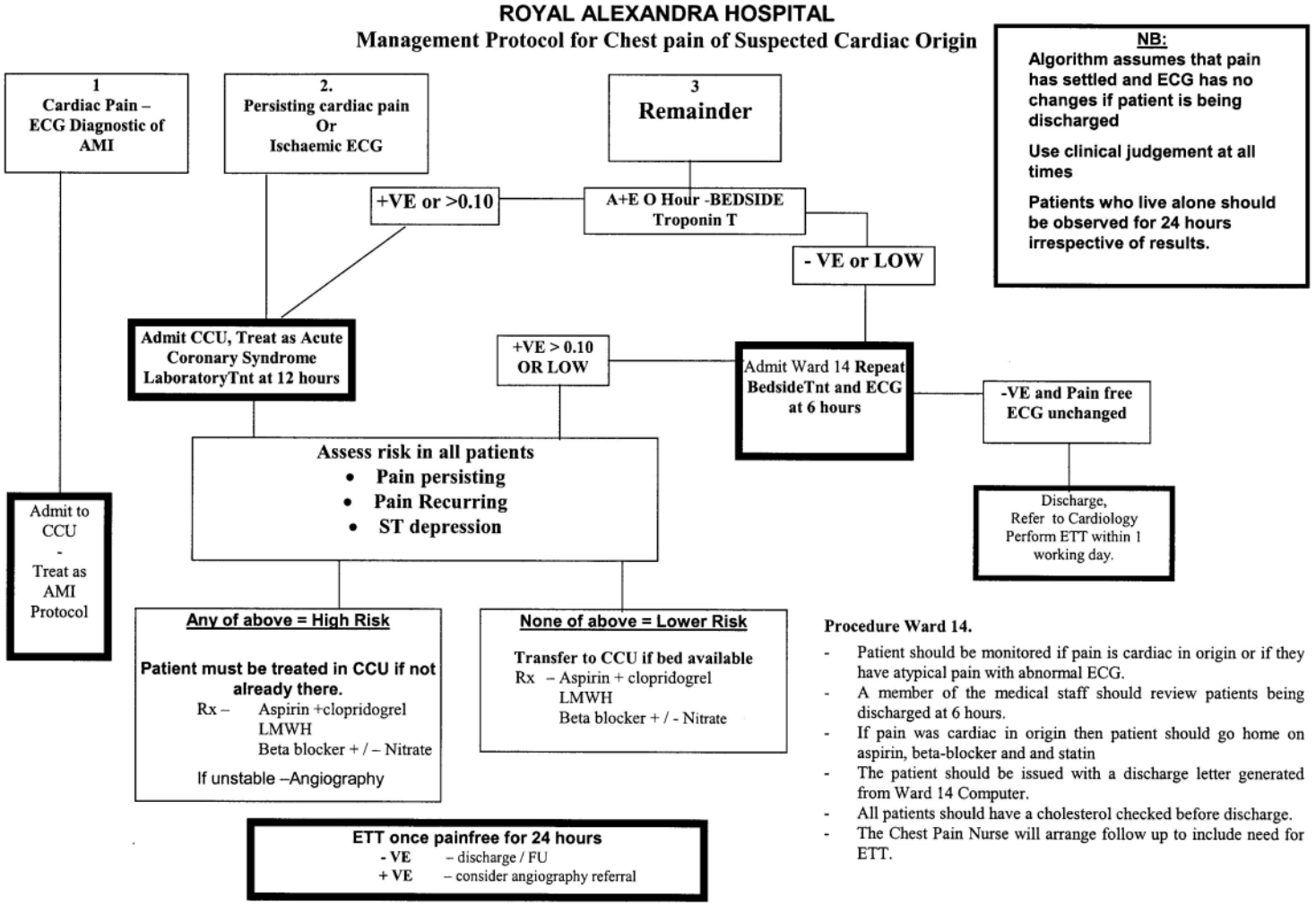

(in use in November 2002)

Appendix 6

THERAPY OPTIONS FOR ACS AND MANAGEMENT STRATEGIES FOR PATIENTS WITH NON-ST ELEVATION ACS

6.1 Therapy options for ACS

6.1.1 Anti-ischaemic agents

β-blockers occupy β-adrenergic receptors thereby preventing the effects of circulating catecholamines. In patients with NSTEMI, β-blocker treatment causes a decrease in myocardial oxygen consumption and is associated with a reduced risk of progressing to AMI (Bertrand *et al*., 2000).

Nitrates may be of value in treating recurrent chest pain in ACS. They act by reducing cardiac workload secondary to venodilation (reducing preload), dilation of normal and atherosclerotic coronary arteries to increase blood flow and also inhibition of platelet aggregation (Bertrand *et al*., 2000).

Calcium-channel blockers may also be of value in treating myocardial ischaemia. There are three subclasses and each varies in the degree to which they cause vasodilation, decreased myocardial contractility and delayed atrioventricular conduction (Bertrand *et al*., 2000). Calcium-channel blockers can be used in patients with contraindications to β-blockers.

6.1.2 Antiplatelet drugs

Aspirin works rapidly by blocking the enzyme cyclooxygenase-1 within platelets, which prevents the formation of thromboxane A2, thereby inhibiting platelet aggregation promoted via this pathway. Aspirin also has an anti-inflammatory effect (Braunwald *et al*., 2002).

Ticlopidine and its derivative *clopidogrel* are adenosine diphosphate inhibitors. These agents inhibit platelet aggregation and can be considered as alternative drugs in those patients with an aspirin intolerance (Bertrand *et al*., 2000). Clopidogrel has fewer side effects associated with use than ticlopidine, and has a more rapid onset of action (Braunwald *et al*., 2002).

Glycoprotein IIb/IIIa inhibitors occupy the glycoprotein IIb/IIIa receptors on the surface of platelets which prevents fibrinogen binding and thereby inhibits platelet aggregation (Braunwald *et al*., 2002). There are three glycoprotein IIb/IIIa inhibitors available in the UK (i.e. abciximab, eptifibatide and tirofiban) and each possesses different pharmacological properties.

6.1.3 Anticoagulant agents

Heparin inhibits coagulation by accelerating the action of circulating antithrombin (Braunwald *et al*., 2002). It also prevents thrombus proliferation. *LMWHs* have several practical advantages over *unfractionated heparins*. These include possessing enhanced anti-Xa activity, being less likely to cause thrombocytopenia, exhibiting decreased sensitivity to platelet Factor 4 and a more predictable and sustained anticoagulant effect (Bertrand *et al*.,

2000). They have a dose-independent clearance with a longer half-life, requiring less frequent administration. Furthermore, they are administered based on a weight-adjusted dose so they do not require regular laboratory monitoring of activity (Braunwald *et al.*, 2002).

6.1.4 Fibrinolytic treatment

Fibrinolytic agents, such as streptokinase and recombinant tissue plasminogen activator, decrease the intracoronary thrombus by breaking down fibrin and have been shown to increase survival in patients with STEMI (Bertrand *et al.*, 2000).

6.1.5 Coronary revascularisation

Surgical interventions are performed to improve the functional capacity of the heart, relieve symptoms and improve patient prognosis (Braunwald *et al.*, 2002). Most commonly used coronary revascularisation procedures are PCI or CABG. The decision on the type of invasive technique undertaken will be determined by the results of the diagnostic coronary angiography examination which establishes the presence and extent of disease (Bertrand *et al.*, 2002). The decision to progress to coronary revascularisation depends on numerous factors such as risk assessment, life expectancy, comorbidity, severity of symptoms, ventricular function and large quantities of irreversible myocardium damage (Braunwald *et al.*, 2002).

6.1.5.1 PCI

The majority of PCIs performed use both balloon dilation and intracoronary stenting (Braunwald *et al.*, 2002). PCI involves the insertion of a catheter through the skin and the inflation of a balloon to dilate the narrowed segment of the artery (Scottish Executive Health Department, 2001). The use of stents helps to improve the patency of the vessel by mechanically stabilising the disrupted plaque at the lesion site and reducing the risk of vessel closure and late stenosis (Braunwald *et al.*, 2002). PCI is advocated for single-, two- or perhaps three-vessel disease and is no longer restricted to the management of stable angina (Bertrand *et al.*, 2000). Patients with ACS should also be considered for PCI (Scottish Executive Health Department, 2001).

6.1.5.2 CABG

CABG involves using veins or arteries from an area other than the heart as conduits for bypassing the diseased coronary arteries (Scottish Executive Health Department, 2001). CABG is used in patients with left main and three-vessel disease, in particular those with left ventricular dysfunction and patients with diabetes mellitus (Bertrand *et al.*, 2000).

6.2 Management strategies in non-ST segment elevation ACS

The ESC guidelines recommend that patients presenting with chest pain with a suspected ischaemic cause but without persistent ST segment elevation have their troponin measured and are initially treated with antiplatelet therapy (aspirin, clopidogrel), LMWH or unfractionated heparins, β-blockers, and nitrates (if chest pain is recurrent or persistent) (Bertrand *et al.*, 2002). Risk assessment during the observational period identifies low- and high-risk patient groups.

6.2.1 Low-risk patients (Bertrand *et al.*, 2002)

Patients in the low-risk group include those:

- who have no recurrence of pain within the observational period
- with normal or minimally abnormal ECG
- without elevated troponin or other biochemical markers at the initial and second measurement.

The ESC guidelines recommend that these patients should continue with antiplatelet therapy, β-blockers and possibly nitrates or calcium-channel antagonists.

If no ECG changes are apparent and the second troponin measurement is negative during the observational period, treatment with LMWH may be discontinued. A stress test (which is usually an ETT but some patients will require myocardial perfusion studies which may involve pharmacological stress) is recommended to help confirm a diagnosis of CAD and to establish prognosis. The results of the stress test, in combination with other factors, may determine whether early angiography is required. If the stress test results are inconclusive, an additional stress echocardiogram or stress myocardial perfusion scintigram may be appropriate. Secondary prevention should also be instituted.

6.2.2 High-risk patients (Bertrand *et al.*, 2002)

Patients at high risk for progression to major MI or death include those:

- with recurrent ischaemia (recurrent chest pain or dynamic ST segment changes)
- with early[2] post-infarction UA
- with elevated troponin levels at either the initial or second measurement
- who develop haemodynamic instability within the observational period
- with major arrhythmias
- with diabetes
- with an ECG pattern that precludes assessment of ST segment changes (pre-existing left bundle branch block or paced rhythm).

The ESC guidelines recommend that, where appropriate, patients judged to be at high risk of progressing to MI or death should receive glycoprotein IIb/IIIa inhibitors prior to angiography and continue on LMWH. The angiography result informs subsequent management decisions about PCI, CABG and conservative management.

[2] 'Early' is not defined by authors.

Appendix 7

TIMI SCORE FOR RISK STRATIFICATION IN PATIENTS WITH NON-ST ELEVATION ACS

The TIMI score for patients presenting with UA or NSTEMI was developed using the database of the TIMI 11B trial (Antman *et al.*, 2000). The TIMI score is a simple quantitative tool for evaluating risk of death and cardiac ischaemic events in patients presenting with UA or NSTEMI. It captures several prognostic variables that can be determined at presentation. The scoring system (www.timi.org) is graded out of seven and assigns one point for the presence of each of the predictor variables:

- age ≥65 years
- three or more coronary artery disease risk factors
- known coronary artery disease (stenosis ≥50%)
- aspirin use within last seven days
- recent severe angina (two or more anginal symptoms within 24 hours)
- elevated cardiac markers
- ST segment deviation ≥0.5 mm.

Appendix 8

LITERATURE SEARCH FOR CLINICAL EFFECTIVENESS

Systematic Search 1 – RCTs

Database: MEDLINE
Coverage: 1966 to July Week 5 2002
Platform: OVID
Search run: 13 August 2002

Strategy:
1. Heart Arrest/
2. exp Myocardial Ischemia/
3. chest pain/
4. ((cardiac or coronary or heart) adj2 arrest$).tw.
5. ((cardiac or coronary or heart) adj2 attack?).tw.
6. (coronary adj2 disease?).tw.
7. angina.tw.
8. "syndrome x".tw.
9. uap.tw.
10. ((cardiac or coronary or heart or myocard$) adj2 aneurysm?).tw.
11. ((cardiac or coronary or heart or myocard$) adj2 arterioscleros?s).tw.
12. ((cardiac or coronary or heart or myocard$) adj2 stenos?s).tw.
13. ((cardiac or coronary or heart or myocard$) adj2 restenos?s).tw.
14. ((cardiac or coronary or heart or myocard$) adj2 thrombos?s).tw.
15. ((cardiac or coronary or heart or myocard$) adj2 vasospasm?).tw.
16. ((cardiac or coronary or heart or myocard$) adj2 spasm?).tw.
17. ((cardiac or coronary or heart or myocard$) adj2 isch?em$).tw.
18. ((cardiac or coronary or heart or myocard$) adj2 infarct$).tw.
19. mi.tw.
20. ami.tw.
21. nqwmi.tw.
22. ((cardiac or coronary or heart or myocard$) adj2 stun$).tw.
23. cardiogenic shock$.tw.
24. acute coronary syndrome?.tw.
25. acs.tw.
26. (ventric$ adj2 fibrillat$).tw.
27. (ventric$ adj2 tachycardia?).tw.
28. (atri$ adj2 fibrillat$).tw.
29. (atri$ adj2 flutter$).tw.
30. (chest adj2 pain$).tw.
31. or/1-30
32. troponin/ or troponin i/ or troponin t/
33. biological markers/
34. (biological adj marker$).tw.
35. (biochemical adj marker$).tw.
36. (clinical adj marker$).tw.
37. (cardiac adj marker$).tw.

38. biomarker$.tw.
39. bio-marker$.tw.
40. troponin?.tw.
41. or/32-40
42. 31 and 41
43. animal/
44. human/ and animal/
45. 43 not 44
46. 42 not 45
47. randomized controlled trial.pt.
48. Randomized Controlled Trials/
49. Random Allocation/
50. Double-Blind Method/
51. Single-Blind Method/
52. or/47-51
53. clinical trial.pt.
54. exp clinical trials/
55. (clin$ adj3 trial$).tw.
56. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
57. PLACEBOS/
58. placebo$.tw.
59. random.tw.
60. rct?.tw. 53
61. or/53-60
62. 46 and (52 or 61)

Systematic Search 2 – Point-of-care testing

Database: MEDLINE
Coverage: 1966 to October Week 5 2002
Platform: OVID
Search run: 04 December 2002

Strategy:
1. Heart Arrest/
2. exp Myocardial Ischemia/
3. chest pain/
4. ((cardiac or coronary or heart) adj2 arrest$).tw.
5. ((cardiac or coronary or heart) adj2 attack?).tw.
6. (coronary adj2 disease?).tw.
7. angina.tw.
8. "syndrome x".tw.
9. uap.tw.
10. ((cardiac or coronary or heart or myocard$) adj2 aneurysm?).tw.
11. ((cardiac or coronary or heart or myocard$) adj2 arterioscleros?s).tw.
12. ((cardiac or coronary or heart or myocard$) adj2 stenos?s).tw.
13. ((cardiac or coronary or heart or myocard$) adj2 restenos?s).tw.
14. ((cardiac or coronary or heart or myocard$) adj2 thrombos?s).tw.

15. ((cardiac or coronary or heart or myocard$) adj2 vasospasm?).tw.
16. ((cardiac or coronary or heart or myocard$) adj2 spasm?).tw.
17. ((cardiac or coronary or heart or myocard$) adj2 isch?em$).tw.
18. ((cardiac or coronary or heart or myocard$) adj2 infarct$).tw.
19. mi.tw.
20. ami.tw.
21. nqwmi.tw.
22. ((cardiac or coronary or heart or myocard$) adj2 stun$).tw.
23. cardiogenic shock$.tw.
24. acute coronary syndrome?.tw.
25. acs.tw.
26. (ventric$ adj2 fibrillat$).tw.
27. (ventric$ adj2 tachycardia?).tw.
28. (atri$ adj2 fibrillat$).tw.
29. (atri$ adj2 flutter$).tw.
30. (chest adj2 pain$).tw.
31. or/1-30
32. troponin/ or troponin i/ or troponin t/
33. biological markers/
34. (biological adj marker$).tw.
35. (biochemical adj marker$).tw.
36. (clinical adj marker$).tw.
37. (cardiac adj marker$).tw.
38. biomarker$.tw.
39. bio-marker$.tw.
40. troponin?.tw.
41. or/32-40
42. 31 and 41
43. animal/
44. human/ and animal/
45. 43 not 44
46. 42 not 45
47. point-of-care systems/
48. point of care.tw.
49. poc.tw.
50. poct.tw.
51. (bedside or bed-side or bed side).tw.
52. (rapid adj (assay? or immuno?assay? or diagnos$ or test$ or whole blood)).tw.
53. (near adj patient).tw.
54. (stick? adj test$).tw.
55. portable.tw.
56. tropt.tw.
57. cardiac status.tw.
58. stratus cs.tw.
59. alpha dx.tw.
60. or/47-59
61. 46 and 60

Systematic Search 3 – Assessment of chest pain

Database: MEDLINE
Coverage: 1966 to October Week 5 2002
Platform: OVID
Date searched: 20 December 2002

Strategy:
1. Heart Arrest/
2. exp Myocardial Ischemia/
3. chest pain/
4. ((cardiac or coronary or heart) adj2 arrest$).tw.
5. ((cardiac or coronary or heart) adj2 attack?).tw.
6. (coronary adj2 disease?).tw.
7. angina.tw.
8. "syndrome x".tw.
9. uap.tw.
10. ((cardiac or coronary or heart or myocard$) adj2 aneurysm?).tw.
11. ((cardiac or coronary or heart or myocard$) adj2 arterioscleros?s).tw.
12. ((cardiac or coronary or heart or myocard$) adj2 stenos?s).tw.
13. ((cardiac or coronary or heart or myocard$) adj2 restenos?s).tw.
14. ((cardiac or coronary or heart or myocard$) adj2 thrombos?s).tw.
15. ((cardiac or coronary or heart or myocard$) adj2 vasospasm?).tw.
16. ((cardiac or coronary or heart or myocard$) adj2 spasm?).tw.
17. ((cardiac or coronary or heart or myocard$) adj2 isch?em$).tw.
18. ((cardiac or coronary or heart or myocard$) adj2 infarct$).tw.
19. mi.tw.
20. ami.tw.
21. nqwmi.tw
22. ((cardiac or coronary or heart or myocard$) adj2 stun$).tw.
23. cardiogenic shock$.tw.
24. acute coronary syndrome?.tw.
25. acs.tw.
26. (ventric$ adj2 fibrillat$).tw.
27. (ventric$ adj2 tachycardia?).tw.
28. (atri$ adj2 fibrillat$).tw.
29. (atri$ adj2 flutter$).tw.
30. (chest adj2 pain$).tw.
31. or/1-30
32. troponin/ or troponin i/ or troponin t/
33. troponin?.tw.
34. or/32-33
35. 31 and 34
36. exp emergency service, hospital/
37. triage/
38. (emergency adj1 (service? or department? or center? or centre? or unit?)).tw.
39. (trauma adj1 (service? or department? or center? or centre? or unit?)).tw.
40. (accident adj1 emergency).tw.

41. triag$.tw.
42. (emergicenter? or emergicentre?).tw.
43. (chest adj pain? adj1 (service? or department? or center? or centre? or unit?)).tw.
44. medical assessment unit?.tw.
45. or/36-44
46. 35 and 45

Sources

Secondary literature, ongoing research, policy documents

- Health Technology Assessment Database
  Via the Cochrane Library
- NICE
  http://www.nice.org.uk/
- NCCHTA (National Coordinating Centre for Health Technology Assessment)
  http://www.ncchta.org/
- NHS Centre for Reviews and Dissemination, University of York
  http://www.york.ac.uk/inst/crd/
- Birmingham Technology Assessment Group, Department of Public Health and Epidemiology, University of Birmingham
  http://www.publichealth.bham.ac.uk/wmhtag/
- ScHARR (School of Health and Related Research), University of Sheffield
  http://www.shef.ac.uk/~scharr/publications.htm
- South and West R&D Directorate, DEC reports
  http://www.doh.gov.uk/research/swro/rd/publicat/dec/
- British Columbia Office of Health Technology Assessment (BCOHTA)
  http://www.chspr.ubc.ca/bcohta/
- Health Services Utilization and Research Commission (HSURC Saskatchewan)
  http://www.hsurc.sk.ca/
- Institute for Clinical and Evaluative Sciences (ICES)
  http://www.ices.on.ca/
- Manitoba Centre for Health Policy (MCHP)
  http://www.umanitoba.ca/centres/mchp/
- ISTAHC (International Society of Technology Assessment in Health Care)
  http://www.istahc.org/
- ECRI (formerly Emergency Care Research Institute)
  http://www.ecri.org/
- HSTAT (Health Services/Technology Assessment)
  http://text.nlm.nih.gov/
- Cochrane Database of Systematic Reviews (CDSR)
  Cochrane Library
- Database of Abstracts of Reviews of Effectiveness (DARE)
  Cochrane Library
- Ongoing Reviews database
  http://www.update-software.com/National/
- SIGN

http://www.sign.ac.uk/
- ARIF (Aggressive Research Intelligence Facility)
  http://www.bham.ac.uk/arif/
- Health Evidence Bulletins Wales
  http://hebw.uwcm.ac.uk/
- Centre for Clinical Effectiveness, Monash Institute of Public Health
  http://www.med.monash.edu.au/healthservices/cce/
- TRiP
  http://www.tripdatabase.com/
- Bandolier
  http://www.jr2.ox.ac.uk/bandolier/
- SEHD
  http://www.scotland.gov.uk/who/dept_health.asp
- SHOW (Scotland's Health On the Web)
  http://www.show.scot.nhs.uk/
- Chief Scientist Office (CSO)
  http://www.show.scot.nhs.uk/cso/
- Clinical Standards Board for Scotland (CSBS)[3]
  http://www.clinicalstandards.org/
- Clinical Resource and Audit Group (CRAG)[1]
  http://www.show.scot.nhs.uk/crag/

RCTs and other primary literature

- MEDLINE (OVID)
- PREMEDLINE (OVID)
- EMBASE (OVID)
- WEB OF SCIENCE (ISI)
- CINAHL (OVID)
- BIOSIS (EDINA)
- Dissertation Abstracts Online (Proquest)
- Cochrane Controlled Trials Register (OVID)
- MRC (Medical Research Council) Funded Research
  http://fundedresearch.cos.com/MRC/
- Current Controlled Trials
  http://www.controlled-trials.com/
- Clinical trials.gov
  http://clinicaltrials.gov/
- NRR (National Research Register)
  http://www.update-software.com/National/
- CRISP (Computer Retrieval of Information on Scientific Projects)
  https://www-commons.cit.nih.gov/crisp/

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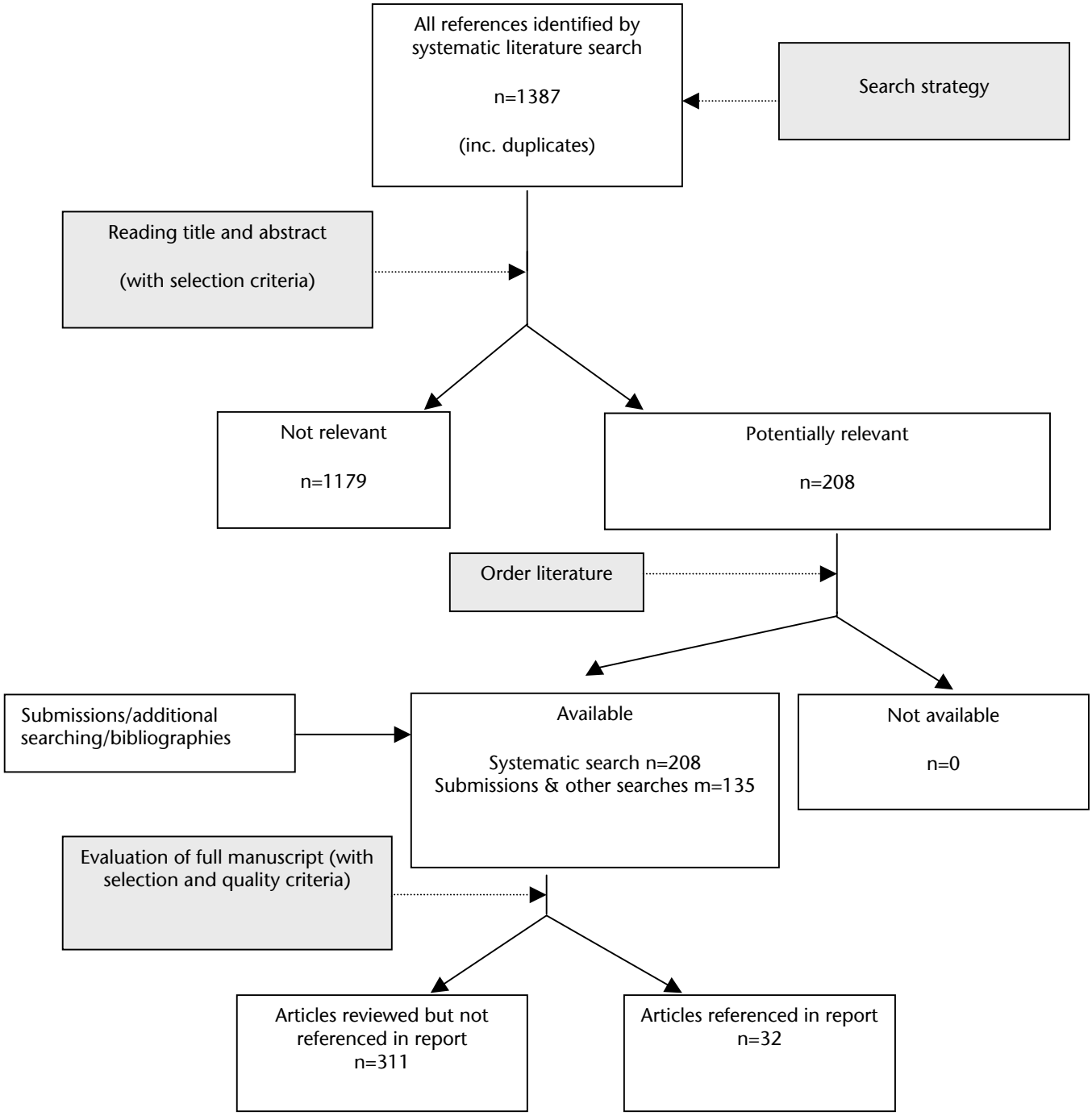
[3] CSBS and CRAG are now a part of NHS Quality Improvement Scotland, http://www.nhshealthquality.org

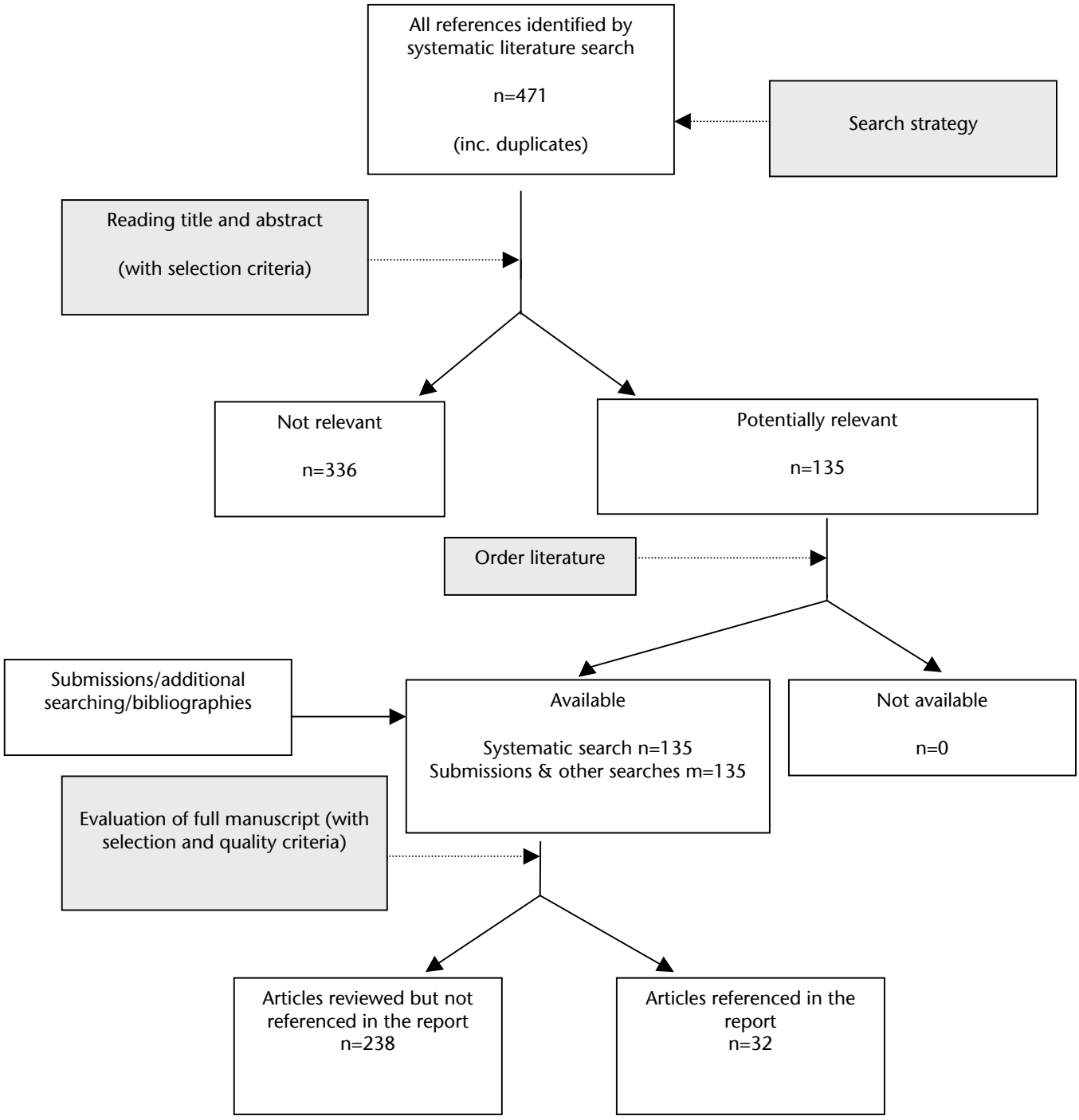
Flow Chart – Search 1

Flow chart of literature selection process
(Outline adapted from CRD 2000)



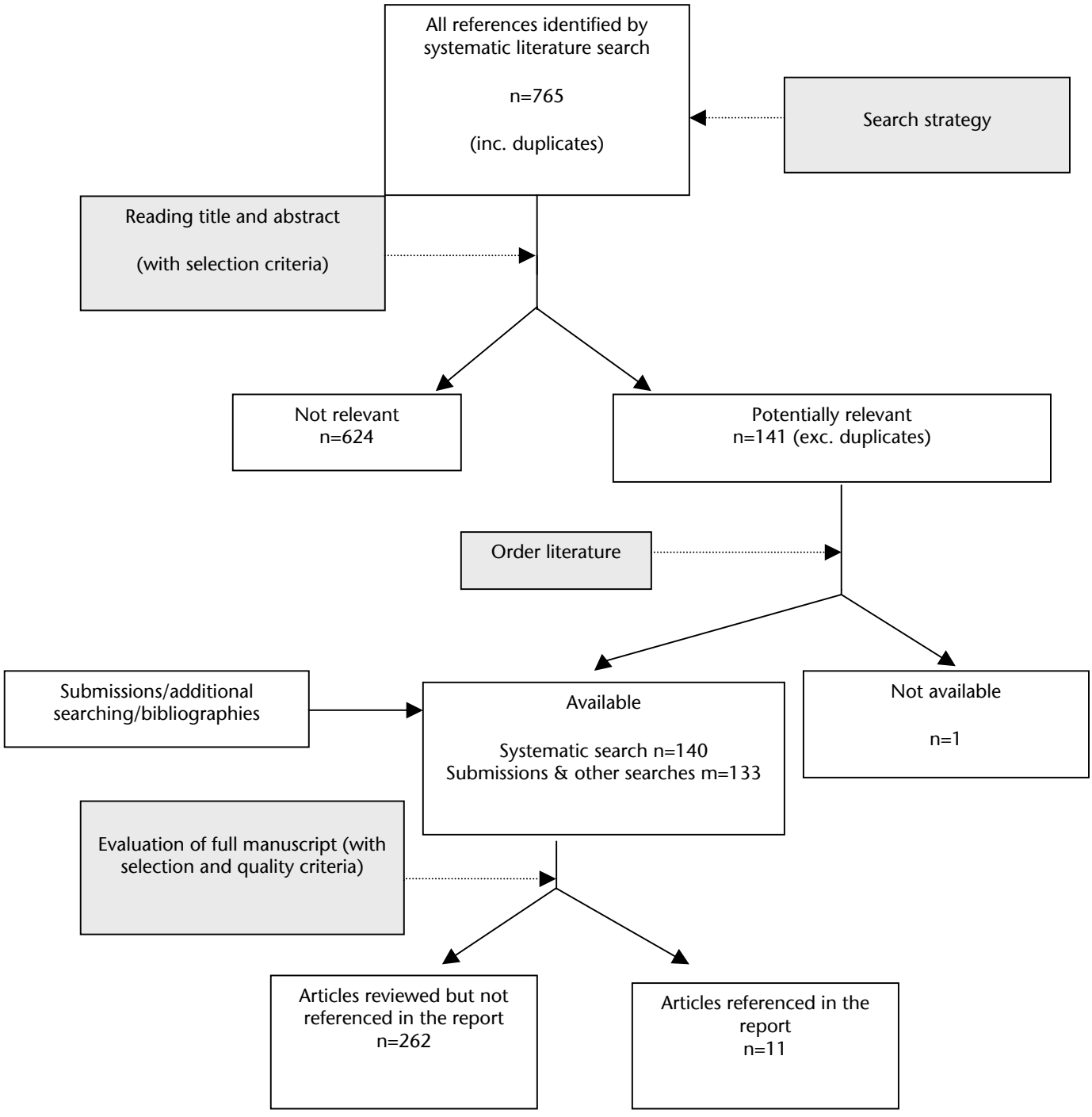
Flow Chart – Search 2

Flow chart of literature selection process
(Outline adapted from CRD 2000)



Flow Chart – Search 3

Flow chart of literature selection process
(Outline adapted from CRD 2000)



Appendix 9

CLINICAL EFFECTIVENESS TABLES

Table A1 Prognostic studies not included in published meta-analyses

Study	Patient source	Number of patients	Troponin assay	Cut-off value	Other predictors	Results
Aguiar *et al.* (2002)	Consecutive patients admitted to CCU with chest pain at rest 'suggestive of ACS'	183	Tn I (Tn I – Access®) (at admission and every 6 hours for 24 hours)	Upper limit of reference: 0.1 μg/L, peak value >0.2 μg/L predicted prognosis (from the receiver operating characteristic [ROC] curve)	12-lead ECG at admission and daily thereafter (deviation of at least 0.1 mV). ST segment monitoring for 24 hours.	30-day death or MI as outcome. Peak Tn I and ST deviation independent risk factors. Tn I: hazard ratio (HR): 2.65 (95% CI 1.01, 6.95) ST segment: HR: 3.07 (95% CI 1.26, 7.46)
Alp *et al.* (2001)	Patients with chest pain of possibly cardiac origin (but not STEMI) referred to CCU of a DGH	400 patients randomised between serial CK + ECG over 24–48 hours (n=182) or admission ECG + 6 hours Tn (n=218)	Tn I – qualitative point-of-care testing (Spectral Cardiac STATus™)	0.1 μg/L	ECG (classified as ischaemic or normal)	Only comparisons between Tn levels reported (outcome was 30-day MI, death or urgent requirement for revascularisation). High Tn: 75% (95% CI 60%, 85%) Low Tn, ischaemic ECG: 15% (95% CI 7%, 28%) Low Tn, normal ECG: 3% (95% CI 1%, 8%)
Aviles *et al.* (2002a)	Participants in the GUSTO IV clinical trial. Selected for one or more of: i) angina at rest ii) ST depression iii) raised troponin.	7800 enrolled, 7033 with Tn and creatinine clearance both measured	Tn T (3rd generation Elecsys®)	Prespecified at 0.1 μg/L 'following experience with 2nd generation assay'	Abnormal renal function (measured by creatinine clearance <58.4 mL/min). Results adjusted for gender, age, ST segment depression, cardiac history and diabetes.	30-day MI or death as outcome. Adjusted OR for positive Tn among patients with normal creatinine clearance was 1.7 (95% CI 1.3, 2.2). OR among patients with low clearance was 2.5 (95% CI 1.8, 3.3).

Study	Patient source	Number of patients	Troponin assay	Cut-off value	Other predictors	Results
Diderholm *et al.* (2002)	Subset of patients from FRISC II study. All had ischaemic ECG (ST depression or T-wave inversion) or elevation of a marker of myocardial damage.	2457 enrolled in trial in total, all with Tn T measurement included: n=2286	Tn T (3rd generation Elecsys)	Functional sensitivity (i.e. level where CV <20%) 0.03 μg/L	Adjusted for age, gender, smoking, hypertension, raised cholesterol, previous MI and treatment.	Death or MI at 12 months as outcome. Raised Tn T: adjusted OR 1.80 (95% CI 1.31, 2.48) Raised Tn T and ST depression: OR 1.80 (95% CI 1.40, 2.40)
Fromm *et al.* (2001)	Consecutive patients at 4 teaching hospitals with chest pain 15 minutes thought to be myocardial in origin	955 enrolled, 825 patients followed until death or for 6 months	Tn T (cardiac Tn T assay Boehringer), Tn I (Stratus® Cardiac Tn I)	Tn T – 0.1 μg/L Tn I – 1.5 μg/L (tested on arrival, at 1 hour, every 2 hours to 6 hours, then every 4 hours up to 24 hours)	Total CK-MB activity, CK-MB subforms	RRs for death or urgent revascularisation within 6 months for a given positive marker are: CK-MB: 2.0 (95% CI 1.3, 2.4) Myoglobin: 1.65 (95% CI 1.1, 2.9) Tn T: 2.2 (95% CI 1.5, 3.2) Tn I: 1.7 (95% CI 1.2, 2.4) CK-MB subforms: 1.8 (95% CI 1.3, 2.6)
Mangione *et al.* (2001) (abstract)	Consecutive patients with >15 minutes chest pain at rest in previous 24 hours and clinically at 'low risk' (≤7%) of AMI	501 (486 of the 498 who survived to discharge were followed up – median 35 months)	Tn I measured at presentation, 3, 6, 8 and 12 hours post admission (machine not specified)	Not stated	Increased risk of long-term serious event was predicted by any raised marker (i.e. also CK-MB mass, myoglobin, myosin light chain-1). Tn I was most useful marker. Only independent prognostic indicator was age.	Outcome was MI or death during follow up. OR for elevated Tn I was 2.3 (95% CI 1.3, 4.2), 11.7% in Tn I-negative group, 26% in Tn I-positive group.

Study	Patient source	Number of patients	Troponin assay	Cut-off value	Other predictors	Results
Sabatine *et al.* (2002)	2 separate data sets: a subset of OPUS-TIMI 16 and a subset of TACTICS TIMI 18. Both trials in patients with confirmed ACS. Models built separately on each data set.	450 OPUS-TIMI – randomly selected from one treatment group, 1635 TACTICS TIMI 18	Tn I (ACS: immunoassay)	0.1 μg/L	C-reactive protein (CRP) and B-type natriuretic peptide. All 3 markers tested at enrolment.	6-month combined endpoint (death, new MI, congestive heart failure) in TACTICS TIMI data, 1 raised biomarker OR: 2.1 ($p<0.01$), 2 raised biomarker OR: 3.1 ($p<0.001$) and 3 raised biomarker OR: 3.7 ($p<0.001$). 10-month combined endpoint (as above) in OPUS-TIMI data, 1 raised biomarker HR: 2.0, 2 raised biomarker HR: 2.3 and 3 raised biomarker HR: 5.3. Only the 95% CI of the latter did not include 1.0. RR was 1.9, 2.5, and 4.7 respectively.
Venge *et al.* (2002)	Subset of patients from FRISC II study. All had ischaemic ECG (ST depression or T-wave inversion).	Of 2457 patients in study, 1763 patients had Tn T and Tn I (x2) measured.	Tn T (Elecsys® 2010), Tn I (AxSYM® and Access® AccuTnI)	2 used: 99th percentile of upper reference limit – Elecsys®: 0.01 μg/L, AxSYM®: 0.6 μg/L, AccuTnI: 0.02 μg/L. Functional sensitivity (i.e. where CV ≤20%) – Elecsys®: 0.03 μg/L, AxSYM®: 1.0 μg/L, AccuTnI: 0.03 μg/L.	None reported	Access® AccuTnI was a better discriminator than Elecsys® and AxSYM®, whose clinical performances were similar. As expected, the 2 Tn I assays correlated better with each other (r_s=0.96) than they did with the Tn T assay (r_s=0.93).

Table A2 Studies showing joint prognostic value of cardiac troponin and other risk factors

Study	Patient source	Number of patients	Troponin assay	Cut-off value	Other predictors	Results
Aguiar *et al.* (2002)	Consecutive patients admitted to CCU with chest pain at rest 'suggestive of ACS'	183	Tn I (Access®) at admission and every 6 hours for 24 hours	Upper limit of reference: 0.1 μg/L, peak value >0.2 μg/L predicted prognosis (from ROC)	12-lead ECG at admission and daily thereafter (deviation of at least 0.1 mV). ST segment monitoring for 24 hours.	30-day death or MI as outcome. Peak Tn I and ST deviation independent risk factors. Tn I: HR: 2.65 (95% CI 1.01, 6.95) ST segment: HR: 3.07 (95% CI 1.26, 7.46)
Antman *et al.* (1996)	Subset of patients enrolled in TIMI IIIB study – patients with diagnosed UA or NSTEMI	1404 of 1473 enrolled in whole study (with plasma specimens from time of enrolment)	Tn I at admission (Stratus® II)	Analysed as continuous variable in multivariate model (minimum detection level 0.4 μg/L)	Age, gender, medical history, smoking status, drug use, duration of pain and ECG	Multivariate analysis showed an increase in RR of mortality by day 42 per 1 μg/L rise in Tn level 1.03 (95% CI 1.00, 1.05) (adjusted for baseline variables).
Antman *et al.* (2000)	Patients from 2 RCTs (TIMI 11B and ESSENCE [Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and non-Q-wave MI] trial). Risk score built using 1 group (unfractionated heparin from TIMI 11B) and validated using 3 remaining groups.	1957 build set, 5124 validation set	Tn I, Tn T and CK-MB used interchangeably as 'biomarker'. (quoted from original work)	'as declared by appropriate laboratory' (quoted from original work)	TIMI score built using age, risk factors for CAD, prior stenosis, ST deviation, prior use of aspirin and elevated markers.	TIMI score was a significant predictor of risk of death, MI or urgent revascularisation in 14 days post randomisation (to enoxaparin or unfractionated heparin) (p-value for trend <0.001).

Study	Patient source	Number of patients	Troponin assay	Cut-off value	Other predictors	Results
Heeschen *et al.* (2000)	Subgroup of placebo group (n=547) from CAPTURE trial (n=1265) with Tn and CRP measured	447 (100 excluded as they had MI within 14 days before enrolment)	Tn T (Elecsys® 2010)	0.1 μg/L ('diagnostic threshold')	CRP, age and history of MI	Tn T and CRP were independent predictors of combined event (MI/mortality) at 6-month follow up (but ST depression was not). Tn T ($p<0.001$) but not CRP ($p=0.41$) was predictive of mortality/MI within the first 72-hour period.
Jernberg *et al.* (2000)	Chest pain or other symptom suggesting ACS. ST segment elevation and uninterpretable ECG were excluded.	598 of 1194 patients admitted to CCU during FAST study	Tn T at admission, 6 and 12 hours (Enzymun-Test System)	0.1 μg/L	ST segment monitoring	Both Tn T and ST episodes predict 30-day combined death and AMI ($p\leq0.01$).
Kerr & Dunt (1997)	Prospective study of patients with angina at rest admitted to CCU (excluded if MI)	164	Tn T measured 14 and 72 hours post-symptom onset ('Boehringer Mannheim assay')	0.05 and 0.1 μg/L	ECG, age, sex and risk factors for coronary artery disease	Tn T >0.05 μg/L was not an independent predictor for in-hospital events (OR 1.3, 95% CI 0.5, 3.6), but was for serious events within 6-month follow up (OR 3.7, 95% CI 1.8, 7.6). Tn T >0.1 μg/L was also a predictor at 6 months.
Lindahl *et al.* (1997a)	Patients from FRISC trial with Tn T and ETT performed	766 (recorded in original publication)	Tn T (peak in first 24 hours) (machine not specified)	0.06 and 0.2 μg/L	Age, ST depression at inclusion, ETT	Tn is an independent predictor of risk of MI/cardiac death at 5 months.
Mangione *et al.* (2001) (abstract)	Consecutive patients with >15 minutes chest pain at rest in previous 24 hours and clinically at 'low risk' (≤7%) of AMI	501 (486 of the 498 who survived to discharge were followed up – median 35 months)	Tn I measured at presentation, 3, 6, 8 and 12 hours post admission (machine not specified)	Not stated	Increased risk of long-term serious event was predicted by any raised marker (i.e. also CK-MB mass, myoglobin, myosin light chain-1). Tn I was most useful marker. Only independent prognostic indicator was age.	Outcome was MI or death during follow up. OR for elevated Tn I was 2.3 (95% CI 1.3, 4.2), 11.7% in Tn I-negative group, 26% in Tn I-positive group.

Study	Patient source	Number of patients	Troponin assay	Cut-off value	Other predictors	Results
Nergaard *et al.* (1999)	Consecutive patients with suspected ACS with ST segment monitoring (substudy of the Thrombin Inhibition in Myocardial Ischemia [TRIM] trial)	232 of 1209 in TRIM trial	Tn T within 24 hours of pain onset (ELISA ES300)	0.2 μg/L (effect of cut-off at 0.1 μg/L also presented in paper)	24-hour ST segment monitoring, previous use of calcium antagonists, age, sex, coronary artery disease risk factors and admission ECG	Tn T is an independent risk factor (RR 3.85, $p<0.05$) (also ST deviation (RR 7.43) and calcium antagonist use (RR 3.31)). 3 groups: low (1.7%, n=117), intermediate (3.1%, n=65) or high (28.5%, n=31) risk of 30-day death or AMI could be identified using a combination of Tn T level and 24-hour ST monitor results (no validation done).
Solomon *et al.* (2002)	Patients (with IHD) randomised to medical management in TIMI IIIB trial	733	Tn I at admission (machine not specified)	0.4 μg/L	Clinical history, ST segment depression >0.1 mV and physical examination	Logistic regression used to construct a risk score to predict endpoint (need for catheterisation within 42 days). Tn I ≥0.4 μg/L: OR 1.4 (95% CI 1.1, 1.9)
Wilcox *et al.* (2001)	All patients presenting to an emergency department of Melbourne teaching hospital in 6-week period with CK-MB requested	424 (excluding those who had a cardiac arrest in the emergency department or were not followed up)	Tn I (AxSYM®)	2.0 μg/L for MI (0.6–0.2 μg/L interpreted as 'minor myocardial damage')	Age, ECG, clinical features and CK-MB	30-day all-cause mortality rates: Tn I and CK-MB raised: 27% (95% CI 13%, 44%) Tn I raised, CK-MB normal: 24% (95% CI 5%, 43%) Both normal: 4.3% (95% CI 2.1%, 6.5%). Multivariate regression indicated that Tn I >2.0 μg/L was an independent predictor of death (OR: 5.1, 95% CI 1.5, 17.1) but CK-MB and Tn I between 0.6 and 2.0 μg/L were not. All 3 were predictive of death in univariate analysis.

Table A3 Studies of the prognostic value of troponin I illustrating the variation in cut-off values

Study	Patient source	Number of patients	Troponin assay	Cut-off value	Other predictors	Results
Antman *et al.* (1996)	Subset of patients enrolled in TIMI IIIB study – patients with diagnosed UA or NSTEMI	1404 of 1473 enrolled in whole study (with plasma specimens from time of enrolment)	Tn I at admission (Stratus® II)	Analysed as continuous variable in multivariate model (minimum detection level 0.4 μg/L)	Age, gender, medical history, smoking status, drug use, duration of pain and ECG	Multivariate analysis showed an increase in RR of mortality by day 42 per 1 μg/L rise in Tn level 1.03 (95% CI 1.00, 1.05) (adjusted for baseline variables).
Boa *et al.* (2000) (abstract)	Consecutive patients with ACS admitted to CCU without ST elevation	110 (10 later excluded as CK/CK-MB mass indicated MI)	Tn I (AxSYM®)	2 μg/L	None reported	Cut-off for risk stratification in ACS (i.e. correlation with endpoint: death, MI or readmission with ACS within 1 year). Other levels of Tn I were tested (0.5 and 1.0 μg/L) but were not correlated to the endpoint at 1 year. None of the 3 cut-offs for Tn I was correlated to risk of endpoint at 1 month.
Collinson & Gaynor (2002) (abstract)	Consecutive admissions to CCU	253 (12-hour Tn result available on 97 patients without ST elevation)	Tn I at admission, 4 and 12 hours (ACS:180®)	0.1 μg/L	None reported	Raised Tn I at admission did not indicate increased risk for endpoint at 4 years (death or MI). Patients with raised 12-hour Tn I had a 4-year combined death or MI rate of 14/50 compared with 3/47 in those without raised Tn I.
Collinson *et al.* (1998) (abstract)	Patients admitted to CCU with suspected ACS	304	Tn I (Opus™ Plus) at admission and 12–24 hours later	1.0 μg/L	None reported	In 121 patients without ST elevation at 6–12 hours Tn I >1.0μg/L predicted 800-day death rates: 9/57 versus 2/64, p=0.033 (Fisher exact test)
Collinson *et al.* (2001a)	Normal subjects	200	AxSYM®	1.7 μg/L		99th percentile of 200 normal subjects

Study	Patient source	Number of patients	Troponin assay	Cut-off value	Other predictors	Results
Collinson *et al.* (2001c)	Consecutive patients with suspected ACS admitted to CCU and a control group undergoing endurance training	279 in cardiac group	Tn I at admission, 4 and 12 hours. (ACS:180®) (Tn T also measured – 12 hours [Elecsys® 1010])	0.1 μg/L (0.15 and 0.2 μg/L also evaluated) (Tn T – 0.1 and 0.2 μg/L)	Tn T >0.1 μg/L	For 97 patients in cardiac group with UA: RR for 6-month combined event (death, AMI or recurrent UA) for Tn I >0.1 μg/L was 2.81 (95% CI 1.26, 6.26), and for Tn I >0.15 μg/L was 2.6 (95% CI 1.21, 5.61). It was not significant for Tn I >0.2 μg/L.
Heeschen *et al.* (1999b)	Patients from the PRISM trial with 3 cardiac marker results (all had diagnosed coronary artery disease)	2222 of 3232 in whole trial	Tn I (AxSYM®) measured at baseline (Tn T also measured [Elecsys® 2010])	1.0 μg/L for risk stratification in ACS	Tn T, age	Cut-off for therapeutic benefit of glycoprotein IIb/IIIa inhibitor
Luscher *et al.* (1997)	Patients with suspected unstable coronary artery disease (component of TRIM study)	516 of 1209 for whole study	Tn I (Opus™ Plus) (Tn T also measured [ELISA ES 300]). Both measured at inclusion, 6, 12, 24, 36, 48 and 72 hours later.	Tn I 2.0 μg/L (1.0, 1.5 and 2.5 μg/L also evaluated) (Tn T 0.1 μg/L; 0.05, 0.15 and 0.2 μg/L also evaluated)	Age, Tn T, ST depression	Tn I >2.0 μg/L within 6 hours predicted mortality at 30 days: 3.2% versus 0.7% (p=0.026). Also predictive of death or MI at 30 days OR 2.15 (95% CI 1.10, 4.18).
Morrow *et al.* (2000b)	Patients from TIMI 11B trial	681	Tn I (Bayer Immuno I®, Dimension® RxL, ACS:180®)	0.1 μg/L		RRs for combined death/non-fatal MI at 43 days: Immuno 1® – 2.2 (95% CI 1.3, 3.6) ACS:180® – 2.8 (95% CI 1.5, 5.1) Dimension® RxL – 3.0 (95% CI 1.5, 5.7)

Table A4 Studies of the relationship between troponin test and LVEF

Study	Patient characteristics	Troponin test	Results
Panteghini *et al.* (2002)	65 patients admitted to CCU with AMI, 55 received thrombolysis and/or PCI	Tn T (3rd generation Elecsys®) measured at discharge (median 72 hours post admission, range 40–160 hours)	Inverse relationship (r=-0.56, p<0.001) between Tn T concentration and LVEF at discharge from CCU and at 3 months (r=-0.70, p<0.001).
Rao *et al.* (1998)	Retrospective study of 50 consecutive patients admitted to hospital with first MI who underwent angiography, 32 of them received thrombolysis	Tn T performed 12–48 hours after presentation ('enzyme linked immunosorbent assay')	Tn T >2.8 μg/L had 100% sensitivity (95% CI 84.6, 100) and 92.9% specificity (95% CI 76.5, 99.1) to predict LVEF <40%.
Rao *et al.* (2003a)	201 consecutive patients admitted to a DGH with suspected ACS (and final diagnosis of MI, WHO definition). Excluded if previous MI, age 80, inadequate ECG obtained.	Tn T performed 12–24 hours after admission (2nd generation Elecsys® 1010)	Tn T ≥2.8 μg/L has 95.5% sensitivity (95% CI 90.5, 98.3) and 88.1% specificity (95% CI 77.8, 94.7) to predict LVEF <40%. The area under the ROC curve is significantly larger for Tn T than for peak CK (0.91 versus 0.069).

Table A5 Studies comparing troponin with CK or CK-MB

Study	Patient source	Number of patients	Troponin assay	Cut-off value	CK cut-off	Results
Appelbaum *et al.* (2000) (abstract)	Retrospective study of first patients with UA presenting to emergency department after 4 months of adoption of Tn I. Excluded if AMI, PCI within 4 weeks, ST elevation at inclusion or abnormal CK-MB.	212 – 32 low risk, 156 intermediate risk, 24 high risk (by AHCPR criteria)	Tn I (machine not specified)	2.0 μg/L (0.4 μg/L: 'mild elevation')	Not stated	Patients at intermediate risk were at significantly higher rate of in-hospital cardiac events if Tn I >2.0 μg/L (12/33) when compared with 0.4–2.0 μg/L (6/123).
Aviles *et al.* (2002b)	Retrospective study of consecutive patients presenting to an emergency department with UA (no recent PCI, no STEMI, normal CK and CK-MB)	724	Tn I (Bayer ACS:180®) – peak level over first 24 hours	0.5 μg/L	CK 336 IU/L for men and 269 IU/L for women. CK-MB 4.3 μg/L.	Tn I >0.5 μg/L predicted increased risk of death (20% versus 8%), HR: (using multivariate analysis) 1.62 (95% CI 1.03, 2.57). Age, gender, diabetes and treatment were also all significant predictors of mortality (Cox regression).
Dulam *et al.* (2000) (abstract)	Consecutive prospective emergency department patients with chest pain. Tn I, CK-MB and CK-MB subforms measured on arrival and 8 hours later (if chest pain <8 hours).	100 (78 with normal CK-MB)	Not stated	Not stated	Not specified	9 of 78 with normal CK-MB had raised Tn I and 8 of the 9 had a major coronary event in hospital; 21 of the same 78 had abnormal CK-MB subforms and 6 of those suffered major events in hospital. Therefore, Tn I was more strongly predictive of in-hospital cardiac events than CK-MB subforms.

Study	Patient source	Number of patients	Troponin assay	Cut-off value	CK cut-off	Results
Morrow *et al.* (2000a)	Patients with normal CK-MB levels from TIMI-11B trial with confirmed NSTEMI ACS, excluded if revascularisation was planned, or patient had undergone recent CABG or PTCA	359 (341 had both Tn I measure-ments) (3910 in whole trial)	Tn I at enrolment and 12–24 hours later (Dimension® RxL)	0.1 μg/L	Not specified	OR for death, non-fatal MI or urgent revascularisation by 14 days for zero or 12–24 hour Tn I >0.1 μg/L was 4.0 (95% CI 2.1, 7.7) (by multivariate analysis). Baseline Tn I measurement alone also predicted combined endpoint at 14 days.
Newby *et al.* (2000a)	Consecutive patients assigned to chest pain unit from emergency department with Tn T measurements, normal/non-diagnostic ECG, normal initial CK/CK-MB	383	Tn T at 0, 4 and 8 hours (2nd generation ES 300)	0.1 μg/L	CK-MB: 9 μg/L	CK-MB >9 μg/L in 8 of 383 patients (7 of whom had Tn >0.1 μg/L). Tn >0.1 μg/L in 39 of 383 patients Median follow up: 29 months Mortality rates: 27% Tn positive, 7% Tn negative ($p<0.001$).
Pettijohn *et al.* (1997)	Consecutive patients in cardiology service with chest pain and normal CK-MB (excluded if renal failure)	129 (94 had normal Tn T, and 35 had raised Tn T)	Tn T (ES300 ELISA) at admission, 8 and 16 hours	0.1 mg/L	CK-MB >5% of total CK	Endpoint was death/MI or revascularisation at 6 months. Tn T <0.1 mg/L: endpoint in 11 of 94 patients. Tn T ≥0.1 mg/L: endpoint in 12 of 35 patients ($p<0.01$). OR 3.9 (95% CI 1.5, 10.1). (No patients were seen with elevated CK-MB and normal Tn I).

Table A6 Studies concerned with the interaction between troponin level and treatment effect of LMWH

Study	Design	Number of patients	Troponin assay	Cut-off value	Other predictors	Results
Lindahl *et al.* (1997b)	Patients with ACS (new/recently increased symptoms plus ECG change) subgroup of FRISC study. Exclusions: high risk of bleeding, indication for thrombolysis or planned CABG or PTCA.	971 (488 placebo, 483 dalteparin) (1506 in whole FRISC study)	Tn T (Enzymun-Test) at inclusion	0.1 μg/L (upper reference for normal 0.06 μg/L)	Not stated	Significant interaction ($p<0.01$) between Tn T level and treatment on endpoint (combined death or MI at 40 days). Tn <0.1 μg/L: rates of endpoint 4.7% (8/170) (placebo) and 5.7% (9/157) (dalteparin) respectively. RR was 1.22 (95% CI 0.5, 3.1). Tn ≥0.1 μg/L: rates of endpoint 14.2% (45/318) (placebo) and 7.4% (24/326) (dalteparin). RR was 0.52 (95% CI 0.3, 0.8).
Morrow *et al.* (2000a)	Patients with normal CK-MB levels from TIMI 11B trial with confirmed NSTEMI ACS, excluded if revascularisation was planned, or patient had undergone recent CABG or PTCA.	359 (341 had both Tn I measurements) (3910 in whole trial)	Tn I at enrolment and 12–24 hours later (Dimen-sion® RxL)	0.1 μg/L	Not specified	Effect of LMWH was significantly greater ($p<0.5$) in high Tn group.

Table A7 Studies concerned with the interaction between troponin level and effect of early intervention (within 72 hours)

Study	Design	Number of patients	Troponin assay	Cut-off value	Other predictors	Results
Diderholm *et al.* (2002)	Subset of patients from FRISC II study. All had ischaemic ECG (ST depression or T-wave inversion) or elevation of a marker of myocardial damage. Patients randomised to conservative or invasive therapy, all received dalteparin.	2457 enrolled in trial in total, all with Tn T measurement were included: n=2286	Tn T (3rd generation Elecsys®) median collection time 39 hours from start of chest pain	Functional sensitivity (i.e. level where CV <20%) 0.03 μg/L	Adjusted for age, gender, smoking, hypertension, raised cholesterol, previous MI and treatment.	Death or MI at 12 months as outcome. Tn ≥0.03 μg/L and ST depression: RR for conservative versus invasive therapy was 0.6 (95% CI 0.43, 0.82). Tn ≥0.03 μg/L, normal ST: RR 0.9 (95% CI 0.60, 1.34). Tn <0.03 μg/L, ST depression: RR 1.13 (95% CI 0.55, 2.39). Both normal: RR 0.70 (95% CI 0.36, 1.38).
Morrow *et al.* (2001)	Patients with ACS TACTICS TIMI 18: randomised trial of invasive versus conservative therapy (all patients given tirofiban) excluded if STEMI, recent CABG or PCI	2220 (1821 with Tn I level measured)	Tn I (ACS:180®) Tn T (Elecsys® 1010)	Tn I 0.1 μg/L (also evaluated 1.5 μg/L [MI] and 0.4 μg/L [10% CV]). Tn T 0.1 μg/L (also evaluated 0.05 μg/L [10% CV]).	None reported	Primary outcome was six-month MI, death or rehospitalisation for ACS. Interaction test significant at p<0.01. Tn I <0.1 μg/L: events in invasive versus conservative group 16.0% versus 12.4% respectively; OR: 1.4 (95% CI 0.9, 2.1). Tn I ≥0.1 μg/L: events in invasive versus conservative group 15.3% versus 25.0% respectively; OR: 0.54 (95% CI 0.4 , 0.7). 'similar results observed with Tn T'.

Table A8 Performance data for TROPT *Sensitive*®

Author/Date	Patient/Sample source	Cut-off level (μg/L)	Readers	True +ve	False -ve	False +ve	True -ve
Azzazy *et al.* (1999)	402 patients (88 with AMI, 77 with UA, 161 with other cardiac conditions, 17 with musculoskeletal damage, 43 with renal failure and 16 others)	0.08		168	6	38	190
Baum *et al.* (1997)	365 samples from suspected ACS, 91 samples from blood donors, 1271 samples from non-cardiac patients (these are all below the limit of detection for laboratory assay)	0.08	Technicians or laboratory physician				
Christenson *et al.* (1997a)	335 patients admitted to an emergency department, 91.4% with cardiac conditions	0.08		197	6	42	221
deFilippi & Parmar (1997)	199 patients with suspected ACS (189 with normal ECG)	0.08	1 trained reader	35	0	6	158
Hirschl *et al.* (2000)	804 samples from 510 patients with suspected ACS, 18 from 15 cardiac surgery patients. Study conducted in 3 laboratories and 2 CCUs – results presented separately.	0.1	Laboratory technicians	438	22	2	360
Hirschl *et al.* (2000)	CCU results	0.1	Nurses	513	37	2	234

Table A9 Performance data for Cardiac STATus™

Author/Date	Patient/ Sample source	Cut-off level (μg/L) and comparator	Readers	True +ve	False -ve	False +ve	True -ve
Christenson *et al.* (2001)	939 chest pain patients presenting to an emergency department	0.1 Dade Behring Dimension® RxL	Emergency depart-ment staff	38	35	29	837
Heeschen *et al.* (1998)	1198 samples from 59 AMI, 321 unstable angina pectoris (UAP), 37 cardiac (not IHD), 120 non-cardiac and 27 renal failure	0.14 laboratory specific device using the same antibody system as Cardiac STATus™	Trained observers	302	0	40	856
Hohnadel *et al.* (2002)	40 patients with possible ACS	1.5 DPC Immulite® Turbo	Not reported	9	7	0	18
Pagani *et al.* (2001)	102 samples from 62 ACS patients	0.07 Beckman Access®	Laboratory technicians	30	0	4	68
Panteghini *et al.* (1997)	Sample from patients with suspected MI (number not specified)	0.2 Sanofi Access ('unimproved' version)	Results given as 'all positive above 0.23 μg/L, all negative below 0.2 μg/L'				

Table A10 Risk stratification results for TROPT *Sensitive*®

Author/Date	Patient details	Assay used	Follow up	Events	Rate troponin positive	Rate troponin negative
deFilippi *et al.* (1998)	199 patients with suspected ACS (189 normal ECG)	TROPT *Sensitive*®	86% follow up (median 361 days)	Death, AMI or re-admission for cardiac cause	10/39	10/132
van Domburg *et al.* (2000a)	77 patients with UAP	TROPT	30 days	Death or AMI	2/11	0/66

Table A11 Data from James *et al.* (2001b) comparing quantitative and qualitative results

Test result	Tn T <0.01 μg/L	Tn T ≥0.01 μg/L
Troponin test strip negative	1269	1107
Troponin test strip positive	219	2166
Death or MI at 30 days		
Troponin test strip negative	34 (2.7%)	111 (10%)
Troponin test strip positive	7 (3.3%)	214 (9.9%)

Table A12 Performance data for TROPT *Quantitative*®

Author/Date	Patient/Sample sources	Comparator	Regression results	Concordance (categorical) results	CV results
Barnes & Collinson (2001)	143 routine serum samples (all analysis done in laboratory)	Elecsys® 2010 (3rd generation)	TROPT *Quantitative*® (Cardiac reader [CR]) Tn T = 0.585 Elecsys® – 0.036	Expected from regression that any samples >0.23 μg/L would be positive on CR – in fact, all >0.27 μg/L positive, between 0.19 and 0.27 μg/L 'some positive', rest became positive on strip after further incubation. All <0.18 μg/L on Elecsys® needed further incubation.	Comment that CR is suitable for rule in, but not rule out.
Collinson *et al.* (2000)	657 patients with chest pain, normal ECG, atypical history and low clinical risk of IHD (data collected prospectively in an emergency department). 453 patients had full clinical data available.	Elecsys® 1010 (2nd generation)	CR TnT = 0.87 Elecsys®	33 classified as AMI by both, 36 as angina pectoris (AP) by CR versus 48 by Elecsys®, 385 non-cardiac pain by CR versus 372 by Elecsys®	
Collinson *et al.* (2001b)	319 samples from patients with known ACS used in method comparison study (200 samples from different group used in calibration study)	Elecsys® 2010 (3rd generation)	CR = 1.07 Elecsys®	Concordance results shown in Table A13. 92% overall concordance.	CV between 9% and 16% (concentration range not specified)

Author/Date	Patient/Sample sources	Comparator	Regression results	Concordance (categorical) results	CV results
Muller-Bardorff *et al.* (1999)	64 healthy volunteers and 252 patients (351 samples from 37 patients with AMI, 354 samples from 44 patients with UAP, 325 samples from 171 patients with no IHD)	Enzymun T ELISA (2nd generation). Note – this is largely a calibration study with premarketing version of the CR. 140 samples from 140 patients with ACS used in method comparison study after calibration.	CR = 0.85 ELISA + 0.002 (Accuracy ± 15%)	For patients with UAP, 126/354 samples >0.1 μg/L from ELISA, 118 of these also positive on CR (all 126 positive visually on re-inspection)	10% CV within-day at 0.16 μg/L; 18% day-to-day CV at 0.33 μg/L.
Muller-Bardorff *et al.* (2000)	281 samples from unselected ACS patients at 7 centres	Enzymun T ELISA (2nd generation)	CR = 0.93 ELISA + 0.02 (Error range ± 25%)	3/281 discordant results when cut-off of 0.1 μg/L used (result pairs in form CR/ELISA are: negative/0.12, 0.14/0.08, 0.14/0.09)	Within instrument CVs in range 10–15% for TnT 0.1–1.2 μg/L between 4% and 9% for same range.

Table A13 Concordance between Elecsys® and TROPT *Quantitative*® (Collinson *et al.*, 2001b)

Elecsys® result (μg/L)				
		0–<0.05	0.05–<0.1	>0.1
TROPT *Quantitative*®	0.1–2.0 μg/L and 'High'	0	9	239
	'Low'	1	5	9
	'Negative'	51	4	1

Table A14 Concordance between Elecsys® and TROPT *Quantitative*® (RAH, Paisley)

Elecsys® result (μg/L)				
		0–<0.05	0.05–<0.1	>0.1
TROPT *Quantitative*®	0.1–2.0 μg/L and 'High'	2	0	25
	'Low'	0	3	1
	'Negative'	165	1	0

Table A15 Performance data for Stratus® CS

Author/Date	Patient/Sample sources	Comparator	Regression results	Concordance (categorical) results	CV results
Altinier *et al.* (1999)	Method comparison study – source of samples not specified	Dimension® RxL (Dade Behring)	Stratus® CS (SCS) Tn I = 0.805 RxL + 0.352 (n=63, range 0–25.91 μg/L)	Not given	Within-run CV 19.3% at 0.07 μg/L; between-run CV 13.99% at 0.08 μg/L.
Altinier *et al.* (2000)	Samples from unspecified number of ACS patients used for method comparison, 85 normals used to assess reference range, Dade Behring controls used to assess CV.	Dimension® RxL (Dade Behring)	SCS = 0.69 RxL + 0.946 High dispersion at large Tn I values (limit of linearity for SCS in dilution assay is 20 μg/L). For 50 samples <16 μg/L, SCS = 0.956 RxL + 0.049.	Not applicable	Within-run CV 14.5% at 0.07 μg/L; between-run CV 14.0%.at 0.08 μg/L. Upper reference limit at 97.5th percentile is 0.03 μg/L, upper reference limit at 99th percentile is 0.05 μg/L.
Beneteau-Burnat *et al.* (2001b)	100 patients (unspecified). Method comparison and imprecision done on plasma samples. Results from 50 paired plasma/whole blood samples suggest no difference.	Stratus® II (Dade Behring)	SCS = 1.01 Stratus® II – 0.12 No correlation seen for values <0.3 μg/L on SCS. Note that limit of detection was 0.03 μg/L for SCS versus 0.35 μg/L for Stratus® II.	Not applicable	Within-assay CV 2.2% at 0.71 μg/L; between-assay CV 3.0% at 0.71 μg/L.
Chapelle *et al.* (2000)	23 suspected AMI (16 yes, 7 no), 12 UAP patients, 9 stable AP patients, 19 cardiac surgery patients, 5 polytrauma patients, 1 non-cardiac surgery patient, 16 haemodialysis patients	AxSYM® (Abbott)	SCS = 0.171 AxSYM® – 0.06 Upper reference limit for SCS given as 0.08 μg/L, for AxSYM® as 0.4 μg/L. If SCS values divided by 0.08 and AxSYM® by 0.4, the mean difference was not statistically different from zero.	4 patients with no evidence of AMI or UAP had AxSYM® Tn I >0.4 μg/L, SCS Tn I <0.08 μg/L. 5 patients with AMI or UAP had SCS Tn I >0.08 μg/L, AxSYM® Tn I <0.4 μg/L.	Not applicable

Author/Date	Patient/Sample sources	Comparator	Regression results	Concordance (categorical) results	CV results
Christenson *et al.* (2002)				99th percentile (from 138 healthy volunteers) was 0.04 μg/L.	10% CV at 0.06 μg/L
Eggers *et al.* (2003)	197 patients with suspected ACS but without ST segment elevation	AxSYM® (Abbott) All point-of-care testing performed by nurses.	Not applicable	Not applicable	CV for SCS 4.2% at 0.45 μg/L. CV for AxSYM® 11.3% at 2.1 μg/L.
El Gendi *et al.* (2002)	30 chest pain patients for method comparison study, control samples	Access® II (Beckman)	SCS = 0.83 Access® II + 0.54 for Tn I in range 0.01–2.0 μg/L, SCS = 1.07 Access® II + 0.003	Not applicable	CV 5.5% at 0.09 μg/L
Gaze & Collinson (2002)	85 patients with confirmed ACS	Opus™ Plus, Dimension® RxL (Dade Behring), Access® (Beckman) and Tosoh AIA 600II (Eurogenetics)	'Good agreement' between SCS and other analysers (r>0.97) for all except Access® (r=0.78)	Not applicable	Not applicable
Heeschen *et al.* (1999a)	412 chest pain patients at an emergency department, chest pain <12 hours pre-admission, no ST segment elevation, no AMI in past 14 days. Analysis on SCS done at point of care by 6 specially trained physicians or paramedics.	Stratus® II (Dade Behring)	SCS = 0.97 Stratus® II + 0.06 For Tn I <4.0 μg/L, low correlation (r=0.62). Detection limit for Stratus® II ~0.5 μg/L versus 0.01 μg/L for SCS.	Decision threshold (97.5th percentile of people without cardiac damage) was 0.08 μg/L. Cut-off for AMI 0.15 μg/L. For 121 UAP patients, 45% SCS above decision threshold, 28% for Stratus® II.	Inter-assay CV 4.5% at 0.1 μg/L Lowest Tn I at 20% CV was 0.03 μg/L.
Moore *et al.* (1998)	37 samples from patients undergoing routine testing used in method comparison, 2 levels of a cardiac marker control used to assess precision.	Stratus® II (Dade Behring)	SCS = 0.84 Stratus® II – 0.02	Not applicable	Total CV 4.0% at 0.6 μg/L

Table A16 Risk stratification results for Stratus® CS

Author/Date	Results
Ferguson *et al.* (2002)	Comparative effects of using SCS or Bayer Immuno 1® on re-definition of AMI using ACC/ESC guidelines (Bertrand *et al.*, 2002). 80 patients admitted to Edinburgh Royal Infirmary with chest pain at rest or minimal exertion, no ST segment elevation, no non-cardiac cause, pain within 24 hours, at least 10 minutes duration, abnormal ECG. Clinical diagnosis from case notes 2 weeks post diagnosis, blind to the SCS result. Median time onset to venepuncture was 15 hours 35 minutes. 86% ischaemic changes (ST depression or T-wave inversion). Clinical diagnosis: 42 UAP, 13 AMI, 9 AP, 5 non-cardiac, 1 pericarditis. 99th percentile: 0.07 μg/L for SCS, not defined for Immuno 1®. 30 patients Tn I (SCS) above this (all AMI patients, 15 UAP, 2 AP) 10% CV: 0.06 μg/L for SCS, 0.35 μg/L for Immuno 1®. For SCS, this was below 99th percentile. For Immuno 1®, 19 above this (12/13 AMI). 20% CV: 0.04 μg/L for SCS, 0.20 μg/L for Immuno 1®. 29 (including all AMI) above this for Immuno 1®, 35 for SCS. High sensitivity assays may identify more patients who would benefit from therapy. Lack of standardisation is an issue, as is the inability of troponin testing to identify everyone who has severe underlying coronary artery disease (Hillis *et al.*, 2001), (Brscic *et al.*, 1998).
Heeschen *et al.* (1999a)	Turnaround time for SCS was 15 minutes. 121 UAP patients – 45% raised Tn I (≥0.08 μg/L) using SCS, 28% raised Tn I (≥0.7 μg/L) using Stratus® II. At 30-day follow up, 25.9% of positive SCS had MI or death versus 28% for Stratus® II. 1.5% (n=1) of SCS-negative patients had an event versus 5.8% (n=5) of Stratus® II-negative patients. Concerns remain about long-term reliability and maintenance of the point-of-care testing analyser; also high throughput laboratory machines offer potential cost savings.

Table A17 Performance data for Biosite Triage®

Author/Date	Patient/Sample sources	Comparator	Regression results	Concordance (categorical) results	CV results
Altinier *et al.* (2001)	44 samples from patients with confirmed ACS used by laboratory staff for method comparison, then point-of-care testing analyser evaluated in an emergency department on 100 consecutive patients with suspected ACS	Dimension® RxL (Dade Behring)	Triage® Tn I = 0.69 RxL + 0.95 (n=44, range 0–50.0 μg/L). Lack of close relationship between Triage® results and laboratory test led to use of Triage® results as positive (≤1 μg/L) or negative (>1 μg/L).	For 5 patients (4 AMI, 1 UAP), Triage® negative when RxL positive (>0.6 μg/L). If a cut-off of 0.4 μg/L used for Triage® (as Apple *et al.* (1999)), this reduced to 2.	CV 21.99% at 0.26 μg/L
Apple *et al.* (1999)	192 chest pain patients (59 MI)	Access® (Beckmann)	Not applicable	89% concordance with Access® for rule out of AMI, using an optimal cut-off point of 0.4 μg/L. (Note this was determined on the same patient group).	CV 12% at 0.4 μg/L
Bachler *et al*. (2002)	87 samples from 77 (unspecified) patients	Access® AccuTnI (Beckman Coulter) AxSYM® (Abbott)	Triage® = 1.91 Access® + 0.05 Triage® = 16.53 AxSYM® – 2.71	1 false negative, 8 false positives for AMI – all 'false positives' had evidence of myocardial damage (denominators and false negatives for myocardial damage not stated).	Not applicable

Table A18 UKNEQAS-Cardiac Markers performance data

System	Number of users[a] in UKNEQAS-Cardiac Markers	CVs[a]
Roche TROPT *Quantitative*®	22	10% at 0.11 μg/L; 15% at 0.15 μg/L
Roche laboratory based	92	20% at 0.05 μg/L; 10% at 0.1 μg/L
Biosite Triage®	14	30% at 0.11 μg/L; 20% at 0.4 μg/L
Bayer ADVIA Centaur®	34	15% at 0.22 μg/L; 7% at 0.75 μg/L
Beckman Coulter Access®	33	15% at 0.05 μg/L; 10% at 0.25 μg/L
Dade Stratus® CS	12	25% at 0.10 μg/L; 15% at 0.4 μg/L
DPC Immulite® 2000	14	20% at 0.30 μg/L; 10% at 1.0 μg/L

[a] Number of UKNEQAS-Cardiac Markers participants and CVs as of 24th October 2003.
Note: The analysers manufactured by Roche measure troponin T and all other analysers measure troponin I.

Table A19 Randomised controlled trials – assessment of chest pain

Author, country of study	Patient group	Testing regimen(s)	Adverse cardiac outcomes	Other outcomes
Dagnone *et al.* (2000), Canada	Chest pain patients with non-diagnostic ECG	1. CK and CK-MB at baseline 2. CK, CK-MB, myoglobin and Tn I at baseline and myoglobin repeated at 2 hours	30-day deaths: 1. n=6 of 150 (4.0%) 2. n=5 of 146 (3.4%) 30-day MI: 1. n=22 of 150 (14.7%) 2. n=18 of 146 (12.3%)	Proportion of patients admitted: 1. 54.0% 2. 45.9% Proportion for whom length of stay >6 hours: 1. 51.8% 2. 50.7%
Zarich *et al.* (2001), US	Chest pain patients without ST segment elevation	1. Serial ECG and CK-MB 2. Serial Tn T at baseline, 3 and 12 hours	30-day combined death or MI: 18 patients in total; not significantly different between control and Tn T group but numbers not specified.	Length of stay in emergency department: 1. 10.3 hours ± 6.7 2. 10.7 days ± 7.8 (p=0.45) Length of stay for whole stay in hospital: 1. 2.3 days ± 3.7 2. 1.8 days ± 3.2 (p=0.14)

Table A20 Observational cohort studies – assessment of chest pain

Author, country of study	Patient group	Testing regimen(s)	Adverse cardiac outcomes	Other outcomes
Conti *et al.* (2002), Italy	All chest pain patients	Chest pain score evaluated using ECG, Tn and cardiac enzyme measurements at baseline to determine risk category: • low risk + chest pain score <4: discharged if negative tests at 6–12 hours after onset of symptoms • low risk + chest pain score ≥4: Tn tested 6–12 hours after onset of symptoms, additional tests if positive, stress test and discharge if negative • intermediate risk: managed in chest pain unit • high risk: referred to CCU.	6-month follow up of chest pain unit patients, in-patient follow up for others. • low risk + chest pain score <4: n=2672; 3 AMI, 1 UA, no deaths • low risk + chest pain score ≥4: n=1755; 885 diagnosed with coronary artery disease in chest pain unit (10 deaths in hospital), 870 discharged, no adverse events • high/intermediate risk: n=9335; 2420 AMI (256 deaths), 3764 UA (41 deaths)	Low risk: 60% were discharged <6 hours 20% were discharged at <24 hours
Goodacre *et al.* (2002), UK	Patients with undifferentiated chest pain	2–6 hour period of observation. Serial ECG, cardiac enzymes measured in accordance with time of onset of pain. ETT performed where appropriate.	6-month follow up of 429 of the 461 discharged patients (93%): 3 cardiac deaths; 2 MI and 60 discharged patients re-attended A&E with related problems (46 of these were admitted).	Mean cost per patient in chest pain unit: £221 (or £323 with interventional cardiology costs). Estimated cost for routine care: £356 (£458). If 65% of chest pain unit patients are admitted and 35% discharged, the costs are identical between chest pain unit and routine care.
Herren *et al.* (2001) UK	Chest pain patients without ST segment elevation	1. 'Gold standard' – serial ECG and cardiac enzymes for 24 hours or Tn T at 48 hours 2. Serial CK-MB measurements and continuous monitoring of ECG ST segment changes	No adverse cardiac events reported at 4 weeks follow up of 292 of 368 patients who completed assessment.	

Author, country of study	Patient group	Testing regimen(s)	Adverse cardiac outcomes	Other outcomes
Mutrie (1999), Canada	Chest pain patients with non-diagnostic ECG	Point-of-care tests for myoglobin, CK-MB and Tn I at presentation. If all negative, myoglobin/CK-MB repeated at 2–3 hours. If either of these is positive, Tn I is repeated at 6 hours after onset of pain otherwise low risk of AMI assumed.	Improved ratio of chest pain patients in the 'other' category compared with the 'MI or UA' category (formerly 8:10, now 3:10). Actual patient numbers not stated.	Reduction in assessment time (by 30%). A decrease in hospitalisation rates resulting in cost savings of $500 000 per year.
Newby *et al.* (2000a), US	Chest pain patients with normal or non-diagnostic ECG	ECG and CK-MB at 0, 4, 8 and 12 hours, and Tn T at 0, 4 and 8 hours.	Deaths during mean follow up of 29.5 months (92% of cohort): 10 troponin positive (27%) 22 troponin negative (7%) ($p<0.0001$)	
Taylor *et al*. (2002), UK	First 100 chest pain patients to enter 'rule out myocardial events on observation ward' assessment	Baseline ECG, Tn I and CK, second ECG before transfer to an observation unit, 12-hour Tn I and ECG. If all negative, ETT prior to discharge.	Mean follow-up of 6.5 months, 67 of 74 patients contacted by questionnaire. 21 patients (31%) had further chest pain, 6 required further cardiology treatment or investigation.	Median length of stay in the observation unit was 23 hours.

Table A21 Rapid assessment/multimarker protocols – assessment of chest pain

Author, country of study	Patient group	Testing regimen(s)	Adverse cardiac outcomes	Other outcomes
Caragher *et al.* (2000), US	Patients with chest pain	1. Serial CK and CK-MB drawn at 8-hour intervals for up to 2 days 2. CK, CK-MB, myoglobin and Tn I at 0, 2 and 6 hours after presentation, and all but myoglobin tested at 9 hours after presentation		Length of stay 1. ACS positive: 5.69 days ACS negative: 2.02 days 2. ACS positive: 4.31 days ACS negative: 1.26 days. Cost saving by using protocol 2: 29.5% for ACS-positive patients, and 29.9% for ACS-negative patients.
Newby *et al.* (2001b), US	Patients with possible myocardial ischaemia within 6 chest pain units	1. Laboratory CK-MB (or Tn or total CK where unavailable) 2. Point-of-care testing of CK-MB and Tn 3. Point-of-care testing of CK-MB, Tn and myoglobin. Point-of-care tests at 0, 3 and 6 hours (timings for samples sent to laboratories not given).	30-day death or MI for baseline test: 1. 6 of 44 positive (13.6%), 44 of 807 negative (5.5%) 2. 28 of 149 positive (18.8%), 19 of 641 negative (3.0%) 3. 25 of 114 positive (21.9%), 22 of 684 negative (3.2%) 30-day death or MI for serial testing: 1. 47 of 85 positive (55.3%), 11 of 883 negative (1.3%) 2. 43 of 228 positive (18.9%), 13 of 725 negative (1.8%) 3. 37 of 180 positive (20.6%), 19 of 775 negative (2.5%)	
Ng *et al.* (2001), US	Patients with symptoms of cardiac ischaemia	Point-of-care testing for myoglobin, Tn I and CK-MB at presentation and at 30, 60 and 90 minutes. Additional marker testing may be done at 3 and 6 hours if admitted to CCU.	66 of 1285 had an AMI. 455 patients discharged within 90 minutes, 8 (2.6%) re-admitted within 30 days (1 MI, 4 UA).	

Appendix 10

POINT-OF-CARE TESTING – CLINICAL EFFECTIVENESS METHODOLOGY

False-positive and false-negative rates were combined separately using the following procedure (see Section 4.3.4.1).

For each study, let p_i denote the false-positive rate and set $\theta_i = \sin^{-1}(\sqrt{p_i})$.

The combined estimate of the false-positive rate is then $p = [\sin(\hat{\theta})]^2$, where

$$\hat{\theta} = \frac{\sum w_i \theta_i}{\sum w_i}$$

$$w_i = \frac{1}{\mathrm{var}(\theta_i)} = \frac{1}{4n}$$

The variance of $\hat{\theta}$ is given by $1/\sum w_i$

Appendix 11

LITERATURE SEARCH FOR ECONOMIC EVALUATION AND MODELLING

Search 1

Database: MEDLINE
Coverage: 1966 to June Week 3 2002
Platform: OVID
Search run: 05 July 2002

Strategy:
1. economics/
2. exp "costs and cost analysis"/
3. exp "economics, medical"/
4. economics, nursing/
5. economics, pharmaceutical/
6. consumer satisfaction/
7. patient acceptance of health care/
8. physician's practice patterns/
9. exp "patient care planning"/
10. health care rationing/
11. quality of life/
12. value of life/
13. quality-adjusted life years/
14. "Outcome and Process Assessment (Health Care)"/
15. "outcome assessment (health care)"/
16. models, economic/
17. markov chains/
18. monte carlo method/
19. economic$.tw.
20. cost?.tw.
21. costing?.tw.
22. costly.tw.
23. costed.tw.
24. price?.tw.
25. pricing?.tw.
26. (pharmacoeconomic? or pharmaco-economic? or (pharmaco adj economic?)).tw.
27. budget$.tw.
28. (value adj1 money).tw.
29. (value adj1 monetary).tw.
30. (expenditure? not energy).tw.
31. fee?.tw.
32. 32. preference?.tw.
33. (satisfaction or satisfied).tw.
34. "quality of life".tw.
35. qol.tw.
36. "quality adjusted life year?".tw.

37. qaly.tw.
38. cba.tw.
39. cea.tw.
40. cua.tw.
41. markov.tw.
42. (monte adj carlo).tw.
43. pathway?.tw.
44. ((clinical or critical or patient) adj path?).tw.
45. (managed adj (care or clinical or network)).tw.
46. (resource? adj1 allocat$).tw.
47. or/1-46
48. (metabolic adj cost?).tw.
49. ((energ$ or oxygen) adj cost?).tw.
50. 48 or 49
51. 47 not 50
52. exp troponin/
53. troponin?.tw.
54. 52 or 53
55. 51 and 54
56. animal/
57. human/
58. 56 not (56 and 57)
59. 55 not 58

Sources

The secondary literature, ongoing research, policy documents sources are listed in Appendix 8.

Primary literature and other data

- MEDLINE (OVID)
- EMBASE (OVID)
- NHS EED
- HEED (OHE CD-ROM)
- WEB OF SCIENCE (ISI)
- PREMEDLINE (OVID)
- CINAHL (OVID)
- BIOSIS (EDINA)
- Dissertation Abstracts Online (Proquest)

Health Economics Research Units:

- Health Economics Research Unit, Aberdeen
  www.abdn.ac.uk/heru
- Centre for Health Economics, York
  www.york.ac.uk/inst/che/
- Health Economics Research Centre, Oxford

www.ihs.ox.ac.uk/herc/

- Health Economics Research Group, Brunel
  http://http1.brunel.ac.uk:8080/departments/herg/home.html
- Health Economics Group (HEG), Newcastle
  www.ncl.ac.uk/deph/hegroup.html
- SCHARR
  www.shef.ac.uk/uni/academic/R-Z/scharr/
- Health Economics Group, East Anglia
  www.uea.ac.uk/menu/acad_depts/hsw/hpp/hegwelc.htm
- LSE (London School of Economics and Political Science)
  www.lse.ac.uk/
- Southampton University Economics Department
  www.soton.ac.uk/~econweb/
- Centre for Health Economics Research and Development (CHERE), University of Sydney and Central Sydney Area Health Service
  www.chere.usyd.edu.au
- Institute of Health Economics (IHE), Alberta, Canada
  www.ihe.ab.ca/
- International Health Economics Association (iHEA)
  www.healtheconomics.org/cgi-bin/WebObjects/ihea
- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University
  www.chepa.org/
- Centre for Health Program Evaluation (CHPE), University of Melbourne and Monash University, Australia
  chpe.buseco.monash.edu.au/
- NetEc
  http://netec.mcc.ac.uk/NetEc.html
- IDEAS (Internet Documents in Economics Access Service)
  http://ideas.uqam.ca/

Appendix 12

SUMMARIES OF SELECTED ECONOMIC EVALUATIONS ON THE ADOPTION OF TROPONIN TESTS

This appendix summarises two business cases, one economic evaluation and seven retrospective studies on the introduction of troponin tests. It also summarises an economic evaluation and a retrospective trial concerning the adoption of point-of-care troponin tests.

Business case for an evidence-based protocol for management of patients with acute chest pain (Collinson *et al.*, 1999)

This study set out the clinical- and cost-effectiveness evidence to support the introduction of a protocol using point-of-care troponin tests to manage patients admitted with chest pain. The main financial savings from using troponins arose from reducing the number of inappropriate admissions. Other benefits included reduced mean waiting time in the emergency setting by at least two hours, lower on-call costs for pathology technicians, reduced mortality in high-risk patients 'missed' by the existing protocol, lower drug costs from improved diagnostic accuracy and improved resource use by improving the identification of patients who would benefit from revascularisation.

Business case for the management of chest pain Royal Alexandra Hospital, Paisley (Fisher *et al.*, 2002)

The business case projected net savings of £0.1 million per annum from implementing a protocol that includes point-of-care troponin tests at zero and six hours from admission to enable the rapid diagnosis and safe discharge of patients with chest pain suspicious of ACS.

Economic aspects of the new biochemical markers for the detection of myocardial damage (Collinson, 1998)

This study developed the Canepa-Anson *et al.* (1998) analysis and costed three strategies and compared their cost effectiveness with the then current strategy of taking CK tests daily for three days.

Cost-minimisation analysis showed that a rapid diagnostic strategy using CK and troponin reduced length of stay and was cost effective, reducing costs by 33% in comparison with the base case. A second rapid diagnostic option using CK and CK-MB produced slightly higher cost savings.

Troponin T as a first-line test: the Royal Liverpool and Broadgreen University Hospital experience (Manning *et al.*, 2001)

In August 1998, the Royal Liverpool and Broadgreen University Hospital replaced CK and CK-MB tests on two to three consecutive days, with a single troponin T

test 12 hours from onset of symptoms, or 12 hours from admission if the earlier time was in doubt. The primary reasons for the change were:

- to allow earlier discharge of non-AMI patients
- to reduce the number of AMIs that were undetected and discharged inappropriately
- to identify high-risk patients who might benefit from early intervention.

Audit data of the outcomes at 12 months of 1400 patients presenting with chest pain in the first three months of the new pathway were provided. A statistically significant higher number of 217 AMIs were diagnosed in comparison with 100 in the corresponding period. A total of 556 patients were discharged from the observation ward within 24 hours. By comparison, many would have waited for enzyme results and stayed three to four days.

Laboratory cost savings were also achieved, with the average monthly cost for troponin being £1983 compared with £3397 for CK and CK-MB. Such savings were realised by ensuring only one troponin sample was analysed per episode of pain.

The effect of a change from conventional cardiac enzymes to troponin I on overall hospital costs in patients with suspected MI (Cavanagh & Cassidy, 2002)

A retrospective study of 245 patients in 1996 and 200 patients in 2000 presenting with chest pain to the Portiuncla Hospital, Galway was undertaken. In 1997, the hospital changed its laboratory testing protocol from traditional cardiac markers such as aspartate aminotransferase, CK and CK-MB to troponin I.

The comparative analysis showed that in 1996, the mean length of stay for 212 patients without a diagnosis of MI was eight days, with 26% having a length of stay of less than three days. In 2000, the mean length of stay for the same group was six days, with 34% discharged in less than three days.

The report attributed the decrease in length of stay to earlier diagnosis aided by the troponin I results.

The net savings were approximately £0.13 million per annum. However, the article noted that the released beds were likely to be occupied by new admissions so no 'real' savings were made (rather the cost per case fell) and there was a more efficient use of beds and services.

Correspondence from McKiernan, Buckley, Pate, Quigley, Reardon and Toddy on the Cavanagh and Cassidy article (McKiernan *et al.*, 2002)

In December 2002, the authors undertook a similar six-month prospective analysis on 336 patients following the introduction of troponin testing at Wexford General Hospital. Their analysis showed that the introduction of troponin testing led to a significant decrease in patients diagnosed with angina (from 42 to 26%) and a corresponding increase in patients with non-cardiac chest pain (from 25 to 44%).

The authors reported a corresponding statistically significant reduction in total bed occupancy leading them to conclude that troponin testing in a general hospital setting is cost effective but no further cost data was provided.

Cardiac troponins: improved diagnosis and cost benefits (Owen, 2001)

This case study demonstrated that the introduction of troponin tests facilitated earlier discharge of the non-cardiac patient group, resulting in financial benefits to the hospital.

The study, conducted over the first six months of 1998, compared using troponin T with aspartate aminotransferase, lactate dehydrogenase and CK in a DGH in Bangor, Wales. Troponin-negative patients were discharged earlier compared with patients who did not have a troponin. The hospital incurred £910 higher troponin test costs but saved £22 515 from fewer bed days and fewer cardiac enzymes, and reduced the cost per patient episode for patients with UA, stable angina and non-cardiac chest pain.

Cost implications of the use of troponin I measurement to diagnose heart conditions (Scullin *et al.*, 2001)

This six-month study (April–September 1999) quantified the savings achieved from replacing CK and CK-MB tests with troponin I tests at Antrim Hospital. The analysis showed that savings of £227 per patient (28% from baseline) were achieved for patients diagnosed as low risk. The major savings per patient were lower LMWH (£79), fewer drugs at discharge (£76) and lower 'hotel' costs (£41).

Cost effectiveness of cardiac troponin I in a systematic chest pain evaluation protocol: use of cardiac troponin I lowers length of stay for low-risk cardiac patients (Anderson *et al.*, 1998)

This 10-month study set in a chest pain unit in Virginia assessed the benefits of adding troponin I to a panel of cardiac markers. Outcomes measured were length of stay, time to catheterisation and hospital and laboratory costs. Outcomes for a test group of 532 patients presenting from May to September 1996 were compared with outcomes for a control group of 490 presenting between December 1995 and April 1996.

The results showed that for low-risk patients (defined as patients with atypical symptoms or no evidence of ischaemia), the test group had a statistically significant decrease in length of stay from 3.0 to 1.9 days, with average hospital costs falling from $6170 to $4550 per patient (26%). Laboratory costs rose by $50 per patient for the test group. Using troponin I did not significantly reduce time to catheterisation.

Effective resource management using a clinical and laboratory algorithm for chest pain triage (Bernstein *et al.*, 1996)

This was a study of the outcomes of 200 emergency department chest pain patients following the introduction of troponin I tests at zero and four hours from

admission at Bridgeport Hospital Connecticut in 1996. The analyses concluded that the introduction of troponin reduced cost per patient with angina or chest pain by $394.

The need for a point-of-care testing: an evidence-based appraisal (Collinson, 1999)

In a prospective RCT of point-of-care and laboratory-based troponin tests, the authors showed that point-of-care troponin tests improved turnaround times (20 minutes versus 72 minutes) and that there was a statistically significant reduction in hospital stay in patients randomised to the point-of-care troponin test arm.

The authors also noted that the benefits from adopting point-of-care troponin tests depended on clinical decision making. A short turnaround time was only helpful within data-driven decision-making protocols and particularly when therapeutic decisions were taken.

A new pain strategy in Thunder Bay (Mutrie, 1999)

The Thunder Bay Regional Hospital developed a chest pain strategy to support its doctors in A&E. The strategy focused on rapid risk stratification using history, ECG, examination and point-of-care testing of myoglobin, CK-MB mass and troponin I. Following the introduction of the strategy in 1997, the hospital realised savings of $0.5 million per annum by a 60% decrease in admission rates and improved capability in the A&E department as well as improving patient care.

Appendix 13

ASSUMPTIONS ADOPTED IN THE ECONOMIC ANALYSIS

This appendix contains detailed information to support the assumptions made in Chapter 5. It explains:

- the cost of secondary prevention
- the composition of the cost estimate for the troponin tests.

Cost of rehabilitation, counselling on risk factor modification and prophylactic medication per patient

Table 5-1 (Chapter 5) sets out high and low costs of rehabilitation, counselling on risk factor modification and prophylactic medication per patient. The cost of rehabilitation was obtained from updating a 2002 ISD estimate for delivering the Heart Manual Rehabilitation Programme (B Graham, ISD, personal communication, 2002). In the low-cost option, it was assumed that the Heart Manual Rehabilitation Programme would be the only source of secondary prevention offered to patients. This is a conservative estimate. Many NHS Boards will provide access to a multidisciplinary team involving community and practice nurses, pharmacists, dieticians and occupational therapy staff. A simple adjustment was made to add a further four hours of nurse time at £22 per hour (Netten *et al.*, 2002) to the base cost to form the high-cost option.

Not all patients offered a rehabilitation programme accept the offer. Analyses of data from the cardiac rehabilitation programme at the RAH in Paisley indicate about 60% of patients will accept classes. The base case assumed 100% of patients would receive counselling.

The Standard for CHD (Clinical Standards Board for Scotland, 2001a) require that all patients admitted to hospital with AMI are prescribed aspirin or another antiplatelet agent, a β-blocker, an ACE inhibitor and a lipid-lowering statin (where appropriate), unless these are contraindicated. The average cost of these drugs depends on the prescribing rate, the prescribing dose and the individual price of drugs.

No prescribing rate data are available by disease category. However, the National Overview of CHD showed that 36 of 37 hospitals prescribe these drugs after an AMI and have protocols in place to ensure this (Clinical Standards Board for Scotland, 2001b). Moreover, the recent *Supporting general practice in prescribing: A progress report* (Audit Scotland, 2003) noted that the defined daily doses for ACE inhibitors, aspirin and statins have increased significantly from 1999 to 2002. In the absence of data showing the average number of patients with AMI who receive these drugs, it was assumed from this evidence that prescribing rates would be high. The analysis assumed that 80% of patients would receive aspirin, a β-blocker and an ACE inhibitor following an AMI, while 60% would receive a lipid-lowering statin.

The cost of each drug prescribed for prophylaxis after an AMI varies, with the main determinants being the manufacturers' charges and dosage. The highest and lowest costs for each indication presented in Table 5-1 (Chapter 5) were obtained from the British National Formulary (British Medical Association (BMA) & Royal Pharmaceutical Society of Great Britain (RPSGB), 2003).

Costs of a troponin test: manufacturers' charges

Manufacturers' charges for troponin tests usually have three components:

- capital purchase or operating lease costs
- maintenance and service costs
- operating costs (primarily reagents and consumables, including those for quality control and calibration of the instrumentation).

The prices quoted for individual sites would be sensitive to several factors that make up a manufacturer's discount structure. Usually the main variables include the volume of tests, the acquisition strategy (e.g. an operating lease is usually cheaper than reagent rental) and other equipment in place with the same manufacturer within the hospital or NHS Board. The actual cost for a specific site may therefore differ from the indicative values assumed in the model.

The cost per tests is also sensitive to the type of the internal quality control adopted and frequency with which it is performed. The main variations arise from the frequency of performing quality control and whether it is an electronic test that does not use reagent or a test of blood sample that uses reagent.

Table A22 sets out the number of troponin tests assumed for the low-, middle- and high-test volumes and derived from discussions with TSG members. Note the laboratory analysers are capable of measuring many different analytes and the costs assume that the analysers are operated as routine clinical chemistry analysers measuring troponin with other chemistry enzymes.

Table A22 Number of troponin tests per annum

	Low	Middle	High
Point-of-care tests	500	1000	2000
Laboratory tests	3000	5000	9000

The costs set out in Table A23 are derived by adding the annual operating lease costs, the annual maintenance and service costs and the total consumable costs for the relevant volume of tests and assumed internal quality control approach, and dividing the grand total by the relevant number of tests.

Table A23 Manufacturer charges for troponin tests

	Cost (£)		
Volume of tests	**Low**	**Middle**	**High**
Troponin I point-of-care test [a]	21	14	9
Troponin T point-of-care test [b]	9	9	9
Troponin I laboratory test	6	3	2
Troponin T laboratory test	4	3	2

Note: [a] Assumes quality control using liquid agent every other day
[b] Assumes quality control using liquid agent once a fortnight

Costs of a troponin test: variable costs

In addition to paying manufacturers for consumables and equipment, settings also incur other variable costs per test, such as the cost of conducting the test, the cost of recording patient and test result details. For the central laboratory-based scenarios, the cost of transporting the blood sample to the laboratory is incurred. The analysis assumed other costs, for example drawing blood, reassuring patients and explaining the test and the result to the patient. These would be common to all scenarios, and were therefore not costed.

TSG members agreed that variable costs for laboratory-based tests are likely to be around £1 per test higher than point-of-care tests because of the double recording of results on a laboratory system and on the patient's records, and the additional transport costs. Where laboratory systems already interface automatically to ward systems, double entry is avoided and thus the cost differences are smaller. At sites with vacuum delivery systems, the marginal cost of sending samples between wards and the central laboratory would also be smaller.

Thus, the base-case run of the economic model adds £1 per laboratory-based test to the costs set out in Table A23 to capture this cost differential and to run a sensitivity test assuming no premium.

Costs of a troponin test: annual fixed costs

The hospital setting is likely to incur additional fixed costs to operate a point-of-care troponin testing service rather than a laboratory-based service. The advice on the management and use of point-of-care tests published by the MDA (2002a) states that there are at least seven activities required prior to the introduction of point-of-care tests. These include preparation of a business case, clinical governance, training, preparation of statements of SOPs, internal and external quality assurance, and accreditation.

TSG members discussed a range of possible costs for each activity and concluded that it is reasonable to assume that point-of-care troponin tests would cost £5000 per annum more to operate than laboratory tests, with the major additional costs being training, quality assurance and governance.

The analysis assumed that the cost of a troponin test would not change with laboratory operating hours. It was considered reasonable to assume that decisions taken in respect of the operating hours of laboratories would balance

many factors but that the availability of troponin tests is unlikely to be a major influence.

Costs of a troponin test: total costs

The total inclusive unit costs per troponin test, which combines the three types of costs, for different numbers of tests are set out in Table A24.

Table A24 Total cost per troponin test for different numbers of test

Volume of tests	**Low**	**Middle**	**High**
Point-of-care tests	500	1000	2000
Laboratory tests	3000	5000	9000
	Costs (£) of tests		
Volume of tests	**Low**	**Middle**	**High**
Troponin I point-of-care test	31	19	11
Troponin T point-of-care test	20	13	9
Troponin I laboratory test	5	4	3
Troponin T laboratory test	4	4	3

Appendix 14

RESULTS OF ECONOMIC MODELLING

This appendix presents:

- the base-case results of the economic modelling for each of the scenarios referred to in Section 5.4.2.3.1.2 for troponin I and T assays
- the results of the sensitivity analyses referred to in Section 5.4.3.2.

Table A25 Troponin I: different strategies ranked by cost – middle, low and high volume use of tests

Middle volume	Scenario	Net costs	Difference from cheapest scenario	Low volume	Scenario	Net costs	Difference from cheapest scenario	High volume	Scenario	Net costs	Difference from cheapest scenario
1 hour turnaround time	S5 24/7	£23 317.80		**1 hour turnaround time**	S2	£28 113.37		**1 hour turnaround time**	S5 24/7	£13 500.20	
	S2	£27 021.16	£3 703.36		S5 24/7	£38 044.20	£9 930.83		S2	£25 928.96	£12 428.76
	S6	£38 514.94	£15 197.14		S6	£39 607.15	£11 493.78		S5	£29 866.58	£16 366.38
	S5	£39 684.18	£16 366.38		S4	£52 931.32	£24 817.95		S4	£31 087.16	£17 586.96
	S4	£39 824.83	£16 507.03		S5	£54 410.58	£26 297.21		S6	£37 422.73	£23 922.53
	S7	£68 448.16	£45 130.36		S7	£69 540.37	£41 426.99		S7	£67 355.95	£53 855.75
	S1	£109 412.19	£86 094.39		S1	£110 504.40	£82 391.03		S1	£108 319.98	£94 819.78
	S3	£121 134.91	£97 817.11		S3	£134 241.41	£106 128.04		S3	£112 397.25	£98 897.05
	S8	£154 056.45	£130 738.65		S8	£155 148.66	£127 035.28		S8	£152 964.24	£139 464.04
2 hour turnaround time	S5 24/7	£23 317.80		**2 hour turnaround time**	S2	£33 286.80		**2 hour turnaround time**	S5 24/7	£13 500.20	
	S2	£32 194.59	£8 876.79		S5 24/7	£38 044.20	£4 757.40		S5	£29 866.58	£16 366.38
	S5	£39 684.18	£16 366.38		S6	£46 362.81	£13 076.01		S4	£31 087.16	£17 586.96
	S4	£39 824.83	£16 507.03		S4	£52 931.32	£19 644.52		S2	£31 102.38	£17 602.18
	S6	£45 270.60	£21 952.80		S5	£54 410.58	£21 123.79		S6	£44 178.39	£30 678.19
	S7	£79 673.38	£56 355.58		S7	£80 765.58	£47 478.79		S7	£78 581.17	£65 080.97
	S1	£115 747.42	£92 429.62		S1	£116 839.63	£83 552.83		S3	£112 397.25	£98 897.05
	S3	£121 134.91	£97 817.11		S3	£134 241.41	£100 954.61		S1	£114 655.21	£101 155.01
	S8	£164 917.79	£141 599.99		S8	£166 010.00	£132 723.20		S8	£163 825.58	£150 325.38

Middle volume	Scenario	Net costs	Difference from cheapest scenario	Low volume	Scenario	Net costs	Difference from cheapest scenario	High volume	Scenario	Net costs	Difference from cheapest scenario
3 hour turnaround time	S5 24/7	£23 317.80		**3 hour turnaround time**	S5 24/7	£38 044.20		**3 hour turnaround time**	S5 24/7	£13 500.20	
	S2	£39 228.86	£15 911.06		S2	£40 321.07	£2 276.87		S5	£29 866.58	£16 366.38
	S5	£39 684.18	£16 366.38		S4	£52 931.32	£14 887.12		S4	£31 087.16	£17 586.96
	S4	£39 824.83	£16 507.03		S6	£54 046.90	£16 002.70		S2	£38 136.66	£24 636.46
	S6	£52 954.70	£29 636.90		S5	£54 410.58	£16 366.38		S6	£51 862.49	£38 362.29
	S7	£89 225.44	£65 907.64		S7	£90 317.65	£52 273.45		S7	£88 133.24	£74 633.04
	S3	£121 134.91	£97 817.11		S1	£124 543.41	£86 499.21		S3	£112 397.25	£98 897.05
	S1	£123 451.20	£100 133.40		S3	£134 241.41	£96 197.21		S1	£122 359.00	£108 858.80
	S8	£174 815.30	£151 497.50		S8	£175 907.51	£137 863.31		S8	£173 723.09	£160 222.89
4 hour turnaround time	S5 24/7	£23 317.80		**4 hour turnaround time**	S5 24/7	£38 044.20		**4 hour turnaround time**	S5 24/7	£13 500.20	
	S5	£39 684.18	£16 366.38		S4	£52 931.32	£14 887.12		S5	£29 866.58	£16 366.38
	S4	£39 824.83	£16 507.03		S5	£54 410.58	£16 366.38		S4	£31 087.16	£17 586.96
	S2	£55 133.33	£31 815.53		S2	£56 225.54	£18 181.34		S2	£54 041.13	£40 540.93
	S7	£96 588.19	£73 270.39		S7	£97 680.40	£59 636.20		S7	£95 495.98	£81 995.78
	S6	£99 670.96	£76 353.16		S6	£100 763.17	£62 718.97		S6	£98 578.75	£85 078.55
	S3	£121 134.91	£97 817.11		S3	£134 241.41	£96 197.21		S3	£112 397.25	£98 897.05
	S1	£138 557.54	£115 239.74		S1	£139 649.75	£101 605.55		S1	£137 465.33	£123 965.13
	S8	£182 258.90	£158 941.10		S8	£183 351.11	£145 306.91		S8	£181 166.70	£167 666.50

Table A26 Troponin I: Different strategies ranked by cost – sensitivity analyses, using base-case data with specified adjustments

Middle volume 2 hour turnaround time	Scenario	Net costs	Difference from cheapest scenario
Base case	S5 24/7	£23 317.80	
	S2	£32 194.59	£8 876.79
	S5	£39 684.18	£16 366.38
	S4	£39 824.83	£16 507.03
	S6	£45 270.60	£21 952.80
	S7	£79 673.38	£56 355.58
	S1	£115 747.42	£92 429.62
	S3	£121 134.91	£97 817.11
	S8	£164 917.79	£141 599.99
Plus £20 ECG	S5 24/7	£23 317.80	
	S2	£38 646.71	£15 328.91
	S5	£42 616.96	£19 299.16
	S4	£43 344.16	£20 026.36
	S6	£54 873.36	£31 555.56
	S7	£97 621.99	£74 304.19
	S1	£145 829.37	£122 511.57
	S3	£147 446.15	£124 128.35
	S8	£207 082.80	£183 765.00
Nurse/consultant costs halved	S2	£18 280.60	
	S5 24/7	£23 317.80	£5 037.20
	S6	£24 817.82	£6 537.22
	S4	£30 288.01	£12 007.41
	S5	£31 500.26	£13 219.66
	S7	£42 017.12	£23 736.52
	S1	£60 051.10	£41 770.51
	S3	£70 937.36	£52 656.76
	S8	£84 633.27	£66 352.67
Plus LMWH £5.81	S5 24/7	£28 838.58	
	S2	£39 589.71	£10 751.13
	S5	£46 056.94	£17 218.36
	S4	£46 367.98	£17 529.39
	S6	£53 580.99	£24 742.40
	S7	£90 408.23	£61 569.65
	S1	£130 007.01	£101 168.42
	S3	£134 299.11	£105 460.53
	S8	£182 687.51	£153 848.93

Table A27 Troponin T: Different strategies ranked by cost – middle, low and high volume use of tests

Middle volume	Scenario	Net costs	Difference from cheapest scenario	Low volume	Scenario	Net costs	Difference from cheapest scenario	High volume	Scenario	Net costs	Difference from cheapest scenario
1 hour turnaround time	S5 24/7	£15 954.60		**1 hour turnaround time**	S5 24/7	£24 545.00		**1 hour turnaround time**	S5 24/7	£11 045.80	
	S2	£27 021.16	£11 066.56		S2	£28 113.37	£3 568.37		S2	£25 928.96	£14 883.16
	S5	£32 320.98	£16 366.38		S6	£39 607.15	£15 062.15		S5	£27 412.18	£16 366.38
	S4	£33 271.58	£17 316.98		S5	£40 911.38	£16 366.38		S4	£28 902.75	£17 856.95
	S6	£38 514.94	£22 560.34		S4	£40 917.03	£16 372.03		S6	£37 422.73	£26 376.93
	S7	£68 448.16	£52 493.56		S7	£69 540.37	£44 995.37		S7	£67 355.95	£56 310.15
	S1	£109 412.19	£93 457.59		S1	£110 504.40	£85 959.40		S1	£108 319.98	£97 274.18
	S3	£114 581.67	£98 627.07		S3	£122 227.12	£97 682.12		S3	£110 212.83	£99 167.03
	S8	£154 056.45	£138 101.85		S8	£155 148.66	£130 603.66		S8	£152 964.24	£141 918.44
2 hour turnaround time	S5 24/7	£15 954.60		**2 hour turnaround time**	S5 24/7	£24 545.00		**2 hour turnaround time**	S5 24/7	£11 045.80	
	S2	£32 194.59	£16 239.99		S2	£33 286.80	£8 741.80		S5	£27 412.18	£16 366.38
	S5	£32 320.98	£16 366.38		S5	£40 911.38	£16 366.38		S4	£28 902.75	£17 856.95
	S4	£33 271.58	£17 316.98		S4	£40 917.03	£16 372.03		S2	£31 102.38	£20 056.58
	S6	£45 270.60	£29 316.00		S6	£46 362.81	£21 817.81		S6	£44 178.39	£33 132.59
	S7	£79 673.38	£63 718.78		S7	£80 765.58	£56 220.58		S7	£78 581.17	£67 535.37
	S3	£114 581.67	£98 627.07		S1	£116 839.63	£92 294.63		S3	£110 212.83	£99 167.03
	S1	£115 747.42	£99 792.82		S3	£122 227.12	£97 682.12		S1	£114 655.21	£103 609.41
	S8	£164 917.79	£148 963.19		S8	£166 010.00	£141 465.00		S8	£163 825.58	£152 779.78

Middle volume	Scenario	Net costs	Difference from cheapest scenario	Low volume	Scenario	Net costs	Difference from cheapest scenario	High volume	Scenario	Net costs	Difference from cheapest scenario
3 hour turnaround time	S5 24/7	£15 954.60		**3 hour turnaround time**	S5 24/7	£24 545.00		**3 hour turnaround time**	S5 24/7	£11 045.80	
	S5	£32 320.98	£16 366.38		S2	£40 321.07	£15 776.07		S5	£27 412.18	£16 366.38
	S4	£33 271.58	£17 316.98		S5	£40 911.38	£16 366.38		S4	£28 902.75	£17 856.95
	S2	£39 228.86	£23 274.26		S4	£40 917.03	£16 372.03		S2	£38 136.66	£27 090.86
	S6	£52 954.70	£37 000.10		S6	£54 046.90	£29 501.90		S6	£51 862.49	£40 816.69
	S7	£89 225.44	£73 270.84		S7	£90 317.65	£65 772.65		S7	£88 133.24	£77 087.44
	S3	£114 581.67	£98 627.07		S3	£122 227.12	£97 682.12		S3	£110 212.83	£99 167.03
	S1	£123 451.20	£107 496.60		S1	£124 543.41	£99 998.41		S1	£122 359.00	£111 313.20
	S8	£174 815.30	£158 860.70		S8	£175 907.51	£151 362.51		S8	£173 723.09	£162 677.29
4 hour turnaround time	S5 24/7	£15 954.60		**4 hour turnaround time**	S5 24/7	£24 545.00		**4 hour turnaround time**	S5 24/7	£11 045.80	
	S5	£32 320.98	£16 366.38		S5	£40 911.38	£16 366.38		S5	£27 412.18	£16 366.38
	S4	£33 271.58	£17 316.98		S4	£40 917.03	£16 372.03		S4	£28 902.75	£17 856.95
	S2	£55 133.33	£39 178.73		S2	£56 225.54	£31 680.54		S2	£54 041.13	£42 995.33
	S7	£96 588.19	£80 633.59		S7	£97 680.40	£73 135.40		S7	£95 495.98	£84 450.18
	S6	£99 670.96	£83 716.36		S6	£100 763.17	£76 218.17		S6	£98 578.75	£87 532.95
	S3	£114 581.67	£98 627.07		S3	£122 227.12	£97 682.12		S3	£110 212.83	£99 167.03
	S1	£138 557.54	£122 602.94		S1	£139 649.75	£115 104.75		S1	£137 465.33	£126 419.53
	S8	£182 258.90	£166 304.30		S8	£183 351.11	£158 806.11		S8	£181 166.70	£170 120.90

Table A28 Troponin T: Different strategies ranked by cost – sensitivity analyses, using base-case data with specified amendments

Middle volume 2 hour turnaround time	Scenario	Net costs	Difference from cheapest scenario
Base case	S5 24/7	£15 954.60	
	S2	£32 194.59	£16 239.99
	S5	£32 320.98	£16 366.38
	S4	£33 271.58	£17 316.98
	S6	£45 270.60	£29 316.00
	S7	£79 673.38	£63 718.78
	S3	£114 581.67	£98 627.07
	S1	£115 747.42	£99 792.82
	S8	£164 917.79	£148 963.19
Plus £20 ECG	S5 24/7	£15 954.60	
	S5	£35 253.76	£19 299.16
	S4	£36 790.91	£20 836.31
	S2	£38 646.71	£22 692.11
	S6	£54 873.36	£38 918.76
	S7	£97 621.99	£81 667.39
	S3	£140 892.90	£124 938.30
	S1	£145 829.37	£129 874.77
	S8	£207 082.80	£191 128.20
Nurse/consultant costs halved	S5 24/7	£15 954.60	
	S2	£18 280.60	£2 326.00
	S4	£23 734.76	£7 780.16
	S5	£24 137.06	£8 182.46
	S6	£24 817.82	£8 863.22
	S7	£42 017.12	£26 062.52
	S1	£60 051.10	£44 096.50
	S3	£64 384.11	£48 429.51
	S8	£84 633.27	£68 678.67
Plus LMWH £5.81	S5 24/7	£21 475.38	
	S5	£38 693.74	£17 218.36
	S2	£39 589.71	£18 114.33
	S4	£39 814.73	£18 339.34
	S6	£53 580.99	£32 105.60
	S7	£90 408.23	£68 932.85
	S3	£127 745.86	£106 270.48
	S1	£130 007.01	£108 531.62
	S8	£182 687.51	£161 212.13

Appendix 15

LITERATURE SEARCH FOR STUDIES EXPLORING PATIENTS' PERCEPTIONS OF CHD

Databases: CINAHL, EMBASE, PREMEDLINE, MEDLINE, PsycINFO
Coverage:
CINAHL 1982 to December Week 4 2002
EMBASE 1980 to 2003 Week 4
PREMEDLINE January 29, 2003
MEDLINE 1966 to January Week 2 2003
PsycINFO 1872 to January Week 4 2003
Platform: OVID Multifile
Search run: 31/01/03

Strategy:
1. heart arrest.sh.
2. myocardial ischemia.sh.
3. coronary disease.sh.
4. angina pectoris.sh.
5. angina, unstable.sh.
6. myocardial infarction.sh.
7. ischemic heart disease.sh.
8. heart muscle ischemia.sh.
9. unstable angina pectoris.sh.
10. impending heart infarction.sh.
11. heart infarction.sh.
12. acute heart infarction.sh.
13. heart infarction size.sh.
14. heart reinfarction.sh.
15. heart muscle necrosis.sh.
16. heart disorders.sh.
17. myocardial infarctions.tw.
18. or/1-17
19. ((cardiac or coronary or heart) adj2 arrest$).tw.
20. ((cardiac or coronary or heart) adj2 attack?).tw.
21. (coronary adj2 disease?).tw.
22. angina.tw.
23. "syndrome x".tw.
24. ((cardiac or coronary or heart of myocard$) adj2 infarct$).tw.
25. ((cardiac or coronary or heart or myocard$) adj2 isch?em$).tw.
26. acute coronary syndrome?.tw.
27. (chest adj2 pain$).tw.
28. or/19-28
29. 18 or 28
30. focus groups.sh.
31. interviews.sh.
32. interview.sh.
33. qualitative research.sh.
34. qualitative analysis.sh.

35. qualitative studies.sh.
36. nursing methodology research.sh.
37. qualitative$.ti.
38. interview$.ti.
39. focus group?.ti.
40. or/30-39
41. 29 and 40
42. remove duplicates from 41

Sources

- MEDLINE (OVID)
- PREMEDLINE (OVID)
- CINAHL (OVID)
- EMBASE (OVID)
- PsycINFO (OVID)
- SOCIAL SCIENCE CITATION INDEX (ISI)

Appendix 16

RESULTS OF THE LITERATURE REVIEW ON PATIENTS' PERCEPTIONS OF CHD

Table A29 Qualitative UK research studies exploring patients' perception of CHD

Study	Main aim	Data	Sample
Cowie (1976)	Describe 'careers' of MI patients from perception of symptoms onwards	Semi-structured interviews	27 married MI patients under 60 years old with first MI Spouses interviewed where possible Does not give details of gender
Thompson *et al.* (1995)	Explore experiences of married men and their partners 1 month after first MI	Semi-structured interviews	20 married men with MI aged 56–72 and their wives
Webster (1997)	Describe experiences and needs of Asian CHD patients, and summarise methodological issues around research on ethnic groups	Semi-structured interviews	40 Gujurati Hindu coronary patients (30 men, 10 women) and their partners/carers, average age was 65
Clark *et al.* (1998)	Review qualitative literature on experiences of CHD, and discuss weaknesses and methodologies	Existing qualitative studies	6 semi-structured or unstructured interview studies that explored patients' experiences of cardiac conditions
Wiles (1998) (see Wiles and Kinmonth (2001))	Describe patients' understandings of an MI and the lifestyle advice they are given	In-depth interviews (at 2 different time points)	25 MI patients (13 men, 12 women) aged 34–80, social class mixture
Miklaucich (1998)	Describe the experience of women with angina	Unstructured interviews (at 2 different time points) and patient diaries	8 women aged 50–70 with diagnosis of angina (after recent acute episode of chest pain and admission to hospital)
Foster & Mallik (1998)	Compare men and women's pre-hospital delay following the onset of acute chest pain	Structured interviews with open-ended questions	24 patients (12 men, 12 women) aged 36–82 admitted to hospital because of chest pain (diagnosis of angina attack or MI)
Ruston *et al.* (1998)	Explore why cardiac patients delay calling for medical help after the onset of symptoms	Semi-structured interviews	43 cardiac patients and 21 others present at cardiac event 28 men and 15 women, social class mix
Gardner & Chapple (1999)	Explore barriers to referral among patients with angina	Semi-structured interviews	16 patients under 75 years with stable angina who have not seen a cardiologist (also 4 GPs), deprived area setting Does not give details of gender mix
White (1999)	Explore the meaning of acute chest pain among men and how their masculinity affects the way they respond to care	Participant observation and in-depth interviews	No details about number or age of participants (although see entry below which seems to relate to the same study)
White & Johnson (2000)	Examine men's experience of chest pain and why they delay in presenting symptoms	Participant observation and in-depth interviews	Participant observation of 25 men admitted to hospital with acute chest pain In-depth interviews with 10 of these men – varied in age, social class, ethnic origin and experiences

Study	Main aim	Data	Sample
Rogers *et al.* (2000)	Explore heart failure patients' experiences, especially their communication with health professionals	In-depth interviews	27 heart failure patients aged 38–90 20 men and 7 women, 21 white and 6 ethnic minority
Tod *et al*. (2001)	Identify factors that influence the use of health services by people with angina	Semi-structured interviews and focus groups	Individual interviews with 14 manual patients (7 women, 7 men) with angina aged 52–73 and with 9 primary care staff 5 focus groups with community groups and 1 with GPs
Wiles & Kinmonth (2001) (see Wiles (1998))	Explore patients' understandings of their MI and identify effective secondary prevention services	In-depth interviews (at 2 different time points)	25 patients (13 men, 12 women) admitted with MI aged 34–80, all white, social class mixture
Clark (2001)	Explore why MI patients delay calling for medical help after the onset of symptoms	Semi-structured interviews (at 4 different time points)	14 MI patients (9 men, 5 women) aged 36–84, varied in terms of social class
Furze *et al*. (2001)	Explore the beliefs of angina sufferers	Semi-structured interviews	20 angina patients (11 men, 9 women), all white (age range not clear)
Roebuck *et al.* (2001)	Examine the effects of MI on health-related quality of life	Semi-structured interviews	31 MI patients (21 men, 10 women) aged 28–74 and 'several' partners
Kennelly & Bowling (2001)	Explore older people's experiences of health care in relation to CHD	Focus groups	5 focus groups with heart support groups A total of 38 patients (26 men, 12 women) aged 56 and over, social class mixture
Ruston & Clayton (2002)	Examine how women distance themselves from the likelihood of developing CHD	In-depth interviews	50 women who had been admitted to hospital with a cardiac event and 88 without CHD No information given on age
Richards *et al.* (2002a)	Explore socio-economic variations in perceptions of, and behavioural responses to, chest pain	Semi-structured interviews	60 respondents (30 men, 30 women) with chest pain aged 45–64, social class mixture
Richards *et al.* (2002b)	Explore gender variations in responses to chest pain	Semi-structured interviews	As above
Tod *et al.* (2002)	Examine what barriers exist for MI patients in accessing cardiac rehabilitation services in a deprived area	Semi-structured interviews and focus groups	Individual interviews with 20 MI patients (16 men, 4 women) aged 43–76 Individual interviews with 15 health professionals (3 men, 12 women) 3 focus groups (1 with health visitors, 2 with lay members of heart support groups)
Pattenden *et al.* (2002)	Explore why MI patients delay seeking medical help after the onset of symptoms	Semi-structured interviews	22 patients (20 men, 2 women) mean age 66 years, already had an MI 11 interviews with relatives

Appendix 17

LITERATURE SEARCH FOR STUDIES WHICH FOCUS ON THE PARTNERS AND/OR FAMILIES OF CHD PATIENTS

Databases: CDSR, ACP Journal Club, DARE, CCTR, CINAHL, EMBASE, PREMEDLINE, MEDLINE
Coverage:
EBM 1st quarter 2003
CINAHL 1982 to April Week 3 2003
EMBASE 1980 to 2003 Week 16
PREMEDLINE April 23 2003
MEDLINE 1966 to April Week 3 2003
Platform: OVID
Date searched: 25 April 2003

Strategy:
1. heart arrest/ use mesz
2. exp myocardial ischemia/ use mesz
3. chest pain/ use mesz
4. heart arrest/ use emez
5. exp ischemic heart disease/ use emez
6. coronary artery disease/ use emez
7. heart arrest/ use cctr,coch,dare
8. exp myocardial ischemia/ use cctr,coch,dare
9. chest pain/ use dare,coch,cctr
10. heart arrest/ use nursing
11. exp myocardial ischemia/ use nursing
12. chest pain/ use nursing
13. ((cardiac or coronary or heart) adj2 arrest$).tw.
14. ((cardiac or coronary or heart) adj2 attack$).tw.
15. ((coronary or heart) adj2 disease?).tw.
16. angina.tw.
17. uap.tw.
18. ((cardiac or coronary or heart or myocard$) adj2 isch?em$).tw.
19. ((cardiac or coronary or heart or myocard$) adj2 infarct$).tw.
20. mi.tw.
21. ami.tw.
22. nqwmi.tw.
23. acute coronary syndrome?.tw.
24. acs.tw.
25. (chest adj2 pain$).tw.
26. or/1-25
27. caregivers/ use mesz
28. home nursing/ use mesz
29. spouses/ use mesz
30. family/ use mesz
31. caregiver/ use emez

32. home care/ use emez
33. exp household/ use emez
34. spouse/ use emez
35. caregivers/ use cctr,coch,dare
36. home nursing/ use cctr,coch,dare
37. spouses/ use cctr,coch,dare
38. family/ use cctr,coch,dare
39. caregiver burden/ use nursing
40. caregivers/ use nursing
41. "caregiver role strain (NANDA)"/ use nursing
42. "risk for caregiver role strain (NANDA)"/ use nursing
43. role stress/ use nursing
44. role change/ use nursing
45. "role change (OMAHA)"/ use nursing
46. caregiver strain index/ use nursing
47. "caregiver home care readiness (Iowa NOC)"/ use nursing
48. "caregiver lifestyle disruption (Iowa NOC)"/ use nursing
49. "caregiver-patient relationship (Iowa NOC)"/ use nursing
50. "caregiver stressors (Iowa NOC)"/ use nursing
51. "caregiving endurance potential (Iowa NOC)"/ use nursing
52. care?giver$.ti.
53. carer$.ti.
54. carer$.ab.
55. or/27-58
56. 26 and 59
57. remove duplicates from 61

Sources

- Cochrane Database of Systematic Reviews (CDSR) (OVID)
- ACP Journal Club (OVID)
- DARE (OVID)
- Cochrane Central Register of Controlled Trials (CCRCT) (OVID)
- CINAHL (OVID)
- EMBASE (OVID)
- PREMEDLINE (OVID)
- MEDLINE (OVID)
- Social Science Citation Index (SSCI) (ISI)
- ASSIA (Applied Social Sciences Index and Abstracts) (CSA)
- BNI (British Nursing Index) (OVID)
- PsycINFO (OVID)

Appendix 18

RESULTS OF THE LITERATURE REVIEW ON PARTNERS AND/OR FAMILIES OF CHD PATIENTS

Table A30 Qualitative research studies which focus on the partners and/or families of CHD patients

Study	Main aim	Data	Sample
Literature reviews			
Nolan & Nolan (1998) (UK)	Provide overview of current deficits in cardiac rehabilitation programmes, including family involvement	Existing literature (quantitative and qualitative)	Not applicable
James (1999) (UK)	Provide overview of literature on the impact of cardioverter defibrillators on patients and their families	Existing literature (quantitative and qualitative)	Not applicable
Fleury & Moore (1999) (USA)	Review research on family-centred care during the acute phase after an MI	Existing literature (quantitative and qualitative)	Not applicable
Van Horn *et al.* (2002) (USA)	Review research on cardiac events that may guide the use of family-centred interventions	Existing literature (quantitative and qualitative)	Not applicable
Empirical studies			
Dougherty (1997) (USA)	Ask survivors and family members about recovery from cardiac arrest, and recommend interventions they received or desired	Interviews at discharge and 4 times over a year	15 survivors of cardiac arrest and 15 relatives Survivors were 13 men and 2 women, mean age 57 Relatives were 'primarily spouses', mean age 53
Theobald (1997) (Australia)	Describe the experiences of respondents whose partners have suffered an MI	In-depth interviews	3 respondents whose partners had experienced a first-time MI 1 man and 2 women, aged 47–73 years
Daly *et al.* (1998) (Australia)	Explore the experiences of women whose spouses had recently experienced an AMI	Semi-structured interviews at 2 and 4 weeks after discharge from hospital	7 English-speaking women of Lebanese origin aged 38–64 years, married to Lebanese-born men All mothers, engaged full-time in domestic duties
Dickerson (1998) (USA)	Investigate the help needed by spouses of cardiac rehabilitation patients	In-depth interviews and focus groups	Individual interviews with 7 wives of cardiac patients, mean age 53 4 focus groups with a total of 17 wives and 2 husbands, mean age 62
Svedlund *et al.* (1999), Svedlund & Axelsson (2000) (Sweden)	Examine the experiences of women with an AMI and their partners	Semi-structured interviews conducted at 3 and 12 months after acute MI	9 men aged 49–65 years, with female partners with acute MI who were under 60 years
James *et al.* (2001a) (UK)	Describe the impact of an imposed medico-legal driving ban on internal cardioverter defibrillator recipients and their partners	Semi-structured interviews	7 patients (5 men and 2 women) who had received an internal cardioverter defibrillator within the previous 18 months and their long-term partners

Study	Main aim	Data	Sample
Stewart *et al.* (2000) (Canada)	Describe stress, coping strategies and social support experienced by survivors of a first-time MI and their spouses	Field notes from 12 support groups and weekly diaries	14 survivors (13 men and 1 woman), mean age 57 and their spouses, mean age 56 All respondents were white
Mahoney (2001) (USA)	Understand the illness experiences of patients with congestive heart failure and their family members	Semi-structured interviews and participant observation	16 patients (men and women, 'ethnically diverse', 50 years or older) and 12 family members Family members were over 12 years of age (no other details given)
Martensson *et al.* (2001) (Sweden)	Describe the experiences of spouses of patients with heart failure	Semi-structured interviews	23 spouses (8 men and 15 women) of patients with severe heart failure. Mean age was 75 for men and 73 for women Chosen to ensure variation in socio-demographic data
Tapp (2001) (Canada)	Describe therapeutic conversations between nurses and families who had a member with IHD	12 clinical sessions (videotaped) with families, discussions by the clinical team, and unstructured interviews with families	Clinical sessions with 3 families (10 individuals) and unstructured interviews with 8 of the same individuals (Information about gender or age is not comprehensive, but the examples suggest both male and female patients were interviewed, with their partner and/or offspring)
Eckert & Jones (2002) (Australia)	Describe the experience of patients with implantable cardioverter defibrillators and their families	Unstructured interviews	3 patients (all men aged 35–70 years) and 3 significant family members (2 women and 1 man)
Murray *et al.* (2002) (UK)	Describe the illness trajectories, needs and service use of patients with advanced cardiac failure and their main informal carers	In-depth interviews at 3-monthly intervals for up to a year	20 patients (average age 74 years) and their main informal carer Patients were chosen to represent the local demography of the condition with respect to age, sex and deprivation category
Brostrom & Dahlstrom (2003) (Sweden)	Describe spouses' support to patients with congestive heart failure in relation to the couple's sleep situation	Semi-structured interviews	25 spouses (10 men and 15 women), all white, aged 35–87 years

Appendix 19

REVIEW OF LITERATURE ON CARERS' NEEDS AND PREFERENCES

There is no comprehensive literature review of qualitative studies which focus on the roles of partners and families of CHD patients. However, four reviews (Fleury & Moore, 1999; James, 1999; Nolan & Nolan, 1998; Van Horn *et al.*, 2002) included some reference to qualitative, as well as quantitative, studies. These reviews found that partners and families try to respond to the patient's need for support in addition to coping with their own grief, shock and fear. They are often unprepared for the transition between hospital and home and their anxieties sometimes manifest as overprotectiveness of the patient. Other concerns included financial worries, changes in social activity and changes in the patient's physical activity. Families' emotional and support needs were often neglected. Families are not given enough information about the illness and are not sufficiently involved in cardiac rehabilitation programmes. Areas of rehabilitation that affect the relationship between patients and partners, such as concerns about sexuality, are often neglected.

There was very little overlap between the papers discussed in these four literature reviews and 14 more recent empirical papers that were identified. However, some of the findings from the empirical papers were similar to those identified in the reviews.

The themes raised by the empirical papers, and considered in the following sections, include:

- problems experienced by relatives
- sources of conflict between relatives and patients
- problems with the health care system
- need for support.

Problems experiences by relatives

Relatives reported a number of adverse effects after the patient's cardiac event. They experienced a variety of distressing emotions including guilt, self-blame, anguish, frustration, resentment, powerlessness and fear (Daly *et al.*, 1998; Svedlund *et al.*, 1999; Theobald, 1997). Daly *et al.* (1998) found that women's health suffered after their husband's MI, but that they hid these health problems in order to protect their families, and that they experienced problems trying to combine their normal roles with the new responsibilities of caring for the patient. Women also reported difficulties in dealing with the mood changes of their husband after an MI (Stewart *et al.*, 2000). Some partners had difficulties with eating, sleeping and concentrating (Theobald, 1997). Others worried about household finances, trying to weigh up whether the patient could afford to give up work against the consequences for their health if they did go back to paid work (Stewart *et al.*, 2000).

Sources of conflict between patients and relatives

These studies identified a number of potential areas of conflict between patients and relatives. Firstly, the need for behavioural change by the patient could be stressful for the family as a whole. Wives reported not knowing what foods would be sufficiently healthy for the patient and had difficulty in creating meals that the whole family would eat (Theobald, 1997; Stewart *et al.*, 2000). Some men reported finding life monotonous as their partner's illness imposed limitations on daily life (Svedlund & Axelsson, 2000). Couples' social lives often changed when the patient was easily tired and did not want to go out, or when they found it difficult to socialise with friends or acquaintances who drank and smoked (Martensson *et al.*, 2001; Svedlund & Axelsson, 2000).

Secondly, the role of the spouse as 'monitor' or 'enforcer' was highlighted. Wives felt they needed to check that their husbands were continuing to eat healthily and this could lead to conflict, especially in a social situation (Daly *et al.*, 1998; Stewart *et al.*, 2000). Spouses also talked about how they spent endless hours observing the patient and how they felt the pressure of constant responsibility (Dickerson, 1998; Mahoney, 2001; Stewart *et al.*, 2000). The balance between supporting patients and letting them lead independent lives was difficult to achieve (Eckert & Jones, 2002). Patients often felt their spouses were being overprotective, while spouses felt isolated and oppressed by the constant responsibility and the need to be close at hand (Daly *et al.*, 1998; Eckert & Jones, 2002; Murray *et al.*, 2002; Stewart *et al.*, 2000). This continual vigilance sometimes resulted in spouses neglecting themselves, being afraid to resume their usual routines and not sleeping as they watched over the patient with CHD (Brostrom & Dahlstrom, 2003).

Thirdly, lack of communication could be an issue. Both spouses and survivors engaged in processes of protective buffering, where they tried to protect the other person from stressful information and hide concerns (Svedlund & Axelsson, 2000; Tapp, 1993). There was also evidence that some patients and some partners distanced themselves from the disease and denied what was happening (Svedlund *et al.*, 2001; Stewart *et al.*, 2000). Relatives found it difficult to know whether to voice their worries about the patient's behaviour, in case it was interpreted as nagging (Tapp, 1993). Unusually, Svedlund and colleagues (Svedlund & Axelsson, 2000; Svedlund *et al.*, 1999) studied the experiences of male partners of women who had suffered an acute MI. They found that men tried to adapt to the women's experiences of the illness and were worried that their partners often withheld their feelings and did not talk to them about their illness. These men felt that their partners wanted to continue to be strong in front of the family and therefore hid their feelings.

Finally, conflict occurred when illness meant that patients could not perform the tasks traditionally associated with their gender. For example, men with CHD found it hard that their spouse had taken over what they perceived as traditional male tasks (e.g. shovelling snow) (Stewart *et al.*, 2000). Similarly, it has been suggested that men with internal cardioverter defibrillators, who are banned from driving, experience this and find it a threat to their self-image (James *et al.*,

2001a). The lack of research on the family relationships of female CHD patients makes it difficult to explore this in relation to women. However, quantitative research suggests that the situation for female CHD patients may be different. For example, Lemos *et al.* (2003) found that men who reported more cardiac symptoms than others tended not to engage in male-stereotyped activities such as repairs and paid employment, but that women who experienced more symptoms continued with their domestic activities. One of the few qualitative studies to focus on men (Svedlund & Axelsson, 2000) found that men let their female partners with CHD decide how much household work to do to prevent the women feeling frustrated and powerless.

Partners and relatives employed a number of coping strategies in order to try to ease these tensions. These included discussing problems with their partners, personal time out, adjusting expectations and 'surrender' (i.e. being philosophical about the situation) (Mahoney, 2001; Stewart *et al.*, 2000). Some spouses assumed responsibility for income generation so the cardiac survivor would not have to go back to work, while others gave up paid employment to care for the patient (Stewart *et al.*, 2000). Finally, some relatives tried to find purpose and meaning in the illness experience (Mahoney, 2001).

Problems dealing with the health care system

Relatives reported a number of problems when dealing with the health care system. They needed most help when the patient was discharged from hospital (Dickerson, 1998). However, discharge sometimes occurred suddenly without adequate preparation (Stewart *et al.*, 2000). This was very stressful as responsibility suddenly shifted from health professionals to the family, who felt very inexperienced in caring for the patient and felt unprepared to handle the side effects of medications at home (Dickerson, 1998; Dougherty, 1997; Murray *et al.*, 2002). Some relatives felt that they were not considered to be an important part of the patient's recovery by health professionals and were not given the information they required (Murray *et al.*, 2002). This lack of information heightened their anxiety. They also wanted health care staff to help resolve problems when patients and family members had different perspectives or opinions about care and recovery (Dougherty, 1997).

Need for support

Relatives expressed a need for support groups, but some felt guilty about asking for help for themselves. Martensson *et al.* (2001) found that elderly female spouses were particularly reluctant to complain or ask for help.

Spouses received support from a number of different sources including offspring, friends, work colleagues, neighbours, health professionals and from their spiritual faith. They needed practical support (e.g. help with domestic chores, transport to hospital) as well as information and emotional support. Dickerson (1998) found that while some spouses had family support, others were expected to provide support to distressed family members. For example, Stewart *et al.* (2000) found that wives perceived that their children felt threatened by their father's MI and

needed reassuring. Martensson and colleagues (2001) found that some friends tended to focus their sympathy on the patient rather than support relatives, and that some spouses did not want to 'bother' their offspring and so did not receive support from them. Other barriers to seeking help included time constraints (Dickerson, 1998).

Gaps in the literature

The four literature reviews identified important gaps in the literature. Firstly, relatively few studies used qualitative methodology to explore the experiences of cardiac patients and their families (James, 1999). Secondly, most research focuses on white, male patients and their wives (Fleury & Moore, 1999; Van Horn *et al*., 2002). Thirdly, samples have often been confined to spouses rather than including partners and other family members (Van Horn *et al*., 2002). Finally, research has neglected the needs and roles of significant friends of CHD patients (Fleury & Moore, 1999).

The empirical papers reviewed confirmed these gaps in the literature. Only 14 qualitative papers that explored the experiences of relatives of cardiac patients were found. Nine papers out of the 14 concentrated solely on the spouse or partner of cardiac patients rather than on the wider family. With regard to gender, eight papers focused exclusively or mainly on female relatives compared with two papers (reporting findings from the same study) which focused exclusively on men. Only one study (Brostrom & Dahlstrom, 2003) had strategically sampled by gender in order to ensure roughly equal numbers of men and women (15 women and 10 men); however, the authors made no comment about differences or similarities in the accounts of male and female spouses. The remaining three papers did not give sufficient detail of the gender of the respondents in their methodology. Only four out of the 14 papers gave any indication of the ethnicity of their respondents. Two studies reported that they focused on the majority white population (Brostrom & Dahlstrom, 2003; Stewart *et al*., 2000), one had 'ethnically diverse' respondents (Mahoney, 2001) and one studied Lebanese-born women in Australia (Daly *et al*., 1998). None of the papers included friends of CHD patients as respondents.

Appendix 20

QUESTIONNAIRE FOR BIOCHEMISTRY LABORATORIES

Health Technology Board for Scotland

NHS SCOTLAND

Laboratory questionnaire to assess the availability of troponin testing services in Scotland

1 Does your laboratory offer any form of cardiac troponin testing?	Yes	No
If 'Yes', *please go to Question 2.*		
If 'No', *please complete the rest of Question 1 only.*		
(i) What biochemical cardiac markers tests are offered? *Please indicate all that apply.*		
Creatine kinase		
Creatine kinase MB		
Aspartate aminotransferase		
Lactate dehydrogenase		
Myoglobin		
Other:		
(ii) Why is troponin testing not offered? *Please indicate all that apply.*		
Clinicians do not wish to use it		
Lack of finance		
Other:		
(iii) Are you planning to introduce troponin testing?	Yes	No

2 What type of cardiac troponin test is offered? *Please indicate all that apply.*	
Laboratory-based troponin I	Analyser/platform/kit used:
	Sample type:
Laboratory-based troponin T	Analyser/platform/kit used:
	Sample type:
Point-of-care testing[1]	Analyser/platform used:
	Sample type(s):

[1] Other terms to describe point-of-care testing include near-patient testing, bedside testing, extra-laboratory testing and disseminated laboratory testing.

3 For laboratory-based troponin testing, *please indicate the following:*		
Is the service offered on demand?	Yes	No
If 'Yes', what are the estimated turnaround times (i.e. time of receipt to reporting) at your institution?		
If 'No', is troponin testing done in batches? *Please describe the process.*		
If your laboratory offers an 'on demand' and 'batch' service, *please describe the process.*		
If the troponin testing service offered at weekends and public holidays is different to that described above, *please describe.*		

4 Does your laboratory provide a troponin testing service to primary care or to remote/rural sites? *Please indicate all that apply.*	
General practices	
Community hospitals	
Satellite institutions	
Other:	

5(a) Does your laboratory provide guidance or a formal protocol to clinicians regarding timing of samples for troponin testing in the setting of an acute coronary admission? *Please circle and then complete appropriate section of Question 5(a).*		Yes	No
(i) If 'Yes', is this:	*Recommended*	*Mandatory*	
Sample taken at time of admission			
Sample taken <6 hours following admission			
Sample taken between 6 and 12 hours following admission			
Other *(please specify)*: *If a written protocol is available, please return with this questionnaire.*			
(ii) If 'No', are clinicians using their own guidance or formal protocol which does not include the laboratory?		Yes	No
If 'Yes', *please provide a contact name.*			
5(b) Do you advise a single blood sample or paired samples for troponin testing? *Please tick appropriate box.*			
Single sample			
Paired sample			

6 Does your laboratory provide guidance or a formal protocol to clinicians regarding interpretation of troponin test results in the setting of an acute coronary event?		Yes	No
Lower and upper cut-off levels *(please specify)*	Lower:	Upper:	
Single action level *(please specify)*			
Other/Comments: *If a written protocol is available, please return with this questionnaire.*			

7(a) Is a troponin point-of-care testing service available in your area?				Yes	No
If 'No', please go to Question 9.					
If 'Yes', *please complete Question 7(b).*					
7(b) What, if any, is the role of your laboratory in the provision of troponin point-of-care services at your institution? *Please indicate all that apply and specify the body responsible for each item.*					
	Location of POCT (*please circle*)	Maintenance of analyser	Analysis and interpretation	QC	QA (*please specify*)
Accident & Emergency	Yes/No				
Wards *(please specify, e.g. Medical Receiving)*	Yes/No				
Primary care	Yes/No				
Other off site (*please specify*)	Yes/No				
Other *(please specify)*	Yes/No				

8 Does your laboratory have specific personnel to conduct training for users of troponin point-of-care testing devices?	Yes	No
If 'Yes', *please specify.*		
If 'No', *please indicate who provides training.*		

9 Has troponin testing superseded conventional cardiac marker testing at your laboratory in the setting of an acute coronary event? *Please indicate where appropriate.*	
'Yes', we do not offer other biochemical cardiac marker tests	
'No', we still offer the following biochemical cardiac markers tests:	
Creatine kinase	
Creatine kinase MB	
Aspartate aminotransferase	
Lactate dehydrogenase	
Other (*please specify*)	

Comments:

This is the end of the questionnaire. Thank you for taking the time to fill it in.

Please return your questionnaire and protocols (if available) to Ms Joyce Craig, Health Technology Board for Scotland, Delta House, 50 West Nile Street, Glasgow G1 2NP.

If you have any queries, please contact Dr Utkarsh Kulkarni, Specialist Registrar, Department of Clinical Biochemistry on 01224 552831 or by email U.V.Kulkarni@arh.grampian.scot.nhs.uk

Appendix 21

QUESTIONNAIRE FOR CARDIOLOGISTS

Cardiologist questionnaire to assess the use of troponin testing services in Scotland

Name _____

Hospital _____

1. Do you have access to the troponin assay in your hospital? Yes No

   If ' No', go to question 7

2. Which of the following is available in your hospital for routine clinical use in patients with suspected acute coronary syndromes? *Tick all that apply.*

Troponin T	Lab	☐	Troponin I	Lab	☐	CK-MB	Lab	☐
	POCT[1]	☐		POCT	☐		POCT	☐

3. On which patients do you perform troponin assay?

	All	Selected *(specify below)*	None	N/A
Patients with unstable angina or NSTEMI	☐	☐	☐	☐
Patients with STEMI	☐	☐	☐	☐
Following angioplasty or other procedures	☐	☐	☐	☐
Other patients (*please specify*)	☐	☐	☐	☐

_____

_____

4. Why do you perform troponin assay?

Risk stratify NSTEMI or unstable angina patients ☐
Change patient management ☐
Confirm or audit clinical decision ☐
Other (*please describe*) ☐

_____

_____

5. Has using troponin enabled:

earlier discharge of admitted patients, presenting with chest pain
and who are troponin negative? ☐
better risk stratification of patients so focus can be on high risk patients? ☐
reduced use of other biochemical markers ☐
other effects? *(please describe below)* ☐

_____

_____

_____

[1] POCT is point-of-care testing kit, also known as near patient testing, bedside testing and extra-laboratory testing.

6. Do you have a formal protocol for the management of patients with chest pain which mentions the use of troponins?

Yes No

If yes, please advise lower and upper cut-off levels	Lower	Upper
If a written protocol is available, please return with this questionnaire		

7. What diagnosis would you currently give the following patient?

Chest pain typical of AMI, non-specific ECG charges, no rise in CK, AST or LDH but a significant rise in troponin

AMI/non STEMI ☐
Unstable angina ☐
Acute coronary syndrome ☐
Other *(please specify)* ☐ _____

_____

This is the end of the questionnaire. Thank you for taking the time to fill it in.

Please return your questionnaire and protocols (if available) to Ms Joyce Craig, Health Technology Board for Scotland, Delta House, 50 West Nile Street, Glasgow, G1 2NP.

If you have any queries, please contact Ms Craig on 0141 225 6985 or by email jcraig@htbs.org.uk

THANK YOU FOR YOUR HELP

Appendix 22

QUESTIONNAIRE FOR COMMUNITY HOSPITALS

Name: _____

Hospital: _____

Please tick applicable responses and provide further information as appropriate

1. (i) Are you able to request troponin tests?
(regardless of restrictions on number/frequency of testing)

☐ yes - please go to question 2

☐ no - please complete the rest of question 1 only

(ii) Which biochemical markers are offered? (*please indicate all that apply)*

☐ creatine kinase

☐ creatine kinase-MB

☐ aspartate aminotransferase

☐ lactate dehydrogenase

☐ myoglobin

(iii) Why is troponin testing not offered? *(please indicate all that apply)*

☐ clinicians do not wish to use it

☐ lack of finance

☐ other: *please explain:*

(iv) Are you planning to introduce troponin testing?

☐ yes

☐ no

(v) Any comments?

2. What type of cardiac troponin test is offered? *Please indicate all that apply and complete related questions.*		
(i) Laboratory-based troponin I	yes ☐ please complete question 3	no ☐
(ii) Laboratory-based troponin T	yes ☐ please complete question 3	no ☐
(iii) Point-of-care testing [1]	yes ☐ please complete question 4	no ☐

3. If you use laboratory-based troponin testing:	
(a) What is the average time from obtaining sample from patient and receipt of results?	
(b) What is the availability of the service at weekends and holidays?	
(c) Does the laboratory provide a protocol for interpretation of troponin test results? ☐ yes - *please provide a copy* ☐ no - *please describe how you determine cut off levels:* --- --- ---	
(d) What is the monthly average number of troponin tests requested?	
(e) Please indicate your level of satisfaction with laboratory based service: ☐ Good ☐ Acceptable ☐ Poor	
(f) Any comments?	

[1] Other terms used to describe point-of-care testing include near-patient testing, bedside testing, extra-laboratory testing and disseminated laboratory testing.

4. If you use point-of-care testing (POCT):

(a) Who carries out the tests?

☐ nurse

☐ other individual. *Please specify*: ----------

(b) (i) Was training provided by the manufacturers?

☐ yes ☐ no

(ii) Is other training required?

☐ yes, *please describe*: ☐ no

(c) Is the service registered with a quality assurance scheme?

☐ yes ☐ no

(d) (i) Does a laboratory provide any services for the POCT?

☐ yes - *please describe:* ☐ no, *please complete part* (ii)

(ii) Would you wish a laboratory to provide services for the operation and maintenance of the POCT?

☐ yes ☐ no

If yes, which services?

(e) What is the monthly average number of POCT requested by:

(i) your practice (if applicable)? ----------

(ii) your hospital? ----------

(f) Please indicate your level of satisfaction with POCT services:

☐ Good ☐ Acceptable ☐ Poor

(g) Any comments?

5. Clinical use of troponin tests

(a) Do you request troponin tests for patients who present with the following?

	all	some	none
Chest pain	☐	☐	☐
Unstable angina or NSTEMI	☐	☐	☐
STEMI	☐	☐	☐
Other conditions? (*please specify):*	☐	☐	☐
----------	☐	☐	☐
----------	☐	☐	☐

6. Why do you perform troponin tests? (p*lease indicate all that apply)*

To enable discharge of 'low risk' patients with negative troponins ☐

To risk stratify NSTEMI or unstable angina patients in hospital ☐

To inform patient management, especially on invasive or conservative management decisions ☐

To audit clinical decision ☐

Other reasons. *Please describe:* ☐

This is the end of the questionnaire. Thank you for taking the time to fill it in.

Please return your questionnaire and protocols (if available) to Ms Joyce Craig, Health Technology Board for Scotland, Delta House, 50 West Nile Street, Glasgow, G1 2NP.

If you have any queries, please contact Ms Craig on 0141 225 6985 or by email jcraig@htbs.org.uk

THANK YOU FOR YOUR HELP

Appendix 23

LABORATORY SURVEY RESULTS

Twenty-two laboratories were identified and surveyed. Eighteen laboratories (82%) responded, although not all questions were applicable to every laboratory. All 18 laboratories offer troponin testing. These laboratories cover most of the population of Scotland but the troponin testing service provided varies.

Ten laboratories measure troponin I using analysers from Bayer, Beckman Coulter, Diagnostics Product Corporation and Johnson & Johnson. Seven laboratories measure troponin T using Roche analysers. One laboratory uses only point-of-care testing to measure troponin, while three laboratories use point-of-care testing in addition to laboratory testing. All four laboratories measure troponin T by point-of-care analysers.

Sixteen laboratories advised clinicians that single blood samples should be used for troponin testing, with two of these indicating that paired samples are recommended in occasional circumstances. The other two laboratories said that they conduct paired sampling.

Seventeen laboratories gave guidance on the timing of troponin testing. Of these 17, six laboratories measure troponin in blood samples taken between 6 and 12 hours after admission, and nine laboratories measure troponin in blood taken between 12 and 24 hours after admission or after the onset of symptoms. One laboratory advises that troponin measurements should be taken less than six hours after the onset of pain, and another laboratory that samples are taken less than 10 hours after admission. In two laboratories, troponin testing at the time of admission is mandatory. One respondent indicated that they have a different testing regimen for different subgroups of patients i.e. low-risk patients undergo a point-of-care troponin test at zero and six hours in contrast to the <12-hour test for other patients.

Of the 13 laboratories that responded to the question, the time from receipt of the sample in the laboratory to reporting the result ranges from 30 minutes to four hours (see Table A31).

Table A31 Time from receipt of specimen in laboratory to result

	Reporting time (hours)					Cannot specify or not given
	0.5	1	2	3	4	
Number of laboratories	3	6	1	1	2	5

Various combinations of testing services were reported e.g. an on-demand service during the week and a batched service at weekends, or a batch service during the week with an on-demand service for specific patients. The survey results indicated that five laboratories offer troponin testing on-demand, four offer batch testing and eight offer an on-demand and batch testing service. The majority of laboratories offer troponin testing at weekends but this tends to be done in batches. Two respondents indicated that a change in their practice is likely e.g. following the introduction of shift work.

Laboratories were later telephoned to clarify whether or not they provide a 24 hours per day, seven days per week troponin testing service to clinicians and five laboratories indicated that they provide this type of service.

Seventeen laboratories have formal guidance or a protocol for troponin testing. Fourteen laboratories provide clinicians with guidance or a formal protocol regarding the interpretation of troponin test results in the setting of an acute coronary event. Taking into account that a variety of analysers were being used, the lowest cut-off level ranges from 0.01 to 0.2 μg/L and the upper cut-off level ranges from 0.1 to 2.0 μg/L.

One laboratory said that troponin testing has superseded conventional cardiac marker testing. An additional three laboratories indicated that other markers are only available in some circumstances. However, 17 laboratories still offer one or more other biochemical cardiac marker tests: 17 offer CK; 11 offer aspartate aminotransferase; nine offer lactate dehydrogenase and five offer CK-MB.

In all four laboratories with point-of-care testing, the analysers are located in one or two hospital wards, specifically the medical receiving ward or the medical assessment unit. In two cases, the analyser is also located in A&E or CCU. In all cases, laboratory staff manage the maintenance of the point-of-care analyser. All four laboratories provide quality assurance and quality control for point-of-care testing. Two laboratories said that their quality assurance for point-of-care testing is provided by SEQAS-CT (now part of UKNEQAS-Cardiac Markers), and another laboratory referred non-specifically to 'internal and external quality assurance'.

One laboratory with point-of-care testing has input into the analysis and interpretation of results, two laboratories mentioned that ward senior house officers, clinicians and clinical support nurses undertake this task, and the fourth laboratory did not respond to this question.

Different specialists, such as clinical scientists and nurse chest pain specialists, provide training for users of the point-of-care analysers. One laboratory said that the manufacturer of the analysers also provides training.

Fourteen laboratories provide a troponin testing service to primary care or remote and rural sites. The service is most commonly used by general practices (12) and community hospitals (10), followed by satellite institutions (eight). Two respondents noted that these services are rarely used.

Appendix 24

CARDIOLOGISTS' SURVEY RESULTS

A survey was sent to 71 Scottish cardiologists and 48 cardiologists responded (68%). Forty six of the 48 cardiologists who responded (96%) have access to troponin tests. Two of these have indirect access, though one hoped to have access to troponin tests in the hospital in the near future. Two cardiologists indicated that they do not have access to troponin. There were no questions on turnaround times in this survey.

The majority of cardiologists have access to laboratory-based troponin (16 use troponin T, 27 use troponin I) or CK-MB (16 use CK-MB). Only three cardiologists have access to troponin T point-of-care testing.

Thirty six cardiologists have a formal protocol that involves troponin testing for the management of patients with chest pain. Thirty six respondents provided one or more cut-off points. Twenty eight of the cut-off points provided were without units, making comparisons impossible. Seven respondents provided cut-off points with units and one of the following single action levels was indicated: 'any detectable troponin'; 0.2 ng/mL; 0.2 ng/L or $\geq$0.03 μg/L.

Of the 46 cardiologists with access to troponin, 42 indicated that all UA or NSTEMI patients are tested and the remaining four reported that some are tested. Twenty-eight cardiologists use troponin tests on all patients with STEMI and a further eight on some patients with STEMI. Twenty cardiologists indicated that troponin testing is used occasionally after angioplasty or other procedures. When asked about the use of troponin testing, 45 responded that the results help to risk stratify NSTEMI or UA patients, 36 to change patient management and 23 to confirm or audit clinical decision.

Cardiologists with access to troponin testing reported that troponin reduces the use of other biochemical markers (27), enables earlier discharge of patients presenting with chest pain and who are troponin negative (34) and allows better risk stratification and focuses more on high-risk patients (43). Other impacts of the use of troponin were noted as an increased workload (e.g. the rate of referral to cardiology services, including catheterisation) and rehabilitation (4), possible increases to the patient's length of stay (2) e.g. due to inadequate catheterisation laboratory capacity, the misinterpretation of a negative troponin result may have led to inappropriate discharge (2) and a more accurate diagnosis of ACS or are less likely to miss an ischaemic event (3). Finally, one respondent noted that the failure 'to agree what exactly a raised troponin means' creates difficulties for cardiologists.

Appendix 25

COMMUNITY HOSPITAL SURVEY RESULTS

A survey was sent to 70 community hospitals throughout Scotland. Fifty-four surveys (77%) were returned, although 17 (33%) of these were marked not applicable i.e. they did not treat CHD patients. Therefore, the number of usable surveys was 37. A follow up of 16 non-responders posed only one question (whether they have access to troponin testing). Nine follow-up surveys were returned, of which one was marked not applicable.

In total, 18 community hospitals (14 respondents to the full survey, four follow-up respondents) indicated that they could request troponin.

The following results refer only to those 37 community hospitals that returned the full survey, of which 14 have access to troponin and 23 do not.

Twenty three of the 37 hospitals do not offer troponin tests. Reasons for this were: clinicians do not wish to use it (1); lack of finance (8); lack of laboratory or clinician willingness (4); transport or distance to the laboratory (4); inappropriateness for their setting or type of patients (7) and 'not aware of sound evidence that a new test will improve current diagnostic process' (1). Of the 23 respondents who do not use troponin testing, 19 said that there are no plans to introduce troponin testing. However, seven respondents indicated that they would like to use it if it is made available, including one who mentioned that a funding bid had been rejected.

In the community hospitals where troponin is not used, 19 have at least one biochemical test available (seven have one or two tests available and 12 have three to five tests). Biochemical tests available are CK (16), CK-MB (5), aspartate aminotransferase (16), lactate dehydrogenase (15) and myoglobin (1).

Of the 14 community hospitals that use troponin testing, the average number of troponin tests requested per month ranges from zero to three. The turnaround times for the 11 community hospitals that use laboratory troponin testing are presented in Table A32. One community hospital reported that their turnaround time is only one hour.

Table A32 Turnaround times in community hospitals

	Turnaround time (hours)					**Cannot specify or not given**
	<12	12–24	24	24–48	48	
Number of laboratories	2	1	2	2	1	3

Of the 10 community hospitals that responded to the question regarding the availability of the laboratory service at weekends, three hospitals have a weekend service. One hospital responded that it is for emergency cases only, one was unsure as they have never tried to use it, and one indicated that a service may be available in exceptional circumstances due to the 'goodwill of staff'.

Four of the 14 community hospitals offering troponin testing have a protocol available for interpretation of the results.

Only four community hospitals offer point-of-care troponin testing. The average number of point-of-care tests requested per month ranges from one to 25. Of these, three classed their satisfaction with the service as 'good' and one as 'acceptable'. Additional comments made were that the troponin point-of-care testing is 'very useful as it is more accurate than CK' and that the 'test items have a short shelf life'.

In the four community hospitals offering point-of-care testing, nurses carry out the tests, although in one hospital 'medical officers' are also involved. Training was said to be necessary by three hospitals and is provided by laboratory staff (1) and manufacturers (2).

One community hospital offering point-of-care testing is registered with a quality assurance scheme, two are not and one did not respond. The laboratory provides some service for point-of-care testing at one of the hospitals. Of the other three hospitals, one hospital would like a laboratory to provide maintenance support while the other two hospitals do not want any laboratory involvement.

Reasons for using troponin testing included early discharge of low-risk patients (7), risk stratification of NSTEMI or UA patients (6), to inform patient management e.g. invasive/conservative management decisions (7) and to audit clinical decision (5). Four hospitals gave other reasons including a test result would assist in the decision to transfer a patient to a DGH.

Appendix 26

GPs' SURVEY RESULTS

The availability of troponin testing in general practice was assessed by distributing a survey to all 36 members of the Scottish General Practitioners Committee i.e. GP representatives covering the whole of Scotland. This is a small sample of the 3500 GPs in Scotland but the responses give an indication of issues faced by GPs in relation to troponin testing.

Fifteen of 36 GPs responded. Seven of the 15 respondents indicated that they have access to troponin tests, seven do not have access and one is unsure. There was some inconsistency in the responses with regard to availability of troponin within some NHS Board areas. Some respondents provided comments, and these were most commonly concerns over the delay in receiving the result e.g. if they suspected an MI, they would send the patient to hospital immediately. Others commented that they feel troponin would be useful in situations where admission to hospital does not appear clinically necessary.

Appendix 27

EMERGENCY ADMISSIONS AND ACCESS TO ANGIOGRAPHY

Table A33 Access of emergency admissions to angiography in hospitals with and without on-site facilities for angiography

		Total angina/AMI patients	% of total patients undergoing angiography	Median gap between admission and angiography	% of total patients undergoing CABG/PCI
Hospitals with on-site angiography facilities					
S226H	Royal Infirmary of Edinburgh	2780	10.29	1	11.08
N101H	Aberdeen Royal Infirmary	2360	19.96	5	15.93
T101H	Ninewells Hospital	1877	3.41	1	3.57
G107H	Glasgow Royal Infirmary	1721	7.90	4	4.13
G516H	Western Infirmary/Gartnavel General Hospital	1661	14.27	2	6.86
A210H	The Ayr Hospital	1231	3.90	7	2.36
S116H	Western General Hospital	1218	21.76	2	15.19
Y104H	Dumfries & Galloway Royal Infirmary	1097	3.83	8	1.64
L302H	Hairmyres Hospital	1091	14.57	2	9.72
C313H	Inverclyde Royal Hospital	954	3.98	8	2.52
H202H	Raigmore Hospital	950	3.16	6	2.42
Total hospitals with on-site angiography facilities		**16940**	**10.48**	**3**	**7.80**
Hospitals without on-site angiography facilities					
L106H	Monklands Hospital	1663	4.99	6	12.57
C418H	Royal Alexandra Hospital	1576	4.31	6	2.28
F704H	Victoria Hospital	1572	8.65	7	6.42
A111H	Crosshouse Hospital	1433	3.07	7	2.30
L208H	Law Hospital	1380	2.25	3	2.17
G306H	Victoria Infirmary	1297	4.63	8	2.16
V102H	Falkirk and District Royal Infirmary	1184	8.61	7	4.65
G207H	Stobhill Hospital	1157	10.20	8	4.41
S308H	St John's Hospital at Howden	1140	1.93	4	2.72
V201H	Stirling Royal Infirmary	1062	5.08	7	3.86
B120H	Borders General Hospital	898	5.35	4	2.67
G405H	Southern General Hospital	889	4.05	8	1.35
T202H	Perth Royal Infirmary	881	4.43	7	12.83
F805H	Queen Margaret Hospital	761	3.02	4	2.23
N411H	Dr Gray's Hospital	645	2.17	7	1.86
C206H	Vale of Leven District General Hospital	587	0.85	6	0.68
T312H	Stracathro Hospital	584	2.23	7	1.03
W107H	Western Isles Hospital	226	3.54	11	1.33

		Total angina/AMI patients	% of total patients undergoing angiography	Median gap between admission and angiography	% of total patients undergoing CABG/PCI
H103H	Caithness General Hospital	224	2.23	11	2.23
C121H	Lorn & Islands District General Hospital	173	1.16	7	0.58
N102H	Woodend General Hospital	131			1.53
Z102H	Gilbert Bain Hospital	131	2.29	8	0.76
H212H	Belford Hospital	130	8.46	6	7.69
Y111H	Garrick Hospital	128	3.13	7	2.34
C106H	Dunoon & District General Hospital	107	2.80	5	
L304H	Stonehouse Hospital	101	5.94	7	2.97
R101H	Balfour Hospital	94	2.13	14	1.06
C122H	Campbeltown Hospital	66	3.03	9	1.52
C110H	Mid Argyll Hospital	58	3.45	8	1.72
S209H	Liberton Hospital	18	5.56	5	
W103H	Dalburgh Hospital	18	5.56	3	5.56
N433H	Turner Memorial Hospital	17	5.88	19	5.88
N335H	Jubilee Hospital	15			6.67
H106H	Lawson Memorial Hospital	13	7.69	20	7.69
	Other hospitals	159	0.63	8	0.63
Total hospitals without on-site angiography facilities		**20518[a]**	**4.55**	**7**	**4.02**

[a] This figure differs from table of 1999–2001 ISD data as it excludes transfer hospitals that did not have patients undergoing angiography.
Source: ISD, 1999–2001 data.

12 Glossary

A&E	Accident and Emergency A specialty of medicine which deals with the provision of immediate care from the point of an acute injury or illness through to the hospital. Most patients will either attend, or be transported to, an A&E department where they will be assessed and treated. If necessary, patients will be referred to an appropriate specialty such as surgery.
ACC	American College of Cardiology
ACE inhibitors	Angiotensin converting enzyme inhibitors These are a group of drugs which lower blood pressure and expand the blood vessels.
ACS	Acute coronary syndromes Acute coronary syndrome is a collective term for the spectrum of acute coronary disease associated with myocardial ischaemia. Clinical presentations recognised within this definition include UA, NSTEMI and STEMI.
Adverse cardiac outcome	Death or non-fatal MI
AHA	American Heart Association
AMI	Acute myocardial infarction See MI
Angina	See AP
Angiography	An X-ray examination of blood vessels whereby a contrast medium is injected into the artery and a rapid series of X-ray recordings is made. In coronary angiography, it identifies the presence and extent of heart disease by assessing the arteries of the heart.
Angioplasty	Surgical widening of the blood vessels to eliminate areas of narrowing or obstruction.
Antibody	A special blood protein produced in response to an antigen.

Antigen	Any substance that the body regards as foreign or potentially dangerous, against which antibodies are produced.
Antiplatelet agent	A medication which thins the blood to prevent clots forming by inhibiting platelet aggregation.
AP	Angina pectoris Chest pain, often radiating to the arms and accompanied by a feeling of suffocation. It is precipitated by exercise, stress or excitement and caused by the imbalance between myocardial demand for oxygen and the available oxygen supply. It is often subdivided into stable and unstable angina.
Arteries	Blood vessels that carry blood away from the heart to supply the tissues.
Assay	A test to measure the amount of a specific constituent of a solution.
Atherosclerosis	The progressive narrowing or occlusion of the arteries due to the build up of atherosclerotic plaques.
Atherosclerotic plaques	The accumulation of cholesterol and fatty material on the wall of a blood vessel.
Audit	The process of setting or adopting standards and measuring performance against those standards, with the aim of identifying both good and bad practice and implementing changes to achieve unmet standards.
Batch service	A service that processes troponin test samples at a fixed time of day for a short period rather than continuously over a longer period.
β-blockers	A group of drugs which can be used to treat raised blood pressure.
BCS	British Cardiac Society
BHF	British Heart Foundation
Bed day	A 24-hour period when a hospital bed is occupied by a patient.

Biochemical markers	Proteins or enzymes (for example, myoglobin, creatine kinase [CK], its MB isoenzyme [CK-MB] and troponins T and I) that appear in abnormally elevated levels in the peripheral circulation as a result of cardiac tissue injury. They serve as indicators of cardiac tissue injury.
BMS	Biomedical scientist
CABG	Coronary artery bypass graft Surgical reconstruction to restore adequate blood supply to the heart by using veins or arteries as conduits for bypassing the diseased arteries in the heart.
CAPTURE	Chimeric c7E3 AntiPlatelet Therapy in Unstable angina Refractory to standard treatment trial
Cardiac rehabilitation	A long-term multidisciplinary programme involving medical evaluation, cardiac risk factor modification, prescribed exercise, education and counselling. It aims to reduce the risk of subsequent cardiac events and promote a return to normal life.
Carer	A person, paid or unpaid, who regularly helps another person, often a relative or friend with all forms of care as a result of illness or disability. This term incorporates spouses, partners, parents, guardians, paid carers, other relatives, and voluntary carers who are not health professionals.
Catheter	A flexible tube that is inserted into a narrow opening to withdraw or introduce fluid.
Catheterisation	Refers to the insertion of a catheter used to visualise the coronary arteries or to perform angioplasty.
CCU	Coronary care unit A specialist unit in a hospital where patients with heart conditions may be cared for.
Central laboratory	A laboratory providing services across a number of hospital wards or departments.

CHD	Coronary heart disease Disease, such as angina, coronary thrombosis or heart attack, caused by the narrowing or blockage of the coronary arteries by atheroma.
CHECKMATE	Chest pain Evaluation by Creatine Kinase-MB, Myoglobin and Troponin I
CI	Confidence interval A confidence interval is an interval likely to contain the true value of an unknown quantity (e.g. the true sensitivity of a test). For a 95% confidence interval, if the experiment were repeated many times 95% of the intervals would contain the value of the unknown quantity that is being estimated.
CK	Creatine kinase A marker of myocardial damage.
CK-MB	An isoform of creatine kinase used to indicate myocardial damage.
Clinical effectiveness	The evaluation of the balance between benefits and risks in a standard clinical setting using outcomes of importance to the patient.
Clinical governance	A framework through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish (Department of Health, 1998).
Clinical trial	Research study conducted with patients, usually to evaluate a new treatment or drug. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease.

Community hospitals	Local hospitals, units or centres providing an appropriate range and format of accessible health care facilities and resources. These will include inpatient, and may include outpatient, diagnostic, day care, primary care and outreach services for patients, provided by multidisciplinary teams. Medical care is normally led by general practitioners in liaison with consultants, nurses and allied health professional colleagues, as necessary. Consultant long-stay beds, primary care nurse-led and midwife services may also be incorporated.
Co-morbidity	The presence of co-existing or additional diseases with reference to either an initial diagnosis or to the index condition that is the subject of study. Comorbidity may affect the ability of affected individuals to function and also their survival; it may be used as a prognostic indicator for length of hospital stay, cost factors, and outcome or survival.
Conservative management	A course of therapy (i.e. usually pharmacological) with possibly less benefit than more risky invasive actions.
Coronary artery disease	See CHD
Coronary revascularisation	Coronary revascularisation procedures include percutaneous coronary intervention or coronary artery bypass graft. These are surgical interventions to improve the functional capacity of the heart.
Coronary stenting	The insertion of a stent (i.e. metal wire or tube) to hold open a coronary artery following dilatation (e.g. by percutaneous transluminal coronary angioplasty), in order to improve blood flow in the vessel and to reduce the risk of vessel re-closure.
Cost effectiveness	Cost effectiveness is used in its broadest form to encompass all forms of economic analysis.
CPA	Clinical Pathology Accreditation
CR	Cardiac Reader (TROPT *Quantitative®*)
CRP	C-reactive protein
CSA	Common Services Agency
CURE	Clopidogrel in Unstable angina to prevent Recurrent Events

Cut-off	A boundary between a positive and a negative result.
CV	Coefficient of variation The ratio of standard deviation to the mean.
Diagnosis	Identification and classification of an illness or disease by means of its signs, symptoms and the results of investigations. This involves ruling out other illnesses and causal factors for clinical manifestations.
DGH	District general hospital Hospitals providing a range of general medical and surgical services (and including services such as A&E, psychiatry, obstetrics and gynaecology and orthopaedics) for a given population. Specialist services such as coronary artery bypass graft would not be available at these types of hospitals.
DVLA	Driver and Vehicle Licensing Agency
ECG	Electrocardiogram A diagnostic test that monitors the electrical activity of the heart.
Echocardiogram	An image and measurement of the heart obtained using ultrasound.
Economic model	This simplifies the patient pathway to a level that describes the essential choices and consequences within treatment options. Linking patient outcomes to resource usage enable different courses of action to be compared from an economic viewpoint.
Elective	Subject to the choice or decision of the patient or physician.
ELISA	Enzyme-linked immunoabsorbent assay
Epitope	A site on any molecule against which an antibody will be produced and to which it will bind.
EQA	External quality assurance
ESC	European Society of Cardiology

ESSENCE	Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and non-Q-wave MI trial
ETT	Exercise tolerance test A test in which an electrocardiogram is monitored whilst a patient walks on a treadmill or exercises on a bicycle. If a patient is unable to perform an exercise tolerance test, they may undergo a pharmacological stress test.
EU	European Union
FDA	Food and Drug Administration
FRISC	Fragmin and fast Revascularisation during Instability in Coronary artery disease trial
GLORIA	Gold-labelled optically read immunoassay
GP	General Practitioner
GRACE	Global Registry of Acute Coronary Events
Grey literature	That which is produced on all levels of government, academics, business and industry in print and electronic formats, not controlled by commercial publishers.
GUSTO	Global Utilization of Strategies To open Occluded coronary arteries trial
Hazard rate	Instantaneous event rate
Health professional	A person qualified in a health discipline.
Heart failure	A condition in which the pumping action of the heart is impaired.
HEED	Health Economics Evaluation Database
Heterophile	An antibody raised against an antigen from one species that also reacts against antigens from other species.
High risk	Refers to patients at high risk of adverse cardiac events (i.e. non-fatal MI or death) within the short term. High-risk patients need urgent treatment.

HR	Hazard ratio The ratio of two hazard rates; for example, the rate of the control group and the rate of the treatment group.
HTA	Health Technology Assessment It is a multidisciplinary field of policy analysis which studies the medical, social, ethical and economic implications of development, diffusion and use of health technology.
HTBS	Health Technology Board for Scotland On 1 January 2003, HTBS became part of NHS Quality Improvement Scotland.
IFCC	International Federation of Clinical Chemistry
IHD	Ischaemic heart disease Disease of the heart associated with deficient blood supply caused by functional constriction or obstruction within the blood vessels.
Immunoassay	An analytical procedure that uses specific binding between antibodies and antigen to measure a chemical substance of interest.
Incidence	The number of new cases of a disease among a certain group of people during a specific period of time.
Inpatient	A person who is admitted to hospital for observation, examination or treatment.
Invasive management	Involves puncture or incision of the skin or insertion of an instrument or foreign material into the body (Dorlands Medical Dictionary, 2000).
Invasive therapy	Angiography followed by a surgical intervention such as PCI or CABG, if appropriate.
IQR	Interquartile range
ISAR-COOL	Intracoronary Stenting with Antithrombotic Regimen Cooling-off
Ischaemia	Reduced blood flow, usually because of narrowing or blockage of an artery.

ISD	Information and Statistics Division
Isoform	A protein with the same function and similar or identical genetic sequence but is tissue specific.
IT	Information and technology
IU	International units
Laboratory testing	Diagnostic testing that is performed in a laboratory.
Left bundle branch block	A defect in the heart conduction of the left bundle branch which is recognised as an ECG abnormality. When present, a diagnosis of recent MI can be more difficult.
LMWH	Low-molecular weight heparin
Low risk	Refers to patients at low risk of adverse cardiac events (i.e. non-fatal MI or death) in the short term. Low-risk patients do not need urgent invasive treatment.
LVEF	Left ventricular ejection fraction A measure of left ventricular contractility.
MCN	Managed Clinical Network A formally organised network of clinicians. The main functions are to facilitate access and to audit performance on the basis of standards and guidelines, with the aim of improving health care across a wide geographic area or for specific conditions.
MDA	Medical Devices Agency
Medical receiving units	An area in a hospital in which patients presenting as urgent medical problems are assessed and treated. After assessment, patients may be discharged, referred to another specialty, reviewed as outpatients, or admitted to medical wards for further treatment.
MeSH	Medical Subject Headings
Meta-analysis	Statistical method to combine the outcomes of more than one randomised controlled trial.
MHRA	Medicines and Healthcare products Regulatory Agency

MI	Myocardial infarction Damage that occurs to the heart muscle when the oxygen supply is disrupted. This is usually as a result of an occluded coronary artery.
Monoclonal antibody	Chemically and immunologically homogeneous antibodies.
Morbidity	The frequency (incidence and/or prevalence) of a particular disease or group of diseases.
Mortality rate	The number of deaths in a given population during a specified period of time.
Myocardial perfusion scan	A test which estimates prognosis and identifies areas of ischaemia in patients at risk of heart disease. It includes a stress test either by exercise or using a short acting medication in those unable to exercise. It also involves the use of a radioisotope and special gamma camera to estimate how well the heart is being nourished.
Myocytes	Muscle cells
Myoglobin	A marker that indicates cardiac damage.
N/A	Not applicable
Necrosis	Cell death caused by disease, injury or interference with blood supply.
NHS Boards	The role of NHS Boards is to ensure the efficient, effective and accountable governance of the local NHS system. There are 15 NHS Boards in Scotland.
NHS EED	NHS Economic Evaluation Database
NHSScotland	National Health Service in Scotland
NICE	National Institute of Clinical Excellence
Non-ST elevation ACS	Patients without ST segment elevation who have a diagnosis that may include UA or NSTEMI.
NSTEMI	Non-ST segment elevation myocardial infarction It is an acute process of myocardial ischaemia with sufficient severity and duration to result in myocardial necrosis.

OR	Odds ratio The association between a random event (E) and some condition (A), expressed as the odds that E occurs when A is true divided by the odds that E occurs when A is not true.
Outpatient	A patient reviewed in a hospital but does not need to be admitted to the hospital.
Oxidation	Loss of electrons.
p-value	The chance that the observed data or some data less probable would be observed under the model being investigated. Values range between zero and one and low values suggest the model is incorrect.
PARAGON	Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in Global Organization Network trial
Pathophysiological cause	An alteration in function.
Patient	A person who is receiving medical treatment (especially in a hospital). Also, a person who is registered with a doctor, dentist, etc and is treated when necessary.
Patient pathway	The pathway taken through the health care system by the patient.
PCI	Percutaneous coronary intervention A procedure involving passing a catheter through the skin into a blood vessel and dilating the narrowed segment of the coronary artery by inflating a balloon on the tip of the catheter. It may also involve the insertion of an intravascular coronary stent.
PDA	Personal digital assistant
Point of care	In the immediate vicinity of a patient.
Point-of-care testing	Diagnostic testing performed at or near site of patient care (Kost, 1995). It is also described as 'near patient test' and 'bedside test'.
Polyclonal antibody	An antibody produced by more than one clone.

Prevalence	The number of existing cases of a disease among a certain group of people, usually at a specified point in time.
Primary prevention	The prevention of the development of a condition, such as coronary heart disease, by avoidance of factors known to contribute to its development, for example, smoking and lack of exercise.
PRISM	Platelet Receptor Inhibition in ischemic Syndrome Management trial
PRISM-PLUS	The Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms trial
Prognosis	An assessment of the expected future course and outcome of a person's disease.
Prophylactic medication	Drugs prescribed to prevent an unwanted outcome.
Protocol	A policy or strategy that defines appropriate action. Also covers the adoption, by all staff, of national or local guidelines to meet local requirements in a specified way, resulting in what are known as local protocols.
PTCA	Percutaneous transluminal coronary angioplasty See PCI
PURSUIT	Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy trial
Quality assurance	Improving performance and preventing problems through planned and systematic activities including documentation, training and review.
r	Pearson's correlation coefficient A measure of how closely related two variables are.
Radioimmunoassay	Any system for testing antigen-antibody reactions in which use is made of radioactive labelling of antigen or antibody to detect the extent of the reaction.
RAH	Royal Alexandra Hospital, Paisley
RCT	Randomised controlled trial

Reduction	Gain of electrons.
Referral	The process whereby a patient is referred from one professional to another, usually for specialist advice or treatment.
Reperfusion therapy	Treatment that restores an adequate blood supply to the heart by administering thrombolytic drugs to break down clots in an artery (thrombolysis) and/or by surgical intervention such as percutaneous coronary intervention.
Risk factor	A clearly defined occurrence or characteristic that increases the possibility that a person will develop a disease or die from a disease he or she already has.
Risk stratification	The initial evaluation to assess whether or not a patient with chest pain is at low or high risk of an adverse cardiac event. It involves careful medical history and a precise description of symptoms, physical examination, ECG and cardiac markers. The risk should be re-assessed regularly.
RITA	Randomised Intervention Trial of unstable Angina
ROC	A receiver operating characteristic curve is used to evaluate the accuracy of any method of predicting a dichotomous outcome.
RR	Relative risk A ratio of two risks.
RTA	Road traffic accident
RxL	Dimension® RxL
SCIN	Scottish Cardiac Intervention Network In 2003, the creation of a National Advisory Committee on CHD was announced and it will take forward the work of SCIN.
Scoring system	A scoring system is a simple quantitative tool for evaluation risk of death and cardiac ischaemic events. An example of a scoring system is the TIMI score.

Scottish Executive	The Scottish Executive is the devolved government for Scotland. It is responsible for most of the issues of day-to-day concern to the people of Scotland, including health, education, justice, rural affairs and transport.
SCS	Stratus® CS
Secondary prevention	All those factors that should be addressed, such as lifestyle changes or drugs, in order to reduce the likelihood of recurrence of, slowing or reversing the progression of disease.
SEHD	Scottish Executive Health Department
SEQAS-CT	Scottish External Quality Assurance Scheme-Cardiac Troponin
Side effect	An effect of treatment in addition to its desired therapeutic effect. A side effect is usually unpleasant and unwanted.
SIGN	Scottish Intercollegiate Guidelines Network
SOP	Standard operating procedure
ST segment	Part of an electrocardiogram tracing that immediately follows the QRS complex.
ST segment depression	A decrease in millivolts in the ST component of an ECG.
ST segment elevation	An increase in millivolts in the ST component of an ECG.
STEMI	ST segment elevation myocardial infarction It is characterised by ST segment elevation on ECG indicating complete occlusion of coronary arteries which leads to myocardial necrosis.
Stenosis	An abnormal narrowing of an opening, such as a coronary artery.
Stress test	This is usually an exercise test but some patients will require myocardial perfusion studies which may involve pharmacological stress.
TACTICS	Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy trial

Tertiary centres	Hospital-based centres which provide specialist services or treatment e.g. percutaneous coronary intervention. Generally, but not always, tertiary centres will be in larger hospitals with appropriate support facilities and are associated with a university or research centre.
TIMI	Thrombolysis in Myocardial Infarction The TIMI score is a simple quantitative tool for evaluating risk of death and cardiac ischaemic events in patients presenting with UA/NSTEMI.
Thrombolysis	A treatment that involves administering drugs to break down clots (thrombolytic agents) to try to dissolve a blockage in an artery, allowing the blood to pass more freely and re-nourish the organ.
Thrombus	A clot caused by the aggregation of platelets, fibrin and other blood factors which may enlarge and obstruct the blood flow in the vessel. It may fragment and occlude smaller vessels downstream, or may dissolve as a result of thrombolysis.
Tn I	Troponin I
Tn T	Troponin T
Triage	A system whereby a group of casualties or patients is sorted according to the seriousness of their injuries or illnesses so that treatment priorities can be allocated to them.
TRIM	Thrombin Inhibition in Myocardial Ischemia trial
Troponin	A complex of proteins involved in the regulation of striated muscle contraction. Cardiac troponins T and I are biochemical markers of myocardial damage.
TSG	Topic Specific Group A group of experts who assist NHS Quality Improvement Scotland with the HTA.
Turnaround time	Time from taking a blood sample to receipt of a troponin result by the decision maker.
UA	Unstable angina See UAP

UAP	Unstable angina pectoris New onset or prior existing angina which is increasing in severity, duration or frequency and may be without provocation.
UK	United Kingdom
UKNEQAS-Cardiac Markers	UK National External Quality Assurance Scheme-Cardiac Markers
US	United States
WEQAS	Welsh External Quality Assurance Scheme
WHO	World Health Organization