

Closer look at white-coat hypertension

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Abstract

This review aims to clarify novel concepts regarding the clinical and laboratory aspects of white-coat hypertension (WCHT). Recent studies on the clinical and biological implications of WCHT were compared with existing knowledge. Studies were included if the WCHT patients were defined according to the 2013 European Society of Hypertension guidelines, *i.e.*, an office blood pressure (BP) of $\geq 140/90$ mmHg, a home BP of $\leq 135/85$ mmHg, and a mean 24-h ambulatory BP of $\leq 130/80$ mmHg. WCHT studies published since 2000 were selected, although a few studies performed before 2000 were used for comparative purposes. True WCHT was defined as normal ABPM and home BP readings, and partial WCHT was defined as an abnormality in one of these two readings. The reported prevalence of WCHT was 15%-45%. The incidence of WCHT tended to be higher in females and in non-smokers. Compared with normotensive (NT) patients, WCHT was associated with a higher left ventricular mass index, higher lipid levels, impaired fasting glucose, and decreased arterial compliance. The circadian rhythm in WCHT patients was more variable than in NT patient's, with a higher pulse pressure and non-dipping characteristics. Compared with sustained hypertension patients, WCHT patients have a better 10-year prognosis; compared with NT patients, WCHT patients have a similar stroke risk, but receive

more frequent drug treatment. There are conflicting results regarding WCHT and markers of endothelial damage, oxidative stress and inflammation, and the data imply that WCHT patients may have a worse prognosis. Nitric oxide levels are lower, and oxidative stress parameters are higher in WCHT patients than in NT patients, whereas the antioxidant capacity is lower in WCHT patients than in NT patients. Clinicians should be aware of the risk factors associated with WCHT and patients should be closely monitored especially to identify target organ damage and metabolic syndrome.

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Key words: White-coat hypertension; Ambulatory blood pressure; Target organ damage; Glucose dysregulation

Core tip: There is contradictory information regarding the clinical presentations and prognosis of white-coat hypertension (WCHT). This review aims to summarize recent research and compare it to existing knowledge about WCHT. Published studies on the prevalence of WCHT, the associated target organ damage and cardiovascular markers, and WCHT patient prognosis were reviewed. WCHT may be a marker of future obesity and metabolic syndrome, is related to glucose dysregulation and left ventricular hypertrophy and may progress to sustained hypertension. Clinicians should be aware of the risk factors associated with WCHT, and patients should be closely monitored, especially to identify target organ damage and metabolic syndrome.

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DEFINITION OF WHITE-COAT HYPERTENSION

According to the 2013 guidelines published by the Euro-

pean Society of Hypertension and the European Society of Cardiology for the management of hypertension white-coat hypertension (WCHT) is defined for patients who are not taking medication as an office blood pressure (BP) of $\geq 140/90$ on at least three occasions in the presence of a health care worker (particularly a physician), with normal 24-h ($\leq 125-130/80$ mmHg) and day ambulatory BP monitoring (ABPM) ($\leq 130-135/85$ mmHg) or a normal home BP (average of several readings, $\leq 130-135/85$ mmHg)^[1]. There were no changes in the definition of WCHT in the JNC8^[2]. The American Heart Association (AHA) recommends home BP monitoring for patients with pre-hypertension (120-139/80-89 mmHg) and for patients diagnosed with hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg)^[3].

It is recommended that at least two 24-h ABPM measurements be recorded to confirm WCHT^[4]. WCHT can be divided into two subgroups: partial WCHT, where either the ABPM or the home BP readings are elevated; and true WCHT, in which both the ambulatory and home BP values are normal^[5].

WCHT should be differentiated from the white coat effect, which is a rise in BP in response to the presence of a medical practitioner and may be observed in all types of patients, from normotensive (NT) persons to patients with sustained hypertension (SHT) in the presence or absence of therapy^[6].

The prevalence of WCHT, its associations with other clinical conditions and vascular biomarkers, the risk of target organ damage and patient prognosis in comparison with other forms of hypertension will be discussed in this review.

Studies were included if the WCHT patients were defined according to the 2013 European Society of Hypertension guidelines. WCHT studies published since 2000 were selected, although a few studies performed before 2000 were used for comparative purposes.

THE PREVALENCE OF WHITE-COAT HYPERTENSION

The Finn-Home study was performed on 1540 untreated participants with an age range of 44 to 75 years. Two hundred thirty-three patients had WCHT. The prevalence of WCHT was 15.1%. The home BP levels of the WCHT patients were higher than those of the NT individuals. The WCHT group was older and had a higher proportion of men; WCHT patients had more metabolic risk factors than NT individuals^[7].

The PAMELA study was a population study performed in Monza, Italy. BP was measured in the office and, twice daily, by subjects at home. The investigators assessed the cardiovascular and all-cause mortality over 16 years (1992-2008) in 2051 patients with an age range of 25-74 years. The prevalence of WCHT among untreated hypertensive patients was estimated at 15%-45%, and WCHT was associated with non-smoking, female gender

and increasing age. The prevalence of partial WCHT was 58%, whereas the prevalence of true WCHT was 42%^[5].

Pickering *et al.*^[8] reported that the prevalence of WCHT was 21% in a 1988 study of 292 patients. WCHT patients tended to be female, be younger, and have a lower body weight.

PREVALENCE OF WHITE-COAT HYPERTENSION IN PATIENTS WITH CHRONIC RENAL DISEASE

The prevalence of WCHT was 15% among 355 long-term hemodialysis patients. When a pre-dialysis BP threshold of 140/90 mmHg was used to classify patients into BP categories, the prevalence of WCHT was 26%^[9].

In a study by Bangash *et al.*^[10], the prevalence of WCHT was 18.3% in 980 patients with chronic renal disease (CRD). The threshold for identifying hypertension based on clinic and ambulatory BP measurements strongly influenced the risk of being diagnosed with masked hypertension (MHT) rather than WCHT. In studies of CRD patients with overt proteinuria, the lower threshold for WCHT ($< 140/90$ mmHg) was responsible for the increased prevalence of WCHT.

PREVALENCE OF WHITE-COAT HYPERTENSION IN TYPE 2 DIABETES MELLITUS PATIENTS

In a Chinese study of 473 patients, the prevalence of WCHT was 7.36% in the overall population, 6.13% in male patients and 8.88% in female patients ($P < 0.05$). Age, etiology of type 2 diabetes mellitus (DM) and male gender were dependent factors, whereas female gender, smoking and alcohol consumption were independent risk factors for WCHT in patients with type 2 DM^[11]. These findings are in accordance with previous studies, and the characteristics of WCHT in diabetic patients are similar to those in the general population.

WHITE-COAT HYPERTENSION AND METABOLIC SYNDROME

According to the 2009 Joint Statement on Metabolic Syndrome, metabolic syndrome is defined as the presence of abnormalities in three of the following five characteristics: waist circumference, triglyceride levels, high-density lipoprotein levels, BP and fasting blood glucose^[12].

Helvaci *et al.*^[13,14] analyzed 955 patients (566 females and 389 males) and suggested that WCHT is not a predisposing factor for hypertension (HT) or atherosclerosis but rather it is an alarm signal. There was an increasing prevalence of obesity, impaired glucose tolerance (IGT) or DM, and coronary heart disease (CHD) between the WCHT and HT groups compared with the NT group. According to this study, the prevalence of dyslipidemia

was the highest in the WCHT group (41.6%, $P < 0.05$), followed by 35.5% in the SHT group and 19.6% in the NT group.

In another study by Björklund *et al.*^[15], 602 male patients aged 50 years and older who had WCHT were followed for 20 years. Their baseline body mass index (BMI) values were similar to those of the individuals in the NT group (23.0 kg/m^2 vs 23.8 kg/m^2) at age 70. However, metabolic abnormalities (insulin sensitivity, elevated blood glucose, and increased serum insulin) and elevated heart rate (HR) developed over time in patients with WCHT and SHT. A lower BMI and a more favorable dietary fat composition predicted the development of WCHT as opposed to SHT.

The PAMELA study demonstrated that patients with WCHT had similar baseline BMI values to patients with SHT ($27 \pm 4.3 \text{ kg/m}^2$ vs $27.4 \pm 5.2 \text{ kg/m}^2$) but had higher fasting glucose levels compared with NT individuals ($93.2 \pm 20.9 \text{ mg/dL}$ vs $85.5 \pm 12.5 \text{ mg/dL}$, $P < 0.05$). At the end of the 10-year follow-up period, patients in the WCHT group were more likely to develop diabetes than those in the NT group (OR = 2.9)^[16].

A study conducted in Turkey by Afsar^[17] revealed that the progression from sustained NT to SHT involves an increase in serum uric acid levels, impaired fasting glucose levels, and increases in BMI and waist circumference. The presence of metabolic syndrome was highest in people with SHT and lowest in those with sustained NT ($P < 0.0001$). This study concluded that the changes in these parameters were not as substantial in the WCHT group as they were when comparing the MHT and SHT groups to the NT group.

Several other studies have shown that the prevalence of impaired fasting glucose levels and abnormal glucose tolerance test results is higher in WCHT patients than in NT individuals. These findings suggest that WCHT is associated with glucose dysregulation and an increased risk for diabetes^[18,19].

Therefore, WCHT is an initial sign of deteriorating health. It commonly accompanies hyperlipidemia, elevated fasting glucose levels and a tendency toward being overweight.

WHITE-COAT HYPERTENSION IN ELDERLY PATIENTS

Two studies have analyzed WCHT in elderly people. In the first study, which was published by Hekman *et al.*^[20], elderly women (age range, 60-83 years; mean age, 69 ± 7 years) with WCHT had a higher SBP than NT elderly women between the hours of 8 am and 12 pm ($133 \pm 8.0 \text{ mmHg}$ vs $123 \pm 9.0 \text{ mmHg}$, $P < 0.001$). The BP variability was higher in the WCHT group only during the wakeful period (between 7 am and 11 pm, $P = 0.02$).

Age and BMI positively correlated with mean SBP at night. In the elderly women with WCHT, a higher SBP was associated with increasing age and BMI ($P = 0.015$ and $P = 0.055$, respectively). Elderly women with WCHT

were more likely to smoke ($P = 0.014$) and snore ($P = 0.046$)^[20].

In the second WCHT study on the elderly, Franklin SS. and colleagues analyzed 1168 untreated subjects with a mean age of 48.8 ± 16.6 years and with isolated systolic hypertension (ISH); 28.6% of the study participants had WCHT. The cardiovascular risk in untreated WCHT patients with ISH was similar to that in NT individuals ($P = 0.63$). Compared with the untreated NT individuals, individuals with WCHT undergoing treatment for ISH as well as treated NT individuals were at a higher cardiovascular risk ($P < 0.01$)^[21]. The results suggested that age, BMI and the need for treatment increased the cardiovascular risk in elderly patients with WCHT.

CIRCADIAN RHYTHMS IN PATIENTS WITH WHITE-COAT HYPERTENSION

BP, HR, cardiac output and serum catecholamine levels increase during the day and decrease during the night. These changes enable an organism to adapt to the need for higher activity levels while awake. The decrease in BP at night is defined as “dipping,” and patients who fail to show this pattern are called “non-dippers”^[22].

A study by Koroboki *et al.*^[22] determined that WCHT patients have the same circadian pattern as NT, MHT and untreated HT patients; however, the daytime and nighttime pulse pressures were higher in WCHT patients than in NT individuals, with nighttime pulse pressures reaching those in MHT patients. Circadian BP and HR profiles in MHT and WCHT patients have been compared with those in NT patients and in treated and untreated SHT patients using ambulatory BP measurements.

Pierdomenico *et al.*^[23] studied 12 NT, 12 WCHT and 12 SHT patients in 2000. The subjects underwent ABPM. Power spectral analyses of the R-R intervals were performed to obtain the low and high frequency components, concomitant with 24-h urine testing for epinephrine and norepinephrine. This study demonstrated that patients with WCHT and SHT have similar circadian patterns based on ABPM; however, the other findings indicated sympathetic overactivity throughout the day in SHT patients but not in WCHT patients, suggesting that the two conditions may have different pathophysiological backgrounds^[23].

Vyssoulis *et al.*^[24] classified WCHT patients according to the presence of accompanying metabolic syndrome traits and thus divided the patients into two groups based on the presence ($n = 522$) or absence ($n = 1778$) of metabolic syndrome. Patients with WCHT and a greater number of metabolic syndrome traits had non-dipping characteristics, along with elevated nighttime SBP levels that are indicative of an increased cardiovascular risk^[24].

WHITE-COAT HYPERTENSION AND TARGET ORGAN DAMAGE

In 2003, Karter *et al.*^[25] studied 50 NT, 90 WCHT and

101 SHT subjects and reported that WCHT patients had a higher BMI and a greater left ventricular mass index (LVMI) than NT individuals ($P < 0.001$). Urinary albumin excretion was similar in WCHT patients and in those with SHT. No difference in renal function between WCHT and HT patients was noted by Pierdomenico *et al.*^[26]

In the PAMELA study, Cardillo, Weber, Mancia and Mulè reported that LVMI was increased in WCHT patients compared with NT patients ($P < 0.01$), whereas Pierdomenico and Hoeghelms found no difference in LVMI^[5,26-31].

Arterial compliance was lower in WCHT patients than in the NT group in studies by Karter's ($P < 0.001$) and Gomez^[25,32]. Turfaner *et al.*^[33] analyzed 47 dipper and 43 non-dipper WCHT patients and determined, that non-dipping in WCHT patients was related to decreased arterial compliance and that the global risk load for target organ damage was higher in non-dipper WCHT subjects.

The carotid artery intimal media thickness (IMT), which is used to measure the progression of atherosclerosis in WCHT patients, has been reported to be similar in NT and WCHT individuals (see studies by Pierdomenico, Karter, Roman and Garipey^[25,34-36]).

In contrast, the HARVEST study by Puato *et al.*^[37] compared the baseline and follow-up IMT values in 35 WCHT, 20 NT and 39 SHT patients over five years. The baseline ($P = 0.004$) and follow-up ($P < 0.01$) IMT values were significantly higher and increased faster in WCHT patients than in NT controls. There was no significant difference between patients with WCHT and those with SHT ($P = 0.27$). This increase in IMT was associated with triglyceride levels, age and mean arterial pressure at ABPM, as determined by multivariate regression analysis^[37].

In a cross-sectional survey that included 2915 Japanese patients aged ≥ 40 years, the carotid IMT was significantly thicker in WCHT patients than in NT patients (0.73 mm *vs* 0.67 mm, $P = 0.001$)^[38].

WHITE-COAT HYPERTENSION AND BIOVASCULAR MARKERS

Studies on endothelial damage and angiogenesis, which indicate an increased risk for a poor prognosis in WCHT patients, have suggested that WCHT is associated with significantly higher endothelin-1 and vascular endothelial growth factor levels^[39].

There is controversy regarding the amount of Nitric Oxide (NO) in WCHT patients. Karter observed higher NO levels in WCHT patients compared with NT patients ($P < 0.001$). Karter *et al.*^[39], Pierdomenico *et al.*^[40] and Güven *et al.*^[41] showed no significant differences in NO levels in WCHT and NT patients. Pierdomenico *et al.*^[40] and Guven *et al.*^[41] demonstrated that NO levels were higher in WCHT patients than in SHT patients ($P < 0.05$). The difference was more significant in the Karter study ($P < 0.001$). In the Karter study, the threshold for clinical WCHT was defined as a DBP > 85 mmHg; in other studies, the threshold was defined as a BP $\geq 140/90$

mmHg, which may result in a difference in endothelial dysfunction parameters.

Homocysteine and asymmetric dimethylarginine levels were examined in two different studies with contradictory results. Pierdomenico found no significant differences in homocysteine levels among WCHT patients and NT patients, whereas Curgunlu *et al.*^[42,43] showed significantly higher homocysteine levels in WCHT patients ($P < 0.001$). Homocysteine levels were significantly higher in SHT patients than in WCHT patients, with P values of 0.0003 and $P < 0.001$ in the studies performed by Pierdomenico *et al.*^[44] and Curgunlu *et al.*^[42,43], respectively. Regarding inflammation, only one of three WCHT studies on C-reactive protein found a significant difference between the WCHT and NT groups^[41,45,46].

The reports on oxidative stress markers in WCHT are conflicting. Among the oxidative stress parameters, paraoxonase (PON-1) levels were significantly lower ($P < 0.001$) and malondialdehyde (MDA) levels were higher ($P < 0.026$) in WCHT patients compared with NT patients, whereas ox-LDL was not significantly different between the NT, WCHT and SHT groups^[47].

A study by Caner *et al.*^[48] on other oxidative stress parameters, such as protein carbonyl (PCO) and antioxidant capacity, showed that PCO was higher ($P < 0.001$) and that antioxidant markers (plasma thiol, plasma CuZn-SOD and erythrocyte glutathione) were lower ($P < 0.01$) in WCHT patients compared with the NT group. Plasminogen activator 1 (PAI-1) and von Willebrand factor levels were not different between the WCHT and NT groups^[45].

PROGNOSIS AND STROKE RISK IN PATIENTS WITH WHITE-COAT HYPERTENSION

Verdecchia *et al.*^[49] reported that the cumulative hazard for stroke in WCHT patients (based on ABPM) tended to increase after 6 years of follow-up and exceeded that of ambulatory hypertensive patients after 9 years of follow-up.

In Japan, 1332 subjects (872 females and 460 males, age ≥ 40 years) who were representative of the Japanese population were followed for 10 years to monitor stroke risk as part of the OHASAMA study. There was no significant difference in outcome between WCHT and NT patients (daytime BP $< 135/85$ mmHg based on ambulatory BP)^[50].

Pierdomenico *et al.*^[51] compared the cardiac and cerebrovascular risks in SHT and WCHT individuals, which were reported to be RR = 4.16, 95%CI: 1.48-11.6, $P = 0.007$, and RR = 4.12, 95%CI: 1.62-10.5, $P = 0.003$, respectively. There was no significant difference between the NT and WCHT individuals in this study, which followed 1732 subjects (1333 SHT, 399 WCHT, and 305 NT) for 6 years.

In another study, Pierdomenico *et al.*^[52] compared the cardiovascular risk in NT and WCHT patients and found no statistically significant differences, regardless of the

NT population type or the follow-up duration. They noted that the WCHT patients were more likely to be receiving drug treatment when compared with the NT patients.

The PAMELA study reported that in partial WCHT patients with either ABPM or home BP monitoring abnormalities, the incidence of fatal events was markedly increased, with a 60% higher fully adjusted risk of cardiovascular and all-cause mortality compared with NT controls; however, the risks of cardiovascular and all-cause mortality were not significantly different from those in NT subjects with true WCHT^[15,29].

TREATMENT

Subjects with WCHT frequently have dysmetabolic risk factors and asymptomatic organ damage, which increase the cardiovascular risk. In these higher-risk individuals with WCHT, drug treatment may be considered in addition to appropriate lifestyle changes. Both lifestyle changes and drug treatment may also be considered when normal ambulatory BP values are accompanied by abnormal home BP values (or vice versa) because this condition is also characterized by increased cardiovascular risk. In the absence of additional cardiovascular risk factors, intervention may be limited to lifestyle changes but should include meticulous follow-up (including periodic out-of-office BP monitoring) because the out-of-office BP is often higher in WCHT patients than in truly NT individuals, and people with WCHT have a greater risk of developing organ damage or progressing to diabetes and SHT^[11,2].

CONCLUSION

WCHT is a sign of deteriorating health. It is often accompanied by hyperlipidemia, elevated fasting glucose levels and a tendency toward being overweight. Based on the clinical and laboratory features, WCHT can be placed on a spectrum of BP disorders that extends between NT and SHT. Commonly, WCHT progresses to SHT, obesity and metabolic syndrome. In the elderly, the cardiovascular risk associated with WCHT increases with age, BMI and the need for treatment^[53].

Patients with WCHT should be assessed for the presence of target organ damage and for the development of cardiovascular risk factors. These assessments should include an oral glucose tolerance test. Patients should be educated regarding increased cardiovascular and diabetes risks, with a special emphasis on maintaining or losing weight. Patients should limit salt intake and should not consume processed food. Patients with WCHT should be monitored for conversion to SHT (ABPM every six months or yearly and/or regular home monitoring).

In the future, with the increased use of ABPM or home monitoring, patients with WCHT will be identified more often and more easily; it may become possible to protect these patients from developing target organ damage^[54].

REFERENCES

- 1 **Mancia G**, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 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 [PMID: 23817082 DOI: 10.1097/01.hjh.0000431740.32696.cc]
- 2 **James PA**, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC, Svetkey LP, Taler SJ, Townsend RR, Wright JT, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; **311**: 507-520 [PMID: 24352797 DOI: 10.1001/jama.2013.28]
- 3 **Pickering TG**, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D. Call to action on use and reimbursement for home blood pressure monitoring: a joint scientific statement from the American Heart Association, American Society Of Hypertension, and Preventive Cardiovascular Nurses Association. *Hypertension* 2008; **52**: 10-29 [PMID: 18497370 DOI: 10.1161/HYPERTENSIONAHA.107.18901]
- 4 **Bairey Merz CN**, Alberts MJ, Balady GJ, Ballantyne CM, Berra K, Black HR, Blumenthal RS, Davidson MH, Fazio SB, Ferdinand KC, Fine LJ, Fonseca V, Franklin BA, McBride PE, Mensah GA, Merli GJ, O'Gara PT, Thompson PD, Underberg JA. ACCF/AHA/ACP 2009 competence and training statement: a curriculum on prevention of cardiovascular disease: a report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Competence and Training (Writing Committee to Develop a Competence and Training Statement on Prevention of Cardiovascular Disease): developed in collaboration with the American Academy of Neurology; American Association of Cardiovascular and Pulmonary Rehabilitation; American College of Preventive Medicine; American College of Sports Medicine; American Diabetes Association; American Society of Hypertension; Association of Black Cardiologists; Centers for Disease Control and Prevention; National Heart, Lung, and Blood Institute; National Lipid Association; and Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol* 2009; **54**: 1336-1363 [PMID: 19778678 DOI: 10.1016/j.jacc.2009.05.019]
- 5 **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 [PMID: 11560854 DOI: 10.1161/hc3701.096100]
- 6 **Agarwal R**, Weir MR. Treated hypertension and the white coat phenomenon: Office readings are inadequate measures of efficacy. *J Am Soc Hypertens* 2013; **7**: 236-243 [PMID: 23523137 DOI: 10.1016/j.jash.2013.02.005]
- 7 **Hänninen MR**, Niiranen TJ, Puukka PJ, Kesäniemi YA, Kähönen M, Jula AM. Target organ damage and masked hypertension in the general population: the Finn-Home study. *J Hypertens* 2013; **31**: 1136-1143 [PMID: 23466942 DOI: 10.1097/HJH.0b013e32835fa5dc]
- 8 **Pickering TG**, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? *JAMA* 1988; **259**: 225-228 [PMID: 3336140 DOI: 10.1001/jama.1988.03720020027031]
- 9 **Agarwal R**, Sinha AD, Light RP. Toward a definition of

- masked hypertension and white-coat hypertension among hemodialysis patients. *Clin J Am Soc Nephrol* 2011; **6**: 2003-2008 [PMID: 21737856 DOI: 10.2215/cjn.02700311]
- 10 **Bangash F**, Agarwal R. Masked hypertension and white-coat hypertension in chronic kidney disease: a meta-analysis. *Clin J Am Soc Nephrol* 2009; **4**: 656-664 [PMID: 19261815 DOI: 10.2215/CJN.05391008]
 - 11 **Zhou J**, Liu C, Shan P, Zhou Y, Xu E, Ji Y. Characteristics of white coat hypertension in Chinese Han patients with type 2 diabetes mellitus. *Clin Exp Hypertens* 2014; **36**: 321-325 [PMID: 24047449 DOI: 10.3109/10641963.2013.827696]
 - 12 **Alberti KG**, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; **120**: 1640-1645 [PMID: 19805654 DOI: 10.1161/circulationaha.105.169404]
 - 13 **Helvaci MR**, Kaya H, Gundogdu M. White coat hypertension may be an initial sign of the metabolic syndrome. *Acta Med Indones* 2012; **44**: 222-227 [PMID: 22983077]
 - 14 **Helvaci MR**, Kaya H, Duru M, Yalcin A. What is the relationship between white coat hypertension and dyslipidemia? *Int Heart J* 2008; **49**: 87-93 [PMID: 18360067]
 - 15 **Björklund K**, Lind L, Vessby B, Andrén B, Lithell H. Different metabolic predictors of white-coat and sustained hypertension over a 20-year follow-up period: a population-based study of elderly men. *Circulation* 2002; **106**: 63-68 [PMID: 12093771 DOI: 10.1161/01.cir.0000019737.87850.5a]
 - 16 **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 [PMID: 19417688 DOI: 10.1097/HJH.0b013e32832832be5f9]
 - 17 **Afsar B**. Comparison of demographic, clinical, and laboratory parameters between patients with sustained normotension, white coat hypertension, masked hypertension, and sustained hypertension. *J Cardiol* 2013; **61**: 222-226 [PMID: 23294898 DOI: 10.1016/j.jcc.2012.11.003]
 - 18 **Hosaka M**, Mimura A, Asayama K, Ohkubo T, Hayashi K, Kikuya M, Sato M, Hashimoto T, Kanno A, Hara A, Obara T, Metoki H, Inoue R, Hoshi H, Satoh H, Oka Y, Imai Y. Relationship of dysregulation of glucose metabolism with white-coat hypertension: the Ohasama study. *Hypertens Res* 2010; **33**: 937-943 [PMID: 20631718 DOI: 10.1038/hr.2010.114]
 - 19 **Martin CA**, Cameron JD, Chen SS, McGrath BP. Two hour glucose post loading: a biomarker of cardiovascular risk in isolated clinic hypertension. *J Hypertens* 2011; **29**: 749-757 [PMID: 21192271 DOI: 10.1097/HJH.0b013e328342eeeb]
 - 20 **Hekman PR**, Barbisan JN, Menezes HS, Antonello V. [24-hour blood pressure in normotensive elderly women and elderly women with white-coat hypertension]. *Arq Bras Cardiol* 2010; **94**: 431-437 [PMID: 20339820 DOI: 10.1590/S0066-782X2010005000010]
 - 21 **Franklin SS**, Thijs L, Hansen TW, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K, Ohkubo T, Jeppesen J, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Imai Y, Wang J, Ibsen H, O'Brien E, Staessen JA. 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 [PMID: 22252396 DOI: 10.1161/hypertensionaha.111.180653]
 - 22 **Koroboki E**, Manios E, Psaltopoulou T, Vemmos K, Michas F, Alexaki E, Zakopoulos N. Circadian variation of blood pressure and heart rate in normotensives, white-coat, masked, treated and untreated hypertensives. *Hellenic J Cardiol* 2012; **53**: 432-438 [PMID: 23178426]
 - 23 **Pierdomenico SD**, Bucci A, Costantini F, Lapenna D, Cuccurullo F, Mezzetti A. Twenty-four-hour autonomic nervous function in sustained and "white coat" hypertension. *Am Heart J* 2000; **140**: 672-677 [PMID: 11011344 DOI: 10.1067/mhj.2000.109643]
 - 24 **Vyssoulis G**, Karpanou E, Adamopoulos D, Kyvelou SM, Gymnopoulou E, Cokkinos D, Stefanadis C. Nocturnal blood pressure fall and metabolic syndrome score in patients with white coat hypertension. *Blood Press Monit* 2008; **13**: 251-256 [PMID: 18799949 DOI: 10.1097/MBF.0b013e32830719c0]
 - 25 **Karter Y**, Curgunlu A, Altinşik S, Ertürk N, Vehid S, Mihmanli I, Ayan F, Kutlu A, Arat A, Oztürk E, Erdine S. Target organ damage and changes in arterial compliance in white coat hypertension. Is white coat innocent? *Blood Press* 2003; **12**: 307-313 [PMID: 14763662 DOI: 10.1080/08037050310021406]
 - 26 **Pierdomenico SD**, Lapenna D, Bucci A, Di Iorio A, Neri M, Cuccurullo F, Mezzetti A. Cardiovascular and renal events in uncomplicated mild hypertensive patients with sustained and white coat hypertension. *Am J Hypertens* 2004; **17**: 876-881 [PMID: 15485748 DOI: 10.1016/j.amjhyper.2004.05.014]
 - 27 **Cardillo C**, De Felice F, Campia U, Folli G. Psychophysiological reactivity and cardiac end-organ changes in white coat hypertension. *Hypertension* 1993; **21**: 836-844 [PMID: 8500864 DOI: 10.1161/01.hyp.21.6.836]
 - 28 **Weber MA**, Neutel JM, Smith DH, Graettinger WF. Diagnosis of mild hypertension by ambulatory blood pressure monitoring. *Circulation* 1994; **90**: 2291-2298 [PMID: 7955186 DOI: 10.1161/01.cir.90.5.2291]
 - 29 **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 [PMID: 23716584 DOI: 10.1161/hypertensionaha.111.00690]
 - 30 **Mulè G**, Nardi E, Cottone S, Cusimano P, Incalcaterra F, Palermo A, Giandalia M, Geraci C, Buscemi S, Cerasola G. Metabolic syndrome in subjects with white-coat hypertension: impact on left ventricular structure and function. *J Hum Hypertens* 2007; **21**: 854-860 [PMID: 17541385 DOI: 10.1038/sj.jhh.1002238]
 - 31 **Høegholm A**, Kristensen KS, Bang LE, Nielsen JW, Nielsen WB, Madsen NH. Left ventricular mass and geometry in patients with established hypertension and white coat hypertension. *Am J Hypertens* 1993; **6**: 282-286 [PMID: 8507447 DOI: 10.1093/ajh/6.4.282]
 - 32 **Gómez-Cerezo J**, Ríos Blanco JJ, Suárez García I, Moreno Anaya P, García Raya P, Vázquez-Muñoz E, Barbado Hernández FJ. Noninvasive study of endothelial function in white coat hypertension. *Hypertension* 2002; **40**: 304-309 [PMID: 12215471 DOI: 10.1161/01.hyp.0000030198.48441.65]
 - 33 **Turfaner N**, Karter Y, Curgunlu A, Ayan F, Mihmanli I, Sipahioglu F. Blunted nocturnal fall of blood pressure in isolated clinical hypertension. *Swiss Med Wkly* 2009; **139**: 251-255 [PMID: 19330562]
 - 34 **Pierdomenico SD**, Lapenna D, Guglielmi MD, Antidormi T, Schiavone C, Cuccurullo F, Mezzetti A. Target organ status and serum lipids in patients with white coat hypertension. *Hypertension* 1995; **26**: 801-807 [PMID: 7591021 DOI: 10.1161/01.HYP.26.5.801]
 - 35 **Roman MJ**, Saba PS, Pini R, Spitzer M, Pickering TG, Rosen S, Alderman MH, Devereux RB. Parallel cardiac and vascular adaptation in hypertension. *Circulation* 1992; **86**: 1909-1918 [PMID: 1451262 DOI: 10.1161/01.CIR.86.6.1909]
 - 36 **Garipey J**, Massonneau M, Levenson J, Heudes D, Simon A. Evidence for in vivo carotid and femoral wall thickening in human hypertension. Groupe de Prévention Cardio-vascu-

- laire en Médecine du Travail. *Hypertension* 1993; **22**: 111-118 [PMID: 8319987 DOI: 10.1161/01.hyp.22.1.111]
- 37 **Puato M**, Palatini P, Zanardo M, Dorigatti F, Tirrito C, Rattazzi M, Pauletto P. Increase in carotid intima-media thickness in grade I hypertensive subjects: white-coat versus sustained hypertension. *Hypertension* 2008; **51**: 1300-1305 [PMID: 18378860 DOI: 10.1161/hypertensionaha.107.106773]
- 38 **Fukuhara M**, Arima H, Ninomiya T, Hata J, Hirakawa Y, Doi Y, Yonemoto K, Mukai N, Nagata M, Ikeda F, Matsumura K, Kitazono T, Kiyohara Y. White-coat and masked hypertension are associated with carotid atherosclerosis in a general population: the Hisayama study. *Stroke* 2013; **44**: 1512-1517 [PMID: 23640825 DOI: 10.1161/STROKEAHA/111000704]
- 39 **Karter Y**, Aydin S, Curgunlu A, Uzun H, Ertürk N, Vehid S, Kutlu A, Simsek G, Yücel R, Arat A, Ozturk E, Erdine S. Endothelium and angiogenesis in white coat hypertension. *J Hum Hypertens* 2004; **18**: 809-814 [PMID: 15215878 DOI: 10.1038/sj.jhh.1001752]
- 40 **Pierdomenico SD**, Cipollone F, Lapenna D, Bucci A, Cucurullo F, Mezzetti A. Endothelial function in sustained and white coat hypertension. *Am J Hypertens* 2002; **15**: 946-952 [PMID: 12441213 DOI: 10.1016/S0895-7061(02)02993]
- 41 **Güven A**, Tolun F, Caliskan M, Ciftci O, Muderrisoglu H. C-reactive protein and nitric oxide level in patients with white coat hypertension. *Blood Press* 2012; **21**: 281-285 [PMID: 22229480 DOI: 10.3109/08037051.2011.649541]
- 42 **Curgunlu A**, Karter Y, Uzun H, Aydin S, Ertürk N, Vehid S, Simsek G, Kutlu A, Oztürk E, Erdine S. Hyperhomocysteinemia: an additional risk factor in white coat hypertension. *Int Heart J* 2005; **46**: 245-254 [PMID: 15876808 DOI: 10.1536/ihj.46.245]
- 43 **Curgunlu A**, Uzun H, Bavunoğlu I, Karter Y, Genç H, Vehid S. Increased circulating concentrations of asymmetric dimethylarginine (ADMA) in white coat hypertension. *J Hum Hypertens* 2005; **19**: 629-633 [PMID: 15829997 DOI: 10.1038/sj.jhh.1001867]
- 44 **Pierdomenico SD**, Bucci A, Lapenna D, Lattanzio FM, Talone L, Cucurullo F, Mezzetti A. Circulating homocysteine levels in sustained and white coat hypertension. *J Hum Hypertens* 2003; **17**: 165-170 [PMID: 12624606 DOI: 10.1038/sj.jhh.1001524]
- 45 **Martin C**, Cameron J, McGrath B. Mechanical and circulating biomarkers in isolated clinic hypertension. *Clin Exp Pharmacol Physiol* 2008; **35**: 402-408 [PMID: 18307729 DOI: 10.1111/j.1440-1681.2008.04886.x]
- 46 **Kamel N**, Gursoy A, Koseoglulari O, Dincer I, Gullu S. Isolated office hypertension: association with target organ damage and cardiovascular risk indices. *J Natl Med Assoc* 2006; **98**: 601-606 [PMID: 16623073]
- 47 **Uzun H**, Karter Y, Aydin S, Curgunlu A, Simsek G, Yücel R, Vehid S, Ertürk N, Kutlu A, Benian A, Yaldiran A, Oztürk E, Erdine S. Oxidative stress in white coat hypertension; role of paraoxonase. *J Hum Hypertens* 2004; **18**: 523-528 [PMID: 14985779 DOI: 10.1038/sj.jhh.1001697]
- 48 **Caner M**, Karter Y, Uzun H, Curgunlu A, Vehid S, Balci H, Yücel R, Güner I, Kutlu A, Yaldiran A, Oztürk E. Oxidative stress in human in sustained and white coat hypertension. *Int J Clin Pract* 2006; **60**: 1565-1571 [PMID: 17109665 DOI: 10.1111/j.1742-1241.2006.00959.x]
- 49 **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 [PMID: 15596572 DOI: 10.1161/01.hyp.0000151623.49780.89]
- 50 **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 [PMID: 16009871 DOI: 10.1001/archinte.165.13.1541]
- 51 **Pierdomenico SD**, Lapenna D, Di Mascio R, Cucurullo F. Short- and long-term risk of cardiovascular events in white-coat hypertension. *J Hum Hypertens* 2008; **22**: 408-414 [PMID: 18288127 DOI: 10.1038/jhh.2008.6]
- 52 **Pierdomenico SD**, Cucurullo 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 [PMID: 20847724 DOI: 10.1038/ajh.2010.203]
- 53 **Verdecchia P**, Angeli F, Gattobigio R, Borgioni C, Castellani C, Sardone M, Reboldi G. The clinical significance of white-coat and masked hypertension. *Blood Press Monit* 2007; **12**: 387-389 [PMID: 18277317 DOI: 10.1097/MBP.0b013e32824958e5]
- 54 **Martin CA**, McGrath BP. White-coat hypertension. *Clin Exp Pharmacol Physiol* 2014; **41**: 22-29 [PMID: 23682974 DOI: 10.1111/1440-1681.12114]

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