Cardio DIGEST
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Editorial

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MICROALBUMINURIA AND CV MORTALITY

With the increasing prevalence of type 2 diabetes, it should not have escaped your attention that the associated increased and early cardiovascular (CV) mortality looks set to climb. Left unchecked, the relentless progression of diabetic renal disease is likely to contribute to this mortality risk. Following a diagnosis of type 2 diabetes, 2 % of patients progress annually to microalbuminuria and thereafter 2.8 % progress to proteinuria annually (Adler et al, 2003). Albuminuria is independently associated with elevated CV mortality risk across the continuum from normal to overt proteinuria levels. Indeed, microalbuminuria carries a two- to four-fold increase in the risk of death, while overt proteinuria carries an even higher risk. Sadly, individuals with proteinuria are more likely to die in any year than to develop renal failure. In only 5 years, 32 % of patients with type 2 diabetes who also have microalbuminuria die. The onset of microalbuminuria reflects systemic vasculopathy. As witnessed in large-scale, randomised, controlled trials such as IRMA2 and MICRO-HOPE (with respect to existing microalbuminuria) as well as IDNT and RENAAL (with respect to proteinuria), inhibitors of the renin–angiotensin system (RAS) significantly reduce albuminuria and delay progression to nephropathy and end-stage renal disease in type 2 diabetes. Encouragingly, recent *post hoc* analysis of RENAAL indicates that short-term albuminuria reduction also affords long-term CV protection, although reduction of albuminuria, per se, was not the primary end point of RENAAL (de Zeeuw et al, 2004). If we are to truly curtail CV mortality in people with type 2 diabetes, slowing the first onset of persistent microalbuminuria appears an increasingly desirable therapeutic goal.

Given that at least 50 % of people with type 2 diabetes are hypertensive, may have other exacerbating comorbidities and typically require aggressive combination antihypertensive therapy, some debate remains over current choice of first-line therapy. However, a recent systemic review of the effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) on mortality in patients with diabetic nephropathy indicates that ACE inhibitors significantly reduce early fatality, but that no such evidence exists for ARBs (Strippoli et al, 2004). This same review confirms that ACE inhibitors reduce the risk of progression from microalbuminuria to proteinuria by 55 % (n=2010) and increase the rate of regression from microalbuminuria to normoalbuminuria by about 3.4-fold. The results of the BErgamo NEphrologic DIabetes Complication Trial (BENEDICT) published in November 2004 should now swing the debate even further in favour of ACE inhibitors.

BENEDICT is the first large-scale trial designed to examine the prevention of development of microalbuminuria in hypertensive patients with type 2 diabetes who have normoalbuminuria at baseline (Ruggenenti et al, 2004). Following a 3- to 6-week washout of any existing antihypertensives, this multicentre, double-blind study randomised 1209 hypertensive patients with type 2 diabetes, aged ≥40 years with normal urinary albumin excretion (UAE; <20 g/min) and normal renal function (serum creatinine ≤1.5 mg/dl) to one of four treatments: the non-hydropyridine calcium-channel blocker verapamil 240 mg/day; the ACE inhibitor trandolapril 2 mg/day; the combination of verapamil 180 mg/day plus trandolapril 2 mg/day; or placebo. The blood pressure target was 120/80 mmHg and the primary end point – development of persistent microalbuminuria (defined as a UAE of 20–200 g/min at two clinic visits) – was assessed over a median of 3.6 years. Trandolapril slowed progression to microalbuminuria by 53 % alone and by 61 % in combination with verapamil, compared with placebo (both *P*=0.01). In contrast, the effect of verapamil alone was similar to that of placebo and not statistically significant. Although there were significant reductions in average trough systolic and diastolic blood pressures, with small significant differences between the trandolapril (with or without verapamil) and placebo groups, the benefit of ACE inhibition with trandolapril exceeded expectations based on changes in blood pressure alone. Current National Institute for Health and Clinical Excellence guidelines already recommend ACE inhibitors as the antihypertensive class of choice in patients with type 2 diabetes and microalbuminuria or proteinuria. Given the CV mortality implications of microalbuminuria – recent data even indicate a dose–response association with risk of atherosclerosis in the general population at levels well below that classified as microalbuminuria (Furtner et al, 2005) – BENEDICT adds to an already compelling case for ACE inhibitors as first-line antihypertensives in people with type 2 diabetes and hypertension. Indeed, it appears that it may never be too early for physicians to initiate ACE inhibitors in these patients.

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Adler AI, Stevens RJ, Manley SE et al (2003) Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney International* **63**(1): 225–32

de Zeeuw D, Remuzzi G, Parving HH et al (2004) Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation* **110**(8): 921–7

Furtner M, Kiechl S, Mair A et al (2005) Urinary albumin excretion is independently associated with carotid and femoral atherosclerosis in the general population. *European Heart Journal* **26**(3): 279–87

Ruggenenti P, Fassi A, Ilieva AP et al (2004) Preventing microalbuminuria in type 2 diabetes. *New England Journal of Medicine* **351**(19): 1941–51

Strippoli GF, Craig M, Deeks JJ et al (2004) Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *British Medical Journal* **329**(7470): 828–31