

# **Using out-of-office blood pressure measurements in established cardiovascular risk scores: implications for practice**

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## **Abstract**

**Background:** Blood pressure (BP) measurement is increasingly carried out through home or ambulatory monitoring, yet existing cardiovascular risk scores were developed for use with measurements obtained in clinic.

**Aim:** To describe differences in cardiovascular risk estimates obtained using ambulatory or home BP measurements instead of clinic readings.

**Design and setting:** Secondary analysis of data from adults aged 30-84 without prior history of cardiovascular disease (CVD) in two BP monitoring studies (BP-Eth and HOMERUS).

**Method:** The primary comparison was Framingham risk calculated using BP measured as in the Framingham study or daytime ambulatory BP measurements. The QRISK2 and SCORE risk equations were also studied. Statistical and clinical significance were determined using the Wilcoxon signed-rank test and scatter plots respectively.

**Results:** In 442 BP-Eth patients (mean age = 58 years, 50% female) the median absolute difference in 10-year Framingham cardiovascular risk calculated using BP measured as in the Framingham study or daytime ambulatory BP measurements was 1.84% (interquartile range 0.65 to 3.63,  $p=0.67$ ). Only 31/442 (7.0%) of patients were reclassified across the 10% risk treatment threshold. In 165 HOMERUS patients (mean age = 56 years, 46% female) the median difference in 10-year risk was 2.76% (IQR 1.19 to 6.39,  $p<0.001$ ) and only 8/165 (4.8%) of patient were reclassified.

**Conclusion:** Estimates of cardiovascular risk are similar when calculated using BP measurements obtained as in the risk score derivation study or through ambulatory monitoring. Further research is required to determine if differences in estimated risk would meaningfully influence risk score accuracy.

**Keywords:** blood pressure, risk, myocardial infarction, stroke, primary health care

**How this fits in:** Out-of-office blood pressure (BP) measurement is increasingly common but cardiovascular risk scores were developed using clinic BP measurements. It is unclear how estimates of cardiovascular risk may be affected by the use of out-of-office measurements in risk prediction algorithms. We have shown that differences in risk are generally small and few patients are reclassified across treatment thresholds when using different BP measurements. Extra care on the part of clinicians may be warranted in subgroups with large BP differences or those with risk estimates close to risk thresholds.

## **Introduction**

Current UK and international guidance recommends that high blood pressure (hypertension) is diagnosed through 24-hour ambulatory blood pressure monitoring (ABPM), or week long home monitoring.(1–5) Furthermore, many patients with hypertension also monitor their blood pressure (BP) at home.(6) Consequently, BP measurements obtained in several settings, may be used to manage hypertension and estimate cardiovascular risk.(7,8)

Risk assessments are recommended in order to treat those at highest risk of cardiovascular disease (CVD). The majority of published cardiovascular risk scores, including the Framingham,(9) QRISK2(10) and SCORE(11) equations, were developed using BP measurements obtained in a clinic setting and, ideally, should be used with measurements obtained similarly. Despite this reflecting the original derivation of the scores, use of clinic BP may systematically over- or underestimate risk in patients with large discrepancies between clinic and out-of-office BP (white coat(12,13) or masked effects(14)). This is because home and ambulatory BP measurements are stronger predictors of CVD than clinic readings.(15–17)

Although masked and white coat hypertension may only affect a minority of the population,(18,19) the extent to which this problem affects risk estimates and subsequent clinical decisions has been little studied. One previous study examined a related problem of end digit preference in clinic BP readings in the Framingham risk score,(20) but was limited to a single risk score and used simulated data. Hence, this study aimed to describe differences in estimated cardiovascular risk when using out-of-office instead of clinic BP measurements and to determine how clinical decisions might be affected by these differences. We used data from the Blood Pressure in different Ethnic groups (BP-Eth) study(21) and the Home versus Office blood pressure MEasurements: Reduction of Unnecessary treatment Study (HOMERUS).(22)

## **Methods**

### **Study population**

The BP-Eth cohort has been described in full previously.(21,23) Briefly, this cross-sectional study compared clinic, home and ambulatory BP in UK patients aged 40 to 74, with or without hypertension, who were white British, white Irish, South Asian or African-Caribbean. For this analysis, patients with a prior history of cardiovascular disease were excluded. Clinic measurement used the BpTRU sphygmomanometer.(24) Measurements on both arms were taken at the first visit and on the higher reading arm at subsequent visits. ABPM (Spacelabs 90217)(25) used half hourly measurement from 0800 to 2300 and hourly measurement overnight. Home BP measurements were obtained twice in the morning and evening over seven days.

HOMERUS was a randomized trial in patients with essential hypertension aged 18 and over from the Netherlands. Patients with history of cardiovascular disease or other severe disease were excluded. Patients were randomized into an office or home monitoring group with antihypertensive treatment adjusted accordingly. Three office BP measurements were taken in the non-dominant arm at each visit using an automated oscillometric device (Omron 705, Japan).(26) Home BP measurements (three in the morning and evening over seven days) were made with the same monitor before each study visit. ABPM was carried out at the beginning and end of the study (following treatment

washout and at optimal titration respectively) with readings every 15 minutes from 0700 to 2300 and every 30 minutes overnight. For this analysis, patients aged 25 to 84 years old from the intervention arm only were included, due to the age restrictions of the QRISK2 risk equation.

### **Statistical analysis**

We estimated cardiovascular risk using the Framingham, QRISK2 and SCORE risk equations, (9–11) which are commonly used in UK general practice.(27) We compared risk estimates calculated using systolic BP values obtained using different measurement techniques in the clinic, at home or through ABPM (Box 1). The primary comparison was risk calculated using BP measured as in the derivation study of each risk score with risk calculated using daytime ambulatory BP (due to its recommended use in diagnosis of hypertension).(1) We calculated Framingham risk in primary analyses as BP measurement in the Framingham study was consistent across patients and well documented.(28) Comparatively, BP measurement in the QRISK2 and SCORE derivation studies varied across patients.(10,11)

Absolute differences in risk were summarized by medians/ interquartile ranges and were compared using the non-parametric Wilcoxon signed-rank test. Clinical significance was determined by calculating the proportion of people reclassified above or below the threshold for statin treatment (10% for all CVD and 5% for CVD mortality) and scatter plots. Analyses were carried out in the BP-Eth and HOMERUS cohorts separately, using Stata 14.2.(29)

### **Missing data**

Analysis was restricted to patients who had complete covariate data and at least three BP readings at visit one in BP-Eth (when measurements were taken in both arms) and visit ten in HOMERUS (when concurrent ABPM and cholesterol measurement occurred). Twelve home BP readings measured on at least three days, and 19 ABPM readings (14 daytime and five night-time) was required.(1,30) Cholesterol data was not collected in BP-Eth, so was simulated from a normal distribution using means and standard deviations in each age-sex strata from the Health Survey for England 2011.(31) Townsend deprivation data (a UK measure of material deprivation based on employment, car ownership, home ownership and household overcrowding) was not available in HOMERUS(32) and hence patients in HOMERUS were assigned non-risk modifying values of deprivation.

## **Results**

A total of 442 patients from the BP-Eth cohort and 165 patients from the HOMERUS cohort were included (Table 1). Patients in the BP-Eth cohort were older and were from a mix of ethnic backgrounds by design. HOMERUS patients were less likely to have risk factors for cardiovascular disease, but had higher clinic BP values. Average differences in BP measurements were small, but there were large differences for some individuals, especially in the HOMERUS cohort (Supplement, Figures S1 and S2).

### **Differences in Framingham risk using ambulatory, home or clinic BP measurements**

In the BP-Eth cohort, comparing estimates of Framingham risk calculated using BP taken to be the mean of 2<sup>nd</sup> and 3<sup>rd</sup> measurements on the left arm or an alternative measure revealed that observed risk differences were generally small. Median absolute differences were less than 2% for all comparisons except night-time ambulatory BP measurement (Table 2). There were no significant differences in Framingham risk when calculated using daytime ambulatory BP ( $p=0.67$ ), home BP excluding the first days readings ( $p=0.08$ ), or BP measured according to current guidance ( $p=0.26$ ).

Figure 1 shows the number of BP-Eth patients reclassified across the 10% 10-year risk threshold when Framingham risk was calculated using daytime ambulatory BP compared to the mean of 2<sup>nd</sup> and 3<sup>rd</sup> clinic measurements on the left arm. In total 31/ 442 (7.0%) of patients were reclassified and those reclassified had risk estimates close to the threshold. Patients were reclassified upwards/ downwards if their ambulatory BP was higher / lower than their clinic BP respectively, reflecting the increased risk associated with higher BP. The largest differences in risk were observed for those already at high risk (Figure S3A) but this pattern was not apparent when considering risk on the log-scale (Figure S3B). Similar patterns were seen when calculating risk using home or guideline recommended clinic BP (Figures S4 and S5).

In the HOMERUS cohort, compared to the BP-Eth cohort, larger median differences in risk were observed when using home or ambulatory BP in the Framingham risk score (Table 3). Differences were statistically significant when using BP measured through daytime ABPM ( $p<0.001$ ), home monitoring excluding the first days readings ( $p<0.001$ ), or according to current guidance ( $p=0.006$ ). As in the BP-Eth cohort, small numbers of people were reclassified across the 10% 10-year risk threshold when calculating risk with daytime ambulatory BP (4.8% reclassified, Figure 2), although estimated risk was lower in the majority of patients. Similar patterns were observed when calculating risk using home or guideline recommended clinic BP (Figures S6 and S7).

### **Differences in QRISK2 risk using ambulatory, home or clinic BP measurements**

Median absolute differences in estimated QRISK2 risk were less than 1.5% in the BP-Eth cohort when using any alternative measures of BP (compared to a single clinic measure) and interquartile ranges were narrower than observed for Framingham risk (Table S1). This suggests that the contribution of BP to overall risk is lower in the QRISK2 equation compared to the Framingham equation. Although differences in risk were statistically significant when using BP measured through ambulatory monitoring ( $p<0.001$ ), home monitoring excluding the first day ( $p<0.001$ ) or as in current guidance ( $p<0.001$ ), fewer people were reclassified across the 10-year risk threshold compared to those observed when using the Framingham equation (Figures S8-S10). Similar results were observed in the HOMERUS cohort, with the majority of patients having lower estimated risk when using ambulatory BP (Table S2, Figures S11-S13).

### **Differences in SCORE risk using ambulatory, home or clinic BP measurements**

Finally, differences in SCORE risk estimates were also small (below 0.5%, Table S3). Differences across risk scores were not directly comparable, since the SCORE equation estimates risk of CVD *death* and absolute risk levels are lower. Differences in risk were statistically significant when calculated using BP measured through ambulatory or home monitoring, or according to current guidance ( $p<0.001$  in all cases). Less than 10% of patients were reclassified above/ below the 5% 10-year CVD mortality risk threshold (Figures S14-S16). The relative variation in risk observed was comparable to/ more than that observed for the Framingham/ QRISK2 equation respectively,

reinforcing the suggestion that BP contributes less to the risk estimate in the QRISK2 equation. In the HOMERUS cohort, use of ambulatory BP primarily resulted in a reduction in estimated risk. No patients were reclassified upwards but 26/165 (15.8%) patients were reclassified from high to low risk (Table S3, Figure S17-S19).

## **Discussion**

This analysis has shown that using BP measurements obtained through ambulatory or home instead of clinic monitoring may have little effect on CVD risk estimates obtained from the Framingham, QRISK2 or SCORE risk equations. Where differences did occur, fewer than 1 in 5 people were reclassified across risk thresholds for treatment and those reclassified tended to have risk estimates close to the thresholds. The relative contribution of BP to risk appeared to be lower in QRISK2 compared to the Framingham or SCORE equation.

### **Strengths and limitations**

The results of this study have been demonstrated in two populations from distinct countries with differing cardiovascular risk profiles and therefore have good face validity. Findings can be considered generalizable to other populations due to the different ethnic composition of the two studies. Results were also similar across the three risk scores studied.

A limitation of this analysis was that outcomes data were not available to allow comparison between estimated and observed risks. Hence, we could not determine whether using one type of BP measurement over another results in more accurate risk assessment. However, since most patients remained at high or low risk, the ability of risk equations to detect those at high risk (discrimination) is likely to be similar regardless of the type of BP measurement used. Calibration (agreement between predicted and observed risk) may well differ and this requires further assessment in formal validation studies.

Data for cholesterol had to be simulated in the BP-Eth dataset, Townsend deprivation scores were fixed at non-risk modifying values in the HOMERUS dataset, and only complete case analyses were carried out. As such, we have described *possible* changes in risk estimates across a range of risk values and BP differences. Further work would be required to estimate risk differences at the population level.

Clinic BP measurements in both cohorts were obtained using automated devices, which likely limited the presence of white-coat effects compared to routine practice.(33) We attempted to mimic routine clinic measurement as far as possible by studying recommended protocols (which have been shown to be followed in a majority of cases in UK primary care)(34) and single BP readings. Larger differences in estimated risk may be observed routinely.

### **Comparisons with the literature**

Previous research carried out in New Zealand examined differences in Framingham risk estimates when BP measurements were subject to zero-end digit preference. The study found that the mean difference in risk was 0.16% and that 2.4% of individuals were reclassified across the 20% risk threshold.(20) This study is a generalisation of the same problem: that of using BP measurements

with differing levels of bias/ measurement error from those used in risk score derivation and our results support the previous findings.

The results of this analysis are also in line with the previous work of several authors, aiming to modify CVD risk scores for use with home instead of clinic BP measurements.(35) Modifications to existing equations were modest and differences in risk between the modified equations and existing risk equations were small. Our results indicate that any changes to risk scores for use with ambulatory measurements would be similarly modest.

Although home and ambulatory BP is predictive of CVD risk over and above clinic BP,(15,16) adding daytime ambulatory BP measurements to the Framingham risk score in a cohort of older men did not improve its accuracy.(36) This suggests that the type of BP measurements included in risk scores may have little influence on accuracy. The small differences in risk observed in this study again support these previous findings.

### **Implications for research and practice**

Broadly, our results indicate that healthcare professionals may not need to be unduly worried about which BP measurements to use when calculating cardiovascular risk and the choice of risk score may be of greater importance. However, there were differences in results between the HOMERUS cohort (a population selected based on high clinic BP) and BP-Eth (a mixed population of normotensive and hypertensive patients). This suggests that greater care may be warranted in those known or likely to have large white-coat/ masked effects and in those with estimated risk close to treatment thresholds, as this combination of characteristics is most likely to lead to reclassification below/ above treatment thresholds respectively.

Although average risk differences were small, up to 1 in 6 people were reclassified in some analyses. If such results are borne out in wider scale analyses, this could have potentially important implications when extrapolated to the population level. However, a recent UK-based study showed that a minority of patients identified at high risk of CVD between 2010 and 2013 were initiated on treatment,(37) indicating that such clinical decisions are influenced by several factors.

The apparent lower contribution of BP to risk in QRISK2 should be further explored. QRISK2 includes more risk factors than Framingham or SCORE, including a term for treated hypertension that may capture part of the BP effect. This is consistent with the relatively smaller hazard ratio for BP in QRISK2 (1.20 per 20 mm Hg for CVD events),(10) compared to hazard ratios of at least 1.49 for CHD and stroke mortality from observational studies,(38) and 1.60 for in primary prevention groups from BP lowering trials.(39)

In conclusion, we have shown that differences in cardiovascular risk estimates, when calculated using BP measurements obtained in a clinical research setting different to that of the risk score derivation studies, are likely to be small in most cases. Further research is required to determine whether meaningful clinically important differences occur in subgroups and at the population level in daily practice.

### **Competing interests**

RJM has received BP monitoring equipment for research purposes from Lloyds Pharmacies and Omron.

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### **Ethical approval**

No ethical approval was required for this secondary analysis of anonymised data.

### **Author contributions**

RJM, PG, SG and MAM (BP-Eth) and WJV, PDL and AAK (HOMERUS) were responsible for the design, conduct and overall data collection of the original studies. SLS devised the analysis plan with input from RJS and RJM. SLS carried out the analysis and drafted the paper, which was revised with input from RJS, RJM, PG, SG, MAM, WJV, PDL and AAK.

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## Box 1: Summary of different blood pressure measurement techniques considered for comparison

### 1. Clinic blood pressure\*

- a. As defined in the derivation studies of each risk score
  - i. Framingham: mean of the 2nd and 3rd clinic measurements in the left arm
  - ii. QRISK2: first clinic measurement in a randomly selected arm
  - iii. SCORE: first clinic measurement in a randomly selected arm
- b. Defined according to current UK guidance. This was defined as the first measurement if less than 140/90mm Hg. If  $\geq 140/90$  mm Hg, then the second measurement was considered. If the second measurement differed from the first by  $>5$  mm Hg systolic then the third measurement was also considered. The minimum of the last two measurements was used in analyses. BP readings were taken from the higher reading arm in patients who had a difference between arms of  $\geq 20$  mm Hg systolic, which was sustained after two readings, or otherwise in a random arm.

### 2. Home blood pressure

- a. Mean of two readings in the morning and two readings in the evening over seven days, excluding the first day's readings.
- b. As in 2a, including the first day's readings.

### 3. Ambulatory blood pressure

- a. Daytime ambulatory BP providing at least 14 valid measurements were available.
- b. Night-time ambulatory BP providing at least five valid measurements were available.
- c. 24-hour ambulatory BP providing at least 19 valid measurements were available.

\* Clinic BP was measured in the non-dominant arm in HOMERUS. Where measurement techniques specify a measurement arm, this was implemented in BP-Eth as specified. In HOMERUS this was implemented using the available measurements, disregarding measurement arm.

**Table 1: Characteristics of the BP-Eth (N=442) and HOMERUS cohorts (N=165)**

	<b>BP-Eth cohort</b>	<b>HOMERUS cohort</b>
<b>Variable</b>	<b>Mean (SD)/ N (%)</b>	<b>Mean (SD)/ N (%)</b>
Age (years)	58.4 (9.4)	55.6 (9.7)
Female	222 (50.2)	75 (45.5)
BMI (kg/m <sup>2</sup> )	29.1 (4.5)	27.5 (4.2)
Current smoker	66 (14.9)	30 (18.2)
Chronic kidney disease	3 (6.8)	0 (0.0)
Atrial fibrillation	16 (3.6)	0 (0.0)
Treated hypertension	249 (56.3)	165 (100.0)
Left ventricular hypertrophy	0 (0.0)	0 (0.0)
Type 1 diabetes	2 (0.5)	6 (3.6)
Type 2 diabetes	57 (12.9)	37 (22.4)
Townsend score	6.1 (4.1)	0.1 (0.06)
Total cholesterol (mmol/L) (simulated)	5.4 (1.1)	5.5 (1.1)
HDL cholesterol (mmol/L) (simulated)	1.5 (0.4)	1.4 (0.4)
Total/HDL cholesterol (mmol/L)	4.0 (1.7)	4.4 (1.4)
Ethnicity: White	203 (45.9)	165 (100.0)
Ethnicity: Indian	79 (17.9)	0 (0.0)
Ethnicity: Pakistani	24 (5.4)	0 (0.0)
Ethnicity: Bangladeshi	5 (1.1)	0 (0.0)
Ethnicity: Black Caribbean	115 (26.0)	0 (0.0)
Ethnicity: Black African	16 (3.6)	0 (0.0)
Systolic BP (mm Hg): single reading (random arm)	136.2 (18.3)	146.5 (19.1)
Systolic BP (mm Hg): mean of 2nd and 3rd readings in left arm	132.4 (17.1)	142.3 (17.1)
Systolic BP (mm Hg): according to current guidance	132.8(15.9)	141.4 (16.2)
Systolic BP (mm Hg): mean of home readings excluding the	133.4 (12.4)	134.0 (10.5)
Systolic BP (mm Hg): mean of daytime ambulatory readings	133.0(14.2)	131.3 (9.9)
QRISK2 10-year CVD risk	16.0 (12.1)	13.2 (8.8)
Framingham 10-year CVD risk	15.6 (10.8)	19.6 (13.5)
SCORE 10-year CVD death risk	3.1 (3.3)	3.3 (3.7)

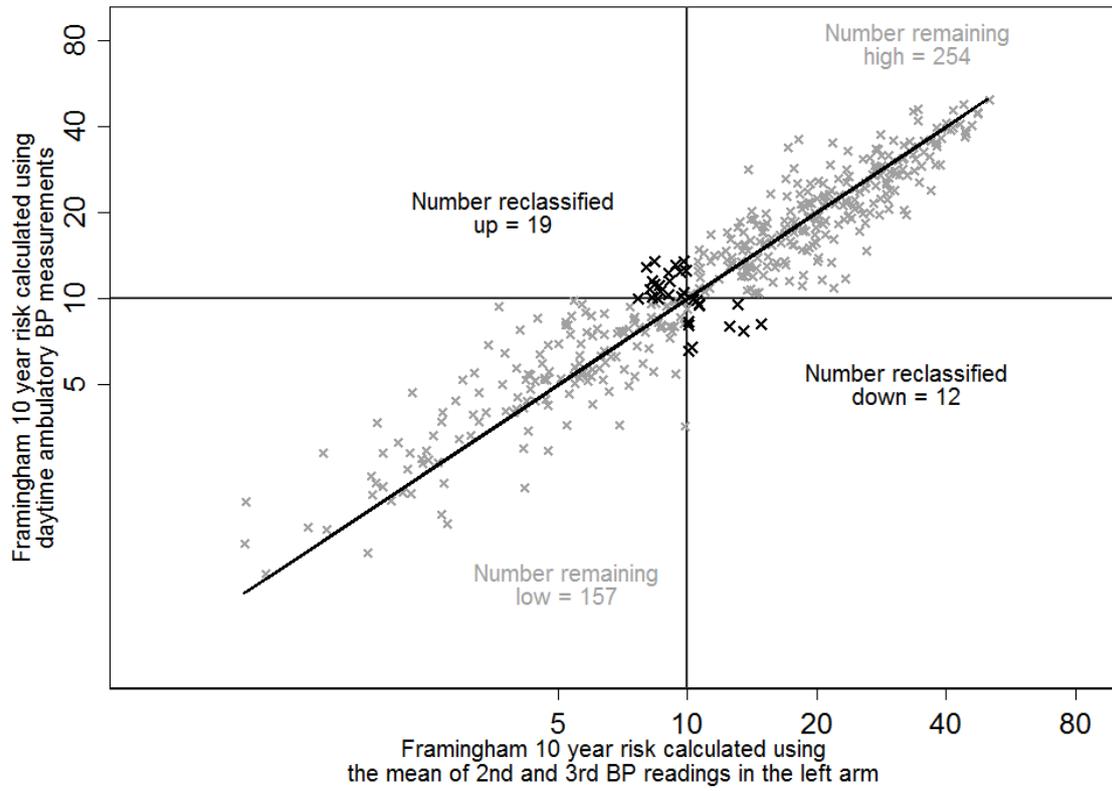
**Table 2: Differences in Framingham risk estimates using alternative summary measures of mean blood pressure in the BP-Eth cohort**

<b>Alternative BP measurement used in risk score</b>	<b>Median absolute difference (%)</b>	<b>Inter-quartile range</b>		<b>Difference range (original – alternative)</b>	
<b>Ambulatory measurements</b>					
Daytime ABPM	1.84	0.65	3.63	-18.04	12.59
Night-time ABPM	2.65	1.09	5.91	-17.96	19.61
24-hour ABPM	1.85	0.76	3.63	-17.61	13.45
<b>Home measurements</b>					
Excluding first days readings	1.66	0.61	3.12	-15.94	11.56
Including first days readings	1.69	0.58	3.09	-16.54	12.23
<b>Clinic measurements</b>					
Current guidance	0.78	0.35	1.62	-15.22	9.15

**Table 3: Differences in Framingham risk estimates using alternative summary measures of mean blood pressure in the HOMERUS cohort**

<b>Alternative BP measurement used in risk score</b>	<b>Median absolute difference (%)</b>	<b>Inter-quartile range</b>		<b>Difference range (original – alternative)</b>	
<b>Ambulatory measurements</b>					
Daytime ABPM	2.76	1.19	6.39	-8.65	18.80
Night-time ABPM	5.35	2.04	11.42	-5.88	28.28
24-hour ABPM	3.05	1.10	7.40	-7.97	20.93
<b>Home measurements</b>					
Excluding first days readings	2.50	0.89	5.32	-8.52	16.33
Including first days readings	2.41	0.92	5.24	-9.03	16.05
<b>Clinic measurements</b>					
Current guidance	0.51	0.21	1.32	-3.56	4.34

**Figure 1: Framingham risk estimates in the BP-Eth cohort calculated using BP measurements obtained as in the Framingham study or through daytime ABPM**



**Figure 2: Framingham risk estimates in the HOMERUS cohort calculated using BP measurements obtained as in the Framingham study or through daytime ABPM**

