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Controversies in Hypertension I: The Optimal Assessment of Blood Pressure Load and Implications for Treatment

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ABSTRACT

The most important factor in treating hypertension is assessing an individual patient's true blood pressure load, the cornerstone being research-grade office determination. Office blood pressure should be supplemented with out-of-office measurement, including home and ambulatory monitoring (if available), which we consider complementary and not interchangeable. Controversy remains for initiation of treatment of white coat hypertension, where cardiovascular risk lies between normotension and sustained hypertension; antihypertensive therapy should be considered unless low cardiovascular risk, wherein pressures should be followed for progression to sustained hypertension. Available data do not support intensification of therapy for the white coat effect due to the similar cardiovascular risk to controlled hypertension. Given the higher cardiovascular risk of the masked effect, initiation of therapy for masked hypertension and intensification for masked uncontrolled hypertension are indicated, acknowledging the dearth of supporting data. Optimally, randomized controlled trials are needed to determine the benefit of treating the 4 incongruous phenotypes between office and out-of-office measurements, that is, those with white coat or masked effects. We make no recommendations regarding chronotherapy pending results of ongoing trials.
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KEYWORDS: Ambulatory blood pressure monitoring; Home blood pressure monitoring; Hypertension; Masked hypertension; White coat hypertension

INTRODUCTION

Hypertension remains a major cause of mortality and loss of quality-adjusted life years.[1] Observational data indicate a graded relationship between usual blood pressure and cardiovascular morbidity/mortality.[2,3] Reduction of high pressure reduces cardiovascular events based on data from multiple randomized controlled trials.[4,5] Lifestyle modifications should be encouraged for all patients.[6] However, there are several aspects of the diagnosis and treatment of hypertension that remain controversial.

Historically, blood pressure was determined in the office in the therapeutic trials proving the benefit of treatment. Out-of-office measurements compared with office measurements, however, show a stronger correlation with cardiovascular events.[7] There are 2 approaches to obtaining out-of-office pressures: 24-hour ambulatory monitoring and self-monitoring by the patient at home.

OFFICE BLOOD PRESSURE MEASUREMENT

Office pressure remains the cornerstone of diagnosis and treatment but should be obtained in a standardized manner. Current American College of Cardiology/American Heart Association guidelines (Guidelines) recommend multiple

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factors required for accuracy (Table 1).[6] An average of ≥2 readings on ≥2 occasions should be used to confirm the diagnosis. Pressures obtained in this manner are considered research grade.

A controversial issue is whether office pressures should be obtained with the patient unattended by office personnel, as in the Systolic Blood Pressure Intervention Trial (SPRINT).[8] Automated oscillometric sphygmomanometers like those used in SPRINT are now available commercially and can be programmed to automatically take multiple readings unattended by staff following a period of rest, termed automated office pressure, and Canadian Guidelines now recommend this as the preferred method.[9] Multiple studies have shown that automated pressure is significantly lower than attended office pressure and more closely approximates daytime ambulatory readings.

Controversy arises when attempting to utilize the intensive target of SPRINT when obtaining attended office pressure, even if research grade. Being unattended removes the "white coat" effect, and pressures are generally lower than if attended. The concern is that the intense unattended target in SPRINT may be significantly higher if obtained attended. Interestingly, nonattendance was not specified in the published protocol[8] and was not universal, as some patients were alone during both rest and measurement, whereas others were never alone.[10] Importantly, the never-alone and always-alone groups attained similar pressures with equivalent numbers of medications and no difference in serious adverse events.

CLINICAL SIGNIFICANCE

- Treatment of hypertension should be based on research-grade office determinations supplemented by out-of-office measurements.
- Comparison of office and out-of-office measurements generates 4 phenotypes in both treated and untreated patients: sustained hypertension, normotension, the white coat effect, and the masked effect.
- Evidence suggests treatment initiation/intensification for the masked effect and no intensification for the white coat effect in treated patients.
- Consider initiation of therapy for untreated white coat hypertension if high cardiovascular risk.

Table 1 Characteristics of Research-Grade Blood Pressure (BP) Determination

1. 5 min of rest
2. Feet on floor
3. Legs uncrossed
4. Back supported
5. Arm supported
6. Bare arm
7. Correct cuff size
8. No talking
9. No mobile phone use
10. Pressure in both arms
11. Notation of arm with higher reading for future use
12. Obtain ≥2 measurements on ≥2 occasions to estimate BP load
13. Separate repeated measurements by 1-2 min
14. Avoid caffeine, exercise, and smoking for at least 30 min
15. Ensure patient has emptied the bladder

A meta-analysis of 31 studies comparing automated pressures with either casual office pressures or pressures obtained as part of a research study found that both the mean casual and research systolic pressures were significantly higher (by 14.5 and 7, all pressures in mm Hg) than the automated pressures when mean automated systolic pressure was <130 mm Hg.[11] Furthermore, the mean automated pressures were nearly identical to daytime ambulatory pressures. Other data indicate that automated pressures may be lower than daytime ambulatory pressures.[12]

Importantly, the difference between office and out-of-office pressures may be affected by age and treatment status. A meta-analysis of 27 studies involving untreated patients found that awake ambulatory pressures were lower than office only after the age of 50 years, whereas in those under 50, daytime ambulatory was higher; home pressures were lower than office at all ages.[13] Subsequent studies in untreated patients with mean ages <50 years found similar results.[14-16] Multiple studies indicate that when treated and controlled, automated pressure is also lower than daytime ambulatory pressure,[12,17,18] similar to untreated adults aged <50 years.[14-16]

The necessary amount of rest prior to obtaining office measurements remains uncertain. Guidelines specify 5 minutes. However, in the Zero to Five study, automated pressures obtained after 0 minutes of rest were closer to daytime ambulatory pressures than after 5 minutes rest, which were 5 lower than ambulatory.[17] In the Best Rest Trial, pressures were measured after 0, 2, or 5 minutes of rest and again after another 5 minutes.[19] Compared with the difference between the 2 5-minute periods, the difference for 0 minutes rest was not inferior, although the 2-minute period was. When dichotomized by systolic pressure, neither the 0 nor 2-minute rest periods were inferior to 5 minutes if systolic pressure was <140 mm Hg, but were inferior if ≥140, suggesting 5 minutes is not necessary if pressure is controlled.

OUT-OF-OFFICE MEASUREMENT

The gold standard for assessing pressure is considered 24-hour ambulatory monitoring,[6] which provides multiple

metrics, including 24-hour average, average daytime, average nighttime, night-day ratio (dipping status), and variability. Multiple studies have shown significant superiority of these metrics over office pressures in predicting cardiovascular events.[7,20] By multivariable analysis, ambulatory pressures retain prognostic significance, whereas office pressures do not.[21] Similarly, when controlled for each other, home pressures remained a significant predictor of cardiovascular events, whereas office pressures did not,[22] and home pressures also have a significantly better correlation than office with both subclinical target organ damage[23] and cardiovascular events.[24] An American Heart Association policy statement on home monitoring was recently published.[25]

HYPERTENSION PHENOTYPES

The threshold for diagnosing and treating hypertension remains arbitrary, with differences between Guidelines.[26] Patients can be above (hypertensive) or below (normotensive) threshold. This dichotomy applies to both office and out-of-office pressures. Patients can also be dichotomized into treated or untreated. The result is 4 potential phenotypes each for both untreated and treated patients (Table 2). If above the threshold both in and out of office, the patient has sustained hypertension if untreated, or sustained uncontrolled hypertension if treated. If below the threshold both in and out of office, the patient has true normotension if untreated, or sustained controlled hypertension if treated. If office measurement is above the threshold but out-of-office is below, the untreated patient has white coat hypertension and the treated patient has a white coat effect. If the office is below threshold, but out-of-office is above threshold, the untreated patient has masked hypertension and the treated patient has masked uncontrolled hypertension.

The appropriate thresholds for both office and out-of-office pressures remain controversial.[27] To designate these thresholds, several methods are available. A distribution-based approach defines each threshold as 2 standard deviations above the mean.[28-30] A regression-based approach utilizes regression models to estimate out-of-office pressures based on office pressures.[31,32] The preferred method utilized by the Guidelines is the outcomes-based approach, which defines each threshold by an equivalent incidence of adverse events in those above it.

Most studies assessing hypertension phenotypes used 140/90 mm Hg for office and either 135/85 (home or ambulatory) for daytime out-of-office or 130/80 for 24-hour (ambulatory) to define hypertension. The Guidelines utilize an office threshold of 130/80 mm Hg. Corresponding out-of-office thresholds based predominantly on the outcomes-based approach are 130/80 mm Hg by home; and by ambulatory, 130/80 (daytime), 110/65 (nighttime), or 125/75 (24-hour average) (Table 3).[6]

Reproducibility of phenotypes is imperfect. The Guidelines call for office measurements on at least 2 occasions for diagnosis. Over 50% of patients deemed hypertensive on one visit may be normotensive on a second visit, perhaps due to measurement error or regression to the mean.[7,33] Reproducibility issues also exist out of office. Bo et al[34] meta-analyzed observational studies where ambulatory monitoring was repeated within 1 month. Reproducibility was excellent on a population level. However, for the individual patient, there were wide limits of agreement, for example, for daytime systolic, −16.7 to 18.4, and 32% had inconsistent dipping results. Mancia et al[35] followed patients with ambulatory pressures repeated yearly for 4 years. About 30% of patients with masked or white coat effects on one visit maintained the same status 1 year later. Only about 5% persisted on all visits.

Multiple studies compared home and ambulatory monitoring for classifying the 4 phenotypes. Stergiou et al[36] found κ values of 0.40 and 0.37 for diagnosing hypertension and white coat hypertension, respectively. Kang et al[37] found κ values of 0.40 to 0.46 for white coat and masked effects, respectively. Ntineri et al[38] found diagnostic agreement on phenotypes in 80% of treated and untreated participants with $\kappa = 0.70$. Similarly, Kim et al[39] found diagnostic agreement of 79% in untreated patients. In contrast, Mancia et al[40] studied 2051 treated/untreated subjects and found that 164 had white coat effects concordantly diagnosed by both ambulatory and home measurement; however, 227 were diagnosed discordantly by only one method. A better correlation with masked hypertension and left ventricular mass was found using home, compared with ambulatory, measurements.[15,16] Shimbo et al[41] performed a systematic

Table 2 Hypertension Phenotypes

	Office BP	Out-of-Office BP	Phenotype
Untreated patient	Below threshold	Below threshold	Sustained normotension
	Above threshold	Above threshold	Sustained hypertension
	Above threshold	Below threshold	White coat hypertension
	Below threshold	Above threshold	Masked hypertension
Treated patient	Below threshold	Below threshold	Controlled hypertension
	Above threshold	Above threshold	Uncontrolled hypertension
	Above threshold	Below threshold	White coat effect
	Below threshold	Above threshold	Masked uncontrolled hypertension

BP = blood pressure.
See Table 3 for comparative office and out-of-office blood pressure (BP).

Table 3 Comparative Blood Pressure Thresholds for Office and Out-of-Office Hypertension Diagnosis*

Office Blood Pressure (mm Hg)	Out-of-Office Blood Pressure (mm Hg)			
	Home Blood Pressure	Ambulatory Blood Pressure		
		Daytime	Nighttime	24-h
120/80	120/80	120/80	100/65	115/75
130/80†	130/80	130/80	110/65	125/75
140/90‡	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

*Adapted from American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines.[6]
†Current ACC/AHA Guideline-recommended comparative thresholds for hypertension diagnosis.
‡Comparative thresholds used by the majority of studies addressing hypertension phenotypes.

review of studies comparing the ability of home and ambulatory measurements to predict cardiovascular events and found no clear superiority. We consider both out-of-office methods complementary, and both could be used. We suggest ambulatory monitoring should be the initial method if available, with home monitoring for confirmation.

Determining the correct phenotype influences initiation or intensification of therapy (Tables 4 and 5).[6] Sustained hypertension in the untreated patient requires initiation, and sustained uncontrolled hypertension in the treated patient necessitates intensification. Sustained normotension in the untreated patient and sustained controlled hypertension in the treated patient do not require initiation or intensification of therapy, respectively. More controversial is the patient with either white coat or masked phenomena.

Table 4 Recommendations for Initiation of Therapy in the Untreated Patient Based on Class (Strength) and Level (Quality) of Evidence*

White Coat Hypertension	Sustained Hypertension
Possibly initiate therapy	Initiate therapy
2C	1A
Sustained Normotension	Masked Hypertension
Do not initiate therapy	Initiate therapy
3C	1C

*Strength of recommendation ranges from 1 (strong recommendation) to 3 (no benefit/potential harm). Level of evidence ranges from A (based on 1 or more high-quality randomized controlled trials or meta-analyses) to C (expert opinion). See Whelton et al, 2017[6] for detailed description of strength and quality scales.

Table 5 Recommendations for Intensification of Therapy in the Treated Patient Based on Class (Strength) and Level (Quality) of Evidence*

White Coat Effect	Uncontrolled Hypertension
Do not intensify	Intensify therapy
3B	1A
Controlled Hypertension	Masked Uncontrolled Hypertension
Do not intensify therapy	Intensify therapy
3C	2C

*Strength of recommendation ranges from 1 (strong recommendation) to 3 (no benefit/potential harm). Level of evidence ranges from A (based on 1 or more high quality randomized controlled trials or meta-analyses) to C (expert opinion). See Whelton et al., 2017[6] for detailed description of strength and quality scales.

ISOLATED OFFICE HYPERTENSION OR THE "WHITE COAT" PHENOMENON

The prevalence of white coat hypertension is quite high, 10%-15% of the general population and 30% of patients with elevated office pressures. The Guidelines recommend not starting antihypertensive drug therapy for white coat hypertension. In our opinion, this remains controversial. Multiple studies assessed the risk of the white coat phenomenon, and multiple meta-analyses have been published.[7,21,42-47] Three earlier meta-analyses concluded there was no increased risk for stroke[42] or total cardiovascular events;[21,43] however, the included studies contained both treated and untreated patients. We will discuss white coat hypertension (untreated) and white coat effect (treated) individually.

A meta-analysis of 8 studies restricted to untreated patients found no increased risk for future cardiovascular events compared with normotensives.[44] A 2015 systematic review evaluated the ability of ambulatory monitoring to predict cardiovascular events in untreated patients after adjustment for office pressures and found similar risk for future cardiovascular events between white coat hypertension and normotension.[7]

Briasoulis et al[45] analyzed 14 studies including some with both treated and untreated patients, and found significantly more cardiovascular events with the white coat phenomenon compared with normotension but significantly less than sustained hypertension. Similarly, cardiovascular mortality was significantly higher compared with normotension and significantly lower than sustained hypertension. If anything, the inclusion of treated patients would have biased results toward the null (vide infra). There were no significant differences regarding all-cause mortality or stroke.

Huang et al[46] restricted analysis to patients with white coat hypertension in 8 studies and found increased risk of cardiovascular events and mortality compared with normotension. Most recently, Cohen et al[47] analyzed 27 studies and found that white coat hypertension was associated with

a significantly increased risk for cardiovascular events, cardiovascular mortality, and total mortality. Sensitivity analyses indicated loss of significance in studies restricted to younger individuals (mean age <55 years) or those without previous cardiovascular disease and attenuated in studies including stroke.

Overall, the data suggest white coat hypertension is not benign, especially in those at higher cardiovascular risk. This may result from several mechanisms. First is misclassification, especially if out-of-office pressure is assessed only once. Prior to withholding treatment, both home and ambulatory measurements should be performed, if possible, to verify out-of-office normotension. Although out-of-office pressure is within the normal range in white coat hypertension, it is higher than that in patients with sustained normotension,[48,49] which increases risk. Second, white coat hypertension has been associated with metabolic abnormalities and new-onset diabetes.[48,50] Third, there is increased risk for conversion to sustained hypertension.[40,51] Finally, subclinical target organ damage may already be present, for example, increased aortic pulse wave velocity, increased urine albumin, or reduced estimated glomerular filtration rate.[51]

Unfortunately, few data exist regarding treatment of white coat hypertension. Mancia et al[52] compared treatment of such patients to those with sustained hypertension. Both groups had similar reductions in office pressure, but only the sustained hypertensives had a decrease in 24-hour pressure. Another study found similar results with reductions only in the clinic pressure with white coat hypertension.[53] Together, these 2 studies suggest that concern for excessive lowering of out-of-office pressure is not warranted when treating white coat hypertension. In the Hypertension in the very Elderly Trial, 50% met criteria for white coat hypertension.[54] The positive results of the overall trial suggest white coat hypertension in the very elderly benefits from treatment.

In treated patients with white coat effect, data indicate cardiovascular risk similar to patients with treated controlled hypertension. In the meta-analysis by Cohen et al,[47] in trials limited to patients on treatment, a white coat effect was not significantly associated with either cardiovascular events or total mortality. The Guidelines do not recommend intensifying therapy and we agree. Patients should be followed with home monitoring to verify maintenance of out-of-office control.

THE MASKED EFFECT

The masked effect portends a significantly worse prognosis for cardiovascular events and death compared with patients with sustained normotension or treated controlled hypertension.[55] Intermediate subclinical endpoints are also increased.[16] In a meta-analysis of untreated patients, the adjusted hazard ratio for any cardiovascular event was 2.09 compared with sustained normotension. The Guidelines recommend initiation (untreated) or intensification (treated) of therapy for the masked effect, and we agree.

A striking feature of the masked effect is the frequency.[56-58] Wang et al[58] imputed a masked hypertension prevalence of 12.3% among 139 million untreated US adults free of cardiovascular disease. Franklin et al[59] found 30% of untreated patients with diabetes had masked hypertension. More concerning is the high prevalence of masked uncontrolled hypertension in those on treatment who otherwise appear to be controlled. Banegas et al[60] found that 31% of 14,840 patients with controlled office hypertension were masked. Sabuncu et al[61] found that 41% of 3212 diabetic patients with hypertension (87% treated) were masked. Of 333 treated veterans with chronic kidney disease, 51% were masked by home monitoring, as were 56% by ambulatory monitoring.[62]

Hence, physicians must be diligent about obtaining out-of-office pressures in those with office pressure <130/80 mm Hg, whether on treatment or not. This would especially apply to those at higher cardiovascular risk with a higher chance of having a masked effect (older, male, diabetes, kidney disease). The only controversial aspect regarding the masked effect is the lack of any trials specifically in those with a masked effect proving the benefit of initiation/intensification of therapy.

NIGHTTIME BLOOD PRESSURE

Nighttime pressure, also referred to as sleep pressure, can be readily obtained with ambulatory monitoring. Whereas monitors for nighttime home monitoring have been developed,[63] none are approved by the US Food and Drug Administration. The Guidelines define nighttime hypertension as ≥110/65 mm Hg. Nighttime pressure normally decreases by 10%-20% compared with daytime (normal "dipping"). A night/day ratio decrease >20% is extreme dipping, <10% is non-dipping, and anything >1 is reverse dipping. Abnormal dipping may occur in 50% or more of hypertensives[64] and 80% of those with concurrent kidney disease.[65] Multiple studies have shown nighttime metrics to be stronger predictors of cardiovascular events and mortality than daytime or 24-hour pressures, whether considered as the absolute level[66-68] or by abnormal dipping status.[64]

Nighttime dosing of antihypertensive medications, termed chronotherapy, has been studied as an alternative to morning dosing. A 2011 Cochrane review found 21 trials, none of which reported on cardiovascular events or mortality.[69] There was no difference in adverse events or withdrawals, but 24-hour pressure was significantly lower. Two subsequent trials showed no benefit of nocturnal dosing on clinic, 24-hour, or nocturnal pressures compared with morning dosing.[70,71] In a meta-analysis of 19 trials comparing nighttime with morning dosing of amlodipine, Luo et al[72] found no significant effect on office, 24-hour, or daytime pressures, but significantly improved nighttime pressure and reduced non-dipper status. Similarly, in a meta-analysis of 5 trials and one comparative study, Wang et al[73] also found a significant decrease in nocturnal systolic/diastolic pressures, a significant increase in awake systolic

pressure, and a significantly reduced non-dipping status. There was little overlap in the trials included in these 2 analyses.

There are 3 trials comparing taking ≥1 medication at bedtime or all in the morning, assessing hard endpoints, all by the same group and all showing reduced cardiovascular events.[74-76] For example, in the Hygia Chronotherapy Trial of 19,084 hypertensive patients, total cardiovascular events were reduced by 45%.[76] Unfortunately, controversy surrounds these impressive results.[77-80] We refrain from making recommendations regarding chronotherapy until ongoing trials are reported.[81,82]

CONCLUSION

The most important factor in treating hypertension is assessing an individual patient's true pressure load. This begins with research-grade office measurement. Whether office pressure should be obtained unattended is uncertain, but consistency should be utilized. Office pressure should optimally be supplemented with out-of-office measurement, including both home and 24-hour ambulatory (if available), which we consider complementary. The cardiovascular risk of white coat hypertension lies in between normotension and sustained hypertension and should prompt consideration of therapy unless low cardiovascular risk (Table 4), wherein patients should be followed for progression to sustained hypertension. Available data do not support intensification of therapy for white coat effect given the similar cardiovascular risk to controlled hypertension (Table 5). Given the higher cardiovascular risk of the masked effect, we recommend initiation of therapy if untreated and intensification if treated, acknowledging the dearth of supporting data. Optimally, trials are needed to determine the benefit of treating the 4 incongruous phenotypes between office and out-of-office measurements, that is, white coat and masked effects. We make no recommendations regarding chronotherapy pending results of ongoing trials.

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