Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association®
Learn and Live℠

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

Stanley S. Franklin, Lutgarde Thijs, Tine W. Hansen, Yan Li, José Boggia, Masahiro Kikuya, Kristina Björklund-Bodegård, Takayoshi Ohkubo, Jørgen Jeppesen, Christian Torp-Pedersen, Eamon Dolan, Tatiana Kuznetsova, Katarzyna Stolarz-Skrzypek, Valérie Tikhonoff, Sofia Malyutina, Edoardo Casiglia, Yuri Nikitin, Lars Lind, Edgardo Sandoya, Kalina Kawecka-Jaszcz, Yutaka Imai, Jiguang Wang, Hans Ibsen, Eoin O'Brien and Jan A. Staessen

Hypertension 2012, 59:564-571: originally published online January 17, 2012
doi: 10.1161/HYPERTENSIONAHA.111.180653
Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0194-911X. Online ISSN: 1524-4563

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

Stanley S. Franklin, Lutgarde Thijs, Tine W. Hansen, Yan Li, José Boggia, Masahiro Kikuya, Kristina Björklund-Bodegård, Takayoshi Ohkubo, Jørgen Jeppesen, Christian Torp-Pedersen, Eamon Dolan, Tatiana Kuznetsova, Katarzyna Stolarz-Skrzypek, Valérie Tikhonoff, Sofia Malyutina, Edoardo Casiglia, Yuri Nikitin, Lars Lind, Edgardo Sandoya, Kalina Kawecka-Jaszcz, Yutaka Imai, Jiguang Wang, Hans Ibsen, Eoin O'Brien, Jan A. Staessen, on behalf of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators

See Editorial Commentary, pp 532–533

Abstract—The significance of white-coat hypertension in older persons with isolated systolic hypertension remains poorly understood. We analyzed subjects from the population-based 11-country International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes database who had daytime ambulatory blood pressure (BP; ABP) and conventional BP (CBP) measurements. After excluding persons with diastolic hypertension by CBP (≥90 mm Hg) or by daytime ABP (≥85 mm Hg), a history of cardiovascular disease, and persons <18 years of age, the present analysis totaled 7295 persons, of whom 1593 had isolated systolic hypertension. During a median follow-up of 10.6 years, there was a total of 655 fatal and nonfatal cardiovascular events. The analyses were stratified by treatment status. In untreated subjects, those with white-coat hypertension (CBP ≥140/<90 mm Hg and ABP <135/<85 mm Hg) and subjects with normal BP (CBP <140/<90 mm Hg and ABP <135/<85 mm Hg) were at similar risk (adjusted hazard rate: 1.17 [95% CI: 0.87–1.57]; $P=0.29$). Furthermore, in treated subjects with isolated systolic hypertension, the cardiovascular risk was similar in elevated conventional and normal daytime systolic BP as compared with those with normal conventional and normal daytime BPs (adjusted hazard rate: 1.10 [95% CI: 0.79–1.53]; $P=0.57$). However, both treated isolated systolic hypertension subjects with white-coat hypertension (adjusted hazard rate: 2.00; [95% CI: 1.43–2.79]; $P<0.0001$) and treated subjects with normal BP (adjusted hazard rate: 1.98 [95% CI: 1.49–2.62]; $P<0.0001$) were at higher risk as compared with untreated normotensive subjects. In conclusion, subjects with sustained hypertension who have their ABP normalized on antihypertensive therapy but with residual white-coat effect by CBP measurement have an entity that we have termed, "treated normalized hypertension." Therefore, one should be cautious in applying the term "white-coat hypertension" to persons receiving antihypertensive treatment. (***Hypertension*. 2012;59:564-571.)** ● **Online Data Supplement**

Key Words: isolated systolic hypertension ■ ambulatory blood pressure ■ white-coat hypertension ■ white-coat effect ■ cardiovascular disease ■ epidemiology

Received August 3, 2011; first decision August 22, 2011; revision accepted December 19, 2011.

From the Heart Disease Prevention Program (S.S.F.), Division of Cardiology, School of Medicine, University of California, Irvine, CA; Studies Coordinating Centre (L.T., T.K., J.A.S.), Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium; Department of Clinical Physiology (T.W.H.), Nuclear Medicine and PET, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; Research for Prevention and Health (T.W.H.), Copenhagen, Denmark; Center for Epidemiological Studies and Clinical Trials and Center for Vascular Evaluation (Y.L., J.W.), Ruijin Hospital, Shanghai Institute of Hypertenson, Shanghai Jiaotong University School of Medicine, Shanghai, China; Departamento de Fisiopatología and Centro de Nefrología (J.B.), Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay; Tohoku University Graduate School of Pharmaceutical Science and Medicine (M.K., T.O., Y.I.), Sendai, Japan; Section of Geriatrics (K.B.-B., L.L.), Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden; Copenhagen University Hospital (J.J., C.T.-P.), Copenhagen, Denmark; Cambridge University Hospitals (E.D.), Addenbrook's Hospital, Cambridge, United Kingdom; First Department of Cardiology and Hypertension (K.S.-S., K.K.-J.), Jagiellonian University Medical College, Kraków, Poland; Department of Clinical and Experimental Medicine (V.T., E.C.), University of Padova, Padova, Italy; Institute of Internal Medicine (S.M., Y.N.), Novosibirsk, Russian Federation; Asociación Española Primera de Socorros Mutuos (E.S.), Montevideo, Uruguay; Aarhus University and Division of Cardiology (H.I.), Holbak Hospital, Holbak, Denmark; Conway Institute of Biomolecular and Biomedical Research (E.O.), University College Dublin, Dublin, Ireland; Department of Epidemiology (J.A.S.), Maastricht University, Maastricht, The Netherlands.

This paper was sent to Ernesto L. Schiffrin, associate editor, for review by expert referees, editorial decision, and final disposition.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.111.180653/-/DC1.

Correspondence to Jan A. Staessen, Studies Coordinating Centre, Laboratory of Hypertension, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35 Block D Level 00, B-3000 Leuven, Belgium. E-mail jan.staessen@med.kuleuven.be

Isolated systolic hypertension (ISH) in older subjects has been associated with a high prevalence of white-coat hypertension as diagnosed by ambulatory blood pressure (BP) monitoring.[1–4] Pickering et al[5] first used the term "white-coat hypertension" in a 1988 publication in subjects who were not receiving antihypertensive treatment. However, more recently in the "real world" of population studies, many individuals with white-coat hypertension, defined as having elevated office BP and normal ambulatory BP, have received antihypertensive treatment because their physicians, rightly or wrongly, felt it was indicated; importantly, this treatment does not have any significant effect on lowering ambulatory BP levels[6] or on morbid events[7] in subjects with bona fide white-coat hypertension.

Despite many previous investigations, controversy persists as to the presence and extent of increased cardiovascular risk in ISH patients with white-coat hypertension as compared with a normotensive population[8–11]; however, few studies addressing this question have been population based, randomly recruited, and with an untreated, normotensive control population that does not contain persons with documented masked hypertension.[2,11,12] Furthermore, many of these older studies had insufficient numbers of persons with ISH, short follow-up periods, and, therefore, a relative low incidence of cardiovascular events and, hence, limited statistical power.

In contrast, the current International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes (IDACO) Study includes a large number of subjects residing in the community from 11 countries with standardized protocols for conventional and ambulatory BP monitoring, a majority free of antihypertensive drug treatment, and a median follow-up of 10.6 years for cardiovascular events.[13,14] The present study assessed the cardiovascular risk in persons with ISH, free of cardiovascular disease at baseline, and stratified by the presence or absence of antihypertensive treatment. We compared incident cardiovascular events by cross-classification of subjects with ISH, using conventional BP (CBP) and daytime ambulatory BP (ABP) measurements. We specifically asked 2 questions. First, is white-coat hypertension associated with increased cardiovascular risk in ISH patients when accounting for antihypertensive drug therapy? Second, what is the incident cardiovascular risk in masked and sustained hypertensives versus normotensives, while stratifying for antihypertensive drug therapy?

Methods

Study Population

Our database was constructed from the 11-country IDACO study groups[15–23] that consisted of random population samples and required available data on conventional and ambulatory BP.[13,14] On July 10, 2010, the IDACO database included 11 785 subjects. We excluded a total of 4490 subjects. The reasons for exclusions were as follows: (1) lack of conventional BP measurements (n=220); (2) <10 daytime ambulatory BP readings (n=164); (3) subjects <18 years at enrollment (n=249); (4) diastolic hypertension (conventional DBP ≥90 mm Hg or daytime DBP ≥85 mm Hg; n=3311); (5) a history of cardiovascular disease (n=545); and (6) unknown treatment status (n=1). Thus, the number of subjects included in the present analysis totaled 7295.

Definition of BP Categories

The conventional BP was the average of 2 consecutive readings obtained either at the subjects' homes[17–19,22,23] or at an examination center.[15,16,20,21] In line with the current guidelines for the diagnosis and management of hypertension,[1,24] we defined conventional ISH as systolic BP (SBP) ≥140 mm Hg with a DBP <90 mm Hg. The thresholds for daytime ambulatory ISH were ≥135 for SBP and <85 mm Hg for DBP.

"Untreated normotension" was defined as a consistently normal BP on both CBP and daytime ABP measurements in subjects not receiving antihypertensive treatment (CBP <140/<90 mm Hg and daytime ABP <135/<85 mm Hg). "Untreated white-coat hypertension" was defined as a raised CBP in the presence of a normal daytime ABP (≥140/<90 and <135/<85 mm Hg). "Untreated masked hypertension" was defined as normal CBP in the presence of raised daytime ABP (<140/<90 and ≥135/<85 mm Hg). "Untreated sustained hypertension" was defined as both elevated CBP and daytime ABP (≥140/<90 and ≥135/<85 mm Hg).

Patients on antihypertensive drug treatment were classified according to their treated BP. "Treated normotension" was defined as having normal values of both CBP and daytime ABP (<140/<90 and <135/<85 mm Hg). Similarly, "treated white-coat," "masked," and "sustained hypertension in subjects with ISH" were defined as both having the same CBP and daytime ABP cutoff points as in untreated subjects. In addition, for subjects with sustained hypertension who had their ABP normalized on antihypertensive therapy but with white-coat effect by CBP measurement (≥140/<90 and <135/<85 mm Hg, subgroup of treated white-coat hypertensives), we introduced an alternative term, "treated normalized hypertension."

Cardiovascular Events

The restricted composite cardiovascular end point included fatal cardiovascular events, myocardial infarction, surgical and percutaneous coronary revascularization, heart failure, and stroke. The broad composite cardiovascular end point included transient ischemic attack, angina, peripheral arterial disease, and all of the events included in the restricted cardiovascular end point. Unless indicated otherwise, results are presented for the broad definition of cardiovascular events.

Statistical Methods

For database management and statistical analysis, we used SAS software, version 9.1.3 (SAS Institute, Cary, NC). All of the analyses were stratified by antihypertensive drug intake. We first compared the incidence of cardiovascular events according to the cross-classification of subjects by conventional and daytime ABP measurement, using Cox models including 3 design variables for the 4 BP categories and standardized to the sex distribution and mean age in the whole study population. Next, we calculated the hazard ratios associated with white-coat, masked, and sustained hypertension versus normotension using Cox proportional hazard models stratified for center and adjusted for age, sex, body mass index, serum cholesterol, current smoking status, and diabetes mellitus. We ascertained that the proportional hazard assumption underlying the Cox regression models was fulfilled by the Kolmogorov-type supremum test and by testing the interaction with follow-up time. We presented hazard ratios as floating absolute risks and calculated their SEs as described by Easton et al.[25] For further details on methods, see the Expanded Methods section in the online-only Data Supplement.

Results

Baseline Characteristics

The 7295 subjects included 3305 men (45.3%). Mean±SD age was 48.8±16.6 years. Table 1 shows the characteristics of the participants divided into 4 study groups by cross-classification of the conventional and daytime ambulatory BP and stratified by antihypertensive treatment status. Of the

Table 1. Baseline Characteristics in Normotensive Subjects and in ISH Subjects With White-Coat, Masked, and Sustained Hypertension Broken Down by Treatment Status

	Untreated				Treated			
Characteristics	Sustained HT (n=314)	White-Coat HT (n=334)	Masked HT (n=520)	Normotension (n=5271)	Sustained HT (n=181)	White-Coat HT (n=162)	Masked HT (n=82)	Normotension (n=431)
No. with characteristic (%)								
Male	216 (68.8)	203 (60.8)	338 (65.0)	2223 (42.2)	82 (45.3)	58 (35.8)	41 (50.0)	144 (33.4)
Diabetes mellitus	23 (7.3)	25 (7.5)	36 (6.9)	170 (3.2)	26 (14.4)	26 (16.0)	16 (19.5)	48 (11.1)
Current smokers	77 (24.7)	69 (21.0)	197 (38.0)	1593 (30.3)	35 (19.4)	26 (16.3)	17 (21.3)	83 (19.3)
Current drinkers	181 (68.0)	131 (45.0)	316 (64.4)	2281 (44.4)	70 (45.5)	43 (32.8)	35 (46.1)	130 (32.8)
Mean±SD								
Age, y	66.9±10.6	61.6±13.6	53.1±15.9	44.1±15.0	69.2±7.8	67.3±8.6	64.9±11.0	59.9±12.8
Body mass index, kg/m^2	26.5±4.0	25.4±4.0	25.8±4.0	24.3±3.8	26.5±4.4	27.0±4.9	26.5±4.9	26.4±4.9
Serum cholesterol, mmol/L	6.0±1.1	5.8±1.2	5.8±1.2	5.4±1.1	5.8±1.1	5.8±1.1	5.7±1.1	5.5±1.1
Systolic blood pressure								
Conventional, mm Hg	152.1±10.8	148.4±9.4	125.8±9.5	116.2±11.2	156.6±13.8	152.0±10.1	128.3±7.3	123.6±10.0
24-h, mm Hg	137.0±9.9	122.0±6.7	131.0±6.2	114.1±7.7	139.4±9.3	122.0±8.0	135.1±7.8	118.2±8.2
Daytime, mm Hg	144.8±8.6	126.2±6.5	140.5±5.1	119.5±8.3	146.1±7.6	125.4±7.2	142.4±6.4	121.7±8.1
Nighttime, mm Hg	122.6±15.0	112.4±11.4	116.2±10.8	104.0±9.3	126.8±15.4	113.3±12.7	121.0±12.4	109.1±11.8
Night:day ratio	0.8±0.1	0.9±0.1	0.8±0.1	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1
Diastolic blood pressure								
Conventional, mm Hg	80.8±6.4	80.5±6.9	76.3±7.4	72.8±7.9	79.8±7.9	80.2±7.0	74.7±8.4	74.8±8.4
24-h, mm Hg	73.4±4.8	70.7±5.2	73.8±4.3	69.0±5.3	74.0±5.4	69.8±5.3	75.0±5.0	69.9±6.1
Daytime, mm Hg	78.0±4.9	74.3±5.7	79.3±4.5	73.8±5.8	78.1±5.2	73.3±5.9	79.1±4.7	73.6±6.4
Nighttime, mm Hg	64.9±6.9	63.4±7.4	64.1±6.6	60.2±6.6	65.4±8.0	62.6±7.7	66.4±7.4	62.3±7.8
Night:day ratio	0.8±0.1	0.9±0.1	0.8±0.1	0.8±0.1	0.8±0.1	0.9±0.1	0.8±0.1	0.9±0.1

ISH indicates isolated systolic hypertension; HT, hypertension.

1168 untreated subjects with ISH, 28.6% had white-coat hypertension, 44.5% had masked hypertension, and 26.9% had sustained hypertension. Of the 425 treated subjects with ISH, 38.1% had white-coat hypertension, 19.3% had masked hypertension, and 42.6% had sustained hypertension. Treated as compared with untreated subjects were, on average, 16.9 years older, had a 2.0-kg/m^2 higher body mass index, and included more subjects with diabetes mellitus (13.6% versus 3.9%; $P<0.001$ for all comparisons).

Incidence of Cardiovascular Events

The total number of cardiovascular events occurring during the 75 464 person-years of follow-up (median: 10.6 years; 5th to 95th percentile interval: 2.5–17.6 years) amounted to 484 according to the restricted definition and 655 according to the broad definition; the latter included 119 fatal events, 169 strokes, 75 transient ischemic attacks, 259 cardiac events, and 33 cases of peripheral artery disease.

Risk in White-Coat Hypertension Versus Normotension by Treatment Status

Figure 1 shows the incidence of cardiovascular events in normotensive subjects and in subjects with white-coat hypertension broken down by treatment status. Incidence was standardized to the sex distribution (45% men) and mean age (48.8 years) in the whole study population. In untreated subjects, the risk in white-coat hypertension was similar to that in normotension ($P=0.38$). Similarly, in treated subjects, white-coat hypertension did not carry an increased risk ($P=0.92$) as compared with persons whose BPs were normalized on treatment. However, both treated patients with white-coat hypertension and treated subjects with normal BP were at higher ($P<0.007$) cardiovascular risk as compared with the untreated normotensive reference group. Repeated analyses using the restricted definition of cardiovascular events (Figure S1, available in the online-only Data Supplement) or using 130/80 mm Hg as cutoff points for the definition of ambulatory normotension (Figure S2) gave similar results.

After stratification for cohort and adjustment for sex, age, body mass index, serum cholesterol, current smoking status, and diabetes mellitus, the risk in white-coat hypertension remained similar to that in normotension (Table 2). The hazard ratio in untreated subjects with white-coat hypertension versus untreated normotensives was 1.17 (95% CI: 0.87–1.57). Compared with treated subjects with normalized BP, the hazard ratio associated with treated white-coat hypertension was 1.09 (95% CI: 0.79–1.52). There was significantly greater ($P<0.0001$) cardiovascular risk in treated normotensives as compared with those who were untreated (hazard ratio: 1.98 [95% CI: 1.49–2.62]). The hazard rates comparing white-coat hypertensives with normotensives were independent of follow-up time (P of supremum test >0.25). Similar findings were obtained for cardio-

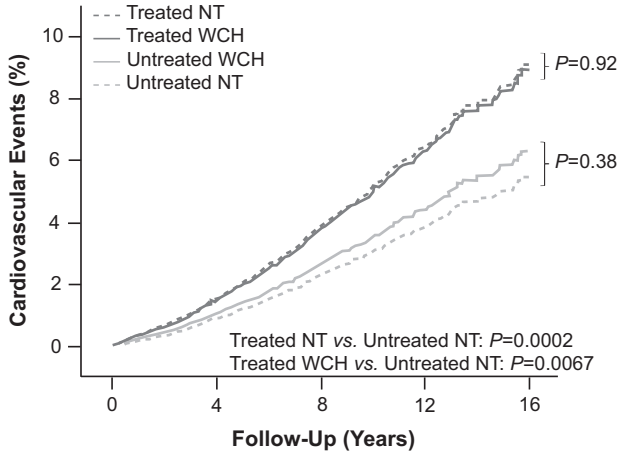


Figure 1. Incidence of cardiovascular events in untreated normotension (untreated NT), untreated isolated systolic hypertension (ISH) subjects with white-coat hypertension (untreated WCH), treated normotension (treated NT), and treated ISH subjects with white-coat hypertension (treated WCH). In untreated subjects with ISH, the risk in white-coat hypertensives was similar to that in normotensives ($P=0.38$). Similarly, in treated subjects with ISH, white-coat hypertension did not carry an increased risk ($P=0.92$) as compared with treated normotension. However, both treated ISH subjects with white-coat hypertension 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.

vascular mortality and for the restricted definition of cardiovascular events (Table S1).

Risk in Masked and Sustained Hypertension Versus Normotension by Treatment Status

Figure 2 shows the incidence of cardiovascular events according to the cross-classification of subjects by conventional and daytime ambulatory BP, stratified by antihypertensive treatment status and standardized to the sex distribution and mean age in the total study population. In the analysis including untreated subjects only (Figure 2, left), the incidence of cardiovascular events was significantly higher in sustained ($P=0.0005$) and masked ($P<0.0001$) hypertension as compared with normotension. Similarly, in treated subjects (Figure 2, right), cardiovascular risk was increased in sustained ($P<0.0001$) and masked hypertension ($P=0.0013$) as compared with treated normotension. In both treated and untreated subjects, cardiovascular risk was similar ($P>0.33$) in masked and sustained hypertension.

After stratification for center and adjustment for the aforementioned covariates, untreated masked and sustained hypertension as compared with untreated normotension were associated with a 67% (95% CI: 33% to 109%) and a 43% (95% CI: 14% to 79%) higher risk, respectively. In treated masked and sustained hypertension as compared with treated normotension, these percentages amounted 102% (95% CI: 40% to 190%) and 98% (95% CI: 55% to 153%), respectively.

Sensitivity Analyses

Table 3 shows the results of the sensitivity analyses for the comparison of the cardiovascular risk in subjects with ISH and white-coat hypertension versus normotension. The analyses were stratified by treatment and adjusted as before.

In subjects ≥60 years of age, the risk in untreated white-coat hypertension (n=226; age 69.4±5.0 years; daytime SBP 126.3±6.7 mm Hg) was similar ($P=0.61$) to that in untreated normotensives (n=971; 66.9±5.4 years; 122.3±7.8 mm Hg). Moreover, the risk in treated white-coat hypertension (n=127; 70.7±5.8 years; 125.9±6.7 mm Hg) was similar ($P=0.70$) to that in treated normotension (n=239; 69.2±5.9 years; 121.9±8.7 mm Hg). In both untreated and treated subjects, the results in younger (<60 years) and older (≥60 years) persons were consistent (P values for interaction >0.36).

There was an interaction ($P=0.04$) between untreated men and women for the hazard rate comparing white-coat hypertension with normotension. Indeed, cardiovascular risk tended ($P=0.06$) to be 44% (95% CI: −1% to 110%) higher in untreated men with white-coat hypertension as compared with untreated normotensive men, whereas the risk in untreated women with white-coat hypertension was similar ($P=0.19$) to the risk in untreated normotensive women. In addition, sensitivity analyses showed a tendency ($P=0.05$) toward an interaction between untreated diabetics and nondiabetics. The hazard rate associated with white-coat hypertension as compared with untreated normotension amounted

Table 2. Hazard Ratios for Cardiovascular Events in ISH Subjects With White-Coat, Masked, and Sustained Hypertension vs Normotension Broken Down by Treatment Status

	Untreated Subjects				Treated Subjects			
Subgroup	Subjects, n	Events, n	Adjusted Hazard Ratio (95% CI)	*P*	Subjects, n	Events, n	Adjusted Hazard Ratio (95% CI)	*P*
Normotensives	5271	232	1.00		431	73	1.98 (1.49–2.62)	<0.0001
Normotensives	5271	232	1.00		431	73	1.00	
White-coat HT	334	47	1.17 (0.87–1.57)	0.29	162	36	1.09 (0.79–1.52)	0.60
Masked HT	520	81	1.67 (1.33–2.09)	<0.0001	82	31	2.02 (1.40–2.90)	0.0002
Sustained HT	314	81	1.43 (1.14–1.79)	0.0020	181	74	1.98 (1.55–2.53)	<0.0001

ISH indicates isolated systolic hypertension; HT, hypertension.

The broad definition of cardiovascular events was used (see Methods section). The hazard ratios in the untreated subjects express the risk vs the untreated normotensive subgroup. The hazard ratios in the treated subjects (bottom rows) express the risk vs the treated subjects with normalized blood pressure. The hazard ratios in the first row express the risk associated with treated normotension as compared with untreated normotension. All of the hazard ratios were stratified for cohort and adjusted for sex, age, body mass index, serum cholesterol, current smoking status, and diabetes mellitus.

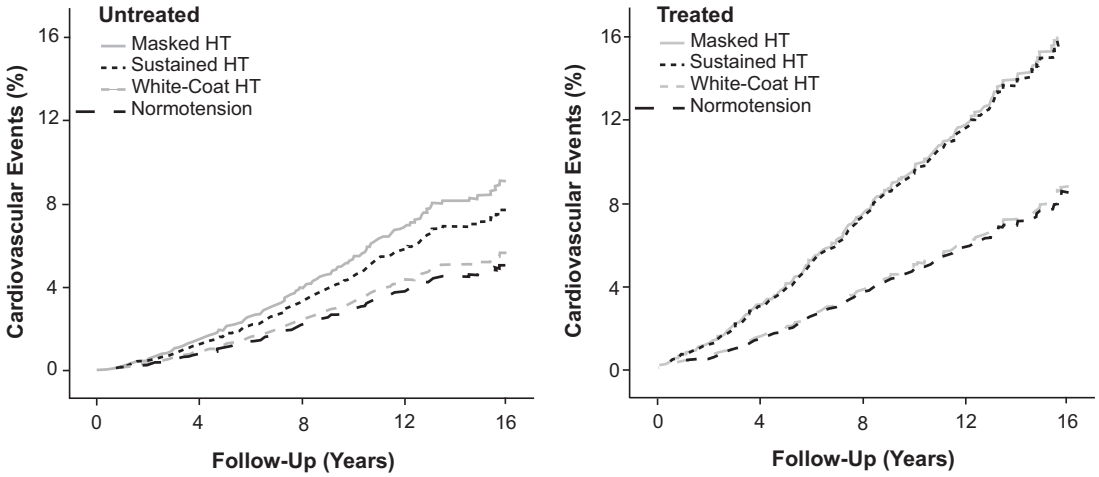


Figure 2. Incidence of cardiovascular events according to the cross-classification of subjects by conventional and daytime ambulatory blood pressure in normotensives and in persons with solated systolic hypertension (ISH) presenting with white-coat hypertension, masked hypertension, and sustained hypertension. The analyses included all of the cardiovascular events according to the broad definition. Incidence was standardized to the sex distribution (45% men) and mean age (48.8 years) in the whole study population. In the analysis including untreated subjects only (left), the incidence of cardiovascular events was significantly higher in sustained ($P=0.0005$) and masked hypertension ($P<0.0001$) as compared with normotension, whereas the risk in white-coat hypertension was similar to that in normotension ($P=0.38$). Similarly, in treated subjects with ISH (right), the incidence of cardiovascular events was significantly higher in sustained ($P<0.0001$) and masked hypertension ($P=0.0013$) as compared with treated normotension, whereas the risk in treated white-coat hypertension was similar to that in treated normotension ($P=0.92$). In both treated and untreated patients with ISH, the risk was similar in sustained and masked hypertension ($P>0.33$).

to 2.68 (95% CI: 1.10–6.54; $P=0.03$) in untreated diabetics and 1.03 (95% CI: 0.72–1.47; $P=0.88$) in untreated nondiabetics.

In further sensitivity analyses, we repeated the analyses while excluding one cohort at a time (Table S2). These analyses were confirmatory and showed that our results were not driven by one particular cohort.

Discussion

Two novel findings were observed in this 11-country IDACO Study. First, in subjects with ISH, those with treated white-coat hypertension had similar cardiovascular risks when compared with treated normotensives but higher risks when compared with untreated normotensives. Second, untreated persons with white-coat hypertension had cardiovascular risk no greater than the untreated normotensive comparator group. These observations were independent of follow-up time.

Because untreated normotensives were, on average, 17.5 years younger than subjects with ISH and untreated white-coat hypertension, we did subgroup analyses in persons ≥60 years of age and found that, first, at comparable ages, there was no significant difference in cardiovascular risk in untreated white-coat hypertension and untreated normotension. Furthermore, the small increase in daytime ambulatory SBP in the older untreated white-coat hypertensive subjects (126.2 mm Hg), in comparison with the younger untreated normotensives (119.5 mm Hg), strengthens our findings because of the expected "normal" gradual increase in SBP with aging. Second, at comparable ages, there was no significant difference in cardiovascular risk in treated white-coat hypertensives and treated normotensives.

Table 3. Hazard Ratios for Cardiovascular Events in ISH Subjects With White-Coat Hypertension vs Normotensive Subjects According to Sex, Age, Pulse Pressure, and Diabetic Status

	Untreated					Treated			
	Events/Subjects, n		Adjusted Hazard Ratio (95% CI)	*P*		Events/Subjects, n		Adjusted Hazard Ratio (95% CI)	*P*
Stratification	Normotensives	White-Coat HT				Normotensives	White-Coat HT		
Women	98/3048	8/131	0.61 (0.29–1.27)	0.19	$P=0.04$	41/287	16/104	0.82 (0.46–1.49)	0.52
Men	134/2223	39/203	1.44 (0.99–2.10)	0.06		32/144	20/58	1.33 (0.74–2.39)	0.34
<60 y	76/4300	4/108	1.66 (0.60–4.56)	0.33		13/192	2/35	0.66 (0.15–2.98)	0.60
≥60 y	156/971	43/226	1.09 (0.77–1.55)	0.61		60/239	34/127	1.09 (0.70–1.69)	0.70
Nondiabetics	219/5101	39/309	1.03 (0.72–1.47)	0.88	$P=0.05$	65/383	32/136	1.12 (0.73–1.74)	0.60
Diabetics	13/170	8/25	2.68 (1.10–6.54)	0.03		8/48	4/26	0.56 (0.16–1.93)	0.36

ISH indicates isolated systolic hypertension; HT, hypertension.

The broad definition of cardiovascular events was used (see Methods section). The hazard ratios in the untreated subjects express the risk vs the untreated normotensive subgroup. The hazard ratios in the treated subjects express the risk vs the treated subjects with normalized blood pressure. All of the hazard ratios were stratified for cohort and adjusted for sex, age, body mass index, serum cholesterol, current smoking status, and diabetes mellitus.

Association of Antihypertensive Treatment With Cardiovascular Risk

In a previous IDACO publication,[26] containing subjects with systolic and/or diastolic hypertension, white-coat hypertension was not associated with increased risk irrespective of treatment. In the present study, subjects with previous cardiovascular events and/or receiving antihypertensive therapy were removed from the normotensive comparator group, thus defining normotensive risk downward, in comparison with previous IDACO studies. The greater risk in treated ISH subjects with white-coat hypertension as compared with low-risk untreated normotensive subjects as observed in the present study is not surprising. Indeed, many of the treated ISH subjects presenting as white-coat hypertension were probably sustained hypertensives whose ambulatory BP was controlled on antihypertensive therapy but whose conventional BP showed a white-coat effect[27]; we propose to use the term "treated normalized hypertension" for this entity, rather than the confusing term of "treated white-coat hypertension."

Previous publications have failed to distinguish persons with treated normalized hypertension from white-coat hypertension because of higher risk in their normotensive comparator groups; this may have resulted from normotensive comparator groups with antecedent cardiovascular events, antihypertensive therapy, inclusion of masked hypertension, insufficient statistical power, or a combination of these factors. Nevertheless, persons with ISH who have "true" white-coat hypertension, but undergo antihypertensive treatment erroneously, have comparable cardiovascular risk as their untreated normotensive counterparts and, therefore, must be distinguished from subjects with treated normalized hypertension that show white-coat effect.[27] For these reasons, one should be cautious in applying the term "white-coat hypertension" to individuals with ISH receiving concurrent antihypertensive therapy.

High Prevalence of White-Coat Hypertension and White-Coat Effect in Older Persons With ISH

BP variability increases from middle age onward in association with increased large artery stiffness, increasing systolic BP, and decreasing diastolic BP with a resulting widening of pulse pressure.[28,29] Importantly, older subjects with widened pulse pressure have increased cardiovascular risk.[30,31] Subjects with ISH, presenting with either white-coat hypertension or white-coat effect, are more likely to have an "alerting" or white-coat response on the measured BP as a result of stiffened arteries and a concomitant reduction in arterial buffering capacity.[32,33]

There is still controversy regarding the concept that white-coat hypertension is a transition state between normotension and sustained hypertension.[1,26,27] Importantly, the influence of the ISH subtype on this possible progression has not been well studied. The present analysis shows similar cardiovascular risk in persons with ISH and untreated white-coat hypertension versus untreated normotension. On the other hand, our subgroup analysis suggests that men and diabetics with untreated white-coat hypertension are at increased cardiovascular risk in comparison with their normotensive counterparts. Indeed, diabetes mellitus has been shown to be a strong risk factor for incident hypertension.[34] Because of the small number of events and the wide confidence limits in our subgroup analyses, however, our results are only hypothesis generating at best; nevertheless, these findings would suggest that individuals with ISH and untreated white-coat hypertension may represent a heterogeneous group, with those with a high cardiometabolic burden (smokers, high low-density lipoprotein cholesterol, metabolic syndrome, and diabetes mellitus) destined to progress over time to sustained hypertension, whereas others with a low cardiometabolic burden may remain white-coat hypertensive indefinitely. Larger, long-term outcome studies are needed to test this hypothesis.

Diagnostic Implications in Subjects With ISH

Importantly, persons with white-coat and masked hypertension, composing 73% of the total number of subjects with ISH in this population study, would not have been diagnosed accurately with exclusive use of conventional clinic or office BP measurements; the ratio of white-coat:sustained:masked hypertension was ≈1:1:1.6. Thus, the exclusive use of conventional office or clinic BP measurements to identify patients with ISH at risk would have resulted in overtreatment of white-coat hypertension and underdiagnosis and undertreatment of masked hypertension. Twenty-four–hour ambulatory BP measurement is the ideal method of diagnosing both masked and white-coat hypertension,[35,36] but other options are available that are less expensive and more easily repeatable for the additional assessment of the response to treatment, including home BP monitoring[35,36] or the use of a repeated automated office BP device with multiple recordings on a single visit.[37,38]

Strengths and Limitations

Our study must be interpreted within the context of its strengths and potential limitations. First, the conventional BP was measured under differing conditions in the cohorts. However, in all but 1 of the cohorts, BP was measured in the sitting position, and in all of the cohorts, the average of only 2 conventional BP measurements was used for analysis. In addition, all of the centers implemented rigorous quality control programs for BP measurement. Second, ambulatory BP monitoring was not standardized in terms of device type and intervals between successive readings. However, all of the ambulatory BP means were weighted for the interval between successive readings. By design, this meta-analysis was based on data from individuals rather than from aggregate data from each individual study. Furthermore, the analysis rested on 11 population-based cohorts over 3 continents with an overrepresentation of European subjects and might, therefore, not be representative for other ethnic groups, in particular blacks. Moreover, we focused our analyses on ISH, which in middle-aged and older subjects is the most prevalent type of hypertension and by far the predominant modifiable risk factor. Our results can, therefore, not be extrapolated to younger patients with combined systolic and diastolic hypertension or isolated diastolic hypertension. Finally, the subgroup analyses of the effects of sex, age, and diabetic status in white-coat hypertension are

hypothesis-generating conclusions that must be tested with additional studies.

Perspectives

Using the 11-country IDACO population database in subjects with ISH undergoing conventional and daytime ambulatory BP measurements, we noted that cardiovascular risk in untreated subjects with white-coat hypertension was no greater than in an untreated normotensive control population, and this finding was independent of follow-up time. Therefore, the present study does not provide support for the thesis that persons with ISH, presenting as untreated white-coat hypertension, represent a transition state between normotension and sustained hypertension; however, subgroup analyses suggest (but do not prove) that untreated white-coat hypertension may be associated with increased cardiovascular risk in some higher-risk groups, such as men and diabetic subjects. Furthermore, subjects with ISH, presenting as treated white-coat hypertension, could be either sustained hypertensives with white-coat effect that had been treated to normotensive daytime ambulatory BP values, an entity that we have termed "treated normalized hypertension," or undiagnosed white-coat hypertensives that had been started on antihypertensive therapy erroneously. Therefore, in the presence of concurrent antihypertensive treatment, one should be cautious in applying the term "white-coat hypertension." Lastly, the exclusive use of conventional clinic BP would result in failure to recognize white-coat and masked hypertension in almost 3 of 4 persons with untreated ISH.

Acknowledgments

We gratefully acknowledge the expert assistance of Sandra Covens and Sonja Zuba (Studies Coordinating Centre, Leuven, Belgium).

Sources of Funding

The European Union (grants IC15-CT98-0329-EPOGH, LSHM-CT-2006-037093, HEALTH-F4-2007-201550, HEALTH-F7-2011-278249 EU-MASCARA, and the European Research Council Advanced Researcher Grant 294713 EPLORE), the Fonds voor Wetenschappelijk Onderzoek Vlaanderen (Ministry of the Flemish Community, Brussels, Belgium; grants G.0575.06 and G.0734.09), and the Katholieke Universiteit Leuven (grants OT/00/25 and OT/05/49) gave support to the Studies Coordinating Centre in Leuven. The European Union (grants LSHM-CT-2006-037093 and HEALTH-F4-2007-201550) also supported the research groups in Shanghai, Kraków, Padova, and Novosibirsk. The Bilateral Scientific and Technological Collaboration between China and Flanders, Ministry of the Flemish Community, Brussels (grant BIL02/10), supported the fellowship of Y.L. in Leuven. The Danish Heart Foundation (grant 01-2-9-9A-22914) and the Lundbeck Fonden (grant R32-A2740) supported the studies in Copenhagen. The Ministries of Education, Culture, Sports, Science, and Technology (grants 15790293, 16590433, 17790381, 18390192, 18590587, 19590929, and 19790423) and of Health, Labor, and Welfare (Health Science Research grants, Medical Technology Evaluation Research grants, H17-Kenkou-007, H18-Junkankitou[Seishuu]-Ippan-012, and H20-Junkankitou[Seishuu]-Ippan-009, 013), a Grant-in-Aid from the Japanese Society for the Promotion of Science (16.54041, 18.54042, 19.7152, 20.7198, 20.7477, and 20.54043), the Japan Atherosclerosis Prevention Fund, the Uehara Memorial Foundation, and the Takeda Medical Research Foundation supported research in Japan, as well as the National Cardiovascular Research Grants and the Biomedical Innovation Grants in Japan. The National Natural Science Foundation of China (grants 30871360 and 30871081), Beijing, China, and the Shanghai Commissions of Science and Technology (grant 07JC14047 and the "Rising Star" program 06QA14043) and Education (grant 07ZZ32 and the "Dawn" Project) supported the JingNing study in China.

Disclosures

None.

References

1. 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, on behalf of the 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.
2. Bjorklund K, Lind L, Zethelius B, Andrén B, Lithell H. Isolated ambulatory hypertension predicts cardiovascular morbidity in elderly men. *Circulation*. 2003;107:1297–1302.
3. 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(part 1):1–6.
4. 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, for the Systolic Hypertension in Europe Trial Investigators. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 99;282:539–546.
5. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? *JAMA*. 1988;259:225–228.
6. Pickering TG, Levenstein M Walmsley P. Differential effects of doxazosin on clinic and ambulatory pressure according to age, gender, and presence of white coat hypertension: results of the HALT study. *Am J Hypertens*. 1994;7:848–852.
7. Fagard RH, Staessen JA, Thijs L, Gasowski J, Bulpitt CJ, Clement D, de Leeuw PW. Dobovisek J, Jaaskivi M, Leonetti G, O'Brien E, Palatini P, Parati G, Rodicio JL, Venhanen H, Webster J. 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.
8. 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.
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. 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.
11. 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.
12. Ohkubo T, Kikuya K, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai K. 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.
13. Kikuya M, Hansen TW, Thijs L, Björklund-Bodegård K, Kuznetsova T, Ohkubo T, Richart T, Torp-Pedersen C, Lind L, Ibsen H, Imai K, Staessen JA, on behalf of the IDACO investigators. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-Year cardiovascular risk *Circulation.* 2007;115:2145–2152.
14. Thijs L, Hansen TW, Kikuya M, Björklund-Bodegård K, Li Y, Dolan E, Tikhonoff V, Seidlerova J, Kuznetsova T, Stolarz K, Bianchi M, Richart T, Casiglia E, Malyutina S, Filipovsky J, Kawecka-Jaszcz K, Nikitin Y, Ohkubo T, Sandoya E, Wang JG, Torp-Pedersen C, Lind L, Ibsen H, Imai K, Staessen JA, on behalf of the IDACO investigators. The International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO): protocol and research perspectives *Blood Press Monit.* 2007;12:255–262.
15. Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure and mortality: a population based study. *Hypertension*. 2005;45:499–504.

16. Ingelsson E, Björklund K, Lind L, Arnlov J, Sundstrom J. Diurnal blood pressure pattern and risk of congestive heart failure. *JAMA*. 2006;295: 2859–2866.
17. Kuznetsova T, Malyutina S, Pello E, Thijs L, Nikitin Y, Staessen JA. Ambulatory blood pressure of adults in Novosibirsk, Russia: interim report on a population study. *Blood Press Monit*. 2000;5:291–296.
18. Kuznetsova T, Staessen JA, Kawecka-Jaszcz K, Babeanu S, Casiglia E, Filipovsky J, Nachev C, Nikitin Y, Peleská J, O'Brien E, on behalf of the EPOGH Investigators. Quality control of the blood pressure phenotype in the European Project on Genes in Hypertension. *Blood Press Monit.* 2002;7:215–224.
19. Li Y, Wang JG, Gao HF, Nawrot T, Wang GL, Qian YS, Staessen JA, Zhu DL. Are published characteristics of the ambulatory blood pressure generalizable to rural Chinese? The JingNing population study. *Blood Press Monit*. 2005;10:125–134.
20. O'Brien E, Murphy J, Tyndall A, Atkins N, Mee F, McCarthy G, Staessen J, Cox J, O'Malley K. Twenty-four-hour ambulatory blood pressure in men and women aged 17 to 80 years: the Allied Irish Bank Study. *J Hypertens*. 1991;9:355–360.
21. Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, Matsubara M, Hashimoto J, Hoshi H, Araki T, Tsuji I, Satoh H, Hisamichi S, Imai Y. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama Study. *J Hypertens*. 2002;20:2183–2189.
22. Schettini C, Bianchi M, Nieto F, Sandoya E, Senra H. Hypertension Working Group. Ambulatory blood pressure: normality and comparison with other measurements. *Hypertension.* 1999;34(part 2):818–825.
23. Staessen JA, Bieniaszewski L, O'Brien ET, Imai Y, Fagard R. An epidemiological approach to ambulatory blood pressure monitoring: the Belgian population study. *Blood Press Monit*. 1996;1:13–26.
24. Chobanian AV, Bakris GL, Black BK, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, and the 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.
25. Easton DF, Peto J, Babiker AGAG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med*. 1991;10:1025–1035.
26. 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 K, Staessen JA, on behalf of the IDACO investigators. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7030 individuals. *J Hypertens.* 2007;25: 1554–1564.
27. Verdecchia P, Staessen JA, White WB, Imai Y, O'Brien ET. Properly defining white coat hypertension. *Eur Heart J*. 2002;23:106–109.
28. Muntner P, Shimbo D, Tonelli M, Reynolds K, Arnett DK, Oparil S. The relationship between visit-to-visit variability in systolic blood pressure and all-cause mortality in the general population: findings from NHANES III, 1988 to 1994. *Hypertension*. 2011;57:150–166.
29. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet*. 2010;375:938–948.
30. Benetos A, Safar M Rudnichi A, Smulyan H, Richard JL, Ducimetiere P, Guize L. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. *Hypertension*. 1997;30:1410–1415.
31. Franklin SS, Lopez VA, Wong ND, Mitchell GF, Larson MG, Vasan RS, Levy D. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009; 119:243–250.
32. Bjorklund K, Lind L, Zethelius B, Berglund L, Lithell H. Prognostic significance of 24-h ambulatory blood pressure characteristics for cardiovascular morbidity in a population of elderly men. *J Hypertens*. 2004;22: 1691–1697.
33. Staessen JA, Thijs L, O'Brien ET, Bulpitt CJ, de Leeuw PW, Fagard RH, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J, Safar ME, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Ambulatory pulse pressure as predictor of outcome in older patients with systolic hypertension. *Am J Hypertens.* 2002;15(part 1):835–843.
34. De Marco M, de Simone G, Roman MJ, Chinali M, Lee Et.Russell M, Howard BV, Devereux RB. Cardiovascular and metabolic predictors of progression of prehypertension into hypertension: the Strong Heart Study. *Hypertension*. 2009;54:974–980.
35. Verdecchia P, Angeli A, Mazzotta G, Gentile G, Reboldi G. Home blood presssure measurements will or will not replace 24-hour ambulatory blood pressure measurement *Hypertension*. 2009;54:188–195.
36. Gaborieau V, Delarche N, Gosse P. Ambulatory blood pressure monitoring versus self-measurement of blood pressure at home: correlation with target organ damage. *J Hypertens.* 2008;26:1919–1927.
37. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Kaczorowski J. Measurement of blood pressure in the office: recognizing the problem and proposing the solution. *Hypertension*. 2010;55:195–200.
38. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Grant FC, Kaczorowski J. Conventional versus automated measurement of blood pressure in primary care patients with systolic hypertension: randomized parallel design controlled trial. *Br Med J*. 2011;342:1–9.

DATA SUPPLEMENT

The Significance of White-Coat Hypertension in Older Persons with Isolated Systolic Hypertension: a Meta-Analysis using the IDACO Population

Short title: White Coat Hypertension in Subjects with ISH

Stanley S. Franklin, Lutgarde Thijs, Tine W. Hansen, Yan Li, José Boggia, Masahiro Kikuya, Kristina Björklund-Bodegård, Takayoshi Ohkubo, Jørgen Jeppesen, Christian Torp-Pedersen, Eamon Dolan, Tatiana Kuznetsova, Katarzyna Stolarz-Skrzypek, Valérie Tikhonoff, Sofia Malyutina, Edoardo Casiglia, Yuri Nikitin, Lars Lind, Edgardo Sandoya, Kalina Kawecka-Jaszcz, Yutaka Imai, Jiguang Wang, Hans Ibsen, Eoin O'Brien, Jan A. Staessen, ᵖ on behalf of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) Investigators

Number: tables 2, figures 2

Correspondence to:
Jan A. Staessen, MD, PhD, FESC, FAHA,
Studies Coordinating Centre,
Laboratory of Hypertension,
University of Leuven,
Campus Sint Rafaël,
Kapucijnenvoer 35 block d level 00,
B-3000 Leuven, Belgium

Telephone: +32-16-34-7104 (office)
+32-15-41-1747 (home)
+32-47-632-4928 (mobile)
Facsimile: +32-16-34-7106 (office)
+32-15-41-4542 (home)
email: jan.staessen@med.kuleuven.be
jan.staessen@epid.unimaas.nl

Expanded methods

Study Population

Our database was constructed from the 11-country IDACO study groups[1-9] that consisted of random population samples and required available data on conventional and ambulatory BP.[10,11] Cardiovascular risk factors were available at baseline and with subsequent follow-up that included fatal and nonfatal outcomes. Further details of the protocol and research perspectives of the IDACO study has been published previously.[11]

On 7/10/2010 the IDACO database included 11,785 subjects. We excluded a total of 4490 subjects. The reasons for exclusions consisted of: lack of conventional BP measurements (n=220), average of fewer than 10 readings of daytime ambulatory BP (n=164), younger than 18-years at enrolment (n=249), diastolic hypertension (conventional DBP ≥ 90 mm Hg or daytime DBP ≥ 85 mm Hg (n=3311), a history of cardiovascular disease (n=545), and unknown treatment status (n=1). Thus the number of subjects included in the present analysis totaled 7295.

The 7295 subjects in the ISH database include 1296 subjects from Copenhagen,[1] 1003 subjects from Ohasama,[7] 1681 subjects from Noorderkempen,[9] 549 subjects from Uppsala,[2] 1141 subjects from Montevideo[8], 215 subjects from JingNing,[5] 163 subjects from Novosibirsk,[3,4] 708 subjects from Dublin,[6] 129 subjects from Pilsen,[4] 218 subjects from Padua,[4] and 192 subjects from Krakow[4]. All studies contributing to the IDACO database received ethical approval and have been described in detail in previous publications.[1-9] All participants provided their informed written consent.

Blood Pressure Measurements

Conventional blood pressure was measured by trained observers with a mercury sphygmomanometer[1-6,9] with validated auscultatory[7] (USM-700F, UEDA Electronic Works, Tokyo, Japan) or oscillometric[8] (OMRON HEM-705CP, Omron Corporation, Tokyo, Japan) devices, using the appropriate cuff size, with participants in the sitting[1,3-9] or supine[2] position. The conventional BP was the average of 2 consecutive readings obtained either at the subjects' home[3-5,8,9] or at an examination center.[1,2,6,7]

We programmed portable monitors to obtain ambulatory blood pressure readings at 30-minute intervals throughout the whole day,[6,7] or at intervals ranging from 15[1] to 30[2] minutes during daytime and from 30[1] to 60[2] minutes at night. The devices implemented an auscultatory algorithm (Accutracker II) in Uppsala[2] or an oscillometric technique (SpaceLabs 90202 and 90207, Nippon Colin, and ABPM-630) in the other cohorts.[1,3-9] While accounting for the daily pattern of activities of the participants, we defined daytime as the interval from 10 AM to 8 PM in Europeans[1-4,6,9] and South Americans,[8,] and from 8 AM to 6 PM in Asians.[5,7] The corresponding nighttime intervals ranged from midnight to 6 AM[1-4,6,8,9] and from 10 PM to 4 AM,[5,7] respectively. We computed the averaged daytime BP weighted for the time interval between consecutive readings.

Other Measurements

We used the questionnaires originally administered in each cohort to obtain information on each subject's medical history, and smoking and drinking habits. Body mass index was body weight in kilograms divided by height in meters squared. We measured serum cholesterol by au-

tomated enzymatic methods. Diabetes mellitus was the use of antidiabetic drugs, a fasting blood glucose concentration of at least 7.0 mmol/L,[1-4,7-9] a random blood glucose concentration of at least 11.1 mmol/L,[5,7,9] a self-reported diagnosis,[5,8,9] or diabetes documented in practice or hospital records.[8]

Ascertainment of Events

In each cohort, outcomes were adjudicated against source documents described in previous publications.[2,5,7,11,12] Fatal and nonfatal stroke (ICD8/9 430–434 and 436, ICD10 I60–I64 and I67–I68) did not include transient ischemic attacks. Cardiac events encompassed death from ischemic heart disease (ICD8 411–412, ICD9 411 and 414, and ICD10 I20 and I24–I25), sudden death (CD8 427.2 and 795, and ICD9 427.5 and 798, and ICD10 I46 and R96), nonfatal myocardial infarction (ICD8/9 410, and ICD10 I21-I22), surgical and percutaneous coronary revascularization and fatal and nonfatal heart failure (ICD8 428 and 427.1–427.2 and 429, and ICD9 429, and ICD10 I50 andJ81). Hospitalizations for unstable angina were coded as ischemic heart disease. In the Danish and Swedish cohorts, the diagnosis of heart failure required admission to hospital. In the other cohorts, heart failure was either a clinical diagnosis or the diagnosis on the death certificate, but in all cases it was validated against hospital files or the records held by family doctors. The restricted composite cardiovascular endpoint included all aforementioned endpoints plus cardiovascular mortality. The broad composite cardiovascular endpoint included TIA, angina, peripheral arterial disease and all events included in the restricted cardiovascular endpoint. In all outcome analyses, we only considered the first event within each category. Unless indicated otherwise, results are presented for the broad definition of cardiovascular events.

Sources of funding

The European Union (grants IC15-CT98-0329-EPOGH, LSHM-CT-2006-037093, HEALTH-F4-2007-201550? HEALTH-F7-2011278249 EU-MASCARA and and the European Research Council Advanced Researcher Grant 294713 EPLORE), the Fonds voor Wetenschappelijk Onderzoek Vlaanderen (Ministry of the Flemish Community, Brussels, Belgium; grants G.0575.06 and G.0734.09), and the Katholieke Universiteit Leuven (grants OT/00/25 and OT/05/49) gave support to the Studies Coordinating Centre in Leuven. The European Union (grants LSHM-CT-2006-037093 and HEALTH-F4-2007-201550) also supported the research groups in Shanghai, Kraków, Padova and Novosibirsk. The Bilateral Scientific and Technological Collaboration between China and Flanders, Ministry of the Flemish Community, Brussels (grant BIL02/10), supported the fellowship of Y.L. in Leuven. The Danish Heart Foundation (grant 01-2-9-9A-22914), and the Lundbeck Fonden (grant R32-A2740) supported the studies in Copenhagen. The Ministries of Education, Culture, Sports, Science, and Technology (grants 15790293, 16590433, 17790381, 18390192, 18590587, 19590929 and 19790423) and of Health, Labor, and Welfare (Health Science Research grants, Medical Technology Evaluation Research grants, H17-Kenkou-007, H18-Junkankitou[Seishuu]-Ippan-012, and H20-Junkankitou[Seishuu]-Ippan-009, 013), a Grant-in-Aid from the Japanese Society for the Promotion of Science (16.54041, 18.54042, 19.7152, 20.7198, 20.7477 and 20.54043), the Japan Atherosclerosis Prevention Fund, the Uehara Memorial Foundation, the Takeda Medical Research Foundation supported research in Japan, the National Cardiovascular Research Grants, and the Biomedical Innovation Grants in Japan. The National Natural Science Foundation of China (grants 30871360 and 30871081), Beijing, China, and the Shanghai Commissions of Science and Technology (grant 07JC14047 and the “Rising Star” program 06QA14043) and Education (grant 07ZZ32 and the “Dawn” project) supported the JingNing study in China.

References

1. Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure and mortality : a population based study. *Hypertension.* 2005;45:499-504.
2. Ingelsson E, Björklund K, Lind L, Arnlov J, Sundstrom J. Diurnal blood pressure pattern and risk of congestive heart failure *JAMA.* 2006;295:2859-2866.
3. Kuznetsova T, Malyutina S, Pello E, Thijs L, Nikitin Y, Staessen JA. Ambulatory blood pressure of adults in Novosibirsk, Russia : interim report on a population study. *Blood Press Monit.* 2000;5:291-296.
4. Kuznetsova T, Staessen JA, Kawecka-Jaszcz K, Babeanu S, Casiglia E, Filipovsky J, Nachev C, Nikitin Y, Peleská J, O'Brien E, on behalf of the EPOGH Investigators. Quality control of the blood pressure phenotype in the European Project on Genes in Hypertension. *Blood Press Monit.* 2002;7:215-224.
5. Li Y, Wang JG, Gao HF, Nawrot T, Wang GL, Qian YS, Staessen JA, Zhu DL. Are published characteristics of the ambulatory blood pressure generalizable to rural Chinese? The JingNing population study. *Blood Press Monit.* 2005;10:125-134.
6. O'Brien E, Murphy J, Tyndall A, Atkins N, Mee F, McCarthy G, Staessen J, Cox J, O'Malley K. Twenty-four-hour ambulatory blood pressure in men and women aged 17 to 80 years : the Allied Irish Bank Study. *J Hypertens.* 1991;9:355-360.
7. Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, Matsubara M, Hashimoto J, Hoshi H, Araki T, Tsuji I, Satoh H, Hisamichi S, Imai Y. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure : the Ohasama study. *J Hypertens.* 2002;20:2183-2189.
8. Schettini C, Bianchi M, Nieto F, Sandoya E, Senra H, Hypertension Working Group. Ambulatory blood pressure. Normality and comparison with other measurements. *Hypertension.* 1999;34 (part 2):818-825.
9. Staessen JA, Bieniaszewski L, O'Brien ET, Imai Y, Fagard R. An epidemiological approach to ambulatory blood pressure monitoring : the Belgian population study. *Blood Press Monit.* 1996;1:13-26.
10. Kikuya M, Hansen TW, Thijs L, Björklund-Bodegård K, Kuznetsova T, Ohkubo T, Richart T, Torp-Pedersen C, Lind L, Ibsen H, Imai K, Staessen JA, On behalf of the IDACO investigators. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-Year cardiovascular risk *Circulation.* 2007;115:2145-2152.
11. Thijs L, Hansen TW, Kikuya M, Björklund-Bodegård K, Li Y, Dolan E, Tikhonoff V, Seidlerova J, Kuznetsova T, Stolarz K, Bianchi M, Richart T, Casiglia E, Malyutina S, Filipovsky J, Kawecka-Jaszcz K, Nikitin Y, Ohkubo T, Sandoya E, Wang JG, Torp-Pedersen C, Lind L, Ibsen H, Imai K, Staessen JA, On behalf of the IDACO investigators. The International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO): protocol and research perspectives *Blood Press Monit.* 2007;12:255-262.
12. 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.

Table S1. Hazard ratios for cardiovascular mortality and restricted cardiovascular events in ISH subjects with white-coat, masked and sustained hypertension versus normotension broken down by treatment status

Subgroup	Untreated subjects				Treated subjects			
	Subjects (n)	Events (n)	Adjusted hazard ratio (95% CI)	*P*-value	Subjects (n)	Events (n)	Adjusted hazard ratio (95% CI)	*P*-value
Cardiovascular mortality								
Normotensives	5271	56	1.00		431	24	1.00	
White coat HT	334	13	1.15 (0.66,2.00)	0.63	162	18	1.48 (0.93,2.36)	0.10
Masked HT	520	23	1.99 (1.30,3.03)	0.0015	82	6	0.99 (0.44,2.23)	0.98
Sustained HT	314	26	1.52 (1.02,2.26)	0.039	181	27	1.96 (1.30,2.96)	0.0014
Cardiovascular events – restricted definition								
Normotensives	5271	160	1.00		431	60	1.00	
White coat HT	334	34	1.14 (0.81,1.61)	0.45	162	30	1.06 (0.74,1.52)	0.76
Masked HT	520	53	1.61 (1.22,2.12)	0.0008	82	26	2.05 (1.38,3.05)	0.0003
Sustained HT	314	58	1.43 (1.10,1.86)	0.0094	181	63	2.10 (1.61,2.73)	<0.0001

ISH, Isolated Systolic Hypertension; HT; hypertension; CI, confidence interval; n, number

The hazard ratios in the untreated subject express the risk versus the untreated normotensive subgroup . The hazard ratios in the treated subjects express the risk versus the treated subjects with normalized blood pressure. All hazard ratios were stratified for cohort and adjusted for sex, age, body mass index, serum cholesterol, current smoking status and diabetes mellitus.

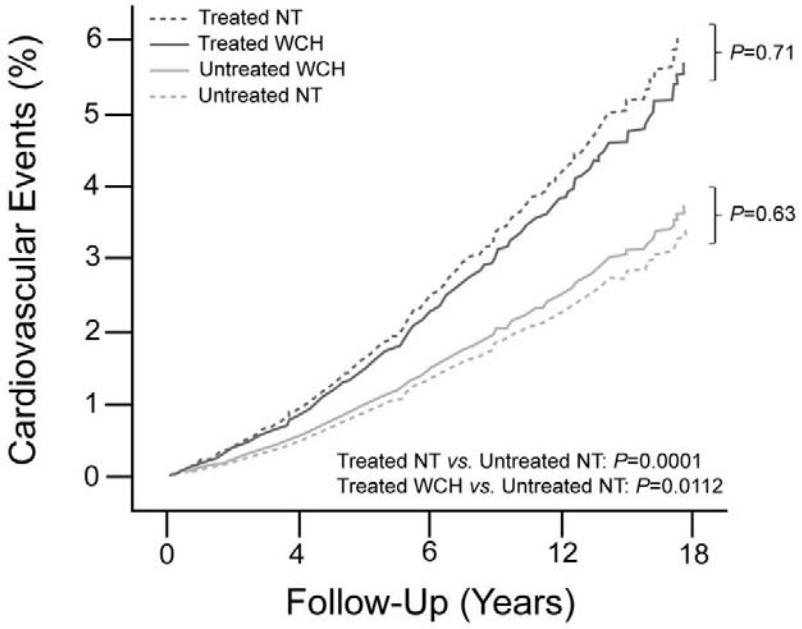
Table S2. Hazard ratios for cardiovascular events in ISH subjects with white coat hypertension versus normotensives obtained after excluding one cohort at a time

Excluded cohort	Untreated				Treated			
	Events/Subjects (n)		Adjusted hazard ratio (95% CI)	*P*-value	Events/ Subjects (n)		Adjusted hazard ratio (95% CI)	*P*-value
	Normotensives	White-coat HT			Normotensives	White-coat HT		
Copenhagen	153/4445	39/298	1.07 (0.74,1.55)	0.71	62/378	34/152	1.12 (0.72,1.73)	0.61
Noorderkempen	199/3881	39/273	1.06 (0.74,1.53)	0.75	72/351	33/129	0.97 (0.63,1.50)	0.90
Ohasama	197/4718	41/270	1.11 (0.85,1.75)	0.29	38/275	22/106	1.20 (0.66,2.17)	0.55
Uppsala	197/5096	29/251	1.19 (0.79,1.80)	0.40	65/405	26/136	0.93 (0.58,1.49)	0.77
Montevideo	194/4360	41/277	1.29 (0.90,1.85)	0.16	59/364	29/138	0.98 (0.62,1.56)	0.93
JingNing	232/5085	47/325	1.15 (0.83,1.61)	0.41	73/428	36/161	1.04 (0.68,1.58)	0.86
Dublin	222/4603	47/322	1.15 (0.82,1.60)	0.41	73/431	36/162	1.04 (0.68,1.58)	0.86
EPOGH cohorts	230/4709	46/322	1.13 (0.81,1.58)	0.48	69/385	36/150	1.11 (0.73,1.69)	0.63

ISH, isolated systolic hypertension; HT, hypertension.

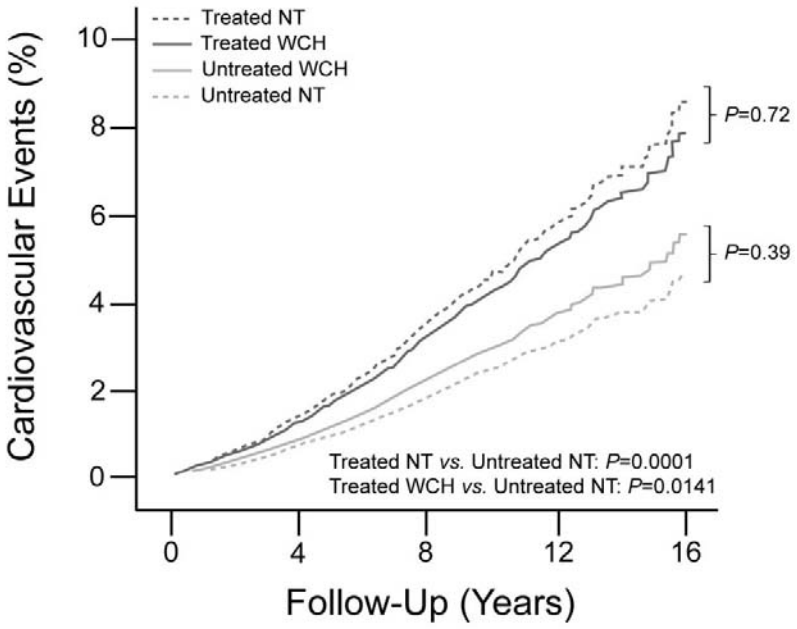
The hazard ratios in the untreated subject express the risk versus the untreated normotensive subgroup . The hazard ratios in the treated subjects express the risk versus the treated subjects with normalized blood pressure. All hazard ratios were stratified for cohort and adjusted for sex, age, body mass index, serum cholesterol, current smoking status and diabetes mellitus. The broad definition of cardiovascular events was used (see methods section). EPOGH includes the cohorts recruited in Kraków (n=176), Novosibirsk (n=158), Padova (n=203) and Pilsen (n=119).

Figure S1. Incidence of restricted cardiovascular events in normotensive subjects and in ISH subjects with white-coat hypertension broken down by treatment status



Incidence of cardiovascular events in untreated normotension (untreated NT), untreated ISH subjects with white coat hypertension (untreated WCH), treated normotension (treated NT) and treated ISH subjects with white-coat hypertension (treated WCH). The restricted definition of cardiovascular events was used (see methods section). Incidence was standardized to the sex distribution (45% men) and mean age (48.8 years) in the whole study population. In untreated subjects with ISH, the risk in white coat hypertensives was similar to that in normotensives (P=0.63). Similarly, in treated subjects with ISH, white-coat hypertension did not carry an increased risk (P=0.71) as compared to treated normotension. However, both treated ISH subjects with white coat hypertension (treated WCH) and treated subjects with normal blood pressure (treated NT) were at higher (P<0.012) cardiovascular risk as compared to the untreated normotensive reference group.

Figure S2. Incidence of broad cardiovascular events in normotensive subjects and in ISH subjects with white-coat hypertension using 130/80 mmHg as cut-off point for daytime normotension and broken down by treatment status



Incidence of cardiovascular events in untreated normotension (untreated NT), untreated ISH subjects with white coat hypertension (untreated WCH), treated normotension (treated NT) and treated ISH subjects with white-coat hypertension (treated WCH). The broad definition of cardiovascular events was used (see methods section). Incidence was standardized to the sex distribution (42% men) and mean age (48.3 years) in the whole study population**.** In untreated subjects with ISH, the risk in white coat hypertensives was similar to that in normotensives (P=0.39). Similarly, in treated subjects with ISH, white-coat hypertension did not carry an increased risk (P=0.72) as compared to treated normotension. However, both treated ISH subjects with white coat hypertension (treated WCH) and treated subjects with normal blood pressure (treated NT) were at higher (P<0.015) cardiovascular risk as compared to the untreated normotensive reference group.