

Letter to the Editor

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Response to Masked Hypertension in Untreated and Treated Patients With Diabetes Mellitus: Attractive But Questionable Interpretations and Response to Is Masked Hypertension Related to Diabetes Mellitus?

We agree with Drs Sobiczewski and Wirtwein that a self-reported diagnosis of diabetes mellitus or the use of antidiabetic drugs may not provide an accurate prevalence of the disease, in particular because of the somewhat different criteria used in the 11 cohorts included in the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO).¹ However, misclassification of diabetes mellitus should weaken, not strengthen, the results of our study. In reply to the comments on ambulatory blood pressure (BP) measurement, we standardized the definitions of daytime and nighttime across cohorts taking into account the differences in the pattern of daily activities between Europe and Asia (see Expanded Methods in the online-only Data Supplement).¹ Moreover, to account for the varying intervals between ambulatory BP readings, we computed time-weighted BP means of the daytime BP (see Expanded Methods in the online-only Data Supplement).¹ In terms of the comparison of cardiovascular risk between untreated diabetic patients with masked hypertension versus untreated diabetic patients with stage-1 hypertension,¹ we wish to correct a misconception. The risk was equal with a hazard ratio of 1.07 (95% confidence interval, 0.58–1.98; $P=0.82$). In addition, the hypothesis that we may have underdiagnosed untreated masked hypertension in the patients with diabetes mellitus by using the daytime rather than the nighttime ambulatory BP was put to the test. Of the 229 untreated diabetic patients with normotension by office reading, there were 67 (29.3%) versus 56 (24.5%) patients with masked hypertension as identified by elevated daytime versus nighttime BP, respectively. However, use of daytime versus nighttime BP to define masked hypertension led to discrepant diagnoses in 22.2% of the untreated patients with diabetes mellitus. There is abundant evidence in the diabetic and other high-risk hypertensive states that nocturnal BP, alone or together with daytime BP, is a superior predictor of cardiovascular risk than daytime BP alone.^{2–4} In the current study in untreated patients with diabetes mellitus, masked hypertension, either defined using daytime BP (hazard ratio, 1.96; confidence interval, 0.97–3.97; $P=0.059$) or nighttime BP (hazard ratio, 3.44; confidence interval, 1.68–7.06; $P<0.001$), predicted increased cardiovascular risk as compared with sustained normotension. However, confidence intervals were wide and overlapping probably because of the relatively small number of events in these subgroups. This limitation was noted in our discussion.¹

Doumas et al raised several issues. The figure used in the Clinical Implications section,⁵ which accompanied our publication,¹ addressed many of these issues. First, in both patients with and without diabetes mellitus, there was a significantly greater cardiovascular risk in the untreated masked hypertensive than in the untreated normotensive comparator group. With adjustment for center, sex, and age, the P value was 0.0091. Second, we hypothesized that antihypertensive treatment converted cases of sustained hypertension into treated masked hypertension. This may explain the higher prevalence of masked hypertension in treated

versus untreated patients. Similarly, treatment may have converted masked hypertension into sustained normotension. This resulted in a higher rate of cardiovascular events during the 11-year follow-up in both treated masked hypertensives and treated normotensives as compared to the untreated normotensive comparator group with no difference in cardiovascular event rate between treated masked hypertensives and treated normotensives. Third, we postulate that the greatest reduction in cardiovascular risk occurs when antihypertensive treatment dosage is titrated upward or additional antihypertensive agents are added, until the majority of patients with masked hypertension reached sustained normotension, that is, when the ambulatory BP was normalized. Not surprisingly, normalization of ambulatory BP with treatment did not eliminate the lifetime cardiovascular burden associated with previous elevated BP, nor did it correct other cardiometabolic risk factors that cluster with the hypertensive state.⁶ Thus, the cardiovascular risk in a patient with treated, normalized BP is always greater than in an untreated subject with the identical BP.⁶ Fourth, antihypertensive treatment increases the prevalence of masked hypertension by decreasing conventional BP versus ambulatory BP by a ratio of ≈ 3 to 2.⁷ This further strengthens our hypothesis that subjects who started with untreated sustained hypertension were converted by treatment into masked hypertension because conventional BP normalized, whereas the ambulatory BP remained elevated. Fifth, because antihypertensive therapy decreases conventional BP more than the ambulatory BP, the reliance on conventional BP as a target treatment goal will result in suboptimal reduction in the cardiovascular event rate. We agree with Doumas et al and so stated in our limitation section: “the confidence intervals around the hazard ratios comparing the risks in masked hypertensives versus normotensives and stage 1 and stage 2 hypertensives were wide, reflecting limited statistical power to accurately assess differences between these subgroups.”¹ Furthermore, the larger nondiabetic IDACO population of patients with masked hypertension was supportive of all the above conclusions and with more robust significant P values.¹ Importantly, follow-up BP data and more information on the type of antihypertensive therapy would have been useful, but the absence of this information did not weaken the conclusions of our study.¹ Similarly, we agree that 24-hour ambulatory BP cannot be justified on a cost–benefit basis for every normotensive diabetic patient, as has been concluded by other investigators.⁸ As we suggested in the Perspectives,¹ home BP monitoring may be a satisfactory substitute for ambulatory BP monitoring in low-risk patients.⁹ Furthermore, others have concluded that patients with diabetes mellitus and masked hypertension have sufficient cardiovascular risk factors, frequently including target organ damage, to warrant antihypertensive therapy.^{10,11} However, we agree with Doumas et al that the benefit of treatment of masked hypertension in patients with and without diabetes mellitus must be confirmed by randomized controlled trials. Finally, as stated in our recent IDACO study,¹ our conclusions are hypothesis generating and need verification by further studies.

Disclosures

None.

*The IDACO investigators are listed in the online-only Data Supplement.¹

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