White-Coat Hypertension Should Not Be Treated in Subjects With Diabetes

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Blood pressure (BP) levels in the doctor's clinic may not always reflect those of daily living, as indicated by 24-h ambulatory or self-monitoring measurements. Simple logic implies that treatment should be guided by the actual BP levels, rather than by imprecise clinic measurements. On average, BP measured in the clinic is higher than out-of-office BP. This difference occurs in a considerable number of patients with white-coat hypertension (WCH). The issue is complicated, since most studies define WCH as an elevated office BP in patients with normal *awake* ambulatory BP. However, the "awake" state may not fully reflect the 24-h BP load. Average 24-h BP, and particularly that during sleep, which is more likely to be higher in subjects with diabetes (1,2), could be elevated in a patient with normal awake BP. The presence of abnormal clinic BP in such a patient discloses true hypertension rather than WCH. Indeed, among 4,121 subjects referred for ambulatory BP monitoring, 4.5% had isolated abnormal sleep BP (>120/70 mmHg) and normal 24-h BP (3). Nevertheless, in this presentation, we assume that the common definition of WCH is elevated clinic readings with normal awake BP.

Assessment of WCH in diabetes is complicated by the fact that normal BP measured at the clinic is defined as <130/80 mmHg (as opposed to 140/90 mmHg in the general population), whereas there are still no accepted thresholds for ambulatory or home-based BP levels.

Characteristics unique to the white-coat response in patients with diabetes, associated prognostic implications, and the need for treatment are discussed.

PREVALENCE OF WCH IN DIABETES

— The issue of prevalence is not marginal: we have found that compared with subjects without diabetes who were referred for 24-h ambulatory BP monitoring, those treated for diabetes were less likely to have WCH (and more likely to have masked hypertension) (1). A similar conclusion was arrived at in a recent Brazilian study where masked hypertension was not only more prevalent (4), but also associated with a higher rate of target organ damage (5).

Among a cohort of 3,995 patients referred to our department for ambulatory BP monitoring, 343 were being medically treated for diabetes. They were older, more obese, and had higher BP, both in the clinic and by ambulatory monitoring, despite the increased likelihood of being treated with medications (1). WCH was defined as awake BP below 135/85 mmHg in the presence of elevated clinic BP. Its prevalence was marginally lower among the subjects with diabetes: 8.5 versus 11.4% among those without diabetes (odds radio [OR] 0.72 [95% CI 0.48–1.06]). For comparison, the OR for normal awake systolic BP among subjects with diabetes (regardless of clinic BP) was lower (0.43 [0.32–0.56]).

Lower prevalence of WCH was also found in a massive multicenter study in Spain, comprising 12,895 treated hypertensive patients, of whom 2,772 had type 2 diabetes. This study had a greater number of subjects and comprised more patients diagnosed with type 2 diabetes than any other, including most combined studies (6). Lower prevalence of WCH among patients with diabetes (0.58 [0.41–0.83]) was also found in a reanalysis of the data in a recent study from Japan, where 301 of 1,267 subjects had diabetes (2). Conversely, the prevalence of WCH was similar among patients with diabetes and normotensive subjects in a population-based study from Japan, where WCH was diagnosed by home-based BP measurements (7).

Overall, it appears that, in type 2 diabetes, the caveat for diagnosis of hypertension may fail to detect masked hypertension (1), rather than failing to notice WCH. White-coat response to measurement of BP by a physician is accompanied by tachycardia and most likely reflects a sympathetic reaction (8), as recently confirmed (9–11). Lower prevalence of WCH in subjects with type 2 diabetes may be explained by the presence of autonomic neuropathy and thus lower reactivity to clinic stress.

Thus, it appears that when subjects with type 2 diabetes—the "prototype" of high-risk subjects—have a normal BP recorded at the clinic, they are more likely to have home-based, or ambulatory, hypertension. Indeed, white-coat and masked hypertension may, in part, reflect "regression toward the mean," depending on whether high (WCH) or low (masked hypertension) levels are recorded at the clinic (12).

PROGNOSIS OF WCH IN DIABETES

— Results of studies on the prognosis of WCH are somewhat controversial (9,13–20). Although most studies find it to be benign (18), this is not a universal finding (9,13–17). The results of several studies demonstrated that subjects with WCH have similar characteristics to those of hypertensive patients, including age, BMI, and metabolic and sympathetic abnormalities, compared with normotensive patients (9,10,14–16). This, in part, could be explained by WCH subjects who have a higher (yet normal) ambulatory BP than normotensive patients. An example could be the

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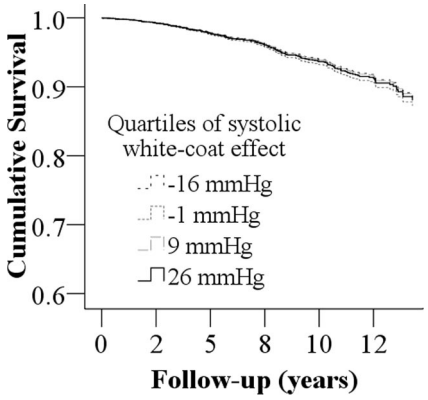

Figure 1—*Survival of patients referred for 24-h ambulatory BP monitoring according to quartiles of the white-coat effect (clinic-awake systolic BP difference) by a Cox proportional hazards model that is adjusted for age, sex, BMI, awake systolic BP, and treatment for hypertension* (P = *0.86*).

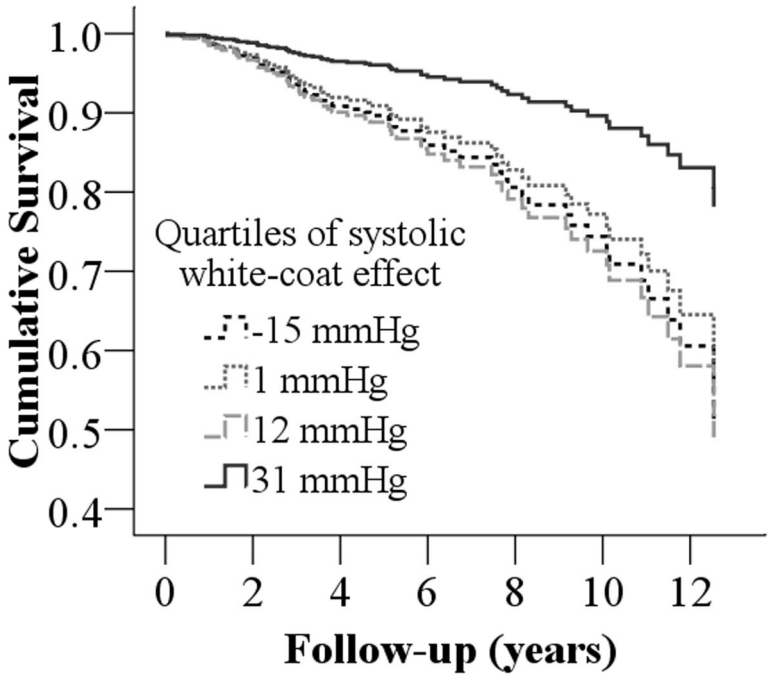

Figure 2—*Survival of patients treated for diabetes who were referred for 24-h ambulatory BP monitoring, according to quartiles of the white-coat effect (clinic-awake systolic BP difference) by a Cox proportional hazards model that is adjusted for age, sex, BMI, awake systolic BP, and treatment for hypertension* (P < *0.04*).

population-based PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) study, where higher ambulatory BP was associated with such abnormalities, as well as with a higher prevalence of diabetes (21). Similar findings appeared in studies of subjects with type 2 diabetes (4,22–24). Even slight BP elevation in high-risk subjects (those with diabetes) may have prognostic implications. Patients with WCH among 2,285 subjects treated for hypertension and referred for 24-h ambulatory BP monitoring at our service had significantly elevated ambulatory BP (although in the normal range), relative to those with controlled BP (20). Accordingly, survival was associated with ambulatory and not manual BP, even after consideration of confounders including diabetes (20). Similar findings were presented in another study (19) and in a recent meta-analysis (18).

The 343 diabetic patients from our cohort of patients referred for ambulatory BP monitoring were older, more obese, and had higher BP both in the clinic and with ambulatory monitoring, despite their greater likelihood of being treated with medications (1). Not surprisingly, their demise was also more likely to occur during follow-up of up to 14 years: their mortality amounted to 27.9/1,000 patient-years, whereas that of subjects without diabetes was almost one-third, at 9.8/1,000 patient-years ($P < 0.0001$). When we analyzed survival of patients referred for ambulatory BP measurements by a Cox proportional hazard model (after adjustment for age, sex, BMI, awake systolic BP, and treatment for hypertension), there was no influence by quartiles of the white-coat effect in subjects without diabetes (Fig. 1). However, a similar analysis in individuals with diabetes found a significant ($P < 0.05$) interaction with systolic white-coat effect quartiles and a substantially improved survival rate in patients with diabetes in the highest systolic white-coat quartile (Fig. 2). Furthermore, in an analysis of the white-coat effect as a continuous variable, with adjustments as above, an increase of 1 SD of the systolic white-coat effect was associated with a significant reduction in the hazard ratio for mortality only in subjects with diabetes (Fig. 3). The conclusion from these results is that taking into account confounding variables (older age, higher BMI, higher ambulatory BP, and their greater propensity to be medically treated for hypertension), diabetic patients with white-coat BP elevation tend to have improved survival. This conclusion is also supported by the findings in Japanese patients with diabetes, where cardiovascular complications were significantly less common in WCH (25).

PERSPECTIVE OF ANTIHYPERTENSIVE THERAPY FOR OFFICE-MEASURED BP IN SUBJECTS WITH DIABETES AND WCH

— Treatment of WCH in general is not believed to be beneficial (9,26–28). Decades ago, it was shown that casual BP, comprising a supplemental component that is rather similar to the

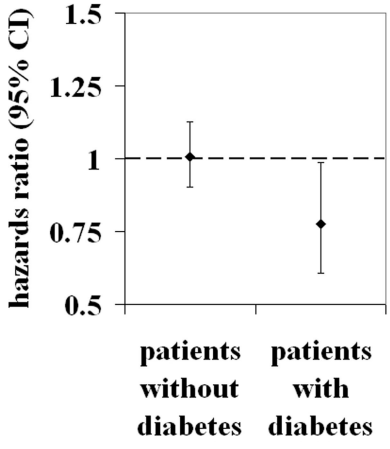

Figure 3—*Mortality hazard ratios associated with 1-SD increase in the white-coat effect (clinic-awake systolic BP difference) adjusted for age, sex, BMI, awake systolic BP, and treatment for hypertension* (P < *0.05*).

white-coat effect (29), does not affect prognosis, whereas basal relaxed BP (similar to sleep BP) soundly predicts outcome (30).

Moreover, treating WCH may produce excessive lowering of the ambulatory BP (28). In the INternational VErapamil SR-trandolapril STudy (INVEST) of 22,576 hypertensive coronary patients, it was found that lowering diastolic BP to <83 mmHg was associated with excess mortality and coronary events. One-third of subjects with clinic systolic BP >140 mmHg (some of whom probably had WCH), and one-third of those with diastolic BP <80 mmHg (prone to consequences of such excessive reduction), had type 2 diabetes (31). Thus, recommendation for treatment of WCH may come at a price of harming patients with diabetes and coronary disease, a common comorbidity, especially among the older group that comprises a substantial section of subjects with type 2 diabetes.

Taking all the aforementioned into consideration, it is unjustified, or at least premature, to treat WCH in diabetes with antihypertensive therapy. Defining diabetes-specific normal ambulatory BP thresholds will facilitate management of the problem in clinical practice.

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