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Factors Influencing Threshold and Choice of Treatment for Hypertension in NIDDM

Cardiovascular Factors

In nondiabetic populations, there is an ~40% increase in stroke risk and a 25% increase in coronary heart disease (CHD) risk with every 6-mmHg increase above 75mmHginusualdiastolicbloodpressure.Diabetesincreases the risk of both conditions by two- to threefold, and in diabetic patients, hypertension further increases these risks. The benefits of lowering blood pressure in nondiabetic subjects have been subjected to meta-analysis, which has demonstrated benefits equivalent to 100% reversal of the excess risk for stroke but with only ~50% of CHD risk reversible after 2–3 yr of treatment. In these analyses, the benefit of treating diastolic blood pressure is similar at all levels >90 mmHg. If these results are extrapolated to diabetic patients, possible benefits of therapy for mild hypertension could be two to three times greater than in nondiabetic subjects, but this could still correspond to 300 person-yr of treatment to prevent one nonfatal stroke and 2500 person-yr of treatment to prevent one CHD death, with treatment that may deleteriously affect quality of life in 36% of all diabetic patients. There may also be risks in treating patients with mild hypertension who have existing CHD or left ventricular hypertrophy, which are more common in diabetes. Despite the theoretical risk of deleterious changes in several cardiovascular risk factors with thiazides or β-blockers, most of the newer agents have not yet been demonstrated to produce similar benefits to the large prospective studies in which the aforementioned agents have been used. It is only with prospective studies in high-risk diabetic populations that the treatments can be compared and the possible risks of a J-shaped curve assessed. ***Diabetes Care* 14 (Suppl. 4):27–32, 1991**

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The problem of managing hypertension in a diabetic patient is much more likely to arise in a patient with non-insulin-dependent diabetes mellitus (NIDDM), because of the relative prevalence of the two main types of diabetes (1,2) and as a result of the frequent coexistence of hypertension and glucose intolerance in the same individual (3). In such patients, cardiovascular disease is a much more frequent cause of morbidity and mortality than renal failure, even in patients with evidence of renal involvement such as microalbuminuria or Albustix-positive proteinuria (4,5). For these reasons, I will discuss only the hypertensive patient with NIDDM. Because intervention studies aimed at assessing the benefits of risk-factor reduction in patients with NIDDM have not been performed, to assess possible benefits it is necessary to extrapolate from studies in nondiabetic subjects while making a number of assumptions that are described in detail below.

EXCESS CARDIOVASCULAR RISK IN DIABETES

In healthy nondiabetic populations, there is a log-linear relationship between the level of diastolic blood pressure and the risk of both coronary heart disease (CHD) and stroke, implying a constant proportionate increase in risk with a standard elevation in blood pressure at any absolute level of pressure (6,7). MacMahon et al. (8) summarized the results of nine major prospective

studies in 420,000 people followed for a mean of 10 yr and calculated that with every 6-mmHg rise in usual diastolic blood pressure, there is an ~35–40% increase in stroke risk and a 20–25% increase in CHD risk (Fig. 1). Moreover, this increase in risk is continuous at all levels of diastolic blood pressure >75 mmHg.

Diabetes increases the risk of both stroke and CHD by two to three times (9–11), although it is unclear whether this excess mortality results simply from a more aggressive atherosclerotic process in diabetic patients, an excess risk of thrombosis, or other processes such as a putative "diabetic cardiomyopathy" (12). Several studies suggest that the relationship between hypertension and risk is proportionately similar in diabetic and nondiabetic populations; i.e., in diabetic subjects, any degree of elevation of blood pressure is associated with the same proportionate increase in risk as in nondiabetic individuals but from a higher baseline (Fig. 2), a so-called *positive interaction* (9–11,13). This implies that

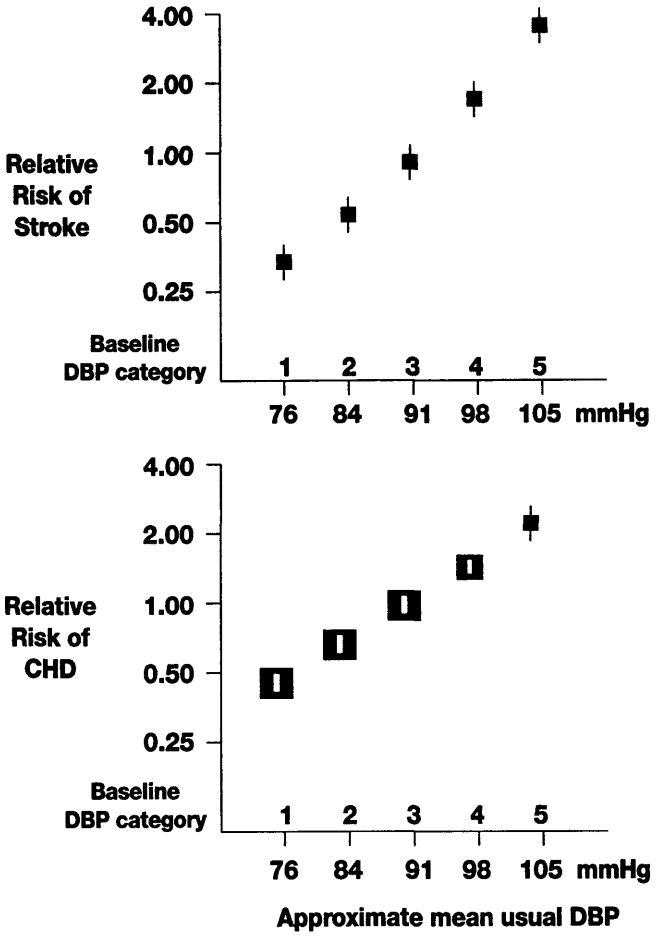

FIG. 1. Relationships between usual diastolic blood pressure (DBP) and relative risks of stroke (7 prospective observational studies with 843 events) and coronary heart diseast (CHD; 9 prospective observational studies with 4856 events) in 5 categories defined by baseline DBP. From MacMahon et al. (8). © by *Lancet*.

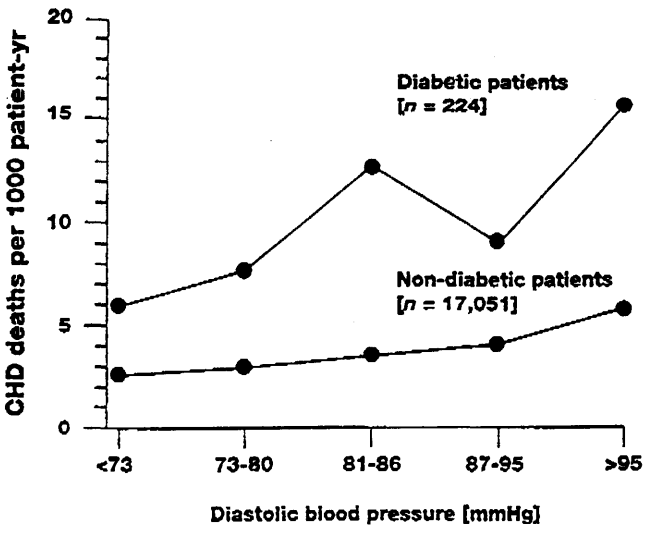

FIG. 2. Relationship between diastolic blood pressure and coronary heart disease (CHD) in diabetic and nondiabetic subjects. Adapted from Fuller et al. (9).

the risk of CHD would double from 2.5 to 5 deaths/1000 person-yr with a rise in diastolic blood pressure from 70 to 95 mmHg in nondiabetic subjects; however, in diabetic patients, the same increase in diastolic blood pressure would increase the risk from 6 to 12 deaths/1000 person-yr, still a doubling of risk but with 6 additional deaths attributable to the increased level of blood pressure compared with 2.5 in nondiabetic subjects. However, it must be pointed out that these studies are based on small numbers of events in diabetic subjects. Data from the 6-yr analysis of Multiple Risk Factor Intervention Trial (MRFIT) screenees suggest the possibility of a smaller proportionate effect of other risk factors in diabetic than in nondiabetic subjects. This would have important implications on the possible maximum benefits of intervention in such subjects (14).

REVERSIBILITY OF EXCESS RISK

Although subjects or populations with low levels of risk factors have a low incidence of cardiovascular disease, the effect of lowering an elevated level of a risk factor is unpredictable and can really be assessed only in the context of prospective randomized controlled intervention studies. It is unusual for the risk to be totally reversed, and more commonly, a partial reduction in excess events is seen. Collins et al. (15) looked at the effects of treating hypertension in nondiabetic subjects by pooling the results from 14 intervention studies, providing data on 37,000 patients treated for 5 yr, with a mean reduction of 5–6 mmHg in diastolic blood pressure. Most patients in these studies were treated with diuretics and β-blockers, and the analysis suggested that the mean ± SD incidence of stroke was reduced by

42 ± 6% and that of CHD by 14 ± 5%. If these reductions are compared with the population study observations of risk and diastolic blood pressure mentioned above, they imply that virtually all of the excess risk of stroke is reversed by treatment, whereas about half of the excess CHD risk is so reversed (Fig. 3). This analysis did not find any significant difference in benefit for either end point according to whether the initial diastolic blood pressure was above or below 110 mmHg.

Whether the finding of complete reversibility for stroke risk is more intriguing than that of ~50% reversibility for CHD risk is debatable, bearing in mind that, even in hypertensive subjects, most strokes are thrombotic and not hemorrhagic in origin (16). However, four possible reasons for the less than complete reversibility of CHD risk in this overview should be mentioned.

- Irreversible damage may have already occurred before treatment.
- Deleterious effects on lipids and insulin resistance may result from treatment with diuretics and β-blockers (17,18). The alterations in lipids produced by thiazides (18) might increase CHD risk by 8–10% if exerted over a 5-yr intervention study (19), although in long-term therapy, the effect of thiazides on lipids may be much less marked (15).
- An increase in CHD mortality has been observed in some studies when blood pressure is reduced below ~85 mmHg in subjects with existing ischemia and left ventricular hypertrophy—the so-called *J-shaped curve* (20,21).
- Hypertension and CHD may be mediated through some common etiological mechanism, e.g., a hormore or growth factor, that produces arteriolar hypertrophy and smooth muscle cell proliferation (22). This implies that hypertension may not be the true pathogenetic mechanism for increased CHD risk but merely an epiphenomenon. It is increasingly clear that the high-risk hypertensive subject is identifiable by echocardiographic evidence of left ventricular hypertrophy (23,24), and it is possible that regression of left ventricular mass (25) may be as important as reduction in blood pressure in reducing the excess CHD risk. However, this hypothesis has not been tested by intervention studies.

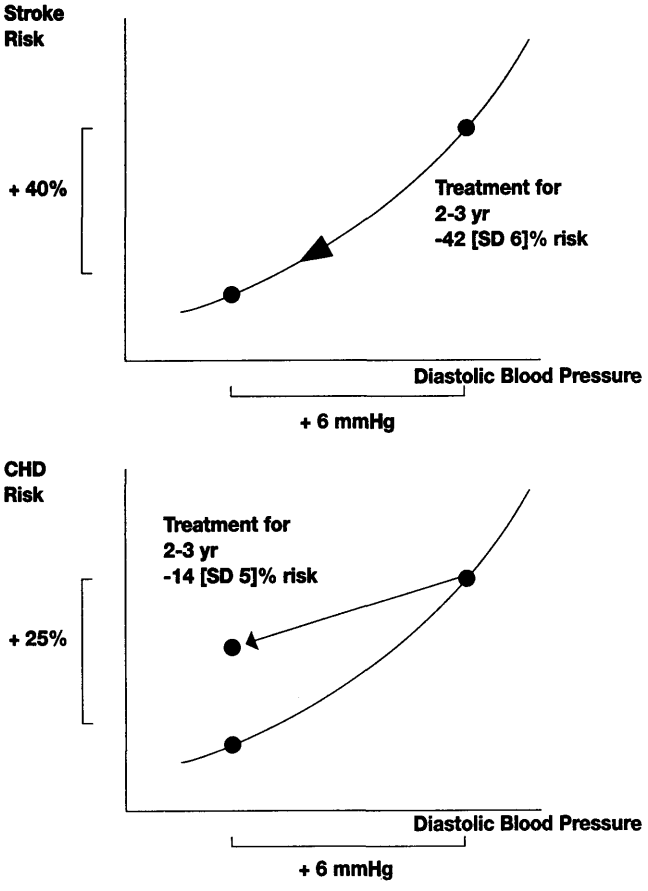

FIG. 3. Benefits of treatment of hypertension in reducing stroke risk and coronary heart disease (CHD) risk compared with epidemiological relationships between diastolic blood pressure, stroke risk, and CHD risk. Adapted from MacMahon et al. (8) and Collins et al. (15).

These four potential explanations would clearly have important, and very different, implications for both the threshold and choice of therapy for hypertension. Nevertheless, what becomes apparent from the meta-analysis is that the maximum benefit that could be expected from a new agent in terms of reversing excess cardiovascular risk is only about twice that provided by current treatments, and that only if any vascular damage caused by the elevated blood pressure is fully reversible.

POTENTIAL BENEFITS OF ANTIHYPERTENSIVE TREATMENT IN DIABETES

There have been no large intervention studies of antihypertensive treatment in diabetic patients, although data from the Hypertension Detection and Follow-up Program study suggest a similar benefit from lowering blood pressure in diabetic and nondiabetic subjects (26). Thus, the only way to assess possible benefits in these subjects is by applying the analysis of results of treatment in nondiabetic patients to observational studies in diabetic individuals, bearing in mind the possibility that not only risk-factor effects but also their reversibility may differ in diabetic and nondiabetic patients. The data of the subjects screened for the MRFIT study (14) were used for this analysis, in which 6-yr CHD mortality was presented for 5245 diabetic and 350,977 nondiabetic men aged 35–57 yr according to initial blood pressure levels. Figure 4 shows CHD mortality in all nondiabetic men and in those 36% of diabetic men with diastolic blood pressure ≥90 mmHg and the effects of treating hypertension in these subjects, assuming exactly the same proportionate reduction in

CHD mortality (11.2%) as calculated in the quoted overview of studies in nondiabetic men (15). Approximately 2.4 fewer CHD deaths would occur as a result of 6 yr of treatment for 1000 men.

The analysis of data from the MRFIT study (14) can also be applied to the possible benefits of other approaches to risk reduction, and in Fig. 5, the comparative theoretical effects of cholesterol (27) and blood pressure reduction (15), aspirin treatment (28), and cessation of smoking (29) on CHD mortality in the diabetic population are shown, with exactly the same method as for hypertension, i.e., multiplying the proportional benefit shown in the overviews of risk-factor reduction in nondiabetic subjects by the observed CHD mortality in the high-risk subgroup of diabetic subjects. Any of the therapeutic interventions may reduce mortality by ~1–3 CHD deaths/1000 men after 6 yr of follow-up. However, what these data do not provide is an estimate of likely benefits on total mortality. Although hypertension and aspirin trials generally show marked benefits on stroke mortality (15,28) and smoking cessation produces reductions in all causes of death (29), there is a question mark over the possible adverse effects of cholesterol reduction on nonvascular causes of death (27).

Many assumptions have been made for these calculations, and several points must be emphasized. First, the implications of a nonfatal stroke are very different from those of a nonfatal myocardial infarction. Although the data are not available to assess the possible reduction in stroke risk from treating hypertension in diabetic subjects, extrapolation from the results of the Medical Research Council study indicates that 300–400 person-yr of treatment would prevent a nonfatal stroke in a mildly hypertensive diabetic patient compared with 724 person-yr for a nonfatal myocardial infarct and 413 person-yr for a death (30). Second, these calculations have been made by assuming that treatment reverses ~50% of the effect of hypertension on CHD risk and 100% on stroke risk. This implies that, even if other agents are employed to overcome any putative iatrogenic blunting of benefit, without effects via other mechanisms, there could be no more than a twofold improvement in CHD event reduction with the same degree of reduction of blood pressure. Moreover, the clear advantages of treating hypertension with diuretics and β-blockers, i.e., the total reversal of the excess risk of stroke (15), have yet to be demonstrated for therapy with other agents. Yet if these new agents are able to safely effect greater reductions in levels of risk factors than currently available drugs, the possible maximal benefits would thereby increase—something the hydroxymethylglutaryl coenzyme A inhibitors are promising in the area of cholesterol reduction. The final point is that these calculations have been made by assuming a positive interaction between diabetes and hypertension; if the interaction is negative, or even additive, the potential benefits of treatment would be further reduced.

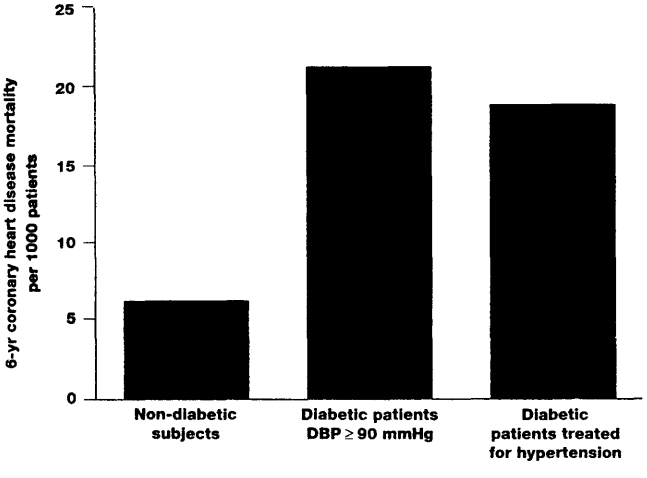

FIG. 4. Estimated benefits of treating hypertension on coronary heart disease mortality in hypertensive diabetic men aged 35–57 yr. DBP, diastolic blood pressure. Adapted from Stamler (14) and Collins et al. (15).

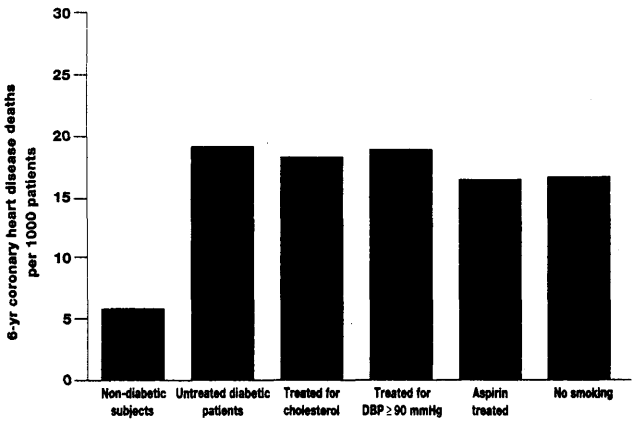

FIG. 5. Comparison of effects of different risk-factor interventions on coronary heart disease mortality in diabetic men aged 35–57 yr. Risk-factor interventions included treatment for cholesterol ≥6.7 mM, treatment of diastolic blood pressure (DBP) ≥90 mmHg, aspirin treatment, and cessation of smoking. Adapted from Stamler (14).

CONCLUSIONS

What, then, are the implications for choice of threshold and agent? The log-linear relationship between risk and blood pressure implies that the benefits of reducing diastolic blood pressure from 95 to 90 mmHg in a nondiabetic subject might parallel the benefits achieved by a reduction from 85 to 80 mmHg in a diabetic patient. However, the higher prevalence of asymptomatic ischemia in diabetic patients may theoretically increase the risks of treatment at a lower level of blood pressure

TABLE 1
United Kingdom Prospective Diabetes Study (UKPDS) hypertension study

	Objective
Methodology: randomization to	
Tight control with atenolol	<150/85 mmHg
Tight control with captopril	<150/85 mmHg
Less tight control	<200/105 mmHg
End points	
Death	6%/yr
Microvascular	6%/yr
Macrovascular	6%/yr

Patient population: 5600 patients included in UKPDS, 43% (n = 2408) with blood pressure >160/90 mmHg.
Power: assuming 15% advantage to active therapy, 71% likelihood of difference at 5% level by 1995.

as a result of the possible existence of a J-shaped curve (20,21). Similar arguments also apply to the degree to which blood pressure should be lowered; any potential gain in reducing stroke risk may be offset by a greater risk of infarction in an already compromised coronary circulation.

With regard to the choice of agent, it is clear that a drug that has beneficial effects on glucose tolerance, insulin sensitivity, lipids, left ventricular hypertrophy, and left ventricular function could have theoretical advantages (31). Angiotensin-converting enzyme (ACE) inhibitors, α-blockers, and Ca^{2+}-channel blockers may offer some or all such advantages. However, there is the hazard that such a drug might not, of necessity, reduce the risk of stroke and, for the reasons considered above, is not likely to produce a >25% reduction in CHD risk unless blood pressure is reduced more than it is by currently available agents. Yet if this putative agent were to have activity on insulin resistance or perhaps ion-transport mechanisms in the cell membrane such as Na^+-H^+ exchange, which may act as the common factor linking glucose intolerance, hypertension, left ventricular hypertrophy, and CHD risk (32,33), it is possible that additional benefit on CHD could become apparent. However, it is clear that it is only in randomized controlled trials that such hypotheses can be tested, and the intention of the United Kingdom Prospective Diabetes Study described in Table 1 is to randomize 2400 hypertensive diabetic patients to treatment with either a β-blocker or an ACE inhibitor, with a target for blood pressure control of ≤150/85 mmHg, and a less tightly controlled group for comparison (34). In recognition of the possibility that of every 100 patients started on therapy, 98 or 99 will not have benefited in terms of a reduction in event rate after 10 yr of treatment, the study is assessing quality of life on the different treatments as well as cardiovascular end points. In conclusion, we may well have identified both the threshold for treatment of hypertension in diabetes and the optimal choice of agent by the time this study is reported in 1995.

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