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Relationship Between Outpatient Clinic and Ambulatory Blood Pressure Measurements and Mortality

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Abstract

Purpose of Review This review aims to summarize and discuss the relationship between outpatient clinic and ambulatory blood pressure (BP) measurements and cardiovascular morbidity and mortality.

Recent Findings Contemporary clinical practice guidelines worldwide recommend ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension. Recent epidemiological studies and systematic reviews showed ABPM predicts cardiovascular events and mortality independent of clinic BP. Ambulatory BP appears to be prognostically superior to clinic BP.

Summary ABPM characterizes BP phenotypes that would not have otherwise identified with clinic BP measurement only. Identification of white coat hypertension, which carries a prognosis almost similar to normotension, and masked hypertension, which carries a prognosis almost similar to sustained hypertension, can be accomplished only by ABPM. Randomize controlled trials to assess the cardiovascular effects of hypertensive patients managed with ABPM vs. clinic BP measurement and cost-effective studies of ABPM are warranted.

Keywords Ambulatory blood pressure monitoring · Hypertension · Cardiovascular diseases · Mortality · White coat hypertension · Masked hypertension

Introduction

Current clinical practice guidelines in North America [1••, 2••, 3••], Europe [4, 5••], Australia [6••], and Asia [7] recommend using ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension in people with suspected hypertension. The recently published guidelines of the European Society of Cardiology and the European Society of Hypertension for management of arterial hypertension [5••] include specific clinical indications for out-of-office blood pressure measurement. Notably, there are two class I recommendations: (a) The diagnosis of hypertension should be based on repeated clinic blood pressure (BP) measurements on more than one visit, except when hypertension is severe, or out-of-office BP measurement with ABPM and/or home blood pressure monitoring if logistically and economically feasible and (b) ABPM or HBPM is recommended for identifying white coat and masked hypertension, quantifying the effects of treatment, and identifying possible causes of side effects such as symptomatic hypotension.

ABPM is more accurate than clinic and home monitoring in diagnosing hypertension because of multiple measurements [8]. In addition, absence of digit preference, absence of observer bias, and lack of white coat effect all contribute to improved accuracy of ambulatory over clinic BP. Utilization of ABPM is expected to reduce unnecessary treatment in people who do not have true hypertension.

Diagnosis and treatment of hypertension has been both historically and currently based largely upon outpatient clinic BP measurement. Variability of BP throughout the day has been well recognized. The advent of non-invasive ABPM about 40 years ago led to identification of white coat hypertension, a phenomenon where individuals have elevated BP during clinic visits yet their ambulatory BP measurements

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remain within normal range, as a distinct phenotype with a unique prognosis in terms of cardiovascular outcomes. Subsequently, another distinct phenotype called masked hypertension was also identified. Masked hypertension is essentially the reverse phenomenon of white coat hypertension, in which BP measurements are within normal range during clinic visits but elevated with ambulatory BP measurements. Classification of individuals on the basis of their clinic and ambulatory BP measurements has an important bearing on formulation of management strategy and prognostication. Four major phenotypes thus emerged as a result of ambulatory BP measurement: (1) sustained normotension, (2) white coat hypertension, (3) masked hypertension, and (4) sustained hypertension.

White Coat Hypertension

One of the major benefits of utilization of ABPM in diagnosis of hypertension is identification of white coat hypertension. White coat hypertension is defined as clinic BP ≥ 130/80 mmHg but < 160/100 mmHg after a 3-month trial of life style modification, and daytime ABPM BP < 130/80 mmHg [1••]. The prevalence of white coat hypertension is reported between 13 and 35% [9, 10]. Many studies demonstrated only a minimal increase in risk of cardiovascular complications or all-cause mortality in individuals with white coat hypertension, leading to some expert panels recommending screening for white coat hypertension with ABPM to minimize the possibility of initiating antihypertensive therapy to a population with an only slightly higher health risk if there is any risk at all.

A population-based cohort study in Italy [11] demonstrated a progressive increase in the risk of cardiovascular mortality in people with white coat hypertension and sustained hypertension during a 16-year follow-up (1% vs. 5% vs. 13%, hazard ratio (HR) 2.04 [0.87–4.78]; $p = 0.099$, and HR 2.94 [1.32–6.57]; $p = 0.008$), compared with normotensive individuals, adjusted for potential confounders. The confounders adjusted were age, gender, blood glucose, total serum cholesterol, smoking, previous cardiovascular events, antihypertensive treatment, and body mass index. A significant increase in adjusted risk for all-cause mortality was also found in either group (6% vs. 20% vs. 30%, HR 1.50 [1.03–2.18]; $p = 0.034$, and HR 1.47 [1.02–2.14]; $p = 0.042$). In these data, white coat hypertension was defined as elevated clinic BP (SBP ≥ 140 mmHg SBP or DBP ≥ 90 mmHg) and a normal 24-h mean (< 125/79 mmHg) or home BP (< 132/83 mmHg). When the definition of white coat hypertension was tightened with the use of ABPM as "true" white coat hypertension, defined by a clinic BP elevation and normal ABPM and home BP, the increase in adjusted risk for all-cause mortality has lost its statistical significance.

A recent retrospective cohort study from a registry-based cohort in Spain [12••] demonstrated that individuals with white coat hypertension had higher risk for cardiovascular mortality (HR 1.96 [1.22–3.15]; $p = 0.005$) and all-cause mortality (HR 1.79 [1.38–2.32]; $p < 0.001$), adjusted for potential confounders. The confounders adjusted were adjusted for age, sex, smoking status, body mass index, and status with respect to diabetes, dyslipidemia, previous cardiovascular disease, number of antihypertensive drugs used, and clinic systolic blood pressure (SBP) and diastolic blood pressure (DBP). White coat hypertension in this study was defined as (clinic SBP ≥ 140 mmHg or DBP ≥ 90 mmHg and 24-h SBP < 130 mmHg and DBP < 80 mmHg).

The difference in risk of cardiovascular and all-cause mortality in the most recent cohort study from previous studies could be due to the difference in defining white coat hypertension.

Masked Hypertension

Another benefit of using ABPM for diagnosis of hypertension is identification of masked hypertension, normal clinic BP measurements with elevated ambulatory or home BP measurement. Masked hypertension is defined as clinic BP of 120–129 mmHg/< 80 mmHg after a 3-month trial of lifestyle modification and consistently elevated daytime BP (≥ 130 mmHg/80 mmHg) on home BP monitoring or ABPM for adults not on drug therapy [1••]. The prevalence of masked hypertension varies between 9 and 54% in registries and population-based studies from different regions of the world [13, 14, 15••]. Although the definitions used to identify masked hypertension varied across the studies, the cut-off used by most of them was clinic BP < 140/90 and ambulatory BP ≥ 135/85 mmHg. A systematic review of 70 cross-sectional observational studies [16•] reported that male gender, current smoking, and increasing body mass index each associated with increased risk of masked hypertension. In addition, a recent cohort study [17•] found that the cumulative incidence of masked hypertension was associated with male gender, older age, higher education, body mass index, smoking, and alcohol intake. Another study [18•] demonstrated that prevalence of masked hypertension was higher in obese individuals. Unlike white coat hypertension, masked hypertension is clearly associated with a higher cardiovascular and all-cause mortality risk, and its risk is almost similar to that of sustained hypertension in some studies. Findings from high-quality contemporary studies within last 5 years are summarized below.

In a participant-level meta-analysis of over 8000 participants from 12 different populations enrolled in the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes [13], the risk of cardiovascular end points including cardiovascular mortality associated with masked hypertension was approximately 1.6–1.8 times higher ($p < 0.0001$) than normotensive population, irrespective of the definition of normotension used. When applying the most stringent definition of normotension as normal conventional BP and normal ambulatory BP for 24 h plus daytime and nighttime, the risk excess was approximately 76% (HR 1.76 [1.39–2.22]; $p < 0.0001$). The HR was were adjusted for sex, age, body mass index, smoking, drinking, total cholesterol, diabetes mellitus, history of cardiovascular disease, and cohort. On the other hand, the risk of cardiovascular endpoints, including cardiovascular mortality, associated with masked hypertension was approximately a third to two-fifths lower ($p < 0.0001$) than sustained hypertensive population, irrespective of the definition of hypertension used. On the other hand, when applying the most stringent definition of hypertension as conventional BP was over the threshold and the ambulatory BP over the thresholds for 24 h plus daytime and nighttime, the risk of masked hypertension was lower than that of sustained hypertension (HR 0.63 [0.50–0.78]; $p \leq 0.001$). However, masked hypertension was associated with an increased risk of all-cause mortality when using stringent definitions of hypertension, 24 h plus nighttime (HR 1.27 [1.04–1.55]; $p < 0.05$) or 24 h plus daytime and nighttime (HR 1.25 [1.03–1.52]; $p < 0.05$).

Analysis of the International Database of HOme blood pressure in relation to Cardiovascular Outcomes (IDHOCO), constructed from over 6000 participants from 5 populations with the median follow-up of 8 years, revealed that the risk of cardiovascular events in treated and untreated masked hypertension was higher than that of normotensive population (HR 1.55 [1.12–2.14]; $p = 0.008$ for untreated masked hypertension; HR 1.76 [1.23–2.53]; $p = 0.0082$ for treated masked hypertension) [19]. HRs were adjusted for cohort, sex, age, body mass index, serum cholesterol, smoking status, cardiovascular disease history, and diabetes mellitus. Participants with both untreated and treated masked hypertension had higher risk of all-cause mortality than that of normotensive individuals ($p \leq 0.031$).

Analysis of data from the Spanish Ambulatory Blood Pressure Registry [12••] showed that masked hypertension was associated with a higher cardiovascular mortality (HR 2.85 [1.66–4.90]; $p < 0.001$) and all-cause mortality (HR 2.83 [2.12–2.79]; $p < 0.001$) than normotensive population. The confounders adjusted in this study were noted in the section of white coat hypertension above.

Isolated Nocturnal Hypertension

Isolated nocturnal hypertension (INH) is another unique phenotype that could be identified by the ABPM, but not by clinic BP measurement. It is defined as nighttime without daytime hypertension on ABPM. It was first identified in a Chinese cohort of over 600 participants enrolled in the JingNing population study [20]. The prevalence of INH in this study was reported as approximately 11%, using the definition of BP > 120/70 mmHg from 10:00 pm to 4:00 am. Only 5% of the participants with INH had elevated clinic BP in this cohort study, underscoring the value of ABPM, which is the only mean by which a diagnosis of INH can be made. Its prevalence is reportedly higher (~ 20%) in individuals with chronic kidney disease (CKD) [21] and its presence is correlated with target-organ damage in CKD population.

Nighttime BP predicted total, cardiovascular, and non-cardiovascular mortality when adjusted for daytime BP in the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) [22]. When adjusted for nighttime BP, daytime BP only predicted non-cardiovascular mortality. Systolic nighttime BP was a stronger predictor of total mortality (HR 1.16 [1.12–1.22]; $p < 0.001$) and all cardiovascular events (HR 1.19 [1.12–1.27]; $p < 0.001$) than systolic daytime BP in hypertensive patients as well as in individuals randomly selected from populations in Asia, Europe, and South America [23]. However, analysis of the Spanish Ambulatory Blood Pressure Registry [12••] revealed that both nighttime BP and daytime BP were predictive total and cardiovascular mortality, and that nighttime BP was no more predictive than daytime BP.

In a multivariate adjusted analysis of the data from over 8000 participants from three continents in the IDACO database [24], INH was associated with a higher risk of all cardiovascular events (HR 1.38 [1.02–1.87]; $p = 0.037$) and total mortality (HR 1.29 [1.01–1.65], $p = 0.045$). Potential confounders adjusted include sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, and diabetes mellitus.

Nondipping Pattern

The average nighttime BP is approximately 15% lower than daytime BP in both normotensive and hypertensive individuals. Failure of the BP to drop by at least 10% percent during sleep is called nondipping pattern [25]. A reverse-dipping BP pattern refers to a phenomenon where the average nighttime BP is higher than daytime BP. It has been considered a variant of nondipping pattern.

Nondippers could have worse cardiovascular outcomes than dippers. ABPM-derived mean BP levels and nondipping pattern are also more closely associated with target-organ damage and worsened cardiovascular outcomes than clinic BP levels in patients with essential hypertension [26, 27]. A recent analysis of a large cohort of over 6000 participants, with an average follow-up period of 10 years [28••], revealed that masked hypertension with reverse-dipping pattern was associated with a higher risk of stroke (odds ratio (OR) 18.660 [1.056–33.813]; $p = 0.046$) in multivariate analysis, adjusted for gender, age, body mass index, smoking status, hypercholesterolemia, and diabetes. In another cohort study with over 2000 participants, nondipping and reverse-dipping patterns were associated with a higher risk of new-incident lacunar infarcts and new microbleeds than dippers in community-based older adults during an average 5-year follow-up [29•].

Nocturnal dipping can be potentially improved by administering the antihypertensive medications in the night. The need for simpler methods to identify dipping status and treatment strategies to improve dipping status have been proposed [30]. Reduction in microalbuminuria has been demonstrated when dipping pattern was restored by administering antihypertensive medication at bedtime [31–33]. The prospective MAPEC study [34] was an open-label, single-center, randomized controlled trial specifically designed to test the hypothesis that bedtime administration of at least one antihypertensive medication would lead to better BP control and CVD risk reduction than morning administration. Individuals who received medication at bedtime had a lower frequency of nondipping (34% vs. 62%; $p < 0.001$) and a higher frequency of controlled ambulatory BP (62% vs. 53%; $p < 0.001$). After a median follow-up of about 6 years, the group which received bedtime medication demonstrated a lower risk of total cardiovascular events than those ingesting all medications in the morning (RR 0.39 [0.29–0.51]; $p < 0.001$). Large, multicenter, randomized double-blind controlled trials are warranted to evaluate whether the improvement of cardiovascular outcomes in the MAPEC study is generalizable.

Ambulatory Blood Pressure and Mortality

A recent systematic review [10] of predictive accuracy of BP screening methods found that systolic 24-h ABPM predicted fatal and nonfatal cardiovascular events and stroke independently of clinic BP measurement. However, association of ABPM with cardiac events and all-cause mortality was somewhat variable. The retrospective cohort study referenced above for white coat hypertension [12••] showed that elevated 24-h ambulatory BP has greater association with mortality than elevated clinic BP. Each increase in ambulatory SBP of 1 standard deviation (14 mmHg) was associated with increased cardiovascular mortality (HR 1.58 [1.56–1.60]; $p < 0.001$) and all-cause mortality (HR 1.58 [1.56–1.60]; $p < 0.001$). However, each increase in clinic SBP of 1 standard deviation (19 mmHg) was associated only with increased all-cause mortality (HR 1.02 [1.00–1.04]; $p = 0.04$). The increased cardiovascular mortality with each increase in clinic SBP of 1 standard deviation did not reach the level of statistical significance (HR 1.02 [1.00–1.04]; $p = 0.08$). Further, a prospective study of individuals with type 2 diabetes in Brazil [35] found that ambulatory SBP was associated with both fatal or nonfatal cardiovascular events and all-cause mortality whereas clinic SBP was associated only with fatal or nonfatal cardiovascular events. These findings are consistent with the results of previous cohort studies from different regions of the world showing ABPM is better correlated with the risk of cardiovascular events than clinic BP [36–41].

In actively treated elderly hypertensives participating in the Second Australian National Blood Pressure study, all-cause or cardiovascular mortality were significantly related to pretreatment ambulatory BP, particularly to nocturnal SBP (HR 1.26 [1.10–1.45]; $p = 0.001$) and pulse pressure (HR 1.18 [1.06–1.31]; $p = 0.003$), but not to clinic BP over long-term (~11 years) follow-up [42••].

Analysis of data from over 7000 participants in the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes [43•] showed no differences in predicted risks when comparing clinic BP and ambulatory BP. The median difference in 10-year risks (1st; 3rd quartile) was −0.01% (−0.3%; 0.1%) for cardiovascular mortality and −0.1% (−1.1%; 0.5%) for cardiovascular events.

It is crucial to appreciate the absolute difference in magnitude of improvement in morality predictive value by using ambulatory BP, in addition to clinic BP. Banegas et al. [44••] further analyzed the data from the ambulatory BP registry [12••] by comparing the absolute risk of cardiovascular mortality for each study participant, using estimates from a model that included cardiovascular risk factors, 24-h ambulatory SBP, and clinic SBP with the risk estimated using the same model without ambulatory SBP. The median absolute risk difference among all the participants during nearly 5-year follow-up was 0.1% (interquartile range, −0.3 to 0.9). It is noteworthy that 14% of all participants had a difference of more than 2% cardiovascular mortality risk, and among these 14%, the absolute cardiovascular mortality was 2.3%. Thus, improvement in cardiovascular mortality predictive value by using ambulatory BP appears to be substantial.

Overall, association between ambulatory BP with cardiovascular events and mortality is rather consistent but its association with all-cause mortality is variable across different studies.

Ambulatory Blood Pressure in Assessing Response to Therapy

The ABPM has a great potential of utility to assess response to antihypertensive therapy although contemporary guidelines give more emphasis on its use in confirmation of diagnosis. Some but not all guidelines also recommend using ABPM to assess the response to therapy. For example, Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines recommend considering ABPM when a clinic-induced elevation in BP (white coat effect) is suspected in treated patients with BP that continues to be above the target despite receiving appropriate chronic antihypertensive therapy, when symptoms suggestive of hypotension are present, or when fluctuating clinic BP readings are observed [3••]. The recommendations from various professional organizations across the world are summarized in Table 1.

As discussed under previous sections, it has been increasingly recognized that nighttime BP is a better of adverse cardiovascular outcomes than daytime BP, it would make sense to aim antihypertensive therapy to achieve BP reduction throughout the 24-h period, and more importantly nighttime, which can be assessed only by using ABPM. It has been proposed to repeat ABPM within 2 to 3 weeks after initiation of antihypertensive therapy to determine whether adequate reduction has been achieved, including reduction of nocturnal BP and return to normal nocturnal dipping pattern [45••]. It has been further proposed to repeat ABPM at 2–3-week intervals, if additional adjustment of antihypertensive therapy is necessary, until a desired control is achieved. Results of the ambulatory blood pressure substudy of the Anglo-Scandinavian cardiac outcomes trial demonstrated that a 1 SD increase in nocturnal SBP increased the likelihood of a cardiovascular event after adjustment for clinic SP by 26% [46], supporting the use of ABPM in assessing effectiveness of antihypertensive therapy. While excessive elevation of nighttime BP imposes an increased risk of adverse cardiovascular outcome, a subset of individuals may be adversely effected by excessive lowering of nighttime BP (extreme dipping) [47], hence another justification for use of ABPM in assessing response to therapy.

An analysis of over 26,000 individual ABPM records from four hypertension centers in Portugal from 1992 to 2015 [48••] found a marked discrepancy between clinic BP and ambulatory BP values. The rates of hypertension control on ABPM are more than double those on clinic BP, underpinning the importance of ABPM in assessing BP control. Further, a recent meta-analysis of 52 randomized controlled trials with more than 9000 participants from five continents found that overall treatment-induced BP reduction is markedly greater for clinic BP than for 24-h BP [49••]. These findings underscore the need to consider the differences in BP reductions by treatment as monitored by clinic vs. ambulatory BP measurements.

These proposals and justifications are based upon various hypertension phenotypes and their unique cardiovascular risks. However, there are no randomized controlled trials assessing the benefits of using ABPM to monitor antihypertensive therapy to aim specific target of nocturnal BP. Such clinical trials will further refine the benefits of ABPM and determine whether widespread clinical utility of ABPM to assess effectiveness of therapy is indeed warranted.

Conclusion

Ambulatory BP appears to be a better indicator of cardiovascular risk compared with clinic BP. In addition to confirming the diagnosis of hypertension in people with elevated BP, it is crucial in distinguishing BP phenotypes. Specifically, identification of white coat hypertension and masked hypertension with ABPM is invaluable since cardiovascular risk of the former is almost the same as or slightly higher than normotension, and that of the latter is remarkably higher than normotension.

ABPM-based clinical algorithms could minimize the frequency of overtreating white coat hypertension and undertreating masked hypertension. ABPM is a significant addition to careful clinic BP measurement in diagnosis of hypertension and perhaps in managing antihypertensive therapy. Nevertheless, most physicians still have to rely on clinic BP measurement for both diagnosis of hypertension and monitoring therapy. ABPM is not available in most outpatient clinics. Multiple factors are responsible for limited availability of such a crucial tool in

Table 1 Recommendations of using ABPM in contemporary clinical practice guidelines

Guideline	Confirmation of diagnosis	Monitoring therapy
ACC/AHA [1••]	Yes	No
USPSTF [2••]	Yes	N/A
Hypertension Canada [3••]	Yes	Yes
UK NICE [4]	Yes	Yes
European Society of Cardiology/European Society of Hypertension [5••]	Yes	Yes
National Heart Foundation of Australia [6••]	Yes	No
Japanese Society of Hypertension [7]	Yes	Yes

identification of multiple phenotypes of hypertension associated with cardiovascular risk. Some of these factors include cost, minimal reimbursement by third-party payers, perceived patient inconvenience, and limited dissemination of information on its utility. In the USA, the expense of ABPM and the limited reimbursement by Medicare and commercial insurance carriers have limited the widespread use of ABPM in day-to-day practice [50•]. Although majority of ABPM procedures for Medicare beneficiaries with suspected white coat hypertension are reimbursed if the ICD-9 diagnosis code of 796.2 (elevated blood pressure without diagnosis of hypertension) is included on the claim, reimbursement amounts are generally below the cost of the procedure [51], which may be prohibitive of utilization of ABPM. In a Markov model-based probabilistic cost-effectiveness analysis applied to the health care system in the UK [52], ABPM was found to be the most cost-effective strategy for the diagnosis of hypertension for men and women of all ages, after an initial elevated BP reading in primary care setting by reducing the misdiagnosis of hypertension. Additional costs of ABPM are counterbalanced by cost savings from better targeted treatment. Future randomized controlled trials assessing cardiovascular outcomes in patients diagnosed and treated using ABPM compared to clinic BP measurement and cost-effective analysis in different health care systems will be critical for the policy makers in establishing reimbursement standards.

At this time, the US Preventive Services Task Force (USPSTF) has established a research plan for screening high blood pressure in adults to be used to guide a systematic review of the evidence by researchers at an Evidence-based Practice Center. Among the key questions related to clinic and ambulatory BP measurement to be systematically reviewed include: (a) What is the accuracy of confirmatory blood pressure measurement in adults who initially screen positive for high blood pressure compared with the reference standard (ABPM)? and (b) What confirmation protocol characteristics define the best diagnostic accuracy? [53•]. The UK NICE Guidelines for Hypertension also recommend future research to answer the question on whether use of ABPM improves response to treatment [4]. The answers to these key questions will further refine the role of ABPM in future clinical practice.

Compliance with Ethical Standards

Conflict of Interest KoKo Aung and Thwe Htay declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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