Original Article

A sudden death risk score specifically for hypertension: based on 25 648 individual patient data from six randomized controlled trials

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See editorial comment on page 2165

Objective: To construct a sudden death risk score specifically for hypertension (HYSUD) patients with or without cardiovascular history.

Methods: Data were collected from six randomized controlled trials of antihypertensive treatments with 8044 women and 17 604 men differing in age ranges and blood pressure eligibility criteria. In total, 345 sudden deaths (1.35%) occurred during a mean follow-up of 5.16 years. Risk factors of sudden death were examined using a multivariable Cox proportional hazards model adjusted on trials. The model was transformed to an integer system, with points added for each factor according to its association with sudden death risk.

Results: Antihypertensive treatment was not associated with a reduction of the sudden death risk and had no interaction with other factors, allowing model development on both treatment and placebo groups. A risk score of sudden death in 5 years was built with seven significant risk factors: age, sex, SBP, serum total cholesterol, cigarette smoking, diabetes, and history of myocardial infarction. In terms of discrimination performance, HYSUD model was adequate with areas under the receiver operating characteristic curve of 77.74% (confidence interval 95%, 74.13–81.35) for the derivation set, of 77.46% (74.09–80.83) for the validation set, and of 79.17% (75.94–82.40) for the whole population.

Conclusion: Our work provides a simple risk-scoring system for sudden death prediction in hypertension, using individual data from six randomized controlled trials of antihypertensive treatments. HYSUD score could help assessing a hypertensive individual's risk of sudden death and optimizing preventive therapeutic strategies for these patients.

Keywords: cardiovascular diseases, cardiovascular risk factor, diabetes, hypertension, risk score, sudden death

Abbreviations: ARIC, Atherosclerosis Risk in Communities; AUROC, area under the receiver operating characteristic curve; CAST, Cardiac Arrhythmia Suppression Trial; CHADS2-VASC, updated score for atrial fibrillation stroke risk; CHS, Cardiovascular Health Study; CI, confidence interval; Duke SCD, Duke Sudden Cardiac Death Risk Score for Patients With Angiographic(>75% Narrowing) Coronary Artery Disease; EWPHE, European Working Party on Hypertension in the Elderly; MRFIT, Multiple Risk Factor Intervention Trial; RCT, randomized controlled trial; ROC, receiver operating characteristic; SCORE, Systemic Coronary Risk Estimation; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients; SYSTEUR, Systolic Hypertension in Europe

INTRODUCTION

Sudden death, a major cardiovascular event which occurs only within 1 h (or 24 h according to other definition) after the first onset of symptoms [1,2], is responsible for approximately 360 000 deaths (half of all cardiovascular deaths) annually in the United States [3]. In France, the annual incidence of sudden death was estimated as 50–70/100 000, thus about 40 000 deaths/year, occur mainly in men (69%), with a mean age of 65 years and at home (75%) [4]. Such event is important to be prevented but unfortunately remains underestimated in public health [5]. Hypertension is considered as a worldwide epidemiology, a well known risk factor for several diseases, and the leading cause for morbidity and mortality, including sudden

Journal of Hypertension 2017, 35:2178–2184

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Received 31 January 2017 **Revised** 17 May 2017 **Accepted** 30 May 2017

DOI:10.1097/HJH.0000000000001451

death, accounting for 7.0% (95% confidence interval (CI) 6.2–7.7) of global disability-adjusted life years and 9.4 (CI 8.6–10.1) million deaths in 2010 [6].

To better protect patients with hypertension regarding sudden death occurrence, a risk score is needed to stratify their risks and to adapt therapy. Up to now, two sudden death risk predictors were developed. One is Duke Sudden Cardiac Death Risk Score for Patients With Angiographic(>75% Narrowing) Coronary Artery Disease (Duke SCD) [7], designed specifically for patients with high coronary risk thus concerns secondary prevention patients. The second one was recently built from two prospective cohorts and for the general population in the United States [3].

We aimed to build here a quantitative and discriminative 5-year sudden death risk predictor from six randomized controlled trials (RCTs) of 25 648 patients with raised blood pressure (BP), treated or not by antihypertensive agents.

METHODS

Participants

The INdividual Data ANalysis of Antihypertensive intervention trials (INDANA) database includes most of major RCTs of antihypertensive drugs vs. placebo or control during the period of 1985–1995, which characteristics detailed elsewhere [8]. We assessed here data from six trials of this database having unbiased information regarding sudden death with 25 648 participants [9–14]. Causes of death were adjudicated in each trial by experts' committee.

Statistical analysis

We used the Cox proportional hazards regression (semiparametric time-to-event) model to establish our sudden death risk score for hypertension. The population was divided randomly into two subpopulations: derivation and validation sets (ratio 2 : 1) to ensure their similar baseline characteristics. Covariable selection was done in two steps. First, we conducted univariable analyses with 29 covariables to evaluate their associations with the sudden death outcome, adjusted on trials (by adding the covariable trial). Second, multivariable analyses were operated, where all covariables were offered simultaneously, but separately for SBP and DBP on one hand, mean BP and pulse BP on the other hand. Similarly, we did not assess serum creatinine in the multivariable testing, considering that glomerular filtration rate did reflect more accurately renal function. We used concurrently 'backward' and 'forward elimination' (stepwise screening) strategies, always adjusted on trials until obtaining the final model (where all the covariables were significant). All these uni and multivariable analyses were done using data of the derivation set.

Tests on time dependence or the linearity of the effect of continuous covariables on log hazard scale were performed using martingale residuals plots, and in comparing the model assuming a linear effect to a model assuming a quadratic effect. We also investigated possible biological interactions among them, particularly interactions with trial and antihypertensive treatment covariables. As well, we explored the impact of the trial covariable on sudden death risk, alone (univariable analysis) or adjusted on other risk factors (multivariable analysis).

The discrimination performance of the final predictive model was assessed by the areas under the receiver operating characteristic curve (AUROC) of the derivation set, the validation set, the whole population, and of each separated trial, with 95% CI [15]. For model calibration and external validation, we used the (k−1) approach: the final 7-risk factor model was rebuilt on five trials and tested on the remaining for six times.

We converted this final model predictor into an integer score using the method of Sullivan *et al.* [16]. Briefly, the score was directly related to an individual's probability of sudden death within 5 years. The zero score (risk of reference) was assigned for an adult at the lowest/most optimal risk represented in the application population. Having grouped each factor into convenient intervals, such as every 10 mmHg for SBP, an individual's score increases by an integer amount for each risk factor level above the reference risk category. Each integer amount is a rounding of the exact figure obtained from the proportional hazards model, thus the risk score is a simple addition of whole points.

All statistical tests were two-sided with a type I error of 0.05. All the analyses were performed with 'survival', 'riskset receiver operating characteristic (ROC)', and 'timeROC' packages on R software, version 3.2.5.

RESULTS

Among 25 648 participants from six RCTs, 345 sudden death occurred during a mean of 5.16 years of follow-up [9–14] (Appendix 1, http://links.lww.com/HJH/A803). All the trials were double blind, except Coope *et al.* [9] and Multiple Risk Factor Intervention Trial (MRFIT) [10], which were open-label trials. The biggest one is MRFIT [10], which recruited 12 866 patients and the smallest one was European Working Party on Hypertension in the Elderly (EWPHE) [11] with 840 participants. Characteristics of the derivation and validation sets are shown in the Table 1.

In univariable analyses, the following parameters were linked significantly with the incidence of sudden death: age, male sex, SBP and pulse BP, smoking status, serum creatinine, glomerular filtration rate, history of myocardial infarction (MI), history of angina pectoris, and baseline diabetes but not antihypertensive treatment (Table 2).

No significant interaction was detected between studied covariables, or between any covariable with antihypertensive treatment and trial ones. As antihypertensive treatment seemed to have no effect on reducing the risk of sudden death in univariable analysis (Table 2) and had no interaction with other covariables, we developed the final model on both treatment and placebo groups in the derivation set.

Using multivariable method, we identified seven significant risk factors of sudden death including age, sex (male), smoking status, serum cholesterol, SBP, baseline of type 2 diabetes, and history of MI, among which serum cholesterol was not statistically significant in univariable analyses (Table 2).

Impact of the trial covariable was tested, indicating a significantly lower sudden death risk (nearly one-third) in

TABLE 1. Baseline characteristics of derivation and validation sets

Covariables	Derivation set	Validation set
Number of patients	17 094	8554
Number of sudden death events (%)	329 (1.6)	170 (1.7)
Trials (*n*, weight % vs. the whole set)		
Coope	589 (3.4)	295 (3.4)
EWPHE	559 (3.3)	281 (3.3)
MRFIT	8577 (50.2)	4289 (50.1)
SHEP	3156 (18.5)	1580 (18.5)
STOP	1084 (6.3)	543 (6.3)
SYSTEUR	3129 (18.3)	1566 (18.3)
Sudden death incidence (*n*, %)		
Coope	14 (2.4)	4 (1.4)
EWPHE	9 (1.6)	4 (1.4)
MRFIT	98 (1.1)	55 (1.3)
SHEP	53 (1.7)	38 (2.4)
STOP	11 (1.0)	5 (0.9)
SYSTEUR	35 (1.1)	19 (1.2)
Treated (%)	50.0	50.0
Male (%)	68.3	69.3
Mean (SD) age (years)	58.9 (14.0)	58.9 (14.1)
Smoker (%)	35.0	35.2
Mean (SD) height (cm)	169.6 (10.3)	169.6 (10.3)
Mean (SD) weight (kg)	79.1 (14.8)	79.0 (14.5)
Mean (SD) BMI (kg/m^2)	27.4 (4.1)	27.4 (4.0)
Mean (SD) SBP (mmHg)	156.4 (25.9)	156.3 (26.0)
Mean (SD) DBP (mmHg)	88.4 (11.3)	88.5 (11.3)
Mean (SD) arterial/mean BP (mmHg)	111.1 (12.4)	111.1 (12.4)
Mean (SD) pulse BP (mmHg)	67.9 (26.4)	67.8 (26.4)
Mean (SD) serum creatinine (μmol/l)	95.1 (17.6)	95.0 (17.4)
Mean (SD) fasting blood glucose (mmol/l)	5.5 (1.2)	5.5 (1.2)
Mean (SD) serum total cholesterol (mmol/l)	6.4 (1.1)	6.4 (1.1)
Mean (SD) serum uric acid (μmol/l)	376.5 (88.7)	376.4 (88.5)
Mean glomerular filtration rate (ml/min)	84.9 (29.0)	84.8 (28.9)
Proteinuria (%)	4.4	4.5
Mean (SD) serum potassium (mmol/l)	4.4 (0.5)	4.4 (0.5)
Mean (SD) heart rate (beats/min)	76.0 (11.7)	76.0 (11.8)
History of angina pectoris (%)	1.6	1.4
History of atrial fibrillation (%)	0.15	0.09
History of leg intermittent claudication (%)	0.4	0.4
Positive dilated fundus examination (%)	27.6	27.3
Baseline of diabetes (%)	5.9	6.1
History of myocardial infarction (%)	4.6	5.0
History of stroke (%)	1.3	1.1
History of antihypertensive treatment (%)	23.5	23.5
History of high BP (%)	72.7	73.4

Baseline characteristics of the 25 648 randomized participants, according to the derivation/validation sets. Values are numbers (percentages) of patients unless stated otherwise.
BP, blood pressure; EWPHE, European Working Party on Hypertension in the Elderly; MRFIT, Multiple Risk Factor Intervention Trial; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients; SYSTEUR, Systolic Hypertension in Europe.

MRFIT trial [10], compared with that of Coope *et al.* [9] trial in univariable analysis. However, this significance disappeared in multivariable analysis (the final model), suggesting the difference of sudden death incidence was explained by the adjustment (Appendix 2, http://links.lww.com/HJH/A803).

The discrimination performance of the final model was quantified by AUROC for the derivation set, validation set, and for each individual trial (Table 3). Overall, our model's performance was good with AUROC at 78, 77, and 79% for the derivation set, validation set, and the whole population, respectively. However, separate assessment for each trial varied considerably from 60% for Systolic Hypertension in the Elderly Program (SHEP) trial [12] to 75% for EWPHE trial [11].

The final model is then converted to an integer score [16]. We took a woman, nonsmoker, aged 37, nondiabetic, total serum cholesterol at 3.5 mmol/l, SBP at 115 mmHg, and without history of MI as the reference profile. The scoring system is presented in the Appendix 3, http://links.lww.com/HJH/A803, allowing to assess the effect of each risk factor on the overall risk of sudden death (the total point). In our sudden death risk score specifically for hypertension (HYSUD) score, one increased year in age was corresponding with one point plus for sudden death risk. In terms of sudden-risk attribution, male sex and history of MI contributed in the same way by 10 points added, followed by smoking (nine points) and baseline diabetes (seven points). For any individual, points scored for each risk factor were cumulated together to estimate their total risk scores.

The model calibration was assessed in comparing the incidence of sudden death predicted vs. observed for each trial in each tertile of predicted risk. Model seemed to work best for EWPHE [11] and Systolic Hypertension in Europe (SYSTEUR) [13] trials for all categories, for Swedish Trial in Old Patients (STOP) [14] except an overestimate in high-risk category; noticeably underestimate for Coope *et al.* [9] and SHEP [12] trials; and largely overestimate for MRFIT [10] trial (Appendix 4, http://links.lww.com/HJH/A803).

Appendix 5, http://links.lww.com/HJH/A803 presents the similarity in predicted 5-year sudden death risks by the scoring system, compared with those obtained by the final Cox proportional hazards model equation. The former was converted from the latter.

Appendix 6, http://links.lww.com/HJH/A803 shows the exponential relation between the risk score and the probability of dying from sudden death in 5 years for men and women of the whole population. Figure 1 presents the distribution of 5-year sudden death risk according to scenarios of sex and age, illustrating higher risks for men comparing with women at the same age categories. Of note, in our database, women accounted for nearly one-third of the population and were older than men (range age 60–98, mean age 72 vs. 35–95, and 53 years old).

DISCUSSION

Our study brings a simple and user-friendly predictor for sudden death risk, specifically for patients of hypertension. HYSUD risk score included seven risk factors: age, male sex, history of MI, smoking status, high BP, high blood cholesterol, and baseline diabetes, ordered by their significant impacts. These factors were well known for cardiovascular events in general [17] and for sudden death in particular [18]. Similarly, according to a recent meta-analysis of 330 376 patients from 47 lipid-modifying trials [19], baseline diabetes is a significant predictor of cardiovascular outcomes including sudden death. The score was built on the point system for an easy assessment of a hypertensive individual's risk of sudden death in 5 years.

Up to now, two sudden death risk predictors were developed: one is Duke SCD [7], designed specifically for secondary coronary prevention and recently, another one

TABLE 2. Univariable analyses and multivariable analysis (final model) for sudden death prediction

Covariables	Univariable analyses		Multivariable analysis (final model)	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (by 5-year increase)	1.33 (1.20–1.48)	<0.001	1.37 (1.23–1.53)	<0.001
Male sex	1.83 (1.47–2.19)	<0.001	2.06 (1.40–3.03)	<0.001
SBP (by 10-mmHg increase)	1.15 (1.05–1.26)	0.002	1.14 (1.04–1.25)	0.006
Pulse BP (by 10-mmHg increase)	1.17 (1.06–1.29)	0.002		
Smoking status	1.55 (1.24–1.87)	0.007	1.81 (1.31–2.51)	<0.001
Serum creatinine (by 10-μmol/l increase)	1.10 (1.02–1.19)	0.01		
Glomerular filtration rate (by 10-ml/min increase)	0.92 (0.85–0.99)	0.02		
History of myocardial infarction	1.74 (1.23–2.25)	0.03	1.71 (1.02–2.85)	0.041
History of angina pectoris	2.51 (1.07–5.90)	0.04		
Baseline diabetes	1.61 (1.13–2.09)	0.05	1.65 (1.02–2.67)	0.040
Mean BP (by 10-mmHg increase)	1.14 (0.99–1.32)	0.08		
Weight (10 kg)	0.93 (1.03–0.84)	0.16		
Heart rate (by 10-beats/min increase)	1.09 (0.96–1.24)	0.17		
BMI (by kg/m^2 increase)	0.98 (0.94–1.01)	0.18		
Serum total cholesterol (by 1-mmol/l increase)	1.08 (0.95–1.20)	0.24	1.17 (1.04–1.33)	0.011
Treatment	0.89 (0.62–1.15)	0.34		
Height (by 10-cm increase)	0.94 (0.80–1.11)	0.49		
Serum potassium (by 1-mmol/l increase)	1.13 (0.78–1.48)	0.49		
History of stroke	0.72 (−0.68–2.12)	0.65		
DBP (by 10-mmHg increase)	1.03 (0.89–1.19)	0.72		

All the univariable analyses were adjusted on trials. Univariable analyses of nine risk factors with frequently lacking data, including fasting blood glucose, serum uric acid, proteinuria, positive dilated fundus examination, history of high BP, history of antihypertensive treatment, history of atrial fibrillation, and history of leg intermittent claudication, gave nonsignificant associations and are not presented in this table. Multivariable analysis was adjusted on trials and treatments. All the analyses were performed on 17 094 individual patient data of the derivation set.
BP, blood pressure; CI, confidence interval.

for the general population [3]. The work of Deo *et al.* [3] was derived from 17 884 individual data free of baseline cardiovascular diseases (some patients had hypertension) from two cohorts in the United States (Atherosclerosis Risk in Communities and Cardiovascular Health Study). Our score included 25 648 patients with hypertension with or without other cardiovascular diseases or histories (diabetes, previous stroke/MI/angina, and so on) from six RCTs and of a wider geographic zone (Europe and the United States). The score of Deo *et al.* [3] contained more significant risk factors than ours (12 vs. 7). However, our HYSUD was transformed into an easy and friendly pointing system, as proposed by the work of Pocock *et al.* [20] for cardiovascular death prediction. A table comparing these two scores is displayed in Appendix 7, http://links.lww.com/HJH/A803.

TABLE 3. Performance and validation of a sudden death risk score specifically for hypertension risk score using areas under the receiver operating characteristic curve

Subset/trial	Number of patients	AUROC (95% CI)
Derivation set	17 094	77.74 (74.13–81.35)
Validation set	8554	77.46 (74.09–80.83)
Coope	884	60.99 (48.55–73.43)
EWPHE	840	75.40 (59.26–91.53)
MRFIT	12 866	65.91 (60.76–71.07)
SHEP	4736	60.12 (53.24–66.99)
STOP	1627	74.07 (60.70–87.45)
SYSTEUR	4695	61.68 (51.72–71.65)
Whole population	25 648	79.17 (75.94–82.40)

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; EWPHE, European Working Party on Hypertension in the Elderly; MRFIT, Multiple Risk Factor Intervention Trial; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients; SYSTEUR, Systolic Hypertension in Europe.

The internal validation of HYSUD risk score indicated a good routine performance for this prognostic prediction type, with AUROC reaching almost 80%. However, model performances differed largely among trials, as was noted in a recent meta-analysis exploring the applicability of the updated score for atrial fibrillation stroke risk score predicting stroke risk in atrial fibrillation patients [21]. These differences could be partially explained by trial heterogeneity regarding: different sudden death definitions: an unexpected death occurring in a time interval of 1 h in SHEP [12] and STOP [14], prolonged to 24 h in MRFIT [10] and SYSTEUR [13], and not given in other trials (details in Appendix 1, http://links.lww.com/HJH/A803); different eligibility criteria for age, BP, etc.; different baseline cardiovascular disease severities that could result in various event rates of cardiovascular death including sudden death [22]; different antihypertensive treatments, geographic zones, periods, follow-up durations; and so on. Nonetheless, pooling data from several studies as we did increases the power of analyses, and allows exploring heterogeneity of information between trials. We also explored the heterogeneity of the links between individual characteristics and sudden death occurrence between trials, as well as its interactions with other covariables on sudden death risk: none was significant. In addition, apparent poor model calibration may come from low incidence of sudden death in our database (only 1.35% during trials' follow-up durations).

Our HYSUD score was built from a database collected in the period of 1970–1990, similarly to classical scores such as Framingham [17] or Systemic Coronary Risk Estimation [23] and hence, should be calibrated before application for nowadays patients, to limit possible bias coming from change in covariable hazards ratio over time or other

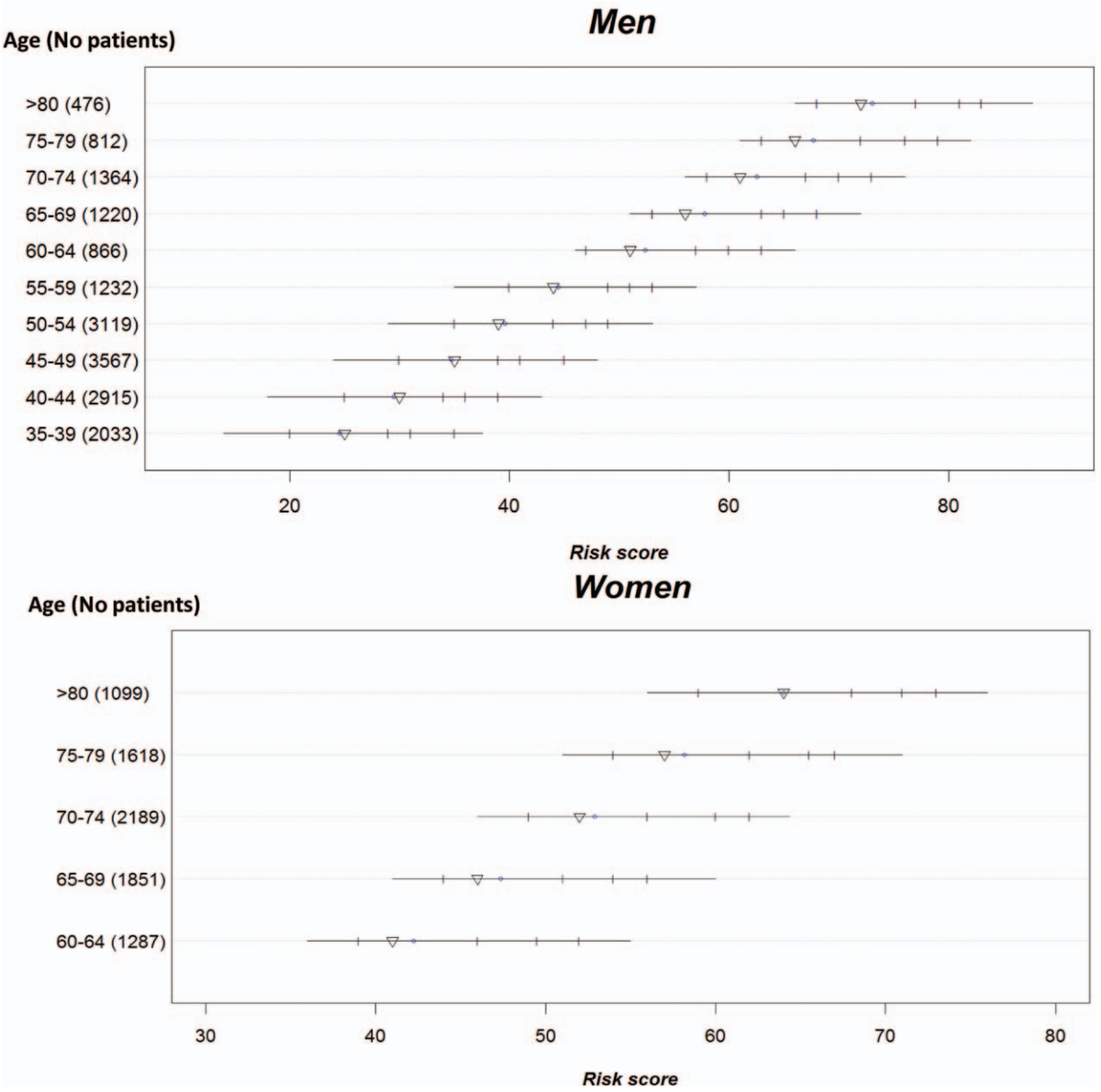

FIGURE 1 Distribution of risk scores by sex and age groups.

reasons. Concerning this point, the risk score of Deo *et al.* [3] which used more updated data (1985–2016, details in appendix 7, http://links.lww.com/HJH/A803) and Duke SCD score [7] which is built from 37 258 patients undergoing coronary angiography in the period of 1 January 1985 to 31 May 2005, could give more accurate estimates.

Another limitation is that our tool was developed in the RCT setting, where individuals have clinical characteristics that are usually different of observational populations and routine practice clinical settings. For example, individuals in the RCT used generally had SBP higher than 160 mmHg and with a lower proportion of men, except MRFIT trial [10]. This latter one [10] recruited only middle-aged men (35–58 years old) and provided approximately half of the studied population (12 866/total of 25 648), one additional reason for caution in potential extrapolation to other individuals. Last but not least, trial-based outcomes are more accurate but they are also limited by a shorter duration of follow-up.

All these elements call for external validations and calibrations of HYSUD score in nowadays hypertensive patients with various cardiovascular risk levels in different countries, before being locally applied. This type of work has been performed for other classical scores by several studies [24,25], strongly suggesting to adapt model predictors for each specific population. Anyway, our HYSUD score could help clinicians estimating individual risk and stratifying patients with regard to their sudden death risks.

As SBP, hypercholesterolemia, and baseline diabetes were significant risk factors, this suggests logically that the use of BP/lipid and glucose-lowering drugs may reduce sudden death risk in these study participants. Paradoxically,

our study, collecting data from six RCTs of antihypertensive drugs, observed no treatment effect on sudden death risk, in agreement with a meta-analysis of 39 908 patients with hypertension [26]. Furthermore, as history of MI was a significant indicator of sudden death risk, the use of antiarrhythmic drugs could appear logical to prevent this event. However, the Cardiac Arrhythmia Suppression Trial (CAST) [27] clearly demonstrated that these drugs significantly increased sudden death and total mortality incidence. These examples illustrate how such risk score must not be used to justify preventive drug prescription, which has to rely on clinical trials' results only. Of note, till now, the prevention of sudden death by pharmacological measures appears effective by β-blockers [28] and antialdosterones [29] for patients with heart failure but again, not by antihypertensive agents for hypertension [26]. Another meta-analysis only showed a modest sudden death risk reduction (one in 10) by statin in populations at risk [30].

Our HYSUD score was built on 17 094 individual data (derivation set) and validated on the remainder 8554 ones (validation set) as well as on each separated trial and on the whole population. This approach integrated the internal and external validations, and illustrated its transportability.

To summarize, sudden death is a major cardiovascular event but remains unfortunately underestimated in public health. This event is associated with considerable loss in terms of health and economy. Our work provides a good-performance, user-friendly predictor to assess 5-year individual sudden death risk in hypertension. This HYSUD risk score could help to stratify patients and thus optimize preventive therapeutic strategies in this population. Local validation process appears important to check that the score was appropriately calibrated.

ACKNOWLEDGEMENTS

François Pillon has done the first draft analyses. H.H.L. would like to thank Professor Hervé Maisonneuve for his advice and his training on scientific writing. We thank the investigators who provided the individual trial data used in our analyses: John Coope (Coope), Eleanor Schron (SHEP), L. L. (STOP), Robert Fagard (EWPHE), Jeffrey Cutler (MRFIT), and Jan Staessen (EWPHE and SYSTEUR).

The whole article was submitted at BMJ but not accepted (January 2017).

Part of the work has been presented as oral/poster communications in the following congresses:

H.H.L., F.S., M.C., M.A., M.F., E. Hénin, P. Janiaud, A. Berrima, M. Girard, S. Erpeldinger, B.K., P. Chevalier, F.G. The first risk score for sudden death prediction in primary prevention patients. Oral presentation at the 35th SFHTA Conference, Paris December 2015 (French Society of Hypertension). Ann Cardiol Angeiol (Paris). December 2015;64 Suppl 1:S5. doi: 10.1016/S0003–3928(16)30005–1.

H.H.L., F.S., M.C., M.A., M.F., I.M., B.K., P. Chevalier, F.G. The first risk scoring system for sudden death prediction in primary prevention patients. Poster presentation at the 26th European Meeting on Hypertension and Cardiovascular Prevention, Paris June 2016 (European Society of Hypertension).

H.H.L., M.F., and M.A. are currently receiving scholarships of the French Ministry of Higher Education and Research, The Academic Agency of La Francophonie (West Africa Regional Office), and The Federal Department of Economic Affairs, Education, and Research (EAER) Switzerland, respectively. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

F.G. proposed the idea of the study. F.S., L.T. made substantial contributions to study conception and design. H.H.L. and M.C. performed the analyses. H.H.L. wrote the article. F.S., M.C., M.A., I.M., L.L., L.T., and F.G. have been involved in revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Fishman GI, Chugh SS, Dimarco JP, Albert CM, Anderson ME, Bonow RO, *et al*. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. *Circulation* 2010; 122:2335–2348.
2. Papadakis M, Sharma S. Sudden cardiac death. *Medicine (Baltimore)* 2010; 38:502–506.
3. Deo R, Norby FL, Katz R, Sotoodehnia N, Adabag S, DeFilippi CR, *et al*. Development and validation of a sudden cardiac death prediction model for the general population. *Circulation* 2016; 134:806–816.
4. Jouven X, Bougouin W, Karam N, Marijon E. [Epidemiology of sudden cardiac death: data from the Paris sudden death expertise center registry]. *Rev Prat* 2015; 65:916–918.
5. Marijon E, Bougouin W, Lamhaut L, Deye N, Jost D, Jouven X. [Sudden death of the adult: do not forget the hidden part of the iceberg!]. *Rev Med Interne* 2012; 33:543–545.
6. Rahimi K, Emdin CA, MacMahon S. The epidemiology of blood pressure and its worldwide management. *Circ Res* 2015; 116:925–936.
7. Atwater BD, Thompson VP, Vest RN, Shaw LK, Mazzei WR, Al-Khatib SM, *et al*. Usefulness of the Duke sudden cardiac death risk score for predicting sudden cardiac death in patients with angiographic (>75% narrowing) coronary artery disease. *Am J Cardiol* 2009; 104:1624–1630.
8. Gueyffier F, Boutitie F, Boissel JP, Coope J, Cutler J, Ekbom T, *et al*. INDANA: a meta-analysis on individual patient data in hypertension. Protocol and preliminary results. *Thérapie* 1995; 50:353–362.
9. Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *Br Med J (Clin Res Ed)* 1986; 293:1145–1151.
10. Multiple Risk Factor Intervention Trial Research Group. Multiple risk factor intervention trial: Risk factor changes and mortality results. *JAMA* 1982; 248:1465–1477.
11. Amery A, Birkenhäger W, Brixko P, Bulpitt C, Clement D, Deruyttere M, *et al*. Mortality and morbidity results from the European working party on high blood pressure in the Elderly trial. *Lancet* 1985; 1:1349–1354.
12. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the systolic hypertension in the elderly program (SHEP) SHEP. *JAMA* 1991; 265:3255–3264; doi: 10.1001/jama.1991.03460240051027.
13. Amery A, Birkenhäger W, Bulpitt CJ, Clément D, De Leeuw P, Dollery CT, *et al*. Syst-Eur. A multicentre trial on the treatment of isolated systolic hypertension in the elderly: objectives, protocol, and organization. *Aging (Milano)* 1991; 3:287–302.
14. Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish trial in old patients with hypertension (STOP-hypertension). *Lancet* 1991; 338:1281–1285.
15. Blanche P, Dartigues JF, Jacqmin-Gadda H. Review and comparison of ROC curve estimators for a time-dependent outcome with marker-dependent censoring. *Biom J* 2013; 55:687–704.

16. Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariate data for clinical use: the Framingham study risk score functions. *Stat Med* 2004; 23:1631–1660.
17. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J* 1991; 121:293–298.
18. Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. *Circulation* 2012; 125:620–637.
19. Hermans MP, Bouenizabila E, Amoussou-guenou DK, Ahn SA, Rousseau MF. Baseline diabetes as a way to predict CV outcomes in a lipid-modifying trial: a meta-analysis of 330 376 patients from 47 landmark studies. *Cardiovasc Diabetol* 2015; 14:60.
20. 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.
21. Quinn GR, Severdija ON, Chang Y, Singer DE. Wide variation in reported rates of stroke across cohorts of patients with atrial fibrillation. *Circulation* 2017; 135:208–219.
22. Zambon A, Arfè A, Corrao G, Zanchetti A. Relationships of different types of event to cardiovascular death in trials of antihypertensive treatment: an aid to definition of total cardiovascular disease risk in hypertension. *J Hypertens* 2014; 32:495–508.
23. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, Backer GD, *et al.*, SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003; 24:987–1003.
24. Marchant I, Boissel JP, Kassaï B, Bejan T, Massol J, Vidal C, *et al.* SCORE should be preferred to Framingham to predict cardiovascular death in French population. *Eur J Cardiovasc Prev Rehabil* 2009; 16:609–615; doi: 10.1097/HJR.0b013e32832da006.
25. Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. *Diabetes Care* 2007; 30:1292–1293.
26. Taverny G, Mimouni Y, LeDigarcher A, Chevalier P, Thijs L, Wright JM, *et al.* Antihypertensive pharmacotherapy for prevention of sudden cardiac death in hypertensive individuals. *Cochrane Database Syst Rev* 2016; 3:CD011745.
27. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, *et al.* Mortality and morbidity in patients receiving encainide, flecainide, or placebo. *N Engl J Med* 1991; 324:781–788.
28. Al-Gobari M, El Khatib C, Pillon F, Gueyffier F. β-blockers for the prevention of sudden cardiac death in heart failure patients: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord* 2013; 13:52; doi: 10.1186/1471-2261-13-52.
29. Le HH, El-Khatib C, Mombled M, Guitarian F, Al-Gobari M, Fall M, *et al.* Impact of aldosterone antagonists on sudden cardiac death prevention in heart failure and post-myocardial infarction patients: a systematic review and meta-analysis of randomized controlled trials. *PloS One* 2016; 11:e0145958.
30. Rahimi K, Majoni W, Merhi A, Emberson J. Effect of statins on ventricular tachyarrhythmia, cardiac arrest, and sudden cardiac death: a meta-analysis of published and unpublished evidence from randomized trials. *Eur Heart J* 2012; 33:1571–1581.

Reviewers' Summary Evaluations

Reviewer 1

Among strengths, good performance of the tool, and the potential educational use of this score (sudden death is quite an impressive outcome, even for older people). Among limitations are the dependence on age and use of data from the 1980s.