Steno-2: Multifactorial intervention in type 2 diabetes and microalbuminuria

Steno-2 study design

- Single-centre, prospective, randomised, open, blinded endpoint trial comparing conventional versus intensive multifactorial therapy.
- 160 participants with type 2 diabetes and metabolic syndrome, including microalbuminuria.
- Study began in 1993, with microvascular endpoint examinations at 4 years and macrovascular examinations at 8 years.
- Thereafter, study continued as an observational follow-up, with participants reassigned so that all had the same intensive treatment targets.
- Mortality outcomes assessed at 13 and 21 years' follow-up.

The Steno-2 study was designed in 1990, while intervention studies, including the UKPDS, were ongoing and there was no evidence base for the treatment of type 2 diabetes. Steno-2 demonstrated significant reductions in mortality and microvascular and macrovascular outcomes in a relatively small cohort of 160 people. How were these results achieved, and what are their implications for our practice?

Take-home messages

- The authors emphasise the importance of early, intensified risk factor control in people with complicated type 2 diabetes.
- The risk reductions achieved in Steno-2 are high compared with those reported in intervention trials targeting single risk factors. Concomitant treatment of multiple risk factors is of profound importance.

4-year follow-up: microvascular

- At a mean follow-up of 3.8 years, significantly fewer people in the intensive treatment group developed nephropathy, the primary endpoint, defined as an albumin excretion rate (AER) of >300 mg/24 hours (8 vs 19 participants; odds ratio [OR], 0.27) compared with conventional treatment (Gaede et al, 1999).

Treatment targets in conventional and intensive therapy groups

Target	Conventional*	Intensive
HbA_{1c} (mmol/mol; %)	<58 (7.5%)	<48 (6.5%)
Triglycerides (mmol/L)	<2.2	<1.7
Total cholesterol (mmol/L)	<6.5	<5.0
HDL-cholesterol (mmol/L)	>0.9	>1.1
Systolic BP (mmHg)	<160	<140
Diastolic BP (mmHg)	<95	<85
ACE inhibitor (irrespective of BP)	No	Yes
Aspirin for primary prevention	No	Yes†

*As per 1988 Danish Medical Association guidelines. †Until 1999, aspirin given only for secondary prevention; thereafter, given to all.
ACE=angiotensin-converting enzyme; BP=blood pressure.

- Retinopathy progression (secondary endpoint) was also reduced (19 vs 33 participants; OR, 0.45).
  - Fewer developed blindness in one eye (1 vs 7).
  - Rates of new-onset retinopathy were lower but not significantly different (12 vs 20).
- Progression of autonomic neuropathy (secondary endpoint) was less common (8 vs 22; OR, 0.31).
  - Rates of progression of peripheral neuropathy were similar (21 vs 26).

8-year follow-up: macrovascular

- The primary endpoint was a composite of death from cardiovascular (CV) causes, non-fatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, non-fatal stroke, amputation as a result of ischaemia or vascular surgery for peripheral atherosclerotic artery disease after 8 years of intervention (Gaede et al, 2003).

Therapies in intervention group (additional therapies added stepwise and target-driven)

Condition	Therapy
All participants	Diet and lifestyle advice ACE inhibitor or ARB Multivitamin and mineral supplement Aspirin
Hyperglycaemia	Metformin (BMI >25 kg/m²) Gliclazide (BMI ≤ 25 kg/m²) Metformin + gliclazide Insulin
Dyslipidaemia	Statins Fibrates
Hypertension	Diuretics Calcium channel blockers Beta-blockers

ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker.

Diet and lifestyle advice – intervention group

- Fat <30% of daily energy intake
- Saturated fat <10% of daily energy intake
- Reduced daily energy intake not a goal
- Light to moderate exercise for ≥30 minutes 3–5 times per week
- Smoking cessation courses
- Multivitamin/mineral supplement (vitamin C, vitamin E, folic acid, chromium picolinate)

- This outcome was significantly reduced in the intensive group (33 events in 19 participants vs 85 events in 35 participants; absolute risk reduction [ARR], 20%).
- This corresponded to a number needed to treat of five people to prevent one CV event over the study period.
- The risk reductions for microvascular outcomes observed at 4 years were maintained.

Observational follow-up

After 8 years, randomisation was ended and all 130 surviving participants were treated similarly to the original intensive treatment arm, in accordance with updated national guidelines. Significant mortality, microvascular and macrovascular benefits persisted in the previously intensively treated group.

Mortality outcomes at mean 13 years

After 5.5 years of observational follow-up, the results were as follows (Gaede et al, 2008):

- Over the total follow-up of 13.3 years, the primary endpoint of death from any cause occurred in 24 participants (30%) in the intensive group compared with 40 (50%) in the conventional group (ARR, 20%).
- Similarly, the ARR for any CV event was 29%.

Clinical perspective – Steno-2 results
Colin Kenny, GP, Dromore, and Editor, *Diabetes Distilled*

There is a good reason why the Steno-2 study is so frequently highlighted at primary care meetings. It was an intensive, multifactorial treatment strategy targeting all known modifiable risk factors for vascular damage in people with type 2 diabetes and microalbuminuria. These interventions are the aspiration of healthcare professionals working in primary care, and are broadly reflected in aspects of the Quality and Outcomes Framework.

Steno-2 was a modest study conducted in one centre, but very actively followed up for long-term microvascular and macrovascular complications, both of which were very significantly reduced. This is perhaps the best study to demonstrate the sustainability of the intensive and multifaceted treatment approach to type 2 diabetes with microalbuminuria, in terms of a major extension of life and a halving of new cardiovascular complications.

Outcomes at mean 21 years

- After a total of 21.2 years (Gaede et al, 2016), mortality was significantly reduced in the intensive group (38 vs 55 participants; ARR, 21%).
  - Median survival time (the primary outcome) was increased by 7.9 years.
- Median time to a first CV event was delayed by 8.1 years (16.1 years vs 8 years).
- The relative risks of retinopathy progression (hazard ratio [HR], 0.67), autonomic neuropathy (HR, 0.59) and progression to nephropathy (HR, 0.52) were all significantly reduced. Peripheral neuropathy risk was similar between the groups.

"At 21.2 years of follow-up of 7.8 years of intensified, multifactorial, target-driven treatment of type 2 diabetes with microalbuminuria, we demonstrate a median of 7.9 years of gain of life. The increase in lifespan is matched by time free from incident cardiovascular disease."

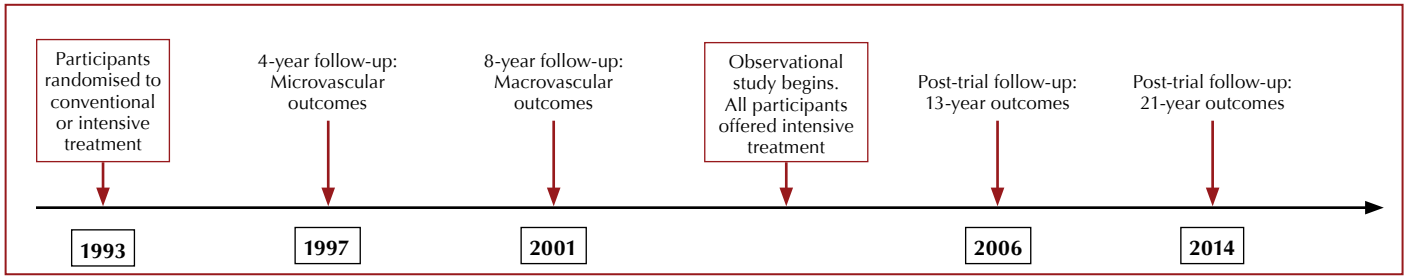
(Gaede et al, 2016)

Gaede P, Vedel P, Parving HH, Pedersen O (1999) Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet* **353**: 617–22

Gaede P, Vedel P, Larsen N et al (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* **348**: 383–93

Gaede P, Lund-Andersen H, Parving HH, Pedersen O (2008) Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* **358**: 580–91

Gaede 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



Steno-2 study timeline.