

Randomized Olmesartan And Diabetes Microalbuminuria Prevention Study (ROADMAP)

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Although a number of interventions have been shown to retard or prevent progression of clinically manifest diabetic nephropathy,^{1,2} once diabetic patients are proteinuric (>300 mg/day), the vast majority of patients progress relentlessly, losing glomerular filtration rate (GFR), increasing the rate of excretion of albuminuria, and ending up in terminal renal failure or succumbing to cardiovascular (CV) accidents (UKPDS [United Kingdom Prospective Diabetes Study]).³

Against this background, it has appeared increasingly attractive not to wait until progressive diabetic nephropathy has set in, but to nip it in the bud, namely, to prevent the very first stage of diabetic nephropathy – microalbuminuria. After the seminal contributions of Mogensen,⁴ Viberti,⁵ and Parving,⁶ it has uniformly been acknowledged that microalbuminuria is the first clinically manifest stage of diabetic nephropathy, although some renal pathology may exist even before the onset of microalbuminuria.^{7,8}

In the past, in the BENEDICT study (Bergamo Nephrologic Diabetes Complications Trial) Ruggenti⁹ had shown that in a sizeable proportion of patients with type 2 diabetes, prevention of microalbuminuria is feasible by blocking the renin-angiotensin system (RAS) using the angiotensin-converting enzyme inhibitor, Trandolapril (2 mg/day); this had been accomplished even though strict normotension was not achieved in all patients.

Against this background, Haller et al.¹⁰ initiated the ROADMAP study (Randomized Olmesartan And Diabetes Microalbuminuria Prevention Study) to address the question whether achievement of more strict normotension and blockade of the RAS by administration of the angiotensin-receptor blocker (Olmesartan) also prevents or retards the onset of microalbuminuria. To this end, type 2 diabetic patients with normoalbuminuria received 40 mg/day Olmesartan or placebo; the high dose was selected

to affect the intrarenal RAS. The primary endpoint was the time to the first onset of microalbuminuria in morning spot urines (with at least 2 of 3 valid tests positive). Important secondary endpoints were CV events, both CV morbidity (acute coronary syndrome, congestive heart failure, silent myocardial infarction [MI], coronary revascularization percutaneous transluminal coronary angioplasty-coronary artery bypass graft [PTCA-CABG], stroke, peripheral vascular disease, new-onset atrial fibrillation, transient ischemic attack) or CV mortality (sudden cardiac death, fatal MI, fatal stroke, congestive heart failure death, death post PTCA or CABG). A further secondary endpoint was loss of renal function, i.e., end-stage renal disease or doubling of serum creatinine.¹⁰ The study was planned to be able to detect a 30% risk reduction in the incidence of microalbuminuria (hazard ratio 1.433) with a power of 90% at 5% significance level.

The inclusion criteria were: age 18–75 years, type 2 diabetes with fasting plasma glucose (>7.0 mmol/l), glycated hemoglobin (HbA_{1c} $>6.5\%$) or treatment for diabetes, normoalbuminuria (<25 mg/g creatinine in men and <35 mg/g creatinine in women), and at least 1 additional CV risk factor (hypercholesterolemia, low high-density lipoprotein cholesterol, high triglycerides, obesity, large waist circumference, hypertension, smoking). The study randomized 4449 patients in Portugal, Spain, France, United Kingdom, Belgium, the Netherlands, Germany, Italy, Czech Republic, Austria, Hungary, Poland, Romania, Bulgaria, Ukraine, Russia, Estonia, and Lithuania. The most relevant baseline characteristics comprised¹¹ HbA_{1c} 7.65% (± 1.62) in the Olmesartan group and 7.66% (± 1.62) in the placebo group; estimated GFR (eGFR) 84.99 ml/min/1.73m² (± 17.01) in the Olmesartan and 84.72 (± 17.30) in the placebo group; mean sitting systolic blood pressure 137 ± 16 mmHg in the Olmesartan and 136 ± 15 mmHg in the placebo group; mean sitting

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diastolic blood pressure 81 ± 10 mmHg in the Olmesartan and 80 ± 9 mmHg in the placebo group. The majority of the patients had 4 to 5 CV risk factors.

In addition to Olmesartan, at physician's discretion, patients received calcium channel blockers, diuretics or β -blockers to reach the target blood pressure goal. At the end of the study, blood pressure was $125.7/74.3$ mmHg in the Olmesartan and $128.7/76.2$ mmHg in the placebo group.

The primary endpoint (i.e., time to first occurrence of microalbuminuria) was significantly reduced (risk reduction 23%, $P = 0.01$). At the end of the study, blood pressure was lower in the Olmesartan group by 3.0 mmHg systolic/1.9 mmHg diastolic, but statistical correction for the blood pressure difference continued to show significance (HR 0.823, $P < 0.05$).

This positive outcome is remarkable because in type 2 diabetic patients treated with Candesartan in the DIRECT trial¹² (where microalbuminuria was not a primary endpoint) and in type 1 diabetic patients treated with Losartan or Enalapril in a small study, RASS (Renin Angiotensin System Study),¹³ a significant reduction of the onset of microalbuminuria had not been achieved.

In the BENEDICT study⁹ the use of Trandolapril had achieved risk reduction by 50% vs. placebo. It is of importance that in this study, baseline blood pressure was considerably higher ($151/87$ mmHg vs. $136/61$ mmHg in ROADMAP) and during the study a blood pressure of $<130/90$ mmHg was achieved in only 15% of patients as compared with 75% of patients in the ROADMAP study.¹⁴ A subsequent analysis of the BENEDICT study¹⁵ had shown that significant benefit was limited to type 2 diabetic patients with systolic blood pressure above 139 mmHg. Therefore, it is of considerable importance that in the ROADMAP study reduction of the onset of microalbuminuria was achieved despite much lower blood pressure values in the course of the study. The risk reduction in the ROADMAP study remained significant after correction for systolic and diastolic blood pressure during the study.

The total mortality in the ROADMAP study was the lowest observed so far in studies on diabetic nephropathy, i.e., $<1\%$ or 2.9 cases per 1000 person/years, compared with past large trials on diabetic nephropathy where mortality was approximately 60 cases per 1000 person/years in IDNT (Irbesartan in Diabetic Nephropathy)² as well as in the RENAAL study (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan).¹

Despite remarkably low overall mortality, there was a difference of CV mortality between the Olmesartan and placebo groups: 15 patients succumbed to CV events in the Olmesartan group compared with 3 patients in the placebo group. Detailed analysis showed that 7 of these cases had a history of coronary heart disease and 11 of these cases had episodes of blood pressure $<110/70$ mmHg before death.

Interestingly, at the end of the study there was a $4.76 \text{ ml/min/1.73m}^2$ difference of eGFR ($P < 0.0001$) between the Olmesartan group and the placebo group; the lower eGFR in the OLMESARTAN group most likely reflects reversal of glomerular hyperfiltration. There was no change in renal events, e.g., for an increase of serum creatinine by 25% or end-stage renal disease.

What are the implications of this study? Increased albuminuria increases the risk of progressive renal disease, but also of increased CV events and of all-cause mortality. For instance, in the HOPE study (Heart Outcomes Prevention Evaluation) and HOPE-TOO (HOPE Study Extension),¹⁶ early intervention with Ramipril, which had lowered albuminuria, had resulted also in fewer cases of MI, stroke, and lower CV mortality.

The study has good news and bad news. The good news is that even in patients with excellent blood pressure control, additional blockade of the RAS with an angiotensin-receptor blocker on top of other antihypertensive medications still lowers the rate of the onset of microalbuminuria.

The bad news is that there was an unexpected and not completely explained excess of CV deaths, which the investigators attribute to episodes of hypotension in patients with preexisting CV disease, although, as mentioned in an editorial,¹⁷ a drug-specific effect cannot be absolutely excluded, but this possibility is definitely unlikely.

To sum up, the ROADMAP study provides further documentation for the postulate that early blockade of the RAS in type 2 diabetic patients, i.e., before the stage of microalbuminuria has set in, retards the onset of microalbuminuria independent of blood pressure. This supports the concept that early intervention is a sensible strategy ("nip it in the bud").

REFERENCES

- 1 Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001; 345: 861-869.
- 2 Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001; 345: 851-860.
- 3 Adler AI, Stevens RJ, Manley SE, et al.; UKPDS GROUP. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int*. 2003; 63: 225-32.
- 4 Mogensen CE. Progression of nephropathy in long-term diabetics with proteinuria and effect of initial anti-hypertensive treatment. *Scand J Clin Lab Invest*. 1976; 36: 383-388.
- 5 Viberti GC, Bilous RW, Mackintosh D, Keen H. Monitoring glomerular function in diabetic nephropathy. A prospective study. *Am J Med*. 1983; 74: 256-264.
- 6 Parving HH, Andersen AR, Smidt UM, Svendsen PA. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet*. 1983; 1: 1175-1179.
- 7 Mac-Moune Lai F, Szeto CC, Choi PC, et al. Isolate diffuse thickening of glomerular capillary basement membrane: a renal lesion in prediabetes? *Mod Pathol*. 2004; 17: 1506-1512.
- 8 Altıparmak MR, Pamuk ON, Pamuk GE, et al. Diffuse diabetic glomerulosclerosis in a patient with impaired glucose tolerance: report on a patient who later develops diabetes mellitus. *Neth J Med*. 2002; 60: 260-262.

- 9 Ruggenenti P, Fassi A, Ilieva AP, et al.; Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med*. 2004; 351: 1941-1951.
- 10 Haller H, Viberti GC, Mimran A, et al. Preventing microalbuminuria in patients with diabetes: rationale and design of the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study. *J Hypertens*. 2006; 24: 403-408.
- 11 Ritz E, Viberti GC, Ruilope LM, et al. Determinants of urinary albumin excretion within the normal range in patients with type 2 diabetes: the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study. *Diabetologia*. 2010; 53: 49-57.
- 12 Bilous R, Chaturvedi N, Sjølie AK, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. *Ann Intern Med*. 2009; 151: 11-20, W3-4.
- 13 Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med*. 2009; 361: 40-51.
- 14 Haller H, Ito S, Izzo JL Jr, et al.; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med*. 2011; 364: 907-917.
- 15 Ruggenenti P, Perna A, Ganeva M, et al.; BENEDICT Study Group. Impact of blood pressure control and angiotensin-converting enzyme inhibitor therapy on new-onset microalbuminuria in type 2 diabetes: a post hoc analysis of the BENEDICT trial. *J Am Soc Nephrol*. 2006; 17: 3472-3481.
- 16 Bosch J, Lonn E, Pogue J, et al.; HOPE/HOPE-TOO Study Investigators. Long-term effects of ramipril on cardiovascular events and on diabetes: results of the HOPE study extension. *Circulation*. 2005; 112: 1339-1346.
- 17 Ingelfinger JR. Preemptive olmesartan for the delay or prevention of microalbuminuria in diabetes. *N Engl J Med*. 2011; 364: 970-971.