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FULL RESEARCH PAPER
Arterial Hypertension

SCORE underestimates cardiovascular mortality in hypertension: insight from the OLD-HTA and NEW-HTA Lyon cohorts

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Aims Current European guidelines recommend the SCORE to estimate 10-year cardiovascular mortality in patients with moderate/low cardiovascular risk. SCORE was derived from the general population. The objective of this study was to investigate the estimated 10-year cardiovascular mortality according to the SCORE in a historic and a contemporary cohort of hypertensive patients.

Methods and results After exclusion of secondary prevention and diabetes, 3086 patients were analysed in the OLD-HTA (1969–90) and 1081 in the NEW-HTA (1997–2014) Lyon cohorts. SCORE was calculated using the low and high cardiovascular risk equations and charts, and patients classified as being at low (0%), moderate (1–4%), high (5–9%), and very high (≥10%) risk. In the OLD-HTA cohort, 10-year cardiovascular mortality was higher (1.2%, 5.5%, 17.7%, and 27.0%) than that predicted by the low-risk equation (0%, 1.7%, 6.4%, and 14.8%). In the NEW-HTA cohort, similar results were observed (1.1%, 4.7%, 15.1%, and 15.2% vs. 0%, 1.9%, 6.2%, and 11.7%, respectively). Using the high-risk equation, mortality was underestimated in both cohorts, but the difference was smaller. The diagnostic performance of the high-risk equation was lower than the low-risk equation in both cohorts, considering the SCORE as a continuous or a categorical variable (Likelihood ratio test $P < 0.05$ for all comparisons in OLD-HTA). Similar results were obtained using SCORE charts.

Conclusion SCORE underestimates the 10-year cardiovascular mortality risk in hypertensive patients in a historic cohort and in a contemporary one. The algorithm to predict cardiovascular mortality in hypertensive patients needs an update given new information since its creation.

Keywords Hypertension • Cardiovascular mortality • Cardiovascular prevention • SCORE • Hypertension-mediated organ damage

Introduction

Risk stratification in hypertensive patients is largely based on the prediction of 10-year cardiovascular mortality by SCORE as recommended by the European guidelines on cardiovascular disease (CVD) prevention.[1,2] Whether SCORE is adapted to hypertensive patients remains uncertain. Indeed, SCORE was developed on large European cohorts issued from the general population in the 70s and in the first part of the 80s,[3] and the prevalence of hypertension or of uncontrolled hypertension in these cohorts was very low.[3] Risk equations were provided for high- and low-risk regions according to different European countries, yet several limitations of SCORE were underlined particularly the absence of separate charts for diabetes, absence of risk estimation for patients <40 years, and lack of screening of hypertension-mediated organ damage (HMOD).[4] Furthermore, some specific subgroups of patients were not fully evaluated in the SCORE project[3]; they were arbitrarily reclassified as high risk (markedly elevated single risk factor, such as blood pressure—BP ≥180/110 mmHg, diabetes mellitus, or HMOD) or very high

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risk (overt CVD, diabetes mellitus with target organ damage, and/or severe chronic kidney disease).[2] This is of great importance as such reclassification has marked implications in terms of risk factor management.[5] In addition, since its publication, the need for its recalibration has been emphasized in some countries including Denmark.[4] In France, the calibration was not confirmed by the analysis of other cohorts, moreover, the low prevalence of hypertension in cohorts used in the SCORE project questions its applicability to this setting.[3]

The prognostic value of SCORE has never been tested in hypertensive patients and particularly those with intermediate or high risk that are not as closely monitored and treated as other conditions, such as diabetes or secondary prevention.[5,6] The aim of this study was to test the performance of SCORE in two different cohorts of hypertensive patients: the OLD-HTA cohort which is contemporary to the studies used for the development of the SCORE and the NEW-HTA cohort, which is more indicative of current hypertensive disease.

Methods

Patients

In the seventies, hypertension was defined by an office BP >160/95 mmHg; since 1977, the threshold was set at 140/90 mmHg.[7] The OLD-HTA Lyon cohort comprises 4061 patients who visited the cardiology department of the Louis Pradel Hospital (Lyon, France) for a work-up of their hypertension between January 1969 and December 1990 and who have extensive followed-up. The first part of this cohort (January 1969–December 1976) have been previously described.[8] Herein, we also used the second period of recruitment of the OLD-HTA cohort (January 1977–December 1990). The NEW-HTA cohort started in the nineties and is still recruiting in the cardiology department of the Croix-Rousse Hospital (Lyon, France).[9] Currently, the data of 1611 patients included from January 1997 to January 2014 are available. In this study, we excluded from both cohorts patients lost to follow-up, those data missing for the calculation of the SCORE, and those at very high risk [secondary prevention for stroke, heart failure, and peripheral or coronary artery disease; diabetes mellitus; or estimated glomerular filtration rate (eGFR) <30 mL/min]. A total of 3086 patients fulfilled these criteria in the OLD-HTA and 1081 in the NEW-HTA (*Figure 1*).

In the OLD-HTA cohort, oral consent was obtained from all patients in accordance with the French legislation prevailing in the 1970s. The study was approved by the local review board and by the national data protection commission (*Commission Nationale Informatique et Liberté*, CNIL). Under French law, as mentioned in several published technical notes, in line with European directives, only the approval of the CNIL is required for single-centre observational usual-care studies, such as the one reported here.[10] The NEW-HTA cohort was approved by the ethics committee and written informed consent was obtained from all patients. The vital status query was approved by national authorities before data extraction by the office for national statistics (*Institut National de la Statistique et des Etudes Economiques*, INSEE).

Baseline work-up

A standardized form, which has modestly changed over the study periods, was filled out for each patient. It included various morphometric characteristics, risk factors for cardiovascular events (smoking status, alcohol intake, salt consumption, etc.), history of CVD, current medication, and known symptoms as previously described.[8,9]

Smoking status was based on current tobacco consumption or stopped <5 years previously. In the OLD-HTA cohort, BP was measured with a manual sphygmomanometer in the supine position. Systolic BP (SBP), diastolic BP, and pulse pressure (PP) were recorded as the mean of six measurements. Mean daytime BP measured with oscillometric devices was used in the NEW-HTA cohort. Three grades of hypertension were defined as proposed by the current guidelines.[1] As mean daytime BP may underestimate office BP from 5 to 20 mmHg, an additional analysis was performed in the NEW-HTA cohort by arbitrarily increasing SBP by 10 mmHg for each patients.[11,12] An overnight fasting blood sample was drawn for haemogram and plasma measurements (electrolytes, creatinine, glucose, and total cholesterol). Diabetes was retrospectively identified by either fasting glucose ≥1.26 g/L (≥7.0 mmol/L) on two separate occasions, or current use of antidiabetic medication. Renal function was estimated using the Modification in Diet in Renal Disease (MDRD) formula to assess the eGFR. CKD-EPI equation was not used as this requires a specific creatinine measurement (isotope dilution mass spectrometry) that was not available during the enrolment of the OLD-HTA cohort. Previous CVD included history of heart failure, coronary artery disease, peripheral arterial disease, and stroke.

Assessment of the SCORE

We measured SCORE using the low-risk equation appropriate for France and described by Conroy *et al.*[3] as it may lead to a different estimation of the SCORE in older patients, in those with very high BP, or high total cholesterol (SCORE equation). These formulas are detailed in the Supplementary material online. SCORE was also calculated according the guidelines using the low cardiovascular risk chart.[1,2] These charts are used to define 10-year cardiovascular mortality risk by selecting the cell nearest to the patient's age, BP, and total cholesterol.[2] For patients younger than 40 years, SCORE was calculated as for those 40 years of age; for those with grade 3 hypertension SCORE was calculated as for those with 180 mmHg of SBP. For exploratory analyses, SCORE was also estimated using the high-risk SCORE equation and chart developed for eastern European countries.[3] Patients were then classified according to four subgroups using the SCORE equation or chart: low risk (SCORE <1%), moderate risk (1% ≤ SCORE <5%), high risk (5% ≤ SCORE <10%), and very high risk (SCORE ≥ 10%).

Assessment of HMOD

HMOD was defined in the present study as previously described[13]: heart involvement in case of electrical left ventricular hypertrophy (LVH) using a Sokolow index >3.5 mV, pulse pressure >60 mmHg in patients >60 years old, and kidney involvement in case of eGFR <60 mL/min/1.73 m^2.

Assessment of outcomes

Deaths at 10 years of follow-up were obtained from the *Répertoire National d'Identification des Personnes Physiques* (RNIPP; a directory maintained by the INSEE). All subjects not officially declared dead were considered to be alive at the end of follow-up. The primary endpoint was cardiovascular death (stroke, heart failure, myocardial infarction, or sudden death) as classified by the French national Epidemiological Center On Medical Causes Of Death (*Centre d'Epidémiologie sur les Causes Médicales de Décès*, CépiDC).[14]

Statistical analyses

Continuous variables approximating normal distributions were summarized as mean ± standard deviation (SD). Continuous variables with skewed distributions were summarized as median (interquartile range, IQR). Categorical variables were expressed as percentages. Analysis of

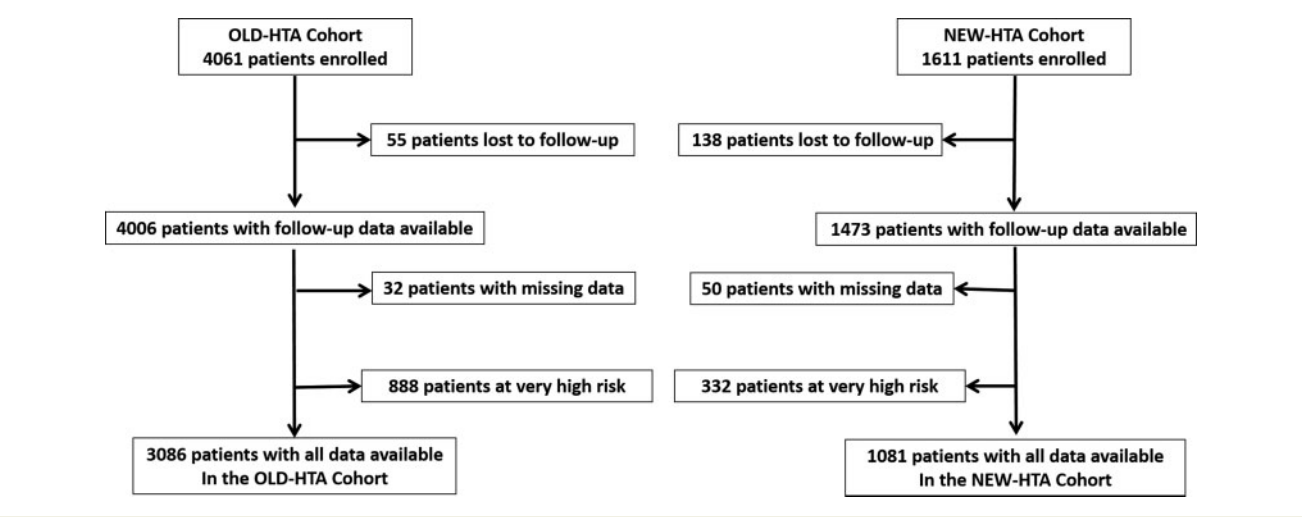

Figure 1 Study flowchart.

Table 1 Baseline characteristics of the OLD and NEW HTA cohorts

Characteristics	OLD-HTA cohort *N* = 3086	NEW-HTA cohort *N* = 1081	*P* values
Demographic			
Mean age (years)	43.2 ± 13.9	48.2 ± 14.3	<0.001
Men, *n* (%)	1747 (56.6)	537 (49.7)	<0.001
Current smoking, *n* (%)	1386 (44.9)	217 (20.1)	<0.001
BMI (kg/m^2)	25.2 ± 4.6	26.3 ± 4.8	<0.001
Cardiac			
SBP (mmHg)	170 ± 33	153 ± 19	<0.001
DBP (mmHg)	99 ± 19	94 ± 13	<0.001
Grade 3 hypertension, *n* (%)	1250 (40.5)	168 (15.5)	<0.001
Target organ damages			
ECG LVH (%)	349 (11.3)	141 (13.0)	0.136
Pulse pressure >60 mmHg in patients aged >60 years (%)	146 (4.7)	102 (9.4)	<0.001
Biochemical			
eGFR (mL/min)	83 (69–99)	88 (74–102)	<0.001
eGFR <60 mL/min, *n* (%)	395 (12.8)	78 (7.2)	<0.001
Total cholesterol (mmol/L)	5.8 ± 1.2	5.3 ± 1.0	<0.001
Number of antihypertensive treatment	0 (0–2.0)	1.0 (0–2.0)	<0.001
Low-risk SCORE equation	1.0 (0.0–3.0)	1.0 (0.0–3.0)	0.060
High-risk SCORE equation	2.0 (1.0–5.0)	2.0 (0.0–5.0)	0.006
Low-risk SCORE chart	1.0 (0.0–3.0)	1.0 (0–3.0)	0.052
High-risk SCORE chart	2.0 (1.0–6.0)	2.0 (1.0–5.0)	0.049

Data are mean ± SD or median (interquartile range, IQR).
BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

variance or non-parametric tests were used as appropriate to compare continuous variables between subgroups. The χ^2 testing was used for between-group comparisons of dichotomous variables.

The prognostic value of SCORE for cardiovascular mortality was examined as a categorical variable [four subgroups: low risk (0%), moderate risk (1–4%), high risk (5–9%), and very high risk (≥10%)] and as a continuous variable for in the OLD-HTA and NEW-HTA cohorts. Considering the SCORE as a categorical variable, cardiovascular deaths were first estimated using the Kaplan–Meier method (log-rank statistic) during a 10-year follow-up period. Then a survival analysis was performed

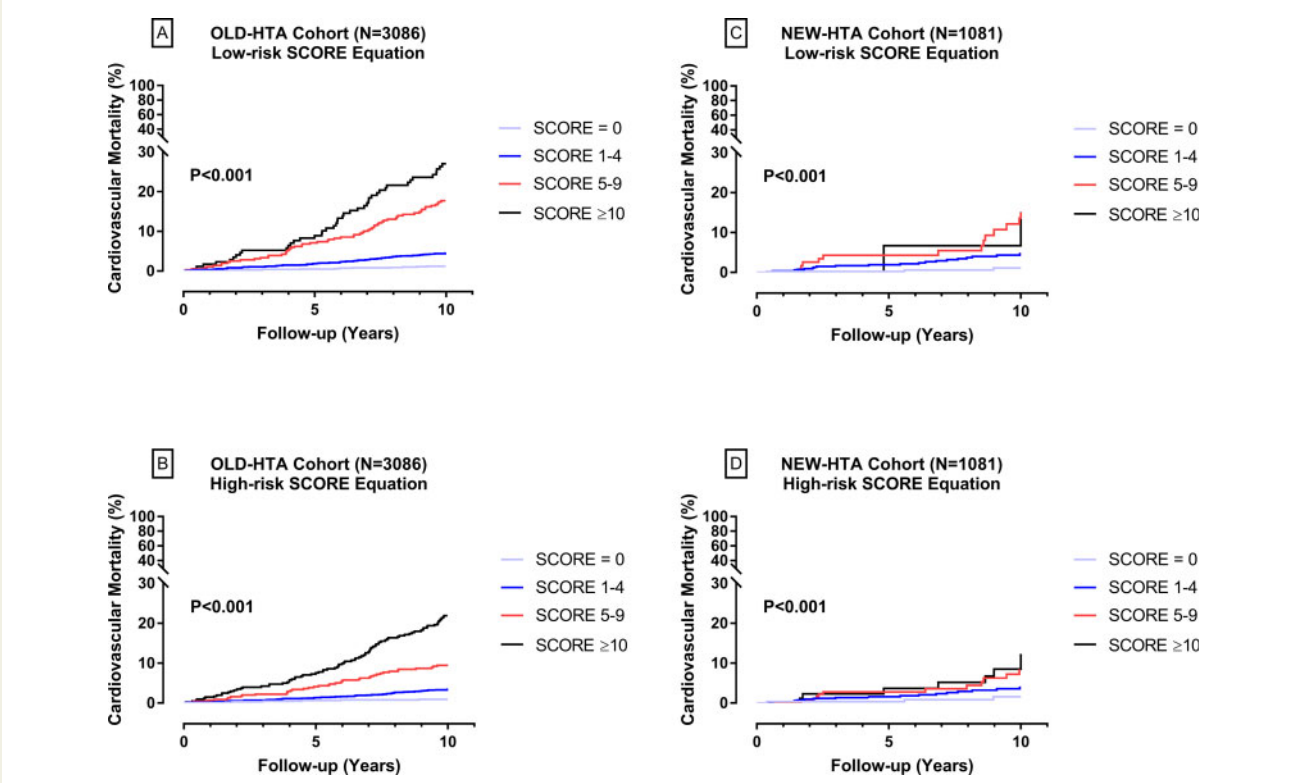

Figure 2 Kaplan–Meier survival curves for cardiovascular mortality according to low-risk and high-risk SCORE equation in the OLD-HTA (*A* and *B*) and in the NEW-HTA cohort (*C* and *D*).

for both SCORE considered as a continuous and a categorical variable using a Cox regression model at 10 years of follow-up.

The predictive accuracy of SCORE was determined using Harrell's C-index.[15] In addition, the information gain in predicting the outcome by high-risk SCORE was compared to the low-risk SCORE using the likelihood ratio test. Analyses were repeated after classifying patients with grade 3 hypertension or HMOD at high risk (SCORE value was extrapolated for all these patients at 7.5%, median between 5% and 10%). Sensitivity analyses were performed after exclusion of patients with grade 3 hypertension or HMOD and by adding arbitrarily 10 mmHg of SBP to the value of each patient in the NEW-HTA. Ten-year cardiovascular mortality predicted by SCORE and observed in the cohorts were plotted on graph.

The analyses were performed using SPSS v20.0.0 (SPSS, Chicago, IL, USA) and STATA 12 (Stata Corporation, College Station, TX, USA). A *P*-value <0.05 was considered for statistical significance.

Results

Baseline patient characteristics in the OLD-HTA (N = 3086) and in the NEW-HTA (N = 1081) Lyon cohorts

Patients in the OLD-HTA cohort were younger, more frequently men, and more frequently smokers; they also had higher BP, cholesterol levels, and SCORE in comparison of those enrolled in the NEW-HTA cohort (*Table 1*). A total of 1444 (46.8%) patients in the OLD-HTA cohort, and 742 (68.6%) in the NEW-HTA cohort received antihypertensive treatment at baseline; notably, none of the OLD-HTA patients received calcium channel blockers, while 544 (50.3%) of the NEW-HTA did so. The drugs used in each cohort are detailed in Supplementary material online, *Table S1*. The patients of the NEW-HTA were preferentially switched, at least 2 weeks before work-up, to antihypertensive treatment that did not interfere to the renin–angiotensin–aldosterone system for detecting secondary forms of hypertension ($n = 907$, 83.9%). In the OLD-HTA cohort, no patient was treated with statins, whereas nine patients received this drug at baseline in the NEW-HTA cohort.

Outcomes according to the SCORE in the OLD-HTA (N = 3086) and in the NEW-HTA (N = 1081) Lyon cohorts

After 10 years of follow-up, there were 182 cardiovascular death in the OLD-HTA cohort and 38 in the NEW-HTA cohort. Outcomes were analysed according to the four SCORE subgroups [low risk (0%), moderate risk (1–4%), high risk (5–9%), and very high risk (≥10%)]. As shown by Kaplan–Meier curves, the cardiovascular mortality increased significantly and gradually with each additional STRATA of SCORE in both cohorts using the low-risk equation or chart (*Figure 2* and Supplementary material online, *Figure S1A* and *C*) and the high-risk equation or chart (*Figure 2* and Supplementary material online, *Figure S1B* and *D*). In univariate Cox regression analyses, SCORE equation and chart were a significant predictor of

cardiovascular mortality when tested as a continuous and as a categorical variable (Supplementary material online, *Table S2*).

The mean observed 10-year cardiovascular mortality rate was 0.9–4.6-fold higher than predicted both in the OLD-HTA and in the NEW-HTA considering SCORE as a categorical variable and the low-risk SCORE equation or chart (*Table 2*; Supplementary material online, *Figures S2* and *S3A* and *C*). The difference was still present but less pronounced when the high-risk SCORE equation or chart was used (*Table 2*; Supplementary material online, *Figures S2* and *S3B* and *D*). The same analyses were also performed for the SCORE as a continuous variable and an underestimation was found when using the low-risk equation for cardiovascular mortality in the OLD-HTA and in the NEW HTA cohorts (*Figure 3A and C*); this underestimation was weaker when the high-risk equation was used (*Figure 3B and D*). Similar observations were observed using SCORE chart instead of the SCORE equation in both cohorts (Supplementary material online, *Figure S4*). An additional analysis was performed in the NEW-HTA cohort after an increase of 10 mmHg of SBP to correct a potential underestimation by mean daytime BP; the results vary marginally with again an underestimation of mortality (Supplementary material online, *Figure S5*).

Diagnostic performance of the low- and high-risk equation or charts to predict cardiovascular mortality

When considering the SCORE as a continuous variable the best performance were observed with the low-risk equation or chart; the same was found when SCORE was considered as a categorical variable (*Table 3*). While the proportion of death predicted seems more appropriate with the high-risk SCORE chart (*Table 2*), the accuracy of the latter was significantly lower than the low-risk equation or chart for all analyses in OLD-HTA and for categorical analyses in the NEW-HTA (C-index and likelihood ratio test; *Table 3*).

Sensitivity analysis after exclusion of grade 3 hypertension and HMOD

After exclusion of patients with grade 3 hypertension and HMOD, a total of 1512 were analysed in the OLD-HTA cohort, and 633 in the NEW-HTA cohort. A greater underestimation of mortality was found with the low-risk SCORE equation or chart in comparison to the high-risk SCORE equation or chart (Supplementary material online, *Table S3*). When considering the SCORE as a continuous variable, the low-risk equation underestimated cardiovascular mortality, while the rate of death seemed more appropriate when using the high-risk equation and chart in both cohorts (Supplementary material online, *Figures S6* and *S7*). The accuracy of the high-risk SCORE equation was not greater than the low-risk SCORE equation to predict cardiovascular mortality except for the categorical equation analysis in NEW-HTA (Supplementary material online, *Table S4*).

Analysis after reclassification of grade 3 hypertension and HMOD

After reclassification of patients with grade 3 hypertension and HMOD as having a SCORE of 7.5, the estimation of mortality by SCORE was, overall, more appropriate. The low-risk SCORE equation or chart underestimated cardiovascular mortality in comparison to the high-risk SCORE (Supplementary material online, *Table S5*), and that the accuracy of the high-risk equation or chart was lower than the low-risk SCORE in the OLD-HTA cohort (Supplementary material online, *Table S6*).

Table 2 Ten-year cardiovascular mortality observed in Kaplan–Meier curves and estimated by the SCORE in the OLD and NEW-HTA cohorts

	Low-risk SCORE		High-risk SCORE	
	Observed	Estimated	Observed	Estimated
OLD-HTA cohort using equations (*N* = 3085)				
SCORE 0	1.2 ± 0.3	0.0	0.9 ± 0.4	0.0
SCORE 1–4	4.5 ± 0.5	1.7 ± 1.0	3.4 ± 0.5	1.9 ± 1.0
SCORE 5–9	17.7 ± 2.1	6.4 ± 1.3	9.5 ± 1.4	6.8 ± 1.4
SCORE ≥10	27.0 ± 3.5	14.8 ± 4.6	21.9 ± 2.1	18.1 ± 8.5
OLD-HTA cohort using charts (*N* = 3085)				
SCORE 0	1.3 ± 0.9	0.0	1.1 ± 0.1	0.0
SCORE 1–4	6.0 ± 1.6	1.7 ± 1.0	6.7 ± 1.6	1.7 ± 0.9
SCORE 5–9	25.6 ± 5.7	6.4 ± 1.2	9.2 ± 3.9	7.0 ± 1.3
SCORE ≥10	33.0 ± 10.3	15.2 ± 4.5	17.3 ± 4.4	17.1 ± 8.2
NEW-HTA cohort using equations (*N* = 1081)				
SCORE 0	1.1 ± 0.7	0.0	1.6 ± 0.9	0.0
SCORE 1–4	4.7 ± 1.0	1.9 ± 1.0	3.9 ± 1.0	2.0 ± 1.1
SCORE 5–9	15.1 ± 4.0	6.2 ± 1.3	8.2 ± 2.4	6.6 ± 1.4
SCORE ≥10	15.2 ± 10.0	11.7 ± 1.6	12.3 ± 4.2	14.1 ± 4.2
NEW-HTA cohort using charts (*N* = 1081)				
SCORE 0	1.0 ± 0.6	0.0	1.6 ± 0.9	0.0
SCORE 1–4	4.8 ± 1.1	2.0 ± 1.0	3.4 ± 0.9	1.9 ± 1.1
SCORE 5–9	15.8 ± 4.1	6.3 ± 1.3	6.9 ± 2.1	6.5 ± 1.4
SCORE ≥10	15.2 ± 6.4	11.8 ± 2.2	15.7 ± 4.7	14.7 ± 4.4

Data are % of death in Kaplan–Meier curves ± SD for observed cardiovascular mortality, data are calculated SCORE ± SD for estimated cardiovascular mortality.

Discussion

In this study, we tested the prognostic value of SCORE in two cohorts of hypertensive patients: the first one (OLD-HTA) recruited during a contemporary period of the SCORE project one and the second one (NEW-HTA) reflecting current practice. We observed that the low-risk equation or chart of SCORE, markedly underestimated cardiovascular death, even after exclusion of grade 3 hypertension, electrical LVH, and moderate CKD. This underestimation was expected for the OLD-HTA cohort considering the higher risk profile and the use of less effective anti-hypertensive treatments[16] but also the higher therapeutic targets[7] and the low proportion of patients with severe hypertension in the cohorts used to construct the SCORE,[3] however, it is more surprising for the NEW-HTA cohort who notably had a better BP and who received modern drugs. This underestimation was observed although the patients were managed in a European Excellence Center for hypertension (exploration of secondary forms, therapeutic optimization), and after exclusion of

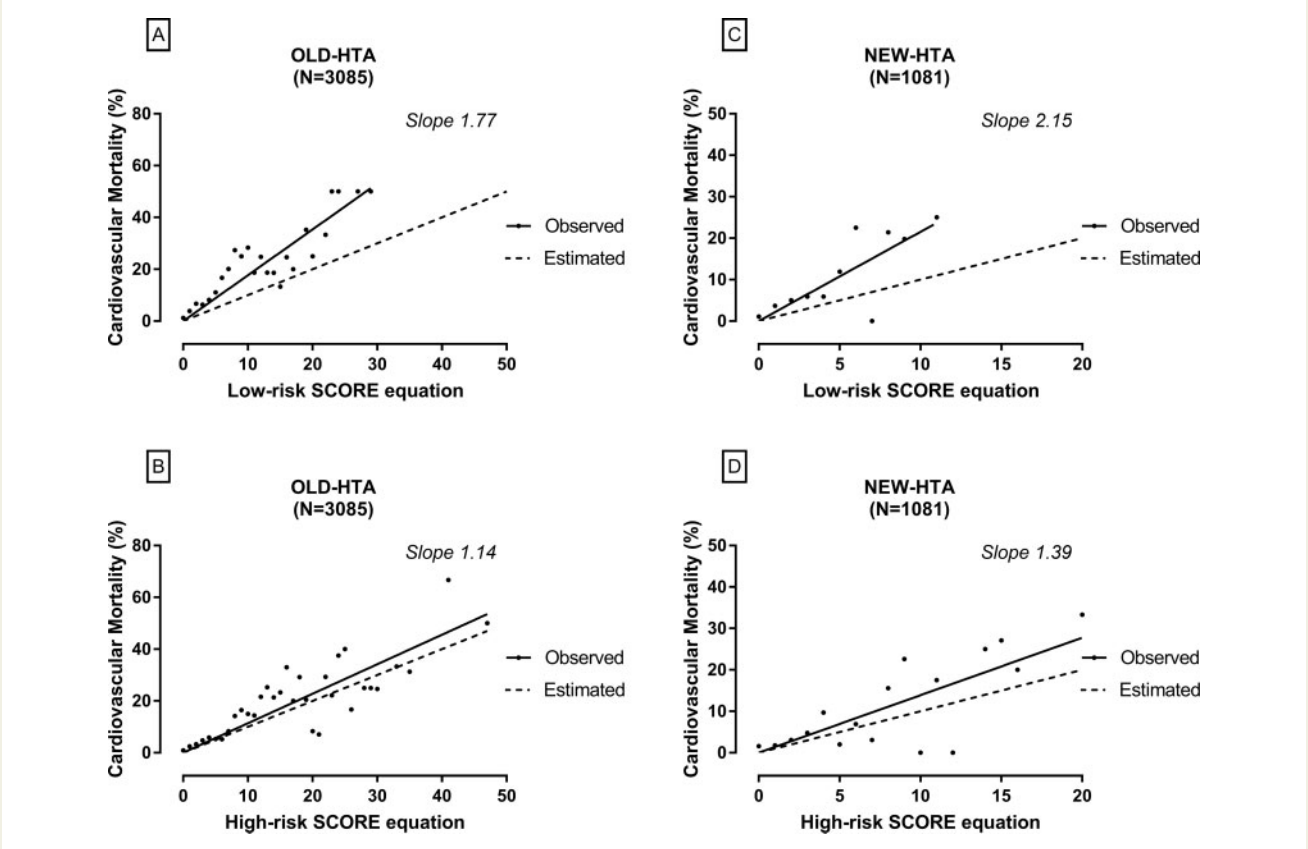

Figure 3 Observed and estimated cardiovascular mortality at 10-year follow-up according to low-risk and high-risk SCORE equation in the OLD-HTA cohort (*A* and *B*) and in the NEW-HTA cohort (*C* and *D*) using SCORE as a continuous variable.

patients at very high cardiovascular risk (established cardiovascular disease, chronic kidney disease stage 4 and diabetes) or high risk (electrical LVH and chronic kidney disease stage 3). Interestingly, the underestimation was not completely corrected when the high-risk equation or chart was used; although predicted cardiovascular mortality seemed closer to that observed when using the high-risk equation or chart there was a higher degree of misclassification (worse accuracy than the low-risk SCORE equation or chart). This observation indicates that moderate to severe hypertensive patients probably required a different cardiovascular risk estimation than SCORE. Our results must be balanced by a low incidence of a cardiovascular mortality which may limit the interpretation of our data in a modern cohort of hypertensive patients and require external validation. Another important point may be related to the misclassification of cause of death as patients did not have verbal autopsy and the real cause of death may be frequently inappropriate.[17] To correct misclassification of death, specific statistical formula have been proposed and demonstrated a lower incidence of events.[18] Taken together our data presented herein use similar method than the SCORE project[3] and bring into question the value of using SCORE as a mandatory step for risk stratification in hypertension.

Other risk stratification scores have been published to predict cardiovascular events, notably the Framingham, QRISK, PROCAM, and PCE, but were also derived from general populations,[19–22] and are likely to also underestimate the risk of hypertensive patients. These scores cannot be tested in this study because we did not have information regarding cardiovascular events and some parameters that are required to calculate these are missing. Some authors have, however, developed scores specifically for hypertensive patients included in randomized trials,[23,24] but these studies have several limitations including a shorter (5 years) prediction risk for ASCOT[24] and also the presence of patients with overt cardiovascular disease for INDANA,[23] and are not included in international guidelines.[1] Another point to consider is that it is also recommended that HMOD be used to guide the classification of cardiovascular risk,[1] the number of which gradually increases this risk.[13] However, this is poorly done, particularly in primary care,[25] owing to the relatively high number of analyses to be conducted for this to be complete. The World Health Organization recommend for all hypertensive patients a plasma creatinine measurement with eGFR and 12-lead electrocardiogram (ECG) for LVH screening[26] that may be easily implemented in a majority of countries. Herein, the reclassification of patients with electrical LVH and moderate chronic kidney disease did not increase the performance of SCORE; other approaches, including simple biomarkers (NT-proBNP or troponin), may be helpful to improve risk stratification of hypertensive patients beyond SCORE evaluation.[9,27]

Table 3 Predictive accuracy and information gain for cardiovascular mortality in the OLD-HTA cohort (*N* = 3086) and in the NEW-HTA cohort (*N* = 1081)

	C-index	95% CI	*P*-value
OLD-HTA cohort using equation (*N* = 3086)			
Low-risk SCORE continuous	0.782	0.749–0.815	—
High-risk SCORE continuous	0.775	0.741–0.809	0.003
Low-risk SCORE categorical	0.758	0.725–0.791	—
High-risk SCORE categorical	0.753	0.720–0.786	0.035
OLD-HTA cohort using chart (*N* = 3086)			
Low-risk SCORE continuous	0.778	0.746–0.812	—
High-risk SCORE continuous	0.770	0.735–0.805	0.012
Low-risk SCORE categorical	0.765	0.733–0.79	—
High-risk SCORE categorical	0.748	0.713–0.782	<0.001
NEW-HTA cohort using equation (*N* = 1081)			
Low-risk SCORE continuous	0.711	0.633–0.789	—
High-risk SCORE continuous	0.700	0.618–0.781	0.171
Low-risk SCORE categorical	0.687	0.617–0.758	—
High-risk SCORE categorical	0.641	0.561–0.722	0.005
NEW-HTA cohort using chart (*N* = 1081)			
Low-risk SCORE continuous	0.724	0.648–0.799	—
High-risk SCORE continuous	0.708	0.627–0.788	0.094
Low-risk SCORE categorical	0.703	0.634–0.773	—
High-risk SCORE categorical	0.657	0.575–0.739	0.011

P-value compared low- and high-risk charts for each variable using the likelihood ratio test.
C-index, Harell's C-index; CI, confidence interval.

Limitations

Given the techniques available at the time of the study, the parameters we used to detect HMOD were less sensitive than those used today.[9,28] Echocardiography and cardiac MRI are more sensitive than electrocardiography in diagnosing LVH, assessing cardiovascular risk, and guiding patient management. Yet, eGFR and ECG still represent the only HMOD recommended in every hypertensive patient. Another limitation of the study is the absence of prediction of non-fatal events that were not reported in the databases used, however, this endpoint was not used in the SCORE project. Furthermore, the results may not be extended to hypertensive patients treated with statins as the vast majority of patients in this study were free of hypolipidaemic drugs. In addition, we did not have information during the follow-up period regarding the adherence to antihypertensive drugs, or the occurrence of obesity and diabetes as it was also the case in the SCORE project.[3] Moreover, the data obtained in the NEW-HTA cohort may be limited by a small number of endpoints. Finally, we should mentioned that we cannot fully excluded some misclassification regarding cause of death and a proportion of patients lost to follow-up.

Conclusion

This study demonstrated that the low-risk SCORE chart underestimated the risk of cardiovascular mortality in 2-Fr cohorts of hypertensive patients, and this was not corrected when the high-risk SCORE chart was used. Taken together, a new risk score is needed, possibly based on both cardiovascular risk factors and HMOD, to better predicted cardiovascular mortality in hypertensive patients without overt cardiovascular disease and diabetes.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Conflict of interest: none declared.

References

1. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I. 2018 ESC/ESH Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018;**36**:1953–2041.
2. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Richard Hobbs FD, Løchen M-L, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Monique Verschuren WM, Binno S; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
3. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM; on behalf of the SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**:987–1003.
4. Mortensen MB, Falk E. Limitations of the SCORE-guided European guidelines on cardiovascular disease prevention. *Eur Heart J* 2017;**38**:2259–2263.
5. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen M-R, Tokgozoglu L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL; Authors/Task Force Members. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 2016;**253**:281–344.
6. Gregg EW, Li Y, Wang J, Rios Burrows N, Ali MK, Rolka D, Williams DE, Geiss L. Changes in diabetes-related complications in the United States, 1990-2010. *N Engl J Med* 2014;**370**:1514–1523.

7. Kotchen TA. Historical trends and milestones in hypertension research. *Hypertension* 2011;**58**:522–538.
8. Courand P-Y, Milon H, Gustin M-P, Froment A, Bricca G, Lantelme P. Effect modification of aortic atheroma on the prognostic value of heart rate in hypertension. *J Hypertens* 2013;**31**:484–491.
9. Grandjean A, Courand P-Y, Mouly-Bertin C, Berge C, Langevin F, Harbaoui B, Garcia D, Lantelme P. Risk stratification in hypertension: NT-proBNP and R wave in aVL lead combination better than echocardiographic left ventricular mass. *J Hypertens* 2020;**38**:65–72.
10. Ministère de l'Enseignement supérieur de la Recherche et de l'Innovation. Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé. 2014. Accessed 12 July 2017.
11. Andreadis EA, Geladari CV, Angelopoulos ET, Savva FS, Georgantoni AI, Papademetriou V. Attended and unattended automated office blood pressure measurements have better agreement with ambulatory monitoring than conventional office readings. *J Am Heart Assoc* 2018;**7**.
12. Staessen JA, O'Brien ET, Atkins N, Amery AK. Short report: ambulatory blood pressure in normotensive compared with hypertensive subjects. The Ad-Hoc Working Group. *J Hypertens* 1993;**11**:1289–1297.
13. Harbaoui B, Courand P-Y, Defforges A, Khettab F, Milon H, Girerd N, Lantelme P. Cumulative effects of several target organ damages in risk assessment in hypertension. *Am J Hypertens* 2016;**29**:234–244.
14. Pavillon G, Laurent F. Certification et codification des causes médicales de décès. *BEH* 2003;**30**:134–138. http://opac.invs.sante.fr/doc_num.php?explnum_id=2065.
15. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**15**:361–387.
16. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Östergren J. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;**366**:895–906.
17. Chandramohan D, Setel P, Quigley M. Effect of misclassification of causes of death in verbal autopsy: can it be adjusted? *Int J Epidemiol* 2001;**30**:509–514.
18. Edwards JK, Cole SR, Moore RD, Mathews WC, Kitahata M, Eron JJ. Sensitivity analyses for misclassification of cause of death in the parametric G-formula. *Am J Epidemiol* 2018;**187**:1808–1816.
19. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;**117**:743–753.
20. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ* 2017;**357**:j2099.
21. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Münster (PROCAM) study. *Circulation* 2002;**105**:310–315.
22. Yadlowsky S, Hayward RA, Sussman JB, McClelland RL, Min Y-I, Basu S. Clinical implications of revised pooled cohort equations for estimating atherosclerotic cardiovascular disease risk. *Ann Intern Med* 2018;**169**:20–29.
23. Pocock SJ, McCormack V, Gueyffier F, Boutitie F, Fagard RH, Boissel JP. A score for predicting risk of death from cardiovascular disease in adults with raised blood pressure, based on individual patient data from randomised controlled trials. *BMJ* 2001;**323**:75–81.
24. Prieto-Merino D, Dobson J, Gupta AK, Chang C-L, Sever PS, Dahlöf B, Wedel H, Pocock S, Poulter N; on Behalf of the ASCOT-BPLA Investigators. ASCORE: an up-to-date cardiovascular risk score for hypertensive patients reflecting contemporary clinical practice developed using the (ASCOT-BPLA) trial data. *J Hum Hypertens* 2013;**27**:492–496.
25. Rossignol P, Hosseini K, Tropeano A-I, Fay R, Tsatsaris A, Guillemin F, Mounier-Vehier C. Target organ damage assessment in French hypertensive patients without established cardiovascular or renal disease: results of the PREVENT-A study. *J Hypertens* 2013;**31**:177–185.
26. Cuspidi C, Meani S, Salerno M, Severgnini B, Fusi V, Valerio C, Catini E, Magrini F, Zanchetti A. Cardiovascular risk stratification according to the 2003 ESH-ESC guidelines in uncomplicated patients with essential hypertension: comparison with the 1999 WHO/ISH guidelines criteria. *Blood Press* 2004;**13**:144–151.
27. Pokharel Y, Sun W, de Lemos JA, Taffet GE, Virani SS, Ndumele CE, Mosley TH, Hoogeveen RC, Coresh J, Wright JD, Heiss G, Boerwinkle EA, Bozkurt B, Solomon SD, Ballantyne CM, Nambi V. High-sensitivity troponin T and cardiovascular events in systolic blood pressure categories: atherosclerosis risk in communities study. *Hypertension* 2015;**65**:78–84.
28. Courand PY, Harbaoui B, Bècle C, Mouly-Bertin C, Lantelme P. Plasma NT-proBNP mirrors the deleterious cardiovascular and renal continuum in hypertension. *Eur J Prev Cardiol* 2017;**24**:452–459.