# How to Define Prehypertension in Diabetes/Metabolic Syndrome

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Hypertension is a powerful risk factor for cardiovascular (CV) morbidity and mortality. The coexistence of hypertension and type 2 diabetes is devastating to the CV system (1). Lowering blood pressure (BP) is especially beneficial in diabetic patients, and therefore the goal BP in these patients is <130/80 mmHg rather than 140/90 mmHg, which is the goal in the general population (2,3). The Joint National Committee (JNC) VII introduced the term "prehypertension," which is defined as BP levels of 120–139 mmHg for systolic and 80–89 mmHg for diastolic BP, respectively (2). Because the goal BP in diabetic patients and in those with metabolic syndrome is <130/80 mmHg, the question arises as to what the definition of prehypertension should be in these patients. The present review analyzes the available data to determine how to define prehypertension in diabetes/metabolic syndrome.

## TYPE 2 DIABETES AND CV RISK

— Despite the advances in CV medicine over the past decades, cardiovascular disease (CVD) remains the major cause of mortality and morbidity in the western world. A similar tendency has been observed over recent years in the developing world as well, where the prevalence of CVD is consistently on the increase. Although multiple factors are responsible for these phenomena, the recent rise in prevalence of type 2 diabetes is significant.

Up to two-thirds of all deaths in diabetic patients are due to a CV event. The high CVD risk of diabetic patients was shown in several studies. The San Antonio Heart Study demonstrated that type 2 diabetes increased CV mortality by about threefold in men (relative risk [RR] 3.2 [95% CI 1.4–7.1]) and by approximately eightfold in women (RR 8.5 [2.8–25.2]) (4). Data from the Framingham longitudinal study showed that type 2 diabetes increases the risk for developing congestive heart failure (CHF) by 1.8-fold in men and 3.7-fold in women (5). Because of the frequency of CVD and the high rate of mortality, type 2 diabetes is considered a coronary heart disease risk equivalent (6).

## METABOLIC SYNDROME AND CV RISK

— The term "metabolic syndrome" refers to a clustering of some CV risk factors in one subject. Although it was recognized almost a century ago, its precise definition and components, and its clinical importance, are still debatable. Several groups generated criteria for the diagnosis of the metabolic syndrome (Table 1) (7,8). These definitions agree on the core components: impaired glucose metabolism, obesity, dyslipidemia, and hypertension. The main purpose of the criteria developers was to give the clinicians a better tool to predict the risk for the development of type 2 diabetes and to prevent CV complications. It seems that the World Health Organization criteria are more accurate in predicting development of type 2 diabetes, and the National Cholesterol Education Program criteria are more sensitive for identification of CV risk. In the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, the risk of CV mortality in nondiabetic subjects was higher in individuals with than in those without the metabolic syndrome (hazard ratio 2.26 in men and 2.78 in women) (8). In the Kuopio Ischemic Heart Disease Risk Factor study, subjects with metabolic syndrome were 2.9- to 4.2-fold more likely to die of coronary heart disease than those without the metabolic syndrome (9). These recent studies demonstrate the increased prevalence, incidence, and risk of CV mortality in subjects with metabolic syndrome, regardless of whether or not they have type 2 diabetes. Therefore, it seems that metabolic syndrome is not just a pre-diabetes syndrome, but is itself, a very high-risk state (10).

## DIABETES AND THE METABOLIC SYNDROME

— It is now clear that both type 2 diabetes and metabolic syndrome are associated with a high rate of CVD. However, it is unclear whether there is any interaction between them. Does the existence of metabolic syndrome in a patient with type 2 diabetes affect prognosis?

The primary prevention arm of the San Antonio Heart Study demonstrated an escalating CV risk based on the presence of type 2 diabetes alone, metabolic syndrome alone, or both (11). In comparison to healthy subjects, the CV risk was increased in patients with metabolic syndrome, was higher in type 2 diabetes, and was the highest in those who had both. A similar pattern was recently shown in the large Chinese cohort study, where more than 30,000 subjects were followed up for 10 years (12). The increased risk for CVD among those who had impaired fasting glucose or type 2 diabetes was largely driven by the coexistence of other components of the metabolic syndrome. These recent studies show that type 2 diabetes and metabolic syndrome are not two different entities, at least in regard to CV risk, but rather a continuum of a primary metabolic disorder. Thus, when considering the CV risk, we need to include patients with type 2 diabetes or metabolic syndrome in the same risk category.

## BP AND CV RISK IN DIABETES AND THE METABOLIC SYNDROME

— The incidence of hypertension in patients with type 2 diabetes is approximately twofold higher than in age-matched subjects with-

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**Table 1—*Various criteria of diagnosis of the metabolic syndrome***

| Clinical measure | World Health Organization (1998) | European Group for the Study of Insulin Resistance (1999) | Adult Treatment Panel III (2001) |
|---|---|---|---|
| Insulin resistance | Impaired glucose tolerance, impaired fasting glucose, type 2 diabetes, or lowered insulin sensitivity + any two of the following | Plasma insulin >75th percentile + any two of the following | None, but any three of the following five features |
| Body weight | BMI >30 kg/m$^2$ or waist-to-hip ratio >0.9 (men) or >0.85 (women) | Waist circumference ≥94 cm (men) or ≥80 cm (women) | Waist circumference ≥94 cm (men) or ≥80 cm (women) |
| Lipid | Triglycerides ≥150 mg/dl and/or HDL cholesterol <35 mg/dl in men or <39 mg/dl in women | Triglycerides ≥150 mg/dl and/or HDL cholesterol <39 mg/dl in men or women | Triglycerides ≥150 mg/dl and/or HDL cholesterol <40 mg/dl in men or <50 mg/dl in women |
| Blood pressure | ≥140/90 mmHg | ≥140/90 mmHg or on hypertension Rx | ≥130/85 mmHg |
| Glucose | Impaired glucose tolerance, impaired fasting glucose, or type 2 diabetes | Impaired glucose tolerance or impaired fasting glucose | >110 mg/dl |
| Other | Microalbuminuria | | |

out the disease (13). According to some reports, the prevalence of hypertension among diabetic patients can reach up to 80% (14). Hypertension has a deleterious effect in type 2 diabetes. It accelerates diastolic and systolic dysfunction and significantly increases mortality (1). Furthermore, in patients with type 2 diabetes, diastolic function may be affected even when BP is in the normal range. Boyer et al. (15) reported a diastolic dysfunction prevalence of 75% in asymptomatic normotensive diabetic patients. Diastolic dysfunction is itself a major risk factor, and even mild diastolic dysfunction increases mortality risk (16). It is well established that one of the important causes, if not the most important, of diastolic dysfunction is left ventricular hypertrophy, mainly caused by chronic elevated BP. Diastolic dysfunction is a major cause of CHF in diabetic patients, but in most patients, heart failure is due to combined systolic and diastolic dysfunction. The prevalence of type 2 diabetes among patients with CHF is increasing (17). In one report, up to 44% of patients with CHF have type 2 diabetes (18). Diabetic patients with CHF or coronary heart disease, have a higher mortality rate than nondiabetic patients. In general, the systolic function at baseline is worse, and systolic dysfunction after myocardial infarction is more severe.

The incidence of CHF among subjects with metabolic syndrome is almost double those without metabolic syndrome (19). In a 20-year follow-up study, Ingelsson et al. (20) showed that metabolic syndrome is a significant predictor of CHF. No data on systolic and diastolic function are available regarding these individuals, but it appears that diastolic dysfunction, and thus hypertension, is a major contributor. Several studies have shown a significant association between metabolic syndrome and increased subclinical target organ damage. In particular, there is an association between metabolic syndrome and left ventricular hypertrophy (21). The recent analysis of metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study showed that metabolic syndrome is common and significantly increases cardiac abnormalities and long-term risk of death (22). BP elevation was the most common component (95.4%) of the metabolic syndrome. Left ventricular mass index was greater and the prevalence of left ventricular hypertrophy higher in those with metabolic syndrome, even after adjustment for BP levels. The contribution of metabolic syndrome components to CV and all-cause mortality was mainly related to BP and glucose abnormalities.

In the Chinese study, elevated BP was the only component of the metabolic syndrome that carried significant CVD risk in the absence of other disorders (12). The prevalence of hypertension was particularly high among subjects with the metabolic syndrome.

The effect of elevated BP on the clinical course and prognosis of patients with type 2 diabetes and metabolic syndrome is remarkable, reinforcing our concept that, at least with regard to CVD risk, type 2 diabetes and metabolic syndrome are one continuum.

## GOALS OF HYPERTENSION TREATMENT IN DIABETES AND METABOLIC SYNDROME

— BP control reduces CV morbidity and mortality in the general population. Guidelines recommended lowering BP to below 140/90 mmHg in the general population and below 130/80 mmHg in diabetic patients (2,3). In patients with type 2 diabetes, several studies have shown the benefit of intensive BP control (23–26). In the Hypertension Optimal Treatment (HOT) study (25), there was evidence that, in hypertensive patients with type 2 diabetes, lowering BP to the lowest target level (diastolic BP ≤80 mmHg) resulted in 51% reduction in major CV events compared with the target group of ≤90 mmHg. Comparing the rate of events in diabetic versus nondiabetic hypertensive patients in the groups with a target diastolic BP ≤80 and ≤90 showed a remarkable benefit in terms of CV and total mortality in the low target BP group, even though the BP differences were considerably smaller than anticipated. These findings were supported by the results from the UKPDS 38 (23). The latter study showed that tight control of BP in hypertensive patients with type 2 diabetes (average of 144/82 mmHg in the "tight" control group vs. 154/87 mmHg in the less "tight" control group) was associated with a reduction of 37% in microvascular end points and 44% in the risk of stroke events. A further report from the UKPDS (27) evaluated the relationship between systolic BP overtime and the risk of macrovascular and microvascular complications. Each 10-mmHg decrease in systolic BP was associated with 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.

In the normotensive Appropriate Blood Pressure Control in Diabetes (ABCD) study (28), 480 type 2 diabetic patients with baseline normal BP (<140/90 mmHg) were randomized into intensive (10 mmHg below the baseline diastolic BP) or moderate (80–89 mmHg) diastolic BP control groups. 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. Based on these data, both the American Diabetes Association and the Joint National Committee (JNC) VII (2,29) recommended a target BP lower than 130/80 mmHg for diabetic patients and 125/75 mmHg for those with proteinuria. 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 (26). After a mean 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). There was no evidence that the effects of the study treatment differed by initial BP levels. The results of this trial further support aggressive lowering of BP in type 2 diabetes.

There are no trials designed to evaluate whether a similar approach should be used in patients with metabolic syndrome. However, since metabolic syndrome and type 2 diabetes share the same underlying pathology and can be viewed as a continuum of a primary metabolic disorder, it is reasonable to recommend the same BP goals of therapy in both conditions. Indeed, the recent European Society of Hypertension/European Society of Cardiology guidelines (3) emphasize the importance of global cardiometabolic risk assessment to determine the goals of hypertension therapy. According to this approach, a patient with metabolic syndrome should be treated as a patient with type 2 diabetes.

**PREHYPERTENSION** — In December 2002, *The Lancet* published a large meta-analysis that changed fundamental definitions in the hypertension field (30). The authors reviewed 61 observational prospective studies that held data on the relationship between BP and vascular mortality. They obtained information from almost 1 million subjects with a total follow-up of 12.7 million person-years. They demonstrated that casual BP is strongly associated with age-specific mortality. In general, a 20-mmHg difference in usual systolic BP is approximately equivalent in its risk to a 10-mmHg difference in usual diastolic BP. Each increase in 20/10 mmHg almost doubles the risk for CV events. The relationships between BP and mortality exist over a wide BP range, starting from 115/75 mmHg.

Based on the meta-analysis and several other studies (31), 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, even in young "so-called" healthy subjects, and that it is associated with metabolic syndrome and other CV risk factors (32,33). Subjects with prehypertension are more obese and have higher levels of triglycerides and LDL cholesterol and lower levels of HDL cholesterol than their counterpart subjects with normal BP (33). Furthermore, during follow-up, subjects with prehypertension are more susceptible to developing true hypertension and coronary atherosclerosis (32,34). Thus, it is clear that subjects with prehypertension are at a considerably high CV risk and require some type of intervention to reduce the risk. It is still debatable whether lifestyle modification or antihypertensive medication should be initiated.

**PREHYPERTENSION IN METABOLIC SYNDROME AND DIABETES** — The term "prehypertension" was defined as a systolic BP level of 120–139 mmHg and/or diastolic BP level of 80–89 mmHg in the general population, where target BP is <140/90 mmHg. Prehypertension in diabetic patients where the target BP is <130/80 mmHg is not yet defined. BP levels that are considered prehypertension in the general population (131–139/81–89 mmHg) are considered hypertension in patients with type 2 diabetes. Thus, a major dilemma is how prehypertension should be defined in diabetic patients and in those with metabolic syndrome.

In an early study, Vasan et al. (31) followed up 6,859 participants of the Framingham Heart Study, as well as the offspring study of participants who were free of hypertension and CVD. Based on BP levels at baseline, the subjects were classified into one of three nonhypertensive BP categories. During a mean follow-up of 11.1 years (75,980 person-years), 397 subjects had a first CV event. CV event rates increased in a stepwise manner across the three BP categories. Compared with optimal BP (<120/80 mmHg), high normal BP (systolic BP of 130–139 mmHg and/or diastolic BP of 85–89 mmHg) was associated with a risk factor adjusted hazard ratio for CV disease of 2.5 among women and 1.6 among men. These results emphasize the CV risk associated with prehypertension.

Other CV risk factors, such as age, BMI, and blood cholesterol, were higher in the "high normal" group than in the optimal BP group. Data on glucose levels were not given, and the rate of type 2 diabetes was low, but even though the rate of type 2 diabetes was higher in the "high normal" than in the optimal BP groups (31).

In the PAMELA study (35), the prevalence of type 2 diabetes, impaired fasting blood glucose, and hypercholesterolemia increased progressively from "optimal" to "normal," "high normal," and elevated office systolic or diastolic BP.

The prevalence of the metabolic syndrome is highly age-dependent. The Third National Health and Nutrition Examination Survey (NHANES III) showed that the prevalence of metabolic syndrome increased from 7% in participants aged 20–29 years to 44% for those aged 60–69 years (36).

These data suggest that the prevalence of metabolic syndrome and type 2 diabetes rises as BP levels increase. Thus, it is possible that the heavy burden of CV disease in prehypertension is driven by the high prevalence of other CV risk factors, such as type 2 diabetes and metabolic syndrome. The high CV risk profile of subjects with prehypertension has been demonstrated by several investigators. A survey of the Israeli Defense Force employees (33) demonstrated that individuals with prehypertension are significantly older and have higher BMI, lower HDL cholesterol, higher triglycerides, and higher fasting glucose. The prevalence of the metabolic syndrome was more than

twofold higher in the prehypertension group than the normal BP group. Similar results were recently described in two studies. In the Strong Heart Study, 2,629 participants free of hypertension and CV disease at baseline were followed-up for 12 years (37). Prehypertension was more prevalent in diabetic than nondiabetic participants (59.4 vs. 48.2%; $P < 0.001$ adjusted for age). Compared with nondiabetic participants with normal BP, the hazard ratios of CVD were 1.80 (1.28–2.54) for those with prehypertension alone, 2.90 (2.03–4.16) for those with type 2 diabetes alone, and 3.70 for those with both prehypertension and type 2 diabetes. Impaired glucose tolerance or impaired fasting glucose also greatly increased the CV disease risk in prehypertensive people. Of 389 CV events, 295 were in subjects with abnormal glucose metabolism, 40 events occurred in normotensive-normoglycemic subjects, and only 54 events were due to prehypertension alone.

In a prospective cohort analysis among 8,960 middle-aged adults in the Atherosclerosis Risk in Communities (ARIC) study, the authors examined the association of prehypertension levels of BP with CVD in several subgroups (38). The authors showed that subjects with prehypertension have an increased risk of developing CVD relative to those with optimal BP levels. The association was more pronounced among individuals with type 2 diabetes and among those with obesity (BMI >30 kg/m$^2$). The CV risk was fourfold higher in diabetic patients with high normal BP (systolic BP 130–139 or diastolic BP 85–89 mmHg) than in those with optimal BP (systolic BP <120 mmHg and diastolic BP <80 mmHg) [RR 4.1, 95% CI 2.26–7.46]). Among individuals with BMI >30 kg/m$^2$, the relative risk was 3.56 (95% CI 1.99–6.35). These findings emphasize that in diabetic patients and in obese subjects, even prehypertensive BP levels are associated with a substantial increased CV risk.

Under these circumstances, the term "prehypertension" should be given an alternative term in subjects with type 2 diabetes or other metabolic risk factors.

## DIABETIC PREHYPERTENSION

— It is clear that systolic BP levels of 130–139 mmHg or diastolic BP levels of 80–89 mmHg that are considered prehypertension in the general population, and require only lifestyle modification, are defined as hypertension that requires drug treatment in patients with type 2 diabetes and in subjects with metabolic syndrome. Thus, prehypertension should be defined differently in patients with type 2 diabetes and metabolic syndrome. To preclude misconception, we suggest using the term "diabetic prehypertension" instead of "prehypertension" in patients with type 2 diabetes and metabolic syndrome. The upper level of diabetic-prehypertension should be 130 mmHg for systolic and 80 mmHg for diastolic BP. The main questions are, what the optimal BP levels for diabetic patients and what should the lower threshold be for diabetic prehypertension?

The Prospective Studies Collaboration demonstrated a strong and direct relationship in the general population between BP and vascular mortality, without any evidence of a threshold down to at least 115/75 mmHg (30). The recent Stop Atherosclerosis in Native Diabetic Study (SANDS) showed that, in diabetic patients, aggressive treatment was more effective than standard treatment in regression of carotid intimal medial thickness and left ventricular mass (39). Aggressive treatment reduced LDL cholesterol to 72 mg/dl (95% CI 69–75) and systolic BP to 117 mmHg (115–118), whereas standard treatment reduced LDL cholesterol to 104 mg/dl (101–106) and systolic BP to 129 mmHg (128–130). SANDS has certain limitations because the compared groups were small, follow-up was short, and no evidence of benefit in clinical events was observed. Nevertheless, the results suggest that reducing systolic BP from 129 to 117 mmHg is beneficial. The evidence from the meta-analysis and the SANDS indicates that a systolic BP target of 115 mmHg is reasonable in diabetic patients. However, since the upper limit of prehypertension in type 2 diabetes is 10/10 mmHg less than the upper limit in the general population (130/80 vs. 140/90 mmHg) and the range of prehypertension is 20/10 mmHg, we believe that a similar range should be maintained for type 2 diabetes and metabolic syndrome. Therefore, we suggest defining diabetic prehypertension as systolic BP of 110–129 mmHg and/or diastolic BP of 70–79 mmHg.

The implication of this definition is that almost all adults with type 2 diabetes will have either hypertension or diabetic prehypertension. However, it does not mean that a diagnosis of diabetes leads necessarily to prescription of an antihypertensive treatment because, in diabetic prehypertension, lifestyle modifications may be enough as long as the BP levels remain in the prehypertension range and target organs are not affected.

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