Atherosclerosis 213 (2010) 345–351

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Predicting the risk of coronary heart disease I. The use of conventional risk markers

T.H.S. Dent*

PHG Foundation, 2 Worts Causeway, Cambridge CB1 8RN, United Kingdom

ARTICLE INFO

Article history:
Received 30 November 2009
Received in revised form 4 June 2010
Accepted 7 June 2010
Available online 16 June 2010

Keywords:
Coronary heart disease
Risk prediction
Conventional risk factors
Novel biomarkers
Genetics

ABSTRACT

This is the first of two articles reviewing recent findings about the risk of coronary heart disease. This paper is concerned with conventional risk factors; the second will review novel molecular biomarkers, genetic markers of risk and the future of risk prediction.

Predicting exactly the future occurrence of coronary heart disease (CHD) is not possible, but the risk can be estimated with models based on cohort studies. Most existing models are based on long-standing research on the residents of Framingham, Massachusetts. The findings from Framingham yield inaccurate results when applied to contemporary populations elsewhere. In particular, they may exacerbate health inequalities. This is because the incidence of and mortality from CHD have fallen recently, the Framingham cohort differs from many groups to which findings from it have been applied, important risk factors such as ethnicity, socio-economic deprivation and family history are absent from the Framingham equations and susceptibility to risk factors varies between populations. Attempts to recalibrate or adjust the Framingham equations to improve their performance have not been shown to overcome these problems.

SCORE, QRISK, PROCAM and ASSIGN are risk prediction models that have been developed based on different cohorts. The group developing NICE's guideline on lipid modification was uncertain about which risk prediction model to recommend for use in the NHS. Eventually they selected a modified version of the Framingham equation. However, QRISK appears to offer the best long-term promise.

Contents

* Tel.: +44 1494 793779.
E-mail address: tomdent07@yahoo.co.uk.

0021-9150/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2010.06.019

1. Introduction

Coronary heart disease (CHD) is a major public health problem. A wide range of preventative interventions for individuals is available, involving either medication or lifestyle change. Both types of intervention are improved by accurate assessment of the individual's risk: the benefits of medication are proportional to the recipient's absolute risk of CHD, while lifestyle change is probably more likely in people who see themselves as at particularly high risk. Inaccurate risk assessment leads to failure to identify, treat and motivate high-risk people, to less cost-effective targeting of treatment to those at lower risk and to the potential for discouragement of all involved if the risk prediction model becomes devalued. Furthermore, if the model is biased, it may exacerbate health inequalities by, for example, systematically under-estimating the risk of CHD in socio-economically deprived people and those from ethnic minorities.

Given the public health importance of CHD, the enormous volume of epidemiological research into its aetiology and the interest of primary care practitioners in its prevention, it is not surprising that a number of tools for assessing individual risk have been developed. However, three problems remain for those seeking an evidence-based approach to choosing and using these tools:

1. How should risk be assessed? There is no consensus as to the most suitable risk prediction model to use.
2. Which biomarkers should be incorporated into risk assessment? There is uncertainty about the potential contribution of novel blood-borne molecular biomarkers to risk assessment, and about whether and how they should be used to identify those at higher risk.
3. Can genetic information improve risk prediction? All available risk prediction models leave an important proportion of individual variance in risk unexplained, and few integrate information on family history. Meanwhile, knowledge of the genetic contribution to risk is increasing.

These papers aim to answer these questions. The second paper goes on to explore the implications of the findings for the appraisal and use of biomarkers more generally.

2. Background

Clinicians and patients need reliable information about an individual's risk of developing CHD. Ideally, they would have entirely accurate data and would be able to use a perfect model to estimate risk. Such a model would be able to categorise people dichotomously into those who would develop CHD and those who would not. Indeed, the perfect model would even be able to predict the timing of the disease's onset. Those destined to develop CHD could receive intensive interventions to reduce their risk and postpone, if not prevent, the disease arising; those who would not develop CHD in the course of their lifetime could be reassured.

Of course, no such perfect model exists. Our knowledge of the disease's aetiology is too incomplete, in terms of both which risk factors are independently important and how they should each be weighted. In any case, many of the risk factors which are known to be important, such as blood pressure and serum cholesterol level, cannot be measured with sufficient accuracy to support risk assessment with this putative degree of certainty. They show considerable intra-individual variation, making repeated measurement necessary for an accurate assessment. This is good clinical practice before treatment decisions are taken, but difficult and expensive in a research setting.

Instead of dichotomising people in this way, the available risk prediction models estimate the probability of CHD arising in a specified future period, usually 10 years. There is an obvious limitation to the value of information from such models, in that it falls far short of providing clarity for individuals about what will happen to them. Most people who go on to develop CHD have estimated risks that indicate that a CHD event is unlikely. More than half of the cardiovascular disease events in the next 10 years among asymptomatic adults in the UK will occur in people below the current drug treatment threshold of 20% over 10 years [1]. This threshold is based on considerations of cost-effectiveness and affordability and so is essentially arbitrary; it certainly excludes from treatment people with capacity to benefit.

A problem with this approach is that the estimation of risk only covers the next 10 years. Among younger and middle-aged adults, there are people with a low 10-year risk but high lifetime risk for cardiovascular disease [2]. It may be appropriate to take into account lifetime risk estimation for cardiovascular disease in deciding whom to treat with lipid-lowering drugs.

Another issue is that global risk assessment is far from universally carried out in primary care. Reimbursement policies may be important in incentivising appropriate assessment and treatment behaviours.

Nevertheless, the outputs of these models can be used to categorise people according to their risk of CHD, and this can in turn be used to decide how intensively to intervene in order to reduce risk. This usefully aligns the inconvenience, risks and costs of intervention with the potential benefits of risk reduction. But, by the same token, risk prediction models which misclassify people can be damaging, leading to a misperception of risk, a misapplication of clinical effort and resources, and costs and harms not offset by commensurate benefits.

So the selection of which model to use is of critical importance. This paper reviews how models are assessed, appraises those available and sets out to identify the most suitable for use.

3. The assessment of risk prediction models: calibration and discrimination

Risk prediction models have usually been assessed using two criteria, calibration and discrimination. Both metrics are important, but they are independent, meaning that whether a model has one characteristic is unrelated to whether it also has the other [3].

A well-calibrated model will correctly estimate the average risk of a group of people. Poor calibration will lead to systematic inaccuracy in a model's performance; this might be universal, or might just occur in certain categories of subject. For example, people of south Asian ancestry living in western countries are at higher risk of CHD than white people. If a model omits ethnicity, it will systematically underestimate risk in south Asian people. The public health importance of this mis-calibration will depend on the proportion of south Asian people in the population in question; in an entirely white population it would not matter, but in a modern multi-ethnic society it might be an important weakness.

A model that discriminates well ranks individuals' risk in the correct order, accurately labelling people as to how their degree of risk relates to that of the population as a whole. Such a model will have high sensitivity and specificity. Discrimination can be illustrated by receiver operator characteristic curves, which display models' discriminatory capacity over the range of possible thresholds. A model which ignored ethnicity could still discriminate well in a population made up entirely of south Asian people or of white people, since in both cases ethnicity is not relevant to their risk relative to one another. In a population of mixed ethnicity, it would discriminate less well the larger the minority group was.