White-Coat Hypertension
New Insights From Recent Studies

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Two statisticians meet.
-How do you do?
-How do I do? Compared to whom?

—Anonymous

Thomas Pickering coined the term white-coat hypertension to denote individuals who were not on treatment for hypertension but who had elevated office blood pressure and normal daytime blood pressure measured with ambulatory blood pressure monitoring (ABPM). Clearly, these individuals would be at low cardiovascular risk.1 The traditional definition of white-coat hypertension is based, therefore, on an elevated office blood pressure with a normal blood pressure during the awake period with ABPM. However, because of the contribution of asleep blood pressure as a predictor of outcome, it seems counterproductive to exclude this period from consideration. The most recent European guidelines2 propose, therefore, an alternative definition of white-coat hypertension, which encompasses subjects with office systolic/diastolic blood pressure readings of ≥140/90 mm Hg and a 24-hour blood pressure <130/80 mm Hg. The purpose of this review is to provide new insights into the characteristics, definitions, and cardiovascular risk assessment in persons with white-coat hypertension, and it will be limited primarily to ABPM with a primary focus on prospective studies.

Characteristics of White-Coat Hypertension
Prevalence and Diagnosis

White-coat hypertension occurs in 15% to 30% of subjects with an elevated office blood pressure,2,3 and the phenomenon is reasonably reproducible.2,4 Although there are no pathognomonic diagnostic features of white-coat hypertension, this condition occurs more frequently in women, older adults, nonsmokers, recently diagnosed patients with hypertension with a limited number of conventional blood pressure measurements in the office setting who have mild hypertension, pregnant women, and subjects without evidence of target organ damage.2,5,6 The misdiagnosis of subjects with white-coat hypertension as being truly hypertensive can result in them being penalized for employment and insurance rating, as well as being prescribed unnecessary lifelong treatment with potential side effects that may be seriously debilitating, especially in the elderly. Moreover, failure to identify the condition results in a large expenditure on unnecessary drugs.7

Role of Ambulatory Monitoring

Blood pressure is characterized by considerable variability. In patients with mild elevation of their office blood pressure on a first visit to a physician, systolic and diastolic blood pressure decrease on average by 15/7 mm Hg by the third visit; indeed, some patients do not reach a stable blood pressure value until the sixth visit.8 This reduction in office blood pressure with subsequent visits represents regression to the mean, placebo or nocebo9 effects, and diminution of the alerting reaction or the fight and flight phenomenon. However, this does not occur in all subjects, leading to the possibility that the phenomenon may be, at least in part, attributable to a conditioning process.1

The Task Force of the Eighth International Consensus Conference on Blood Pressure Monitoring10 recommends ambulatory monitoring to exclude white-coat hypertension in untreated patients when (1) the office blood pressure is ≥140/90 mm Hg on ≥3 separate office visits; (2) ≥2 blood pressure measurements taken outside the office are <140/90 mm Hg, frequently using home blood pressure monitoring; and (3) there is no evidence of hypertensive target organ damage. For patients with a confirmed daytime ABPM of ≥135/85 mm Hg, physicians may wish to consider starting antihypertensive drug treatment.10 The recent British National Institute for Health and Clinical Excellence (NICE) guidelines11 advocate that every person with elevated office blood pressure aged >18 years undergo ABPM to rule out a diagnosis of white-coat hypertension with the potential for savings in health costs by virtue of unnecessary treatment with antihypertensive drugs.

Management

Once ABPM has confirmed the diagnosis of white-coat hypertension, the European Society of Hypertension Working...
Group on Blood Pressure Monitoring recommends that the diagnosis be reconfirmed in 3 to 6 months and followed up yearly with ambulatory monitoring to detect any evidence of progression to sustained hypertension.

Differential Diagnosis
White-coat hypertension should not be confused with high-normal blood pressure (the upper end of prehypertension [Table 2]); however, the distinction is not clear-cut. Indeed, patients with white-coat hypertension may share 2 characteristics with bona fide high-normal blood pressure: (1) progression over a short interval of time to sustained hypertension, in particular in middle-aged and older individuals; and (2) increased cardiovascular risk compared with a normotensive comparator group of blood pressure levels <120 mm Hg systolic and <80 mm Hg diastolic. In 1 study, 37% of subjects with white-coat hypertension developed sustained hypertension over a mean follow-up time of 2.5 years with an accompanying rise in left ventricular mass.

What could account for increased cardiovascular risk over time in persons with white-coat hypertension (office blood pressure of ≥140/90 mm Hg and daytime ABPM of <135/85 mm Hg)? Blood pressure is a continuous variable with no specific separation between normal and abnormal values. Similarly, there is a spectrum of definitions for daytime ABPM that separate true sustained hypertension from white-coat hypertension (Table 1): <120 to 130/<75 to 80 mm Hg as optimal daytime ABPM and 130 to 135/80 to 85 mm Hg as normal/high-normal daytime ABPM. Hypertension is defined by daytime ABPM ≥135/85 mm Hg in association with conventional office elevation of ≥140/90 mm Hg.

In retrospect, the propensity of subjects with white-coat hypertension to progress to sustained hypertension may be associated with at least 3 clinical states: (1) those persons on the upper end of the blood pressure spectrum, that is, high-normal daytime ABPM, especially in the middle-aged and older group have the greatest propensity to develop sustained hypertension over a relatively short time; (2) subjects with night-time elevation in ABPM in association with normal/high-normal daytime ABPM of 130 to 135/80 to 85 mm Hg, often associated with obstructive sleep apnea, autonomic dysfunction, diabetes mellitus, or chronic kidney disease, might really have masked hypertension rather than white-coat hypertension; and (3) the high number and severity of cardiometabolic abnormalities associated with normal/high-normal ABPM values in persons with white-coat hypertension may predispose to increased cardiovascular disease risk over time (see below).

Recently, Sung et al reported that white-coat hypertension might be more risky than prehypertension. However, they defined prehypertension as a conventional blood pressure between 120/80 and 140/90 mm Hg with a daytime ABPM of <135 mm Hg systolic and <85 mm Hg diastolic. Their definition of prehypertension was not consistent with current guidelines that do not impose constraints on the upper levels of daytime ambulatory blood pressure. Indeed, their mean daytime systolic blood pressure was 123 mm Hg for white-coat hypertension and only 118 mm Hg for prehypertension. Prehypertension as defined by Sung et al resembles a mild form of white-coat hypertension, unlikely to yield higher risk than white-coat hypertension. The article by Sung et al highlights, therefore, the necessity for more consistency and communication between expert committees in labeling the different categories of hypertension (Tables 1 and 2).

Resistant Hypertension
Patients whose conventional blood pressure remains uncontrolled by 3 classes of antihypertensive agents, including a diuretic, have so-called resistant hypertension. However, when ABPM is performed, in as many as one third of patients with apparent resistant hypertension, the resistance is a manifestation of conventional blood pressure measurement and ABPM levels are lower, showing that the blood pressure elevation is in fact a white-coat effect (see below).20,21 Characteristics of true resistant hypertension include male sex, longer duration of hypertension, a worse cardiovascular risk profile, smoking, diabetes mellitus, target organ damage, and a history of cardiovascular disease or chronic kidney disease.20,21 Importantly, the clinical picture alone does not distinguish between truly resistant and white-coat resistant hypertension, so that ABPM must be applied as a diagnostic and prognostic procedure in patients suspected of having resistant hypertension.20,21 Indeed, by establishing a diagnosis of white-coat resistant hypertension, one can simplify what may be excessive antihypertensive drug treatment.

### Table 2. Classification of the Conventional Blood Pressure According to European and US Guidelines

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic BP, mm Hg</th>
<th>Diastolic BP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>European guidelines17,*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Normal</td>
<td>120–129</td>
<td>80–84</td>
</tr>
<tr>
<td>High normal</td>
<td>130–139</td>
<td>85–89</td>
</tr>
<tr>
<td>Grade 1 hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Grade 2 hypertension</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Grade 3 hypertension</td>
<td>≥180</td>
<td>≥110</td>
</tr>
</tbody>
</table>

| US guidelines17,*         |                    |                    |
| Normotension              | <120               | <80                |
| Prehypertension           | 120–139            | 80–89              |
| Stage 1 hypertension      | 140–159            | 90–99              |
| Stage 2 hypertension      | ≥160               | ≥100               |
| Stage 3 hypertension      |                    |                    |

*The blood pressure (BP) category is defined by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension should be graded 1, 2, or 3 according to systolic BP values in the ranges indicated.
Cardiovascular Risk Associated With White-Coat Hypertension

Longitudinal Studies

The issue of cardiovascular risk in subjects with untreated white-coat hypertension is controversial. The 2012 International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) study,22 which totaled 7295 persons, is the most contemporary of the event-based cohort studies and illustrates many of the pitfalls in determining risk in white-coat hypertension. It may provide, therefore, a “standard against which previous studies may be assessed.” The 2012 IDACO population included older individuals (mean age, 64 years) with isolated systolic hypertension stratified by the presence or absence of antihypertensive therapy and who had conventional and 24-hour ABPM. The normotensive comparator group was at low risk, because subjects with prior cardiovascular events, subjects on antihypertensive drug treatment, and patients with masked hypertension were excluded. The major finding of this study with a mean follow-up time of 10.6 years was that the sex- and age-standardized incidence rate of cardiovascular events in 334 participants with untreated white-coat hypertension (Figure) was no greater than in the untreated normotensive control population (P=0.38). When adjusted for all covariables, the hazard ratio was 1.17 (95% confidence interval, 0.87–1.57; P=0.29).22 Furthermore, failure to show a progressive increase in cardiovascular risk over time in untreated people with white-coat hypertension was evidence against these subjects progressing to sustained hypertension or having been selected inappropriately with high-normal blood pressure.

Moreover, 162 subjects with a diagnosis of white-coat hypertension who had been prescribed antihypertensive drugs had similar cardiovascular risk as compared with treated normotensive comparators (P=0.92; Figure). With adjustment for all covariables, the hazard ratio was 1.10 (95% confidence interval, 0.79–1.53; P=0.53). In contrast, subjects with treated white-coat hypertension had about twice the cardiovascular risk when compared with untreated normotensives (P=0.0067); the adjusted hazard ratio was 1.98 (95% confidence interval, 1.49–2.62; P<0.0001).22 These findings are not unexpected because treatment is a good marker for identifying higher risk people in observational studies.23 Restoring normal blood pressure levels with treatment neither eliminated the lifetime cardiovascular disease burden associated with prior elevation of blood pressure nor corrected other cardiometabolic risk factors that are associated with hypertension. Thus, antihypertensive drug treatment can normalize the daytime ambulatory blood pressure and mimic white-coat hypertension, but the damage done by pre-existing hypertension persists and exerts its toll. Two considerations are important, therefore, in the assessment of risk associated with treated white-coat hypertension in outcome studies.

First, definition of the low-risk normotensive comparator group is a key issue. The potential cardiovascular risk of treated subjects with elevated office blood pressure and normal daytime ABPM that simulates white-coat hypertension depends, in part, on the cardiovascular risk in the normotensive comparator group, that is, one must ask the question: “compared with whom?” (Table 3).24 For example, in a 2007 IDACO publication,27 white-coat hypertension was not associated with increased cardiovascular risk over a 10.6-year follow-up period after adjusting for treatment. However, the normative comparator group included patients with prior cardiovascular events and receiving antihypertensive drug treatment.27 In retrospect, removal of high-risk participants from the comparator group in the 2007 IDACO study would have unmasked the increased risk in the treated patients with white-coat hypertension.27

Second, the white-coat effect or white-coat phenomenon manifests itself in 2 ways: either as the white-coat effect or as white-coat hypertension, and there is no automatic association between these 2 conditions.28–30 The white-coat effect is a measure of blood pressure change from before to during the visit in office/clinic when the blood pressure is recorded by a physician or nurse; this was first described in 1983 by Mancia et al11 with the use of cuff and intra-arterial bedside measurements. White-coat effect is present in almost all persons and can vary from minimal to marked in a given individual with an overall mean increase of 27 mm Hg systolic blood pressure.31 The pathogenesis of white-coat effect is an alerting reaction working through reflex activation of the sympathetic nervous system.32 The white-coat effect is more prominent in older people, women, and patients labeled (diagnosed) as hypertensive.33 A clinically significant white-coat effect is an office or clinic blood pressure exceeding the daytime ABPM by 20 mm Hg systolic or 10 mm Hg diastolic, either in the absence or presence of antihypertensive drug treatment.28–31 The white-coat effect might lead to subjects with normotension being classified as stage 1 or even stage 2 patients with hypertension, and stage 1 patients with hypertension being classified as stage 2 patients with hypertension.

White-coat resistant hypertension (see above) is another form of the white-coat effect in patients on antihypertensive drug
treatment. Furthermore, there is no correlation between white-coat effect and left ventricular mass, a measure of cardiovascular disease risk.\(^{29,30}\) As pointed out by Pickering,\(^{25}\) individuals with untreated white-coat hypertension as currently defined, and who then undergo antihypertensive treatment unnecessarily, may show partial reduction in white-coat effect but continue to be without increased risk when compared with the low-risk normotensive comparator group. Because white-coat effect does not define risk (Table 3), it does not distinguish between subjects with unnecessarily treated true white-coat hypertension and subjects with sustained hypertension before starting antihypertensive therapy and whose ambulatory, but not conventional, blood pressure became normal on treatment and therefore mimic white-coat hypertension; we have termed the latter entity “treated normalized hypertension with white-coat effect,”\(^{22}\) and it represents one of many causes of pseudoresistant hypertension.\(^{34}\)

There are 3 observational event-based cohort studies of long duration\(^ {35-37}\) involving European and Asian populations and 2 extensive meta-analyses\(^ {38,39}\) (Table 4) that addressed the question of cardiovascular morbidity and mortality and showed little or no increased risk when compared with the low-risk normotensive comparator group. Because white-coat effect does not define risk (Table 3), it does not distinguish between subjects with unnecessarily treated true white-coat hypertension and subjects with sustained hypertension before starting antihypertensive therapy and whose ambulatory, but not conventional, blood pressure became normal on treatment and therefore mimic white-coat hypertension; we have termed the latter entity “treated normalized hypertension with white-coat effect,”\(^ {22}\) and it represents one of many causes of pseudoresistant hypertension.\(^ {34}\)

Table 3. Cardiovascular Risk According to the Cross-Classification by Conventional and Daytime Ambulatory Blood Pressure and Treatment Status

<table>
<thead>
<tr>
<th>Definition of Blood Pressure Category in Outcome Studies</th>
<th>Cutoff for Office Blood Pressure, mm Hg</th>
<th>Cutoff for Daytime Ambulatory Blood Pressure, mm Hg</th>
<th>Cardiovascular Risk as Compared With Low-Risk Comparator Group*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained normotension</td>
<td>&lt;140/90</td>
<td>&lt;135/85</td>
<td>Equal[^2]</td>
</tr>
<tr>
<td>White-coat hypertension</td>
<td>≥140/90</td>
<td>&lt;135/85</td>
<td>Equal[^2][^4]</td>
</tr>
<tr>
<td>Masked hypertension</td>
<td>&lt;140/90</td>
<td>≥135/85</td>
<td>Higher[^4]</td>
</tr>
<tr>
<td>Sustained hypertension</td>
<td>≥140/90</td>
<td>≥135/85</td>
<td>Higher[^2]</td>
</tr>
<tr>
<td>Treated subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained normotension</td>
<td>&lt;140/90</td>
<td>&lt;135/85</td>
<td>Higher[^25]</td>
</tr>
<tr>
<td>Unnecessarily treated white-coat hypertension</td>
<td>≥140/90</td>
<td>&lt;135/85</td>
<td>Equal[^25]</td>
</tr>
<tr>
<td>Treated normalized hypertension with white-coat effect</td>
<td>≥140/90</td>
<td>&lt;135/85</td>
<td>Higher[^22]</td>
</tr>
<tr>
<td>Masked hypertension</td>
<td>&lt;140/90</td>
<td>≥135/85</td>
<td>Higher[^17]</td>
</tr>
<tr>
<td>Sustained hypertension</td>
<td>≥140/90</td>
<td>≥135/85</td>
<td>Higher[^17]</td>
</tr>
</tbody>
</table>

[^2]: Low-risk normotensive comparator group: absence of prior cardiovascular events, hypertensive target organ damage, significant cardiometabolic risk factors, masked hypertension, and antihypertensive drug treatment.
[^4]: Risk of white-coat hypertension increases in the presence of associated cardiometabolic risk factors.

The first Pressioni Arteriose Monitorate E Loro Associazioni study (PAMELA)^{40} involved participants with white-coat hypertension of whom many were receiving antihypertensive treatment. There was no adjustment or stratification by treatment status, thus making a true analysis of cardiovascular risk difficult. However, a subsequent 2009 PAMELA report\(^ {41}\) did stratify by treatment status and showed that untreated subjects with white-coat hypertension more frequently developed sustained hypertension, suggesting the potential for increased long-term risk. Similarly, the Ohasama study\(^ {42}\) using home blood pressure monitoring showed a transition in risk from untreated white-coat hypertension to sustained hypertension.

Miscellaneous Studies

The majority of evidence supports increased target organ damage in cross-sectional studies of subjects with white-coat hypertension. Early studies correlated white-coat hypertension with left ventricular hypertrophy\(^ {43-45}\) and more recently with increased carotid intimal-media thickness.\(^ {46-48}\) In contrast, in 958 elderly Japanese subjects\(^ {40}\) who were followed for 42 months (median) and whose baseline conventional and ambulatory blood pressures were measured in the absence of antihypertensive therapy, the incidence of stroke was similar in white-coat hypertensives and normotensives but was one fourth of the risk in sustained hypertensives. Similarly, the 2-year mortality in white-coat hypertensive patients with end-stage

Table 4. Prospective Outcome Studies of White-Coat Hypertension

<table>
<thead>
<tr>
<th>Authors (Reference)</th>
<th>Journal, Year</th>
<th>Subjects, n</th>
<th>Follow-Up, y</th>
<th>White-Coat Hypertension, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khatr et al(^ {35})</td>
<td>Circulation, 1998</td>
<td>479</td>
<td>9.1</td>
<td>136</td>
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<tr>
<td>Fagard et al(^ {36})</td>
<td>Circulation, 2000</td>
<td>695</td>
<td>10.9</td>
<td>167</td>
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<tr>
<td>Kario et al(^ {37})</td>
<td>J Am Coll Cardiol, 2001</td>
<td>958</td>
<td>3.5</td>
<td>236</td>
</tr>
<tr>
<td>Verdecchia et al(^ {38})</td>
<td>Hypertension, 2005</td>
<td>4406</td>
<td>5.4</td>
<td>398</td>
</tr>
<tr>
<td>Pierdomenico and Cuccurullo(^ {29})</td>
<td>Am J Hypertens, 2011</td>
<td>7961</td>
<td>6.6</td>
<td>1279</td>
</tr>
</tbody>
</table>
renal disease requiring hemodialysis was less than in masked and sustained hypertensives, but somewhat higher than in sustained normotension as diagnosed by ABPM. Clearly, ABPM was more useful than pre- or posthemodialysis blood pressure measurements in determining cardiovascular risk.

Use of pulse wave analysis as a marker of arterial stiffness in persons with white-coat hypertension versus normotensive controls showed a higher augmentation index in the former; however, it is possible that high white-coat effect, so characteristic of subjects with white-coat hypertension, could explain these findings. In summary, some persons with white-coat hypertension show progression over time to sustained hypertension, but the majority of longitudinal studies and meta-analysis show no evidence of significant increased cardiovascular event risk as compared with normotensive controls.

The role of metabolic risk factors in patients with white-coat hypertension was first outlined in 2000 by Kario and Pickering. When metabolic risk factors are present in association with white-coat hypertension, the increased risk of target organ damage is determined not only by the blood pressure characteristics but also by the metabolic abnormalities. Weber et al were the first to describe an association between white-coat hypertension and metabolic abnormalities in a 1994 cross-sectional study. Indeed, in persons with untreated white-coat hypertension from the PAMELA study, there was a significantly higher risk of new onset diabetes mellitus during a 10-year follow-up as compared with participants with normotension. Whether there was a direct association between white-coat hypertension and prehypertension progressing to sustained hypertension and the onset of diabetes mellitus or a confounding relation through an indirect causative pathway is unclear from this study. Interestingly, as shown in the 2012 IDACO study, as proof of concept, untreated white-coat hypertension was associated with increased risk in men and subjects with diabetes mellitus.

When Should White-Coat Hypertension Be Treated and What Is the Target ABPM Goal?

The premise that it may be beneficial to treat high-risk patients with white-coat hypertension, as outlined earlier, is untested by randomized controlled trials. In a subgroup of the double-blind, placebo controlled Syst-Eur trial in elderly patients with isolated systolic hypertension, active treatment reduced the conventional but not the ambulatory blood pressure in 167 subjects with white-coat hypertension. In this subgroup, there was no evidence for a beneficial effect of active treatment on ECG voltages or stroke incidence. Currently, clinical decisions to begin antihypertensive treatment and to decide on target goals remain empirical. Randomized trials need to be performed using different ABPM treatment thresholds to establish optimal treatment guidelines. Therefore, current treatment decisions, beyond instituting lifestyle changes, should be based on documentation of elevated 24-hour ABPM (or home blood pressure monitoring) values in patients with high absolute cardiovascular risk and evidence of hypertensive target organ damage.

Perspectives

This review highlights what clinicians should know about white-coat hypertension. They should not confuse high-normal blood pressure with white-coat hypertension. They should be aware that untreated subjects with white-coat hypertension may still be at increased cardiovascular risk, albeit small compared with subjects with sustained hypertension, which will be dependent on associated cardiometabolic risk factors. For researchers of cardiovascular outcomes and health economists, our review highlights the necessity to define the risk associated with white-coat hypertension and to define a true low-risk normotensive comparator group. This includes elimination of subjects with prior cardiovascular events, target organ damage, cardiometabolic risk factors, and patients on antihypertensive drug treatment. Experts writing guidelines for the diagnosis and management of hypertension should examine carefully the definitions used to categorize patients with hypertension. As shown by the report of Sung et al, not uniformly labeling categories of blood pressure (Table 2) confuses both clinicians and researchers. Furthermore, expert committees should reflect outcome-driven rather than arbitrary thresholds for out-of-the-office blood pressure measurement, the diurnal intervals (24-hour versus daytime versus night-time) or the number of self-measurements to be considered to quantify the white-coat effect or to diagnose white-coat hypertension by ABPM or home blood pressure monitoring, respectively. Finally, in the presence of concurrent antihypertensive treatment, one should be cautious in applying the term white-coat hypertension to an individual with increased office blood pressure and normal ABPM. Thus, the determination of true white-coat hypertension requires a clear answer to the question: “compared to whom?”

Disclosures

None.

References


