

# Should White-Coat Hypertension in Diabetes Be Treated? Pro

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**W**hite coat hypertension, which should be more descriptively termed “isolated clinic hypertension” (1), consists of a condition in which clinic (or office) blood pressure is repeatedly  $\geq 140$  mmHg systolic or 90 mmHg diastolic, whereas 24-h mean blood pressure is below its generally accepted upper limit of normality, i.e.,  $< 125/80$  mmHg (1,2). This article will first show evidence from the PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) population study that isolated clinic hypertension is associated with a prevalence of organ damage and a risk of cardiovascular morbidity and mortality, which, although less than those of patients with in- and out-of-office hypertension, are distinctly greater than those displayed by truly normotensive subjects. It will then emphasize that in diabetic subjects, limited evidence is available on the prevalence of isolated clinic hypertension as well as on its association with diabetic-related microvascular and macrovascular disease. In this context, some specific difficulties exist, i.e., 1) the uncertainty about whether the cut-off clinic and ambulatory blood pressure values to use should (or should not) be different from those used in non-diabetic individuals, 2) the small number of subjects and events in the few studies that have addressed this issue, and 3) the confounding effect of factors such as the duration of diabetes, the extent and type of blood pressure-lowering treatments, and the more or less effective blood glucose control when subjects with and without isolated clinic hypertension are compared.

It will be concluded, however, that

recommendations on this matter should take into due account that, in diabetes, cardiovascular and renal protection are enhanced by aggressive reductions in clinic blood pressure ( $< 130/80$  mmHg) and that lowering blood pressure is beneficial even when the initial clinic value is within the normal blood pressure range, i.e., 130–139 mmHg (2). This scores in favor of a systematic blood pressure-lowering intervention in this condition.

## CLINICAL SIGNIFICANCE OF ISOLATED CLINIC HYPERTENSION IN THE POPULATION

— PAMELA (3,4) is an observational study on a population representative of Monza, a town in the northeast outskirts of Milan. In 2,052 subjects aged 25–74 years, 356 were diagnosed as having an isolated clinic hypertension, i.e., a high clinic together with a normal 24-h average blood pressure (3,4). This represented 8.5% of the total population as well as 41.8% of the number of individuals defined as hypertensive because of an elevation in clinic blood pressure. The isolated clinic blood pressure condition was not without clinical consequences. First, the prevalence in these subjects of echocardiographic left ventricular hypertrophy amounted to 15%, which was less than the 25% prevalence seen in subjects with sustained (i.e., both clinic and 24-h) hypertension, but greater than the 4% prevalence of normotensive individuals (4). Furthermore, as shown in Fig. 1, over an about 12-year follow-up, subjects with isolated clinic hypertension had an incidence of cardiovascular and all-cause mortality that was

also intermediate between that of the two other conditions (3). This was the case even when combined cardiovascular morbid (hospital diagnosis) and fatal events were considered. Compared with the normotensive group, the age- and sex-adjusted increase in the risk of a cardiovascular event was significantly greater in subjects with isolated clinic hypertension, although less than the more marked increase seen in the “sustained” hypertensive group. Similar findings were obtained when isolated clinic hypertension was diagnosed by office versus home blood pressure, which was made possible by the semiautomatic morning and evening self-measurements of blood pressure performed by all subjects of the PAMELA cohort.

## MECHANISMS RESPONSIBLE FOR THE INCREASED CARDIOVASCULAR RISK ASSOCIATED WITH ISOLATED CLINIC HYPERTENSION

— It has long been shown that subjects with isolated clinic hypertension exhibit metabolic abnormalities of prognostic significance (5). However, because the association with an increased incidence of cardiovascular events had failed to be documented in some studies (6), the clinical relevance of this condition remained for a long time controversial. As shown in Fig. 2, in subjects with isolated clinic hypertension of the PAMELA cohort, total serum cholesterol, serum triglycerides, and BMI were all higher than in normotensive subjects, whereas serum HDL cholesterol was lower, the values often being indistinguishable from the abnormal ones seen in “sustained” hypertension (3). This was the case also for blood glucose and the prevalence of a metabolic syndrome, overt diabetes, and an impaired fasting blood glucose state. Furthermore, as reported above, in subjects with isolated clinic hypertension, there was a greater prevalence of left ventricular hypertrophy (7), in line with evidence from other studies that this condition is associated with the presence of subclinical organ damage (6,8,9). Finally, as shown in Fig. 3, ambulatory and home blood pressure values

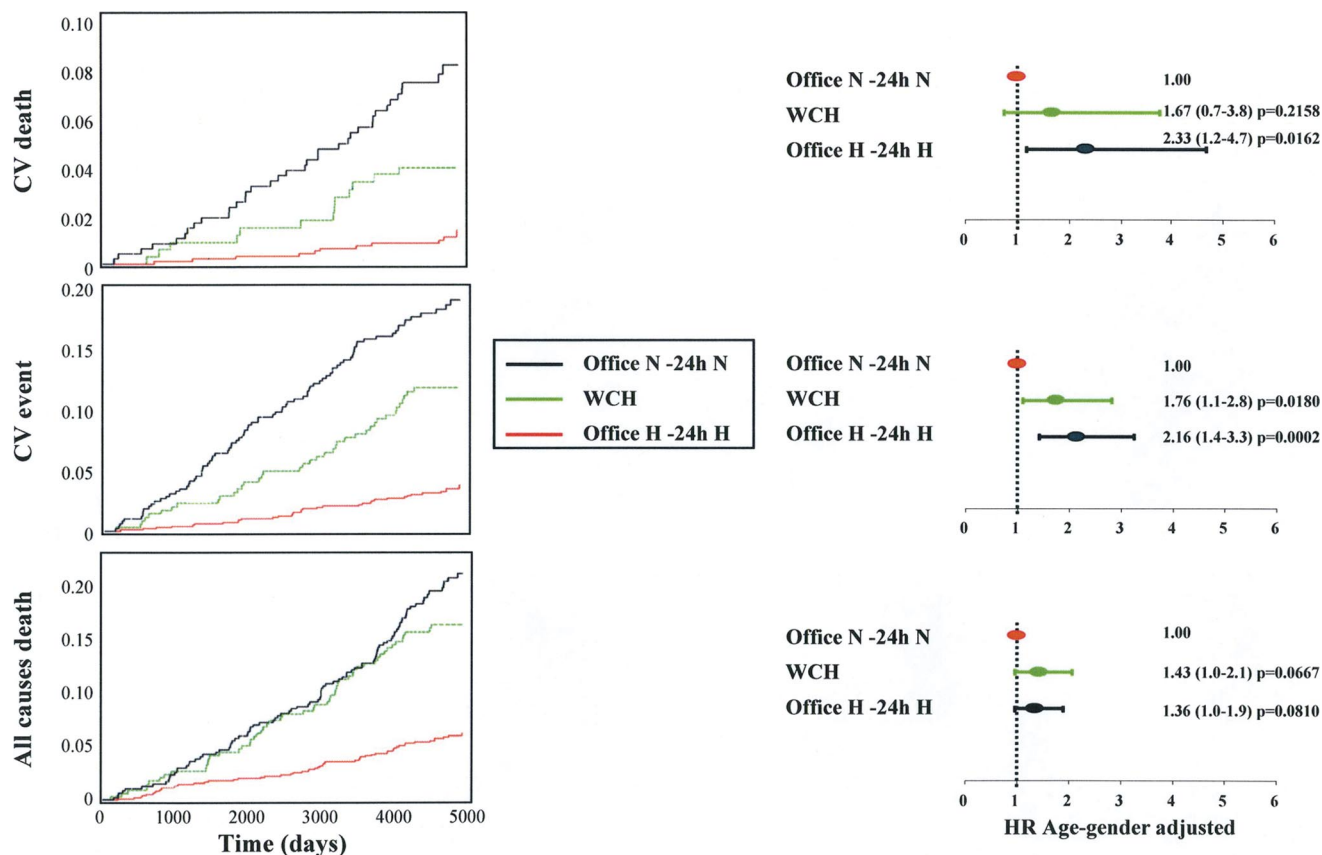
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**Figure 1**—Left panels: Incidence of cardiovascular (CV) death, cardiovascular events, and all-cause death in normotensive subjects (Office N and 24-h N) and in patients with white-coat hypertension (WCH) and sustained hypertension (Office H and 24-h H). 24-h, 24-h ambulatory blood pressure; H, hypertension; N, normotension. Right panels: Hazard ratio (HR), adjusted for age and sex, for cardiovascular death (upper panel), cardiovascular events (middle panel), and all-cause death (lower panel). Data were collected in the follow-up (12 years) of the PAMELA study. Reprinted with permission from Mancina et al. (3).

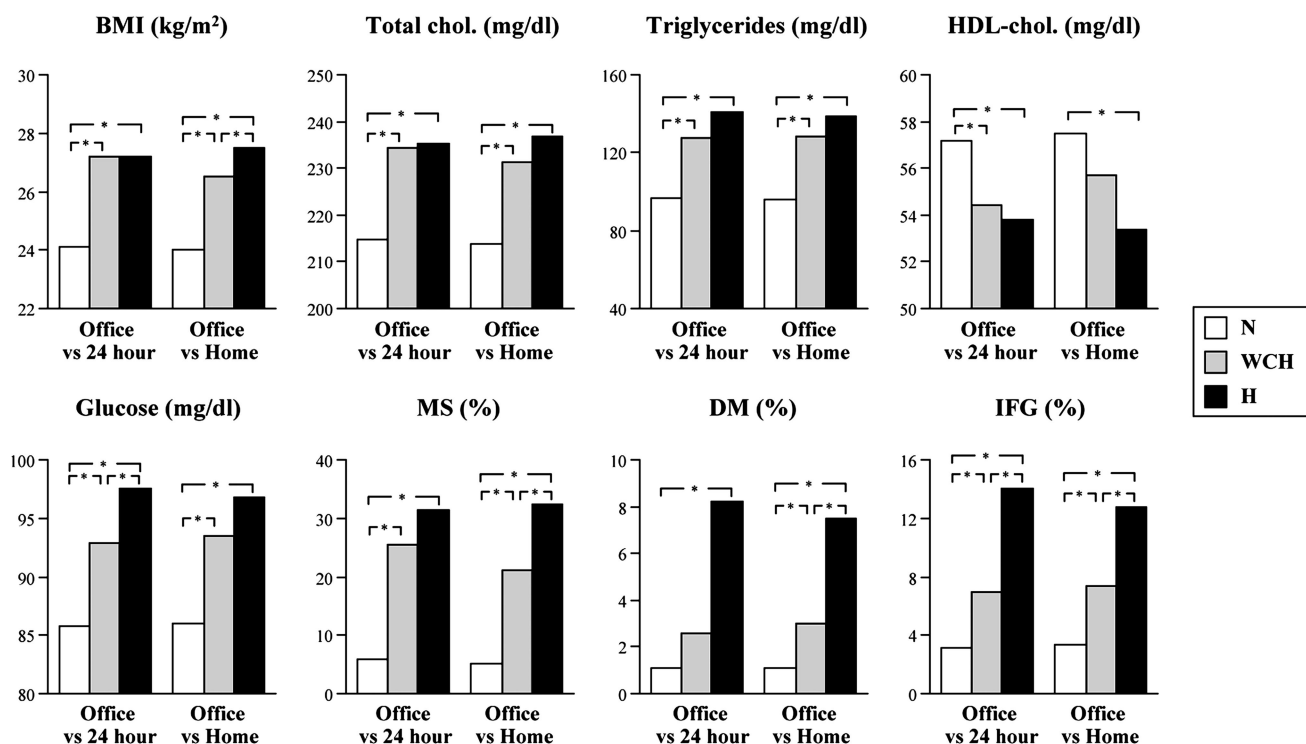
were higher than those displayed by “truly” normotensive subjects (3). Because the relationship between clinic, ambulatory, or home blood pressure and the incidence of cardiovascular events is a continuous one from low to high values (10), this argues against the conclusion that this condition is clinically innocent. It also suggests that this increased risk may materialize even in individuals in whom isolated clinic hypertension is diagnosed in the absence of metabolic abnormalities or organ damage. Further support to this hypothesis comes from the observation that in subjects with isolated clinic hypertension, 24-h blood pressure variability is increased and that this increase has a long-term adverse prognostic significance, independently of 24-h mean values (11).

**ISOLATED CLINIC HYPERTENSION AND ANTIHYPERTENSIVE DRUG TREATMENT**

Whether antihypertensive drug treatment has the same fa-

vorable impact in patients with isolated clinic versus sustained hypertension is an issue that has been even rarely addressed. From data obtained in a subgroup of patients from a trial on treatment of systolic hypertension, Fagard et al. (12) reported that, in patients with isolated clinic hypertension, the blood pressure reduction was limited to clinic blood pressure values with a decrease in cardiovascular event rate that was less than that seen in the group, in which both clinic and ambulatory blood pressure were initially elevated and then reduced by treatment. Furthermore, in a large number of treated hypertensive patients followed for 14 years, Ben-Dov et al. (13) showed that subjects in whom ambulatory or ambulatory plus clinic blood pressure was not controlled showed the highest mortality rate, which was lowest in the condition termed “white-coat uncontrolled hypertension” because control involved ambulatory but not clinic blood pressure. Because isolated clinic hypertension carries a lower level of risk than sustained

hypertension, a lesser benefit in the former than in the latter condition is predictable. These results, however, go somewhat further insofar as they suggest that cardiovascular protection by antihypertensive drug treatment depends on ambulatory blood pressure control. They also imply that concomitant control or lack of control of clinic blood pressure may have a lesser importance. However, because it was based on a relatively small group of nonrandomized patients, the study by Fagard et al. (12) had no sufficient statistical power. Furthermore, in the treated patients of the study of Ben-Dov et al. (13), the clinic and ambulatory blood pressure values might have reflected the greater or the lesser difficulty of the drugs used to control “in-office” and “out-of-office” blood pressure, possibly because of a difference in the baseline cardiovascular risk. This may be supported by an internal inconsistency of the data, i.e., that, although the difference was not significant, the risk of death was 42% less in the group in which both clinic



**Figure 2**—Values of BMI, total cholesterol (Chol), triglycerides, HDL cholesterol, and plasma glucose in normotensive (N), white-coat hypertensive (WCH), and sustained hypertensive (H) of the PAMELA study. Prevalence of metabolic syndrome (MS), diabetes (DM), and impaired fasting glucose (IFG) in the three groups of patients are also shown. Data are superimposable when the diagnosis of the three blood pressure states is based on office versus 24-h ambulatory blood pressure monitoring or on office versus home blood pressure. \* $P < 0.05$  and refers to the statistical significance between groups. Reprinted with permission from Mancia et al. (3).

and ambulatory blood pressures were controlled by treatment than in the white-coat uncontrolled hypertension, in which clinic blood pressure values remained elevated.

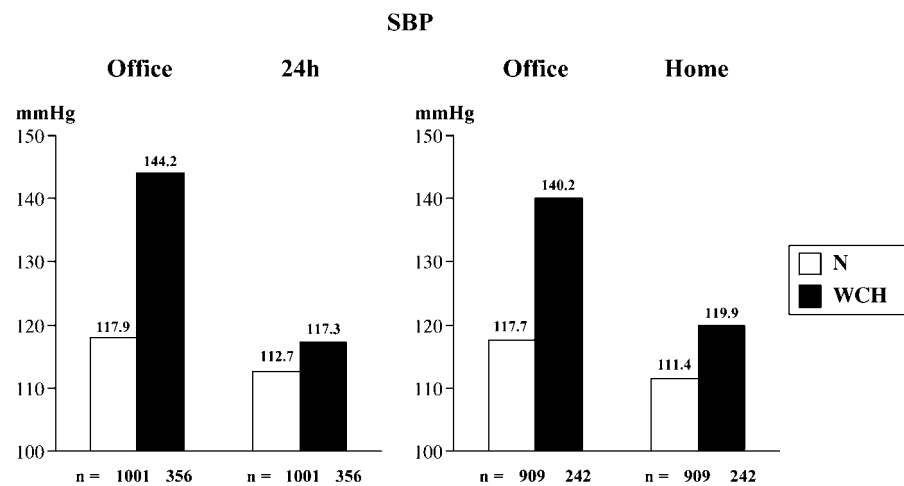
### ISOLATED CLINIC HYPERTENSION AND DIABETES

— Only few studies have explored the clinical significance of iso-

lated clinic hypertension in diabetes (14–17), and in almost all cases, the number of subjects identified as having this condition was limited. This led to a small number of events and opened the results and conclusions to the risk of chance. The largest study performed (18) is the one carried out on 1,207 consecutive hypertensive patients who were followed for an average of ~4 years to determine the risk

of events such as myocardial infarction, stroke, and sudden cardiac death. Out of 262 patients with type 2 diabetes, only 56 were found to have an isolated clinic hypertension based on clinic blood pressure values  $\geq 140/90$  mmHg and an average daytime blood pressure  $< 135/85$  mmHg. In the group with isolated clinic hypertension and diabetes, the risk of a cardiovascular event was lesser than in the group with sustained hypertension without or with diabetes. However, it was surprisingly similar to the risk of nondiabetic subjects with isolated clinic hypertension, thus apparently denying the well-known prognostic importance of diabetes per se at all blood pressure values (19). This paradoxical finding may have resulted from the low number of events in the various groups. In the group with isolated clinic hypertension and diabetes, for example, during the follow-up, there were only 4.2% of the 97 recorded events, i.e., four events in all.

An additional set of data provided by the PAMELA study may be of interest (20). Independently from use of antihypertensive drugs, in subjects with isolated clinic hypertension, the 10-year risk of developing a new-onset diabetes was 2.89



**Figure 3**—Office systolic blood pressure (SBP) in normotensive (N) and white-coat hypertensive (WCH) patients as defined by an elevation in office versus 24-h SBP (left panel) or in office versus home SBP (right panel). Reprinted with permission from Mancia et al. (3).

greater than that of normotensive subjects (95% CI 1.34–6.22,  $P = 0.007$ ), the increase being similar to that of sustained hypertensive patients. Furthermore, the risk of developing an impaired fasting glucose state in subjects with an initial blood glucose  $<100$  mg/dl was about four times (relative risk 3.72, 95% CI 2.10–6.60,  $P < 0.001$ ) greater in the isolated clinic hypertensive subjects than in the normotensive group. Thus, subjects with isolated clinic hypertension have a much greater chance of developing high cardiovascular risk conditions such as pre-diabetes and diabetes over the years following identification of their abnormal blood pressure pattern. This is further reason not to take this identification lightly.

**CONCLUSIONS** — The limited amount of data available on isolated clinic hypertension and diabetes should not divert attention from the large body of evidence that diabetes per se carries a high cardiovascular risk (19) and that antihypertensive treatment has cardiovascular and nephroprotective effects (21,22) when initial blood pressure is well below the values that traditionally define isolated clinic hypertension (2). It should also be remembered that the finding that low blood pressure is protective against diabetes-related microvascular complications has a pathophysiological explanation. In those with diabetes, there is an early loss of small artery autoregulation (23), which exposes microcirculation to a higher blood pressure than that of nondiabetic subjects, favoring rather than damaging the vessel wall. This calls for antihypertensive drug treatment also in diabetic subjects with isolated clinic hypertension. Nevertheless, trying to define the risk and the benefit of treatment in this condition vis à vis those of sustained hypertensives is valuable because it may allow to distinguish categories of patients in whom treatment and blood pressure goals should be more or less aggressive.

However, the studies addressing this issue will have to overcome several problems. The first problem is whether the cutoff clinic blood pressure values used to diagnose isolated clinic hypertension in the general hypertensive population hold for diabetic subjects, in whom the threshold for antihypertensive drug treatment (and thus the operational definition of hypertension) is 130/80 mmHg rather than 140/90 mmHg (2). Whether cutoff ambulatory blood pressure values should also

be different in diabetic and nondiabetic subjects is another important question. It is relevant to this issue that in diabetic subjects the nocturnal blood pressure decline undergoes an early attenuation (24) caused by early subclinical dysautonomia (25), making the average 24-h values relatively higher than those for nondiabetic subjects with preserved nocturnal hypotension. Future studies will require a larger number of events to provide conclusions that have sufficient statistical power. The studies will also require properly matched groups for factors important for patient prognosis, such as duration of diabetes, achieved blood pressure control, and type of antihypertensive drugs used, given their differential importance for protection against diabetes-related cardiovascular complications (2). Matching should also be sought for the magnitude of nocturnal blood pressure decline because nighttime blood pressure is a more sensitive predictor of patient outcome than daytime blood pressure (10,26,27). Failure to take this into account may lead to the recruitment of higher-risk patients in the sustained hypertension group (in which nocturnal blood pressure decline is more likely), endangering the demonstration of the different effects of treatment in the two conditions.

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