

Nephropathy in type 2 diabetes mellitus: further implications for the benefits of intensive glucose control in the advance trial

Diabetic nephropathy is a frequent and progressive long-term complication of type 2 diabetes mellitus (T2DM).

Aside from nonmodifiable factors, ie, diabetes duration and genetic susceptibility, major determinants include chronic hyperglycemia and blood pressure.¹ Prevention of diabetic nephropathy is a first priority goal for public health, and recent results for the intensive glucose arm of the ADVANCE trial (Action in Diabetes and Vascular disease: Preterax and DiamicroN MR Controlled Evaluation) offer many hopes for the future.

Nephropathy: a progressive complication with a severe prognosis

It is well established that diabetic nephropathy progresses over time in T2DM. According to the United Kingdom Prospective Diabetes Study (UKPDS),² the annual risk for progression from a normal to elevated urinary albumin excretion rate (microalbuminuria; 30-300 mg/24h) is 2.0%; progression from microalbuminuria to proteinuria (≥ 300 mg/24h) is 2.8%, and from proteinuria to renal failure (defined as a plasma creatinine level ≥ 175 $\mu\text{mol/L}$ or the need for renal replacement or graft) is 2.3%.

During the last 20 years in the USA and Europe, diabetes has become one of the first causes of end-stage renal failure (ESRF), the majority of patients having T2DM.² Diabetes is now the only increasing cause of ESRF.¹ Some ethnic groups are more disposed to nephropathy, including Native Americans in the USA, South Asians in the UK, and patients of African descent in France.

Progression of nephropathy is associated with a worsened cardiovascular prognosis. The annual death rate increases from 1.4% in patients with normal renal parameters to 3.0% when microalbuminuria is present, 4.6% in patients with macroproteinuria, reaching 19.2% in ESRF. A similar increased death rate was reported in the Wisconsin study,³ with an adjusted relative risk (RR) for coronary death of 1.96 in patients with microalbuminuria and 2.73 in patients with proteinuria.

Furthermore, an increase in the death rate has been reported to occur when the estimated glomerular filtration rate (GFR) decreases, with the RR of all-cause mortality increasing by 2.58 when the GFR is between 30 to 60 ml/min, and by 6.42 when the GFR is below 30 ml/min.⁴ The mean life expectancy for type 2 diabetics entering a dialysis program is reduced, with less than 1 in 5 surviving after 5 years—cardiovascular disease being the main cause of death.²

These data permit us to conclude that prevention of kidney deterioration is of primary importance for reducing cardiovascular complications and death, and thus improving life expectancy in T2DM.

Intervention studies: intensive glucose control

In UKPDS, after a 6-year follow-up, microalbuminuria development was reduced by 12% ($P=0.043$) in the intensive group, with no reduction in macroproteinuria ($P=0.61$) or the doubling of creatinine levels ($P=0.09$).^{5,6} A 9-year follow-up was required to observe

a significant improvement in these parameters.⁵ In ADVANCE,⁷ in which there was a mean 0.67% difference in HbA1C levels between the intensive group receiving DIAMICRON MR-based therapy and the conventional group (6.5% vs 7.3%, P< 0.001), a significant improvement in all renal parameters was obvious after only a 5-year median follow-up. A 21% reduction in the development or progression of nephropathy (macroproteinuria [albumin-creatinine ratio >300 µg/mg], doubling of creatinine in excess of 200 µmol/L, dialysis, or renal death) (P=0.006) was observed. In the intensive group, the risk for developing microalbuminuria was reduced by 9% (P=0.02), and macroproteinuria by 30% (P=0.01). The progression rate from microalbuminuria to macroproteinuria decreased by 22% (P=0.0001).

The implication of these results is of major importance with respect to the expected long-term reduction in cardiovascular events and cardiovascular death in the ADVANCE population. The long-term sustained effect of improving glucose control was recently evidenced by a 10-year post trial follow-up of patients included in UKPDS.⁸ In the intensive glucose control group, the benefit of improving glucose control on the incidence of myocardial infarction and all-cause mortality became obvious only after 15 years.

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References:

1. Gross JL, Canani LH, de Azevedo MJ, et al. Diabetes Care. 2005;28:164-76.
2. Bilous R. Diabet Med. 2008;25(suppl 2):25-29.
3. Valmadrid CT, Klein R, Moss SE, et al. Arch Intern Med. 2000;160:1093-1100.
4. Nag S, Bilous R, Kelly W, et al. Diabet Med. 2007;24:10-17.
5. UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837-853.
6. Stratton IM, Adler AI, Neil AW, et al. BMJ. 2000;321:405-412.
7. The ADVANCE Collaborative Group. N Engl J Med. 2008;358:2560-2572.
8. Holman RR, Paul SK, Bethel MA, et al. N Engl J Med. 2008;359:1577-1589.