ARTICOLI ORIGINALI

Preventing nephropathy in type 2 diabetes

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Corrispondenza a: ;

Nephropathy of type 2 diabetes is the leading cause of end stage renal disease (ESRD) [1].Currently, more than 50% of patients on renal replacement therapy in the US are diabetics. The yearly incidence of diabetics progressing to ESRD and the proportion of ESRD patients with diabetes is progressively increasing due to the ongoing epidemic of type 2 diabetes. According to the World Health Organization (WHO), diabetes affects over 170 million people, and, due to progressive ageing of the population, life-style modifications and increasing burden of obesity, this number is expected to rise to 370 millions by 2030 [2]. About one third of those affected will eventually have progressive deterioration of renal function [2]. Untreated, these patients progress to ESRD within 10 years or die prematurely because of cardiovascular complications (that are 10-fold more frequent than in those without and the general population) [1]. Costs for renal replacement therapy of these patients – and for treatment of related complications - are also progressively increasing. Where renal replacement therapy is available only for a small minority of subjects, these patients already die because of uremia.

The first clinical sign of renal dysfunction in diabetic patients is persistent microalbuminuria [3] which develops in 2 to 5 percent of patients per year [4] [5] and progresses to overt proteinuria in 20 to 40 percent of cases [6] [7]. In 10 to 50 percent of patients with proteinuria, chronic kidney disease develops that ultimately requires dialysis or transplantation [8] [9] [10]. Of great concern, 40 to 50 percent of type 2 diabetic patients with microalbuminuria eventually die of cardiovascular disease [6] [11] [12]. This is three times as a high rate of death from cardiac causes as among patients who have diabetes but have no evidence of renal disease. Thus, preventing (or delaying) the development of microalbuminuria is a key treatment goal for renoprotection and, possibly, for cardioprotection.

A small study found that the ACE inhibitor Enalapril decreased the incidence of microalbuminuria in patients with type 2 diabetes and normal blood pressure, as compared with placebo [13]. This study, however, included only non obese subjects. Most important, the blood pressure was lower in patients on Enalapril than in those on placebo throughout most of the study period and the study was underpowered to evaluate whether the effect of Enalapril in preventing microalbuminuria was explained by ACE inhibition or, rather, by more effective blood pressure control. More recently, the BErgamo NEphrologic DIabetes Complications Trial (BENEDICT) found that treatment with the ACE-inhibitor Trandolapril (either alone or combined to the calcium channel blocker Verapamil) significantly reduced the incidence of microalbuminuria in 1204 patients with type 2 diabetes and hypertension, but normal urinary albumin excretion, as compared with placebo [14]. The effect of preventing microalbuminuria exceeded expectations based on changes in blood pressure alone and was not enhanced by combined calcium channel blocker therapy.

Studies in patients with type 2 diabetes and micro - or macro - [8] [9] albuminuria clearly show that ARBs may shear with ACE inhibitors a similar renoprotective effect in this typology of patients. Indeed, ARBs decreased the incidence of macroalbuminuria in patients with microalbuminuria [15], and slowed the progression to ESRD in those with macroalbuminuria at study entry [8] [9]. Recently one large randomized trial reported that the ARB Olmesartan reduced the onset of microalbuminuria in more than 4000 patients with type 2 diabetes and hypertension with normal urinary albumin excretion. However, treatment effect was no longer statistically significant when the analyses were adjusted for blood pressure control throughout the observation period. Moreover, Olmesartan therapy was burdened by an excess cardiovascular mortality compared to placebo [16]. These findings challenge the protective effect of ARB therapy against progression to microalbuminuria and raise concern on their safety profile in this population. Whether the beneficial effect against the development of microalbuminuria is enhanced when ACE inhibitors and ARBs are given in combination is not established so far. However, finding that combined ACE inhibitor and ARB therapy more effectively than single drug RAS blockade reduced albuminuria [17] or proteinuria [18] in subjects with type 2 diabetes, suggests that the renoprotective effect of combined therapy could be superior to that of single drug blockade of the RAS also in diabetic patients with no evidence of renal disease.

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