Cardiovascular Risk Associated With White-Coat Hypertension

Con Side of the Argument

Kei Asayama, Yan Li, Stanley S. Franklin, Lutgarde Thijs, Eoin O'Brien, Jan A. Staessen

Building on the work of Mann et al[1] at Northwick Park Hospital in London, Coats et al[2] at the John Radcliffe Hospital in Oxford, and Perloff et al[3] at the San Francisco Medical Center, in 1988, Thomas Pickering coined the term white-coat hypertension, to describe patients whose blood pressure was elevated in the medical environment, but not during daytime ambulatory monitoring.[4,5] Early pioneering studies[1–3] unambiguously established that ambulatory blood pressure is a better predictor of cardiovascular outcome than the in-office blood pressure and consequently surmised that white-coat hypertension must be associated with low cardiovascular risk. A seminal article by Pickering et al[4] included a statement that patients who showed an exaggerated response to the clinic environment might also exhibit a similar response to more regularly occurring types of stress, which could support the continued use of clinic blood pressure for making therapeutic decisions. However, observations by Pickering et al[4] did not support this preposition.

The first longitudinal study on the prognostic values of white-coat hypertension was reported in 1994.[6] On the basis of these early studies[1–6] and confirmatory reports in patients[7] and populations,[8–12] the currently prevailing point of view is that white-coat hypertension carries little cardiovascular risk.[13] However, some researchers[14] suggested that white-coat hypertension is a heterogeneous condition. In making this statement, they did not refer to the loose criteria in the literature used to diagnose white-coat hypertension. They alluded to the fact that in some studies, white-coat hypertension, compared with true normotension, was associated with a higher prevalence of cardiovascular risk factors and target organ damage,[15] increased mortality,[15] more cardiovascular events,[16] and higher out-of-the-office blood pressure.[15,16] In this article, we will demonstrate that labeling white-coat hypertension in this sense as a heterogeneous condition is erroneous because it is based on a combination of imprecise diagnostic criteria that overlook the true nature of white-coat hypertension and that white-coat hypertension is associated with low cardiovascular risk in the absence of other risk factors.

Determinants of White-Coat Hypertension

In 1994, in an analysis of the International Database of Ambulatory Blood Pressure Monitoring, we demonstrated that the probability of patients with office hypertension having a normal 24-hour blood pressure was higher in women than in men, increased with age, and was 2- to 4-fold greater if the office blood pressure had only been measured at a single visit or if fewer than 3 readings had been averaged.[17] In untreated participants with mild hypertension enrolled in the HARVEST (Hypertension and Ambulatory Recording Venetia Study) or the PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) studies, white-coat hypertension was most frequent among women, nonsmokers, and individuals with low clinic blood pressure and smaller left ventricular mass.[18] In a more recent participant-level meta-analysis,

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan (K.A.); Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Sciences, Sendai, Japan (K.A.); Center for Epidemiological Studies and Clinical Trials and Center for Vascular Evaluations, Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, China (Y.L.); Heart Disease Prevention Program, Division of Cardiology, School of Medicine, University of California-Irvine (S.S.F.); Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Belgium (L.T., J.A.S.); Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Ireland (E.O.); and R&D Group VitaK, Maastricht University, The Netherlands (J.A.S.).

This paper was sent to Theodore A. Kotchen, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Correspondence to Jan A. Staessen, Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, Box 7001, BE-3000 Leuven, Belgium. E-mail jan.staessen@med.kuleuven.be or ja.staessen@maastrichtuniversity.nl

(*Hypertension*. 2017;70:676-682. DOI: 10.1161/HYPERTENSIONAHA.117.08902.)

we refined the assessment of the association of white-coat hypertension with age by combining 9550 individuals not taking any antihypertensive medications enrolled in the IDACO (International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes; n=7506) with the study of GAPP (Genetic and Phenotypic Determinants of Blood Pressure and Other Cardiovascular Risk Factors; n=2044).[11] Among individuals aged 18 to 30, 30 to 40, and 40 to 50 years, mean daytime blood pressure was higher than the corresponding office blood pressure. The differences averaged 6.0, 5.2, and 4.7 mm Hg for systolic, and 2.5, 2.7, and 1.7 mm Hg for diastolic pressure. In contrast, in individuals aged 60 to 70 and ≥70 years, office blood pressure was 5.0 and 13.1 mm Hg systolic and 2.0 and 4.2 mm Hg higher than the daytime ambulatory blood pressure (Figure 1).[11] The prevalence of white-coat hypertension exponentially increased from 2.2% to 19.5% from age 18 to 30 to ≥70 years, with little sex differences.[11] Along similar lines, in untreated participants enrolled in the SKIPOGH study (Swiss Kidney Project of Genes in Hypertension), older age was the sole determinant of white-coat hypertension with education, family history of hypertension, and physical activity having no influence.[19] Other studies[20,21] confirmed that the relation between office and home blood pressure, as other modality of out-of-the-office blood pressure measurement, changes according to age in a way similar as the relation between office and the ambulatory blood pressure does.[11]

We recently assessed in 8237 untreated IDACO participants to what extent the time intervals, during which the ambulatory blood pressure is measured, affects cardiovascular risk.[12] We used the following hypertension thresholds ≥140/≥90, ≥130/≥80, ≥135/≥85, and ≥120/≥70 mm Hg for the office, 24-hour, daytime, and nighttime blood pressures, respectively (Table). The prevalence of white-coat hypertension ranged from 6.3% to 12.5% depending on the time periods chosen. During 91 046 person-years, 729 cardiovascular events occurred. In multivariable-adjusted analyses, hazard ratios associated with white-coat hypertension progressively weakened (Figure 2), considering daytime only (1.38; *P*=0.033), nighttime only (1.43; *P*=0.0074), 24 hours only (1.21; *P*=0.20), 24 hours plus daytime (1.24; *P*=0.18), 24 hours plus nighttime (1.15; *P*=0.39), and 24 hours plus daytime and nighttime (1.16; *P*=0.41).[12] Being normotensive over the whole 24-hour period was therefore associated with the lowest cardiovascular risk.[12] Within the daytime-based white-coat hypertension, Considering daytime-defined white-coat hypertension, Verdecchia et al[23] suggested that lowering the threshold of daytime hypertension (eg, from 131/86 mm Hg in women and 136/87 mm Hg in men to 130/80 mm Hg in both sexes) would result in a lower event rate associated with white-coat hypertension.

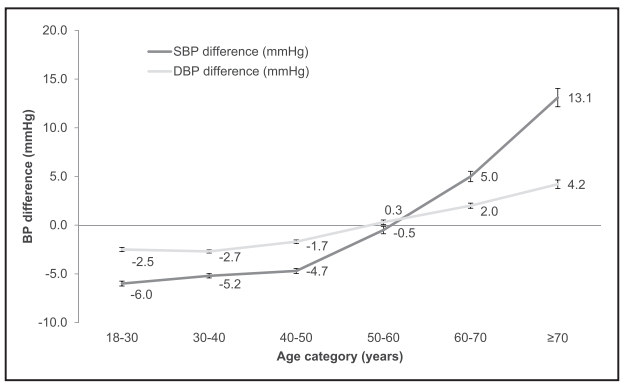

Figure 1. Differences between office and ambulatory daytime blood pressures according to age categories. Data are mean±SE differences of office minus daytime blood pressure. DBP indicates diastolic blood pressure; and SBP, systolic blood pressure. Reprinted from Conen et al.[11] Copyright © 2014, American Heart Association, Inc.

Blood pressure self-measurement offers several of the well-recognized advantages of the more complex approach of ambulatory blood pressure monitoring.[24] The greater number of readings and the minimization of the white-coat effect contribute to a better diagnostic accuracy, compared with office blood pressure measurement.[24] If automated devices are used and if patients apply a standardized protocol for the timing of the measurements rather than initiating recordings based on symptoms, self-recorded blood pressure values are to a large extent free of observer bias. However, in 831 untreated Chinese outpatients, using daytime ambulatory instead of home blood pressure confirmed the cross-classification with office blood pressure only in 575 patients (69.2%), downgraded risk from masked hypertension to normotension (n=24) or from sustained to white-coat hypertension (n=9) in 33 patients (4.0%), but upgraded the risk from normotension to masked hypertension (n=179) or from white-coat to sustained hypertension (n=44) in 223 patients (26.8%).[25] These observations,[25] along with the IDACO data article referred to before,[12] indicate that the method of measuring out-of-the-office blood pressure substantially affects the prevalence of white-coat hypertension.

Although confined by definition to the normal blood pressure range, both ambulatory and home blood pressure are several mm Hg higher in white-coat hypertensive patients than in normotensive people.[14] However, this interpretation[14] disregards the effects on estimates of the prevalence of white-coat hypertension related to the frequency of office blood pressure measurements,[17] age,[11,17] the modality used to measure the out-of-the-office blood pressure,[25] or the time intervals applied during ambulatory monitoring to diagnose white-coat hypertension.[12]

Influence of Treatment

In the literature, white-coat hypertension is varyingly defined based on the ambulatory blood pressure levels irrespective of treatment status[8] or in untreated persons only.[11,12,19] Initial analyses of the IDACO database did not account for treatment status. Using thresholds as proposed in current guidelines[22,26] and office and daytime normotension as reference, the multivariable-adjusted hazard ratio for a cardiovascular event associated with white-coat hypertension was 1.22 (*P*=0.095).[8] Median follow-up was 9.5 years. If the Cox models were censored at 6, 9, and 12 years, the hazard ratios associated with white-coat hypertension were 1.08 (*P*=0.79), 1.20 (*P*=0.29), and 1.30 (*P*=0.043), respectively.[8] Compared with sustained hypertension, the hazard ratio for a cardiovascular end point associated with white-coat hypertension was consistently <0.73 (*P*≤0.014) lower, irrespective of the follow-up period considered.[8] Thus, follow-up duration is another key factor

Table. Systolic and Diastolic Blood Pressure Thresholds for Blood Pressure

Category	Office Blood Pressure		Out-of-the-Office Blood Pressure		
	Conventional	Automated	Ambulatory		Home
Normotension	<140 and < 90	<135 and <85	Daytime	<135 and <85	<135 and <85
			Nighttime	<120 and <70	
			24 h	<130 and <80	
Optimal	<120 and <80				
Normal	120–129 or 80–84				
High–normal	130–139 or 85–89				
Hypertension	≥140 or ≥90	≥135 or ≥85	Daytime	≥135 or ≥85	≥135 or ≥85
			Nighttime	≥120 or ≥70	
			24 h	≥130 or ≥80	

Blood pressure thresholds are given in mm Hg. Automated office blood pressure is the mean of multiple blood pressure readings recorded with a fully automated device with the patient resting silently, alone, in a quiet room at the doctor's office or clinic. Consensus classification proposed by the 2013 European guidelines.[22]

to be considered in relating cardiovascular risk to white-coat hypertension. Until now, there is no proof that in studies with a sufficiently lengthy follow-up risk estimates are higher in white-coat hypertensive than normotensive people.

Subsequent IDACO analyses only included untreated people[9,10,12] and most recently[10] accounted for the huge effect of age on the prevalence of white-coat hypertension and the clustering of risk factors with both aging and white-coat hypertension. We scored cardiovascular risk by applying European Society Hypertension guidelines[22] to 653 untreated white-coat hypertensive patients matched with 653 normotensive controls by cohort and age (within 5 years),[10] an approach that is more bias-free than trying to adjust away the huge confounding effect of age. Over a median follow-up of 10.6 years, the incidence of cardiovascular end points was higher in 159 high-risk white-coat hypertensive patients compared with cohort- and age-matched high-risk normotensive people (adjusted hazard ratio, 2.06; *P*=0.023). The corresponding hazard ratio in 494 low-risk participants was not significant (1.06; *P*=0.80). After stratification for age (<60 versus ≥60 years), the association between cardiovascular risk and white-coat hypertension was limited to senior high-risk white-coat hypertensive patients.[10] The hazard ratio associated with white-coat hypertension was higher (*P*=0.044) in older high-risk compared with older low-risk individuals (2.19 versus 0.88; *P*=0.027 versus 0.66). Below 60 years of age, the incidence of cardiovascular events in white-coat hypertensive participants was low without any tendency for increased risk compared with their cohort- and age-matched normotensive controls. Overall, there were 70 incident cardiovascular events in the white-coat hypertensive patients versus 48 in the cohort- and age-matched normotensive participants, meaning that there was an excess of only 22 new cardiovascular events, affecting only 3.4% of the 653 white-coat hypertensive patients and leaving 96.6% of the white-coat population at no greater risk than cohort- and age-matched normotensive controls.[10]

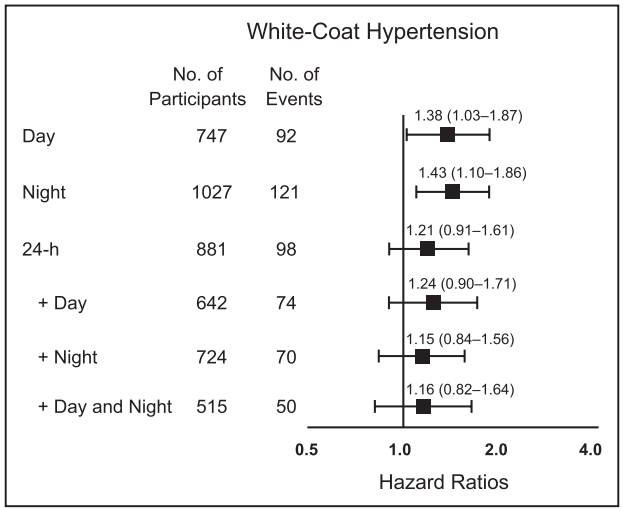

Figure 2. Risk of a cardiovascular outcome associated with white-coat hypertension as recorded during varying intervals during the day. White-coat hypertension was office hypertension in the presence of a normal ambulatory blood pressure. When systolic or diastolic blood pressure was in different categories (normotensive vs hypertensive), participants were classified as hypertensive. Hazard ratios were multivariable adjusted. Horizontal bars denote the 95% confidence interval. Reprinted from Asayama et al.[12] Copyright © 2014, American Heart Association, Inc.

Pierdomenico and Cuccurullo[13] did a meta-analysis of summary statistics to assess the prognostic impact of white-coat hypertension in initially untreated people free of cardiovascular complications, which included the availability of covariables to adjust the hazard ratios for confounders. They identified 6 studies,[6,7,27–30] including untreated participants with white-coat hypertension. Four studies[7,28–30] used <135/<85 mm Hg as daytime ambulatory threshold, one[27] used <130/<80 mm Hg as 24-hour threshold, and one[6] applied sex-specific thresholds for the daytime blood pressure (<131/86 mm Hg in women and <136/87 mm Hg in men). In this meta-analysis, 1 study by Hansen et al[29] provided updated data for untreated participants. Compared with normotension, the pooled hazard ratio of white-coat hypertension for the incidence of cardiovascular events was 0.96 (95% confidence intervals [CIs], 0.65–1.42; *P*=0.85) without any heterogeneity

between studies (P>0.65; Figure 3), and follow-up duration did not affect this conclusion. This exemplary meta-analysis[13] accurately dealt with the problem of confounding by antihypertensive drug treatment.

Total and Cardiovascular Risk

In each participant of the population in the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni),[31] 3 office blood pressure readings at a single visit, a 24-hour ambulatory blood pressure recording, and 2 home blood pressure measurements, one in the morning and one in the evening, were obtained. The proportion of participants on antihypertensive drug treatment was 4.3% in 825 normotensive people and 31.0% in 227 patients with partial white-coat hypertension, as diagnosed by either ambulatory or home blood pressure monitoring, and 22.0% in 164 true white-coat hypertensive patients, who had a normal out-of-the-office blood pressure both on ambulatory and home blood pressure monitoring. It is not surprising that by including treated participants, the results were contradictory. With normotension as the reference group, the hazard ratios for total mortality were 1.35 (CI, 0.81–2.23; P=0.25) and 1.58 (CI, 1.05–2.38; P=0.027) in true (22 deaths) and partial (55 deaths) white-coat hypertensive participants; for cardiovascular mortality, the corresponding estimates were 0.67 (CI, 0.14–3.18; P=0.61; 2 deaths) and 2.76 (CI, 1.16–6.59; P=0.022; 19 deaths).[31] The partial white-coat hypertensive group probably included a proportion of patients with sustained hypertension. The models, including 4 blood pressure groups, were adjusted for sex, age, body mass index, blood glucose, serum total cholesterol, smoking, previous cardiovascular disease, and antihypertensive drug treatment. There were few events, in particular, from cardiovascular mortality, relative to the number of independent variables possibly leading to uncertain results. Moreover, the introduction of stroke units and invasive coronary procedures in routine clinical care has substantially decreased the case fatality rates of most cardiovascular complications of hypertension. Not accounting for nonfatal events, therefore, limits the generalizability of the PAMELA results.[31]

A Taiwanese study included 1257 never-treated volunteers from a community-based survey.[32] Of those, 250 were normotensive people with an office blood pressure of <120 mm Hg systolic and 80 mm Hg diastolic; 318 were participants with prehypertension, who had an office blood pressure between 120/80 and 140/90 mm Hg and normal daytime ambulatory blood pressure; and 153 were white-coat hypertensive patients. During a median follow-up period of 15 years, 272 died, but only 73 (26.8%) from cardiovascular disease.[32] The incidence of all-cause and cardiovascular mortality expressed per 1000 person-years of follow-up was 9.7 and 0.6 in normotensive people, 11.0 and 1.4 in prehypertensive participants, and 24.6 and 6.5 in white-coat hypertensive patients.[32] Multivariable models were adjusted for sex, age, body mass index, smoking, fasting plasma glucose, and the total:high-density lipoprotein serum cholesterol ratio. Compared with normotension, the hazard ratios associated with white-coat hypertension were 1.30 (CI, 0.81–2.09) and 5.59 (CI, 1.22–25.6) for total and cardiovascular mortality, respectively.[32] As in the PAMELA study,[31] the Taiwanese study[32] was underpowered to assess cardiovascular mortality, resulting in extremely wide CIs and did also not account for the incidence of nonfatal cardiovascular events.

That cardiovascular mortality in the Taiwanese study[32] represented only one fourth of all-cause mortality highlights the relevance of the latter issue. Moreover, prehypertensive participants were excluded from the control group, leading to an underestimation of the risk associated with normotension.[32] White-coat hypertensive participants were significantly older and had greater body mass index, blood pressure values, intima-media thickness, carotid-femoral pulse wave velocity, central augmentation index, amplitude of the backward pressure wave, and a lower estimated glomerular filtration compared with prehypertensive individuals.[32] This illustrates the superiority of the IDACO approach,[10] in which normotensive and white-coat hypertensive participants were matched by age with normotensive controls and in which analyses were stratified by age and cardiovascular risk.[10]

The results of another study, the DHS (Dallas Heart Study), which attempts to determine hypertensive target organ damage and adverse cardiovascular outcomes associated with white-coat hypertension, is also flawed.[16] This study includes a probability-based population cohort (n=3027 at baseline) with oversampling of blacks (50.0%). The sample-weighted prevalence rate of white-coat hypertension at baseline (3.3%) was ≈4-fold lower than in other population studies.[12] The obvious explanation is that the same observers measured blood pressure at the homes of the participants and subsequently at the clinic and that of 5 blood pressure readings at each occasion, only the third to fifth were averaged for analysis. In 2073 participants followed up for a median of 9.4 years, 52 composite cardiovascular events occurred in 1627 normotensive

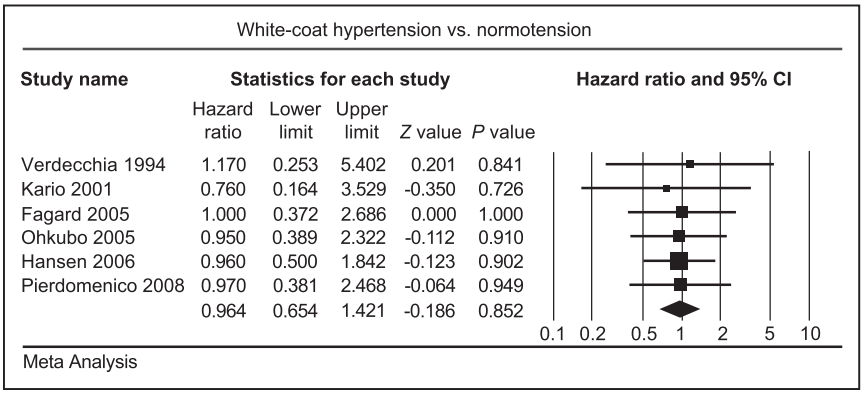

Figure 3. Adjusted hazard ratio and 95% confidence intervals (CIs, horizontal bars) in white-coat hypertension for the incidence of cardiovascular events compared with normotension. Reprinted from Pierdomenico and Cuccurullo[13] with permission of the publisher. Copyright © 2011, Oxford University Press.

participants but only 10 in 109 white-coat hypertensive patients. The cardiovascular end point included cardiovascular death, coronary heart disease, stroke, heart failure, but also the weaker outcome of atrial fibrillation.[16] The contribution of each of these outcomes to the composite end point was not reported.[16] Outcome analyses did not include patients with a previous history of cardiovascular disease and were adjusted for ethnicity, sex, age, body mass index, diabetes mellitus, serum cholesterol, smoking, self-reported history of hypertension, and antihypertensive treatment. With these adjustments applied, the hazard ratio, as the authors stated,[16] trended to significance, amounting to 1.98 (CI, 0.99–3.95; *P*=0.051).

Briasoulis et al[33] published a meta-analysis of summary statistics extracted from 14 studies including 13 538 normotensive and 4806 white-coat hypertensive patients. The incidence of cardiovascular events was 6% in white-coat hypertensive patients and 4% in normotensive people. The odds ratio of a cardiovascular event associated with white-coat hypertension compared with normotension was 1.73 (CI, 1.27–2.36; *P*=0.006). However, this study[33] is uninterpretable because the authors pooled studies based on daytime and home blood pressure monitoring to define white-coat hypertension, and the analyses were completely unadjusted and notably did not account for age or treatment status. By way of comparison, the Ohasama study group originally reported that the multivariable-adjusted cardiovascular risk among participants with white-coat hypertension, including both treated and untreated residents, was much lower, that is, 1.28 (CI, 0.76–2.14; *P*=0.40).[28]

More recently, Huang et al[34] conducted a similar meta-analysis[33] and had it published in the *Journal of Hypertension*. The reference list of the publication by Huang et al[34] confirmed that our search strategy based on >30 years of working in the field of blood pressure measurement had covered most—if not all—of the relevant publications. The report by Huang et al[34] included 23 (20 445 individuals), 11 (8 656), and 12 (21 336) cohorts for analysis of cardiovascular risk, respectively, associated with white-coat hypertension in patients without or under antihypertensive treatment at baseline or including both untreated and treated participants. In untreated cohorts, compared with normotension, white-coat hypertension was associated with 38% and 20% risk increments of cardiovascular disease and total mortality. However, in treated patients, neither the risk of cardiovascular disease nor total mortality was increased in white-coat hypertension. As highlighted before, total mortality is an administrative end point, easily obtained from population registries and since the introduction of invasive therapies in cardiovascular disease carrying little information. In subgroup analyses, white-coat hypertension was suboptimally defined using varying approaches to measure blood pressure or to define a composite cardiovascular end point. For instance, Huang et al[34] included a recent IDACO analysis,[12] but selected the daytime only or 24-hour only ambulatory blood pressure-based statistics, thereby overestimating the risk of white-coat hypertension compared with ambulatory normotension over the whole day. They also referenced our home blood pressure–based individual participant database, including 5007 untreated and 1451 treated participants enrolled in 5 cohorts,[35] who monitored their home blood pressure for a single day up to >3 weeks (7 days in 84% of the participants). If participants were analyzed with ≥7 days of home blood pressure monitoring, as recommended by present-day guidelines,[22,36] home blood pressure–based white-coat hypertension was no longer associated with an increased cardiovascular risk.[37]

Conclusions

White-coat hypertension is commonly defined as a raised in-office blood pressure in the presence of a normal out-of-the-office blood pressure. In the light of the evidence reviewed in this debate, we propose that this definition be refined. One possibility, as suggested by Myers and Stergiou,[38] is to change the nomenclature from white-coat hypertension to white-coat phenomenon to remove the stigma of hypertension. Although the white-coat phenomenon rightly denotes the white-coat effect, it is, in our opinion, a misnomer to refer to white-coat hypertension because the this condition may be present both in untreated and treated individuals. Alternatively, an elevated office pressure in the presence of a normal out-of-the-office blood pressure in untreated people might be called masked normotension, a term proposed previously by others[39] although not accounting for treatment status. Masked normotension, which is not associated with increased cardiovascular risk, and which should not be treated by blood pressure–lowering drugs, does requires management of cardiovascular risk factors and further follow-up. The widespread assumption that masked normotension predisposes to the development of sustained hypertension,[40,41] to our knowledge, has never been tested by long-term follow-up of truly normotensive and masked normotensive people, matched for age at baseline. An elevated office pressure in the presence of a normal out-of-the-office blood pressure in treated patients reflects hypertension controlled under out-of-the-office conditions, but uncontrolled in a medical environment. For this group, the term white-coat hypertension might still be appropriate on condition that treatment is given correctly, as recommended by current guidelines. Unfortunately, this is not always the case.

We agree with 1 point raised by Mancia and Grassi,[14] who state that white-coat hypertension is a heterogeneous condition. For this very reason, studies should account for age,[11,17] for the presence of cardiovascular risk factors, for the number of visits and the number of blood pressure readings used to define the office blood pressure,[17] the modality of out-of-the-office measurement,[25] the number and definition of end points available for analysis,[31,32] and the proportionality between the number of end points and confounders adjusted for.[31,32] Furthermore, definition of white-coat hypertension differs across the studies, which affect the risk of white-coat hypertension.[12,23] If ambulatory blood pressure measurement is used to define white-coat hypertension, the period of the day during which blood pressure was within the normal range must be stated[12]; if home blood pressure monitoring is applied, current guidelines recommend at least 3 to 4[22] but preferably 5 to 7 consecutive days of measurement per week.[22,36] These quality standards might inform the future research agenda and the criteria to be met for new publications on the subject and for truly evidence-based guidelines for the diagnosis and management of white-coat hypertension.

Acknowledgments

Renilde Wolfs and Vera De Leebeeck provided expert clerical assistance.

Sources of Funding

The European Union (HEALTH-F7-305507 HOMAGE) and the European Research Council (Advanced Researcher Grant 2011-294713-EPLORE and Proof-of-Concept Grant 713601-uP-ROPHET) currently support research at the Studies Coordinating Centre in Leuven.

Disclosures

None.

References

1. Mann S, Millar Craig MW, Raftery EB. Superiority of 24-hour measurement of blood pressure over clinic values in determining prognosis in hypertension. *Clin Exp Hypertens A*. 1985;7:279–281.
2. Coats AJ, Conway J, Sleight P, Meyer TE, Somers VK, Floras JS, Vann Jones J. Interdependence of blood pressure and heart period regulation in mild hypertension. *Am J Hypertens*. 1991;4(3 pt 1):234–238.
3. Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressures. *JAMA*. 1983;249:2792–2798.
4. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? *JAMA*. 1988;259:225–228.
5. O'Brien E. First Thomas Pickering memorial lecture*: ambulatory blood pressure measurement is essential for the management of hypertension. *J Clin Hypertens*. 2012;14:836–847. doi: 10.1111/j.1751-7176.2012.00698.x.
6. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, Santucci C, Reboldi G. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension*. 1994;24:793–801.
7. Fagard RH, Van Den Broeke C, De Cort P. Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. *J Hum Hypertens*. 2005;19:801–807. doi: 10.1038/sj.jhh.1001903.
8. 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. doi: 10.1097/HJH.0b013e3281c49da5.
9. 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. doi: 10.1161/HYPERTENSIONAHA.111.180653.
10. Franklin SS, Thijs L, Asayama K, et al; IDACO Investigators. The cardiovascular risk of white-coat hypertension. *J Am Coll Cardiol*. 2016;68:2033–2043. doi: 10.1016/j.jacc.2016.08.035.
11. Conen D, Aeschbacher S, Thijs L, et al. Age-specific differences between conventional and ambulatory daytime blood pressure values. *Hypertension*. 2014;64:1073–1079. doi: 10.1161/HYPERTENSIONAHA.114.03957.
12. Asayama K, Thijs L, Li Y, et al; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) Investigators. Setting thresholds to varying blood pressure monitoring intervals differentially affects risk estimates associated with white-coat and masked hypertension in the population. *Hypertension*. 2014;64:935–942. doi: 10.1161/HYPERTENSIONAHA.114.03614.
13. 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. doi: 10.1038/ajh.2010.203.
14. Mancia G, Grassi G. The heterogeneous nature of white-coat hypertension. *J Am Coll Cardiol*. 2016;68:2044–2046. doi: 10.1016/j.jacc.2016.08.043.
15. 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. doi: 10.1161/01.HYP.0000215363.69793.bb.
16. Tientcheu D, Ayers C, Das SR, McGuire DK, de Lemos JA, Khera A, Kaplan N, Victor R, Vongpatanasin W. Target organ complications and cardiovascular events associated with masked hypertension and white-coat hypertension: analysis from the Dallas Heart Study. *J Am Coll Cardiol*. 2015;66:2159–2169. doi: 10.1016/j.jacc.2015.09.007.
17. Staessen JA, O'Brien ET, Amery AK, Atkins N, Baumgart P, De Cort P, Degaute JP, Dolenc P, De Gaudemaris R, Enström I. Ambulatory blood pressure in normotensive and hypertensive subjects: results from an international database. *J Hypertens Suppl*. 1994;12:S1–S12.
18. 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.
19. Alwan H, Pruijm M, Ponte B, et al. Epidemiology of masked and white-coat hypertension: the family-based SKIPOGH study. *PLoS One*. 2014;9:e92522. doi: 10.1371/journal.pone.0092522.
20. Ishikawa J, Ishikawa Y, Edmondson D, Pickering TG, Schwartz JE. Age and the difference between awake ambulatory blood pressure and office blood pressure: a meta-analysis. *Blood Press Monit*. 2011;16:159–167. doi: 10.1097/MBP.0b013e328346d603.
21. Ntineri A, Stergiou GS, Thijs L, et al. Relationship between office and home blood pressure with increasing age: The International Database of HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO). *Hypertens Res*. 2016;39:612–617. doi: 10.1038/hr.2016.32.
22. 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. doi: 10.1093/eurheartj/eht151.
23. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Porcellati C. White-coat hypertension. *Lancet*. 1996;348:1444–1445; author reply 1445. doi: 10.1016/S0140-6736(04)70084-7.
24. Staessen JA, Thijs L, Ohkubo T, Kikuya M, Richart T, Boggia J, Adiyaman A, Dechering DG, Kuznetsova T, Thien T, de Leeuw P, Imai Y, O'brien E, Parati G. Thirty years of research on diagnostic and therapeutic thresholds for the self-measured blood pressure at home. *Blood Press Monit*. 2008;13:352–365. doi: 10.1097/MBP.0b013e3283108f93.
25. Zhang L, Li Y, Wei FF, Thijs L, Kang YY, Wang S, Xu TY, Wang JG, Staessen JA. Strategies for classifying patients based on office, home, and ambulatory blood pressure measurement. *Hypertension*. 2015;65:1258–1265. doi: 10.1161/HYPERTENSIONAHA.114.05038.
26. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P; European Society of Hypertension Working Group on Blood Pressure Monitoring. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens*. 2005;23:697–701. doi: 10.1097/01.hjh.0000163132.84890.c4.
27. 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.
28. Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol*. 2005;46:508–515. doi: 10.1016/j.jacc.2005.03.070.
29. Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure monitoring and risk of cardiovascular disease: a population based study. *Am J Hypertens*. 2006;19:243–250. doi: 10.1016/j.amjhyper.2005.09.018.
30. Pierdomenico SD, Lapenna D, Di Mascio R, Cuccurullo F. Short- and long-term risk of cardiovascular events in white-coat hypertension. *J Hum Hypertens*. 2008;22:408–414. doi: 10.1038/jhh.2008.6.
31. Mancia G, Bombelli M, Brambilla G, Facchetti R, Sega R, Toso E, Grassi G. Long-term prognostic value of white coat hypertension: an insight from diagnostic use of both ambulatory and home blood pressure measurements. *Hypertension*. 2013;62:168–174. doi: 10.1161/HYPERTENSIONAHA.111.00690.
32. 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. doi: 10.1161/HYPERTENSIONAHA.111.00569.
33. Briasoulis A, Androulakis E, Palla M, Papageorgiou N, Tousoulis D. White-coat hypertension and cardiovascular events: a meta-analysis. *J Hypertens*. 2016;34:593–599. doi: 10.1097/HJH.0000000000000832.

34. Huang Y, Huang W, Mai W, Cai X, An D, Liu Z, Huang H, Zeng J, Hu Y, Xu D. White-coat hypertension is a risk factor for cardiovascular diseases and total mortality. *J Hypertens*. 2017;35:677–688. doi: 10.1097/HJH.0000000000001226.
35. Stergiou GS, Asayama K, Thijs L, Kollias A, Niiranen TJ, Hozawa A, Boggia J, Johansson JK, Ohkubo T, Tsuji I, Jula AM, Imai Y, Staessen JA; International Database on HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO) Investigators. Prognosis of white-coat and masked hypertension: International Database of HOme blood pressure in relation to Cardiovascular Outcome. *Hypertension*. 2014;63:675–682. doi: 10.1161/HYPERTENSIONAHA.113.02741.
36. Shimamoto K, Ando K, Fujita T, et al; Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). *Hypertens Res*. 2014;37:253–390. doi: 10.1038/hr.2014.20.
37. Niiranen TJ, Asayama K, Thijs L, Johansson JK, Hara A, Hozawa A, Tsuji I, Ohkubo T, Jula AM, Imai Y, Staessen JA; IDHOCO Investigators. Optimal number of days for home blood pressure measurement. *Am J Hypertens*. 2015;28:595–603. doi: 10.1093/ajh/hpu216.
38. Myers MG, Stergiou GS. White coat phenomenon: removing the stigma of hypertension. *Hypertension*. 2016;67:1111–1113. doi: 10.1161/HYPERTENSIONAHA.116.07322.
39. Hermida RC, Smolensky MH, Ayala DE, Portaluppi F. Ambulatory Blood Pressure Monitoring (ABPM) as the reference standard for diagnosis of hypertension and assessment of vascular risk in adults. *Chronobiol Int*. 2015;32:1329–1342. doi: 10.3109/07420528.2015.1113804.
40. 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. doi: 10.1001/archinte.165.13.1541.
41. Sivén SS, Niiranen TJ, Kantola IM, Jula AM. White-coat and masked hypertension as risk factors for progression to sustained hypertension: the Finn-Home study. *J Hypertens*. 2016;34:54–60. doi: 10.1097/HJH.0000000000000750.

Response to Cardiovascular Risk Associated With White-Coat Hypertension: Con Side of the Argument

Giuseppe Mancia, Michele Bombelli, Cesare Cuspidi, Rita Facchetti, Guido Grassi

Any controversy on the clinical value of white-coat hypertension (WCH) cannot deny a simple fact, namely, that when physicians (who are not asked to adjust their observations for covariates!) see a patient with an elevation of office blood pressure and an out-of-office blood pressure within the accepted normal limits, they must suspect a clinically abnormal condition and proceed to clinical investigations that are not required in patients in whom the above pressures are both normal. This will disclose considerably more often than in normotensive individuals an array of associated metabolic risk factors but also organ alterations that are normally caused by a blood pressure elevation such as left ventricular hypertrophy, suggesting that the abnormal in-office and out-of-office blood pressure pattern is involved. We think that the clinical abnormality of WCH has received confirmation from (1) meta-analyses of longitudinal outcome studies that have documented its association with an increased cardiovascular risk and (2) evidence that WCH individuals' progression to high cardiovascular risk conditions (established hypertension and diabetes mellitus) is substantially more frequently than in normotensive people. This is the case also for the development of organ damage in patients who do not have it originally, that is, a condition regarded by our opponents as of no risk.

We think it is time to move from this established background to research on issues of mechanistic and clinical relevance that are not clear. One of them may be the identification of WCH subgroups at higher or lower risk, perhaps acknowledging, however, that in several instances (eg, treated WCH), the nature of the available information makes unequivocal evidence difficult to be obtained. Another is to determine whether and to what extent in WCH drug treatment of the abnormal risk profile can reduce the cardiovascular risk and slow down progression to high-risk conditions that will inevitably affect their life time prognosis.

Cardiovascular Risk Associated With White-Coat Hypertension: Con Side of the Argument

Kei Asayama, Yan Li, Stanley S. Franklin, Lutgarde Thijs, Eoin O'Brien and Jan A. Staessen

Hypertension. 2017;70:676-682; originally published online August 28, 2017;
doi: 10.1161/HYPERTENSIONAHA.117.08902
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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

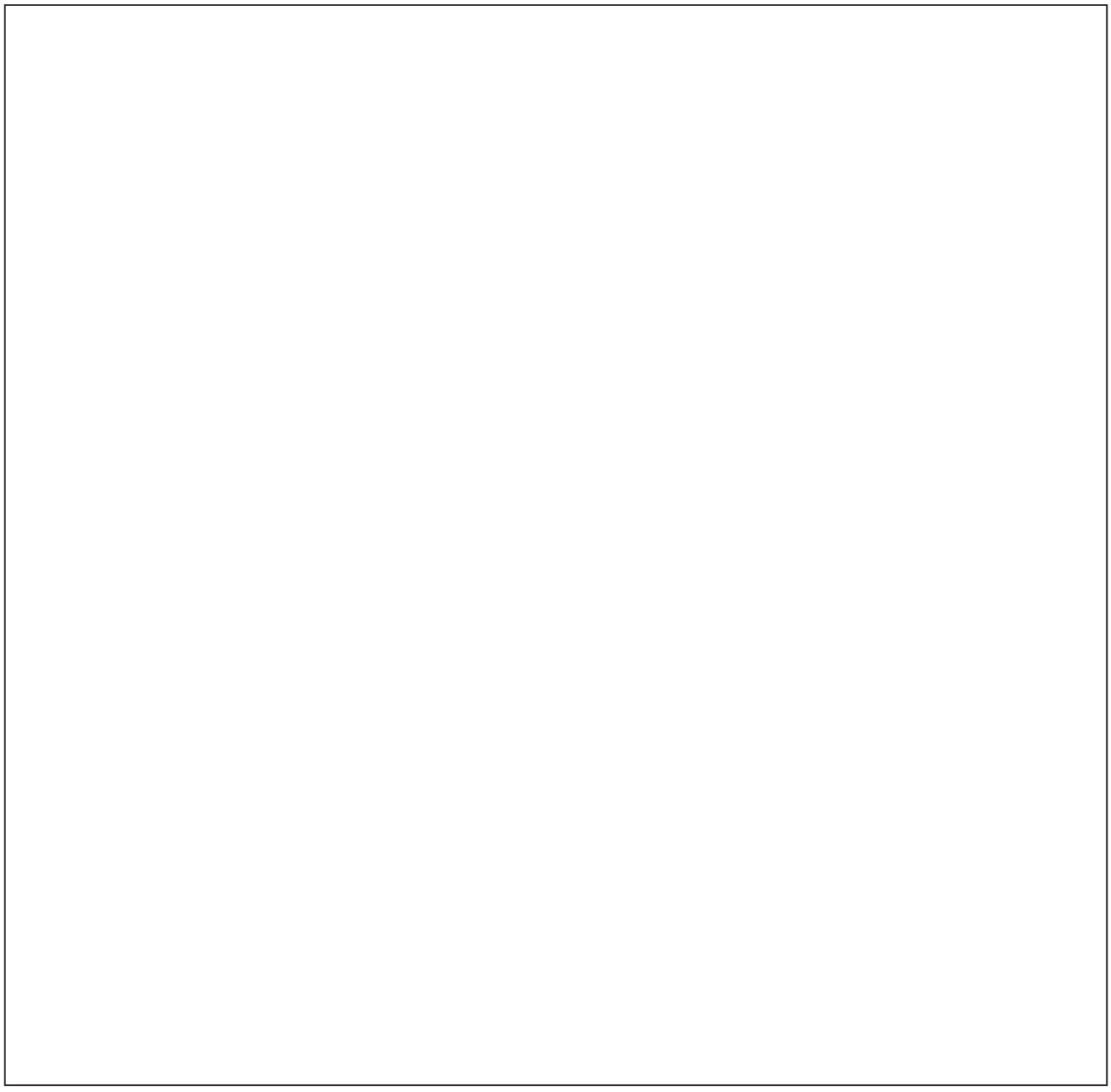

Figure 2. Cardiac and vascular alterations in (1) white-coat hypertension (WCH) vs normotension (NT; **top**) and (2) WCH vs sustained hypertension (SH; **bottom**). Data from meta-analyses of available studies. A indicates atrial dependent ventricular filling; E, early ventricular filling; IMT, intima–media thickness; LAD, left atrial diameter; LVMI, left ventricular mass index; and SMD, standardized mean difference between groups. Adapted from Cuspidi et al[11,12] with permission of the publisher.

the cardiovascular risk of WCH was reported not to differ significantly from normotension (hazard ratio, 1.12; 95% confidence intervals, 0.84–1.50, in one and hazard ratio, 0.96; 95% confidence intervals, 0.65–1.42, in the other),[23–25] in the most recent ones, the event risk of WCH has been found to be greater than that in normotension. Years ago, this was reported for cerebrovascular events in a meta-analysis based on >200 strokes,[26] the risk of which became greater in WCH than in normotensive subjects after several years of follow-up, suggesting that a selective office BP elevation may adversely affect cerebral vascular integrity over the long term. It has been further documented in the large meta-analyses recently published by Briasoulis et al[27] and Huang et al.[28] In the meta-analysis of Briasoulis et al,[27] WC hypertensives showed, during an average follow-up of 8 years, a significant increase in the risk of cardiovascular events (hazard ratio, 1.73; 95% confidence intervals, 1.27–2.36; 722 events) and cardiovascular mortality (hazard ratio, 2.79; 95% confidence intervals, 1.62–4.80; 153 events) compared with normotensive controls. A significant, albeit smaller, risk increase has also been found in the similarly large meta-analysis of Huang et al,[19] which has shown the risk of cardiovascular events (follow-up 9.6 years) to be 38% and 19% greater in WC hypertensives

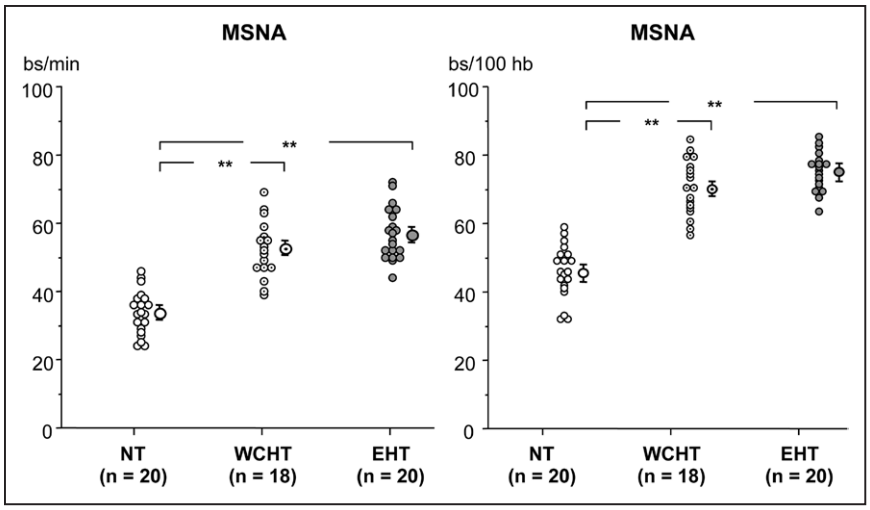

Figure 3. Individual and mean muscle sympathetic nerve activity (MSNA) values in normotensives (NT), white-coat hypertensives (WCH), and sustained essential hypertensives (EH). Data are shown as number of sympathetic bursts per min or per 100 beats. Adapted from Grassi et al[13] with permission of the publisher. Copyright © 2007, American Heart Association, Inc. 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.

than in normotensives ($P<0.0006$ and 0.04) when assessed in untreated or mixed (treated and untreated) cohorts, respectively. In this meta-analysis, the greater risk of WC hypertensives over the normotensive population included a 20% increase of all-cause mortality as well ($P<0.02$; Figure 5).

Muntner et al[29] have criticized the meta-analysis of Briasoulis et al[27] because, at variance from other meta-analyses, the results were not adjusted for demographic and clinical covariates that may contribute to the overall risk. We agree that adjustment for demographic covariates is necessary because WCH tends to be more common as age advances[30] with an obvious impact on the WCH risk, which was thus presumably overestimated in the meta-analysis of Briasoulis et al.[27] We do not share the view, however, that adjustment should be necessarily extended to concomitant risk factors and indeed think that presenting the main results after adjustment for concomitant metabolic risk factors may be somewhat misleading. This is the case because neutralizing the contribution to the risk of concomitant metabolic and other risk factors prevents a correct appreciation of the clinical significance of WCH in its natural multifactorial phenotype, favoring the erroneous conclusion that it does not prognostically differ from normotension, as it has happened in some guidelines.[31] We also do not agree that in WCH adjustments for concomitant cardiovascular risk factors is needed to decide about the use of antihypertensive treatment[29] because the adjustment procedure represents an attempt to approximately ascribe the overall risk to individual variables, with no possibility to determine risk reversibility by treatment.

Heterogeneity of Cardiovascular Risk in WCH

Pooling data from several cohorts, the International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome group has provided evidence of an increased cardiovascular risk in patients in whom WCH was limited to a systolic BP elevation[32] and in elderly WCH individuals at high cardiovascular risk.[33] On the contrary, no cardiovascular risk increase was seen in younger WCH patients[33] and, somewhat inconsistently, in WC patients with diabetes mellitus,[34,35] generating the hypothesis that this condition may have a different prognostic significance in different demographic and clinical circumstances.[36] An alternative explanation, however, is that documenting the adverse clinical significance of WCH is easier when the risk of the population at study is greater. This is supported by the results of the large meta-analysis by Huang et al,[28] which has shown WCH to be accompanied by an increased risk of cardiovascular events in various subgroups, including those above or below 55 years of age and with or without a history of cardiovascular disease. It, thus, seems likely that patients with an increase of office but not of out-of-office BP are exposed to a greater outcome risk regardless their demographic and clinical characteristics.

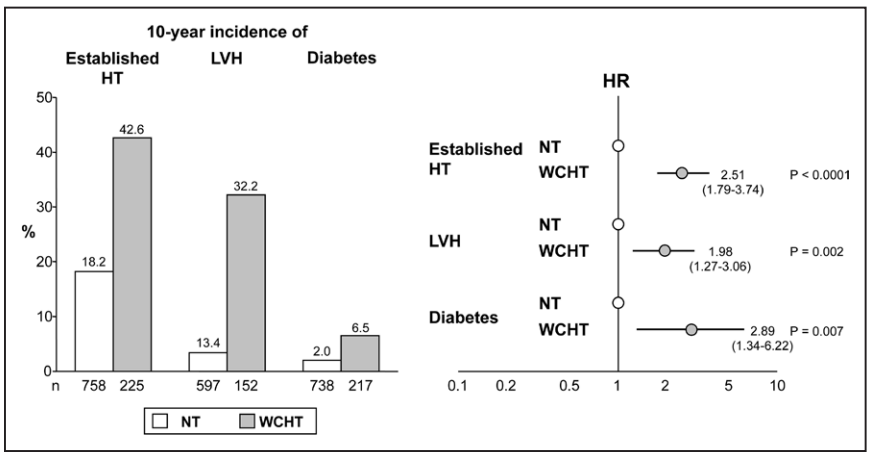

Figure 4. Ten-year incidence and adjusted risk of developing sustained hypertension (HT), diabetes mellitus, and echocardiographic left ventricular hypertrophy (LVH) in white-coat hypertensive (WCHT) and normotensive (NT) subjects of the PAMELA population. For each condition, data were adjusted for relevant confounders. Reprinted from Zanchetti and Mancia[21] with permission of the publisher. Copyright © 2012, Wolters Kluwer Health, Inc.

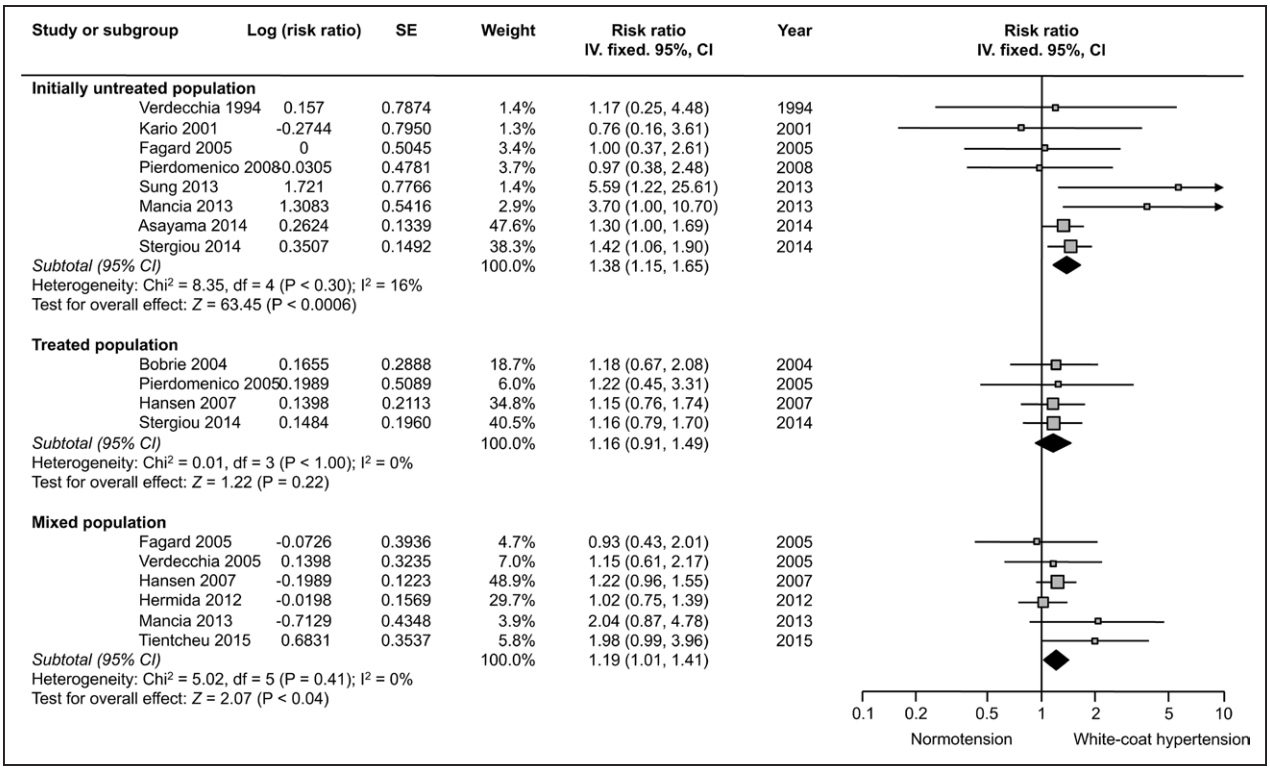

Figure 5. Risk of cardiovascular outcomes in white-coat hypertension vs normotension. Data are separately shown as meta-analyses from cohorts of subjects under no antihypertensive treatment (8656 subjects), cohorts under antihypertensive treatment, and mixed (untreated and treated) cohorts. CI indicates confidence intervals. Reprinted from Huang et al[28] with permission of the publisher. Copyright © 2017, Wolters Kluwer Health, Inc.

Treated patients with an uncontrolled office but a normal ambulatory or home BP represent a special case because either individual studies[32] or data provided by large meta-analyses[28] have reported their cardiovascular risk not to differ significantly from that of the treated population in which both office and out-of-office BP achieved control. The significance of these results is unclear, however. First, in absence of any information on their original BP and cardiovascular risk pattern, the category to which patients in whom control is limited to out-of-office BP cannot be determined. Furthermore, given the persisting uncertainty of the optimal office BP target in different clinical conditions,[37] the possibility exists that what is regarded as an uncontrolled office BP actually represents the optimal (or maximally protective) value for this group. Finally, it should be emphasized that studies on WCH have a limitation that is particularly relevant for treated individuals. Namely, they are usually based on a single temporal out-of-office and office BP assessment, which can hardly provide a precise estimate of the prevailing BP value over prolonged (years!) treatment periods usually characterized by multiple treatment changes and a low and variable adherence to the prescribed treatment regimens.[38,39]

Unmet Needs

Factors Responsible for Increased Risk of WCH

In the earliest meta-analyses, adjusting the data for metabolic variables led to an attenuation or a disappearance of the extrarisk

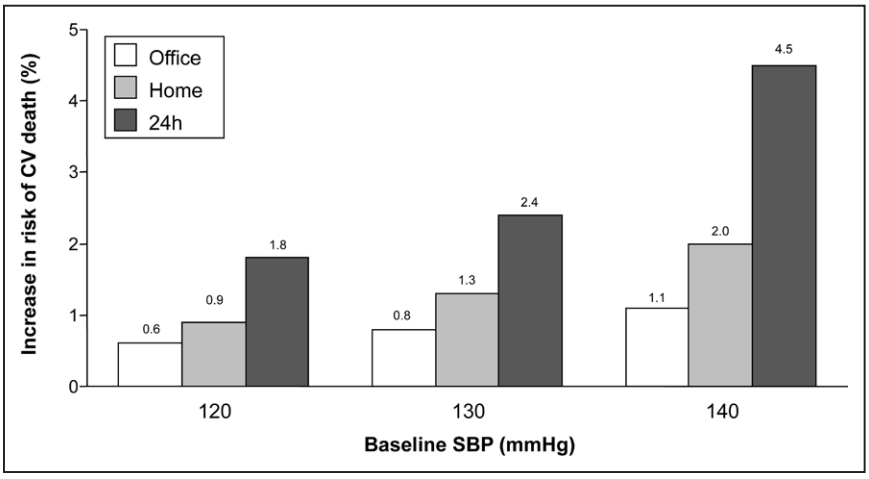

Figure 6. Eleven-year increase in risk of cardiovascular mortality for 10 mm Hg increase in office, home, 24-h mean systolic blood pressure (SBP) and different baseline SBP values. Reprinted from Sega et al[42] with permission of the publisher. Copyright © 2005, American Heart Association, Inc.

exhibited by WC hypertensives.[23–26] As shown by the more recent large meta-analysis of Huang et al,[28] however, even after extensive covariate adjustment, the risk of WCH individuals remained higher than that of normotensive controls, suggesting that their BP pattern is also involved. The question remains whether this BP contribution is because of the office BP elevation, the ambulatory and home BP values, or both. In this context, it is important to mention that, although confined by definition to the normal range, in WCH, both ambulatory and home BP values are few mm Hg higher than in the control normotensive population.[4,28] Because both pressures have a clear-cut relationship with cardiovascular events[40–45] even when their value is in the normal range[42] (Figure 6), this speaks in favors of their involvement.[46] A contribution of office BP should by no means be excluded, however. In the WCH patients of the PAMELA study, for example, office rather than out-of-office BP showed the ability to predict progression to sustained hypertension or diabetes mellitus.[19,20,22] Furthermore, for a similar 24-hour BP value, the cardiovascular risk of WCH subjects was greater when office BP was higher.[47]

Cardiovascular Risk Discrimination in the WCH Population

An important practical issue is to distinguish, within the overall WCH category, patients in whom the cardiovascular risk is higher to decide about the closeness of the follow-up, the intensity of the lifestyle interventions, and perhaps also the need of cautionary drug treatment. A careful history, a thorough assessment of metabolic risk factors, and a precise identification of structural and functional organ alterations can obviously be of help together, however, with 2 other diagnostic approaches. One is to measure either ambulatory and home BP because evidence has been obtained that cardiovascular risk is less in WCH subjects in whom both these pressures are within the normal range,[48] an observation that incidentally suggests that these 2 out-of-office BP may have a complementary prognostic value.[4] The other is to measure office BP at different visits because subjects with a persistent office BP elevation have been found to be at greater risk than those in whom the elevation has been inconsistent from one visit to another.[47] Future studies will have to also investigate the possibility for the WCH-related risk to have a genetic background. This has been suggested in an early investigation by Julius et al[49] who found patients with WCH (high office and normal home BP) to have parents with office BP elevations as well.

Antihypertensive Treatment

Unfortunately, no evidence is available on whether the risk of WCH is reduced by antihypertensive drugs, possibly with a return to the risk level of the normotensive population. To date, data can count on a 4-year follow-up of the patients recruited for the European Lacidipine Study on Atherosclerosis, which has shown antihypertensive drugs to (1) persistently lower office BP almost as much in WCH (high office and normal ambulatory BP) and sustained hypertensive patients[18] and (2) have a strikingly different effect on ambulatory BP, which was effectively reduced in sustained but unchanged or slightly increased in WC hypertensives. They can also count on the follow-up of patients with WC systolic hypertension recruited for the SYSTEUR trial (Systolic Hypertension in Europe) in which drug treatment did not reduce cardiovascular outcomes more than placebo.[50] Unfortunately, in this study, the number of events was so small as to make the results inconclusive and leave the question whether BP should be lowered in WCH unanswered. It should be mentioned, however, that based on epidemiological data,[2] in the large number of randomized trials that have documented the protective effect of antihypertensive treatment,[51] the prevalence of WCH was far from marginal. This might have been particularly the case in the trials that have shown BP reduction to lower cardiovascular outcomes in grade 1, low-to-moderate risk hypertensives,[52–54] ≤40% of whom may have a WCH condition.[2] It was definitively the case in patients (aged ≥80 years) with an office BP elevation recruited for the HYVET (Hypertension in the Very Elderly Trial),[55] in whom treatment was accompanied by a marked reduction of cardiovascular events, despite a documented (55%) high prevalence of WCH.[56] Thus, it can be argued that, until evidence for the contrary is obtained, WCH patients share the benefit of treatment of the overall hypertensive population and should not be denied a BP-lowering intervention. A randomized properly powered outcome-based trial will be necessary to give this important question a conclusive answer.

Understanding the Nature of WCH

A better understanding of the factors involved in the difference between office and out-of-office BP will also be desirable and perhaps helpful in designing the proper trials to perform. To date, this difference is ascribed to the alerting response to the environmental conditions where office BP is taken, but several arguments suggest that this may not be the only factor involved.[44] One, the alerting response to office BP measurements is accompanied by a marked tachycardia,[57] which is hardly compatible with the regularly reported similarity of office and daytime heart rates.[30] Two, the difference between office and out-of-office BP increases markedly with patient's age, which should imply a hyperreaction of elderly patients to office BP measurements or, more in general, stress. This has not been found in studies that have addressed the patients' BP response to laboratory-elicited emotional stimuli. Furthermore, in patients under intra-arterial ambulatory BP monitoring, the BP increase seen during a physician's visit (ie, the directly quantified WC effect) has shown no relationship with patients' age.[58] Three, the difference between office and out-of-office BP is directly related to office, but it exhibits a steep inverse relationship with out-of-office values, thereby being under the influence of emotional factors but also of factors that govern daily life BP and have little or no relationship with the emotional response to the physician's visit.[59] Indeed, years ago, we showed the office daytime BP difference to bear no significant relationship with the WC effect as directly quantified by beat-to-beat BP monitoring before, during, and after the physician's visit,[60] suggesting that the alerting component of this effect may not even be the most important one. This may perhaps be especially the case in elderly patients in whom an impairment of the mechanisms involved in BP homeostasis might lead to frequent daytime hypotensive episodes, lowering the mean ambulatory value. According to these arguments, the term WCH may be not entirely correct, favoring its replacement with a more neutral descriptive term such as isolated office hypertension. However, history provides multiple examples that trying to change popular names is an exercise in futility. Use of the term WCH for defining the condition of selective office BP elevation should not imply, however, that its mechanistic nature has been clarified, and no further studies in this direction are needed.

Disclosures

None.

References

1. Pickering TG, Harshfield GA, Devereux RB, Laragh JH. What is the role of ambulatory blood pressure monitoring in the management of hypertensive patients? *Hypertension*. 1985;7:171–177.
2. Mancia G, Fagard R, Narkiewicz K, et al; Task Force Members. 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). *J Hypertens*. 2013;31:1281–1357. doi: 10.1097/01.hjh.0000431740.32696.cc.
3. Weber MA, Neutel JM, Smith DH, Graettinger WF. Diagnosis of mild hypertension by ambulatory blood pressure monitoring. *Circulation*. 1994;90:2291–2298.
4. 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. doi: 10.1161/01.HYP.0000215363.69793.bb.
5. Borghi C, Rosei EA, Bardin T, Dawson J, Dominiczak A, Kielstein JT, Manolis AJ, Perez-Ruiz F, Mancia G. Serum uric acid and the risk of cardiovascular and renal disease. *J Hypertens*. 2015;33:1729–1741. doi: 10.1097/HJH.0000000000000701.
6. Pickering TG, Coats A, Mallion JM, Mancia G, Verdecchia P. Blood pressure monitoring. Task force V: white-coat hypertension. *Blood Press Monit*. 1999;4:333–341.
7. Kotsis V, Stabouli S, Toumanidis S, Papamichael C, Lekakis J, Germanidis G, Hatzitolios A, Rizos Z, Sion M, Zakopoulos N. Target organ damage in "white coat hypertension" and "masked hypertension". *Am J Hypertens*. 2008;21:393–399. doi: 10.1038/ajh.2008.15.
8. Høegholm A, Bang LE, Kristensen KS, Nielsen JW, Holm J. Microalbuminuria in 411 untreated individuals with established hypertension, white coat hypertension, and normotension. *Hypertension*. 1994;24:101–105.
9. 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.
10. Sega R, Trocino G, Lanzarotti A, Carugo S, Cesana G, Schiavina R, Valagussa F, Bombelli M, Giannattasio C, Zanchetti A, Mancia G. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). *Circulation*. 2001;104:1385–1392.
11. Cuspidi C, Rescaldani M, Tadic M, Sala C, Grassi G, Mancia G. White-coat hypertension, as defined by ambulatory blood pressure monitoring, and subclinical cardiac organ damage: a meta-analysis. *J Hypertens*. 2015;33:24–32. doi: 10.1097/HJH.0000000000000416.
12. Cuspidi C, Sala C, Tadic M, Rescaldani M, Grassi G, Mancia G. Is white-coat hypertension a risk factor for carotid atherosclerosis? A review and meta-analysis. *Blood Press Monit*. 2015;20:57–63. doi: 10.1097/MBP.0000000000000094.
13. Grassi G, Seravalle G, Trevano FQ, Dell'oro R, Bolla G, Cuspidi C, Arenare F, Mancia G. Neurogenic abnormalities in masked hypertension. *Hypertension*. 2007;50:537–542. doi: 10.1161/HYPERTENSIONAHA.107.092528.
14. Mancia G, Grassi G. The autonomic nervous system and hypertension. *Circ Res*. 2014;114:1804–1814. doi: 10.1161/CIRCRESAHA.114.302524.
15. Schlaich MP, Kaye DM, Lambert E, Sommerville M, Socratous F, Esler MD. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. *Circulation*. 2003;108:560–565. doi: 10.1161/01.CIR.0000081775.72651.B6.
16. Bevan RD. Trophic effects of peripheral adrenergic nerves on vascular structure. *Hypertension*. 1984;6(6 pt 2):III19–III26.
17. Mancia G. Short- and long-term blood pressure variability: present and future. *Hypertension*. 2012;60:512–517. doi: 10.1161/HYPERTENSIONAHA.112.194340.
18. Mancia G, Facchetti R, Parati G, Zanchetti A. Effect of long-term antihypertensive treatment on white-coat hypertension. *Hypertension*. 2014;64:1388–1398. doi: 10.1161/HYPERTENSIONAHA.114.04278.
19. 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. doi: 10.1161/HYPERTENSIONAHA.109.129882.
20. 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. doi: 10.1097/HJH.0b013e32832be5f9.
21. Zanchetti A, Mancia G. Longing for clinical excellence: a critical outlook into the NICE recommendations on hypertension management–is nice always good? *J Hypertens*. 2012;30:660–668. doi: 10.1097/HJH.0b013e328351b4e4.
22. 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. doi: 10.1001/archinte.165.13.1541.
23. Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. *J Hypertens*. 2007;25:2193–2198. doi: 10.1097/HJH.0b013e3282ef6185.
24. Pierdomenico SD, Lapenna D, Di Mascio R, Cuccurullo F. Short- and long-term risk of cardiovascular events in white-coat hypertension. *J Hum Hypertens*. 2008;22:408–414. doi: 10.1038/jhh.2008.6.
25. 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. doi: 10.1038/ajh.2010.203.
26. 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. doi: 10.1161/01.HYP.0000151623.49780.89.
27. Briasoulis A, Androulakis E, Palla M, Papageorgiou N, Tousoulis D. White-coat hypertension and cardiovascular events: a meta-analysis. *J Hypertens*. 2016;34:593–599. doi: 10.1097/HJH.0000000000000832.
28. Huang Y, Huang W, Mai W, Cai X, An D, Liu Z, Huang H, Zeng J, Hu Y, Xu D. White-coat hypertension is a risk factor for cardiovascular diseases and total mortality. *J Hypertens*. 2017;35:677–688. doi: 10.1097/HJH.0000000000001226.
29. Muntner P, Booth JN 3rd, Shimbo D, Schwartz JE. Is white-coat hypertension associated with increased cardiovascular and mortality risk? *J Hypertens*. 2016;34:1655–1658. doi: 10.1097/HJH.0000000000000983.
30. Sega R, Cesana G, Milesi C, Grassi G, Zanchetti A, Mancia G. Ambulatory and home blood pressure normality in the elderly: data from the PAMELA population. *Hypertension*. 1997;30(1 pt 1):1–6.
31. National Institute for Health and Care Excellence (NICE). Hypertension in Adults: Diagnosis and Management. Clinical Guideline 127. Published date: August 2011. Last updated: November 2016. https://www.nice.org.uk/guidance/cg127.
32. 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. doi: 10.1161/HYPERTENSIONAHA.111.180653.
33. Franklin SS, Thijs L, Asayama K, et al; IDACO Investigators. The cardiovascular risk of white-coat hypertension. *J Am Coll Cardiol*. 2016;68:2033–2043. doi: 10.1016/j.jacc.2016.08.035.
34. Ben-Dov IZ, Kark JD, Mekler J, Shaked E, Bursztyn M. The white coat phenomenon is benign in referred treated patients: a 14-year ambulatory blood pressure mortality study. *J Hypertens*. 2008;26:699–705. doi: 10.1097/HJH.0b013e3282f4b3bf.
35. Eguchi K, Hoshide S, Ishikawa J, Ishikawa S, Pickering TG, Gerin W, Ogedegbe G, Schwartz JE, Shimada K, Kario K. Cardiovascular prognosis of sustained and white-coat hypertension in patients with type 2 diabetes mellitus. *Blood Press Monit*. 2008;13:15–20. doi: 10.1097/MBP.0b013e3282f13f4a.
36. Mancia G, Grassi G. The heterogeneous nature of white-coat hypertension. *J Am Coll Cardiol*. 2016;68:2044–2046. doi: 10.1016/j.jacc.2016.08.043.
37. Mancia G, Grassi G Aggressive blood pressure lowering is dangerous. The J-curve. Pro-side of the argument. *Hypertension* 2013,63:29–36.
38. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, Stricker B, Mendis S, Hofman A, Mant J, Franco OH. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J*. 2013;34:2940–2948. doi: 10.1093/eurheartj/eht295.
39. Corrao G, Zambon A, Parodi A, Poluzzi E, Baldi I, Merlino L, Cesana G, Mancia G. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. *J Hypertens*. 2008;26:819–824. doi: 10.1097/HJH.0b013e3282f4edd7.
40. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional vs ambulatory

blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA*. 1999;282:539–546.
41. Dolan E, Stanton AV, Thom S, Caulfield M, Atkins N, McInnes G, Collier D, Dicker P, O'Brien E; ASCOT Investigators. Ambulatory blood pressure monitoring predicts cardiovascular events in treated hypertensive patients–an Anglo-Scandinavian cardiac outcomes trial substudy. *J Hypertens*. 2009;27:876–885. doi: 10.1097/HJH.0b013e328322cd62.
42. Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation*. 2005;111:1777–1783. doi: 10.1161/01.CIR.0000160923.04524.5B.
43. Mancia G, Verdecchia P. Clinical value of ambulatory blood pressure: evidence and limits. *Circ Res*. 2015;116:1034–1045. doi: 10.1161/CIRCRESAHA.116.303755.
44. Boggia J, Li Y, Thijs L, et al; International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) investigators. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *Lancet*. 2007;370:1219–1229. doi: 10.1016/S0140-6736(07)61538-4.
45. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Predictors of all-cause mortality in clinical ambulatory monitoring: unique aspects of blood pressure during sleep. *Hypertension*. 2007;49:1235–1241. doi: 10.1161/HYPERTENSIONAHA.107.087262.
46. Myers MG. Statistical analysis as a cause of white-coat hypertension. *J Hypertens*. 2017;35:707–709. doi: 10.1097/HJH.0000000000001232.
47. Mancia G, Facchetti R, Grassi G, Bombelli M. Adverse prognostic value of persistent office blood pressure elevation in white coat hypertension. *Hypertension*. 2015;66:437–444. doi: 10.1161/HYPERTENSIONAHA.115.05367.
48. Mancia G, Bombelli M, Brambilla G, Facchetti R, Sega R, Toso E, Grassi G. Long-term prognostic value of white coat hypertension: an insight from diagnostic use of both ambulatory and home blood pressure measurements. *Hypertension*. 2013;62:168–174. doi: 10.1161/HYPERTENSIONAHA.111.00690.
49. Julius S, Mejia A, Jones K, Krause L, Schork N, van de Ven C, Johnson E, Petrin J, Sekkarie MA, Kjeldsen SE. "White coat" versus "sustained" borderline hypertension in Tecumseh, Michigan. *Hypertension*. 1990;16:617–623.
50. 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.
51. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957–967. doi: 10.1016/S0140-6736(15)01225-8.
52. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels–overview and meta-analyses of randomized trials. *J Hypertens*. 2014;32:2296–2304. doi: 10.1097/HJH.0000000000000379.
53. Five-year findings of the hypertension detection and follow-up program. III. Reduction in stroke incidence among persons with high blood pressure. Hypertension Detection and Follow-up Program Cooperative Group. *JAMA*. 1982;247:633–638.
54. MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. *Br Med J (Clin Res Ed)*. 1985;291:97–104.
55. Beckett NS, Peters R, Fletcher AE, et al; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358:1887–1898. doi: 10.1056/NEJMoa0801369.
56. Bulpitt CJ, Beckett N, Peters R, Staessen JA, Wang JG, Comsa M, Fagard RH, Dumitrascu D, Gergova V, Antikainen RL, Cheek E, Rajkumar C. Does white coat hypertension require treatment over age 80?: Results of the hypertension in the very elderly trial ambulatory blood pressure side project. *Hypertension*. 2013;61:89–94. doi: 10.1161/HYPERTENSIONAHA.112.191791.
57. Mancia G, Zanchetti A. White-coat hypertension: misnomers, misconceptions and misunderstandings. What should we do next? *J Hypertens*. 1996;14:1049–1052.
58. 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.
59. Parati G, Omboni S, Staessen J, Thijs L, Fagard R, Ulian L, Mancia G. Limitations of the difference between clinic and daytime blood pressure as a surrogate measure of the 'white-coat' effect. Syst-Eur investigators. *J Hypertens*. 1998;16:23–29.
60. Parati G, Ulian L, Santucciu C, Omboni S, Mancia G. Difference between clinic and daytime blood pressure is not a measure of the white coat effect. *Hypertension*. 1998;31:1185–1189.

Response to Increased Cardiovascular Risk of White-Coat Hypertension: Pro Side of the Argument

Kei Asayama, Yan Li, Stanley S. Franklin, Lutgarde Thijs, Eoin O'Brien, Jan A. Staessen

Mancia et al have put forward a good case, but in our opinion, it falters on the basis of definition and measurement. At the end of their argument, the reader is confronted with varying flavors of a condition loosely characterized by an elevated in-office and a normal out-of-the-office blood pressure without clear guidance as to how, and how often, both these blood pressures should be measured. White-coat hypertension has been presented as a constellation of metabolic dysregulation, cardiovascular risk factors, renal dysfunction, and subclinical cardiovascular disease, in which blood pressure becomes an epiphenomenon. Given this background, it should not come as a surprise that in some, albeit not all, studies reviewed by Mancia et al, white-coat hypertension was a forerunner of sustained hypertension with all its well-documented cardiovascular complications. In our review, we have emphasized the critical importance of age matching rather than age adjusting[1]—a point that Mancia et al totally ignored, thereby increasing the disparity of total cardiovascular risk in older white-coat hypertensive patients versus their younger normotensive comparators. We also underscored the importance of the presence of cardiovascular risk factors, the number of visits, and the number of blood pressure readings used to define the office blood pressure, the modality of out-of-the-office measurement, and concomitant drug treatment. In the absence of a precise definition that allows for these confounding factors, physicians do not know what they are really measuring, cannot understand what is being measured, and, even worse, cannot control such an inaccurate phenomenon. A precise definition, such as we propose, by removing the noise from the data in Mancia's review, renders the case for a damaging outcome from white-coat hypertension as being weak indeed. A precise definition of white-coat hypertension is also a sine qua non to reaching a consensus on how this condition should be managed, which should be more dependent on lifestyle modification and risk factor control than the pharmacologically lowering of blood pressure.

Reference

1. Franklin SS, Thijs L, Asayama K, et al; IDACO Investigators. The cardiovascular risk of white-coat hypertension. *J Am Coll Cardiol*. 2016;68:2033–2043. doi: 10.1016/j.jacc.2016.08.035.