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Is there a need for novel cardiovascular risk factors?

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Introduction

Atherosclerosis is a multifactorial disease whose age of onset and progression are strongly influenced by inborn and acquired risk factors. Since the pioneering work of the Framingham study, many prospective population and clinical studies have identified a series of independent risk factors for myocardial infarction, stroke and peripheral vascular disease, among which the preexistence of atherosclerotic vascular disease, age, male gender, a positive family history of premature

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atherosclerotic disease, smoking, diabetes mellitus, hypertension, hypercholesterolaemia, hypertriglyceridaemia and low HDL cholesterol are considered as classical risk factors. Moreover, several large randomized and prospective intervention studies have demonstrated that smoking cessation as well as antihypertensive and lipid-lowering drug therapies help to reduce cardiovascular morbidity and mortality by ~30% in both secondary and primary prevention. Despite these advances, we currently witness a controversy concerning the introduction of novel risk factors into clinical practice, specifically lipoprotein(a) [Lp(a)], C-reactive protein (CRP), fibrinogen, homocysteine and microalbuminuria.

Advances and limitations of classical risk factors and global risk estimation

Two recent reports on the data analysis of more than 500 000 participants in 14 intervention trials and three observational studies showed that 80–90% of patients who developed clinically significant coronary heart disease had at least one of four classical risk factors, namely hypercholesterolaemia (serum cholesterol >240 mg/dl/6.22 mmol/l), hypertension (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg), diabetes mellitus or smoking [1,2]. However, counting of risk factors has a low sensitivity and specificity because it does not take into account the graded and dose-dependent influence of risk factors and the overproportional effect of risk factor interaction. In a given individual, the presence of a single risk factor has a low positive predictive value. In contrast, the presence of several moderately expressed risk factors can produce a significant increase in cardiovascular risk. Therefore, at present the most advanced strategy for coronary risk assessment is to combine the information of several risk factors in algorithms or scores. This procedure allows calculation of an individual's absolute risk of experiencing a cardiovascular event within the next 10 years. The best accepted and evaluated algorithms are those derived from the US-American Framingham study and the German PROCAM study [3,4]. Current international guidelines base their recommendations for the indication of hypolipidaemic or anti-hypertensive drug treatment in clinically asymptomatic patients ('primary prevention') on the estimation of global risk. An estimated global risk of >20% per 10 years in an asymptomatic patient is considered to be high. The affected patient is given advice to be treated as aggressively as a symptomatic patient with vascular disease. This implies lowering of LDL cholesterol below 100 mg/dl (2.6 mmol/l) and systolic blood pressure below 130 mm Hg. An estimated risk ranging between 10 and 20% in 10 years is considered as moderate, and treatment targets for LDL cholesterol and systolic blood pressure are <130 mg/dl (<3.4 mmol/l) and 140 mm Hg, respectively. An estimated risk <10% is considered as low. In this case, drug treatment recommendations are not offered to the majority of individuals [International Task Force for Prevention of Coronary Heart Disease. Pocket Guide to Prevention of Coronary heart disease. http://www.chd-taskforce.de/guide.htm; 5,6].

Using the PROCAM algorithm, 7.5% of German men aged 35 to 65 years have a risk estimate of >20%, 15% a risk estimate of 10–20% and 72.5% a risk estimate of <10%. Each group accounts for about one-third of all coronary events that will occur during 10 years of follow up. Using the PROCAM algorithm, the finding of an estimated global risk above 20% in a 35- to 65-year-old asymptomatic German man has a positive predictive value of 32%. The finding of an estimated global risk of <10% has a negative predictive value of 97%. The intermediate risk of 10–20% has positive and negative predictive values of 14 and 86%, respectively (http://www.chd-taskforce.de/guide.htm). The Framingham algorithm has an even lower positive predictive value and, hence, overestimates cardiovascular risk in asymptomatic German middle-aged men [7].

The predictive values summarized above give rise to a conceptual misunderstanding by many scientists, physicians and patients, who believe that the assessment of classical risk factors leads to an underestimation of coronary risk in many individuals. The opposite is the case. The detection of the relatively small percentage of individuals, who will develop atherosclerotic vascular disease despite estimated low global risk, would require cost-intensive screening of large populations with a low case-finding probability. The more relevant problem is the high false-positive rate in individuals with a high or intermediate estimated global risk.

The use of neural network statistics rather than conventional Cox-proportional hazard statistics can improve the diagnostic efficacy of global risk estimation. However, this strategy does not provide freely accessible algorithms and scores, but requires the communication with a central data manager for the calculation of an individual's risk [8]. Moreover, even this approach does not eliminate the problem of false-positive risk assignment, so that there is still considerable need for improving global risk assessment.

Requirements for novel risk factors

The interest in improving cardiovascular risk assessment, resulting from a better understanding of the pathogenesis of atherosclerosis and identification of new targets for anti-atherosclerotic drug therapy has always stimulated the search for novel risk factors. Thousands of cross-sectional case-control studies have identified hundreds of clinical, biochemical or genetic markers that showed statistically significant associations with coronary heart disease, stroke or peripheral vascular disease. Most of these associations were either not reproducible in other studies or not independent of classical risk factors. However, some of these

emerging risk factors turned out to be robust and independent. Currently there is an intense discussion whether they should be introduced into routine risk assessment. This especially concerns Lp(a), CRP, fibrinogen, homocysteine and microalbuminuria.

Before these and other emerging risk factors are widely introduced into clinical routine, they must fulfil pre-defined criteria [5,9,10]. (i) The methods for their measurement must be precise, accurate, and internationally standardized so that the results are reliable and independent from the manufacturer and the laboratory. (ii) The analyte should be biologically stable so that single measurements within an individual are representative and no special pre-analytical requirements are to be fulfilled. (iii) Consensus must have been obtained on diagnostic cut-offs so that clinical decisions can be drawn in daily practice. (iv) The novel risk factor must interact with the classical risk factors so that they improve the diagnostic efficacy of global risk estimation, preferably as discussed before, in the high- and intermediate-risk groups. In addition or alternatively, they should be of special importance in subgroups of patients, e.g. in women or patients with diabetes mellitus or kidney disease, or in association with specific vascular diseases, e.g. stroke or peripheral vascular disease. (v) The assessment of the risk factor should have therapeutic implications that in the ideal case are specific. (vi) The marker should exhibit a good cost-benefit relationship by fulfilling the criteria listed before and by being measured by easy-to-use and inexpensive tests.

How do these criteria apply to the emerging risk factors most intensively discussed?

Lipoprotein(a) [11]

An international Lp(a) standard has become available only recently. However, the use of this standard by different tests still give discrepant results so that Lp(a) data of different laboratories give discrepant results [12]. By convention the majority of laboratories agree on a cut-off of 30 mg/dl, above which cardiovascular risk is considered as increased. Because of its strong genetic determination, Lp(a) levels show little intra-individual variation. However, renal insufficiency and proteinuria cause increases in Lp(a) levels. Consequently, it is not the Lp(a) level but the size polymorphism of its protein constituent, apolipoprotein(a), which shows a significant association with coronary events in patients with renal disease [13]. In the asymptomatic male population, Lp(a) interacts with traditional risk factors so that elevated Lp(a) further increases the coronary risk of men with intermediate and high global risk but not in men at low risk [14]. Because of the high risk of venous thromboembolism in patients with renal insufficiency or nephrotic syndrome, it is also interesting to note that Lp(a) further increases the risk of stroke and venous thromboembolism in children and adolescents with genetic thrombophilic risk factors [15,16]. Lp(a) levels are little influenced by currently available drugs except sex steroids. In *post hoc* analyses of some intervention trials, individuals with high Lp(a) levels were found to derive an excessive benefit from statin or postmenopausal hormone replacement therapy. However, this finding has not been reproduced in the analyses of other large intervention trials [17,18].

C-reactive protein [19]

CRP levels can be measured with precise, accurate, standardized and relatively inexpensive tests. A CRP level above 1 mg/l is considered to indicate a moderate increase in risk and a CRP level above 3 mg/l is considered as an indicator of high risk [20]. However, CRP levels are strongly influenced by acute and chronic inflammation so that levels >10 mg/l must not be used for cardiovascular risk assessment [21]. In this case, repeated blood samples for analysis must be taken after recovery from the acute disease. As yet, only one published study performed in women has assessed the interaction of CRP with global risk estimates. In this study, elevated CRP levels further increased the cardiovascular risk of women being at low risk as well as at combined intermediate and high risk (i.e. >10% in 10 years as estimated with the Framingham risk score) [22]. In the data from the Augsburg cohort of the MONICA study, (W. V. König, unpublished data presented at the European Society of Cardiology Congress in Vienna, 2003) found that CRP improves the diagnostic efficacy in men with intermediate global risk but not in men with high global risk. Post hoc analyses of intervention trials indicate that men with elevated CRP have an overproportional benefit from aspirin and statin therapy [23,24]. CRP-directed statin intervention studies have been initiated.

Fibrinogen [24]

Fibrinogen measurements have not been internationally standardized. The analyte requires citrate plasma as a special specimen. Like CRP, fibrinogen is an acute phase reactant, which is not clinically useful for cardiovascular risk assessment in patients with acute disease. There is no international consensus on a diagnostic cut-off although in the majority of studies 3.5 g/l has been used. Fibrinogen was found to further increase the risk of men with a high estimated cardiovascular risk as estimated with the Framingham score [25]. Likewise in the PROCAM study, fibrinogen was found to further increase the risk of men with low and combined intermediate and high risk (G. Assmann, H. Schulte, A. von Eckardstein, unpublished data). Information on therapeutic interventions based on elevated fibrinogen is not available.

Homocysteine [26]

Homocysteine can be measured by precise, accurate and standardized assays. In healthy individuals, the analyte shows little intraindividual variation. However, it is strongly influenced by renal function and several drugs [26]. Although the analyte does not require special specimens, care has to be taken that serum or plasma is quickly separated from cells, since erythrocytes produce homocysteine so that prolonged full blood storage causes an increase in homocysteine levels [27]. Alternatively, fluoride can be added for the inhibition of erythrocyte metabolism. So far there is no consensus on cut-offs for homocysteine levels so that they vary from 10 to 16 μmol/l. Despite its moderate association with coronary risk, homocysteine was found to further increase the risk of high-risk individuals such as those with pre-existing coronary heart disease or those with a high estimated Framingham score risk [25]. Homocysteine is the only one of the novel risk factors discussed here which is connected with a specific therapeutic intervention, namely the application of folate either alone or in combination with vitamins B6 and B12 [26]. In one study, treatment of patients undergoing coronary angioplasty with this vitamin combination reduced restenosis rates after 6 and 12 months of follow up. In contrast, the number of fatal and non-fatal myocardial infarctions was not reduced [28,29]. Surprisingly, however, the rates of restenosis as well as clinical events were increased upon folate/vitamins B6 and B12 treatment in another study of similar design [9]. We therefore urgently need the outcomes of several ongoing large intervention trials assessing the clinical effects of homocysteine-lowering vitamins to judge the clinical relevance of this marker.

Microalbuminuria

Microalbuminuria is a well-accepted marker for micro and macrovascular damage in patients with diabetes mellitus or hypertension [30,31]. Therefore, and because of the proven benefit of treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists in patients with microalbuminuria, consensus guidelines recommend the measurement of albuminuria in hypertensive or diabetic patients [30,31]. More and more evidence is accumulating that microalbuminuria is an important cardiovascular risk factor even in the general population [32]. It interacts with classical risk factors. It has not yet been shown, however, whether and how it further increases the risk within estimated global risk categories [33]. Another major drawback for the wider use of microalbuminuria is the lack of agreement on the optimal specimen and the large intraindividual variation because of the great impact of fever, physical stress and menstrual bleeding on renal albumin excretion. The gold standard specimen, the 24 h urine, is neither practical nor well-accepted by patients. Albumin concentrations in spot urine show a good correlation with 24 h albumin excretion if taken at a defined time point (second morning urine). However, disagreement exists on whether the albumin over creatinine ratio or absolute albumin concentration should be determined. The former takes into consideration muscle mass and needs the definition of age and sex specific cut-offs; the latter is confounded by intraindividual variation in diuresis [34,35].

Conclusion

The classical risk factors have a high negative predictive value especially if combined in scores and algorithms the use of which is currently advocated in international consensus guidelines for primary prevention of cardiovascular disease. Because costs are high relative to the small chance of finding cases, novel risk factors should not be included in unselected population-wide screening programs. However, the global risk estimates have insufficient positive predictive value so that there is a clear need for improving risk estimation in individuals at high and intermediate risk. This appears to be 20–25% of the population. These individuals are the proper target for any novel risk factor (and non-invasive imaging method for the early detection of clinically relevant atherosclerosis). As yet, all emerging risk factors have to be investigated along these lines, before they are introduced into clinical practice. Among the novel risk factors currently under discussion, CRP has apparently been evaluated best.

Several authors advocate the use of novel risk factors in patients with existing coronary heart disease who lack any classical risk factors [9]. However, in this secondary prevention setting, a novel risk factor is of limited usefulness if it does not lead to specific treatment. For example, so far it is not justified to make decisions concerning the use of statins or aspirin in patients with manifest atherosclerosis dependent on CRP or Lp(a) levels. In this setting, parameters connected with specific treatment decisions have a great potential. However, randomized intervention studies are needed to prove the relevance of these risk factors and the benefit of the intervention based on their results.

Conflict of interest statement. None declared.

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