



TITLE: Utility of Ambulatory Blood Pressure Monitoring

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UTILITY OF AMBULATORY BLOOD PRESSURE MONITORING IN CLINICAL PRACTICE

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of ambulatory blood pressure monitoring (ABPM) in clinical practice. The review will focus primarily on the risks and benefits associated with using ABPM to diagnose white-coat hypertension (WCH). Other topics, such as improved prediction of future cardiovascular events and the use of ABPM to guide antihypertensive therapy, will be discussed, but not reviewed in detail because of the limited data available for assessment.

BACKGROUND

Hypertension

Elevated blood pressure is a common, independent risk factor for stroke, coronary heart disease (CHD), congestive heart failure and kidney disease. The risk relationship is progressive and graded throughout the range of blood pressure including the “normal” range (MacMahon *et al.* 1990; Chobanian *et al.* 2003). Risk approximately doubles for each increase of 20/10 mm Hg beginning at 115/75 mm Hg (Vasan *et al.* 2001a; Lewington *et al.* 2002). About 25% of all American adults (> 50 million people) have hypertension, defined as a systolic blood pressure (SBP) \geq 140 mm Hg and or a diastolic blood pressure (DBP) \geq 90 mm Hg. Risk increases with age- over 50% of Americans 60 years and older have hypertension (Stamler *et al.* 1993; Burt *et al.* 1995). The lifetime risk of hypertension is greater than 90%, even for people without hypertension at age 55 (Vasan *et al.* 2002).

A substantial body of literature documents, with randomized clinical trials, that drug therapy to lower blood pressure prevents stroke, CHD and heart failure (Collins *et al.* 1990; Kostis *et al.* 1997). All of the clinical trials with clinical endpoints identified patients for randomization using office blood pressure measurements.

The relationship between blood pressure and future events has been based on office blood pressure readings. However, office blood pressure measurement is often imprecise. In order to minimize errors and variability, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood pressure (JNC) recommends a standard protocol for measurement of blood pressure in the office. The patient should be seated in a chair with arm supported at heart level. The most recent caffeine, smoking and exercise should be more than 30 minutes prior to measurement. At least two measurements should be made and the average recorded (Chobanian *et al.* 2003).

Table 1 lists the current categorization of blood pressure for adults, as recommended by JNC VII. These categories should reflect the average of at least two office readings following the standard protocol on each of at least two separate visits (Chobanian *et al.* 2003).

TABLE 1. Classification of Blood Pressure (BP) for Adults

BP Classification	SBP mm Hg	DBP mm Hg
Normal	<120	And <80
Prehypertension	120-139	Or 80-89
Stage 1 hypertension	140-159	Or 90-99
Stage 2 hypertension	≥160	Or ≥100

The definition of normal is changing, in part based on the observation that risk of heart attacks, strokes, kidney disease and death is continuous through what was previously considered the normal range of blood pressure. Thus, a person with a blood pressure of 135/85 has twice the risk of cardiovascular disease compared to a patient with a blood pressure of 115/80. Furthermore, investigators estimate that the four-year rate of progression from prehypertension to hypertension ranges from 25% to 50% (Vasan *et al.* 2001b). Based on this data, the latest consensus guidelines recommend non-pharmacologic interventions for all persons with “prehypertension” and consideration of pharmacologic therapy for patients with diabetes or kidney disease (Chobanian *et al.* 2003).

Patient awareness and treatment of hypertension is improving, but is far from optimal. In the United States, awareness of hypertension increased from 51% to 70% between 1980 and 2000. Over the same period, treatment increased from 31% to 59%, but blood pressure targets were achieved in only 34% of patients in 2000 (Chobanian *et al.* 2003).

Ambulatory Blood Pressure Monitoring (ABPM)

Office-based blood pressure monitoring has several limitations, even if measured in accordance with recommended guidelines. Blood pressure fluctuates tremendously within a single day and over time, making accurate classification of an individual’s blood pressure difficult. Furthermore, the blood pressure measured in the office may not represent the usual blood pressure of an individual outside of the medical setting. -ABPM was developed to address some of these issues.

ABPM provides information about blood pressure during a person’s usual daily activities and sleep (Pickering 1996). There is a clear pattern of blood pressure throughout the day. Blood pressure is highest while a person is awake and active, with lower values during rest and sleep. Blood pressure begins to rise in the morning about three hours before awakening, concordant with diurnal variation in cortisol levels (Kario *et al.* 2003). Ambulatory blood pressure (ABP) values are usually lower than office readings. The level of ABPM correlates with measures of organ damage from hypertension better than office measurements (Franklin *et al.* 1997) and is also a more precise predictor of future cardiovascular events (Clement *et al.* 2003).

Devices that measure ABP either use a microphone to measure Korotkoff sounds or a cuff that uses arterial wave forms to calculate blood pressures by algorithms, using oscillometric techniques. The equipment includes the cuff, a small monitor that the patient wears and tubes connecting the monitor to the cuff. A trained technician attaches the device and calibrates the ABPM pressures to those from standard sphygmomanometer readings. Blood pressure is measured and recorded every 15 to 60 minutes throughout a 24-hour period. When the subject returns, the technician downloads data from the monitor for analysis. The final report summarizes maximum, minimum and average determinations for systolic and diastolic blood pressures for the daytime, nighttime and 24-hour intervals.

Current devices are small, about the size of a personal cassette player, light and quiet. Most units recognize arm movements as potentially confounding and reassess the blood pressure several minutes later for more reliable determination. Most units also inflate the cuff to incrementally higher pressures until the systolic peak appears unambiguously. This procedure may result in over-inflations that are painful, distracting or inconvenient. When evaluated in general practice, 49% of patients reported some interference with normal activity and 76% reported some disruption of sleep. Bed partners may also complain of interrupted sleep. There have been some reports of adverse events associated with ABPM, in particular redness of the arm, petechial skin lesions and compartment syndrome, although the overall rate of complications seems to be low (Tapolyai *et al.* 2001).

Currently, there are no accepted standards for the processing of data obtained from ABPM. For example, the definition of daytime and nighttime varies, with some investigators and device manufacturers using fixed times of day based on societal norms while others use times based on patient report. Manufacturers also use proprietary algorithms to detect artifacts and have different rules for handling unusually high or low readings (Winnicki *et al.* 1997).

Several patterns of ABP have been highlighted that may be clinically important. Blood pressure usually drops at least 10% from daytime to nighttime. Persons whose blood pressure does not decline during usual sleep hours are termed "non-dippers." Non-dippers may be at increased risk for cardiovascular disease compared with "dippers" (those whose pressure drops at least 10%) (O'Brien *et al.* 1988; Verdecchia *et al.* 1991). Older persons, persons with diabetes and persons with chronic kidney disease are more likely to be classified as non-dippers.

ABPM has been proposed to help diagnose suspected WCH, assess patients with apparent drug resistant hypertension, evaluate hypertensive symptoms in patients on antihypertensive medications, evaluate episodic hypertension and autonomic dysfunction and to guide management of hypertension. Less common indications include monitoring for episodic hypotension, pre-syncope and medication-related lability of blood pressure.

White-coat Hypertension (WCH)

The white-coat effect is an increase in blood pressure primarily in the medical care environment. This can be documented (depending on the definition) in 15% to 30% of patients diagnosed with hypertension (Pickering *et al.* 1999). WCH is usually defined as hypertension in the office (BP > 140/90 averaged over several office visits) with normal blood pressure on ABPM. However, there is no accepted standard for normal ABP. Many define this as a daytime ABP <135/85, but some use a lower cut off value and some use the 24-hour average blood pressure to define normal.

Identification of WCH may benefit patients by sparing them the expense and side effects associated with treatment of hypertension. Patients may also avoid the ill effects of being labeled as having hypertension. On the other hand, patients with WCH may still benefit from treatment to lower their blood pressure. It is possible that persons with WCH may also suffer from traffic hypertension, frustration hypertension and “just got yelled at by the boss” hypertension, suggesting that based on the density of high intensity periods, the time averaged blood pressures may be relatively high and anti-hypertensive therapy may be of benefit.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

There are several manufacturers of ABPM devices. These devices have been cleared by the FDA for marketing under the 510(k) process. The predicate device was a normal non-invasive BP monitor.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words ambulatory blood pressure monitoring, 24 hour blood pressure monitoring. These were cross-referenced with the keywords hypertension and cardiovascular disease. The search was performed for the period from 1966 through August 2004. The bibliographies of systematic reviews and key articles were manually searched for additional references. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

WCH

The most important health outcomes related to hypertension are death, heart attack, stroke, heart failure and kidney failure. Ideally, these outcomes would be evaluated in patients with WCH randomized to antihypertensive treatment or no treatment. Cohort studies that compare outcomes in patients with WCH to patients who are normotensive would also be useful in determining whether WCH is a benign condition, although the results could be confounded by selection bias.

Intermediate outcomes are often used in cross sectional studies. Measures of organ damage associated with hypertension include left ventricular mass, measures of diastolic dysfunction such as the E/A ratio, carotid artery intimal medial thickness, urine albumin excretion as a measure of kidney disease and retinopathy on fundoscopy.

Randomized Clinical Trials

A subgroup of one randomized clinical trial, the Systolic Hypertension in Europe Trial (Syst-Eur Trial), addressed whether patients with WCH who are treated with blood pressure lowering medications have outcomes that are equivalent to similar patients who are not treated (Fagard *et al.* 2000). However, the study was inadequately powered to answer why, out of the 4,695 patients randomized, 458 had useable ABPM data and only 167 patients met criteria for WCH?

Cohort Studies

Only two of six prospective cohort studies that evaluated cardiovascular outcomes for patients with WCH met criteria for inclusion in this review. One study (Perloff *et al.* 1989) did not assess WCH as it is usually defined: all patients with ABP lower than office blood pressure were grouped together rather than grouping the patients with elevated office blood pressure and normal ABP. Another used intra-arterial measurements and did not have a normotensive control group for comparison of event rates (Khattar *et al.* 1998). The third study used a standard ABPM device, but again did not have a normotensive control group (Celis *et al.* 2002). The fourth (Bjorklund *et al.* 2003) primarily focused on a group of normotensive patients with elevated ambulatory pressure. It is accepted that higher blood pressure levels, measured in the office or by ambulatory monitoring, are associated with higher rates of cardiovascular outcomes. The important question to answer is whether patients with WCH have rates of adverse cardiovascular outcomes that are similar to patients without hypertension and can they be safely left untreated?

The first of the informative cohort studies (Verdecchia *et al.* 1994) followed 228 patients with WCH and 205 healthy controls from office staff and students for an average of 3.2 years. The second (Gustavsen *et al.* 2003) followed 76 patients with WCH and 146 normotensive controls for an average of 10.2 years. Both report analyses adjusted for known cardiovascular risk factors.

Cross-sectional Studies

At least twenty-one cross-sectional studies (White *et al.* 1989a; White *et al.* 1989b; Verdecchia *et al.* 1992; Cardillo *et al.* 1993; Hoegholm *et al.* 1993; Kuwajima *et al.* 1993; Hoegholm *et al.* 1994; Weber *et al.* 1994; Cavallini *et al.* 1995; Cerasola *et al.* 1995; Pierdomenico *et al.* 1995; Glen *et al.* 1996; Pose-Reino *et al.* 1996; Soma *et al.* 1996; Chang *et al.* 1997; Ferrara *et al.* 1997; Hoegholm *et al.* 1998; Nalbantgil *et al.* 1998; Torrisi *et al.* 1999; Zakopoulos *et al.* 1999; Muldoon *et al.* 2000; Palatini *et al.* 2002; Pose-Reino *et al.* 2002; Karter *et al.* 2003) compare evidence of hypertensive target organ damage patients with WCH to controls with normal blood pressure. The most common outcome used was some measurement of left ventricular mass. Definitions of WCH varied widely across the studies. These studies were based on intermediate or surrogate outcomes rather than clinical outcomes. Thus, the results of these studies have been given little weight in balancing the overall benefits and harms associated with the use of ABPM to diagnose WCH.

Prediction of Cardiovascular Events

A large number of studies have demonstrated that ABP level predicts future cardiovascular outcomes and several have shown that it is still predictive of future events after adjusting for office blood pressure measurements (Mallion *et al.* 1999; Mancia *et al.* 2000; Verdecchia 2000). This is not surprising because estimating a highly variable quantity with the average of 25-50 measurements (ABPM) is always more precise than averaging two to six measurements (office blood pressure). The key question is whether this additional precision significantly improves predictive accuracy. There are over 40 measurements, such as coronary artery calcification, c-reactive protein, lipoprotein-a and homocysteine, that are independent risk factors for future cardiovascular events. However, few have become part of routine risk assessment.

The current standard for cardiovascular event prediction is the Framingham risk score (Wilson *et al.* 1998), a complex calculation using age, sex, office blood pressure level, cholesterol levels, diabetes, tobacco use and left ventricular hypertrophy (LVH) to predict an individual's ten-year risk for future events. There is no equivalent equation that incorporates ABP measurements or compares predictions from ABPM to the Framingham predictions. In order to be of clinical value, studies need to demonstrate that ABPM significantly improves the discriminatory accuracy of the Framingham risk score, as assessed by the concordance index (Ridker *et al.* 2002; Greenland *et al.* 2004). None of the published studies of ABPM have addressed this question.

Management of Hypertension

One randomized clinical trial (Staessen *et al.* 1997) compared ABP with office blood pressure for the management of hypertension. The investigators randomized 419 patients with untreated diastolic hypertension to treatment based on daytime diastolic ABP or the average of three sitting office blood pressure measurements. The average follow-up was six months. The primary outcomes were the intensity of medical therapy and changes in left ventricular mass.

Level of Evidence: 2, 3, 4, 5

TA Criterion 2 is met

TA Criterion 3: The technology must improve the net health outcomes.

WCH

Randomized Clinical Trials

The Syst-Eur Trial (Fagard *et al.* 2000) randomized patients who were ≥ 60 years old with systolic BP of 160 to 219 mm Hg and diastolic BP of < 95 mm Hg, to nitrendipine or identical placebo. Patients enrolled in the Ambulatory Blood Pressure Monitoring Side Project were classified according to daytime systolic ABP into one of three subgroups: WCH (< 140 mm Hg), mild sustained hypertension (140 to 159 mm Hg) and moderate sustained hypertension (≥ 160 mm Hg). At baseline, patients with WCH had smaller electrocardiogram (ECG) voltages ($P < 0.001$) and during follow-up, a lower incidence of stroke ($P < 0.05$) and of cardiovascular complications ($P = 0.01$) than other groups. Active treatment reduced ABP and office blood pressure in patients with sustained hypertension but only office blood pressure in patients with WCH ($P < 0.001$). The influence of active treatment on ECG voltages ($P < 0.05$) and on the incidence of stroke ($P < 0.05$) and cardiovascular events ($P = 0.06$) was more favorable than that of placebo only in patients with moderate sustained hypertension. However, even in the white-coat or WCH group, there was a trend towards benefit. None of the patients with WCH, who were treated with antihypertensive medication, suffered a stroke during follow-up compared to two among patients randomized to placebo ($p = 0.16$). Similarly, only two of the treated patients with WCH suffered a cardiovascular event, compared to six of those randomized to placebo ($p = 0.17$). The relative risk reduction (RRR) from treatment was greater for patients with WCH (approximately 69% RRR) compared with patients with mild or moderate hypertension (approximately 35%). However, the absolute benefit was greater for patients with moderate hypertension because of their higher absolute rate of cardiovascular events. Still, the absolute risk reduction (ARR), estimated from Figure 4 of the paper, is 14.5 events/1,000 patients treated for one year or a number needed to treat (NNT) of 69. This is more favorable than the reduction seen for nitrendipine in the full study (ARR for all cardiovascular events 10.4/1000 person years, NNT 96) (Staessen *et al.* 1999). The NNT for treatment of WCH in this study is similar to pravastatin (NNT = 55) for preventing CHD events (Lewis *et al.* 1998) and lower than aspirin (NNT = 669) for preventing CHD events in hypertensive patients (Hansson *et al.* 1998).

The study was underpowered to reach a definitive conclusion, but there was a clear trend towards benefit in patients with WCH. The definition of WCH used in this study (daytime SBP < 140 mm Hg) uses a higher cutoff than that used in other studies (135 or 130 mm Hg). These results may not generalize to patients with lower ambulatory blood pressures. On the other hand, there is no evidence from this study to support a lower RRR from antihypertensive treatment in patients with WCH. This suggests that decisions on whether to treat should be based on an individual

patient's absolute risk of cardiovascular events rather than an arbitrary blood pressure cutoff derived either from office or ABP measurements. Furthermore, there was no assessment of the impact of the two interventions on patient quality of life.

Cohort Studies

The first cohort study (Verdecchia *et al.* 1994) to compare patients with WCH to patients with normal blood pressure enrolled 1,187 patients with an office blood pressure > 140/90 and 205 controls with normal blood pressure selected from clinic staff and students. All patients had ABPM. Patients were diagnosed with WCH if their daytime ABP was < 131/86 for women and <136/87 for men (n=228). The average follow-up was 3.2 years. The primary outcome measure was all cardiovascular events defined as fatal and non-fatal heart attacks, stroke, sudden cardiac death, angina, heart failure or renal failure. The incidence of cardiovascular events was similar in patients with WCH (4.9/1,000 person-years) and patients with normal blood pressure (4.7/1,000 person-years). In a multivariable Cox proportional hazards analysis of the data, WCH was not associated with increased risk of cardiovascular events (relative risk (RR) 1.2, 95% CI 0.25-5.3). However, the study was not designed or powered to demonstrate equivalency between the two groups. The confidence interval (CI) suggests that WCH could still be associated with a large increase in risk of cardiovascular events. Furthermore, the study is likely subject to confounding. At baseline, 29% of the patients in the WCH group were receiving treatment for hypertension. This number likely increased over time, although no further assessment of antihypertensive medication use was made. Medication use was not adjusted in the multivariable model used in the analysis. However, LVH was adjusted in the model. Left ventricle (LV) mass was significantly greater in the WCH group (92 versus 86 g/m², p=0.004, from Table 1 data) and LVH predicted cardiovascular events (RR 1.7, 95% CI 0.98-3.04). Given that LVH is likely on the causal pathway between elevated blood pressure and CHD, adjusting for LVH likely decreased the strength of the association between WCH and cardiovascular disease in this analysis.

The second cohort study (Gustavsen *et al.* 2003) was a 10-year follow-up study on 420 patients with hypertension newly diagnosed by their general practitioner and 146 normal controls. ABPM was performed at baseline. WCH was defined as daytime ABP >135/90 mmHg. Of the 420 patients, 76 (18.1%) met this definition. The remaining 344 were called established hypertensives. With a lower cutoff of 135/85 mmHg, 40 (9.5%) would have WCH. Complete follow-up data was obtained for all 566 subjects. The mean duration of follow-up was 10.2 years (range 9.0-12.5). In the WCH group, 14 (18.4%) first events were recorded consisting of cardiovascular deaths and 12 nonfatal cardiovascular events. In the established hypertensive group, the corresponding number of events were 56 (16.3%) first events, 12 (3.5%) cardiovascular deaths and 44 (12.8%) nonfatal cardiovascular events. In the normal control group, 10 (6.8%) were first events, 2 (1.4%) cardiovascular deaths and 8 (5.5%) nonfatal cardiovascular events. The event rate was similar between the WCH group and the established hypertensive group but significantly lower in the normal control group (P<0.05). When corrected for daytime-ABP, age and other confounders, the difference in

cardiovascular event rates remained statistically significant. When using the lower cutoff of 135/85 mmHg, WCH was still associated with a significantly higher cardiovascular event rate compared to normal controls ($p < 0.01$). It is interesting to note that the earlier cross-sectional analyses, using the same patients, reported that cardiac and renal target organ damage in the WCH group was lower than in established hypertensive patients and similar to that observed in the normal control group (Hoegholm *et al.* 1993; Hoegholm *et al.* 1994; Hoegholm *et al.* 1998).

This study is remarkable for the high rate of cardiovascular events in the WCH group even though 60% of the group were treated for hypertension during the follow-up period. The RR of WCH for cardiovascular events in their multivariable analysis was 6.6 ($p < 0.001$, 95% CI not given), which is much higher than the 1.2 (95% CI .25-5.3) reported by Verdecchia *et al.* (1994). The primary outcome was defined similarly in the two studies, though the length of follow-up was much longer in the second study (10.2 versus 3.2 years). Both studies controlled for age, sex, blood pressure, diabetes, smoking, body mass index and prior CHD in their analyses. Neither controlled for use of anti-hypertensive medications, while Verdecchia *et al.* controlled for both LVH and serum cholesterol level. The cutoff used to diagnose WCH was different in the two studies and likely explains part of the large difference between the two studies. However, Gustavsen *et al.* (2003) also analyzed their data using a cutoff of 135/85 for WCH. Patients with WCH still had a significantly higher cardiovascular event rate ($p < 0.01$), though the authors did not report the adjusted RR from this analysis.

Cross-sectional Studies

As with the prospective studies above, the definition of WCH varies from study to study in the cross-sectional literature. Examples of WCH include office blood pressure $> 140/90$ with daytime ABP $< 140/90$, office blood pressure $> 160/90$ with ABP < 130 systolic and office blood pressure $> 140/90$ with awake ABP $< 134/90$ or $< 142/90$ if age > 65 years old. There were 13 different definitions of WCH among the 21 studies. The lack of a common definition highlights the general lack of consensus in this field.

Blood pressure cutoffs for the comparison groups also differ considerably. Hypertension is sometimes defined by DBP alone or a combination of office and ambulatory measures. Similarly, the normal blood pressure group is usually defined as office blood pressure $< 140/90$, but sometimes as DBP < 90 or 95. One study defined normal as office blood pressure $< 135/85$ and ABP $< 130/80$. Six different definitions of normal were used in these studies. Given the linear association of blood pressure (both office and ambulatory) with target organ damage and cardiovascular events from at least 110/60 and higher (MacMahon *et al.* 1990; Ohkubo *et al.* 2000), the definition of hypertension, WCH and normal blood pressure will be a key factor in observed differences between the groups.

Clearly, other clinical factors such as age, sex, smoking, diabetes and cholesterol level, are associated with most of the surrogate outcomes used in these cross sectional studies. Only four of the 21 studies matched patients on clinical characteristics.

The most common surrogate measure used to compare patients with WCH to patients with normal blood pressure was left ventricular mass either as mass in grams or mass indexed to body surface area. In the majority of the studies (15/18) left ventricular mass was higher in patients with WCH, though usually less than that of true hypertensives.

The ventricles stiffen in response to prolonged hypertension leading to diastolic dysfunction. Echocardiographic phases of ventricular filling have been described as early (E) and late, or atrial (A). Characteristically, when diastolic dysfunction is present, a greater portion of end-diastolic volume is the result of late filling rather than early filling. Thus the E/A ratio is reduced in diastolic dysfunction. In all seven studies that reported the E/A ratio, it was intermediate between normotensive and hypertensive patients for patients with WCH.

Carotid artery intimal medial thickness was measured in six studies. In all six, the thickness for white-coat hypertensives was intermediate between the other two groups. Similarly, albumin excretion, a measure of kidney damage, was higher in white-coat hypertensives than normotensives, in four of five studies reporting renal function. Finally, retinopathy was more common in white-coat hypertensives in all three studies that compared retinal exams to normotensives.

Taken together, these 21 studies provide evidence that the risk of adverse events with WCH lies somewhere between the risk of patients with normal blood pressure and those with persistently elevated blood pressure. There is tremendous variability in the target organ damage reported by these studies. This likely reflects the heterogeneity of the patients included in the various studies, as well as the lack of consensus in blood pressure cutoffs used to define WCH, persistent hypertension and normal blood pressure.

Management of Hypertension

One randomized clinical trial (Staessen *et al.* 1997) compared ABP with office blood pressure for the management of hypertension. The investigators randomized 419 patients with untreated diastolic hypertension to treatment based on daytime diastolic ABP or the average of three sitting office blood pressure measurements. The average follow-up was six months. More patients in the ABPM arm were able to discontinue medications (26% versus 7%, $p<0.001$) and fewer patients were using multiple medications (27% vs. 43%, $p<0.001$). However, there was a greater reduction in both SBP and DBP in the office blood pressure arm whether assessed by office blood pressure ($-3.3/1.4$, $p=0.06$) or by ABPM ($-2.8/1.6$, $p=0.03$). Quality of life measures were identical in the two arms for the study. Symptom scores fell from 1.62 to 1.42 in the office blood pressure arm and from 1.61 to 1.43 in the ABPM arm. ECG and echocardiographic changes were similar in the two groups. For example, the estimate of LV mass fell from 203 to 201 g in the office blood pressure arm and from 196 to 190 g in the ABPM arm ($p=0.56$). Overall, treatment costs were not significantly different (office blood pressure \$5194 versus ABPM \$5366, $p=0.48$).

Follow-up was short, so the study was not powered to evaluate important clinic events like heart attacks and strokes. One patient in the office blood pressure arm suffered a heart attack compared with two in the ABPM arm. One patient in each arm developed heart failure. Thus, the trend was towards fewer events in the clinical blood pressure arm compared with the ABP arm. The observed differences in blood pressure between the two arms of the study, while small, have been estimated to reduce stroke mortality by more than 8%, CHD mortality by 5% and total mortality by 4% (Whelton *et al.* 2002). Larger studies with longer follow-ups are needed to better assess the effect of ABPM guided therapy on patient outcomes.

TA Criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

WCH

The only established alternative to ABPM is office blood pressure with treatment of office blood pressure >140/90, regardless of suspicion for WCH. The only study which addresses the comparison directly is the subgroup of patients in the Syst-Eur Trial (Fagard *et al.* 2000) with WCH. As noted above, the study was underpowered to reach a definitive conclusion, but there was a clear trend towards benefit in treating patients with WCH. Further clinical trials need to be performed to definitively answer the question, but current data suggests that patients with WCH benefit from treatment.

Management of Hypertension

The other randomized clinical trial (Staessen *et al.* 1997), described above, compared ABP with office blood pressure for the management of hypertension during six months of follow-up. Patients in the ABPM arm were treated less intensively ($p < 0.001$), but had less of a reduction in both SBP and DBP ($p < 0.05$). Quality of life measures and costs were identical in the two arms for the study. Follow-up was too short to assess clinical outcomes.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Ambulatory blood pressure monitors are not difficult to learn to use. Medical staff or technicians can be trained to properly calibrate the devices, explain their use to patients and attach them to patients. They have been used at many centers around the world. At least one study has documented that general practice offices can be taught to use the device with high quality results (Omvik *et al.* 2003). However, the use of ABPM has not been shown to improve patient outcomes in research centers. Thus, TA criterion 5 is not met.

TA Criterion 5 is not met.

OPINIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

In 1999, the BCBSA Technology Evaluation Center conducted a review of Ambulatory Blood Pressure Monitoring for the Diagnosis of Hypertension in Patients with Elevated Office Blood Pressure and determined that TEC criteria were not met. In 2001, a reanalysis was performed for the Centers for Medicare and Medicaid Services. TEC criteria were not met.

Centers for Medicare and Medicaid Services (CMS)

In 2001, CMS published a National Coverage Determination that the use of ABPM is appropriate for those patients with suspected WCH. It read as follows:

Suspected WCH is defined as office BP > 140/90 mm Hg on at least three separate clinic/office visits with two separate measurements made at each visit. In addition, there should be at least two BP measurements taken outside the office which are < 140/90 mm Hg. There should be no evidence of end-organ damage. The information obtained by ABPM is necessary in order to determine the appropriate management of the patient.

American College of Cardiology, California Chapter (ACC)

In 1994, the ACC re-approved a Position Statement regarding ABPM. The full statement is published on the ACC web site (<http://www.acc.org/clinical/position/72530.pdf>). The recommendations note:

Ambulatory blood pressure monitoring has become a mature, clinically applicable technology, with available standards developed by the Association for the Advancement of Medical Instrumentation and the British Hypertension Society. American and international consensus meetings have developed clinical indications and guidelines for this procedure.

A representative of the ACC was not able to attend the meeting.

American Society of Hypertension, Inc., California Chapter (ASH)

A society representative was not able to attend the meeting to provide testimony. However, a statement that the ASH does not have a specific position statement regarding the use of ABPM, was provided.

Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC)

In May of 2003, the National Institutes of Health published JNC-7. This document notes:

ABPM is warranted for evaluation of "white-coat" hypertension in the absence of target organ injury. It is also helpful to assess patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, episodic hypertension, and autonomic dysfunction.

U.S. Preventive Services Task Force (USPSTF)

In a 2003 statement, the USPSTF noted that "There are some data to suggest that ambulatory blood pressure measurement (that provides a measure of the average blood pressure over 24 hours) may be a better predictor of clinical cardiovascular outcome than clinic-based approaches; however, ambulatory blood pressure measurement is subject to many of the same errors as office blood pressure measurement."

CONCLUSION

There is no randomized, controlled trial evidence to support the use of ABPM for any indication. Randomized trials, with adequate design and sample sizes, are needed to evaluate the possible advantages and risks of ABPM. These trials should evaluate not only clinical outcomes, but also use of health care resources and quality of life.

WCH

The lack of a commonly accepted definition of WCH makes any attempt to synthesize the literature extremely difficult. The primary use that has been advocated for ABPM, is the detection of WCH with the implication that patients with WCH could avoid the cost and side effects associated with unnecessary treatment. This assumes that the harms of treatment in this population outweigh any potential benefits of treatment. Only one randomized trial compared outcomes in patients with WCH who were treated with similar patients who were not treated. Although the study was underpowered, treated patients with WCH had no strokes during follow-up (versus two in the untreated group) and had one third the number of cardiovascular events (RR estimated 0.31). Although not statistically significant, the ARR in cardiovascular events for treatment of WCH (14.5/1000 person-years) was larger than that for hypertensive treatment of all patients with isolated systolic hypertension in the full Syst-Eur Trial (10.4/1000 person-years, $p < 0.001$). Of the two prospective cohort studies comparing patients with WCH to patients with normal blood pressure, one reported that cardiovascular event rates were similar in the two groups, while the other reported that the event rates were significantly higher for patients with WCH. Case-control studies generally reported that the risk of target organ damage associated with WCH fell between that of hypertension and normal blood pressure. Taken together, the current evidence base suggests that patients with WCH should be treated with anti-hypertensive therapy, as they have in all of the major trials demonstrating benefit to the treatment of hypertension.

Prediction of Cardiovascular Events

ABPM clearly is a more precise measurement of blood pressure than office blood pressure measurements and is an independent predictor of future cardiovascular events. The current standard for estimating a patient's risk of future cardiovascular events is the Framingham risk score. Both the USPSTF and the National Cholesterol Education Program recommend using Framingham risk calculations to guide decisions about the use of aspirin and cholesterol lowering therapy for primary prevention. No studies to date have investigated whether ABP improves the predictive accuracy of the Framingham risk scores. Thus, there is no evidence that the use of ABPM for prognosis improves patient outcomes.

Management of Hypertension

Finally, one clinical trial investigated whether using ABPM to guide anti-hypertensive therapy improved patient outcomes over six months. Adjustment based on ABP led to less intensive drug treatment, but less of a reduction in blood pressure. Quality of life measures were identical in the two arms for the study. ECG and echocardiographic

changes were similar in the two groups as were overall costs. Follow-up was short, so the study was not powered to evaluate important clinical events like heart attacks and strokes. However, the trend was toward fewer events in the clinical blood pressure arm compared with the ABP arm. Thus, the study provided no evidence of important short term benefits gained from the use of ABPM to guide therapy. Larger studies with longer follow-up are needed to better assess the effect of ABPM guided therapy on patient outcomes.

RECOMMENDATION

It is recommended that the use of ABPM to diagnose WCH, predict cardiovascular events, or guide therapy for hypertension does not meet technology assessment criteria 3, 4, or 5 for safety, effectiveness and improvement in health outcomes.

The California Technology Assessment Forum approved the recommendation as written.

Abbreviations used in this assessment

ABPM	Ambulatory blood pressure monitoring
ABP	Ambulatory blood pressure
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
ECG	Electrocardiogram
JNC	Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure
CHD	Coronary heart disease
LV	Left ventricle
LVH	Left ventricular hypertrophy
CI	Confidence interval
ARR	Absolute risk reduction
NNT	Number needed to treat
RRR	Relative risk reduction
WCH	White-coat hypertension
RR	Relative risk
BP	Blood pressure

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