White-coat hypertension: growing evidence in favour of its adverse prognostic significance

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In the last 10 years, several meta-analyses have looked at the risk of cardiovascular outcomes in white-coat hypertension (WCH), that is the condition in which office blood pressure (BP) is elevated, whereas ambulatory or home BP is normal [1]. In two earlier meta-analyses, respectively, published in 2007 and 2008, cardiovascular risk was found not to differ significantly in WCH and normotension [2,3]. This was not the case in a meta-analysis published in 2016, in which individuals with WCH were found to have a significantly greater risk of cardiovascular events and mortality (+7.5 and 179%) compared with normotensive controls [4]. It is now shown not to be the case also in a comprehensive meta-analysis of 12 cohorts (21,336 patients) published by Huang et al. [5] in this issue of the *Journal of Hypertension*, in which WCH exhibited, over an average follow-up of about 8 years, a slight but significant increase of cardiovascular diseases (19%) and all-cause death (50%) compared with normotensive controls. This reinforces the conclusion that WCH is not clinically innocent [6] but that it rather identifies patients in whom the risk of clinically manifesting cardiovascular disease or death over the following few years is greater than that of the normotensive population. It also confirms the appropriateness of the recommendation of European Hypertension Guidelines that WCH needs a follow-up closer than that reserved to individuals in whom office and out-of-office BP are within the normal range [1]. This is further supported by the evidence that in WCH there is a significant increase in the risk of developing a true hypertensive condition (i.e. an in and out-of-office BP elevation) or diabetes over a 10-year time interval, with thus a more frequent mid-term progression to a high cardiovascular risk state [7,8].

Several aspects of WCH require further studies and clarification, however. It is not clear whether all or most subgroups of patients with WCH exhibit an increased risk or this is restricted to individuals with specific BP, demographic or clinical phenotypes. In the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) population, an increased cardiovascular risk was only visible in WCH patients in whom the elevation of office BP was confirmed at two visits [9] or normal out-of-office values did not extend to both ambulatory and home BP [10]. In addition, in the International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome (IDACO) database, an association between WCH and a greater cardiovascular risk has been reported to occur in elderly patients with a high cardiovascular risk but not in younger low-risk individuals [11] and affect patients without but not those under antihypertensive treatment [12], an observation replicated by the meta-analysis of Huang et al. [5] in which cardiovascular diseases increased by almost 40% in 20,445 untreated white-coat hypertensive patients, whereas it was superimposable to normotensive patients in the 8,656 treated white-coat hypertensive patients. This supports the conclusion that WCH may be a heterogeneous clinical condition in which patients at lower and higher cardiovascular risk coexist [13]. A caveat to this conclusion, however, is that in the IDACO database younger low cardiovascular risk patients had, predictably, very few outcomes, with thus a limited ability to detect between-group differences. It is also that in most studies, out-of-office BP was measured only in one occasion. Given the high rate of antihypertensive treatment modifications and low adherence to antihypertensive drugs [14], this may have failed to reliably establish the prevailing on-treatment BP values across observational periods of several years, weakening the conclusion that when WCH does not represent a spontaneous office and out-of-office BP pattern but rather the consequence of a greater out-of-office effect of antihypertensive medications that leave office BP selectively uncontrolled, patients’ risk can nevertheless be normalized. Before disregarding office BP reductions as a marker of cardiovascular protection by treatment (in disagreement with the information provided by a huge number of trials) [15], studies providing more precise information on the long-term ambulatory BP values during treatment are needed.

The factors involved in the increased risk of WCH are also not entirely clear. As WCH is accompanied by an
increased prevalence of dyslipidaemias, diabetes, glucose intolerance and overweight [16], metabolic abnormalities are likely to play a role. BP values, however, are also likely to be involved because, as shown by Huang et al. [5] in their meta-analysis, the cardiovascular risk of WCH patients remained elevated despite adjustment for ‘metabolic’ factors. It remains to be determined which BP may have the main prognostic impact because, as documented years ago in the PAMELA population [16] and now confirmed by Huang et al. [5] on a greater numerical basis, in WCH office BP elevation is accompanied by ambulatory and home BP values that, although confined to the normality range, are both several mmHg higher than in normotensive controls. There is no question that this makes out-of-office BP an adverse prognostic candidate because a several mmHg increase of out-of-office BP is associated with a measurable increase of cardiovascular risk also within the range of values typical of WCH [17] and this is even more the case for a combined increase of ambulatory and home BP, which appears to carry a greater adverse significance than an increase of one of these two pressures alone [16]. However, this should not lead, as in an Editorial by Myers [18] also published in the current issue of the Journal of Hypertension, to a denial of any prognostic role of office BP. There is in the literature evidence that 24-h, daytime and home BP are prognostically superior to office BP, although, in several studies, this has been inferred from their steeper relationship with outcomes, a phenomenon that may be explained by the narrower distribution of means compared with few or isolated values in the population [19]. There is, on the other hand, no evidence that office BP has no independent prognostic value whatsoever. The contrary is indeed suggested by the observation that in WCH, office BP independently predicts the risk of progression to true hypertension [8] and cardiovascular mortality is greater when office BP is more clearly elevated, for a similar 24-h ambulatory BP [9]. A current hypothesis, to be further tested, is that ambulatory, home and office BP are prognostically complementary [19], possibly because they reflect the BP behaviour in partly different environmental conditions.

As pointed out by Myers [18], a third unresolved problem is the absence of any valid information on the effects of antihypertensive drug treatment on the risk of WCH patients. Thanks to the European Lacidipine Study on Atherosclerosis, it is now clearly established that in WCH antihypertensive treatment can lead to an effective long-term (4 years) office BP reduction, with no reduction, however, of ambulatory BP, at variance from true hypertension in which treatment modifies effectively both pressures [20]. This is not the case, however, for the effects of treatment on cardiovascular outcomes that can at present mainly count on an analysis of the patients of the Systolic Hypertension in Europe (Syst-Eur) trial in whom ambulatory BP monitoring allowed identification of WCH. Antihypertensive drug administration was found to reduce office BP, have little effect on ambulatory BP and affect cardiovascular outcomes to a degree that was not significantly different from what was observed in the placebo group, the number of events being so small, however, as to make no safe conclusion possible [21]. Whether antihypertensive treatment protects WCH patients will thus have to be suitably addressed by future studies, which will hopefully clarify if treatment-dependent protection mandatorily requires an out-of-office BP reduction or can, at least in part, be achieved by a selective effect on office BP as well (see above). A consensus exists that this should be regarded as a priori research goal because WCH may involve up to 30–40% of hypertensive patients [1], including those with a resistant hypertension state [22] and that research should be extended to the protective effect of treatment on masked hypertension, a condition in which an increased cardiovascular risk is associated with a selective elevation of out-of-office BP [1] for which the effects of treatment in cardiovascular outcomes are completely unknown.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES


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