A Summary of the ADVANCE Trial

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The publication of the U.K. Prospective Diabetes Study (UKPDS) in 1998 helped to shape the management of type 2 diabetes in recent years (1). The study demonstrated several points. First, sulfonylureas are as safe as insulin in controlling blood glucose. Second, metformin reduced cardiovascular disease in an overweight subgroup. Third, the same benefit of glycemic control in reducing microvascular disease (previously noted in type 1 diabetes) is applied equally to patients with type 2 diabetes. A separation in A1C of ~1% in the UKPDS reduced the risk of microvascular disease (largely diabetic retinopathy) by ~25%. This reflected the data from the Diabetes Control and Complications Trial, where a separation in A1C of 2% in intensive and standard groups led to a reduction in microvascular disease of ~50% (2).

A fourth demonstration was that there was no significant reduction in macrovascular disease but a trend toward fewer myocardial infarctions with more intensive glucose control. Fifth, using the current treatment of the time (first-generation sulfonylureas, human ultratard insulin, or metformin), it proved impossible to maintain glucose control, which tended to deteriorate throughout the study. It is now generally believed that the progressive fall in endogenous insulin production as β-cell numbers decline makes it difficult, if not impossible, to maintain tight control using standard treatment. Sixth, the UKPDS also showed that in those patients with hypertension, lowering blood pressure (BP) to moderate levels with either captopril or atenolol could reduce microvascular disease (3).

In a subsequent study, the UKPDS investigators presented the rates of both micro- and macrovascular disease according to the achieved levels of A1C during the study (4). They showed a linear relationship between A1C and both groups of complications. The implication of the article was that if glycemic control could be tightened below the levels achieved in the UKPDS, then it might be possible to reduce rates, not only of microvascular complications, but also cardiovascular disease as well.

The aim of the glucose arm of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (5) was to build on the information gained by the UKPDS and to answer the question as to whether intensifying glucose control to achieve an A1C of <6.5% would provide additional benefit in reducing the risk of both micro- and macrovascular disease.

ADVANCE also asked questions about BP lowering in patients with type 2 diabetes. The aims of the BP arm were to establish whether routine provision of BP-lowering therapy produced additional benefits in terms of macro- and microvascular disease, irrespective of baseline BP, and added to the benefits produced by other cardiovascular preventive therapies, including ACE inhibitors.

TRIAL DESIGN — The trial involved 215 collaborating centers in 20 countries from Asia, Australia, Europe, and North America. It was designed to randomize over 10,000 patients with established type 2 diabetes in a factorial design (Table 1), resulting in treatment in four categories: *1*) intensive glucose lowering (including gliclazide MR) and additional "routine" BP lowering (perindopril/indapamide combination), *2*) standard glucose therapy and routine BP lowering, *3*) intensive glucose lowering and placebo; and *4*) standard glucose therapy and placebo (6).

Patients were included if they had type 2 diabetes and were aged ≥55 years with an additional risk factor for a vascular event, any level of BP, and any level of glucose control with no immediate indication for insulin treatment. After a 6-week prerandomization run-in, during which they received a fixed combination of perindopril (2 mg) and indapamide (0.625 mg) and standard guidelines-based blood glucose control, patients were randomized in a factorial design to either a perindopril/indapamide combination or placebo and either an intensive glucose-lowering strategy aiming for an A1C target of ≤6.5% or standard glucose-lowering strategy.

Subjects in the intensive glucose control arm received gliclazide MR and any other additional therapy to achieve these glucose targets. Subjects in the standard arm received therapy according to local guidelines; although if they required a sulfonylurea, then any medication other than gliclazide could be used.

Patients in the intensive glucose arm made clinic visits more frequently, attending three monthly after the first 6 months compared with 6 monthly visits in patients allocated to standard therapy.

Other measures that were used to tighten control in the intensive arm included encouraging investigators to promote lifestyle management such as weight loss and exercise; maximizing the dose of gliclazide MR, adding other oral agents; and adding long-acting insulin, used as basal bedtime insulin, with rapid-acting insulin added as required, starting with the main meal of the day.

Those allocated to standard therapy received treatment according to local practice. Outcomes were recorded at 6 monthly intervals with the exception of retinopathy, albumin-to-creatinine ratio, mini mental scores, and quality of life,

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Table 1—*Factorial design: description of the possible assigned therapies*

Intensive glucose control	Standard glucose control
Routine BP-lowering therapy	Routine BP-lowering therapy
Intensive glucose control	Standard glucose control
Placebo	Placebo

which were recorded at 2 years, 4 years, and at the end of the study.

The primary outcome was a composite of macrovascular (myocardial infarction, stroke, or cardiovascular death) and microvascular (retinopathy or nephropathy) events. Secondary outcomes included heart failure, hospitalization, all-cause mortality, and dementia.

The sample size was calculated based on epidemiological studies reporting the association of A1C with vascular events and assumed a 1% reduction in A1C between groups and 6 mmHg reduction in systolic BP, a 16% reduction in microvascular or macrovascular events based on an annual event rate of 3% for each. The analysis was based on the intention-to-treat principle. After 3 years of the trial, overall event rates were occurring at around 2% and separation of A1C was <1%. Without access to unblinded data, it was therefore decided to combine the analysis of the primary end point (i.e., macrovascular and microvascular disease) and extend the duration of the glucose-control arm by 18 months.

RESULTS

Patient characteristics

The progress of subjects through the trial is shown in Fig. 1. A total of 11,140 patients were randomized into the two glucose arms with a median follow-up of 5 years. Baseline characteristics are shown in Table 1. The mean age was 66 years,

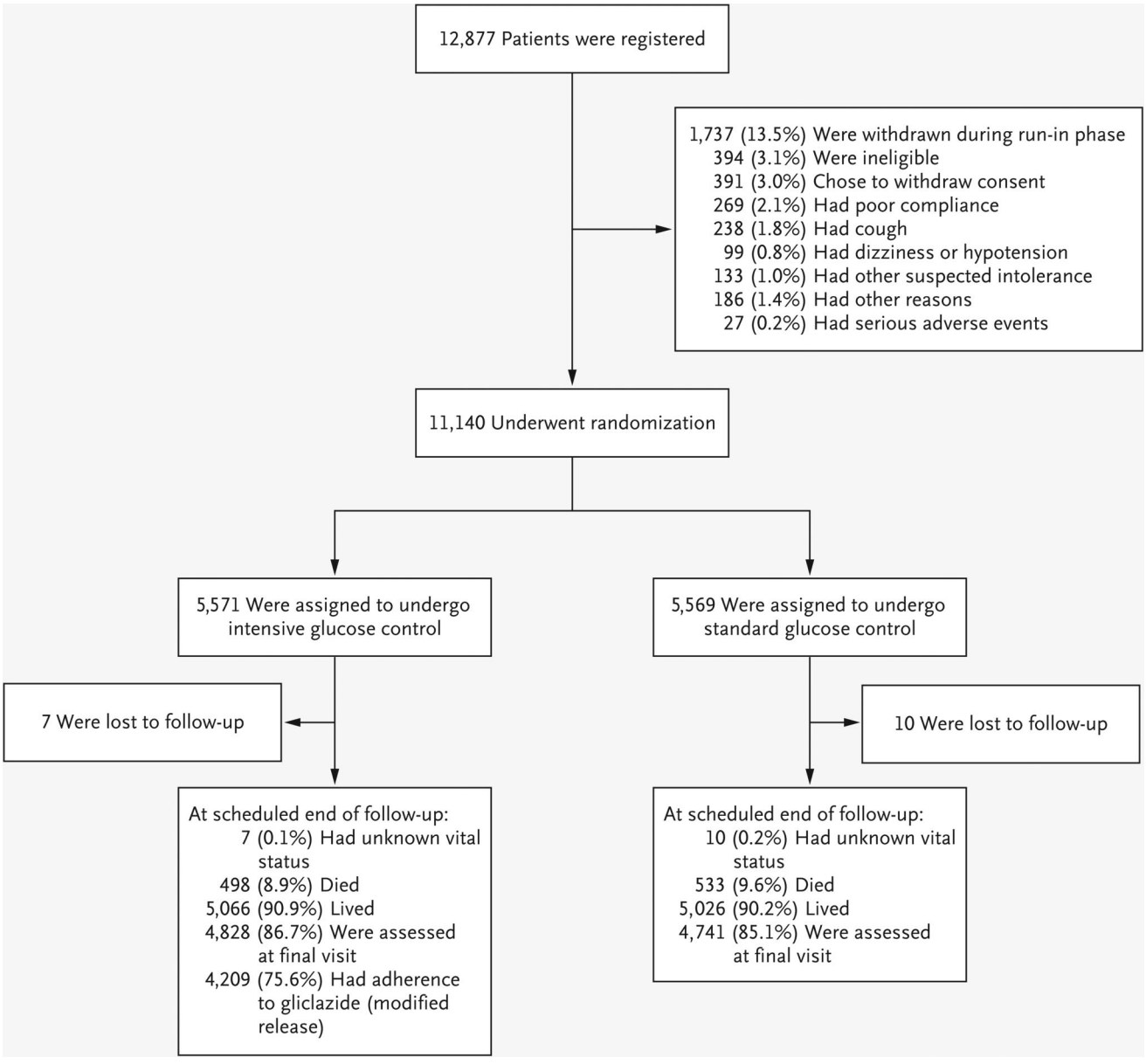

Figure 1—*Enrollment, randomization, and follow-up of study participants.*

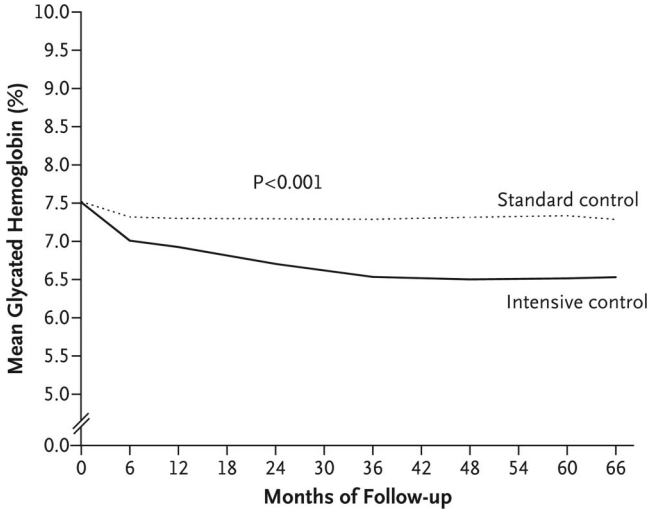

Figure 2—*A1C at baseline and during follow-up, according to glucose-control strategy. Data are shown for mean glycated hemoglobin. The average difference between the intensive-control group and the standard-control group for the follow-up period was 0.67 percentage points (95% CI 0.64–0.70).*

known duration of diabetes 8 years, and BMI 28 kg/m^2. Mean A1C at entry was 7.5%. About one-third of the patients had a history of previous macrovascular disease, 71% were taking sulfonylureas at entry, and 60% were on metformin.

The BP arm of the study ran for an average of 4.3 years: the results, published in *The Lancet* in 2007 (7), showed that a combination of indapamide and perindopril reduced mortality, coronary events, and diabetic nephropathy regardless of the initial BP.

A1C and glucose-lowering therapy

By the end of follow-up, A1C in the intensive group had fallen to a mean of 6.5% compared with 7.3% in the standard group (Fig. 2). A1C fell progressively in the intensive group, reaching 6.5% after 2–3 years' duration of the trial. By the end of the trial, over 90% of patients were still taking a sulfonylurea (gliclazide MR) in the intensive group compared with 69% in those allocated to standard therapy. A total of 74% were taking metformin (vs. 67% in the standard group), 40% were on insulin (vs. 24%), and 17% were taking a glitazone compared with 11% in the standard group.

Effect of glycemic control on other risk factors

Systolic BP was significantly lower in individuals allocated to intensive glucose control by the end of follow-up (135.5 vs. 137.9 mmHg, average difference during follow-up 1.6 mmHg; $P < 0.001$). The difference was present at the 3-month visit and all subsequent visits. There were no differences in diastolic BP or lipids. The weight of those assigned to intensive control remained generally stable, whereas those in the standard group had a mean reduction in weight of 0.69 kg compared with the intensive group ($P < 0.001$).

Primary outcomes

A total of 2,125 participants had a major macrovascular or microvascular event during follow-up: 18.1% in the intensive control group and 20.0% in the standard control group (hazard ratio 0.90 [95% CI 0.82–0.98]; $P = 0.013$) (Fig. 3). There were no significant differences in the number of macrovascular events between the two groups during the trial (hazard ratio 0.94 [0.84–1.06]; $P = 0.32$) (Fig. 3). Thus, the differences were due to fewer microvascular events (14% relative risk reduction, $P = 0.01$), essentially a reduction in diabetic nephropathy (Fig. 4).

Secondary outcomes (including sudden death)

There were 1,031 deaths during the trial, but there were no significant differences between the two groups (8.9% in the intensive control group and 9.6% in the standard control group (hazard ratio 0.93 [0.83–1.06]; $P = 0.28$) (Fig. 3). Hospitalization was more frequent in the intensive control group, but there were no other significant differences in secondary end points.

Hypoglycemia

Severe hypoglycemia was more frequent in the intensive-control group than in the standard-control group: 150 patients (2.7%) had at least one episode of severe hypoglycemia compared with 81 (1.5%) in the standard group (hazard ratio 1.86 [1.42–2.40]; $P < 0.001$).

Minor hypoglycemia was also more frequent in the intensive control group (120 events per 100 patients per year, versus 90 with standard control).

CONCLUSIONS — The ADVANCE study has answered a number of important questions regarding glycemic control in patients with type 2 diabetes. It has clearly demonstrated that it is possible to achieve tight levels of glycemic control safely using conventional agents. The glucose-lowering approach reflected conventional "real-life" strategies using sulfonylureas (gliclazide MR), metformin, and insulin. Yet, A1C levels fell progressively to a mean of 6.5% and remained there for the duration of the study. This is in contrast to the glycemic profile of the UKPDS, where glucose control deteriorated gradually for the length of the trial (2). It is possible that the differences between the populations of patients studied in the two trials might account for some of these findings. Patients in the UKPDS were newly diagnosed, and it is conceivable that in recruiting for ADVANCE, local investigators excluded those whose glycemic control was likely to deteriorate. The ADVANCE study also included a large group of individuals from Asia whose diabetes might be expected to behave differently from a U.K. population. However, preliminary analyses do not suggest that the European patients in ADVANCE behaved significantly differently in terms of glycemic control. It may be that the incremental approach to glycemic therapy in type 2 diabetes that has developed over the last 15 years and uses metformin early together with basal insulin in combination with oral agents is reasonably effective at maintaining tight levels of glycemic control.

Importantly, the intensive glucose-lowering strategy used in ADVANCE was apparently safe. The incremental approach with increasing number of oral agents and the use of basal insulin lowered A1C levels in the intensive group gradually and the target A1C of 6.5% was

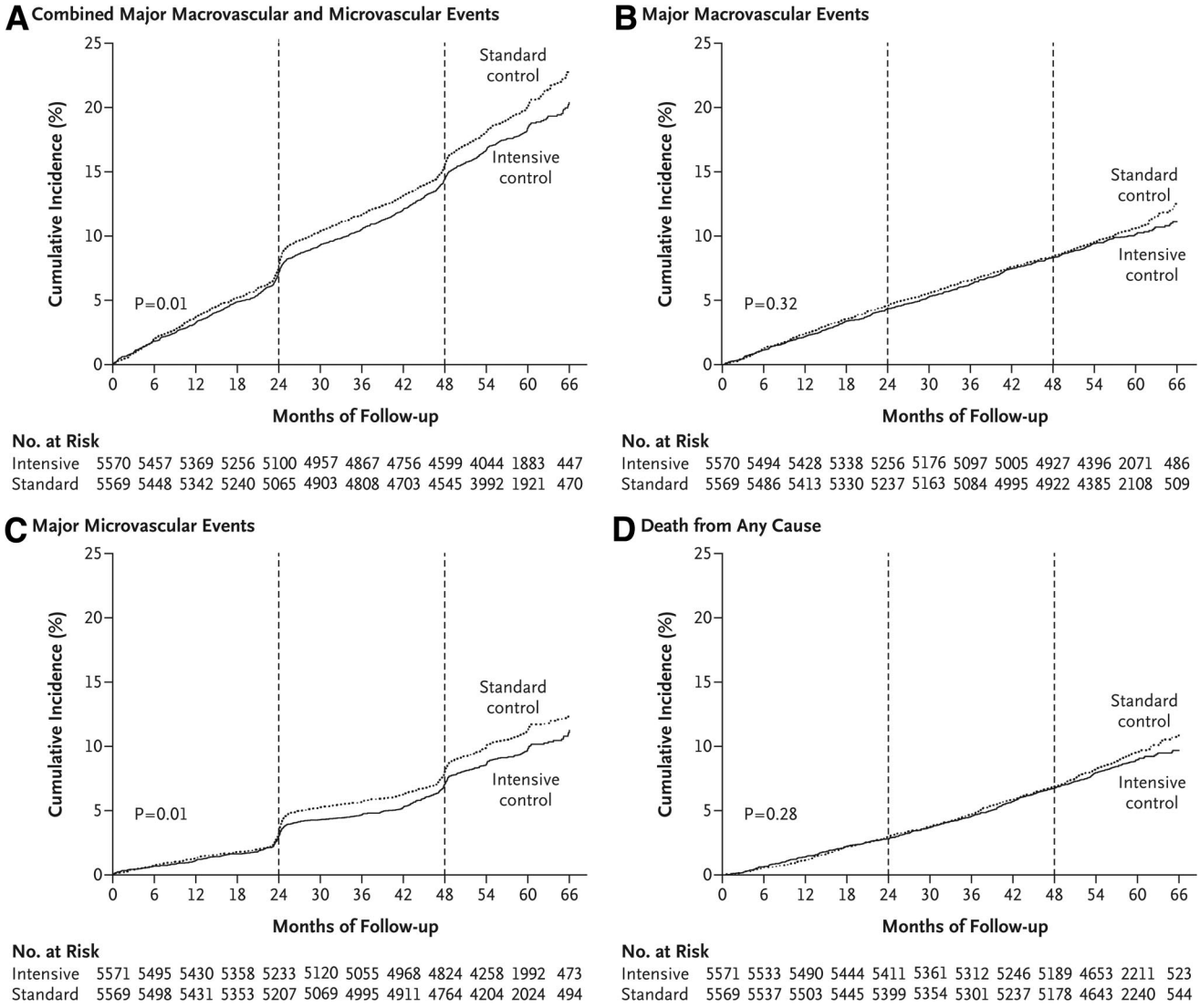

Figure 3—*Cumulative incidences of events, according to glucose-control strategy. The hazard ratios for intensive glucose control compared with standard glucose control were as follows: for combined major macrovascular or microvascular events, 0.90 (95% CI 0.82–0.98)* (A)*; for major macrovascular events, 0.94 (0.84–1.06)* (B)*; for major microvascular events, 0.86 (0.77–0.97)* (C)*; and for death from any cause, 0.93 (0.83–1.06)* (D)*. The vertical dashed lines indicate the 24- and 48-month study visits, at which additional data on microvascular events were collected, specifically the ratio of urinary albumin to creatinine and results of a retinal examination. For events relating to these data, the event time was recorded as the date of the visit. The curves were truncated at month 66, by which time 99% of the events had occurred. The effects of treatment (hazard ratios and* P *values) were estimated from unadjusted Cox proportional-hazard models that used all the available data.*

achieved over 2 years after the start of the trial. Perhaps as a result of this relatively slow fall in A1C, the side effects of glucose-lowering therapy were relatively limited. Severe hypoglycemia was not common and less than that reported in the UKPDS. Indeed, rates of severe hypoglycemia in those patients assigned to intensive control in ADVANCE were below those reported in the standard arm of the UKPDS. It is not clear which aspects of the glucose control strategy were responsible for the low risk of severe hypoglycemia. It is possible that the use of basal insulin rather than quick-acting insulin, which is associated with lower rates of hypoglycemia compared with other insulin regimens (8), partly explains this finding.

The lack of weight gain in the trial was noteworthy and unexpected. It is possible that the use of basal insulin as a strategy in combination with metformin and sulfonylureas was partially responsible (9). The high proportion of Asian patients and thus the slightly lower BMI in the trial compared with other large studies of type 2 diabetes might also have contributed. However, perhaps the relatively low A1C in the recruited population on entry into the trial is the most likely explanation. Such individuals would be losing relatively small amounts of glucose in their urine so that tightening their control would not have caused weight gain due to a loss of glycosuria, an important cause of increased weight among patients with type 2 diabetes when diabetic control is tightened (10).

This trial and others (11) have demonstrated clearly that at least in the short term (3–5 years), tightening glycemic control from moderate to fairly tight levels of A1C (6–6.5%) has no significant effect in reducing macrovascular disease. The results of ADVANCE do not exclude a minor effect on cardiovascular disease; indeed cardiovascular mortality was reduced by 12%, albeit nonsignificantly.

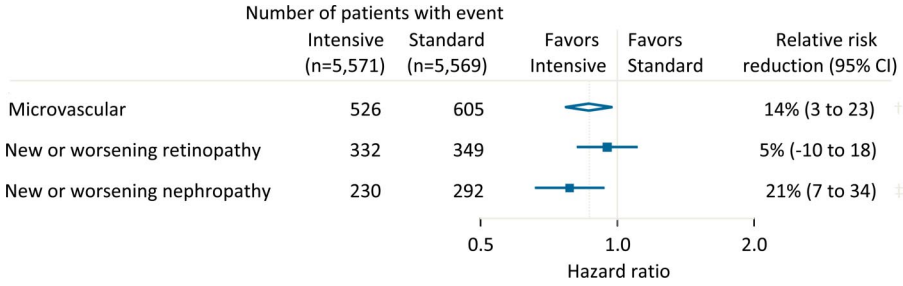

Figure 4—*Relative effects of glucose-control strategy on microvascular disease. The diamonds incorporate the point estimates, represented by the vertical dashed lines, and the 95% CIs of the overall effects within categories; for subcategories, black squares represent point estimates (with the area of the square proportional to the number of events), and horizontal lines represent 95% CIs. The hazard ratios and relative risk reductions are given for intensive glucose control compared with standard glucose control.*

However, clinicians can now concentrate on targeting other aspects of type 2 diabetes, particularly BP and cholesterol reduction in the clear knowledge that this will have a larger effect in preventing macrovascular complications.

Nevertheless, it may be that the fall in the incidence of nephropathy that was demonstrated in ADVANCE might have longer-term downstream benefits on cardiovascular disease. Patients with diabetic nephropathy have a much higher risk of macrovascular disease, and so a 20% reduction could be expected to affect cardiovascular disease over a longer time frame (12). It is noteworthy that the STENO-2 trial, which tested an aggressive strategy targeting glucose, BP, and lipids in high-risk individuals with type 2 diabetes, only demonstrated clinically relevant reductions in cardiovascular disease after 8 years and mortality after 13 years (13).

Clinicians will need to decide whether the reduction in diabetic nephropathy among patients with type 2 diabetes when A1C levels are lowered to ~6.5% is worthwhile. However, since glycemic control was achieved in ADVANCE across multiple centers worldwide with relatively few side effects, this level of glycemic control appears to be both practical and provides useful clinical benefit. Current clinical guidelines that recommend A1C levels of between 6.5 and 7% are supported by the data from ADVANCE.

In conclusion, the ADVANCE trial has demonstrated in over 10,000 patients with type 2 diabetes, that an intensive strategy with conventional agents can achieve mean A1C levels of 6.5% safely with no increase in mortality and has no significant effect in reducing macrovascular disease, but reduces diabetic nephropathy by ~20%.

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