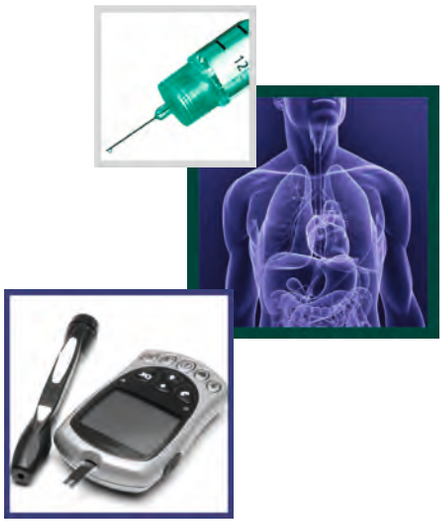

Reducing renal failure: how low do glucose levels need to go?

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Practice Points

- Diabetic kidney disease is the commonest cause of end-stage kidney disease worldwide and leads to significant morbidity and mortality, increased cardiovascular risk and increased economic health costs due to the need for dialysis.
- Major risk factors for diabetic nephropathy include hyperglycemia, hypertension, dyslipidemia and duration of diabetes.
- There are both albuminuric and nonalbuminuric pathogenetic pathways to renal dysfunction in diabetic nephropathy.
- Studies in both Type 1 and Type 2 diabetes show a relationship between tighter glucose control and a lower risk of the development and progression of albuminuria and diabetic nephropathy.
- While older trials such as the UKPDS and DCCT aimed for a glycated hemoglobin (HbA1c) approaching 7%, more contemporary trials such as ACCORD, ADVANCE and VADT lowered the HbA1c to less than 7%.
- The major side effect of lowering glucose levels is hypoglycemia.
- The renal benefits of intensive blood glucose control have to be balanced with the patient's age, comorbidities and the risk of hypoglycemia.
- A general glycemic target of HbA1c of 7% to prevent onset and progression of diabetic nephropathy is appropriate in most patients.
- Other risk factor modification such as treating hypertension, the use of renin–angiotensin system blockade and treating dyslipidemia are equally as important as glycemic control in the management of the patient with diabetic nephropathy.

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SUMMARY Diabetic kidney disease is the commonest cause of end-stage kidney disease worldwide. One strategy to prevent the development and progression of diabetic kidney disease is intensive blood glucose control. Randomized controlled trials such as the UKPDS and DCCT have demonstrated that a target HbA1c level of 7% improves renal outcomes. More recently, ACCORD, ADVANCE and VADT have explored the effects of targeting even lower HbA1c levels of 6.0–6.5%. These contemporary trials have universally reported improvements in albuminuria but no clear effects on preventing end-stage kidney disease. Thus, the additional and likely long-term renal benefits of intensive glucose lowering to achieve HbA1c levels ≤7% need to be balanced against the potential risks of intensive therapy such as severe hypoglycemia. An individualized approach is required with the understanding that the greatest renal benefits are likely to be achieved at a HbA1c level of ≤7%. Other risk factors for renal impairment should also be addressed.

Diabetes is now the commonest cause of end-stage kidney disease in both the developed and developing world [1]. Chronic kidney disease causes significant morbidity and mortality, and further increases cardiovascular risk in people with diabetes [2]. It also results in significant individual and economic health costs due to the need for renal replacement therapy. Measures to decrease the development and progression of chronic kidney disease in people with diabetes are thus urgently needed, particularly as the prevalence of Type 2 diabetes continues to increase globally.

Pathophysiology

Major risk factors for diabetic nephropathy include hyperglycemia, hypertension, dyslipidemia and duration of diabetes. Classic diabetic nephropathy develops over 20 years. The onset of diabetic nephropathy is usually marked by glomerular hyperfiltration, which is then followed by the development of worsening albuminuria progressing from normoalbuminuria (<30 mg/24 h) to microalbuminuria (30–300 mg/24 h) and then to proteinuria (>300 mg/24 h). The glomerular filtration rate usually remains stable until the development of proteinuria, and then progressively falls by an average of 10–12 ml/min/1.73 m^2/year, ultimately leading to renal failure **(Figure 1)** [3–5]. This pathway is classically seen in Type 1 diabetes and in some patients with Type 2 diabetes, although there are exceptions. On kidney biopsy, some patients with Type 2 diabetes labeled as having diabetic nephropathy do not exhibit the classical pathological renal findings or have mixed disease. Furthermore, microalbuminuria can regress either as part of the natural history of the disease or with the use of renin–angiotensin system blockade. Some patients may also be observed to develop a decline in renal function without progressive albuminuria. Thus, it is believed that both classical albuminuric and nonclassical nonalbuminuric pathways lead to decline of renal function in people with diabetes [6,7].

Epidemiological studies have established a clear link between glycemic control and the development and progression of diabetic kidney disease. The recent publication of three landmark trials (ACCORD, ADVANCE and VADT) [8–11] has added to our understanding of the relationship between glycemic control and kidney disease. Here, we review these three trials, as well as other major studies that provide evidence for the important role of glucose control in the prevention of diabetic kidney disease and renal failure.

Studies of patients with Type 1 diabetes

The DCCT assessed the effect of intensive glucose control on the development of diabetic nephropathy and decline in renal function in young patients with Type 1 diabetes [12].

A total of 1441 patients with Type 1 diabetes, a mean glycated hemoglobin (HbA1c) of 8.9% and a mean age of 27 years were randomized. The cohort consisted of two groups: a primary prevention group with no retinopathy, mild microalbuminuria (<40 mg/day) and a mean diabetes duration of 2.6 years; and a secondary prevention group with mild-to-moderate nonproliferative retinopathy or microalbuminuria (<200 mg/day) and a mean diabetes duration of 8.8 years. The effect of intensive insulin therapy (median HbA1c reached was approximately 7%) was compared with conventional therapy (median HbA1c reached was approximately 9%). The primary outcome was the development and progression of retinopathy; other secondary outcomes included macrovascular and renal outcomes. After a mean follow-up of 6.5 years, intensive control as compared with conventional

control, led to a 39 and 54% reduction in the occurrence of new microalbuminuria and new macroalbuminuria, respectively (95% CI: 21–52 and 19–74%, respectively).Moreover, when the patients were followed for a further 8 years in the post trial, EDIC study, the effects of the former intensive control compared with conventional control, further reduced the occurrence of new microalbuminuria by 59% (despite the HbA1c levels converging after 4 years) [13] contributing to a decreased risk of any cardiovascular disease by 42% (p = 0.02) [14]. There was a two- to three-fold increased risk of major hypoglycemia in the intensive control group compared with the conventional group.

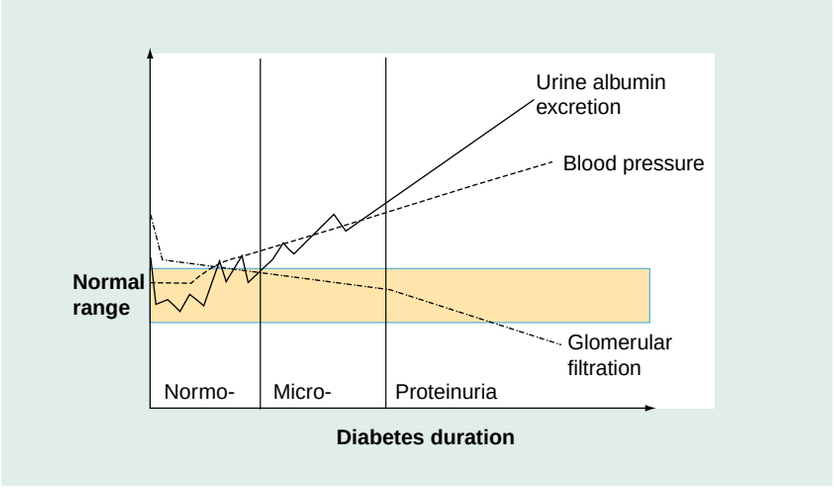

Figure 1. Natural history of classical diabetic nephropathy.
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Studies of patients with Type 2 diabetes

The UKPDS [15], an open label trial of 3867 newly diagnosed patients with Type 2 diabetes, compared the effects of intensive glycemic control with either sulfonylurea, or insulin versus conventional dietary therapy on the development of microvascular and macrovascular complications. Primary aggregate end points were any diabetes-related end point (including renal failure defined as requirement for dialysis or a plasma creatinine greater than 250 µmol/l); diabetes-related death (including death from renal disease) and all-cause mortality. Subclinical renal end points were also assessed every 3 years and included microalbuminuria, proteinuria and a twofold increase in plasma creatinine. After 10 years, the mean HbA1c was 7% in the intensive therapy group compared with 7.9% in the conventional therapy group. The risk of any diabetes-related end point was 12% lower in the intensive therapy group compared with the conventional therapy group. This was primarily driven by a 25% reduction in risk of microvascular complications (defined as vitreous hemorrhage, retinal photocoagulation or renal failure). After 9 years, fewer patients in the intensive group compared with the conventional group developed microalbuminuria (19.2 vs 25.4%; relative risk [RR]: 0.76; p = 0.00062), proteinuria (4.4 vs 6.5%; RR: 0.67; p = 0.026) and doubling in serum creatinine (0.71 vs 1.76%; RR: 0.4; p = 0.027). However, more weight gain and a greater number of total and major hypoglycemic episodes were reported in the intensive versus the conventional group, especially in those patients receiving insulin (3% of patients on insulin had a major hypoglycemic episode, and 40% had either a major or minor episode). The 10 year post-trial follow-up has subsequently reported maintained benefits on microvascular complications (vitreous hemorrhage, retinal photocoagulation or renal failure) in the intensive group, despite early loss of the glycemic difference between the two treatment groups [16].

The Kumamoto trial [17], studied the effect of intensive glucose control with insulin therapy on the development of microvascular complications in 110 Japanese patients with Type 2 diabetes (55 patients who had diabetes without microvascular complications in the primary prevention cohort and 55 patients who had mild retinopathy and microalbuminuria in the secondary intervention cohort). Patients were randomized to either an intensive regimen of rapid-acting insulin with meals and basal intermediate insulin at night, or a conventional regimen of an intermediate acting insulin once or twice daily. The primary prevention group had a mean age of 40 years, average duration of diabetes of 6.5 years and mean HbA1c of 9%. The secondary intervention group had a mean age of 50.5 years, average duration of diabetes of 10.3 years and mean HbA1c of 9.2%. After 6 years, a mean HbA1c of 7.1% was achieved in the intensive group versus 9.4% in the conventional group. Compared to the conventional group, the intensive group had a significantly lower rate of development of nephropathy. In particular, in the primary prevention group, 7.7% of those receiving intensive therapy developed albuminuria compared with 28% of those receiving conventional therapy

(p = 0.03). Unlike the UKPDS and DCCT, this study only reported an increased risk of mild hypoglycemia in the intensive versus the conventional therapy groups.

The Veteran Affairs Cooperative Study on Glycemic Control and Complications in Type 2 diabetes [18] was of similar size to the Kumamoto study, and examined the effects of intensive glucose control on microalbuminuria and creatinine clearance. Investigators assigned 153 male patients of mean age 60 years, with diabetes of mean duration 7.8 years and with a mean HbA1c of 9.8%, to either intensive control (mean achieved HbA1c was 7.1%) or standard control (mean HbA1c achieved was 9.1%). Of the cohort 38% had microalbuminuria, and were evenly assigned to both groups. Both groups received insulin, however while patients in the standard group could only receive a maximum of two injections of insulin, the intensive group could be on a multidose regimen. At 2 years of follow-up, intensive therapy slowed the progression of microalbuminuria significantly with the changes in the albumin:creatinine ratio from baseline to 2 years being 0.045 in the intensive group compared with 0.141 in the standard group (p = 0.046). This effect was demonstrated most in patients with evident microalbuminuria at study entry. The intensive group also had a slower decline in creatinine clearance compared with the standard control. For patients without baseline microalbuminuria, the decline was nonsignificant in both the intensive and standard groups. In patients with microalbuminuria, the intensive group showed a significant 12% reduction in creatinine clearance (p = 0.0001) compared with a significant 17% decline (p = 0.009) in the standard control.

The majority of older trials have studied the effects of targeting a HbA1c level of close to 7% compared with levels of 8% or greater. More recently, three major randomized trials, the ACCORD, the ADVANCE and the VADT, have examined the effects of targeting a HbA1c level less than 7%, compared with levels of greater than 7% on the development of both macrovascular and microvascular complications, including renal outcomes **(Table 1)**.

The ACCORD [8] glycemic control arm randomized 10,251 North American patients with Type 2 diabetes of median duration 10 years, average HbA1c of 8.1%, mean age 62 years, and either with prevalent cardiovascular disease or at high risk of cardiovascular disease, to either intensive glycemic control (median achieved HbA1c was 6.4%) or standard glycemic control (median achieved HbA1c was 7.5%). The primary outcome was a composite of major cardiovascular events, defined as nonfatal myocardial infarction, nonfatal stroke and death from cardiovascular causes. Secondary outcomes included two prespecified composite microvascular end points. The first composite end point was the development of renal failure (defined as initiation of dialysis or end-stage renal disease, renal transplantation, or rise of serum creatinine >291.72 µmol/l) or retinopathy (requiring retinal photocoagulation or vitrectomy). The second composite end point added peripheral neuropathy to the first composite outcome. In the intensive control group, therapy was titrated monthly for 4 months, and 2 months thereafter, to achieve and maintain the proposed glycemic target. In the standard control group, therapy and targets were reviewed every 4 months. HbA1c was rapidly reduced within the first 6 months with combinations of insulin and other oral glucose-lowering agents. After an average 3.5 years of follow-up, the trial was terminated prematurely due to an increased risk of all-cause and cardiovascular mortality in the intensive control group. At this time, there was no significant difference between the groups for either the first composite microvascular (HR: 1.00; 95% CI: 0.88–1.14; p = 1) or the second composite outcome (HR: 0.95; 95% CI: 0.80–1.02; p = 0.19) or the rate of overt renal failure (HR: 0.95; 95% CI: 0.73–1.24; p = 0.713). Compared with the conventional group, the intensive group had a 21% reduction in risk of microalbuminuria (p = 0.0005), 31% reduction in risk of macroalbuminuria (p = 0.0007) but a 7% increase in the risk of doubling of serum creatinine or decrease in estimated glomerular filtration rate (eGFR; p = 0.016) and a threefold increased risk of severe hypoglycemia. This difference in the risk of doubling of serum creatinine was absent after a median follow-up of 5 years postcessation of intensive glycemic control. The initial decline in eGFR was thought to be due to a decrease in glomerular hyperfiltration associated with improved glycemic control [9].

ADVANCE [10] was a multinational trial that randomized 11,140 patients with Type 2 diabetes of median duration of 7 years, mean HbA1c of 7.5%, mean age of 66 years and with major macrovascular or microvascular complications or at least one other risk factor, to either standard or intensive glucose control. The composite primary

Table 1. Summary of major randomized controlled trials in patients with diabetes pertaining to glycemic lowering and renal outcomes.

Trial	Sample size (n)	Type of diabetes	Duration of diabetes at baseline (years)	Study duration (years)	HbA1c achieved in intensive group (%)	HbA1c achieved in conventional or standard group (%)	Difference in HbA1c between groups (%)	Renal outcomes in intensive group vs conventional group	Complications	Ref.
DCCT	1441	1	5.7	6.5	7	9	2	39% lower rate of microalbuminuria 54% reduction in the occurrence of albuminuria	Increased risk of major hypoglycemia and mean 4.6 kg more weight gain at 5 years in intensive vs conventional group	[12]
UKPDS 33	3867	2	0	10	7	7.9	0.9	Development of microalbuminuria decreased by 24% and doubling of Cr decreased by 60% at 9 years of follow-up	More weight gain and increased risk of major hypoglycemia in the intensive vs conventional group	[15]
Kumamoto Study	110	2	6.5	6	7.1	9.4	2.3	Lower progression of albuminuria 7.7 vs 28%	No significant increase in weight gain or severe hypoglycemia in the intensive insulin vs conventional insulin group	[17]
VA Co-operative Study	153 (male only)	2	8	2	7.1	9.1	2	Lower progression of microalbuminuria Changes in Alb:Cr ratio from baseline were 0.045 vs 0.141; p = 0.046	Weight gain and hypoglycemia risks were not reported	[18]
ACCORD glycemic arm	10,251	2	10	3.5	6.4	7.5	1.1	21% reduction in development of microalbuminuria 31% reduction in the development of macroalbuminuria	Significantly increased risk of mortality causing premature termination of study at 3.5 years	[8,9]
ADVANCE glycemic arm	11,140	2	8	5	6.5	7.3	0.8	21% reduction in the development of macroalbuminuria, doubling of Cr, need for renal replacement therapy or renal death	Increased risk of severe hypoglycemia in the intensive vs standard group	[10]
VADT	1791	2	11.5	5.6	6.9	8.4	1.5	Reduction in albuminuria progression 9.1 vs 13.8%	More weight gain and increased risk of severe hypoglycemia in the intensive vs standard group	[11]

Alb: Albumin; Cr: Creatinine; HbA1c: Glycated hemoglobin.

outcome was major macrovascular events (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy) assessed both together and separately. The intensive group received gliclazide modified release plus other glucose lowering agents as required, to achieve a target HbA1c of ≤6.5%. The standard therapy group received sulfonylureas other than gliclazide, plus other drugs and insulin as required, as per local guidelines. In comparison to ACCORD, the HbA1c level was gradually reduced over 3 years to a mean of 6.5% in the intensive group compared with 7.3% in the standard group. After a median 5-years follow-up, the incidence of the combined major macrovascular and microvascular outcome was reduced by 10% (95% CI: 2–18%; p = 0.01). Similarly to the UKPDS, most of this effect was due to a reduction in microvascular complications, particularly a significant 21% reduction in the incidence of new or worsening nephropathy defined as the development of macroalbuminuria (urine albumin:creatinine ratio >33.9 mg/mmol), doubling of serum creatinine ≥200 µmol/l, need for renal replacement therapy or death due to renal disease. Intensive glycemic control was associated with a modestly increased rate of severe hypoglycemia.

The VADT was a smaller randomized control trial that studied the effect of intensive versus standard glucose control on 1791 USA military veterans with a mean age of 60 years, Type 2 diabetes of mean duration of 11.5 years, and mean HbA1c of 9.4% [11]. The primary outcome was the time to first occurrence of a major cardiovascular event. Secondary outcomes included microvascular complications such as nephropathy, retinopathy and neuropathy. Glucose-lowering strategies included the use of oral glucose lowering agents and insulin. After a median follow-up of 5.6 years, the intensive group achieved an HbA1c of 6.9% compared with 8.4% in the standard group. This did not result in a significant difference in the primary composite major cardiovascular event end point. However, a significant reduction in albuminuria progression was observed (9.1 vs 13.8%; p < 0.01). No other renoprotective effects of intensive therapy were reported. Similar to the ACCORD trial, severe hypoglycemia was increased fourfold with intensive glucose lowering.

Conclusion

While differing in design, as well as extent and intensity of glucose control, the available evidence from trials would suggest that over several years, more intensive glucose control will improve a range of renal outcomes in particular the development and progression of albuminuria and thus future development of diabetic nephropathy and end-stage kidney disease in patients with Type 1 and 2 diabetes. The optimal HbA1c target for preventing kidney disease is likely to be less than 7% based on current trial evidence. The benefits of aiming for such intensive glucose control must be weighed up against the increased risks of major hypoglycemia with agents in common use at this time. In older patients or those with other comorbidities, a low HbA1c target may be impractical and unsafe. Thus the control of other risk factors for nephropathy such as hypertension, and dyslipidemia may be more critical for these patients [19,20].

Limitations of current evidence

There are several limitations to the inferences that can be drawn from available glucose lowering trials.

First, while intensive glucose control results in better renal outcomes, the lowest HbA1c achieved in trials was 6.4%. Whether further renal benefits can be safely achieved by lowering the HbA1c to even closer to 6% is currently unknown.

Second, in most trials, the only renal outcome observed to significantly improve with intensive glucose control was the development of albuminuria. This is because most of the trials were underpowered and too short to detect any effects on the development of more advanced kidney disease such as end-stage kidney disease requiring dialysis or transplantation. It is not known whether nonalbuminuric pathogenetic pathways of diabetic nephropathy are modulated by strict glycemic control. Long-term follow-up of the ACCORD, VADT and ADVANCE cohorts will address the question of legacy or metabolic memory in those with long standing diabetes including the effects on more advanced kidney disease outcomes.

Future perspective

Current strategies for glucose lowering often include oral glucose lowering agents and insulins that increase the risk of hypoglycemia. As a result, there is a trade-off between tight glucose control and the experience of hypoglycemia. This is especially the case when these agents are

used in the setting of impaired renal function. The exceptions are metformin, DPP4 inhibitors and GLP1 agonists, which have a negligible risk of hypoglycemia when used alone or in combination with each other. However, these agents are contraindicated (apart from some currently available DPP4 inhibitors) once the eGFR declines to less than 30 ml/min or may require dose reduction once the eGFR is less than 60 ml/min. Furthermore, when used alone these agents are unlikely to achieve tight glucose control in the majority of patients [21]. Therefore, there is a need for more physiological methods of insulin replacement and the development of novel agents that target the different pathologic pathways resulting in diabetes and that can be used in those with renal impairment with minimal risk of hypoglycemia [1,22–23]. This will make the achievement of an HbA1c level of less than 7% and closer to euglycemia, a reality for more patients with diabetes.

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References

Papers of special note have been highlighted as:

- ■ of interest
- ■■ of considerable interest

1 Atkins RC, Zimmet P. Diabetic kidney disease: act now or pay later. *Diab. Res. Clin. Pract.* (90), e54–e56 (2011).

2 Hahr A, Molitch ME. Diabetes, cardiovascular risk and nephropathy. *Cardiol. Clin.* (28), 467–475 (2010).

3 Marshall SM, Flyvbjerg A. Diabetic nephropathy. In: *Textbook of Diabetes (4th Edition)*. Holt RIG, Cockram CS, Flyvbjerg A *et al*. (Eds). Blackwell Publishing Ltd., West Sussex, UK, 599–614 (2010).

■■ **Good review chapter on pathophysiology and treatment of diabetic nephropathy.**

4 Zelmanovitz T, Gerchman F, Balthazar AP *et al.* Diabetic nephropathy. *Diabetol. Metab. Syndr.* 1(1), 10 (2009).

5 Chadban S, Howell M, Twigg S *et al.* National evidence based guidelines for diagnosis, prevention and management of chronic kidney disease in Type 2 diabetes. Diabetes Australia and the NHMRC. Canberra, Australia (2009).

■■ **Excellent evidence-based guidelines on management of chronic kidney disease in Type 2 diabetes.**

6 Jerums G, Panagiotopoulos S, Premaratne E, MacIsaac RJ. Integrating albuminuria and GFR in the assessment of diabetic nephropathy. *Nat. Rev. Nephrol.* (5), 397–406 (2009).

■ **Good review article on the concept of albuminuric and nonalbuminuric pathways of diabetic nephropathy.**

7 Jerums G, Premaratne E, Panagiotopoulos S, Clarke S, Power DA, MacIsaac RJ. New and old markers of progression of diabetic nephropathy. *Diabetes Res. Clin. Pract.* (82S), S30–S37 (2008).

8 Gerstein HC, Miller ME, Byington RP *et al.*; ACCORD Study Group. Effects of intensive glucose lowering in Type 2 diabetes. *N. Engl. J. Med.* 358(24), 2545–2559 (2008).

9 Ismail-Beigi F, Craven T, Banerji MA *et al.*; ACCORD Study Group. Effect of intensive treatment of hyperglycemia on microvascular outcomes in Type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 376, 419–430 (2010).

10 ADVANCE collaborative group. Intensive blood glucose control and vascular outcomes in patients with Type 2 diabetes. *N. Engl. J. Med.* 358(24), 2560–2572 (2008).

11 Duckworth W, Abraira C, Moritz T *et al.* Glucose control and vascular complications in veterans with Type 2 diabetes. *N. Engl. J. Med.* 360(2), 129–139 (2009).

12 The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N. Engl. J. Med.* 329(14), 977–986 (1993).

■ **Landmark trial on the effects of glucose lowering on renal function in Type 1 diabetes.**

13 Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of Type 1 diabetes mellitus on the development and progression of diabetic nephropathy. Epidemiology of diabetes interventions and complications (EDIC) study. *JAMA* 290, 2159–2167 (2003).

14 Nathan DM, Cleary PA, Backlund JY *et al.* Intensive diabetes treatment and cardiovascular disease in patients with Type 1 diabetes. *N. Engl. J. Med.* 353, 2643–2653 (2005).

15 Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* (352), 837–853 (1998).

■ **Landmark trial on the effects of glucose lowering on renal function in Type 2 diabetes.**

16 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10 year follow-up of intensive glucose control in Type 2 diabetes. *N. Engl. J. Med.* 359(15), 1577–1589 (2008).

17 Ohkubo Y, Kishikawa H, Araki E *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin dependent diabetes mellitus: a randomised prospective 6 year study. *Diabetes Res. Clin. Pract.* (28), 103–117 (1995).

18 Levin SR, Coburn JW, Abraira C *et al.* Effect of intensive glycemic control on microalbuminuria in Type 2 diabetes. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial Investigators. *Diabetes Care* 23(10), 1478–1485 (2000).

19 Gaede P, Vedel P, Larsen N *et al.* Multifactorial intervention and cardiovascular disease in patients with Type 2 diabetes. *N. Engl. J. Med.* 348, 383–393 (2003).

■ **Also called the STENO2 study. Major study showing the effectiveness of multifactorial intervention in decreasing progression of renal impairment in Type 2 diabetes.**

20 Gaede P, Lund-Andersen H, Parving HH *et al.* Effect of multifactorial intervention on mortality in Type 2 diabetes. *N. Engl. J. Med.* 358(6), 580–591 (2008).

21 Nathan DM, Buse JB, Davidson MB *et al.* Medical management of hyperglycemia in Type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care* 32(1), 193–203 (2009).

22 Rossing P, de Zeeuw D. Need for better diabetes treatment for improved renal outcome. *Kidney Int. Suppl.* (79), S28–S32 (2011).

23 Seaquist ER, Ibrahim HN. Approach to the patient with Type 2 diabetes and progressive kidney disease. *J. Clin. Endocrinol. Metab.* 95(7), 3103–3110 (2010).

■ **Good review article on management of diabetic nephropathy.**