Cost-Effectiveness of Secondary Screening Modalities for Hypertension

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Abstract

Background—Clinic-based blood pressure (CBP) has been the default approach for diagnosing hypertension, but patients may be misclassified due to masked hypertension (false negative) or "white coat" hypertension (false positive). The incorporation of other diagnostic modalities, such as home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM), holds promise to improve diagnostic accuracy and subsequent treatment decisions.

Method—We reviewed the literature on the costs and cost-effectiveness of adding HBPM and ABPM into routine blood pressure screening in adults. We excluded letters, editorials, and studies of pregnant and/or pre-eclamptic patients, children, and patients with specific conditions (e.g. diabetes).

Results—We identified 14 original, English language studies that included cost outcomes and compared two or more modalities. ABPM was found to be cost-saving for diagnostic confirmation following an elevated CBP in 6 studies. Three of 4 studies found that adding HBPM to an elevated CBP was also cost-effective.

Conclusion—Existing evidence supports the cost-effectiveness of incorporating HBPM or ABPM following an initial CBP-based diagnosis of hypertension. Future research should focus on their implementation in clinical practice, long-term economic values, and potential roles in identifying masked hypertension.

INTRODUCTION

According to the Centers for Disease Control and Prevention, approximately one out of every three United States (US) adults is hypertensive [1]. Uncontrolled hypertension is associated with higher cardiovascular and overall mortality [2] and is present in nearly 75% of US adults diagnosed with coronary artery disease, congestive heart failure, cerebrovascular disease, or diabetes mellitus [3]. In 2010, hypertension was estimated to cost the US $76.6 billion in health care services, medications, and missed work days [4].

The U.S. Preventive Services Task Force endorses a Grade A recommendation for screening adults age 18 and older for hypertension [5]. In a previous review, researchers found several studies that demonstrated the efficacy and effectiveness of detecting elevated blood pressure and introducing anti-hypertensive treatment as part of routine health visits for reducing future mortality and morbidity; however, evidence on the cost-effectiveness of various blood pressure monitoring techniques was not available [6].

Traditionally, the diagnosis of hypertension or "pre-hypertension" is made by taking blood pressure measurements in the clinic. According to the Joint National Committee VII (JNC-7) report [7], the diagnosis of hypertension in adults is made when the average of two or more diastolic blood pressure measurements on at least 2 visits is 90 mmHg or when the average of two or more systolic blood pressure measurements on at least 2 visits is 140 mmHg. In addition, 'prehypertension' is defined as having an average diastolic blood pressure of 80–89 mmHg or average systolic blood pressure of 120–139 mmHg.

However, there are two major caveats to the diagnosis and treatment of hypertension based solely upon clinic blood pressure: namely, the possibilities of false positive and false negative diagnoses (Figure 1). "White coat" hypertension is defined as clinic hypertension (mean SBP is 140 mmHg or mean DBP 90 mmHg) without ambulatory hypertension (defined as mean awake blood pressure 135/85 mmHg) [8]. In the absence of ABPM, these patients are likely to be treated despite having normal "true" or "usual" blood pressure, and thus are exposed to unnecessary risks for adverse effects and treatment costs. Conversely, "masked hypertension" is present when the clinic blood pressure is below 140/90 mmHg but the average blood pressure in one's normal living environment meets the criterion for hypertension [9] – i.e., where CBP yields a false negative diagnosis. These patients are left untreated in spite of their elevated blood pressure levels. In general, patients with white coat hypertension are shown to have better prognosis than those with true hypertension, and patients with masked hypertension appear to experience worse outcomes than those truly normotensive [10]. These observations underlie the limitations of relying on CBP alone for diagnosing treatment-eligible patients and the opportunities for out-of-clinic blood pressure measurement modalities to optimize patient outcomes.

Support for the addition of ambulatory blood pressure monitoring (ABPM) and/or home blood pressure monitoring (HBPM) measures to the diagnostic algorithms as part of routine care has been modest [5]. However, the UK National Health Services recently revised their blood pressure screening guideline to support the routine use of ABPM to confirm a new diagnosis of hypertension. The new guideline estimated a potential savings of £10 million ($16 million) over 4–5 years, mainly from the identification of white-coat hypertension and subsequent reduction in treatment-associated costs [11]. Others advocate for using HBPM as a cost-effective strategy to augment CBP-based usual care with fewer physician visits [12–16], citing its greater accuracy as a measure of "usual blood pressure", greater reproducibility, greater prognostic value for cardiovascular outcomes, and low cost [16]. JNC-7 guidelines suggested a potential role of blood pressure self-measurement of hypertensive patients [7], but did not endorse its routine use; international guidelines

endorse a wider use of HBPM for monitoring treatment [17–19]. The limited uptake and reimbursement for ABPM and HBPM may be due to a knowledge gap about its cost-effectiveness compared to CBP. In this article, we provide an overview of the existing literature on the comparative cost and cost-effectiveness of ABPM and CBP for hypertension screening.

METHOD

Independent searches of PubMed, Medline, and the Tufts Cost Effectiveness Analysis (CEA) Registry were carried out by authors AK and MN for studies published in the past 25 years. Citations and reference lists were also reviewed to identify additional studies. We used the following search terms: adult, hypertension, blood pressure, screening, diagnosis; cost-effectiveness, cost-benefit, cost analysis, cost utility, cost impact; clinic, ambulatory, home; multiple combinations of search terms were used to maximize results from the searches. We included original English-language studies that compared two or more modalities of blood pressure measurement, for the purposes of primary prevention. Letters and editorials were excluded. We also excluded studies that were restricted to subpopulations of pregnant and/or pre-eclamptic patients; patients with specific comorbidities (i.e., diabetes, coronary artery disease); and/or patients undergoing treatment using a particular drug or device. All eligible articles were audited by AK and JN independently, and disagreements were resolved by all authors.

We report the year of publication, country, study population, study design, time horizon, and main findings. We also report the original cost figures as well as standardized 2011 US dollars to allow comparisons across studies including various currencies and years of analysis.

RESULTS

Fourteen studies were identified as meeting our eligibility criteria (Table 1). Nine of the 14 studies are clinical trials, while five are model-based decision analyses. The earliest study was published in 1988[20]. Seven out of 14 of the studies were conducted in Europe; 4 were conducted in the US; 2 were conducted in Japan; and one was conducted in Australia. Nine studies compared ABPM to CBP alone[20–28], four studies compared HBPM to CBP [12–15], and one study compared all three [11].

Comparing ABPM to CBP

In general, compared to CBP alone, most researchers found ABPM to be cost-saving. This cost-saving was achieved mainly through increases in diagnostic accuracy resulting in a reduction in overtreatment due to false-positive diagnoses of hypertension based on CBP alone [11, 21–23, 25, 27, 28]. For example, in two separate studies, Krakoff *et al* found that over a period of three years the cumulative costs of treatment for mild hypertension are lower for those using ABPM compared to CBP only [20, 27]. These researchers also estimated a 3–14% reduction in medical costs (which correlated with a 10–23% reduction in treated patient-days) as long as annual treatment costs are no more than $300. Yarows *et al* estimated that the cessation of unnecessary anti-hypertensives in patients with white-coat hypertension could offset the cost of ABPM after one year when ABPM costs $188 or less [29]. When ABPM was used as a secondary diagnostic modality, Pierdomenico *et al* found a savings of $110,819 by using ABPM every two years over a six-year period, compared to annual screening using CBP alone [22]. Rodriguez-Roca *et al* found that the cost of achieving a well-controlled hypertension case is €940 ($1,169) with CBP and €238 ($296) with ABPM, resulting in in €115 ($143 in 2011 US dollars) per additional well-controlled case achieved [28]. In a secondary prevention study by Lorgelly *et al*, ABPM successfully

identified patients with white coat hypertension, but at an annual cost of £3612 ($6641 in 2011 US dollars) [26]. Long-term savings were also found by a number of additional ABPM studies [23, 25]. After measuring both consultation and medication costs, Aitken *et al* demonstrated that the initial costs of ABPM were recouped after 1–2 years [23]. Similarly, Ewald and Pekarsky constructed a model to evaluate the cost and effectiveness of ABPM conducted every one, two, or three years [25]. Over a seven-year period, all three strategies broke even after the third year, with subsequent savings ranging from $34 to $53 per year per patient.

On the other hand, two research teams found no net savings of ABPM compared to CBP. In a randomized control trial published in 1997 by Staessen et al., the researchers found that despite more patients in the ABPM arm being considered a false positive and having their anti-hypertensive treatment discontinued than in the CBP arm and more patients in the CBP arm progressing to multi-drug treatment than in the ABPM arm, the savings at 1 year was not sufficient to offset the cost of ABPM [24]. However, the range of follow-up for this study was only 85–258 days, which might be an inadequate time period in which to observe savings. Similarly, Lorgelly et al. [26] found that ABPM increased the cost of hypertension control at a rate of £31 ($57 in 2011 US dollars) per patient over one year.

Comparing HBPM to CBP

There were two randomized controlled trials comparing HBPM to CBP. Staessen *et al*, 2004 [15] found that HBPM was associated with worse hypertension management despite marginally lower costs. At one month, average medical costs per 100 patients were $4473 with HBPM versus $4921 without HBPM; however, mean blood pressure was also <u>higher</u> in the HBPM group. General well-being and left ventricular mass did not appear to differ between the two groups. Note, however, that the authors used a threshold for HBPM of 140/90 mmHg to define hypertension control, rather than the generally accepted 135/85 mmHg cut-off. In contrast, in their year-long clinical trial Soghikian *et al* found that the mean costs for hypertension care were 29% less in patients managed via HBPM compared to usual clinic-based care [14].

Three of the four modeled analyses comparing HBPM to CBP found HBPM to be cost-effective [12–15]. Using data from the Ohasama study and a Markov model, Fukunaga *et al* estimated the cost of incorporating HBPM into the diagnosis of hypertension in the Japanese population [12]. They estimated that the incorporation of HBPM could reduce medical costs by $US 1.56 million for every 1,000 patients over 5 years. When they varied the assumed prevalence of white coat hypertension from 8.2 to 24.7% in the sensitivity analysis, the resulting cost reduction ranged from $0.8 to 2.0 million. Using the same data but modeling a decision tree analysis, Funahashi *et al* estimated that broad implementation of HBPM could result in a saving of $9.3 billion US dollars in hypertension-related medical costs in Japan[13]. These cost savings came mainly from identifying white coat hypertension. Moreover, HBPM also contributes to better control and prognosis of true hypertensives, saving approximately $28 million in annual medical costs from the prevention of hypertension-related complications and $39 million annually from stroke prevention. It is worth noting that, because stroke occurs at greater incidence in the Japanese population relative to coronary heart disease (whereas coronary artery disease and MIs are much more prevalent than stroke in the U.S. and Western European societies), their study placed a greater emphasis on the role of hypertension control on stroke prevention.

Comparing ABPM, HBPM and CBP

Using a state-transition Markov model, Lovibond et al. [11] is the only study that compared ABPM, HBPM and CBP. The study based the sensitivity and specificity of CBP (sensitivity

85.6% (95% CI 81.0–89.2); specificity 45.9% (95% CI 33.0–59.3)), HBPM (sensitivity 85.7% (95% CI 78.0–91.2); specificity 62.4% (95% CI 48.0–75.0)), and ABPM (both 100%, considered gold standard) on a published meta-analysis[30]. From the perspective of the British National Health Services, the study found that ABPM was cost-saving in reducing unnecessary treatment and future risks of coronary heart disease and stroke for men and women of all ages.

DISCUSSION

Based on our review, existing studies suggest that supplementing CBP with HBPM or ABPM is cost-effective for improving the diagnosis of hypertension and subsequent treatment decisions. While differences in the study population and analytic methods exist, this conclusion is consistent across the literature reviewed. These economic evaluations suggested that adding HBPM or ABPM after detecting elevated BP in the clinic setting could be worthwhile for identifying white coat hypertension and avoiding unnecessary treatment.

Despite these consistent findings on the comparative value of HBPM and ABPM, the translation of these findings into practice is modest and broad implementation of these modalities into clinical practice have not occurred. This may be due to the marginal cost savings found in some studies.

As the clinical benefit of BP measures hinges on the probabilities of false positive and false negatives (Figure 1), identifying subpopulations most likely to be misclassified by CBP alone will be important in maximizing cost-effectiveness. As noted by Krakoff [27], the use of ABPM to diagnose hypertension may be most cost-effective when the prevalence of white coat hypertension is high and when the annual incidence of new hypertension is low. In four population-based European studies, researchers found that ambulatory pressure shows much less increase with age than CBP [31–34]. We found few studies examining the compliance issues associated with HBPM/ABPM. As the utility of these modalities depends on patient cooperation, existing studies based on trial populations or modeling assumptions are likely to represent an overestimate of the cost-effectiveness of these modalities.

Both ABPM and HBPM can add accuracy and value beyond simply correcting the CBP measurement. For instance, ABPM can reveal nocturnal hypertension, a relatively new marker of cardiac risk that has been shown to refine cardiovascular risk stratification above and beyond that of conventional BP measurement, both in untreated subjects with white coat hypertension and those with resistant hypertension [35, 36]. ABPM is also currently regarded as the 'gold standard' for the prediction of risk; however, the role of ABPM in diagnosing masked hypertension is uncertain, and it remains the most expensive of the 3 modalities [37]. The degree to which HBPM, a less expensive out-of-office option, can adequately substitute for ABPM is unknown. However, there is increasing evidence that HBPM is a good predictor of left ventricular hypertrophy and cardiovascular events, including mortality. HBPM also has better prognostic accuracy than CBP for predicting the future development of hypertension, and may be particularly useful for monitoring anti-hypertensive treatment effects [29, 38, 39]. HBPM has the added bonus of eliminating the white coat effect entirely, and can substantially increase patients' awareness of their own blood pressure, which may lead to better compliance with treatment [40]. However, HBPM may not be suitable for all patients (e.g., obese patients with large arm sizes or the elderly) and is subject to the same operator issues as CBP. While most studies show that HBPM lowers costs, one study (but not others) also found that when used alone, it decreased BP control [15].

Based on our review, existing studies have characterized the clinical benefits of HBPM and ABPM for identifying white coat hypertension (false positives); however, more research is needed to assess how HBPM and ABPM may best be used to identify masked hypertension (false negatives). A reasonable approach may be to prescribe ABPM or HBPM for patients with CBP in the high-normal range (130–139/85–89 mmHg) or pre-hypertensive (120–139/80–89 mmHg) range. One might also consider the presence/absence of other cardiovascular risk factors in deciding who could benefit most from ABPM or HBPM following a normal CBP. The value of identifying individuals with masked hypertension parallels the well-established clinical benefit and cost-effectiveness of treating previously undiagnosed hypertension. However, unlike observing cost savings from avoiding treatment among white-coat hypertensives, the cost savings will come from downstream events avoided and therefore the research will require a longer follow-up time. This need for a long-term perspective highlights the value of model-based studies that enable us to weigh immediate set-up costs with downstream treatment costs avoided, possibly several decades later [11–13, 27].

It is worth noting that researchers and clinicians should not overlook ways to improve the accuracy of CBP. CBP employs the traditional auscultatory technique with a trained technician and a sphygmomanometer. Various types of equipment are still used, including mercury (rarely); aneroid devices (require frequent calibration); and automatic devices with electronic transducers, which are becoming more and more common [41] and can potentially minimize the white coat effect of CBP at a reasonable cost [42]. Training of the operator, positioning of the patient, and cuff size can all make a difference in measurement, and are all factors that contribute to the poor correlation between CBP and other types of blood pressure measurement, especially outside the research setting. Additionally, there needs to be greater recognition of the fact that BP is a dynamic variable, of which CBP provides only a snapshot. Even if CBP is the sole diagnostic assessment method, treatment decisions should be based on multiple visits with multiple readings taken during each visit.

As the UK National Health Services begins to cover ABPM following an initial CBP assessment as part of routine care [11], we anticipate increased discussion about the potential utility of following similar diagnostic algorithms in U.S. clinical guidelines. Additional population-based evidence from the UK will also fill key knowledge gaps on the longer-term merits and unintended consequences of these practices. Furthermore, as the field of cardiovascular prevention moves towards a global risk-based approach rather than single risk factor approach, diagnostic accuracy of blood pressure may have implications beyond hypertension treatment. For instance, the Adult Treatment Panel (ATP) 3 cholesterol treatment guideline determines candidacy and treatment goal for lipid-lowering therapy based on predicted 10-year Framingham risk for coronary heart disease. If one has 2 or more non-cholesterol risk factors such as elevated blood pressure, even borderline LDL levels may be sufficient to be classified as statin-eligible. Considering the day-to-day variability and diagnostic inaccuracies of blood pressure measures, it is possible that a false positive CBP reading results in both unnecessary anti-hypertensive and cholesterol-lowering medications. Future research should evaluate the full spectrum of clinical and cost implications of implementing secondary modalities in clinical practice, for both primary and secondary prevention, and for a sufficiently long time frame. The identification of optimal thresholds for secondary measurement modality and for treatment initiation, possibly for different demographic subgroups, will have tremendous impact on driving the cost efficiency of hypertension screening at the population level.

Acknowledgments

REFERENCES

1. Health, United States. 2008. [http://www.cdc.gov/nchs/hus.htm]

2. Gu Q, Dillon CF, Burt VL, Gillum RF. Association of hypertension treatment and control with all-cause and cardiovascular disease mortality among US adults with hypertension. Am J Hypertens. 2010; 23(1):38–45. [PubMed: 19851295]

3. Wong ND, Lopez VA, L'Italien G, Chen R, Kline SE, Franklin SS. Inadequate control of hypertension in US adults with cardiovascular disease comorbidities in 2003–2004. Arch Intern Med. 2007; 167(22):2431–2436. [PubMed: 18071164]

4. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation. 2010; 121(7):e46–e215. [PubMed: 20019324]

5. Guide to Clinical Preventive Services. [http://www.preventiveservices.ahrq.gov/]

6. Sheridan S, Pignone M, Donahue K. Screening for high blood pressure: a review of the evidence for the U.S. Preventive Services Task Force. Am J Prev Med. 2003; 25(2):151–158. [PubMed: 12880884]

7. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003; 42(6):1206–1252. [PubMed: 14656957]

8. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? JAMA. 1988; 259(2):225–228. [PubMed: 3336140]

9. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. Hypertension. 2002; 40(6):795–796. [PubMed: 12468559]

10. Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, Gheeraert PJ, Missault LH, Braun JJ, Six RO, et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. N Engl J Med. 2003; 348(24):2407–2415. [PubMed: 12802026]

11. Lovibond K, Jowett S, Barton P, Caulfield M, Heneghan C, Hobbs FD, Hodgkinson J, Mant J, Martin U, Williams B, et al. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. Lancet. 2011; 378(9798):1219–1230. [PubMed: 21868086]

12. Fukunaga H, Ohkubo T, Kobayashi M, Tamaki Y, Kikuya M, Obara T, Nakagawa M, Hara A, Asayama K, Metoki H, et al. Cost-effectiveness of the introduction of home blood pressure measurement in patients with office hypertension. J Hypertens. 2008; 26(4):685–690. [PubMed: 18327077]

13. Funahashi J, Ohkubo T, Fukunaga H, Kikuya M, Takada N, Asayama K, Metoki H, Obara T, Inoue R, Hashimoto J, et al. The economic impact of the introduction of home blood pressure measurement for the diagnosis and treatment of hypertension. Blood Press Monit. 2006; 11(5):257–267. [PubMed: 16932035]

14. Soghikian K, Casper SM, Fireman BH, Hunkeler EM, Hurley LB, Tekawa IS, Vogt TM. Home blood pressure monitoring. Effect on use of medical services and medical care costs. Med Care. 1992; 30(9):855–865. [PubMed: 1518317]

15. Staessen JA, Den Hond E, Celis H, Fagard R, Keary L, Vandenhoven G, O'Brien ET. Antihypertensive treatment based on blood pressure measurement at home or in the physician's office: a randomized controlled trial. JAMA. 2004; 291(8):955–964. [PubMed: 14982911]

16. Padfield PL. The case for home monitoring in hypertension. BMC medicine. 2010; 8:55. [PubMed: 20875117]

17. Imai Y, Otsuka K, Kawano Y, Shimada K, Hayashi H, Tochikubo O, Miyakawa M, Fukiyama K. Japanese Society of H. Japanese society of hypertension (JSH) guidelines for self-monitoring of blood pressure at home. Hypertension research : official journal of the Japanese Society of Hypertension. 2003; 26(10):771–782. [PubMed: 14621179]

18. Cappuccio FP, Kerry SM, Forbes L, Donald A. Blood pressure control by home monitoring: meta-analysis of randomised trials. Bmj. 2004; 329(7458):145. [PubMed: 15194600]

19. Parati G, Stergiou GS, Asmar R, Bilo G, de Leeuw P, Imai Y, Kario K, Lurbe E, Manolis A, Mengden T, et al. European Society of Hypertension practice guidelines for home blood pressure monitoring. Journal of human hypertension. 2010; 24(12):779–785. [PubMed: 20520631]

20. Krakoff LR, Eison H, Phillips RH, Leiman SJ, Lev S. Effect of ambulatory blood pressure monitoring on the diagnosis and cost of treatment for mild hypertension. Am Heart J. 1988; 116(4):1152–1154. [PubMed: 3177190]

21. Yarows SA, Khoury S, Sowers JR. Cost effectiveness of 24-hour ambulatory blood pressure monitoring in evaluation and treatment of essential hypertension. Am J Hypertens. 1994; 7(5): 464–468. [PubMed: 8060582]

22. Pierdomenico SD, Mezzetti A, Lapenna D, Guglielmi MD, Mancini M, Salvatore L, Antidormi T, Costantini F, Cuccurullo F. 'White-coat' hypertension in patients with newly diagnosed hypertension: evaluation of prevalence by ambulatory monitoring and impact on cost of health care. Eur Heart J. 1995; 16(5):692–697. [PubMed: 7588903]

23. Aitken L, Addison C. The cost-effectiveness of ambulatory blood pressure monitoring. Prof Nurse. 1996; 12(3):198–202. [PubMed: 9128668]

24. Staessen JA, Byttebier G, Buntinx F, Celis H, O'Brien ET, Fagard R. Antihypertensive treatment based on conventional or ambulatory blood pressure measurement. A randomized controlled trial. Ambulatory Blood Pressure Monitoring and Treatment of Hypertension Investigators. JAMA. 1997; 278(13):1065–1072. [PubMed: 9315764]

25. Ewald B, Pekarsky B. Cost analysis of ambulatory blood pressure monitoring in initiating antihypertensive drug treatment in Australian general practice. Med J Aust. 2002; 176(12):580–583. [PubMed: 12064956]

26. Lorgelly P, Siatis I, Brooks A, Slinn B, Millar-Craig MW, Donnelly R, Manning G. Is ambulatory blood pressure monitoring cost-effective in the routine surveillance of treated hypertensive patients in primary care? Br J Gen Pract. 2003; 53(495):794–796. [PubMed: 14601356]

27. Krakoff LR. Cost-effectiveness of ambulatory blood pressure: a reanalysis. Hypertension. 2006; 47(1):29–34. [PubMed: 16344364]

28. Rodriguez-Roca GC, Alonso-Moreno FJ, Garcia-Jimenez A, Hidalgo-Vega A, Llisterri-Caro JL, Barrios-Alonso V, Segura-Fragoso A, Clemente-Lirola E, Estepa-Jorge S, Delgado-Cejudo Y, et al. Cost-effectiveness of ambulatory blood pressure monitoring in the follow-up of hypertension. Blood Press. 2006; 15(1):27–36. [PubMed: 16492613]

29. Yarows SA, Julius S, Pickering TG. Home blood pressure monitoring. Arch Intern Med. 2000; 160(9):1251–1257. [PubMed: 10809027]

30. 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. 2011; 342:d3621. [PubMed: 21705406]

31. Rasmussen SL, Torp-Pedersen C, Borch-Johnsen K, Ibsen H. Normal values for ambulatory blood pressure and differences between casual blood pressure and ambulatory blood pressure: results from a Danish population survey. Journal of hypertension. 1998; 16(10):1415–1424. [PubMed: 9814611]

32. O'Brien E, Murphy J, Tyndall A, Atkins N, Mee F, McCarthy G, Staessen J, Cox J, O'Malley K. Twenty-four-hour ambulatory blood pressure in men and women aged 17 to 80 years: the Allied Irish Bank Study. J Hypertens. 1991; 9(4):355–360. [PubMed: 1646262]

33. Wiinberg N, Hoegholm A, Christensen HR, Bang LE, Mikkelsen KL, Nielsen PE, Svendsen TL, Kampmann JP, Madsen NH, Bentzon MW. 24-h ambulatory blood pressure in 352 normal Danish

subjects, related to age and gender. Am J Hypertens. 1995; 8(10 Pt 1):978–986. [PubMed: 8845079]

34. Schettini C, Bianchi M, Nieto F, Sandoya E, Senra H. Ambulatory blood pressure: normality and comparison with other measurements. Hypertension Working Group. Hypertension. 1999; 34(4 Pt 2):818–825. [PubMed: 10523367]

35. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. JAMA. 1999; 282(6):539–546. [PubMed: 10450715]

36. Verdecchia P. Prognostic value of ambulatory blood pressure : current evidence and clinical implications. Hypertension. 2000; 35(3):844–851. [PubMed: 10720605]

37. Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. N Engl J Med. 2006; 354(22):2368–2374. [PubMed: 16738273]

38. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Menard J, Mallion JM. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA. 2004; 291(11):1342–1349. [PubMed: 15026401]

39. Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Kikuya M, et al. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. J Hypertens. 1998; 16(7):971–975. [PubMed: 9794737]

40. Verberk WJ, Kroon AA, Kessels AG, de Leeuw PW. Home blood pressure measurement: a systematic review. Journal of the American College of Cardiology. 2005; 46(5):743–751. [PubMed: 16139119]

41. 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(5):697–716. [PubMed: 15699287]

42. Rafey M. Beyond office sphygmomanometry: ways to better assess blood pressure. Cleveland Clinic journal of medicine. 2009; 76(11):657–662. [PubMed: 19884295]

43. Bidlingmeyer I, Burnier M, Bidlingmeyer M, Waeber B, Brunner HR. Isolated office hypertension: a prehypertensive state? Journal of hypertension. 1996; 14(3):327–332. [PubMed: 8723986]

		AVERAGE OUT-OF-CLINIC BLOOD PRESSURE STATUS*	
		Hypertensive (Should be treated)	**Normal** (Should NOT be treated)
CLINIC BLOOD PRESSURE	>140/90 mmHg	**Sustained hypertension** "True Positive"	**White coat hypertension‡** "False Positive"
	≤140/90 mmHg	**Masked hypertension†** "False Negative"	**Sustained Normotension** "True Negative"

Figure 1.
Misclassification of Hypertension Status

*Typically defined as the average blood pressure during awake hours. ABPM is usually viewed as the gold standard to reflect the average out-of-clinic blood pressure status.

†Masked hypertension carries higher risk for future cardiovascular events from untreated hypertension[10]

‡ White coat hypertension results in unnecessary treatment costs and risk for adverse effects. They constitute ~20% of newly diagnosed hypertensive patients [8] with 10% per year progression rate to sustained hypertension [43]

Table 1

Summary of Studies Meeting Eligibility Criteria

Study	Year	Country	Study Population	Study Design	Modality Compared	Time Horizon	Main Findings
Studies comparing ABPM to CBP							
				Trials & Observational Studies			
Krakoff [20]	1988	USA	Patients referred for management of hypertension, diagnosed on 2+ occasions (N=60). Age 18–68 y	Observational Study; Case series	ABPM vs. CBP	5 years	ABPM is $100 ($191 in 2011 dollars) cost-saving compared to CBP over 5 years.
Yarows [21]	1994	USA	Patients being assessed for hypertension control in a single practice (N=192). Mean age 61 y (intervention) & 54 y (control).	Observational Study; patient Survey	ABPM vs. CBP	1 year	The fee for ABPM that would offset the savings of antihypertensive therapy if no treatment was used for patients with elevated CBP and normal ABP was $188 ($325 in 2011 dollars).
Pierdimenico [22]	1995	Italy	Untreated, newly diagnosed patients with arterial hypertension (N=255) in a secondary referral center. Age range 33–65 y.	Observational Study	ABPM (every 2y for untreated patients, every 1y for white coat hypertensive s) vs. CBP	6 years	ABPM resulted in net saving of $110,819 (untreated, $172,878 in 2011 dollars) & $100,348 (white coat hypertensives, $156,542 in 2011 dollars) compared to CBP alone.
Aitken [23]	1996	UK	Patients referred for ABPM as a result of elevated CBP (N=69). Mean age 50 y.	Observational Study	ABPM vs. CBP	2 years	ABPM is cost-saving by £381 ($857 in 2011 US dollars) compared with CBP over 2 years.
Staessen [24]	1997	Belgium	Adults with average clinic diastolic BP >= 95 mmHg (N=419). Mean age 51.3 y in CBP arm; 53.8 y in ABPM arm.	Randomized Clinical Trial	ABPM vs. CBP	1 year	No difference in cost ($5366 ($7,566 in 2011 dollars) in ABPM arm vs. $5194 ($7,479 in 2011 dollars) in CBP arm) at one month.
Lorgelly [26]	2003	UK	Treated hypertensive patients attending a nurse-led cardiovascular risk reduction clinic (N=374). Aged range 50–70 y	Observational study	ABPM vs. CBP	1 year	Compared to CBP alone, adding ABPM increased rates of adequate hypertension control at £31 ($57 in 2011 US dollars) per patient.
Rodriguez-Roca [28]	2006	Spain	Patients previously diagnosed with hypertension by repeated CBP (N=266). Age range 17–91 y.	Cross-sectional Study	ABPM vs. CBP	1 year	Average cost per patient with well controlled hypertension is almost four times higher with CBP than ABPM (€40 ($1,169) vs. €238 ($296)), resulting in €15 ($143 in 2011 US dollars) per additional well-controlled case achieved.
				Model-based or Hybrid Studies			

Study	Year	Country	Study Population	Study Design	Modality Compared	Time Horizon	Main Findings
Ewald [25]	2002	Australia	Newly diagnosed hypertensive adults based on CBP (N=100 simulated based on 62 real patients).	Model informed by small patient cohort	ABPM- (1)Annual, (2) biennial, and (3) Triennial vs. CBP	7 years	Cost-saving of $23 ($29 in 2011 dollars) in strategy 1, $35 ($44 in 2011 dollars) in strategy 2, and $40 ($50 in 2011 dollars) in strategy 3 per patient per year compared with No ABPM.
Krakoff [27]	2006	US	Patients newly categorized as hypertensive based on CBP (N=1000).	Simulation Model	ABPM vs. CBP	5 years	Expected 3–14% ($45,322–$210,024 in 2011 US dollars) cost savings and 10–23% reduction in treated person-days when adding ABPM to CBP.
Studies comparing HBPM to CBP							
				Trials & Observational Studies			
Soghikian [14]	1992	USA	Patients with uncomplicated hypertension from 4 medical centers in Northern California (N=430). Mean age 54.2 y.	Clinical Trial	HBPM vs. CBP	1 year	Cost of hypertension care per patient in the HBPM arm was $116.59 ($240 in 2011 dollars) -- 6% less than in the CBP group.
Staessen [15]	2004	Belgium Ireland	Patients with clinic diastolic BP >= 95 mmHg (N=400). Average age 53.4 y.	Clinical Trial	HBPM vs. CBP	1 year	Costs per 100 patients followed up for 1 month were only slightly lower in the HBPM group, €875 ($4805 in 2011 US dollars) vs. €473 ($5547 in 2011 US dollars).
				Model-based or Hybrid Studies			
Funahashi [13]	2006	Japan	Adults >= 30y living in Japan (N=85,750,000).	Decision Tree Model	HBPM vs. CBP	1 year	Break-even cost for using HBPM in 22.9 million hypertensive individuals: $409 ($511 in 2011 US dollars) per person.
Fukunaga [12]	2008	Japan	Subjects initially diagnosed as hypertensive based on screening CBP (N=1000).	Markov Model	HBPM vs. CBP	5 years	Break even cost for introducing HBPM is $1562/year ($1749 in 2011 US dollars) when prevalence of WCHT is 16.5% and annual incidence of new HTN is 7.4%
Studies comparing CBP, HBPM and ABPM							
Lovibond [11]	2011	UK	Hypothetical primary care population with clinic BP >=140/90 mmHg. Age 40+ y.	Markov Cohort Model	ABPM, HBPM, CBP	60 years	ABPM is cost saving for all groups (from –£56 ($90 in 2011 US dollars) in men aged 75+ y to –£323 ($519 in 2011 US dollars) in women aged 40 y) and resulted in more QALYs for men and women older than 50 y.