A discussion of the most recent European and American guidelines to assess cardiovascular risk

Cardiovascular risk factors: a critical issue of preventive cardiology

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Introduction

Acute cardiovascular diseases (CVD) are the leading cause of mortality worldwide and this still occurs despite the development of quite effective therapeutic strategies. Recent epidemiological data have increased awareness that prevention-based programmes might dramatically decrease the burden of CVD [1]. Relying on these assumptions, the most recent European Society of Cardiology (ESC) guidelines defined CVD prevention as “a co-ordinated set of actions, at public and individual level, aimed to eradicating, eliminating, or minimising the impact of CVD and their related disability” [2]. However, this strategy requires a great effort (involving individuals, politicians and healthcare systems), but to date only few resources have been allocated to this challenge [3], especially in developing countries, where the incidence of CVD is increasing [4].

The use of score prediction models has become the cornerstone for CVD risk assessment and represents the first step for patient risk stratification and decision-making about preventive management and treatment [2, 5]. Some intervention on risk factors has been largely recognised to decrease the CV event rate, but there is an ongoing need to improve these algorithms [6]. The main challenge remains to balance the usefulness of new powerful predictors with their financial and social costs in clinical practice. Focusing on this topic, this review updates current CVD risk stratification strategies and discusses some novel and promising predictors potentially useful in combination with the available algorithms.

Summary

In the last decades, relevant financial investments in cardiovascular research have been made to reduce acute ischaemic cardiovascular diseases (CVD), which still represent the first cause of mortality worldwide. The assessment of a “global” cardiovascular (CV) risk combining different risk factors has been suggested by international guidelines that regularly update Score Charts. However, all available algorithms lose predictive power in clinical translation mainly because patient-tailored information is included in models mainly based on high-risk populations. Therefore, the assessment of CV risk in the general population using available scores might present some intrinsic limitations. Furthermore, the knowledge of pathophysiological processes underlying atherogenesis and atherosclerotic plaque vulnerability is constantly evolving. Thus, all available predictive models based on traditional risk factors (i.e., age, smoking, gender, blood pressure and lipid profile) might not appropriately consider the pathophysiological relevance of soluble pro-atherosclerotic biomarkers, such as pro-atherosclerotic mediators. These limitations might confer to the physician a quite arbitrary role in the decision-making process to prevent acute cardiovascular diseases in patients at low/moderate CV risk. This narrative review aims at reporting and discussing the most recent European and American guidelines to assess cardiovascular risk. An update on novel and promising CV risk factors was also performed.

Key words: cardiovascular diseases; risk factors; coronary arteries

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>ARIC</td>
<td>Atherosclerosis risk in communities</td>
</tr>
<tr>
<td>ASCVD</td>
<td>Atherosclerotic cardiovascular disease</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>CAC</td>
<td>Coronary artery calcium</td>
</tr>
<tr>
<td>CARDIA</td>
<td>Coronary Artery Risk Development in Young Adults</td>
</tr>
<tr>
<td>CHS</td>
<td>Cardiovascular Health Study</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>EUROASPIRE</td>
<td>EUROpean Action on Secondary and primary Prevention by Intervention to Reduce Events</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendation Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>JUPITER</td>
<td>Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin</td>
</tr>
<tr>
<td>LDL-c</td>
<td>Low density lipoprotein-cholesterol</td>
</tr>
<tr>
<td>MESA</td>
<td>Multi-Ethnic Study of Atherosclerosis</td>
</tr>
<tr>
<td>SCORE</td>
<td>Systematic Coronary Risk Evaluation</td>
</tr>
</tbody>
</table>

An article from the series “Atherosclerosis and inflammation”
Current trends about the traditional predictor of cardiovascular risk

As suggested by the leading guidelines, the first step in CVD prevention is the estimation of the “individual” total risk [2, 5]. Accordingly, several score systems have been developed taking into account that the greatest benefit is expected from the higher absolute risk. ESC consolidated the use of Systematic Coronary Risk Evaluation (SCORE) system, calibrated on epidemiological data from different countries. Such a model is addressed to estimate the 10-year risk of fatal atherosclerotic events, thus avoiding confounders from definition, diagnosis and standardisation of non-fatal events. In addition, only two levels of recommendation (“strong” and “weak”) were provided accordingly to the Grading of Recommendation Assessment, Development and Evaluation (GRADE) [2]. Conversely, preventive cardiology in North America relies on the guidelines of American Heart Association (AHA) recently updated by introducing a new pooled cohort risk equation model. Traditional Framingham Original and Offspring Study cohorts have been combined with other large and more representative cohorts (including Atherosclerosis Risk in Communities [ARIC], Cardiovascular Health Study and Coronary Artery Risk Development in Young Adults [CARDIA] study and Cardiovascular Health Study [CHS]) in order to improve the 10-year risk estimation for atherosclerotic CVD (ASCVD) in African-American and White men and women 40 to 79 years of age [5]. In addition, these new guidelines lowered the high-risk threshold to 7.5% risk for 10-year ASCVD. As a consequence, AHA guidelines extended the “treatment recommended group” in contrast to ESC guidelines that maintain a larger “treatment considered” group, emphasising the lifelong development of CVD. Table 1 summarises some discrepancies between ESC and AHA guidelines and the following paragraphs will update the current knowledge about traditional predictors of CVD, thus providing insights to improve current risk prediction algorithms.

Table 1: Epidemiological models and strategies for CVD risk estimation in ESC and AHA/ACC guidelines.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Risk assessment tool</td>
<td>SCORE system (pooled dataset of 69 cohort studies from 12 European countries) [7]</td>
<td>Pooled cohort equations (including Framingham Original and Offspring data, ARIC, CARDIA and CHS cohorts) [5]</td>
</tr>
<tr>
<td>Population (sample size)</td>
<td>General population and some occupational cohorts (117,098 men and 88,080 women, aged 40 to 65 years)</td>
<td>Large community-based epidemiologic cohort (9,098 White men, 11,240 White women, 1,647 African-American men, 2,641 African-American women)</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Age, Gender, Total cholesterol, Low HDL, Smoking status, BP, Diabetes</td>
<td>Age, Gender, Total cholesterol, Smoking status, BP</td>
</tr>
<tr>
<td>Outcomes</td>
<td>10-year risk of ASCVD*</td>
<td>10-year risk of CVD mortality</td>
</tr>
<tr>
<td>Risk categories</td>
<td>&lt;7.5%: low risk, 7.5%–10%: intermediate risk, &gt;10%: high risk</td>
<td>&lt;1%: low risk, 1%–5%: moderate risk, 5%–10%: high risk, &gt;10%: very high risk</td>
</tr>
<tr>
<td>Additional tools</td>
<td>Family history, hs-CRP, CAC score and ABI may be considered if treatment decision remains uncertain.</td>
<td>Strong GRADE recommendation for including cIMT (class IIa, level B), ABI (class IIa, level B) and cardiorespiratory fitness (class IIb, level B), but also CKD (class I, level C)</td>
</tr>
</tbody>
</table>

ABI = Ankle Brachial Index; AHA/ACC = American Heart Association / American College of Cardiology; ARIC = Atherosclerosis risk in communities; ASCVD = Atherosclerotic Cardiovascular Disease; BP = Blood pressure; CAC = Coronary artery calcium; CARDIA = Cardiovascular Health Study and Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; cIMT = carotid Intima Media Thickness; CKD = Chronic kidney disease; CVD = Cardiovascular disease; ESC = European Society of Cardiology; GRADE = Grading of Recommendation Assessment, Development and Evaluation; HDL = High density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; SCORE = Systematic Coronary Risk Evaluation system. *ASCVD: defined as coronary death or non-fatal myocardial infarction, or fatal or non-fatal stroke.
**Age**

Age has been intuitively included in CVD score systems as an indicator of the progressive exposure to CVD risk factors. Furthermore, calculation of the risk age corresponding to each combination of CVD risk factor has been recently introduced as a new concept, termed as “CVD risk age” [8]. In other words, a young person with a low absolute risk score may have significantly increased risk compared to others of the same age but without any risk factor. ESC guidelines applied this concept of CVD risk age in specific SCORE charts [2], also expecting to be useful for CVD prevention in young people. Considering the increasing evidence about the progressive lifetime development of CVD (process starting at very young age, virtually also during pregnancy [9]), it has become crucial to promote healthy lifestyles as well as to recognise CVD-related diseases very early. Both cross-sectional [10–12] and short-term prospective studies [13] focused on this topic and emphasised the clustered incidence of CVD risk factors in young people. However, the only long-term longitudinal cohort available in this field is the CARDIA study. Table 2 reports the most recent studies from this cohort of 5,115 healthy people baseline aged 18 to 30 years, in which the long-term effects of CVD risk factors were investigated at different follow-up times up to 25 years [14]. Overall, these findings support the need to treat very early traditional modifiable risk factors, especially overweight [5, 18], lipid profile [19], inflammatory markers [16, 21] and unhealthy lifestyles [22, 23]. On the other hand, new AHA guidelines on the elderly population have raised many concerns. Although there are no solid data on primary prevention in patients over age 75, the task force suggested that pooled equation model may drive decisions about statin therapy up to 79 years. Furthermore, age emerged as a major determinant of starting statin treatment [27]. Also considering the potential risk of adverse drug reactions in the geriatric population, as well as the lack of indications about statin therapy discontinuation in long-term-

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients*</th>
<th>Risk factors (follow-up)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reis, et al. [15]</td>
<td>2013</td>
<td>5,115</td>
<td>Waist circumference (25 years)</td>
<td>Abdominal obesity was associated with diabetes development (adjusted HR 1.04 [95% CI 1.02–1.07]; p &lt; 0.05).</td>
</tr>
<tr>
<td>Catov, et al. [16]</td>
<td>2013</td>
<td>916 women</td>
<td>Biomarkers, cIMT and BP (20 years)</td>
<td>Preterm birth had higher BP before pregnancy (p &lt; 0.03) and more rapid increase of BP (p &lt; 0.01).</td>
</tr>
<tr>
<td>Bansal, et al. [17]</td>
<td>2013</td>
<td>3,070</td>
<td>eGFRcys and CAC (20 years)</td>
<td>Decrease of eGFRcys was inversely associated with higher CAC (RR 33% to 51%; p = 0.01).</td>
</tr>
<tr>
<td>Reis, et al. [18]</td>
<td>2013</td>
<td>3,275</td>
<td>BMI and waist circumference (25 years)</td>
<td>Both overall and abdominal obesity were associated with CAC occurrence as well as increased CAC progression (p &lt; 0.05 for all).</td>
</tr>
<tr>
<td>Raynor, et al. [19]</td>
<td>2013</td>
<td>2,435</td>
<td>Total Ch, LDL-c, HDL-c and TAG (20 years)</td>
<td>At interquartile comparison all lipids both at recruitment and after follow-up were significantly associated with CAC and cIMT (p &lt; 0.05 for all).</td>
</tr>
<tr>
<td>Gidding, et al. [20]</td>
<td>2013</td>
<td>2,426</td>
<td>Echocardiography (20 years)</td>
<td>LVM and LV wall thickness increase was dependent of different risk factors including BMI and mean BP (p &lt; 0.05 for both).</td>
</tr>
<tr>
<td>Majka, et al. [21]</td>
<td>2013</td>
<td>2,203</td>
<td>Anti-β2-GPI and aCL Ab (8 and 13 years)</td>
<td>At adjusted analysis both aPL Ab were associated with CAC (p &lt; 0.05 for all).</td>
</tr>
<tr>
<td>Shikany, et al. [22]</td>
<td>2013</td>
<td>2,832</td>
<td>Scored diet history</td>
<td>A good diet-quality score was directly associated with CRF (p &lt; 0.05).</td>
</tr>
<tr>
<td>Gibbs, et al. [23]</td>
<td>2014</td>
<td>2,854</td>
<td>Cross-sectional analysis of sedentary lifestyle</td>
<td>Sedentary lifestyle was associated with higher LVM in white people (p &lt; 0.001).</td>
</tr>
<tr>
<td>Armstrong, et al. [24]</td>
<td>2013</td>
<td>2,903</td>
<td>Echocardiography (20 years)</td>
<td>Increases of BP and BMI were independently related to LA enlargement (p = 0.011 and &lt;0.001, respectively).</td>
</tr>
<tr>
<td>Kishi, et al. [25]</td>
<td>2014</td>
<td>2,339</td>
<td>LVM and LVEF (20 years)</td>
<td>High LVM at baseline predicted a reduced LVEF (&lt;50%) at the end of follow-up (OR 1.59 [95% CI 1.30–1.94]; p&lt; 0.001).</td>
</tr>
<tr>
<td>Armstrong, et al. [26]</td>
<td>2014</td>
<td>3,980</td>
<td>FRS and LVM (20 years)</td>
<td>CV events were significantly predicted by LVM at baseline (adjusted HR 1.55 [95% CI 1.07–2.22]; p = 0.02) with AUC of 0.87.</td>
</tr>
</tbody>
</table>

aCL Ab = anti-CarDioLipin antibodies; anti-β2-GPI Ab = anti-β2-GlycProtein I antibodies; aPL Ab = anti-PhosphoLipid antibodies; AUC = Area under the curve; BMI = Body Mass Index; BP = Blood pressure; CAC = Coronary artery calcium; Ch = Cholesterol; CI = Confidence interval; cIMT = carotid Intima Media Thickness; CRF = CardioRespiratory Fitness; eGFRcys = Cystatin C-derived estimated glomerular filtration rate; FRS = Framingham Risk Score; HDL-c = High density lipoprotein-cholesterol; HR = Hazard ratio; LA = Left atrium; LDL-c = Low-density lipoprotein-cholesterol; LV = Left ventricle; LVEF = Left ventricular ejection fraction; LVM = Left ventricular mass; MRF = Modifiable cardiovascular risk factors; OR = Odds ratio; RR = Relative risk; TAG = Triglyceride. * All studies included men and women of both Caucasian and African-American race.
treated patients, these recommendations might suggest to better investigate lipid-lowering drugs in elderly that are commonly excluded from major clinical trials [28]. To date, only a sub-analysis study from the Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study showed that rosuvastatin treatment was able to reduce the CV risk in primary prevention in elderly patients [29].

Smoking
Programmes targeting early smoking cessation particularly impacted the benefits of CVD prevention, as recently extrapolated in a cohort of 216,917 adults aged ≥25 years and enrolled in the United States National Health Interview Survey between 1997 and 2004 [30]. In addition to further confirm the increased mortality in persistent smokers [31, 32], this study proved that the benefit of smoking cessation was greater when it was done earlier (cessation at 25–34, 35–44, or 45–54 years of age increased life expectancy of 10, 9, and 6 years, respectively).

Gender
Gender differences in the natural history of CVD are justified by specific pathophysiological mechanisms and hormonal influences. However, higher incidence of certain pathological conditions (e.g., autoimmune diseases) was recently shown to increase CVD risk in women [33]. The awareness of gender differences in CVD has progressively increased in the last decades and the development of specific guidelines since 1999 had promoted a significant decrease of CVD-related mortality in women over this time. However, guidelines are biased by a widespread under-representation of women in longitudinal studies and clinical trials [34], so that substantial work still needs to be done to close this gender gap [35]. Accordingly, also for current guidelines the validation of woman-specific charts for risk stratification is still a matter of debate, especially about the new pooled cohort equations model suggested by AHA. Furthermore, although the assessment of gender-specific diseases (i.e., systemic autoimmune collagen-vascular disease, pre-eclampsia, gestational diabetes, pregnancy-induced hypertension and depression) is now recommended by AHA [36], it would be uncomfortable to add such diseases in the algorithm of CVD risk stratification [37]. Ultimately, these limitations emphasise the arbitrary role of physicians in making a patient-tailored CVD risk stratification.

Blood pressure
Monitoring of blood pressure (BP) and treatment of hypertension are well-recognised cornerstones in both primary and secondary CVD prevention. Several studies investigated pre-hypertension as an increasing prevalent condition in the general population [38]. The impact of pre-hypertension on CVD risk has also been confirmed by meta-analyses [39–45] and a large longitudinal study [46]. Therefore, since the use of the Framingham hypertension risk prediction model performed by Parikh and co-workers [47] has been recently validated in the CARDIA study [48], the upcoming challenge is to promote screening programmes for pre-hypertension in children and young adults. Currently, the prevalence of pre-hypertension in this setting has been assessed in small observational studies [49–53], but several clinical trials are ongoing [54–56].

Lipid profile
Statin treatment is recommended in addition to lifestyle intervention to reduce low-density lipoprotein-cholesterol (LDL-c) levels [57, 58]. The efficacy of statin treatment has also recently been confirmed by a meta-analysis including 22 large clinical trials [59]. In this study each 1 mmol/l reduction in LDL-c was associated with a reduced CVD event rate of about 11 per 1,000 over 5 years. Consistent with this evidence, AHA guidelines have recently reduced the threshold to start statin therapy at a 10-year risk of ASCVD ≥7.5% [5]. Accordingly, this AHA statement resulted in a larger “treatment recommended” portion of patients, in contrast with the prevalent “treatment considered” group supported by the ESC guidelines. Since more than one billion people worldwide would be included in the treatment group, as recently estimated by Ioannidis [60], the great impact of this new approach raised many concerns involving the validation of pooled cohort equations methods [61, 62], the conflict interest of panellists [63] and the socio-economic burden. In addition, new AHA guidelines still lack therapeutic targets for cholesterol lowering, in contrast with ESC recommendations [2] (Table 3). These apparent discrepancies may worry physicians in prescribing a lifelong treatment, in addition to impairing patient compliance. Although ongoing trials may provide further insights [65], these new AHA guidelines should be considered as an intermediate step, expecting a feedback from the clinical translation [66].

Overweight and physical inactivity
ESC and AHA guidelines evaluated the CV risk related to obesity and overweight. Obesity (defined as body mass index (BMI) ≥30), and more generally overweight (25 ≤BMI ≤29.9), have been indicated as conditions associated with an increased CV risk [67–69]. These pathologies represent leading public health problems, also
considering their dramatic epidemiological increase during the last decades [70, 71]. ESC guidelines recommended the weight reduction in overweight and obese patients, since it is associated with favourable effects on BP and dyslipidaemia (class of recommendation 1, level of evidence A: strong GRADE recommendation) [2]. Similarly, AHA guidelines supported the meaningful health benefits of weight loss including an improved metabolic profile as well as a reduced need for medications (class of recommendation 1, level of evidence A) [72]. Recent discoveries showing a paradoxical cardiovascular protection in overweight elderly [73, 74] and morbidly obese patients might imply the need to review both ESC and AHA guidelines. In addition, the emerging role of visceral adiposity [75] increased the debate on the use of BMI instead of other anthropometric measures (including simple waist circumference, waist/hip ratio and waist-to-height ratio) to assess obesity [67, 76]. Although there are no data supporting the use of these alternative measures in clinical practice (class of recommendation IIa, level of evidence B according to AHA guidelines), this field of research is constantly growing and currently focuses on the assessment of some regional adiposity, especially the epicardial fat [77]. Unfortunately, this approach still requires expensive and time-consuming techniques (such as computed tomography, ultrasound and magnetic resonance), thus limiting translation into clinical practice [78]. On the other hand, ESC and AHA guidelines differ about therapeutic approaches to overweight. AHA did not recommend pharmacotherapy, but emphasised the beneficial role of diet and lifestyle intervention for weight loss, whereas bariatric surgical treatment received a class of recommendation IIa [72]. ESC guidelines underlined the long-term failure of diet and lifestyle modifications, thus providing a modest endorsement for the pharmacological and surgical approach to obesity [2]. In addition, both guidelines strongly encouraged sedentary subjects to start exercise programmes, recommending at least 2.5 hours per week of physical activity [2], as indicated also in epidemiological [79, 80] and clinical studies investigating myocardial performance [81], cholesterol levels, BP and insulin resistance [82].

### Table 3: Strategies and targets in the management of dyslipidaemia.

<table>
<thead>
<tr>
<th>ESC guidelines (updated in 2012) [5, 57]</th>
<th>AHA/ACC risk score (updated in 2013) [2, 64]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical risk categories</strong></td>
<td><strong>Treatment (target)</strong></td>
</tr>
<tr>
<td>No Consider treatment if LDL-c ≥5 mmol/l.</td>
<td>Low risk (&lt;1%)</td>
</tr>
<tr>
<td>No Consider treatment if LDL-c ≥4 mmol/l. (LDL-c &lt;3 mmol/l)</td>
<td>Moderate risk (1%–5%)</td>
</tr>
<tr>
<td>Yes if LDL-c ≥4 mmol/l Consider treatment also independently of LDL-c levels. (LDL-c &lt;2.5 mmol/l)</td>
<td>High risk (5%–10%)</td>
</tr>
<tr>
<td>Yes if LDL-c ≥2.5 mmol/l Consider treatment also independently of LDL-c levels. (LDL-c &lt;1.8 mmol/l or reduction ≥50%)</td>
<td>Very high risk (&gt;10%)</td>
</tr>
<tr>
<td>Yes independently of LDL-c levels. (LDL-c &lt;1.8 mmol/l or reduction ≥50%)</td>
<td>Established CVD</td>
</tr>
<tr>
<td>Yes (LDL-c &lt;2.5 mmol/l in patients without CVD and &lt;1.8 mmol/l or ≥50% reduction in patients at very high CVD risk)</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Yes in stages 2–5 (eGFR &gt;90 ml/min/1.73 m²) considered a CAD risk equivalent. (LDL-c &lt;1.8 mmol/l or reduction ≥50%)</td>
<td>CKD</td>
</tr>
<tr>
<td>Yes, since they are considered as high CVD risk patients. (LDL-c &lt;1.8 mmol/l or reduction ≥50%) Dyslipidaemia (LDL-c &gt;4.9 mmol/l)</td>
<td>High-intensity treatment (target not available)</td>
</tr>
</tbody>
</table>

AHA/ACC = American Heart Association / American College of Cardiology; CKD = Chronic kidney disease; CVD = Cardiovascular disease; ESC = European Society of Cardiology; LDL-c = Low density lipoprotein cholesterol. * Moderate-intensity treatment: daily dose of statins lowers LDL cholesterol level by approximately 30% to <50% on average. ** High-intensity treatment: daily dose of statins lowers LDL cholesterol level by approximately ≥50% on average.
Diabetes

Diabetes is a recognised CV risk factor [83] and both ESC and AHA guidelines tailored a specific therapeutic approach for diabetic patients. AHA guidelines even included diabetes as an independent predictor variable [2, 5]. Although very difficult to achieve, BP target of 140/80 is recommended also through a combination therapy (class of recommendation I, level of evidence A) for both ESC and AHA guidelines; strong GRADE recommendation according to ESC guidelines. In addition, in diabetic patients, a lipid-lowering drug independent of basal level of LDL-c should be administered (table 3). Finally, whereas the role of antithrombotic therapy with aspirin remains unproved [84], a target of HbA1c <7% (but not a further reduction below 6.5%) is recommended [85, 86].

New promising predictors

Traditional risk factors showed some inconsistency in CVD risk stratification, but current guidelines provide only a tepid endorsement for the introduction of new markers in CVD risk assessment. High-sensitivity C-reactive protein, apolipoproteins, carotid intima media thickness, cardiorespiratory fitness, ankle-brachial index and chronic kidney disease were not recommended as screening tools in low-risk patients [2, 5]. About genetic testing, ESC guidelines emphasised the need for screening familial prevalence of atherosclerotic diseases and/or major risk factors. However, clinical benefits and relevance of genetic tests have not been established yet (class of recommendation III, level of evidence B; strong GRADE recommendation). On the other hand, the assessment of coronary artery calcium (CAC) score by computed tomography is emerging as a cost-effective way for CVD prediction, also in low-risk patients. Substantial evidence of CAC score effectiveness was provided by the Multi-Ethnic Study of Atherosclerosis (MESA) and further confirmed in other recent studies [87–94] (table 4). Accordingly, the inclusion of CAC scores in different validated CVD risk algorithms, including Framingham ARIC and Reynolds score, was shown to improve the absolute risk estimation [87]. Furthermore, also the potential cost effectiveness of CAC assessment has been recently highlighted. Martin and

Table 4: Recent analyses from Multi-Ethnic Study of Atherosclerosis (MESA).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Outcome (follow-up)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Goma, et al.</td>
<td>2013</td>
<td>52,318 subjects from different cohorts (95–99)</td>
<td>Pooling ARIC, Reynolds or CAC* equations to Framingham risk score (10 years)</td>
<td>The implementation of Framingham CV risk algorithm with CAC score greatly changed absolute risk estimation.</td>
</tr>
<tr>
<td>Desai, et al.</td>
<td>2013</td>
<td>6,581</td>
<td>CVD incidence according to CAC score**</td>
<td>In women, CVD incidence was high compared to low-risk group (HR 3.18 [95% CI: 2.14–4.72]; p &lt;0.05). Similar results were observed in men (HR 2.65 [95% CI: 2.55–5.22]; p &lt;0.05).</td>
</tr>
<tr>
<td>Polak, et al.</td>
<td>2013</td>
<td>5,445</td>
<td>Relationship between cIMT-CAC score (2.4 years)</td>
<td>cIMT strongly predicted CAC (RR 1.37 [95% CI: 1.12–1.67]; p &lt;0.05), whereas CAC was associated with cIMT progression (RR 1.13 [95% CI: 1.03–1.25]; p &lt;0.05).</td>
</tr>
<tr>
<td>Budoff, et al.</td>
<td>2013</td>
<td>5,328</td>
<td>CV events (5 years)</td>
<td>Higher levels of CAC* score were strong predictors of CV events (HR 5.36 [95% CI: 2.46–11.7]; p &lt;0.001).</td>
</tr>
<tr>
<td>Martin, et al.</td>
<td>2014</td>
<td>5,534</td>
<td>CVD according to CAC score** (7.6 year follow-up)</td>
<td>CVD events were best predicted by high CAC score compared with dyslipidaemia.</td>
</tr>
<tr>
<td>Bittencourt, et al.</td>
<td>2014</td>
<td>6,522</td>
<td>CAC score*** and polypill therapy (5 years)</td>
<td>High CAC scores were recognised in subjects eligible for polypill therapy.</td>
</tr>
<tr>
<td>Criqui, et al.</td>
<td>2014</td>
<td>3,398</td>
<td>CVD according to CAC score for density* and volume (7.6-year follow-up)</td>
<td>Both CAC assessment strategies significantly predicted CVD occurrence. However, ROC analysis showed that the addition of density and volume scores improved risk prediction for CVD (p-value for AUC increase = 0.02).</td>
</tr>
<tr>
<td>Silverman, et al.</td>
<td>2014</td>
<td>6,540</td>
<td>PCI and CABG according to CAC score* and CAC distribution (8.5-year follow-up)</td>
<td>CAC was predicted by CAC burden (HR 17.5 [95% CI: 10.1–30.3]; p &lt;0.001) and distribution (HR 16.8 [95% CI: 9.6–29.6]; p &lt;0.001). CAC score predicted both PCI (HR 4.1 [95% CI: 2.2–7.7]; p &lt;0.001) and CABG (p &lt;0.001).</td>
</tr>
</tbody>
</table>

AUC = Area under the curve; ARIC = Atherosclerosis risk in communities; CV = Cardiovascular; cIMT = Carotid Intima Media Thickness; CHD = Chronic heart disease; CI = Confidence interval; CAC = Coronary artery calcium; CVD = Cardiovascular disease; C = Coronary; HR = Hazard ratio; HNR = Heinz Nixdorf RECALL study; MESA = Multi-Ethnic Study of Atherosclerosis; PHS = Physician’s Health Study; PCI = Percutaneous coronary intervention; ROC = Receiver operator curve; RR = Relative risk; WHS = Women’s Health Study. * Low-, high-, and very-high-risk values of CAC were defined as: 0, 100 and >400 Agatston units. Conversely, ARIC risk score incorporates carotid intima media thickness and Reynolds risk score incorporates high-sensitivity C-reactive protein. ** Low-, intermediate- and high-risk values of CVD were defined as: 0, 1–100 and >100 Agatston units. *** Low-, intermediate- and high-risk values of CAC were defined as: 0, 1–100 and >100 Agatston units.
co-workers reported that CAC may potentially narrow the field of statin treatment by helping to match it with the absolute CVD risk \[91\]. Similarly, it has been observed that the screening by CAC might reduce the burden of polypill-treated patients according to different criteria \[92\]. However, the substantial lowering of risk threshold in AHA guidelines (from <10% to <7.5% 10-year risk of ASCVD) has consistently limited the potential role of CAC in decision-making about statin therapy initiation. Thus, the assessment of CAC was recommended as class IIb, according to previous 2010 AHA guidelines and consistent with ESC recommendations (class of recommendation Ila, level of evidence B; weak GRADE recommendation). Table 5 lists the potential new biomarkers of increased CV risk.

Lost in translation

Limitation of the algorithm-based prediction of cardiovascular disease

Despite decades of work, a broad range of CVD predictors and several different algorithms, none of the models so far developed seems to be satisfactory. On the other hand, cornerstones of CVD risk prevention still remain the same risk factors known since the 1960s: age, gender, race, lipid profile, diabetes, smoking and hypertension. The reasons underlying these limitations are complex and not fully understood. Leading concerns rely on the combination of stochastic effects and incomplete knowledge of different predictors. Furthermore, extracting a personalised risk from a population-based risk model algorithm represents an intrinsic methodological limitation. The efforts of preventive cardiology aimed at improving the accuracy of prediction models (current ranging between 0.60 and 0.70, according to c-index \[100\]). Additional predictors may increase accuracy up to 0.80 \[101\], but a further rise would lead to a lack of calibration \[102\]. In addition, the available predictive models do not fit well with different populations or time periods (i.e., the exposure time to risk factors). On the other hand, a risk-prediction model tailored on event occurrence (i.e., myocardial infarction) rather than the underlying disease (i.e., atherosclerosis) may lead to missing a large amount of therapeutic opportunities. Therefore, as recently suggested by McEvoy and co-workers, it might be time to shift the target from risk estimation to screening strategy \[103\]. A screening-based approach potentially burdens CVD overestimation and would require a large prospective validation.

Poor implementation of guidelines in cardiovascular prevention

Despite many efforts to improve CV risk assessment, current guidelines are still far from being implemented into clinical practice. From 1995, EUROASPIRE (European Action on Secondary and primary Prevention by Intervention to Reduce Events) surveys I, II and III provided an overview on clinical standards in preventive cardiology and documented a constant gap between clinical management and guidelines \[104\]. In 2009, Kotseva and colleagues comparing EUROASPIRE surveys suggested a limited focus of health care programmes on preventive cardiology \[105\]. The leading concern was represented by adverse lifestyle trends (such as an increase in smoking in young and female subjects and

Table 5: New potential biomarkers for CV risk stratification.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>ESC recommendation</th>
<th>AHA/ACC recommendation</th>
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<tr>
<td></td>
<td>COR</td>
<td>LOE</td>
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<tr>
<td>hs-CRP</td>
<td>Iib</td>
<td>B</td>
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<tr>
<td>Fibrinogen</td>
<td>III</td>
<td>B</td>
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<tr>
<td>Homocysteine</td>
<td>Iib</td>
<td>B</td>
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<tr>
<td>LpPLA2</td>
<td>Iib</td>
<td>B</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>III</td>
<td>B</td>
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<tr>
<td>cIMT</td>
<td>Iia</td>
<td>B</td>
</tr>
<tr>
<td>CAC</td>
<td>Iia</td>
<td>B</td>
</tr>
<tr>
<td>Cardiorespiratory fitness</td>
<td>Iib</td>
<td>B</td>
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<td>ABI</td>
<td>Iia</td>
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<td>CKD</td>
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</table>

AHA/ACC = American Heart Association / American College of Cardiology; ABI = Ankle Brachial Index; CAC = Coronary artery calcium; cIMT = Carotid Intima Media Thickness; CKD = Chronic kidney disease; COR = Class of recommendation; ESC = European Society of Cardiology; GRADE = Grading of Recommendation Assessment, Development and Evaluation; hs-CRP = high-sensitivity C-reactive protein; LOE = Level of evidence; LpPLA2 = Lipoprotein-associated phospholipase A2.
pandemic obesity) [106, 107]. In addition, the EU-ROASPIRE surveys reported the failure of achieving therapeutic targets despite an increased prescription rate of anti-hypertensive and cholesterol lowering drugs [108, 109]. Considering this evidence, we believe that health-care systems should develop lifestyle programmes and medical technology to further implement international recommendations in clinical management.

Conclusion

Although proof-of-concept trials are needed to validate the potential role of screening strategies, there is no doubt that targeting atherogenesis will be the next goal in preventive cardiology to potentially identify some novel and promising risk factors. According to several lines of evidence, early intervention has also been shown to promote athero-regression so that resetting the vascular aging clock might be the aim of future research, as recently stated by Robinson and Gidding [110]. Meanwhile, we believe that current methodologies for disease detection and quantification (especially CAC) have achieved high levels of accuracy and may provide further information before committing patients to lifelong treatments. Thus, it is expected that combining CVD screening and risk estimation might be a potential step forward in cardiovascular prevention. This would improve clinical translation of current algorithms, thus promoting personalised decision-making by physicians.

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The complete list of references is attached to the online version at www.cardiovascmed.ch

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