

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

H Hemingway,^{1*} M Henriksson,^{2,3} R Chen,¹ J Damant,¹ N Fitzpatrick,¹ K Abrams,⁴ A Hingorani,¹ M Janzon,⁵ M Shipley,¹ G Feder,⁶ B Keogh,⁷ U Stenestrand,⁵ K McAllister,¹ J-C Kaski,⁸ A Timmis,⁹ S Palmer³ and M Sculpher³

¹Department of Epidemiology and Public Health, University College London, UK

²Centre for Medical Technology Assessment, Linköping University, Sweden

³Centre for Health Economics, University of York, UK

⁴Department of Health Sciences, University of Leicester, UK

⁵Department of Cardiology, Linköping University, Sweden

⁶Department of Primary Health Care, University of Bristol, UK

⁷Department of Health, London, UK

⁸Cardiovascular Biology Research Centre, St George's, University of London, UK

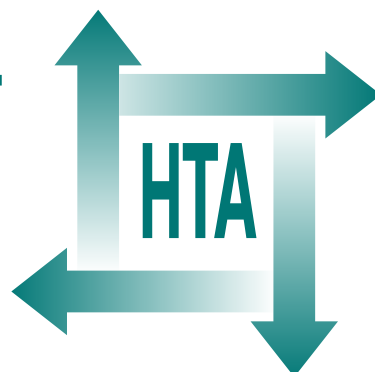
⁹Barts and the London NHS Trust, London, UK

*Corresponding author



Executive summary

Health Technology Assessment 2010; Vol. 14: No. 9
DOI: 10.3310/hta14090





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

Hemingway H, Henriksson M, Chen R, Damant J, Fitzpatrick N, Abrams K, *et al.* The effectiveness and cost-effectiveness of biomarkers for the prioritisation of patients awaiting coronary revascularisation: a systematic review and decision model. *Health Technol Assess* 2010;**14**(9).



How to obtain copies of this and other HTA programme reports

An electronic version of this title, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable DVD is also available (see below).

Printed copies of HTA journal series issues cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our despatch agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per issue and for the rest of the world £3 per issue.

How to order:

- fax (with **credit card details**)
- post (with **credit card details** or **cheque**)
- phone during office hours (**credit card** only).

Additionally the HTA website allows you to either print out your order or download a blank order form.

Contact details are as follows:

Synergie UK (HTA Department)
Digital House, The Loddon Centre
Wade Road
Basingstoke
Hants RG24 8QW

Email: orders@hta.ac.uk

Tel: 0845 812 4000 – ask for 'HTA Payment Services'
(out-of-hours answer-phone service)

Fax: 0845 812 4001 – put 'HTA Order' on the fax header

Payment methods

Paying by cheque

If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *University of Southampton* and drawn on a bank with a UK address.

Paying by credit card

You can order using your credit card by phone, fax or post.

Subscriptions

NHS libraries can subscribe free of charge. Public libraries can subscribe at a reduced cost of £100 for each volume (normally comprising 40–50 titles). The commercial subscription rate is £400 per volume (addresses within the UK) and £600 per volume (addresses outside the UK). Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

How do I get a copy of HTA on DVD?

Please use the form on the HTA website (www.hta.ac.uk/htacd/index.shtml). *HTA on DVD* is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

Editor-in-Chief: Professor Tom Walley CBE
Series Editors: Dr Martin Ashton-Key, Dr Aileen Clarke, Professor Chris Hyde,
Dr Tom Marshall, Dr John Powell, Dr Rob Riemsma and Professor Ken Stein

ISSN 1366-5278

© 2010 Queen's Printer and Controller of HMSO

This journal may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to: NETSCC, Health Technology Assessment, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.

G