

Should Out-of-Office Monitoring Be Performed for Detecting White Coat Hypertension?

The only certainty is that nothing is certain.
—Pliny the Elder, book II, section 7, *Natural History*

Office blood pressure (BP) measurements have been the primary method for identifying persons with hypertension and monitoring their response to antihypertensive medication. Blood pressure measured in the office setting may differ substantially from BP measured outside of it, and several studies have demonstrated that out-of-office BP measured by ambulatory and home BP monitoring has a stronger association with a person's risk for cardiovascular disease (CVD) events than office BP measurement (1).

Four phenotypes have been defined by cross-classifying office BP and out-of-office BP. Two phenotypes, sustained normotension and sustained hypertension, are defined by agreement between office BP and out-of-office BP levels with both sets of readings being not high for sustained normotension and high for sustained hypertension. The 2 other phenotypes are defined by a mismatch between office and out-of-office BP. White coat hypertension (WCH) is defined as office BP that is high and out-of-office BP that is not high, whereas masked hypertension is defined as office BP that is not high and out-of-office BP that is high. The term *WCH* is applied to persons not taking antihypertensive medication. For those taking antihypertensive drugs, the term *treated WCH* or *white coat effect (WCE)* is used. In several early studies, WCH and WCE were not associated with an increased risk for CVD events compared with sustained normotension (2, 3). The 2011 U.K. National Institute of Health and Clinical Excellence guideline (4) and the 2015 U.S. Preventive Services Task Force guideline (5) both recommended out-of-office BP monitoring to confirm that WCH is not present before initiating antihypertensive medication for patients with high office BP. More recent hypertension guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) in 2017 and European Society of Cardiology and European Society of Hypertension in 2018 recommend out-of-office BP monitoring to screen for WCH and WCE (1, 6).

The systematic review and meta-analysis from Cohen and colleagues (7) examines the associations of WCH and WCE with CVD events and mortality. The authors identified 27 observational studies that followed 25 786 participants with either WCH or WCE and 38 487 with sustained normotension for nonfatal and fatal CVD events and all-cause mortality. Compared with sustained normotension, WCH was associated with a moderately increased risk for CVD events (hazard ratio [HR], 1.36 [95% CI, 1.03 to 2.00]) and all-cause mortality (HR, 1.33 [CI, 1.07 to 1.67]). In contrast, WCE was not asso-

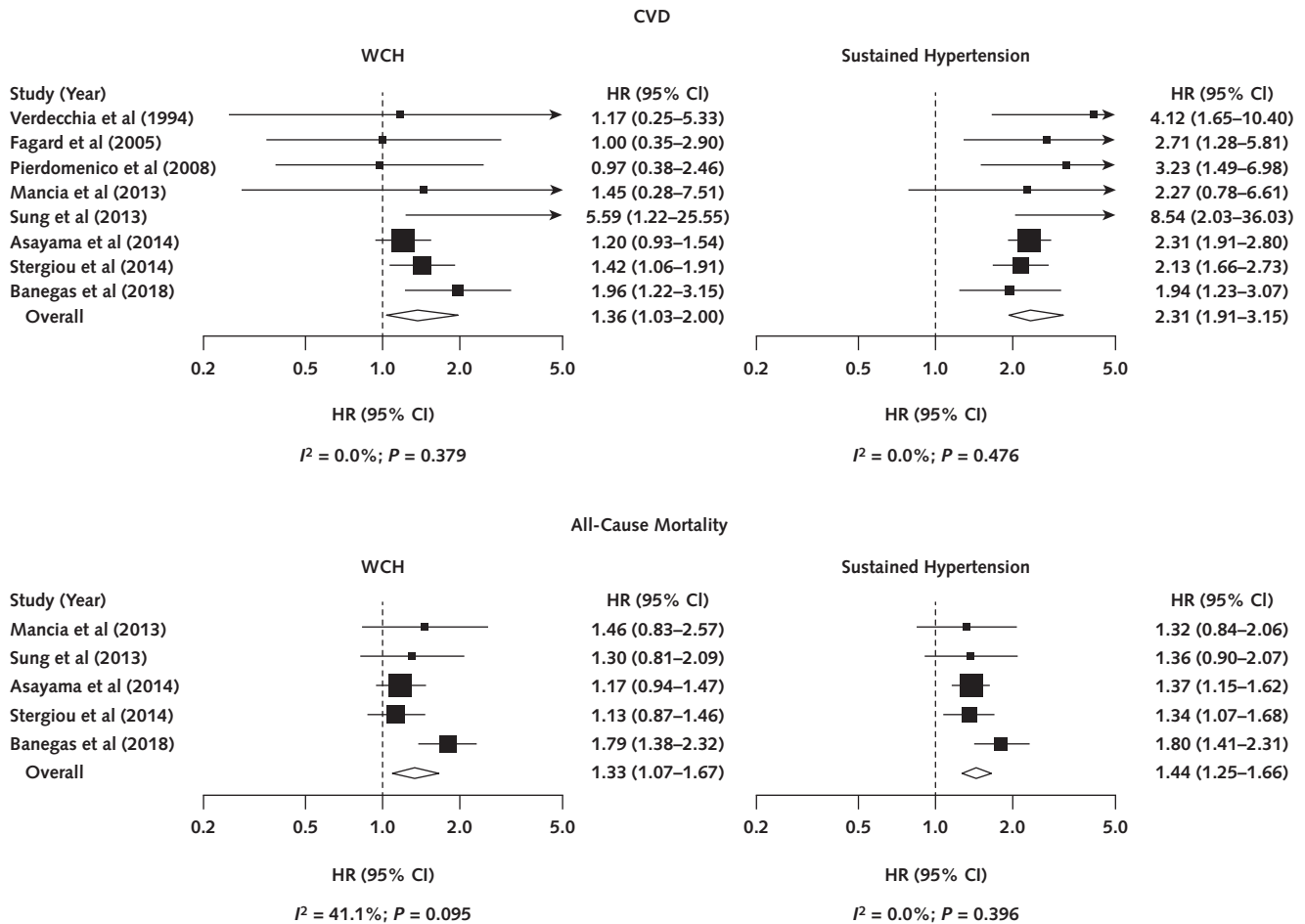
ciated with CVD events or all-cause mortality. The meta-analysis has several strengths: The literature search was comprehensive and included several recently published studies, it included only studies that adjusted for potential confounders, and analyses were performed demonstrating that the results were not highly influenced by any one study.

Several sensitivity analyses were conducted to determine whether the results were consistent across different study design elements and study populations. Although the results were consistent in most subgroup analyses, the association between WCH and CVD risk was present only in studies in which the mean age of participants was at least 55 years and in those that included persons with a history of CVD or persons with chronic kidney disease or diabetes. Therefore, the increased CVD risk associated with WCH may be present only among older persons who have high CVD risk. This finding is consistent with a previous analysis of the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome and suggests that WCH may be benign in persons with a lower CVD risk (8).

Although the study by Cohen and associates (7) provides informative data about WCH and WCE, knowledge gaps remain. The results may have been affected by residual confounding, because the studies typically did not adjust for out-of-office BP. In previous studies, out-of-office BP was higher among participants with WCH than in their counterparts with sustained normotension, which may partially explain the increased CVD risk associated with WCH (9). Only 2 studies in the meta-analysis were conducted in the United States, and the applicability of these findings to non-Hispanic black and Hispanic adults in the United States is unknown. Despite the strong association between office and out-of-office BP and stroke, WCH was not associated with this outcome. This unexpected finding may benefit from further investigation. Whether WCH—when defined by using the BP thresholds recommended in the 2017 ACC/AHA BP guideline (1): office BP of 130/80 mm Hg or greater and daytime BP less than 130/80 mm Hg—is associated with an increased risk for CVD events or all-cause mortality is unknown.

To provide a context for the excess CVD and all-cause mortality risk associated with WCH, we abstracted and pooled the HRs associated with sustained hypertension from the studies included in Cohen and colleagues' meta-analysis (Figure). Consistent with previous meta-analyses (10), sustained hypertension was associated with a substantially higher HR of CVD events and mortality than either sustained normotension or WCH.

Figure. Hazard ratios for CVD events and all-cause mortality associated with WCH and sustained hypertension versus sustained normotension.



Data were extracted from the same articles used in the meta-analysis by Cohen and colleagues (7). Hazard ratios and 95% CIs for CVD and all-cause mortality associated with sustained hypertension vs. sustained normotension from the articles by Fagard et al and Mancia et al were obtained by personal communication with the authors. Hazard ratios and 95% CIs for CVD events associated with sustained hypertension vs. sustained normotension for the article by Verdecchia et al were determined by pooling published results and a simulation analysis. The results for sustained hypertension from the article by Sung et al compare sustained hypertension and masked hypertension, pooled together, vs. sustained normotension. Solid squares are the point estimates of HR for each study. The open diamond shapes include the pooled HR (the top and bottom points of the diamond); the left and right points of each diamond form the 95% CI of the pooled HR. CVD = cardiovascular disease; HR = hazard ratio; WCH = white coat hypertension.

An important consideration is the impact of Cohen and colleagues' meta-analysis on recent U.S. and European hypertension guideline recommendations for out-of-office BP monitoring for patients with high office BP (1, 6). For adults taking antihypertensive medication, the results are clear. White coat effect is not associated with increased risk, and out-of-office monitoring seems warranted to prevent intensification of antihypertensive treatment. For adults not taking antihypertensive medication, the risk for CVD events and all-cause mortality is only moderately increased, and this risk is substantially lower than that associated with sustained hypertension. Therefore, out-of-office BP monitoring is useful for distinguishing between WCH and sustained hypertension among persons with high office BP. Overall, the meta-analysis by Cohen and colleagues makes an important contribution and provides contemporary data

supporting recent U.S. and European guidelines that recommend out-of-office BP monitoring to screen for WCH and WCE.

Daichi Shimbo, MD
Columbia University Medical Center
New York, New York

Paul Muntner, PhD
University of Alabama at Birmingham
Birmingham, Alabama

Disclaimer: The National Institutes of Health (NIH) had no role in the design of the study; the collection, analysis, and interpretation of the data; or the decision to approve publication of the finished manuscript.

Grant Support: By NIH grants R01 HL136445, R01 HL139716, R01 HL047540, and K24 HL125704 from the National Heart, Lung, and Blood Institute.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-1134.

Corresponding Author: Daichi Shimbo, MD, Columbia University Medical Center, 622 West 168th Street, PH 9-310, New York, NY 10032; e-mail, ds2231@cumc.columbia.edu.

Current author addresses are available at Annals.org.

Ann Intern Med. doi:10.7326/M19-1134

References

- Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol.* 2018;71:e127-e248. [PMID: 29146535] doi:10.1016/j.jacc.2017.11.006
- Fagard RH, Van Den Broeke C, De Cort P. Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. *J Hum Hypertens.* 2005;19:801-7. [PMID: 15959536]
- Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension.* 1994;24:793-801. [PMID: 7995639]
- Krause T, Lovibond K, Caulfield M, McCormack T, Williams B; Guideline Development Group. Management of hypertension: summary of NICE guidance. *BMJ.* 2011;343:d4891. [PMID: 21868454] doi:10.1136/bmj.d4891
- Siu AL; U.S. Preventive Services Task Force. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2015;163:778-86. [PMID: 26458123] doi:10.7326/M15-2223
- Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J.* 2018;39:3021-104. [PMID: 30165516] doi:10.1093/eurheartj/ehy339
- Cohen JB, Lotito MJ, Trivedi UK, Denker MG, Cohen DL, Townsend RR. Cardiovascular events and mortality in white coat hypertension. A systematic review and meta-analysis. *Ann Intern Med.* 2019. [Epub ahead of print]. doi:10.7326/M19-0223
- Franklin SS, Thijs L, Asayama K, Li Y, Hansen TW, Boggia J, et al; IDACO Investigators. The cardiovascular risk of white-coat hypertension. *J Am Coll Cardiol.* 2016;68:2033-43. [PMID: 27810041] doi:10.1016/j.jacc.2016.08.035
- 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;47:846-53. [PMID: 16567588]
- Stergiou GS, Asayama K, Thijs L, Kollias A, Niiranen TJ, Hozawa A, et al; International Database on HOME blood pressure in relation to Cardiovascular Outcome (IDHOCO) Investigators. Prognosis of white-coat and masked hypertension: International Database of HOME blood pressure in relation to Cardiovascular Outcome. *Hypertension.* 2014;63:675-82. [PMID: 24420553] doi:10.1161/HYPERTENSIONAHA.113.02741

Current Author Addresses: Dr. Shimbo: Columbia University Medical Center, 622 West 168th Street, PH 9-310, New York, NY 10032.

Dr. Muntner: University of Alabama at Birmingham, Department of Epidemiology, 1665 University Boulevard, Suite 230J, Birmingham, AL 35294.