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Ambulatory blood pressure adds little to Framingham Risk Score for the primary prevention of cardiovascular disease in older men: secondary analysis of observational study data

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ABSTRACT

Objective: To determine the incremental value of ambulatory blood pressure (BP) in predicting cardiovascular risk when the Framingham Risk Score (FRS) is known.

Methods: We included 780 men without cardiovascular disease from the Uppsala Longitudinal Study of Adult Men, all aged approximately 70 years at baseline. We first screened ambulatory systolic BP (ASBP) parameters for their incremental value by adding them to a model with 10-year FRS. For the best ASBP parameter we estimated HRs and changes in discrimination, calibration and reclassification. We also estimated the difference in the number of men started on treatment and in the number of men protected against a cardiovascular event.

Results: Mean daytime ASBP had the highest incremental value; adding other parameters did not yield further improvements. While ASBP was an independent risk factor for cardiovascular disease, addition to FRS led to only small increases to the overall model fit, discrimination (a 1% increase in the area under the receiver operating characteristic (ROC) curve), calibration and reclassification. We estimated that for every 10 000 men screened with ASBP, 141 fewer would start a new BP-lowering treatment (95% CI 62 to 220 less treated), but this would result in 7 fewer cardiovascular events prevented over the subsequent 10 years (95% CI 21 fewer events prevented to 7 more events prevented).

Conclusions: In addition to a standard cardiovascular risk assessment it is not clear that ambulatory BP measurement provides further incremental value. The clinical role of ambulatory BP requires ongoing careful consideration.

Strengths and limitations of this study

- Strengths include the high event rate and good precision for our estimates, reliable ascertainment of outcomes with minimal losses to follow-up, relatively untreated population rigorous statistical analysis and clinically relevant results
- Limitations include an older age all male population who were all very close in age, home advantage to ambulatory systolic blood pressure (ASBP) in the models, assumption of 20% risk reduction with treatment. In combination these limitations mean our estimates are 'best case' estimates for this population, and the incremental value of ASBP may be even lower in other populations.

INTRODUCTION

There is increasing interest in measuring patients' ambulatory blood pressure (BP), both to confirm a diagnosis of hypertension and to monitor response to treatment. For example, the UK's National Institute for Health and Care Excellence (NICE) 2011 guidelines on hypertension recommend the use of ambulatory BP measurement to confirm the diagnosis of hypertension in all patients using the mean of measurements taken during waking hours.[1] Ambulatory BP monitoring (ABPM) uses measurements made by an automated device over a 24 h period and has a number of potential advantages. There is less likely to be 'white coat hypertension' where BP is raised because the patient is anxious about the measurement and the 'usual' BP level is more accurately estimated by averaging several measurements over 1 day. In addition, the within-day variability of the patient's BP is able to be estimated because multiple measurements are taken. The amount of BP variability and the presence of BP that does not decrease at night (non-dipping) appear to be independent risk factors for cardiovascular disease (CVD).[2 3] If BP alone is considered (separate to other cardiovascular risk factors), then ambulatory BP measurements are better at predicting CVD than clinic measurements.[4–9]

In parallel, clinical guidelines are increasingly recommending that the decision to start therapy to lower BP be based at least partly on the individual's overall absolute risk of CVD[10–15] using risk prediction scores such as the Framingham equation,[16] rather than just considering the BP level alone. Other CVD risk equations include PROCAM,[17] SCORE,[18] ASSIGN[19] and QRisk.[20] These risk scores incorporate information about the individual's gender, age, total cholesterol, high-density lipoprotein (HDL) cholesterol, diabetes and smoking status in addition to systolic BP (SBP) to arrive at their absolute risk of a cardiovascular event within the next 5–10 years.[21] Ambulatory BP measurements are only likely to be taken after an initial BP screening in the clinic.[22] Therefore, to properly assess the value of ambulatory BP measurement, we need to estimate the incremental value in predicting cardiovascular disease, above and beyond risk prediction that includes clinic BP measurement.

There is some evidence that adding ambulatory SBP (ASBP) values to clinic SBP, but ignoring other risk factors, significantly improves the prediction of individuals' cardiovascular risk.[23] Other evidence suggests that additional measurements of clinic SBP only marginally add to a single clinic SBP measurement when this is combined with traditional risk factors in the prediction of an individual's cardiovascular risk.[24] The incremental value of ASBP above and beyond risk scores based on the Framingham equation is unknown.

We aimed to estimate the incremental value of ambulatory BP measurement to 10-year cardiovascular risk scores based on the 2008 Framingham equation.[16] We tested ambulatory BP measures representing the average and the variability of BP (see Methods section, statistical analysis for details).

METHODS

Study design and sample

We used data from the Uppsala Longitudinal Study of Adult Men (ULSAM). The methods for this study have been described previously.[25] Briefly, ULSAM is an ongoing longitudinal epidemiological study based on all available men born between 1920 and 1924 in Uppsala county, Sweden. The current paper uses baseline data from the age 70 survey which was conducted during 1991–1995. Of the original 1681, 1221 men in the ULSAM study who were still alive and residing in Uppsala took part in the age 70 reinvestigations. Of these, 835 men were free of CVD at baseline and a total of 780 men (93.4%) had valid data for 24 h ASBP and all Framingham covariates (age, total cholesterol, HDL cholesterol, clinic SBP, smoking status, diabetes status, BP-lowering treatment).

At baseline, approximately 9% and 35% were on lipid and BP-lowering treatment, respectively.

Measurement of risk factors

Twenty-four hour ASBPs were recorded using Accutracker 2 equipment (Suntech Medical Instruments Inc, Morrisville, North Carolina, USA). The device was attached to the patient's non-dominant arm by a skilled laboratory technician, and BP recordings were made every 20 min for 24-h starting at 1100 h. SBP data were edited by omitting all readings of zero and >270 and <80 mm Hg, and all readings where the difference between SBP and diastolic BP was less than 10 mm Hg. Short fixed clocktime intervals were used, defining daytime as 10:00 to 20:00 and night-time as midnight to 06:00 as previously suggested.[26] The median number of daytime measurements available for analysis per man was 30 (IQR 25–33, five men had less than 14 measurements).

Clinic BP was measured in the right arm of supine patients with a sphygmomanometer using the appropriate cuff size; recordings were made to the nearest 2 mm Hg twice after 10 min rest, and the mean of the two measurements was used for the analyses. Serum total and HDL cholesterol levels were determined with standardised enzymatic methods. Cigarette smoking status was ascertained through interview reports. Diabetes was defined by applying 1985 WHO criteria to fasting glucose and oral glucose tolerance test. BP-lowering treatment was determined using a questionnaire.

Follow-up and outcome events

The population was followed for up to 17.3 years since the start of the investigation at age 70 years. The median follow-up period was 14 years (IQR 6.6–15.5 years). End of follow-up was at the first of: cardiovascular event, loss to follow-up, last follow-up visit.

Outcome variables were defined using data from the Swedish Hospital Discharge and Cause of Death Registries. Cardiovascular morbidity was defined as a composite end point, including death or first hospitalisation from coronary heart disease (ICD-9 codes 410–414, or ICD-10 codes I20–I25) and stroke (ICD-9 codes 431–436, or ICD-10 codes I61–I66). A quality control study by the Swedish centres of the WHO MONICA study previously showed good agreement between official routine mortality statistics and registration of myocardial infarction.[27]

Statistical analysis

We used Cox proportional hazard models for analysis. The proportional hazards and linearity assumptions were tested for each covariate and found to hold.

We applied a log transformation to all ASBP variables for consistency with the Framingham risk equation. We included these in the models as continuous variables. Framingham Risk Scores (FRS) were calculated using the published equation for 10-year risk.[16]

Descriptive statistics were performed for traditional risk factors and calculated FRS and unadjusted HRs estimated. We built a base model for comparison which included only FRS. We then screened a number of different ambulatory BP measures for incremental

prediction by adding them one at a time to the base model. We used likelihood ratio tests and improvements in discrimination (c-statistic) to select ASBP measures that were most predictive of cardiovascular risk above and beyond FRS. Measures tested were: mean daytime, mean night-time, minimum night-time, maximum night-time, maximum daytime, minimum daytime, Range daytime, coefficient of variation (CV) daytime, SD night-time, CV night-time, SD daytime, IQR daytime, IQR night-time and the range of night-time BP. We fitted each ambulatory BP measure as one covariate (regardless of whether men were on BP-lowering treatment or not). The best 'average' measure and the best 'variability' measure for each of daytime and night-time were then added together to the model, as well as the best average measures for daytime and night-time together to evaluate for further improvements. We also evaluated equivalent diastolic BP measures in this way.

After selecting the best ASBP measures, we estimated other metrics of incremental value compared to the base model including HRs, measures of overall risk prediction and estimated clinical effects of screening with ambulatory BP. We estimated standardised HRs (per SD), before and after adjustment for the FRS. We estimated equivalent HRs for FRS for comparison.

The 10-year predicted risk for each man was calculated from models that included (1) FRS only and (2) FRS and ASBP. The probability of a cardiovascular event within 10 years was estimated by raising 10-year baseline survival to the exponential of the sum of the linear predictors. The predicted 10-year risk from the Cox model including FRS only tended to be higher than the actual FRS itself. By including FRS as a covariate in the model based on outcome data from this cohort, we were in effect recalibrating their risk.

We assessed improvements in overall prediction by estimating calibration (Groennesby-Borgan tests[28]) in addition to the likelihood ratio tests and changes in discrimination (c-statistic) calculated already. We also examined reclassification by calculating the number of cases (CVD within 10 years) and non-cases (no CVD within 10 years) who moved up or down across the 20% treatment threshold) and constructed reclassification plots.

We estimated the difference in number of men who would be started on treatment (or have treatment escalated for those already on treatment) by comparing the number of men above the 20% 10-year threshold when just FRS was used in the model with the number of men above the 20% 10-year threshold when ASBP and FRS were used. We calculated 95% confidence limits using standard formula for paired data.[29]

Finally, we calculated the potential difference in the number of cardiovascular events for every 10 000 men screened with ASBP, using a modified version of the method described in ref. [30] We assumed that men above the 20% 10-year threshold would be started on treatment, or have treatment escalated. We assumed that treatment (or escalation in treatment) would have an effect of 0.2 relative risk reduction (based on data from ref. 31).

We first calculated the mean of the 10-year predicted risks for the models with the Framingham scores. We then applied a treatment effect with a reduction in risk of 20% to those people with estimated 10-year predicted risks greater than 20%. Combining these treatment reduced risks with the unchanged risks for people who had calculated risks below the treatment threshold, we calculated a second mean. The difference in these means, multiplied by 10 000, provides the number of events prevented per 10 000 screened when the risk prediction models with the Framingham scores are used. We carried out the same calculations for the models with Framingham scores and ASBP. The number of events prevented was compared and the difference between Framingham only models and Framingham and ambulatory BP calculated.

$$\begin{aligned}&\text{Events prevented with addition of ASBP} =\\&(\text{Events prevented using ASBP and clinic SBP}\\&-\text{Events prevented using clinic SBP})\\&\times \text{proportion who had an event} \times 10000\\&((\overline{\text{risk}}_{2,\text{all untreated}} - \overline{\text{risk}}_{2,\text{treatment reduced and unchanged}})\\&-(\overline{\text{risk}}_{1,\text{all untreated}} - \overline{\text{risk}}_{1,\text{treatment reduced and unchanged}}))\\&\times 10000\end{aligned}$$

We calculated 95% CIs for number of events prevented using 2000 bootstrap samples.

SAS V.9.3 was used for all analyses.

RESULTS

We included 780 men with 412 events in our analysis where data were available on ambulatory BP and all traditional risk factors. Summary statistics are presented in table 1. Age was not significantly associated with CVD in this dataset, probably because of its small variability (most men were aged very close to 71 years). Total cholesterol was also not significantly associated with CVD. Other traditional risk factors had significant associations with CVD in expected directions.

Table 2 shows the improvement in CVD risk prediction when different ASBP measures were added to a model that included calculated FRS. The largest improvements in overall model fit and discrimination were from mean daytime SBP. Substitution for, or addition of other, ASBP variables did not lead to further improvements. Evaluation of diastolic BP measures instead of SBP did not result in further improvements.

Table 3 shows the association between FRS, mean daytime ASBP and CVD. Before adjustment for the other risk factor the HR was 1.43 per SD increase in FRS and 1.31 per SD increase in ASBP. After adjustment for the other risk factor, the HR was 1.34 per SD increase in

Table 1 Summary data for traditional cardiovascular risk factors and ambulatory systolic BP

Characteristic	Summary measure*	Unadjusted HR per SD
Age (years)	71.1 (0.77)	1.04 (0.94 to 1.15)
Total cholesterol (mmol/L)	5.7 (1.3)	0.97 (0.88 to 1.07)
HDL cholesterol (mmol/L)	1.3 (0.43)	0.87 (0.79 to 0.97)
BP treatment	210/780 [26.9]	1.85 (1.51 to 2.27)
Smoking	166/780 [21.2]	1.52 (1.21 to 1.91)
Diabetes	80/780 [10.2]	1.59 (1.19 to 2.10)
Office systolic BP (mm Hg)	146 (26)	1.31 (1.19 to 1.44)
10-year FRS	0.37 (0.22)	1.46 (1.32 to 1.62)
10-year FRS>20%	733/780 [94.0]	1.75 (1.07 to 2.84)
Subsequent CVD events	412/780 [52.7]	

*Values are median (IQR) or n [%].
BP, blood pressure; CVD, cardiovascular disease; FRS, Framingham Risk Score; HDL, high-density lipoprotein.

FRS and 1.20 per SD increase in ASBP, demonstrating that both were independent risk factors, but FRS was the stronger predictor of the two.

Table 4 summarises the small improvements in overall risk prediction for an individual when mean daytime ASBP was added to calculated FRS in the risk model (ie, where there is one new test that combines FRS and ASBP). The overall calibration was better when ASBP was added to FRS, but the actual number of events observed vs predicted for each risk decile (used in the Gronnesby test) appeared similar for both models (see figure 1A, B). The very small improvements in reclassification are illustrated in figure 2A, B: most men were not reclassified downwards or upwards across the treatment threshold when ASBP was used as well as FRS. There would have been no change in the recommendation of treatment for 98.2% (491/500) of men who did not have an event within 10 years and 99.3% (278/280) of men who did have an event within 10 years. These percentages were the same when Kaplan-Meier life table estimates were used and allowance made for censoring (70 men without CVD died of other causes before 10 years). Figure 2A shows that of the 500 men who did not have a cardiovascular event, 9 were correctly

Table 2 Impact of adding ambulatory systolic BP measures to 10-year Framingham CVD risk

Ambulatory BP measure added to base model*	Improvement in overall fit (likelihood ratio test, p value)	Improvement in discrimination (c-statistic)
One ABPM covariate		
Mean daytime SBP	0.0006	0.011
Mean night-time SBP	0.0008	0.007
Minimum night-time SBP	0.003	0.003
Maximum night-time SBP	0.009	0.003
Maximum daytime SBP	0.04	0.003
Minimum daytime SBP	0.11	0.003
CV daytime SBP	0.39	–
SD night-time SBP	0.41	–
SD daytime SBP	0.60	–
Range daytime SBP	0.62	–
IQR daytime SBP	0.62	–
IQR night-time SBP	0.74	–
CV night-time SBP	0.74	–
Range night-time SBP	0.76	–
Two ABPM covariates		
Mean daytime SBP and mean night-time SBP	0.0008	0.010
Mean night-time SBP+minimum night-time SBP	0.004	0.007
Mean daytime SBP+maximum daytime SBP	0.003	0.010
Ratio mean daytime SBP to mean night-time SBP	0.32	–

*Reference model: Framingham 10-year risk score.
ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CVD cardiovascular disease; SBP, systolic blood pressure.

Table 3 Associations between FRS, ASBP and cardiovascular disease

Association	HR per SD (95% CI)
FRS, unadjusted	1.43 (1.30 to 1.57)
FRS, adjusted for ASBP*	1.34 (1.22 to 1.48)
ASBP, unadjusted	1.33 (1.21 to 1.46)
ASBP adjusted for FRS*	1.21 (1.10 to 1.34)

*Adjusted predictions, allowing for effects of FRS and ASBP.
BP, blood pressure; FRS, 10-year Framingham Risk Score; ASBP, mean daytime ambulatory systolic blood pressure.

reclassified downwards when ASBP was included in the model (including one man who died at just over 8.5 years of follow-up). None were incorrectly reclassified upwards when ASBP was included in the model. Figure 2B shows that of the 280 men who did have a cardiovascular event, 2 were incorrectly reclassified downwards and none correctly reclassified upwards when ASBP was included in the model.

Using a risk model with just FRS, we estimated that for every 10 000 men screened with ASBP, all 10 000 would be treated and 723 cardiovascular events prevented (95% CI 650 to 796 events prevented). Using a risk model that combines FRS and ASBP, 9859 would be treated (95% CI 9776 to 9942 treated) and 715 cardiovascular events prevented (95% CI 635 to 795 events prevented). Using FRS and ASBP, 141 fewer men would be treated (95% CI 58 to 224 less treated) and 7 fewer events prevented (95% CI 20 fewer events prevented to 6 more events prevented).

DISCUSSION

Our analysis of data from the ULSAM found that 24-h ABPM added little to the CVD risk prediction of the FRS. The addition of mean daytime ASBP might lead to fewer men started on treatment, but this may be at the expense of fewer cardiovascular events prevented. The estimated size of these differences is small, and the clinical significance unclear: for every 10 000 men screened with ASBP, approximately 141 fewer men would be started on treatment (95% CI 58 to 224 less treated) but 7 fewer cardiovascular events would be prevented (95% CI 20 fewer events prevented to 6 more events prevented).

Our study has several strengths. The underlying methods used in the ULSAM study are robust. Although this is a modestly sized study, the event rate was high and hence our estimates had good precision. The study population was recruited prior to widespread use of statins and with a relatively low use of BP-lowering drugs which means it is an appropriate population for understanding prognosis in an untreated population. There were minimal exclusions due to missing data on risk factors (less than 7% of men were missing data on ambulatory BP or one of the FRS covariates). There was reliable ascertainment of outcomes with minimal losses to follow-up. We used rigorous statistical analysis using methods that allow interpretation of the clinical significance of results.

There are also some limitations to our study. Our study population consisted of men over the age of 65 years and most were at high risk of a cardiovascular event. At the same time, the men in our study were all very close in age which meant that age was not a significant predictor in this study. In populations without age restriction, age is the most powerful predictor of cardiovascular risk. There is also evidence that the FRS is less accurate for older age groups, and this may have also caused ambulatory BP to have had more effect in our study than in younger populations. We used the FRS as the initial predictor for our models but this will result in a 'home' advantage to ASBP (where the contribution was decided by the data) over traditional risk factors including clinic BP (where the contribution is fixed as decided by the Framingham Risk equation, which may not be ideal for this data set). We assumed that treatment to lower BP resulted in a 20% reduction in risk of a cardiovascular event.[31] The risk reduction may be less for escalation of treatment (for patients who were already on some treatment at baseline or were started on treatment during follow-up). However, if cholesterol-lowering effects are also considered,[32] there is a

Table 4 Improvements in the overall prediction of an individual's cardiovascular risk and effects on treatment and cardiovascular events when mean daytime ASBP is added to FRS

Overall model fit (LRT)	Discrimination (change in c-statistic)	Calibration (p value)	Reclassification*	Treatment	CVD events
X^2=12.29,1df, p=0.0006	0.011	0.27 (FRS) vs 0.54 (FRS+ASBP)	1.8% (9/500) non-cases correctly classified downwards 0.7% (2/280) cases incorrectly classified downwards	141 less treated per 10 000 men screened with ASBP (95% CI 58 to 224 less treated)	7 fewer events prevented per 10 000 men screened with ASBP (95% CI 20 fewer events prevented to 6 more events prevented)

*Adjusting for censoring using Kaplan–Meier life table estimates did not change per cent estimates for reclassification.
ASBP, ambulatory systolic blood pressure; CVD, cardiovascular disease; FRS, Framingham Risk Score; LRT, likelihood ratio test.

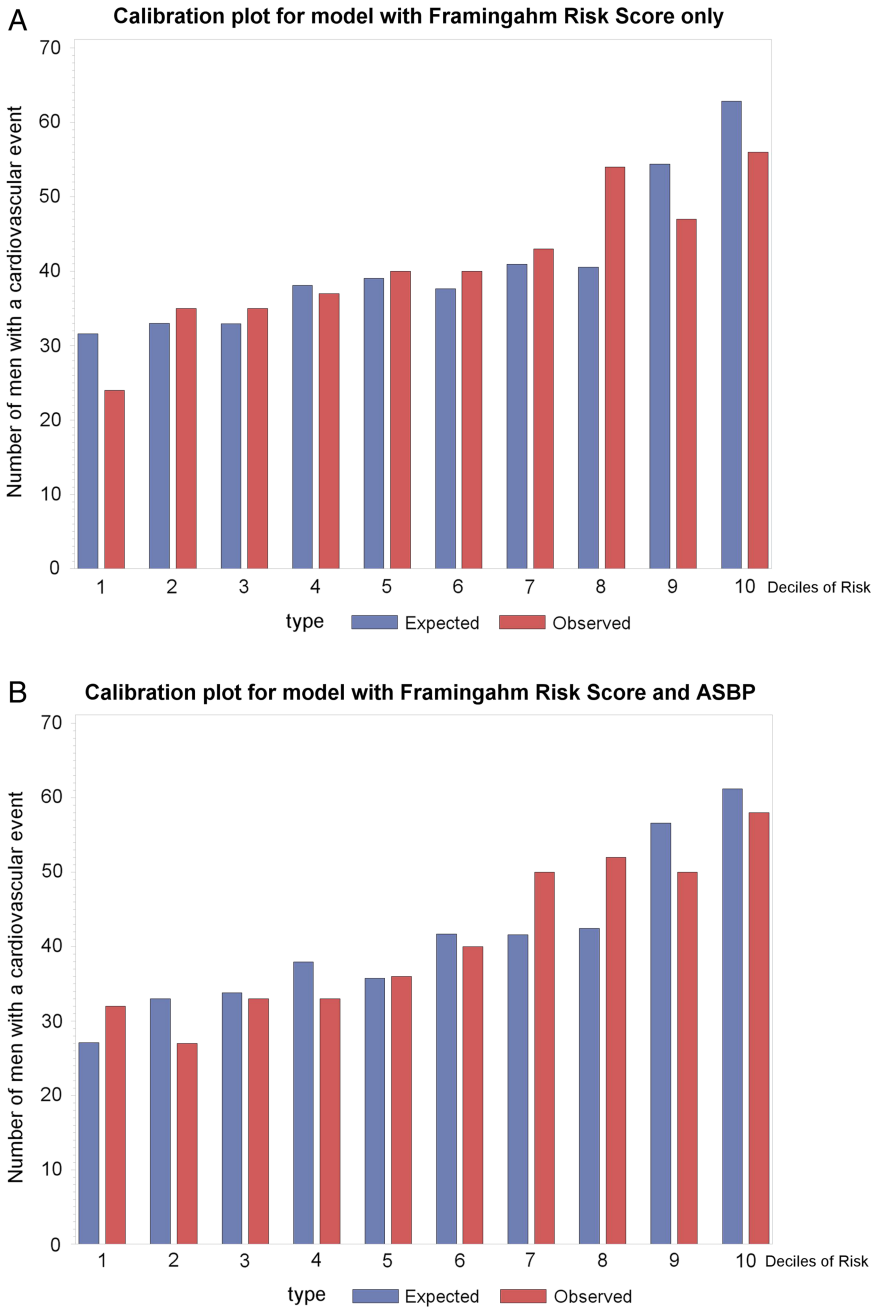

Figure 1 (A and B) Calibration graph showing observed and predicted number of cardiovascular events within 10 years, in each decile of the risk score (A, FRS only; B, FRS and ASBP). ASBP, ambulatory systolic blood pressure; FRS, Framingham Risk Score.

significantly larger risk reduction with treatment, which would more than offset this. On balance, even more events would be prevented in the FRS alone model relative to the FRS and ASBP one. We based our estimations of treatment effect on the assumption of one cardiovascular risk assessment, but this may be repeated before 10 years, which would be likely to lead to more patients crossing the treatment threshold with ASBP and even smaller difference in reclassification. Also, participants below the absolute risk threshold who have elevated BP may still be started on treatment, meaning less of a difference in numbers started on treatment and events prevented. Finally, it is likely that not all people above the threshold would be offered and accept treatment to lower cardiovascular risk; again, this would lessen the difference in treatment and events prevented between the two risk models.

In combination, these factors mean that our estimates are 'best-case' estimates for this population and the incremental value of ASBP may be even lower in other populations, including younger populations and women. The generalisability of these estimates is further supported by the fact that (1) Ambulatory BP did just as badly on the performance measures that were not looking at movement across treatment threshold, such as change in c-statistic and likelihood ratio and (2) the risk plots in figure 2A, B suggest that adding ambulatory BP may still have little effect on reclassification even if

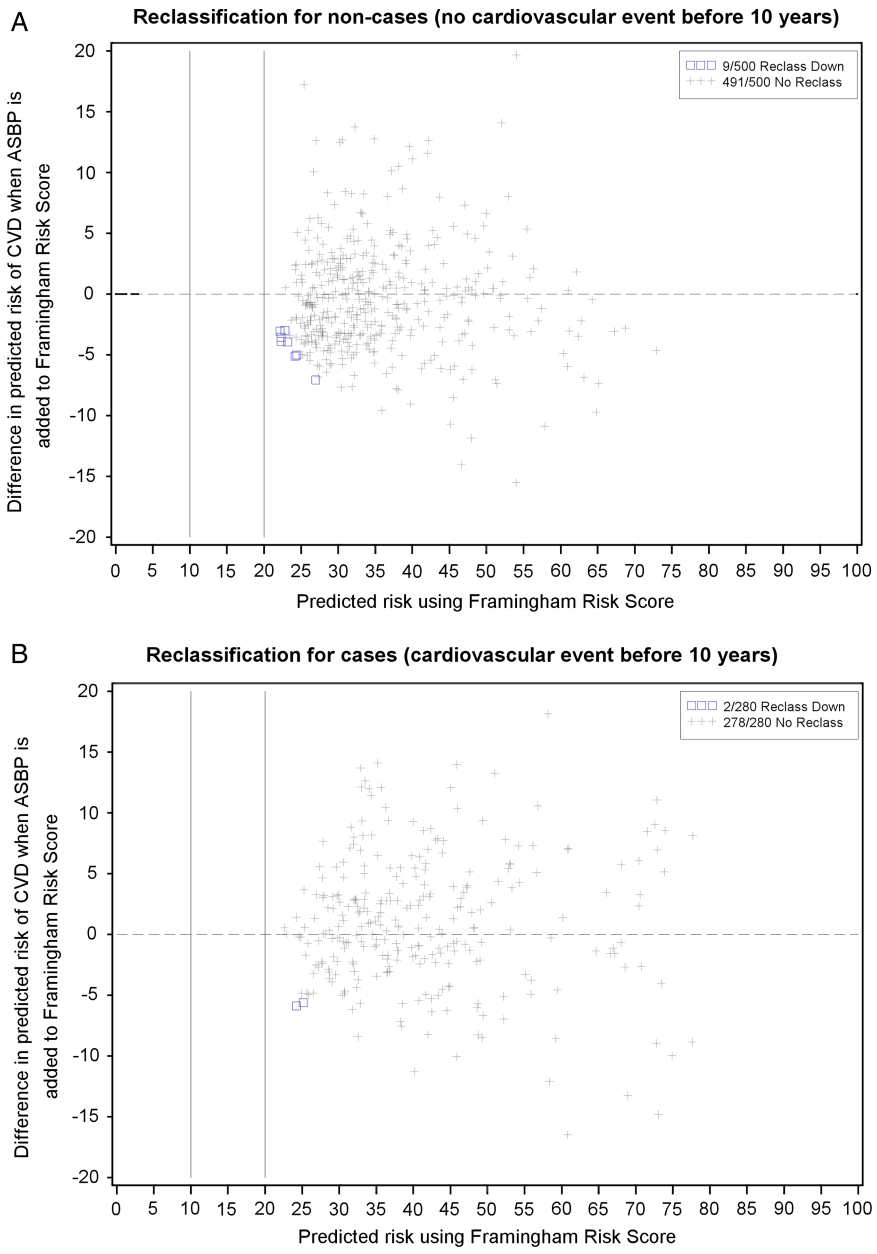

Figure 2 (A and B) Reclassification of risk across 20% (treatment) threshold when ambulatory systolic blood pressure (ASBP) is included in the prediction of 10-year risk of a cardiovascular event (A, men who did not develop cardiovascular disease (CVD); B, men who did develop CVD.

thresholds were shifted so that more men were under threshold on the basis of FRS. A recent study using simulated data to evaluate the effects of changes in mean risk on predictive and utility measures found that adding a new predictor with HR of 1.2 per SD (similar to the HR for ASBP in our study), resulted in little difference in the percentage reclassified across all mean risk levels.[33]

We found that mean daytime ASBP had the highest incremental value and that other ASBP measures, including variability of BP did not add to this. Other studies have found that visit-to-visit variation independently predicts risk of cardiovascular events[3 34] and it may be that day-to-day variation has more prognostic importance than within day variation. We note that the overall incremental value of these variability measures has not been assessed in a similar way to the present study.

We have previously found that one additional clinic BP (and cholesterol) measurement only minimally improved risk prediction compared to risk factors from the Framingham Risk equation.[24] The PAMELA study looked at improvements in the overall model fit when out of office BP was added to clinic BP without considering other traditional risk factors.[35] They found that there was improved overall prediction, but the clinical meaning of this is unclear. Our conclusions on the clinical utility of ABPM differ from the conclusions of a cost-effectiveness analysis undertaken in relation to the use of ambulatory BP measurement for diagnosis of hypertension.[22] This modelling study assumed that patients below the treatment threshold derived no cardiovascular risk reduction from treatment whereas those above the treatment threshold did. This is at odds with research

showing a similar relative risk reduction with BP-lowering treatment for individuals irrespective of their pretreatment BP (down to a SBP of 110, below which data become sparse).[31]

Our findings need validation in other data sets, in particular populations including women, younger people and a wider range in age. We need to compare the incremental value of ASBP with that of home BP measurement. Future research may also assess the incremental effects of ASBP and home BP measurements on the short term measurement variability of risk scores.

In summary, the incremental value of ASBP above FRS appears to be at most small, at least in older men. While selective use is reasonable, we question the recommendation for universal assessment of all those being considered for use of BP-lowering therapy. FRS scores alone are sufficient to decide on the need for starting BP and cholesterol-lowering therapy.

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Contributors KJLB contributed to the concept and design, analysis, interpretation of data, was responsible for drafting and revising the manuscript and is guarantor for the study. EB and KMG contributed to the analysis of the data, interpretation of data and revising the manuscript. JS facilitated access to the data, contributed to interpretation of data and revision of the manuscript. AH contributed to interpretation of data and revision of the manuscript. LI, BN and PG contributed to the concept and design, interpretation of data, revision of the manuscript.

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