Nephropathy

The Steno-2 study comes of age

Rudy Bilous
Professor of Clinical Medicine, Newcastle University, Newcastle, and Clinical Dean at Newcastle University Medical School, Malaysia

In 1993, 160 people with type 2 diabetes and microalbuminuria were randomised in Denmark to an intensive or conventional treatment protocol. Those in the intensive arm attended the Steno specialist hospital every three months. As well as being provided with lifestyle advice on diet, exercise and smoking cessation, they all received renin–angiotensin system blockade therapy, a low dose of aspirin (after 5 years), vitamins A and E, folic acid and trace element supplements. They were also set more stringent blood glucose, blood pressure and blood lipid targets. At the end of the initial study period (median 7.8 years), there were significant reductions in microvascular and macrovascular endpoints in the intensive treatment group. All of the surviving patients were then set the same targets, but the intensive lifestyle interventions and supplements were stopped. By the next study point at 13.3 years, levels of glycaemia, blood pressure and lipids in the two groups were the same. What had happened to the participants after 21 years? A new study (summarised alongside) provides the answers.

In the two groups, 38 vs 55 participants had died (intensive vs conventional), with an absolute risk reduction (ARR) for mortality of 21%. The median survival benefit for intensive therapy was 7.9 years. For a first cardiovascular (CV) event, the ARR was 20% and median time was delayed by 8.1 years. In the intensive group 28 participants had no recorded CV event, compared to 13 in the conventional group. Looking at the Kaplan–Meier curves, there is a separation for CV events (including mortality) at around 4 years, and for mortality alone at 9–10 years. Cardiovascular event rates after the initial study period were more or less parallel, but mortality rates continued to diverge. There was a marked reduction in stroke and myocardial infarction (MI) rates in the intensive group. How were such remarkable results achieved with such a relatively small cohort?

In the intervention period there were modest reductions in glycaemia (absolute difference in HbA_{1c}, 8 mmol/mol; 0.7%), with greater reductions in systolic blood pressure (SBP) of 11 mmHg and serum low-density lipoprotein cholesterol (LDL-C) of 1.1 mmol/L. Disappointingly, there was no significant impact on smoking rates, BMI or lifestyle. By the time of the first post-intervention follow-up at 13.3 years, there was no longer any difference between groups, although we do not know at what precise time this occurred. If we assume that this happened midway, then the intervention group could have had more than 10 years of better glycaemia, blood pressure and lipid control. Using the UKPDS data (Stevens et al, 2004), the lower HbA_{1c} would have reduced the odds for an MI by around 12% and stroke by 26%. The SBP reduction would have reduced relative risk (RR) for a major CV event (including mortality) by ~13% (Ettehad et al, 2015) and the LDL-C reduction by 23% (Cholesterol Treatment Trialists' [CTT] Collaboration et al, 2015). The lower SBP reduces the RR for stroke by nearly 29%. Most interesting is the finding that the difference between treatment groups was only seen in those with no history of a CV event over 21 years. Once an individual had experienced one, then there was no benefit of intensive therapy.

What can we take from all this? Firstly, the report highlights the high CV risk in these patients – 50% in the conventional group had a major CV event by 8 years and nearly 70% had died by 20 years. Secondly, improving glycaemia and lowering SBP and serum LDL-C all have a major beneficial effect on CV events in people with type 2 diabetes who are at relatively high risk. The data thus support current guidance with regard to treatment targets. Thirdly, primary prevention of a CV event seems critical. Finally, and perhaps most depressingly in the light of the current NHS Diabetes Prevention Programme, even in the context of a clinical trial delivered by an international centre of excellence, it is hard to influence lifestyle and smoking habits. ■

References on next page

Diabetologia

Steno-2 follow-up: years of life gained and free of CVD

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 In 1993, the Steno-2 study enrolled 160 individuals with T2D and microalbuminuria. They were randomised to receive either conventional multifactorial treatment or intensified multifactorial treatment.

2 After 7.8 years, all surviving participants were offered intensive treatment in an observational post-trial follow-up. The primary endpoint was difference in median survival time between the original treatment groups with and without incident cardiovascular disease (CVD).

3 At the end of the follow-up (median time 21.2 years after the start of the invention), 38 (48%) of the participants from the original intensive-therapy group had died, compared with 55 (69%) from the conventional group (hazard ratio, 0.55 [95% confidence interval (CI), 0.36–0.83; P=0.005]). Those in the intensive group survived for a median of 7.9 years longer than those in the conventional group.

4 The median time to first CVD event or death after randomisation was 16.1 years in the intensive group and 8.0 years in the conventional group (95% CI, 4.0–12.6; P=0.001). Death from cardiovascular causes was reduced by 62% in the intensive-therapy group.

5 The increased lifespan in the intensive-therapy group was matched by the years gained free from cardiovascular complications.

6 The findings provide further evidence of the significance of early, intensified risk factor control in people with complicated T2D.

Gæde P, Oellgaard J, Carstensen B et al (2016) Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. *Diabetologia* **59**: 2298–307

Am J Kidney Dis

Safety and efficacy of incretin-based therapies

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 These authors carried out a systematic review and meta-analysis of randomised controlled trials to assess the safety and efficacy of incretin-based therapies in individuals with T2D and moderate or severe chronic kidney disease (CKD).

2 After a comprehensive search of databases, 13 studies, which included a total of 6848 people, were selected for inclusion. Eleven studies used a dipeptidyl peptidase-4 (DPP-4) inhibitor, while two used a glucagon-like peptide-1 (GLP-1) receptor agonist.

3 Compared to placebo, incretin-based therapies significantly reduced HbA_{1c} levels, although they did not reduce HbA_{1c} when compared with an active comparator (defined as antidiabetic medication other than an incretin-based therapy).

4 Analysis of hypoglycaemic events showed a significant risk for incretins versus placebo, but no effect versus active comparators. Limited evidence was found on the effect on all-cause mortality, end-stage renal disease and cardiovascular events.

5 This review provides further evidence that incretin-based therapies are effective in reducing glycaemia without substantially increasing the risk for hypoglycaemia in those with T2D and CKD.

6 The authors conclude that future collaborative meta-analyses, incorporating subgroup analysis based on CKD stage, would help to elucidate further the safety and efficacy of these therapies in this subgroup.

Howse PM, Chibrikova LN, Twells LK et al (2016) Safety and efficacy of incretin-based therapies in patients with type 2 diabetes mellitus and CKD: a systematic review and meta-analysis. *Am J Kidney Dis* **68**: 733–42

JAMA

Manifestations of disease in US adults

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 This study examined changes in clinical manifestations of kidney disease among US adults with diabetes.

2 In serial cross-sectional studies of individuals participating in national surveys between 1988 and 2014, no change in the prevalence of diabetic kidney disease was observed.

3 There was a significant, progressive decrease in the prevalence of albuminuria over time (20.8% to 15.9%; $P=0.001$).

4 The prevalence of reduced estimated glomerular filtration rate (eGFR) increased (9.2% to 14.1%; $P=0.001$), as did severely reduced eGFR (1.0% to 2.7%; $P=0.004$).

5 Therapy improvements may be responsible for the reduced prevalence of albuminuria. Reasons for the increased prevalence of reduced eGFR could not be conclusively discerned from the data.

Afkarian MD, Zelnick LR, Hall YN et al (2016) Clinical manifestations of kidney disease among US adults with diabetes, 1988–2014. *JAMA* **316**: 602–10

Eur J Endocrinol

eGFR trajectory and mortality in T2D

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 This longitudinal observational study investigated the association between estimated glomerular filtration rate (eGFR) and all-cause mortality, and between eGFR trajectories and all-cause death in individuals with T2D.

2 Participants ($n=1296$) from the Fremantle Diabetes Study Phase 1 were assessed between 1993 and 1996, and followed until December 2012.

3 The authors confirmed a U-shaped relationship between all-cause death and eGFR category.

4 Statistical modelling identified a subgroup with a relatively high eGFR initially, but whose renal function declined rapidly over the next 5 years.

5 This subgroup's eGFR profile over time may be a marker of vulnerability that is not otherwise apparent.

6 The authors conclude that eGFR should be monitored even in those well away from clinically concerning renal impairment.

Davis TME, Chubb SAP, Davis WA (2016) The relationship between estimated glomerular filtration rate trajectory and all-cause mortality in type 2 diabetes: the Fremantle Diabetes Study. *Eur J Endocrinol* **175**: 273–85

Diabetologia

Effects of SGLT2 inhibition on UACR

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 This study examined the effect of empagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, on urine albumin-to-creatinine ratio (UACR).

2 Phase III trial data from people with T2D and prevalent microalbuminuria ($n=636$) or macroalbuminuria ($n=215$) were examined.

3 After controlling for confounders, it was found that treatment with empagliflozin resulted in a clinically significant reduction in UACR in those with microalbuminuria (–32% vs placebo; $P<0.001$) or macroalbuminuria (–41% vs placebo; $P<0.001$).

4 Most of the improvement was not explained by SGLT2 inhibition-related improvements in HbA_{1c}, weight or blood pressure.

5 The results further support a direct renal effect of SGLT2 inhibition.

Cherney D, Lund SS, Perkins BA et al (2016) The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. *Diabetologia* **59**: 1860–70

"The authors conclude that estimated glomerular filtration rate should be monitored even in those well away from clinically concerning renal impairment."

References from commentary

Cholesterol Treatment Trialists' (CTT) Collaboration, Fulcher J, O'Connell R et al (2015) Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* **385**: 1397–405

Ettehad D, Emdin CA, Kiran A et al (2015) Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* **387**: 957–67

Stevens RJ, Coleman RA, Adler AI et al (2004) Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. *Diabetes Care* **27**: 201–7