Should We Treat Prehypertension in Diabetes?

What are the cons?

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Elevated blood pressure (BP), even within the normal range, is associated with cardiovascular (CV) morbidity and mortality. Therefore, the Joint National Committee (JNC) VII introduced the term "prehypertension" in the general population, which is defined as BP levels of 120–139 mmHg and 80–89 mmHg for systolic and diastolic BP, respectively (1). Prehypertension includes two different categories of BP: normal (systolic of 120–129 mmHg or diastolic BP of 80–84 mmHg) and high-normal (systolic of 130–139 mmHg or diastolic BP of 85–89 mmHg). The risk of CV events is increased by two- to fourfold with the coexistence of hypertension and type 2 diabetes. Lowering BP is particularly effective in patients with type 2 diabetes. Therefore, guidelines recommend lowering BP to below 130/80 mmHg in diabetic patients. Thus, the term "prehypertension" is inadequate for patients with type 2 diabetes. It is clear from guidelines that in diabetic patients, the high-normal BP category of prehypertension should be pharmacologically treated. However, there is no evidence that drug treatment is beneficial in the normal BP category of prehypertension. Therefore, despite the devastating effect of elevated BP in type 2 diabetes, drug treatment is not always recommended for all diabetic patients with prehypertension.

Hypertension is perhaps best defined by the BP level that has a negative impact on the CV system. Thus, numerical definitions, although hotly debated by numerous guideline committees, are not helpful to practicing physicians. Recent guidelines set the target level of BP for uncomplicated hypertension to below 140/90 mmHg and in the diabetic hypertensive patient to below 130/80 mmHg (1,2). Solid evidence exists showing that the benefits of BP lowering are far more pronounced in the diabetic than in the nondiabetic hypertensive patient. In light of the benefits of BP lowering in diabetic patients, there is a dilemma as to whether diabetic patients with prehypertension should be medically treated to lower BP. I will endeavor to analyze the available data to determine what therapeutic approach should be adopted for diabetic patients with prehypertension.

RISK OF HYPERTENSION IN DIABETES — Hypertension is a major modifiable risk factor for CV morbidity and mortality. Diabetes is associated with a high risk of CV disease and is the leading cause of end-stage renal disease, blindness, and nontraumatic amputations in western countries (3). Although the effects of diabetes and hypertension on the CV system vary somewhat, and are often distinct, their combined presence in the same patient is destructive (4).

Coronary artery disease is far more common in diabetic hypertensive patients than in patients suffering from hypertension or diabetes alone (5). For all 2,681 men in the PROCAM trial who had none of the three risk factors (i.e., hypertension, diabetes, or hyperlipidemia), the coronary artery disease incidence was 6/1,000 over 4 years. In contrast, the incidence of coronary artery disease in participants who were suffering from hypertension or diabetes was 14 and 15 per 1,000 over 4 years, respectively. When both risk factors were present in the same patient, the incidence rate increased to 48 per 1,000 (5).

Several clinical studies have indicated that diabetes is associated with cardiomyopathy that is independent of atherosclerotic coronary artery disease (6). Congestive heart failure is substantially increased in diabetic patients irrespective of coronary artery disease and hypertension (7). The Framingham study data revealed a fourfold greater incidence of congestive heart failure in diabetic men and an eightfold increase in diabetic women, compared with nondiabetic subjects (8). In the DIGAMI (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) trial, congestive heart failure accounted for up to 66% of mortality during the first year postmyocardial infarction in diabetic patients (9).

Longstanding hypertension leads to the development of cardiomyopathy, which is associated with impaired cardiac function (10). We showed that in hypertensive patients, contractility deteriorated as left ventricular mass increased (11). A progressive decline in ventricular function may lead to congestive heart failure. Data from the Framingham study showed that hypertension was the primary cause of congestive heart failure in 35% of cases and played a role in this condition in another 40% (12).

The coexistence of diabetes and hypertension results in more severe cardiomyopathy than would be expected with either hypertension or diabetes alone (10). Clinical studies with echocardiography also showed an increased left ventricular mass in diabetic hypertensive patients (13) increased septal and posterior wall thickness in patients with hypertension and diabetes, compared with nondiabetic hypertensive patients (13). Prevalence of left ventricular hypertrophy was 72% in diabetic hypertensive patients and only 32% in the nondiabetic hypertensive patients who had a similar degree of hypertension. Because left ventricular hypertrophy is known to predispose patients with hypertension to CV morbid and fatal events, the finding of a high

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prevalence of left ventricular hypertrophy in diabetic hypertensive patients may partially explain their increased morbidity and mortality. Cardiomyopathy of diabetes and hypertension is associated with impaired ventricular function and a high prevalence of congestive heart failure (10).

Diabetes is one of the leading causes for end-stage renal disease (ESRD) (14). Hypertension is a well-defined risk factor for end-stage renal disease and accounts for 27% of all end-stage renal disease cases in the U.S. and 33.4% of end-stage renal disease cases among African Americans (14).

When hypertension is superimposed on diabetes, it accelerates the decrease in renal function. Blood pressure control can slow the progression of renal disease in diabetic patients (15).

Diabetes adversely affects cerebrovascular arterial circulation. The risk of stroke is increased by 150–400% for patients with diabetes (16). In the Multiple Risk Factor Intervention Trial, subjects taking medications for diabetes were three times as likely to suffer a stroke (17). In particular, diabetes increases the risk of stroke among younger patients. The prevalence of diabetes increases the risk of stroke-related dementia more than threefold (18), doubles the risk of recurrence, and increases total and stroke-related mortality (19).

Hypertension, mainly systolic, is strongly and directly related to stroke in all age-groups (20), and lowering BP reduces the rate of stroke remarkably (21). The occurrence of diabetes more than doubles the risk of stroke in hypertensive patients (22), and lowering BP in these patients reduces the risk of stroke by 44% (23).

Diabetes may cause diabetic retinopathy that is characterized by neovascularization and formation of microaneurysms. Hypertension accelerates the development of diabetic retinopathy. Knowler et al. (24) found that in diabetic subjects not taking insulin, the incidence of exudates in those with systolic BP of >145 mmHg was more than twice that of those with pressures of <125 mmHg. The combination of hypertensive and diabetic retinopathy is often devastating and remains one of the leading causes of blindness.

PREHYPERTENSION — A recent meta-analysis showed that casual BP is strongly associated with age-specific mortality (20). The relationships between BP and mortality exist over a wide BP range, starting from 115/75 mmHg. On this basis, the JNC VII introduced a new category of "prehypertension." This category is defined as a systolic BP level of 120–139 mmHg and/or diastolic BP level of 80–89 mmHg. Several studies showed that "prehypertension" is common and is associated with the metabolic syndrome and other CV risk factors (25,26), such as obesity, elevated triglycerides, elevated LDL cholesterol, and low levels of HDL cholesterol. Furthermore, during follow-up, subjects with prehypertension are more susceptible to developing true hypertension and coronary atherosclerosis (25,27). Prehypertension includes two different categories of BP that are used by the European Society of Hypertension: normal BP (systolic 120–129 mmHg, or diastolic 80–84 mmHg) and high-normal BP (systolic 130–139 mmHg or diastolic 85–89 mmHg) (2). Grotto et al. (26) showed that subjects with high prehypertension, which is equivalent to high-normal BP, have elevated levels of glucose, total cholesterol, triglycerides, and BMI and lower levels of HDL cholesterol than those with low prehypertension equivalent to normal BP. Vasan et al. (28) showed that the risk for CV disease is 2.5- and 1.6-fold higher among women and men, respectively, with high-normal BP than in those with optimal BP (<120/80 mmHg). Thus, prehypertension is associated with other metabolic abnormalities and increased CV risk. Within the prehypertension group, there is further stratification into two risk categories: normal and high-normal BP.

DIABETIC PREHYPERTENSION — In patients with type 2 diabetes, elevated BP is more harmful than in nondiabetic subjects. There is clear evidence that lowering BP is more beneficial in diabetic than in nondiabetic patients. Aggressive lowering of BP is beneficial in type 2 diabetes, even in patients without hypertension. High-normal BP or high prehypertension is considered hypertension in type 2 diabetes and requires antihypertensive treatment. Regarding this issue, elsewhere we suggested that diabetic prehypertension should be defined as systolic BP of 110–129 mmHg and/or diastolic BP of 70–79 mmHg (29).

The question, therefore, should not be whether to treat prehypertension in patients with type 2 diabetes, but whether to initiate antihypertensive treatment in diabetic patients with diabetic prehypertension.

TREATMENT OF PREHYPERTENSION — In the general population, there are no outcome studies showing any benefit of drug treatment in prehypertension. Only two studies evaluated the efficacy of drug treatment in prehypertension (30,31). The Trial of Preventing Hypertension (TROPHY) study investigated whether pharmacologic treatment of prehypertension prevents or postpones stage 1 hypertension (30). A total of 809 subjects with high-normal BP (high prehypertension) were randomly assigned to receive 2 years of either candesartan (409 subjects) or placebo (400 subjects), followed by 2 years of placebo for everyone. All subjects were instructed to change their lifestyles to reduce BP. During the first 2 years, candesartan reduced the risk of incident hypertension by 66.3% ($P < 0.001$); hypertension had developed in 154 subjects in the placebo group and 53 of those in the candesartan group. After 4 years, candesartan reduced the risk of incident hypertension by 15.6% ($P < 0.007$); hypertension had developed in 240 subjects in the placebo group and 208 of those in the candesartan group. In the recent Prevention of Hypertension study, using the ACE inhibitor ramipril in patients with high-normal BP (PHARAO), a total of 1,008 subjects with high-normal office BP were randomized to treatment with either ramipril ($n = 505$) or placebo ($n = 503$) and were followed up for 3 years (31). Treatment with ramipril reduced the risk of progression to hypertension by 34.4% (155 subjects with ramipril vs. 216 subjects with placebo). Despite the reduction in progression to hypertension, ramipril failed to reduce CV events and death. Both studies succeeded in showing that blockers of the renin angiotensin system reduce progression to hypertension, but they did not show a reduction of CV events. Further long-term studies with additional antihypertensive agents are required to evaluate whether pharmacological treatment can improve clinical outcomes in patients with prehypertension.

TREATMENT OF DIABETIC PREHYPERTENSION — Several studies evaluated the effect of pharmacological treatment in diabetic patients with normal BP (32,33). In the normotensive Appropriate Blood Pressure Control in

Diabetes (ABCD) study (33), 480 type 2 diabetic patients with baseline normal BP (<140/90 mmHg) were randomized to intensive (10 mmHg below the baseline diastolic BP) or moderate (80–89 mmHg) diastolic BP control. Over a 5-year follow-up period, intensive BP control (average of 128/75 mmHg) was associated with less progression to incipient or overt diabetic nephropathy, less progression to diabetic retinopathy, and less incidence of stroke than moderate (137/81 mmHg) BP control. In the recent Action in Diabetes and Vascular disease preterAx and diamicorN MR Controlled Evaluation (ADVANCE) trial, 11,140 patients with type 2 diabetes were randomized to treatment with a fixed combination of perindopril and indapamide or matching placebo (32). After a mean of 4.3 years of follow-up, active treatment (BP 136/73 mmHg) reduced the relative risk of a major macrovascular or microvascular event by 9%, compared with the placebo treatment (BP 140/73 mmHg). The authors stated that the study treatment was not affected by the initial BP levels. However, the mean initial BP of the studied population was 145/81 mmHg, which is clearly hypertension in type 2 diabetes, and 7,655 (68.5%) patients had a history of current antihypertensive treatment. Moreover, analysis of subgroups revealed that in patients with no history of hypertension, active treatment did not reduce CV events.

SHOULD WE USE PHARMACOLOGICAL TREATMENT IN DIABETIC PREHYPERTENSION?

— There is no evidence that antihypertensive treatment is beneficial in patients with diabetic prehypertension. Data from the U.K. Prospective Diabetes Study (UKPDS)-23 showed that a 10-mmHg decrease in systolic BP was associated with a 12% reduction in risk of any complication related to type 2 diabetes. The lower the systolic BP, the lower the risk of complications, and no threshold of systolic BP was observed for a substantive change in risk for any of the outcomes examined. These findings do not necessarily mean that we need to force BP treatment to a goal <130/80 mmHg. When considering lowering the BP goal in type 2 diabetes, and medically treating patients with diabetic prehypertension, the cost and benefit of drug treatment should be taken into account. It seems that the benefit, if any, of lowering BP in diabetic patients below 130/80 mmHg is marginal. Thus, it seems that with the present evidence, it would be unjustified to recommend drug treatment in diabetic prehypertension.

CONCLUSIONS

— The definition of prehypertension in type 2 diabetes is different from that in the general population. High-normal BP (high prehypertension) is considered hypertension in type 2 diabetes and requires drug treatment. However, diabetic-prehypertension requires lifestyle modification and not pharmacological treatment. Long-term studies with antihypertensive treatment in diabetic prehypertension will be beneficial in teaching us whether or not to modify our current approach.

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