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Is there a need for other cardiovascular risk factors besides the established risk factors?

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Cardiovascular disease (CVD) represents the leading cause of mortality in high-income countries.[1] The cornerstone of both primary and secondary prevention of CVD (i.e. prevention of cardiovascular events in patients without and with established CVD, respectively) is the multifactorial management of all cardiovascular risk factors. In turn, the aggressiveness of management of cardiovascular risk factors is based on the cardiovascular risk. Patients with established CVD are at very high cardiovascular risk. Patients with chronic kidney disease (CKD, i.e. with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2) and/or type 2 diabetes mellitus (T2DM) are also considered to have cardiovascular risk comparable to those with established CVD and should therefore be treated as aggressively as those with established CVD.[2,3] In all other patients, estimation of cardiovascular risk is essential for determining the targets of lipid-lowering, antihypertensive and antidiabetic treatment and to decide whether antiplatelet treatment is required.

Regarding lipid-lowering treatment, European guidelines recommend the use of SCORE to estimate cardiovascular risk in primary prevention. SCORE provides the 10-year risk for a fatal cardiovascular event based on age, gender, systolic blood pressure (SBP), total cholesterol and on whether the subject is a current smoker or not.[4] On the other hand, US guidelines recommend the use of the Pooled Cohort Risk Assessment Equations, which estimates the 10-year risk for a cardiovascular event (nonfatal and fatal myocardial infarction (MI) and nonfatal and fatal stroke) based on age, gender, race, SBP, total cholesterol, high-density lipoprotein cholesterol, presence of T2DM and on whether the subject is current smoker or not and on whether the patient is receiving antihypertensive treatment or not.[5] However, it has been reported that the Pooled Cohort Risk Assessment Equations overestimate cardiovascular risk.[6] Moreover, these Equations were derived from the US population, which is different from the European populations in the prevalence of many cardiovascular risk factors, including obesity, hypertension and smoking.[6] Therefore, it is

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unclear whether the Pooled Cohort Risk Assessment Equations can be applied in non-US populations. On the other hand, it should also be mentioned that the SCORE also appears to overestimate cardiovascular risk in contemporary European populations.[6]

Regarding antihypertensive treatment, current European guidelines recommend that blood pressure target should be <140/90 mmHg in all hypertensive patients, except in those with T2DM, in whom a target of <140/85 mmHg is proposed.[7] However, the recently published Systolic Blood Pressure Intervention Trial (SPRINT) showed that targeting a SBP <120 mmHg compared with a SBP <140 mmHg reduces cardiovascular and all-cause mortality by 43 and 27%, respectively.[8] The SPRINT trial included patients with clinical or subclinical CVD other than stroke, CKD (eGFR 20-60 ml/min/1.73 m^2), an age of 75 years or older or a 10-year risk of CVD≥ 15% on the basis of the Framingham risk score.[8] Therefore, the SPRINT also suggested that hypertension should be managed more aggressively in high-risk patients.[8] However, this trial used the Framingham risk score to estimate cardiovascular risk, which is also based on a US population and does not appear to predict cardiovascular risk accurately in European populations.[9] Therefore, it is unclear which patients younger than 75 years without CVD or CKD should be managed more aggressively outside US. It is also unclear whether the findings of the SPRINT trial apply to patients with low cardiovascular risk.

Regarding antiplatelet treatment, European guidelines recommend against using antiplatelet agents in patients without established CVD.[10] However, according to recent US guidelines, the choice whether to administer antiplatelet agents in primary prevention should depend on the cardiovascular risk.[11] Subjects aged 50-59 years with estimated 10-year risk for CVD≥ 10%, without increased risk for bleeding and with a life expectancy ≥ 10 years should receive low-dose aspirin.[11] In subjects 60-69 years and 10-year risk for CVD ≥ 10%, the decision to administer aspirin should be individualized.[11] On the other hand, in subjects older than 70 years or younger than 50 years, there is insufficient evidence to recommend aspirin treatment.[11] However, the estimation of 10-year cardiovascular risk is also based on the Pooled Cohort Risk Assessment Equations, with all the limitations detailed above. It should be mentioned that these US recommendations are also partly due to the reduction in the incidence of and mortality from colorectal cancer in patients receiving long-term aspirin treatment.[12]

Finally, regarding antidiabetic treatment, current guidelines mention that patients with established CVD should have less stringent HbA_{1c} targets.[13]

Despite the limitations of current algorithms for estimating cardiovascular risk, there is a clear rationale for using them in clinical practice. These algorithms incorporate the most important cardiovascular risk factors, including age, gender, blood pressure, lipid profile, smoking and/or T2DM, which are responsible for the vast majority of cardiovascular events. Indeed, in the INTERHEART study (n= 15,152 patients with MI and 14,820 controls from 52 countries), blood pressure, lipid profile, smoking and T2DM accounted for more than 90% of cases of MI in both genders and at all ages.[14] In the INTERSTROKE study (n= 10,388 patients with ischemic stroke and 13,472 controls from 32 countries), blood pressure, lipid profile and smoking also accounted for more than 87% of cases of ischemic stroke in both genders and at all ages.[15] In a more recent meta-analysis of 18 cohort studies (n= 257,384), subjects 55 years-old with optimal blood pressure (<120/80 mmHg) and lipid levels (total cholesterol <180 mg/dl) who did not smoke and did not have T2DM, had extremely low lifetime risk for cardiovascular events.[16]

In the last decades, several novel cardiovascular risk factors have been identified. Many of these risk factors predict cardiovascular events independently of the established risk factors (i.e. age, gender, blood pressure, lipid profile and smoking) that are included in the SCORE and Pooled Cohort Risk Assessment Equations. However, most of these novel risk factors do not appear to be able to affect the management of patients without established CVD. Indeed, the addition of these risk factors to the cardiovascular risk estimation equations does not appear to increase the ability of these equations to discriminate risk and does not reclassify patients to a different risk category (low, intermediate or high-risk). This is particularly relevant for patients who are at intermediate cardiovascular

risk and for which it is difficult to decide on the targets of antihypertensive and lipid-lowering treatment and on whether antiplatelet agents are recommended. None of these novel risk factors appear to be able to reclassify a clinically meaningful proportion of intermediate risk patients to the higher risk category.

Elevated high-sensitivity C-reactive protein (hsCRP) levels are a marker of subclinical inflammation and are independently associated with increased cardiovascular risk.[17] However, in a recent analysis of 52 prospective studies (n= 246,699 subjects without a history of CVD), the addition of hs-CRP levels to the traditional cardiovascular risk factors improved the C-statistic, a marker of risk discrimination, by only 0.004 and resulted in a net reclassification improvement of only 1.5%.[18] The same analysis showed that measuring hsCRP levels in intermediate risk patients would help prevent only one CVD event over a period of 10 years for every 440 patients screened.[18]

Several other circulating biomarkers have been associated with increased cardiovascular risk, e.g. brain natriuretic peptide and lipoprotein(a).[19,20] However, evaluating several biomarkers in the same subject also does not appear to improve risk discrimination. In the Framingham Heart Study (n= 3,209), the addition of 10 biomarkers, including hsCRP, brain natriuretic peptide, and fibrinogen levels and the urinary albumin/creatinine ratio did not affect risk classification over that provided from traditional cardiovascular risk factors.[21] In the Cardiovascular Health study (n= 5,808), the evaluation of 6 biomarkers, including hsCRP, interleukin 6 and lipoprotein(a), also did not improve risk stratification.[22]

Increased carotid intima-media thickness (cIMT) is a marker of subclinical atherosclerosis and is independently associated with increased cardiovascular risk.[23] However, in a recent meta-analysis of 14 population-based cohorts (n= 45,828), the addition of cIMT to the Framingham risk score did not change the C-statistic.[24] Moreover, in intermediate risk patients, measuring cIMT resulted in a net reclassification improvement of only 3.8%.[24]

Coronary artery calcification (CAC) is another marker of subclinical atherosclerosis that independently predicts cardiovascular risk.[25] In a recent systematic review of 9 studies (total n= 31,397), it was reported that adding CAC to a cardiovascular risk prediction equation improved the C-statistic by 0.04 to 0.09.[26] In addition, in 4 studies that evaluated the net reclassification improvement conferred by measuring CAC (total n= 13,969), this improvement ranged between 14 and 24%.[26] Therefore, CAC appears to be more promising than other cardiovascular risk factors in improving risk discrimination. However, measurement of CAC incurs the risk of radiation exposure and is expensive.[26] Moreover, CAC represents a later stage of atherosclerosis and is frequently absent in young subjects, limiting its value in this age group.[27]

In view of these data, recent guidelines issued by the American College of Cardiology and the American Heart Association state that if treatment decision is uncertain after estimating cardiovascular risk with the Pooled Cohort Risk Assessment Equations, measurement of hsCRP or CAC score may be considered (Grade E (expert opinion), Class of recommendation IIb (usefulness less well established), level of evidence B (limited populations evaluated).[27] In contrast, routine measurement of cIMT is not recommended in patients without established CVD (level of evidence B (limited populations evaluated).[27]

In conclusion, estimation of cardiovascular risk is essential for deciding whether to administer antihypertensive, lipid-lowering and antiplatelet treatment and to define treatment targets. The traditional cardiovascular risk factors, i.e. age, gender, blood pressure, lipid profile, smoking and T2DM are present in almost all patients who suffer a cardiovascular event. Therefore, risk prediction equations that incorporate these risk factors and are derived from the population in question should be used to estimate cardiovascular risk. On the other hand, other cardiovascular risk factors and markers of subclinical atherosclerosis do not appear to be useful in risk discrimination despite their independent association with cardiovascular events.

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