Recent developments in cardiovascular risk assessment: relevance to the nephrologist

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Chronic kidney disease (CKD) is a major global public health problem and is associated with increased cardiovascular and total mortality [1]. This applies even to patients with only modestly decreased estimated glomerular filtration rate (eGFR). The prevalence of moderate forms of CKD is increasing in the general population due to the epidemic of hypertension and obesity/Type 2 diabetes mellitus. Therefore, such patients should be identified early and appropriate treatment should be initiated to improve long-term prognosis in this high-risk group for cardiovascular complications.

Present risk assessment strategies: advantages and limitations

Based on current guidelines by the American Heart Association/American College of Cardiology [2] and the European Society of Cardiology [3] risk assessment in primary prevention should be done by using one of the available scores to estimate the total 10-year coronary heart disease (CHD) or cardiovascular disease (CVD) risk. Several scores like the Framingham risk score (FRS, 4), the European Society of Cardiology (ESC) SCORE [3] or the PROCAM score [5] and various others are available. Although they are easy to apply, all of them are based on a limited number of risk factors, which are not identical, and poor calibration, e.g. has been found to be an issue limiting the application of the FRS outside the USA. Thus, these scores may miss important pathological conditions in certain patients, but in general, the use of any score is better than not to use such a score at all. Yet it is important to mention that in CKD patients, the FRS in particular is less accurate than in non-CKD patients [6], but data for other scores in CKD patients do not exist. Of note, in a recent report from a large population-based sample of subjects without CVD or diabetes, the addition of the urine albumin/creatinine ratio (UACR) as a marker of subclinical organ damage to the ESC SCORE was associated with improved risk prediction [7]. Major cardiovascular risk factors like age, gender, elevated total cholesterol, decreased high-density lipoprotein (HDL) cholesterol, hypertension, smoking and in some scores also diabetes mellitus, and family history of CHD, represent the crucial elements. Age is the strongest predictor of absolute risk in all these scores and thus they work well in higher age groups but are of limited value in middle-aged patients who may have already acquired a cluster of risk factors but typically are categorized as low risk. Thus, recent research in this area has focused on the development of the so-called 'life-time risk'.

Traditionally, patients are characterized to be either at high cardiovascular risk if, e.g. the FRS over 10 years is >20% or at low risk if the risk is <10%. This leaves a significant group at intermediate risk for which no clear guidelines exist. Low-risk patients would be re-invited in 3–5-years intervals and high-risk patients would need advice regarding life-style changes and potentially the prescription of a statin and also antihypertensive medication. Those at intermediate risk would be candidates for additional testing using new risk markers, but this still represents a controversial area and there are further issues that question current traditional and emerging strategies. Data from the large National Health and Nutrition Examination Survey study in the USA [8] have shown that in the general population, ~80% are at low risk, 15% at intermediate and only 5% at high risk. However, about two-thirds of CHD events come from those at low risk and only one-third would have been characterized as intermediate or high risk. Thus, current scoring systems are unable to identify a large proportion of the patients who will eventually suffer a cardiovascular event.

Improving risk assessment strategies: possible approaches

Attempts have been made to refine risk assessment strategies by introducing various emerging risk markers, either blood biomarkers, markers of subclinical atherosclerosis or genetic markers. Concerning blood biomarkers, a large panel of molecules has been tested in a variety of well-designed large prospective epidemiological studies separately or in combination. At present, results from these studies have limited our enthusiasm because even the
combination of 30 different markers in addition to global risk assessment, as recently published by Blankenberg et al. [9], has contributed only modestly to improved identification of future CHD cases [10, 11]. This also applies to several imaging methods which have been studied in a variety of prospective cohorts, in particular the measurement of carotid intima-media thickness (IMT) by high-resolution transcutaneous ultrasound [12] and the assessment of coronary artery calcium (CAC) by computed tomography [13], although both methods have recently received a Class II a, level of evidence B recommendation by AHA/ACC [14] in those at intermediate risk. Based on high-throughput genome-wide association studies, a large number of potential genetic markers (single-nucleotide polymorphism, SNP) have been identified which certainly have improved our pathophysiological understanding of atherosclerosis. But none of the identified SNPs, either alone or in combination, has been able to significantly improve risk prediction [15]. Thus, at present, a family history of premature CHD or CVD still represents the best genetic information. Particular subgroups at increased risk, which would need an improved strategy are those at intermediate risk and patients with diabetes and/or impaired renal function.

Which markers may be promising in the future for clinical practice?

From the large number of emerging biomarkers at present, only a small set of molecules may be potentially suitable for translation into clinical practice. Candidates include additional lipid markers like HDL cholesterol and lipoprotein (Lp) (a), C-reactive protein (CRP), a classical sensitive marker of systemic inflammation, natriuretic peptides as markers of haemodynamic stress, which are particularly relevant to the diabetic and hypertensive population and more sensitive markers of renal function like cystatin C or the UACR as a surrogate of CVD. Finally, the most recent data reporting on high-sensitivity troponin assays have shown that even small elevations of this marker of myocyte necrosis are associated with increased adverse outcome.

Extended lipid profile

In addition to low-density lipoprotein (LDL) cholesterol which has to be measured and treated to target in all patients if elevated, there is compelling epidemiologic evidence that HDL cholesterol levels are inversely associated with cardiovascular risk. However, at present, treatment options are limited to nicotinic acid or fibrates, but extensive experimental and clinical research focuses on an improved understanding of the effects of HDL cholesterol besides its involvement in reverse cholesterol transport and evaluates new therapeutic strategies (cholesterolytransfer protein inhibition). Furthermore, Lp (a) a strongly genetically determined molecule consisting of the glycoprotein apolipoprotein (a) [Apo (a)] covalently linked to LDL cholesterol has been shown to add to cardiovascular risk in addition to elevated LDL cholesterol. A recent consensus paper issued by the European Atherosclerosis Society has suggested its measurement in several specified patient groups [16].

Markers of inflammation

A most recent meta-analysis of >100 000 subjects has shown that the predictive value of CRP is at least as strong as systolic blood pressure or non-HDL cholesterol for CHD and ischaemic stroke in multivariate models [17]. In addition, the recent JUPITER study has convincingly demonstrated that the presence of elevated CRP is able to identify a high-risk population that would benefit from statin treatment, which has not been considered so far based on current guidelines [18]. After only 1.9 years in trial, there was a significant 44% relative reduction for the primary end point in this study. Additional analyses have shown that statin treatment in this patient group defined only by age (women >60 years, men >50 years, LDL cholesterol <130 mg/dL and CRP >2 mg/L) was beneficial for stroke and in general showed fairly low numbers needed to treat for various end points [19]. Rosuvastatin showed a similar large benefit in those at intermediate risk as in the total population [20] and was also beneficial in patients with modest CKD [21]. The SHARP study has assessed the effects of lipid-lowering therapy with simvastatin + ezitimibe versus matching placebo in ~9500 patients with advanced CKD [22]. Ezitimibe + simvastatin significantly reduced major atherosclerotic events (relative risk reduction 17%) irrespective of the severity of their disease and there were no safety concerns.

Markers of haemodynamic stress

In addition to CRP, there is a large body of literature on natriuretic peptides (BNP or NT-proBNP) and prediction of risk. Increased levels of either NT-proBNP or BNP predict cardiovascular outcome in the general population, in patients with acute coronary syndrome, in stable CHD patients, in patients with congestive heart failure and other high-risk groups. Therefore, measurement of natriuretic peptides may add important information to the currently measured risk factors. However, the fact that NT-proBNP and BNP levels are increased in those with CKD represents a clinically important issue that needs to be considered when interpreting this marker [23].

More sensitive markers of CKD

EGFR based on various formulas using creatinine are measured routinely in outpatients as well as in hospitalized patients. More recently, formulas have been developed based on cystatin C, a molecule that has been shown to be more sensitive than creatinine in detecting even small impairments of renal function [24]. We have recently published a study in 1200 patients with stable CHD after an acute event and followed them for 8 years. Based on creatinine or cystatin C, we calculated six different formulas and compared these head to head for the prediction of recurrent
Markers of subclinical atherosclerosis

Finally, in cases where there is still uncertainty, either CAC scoring which does not need the application of contrast medium or the measurement of IMT might represent additional diagnostic tools in patients at intermediate risk [14].

Conclusions

Our present approach regarding risk stratification for major cardiovascular events is imperfect, although there has been considerable progress through the introduction of global risk assessment. Since these scores have several limitations, there is a need for improved risk stratification by identifying new biomarkers that may complement the information based on traditional risk factors. In particular, the OMICS technology may yield new promising candidates. However, at present, the following strategy might be recommended.

Despite the above-mentioned limitations, global risk assessment should be performed in all patients at cardiovascular risk using one of the available scores and for patients with even modest CKD, full cardiovascular evaluation is needed due to the increased risk. If patients are at high risk, consider life-style changes and treatment with a statin as well as optimizing blood pressure using a compound interfering with the renin–angiotensin system as first line treatment. If a patient is diabetic or hypertensive, also measure renal function, preferably using cystatin C and/or the UACR. In selected cases, imaging the IMT and/or measurement of CAC might be justified.

Conflict of interest statement. None declared.

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