Biomarkers for the prioritisation of patients awaiting coronary revascularisation

# 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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## *Executive summary*

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# 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.

## Publication

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 05/40/04. The contractual start date was in November 2006. The draft report began editorial review in August 2008 and was accepted for publication in March 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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