Coronary artery disease: seeing or foreseeing?

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This editorial refers to ‘Discordance between Framingham Risk Score and atherosclerotic plaque burden’, by A. Pen et al., on page 1075

The prevention of cardiovascular disease (CVD) has been a major priority and challenge for policy-makers and healthcare workers for at least five decades. In this ‘co-ordinated set of actions, at public and individual level, aimed at eradicating, eliminating, or minimizing the impact of CVDs and their related disability’, the capacity to predict the presence of coronary atherosclerosis obviously plays a central role.

Studies show that the combination of a few major risk factors is an easily accessible proxy for risk stratification: the European Society of Cardiology (ESC) EUROSCORE tables use sex, smoking, blood pressure, diabetes, blood cholesterol levels, and nationality (high- vs. low-risk countries, or nation-specific charts) to provide direct and intuitively useful information on the risk of individuals belonging to specific risk strata. Under the guidance of these epidemiological data, a set of interventions aimed at the prevention of cardiovascular disease can be developed: as the 2012 ESC guidelines emphasize, such efforts are a life-long commitment for both patients (or healthy individuals) and healthcare workers: CVD prevention ideally starts before birth and lasts until the end of life. At a population level, governments and scientific societies have been promoting for > 50 years ad hoc policies and community interventions aimed at reducing the incidence and consequences of CVD through lifestyle and environmental changes targeted at the population at large. Examples of these policies include smoking bans, awareness campaigns on the importance of high blood pressure, CVD in women, or ‘heart days’, where the population is offered the possibility to undergo a free cardiovascular check-up. These interventions appear to be at least as effective in reducing cardiovascular mortality as the improvements in medical technologies and drug development. Aggressive interventions focused on major risk factors, in particular smoking, blood pressure, and diet, account for more than half of the decrease in CVD (Figure 1). The rising prevalence of obesity and type 2 diabetes suggests, however, that future efforts need to be made in this direction.

While the impact of these strategies is evident at a population level, it may offer little to the single individual, and will not address the needs of practising clinicians, challenged in their everyday routine by complex cases. As clinicians, we are daily confronted with questions such as ‘why did it happen to me?’, or with the more challenging version ‘what did I do wrong?’, which often remain unanswered, for instance when asked by a young patient with small children and no known risk factors. In clinical practice, cost and feasibility considerations limit our possibility of intervening, and our efforts—at least at the level of single clinicians—focus on those patients who are at higher risk, whether they are individuals with multiple factors or patients with established CVD. In sum, despite the evidence available to justify the intensification of public health and individual preventive efforts, reflecting the complexity of the biology of atherosclerosis and related diseases, important gaps in our understanding and in the capacity to predict the presence of CVD at an individual level still exist.

In the last years, a number of approaches have been proposed to investigate, directly or indirectly, parameters related to the biology of the atherosclerotic plaque which might reflect the predisposition to CVD events. For instance, the study of endothelial function has been proposed by many as a possible compound measure of the interaction among known and unknown risk factors, and as such a ‘barometer of cardiovascular health’. Since endothelial dysfunction temporally precedes the development of morphological changes and can be measured non-invasively, it has been proposed that it might assist in the stratification of individual risk. Unfortunately, only a very limited number of studies have investigated whether these methods provide information that is additional to that of traditional risk factors, and whether they provide information in populations that would not be classified as being at high risk. This issue will be addressed for the first time at a whole population level in the Gutenberg Health Study, a prospective, single-centre cohort study that started in 2007 at the University Medical Center Mainz. The study aims to test the associations and predictive power of three different methodologies to assess endothelial function directly or indirectly (flow-mediated dilation, finger pulse plethysmography, and pulse wave reflection). A total
of 15,000 individuals aged 35–74 years were included in this study by May 2012. This is followed by a computer-assisted telephone interview with a standardized interview and assessment of end-points after 2.5 years. After 5 years, a detailed follow-up examination comparable with the visit at study inclusion will be performed. In our previous study, endothelial function assessment provided information on top of traditional risk factors in predicting the presence of coronary artery disease (CAD), although the demonstrated increase in diagnostic accuracy was relatively small. While the study of endothelial function tackles the biology of CAD, and both practical and theoretical issues limit its application, coronary computer tomography (CT) provides a direct, more informative, and organ-specific assessment of the status of the coronary artery. Several studies have demonstrated the accuracy of CT in detecting the presence and fate of CAD, and the introduction of CT-based non-invasive fractional flow reserve has already been shown to be associated with an improved discrimination vs. CT alone. Pen et al. have now extended these data reporting on the association between the presence of CAD (quantified as total plaque score by CT) and the Framingham Risk Score. Thirdly, the definition of CAD (particularly when one introduces the concept of rupture-prone plaque) is particularly challenging. As shown by Pen et al., the Framingham risk equation underestimates CAD in low-risk and/or intermediate risk populations. The problem here is, however, the gold standard: are we searching for CAD or for the lesions at risk of clinical events? It is well known that myocardial ischaemia and infarction may occur in the absence of angiographically visible CAD. Even the

There are some limitations to the research, which need to be mentioned. First of all, patients had a clinical indication for the assessment of CAD, with the majority of patients reporting angina or dyspnoea, or a combination of the two. In Bayesian terms, their pre-test probability of having CAD was therefore relatively high, which is confirmed by the high prevalence of CAD at CT (63%). The present results should therefore not be extrapolated to the early detection of coronary atherosclerosis in the population at large and in non-university settings. In other terms, we remain with the question of who should undergo CT (especially in consideration of the risks associated with this exam). In patients with suspected CAD, other non-invasive tests (stress echocardiography for instance) have the advantage of being safer (no need for X-rays and contrast) and less expensive, and they provide functional information (as fractional flow reserve clearly shows, not all angiographically severe stenoses are haemodynamically relevant).

Secondly (and clinically most importantly), the Framingham Risk Score was not developed to predict the presence of CAD. In this sense, this was probably the wrong comparator to use, and a more crude multivariate logistic regression analysis including as many known risk factors as possible might have provided additional information. In clinical practice, however, these data need to be summarized in an easily accessible scoring system.

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invasive assessment of CAD has important limitations, and it needs to be emphasized that coronary atherosclerosis is a biological, not a mechanical, phenomenon: it is not the progressive apposition of lipids that causes plaque rupture and infarction, but their interaction with a number of factors such as platelet activation, oxidative stress, inflammation, and many others. Biological, yet poorly predictable, phenomena determine plaque stability and the risk of coronary events. In this sense, we fall short of the most important information, namely what best predicts plaque instability (rather than presence). Once again, as clinicians, we are not interested in the general rule: it is intuitive to all that the presence of CAD predicts a worse prognosis than its absence. As empathic persons even more than as treating physicians, what we would like to be able to predict are the exceptions (e.g. a plaque rupture in the absence of angiographically visible CAD) which we encounter daily in our practice.

In sum, we need to accept that all current risk stratification methods—including the Framingham Risk Score—predict risk in large populations but may only have moderate or limited predictive value for an individual patient. While working well in epidemiology settings (and in directing policy-makers), Bayesian considerations are poorly applied in clinical routine. In this sense, the further refinement of (ideally non-invasive, X-ray- and contrast medium-free) screening methods that investigate the structure and biology of coronary plaques are the true challenge of modern cardiovascular medicine. For the moment, we still need to see (and measure) in order to believe.

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References