Decision Memo for Ambulatory Blood Pressure Monitoring (CAG-00067N)

Decision Summary

At this point in time, ABPM will be covered for those patients with suspected WCH. Suspected WCH will be 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.

We encourage physicians to study the guidelines on the management of WCH. For those patients that undergo ABPM, and have an ambulatory BP < 135/85 with no evidence of end-organ damage, it is likely that their cardiovascular risk is similar to normotensives. They should be followed over time. For those patients for which ABPM demonstrates BP > 135/85, they may be at increased cardiovascular risk, and a physician may wish to consider antihypertensive therapies.

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Decision Memo

To: Administrative File: CAG-00067N
Ambulatory Blood Pressure Monitoring

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Re: National Coverage Decision

Date: October 17, 2001

This memorandum serves five purposes: (1) provides a brief outline of hypertension and its management; (2) describes the various methods of blood pressure monitoring, with an emphasis upon ambulatory blood pressure monitoring (ABPM); (3) reviews Medicare's past and current coverage policy regarding ABPM; (4) presents and analyzes the relevant scientific and clinical literature on the use of ABPM in certain patient populations; and (5) delineates the reason for a limited national coverage decision for patients with suspected white coat hypertension.

Clinical Background

Hypertension (high blood pressure) is defined as having a systolic blood pressure (BP) of <140 mm Hg and/or a diastolic BP of <90 mm Hg.[1] Elevated BP is a significant risk factor for a number of disorders, including cerebrovascular disease, coronary artery disease, congestive heart failure, renal failure, and peripheral vascular disease. Evidence has shown that, if detection and treatment of people with elevated BP can be achieved, the risk of morbidity and mortality for those people can be reduced. Hypertension can be successfully managed (the goal being to achieve and maintain a systolic BP below 140 mm Hg and a diastolic BP below 90 mm Hg) with the use of anti-hypertensive drug therapy, in addition to changes in lifestyle (e.g. weight loss, moderation of alcohol consumption, increase in physical activity). It should be noted that hypertension is a major concern in the Medicare population since the prevalence of hypertension is particularly high in older Americans.[2]

Methods of Blood Pressure Measurement

There are at least four methods of measuring BP:

1. Arterial (invasive) measurement (usually done in a hospital setting)
2. Conventional measurement through the use of a sphygmomanometer, or digital device (measurement taken in the clinic setting)
3. Conventional measurement through the use of a sphygmomanometer, or digital device (measurement performed outside the clinic setting)
4. ABPM

An ambulatory blood pressure monitor is a non-invasive device used to measure BP in 24-hour cycles. The device consists of a portable sphygmomanometer attached to a recording device. The ABPM is fitted to and removed from the patients by a trained technician. The sphygmomanometer inflates at predetermined times, generally every 30 minutes, and the BP recorded at each inflation are stored. The patient performs his/her normal activities while wearing the monitor.

This is distinct from the current standard measurement and assessment of BP, i.e. clinic measurement, where random isolated measurements are taken during office visits (occurring during daytime hours). Both ABPM and clinic measurements are, however, conducted through the supervision of a physician or other clinician (ABPM is not a self-monitoring device). A clinician is required to allow for the adequate evaluation of data from an ABPM. The patient is instructed on how to wear the device, but it is up to the clinician to interpret the collected data. The clinician does this by uploading the data onto a computer where device-specific programs are used to categorize and analyze the measurements. ABPM differs from self-measurement (home monitoring), as the latter is performed by the patient who takes his or her own BP readings.

It is generally thought that if readings are obtained at frequent intervals throughout the day and night, then the physician is better able to manage the patient's case.

It is important to note that self-measurement of home BP is not considered as a true alternative to ABPM. Automated ABPM is more accurate than patient self-monitoring. Several groups have raised concerned about the ability of patients to accurately measure BP at home. Patient self-monitoring often does not provide the same degree of information that is necessary for a physician to make an informed decision about the patient's cardiovascular risk, and subsequent need for treatment. Some home devices have been shown to be inaccurate, and patients' ability to correctly utilize them has been variable. Moreover, the validity of patient self-measurement is not known, since patients choose their own time to record BP, and may do so based on convenience, or when values are expected to be lower, such as when resting quietly at home.

Physician interest and use of ABPM is quite variable. ABPM is not a diagnostic tool to be used on every patient where the diagnosis of hypertension is being considered. In a large-scale cross-sectional study, Grin *et al.* looked at physician's practice habits in the use of this technology. [3] The authors found that only 9% of physicians indicated on a questionnaire that they would consider using ABPM in the standard evaluation of hypertension. When physicians used the device for a select group of patients, information obtained by ABPM affected patient management of many patients: 41% led to a change of diagnosis, and 46% led to an adjustment of anti-hypertensive therapy.

FDA Approval/Clearance

ABPM devices have been cleared for marketing under a 510 (k). The predicate device was a normal non-invasive BP monitor. Data were focused on the accuracy and technical performance of the device, and not clinical outcomes related to the diagnosis and treatment of hypertension.

History of the Medicare Coverage Process and Timeline of Recent Activities

History of Medicare Coverage of ABPM

Presently, ABPM devices are non-covered. The *Coverage Issues Manual* (CIM) 50-42, "Ambulatory Blood Pressure Monitoring with Fully and Semi-Automatic (Patient-Activated) Portable Monitors - Not Covered" states: "While ABPM in hypertensive patients using these monitors is a safe and accurate means of measuring blood pressure, the clinical usefulness of the data obtained from such devices is not clearly established. Researchers and clinicians cite the need for standardization of instrumentation and further study of this technology to better ascertain its role in hypertensive therapy. Accordingly, program payment may not be made for the use of such devices at this time."

ABPM was last considered by the Centers for Medicare & Medicaid Services (CMS) in April 1981 and was followed by a technology assessment by the Office of Health Research, Statistics, and Technology (a sector of the Pubic Health Service) in May of 1982. The submission requested coverage only for selected patients - persons with mild to moderate hypertension and some indication of cardiovascular disease. The assessment stated that ABPM is considered a safe and effective method of obtaining multiple BP measurements away from the physician's office. The assessment further stated that while the rationales for ABPM and aggressively treating patients with sustained hypertension based on ABPM appear reasonable, there was no evidence currently available to demonstrate any improvement in patient outcomes due to such differential treatment. Based on this assessment and internal review, a non-coverage decision was issued.

Timeline of Recent Activities

June 22, 2000 - Spacelabs Medical Inc. (Redmond, Washington) made the current request for a national coverage decision on ABPM. They requested coverage of ABPM for use in patients with the following indications : 1) suspected white coat hypertension (WCH); 2) apparent drug resistance; 3) hypotensive symptoms with antihypertensive medications; 4) episodic hypertension; 5) autonomic dysfunction.

October 25, 2000 - After internal review and analysis, it was believed that the present evidence was unclear as to the medical necessity and appropriateness. Therefore, CMS referred the issue to the Medicare Coverage Advisory Committee (MCAC). On January 8, 2001, the MCAC panel to which the issue would be sent was specified to be the Medical Devices and Prosthetics Panel.

January 2001 - CMS requested that an update be made to a previous technology assessment on ABPM for diagnosis of hypertension in adults that had been completed in 1999 by Blue Cross Blue Shield Technology Evaluation Center (BC/BS TEC). CMS received TEC's updated report in February 2001.

February 21, 2001 - MCAC Medical Devices and Prosthetics Panel met to discuss the topic of ABPM.

June 14, 2001 - MCAC Executive Committee met to ratify the recommendations of the Medical Devices and Prosthetics Panel.

July 23, 2001 - Signed minutes from Executive Committee received.

Summary of Evidence

Technology Assessments

BC/BS TEC 1999/2001

In June 1999, BC/BS TEC conducted a technology assessment on ABPM for diagnosis of hypertension in adults. The objective of the assessment was to determine whether the use of ABPM in adults with untreated elevated office BP improves health outcomes. No clinical trials comparing "...office BP directed diagnosis and treatment with ABPM directed diagnosis and treatment in patients previously untreated for hypertension" existed. The TEC therefore attempted to answer the assessment question indirectly by examining whether patients with elevated office BP and normal ambulatory BP have a risk of adverse cardiovascular outcomes (e.g. myocardial infarction, stroke) that is similar to normotensive patients (as shown by the amount of end organ damage [e.g. left ventricular hypertrophy] present) or whether that risk is distinct from that of normotensive patients.

To determine whether those patients with white coat hypertension, identified through ABPM, have a risk profile similar to that of normotensive patients, BC/BS TEC conducted a review on the data from one prospective cohort study (Verdecchia, *et al.* [1994]) and fourteen cross-sectional studies. The cohort study suggested that patients with white coat hypertension may have a risk profile similar to that of normotensives. However, the TEC notes that drawing conclusions from this study is problematic because the results are "...potentially confounded by the effect of treatment and unmeasured covariates on outcomes."

The 14 cross-sectional studies compared patients with white coat hypertension (as diagnosed through ABPM) and true hypertensives and normotensives. The results of these studies (although not unvarying) suggested that ABPM selects a group of patients (those with white coat hypertension) who have a risk profile different from that of normotensive patients. Specifically, the TEC states that: "...(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."

Based upon this review, the TEC concluded that given the available evidence, the effect of changing treatment NCDs based on the use of ABPM is uncertain. The technology assessment indicated that the available evidence suggests ABPM selects a group (white coat hypertensives) with a risk profile similar to that of normotensives. In summation, the technology assessment concluded that it was not possible to determine whether or not the use of ABPM improves health outcomes.

In 2001, CMS requested that the 1999 technology assessment be updated to include new articles on suspected white coat hypertension, as well as to review any literature on other uses of ABPM. This updated technology assessment looked at four additional cross-sectional studies, but came to the same conclusions as the 1999 TEC report. Moreover, no studies meeting the technology's inclusion/exclusion criteria were met addressing any indication other than white coat hypertension.

Articles In Addition to the BCBS Technology Assessment

In addition to the BCBS technology assessment, CMS' Coverage and Analysis Group (CAG) conducted literature searches for scientific articles regarding ABPM and the five requested indications. In reviewing the literature, we asked the following questions:

- Assuming that ABPM is an accurate, reliable, and valid form of measurement, is the scientific and clinical evidence adequate to draw conclusions about the usefulness of ABPM in routine clinical settings in the Medicare population for the following independent indications: a) suspected WCH; b) apparent drug resistance; c) hypotensive symptoms while on antihypertensive therapy; d) episodic hypertension; and e) autonomic dysfunction?
- Considering the available clinical and scientific literature, does the use of ABPM alter management for each of the following independent indications: a) suspected WCH; b) apparent drug resistance; c) hypotensive symptoms while on antihypertensive therapy; d) episodic hypertension; and e) autonomic dysfunction?
- Considering the available clinical and scientific literature, is the use of ABPM likely to improve patient outcomes (e.g. increase survival, decrease cardiovascular morbidity/mortality) for each of the following independent indications? a) suspected WCH; b) apparent drug resistance; c) hypotensive symptoms while on antihypertensive therapy; d) episodic hypertension; and e) autonomic dysfunction?

Inclusion Criteria

- Articles must be published in English language
- Study must have evaluated human subjects
- Study must have evaluated _ 20 subjects
- Study must have utilized 24-hour ABPM
- Study must have included at least one outcome measure, either direct (e.g. cardiovascular morbidity/mortality) or indirect (e.g. changes in the cardiovascular system such as left ventricular hypertrophy)

Exclusion Criteria

- Editorials
- Abstracts
- Review Articles
- Letters/Comments
- Article focused on the use of ABPM as a research tool
- Study did not pertain to the Medicare population
- Study involved the validation, accuracy, and/or reliability of ABPM

A combination of the following search terms were used:

- Ambulatory blood pressure monitoring
- 24-hour blood pressure monitoring
- White coat hypertension
- White coat effect
- Resistant hypertension
- Apparent drug resistance
- Hypotension
- Autonomic dysfunction

As a result of the aforementioned search terms, as well as consideration of the articles submitted by Spacelabs, 13 additional articles in addition to those in the BC/BS TEC report were reviewed. These 13 articles included the following study types:

- 2 Randomized Controlled Trials
- 3 Cohorts
- 7 Case-Series
- 1 Case Control

Of these studies, 5 articles addressed primary outcomes such as cardiovascular morbidity and mortality and 8 addressed intermediate outcomes such as left ventricular (LV) wall thickness, LV systolic function, and LV wall mass.

An analysis of each article can be found in **Appendix A**. The following represents a brief summary of the studies.

Staessen (1997) reported on 419 patients whose untreated diastolic BP on clinic BP measurement averaged _95 mm Hg in a randomized controlled trial (RCT). These patients were randomized to clinic (conventional) or ambulatory BP groups. Patients in the ambulatory group were treated based on ambulatory BP measurements. Patients in the clinic group were treated based on clinic BP measurements. Antihypertensive drug therapy was modified according to either ambulatory or clinic BP measurements. The objective of the study was to compare conventional BP and ambulatory BP measurement in the management of hypertensives. Median follow-up time was 182 days. More patients in the ambulatory BP group (26.3%) than in the clinic BP group (7.3%) had stopped anti-hypertensive drug therapy at the end of the study. ($p<.001$) Furthermore, a smaller number of patients in the ambulatory BP group (27.2% vs. 42.7%) had advanced to sustained multiple drug therapy. ($p<.001$).

Staessen (1999) was a sub-study to the double-blind placebo-controlled trial. The aim of the study was to compare the prognostic significance of conventional and ambulatory blood pressure measurement in elderly patients with systolic hypertension (SBP 160-219, DBP < 95). The authors studied 808 patients, with a mean age of 69.6 years. Authors concluded that in untreated elderly patients with isolated systolic hypertension, ambulatory systolic blood pressure was a significant predictor of cardiovascular risk over and above conventional BP.

Redon (1998) investigated whether ambulatory BP offers a better estimate of cardiovascular risk than does clinic BP in resistant (refractory) hypertension in a cohort study. There were 86 patients involved in this study. All patients were diagnosed as having refractory hypertension. The authors evaluated the incidence of cardiovascular events over an average follow-up time of 49 months. The patients were referred to specialized hypertension clinics where ABPM was performed at the time of entrance. End-organ damage was monitored yearly, and the incidence of cardiovascular events was chronicled. The patients were divided into three groups based on diastolic ambulatory BP level; low, medium, and high BP. Results indicated that patients who had a higher ambulatory BP at baseline had a higher risk of cardiovascular events. There was a significant difference in the relative risk for cardiovascular morbid events between the group with low ambulatory BP and the group with high ambulatory BP ($p=.017$; Relative Risk=6.42). The relative risk for cardiovascular morbid events was not significantly different between the low ambulatory BP group and the medium ambulatory BP group. ($p=.098$; Relative Risk=3.69). The comparison of survival curves among the groups shows significant differences between the low ambulatory BP group and the medium ambulatory BP group ($p<.04$), and between the low ambulatory BP and high ambulatory BP groups. ($p<.006$) No differences between the medium ambulatory BP and high ambulatory BP groups were observed. ($p<.26$) The authors suggest that ABPM is useful in stratifying the risk in patients with refractory hypertension measured by conventional BP.

Ohkubo (1997) reported on a general Japanese population of 1542 men and women in a cohort study. Follow-up time was 8.1 years. The objective of the study was to compare ABPM and clinic BP to determine if one was a better predictor of mortality than the other. All subjects underwent ABPM and clinic BP measurement. Subjects were divided into five groups, based on their ambulatory and clinic BP levels. Results indicated that the subgroup with the highest ambulatory systolic BP had a significantly increased risk of overall and cardiovascular mortality (overall mortality Relative Hazard = 2.36, p=.017; cardiovascular mortality Relative Hazard = 4.61, p=.015). The subgroup with the highest clinic systolic BP had a significantly increased risk of overall mortality (Relative Hazard = 2.25, p<.05) but the increase in cardiovascular mortality for this group based on clinic systolic BP was not significant. The subgroup with the highest ambulatory diastolic BP had a significantly increased risk of cardiovascular mortality (Relative Hazard = 3.39, p<.05). No other significant associations were found for diastolic ambulatory or clinic BP. The ambulatory systolic BP was the only variable which was significantly related to the risk of mortality (Relative Hazard = 1.047, p<.01). The clinic systolic and diastolic BP's and the diastolic ambulatory BP did not show a significant association with mortality.

Verdecchia (1997) investigated the prognostic significance of the difference between clinic and ambulatory BP's before treatment (this difference was taken as a surrogate measure of the white coat effect) in a case-series study. The database of another study (the PIUMA study) was analyzed in order to carry out the investigation of the prognostic significance of the white coat effect. 1522 subjects with a mean age of 52 years were observed for a period of up to 9 years. All subjects underwent ABPM and clinic BP measurement. Subjects were divided into four groups, based on their clinic-ambulatory BP difference. Results indicated the clinic-ambulatory difference (a measure of the white coat effect) does not predict morbidity and mortality in subjects with essential hypertension. Authors reported that the rate of total cardiovascular morbid events did not differ among the four quartiles (2.13, 2.92, 2.10, and 2.83 events per 100 patient-years for systolic BP and 2.94, 2.14, 2.58, and 2.16 events per 100 patient-years for diastolic BP). The rate of fatal cardiovascular events also did not differ among the four quartiles (0.38, 0.69, 0.67, and 0.31 events per 100 patient-years for diastolic BP).

Imai (1996) studied the risks of high and low BP levels determined by ABPM and home BP measurements. In a prospective cohort design, the authors studied over 3000 patients (1192 patients in the ABPM group, 1962 patients in the home BP group) in northeastern Japan. Maximum observation time was > 6 years. Both groups were stratified into quintiles. The ABPM group showed decreased survival in the highest quintile of SBP and in the highest and lowest quintiles of DBP. The casual measurement group only showed a decrease in the highest quintile of SBP. In addition, cerebrovascular and cardiovascular mortalities were higher in the highest and lowest quintiles of ABPM that was not similarly recognized by the casual blood pressure levels. The authors proposed that there is a significant risk associated with low BP that can be determined only by ABPM and home BP measurements, not by casual BP measurements.

Lemne (1995) studied whether 24-hr ABPM is a better predictor of left ventricular hypertrophy (LVH) in borderline hypertensives than casual BP measurements. Eighty-one borderline hypertensives were compared to 80 normotensives. The study was conducted in Sweden, and all patients were men. Casual BP levels did not correlate with LVH indices, while ABPM did correlate with systolic levels in the borderline group, but not the normotensive group. Asymmetric structural changes were detected with ABPM but not casual BP. The authors concluded that the casual BP levels correlate poorly with the degree of LVH in borderline hypertension, while ABPM correlate much more closely with LV wall dimensions.

Boley (1997) attempted to assess the relationship of BP measured through ABPM to left ventricular (LV) and arterial function. The authors studied a total of 280 people, both normotensive subjects and hypertensive patients who had not been previously treated for hypertension. On echocardiography, there were no differences detected relating to LV chamber size, cardiac output, mean wall stress, or circumferential end-systolic stress; there were differences relating to wall thickness, LV mass index, and total peripheral resistance. The authors concluded that, for a population of predominantly hypertensive, unmedicated adults, ambulatory BP's during waking hours and at home are related to left ventricular and arterial function. Such information could lead to better patient management.

Lantelme (2000) attempted to use ABPM to compare the real white coat effect and the estimated white coat effect in terms of magnitude and consequences on target organs. The authors studied 88 patients, 64 of which had never been treated for hypertension. At the end of the study, the authors concluded that true white coat effect and its estimation are not equivalent. In addition, the way in which the white coat was defined did not alter its effect on target organs or cardiovascular risk profile.

Lin (1995) studied 171 patients stratified into four groups: normotensive, isolated diastolic hypertensive, isolated systolic hypertension, and combined hypertension. The authors found that there was a lower incidence of damage in the normotensive group, and that the incidence was higher in isolated systolic than isolated diastolic groups. This suggests that the severity of hypertensive complications is more closely related to mean ambulatory systolic BP than mean ambulatory diastolic BP.

Musialik (1998) compared blood pressure measurements by 24 hr ABPM in young vs elderly hypertensives, and related LVM and different BP ratios. The authors studied 15 patients aged 22 to 45 years, and 15 patients aged 65 to 79 years. Results showed that there were 10 non-dippers in the young group, and seven non-dippers in the elderly group. LVM was similar in both groups.[4] There was a correlation of the nocturnal MAP with LVM in elderly hypertensives and a dependency of nocturnal BP load with LVM. ABPM allowed this correlation to be determined.

Palatini (1997) investigated the prevalence of cardiac and renal changes among subjects with borderline-to-mild hypertension, and assessed the relationship of hypertensive end organ damage to office and ambulatory BP's. Authors studied 1095 patients as part of the Hypertension and Ambulatory Recording Venetia Study (HARVEST). WCH was defined as those with office BP > 140/90 mm Hg and mean day-time BP < 140/90. The authors concluded that ABPM is useful in identifying those patients with WCH. Treatment for hypertension should be based not only on their office BP but also their ambulatory BP, and whether the patient has target organ damage.

Prisant (1990) attempted to examine whether 24-hour ABPM measurement is a better predictor of echocardiographic LV wall thickness than either isolated or multiple averaged office visits. Authors studied a total of 55 hypertensive patients. 24-hr ABPM was more strongly associated with various echocardiographic indices of cardiac target organ damage in stable hypertensive patients than multiple or single office visit BP.

Clinical Consensus and Position Statements of Outside Organizations

Clinical consensus and position statements by specialty societies are an important consideration in determining a national coverage decision. CMS received 14 consensus and position statements. All are available on the CMS website. The most recent policies, and those that specified an evidence-based process to develop the guideline, are highlighted below.

Canadian Hypertension Society and the Canadian Coalition for High Blood Pressure Prevention and Control

The Canadian Hypertension Society and the Canadian Coalition for High Blood Pressure Prevention and Control published a guideline in 1999 with recommendations on the management of hypertension. Using an evidence-based decision-making process, authors first rated the evidence on diagnosis and/or treatment. They then graded their recommendations. [5] Relating to ambulatory blood pressure monitoring for suspected WCH, the following recommendations were made:

1. Physicians should use only ambulatory blood pressure monitoring devices that have been validated independently using established protocols (Grade A)
2. A decision to withhold drug therapy, based upon the ambulatory blood pressure, should take into account normal values for 24 hours, and awake ambulatory blood pressure (Grade B)
3. Ambulatory blood pressure monitoring should be considered for untreated patients whenever an office-induced increase in blood pressure is suspected, including patients with mild-to-moderate blood pressure elevations in the clinic, without target-organ damage (Grade A)

In additional text, the authors note the Ohkubo study that a mean 24-hour ambulatory BP > 134/78 was predictive of increased total and cardiovascular mortality. They also noted the Verdecchia study where normal ambulatory blood pressure was defined as < 136/87 for men, and < 131/86 for women. People with normal blood pressure on 24-hr monitoring have a prognosis similar to those with normal office blood pressure. These guidelines also note that the American Society of Hypertension suggesting that daytime ambulatory blood pressure < 135/85 be considered normal.

Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, sponsored by the National Institutes of Health, used evidence-based medicine and consensus, to provide guidance for primary care physicians. In the section on ambulatory blood pressure monitoring published in 1997, the authors note that the Verdeechia and Perloff studies are the best prospective studies that relate ambulatory blood pressure to prognosis. "These studies suggest that, in patients in whom an elevated clinic pressure is the only abnormality, ambulatory monitoring may identify a group at relatively low risk of morbidity. Ambulatory blood pressure monitoring is most clinically helpful and most commonly used in patients with `suspected white coat hypertension'..." Authors note that 135/85 outside the office should be considered elevated.

British Hypertension Society

The British Hypertension Society published recommendations in April 2000 on the use of ambulatory blood pressure monitoring. The authors point out that ABPM is a more sensitive predictor of cardiovascular outcome than conventional measurement, and that the information obtained is only one factor in determining a patient's risk profile, and must be assessed in relation to concomitant disease, and degree of target organ damage. Relating to white coat hypertension, the authors define it as BP > 140/90 in office, < 135/85 out of office. With this definition, the authors note that WCH is "probably small risk when compared with normal blood pressure." In terms of clinical implication, the guideline recommends that WCH should be considered before drug treatment is prescribed, and information obtained by ABPM must be placed in context of the overall risk profile.

American Society of Hypertension

The American Society of Hypertension (ASH) issued recommendations for the use of ambulatory blood pressure monitoring. An Ad Hoc panel was established in 1996, with Dr. Thomas Pickering as its Chair. Using the Perloff and Verdeechia studies as the best available evidence, ASH concluded that patients in whom an elevated clinic pressure is the only abnormality, ABPM can identify a group at relatively low risk of morbidity. ASH offered the following strategy:

Persistently elevated clinic BP

140-160/90-104

Target organ damage

Home blood pressure

Normal is <134/90

24-hr ambulatory blood pressure

Continue to monitor clinic and home blood pressure

The guideline directly addresses the issue of cardiovascular risk of white coat hypertension. The authors acknowledge that there are two opposing views: the majority of groups consider the prognosis to be benign, while a minority have suggested that the risk in WCH is similar to the risk of patients with sustained hypertension. Overall, the guideline suggests that patients with elevated office BP > 140/90, with no evidence of end-organ damage, and normal ABP < 134/90, should be followed, and not necessarily treated, since they are at low risk.

American College of Cardiology

The American College of Cardiology first put out a position statement on ABPM in 1994. At that time, the ACC recommended ABPM as a "mature, clinically applicable (useful) technology for the management of selected hypertensive patients. The ACC made no further qualifications until September, 2000 when in a letter to the Agency, the College did note that it believed the literature supported the use of ABPM in evaluation of patients with suspected WCH, evaluation of subjects with normal clinic BP but evidence of hypertension-related target-organ damage, and evaluation of autonomic dysfunction. All other indications were not supported or uncertain .[6] Although the letter stated it was not an official position, in subsequent testimony to the MCAC, the ACC did reiterate support of these indications, and specified such as official College policy.

The American College of Physicians /American Society of Internal Medicine

The ACP/ASIM stated in 1994 that ABPM may in theory have a specific role in the diagnosis, prognosis, and management of hypertension, but that evidence to support this role is mostly indirect and that further direct evidence is needed. They assert that the available evidence does not warrant widespread dissemination or routine use of ABPM. However, they support a more circumspect use of ABPM for research and for the care of subgroups of hypertensive patients with specific clinical problems.

Summary of Position Statements

For those guidelines that are more recent, and specified an evidence-based process and rating of evidence as part of their development, there is a significant amount of consistency. Almost all of them support the use of ABPM in the diagnosis of WCH with a general definition of suspected WCH as being > 140/90 in the clinic, < 135/85 outside the office. Several of the guidelines also consider ABPM useful in other indications such as drug resistance and episodic hypertension.

Medicare Coverage Advisory Committee Deliberations

Due to the complexity of the available evidence and lack of clear consensus, this issue was sent to the Medicare Coverage Advisory Committee (MCAC). On February 21, 2001, the Medical Devices and Prosthetics Panel of the MCAC met to discuss the use of ABPM for patients with WCH, patients with refractory (treatment resistant) hypertension, and patients with hypotensive symptoms while on anti-hypertensive therapy. The panel was sent the BC/BS TEC updated technology assessment (updated through January 2001), all articles contained in the bibliographies of the original BCBS TEC assessment and the updated BCBS TEC assessment, CMS literature review tables, all articles contained in CMS literature review tables (13 total), position and consensus statements (14 total).

During the panel meeting, ten people spoke, representing a wide range of interests, including professional societies, physicians and other providers, device companies, and patients.

Dr. Harold Sox, chair of the committee, presented an analytical framework for use in guiding panel discussions on evaluating ABPM. Most of the discussion centered around white coat hypertension, since the panel agreed that no evidence was submitted for the use of ABPM in patients with hypotensive symptoms while on antihypertensive therapy and the panel believed there was inadequate evidence to make a clear judgement about the use of ABPM in patients with refractory hypertension.

There were 5 key questions regarding WCH:

1. *Does ABPM detect patients who have office hypertension but normal BP at home?*

   The panel agreed that yes, ABPM does this.

2. *Do physicians withhold treatment when BP is normal at home but elevated in the office?*

   The panel agreed that there is not much information available concerning what doctors do when they incorporate ABPM into their treatment regimens.

3. *Do patients with untreated WCH have intermediate health outcomes that are the same as people with normal office BP?*

   The panel acknowledged that the prevalence of intermediate outcomes (e.g. left ventricular hypertrophy; intermediate outcome markers that predict cardiovascular disease endpoints) in patients with white coat hypertension is intermediate between normotensives and patients with sustained hypertension. The panel thus acknowledged that white coat hypertension is not necessarily a benign condition.

4. *Do patients with untreated WCH and intermediate health outcomes have final health outcomes (stroke, coronary artery disease) that are the same as people with normal office BP?*

   The panel acknowledged that no studies were available to address this question

5. *Will basing treatment of suspected WCH on the results of ABPM result in health outcomes that are similar to people with normal office BP?*

   The panel concluded that it is not clear what effect the use of ABPM for patients with suspected WCH has on health outcomes due to insufficient data.

The panel also acknowledged that although ABPM is useful in defining a group of hypertensive patients who may require different treatment goals than sustained hypertensives, there is not yet a satisfactory body of evidence to definitively guide further management, or to conclude that treatment alters cardiovascular outcomes. The panel also struggled with the definition of WCH, noting the variability in definitions across studies.

There were 4 key questions regarding apparent drug resistance.

1.

Does ABPM detect treated hypertension patients who have inadequate BP control when measured in the office but adequate BP control when measured at home?

The panel voted yes.

2.

Do physicians maintain treatment regimen when BP control is adequate at home but not adequate as measured in the office?

The panel agreed that there is not much information available concerning what doctors do when they incorporate ABPM into their treatment regimens.

3.

Does treating to achieve adequate BP control as measured at home, despite poor control as measured in the office, lead to the same health outcomes (stroke, coronary artery disease, side effects of treatment) as experienced by patients with adequate control as measured in the office?

The panel concluded that the available evidence does not address this question.

4.

Will basing treatment of treatment-resistant hypertension on the results of ABPM result in health outcomes that are similar to treatment-responsive hypertension as measured in the office?

The panel concluded that it is not clear what affect the use of ABPM for patients with apparent drug resistance has on health outcomes due to insufficient data.

There were 6 key questions presented on hypotensive symptoms while on antihypertensive therapy. However, it was not possible to address any of these questions due to the lack of available evidence.

In general, the panel thought the device could be beneficial. However, the panel acknowledged that there is difficulty in defining the population for whom ABPM should be used. The panel voted and unanimously approved the following statement and recommendation: "The panel believes that the evidence from cross-sectional studies indicates that people with white coat hypertension have intermediate harmful health outcomes (left ventricular hypertrophy, nephropathy, retinopathy) compared with normotensive people. Although higher quality evidence (e.g., randomized clinical trials) is lacking and data on true health outcomes (e.g., mortality, cardiovascular disease morbidity) are sparse and of relatively low quality, the panel believes that the use of ABPM in diagnosing white coat hypertension can help guide individualized treatment of persons with white coat hypertension (e.g., whether and when to initiate medication, deciding which medication(s) to use), which may in turn improve health outcomes. Therefore, the panel supports ABPM for diagnosis of white coat hypertension in patients with suspected white coat hypertension if guidelines are developed for selecting patients for ABPM and managing white coat hypertension. The panel recommends that studies be done to better define white coat hypertension and low-risk patients."

On June 14, 2001, the MCAC Executive Committee met and ratified the recommendation of the Medical Devices and Prosthetics Panel. However, the executive committee changed the wording in a section of the recommendation. They changed the sentence, "Therefore, the panel supports ABPM for diagnosis of white coat hypertension in patients with suspected white coat hypertension if guidelines are developed for selecting patients for ABPM and managing white coat hypertension" to "Therefore, the panel supports ABPM for diagnosis of white coat hypertension in patients with suspected white coat hypertension when guidelines are developed for selecting patients for ABPM and managing white coat hypertension". This decision was submitted to CMS on July 23, 2001.

CMS Analysis

After a careful review of the available clinical and scientific evidence, there are five outstanding questions that remain in determining whether ABPM are "medically reasonable and necessary" diagnostic tests:

- Is there sufficient evidence available on each of the five requested indications to conduct an effective evidence-based review of ABPM?
- How appropriate are surrogate measures?
- How does one identify a population at risk for having WCH?
- Does the use of ABPM alter management in patients with suspected WCH?
- Is the use of ABPM in patients with suspected WCH likely to improve patient outcomes?

There is little uncertainty that ABPM produces a valid and potentially more accurate and reproducible BP measurement than does clinic measurement, since the device is able to monitor BP during activity and sleep states. [7] In addition, more frequent measurement would in general lead to a more accurate reading. More readings would reduce random error and allow for more accurate diagnosis. The medical appropriateness and reasonableness of such devices remains to be addressed.

Is there sufficient evidence available on each of the five requested indications to conduct an effective evidence-based review of ABPM?

As noted earlier, the original request for a national coverage determination addressed five indications:

1. suspected WCH;
2. apparent drug resistance;
3. hypotensive symptoms while on antihypertensive therapy;
4. episodic hypertension;
5. autonomic dysfunction

Of the information presented, the overwhelming majority of information addressed the use of ABPM in patients with suspected WCH. The BC/BS TEC exclusively looked at WCH since no articles of adequate quality (as determined by the inclusion/exclusion criteria) were found on the other indications. [8] CMS' internal literature search provided a total of 13 articles, 3 of which addressed WCH. One of the 13 articles addressed resistant hypertension, while the remaining 9 articles concentrated on the use of ABPM for hypertension in general.

Moreover, the position statements primarily addressed WCH. The MCAC also was unable to appropriately answer the questions posed to them concerning the last 4 indications due to a lack of adequate information. Given the lack of well-designed studies on the other indications and the fact that the studies on the use of ABPM in WCH are not necessarily generalizable for the other indications, this decision memorandum will only address the use in suspected WCH. It is important to note that the lack of sufficient evidence does not imply that the use of ABPM in these indications is not of benefit, but rather, simply states that there is not adequate evidence to make a definitive determination about effectiveness.

How appropriate are surrogate measures?

Of the 31 studies reviewed, 27 used surrogate outcomes measures. The most important outcomes of chronic hypertension are morbidity and mortality associated with stroke and myocardial events. In general, these outcomes occur infrequently, and are difficult to demonstrate in small studies that are typically only a few years in duration. At the same time, there is conclusive evidence that elevated BP increases cardiovascular risk. As a result, markers of damage to organs such as the left ventricle of the heart, the kidney, the eye, and the arterial system are recognized as appropriate surrogate outcomes. Some of the most common surrogate endpoints in the studies reviewed were left ventricular mass, left ventricular hypertrophy, wall thickness, proteinuria, and retinopathy. Although ideally, we would like to have seen primary outcome measures, in this particular circumstance, the surrogate measures used are appropriate and acceptable to serve as the basis for determining coverage.

How does one identify a population at risk for having WCH?

A standard definition for WCH remains unclear. However, there is some consensus developing in the medical literature. As noted earlier, WCH is the most common term for the occurrence of elevated BP when measured in a physician's office in an otherwise normotensive individual. The etiology is believed to be a rise in adrenal activity, and catecholamine release, brought upon by the stress associated with the appearance of the physician. Other terms include isolated clinic hypertension, isolated office hypertension, and non-sustained hypertension. Although precise numbers remain elusive, there appears to be consensus in the studies reviewed. As Table 1 demonstrates, the overwhelming majority of studies defined WCH as office BP > 140/90 with measurements outside the office BP < 140/90. In addition, there typically were at least three separate measurements prior to use of the device.

Table 1: Definitions of WCH

Study	Definition of WCH
Cardillo, 1993	Office DBP > 90 and ambulatory BP < 134/90
Cavallini, 1995	Office BP 140/90 and awake ambulatory BP < 134/90 (< 142/90 if > 65yo)
Ceresola, 1995	Office BP > 145/90 and day ambulatory BP < 134/90
Chang, 1997	Office BP > 140/90 and ambulatory BP < 127/81
Ferrara, 1997	Office BP > 140/90 and ambulatory BP < 130/85
Glen, 1996	Office DBP > 95, ambulatory DBP < 95

Study	Definition of WCH
Hoegholm, 1994	Office DBP > 90 and daytime ambulatory DBP < 90
Kuwajima, 1993	Office BP > 160/90 and ambulatory systolic BP < 140
Muldoon, 2000	Clinic BP > 140/90 and daytime ambulatory BP < 140/90
Nalbantgil, 1998	Office BP > 140/90 and awake ambulatory BP < 134/90 (< 142/90 if > 65yo
Palatini, 1997	Office BP >140/90 and mean daytime BP <135/85 or <140/90
Palatini, 1998	Office BP 140-159/90-99 and ambulatory BP < 130/80 or < 135/85
Pierdomenico, 1995	Office BP > 140/90 and ambulatory BP < 135/85
Pose-Reino, 1996	Office BP > 140/90; Mean ambulatory BP < 135/90; day ambulatory BP < 140/90; night ambulatory BP < 120/80
Soma, 1996	Office DBP > 90 and daytime ambulatory BP < 140/90

Study	Definition of WCH
Verdecchia, 1992	Clinic DBP > 90 and ambulatory BP < 136/87 for men and < 131/86 for women
Verdecchia, 1994	Office BP > 140/90 and daytime ambulatory BP < 131/86 (women), < 136/87 (men)
Weber, 1994	Ambulatory DBP < 85, and at least 15 mm lower than office BP
White, 1989	CBP > 140/90 and ambulatory BP < 130/80
Zakopoulos, 1999	Clinic BP > 160/90, and ambulatory SBP < 130

In addition, the various guidelines reviewed address the definition of WCH with the general definition of > 140/90 in the office, < 135/85 on 24 hour ambulatory blood pressure monitoring. Testimony at the MCAC also focused on these same parameters. Furthermore, in a review by Pickering looking at 23 studies from 1988 to 1998 dealing with WCH, 20 studies used 140/90 as the cutoff point for clinic measurements; almost all used either < 140/90 or < 135/85 as the cutoff for the ambulatory measurement.[9] Given this considerable consensus in the scientific literature and clinical community and the guidance thereof, we will define suspected WCH as BP > 140/90 in the physician's office, and < 140/90 outside the physician's office. The measurements outside the physician's office can be from various methods, but it needs to be a method, which the physician believes to be reliable for the information it is providing. Such an approach would be comparable to the studies and guidelines reviewed. There are some studies that have a slightly more restrictive definition, but we are choosing the definition upon which there is most consensus, and from which more patients can benefit. In addition, most studies included the lack of target organ damage as part of the definition. Target organ damage typically is indicated by left ventricular hypertrophy, proteinuria, and retinopathy.

Does the use of ABPM alter management in patients with suspected WCH?
Is the use of ABPM in patients with suspected WCH likely to improve patient outcomes?

The studies reviewed demonstrated that ABPM could identify patients with suspected WCH. ABPM can therefore serve a useful role in identifying patients who have an elevated BP in the office, but otherwise are normotensive. This device would not be useful for the typical patient who presents with an elevated BP but only those patients where the diagnosis of WCH is suspected.

As noted earlier, ABPM can provide more accurate information regarding a patient's risk of cardiovascular events compared to office BP measurements alone. Given that ABPM accurately measures BP, and can identify a patient with suspected WCH, does this information help physicians in the management of patients? That is, should physicians change the management of patients based on the diagnosis of WCH? [10] To answer these questions, one must also address whether the use of ABPM in patients with WCH leads to improved patient outcomes. After all, the collection of data for its own sake is not sufficient to warrant coverage.

The answer lies in determining the cardiovascular risk associated with WCH. It becomes less clear because there is some uncertainty about the risk of patients with WCH. The BC BS TEC assessment is equivocal in determining the risk associated with WCH: "Some studies report values close to, or equivalent to normotensive patients, while others report values far greater than normotensive patients and closest to the values for patients with sustained hypertension." The report does state that "reported results of these studies do not support the hypothesis that the risk of adverse outcomes is similar to normotensive patients. For patients with WCH, the mean values on measures of end-organ damage are consistently higher than those for normotensive patients, and lower for patients with sustained hypertension. This raises the possibility that patients with WCH will have rates of adverse cardiovascular events that are higher than normotensive patients. However, the degree of risk that might be associated with WCH cannot be estimated from these data."

The MCAC also debated this issue of risk; there was concern that such information obtained by ABPM might misguide physicians in withholding treatment from patients who would benefit from antihypertensive therapy. Therefore, the MCAC felt there should be some guidance. Using the definition of suspected WCH discussed earlier, considerable guidance does exist, based on stratified risk. That is, we know from epidemiological studies, the different levels of cardiovascular risk based on certain systolic and diastolic blood pressure. The most well-designed studies in this field are Verdecchia, Fagard, Perloff, and Ohkubo, which are, in general, used as the basis for most of the guidelines/recommendations by specialty societies. As noted earlier, Verdecchia showed in a prospective cohort study design that men with BP < 136/87 and women with BP < 131/86 on ABPM did not have increased cardiovascular risk, as compared to patients with normal office blood pressure. Fagard studied 353 subjects in a randomized double blind placebo controlled trial. [11] He demonstrated that subjects with nonsustained hypertension were at lower risk of poor outcome than subjects with sustained hypertension. Fagard also found that active treatment reduced the outcome of cardiovascular events to a statistically significant extent only in the group with moderate sustained hypertension and not in the group with nonsustained hypertension. Okhubo concluded that ambulatory BP > 134/78 was predictive of increased cardiovascular risk.

The guidelines have used this information and developed the treatment recommendations discussed earlier in this document. In general, if a patient has a 24-hour ambulatory blood pressure < 135/85, they are unlikely to be at increased risk, and should be followed over time.

One of the potential benefits of accurate diagnosis of WCH is that a patient may be able to avoid medication, with the subsequent adverse events associated with antihypertensives. Although serious adverse events are infrequent, such events can be particularly dangerous in elderly patients, since causing hypotension can lead to falls, dizziness, and myocardial infarction. Avoiding these adverse events is desirable, and would improve a patient's health outcomes.

In addition, a physician may better assess a patient's overall cardiovascular risk with the information provided by ABPM, and decide how best to manage elevated BP. After all, informed decision making is enhanced by full knowledge of disease and its risks. Based upon the diagnosis of WCH, a physician can then decide whether or not he wishes to treat the patient. The physician needs this information in order to make an effective treatment decision; ABPM will provide this data.

Conclusion

ABPM provides an accurate and reliable method for measuring blood pressure. It can provide useful information to a physician, to determine whether a patient is truly hypertensive, or is exhibiting white coat hypertension. With that information, a physician can better manage the patient. ABPM will provide more information on a patient's cardiovascular risk, and with such information, a physician can more appropriately treat the patient. Although there are other potential uses for ABPM, we will not issue a national coverage decision on such indications at this time, until more data becomes available as to how it affects patient management. We welcome interested parties to speak with CMS about study design and outcome measures.

DECISION:

At this point in time, ABPM will be covered for those patients with suspected WCH. Suspected WCH will be 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.

We encourage physicians to study the guidelines on the management of WCH. For those patients that undergo ABPM, and have an ambulatory BP < 135/85 with no evidence of end-organ damage, it is likely that their cardiovascular risk is similar to normotensives. They should be followed over time. For those patients for which ABPM demonstrates BP > 135/85, they may be at increased cardiovascular risk, and a physician may wish to consider antihypertensive therapies.

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1 The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI), National Heart, Lung, and Blood Institute: National High Blood Pressure Education Program, NIH Publication No. 98-1080, November 1997

2 JNC VI, (1997)

3 Grin JM, McCabe EJ, White WB. Management of hypertension after ambulatory blood pressure monitoring. *Annals of Internal Medicine* 1993;118:833-837.

4 Dippers refers to the phenomenon that blood pressure rises in the early morning, remains elevated during the day, and decreases during the night. About 10% of people do not show a decrease in BP at night. These are referred to as non-dippers.

5 Grading system for recommendations:
A The recommendation is based on one or more studies at Level I
B Best evidence available was a Level II
C Best evidence available was at least Level III
D Best evidence available was lower than Level III and included expert opinion

6 This letter is signed by College President, Dr. George Beller. He specifies that the document is not an official ACC clinical statement or guideline.

7 This review did not focus on the accuracy and reliability of these devices. The FDA clearance process has assured that these devices are accurate and reliable in measuring blood pressure.

8 This is not to say that no articles exist on the use of ABPM for these other indications, or that ABPM has no use in these other indications. Rather, CMS believes the studies were not adequately designed, to allow for adequate conclusions.

9 Pickering TG, Coats A, Mallion JM, Mancia G, Verdecchia P. Task Force V: White coat hypertension. *Blood Pressure Monitoring* 1999;4:333-341.

10 In addressing coverage of diagnostic tests, it is important that these tests accurately diagnose a condition, but the information obtained from these tests should affect patient management.

11 Fagard RH et al. Response to antihypertensive therapy in older patients with sustained and nonsustained systolic hypertension. *Circulation* 2000;102:1139-

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