White-Coat Hypertension: New Insights From Recent Studies

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Hypertension. 2013;62:982-987; originally published online September 16, 2013;
doi: 10.1161/HYPERTENSIONAHA.113.01275
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

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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 guidelines[2] 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[8]; 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 nocebo[9] 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 Monitoring[10] 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) guidelines[11] 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

Received May 26, 2013; first decision June 15, 2013; revision accepted August 20, 2013.

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This paper was sent to Takayoshi Ohkubo, Guest editor, for review by expert referees, editorial decision, and final disposition.

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(*Hypertension*. 2013;62:982-987.)

***Hypertension* is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.113.01275**

Group on Blood Pressure Monitoring[2] 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.[2]

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[12,13]; and (2) increased cardiovascular risk compared with a normotensive comparator group of blood pressure levels <120 mm Hg systolic and <80 mm Hg diastolic.[14] 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.[15]

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.[2,16]

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,[2,17] 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).

Table 1. Ambulatory Blood Pressure Thresholds,[2] in Part, Population Based[16]

Interval	Optimal	Normal/High Normal	Elevated
Awake (daytime)* average	<120–130/80	130–135/80–85	≥135/85
Asleep (night-time) average	<100–115/65	115–120/65–70	≥120/70
24-h average	<115–125/75	125–130/75–80	≥130/80

*Same values pertain to home blood pressure monitoring.

Recently, Sung et al[18] 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[18] resembles a mild form of white-coat hypertension, unlikely to yield higher risk than white-coat hypertension. The article by Sung et al[18] highlights, therefore, the necessity for more consistency and communication between expert committees[17,19] 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

Category	Systolic BP, mm Hg	Diastolic BP, mm Hg
European guidelines[17,*]		
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Grade 1 hypertension	140–159	90–99
Grade 2 hypertension	160–179	100–109
Grade 3 hypertension	≥180	≥110
US guidelines[19,*]		
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.

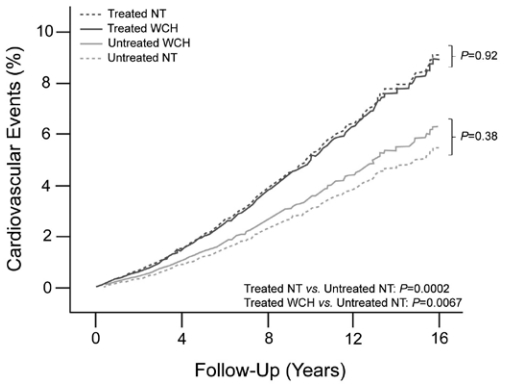

Figure. Incidence of cardiovascular events in untreated normotension (untreated NT), untreated patients with isolated systolic hypertension (ISH) and white-coat hypertension (untreated WCH), treated normotension (NT), and treated ISH patients with white-coat hypertension (treated WCH). In untreated ISH subjects, the risk related to white-coat hypertension was similar to that in normotension (P=0.38). Similarly, in treated ISH subjects, white-coat hypertension did not carry an increased risk (P=0.92) as compared with treated normotension. However, both treated WCH subjects and treated subjects with normal blood pressure (treated NT) were at higher (P<0.007) cardiovascular risk as compared with the untreated normotensive reference group. Reproduced with permission from Franklin et al.[22] Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

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).[26] 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 al[31] 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

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

Definition of Blood Pressure Category in Outcome Studies	Cutoff for Office Blood Pressure, mm Hg	Cutoff for Daytime Ambulatory Blood Pressure, mm Hg	Cardiovascular Risk as Compared With Low-Risk Comparator Group*
Untreated subjects			
Sustained normotension	<140/90	<135/85	Equal[2]
White-coat hypertension	≥140/90	<135/85	Equal[2,24]†
Masked hypertension	<140/90	≥135/85	Higher[2]
Sustained hypertension	≥140/90	≥135/85	Higher[2]
Treated subjects			
Sustained normotension	<140/90	<135/85	Higher[23]
Unnecessarily treated white-coat hypertension	≥140/90	<135/85	Equal[25]
Treated normalized hypertension with white-coat effect (1 type of pseudoresistant hypertension)	≥140/90	<135/85	Higher[22]
Masked hypertension	<140/90	≥135/85	Higher[17]
Sustained hypertension	≥140/90	≥135/85	Higher[17]

*Low-risk normotensive comparator group: absence of prior cardiovascular events, hypertensive target organ damage, significant cardiometabolic risk factors, masked hypertension, and antihypertensive drug treatment.

†Risk of white-coat hypertension increases in the presence of associated cardiometabolic risk factors.

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 between untreated patients with white-coat hypertension and their normotensive comparators and hence most resembled the 2012 IDACO study.[22] However, almost invariably, persons with white-coat hypertension will have a slightly higher cardiovascular risk when compared with persons with sustained normotension. In contrast, 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[36] 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

Authors (Reference)	Journal, Year	Subjects, n	Follow-Up, y	White-Coat Hypertension, n
Khattar et al[35]	*Circulation*, 1998	479	9.1	136
Fagard et al[36]	*Circulation*, 2000	695	10.9	167
Kario et al[37]	*J Am Coll Cardiol*, 2001	958	3.5	236
Verdecchia et al[38]	*Hypertension*, 2005	4406	5.4	398
Pierdomenico and Cuccurullo[39]	*Am J Hypertens*, 2011	7961	6.6	1279

renal disease requiring hemodialysis was less than in masked and sustained hypertensives, but somewhat higher than in sustained normotension as diagnosed by ABPM.[49] Clearly, ABPM was more useful than pre- or posthemodialysis blood pressure measurements in determining cardiovascular risk.[49] 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[50]; 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.[24] 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.[24] Weber et al[51] 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.[52] 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.[53] Interestingly, as shown in the 2012 IDACO study,[22] 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.[36] In this subgroup, there was no evidence for a beneficial effect of active treatment on ECG voltages or stroke incidence.[36] 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,[18] not uniformly labeling categories of blood pressure (Table 2) confuses both clinicians and researchers. Furthermore, expert committees should reflect outcome-driven[2,17] 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

1. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? *JAMA*. 1988;259:225–228.
2. O'Brien E, Parati G, Stergiou G, et al; on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens*. 2013;31:1731–1767.
3. O'Brien E, Coats A, Owens P, Petrie J, Padfield PL, Littler WA, de Swiet M, Mee F. Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British hypertension society. *BMJ*. 2000;320:1128–1134.
4. Ben-Dov IZ, Ben-Arie L, Mekler J, Bursztyn M. Reproducibility of white-coat and masked hypertension in ambulatory blood pressure monitoring. *Int J Cardiol*. 2007;117:355–359.
5. Verdecchia P, Palatini P, Schillaci G, Mormino P, Porcellati C, Pessina AC. Independent predictors of isolated clinic ('white-coat') hypertension. *J Hypertens*. 2001;19:1015–1020.
6. Dolan E, Stanton A, Atkins N, Den Hond E, Thijs L, McCormack P, Staessen J, O'Brien E. Determinants of white-coat hypertension. *Blood Press Monit*. 2004;9:307–309.
7. Lovibond K, Jowett S, Barton P, Caulfield M, Heneghan C, Hobbs FD, Hodgkinson J, Mant J, Martin U, Williams B, Wonderling D, McManus RJ. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. *Lancet*. 2011;378:1219–1230.
8. Watson RD, Lumb R, Young MA, Stallard TJ, Davies P, Littler WA. Variation in cuff blood pressure in untreated outpatients with mild hypertension–implications for initiating antihypertensive treatment. *J Hypertens*. 1987;5:207–211.
9. Colloca L, Finniss D. Nocebo effects, patient-clinician communication, and therapeutic outcomes. *JAMA*. 2012;307:567–568.
10. Staessen JA, Asmar R, De Buyzere M, Imai Y, Parati G, Shimada K, Stergiou G, Redón J, Verdecchia P; Participants of the 2001 Consensus Conference on Ambulatory Blood Pressure Monitoring. Task Force II: blood pressure measurement and cardiovascular outcome. *Blood Press Monit*. 2001;6:355–370.
11. National Institute for Health and Clinical Excellence (NICE). *The Clinical Managment of Primary Hypertension in Adults*. London, United Kingdom: National Institute for Health and Clinical Excellence (NICE); 2011.

12. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. *Lancet*. 2001;358:1682–1686.
13. Zhang H, Thijs L, Kuznetsova T, Fagard RH, Li X, Staessen JA. Progression to hypertension in the non-hypertensive participants in the Flemish Study on Environment, Genes and Health Outcomes. *J Hypertens*. 2006;24:1719–1727.
14. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med*. 2001;345:1291–1297.
15. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Sacchi N, Guerrieri M, Comparato E, Porcellati C. Identification of subjects with white-coat hypertension and persistently normal ambulatory blood pressure. *Blood Press Monit*. 1996;1:217–222.
16. Kikuya M, Hansen TW, Thijs L, Björklund-Bodegård K, Kuznetsova T, Ohkubo T, Richart T, Torp-Pedersen C, Lind L, Ibsen H, Imai Y, Staessen JA; International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes Investigators. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. *Circulation*. 2007;115:2145–2152.
17. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159–2219.
18. Sung SH, Cheng HM, Wang KL, Yu WC, Chuang SY, Ting CT, Lakatta EG, Yin FC, Chou P, Chen CH. White coat hypertension is more risky than prehypertension: important role of arterial wave reflections. *Hypertension*. 2013;61:1346–1353.
19. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252.
20. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, Oliveras A, Ruilope LM. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension*. 2011;57:898–902.
21. de la Sierra A, Banegas JR, Oliveras A, Gorostidi M, Segura J, de la Cruz JJ, Armario P, Ruilope LM. Clinical differences between resistant hypertensives and patients treated and controlled with three of less drugs. *J Hypertens*. 2012;30:1211–1216.
22. Franklin SS, Thijs L, Hansen TW, et al; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Significance of white-coat hypertension in older persons with isolated systolic hypertension: a meta-analysis using the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes population. *Hypertension*. 2012;59:564–571.
23. Isles CG, Walker LM, Beevers GD, Brown I, Cameron HL, Clarke J, Hawthorne V, Hole D, Lever AF, Robertson JW. Mortality in patients of the Glasgow Blood Pressure Clinic. *J Hypertens*. 1986;4:141–156.
24. Kario K, Pickering TG. White-coat hypertension or white-coat hypertension syndrome: which is accompanied by target organ damage? *Arch Intern Med*. 2000;160:3497–3498.
25. Pickering TG. White coat hypertension. *Curr Opin Nephrol Hypertens*. 1996;5:192–198.
26. Verdecchia P, Angeli F, Staessen JA. Compared with whom? Addressing the prognostic value of ambulatory blood pressure categories. *Hypertension*. 2006;47:820–821.
27. Hansen TW, Kikuya M, Thijs L, Björklund-Bodegård K, Kuznetsova T, Ohkubo T, Richart T, Torp-Pedersen C, Lind L, Jeppesen J, Ibsen H, Imai Y, Staessen JA; IDACO Investigators. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7,030 individuals. *J Hypertens*. 2007;25:1554–1564.
28. Verdecchia P, Staessen JA, White WB, Imai Y, O'Brien ET. Properly defining white coat hypertension. *Eur Heart J*. 2002;23:106–109.
29. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Zampi I, Gattobigio R, Sacchi N, Porcellati C. White coat hypertension and white coat effect. Similarities and differences. *Am J Hypertens*. 1995;8:790–798.
30. Parati G, Ulian L, Sampieri L, Palatini P, Villani A, Vanasia A, Mancia G. Attenuation of the "white-coat effect" by antihypertensive treatment and regression of target organ damage. *Hypertension*. 2000;35:614–620.
31. Mancia G, Bertinieri G, Grassi G, Parati G, Pomidossi G, Ferrari A, Gregorini L, Zanchetti A. Effects of blood-pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet*. 1983;2:695–698.
32. Grassi G, Turri C, Vailati S, Dell'Oro R, Mancia G. Muscle and skin sympathetic nerve traffic during the "white-coat" effect. *Circulation*. 1999;100:222–225.
33. Manios ED, Koroboki EA, Tsivgoulis GK, Spengos KM, Spiliopoulou IK, Brodie FG, Vemmos KN, Zakopoulos NA. Factors influencing white-coat effect. *Am J Hypertens*. 2008;21:153–158.
34. Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. *J Am Coll Cardiol*. 2008;52:1749–1757.
35. Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension: a 10-year follow-up study. *Circulation*. 1998;98:1892–1897.
36. Fagard RH, Staessen JA, Thijs L, et al. Response to antihypertensive therapy in older patients with sustained and nonsustained systolic hypertension. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Circulation*. 2000;102:1139–1144.
37. Kario K, Shimada K, Schwartz JE, Matsuo T, Hoshide S, Pickering TG. Silent and clinically overt stroke in older Japanese subjects with white-coat and sustained hypertension. *J Am Coll Cardiol*. 2001;38:238–245.
38. Verdecchia P, Reboldi GP, Angeli F, Schillaci G, Schwartz JE, Pickering TG, Imai Y, Ohkubo T, Kario K. Short- and long-term incidence of stroke in white-coat hypertension. *Hypertension*. 2005;45:203–208.
39. Pierdomenico SD, Cuccurullo F. Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta analysis. *Am J Hypertens*. 2011;24:52–58.
40. Mancia G, Facchetti R, Bombelli M, Grassi G, Sega R. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension*. 2006;47:846–853.
41. Mancia G, Bombelli M, Facchetti R, Madotto F, Quarti-Trevano F, Polo Friz H, Grassi G, Sega R. Long-term risk of sustained hypertension in white-coat or masked hypertension. *Hypertension*. 2009;54:226–232.
42. Ugajin T, Hozawa A, Ohkubo T, Asayama K, Kikuya M, Obara T, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Tsuji I, Imai Y. White-coat hypertension as a risk factor for the development of home hypertension: the Ohasama study. *Arch Intern Med*. 2005;165:1541–1546.
43. Glen SK, Elliott HL, Curzio JL, Lees KR, Reid JL. White-coat hypertension as a cause of cardiovascular dysfunction. *Lancet*. 1996;348:654–657.
44. Owens PE, Lyons SP, Rodriguez SA, O'Brien ET. Is elevation of clinic blood pressure in patients with white coat hypertension who have normal ambulatory blood pressure associated with target organ changes? *J Hum Hypertens*. 1998;12:743–748.
45. Muscholl MW, Hense HW, Bröckel U, Döring A, Riegger GA, Schunkert H. Changes in left ventricular structure and function in patients with white coat hypertension: cross sectional survey. *BMJ*. 1998;317:565–570.
46. Zakopoulos N, Papamichael C, Papaconstantinou H, Dubbins PA, Burrell CJ, Lekakis J, Stamatelopoulos S, Moulopoulos S. Isolated clinic hypertension is not an innocent phenomenon: effect on the carotid artery structure. *Am J Hypertens*. 1999;12:245–250.
47. Hara A, Ohkubo T, Kikuya M, et al. Detection of carotid atherosclerosis in individuals with masked hypertension and white-coat hypertension by self-measured blood pressure at home: the Ohasama study. *J Hypertens*. 2007;25:321–327.
48. Puato M, Palatini P, Zanardo M, Dorigatti F, Tirrito C, Rattazzi M, Pauletto P. Increase in carotid intima-media thickness in grade I hypertensive subjects: white-coat versus sustained hypertension. *Hypertension*. 2008;51:1300–1305.
49. Agarwal R, Sinha AD, Light RP. Toward a definition of masked hypertension and white-coat hypertension among hemodialysis patients. *Clin J Am Soc Nephrol*. 2011;6:2003–2008.
50. Wimmer NJ, Sathi K, Chen TL, Townsend RR, Cohen DL. Comparison of pulse wave analysis between persons with white coat hypertension and normotensive persons. *J Clin Hypertens (Greenwich)*. 2007;9:513–517.
51. Weber MA, Neutel JM, Smith DH, Graettinger WF. Diagnosis of mild hypertension by ambulatory blood pressure monitoring. *Circulation*. 1994;90:2291–2298.
52. Mancia G, Bombelli M, Facchetti R, Madotto F, Quarti-Trevano F, Grassi G, Sega R. Increased long-term risk of new-onset diabetes mellitus in white-coat and masked hypertension. *J Hypertens*. 2009;27:1672–1678.
53. de Leeuw PW. Variable hypertension and latent diabetes: two of a kind? *J Hypertens*. 2009;27:1536–1537.