Risk prediction is improved by adding markers of subclinical organ damage to SCORE

Thomas Sehestedt1,2*, Jørgen Jeppesen1, Tine W. Hansen2,3, Kristian Wachtell4, Hans Ibsen5, Christian Torp-Petersen6, Per Hildebrandt1, and Michael H. Olsen1

1Department of Internal Medicine, The Cardiovascular Research Unit, Glostrup University Hospital, Nordre Ringvej 57, Glostrup 2600, Denmark; 2Research Center for Prevention and Health, Copenhagen, Denmark; 3Department of Clinical Physiology and Nuclear Medicine, Hvidovre University Hospital, Hvidovre, Denmark; 4Department of Cardiology, Rigshospitalet, Denmark; 5Department of Internal Medicine, Holbæk Hospital, Holbæk, Denmark; and 6Department of Cardiology, Gentofte University Hospital, Gentofte, Denmark

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Aims
It is unclear whether subclinical vascular damage adds significantly to Systemic Coronary Risk Evaluation (SCORE) risk stratification in healthy subjects.

Methods and results
In a population-based sample of 1968 subjects without cardiovascular disease or diabetes not receiving any cardiovascular, anti-diabetic, or lipid-lowering treatment, aged 41, 51, 61, or 71 years, we measured traditional cardiovascular risk factors, left ventricular (LV) mass index, atherosclerotic plaques in the carotid arteries, carotid/femoral pulse wave velocity (PWV), and urine albumin/creatinine ratio (UACR) and followed them for a median of 12.8 years. Eighty-one subjects died because of cardiovascular causes. Risk of cardiovascular death was independently of SCORE associated with LV hypertrophy [hazard ratio (HR) 2.2 (95% CI 1.2–4.0)], plaques [HR 2.5 (1.6–4.0)], UACR ≥90th percentile [HR 3.3 (1.8–5.9)], PWV >12 m/s [HR 1.9 (1.1–3.3)] for SCORE ≥5% and 7.3 (3.2–16.1) for SCORE <5%. Restricting primary prevention to subjects with SCORE ≥5% as well as subclinical organ damage, increased specificity of risk prediction from 75 to 81% (P < 0.002), but reduced sensitivity from 72 to 65% (P = 0.4). Broaden primary prevention from subjects with SCORE ≥5% to include subjects with 1% ≤SCORE <5% together with subclinical organ damage increased sensitivity from 72 to 89% (P = 0.006), but reduced specificity from 75 to 57% (P < 0.002) and positive predictive value from 11 to 8% (P = 0.07).

Conclusion
Subclinical organ damage predicted cardiovascular death independently of SCORE and the combination may improve risk prediction.

Keywords
Risk stratification • SCORE • Atherosclerotic plaques • Albuminuria • Pulse wave velocity • Left ventricular hypertrophy

Introduction
Systemic Coronary Risk Evaluation (SCORE) is one of the most used risk charts for cardiovascular risk stratification of healthy subjects. It is based on a risk function derived from the analysis of 12 European cohort studies and calculates 10-year risk of cardiovascular death using five traditional risk factors: age, gender, systolic blood pressure, cholesterol, and smoking.1 Furthermore, through combining national mortality statistics, SCORE also provides risk charts calibrated to each country. Subjects with a SCORE ≥5% are considered eligible for primary prevention.2 Although the vast majority of cardiovascular events occur among subjects with at least one elevated traditional risk factor,3 the positive predictive values of the traditional cardiovascular risk factors are low in healthy subjects. As most subjects have a SCORE <5%, the majority of cardiovascular endpoints may actually occur in this low-risk group emphasizing the need for new and better risk markers. Therefore, European Society of Cardiology recommends in their guidelines for prevention of cardiovascular disease that subjects with markers of subclinical organ damage are allocated to a higher risk category than that calculated with SCORE.2 These markers are believed to be precursors and predictors of cardiovascular disease and are an integrated part of the risk chart for hypertension from the European Society of Hypertension (ESH).4

* Corresponding author. Tel: +45 305 40 515, Fax: +45 432 33 950, Email: ts@heart.dk
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The aim of this study was to investigate whether markers of subclinical organ damage predict cardiovascular death independently of SCORE and whether they together with SCORE improve the selection of apparently healthy subjects for primary intervention. To clarify this issue, we examined 1968 subjects in a Danish random population and recorded cardiovascular events during a median follow-up of 12.8 years. In addition to the risk factors used in SCORE, we measured four different types of subclinical organ damage at baseline, all previously being associated with increased cardiovascular risk in the general population: increased pulse wave velocity (PWV), as a marker of increased arterial stiffness; presence of atherosclerotic plaques, as a marker of atherosclerosis; increased urine albumin/creatinine ratio (UACR), as a marker of vascular damage; and increased left ventricular (LV) mass, as a marker of cardiac hypertrophy.

**Methods**

The participants in our study originated from a population survey in Glostrup County, Copenhagen, started in 1982–1984 as part of the MONItoring of Trends and Determinants in CArdiovascular Disease (MONICA) health surveys. A total of 3971 (82.6%) accepted the original invitation. In 1993–1994, 3783 previous participants were re-invited for a follow-up examination and 2656 (70.2%) accepted the invitation. At that time, they were aged exactly 41, 51, 61, or 71 years. We wanted to risk stratify healthy subjects so we excluded 688 (25.9%) subjects with self-reported previous myocardial infarction, stroke, diabetes, or a fasting plasma glucose ≥7.0 mmol/L at baseline examination, subjects taking cardiovascular, anti-diabetic, or lipid-lowering drugs as well as subjects with missing information on risk factors or measurements of subclinical damage as described below. This left us with 1968 subjects for this study.

All participants have given informed written consent and the study was conducted in accordance with the Helsinki Declaration and approved by the local Ethics Committee.

Anthropometric characteristics were measured by a trained nurse. Body mass index was calculated. Waist circumference was measured as the largest circumference located between the lower rib and the iliac crest. Office blood pressure was measured sitting after 5 min of rest with a random zero mercury sphygmomanometer fitted with a correct cuff size, and the mean of two consecutive measurements was recommended. Hypertension was defined as blood pressure ≥140/90 mmHg. Venous blood samples collected after overnight fasting were analysed for lipids and blood glucose by standard automated methods. All participants were encouraged to complete a questionnaire concerning previous and current cardiovascular disease, diabetes, intake of medication, and lifestyle.

**Echocardiography**

Using M-mode and two-dimensional techniques, one experienced physician blinded for all other information carried out and read all measurements. The internal dimension of the left ventricle and wall thickness were measured at end-diastole and LV mass was calculated according to the guidelines from the American Society of Echocardiography. Left ventricular mass index (LVMI) was LV mass divided by body surface area, calculated with the Dubois’ formula.

**Pulse wave velocity**

Two transducers were placed over the common carotid artery and the femoral artery, and PWV was calculated as the distance between the two transducers divided by the recorded time delay for the pulse wave.

**Arteriosclerotic plaques**

Using B-mode ultrasound, the common carotid artery on both sides was examined identifying arteriosclerotic plaques defined as a local thickening of the intima-media layer of more than 50% or a local, sharp increase in echo-density with shadowing.

**Urine albumin/creatinine ratio**

Urine albumin concentration was measured by standard methods using a turbidimetric method (Hitachi 717 analyzer, Roche Diagnostics, Mannheim) on a single morning urine sample. Urine creatinine was analysed using the Jaffé reaction without deproteinizing and then quantified by a photometric method (Hitachi 717 analyzer, Roche Diagnostics).

Subclinical organ damage was defined according to the guidelines from the ESH as LVMI ≥125 g/m² for men or ≥110 g/m² for women, PWV > 12 m/s or presence of one or more arteriosclerotic plaques. However, based on recent data, we used a cut-off value of 0.73 mg/mmol for men and 1.09 mg/mmol for women for UACR corresponding to the 90th percentile in our sample of 1968 healthy subjects.

**SCORE**

We calculated the 10-year risk of cardiovascular death using the risk chart for a high risk population. The age of the participants in our study were fitted to the age categories in SCORE and subjects aged 41, 51, 61, and 71 were set to 40, 50, 60, and 65 years, respectively. SCORE < 1% corresponds to low risk, ≥1 and <5% to moderate risk, ≥5% and <10% to high risk, and ≥10% to very high risk. For simplification, we divided the results into SCORE < 5% and SCORE ≥ 5%, combining the low and moderate risk categories as well as the high and very high risk categories, respectively.

We constructed three new risk chart models for primary prevention. Model 1 required presence of both SCORE ≥ 5% and subclinical organ damage, whereas Model 2 required presence of either SCORE ≥ 5% or subclinical organ damage before primary prevention was recommended. Model 3 required SCORE ≥ 5% alone or 1% ≤ SCORE < 5% plus presence of subclinical organ damage. These three models were compared with the SCORE risk chart where primary prevention is recommended if SCORE ≥ 5%.

Vital status of all participating individuals was ascertained through the Danish Civil Registration System until December 2006. The endpoint was cardiovascular death (ICD-10 codes I00-79 and R95-99) and information on cardiovascular mortality was obtained from the Central Death Registry. Eleven subjects were lost to follow-up.

**Statistics**

Data are presented as mean ± standard deviation and median with inter-quartile range for continuous variables and proportions for categorical variables. The 95% confidence intervals for proportions and for differences between proportions were calculated with methods described by Newcombe. The z-ratio was used to test if differences between proportions were significant. Hazard ratios (HRs) for cardiovascular death were assessed using multiple Cox-regression analysis. All variables in the models were tested for linearity and proportional hazard assumption. The prognostic importance of the different types of subclinical organ damage was tested for interaction with age, gender, hypertension, and SCORE. In case of interaction, the population was divided based on the
interactive factor. When evaluating cardiovascular mortality according to total number of different types of subclinical damage and according to SCORE categories and presence of subclinical organ damage, subjects experiencing any other mode of death were censored. The Kaplan–Meier estimator is not applicable for estimating probabilities of particular modes of death in a competing risk model and the cumulative incidence functions were estimated from the cause-specific Cox-models using a custom-built program. The incremental value of adding markers of subclinical organ damage to SCORE was summarized by means of the Harrell’s C-statistic from a Cox-model, which is conceptually analogous to the C-statistic estimated from logistic models, but it allows for right-censored data and variable follow-up. In that analysis, subclinical organ damage was analysed as a continuous variable (0–4). The confidence interval for the difference in C-statistics between models was calculated by bootstrap sampling. From the same Cox-models, the net reclassification improvement (NRI) measure was calculated to assess the extent to which addition of subclinical organ damage to SCORE reassigned subjects to risk categories that better reflected their final outcome. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC, USA) and R, version 2.8.1. A P-value of <0.05 on two-sided tests was considered statistical significant.

Results

During a median follow-up of 12.8 years (5–95th percentile 12.1–13.4), a total of 253 deaths occurred. Of the 81 deaths due to cardiovascular diseases, 12 were due to stroke and 22 were due to ischaemic heart disease, of which 15 had fatal myocardial infarction. There was an equal sex distribution and 47% were smokers in our sample. Four hundred and twenty-nine (22%) had SCORE, 1% 15 (52%) 1% ≤ SCORE < 5%, 322 (16%) 5% ≤ SCORE < 10%, and 202 (10%) SCORE ≥ 10%. The corresponding absolute event rates of cardiovascular death were 0.2, 1.8, 7.2, and 14.7 per 1000 person-years, respectively. Eighty percentage of the subjects with SCORE ≥ 5% had subclinical organ damage and only 29% in the group with SCORE < 5%. The different subtypes of subclinical damage in subjects with SCORE ≥ 5%/SCORE < 5% were distributed in the following way: 85 (16.2%)/113 (7.8%) subjects had UACR ≥ 90th percentile, 293 (55.9%)/171 (11.8%) subjects had PWV > 12 m/s, 63 (12.0%)/38 (2.6%) subjects had LV hypertrophy, and 258 (49.2%)/182 (12.6%) subjects had presence of atherosclerotic plaques. Baseline characteristics of participants with and without an event are shown in Table 1. All four measured markers of subclinical organ damage were significantly associated with increased cardiovascular risk in a multiple Cox regression.
Table 2 Hazard ratios for cardiovascular death for markers of subclinical organ damage in multiple Cox regression models

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each marker separately, adjusted for age and gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV hypertrophy (n = 101)</td>
<td>2.2</td>
<td>(1.2–4.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Atherosclerotic plaques (n = 440)</td>
<td>2.1</td>
<td>(1.3–3.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>PWV &gt; 12 m/s (n = 464)</td>
<td>2.0</td>
<td>(1.2–3.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>UACR &gt; 90th percentile (n = 198)</td>
<td>2.4</td>
<td>(1.4–4.0)</td>
<td>0.0009</td>
</tr>
<tr>
<td>SCORE plus each marker separately SCORE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV hypertrophy ≥5%</td>
<td>2.2</td>
<td>(1.2–4.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>LV hypertrophy &lt;5%</td>
<td>1.9</td>
<td>(1.3–13.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Atherosclerotic plaques ≥5%</td>
<td>2.1</td>
<td>(1.2–3.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Atherosclerotic plaques &lt;5%</td>
<td>3.9</td>
<td>(1.7–9.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>PWV &gt; 12 m/s</td>
<td>1.9</td>
<td>(1.1–3.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>PWV &gt; 12 m/s</td>
<td>7.3</td>
<td>(3.2–16.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UACR &gt; 90th percentile ≥5%</td>
<td>2.2</td>
<td>(1.2–4.0)</td>
<td>0.008</td>
</tr>
<tr>
<td>UACR &gt; 90th percentile &lt;5%</td>
<td>3.4</td>
<td>(1.3–9.3)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

LV hypertrophy, left ventricular hypertrophy; PWV, pulse wave velocity; UACR, urine/albumin creatinine ratio.

*Only PWV had a significant interaction with SCORE (P = 0.008).

Model adjusted for age and gender with HR's between 2.0 and 2.4 (Table 2). The association with increased cardiovascular risk remained significant for all markers in a regression model including SCORE in two categories (<5% or ≥5%) and each marker separately (Table 2). The HR for SCORE itself varied between 5.5 (95% CI 3.3–9.3, P < 0.0001) and 7.4 (95% CI 4.6–12.0, P < 0.0001) in models with presence of plaques and UACR > 90th percentile, respectively. There were no interactions between the different types of subclinical organ damage and age, gender, or hypertension. However, there was a significant interaction between the different types of subclinical organ damage and age, gender, or hypertension. The results of the new risk chart models which added subclinical organ damage to SCORE are shown in Table 4. Model 1 reduced the number of individuals recommended for prevention by 20% and increased specificity significantly by 5% (95% CI 3–8, P < 0.002) compared with SCORE. The positive predictive value increased insignificantly by 2% (95% CI 0.3–7, P = 0.5), but sensitivity was reduced insignificantly by 7% (95% CI 8 to 20, P = 0.4) due to the fact that five events occurred in the 104 subjects who were reclassified into the group without recommendation of primary prevention. Model 2 increased sensitivity significantly by 17% (95% CI 5–29, P = 0.006). However, specificity and the positive predictive value were significantly reduced by 22% (95% CI 19–25, P < 0.002) and 3% (95% CI 0.4–7, P = 0.03), respectively. Model 3 also increased sensitivity significantly by 17% and reduced specificity significantly by 18% (95% CI 15–21, P < 0.002) and positive predictive value insignificantly by 3% (95% CI 0.3 to 6, P = 0.07). Furthermore, Model 3 had 4% (95% CI 0.3–7, P = 0.03) higher specificity than Model 2. All models had high negative predictive values between 98 and 99%. In the different models, it would only be necessary to measure subclinical organ damage in the subjects where the eligibility for primary prevention depended on whether there was presence of subclinical organ damage or not. Since measuring subclinical organ damage can be time-consuming and expensive, it was noteworthy that there was a considerable difference in the total number of subjects in whom examination for subclinical organ...
damage was required: 524, 1444, and 1015 in Model 1, Model 2, and Model 3, respectively.

**Discussion**

In an apparently healthy population sample, we found that the presence of subclinical organ damage as well as the number of organs damaged was associated with increased cardiovascular risk independently of SCORE. Combined risk models of SCORE and subclinical organ damage had major influence on risk stratification and recommendations on primary prevention.

The age and gender adjusted HRs of the individual types of subclinical organ damage varied between 2.0 and 2.4 and were comparable to the age and gender adjusted HRs associated with blood pressure $\geq 140/90$ mmHg, HR 1.7 (95% CI 1.0–2.6), and smoking, HR 2.0 (95% CI 1.3–3.1). However, the association between cardiovascular risk and UACR, LVMI, and PWV is continuous, and the thresholds used in this study and by ESH are arbitrary that makes comparisons of HRs between types questionable and suggest that results may have been different with different thresholds. Furthermore, we found that risk increased with total number of types of organ damage, suggesting a broad examination program including all four types of organ damage. However, the majority only had one or two types of subclinical organ damage and from a practical clinical point of view measuring all four types would not be rational. Measurement of UACR and PWV, which would identify 70% of all subjects with subclinical organ damage, would be favourable as they are both fairly low cost and do not require highly trained personnel in contrast to examining for LV hypertrophy and atherosclerotic plaques. Furthermore, we did not find any difference in type of cardiovascular events in subjects who had increased UACR and PWV compared with subjects with LV hypertrophy and presence of atherosclerotic plaques (data not shown). Other types of subclinical organ damage cost even less and are easier to measure such as the ankle/brachial blood pressure index or electrocardiographic LV hypertrophy. However, these measurements and other modifiers of SCORE such as information on family history of cardiovascular disease, which can be obtained free of cost, were not included in our study and it remains uncertain how this information would have influenced our results.

We found an interaction between PWV and SCORE with higher HR in subjects with SCORE $< 5\%$. This suggests that PWV measurement may be particularly useful in low-risk subjects for instance in younger individuals with genetic disposition for
Figure 2  The cumulative probability (%) and hazard ratios of cardiovascular death in subgroups, according to SCORE and presence of subclinical organ damage. Dotted lines denote the 10 years 5% cumulative probability of cardiovascular death. Subjects with SCORE < 5% and no subclinical organ damage were the reference group. Abbreviation: SOD, subclinical organ damage.

Table 3  Net reclassification improvement using SCORE with and without markers of subclinical organ damage using four risk categories for 10-year risk of cardiovascular death

<table>
<thead>
<tr>
<th>SCORE (%)</th>
<th>Predicted 10-year risk of cardiovascular death: SCORE plus subclinical organ damage</th>
<th>Number of subjects</th>
<th>Reclassified</th>
<th>Increased risk</th>
<th>Decreased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;1</td>
<td>1–5</td>
<td>5–10</td>
<td>≥10</td>
</tr>
<tr>
<td>Subjects without an event (n = 1887)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>406</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>69</td>
</tr>
<tr>
<td>1–5%</td>
<td>307</td>
<td>665</td>
<td>19</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>5–10%</td>
<td>0</td>
<td>163</td>
<td>106</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>≥10%</td>
<td>0</td>
<td>26</td>
<td>68</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Subjects with an event (n = 81)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>1–5%</td>
<td>5</td>
<td>12</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>5–10%</td>
<td>0</td>
<td>9</td>
<td>13</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>≥10%</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>NRI (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
 cardio vascular disease or obese smokers with SCORE < 5% and could provide essential information that would influence life-style counselling. This is in line with a previous study where PWV had higher predictive value among subjects with a low Framingham risk score.18

Measurements of subclinical organ damage have improved risk classification considerably in smaller studies in hypertensive patients,19,20 but there are no larger prospective studies in a healthy population. We did not find any interactions with subclinical organ damage and hypertension, suggesting an equal value of subclinical organ damage as risk predictor in the hypertensive and normotensive population. However, we had excluded subjects who were taking antihypertensive medication and consequently were the hypertensive subjects in our study not necessarily representative of the whole hypertensive population.

We have evaluated three new risk prediction models where information on subclinical organ damage was added to SCORE and used to classify subjects with respect to recommending primary prevention or not. Not surprisingly, none of the new models resulted in increases in both sensitivity and specificity, thus making any firm conclusions on their practical value difficult. Sensitivities and specificities of predictive models represent different clinical values and costs.21 Therefore, an increase in sensitivity in a predictive model at the expense of a reduction in specificity can be acceptable in the context of prevention of fatal outcomes, if the costs of examination and false-positive test results are low.

Presence of subclinical organ damage in subjects with SCORE ≥ 5% identified a subgroup at particular high risk. Consequently, restricting primary prevention to this group (Model 1) reduced the number eligible for primary prevention by 20% and increased specificity compared with using SCORE alone. However, it was accompanied by a 7% reduction in sensitivity which we do not find recommendable. Alternatively, measurement of subclinical organ damage in subjects with SCORE ≥ 5% could be used to identify subjects eligible for particular intensive primary prevention.

Presence of subclinical organ damage in subjects with SCORE < 5% also identified subjects with higher risk than according to SCORE measurements. However, the 10-year event rate of a cardiovascular death did not exceed the 5% threshold in subjects with SCORE < 5% or 1% ≤ SCORE < 5%, unless in the rare occasion that all four types of damage was present in the same individual (data not shown). European Society of Cardiology recommends that subjects with presence of subclinical organ damage should be allocated to higher risk categories in SCORE which resembles Model 3. When compared with Model 2, Model 3 reduced the number needed to be examined for subclinical organ damage by 30% and had significantly higher specificity and similar sensitivity, suggesting that the most efficient approach would be only to measure subclinical damage in subjects with 1% ≤ SCORE < 5% and not in subjects with SCORE < 1%. This would result in recommendation of primary prevention with, for example, a cheap, well-tolerated medication like statins in 70% more subjects (879 vs. 524) in order to intervene against ~25% more future major cardiovascular events (72 vs. 58) compared with using SCORE alone. Measuring only UACR and PWV would decrease cost of the examination program even further and would still identify 12 of the 14 registered events in subjects with 1% ≤ SCORE < 5%.

### Table 4

<table>
<thead>
<tr>
<th>Risk model</th>
<th>SCORE ≥ 5%</th>
<th>SCORE ≥ 5% plus subclinical organ damage present</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCORE ≥ 5%</td>
<td>SCORE ≥ 5% or 1% ≤ SCORE &lt; 5%</td>
<td>SCORE ≥ 5% or 1% ≤ SCORE &lt; 5% plus subclinical organ damage present</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SCORE ≥ 5%</td>
<td>SCORE ≥ 5% or 1% ≤ SCORE &lt; 5%</td>
<td>SCORE ≥ 5% or 1% ≤ SCORE &lt; 5% plus subclinical organ damage present</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- **No**: Cardiovascular deaths 2313444 58524 15484 20 1023 895 495 3 895 495 3
- **Yes**: Cardiovascular deaths 9 72 9 72 9 72 9 72 9

**Score values**: Sensitivity, pct (95% CI) 72 (61–80) 65 (55–75) 89 (80–94)* 89 (80–94)* Specificity, pct (95% CI) 75 (73–77) 81 (79–82)* 54 (51–56)* 57 (55–59)* Positive predictive value, pct (95% CI) 11 (9–14) 13 (10–16) 8 (6–9)* 8 (7–10) Negative predictive value, pct (95% CI) 98 (98–100) 98 (97–99) 99 (98–100) 99 (98–100)

*P < 0.005 for comparison with Model 1.
This would result in a small reduction in sensitivity from 89 to 86%, but an increase in specificity from 57 to 64% with positive and negative predictive values of 9.4 and 99%, respectively.

Our study must be interpreted within the context of its potential limitations. Owing to the small number of events, our results are only hypothesis generating and must be confirmed in a larger prospective study which could also include other markers of subclinical organ damage than the ones used in our study such as ankle/brachial blood pressure index and electrocardiographic LV hypertrophy. Some established disease may have gone unrecognized. However, all subjects taking any cardiovascular, anti-diabetic, or lipid-lowering medication and subjects with missing data were excluded minimizing the problem. We excluded subjects with diabetes, this was not possible in the original SCORE dataset and consequently SCORE may overestimate risk in our population. There was no independent endpoint committee assessing outcome. However, the Danish Central Death Registry has high sensitivity regarding cardiovascular risk. We measured only single-spot urine and UACR has considerably individual variation. However, our spot urine correlated as expected with plasma glucose and blood pressure and predicted outcome in a previous study. Furthermore, we did not evaluate the reproducibility of the PWV measurements at baseline, but the recordings were managed solely by one-trained observer and an intra-observer repeatability of 9.0% has previously been reported. Participant’s blood pressure was classified based on only two blood pressure readings on one single occasion. However, this is in line with previous studies. Finally, we did not have information on initiation of medication during follow-up and are therefore unable to report if there were any differences between groups.

In conclusion, subclinical organ damage predicted cardiovascular death independently of SCORE and the combination may improve risk prediction especially in subjects with 1% < SCORE < 5% as risk prediction of UACR (men/women) ≥ 0.73/1.09 mg/mmol or PWV ≥ 12 m/s in this subgroup in our population identified ~20% more major cardiovascular events by increasing the amounts of subjects at risk by ~40%. However, this will only have clinical relevance if a cheap, well-tolerated, and effective prevention exists.

Funding
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Conflict of interest: none declared.

References
22. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of
A 36-year-old patient was sent for diagnostic work-up of dry cough, chest tightness, and 2 years of increasing dyspnoea. Previously, the patient was physically well and only known for an asymptomatic heart murmur since childhood. A grade III/VI systolic murmur was heard at the left sternal border. Electrocardiogram revealed right ventricular hypertrophy and occasional atrial premature beats. Chest radiograph revealed prominent left pulmonary trunk with increased vascular markings (Panel A), and echocardiography showed enlargement of right atrium and ventricle, moderate tricuspid regurgitation, and pulmonary hypertension (estimated pulmonary pressure 85 mmHg). Cardiac magnetic resonance imaging suspected right pulmonary artery agenesis. We then performed cardiac catheterization for pulmonary hypertension workup. Pulmonary artery pressure was elevated (84/19/46) and angiography showed a total absence of right pulmonary artery (RPA) with left pulmonary artery (LPA) engorgement (Panel B). Incidentally, we found a tortuous coronary fistula raising from the right coronary artery (RCA) supplying the right lung field (Panels C and D). To reveal a possible coronary steal, we suggested further stress study by Treadmill exercise test but the patient refused and was treated with oral nifedipine for control of pulmonary hypertension thereafter. Her estimated pulmonary pressure was the same during half-year follow-up, and her symptoms were stationary.

In patients with pulmonary atresia with ventricular septal defect, unilateral pulmonary artery hypoplasia with collateral blood flow, mostly from systemic and rarely from coronary artery supplying the corresponding lung territory, is common. The anomaly was thought to result from early recanalization of coronary artery to bronchopulmonary anastomoses due to regional reduction in pulmonary blood flow. Here, we report a rare case of isolated RPA agenesis with right lung blood supply mainly from RCA possibly through the same embryologic mechanism.

Supplementary material is available at European Heart Journal online.