Cardiovascular risk assessment beyond Systemic Coronary Risk Estimation: a role for organ damage markers

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Background: Cardiovascular risk assessment in the clinical practice is mostly based on risk charts, such as Framingham risk score and Systemic Coronary Risk Estimation (SCORE). These enable clinicians to estimate the impact of cardiovascular risk factors and assess individual cardiovascular risk profile. Risk charts, however, do not take into account subclinical organ damage, which exerts independent influence on risk and may amplify the estimated risk profile. Inclusion of organ damage markers in the assessment may thus contribute to improve this process.

Objective: Our aim was to evaluate the influence of implementation of SCORE charts with widely available indexes of organ damage, with the purpose to ameliorate individual risk assessment.

Methodology: We searched www.Pubmed.gov for evidence about the predictive value of left ventricular hypertrophy (LVH), estimated glomerular filtration rate (eGFR), microalbuminuria (MAU) and metabolic syndrome on different risk profiles estimated by SCORE. Interventional and observational trials including at least 200 patients and published after 2000 were selected.

Results: The presence of organ damage as well as the number of abnormal parameters indicating organ damage is associated with increased cardiovascular risk, independently of SCORE. In the area of high risk, the impact of different markers of organ damage is heterogeneous. Combined risk models of SCORE and subclinical organ damage have major impact on risk stratification and may impact on recommendation in primary prevention in all SCORE categories.

Conclusion: Available evidence suggests a tangible clinical advantage of adding the evaluation of simple organ damage markers to risk charts in cardiovascular risk prediction.

Keywords: cardiovascular risk, estimated glomerular filtration rate, left ventricular hypertrophy, metabolic syndrome, microalbuminuria, prevention, SCORE, target organ damage

Abbreviations: ACR, albumin/creatinine ratio; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology collaboration; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; MAU, microalbuminuria; MDRD, modification of diet in renal disease; MetS, metabolic syndrome; MI, myocardial infarction; PRISMA, preferred reporting items for systematic review and meta-analysis; SCORE, Systemic Coronary Risk Estimation; TOD, target organ damage; UACR, urinary albumin/creatinine ratio

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, leading to 4.3 million of deaths per year in Europe [1]. Particularly, in Italy, CVD accounts for 44% of total deaths (Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute).

Over the last years, different algorithms concerning cardiovascular risk stratification have been developed to prospectively estimate the risk of cardiovascular mortality. Such scores are based mainly on the presence or the absence of traditional modifiable and nonmodifiable cardiovascular risk factors. Framingham Risk Score and Systemic Coronary Risk Estimation (SCORE) projects have been thoroughly validated and largely used in clinical practice. However, despite the availability of a large number of scores, it is still hard to identify powerful

Journal of Hypertension 2012, 30:1056–1064

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Received 22 July 2011 **Revised** 21 November 2011 **Accepted** 8 February 2012

J Hypertens 30:1056–1064

DOI:10.1097/HJH.0b013e3283525715

determinants discriminating among different categories of cardiovascular risk. The lack of any clue on subclinical organ damage in the available risk charts exemplifies the failure to intercept patients with significant cardiovascular risk. As a result, treatment strategies aimed at preventing CVD are not always tailored on the real individual risk profile.

Although preventive strategies for high-risk patients are well defined by current guidelines, the challenge of CVD risk prediction is mostly focused on those patients defined at intermediate risk. This category of patients could be better addressed at the individual clinical level by a more accurate risk stratification including cost-effective, second-level tests that have recently shown a high predictive value for cardiovascular events [2,3]. As suggested by 2007 European Society of Hypertension/European Society of Cardiology (ESH/ESC) hypertension guidelines, the evaluation of global cardiovascular risk should take into account subclinical target organ damage beyond traditional cardiovascular risk factors [3]. However, the impact of organ damage among different risk categories is still not clear. Also, the identification of metabolic syndrome (MetS), an easy and practical clinical task, has been advocated in the guidelines as a potential cardiovascular risk predictor to be integrated with traditional charts [3]. However, its discrete influence on estimation of global risk has not been defined. Only few studies have investigated whether the assessment of cardiovascular risk by risk charts can be ameliorated by adding target organ damage (TOD) and MetS.

According to available literature, we attempted to critically discuss current evidence supporting the additional predictive value of left ventricular hypertrophy (LVH), reduction of estimated glomerular filtration rate (eGFR) and microalbuminuria (MAU) as TOD markers, and MetS beyond the SCORE project. The aim of this work is to propose an updated and documented viewpoint on the need to modify SCORE charts to better define the individual cardiovascular risk on a large-scale population based on the addition of simple and low-cost parameters, easily and widely available in the routine clinical setting.

SEARCH METHODOLOGY

On the basis of the vast amount of evidence existing in literature, we selected the following markers of organ damage for our search: LVH, eGFR, MAU. We also searched for MetS. All articles in English available until March 2011 on www.Pubmed.com by introducing the terms 'left ventricular hypertrophy/estimated glomerular filtration rate/microalbuminuria/metabolic syndrome and cardiovascular risk', 'left ventricular hypertrophy/estimated glomerular filtration rate/microalbuminuria/metabolic syndrome and cardiovascular events', 'left ventricular hypertrophy/estimated glomerular filtration rate/microalbuminuria/metabolic syndrome and risk score' were screened for our search. Out of the results retrieved, we eliminated duplicates and substudies, then we selected interventional and observational studies electing those with population of at least 200 patients, particularly those studies published after 2000 and meta-analyses most representative for our purpose. Our decisional process actually adhered to all the steps of the four-phase flow diagram published by Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) [4] in 2009. Most of the studies reported used hazard ratio and relative risk as index of the association between TOD and outcomes. Our analysis largely reflects the checklist and methodology recently proposed by PRISMA.

THE SYSTEMIC CORONARY RISK ESTIMATION PROJECT

SCORE is a widely used risk chart for cardiovascular risk stratification in healthy individuals. It is based on risk functions derived from the analysis of 12 European cohort studies and calculates 10-year risk of cardiovascular death based on age, sex, SBP, cholesterol and smoking. SCORE also provides risk charts calibrated to each geographic region in Europe. Two parallel SCORE models have been developed: one based on total cholesterol and the other on total cholesterol/high-density lipoprotein (HDL) cholesterol ratio. The risk estimations are displayed graphically in simple risk charts [5].

LEFT VENTRICULAR HYPERTROPHY

Data about the importance of the presence of LVH as well as of other markers of TOD in hypertensive patients appear to be relevant because hypertension is a very common risk condition in the general population. The analysis of this subgroup of patients could indeed represent a gateway for the analysis of TOD also in other population subgroups. Electrocardiography is commonly used in the routine assessment of individuals with high blood pressure as well as practically in all other groups of individuals carrying cardiovascular risk factors. Although sensitivity is low, LVH detected by the Sokolow–Lyons index (SV1 + RV5–6 >38 mm) or by the Cornell voltage QRS duration product (>2440 mm/ms) is an independent predictor of cardiovascular events [3,5–16]. LVH has been shown to be predictive of major cardiovascular events (including stroke) and all-cause mortality, independent of blood pressure, and across all racial groups that have been studied. In the Framingham Study, for every 50 g/m^2 LVH increase, there was a relative risk (RR) of death of 1.73 [95% confidence interval (CI) 1.19–2.52] independent of blood pressure level [17]. In the African–American population enrolled in the ARIC study, LVH conferred an increased risk for CVD events [nonfatal myocardial infarction (MI), cardiac death, coronary revascularization, and stroke] even after adjusting for other risk factors with a hazard ratio of 1.88 in men and 1.92 in women. Among American Indians enrolled in the Strong Heart Study (64% women, mean age 58 years), the LVH prevalence on echocardiography was 9.5% and conferred a seven-fold increase in cardiovascular mortality and a four-fold increase in all-cause mortality [17]. Of note, in hypertensive individuals, left ventricular mass showed a linear correlation with cardiovascular risk, which extended even below the conventional cut-off levels for LVH [11]. Specifically, regarding the ECG-detected LVH, the Framingham cohort individuals in the highest quartile of ECG–LVH displayed a three-fold increase in risk of CVD as compared

with those in the lowest quartile [8]. In Italy, the ECG-derived Perugia score for definition of LVH carried the highest population-attributable risk for cardiovascular morbidity and mortality compared with classic methods for detection of LVH [9]. Moreover several studies have shown that reduction of ECG–LVH is significantly associated with reduced cardiovascular risk [8,18,19]. Recently, a LIFE (Losartan Intervention for Endpoint reduction in Hypertension) substudy showed that in individuals with low in-treatment ECG–LVH, the rate of fatal and nonfatal cardiovascular events was strongly reduced, regardless of blood pressure reduction [20]. In fact, after controlling for possible confounders in Cox regression models, the composite cardiovascular end point (cardiovascular death, fatal or nonfatal MI, and fatal or nonfatal stroke) was 14% lower for every decrease in 1 SD (1050 mm ms) in Cornell product and 17% lower for every decrease in 1 SD (10.5 mm) in Sokolow–Lyon voltage. Further observations using the more sensitive echocardiographic technique have shown that patients who achieve LVH regression during follow-up are much less likely to experience morbid events as compared with those with persistence of LVH [21,22]. These observations have been reinforced by other studies and by the results of the echocardiographic substudy of LIFE in which a reduction of 25 g/m^2 in left ventricular mass (corresponding to 1 SD of baseline value) was associated with a reduction of 22% in the primary composite end point during 4.6 years of follow-up, even after adjusting for possible confounders [23].

In a recent meta-analysis that involved five prospective studies (2449 individuals with a follow-up duration ranging from 3 to 9 years), it has been shown that echocardiographic LVH regression in hypertension is associated with reduced risk of future cardiovascular events. The overall adjusted hazard ratio was 0.54 for LVH regression/persistent normal left ventricular mass vs. LVH persistence/LVH development [24].

It should also be mentioned that without ultrasound investigations for LVH and vascular thickening or plaques, a significant portion of hypertensive individuals, especially men older than 50 years, may be mistakenly classified as at low or moderate added risk, whereas the presence of cardiac or vascular damage classifies them within a higher risk group [3,25]. Despite this, it is still necessary to perform new specific studies that would address the definition of the usefulness of ECG-LVH in reclassifying the added relative risk of individuals through specific Bayesian statistic methods such as receiving–operating curves. In our opinion, an electrocardiographic screening for LVH could be the best strategy in a primary prevention setting, given also the high cost-effectiveness of echocardiography [25].

ESTIMATED GLOMERULAR FILTRATION RATE

The US National Kidney Foundation has provided guidelines for the chronic kidney disease (CKD) evaluation, classification and stratification. Definitions of stages 1–5 of CKD correspond to eGFR levels of at least 90, 60–89, 30–59, 15–29 and less than 15 ml/min per 1.73 m^2. Stage 3 (eGFR <60 ml/min per 1.73 m^2) is generally the stage at which patients show symptoms of renal insufficiency, and it is considered as the cut-off point for moderate–severe CKD [26].

Reduced eGFR is associated with high prevalence of CVD risk factors, CVD surrogates and clinical CVD [27] and has been repeatedly found to be an independent risk factor for CVD outcome in high-risk populations [28–33] and in hypertensive patients [34–36]. Shara *et al*. [33] showed in a large cohort with high prevalence of diabetes that, compared with individuals whose eGFR was at least 90 ml/min per 1.73 m^2 at baseline, those with eGFR less than 30, 30–59 and 60–89 ml/min per 1.73 m^2 using either modification of diet in renal disease (MDRD) and Cockcroft–Gault equation, had increased risk of incident CVD.

In 2006, a pooled analysis of four community-based studies involving 26147 individuals showed that the presence of stage 3 of CKD was an independent risk factor for cardiac events, stroke and death (hazard ratio 1.26; CI 95% 1.16–1.35; $P < 00001$) [37]. Similar results were reinforced in 2007 by a meta-analysis of six previous reports involving a total of 4720 incident coronary heart disease cases which yielded a combined risk ratio of 1.41 in individuals with baseline eGFR less than 60 ml/min per 1.73 m^2 compared with those with higher values [38]. In 2010, the Chronic Kidney Disease Prognosis Consortium published a collaborative meta-analysis involving 105 872 individuals from 21 general population cohorts. This meta-analysis showed that eGFR and albuminuria were associated with all-cause mortality and cardiovascular mortality, independently of each other and of traditional cardiovascular risk factor. The risk for cardiovascular mortality became significant around eGFR 60 ml/min per 1.73 m^2 (hazard ratio 1.40) and even grew for smaller value of eGFR (hazard ratio 1.99 when eGFR 45 ml/min per 1.73 m^2; hazard ratio 2.66 when eGFR 15 ml/min per 1.73 m^2). In addition, eGFR lower than 60 ml/min per 1.73 m^2 showed a similar association with risk of mortality across all levels of albuminuria and *vice versa*, suggesting a role of multiplicative independent risk factor for mortality [39].

A relationship between eGFR less than 60 ml/min per 1.73 m^2 values and the risk of cardiovascular mortality and morbidity has been reported even in low-risk population [40–45]. A study involving more than 1 million individuals showed that the progressive decline of eGFR was associated with an increase in the risk of mortality. eGFR values ranging from 45 to 59, 30 to 44, 15 to 29 and less than 15 ml/min per 1.73 m^2 were associated with 1.2-fold, 1.8-fold, 3.2-fold and 5.9-fold increase in mortality, when compared with individuals with preserved renal function (eGFR $\geq$60 ml/min per 1.73 m^2). Similarly, the hazard ratios for cardiovascular events progressively increased with the impairment of glomerular filtration [41]. Interestingly, evidence also suggest that even minor declines of renal function, can be associated with increased risk of cardiovascular mortality and morbidity [46–48]. It has been calculated that a decrease in eGFR of 5 ml/min per 1.73 m^2 within the 116.9 and 16.8 ml/min per 1.73 m^2 range is associated with a 26% increase in cardiovascular mortality risk [47]. Similar results were obtained also in a cohort of healthy people [49] and in elderly individuals [26]. The Atherosclerotic Risk in Communities Study found a 16% increase cardiovascular risk for

those individuals with an eGFR value above 60 ml/min per 1.73 m^2 as compared with those displaying a normal renal function (eGFR above 90 ml/min per 1.73 m^2) [48].

More recently, a cohort study involving hypertensive patients showed that eGFR less than 60 ml/min per 1.73 m^2 was related to the presence of CVD regardless of cardiovascular risk profile as defined by SCORE. Interestingly, the evaluation of eGFR in addition to the SCORE increased the accuracy in identifying patients with CVD (AUC of ROC analyses of individual probability to have total CVD for SCORE alone was 0.66, instead for SCORE + CKD was 0.69) [50]. Moreover, in 2010, it has been suggested that a new equation for eGFR recently published by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) could categorize more appropriately individuals with respect to long-term cardiovascular risk compared with MDRD study equation, suggesting improved clinical usefulness [51]. However, prospective studies addressing the predictive value of eGFR beyond SCORE in clinical practice are still lacking. This aspect is of outmost importance since a simple and reliable index of renal function as eGFR could increase disproportionately the accuracy of available scores in the prediction of cardiovascular events in primary prevention.

MICROALBUMINURIA

Due to its low molecular weight, albumin can be filtered through the glomerular capillaries, then it is reabsorbed by the proximal tubular cells till a maximal capacity. When the system is exhausted, because of increased glomerular leakage low quantities of albumin can be detected in the urine, MAU, which is defined as excretion of urinary albumin above 20 μg/min or between 30 and 300 mg/24 h or 20–200 mg/l in spot urine collection or as urinary albumin/creatinine ratio (UACR) above 2.5–25 mg/mmol in men and 3.5–25 mg/mmol in women or at least 22 mg/g (men) and at least 31 mg/g (women) and less than 300 mg/mmol [52]. Excretion of urinary albumin in the MAU range can be considered a candidate prediction biomarker for CVD risk for several reasons. Standard CVD risk factors are associated with MAU and this is associated with incident hypertension, progression to a higher blood pressure category and incident diabetes [17]. In the past decade, a large body of evidence has been published suggesting that the value of MAU as predictor of cardiovascular events and total mortality may be extended to diabetic and nondiabetic individuals, hypertensive patients and general population [52–63]. A meta-analysis of 26 cohort studies including 169 949 participants reported that after accounting for standard CVD risk factors, there was a stepwise relationship between albuminuria and risk of CHD. Compared with individuals without albuminuria, macroalbuminuria was associated with a doubling of risk (RR 2.17; 95% CI 1.87–2.52) and MAU was associated with a nearly 50% greater risk (RR 1.47; 95% CI 1.30–1.66) of CHD [64].

Recently, a LIFE substudy showed that in hypertensive patients with LVH fatal and nonfatal cardiovascular events increased disproportionately across deciles of MAU, strongly suggesting a linear relation between MAU and raised cardiovascular risk [65]. Moreover, it has been shown that MAU is independently associated with cardiovascular mortality with such a relationship maintained even within normal range of UACR [66–68]. Indeed, in the large the Netherlands cohort of the PRevention of Renal and Vascular End Stage Disease study, after adjustment for cardiovascular risk factors, a two-fold increase in urinary albumin excretion (UAE) was associated with a 29% increased risk of death from CVD. Across the whole spectrum of UAE, there was a continuous association between CVD and increasing albuminuria [67]. Similar results have been supported in 2010 by a collaborative meta-analysis by Chronic Kidney Disease Prognosis Consortium. Albumin/creatinine (ACR) ratio was associated with risk of cardiovascular mortality linearly without threshold effect. Compared with ACR 0.6 mg/mmol, hazard ratio for cardiovascular mortality were 1.27 for ACR 1.1 mg/mmol, 1.77 for 3.4 mg/mmol and 2.43 for 33.9 mg/mmol [39].

METABOLIC SYNDROME

According to Adult Treatment Panel III, the diagnosis of MetS can be made whenever three or more of the following parameters are met: triglycerides 150 mg/dl or more; HDL cholesterol less than 40 mg/dl for men and less than 50 mg/dl for women; blood pressure 130/85 mmHg or more; obesity as defined by a waist circumference 88 cm or more for women and 102 cm or more for men; and abnormal glucose metabolism as defined by a fasting glucose 110 mg/dl or more [69].

The relationship between MetS, as defined by the WHO [70–72], the IDF [70,73] and the ATPIII [69,72–80], and cardiovascular events has been reported. In this regard, analysis of large cohorts has proved that MetS is associated with increased risk for coronary heart disease and stroke [71,73,78,81], but recent studies failed to show superiority of the MetS in predicting future CVD above and beyond its single components, especially fasting glucose or hypertension [70,82].

Several European [72,74,77] and American longitudinal studies [75,76,79] explored the relation between MetS and cardiovascular mortality, observing a 2.1-fold increase in the risk of all-cause mortality and a 3.6 increase in cardiovascular mortality, in patients free of CVD and diabetes [72]. An association between the number of MetS criteria and mortality from CVD has been also reported [79,83]. Even if MetS could be an independent risk factor for mortality associated with a worse prognosis than its individual components [76,83], Mancia *et al.* [74] recently reported that increased risk for cardiovascular and all-cause mortality in MetS patients was related only to blood pressure and to blood glucose component of the syndrome, with no contribution of the remaining components. Since evidence about the ability of MetS to assess cardiovascular risk is quite conflicting, its usefulness in predicting cardiovascular mortality beyond risk chart is still largely debated. A work from the Diabetes Epidemiology: Collaborative analysis of Diagnostic Criteria in Europe study (the DECODE study group 2006) supported a possible role of MetS in detecting more patients at high risk of cardiovascular death beyond those identified by SCORE. A total of 2790 middle-aged men without diabetes have been

followed for cardiovascular mortality recording over a 10-year follow-up. The main purpose was to determine whether men at low risk (SCORE <5%) with MetS, as defined by NCEP, had significantly higher cardiovascular mortality than those without. Low-risk men with MetS had a hazard ratio 2.26 (CI 95% 1.09–468) for the endpoint as compared with men without MetS. In contrast, in the high-risk population (SCORE ≥5%), hazard ratio for cardiovascular death in presence of MetS was 1.08 (CI 95% 0.68–1.72, NS). Most likely, in this, the later risk was mainly driven by the classic cardiovascular risk factors. Furthermore, people at low cardiovascular risk (SCORE <5%) with MetS have the same cumulative hazards for cardiovascular death than people at high risk (SCORE ≥5%) without MetS [84].

THE ADDITION OF SUBCLINICAL ORGAN DAMAGE TO SYSTEMIC CORONARY RISK ESTIMATION

Sehestedt *et al.* [85] investigated whether organ damage could improve cardiovascular risk prediction beyond SCORE. In an apparently healthy population, subclinical organ damage as well as the number of damaged organs was associated with increased cardiovascular risk, independently of SCORE. However, combining risk models of SCORE and subclinical organ damage yielded greater performance on risk stratification and recommendation for primary prevention. In particular, the presence of subclinical organ damage in patients with SCORE 5% or more identified a subgroup at particular high risk. Consequently, restricting primary prevention to this group reduced the number eligible for primary prevention by 20% and incremented specificity compared with using SCORE alone. Of note, measurement of subclinical organ damage in patients with SCORE 5% or more could be used to identify patients eligible for particular intensive primary prevention. Even in individuals with SCORE less than 5%, the risk estimation tended to be higher when organ damage was factored in. In contrast, subclinical organ damage detection did not improve cardiovascular risk prediction among patients with SCORE less than 1%. On the basis of these findings, the authors concluded that the most efficient approach would be only to measure subclinical organ damage in patients with SCORE between 1 and 5% rather than in those with SCORE less than 1%.

Other studies have investigated the predictive value of TOD on cardiovascular risk, showing, for instance, a strong association of MAU in patients with hypertension. Leoncini *et al.* [86], in a cross-sectional study, classified 58% of their cohort in the high/very high added risk stratum according to the 2007 ESH/ESC guidelines [3], by a simple routine clinical workup. The simultaneous evaluation of urinary albumin excretion and creatinine clearance resulted in a significantly greater change in risk stratification, because 68% of the patients were reclassified in the high/very high risk class. Viazzi *et al.* [87] reported that the combination of albuminuria assessment and cardiovascular ultrasonography greatly improved detection of target organ damage, therefore allowing identification of a larger proportion of patients at high risk as compared with those undergoing by routine workup (73 vs. 42%) [86].

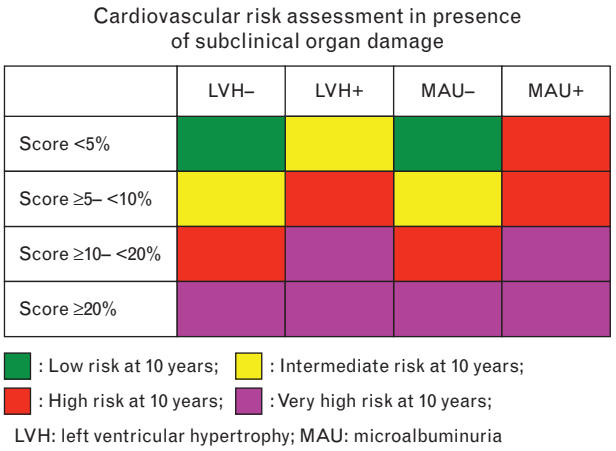

FIGURE 1 The reassessment of cardiovascular risk using indexes of target organ damage in groups of patients with different Systemic Coronary Risk Estimation (SCORE).

Results provided by Sehestedt *et al.* [85] allow reclassification of the cardiovascular risk as defined by SCORE by simply adding LVH and MAU figures (Fig. 1). In patients with a SCORE 5% or more, the cardiovascular risk would actually be doubled, when taking into account the presence of each these two markers of TOD. In patients with a SCORE less than 5%, the presence of LVH almost doubles the cardiovascular risk. Of note, the most relevant information is reported by adding the evaluation of MAU to SCORE in the subgroup of patients with a SCORE less than 5%. In fact, these patients in the presence of MAU would be at high cardiovascular risk by having cardiovascular death odds more than three-fold higher compared with those without MAU. Although these initial observations are encouraging, it should be pointed out that there are still very few studies, particularly in the light of the heterogeneity of the risk populations.

LIMITATIONS

Our work has some possible limitations. For the purpose our analysis, we selected from www.Pubmed.gov those most relevant studies, including meta-analysis, published between 2000 and 2011 about the cardiovascular prognostic implications of the presence of TOD. We excluded small investigations and substudies and did not use other search database. As we searched the literature for studies with at least 200 individuals, relevant small studies could have been missed, partially biasing our search methodology. However, our literature search to support a viewpoint, based on meta-analyses and the most representative and large studies, reflects overall a straightforward approach.

All the studies selected had different designs and included nonhomogeneous population.

With regard to LVH, follow-up terms varied from one study to another (from decades to months), some researchers did serial ECG and blood pressure analysis, whereas others did not; only some excluded with an explicit statement the possible influence of significant valvular defects on LVH. At last, racial differences in assessing ECG criteria for LVH have been reported, so the results derived in a

particular population may not be applicable to other racial groups.

With regard to renal damage, some studies evaluated glomerular filtration rate by using MDRD formula, whereas others used Cockcroft–Gault equation, some obtained serial measurement of serum creatinine/UACR/MAU, whereas others did not, leading to misclassification of CKD status. Moreover, the prevalence of different degrees of chronic kidney impairment across the population collected varied from one study to another. Finally, in some trials, the severity of comorbid medical conditions and information on physical activity, tobacco/alcohol use were not known.

MetS was defined using different definition (ATPIII-IDF-WHO) across studies, possibly leading to misclassification of the relationship with outcomes. However, this is a common, generally accepted limit of most meta-analytical studies on MetS.

In particular, in the study by Sehestedt *et al.*, a small number of events was recorded and it was not assessed by an independent committee, also excluding diabetic patients. This is different from the original SCORE dataset, thus the SCORE could overestimate the risk in population of Sehestedt *et al.*.

CONCLUSION

The search of the best possible estimate of cardiovascular risk in an individual patient represents a major need of modern management of CVD and is at the same time a daily clinical challenge for all physicians, specialists or general practitioners. Risk charts are commonly used and referred to as reliable way of cardiovascular risk stratification. Nonetheless, they are not voided of pitfalls and weaknesses and the clinical yield is often not sufficient especially in patients with subclinical cardiorenal organ damage. A better definition of the individual risk on a large-scale population may in fact be achieved by evaluation of subclinical organ damage by means of cost-effective tools that can be used in primary prevention. The literature data suggest that by diagnosing LVH and MAU, a reliable reclassification of each patient is obtained. However, more solid evidence is needed particularly in larger cohorts with longer follow-up because there are still nonconclusive prospective studies comparing different cardiovascular risk assessment strategies with and without the inclusion of parameters of target organ damage with sufficient follow-up data.

More sophisticated and expensive markers of TOD have also showed a predictive role in cardiovascular risk assessment. For instance, carotid atherosclerosis, defined as intima–media thickness or plaques, has been proven to ameliorate the predictive ability of the Framingham risk score [88], the SCORE [85] and the Progetto Cuore [89,90] charts. Despite this, its usefulness in large-scale population screening is actually limited by its elevated costs and high dependence on operator and machine availability.

We can conclude that today there is much interest and need to test the ability of new indexes of target organ damage that are largely available, easy to obtain and cheap.

ACKNOWLEDGEMENTS

Authors represent: M.V. for Italian Society of Cardiovascular Prevention (SIPREC); E.A.R. for Italian Society of Hypertension (SIIA); A.C. for Italian Society of Clinical and Experimental Therapy (SITeCS); R.C. for Italian Society of Nephrology (SIN); S.D.P for Italian Society of Diabetes (SID); S.G. for Italian Association of Clinical Diabetologist (ADM); E.M. for Italian Society for the Study of Atherosclerosis (SISA); S.N. for Italian Society of Cardiology (SIC); D.P. for Italian Society for the Study of Haemostasis and Thrombosis (SISET).

The authors also wish to thank Dr Giuliano Buzzetti for the significant organizing support.

Conflicts of interest

Cooperative work supported by Consulta delle Società Scientifiche per la Riduzione del Rischio Cardiovascolare (CSCV).

Research fee 2010 from Roche SPA and Roche Diagnostics, Milan, Italy (S.G.); Honoraria for advisory boards or congresses by GSK and Bayer (D.P.); no other potential conflicts of interest to disclose.

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Reviewers' Summary Evaluations

Reviewer 1

In their retrospective analysis Volpe and coworkers review the additional predictive contribution of left ventricular hypertrophy, eGFR, microalbuminuria, metabolic syndrome to standard cardiovascular risk assessment charts such as Framingham or SCORE. The authors conclude that there is some additional benefit of the above mentioned parameters for the assessment of cardiovascular risk, as compared to cardiovascular risk assessment by standard risk charts. However, there is a large amount of evidence in favour of better cardiovascular risk prediction when parameters of target organ damage are measured. Therefore conclusive prospective studies comparing different cardiovascular risk assessment strategies with and without the inclusion of parameters of target organ damage are warranted.

Reviewer 2

The strong point in the analysis by Volpe and coworkers is that they only included studies with a large patient group and that all had been published after the year 2000 so that the assessment of damage across the studies was done with sound methods. A weak point, duly acknowledged by the authors, is that outcome studies varied markedly in duration of follow-up and sometimes methodology. Also, the type of patients in the studies varied substantially. Nevertheless, the paper provides a good starting point for future prospective studies in this area.