Efficacy of antihypertensive therapy in decreasing renal and cardiovascular complications in diabetes mellitus

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Abstract. The mechanism underlying the pathogenesis of microangiopathy and macroangiopathy in diabetes mellitus is hypothesized to be chronic hyperglycaemia. However, the values of blood glucose at which chronic diabetic complications develop at the renal and cardiac level are quite different. It is not clear whether this is due to different responses of kidney and heart tissues to the metabolic challenge of diabetes, or to the simultaneous role of other mechanisms contributing differently to the pathogenesis of chronic diabetic complications in renal and cardiac tissues. One of these mechanisms could be the simultaneous occurrence of arterial hypertension along with hyperglycaemia in diabetic patients.

We reviewed the available evidence in the recent medical literature and provide information on the relationships between hyperglycaemia and cardiovascular and renal complications in insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). The majority of reports indicate that the values of blood glucose appearing to be at threshold level for the development of cardiovascular complications are significantly lower than those determining renal complications (5.4 vs 10.0 mmol/l blood glucose concentrations 2 h after an oral glucose tolerance test). This was the case both in cross-sectional and prospective studies and also in intervention studies aimed at decreasing blood glucose concentrations by using strict metabolic control methods (The Diabetes Control and Complications Trial Research Group), which succeeded in delaying the rate of occurrence of microangiopathic complications at the kidney and retinal level but not so effectively at the cardiac level. Therefore, alternative therapeutic or supplementary strategies to blood glucose control should be adopted in diabetes to prevent diabetic complications. To date, the most effective approach, from our point of view, is antihypertensive therapy in order to prevent end-stage renal disease. We extensively reviewed the available literature which reported comparisons between angiotensin-converting enzyme inhibitors (ACE inhibitors) and calcium channel blockers (CCBs) in the treatment of arterial hypertension in diabetes. Intensified antihypertensive therapy achieving a blood pressure level below 130/85 mmHg has been shown to be useful in decreasing the rate of occurrence of chronic diabetic complications in diabetes mellitus. Both ACE inhibitors and CCBs have been shown to significantly improve the course of renal function in diabetic patients with incipient and overt nephropathy.

Key words: angiotensin-converting enzyme inhibitors; calcium channel blockers; cardiovascular complications; diabetes mellitus; diabetic nephropathy

Does a blood glucose threshold for the development of cardiovascular disease exist?

Cardiovascular disease (CVD), which includes heart disease (CHD), cerebrovascular disease and peripheral vascular disease, occurs with greater than normal frequency in diabetes [1], and CHD accounts for as much as 75% of the mortality in non-insulin-dependent diabetes mellitus (NIDDM) [2]. Raised blood glucose concentrations, much lower than those necessary to diagnose diabetes or even impaired glucose tolerance, have not been recognized fully and are also associated with an increased risk of CVD [3]. Glucose concentrations, which are also linked to an increased risk of CVD, are lower than those associated with microvascular disease. This is not surprising because the glucose dose concentration criterion was higher for patients who were at risk of developing retinal and renal disease [4]. However, the diagnostic criteria for diabetes mellitus have been revised recently, and a cut-off point of 126 and 110 mg/dl was indicated for the fasting plasma glucose value in the diagnosis of diabetes and impaired glucose tolerance respectively [5]. It is uncertain whether hyperglycaemia may explain...
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CVD in diabetes, although it is clearly related to diabetic micro- and macrovascular complications. The Honolulu Heart Study [6] demonstrated that a 12 year rate of fatal and non-fatal CHD events accounted for >1.45% in patients with a glucose concentration >6.4 mmol/l 1 h after a 50 g glucose challenge, during which a more advanced degree of glucose intolerance accounted for an excess incidence of only 0.37% (>10.6 mmol/l 1 h after oral glucose tolerance test). These findings are in keeping with the Whitehall Study’s results, suggesting that the post-prandial glucose value at which patients are at increased cardiac risk may be as low as 5.4 mmol/l [4].

A continuous graded association between blood glucose and the risk of CHD was also observed in patients not previously diagnosed with diabetes in the Framingham Offspring Study [7], where patients with normal glucose tolerance were categorized by quintiles of their fasting blood glucose. The mean values for the proportions of patients with CHD show a continuous, graded increase amongst the non-diabetic glucose tolerance categories, starting at the lowest fasting-glucose quintiles and increasing substantially for impaired glucose tolerance and previously unrecognized NIDDM. This observation disguises the categorical distinction between normal glycaemia, impaired glucose tolerance and NIDDM, at least from the CHD perspective, in which the risk appears to be a continuum.

During a recent analysis of the Paris Prospective Study, the incidence of fatal coronary heart disease was related to both fasting plasma glucose (FPG) and a 2 h oral glucose tolerance plasma test (2hPG), determined at a baseline examination [1,2]. Incidence rates were markedly increased at FPG ≥6.9 mmol/l (125 mg/dl) or 2hPG ≥7.8 mmol/l (140 mg/dl). With regard to the results of the intervention trials aimed at lowering blood glucose levels in IDDM and NIDDM patients, contrasting findings were reported.

However, the striking reduction in microvascular complications amongst IDDM patients in the Diabetes Control and Complications Trial (DCCT) [8] has renewed interest in the intensive glycaemic control in CHD and, initially, this trial was not designed to address the impact of intensive diabetes therapy on macrovascular complications. Although there was a 41% decrease in major cardiovascular complications among the DCCT patients in the intensive treatment cohort, the number of events was by no means small and the reduction was not statistically significant (P = 0.08). The few randomized controlled trials of intensive glycaemic control in patients with NIDDM have proved to be somewhat limited and have not shown any reduction in CHD end-points.

Observational analyses of the relationship between hyperglycaemia and CHD in established NIDDM need to take into account the co-existence of multiple related risk factors. Cross-sectional and prospective observa-

![Fig. 1. Cumulative risk of progression to proteinuria from microalbuminuria in 92 normotensive IDDM patients with incipient diabetic nephropathy during placebo, lisinopril and nifedipine treatments. The small table below indicates the number of patients in each group at risk for progression to proteinuria at baseline and after 1–2 years of follow-up (reproduced with permission of Crepaldi et al. [17]).](image)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Duration (years)</th>
<th>Drug</th>
<th>AER (µg/min)</th>
<th>P</th>
<th>GFR (ml/min)</th>
<th>P</th>
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<tr>
<td>MDNSG</td>
<td>43 IDDM and NIDDM</td>
<td>1</td>
<td>Perindopril</td>
<td>34</td>
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<td>35</td>
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<td>Chan et al.</td>
<td>102 NIDDM</td>
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<td>Enalapril</td>
<td>48</td>
<td>22</td>
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<td>92 IDDM</td>
<td>3</td>
<td>Lisinopril</td>
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<td>29</td>
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<td>Cilazapril</td>
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<td>Lisinopril</td>
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<td>Rossing et al.</td>
<td>IDDM</td>
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<td>Lisinopril</td>
<td>1047</td>
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tional studies, which have assessed specifically the multivariate, independent relationship between glycaemia and CHD in NIDDM patients, have not uniformly supported such an affinity. Of the five cross-sectional studies, only one was found to demonstrate an independent link between glycaemia (i.e., the glycohaemoglobin concentration) and overall macrovascular disease. The failure to show an association in cross-sectional studies could be the result of survival bias (e.g., patients particularly sensitive to hyperglycaemia may have died, leaving resistant survivors), inadequate measurements of long-term glycaemia, or no living relative.

No consistent association between hyperglycaemia and CHD mortality in NIDDM was demonstrated in prospective studies. Of eight studies, two discovered no association between blood glucose or glycohaemoglobin and CHD mortality on univariate or multivariate analysis. Furthermore, in two other studies, a significant univariate association disappeared after adjustment for age or other CHD risk factors [2–4]. Two studies of Finnish patients with NIDDM showed that either the fasting blood glucose or HbA1c at baseline predicted CHD mortality. However, neither blood pressure nor hyperlipidaemia had an independent relationship to the incidence of CHD, which calls the generalization of these studies into question. In a 4 year follow-up study of NIDDM patients from Taiwan, both total cholesterol and HbA1c were associated with the incidence of self-reported CHD and with ischaemic ECG changes [1–3]. This report was not clear enough in defining whether patients with pre-existing CHD were excluded from incidence analyses. Amongst maturity-onset diabetic patients in the Wisconsin Epidemiological Study of Diabetic Retinopathy, glycohaemoglobin concentrations predicted an 8 year CHD mortality after checking the systolic blood pressure and smoking habits in the analysis. However, there was no control for lipid concentrations and diabetes therapy. Hypoglycaemic therapy is an important factor due to the effect of glycaemic control on cardiovascular disease, and this could be masked if sulfonylurea or insulin therapy increased the risk of cardiovascular disease, either directly or through an increase in body weight [9].

**Strategies for the prevention of cardiovascular and renal complications in diabetes mellitus**

Our reasons for explaining these findings may not be fully understood. On the one hand, NIDDM commonly is accompanied by the established risk factors, such as hypertension and obesity, which are well-recognized hazards for cardiovascular disease in non-diabetic populations. On the other hand, factors specific to diabetes, either the direct or indirect consequence of hyperglycaemia, such as diabetic renal disease, may have an important role in the increased risk of cardiovascular disease, especially in IDDM, in which the non-specific risk factors are less prevalent.

To date, large intervention trials showing clear-cut evidence that the rate of development of CVD and CHD is decreased by antihypertensive therapy are still lacking in diabetic patients, at variance with non-diabetic subjects. The most effective intervention trial performed in diabetic patients aimed at ameliorating cardiovascular prognosis has been that of hypochondro-vascular agents. Indeed, a significant decrease in major cardiac events was achieved in a group of 105 NIDDM patients taking simvastatine therapy compared with 97 NIDDM patients on placebo in the 5.3 year study reported by Pyorala et al. [10].

The lack of a definite threshold of hyperglycaemia for the occurrence of CHD attracts several comments. From one point of view, the emphasis on the need for a major effort to accomplish and maintain blood glucose as close as possible to normal is strengthened. However, it is also likely that our efforts to decrease the rate of occurrence of CHD in diabetes would be somewhat unsuccessful both in IDDM and NIDDM patients, since extensive trials such as the DCCT study were capable of achieving an average HbA1c of 7.5%. The drawback of metabolic therapy of diabetes is particularly true in NIDDM, where the mechanism of impaired insulin action is not yet fully understood.

Therefore, additional therapeutic approaches need to be designed to prevent the development of complications in diabetic patients. At the moment, the most successful intervention has been that of antihypertensive therapy, particularly with regard to renal complications. As far as cardiovascular complications are concerned, the rate of occurrence of both stroke and CHD is related inversely to the diastolic blood pressure in the general population. It is conceivable that these results may be extrapolated to diabetic patients, although it has to be pointed out that unequivocal evidence concerning these issues has not yet been reported.

**Antihypertensive therapy with angiotensin-converting enzyme inhibitors and calcium channel blockers**

The first reports showing a long-term comparison between angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) in diabetic patients with incipient nephropathy were from the Melbourne Diabetic Nephropathy Study (MDNS) [11] and Chan et al. [12]. The MDNS was a randomized study of hypertensive and normotensive IDDM and NIDDM patients with persistent microalbuminuria [albumin excretion rate (AER) between 20 and 200 μg/ min]. The patients were assigned randomly to treatment with perindopril or nifedipine in doses aimed at achieving equivalent hypotensive efficacy. The effects on blood pressure, albuminuria and glomerular filtration rate (GFR) were analysed.

No significant differences were observed in the blood pressure or albuminuria response of patients, whether hypertensive or normotensive, treated with perindopril.
or nifedipine over 1 year. No vital differences were observed with either treatment regarding the GFR. These authors also evaluated the hypothesis that chronic ACE inhibition leads to angiotensin II suppression with resultant compensatory vasoconstrictor mechanisms to maintain blood pressure. If this is the case, cessation of ACE inhibition would restore angiotensin II levels and result in a rebound in blood pressure at variance with CCBs treatment. However, albuminuria increased significantly, with no difference between the two treatment groups 1 month after stopping antihypertensive therapy.

Similar results in NIDDM patients were noticed during a 6 month period of treatment using enalapril as compared with nifedipine [12]. Previous reports [13] on much smaller cohorts of patients during a follow-up period of 6 weeks showed a lower effect of nifedipine as compared with captopril on the AER in diabetic patients with incipient nephropathy. However, these findings were also at variance with a 4 week study comparing the capacity of nicardipine and enalapril to inhibit AER in hypertensive microalbuminuric diabetic patients.

CCBs inhibit the vasoconstrictor and also the hypertrophic and hyperplastic effects of angiotensin II and other mitogens in mesangial and vascular smooth muscle cells through blockade of a calcium-dependent mechanism [14]. Earlier studies, however, demonstrate marked differences between antiproteinuric effects of dihydropyridine (such as nifedipine) and non-dihydropyridine (such as verapamil-diltiazem) CCBs. Bakris et al. [15] recently randomized 52 NIDDM patients with proteinuria >2.0 g/day and creatinine clearance <70 ml/min to atenol, CCBs and lisinopril then followed them for an average period of 5 years. Their findings showed that lisinopril and CCBs were both similarly more effective than atenol in delaying the decay of creatinine clearance and in lowering the excretion rate of proteins.

Our research group recently investigated [16] the course of renal function in two cohorts of hypertensive NIDDM patients, measuring plasma clearance of 51 patients (Cr-EDTA) every 6 months during antihypertensive double blind, randomized therapy, either with cilazapril or with amlodipine. The rate of decline of the GFR was 2.0 ml/min/year in hypertensive NIDDM patients without microalbuminuria and 2.3 ml/year in hypertensive NIDDM patients with microalbuminuria during a 3 year treatment [16]. No differences were observed between the groups treated by a dihydropyridine CCBs (amlodipine) and an ACE inhibitor (cilazapril). The characteristic of this latter study was the strict antihypertensive control aiming at a target blood pressure level below 135 and 85 mmHg for systolic and diastolic blood pressure respectively.

More recently, Rossing et al. [17] treated a group of IDDM patients with overt albuminuria with either nisoldipine or lisinopril and evaluated the change in the GFR and AER during a 12 month period. The AER decrease was markedly greater with lisinopril than with nisoldipine. However, the decline in GFR improved significantly with nisoldipine rather than with lisinopril.

Two comments can be made concerning this latter report. Firstly, a decrease in the protein excretion rate is not always necessarily associated with a more favourable course of renal function. The findings of Rossing et al. [17] are in keeping with those of Chan et al. [12], who also observed a significant improvement in plasma creatinine with nifedipine, and in comparison with enalapril, despite a more marked reduction in the protein excretion rate than with ACE inhibitors. This observation is noteworthy also from a pathophysiological angle as it does not support the tenet that altered albumin and protein excretion rates are not only an effect but also a determining factor in the development of renal damage.

More recently, a multicentre trial in Italy [18] recruited a large cohort of IDDM patients with normal blood pressure, and AER in the range of microalbuminuria [18]. The results of this latter study showed that the rate of occurrence of proteinuria among these microalbuminuric patients was delayed similarly by nifedipine and lisinopril during a 3 year period of treatment (Figure 1 and Table 1).

To summarize, it seems plausible to conclude that ACE inhibitors and CCBs are similarly effective in protecting the kidney from the progression of renal damage in diabetes and may suggest that the degree of blood pressure control is the most important factor to be taken into consideration.

This view is also in agreement with the conclusions of the Sixth Joint National Committee Report [19] on the diagnosis, definition and treatment of arterial hypertension, which considers both ACE inhibitors and CCBs favourably for the treatment of diabetic patients on the basis of the two reports [16,17], cited in Table 1, and indicates values of 130/85 mmHg as a cut-off point for the diagnosis and as a treatment target of arterial hypertension. As a word of caution, although prospective confirmation is still required, a higher number of cardiovascular events associated with the use of isradipine were found among hypertensive patients taking CCBs than in those on diuretic therapy [20].

However, a possible bias of this latter report is that patients with known diabetes, and thus being treated by diet, oral agents or insulin, were not included, whereas patients with undiagnosed diabetes, and, therefore, untreated, were included. Therefore, one can suggest that the worst cardiovascular outcome observed was not due to the omission of treatment for diabetes, but rather to diabetes itself [20].

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