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PREDICTING OUT-OF-OFFICE BLOOD PRESSURE (PROOF-BP) IN THE CLINIC FOR THE DIAGNOSIS OF HYPERTENSION IN PRIMARY CARE: AN ECONOMIC EVALUATION

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Abstract

Clinical guidelines in the US and UK recommend that individuals with suspected hypertension should have ambulatory blood pressure (BP) monitoring (ABPM) to confirm the diagnosis. This approach reduces misdiagnosis due to white coat hypertension but will not identify people with masked hypertension who may benefit from treatment. The Predicting Out-of-Office Blood Pressure (PROOF-BP) algorithm predicts masked and white coat hypertension based on patient characteristics and clinic BP, improving the accuracy of diagnosis whilst limiting subsequent ABPM. This study assessed the cost-effectiveness of using this tool in diagnosing hypertension in Primary Care. A Markov cost-utility cohort model was developed to compare diagnostic strategies: the PROOF-BP approach, including those with clinic BP ≥130/80mmHg who receive ABPM as guided by the algorithm, compared to current standard diagnostic strategies including those with clinic BP ≥140/90mmHg combined with further monitoring (ABPM as reference, clinic and home monitoring also assessed). The model adopted a lifetime horizon with a three month time-cycle, taking a UK Health Service/Personal Social Services perspective. The PROOF-BP algorithm was cost-effective in screening all patients with clinic BP ≥130/80mmHg compared to current strategies which only screen those with clinic BP ≥140/90mmHg, provided healthcare providers were willing to pay up to £20,000 ($26,000)/quality-adjusted life year gained. Deterministic and probabilistic sensitivity analyses supported the base-case findings. The PROOF-BP algorithm appears to be cost-effective compared to the conventional BP diagnostic options in Primary Care. Its use in clinical practice is likely to lead to reduced cardiovascular disease, death and disability.

Key words: raised blood pressure; general practice; cohort simulation; cost utility analysis

Introduction

Hypertension is one of the most important modifiable risk factors for cardiovascular morbidity and mortality.[1] Accurate measurement of blood pressure (BP) is essential to ensure that treatment is targeted appropriately. In the UK, the National Institute for Health and Care Excellence (NICE) published new guidelines on the diagnosis of hypertension in Primary Care in 2011.[2] These recommended that all individuals with high BP readings in the clinic should be referred for ambulatory BP monitoring (ABPM) to confirm a diagnosis of hypertension, before initiating treatment. This recommendation was based on a systematic review of the clinical evidence and a Markov model-based cost-utility analysis comparing three different BP monitoring methods (clinic [CBPM], self-monitoring at home [HBPM] and ABPM) for making a diagnosis of hypertension in individuals with a screening clinic BP measurement equal-to-or-above 140/90 mm Hg.[3,4] ABPM was found to be the most cost-effective option across all age and gender subgroups. Despite ABPM being more expensive in terms of diagnostic costs, better targeting of treatment meant that it saved money in the long term by treating fewer individuals with white coat hypertension. Similar arguments have since been used in North America and Japan where out-of-office measurement is now also recommended.[5,6]

White coat hypertension is the term used to describe when an individual has raised clinic BP (≥140/90 mm Hg) but is normotensive on ABPM (≤135/85 mm Hg).[7] Individuals with white coat hypertension are at lower cardiovascular disease risk compared to individuals with sustained hypertension.[8] Conversely, individuals with normotensive clinic BP measurements (<140/90 mm Hg) but hypertensive ambulatory BP measurements (>135/85 mm Hg) are referred to as having masked hypertension and have an increased risk of cardiovascular

events which approaches that of overt hypertension.[9,10] Individuals with potential masked hypertension were not included in the population assessed in the health economics analysis that informed the NICE guideline[2] as their screening clinic BP measurement would have been less than 140/90 mm Hg.

The Predicting Out-of-Office Blood Pressure (PROOF-BP) algorithm calculates a predicted home clinic BP difference based on an individuals' characteristics (age, sex, body mass index, past diagnosis of hypertension, cardiovascular disease, and antihypertensive prescription) and clinic BP, to guide utilisation of ABPM (Table S1 in the online-only Data Supplement). Adding this predicted difference to the known clinic BP of an individual provides the 'adjusted clinic BP' which has been shown to be closer to the true out-of-office blood pressure.[11] Used as a triaging tool for ABPM (Figure 1), it has been shown to improve the accuracy of hypertension diagnosis (masked hypertension, sustained hypertension and white coat hypertension) without appreciably increasing use of ABPM.[11] This study aimed to assess the cost-effectiveness of a strategy of targeted use of ABPM using the PROOF-BP algorithm in the diagnosis of hypertension in a primary care setting using an adaptation of the cost-effectiveness model used to inform the 2011 NICE guideline.

Methods

Full methods of the original health economic assessment that informed the NICE guideline have been described elsewhere.[3,4] The original model assessed the cost-effectiveness of each BP monitoring method (CBPM, HBPM & ABPM) for confirming a diagnosis in people with suspected hypertension (clinic BP ≥140/90 mm Hg). This model, developed in Microsoft Excel, was modified by comparing the original diagnostic strategies with use of the PROOF-

BP algorithm as a comparator. The base case model entry population was expanded to men and women aged 40 to 75 years with a screening clinic BP of ≥130/80 mm Hg although the management of those with clinic BP between 130-139/80-89 mm Hg was only affected in the PROOF-BP arm (see below). Model inputs were also updated where appropriate.

Study population

Data for the screening patient population, defined according to their clinic BP (Table S3 in the online-only Data Supplement), were taken from the Health Survey for England[12] and adjusted clinic BPs were calculated using the PROOF-BP risk algorithm.[11]

Model comparators

The new model compared four methods of BP monitoring in the diagnosis of hypertension. Those approaches examined in the original model – CBPM [monthly measurements over 3 months], HBPM [measurements over a week] and ABPM [measurements over 24 hours] – were compared to the new PROOF-BP diagnostic strategy (Figure 1):

- The CBPM, HBPM, or ABPM diagnostic strategies were unchanged from the original model:
    - Individuals were not considered for diagnosis or treatment if their screening clinic BP was less than 140/90 mm Hg.
    - For those with a screening clinic BP of 140/90 mm Hg or over, they either underwent further clinic measurement, home monitoring or ABPM, exactly as in the original model.

- The PROOF BP strategy operated for all with a screening clinic BP of 130/80 mm Hg or over (i.e. everyone). They had an adjusted BP calculated using the PROOF BP algorithm and then proceeded as follows:
    - If the individual had an adjusted clinic BP < 130/80 mm Hg, no further action was required and they were measured again at the next check-up period.
    - If the individual had an adjusted clinic BP between 130/80-144/89 mm Hg, they received ABPM for confirmatory diagnosis.
    - If the individual had an adjusted clinic BP ≥145/90 mm Hg, true hypertensive status was assumed and treatment was offered without confirmatory ABPM diagnosis.

Model structure

A simplified Markov model diagram of the health states and the movements between states allowed to occur in a cycle is shown in Figure 2. In keeping with the original model, a model cycle length of three months was chosen as that approximated the average length of time for a complete CBPM diagnosis.[2] HBPM, ABPM and the PROOF-BP algorithm were assumed to take one month for a complete diagnosis. In the suspected and diagnosed stages of the model, individuals could suffer a fatal or non-fatal cardiovascular event (stable angina, unstable angina, stroke, myocardial infarction [MI], and transient ischemic attack [TIA]). As per the original model, after suffering a non-fatal cardiovascular event, repeat clinical events were not modelled and individuals remained in a post-cardiovascular event state until they died.

In the model, normotensive individuals could become hypertensive over time and those with an initial screening clinic BP of <140/90 mm Hg could move to >140/90 mm Hg. For model simplification purposes, it was assumed individuals could not become hypertensive while being assessed in the diagnostic pathway. Individuals not diagnosed with hypertension were assumed to have a BP check-up with CBPM at least every 5 years. In common with the original model, a failure rate was incorporated into ABPM. If ABPM failed (any cause of failure from a technical or a patient's view), individuals were assumed to be put on HBPM. In the PROOF-BP algorithm strategy, if individuals had a screening clinic BP of less than 140/90 mm Hg and ABPM failed, it was assumed they remained undiagnosed (as in the HBPM strategy where these individuals were not considered for hypertension diagnosis) and their BP was rechecked every five years. This was due to a lack of data on the sensitivity and specificity of HBPM for those with a clinic BP of less than 140/90 mm Hg.

Clinical model parameters are detailed in Table 1. Correct diagnosis of hypertension depended on the sensitivity and specificity of the test strategy used. As in the original model, test characteristics for CBPM and HBPM were taken from a meta-analysis[13] with ABPM assumed to be the reference standard (100% sensitivity & 100% specificity). The test characteristics of the PROOF-BP algorithm with respect to their clinic BP and adjusted clinic BP categories are shown in Table S2 in the online-only Data Supplement.

Model outcomes

Risk of coronary heart disease and stroke were calculated using the Framingham risk equations[14] by combining age, sex, and BP with the general population prevalence of risk factors in the Health Survey for England.[12] Individuals with masked hypertension were assumed to have the same higher risk of cardiovascular events as sustained hypertensives.[15]

A hypertension diagnosis resulted in prescription of antihypertensive drug therapy and true hypertensive individuals received benefit in terms of cardiovascular risk reduction from such treatment. True normotensive individuals were assumed to receive no risk reduction from treatment (this assumption is relaxed in a sensitivity analysis). The proportion of individuals on different antihypertensive drug classes was based on treatment guidelines.[2]

Quality of life and cost data are shown in Table 2. Baseline gender and age specific quality of life (utility) weights were taken from the Health Survey for England[16] and applied to the cohorts. In the base case, individuals were assumed not to suffer any quality of life reductions (disutility) as a result of antihypertensive treatment.

Model costs

A more detailed description of costs is given in the extended methods in the online appendix. Costs were updated where necessary to 2013-2014 prices using the Hospital & Community Health Services (HCHS) index.[17] Resource usage by diagnostic method and device usage assumptions were in line with the original model.[4]

Analysis

Results were presented as the total costs and effects of each diagnostic strategy (ordered by increasing cost). Effectiveness was measured in quality-adjusted life years (QALYs). Incremental Cost-Effectiveness Ratios (ICERs) were calculated from the difference in costs and effects between two options. Cost-effectiveness was assessed in relation to the NICE lower threshold of £20,000 per QALY.[18] More costly and less effective (dominated) options were excluded from consideration. The analysis adopted a lifetime horizon and all costs and outcomes were discounted at the standard 3·5% rate.[19] Costs and outcomes were

considered from a UK National Health Service (NHS)/Personal Social Services (PSS) perspective.

Sensitivity analyses

Uncertainty was explored via sensitivity analyses. Additional model runs were undertaken to determine the impact of changing key parameters on the model results. The following univariate sensitivity analysis was undertaken on all cohorts: model entry criteria were varied up and down, expanded to a screening clinic BP ≥120/70 mm Hg population (Table S4 in the online-only Data Supplement) and then restricted to a screening clinic BP ≥140/90 mm Hg population (Table S5 in the online-only Data Supplement). In line with the original model, sensitivity analyses were performed using the males aged 60 years subgroup. The following scenarios were explored:

(i) A treatment disutility of 1% was assumed. This was equivalent to a quarter of the individuals suffering a quality of life reduction of 4% and everyone else suffering no ill effects of treatment.

(ii) A treatment disutility of 2% was assumed. This was equivalent to a quarter of the individuals suffering a quality of life reduction of 8% and everyone else suffering no ill effects of treatment;

(iii) Antihypertensive treatment risk reduction was based on half doses of medication;

(iv) Antihypertensive drug costs were increased by 30%;

(v) ABPM (reference) strategy to confirm diagnosis was undertaken in all patients with a screening clinic BP of ≥130/80 mm Hg;

(vi) The BP check-up frequency for those not diagnosed with hypertension was reduced from every five years to every three years;

(vii) The prevalence of masked hypertension was increased and decreased by 25% respectively;

(viii) Antihypertensive treatment risk reduction for masked hypertension was based on half doses;

(ix) Antihypertensive treatment risk reduction for all treated people (i.e. those who are not truly hypertensive also gain benefit from BP reduction);

(x) Antihypertensive treatment risk reduction assumed to be same as intensive treatment from the SPRINT trial.[20]

(xi) The failure rate of ABPM was increased from 5% to 17%[21]

Where available, data were inputted into the model as distributions in order to fully incorporate the uncertainty around parameter values for a probabilistic sensitivity analysis (PSA). The PSA ran for 1000 iterations across all cohorts for the three different model entries respectively. The number of times a strategy was the most cost-effective diagnostic option for each simulation (i.e. produced the highest net benefit) was expressed as a percentage for all cohorts. Positive count data from the PROOF-BP risk algorithm test characteristics formed the parameters for a Dirichlet distribution.

Results

In the base-case analysis (Table 3), the use of the PROOF-BP algorithm to triage for ABPM was cost-effective in all age and gender cohorts compared to the current NICE standard ABPM strategy and dominated the other comparators (saved costs and increased QALYs).

This was because of the influence of treating otherwise unrecognised cases of masked hypertension (see Table S6 in the online-only Data Supplement for number of initial misdiagnosis by strategy). For example, in a cohort of 1000 males aged 60, with a screening BP of 130/80 mm Hg or above, using the PROOF-BP algorithm would result in 62 more true hypertension cases detected, 5 more CVD events prevented (excluding fatal CHD & CVD deaths), 19.6 QALYs gained and increased total costs by £32,929 compared to standard ABPM (£1,680 per QALY gained). A detailed breakdown of costs and events for all age cohorts can be seen in Tables S7-S8. Using the PROOF-BP algorithm, with a screening BP of 130/80 mm Hg or above, reduced the number of ABPM investigations in all age cohorts except for 40 year old (male & female) and 50 year old females compared with the NICE standard ABPM strategy (Table S9 in the online-only Data Supplement).

The PROOF-BP algorithm was also cost-effective when the model entry was widened to individuals with a screening BP ≥120/70 mm Hg (Table S10 in the online-only Data Supplement). The PSA results indicated that for the base-case and ≥120/70 mm Hg model populations, PROOF-BP was the most cost-effective option in all iterations. When entry to the model was restricted to individuals with a screening BP ≥140/90 mm Hg (Table S11 in the online-only Data Supplement), PROOF-BP was the most cost-effective option except in the 40 year female old cohort. Univariate sensitivity analysis (Table 4) demonstrated that the model was sensitive to the assumption of quality of life reduction from treatment. For example, if a quarter of the individuals suffered a quality of life reduction of 8% and everyone else suffered no ill effects of treatment, PROOF-BP was dominated (more costly, less health gain) by the standard ABPM strategy. Use of the PROOF-BP algorithm was also

cost-effective compared to a strategy of utilising ABPM in all individuals with a screening BP of ≥130/80 mm Hg, which was cheaper, but resulted in fewer QALYs gained.

Discussion

This represents the first economic evaluation to compare the cost-effectiveness of using the PROOF-BP algorithm with strategies to diagnose hypertension which includes the consideration of individuals with potential masked hypertension. Targeted use of ABPM using the PROOF-BP algorithm was the most cost-effective diagnostic option for individuals presenting with a screening clinic BP of 130/80 mm Hg or above. The increased quality of life arising from use of the PROOF-BP algorithm was mainly due to identification and treatment of masked hypertension (and the subsequent CVD events avoided) which was ignored by the other strategies. The results were robust to several sensitivity analyses examining treatment disutility caused by side-effects to medication, adjusting the masked hypertension prevalence, higher treatment costs and increased use of ABPM in individuals with apparently normal screening BPs (<140/90 mm Hg). The findings suggest that a strategy of targeted use of ABPM in individuals with high or high-normal screening BP is likely to be cost-effective at a willingness to pay of £20,000 per QALY gained, and results in increased quality of life and lower mortality rate for individuals with hypertension.

Strengths and weaknesses

The major strength of this work is that it represents a direct update of the cost-effectiveness model that informed the NICE hypertension guidance and which currently underpins the use of ABPM in routine clinical practice in the UK.[2] This means that this new strategy of targeted

use of ABPM using the PROOF-BP algorithm can be directly compared to the current UK reference standard approach for diagnosis of hypertension. A large number of sensitivity analyses were considered to test the robustness of assumptions in the model and consistently supported the base-case findings.

The original analysis included a detailed discussion including potential limitations with the original model and these are not repeated here.[4] Additional points are discussed below.

One limitation of the model as used here, is that it assumed that individuals derived the same benefit from treatment of masked hypertension as applies to those with sustained hypertension. Although this has been suggested in a number of observational studies,[15,22] no randomised trial of treatment versus no treatment in individuals with masked hypertension has yet been reported. One previous study did examine the efficacy of treatment based on ABPM rather than clinic readings and reported similar levels of BP control at follow-up but less treatment in the intervention arm.[23] However, this study did not include individuals with masked hypertension. A trial of treatment of masked hypertension is currently underway in the US,[24] however this plans to enrol individuals with existing hypertension who are apparently controlled according to clinic BP, so the findings will not be directly relevant in the diagnostic scenario examined here. Until a randomised clinical trial of treatment in drug naïve individuals with masked hypertension is conducted, the true benefits of treatment will remain unknown. However, since the relationship between BP and vascular outcomes appears log-linear and predictable in epidemiological studies,[25] it is reasonable to assume that treatment of masked (but true) hypertension carries similar benefit.

The present study used a prevalence of masked hypertension from the International Database on Ambulatory BP in relation to Cardiovascular Outcomes (IDACO).[26] In fact, due to the difficulty recognising masked hypertension in routine clinical practice, the true prevalence has been shown to vary, with estimates ranging from 8·5 to 16·6%.[22,27] We examined the impact of varying prevalence in a sensitivity analysis and the PROOF-BP algorithm remained cost-effective across the range assessed.

As with the previous model that informed the latest NICE hypertension guidance,[4] and in keeping with the results of the recent HOPE-3 trial ,[28] the present analysis assumed that there was no benefit from treatment in individuals who were truly normotensive. This assumption has been challenged by the meta-analysis by Law and colleagues[25] and more recently the SPRINT trial[29] which support the prescription of treatment to those with BP levels of ≥130/80 mm Hg. However, SPRINT was a trial of individuals at high risk and less than 10% were treatment naïve at baseline, limiting the applicability of those results to a modelled population of undiagnosed individuals undergoing screening for hypertension. Sensitivity analyses undertaken in the present study also revealed assuming equal risk reduction in normotensive patients, or those undergoing intensive blood pressure lowering regimes would actually reduce the ICER in favour of the PROOF-BP algorithm.

While the PROOF-BP algorithm was cost-effective when the model entry was widened to individuals with a screening BP ≥120/70 mm Hg, the increased primary care workload burden from the additional ABPM investigations (Table S9 in the online-only Data Supplement) would likely make implementation infeasible (between 1·57 to 6·85 times more ABPM investigations by cohort than current practice).

Findings in the context of existing literature

There are a number of economic analyses examining the cost-effectiveness and cost benefit of different BP monitoring strategies in the diagnosis of hypertension. Previous studies from Australia, USA and Europe have compared ABPM with CBPM[30-33] and further studies from Japan and the USA have compared HBPM with CBPM.[34,35] The original cost-effectiveness model developed for NICE,[2] which formed the basis for the present analyses, was the first to compare all three strategies. All previous analyses found diagnosis with out-of-office monitoring to be cost-effective, but only examined individuals with a high screening BP and examined strategies which targeted the use of ABPM or HBPM monitoring at those most likely to benefit. A recent analysis compared the cost-effectiveness of central BP monitoring with CBPM and found the former to be cost-effective, although they did not compare it with ABPM or HBPM.[36]

The present analysis examined the cost-effectiveness of a new strategy designed to target the use of ABPM at those displaying a potential white coat or masked effect, something which has not been attempted before. Utilisation of the PROOF-BP algorithm was found to be cost-effective at all ages and in males and females, primarily due to treatment of masked hypertension. Some variation by gender was observed, which may be attributable to the varying Framingham risk profile[14] between genders: females had a lower cardiovascular risk which limited the benefits of antihypertensive treatment.

Scenarios where the PROOF-BP risk algorithm was not the most cost-effective option centred on adjustments in treatment disutility. All strategies that increased the proportion of individuals receiving treatment (in the case of PROOF-BP, treating masked hypertension) were disadvantaged when quality of life decrement penalties due to treatment side-effects were assumed. The level of treatment disutility associated with antihypertension

medication is a matter of debate and may vary with age. The non-inclusion of disutility in the present analysis base-case was consistent with previous modelling which argued that where side effects exist, individuals can switch to alternative drugs.[4]

Implications for clinical practice

The present analyses suggest that using the PROOF-BP algorithm was likely to result in slightly higher healthcare costs (due to increased utilisation of treatment in masked hypertensives) but improved quality of life in individuals screened for hypertension. The PROOF-BP algorithm is not currently utilised in routine clinical practice but implementation would be possible with relative ease: automated BP monitors which take up to three consecutive readings (required for the decision tool) are now cheap and routinely available. The prediction algorithm is already available as an online calculator (https://sentry.phc.ox.ac.uk/proof-bp) and could easily be incorporated into general practice computer systems or built into smartphones linked to BP monitors. This strategy has the potential for individuals with apparently normal clinic BP to end up on treatment (if they have masked hypertension), which represents a notable shift from the current practice model and therefore would require some 'buy in' from both patients and practitioners. Presenting the evidence and treatment options clearly, perhaps through formal patient and practitioner education may be required, in much the same way that it accompanied the adoption of ABPM into routine Primary Care.

Perspectives

Current guidelines recommend use of out-of-office measurements to confirm hypertension diagnosis for individuals with raised clinic BP readings. The PROOF-BP algorithm considers both normal and raised clinic BP individuals with less reliance on out-of-office

measurements to confirm hypertension diagnosis. Targeted use of ABPM (PROOF-BP algorithm) in the diagnosis of hypertension appears to be cost-effective compared to the conventional BP diagnostic options in Primary Care and would lead to reduced death and disability. Limitations of the model include the lack of data on the assumed efficacy of antihypertensive treatment for masked hypertension, which requires further investigation.

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Williams works in academic collaboration with Healthstats, Singapore, in developing novel blood pressure–monitoring approaches. The other authors report no conflicts.

Data sharing

Individuals wishing to use the data in this study should contact the corresponding author.

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Novelty and Significance

What Is New?

- This study considered the merits (cost-effectiveness) of using the PROOF-BP algorithm to triage for Ambulatory Blood Pressure Monitoring (ABPM) in the diagnosis of hypertension
- This is the first economic evaluation of different methods of diagnosing hypertension which includes the consideration of individuals with potential masked hypertension

What Is Relevant?

- PROOF-BP algorithm considered a broader screening population in terms of clinic BP for diagnosis but necessitated less ABPM investigations in most age cohorts compared with current guidelines.

Summary

- Economic modelling suggest such an approach would be cost-effective compared with conventional BP diagnostic options in Primary Care

Figure Legends

Figure 1. Diagnostic strategies examined

Figure 2. Markov state transition diagram

Tables

Table 1. Clinical data inputs for the model

Clinical data for the model	Data	Source
Prevalence of true hypertension in population suspected of having hypertension* (Clinic BP ≥140/90 mm Hg)	17-64% (age and sex dependent)	Estimated with meta-analysis by Hodgkinson and colleagues[13] and HSE 2013[12]
Prevalence of masked hypertension in screening population (Clinic BP ≥130/80 mm Hg)	1-15% (age and sex dependent)	Estimated from Conen and colleagues[26] and HSE 2013[12]
Diagnosis inputs		
Clinic BP ≥140/90 mm Hg Sensitivity	CBPM 85·6% (95% CI 81·0-89·2); HBPM 85·7% (95% CI 78·0-91·0); ABPM 100·0%; PROOF-BP 100·0%	Meta-analysis sensitivity analysis by Hodgkinson and colleagues[13] (excluding populations with low mean BP); ABPM was assumed to be reference standard with 100% sensitivity and specificity. PROOF-BP data taken from Sheppard and colleagues[11]
Clinic BP ≥140/90 mm Hg Specificity	CBPM 45·9% (95% CI 33·0-59·3); HBPM 62·4% (95% CI 48·0-75·0) ABPM 100·0%; PROOF-BP 65·5%	As above
Clinic BP between 130/80 mm Hg & 140/90 mm Hg Sensitivity	CBPM, HBPM, ABPM 0% PROOF-BP 97·3%	Assumed not hypertensive in conventional strategies. PROOF-BP data taken from Sheppard and colleagues[11]
Clinic BP between 130/80 mm Hg & 140/90 mm Hg Specificity	CBPM, HBPM, ABPM 100% PROOF-BP 96·2%	As above
Sensitivity Analysis: Clinic BP between 120/80 mm Hg & 140/90 mm Hg Sensitivity	CBPM, HBPM, ABPM 0% PROOF-BP 89·5%	As above
Sensitivity Analysis: Clinic BP between 120/80 mm Hg & 140/90 mm Hg Specificity	CBPM, HBPM, ABPM 100% PROOF-BP 97·6%	As above
Time until diagnosis complete	CBPM 3 months; HBPM 1 month; ABPM 1 month; PROOF-BP 1 month	Assumption based on guideline recommendations
Diagnostic device failure rate	ABPM 5%	Assumption
Mortality and risk of cardiovascular disease		

Probability of non-cardiovascular death	Age and sex dependent	England and Wales 2011-2013 lifetables without circulatory death[37,38]
Probability of coronary heart disease event if truly normotensive within 10 years	0·8-14·9% (age and sex dependent)	Calculated with Framingham coronary heart disease and stroke risk equations[14] and risk factor profile based on HSE 2013[12]
Probability of coronary heart disease event if truly hypertensive within 10 years	1·7-22·2% (age and sex dependent)	As above
Probability of stroke event if truly normotensive within 10 years	0·3-4·8% (age and sex dependent)	As above
Probability of stroke event if truly hypertensive within 10 years	0·8-14·8% (age and sex dependent)	As above
Coronary heart disease event distribution (age and sex dependent)	MI 14·3-37·8%; unstable angina 10·4-20·9%; stable angina 37·7-62·9%; coronary heart disease death 6·6-17·8%	Ward and colleagues[39]
Stroke event distribution (age and sex dependent)	Stroke 51·7-70·1%; TIA 13·4-36·1%; stroke death 12·2-16·5%	Ward and colleagues[39]
Relative Risk of coronary heart events on treatment – true positives	0·639-0·721 (age and sex dependent)	Calculated with meta-analysis by Law and colleagues[25] and HSE distribution of people on 1-3 drugs[12]
Relative Risk of coronary heart events on treatment – false positives	1	Assumption that people without raised BP get no treatment benefit
Relative Risk of stroke events on treatment—true positives	0·533-0·721 (age and sex dependent)	Calculated with meta-analysis by Law and colleagues[25] and HSE distribution of people on 1-3 drugs[12]
Relative Risk of stroke events on treatment—false positives	1	Assumption that people without raised BP get no treatment benefit
Standardized Mortality Rate (SMR) after myocardial infarction	2·68 (95% CI 2·48-2·91)	Brønnum-Hansen and colleagues[40]
SMR after unstable angina	2·19 (95% CI 2·05-2·33)	NICE guidelines[41]
SMR after stable angina	1·95 (95% CI 1·65-2·31)	Rosengren and colleagues[42]
SMR after stroke	2·72 (95% CI 2·59-2·85)	Brønnum-Hansen and colleagues[40]

SMR after transient ischaemic attack	1·40 (95% CI 1·1-1·8)	Oxfordshire Community Stroke Project[43]
BP over time and ongoing monitoring		
Probability of raised BP (true positive and false positive)	13-34% (age and sex dependent)	Calculated based on HSE 2013[12]
Proportion of masked hypertension that progress to sustained hypertension by 3 years	26·3%	Trudel and colleagues[44]
Proportion of masked hypertension that progress to sustained hypertension by 5 years	34·9%	Trudel and colleagues[44]
Check-up frequency if diagnosed not hypertensive	Every 5 years	Assumption based on present UK practice
Diagnosis method following check-up	Same as initial diagnosis method	

CBPM, Clinic Blood Pressure Monitoring; HBPM, Home Blood Pressure monitoring; ABPM, Ambulatory Blood Pressure Monitoring; PROOF-BP, Predicting out-of-office blood pressure; TIA, Transient Ischaemic Attack; MI, Myocardial infarction; NICE, National Institute for Health and Care Excellence; HSE, Health Survey for England;
*Left ventricular hypertrophy risk input assumed to be 0%

Table 2. Quality of life and cost data inputs for the model

Quality of life weights	**Data**	**Source**
No cardiovascular event	0·737-0·905 (age and sex dependent)	General population utilities from analysis of EQ-5D (UK tariff) from HSE 2012[16]
Quality of life multipliers		
Stroke	0·629	Ward and colleagues.[39] Applied multiplicatively to general population age-dependent and sex-dependent utilities
Myocardial infarction	0·760	As above
Unstable Angina	0·770	As above
Stable Angina	0·808	As above
Transient Ischaemic Attack	1	As above
On hypertension treatment	1	Assumption that no quality of life loss to treatment in base-case
Costs		
Cost of diagnosis CBPM	£46·37	Calculated based on resource-use assumptions from Lovibond and colleagues[4] and UK unit costs below
Cost of diagnosis HBPM	£47·59	As above
Cost of diagnosis ABPM	£63·61	As above
Cost of diagnosis PROOF-BP	£0-£63·61	Cost of diagnosis of ABPM if decision rule suggests confirmatory investigation, zero otherwise (zero assumed cost of using algorithm)
Practice nurse consultation	£11·37	PSSRU 2014 unit costs[17]
GP consultation	£35·00	PSSRU 2014 unit costs[17]
HBPM device	£46·00	Median price of approved HBPM devices from NHS supply chain catalogue; only monitors also on the British Hypertension Society list of validated devices suitable for home use were used
ABPM device	£1,105	Median price from NHS supply chain catalogue
HBPM calibration/services per year	£10·00	Data on File at Greenridge Surgery, South Birmingham primary-care trust (Richard J McManus, unpublished,2011)
ABPM calibration/service/parts per	£413	Mean of two estimates (£460·00 and £300·00) updated

year		to 2013-14[17]
Battery (1·5 volt size AA/LR6 high power alkaline)	£0·29	NHS supply chain catalogue
Adult cuff	£17·41	Median price in NHS supply chain catalogue
Nurse practitioner consultation	£22·00	PSSRU 2014 unit costs[17]
Annual hypertension treatment cost	£58·01-64·90	Calculated based on recommended treatment and UK unit costs[2,12,17]
Initial stroke costs (3 months)	£8,390	Luengo-Fernandez and colleagues[45]
Post-stroke costs (3 months)	£336	Luengo-Fernandez and colleagues[45]
Initial cost of TIA (3 months)	£1,045	Diagnostic tests and procedures: Ward and colleagues inflated to 2013-14;[17] drug costs: relevant NICE guidance[46,47] and British National Formulary 69[48]
Costs after TIA (3 months)	£19·56	Relevant NICE guidance[46,47] and British National Formulary 69[48]
Initial myocardial infarction costs (3 months)	£5,183	Palmer and colleagues inflated to 2013-14[17]
Costs after myocardial infarction (3 months)	£152	Taylor and colleagues[49]
Initial unstable angina costs (3 months)	£3,110	Assumed to be 60% of initial costs of myocardial infarction
Costs after unstable angina (3 months)	£91	Assumed to be 60% of costs after myocardial infarction
Initial stable angina cost (3 months)	£397	An outpatient cardiology assessment (service code 320) plus non-invasive imaging SPECT scan (service code RA37Z)[50]
Costs after stable angina (3 months)	£8	Relevant NICE guidelines[51] and British National Formulary 69[48]
Check-up	£35	PSSRU 2014 unit costs[17]

CBPM, Clinic Blood Pressure Monitoring; HBPM, Home Blood Pressure monitoring; ABPM, Ambulatory Blood Pressure Monitoring; GP, General Practitioner; PROOF-BP, Predicting out-of-office blood pressure; NICE, National Institute of Health and Care Excellence; PSSRU, Personal Social Services Research Unit; TIA, Transient Ischaemic Attack

Table 3. Base-case model results when entry is restricted to clinic BP ≥130/80 mm Hg

Strategy	QALYs (95% CI)	Costs (95% CI)	ICER	Most CE strategy probability	Strategy	QALYs (95% CI)	Costs (95% CI)	ICER	Most CE strategy probability
40 years, Male					40 years, Female				
ABPM	18·116 (17·867 to 18·34)	£3275 (£3181 to £3440)		0%	ABPM	18·006 (17·807 to 18·209)	£1989 (£1911 to £2132)		0%
PROOF-BP	18·153 (17·906 to 18·377)	£3389 (£3301 to £3540)	£3081	100%	HBPM	18·007 (17·808 to 18·209)	£2148 (£2064 to £2257)	Dominated	0%
HBPM	18·115 (17·865 to 18·340)	£3397 (£3310 to £3520)	Dominated	0%	PROOF-BP	18·020 (17·823 to 18·222)	£2153 (£2067 to £2286)	£11363	100%
CBPM	18·115 (17·864 to 18·339)	£3427 (£3345 to £3537)	Dominated	0%	CBPM	18·007 (17·808 to 18·210)	£2188 (£2112 to £2288)	Dominated	0%
50 years, Male					50 years, Female				
ABPM	15·604 (15·365 to 15·858)	£3405 (£3269 to £3597)		0%	ABPM	15·426 (15·207 to 15·627)	£2269 (£2154 to £2453)		0%
PROOF-BP	15·633 (15·399 to 15·884)	£3468 (£3344 to £3640)	£2094	100%	PROOF-BP	15·442 (15·223 to 15·643)	£2372 (£2262 to £2544)	£6232	100%
HBPM	15·599 (15·360 to 15·855)	£3504 (£3390 to £3649)	Dominated	0%	HBPM	15·425 (15·207 to 15·627)	£2385 (£2277 to £2534)	Dominated	0%

CBPM	15·598 (15·359 to 15·854)	£3530 (£3424 to £3668)	Dominated	0%	CBPM	15·426 (15·205 to 15·628)	£2416 (£2314 to £2556)	Dominated	0%
60 years, Male					60 years, Female				
ABPM	12·842 (12·624 to 13·060)	£3193 (£3018 to £3428)		0%	ABPM	12·528 (12·315 to 12·735)	£2346 (£2161 to £2634)		0%
PROOF-BP	12·862 (12·646 to 13·079)	£3226 (£3069 to £3449)	£1680	100%	PROOF-BP	12·537 (12·325 to 12·743)	£2383 (£2217 to £2651)	£3865	100%
HBPM	12·835 (12·618 to 13·054)	£3280 (£3120 to £3483)	Dominated	0%	HBPM	12·525 (12·314 to 12·729)	£2459 (£2289 to £2696)	Dominated	0%
CBPM	12·833 (12·617 to 13·053)	£3305 (£3161 to £3500)	Dominated	0%	CBPM	12·525 (12·314 to 12·730)	£2490 (£2344 to £2711)	Dominated	0%
70 years, Male					70 years, Female				
ABPM	9·821 (9·569 to 10·026)	£2686 (£2440 to £2989)		0%	ABPM	9·357 (9·120 to 9·590)	£2021 (£1797 to £2314)		0%
PROOF-BP	9·830 (9·577 to 10·038)	£2695 (£2472 to £2988)	£955	100%	PROOF-BP	9·364 (9·128 to 9·596)	£2040 (£1832 to £2314)	£2789	100%
HBPM	9·812 (9·558 to 10·019)	£2765 (£2552 to £3043)	Dominated	0%	HBPM	9·351 (9·115 to 9·584)	£2088 (£1892 to £2344)	Dominated	0%

CBPM	9·810 (9·556 to 10·017)	£2790 (£2588 to £3055)	Dominated	0%	CBPM	9·350 (9·112 to 9·585)	£2110 (£1914 to £2356)	Dominated	0%
75 years, Male					75 years, Female				
PROOF-BP	8·235 (7·987 to 8·490)	£2430 (£2175 to £2755)	Dominant	100%	PROOF-BP	7·689 (7·412 to 7·975)	£1818 (£1583 to £2164)	Dominant	100%
ABPM	8·230 (7·981 to 8·484)	£2434 (£2166 to £2773)	Dominated	0%	ABPM	7·687 (7·411 to 7·973)	£1822 (£1584 to £2183)	Dominated	0%
HBPM	8·222 (7·972 to 8·476)	£2495 (£2250 to £2815)	Dominated	0%	HBPM	7·682 (7·406 to 7·970)	£1884 (£1664 to £2215)	Dominated	0%
CBPM	8·219 (7·969 to 8·470)	£2516 (£2273 to £2829)	Dominated	0%	CBPM	7·681 (7·403 to 7·967)	£1906 (£1687 to £2228)	Dominated	0%

Results are per patient & strategies are ordered by ascending costs; CBPM, Clinic Blood Pressure Monitoring; HBPM, Home Blood Pressure monitoring; ABPM, Ambulatory Blood Pressure Monitoring; PROOF-BP, Predicting out-of-office blood pressure; QALYs, quality-adjusted life years; ICER= Incremental Cost-Effectiveness Ratio

Table 4. Sensitivity Analysis Scenarios

Strategy	QALYs	Costs	ICER	Strategy	QALYs	Costs	ICER
Base-case				Risk reduction based on half doses for masked hypertensives			
ABPM	12·842	£3193		ABPM	12·840	£3,199	
PROOF-BP	12·862	£3226	£1680	PROOF-BP	12·857	£3,240	£2504
HBPM	12·835	£3280	Dominated	HBPM	12·833	£3,286	Dominated
CBPM	12·833	£3305	Dominated	CBPM	12·831	£3,310	Dominated
1% utility decrement on treatment				Higher prevalence of masked hypertension (125%)			
ABPM	12·786	£3,193		ABPM	12·837	£3,213	
PROOF-BP	12·790	£3,226	£7620	PROOF-BP	12·861	£3,240	£1193
HBPM	12·764	£3,280	Dominated	HBPM	12·830	£3,300	Dominated
CBPM	12·757	£3,305	Dominated	CBPM	12·828	£3,325	Dominated
2% utility decrement on treatment				Lower prevalence of masked hypertension (75%)			
ABPM	12·730	£3,193	Dominant	ABPM	12·847	£3,174	
PROOF-BP	12·719	£3,226	Dominated	PROOF-BP	12·863	£3,212	£2375
HBPM	12·693	£3,280	Dominated	HBPM	12·839	£3,261	Dominated
CBPM	12·682	£3,305	Dominated	CBPM	12·838	£3,286	Dominated
Higher hypertension treatment costs				Antihypertensive treatment benefits assumed for all people			
ABPM	12·842	£3,277		ABPM	12·846	£3,185	
PROOF-BP	12·862	£3,326	£2470	PROOF-BP	12·878	£3,185	£20
HBPM	12·835	£3,380	Dominated	HBPM	12·862	£3,214	Dominated
CBPM	12·833	£3,409	Dominated	CBPM	12·867	£3,223	Dominated
Risk reduction based on half doses				Antihypertensive intensive treatment assumed			
ABPM	12·811	£3,276		ABPM	12·903	£3,093	
PROOF-BP	12·827	£3,318	£2572	PROOF-BP	12·930	£3,115	£852
HBPM	12·805	£3,361	Dominated	HBPM	12·893	£3,183	Dominated
CBPM	12·803	£3,385	Dominated	CBPM	12·891	£3,208	Dominated
ABPM strategy considers individuals with a screening clinic BP of 130/80 mm Hg				ABPM failure rate increased from 5% to 17%			

ABPM	12·860	£3,219		ABPM	12·841	£3,224	
PROOF-BP	12·862	£3,226	£5153	PROOF-BP	12·861	£3,250	£1287
HBPM	12·835	£3,280	Dominated	HBPM	12·835	£3,280	Dominated
CBPM	12·833	£3,305	Dominated	CBPM	12·833	£3,305	Dominated
BP check-up frequency is reduced from every 5 years to every 3 years							
ABPM	12.847	£3,253					
PROOF-BP	12.865	£3,294	£2,315				
HBPM	12.842	£3,320	Dominated				
CBPM	12.840	£3,333	Dominated				

Results are per patient & strategies are ordered by ascending costs; CBPM, Clinic Blood Pressure Monitoring; HBPM, Home Blood Pressure monitoring; ABPM, Ambulatory Blood Pressure Monitoring; PROOF-BP, Predicting out-of-office blood pressure; QALYs, quality-adjusted life years; ICER= Incremental Cost-Effectiveness Ratio

Figures

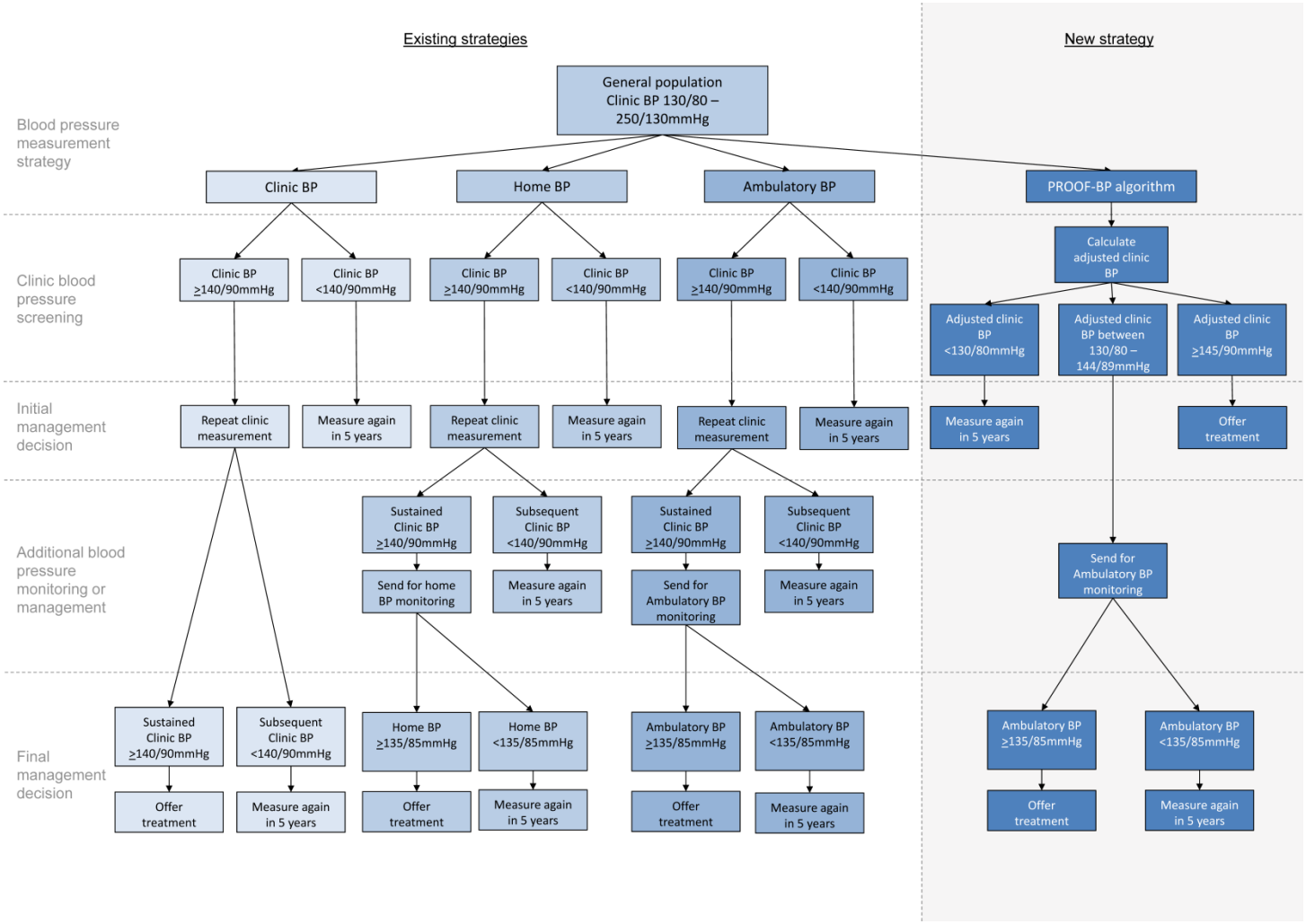

Figure 1. Diagnostic strategies examined

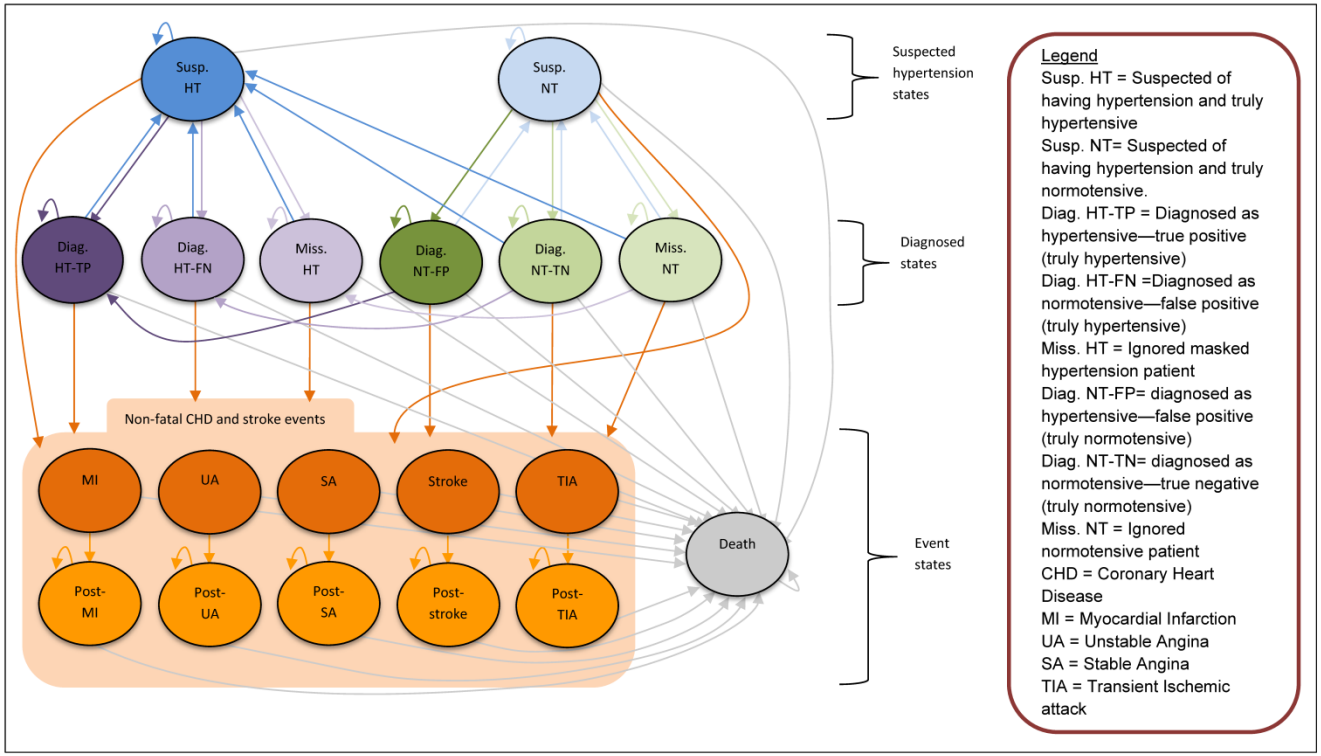

Figure 2. Markov state transition diagram