Prevalence of microalbuminuria in type 2 diabetes: lessons learned from the ROADMAP study

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It is plausible to assume that the earlier the stage of diabetic nephropathy the greater is the chance of successful intervention; this is suggested e.g. by the observation of Siragy and Carey [1], who report that in diabetic nephropathy the efficacy of delayed RAS blockade is limited. In the past, it had commonly been assumed that kidney disease in diabetes starts with an increase in albuminuria and progresses to the stages of microalbuminuria and subsequently to overt proteinuria and progressive loss of renal function. Although recent observations indicate that this is not true in all cases of type 2 [2, 3] or type 1 diabetes, this scheme is certainly valid in the majority of patients. The urinary albumin excretion in diabetes constitutes a continuum so that the diagnosis of microalbuminuria is somewhat arbitrary—which led to the proposal to abandon the concept of microalbuminuria [5], because in type 2 diabetics renal and cardiovascular (CV) risks increase progressively with increasing albumin excretion even within the normal range [6]. Nevertheless, the onset of microalbuminuria remains [1] a valid parameter for intervention studies.

The currently available interventions to reduce albuminuria are mainly based on two interventions, i.e. lowering of blood pressure (BP) and blockade of the renin–angiotensin system by ACE inhibitors (ACEi) or angiotensin receptor blockers (ARB).

In the BENEDICT trial, Ruggenenti and Remuzzi [7] documented the efficacy of RAS blockade with ACE inhibitors (ACEi) for the prevention of microalbuminuria in patients with type 2 diabetes. The situation had remained less clear for the effect of angiotensin receptor blockers (ARB), because negative outcomes had been reported by several authors [8, 9].

In order to clarify this issue, the ROADMAP study [10, 11] was designed to prove or disprove the hypothesis that early intervention with an ARB—in this study with Olmesartan—delays the time to onset of microalbuminuria. To this end, 4447 normoalbuminuric patients with type 2 diabetes and at least one additional CV risk factor were randomized to receive either placebo (on top of BP medication other than RAS blockers) or Olmesartan 40 mg (in addition to BP medication other than RAS blockade). The two groups comprised 2215 and 2232 patients, respectively.

The primary endpoint was the time to the first onset of microalbuminuria (assessed by morning spot-urine measurements with at least two out of three valid tests being positive).

The secondary endpoints were CV events: CV morbidity such as acute coronary syndrome, congestive heart failures, silent MI, coronary vascularization (PTCA/CABG), stroke, peripheral vascular disease, new-onset atrial fibrillation, transient ischemic attack and CV mortality (i.e. sudden cardiac death, fatal MI, fatal stroke, congestive heart failure, death after PTCA or CABG).

In addition, renal function was a second endpoint, i.e. end-stage renal disease, doubling of serum creatinine and change in the estimated glomerular filtration rate (eGFR). Forty-six percent of study participants were male, the median age was overall 58 years (± 8.7), body mass index 31.0 kg/m² (± 4.9), duration of diabetes 73.3 months (±72.4), serum creatinine 77.5 μmol/L (16.2), HbA1c 7.7% (± 1.6) and eGFR 84.9 mL/min/1.73 m² (± 17.2). The CV risk factors were well balanced at baseline with four to five CV risk factors in >50% of the patients. At baseline, the BP was 136/81 mmHg [10, 11].

The study results [10] showed that on Olmesartan 40 mg/day the risk of de novo onset of microalbuminuria was reduced by 23%; the hazard ratio was 0.770 (0.63–0.94) with P = 0.01. Of note, the greatest benefit was seen (i) in individuals with higher BP (similar to what was seen in the BENEDICT trial), (ii) with eGFR <83 mL/min/1.73 m², (iii) with lower HbA1c and (iv) with higher baseline albuminuria. The eGFR at last assessment was lower by 3.6 mL/min/1.73 m² (P < 0.0001) in the Olmesartan group compared with the placebo group. It is plausible to assume that this was the result of reversal of glomerular hyperfiltration.

On treatment, the BP was 125.7/74.3 mmHg in the Olmesartan and 128.7/76.2 mmHg in the placebo group. Of note, this was the study in diabetic nephropathy with the so far most stringent BP control at baseline, i.e. 136/81 mmHg. The values are similar to what was achieved...
overall also in the ACCORD study including patients with diabetic nephropathy [12].

The number of patients developing microalbuminuria was 178 in the Olmesartan and 210 in the placebo arm (hazard ratio 0.770, CI 0.630–0.941) P = 0.01. Specifically in the subpopulation with hypertension, Olmesartan delayed the time to onset of microalbuminuria by 25% and patients with reduction of systolic pressure >17.5 mmHg (median) had a lower incidence of microalbuminuria [13].

The positive outcome of the ROADMAP trial with respect to the onset of microalbuminuria is of particular note in view of past studies in which ARB had failed to reduce the onset of microalbuminuria. In the DIRECT trial [9], the primary endpoint of retinopathy was less frequent on Candesartan and the onset of microalbuminuria was also reduced in type 2 diabetic patients—but this difference was not statistically significant. It is of note, however, that microalbuminuria was not the primary endpoint.

The RASS trial [8] was a study in type 1 diabetic patients; retinopathy and nephropathy were assessed. In this study, Losartan reduced the onset of microalbuminuria, but this was not statistically significant in this very small study.

The study with the ARB Olmesartan complements the BENEDICT trial [7] in which ACE inhibition using Trandolapril reduced the progression of microalbuminuria significantly in type 2 diabetic patients. The risk was reduced by 50%. It is of note, however, that benefit was seen only in patients with systolic BP >139 mmHg, while no significant effect was seen in patients with systolic BP <139 mmHg. Comparing the efficacy of RAS blockade in the ROADMAP study (using the ARB Olmesartan) with the BENEDICT study (using the ACE inhibitor Trandolapril), the efficacy in individuals with systolic BP <130 mmHg was higher in the ROADMAP than in the BENEDICT trial.

Total mortality in the ROADMAP study was <1%, i.e. 2.9 cases per 1000 person-years, the lowest in large trials of diabetic nephropathy and comparable with the BENEDICT trial with three cases per 1000 person-years; this contrasts with the IDNT and RENAL studies on patients with advanced diabetic nephropathy [14, 15] where total mortality was 60 cases per 1000 patient-years.

What is the potential explanation for the unanticipated higher frequency of acute cardiac death in the ROADMAP trial? In the ONTARGET trial, Sleight [16] had shown that the systolic BP values <120 mmHg at follow-up were associated with a higher adjusted 4.5 year risk of adverse events. In addition, Messerli [17] showed in the INVEST trial of patients with coronary heart disease, treated with beta blockers or calcium channel blockers, that mortality at follow-up was increased in patients with a diastolic BP <70 mmHg. These observations support the recommendation of Mancia [18] that systolic BP should not be lowered to values <120 mmHg in patients with cardiac disease. This consideration is important to interpret the findings that—although overall CV morbidity was, if anything, lower in the Olmesartan arm (81 versus 91 events, P = 0.37)—CV mortality was higher in the Olmesartan arm (15 versus 3, P = 0.01). The number is too small to draw reasonable statistical conclusions, but assessment of the individual cases showed that the two most frequent modalities were sudden cardiac death and fatal myocardial infarction, occurring in patients with pre-existing coronary heart disease.

In the ROADMAP study, a trend towards a higher CV mortality was observed in patients with pre-existing coronary heart disease in whom the BP was in the lowest quartile during follow-up or who had the strongest BP reduction.

In conclusion, in subjects with type 2 diabetes and BP controlled as recommended by the guidelines, early treatment with the ARB Olmesartan significantly reduces the risk of developing microalbuminuria.

Olmesartan had no detrimental effects on hard renal outcomes in the ROADMAP study.

Fatal CV events were few, but more frequent in the Olmesartan group, possibly due to the episodes of hypertension in some patients with pre-existing CHD.

Conflict of interest statement. None declared

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