Assessment of cardiovascular risk: time to apply genetic risk factors?

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Decision making in clinical practice requires appropriate risk assessment in a given patient. The estimated risk of a patient having cardiovascular disease or of developing complications such as myocardial infarction, sudden death or stroke will often determine which diagnostic tests should be performed and whether or not certain therapeutic interventions should be adopted.

Prognosis is difficult, particularly if it relates to the future. The saying of Niels Bohr applies to medicine and cardiovascular disease in particular. Although in populations reasonable estimates can be obtained, it remains difficult to determine risk in an individual patient. However, in clinical practice, the risk factor concept has proved to be helpful[1]. Age, male sex, personal history of cardiac events, and major risk factors such as blood pressure, cholesterol levels, smoking and diabetes allow physicians to estimate the risk increase of a given patient[2,3]. In addition, a number of factors have been proved to reduce the risk such as physical activity[4] and light to moderate alcohol consumption[5]. In spite of this, up to half of the events cannot be attributed to traditional risk factors[6]. Certain patients suffer a heart attack in the absence of any known risk factors, while others remain healthy although they smoke and have an elevated cholesterol.

Because of the lack of precision of individual classification, the search for new cardiovascular risk factors is important. Epidemiological research has indeed provided new biochemical parameters that are associated with cardiovascular diseases such as C reactive protein[7], fibrinogen[8], homocysteine[9], lipoprotein(a)[10] and many others. Although some of these new risk factors are not amenable to therapy, they may still be important in leading clinical decision making as — particularly with increasingly limited resources in health care — we are forced to focus diagnostic and therapeutic measures to those at highest risk. Indeed, although the relative risk reduction with many interventions — for instance with lipid-lowering therapy — is similar in many subgroups, the absolute risk reduction and consequently the number needed to treat[11] and the cost-effectiveness[12] differs considerably according to the baseline risk.

It has been common knowledge for centuries that certain diseases run in families. Also in cardiovascular medicine, many prospective studies indicate that a family history of coronary heart disease doubles the cardiovascular risk[13]. Given this information, it would appear to be straightforward to search for genetic variations, which may mediate the risk. In monogenetic diseases such as the long QT syndrome or hypertrophic cardiomyopathy, the situation could be resolved by identifying single mutations that fully account for the presence of the respective disease[14,15]. Polygenic diseases such as atherosclerosis are much more complex. Within the same individual, several polymorphisms may increase the risk to a different extent. Moreover, some genetic polymorphisms may only increase the risk in the presence of other genetic variations, i.e. there may be an interaction between different polymorphisms. Therefore, several potential candidate polymorphisms should probably be tested simultaneously, which requires large patient populations.

One polymorphism reported to increase the risk for myocardial infarction was the insertion/deletion (I/D) polymorphism of the angiotensins converting enzyme (ACE) gene[16]. This polymorphism consists of either the presence or absence of a DNA fragment inside intron 16. Carriers of the D allele tend to have higher ACE levels in blood, and hence may have an activated ACE system. The renin-angiotensin system is known to regulate blood pressure and may be involved in the pathogenesis of certain forms of hypertension. Within the blood vessel wall, the renin-angiotensin system plays a role in endothelial function[17,18] and vascular structure[19]. The concept is supported by the clinical effectiveness of ACE inhibitors in the treatment of hypertension and heart failure[20,21] and in their ability to reduce the incidence of myocardial infarction and stroke in patients with coronary heart disease[22].

After the first report of a risk increase among carriers of the D allele[16], subsequent studies reported conflicting results. While some found a several-fold increase in the risk for coronary heart disease, in other studies the presence of a D allele was not associated with coronary heart disease. A recent meta-analysis found a significant 30% increase in risk for coronary heart disease in the pooled risk estimate, but there was a significant heterogeneity among the different studies[23]. Moreover, there was evidence of

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a publication bias among the smaller studies, in favour of publishing reports showing a risk increase. At the XXIst congress of the European Society of Cardiology in Barcelona on 29 August 1999, large patient populations in which the ACE genotype had been determined, were presented. In a study including about 5000 myocardial infarction cases and controls from Germany\(^\text{[24]}\), the D-allele was not more frequent among those with myocardial infarction (52.6%) than in controls (55.4%). Similarly, among over 10 000 myocardial infarction cases and controls from the U.K.\(^\text{[25]}\), the frequency of subjects with the DD genotype where similar in cases (29.4%) and controls (27.6%; OR 1.09). These results suggest that the D allele variant of the ACE gene is not likely to substantially increase the coronary heart disease risk.

In their study published in this issue Fatini et al. investigated 205 patients with documented coronary artery disease and 209 unmatched controls\(^\text{[26]}\). They studied genetic variants of the renin-angiotensin system including angiotensinogen polymorphisms (ATG M235T and T174M), the ACE I/D polymorphism and the A1166C polymorphism of the AT1R gene. The authors found an association between coronary heart disease and the ACE DD and the AT1R CC genotype both in the univariate and multivariate analyses (odd ratios 1.8–2.5). Moreover, they describe a significant effect modification of the risk of the ACE DD genotype according to the presence of the AT1R C allele (AT1R AA genotype: OR 0.9; AC genotype: OR 2.3; CC genotype: OR 4.4) as observed in a previous larger study\(^\text{[27]}\). They conclude from their study that the ACE DD and the AT1R CC genotypes are independent coronary heart disease predictors in Italians and that screening for genetic risk factors may be clinically useful.

What should we do with this information? The large effect of the ACE DD genotype on coronary artery disease risk in this small population is at variance with what has been reported in recently presented large-scale studies\(^\text{[24,25]}\). There are three possible explanations: (1) the results may be an accidental finding; (2) the role of the DD polymorphism may be particularly important in some populations due to different environmental factors; (3) there may be an interaction or linkage between the I/D polymorphism and other, still unknown polymorphisms of the renin-angiotensin system having different allele frequencies in certain populations. Whatever is true, given heterogeneous study results, the negative results of the two largest studies, and the limited sample size of the current study, the results should be interpreted with care. While small studies are important to explore the potential effects of genetic variation, large studies are needed for definitive assessment of genetic risk factors. If a potential risk factor is consistently associated with a risk increase in large-scale studies, the gain in risk prediction has to be tested in prospective studies. Until then, in clinical practice, we still have to rely on prediction rules derived from established risk factors.

### References


