Curr Cardiol Rep (2012) 14:79–88
DOI 10.1007/s11886-011-0238-6

Does Aggressive Glycemic Control Benefit Macrovascular and Microvascular Disease in Type 2 Diabetes?: Insights from ACCORD, ADVANCE, and VADT

Toni Terry · Kalyani Raravikar · Nalurporn Chokrungvaranon · Peter D. Reaven

Published online: 13 December 2011

Abstract Diabetes is increasing rapidly worldwide and frequently results in severe vascular complications. A target glycated hemoglobin of less than 7% has commonly been recommended in hopes of preventing both macrovascular and microvascular complications. Although results from trials of intensive glycemic control have generally supported the notion that lower glycated hemoglobin values reduce microvascular disease, the evidence for similar benefits for macrovascular disease has been less clear. As macrovascular disease is the major cause of morbidity and mortality in type 2 diabetes, this remains one of the more important unresolved clinical questions. Recent results from the ACCORD, ADVANCE, and VADT studies have challenged the conventional believe that lower glycated hemoglobin values should be pursued in all diabetic patients. Factors that may influence whether intensive glucose management is advisable include duration of diabetes, pre-existing macrovascular disease, hypoglycemic unawareness, and significant comorbidities. Glycated hemoglobin goals should account for these factors and be individualized for each patient.

Keywords Type 2 diabetes · Macrovascular disease · Microvascular disease · Intensive glycemic control · UGDP · UKPDS · ACCORD · ADVANCE · VADT · Coronary artery calcium · Atherosclerosis · Diabetes duration · Hypoglycemic unawareness · Glycated hemoglobin · Advanced glycation end products · Metabolic memory

T. Terry (✉) · P. D. Reaven
Division of Endocrinology,
Phoenix VA Health Care System,
650 East Indian School Road,
Phoenix, AZ 85012, USA
e-mail: toni.terry@va.gov

P. Reaven
e-mail: peter.reaven@va.gov

K. Raravikar
Research Department, Endocrine Section,
Phoenix VA Health Care System,
650 East Indian School Road,
Phoenix, AZ 85012, USA
e-mail: kate2kalyani@gmail.com

N. Chokrungvaranon
Endocrinology, University of Missouri Kansas City,
2301 Holmes Street,
Kansas City, MO 64108, USA
e-mail: nalurporn@yahoo.com

P. D. Reaven
Arizona State University,
Tempe, AZ, USA

P. D. Reaven
University of Arizona,
Phoenix, AZ, USA

Clinical Trial Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
DCCT	Diabetes Control and Complications Trial
UGDP	University Group Diabetes Program
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial

Introduction

By the year 2030, it is estimated that 366 million people worldwide will have diabetes mellitus [1]. This predicted increase parallels the advancing age of the population, rising rates of obesity throughout the world, and sedentary lifestyles. Diabetes can result in significant macrovascular

and microvascular complications. Coronary artery disease, peripheral vascular disease, and stroke are well-recognized macrovascular complications, whereas retinopathy, nephropathy, and neuropathy are the more common microvascular disease manifestations.

The impact of hyperglycemia and its association with macrovascular disease has been examined in numerous studies. Several cohort studies, including the Diabetes Intervention Study [2], the San Antonio Heart Study [3], and the Framingham Study [4], have demonstrated a two- to fourfold increase in cardiovascular disease risk associated with either elevated glycated hemoglobin or fasting glucose. The consequences of cardiovascular disease are greater in patients with diabetes because death after acute myocardial infarction is 50% more common [5] and congestive heart failure is more common after acute myocardial infarction compared with nondiabetic patients [6]. Cardiovascular disease and stroke account for the highest percentage of deaths in people with diabetes even when other risk factors such as smoking, hyperlipidemia, and hypertension are considered.

Intensive glycemic control has been suggested as an effective treatment to reduce the burden of both macrovascular and microvascular disease. Until recently, guidelines by most health organizations have recommend a glycated hemoglobin goal of 7% or below without clear guidance as to whether other patient characteristics such as duration of diabetes, patient frailty, presence of pre-existing vascular disease, or concomitant illnesses should modify this goal. However, the optimal goal for glycemic control has been disputed since the publication of results from several recent studies including ACCORD, ADVANCE, and VADT.

This article reviews earlier studies as well as recent pivotal studies to help place these many diverse findings into a broader clinical context. An additional goal of this review is to help identify which subgroups may or may not benefit from more aggressive glycemic control.

Earlier Studies in Type 2 Diabetes: UGDP and UKPDS

UGDP

The UGDP completed in 1969 was one of the first randomized controlled trials conducted to assess the benefit of lowering blood glucose on the incidence of diabetes complications [7]. A total of 823 type 2 diabetic patients were randomly assigned to placebo, sulfonylurea (tolbutamide), or insulin to determine if use of a hypoglycemic agent could decrease vascular complications compared with placebo and insulin. The study failed to demonstrate a benefit for cardiovascular risk reduction. In fact, patients on tolbutamide had a higher rate of death from cardiovascular causes (12.7% vs 4.9%) than the placebo group. Even though there has been widespread criticism of UGDP, this study was one of the first to raise concern about glycemic management and its impact on cardiovascular mortality.

UKPDS

The UKPDS randomized 4209 patients with newly diagnosed type 2 diabetes in 23 centers within the United Kingdom between 1977 and 1991 [8]. Consistent with their recent diagnosis of diabetes, participants were younger than those in ACCORD, ADVANCE, and VADT with a mean age of 53.3 years (Table 1). Baseline mean glycated hemoglobin was similar to mean entry values in the ADVANCE study at 7.1% but lower than those found in ACCORD and VADT studies. Participants in the UKPDS were assigned to receive conventional therapy with dietary restriction or intensive therapy (either sulfonylurea or insulin, or, in overweight patients, metformin). The UKPDS was designed to establish whether intensive blood glucose control reduced the risk of macrovascular or microvascular complications in type 2 diabetes. Although glucose levels fluctuated over the 10-year study duration, the median glycated hemoglobin in the intensive group was 7.0% compared with 7.9% in the conventional group. Intensive glycemic therapy was associated with a 25% reduction in microvascular disease; however, most of this reduction was attributed to fewer patients requiring photocoagulation. There was a nonsignificant reduction in relative risk of myocardial infarction (16% risk reduction; $P=0.052$), but no overall decrease in macrovascular disease. In subgroup analyses of intensive therapy patients allocated to metformin there was a risk reduction of 32% ($P=0.0023$) for any diabetes-related end point including macrovascular and microvascular complications, a 42% risk reduction ($P=0.017$) for diabetes-related death, and a 36% risk reduction for all-cause mortality ($P=0.011$) compared with the conventional group. This data suggests that intensive glucose control with metformin appears to decrease the risk of diabetes-related end points in overweight diabetic patients [9].

UKPDS Follow-Up

After completion of the active intervention study, differences in glycated hemoglobin levels between the standard and intensive glycemic groups disappeared after the first year. Participants were followed for an additional 10 years, either at annual clinic visits for the first 5 years, or with follow-up questionnaires subsequently. In the combined group assigned to treatment with either sulfonylurea or insulin, persistent and now significant relative risk reduc-

Table 1 Baseline and on-study characteristics of subjects in the UKPDS, ACCORD, ADVANCE, and VADT studies

	UKPDS		ACCORD		ADVANCE		VADT	
Baseline characteristics								
N	3867		10,251		11,140		1791	
Gender male/female (%)	61/39		61/39		57/43		97/3	
Mean age (y)	53.3		62.2		65.8		60.4	
Duration of diabetes (y)	Newly diagnosed		10		8		11.5	
History of macrovascular disease (%)	6		35		32		40	
Mean HbA_{1c} (%)	7.1		8.3		7.5		9.4	
On insulin (%)	0		35		1.5		52	
Study protocol	Intensive	Standard	Intensive	Standard	Intensive	Standard	Intensive	Standard
HbA_{1c} goal (%)	FPG <108 mg/dL	Best achievable with diet	<6	7.0–7.9	≤ 6.5	Goal based on local guidelines	<6 (action if > 6.5)	Planned separation of 1.5
Treatment strategy	Sulfonylurea, insulin, metformin	Diet, if FPG > 270 mg/dL then addition of drugs	Different glucose-lowering agent and/or insulin at the discretion of physician		Gliclazide + other treatment at the discretion of physician	No gliclazide, other treatment at discretion of physician	BMI > 27 kg/m^2: max dose of metformin + rosiglitazone. BMI <27 kg/m^2: glimepiride + rosiglitazone. Insulin if HbA_{1c} of ≥ 6%	Half doses of intensive treatment. Insulin if HbA_{1c} ≥ 9%
On-study characteristics								
Median follow-up (y)	10	10	3.4	3.4	5.0	5.0	5.6	5.6
Median HbA_{1c} achieved	7.0[a]	7.9[a]	6.4	7.5	6.5	7.3	6.9	8.4
On insulin at study end (%)	55	23	77	55	41	24	NS	
On TZD at study end (%)	NS	NS	91	58	17	11	53	42
On statin at study end (%)	NS	NS	88	88	46	48	85	83
On aspirin at study end (%)	NS	NS	76	76	57	55	88	86
Mean blood pressure at study end (mm Hg)	NS	NS	126/67	127/68	136/74	138/74	127/69	125/69
Weight changes (kg)	NS	NS	+3.5	+0.4	−0.1	−1.0	+7.8	+3.4

[a] Median achieved HbA1c over 10 years

ACCORD Action to Control Cardiovascular Risk in Diabetes; *ADVANCE* Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; *BMI* body mass index; *FPG* fasting plasma glucose; *HbA1c* hemoglobin A1c; *NS* not stated; *TZD* thiazolidinedione; *UKPDS* United Kingdom Prospective Diabetes Study; *VADT* Veterans Affairs Diabetes Trial

tions of 15% for myocardial infarction and 13% for death of any cause were seen as more events occurred over time [10••]. Furthermore, the significant reduction of 25% in the risk of microvascular disease observed during the interventional trial in the intensive therapy group persisted throughout the post-trial period (Table 2).

Thus, the UKPDS showed a benefit of improved glycemic control in reducing the risk of microvascular disease during the interventional trial, but the risk reduction for myocardial infarction and death from any cause were observed only with extended post-trial follow-up. Persistent and long-term benefits for microvascular disease reduction noted in the post-trial UKPDS follow-up, despite the early loss of within-trial differences in glycated hemoglobin between the intensive therapy group and the conventional therapy group in the first year after trial completion, have been termed a "legacy effect." One of the proposed concepts to explain this purported extended legacy effect is metabolic memory. This is the concept whereby the early glycemic environment is remembered by target organs and affects future vascular changes [11–13]. The legacy effect is also supported by long-term monitoring data after completion of the DCCT. Results from this epidemiologic follow-up demonstrated that prior intensive diabetes therapy in type 1 diabetes reduced the risk of any cardiovascular disease event by 42% (P=0.02) and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57% (P=0.02) [14].

ACCORD

The ACCORD trial was specifically designed to determine whether targeting normal glycated hemoglobin levels (<6.0%) would reduce the rate of cardiovascular events compared with targeting levels from 7.0% to 7.9% in type 2 diabetic patients with established cardiovascular disease or additional risk factors [15••]. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After recruitment, 10,251 participants were randomized to receive intensive glucose-lowering therapy with oral agents, insulin, or both to achieve specified glycated hemoglobin values. Participants had long-standing diabetes (~10 years), a mean age of 62.2 years, and a mean glycated hemoglobin level of 8.3% (Table 1). Previous cardiovascular events were reported in 35% of the study participants. Intensive and standard therapeutic strategies rapidly achieved differ-

Table 2 Outcomes for subjects in the UKPDS, ACCORD, ADVANCE, and VADT studies

Outcomes				
	UKPDS	ACCORD	ADVANCE	VADT
Primary outcome	Aggregate of any diabetes-related end point, diabetes-related death, all-cause mortality	Composite of nonfatal MI, nonfatal stroke, and CV death	Composite of major macrovascular and microvascular events	Composite of major CV events
Risk for primary outcome (95% CI)	RR any diabetes-related end point 0.88 (0.79–0.99) RR diabetes-related death 0.90 (0.73–1.11)	HR 0.90 (0.78–1.04)	HR 0.90 (0.82–0.98)	HR 0.88 (0.74–1.05)
Risk for total mortality (95% CI)	RR 0.94 (0.8–1.1)	HR 1.22 (1.01–1.46)	HR 0.93 (0.83–1.06)	HR 1.07 (0.81–1.42)
Risk for CV mortality (95% CI)	NS as combined end point RR fatal MI 0.94 (0.68–1.30) RR fatal stroke 1.17 (0.54–2.54)	HR 1.35 (1.04–1.76)	HR 0.88 (0.74–1.04)	HR 1.32 (0.81–2.14)
Risk for nonfatal MI (95% CI)	RR 0.79 (0.58–1.09)	HR 0.76 (0.62–0.92)	HR 0.98 (0.78–1.23)	NS
Risk for nonfatal stroke (95% CI)	RR 1.07 (0.68–1.69)	HR 1.06 (0.75–1.50)	HR 1.02 (0.85–1.24)	NS
Risk for microvascular disease (95% CI)	RR 0.75 (0.6–0.93)	NS	HR 0.86 (0.77–0.97)	NS
Follow-up studies				
	Microvascular intensive	Microvascular intensive	Macrovascular intensive	Macrovascular intensive
UKPDS	Sulfonylurea-insulin	Metformin	Sulfonylurea-insulin	Metformin
	After 16.8 y, 25% relative reduction in risk of microvascular complication	No significant risk reductions during or after the trial in microvascular disease	After 16.8 y, 15% risk reduction for MI 13% risk reduction from death of any cause	After 17.7 y, 33% risk reduction in MI, 27% reduction from death of any cause
ACCORD			After 5 y, reduced nonfatal MIs but increased 5-y mortality	

ACCORD Action to Control Cardiovascular Risk in Diabetes; *ADVANCE* Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; *CV* cardiovascular; *HR* hazard ratio; *MI* myocardial infarction; *NS* not stated; *RR* relative risk; *UKPDS* United Kingdom Prospective Diabetes Study; *VADT* Veterans Affairs Diabetes Trial

ent glycated hemoglobin levels, and within 4 months of randomization the level had fallen from 8.1% at baseline to 6.7% in the intensive therapy group and to 7.5% in the standard therapy group. At 1 year, stable median levels of 6.4% in the intensive group and 7.5% in the standard group had been achieved and were maintained until increased mortality was observed in the intensive therapy group. Differences in mortality emerged 1–2 years after randomization. Compared with the standard therapy group, the intensive therapy group had a relative increase in mortality of 22%. The finding of higher mortality in the intensive therapy group led to discontinuation of intensive therapy after a mean of 3.5 years of follow-up. The increase in mortality was equivalent to approximately one extra death (primarily from cardiovascular causes) for every 95 patients treated for 3.5 years. As a result of these findings, intensive therapy group subjects were subsequently transitioned to standard therapy and followed until study completion (median of 5 years). After this transition, the median glycated hemoglobin level in the intensive group rose from 6.4% to 7.2%.

The lower glycated hemoglobin levels in the intensive therapy group were associated with a greater exposure to diabetes medications and participants within this group had more frequent changes in the dose or the number of study drugs used. In contrast to the standard therapy group, the intensive therapy group had significantly higher rates of hypoglycemia, weight gain, and fluid retention. Although many explanations for the increased mortality in ACCORD have been proposed, including rapid reduction of high glycated hemoglobin values or maintenance of glycated hemoglobin at near-normal levels, hypoglycemia, effects of drugs or drug combinations, and weight gain [16], none have been definitively supported in post hoc analyses. Of note, analyses by Riddle et al. [17] have implicated factors associated with persistent higher glycated hemoglobin levels rather than low glycated hemoglobin levels as likely contributors to the increased mortality associated with intensive glycemic control. Specifically, the risk of death appeared to be greater with intensive glycemic control compared with the standard therapy group only when the average glycated hemoglobin was greater than 7%.

ACCORD Macrovascular Results

At 3.5 years of follow-up, the primary outcome occurred in 352 participants in the intensive therapy group compared with 371 participants in the standard therapy group (Table 2; hazard ratio, 0.90; P=0.16). Thus, the use of intensive therapy to target normal glycated hemoglobin levels resulted in increased mortality and did not significantly reduce major cardiovascular events. As previously mentioned, participants in the intensive therapy group were transitioned to the standard therapy regimen and followed for the remaining 17 months to complete the planned 5-year trial. At the end of the 5-year trial, the median glycated hemoglobin levels were 7.2% in the intensive therapy group and 7.6% in the standard therapy group. The overall rate of nonfatal myocardial infarction in the intensive therapy group was lower than in the standard therapy group (1.18% vs 1.42%; hazard ratio, 0.82; 95% CI, 0.70–0.96; P=0.01) [18••]. However, analysis at the end of 5 years showed a 19% higher rate of death from any cause in the intensive therapy group compared with the standard therapy group (1.53% vs 1.27%; 95% CI, 1.03–1.38; P=0.02). There were no clear differences in any of the other predefined cardiovascular outcomes. Thus, the use of intensive therapy for 3.5 years to target a glycated hemoglobin level below 6% reduced 5-year nonfatal myocardial infarctions but increased 5-year mortality. Based on results from ACCORD, a similar strategy of intensive glycemic control aiming toward a glycated hemoglobin of less than 6% cannot be recommended in patients with advanced type 2 diabetes and a high risk of cardiovascular disease.

Although there was no overall benefit for the whole group, prespecified subgroup analyses indicated there were fewer cardiovascular events in patients without a previous history of cardiovascular disease events (~5% vs 11%) or with a baseline glycated hemoglobin of 8.0% or less (~6% vs 8%). This indicates that participants with less “advanced” diabetes may in fact benefit from intensive glycemic control. In contrast, those with pre-existing cardiovascular disease or higher baseline glycated hemoglobin levels may be at greater risk of cardiovascular events if aggressive glycemic control is rapidly achieved following the ACCORD approach.

ACCORD Microvascular Results

ACCORD also had predefined secondary end points to assess the effect of intensive therapy on the incidence and progression of retinopathy, nephropathy, and neuropathy. Composite outcomes of advanced nephropathy, diabetic eye complications, and neuropathy did not differ between groups at the point of transition or at the official study end. However, intensive therapy was associated with a 21% reduction in the development of microalbuminuria at the point of transition and a 15% reduction at the end of the 5-year study. Furthermore, the risk of development of macroalbuminuria was 31% lower with intensive therapy at transition and 28% lower at study end. Macroalbuminuria is a known risk factor for renal insufficiency [19] and cardiovascular disease [20]. These findings support the

benefits of glycemic control for reduction of albuminuria and raise the possibility that longer-term follow-up may reveal improvements in clinical renal disease and possibly macrovascular outcomes.

ADVANCE

The ADVANCE trial was designed to assess the effects of lowering the glycated hemoglobin value to a target of 6.5% or less on major macrovascular and microvascular outcomes in an international cross-section of patients with type 2 diabetes [21]. The global study included 11,140 participants whose original diagnosis of diabetes occurred at ≥ 30 years of age. Participants were older with a longer duration of diabetes, had a history of microvascular (27% of participants had microalbuminuria) or major macrovascular disease (32% of participants), or at least one other risk factor for vascular disease (Table 1). Subjects were randomized to intensive glucose-lowering therapy (target glycated hemoglobin of ≤6.5%) or standard therapy where target glycated hemoglobin was locally established.

After a mean of 5 years of follow-up, the glycated hemoglobin was lower in the intensive control group (6.5%) than in the standard control group (7.3%).

There was a significant 10% relative reduction in the combined outcome of major macrovascular and microvascular events seen in the intensive glucose control group in this study. However, this was mainly the result of a 21% relative reduction in the risk of new or worsening nephropathy. There were no significant differences between intensive and standard control groups in all-cause mortality (hazard ratio with intensive control, 0.93; 95% CI, 0.83–1.06; P=0.28) or death from cardiovascular causes (hazard ratio with intensive control, 0.88; 95% CI, 0.74–1.04; P=0.12). The development of macroalbuminuria (2.9% vs 4.9%; hazard ratio, 0.70; 95% CI, 0.57–0.85; P<0.001) was significantly reduced in the intensive therapy arm compared with the standard control. No significant treatment effect was seen with retinopathy. Rates of severe hypoglycemia were 2.7% in the intensive therapy group compared with 1.5% in the standard control group (P<0.001).

Even though ADVANCE participants were diverse in locality and ethnicity, the effects of intensive glycemic control were not significantly different between regions for any outcome, including mortality, vascular end points, and severe hypoglycemic episodes [22•]. Similar to the ACCORD study, ADVANCE participants without a history of macrovascular disease tended to have slightly better responses to intensive glycemic control; specifically, a nonsignificant 14% versus 4% relative risk reduction for combined major macrovascular and microvascular events. Overall, there was a clear benefit for microvascular reduction (particularly albuminuria) with intensive therapy but there was no significant difference in major macrovascular events or all-cause mortality between intensive therapy and standard control groups.

VADT

The VADT randomized 1791 military veterans with type 2 diabetes who had a suboptimal response to therapy (mean baseline glycated hemoglobin 9.4%). The mean age of participants was 60.4 years, mean number of years since the diagnosis of diabetes was 11.5, and 40% had a previously documented cardiovascular event (Table 1). Participants were randomized to either intensive therapy (goal of absolute reduction by 1.5 percentage points in the glycated hemoglobin level) or standard therapy. The primary outcome was the time from randomization to the first occurrence of any composite of cardiovascular events with all-cause mortality assessed as a secondary outcome [23••]. Median follow-up for participants was 5.6 years. The median glycated hemoglobin levels stabilized after 6 months of treatment at 8.4% in the standard therapy group and 6.9% in the intensive therapy group.

Comparison between intensive therapy and standard therapy failed to show any statistical differences in both primary and secondary outcomes. The primary outcome was observed in 264 patients in the standard therapy group versus 235 patients in the intensive therapy group (Table 2, hazard ratio, 0.88). Death from any cause was nonsignificantly higher in the intensive therapy group (hazard ratio, 1.07). Although intensive glycemic control did not show any significant benefit with regard to reduction in retinopathy, major nephropathy, or neuropathy compared with standard therapy, there was a significant reduction in worsening of albuminuria. In particular, participants with pre-existing microvascular eye disease, greater body weight, lower diastolic blood pressure, and higher levels of baseline albuminuria appeared to have the greatest attenuation in progression of albuminuria when intensive glucose-lowering therapy was pursued [24•].

As in several other intensive glucose-lowering therapy trials, there was a significant amount of hypoglycemia observed in the VADT trial (1566 hypoglycemic episodes per 100 patient-years in the intensive control group vs 432 hypoglycemic episodes per 100 patient-years in the conventional control group). A recent severe hypoglycemic episode was an important predictor for cardiovascular death (hazard ratio, 3.72; 95% CI, 1.34–10.4; P<0.01) and all-cause mortality (hazard ratio, 6.37; 95% CI, 2.57–15.8; P=0.001) as reported by Duckworth et al. [25] at the American Diabetes Association Scientific Sessions in 2009 in New Orleans, Louisiana. In summary, in the whole cohort, the

overall benefit of decreasing glycated hemoglobin from 8.4% to 6.9% over a period of 5–6 years was modest and was primarily limited to reduced progression of albuminuria. Since 97% of participants were men, one cannot extrapolate these findings to women; although the results are consistent with those in the ACCORD and ADVANCE studies.

Baseline Atherosclerosis Indicates Response to Therapy in the VADT

In a substudy cohort of 301 type 2 diabetes participants in VADT, baseline coronary atherosclerosis was assessed using coronary artery calcium (CAC) measured by computed tomography to determine whether the initial extent of vascular disease influenced responsiveness to glucose-lowering therapy [26•]. In fact, the benefit of intensive glycemic control was impressive (hazard ratio, 0.08; 95% CI, 0.008–0.77; $P=0.03$) for those with lower CAC (<100 Agatston units) but no significant improvement in cardiovascular outcomes was seen between intensive therapy and standard therapy when CAC scores were greater than 100. Importantly, the level of risk factors was not significantly different between these two groups of subjects, and adjustment for relevant risk factors did not reduce the importance of baseline CAC as a predictor of response to therapy. Thus, this subgroup analysis indicates that intensive glycemic therapy may be most effective in those with less extensive coronary atherosclerosis, whereas those with more extensive underlying atherosclerosis may not experience a significant reduction in macrovascular outcomes. As nearly 60% of this VADT subset of participants had CAC greater than 100 units, and this group appeared representative of the entire VADT cohort, this may explain the overall negative results in the VADT.

Just as underlying cardiovascular disease may predict whether a patient benefits from intensive glycemic control, duration of diabetes may also be an important factor to consider. In post hoc analyses of the VADT data, duration of diabetes at baseline was significantly related to cardiovascular outcomes with intensive glucose-lowering treatment. In subjects with less than 15 years of diabetes at the time of enrollment, intensive glycemic control significantly reduced cardiovascular outcomes. In contrast, with more than 15 years of diabetes, intensive treatment was associated with increased cardiovascular events and was significantly worse than standard therapy after 20 years or more of diabetes [25]. One possible explanation for this lack of benefit in those with a greater duration of diabetes may involve the accumulation of advanced glycation end products (AGEs) that exert atherogenic effects [27, 28]. Prolonged elevation of glucose concentrations over many years results in increased accumulation of AGEs, which may take years to be cleared. This phenomenon could potentially account for the limited reduction in macrovascular disease seen with intensive glycemic control in patients with poorly controlled, well-established diabetes.

Meta-Analyses of Trials of Intensive Glucose-Lowering Therapy

Whether intensive glucose lowering affects all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes has also been evaluated in several meta-analyses of randomized controlled trials. In the largest and most recent meta-analysis by Boussageon et al. [29••], 13 studies were included. Of the 34,533 patients evaluated, 18,315 received intensive glucose-lowering treatment and 16,218 standard treatment. Intensive treatment did not significantly affect all-cause mortality or cardiovascular death. However, intensive therapy was associated with reductions in the risk of nonfatal myocardial infarction (hazard ratio, 0.85; 99% CI, 0.74–0.96; $P<0.001$) and microalbuminuria (hazard ratio, 0.90; 99% CI, 0.85–0.96; $P<0.001$). Over a treatment period of 5 years, 117–150 patients would need to be treated to avoid one nonfatal myocardial infarction and 32–142 patients treated to avoid one episode of microalbuminuria. Moreover, a greater than twofold increase in the risk of severe hypoglycemia was seen with intensive therapy compared with standard therapy. With intensive therapy, one severe episode of hypoglycemia would occur for every 15–52 patients. When analyses were restricted to high-quality studies, intensive treatment was not associated with any reduction in microvascular or macrovascular complications but instead was associated with a 47% increase in the risk of congestive heart failure. In summary, the results of this meta-analysis showed limited benefit of intensive glucose-lowering therapy on all-cause mortality and deaths from cardiovascular causes and a 10% reduction in the risk of microalbuminuria.

A separate meta-analysis by Turnbull et al. [30••] included a total of 27,049 participants and 2370 major vascular events. Allocation to more intensive glucose control reduced the risk of major cardiovascular events by 9% (hazard ratio, 0.91; 95% CI, 0.84–0.99) during an average follow-up of 4.4 years, primarily because of a 15% reduced risk of myocardial infarction. Mortality was not decreased, with nonsignificant hazard ratios for all-cause mortality and cardiovascular death. However, in subgroup analysis, participants who did not have a history of macrovascular disease prior to randomization appeared to benefit from more intensive glycemic control (major cardiovascular events hazard ratio, 0.84; 95% CI, 0.74–0.94; $P=0.04$), whereas those with pre-existing macrovascular disease did not appear to benefit (major cardio-

vascular events hazard ratio, 1.00; 95% CI, 0.89–1.19; P= 0.04). Once again, intensively treated participants had significantly more major hypoglycemic events. Because of significant heterogeneity among the four studies (UKPDS, ACCORD, ADVANCE, VADT), the possibility of harm with more intensive glycemic treatment cannot be ruled out.

Translating Results from UKPDS, ACCORD, ADVANCE, and VADT to Improve Clinical Practice for Type 2 Diabetes

Results from the ACCORD, ADVANCE, and VADT strongly indicate that, at least over the 3- to 5-year active study duration available to date, older patients with more advanced diabetes and a greater prevalence of macrovascular disease do not derive significant benefit from intensive glycemic control trying to achieve near-normal glucose levels. In fact, there was a clear indication that, at least when following the treatment approach used in the ACCORD study, targeting near-normal glucose levels could increase mortality. Importantly, intensive glycemic control in the ACCORD and VADT resulted in more frequent and severe episodes of hypoglycemia, which not surprisingly was a strong risk factor for cardiovascular complications. Thus, one clear message from these recent studies appears to be that more moderate glucose control may be advisable in patients who resemble those in the ACCORD, ADVANCE, and VADT studies, in particular among those with baseline macrovascular disease and/or advanced or poorly controlled diabetes. Of course, we await longer-term observational follow-up from these studies to determine if future benefits become more apparent.

In contrast to these relatively negative findings, results from the UKPDS indicate that participants with newly diagnosed diabetes and absence of obvious macrovascular complications may derive the greatest benefit from intensive glycemic control. Early and aggressive glucose management in these types of patients appears to translate into long-term risk reduction for myocardial infarction, death from any cause, and microvascular disease. However, it is important to recognize that glycated hemoglobin goals targeted and those actually achieved were higher (> 7%) than in the more recent studies conducted in more advanced type 2 diabetes patients—perhaps reducing the frequency of adverse events in the intensive-treated group. Moreover, blood pressure and cholesterol levels obtained in the UKPDS were also higher than those in more current studies, potentially enhancing the importance of glucose control in a population with less than optimal risk factor control. Nonetheless, the favorable results in new-onset type 2 diabetes patients in the UKPDS are quite consistent with results from the DCCT in relatively young type 1 diabetes patients [31]. Moreover, subset analyses from the ACCORD and VADT studies also support this notion, and highlight the importance of considering factors such as diabetes duration, extent of coronary atherosclerosis, and prevalence of cardiovascular disease in determining how low the glycemic target should be.

Results from these above described trials point out that selecting the optimal glycated hemoglobin goal for individual patients is challenging and should take multiple factors into consideration. In recognition of these newer findings, and findings in many other studies not discussed, there is increased recognition among health organizations that more nuanced goals for glucose lowering are required. For example, the American Diabetes Association supports less aggressive glycated hemoglobin goals for certain subsets of diabetes patients, such as those with a very long duration of diabetes, history of severe hypoglycemia, advanced atherosclerosis, significant comorbidities, and advanced age/frailty [32••]. Thus, aiming for a glycated hemoglobin of 7%–8% may be a reasonable goal in patients with these conditions. In younger patients without documented macrovascular disease or the above-mentioned conditions, pursuing glycated values of less than 7% may provide long-lasting benefits. In patients with limited life expectancy, more liberal glycated hemoglobin values can be pursued.

Although many studies have focused on intensive glycemic control to decrease the risks of macrovascular and microvascular disease, glucose control is only one of the factors to consider. Comprehensive risk factor management including blood pressure control, lipid management, weight reduction in overweight or obese individuals, and smoking cessation are also needed. The Steno-2 study showed that a long-term, intensified intervention aimed at reduction of glycated hemoglobin, blood pressure, serum cholesterol and triglycerides levels, and urinary albumin excretion can reduce the risk of cardiovascular and microvascular events by nearly 50% [33]. Thus, to significantly reduce macrovascular and microvascular events in type 2 diabetes, comprehensive risk factor reduction must be addressed.

Conclusions

The ACCORD, ADVANCE, and VADT trials all showed that intensive glucose control does not reduce macrovascular disease in older patients with long-standing diabetes who are either at risk for, or have, cardiovascular disease. In fact, mortality findings in ACCORD and subgroup analyses of VADT suggest that aggressive glycemic control should be avoided in type 2 diabetic patients with long-standing diabetes, hypoglycemic un-

awareness, significant comorbidities and/or macrovascular disease, and advanced age/frailty. Similarly, although microvascular disease (particularly retinopathy) was reduced significantly in the UKPDS, improvements in microvascular complications in the ACCORD, ADVANCE, and VADT were relatively modest and were limited to reduced proteinuria. It remains unknown whether these improvements in microalbuminuria will eventually translate to reduced macrovascular and microvascular disease. Results from ongoing long-term, post-intervention follow-up of the ACCORD and VADT studies will be critical to determine if the benefits of intensive glycemic control outweigh the potential risks and consequences of this approach in individuals with characteristics of more advanced diabetes.

Although no clear macrovascular benefit was seen in the cohort analyses of these studies, subset analyses and results from earlier studies in young type 1 and type 2 diabetic patients have suggested a significant benefit of intensive glycemic control in those participants with shorter duration of diabetes, lower glycated hemoglobin at entry, and/or the absence of pre-existing macrovascular disease. Therefore, aggressive management of younger, newly diagnosed diabetic patients without underlying cardiovascular disease may provide long-lasting benefits and reduce the future burden of macrovascular and microvascular disease.

In conclusion, glycated hemoglobin goals for type 2 diabetes should be individualized based on the duration of diabetes, pre-existing macrovascular disease, hypoglycemic unawareness, comorbidities, and frailty. Macrovascular and microvascular risk reduction require comprehensive assessment and management of all known contributing risk factors.

Disclosure Conflicts of interest: T. Terry: none; K. Raravikar: none; N. Chokrungvaranon: none; P. Reaven: has received grant support from Amylin and Takada.

Disclaimer This material is based upon work supported in part by the Department of Veterans Affairs Cooperative Studies Program. The contents do not represent the views of the Department of Veterans Affairs or the United States Government.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27:1047–53.
2. Hanefeld M, Fischer S, Schmechel H, et al. Diabetes intervention study: multi-intervention trial in newly diagnosed NIDDM. Diabetes Care. 1991;14:308–17.
3. Wei M, Gaskill SP, Haffner SM. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. The San Antonio Heart Study. Diabetes Care. 1998;21:1167–72.
4. Wilson PW, Cupples LA, Kannel WB. Is hyperglycemia associated with cardiovascular disease? The Framingham Study. Am Heart J. 1991;121:586–90.
5. Sprafka JM, Burke GL, Folsom AR. Trends in prevalence of diabetes mellitus in patients with myocardial infarction and effect of diabetes on survival. The Minnesota Heart Survey. Diabetes Care. 1991;14:537–43.
6. Jaffe AS, Spadaro JJ, Schechtman K, et al. Increased congestive heart failure after myocardial infarction of modest extent in patients with diabetes mellitus. Am Heart J. 1984;108:31–7.
7. Meinert CL, Knaterud GL, Prout TE, et al. A study of the effects of hypoglycemic agents on vascular complications in patients with adult onset diabetes. II. Mortality results. Diabetes 1970, 19: Suppl:789–830.
8. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998, 352:837–853.
9. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998, 352:854–865.
10. •• Holman R, Paul S, Bethel M, et al. 10-Year follow-up of intensive glucose control in type 2 diabtes. N Engl J Med 2008, 359:1577–1589. *This article contains the 10-year follow-up of intensive glucose control in type 2 diabetes for the UKPDS.*
11. Ceriello A, Esposito K, Ihnat M, et al. Long-term glycemic control influences the long-lasting effect of hyperglycemia on endothelial function in type 1 diabetes. J Clin Endocrinol Metab. 2009;94:2751–6.
12. Ceriello A, Ihnat M, Thorpe J. Clinical review 2: the "metabolic memory": is more than just tight glucose control necessary to prevent diabetic complications? J Clin Endocrinol Metab. 2009;94:410–5.
13. Ceriello A. Hypothesis: the "metabolic memory", the new challenge of diabetes. Diabetes Res Clin Pract. 2009;86 Suppl 1: S2–6.
14. Intensive diabetes treatment and cardiovasculoar disease in patients with type 1 diabetes. The diabetes control and complications trial/epidemiology of diabetes interventions and complications (DCCT/EDIC) study research group. N Engl J Med 2005, 353:2643–2653.
15. •• Effects of intensive glucose lowering in type 2 diabetes. The action to control cardiovascular risk in diabetes study group. N Engl J Med 2008, 358:2545–2559. *This article contains the data from the ACCORD trial*.
16. Riddle M. Effects of intensive glucose lowering in the management of patients with type 2 diabetes mellitus in the action to control cardiovascular risk in diabetes (ACCORD) trial. Circulation. 2010;122:844–6.
17. Riddle M, Ambrosius W, Brillon D, et al. Epidemiologic relationships between A1c and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care. 2010;33:983–90.
18. •• Long-term effects of intensive glucose lowering on cardiovascular outcomes. The ACCORD study group. N Engl J Med 2011, 364:818–828. *This article contains the 5-year outcomes from the ACCORD trial.*
19. Meguro S, Shigihara T, Kabeya Y, et al. Increased risk of renal deterioration associated with low e-GFR in type 2 diabetes mellitus only in albuminuric subjects. Intern Med. 2009;48:657–63.
20. Sayage S, Estacio R, Jeffers B, et al. Urinary albumin excretion as a predictor of diabetic retinopathy, neuropathy, and cardiovascular disease in NIDDM. Diabetes Care. 1996;19:1243–8.

21. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. The ADVANCE collaborative group. N Engl J Med 2008, 358:2560–2572.
22. • Woodward M, Patel A, Zoungas S, et al. Does glycemic control offer similar benefits among patients with diabetes in different regions of the world? Diabetes Care publish ahead of print, published online October 4, 2011. *This article shows that irrespective of absolute risk, the effects of intensive glycemic control with the gliclazide modified release–based regimen used in ADVANCE were similar across Asia, established market economies, and eastern Europe and can be safely recommended for patients with type 2 diabetes in all these regions.*
23. •• Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129–39. *This article contains the data from the VADT trial*.
24. • Agrawal L, Azad N, Emanuele N, et al. Observation on renal outcomes in the veterans affairs diabetes trial. Diabetes Care 2011, 34:2090–2094. *This article shows that intensive glucose control had no significant effect on the progression of renal disease but was associated with some protection against increasing microalbuminuria in certain individuals.*
25. Duckworth W, Abraira C, Moritz T, et al. The duration of diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial. Presented at the June 2009 annual meeting of the ADA in New Orleans, LA.
26. • Reaven P, Moritz T, Schwenke D, et al. Intensive glucose-lowering therapy reduces cardiovascular disease events in veterans affairs diabetes trial participants with lower calcified coronary atherosclerosis. Diabetes 2009, 58:2642–2648. *These data indicate that intensive glucose lowering reduces cardiovascular events in those with less extensive calcified coronary atherosclerosis.*
27. Goldin A, Beckman J, Schmidt A, et al. Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation. 2006;114:597–605.
28. Yan S, Ramasamy R, Schmidt A. The RAGE axis: a fundamental mechanism signaling danger to the vulnerable vasculature. Circ Res. 2010;106:842–53.
29. •• Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomized controlled trials. BMJ 2011;343:d4169 doi:10.1136/bmj.d4169. *This is the largest and most recent met-analysis to examine whether intensive glucose lowering affects all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes.*
30. •• Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009, 52:2288–2298. *This is another recent, large meta-analysis that suggests that participants who do not have a history of macrovascular disease may benefit from more intensive glycemic control.*
31. 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 goup. N Engl J Med 1993, 329:977–986.
32. •• Standards of Medical Care in Diabetes—2011. American Diabetes Association. Diabetes Care 2011, 34:S11-S61. *These are the most recent guidelines published by the American Diabetes Association.*
33. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003;348:383–93.