EDITORIAL COMMENT

The Heterogeneous Nature of White-Coat Hypertension*



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ince its identification in the early 1980s (1), white-coat hypertension (WCH) has largely been regarded as a clinically innocent phenomenon, (i.e., a condition for which the normality of blood pressure [BP] in daily life makes its prognostic value similar to normotension) (2). Some dissenting views have also been expressed, however, because, compared with normotensives, WCH patients exhibit a greater prevalence of dysmetabolic risk factors, as well as of cardiac, vascular, and other types of organ damage (3). Furthermore, although confined by definition to the normal range, both ambulatory and home BP are several mm Hg higher in WCH than in normotensive subjects (3). Finally, although in most longitudinal studies the cardiovascular (CV) risk of WCH and normotension has not exhibited a significant difference (4), in a few cases, an elevation of conventional, but not of home or ambulatory, BP has been associated with a CV morbidity and mortality that is less than that seen in "true" hypertension (BP elevation in and out of the doctor's office), but distinctly greater than that of "true" normotensive subjects (3,5).

Reconciling the discrepant views of the prognostic significance of WCH will require studies that avoid a main problem of previous investigations, that is, the limited number of events (and thus, the insufficient statistical power) obtained in the subjects under observation, even when extended to follow-ups of >10 years. In the meantime, however, attention has

shifted toward the possibility that, in WCH, subjects at normal risk coexist with those at an increased CV risk, in the belief that the identification of high-risk WCH subgroups may help, perhaps more than establishing the CV risk of the WCH population as a whole, in proper management of this condition in medical practice. The paper by Franklin at al. (6) published in this issue of the Journal offers a contribution in this direction. The investigators have used the large database provided by the 11 population cohorts of the IDACO (International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes) collaboration, from which they extracted 653 untreated subjects with WCH (conventional, but not daytime ambulatory BP elevation) who were compared with 653 normotensive subjects to whom they were matched for several variables.

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The results showed that, over a 10.6-year follow-up, subjects with 0 to 2 CV risk factors exhibited a risk of CV outcomes that did not significantly differ between WCH and normotensive subjects. By contrast, in patients with \geq 3 risk factors, diabetes, or a history of CV events, WCH was associated with a CV risk that exceeded (106% risk increase; 95% confidence interval: 10% to 184%; p = 0.023) that of normotensive comparators. Interestingly, this appeared to be the case only when a high CV risk was associated with advanced age because in high-risk subjects ≥ 60 years of age, WCH elevated the CV risk by 109% (p = 0.027), whereas it did not make the patients' prognosis worse than that of normotensive subjects in younger high-risk subjects. Thus, within the large number of subjects affected by WCH (up to 30% to 40% of the hypertensive population) (7), elderly subjects with a high background CV risk may require special attention because, in this subgroup, a selective elevation of conventional BP may have a further

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adverse impact on their well-being and survival. Special attention may mean a more in-depth assessment of their organ damage, more frequent visits during the follow-up, and more rigorous control of risk factors. It may, perhaps, also mean a conventional BP reduction by treatment, although unfortunately, no evidence is so far available that conventional BP reduction has a protective effect in WCH (8).

One of the merits of the analysis of the IDACO database made by Franklin et al. (6) is that WCH and normotensive subjects were matched for age and CV risk level, a procedure that, as emphasized by the investigators, is superior to the adjusting approach used to neutralize the confounding effect of the multiple WCH/normotension differences adopted in previous studies. There are, however, also limitations that introduce some elements of weakness to the study. First, due to its origin from many population cohorts, the database appears to have a pronounced heterogeneity, as exemplified by the huge between-cohort differences in WCH prevalence, from 3% to 38%. Second, patients were accepted for analysis if at least 10 BP values were available during the daytime, a number of measurements so low as to leave BP potentially undetected for several hours. Third, although the original database was large, the number of WCH patients suitable for analysis was small, and so was the number of events. Predictably, this was particularly the case for the younger subgroup of patients, in which the availability of only 12 CV events make the lack of prognostic difference between WCH and normotension of uncertain significance. This is pertinent to one of the conclusions of the study, that the adverse prognostic significance of WCH is limited to the elderly high-risk subgroup, which the authors calculate to be no more than 14% of the overall WCH population. As mentioned previously, the extremely small number of events did not allow proper analysis of the CV risk in the younger population strata. We are also not sure that elderly subjects with a high CV risk are so few. An advanced age can lead to a high CV risk condition almost "per se," that is, without the contribution of ≥ 3 risk factors, diabetes, or previous CV events. Furthermore, in the elderly, there is a high prevalence of subclinical organ damage (not reported and perhaps not available in the IDACO database), which is associated with high CV risk (7,9). Within the WCH population, subgroups and patients with a higher CV risk than that of normotension may thus be more common than was calculated in the present study. This would be in line with previous data from the

PAMELA (Pressioni Arteriose Monitorate e Loro Associazioni) population and even the IDACO database, which reported a higher CV risk to characterize WCH with a stable conventional BP elevation (10), discrepant ambulatory and home BP values (11), or a selective systolic BP increase (12).

A final contribution of the study by Franklin et al. (6) is the description of the factors related to the WC effect, namely, the difference between conventional and daytime BP, which, in agreement with previous investigations (13,14), is found to be closely associated with increasing age and has no relationship with CV risk. Franklin et al. (6), however, also discuss the nature of the white-coat effect, which they ascribe to the alerting response of the patient to the doctor's visit, thus primarily involving sympathetic activation, possibly without a proper counteracting influence of the baroreflex. This may well be the case, but several considerations cast some doubts on the CV effect of stress as the only explanation for the difference between conventional and ambulatory BP. For example, the alerting reaction to the physician's visit includes a pronounced tachycardia (15), which is at odds with the observation that office and daytime heart rate values do not normally show any substantial difference (13). Furthermore, the alerting reaction-based explanation of the difference between office and daytime BP means that as the patient's age advances, so does the patient's reactivity to the doctor's visit. But direct quantification of the white-coat effect (beat-to-beat BP measurement before, during, and after the visit) has shown that it does not increase in magnitude with age, which also is not characterized by a greater response to laboratory stressors (16). Finally, the office/daytime BP difference is positively related to conventional BP measurements. It has also been found, however, to bear an inverse relationship with daytime BP (17), which means that its magnitude increases if ambulatory BP is reduced, for example, in elderly patients who are less physically active or have orthostatic hypotension. A more in-depth assessment of the factors involved in the determination of conventional ambulatory BP differences, not only may lead to a more evidence-based definition of the whitecoat effect, but also, beyond semantics, may provide a better understanding of the perhaps complex nature of WCH, and thus more properly deal with this condition from a medical standpoint.

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