Epidemiology of Hypertension in Diabetic Patients and Implications for Treatment

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We review the epidemiology of hypertension in diabetic patients and discuss the implications for treatment. The relationship between coronary heart disease (CHD) mortality and blood pressure (BP) in the World Health Organization Multinational Study of Vascular Disease in Diabetics (WHO MSVDD) is evaluated. One thousand two hundred seventy-seven patients with insulin-dependent diabetes mellitus (IDDM) and 3463 patients with non-insulin-dependent diabetes mellitus (NIDDM), aged 35–55 yr at baseline, from 10 centers throughout the world were evaluated. CHD mortality after a follow-up of 6–7 yr was measured. Estimates of usual diastolic BP were made with data from the Framingham study. The relative risk (RR) of CHD death was plotted against usual diastolic BP for IDDM and NIDDM, and the shapes of the relationship were compared with a meta-analysis of nine prospective studies in nondiabetic populations. For the NIDDM group, the CHD RRs were significantly >1.0 only for the uppermost diastolic BP category (RR 2.23, 95% confidence interval 1.14–4.40). For the IDDM group, the shape of the diastolic BP-CHD relationship was difficult to assess in view of the small number of events. In neither diabetic group was the evidence for a J-shaped relationship. Elevated BP is associated with increased cardiovascular/renal mortality in both types of diabetes. However, the efficacy of antihypertensive therapy in the prevention of these outcomes remains unclear. Prospective data from the WHO MSVDD do not provide clear evidence of benefit from treating diastolic BP <95–100 mmHg in NIDDM patients. The cost-benefit implications of aggressive BP treatment in IDDM must be more clearly defined before such treatment policies are accepted. *Diabetes Care* **14 (Suppl. 4):8–12, 1991**

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The degree to which hypertension and diabetes mellitus are associated has received much attention over the years and has raised several important methodological issues that have recently been reviewed (1). Population-based studies, particularly of non-insulin-dependent diabetes mellitus (NIDDM), have shown that the elevated levels of blood pressure (BP) associated with diabetes are not as substantial as those claimed by clinic-based studies, which are often susceptible to several forms of bias (2–6).

Prospective studies continue to demonstrate that raised BP is an important risk factor for the macrovascular complications of diabetes (2,7). Studies mainly in insulin-dependent diabetes mellitus (IDDM) indicate that hypertension is significantly involved in the progression and perhaps the onset of diabetic nephropathy (8). BP may also be an important factor in the development and progression of diabetic retinopathy (9,10). These associations of raised BP with the major life-threatening and incapacitating complications of diabetes clearly raise important preventive and therapeutic issues. This article discusses the aims of treatment of BP in diabetic patients from an epidemiologic standpoint, dealing with the two major forms of the disease separately.

NIDDM

Several prospective studies in developed countries have confirmed that subjects with NIDDM have at least two-

TABLE 1
Mean diastolic blood pressure (DBP) at baseline compared with estimation of usual DBP to correct for regression dilution bias

Baseline DBP category (mmHg)	Framingham study mean baseline DBP (mmHg)*		WHO MSVDD mean baseline DBP (mmHg)		Framingham study estimated mean usual DBP (mmHg)	
≤79	70.8		71.2		76.2	
		(12.8)		(12.3)		(7.7)
80–89	83.6		83.5		83.9	
		(9.9)		(10.5)		(7.4)
90–99	93.5		93.0		91.3	
		(9.9)		(9.6)		(7.2)
100–109	103.4		102.6		98.5	
		(13.0)		(12.5)		(6.2)
≥110	116.4		115.1		104.7	

Difference in mean DBP between categories is given in parentheses. WHO MSVDD, World Health Organization Multinational Study of Vascular Disease in Diabetics.
*Data from ref 17, Table 3, based on 3776 men and women in the Framingham study.

fold the risk of death from cardiovascular disease compared with the nondiabetic population (11). Earlier cohort and insurance studies indicated that elevations of both systolic and diastolic BP are important predictors of mortality in diabetic patients (12,13). In the London Whitehall study of male middle-aged civil servants, systolic and diastolic BP had a more consistent relationship to coronary heart disease (CHD) mortality in those with diabetes and glucose intolerance than blood cholesterol, degree of obesity, and cigarette smoking (14). The German Schwabing study of mainly NIDDM patients showed that systolic BP was a major risk factor for fatal or nonfatal cardiovascular events (15).

In the World Health Organization Multinational Study of Vascular Disease in Diabetics (WHO MSVDD), 4740 diabetic men and women, aged 35–55 yr at baseline, were followed up for mortality for 6–7 yr (16). Sitting arterial BP was measured at baseline with a standard sphygmomanometer with diastolic BP recorded at the point of disappearance of sound (Korotkoff phase 5). Both systolic and diastolic BP at baseline were significantly predictive of cardiovascular death in this study. Hypertensive subjects were defined according to WHO recommendations as those with systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg or on antihypertensive therapy. When hypertensive subjects were compared with normotensive subjects, the relative risks of cardiovascular death in NIDDM patients were 2.2 for men and 3.7 for women (7).

A recent meta-analysis of results from nine major prospective studies in nondiabetic populations examined the direction and size of the effects of prolonged differences in diastolic BP on CHD and stroke risk (17). Previous studies, with baseline levels of BP, have tended to underestimate the true associations of diastolic BP with disease rates. An estimate of usual diastolic BP categories compared with baseline BP levels has been obtained from remeasurements of diastolic BP after 4 yr of follow-up in 3776 men and women in the Framingham Study (18; Table 1). An effect of "regression dilution bias" is that the difference in mean diastolic BP between the top and bottom categories is ~60% greater for baseline BPs than for estimated usual diastolic BPs. This means that when usual BPs are analyzed, the slopes of the diastolic BP–CHD association will be at least 60% steeper than when baseline BPs are utilized (17). This meta-analysis of nine prospective studies included 420,000 individuals, 4856 of whom suffered a fatal or nonfatal CHD event. The relationship between the relative risk of CHD and usual diastolic BP was positive and continuous, with no evidence of any threshold below which lower levels of diastolic BP were not associated with lower risks of CHD (Fig. 1). In particular,

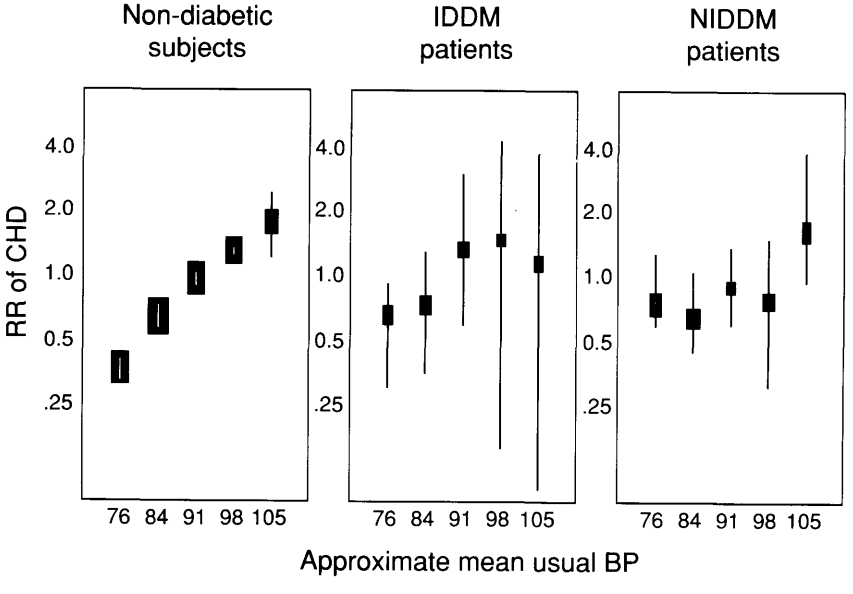

FIG. 1. Relative risk (RR) of coronary heart disease (CHD) and usual diastolic blood pressure (BP) in insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) subjects and nondiabetic subjects. *Vertical lines*, 95% confidence intervals for estimates of RR. Data on nondiabetic individuals are reproduced from MacMahon et al. (17). © by *Lancet*.

there was no evidence of a J-shaped relationship seen in some smaller studies, which have often included subjects with preexisting CHD (19). This analysis demonstrated that in nondiabetic populations, prolonged differences in usual diastolic BP of 5, 7.5, and 10 mmHg were associated with at least 21, 29, and 31% less CHD, respectively (17).

A similar analysis of the relationship between diastolic BP and CHD mortality was carried out for the 4740 diabetic subjects in the WHO MSVDD. The distribution of baseline diastolic BP in this study was very similar to that in the Framingham population (Table 1). The Framingham study estimates of usual diastolic BP have therefore been applied to the diabetic sample. Age-standardized CHD death rates were calculated by the direct method of standardization for each category of diastolic BP for the 1277 IDDM and 3463 NIDDM subjects separately, excluding those already on antihypertensive therapy. The relative risks (RRs) of CHD mortality, (relative to the risk of the total population) were calculated for each diastolic BP category. These RRs are plotted in Fig. 1 by the usual diastolic BP categories, with their 95% confidence intervals (CIs), estimated by the method described by MacMahon et al. (17).

In contrast to the nondiabetic sample, the CHD RRs in the NIDDM group are significantly >1 only for the uppermost diastolic BP category (RR 2.23, 95% CI 1.14–4.40). CHD relative risks for diastolic BP below this upper level of ~105 mmHg are not significantly different from 1, but there is no convincing evidence of a J-shaped relationship. However, there are good reasons for exercising caution in interpreting these data. First, only 112 fatal CHD events occurred in the NIDDM sample, resulting in relatively large CIs around the RR estimations. Other mortality studies in diabetic patients have reported an even smaller number of CHD events (e.g., 25 in the Whitehall study [14]), thus making their estimates of the shape and magnitude of the BP-CHD mortality relationship rather uncertain. Second, the demonstrated association between BP and CHD mortality would be influenced by the exclusion of those on antihypertensive therapy at baseline, comprising 17% of male and 23% of female NIDDM subjects in the WHO study (7). With these important caveats in mind, these analyses of prospective observational data, in a large group of NIDDM patients, do not support a strategy of treating diastolic BP <95–100 mmHg in terms of improving CHD risk status. Hopefully, an ongoing longer followup of the WHO MSVDD cohort, examining both fatal and nonfatal CHD and stroke events, will provide a more accurate characterization of the BP-disease relationship in NIDDM.

Unfortunately, direct evidence on the possible benefit of antihypertensive treatment in diabetic patients is available from only one randomized controlled trial. In the large Hypertension Detection and Follow-up Program (HDFP) study (20), a diabetic subgroup had a similar reduction in mortality of 25% compared with the whole study population when a stepped-care group was compared with a referred-care group. However, this benefit of treatment has not been confirmed by other randomized trials in nondiabetic populations as far as CHD events are concerned (21,22), and the design of the HDFP is such that no definite conclusions can be drawn about the optimum level of diastolic BP to be attained by antihypertensive therapy (22).

Information on the specific efficacy of BP reduction in the prevention of macrovascular disease in diabetes is so sparse that a recent consensus statement recommended that "the indications for initiating antihypertensive treatment should be the same as for non-diabetic hypertensive patients" (23). However, in the same section of the consensus statement, a recommendation for (undefined) "aggressive" treatment of hypertension in diabetes was made. Expert groups concerned with the formulation of guidelines for the management of hypertension in the general (nondiabetic) population have wisely avoided such unjustified and possibly harmful suggestions. The most recent WHO/International Society for Hypertension guidelines advised that drug treatment should be considered for those individuals whose diastolic BPs remain between 90 and 94 mmHg "after prolonged observation" in the presence of an additional cardiovascular risk factor, such as diabetes (24). From a study of BP levels in >5000 diabetic patients in London, it can be estimated that a diastolic BP treatment threshold of 90 mmHg would result in at least 25% of male NIDDM patients requiring lifelong antihypertensive therapy (1).

Before this BP treatment policy is accepted, notwithstanding the lack of evidence from randomized controlled trials, it should be realized that hypertension contributes only a small proportion of the excess coronary risk associated with diabetes (14), and prospective studies are revealing that elevated BP and other cardiovascular risk factors may precede the diagnosis of NIDDM by many years (25–27). The "clock for CHD may have been ticking" for too many years before the onset of clinical diabetes for BP intervention to have any significant impact after the diagnosis of NIDDM (26).

IDDM

Cohort studies of IDDM patients have shown that they have considerable excess mortality compared with the background population, and the major causes of death are cardiovascular disease and nephropathy (28). The presence of proteinuria and elevated urinary albumin excretion rates are important predictors of macrovascular disease in this group (8,29). In the IDDM subgroup of the WHO MSVDD cohort, the age-adjusted relative risks for cardiovascular mortality, comparing WHO-defined hypertensive subjects with nonhypertensive subjects, were 3.5 for men and 2.5 for women (7), and the relationship of BP to mortality was independent of the effect of proteinuria. Age-adjusted relative risks for CHD mortality have been calculated as described above for the NIDDM group and are plotted against usual diastolic

BP in Fig. 1. The shape of the diastolic BP–CHD relationship is rather difficult to assess with any degree of confidence, because the total number of CHD deaths is small at 35 and the CIs are rather large in all the RR estimates. Compared with NIDDM, in the IDDM group, a smaller proportion were excluded from the analysis because they were on antihypertensive therapy: 8.7% of men and 13.1% of women (7). Despite the uncertainty associated with the small number of events, it can again be cautiously concluded that a J-shaped relationship of diastolic BP to CHD mortality does not seem likely in this sample.

Apart from its importance as a predictor of cardiovascular disease in IDDM, much attention has focused on the role of elevated BP in the onset and progression of diabetic nephropathy (8). In the WHO MSVDD, hypertension was a significant predictor of renal death in both IDDM and NIDDM subgroups (30). However, the question of whether elevated BP precedes, accompanies, or follows the increase in urinary albumin excretion associated with the development of diabetic nephropathy remains a matter of intense debate (31,32). There is a regrettable lack of large well-designed controlled intervention studies of BP reduction in IDDM patients with clinical end points, including the need for renal replacement therapy, renal death, or cardiovascular fatal and nonfatal events. It is therefore difficult to come to firm conclusions about the level of BP requiring drug therapy, the target BPs that should be aimed for during treatment, and the cost-benefit implications of such treatment in IDDM patients.

Uncertainty in this area of clinical decision making is reflected by the wide range of responses to questions on BP treatment in IDDM patients received from 20 European diabetes centers participating in the EURODIAB IDDM complications study. Table 2 shows that for patients aged 30–44 yr, for example, physicians would give drug treatment for systolic BP levels between 140 and 160 mmHg and diastolic levels between 85 and 95 mmHg. For the same age range, target BP levels varied more widely, from 110 to 150 mmHg for systolic BPs and from 70 to 95 mmHg for diastolic BPs. The clinical implications of these treatment strategies can again be deduced from the percentile distribution of BPs in 1352 London IDDM patients (1). A treatment level of 140/85 mmHg corresponds to the upper 75th percentile of the BP distribution and would result in at least 25% of male IDDM patients, aged 30–44 yr, being subjected to lifelong antihypertensive therapy. A target treated BP level of 110/70 mmHg would result in BP reduction to the 25th percentile of the BP distribution, but from Fig. 1, it can be seen that there is no evidence of further reduction of cardiovascular risk for diastolic BPs below ~85 mmHg for IDDM patients.

The implications of these "aggressively" low BP target levels recommended for the prevention of diabetic nephropathy are impossible to determine with any confidence because of the lack of any adequately sized controlled intervention studies with clinical end points.

TABLE 2
Responses to questions on blood pressure (BP) treatment from 20 European diabetes centers

Age range (yr)	Systolic BP (mmHg)	Diastolic BP (mmHg)
What level of BP would you consider it important to treat with drugs, in an insulin-dependent patient with no other cardiovascular risk factors?		
15–29	141 (130–160)	90 (85–95)
30–44	145 (140–160)	91 (85–95)
45–59	153 (140–190)	93 (85–100)
What level of BP would you aim to achieve on treatment (target BP)?		
15–29	129 (110–140)	82 (70–95)
30–44	134 (110–150)	84 (70–95)
45–59	139 (110–160)	85 (70–95)

Values are means with ranges in parentheses.

CONCLUSIONS

Raised BP levels are clearly associated with an increased risk of cardiovascular and renal disease in both types of diabetes. However, the efficacy of antihypertensive therapy in the prevention of the major life-threatening long-term complications of the condition and the exact levels of BP that require treatment remain unclear. As far as NIDDM patients are concerned, a lack of diabetes-specific data has led consensus groups to recommend the application of BP treatment strategies accepted for the nondiabetic population (23). In addition, the cost-benefit implications of this policy have not been adequately addressed, and the prospective data presented here provide no clear evidence for the benefit of treating diastolic BPs <95–100 mmHg.

Recommendations for BP reduction in patients with IDDM have mainly concentrated on the role of hypertension in the progression and, perhaps, the onset of the complex processes leading to diabetic nephropathy. Those who continue to recommend aggressive BP treatment for either type of diabetes should define what they mean by such admonitions and back up their advice with more evidence to convince the scientific community that these policies will do more good than harm to our patients (22).

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