AMBULATORY BLOOD PRESSURE MONITORING FOR ADULTS WITH ELEVATED OFFICE BLOOD PRESSURE

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ASSESSMENT OBJECTIVE

The objective of this technology assessment is to determine whether using 24-hour ambulatory blood pressure monitoring (ABPM) in adult patients with elevated office blood pressure improves health outcomes. The rationale for ABPM in this setting is to identify a subgroup of patients with elevated office blood pressure and "normal" ambulatory blood pressure (i.e., "white coat hypertensives") whose risk for adverse cardiovascular events is similar to normotensive patients. If ABPM can accurately identify such a subgroup of patients, health outcomes would be improved by avoiding unnecessary medications.

There is a wide variability of blood pressure among individuals and some patients with an office blood pressure greater than 140/90 mm Hg may not have sustained hypertension. Some patients may also experience a heightened "white coat effect," which refers to the phenomenon that blood pressure tends to be higher when taken in the doctor's office. Thus, office readings may not be a good indicator of a patient's true average blood pressure. The use of ABPM offers the opportunity to obtain a greater number of blood pressure readings over a longer period of time and in an environment unlikely to stimulate a white coat effect.

The most important adverse outcomes of chronic hypertension are morbidity and mortality from cardiovascular events, mainly stroke and myocardial infarction (MI). Blood pressure is a well-established predictor of the cardiovascular event risk. Markers of damage to organs such as the left ventricle of the heart, the kidney, and other arterial structures are often used as surrogate endpoints, i.e., intermediate outcomes, in short-term studies of adverse cardiovascular effects. The most common intermediate outcome used in studies of hypertension is left ventricular mass (LVM). LVM is increased as a result of sustained hypertension and is strongly linked to the incidence of adverse cardiovascular outcomes.

The best evidence on the utility of ABPM would be from a well-designed randomized controlled trial comparing outcomes of patients in whom antihypertensive treatment was initiated based on office or ABPM readings. For patients known to have an elevated office blood pressure and a "normal" ambulatory blood pressure, randomized, controlled trials of treatment versus watchful waiting and placebo would provide direct evidence on the question of interest. Lacking this level of evidence, this assessment will attempt to determine whether patients with elevated office blood pressure and "normal" ambulatory blood pressure have a risk of adverse cardiovascular outcomes that is similar to normotensive patients, as evidenced by the presence of hypertensive end-organ damage.

BACKGROUND

Hypertension

Hypertension (HTN) is a common chronic health condition, affecting as many as 50 million persons in the U.S. (Perloff et al. 1993). Epidemiologic evidence has confirmed that elevated blood pressure causes damage to multiple organ systems, and with cardiovascular morbidity and mortality (Working Group on Risk and High Blood Pressure 1985; Stamler et al. 1989; MacMahon et al. 1990; Collins et al. 1990). In the heart, prolonged hypertension leads to hypertrophy of the left ventricle, and abnormalities in diastolic filling of the left ventricle. Damage to the kidney, or nephropathy, is first manifested by proteinuria, which progresses to nephrosclerosis and renal failure. Prolonged increased blood pressure leads to decreased compliance, or stiffening, of arterial vessels. This leads to accelerated arteriosclerosis in the heart, the central nervous system and the peripheral blood vessels. These vascular changes predispose hypertensive individuals to myocardial infarction (MI), stroke, and peripheral vascular disease.

The risk of cardiovascular events increases continuously with increasing blood pressure, at least above a level of 120/80 mm Hg (Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure 1997). An evaluation of 9 prospective cohort studies by McMahon et al. (1990) is summarized in Tables 1a and 1b. A consistent finding was that the risk of cardiovascular outcomes increased continuously with increasing diastolic blood pressure. Furthermore, there was no threshold identified below which a lower diastolic blood pressure was not associated with a decrease in the risk of cardiovascular outcomes. For patients with average blood pressures, decreases in usual diastolic blood pressure of 5, 7.5, and 10 mm Hg were associated with 34%, 46%, and 56% lower risks of stroke, and 21%, 29%, and 37% lower risks of coronary heart disease, respectively.

These data indicating a continuous relationship between blood pressure and morbidity challenges the concept of "normality" in blood pressure measurement. Any cutoff used to define normal versus abnormal blood pressure will not be characterized by sharp demarcations in risk above and below this level.

The relationship between blood pressure and risk has to date been defined entirely by office blood pressure measurements. Because of potential errors associated with office blood pressure measurement that are related to the normal fluctuations of blood pressure, it has been recommended that a standardized protocol be used for measurement of blood pressure in the office (Perloff et al. 1993; Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure 1993). The recommended protocol calls for taking the average of 2 or more readings taken at each of 2 or more visits following an initial screening. Before the measurement, the patient should rest comfortably for at least 5 minutes, and have refrained from cigarettes or caffeine for at least 30 minutes. The measurement should be taken while the patient is seated, and should be performed with a mercury sphygmomanometer, or a recently calibrated aneroid or electronic device.

Table 1a. Incidence rates of coronary heart disease events by diastolic blood pressure strata in prospective cohort studies[1]

Study/Yr	N	F/U (yrs)	£ 69	70-79	80-89	90-99	100-109	³110
Stamler 1989	350,977	6	0.3%	0.4%	0.5%	0.8%	1.2%	2.0%
Stamler 1975	22,777	12	0.9%	1.1%	2.0%	3.4%	4.9%	6.6%
Reid 1976	16,372	10	1.7%	2.5%	3.0%	3.7%	6.2%	9.3%
Garcia-Palmeiri 1986	8158	6	1.2%	1.9%	2.7%	4.1%	4.4%	8.7%
Kagan 1974	7317	12	2.2%	4.1%	5.3%	6.9%	8.2%	14.0%
LRC group 1980	4674	9	.6%	1.1%	1.1%	2.5%	3.3%	10.2%
Dawber 1980	4641	6	2.1%	1.9%	3.2%	4.8%	7.3%	7.8%
Paul 1963	2025	25	7.7%	12.8%	15.6%	18.8%	25.0%	30.2%
Dyer 1975	1402	25	15.1%	13.7%	20.0%	27.5%	31.1%	40.6%
Combined RR[2]			**(0.46)[3]**	**0.46**	**0.74**	**0.98**	**1.75**	**2.25**

[1] Adapted from MacMahon et al 1990
Incidence rates are reported as the percentage of patients with the outcome over the entire duration of the study.
[2] Compared to whole population. Estimated from graphical data in MacMahon et al 1990
[3] diastolic blood pressure groups ≤ 69mm Hg and 70-79mm Hg combined for RR calculations. Reported RR is for all patients with diastolic blood pressure ≤ 79mm Hg.

Table 1b. Incidence rates of stroke by diastolic blood pressure strata in prospective cohort studies[1]

Study/Yr	N	F/U (yrs)	£ 69	70-79	80-89	90-99	100-109	³110
Stamler 1989	350,977	6	0.03%	0.03%	0.04%	0.09%	0.2%	0.5%
Stamler 1975	22,777	12	0.2%	0.2%	0.1%	0.6%	1.0%	1.7%
Reid 1976	16,372	10	0.2%	0.2%	0.3%	0.5%	1.8%	1.8%
Garcia-Palmeiri 1986	8158	6	NR	NR	NR	NR	NR	NR
Kagan 1974	7317	12	1.0%	2.2%	3.7%	3.7%	8.2%	13.2%
LRC group 1980	4674	9	NR	NR	NR	NR	NR	NR
Dawber 1980	4641	6	0.4%	0.5%	0.8%	1.4%	1.8%	5.9%
Paul 1963	2025	25	1.9%	0.7%	1.9%	3.5%	3.3%	6.3%
Dyer 1975	1402	25	0%	3.4%	0.4%	6.5%	10.8%	9.4%
Combined RR[2]			**(0.35)[3]**	**0.35**	**0.52**	**0.90**	**1.8**	**3.6**

[1] Adapted from Macmahon et al 1990
Incidence rates are reported as the percentage of patients with the outcome over the entire duration of the study.
[2] Compared to whole population. Estimated from graphical data in Macmahon et al 1990
[3] diastolic blood pressure groups ≤ 69mm Hg and 70-79mm Hg combined for RR calculations. Reported RR is for all patients with diastolic blood pressure ≤ 79mm Hg.

In clinical practice, hypertension is usually defined as an office blood pressure above 140/90 mm Hg. This definition was used in seminal studies of hypertension treatment, such as the Veterans Administration (VA) cooperative study performed in the late 1960s (VA Cooperative Study 1970a and 1970b). This study demonstrated that, considering all patients with an office blood pressure greater than 140/90, there was benefit to pharmacologic treatment in reducing adverse cardiovascular events. The study also found on subgroup analysis that patients with higher levels of blood pressure derived greater benefit from treatment. The benefit of treating patients with mild hypertension (diastolic blood pressure 90–104) was not definitively established by this study.

Subsequent studies focused on patients with milder elevations of diastolic blood pressure. The Working Group on Risk and High Blood Pressure (1985), a subcommittee of the National High Blood Pressure Education Program, evaluated four trials of patients with mild hypertension. The main results, which are summarized in Table 2, show that there is a significant relative risk reduction for patients in all ranges of diastolic blood pressure above 90. However, the absolute reduction in risk for patients with higher levels of blood pressure will be greater, considering the higher incidence of adverse events with increasing blood pressure (Table 1). These and other studies have clearly established that the benefit of treatment is proportional to the degree of elevation in blood pressure, and that treatment of diastolic blood pressure of 90 or higher is of benefit.

While there are no clinical trials that have evaluated the benefit of treating patients with blood pressures in the range of 120/80 to 140/90, many experts now consider the "optimal" blood pressure to be less than 120/80 (Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure 1993, Alderman 1993). This is based on the epidemiologic evidence of cardiovascular risk. Blood pressure readings between 120/80 and 140/90 are considered to be "normal" but are recognized to be associated with an increased risk for adverse cardiovascular events. Currently there is greater attention toward assessing a patient's overall risk for cardiovascular events, including other risk factors such as diabetes, smoking, family history, elevated cholesterol, and obesity in making treatment decisions, rather than relying on an absolute blood pressure level for making treatment decisions (Alderman 1993).

Table 2. Relative risk reduction in cardiovascular events in antihypertensive treatment trials by diastolic blood pressure strata

Study/yr	diastolic BP eligibility	N		Relative risk reduction by diastolic BP strata			
		Treated	Control	90-94	95-99	100-104	>104
Smith 1977	90-115	379	390	(35%)	(35%)	35%[1]	75%
Helgeland 1980	90-110	812	758	(9%)	9%[2]	54%[2]	(54%)
Australian National BP study 1980	95-110	1721	1706	--	30%	29%	32%
HTN Detection and FU Program 1979	≥ 90	5485	5455	22%	23%	14%	--

[1] Combined risk reduction for all patients with diastolic BP < 105
[2] Combined risk reduction for all patients with diastolic BP < 100 and all patients with diastolic BP > 100

Current established treatment recommendations are defined by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The latest report of this committee makes the following general recommendations (Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure 1997; Table 3):

> Of primary importance for this Assessment are the recommendations for stage I hypertension, as most patients evaluated by ABPM will fall into this category. Since the absolute risk for adverse events in this range of blood pressure is low, the recommendations allow for a period of lifestyle modifications over a period of several months to a year, prior to the institution of antihypertensive medications. This report by the JNC also discusses the value of assessing other risk factors for adverse cardiovascular events, and taking these into account in treatment decisions, rather than relying solely on a blood pressure threshold.

Table 3. JNC VI Treatment Recommendations

BP mm Hg systolic BP	diastolic BP	Category	Recommendations
<120	<80	Optimal	Recheck in 2 years
<130	<85	Normal	Recheck in 2 years
130-139	85-89	High-normal	Recheck in 1 year Provide advice about lifestyle modifications
140-159	90-99	HTN – Stage 1	Confirm within 2 months Provide advice about lifestyle modifications Consider antihypertensive medication based on response to lifestyle modifications and other cardiovascular risk factors
160-179	100-109	HTN – Stage 2	Confirm within one month Begin antihypertensive medication
>179	>109	HTN – Stage 3	Begin antihypertensive medication immediately

Ambulatory Blood Pressure Monitoring (ABPM)

Automated devices to measure blood pressure repeatedly over a 24-hour period have been available since the 1960s. These devices consist of a portable sphygmomanometer attached to a recording device. The ABPM device is fitted to the patient and removed by a trained technician. The sphygmomanometer inflates at predefined times, generally every 15–30 minutes, and the blood pressures recorded at each inflation are stored. The patient is instructed to perform his/her usual activities while wearing the blood pressure monitor. After the monitoring period is complete, a printout of the blood pressure measurements is obtained and mean blood pressure readings calculated.

Initial research with ABPM revealed that the average blood pressure readings are consistently lower than those measured in the office. Patient self-measurement tends to yield values that are between those taken in the office and by ABPM. These observations have been repeated in numerous subsequent studies.

Since the readings on ABPM differ consistently from those obtained with office blood pressure measurement, the question of what constitutes a "normal" ABPM reading has been problematic, and is not yet definitively resolved. A number of studies have evaluated the comparison between office, self-measurement and ABPM in a referral population of hypertensive patients. A smaller number of population-based studies, each with substantially larger numbers than the referral populations, have compared clinic blood pressure with ambulatory blood pressure and self-measurement (Table 4).

Table 4. Comparisons of ABPM, patient self-measurement, and ABPM[1]

Study/yr	N	Mean Systolic BP			Mean Diastolic BP		
		Office	Self-measure	ABPM	Office	Self-measure	ABPM
Referral populations							
Kleinert 1984	93	148	138	131	94	89	89
Flapan 1987	24	167	151	126	95	92	83
Kenny 1987	19	156	147	139*	98	94	90*
Marolf 1987	31	147	134	130	94	88	85
Bialy 1988	15	129	131	130*	89	87	86*
James 1988	13	155	141	133	92	86	85
O'Brien 1988	18	160	153	148*	96	94	97
Mengden 1992	51	153	147	149	101	97	96
Population based studies							
Mancia 1995	1438	128	119	118	82	75	74
Schettini 1999	577	124	115	118	79	72	74

[1] Adapted from Appel 1993 * Daytime mean ABP

The largest population study to date evaluating the normal distribution of ambulatory blood pressure is the "Pressioni Arteriose Monitorate e Loro Associazioni" or "PAMELA" study (Mancia et al. 1995), completed in Italy. In this study, a random sample of 2,400 subjects was obtained, stratified by sex and age deciles, with a response rate of 69%. Individuals currently receiving antihypertensive medications were excluded (n=213), leaving 1,438 subjects for analysis. In all subjects, clinic blood pressure, home self-measured blood pressure, and 24-hour ABPM results were recorded.

The mean 24-hour ambulatory blood pressure level for the entire population was 118 (±11)/74 (±7). There was significant differences in blood pressure readings by gender and age. For men, the average 24-hour ambulatory blood pressure was 121(±10)/77 (±7), while the average for women was 114 (±11)/70 (±8). In a second population-based study, Schettini et al. (1999) evaluated 577 patients with clinic, ambulatory and self-measurements, drawn from a larger cohort of 1573 patients in Uraguay. Their mean ambulatory blood pressure for the entire population was 118 (±12)/74 (±8.8), very similar to that found in the PAMELA study.

Both of these studies attempted to define the upper limit of normal ambulatory blood pressure as the level that corresponds to an office blood pressure of 140/90. For the PAMELA study, this value was found to lie between a systolic blood pressure of 121–132 and a diastolic blood pressure of 75–81, with slight variability depending on age and gender. For the Schettini et al. study, these values were

estimated as 125/80 (range of 122–128/77–83) for 24-hour ambulatory blood pressure and 129/84 (127–132/81–86) for daytime ambulatory blood pressure.

From these studies, it can be concluded that a lower threshold for "normality" should be used for ambulatory blood pressure measurements. An ambulatory blood pressure that corresponds to an office blood pressure of 140/90 may be roughly in the range of 120–130/75–85. However, these values represent population means, and it is not possible to apply these conversions to an individual patient. There is a large individual variability in the difference between office and ambulatory blood pressure readings (Palu 1999), due, in part, to high variability in the "white coat effect" among individuals. Other factors, such as random fluctuations, different blood pressure patterns during sleep, and lability at other times in the day also contribute to this variability As a result, extrapolation of one parameter to the other in individual patients is not possible.

The American Society of Hypertension has issued recommendations for interpreting ambulatory blood pressure measurements, classifying levels of ambulatory blood pressure measurements into categories of "probably normal," "borderline," and "probably abnormal," as follows:

Table 5. American Society of Hypertension Thresholds for Ambulatory Blood Pressure (ABP) Readings

ABP Measure	"Probably normal"	"Borderline"	"Probably abnormal"
24-hour systolic BP	<130	130-135	>135
Daytime systolic BP	<135	135-140	>140
24-hour diastolic BP	<80	80-85	>85
Daytime diastolic BP	<85	85-90	>90

Adapted from Myers et al. 1999

These recommended thresholds apply to the general population. Extrapolation of these data to the specific subpopulation of patients with elevated office blood pressure and "normal" ambulatory blood pressure should be avoided. This subpopulation of patients with elevated office blood pressure and normal ambulatory blood pressure may have different risk profiles at any baseline level of ambulatory blood pressure compared to the general population.

There is limited epidemiologic evidence relating ambulatory blood pressure measurements to cardiovascular risk. Ohkubo et al. (1998) is the single longitudinal study available relating ABPM results to cardiovascular mortality. In this study, all working residents of Ohasama, Japan aged 40 and over were offered ABPM and participation in the study. Of 1,989 eligible individuals, 1,542 (78%) agreed to participate. All patients had a baseline evaluation with ABPM and filled out a written questionnaire to assess other cardiovascular risk factors (e.g., previous heart disease, hypertension, smoking, diabetes, and hypercholesterolemia). Patients were followed for a mean of 6.2 years, and the effect of ambulatory blood pressure level on mortality was examined. The ambulatory blood pressure range associated with the best prognosis was a systolic blood pressure of 120–133 mm Hg and a diastolic blood pressure of 65–78 mm Hg. Above this range, there was an increase in mortality that was related primarily to

cardiovascular events. Below this range, there was an increase in mortality that was related to non-cardiovascular events. A follow-up report on this same cohort (Ohkubo et al. 2000) evaluated the relationship of ABPM to stroke. This analysis determined that there was a linear relationship between ABPM and stroke above a systolic blood pressure of 110 and a diastolic blood pressure of 63.

As more epidemiologic evidence on ABPM accumulates in different populations, interpretation of ABPM results will become more clear. However, at the present time, this small body of epidemiologic evidence relating ABPM to risk is not sufficient to define the ABPM thresholds that warrant treatment with antihypertensive agents.

FDA Status. Several ABPM monitors (e.g., DynaPulse 200M, DynaPulse 5000A) have been cleared for marketing via the 510(k) process.

Rationale for Use of ABPM

Increased Precision of ABPM Versus Office Blood Pressure Measurement. Blood pressure fluctuates substantially throughout a typical day, from day to day, and over longer periods of time. Multiple physical, emotional, and psychological factors may influence blood pressure, such as degree of arousal, physical activity, mood, and temperature. Therefore, if only a few readings are done, there is a risk of misclassifying a patient based on random error. With ABPM, the increased number of total readings over a longer period of time should decrease the amount of random error (Palu and Pessina 1999; Mallion et al. 1999).

Mar et al. (1998) used a Bayesian approach in a group of 129 patients with newly diagnosed mild hypertension to estimate the improvement in precision with the use of ABPM. The authors compared the accuracy of three blood pressure measurements, as is routinely done in the office, with 24 blood pressure measurements, the typical number of daytime blood pressure values obtained with ABPM. Results indicated that the accuracy of diagnosing patients with mild hypertension was substantially improved with the larger number of measurements. The positive predictive value for mild hypertension rose from 0.64 with 3 measurements to 0.84 with 24 measurements. This study suggests that there may be a substantial difference in accuracy with the two approaches.

However, given the continuous association of blood pressure levels with risk, the utility of precisely defining whether the "true" blood pressure is above or below a particular threshold may be of limited benefit (Palu and Pessina 1999). The benefit of treatment for a patient who is slightly above a given threshold will likely be similar to a patient who is slightly below that threshold.

Confounding of "True" Blood Pressure by White Coat Effect. Another factor that may cause an elevated office blood pressure when sustained hypertension is not present, apart from random variability, is the "white coat effect." This is defined as an increase in blood pressure associated with measurement in the doctor's office. Some degree of a white coat effect is present in most individuals, however the magnitude of increase is very variable among individuals. The white coat effect has been

attributed to an "alerting," or stress reaction associated with measurement of blood pressure in the office, especially when taken by a physician.

White coat hypertension refers to an exaggerated increase in blood pressure, i.e., a large white coat effect. White coat hypertension is an ill-defined term, as the parameters for white coat hypertension differ substantially across the available studies. The clinical significance of white coat hypertension is controversial (Mansoor and White 1999; Pickering 1992; Zanchetti 1997; Gibbs et al. 1998). There is not a standardized definition for what constitutes white coat hypertension, and there are no clinical trials that evaluate the benefits of treating patients who have white coat hypertension.

Because of the large individual variability of the white coat effect, it is difficult to predict ABPM-derived measures from office blood pressure and vice-versa (Palu 1999). ABPM measures in patients with a minimal white coat effect will be very close to office blood pressure. In contrast, ABPM in patients with a large white coat effect may differ from office blood pressure by 20–30 mm Hg or more. In this regard, office blood pressure can be conceptualized as measuring both baseline blood pressure and the white coat effect, but it is not possible to determine the degree of white coat effect present by office blood pressure alone. ABPM, on the other hand, largely eliminates the white coat effect and reflects primarily baseline blood pressure.

Increased Accuracy of ABPM Versus Office Blood Pressure. The increased accuracy of ABPM is supported by studies that have compared ABPM and office blood pressure on the degree of correlation with outcomes or with markers of hypertensive end organ. The evidence, consisting of one longitudinal study and numerous cross-sectional studies demonstrates that ABPM correlates more strongly with end-organ damage than does office blood pressure, and ABPM may be a better predictor of subsequent adverse events (Mancia and Parati 2000; Mallion et al. 1999; Verdecchia 2000).

Perloff et al. (1983), performed a prospective cohort study of 1,076 patients with essential hypertension, evaluating both ABPM and office blood pressure at baseline. Based on the ABPM results, they classified patients into those who had a ambulatory blood pressure lower than predicted by office blood pressure, the same as predicted, or higher than predicted. The authors evaluated overall mortality and the combined cardiovascular event rate as their main outcome measures with an average duration of follow-up of 5.5 years. Patients in the group whose ambulatory blood pressure was lower than predicted had a significantly lower overall mortality and cardiovascular event rate as compared to those patients with a higher than average ambulatory blood pressure. This study was subsequently reanalyzed (Perloff et al. 1989) by logistic regression analysis. In this analysis, ambulatory blood pressure was found to add predictive ability above that obtained by office blood pressure. Results were stratified by office blood pressure. At each level of office blood pressure examined, the ambulatory blood pressure reading was an independent predictor of outcomes.

Numerous cross-sectional studies have compared ABPM to office blood pressure in predicting intermediate outcomes, i.e., hypertensive end-organ damage. The most common intermediate outcome used in these studies are measures of left ventricular mass (LVM) by echocardiography. A meta-analysis of the relationship between ambulatory blood pressure, office blood pressure, and left

ventricular mass was performed by Fagard et al. (1995). This analysis included 21 studies, with both treated and untreated patients. The combined average correlation coefficient for ABPM was 0.50, which was significantly higher than that for office blood pressure (0.35, $p<0.001$). The authors noted that the correlation between office blood pressure and LV mass was highly dependent on the number of office measures and the care taken during office measurement. When only studies where clinic pressure was measured by multiple readings under well standardized conditions, the correlation approached that seen with ABPM (0.45–0.53). Since that time, at least two additional studies in untreated patients (Fagard et al. 1997; Veerman et al. 1996) have found that ambulatory blood pressure is a better predictor of LVM as compared to office blood pressure.

Improved Ability to Assess Response to Treatment. A final study, the only available randomized, controlled trial, provides additional rationale for use of ABPM (Staessen et al. 1997). This trial is notable in that it suggested a benefit for ABPM. Four hundred-nineteen patients whose diastolic blood pressure averaged 95 mm Hg or higher based on clinic measurement were randomized to treatment based on either conventional office blood pressure or ambulatory blood pressure. Antihypertensive medication was adjusted in a stepwise fashion based on either the ABPM results or the average of three office diastolic blood pressure measurements. The main outcome measures were the final blood pressure levels, the level of antihypertensive medication use, and the left ventricular mass on echocardiography.

After a mean follow-up of 182 days, more patients in the ambulatory blood pressure group were able to discontinue medications (26.3% versus 7.3%, $p<0.001$), and fewer patients had progressed to multiple medications (27.2% versus 42.7%, $p<0.001$). There was no significant difference seen in the final blood pressure or in the degree of change in LVM between the two groups. This study suggests that the use of ABPM can lead to lower medication use without short-term adverse effects on blood pressure level and LV mass. However, the study did not directly address the question of diagnosing hypertension in untreated patients and whether the results can be extrapolated to untreated patients is unclear.

Alternatives to ABPM

The main alternative to use of ABPM is following the recommended protocols for office measurement of blood pressure (Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure 1997). This involves repeat measurement of an elevated office blood pressure multiple times over successive visits in a standardized fashion, and basing treatment decisions on the average readings obtained from these measurements. This is the current standard of care in hypertension evaluation and treatment.

Patient self-measurement of blood pressure is another alternative to ABPM. Numerous commercial devices are available that patients can use to monitor their own blood pressure. Patient self-monitoring of blood pressure is commonly used in patients with suspected white coat hypertension, and in treated hypertensive patients to assist in monitoring response to treatment.

Self-measurement of home blood pressure will not be considered a true alternative to ABPM for several reasons. First, self-measurement can be viewed as a simplified form of ambulatory blood pressure measurement, or a less expensive surrogate for ABPM. In this context, automated ABPM will always be as good, or better, than patient self-monitoring. Concerns about the appropriateness of patient self-measurement of blood pressure have been raised (American College of Physicians 1993). Some devices have been shown to be inaccurate, and patients' ability to correctly utilize them has been variable. Also, the validity of patients self-measurement is not known, since patients choose their own time to record blood pressure, and may do so based on convenience or when values are expected to be lower, for example, when resting quietly at home.

Position Statements

Several position papers on the use of ABPM in the diagnosis of hypertension have been published over the last decade. Most recently, the American Society of Hypertension (ASH) published a report in 1996. Other recent, position papers by major medical societies have included reports by the American College of Cardiology (ACC) in 1994 and by the American College of Physicians in 1993.

The ASH paper enumerated several clinical situations in which ABPM was believed to be helpful. The main indication was suspected white coat hypertension in patients with mild hypertension and no end-organ damage. The authors acknowledged limitations in the literature for this indication, including the lack of a standardized definition for white coat hypertension. Other clinical situations for which ABPM was thought to be useful were evaluation of apparent drug resistance, hypotensive symptoms in treated patients, episodic hypertension, and autonomic dysfunction.

The ACC position stated that ABPM "has become a mature, clinically applicable technology," but did not include specific recommendations for the clinical use of ABPM. Rather, this paper referred to recommendations made by other medical societies to further define clinical indications (Sheps et al. 1994). The ACP position paper stated that ABPM "may, in theory, have a specific role in the diagnosis, prognosis, and management of hypertension." They stated that the evidence to support the role of ABPM is mostly indirect and that further direct evidence is needed. These authors concluded that "the available evidence does not warrant widespread dissemination or routine use of automated ambulatory blood pressure measurement at this time." However, they "support a more circumspect use of such devices for research and for the care of subgroups of hypertensive patients with specific clinical problems."

In addition to the above specialty society position papers, the Working Group on Ambulatory Blood Pressure Monitoring, a subcommittee of the National High Blood Pressure Education Program, published a report with recommendations for the clinical use of ABPM in 1990. This report recommended that ABPM is not necessary for the diagnosis of hypertension in most patients. They stated that "The clinical use of ABPM should be limited, at present, to selected clinical circumstances." The clinical situations listed that involved the diagnosis of hypertension were the evaluation of white coat hypertension, borderline hypertension with end-organ damage, and episodic hypertension. Other clinical indications given were the evaluation of drug resistance, hypotensive symptoms in patients on

antihypertensive medication, evaluation of blood pressure changes in nocturnal angina and pulmonary congestion, autonomic dysfunction, carotid sinus syncope and pacemaker syndromes, and exclusion of placebo reactors when determining efficacy of antihypertensive drug therapy in controlled clinical trials.

The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, published in 1997, included a brief discussion of the use of ABPM. They stated that ABPM was "most clinically helpful" in patients with suspected white coat hypertension. They stated that it is also helpful in patients with apparent drug resistance, hypotensive symptoms on medications, episodic hypertension, and autonomic dysfunction.

Guidelines for use of ABPM have also been issued by professional societies outside of the U.S. The British Hypertension Society recently released recommendations (O'Brien et al. 2000) that include the following three summary points: 1) One of the most important indications for ABPM is to exclude "white coat hypertension"; 2) ABPM is also valuable in diagnosing and treating elderly patients and is used increasingly in pregnancy; 3) Practices should consider carefully the validity of individual monitors and the way in which data is interpreted and analyzed. Guidelines released by the Canadian Hypertension Society (Myers et al. 1999) include the following on the use of ABPM: 1) ABPM should be considered for untreated patients whenever an office-induced increase in blood pressure is suspected; and 2) A decision to withhold drug therapy based on ambulatory blood pressure readings should take into account normal values for 24-hour and awake ambulatory blood pressure.

METHODS

Search Methods

MEDLINE was searched over the period of 1980 through January 2001 using the text words "ambulatory blood pressure monitoring" and "24 hour blood pressure monitoring," as well as the Medical Subject Heading (MeSH) term "blood pressure/monitoring" cross-referenced with the textword "ambulatory." The search was limited to English-language articles of human subjects. A total of 436 articles were identified by this method.

The abstracts of all identified articles were reviewed. Articles were excluded if they were reviews, or if ABPM was used as a research tool (such as to compare two antihypertensive agents or to classify subgroups of patients for comparison purposes). Articles were also excluded that evaluated ABPM in the pediatric population. This left a total of 132 articles for retrieval.

The bibliographies of review articles published since 1995 were reviewed for relevant citations. The Cochrane Library and *Current Contents* were searched for randomized controlled trials evaluating the use of ABPM. A total of 55 citations were identified by these approaches, leaving a total of 187 articles retrieved for review.

Study Selection

Inclusion criteria for studies in this technology assessment were as follows:

1. Evaluated at least 20 patients;
2. population consisted primarily of patients not being treated for hypertension; where a mixed population was included, the majority of patients had to be untreated at the beginning of the study;
3. utilized an automatic 24-hour ambulatory blood pressure monitor to select a group of patients who were hypertensive on office blood pressure and normotensive on ABPM (usually termed white coat hypertensives);
4. included at least one outcome measure, either a direct health outcome (e.g., cardiovascular morbidity and mortality), or an intermediate health outcome (end-organ damage associated with hypertension, reduction in blood pressure);
5. compared the group of patients identified by ABPM with normotensive patients and true hypertensive patients on at least one relevant outcome measure.

FORMULATION OF THE ASSESSMENT

Patient Indications

Patients eligible for 24-hour ABPM will have an average office blood pressure greater than 140/90 after standardized assessment of clinic blood pressure. In addition, patients considered for ABPM are those whom the clinician suspects may not have sustained hypertension outside of the clinic setting.

Technologies to Be Compared

For patients with an office blood pressure greater than 140/90 after 3 successive readings at different times and either suspected white coat hypertension or borderline readings, two alternatives will be compared. The standard approach will involve treatment of elevated blood pressure based only on office blood pressure measures, using recommendations from JNC VI as guidelines. The second strategy will be to evaluate patients who fall into one of the two above categories with ABPM. Subsequent treatment decisions are then made on the basis of ABPM results.

Health Outcomes

Beneficial Outcomes. If patients are accurately identified as normotensive (true negative), unnecessary treatment with antihypertensive medications can be avoided. If patients are accurately identified as hypertensive (true positive), antihypertensive treatment can be initiated resulting in reduced risk of mortality and morbidity from cardiovascular events such as stroke or myocardial infarction.

Harmful Outcomes. The most harmful outcome is failure to initiate appropriate antihypertensive treatment. If patients are inaccurately identified as normotensive (false negative), there will be failure to initiate necessary antihypertensive treatment potentially resulting in increased risk of mortality and morbidity from cardiovascular events such as stroke or myocardial infarction . If patients are inaccurately identified as hypertensive (false positive), unnecessary antihypertensive treatment will result.

However, in the patient group of interest, this outcome would be no more likely than if office blood pressure readings had been used for treatment decisions. Thus, no additional harm would result.

The adverse effects of ABPM itself are minimal, and are limited to discomfort with the device, skin irritation, sleep disturbances, and other minor annoyances.

Intermediate outcomes. The main intermediate outcomes used in the evaluation of hypertension are measures of end-organ damage associated with hypertension. These outcomes are usually measured as changes in the cardiovascular system (e.g., left ventricular hypertrophy [LVH], diastolic dysfunction, carotid artery intimal medial thickness), the kidney (e.g., nephropathy), or the eyes (e.g., retinopathy).

The presence of end-organ damage such as LVH, retinopathy, or nephropathy in hypertensive patients is associated with an increase in cardiovascular morbidity and mortality. In particular, there is a strong link established between LVH and adverse outcomes. For the purposes of this technology assessment, the following intermediate outcomes will be considered:

1. Cardiovascular
    a. Left ventricular mass
    b. E/A ratio (diastolic dysfunction)
    c. Carotid artery intimal medial thickness
2. Nephropathy
    a. Mean urinary albumin excretion
    b. Percent of patients with albuminuria
3. Retinopathy
    a. Percent of patients with retinopathy on fundoscopy

Reduction in blood pressure is a common physiologic outcome that is reported, and also represents an intermediate outcome. Evidence exists that lowering blood pressure in patients with hypertension decreases end-organ damage from hypertension and decreases cardiovascular morbidity and mortality. However, evidence on the beneficial outcomes of lowering blood pressure in the general population of hypertensive patients cannot be extrapolated to the group of patients with white coat hypertension. Therefore, lowering blood pressure in and of itself will not be considered a valid outcome measure for this review.

Specific Assessment Question

In untreated patients with an office blood pressure of greater than 140/90, in whom it is suspected that the hypertension may not be sustained outside the office setting, can the use of ABPM identify a subgroup of patients who have a risk for adverse cardiovascular outcomes equivalent to normotensive patients?

REVIEW OF EVIDENCE

There is a lack of high-quality, prospective studies that address this specific question. There are no controlled trials of treatment in patients with an elevated office blood pressure and normal ambulatory pressure. A number of cohort studies have been published, but these either do not address the specific population for this evidence review, or contain serious methodologic limitations that limit the validity of the conclusions. Therefore, the primary focus of the review of evidence will be on the cross-sectional studies published in the peer-reviewed literature that compare markers of cardiovascular risk.

Of the three prospective cohort studies (Perloff et al. 1989; Verdecchia et al. 1994; Khattar et al. 1998) evaluating cardiovascular outcomes for patients with white coat hypertension, two (Perloff et al. 1989; Khattar et al. 1998) did not meet the selection criteria for inclusion in this review of evidence. Perloff et al (1989) did not specifically study patients with "white coat hypertension, as defined by having an elevated office blood pressure and a "normal" ambulatory blood pressure. Rather, they used ABPM to identify patients whose ambulatory blood pressure was higher than clinic blood pressure, the same as clinic blood pressure, or lower than clinic blood pressure. Although the population with ambulatory blood pressure lower than clinic blood pressure has been interpreted as "white coat hypertension," this is not accurate. Patients in this category may have had both clinic and ambulatory blood pressure within the hypertensive range, or both within the normotensive range. This study is more accurately interpreted as evaluating the additional prognostic ability of ambulatory blood pressure monitoring above clinic blood pressure readings across the entire range of blood pressure.

The second prospective cohort study that did not meet the selection criteria (Khattar et al. 1998) compared patients with white coat hypertension to patients with sustained hypertension. This study used intra-arterial measurement of ambulatory blood pressure, as opposed to the more conventional use of blood pressure by sphygmomanometer, and did not include a comparison with normotensive patients, which is the primary focus for this evidence review.

The prospective cohort study that did meet the inclusion criteria (Verdecchia et al. 1994) enrolled 1,187 patients from three hospital sites with essential hypertension, as defined by an office blood pressure of greater than 140/90. All patients underwent ABPM, and patients were classified as having white coat hypertension if their daytime ambulatory blood pressure was less than 131/86 for women and less than 136/87 for men. Two hundred-five normotensive individuals were included for a control group and patients were followed for a mean of 5 years. A variety of cardiovascular outcomes were endpoints in this study, including both true health outcomes and intermediate outcomes (Table 6a).

The incidence of adverse cardiovascular outcomes in the white coat hypertension group was close to that seen in the normotensive control group, while the rate for the sustained hypertension group was significantly higher. Among patients with sustained hypertension, those who were "dippers" (blood pressure decreases significantly with sleep) had better outcomes than hypertensive patients who were "non-dippers" (no blood pressure decrease with sleep).

Table 6a. Evaluation of white coat hypertension by ABPM – longitudinal studies

Study/yr	Patients	Study Design	Protocol	Outcome measures	Results
Verdecchia 1994	1187 patients diagnosed with essential HTN at one of three hospitals. 205 control patients, healthy and normotensive, drawn from clinic staff and students. 228 pts identified as having white coat HTN	Prospective, comparative cohort study	Patients classified into four cohorts: 1. Hypertensive patients (non-dippers) 2. Hypertensive patients (dippers) 3. "WC HTN" – office BP >140/90, Daytime ambulatory BP < 131/86 (women); < 136/87 (men) 4. Normotensive controls All patients in groups 2,3,4 treated at discretion of individual physicians, based on office BP, with goal of office BP <140/90. Patients in all four groups followed for a mean of 3.2 yrs (range 0.5-7.5)	Cardiovascular morbidity and mortality (fatal and non-fatal MI, stroke, sudden cardiac death, angina, revascularization procedure, TIA, aortoiliac occlusive disease, retinal thrombosis, progressive cardiac or renal failure). Outcomes ascertained by telephone interview	Incidence of cardiovascular morbidity by group (events per 100 person/years): 1. HTN –non-dippers 4.99 2. HTN –dippers 1.79 3. "WC HTN" 0.49 4. NORM 0.47 Incidence rates significantly different among groups ($p<0.0001$). *Not designed or powered as an equivalency study. Many patients in white coat hypertension treated (29% at beginning of study; drug usage not subsequently tracked). Comparisons between cohorts may be confounded by treatment effect. Covariates (e.g., weight, exercise) not well-controlled for.*

There are several methodologic weaknesses to this study that limit the ability to compare the white coat hypertensive patients with the normotensive patients. The study was not designed or powered as an equivalency study, so that the finding of no difference between the normotensive and white coat hypertension groups may be prone to a type II statistical error. The results of the study are potentially confounded by an effect of antihypertensive treatment in the white coat hypertension patients. Patients in both the white coat and hypertensive groups were treated at the discretion of their individual doctors. At the start of the study, 29% of patients in the white coat hypertension group were under treatment, as compared to 56% of the patients in the hypertension group. Only a minority of patients (30%) completed regular follow-up visits, so the percentage of white coat hypertension patients treated over the course of the study, as well as the adequacy of blood pressure control in all patients, could not be assessed. Finally, the results of this study may also be confounded by other variables, such as exercise, diet, cholesterol level, smoking, and diabetes, which were not adequately measured or controlled for. Unmeasured differences in these variables could also potentially confound the results reported.

Eighteen cross-sectional studies met the inclusion criteria for review; these are summarized in Tables 6b and 6c. In each of these studies, a group of patients with "white coat hypertension" is selected on the basis of a discrepancy between office blood pressure and ABPM. However, the definition of white coat hypertension varies considerably. For example, in some studies a simple definition of office blood pressure above a threshold level (diastolic blood pressure = 90 or 95 mm Hg) and an ambulatory blood pressure below that level is used (Glen et al. 1996). In other studies, a stricter definition is used. White et al. (1989) required the ambulatory blood pressure mean values to be below 130/80, together with an office blood pressure of greater than 140/90. Weber et al. (1994) required the ambulatory diastolic blood pressure to be both below 85 mm Hg and at least 15 mm Hg less than the office diastolic blood pressure in order to be labeled as white coat hypertension.

Among these studies, there are also differences in the definition of the hypertension group that may be important. Some studies (Pose-Reino et al. 1996; Cuspidi et al. 1995; Palatini et al. 1998) specifically selected patients with mild hypertension as the comparison group. In numerous studies (White et al. 1989; Verdecchia et al. 1992; Cardillo et al. 1993; Ceresola et al. 1995; Cavallini et al. 1995; Lue et al. 1996; Glen et al. 1996), eligible patients were those referred to a hypertension clinic. This referral population may have more severe hypertension as compared to the aforementioned studies. Three studies (Muldoon et al. 2000; Chang et al. 1997, Ferrara et al. 1997) used populations that were matched for factors such as age, sex, and body mass index.

Of the eighteen studies, fifteen compared LVM among groups, most commonly as LVM index (LVMI = LVM indexed to body surface area). In the majority of these studies (13/15), the LVMI for patients with white coat hypertension was higher than that of normotensive patients and lower than that of hypertensive patients. In the remaining two studies, LVMI for white coat hypertensive patients was identical to that of normotensive patients in one (Chang et al. 1997), and 3.6% less than normotensive in the other (Glen 1996). For the thirteen studies in which LVMI was higher than normotensives, the percent increase in LVMI for white coat hypertensive patients ranged from 1.3–30.8%. Eight studies had an increase in LVMI of 0–10% above

Table 6b. Evaluation of white coat hypertension by ABPM in cross-sectional studies: Study description

Study/yr	Patients	Study Design	Definitions/Protocol	Outcome Measures				
				LVM	E/A ratio	Carotid IMT	Nephro	Retin
Muldoon 2000	120 patients recruited from mailings to general population, age 40-70 with no prior treatment for HTN, no clinical heart disease	Cross-sectional study with groups matched by race, gender and baseline BP	1. Hypertensive – Clinic BP 140-180/90-120 and daytime ambulatory BP >140/90 (n=40). 2. WC HTN - Clinic BP >140/90 and daytime ambulatory BP <140/90 (n=40). 3. Normotensives – Clinic BP <140/90 and daytime ambulatory BP <140/90 (n=40) Hypertensive and WC HTN group matched for baseline clinic BP. WC HTN group and normotensive group matched for daytime ambulatory BP. All patients underwent ultrasound imaging of the carotid artery			X		
Zakopoulos 1999	66 asymptomatic patients with clinic BP >160/90, with no clinical cardiac or renal disease, and not previously treated for HTN. 17 healthy, normotensive control patients matched for age and gender	Cross-sectional study	1. Hypertensive – Clinic BP >160/90 and ambulatory SBP >130 (n=42). 2. WC HTN - Clinic BP >160/90 and ambulatory SBP <130 (n=21). 3. Normotensives – BP parameters not specified All patients underwent ultrasound imaging of the carotid artery.			X		
Palatini 1998	772 patients with echos from among 942 pts taking part in multisite HARVEST study, (mild HTN and not previously treated) 95 normotensive controls recruited from medical staff and relatives matched for age and sex.	Cross-sectional study	1) Hypertensive – office BP 140-159/90-99 and ambulatory BP above threshold (n=792) 2) WC HTN – office BP 140-159/90-99 and a) ambulatory BP < 130/80 (n=150), or b) ambulatory BP <135/85 (n=331) 3) Normotensives – office BP < 140/90 (n=95) All patients underwent echo and 24 hour urine collection.	X	X		X	

Table 6b. Evaluation of white coat hypertension by ABPM in cross-sectional studies: Study description (cont'd)

Study/yr	Patients	Study Design	Definitions/Protocol	Outcome Measures				
				LVM	E/A ratio	Carotid IMT	Nephro	Retin
Nalbantgil 1998	542 pts without evidence of heart disease (population not described further)	Cross-sectional study	1. Hypertensive – office BP >140/90 (>160/90 if >65yo) (n=164) 2. WC HTN – office BP > 140/90 and awake ambulatory BP <134/90 (<142/90 if >65yo) (n=106) 3. Normotensives – office BP < 140/90 (n=272) All patients underwent echo and ambulatory ECG monitoring.	X				
Ferrara 1997	76 pts with newly diagnosed HTN. 32 age-matched normotensive control pts	Cross-sectional study	1) Hypertensive – office BP >140/90 and ambulatory BP above 130/85 (n=56) 2) WC HTN – office BP > 140/90 and ambulatory BP < 130/85 (n=20) 3) Normotensives – office BP < 140/90 (n=32) All patients underwent echocardiography.	X	X			
Chang 1997	100 patients selected from 235 consecutive patients seen at a HTN clinic; matched for age, sex and BMI; excluded patients with LVH. Age 28-49 yrs.	Cross-sectional study	1) Hypertensive – office BP >140/90 (n=50) 2) WC HTN – office BP > 140/90 and ambulatory BP < 127/81 and 18/16 lower than office BP (n=25) 3) Normotensives – office BP < 140/90 (n=25) All patients underwent echocardiography.	X	X			
Soma 1996	80 pts referred to a HTN clinic, never previously treated with medications.	Cross-sectional study	1) Hypertensive – Office diastolic BP 90-115 and daytime Amb diastolic BP > 90 (n=22) 2) WC HTN – Office diastolic BP >90 and daytime ambulatory BP < 140/90 (n=26) 3) Normotensives – office BP < 140/90 (n=32) All patients underwent echo	X	X			

Table 6b. Evaluation of white coat hypertension by ABPM in cross-sectional studies: Study description (cont'd)

Study/yr	Patients	Study Design	Definitions/Protocol	Outcome Measures				
				LVM	E/A ratio	Carotid IMT	Nephro	Retin
Glen 1996	65 consecutive patients referred for assessment of HTN. Age 45-73 yrs.	Cross-sectional study	1) Hypertensive – diastolic BP >95 on office BP and on ABPM (n=20) 2) WC HTN – diastolic BP >95 on office BP and diastolic BP <95 on ABPM (n=22). 3) Normotensive – diastolic BP <95 on office BP and ABPM All patients underwent echocardiography and measures of carotid artery compliance	X	X	X		
Pose-Reino 1996	51 pts with mild hypertension (diastolic BP<105) recruited from internal medicine clinic. 51 normotensive pts recruited from same clinic	Cross-sectional study	Divided pts into three groups: 1) Hypertensive – office BP >140/90 and do not meet criteria for WC HTN (n=24) 2) WC HTN – office BP > 140/90 and: Mean ambulatory BP < 135/80; day ambulatory BP < 140/90: night ambulatory BP < 120/80 (n=27) 3) Normotensives – office BP < 140/90 (n=51) All patients underwent echocardiography.	X				X
Pierdomenico 1995	Three groups of patients matched for age, sex, body mass index and smoking status: 50 sustained hypertensives; 25 WC hypertensives; 25 normotensives	Cross-sectional study with matched comparison groups	1. Hypertensive – office BP >140/90 and ambulatory BP >135/85 (n=50) 2. WC HTN – office BP > 140/90 and ambulatory BP <135/85 (n=25) 3. Normotensives – office BP < 140/90 (n=25)	X		X	X	
Ceresola 1995	61 outpatients with essential HTN seen at HTN clinic, ages 30-55. 35 normotensives matched for age and body mass index.	Cross-sectional study with matched control group	1. Hypertensive – office BP >145/90 and day ambulatory BP >134/90 (n=34) 2. WC HTN – office BP > 145/90 and day ambulatory BP <134/90 (n=27)	X			X	

			3. Normotensives – office BP < 145/90 (n=35)					

Table 6b. Evaluation of white coat hypertension by ABPM in cross-sectional studies: Study description (cont'd)

Study/yr	Patients	Study Design	Definitions/Protocol	Outcome Measures				
				LVM	E/A ratio	Carotid IMT	Nephro	Retin
Cavallini 1995	24 pts with WC hypertension seen at a HTN clinic. 24 pts with sustained HTN at same clinic, matched for age and sex. 24 normotensive control pts matched on age and sex, drawn from participants in a longitudinal study	Cross-sectional study	1. Hypertensive – office BP >140/90 (>160/90 if >65yo) and do not meet criteria for WC HTN (n=24) 2. WC HTN – office BP > 140/90 and awake ambulatory BP <134/90 (<142/90 if >65yo) (n=24) 3. Normotensives – office BP < 140/90 (n=24) All patients underwent echocardiography.	X		X		
Hoegholm 1994	284 patients with newly diagnosed mild to moderate HTN, with no renal disease, diabetes, or previous treatment with antihypertensive drugs	Cross-sectional study	1. Hypertensive – office DBP >90 and daytime ambulatory DBP >90 (n=173) 2. WC HTN – office DBP > 90 and daytime ambulatory DBP <90 (n=111) 3. Normotensives – office DBP < 90 (n=127)				X	
Weber 1994	171 hypertensive pts who had never been treated or off treatment at least 6 months, without evidence of hypertensive end-organ damage. Age 23-54 yrs 88 normotensive volunteers.	Cross-sectional study with matched comparison group	WC hypertension defined as ABPM reading of diastolic BP<85 and at least 15 mm lower than office BP (n=58). WC hypertensives matched with control patients on ABP, gender, age, weight (n=40 pairs). WC hypertensives matched with hypertensive patients on office BP, gender, age, weight (n=51 pairs)	X	X			
Cardillo 1993	56 consecutive patients with mild to moderate hypertension referred to HTN clinic	Cross-sectional study	1) Hypertensive – Office diastolic BP >90 and ambulatory BP >134/90 (n=36) 2) WC HTN – Office diastolic BP >90 and ambulatory BP <134/90 (n=20) 3) Normotensive – Office BP <140/90 (n=18)	X	X			X
Kuwajima 1993	51 elderly pts (>60yo) with essential hypertension. Excluded: CHF, CAD, stroke,	Cross-sectional study	1. Hypertensive – office BP >160/90 and amb systolic BP >140 (n=34) 2. WC HTN – office BP >160/90 and amb systolic BP	X	X			

	DM, autonomic neuropathy.		<140 (n=17) 3. Normotensive – not defined (n=16)					

Table 6b. Evaluation of white coat hypertension by ABPM in cross-sectional studies: Study description (cont'd)

Study/yr	Patients	Study Design	Definitions/Protocol	Outcome Measures				
				LVM	E/A ratio	Carotid IMT	Nephro	Retin
Verdecchia 1992	346 pts with untreated HTN evaluated at a HTN clinic, without cardiac or renal disease. 47normotensive controls from same clinic	Cross-sectional study	1. Hypertensive – clinic diastolic BP >90 and awake ABPM >136/87 for men and >131/86 for women (n=304) 2. WC HTN – Clinic diastolic BP >90 and ambulatory BP <136/87 for men and <131/86 for women (n=42) 3. Normotensive – Clinic diastolic BP <90 (n=47)	X				
White 1989	77 patients who were never previously treated selected from 720 patients who underwent ABPM at HTN clinic. HTN and WC HTN groups matched for age, height weight.	Cross-sectional study	1. Hypertensive – BP >140/90 on CBP and on awake ABPM (n=18) 2. WC HTN – CBP >140/90 and ambulatory BP <130/80 (n=18) 3. Normotensive – CBP <135/85 and ambulatory BP <130/80 (n=41) All patients underwent echocardiography	X				

Table 6c. Evaluation of white coat hypertension by ABPM in cross-sectional studies: Outcome measures

Study/yr	Groups	Outcome measures					
		LVMI % above normal	E/A ratio % below normal	Carotid IMT % above normal	Nephro pathy % above normal	Retino Pathy % above normal	Comments
Muldoon 2000	1. HTN 2. WC HTN 3. Norm 1. HTN 2. WC HTN 3. Norm			<u>mean</u> 0.90 5.9% 0.88 3.5% 0.85 <u>maximum</u> 1.16 9.4% 1.16 9.4% 1.06* *p<0.05 as compared to groups 1 and 2			
Zakopoulos 1999	1. HTN 2. WC HTN 3. Norm			0.69 35% 0.68 33% 0.51* *p<0.05 as compared to hypertensive and WC HTN group.			Data estimated from graphical representation.
Palatini 1998	1. HTN 2. WC HTN 3. Norm 1. HTN 2. WC HTN 3. Norm	<u>ABP <130/80:</u> 92.9 ± .7 13.2% 88.0 ± 1.6 7.2% 82.1 ± 1.9* <u>ABP< 135/85:</u> 93.8 ± 0.8 14.3% 89.1 ± 1.0 8.5% 82.1 ± 1.9* * p<0.001 for differences among groups by ANCOVA	1.42 ± .02 4.7% 1.36 ± .04 87% 1.49 ± .05 1.41 ± .02 5.4% 1.40 ± .03 6.0% 1.49 ± .05		<u>AER</u> 12.7 ± 42 60.8% 7.9 ± 11 0% 7.9 ± 8 13.7 ± 46 73.4% 8.7 ± 21 10.1% 7.9 ± 8		

Table 6c. Evaluation of white coat hypertension by ABPM in cross-sectional studies: Outcome measures (cont'd)

Study/yr	Groups	Outcome measures					
		LVMI % above normal	E/A ratio % below normal	Carotid IMT % above normal	Nephro pathy % above normal	Retino Pathy % above normal	Comments
Nalbantgil 1998	1. HTN 2. WC HTN 3. Norm	84.6 ± 12.4†* 11.9% 77.3 ± 9.3* 2.2% 75.6 ±8.7* *Significant differences among groups at p<.05 or less.					Silent ischemia (%) 1. HTN 26.2* 2. WC 18.8* 3. NORM 6.4* † Apparent typographical error reported as 64.6 in text, but stated that LVMI for HTN higher than other groups.
Ferrara 1997	1. HTN 2. WC HTN 3. Norm	LVM 183.9 ± 47 11.6% 166.9 ± 40 1.3% 164.8 ± 41	1.04 ± .3* 27.3% 1.08 ± .3 24.5% 1.43 ± .3 * p < 0.05 compared to groups 2 and 3				
Chang 1997	1. HTN 2. WC HTN 3. Norm	78 ± 10 2.6% 76 ± 8 0% 76 ± 9	0.88 ± .44 35% 0.93 ± .39 32% 1.35 ± .12* * p<0.05 compared to groups 1 and 2				
Soma 1996	1. HTN 2. WC HTN 3. Norm	126 ± 22* 23.5% 106 ± 21 3.9% 102 ± 20 * p<0.05 as compared	1.12 ± .25 5.9% 1.16 ± .32 2.5% 1.19 ± .27				

		to normotensive group					

Table 6c. Evaluation of white coat hypertension by ABPM in cross-sectional studies: Outcome measures (cont'd)

Study/yr	Groups	Outcome measures					
		LVMI % above normal	E/A ratio % below normal	Carotid IMT % above normal	Nephro pathy % above normal	Retino Pathy % above normal	Comments
Glen 1996	1. HTN 2. WC HTN 3. Norm	LVM 209 ± 47* 23.7% 163 ± 32 -3.6% 169 ± 53 * p<0.05 compared with normotensives		6.3 ± 0.7* 12.5% 6.3 ± 0.9* 12.5% 5.6 ± 0.8 * p<0.05 compared with normotensives			
Pose-Reino 1996	1. HTN 2. WC HTN 3. Norm 1. HTN 2. WC HTN 3. Norm	142 ± 45* 34.0% 132 ± 46* 24.5% 106 ± 25 <u>% with LVH</u> 63%* 45% 41%* 23% 18% * p<0.05 for groups 1 and 2 compared to normotensive group				58.3% 33.3% NR	
Pierdomenico 1995	1. HTN 2. WC HTN 3. Norm	126 ± 20* 34.0% 98 ± 12 4.3% 94 ± 11 * p<0.05 compared with groups 2 and 3		.85± .18* 21.4% .71 ± .15 1.4% .70 ± .14 * p<0.05 compared with groups 2 and 3	<u>UAE</u> 15.0 ± 14* 237% 4.5 ± 1.5 4.7% 4.3 ± 1.1 * p<0.0001 compared to groups 2 and 3		
Ceresola 1995	1. HTN 2. WC HTN 3. Norm	110 ± 29* 48.1% 93 ± 29† 9.9% 81 ± 18			<u>AER</u> 13.1 ± 9.2* 95.5% 7.5 ± 2.9 11.9% 6.7 ± .6		

		* p<0.05 group 1 vs. groups 2 and 3 † p<0.05 group 2 vs. group 3			* p<0.05 group 1 vs. groups 2 and 3		

Table 6c. Evaluation of white coat hypertension by ABPM in cross-sectional studies: Outcome measures (cont'd)

Study/yr	Groups	Outcome measures					
		LVMI % above normal	E/A ratio % below normal	Carotid IMT % above normal	Nephro pathy % above normal	Retino Pathy % above normal	Comments
Cavallini 1995	1. HTN 2. WC HTN 3. Norm	173 ± 44* 20.2% 145 ± 32 5.1% 138 ± 33 * p<0.02 as compared to groups 2 and 3		.98 ± .21* 28.9% .84 ± .16 10.5% .76 ± .18 * p<0.02 as compared to groups 2 and 3			
Hoegholm 1994	1. HTN 2. WC HTN 3. Norm 1. HTN 2. WC HTN 3. Norm				UAE .38 ± .81 81.0% .24 ± .41 14.3% .21 ± .70 log UAE 1.09 ± .44* 31.3% .96 ± .42* 15.7% .83 ± .40* * Significant difference between all groups by ANOVA		
Weber 1994	1. HTN 2. WC HTN WC HTN 3. Norm	135 ± 4 14.4% 131 ± 5 131 ± 4 11.0% 118 ± 5	1.01 ± .05* 32.9% .82 ± .04 .78 ± .05 2.6% .76 ± .04 *p<0.05 relative to comparison group				Results reported as HTN pts vs. matched WC HTN; and WC HTN vs. matched controls, giving two slightly different WC HTN groups
Cardillo 1993	1. HTN 2. WC HTN 3. Norm	122 ± 25 48.8% 103 ± 14 25.6% 82 ± 17*	1.01 ± .29 23.5% 1.06 ± .27 19.7% 1.32 ± .37*			% abn fundus 40 40% 15 15% 0	

		p<0.05 for group 3 vs. groups 1 and 2	p<0.05 for group 3 vs. groups 1 and 2				

Table 6c. Evaluation of white coat hypertension by ABPM in cross-sectional studies: Outcome measures (cont'd)

Study/yr	Groups	Outcome measures									
		LVMI	% above normal	E/A ratio	% below normal	Carotid IMT	% above normal	Nephro pathy	% above normal	Retino Pathy	% above normal	Comments
Kuwajima 1993	1. HTN 2. WC HTN 3. Norm	134 ± 43* 119 ± 40* 91 ± 16* * p<0.001 for differences between groups by ANOVA	47.3% 30.8%	0.61 ± .44* 0.67 ± .35* 0.76 ± .23* * p<0.01 for differences between groups by ANOVA	19.7% 11.8%							
Verdecchia 1992	1. HTN 2. WC HTN 3. Norm	108 ± 34* 85 ± 20 77 ± 19 * p<0.01 compared to groups 2 and 3	40.3% 10.4%									
White 1989	1. HTN 2. WC HTN 3. Norm	135 ± 21* 97 ± 30 91 ± 19 * p< 0.001 compared to groups 2 and 3	48.4% 6.6%									

Tables key:

ABPM	Ambulatory Blood Pressure Monitoring;	ABP	Ambulatory Blood Pressure;	ACR	Albumin/Creatinine ratio;
AER	Albumin excretion ratio (mcg/min);	BMI	Body mass index;	CVA	Cerebrovascular accident
IMT	Intimal medial thickness;	LV	Left ventricular;	LVH	Left ventricular hypertrophy
MI	Myocardial infarction;	NR	Not reported;	TIA	Transient ischemic attack
"WC HTN"	White coat hypertension;	UAE	Urinary albumin excretion (mg/24hr)		

Echocardiographic measures:

LVM	Left ventricular mass
LVMI	Left ventricular mass index (LVM corrected for height and weight)
A/E ratio	A to E ratio – sometimes expressed as E/A ratio (measure of ventricular filling/compliance)

normotensives, two studies had an increase of 10–20% and three studies had an increase of greater than 20%.

The E/A ratio, which is a measure of diastolic dysfunction often associated with hypertension, was measured in seven studies. In all seven studies, the E/A ratio for patients with "white coat hypertension" was intermediate to that of normotensive and hypertensive patients. The percent below normal (lower values indicating greater dysfunction) ranged from 2.5–32%. Three studies reported an decrease below normal in the range of 0–10%, two studies in the range of 10–20%, and two greater than 20%.

Carotid artery intimal medial thickness (IMT) was measured in five studies and in all cases was intermediate for the white coat hypertension patients compared to the other groups. The percent above normal for the white coat hypertension patients in these five studies was 1.4%, 3.5%, 10.5%, 12.5%, and 33%. Albumin excretion in the urine, a measure of nephropathy, was measured in four studies. In one study (Palatini et al. 1998), the albumin excretion for white coat hypertension patients was equal to that of normotensive patients. In the other three studies, the albumin excretion for white coat hypertension patients was intermediate, relative to the other groups. The percent above normotensive was 4.7%, 11.9%, and 14.7%. The final outcome measure, retinopathy, was evaluated in two studies. In one study, 15% of patients with white coat hypertension" exhibited signs of retinopathy on fundoscopic exam, compared to 0% of normotensive patients. In the second study, 32% of patients with white coat hypertension had retinopathy. The percentage of normotensive patients with retinopathy was not reported in this trial.

Reported results of these 15 studies do not support the hypothesis that the risk of adverse outcomes is similar to normotensive patients. For patients with white coat hypertension, the mean values on these measures of end organ damage are consistently higher than those for normotensive patients, and lower than those for patients with sustained hypertension. This raises the possibility that patients with white coat hypertension will have rates of adverse cardiovascular events that are higher than normotensive patients. However, the degree of risk that might be associated with white coat hypertension cannot be estimated from these data.

There is a large degree of variability in the data from these studies. Some studies report values close to, or equivalent to, normotensive patients, while others report values far greater than normotensive patients and closer to the values for patients with sustained hypertension. There are several possible reasons why the group comparisons may vary in these studies. Differences in the definition of white coat hypertension may be the most important factor. To the extent that definitions of white coat hypertension differ, these studies will include different populations of patients that are labeled as "white coat hypertension." Verdecchia et al. (1992) varied the definition of white coat hypertension in a single population and demonstrated the differences in risk as defined by LVH. As shown in Table 7, the definition of white coat hypertension may impact on these parameters substantially.

Table 7. Effect of definition of white coat hypertension on prevalence and end-organ damage

Definition of white coat HTN	% with WC HTN	LVMI (gm/m^2)	% with LVH
office diastolic BP>90 and day ambulatory BP <136/87 for men and <131/86 for women	12.1%	85 ± 20	2.4%
office diastolic BP>90 and day ambulatory BP <134/90	16.5%	85 ± 25	3.5%
office diastolic BP>90 and day ambulatory BP < 146/91	28.9%	90 ± 27	9.0%
office diastolic BP>90 and day ambulatory BP defined by age and gender[1]	53.2%	98 ± 29	14.7%

[1] Age 17-29 <144/88 for men, 131/83 for women Age 30-39 <143/91 for men, 132/85 for women
Age 40-49 <150/98 for men, 150/94 for women Age 50-79 <155/103 for men, 177/97 for women

Thus, it is likely that studies with a stricter definition of white coat hypertension, such as an ambulatory blood pressure less than 130/80 will tend to select patients who more closely resemble normotensive patients. Conversely, studies with a more permissive definition of white coat hypertension, such as an average ambulatory blood pressure of less than 140/90, are more likely to find that their population more closely resembles patients with true hypertension.

Differences in the comparison population, especially in the sustained hypertension group, may also affect comparisons with the group identified as having white coat hypertension, since the degree of end-organ damage will increase with the severity of hypertension. If the comparison population includes patients with severe hypertension, then the risk profile will tend to be skewed higher, and away from the group identified by ABPM. Where the population of hypertension patients consists only of patients with mild hypertension, it is more likely that the risk profile will be closer to that of the group identified by ABPM.

In summary, the data from these studies allow the following conclusions concerning the group of patients with elevated office blood pressure and "normal" ambulatory blood pressure (i.e., "white coat hypertension"):

1) The risk profile of these patients appears to be less favorable than that of normotensive patients;
2) The risk profile for these patients appears to be more favorable than that of patients with sustained hypertension; and
3) The risk profile of these patients is partially dependent on the definition used to define this population.

Finally, the effect of altering treatment decisions based on ABPM results is uncertain. If patients with elevated office blood pressures and "normal" ambulatory pressures are not treated, then incorporating ABPM results into treatment decisions will result in fewer patients being labeled as hypertensive, resulting in less medication use. From the evidence reviewed in this technology assessment, the patients who are not treated may have an increased risk of adverse cardiovascular outcomes. If this is the case,

then there may be a negative impact on health outcomes with this approach. On the other hand, if the increase in risk for white coat hypertension patients is not real or is not clinically significant, then avoiding or deferring treatment for these patients will improve health outcomes by reducing unnecessary medication use. The evidence available at the present time is not sufficient to distinguish between these two possibilities.

SUMMARY AND CONCLUSIONS

Adequacy of Evidence. There are no clinical trials in untreated patients that directly evaluate the effect on health outcomes of using ABPM versus office blood pressure measurement to identify and/or treat patients with an elevated office blood pressure and a normal ambulatory blood pressure. There is one prospective cohort study that suggests that this specific group of patients may have a risk similar to normotensive patients. However, the results of this study are limited in that the study was not designed or powered as an equivalence study, the results may have been confounded by treatment of patients with white coat hypertension, and that other potentially important confounding risk factors were not measured.

Numerous cross-sectional studies compare patients labeled as having "white coat hypertension" with true hypertensive patients and normotensive patients. These studies primarily compare the extent of end-organ damage, usually left ventricular mass, among the three groups. Although results of these studies vary in degree, they are consistent in reporting that white coat hypertensive patients selected by ABPM generally have measurements of end-organ damage, such as left ventricular mass index, that are higher than normotensive patients and lower than patients with sustained hypertension. Therefore, the evidence is adequate to determine that the use of ABPM selects a group with a risk profile, as reflected by measures of hypertensive end-organ damage, that is different from normotensive patients. The clinical significance of this different risk profile is uncertain.

Benefits/Risks. Estimation of benefits and risks depends on clinical decisions made as a result of ABPM. Given the available scientific evidence, the effect of altering treatment decisions based on ABPM results is uncertain. If treatment is withheld for patients identified as having white coat hypertension by ABPM, then incorporating ABPM results into treatment decisions will result in fewer patients being labeled as hypertensive and less medication use. However, from the evidence available, the patients who are not treated may have an increased incidence of adverse cardiovascular outcomes. If this population does have an increased risk for adverse cardiovascular outcomes, then withholding medications may result in a net harm. On the other hand, if the increase in risk for patients with white coat hypertension is not real or is not clinically significant, then withholding treatment for these patients will improve health outcomes by reducing unnecessary medication use. The evidence available at the present time is not sufficient to distinguish between these two possibilities. However, the available evidence does suggest that the hypothesis that patients who have white coat hypertension have a risk equivalent to normotensive patients should viewed with caution.

Magnitude of Benefit. The evidence is not adequate to determine whether the use of ABPM for identifying patients with white coat hypertension leads to a net benefit or a net harm. Therefore, the magnitude of benefit cannot be estimated.

Relevance to Medicare Population. The specific assessment question is directly relevant to the Medicare population, as well as to younger populations. It is possible that with advancing age, the risk of adverse effects of medication increase, and as a result, avoiding unnecessary medication use in this population is of greater relative benefit than in younger patients. However, the benefits of treating true, sustained hypertension are substantial, especially when the severe and irreversible morbidities of cardiovascular disease and stroke are considered. Thus, issues raised in this Assessment are of particular importance to the Medicare population,, as well as to younger populations.

REFERENCES

Alderman MH. (1993). Blood pressure management: individualized treatment based on absolute risk and the potential for benefit. *Ann Intern Med,* 119(4):329-35.

American College of Physicians. (1993). Automated ambulatory blood pressure and self-measured blood pressure monitoring devices: their role in the diagnosis and management of hypertension. *Ann Intern Med,* 118(11):889-92

Appel LJ, Stason WB. (1993). Ambulatory blood pressure monitoring and blood pressure self-measurement in the diagnosis and management of hypertension. *Ann Intern Med,* 118(11):867-82.

Bauwens F, Duprez D, De Buyzere M et al. (1992). Blood pressure load determines left ventricular mass in essential hypertension. *Int J Cardiol,* 34(3):335-8.

Bikkina M, Levy D, Evans JC et al. (1994). Left ventricular mass and risk of stroke in an elderly cohort. The Framingham Heart Study. *JAMA,* 272(1):33-6.

Cardillo C, De Felice F, Campia U et al. (1993). Psychophysiological reactivity and cardiac end-organ changes in white coat hypertension. *Hypertension,* 21(6 Pt 1):836-44.

Casale PN, Devereaux RB, Milner M et al. (1986). Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. *Ann Intern Med,* 105(2):173-8.

Cavallini MC, Roman MJ, Pickering TJ et al. (1995). Is white-coat hypertension associated with arterial disease or left ventricular hypertrophy? *Hypertension,* 26(3):413-9.

Ceresola G, Cottone S, Nardi E et al. (1995). White-coat hypertension and cardiovascular risk. *J Cardiovasc Risk,* 2(6):545-9.

Chang NC, Lai ZY, Chan P et al. (1997). Left ventricular filling profiles in young white-coat hypertensive patients without hypertrophy. *Hypertension,* 30(3 Pt 2):746-52.

Collins R, Peto R, MacMahon S et al. (1990). Blood pressure, stroke and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet,* 335(8693):827-38.

Cuspidi C, Marabini M, Lonati L et al. (1995). Cardiac and carotid structure in patients with established hypertension and white-coat hypertension. *J Hypertens,* 13(12 Pt 2):1707-11.

Devereaux RB, Alderman MH. (1993). Role of preclinical cardiovascular disease in the evolution from risk factor exposure to development of morbid events. *Circulation,* 88(4 Pt 1):1444-55.

Fagard R, Staessen J, Thijs L et al. (1995). Multiple standardized clinic blood pressures may predict left ventricular mass as well as ambulatory monitoring. A metaanalysis of comparative studies. *Am J Hypertens,* 8(5 Pt 1):533-40.

Fagard RH, Staessen JA, Thijs L. (1997). Prediction of cardiac structure and function by repeated clinic and ambulatory blood pressure. *Hypertension,* 29(1 Pt 1):22-9.

Ferrara LA, Guida L, Pasanisi F et al. (1997). Isolated office hypertension and end-organ damage. *J Hypertens,* 15(9):979-85.

Gibbs CR, Murray S, Beevers DG. (1998). The clinical value of ambulatory blood pressure monitoring. *Heart,* 79(2):115-7

Glen SK, Elliot HL, Curzio JL et al. (1996). White-coat hypertension as a cause of cardiovascular dysfunction. *Lancet,* 348(9028):654-7.

Gosse P, Desrumeau GC, Roudaut R et al. (1989). Left ventricular mass in normotensive subjects. Importance of blood pressure response to activity. *Am J Hypertens,* 2(2 Pt 1):78-80.

Hoegholm A, Bang LE, Krsitensen KS, et al (1994). Microalbuminauria in 411 untreated individuals with established hypertension, white coat hypertension, and normotension. *Hypertension*, 24:101-105

Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. (1993). The fifth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med,* 153(2):154-83.

Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. (1997). The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med,* 157(21):2413-45.

Khattar RS, Senior R, Lahiri A. (1998). Cardiovascular outcome in white-coat hypertension versus sustained mild hypertension. *Circulation,* 98:1892-1897.

Koren MJ, Devereaux RB, Casale PN et al. (1991). Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 114(5):345-52.

Kuwajima I, Suzuki Y, Fujisawa A et al. (1993). Is white coat hypertension innocent? Structure and function of the heart in the elderly. *Hypertension,* 22(6):826-31.

Lue BH, Hsu KL, Tseng YZ. (1996). Cardiac end-organ changes: comparison between white coat hypertension and persistent mild hypertension. *J Formos Med Assoc,* 95(6):440-5.

MacMahon S, Peto R, Cutler J et al. (1990). Blood pressure, stroke and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet,* 335(8692):765-74.

Mallion JM, Baguet JP, Siche JP et al. (1999). Clinical value of ambulatory blood pressure monitoring. *J Hypertens,* 17:585-595.

Mancia G, O"Brien E, Imai Y. (1999). Task Force II: Ambulatory blood pressure monitoring in population studies. *Blood Pressure Monitoring,* 4:295-301.

Mancia G, Parati G. (2000). Ambulatory blood pressure monitoring and organ damage. *Hypertension,* 36:894-900.

Mancia G, Sega, R, Bravi C et al. (1995). Ambulatory blood pressure normality: results from the PAMELA study. *J Hypertens,* 13(12 Pt 1):1377-90.

Mansoor GA, White WB. (1999). Is white coat hypertension innocent or detrimental? *Blood Pressure Monitoring,* 4:241-247.

Mar J, Pastor R, Abasola R et al. (1998). Ambulatory blood pressure monitoring and diagnostic errors in hypertension: a Bayesian approach. *Med Decis Making,* 18(4):429-35.

Marabotti C, Genovesi-Ebert A, Palombo C et al. (1991). Casual, ambulatory and stress blood pressure: relationships with left ventricular mass and filling. *Int J Cardiol,* 31(1):89-96.

Muldoon MF, Nazzaro P, Sutton-Tyrell K et al. (2000). White coat hypertension and carotid artery atherosclerosis. *Arch Int Med,* 160:1507-1512.

Myers MG, Haynes RB, Rabkin SW. (1999). Canadian Hypertension Society Guidelines for Ambulatory Blood Pressure Monitoring. *Am J Hypertens,* 12:1149-1157

Nalbantgil I, Onder R, Nalbantgil S et al. (1998). The prevalence of silent myocardial ischaemia in patients with white-coat hypertension. *J Hum Hypertens,* 12(5):337-41.

National High Blood Pressure Education Program Coordinating Committee. (1990). National High Blood Pressure Education Program Working Group report on ambulatory blood pressure monitoring. *Arch Intern Med,* 150(11):2270-80.

O'Brien E, Coats A, Owens P et al. (2000). Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British Hypertension Society. *Br Med J,* 320:1128-1134.

Ohkubo T, Hozawa A, Nagai K et al. (2000). Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. *J Hypertens,* 18(7):847-54.

Ohkubo T, Imai Y, Ichiro T et al. (1998). Reference values for 24-hour ambulatory blood pressure monitoring based on a prognostic criterion. *Hypertension,* 32:255-259.

Palatini P, Mormino P, Santonastaso M et al. (1998). Target-organ damage in stage I hypertensive subjects with white coat and sustained hypertension. *Hypertension,* 31(1):57-63.

Palu CD. (1999). Ambulatory blood pressure monitoring: a criticism. *J Hum Hypertens,* 13(11):743-5.

Palu CD, Pessina AC. (1999). Clinical utility of ambulatory blood pressure monitoring. *Blood Pressure Monitoring,* 4:223-226.

Pearce KA, Grimm RH, Rao S et al. (1992). Population-derived comparisons of ambulatory and office blood pressures. Implications for the determination of usual blood pressure and the concept of white coat hypertension. *Arch Intern Med,* 152(4):750-6.

Perloff D, Sokolow M, Cowan RM. (1983). The prognostic value of ambulatory blood pressures. *JAMA,* 249(20):2792-8.

Perloff D, Sokolow M, Cowan RM et al. (1989). Prognostic value of ambulatory blood pressure measurements: further analyses. *J Hypertens Suppl,* 7(3):S3-10.

Perloff D, Grim C, Flack J, et al. (1993). Human blood pressure determination by sphygmomanometry. *Circulation,* 88(5 Pt 1):2460-9.

Phillips RA, Goldman ME, Eison HB et al. (1989). Noninvasive ambulatory blood pressure monitoring in patients with recently detected systemic hypertension. *Am J Cardiol,* 64(11):62F-64F.

Pickering TG. (1992). Differing perspectives on white coat hypertension. *Arch Intern Med,* 152(4):691-2.

Pickering T. (1996). Recommendations for the use of home (self) and ambulatory blood pressure monitoring. American Society of Hypertension Ad Hoc Panel. *Am J Hypertens,* 9(1):1-11.

Pierdominico SD, Lapenna D, Guglielmi MD et al. (1995). Target organ status and serum lipids in patients with white coat hypertension. *Hypertension,* 26(5):801-7.

Pose-Reino A, Gonzalea-Juanatey JR, Pastor C et al. (1996). Clinical implications of white coat hypertension. *Blood Press,* 5(5):264-73.

Rizzoni D, Muiesan ML, Montani G et al. (1992). Relationship between initial cardiovascular structural changes and daytime and nighttime blood pressure monitoring. *Am J Hypertens,* 5(3):180-6.

Schettini C, Bianchi M, Nieto F et al. (1999). Ambulatory blood pressure: Normality and comparison with other measurements. *Hypertension,* 34:818-825.

Sheps SG, Pickering TG, White WB et al. (1994). Ambulatory blood pressure monitoring. Hypertensive Diseases Committee, American College of Cardiology. *J Am Coll Cardiol,* 23(6):1511-3.

Soma J, Wideroe TE, Dahl K et al. (1996). Left ventricular systolic and diastolic function assessed with two-dimensional and Doppler echocardiography in "white coat" hypertension. *J Am Coll Cardiol,* 28(1):190-6.

Stamler J, Neaton JD, Wentworth DN. (1989). Blood pressure (systolic and diastolic) and risk of fatal coronary heart disease. *Hypertension,* 13(5 suppl):I2-12.

Staessen JA, Byttebier G, Buntix F et al. (1997). Antihypertensive treatment based on conventional or ambulatory blood pressure measurement. A randomized controlled trial. Ambulatory Blood Pressure Monitoring and Treatment of Hypertension Investigators. *JAMA,* 278(13):1065-72.

VA Cooperative Study Group on Antihypertensive Agents. (1970a). Effects of treatment on morbidity in hypertension. I. Results in patients with diastolic blood pressure averaging 115 through 129 mm Hg. *JAMA,* 202(11):116-122.

VA Cooperative Study Group on Antihypertensive Agents. (1970b). Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA,* 213(7): 1143-52.

Veerman DP, de Blok K, Delemarre BJM et al. (1996). Office, nurse, basal and ambulatory blood pressure as predictors of hypertensive target organ damage in male and female patients. *J Hum Hypertens,* 10(1):9-15.

Verdecchia P, Schillaci G, Boldrini F et al. (1992). Variability between current definitions of 'normal' ambulatory blood pressure. *Hypertension,* 20(4):555-62.

Verdecchia P, Porcellati C, Schillaci G et al. (1994). Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension,* 24(6):793-801.

Verdecchia P. (2000). Prognostic value of ambulatory blood pressure: Current evidence and clinical implications. Hypertension, 35:844-851.

Weber MA, Neutel JM, Smith DHG et al. (1994). Diagnosis of mild hypertension by ambulatory blood pressure monitoring. *Circulation,* 90(5):2291-8.

White WB, Dey HM, Schulman P. (1989a). Assessment of the daily blood pressure load as a determinant of cardiac function in patients with mild-to-moderate hypertension. *Am Heart J,* 118(4):782-95.

White WB, Schulman P, Dey HM et al. (1989b). Effects of age and 24-hour ambulatory blood pressure on rapid left ventricular filling. *Am J Cardiol,* 63(18):1343-7.

White WB, Schulman P, McCabe EJ et al. (1989c). Average daily blood pressure, not office blood pressure, determines cardiac function in patients with hypertension. *JAMA,* 261(6):873-7.

Working Group on Risk and High Blood Pressure. (1985). An epidemiological approach to describing risk associated with blood pressure levels. *Hypertension,* 7(4):641-51.

Zakopoulos N, Papamichael C, Papaconstantinou H, et al (1999). Isolated clinic hypertension is not an innocent phenomenon: effect on the carotid artery structure. *Am J Hypertens*, 12:245-250.

Zanchetti A. (1997). The role of ambulatory blood pressure monitoring in clinical practice. *Am J Hypertens,* 10(9 Pt 1):1069-80.

Zawadzka A, Bird R, Casadei B et al. (1998). Audit of ambulatory blood pressure monitoring in the diagnosis and management of hypertension in practice. *J Hum Hypertens,* 12(4):249-52.