Cardiovascular risk assessment beyond SCORE: a role for organ damage markers

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Abstract
Background: Cardiovascular (CV) 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 CV risk factors and to assess individual CV 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 (MetS) on different risk profiles estimated by SCORE. Interventional and observational studies with at least 200 subjects included, published after 2000 were selected.

Results: The presence of organ damage as well as the number of abnormal parameters indicating organ damage are associated with increased CV 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 suggest a tangible clinical advantage of adding the evaluation of simple organ damage markers to risk charts in cardiovascular risk prediction.

Condensed abstract
Current evidence suggests that the risk assessment derived by available cardiovascular risk charts may benefit from adding the evaluation of target organ damage indexes, such as left ventricular hypertrophy, microalbuminuria and other simple clinical parameters. The inclusion of these elements in the risk assessment may permit to refine better the estimation of individual risk and to improve practical clinical strategies on a large-scale population.

Key words: cardiovascular risk, prevention, SCORE, target organ damage, left ventricular hypertrophy, microalbuminuria, estimated glomerular filtration rate, metabolic syndrome
**Introduction**

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

Over the last years different algorithms concerning cardiovascular (CV) risk stratification have been developed to prospectively estimate the risk of CV mortality. Such scores are based mainly on the presence or the absence of traditional modifiable and non-modifiable CV 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 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 CV risk. As a result, treatment strategies aimed at preventing CVD are not always tailored on the real individual risk profile.

While preventive strategies for high-risk patients are well defined by current guidelines the challenge of CVD risk prediction is mostly focused on those subjects 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 which have recently shown a high predictive value for cardiovascular events [2-3]. As suggested by 2007 ESH/ESC hypertension guidelines, the evaluation of global cardiovascular risk should take into account subclinical target organ damage beyond traditional CV risk factors [3]. However, it is still not clear the impact of organ damage among different risk categories. Also the identification of metabolic syndrome, an easy and practical clinical task, has been advocated in the guidelines as a potential CV 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 CV risk by risk charts can be ameliorated by adding target organ damage (TOD) and metabolic syndrome.

According to available literature we attempted to critically discuss in this article 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 metabolic syndrome (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 CV 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**

Based on 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 papers in English available until March 2011 on www.Pubmed.com by introducing the following 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 200 subjects at least, with priority for those study published after 2000 and for 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 SCORE project
SCORE is a widely used risk charts for CV risk stratification in healthy subjects. It is based on risk functions derived from the analysis of 12 European cohort studies and calculates 10-year risk of CV death based on: age, gender, systolic blood pressure, 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 second one on total cholesterol/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 since 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 populations subgroups. Electrocardiography is commonly used in the routine assessment of subjects with high blood pressure as well as practically in all other groups of subjects carrying CV risk factors. Though sensitivity is low, LVH detected by the Sokolow-Lyons index (SV1+RV5–6 >38 mm) or by the Cornell voltage QRS duration product (>2440mm*ms) is an independent predictor of cardiovascular events [3;5-16]. LVH has been shown to be predictive of major CV 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 50g/m2 LVH increase, there was a RR of death of 1.73 (95% CI 1.19 to 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 (non fatal MI, cardiac death, coronary revascularization, and stroke) even after adjusting for other risk factors with a HR of 1.88 in men and 1.92 in women. Among American Indians enrolled in the Strong Heart Study (64% female, mean age 58 years), the LVH prevalence on echocardiography was 9.5% and conferred a 7-fold increase in CV mortality and a 4-fold increase in all-cause mortality [17]. Of note, in hypertensive subjects left ventricular mass showed a linear correlation with CV risk, which extended even below the conventional cut-off levels for LVH [18]. Specifically, regarding the ECG-detected LVH, the Framingham cohort subjects in the highest quartile of ECG-LVH displayed a 3-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 CV 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 CV risk [8; 19-20]. Recently, a LIFE substudy showed that in subjects with low in-treatment ECG-LVH the rate of fatal and non-fatal CV events was strongly reduced, regardless of blood pressure reduction [21]. In fact, after controlling for possible confounders in Cox regression models, the composite CV end point
(cardiovascular death, fatal or non-fatal myocardial infarction, and fatal or non fatal stroke) was 14% lower for every decrease in one standard deviation (1050- mm*ms) in Cornell product and 17% lower for every decrease in one standard deviation (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 [22-23]. 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/m2 in LV mass (corresponding to one standard deviation of baseline value) was associated with a reduction of 22% of the primary composite end point during 4.6 years of follow-up, even after adjusting for possible confounders [24]. In a recent meta-analysis that involved five prospective studies (2,449 subjects 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 CV events. The overall adjusted HR was 0.54 for LVH regression/persistent normal LV mass vs LVH persistence/LVH development [25]. It should also be mentioned that without ultrasound investigations for left ventricular hypertrophy and vascular thickening or plaques, a significant portion of hypertensive subjects, especially if men older than 50 years old, 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; 26]. Despite this it is still necessary to perform new specific studies, which 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 [26].

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 to 5 of CKD correspond to eGFR levels of ≥90, 60-89, 30-59, 15-29 and less than 15 ml/min/1.73m2. Stage 3 (eGFR <60 ml/min/1.73m2) 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 [27]. Reduced eGFR is associated with high prevalence of CVD risk factors, CVD surrogates and clinical CVD [28] and it has been repeatedly found to be an independent risk factor for CVD outcome in high-risk populations [29-34] and in hypertensive patients [35-37]. Shara et al. showed in a large cohort with high prevalence of diabetes that, compared with subjects whose eGFR was ≥90 at baseline, those in the <30, 30-59 and 60-89 categories using either Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault (CG) equation, had increased risk of incident CVD [34]. In 2006 a pooled analysis of four community-based studies involving 26147 subjects showed that the presence of stage 3 of CKD was an independent risk factor for cardiac events, stroke and death (HR: 1.26; CI 95%; 1.16 to 1.35; P<0.0001) [38]. 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 < 60ml/min/1.73m2 compared with those with higher values [39]. In 2010 the Chronic Kidney Disease Prognosis Consortium published a collaborative meta-analysis involving 105872 subjects from 21 general
population cohorts. This meta-analysis showed that eGFR and albuminuria were associated with all cause mortality and CV mortality, independently of each other and of traditional CV risk factor. The risk for CV mortality became significant around eGFR 60ml/min/1.73m² (HR 1.40) and even grew for smaller value of eGFR (HR: 1.99 when eGFR 45ml/min/1.73m²; HR: 2.66 when eGFR 15ml/min/1.73m²). Besides, eGFR lower than 60ml/min/m² 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 [40].

A relationship between eGFR <60 ml/min/1.73m² values and the risk of CV mortality and morbidity has been reported even in low risk population [41-46]. A study involving more than 1 million subjects showed that the progressive decline of eGFR was associated with an increase in the risk of mortality. EGFR values ranging 45-59, 30-44, 15-29 and <15 ml/min/1.73m², were associated with 1.2, 1.8, 3.2 and 5.9 fold increase in mortality, when compared with individuals with preserved renal function (eGFR≥60ml/min/1.73m²). Similarly, the hazard ratios for CV events progressively increased with the impairment of glomerular filtration [42]. Interestingly, evidence also suggest that even minor declines of renal function, can be associated with increased risk of CV mortality and morbidity [47-49]. It has been calculated that a decrease in eGFR of 5ml/min/1.73m² within the 116.9 and 16.8 ml/min/1.73m² range is associated with a 26% increase in CV mortality risk [48]. Similar results were obtained also in a cohort of healthy people [50] and in elderly subjects [27]. The Atherosclerotic Risk in Communities Study found a 16% increase CV risk for those subjects with a eGFR value above 60 ml/min/1.73m² as compared with those displaying a normal renal function (eGFR above 90 ml/min/1.73m²) [49].

More recently, a cohort study involving hypertensive patients showed that eGFR <60 ml/min/1.73m² was related to the presence of CVD regardless of CV 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) [51]. 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 CV risk compared with MDRD Study equation, suggesting improved clinical usefulness [52]. However, prospective studies addressing the predictive value of eGFR beyond SCORE in clinical practice are still lacking. This aspect is of utmost importance since a simple and reliable index of renal function as eGFR could increase disproportionately the accuracy of available scores in the prediction of CV 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 microgr/min or between 30-300mg/24h or 20-200mg/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 ≥ 22 mg/gr (males) and ≥ 31 mg/gr (females) and less than 300 mg/mmol [53]. Excretion of urinary albumin in the MAU range can be considered a candidate prediction biomarker for CVD risk for several reasons.
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 CV events and total mortality may be extended to diabetic and non diabetic individuals, hypertensive patients and general population [53-64]. 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 to 2.52), and MAU was associated with a nearly 50% greater risk (RR 1.47; 95% CI 1.30 to 1.66) of CHD [65]. Recently a LIFE substudy showed that in hypertensive patients with LVH fatal and non fatal cardiovascular events increased disproportionately across deciles of MAU, strongly suggesting a linear relation between MAU and raised CV risk [66]. Moreover it has been shown that MAU is independently associated with CV mortality with such a relationship maintained even within normal range of UACR [67-69]. Indeed, in the large Netherlands cohort of the PREVEND study, after adjustment for CV 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 [68]. Similar results have been supported in 2010 by a collaborative meta-analysis by Chronic Kidney Disease Prognosis Consortium. Albumin to Creatinine (ACR) ratio was associated with risk of CV mortality linearly without threshold effect. Compared with ACR 0.6 mg/mmol, hazard ratio for cardiovascular mortality were 1.27 for ACR 1.1 mllg/mmol, 1.77 for 3.4 mg/mmol and 2.43 for 33.9 mg/mmol [40].

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: (1) triglycerides ≥150 mg/dl; (2) HDL cholesterol <40 mg/dl for men and <50 mg/dl for women; (3) blood pressure ≥130/85 mm Hg; (4) obesity as defined by a waist circumference ≥88 cm for women and ≥102 cm for men; and (5) abnormal glucose metabolism as defined by a fasting glucose ≥110 mg/dl [70].

The relationship between MetS, as defined by the WHO [71-73], the IDF [71; 74] and the ATPIII [70; 73-81], and CV 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 [72; 74; 79; 82] 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 [71; 83]. Several European [73; 75; 78] and American longitudinal studies [76-77, 80] explored the relation between MetS and CV mortality, observing a 2.1 fold increase in the risk of all-cause mortality and a 3.6 increase in CV mortality, in patients free of CVD and diabetes [73]. An association between the number of MetS criteria and mortality from CVD has been also reported [80; 84]. Even if MetS could be an independent risk factor for mortality associated with a worse prognosis than its individual components [77; 84], Mancia et al. recently reported that increased risk for CV and all-cause mortality in MetS subjects was related only to blood pressure and to blood glucose component of the syndrome, with no contribution of the remaining components [75]. Since evidence about the ability of MetS to assess CV risk is quite conflicting, its usefulness in predicting
CV 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 subjects at high risk of CV death beyond those identified by SCORE. A total of 2790 middle age men without diabetes have been followed for CV 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 CV mortality than those subjects without. Low risk men with MetS had an HR 2.26 (CI 95%: 1.09-4.68) for the endpoint as compared to men without MetS. In contrast, in the high-risk population (SCORE ≥5%) HR for CV death in presence of MetS was 1.08, (CI 95%: 0.68-1.72, n.s.). Most likely, in this the later risk was mainly driven by the classic CV risk factors. Furthermore, people at low cardiovascular risk (SCORE<5%) with MetS have the same cumulative hazards for CV death than people at high risk (SCORE ≥5%) without MetS [85].

The addition of subclinical organ damage to SCORE
Sehestedt et al. [86] investigated whether organ damage could improve CV risk prediction beyond SCORE. In an apparently healthy population subclinical organ damage as well as the number of damaged organs was associated with increased CV 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 subjects with SCORE ≥5% 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 subjects with SCORE ≥5% could be used to identify subjects eligible for particular intensive primary prevention. Even in individuals with SCORE <5%, the risk estimation tended to be higher when organ damage was factored in. In contrast, subclinical organ damage detection did not improve CV risk prediction among subjects with SCORE <1%. Based on these findings the authors concluded that the most efficient approach would be only to measure subclinical organ damage in subjects with SCORE between 1 and 5% rather than in subjects with SCORE <1%.

Other studies have investigated the predictive value of TOD on CV risk, showing, for instance, a strong association of MAU in patients with hypertension. Leoncini et al. 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 work up. The simultaneous evaluation of urinary albumin excretion and creatinine clearance resulted in a significantly greater change in risk stratification, since 68% of patients were reclassified in the high/very high risk class [87]. Viazzi et al. reported that the combination of albuminuria assessment and CV 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 work-up (73% versus 42%) [87-88].

Results provided by Sehestedt et al. allow reclassification of the CV risk as defined by SCORE by simply adding LVH and MAU figures (figure 1). In subjects with a SCORE ≥5% the CV risk would actually be doubled, when taking into account the presence of each these two markers of TOD. In patients with a SCORE <5% the presence of LVH almost double the CV 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<5%. In fact, these patients in the presence of MAU would become at high CV risk by having CV death odds more than three-fold higher compared to those patients without MAU [86]. 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 of our analysis, we selected from www.Pubmed.gov those most relevant studies, including meta-analysis, published between 2000-2011 about the cardiovascular prognostic implications of the presence of TOD. We excluded small investigations and substudies and we not use other search database. Since we searched the literature for studies with at least 200 subjects included, 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 non homogenous 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 while 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 while 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 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 Sehestedt’s population.

Conclusions:
The search of the best possible estimate of CV risk in individual subjects represents a major need on 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 CV 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 since there are still non conclusive prospective studies comparing different CV 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 CV 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 [89], the SCORE [86] and the Progetto Cuore [90-91] 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 largely available, easy to obtain and cheap.

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Figure 1 Legend: The reassessment of cardiovascular risk using indexes of TOD in groups of subjects with different SCORE

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<th>Cardiovascular risk assessment in presence of subclinical organ damage</th>
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: low risk at 10 years;  : intermediate risk at 10 years;
: high risk at 10 years;  : very high risk at 10 years

LVH: left ventricular hypertrophy; MAU: microalbuminuria