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Prediction of cardiovascular events from systolic or diastolic blood pressure

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Abstract

Over time, a focus on blood pressure has transferred from diastolic pressure to systolic pressure. Formal analyses of differences in predictive value are scarce. Our goal of the study was whether office SBP adds prognostic information to office DBP and whether both 24-h ambulatory SBP and 24-h ambulatory DBP is specifically important. The authors examined 2097 participants from a population cohort recruited in Copenhagen, Denmark. Cause-specific Cox regression was performed to predict 10-year person-specific absolute risks of fatal and non-fatal cardiovascular (CV) events. Also, the time-dependent area under the receiver operator curve (AUC) was utilized to evaluate discriminative ability. The calibration plots of the models (Hosmer-May test) were calculated as well as the Brier score which combines (discrimination and calibration). Adding both 24-h ambulatory SBP and 24-h ambulatory diastolic blood pressure did not significantly increase AUC for CV mortality and CV events. Moreover, adding both office SBP and office DBP did not significantly improve AUC for both CV mortality and CV events. The difference in AUC (95% confidence interval; *p*-value) was .26% (-.2% to .73%; .27) for 10-year CV mortality and .69% (-.09% to 1.46%; .082) for 10-year risk of CV events. The difference in AUC was .12% (-.2% to .44%; .46) for 10-year CV mortality and .04% (-.35 to .42%; .85) for 10-year risk of CV events. Moreover, for both CV mortality and CV events, office SBP did not improve prognostic information to office DBP. In addition, the Brier scores of office BP in both CV mortality and CV events were .078 and .077, respectively. Furthermore, the Brier scores were .077 and .078 in CV mortality and CV events of 24-h ambulatory. For the average population as those participating in a population survey, the 10-year discriminative ability for long-term predictions of CV death and CV events is not improved by adding systolic to diastolic blood pressure. This finding is found for ambulatory as well as office blood pressure.

KEYWORDS
Brier score, cardiovascular risk, competing risks, diastolic blood pressure, predictive value, systolic blood pressure

1 | INTRODUCTION

Hypertension is a contributing risk factor for cardiovascular disease (CVD).[1] In recent European Society of Cardiology (ESC) guideline, main recommendation for antihypertensive treatment of patients was regarded by the future risk of CV mortality, CV disease, or total mortality. The guideline state that decision on treatment should be according to risk estimates over 10 years.[2] In the 1970s and early 1980s, diastolic blood pressure (DBP) was regarded as superior to systolic blood pressure (SBP) to estimate future CV risk.[3] Later studies have challenged the importance of DBP in predicting coronary heart disease (CHD).[4] Along this line, Framingham Study data have indicated that SBP was superior to DBP for estimating future risk.[5] In particular, studies of the elderly have reported the importance of SBP.[6] A new study of adults reveals both systolic and diastolic blood pressures have great effects on the risk of adverse CV events.[7] A study was performed on population of 70–78-year-old in the Netherlands based on survival analysis approaches.[8]

Current knowledge on the importance of treating hypertension is partly based on older studies focusing on treating DBP and in part on newer studies focusing on treating SBP.[2] Therefore, it is crucial to have an international data and perform some analyses on whether BP estimation is more important than the other. The problem with available studies is that they all concentrated on estimates of hazard ratios from Cox models, including both SBP and DBP.[9] The analyze in several issues given that the goal is to examine 10-year risk prediction. First, the association between hazard ratio and prediction is known to be weak and also SBP and DBP are highly correlated, which is again a problem in comparative analysis.[10] Since Cox model consider the two correlated variables (SBP and DBP) and generally one of them will regarded more essential than the other, we used this model that the result does not necessarily lead to a significant more important effect on long-term prediction. The proper examination of the added value of, for example, SBP over DBP is to demonstrate that the area under the receiver operator curve (AUC) for 10-year prediction is improved by adding one BP to another.[10] AUC is used as the probability that a person who experiences the outcome, including CV mortality and CV events, received a higher predicted 10-year risk in comparison to a person who either died due to non-CV causes or were alive 10 years after the BP measurements. Differences in AUC were obtained to assess the influence of adding 24-h ambulatory SBP to 24-h ambulatory DBP office BP and adding office SBP to office DBP.

Such analysis of SBP versus DBP is not available.[8] Therefore, we have used an extensive population survey to examine whether the predictive importance of SBP and DBP differs when measured either as clinic BP or as 24-h ambulatory BP.

2 | MATERIALS AND METHODS

2.1 | Population characteristics

The cohort data included 2097 participants in the municipality of Glostrup.[11] At enrolment, BP measurements, including ambulatory SBP and DBP measurements during a 24-h period and office BP were registered. Additionally, the recorded data information consisted of baseline risk factors of CV outcomes and follow-up information CV events of participants. The participants' information about baseline CV risk factors were obtained with questionnaires.[9] Information about treatment for antihypertensive drugs, history of CVD and diabetes were registered.

2.2 | Main outcomes

The condition of fatal and non-fatal complications and survival status were reported based on register follow-up.[9] The main outcomes were CV mortality and CV events. The CV events included in both fatal and non-fatal CV complications. The combination of fatal and non-fatal CV events was considered as cerebrovascular death and non-fatal stroke; coronary events (death from ischemic heart disease, sudden death, non-fatal myocardial infarction, or coronary revascularization). Also, cardiac events were specified as the fatal or non-fatal heart failure and coronary events. Moreover, each of the aforementioned fatal and non-fatal CV events individually were done as the secondary outcomes.

2.3 | Measuring blood pressure

Office BP was recorded at least two times by random zero mercury sphygmomanometer for each participant. In the sitting position, office BP was registered after 5 min of rest and then the mean of two measurements were recorded. The portable device for BP monitoring was used to measure 24-h ambulatory BP during 24-h using a Takeda TM-2421 (A&D, Tokyo, Japan) device. Oscillometric AMBP measurements were used, which have passed validation tests.[12] BP measurements were performed from as 10.00 a.m. to 8.00 p.m., every 15 min during daytime and between 10.00 p.m. and 4.00 a.m., every 20 or 30 min during night-time.

Definition of hypertension with different types of BP measurement

(I) Systolic hypertension was defined when either the average daytime ambulatory SBP was equal or greater than 135 mmHg or

the average night-time ambulatory SBP was equal or greater than 120 mmHg.

(II) Normal systolic blood pressure was defined when the average daytime ambulatory SBP was less than 135 mmHg and the average night-time ambulatory SBP was less than 120 mmHg.

(III) Diastolic hypertension was defined when either the average daytime ambulatory DBP was equal or greater than 85 mmHg or the average night-time ambulatory DBP was equal or greater than 70 mmHg.

(IV) Normal diastolic blood pressure was defined when the average daytime ambulatory DBP was less than 85 mmHg and the average night-time ambulatory DBP was less than 70 mmHg.

(V) Isolated systolic nocturnal hypertension was defined when the average daytime ambulatory SBP was less than 135 mmHg and the average night-time ambulatory SBP was equal or greater than 120 mmHg.

(VI) Isolated diastolic nocturnal hypertension was defined when the average daytime ambulatory DBP was less than 85 mmHg and the average night-time ambulatory DBP was equal or greater than 70 mmHg.

(VII) Isolated systolic hypertension was defined as office SBP equal or greater than 140 mmHg and office DBP was less than 90 mmHg.[2]

2.4 | Statistical data analyses

In this cohort study, the reverse Kaplan–Meier estimator was used to calculate median follow-up time.[13] The average of 24-h ambulatory SBP and 24-h ambulatory DBP were obtained for each person. Imputations were conducted to account for missing values, including history of CVD ($n = 1$), current smoking ($n = 4$) and drinking habits ($n = 12$) and total serum cholesterol level ($n = 1$). Missing values of categorical and continuous variables were imputed by the mean and predicted value from a linear regression of non-missing observations with stratifying on sex.[14] We used two cause-specific Cox regression models for CV endpoints and non-CV, using formula represented in Supplementary material online to calculate the hazard rates[13] of the two primary outcomes (CV mortality and CV events).[15–17] For each cause-specific Cox regression model, these models were using (I) either 24-h ambulatory DBP, 24-h ambulatory SBP, or both 24-h ambulatory SBP and DBP as well as (II) either office DBP, office SBP, or both office SBP and DBP. The variables are, including sex, age, body mass index (BMI), current drinker and smoker status, cholesterol level, history of diabetes and CVD, antihypertensive drugs, interactions between treatment with antihypertensive drugs and the BP variables, including 24-h ambulatory SBP, 24-h ambulatory DBP, office SBP and office DBP. Reported are hazard ratios (HRs) with 95% confidence interval (CI) for one standard deviation (SD) increase in each BP variable. Using the Cox regression models and based on a formula of prior research,[16] we estimated the 10-year absolute risk of the primary outcomes.[15–17] The quantiles of violin plots are drawn by person-specific prediction to risks and changes in predicted 10-year risks. The quantiles change of predicted 10-year risks are acquired in both retrospectively and conditional on outcome after 10 years by inverse probability of censoring weighting approach. Results are demonstrated by the median difference (Q2), 1st quartile (Q1) and 3rd quartile (Q3) of predicted risks. The scatter plots are represented to reveal the changes in person-specific 10-year CV risk predictions when 24-h ambulatory SBP/ office SBP is added to 24-h ambulatory DBP/office DBP. Discrimination ability was calculated through time-dependent AUCs to evaluate discriminative ability in competing risk.[18,19] The time-dependent AUC of a risk prediction model is the probability that an individual who experienced the CV event within 10-years receives a higher predicted 10-year risk than an individual who either was alive and event-free 10 years after the BP measurements or died due to non-CV causes within 10-years after the blood pressure measurement. The predicted 10-year risks of CV events are given in separated groups, including age, history of CVD, antihypertensive treatment, diastolic and systolic hypertension, nocturnal diastolic hypertension and isolated systolic hypertension. To evaluate the significance of adding 24-h ambulatory SBP to 24-h ambulatory DBP together with adding office SBP to office DBP, the differences in AUC were obtained with their 95% confidence limits. The Brier score measures average discrepancies between the true disease outcome and the predictive values from the model.[19,20] The R software version 3.5.1 was used for statistical analysis.[21]

3 | RESULTS

3.1 | Baseline characteristics of study participants

The median (Q1-Q3) follow-up time was 11.6 (12.6-12.7) years and the mean (SD) of participants' age at baseline was 56.4 (10.3). During follow-up, 283 were diagnosed with a fatal or non-fatal CV event and 127/187 died because of CV/non-CV causes. Table 1 shows the descriptive information of the subject characteristics in the cohort study.

3.2 | The changes of person-specific 10-year risk predictions

Figure 1A reveals the changes in predicted 10-year risks by median difference (Q1-Q3) in CV mortality and CV events. The violin plot of Figure 1A shows the median change (Q1–Q3) of person-specific risks was .00009% (-.1% to .08%) and .09% (-1%, .5%) in CV mortality and CV events, respectively. Figure 1B,C shows predicted person-specific 10-year risks by adding 24-h ambulatory SBP to 24-h ambulatory DBP and conventional risk factors in CV mortality and CV events, respectively. That is to say; it demonstrates the rate of changes of person-specific 10-year risk predictions when 24-h SBP is added to 24-h DBP and conventional risk factors. The scatter plots reveal that the information obtained by adding 24-h SBP did not have any effect on the majority of people. In 90% of the individuals, the predicted 10-year risk of CV mortality (CV events) changed by less than .7% (4%). It means that the

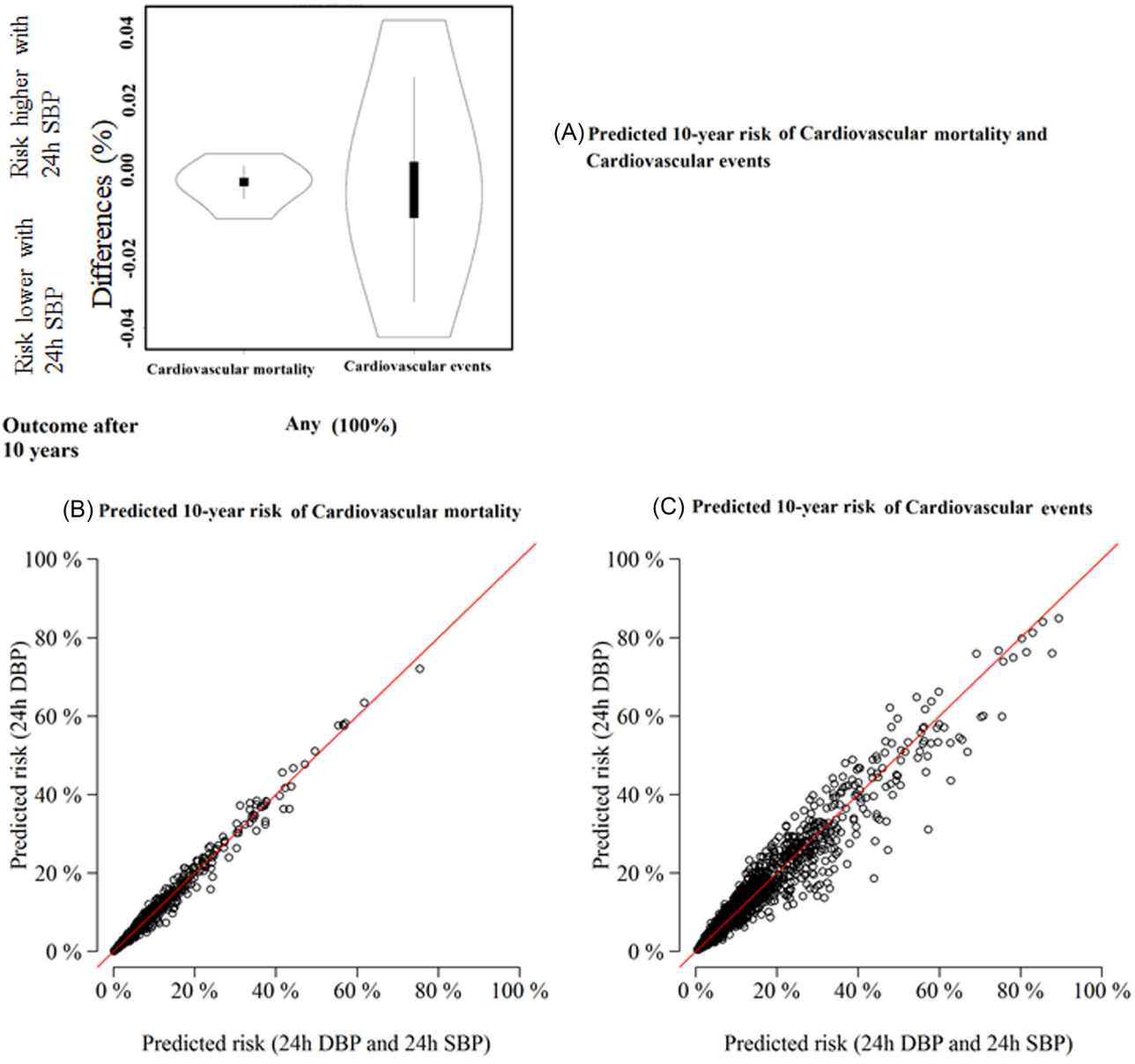

FIGURE 1 Diastolic 24-h blood pressure and systolic 24-h blood pressure predict person-specific 10-year absolute risk in CV mortality and CV events (A). Violin plots reveal median, interquartile range, CI 95%, higher and lower probabilities to predict of absolute risks according to both diastolic 24-h ambulatory BP and systolic 24-h ambulatory BP vs. only diastolic ambulatory 24-h BP. Diastolic 24-h blood pressure and systolic 24-h blood pressure predict person-specific 10-year absolute risk in CV mortality (B) and CV events (C). Scatter plots reveal person-specific predictions based on both diastolic 24-h ambulatory BP and systolic 24-h ambulatory BP vs. only diastolic 24-h ambulatory BP

prognostic information for evaluating the 10-year risk of CV complications is not substantially improved by adding 24-h ambulatory SBP to diastolic 24-h ambulatory DBP.

Figure 2A reveals the changes in predicted 10-year risks by median difference (Q1-Q3) in CV mortality and CV events. The violin plot of Figure 2A shows the median change (Q1–Q3) of person-specific risks was .00007% (-.08% to .04%) and -.01% (-.3%, .2%) in CV mortality and CV events, respectively.

Figure 2B,C predicts person-specific 10-year risks by adding systolic office BP to diastolic office BP in CV mortality and CV events, respectively. Simply put, it illustrated the changes in person-specific 10-year risk predictions when office SBP is added to office DBP and conventional risk factors. More specifically, the figure demonstrates that the information provided by adding office SBP did not affect the greater number of individuals. For 90% of the individuals, the amount of change in predicting the 10-year absolute risk of CV mortality (CV events) obtained .7% (2%). The finding indicates that predictive value for assessing the 10-year risk of CV complications is not substantially improved by adding office SBP to office DBP.

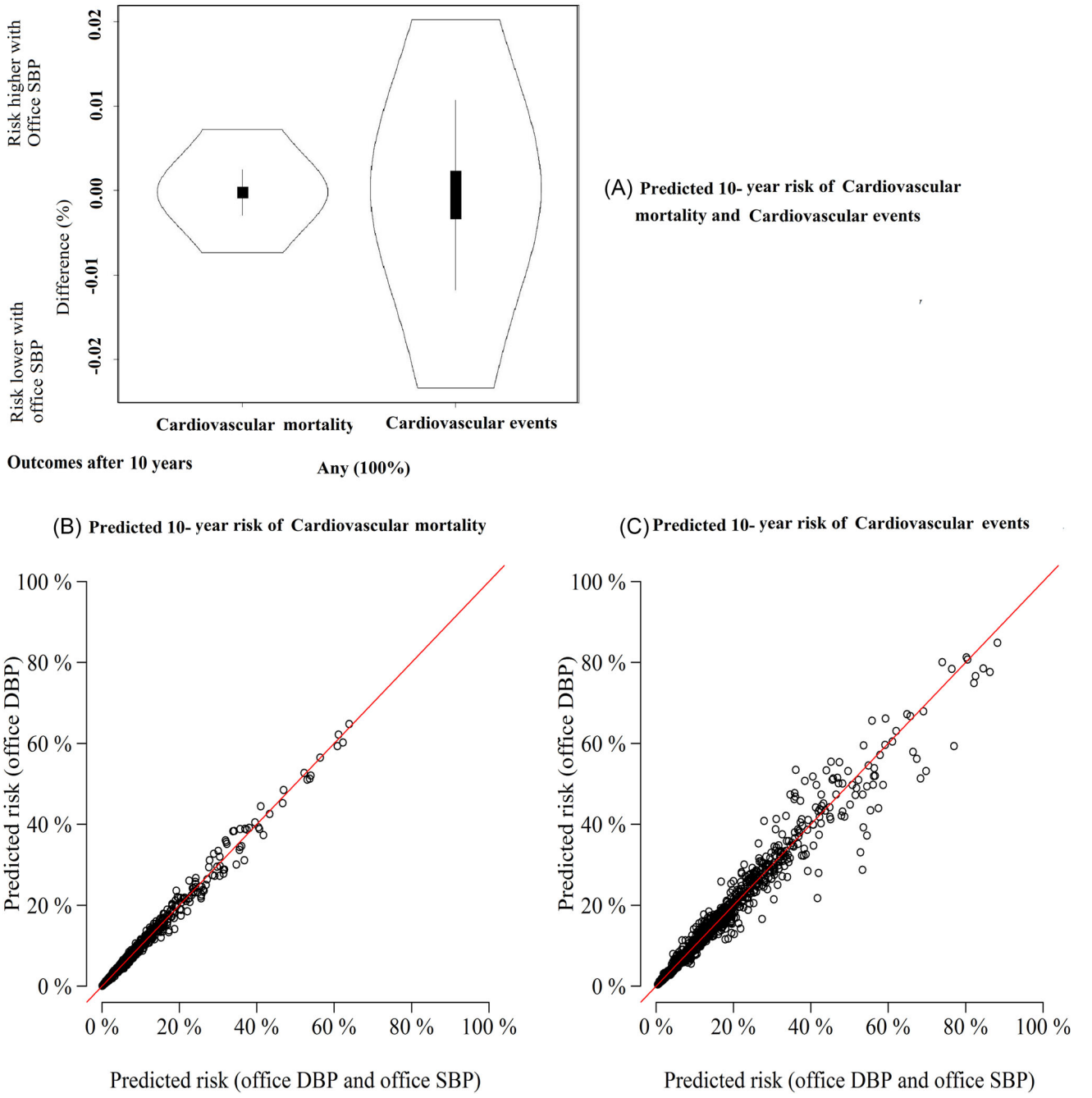

FIGURE 2 Diastolic office blood pressure and systolic office blood pressure predict person-specific 10-year absolute risk in CV mortality and CV events (A). Violin plots reveal median, interquartile range, CI 95%, higher and lower probabilities to predict of absolute risks according to both diastolic office blood pressure and systolic office blood pressure vs. only diastolic office BP. Diastolic office blood pressure and systolic office blood pressure predict person-specific 10-year absolute risk in CV mortality (B) and CV events (C). Scatter plots reveal person-specific predictions based on both diastolic office and systolic office BP versus only diastolic office BP

3.3 | The differences in AUC

Table 2 reveals that by adding 24-h SBP to 24-h DBP and also adding office SBP to office DBP, how much does AUC change in both cases CV mortality and CV events.

In both outcomes and BPs, the AUC for each 10-year outcome (%) obtained from predictions completed by combined cause-specific Cox regression (including 24-h DBP and conventional risk factors) was shown in the first row of Table 1. Also, the differences in AUC (%) for predictions (including 24-h SBP rather than 24-h DBP and predictions obtained by adding 24-h SBP, 24-h DBP and conventional risk factors) were shown in other two rows.

The table shows the differences in AUC predicted 10-year absolute risks by adding 24-h ambulatory SBP to 24-h ambulatory DBP. When

TABLE 1 Demographic and basic features of the subjects in the cohort study

Characteristics	*N* = 2097
Male sex, *n* (%)	1091 (52)
Smoker, *n* (%)	907 (43.3)
Currently alcohol intake, *n* (%)	1803 (86.5)
Hypertension treatment, *n* (%)	312 (14.9)
History of cardiovascular disease, *n* (%)	126 (6)
Diabetes, *n* (%)	70 (3.3)
Systolic and diastolic blood pressure, *n* (%)	
Normal systolic blood pressure	957 (45.6)
Nocturnal systolic blood pressure	91 (4.3)
Normal diastolic blood pressure	1277 (60.9)
Nocturnal diastolic blood pressure	204 (9.7)
Isolated systolic hypertension	251 (12.0)
Age (years), mean (SD)	56.4 (10.3)
Body mass index (kg/m^2), mean (SD)	26.0 (4.1)
Total cholesterol (mmol/L), mean (SD)	6.2 (1.1)
Systolic and diastolic blood pressure (mmHg), mean (SD)	
Systolic office BP	131.2 (19.3)
Systolic 24-h ambulatory BP	128.6 (12.8)
Diastolic office BP	83.27 (10.72)
Diastolic 24-h ambulatory BP	75.11 (8.5)
Follow-up time, years, median (IQR)	12.7 (12.6,12.7)

24-h ambulatory SBP is added to 24-h ambulatory DBP, it did not significantly increase AUC for 10-year predictions of CV mortality (change at AUC, .26%; 95% CI, -.2% to .73%; *p*-value = .27). In addition, by adding 24-h ambulatory SBP to 24-h ambulatory DBP did not significantly enhance AUC for CV events (change at AUC, .69%; 95% CI, -.09% to 1.46%; *p*-value = .082). Moreover, if office SBP is added to office DBP, it did not significantly improve AUC for 10-year predictions of CV mortality (change at AUC, .12%; 95% CI, -.2% to .44%; *p*-value = .46) and also in CV events (change at AUC, .04%; 95% CI, -.35% to .42%; *p*-value = .854).

3.4 | Calibration and discrimination

Figure 3 demonstrates the calibration plots of the two cases, including CV mortality and CV events in 24-h ambulatory BP. Also, the Brier scores of office BP in both CV mortality and CV events cases were .077 (CI: .068, .086) and .078 (CI: .069, .087), respectively.

In addition, the calibration plots of the two approaches, CV mortality and CV events of office BP are represented in Figure 4, which the Brier scores are .078 (CI: .068, .87) and .077 (CI: .068, .086) in CV mortality and CV events

3.5 | Supplemental material online

The changes in AUC based on secondary outcomes and subgroup outputs based on some essential variables, including age, history of CVD,

TABLE 2 AUC and differences in AUC in 24-h ambulatory DBP versus SBP and office DBP versus SBP

	24-h DBP and 24-h SBP	
Cardiovascular mortality	**Δ AUC [95% CI]**	***p*-Value**
10-year risk predictions 24-h DBP	85.03	–
10-year risk predictions 24-h SBP	.45 [-.28, 1.17]	.228
10-year risk predictions 24-h DBP and 24-h SBP	.26 [-.2, .73]	.266
Cardiovascular events		
10-year risk predictions 24-h DBP	80.47	–
10-year risk predictions 24-h SBP	.69 [-.11, 1.49]	.091
10-year risk predictions 24-h DBP and 24-h SBP	.69 [-.09, 1.46]	.082
	Office DBP and office SBP	
Cardiovascular mortality	**Δ AUC [95% CI]**	***p*-value**
10-year risk predictions office DBP	85.1	–
10-year risk predictions office SBP	-.04 [-.68, .59]	.896
10-year risk predictions office DBP and office SBP	.12 [-.2, .44]	.461
Cardiovascular events		
10-year risk predictions office DBP	80.41	–
10-year risk predictions office SBP	-.25 [-.85, .35]	.413
10-year risk predictions office DBP and office SBP	.04 [-.35, .42]	.854

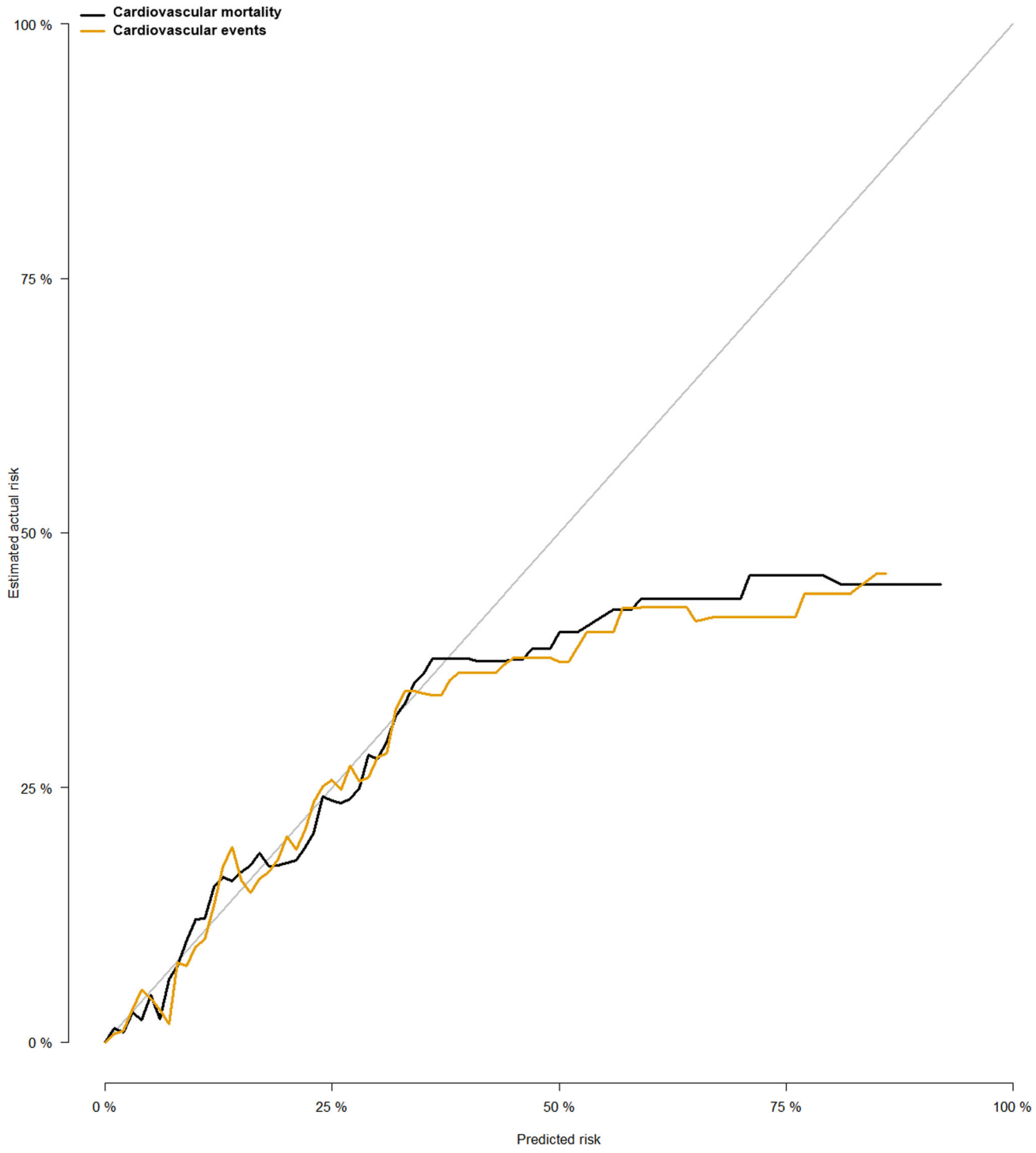

FIGURE 3 Calibration plots of the models (CV mortality and CV events) based on 24-h ambulatory BP

antihypertensive treatment, hypertension, nocturnal hypertension and isolated hypertension effect on person-specific 10-year absolute risks of CV mortality vs. non-CV mortality and CV events vs. non-CV mortality are given in Tables S1-S3 and Figure S1 in Supplemental material part.

4 | DISCUSSION

In this Glostrup cohort study, the findings show that (I) adding 24-h ambulatory SBP to 24-h ambulatory DBP does not provide any extra prognostic information for 10-year person-specific absolute risks of

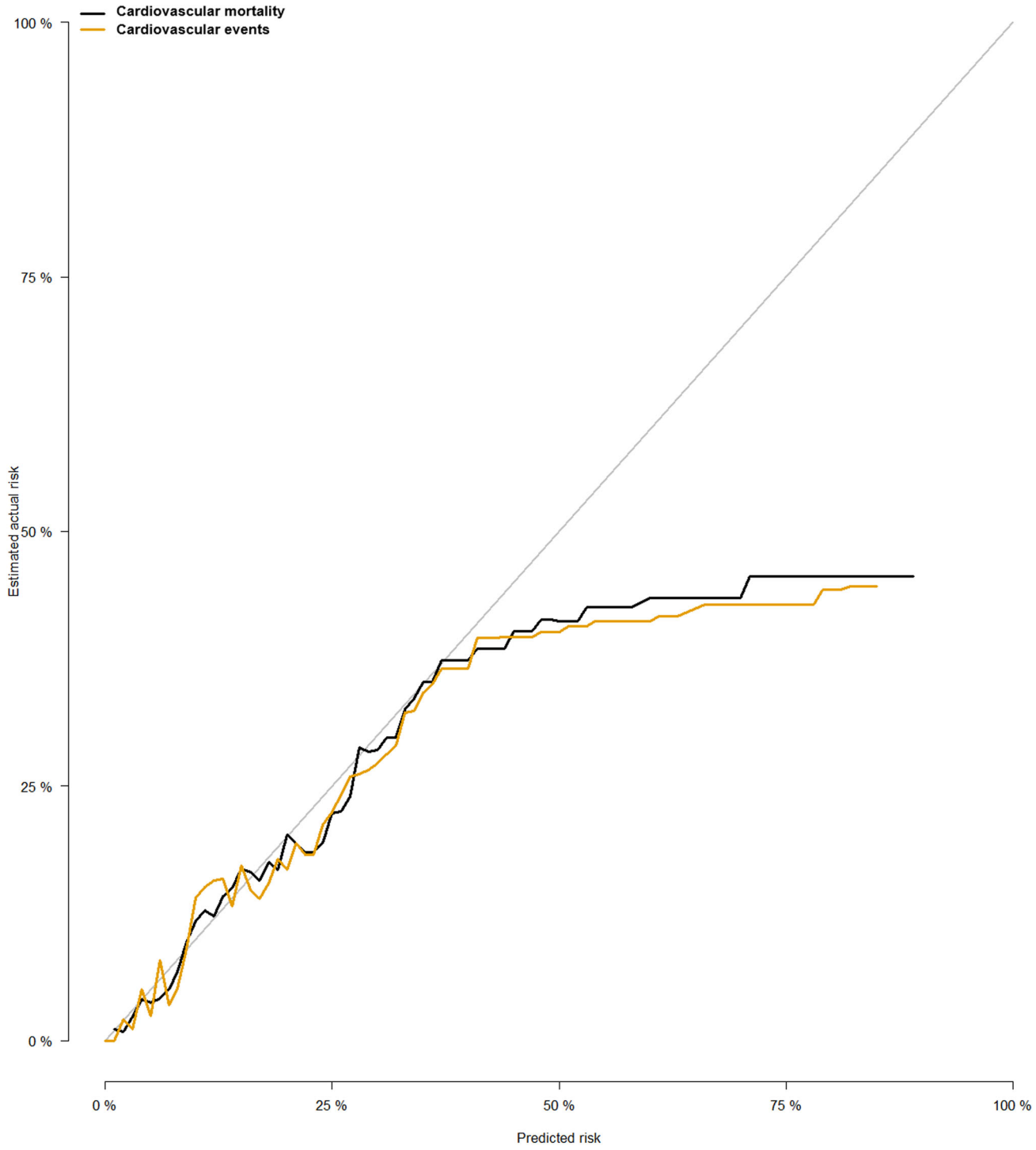

FIGURE 4 Calibration plots of the models (CV mortality and CV events) based on office BP

CV complications (II) adding office SBP to office DBP does not obtain additional predictive accuracy for 10-year risks of CV events. In other words, the average population 10-year risk of CV complications is identically predicted from SBP and DBP for both 24-h ambulatory BP and office BP.

Previous studies focused on estimating hazard ratios using Cox models.[9] These methods have some fundamental weaknesses, including to choose one important variable between two correlated variables and to ignore the distribution of events during the follow-up by using average HR. For these reasons, it seems that using a more advanced model is necessary to estimate of person-specific predicted 10-year risks and cause-specific hazard ratios. Also, a few studies have been done based on discriminative ability to assess predictive performance.[8,14] This long-term risk prediction of person-specific is

related to both approaches, including non-CV mortality in competing risk and the relationship between BP and CV event. Also, our model is well able to survey two correlated variables, including DBP and SBP and necessarily show a significantly more essential effect on long-term prediction.

The present study obtained the hazard ratios using cause-specific cox regression and considered person-specific predictions for 10-year absolute risks of CV outcomes. Moreover, the current cohort study assessed the statistical significance of hazard ratios and predictive accuracy of long-term person-specific predictions. Although high significant hazard ratios, it does not lead to substantial changes for long-term predictions.

According to the findings, the prognostic information for assessing the 10-year risk of CV complications is not improved by adding 24-h ambulatory SBP to 24-h ambulatory DBP and also adding office SBP to office DBP is to absolute risks obtained by office DBP alone. In both comparisons, the prognosis information does not change when the information of SBP is added to DBP in the greater number of persons (Figures 1 and 2).

The results indicate the application of discriminative ability by using a time-dependent area under the receiver operating characteristic curve (AUC) for competing risks to evaluating predictive accuracy. Despite high hazard ratios in the cause-specific Cox regression model, the effects do not change into statistically significant improvements for long-term person-specific predictions (Table 2). The concept of AUC is the probability that an individual who experiences the CV events or CV mortality received a higher predicted 10-year risk than an individual who was alive 10 years after the BP measurements or died due to non-CV causes. Based on the results, 24-h ambulatory SBP is not able to add additional prognostic information to 24-h ambulatory DBP using time-dependent AUC of discrimination ability in both CV mortality and CV events (Table 2). Also, office SBP cannot add prognostic information to office DBP in CV mortality and CV events (Table 2).

To our knowledge, this study can calculate the long-term risk predictions of individuals. Our research also takes a step further by evaluating the cause-specific Cox regression model to predict 10-year person-specific absolute risks of CV events.

5 | CONCLUSIONS

It is concluded from the findings of our study that adding SBP to DBP does not improve the 10-year predictions of fatal and non-fatal CV events for both 24-h ambulatory BP and office BP

6 | RESEARCH LIMITATIONS

The main implication of the study is that it can probably be concluded that it is not crucial whether SBP or DBP is used to screen an average population, both BPs are equally important for physicians in other words. The long-term follow-up on CV events and the large sample size are the strong points of the study. The study's critical weakness is to participate in healthier people than general people because of taking part by invitation and it returns to the nature of population study. Therefore, healthier people attend more than the general population in the study. Besides, a lack of patients with established hypertensive diseases is another main limitation. Moreover, it should be noted that these findings resulted from healthy individuals without CV disease and more studies on patients with different clinical characteristics are needed to conclude about the assumption.

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CONFLICT OF INTEREST DISCLOSURE

The authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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