

White Coat Hypertension: Addressing the 10 Most Important Questions

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Abstract The term ‘white coat’ hypertension (WC-HTN) is intended to reflect the situation in which measurement of blood pressure (BP) by a health professional (often a physician in a white coat) in an office setting is found to be elevated in comparison with BP measured by a more consistent and less error-prone method such as ambulatory BP monitoring (ABPM), or home BP monitoring (HBPM). Office BP (also sometimes called ‘casual BP’) has formed the basis of clinical trials that confirm meaningful reductions in MI (25 %), stroke (40 %), and heart failure (50 %) with pharmacotherapy. Nonetheless, within clinical trials, a substantial minority of patients have been determined to have WC-HTN, for which treatment is not known to be of benefit, and is hence not indicated. Clinicians continue to have a good deal of uncertainty about the definition, consequences, course, and best management of WC-HTN. The intention of this communication is to address the top priority questions about WC-HTN to enable clinicians to become more confident in its identification and management.

Keywords White coat hypertension · Home blood pressure · Ambulatory blood pressure · Resistant hypertension

Abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
AKA	Also Known As
BP	Blood Pressure
CIMT	Common Carotid Intimal-Medial Wall Thickness
HBPM	Home Blood Pressure Monitoring
HTN	Hypertension

MI	Myocardial Infarction
M-HTN	Masked Hypertension
R-HTN	Resistant Hypertension
S-HTN	Sustained Hypertension
WCE	White Coat Effect
WC-HTN	White Coat Hypertension

Introduction

That BP measured at home is typically lower than BP measured in the office has been recognized for more than 70 years [1]. WC-HTN is felt to reflect an alerting response of the autonomic nervous system that is not reflective of the steady-state autonomic tone sustained in the individual. BP measurements obtained during such periods of transient autonomic activation are typically elevated compared with measurements obtained in other environs. The situational elevation of BP, when not accompanied by sustained BP elevation elsewhere, is therefore a spurious indicator of true hypertension (aka ‘sustained HTN’), though as we shall see, it may not be entirely innocuous. Any situation that provokes autonomic activation may be anticipated to produce a rise in blood pressure, but this communication will focus upon the specific situation of autonomic activation in medical settings, the area of most interest to clinicians (Figure 1).

WC-HTN is important for several reasons, even if it is not associated with adverse outcomes. First, the ‘labeling effect’ (the negative impact upon a person resulting from being informed that one has a meaningful medical malady) is in itself of some gravity. Second, insurability and its costs may be affected. Third, there can be major skewing of the results of clinical trials if WC-HTN patients comprise a significant cohort. Specifically, because WC-HTN has such a benign prognosis, a population selected for a clinical trial that was incidentally WC-HTN-rich would understandably

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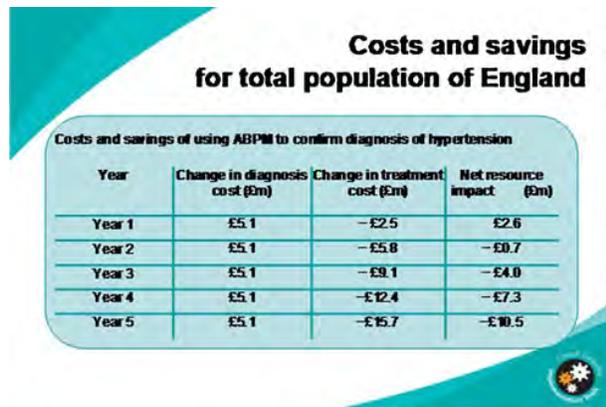


Fig. 1 In year 1 it is estimated the recommendation will cost the NHS around £2.6 million. In future years, as more people benefit from more accurate diagnoses using ABPM, a cumulative effect of people not receiving antihypertensive drugs inappropriately starts to be seen. Savings from reduced treatment costs will start to outweigh the additional costs of diagnoses. Expected savings are £4.0 million in year 3 and £10.5 million in year 5. Saving may increase further from a continuation of this cumulative effect. Source: <http://nice.org.uk/guidance/CG127/slideset/ppt/English> (accessed July 10, 2012)

see a lower-than-anticipated event rate over time, simply because these WC-HTN patients are not at increased risk for CV events. Similarly, HTN treatments being tested might appear less effective compared with placebo if the placebo group has many WC-HTN patients whose BP returns to normal over time, and who remain event-free, without treatment.

What is the Definition of WC-HTN?

Although definitions vary, the most recent United Kingdom Hypertension Guidelines define a discrepancy ≥ 20 mm Hg systolic BP or 10 mm Hg diastolic BP between office BP, and ABPM, or HBPM as fulfilling the criteria for WC-HTN, wherein ABPM/HBPM are lower than office BP. Since many articles that address WC-HTN use the terminology ‘sustained hypertension’ (S-HTN) to distinguish HTN confirmed both by office and ABPM/HBPM from WC-HTN (office BP elevated but normotensive by ABPM/HBPM), we will follow that same convention. Clinicians may commonly suspect WC-HTN when patients report substantially lower out-of-office BP readings than that obtained in the office. Of course, mismeasurement of BP out of the office can also be a reason for discrepant office/out of office readings. The definition of WC-HTN presumes accurate in-office as well as out-of-office readings. Commonplace errors in measurement of BP, which can lead to discrepant readings (eg, wrong size cuff, caffeine preceding measurement, etc) will not be the subject of this communication, but can simulate WC-HTN.

A similar office-to-ambulatory BP discrepancy may occur when the ABPM/HBPM is higher than office BP, termed ‘masked hypertension’ (M-HTN). M-HTN is a fairly recently identified entity. In contrast to WC-HTN, for which the preponderance of evidence suggests relative benignity, the prognosis of M-HTN appears to be as bad as or even worse than S-HTN. M-HTN appears to be physiologically the reverse of WC-HTN: M-HTN patients experience an autonomic calming in the medical setting, which is lost when they enter the ‘real world’.

Is the Epidemiologic Presence of WC-HTN Important Enough That I Should Care About It?

If your practice is reflective of most, at least 20 % of your patients initially diagnosed with HTN in the office have WC-HTN. The most recent guidelines on HTN from the United Kingdom (August 2011) have suggested that all HTN patients undergo either ABPM or HBPM [2•]. This position is based upon the observation that a substantial minority of patients diagnosed with HTN will ultimately be determined to have WC-HTN, and have in the past received chronic unnecessary pharmacotherapy. According to their cost-effectiveness analysis (Fig.), identification of WC-HTN patients—who at the current time are felt not to merit pharmacotherapy—will ultimately save millions of dollars for their national health care service and obviate unnecessary treatment.

The literature suggests that 20 % to 40 % of patients initially diagnosed as HTN may have WC-HTN, but it is difficult to put forth a precise number due to variation in prevalence found in different populations [3]. As an example of very high prevalence results, a study of adults diagnosed by office BP as hypertensive in Tecumseh, Michigan found that over half had normal home BP readings [4]. A recent study of randomly selected adult male and female patients attending internal medicine clinics for any medical reason found that 43 % of subjects ($n=438$) had WC-HTN as determined by comparing office BP with HBPM and ABPM [5].

Because the prevalence of WC-HTN may be setting-specific (eg, primary care vs tertiary, ethnic variation, socioeconomic variation, age variation), it is worthwhile looking at the frequency of WC-HTN in the primary care setting, in which the overall largest proportion of HTN care is provided. In a study of adult primary care patients who had been diagnosed with mild-moderate HTN based upon office measurements, Martinez et al performed ABPM and found a 39% prevalence of WC-HTN [6]. A study in Romanian adults with HTN evaluated by ABPM determined that 30 % of subjects designated as hypertensive had WC-HTN [7]. Studies in hypertensive children (defined as BP above the

95th percentile), which compare office BP with ABPM, have found almost half were reclassified as having WC-HTN [8].

WC-HTN: Does the Phenomenon Only Occur in Truly Normotensive Individuals?

Identification of WC-HTN amongst truly normotensive individuals provides the opportunity to avoid unnecessary treatment. The alerting response to which WC-HTN is attributed can also occur in patients with HTN or pre-HTN [3]. In a Canadian study of 71 on-treatment HTN patients undergoing ABPM, white coat effect (WCE) was seen in 73 %; ‘marked’ WCE (their definition: 40/20 mm Hg discrepancy) was seen in 31 % [9]. The WCE in hypertensive patients might lead unwary clinicians to intensify antihypertensive regimens needlessly, unless the WCE is suspected and out-of-office BP measurements (ABPM/HBPM) are scrutinized to clarify the patient’s true steady-state BP.

WCE: Does it Disappear Over Time?

It may depend upon whether you are talking about the short-term or long-term perspective. Although the WCE may commonly diminish or abolish entirely over time, some patients continue to exhibit an alerting response despite repeat visits with the same physician [10]. In a study of patients who received repeat visits over 2 days during continuous intraarterial monitoring, the WCE (22.6 mm Hg increase in mean BP) did not diminish over a 2-day interval [11].

The long-term perspective may be more sanguine. The Australian National Blood Pressure Trial ($n=3427$) [12] made headlines in the United States when it was reported that 20 %- to 25 % of all subjects in the placebo group had become normotensive during the trial [13]. Of subjects with mild HTN, most of the almost 50 % who achieved normotension on placebo had done so within the first 4 months of the study; The Management Committee of the Australian National Blood Pressure Study commented “Such subjects clearly do not require drug therapy. This suggests that repeated BP measurements over an observation period of some 4 months...can identify a large proportion of subjects with suspected mild hypertension in whom drug therapy can be withheld” [14]. Although the placebo group did receive advice on lifestyle modification, it would be difficult to conceive that so large a subset of individuals were sufficiently compliant with diet and exercise as to attain control of sustained hypertension without pharmacotherapy.

The more contemporary Second Australian National Blood Pressure Study (ANBP2) provided still another

perspective from a larger population of hypertensives. During the ANBP2 run-in phase, 6291 participants who were on treatment for HTN completed drug withdrawal; of these, 18 % (1228) maintained normotension for up to 76 weeks (median 4 weeks) [15]. The ability to remain normotensive despite withdrawal of antihypertensive medication reflects a likely substantial population of WCE.

Does It Make a Difference Who Measures the BP?

For some individuals, the ‘category’ of person taking their blood pressure makes an impact on the degree of WCE. In a study that utilized subjects ($n=46$) undergoing prolonged intra-arterial BP monitoring, in whom the baseline BP was well established, comparisons of WCE between physician visits and nurse visits were dramatically different: nurse-administered BP measurement showed only about half the degree of WCE as physicians, both in BP elevation and heart rate [11].

Does Having WC-HTN Put Patients at Increased Risk?

The literature to date is insufficient to definitively dismiss WC-HTN as a pathologic entity. Although the disquieting results are clearly outweighed by the reassuring ones, there continues to be enough controversy that it would be wise to assume a non-dogmatic position on the issue at this point.

The Microscopic View

Endothelial function does not appear to be impaired in WCH. A study that evaluated endothelial function in normotensives ($n=22$), S-HT ($n=22$), and WC-HTN ($n=22$) found no difference between normotensives and WC-HTN, but reduced endothelium-dependent vasodilation in sustained S-HTN [16].

The Macroscopic View

Numerous clinical trials have indicated that out-of-office BP measurements (HBPM, ABPM) correlate better with adverse outcomes than office BP. Accordingly, one would intuitively expect that persons with normal out-of-office BP would be unlikely to suffer target organ damage. A study of cardiac function and size that compared WC-HTN patients with normotensives did not find any meaningful difference between the groups [17].

Some experts utilize common carotid intimal-medial wall thickness (CIMT) as a surrogate marker for vascular disease.

If this philosophy is correct (ie, that one might rely upon the presence, absence, or progression of CIMT as an indicator), then WC-HTN might not be entirely innocent. For instance, a study of CIMT ($n=80$) that compared normotensives, WC-HTN, and S-HTN patients (ie, both office and ABPM elevated) found that CIMT was similar in the WC-HTN and hypertensive group, both of which had greater CIMT than normotensives [18]. A trial evaluating carotid elasticity (another marker of vascular health) found similar deleterious changes in HTN and WC-HTN study subjects [19]. Most recently, a 5-year prospective study of 74 never-treated Stage 1 HTN patients, approximately half of whom had WC-HTN, found similar untoward CIMT changes in both groups compared with normotensives [20]. Whether such associations will ultimately lead to greater incidence of cardiovascular (CV) events remains to be determined.

One of the largest prospective observational trials enrolled patients ($n=479$) who had persistent office HTN, but normal 24-hour intra-arterial ABPM. An initial deficit in this study is that patients were enrolled not based upon the current definition of WC-HTN ($>20/10$ mm Hg difference between office BP and HBPM/ABPM), but rather, included all patients with office HTN whose ABPM was $<140/90$ mm Hg. Nonetheless, after 9 years of follow-up, the CV event rate was essentially half amongst the WC-HTN group as in the sustained HTN group (1.32 events/100 pt-years vs 2.56 events/100 pt-years, respectively). These data demonstrate that WC-HTN is of substantially lesser CV risk than HTN, but in the absence of a normotensive group, cannot establish whether CV risk in WC-HTN is greater than normotensives [21].

To date, there have been no large prospective randomized trials of persons with WC-HTN compared with normotensives or hypertensives with outcomes data that could definitively ascertain the long-term risk of WC-HTN. That WC-HTN is less risky than HTN is quite clear: a 5-year follow-up comparing these 2 populations found the CV event rate is essentially twice as high in the HTN group, but this does not clarify for us whether the WC-HTN group had a higher event rate than normotensives [22].

Some insight about the relatively benign course of WC-HTN can be gained from a prospective observational study ($n=118$) performed in Portugal. Using ABPM, normotensive subjects (ie, office and ABPM both normal), as well as WC-HTN subjects who underwent ABPM periodically over a 90-month follow-up period, seeking to determine the rate of conversion from normotension to HTN. At the end of the trial, the rate of conversion to HTN was not statistically significantly greater in WC-HTN patients than in normotensives, nor was the rate of CV events greater [23].

Martinez performed ABPM on 345 patients who had been diagnosed with mild-moderate HTN in primary care offices [6]. At the same time echocardiography, lipids, glucose, uric acid, glucose, and albuminuria were measured;

amongst these metrics, no detrimental signals were found in the WC-HTN subjects. According to these data, predictors of WC-HTN were female gender and low educational level. In addition, the frequency of WC-HTN was inversely proportional to the severity of BP: ie, those with the highest BP were least likely to have WC-HTN.

The most reassuring data on the benignity of persons with normal home BP in the face of elevated office BP comes from a meta-analysis reported in 2012. Pooling data from 8 prospective studies ($n=17,688$; nearly 100,000 person-years of follow-up) affirmed that home BP—but not office BP—predicted all-cause and CV mortality, leading to the conclusion that from the preponderance of evidence, high BP in the office, but not at home, is not associated with adverse CV outcomes [24]. Recent editorialists have gone so far as to suggest that HBPM may indeed make office blood pressure measurement obsolete [25•]!

WCE Is Seen in Normotensives and Hypertensives. What About Patients with Resistant Hypertension?

Resistant HTN (R-HTN) is defined as BP $>140/90$ while being treated with optimized doses of at least 3 antihypertensive medications, including a diuretic [26]. The largest data set to examine the prevalence of WC-HTN actually comes from a recent study of persons with R-HTN in Spain ($n=8295$) [27••]. It has been reported that 12 % of adult hypertensives in Spain have R-HTN [27••]. Using ABPM, 37.5 % of patients initially classified by office BP as having R-HTN were ultimately determined to have WC-HTN. As might be intuitive from the preceding discussion, target organ damage was substantially less common in WC-HTN than R-HTN. There were a number of characteristics that were more prevalent in persons with R-HTN than WC-HTN (eg, diabetes, cigarette smoking, microalbuminuria), however, none of these features were sufficient to predict which persons diagnosed by office BP with R-HTN should be suspected of having WC-HTN.

What Should Be Done About WC-HTN?

The preponderance of data suggests that WC-HTN is one of the wide range of normal responses to being placed in the medical setting, including the phenomenon of ‘masked hypertension,’ in which office BP is normal yet BP is consistently elevated outside of the office, as if the medical environment is found to be stabilizing to the autonomic nervous system of these individuals.

The author agrees with the most recently published international guideline on HTN by the British Hypertension Society that HBPM or ABPM should be routinely

performed at the initial diagnosis of HTN. HBPM is reliable when performed by persons who have been carefully instructed and use validated devices. Given the generally benign outcomes of WC-HTN, clinicians should confirm that BP measurement technique is appropriate, and make therapeutic changes based upon BP measured at home rather than in the office [5]. In the event that HBPM provides inconsistent or poorly interpretable data, ABPM may be used alternatively. Were ABPM to be available at a cost affordable to all patients with HTN, it might be the preferable tool, yet HBPM offers some long-term insights about BP management not available from the brief window of time assayed by ABPM. Subsequent to the clarification of WC-HTN in a patient initially suspected of having S-HTN, annual BP monitoring without treatment is appropriate unless sustained hypertension ensues, in the opinion of the author.

Would It Make Sense to Provide Any Intervention to Address WC-HTN?

If it were entirely clear that WC-HTN is non-pathologic, there would be no reason to treat it. On the other hand, since WC-HTN is sometimes mistaken for S-HTN, since elevated BP in the office setting may be unsettling for the clinician and/or the patient, and since innocent mislabeling as hypertensive has its own set of consequences, were there an easy, non-toxic intervention that would alleviate the elevated office BP measurements seen in WC-HTN, it might be worthwhile considering, even if only under the philosophical position of alleviating a troublesome artifactual finding.

Cohort studies have shown that exercise reduces BP. Might exercise also reduce BP in WC-HTN? Tsai et al enrolled 42 WC-HTN patients and randomized half to moderately intense exercise, the other half to placebo for 12 weeks [28]. Exercise produced a prompt (within 4 weeks), durable (lasting 12 weeks), and potent (SBP decreased >10 mm Hg) reduction in office BP. Such changes could help reduce the likelihood that a patient might be misdiagnosed with WC-HTN.

Conclusions What is the Bottom Line in 2012 on WC-HTN?

The author is in agreement with Helvaci et al [5], who came to the conclusion that WC-HTN "...should be thought of as a normal response of the body against various stresses and its management should be limited to annual follow-up with HBPM." We can capitalize upon this understanding by routinely employing either ABPM or (preferentially) HBPM in anyone with office HTN. Because of cost, convenience, and advocacy from major consensus groups, the author suggests HBPM as the preferred tool.

Patients with WCE should be reassured that the preponderance of current evidence does not confirm an increased burden of CV risk attributable to WC-HTN. Because, like all other adults, some persons with WC-HTN will progress to develop sustained HTN (though not convincingly more often than the general normotensive population), annual surveillance of BP is suggested. Persons with R-HTN suffer a greater burden of medical cost and medication burden. Because as many of 1/3 or more of them may have WC-HTN, current guidelines recommend ABPM or HBPM for all persons with R-HTN. By identifying WCE in patients with elevated BP, we can avoid unnecessary labeling, reduce office visits, and decrease the medication burden shouldered by our patients for this very common condition.

Disclosure No potential conflicts of interest relevant to this article were reported.

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