

Long-Term Renoprotective Effect of Nisoldipine and Lisinopril in Type 1 Diabetic Patients With Diabetic Nephropathy

Response to Tarnow et al.

Over the last 20 years, the importance of antihypertensive therapy in retarding the progression of diabetic nephropathy has been extensively investigated. Initial studies emphasized the use of conventional agents, such as vasodilators (e.g., hydralazine), β -blockers, and diuretics, in reducing urinary albumin excretion and slowing the decline in glomerular filtration rate (GFR) in type 1 diabetic patients with overt nephropathy (1,2). Subsequent studies supported by findings from various animal experiments (3) have suggested a possible superiority of ACE inhibitors over other antihypertensive agents in retarding the progression of diabetic renal disease (4). This was most clearly demonstrated by the Collaborative Study Group, which showed that captopril treatment was associated with reduced progression to end-stage renal failure (5). In that large study, the authors postulated an independent renoprotective effect of captopril, but this issue has never been fully resolved because captopril treatment in that study may have been associated with a modest reduction in blood pressure of <5 mmHg.

Calcium channel blockers (CCBs) are widely used as antihypertensive agents, yet their specific effects as renoprotective agents remain controversial. Some relatively short-term studies have suggested that in contrast to ACE inhibitors, CCBs and in particular the dihydropyridine class (e.g., nifedipine or amlodipine) are associated with an increase in albuminuria (6,7). Indeed, several meta-analyses that have included type 1 and type 2 diabetic patients with and without hypertension and with early or overt nephropathy have suggested that dihydropyridine CCBs and nifedipine in particular do not reduce albuminuria as effectively as ACE inhibitors, despite similar efficacy as antihypertensive agents (8,9). Nevertheless, the data on these agents in preventing decline in renal function, the

major clinical end point relevant to the progression on renal disease, have been rather limited particularly in type 1 diabetes. The recent study by Tarnow et al. (10) described in this issue has directly addressed this issue and specifically included 24-h ambulatory blood pressure monitoring to determine if both the ACE inhibitor lisinopril and the long-acting dihydropyridine CCB nisoldipine had similar effects on blood pressure (10). In this 4-year prospective study in 48 hypertensive type 1 diabetic patients with overt nephropathy, similar reductions in blood pressure were observed with both drugs. Like the predictions from experimental studies and previous clinical studies in other diabetic populations, ACE inhibition was associated with a 50% decrease in albuminuria, yet CCB treatment was associated with no decrease in this parameter. By contrast, no difference in decline in renal function was detected between the two drugs. These findings suggest that a reduction in albuminuria cannot be considered a reliable surrogate for renal protection, and it contrasts with previous findings from Parving's group who suggested that reduction in proteinuria ultimately translated to benefits in terms of slowing the decline in GFR in this population (11). Indeed, it is likely that this link between effects on albuminuria and renal function—though clearly detectable in natural history studies or in patients prescribed with ACE inhibitors—cannot be assumed in the setting of dihydropyridine calcium antagonist therapy.

One must be cautious in concluding from this relatively small study that CCBs and ACE inhibitors have similar renoprotective properties. The authors indicate in their study that they had 80% power to detect a $2 \text{ ml} \cdot \text{min}^{-1} \cdot \text{year}^{-1}$ difference in effect on GFR between the two treatments. However, this was a population with rela-

tively preserved renal function, despite hypertension and overt proteinuria. It is possible that in a population with more advanced renal impairment, a superiority of the ACE inhibitor in retarding nephropathy may have been detected. In a range of studies by Bakris et al. (12) in proteinuric diabetic patients with advanced nephropathy, it appeared that ACE inhibitor treatment, in addition to reducing urinary protein excretion, was associated with a less rapid decline in GFR when compared with the group treated with the β -blocker atenolol. Interestingly, in that study, similar beneficial effects on renal function were also observed with the nondihydropyridine CCBs verapamil and diltiazem (12). These investigators have suggested significant differences in terms of renoprotection between different classes of CCBs in diabetic nephropathy, and this issue remains unresolved (13). It must be appreciated that the studies performed by the Bakris group were in type 2 diabetic subjects, which could represent an additional potential confounding factor.

Ultimately, these antihypertensive drugs must be considered not only in terms of renal protection, but also in terms of cardiovascular protection (14). This context is particularly relevant when considering dihydropyridine CCB treatment. These agents have recently been subjected to intensive investigation in the setting of diabetes with a number of studies, suggesting a possible deleterious effect of dihydropyridine CCBs on cardiovascular mortality in diabetic subjects (15). These studies have generally been performed in type 2 diabetic patients and cannot be extrapolated to the type 1 diabetic population. Furthermore, the recent HOPE study has suggested a specific cardioprotective effect of the ACE inhibitor ramipril in high-risk type 2 diabetic patients (16). These findings must be considered in the context that cardiovascu-

lar disease remains a major cause of morbidity and mortality in the type 1 diabetic population with proteinuria (17). It is intriguing that there appeared to be a trend, although it was not statistically significant in the study by Tarnow et al. (10), for more vascular events and death in the CCB-treated group (10). It is hoped that in the future interventional studies in the type 1 diabetic population addressing choice of antihypertensive therapy will explore not only renal but other complications, including retinopathy and macrovascular disease.

CCBs have not generally been considered first-line treatment for hypertension in diabetic subjects or in those with diabetic renal disease, as outlined in the recently published guidelines from the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (18), the World Health Organization (19), and the International Society of Hypertension (19). However, these agents appear to be effective blood pressure-lowering drugs that, as suggested in the study by Tarnow et al. (10), may confer more renal protection than generally assumed. The data available in type 1 diabetes are still rather scant and restricted to small groups of patients with relatively preserved renal function. In regard to type 2 diabetic patients with overt nephropathy, it is anticipated that the role of CCBs will be further clarified over the next 12–18 months with the imminent completion of several multicentered studies (RENAAL [20] and the Irbesartan Type II Diabetic Nephropathy Trial [21]) in this population.

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