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Predicting Out-of-Office Blood Pressure in the Clinic (PROOF-BP)

Derivation and Validation of a Tool to Improve the Accuracy of Blood Pressure Measurement in Clinical Practice

James P. Sheppard, Richard Stevens, Paramjit Gill, Una Martin, Marshall Godwin, Janet Hanley, Carl Heneghan, F.D. Richard Hobbs, Jonathan Mant, Brian McKinstry, Martin Myers, David Nunan, Alison Ward, Bryan Williams, Richard J. McManus

See Editorial Commentary, pp 834–835

Abstract—Patients often have lower (white coat effect) or higher (masked effect) ambulatory/home blood pressure readings compared with clinic measurements, resulting in misdiagnosis of hypertension. The present study assessed whether blood pressure and patient characteristics from a single clinic visit can accurately predict the difference between ambulatory/home and clinic blood pressure readings (the home–clinic difference). A linear regression model predicting the home–clinic blood pressure difference was derived in 2 data sets measuring automated clinic and ambulatory/home blood pressure (n=991) using candidate predictors identified from a literature review. The model was validated in 4 further data sets (n=1172) using area under the receiver operator characteristic curve analysis. A masked effect was associated with male sex, a positive clinic blood pressure change (difference between consecutive measurements during a single visit), and a diagnosis of hypertension. Increasing age, clinic blood pressure level, and pulse pressure were associated with a white coat effect. The model showed good calibration across data sets (Pearson correlation, 0.48–0.80) and performed well-predicting ambulatory hypertension (area under the receiver operator characteristic curve, 0.75; 95% confidence interval, 0.72–0.79 [systolic]; 0.87; 0.85–0.89 [diastolic]). Used as a triaging tool for ambulatory monitoring, the model improved classification of a patient's blood pressure status compared with other guideline recommended approaches (93% [92% to 95%] classified correctly; United States, 73% [70% to 75%]; Canada, 74% [71% to 77%]; United Kingdom, 78% [76% to 81%]). This study demonstrates that patient characteristics from a single clinic visit can accurately predict a patient's ambulatory blood pressure. Usage of this prediction tool for triaging of ambulatory monitoring could result in more accurate diagnosis of hypertension and hence more appropriate treatment. **(*Hypertension*. 2016;67:941-950. DOI: 10.1161/HYPERTENSIONAHA.115.07108.)** • **Online Data Supplement**

Key Words: ambulatory blood pressure monitoring ■ hypertension ■ masked hypertension ■ white coat hypertension

High blood pressure (hypertension) is an important risk factor for cardiovascular disease, a significant cause of morbidity and mortality worldwide.[1] The diagnosis and management of hypertension depend on accurate measurement of blood pressure so that antihypertensive treatment can be targeted appropriately and unnecessary adverse effects and healthcare costs can be avoided.[2] Traditionally, blood pressure measurement has taken place in the primary care physician's office or clinic using an electronic oscillometric or aneroid sphygmomanometer (clinic blood pressure; Table 1), but it has long been recognized that home or ambulatory (out-of-office) blood pressures provide more accurate estimates of a patient's true mean blood pressure.[3] This is in part because multiple readings are taken and it correlates with a range of

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cardiovascular outcomes and end-organ damage better than clinic blood pressure.[4,5]

Clinic blood pressure values are often different from out-of-office blood pressure and can lead to incorrect classification of blood pressure status and hence inappropriate management.[6,7] Patients with higher clinic blood pressure than the corresponding out-of-office pressure will have a negative home–clinic blood pressure difference (white coat effect) and are at risk of overtreatment (Figure S1 in the online-only Data Supplement).[8] Conversely, patients with higher out-of-office blood pressures than the corresponding clinic blood pressure would be expected to have a positive home–clinic blood pressure difference (masked effect), and often remain unrecognized and therefore potentially undertreated (Figure S1).[9] Such patients are at increased risk of target-organ damage[10] and have cardiovascular morbidity and mortality not dissimilar to sustained hypertension.[11]

Strategies to reduce these misclassifications are emerging and include the use of multiple automated clinic blood pressure readings which have been shown to reduce the white coat effect.[12,13] In the United States, the Preventive Services Task Force[14] have recently released guidelines recommending that home or ambulatory blood pressure monitoring is used to confirm a diagnosis of hypertension, an approach which has already been adopted in the United Kingdom,[15] where it is considered cost-effective because of a reduction in misdiagnosis caused by the white coat effect.[2] However, this approach will result in some patients with sustained hypertension identified by clinic blood pressure readings being sent for arguably unnecessary out-of-office monitoring, which some patients find uncomfortable, and importantly, this strategy will not capture those patients with masked hypertension.

Recent work by some of the authors has shown that the change in clinic blood pressure compared with multiple automated clinic readings from a single visit can predict the home–clinic blood pressure difference.[16] This study aimed to use patient characteristics and details of repeated clinic blood pressure measurements to derive a model for predicting this home–clinic blood pressure difference. Furthermore, we aimed to validate this model and examine its application as a means to target ambulatory blood pressure monitoring more efficiently in routine clinical practice.

Methods

An extended version of the Methods is available in the online-only Data Supplement. Blood pressure definitions and terminology used are summarized in Table 1.

Study Design and Source Data

The present study was an individual patient data analysis of cohort studies conducted in a primary care setting.[12,17–21] A linear regression model predicting the home–clinic blood pressure difference was derived in 2 data sets using candidate predictors identified from a literature review. All included studies collected relevant data including clinic, home, and daytime ambulatory blood pressure readings, using a validated electronic oscillometric blood pressure monitor, and details of patient characteristics and medical history. The characteristics of patients from included studies are detailed in Table 2. Individual clinic readings were available in each study permitting estimation of a variety of different definitions of clinic blood pressure. Patients in the Conventional Versus Automated Measurement of Blood Pressure in the Office (CAMBO) study[12] had their clinic blood pressure measured with a BpTRU device with either the doctor or nurse taking the first reading and then leaving the room for the remaining measurements. In all other studies, multiple clinic readings were taken in the presence of a nurse or practice reception staff.[17–20] Because our study involved secondary analysis of existing data, it was not possible to standardize protocols for blood pressure measurement across studies, and specific protocols for the measurement of home and daytime ambulatory blood pressures did vary to some degree (Table S1).

Patients were selected for the derivation cohort from the Blood Pressure in Ethnic groups (BP-Eth)[17] and Telemonitoring and Self-Management in the Control of Hypertension (TASMINH2)[19] studies (n=991) because these were considered to be sufficiently large and representative of the population likely to undergo blood pressure monitoring for diagnosis and management of hypertension. Patients from the remaining 4 studies[12,18,20,21] were used in the validation cohort (n=1172).

Statistical Analysis

Selection of Candidate Predictors

Candidate predictors considered for inclusion in the model were identified by literature review.[22] Of the 60 identified, a total of 14 variables were considered for inclusion in the model, including age, sex, body mass index, diagnosis of hypertension and time from diagnosis, antihypertensive prescription, smoking status, alcohol consumption, diagnosis of cardiovascular disease, clinic blood pressure level (systolic/diastolic), and multiple clinic blood pressure characteristics defined as previously described.[16] These characteristics were the difference between the first and last clinic blood pressure reading (referred to as the clinic blood pressure change [estimated from 3 or 6 readings]), the rate of the change in clinic blood pressure (referred

Table 1. Definitions of Blood Pressure Measurements Described in the Present Study

Term	Definition
Clinic blood pressure	First clinic blood pressure reading from a single clinic visit using an electronic oscillometric sphygmomanometer
Multiple clinic blood pressure readings	3–6 clinic blood pressure readings from a single clinic visit using an automated oscillometric sphygmomanometer
Clinic blood pressure change	Difference between the first and third (or sixth) clinic blood pressure reading taken in a single clinic visit using an automated oscillometric sphygmomanometer
Daytime ambulatory blood pressure	Ambulatory blood pressure measured at 15–60 minute intervals during the daytime (definition of daytime and interval varies between studies)
Home blood pressure	Mean of 6 days of readings (2 readings per day taken in the morning) after discarding the first day's readings
Out-of-office blood pressure	Daytime ambulatory blood pressure or home blood pressure (if daytime ambulatory blood pressure is not available)
Out-of-office hypertension	Daytime ambulatory blood pressure or home blood pressure ≥135/85 mm Hg
Home–clinic blood pressure difference	The difference between out-of-office blood pressure and automated blood pressure measured in the clinic
Model-adjusted clinic blood pressure	First clinic blood pressure reading added to the predicted home–clinic blood pressure difference (estimated by the PROOF-BP prediction algorithm).

PROOF-BP indicates Predicting Out-of-Office Blood Pressure in the clinic.

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Table 2. Characteristics of Studies Used for Model Derivation and Validation

Study	Author (Year)	Total Population	Used in Analysis	Age (Mean±SD)	Sex (% Men)	Population	CHD	Stroke	Diabetes Mellitus	Hypertensive*	Years With High BP (Mean±SD)	Treatment for Hypertension	White Coat Hypertension†	Masked Hypertension†
BP-Eth‡	Martin et al[17]	771	771	59±10	375 (49%)	Unselected	81 (11%)	33 (4%)	130 (17%)	344 (45%)	10±8	484 (63%)	83 (11%)	136 (19%)
CAMBO	Myers et al[12]	555	379§	64±10	131 (35%)	Isolated systolic hypertensives	0 (0%)	0 (0%)	0 (0%)	166 (44%)	9±9	364 (96%)	52 (16%)	64 (19%)
HITS	Mckinstry et al[18]	401	401	61±11	237 (59%)	Uncontrolled hypertensives	N/A	0 (0%)	0 (0%)	379 (95%)	N/A	352 (88%)	23 (6%)	42 (10%)
Oxford self-monitoring study	Nunan et al[21]	203	203	56±10	107 (53%)	Untreated, clinic BP ≥130/80 mm Hg	0 (0%)	0 (0%)	11 (5%)	109 (54%)	0±0	0 (0%)	67 (33%)	13 (6%)
TASMINH2‡	McManus et al[19]	527	220‖	67±9	103 (47%)	Uncontrolled hypertensives	20 (9%)	12 (5%)	18 (8%)	172 (78%)	10±8	220 (100%)	42 (21%)	11 (5%)
TASMINH-SR	McManus et al[20]	552	189‖	69±9	115 (61%)	Uncontrolled, high-risk hypertensives	58 (31%)	30 (16%)	81 (43%)	134 (71%)	11±9	160 (85%)	18 (10%)	53 (29%)

Hypertension defined as daytime out-of-office blood pressure (home or ambulatory monitoring) of ≥135/85 mm Hg. White coat systolic hypertension defined as a clinic blood pressure ≥140 mm Hg (mean of second and third readings) but an out-of-office blood pressure of <135 mm Hg. Masked systolic hypertension defined as a clinic blood pressure (mean of second and third readings) <140 mm Hg but an out-of-office blood pressure of ≥135 mm Hg. All percentages are given as a proportion of those patients with available data. BP indicates blood pressure; BP-Eth, Blood Pressure in Ethnic groups; CAMBO, Conventional Versus Automated Measurement of Blood Pressure in the Office; CHD, coronary heart disease; HITS, Telemonitoring-Based Service Redesign for the Management of Uncontrolled Hypertension; N/A; not available; TASMINH2, Telemonitoring and Self-Management in the Control of Hypertension; and TASMINH-SR, Targets and Self-Management for the Control of Blood Pressure in Stroke and at Risk Groups.

*Hypertensive according to home or ambulatory blood pressure monitoring.

†Defined according to systolic blood pressure.

‡Studies used for model derivation.

§Missing patients were those in the control arm (multiple clinic BP readings not taken) and those recruited from centers where complete clinic BP readings were not documented.

‖Missing patients were those in the control arm of the trial and those with missing home BP data.

to as the blood pressure slope [estimated from 3 or 6 readings]), and the curvature of this change in clinic blood pressure (referred to as the blood pressure quadratic [estimated from 6 readings]). Age, sex, and clinic blood pressure variables were included in the final model a priori because they were cited as significant predictors of white coat or masked hypertension in more than twice as many published studies compared with other predictors in a previous literature review.[22,23] Backward stepwise selection was used to select the remaining candidate predictors for the final model. Only predictors reaching a significance level of $P<0.05$ were included.

Model Derivation

A complete case analysis was conducted because of low amount of missing data. Two separate linear regression models were constructed examining factors that predict the systolic and diastolic home–clinic blood pressure difference (the difference between the first clinic blood pressure reading and mean out-of-office blood pressure). Out-of-office blood pressure was taken to be mean daytime ambulatory blood pressure where available; otherwise, mean home blood pressure was used (Table 1).[19,20] Because of colinearity between some of the candidate predictors listed above, separate models were compared in 3 stages using likelihood ratio tests. The best fitting model at each stage was considered in the next stage and where there was no significant difference in model fit, the most parsimonious model was selected. Stage 1 compared 5 different prediction models examining combinations of clinic blood pressure characteristic. Stage 2 compared the best fitting model from the first step using different definitions of clinic blood pressure (first clinic reading; mean of 1–3 readings; mean of 2–3 readings; mean of 1–6 readings; or the mean of 2–6 readings). The final stage explored prespecified interactions of all candidate predictors with age, sex, and diagnosis of hypertension, and the interaction between clinic blood pressure and the characteristics of the change in clinic blood pressure. Ninety-five percent confidence intervals (CIs) for model coefficients were estimated with bootstrap resampling (200 replications). Model coefficients are presented for centered continuous variables in the final model.

Model Validation and Performance

The agreement between predicted and actual home–clinic blood pressure differences was examined in both derivation and validation cohorts using Pearson correlation coefficient and Bland–Altman plots. A model-adjusted clinic blood pressure value was calculated by combining the original clinic pressure (first clinic reading) with the home–clinic blood pressure difference estimated from the model. The ability of the model-adjusted clinic blood pressure to predict out-of-office hypertension was assessed using area under the receiver operator characteristic (AUROC) curve statistics. High AUROC values (closer to 1) indicate better model discrimination.

Potential strategies for referral for out-of-office monitoring were explored in the derivation cohort (Tables S2 and S3), with the optimal strategy defined as a threshold which produced an overall classification error of ≤10% with the lowest proportion of patients referred for out-of-office monitoring. Model performance detecting true out-of-office hypertension was compared with existing strategies for blood pressure measurement described in international hypertension guidelines (Table S4).[15,24–26] The model was also applied to a nominal population from our validation cohort, with a comparable distribution of clinic blood pressures to that documented in the Health Survey for England. Using this nominal population, the number of patients being correctly diagnosed with hypertension per 1000 individuals was compared with the current National Institute for Health and Care Excellence (NICE) diagnostic algorithm[15] (considered best of the rest).

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Sensitivity analyses explored the model performance by individual study, predicting home or daytime ambulatory blood pressure, in patients with raised clinic blood pressure and those with controlled or normal clinic blood pressure. We also examined a revised diagnostic strategy which does not use the Predicting Out-of-Office Blood Pressure (PROOF-BP) algorithm, but in which patients with a clinic blood pressure between 130/85 and 160/100 mm Hg were referred for out-of-office monitoring. All sensitivity analyses were conducted in the validation cohort (except those by individual study which compared all available data).

All analyses were performed in STATA version 13.1 (MP parallel edition, StataCorp, TX). Data are presented as proportions of the total study population or means with SD or 95% CIs unless otherwise stated. Ethical approval was given for all individual studies contributing data, but approval for secondary analysis using anonymized data was not required.

Results

Characteristics of the Study Cohort

Of the 2470 patients with out-of-office blood pressure measurements enrolled across the 6 studies, relevant data were available for analysis in a total of 2163 patients (991 patients in the derivation cohort; 1172 patients in the validation cohort). Relevant data were not available in some patients enrolled in the CAMBO study[12] because not all centers recorded the individual automated clinic blood pressure readings required for this analysis (Table 2; Table S1). Characteristics of the derivation and validation cohorts were similar in terms of age, sex, the prevalence of systolic white coat hypertension and systolic masked hypertension (Table S5).

Model Derivation

Goodness-of-fit was similar between models examining 3 or 6 clinic blood pressure readings (derivation stage 1; adjusted R^2, 0.50–0.52) and those using different definitions of clinic blood pressure (derivation stage 2; adjusted R^2, 0.50–0.52). The most parsimonious model selected at each stage was that which used patient characteristics along with the clinic blood pressure change (estimated from 3 clinic readings), with the first clinic reading as an estimate of clinic blood pressure.

The systolic masked effect (a positive home–clinic difference) was associated with male sex and a positive clinic blood pressure change (Figure 1). The clinic blood pressure change and a history of hypertension were predictive of a diastolic masked effect. The systolic white coat effect (negative home–clinic blood pressure difference) was associated with increasing clinic blood pressure only (Figure 1). The diastolic white coat effect was associated with increasing clinic blood pressure, increasing age, and increasing pulse pressure. The final model included significant interactions between age, sex, clinic blood pressure, the clinic blood pressure change, pulse pressure, body mass index, history of cardiovascular disease, presence of an antihypertensive prescription, history of hypertension, and duration of hypertension. The final model (centered) coefficients are presented in Table 3 and the full equation is given in Figure S6.

Model Validation and Performance

The final model showed good calibration across all derivation and validation data sets (Pearson correlation, 0.62–0.80 [systolic]; 0.48–0.80 [diastolic]; $P<0.001$; Figures S2 and S3). At the extremes of home–clinic blood pressure difference, the model was less accurate, as evidenced by the slight skew observed in the Bland–Altman plots (Figures S4 and S5), suggesting that the model underpredicts those with a large masked effect and overpredicts those with a large white coat effect.

The model was good at discriminating out-of-office hypertension (masked or sustained hypertension) in the derivation cohort (AUROC, 0.80; 95% CI, 0.78–0.83 [systolic model]; 0.82; 95% CI, 0.80–0.85 [diastolic model]) and this discrimination was maintained in the validation cohort (AUROC, 0.75; 95% CI, 0.72–0.79 [systolic model]; 0.87; 95% CI, 0.85–0.89 [diastolic model]; Figure 2). Using the model-adjusted clinic blood pressure, the optimal thresholds for referral for out-of-office monitoring were ≥130/80 and <145/90 mm Hg. In other words, in a model-adjusted blood pressure of <130/80 mm Hg, patients were confidently predicted as normotensive and those with a model-adjusted blood pressure of ≥145/90 mm Hg were considered hypertensive. Anyone with a model-adjusted blood pressure between the 2 required out-of-office measurements. Using

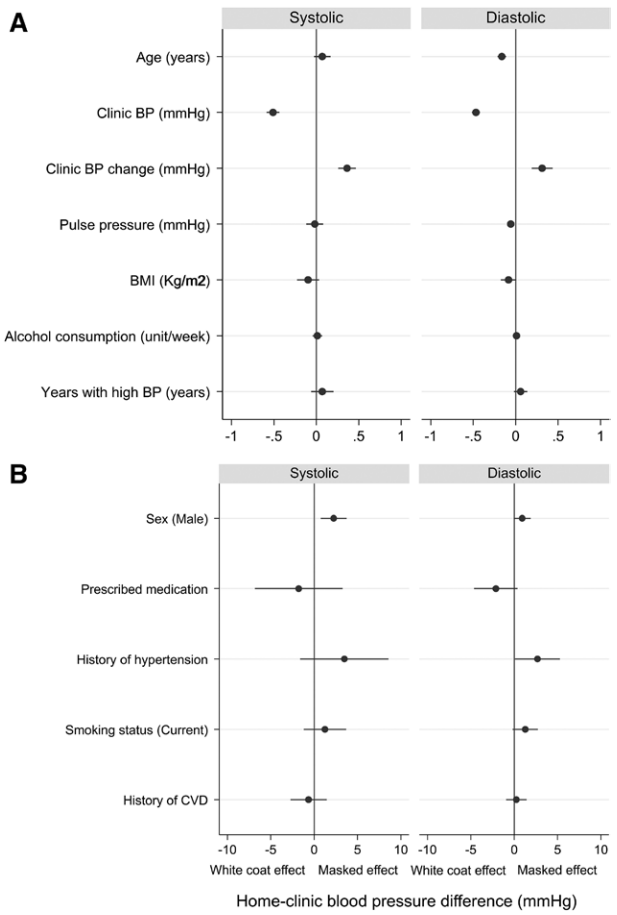

Figure 1. Coefficient plot showing predictors of the systolic and diastolic home–clinic blood pressure difference. **A**, Continuous predictors. **B**, Binary predictors. All coefficients are presented from the model before stepwise selection. Coefficients for continuous variables are presented as centered values per unit increase. BMI indicates body mass index; BP, blood pressure; and CVD, cardiovascular disease.

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Table 3. Linear Regression Model for Prediction of the Systolic/Diastolic Home–Clinic Blood Pressure Difference

	Prediction Model With Interaction Terms					
	Systolic Prediction Model			Diastolic Prediction Model		
Model Term	β	95% CI	*P* Value	β	95% CI	*P* Value
Age, y	0.07	−0.02 to 0.17	0.134	−0.33	−0.62 to −0.05	0.022
Sex, (men)	3.41	0.23 to 6.60	0.036	3.33	1.78 to 4.87	<0.001
Clinic blood pressure (first reading), mm Hg	−0.50	−0.58 to −0.43	<0.001	−0.47	−0.51 to −0.42	<0.001
Clinic blood pressure change (readings 1–3), mm Hg	0.36	0.26 to 0.46	<0.001	0.31	0.21 to 0.42	<0.001
Body mass index, kg/m^2	−0.21	−0.37 to −0.04	0.012	−0.07	−0.16 to 0.01	0.096
Previous diagnosis of hypertension (yes)	−5.07	−12.15 to 2.01	0.161	−0.03	−3.55 to 3.49	0.987
Time from diagnosis of hypertension, y	0.18	0.00 to 0.35	0.053	…	…	…
Antihypertensive prescription (yes)	6.94	0.42 to 13.46	0.037	2.37	−1.30 to 6.04	0.206
History of cardiovascular disease (yes)	…	…	…	−0.40	−1.69 to 0.89	0.543
Pulse pressure (first reading), mm Hg	−0.04	−0.13 to 0.05	0.397	−0.06	−0.09 to −0.03	<0.001
Age×clinic blood pressure	−0.01	−0.01 to −0.00	0.027	…	…	…
Age×pulse pressure	0.01	0.00 to 0.02	0.030	…	…	…
Age×clinic blood pressure change	…	…	…	0.01	0.00 to 0.02	0.014
Age×body mass index	…	…	…	0.01	0.00 to 0.02	0.039
Age×history of cardiovascular disease	…	…	…	0.18	0.02 to 0.33	0.023
Age×antihypertensive prescription at baseline	…	…	…	−0.13	−0.24 to −0.03	0.010
Sex×body mass index	0.30	0.01 to 0.58	0.041	…	…	…
Sex×time from diagnosis of hypertension	−0.26	−0.50 to −0.02	0.034	…	…	…
Sex×antihypertensive prescription at baseline	−14.74	−23.33 to −6.15	0.001	−8.00	−12.45 to −3.54	<0.001
Sex×previous diagnosis of hypertension	13.39	4.57 to 22.21	0.003	4.63	0.40 to 8.85	0.033
Constant	−9.09	−11.55 to −6.64	<0.001	−6.98	−8.24 to −5.72	<0.001

β-Coefficients and 95% confidence intervals given in mm Hg. β-Coefficients for continuous variables are presented as centered values per unit increase unless otherwise stated. CI indicates confidence intervals.

this model-adjusted blood pressure to triage patients for out-of-office monitoring, 93% of cases were correctly classified (Table 4). This was an improvement of ≤29% compared with strategies recommended in current clinical guidelines (PROOF-BP, 93% [92% to 95%]; American Heart Association, 73% [70% to 75%]; Canadian Hypertension Education Program, 74% [71% to 77%]; European Society of Hypertension, 73% [70% to 75%]; NICE, 78% [76% to 81%]) with similar usage of out-of-office monitoring (PROOF-BP, 58% referred [55% to 61%] versus NICE, 54% referred, [51% to 57%]; Table 4). In a nominal representative population, for every 1000 people aged from 45 to 74 years screened with the new algorithm, correct classification would be gained for 910 patients with 395 diagnosed as hypertensive, compared with the next best strategy (NICE algorithm) where 853 would be correctly classified and only 274 diagnosed as hypertensive. The additional 121 diagnoses of hypertension result from the detection of those patients with masked hypertension.

Sensitivity Analyses

The results of the sensitivity analyses are detailed in the Appendix S1 (Table S6). Model performance was consistent across individual studies (AUROC, 0.61–0.78 [systolic model]; 0.74–0.91 [diastolic model]) and the new algorithm resulted in better targeting of out-of-office blood pressure compared with a revised diagnostic strategy using clinic blood pressure alone to triage patients for out-of-office monitoring. Using the new algorithm to triage only those patients with raised clinic blood pressure (ie, only considering those patients with a potential white coat effect) resulted in correct classification of 94% of patients with only 45% requiring out-of-office monitoring (Table S6).

Discussion

This study describes a clinical prediction model which combines patient characteristics (age, sex, body mass index, history of hypertension, cardiovascular disease, and

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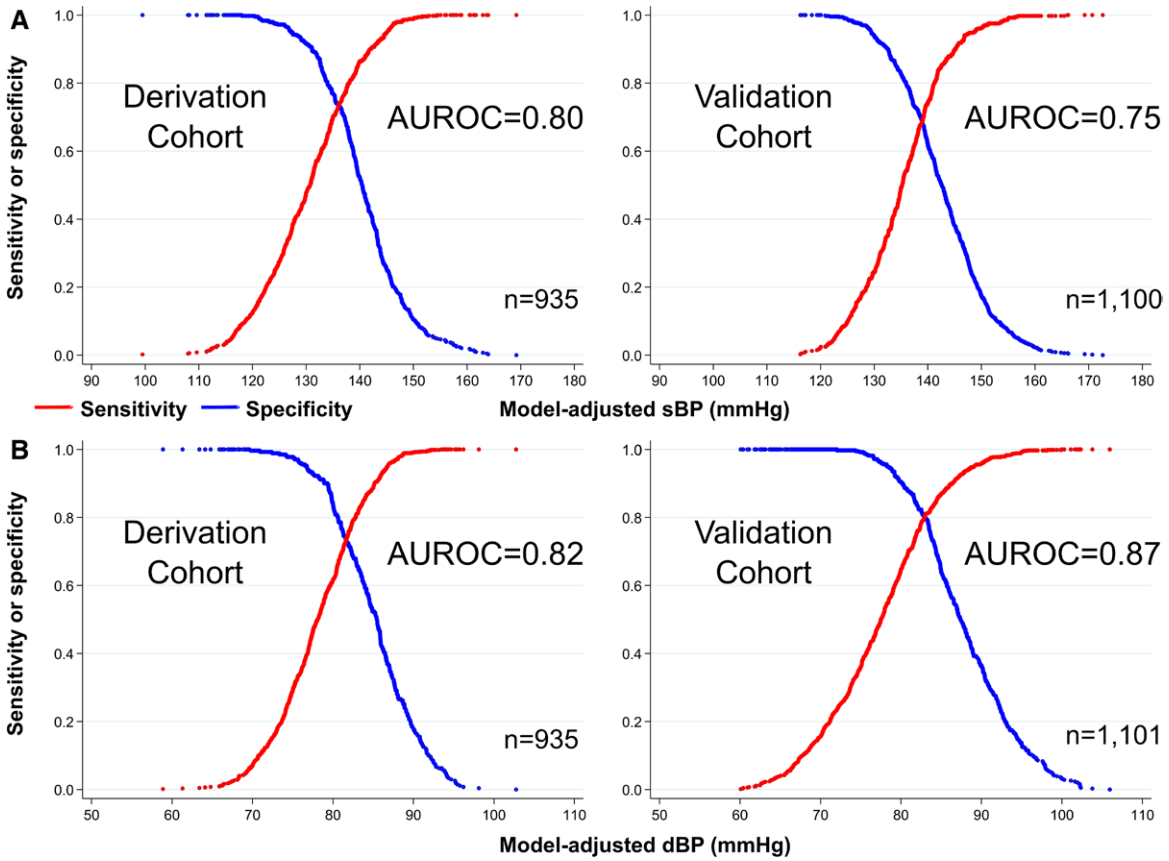

Figure 2. Area under the receiver operator characteristic curve (AUROC) analysis showing performance of systolic/diastolic blood pressure (sBP/dBP) prediction models for discrimination of out-of-office hypertension. **A**, sBP prediction model. **B**, dBP prediction model.

antihypertensive treatment) and 3 clinic blood pressure measurements from a single visit to accurately predict a patient's out-of-office blood pressure. Used as a triaging tool for out-of-office monitoring, detection of hypertension or uncontrolled blood pressure was markedly improved from existing diagnostic and management strategies, specifically including those with previously unrecognized masked hypertension.

Strengths and Limitations

This retrospective study used a large cohort of patients from 6 previous studies providing a population representative of individuals from the United Kingdom and North America undergoing blood pressure measurement in primary care. Sensitivity analyses revealed consistent model performance across individual studies, suggesting that it would be effective regardless of the electronic blood pressure monitoring

Table 4. Comparison of Model Performance With Current Clinical Practice in the Validation Cohort (n=1100)

Guideline (year)	Systolic AUC (95% CI)	Diastolic AUC (95% CI)	Hypertensive (True-Positive)	Normotensive (True-Negative)	White Coat Hypertensive (False-Positive)	Masked Hypertensive (False-Negative)	Correctly Classified	Referral for ABPM
AHA[24]	0.74 (0.71–0.77)	0.85 (0.83–0.87)	625 (57%)	173 (16%)	178 (16%)	124 (11%)	798 (73%)	0 (0%)
CHEP[25]	0.76 (0.73–0.79)	0.87 (0.85–0.89)	642 (58%)	172 (16%)	179 (16%)	107 (10%)	814 (74%)	0 (0%)
ESH[26]*	0.74 (0.71–0.77)	0.86 (0.84–0.88)	596 (54%)	203 (18%)	148 (13%)	151 (14%)	799 (73%)	0 (0%)
NICE[15]	0.73 (0.70–0.76)	0.84 (0.82–0.87)	513 (47%)	349 (32%)	2 (0.2%)	236 (21%)	862 (78%)	590 (54%)
PROOF-BP (2016)	0.75 (0.72–0.78)	0.87 (0.85–0.89)	720 (65%)	306 (28%)	45 (4%)	29 (3%)	1026 (93%)	640 (58%)

Data were from the Telemonitoring-Based Service Redesign for the Management of Uncontrolled Hypertension (HITS),[18] Telemonitoring and Self-Management in the Control of Hypertension,[20] Conventional Versus Automated Measurement of Blood Pressure in the Office (CAMBO),[12] and Oxford self-monitoring studies.[21] ABPM indicates ambulatory blood pressure monitoring; AHA, American Heart Association; AUC, area under the receiver–operator characteristic curve; CHEP, Canadian Hypertension Education Program; CI, confidence intervals; ESH, European Society of Hypertension; NICE, National Institute for health and Care Excellence; and PROOF-BP, Predicting Out-of-Office Blood Pressure in clinic tool.

*Analysis conducted in only 1098 patients because of missing data.

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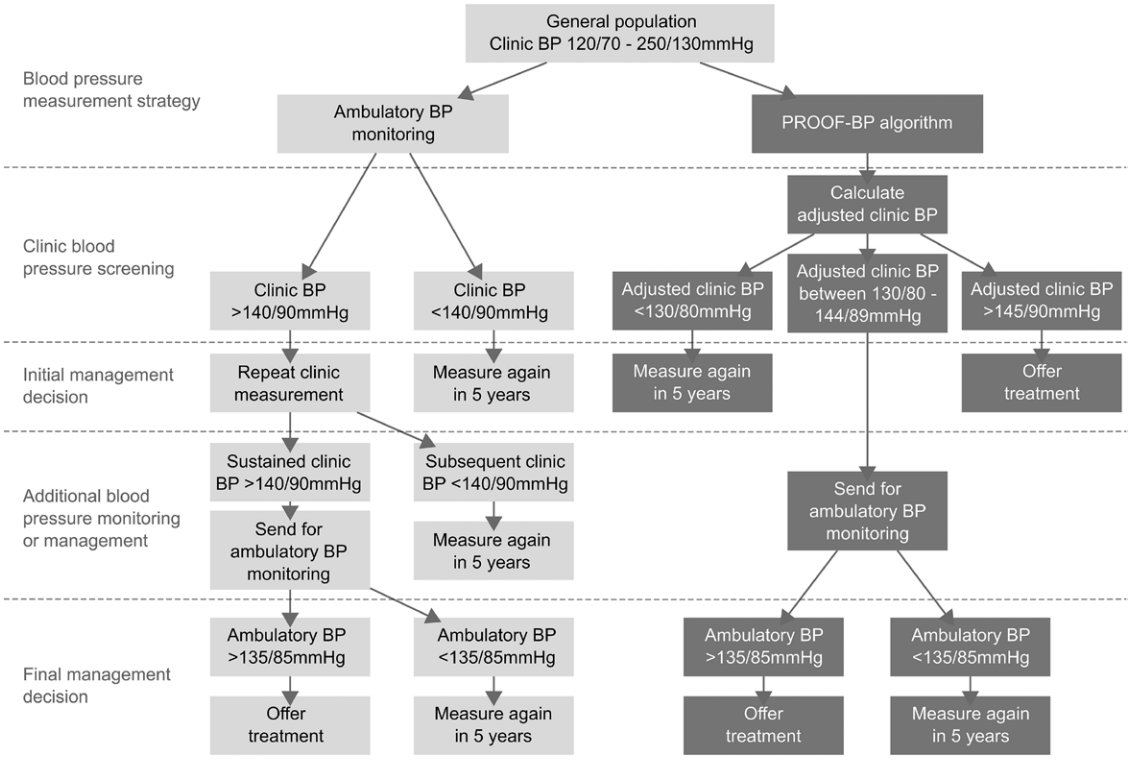

Figure 3. Algorithm for using the Predicting Out-of-Office Blood Pressure in clinic tool (PROOF-BP) prediction model to triage patients for out-of-office blood pressure monitoring. Existing strategies are based on the hypertension diagnostic pathway specified by the US Preventive Services Task Force and the National Institute for Health and Care Excellence. BP indicates blood pressure.

device (BpTRU; Stabil-O-Graph) or measurement protocol used (rest period versus no rest period; nurse present during measurement versus nurse not present; automatic readings versus patient/nurse-initiated readings; 1-minute versus 2-minute intervals between readings). It is well known that blood pressure measurements made under controlled conditions in a research setting are not necessarily comparable with those made by a physician in routine clinical practice.[24,27,28] Differences occur for a variety of reasons, including the use of inadequate or uncalibrated devices[29–31] and suboptimal measurement techniques.[32–34] Indeed, the present algorithm requires 3 consecutive blood pressure readings to be taken at a single clinic visit and although this is recommended in most hypertension guidelines,[15,24–26] ensuring this approach is adhered to in routine practice may require some education of physicians and nurses. Therefore, although this prediction model is shown to be accurate in a research setting, it is not guaranteed to work in routine clinical practice, and prospective validation of the PROOF-BP prediction tool in a clinical setting warrants further investigation.

Bland–Altman plots demonstrated that the PROOF-BP prediction model tends to underestimate those with a large masked effect and overestimate those with a large white coat effect. This is likely to be explained by the underlying population in the derivation cohort which contained a higher proportion of hypertensive (defined by clinic readings) patients on treatment (704 [71%]), a population known to have an exaggerated white coat effect compared with normotensives (Figure S1).[35] Although the model was less accurate at extremes of home–clinic blood pressure difference, it showed good performance detecting out-of-office hypertension around the clinical threshold (140/90 mm Hg) where the average home–clinic blood pressure difference is smaller.[35]

The present analyses used home blood pressure data to define out-of-office blood pressure, where daytime ambulatory measurements were not available (Table 1). Some argue that 24-hour ambulatory blood pressure should be used as the gold standard measure of blood pressure[26] because it contains information about night-time blood pressure which includes additional prognostic information. However, the recent review by the US Preventive Services Task Force found no apparent difference among 24-hour, daytime, and night-time ambulatory blood pressure measurement protocols for prediction of cardiovascular outcomes,[14] and a sensitivity analysis in the present study demonstrated no change in the accuracy of the PROOF-BP prediction model using home or daytime ambulatory readings.

Comparison With Previous Literature

Many studies have examined the association between patient characteristics and the home–clinic blood pressure difference, noting age,[36–38] sex,[36–39] and clinic blood pressure level,[36–39] along with anxiety,[40,41] stress,[42] and other factors[22] as significant independent predictors of white coat or masked hypertension. The findings of the present study were consistent with previous literature, showing age, sex, clinic blood pressure, pulse pressure, and a history of hypertension as significant predictors of the home–clinic blood pressure difference. Interestingly, female sex was not a significant predictor of the white coat effect, although it was included a priori in the

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final prediction model because this association has been well-defined in the previous literature.[36,38]

Few studies have suggested a strategy for targeted use of out-of-office blood pressure in routine clinical practice. Myers et al[43] and Godwin et al[44] have proposed the use of multiple (automated) office blood pressure readings taken using the BpTRU device to identify patients with high normal blood pressure (130/80 to 139/89 mm Hg) who could be referred for ambulatory blood pressure to confirm the presence of masked hypertension. Similarly, Viera et al[45] examined optimal automated clinic blood pressure levels for referral for out-of-office monitoring in patients with normal clinic pressure for detection of masked hypertension. However, they concluded that using clinic blood pressure alone was not sufficient because of high referral rates, and suggested that a combination of factors including patient characteristics might be more effective at targeting out-of-office blood pressure more efficiently.

Implications for Clinical Practice

The US Preventive Services Task Force[14] recently released guidelines recommending that ambulatory blood pressure monitoring is used to confirm a diagnosis of hypertension. It is anticipated that these guidelines will follow a similar approach to that advocated in the United Kingdom by NICE, which does not capture those patients with masked hypertension. The present analyses propose a method for capturing nearly all patients with truly raised out-of-office blood pressure which is likely to result in a small increase in the amount of out-of-office monitoring required in routine practice but could still be cost-effective if it reduces the present best practice involving indiscriminate application of ambulatory monitoring.[2,14,15] Indeed, our sensitivity analyses show that in patients with raised clinic readings, the PROOF-BP prediction model could potentially reduce the proportion of referrals for daytime ambulatory monitoring by more than half to 285/629 (45%), with nearly all patients being accurately diagnosed (589/629 [94%] correctly classified) and acceptable false-positive and false-negative rates (6% and 0%, respectively). Importantly, this new method identifies patients with possible masked hypertension which is otherwise unsuspected unless there is evidence of unexpected end-organ damage.

An algorithm for using the PROOF-BP prediction tool in routine clinical practice is presented in Figure 3. Electronic blood pressure monitors which take 3 consecutive readings (at 1-minute intervals) are now cheap and routinely available, permitting use of this algorithm before, during, or after a standard physician consultation in primary care. The prediction model could easily be incorporated into general practice computer systems, accessed as an online calculator or even built into smartphones linked to blood pressure monitors to facilitate implementation in routine clinical practice. This novel approach to measurement and management would require buy in from both patients and practitioners and therefore some degree of education may be required during implementation.

Perspectives

The present study shows that a combination of simple patient characteristics with 3 clinic blood pressure measurements from a single visit can accurately identify those patients requiring out-of-office blood pressure monitoring for suspected white coat hypertension and arguably most importantly masked hypertension. This prediction model has the potential to improve the accuracy of diagnosis and management of hypertension in primary care, and prospective validation in routine clinical practice along with analysis of cost-effectiveness are now warranted.

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R.J. McManus has received equipment for research purposes from Omron and Lloyds Healthcare. C. Heneghan has received expenses and payments for his media work from Channel 4, British Broadcasting Corporation, FreshOne Television productions and the Guardian, and also expenses from the World Health Organization and the US Food and Drug Administration. He is also an expert witness in an ongoing medical device legal case, has received payment from British United Provident Association for analyzing and appraising guidelines and income from the publication of a series of tool kit books published by Blackwells. F.D.R. Hobbs has received limited research support in terms of blood pressure devices from Microlife and BpTRU. B. Williams works in academic collaboration with Healthstats, Singapore, in developing novel blood pressure–monitoring approaches. The other authors report no conflicts.

References

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913. doi: 10.1016/S0140-6736(02)11911-8.
2. Lovibond K, Jowett S, Barton P, Caulfield M, Heneghan C, Hobbs FD, Hodgkinson J, Mant J, Martin U, Williams B, Wonderling D, McManus RJ. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. *Lancet*. 2011;378:1219–1230. doi: 10.1016/S0140-6736(11)61184-7.

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3. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension*. 2005;46:156–161. doi: 10.1161/01.HYP.0000170138.56903.7a.
4. Ohkubo T, Hozawa A, Nagai K, Kikuya M, Tsuji I, Ito S, Satoh H, Hisamichi S, Imai Y. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. *J Hypertens*. 2000;18:847–854.
5. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J; Systolic Hypertension in Europe Trial Investigators. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA*. 1999;282:539–546. doi: 10.1001/jama.282.6.539.
6. Hodgkinson J, Mant J, Martin U, Guo B, Hobbs FD, Deeks JJ, Heneghan C, Roberts N, McManus RJ. Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: systematic review. *BMJ*. doi: 10.1136/bmj.d3621.
7. Jin Y, Bies R, Gastonguay MR, Stockbridge N, Gobburu J, Madabushi R. Misclassification and discordance of measured blood pressure from patient's true blood pressure in current clinical practice: a clinical trial simulation case study. *J Pharmacokinet Pharmacodyn*. 2012;39:283–294. doi: 10.1007/s10928-012-9250-8.
8. Pickering TG, Coats A, Mallion JM, Mancia G, Verdecchia P. Blood Pressure Monitoring. Task force V: white-coat hypertension. *Blood Press Monit*. 1999;4:333–341.
9. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. *Hypertension*. 2002;40:795–796. doi: 10.1161/01.HYP.0000038733.08436.98.
10. Sega R, Trocino G, Lanzarotti A, Carugo S, Cesana G, Schiavina R, Valagussa F, Bombelli M, Giannattasio C, Zanchetti A, Mancia G. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). *Circulation*. 2001;104:1385–1392. doi: 10.1161/hc3701.096100.
11. Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol*. 2005;46:508–515. doi: 10.1016/j.jacc.2005.03.070.
12. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Grant FC, Kaczorowski J. Conventional versus automated measurement of blood pressure in primary care patients with systolic hypertension: randomised parallel design controlled trial. *BMJ*. 2011;342:d286. doi: http://dx.doi.org/10.1136/bmj.d286.
13. Myers MG, Valdivieso M, Kiss A. Use of automated office blood pressure measurement to reduce the white coat response. *J Hypertens*. 2009;27:280–286. doi: 10.1097/HJH.0b013e32831b9e6b.
14. Piper MA, Evans CV, Burda BU, Margolis KL, O'Connor E, Whitlock EP. Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2015;162:192–204. doi: 10.7326/M14-1539.
15. National Clinical Guideline Centre; National Institute for Health and Clinical Excellence Guidance (CG127). *Hypertension. The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34*. London, United Kingdom: Royal College of Physicians; 2011.
16. Sheppard JP, Holder R, Nichols L, Bray E, Hobbs FD, Mant J, Little P, Williams B, Greenfield S, McManus RJ. Predicting out-of-office blood pressure level using repeated measurements in the clinic: an observational cohort study. *J Hypertens*. 2014;32:2171–2178; discussion 2178. doi: 10.1097/HJH.0000000000000319.
17. Martin U, Haque MS, Wood S, Greenfield SM, Gill PS, Mant J, Mohammed MA, Heer G, Johal A, Kaur R, Schwartz C, McManus RJ. Ethnicity and differences between clinic and ambulatory blood pressure measurements. *Am J Hypertens*. 2015;28:729–738. doi: 10.1093/ajh/hpu211.
18. McKinstry B, Hanley J, Wild S, Pagliari C, Paterson M, Lewis S, Sheikh A, Krishan A, Stoddart A, Padfield P. Telemonitoring based service redesign for the management of uncontrolled hypertension: multicentre randomised controlled trial. *BMJ*. 2013;346:f3030. doi: http://dx.doi.org/10.1136/bmj.f3030.
19. McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, Kaambwa B, Banting M, Bryan S, Little P, Williams B, Hobbs FD. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. *Lancet*. 2010;376:163–172. doi: 10.1016/S0140-6736(10)60964-6.
20. McManus RJ, Mant J, Haque MS, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. *JAMA*. 2014;312:799–808. doi: 10.1001/jama.2014.10057.
21. Nunan D, Thompson M, Heneghan CJ, Perera R, McManus RJ, Ward A. Accuracy of self-monitored blood pressure for diagnosing hypertension in primary care. *J Hypertens*. 2015;33:755–762; discussion 762. doi: 10.1097/HJH.0000000000000489.
22. Sheppard JP, Fletcher B, Gill P, Martin U, Roberts N, McManus RJ. Predictors of the home-clinic blood pressure difference: a systematic review and meta-analysis [published online ahead of print September 22, 2015]. *Am J Hypertens*. doi: 10.1093/ajh/hpv157. http://ajh.oxfordjournals.org/content/early/2015/09/20/ajh.hpv157.long. Accessed September 22, 2015.
23. Steyerberg EW. Restriction on candidate predictors. *Clinical Prediction Models*. New York: Springer Science+Business Media; 2010: 175–187.
24. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation*. 2005;111:697–716. doi: 10.1161/01.CIR.0000154900.76284.F6.
25. Dasgupta K, Quinn RR, Zarnke KB, et al; Canadian Hypertension Education Program. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol*. 2014;30:485–501. doi: 10.1016/j.cjca.2014.02.002.
26. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159–2219. doi: 10.1093/eurheartj/eht151.
27. Sebo P, Pechère-Bertschi A, Herrmann FR, Haller DM, Bovier P. Blood pressure measurements are unreliable to diagnose hypertension in primary care. *J Hypertens*. 2014;32:509–517. doi: 10.1097/HJH.0000000000000058.
28. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Kaczorowski J. Measurement of blood pressure in the office: recognizing the problem and proposing the solution. *Hypertension*. 2010;55:195–200. doi: 10.1161/HYPERTENSIONAHA.109.141879.
29. Rouse A, Marshall T. The extent and implications of sphygmomanometer calibration error in primary care. *J Hum Hypertens*. 2001;15:587–591. doi: 10.1038/sj.jhh.1001241.
30. Coleman AJ, Steel SD, Ashworth M, Vowler SL, Shennan A. Accuracy of the pressure scale of sphygmomanometers in clinical use within primary care. *Blood Press Monit*. 2005;10:181–188.
31. A'Court C, Stevens R, Sanders S, Ward A, McManus R, Heneghan C. Type and accuracy of sphygmomanometers in primary care: a cross-sectional observational study. *Br J Gen Pract*. 2011;61:e598–e603. doi: 10.3399/bjgp11X593884.
32. Manzoli L, Simonetti V, D'Errico MM, De Vito C, Flacco ME, Forni C, La Torre G, Liguori G, Messina G, Mezzetti A, Panella M, Pizzi C, Siliquini R, Villari P, Cicolini G. (In)accuracy of blood pressure measurement in 14 Italian hospitals. *J Hypertens*. 2012;30:1955–1960. doi: 10.1097/HJH.0b013e3283577b20.
33. McVicker JT. Blood pressure measurement–does anyone do it right?: an assessment of the reliability of equipment in use and the measurement techniques of clinicians. *J Fam Plann Reprod Health Care*. 2001;27:163–164. doi: 10.1783/147118901101195407.
34. Veiga EV, Nogueira MS, Cárnio EC, Marques S, Lavrador MA, de Moraes SA, Souza LA, Lima NK, Nobre F. Assessment of the techniques of blood pressure measurement by health professionals. *Arq Bras Cardiol*. 2003;80:89–93, 83. doi: 10.1590/S0066-782X2003000100008.
35. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Zampi I, Gattobigio R, Sacchi N, Porcellati C. White coat hypertension and white coat effect. Similarities and differences. *Am J Hypertens*. 1995;8:790–798. doi: 10.1016/0895-7061(95)00151-E.
36. Abir-Khalil S, Zaîmi S, Tazi MA, Bendahmane S, Bensaoud O, Benomar M. Prevalence and predictors of white-coat hypertension in a large

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database of ambulatory blood pressure monitoring. *East Mediterr Health J*. 2009;15:400–407.
37. Andalib A, Akhtari S, Rigal R, Curnew G, Leclerc JM, Vaillancourt M, Tardif JC. Determinants of masked hypertension in hypertensive patients treated in a primary care setting. *Intern Med J*. 2012;42:260–266. doi: 10.1111/j.1445-5994.2010.02407.x.
38. Lindbaek M, Sandvik E, Liodden K, Mjell J, Ravnsborg-Gjertsen K. Predictors for the white coat effect in general practice patients with suspected and treated hypertension. *Br J Gen Pract*. 2003;53:790–793.
39. Sobrino J, Domenech M, Camafort M, Vinyoles E, Coca A; ESTHEN Group Investigators. Prevalence of masked hypertension and associated factors in normotensive healthcare workers. *Blood Press Monit*. 2013;18:326–331. doi: 10.1097/MBP.0000000000000002.
40. Jhalani J, Goyal T, Clemow L, Schwartz JE, Pickering TG, Gerin W. Anxiety and outcome expectations predict the white-coat effect. *Blood Press Monit*. 2005;10:317–319.
41. Spruill TM, Pickering TG, Schwartz JE, Mostofsky E, Ogedegbe G, Clemow L, Gerin W. The impact of perceived hypertension status on anxiety and the white coat effect. *Ann Behav Med*. 2007;34:1–9. doi: 10.1080/08836610701495581.
42. MacDonald MB, Laing GP, Wilson MP, Wilson TW. Prevalence and predictors of white-coat response in patients with treated hypertension. *CMAJ*. 1999;161:265–269.
43. Myers MG. A proposed algorithm for diagnosing hypertension using automated office blood pressure measurement. *J Hypertens*. 2010;28:703–708. doi: 10.1097/HJH.0b013e328335d091.
44. Godwin M, Birtwhistle R, Delva D, Lam M, Casson I, MacDonald S, Seguin R. Manual and automated office measurements in relation to awake ambulatory blood pressure monitoring. *Fam Pract*. 2011;28:110–117. doi: 10.1093/fampra/cmq067.
45. Viera AJ, Lin FC, Tuttle LA, Shimbo D, Diaz KM, Olsson E, Stankevitz K, Hinderliter AL. Levels of office blood pressure and their operating characteristics for detecting masked hypertension based on ambulatory blood pressure monitoring. *Am J Hypertens*. 2015;28:42–49. doi: 10.1093/ajh/hpu099.

Novelty and Significance

What Is New?

- This study shows that a simple linear regression model incorporating patient characteristics and 3 consecutive clinic blood pressure measurements from a single clinic visit can accurately identify those patients requiring out-of-office blood pressure monitoring for suspected white coat or masked hypertension.
- The model performance was consistent across populations, and in studies using different blood pressure monitors and measurement techniques, suggesting that the results are widely applicable across Primary Care.

What Is Relevant?

- This prediction model could be used as an online calculator or integrated into practice computer systems for triaging of out-of-office monitoring to permit detection of those patients with white coat or masked hypertension in routine clinical practice.
- The present analyses suggest such an approach would improve the detection of hypertension and provide a strategy for capturing patients with apparent masked hypertension for the first time.

Summary

Our findings suggest that it is possible to predict which patients are most likely to display a white coat or masked effect, using patient characteristics and multiple clinic blood pressure measurements from a single clinic visit.

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Predicting Out-of-Office Blood Pressure in the Clinic (PROOF-BP): Derivation and Validation of a Tool to Improve the Accuracy of Blood Pressure Measurement in Clinical Practice

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PRedicting Out-of-OFfice Blood Pressure in the clinic (PROOF-BP): Derivation and validation of a tool to improve the accuracy of blood pressure measurement in clinical practice

Sheppard, Predicting out-of-office blood pressure

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Supplemental Material

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Extended methods

Study design and source data

The present study was an individual patient data analysis of cohort studies conducted in a Primary Care setting.[1-6] A linear regression model predicting the home-clinic blood pressure difference was derived in two datasets using candidate predictors identified from a literature review. All included studies collected relevant data including clinic, home and/or daytime ambulatory blood pressure readings using a validated electronic oscillometric blood pressure monitor and details of patient characteristics and medical history. The characteristics of patients from included studies are detailed in table 1. Patients in the CAMBO study[5] had their clinic blood pressure measured with a BpTRU device with either the doctor or nurse taking the first reading and then leaving the room for the remaining measurements. In all other studies, multiple clinic readings were taken in the presence of a nurse or practice reception staff.[1-4] Individual clinic readings were available in each study permitting estimation of a variety of different definitions of clinic blood pressure. Since this study involved secondary analysis of existing data, it was not possible to standardise protocols for blood pressure measurement across studies and thus specific definitions of home and daytime ambulatory blood pressure varied to some degree (eTable 1).

Patients were selected for the derivation cohort from the BP-Eth[1] and TASMINH2[3] studies (n=991) because these were considered to be sufficiently large and representative population of patients likely to undergo blood pressure monitoring for diagnosis and management of hypertension in routine clinical practice. The remaining four studies[2, 4-6] were utilised in the validation cohort (n=1,172).

Selection of candidate predictors

Candidate predictors considered for inclusion in the model were identified by literature review.[7] Of the 60 identified, 24 were excluded because they were not considered routinely available in Primary Care. A further 19 predictors were excluded due to a lack of availability in the datasets used. Five variables describing history of cardiovascular disease and the number of antihypertensive medications prescribed were simplified to the presence of disease/medication or not, due to missing data in some studies. In total, 14 variables were considered in the model derivation and comprised age (continuous), sex (male/female), body mass index (BMI; continuous), diagnosis of hypertension (yes/no), time since diagnosis of hypertension (continuous), antihypertensive prescription (yes/no), smoking status (current/non-smoker), alcohol consumption (yes/no), diagnosis of cardiovascular disease (yes/no), clinic systolic and diastolic blood pressure (continuous) and multiple clinic blood pressure characteristics defined as previously described.[8] These characteristics were the difference between the first to last clinic blood pressure reading ('clinic blood pressure change', continuous; estimated from 3 or 6 readings), the rate of the change in clinic blood pressure (referred to as the 'clinic blood pressure slope' [continuous; estimated from 3 or 6 readings]) and the 'curvature' this change in clinic blood pressure (referred to as the 'clinic blood pressure quadratic' [continuous; estimated from 6 readings]). Continuous variables were centred before use. Age, sex and clinic blood pressure variables were included in the

final model a priori because they were cited as significant predictors of white coat or masked hypertension in more than twice as many published studies compared to other predictors in previous literature review.[7, 9] Backwards stepwise selection was used to select the remaining candidate predictors for the final model. Only predictors reaching a significance level of $p < 0.05$ were included.

Data cleaning

Where necessary, variables of interest were recoded to ensure consistency across datasets. For example, smoking status was standardised to 'current smoker' vs. 'non-smoker' with ex-smokers classed as non-smokers where appropriate. History of hypertension was defined as a documented diagnosis of hypertension prior to enrolment in a given study. This could have been based on clinic or out-of-office readings or a combination of both. History of cardiovascular disease was defined as any coronary artery disease (CHD; including myocardial infarction, angina or coronary artery bypass graft), stroke, peripheral vascular disease or heart failure. Patients enrolled in the HITS study[2] (where presence of CHD was not recorded) were assumed to have no history of CHD for the purposes of model validation.

Data were cleaned and outlying values were excluded where appropriate. Blood pressure outliers were defined a systolic blood pressure of <70mmHg or >260mmHg and a diastolic blood pressure of <40mmHg or >150mmHg as previously described.[10] BMI values of zero or >75 were recoded to missing. Data from patients which did not appear to meet the original study inclusion criteria were also recoded to missing (e.g. age 7 years when inclusion criteria specifies age 45 and above).

Model derivation

Because data in each study were collected specifically for clinical trials or cohort studies, data completeness was high (>95%) in all variables of interest. Thus, a compete case analysis was possible and no attempt was made to impute missing data. A linear regression model was constructed examining factors that predicted the home-clinic blood pressure difference (1st clinic blood pressure reading minus mean out-of-office blood pressure). Out-of-office blood pressure was taken to be mean daytime ambulatory blood pressure where available, otherwise home blood pressure was used.[3, 4] Due to co-linearity between some of the candidate predictors listed above, separate models were compared in three stages using likelihood ratio tests. The best fitting model at each stage was considered in the next stage and where there was no significant difference in model fit, the most parsimonious model was selected. Stage one compared five different prediction models examining different combinations of automated clinic blood pressure characteristic:

- Model 1 = the slope and quadratic of the change in clinic blood pressure across 6 readings;[8]
- Model 2 = the slope of the change in clinic blood pressure across 6 readings;[8]
- Model 3 = the clinic blood pressure change across 6 readings;
- Model 4 = the slope of the change in clinic blood pressure across 3 readings;[8]
- Model 5 = the clinic blood pressure change across 3 readings.

Stage two compared the best fitting model from the first step using different definitions of mean automated clinic blood pressure (1st clinic reading; mean of 1-3 readings; mean of 2-3 readings; mean of 1-6 readings; or the mean of 2-6 readings). The final stage explored pre-specified interactions of all candidate predictors with age, sex and diagnosis of hypertension and the interaction between clinic blood pressure and the characteristics of the change in clinic blood pressure. Ninety-five percent confidence intervals (CIs) for model coefficients were estimated with bootstrap resampling (200 replications). Model coefficients are presented for centred continuous variables in the final model.

Model validation and performance

The agreement between predicted and actual home-clinic blood pressure differences was examined in both derivation and validation cohorts using Pearson's correlation coefficient and Bland-Altman plots. The ability of the model-adjusted clinic blood pressure to predict out-of-office hypertension was assessed using Area Under the Receiver Operator Characteristic (AUROC) curve statistics. High AUROC values (up to 1) indicate better model discrimination. The 'model-adjusted' clinic blood pressure value was calculated by combining the original clinic pressure (1st clinic reading) with the home-clinic blood pressure difference estimated from the model.

Potential strategies for referral for out-of-office monitoring were explored in the derivation cohort (see appendix, eTables 2 and 3), with the optimal strategy defined as a threshold which produced an overall classification error of <10% with the lowest proportion of patients referred for out-of-office monitoring. Optimal thresholds were identified in the derivation cohort (prevalence of out-of-office hypertension = 46%) and examined in the validation cohort (prevalence of out-of-office hypertension = 68%). Model performance detecting true out-of-office hypertension was compared to existing strategies for blood pressure measurement described in international hypertension guidelines from the American Heart Association (AHA),[11] Canadian Hypertension Education Programme (CHEP),[12] European Society of Hypertension (ESH)[13] and NICE[14] (see appendix, eTable 2). The model was also applied to a nominal population from our validation cohort, with a comparable distribution of clinic blood pressures to that documented in the Health Survey for England. Using this nominal population, the number of patients being correctly diagnosed with hypertension per 1,000 individuals was compared to the current NICE diagnostic algorithm[14] (considered best of the rest).

Sensitivity analyses explored the model performance by individual study, predicting home versus ambulatory blood pressure, in patients with raised clinic blood pressure and those with controlled or normal clinic blood pressure (clinic blood pressure of ±140/90mmHg using the NICE definition).[14] In addition, model performance was compared to a revised 'NICE' diagnostic strategy in which patients with a clinic blood pressure between 130/85mmHg and 160/100mmHg are referred for out-of-office monitoring (identified as the optimal referral strategy using method described above). All sensitivity analyses were conducted in the validation cohort (except those by individual study which compared all available datasets).

All analyses were conducted in STATA version 13.1 (MP parallel edition, StataCorp, Texas, USA). Data are presented as proportions of the total study population or means with standard deviation or 95% CIs unless otherwise stated. Ethical approval was given for all individual studies contributing data but approval for secondary analysis on anonymised data was not required.

References

1. Martin U, Haque MS, Wood S, Greenfield SM, Gill PS, Mant J, Mohammed MA, Heer G, Johal A, Kaur R, Schwartz C, McManus RJ. Ethnicity and Differences Between Clinic and Ambulatory Blood Pressure Measurements. *American Journal of Hypertension*. 2015;28:729-738.

2. McKinstry B, Hanley J, Wild S, Pagliari C, Paterson M, Lewis S, Sheikh A, Krishan A, Stoddart A, Padfield P. Telemonitoring based service redesign for the management of uncontrolled hypertension: multicentre randomised controlled trial. *BMJ*. 2013;346:f3030.

3. McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, Kaambwa B, Banting M, Bryan S, Little P, Williams B, Hobbs FD. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. *Lancet*. 2010;376:163-172.

4. McManus RJ, Mant J, Haque MS, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. *JAMA*. 2014;312:799-808.

5. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Grant FC, Kaczorowski J. Conventional versus automated measurement of blood pressure in primary care patients with systolic hypertension: randomised parallel design controlled trial. *BMJ*. 2011;342:d286.

6. Nunan D, Thompson M, Heneghan C, Perera R, McManus RJ, Ward AM. Accuracy of self-monitored blood pressure for diagnosing hypertension in primary care. *Journal of Hypertension*. 2015;33:755-762.

7. Sheppard JP, Fletcher B, Gill P, Martin U, Roberts N, McManus RJ. Predictors of the Home-Clinic Blood Pressure Difference: A Systematic Review and Meta-Analysis. *American Journal of Hypertension*. Epub 2015 Sep 22. pii: hpv157

8. Sheppard JP, Holder R, Nichols L, Bray E, Hobbs FD, Mant J, Little P, Williams B, Greenfield S, McManus RJ. Predicting out-of-office blood pressure level using repeated measurements in the clinic: an observational cohort study. *Journal of Hypertension*. 2014;32:2171-2178; discussion 2178.

9. Steyerberg EW. Restriction on candidate predictors. *Clinical Prediction Models* New York: Springer Science+Business Media; 2010: 175-187.

10. Stergiou GS, Zourbaki AS, Skeva II, Mountokalakis TD. White coat effect detected using self-monitoring of blood pressure at home: comparison with ambulatory blood pressure. *American Journal of Hypertension*. 1998;11:820-827.

11. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation*. 2005;111:697-716.

12. Dasgupta K, Quinn RR, Zarnke KB, et al. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *The Canadian Journal of Cardiology*. 2014;30:485-501.

13. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Journal of Hypertension*. 2013;31:1281-1357.

14. National Clinical Guideline Centre. National Institute for Health and Clinical Excellence Guidance (CG127). *Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34.* London: Royal College of Physicians (UK); 2011(CG127).

Table S1. Methods of blood pressure measurement in studies used for model derivation and validation

Study	Clinic BP monitor	Number of Clinic readings	Method of clinic measurement	Out-of-office monitoring	Home BP monitor	Min number of Home readings	Definition of home BP	ABPM monitor	Min number of ABPM readings	Definition of daytime ABPM
BP-Eth[1a]	BpTRU	6	6 readings, taken at 1 minute intervals after 5 minutes of rest; nurse present	Home & ABPM	Omron 705IT	12	Mean of 6 days of readings (2 readings per day taken in the morning) after discarding the 1st days' readings	SpaceLabs 90217	14	Readings taken between 6:00am and 10:00pm
CAMBO[5]	BpTRU	6	6 readings taken at 2 minutes intervals; no rest period, patient left alone after 1st reading	ABPM	n/a	n/a	n/a	SpaceLabs 90207	64	Readings whilst patient was awake, documented in a patient diary
HITS[2]	Stabil-O-Graph, SpaceLabs 90207	3	BP measured once in both arms using the Stabil-O-Graph and then twice more using the SpaceLabs 90207 after 5 minutes of rest; nurse present	Home & ABPM	Stabil-O-Graph	12	Mean of 6 days of readings (2 readings per day taken in the morning) after discarding the 1st days' readings	SpaceLabs 90207	20	Readings taken between 6:00am and 10:00pm
Oxford self-monitoring study[6]	Stabil-O-Graph	8	BP measured once in both arms, then 6 readings taken one after the other in selected arm, after 5 minutes of rest; nurse/receptionist present	Home & ABPM	Stabil-O-Graph	8	Mean of 6 days of readings (2 readings per day taken morning & evening) after discarding the 1st days' readings	Microlife Watch BP 03	14	Readings taken between 7:00am and 11:00pm
TASMINH2[3a]	BpTRU	6	6 readings, taken at 1 minute intervals after 5 minutes of rest; nurse present	Home	Omron 705IT	12	Mean of 6 days of readings (2 readings per day taken in the morning) after discarding the 1st days' readings	n/a	n/a	n/a
TASMINH-SR[4]	BpTRU	6	6 readings, taken at 1 minute intervals after 5 minutes of rest; nurse present	Home	Omron 705IT	12	Mean of 6 days of readings (2 readings per day taken in the morning) after discarding the 1st days' readings	n/a	n/a	n/a

[a]Studies utilised for model derivation

BP = blood pressure; ABPM = ambulatory blood pressure monitoring

Table S2. AUROC analyses for model adjusted systolic blood pressure thresholds for referral of ambulatory blood pressure monitoring (n=935)

Lower/upper thresholds of model adjusted systolic blood pressure	Hypertensive (True positive)		Normotensive (True negative)		White coat hypertensive (False positive)		Masked hypertensive (False negative)		Total error rate		Patients referred for ABPM	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<120 mmHg ≥165 mmHg	1	0%	61	7%	0	0%	1	0%	1	0%	872	93%
<120 mmHg ≥160 mmHg	9	1%	61	7%	0	0%	1	0%	1	0%	864	92%
<120 mmHg ≥155 mmHg	21	2%	61	7%	0	0%	1	0%	1	0%	852	91%
<120 mmHg ≥150 mmHg	46	5%	61	7%	6	1%	1	0%	7	1%	821	88%
<120 mmHg ≥145 mmHg	110	12%	61	7%	26	3%	1	0%	27	3%	737	79%
<125 mmHg ≥165 mmHg	1	0%	137	15%	0	0%	12	1%	12	1%	785	84%
<125 mmHg ≥160 mmHg	9	1%	137	15%	0	0%	12	1%	12	1%	777	83%
<125 mmHg ≥155 mmHg	21	2%	137	15%	0	0%	12	1%	12	1%	765	82%
<125 mmHg ≥150 mmHg	46	5%	137	15%	6	1%	12	1%	18	2%	734	79%
<125 mmHg ≥145 mmHg	110	12%	137	15%	26	3%	12	1%	38	4%	650	70%
<130 mmHg ≥165 mmHg	1	0%	239	26%	0	0%	36	4%	36	4%	659	70%
<130 mmHg ≥160 mmHg	9	1%	239	26%	0	0%	36	4%	36	4%	651	70%
<130 mmHg ≥155 mmHg	21	2%	239	26%	0	0%	36	4%	36	4%	639	68%
<130 mmHg ≥150 mmHg	46	5%	239	26%	6	1%	36	4%	42	4%	608	65%
<130 mmHg ≥145 mmHg	110	12%	239	26%	26	3%	36	4%	62	7%	524	56%
<135 mmHg ≥165 mmHg	1	0%	351	38%	0	0%	100	11%	100	11%	483	52%
<135 mmHg ≥160 mmHg	9	1%	351	38%	0	0%	100	11%	100	11%	475	51%
<135 mmHg ≥155 mmHg	21	2%	351	38%	0	0%	100	11%	100	11%	463	50%
<135 mmHg ≥150 mmHg	46	5%	351	38%	6	1%	100	11%	106	11%	432	46%
<135 mmHg ≥145 mmHg	110	12%	351	38%	26	3%	100	11%	126	13%	348	37%
<140 mmHg ≥165 mmHg	1	0%	434	46%	0	0%	206	22%	206	22%	294	31%
<140 mmHg ≥160 mmHg	9	1%	434	46%	0	0%	206	22%	206	22%	286	31%
<140 mmHg ≥155 mmHg	21	2%	434	46%	0	0%	206	22%	206	22%	274	29%
<140 mmHg ≥150 mmHg	46	5%	434	46%	6	1%	206	22%	212	23%	243	26%
<140 mmHg ≥145 mmHg	110	12%	434	46%	26	3%	206	22%	232	25%	159	17%

Area under the receiver operator characteristic = 0.80 (95% CI 0.78 to 0.83)

Table S3. AUROC analyses for model adjusted diastolic blood pressure thresholds for referral of ambulatory blood pressure monitoring (n=935)

Lower/upper thresholds of model adjusted systolic blood pressure	Hypertensive (True positive)		Normotensive (True negative)		White coat hypertensive (False positive)		Masked hypertensive (False negative)		Total error rate		Patients referred for ABPM	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
<70 mmHg ≥100 mmHg	1	0%	45	5%	0	0%	1	0%	1	0%	888	95%
<70 mmHg ≥85 mmHg	142	15%	45	5%	76	8%	1	0%	77	8%	671	72%
<70 mmHg ≥90 mmHg	49	5%	45	5%	6	1%	1	0%	7	1%	834	89%
<70 mmHg ≥95 mmHg	8	1%	45	5%	0	0%	1	0%	1	0%	881	94%
<75 mmHg ≥100 mmHg	1	0%	194	21%	0	0%	6	1%	6	1%	734	79%
<75 mmHg ≥85 mmHg	142	15%	194	21%	76	8%	6	1%	82	9%	517	55%
<75 mmHg ≥90 mmHg	49	5%	194	21%	6	1%	6	1%	12	1%	680	73%
<75 mmHg ≥95 mmHg	8	1%	194	21%	0	0%	6	1%	6	1%	727	78%
<80 mmHg ≥100 mmHg	1	0%	410	44%	0	0%	43	5%	43	5%	481	51%
<80 mmHg ≥85 mmHg	142	15%	410	44%	76	8%	43	5%	119	13%	264	28%
<80 mmHg ≥90 mmHg	49	5%	410	44%	6	1%	43	5%	49	5%	427	46%
<80 mmHg ≥95 mmHg	8	1%	410	44%	0	0%	43	5%	43	5%	474	51%

Area under the receiver operator characteristic = 0.82 (95% CI 0.80 to 0.85)

Table S4. Strategy for blood pressure measurement according to guidelines

Guideline	Year	Clinic blood pressure definition	ABPM	Threshold for hypertension
American Heart Association (AHA)[11]	2005	Mean of the 1st & 2nd readings or mean of 3 if the initial pair of readings are >5mmHg apart	Not routinely recommended	≥140/90mmHg
Canadian Hypertension Education Programme (CHEP)[12]	2014	Mean of 2nd to the 6th readings taken using an automated blood pressure monitor	Not routinely recommended	≥135/85mmHg
European Society for Hypertension (ESH)[13]	2013	Mean of the 2nd & 3rd readings	Not routinely recommended	≥140/90mmHg
National Institute for health Clinical Excellence (NICE)[14a]	2011	Lowest of the 1 & 2nd or 3rd if the initial pair of readings are both raised	Daytime	≥180/110mmHg (clinic) or ≥135/85mmHg (ABPM)
PRedicting Out-of-OFfice Blood Pressure in the clinic algorithm (PROOF-BP)[b]	2015	Adjusted clinic blood pressure using the PROOF-BP algorithm	Daytime	≥145/90mmHg (adjusted clinic) or ≥135/85mmHg (ABPM)

ABPM = ambulatory blood pressure monitoring

[a]Patients with raised clinic BP (≥140/90 mmHg) should be referred for out-of-office monitoring (diagnosis only)

[b]Patients with an adjusted clinic BP between ≥130/80 and 144/89 mmHg should be referred for out-of-office monitoring

Table S5. Characteristics of the study population

Characteristic	Derivation cohort	Validation cohort
Total population	991	1,172
Age (years) (mean±SD)	60±10	62±11
Sex (male)	478 (48%)	590 (50%)
BMI (kg/m^2) (mean±SD)	30±6	29±6
Smoking status (current)	125 (13%)	186 (16%)
Diabetes (yes)	148 (15%)	92 (8%)
History of stroke (yes)	45 (5%)	30 (3%)
History of hypertension (yes)	701 (71%)	942 (80%)
On treatment for hypertension (yes)	704 (71%)	876 (75%)
Office blood pressure (mmHg) (mean±SD)	137/83±19/10	145/85±17/13
Out-of-office blood pressure (mmHg) (mean±SD)	135/80±15/9	139/81±13/11
White coat systolic hypertension (yes)	125 (13%)	160 (14%)
Masked systolic hypertension (yes)	147 (16%)	172 (15%)

BMI = body mass index; SD = standard deviation; Office blood pressure defined as the mean of the 2^{nd} & 3^{rd} readings. White coat systolic hypertension defined as a clinic blood pressure $\geq$140mmHg (mean of 2^{nd} & 3^{rd} readings) but an out-of-office blood pressure of <135mmHg. Masked systolic hypertension defined as a clinic blood pressure (mean of 2^{nd} & 3^{rd} readings) <140mmHg but an out-of-office blood pressure of $\geq$135mmHg

Table S6. Sensitivity analyses

Sensitivity analysis	Total population	Prevalence of (uncontrolled) hypertension†	Systolic AUC† (95% CI)	Diastolic AUC† (95% CI)	True positive (hypertensive)	True negative (normotensive)	False positive (white coat hypertensive)	False negative (masked hypertensive)	Correctly classified†	Referral for home/ ABPM[d]
BP-Eth	715	331 (46%)	0.78 (0.75-0.81)	0.83 (0.80-0.86)	299 (42%)	368 (51%)	16 (2%)	32 (4%)	667 (93%)	423 (59%)
CAMBO	321	137 (43%)	0.68 (0.63-0.74)	0.85 (0.80-0.91)	119 (37%)	164 (51%)	20 (6%)	18 (6%)	283 (88%)	189 (59%)
HITS	398	376 (94%)	0.77 (0.70-0.85)	0.91 (0.89-0.94)	364 (91%)	30 (8%)	2 (0.5%)	2 (0.5%)	394 (99%)	195 (49%)
Oxford self-monitoring	200	108 (54%)	0.73 (0.66-0.80)	0.74 (0.67-0.81)	105 (53%)	74 (37%)	18 (9%)	3 (2%)	179 (90%)	121 (61%)
TASMINH2	220	172 (78%)	0.66 (0.57-0.75)	0.81 (0.75-0.88)	172 (78%)	37 (17%)	11 (5%)	0 (0%)	209 (95%)	144 (65%)
TASMINH-SR	181	128 (71%)	0.61 (0.52-0.69)	0.83 (0.77-0.90)	122 (67%)	48 (27%)	5 (3%)	6 (3%)	170 (94%)	135 (75%)
Home BP[a]	398	325 (82%)	0.71 (0.65-0.76)	0.84 (0.80-0.88)	323 (81%)	70 (18%)	3 (1%)	2 (1%)	393 (99%)	295 (74%)
ABPM[a]	398	294 (74%)	0.77 (0.72-0.82)	0.82 (0.77-0.86)	293 (74%)	102 (26%)	2 (1%)	1 (0.3%)	395 (99%)	295 (74%)
PROOF-BP tool[b]	1100	749 (68%)	0.75 (0.72-0.78)	0.87 (0.85-0.89)	720 (65%)	306 (28%)	45 (4%)	29 (3%)	1,026 (93%)	640 (58%)
Clinic BP (revised thresholds)[b c]	1100	749 (68%)	0.73 (0.70-0.76)	0.84 (0.82-0.87)	676 (61%)	330 (30%)	21 (2%)	73 (7%)	1006 (91%)	709 (64%)
Patients with raised clinic BP[b e]	629	513 (82%)	0.70 (0.65-0.75)	0.85 (0.83-0.89)	513 (82%)	76 (12%)	40 (6%)	0 (0%)	589 (94%)	285 (45%)
Patients with controlled clinic BP[b e]	471	236 (50%)	0.66 (0.61-0.71)	0.83 (0.79-0.87)	207 (44%)	230 (49%)	5 (1%)	29 (6%)	437 (93%)	355 (75%)

AUC=Area Under the receiver operator characteristic Curve; CI=Confidence Intervals; ABPM=Ambulatory blood pressure monitoring; BP=blood pressure

[a]Data from the HITS[2] and Oxford self-monitoring studies (combined);

[b]Data from validation cohort - HITS,[2] TASMINH-SR,[4] CAMBO[5] and Oxford self-monitoring study;[6]

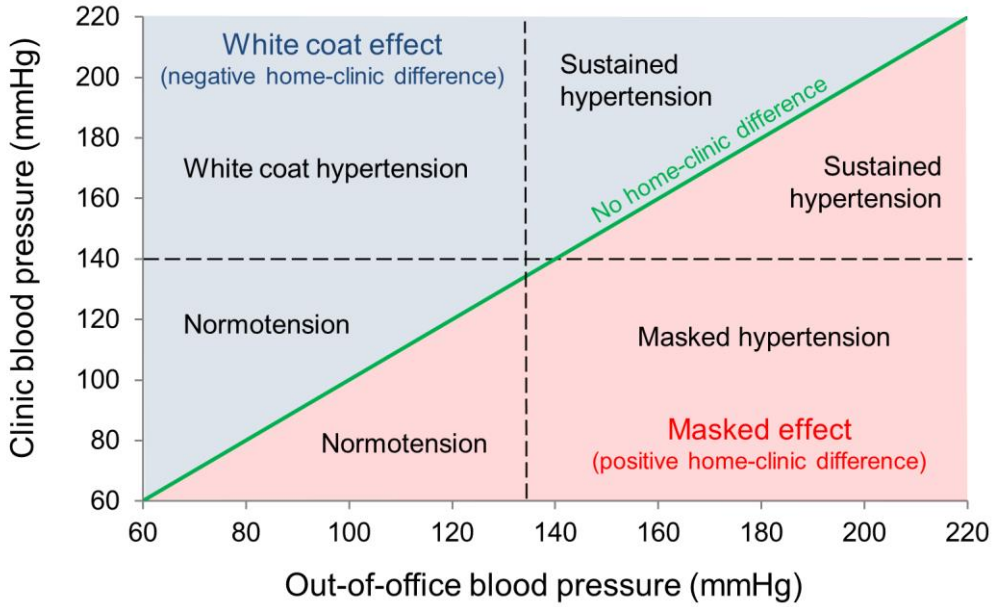
[c]Revised referral thresholds defined as a clinic blood pressure between 130/85mmHg and 160/100mmHg

[d]For detection of out-of-office hypertension (≥135/85mmHg)

[e]Clinic blood pressure ≥140/90mmHg

[f]Clinic blood pressure <140/90mmHg

Figure S1. Definitions of normotension, hypertension and the home-clinic blood pressure difference

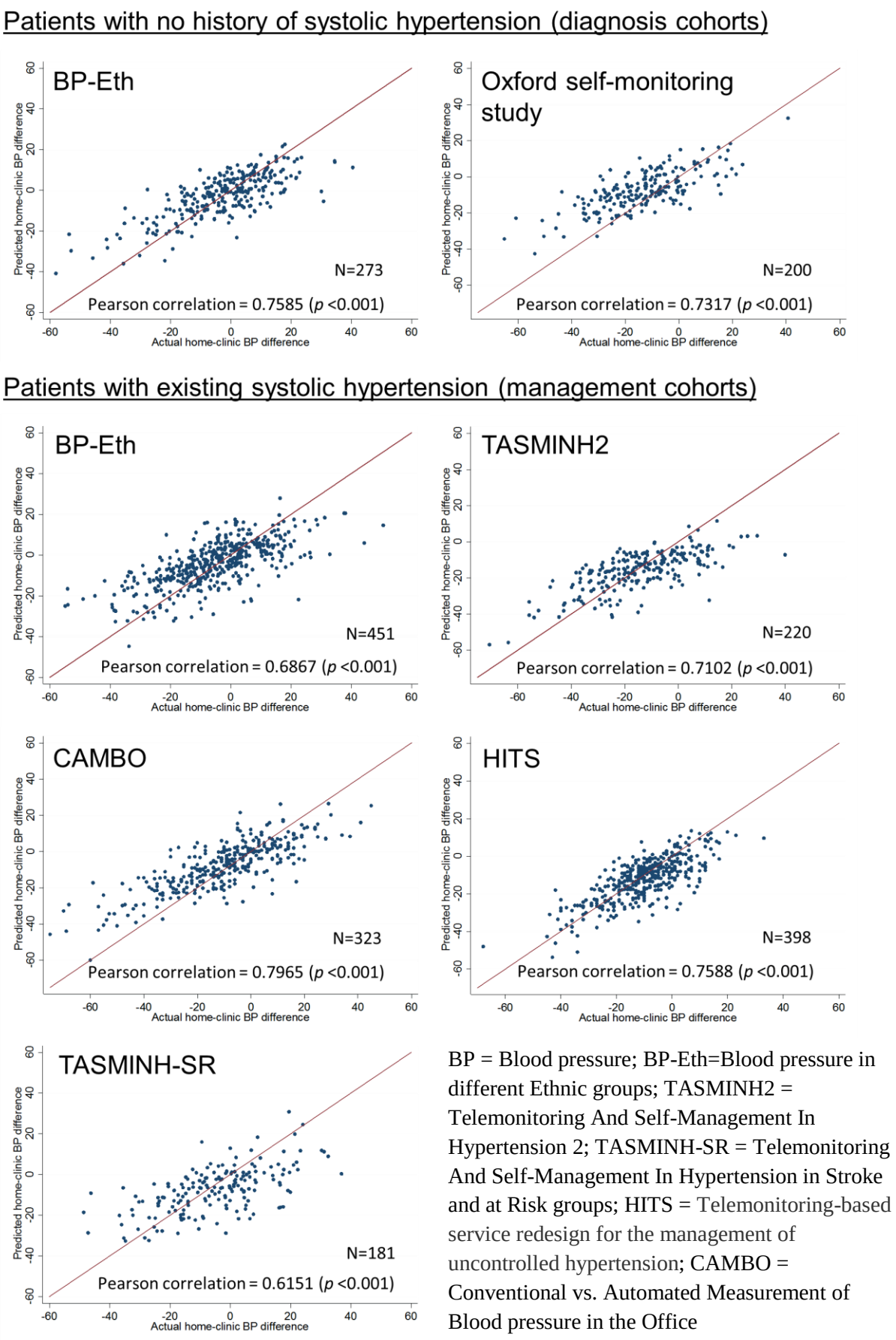


Condition	Clinic blood pressure	Out-of-office blood pressure	Home-clinic blood pressure difference
Normotension	<140/90mmHg	<135/85mmHg	Positive or negative
Sustained hypertension	≥140/90mmHg	≥135/85mmHg	Positive or negative
White coat hypertension	≥140/90mmHg	<135/85mmHg	Negative
Masked hypertension	<140/90mmHg	≥135/85mmHg	Positive
White coat effect	> out-of-office BP	< clinic BP	Negative
Masked effect	< out-of-office BP	> clinic BP	Positive

BP =Blood pressure; Out-of-office blood pressure may be defined by home or daytime ambulatory blood pressure measurements.

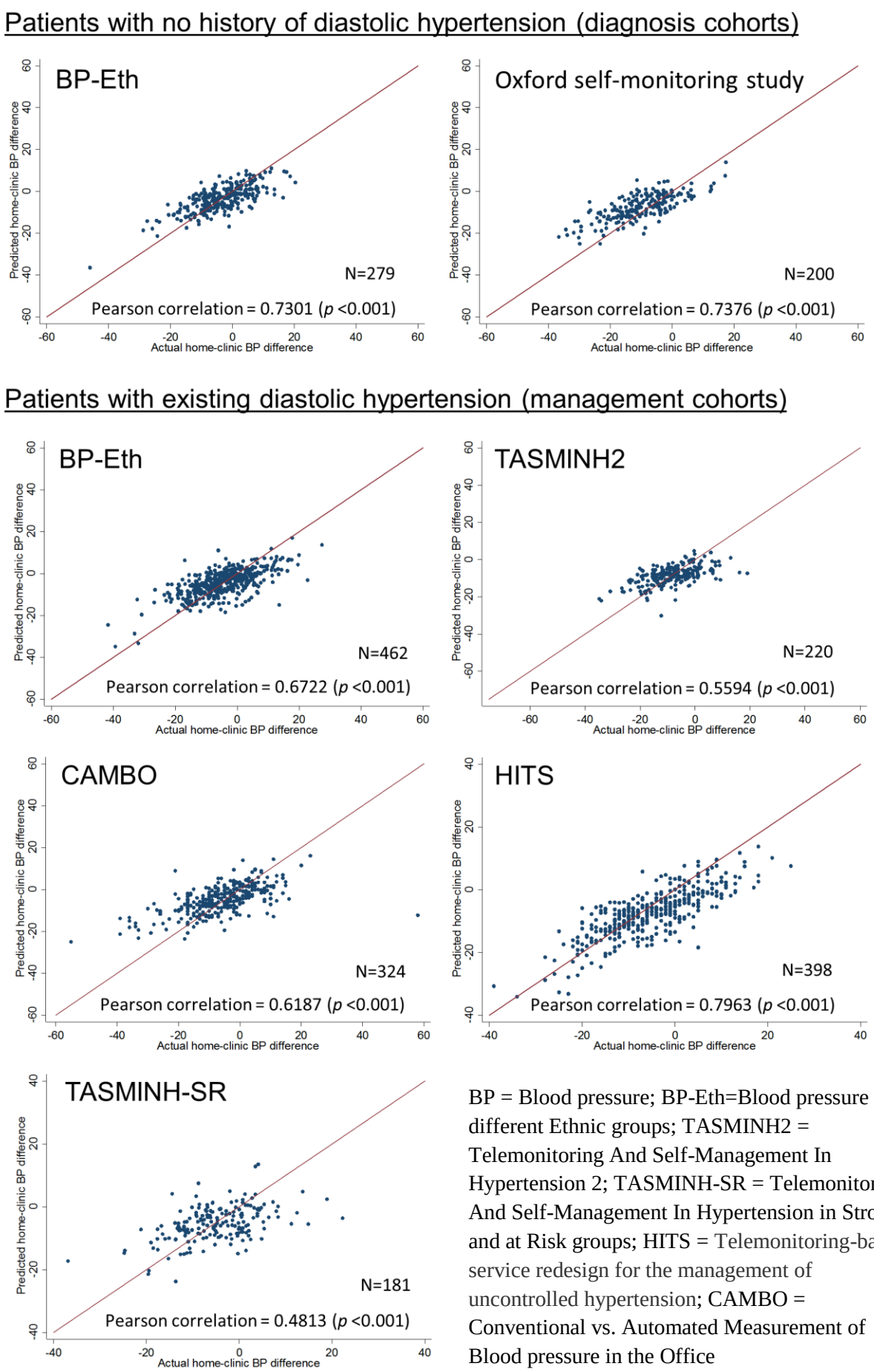
Individuals with a white coat effect (negative home-clinic difference) may be normotensive, hypertensive or white coat hypertensive. Those with a masked effect (positive home-clinic difference) may be normotensive, hypertensive or masked hypertensive. Those with an out-of-office ≥135/85mmHg (hypertension) may be masked or sustained hypertensives.

Figure S2. Graphs showing model calibration in derivation (BP-Eth, TASMINH2) & validation (Oxford self-monitoring study, CAMBO, HITS, TASMINH-SR) datasets for prediction of systolic blood pressure.



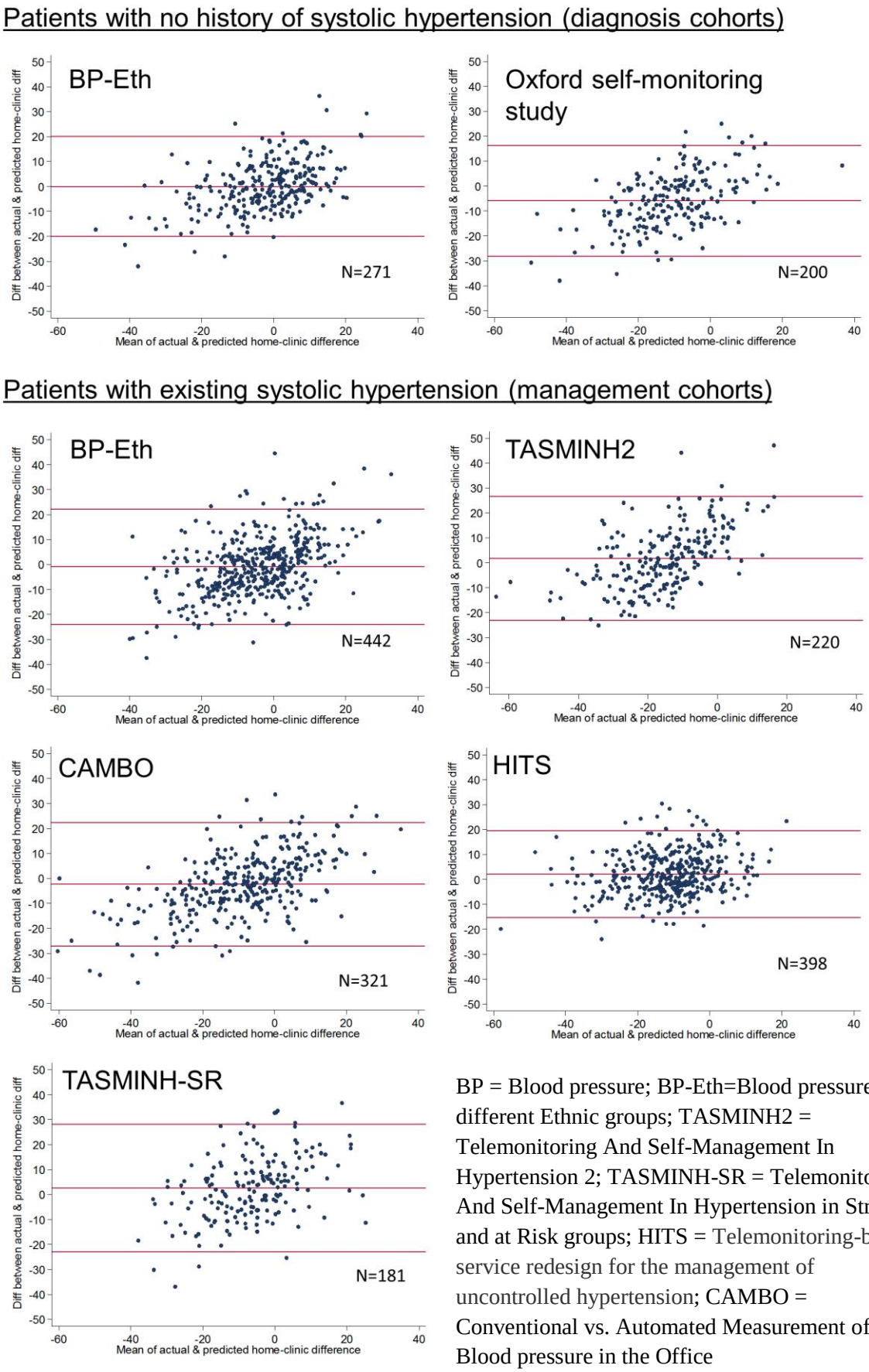
BP = Blood pressure; BP-Eth=Blood pressure in different Ethnic groups; TASMINH2 = Telemonitoring And Self-Management In Hypertension 2; TASMINH-SR = Telemonitoring And Self-Management In Hypertension in Stroke and at Risk groups; HITS = Telemonitoring-based service redesign for the management of uncontrolled hypertension; CAMBO = Conventional vs. Automated Measurement of Blood pressure in the Office

Figure S3. Graphs showing model calibration in derivation (BP-Eth, TASMINH2) & validation (Oxford self-monitoring study, CAMBO, HITS, TASMINH-SR) datasets for prediction of diastolic blood pressure.



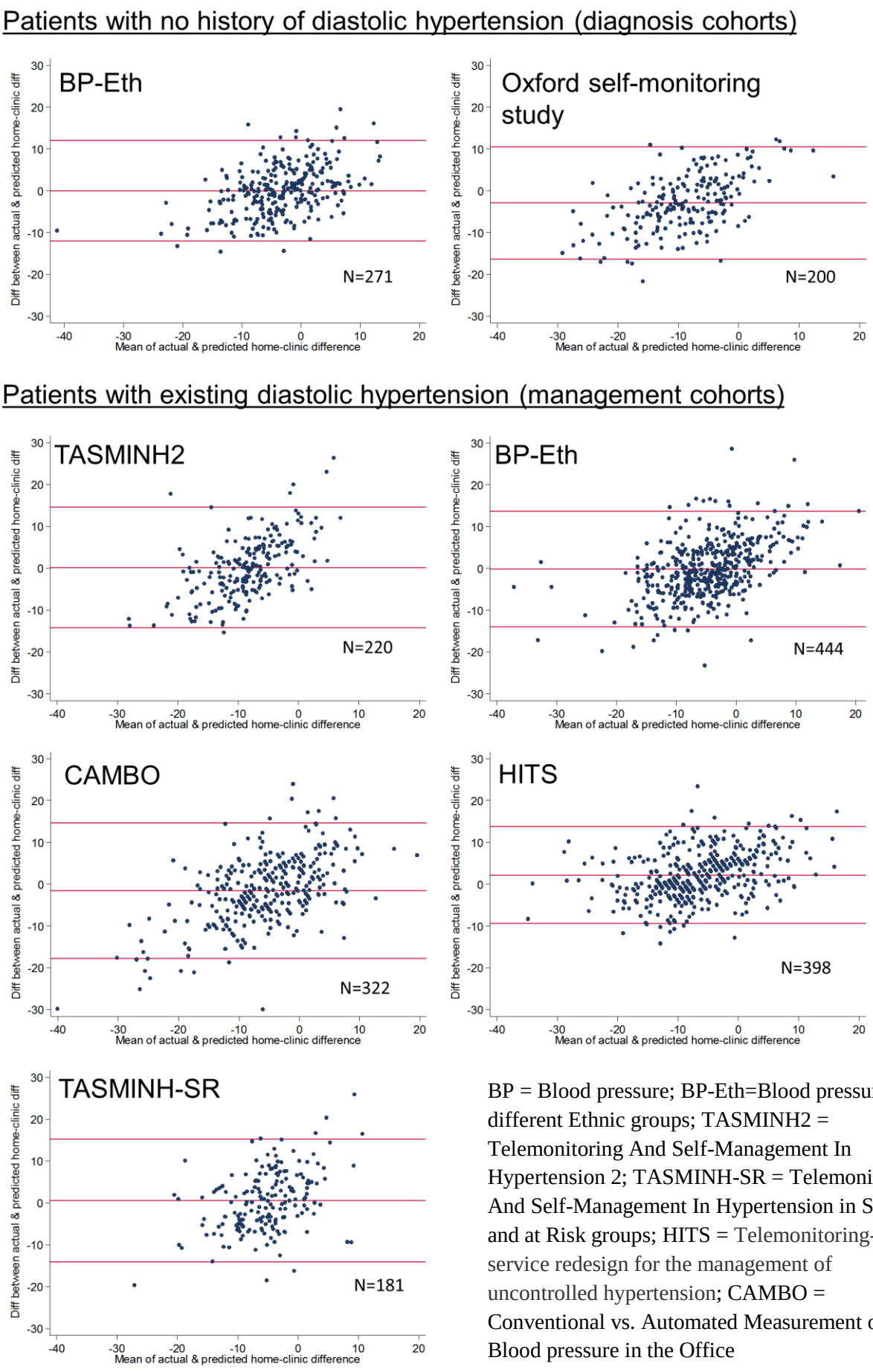
BP = Blood pressure; BP-Eth=Blood pressure in different Ethnic groups; TASMINH2 = Telemonitoring And Self-Management In Hypertension 2; TASMINH-SR = Telemonitoring And Self-Management In Hypertension in Stroke and at Risk groups; HITS = Telemonitoring-based service redesign for the management of uncontrolled hypertension; CAMBO = Conventional vs. Automated Measurement of Blood pressure in the Office

Figure S4. Bland-Altman plots showing agreement between actual & predicted home-clinic systolic blood pressure differences in derivation (BP-Eth, TASMINH2) & validation (Oxford self-monitoring study, CAMBO, HITS, TASMINH-SR) datasets



BP = Blood pressure; BP-Eth=Blood pressure in different Ethnic groups; TASMINH2 = Telemonitoring And Self-Management In Hypertension 2; TASMINH-SR = Telemonitoring And Self-Management In Hypertension in Stroke and at Risk groups; HITS = Telemonitoring-based service redesign for the management of uncontrolled hypertension; CAMBO = Conventional vs. Automated Measurement of Blood pressure in the Office

Figure S5. Bland-Altman plots showing agreement between actual & predicted home-clinic diastolic blood pressure differences in derivation (BP-Eth, TASMINH2) & validation (Oxford self-monitoring study, CAMBO, HITS, TASMINH-SR) datasets



BP = Blood pressure; BP-Eth=Blood pressure in different Ethnic groups; TASMINH2 = Telemonitoring And Self-Management In Hypertension 2; TASMINH-SR = Telemonitoring And Self-Management In Hypertension in Stroke and at Risk groups; HITS = Telemonitoring-based service redesign for the management of uncontrolled hypertension; CAMBO = Conventional vs. Automated Measurement of Blood pressure in the Office

Figure S6. Final model equations

$$\textbf{out of office sBP} = clinic\ sBP + \big(33.57 + (0.63 \times age) + (-3.60 \times male\ sex) + (-0.04 \times clinic\ sBP) + (0.36 \times sBP\ change) + (-0.21 \times BMI) + (-5.07 \times diagnosis\ of\ hypertension) + (0.18 \times duration\ of\ hypertension) + (6.94 \times antihypertensive\ prescription) + (-0.62 \times pulse\ pressure) + (-0.01 \times [age * clinic\ sBP]) + (0.01 \times [age * pulse\ pressure]) + (0.30 \times [sex * BMI]) + (-0.26 \times [sex * diagnosis\ of\ hypertension]) + (-14.74 \times [sex * duration\ of\ hypertension]) + (13.39 \times [sex * antihypertensive\ prescription])\big)$$

$$\textbf{out of office dBP} = clinic\ dBP + (59.34 + (-0.33 \times age) + (3.32 \times male\ sex) + (-0.47 \times clinic\ dBP) + (-0.40 \times dBP\ change) + (-0.66 \times BMI) + (-0.03 \times diagnosis\ of\ hypertension) + (10.46 \times antihypertensive\ prescription) + (-11.07 \times diagnosis\ of\ cardiovascular\ disease) + (-0.06 \times pulse\ pressure) + (0.01 \times [age * dBP\ change]) + (0.01 \times [age * BMI]) + (0.18 \times [age * diagnosis\ of\ cardiovascular\ disease]) + (-0.13 \times [age * antihypertensive\ prescription]) + (-8.00 \times [sex * antihypertensive\ prescription]) + (4.63 \times [sex * diagnosis\ of\ hypertension]))$$

sBP=systolic blood pressure; dBP=diastolic blood pressure; BMI=body mass index
Binary variables coded as yes (1) or no (0)
ß coefficients given for continuous explanatory variables which have not been centred.