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Abstract

The effectiveness and cost-effectiveness of biomarkers for the prioritisation of patients awaiting coronary revascularisation: a systematic review and decision model

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Objective: To determine the effectiveness and cost-effectiveness of a range of strategies based on conventional clinical information and novel circulating biomarkers for prioritising patients with stable angina awaiting coronary artery bypass grafting (CABG).
Data sources: MEDLINE and EMBASE were searched from 1966 until 30 November 2008.
Review methods: We carried out systematic reviews and meta-analyses of literature-based estimates of the prognostic effects of circulating biomarkers in stable coronary disease. We assessed five routinely measured biomarkers and the eight emerging (i.e. not currently routinely measured) biomarkers recommended by the European Society of Cardiology Angina guidelines. The cost-effectiveness of prioritising patients on the waiting list for CABG using circulating biomarkers was compared against a range of alternative formal approaches to prioritisation as well as no formal prioritisation. A decision-analytic model was developed to synthesise data on a range of effectiveness, resource use and value parameters necessary to determine cost-effectiveness. A total of seven strategies was evaluated in the final model.
Results: We included 390 reports of biomarker effects in our review. The quality of individual study reports was variable, with evidence of small study (publication) bias and incomplete adjustment for simple clinical information such as age, sex, smoking, diabetes and obesity. The risk of cardiovascular events while on the waiting list for CABG was 3 per 10,000 patients per day within the first 90 days (184 events in 9935 patients with a mean of 59 days at risk). Risk factors associated with an increased risk, and included in the basic risk equation, were age, diabetes, heart failure, previous myocardial infarction and involvement of the left main coronary artery or three-vessel disease. The optimal strategy in terms of cost-effectiveness considerations was a prioritisation strategy employing biomarker information. Evaluating shorter maximum waiting times did not alter the conclusion that a prioritisation strategy with a risk score using estimated glomerular filtration rate (eGFR) was cost-effective. These results were robust to most alternative scenarios investigating other sources of uncertainty. However, the cost-effectiveness of the strategy using a risk score with both eGFR and C-reactive protein (CRP) was potentially sensitive to the cost of the CRP test itself (assumed to be £6 in the base-case scenario).
Conclusions: Formally employing more information in the prioritisation of patients awaiting CABG appears to

be a cost-effective approach and may result in improved health outcomes. The most robust results relate to a strategy employing a risk score using conventional clinical information together with a single biomarker (eGFR). The additional prognostic information conferred by collecting the more costly novel circulating biomarker CRP, singly or in combination with other biomarkers, in terms of waiting list prioritisation is unlikely to be cost-effective.

Contents

List of abbreviations

ACM	all-cause mortality
apoA-I	apolipoprotein A-I
apoB	apolipoprotein B
BNP	brain natriuretic peptide
CABG	coronary artery bypass graft
CI	confidence interval
CHD	coronary heart disease
CRP	C-reactive protein
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
HDL	high density lipoprotein
ICER	incremental cost-effectiveness ratio
IL-6	interleukin 6
LDL	low density lipoprotein
Lp(a)	lipoprotein a
NICE	National Institute for Health and Clinical Excellence
NT-proBNP	N-terminal brain natriuretic peptide
PCI	percutaneous coronary intervention
QALY	quality-adjusted life-year
RR	relative risk
SCAAR	Swedish Coronary Angiography and Angioplasty Register
SD	standard deviation
TC	total cholesterol
TG	triglycerides

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Circulating biomarkers have been recommended as potentially useful measures in the management of patients with coronary artery disease. Coronary artery bypass grafting (CABG) is an effective treatment for chronic stable angina, but is usually carried out after an interval of days or weeks from the date the decision for surgery is made. During this waiting interval the patient is at risk of death or heart attack. Current usual practice in many health systems is to use simple clinical information informally to prioritise the queue. It is not known whether formal scoring methods using simple clinical information (scores of urgency or risk of event) might be cost-effective. Further, it is not known whether collecting new information on circulating biomarkers might better prioritise the clinical acuity of patients awaiting CABG in terms of health outcomes for a given cost.

Aim

The aim of this study was to determine the effectiveness and cost-effectiveness of a range of strategies based on conventional clinical information and novel circulating biomarkers for prioritising patients with stable angina awaiting CABG.

Objectives

1. To estimate the prognostic value of circulating biomarkers in predicting events among patients with stable coronary disease.
2. To develop and populate a decision-analytic model to compare circulating biomarkers with alternative approaches to prioritisation in terms of cost-effectiveness based on lifetime costs and quality-adjusted life-years (QALYs).

Methods of systematic review and meta-analyses

We carried out systematic reviews and meta-analyses of literature-based estimates of the prognostic effects of circulating biomarkers in stable coronary disease. We assessed five routinely measured biomarkers [estimated glomerular filtration rate (eGFR), fasting glucose, haemoglobin, total cholesterol and low density lipoprotein (LDL) cholesterol] and the eight emerging (i.e. not currently routinely measured) biomarkers recommended by the European Society of Cardiology Angina guidelines {highly sensitive C-reactive protein (CRP), fibrinogen, lipoprotein a [Lp(a)], apolipoprotein A-I (apoA-I), apolipoprotein B (apoB), homocysteine, brain natriuretic peptide (BNP) and interleukin 6 (IL-6)}. We searched MEDLINE and EMBASE from 1966 until 30 November 2008.

Results of meta-analyses

We included 390 reports of biomarker effects in our review. For routinely measured biomarkers, relative risks were 2.00 [95% confidence interval (CI) 1.65 to 2.42] for eGFR below 60 ml/min (based on 12 studies, 31,839 patients, 1639 outcome events), 1.74 for fasting glucose higher than 7 mmol/l, 2.92 for haemoglobin less than 13 g/dl, and 1.30 and 1.33 for total and LDL cholesterol (top versus bottom tertile) respectively.

For novel circulating biomarkers, relative risks comparing the top with the bottom third were: 1.96 (95% CI 1.76 to 2.17) for CRP and, based on a smaller literature, 2.93 for BNP, 2.06 for homocysteine, 1.63 for IL-6, 1.59 for fibrinogen, 1.39 for apoB, 1.24 for Lp(a) and 0.81 for apoA-I. The quality of individual study reports was variable, with evidence of small study (publication) bias and incomplete adjustment for simple clinical information such as age, sex, smoking, diabetes and obesity.

Methods of decision model and cost-effectiveness analysis

The cost-effectiveness of prioritising patients on the waiting list for CABG using circulating biomarkers was compared against a range of alternative formal approaches to prioritisation as

well as no formal prioritisation. A decision-analytic model was developed to synthesise data on a range of effectiveness, resource use and value parameters necessary to determine cost-effectiveness. A total of seven strategies were evaluated in the final model: (i) no formal prioritisation (i.e. usual clinical practice); (ii–iii) urgency scores (Ontario and New Zealand algorithms); (iv) risk score without the use of biomarkers; and (v–vii) three approaches using a risk score with biomarkers – the use of either a single routine eGFR or novel CRP biomarker as well as a combination of these biomarkers.

The risk of cardiovascular events while on the waiting list for CABG, procedural risk and risk after CABG were estimated for 9935 patients registered in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) between the years 2000 and 2005. eGFR was the only circulating biomarker available in SCAAR; we imputed values of CRP, the novel biomarker, using another data set from St George's Hospital, London. The impact of biomarkers on these risks was estimated from our meta-analyses together with additional adjustments required to evaluate the independent effect of biomarker information. Costs and health-related quality of life associated with procedures and different health states in the model were estimated from the literature.

Lifetime costs and QALYs associated with each strategy were established in a three-step procedure: first, patients in a representative cohort were ranked and assigned a day of CABG according to each prioritisation strategy; second, costs and QALYs were determined for each patient conditional on the assigned day of CABG within each strategy; and third, cost-effectiveness was determined by comparing the mean costs and QALYs for each strategy based on their incremental cost-effectiveness ratio (ICER).

The analysis was undertaken in the context of a maximum waiting time of 3 months. Additional scenarios were also considered to determine the robustness of the results to shorter waiting times (6 weeks and 2 weeks) as well as other sources of uncertainty.

Results of decision model

The risk of cardiovascular events while on the waiting list for CABG was 3 per 10,000 patients per day within the first 90 days (184 events in 9935 patients with a mean of 59 days at risk). Risk factors associated with an increased risk and included in the basic risk equation were age, diabetes, heart failure, previous myocardial infarction and involvement of the left main coronary artery or three-vessel disease.

Three prioritisation strategies were excluded as they were dominated (more costly and less effective than one or more of the other strategies) or extendedly dominated (a combination of other strategies being more cost-effective). Of the remaining four prioritisation strategies, a risk score using eGFR was the most effective strategy with an ICER below a £20,000–30,000 per additional QALY threshold range (the ICER compared with Ontario urgency score was £405 per QALY). A prioritisation strategy with a risk score employing information from CRP and eGFR is unlikely to be cost-effective as the ICER was well above the threshold value when compared with a risk score using eGFR alone. The optimal strategy in terms of cost-effectiveness considerations was therefore a prioritisation strategy employing biomarker information.

Evaluating shorter maximum waiting times did not alter the conclusion that a prioritisation strategy with a risk score using eGFR was cost-effective. These results were robust to most alternative scenarios investigating other sources of uncertainty. However, the cost-effectiveness of the strategy using a risk score with both eGFR and CRP was potentially sensitive to the cost of the CRP test itself (assumed to be £6 in the base-case scenario). If this cost was reduced to £3, then the ICER of a strategy employing both eGFR and CRP, assuming a 90-day maximum waiting time, would be within the £20,000–30,000 threshold range. For shorter maximum waiting times, the cost of CRP would have to be less than £1.30 for a strategy using a risk score with both eGFR and CRP to be considered cost-effective. Furthermore, the scenario employing the lower bound of the 95% CI of the biomarker coefficients did not change the results substantially. It could be argued that the lower bound of the 95% CI is likely to be closer to the true biomarker effect because of adjustment and publication biases.

Discussion

We present a framework for evaluating the cost-effectiveness of formally incorporating biomarkers – routine, novel or both – into clinical decision-making. This framework evaluates methods of prioritising patients with respect to long-term costs

and health outcomes. Biomarkers must provide enough information to change the order (i.e. the waiting time) in which patients are assigned CABG if they are to provide additional value in prioritising patients.

Our findings indicate that a prioritisation strategy employing a single, routinely available biomarker (eGFR) appears cost-effective and robust to alternative assumptions, including variation in the maximum waiting list times.

Importantly, the results emphasise the potential clinical and economic value of prioritisation approaches to the management of waiting lists more generally. However, the increased precision provided by multiple biomarkers, over and above that achievable from an approach based on estimating prognostic risk based on conventional clinical information and a single biomarker, appears unlikely to be cost-effective. Although precision increases with more information, there is a potential trade-off against the additional costs of obtaining this information.

Although the magnitude of differences in QALYs between strategies was modest, they are worthy of clinical policy interest because the adoption of formal protocols has recently been recommended by the National Confidential Enquiry into Patient Outcome and Death, and risk scoring may be seen as part of wider quality initiatives.

Limitations

The results need to be considered in relation to a number of potential limitations. These include:

1. The quality of individual studies, and their reports, in the biomarker systematic reviews.
2. The lack of individual participant data with novel biomarkers for patients awaiting CABG (necessitating imputation of CRP levels in SCAAR).
3. The restricted range of strategies considered in the decision model and the limitations of the approaches to dealing with uncertainties within the model.

Conclusions

Formally employing more information in the prioritisation of patients awaiting CABG appears to be a cost-effective approach and may result in improved health outcomes. The most robust results relate to a strategy employing a risk score using conventional clinical information together with a single biomarker (eGFR). The additional prognostic information conferred by collecting the more costly novel circulating biomarker CRP, singly or in combination with other biomarkers, is unlikely to be cost-effective in terms of waiting list prioritisation.

Recommendations for further research

1. To establish and develop a national register of coronary angiography in the UK, which would provide a platform for health technology appraisal and other outcomes-based research relevant to the NHS. Such a register should include details of angiographic findings, clinical details required for estimating risk equations, circulating biomarker information and follow-up for events and revascularisation (electronic patient record, Connecting for Health).
2. To develop the decision-analytic framework by incorporating a more comprehensive range of biomarker strategies, and to reflect more formally the uncertainties in the various input sources estimates with probabilistic sensitivity analysis. To consider these in relation to a broader set of approaches to the overall management of stable disease including a policy of shortening overall waiting times.
3. To consider the consequences of uncertainty in the model more formally using value of information analysis to target specific areas where further research appears most worthwhile.
4. To develop initiatives for improving the quality of biomarker prognosis research, for example by developing standards for reporting [e.g. CONSORT (CONsolidated Standards Of Reporting Trials) has been influential in other types of research], and to foster collaborations that pool individual participant data sets.

Chapter 1
Background

Biomarkers

There is intense interest in the measurement and evaluation of biomarkers in order to better target clinical care for many diseases.[1,2] The hope is that biomarkers will provide new information about the patient and his or her disease condition, which will help optimise the type, amount or timing of subsequent intervention. The development, evaluation and use of biomarkers represents a major technology in health care, with growing investment from large companies, including Dade Behring, Roche Diagnostics, Abbott Diagnostics, Acon International and Beckman Instruments. Within the last decade there have been rapid increases in the number of reports of individual biomarkers and their incorporation into prognostic risk scores.[3] This interest has in part been stimulated by the high cost and long timescales involved in the development of new therapeutic drugs and devices. The concept of 'personalised medicine' seeks to exploit information from biomarkers in order to maximise the probability of benefit and minimise harms for a given treatment.

A biomarker has been defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.'[4] Thus the term 'biomarker' encompasses a range of measures; biomarkers that are circulating – that is, assessed from a blood sample – have been the focus of most interest in prognosis research. Compared with imaging biomarkers (e.g. computed tomography or magnetic resonance imaging), circulating biomarkers have the advantages of being relatively low cost, low burden (patients expect to have blood taken) and no risk (compared with the radiation exposure of computed tomography). Clinicians are used to interpreting and acting on a single numerical value from a blood test (e.g. low haemoglobin defines anaemia), and are increasingly using numerical values derived from scores. In the setting of coronary artery disease, more than 100 measures (beyond those widely made in routine clinical practice) have been related to the risk of subsequent death or heart attack in one or more study.[1]

Prognosis, outcomes and NHS quality initiatives

Clinicians are increasingly invited to scrutinise the outcomes of their care, in an effort to improve quality. Cardiac surgery in children,[5] and subsequently in adults, has been the subject of high profile inquiries into the performance of individual units and clinicians. Under the Darzi review,[6] from April 2010 all health-care providers working for the NHS will be legally obliged to publish 'quality accounts' on safety, patients' experience and clinical outcomes, in the same way that they publish financial accounts. Indeed, the 2007 White Paper *Trust, Assurance and Safety*[7] states that 'recertification will be supported by information that shows how clinically effective each doctor's treatment of his or her patients has been' requiring 'analysis of the outcomes of their treatment'.

Coronary artery bypass grafting and the NCEPOD Report

Coronary artery bypass grafting (CABG) remains the standard of care for patients with three-vessel or left main coronary artery disease, because the use of CABG, as compared with percutaneous coronary intervention (PCI), resulted in lower rates of the combined end point of major adverse cardiac or cerebrovascular events.[8] The 2008 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report on death after CABG[9] found that 'in the opinion of the advisors for 57/821 (7%) of cases there was a delay from referral to the first cardiothoracic review and in 33 of these patients outcome was adversely affected.' One of the principal recommendations was to 'use protocols for referrals. These protocols should be standardised nationally for patients who require coronary artery bypass graft surgery. The degree of urgency of referral should be emphasised within these protocols.'

Thus, cost-effective means of improving institutional performance are of considerable interest. There is an established culture of using risk prediction scores (the euroSCORE; European

System for Cardiac Operative Risk Evaluation)[10] for operative mortality after CABG, for the purposes of risk-adjusting comparisons between institutions and individual surgeons. This score does not use novel biomarkers and is not designed to assess event rates on the waiting list.

Stable angina

In women and men, coronary heart disease (CHD) is the most common cause of premature death in the UK and most Western countries,[11] and is predicted to remain so at least until the next decade. Coronary disease commonly presents as angina pectoris, which is characterised by chest pain or discomfort typically on exertion and relieved by rest, in association with atherosclerotic narrowing of the coronary arteries (assessed at angiography). Between 1991 and 2003, while the incidence of heart attack declined rapidly (about 8% per year), the prevalence of angina pectoris diagnosed by a doctor based on five waves of Health Survey for England data showed no evidence of decline,[12] suggesting that the relative importance of chronic symptomatic coronary disease may be increasing. The prevalence of angina in the UK is about 3–5% for women and men,[13] suggesting that approximately 1.3 million people have symptoms (www.heartstats.org/datapage). The economic burden of angina is high, estimated at 1.3% of the NHS budget in the UK[14] and costing $75 billion in 2000 in the USA.[15]

Angina prognosis

The public health impact of angina comes from its immediate impact on health functioning and disability, as well as the elevated risk of future acute vascular events including myocardial infarction, other acute coronary syndromes, sudden death and stroke. Overall, coronary mortality is estimated at about 1–2% per annum among people with angina in primary care, and approximately 3% of annual all-cause mortality (ACM).[16] An important feature of angina is the wide variation in risk; while some patients die within the first 3 months of diagnosis, others live a normal life expectancy. Recently, efforts have been made to develop risk scores to discriminate between such very high and very low risk groups of patients. For example, the ACTION (A Coronary Disease Trial Investigating Outcome with Nifedipine GITS) trial data were re-analysed to generate a risk score for which those in the bottom 10th of the risk score distribution had a 5-year risk of death, non-fatal myocardial infarction or disabling stroke of 4%, compared with a 35% risk for patients in the top decile.[17] Efforts to improve the precision of such risk prediction scores have focused on the use of emerging blood-based markers. However, these efforts have been hampered by a lack of precise, unbiased estimates of the independent strength of effect for each biomarker.

Current use of circulating biomarkers in coronary disease

Several types of blood measurement are widely used in the management of coronary disease. These include markers of myocardial necrosis – evolving from aspartate transaminase in the 1950s, creatinine kinase (CK) in the 1960s, CK-MB in the 1970s, and troponins in the 1980s – which are used primarily as diagnostic tests with high negative and positive predictive value. This is one of the clearest examples in clinical medicine where marker measurement and urgent clinical decision-making are closely related. However, a range of other blood markers are routinely 'taken' among patients with coronary disease, but their use, if any, in clinical decision-making is less clear. For example, a measure of kidney function, the serum creatinine, has been estimated among people with suspected coronary disease for decades, but only in the last decade has its potential prognostic value been considered.

Proposed use of circulating biomarkers in stable angina

Circulating biomarkers have been recommended as potentially useful measures in the management of patients with stable angina. For example, the Centers for Disease Control/American Heart Association statement for health-care professionals recommended that, among patients with stable coronary disease, one biomarker, C-reactive protein (CRP), 'may be useful as an independent prognostic marker'.[18] The costs and other characteristics of selected biomarkers are shown in *Table 1*. The European Society of Cardiology angina guidelines recommend (class IIb, strength of evidence B) measurement of CRP, lipoprotein a [Lp(a)], apoA-I (apolipoprotein A-I), apoB (apolipoprotein B), homocysteine, N-terminal brain natriuretic peptide (NT-proBNP), fibrinogen and interleukin 6 (IL-6).[19] Although there are no surveys on the variability between clinicians

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TABLE 1 *Cost and other characteristics of five routinely measured and eight novel circulating biomarkers*

Biomarker	What is the molecule?	Why might it cause cardiovascular events?	Usual range in healthy populations[a]	Higher levels associated with	What can be done to improve levels?	Cost of test in research[b]
Widely performed in routine care						
eGFR estimated from creatinine	Breakdown product of creatinine phosphate in muscle	Hypertension, dyslipidaemia, inflammation, calcification	> 60 ml/min	Increased risk: threshold?	Avoid causes of renal disease	Routine
Haemoglobin	Protein carrying oxygen in blood	Carries oxygen to heart muscle and all organs	> 13 g/dl	Decreased risk: threshold?	Avoid causes of anaemia	Routine
Fasting glucose	Sugar, a small molecule	Dyslipidaemia, hyperinsulinaemia	< 7 mmol/l	Increased risk: threshold?	Avoid causes of diabetes	Routine
Total cholesterol	Fat	Atherosclerosis	< 5.2 mmol/l	Increased risk	Statins lower levels and risk	Routine
LDL cholesterol	Lipoprotein	Atherosclerosis	< 3.3 mmol/l	Increased risk	Statins lower levels and risk	Routine
Novel: often not measured in routine care						
CRP	Inflammatory protein	Degree of inflammatory activity may be related to plaque instability	< 1 mg/l	Increased risk	No specific agents but statins and aspirin may non-specifically lower CRP	£6
Fibrinogen	Clotting protein	Formation of clot; inflammatory activity	2–4 g/l	Increased risk	No specific agents but fibrates lower fibrinogen	£10
Lp(a)	Lipoprotein	Reduces fibrinolysis; stimulates thrombogenesis; atherosclerosis (because of LDL cholesterol content)	130 mg/l	Increased risk	No specific agents, but niacin and aspirin may reduce levels	£8

continued

TABLE 1 *Cost and other characteristics of five routinely measured and eight novel circulating biomarkers (continued)*

Biomarker	What is the molecule?	Why might it cause cardiovascular events?	Usual range in healthy populations[a]	Higher levels associated with	What can be done to improve levels?	Cost of test in research[b]
ApoA-1	Lipoprotein	The major protein component of HDL cholesterol	1.4 g/l	Decreased risk	Cholesterol ester transfer protein inhibitors raise HDL, but concerns over safety	£10
ApoB	Lipoprotein	The major protein component of LDL cholesterol	1 g/l	Increased risk	RCTs of statins show risk lowering	£10
Homocysteine	Amino acid	Oxidises low-density lipoprotein; pro-thrombotic	1.6 mg/l	Increased risk	RCTs of B vitamins decrease levels, but do not improve events	£25
BNP	Peptide	Released from ventricular myocardium as a response to ventricular dilatation and pressure overload in patients with heart failure and acute coronary syndrome	< 80 ng/l	Increased risk	No specific agents but ACE inhibitors beneficial in heart failure	£35
IL-6	Cytokine (signalling protein)/glycoprotein	Inflammation	< 5 ng/l	Increased risk	No specific agents	£36

ACE, angiotensin-converting enzyme; ApoA-I, apolipoprotein A-1; ApoB, apolipoprotein B; BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; IL-6, interleukin 6; LDL, low density lipoprotein; LP(a), lipoprotein a; RCTs, randomised controlled trials.

a Prefix n denotes nano 10^{-9}, and p denotes pico 10^{-12}.

b Costs based on research collaborator costs.

and centres in which biomarkers are measured, anecdotal evidence suggests that in NHS practice in 2008 most, if not all, of these eight biomarkers are not routinely evaluated among patients with angina. The biological mechanisms by which these markers may influence prognosis are varied, and span molecules with differing function, including markers of inflammation, lipids, hormones and vitamins. For the purposes of the evaluation of biomarkers, their biological functions are of secondary importance; the question is the extent to which they predict risk, not how.

Biomarkers and specific clinical decisions

Existing biomarker measurement recommendations, remarkably, do not specify which clinical decisions might be influenced in the light of the biomarker information. It is implicitly assumed that more information might lead to better clinical decision-making in general. Specifically, there are no professional body or government recommendations for the measurement of biomarkers in the invasive management of angina pectoris.

Revascularisation for angina

The goals of treatment for angina are to reduce mortality, lower the risk of major non-fatal events (heart attack and stroke) and to improve symptoms and quality of life. In both women and men, the diagnosis of angina is associated with markedly increased death rates from coronary disease compared with the general population: five-fold excesses among patients aged 45–55 years, and three-fold excesses among patients aged 65–75 years.[16] Coronary angiography – one of the most widely performed procedures in clinical medicine (annual numbers estimated at around 1 million in the USA, and 100,000 in the UK) – is the invasive X-ray used to diagnose coronary artery disease; without this test revascularisation cannot be considered. Among patients with angiographic luminal narrowings, coronary revascularisation is effective at relieving symptoms and improving quality of life, compared with medical management. Revascularisation with PCI with balloon angioplasty, with or without stenting, was initially proposed for patients with single- or double-vessel disease. CABG is a major surgical procedure carried out under general anaesthetic, in which the narrowings in the coronary arteries are bridged using vessels from the patient – leg veins (saphenous) or an artery from the inside of the chest wall (internal mammary). CABG is a higher cost procedure, which is associated with improvements in survival[20] (unlike PCI), and tends to be associated with longer waiting times.

NHS waiting time initiatives for coronary artery bypass grafting

Coronary artery bypass grafting is carried out after an interval of days or weeks from the date the decision for surgery is made. In the 2003 report from the National Adult Cardiac Database there were about 25,000 CABG procedures carried out annually between 1997 and 2003,[21] with no evidence of a decline in this number of procedures. There have been dramatic falls in the waiting time – defined as starting from the date of angiography to CABG – since the median waiting times of 214 days in 1994/5.[22] The implementation of the National Service Framework for CHD in 2000 led to declines in waiting time, and since March 2005 no NHS patient has waited longer than 3 months for CABG.[7] The most recent figures (August 2008) from the Department of Health suggest that about half the patients waiting for CABG have been waiting for between 1 and 3 months, and about half for up to 1 month. Previous policy was based on waiting from the time of angiography – which represents only one segment of patients' waiting experience. The most recent policy focuses on the whole wait, from time of initial referral to receipt of definitive treatment, in this case CABG, with a ceiling of 18 weeks.

International comparisons in waiting times

Internationally and across different systems of health-care provision, waiting times for CABG have been the subject of targets set by politicians and by professional bodies.[23] Waiting times continue to vary within and between countries, with published comparisons between the USA, Sweden and Netherlands[24] and other countries.[25] Recent Canadian guidelines state: 'The target for bypass surgery in those with high-risk anatomy is 14 days; for all others, the target is six weeks … there is an ongoing need to continually reassess current risk stratification methods to limit adverse events in patients on waiting lists and assist clinicians in triaging patients for invasive therapies.'[26]

Events on waiting list

People with stable coronary disease are at increased risk of death or heart attack,[16] compared with the general population. Being on a waiting list for CABG per se probably has no measurable impact on these event rates.[27] Patients awaiting CABG experience continued symptoms, and some, but not all, studies suggest longer waits are associated with more anxiety and disutility.[28] There is no evidence of any benefit in deferring surgery among patients with stable coronary disease without acute myocardial infarction history. Among patients in whom there is a history of recent acute myocardial infarction, the possible increased risk of early surgery may be balanced against the potential for improved remodelling, improved quality of life and decreased hospital stay costs.[29]

Need for prioritising waiting lists

Irrespective of whether target waiting times for CABG are 14 days, 6 weeks or 3 months from the date of angiography, clinicians (and the administrative systems in which they work) are faced with deciding whether an individual patient merits listing for surgery sooner. That is, does a strategy of ordering the waiting interval, according to formal scores, improve clinical outcomes and, if so, is this strategy cost-effective? However the cost-effectiveness of any strategy may be hypothesised to be lower in countries with lower median waiting times.

Usual practice

Clinicians informally prioritise waiting lists. Without recourse to formal scores, published evidence suggests that time to invasive management of coronary disease is not random but, on average, is ordered at least according to urgent, semi-urgent and non-urgent categories.[30,31] But the rules for deciding which combination of simple clinical information would place a patient in one group or another are not explicit. Although enough information is routinely collected that would allow calculation of a formal urgency or risk score (including information on some circulating biomarkers), these formal scores are seldom derived in NHS practice.

Different formal prioritisation strategies

The dominant technology, which has been proposed as a means of improving on such implicit means of prioritising waiting lists, has been the use of 'urgency' or 'acuity' scores. These scores have been developed, and to some extent implemented,[31] in Canada[32] and New Zealand.[33] These urgency scores apply weightings to clinical covariates based on anatomical disease severity and symptom severity, both of which are predictors of mortality.[34] The principle is that higher risk patients should undergo an operation sooner. Biomarkers are not included in these urgency scores. Scores that predict the long-term risk of events among people with stable coronary disease have been developed,[17] but are not widely used and were not developed among patients awaiting CABG.

Framework for evaluation

Conventionally, the effectiveness of different health-care technologies is rigorously evaluated in randomised controlled trials, in order to address confounding. There are no randomised trials comparing different prioritisation strategies for CABG in stable coronary disease, and these are unlikely ever to be performed. Thus, observational data with decision modelling has been demonstrated as a robust, evidence-based method of evaluation that can inform policy-making and clinical decision-making. Thus, observational studies are likely to be the main basis for estimating the effects of biomarkers in the context of prioritising patients on waiting lists. It is increasingly recognised that, to inform decisions about the effectiveness and cost-effectiveness of new technologies and health-care programmes, decision-analytic models provide a valuable framework.[35] These methods are now central to the National Institute for Health and Clinical Excellence's (NICE's) technology appraisal programme.[36] Decision analysis is a framework for supporting decisions rather than a source of data as provided by randomised trials and observational methods. To inform decisions, these methods facilitate the synthesis of available evidence and explicit assumptions and judgements about, for example, the duration of treatment effects. Importantly, decision analysis provides a means of quantifying the uncertainty in existing evidence and hence prioritising future research.

Scientific uncertainties addressed in this monograph

The following is not known:

- The quality of individual studies reporting biomarkers in the prognosis of stable coronary disease, and the potential for biasing meta-analytic estimates of the effects of biomarkers.
- The strength of effect (relative risks) and precision of these estimates [95% confidence intervals (CIs)] of five routinely assessed and eight novel biomarkers in the prediction of CHD, cardiovascular disease (CVD) and ACM events among people with stable coronary disease.
- The most appropriate structure and input parameters for a decision-analytic model to evaluate alternative prioritisation strategies.
- Are circulating biomarkers cost-effective at prioritising the clinical acuity (urgency) of patients awaiting CABG?
- What is the incremental cost-effectiveness ratio (ICER) of adding one novel biomarker, one routinely assessed biomarker or both to a risk score to prioritise patients awaiting CABG?

Chapter 2

Aims, objectives and overview of decision problem

We sought to address the absence of previous meta-analyses of the prognostic value of circulating biomarkers in stable coronary disease, and the absence of previous decision models to establish the cost-effectiveness of such biomarkers. We carried out systematic reviews and meta-analyses of biomarkers (currently measured and novel) to structure and populate a decision-analytic model as a framework for addressing the policy question regarding the value of differences in long-term costs and quality-adjusted survival duration predicted between alternative prioritisation strategies.

Aim

To determine the clinical effectiveness and cost-effectiveness of a range of formal strategies based on conventional clinical information and novel circulating biomarkers (singly or in combination) for prioritising patients with stable angina awaiting CABG.

Objectives

1. To estimate the prognostic value of circulating biomarkers in predicting events among patients with stable coronary disease. The prognostic value was determined using systematic review and meta-analytic approaches in order to estimate summary relative risks of effects on prognosis for biomarkers for which measurement in angina patients in NHS practice is widespread [e.g. estimated glomerular filtration rate (eGFR)], and is recommended but not routine (e.g. highly sensitive CRP).
2. To explore sources of uncertainty in the estimates of effect of the biomarkers which may influence the clinical effectiveness and cost-effectiveness estimates, specifically to assess the precision of estimates, the quality of individual studies, publication bias and other sources of heterogeneity.
3. To develop a decision-analytic model to compare alternative approaches to prioritisation in terms of cost-effectiveness using lifetime costs and quality adjusted life-years (QALYs). The strategies of interest in relation to circulating biomarkers were:
   - single routine biomarker (e.g. eGFR)
   - single novel biomarker (e.g. CRP)
   - combination of routine and novel biomarkers (e.g. eGFR + CRP),

   added to a risk equation, as compared with other alternative approaches which are relevant comparators. These alternatives include both current practice and the more formal use of alternative methods or prioritisation based on conventional clinical information and urgency scores (e.g. New Zealand and Ontario algorithms).
4. To estimate the contemporary rates of events (death, non-fatal myocardial infarction and non-fatal stroke) among patients with chronic stable angina on a waiting list for CABG, and the extent to which conventional clinical information predicts these event rates, and thereby offer a means of prioritisation.
5. To estimate the costs of gathering prognostic information, the costs of alternative management interventions, the long-term outcomes (fatal, non-fatal and health-related quality of life), and the efficacy of revascularisation with respect to patients' baseline risks and over time.
6. To populate the decision-analytic model using robust estimates of the full range of relevant inputs required to estimate mean lifetime costs, QALYs and overall cost-effectiveness of the alternative strategies in the context of a representative cohort of patients on a waiting list for CABG.
7. To undertake sensitivity analysis to examine the robustness of the results of the decision-analytic model to alternative input values and assumptions in relation to potentially important drivers of cost-effectiveness.

Overview of decision problem

This section summarises the key elements of the decision problem considered.

- *Patient population* Patients with stable coronary artery disease who have been placed on the waiting list for CABG. It is assumed that all patients will undergo CABG within 3 months of being placed on the waiting list but, within this period, prioritisation between patients is possible. Alternative scenarios representing shorter target waiting times for CABG of 15 and 40 days are also considered.
- *Technology of interest* Standard clinical information together with circulating biomarkers singly and in combination as a basis of prioritisation. This is represented in the form of a risk score combining information relating to clinical parameters and circulating biomarkers.
- *Comparators* Alternative forms of prioritisation: no formal prioritisation (routine clinical practice), urgency scores (New Zealand and Ontario algorithms), a formal risk score based on standard clinical information (without biomarkers).
- *Basis of evaluation* To establish which approach to prioritisation is the most cost-effective. Cost-effectiveness is determined based on a comparison of the expected (mean) estimates of costs and QALYs for the alternative strategies considered. The alternative strategies are then compared by estimating the differential costs and outcomes between successively more expensive (or more effective) strategies, expressed in terms of an ICER representing the incremental cost per additional QALY gained. The ICER can then be compared with external thresholds used to establish whether or not this represents potential value for money to the NHS. The threshold applied here is in the region of £20,000–30,000 per additional QALY, based on decisions made by NICE.

Overview of analytical approach

In order to determine the cost-effectiveness of alternative strategies (including the use of biomarkers) for prioritising patients on the waiting list for CABG, several analytical steps are required. These are outlined schematically in *Figure 1*. These steps are broken down into *four inter-related elements*, comprising:

1. *Defining the baseline characteristics of the representative cohort* This represents variation in baseline characteristics and risk factors among patients on a waiting list for CABG. In the base-case analysis, all patients in the cohort are assumed to have the procedure within 3 months, but the order in which they undergo the procedure is then determined by the alternative methods of prioritisation under investigation. A different ordering of patients may result in different costs and health outcomes, as these are determined by the risk of cardiovascular events while awaiting CABG, the risk of the procedure itself and the risk of cardiovascular events after CABG. These costs and health outcomes will vary according to the baseline characteristics and risk factors of the representative cohort. It should be noted that we modelled a waiting list based on a fixed cohort of patients. The reason we did not model a more complex, dynamic situation (in which patients enter and leave the cohort over time) is because once patients are given a date for their operation it is rarely appropriate to change this.
2. *Establishing the clinical effectiveness of the alternative strategies for prioritisation* Systematic review and appropriate evidence synthesis approaches are required to generate measures of clinical effectiveness (in terms of relative risks) for the alternative strategies considered, reflecting the effects on prognosis for biomarkers. Ultimately, what is of interest is the extent to which utilising such information actually changes the order in which patients are prioritised for CABG and the subsequent costs and outcomes of such an approach.
3. *Developing and populating a decision-analytic model in order to evaluate the lifetime costs and health outcomes of the alternative strategies* The decision-analytic model provides an explicit analytical framework to combine data on a range of effectiveness, resource use and value parameters necessary to provide guidance on optimal reimbursement decisions. The decision-analytic model is used to structure the decision problem to identify the relevant parameters, and the amount and quality of available evidence can then be reflected in the inputs assigned to these parameters. The model is structured around the patient

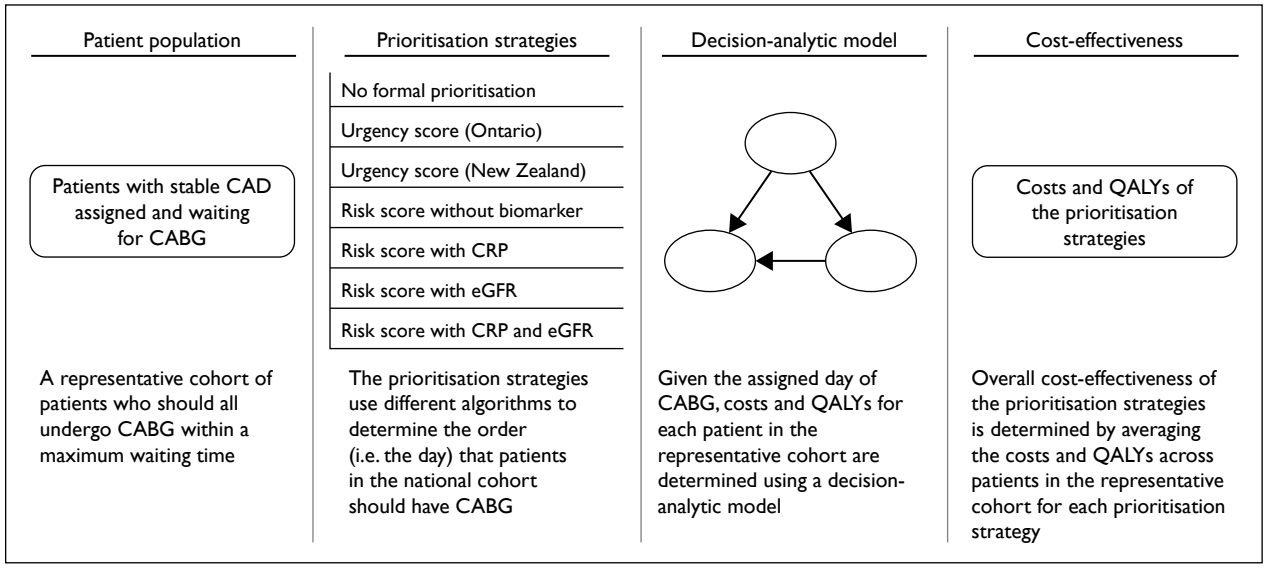

FIGURE 1 *Overview of the analytical approach. CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; QALY, quality-adjusted life-year.*

population of interest, characterising the potential events that may occur within both the short-term (e.g. events on a waiting list and procedural risk) and the longer term (e.g. subsequent prognosis after CABG) in terms of overall quality-adjusted life expectancy and costs and also reflecting the specific effect of the alternative strategies on these elements. This process inevitably involves methods for synthesising evidence for a range of parameters beyond simply the effectiveness of an intervention, including generating baseline event rates (e.g. to represent current practice), quality of life estimates and costs.

4. *Estimation of the mean lifetime cost and health outcomes of the different prioritisation strategies in order to determine overall cost-effectiveness* Propagation of the full range of input parameters into the decision-analytic model enables the expected lifetime costs and health outcomes for patients with different characteristics and risk factors to be established, conditional on the assigned day of CABG. For example, a particular patient in the representative cohort could be assigned CABG at day 10 with one prioritisation strategy and day 20 with an alternative prioritisation strategy. In this case it is necessary to estimate the costs and health outcomes associated with undergoing CABG at day 10 and day 20 for this particular patient. Overall cost-effectiveness of the prioritisation strategies can then determined by averaging the costs and health outcomes across patients in the representative cohort for each prioritisation strategy and comparing the subsequent ICER estimates with external thresholds representing value for money to the NHS.[36]

Major data inputs

Several data sources and analytical approaches are required in order to carry out the analyses outlined above. The two major elements required to populate the decision model are: (1) systematic review and synthesis of existing evidence related to the clinical effectiveness of biomarkers themselves and (2) other evidence necessary to populate the decision-analytic model and the range of alternative strategies including the risk of cardiovascular events (on the waiting list, procedural and after CABG) as well as the effect on costs and health-related quality of life. The methods and results of the systematic review and synthesis of existing evidence related to clinical effectiveness of biomarkers are described in detail in Chapters 3 and 4. The results from this review provide one of the major inputs required for the overall decision model. The methods, range of data sources and results of the decision model are reported in Chapters 5 and 6. The key data source for a number of separate elements of the decision model, including the characteristics and risk factors of the representative cohort, was the Swedish Coronary Angiography and Angioplasty

Registry (SCAAR).[37] This registry includes consecutive patients without exclusion criteria in all 30 centres in Sweden, and covers a total of 201,000 angiographies. Furthermore, the decision on further management after angiography is also available in SCAAR, making it possible to identify a representative cohort of patients with a decision to perform CABG as well as longer term prognosis. The SCAAR registry, alongside other published sources used to populate the decision model, is presented in detail in Chapter 5.

Chapter 3

Methods of systematic review of circulating biomarkers

We carried out systematic reviews and meta-analyses of literature-based estimates of the effects of circulating biomarkers on the prognosis of stable coronary disease. We carried out the systematic reviews and meta-analyses in accordance with standards for reporting set out by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.[38] The MOOSE standards are focused on healthy population studies; there are no standards for the design and reporting of meta-analyses for prognostic studies (i.e. among patients with established disease).

Inclusion criteria

An eligible publication had to meet five criteria:

- prospective study design
- patients with stable coronary disease
- one (or more) eligible biomarker
- eligible outcome
- relative risk and 95% CI reported.

Appendix 3 shows the proforma used to assess articles for eligibility.

Eligible study designs

We included any prospective study (observational cohort studies, prospective nested case–control studies, randomised controlled trials) that assessed biomarkers at one time point, and patients were followed up for outcomes at a later time point. Cross-sectional studies were not eligible.

Eligible patient populations

We included patient populations that had stable coronary disease, defined as clinically diagnosed chronic stable angina pectoris or coronary artery disease defined by luminal narrowing at coronary angiography, or a history of previous acute coronary syndrome at least 2 weeks prior to biomarker measurement. We excluded studies in which the biomarker was measured during an admission with an acute coronary syndrome. We also excluded studies in which the biomarker was measured after a coronary procedure had been performed but before discharge from hospital. The ideal population (most relevant to the decision model) was defined as patients who had undergone an angiogram and were waiting for CABG.

Eligible biomarkers

We defined five routinely measured circulating biomarkers as eligible for systematic review: serum creatinine, eGFR, fasting glucose, haemoglobin, total cholesterol, and low density lipoprotein (LDL) cholesterol.

We defined eight novel circulating biomarkers as eligible for systematic review: CRP, brain natriuretic peptide (BNP), IL-6, fibrinogen, ApoA-I, ApoB, Lp(a) and homocysteine. These were chosen because of policy relevance and inclusion in the 2006 guidelines for the management of angina published by the European Society of Cardiology.[19] They represent a range of costs (see *Table 1*).

Eligible outcomes

Eligible outcomes were defined as CHD events (including coronary mortality, sudden cardiac death, acute non-fatal myocardial infarction, unplanned emergency admissions with unstable angina, acute coronary revascularisation, or the development of severe, worsening or rest pain), CVD events (where acute coronary events were reported in combination with other non-coronary events including heart failure, stroke and peripheral arterial disease) and ACM. For the decision model, the most important outcomes were those for which risk might be reduced by CABG – coronary death and acute coronary events. We therefore defined a hierarchy where biomarker effects on specifically coronary causes and death were given the highest preference, and non-fatal events and ACM were used in their absence. As

many papers reported two or more different end points, we present end points according to the hierarchy:

Death	Non-fatal events	Abbreviation used in tables
1. Coronary	None	CHD
2. Coronary	+ Coronary	
3. Cardiovascular	None	CVD
4. Cardiovascular	+ Cardiovascular	
5. All cause	+ Cardiovascular	ACM
6. All cause	None	
7. None	+ Cardiovascular	Morbidity

Exclusion criteria

We did *not* exclude any studies based on methodological standards, sample size, duration of follow-up, publication year or language of publication.

Search strategies

We searched MEDLINE (PubMed) and EMBASE databases between 1966 and 30 November 2008 using a strategy developed with an expert librarian (who has a Postgraduate Diploma in Information and Library Science and 10 years experience as a medical librarian) based on terms for coronary disease (Cochrane Library of Systematic Reviews and Protocols), prognostic studies[39] and biomarker. The final search combined these three searches with the connector word 'AND'. Details of the search terms are shown in Appendix 2.

Reference management

Titles and abstracts were downloaded to REFERENCE MANAGER (version 10.0) into separate databases for the MEDLINE and EMBASE results, which were then merged and checked for duplicates. Unique study identifiers were assigned to each article based on the REFERENCE MANAGER reference identifier (Ref ID). The duplicated references were then eliminated.

Reviewing titles and abstracts for eligibility

Three reviewers (NF, JD and KM) reviewed article titles and abstracts for eligibility and obtained full text articles where eligibility was definite or unclear. Multiple publications from one study data set were eligible where they reported results from two or more different biomarkers.

Data extraction

Two reviewers (NF and JD) independently abstracted data from eligible articles using a pre-defined coding protocol (see Appendix 4). Non-English articles were translated. Individual item disagreement between the two reviewers was resolved by consensus or, rarely, adjudication by a third reviewer (HH). The main details extracted were the year of publication; the number of patients at baseline that were included in the analysis, their mean age and the percentage of women; the baseline coronary morbidity (proportion with symptoms of angina, angiographic disease or previous myocardial infarction); mean [standard deviation (SD)] levels of biomarker at baseline [or median (interquartile range)]; type of assay; follow-up duration; the number and type (CHD, CVD, or ACM) of outcome events; the crude annual risk of these events calculated; whether or not the multivariate adjustment models included terms for age, sex, smoking status, obesity (nearly always body mass index), diabetes and one or more lipid variable [from total cholesterol, LDL cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides]; and the comparisons (grouped or continuous).

Selection of relative risks

Within one study, two or more relative risks were commonly reported, based on different combinations of outcomes (e.g. reporting effects for coronary death and all-cause death separately) or different combinations of adjustment factors. We identified and extracted the relative risk and 95% CIs for the most specific cardiac end point combination according to the seven-level hierarchy defined above. Where two or more relative risks were reported for the most specific end point combination, we selected the most highly adjusted relative risk (i.e. with the largest number of adjustment variables). Where men and women were reported separately, these were taken as two separate study populations. Where separate effects were reported in active treatment and placebo arms of randomised trials, we selected the effect from the placebo arm.

Data extraction for study quality

There are no widely used, validated methods of scoring the overall quality of individual reports from studies of prognostic biomarkers. We based our definitions of quality items on those in the guidelines for reporting tumour biomarkers (REMARK)[40] and those discussed in Hayden.[41] Such approaches assess the quality of the reporting of the study, rather than the quality of the study per se. However, the quality of reporting is related to the quality of the research in some, but not all, studies.

We summarised the quality of individual studies according to *whether there was a clear statement or description or evidence* of each item. A clear description is indicated in the table with a '•' in the study row, and absence of adjustment for a factor or lack of a clear description was indicated with a '○'. The actual content of the descriptions among those with a '•' are not summarised in this monograph (details are available from the authors on request), because they bear no simple relation with quality. For example, whether a data set is drawn from a randomised trial or a registry does not have a necessary relation to study quality.

The following quality items were systematically extracted from each paper included in the meta-analysis:

- *Pre-specified research question*: a bibliographic reference stating that studying the relation of the biomarker on coronary events was part of the rationale for collecting the patient sample at the outset of the study.

Population

- *Setting:* the clinic or hospital circumstances in which the cohort was recruited (e.g. primary care, at the time of angiography, or combinations thereof).
- *Duration of CHD:* the average length of time since the first symptomatic clinical presentation of CHD (years).
- *Flow diagram of patient inclusion:* illustrating the reasons for exclusion and numbers of patients.
- *N eligible patients:* the total number of patients who were invited to participate in the study, i.e. before exclusion criteria or missing data on covariates reduces the number of patients available for analysis.
- *Exclusion criteria:* relating to other conditions which, for example, might influence inflammatory markers.
- *Consent*: written informed patient consent.

Biomarker measurement

- *Fasting status:* the fasting status of the patients when blood tests were drawn.
- *Storage:* fresh sample or if the blood is stored, at what the temperature (fresh/temperature/no statement/not applicable).
- *Manufacturer:* the name of the company that makes the assay for the biomarker.
- *Assay:* the type of assay used to measure the biomarker (e.g. turbidimetric, ELISA, nephelometry).

Outcomes

- *Masking:* if clinical details were masked during the appraisal of outcome events.
- *Validation:* outcome events were cross-checked by independent sources.
- *Primary outcome:* a single disease end point, or a single combination of end points, for the analysis. The report must use the word 'primary'.
- *Pre-specified primary outcome:* the primary outcome was pre-specified in the study protocol.

Confounders

- *Confounder measurement:* were the following potential confounders measured: age, sex, smoking status, LDLs and triglycerides, body mass index and diabetes? However, these confounders do not necessarily have to be included in the multivariate analysis to be included.
- *Rationale for including adjustment variable:* states the method by which factors were selected to be in the multivariate adjustment models (response categories: a priori, stepwise procedures, univariate *p*-values).

Analytical decisions

- *Missing values:* how were patients without valid information on the biomarker or confounders were dealt with in the analysis (response categories: complete case analysis, multiple imputation)?
- *Cut-point rationale:* how were the cut-points for the biomarker determined for the estimation of relative risks (response categories: a priori, quantiles)?
- *Power:* statistical sample size or power calculation (yes/not stated).
- *Multiple publications:* other publications using the same study population report other relative risks for the same biomarker.

Statistical analysis

Different categorical and continuous scales of effect

Studies reported relative risk on continuous and categorical scales, and within each a wide variety of approaches was used (*Table 2*). Thus, for continuous scales some studies reported per SD of untransformed data, while others reported per unit, or per unit on the log scale. These relative risks are not directly comparable. For categorical scales, some studies reported for two, three, four or five equally sized groups, and for others the group size was not clear. Clearly, assuming a linear relation between biomarker and events, the effects for the top versus the bottom fifth of the distribution will, for example, be more extreme than for the portion above and below the median.

Conversion of literature estimates of relative risk to a common scale (tertiles)

We therefore needed to convert continuous and categorical relative risks on to a common scale of effect. We chose thirds of the biomarker distribution (tertiles) because this has been the approach in the large-scale meta-analyses of these biomarkers in aetiological (healthy population) studies,[52] and because the number of events in, for example, fifths of the distribution would become very small given the average size of study.

Converting continuous scales

For a normally distributed variable, the difference between the means of the top (T3) and bottom (T1) third of the distribution is 2.18 SD units. Thus to estimate the relative risk for T3 versus T1, relative risks reported per SD of log CRP were raised to the power of a *scaling factor* of 2.18, as previously reported.[53] This method assumes that CRP is log normally distributed and that the association with disease risk is log linear; both these assumptions have empirical support in healthy population studies of CRP.[54] Similarly, for relative risks expressed as either top 50% versus bottom 50% or by quartiles, scaling factors equal to 1.37 (2.18/1.59) and 0.86 (2.18/2.54) respectively, were used. 1.59 is the difference, in SD units, between the means of the top and bottom (T1) halves of the distribution; 2.54 is the difference, in SD units, between the top (T4) and bottom quarters of the distribution. Where two groups were of unequal size, we calculated the means in the groups, assuming the underlying distribution to be normal and used these differences as the scaling factor.

However, for a log normally distributed variable, the difference in means between T3 and T1 depends upon both the mean and SD of the untransformed distribution. The implication of this is that for relative risks reported per unit or SD of CRP (untransformed), we needed to obtain study-specific scaling factors, based on the means and SD of the untransformed data. Simulating one million observations from a log normal distribution with specified mean and SD allowed us to compute the difference in means between T3 and T1 for any combination of mean and SD. In addition, as there is an exact relationship between the means and SD of the normal and log normal distributions, the T3 versus T1 differences could be computed whenever means and SD were specified for either CRP or log CRP. In the absence of reported estimates of the mean and SD, these were estimated for the log CRP distribution from the interquartile range (IQ_l, IQ_u) as: mean = $(IQ_l + IQ_u)/2$, SD = $(IQ_u - IQ_l)/1.349$, where 1.349 is the distance in SD units between the 25th and 75th centile of the normal distribution.

Some studies reported the mean and SD within subgroups, rather than of the overall sample. In this situation where we knew the sufficient statistics (*N*, mean, SD) within groups, we calculated the mean and SD of the overall sample from these values.

Relative risks reported per mg/l were converted first to an SD change, using the study-specific SD, and thence to tertiles as above. For those studies that provided regression-based estimates per tertile, i.e. assuming a log linear relationship for CRP, the relative risk for the comparison of the highest third with the lowest third of the CRP distribution was obtained by using a scaling factor of 2. The middle tertile estimate was obtained by taking the square root of the T3 versus T1 estimate from the summary estimate of the meta-analysis.

Conversion of literature estimates of relative risk to a common cut-point

For eGFR, fasting glucose and haemoglobin, a single value is used to define chronic kidney disease, diabetes and anaemia respectively. However, reports used different single cut-points, and two or more cut-points. Therefore, in order to obtain an estimate for the presence versus absence of these diseases, we illustrate the method with chronic kidney disease, as defined by an eGFR

TABLE 2 *Methods for converting the relative risks reported in the literature to a common scale of top and middle tertile vs bottom tertile*

RR comparison reported in the paper	Number of studies	Method	Example		
			Study reference	Reported RR (95% CI)	Scaled RR Top vs bottom (95% CI)
Continuous					
Per SD	7	Scaling factor is 2.18 (the difference in means between T3 and T1)	Blankenberg 2006[42]	1.10 (0.99 to 1.23)	1.23 (0.98 to 1.57)
Per tertile	4	Scaling factor is 2.00	Anderson 2000[43]	1.42 (1.12 to 1.80)	2.02 (1.25 to 3.24)
Per quartile	3	Scaling factor is 2.32	Chan 2003[44]	1.32 (1.12 to 1.56)	2.04 (1.34 to 3.14)
Per standard unit (e.g. mg/l for CRP)	8	First convert to SD using study-specific SD	Inaguma 2007[45]	1.05 (1.02 to 1.08)	1.40 (1.14 to 1.69)
Per log 10 (biomarker)	14	First convert to SD, and then to natural log scale	Aguilar 2006[46]	1.70 (1.39 to 2.08)	1.76 (1.42 to 2.19)
Equal size groups: top vs bottom					
Two groups	10	Scaling factor is 1.37 (2.18/1.59; difference in means is between top 50% vs bottom 50%	Huang 2008[47]	1.66 (1.04 to 2.64)	2.00 (1.06 to 3.78)
Three groups (tertiles)	9	Reported (no scaling required)	Fathi 2005[48]	1.85 (1.13 to 3.03)	1.85 (1.13 to 3.03)
Four groups (quartiles)	11	Scaling factor 0.858 (2.18/2.54; difference in means between T4 and T1)	Chew 2001a[49]	3.68 (1.51 to 8.99)	3.06 (1.42 to 6.58)
Unequal size groups: top vs bottom					
Two groups	35	Calculated the means in the groups, assuming the underlying distribution to be normal and use these differences as the scaling factor	Crea 2002[50]	2.51 (1.30 to 4.8)	3.27 (1.40 to 7.53)
Three groups	2	Calculated the means in three groups, assuming the underlying distribution to be normal and use these differences as the scaling factor	Morrow 2006[51]	3.90 (1.8 to 5.6)	2.93 (1.59 to 3.91)

RR, relative risk.

lower than 60, versus its absence (eGFR ≥ 60). eGFR differs further from the situation with CRP, because eGFR is normally distributed and the relation between eGFR and CHD risk is not linear, as demonstrated in a previous meta-analysis in healthy population studies.[55]

Where the relative risk was reported on a continuous scale, we used the mean and SD to estimate the proportion of the sample lying above and below the cut-point of 60 ml/min. Then we calculated the difference in means, expressed on the standard normal deviate scale, between these two groups and multiplied this by the reported eGFR SD to obtain the scaling factor.

Where the relative risk was reported in categories with the reference group as greater than or equal to 60 ml/min, we combined the two (or three) risk groups by weighting the relative risk estimates by the inverse of their variance. When the reference group was greater than or equal to 90 or to 75, we used that as reference group.

Meta-analysis

For each study, the relative risk estimate and its corresponding standard error were transformed to their natural logarithms to stabilise the variance and normalise the distributions. Summary relative risk estimates and their 95% CIs were estimated from a random effects model that considers both within- and between-study variation.[56] Statistical heterogeneity among studies was evaluated using the Cochran's Q and I^2 statistics.[57] Small study bias, consistent with publication bias was assessed with funnel plot (i.e. a plot of study results against precision), by Begg's adjusted rank correlation test, and by Egger's regression asymmetry test.[58]

To explore other potential sources of study heterogeneity, such as age, sex, annual risk rate, CRP levels, sample size, degree of covariates adjustment, duration of follow-up, study start year, events number and type of adjustment, we employed a meta-regression model that included these variables as covariates in categorical forms. We also performed meta-regression for continuous covariates, but due to the fact that these were often aggregated individual-level covariates, the results were interpreted with caution because of possible ecological bias. All analyses were conducted using STATA, version 8.0 (StataCorp, College Station, TX, USA). All statistical tests were two-sided.

Chapter 4

Results of systematic review of circulating biomarkers

Results of searches

We reviewed a total of 14,723 unique titles and abstracts for eligibility and included 390 reports (see *Figure 2* and Appendix 2). We translated studies from French, German, Italian, Portuguese, Spanish, Russian, Farsi, Japanese, Mandarin and Czech. A list of full text articles reviewed and rejected is given in the appendices.

We identified no previous meta-analyses, or systematic reviews, of any circulating biomarker in the prognosis of stable coronary disease. We identified no eligible studies in the 'ideal' population – among patients on the waiting list for CABG – in relation to novel circulating biomarkers.

Quality of individual studies

We included 390 reports of biomarker effects in our review. The number of events per study, and the demographic and clinical characteristics of patients were similar across biomarkers. The quality of individual study reports was similar across different biomarkers, and is summarised for the CRP studies in *Table 3*. Given that one data set commonly reported relative risks for the effects of more than one biomarker, and given that the quality of studies did not vary substantially between biomarkers, we show the 109 studies that reported results for CRP, the biomarker with the most eligible studies. No (0%) studies reported a clear statement of pre-specified research question.

Quality of reports of study populations

The clinical setting of the studies was clearly described, but there were concerns about how the final study population available for analysis was derived. Thus, only five (5%) studies reported the duration of history of coronary disease and 3% reported a flow diagram of patient inclusion. However, 85% reported the number of eligible patients as distinct from the number of patients included in the final analysis.

Quality of reports of biomarker measurement

Minimal standards for reporting biomarker measurement methods were not universally applied. Thus, 39% of studies reported a clear description of the fasting status of the patient and 63% gave details of sample storage.

Quality of reports of confounders

There was not always clarity about which confounders were measured and, among those that were, what rationale directed their inclusion in multivariate models. Thus, 50% of studies reported any rationale guiding the inclusion of confounders in multivariate models.

Quality of reports of outcomes (end points)

Given that nearly all studies used a combination of disease processes as an outcome event (e.g. combining different types of fatal and non-fatal events, with different combinations of non-fatal events) it was of particular concern that 35% of studies defined a primary outcome, but in only 3% of studies was this primary outcome pre-specified. Likewise, validation of outcome events, or masking of the event ascertainment or classification to clinical details, was seldom reported.

For these reasons, few studies reported on precisely the end point combination that we implement in the decision model (ACM + non-fatal myocardial infarction + non-fatal hospitalised stroke).

Quality of reporting of analytical decisions

No study reported pre-specified hypotheses or analytical plans. Four per cent of studies commented on missing values of biomarkers. Most studies that reported relative risks for cut-points of biomarkers gave a rationale for the choice of cut-point. However, few studies gave a rationale as to prior decision of whether to analyse the biomarker

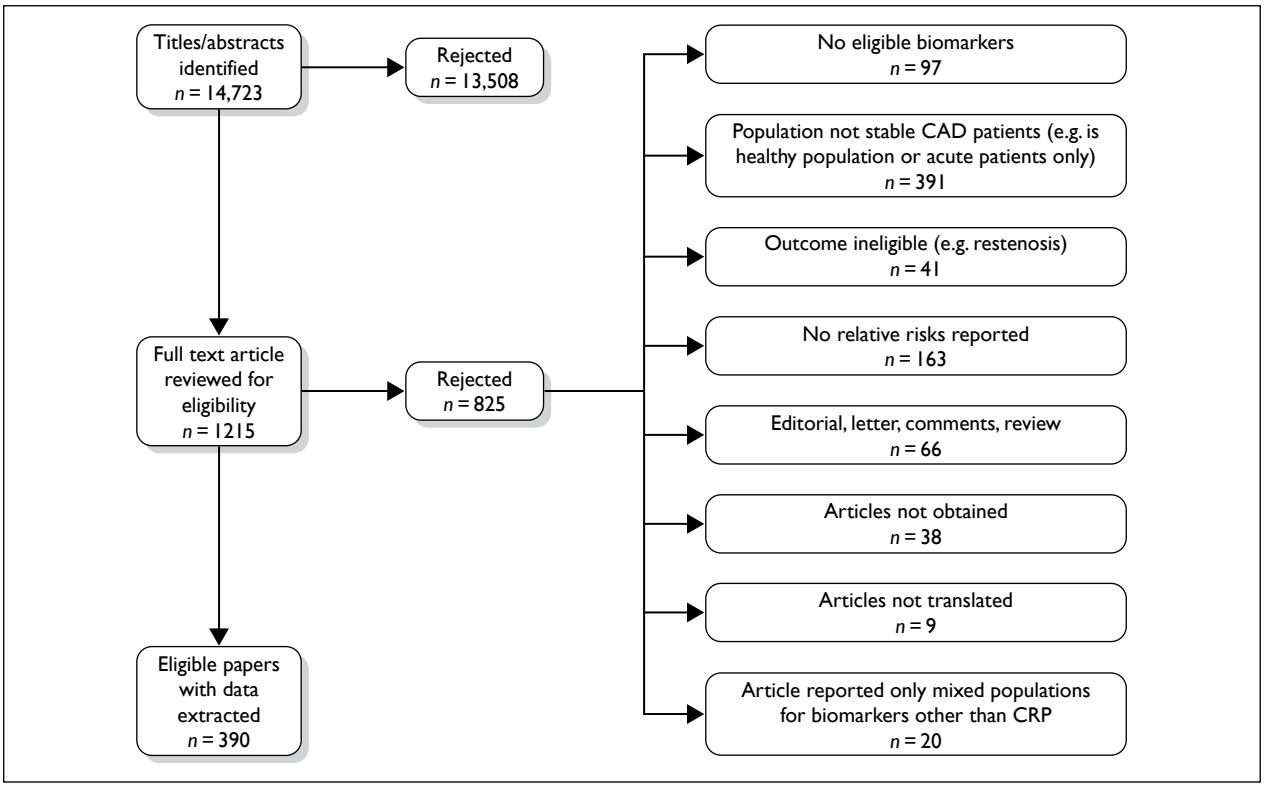

FIGURE 2 *Flow chart of search results and selection of eligible studies.*

as a continuous or a categorical exposure. Five per cent of studies reported a sample size or power calculation.

C-reactive protein systematic review

We identified a total of 109 reports among patients with stable coronary disease where CRP was related to the risk of subsequent events (*Table 4*). Current angina symptoms were present in median 70.5 (range 9–100%) among the 45 studies providing data. Previous myocardial infarction was present in median 39 (range 8–100%) of patients in the 65 studies providing data. The mean age of patients across studies was a median of 62 years, and only one study had a mean age above 70 years. The median proportion of women in studies was 24.1%, and only three studies reported separate estimates among women. Eight thousand three hundred and sixty-nine outcome events were reported, with a median number of events per study of 51 (range 4–825).

C-reactive protein meta-analysis

The 109 study reports came from 77 unique studies. The pooled relative risk from the random effects model of top versus bottom third of CRP based on 77 unique studies was 1.96 (95% CI 1.76 to 2.17). There was marked heterogeneity, with an *I*-squared value of 79.1%. Evidence of small study bias is seen with smaller studies showing more extreme (positive) results. The funnel plot (not shown) was asymmetrical and the Egger test was significant ($p < 0.001$). This overall effect was weaker among those with more adjustment variables and earlier studies, but study characteristics did not account for the substantial heterogeneity between studies. Effects did not differ according to morbidity at baseline or among studies which reported CHD, CVD or ACM outcome events (data not shown).

Estimated glomerular filtration rate systematic review and meta-analysis

The systematic review of eGFR is shown in *Table 5* and serum creatinine in *Table 6*. Given that eGFR is a more accurate reflection of renal function, taking account of age and sex, we did not meta-analyse the serum creatinine results. For routinely measured biomarkers, relative risks were 2.00 (95% CI 1.65 to 2.42) for eGFR below versus above 60 ml/min (based on 12 studies, 31,839 patients, 1639 outcome events).

Summary of systematic review for five routinely measured and eight novel biomarkers

We included 390 reports of biomarker effects in our review (*Table 7*), and Appendix 1 contains the results of the systematic reviews of each of the biomarkers. The number of events per study, and age, sex and baseline morbidity characteristics were similar across all the biomarkers. The quality issues identified for the CRP studies were likewise found for the other biomarkers (data not shown). Routinely assessed biomarkers contributed fewer studies than did novel biomarkers. Thus, CRP had 109 reports in the systematic review and 100 in the meta-analysis, by contrast with haemoglobin (15 and 4 respectively).

The estimated summary relative risks were 1.74 for fasting glucose higher than 7 mmol/l, 2.92 for haemoglobin lower than 13 g/dl, and 1.30 and 1.33 for total and LDL cholesterol (top versus bottom tertile) respectively.

For novel circulating biomarkers, relative risks comparing the top and bottom third were: 1.96 (95% CI 1.76 to 2.17) for CRP (based on 77 studies, 56,496 patients, 5798 outcome events) and, based on a smaller literature, 2.93 for BNP, 2.06 for homocysteine, 1.63 for IL-6, 1.59 for fibrinogen, 1.39 for ApoB, 1.24 for Lp(a) and 0.81 for ApoA-I. The quality of individual study reports was variable with many studies lacking clear description of population selection, and variable adjustment for simple clinical information – age, sex, smoking, diabetes, obesity and lipids.

TABLE 3 *Quality of 109 individual reports of CRP and prognosis: presence of clear description on items related to study population, biomarker measurement, confounders, outcome measurement and analytical decisions (see Appendix 1 for references)*

		Population							Biomarker measurement				Confounders		Outcomes				Analytical decisions		
Author/publication year (study name)	**Pre-specified research question**	**Multiple publications**	**Setting**	**Duration of CHD**	**Number of eligible patients**	**Flow diagram for patient inclusion**	**Exclusion criteria**	**Informed consent**	**Fasting status**	**Storage temperature**	**Manufacturer**	**Assay**	**Confounders measured**	**Rationale for adjustments**	**Masking of clinical details**	**Validation**	**A primary outcome**	**Pre-specification of primary outcome**	**Missing values**	**Cut-point rationale**	**Power**
Aguilar 2006[46] (WIZARD)	○	○	●	○	●	○	●	●	●	○	●	●	○	○	●	●	●	○	○	●	○
Anderson 2000[43] (–)	○	○	●	○	○	○	○	●	●	●	●	●	○	●	○	●	○	○	○	●	○
Arroyo-Espliguero 2004[84] (–)	○	○	●	○	○	○	●	●	●	○	●	○	○	●	○	●	○	○	○	●	○
Arroyo-Espliguero 2008[94] (–)	○	○	●	●	●	○	●	●	●	●	●	●	●	●	○	○	○	○	○	●	○
Artieda 2007[90] (–)	○	○	●	○	○	○	●	●	●	○	●	●	○	○	●	●	○	○	○	●	○
Aytekin 2003[130] (–)	○	○	●	○	○	○	●	○	○	●	○	○	○	○	●	○	●	○	○	○	○
Biancari 2003[135] (–)	○	○	●	○	●	○	●	○	○	○	●	●	○	●	○	○	○	○	●	●	○
Bickel 2002[73] (Atherogene)	○	●	●	○	●	○	●	●	●	●	●	●	●	●	○	○	○	○	●	○	○
Blankenberg 2001a[82] (Atherogene)	○	●	●	○	●	○	●	●	○	●	●	●	●	●	○	○	○	○	○	○	○
Blankenberg 2001b[113] (Atherogene)	○	●	●	○	●	○	●	●	●	●	●	●	●	○	○	○	○	○	○	○	○
Blankenberg 2002[68] (Atherogene)	○	●	●	○	●	○	●	●	○	●	●	●	●	○	○	○	○	○	○	●	○
Blankenberg 2003[67] (Atherogene)	○	●	●	○	●	○	○	●	○	●	●	●	○	○	○	○	○	○	○	●	○
Blankenberg 2006[42] (HOPE)	○	●	●	○	●	○	●	●	○	●	●	●	●	●	●	○	●	○	○	●	○
Bogaty 2001[77] (–)	○	●	●	○	○	○	●	●	●	○	●	●	●	○	○	○	○	○	○	○	○
Bogaty 2008[88] (–)	○	○	●	○	●	○	●	○	○	●	●	●	●	●	○	●	●	○	○	●	●

	Population									Biomarker measurement				Confounders		Outcomes				Analytical decisions		
Author/publication year (study name)	**Pre-specified research question**	**Multiple publications**	**Setting**	**Duration of CHD**	**Number of eligible patients**	**Flow diagram for patient inclusion**	**Exclusion criteria**	**Informed consent**	**Fasting status**	**Storage temperature**	**Manufacturer**	**Assay**	**Confounders measured**	**Rationale for adjustments**	**Masking of clinical details**	**Validation**	**A primary outcome**	**Pre-specification of primary outcome**	**Missing values**	**Cut-point rationale**	**Power**
Brilakis 2005[75] (–)	○	○	●	○	○	○	●	●	○	○	●	●	○	○	○	○	○	○	○	●	○
Chan 2003[44] (–)	○	○	●	○	○	○	●	○	○	○	○	○	●	●	○	●	○	○	○	●	○
Chew 2001b[225] (–)	○	○	●	○	●	○	●	○	○	○	○	○	○	●	○	○	○	○	○	●	○
Chirinos 2005a[78] (–)	○	●	●	○	●	○	●	●	○	●	●	●	○	○	○	○	○	○	○	●	○
Chirinos 2005b[76] (–)	○	●	●	○	○	○	○	●	○	●	●	●	○	●	○	●	○	○	○	●	○
Crea 2002[50] (4S Study)	○	●	●	○	●	○	●	○	○	●	●	●	●	●	●	○	●	○	○	●	○
Dai 2007[86] (–)	○	●	●	○	○	○	●	●	○	●	●	●	●	○	○	●	○	○	○	●	○
Dai 2008[87] (–)	○	●	●	○	○	○	●	●	○	○	●	●	●	●	○	○	○	○	○	●	○
de Winter 2002[226] (–)	○	●	●	○	○	○	●	○	○	●	●	●	○	○	○	○	○	○	○	●	○
de Winter 2003[227] (–)	○	●	●	○	○	○	●	○	○	●	●	●	○	○	○	○	○	○	○	●	○
de Winter 2004[228] (–)	○	●	●	○	○	○	●	○	○	●	●	●	○	●	○	○	○	○	○	●	○
Dibra 2003[111] (–)	○	○	●	○	○	○	●	●	○	●	●	○	○	●	○	○	○	○	○	●	○
Espinola-Klein 2007[98] (–)	○	○	●	○	●	○	○	●	●	○	●	●	●	○	○	○	○	○	○	●	○
Fathi 2005[48] (–)	○	○	●	○	●	○	●	○	○	○	○	●	○	●	○	○	○	○	○	●	○
Falcone 2006[61] (–)	○	○	●	○	●	○	●	●	○	●	●	○	●	○	○	○	○	○	○	●	○
Fang 2007[101] (–)	○	○	●	○	○	○	○	●	●	○	●	●	●	○	○	○	○	○	○	●	○
Gach 2007[121] (–)	○	○	●	○	○	○	●	●	●	○	●	●	●	○	○	○	○	○	○	●	○
Garcia-Moll 2000[81] (–)	○	○	●	○	○	○	●	●	●	●	●	●	○	●	○	○	○	○	○	●	○
Gaspardone 1998[136] (–)	○	○	●	○	○	○	○	○	○	●	●	●	○	○	○	○	○	○	○	●	○
Grander 2004[148] (–)	○	○	●	○	○	○	●	●	●	●	●	○	○	○	●	○	○	○	○	●	○
Haim 2007[89] (BIP)	○	○	●	●	●	○	○	●	●	●	●	●	●	○	●	○	●	○	○	●	○

continued

TABLE 3 *Quality of 109 individual reports of CRP and prognosis: presence of clear description on items related to study population, biomarker measurement, confounders, outcome measurement and analytical decisions (see Appendix 1 for references) (continued)*

	Population								Biomarker measurement				Confounders		Outcomes				Analytical decisions		
Author/publication year (study name)	**Pre-specified research question**	**Multiple publications**	**Setting**	**Duration of CHD**	**Number of eligible patients**	**Flow diagram for patient inclusion**	**Exclusion criteria**	**Informed consent**	**Fasting status**	**Storage temperature**	**Manufacturer**	**Assay**	**Confounders measured**	**Rationale for adjustments**	**Masking of clinical details**	**Validation**	**A primary outcome**	**Pre-specification of primary outcome**	**Missing values**	**Cut-point rationale**	**Power**
Harb 2002[152] (THROMBO)	○	○	●	○	●	○	●	○	●	●	○	○	●	●	○	○	●	●	○	●	○
Haverkate 1997[64] (ECAT)	○	●	●	○	●	●	●	○	○	○	●	●	○	○	●	●	○	○	○	●	○
Hoffmeister 2005[153](–)	○	●	●	○	○	○	●	●	○	●	●	●	○	○	○	●	○	○	○	●	○
Horne 2000[66] (–)	○	○	●	○	○	○	●	●	○	○	●	●	○	●	○	●	○	○	○	●	○
Huang 2006[138] (–)	○	○	●	○	○	○	●	○	●	○	○	●	○	○	○	○	○	○	○	○	○
Huang 2008[47] (–)	○	○	●	○	●	○	●	●	●	●	●	●	●	○	○	○	●	○	○	●	○
Ijsselmuiden 2003[115] (–)	○	○	●	○	○	○	●	●	○	○	○	○	○	○	○	○	●	○	○	○	●
Ikonomidis 2005[124] (–)	○	○	●	○	○	○	●	●	○	●	●	●	○	●	○	●	●	○	○	●	●
Inaguma 2007[45] (–)	○	○	●	○	○	○	●	○	○	○	○	○	●	○	○	○	○	○	○	○	○
Inoue 2007[99] (–)	○	○	●	●	●	○	●	●	●	●	●	●	●	●	○	○	○	○	○	○	○
Inoue 2008[96] (–)	○	○	●	○	●	○	●	●	●	●	●	●	○	○	○	○	○	○	○	●	○
Janoskuti 2005[118] (–)	○	○	●	○	○	○	●	●	●	●	●	●	●	○	○	○	○	○	○	●	○
Kangasniemi 2006[108] (–)	○	○	●	○	●	○	●	○	○	○	●	●	○	●	○	○	○	○	○	○	○
Karha 2006[125] (–)	○	○	●	○	○	○	●	●	○	○	●	●	○	○	○	○	○	○	○	●	○
Khor 2004[102] (Intermountain Heart Collaborative Study)	○	○	●	○	●	○	●	●	○	●	●	●	○	●	○	○	○	○	○	○	○
Kinjo 2003[126] (OACIS)	○	●	●	○	●	○	○	○	○	○	○	●	○	○	●	○	○	○	○	●	○
Kinjo 2005[133] (OACIS)	○	●	●	○	●	○	○	●	○	●	●	●	●	●	●	○	○	○	○	●	○
Kip 2005[151] (WISE)	○	●	●	○	●	○	●	●	●	●	●	○	○	○	○	○	●	○	○	●	●
Krzewina 2003[157] (–)	○	○	●	○	○	○	●	●	○	●	○	●	○	○	○	○	○	○	●	●	○
Kubica 2005[146] (–)	○	○	●	○	○	○	●	●	○	●	●	●	●	○	○	○	●	○	○	●	○

	Population									Biomarker measurement				Confounders		Outcomes				Analytical decisions		
Author/publication year (study name)	**Pre-specified research question**	**Multiple publications**	**Setting**	**Duration of CHD**	**Number of eligible patients**	**Flow diagram for patient inclusion**	**Exclusion criteria**	**Informed consent**	**Fasting status**	**Storage temperature**	**Manufacturer**	**Assay**	**Confounders measured**	**Rationale for adjustments**	**Masking of clinical details**	**Validation**	**A primary outcome**	**Pre-specification of primary outcome**	**Missing values**	**Cut-point rationale**	**Power**
Kwaijtaal 2005[127] (EXIT)	○	●	●	○	●	●	●	●	○	●	●	●	○	○	○	●	○	○	○	●	○
Lee 2006[149] (–)	○	●	●	○	○	○	○	●	○	●	●	●	●	○	○	○	○	○	○	●	○
Leu 2004[122] (–)	○	○	●	○	○	○	●	●	●	●	●	●	○	○	○	○	○	○	○	○	○
Liu 2003[110] (–)	○	○	●	○	○	○	●	○	●	●	●	○	●	●	○	○	○	○	○	●	○
Low 2004[120] (–)	○	○	●	○	○	○	●	●	●	●	●	●	○	●	○	●	○	○	○	●	○
Lu 2003[134] (–)	○	○	●	○	○	○	●	●	●	●	●	●	○	●	○	○	○	○	○	●	○
Lubos 2006[62] (Atherogene)	○	●	●	○	●	○	●	●	○	●	●	●	●	○	○	●	●	○	○	●	○
Marcinkowski 2007[100] (–)	○	○	●	○	●	○	●	○	●	●	●	●	●	●	○	○	○	○	○	○	○
Milazzo 1999[139] (–)	○	○	●	○	○	○	●	●	○	●	●	●	○	○	●	○	○	○	○	○	○
Minoretti 2006[83] (–)	○	○	●	○	●	○	●	●	●	●	●	○	●	●	○	●	●	○	○	●	○
Morrow 2006[51] (AtoZ)	○	○	●	○	○	○	●	●	○	●	●	●	○	●	●	○	○	○	○	●	○
Muhlestein 2000[109] (Intermoutain Heart Collaborative Study)	○	●	●	○	●	○	●	●	○	○	●	●	○	●	○	○	○	○	○	●	○
Muhlestein 2004[141] (Intermountain Heart Collaborative Study)	○	●	●	○	●	○	●	●	○	○	●	○	○	●	○	○	○	○	○	●	○
Ndrepepa 2006a[71] (–)	○	●	●	○	○	○	●	●	○	●	●	●	●	●	●	●	○	○	○	●	○
Ndrepepa 2006b[71] (–)	○	●	●	○	●	○	●	●	○	●	●	●	○	○	○	●	○	○	○	●	○
Niccoli 2007[112] (–)	○	○	●	○	●	○	●	●	○	○	●	●	○	○	○	○	○	○	○	●	○
Otsuka 2002[72] (–)	○	○	●	○	○	○	●	●	○	○	○	●	○	○	○	●	○	○	○	●	○

continued

TABLE 3 *Quality of 109 individual reports of CRP and prognosis: presence of clear description on items related to study population, biomarker measurement, confounders, outcome measurement and analytical decisions (see Appendix 1 for references) (continued)*

	Population								Biomarker measurement				Confounders		Outcomes				Analytical decisions		
Author/publication year (study name)	**Pre-specified research question**	**Multiple publications**	**Setting**	**Duration of CHD**	**Number of eligible patients**	**Flow diagram for patient inclusion**	**Exclusion criteria**	**Informed consent**	**Fasting status**	**Storage temperature**	**Manufacturer**	**Assay**	**Confounders measured**	**Rationale for adjustments**	**Masking of clinical details**	**Validation**	**A primary outcome**	**Pre-specification of primary outcome**	**Missing values**	**Cut-point rationale**	**Power**
Palazzuoli 2006[140] (–)	○	○	●	○	●	○	●	●	○	●	●	●	○	●	●	○	●	○	○	●	○
Palmerini 2005[132] (–)	○	○	●	○	○	○	●	●	○	○	●	●	○	●	○	○	○	○	○	●	○
Palmerini 2007[92] (Bologna Registry)	○	●	●	○	○	○	●	●	●	○	●	●	●	●	○	○	●	○	○	●	○
Papa 2008[95] (–)	○	○	●	○	●	○	●	●	●	○	●	●	○	●	○	○	○	○	○	●	○
Park 2007[147] (–)	○	○	●	○	○	○	●	●	○	○	●	●	○	●	○	○	●	●	○	●	●
Patti 2002[49] (–)	○	○	●	○	○	○	●	○	●	●	●	●	○	○	○	○	○	○	○	●	○
Qi 2003a[79] (–)	○	○	●	○	●	○	●	●	○	●	●	●	○	○	○	○	○	○	○	●	○
Qi 2003b[80] (–)	○	○	●	○	○	○	●	●	○	●	●	●	○	○	○	○	○	○	○	●	○
Rahel 2003[144] (–)	○	○	●	○	●	○	●	●	●	●	●	●	○	●	○	○	○	○	○	●	○
Retterstol 2002[154] (–)	○	●	●	○	●	○	●	●	●	●	●	●	○	●	○	○	●	○	○	●	○
Rothenbacher 2006[150] (–)	○	○	●	○	●	○	○	●	●	●	●	●	○	●	○	○	○	○	○	●	○
Sabatine 2007[142] (PEACE)	○	○	●	○	●	○	○	○	○	●	●	●	○	●	●	●	○	○	○	●	○
Saleh 2005[143] (–)	○	●	●	○	●	○	●	●	○	○	●	●	○	●	○	○	○	○	○	●	○
Saleh 2006[74] (–)	○	●	●	○	○	○	○	●	●	○	●	●	○	●	○	○	○	○	○	●	○
Sargento 2002[131] (–)	○	○	●	○	○	○	○	●	○	○	●	○	○	○	○	○	○	○	○	●	○
Schaan 2007[69] (–)	○	○	●	●	○	○	●	●	●	●	●	●	●	●	○	○	○	○	○	●	○
Schnabel 2005a[107] (Atherogene)	○	●	●	○	○	○	●	●	●	●	●	●	●	●	○	○	●	○	○	●	○
Schnabel 2005a[107] (Atherogene)	○	●	●	○	○	○	●	●	○	○	●	●	○	●	○	○	○	○	○	○	○
Schnabel 2005b[155] (Atherogene)	○	●	●	○	●	○	●	●	○	●	●	●	○	●	○	○	○	○	●	●	○

Author/publication year (study name)	Population									Biomarker measurement				Confounders		Outcomes					Analytical decisions		
	Pre-specified research question	Multiple publications	Setting	Duration of CHD	Number of eligible patients	Flow diagram for patient inclusion	Exclusion criteria	Informed consent	Fasting status	Storage temperature	Manufacturer	Assay	Confounders measured	Rationale for adjustments	Masking of clinical details	Validation	A primary outcome	Pre-specification of primary outcome	Missing values	Cut-point rationale	Power	
Shlipak 2008[97] (Heart and Soul)	○	●	●	○	●	○	●	○	●	●	○	●	●	●	○	●	○	○	○	●	○		
Sinning 2006[59] (Atherogene)	○	●	●	○	●	○	●	●	○	●	●	●	●	○	○	○	○	○	○	●	○		
Soeki 1999[65] (–)	○	○	●	○	○	○	●	●	●	○	●	●	○	○	○	○	○	○	○	●	○		
Spiedl 2002[145] (–)	○	○	●	○	●	○	●	○	○	●	●	○	●	○	○	○	●	○	○	●	○		
Susen 2005[85] (–)	○	○	●	○	●	○	●	●	○	●	●	●	●	○	○	○	●	○	○	●	○		
Thompson 1995[60] (–)	○	●	●	○	●	●	●	○	○	●	○	●	○	○	●	○	●	○	○	●	○		
van der Harst 2006[137] (QUOVADIS)	○	○	●	○	●	○	●	●	○	●	○	●	●	●	○	●	○	○	○	●	○		
Veselka 2004[229] (–)	○	○	●	○	●	○	●	●	○	○	●	●	○	○	○	○	●	○	○	○	○		
West 2008[91] (LIPID)	○	●	●	●	○	○	○	○	●	●	●	●	●	●	●	○	●	○	○	●	○		
Wolk 2004[63] (–)	○	○	●	○	○	○	●	●	●	○	●	●	○	○	○	○	○	○	○	●	○		
Wu 2005[117] (–)	○	○	●	○	○	○	●	●	●	●	●	○	○	○	○	●	○	○	○	●	○		
Zairis 2002[129] (GENERATION)	○	●	●	○	●	○	●	●	○	●	●	●	○	●	○	○	●	●	○	●	○		
Zairis 2004[128] (GENERATION)	○	●	●	○	●	○	●	●	○	●	●	●	○	○	○	○	●	○	○	●	○		
Zebrack 2002[103] (–)	○	●	●	○	●	○	●	●	○	○	●	●	○	●	○	○	●	○	○	●	○		
Zebrack 2002b[105] (–)	○	●	●	○	●	○	●	●	○	○	●	●	○	●	○	○	●	○	○	●	○		
Zebrack 2003[104] (–)	○	●	●	○	○	○	○	●	○	○	●	●	○	●	○	○	●	○	○	●	○		
Zhu 2001[70] (–)	○	○	●	○	○	○	○	●	○	●	●	●	○	○	○	○	○	○	○	●	○		
Number of '●' from total of 109 reports	0	43	109	5	55	3	93	84	42	69	95	92	39	56	17	20	38	3	4	91[a]	5		
(%)	0	39	100	5	50	3	85	77	39	63	87	84	36	50	16	18	35	3	4	83[a]	5		

TABLE 4 *Systematic review of 109 study reports reporting the effect of CRP on prognosis among patients with stable coronary disease*

Author/publication year (study name)	Number of patients	Age (years)	% Women	Baseline coronary morbidity (%)			CRP mean (mg/l)	Assay type	Follow-up (years)	Event combination	Number of events
				Angina	Angiographic CAD	Prior MI					
Blankenberg 2006[43] (HOPE)	3199	65.4	23.2	–	100	–	2.7	N	4.5	CVD	501
Sinning 2006[59] (Atherogene)	1806	61.7	21.3	100	100	47.5	2.8	LPE	3.5	CVD	131
Thompson 1995[60] (ECAT)	2806	53.8	14.8	37.0	75.8	44.3	1.6	N	2	CHD	106
Falcone 2006[61] (–)	1014	64.6	27.2	82.9	100	44.9	0.6	–	2.7	CVD	105
Lubos 2006[62] (Atherogene)	1945	61.2	21.1	–	100	37.5	3.2	LPE	2.6	CVD	75
Wolk 2004[63] (–)	382	62.0	30.0	–	100	20	1.1	LPE	4	CVD	44
Haverkate 1997[64] (ECAT)	743	56	14.1	100	–	42	1.7	MEIA	2	CHD	29
Soeki 1999[65] (–)	106	62.3	25.5	–	–	35.8	2.4	LXAG	4.17	CHD	11
Anderson 2000[43] (–)	1002	64.9	22.7	–	100	–	23.4	FP	3.0	ACM	118
Horne 2000[66] (–)	172	63	29	45	100	23	22	FP	3	ACM	–
Chan 2003[44] (–)	937	69.5	31.1	–	100	28.4	4.0	–	1	ACM	149
Blankenberg 2003[67] (Atherogene)	771	61.7	23.3	70.5	100	48.7	–	LPE	4.1	CVD	97
Blankenberg 2002[68] (Atherogene)	1229	61.8	25.5	65.8	100	47.0	4.0	LPE	3.9	CVD	95
Inaguma 2007[45] (–)	790	67.7	27.1	–	–	64.1	3.2	–	2.31	CVD	110
Schaan 2007[69] (–)	123	58.2	48.9	–	37.8	100	5.8	N	2.27	CHD	–
Zhu 2001[70] (–)	890	65.3	22.9	–	100	–	23.4	FP	3	ACM	167
Ndrepepa 2006[71] (–)	507	69.1	33.9	–	100	45.6	7.8	T	4	ACM	103
Otsuka 2002[72] (–)	363	65.3	29.5	–	100	27.5	3.9	LXAG	0.54	CVD	89
Bickel 2002[73] (Atherogene)	791	61.9	24.7	–	100	49.1	14	LPE	2.9	CHD	88
Saleh 2005[74] (–)	891	65	32	58	100	39	2.3	N	2.6	ACM	75
Brilakis 2005[75](–)	466	60.1	38	–	75.8	15	2.9	T	4	ACM	61
Chirinos 2005a[76] (–)	160	62.1	0	–	81.9	–	–	AUTO	4.4	ACM	37
Bogaty 2001[77] (–)	100	57.6	10	–	100	50	4.4	N	4	Morbidity	23
Chirinos 2005[78] (–)	122	63.9	0	–	100	39	0.7	N	3	ACM	–
Qi 2003a[79] (–)	134	64.1	19.4	48.5	100	34.4	3.3	EIA	1	CHD	32
Qi 2003b[80] (–)	121	64.1	21.5	43.8	100	30.6	3.4	EIA	0.08	ACM	16
Aguilar 2006[46] (WIZARD)	3319	62	18.3	–	–	100	2.6	N	3.08	ACM	825
Garcia-Moll 2000[81] (–)	911	63.1	35.9	100	23.9	31.7	4.01	–	1.6	CVD	89

Crude annual risk	Adjustments: Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes	Comparison group	RR	95% CI
3.48	●	●	○	●	○	●	Continuous (per SD)	1.1	0.99 to 1.23
2.07	●	●	●	●	●	●	Continuous (per SD)	1.13	1.0 to 1.26
1.89	●	●	●	●	●	●	Continuous (per SD)	1.24	1.00 to 1.55
3.84	●	●	○	○	○	○	Continuous (per SD)	1.50	1.21 to 1.69
1.48	●	●	●	●	●	●	Continuous (per SD)	1.80	154 to 2.2
2.88	Crude						Continuous (per SD)	1.39	0.84 to 1.05
1.95	●	○	○	○	○	○	Continuous (per SD)	1.5	1.01 to 2.18
2.49	●	●	○	○	○	○	Continuous (per SD)	1.55	1.08 to 2.23
3.93	●	○	○	●	○	●	Continuous (per tertile)	1.42	0.80 to 1.12
–	–	–	–	–	–	–	Continuous (per tertile)	0.97	–
15.9	○	●	●	○	○	●	Continuous (per quartile)	1.32	1.12 to 1.56
3.07	●	●	●	●	●	●	Continuous (per quartile)	0.8	0.6 to 1.1
1.88	●	○	○	●	○	●	Continuous (per quartile)	0.94	0.70 to 1.25
6.03	●	●	○	○	○	○	Continuous (per mg/dl)	1.05	1.02 to 1.08
–	●	○	○	○	○	○	Continuous (per mg/dl)	1.059	1.00 to 1.12
6.25	●	●	●	●	○	●	Continuous (per mg/dl)	1.08	1.03 to 1.14
5.08	●	○	○	○	○	○	Continuous (per 5-mg/l increase)	1.04	1.00 to 1.08
45.4	–	–	–	–	–	–	Continuous (per mg/dl)	1.14	0.82 to 1.58
3.84	●	●	●	●	●	●	Continuous (per mg/dl)	1.8	1.14 to 2.83
3.23	●	○	○	○	○	●	Continuous (per mg/l)	1.04	0.99 to 1.09
3.27	●	●	●	●	○	○	Continuous (per 1.32mg/dl)	1.34	1.05 to 1.72
5.26	Crude						Continuous (per mg/dl)	1.15	1.00 to 1.33
5.75	○	○	○	●	○	○	Continuous (per mg/dl)	5.4	1.9 to 17.2
–	●	●	○	○	○	○	Continuous (per mg/dl)	1.26	1.02 to 1.55
23.9	–	–	–	–	–	–	Continuous (per unit increase)	2.03	1.13 to 2.05
165.3	–	–	–	–	–	–	Continuous (per unit increase)	1.06	0.80 to 1.18
8.07	●	●	●	●	●	●	Continuous (log10 mg/l)	1.52	1.30 to 1.76
6.11	●	●	○	○	○	○	Continuous (log10)	1.68	1.04 to 2.72

continued

TABLE 4 *Systematic review of 109 study reports reporting the effect of CRP on prognosis among patients with stable coronary disease (continued)*

Author/publication year (study name)	Number of patients	Age (years)	% Women	Baseline coronary morbidity (%)			CRP mean (mg/l)	Assay type	Follow-up (years)	Event combination	Number of events
				Angina	Angiographic CAD	Prior MI					
Blankenberg 2001[82] (Atherogene)	1240	61.9	24.7	–	100	49.1	5.0	LPE	2.7	CHD	88
Minoretti 2006[83] (–)	799	64.9	25.6	100	100	46.3	0.5	–	2.7	CVD	69
Arroyo-Espliguero 2004[84] (–)	700	63	25.0	100	–	39	2.3	–	1.0	CHD	68
Susen 2005[85] (–)	488	61.0	22.0	69.0	100	19.0	2.6	N	1.24	CHD	44
Dai 2007[86] (–)	568	62.5	33.8	100	100	–	2.0	N	1.85	CVD	61
Dai 2008[87] (–)	345	64.6	26.7	–	100	15	4.2	N	3	CHD	56
Bogaty 2008[88] (–)	1210	62	25	37	–	28	4.97	N	1	ACM	142
Haim 2007[89] (BIP)	2979	60	8.6	57.3	–	78	4.96	CL	6.2	CHD	–
Artieda 2007[90] (–)	132	55.2	0	100	72.7	0	0.5	N	3.98	CVD	33
West 2008[91] (LIPID)	500	63	15	–	100	–	–	LPE	2.5	CVD	250
Palmerini 2007[92] (Bologna Registry)	108	69.1	23	28.7	100	32.5	–	N	0.75	ACM	11
Niccoli 2007[93] (–)	40	61	15	35	–	–	2.7	N	0.5	ACM	14
Arroyo-Espliguero 2008[94] (–)	790	63.1	29.5	100	100	31	–	LPE	1	CHD	71
Papa 2008[95] (–)	422	64	19.9	–	100	–	–	FP	3	CHD	13
Inoue 2008[96] (–)	158	63	28	53	82.9	29.7	0.6	N	7	CVD	56
Shlipak 2008[97] (Heart and Soul)	979	67	18	–	100	53.7	–	T	3.7	CHD	142
Espinola-Klein 2007[98] (–)	694	62.4	27.4	–	92.1	43.3	4.8	LPE	6.5	CVD	75
Huang 2008[47] (–)	205	68	11.5	–	62.9	0	2.3	N	4	Morbidity	84
Inoue 2007[99] (–)	149	63	29	53.7	83.2	29.5	2.1	LPE	7	CVD	58
Marcinkowski 2007[100] (–)	100	58.3	22.4	–	–	0	4.4	N	1.48	CHD	15
Fang 2007[101] (–)	258	58.7	36.8	26.7	100	–	1.9	–	1.01	CHD	102
Khor 2004[102] (Intermountain Heart Study)	2254	66	23.8	–	100	20	13.4	FP	3.1	ACM	570
Zebrack 2002a[103] (Intermountain)	1848	65.5	22.6	–	100	–	12.2	FP	2.1	CHD	235
Zebrack 2003[104] (Intermountain)	1484	64.0	33.0	72.0	76.0	–	13	FP	3	ACM	205
Crea 2002[50] (4S)	258	61.9	10.9	–	–	–	–	N	5	ACM	129
Zebrack 2002b[105] (Intermountain)	285	66.3	23.0	100	100	–	13.1	FP	2.8	ACM	117
Schnabel 2005[106] (Atherogene)	1872	61	20.9	–	100	–	3.14	LPE	2.6	CVD	114

Crude annual risk	Adjustments						Comparison group		RR	95% CI
	Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes				
2.63	–	–	–	–	–	–	Continuous (log mg/dl)		1.34	1.09 to 1.9
3.20	●	●	●	●	●	●	Continuous (log transformed mg/dl)		1.42	1.12 to 1.81
9.71	●	●	○	○	○	●	Continuous (log mg/l)		1.9	1.1 to 3.5
7.27	●	●	●	●	●	○	Continuous (per unit by log transformation)		2.05	1.21 to 3.47
5.8	●	●	●	●	○	○	Continuous (log transformed)		1.51	1.28 to 1.77
5.41	●	●	●	●	○	●	Continuous (–)		1.99	1.11 to 3.56
11.74	●	○	○	○	○	●	Continuous (log transformed)		1.12	0.93 to 1.34
–	●	●	●	●	●	●	Continuous (per natural log unit)		1.28	1.04 to 1.59
6.28	●	○	●	●	○	●	Continuous (log mg/dl)		2.17	0.87 to 5.43
20	●	○	○	○	○	●	–	–	0.9	0.40 to 1.50
13.58	●	○	○	○	○	●	< 1.22	≥ 1.22	5.87	1.67 to 20.62
70	○	○	○	○	○	○	≤ 3	> 3	10.9	1.0 to 119
8.99	●	○	○	○	○	○	< Median (median not specified)	> Median (median not specified)	1.9	1.1 to 3.2
1.03	–	–	–	–	–	–	≤ 0.8	> 0.8	10.15	1.26 to 81.79
5.06	–	–	–	–	–	–	–	–	1.45	0.88 to 2.77
3.92	●	●	●	○	●	●	≤ 4.93	> 4.93	1.82	1.24 to 2.67
1.66	●	●	●	●	●	●	< 4.8	≥ 4.8	1.2	0.8 to 2.2
10.24	●	○	●	○	●	●	< 1.1	≥ 1.1	1.66	1.04 to 2.64
5.56	○	○	●	○	○	○	–	–	2.28	0.92 to 6.81
10.14	Crude						≤ 1.83	> 1.83	14.39	1.94 to 106.7
39.14	–	–	–	–	–	–	< 2.64	> 2.64	2	0.9 to 6.7
8.16	●	○	●	●	●	●	< 1.2	≥ 1.2	1.6	1.3 to 1.9
6.01	●	●	●	●	○	●	< 1.0	≥ 1.0	1.9	1.3 to 2.8
4.6	–	–	–	–	–	–	< 1.0	≥ 1.0	1.9	1.2 to 2.8
10.00	○	○	●	●	○	○	< 4.1	≥ 4.1	2.51	1.3 to 4.8
14.7	●	●	●	●	○	●	< 1.15	≥ 1.15	2.3	1.1 to 4.6
2.34	●	●	●	●	●	●	≤ 5.44	> 5.44	1.51	0.98 to 2.2

continued

TABLE 4 *Systematic review of 109 study reports reporting the effect of CRP on prognosis among patients with stable coronary disease (continued)*

Author/publication year (study name)	Number of patients	Age (years)	% Women	Baseline coronary morbidity (%)			CRP mean (mg/l)	Assay type	Follow-up (years)	Event combination	Number of events
				Angina	Angiographic CAD	Prior MI					
Schnabel 2005a[107] (Atherogene)	639	61.7	27.8	79.3	86.8	–	3.8	LPE	7.1	CVD	112
Kangasniemi 2006[108] (–)	843	60.6	21.2	–	–	9.5	–	T	12	CHD	119
Muhlestein 2000[109] (Intermountain)	985	65.8	23.0	44.4	100	23.0	23.0	FP	2.7	ACM	110
Liu 2003[110] (–)	247	62	27	–	100	20	37.0	–	1.6	CHD	87
Dibra 2003[111] (–)	1152	66.1	26.6	100	100	31.5	–	–	1	ACM	86
Ndrepepa 2006b[112] (–)	989	66.3	21.0	–	100	39.9	1.2	T	3.6	ACM	85
Blankenberg 2001a[113] (Atherogene)	983	62.2	26.4	78.4	100	51.8	–	LPE	3.1	CHD	70
de Winter 2002[114] (–)	501	61.8	26.1	14.2	100	–	3.48	N	1.16	CHD	69
Ijsselmuiden 2003[115] (–)	400	60.7	19	67.5	100	38.0	–	–	0.5	CVD	64
de Winter 2003[116] (–)	1458	61.5	27.6	–	100	–	6.6	N	1.16	CHD	55
Wu 2005[117] (–)	150	67.8	9.3	100	100	19.7	–	–	1.5	CHD	48
Janoskuti 2005[118] (–)	387	59	26.9	–	–	48.1	3.89	N	5.06	ACM	41
Veselka 2005[119] (–)	300	63.5	31.0	100	99.5	57.0	–	N	0.5	ACM	40
Low 2004[120] (–)	347	58	34.6	69.2	–	16.5	–	IPA	2.5	CVD	37
Gach 2007[121] (–)	89	60.2	24.7	100	100	25.8	3.4	N	6.6	CHD	36
Leu 2004[122] (–)	75	68.1	12	100	100	25.3	1.02	ELISA	3.33	CVD	33
de Winter 2004[123] (–)	1172	62.0	33.0	78.0	100	46.5	6.4	N	1.16	ACM	32
Ikonomidis 2005[124] (–)	100	54	16	100	100	52	–	N	6	CHD	31
Karha 2006[125] (–)	652	65.4	32.4	–	–	–	3.3	T	1	ACM	31
Kinjo 2003[126] (OACIS)	1307	63.4	22.0	–	–	12.5	1.3	N	1.4	CVD	29
Kwaijtaal 2005[127] (EXIT)	213	53.6	21.8	9.9	100	26.8	3.7	ELISA	2	CHD	25
Zairis 2004[128] (Generation)	474	59.3	18.1	22.6	100	8.6	7.0	N	3	CHD	25
Zairis 2002a[129] (Generation)	483	59.3	18.0	22.2	100	8.7	5.8	T	3	CHD	20
Aytekin 2003[130] (–)	116	56.5	22.4	34.5	100	14.7	–	–	0.5	CHD	19
Sargento 2002[131](–)	64	58	7.8	–	–	100	–	–	1.67	ACM	19
Palmerini 2005[132] (–)	83	72.0	40.0	25.0	100	33.0	–	N	0.75	ACM	18
Kinjo 2005[133] (OACIS)	1191	62.4	25.9	–	–	15.4	9.2	N	1	ACM	14
Lu 2003[134] (–)	153	71.0	13.1	100	100	30.1	–	N	1.33	CVD	14
Biancari 2003[135] (–)	764	64	24.9	–	100	43.7	–	–	0.014[a]	ACM	13

Crude annual risk	Adjustments						Comparison group		RR	95% CI
	Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes				
2.47	●	●	●	○	○	●	< 10.1	≥ 10.1	1.27	0.80 to 2.01
1.18	●	○	○	○	○	●	< 1.0	≥ 1.0	1.65	0.95 to 2.88
4.14	●	●	●	●	○	●	< 1.2	< 1.2	2.40	1.4 to 4.1
22.01	Crude						≤ 7.5	> 7.5	1.8	1.2 to 3.8
7.47	●	○	●	●	○	●	≤ 5	> 5	1.8	1.1 to 2.9
2.39	●	●	●	●	●	●	< 1.2	≥ 1.2	2.3	1.40 to 3.78
2.30	●	●	●	●	●	●	< 9.6	≥ 9.6	3.10	1.2 to 8.1
11.87	–	–	–	–	–	–	≤ 3	> 3	2.54	1.44 to 4.47
32.0	–	–	–	–	–	–	≤ 10.0	> 10.0	1.94	1.0 to 3.7
3.25	●	●	●	○	○	●	≤ 3	> 3	3.60	1.8 to 7.2
21.3	○	○	○	○	○	○	< 1.0	≥ 1.0	1.91	0.98 to 3.74
2.09	●	●	●	○	●	○	< 6.24	≥ 6.24	5.21	1.76 to 5.43
26.7	●	○	●	●	○	●	≤ 3.0	> 3.0	1.00	0.51 to 1.95
4.27	○	○	○	○	○	○	< 1.0	≥ 1.0	3.47	1.76 to 6.84
6.13	–	–	–	–	–	–	< 3.0	≥ 3.0	1.05	0.09 to 1.02
13.2	●	●	●	●	○	○	≤ 1.0	> 1.0	2.78	1.21 to 6.41
2.35	–	–	–	–	–	–	≤ 3	> 3	2.02	0.91 to 4.48
5.17	●	○	●	○	○	○	< 2.4	≥ 2.5	6.24	1.74 to 22.42
4.75	●	●	○	○	○	●	< 3.3	≥ 3.3	6.5	2.2 to 19.3
1.58	●	●	●	●	●	●	< 0.38	≥ 0.38	9.58	1.17 to 78.4
5.34	●	●	●	○	●	●	≤ 3.0	> 3.0	2.50	1.1 to 5.7
1.76	–	–	–	–	–	–	< 0.68	≥ 0.68	4.0	1.8 to 8.9
1.38	–	–	–	–	–	–	< 0.68	≥ 0.68	3.16	1.25 to 7.98
32.8	Crude						≤ 0.5	> 0.5	–	–
17.8	–	–	–	–	–	–	< 97%	≥ 97%	9	–
28.9	●	○	○	○	○	●	< 10.36	≥ 10.36	11.5	2.5 to 52
1.18	●	●	●	●	●	●	< 2.9	≥ 2.9	1.28	0.21 to 7.23
6.88	Crude						≤ 0.5	> 0.5	0.77	0.17 to 3.47
121.5	–	–	–	–	–	–	< 1.00	≥ 1.00	6.97	1.45 to 33.42

continued

TABLE 4 *Systematic review of 109 study reports reporting the effect of CRP on prognosis among patients with stable coronary disease (continued)*

Author/publication year (study name)	Number of patients	Age (years)	% Women	Baseline coronary morbidity (%)			CRP mean (mg/l)	Assay type	Follow-up (years)	Event combination	Number of events
				Angina	Angiographic CAD	Prior MI					
Gaspardone 1998[136] (–)	76	58.7	14.5	100	100	–	2.3	T	1	CHD	13
van der Harst 2006[137] (QUO VADIS)	87	62.9	14.9	7.4	100	41.4	1.9	ELISA	7.6	CVD	11
Huang 2006[138] (–)	185	69.4	47	–	100	–	–	ELISA	3	CVD	10
Milazzo 1999[139] (–)	86	64.7	14.3	17.4	100	47.7	–	N	3.2	ACM	4
Palazzuoli 2006[140] (–)	208	70.6	33.7	21.2	–	31.7	–	N	1	Morbidity	–
Fathi 2005[48] (–)	4522	65	29.1	–	100	42.4	–	T	1.7	ACM	332
Muhlestein2004[141] (Intermountain Heart Study)	2924	65.0	24.0	43.0	100	26.0	–	–	2.4	ACM	277
Sabatine 2007[142] (PEACE)	3771	63.7	18.9	–	–	56.1	1.7	T	4.8	CVD	131
Saleh 2005[143] (–)	891	63.6	27.0	68	100	43	2.25	N	2.6	ACM	76
Rahel 2003[144] (–)	600	61.6	31.3	–	100	–	4.5	ELISA	0.67	ACM	54
Speidl 2002[145] (–)	119	39.3	23.5	–	100	78.2	–	–	4.5	CHD	30
Kubica 2005[146] (–)	80	56.0	27.5	87.5	100	50	1.2	N	1	CHD	28
Park 2007[147] (–)	1650	60.3	28.7	53.7	100	8.0	–	LPE	1	CHD	23
Grander 2004[148] (–)	81	61.6	30.9	–	100	–	4.3	–	0.57	CVD	17
Morrow 2006[51] (AtoZ)	3817	60.7	24.1	–	–	39	2.4	T	2	CVD	–
Lee 2006[149] (–)	1050	60.8	27.1	–	–	–	–	CL	8.5	ACM	231
Rothenbacher 2006[150] (–)	1051	58.5	15.1	–	100	58.2	–	LPE	4.1	CVD	95
Kip 2005[151] (WISE)	580	58	100	–	61	–	2.9	–	4.7	CVD	92
Chew 2001b[149] (–)	727	65.9	28.6	–	100	30.9	5.0	–	0.082	ACM	71
Harb 2002[152] (THROMBO)	957	–	24.6	32.2	–	100	–	–	2.17	CHD	69
Hoffmeister 2005[153] (–)	300	57.9	14.4	–	100	61.3	–	N	3.2	CVD	60
Retterstol 2002[154] (–)	247	52.7	21.9	–	–	100	2.4	LPE	10	CHD	36
Schnabel 2005b[155] (Atherogene)	570	–	–	100	100	–	–	LPE	2	CVD	31
Patti 2002a[156] (–)	73	6.0	15.0	51.0	100	55.0	2.5	N	1.5	CHD	12
Krzewina 2003[157] (–)	154	57.1	25.3	89.6	–	41	–	N	1	CHD	31

AUTO, autoanalyser; CAD, coronary artery disease; CL, chemiluminescence; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; FP, fluorescence polarisation; IPA, infrared particle assay; LPE, latex particle enhanced; LXAG, latex agglutination; MEIA, microparticle enzyme immunoassay; MI, myocardial infarction; N, nephelometry; RR, relative risk; T, turbidimetric; TC, total cholesterol; TG, triglycerides.

Crude annual risk	Adjustments: Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes	Comparison group				RR	95% CI
17.11	Crude						≤0.5	>0.5			–	–
1.66	●	●	●	●	●	●	≤1.9	>1.9			4.3	0.75 to 24.55
1.80	○	○	●	●	●	○	≤3.0	>3.0			4.6	2.51 to 6.47
1.45	Crude						<3.0	≥3.0			–	–
–	●	●	●	●	●	●	≤5.0	>5.0			1.4	1.14 to 2.08
4.32	●	●	●	○	●	●	<1.0	1.0–3.0	>3.0		1.85	1.13 to 3.03
3.95	–	–	–	–	–	–	<1.2	1.2–1.7	>1.7		2.30	1.6 to 3.2
0.724	●	●	●	●	●	●	<1.0	1.0–3.0	>3.0		1.67	1.00 to 2.78
3.28	●	●	○	○	○	●	≤1.0	1.1–3.1	>3.2		1.41	0.77 to 2.60
13.4	●	○	●	○	○	○	–	–	–		1.39	0.62 to 3.10
5.60	●	●	●	●	●	●	<1.59	1.69–5.51	>5.58		2.7	0.94 to 7.75
35.0	–	–	–	–	–	–	<0.85	0.85–2.0	>2.00		4.17	1.27 to 13.65
1.39	●	○	●	○	○	○	<1.2	1.2–3.1	>3.1		9.94	1.28 to 77.14
36.82	○	○	○	○	○	○	0.7–4.8	0.23–0.69	≤0.22		0.045	0.004 to 0.522
–	●	●	●	●	○	●	<1.0	1.0–3.0	>3.0		3.9	1.8 to 5.6
2.59	●	●	●	●	●	●	≤0.88	0.88–1.97	1.97–5.16	≥5.16	2.12	1.38 to 3.27
2.20	●	●	●	●	○	●	≤1.24	1.25–3.51	3.52–8.61	>8.61	1.6	0.91 to 2.83
3.37	●	○	●	○	○	●	<0.17	0.17–0.36	0.37–0.83	≥0.84	1.92	1.04 to 3.54
119.1	–	–	–	–	–	–	<0.16	0.16–0.40	0.41–1.10	>1.10	3.68	1.51 to 8.99
3.32	○	●	○	○	○	●	≤0.09	0.10–0.23	0.24–0.58	>0.59	1.22	0.58 to 2.55
6.25	●	●	●	●	●	●	<0.69	0.70–1.27	1.28–2.84	>2.85	1.3	0.6 to 2.8
1.46	●	○	●	●	○	○	≤1.19	1.20–2.36	2.37–4.19	≥4.20	4.09	1.20 to 3.93
2.72	●	●	●	●	●	●	–	–	–	>6.1	2.40	1.1 to 4.6
11.0	Crude						–	–	–	–	5.28	0.68 to 40.92
20.1	–	–	–	–	–	–	Unclear				2.10	–

a Estimated length of hospital stay for coronary event is 5 days = 0/014 years.

TABLE 5 *Systematic review of studies reporting eGFR and prognosis of stable coronary disease*

Author/publication year (study name)	Number of patients	Age (years)	% Women	Baseline coronary morbidity (%)			Creatinine mean (ml/min)	Measurement type	Follow-up (years)	Event combination
				Angina	Angiographic CAD	Prior MI				
Inaguma 2007[45] (–)	790	67.7	27.1	–	–	64.1	66.1	eGFR-MD	2.31	CVD
Gibson 2007[158] (–)	1938	65	23	–	–	49	63.9	Autoanalyser	3.6	CHD
Deckers 2006[159] (EUROPA)	12,218	60	15	–	25	65	85	eGFR-CG	4.1	CHD
Lipsic 2005[160] (Intervention Cardiology Risk Stratification Study)	143	61.5	28.7	100	100	32.9	79.51	–	3.7	CVD
Reinecke 2003[161] (–)	689	62.6	0	–	100	30.2	79.48	eGFR-CG	2	ACM
Hillis 2006[162] (–)	2067	66	23	100	100	50	64.1	eGFR-MD	2.3	ACM
Reddan 2003[163] (–)	4584	63	33.5	–	100	50.8	–	eGFR-CG	5	ACM
Tang 2007[164] (–)	1472	61.6	28.2	26	100	33.3	–	–	1	ACM
Vittinghoff 2003[165] (HERS)	2763	66.6	100	26.4	100	–	–	eGFR-CG	4.1	CHD
Zebrack 2003[104] (–)	1484	64	33	72	76	–	73	eGFR-MD	3	ACM
de Winter 2004[123] (–)	1172	62	32.9	78	100	46.5	–	eGFR-CG	1.16	ACM
Zakeri 2005[166] (–)	4403	63.4	21	–	100	50.6	–	eGFR-CG	2.4	ACM
Shlipak 2001[167] (HERS)	2763	66.5	100	–	100	51.9	–	eGFR-CG	4.1	CHD
Rothenbacher 2006[150] (–)	1051	58.5	15.1	–	100	58.3	–	eGFR-CG	4.1	CVD
Almquist 2006[168] (APSIS)	808	59.4	31	100	–	16	77.6	eGFR-CG	3.4	CVD
Shlipak 2004[169] (HERS II)	2266	71.0	100	–	100	–	–	eGFR-MD	6.8	CHD
Solomon 2006[170] (PEACE/Placebo)	4127	63.8	18	–	70.5	54.9	77.6	eGFR-MD	4.8	CVD
Fathi 2005[148] (–)	4522	65	29.1	–	100	42.4	77	eGFR-MD	1.7	ACM
Chen 2006[171] (ACRE)	1144	60.7	0	–	80.5	–	–	eGFR-MD	7	ACM
Chen 2006[171] (ACRE)	465	60.7	100	–	55.1	–	–	eGFR-MD	7	ACM
Dai 2008[87] (–)	345	64.6	26.7	–	100	15	70.9	eGFR-MD	3	CHD

CAD, coronary artery diseases; eGFR-CG, estimated glomerular filtration rate calculated with the Cockcroft–Gault formula; eGFR-MD, estimated glomerular filtration rate calculated with the Modification of Diet Renal Disease equation; MI, myocardial infarction; RR, relative risk; TC, total cholesterol; TG, triglycerides.

Number of events	Crude annual risk (%)	Adjustments						Comparison group				RR	95% CI
		Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes						
110	6.03	●	●	○	○	○	○	Continuous (per ml/min)				0.97	0.96 to 0.98
–	–	●	●	●	○	○	●	Continuous (per ml/min)				0.97	-
1091	2.18	●	●	●	●	○	●	Continuous (per ml/min)				1.01	1.01 to 1.02
19	3.59	○	○	○	○	○	○	Continuous (per ml/min)				1.0	0.98 to 1.02
62	4.50	○	○	○	○	○	○	Continuous (per mg/dl)				1.76	1.40 to 2.21
158	3.32	●	●	○	○	○	●	Continuous (per ml/min per 1.73 m^3)				0.98	0.97 to 0.99
–	–	●	○	○	○	○	●	Continuous (per 10 ml/min decline)				1.14	1.09 to 1.20
141	9.58	●	●	●	○	●	●	Continuous				0.01	0.99 to 1.00
361	3.19	●	○	●	●	●	●	>40	≤40			1.56	1.16 to 2.11
159	3.57	○	○	○	○	○	○	≥60	<60			3	2.1 to 4.2
32	2.35	○	○	○	○	○	○	>51	≤51			3.06	1.22 to 7.64
–	–	–	–	–	–	–	–	≥60	<60			1.56	1.14 to 2.13
127	1.12	●	●	●	●	●	●	>60	40–60	<40		2.56	1.5 to 4.3
95	2.20	●	●	●	●	○	●	≥90	60–90	<60		1.39	0.59 to 3.23
69	2.51	●	●	○	○	○	●	≥90	60–89	<60		1.99	0.87 to 4.56
–	–	●	●	○	●	○	●	≥60	40–60	<40		2.97	1.49 to 5.93
352	1.78	●	●	○	○	○	●	>75	60–74.9	45–59.9	<45.0	2.8	1.70 to 4.60
332	4.32	●	●	●	○	●	●	≥90	60–89	30–59	≤29	3.65	2.24 to 5.94
280	3.50	●	●	●	○	●	●	≥60	45–59.9	30.0–44.9	<30	4.77	2.95 to 7.70
102	3.13	●	●	●	○	●	●	≥60	45–59.9	30.0–44.9	<30	10.4	3.97 to 27.4
56	5.41	●	●	●	●	○	●	–				0.99	0.98 to 1.01

TABLE 6 *Systematic review of studies reporting serum creatinine concentration in relation to the prognosis of stable coronary disease*

Author/publication year (study name)	Number of patients	Age (years)	% Women	Baseline coronary morbidity (%)			Creatinine mean (μmol/l)	Measurement type	Follow-up (years)	Event combination	Number of events
				Angina	Angiographic CAD	Prior MI					
Dai 2008[87] (–)	345	64.6	26.7	–	100	15	1.3 mg/dl	SCr	3	CHD	56
Assmus 2007[172] (TOPCARE-CHD trial)	121	62	13	–	100	100	1.17 mg/dl	SCr	1.58	ACM	14
Falcone 2006[61] (–)	1014	64.6	27.2	82.9	100	44.9	79.6	SCr	2.7	CVD	105
Shah 2008[173] (–)	2886	66.2	–	–	100	31.8	1.3 mg/dl	–	5.025	ACM	961
Ruilope 2007[174] (ACTION)	7665	63.4	20.5	100	–	51	1.09 mg/dl	–	4.94	CVD	784
Clayton 2005[17] (ACTION)	7311	63.5	20.6	100	70	50.8	96.4	SCr	3	ACM	569
Exaire 2006[175] (REPLACE-2)	6002	62	25.6	–	100	8.2	–	SCr	1	ACM	128
Minoretti 2006[83] (–)	799	64.9	25.6	100	100	46.3	79.6	SCr	2.7	CVD	69
Matts 1993[176] (POSCH)	416	50.6	7.7	–	–	100	98.1	SCr	7	CHD	32
Chirinos 2005[78] (–)	122	63.9	0	–	100	39	123.8	SCr	3	ACM	–
Hu 2006[177] (DESIRE)	1280	59.8	24.5	–	100	9.4	132.6	SCr	2.27	ACM	158
Stassano[178] 2006 (–)	175	62.7	22.9	–	100	16.6	106.1	SCr	2	ACM	11
DiMauro 2007[179] (–)	1884	64.5	16.9	–	100	46.6	1.1 mg/dl	SCr	7.5	ACM	117
McKechnie 2004[180] (–)[b]	45,165	63.1	33.9	–	100	34.2	106.1	SCr	0.014[a]	ACM	641
Duffy 2006[181] (–)[b]	1046	62.3	29.3	–	100	23.6	–	–	2.58	ACM	144
Elisheva 2000[182] (ISCAB)[b]	4738	64.7	21.3	–	100	–	–	SCr	0.083	ACM	147
Schnabel 2005[106] (Atherogene)[b]	1872	61	20.9	–	100	–	83.1	–	2.6	CVD	114
Cesena 2004[183] (–)[b]	574	61	27.5	97.4	100	65.9	106.1	SCr	0.47	CHD	107
Van Domburg 2002[184] (–)	832	62.8	24	32	100	26	–	–	5.2	ACM	92
Szczech 2002[185] (BARI)[b]	3608	61.5	26.0	71.2	100	52.0	–	SCr	7	CHD	–

Crude annual risk (%)	Adjustments: Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes	Comparison group		RR	95% CI
5.41	Crude						–		1.17	1.03 to 1.32
7.32	●	○	○	○	○	●	–		4.7	1.8 to 12.1
3.84	○	●	●	○	○	○	Continuous (per SD)		1.04	0.99 to 1.85
6.63	●	○	○	○	●	○	Continuous (per mg/dl)		0.841	–
2.07	●	●	●	○	○	●	Continuous (per mg/dl)		1.75	1.27 to 2.40
2.59	●	●	○	○	○	○	Continuous (per mg/dl)		1.09	1.04 to 1.14
2.13	–	–	–	–	–	–	Continuous (per mg/dl)		1.66	1.23 to 2.24
3.20	●	●	●	●	●	●	Continuous (per mg/dl)		1.01	0.98 to 1.31
1.10	–	–	–	–	–	–	Continuous (per mg/dl)		1.59	–
–	○	○	○	○	○	○	Continuous (per mg/dl)		1.37	0.94 to 1.99
5.34	●	●	○	●	○	○	Continuous (per mg/l)		1.32	0.90 to 1.67
3.14	–	–	–	–	–	–	Continuous (per unit increase by log transformation)		1.48	1.03 to 2.11
0.83	–	–	–	–	–	–	< 2.0	≥ 2.0	4.1	2.6 to 6.4
101.3	●	○	○	○	○	●	≤ 132.6	> 132.6	2.14	1.75 to 2.63
5.34	●	○	○	○	○	○	≤ 132.6	> 132.6	1.26	1.16 to 1.37
3.74	●	●	○	○	○	●	< 123.8	≥ 123.8	2.28	–
2.34	●	●	●	●	●	●	< 90.2	≥ 90.2	1.8	1.1 to 2.5
3.97	○	○	○	○	○	○	< 132.6	≥ 132.6	1.60	1.0 to 2.8
2.13	●	●	○	●	○	●	≤ 150	> 150	2.8	1.4 to 5.5
–	●	●	●	○	●	●	≤ 132.6	> 132.6	3.00	1.87 to 4.82

continued

TABLE 6 *Systematic review of studies reporting serum creatinine concentration in relation to the prognosis of stable coronary disease (continued)*

Author/publication year (study name)	Number of patients	Age (years)	% Women	Baseline coronary morbidity (%)			Creatinine mean (μmol/l)	Measurement type	Follow-up (years)	Event combination	Number of events
				Angina	Angiographic CAD	Prior MI					
Yamamuro 2000[186] (–)[b]	739	74.0	20.8	–	100	58.6	118.5Ψ	SCr	4.25	ACM	–
Zakeri 2005[166] (–)	4403	63.4	21	–	100	50.6	–	–	2.4	ACM	–
Weerasinghe 2001[187] (–)	1197	–	16.2	–	100	56.6	98.0	SCr	0.025	ACM	45
Wattanakit 2005[188] (ARIC)[b]	766	57.1	24.7	0	–	86.0	–	SCr	8.7	CVD	313
Schnabel 2005A[107] (Atherogene)[b]	639	61.7	27.8	86.8	–	27.8	97.2	SCr	7.1	CVD	112
Nygard 1997[189] (–)	578	62	18.6	–	100	57.4	–	SCr	4.6	ACM	64
Kaplan 2002[190] (–)	2677	63.8	37.9	40.1	–	100	110.6	SCr	3.4	CHD	445
Matts 1993[176] (POSCH)[b]	416	50.6	7.7	–	–	100	98.1	SCr	7	CHD	32
Reinecke 2003[161] (–)	689	62.6	0	–	100	30.2	79.48 (5 SDs) (23.4)	eGFR-CG	2	ACM	62

CAD, coronary artery diseases; eGFR-CG, estimated glomerular filtration rate calculated with the Cockcroft–Gault formula; MI, myocardial infarction; RR, relative risk; SCr, serum creatinine concentration; TC, total cholesterol; TG, triglycerides.

Crude annual risk (%)	Adjustments: Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes	Comparison group				RR	95% CI
–	○	○	○	○	○	○	≤ 141.4	> 141.4			1.73	1.14 to 2.61
–	–	–	–	–	–	–	< 130	≥ 130			1.65	1.25 to 2.18
150.4	●	●	●	●	○	●	< 130	130–149	≥ 150		7	to 1
4.70	●	●	●	●	○	●	< 88.4	88.4–97.2	106.1–114.9	≥ 123.8	1.66	1.1 to 2.6
2.47	●	●	●	●	○	●	< 83.1	83.1–91.9	91.9–105.2	> 105.2	2.48	1.22 to 5.02
2.41	●	●	●	●	○	●	< 80	80–119	120–149	≥ 150	2.55	0.82 to 7.92
4.89	●	●	●	●	●	●	94.4–104.3	< 84	84–94.3	104.4–120.5	> 120.5	1.77	1.31 to 2.38
1.10	–	–	–	–	–	–	≤ 0.9	88.4	97.2	106.1	≥ 114.9	1.54	–
4.50	○	○	○	○	○	○	Continuous (per mg/dl)	1.76	1.40–2.21				

a Estimated average length of stay for coronary event admission is 5 days.
b Paper reported serum creatinine in mg/dl. Reported value multiplied by 88.4 to convert to μmol/l.

TABLE 7 *Summary of meta-analyses of five routine and eight novel circulating biomarkers*

	Number of studies in systematic review	Number of studies in meta-analysis[a]	Number of patients	Number of events[b]	Comparison	Relative risk (95% CI)
Widely performed in routine clinical care						
eGFR	15	12	31,839	1639	Chronic kidney disease < 60 ml/min	2.00 (1.65 to 2.42)
Fasting glucose	28	11	63,957	14716	Diabetes > 7 mmol/l	1.74 (1.15 to 2.63)
Haemoglobin	15	4	52,113	1741	Anaemia (haemoglobin < 13g/dl)	2.92 (0.40 to 21.1)
Total cholesterol	47	31	53,129	4441	T3 vs T1	1.30 (1.16 to 1.45)
LDL cholesterol	39	29	33,817	5874	T3 vs T1	1.33 (1.16 to 1.52)
Novel biomarkers						
hs-CRP[c]	109	77	56,496	5798	T3 vs T1	1.96 (1.76 to 2.17)
Fibrinogen	40	31	36,739	3692	T3 vs T1	1.59 (1.39 to 1.82)
Lp(a)[c]	20	17	17,602	2322	T3 vs T1	1.24 (1.12 to 1.38)
Apolipoprotein A-I[c]	14	11	15,044	1398	T3 vs T1	0.81 (0.71 to 0.92)
Apolipoprotein B[c]	13	12	16,706	1645	T3 vs T1	1.39 (1.07 to 1.79)
Homocysteine[c]	16	12	6100	817	T3 vs T1	2.06 (1.69 to 2.50)
NT-BNP[c]	20	14	18,326	1620	T3 vs T1	2.93 (2.03 to 4.23)
Il-6	14	9	8200	1148	T3 vs T1	1.63 (1.09 to 2.43)

hs, high sensitivity.
a Fewer studies used in meta-analysis than in systematic review because no CIs were reported, or for eGFR, fasting glucose and haemoglobin only continuous effects were reported.
b A few studies did not give the number of events.
c Currently recommended for measurement according to the European Society of Cardiology Angina guidelines 2006.

Chapter 5
Methods of decision model

Introduction

As outlined in Chapter 2, several analytical steps are required in order to determine the cost-effectiveness of alternative strategies for prioritising patients on the waiting list for CABG. While the results of the systematic review provide the most appropriate basis for estimating the clinical effectiveness of single and combination biomarkers (both routine and novel) in terms of their prognostic value in predicting events among patients with stable coronary disease, this addresses only one element of the overall decision problem. These results do not directly consider the effect of employing biomarkers in terms of their effect on final health outcomes expressed in generic terms (e.g. QALYs gained), subsequent health-care resource utilisation and costs; neither do these results provide a comparison against a range of alternative approaches to prioritisation which may be considered relevant comparators. Hence, in order to address the overall decision problem outlined in Chapter 2, a number of additional steps are subsequently required to determine the cost-effectiveness of alternative prioritisation strategies.

The additional steps comprise the methods and analytical approaches of the decision-analytic model itself, as well as the additional approaches required to integrate the results from the systematic review of circulating biomarkers within this framework. This chapter provides details of the methods, analytical approaches and sources of input data into the decision-analytic model. The chapter also outlines the approaches required to incorporate the results from Chapter 4 within the broader evaluation of cost-effectiveness. The results of the separate analyses, alongside the final estimates of cost-effectiveness, are reported in detail in Chapter 6.

Cost-effectiveness analysis

The cost-effectiveness analysis was undertaken from a UK health service perspective and costs were expressed in UK pounds sterling (GBP) at 2006/7 prices. A lifetime time horizon was employed and health outcomes were estimated in terms of QALYs. Costs and QALYs were discounted by 3.5% per annum.[191]

Prioritisation strategies

There are several ways of formally prioritising patients waiting for revascularisation, of which circulating biomarkers represent one potential approach. It is not possible to establish the cost-effectiveness of using biomarkers without an explicit comparison against other formal approaches to prioritisation that are considered relevant and feasible options which could also be implemented in the NHS. Similarly, the use of any formal approach to prioritising waiting lists for CABG also needs to be evaluated in the context of current NHS practice. That is, any additional costs that may be imposed on the NHS because of the use of novel biomarkers (or any formal approach to prioritising waiting lists) need to be considered in relation both to the additional gains in health outcomes that may subsequently be achieved as well as to other ways in which these resources might be productively used elsewhere within the NHS. It is only through such an explicit comparison that the cost-effectiveness of alternative prioritisation strategies can subsequently be determined.

We identified four general approaches to the prioritisation of patients on a waiting list for CABG. These approaches comprised: (1) no formal prioritisation (routine clinical practice); (2) urgency scores; (3) risk score without the use of biomarkers; and (4) risk score with biomarkers. Within several of the general approaches there also exists a number of alternative approaches that could be considered (e.g. different approaches to evaluating urgency scores, different single and combination biomarkers comprising both novel and routine biomarkers, etc.). Each of these general approaches (and variants therein) represents potentially relevant and separate *strategies* that should be considered as part of an overall evaluation of cost-effectiveness.

While it remains desirable to evaluate all plausible strategies in the context of the decision problem, this also needs to be balanced against the analytical

feasibility and data requirements required to provide robust inputs into such a comprehensive evaluation that would then provide a robust basis for informing NHS policy. This issue is particularly pertinent to the evaluation of alternative strategies that could be considered within the general approach of using risk score approaches with biomarkers. The five routine and eight novel biomarkers considered in Chapter 4 could feasibly be used either singly or in combination with any one or more of the remaining biomarkers. Consequently, there exists a large number of potentially relevant strategies – even with the eight novel biomarkers there are over 40,000 possible combinations that could be considered, and when combined with the five routine biomarkers this increases to 16 factorial. Ultimately, any attempt to comprehensively evaluate all of these strategies is likely to be a relatively futile exercise, the problems of which will also be compounded by the lack of robust clinical data on the majority of these strategies and the potential difficulties that may subsequently be encountered in terms of linking this evidence to the broader decision model itself.

Hence, rather than attempting to be comprehensive in terms of the strategies considered, with particular reference to the biomarker strategies, the decision model evaluates a more restrictive range of strategies. The strategies that were finally selected were chosen on the basis that these were considered to be particularly important questions relevant to existing NHS decision-making in terms of routine biomarkers that are already widespread (e.g. eGFR) and those whose use remains variable (e.g. CRP). A total of seven separate strategies, within the four general approaches, were thus evaluated in detail as part of the decision model. These separate strategies are summarised below.

Strategy 1: No formal prioritisation (routine clinical practice) This strategy reflects how prioritisation is currently undertaken in routine clinical practice. Routine clinical practice will inevitably reflect the variability that exists in different centres in terms of the approaches employed to prioritising patients on a waiting list. This variability will reflect differences in the formal and informal approaches to ordering waiting lists that are currently being applied. This provides an appropriate baseline with which to assess the alternative prioritisation strategies that are based on a more formal and systematic approach to prioritisation.

Strategies 2–3: Urgency scores Within this general approach, formal prioritisation is guided by the use of urgency scores. Explicit urgency scores, where those with the most disabling symptoms and worst prognosis should be prioritised first, have been proposed as a formal approach to the prioritisation of waiting lists. The two particular algorithms considered here are based on the Ontario[31] and New Zealand[168] scoring systems. These algorithms are subsequently evaluated as two separate strategies within the decision model.

Strategy 4: Risk score without biomarkers An alternative to the use of urgency scores based primarily on symptom measures is to consider formal prioritisation approaches guided entirely by the predicted risk of cardiovascular events. Such an approach could be implemented by employing a risk equation based on routinely measured and/or observable risk factors (excluding information based on biomarkers) which can be demonstrated to be predictive of the potential risk of experiencing a cardiovascular event. The use of such an approach would mean that individuals within a cohort of subjects on a waiting list could be stratified according to their individual risk score, with patients predicted to be at a higher absolute risk of experiencing a cardiovascular event on the waiting list subsequently prioritised above individuals predicted to be at a lower absolute risk.

Strategies 5–7: Risk score with biomarkers This general approach is similar to that outlined for Strategy 4. However, in addition to the routinely available information considered within Strategy 4, the risk score is refined by including additional prognostic information provided by the biomarkers themselves. A total of three separate strategies are considered based on a risk prediction equation that also incorporates the additional prognostic information generated by biomarkers. The three strategies considered were: (1) adding a single, routinely available biomarker to the risk prediction equation (eGFR); (2) adding a single, novel biomarker (CRP); and (3) adding a combination of biomarkers (both CRP and eGFR). Hence, the strategies reflect the use of a single routine or a novel biomarker as well as employing a combination of biomarkers.

Choice of biomarkers

We focused on two biomarkers: CRP, because our systematic reviews demonstrated that it has been investigated in many more studies than

any of the other eight biomarkers assessed, and thus the available evidence is likely to be more reliable. eGFR was chosen because renal function is currently routinely assessed and used by surgeons to assess operative risk (e.g. euroSCORE). Thus, if cost-effective, extension of its use in prioritisation is likely to be feasible.

In order to evaluate the separate strategies, obtaining contemporary data representative of current clinical practice is critical. This provides an appropriate baseline which can then be used to evaluate potential changes in health outcomes and costs related to the application of more formal approaches to the prioritisation of waiting lists. Ultimately, the value of the formal prioritisation strategies will be determined by three main issues: (1) the degree to which the additional prognostic information they provide alters the subsequent ordering of individual subjects in terms of their position on a waiting list from that based on current practice; (2) the degree to which a different ordering results in meaningful improvements in terms of subsequent long-term health outcomes and costs; and (3) the costs of generating and applying this prognostic information.

The primary analysis considered here (hereafter referred to as the 'base-case' analysis) evaluates the impact of alternative prioritisation approaches within the context of a maximum waiting time of 3 months (90 days). However, separate scenarios are also presented that consider the value of prioritisation approaches for shorter proposed maximum waiting times (2 weeks and 6 weeks). Consequently, the results are generalisable to different settings with longer and shorter maximum waiting times.

Details of how the prioritisation strategies were implemented and evaluated in the present analysis are provided in the following sections. Given that the decision-analytic model provides the overall analytical framework for the cost-effectiveness analysis, a detailed description of the structure of the model is provided initially.

Model structure

The decision-analytic model reflects both the overall structure of the decision problem as well as the analytical framework necessary to combine the various inputs required to evaluate expected lifetime costs and QALYs for patients on a waiting list for CABG. Given that the overall objective is to assess the impact of alternative prioritisation approaches in terms of the effect they have on the ordering of a waiting list (and hence in terms of the overall time an individual experiences on a waiting list prior to the procedure), the model needs to evaluate the expected lifetime costs and QALYs based on a CABG procedure undertaken anytime between day 1 and day 90, representing the minimum and maximum waiting times possible in the context of the base-case analysis. To assess the cost-effectiveness of the different prioritisation strategies, the decision model also needs to evaluate the potential impact each prioritisation strategy has on the proposed timing of the procedure and how this subsequently affects the expected lifetime estimates of costs and QALYs.

Central to this is the structure of the decision-analytic model itself. The model developed here has a Markov structure,[35] employing a similar structure to previously developed decision-analytic models in the cardiovascular field.[193,194] In a Markov structure, hypothetical individuals reside in one out of a set of mutually exclusive health states at particular points in time. During discrete time intervals of equal length (normally referred to as Markov cycles), individuals can either remain in a particular health state or move to a separate health state (e.g. because of a patient experiencing a particular clinical event). The movements between states represent the potential clinical pathways that a patient may follow at different time points and over his or her remaining lifetime. The likelihood that an individual remains in a particular health state, or moves to a separate state, is estimated in terms of transition probabilities. Defining and subsequently estimating these transition probabilities represent both key structural and analytical elements of the decision model.

In addition to defining the potential health states and estimating the transition probabilities, the costs and the quality of life effect of the states themselves also need to be evaluated. For the purpose of cost-effectiveness analysis, it is essential that quality of life is assessed in terms of a generic measure. Decisions concerning resource allocation typically need to be taken across specialties and disease areas. If these decisions are to be informed by cost-effectiveness analysis then it is crucial that the outcome measure adopted is generic, i.e. that it has meaning outside the clinical area within which it is used. The use of QALYs as the primary outcome of the model allows the cost-effectiveness of the different strategies to be compared with other potential uses of these resources within

the NHS. In order to estimate QALYs, it is necessary to quality adjust the period of time the average patient is alive within the model using an appropriate utility or preference score. The utility scores represent the quality of life of the separate states in the model. The costs and health outcomes from each Markov cycle are then accumulated and summarised for the cohort of hypothetical individuals at the termination of the analysis. These estimates then provide the basis for the cost-effectiveness estimates.

The Markov structure is shown in detail in *Figure 3*. The health states comprising the structure of the model are illustrated by ovals in the figure. The boxes indicate events occurring during a Markov cycle. For instance, the box named 'CABG day 1–90' illustrates that revascularisation has occurred during a cycle. Similarly, the boxes named 'Stroke/MI/death' are used to illustrate that a patient has experienced a composite clinical event. However, these events do not represent health states as such, instead they simply provide the mechanism by which the specific health state (e.g. stroke, myocardial infarction or death) in which a patient resides at the end of a cycle is estimated. The arrows represent the possible movements between health states in any given cycle.

For the first 90 days of the model, representing the total period in which all patients are assumed to undergo CABG in the base-case analysis, daily cycles are applied. After 90 days, annual cycles are applied. All patients in the representative cohort start in the 'no event/no CABG' state. Patients face a risk of a composite end point (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) while awaiting CABG (denoted transition 1 in *Figure 3*). This transition is implemented in the model as a daily probability of the composite end point. This probability is applied in the model *before* patients receive CABG. When CABG is performed (note that CABG can be performed any day between day 1 and 90 as determined by the prioritisation strategies), patients face a procedural risk (denoted transition 2 in *Figure 3*). This risk is applied as an instant 'one-off' risk in the cycle where CABG is performed, although this actually represents the probability of an event up to 30 days after the procedure has been performed. Patients who have a successful CABG (i.e. without a procedural event) make a transition to the 'no event/post CABG' state. In this state, patients still face an ongoing risk of experiencing the composite end point (denoted transition 3 in *Figure 3*), although this risk is now lower than the risk for those on the waiting list as the protective effect of

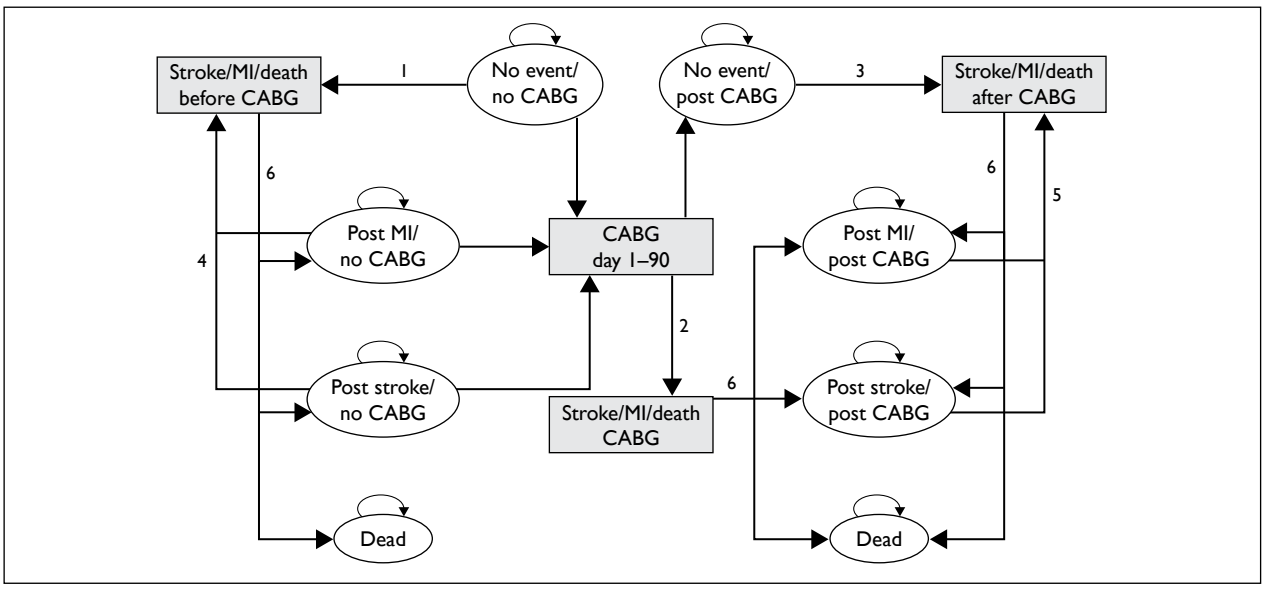

FIGURE 3 *Model structure showing key transitions before and after CABG. 1. Rates of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke on the waiting list for CABG. 2. Procedural risk of death, non-fatal myocardial infarction or non-fatal stroke. 3. Rates of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke after successful CABG. 4. Rates of subsequent cardiovascular events while on the waiting list for CABG. 5. Rates of subsequent cardiovascular events after successful CABG. 6. Conditional probability of a composite event being non-fatal myocardial infarction, non-fatal stroke or death. Note, at any point in time, all patients (regardless of their health state) are also at risk of dying from non-cardiovascular causes. This risk is assumed to be independent of particular health states and so these transitions are not illustrated separately in the schematic. MI, myocardial infarction.*

revascularisation is incorporated into this estimated risk. This transition is implemented in the model as a daily probability between the day of CABG and 90 days, and as an annual probability thereafter.

Patients suffering a non-fatal stroke or a non-fatal myocardial infarction anywhere in the model make a transition to the post-stroke and post-myocardial infarction states respectively. In these states, patients are at risk of a further composite end point (denoted transitions 4 and 5 in *Figure 3*). As for patients without an event, this risk is different depending on whether or not CABG has been performed. Patients suffering a non-fatal myocardial infarction or stroke before CABG are assumed to undergo CABG as planned. If a composite end point occurs at any time in the model, a further calculation determines whether this event is fatal, a non-fatal stroke or a non-fatal myocardial infarction (denoted transition 6 in *Figure 3*). At any point of time, patients are also at risk of mortality from other than cardiovascular causes (transitions not shown in *Figure 3*).

Data sources – Swedish Coronary Angiography and Angioplasty Registry

Transition probabilities

In addition to the systematic review of circulating biomarkers presented previously, the key data source for estimating transition probabilities was a registry of coronary angiography. The ideal registry in which to develop our decision-analytic model has several characteristics. It should: identify large numbers of patients at the time of angiography and record details of the intention to perform CABG and baseline clinical information including biomarkers; be multicentre or national; reflect contemporary practice; and have follow-up for fatal and non-fatal events. No such registry exists in the UK. One of the few registries in the world that meets these criteria is SCAAR.[37]

The Swedish Coronary Angiography and Angioplasty Registry is a national registry that includes all angiographies performed in Sweden. The registry covers high volume dedicated research centres as well as low volume centres. Data for this analysis were available from 2000 to 2005. The registry covers a total of 201,000 angiographies. In 2005, a total of 9500 angiographies in patients with stable coronary artery disease were reported. In SCAAR the decision on further management after angiography is also available, making it possible to identify patients with a decision to undergo CABG, which comprises the patient population of interest in the present analysis. Follow-up for death, non-fatal myocardial infarction and non-fatal stroke was carried out through linkage to national hospitalisation registers. As the SCAAR registry is contemporary, has good coverage, and reflects current clinical practice, this data source was considered to represent the best available evidence to inform the decision model, despite not being from a UK population. Furthermore, we had access to comprehensive individual-patient data from SCAAR, which is required in order to estimate event risks with sufficient detail to be useful in the decision-analytic model.

Data from the SCAAR registry were employed to develop risk equations which were used to define several of the prioritisation strategies (discussed further below) and also to estimate transition probabilities in terms of the risk of cardiovascular events on the waiting list for CABG, procedural risk and the risk after CABG to be applied within the decision-analytic model. Furthermore, SCAAR was also used to define the cohort representing the characteristics and baseline risk factors of a representative cohort on a waiting list for CABG patients. We used the full SCAAR sample to generate the risk equations in order to obtain reliable estimates for the risk factor coefficients. Prioritisation strategies were applied to a cohort of patients in SCAAR with complete data including time to CABG (required to implement a strategy of no formal prioritisation) and eGFR (added to the data set in 2005). In terms of age, sex and coronary anatomy, this cohort ($n = 338$) was representative of the earlier sample (data not shown).

The baseline characteristics of patients in SCAAR with stable coronary artery disease and a decision to undergo CABG after angiography between 2000 and 2005 are shown in *Table 8*.

Data from SCAAR were subsequently used to estimate the separate transition probabilities illustrated in *Figure 4*. The approaches employed to estimation are described in detail below. The results themselves are reported in Chapter 6.

Transition 1: Rates of cardiovascular events while on the waiting list for CABG

All patients in SCAAR between 2000 and 2005 with stable coronary artery disease and who

TABLE 8 *Baseline characteristics of patients in SCAAR assigned CABG after angiography*

Variable	Total number of patients	Number of patients with characterisation	Mean
Age	10,129	Continuous	66.02
Gender (male)	10,130	8025	0.79
Smoker (previous or current)	1117	623	0.56
Hypertension treatment	1149	688	0.60
Lipid lowering treatment	1148	842	0.73
Diabetes	10,130	1461	0.14
Body mass index	783	Continuous	27.28
Angina symptoms Canadian class (3 or 4)	5097	2261	0.44
Left main vessel or three-vessel disease	9936	7801	0.79
Previous myocardial infarction	10,130	3008	0.30
Previous PCI	6254	694	0.11
Previous CABG	6254	211	0.03
Previous stroke	10,130	617	0.06
Heart failure	10,130	839	0.08
Peripheral vascular disease	10,130	446	0.04
S-creatinine (μmol/l)	857	Continuous	88.95
Renal failure	10,130	96	0.01
Chronic obstructive lung disease	10,130	326	0.03
Cancer diagnosis	10,130	210	0.02

Data from 2000 to 2005.

were assigned a primary decision of CABG after angiography were included in this analysis. In order to facilitate the incorporation of the estimated risks as transition probabilities in the decision-analytic model, a parametric time-to-event model with an exponential distribution was estimated.[195] The event considered in this analysis was the composite end point of death, myocardial infarction or stroke. Patients not reaching the composite end point were censored at date of CABG, date of PCI or the date 90 days after the decision to undergo CABG. The candidate covariates for the time-to-event model are shown in *Table 8*. The choice of covariates to be included in the final model was based on availability and statistical significance. Some covariates had to be dropped on the basis that they were not reported for a large enough number of patients. The general rule was to keep covariates that were statistically significant at the 5% level. The transition probabilities needed to populate the Markov structure were derived from the results of the final exponential time-to-event model. Furthermore, the additional prognostic information provided by biomarkers was added to the predicted risk of the composite end point (see Implementing prioritisation strategies and Adjustment factors for details).

Transition 2: Procedural risk of cardiovascular events

For this analysis, the patients assigned and actually undergoing CABG were included. The same composite end point of death, myocardial infarction or stroke was used in this analysis. For the purpose of this analysis, events occurring within 30 days of CABG were defined as procedural. A standard logistic regression was applied in order to estimate procedural risk for patients with different characteristics and risk factors. This analysis included the same covariates as those included in the time-to-event model estimated for the risk of a composite event while on the waiting risk.

The logistic regression estimates the odds of particular events. It should be noted that the odds of an event is the ratio of two complementary probabilities, and therefore does not represent a probability required to populate the cost-effectiveness model. To obtain the relevant probabilities (p) from the logistic regression, the

inverse logistic transformation was used,[196] given by:

$$p = \frac{e^{X\beta}}{1 + e^{X\beta}}$$

for the covariates, X, and the estimated coefficients on the log scale, β.

Transition 3: Rates of cardiovascular events after successful CABG

In estimating this risk, we used the patients assigned and undergoing CABG and not experiencing a composite procedural event. Hence, the starting date for this analysis was the date of CABG plus 30 days. A parametric time-to-event model employing an exponential distribution was estimated using the same end point and risk factors as in the statistical models used for the other transitions. Patients not experiencing the composite end point were censored at 31 December 2005. In a similar manner to the equation estimating transition 1, the additional prognostic information provided by biomarkers was added to the predicted risk of the composite end point. Transition probabilities were derived from this time-to-event model employing the same formulas outlined for transition 1.

Transition 4: Rates of subsequent cardiovascular events while on the waiting list for CABG

Patients suffering a non-fatal event in the model are at risk of further cardiovascular events (transition 4) in the model. We did not have sufficient data to estimate this risk for patients on the waiting list for CABG. Instead, the time-to-event model estimated for transition 1 was used, updating the covariates of previous myocardial infarction and previous stroke to provide an estimate of this risk.

Transition 5: Rates of subsequent cardiovascular events after successful CABG

Similar to patients on the waiting list for CABG, patients with a non-fatal event post CABG are at risk of further cardiovascular events (transition 5). As for transition 4, there were not sufficient data for estimating this risk. Similar to transition 4, the time-to-event model estimated for transition 3 was used, updating the covariates of previous myocardial infarction and previous stroke to provide an estimate of this risk.

Transition 6: Conditional probability of a composite event being non-fatal myocardial infarction, non-fatal stroke or death

In order to determine whether a composite event was fatal, a non-fatal myocardial infarction or a non-fatal stroke, the proportions of the observed events in the estimated equations were used.

Death from non-cardiovascular causes

The probability of death from non-cardiovascular causes was also included. This was assumed to be independent of the (non-fatal) health states considered in the overall model. Hence, the same probability of non-CVD mortality was assigned to each health state in the model. The respective probability of non-CVD mortality was estimated using UK sex- and age-specific life tables adjusted to exclude cardiovascular mortality.[197,198]

Costs

The estimated costs for different states in the model are reported in *Table 9*, together with the cost of the procedure itself. The cost of CABG is derived from NHS reference costs,[199] and the estimated costs associated with the health states in the model are based on previous detailed costing work undertaken using the Nottingham Heart Attack Registry.[200] The cost of the CRP was estimated to be £6 (see *Table 1*). No additional cost was assigned to eGFR on the basis that this is already routinely collected and hence the opportunity cost of using this for the purposes of prioritising a waiting list for CABG would be negligible.

Health-related quality of life

The estimated utilities, or quality adjustment weights, representing the health-related quality of life of the separate health states in the model are shown in *Table 10*. These estimates are based on previous work[201] which employed systematic approaches to identify appropriate utility estimates to apply to patients with ischaemic heart disease, myocardial infarction and stroke, representing the major health states of the model.

TABLE 9 *Cost inputs applied in the model*

Cost item	Mean value
Annual cost of ischaemic heart disease without an event	£483
Annual cost of the first year after a myocardial infarction	£2201
Annual cost of the second and subsequent years after a myocardial infarction	£774
Annual cost of the first year after a stroke	£9845
Annual cost of the second and subsequent year after a stroke	£2597
Cost of CABG	£8203
Costs are at 2006/7 prices.	

TABLE 10 *Estimated utilities associated with health states in the mode*

Health state	Mean utility
Ischaemic heart disease (no event state)	0.718
First year after myocardial infarction	0.683
Second and subsequent years after myocardial infarction	0.718
Post stroke (combining disabling and non-disabling stroke)[a]	0.612

a Assuming 31% disabling (with utility 0.38) and 69% non-disabling (with utility 0.74) based on the European Stroke Prevention Study 2 (ESPS-2).[202]

Defining the representative cohort

In order to determine costs and health outcomes of the prioritisation strategies, a cohort of patients to be prioritised is required. As previously described, a representative cohort is an important element of the model and is used to characterise the variation in the baseline characteristics and risk factors of a representative group of patients on a waiting list for CABG. Ultimately, it is this cohort that provides the basis for estimating the order in which individuals are assumed to receive the CABG procedure for each of the alternative methods of prioritisation under investigation. Similarly, the baseline covariates of this cohort determine the subsequent effect of the separate risk equations in terms of health outcomes and costs. These costs and health outcomes will vary according to the baseline characteristics and risk factors of the representative cohort as well as to the different ordering of this cohort predicted by the alternative strategies.

A total of 338 patients from the SCAAR registry who underwent CABG were used to define the representative cohort. As noted previously, these patients did not differ in terms of baseline covariates from the larger sample. A further 22 patients were sampled randomly and reintroduced as 'duplicate' patients to make a total of 360 patients and an even number of procedure 'slots' per day over 90 days (i.e. four operations per day) to simplify the subsequent analytical implementation of the model. The 338 patients from SCAAR were those with complete covariate data (i.e. ensuring that the complete set of risk equations could be applied for these patients), and their times to CABG from angiography were available (i.e. making it possible to implement a strategy of clinical practice in the representative cohort). For example, creatinine was only routinely reported in SCAAR from 2005, thus substantially reducing the number of patients eligible for the representative cohort as creatinine was required to implement the prioritisation strategy using a risk score with eGFR. Finally, the presence of complete covariates was also necessary because of the additional analytical steps that were needed to impute CRP levels for the SCAAR patients. This imputation was required as this biomarker was not actually collected as part of the SCAAR registry. Further details of the imputation approaches are reported in later sections. There were 680 patients with complete covariates in SCAAR. Of these 680 patients, 338 also had a time to CABG registered and were thus included in the representative cohort.

Implementing prioritisation strategies

This following section outlines how the prioritisation strategies were implemented in relation to the representative cohort. For several of the proposed strategies, a number of additional assumptions and analytical approaches were required to generate the appropriate estimates necessary to implement the strategies within the decision model.

No formal prioritisation

For all patients in the representative cohort, the time to CABG is actually reported in the SCAAR registry (i.e. the time from decision to when the actual procedure was performed). Hence, the strategy of no formal prioritisation simply reflects the implicit ordering of patients based on these reported waiting times. While this approach does not comprise an explicit approach to formally ordering the waiting list, it reflects the reality of existing practice and the subsequent ordering that this implies. Hence, patients in the representative cohort with a shorter reported time to CABG are prioritised first when the strategy of no formal prioritisation is modelled.

Urgency scores

The complete set of variables needed to implement either the Ontario or the New Zealand urgency scoring systems was not available in the SCAAR data set. However, given the importance of including a range of alternative formal approaches to prioritisation of the waiting list, separate mapping exercises were undertaken between the variables reported in the SCAAR registry and those included in both the Ontario and the New Zealand urgency scoring algorithms.

The algorithm for mapping Ontario into the SCAAR patients is shown in *Figure 4*. The results of the mapping were used to estimate the urgency scores for each of the individual patients within the representative cohort. The ordering of patients in terms of the Ontario score was thus determined by the estimated scores of the individual patients within this cohort, with a lower Ontario score indicating a higher prioritisation and hence an earlier position on the scheduling of CABG within the 3 months considered.

The algorithm for mapping New Zealand into the SCAAR patients is shown in *Figure 5*. A similar approach was employed to that used for the strategy based on Ontario urgency scores, except that patients with higher New Zealand scores are prioritised first within this strategy.

Risk score without biomarkers

With this strategy, patients were prioritised according to their predicted risk of cardiovascular events while on the waiting list for CABG. To implement this strategy in the representative cohort, the risk estimated by the time-to-event model used to derive the probability of transition 1 was used. A daily rate of the composite end point was derived for each patient in the representative cohort. With this strategy the information from biomarkers was not included in the equation. Patients within the representative cohort with the

Ontario variables

Anatomical equivalent	Mapping into SCAAR
Left main stenosis	All with left main disease in SCAAR
Multivessel including proximal LAD stenosis	All with three-vessel disease in SCAAR
Three-vessel, without proximal LAD stenosis	
Single-vessel, proximal LAD stenosis	All with two-vessel disease in SCAAR
One- or two-vessel disease, no proximal LAD stenosis	All with one-vessel disease in SCAAR
Number to be subtracted if non-invasive test suggests high ischaemic risk	Not available in SCAAR

SCAAR variables	Derived Ontario score from SCARR: Based on angiographic findings and Canadian class		
	Angiography finding	Canadian class score I–II	III	IV
Inconclusive	0	6.95	6.65	6.15
Normal	1	6.95	6.65	6.15
One-vessel not left main	2	6.95	6.65	6.15
Two-vessel not left main	3	6.80	6.55	5.80
Three-vessel not left main	4	6.15	6.00	5.50
Left main + one-vessel	5	5.40	4.85	4.75
Left main + two-vessel	6	5.40	4.85	4.75
Left main + three-vessel	7	5.40	4.85	4.75
Left main	8	5.40	4.85	4.75

FIGURE 4 *Implementation of the Ontario algorithm into SCAAR. LAD, left anterior descending.*

New Zealand variables and scoring system	Score	Mapping into SCAAR
Degree of coronary artery obstruction		
No CAD ≥ 50%	0	
1 CAD 50–74%	6	All with one-vessel disease in SCAAR Score = 7
>1 VD 50–75%	7	
1 VD (75%)	7	
1 VD (≥ 90%)	10	
2 VD (50–89%)	12	
2 VD (both ≥ 90%)	13	All with two-vessel disease in SCAAR Score = 15
1 VD, ≥ 90% proximal LAD	15	
2 VD, ≥ 90% LAD	15	
2 VD, ≥ 90% proximal LAD	18	
3 VD	18	
3 VD, ≥ 90% in at least 1	20	All with three-vessel disease in SCAAR Score = 21
3 VD, 75% proximal LAD	21	
3 VD, ≥ 90% proximal LAD	24	
Left main (50%)	25	
Left main (75%)	26	All with left main disease in SCAAR Score = 28
Left main (≥ 90%)	32	
Left ventricular ejection fraction		
<35%	10	Previous heart failure Score = 6
35–50%	6	
>50%	0	
Angina class		
I	1	
II	2	
III	7	Apply as in SCAAR
IVa	16	
IVb	20	
IVc	23	
Exercise stress test		
Markedly positive	20	
Very positive	16	Not available in SCAAR
Positive	8	
Mildly positive	4	
Negative	0	
Ability to work, give care to dependents or live independently		
Immediately threatened	15	
Threatened, but not immediately	8	Not available in SCAAR
Not threatened, but more difficult	4	

Deriving New Zealand score from SCARR		
SCAAR variables	SCAAR entry	Score
Inconclusive	0	7
Normal	1	7
One vessel not left main	2	7
Two vessel not left main	3	15
Three vessel not left main	4	21
Left main + one vessel	5	28
Left main + two vessel	6	28
Left main + three vessel	7	28
Left main	8	28
No previous heart failure	0	0
Previous heart failure	1	6
Canadian class = 1	1	1
Canadian class = 2	2	2
Canadian class = 3	3	7
Canadian class = 4	4	16

FIGURE 5 *Implementation of the New Zealand algorithm into SCAAR. CAD, coronary artery disease; LAD, left anterior descending; VD, vessel disease.*

highest estimated risk of the composite end point were prioritised first within this strategy.

Risk score with biomarkers

This prioritisation approach is implemented in a similar way to the use of a risk score without biomarkers. The only difference with this set of strategies is that the additional prognostic information provided by the biomarkers is included in the risk equation for estimating transition 1. As stated earlier in this section, the three strategies considered within this general approach were: (1) adding a single, routinely available biomarker to the risk prediction equation (eGFR); (2) adding a single, novel biomarker (CRP); and (3) adding both CRP and eGFR to the risk equation. As with the approach to prioritisation without biomarker information, patients with the highest predicted risk (including the additional prognostic information provided by the biomarkers) of a composite event were prioritised first.

The additional prognostic value of the separate biomarker strategies was derived from the estimates of relative risk presented in Chapter 4. However, several additional steps were subsequently required in order to implement these results within the decision model itself. These additional steps were required to address two specific issues that prevented these results being incorporated directly into the proposed decision model framework and into the proposed risk equations.

The first issue represents the need to consider the prognostic effect of the biomarkers, represented by the other covariates within the risk equation. Hence, a set of adjustment factors was required to account for the changes to the regression coefficients of the other covariates included in the risk equations when the biomarker covariates were added. The second issue concerns the absence of CRP data within the SCAAR registry. Hence, in order to implement a prioritisation strategy incorporating this biomarker, it was necessary to impute CRP levels for patients in the representative cohort based on the covariate data that were available within the SCAAR registry. Both of these issues required access to an additional data set to address these issues and to provide appropriate estimates to populate the final model.

Methods of incorporating biomarker information within the decision model

An additional data set (St George's Hospital, London, Principal Investigator Kaski) was obtained in order to generate the adjustment factors and to impute CRP values in the representative cohort derived from the SCAAR registry. St George's data set consists of 643 patients with chronic stable angina undergoing coronary angiography at St George's Hospital, London, in whom CRP was measured along with the same covariates as are available in the SCAAR registry. Patients in this data set were followed up for mortality over 7 years. Details of the St George's data set have been previously published.[203] The St George's data did not include waiting list information or date of CABG receipt and thus were not suitable for running the decision model.

Adjustment factors

Further to the risk equations estimated from SCAAR data, the impact of biomarker information on the risk of the composite end point was added. These estimates were obtained from the systematic review outlined in Chapter 3. Integrating the literature-based estimates of the impact of biomarker information on the composite end point with the time-to-event model developed from the SCAAR data may potentially influence the parameter estimates in the time-to-event model estimated from SCAAR data. To account for this, adjustment factors were employed.[204,205]

Using the St George's data set, adjustment factors were calculated by fitting parametric proportional hazards regression models using a constant baseline hazard function, i.e. assuming that time to an event followed an exponential distribution, with and without one or more novel biomarkers included as a three-level categorical variable, with levels representing tertiles, with the exception of eGFR which was included as a binary covariate using a cut-off of 60 ml/min. Thus, equation [1] estimates the hazard ratios, i.e. $\exp(\beta_1)$, …, $\exp(\beta_p)$ associated with p covariates, while equation [2] estimates the hazard ratios, i.e. $\exp(\beta_1^*)$, …, $\exp(\beta_p^*)$ associated with the same p covariates when a biomarker, BM_1 is included in the model.

$$\lambda(\tau) = \exp(\beta_0 + \beta_1 x_1 + \ldots + \beta_p x_p) \quad [1]$$

$$\lambda(\tau) = \exp(\beta_0^* + \beta_1^* x_1 + \ldots + \beta_p^* x_p + BM_1) \quad [2]$$

The adjustment factors, $\alpha_0, \ldots, \alpha_p$, for the p covariates and the baseline hazard, are then calculated by equation [3].

$$\alpha_0 = \beta_0 - \beta_0^*$$
$$\alpha_p = \beta_p - \beta_p^* \quad [3]$$

The hazard ratios obtained from fitting the corresponding model in SCAAR (without a biomarker) were then adjusted, when the relative risks from the meta-analysis in Chapter 3 were applied, by $\exp(\alpha_0), \ldots, \exp(\alpha_p)$.

Imputation of C-reactive protein in SCAAR

As CRP was not available in the SCAAR registry, the level of CRP of patients in the representative cohort had to be imputed. The St George's data set was used to develop a prediction model using covariates common to both St George's and the SCAAR registry. An ordinal logistic model was used to estimate the tertiles of CRP.[206] Applying this model, the following cumulative odds can be defined:

θ_1 = probability(1st tertile of CRP)/ probability(2nd or 3rd tertile of CRP)

θ_2 = probability(1st or 2nd tertile of CRP)/ probability(3rd tertile of CRP)

which can then be modelled in terms of q covariates as in equation [4].

$$\log_e(\theta_j) = \alpha_j - \gamma_1 x_1 + \ldots + \gamma_q x_q \quad j = 1,2 \qquad [4]$$

Hence, after estimating the parameters of equation [4], the cumulative probabilities of a specific patient being in either the first or the first or second tertile are given by:

$$P_1 = \text{probability(1st tertile of CRP)} = 1/(1 + e-(\alpha_1 - \gamma_1 x_1 + \ldots + \gamma_q x_q))$$

$$P_{1,2} = \text{probability(1st or 2nd tertile of CRP)} = 1/(1 + e-(\alpha_2 - \gamma_1 x_1 + \ldots + \gamma_q x_q)) \qquad [5]$$

Thus, the probabilities of a specific patient having a CRP value within each tertile are given by:

$$\begin{aligned} &\text{Probability(1st tertile)} = \pi_1 = P_1 \\ &\text{Probability(2nd tertile)} = \pi_2 = P_{1,2} - P_1 \\ &\text{Probability(3rd tertile)} = \pi_3 = 1 - P_{1,2} \end{aligned} \qquad [6]$$

The meta-analysis outlined in Chapter 3 estimates the relative risk of an event for a patient being in the second tertile compared with the first, $RR_{1,2}$, and the relative risk of an event for a patient being in the third tertile compared with the first, $RR_{1,3}$, using meta-analysis techniques.

Using equations [4], [5] and [6], the probability that each individual patient in the SCAAR registry is in each CRP tertile is estimated. Following this, the baseline risk for each individual patient of an event in each of the three tertiles is estimated, adjusted for the fact that CRP is now included in the model, thus:

$$\begin{aligned} \lambda_1 &= \exp(\beta_0^* \alpha_0 + \beta_1^* \alpha_1 x_1 + \ldots + \beta_p^* \alpha x_p) \\ \lambda_2 &= \exp(\beta_0^* \alpha_0 + \beta_1^* \alpha_1 x_1 + \ldots + \beta_p^* \alpha x_p) RR_{1,2} \\ \lambda_3 &= \exp(\beta_0^* \alpha_0 + \beta_1^* \alpha_1 x_1 + \ldots + \beta_p^* \alpha x_p) RR_{1,3} \end{aligned} \qquad [7]$$

Having estimated the hazard of an event (using CRP and clinical information) using equation [7] for a patient being in each of the tertiles, this hazard is then averaged according to the probability of a patient being in each tertile, to yield λ^*, i.e. $\lambda^* = \pi_1\lambda_1 + \pi_2\lambda_2 + \pi_3\lambda_3$. The averaged estimate is then used to rank patients in the representative cohort for the strategy using a risk score with CRP alone and the strategy using a risk score with both eGFR and CRP.

The transition probabilities needed to populate the Markov structure were derived from the results of the final exponential time-to-event model including the integrated biomarker information. The survivor function of the exponential distribution is given by $S(t) = e^{-\lambda t}$ and thus the transition probability of a composite end point in Markov cycle t, $tp(t)$, is given by $tp(t) = 1 - \exp(\lambda(t-1) - \lambda t)$ [8]. When evaluating the decision model, transition probabilities were derived for each tertile of CRP, thus providing three estimates of costs and QALYs for each patient. These estimates were then averaged according to the probability of a patient being in each tertile to generate a cost and QALY estimate for a particular patient (operated on a particular day within the maximum waiting time).

Analysis of decision model

Several analytical steps are required in order to estimate the cost-effectiveness of the different prioritisation strategies according to the methods outlined above. In the first step, the statistical risk prediction equations are populated based on the SCAAR registry data, with the results of the systematic review incorporated using the adjustment factors. The final risk equations represent our best prediction of clinical events based on the various data sources, and provide the basis for the subsequent transition probabilities applied in the model itself. It is important to note that the transition probabilities for each strategy are actually populated using the same risk equations representing: (1) the risk on the waiting list for CABG; (2) the procedural risk; and (3) the risk after the CABG procedure. The differences between strategies will actually be reflected in the different ordering of patients on the waiting list. This ordering determines the predicted time at which a given individual will 'switch' between the separate equations in the model for each separate strategy. The ordering of patients on the waiting list and how this varies by strategy comprises the next step.

In the second step of the analysis the prioritisation strategies are implemented in the representative cohort in order to assign each patient in the cohort a day of CABG with the alternative prioritisation strategies. The different approaches to prioritisation will imply a different ordering of the waiting list and hence a potentially different day on which the procedure would be undertaken. In the base-case analysis it is assumed that all patients in the representative cohort should have their procedure within 90 days (i.e. four procedures per day), representing the maximum waiting time being considered. The importance of the maximum waiting time itself on overall results of cost-effectiveness was subsequently investigated in

alternative scenarios by decreasing the number of maximum days on the waiting list to 40 (i.e. nine procedures per day) and 15 days (i.e. 24 procedures per day). Regardless of which time period is chosen to represent the maximum waiting time, the ordering of the representative cohort will remain the same in each strategy.

In the third step of the analysis, costs and health outcomes are determined for each patient given the assigned day of CABG with the different prioritisation strategies. Hence, if a particular patient is assigned to undergo CABG at day 20 by a specific means of prioritisation, the costs and health outcomes for this particular patient are determined by running the decision-analytic model with the day of CABG set to 20 and applying the covariate pattern of this particular patient. This procedure is then repeated for all patients in the representative cohort and for all prioritisation strategies. It should be noted that alternative prioritisation strategies will differ in terms of the different assigned days of CABG and thus different estimates of the subsequent costs and health outcomes for the same patient. However, given that the same risk equations are employed for each strategy, if the timing of receipt of CABG for a given individual is the same for particular strategies, then the subsequent estimates of lifetime costs and QALYs will be identical. The overall cost-effectiveness of the prioritisation strategies is subsequently determined by averaging the costs and health outcomes across patients in the representative cohort for each prioritisation strategy and evaluating the associated ICERs.

Chapter 6
Results of decision model

The results of the decision model are presented as follows: (1) the final risk equations and the associated set of transition probabilities; (2) the impact of the different prioritisation strategies in terms of the actual ordering of the representative cohort within the waiting list for CABG; and (3) the overall costs and health outcomes of the alternative prioritisation strategies and their relative cost-effectiveness.

Final risk equations

Risk on the waiting list

The observed events and estimated hazard ratios while on the waiting list for CABG are shown in *Table 11*. Age, heart failure, diabetes and previous stroke were all associated with a statistically significant elevated risk of the composite end point. Previous myocardial infarction and left main vessel disease and/or three-vessel disease were very close to statistical significance at the 5% level and were retained in the time-to-event model. The hazard ratios of biomarker information (CRP and eGFR), estimated from the systematic review and meta-analysis, are also shown in *Table 11*. In the last column of the table, the adjusted hazard ratios are presented.

This is the final equation applied when determining transition probabilities for the decision-analytic model. The equation also provides the basis for the ordering of patients using the prioritisation strategy based on absolute clinical risk with biomarkers. The unadjusted equation in the first column, without the biomarker coefficients, was used when ordering patients for the prioritisation strategy based on absolute risk without biomarkers.

It should be noted that the assumption of a constant hazard within the exponential distribution was tested by employing an alternative distribution (Weibull) for this time-to-event model in order to investigate whether there was indication of a changing hazard from time of the decision to perform CABG to the censoring date. The separate analysis employing a Weibull distribution did not support a time-dependent hazard function, thus providing additional justification for the distributional assumption made.

Procedural risk

The number of procedural events and estimated procedural risk are shown in *Table 12*. The covariates included in the 'waiting list model' described above were also significant in the logistic model estimated to predict procedural risk associated with CABG. It should be noted that the results in *Table 12* are based on all patients included in the 'waiting list model' who went on to have CABG regardless of the time from the decision to CABG to the actual procedure. Of all procedures included in the analysis, 77% were performed within 90 days of the decision to perform CABG. The proportion of patients in this group suffering a composite end point was 5.1% compared with 6.1% for those patients having the procedure more than 90 days after the decision to perform CABG. The overall estimate based on the events reported in *Table 12* was 5.4%.

Risk after coronary artery bypass grafting

The observed events and estimated hazard ratios after the CABG procedure are shown in *Table 13*. All covariates included in the 'waiting list model' were statistically significant at the 5% level, with the exception of previous myocardial infarction. However, previous myocardial infarction was very close to statistical significance and was retained in the time-to-event model. As for the 'waiting list model', the hazard ratios of biomarker information (CRP and eGFR), as estimated from the meta-analysis, were integrated in this model. In the last column of the table, the adjusted hazard ratios are presented. This is the final equation applied when determining transition probabilities for the decision-analytic model.

A separate analysis was undertaken, employing a Weibull distribution in order to investigate whether the assumption of a constant hazard, from the starting time of the analysis to the censoring date, was appropriate. The analysis indicated that the assumption of a constant hazard was appropriate.

TABLE 11 *Events and estimated hazard ratios while on the waiting list for CABG (n = 9935)*

Events[a]	Number of events/total number of patients	Hazard ratio	95% CI	Adjusted hazard ratio
Dead	83/9935			
Myocardial infarction	84/9935			
Stroke	30/9935			
Dead, myocardial infarction or stroke	184/9935			
Variables in survival model	Number of patients with characteristic/total number of patients[b]			
Age (per year)	66.03	1.05	1.03 to 1.06	1.04
Heart failure	816/9935	2.43	1.69 to 3.50	2.45
Previous myocardial infarction	2947/9935	1.32	0.97 to 1.80	1.29
Diabetes	1432/9935	1.57	1.11 to 2.23	1.56
Previous stroke	598/9935	1.85	1.21 to 2.83	1.89
Left main or three-vessel disease	7801/9935	1.51	0.99 to 2.31	1.51
CRP 2nd tertile		1.40	1.33 to 1.47	1.40
CRP 3rd tertile		1.96	1.76 to 2.17	1.96
eGFR		2.00	1.65 to 2.42	2.00

a Events occurring within 90 days of assignment of CABG, patients censored at revascularisation or 90 days, mean time at risk is 59 days.
b Mean for the continuous age variable.
Results are for patients with all covariates, some are excluded from the survival analysis because of missing covariates.

TABLE 12 *Events and estimated procedural risk of CABG*

Events[a]	Number of events/ total number of patients	Odds ratio	95% CI
Dead	90/7375		
Myocardial infarction	224/7375		
Stroke	106/7375		
Dead, myocardial infarction or stroke	395/7375		
Variables in logistic model	Number of patients with characteristic/total number of patients[b]		
Age (per year)	65.71	1.04	1.02 to 1.05
Heart failure	554/7375	1.82	1.35 to 2.44
Previous myocardial infarction	2124/7375	1.52	1.22 to 1.89
Diabetes	1015/7375	2.00	1.56 to 2.56
Previous stroke	422/7375	2.14	1.55 to 2.95
Left main or three-vessel disease	5768/7375	1.62	1.20 to 2.18

a Events occurring within 30 days of the procedure.
b Mean for the continuous age variable.

Transition probabilities

Transition probabilities to be applied in the decision-analytic model were derived from the equations presented in Chapter 5. These were estimated for each individual in the representative cohort. For illustrative purposes, the estimated transition probabilities for patients with selected baseline characteristics and risk factors are shown in *Table 14*.

TABLE 13 *Events and estimated risk post CABG procedure*

Events[a]	Number of events/total number of patients	Hazard ratio	95% CI	Adjusted hazard ratio
Dead	478/6980			
Myocardial infarction	137/6980			
Stroke	161/6980			
Dead, myocardial infarction or stroke	680/6980			
Variables in survival analysis	Number of patients with characteristic/total number of patients[b]			
Age (per year)	65.55	1.05	1.04 to 1.06	1.05
Heart failure	485/6980	2.23	1.81 to 2.75	2.25
Previous myocardial infarction	1957/6980	1.15	0.98 to 1.36	1.13
Diabetes	912/6980	1.68	1.39 to 2.03	1.67
Previous stroke	372/6980	2.07	1.63 to 2.62	2.11
Left main or three-vessel disease	5426/6980	1.22	1.00 to 1.49	1.22
CRP 2nd tertile		1.40	1.33 to 1.47	1.40
CRP 3rd tertile		1.96	1.76 to 2.17	1.96
eGFR		2.00	1.65 to 2.42	2.00

a Events occurring more than 30 days after CABG was performed, mean time at risk is 3.8 years.
b Mean for the continuous age variable.

In *Table 15*, the number of composite end points being fatal, non-fatal myocardial infarction and non-fatal stroke are shown together with the probabilities applied for this transition in the decision-analytic model.

Implementation of strategies and impact on the ordering of the waiting list

As previously described, the value of the formal prioritisation strategies will be determined by the degree to which they alter the subsequent ordering of individual subjects in terms of their position on a waiting list based on no formal prioritisation and, in turn, whether the different ordering results in meaningful improvements in terms of subsequent long-term health outcomes and costs.

The derived scores by the alternative means of prioritisation and assigned day of CABG for 12 selected patients in the representative cohort are shown in *Table 16*. The derived scores are the result of implementing the prioritisation strategies on the patients in the cohort using the approaches outlined in Chapter 5. The scores are then used to rank patients from highest to lowest risk, where the patients with higher risk are prioritised to receive CABG at an earlier time than lower risk patients. The position on the waiting list and hence the timing of the procedure are illustrated by the assigned day of CABG reported in the table. In the event that a prioritisation strategy produced the same score for patients in the representative cohort, then the subsequent ranking within these clusters of patients was assigned randomly. Hence, randomness is more pertinent in the somewhat crudely implemented Ontario and New Zealand urgency scores (as indicated by the scores in columns three and four of the table). It should be noted that for the strategy of no formal prioritisation, the derived 'score' is simply the actual number of days on the waiting list that particular patient actually experienced in the representative cohort.

The decision model is then used to estimate the resulting differences in costs and QALYs obtained through the different orderings of the waiting list for each individual strategy.

TABLE 14 *Probabilities of composite end point applied in the decision-analytic model: illustration in five patients*

Patient characteristics	Waiting list before CABG[a]			CABG[b]	After CABG[c]		
	No event	Post MI	Post stroke		No event	Post MI	Post stroke
65 years, male	0.00008	0.00010	0.00015	0.0229	0.009	0.010	0.019
55 years, male, heart failure, previous MI	0.00017	0.00021	0.00031	0.0439	0.014	0.016	0.029
65 years, male, heart failure, previous MI	0.00025	0.00033	0.00048	0.061	0.023	0.026	0.048
55 years, male, diabetes, heart failure, previous MI, main-vessel and/or three-vessel disease	0.00039	0.00050	0.00074	0.129	0.028	0.032	0.058
65 years, male, diabetes, heart failure, previous MI, main-vessel and/or three-vessel disease	0.00060	0.00078	0.00114	0.173	0.046	0.053	0.095

MI, myocardial infarction.
a Daily probabilities.
b One-off probability assigned at the time of CABG but representing the probability of a procedural risk over a 30-day period.
c Annual probabilities shown in table; note that these are also implemented as daily probabilities in the model between day of CABG and 90 days.
Note that the coefficients for the biomarkers are not updated in this illustrative example.

TABLE 15 *Distribution of composite end points*

	Waiting list		CABG procedure		After CABG	
	Number of events	Probability	Number of events	Probability	Number of events	Probability
Non-fatal stroke	26	0.14	100	0.25	152	0.22
Non-fatal myocardial infarction	83	0.45	222	0.56	130	0.19
Death	75	0.41	73	0.19	398	0.59
Total	184	1	395	1	680	1

Cost-effectiveness

To estimate lifetime costs and QALYs, the model is run for a period of 60 cycles (equivalent to 60 years), after which the vast majority of patients will have died in the model. Therefore, the mean QALYs per patient can be calculated for each strategy, as well as the mean lifetime costs. With the assigned day of CABG (as illustrated in *Table 16*), the cost and health outcomes with each prioritisation strategy for each individual patient in the representative cohort were estimated. The costs and health outcomes across the individual patients in the cohort for each prioritisation strategy were then averaged to obtain a mean (per patient) estimate of costs and QALYs, and the relative cost-effectiveness of the different strategies was then estimated.

The results of the cost-effectiveness analysis are presented in two ways. Firstly, mean costs and QALYs for the various comparators are presented. Secondly, the cost-effectiveness of the different strategies is compared using standard decision rules, estimating ICERs as appropriate.[207] The ICER examines the additional costs that one strategy incurs over another and compares this with the additional benefits. The ICER estimate reports the additional cost required to generate one additional unit of health outcome (QALY). When more than two strategies are being compared, the ICERs are calculated using the following process:

- The strategies are ranked in terms of mean QALYs (from the least effective to the most effective).
- If a strategy is more expensive and less effective than any previous strategy, then this strategy is

TABLE 16 *Derived scores by different means of prioritisation and assigned day of CABG illustrated for 12 selected patients in the notional cohort*

	Derived scores for prioritisation							Assigned day of CABG						
Patient	Clin pract	Urg Ont	Urg NZ	Risk no biom	Risk CRP	Risk eGFR	Risk eGFR + CRP	Clin pract	Urg Ont	Urg NZ	Risk no biom	Risk CRP	Risk eGFR	Risk eGFR + CRP
1	10	6.15	23	0.000508	0.000426	0.000301	0.000426	6	63	58	7	11	15	18
2	46	5.40	30	0.000197	0.000188	0.000122	0.000188	55	25	23	57	56	59	55
3	29	6.15	23	0.000121	0.000119	0.000076	0.000119	34	61	63	80	78	81	78
4	22	6.15	23	0.000165	0.000162	0.000103	0.000162	22	52	59	67	65	67	65
5	42	6.15	23	0.000216	0.000224	0.000267	0.000447	53	51	70	49	43	18	16
6	24	6.15	23	0.000260	0.000233	0.000161	0.000233	26	49	69	38	40	39	43
7	34	6.80	17	0.000109	0.000099	0.000068	0.000099	43	85	86	84	83	84	84
8	60	6.00	28	0.000258	0.000266	0.000317	0.000532	65	45	42	40	33	13	12
9	42	6.15	23	0.000197	0.000188	0.000245	0.000376	52	59	70	56	55	21	23
10	70	6.15	23	0.000236	0.000189	0.000145	0.000189	69	69	64	44	54	46	55
11	35	6.15	23	0.000151	0.000130	0.000094	0.000130	46	65	54	71	75	72	75
12	27	6.15	23	0.000270	0.000289	0.000165	0.000289	30	53	55	35	28	37	33

Scores: No formal prioritisation (Clin pract) = time to CABG observed in SCAAR; Ontario (Urg Ont) = derived from mapping, low score indicates high risk; New Zealand (Urg NZ) = derived from mapping, high score indicates high risk; risk score without biomarker (Risk no biom) = daily rate estimated by risk equation; risk score with biomarker (Risk CRP/eGFR/eGFR+CRP) = daily rate estimated by risk equation including biomarker information.

said to be dominated and is excluded from the calculation of the ICERs.
- The ICERs are calculated for each successive alternative, from the least effective to the most effective. If the ICER for a given strategy is higher than that of any more effective strategy, then this strategy is ruled out on the basis of extended dominance.
- Finally, the ICERs are recalculated, excluding any strategies that are ruled out by principles of dominance or extended dominance.

The resulting ICERs then provide the basis for establishing which strategy appears optimal based on cost-effectiveness considerations. That is, which strategy (or strategies) appears to provide good value for money to the NHS. Guidance from NICE suggests that an incremental cost per additional QALY of around £20,000–30,000 is considered to represent an appropriate threshold to establish value for money to the NHS.

The model was run several times, once for the main base-case analysis and then for a number of alternative scenarios to consider alternative assumptions related to key aspects of the base-case approach.

Base-case analysis

Table 17 reports the results of the mean lifetime costs, life-years, QALYs and ICERs for the base-case analysis using a 3-month (90-day) maximum waiting time for CABG. Mean estimates of the lifetime costs and QALYs are reported in detail for each strategy, together with the associated ICER estimates for non-dominated strategies.

Each of the alternative formal prioritisation strategies appears more costly and more effective than no formal prioritisation. Therefore, the comparison of ICERs is an important consideration. Applying the decision rules outlined in the previous section, one prioritisation strategy is ruled out based on dominance considerations and hence excluded from the final ICER estimates. The strategy of using a risk score with CRP is dominated by the risk score employing eGFR. This means that the single novel biomarker strategy is associated with additional costs (principally the additional £6 cost of the biomarker itself) and the prognostic information based on this strategy appears less informative than that based on a strategy incorporating the routine biomarker. Furthermore, the prioritisation strategies using a risk score without biomarker information and New Zealand urgency score are extendedly dominated by the strategy based on a risk score with eGFR.

Hence, of the seven initial strategies considered, four remain after dominance considerations. These four strategies provide the basis for the final ICER estimates in the base-case analysis. No formal prioritisation is associated with the lowest mean cost and QALY estimates. Given that this is the least effective (and non-dominated) strategy considered, this provides the initial reference point for the subsequent ICER estimates. Compared with no formal prioritisation, the strategy with Ontario urgency score is more effective and more costly.

TABLE 17 *Cost-effectiveness results from the base-case analysis*

	90-day maximum waiting time			
Strategy	**Cost (£)**	**Life-year**	**QALY**	**ICER (£)[a]**
No formal prioritisation	16099.77	11.6611	8.2796	
Ontario urgency score	16100.00	11.6646	8.2822	88
New Zealand urgency score	16100.87	11.6663	8.2835	ED
Risk score without biomarker	16101.98	11.6713	8.2871	ED
Risk score with CRP	16107.99	11.6714	8.2872	D
Risk score with eGFR	16102.22	11.6721	8.2877	405
Risk score with CRP + eGFR	16108.19	11.6723	8.2878	57,842

D, dominated (meaning that a comparator strategy has lower cost and better health outcome, e.g. a risk score with CRP is associated with lower mean QALYs and higher mean costs than a risk score using eGFR); ED, extendedly dominated (meaning that a combination of two other comparators has lower costs and better health outcome, e.g. a combination of Ontario urgency score and a risk score with eGFR will always be more cost-effective than a risk score without a biomarker).
a ICERs are calculated as cost per QALY.

The ICER of a strategy based on Ontario urgency score compared with no formal prioritisation is £88 per additional QALY. As this is below the threshold used to establish cost-effectiveness, the next consideration is whether the additional costs and health outcomes generated by the next non-dominated strategy are cost-effective. This comparison is now made against the Ontario urgency score. That is, as it has been established that a risk equation with Ontario urgency score is potentially cost-effective, the relevant question becomes whether the remaining strategy is cost-effective with reference to this strategy? The ICER of a risk score with eGFR compared with Ontario urgency score is £405 per additional QALY. Given that this is also below the threshold used to establish cost-effectiveness, it has to be considered whether the remaining strategy of a risk score with CRP and eGFR is cost-effective compared with a risk score with eGFR alone. The ICER for this comparison is £57,842 per additional QALY.

Applying a threshold of between £20,000 and £30,000 per QALY, a strategy employing a risk score with both CRP and eGFR cannot be considered cost-effective. In contrast, the most effective prioritisation strategy with an ICER below the threshold is a risk score based on the routinely collected biomarker eGFR. This indicates that a risk score with eGFR is the most cost-effective prioritisation strategy.

The increasing ICER estimates between the single and combination biomarker strategies clearly demonstrate that while additional predictive information is informative in terms of deriving more precise estimation of a patient's individual risk, the actual value of this increased precision will ultimately be determined by the difference this information then makes to the ordering of a waiting list (and hence to the resulting estimates of costs and QALYs). This is most evident in the comparison between the strategies based on a risk score with eGFR alone and a risk score with both eGFR and CRP. While the latter risk score provides a more precise estimate of an individual's predicted risk, the resulting difference in outcomes between the strategies is 0.0001 QALYs. Putting this into context, this is equivalent to a mean, per patient, gain of 0.04 days of perfect health over a patient's lifetime. Hence, although the additional cost imposed by the use of a novel biomarker appears relatively minor (£6), the subsequent impact in terms of the ordering of the waiting list and on longer-term costs and QALYs appears marginal. Consequently, when the additional costs of such a strategy are compared with the additional predicted gain in QALYs, the resulting ratio of costs to benefits leads to an ICER of approximately £58,000 per QALY.

Separate analyses were also undertaken to examine the impact of the uncertainty in the relative effectiveness estimates for biomarkers reported in Chapter 4, as well as variation that may exist in relation to the cost of the biomarkers themselves.

Sensitivity analyses

Cost-effectiveness results comparing alternative maximum waiting times

Table 18 compares the results of the mean lifetime costs, life-years, QALYs and ICERs for the base-case analysis using a 3-month (90-day) maximum waiting time for CABG, with similar estimates based on maximum waiting times of 40 days and 15 days. In each of these analyses, the same strategies are ruled out on the grounds of dominance and extended dominance. Interestingly, the ICER for a strategy of using a risk score with eGFR remains remarkably stable and well below the conventional threshold of value for money in the NHS.

Cost-effectiveness results comparing alternative relative risk estimates for biomarkers

The results of the systematic review of the clinical effectiveness of circulating biomarkers demonstrated a relatively high level of uncertainty surrounding the estimated hazard ratios representing the prognostic importance of the various biomarkers. The results from the base-case analysis are based on the mean estimates of the hazard ratios. In order to examine the robustness of the cost-effectiveness results to this source of uncertainty, additional scenarios were considered based on the lower and upper bounds of the 95% CIs for the estimates of the hazard ratio associated with the biomarker information. The results of these analyses are shown in *Tables 19* and *20* respectively, presented in the context of maximum waiting times of 90, 40 and 15 days.

Table 19 shows the results when the biomarker coefficients in the risk equations are set to the lower 95% CI value (i.e. biomarkers carrying less information). This approach results in a decrease in the absolute risk of clinical events for all patients regardless of the prioritisation strategy employed, relative to those applied in the base-case analysis.

TABLE 18 *Cost-effectiveness results comparing alternative maximum waiting times*

	90-day maximum waiting time				40-day maximum waiting time				15-day maximum waiting time			
Strategy	**Cost (£)**	**Life-years**	**QALY**	**ICER[a]**	**Cost (£)**	**Life-years**	**QALY**	**ICER[a]**	**Cost (£)**	**Life-years**	**QALY**	**ICER[a]**
No formal prioritisation	16099.77	11.6611	8.2796		16095.47	11.6845	8.2973		16093.22	11.6963	8.3062	
Ontario urgency score	16100.00	11.6646	8.2822	88	16095.53	11.6861	8.2984	55	16093.24	11.6969	8.3066	31
New Zealand urgency score	16100.87	11.6663	8.2835	ED	16095.91	11.6868	8.2990	ED	16093.38	11.6972	8.3068	ED
Risk score without biomarker	16101.98	11.6713	8.2871	ED	16096.37	11.6891	8.3006	ED	16093.53	11.6980	8.3074	ED
Risk score with CRP	16107.99	11.6714	8.2872	D	16102.37	11.6891	8.3007	D	16099.54	11.6980	8.3074	D
Risk score with eGFR	16102.22	11.6721	8.2877	405	16096.47	11.6894	8.3009	380	16093.57	11.6981	8.3075	362
Risk score with CRP + eGFR	16108.19	11.6723	8.2878	57,842	16102.46	11.6895	8.3009	133,287	16099.57	11.6982	8.3075	374,371

D, dominated; ED, extendedly dominated.
a ICERs are calculated as cost per QALY.

Furthermore, a strategy of no formal prioritisation is now dominated by the strategy of Ontario urgency score. Hence, Ontario urgency score is now the least effective (and non-dominated) strategy considered, and provides the initial reference point for the subsequent ICER estimates. The ICER comparing a risk score using eGFR with the Ontario urgency is £306 per additional QALY. The ICER of a risk score with CRP and eGFR compared with a risk score using eGFR alone was well above the threshold of value for money in the NHS (£79,000–552,000 for different maximum waiting times). Hence, even when eGFR carries less information than in the base-case scenario, this prioritisation strategy was associated with the highest ICER below the NHS threshold, and is still the most cost-effective strategy. It should be noted that the meta-analysis showed evidence of small study (publication) bias and incomplete adjustment for simple clinical information such as age, sex, smoking, diabetes, and obesity, suggesting that the estimated coefficients for biomarkers may be lower than those reported in the base-case meta-analysis. Hence, the lower bound of 95% CI is more likely to be closer to the true biomarker effect than the point estimate used in the base-case estimates; our conclusions regarding cost-effectiveness are unlikely to change with such a scenario.

In *Table 20*, the results of setting all biomarker coefficients in the risk equation to their upper 95% CI value are presented. This scenario results in an associated increase in the absolute risk of clinical events for all patients regardless of the prioritisation strategy employed, resulting in a reduction in the mean QALY estimates for all strategies compared with the base-case analysis. With this scenario, the results are similar to the results of the base-case scenario. The estimates of the ICER for the risk score with CRP and eGFR, compared with the risk score with eGFR alone, are more favourable in this scenario. However, using a 90-day maximum waiting time the ICER is £39,000, which is still above the threshold level of £20,000–30,000 per QALY. Thus, a prioritisation strategy with a risk score using both CRP and eGFR is unlikely to be cost-effective.

In *Figure 6*, the difference in the assigned day of CABG between non-dominated prioritisation strategies is plotted for the three different maximum waiting times. Hence, the figure illustrates the degree to which a prioritisation strategy actually alters, when compared with a relevant comparator, the subsequent ordering of individual subjects in terms of their position on a waiting list. Furthermore, the ICERs for the relevant comparisons are given, illustrating the link between different ordering of the waiting list and cost-effectiveness. In *Figure 6* it is demonstrated that adding the novel circulating biomarker CRP to the routinely measured eGFR has little scope for improved effectiveness (changing day of CABG) with 90-day maximum waiting times, and almost none for shorter maximum waiting times.

Cost-effectiveness results comparing alternative prices

The base-case results are based on a cost of £6 for CRP derived from the costs of the test in a research setting. However, this cost may vary depending upon the setting and may also differ if novel biomarkers become more widely used in the NHS. The potential robustness of the cost-effectiveness results to this issue is an important consideration. Clearly, if the costs of CRP are lower than £6, then the subsequent cost-effectiveness of a prioritisation approach employing a risk score with eGFR and CRP will become more favourable. Considering a 90-day waiting time, lowering the cost of CRP to £3 (£6 in the base-case analysis) reduces the ICER for the comparison of the risk score with eGFR and CRP with the risk score based on CRP alone to approximately £29,000 per QALY. At a cost of £2 for CRP, the subsequent ICER reduces to below the lower bound of the NICE threshold (approximately £19,000 per QALY). The cost-effectiveness of employing a risk score with eGFR and CRP is therefore somewhat sensitive to the cost of the test itself if the maximum waiting time is 90 days. Employing shorter waiting times, the cost of CRP has to be less than £1.30 for a strategy with eGFR and CRP to be cost-effective with a 40-day maximum waiting time (ICER approximately £22,000 with a CRP cost of £1) and below £0.5 with a 15-day maximum waiting time (ICER approximately £21,500 with a CRP cost of £0.35).

Organisation and training issues

A related issue also concerns the potential organisational and training implications (including costs) of using any formalised approach to prioritisation that has not been formally quantified here and would need to be considered against expected health gains. Given that the risk equations (including and excluding eGFR) are derived from routinely collected data, we have assumed that the opportunity cost of acquiring this

TABLE 19 *Cost-effectiveness results based on lower 95% CIs for relative risk estimates for biomarkers*

	90-day maximum waiting time			40-day maximum waiting time			15-day maximum waiting time		
Strategy	**Cost (£)**	**QALY**	**ICER[a]**	**Cost (£)**	**QALY**	**ICER[a]**	**Cost (£)**	**QALY**	**ICER[a]**
No formal prioritisation	16125.44	8.4148		16120.43	8.4309	D	16117.85	8.4390	D
Ontario urgency score	16125.44	8.4172	0.4	16120.40	8.4320		16117.83	8.4394	
New Zealand urgency score	16126.08	8.4183	ED	16120.67	8.4325	ED	16117.93	8.4396	ED
Risk score without biomarker	16126.71	8.4213	ED	16120.93	8.4338	ED	16118.02	8.4401	ED
Risk score with CRP	16132.71	8.4214	D	16126.93	8.4339	D	16124.02	8.4401	D
Risk score with eGFR	16126.80	8.4216	306	16120.97	8.4340	285	16118.03	8.4402	268
Risk score with CRP + eGFR	16132.78	8.4217	78,915	16126.96	8.4340	165,707	16124.03	8.4402	552,300

D, dominated; ED, extendedly dominated.
a ICERs are calculated as cost per QALY.

TABLE 20 *Cost-effectiveness results based on upper 95% CIs for relative risk estimates for biomarkers*

	90-day maximum waiting time			40-day maximum waiting time			15-day maximum waiting time		
Strategy	**Cost (£)**	**QALY**	**ICER[a]**	**Cost (£)**	**QALY**	**ICER[a]**	**Cost (£)**	**QALY**	**ICER[a]**
No formal prioritisation	16064.57	8.1424		16061.23	8.1616		16059.44	8.1713	
Ontario urgency score	16065.09	8.1452	182	16061.41	8.1629	141	16059.49	8.1718	111
New Zealand urgency score	16066.22	8.1466	ED	16061.90	8.1635	ED	16059.67	8.1720	ED
Risk score without biomarker	16067.96	8.1508	ED	16062.63	8.1654	ED	16059.93	8.1727	ED
Risk score with CRP	16073.98	8.1510	D	16068.63	8.1655	D	16065.93	8.1728	D
Risk score with eGFR	16068.44	8.1518	511	16062.83	8.1658	480	16060.00	8.1729	460
Risk score with CRP + eGFR	16074.42	8.1519	39,111	16068.83	8.1659	81,830	16066.00	8.1729	229,083

D, dominated; ED, extendedly dominated.
a ICERs are calculated as cost per QALY.

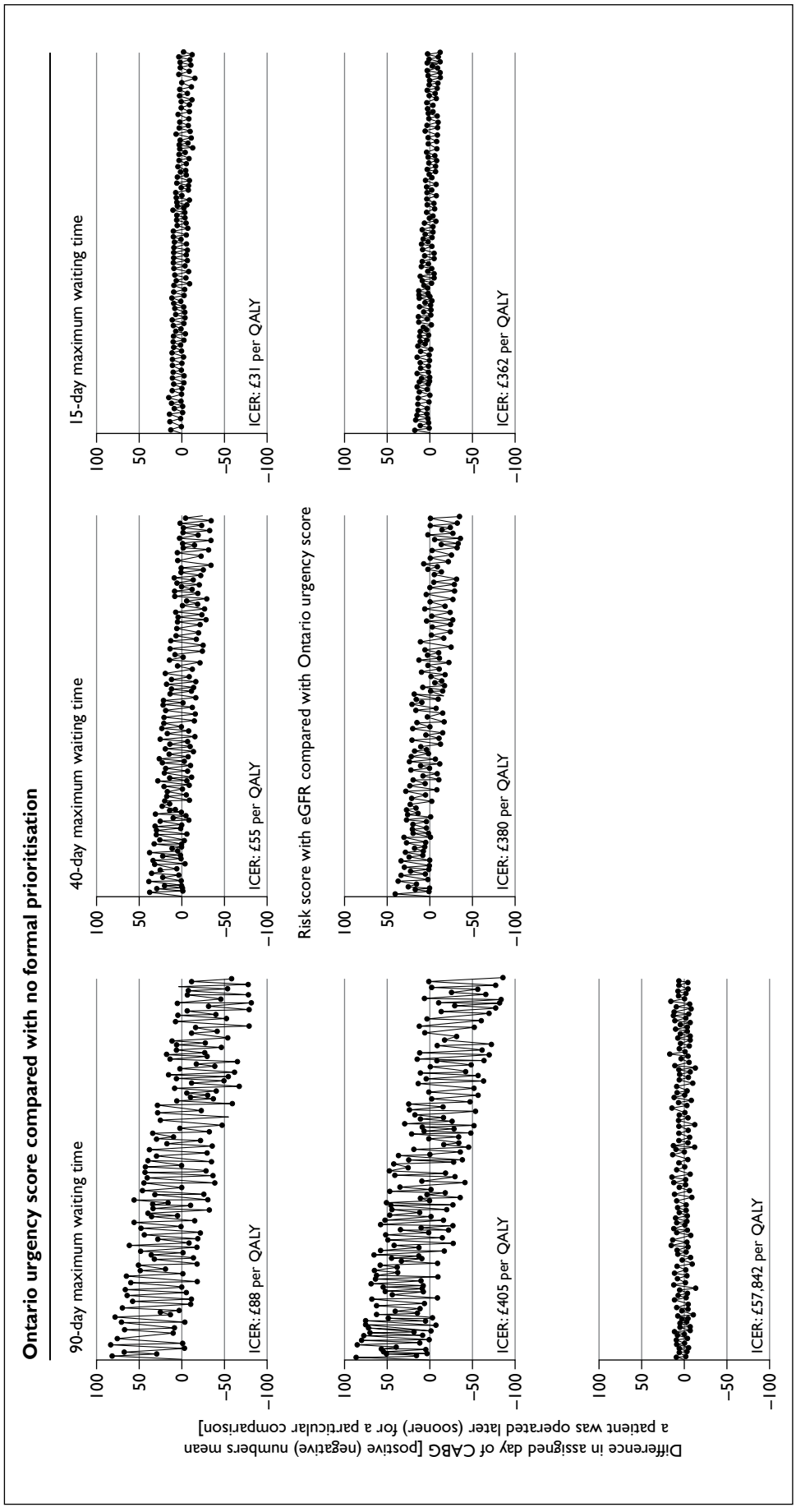

FIGURE 6 *Difference in assigned day of CABG and ICERs for non-dominated prioritisation strategies. Each dot represents a patient in the representative cohort and shows the change in assigned day of CABG for the particular comparison. Comparing Ontario urgency score with no formal prioritisation employing a 90-day maximum waiting time (top left panel) resulted in 48.6% of patients undergoing operation on average 28.2 days later and 50.0% of patients undergoing operation on average 27.4 days sooner. Comparing a risk score with eGFR and CRP with a risk score using eGFR alone employing a 15-day maximum waiting time (bottom right panel) resulted in 23.3% of patients undergoing operation on average 1.2 days later and 24.2% of patients undergoing operation on average 1.1 days sooner.*

information for the purposes of risk stratification of a waiting list would be zero. However, the subsequent application of this information within a formal risk scoring system could incur additional costs, as could the aforementioned organisational and training implications that would arise from a more systematic approach to prioritising waiting lists more generally. Equally, it should be recognised that while such changes may impose additional 'up front' costs to the NHS, at the level of an individual patient these costs may be negligible as such costs would ultimately be shared among the large number of patients who would then benefit from this approach. However, to more formally consider this issue and to explore the robustness of the base-case results to it, additional analyses were undertaken to identify the threshold cost at which the application of a formal prioritisation strategy would cease to become cost-effective compared with current practice. This analysis demonstrated that the per patient cost of implementing a risk equation incorporating eGFR would have to exceed £190 for the ICER estimate to exceed £30,000 per QALY. Hence, the results appear likely to be robust to this issue.

Other novel biomarkers not formally considered in decision model: the example of brain natriuretic peptide

Our results provide a provisional basis to consider the potential cost-effectiveness of the other ($n = 7$) novel biomarkers that were included in the systematic review, but were not formally considered in the model. The evaluation of the risk equations employing eGFR and one based on a combination of eGFR and CRP provides a suitable reference point to consider the necessary requirements that need to hold for an alternative novel biomarker to be cost-effective. The first requirement is that an alternative novel biomarker is both cheaper and at least as effective as CRP. However, as CRP is the cheapest of the novel biomarkers considered (see *Table 1*), this requirement is not met by any of the current alternatives to CRP. Thus, the second requirement is a more important consideration; an alternative and more expensive biomarker must provide comparatively greater gains in QALYs than those obtained using CRP to justify value for money. The summary results presented in *Table 7* suggest that only BNP appears to meet this requirement as it may provide additional prognostic value compared with CRP (it has a higher point estimate of relative risk – 2.93). However, the cost of BNP is also markedly higher at £35. Consequently, the additional health gains that would be required to justify this additional cost compared with CRP will inevitably need to be markedly higher than those achieved using CRP. The results from the current model suggest that the gains in QALYs using BNP would need to be approximately 5.5 times greater than those obtained using CRP, to demonstrate value for money. Although it is not possible to directly link the relative risk estimates reported in *Table 1* and subsequent QALY gains without formally modelling this strategy, the size of the relative risk estimates suggest that it is unlikely that BNP would be a cost-effective alternative to CRP.

Chapter 7
Discussion

Objective addressed

We developed a novel framework for evaluating the cost-effectiveness of formally incorporating biomarkers – routine, novel or both – into clinical decision-making. This framework evaluates methods of prioritising patients with respect to long-term costs and health outcomes. We found that a prioritisation strategy employing a single, routinely available biomarker (eGFR) appears cost-effective and robust to alternative assumptions, including variation in the maximum waiting list times. However, the additional costs and value of more precise information obtained from employing multiple biomarkers (e.g. eGFR and CRP) appears less clear and is unlikely to be cost-effective in the context of shorter waiting list times.

Systematic review of pooled relative risks

We report the first meta-analysis of any circulating biomarker in the prognosis of stable coronary disease, offering a synopsis of the field. Analysing 390 biomarker prognosis relative risks, we present a comparison of the strength of reported effects across a wide range of routinely recorded and novel biomarkers. The pooled relatives risks estimated from random effects models ranged from 2.00 (eGFR) to 1.96 (CRP) to 2.93 (BNP). However, these estimates are subject to a range of biases.

Systematic review of publication bias and missing studies

We found evidence that small studies were likely to report stronger effects, consistent with publication bias. Selective reporting within publications may also operate: those CRP results not mentioned in the abstract were less likely to be positive. More extreme effects were also observed among recently started studies, opposite to the widely observed situation where early literature tends to report inflated relative risks.[208] Subgroups of literature-based meta-analyses are unreliable means to explain such findings, and they should be seen as hypothesis generating.

Systematic review of the relative lack of evidence on routinely assessed biomarkers

Novel biomarkers contributed more studies than did routinely assessed markers. Thus, in the meta-analysis there were 77 studies available for CRP and four for haemoglobin. Biases may operate from funders of research, researchers and journal editors favouring enquiry into new markers at the expense of more robustly understanding the prognostic importance of widely performed measures. Further, the effects of novel markers are commonly not adjusted for routinely available biomarkers. Other routine markers fell outside our review, e.g. serum potassium, albumin, urate.

Systematic review of the relevance of the literature identified

We identified no studies in which a novel biomarker was related to prognosis among patients on the waiting list for CABG. Many studies reported only that patients had anatomical evidence of coronary artery disease but make no statement about the proportion of them with symptoms of angina or the severity of these symptoms. This reflects the lack of internationally agreed case definitions for what constitutes stable angina pectoris. This is of particular importance when considering the generalisability of findings to symptomatic patients awaiting CABG. Very few studies (with the possible exception of the European Concerted Action on Thrombosis and Disabilities study)[209] were designed with the purpose of assessing the incremental prognostic value of biomarkers. No studies were identified that reported the incremental prognostic value of biomarkers in relation to a clearly defined clinical decision. Instead, the focus of many of the reports was assessing biological hypotheses such as plaque stability. Notwithstanding these caveats, the estimates lie within plausible ranges, consistent with those observed in healthy population (aetiologic) studies, which reported an effect of 1.5 for CRP[41] and 1.41 for eGFR.[210]

Systematic review of the quality of individual studies

Of those studies that were included, we identified concerns about the quality of reports of individual studies with potential for bias at each stage of population selection, biomarker measurement, rationale for inclusion of confounders, lack of primary outcome specification and post hoc analytical decisions over the choice of statistical model. Such potential biases have been identified in systematic reviews of cancer prognostic markers.[211,212] The extent and direction of these potential biases is not always clear but previous meta-analyses of observational studies of novel risk factors have suggested that they are likely to inflate estimates. Thus, more precise, less biased estimates of the relative risk would be hypothesised to be weaker than those observed.

Systematic review of the incremental prognostic value

A goal of novel biomarker estimation is to contribute information beyond that already provided by routinely measured markers. We found that the quantity and quality of adjustments for potential confounding factors in the systematic review was highly variable, and as few studies systematically adjusted for the routinely recorded factors known to relate to both CRP and outcome (including smoking, diabetes, obesity and lipids), residual confounding of the relative risks cannot be excluded. Thus, better use of information already obtained in clinical practice (i.e. at zero marginal cost) might contribute at least part of the prognostic information reported for CRP. No study assessed whether CRP might add discrimination to standard clinical factors in the prognostic risk scores for patients with angina developed in the ACTION[17] and EuroAngina[213] studies.

Angiography registry: SCAAR

The ideal registry in which to develop our decision-analytic model has several characteristics. It should identify large numbers of patients at the time of angiography and record details of the intention to perform CABG and baseline clinical information including biomarkers; be multicentre or national; reflect contemporary practice; and have follow-up for fatal and non-fatal events. No such registry exists in the UK. One of the few registries in the world that meets these criteria is SCAAR.[36] The Swedish angiography patients observed in SCAAR are likely to be generalisable to the UK because patient characteristics are similar to those reported in UK series.[214] Sweden has a similar health-care system (free at the point of use), and broadly comparable rates of coronary heart disease and rates of angiography and CABG. Sweden does differ from the UK in not having comparable ethnic minority populations; 14% of patients appropriate for CABG in the UK are reported as being of South Asian ethnicity.[215] Such ethnic differences are unlikely to significantly alter our conclusions because ethnicity is not associated with event rates nor with waiting time up to 90 days.[215] In Sweden, as in the UK, routine clinical practice involves informal, implicit prioritisation in which patients are given a qualitative order (urgent, semi-urgent and routine) after a joint clinical meeting between cardiologists and surgeons. However, there is a lack of national comparative research into the processes of current practice.

Smoking was not included in our risk model, despite its association with risk among patients with coronary disease,[216] because it would serve to bring smokers forward in the queue. The contrary position – that smokers should be put to the back of the queue – which has attracted interest from media and ethicists is not addressed by our model. But our score could be used to investigate whether smokers are being given different priority and (according to viewpoint) discriminated against.

Cost-effectiveness: general methods

In order to assess the value of circulating biomarkers in prioritising CABG waiting lists, it is necessary to estimate their effect on health system costs and patients' quality-adjusted life expectancies compared with other forms of prioritisation. It is then necessary to assess how any improvement in patients' health compares with the health decrement associated with removing or reducing the use of other interventions or programmes elsewhere in the NHS to fund the use of biomarkers in this way (i.e. opportunity costs). The choice of all the relevant options for prioritising CABG waiting lists is critical in understanding the value of the specific strategies associated with biomarkers. The need to include routine clinical practice as an option is clear; although no formal prioritisation strategy may be

used, decisions are inevitably taken about the order in which patients receive their procedure.

Urgency scores incorporate symptom severity which is an example of a (non-circulating) biomarker, which is routinely assessed. We also evaluated a strategy of ordering the CABG waiting list based on a risk prediction equation without biomarkers. Although formal use of risk scores is likely to be rare in routine practice, they essentially make explicit what clinicians would be expected to do routinely – assess the chance of a patient experiencing a fatal or severe non-fatal event while on the CABG waiting list. There are no risk prediction scores that are in widespread use in any aspect of the management of stable angina in general. Recently, two prognostic risk scores have been developed among patients with stable angina,[17,217] but neither were suitable for use in the decision model because they were not developed in populations with severe coronary artery disease awaiting CABG; the scores did not assess 90-day risk (they assessed long-term risk over 1–5 years); and they used clinical covariates that are not routinely available (e.g. exercise electrocardiographic findings, left ventricular ejection fraction).

Changing the day of CABG is a surrogate of biomarker effectiveness

To assess the cost-effectiveness of circulating biomarkers, it is then necessary to establish their value, over and above routinely collected information incorporated into the risk equation, in predicting serious events.

To be able to demonstrate their cost-effectiveness in informing the prioritisation of patients on the CABG waiting list, it is necessary to show that information on biomarkers (as part of a risk prediction equation) will achieve a change in the order in which patients receive their procedure. In effect, 'order' becomes a surrogate of the effectiveness of biomarker information in this context. As with any surrogate, it is necessary to assess its link with final changes in patients' health and with costs. The decision-analytic model quantifies this link by estimating the rate of prognostic events (death, non-fatal myocardial infarction and non-fatal stroke) for patients with different baseline characteristics while on the waiting list, during the procedure and beyond the procedure. Each event affects health service costs and patients' quality-adjusted life expectancy.

Hence, the key to biomarkers showing value is the extent to which they affect the order in which CABG is given and this change in order affects event rates.

Cost-effectiveness: base-case results

The base-case results of the cost-effectiveness analysis suggest that the choice of prioritisation strategy is between no formal prioritisation, Ontario urgency score, a risk score with eGFR and a risk score with both eGFR and CRP, with the other options being subject to dominance or extended dominance. Given the cost-effectiveness thresholds used by NICE (£20,000–30,000 per QALY),[36] the base-case results suggest that incorporating eGFR into the risk model would be cost-effective, while using both eGFR and CRP is unlikely to be cost-effective.

It should be emphasised that the differences in mean costs and QALYs between current practice and the full range of formal prioritisation strategies are relatively small. Hence, although the ICER estimates indicate that the use of a formal prioritisation approach based on a risk score with eGFR appears to represent good value for money to the NHS, the predicted difference in health outcomes at the level of an individual needs to be considered in terms of whether this is clinically meaningful. Clearly, the biggest difference in outcomes between strategies is that observed based on current clinical practice and the most precise strategy based on a risk prediction equation including information generated by a combination of biomarkers. For this comparison, the resulting difference in mean QALYs is approximately 0.008 (equivalent to an additional 2.9 days of good health over a patient's lifetime).

The relatively minor differences in terms of health outcomes estimated between the different strategies may not be entirely surprising given the nature of the decision problem under investigation. Ultimately, the different prioritisation strategies can result in a different ordering of patients only within the waiting list itself, and all patients (except those experiencing a fatal event on the waiting list) will eventually receive a CABG within 90 days. Equally, it should be noted that although the differences in quality-adjusted survival are small between strategies, formally employing more information in the prioritisation of patients appears to result in improved health outcomes.

Cost-effectiveness: alternative scenarios

Given that all surviving patients will eventually receive CABG, the maximum waiting time represents an important consideration with respect to the additional value that formal prioritisation approaches will have in the context of prioritising waiting lists. While the base-case analysis has been undertaken within the context of a maximum waiting list time, the value of alternative approaches to prioritisation within shorter waiting list times is an important consideration. To explore the robustness of the base-case results to this aspect, additional scenarios were considered based on a reduction in the maximum waiting list time (see *Table 18*). The results suggest that the use of a risk score with eGFR is cost-effective (subject to a £20,000–30,000 cost-effectiveness threshold) for maximum waiting list timing ranging from 15 days to 90 days. The use of the risk score with both eGFR and CRP would, however, have an ICER above NICE thresholds for maximum waiting times of 40 days and 15 days.

As noted above, less-biased estimates of the relative risk of biomarkers would be hypothesised to be weaker than those observed. The sensitivity scenario applying the lower 95% confidence limit value gives an indication of how these biases may influence the cost-effectiveness results. With biomarkers carrying less information, the risk score with eGFR and CRP appears even less cost-effective. However, the strategy employing a risk score with eGFR is still cost-effective employing the 95% lower limit value. It is difficult to estimate the magnitude of the bias on the biomarker estimates. A weaker estimate for CRP will clearly make the conclusions of this study stronger, as a risk score including CRP will look even less cost-effective. It is less clear how this bias will influence the cost-effectiveness of a risk score with eGFR. Clearly, the bias needs to have a large effect on the estimated coefficient to make the strategy employing a risk score with eGFR alone cost-ineffective.

Cost-effectiveness: limitations

It is important to be aware of limitations in the cost-effectiveness analysis. All parameters in the model are estimated with uncertainty – some of these are estimated with considerable imprecision (e.g. the predictive effects of biomarkers). Ideally, the model would have been subject to probabilistic sensitivity analysis in which the uncertainty in all parameters is systematically propagated through the model using simulation to show the consequent uncertainty in cost-effectiveness results. Given the complexity of the model – in effect the model is run for each patient in the notional cohort – probabilistic sensitivity analysis using the existing modelling platform would have taken large periods of time to compute. The authors have been funded by the National Institute for Health Research to establish a large new patient cohort of patients with angina, and assess a range of biomarkers in relation to prognosis and use of probabilistic sensitivity analysis in decision-analytic models. In the absence of probabilistic sensitivity analysis, a series of scenario analyses are presented including a sensitivity analysis on the value of the parameters relating to the relative risk with biomarkers.

We imputed values of CRP in SCAAR and cannot exclude the possibility that this diluted its effect. However, our conclusions are likely to be robust to this possibility because the literature-based estimates are likely to be inflated because of publication bias and inadequate adjustment for the routinely recorded factors known to relate to both CRP and outcome (including smoking, diabetes, obesity and lipids). Furthermore, even when using the upper 95% confidence limit for the effect, CRP had an ICER exceeding £40,000 per QALY, and is thus unlikely to be considered cost-effective. However, the manner in which we imputed the effect of CRP on risk, i.e. by averaging over tertiles, will capture some of the uncertainty associated with having to use imputation.

A further limitation is that we have simplified the process of prioritisation. In the modelling, it is assumed that prioritisation is undertaken on a single cohort of patients who join the list simultaneously and who receive their CABG in the order determined by the model. In reality, there is a dynamic process to a waiting list, in that new patients are being added to existing patients over time. In principle, this means that a formal prioritisation strategy would have to be run every time someone leaves or joins the list. A number of decision rules could be used in this more complex situation which may involve a patient's anticipated day for surgery changing a number of times, or there may be constraints on how many changes are permitted. Revising the date of operation with changes in the pool of people waiting has its own information and scheduling costs, and the feasibility of such an approach as well as its acceptability to the patient are likely to be limited.

Further research is needed to include these more complex prioritisation algorithms into our modelling framework.

Furthermore, the model has not compared all the feasible strategies that could be used to prioritise patients on the waiting list for CABG. Specifically, as discussed in Chapter 4, there is a very large number of potential strategies involving different biomarkers individually or jointly. We focused on a circulating biomarker that is either routinely available (eGFR) or is beginning to be used in some centres to inform the care of stable angina patients (CRP). The model reported here provides a framework that can be adapted to look at other prioritisation strategies. Importantly, it provides a general approach to evaluating the cost-effectiveness of biomarkers to stratify patients by risk in a number of contexts which might include, for example, revascularisation versus best medical management and choice of revascularisation.

Implications for policy-makers

Notwithstanding these caveats, we expect our results to inform changes in clinical practice. The widespread practice of using only implicit or informal means of clinically ordering the waiting list may be harmful and we hope would be replaced with formal prioritisation approaches. The recently published Syntax trial compared CABG and PCI in the management of severe coronary artery disease and reported lower primary end point rates in those randomised to CABG.[8] It is possible that this positive trial will increase the number of patients referred for surgery, increase pressure on waiting time, and further emphasise the importance of our findings.

In our decision model we found that incorporation of a routinely available biomarker (eGFR) to a risk score was associated with changes in the day of assigned CABG, leading to higher QALYs at modest additional cost. This explicit strategy of formally prioritising the waiting list was cost-effective and robust to alternative assumptions, including maximum waiting list times of only 14 days. Although the QALY gains averaged across patients are small, our findings suggest that implementing the eGFR strategy would offer worthwhile gains in health – 780 QALYs per 100,000 patients.

This gain in health needs to be set against the organisational and training implications (including costs) of using any formalised approach to prioritisation, which we did not quantify. Several lines of evidence suggest that cost and organisational barriers to implementation of formal prioritisation scores, while real, may not be large. First, use of routinely collected data for scores for calculating operative mortality risk (e.g. euroSCORE[24]) is already widespread, suggesting that the information technology infrastructure and clinical culture for implementing scores already exist. Second, 'formal protocols' for prioritisation have recently been recommended.[25]

This estimated change in health related to the cheapest biomarker compared with routine clinical practice. In moving from eGFR to potentially more effective novel biomarkers in terms of risk prediction, the *incremental* gains in health are likely to be quite small and their scope to be cost-effective given an additional acquisition cost may be quite limited.

Brain natriuretic peptide and other biomarkers not formally included in decision model

Our results provide a provisional basis to consider the potential cost-effectiveness of the other biomarkers that were included in the systematic review but were not formally considered in the model. Haemoglobin was the routine biomarker with the highest relative risk (2.9) and given its (zero) cost, further research that reduced the uncertainty around this estimate would be worthwhile. Given that all the other novel biomarkers are more expensive than CRP, an alternative and more expensive biomarker must provide comparatively greater gains in QALYs than those obtained using CRP to justify value for money. The summary results presented in *Table 7* suggest that only BNP appears to have a stronger relative risk (2.93 for BNP versus 1.96 for CRP). However, the cost of BNP is also markedly higher at £35. Consequently, the additional health gains that would be required to justify this additional cost compared with CRP will inevitably need to be markedly higher (more than five-fold) than those achieved using CRP. Our model suggests that it is unlikely that BNP would be a cost-effective alternative to CRP. The predictive ability of multiple biomarkers has not been widely assessed and, to date, findings are conflicting.[218,219] Findings from our model suggest that combinations of costly biomarkers are unlikely to be cost-effective.

Whether common genetic polymorphisms might contribute prognostic information is also not known, but the marginal cost of adding multiple genetic variants to a testing panel is low.

The issue of the maximum waiting time is important to consider for two reasons. The first is that the maximum waiting time will influence the cost-effectiveness of different prioritisation strategies (see *Table 19*) – in general, the shorter the maximum wait the smaller the scope for re-allocation of time slots with a prioritisation strategy with or without biomarkers, and hence the smaller the potential health gains to set against any cost of the prioritisation. The second reason for the importance of the maximum waiting time is that it may be a better use of NHS resources to reduce this time further rather than to invest in prioritisation strategies with a fixed maximum waiting time. This is because reducing the maximum wait will itself improve health outcomes – for example, *Table 18* shows that a move from a maximum wait of 90 days to a maximum of 40 days, with patients' order determined by routine practice, would increase QALYs by 0.03 for the average patient, i.e. a relatively large effect. This gain would have to be set against the cost of reducing waiting times. Figures released in August 2008 from the Department of Health suggest that about half the patients waiting for CABG have been waiting for between 1 and 3 months, and about half for up to 1 month.

Recommendations for further research

1. To establish and develop a national register of coronary angiography in the UK, which would provide a platform for health technology appraisal and other outcomes-based research. Such a register should include details of angiographic findings, clinical details required for basic risk equation, routinely estimated circulating biomarker information (eGFR) and follow-up for events and revascularisation (electronic patient record, Connecting for Health).
2. To develop initiatives for improving the quality of biomarker prognosis research,[230] for example by developing standards for reporting which have been influential in other types of research and to foster collaborations of individual participant data sets. The potential shortfalls in the design, conduct, analysis and reporting of the studies highlighted in this review are consistent with those reported in meta-analyses of biomarkers in the prognosis of cancer.[220,221] Reporting standards, when adopted by journal editors, have been instrumental in reporting the quality of randomised trials (CONSORT) and although standards for observational aetiological studies (STROBE)[222] exist, there is no counterpart for prognosis research.[223] A promising approach has been applied by Hayden[41] and REMARK guidelines.[40] Ultimately, registration of prognosis research studies may prove as important as it has been for trials,[224] especially because the rationale for many of the patient collections in this review was unclear.
3. To develop the decision-analytic framework by incorporating estimates of parameter uncertainty with probabilistic sensitivity analysis.
4. To use 'value of information' analysis to target where better research is needed. For example, to overcome problems of imputed data and parameters estimated from 'non-optimal' sources.

Conclusions

Formally employing more information in the prioritisation of patients awaiting CABG appears to be a cost-effective approach and may result in improved health outcomes. The most robust results relate to a strategy employing risk stratification using conventional clinical information together with a single biomarker (eGFR). The additional prognostic information conferred by collecting a novel circulating biomarker (CRP) or multiple biomarkers in terms of waiting list prioritisation is likely to be a cost-effective approach only in those countries with particularly long waiting lists.

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Contributions of authors

Harry Hemingway (Professor of Clinical Epidemiology) was principal investigator on the grant, led the systematic reviews and co-ordinated the first and final draft of the manuscript; he also acts as guarantor of the study. Martin Henriksson (Research Fellow) designed, implemented and analysed the decision model and wrote drafts of Chapters 2, 5 and 6. Ruoling Chen (Statistician) carried out the meta-analyses of the biomarkers. Jacqueline Damant (Research Officer) is a systematic reviewer who carried out the searches, reviewed titles and abstracts for eligibility and extracted study data. Natalie Fitzpatrick (Research Programme Co-ordinator) is a systematic reviewer and project co-ordinator who reviewed titles and abstracts for eligibility and extracted study data. Keith Abrams (Professor of Medical Statistics) supervised the statistical aspects of the meta-analyses and the decision-analytic modelling. Aroon Hingorani (Professor of Genetic Epidemiology) advised on the scope of the biomarkers to include and on the interpretation of the biomarker results in biological and clinical context. Magnus Janzon (Cardiologist) was instrumental in obtaining the necessary ethical clearance for the use of SCAAR data and its linkage to the Swedish death and hospital admission registries. Martin Shipley (Statistician) derived study-specific scaling factors for the meta-analysis. Gene Feder (GP) was a co-applicant on the grant and advised on clinical aspects. Sir Bruce Keogh (Professor of Cardiac Surgery, University College London; NHS Medical Director) stimulated initial interest in the project and contributed the perspective of a cardiothoracic surgeon as well as, now, a policy-maker. Ulf Stenestrand (Cardiologist), as principal investigator on the SCAAR registry, obtained permission to use these data for this project, and helped in their appropriate interpretation. Kate McAllister (Research Assistant) was involved at inception and at study end in compiling and checking the report and study references, and updating the systematic review. Juan-Carlos Kaski (Professor of Cardiovascular Science) made the St George's angina data set available for sharing, which allowed imputation of CRP in SCAAR and the calculation of adjustment factors. Adam Timmis (Professor of Clinical Cardiology) contributed clinical insights into the design and analysis of the meta-analyses and the decision-analytic modelling. Stephen Palmer (Senior Research Fellow of Health Economics) contributed to the overall design and implementation of the decision model and wrote much of the discussion. Mark Sculpher (Professor of Health Economics) led the overall design of the decision-analytic and cost-effectiveness models.

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Appendix 1

A systematic review of four routine and seven novel biomarkers

TABLE 21 *Systematic review of haemoglobin (15 studies)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			Hb (g/dl)	Assay type	Follow-up (years)	Event combination	Number of events
				Angina	Angiographic CAD	Prior MI					
Burr 1992[1] (DART)	1755	60.3	0	–	–	100	15	–	1.5	ACM	92
Arant 2004[2] (WISE)	864	58.4	100	–	63.9	–	–	–	3.3	ACM	155
Duffy 2006[3] (–)	1046	62.3	29.3	–	100	23.6	13.2	–	2.58	ACM	144
Exaire 2006[4] (REPLACE-2)	6002	62	25.6	–	100	8.2	–	–	1	ACM	128
Rajagopal 2004[5] (EPIC/ EPISTENT/EPILOG)[b]	2982	60.2	28.9	84.4	100	57.7	–	–	3	ACM	219
Fathi 2005[6] (–)	4522	65	29.1	–	100	42.4	13.6	–	1.7	ACM	332
daSilveira 2008 [7] (–)	310	63	38.7	–	–	51.5	13.4	–	3.67	CVD	43
Elisheva 2000[8] (ISCAB)°	4644	64.7	21.3	–	–	–	–	–	0.083	ACM	115
Lipsic 2005[9] (Intervention Cardiology Risk Stratification Study)°	143	61.5	28.7	–	100	32.9	14.02	–	3.7	CVD	19
McKechnie 2004[10] (–)	45,165	65.4	33.9	–	100	34.2	13.6	–	0.014a	ACM	1553
Muzzarelli 2006[11] (TIME)	253	79.1	43	100	89.3	50	13.3	–	4	CHD	51
Lee 2004[12] (–)	6116	65.4	31.6	31.1	100	27.6	–	–	0.083	ACM	107
Skinner 1999[13] (–)[b]	353	57.2	15.9	98	100	61	–	EDTA	5	CHD	16
Martin 1991[14] (–)[c]	1716	–	0	–	–	100	15.0	–	2	CHD	126
Reinecke 2003[15] (–)	689	62.6	0	–	30.2	100	–	–	2	ACM	62

CAD, coronary artery disease; EDTA, ethylenediaminetetraacetic acid; Hb, haemoglobin; MI, myocardial infarction; RR, relative risk; TC, total cholesterol; TG, triglycerides.
Note: References and the key to the footnotes are listed at the end of this appendix.

Crude annual risk (%)	Adjustments						Comparison groups					RR	95% CI
	Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes							
3.49	●	○	●	○	○	○	Continuous (per SD)					0.72	–
5.44	●	○	○	●	○	●	Continuous (per g/dl)					1.20	–
5.34	●	○	○	○	○	○	Continuous (per g/dl)					0.82	0.74 to 0.9
2.13	Adjustment variables unclear						Continuous (per mg/dl)					0.76	0.68 to 0.86
2.45	●	●	●	○	●	○	Continuous (per unit increase)					0.90	0.81 to 0.98
4.32	●	●	●	○	●	●	Continuous (per g/dl by log transformation)					0.74	0.69 to 0.79
3.78	●	●	●	●	●	●	≥ 12 women; ≥ 13 men	< 12 women, < 13 men				3.28	1.66 to 6.50
29.8	○	○	○	○	○	○	> 12.9	≤ 12.9				6.85	–
3.59	●	●	●	●	○	●	> 13.0	≤ 13.0				5.74	1.49 to 22.13
245.6	●	○	○	○	○	●	> 13.0	≤ 13.0				1.2	1.05 to 1.34
5.04							> 13.0	≤ 13.0				1.76	–
21.1	●	●	○	○	○	●	> 12	10–12	< 10			1.9	1.2 to 6.0
0.91	Crude						–	–	–			0.20	0.04 to 0.95
3.67	●	○	○	○	○	○	–	–	–	–		0.5	–
4.5	●	○	●	○	○	●	≤ 12.9	13.0–13.8	13.9–14.5	14.6–15.2[k]	≥ 15.3	4.09[p]	1.52 to 11.05

TABLE 22 *Systematic review of fasting glucose (28 studies)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			Fasting glucose (mmol/l)	Assay type	Follow-up (years)	Event combination
				Angina	Angiographic CAD	Prior MI				
Shah 2008[16] (–)	2886	66.2	–	–	100	31.8	7.48	–	5.025	ACM
Munoz 2007[17] (ICAR)	983	63.9	25.5	–	–	–	5.7	–	3	CVD
Vaidya 2007[18] (WAVE)	400	65.1	100	–	100	42.5	5.73	Glucose oxidase method	2.6	ACM + nf MI
Karlson 2000[19] (–)	624	63	33	49	–	100	4.8	–	10	ACM
Zindrou 2001[20] (–)	878	61.7	17.7	38.2	100	6.9	5.3	Colorimetric oxidase	0.082	ACM
Dankner 2003[21] (BIP)[m]	14,539	60.3	18.9	–	100	72.2	6.34	–	5.2	CHD
Wong 1989[22] (Framingham)[m]	344	62.2	31.7	–	–	100	5.33	–	32	CHD
Shah 2005[23] (–)[m]	1746	65.3	0.8	–	100	20.9	6.99	–	–	ACM
de Lorgeril 1999[24] (Lyon Diet Heart Study)[m]	423	–	–	–	–	100	–	–	3.8	CVD
Stewart 2008[25] (LIPID)	8733	61	16.6	–	–	72	–	–	7.8	CVD
Leander 2007[26] (Stockholm Heart Epidemiology Program)	1105	58.6	0	–	–	0	5.3	–	7.2	CHD
Leander 2007[26] (Stockholm Heart Epidemiology Program)	538	62.1	100	–	–	0	5.2	–	7.2	CHD
Corsetti 2007[27] (THROMBO)	173	60.3	32.9	–	–	24.3	8.69	–	2.17	CHD
Nigam 2006[28] (CASS)[m]	24,958	52.9	24.4	–	72.3	–	5.79	–	12.6	ACM
Arcavi 2004[29] (BIP)[m]	3122	60.1	8.6	57	–	100	5.58	–	6.2	Morbidity
The Coronary Drug Project Research Group 1975[30] (–)[m]	2789	47	0	–	–	100	5.61	–	5	ACM
Schlant 1982[31] (Coronary Drug Project)	2789	52.4	0	–	–	100	–	–	5	CHD
Dibra 2005[32] (–)[m]	990	65.4	20.3	100	100	39.8	–	Dehydrogenase method	1	ACM

Number of events	Crude annual risk (%)	Adjustments						Comparison groups		RR	95% CI
		Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes				
961	6.63	●	○	○	○	●	○	Continuous (per mg/dl)		0.999	–
32	1.09	●	●	○	○	○	○	Continuous (per mmol/l)		1.01	1.00 to 1.02
26	2.5	●	○	○	○	○	○	Continuous (per 10 mg/dl)		1.11	1.06 to 1.16
41	0.66	●	●	●	○	○	●	Continuous (per quartile)		1.07	1.02 to 1.12
30	41.2	Crude						Continuous (per quartile)		1.39	1.15 to 1.67
1055	1.39	●	●	●	●	●	●	Continuous (per 40 mg/dl)		1.21	1.16 to 1.26
126	1.14	●	○	○	○	○	○	Continuous (per 25 mg/dl)		1.11	1.03 to 1.20
–	–	●	○	○	○	●	●	Continuous (per 10 mg/dl)		1.03	1.02 to 1.05
58	3.61	Crude						Continuous (per mmol/l)		1.11	0.89 to 1.36
–	–	●	●	○	○	○	○	≤ 7.0	> 7.0	1.59	1.33 to 1.90
320	4.02	○	○	●	●	●	●	< 6.0	≥ 6.0	1.2	0.7 to 1.8
141	3.64	○	○	●	●	●	●	< 5.8	≥ 5.8	2.00	0.9 to 4.7
51	13.59				Crude			≤ 10.55	> 10.55	1.99	1.13 to 3.52
10,302	3.28	●	●	●	●	○	●	< 6.1	≥ 6.1	1.33	1.25 to 1.41
847	4.38	●	●	●	●	●	●	< 7.0	≥ 7.0	1.4	1.18 to 1.77
584	4.19	Crude						< 5.6	≥ 5.6	–	–
461	3.31	Crude						< 5.6	≥ 5.6	–	–
54	5.45	●	●	●	●	●	●	< 5.6	5.6–6.05	2.3	1.29 to 4.06

continued

TABLE 22 *Systematic review of fasting glucose (28 studies) (continued)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			Fasting glucose (mmol/l)	Assay type	Follow-up (years)	Event combination
				Angina	Angiographic CAD	Prior MI				
Held 2005[33] (APSIS)	740	59.2	30.9	100	6.4	22.8	5.2	Autoanalyser	3.4	CVD
Yun 2006[34] (–)[m]	98	59.8	35.7	29.6	–	5.6	5.72	–	3	ACM
Hu 2006[35] (DESIRE)[m]	1280	59.8	24.5	–	100	9.4	6.21	–	2.27	ACM
Anderson 2004[36] (Intermountain Heart Collaborative study)[m]	2035	65	24	1	100	17	–	–	2.8	ACM
Wilhelmsen 2001[37] (4S)	1468	58.7	0	–	100	100	–	–	5.4	CHD
Rubins 2002[38] (VA-HIT)[m]	1260	64.4	0	–	–	61.1	6.42	–	5.1	CHD
Van de Veire 2006[39] (–)[m]	160	65.3	0	–	100	73	5.72	–	2.7	ACM
Canner 2005[40] (Coronary Drug Project)[m]	3906	–	0	–	–	100	–	–	6.2	CHD
Kanaya 2005[41] (HERS)[m]	2763	67.2	100	–	100	17.2	6.05	Hexokinase enzymaticmethod	6.8	CHD
Fisman 2004[42] (BIP)[m]	14670	59.8	18.9	–	–	71.5	6.13	Autoanalyser	8	CHD
The Coronary Drug Project Research Group 1977[43] (–)[m]	2770	47	0	–	–	100	5.65	Autoanalyser	5	CHD

CAD, coronary artery disease; MI, myocardial infarction; RR, relative risk; TC, total cholesterol; TG, triglycerides.
Note: References and the key to the footnotes are listed at the end of this appendix.

Number of events	Crude annual risk (%)	Adjustments						Comparison groups					RR	95% CI
		Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes							
55	2.19	●	○	●	○	○	●	< 6.1	≥ 6.1				2.79	1.97 to 3.84
6	2.04	Adjustment variables unclear						< 6.1	≥ 6.1				4.58	0.28 to 84.0
158	5.43	●	●	○	●	○	○	< 5.6	≥ 5.6				1.43	1.04 to 1.87
345	6.05	●	●	●	●	●	●	< 6.1	6.1–6.9	≥ 6.9			1.68	1.48 to 1.90
431	5.44	Crude						< 5.0	5.0–5.9	≥ 6.0			1.34	1.05 to 1.70
328	5.10	●	●	●	●	●	●	< 6.1	6.1–6.9	≥ 7.0			1.72	1.01 to 2.68
25	5.79	Crude						< 6.1	6.1–6.9	≥ 7.0			–	–
1194	6.22	Crude						< 5.3	5.3–5.8	5.8–6.9	≥ 7.0		–	–
254	1.35	●	●	●	○	●	●	< 5.6	5.6–6.0	6.1–6.9	≥ 7.0		2.11	1.55 to 2.88
1470	1.25	●	●	●	●	●	●	≤ 3.8	3.9–4.4	4.4–6.0[k]	6.1–6.9	7.0–7.7	≥ 7.7	2.27	2.00 to 2.57
449	3.24	●	●	●	●	○	●	< 5.0	5.0–5.5	5.6–6.0	6.1–6.6	6.7–7.7	≥ 7.8	–	–

TABLE 23 *Systematic review of total cholesterol (47 studies)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			TC (mmol/l)	Assay type	Follow-up (years)	Event combination
				Angina	Angiographic CAD	Prior MI				
Asztalos 2008[44] (VA-HIT)	754	64	–	–	–	–	4.32	Standard enzymatic methods	5.1	CHD
Inaguma 2007[45] (–)	790	67.7	27.1	–	–	64.1	4.61	–	2.31	CVD
Munoz 2007[17] (ICAR)	983	63.9	25.5	–	–	–	5.4	–	3	CVD
Inoue 2007[46] (–)	149	63	29	53.7	83.2	29.5	4.77	–	7	CVD
Bolibar 2000[47] (ECAT)	2806	55.8	15.9	36.0	–	45.0	6.57	–	2	CHD
Falcone 2006[48] (–)	1014	64.6	27.2	82.9	100.0	44.9	5.08	Autoanalyser	2.7	CVD
Soeki 1999[49] (–)[n]	106	62.3	25.5	–	–	35.8	5.26	EIA	4.2	CHD
Retterstol 2002[50] (–)	247	52.7	21.9	–	–	100.0	6.9	EIA	10	CHD
Retterstol 2001[51] (–)	247	52.7	21.9	44.5	–	100.0	6.9	EIA	10	CHD
Deckers 2006[52] (EUROPA)	12,218	60.0	15	–	–	65.0	5.4	–	4.1	CHD
Minoretti 2006[53] (–)	799	64.9	25.6	100.0	100.0	46.3	5.1	Autoanalyser	2.7	ACM
Brilakis 2005[54] (–)	466	60.1	38	–	75.8	15	5.4	EIA	4	ACM
de Lorgeril 1999[24] (Lyon Diet Heart Study)	423	–	–	–	–	100.0	6.16	–	3.8	CVD
Tervahauta 1995[55] (Seven Countries Study)	171	72.2	0.0	–	100.0	–	6.2	EIA	5	CHD
Bittner 2002[56] (BARI)	1514	61.2	27	96.0	100.0	53.0	5.57	–	5.4	Morbidity
Simes 2002[57] (LIPID)	4502	53.0	–	–	–	–	5.65	–	5	CHD
Qi 2003a[58] (–)	134	64.1	19.4	48.5	100.0	34.4	3.83	–	1	ACM
Qi 2003b[59] (–)	121	64.1	21.5	43.8	100.0	30.6	3.87	–	0.077	ACM
Hu 2006[35] (DESIRE)	1280	59.8	24.5	–	100	9.4	4.80	–	2.27	ACM

Number of events	Crude annual risk(%)	Adjustments						Comparison groups	RR	95% CI
		Age	Sex	Smoking	Lipids (TC/LDL/HDL/TG)	Obesity	Diabetes			
168	4.37	●	○	●	●	●	●	Continuous (per SD)	1.13	0.95 to 1.33
110	6.03	●	●	○	○	○	○	Continuous (per mg/dl)	0.99	0.99 to 1.00
32	1.09	●	●	○	○	○	○	Continuous (per mmol/l)	1.0	0.99 to 1.01
58	5.56	Crude						Method unclear	1.5	0.5 to 2.8
106	1.89	●	●	●	●	●	●	Continuous (per SD)	1.17	0.97 to 1.42
105	3.84	●	●	○	●	○	○	Continuous (per SD)	1.31	1.09 to 1.58
11	2.47	Crude						Continuous (per SD)	0.92	0.51 to 1.66
36	1.46	●	○	●	●	○	○	Continuous (per quartile)	1.07	0.78 to 1.45
35	1.42	●	○	●	●	○	○	Continuous (per quartile)	1.10	0.8 to 1.6
1091	2.18	●	●	●	●	●	●	Continuous (per mmol/l)	1.15	1.09 to 1.21
69	3.20	●	●	●	●	●	●	Continuous (per mmol/l log increase)	1.21	0.96 to 1.54
61	3.27	●	●	●	●	○	○	Continuous (per 1.17 mmol/l)	0.75	0.55 to 1.04
58	3.61	Crude						Continuous (per mmol/l)	1.31	1.05 to 1.65
42	4.91	●	●	●	●	●	○	Continuous (per mmol/l)	1.30	1.0 to 1.7
–	–	●	●	●	●	●	●	Continuous (per 0.26 mmol/l)	1.04	1.00 to 1.09
–	–	●	●	●	●	○	●	Continuous (per mmol/l)	1.24	1.08 to 1.44
32	23.88	Crude						Continuous (method unclear)	0.98	0.93 to 1.06
16	171.73	Crude						Continuous (method unclear)	1.03	0.96 to 1.05
158	5.43	●	●	○	●	○	○	Continuous (per mg/l)	1.00	0.99 to 1.01

continued

TABLE 23 *Systematic review of total cholesterol (47 studies) (continued)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			TC (mmol/l)	Assay type	Follow-up (years)	Event combination
				Angina	Angiographic CAD	Prior MI				
Dankner 2003[21] (BIP)[n]	14,539	60.3	18.9	–	100.0	72.2	5.80	–	5.2	CHD
Wong 1989[22] (Framingham)[n]	344	62.2	31.7	–	–	100.0	6.31	–	32	CHD
Susen 2005[60] (–)[n]	488	61.0	22	69.0	100.0	19.0	5.23	–	1.24	ACM
Dibra 2003[61] (–)[n]	1152	66.1	26.6	100.0	100.0	31.5	5.26	–	1	ACM
Buchwald 2001[62] (POSCH)[b]	838	–	–	–	–	100.0	–	–	9.7	CHD
Lundstam 2002[63] (–)	963	59.0	23	93.9	100.0	51.0	–	EIA	11.7	ACM
Arcavi 2004[29] (BIP)[n]	3122	60.1	8.6	57.0	–	100.0	5.50	–	6.2	Morbidity
van Lennep 2000[64] (–)	838	64.8	20.4	–	100.0	47.2	7.1	EIA	2.99	ACM
Bosevski 2005[65] (–)	90	62.3	27	–	100.0	54.4	5.64	–	3	ACM
Schlant 1982[31] (Coronary Drug Project)[n]	2789	52.4	0.0	57.8	100.0	–	–	–	5	ACM
The Coronary Drug Project Research Group 1975[30][n]	2789	47.0	0	–	–	100.0	6.45	–	5	ACM
Behar 1997[66] (BIP)[n]	11,563	59.8	21.7	28.9	–	70.6	5.85	EIA	3.3	CHD
Zhukovskii 1982[67] (–)[n]	475	49.5	0.0	28.0	–	27.6	–	–	3.8	CHD
Glader 2002[68] (–)	1196	59.4	18.2	100.0	100.0	53.0	6.9	EIA	6.7	CVD
Frank 1973[69] (–)[n]	745	44.0	0.0	36.9	–	63.0	–	–	4.5	CHD
Berge 1982[70] (The Coronary Drug Project)[n]	354	47.0	0	–	–	100.0	–	Autoanalyser	5	ACM
Takahashi 1997[71] (–)[n]	312	60.0	24.8	–	100.0	48.0	4.98	EIA	4	CVD
Wu 2005[72] (–)[n]	150	67.8	9.3	100.0	100.0	19.7	4.70	ELISA	1.48	CHD

Number of events	Crude annual risk(%)	Adjustments						Comparison groups		RR	95% CI
		Age	Sex	Smoking	Lipids (TC/LDL/HDL/TG)	Obesity	Diabetes				
1055	1.40	●	●	●	●	●	●	Continuous (per 40 mg/dl)		1.09	1.02 to 1.15
126	1.14	●	●	○	●	○	●	Continuous (per 50 mg/dl)		1.34	1.12 to 1.59
44	7.27	Crude						Continuous (per mg/dl log increase)		1.00	0.99 to 1.00
86	7.46	●	●	○	●	○	●	Continuous (per 50 mg/dl)		1.10	0.90 to 1.40
119	1.46	●	●	○	○	○	○	Continuous (per unit increase)		1.00	–
363	3.22	Adjustment variables unclear						Continuous (ln)		0.50	0.3 to 0.8
847	4.38	●	●	●	●	●	●	Continuous (–)		1.01	1.00 to 1.01
101	4.03	●	●	●	●	○	●	Continuous (–)		0.73	0.38 to 1.38
–	–	●	●	●	●	○	●	Continuous (–)		0.05	–
591	4.24	Crude						<6.48	≥6.48	–	–
583	4.18	Crude						<6.48	≥6.48	–	–
535	1.40	●	●	●	●	○	●	≤4.14	>4.14	1.09	0.76 to 1.56
186	10.30	Adjustment variables unclear						<7.0	≥7.0	–	–
152	1.90	Crude						<6.5	≥6.5	0.90	0.7 to 1.3
105	3.13	Crude						≤7.0	>7.0	–	
80	4.52	Crude						<6.48	≥6.48	–	–
53	4.25	●	○	○	○	○	○	<5.70	≥5.70	2.30	1.2 to 4.2
48	21.62	Crude						<5.18	≥5.18	1.42	0.80 to 2.56

continued

TABLE 23 *Systematic review of total cholesterol (47 studies) (continued)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			TC (mmol/l)	Assay type	Follow-up (years)	Event combination
				Angina	Angiographic CAD	Prior MI				
Fukushima 2004[73] (–)[n]	120	65.6	37.5	–	100.0	–	5.23	–	1.7	CHD
Chikamori 2000[74] (–)[n]	392	60.6	25.3	–	100.0	–	5.26	EIA	1.4	CHD
Janoskuti 2005[75] (–)	387	59.0	26.9	–	–	48.1	5.9	EIA	5.1	ACM
Lipsic 2005[9] (Intervention Cardiology Risk Stratification Study)	143	61.5	28.7	–	100.0	32.9	–	–	3.7	CVD
Cesena 2004[76] (–)[n]	574	61.0	27.5	97.4	100.0	65.9	5.57	–	0.47	CHD
Zotz 2000[77] (–)[n]	251	64.5	19.5	–	100.0	64.0	6.37	–	1	ACM
Wilhelmsen 2001[37] (4S)	1490	–	0.0	–	100.0	–	–	EIA	5.4	CHD
Hoffmann 1980[78] (–)[n]	1414	65.6	0.0	–	100.0	65.5	6.86	Autoanalyser	5	ACM
Nygard 1997[79] (–)	574	62.0	18.6	–	100.0	57.4	–	Chemical assay	4.6	ACM
Ulvenstam 1984[80] (–)	1204	53.2	0.0	–	–	100.0	7.01	EIA	11	ACM

CAD, coronary artery disease; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; MI, myocardial infarction; RR, relative risk; TC, total cholesterol; TG, triglycerides.
Note: References and the key to the footnotes are listed at the end of this appendix.

Number of events	Crude annual risk(%)	Adjustments						Comparison groups					RR	95% CI
		Age	Sex	Smoking	Lipids (TC/LDL/HDL/TG)	Obesity	Diabetes							
44	21.57	Crude						≤5.70	>5.70				1.20	0.6 to 2.3
43	7.84	Adjustment variables unclear						≤5.18	>5.18				1.50	0.80 to 2.70
41	2.08	●	●	●	●	●	○	≥5.2	<5.2				2.90	1.02 to 8.42
19	3.59	●	●	●	●	○	●	≤6.5	>6.5				3.74	1.26 to 11.04
12	4.45	Crude						<6.22	≥6.22				3.68	–
10	3.98	Crude						≤5.18	>5.18				–	–
431	5.36	Crude						≤6.40	6.41–7.00	≥6.5			1.22	1.00 to 1.49
175	2.48	Crude						<6.48	6.48–9.07	>9.07			–	–
64	2.42	●	●	●	●	○	●	<5.50	5.50–6.99	7.00–8.99	≥9.0		1.59	0.50 to 5.07
254	1.92	Crude						≤5.99	6.0–6.69	6.7–7.29	7.3–8.03	≥8.04	–	–

TABLE 24 *Systematic review of low density lipoprotein (39 studies)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			LDL (mmol/l)	Assay type	Follow-up (years)
				Angina	Angiographic CAD	Prior MI			
Vittinghoff 2003[81] (HERS)	2763	66.6	100	26.4	100	–	3.8	–	4.1
Bolibar 2000[47] (ECAT)	2806	55.8	15.9	36	–	45	4.7	–	2
Falcone 2006[48] (–)	1014	64.6	27.2	82.9	100	44.9	3.46	Autoanalyser	2.7
Asztalos 2008[44] (VA-HIT)	754	64	–	–	–	–	2.89	Friedwald formula	5.1
Munoz 2007[17] (ICAR)	983	63.9	25.5	–	–	–	2.68	–	3
vonEnyatten 2008[82] (–)	1051	59	15.1	–	95.2	58.2	2.59	Friedwald formula	4.7
Volzke 2007[83] (–)	988	61.2	21.7	–	100	67	3.9	Friedwald formula	8
Glader 2002[68] (–)	1046	59.4	18.2	100	100	53	4.8	Friedwald formula	6.7
Bittner 2002[56] (BARI)	1514	61.2	27	96	100	53	3.66	Friedwald formula	5.4
Simes 2002[57] (LIPID)	4502	53	–	–	–	–	3.88	Friedwald formula	5
LaRosa 2007[84] (TNT)	9769	61	19	81.5	–	58.4	2.53	–	4.9
Aronow 2002A[85] (–)[n]	1410	80.5	65.4	–	–	100	3.97	–	3
Kastelein 2008[86] (TNT/IDEAL)	18,018	61.4	18.9	–	–	–	2.32	Friedwald formula	4.8
Sacks 1998[87] (CARE)[n]	4159	59.0	14.0	–	–	100	3.60	–	2
Aronow 2002[88] (–)[n]	529	79	67.7	–	–	100	4.01	–	2.42
Olsson 2005[89] (MIRACL)	2739	65	33.3	–	–	54	–	Friedwald formula	0.31
Yanase 2004[90] (–)[n]	102	61.3	16.7	–	100	76.5	3.34	–	4
Buchwald 2001[62] (POSCH)[n]	838	–	–	–	–	100	–	–	9.7
Linden 1998[91] (–)	964	60.8	23	–	–	50.6	4.57	Friedwald formula	5.2
Minoretti 2006[53] (–)	799	64.9	25.6	100	100	46.3	3.47	Friedwald formula	2.7
Susen 2005[60] (–)[n]	488	61.0	22.0	69	100	19	3.42	–	1.24

Event combination	Number of events	Crude annual risk (%)	Adjustments						Comparison groups	RR	95% CI
			Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes			
CHD	361	3.19	●	●	●	●	●	●	Continuous (per SD)	1.10	1.00 to 1.22
CHD	106	1.89	●	●	●	●	●	●	Continuous (per SD)	1.23	0.99 to 1.53
CVD	105	3.84	●	●	●	●	●	●	Continuous (per SD)	1.28	1.09 to 1.52
CHD	168	4.37	●	○	●	●	●	●	Continuous (per SD)	1.08	0.93 to 1.26
CVD	32	1.09	●	●	○	○	○	○	Continuous (per mmol/l)	1.0	0.99 to 1.02
CVD	95	1.92	●	●	●	○	●	●	Continuous (per mmol/l)	1.4	1.07 to 1.84
ACM	535	6.77	Crude						Continuous (per mmol/l)	1.12	1.05 to 1.20
CVD	152	2.19	Crude						Continuous (per mmol/l)	0.98	0.84 to 1.14
Morbidity	–	–	●	●	●	●	●	●	Continuous (per mmol/l)	1.033	0.98 to 1.09
CHD	–	–	●	●	●	●	○	●	Continuous (per mmol/l)	1.28	1.10 to 1.46
CHD	–	–	●	●	●	○	●	●	Continuous (per mg/dl)	1.15	1.1 to 1.2
CHD	838	19.8	●	○	●	●	○	●	Continuous (per mg/dl)	1.01	1.007 to 1.012
CHD	1783	2.06	●	●	○	○	○	○	Continuous (per 27.4 mg/dl)	1.15	1.10 to 1.20
CHD	486	5.84	●	●	●	●	○	●	Continuous (per 25 mg/dl)	1.21	1.11 to 1.31
CHD	405	34.2	●	○	●	●	○	○	Continuous (per mg/dl)	1.01	1.005 to 1.011
ACM	121	14.3	–	–	–	–	–	–	Continuous (mg/dl)	1.001	0.996 to 1.007
ACM	23	5.64	Crude						Continuous (per mg/dl)	0.99	0.98 to 1.01
CHD	119	1.46	●	●	○	○	○	○	Continuous (per unit increase)	1.01	–
ACM	168	3.35	Crude						Continuous (per unit increase by log transformation)	0.84	0.72 to 0.97
CVD	69	3.20	●	●	●	●	●	●	Continuous (per unit increase by log transformation)	1.21	0.81 to 1.56
ACM	44	7.27	Crude						Continuous (per unit increase by log transformation)	1.00	0.99 to 1.00

continued

TABLE 24 *Systematic review of low density lipoprotein (39 studies) (continued)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			LDL (mmol/l)	Assay type	Follow-up (years)
				Angina	Angiographic CAD	Prior MI			
Guang-da 2004[92] (–)	131	65.0	49.6	–	100	–	3.04	EIA	7
Lundstam 2002[63] (–)	908	59	23	100	–	51	–	Friedwald formula	11.7
Qi 2003a[58] (–)	134	64.1	19.4	48.5	100	34.4	1.69	–	1
Qi 2003b[59] (–)	121	64.1	21.5	43.8	67	30.6	1.66	–	0.077
Benchimol 2000[93] (–)	319	57	14.1	56.4	100	43.6	4.5	Precipitation	2
Bosevski 2005[65] (–)	90	62.3	27	–	–	100	3.52	–	3
Aronow 2001[94] (–)[n]	613	79.1	67.7	–	–	100	–	–	2.42
Fukushima 2004[73] (–)[n]	120	65.6	37.5	–	100	–	3.32	–	1.7
Janoskuti 2005[75] (–)	387	59	26.9	–1	100	44.9	3.7	Friedwald formula	5.1
Leu 2004[95] (–)[n]	75	68.1	12	100	100	25.3	2.97	Friedwald formula	3.33
Zotz 2000[77] (–)[n]	251	64.5	19.5	–	100	64	4.10	–	1
Wilhelmsen 2001[37] (4S)	1490	58.7	0	–	100	–	–	Friedwald formula	5.4
van Lennep 2000[64] (–)	848	64.8	20.4	–	100	47.2	4.9	Friedwald formula	2.99
Wattanakit 2005[96] (ARIC)[n]	766	57.1	24.7	–	100	81	–	–	8.7
Schlitt 2005[97] (–)[n]	1294	61.8	25.8	–	100	–	3.65	EIA	3.9
Sacks 2000[98] (CARE)[n]	788	60.0	13.0	–	–	–	3.6	EIA	5
Inoue 2007 [46] (–)	149	63	29	53.7	83.2	29.5	3.13	–	7

CAD, coronary artery disease; EIA, enzyme immunoassay; MI, myocardial infarction; RR, relative risk; TC, total cholesterol; TG, triglycerides.
Note: References and the key to the footnotes are listed at the end of this appendix.

Event combination	Number of events	Crude annual risk (%)	Adjustments						Comparison groups					RR	95% CI
			Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes							
CHD	39	4.25	●	○	○	●	○	○	Continuous (per unit increase by log transformation)					1.25	0.98 to 1.58
ACM	363	3.42	–	–	–	–	–	–	Continuous (ln)					0.5	0.3 to 0.7
ACM	32	23.9	Crude						Continuous					0.46	0.31 to 1.12
ACM	16	171.73	Crude						Continuous					0.88	0.12 to 1.16
CHD	12	1.89	○	○	○	○	○	○	Continuous					1.8	1.1 to 3.0
ACM	–	–	●	●	●	●	○	●	Continuous					0.25	–
CHD	460	31.0	●	●	●	●	●	○	< 3.24	≥ 3.24				1.42	1.15 to 1.75
CHD	44	21.57	Crude						≤ 3.57	> 3.57				1.0	0.6 to 1.8
ACM	41	2.08	●	●	●	●	●	○	≥ 0.92	< 0.92				0.63	0.25 to 1.55
CVD	33	13.2	Crude						≤ 4.14	> 4.14				2.92	1.19 to 7.13
CVD	10	3.98	Crude						≤ 3.89	> 3.89				–	–
CHD	431	5.36	Crude						≤ 4.5	4.51–5.15	≥ 5.16			1.16	0.95 to 1.42
ACM	101	3.98	●	○	○	○	○	○	–	–	Median			1.16	0.80 to 1.67
CVD	313	4.70	●	●	○	○	○	○	< 3.2	3.2–3.8	3.9–4.4	≥ 4.4		1.84	1.2 to 2.7
CVD	158	3.13	●	●	●	●	●	●	≤ 3.0	3.0–3.6	3.6–4.3	> 4.3		1.66	0.67 to 4.1
CHD	418	10.6	●	○	●	●	○	○	–	–	–	–	–	1.73	1.1 to 2.7
CVD	58	5.56	Crude						–					1.5	0.8 to 2.45

TABLE 25 *Systematic review of fibrinogen (40 studies)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			Fibrinogen mean (mg/dl)	Assay type	Follow-up (years)	Event combination
				Angina	Angiographic CAD	Prior MI				
Blankenberg 2006[99] (HOPE)	3199	65.4	23.2	–	100	–	353	von Claus method	4.5	CVD
Sinning 2006[100] (Atherogene)[c]	1806	61.7	21.3	100	100	47.5	314	Derived method	3.5	CVD
Thompson 1995[101] (ECAT)[c]	2806	53.8	14.8	37.0	75.8	44.3	301	–	2	CHD
Falcone 2006[48] (–)	1014	64.6	27.2	82.9	100	44.9	341	–	2.7	CVD
Morange 2006[102] (Atherogene)[b]	1057	61.5	23.2	69.8	100	48.5	–	Derived method	6.6	CVD
Soeki 1999[49] (–)[j]	106	62.3	25.5	–	–	35.8	–	Claus method	4.17	CHD
Burr 1992[1] (DART)[c]	1706	60.3	0	–	–	100	450	N	1.5	ACM
Thompson 1996[102] (–)[c]	209	53	20	100	–	47	320	Von Claus method	9	ACM
Cooper 1991[104] (PARIS I)[h]	70	52	–	–	–	100	–	–	4	ACM
Soeki 1999[49] (–)[j]	106	62.3	25.5	–	–	35.8	–	Claus method	4.17	CHD
Hartmann 2006[105] (–)	60	58	17	100	100	35	278	N	1.5	Morbidity
Wolk 2004[106] (–)	382	62.0	30.0	–	100	20	467	–	4	CVD
Retterstol 2002[50] (–)[c]	247	52.7	21.9	–	–	100	340	–	10	CHD
Glader 2002[68] (–)[c]	1150	59.4	18.2	100	100	53	340	Thrombin reaction rate method	6.7	CVD
Benchimol 2000[93] (–)[c]	319	57	14.1	56.4	100	43.6	350	Von Claus method	9	CHD
Otsuka 2002[107] (–)	363	65.3	29.5	–	100	27.5	313.5	Von Claus method	0.54	CVD
Blankenberg 2001[108] (Atherogene)	1240	61.9	24.7	–	88.4	49.1	334	Derived method	2.7	CHD
Minoretti 2006[53] (–)	799	64.9	25.6	100	100	46.3	341	–	2.7	CVD
Bosevski 2005[65] (–)[c]	90	62.3	27	–	100	54.4	429	Von Claus method	3	ACM
Palmerini 2007[109] (Bologna Registry)	108	69.1	23	28.7	100	32.5	–	Von Claus method	0.75	ACM
Shlipak 2008[110] (Heart and Soul)	979	67	18	–	100	53.7	–	Von Claus method	3.7	CHD
Espinola-Klein 2007[111] (–)	694	62.4	27.4	–	92.1	43.3	335.6	LPE	6.5	CVD
Sjoland 2007[112] (–)	589	63.4	18.9	99	100	57.3	360	Von Claus method	10	ACM

Number of events	Crude annual risk (%)	Adjustments						Comparison groups	RR	95% CI
		Age	Sex	Smoking	Lipids	Obesity	Diabetes			
501	3.48	●	●	○	●	○	●	Continuous (per SD)	1.15	1.01 to 1.25
131	2.07	●	●	●	●	●	●	Continuous (per SD)	1.26	1.09 to 1.46
106	1.89	●	●	●	●	●	●	Continuous (per SD)	1.31	1.07 to 1.61
105	3.84	●	●	○	○	○	○	Continuous (per SD)	1.87	0.32 to 4.21
135	1.94	●	●	●	●	●	●	Continuous (per SD)	1.27	1.04 to 1.55
11	2.47	Crude						Continuous (per SD)	1.07	0.61 to 1.87
85	3.32	●	○	●	○	○	○	Continuous (per SD)	1.34	–
45	2.39	●	●	●	○	○	○	Continuous (per SD)	1.29	0.96 to 1.73
20	7.14	●	●	●	○	○	○	Continuous (per SD)	1.69	0.96 to 2.97
11	2.47	Crude						Continuous (per SD)	1.07	0.61 to 1.87
19	21.1	●	●	●	●	○	●	Continuous (per SD)	1.01	1.00 to 1.03
44	2.88	Crude						Continuous (per SD)	1.39	1.10 to 1.75
36	1.45	●	○	●	●	○	○	Continuous (per quartile)	1.03	0.72 to 1.47
152	1.97	●	●	●	●	●	●	Continuous (per g/l)	1.21	0.98 to 1.48
13	0.45	○	○	○	○	●	○	Continuous (per g/l)	2.0	1.15 to 3.46
89	45.4	Adjustment variables unclear						Continuous (per 100 mg/dl)	1.82	1.35 to 2.46
88	2.63	●	●	○	○	●	○	Continuous (log transformed)	0.6	0.6 to 7.8
69	3.20	●	●	●	●	●	●	Continuous (log transformed)	1.01	0.98 to 1.10
8	2.96	●	●	●	●	○	●	Continuous	2.78	–
11	13.58	Crude						< 439 ≥ 439	5.24	1.39 to 19.77
142	3.92	●	●	●	○	●	●	≤ 443 > 443	1.15	0.78 to 1.69
75	1.66	●	●	●	●	●	●	< 332 ≥ 332	2.1	1.2 to 3.7
–	–	●	●	●	●	●	●	≤ 360 > 360	1.39	0.99 to 1.96

continued

TABLE 25 *Systematic review of fibrinogen (40 studies) (continued)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			Fibrinogen mean (mg/dl)	Assay type	Follow-up (years)	Event combination
				Angina	Angiographic CAD	Prior MI				
Marchioli 2001[113] (GISSI-Prevenzione)	9601	56.1	0	–	–	100	–	–	4	ACM
Marchioli 2001[113] (GISSI-Prevenzione)	1647	63.9	100	–	–	100	–	–	4	ACM
Bickel 2002[114] (Athrerogene)	1240	61.9	24.7	–	100	49.1	360	Derived method	2.9	CHD
Retterstol 2001[51] (–)[c]	247	52.7	21.9	44.5	–	100	–	Semi-automatically	10	CHD
Volzke 2003[115] (–)[c]	220	63.9	21.7	–	100	–	350	Von Claus method	2	ACM
Huang 2006[116] (–)[c]	185	69.4	47	–	100	–	380	EIA	3	CVD
Liem 2003[117] (–)[c]	593	65.2	22.1	–	100	56	399	EIA	2	ACM
Held 2000[118] (APSIS)	714	59	31	100	5	16	391	Modified thrombin time	3.3	CVD
Behar 1999[119] (BIP)	3011	59.5	–	–	–	70	364	Kinetic method	6.25	CHD
Benderly 1996[120] (–)	3092	59	0	–	–	76	346	Kinetic method	3.2	CHD
Haim 2007[121] (BIP)[e]	138	62.1	6	57.2	–	75.4	479.59	Liquid chromatography	6.2	CHD
Rahel 2003[122] (–)[c]	600	61.6	31.3	–	100	–	313	ELISA	0.67	ACM
Haim 2002[123] (BIP)	272	61.5	5	61.4	–	80.9	356.5	–	6.2	CHD
Martin 1991[14] (–)[c]	1716	–	0	–	–	100	446	N	2	CHD
Redondo 2001[124] (–)[c]	194	57.4	12.4	–	97	–	280	Von Claus method	2	CHD
Wattanakit 2005[96] (ARIC)	766	57.1	24.7	–	100	81	–	–	8.7	CVD
Papa 2008[125] (–)	422	64	19.9	–	100	–	344	–	3	CHD

CAD, coronary artery disease; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; LPE, latex particle enhanced; MI, myocardial infarction; N, nephelometry; RR, relative risk; TC, total cholesterol; TG, triglycerides.
Bolibar 2000 was omitted from this table as it presents the same values as Thompson 1995.
Note: References and the key to the footnotes are listed at the end of this appendix.

Number of events	Crude annual risk (%)	Adjustments						Comparison groups				RR	95% CI
		Age	Sex	Smoking	Lipids	Obesity	Diabetes						
904	2.35	●	●	●	●	○	●	< 400	≥ 400			1.62	1.41 to 1.86
167	2.53	●	●	●	●	○	●	< 400	≥ 400			1.12	0.81 to 1.53
88	2.45	●	●	●	●	●	●	< 410.3	≥ 410.3			1.7	1.01 to 2.8
35	1.42	●	○	●	●	○	○	≤ 390	≥ 400			2.2	1.1 to 4.4
20	4.55	Adjustment variables unclear						< 350	≥ 350			1.59	1.08 to 2.33
10	1.80	○	○	●	●	●	○	≤ 400	400			2.98	1.22 to 3.78
–	–	○	●	○	○	○	●	< 500	≥ 500			2.1	1.23 to 3.56
60	2.54	○	○	●	○	○	●	≤ 345	3.46–425	> 425		2.61	0.99 to 6.86
173	0.91	●	○	●	●	○	○	< 314	315–373	> 373		1.44	0.99 to 2.09
111	1.12	●	○	●	○	○	●	< 308	308–368	> 368		1.75	1.06 to 2.88
69	8.06	○	○	●	○	○	●	< 408.2	408.2–530.6	> 530.6		2.3	0.87 to 5.64
54	13.4	●	○	●	○	○	○	–	–	–		3.74	1.08 to 12.95
136	8.06	Crude						–	–	–	–	1.4	0.73 to 2.75
126	3.67	●	○	○	○	○	○	–	–	–	–	2.5	–
37	9.53	●	●	●	●	●	●	–	–	–	–	1.3	0.47 to 3.70
313	4.70	●	●	●	●	●	●	< 277	277–310	311–357	≥ 358	1.13	0.8 to 1.7
13	1.03	Crude						–				3.77	1.04 to 13.73

TABLE 26 *Systematic review of lipoprotein (a) (20 studies)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			Lp(a) (mg/dl)	Assay type	Follow-up (years)	Event combination	Number of events
				Angina	Angiographic CAD	Prior MI					
Bolibar 2000[47] (ECAT)[c]	2806	55.8	15.9	36	–	45	105	–	2	CHD	106
Falcone 2006[48] (–)	1014	64.6	27.2	82.9	100	44.9	21.0	EIA	2.7	CVD	105
Soeki 1999[49] (–)	106	62.3	25.5	–	–	35.8	29.7	T	4.17	CHD	11
Saely 2006[126] (–)	451	62.3	30.2	–	–	–	16.0	T	3.9	CVD	81
Corsetti 2008[127] (THROMBO)	215	58.9	24.7	–	–	23	0.79[q]	EIA	2.17	CHD	42
Minoretti 2006[53] (–)	799	64.9	25.6	100	100	46.3	18.0	EIA	2.7	CVD	69
Guang–Da 2004[92] (–)[b]	131	65	49.6	–	100	–	31.64	ELISA	7	CHD	39
Hartmann 2006[105] (–)	60	58	17	100	100	35	25.0	N	1.5	Morbidity	19
Lundstam 2002[63] (–)[b]	964	59	23	93.9	100	51	–	ELISA	11.7	ACM	363
Vittinghoff 2003[81] (HERS)	2763	66.6	100	26.3	100	–	25.3	–	4.1	CHD	361
Glader 2002[68] (–)[b]	1216	59.4	18.2	100	100	53	25.1	EIA	6.7	CVD	152
Zairis 2002[128] (GENERATION)	483	59.3	18	22.2	100	8.7	19	N	3	CHD	20
Maher 1995[129] (FATS)	146	–	0	–	100	–	30.8	ELISA	2.5	ACM	15
Wehinger 1999[130] (–)	2223	62.9	23.3	–	100	–	14.4	N	1	CHD	–
Wilhelmsen 2001[37] (4S)	1490	–	0	–	100	–	–	ELISA	5.4	CHD	431
Rahel 2003[131] (–)[b]	600	61.6	31.3	–	100	–	19.99	–	0.67	ACM	54
Skinner 1997[132] (–)[b]	347	57.2	16	98	100	61	–	ELISA	5	CHD	16
Wattanakit 2005[96] (ARIC)[i]	766	57.1	24.7	–	100	86	–	–	8.7	CVD	313
Shlipak 2000[110] (HERS)	1383	66.7	100	–	–	–	25.3	EIA	4.1	CHD	182
Lloyd 2001[133] (FLARE)[c]	823	60.8	17	–	100	32.8	13.0	ELISA	0.82	ACM	190

CAD, coronary artery disease; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; MI, myocardial infarction; N, nephelometry; RR, relative risk; T, turbidimetric; TC, total cholesterol; TG, triglycerides.
Note: References and the key to the footnotes are listed at the end of this appendix.

Crude annual risk (%)	Adjustments						Comparison groups					RR	95% CI
	Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes							
1.89	●	●	●	○	●	●	Continuous (per SD)					1.02	0.79 to 1.31
3.84	●	●	○	○	○	○	Continuous (per SD)					1.8	1.26 to 2.56
2.47	Crude						Continuous (per SD)					0.98	0.48 to 1.70
4.61	●	●	●	●	●	○	Continuous (per SD)					1.41	1.12 to 1.90
9.00	–	–	–	–	–	–	Continuous (per μmol/l)					1.67	1.26 to 2.22
3.20	●	●	●	●	●	●	Continuous (per unit increase by log transformation)					1.2	0.98 to 1.47
4.25	●	○	○	●	○	○	Continuous (per unit increase by log transformation)					1.56	1.14 to 2.12
21.1	●	●	●	●	○	●	Continuous (per unit increase by log transformation)					10.2	2.36 to 44.13
3.22	Adjustment variables unclear						≤3	>3				1.04	0.8 to 1.3
3.19	●	●	●	●	●	●	≤25.3	>25.3				1.44	1.06 to 1.96
1.87	●	●	●	●	●	●	<300	≥300				1.40	1.0 to 2.0
1.38	Adjustment variables unclear						<25	≥25				1.27	0.48 to 3.34
4.11	Adjustment variables unclear						<46.2	≥46.2				–	–
–	●	●	○	○	○	○	≤56	>56				1.04	0.85 to 1.28
5.36	●	○	●	●	●	●	≤120	121 to 400	≥181			1.09	0.89 to 1.32
13.4	●	○	●	○	○	○	–	–	–			1.66	0.73 to 3.76
0.92	Adjustment variables unclear						<12.3	12.3–33.1	>33.1			0.4	0.08 to 2.06
4.7	●	●	●	●	○	●	<2.6	2.6–7.1	7.2 to 18.0	≥18.1		1.41	1.0 to 2.1
3.21	○	●	●	●	●	●	≤7.0	7.1–25.3	25.4 to 54.9	55.0–236.0		1.54	1.0 to 2.4
25.2	Adjustment variables unclear						≤4	5–10	11–19	20–52	>53	–	–

TABLE 27 *Systematic review of apolipoprotein A (14 studies)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			ApoA (g/l)	Assay type	Follow-up (years)	Event combination	Number of events
				Angina	Angiographic CAD	Prior MI					
Asztalos 2008[44] (VA-HIT)	754	64	–	–	–	–	1.096	T	5.1	CHD	168
Bolibar 2000[47] (ECAT)	2806	55.8	15.9	36	–	45	1.28	–	2	CHD	106
Soeki 1999[49] (–)[f]	106	62.3	25.5	–	–	35.8	1.138	T	4.2	CHD	11
Simes 2002[57] (LIPID)	4502	53	–	–	–	–	1.3	N	5	CHD	–
van Lennep 2000[64] (–)	848	64.8	20.4	–	100	47.2	1.4	N	2.99	ACM	101
Lundstam 2002[63] (–)	871	59	23	93.9	100	51	–	N	11.7	ACM	363
Harb 2002[134] (THROMBO)[b]	957	–	24.6	32.2	–	100	–	–	2.17	CHD	69
Skinner 1999[13] (–)[b]	353	57.2	15.9	98	100	61	–	N	5	CHD	16
Leander 2007[26] (Stockholm Heart Epidemiology Program)	1105	58.6	0	–	–	0	1.5	–	7.2	CHD	320
Leander 2007[26] (Stockholm Heart Epidemiology Program)	538	62.1	100	–	–	0	1.5	–	7.2	CHD	141
Wilhelmsen 2001[37] (4S)[d]	1476	–	0	–	100	–	–	T	5.4	CHD	426
Held 1997[118] (APSIS)	786	60	31	100	6	16	1.35	N	3.3	CVD	67
Schlitt 2005[97] (–)	1294	61.8	25.8	–	100	–	1.33	T	3.9	CVD	158
Moss 1999[135] (–)[f]	1045	–	24	–	–	100	1.19	Immunochemical	2.2	CHD	81
van der Steeg 2008[136] (IDEAL)	8564	61.7	19.1	–	–	100	1.39	N	4.8	CVD	679

CAD, coronary artery disease; MI, myocardial infarction; N, nephelometry; RR, relative risk; T, turbidimetric; TC, total cholesterol; TG, triglycerides.
Note: References and the key to the footnotes are listed at the end of this appendix.

Crude annual risk (%)	Adjustments						Comparison groups				RR	95% CI
	Age	Sex	Smoking	Lipids (TC, LDL,HDL,TG)	Obesity	Diabetes						
4.37	●	○	●	●	●	●	Continuous (per SD)				0.93	0.76 to 1.14
1.89	●	●	●	○	●	●	Continuous (per SD)				0.66	0.54 to 0.81
2.47	Crude						Continuous (per SD)				0.54	0.23 to 1.22
–	●	●	●	○	○	●	Continuous (g/l)				0.41	0.24 to 0.69
3.98	Adjustment variables unclear						Continuous (g/l)				0.29	0.09 to 0.97
3.56	Adjustment variables unclear						Continuous (ln)				0.3	0.2 to 0.5
3.32	○	●	○	○	○	●	–	–			2.14	1.24 to 3.69
0.91	Crude						–	–	–		0.13	0.02 to 1.01
4.02	○	○	●	●	●	●	> 1.3	≤ 1.3			0.9	0.6 to 1.3
3.64	○	○	●	●	●	●	> 1.3	≤ 1.3			2.3	1.1 to 5.0
5.34	●	○	●	●	●	●	≤ 1.3 mmol/l	1.1–1.2 mmol/l	≤ 1.0 mmol/l		1.13	0.90 to 1.43
2.58	●	●	●	○	○	●	> 1.54	1.34–1.54	< 1.34		1.6	0.82 to 3.09
3.13	●	●	●	○	●	●	≤ 1.16	1.16–1.31	1.31–1.47	> 1.47	0.41	0.22 to 0.78
3.52	○	●	○	○	○	●	–	–	–	< 1.01	1.73	0.86 to 3.46
1.65	●	●	●	●	●	○	< 1.25	1.25–1.45	1.45–1.65	1.65–1.80	1.80–1.95	> 1.95	0.71	0.29 to 1.75

TABLE 28 *Systematic review of apolipoprotein B (13 studies)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			ApoB (g/l)	Assay type	Follow-up (years)	Event combination	Number of events
				Angina	Angiographic CAD	Prior MI					
Bolibar 2000[47] (ECAT)	2806	55.8	15.9	36	–	45	1.28	–	2	CHD	106
Soeki 1999[49] (–)[f]	106	62.3	25.5	–	–	35.8	1.142	T	4.2	CHD	11
Lee 2006[137] (–)	1050	60.8	27.1	–	–	–	0.97	–	8.5	CHD	95
Simes 2002[57] (LIPID)	4502	53	–	–	–	–	1.32	N	5	CHD	–
Lundstam 2002[63] (–)	872	59	23	93.9	100	51	–	N	11.7	ACM	363
Linden 1998[91] (–)	964	60.8	23	–	–	50.6	1.48	N	5.2	ACM	168
van Lennep 2000[64] (–)	848	64.8	20.4	–	100	47.2	1.5	N	2.99	ACM	101
Kastelein 2008[138] (TNT/IDEAL)	18,018	61.4	18.9	–	–	–	0.989	N	4.8	CHD	1783
Harb 2002[134] (THROMBO)[b]	957	–	24.6	32.2	–	100	–	–	2.17	CHD	69
Wilhelmsen 2001[37] (4S)[d]	1476	–	0	–	100	–	–	T	5.4	CHD	426
Held 1997[118] (APSIS)	786	60	31	100	6	16	1.35	N	3.3	CVD	67
Schlitt 2005[97] (–)	1294	61.8	25.8	–	100	–	1.2	T	3.9	CVD	158
Moss 1999[135] (–)[f]	1045	–	24	–	–	100	1.23	EIA	2.2	CHD	81

CAD, coronary artery disease; EIA, enzyme immunoassay; MI, myocardial infarction; N, nephelometry; RR, relative risk; T, turbidimetric; TC, total cholesterol; TG, triglycerides.
Note: References and the key to the footnotes are listed at the end of this appendix.

Crude annual risk (%)	Adjustments						Comparison groups				RR	95% CI
	Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes						
1.89	●	●	●	○	●	●	Continuous (per SD)				1.27	1.03 to 1.56
2.47	Crude						Continuous (per SD)				1.59	0.97 to 2.58
1.06	●	●	●	●	●	●	Continuous (per 0.2 g/l)				1.36	1.17 to 1.59
–	●	●	●	○	○	●	Continuous (g/l)				2.07	1.32 to 3.22
3.56	Adjustment variables unclear						Continuous (ln)				0.6[l]	0.3 to 1.0
3.35	○	●	●	●	○	●	Continuous (g/l)				0.41	0.20 to 0.83
3.98	Adjustment variables unclear						Continuous (g/l)				7.94	1.09 to 57.72
2.06	●	●	○	○	○	○	Continuous (per 27.2 mg/dl)				1.19	1.14 to 1.24
3.32	○	●	○	○	○	●	–	–			1.9	1.11 to 3.25
5.34	●	○	●	●	●	●	≤ 1.0	1.1–1.2	≥ 1.3		1.23	0.99 to 1.53
2.58	●	●	●	○	○	●	< 1.31	1.31–1.60	> 1.60		1.2	0.67 to 2.16
3.13	●	●	●	○	●	●	≤ 1.01	1.01–1.17	1.17–1.37	> 1.37	0.78	0.42 to 1.46
3.52	○	●	○	○	○	●	–	–	–	> 1.4	1.93	1.03 to 3.62

TABLE 29 *Systematic review of homocysteine (16 studies)*

Author publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			Homocysteine mean (µmol/l)	Assay type	Follow-up (years)	Event combination	Number of events	Crude annual risk (%)
				Angina	Angiographic CAD	Prior MI						
Lee 2006[137] (–)	1050	60.8	27.1	–	–	–	14.2	CLIMA	8.5	CHD	95	1.06
Lu 2003[139] (–)	153	71.0	13.1	100	100	34	13.1	EIA	1.33	CVD	51	25.1
Ndrepepa 2006[140] (–)	507	69.1	33.9	–	100	45.6	12.9	FP	4	CVD	62	30.6
Retterstol 2003[141] (–)	247	52.7	21.9	–	–	100	–	LC	10	CHD	36	1.46
Schnyder 2002[142] (–)	549	62	19.7	–	100	54.6	10.1	LC	1.12	CHD	6	0.956
Zebrack 2003[143] (Intermountain)	1128	64.0	33.0	72.0	76.0	–	6.8	–	3	ACM	208	6.15
Anderson 2000[144] (–)	1002	64.9	22.7	–	100	–	15.5	FP	3.0	ACM	118	2.78
Leu 2004[95] (–)	75	68.1	12	100	100	25.3	12.61	ELISA	3.33	CVD	33	13.2
Palma Reis 2000[145] (–)	110	48.1	8	–	–	100	–	–	7	CVD	28	3.64
Liem 2003[146] (–)	593	65.2	22.1	–	100	56	12.1	FP	2	ACM	–	–
Schnyder 2002a[147] (–)	205	61	23.5	–	100	54.6	9.9	–	0.38	CHD	47	60.3
Rossi 2006[148] (GENICA)	262	66.3	100	–	54.6	–	11.6	LC	3.6	CVD	15	1.59
Nygard 1997[149] (–)	587	62	18.6	–	100	57.4	11.2	LC	4.6	ACM	64	2.37
Schnabel 2005a[150] (Atherogene)	639	61.7	27.8	79.3	86.8	–	14.2	LC	7.1	CVD	112	2.47
Knekt 2001a[151] (Mobile Clinic Health Examination Survey)[s]	477	55.7	0	–	–	–	0.154	LC	12	CHD	166	2.9
Knekt 2001b[152] (Mobile Clinic Health Examination Survey)	221	58.8	100	–	–	–	11.7	LC	12	CHD	74	2.79

CAD, coronary artery disease; CLIMA, Cell Line Integrated Molecular Authentication; ELISA, enzyme-linked immunosorbent assay; FP, fluorescence polarisation; LC, liquid chromatography; MI, myocardial infarction; RR, relative risk; TC, total cholesterol; TG, triglycerides.
Note: References and the key to the footnotes are listed at the end of this appendix.

Adjustments												
Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes	Comparison group					RR	95% CI
●	●	●	●	●	●	Continuous (μmol/l)					1.05	1.02 to 1.08
Crude						Continuous (μmol/l)					1.01	0.93 to 1.09
●	○	○	○	○	○	Continuous (per 5 μmol/l)					1.04	0.80 to 1.36
○	○	●	●	○	○	Continuous (per quartile)					1.40	1.03 to 1.90
Crude						Continuous (per μmol/l)					1.2	1.08 to 1.33
●	○	●	●	○	●	≤ 15	> 15				1.3	–
●	○	○	●	○	●	< 11.83	11.83–16.1	≥ 16.2			1.64	1.13 to 2.38
Crude						≤ 12	> 12				2.83	1.21 to 6.62
Crude						< 10.10	≥ 10.10				–	–
○	●	○	○	○	●	< 13.1	≥ 13.1				1.96	1.15 to 3.33
Crude						< 9.0	≥ 9.0				–	–
Adjustment variables unclear						≤ 8.7	8.8–12.4	≥ 12.5			–	–
●	●	●	●	○	●	< 9.0	9.0–14.9	15.0–19.9	≥ 20.0		4.51	1.22 to 16.6
●	●	●	●	○	●	< 11.3	11.3–13.7	13.7–16.8	> 16.8		3.00	1.35 to 6.66
○	●	●	●	●	●	< 7.9	7.9–9.1	9.2–10.4	10.5–12.3	≥ 12.4	2.23	1.03 to 4.85
●	●	●	●	●	●	< 8.1	8.1–9.8	9.9–11.3	11.4–13.4	> 13.5	3.32	1.05 to 10.5

TABLE 30 *Systematic review of N-terminal pro-B natriuretic peptide (20 studies)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)				NT-proBNP (pg/ml)	Assay type	Follow-up (years)	Event combination
				Heart Failure	Angina	Angiographic CAD	Prior MI				
Lubos 2006[153] (Atherogene)	1945	61.2	21.1	–	–	100	37.5	50.9	FP	2.6	CVD
Bibbins-Domingo 2007[154] (Heart and Soul)	987	67	18.5	17.5	–	–	53.4	174.8	EIA	3.7	CHD
Tang 2007[155] (CREDO)	1472	61.6	28.2	8.4	26	100	33.3	131	Electrocheminescence	1	ACM
Dai 2008[156] (–)	345	64.6	26.7	–	–	100	15	212.2	ELISA	3	CHD
Schnabel 2005[157] (Atherogene)	1872	61	20.9	–	–	100	–	52.55	FP	2.6	CVD
Shlipak 2008[110] (Heart and Soul)	979	67	18	17.6	–	100	53.7	–	CL	3.7	CHD
Ndrepepa 2006b[158] (–)[g]	989	66.3	21.0	100	–	100	39.9	279.9	Autoanalyser	3.6	ACM
Richards 2006[237] (ANZ Heart Failure trial and Christchurch Cardioendocrine post-myocardial infarction cohort)	1049	63.4	21.0	27.8	–	–	97	819.8	ELISA	1	ACM
Saleh 2006[160] (–)	891	65	32	21	58	100	39	179	SEISA	2.6	ACM
Ndrepepa 2005[161] (–)[g]	1059	66.6	21.1	100	100	100	40.6	369.4	Autoanalyser	3.6	CVD
de Winter 2004[162] (–)	1172	62.0	33.0	46.1	78.0	100	46.5	321.5	–	1.16	ACM
Lindahl 2005[163] (FRISC-II)[g]	1189	68	29	63.0	–	–	29	343	EIA	2	ACM
Blankenberg 2006[99] (HOPE)	3199	65.4	23.2	–	–	100	–	160.2	SEISA	4.5	CVD
März 2007[164] (LURIC)	1640	61.1	30.7	–	–	100	32.2	–	CL	5.45	CVD
West 2008[165] (LIPID)	500	63	15	–	–	100	–	689	SEISA	2.5	CVD
Omland 2007[166] (PEACE)	3761	63.6	19	–	–	100	56.2	139.3	CL	4.8	CHD

Number of events	Crude annual risk (%)	Adjustments						Comparison group				RR	95% CI
		Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes						
75	1.48	●	●	●	●	●	●	Continuous (per SD)				2.7	2.0 to 3.9
34	0.93	●	●	●	●	○	●	Continuous (per SD)				2.6	1.3 to 5.0
141	9.58	●	●	●	○	●	●	Continuous (per unit increase by log transformation)				1.25	1.07 to 1.46
56	5.41	●	●	●	●	○	●	Continuous (per unit increase by log transformation)				2.68	1.74 to 4.13
114	2.34	●	●	●	●	●	●	≤ 102.31	> 102.31			1.96	1.28 to 3.0
142	3.92	●	●	●	○	●	●	≤ 459	> 459			2.13	1.43 to 3.18
85	2.39	●	●	●	●	●	●	< 279.9	≥ 279.9			2.0	1.05 to 3.58
79	7.53	●	●	○	○	○	●	Below median	Above median			2.08	1.12 to 3.89
75	3.23	●	○	○	○	○	●	≤ 490	> 490			3.72	1.44 to 9.65
70	1.84	●	●	○	●	●	●	< 120.6	–	–	≥ 808.4	5.98	1.55 to 23.13
32	2.35	Crude						≤ 456	> 456			7.06	3.30 to 15.08
–	–	●	●	○	○	○	●	Reference group	Double reference group			1.46	1.06 to 2.03
501	3.48	●	●	○	●	○	●	–	–	–		2.25	1.74 to 2.89
129	1.44	●	●	●	●	●	●	5–81	82–194	195–521	522–35000	3.92	1.76 to 8.74
250	20	●	○	○	○	○	●	< 117	117–268	268–646	> 646	2.22	1.15 to 4.29
241	1.33	●	●	●	●	●	●	Men 5–66; women 5–105	Men 66–127; women 105–196	Men 127–253; women 196–372	Men 253–5590; women 372–4593	1.19	0.77 to 1.83

continued

TABLE 30 *Systematic review of N-terminal pro-B natriuretic peptide (20 studies)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)				NT-proBNP (pg/ml)	Assay type	Follow-up (years)	Event combination
				Heart Failure	Angina	Angiographic CAD	Prior MI				
Kragelund 2005[167] (–)	1034	58.7	22.3	100	89.6	80.1	531	169	EIA	9.2	ACM
Rothenbacher 2006[168] (–)[g]	1051	58.5	15.1	20.4	–	100	58.2	568.4	EIA	4.1	CVD
Schnabel 2005b[169] (Atherogene)	417	–	–	–	100	100	–	–	EIA	2	CVD
Assmus 2007[170] (TOPCARE-CHD)	121	62	13	–	–	100	100	–	SEISA	1.58	ACM

CAD, coronary artery disease; CL, chemiluminescence; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; FP, fluorescence polarisation; MI, myocardial infarction; RR, relative risk; SEISA, sandwich enzyme immunosorbent assay; TC, total cholesterol; TG, triglycerides.
Note: References and the key to the footnotes are listed at the end of this appendix.

Number of events	Crude annual risk (%)	Adjustments						Comparison group				RR	95% CI
		Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes						
288	3.03	●	●	●	●	●	●	< 63	63–169	170–456	> 456	2.4	1.5 to 4.0
95	2.20	●	●	●	●	○	●	≤ 278.3	278.3–564.7	564.7–1097	> 1097	2.35	1.14 to 4.88
31	2.72	●	●	●	●	●	●	< 86.7	86.7–192.0	192.0–487.9	> 487.9	3.96	1.13 to 13.9
14	7.32	●	○	○	○	○	●	–				7.2	2.4 to 22.2

TABLE 31 *Systematic review of interleukin 6 (14 studies)*

Author/publication year (study name)	Number of patients	Age	% Women	Baseline coronary morbidity (%)			IL-6 mean (pg/ml)	Assay type	Follow-up (years)	Event combination	Number of events
				Angina	Angiographic CAD	Prior MI					
Blankenberg 2006[99] (HOPE)	3199	65.4	23.2	–	100	–	3.27	EIA	4.5	CVD	501
Blankenberg 2003[171] (Atherogene)[b]	771	–	–	70.5	100	48.7	–	LPE	4.1	CVD	97
Blankenberg 2002[172] (Atherogene)	1229	61.2	25.5	65.8	100	46.9	8.4	ELISA	3.9	CVD	95
Lee 2006[137] (–)[g]	1050	60.8	27.1	–	–	–	2.3	EIA	8.5	CHD	95
Ikonomidis 2008[173] (–)	106	62	14	100	100	53	2.27	Highly sensitive immunoassay	5.3	CHD	36
Shlipak 2008[110] (Heart and Soul)	979	67	18	–	100	53.7	–	CL	3.7	CHD	142
Espinola–Klein 2007[111] (–)	694	62.4	27.4	–	92.1	43.3	11.6	LPE	6.5	CVD	75
Kwaijtaal 2005[174] (Exhaustion Intervention trial)	213	53.6	21.6	9.9	100	26.8	2.01	ELISA	2	CHD	25
Inoue 2008[175] (–)	158	63	28	53	82.9	29.7	9.25	SEISA	7	CVD	56
West 2008[165] (LIPID)	500	63	15	–	100	–	25.5 (unit not specified)	ELISA	2.5	CVD	250
Rahel 2003[122] (–)	600	61.6	31.3	–	100	–	2.88	ELISA	0.67	ACM	54
Kip 2005[176] (WISE)	580	58	100	–	61	–	–	EIA	4.7	CVD	92
Hoffmeister 2005[177] (–)	300	57.9	14.3	–	100	61.3	2.6	ELISA	3.2	CVD	60
Fisman 2006[178] (BIP)	258	61	4.7	59.7	100	79	3.53	CLIMA	6.3	CHD	129

CAD, coronary artery disease; CL, chemiluminescence; CLIMA, Cell Line Integrated Molecular Authentication (database); EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; LPE, latex particle enhanced; MI, myocardial infarction; RR, relative risk; SEISA, sandwich enzyme immunosorbent assay; TC, total cholesterol; TG, triglycerides.
Note: References and the key to the footnotes are listed at the end of this appendix.

Crude annual risk (%)	Adjustments						Comparison groups					RR	95% CI
	Age	Sex	Smoking	Lipids (TC, LDL, HDL, TG)	Obesity	Diabetes							
3.48	●	●	○	●	○	●	Continuous (per SD)					0.9	0.8 to 1.1
3.07	●	●	●	●	●	●	Continuous (per quartile)					1.10	0.80 to 1.45
1.98	●	○	○	●	○	●	Continuous (per quartile)					1.15	0.90 to 1.49
1.06	●	●	●	●	●	●	Continuous (ng/l)					1.08	1.01 to 1.16
6.41	●	●	●	●	○	○	Continuous (per unit increase)					1.17	0.94 to 1.45
3.92	●	●	●	○	●	●	≤ 4.2	> 4.2				1.76	1.22 to 2.53
1.66	●	●	●	●	●	●	< 11.3	≥ 11.3				1.3	0.8 to 2.1
5.87	●	●	●	○	●	●	–	–				3.9	1.70 to 9.0
5.06	–	–	–	–	–	–	–	–				0.92	0.27 to 3.57
20	●	○	○	○	○	●	Lower quartile (not specified)	Upper quartile (not specified)				1.0	0.50 to 1.80
13.4	●	○	●	○	○	○	–	–	–			0.75	0.35 to 1.62
3.37	●	●	●	○	○	●	< 1.68	1.68–2.92	2.93–5.27	≥ 5.28		2.31	1.20 to 4.44
6.25	●	●	●	●	●	●	< 1.50	1.51–2.09	2.10–3.58	> 3.59		1.8	0.90 to 3.60
7.94	○	○	○	○	●	○	< 1.05	1.05–1.61	1.61–2.33	2.33–3.67	≥ 3.67	3.33	1.47 to 8.13

Key to tables

a Estimated average length of stay for coronary event admission = 5 days.
b Original units mg/l.
c Original units g/l.
d Original units mmol/l – unchanged on this table.
e (Fibrinogen) converted from μmol/l to mg/dl by dividing by 0.0294.
f Original units mg/dl.
g Original units ng/l.
h Original units mg/ml.
i Original units μg/ml.
j Omitted from table, as quoted as a percentage.
k Reference group.
l Men 0.4 (0.2 to 0.7); women 2.1 (0.6 to 6.3).
m (Fasting glucose) converted from mg/dl to mmol/l by multiplying by 0.0555.
n (LDL/total cholesterol) converted from mg/dl to mmol/l by multiplying by 0.0259.
o (Hb) converted from mmol/l to g/dl by dividing by 0.6206.
p Relative risk first vs fourth quartile (low vs high).
q Original units pmol/l – unchanged.
r (Creatinine) converted from mg/dl to μmol/l by multiplying by 88.4.
s (Homocysteine) converted from mg/dl to μmol/l by multiplying by 73.97.

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Appendix 2

Search strategy for disease, study design and biomarkers in MEDLINE and EMBASE

Our original search was performed on all the literature until April 2007. At the invitation of the reviewers, we updated this in November 2008. The updated search was performed using the date parameters 1 January 2007 to 31December 2008 in order to (1) identify any papers published January–April 2007 that were not stored on databases at that time and (2) identify any papers in the public domain that had dates after the search date (e.g. advanced publications online).

Search terms as performed in April 2007

PubMed	Results	EMBASE	Results
SEARCH 1: ACS OR ANGINA			
"Angina, Unstable"[MeSH]	295,088 hits	Exp "unstable-angina-pectoris"[SU]	196,727 hits
OR unstable angina*[tw]			
OR "Myocardial Ischemia"[MeSH]		Exp "Heart-muscle-ischemia"[SU]	
OR coronary disease[tw]			
OR coronary syndrome[tw]			
OR myocardial infarct*[tw]			
OR myocardial ischemi*[tw]		Myocardial isch?emi*[tw]	
OR myocardial ischaemi*[tw]			
OR "Coronary Thrombosis"[MeSH]		Exp "Coronary-Artery-Thrombosis"[SU]	
OR coronary thrombos*[tw]			
OR non q-wave[tw]		Non?q?wave	
OR non q wave[tw]			
OR nstemi[tw]			
OR stemi[tw]			
OR heart infarct*[tw]			
OR coronary arteriosclerosis[tw]			
OR acute coronary[tw]			
OR "Angina Pectoris"[MeSH]		Exp "angina-pectoris"[SU]	
OR "Angina Pectoris, variant"[MeSH]		Exp "variant-angina-pectoris"[SU]	
OR angina*[tw]			
SEARCH 2: STUDY DESIGN			
"Prognosis"[MeSH]	1,559,421 hits	Exp "Prognosis"[SU]	642,517 hits
OR Diagnosed[tw]			
OR "Cohort Studies"[MeSH]		Exp "Cohort-analysis"[SU]	
OR predictor*[tw]			
OR death[tw]			
OR "Models, statistical"[MeSH]		Exp "statistical-model"[SU]	

PubMed	Results	EMBASE	Results
SEARCH 3: CRP			
"C-reactive protein"[MeSH]	20,582 hits	Exp "C reactive protein"[SU]	20,027 hits
OR C reactive protein[tw]		OR C?reactive?protein	
		OR Hs?c?reactive protein	
		OR High?sensitivity?c?reactive?protein	
		OR Hs?CRP	
		OR High?sensitivity?CRP	
SEARCH 3: BIOMARKERS			
"C-reactive protein"[MeSH]	626,118 hits	Exp "C reactive protein"[SU]	446,082 hits
OR C reactive protein[tw]		OR C?reactive?protein	
		OR Hs?c?reactive protein	
		OR High?sensitivity?c?reactive?protein	
		OR Hs?CRP	
		OR High?sensitivity?CRP	
OR "Serum albumin"[MeSH]		OR Exp "albumin"[SU]	
OR Albumin[tw]			
OR "Apolipoproteins A"[MeSH]		OR Exp "Apolipoprotein A"[SU]	
OR Apolipoprotein* A[tw]		Apolipoprotein?A	
OR ApoA[tw]			
OR "Apolipoproteins B"[MeSH]		OR "Apolipoprotein B"[SU]	
OR Apolipoprotein* B[tw]		Apolipoprotein?B	
OR ApoB[tw]			
OR "Creatinine"[MeSH]		Exp "Creatinine"[SU]	
OR Creatinine[tw]			
Or "Blood Glucose"[MeSH]		Exp "Glucose-blood-level"[SU]	
OR Fasting glucose[tw]			
OR 2 hour glucose[tw]		n/a	
OR Fasting blood sugar[tw]			
OR 2-hour postprandial blood sugar[tw]		n/a	
OR "Fibrinogen"[MeSH]		Exp "Fibrinogen"[SU]	
OR Fibrinogen[tw]			
OR "Hemoglobins"[MeSH]		Exp "Hemoglobin"[SU]	
OR Haemoglobin[tw]		H?emoglobin[tw]	
OR Hemoglobin[tw]		–	
OR Hgb[tw]			
OR "Hemoglobin A, glycosylated"[MeSH]		Exp "Hemoglobin-A1c"[SU]	
OR Glycated hemoglobin[tw]		Glycated h?emoglobin	
OR Glycated haemoglobin[tw]		–	
OR Hemoglobin A1c[tw]		H?emoglobin A1c	
OR Haemoglobin A1c[tw]		–	
OR Glycohaemoglobin[tw]		Glycoh?emoglobin[tw]	
OR Glycohemoglobin[tw]		–	

PubMed	Results	EMBASE	Results
OR HbA1c[tw]			
OR Glycosylated hemoglobin[tw]		Glycosylated h?emoglobin[tw]	
OR Glycosylated haemoglobin[tw]		–	
OR "Lipoproteins, HDL"[MeSH]		Exp "high-density-lipoprotein"[SU]	
OR High density lipoprotein[tw]		OR High?density?lipoprotein[tw]	
OR HDL[tw]			
OR "Lipoproteins, LDL"[MeSH]		Exp "low-density-lipoprotein"[SU]	
OR Low density lipoprotein[tw]		OR Low?density?lipoprotein[tw]	
OR LDL[tw]			
OR "Homocysteine"[MeSH]		Exp "homocysteine"[SU]	
OR Homocysteine[tw]			
		tHcy[tw]	
OR "Interleukin-6"[MeSH]		Exp "Interleukin-6"[SU]	
OR Interleukin-6[tw]		Interleukin?6[tw]	
OR IL-6[tw]		IL?6[tw]	
OR IL 6[tw]		–	
OR "Lipoprotein(a)"[MeSH]		Exp "lipoprotein-A"[SU]	
OR "lipoprotein(a)"[tw]		OR lipoprotein?(a)[tw]	
OR lipoprotein a[tw]		OR Lp?(a)[tw]	
OR "Lp(a)"[tw]		OR lipoprotein?a[tw]	
OR "Lp a"[tw]		OR Lp?a[tw]	
OR Pro-brain natriuretic peptide (1–76) [Substance name]			
OR N-terminal pro-BNP[tw]			
OR NT-BNP[tw]			
OR NTproBNP[tw]		NT?proBNP	
OR NT-proBNP[tw]		–	
OR Amino-terminal pro-brain natriuretic peptide[tw]			
OR "Cholesterol"[MeSH]		Exp "Cholesterol-blood-level"[SU]	
OR total cholesterol[tw]			
OR "Triglycerides"[MeSH]		Exp "Triacyglycerol"[SU]	
		Triacyglycerol[tw]	
OR triglycerides[tw]			
OR "Leukocyte count"[MeSH]		Exp "Leukocyte count"[SU]	
OR leukocyte count[tw]			
OR white blood cell count[tw]			
OR WBC[tw]			

MeSH, (MEDLINE) Medical Subject Heading; SU, (EMBASE) subject; TW, text word.

Search terms as performed in November 2008 (with date parameters set 1 January 2007 to 31 December 2008)

EMBASE standard search terms had changed in the intervening period so the initial search strategy could not be replicated exactly.

PubMed	Results	EMBASE	Results
SEARCH 1: ACS OR ANGINA			
"Angina, Unstable"[MeSH]	21,594 hits	exp Unstable Angina Pectoris/	8501 hits
OR unstable angina*[tw]		unstable angina pectoris.mp	
OR "Myocardial Ischemia"[MeSH]		exp Heart Muscle Ischemia/	
OR coronary disease[tw]		Heart Muscle Ischemia.mp	
OR coronary syndrome[tw]			
OR myocardial infarct*[tw]			
OR myocardial ischemi*[tw]			
OR myocardial ischaemi*[tw]		myocardial isch?emi?.mp	
OR "Coronary Thrombosis"[MeSH]		exp Coronary Artery Thrombosis/	
OR coronary thrombos*[tw]		Coronary Artery Thrombosis.mp	
OR non q-wave[tw]		non q-wave.mp	
OR non q wave[tw]		non q wave.mp	
OR nstemi[tw]		non-q-wave.mp	
OR stemi[tw]		non-q wave.mp	
OR heart infarct*[tw]		exp Angina Pectoris/	
OR coronary arteriosclerosis[tw]		angina pectoris.mp	
OR acute coronary[tw]		exp Variant Angina Pectoris/	
OR "Angina Pectoris"[MeSH]		Variant Angina Pectoris.mp	
OR "Angina Pectoris, variant"[MeSH]			
OR angina*[tw]			
SEARCH 2: STUDY DESIGN			
"Prognosis"[MeSH]	227,140 hits	exp Prognosis/	47,362 hits
OR Diagnosed[tw]		prognosis.mp	
OR "Cohort Studies"[MeSH]		exp Cohort Analysis/	
OR predictor*[tw]		cohort analysis.mp	
OR death[tw]		exp Statistical Model/	
OR "Models, statistical"[MeSH]		statistical model.mp	
SEARCH 3: CRP			
"C-reactive protein"[MeSH]	5980 hits	exp C Reactive Protein/	7914 hits
OR C reactive protein[tw]		C?Reactive?Protein.mp	
		c reactive protein.mp	
		CRP.mp	
		Hs?c?reactive protein.mp	
		high?sensitivity?c?reactive?protein.mp	
		Hs?CRP.mp	
		high?sensitivity?CRP.mp	

PubMed	Results	EMBASE	Results
SEARCH 3: BIOMARKERS			
"C-reactive protein"[MeSH]	53,951 hits	exp C Reactive Protein/	82,067 hits
OR C reactive protein[tw]		C?Reactive?Protein.mp	
		c reactive protein.mp	
		CRP.mp	
		Hs?c?reactive protein.mp	
		high?sensitivity?c?reactive?protein.mp	
OR "Serum albumin"[MeSH]		Hs?CRP.mp	
OR Albumin[tw]		high?sensitivity?CRP.mp	
OR "Apolipoproteins A"[MeSH]		exp Albumin/	
OR Apolipoprotein* A[tw]		albumin.mp	
OR ApoA[tw]		serum albumin.mp	
OR "Apolipoproteins B"[MeSH]		exp Serum Albumin/	
OR Apolipoprotein* B[tw]		exp Albumin Blood Level/	
OR ApoB[tw]		albumin blood level.mp	
OR "Creatinine"[MeSH]		apolipoprotein a.mp	
OR Creatinine[tw]		Apolipoprotein A/	
Or "Blood Glucose"[MeSH]		Apolipoprotein A1/	
OR Fasting glucose[tw]		apolipoprotein a1.mp	
OR 2 hour glucose[tw]		Apolioprotein B/	
OR Fasting blood sugar[tw]		apolipoprotein b.mp	
OR 2-hour postprandial blood sugar[tw]		Creatinin Blood Level/or Creatinine/	
OR "Fibrinogen"[MeSH]		Creatinine.mp	
OR Fibrinogen[tw]		creatinine blood level.mp	
OR "Hemoglobins"[MeSH]		Glucose/	
OR Haemoglobin[tw]		Glucose Blood Level/	
OR Hemoglobin[tw]		Glucose.mp	
OR Hgb[tw]		Glucose Blood Level.mp	
OR "Hemoglobin A, glycosylated"[MeSH]		Fibrinogen Blood Level/or Fibrinogen/	
OR Glycated hemoglobin[tw]			
OR Glycated haemoglobin[tw]		Glycosylated Hemoglobin/of Hemoglobin/	
OR Hemoglobin A1c[tw]		h?emoglobin.mp	
OR Haemoglobin A1c[tw]		glycated h?emoglobin.mp	
OR Glycohaemoglobin[tw]		glycoh?emoglobin.mp	
OR Glycohemoglobin[tw]		Hemoglobin Blood Level/	
OR HbA1c[tw]		h?emoglobin blood level.mp	
OR Glycosylated hemoglobin[tw]		High Density Lipoprotein/	
OR Glycosylated haemoglobin[tw]		high density lipoprotein.mp	
OR "Lipoproteins, HDL"[MeSH]		Low Density Lipoprotein/	
OR High density lipoprotein[tw]		low density lipoprotein.mp	
OR HDL[tw]		hdl.mp	

PubMed	Results	EMBASE	Results
OR "Lipoproteins, LDL"[MeSH]		ldl.mp	
OR Low density lipoprotein[tw]		homopcysteine.mp	
OR LDL[tw]		Homocysteine/	
OR "Homocysteine"[MeSH]		tHcy.mp	
OR Homocysteine[tw]		Interleukin 6/	
		Interleukin 6.mp	
OR "Interleukin-6"[MeSH]		il?6.mp	
OR Interleukin-6[tw]		interleukin?6.mp	
OR IL-6[tw]		Lipoprotein A/	
OR IL 6[tw]		lipoprotein a.mp	
OR "Lipoprotein(a)"[MeSH]		lipoprotein a?mp	
OR "lipoprotein(a)"[tw]		lipoprotein?a?.mp	
OR lipoprotein a[tw]		Lp a.mp	
OR "Lp(a)"[tw]		Lp?a?.mp	
OR "Lp a"[tw]		Amino Terminal Pro Brain Natriuretic Peptide/or Brain Natriuretic Peptide/	
OR Pro-brain natriuretic peptide (1–76) [Substance name]		Brain Natriuretic Peptide.mp	
OR N-terminal pro-BNP[tw]		Amino Terminal Pro Brain Natriuretic Peptide.mp	
OR NT-BNP[tw]		NT?pro?BNP.mp	
OR NTproBNP[tw]		BNP.mp	
OR NT-proBNP[tw]		Cholesterol Blood Level/	
OR Amino-terminal pro-brain natriuretic peptide[tw]		Cholesterol/	
OR "Cholesterol"[MeSH]		cholesterol.mp	
OR total cholesterol[tw]		cholesterol blood level.mp	
OR "Triglycerides"[MeSH]		Triacylglycerol/	
		Triacylglycerol.mp	
OR triglycerides[tw]		Leukocyte Count/	
OR "Leukocyte count"[MeSH]		leukocyte count.mp	
OR leukocyte count[tw]			
OR white blood cell count[tw]			
OR WBC[tw]			
MeSH, (MEDLINE) Medical Subject Heading; TW, text word			

Appendix 3

Eligibility criteria for biomarker studies in systematic review

Criterion	Definition	Example of ineligible articles
Prospective design	Any prospective study including observational cohort studies, prospective nested case–control, randomised controlled trials	Cross-sectional studies, meta-analyses, editorials, reviews, comments
Patients with stable coronary disease	Studies which include patients described as having stable coronary disease, chronic stable angina, or a history of acute coronary syndromes for at least 2 weeks prior to biomarker measurement	Patients with: unstable angina, acute coronary syndrome, acute myocardial infarction, emergency revascularisation, undiagnosed coronary disease at biomarker measurement (i.e. healthy population)
One or more eligible biomarker	The article must discuss one or more of the following biomarkers: total cholesterol, low density lipoprotein, high density lipoprotein, triglycerides, fasting glucose, haemoglobin, white cell count, creatinine (serum creatinine, creatinine clearance or glomerular filtration rate), apolipoprotein A, apolipoprotein B, lipoprotein (a), fibrinogen, homocysteine, C-reactive protein, N-terminal B natriuretic protein, interleukin 6	Studies measuring other circulating biomarkers
Eligible outcomes	Any prospective study which measured the following outcomes: coronary death, non-fatal coronary event, coronary revascularisation, cardiovascular death, all-cause mortality (these can be in combination with non-fatal vascular events)	Studies which measure ONLY non-fatal vascular events (e.g. stroke, heart failure, peripheral arterial disease)
Relative risks and 95% confidence intervals	Any prospective study which reported a hazard/odds ratio OR studies which provide the number of events and number of patients in two or more biomarker comparison groups	

Appendix 4

Coding protocol for extraction of eligible studies

Variable name	Definition	Coding
General		
RefmanID	REFERENCE MANAGER ID for the article	
Study number	Unique number given to the article by the reviewers	
Author	Last name of the first author of the article	
Pubyear	Publication year of the article	
Studyname	Name of study discussed in the article	
Startyear	Year the study began (i.e. when first patients were recruited)	When the start year is not stated, give an estimate of 5 years before publication date
Country	Country where study was conducted	
Population/design		
Prespec	Whether the research question was pre-specified in a peer-reviewed, dated protocol or grant	1 = Yes –1 = Not stated
Designcom	The sources of data collection reported in the article. From the list opposite, indicate the sources of data collection reported in the article. Each source has a three-digit number; <designcom> is written as a string of one or several three-digit numbers	101 = Randomised controlled trial 102 = Observational: bespoke prospective baseline collection, assessing more variables than routine clinical care 103 = Extraction of clinical records 104 = Extraction from routinely collected electronic data 105 = Ongoing coronary disease registry 106 = Retrospective 108 = Nested case–control 109 = Cross-sectional
Multiplepub	Whether the biomarker of interest is analysed for the same data set in a separate article	1 = Yes –1 = Not stated
Sample	The method by which the study sample of the article was selected	
Multicentre	Indicates the number of patient centres in the study (e.g. hospital units, clinics)	1 = 1 2 = 2 3 = 3 or more –1 = Not stated
Negligible	The total number of patients who were invited to participate in the study, i.e. the number before exclusion criteria or missing data reduced the number of analysed patients in the article	
Npatients	Number of patients included in the analysis of the biomarker	

Variable name	Definition	Coding
Nsampleclear	Whether there is a clear description of how the number analysed was derived from the number eligible	1 = Yes –1 = Not stated
Excritcom	The combination of exclusion criteria reported in the article. Each reason for exclusion is a three-digit number; <excritcom> is written as a string of one or several three-digit numbers. The codes for the exclusion criteria were categorised as follows: Acute coronary or cardiovascular events: codes 101–129 Treatment: 201–236 Infections: 301–305 Inflammatory disorder: 401–408 Malignancy: 501 Other: 601–627	
Ptresponse	The percentage of <N eligible> patients who agreed to be part of the study	
Consent	Was written informed patient consent obtained?	1 = Stated –1 = Not stated
Age	Average age of <N patients>	
Ageavetype	How was <Age> estimated	1 = Mean, as stated in the article 2 = Median, as stated in the article 3 = Calculated weighted mean 4 = Calculated weighted median 5 = Mid-point of stated age range –1 = Not stated
Pctwomen	Percentage of <N patients> who were women	
Settcom	From the list opposite, indicate the setting in which the patients were recruited and the study was carried out	101 = Patients presenting to and diagnosed in primary care 201 = Patients undergoing an exercise electrocardiogram or other non-invasive ischaemic test 202 = Patients presenting to chest pain clinics 203 = Patients referred to other hospital outpatient departments 204 = Patients undergoing coronary angiography 205 = Patients undergoing revascularisation: PCI, CABG 301 = Patients recruited AFTER coronary event 401 = Randomised controlled trial –1 = Not stated
Ptcom	The combination of types of patients analysed in the article Articles with patients with 300 or 400 codes ONLY were considered ineligible	From the list below, indicate the combination of characteristics that make up the patient population of the article. Each characteristic is a three-digit number; <ptcom> is written as a string of one or several three-digit numbers, e.g. the string 100301105 indicates stable and unstable angina patients admitted for an elective PCI

Variable name	Definition	Coding

Stable/chronic disease	History of previous coronary heart disease	Acute or unstable disease at time of biomarker measurement	Other vascular disease	Subgroup identification
100 = Stable angina 101 = Stable coronary artery disease/ ischaemic heart disease 102 = Patients admitted for angiogram 103 = Patients with luminal narrowing 104 = Patients without luminal narrowing 105 = Patients admitted for an elective revascularisation (non-emergency PCI or CABG)	200 = Acute coronary syndrome 201 = Unstable angina 202 = Myocardial infarction 203 = Silent ischaemia	300 = Acute coronary syndrome 301 = Unstable angina 302 = Myocardial infarction 303 = ST elevation myocardial infarction 304 = Non-ST elevation myocardial infarction 305 = Emergency revascularisation	400 = Heart failure 401 = Stroke 402 = Peripheral vascular disease 403 = Peripheral arterial disease	500 = Placebo subgroup 501 = Treatment subgroup

AveHx	Time since the first presentation of coronary disease (in average years)	
MinHx	The minimum known time of patients having coronary disease (in years)	
PctMI	Percentage of <N patients> who have suffered a previous myocardial infarction	
PctCAD	Percentage of <N patients> with angiographically confirmed coronary artery disease	100 if cohort admitted for revascularisation
Pctangina	Percentage of <N patients> with stable angina at the time of recruitment	
Pctstatin	Percentage of <N patients> on statins at time of recruitment	
FU	Follow-up time, in years	
FUtype	Type of measure for follow-up time	1 = Mean 2 = Median 3 = Maximum follow-up time stated in the analysis 4 = Average length of hospital stay for coronary event (5 days) –1 = Not stated
PctlostFU	Percentage of patients lost to follow-up	Percentage stated in the article –1 = Not stated
CharaclostFU	Whether the article states the characteristics of patients followed up compared with those lost to follow-up	1 = Stated –1 = Not stated

Variable name	Definition	Coding
Biomarker measurement		
Biomarker identification number	Identification number of biomarker reported in article. If there is more than one biomarker analysed in the article, begin a new row of data entry	1 = Total cholesterol 2 = Low density lipoprotein 3 = High density lipoprotein 4 = Triglycerides 5 = Fasting glucose 6 = Haemoglobin 7 = White blood cell count 8 = Creatinine (including serum creatinine, glomerular filtration rate, creatinine clearance) 9 = Apolipoprotein A-1 10 = Apolipoprotein B 11 = Lipoprotein (a) 12 = Fibrinogen 13 = Homocysteine 14 = C-reactive protein 15 = N-terminal pro-B type natriuretic peptide 16 = IL-6
BMmeascom	From the list opposite, indicate which biomarkers have been measured in the article. Each biomarker has a three-digit number; <BMmeascom> is written as a string of one or several three-digit numbers. For example, when both C-reactive protein and triglycerides are measured in the blood analysis, the entry is 114104	101 = Total cholesterol 102 = Low density lipoprotein 103 = High density lipoprotein 104 = Triglycerides 105 = Fasting glucose 106 = Haemoglobin 107 = White blood cell count 108 = Creatinine, glomerular filtration rate, creatinine clearance 109 = Apolipoprotein A 110 = Apolipoprotein B 111 = Lipoprotein (a) 112 = Fibrinogen 113 = Homocysteine 114 = C-reactive protein 115 = N-terminal pro-B natriuretic peptide 116 = Interleukin-6
Fasting	Whether the blood sample was taken while patients were fasting	1 = Fasting 2 = Casual –1 = Not stated
Tempstor	The temperature at which the blood samples were stored	1 = Fresh (i.e. sample assayed immediately and not frozen) 2 = Sample frozen at –80°C 3 = Sample frozen at –79°C to –60°C 4 = Sample frozen at–59°C to –40°C 5 = Sample frozen at –39°C to –1°C 6 = Refrigerated at 0°C to 10°C

Variable name	Definition	Coding
Manufacturer	The reagent manufacturer biomarker measurement	Write in free text the name of the company source (e.g. Dade Behring, Abbott Diagnostics) or in house
Assay	The method of assay of biomarker measurement	1 = Turbidimetric 2 = Nephelometric 3 = EIA (Enzyme immunoassay) 4 = ELISA (Enzyme linked immunoradiometric assay) 5 = Fluorescence polarisation 6 = Chemiluminescent 7 = Latex particle enhanced 8 = Autoanalyser 9 = HPLC (high pressure liquid chromatography) 10 = Latex agglutination 11 = von Claus method 12 = Precipitation with sodium/ magnesium/phosphates 13 = Infrared particle immunoassay 14 = Sandwich enzyme linked immunosorbent assay 15 = MEIA (microparticle capture enzyme immunoassay)
BMrepmeas	The number of times the biomarker was measured	1 = Biomarker was measured one time only 2 = Biomarker was measured at two different time points 3 = etc. –1 = Not stated
BMave	The average value of the biomarker at baseline irrespective of subsequent outcome events status	
BMavetype	How was <BMave> obtained?	1 = Mean, as stated in the article 2 = Median, as stated in the article 3 = Calculated weighted mean 4 = Calculated weighted median 5 = Geometric mean 6 =Weighted average of geometric mean 7 =Average of geometric mean –1 = Not stated –2 = Not applicable

Variable name	Definition	Coding
BMSD	Standard deviation of the biomarker	
BMunit	Measurement unit of the biomarker used in the article	1 = mg/l 2 = g/l 3 = µg/l 4 = ng/l 5 = mg/dl 6 = g/dl 7 = mg/ml 8 = µg/ml 9 = ng/ml 10 = pg/ml 11 = mmol/l 12 = µmol/l 13 = pmol/l 14 = ml/min 15 = ml/min/m^2
BMavewithev	Average value of the biomarker at baseline for patients who had subsequent outcome event	
BMavetypewithevt	How was <BMavewithev> obtained for patients who had an outcome event	1 = Mean 2 = Median 3 = Weighted average of means 4 = Weighted average of medians –1 = Not stated
BMevtSD	Standard deviation for the biomarker at baseline for patients who did not experience an event over the follow-up period	
BMavenoevt	The average value of the biomarker for patients without an event	
BMavetypenoevt	How was this <BMavenoevt> obtained for patients who had an outcome event	1 = Mean 2 = Median 3 = Weighted average of means 4 = Weighted average of medians –1 = Not stated
BMnoevtSD	Standard deviation for biomarker for patients without an outcome event	
Blindisease	Whether the measurement of biomarker measurements was blinded to disease status	1 = Stated –1 = Not stated
hsCRP	Whether CRP was measured by high-sensitivity method	1 = CRP 2 = high-sensitivity CRP –1 = Not stated –2 = Not applicable (i.e. if biomarker other than CRP is analysed, e.g. total cholesterol)

Variable name	Definition	Coding
Outcomes		
Evcom	The combination of events (i.e. outcomes/end points) analysed in the article. Articles which reported outcomes with 300 codes ONLY were considered ineligible	From the list below, indicate the combination of outcomes events analysed in the article. Each event is a three-digit number; <evcom> is written as a string of one or several three-digit numbers, e.g. when analysed events are cardiovascular death and myocardial infarction, the entry is 105200

Death	Non-fatal coronary outcomes	Other non-fatal vascular outcomes
100 = Fatal coronary heart disease	200 = Myocardial infarction	300 = Stroke
101 = Cardiac mortality	201 = Acute coronary syndrome	301 = Heart failure
102 = Fatal myocardial infarction	202 = Unstable angina	302 = Peripheral arterial disease
103 = Sudden cardiac death	203 = Recurrent ischaemia	303 = Peripheral thrombolism
104 = Fatal stroke	204 = Resuscitated cardiac arrest	304 = Peripheral revascularisation
105 = Cardiovascular mortality	205 = Target vessel revascularisation/ emergency revascularisation (PCI or CABG)	305 = All cause hospitalisation
106 = All-cause mortality	206 = Cardiac hospitalisation	

EvN	Number of patients experiencing an event, used in the analysis	
Masking	Whether the assessment of outcomes/events was blinded to biomarker results and other clinical details	1 = Stated –1 = Not stated
Power	Whether there was evidence of power, or a statistical sample size calculation	1 = Stated –1 = Not stated
Validation	Whether the outcomes/events were validated by two independent assessors	1 = Stated –1 = Not stated
Primary outcome	Whether a single disease end point, or a single combination of end points, for the analysis. The report must use the word 'primary'	1 = Stated –1 = Not stated
Pre-specified primary outcome	Whether the primary outcome was pre-specified in the study protocol	1 = Stated –1 = Not stated
Adjustments		
Adjcom	Combination of adjustment variables reported in the analysis. Each adjustment variable is a three-digit number; <adjcom> is written as a string of one or several three-digit numbers. The codes were categorised as follows: Patient history: codes 100–111 Comorbidity: 200–225 Physical examination: 300–310 Routine blood tests: 400–423 Non-invasive ischaemic testing: 500–509 Invasive imaging: 600–611 Treatment: 700–731 Novel biomarkers: 800–832	

Variable name	Definition	Coding
Confounder measurement	Were the following potential confounders measured: age, sex, body mass index, smoking status, diabetes, low density lipoproteins and triglycerides? However, these confounders do not necessarily have to be included in the multivariate analysis	1 = Yes –1 = Not stated
Adjrational	Rationale given for the inclusion of the adjustment variables	1 = A priori 2 = Stepwise selection 3 = Univariate *p*-value –1 = Not stated (i.e. no rationale provided) –2 = Not applicable (e.g. if the analysis was univariate)
Analytical		
Rowno	Number given to the row for each relative risk reported in the article A new row of data is created for: each biomarker each outcome event men and women subgroups placebo and treatment subgroups each analysis (i.e. if the biomarker is analysed both continuously and categorically)	
RowID	A unique identifier for each row was created by merging the study number (integer) and the corresponding row numbers (decimal)	e.g. Study number 23 has five rows. The respective rows IDs are: 23.1, 23.2, 23.3, 23.4, 23.5
RRtype	Indicate the type of relative risk reported in the article	1 = Odds ratio 2 = Hazard ratio 3 = Relative risk
MissBMan	Method used to deal with missing biomarker values in the analysis	1 = Imputation 2 = Complete case analysis –1 = Not stated
Missadjan	Method used to deal with missing values of confounders in the analysis	1 = Imputation 2 = Complete case analysis –1 = Not stated
Nriskgr	Number of risk groups reported in the article	1 = Continuous (per SD or incremental unit increase) 2 = With one cut-off point, median 3 = Tertiles, two cut-off points 4 = Quartiles, etc.
Quant	Whether the article reports risk groups in 'quan'tiles (e.g. tertiles, quartiles, quintiles, etc.)	0 = No: derived cut-points, continuous analysis 1 = Yes (risk groups are equal numbers: 'quan'tiles) –1 = Not stated/unclear

Variable name	Definition	Coding
Cut-point rationale	How were the cut-points for the biomarker determined for the estimation of relative risks (response categories: a priori, quantiles)	1 = A priori: using estimates from other general population study or review (e.g. cites reference, World Health Organization, etc.) 2 = Median (50th centile) 3 = Quantile 4 = Value of top quantile vs combined lower quantiles (e.g. Q4 vs Q1–3) –1 = Not stated –2 = Continuous
Refdef	Range of biomarker values for the reference group of the analysis	e.g. < 1.0 (mg/dl) If continuous: per SD, log transformation, per unit increase
Refn	Number of events in the reference group	
Refn_1	Number of patients in the reference group	
R1def	Range of biomarker values for group 1	e.g. 1.0–3.0 (mg/dl); or ≥ 1.0 (mg/dl)
R1n	Number of events in risk group 1	
R1n_1	Number of patients in risk group 1	
R1RR	Relative risk reported for risk group 1 compared with reference group	
R195_CI	95% confidence interval reported for relative risk for group 1 versus reference group	
There will be subsequent Refn_x, Rxdef, Rxn, Rxn_1, RxRR and Rx95_CI variables depending on the number of analysis groups; e.g. if there are three groups, the third group variables are entered in Refn_2, etc. If there are four groups, fourth group variables are entered in Refn 3, etc., and so on.		

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We look forward to hearing from you.

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