Glycemic control and vascular complications in type 2 diabetes mellitus

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INTRODUCTION

The importance of intensive glycemic control for protection against microvascular and cardiovascular disease (CVD) in diabetes was established for type 1 diabetes in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study [1,2]. Although the benefit of glycemic control on microvascular disease in type 2 diabetes was documented in the United Kingdom Prospective Diabetes Study (UKPDS), its role in reducing cardiovascular risk has not been similarly established.

Glycemic targets and the effects of glycemic control on microvascular and macrovascular complications in type 2 diabetes will be reviewed here. Glycemic control and vascular complications in type 1 diabetes, the mechanism by which hyperglycemia might cause these complications, and an overview of the treatment of diabetes are discussed separately. (See "Glycemic control and vascular complications in type 1 diabetes mellitus" and "Overview of general medical care in nonpregnant adults with diabetes mellitus".)

CHOOSING A GLYCEMIC TARGET

Selecting an appropriate target glycated hemoglobin (A1C; intensive versus moderate control) should be individualized based upon comorbid conditions and functional status, balancing the potential benefit of improved glycemic control with the risks of hypoglycemia and weight gain.

- **Most patients** – A reasonable goal of therapy for most patients might be an A1C value of ≤7 percent (using a Diabetes Control and Complications Trial [DCCT]/United Kingdom Prospective Diabetes Study [UKPDS]-aligned assay in which the upper limit of normal is 6 percent). In order to achieve the A1C goal, a fasting glucose of 80 to 130 mg/dL (4.4 to 7.2 mmol/L) and a postprandial glucose (90 to 120 minutes after a meal) less than 180 mg/dL (10 mmol/L) have been given as targets, but higher achieved levels may suffice (table 1) [3,4].

- **Older patients or those with complications or comorbidities** – The A1C goal should be set somewhat higher (eg, <8 percent or higher) for patients with a history of severe hypoglycemia, patients with limited life expectancy, very young children or older adults, and individuals with advanced complications or comorbid conditions.

Improved glycemic control lowers the risk of microvascular complications in patients with type 2 diabetes (figure 1 and table 2) [5-12]. However, the absolute risk for microvascular complications and the incremental benefit of intensively lowering A1C must be balanced against the diminishing returns and the heightened risk of hypoglycemia at A1C levels less than 6.5 percent. (See 'Microvascular disease' below.)

Only limited clinical trial data (the long-term follow-up of the UKPDS) has demonstrated a macrovascular benefit with intensive therapy in patients with newly diagnosed type 2 diabetes [6]. The results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial suggest that a target A1C of 7.0 to 7.9 percent (achieving a median of 7.5 percent) may be safer for patients with longstanding type 2 diabetes and who are at high risk for cardiovascular disease (CVD) than a target A1C of less than 6.0 percent (achieving a median of 6.4 percent) [7]. (See 'Macrovascular disease' below.)

A target of 7.0 to 7.9 percent is also supported by the results of a retrospective cohort study of approximately 48,000 patients with type 2 diabetes, aged 50 years and older, whose treatment had been intensified [13]. After a mean follow-up of approximately 4.5 years, all-cause mortality was highest in those with the lowest (less than 6.7 percent) and highest (9.9 percent) A1C values. An A1C level of 7.5 percent was associated with the

lowest all-cause mortality. Similar findings were reported in a population-based cohort study of patients with diabetes and chronic kidney disease (estimated glomerular filtration rate [eGFR] 15 to 59.9 mL/min/1.73 m^2) [14]. There was a U-shaped relationship between A1C and mortality, with risk of mortality increasing with A1C values below 6.5 or above 8 percent.

All guidelines recommend tailoring A1C goals for individual patients. The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus algorithm recommend an A1C of less than 7 percent for most nonpregnant adults due to the benefits of reducing microvascular complications [4,15]. The American College of Physicians recommends an A1C between 7 and 8 percent [16]. The American Geriatrics Society suggests an A1C target of 8 percent for frail older adults and individuals with life expectancy of less than five years. These recommendations are supported by a decision analysis integrating multiple prediction models [17]. In this analysis, comorbid conditions and functional impairment were better predictors of both life expectancy and less benefit from intensive glucose control than age alone. (See "Treatment of type 2 diabetes mellitus in the older patient".)

INTENSIVE GLYCEMIC CONTROL

Benefits

Microvascular disease — Improved glycemic control lowers the risk of microvascular complications in patients with type 2 diabetes (primarily retinopathy, nephropathy) as illustrated by the findings of the United Kingdom Prospective Diabetes Study (UKPDS), Kumamoto, Action in Diabetes and Vascular Disease (ADVANCE), and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials (table 2) [5-11]. In a meta-analysis of these and other randomized trials (34,912 participants), there was a reduction in the risk of microvascular complications (a composite outcome including progression of nephropathy, manifestation and progression of retinopathy, and retinal photocoagulation) in the intensive compared with standard glycemic control group (risk ratio [RR] 0.88, 95% CI 0.82-0.95) [18]. There were significant reductions in risk for each of the individual components.

In other meta-analyses of trials (over 28,000 adults) evaluating the benefits of intensive versus conventional glycemic control specifically on renal outcomes, there was a

statistically significant reduction in the risk of microalbuminuria and macroalbuminuria in patients randomly assigned to intensive glycemic control (RRs of 0.86 and 0.74, respectively) [19-21]. The reduction in risk of end-stage kidney disease did not reach statistical significance (RR 0.69, 95% CI 0.46-1.05). There was no reduction in the risk of doubling of the serum creatinine level or death from renal disease (RRs 1.06 and 0.99, respectively) [20]. Of note, the majority of the trials in the meta-analyses were not of long enough duration to show a beneficial effect of glycemic control on end-stage kidney disease, which typically manifests after 10 to 20 years of diabetes duration [22]. In the trials included in the meta-analyses, the absolute rates of severe renal outcomes were low in both the intensive therapy and conventional therapy groups, reducing the ability of the analysis to demonstrate a benefit, if one exists. In the one trial with longer-term follow-up (UKPDS cohort followed for 22 years), there was a beneficial effect of intensive therapy on the development of more advanced clinical outcomes, including renal disease [6].

The importance of glycemic control in reducing the risk of microvascular disease is not disputed (although intensive compared with moderate glycemic control is debated) [23]. In UKPDS, every 1 percent decrease in A1C was associated with improved outcomes over the long term with no threshold effect (figure 1) [5]. In addition, the results of the post-trial monitoring phase of the UKPDS (median follow-up 17 years) showed that a sustained period of glycemic control in newly diagnosed patients with type 2 diabetes has lasting benefit in reducing microvascular disease [6]. The reduction in microvascular complications in patients receiving intensive therapy was of a smaller magnitude than in patients with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) [1]. One possible explanation for this difference is that the difference in A1C values was smaller between the intensive and conventional therapy groups in UKPDS (7.0 versus 7.9 percent) compared with the DCCT (7.2 versus 9.1 percent).

The lack of overall benefit of intensive control in the Veterans Affairs Diabetes Trial (VADT) on microvascular outcomes (although there were consistent, significant benefits with regard to albuminuria) may be secondary to the duration of diabetes in patients participating in VADT (mean 11.5 years versus newly diagnosed in UKPDS) and the time required to show benefit (delayed benefit may require longer follow-up) [24]. In addition, aggressive treatment of hypertension and hyperlipidemia in all VADT participants may have contributed to the inability to show a microvascular benefit of intensive glucose control.

Macrovascular disease — Although epidemiologic analyses (observational studies or secondary analyses of trials) suggest a correlation between higher rates of cardiovascular disease (CVD) and chronic hyperglycemia [25-30], most randomized clinical trials have not demonstrated a beneficial effect of intensive therapy on macrovascular outcomes in type 2 diabetes.

- **Longstanding diabetes** – The VADT, ACCORD, and ADVANCE trials were designed to study the effects of intensive versus conventional therapy (achieved A1C levels of approximately 6.5 compared with 7.5 to 8.5 percent) on cardiovascular outcomes in patients with **longstanding** diabetes (duration 8 to 12 years) [7,9-11,24,31,32]. None show a benefit of intensive control, and results from ACCORD showed a significant increase in total (hazard ratio [HR] 1.22) and CVD (HR 1.35) mortality with intensive therapy (table 3) [7,31,33,34]. Of note, ACCORD aimed for an A1C <6 percent, used as many as five diabetes medications to reach its glycemic goals, and secondary analyses did not identify lower A1C or hypoglycemia as risk factors for the excess mortality in the intensive intervention group [35,36].

- **Newly diagnosed diabetes** – In contrast to these trials, the UKPDS was designed to investigate the role of glycemic control (achieved mean A1C values of 7.0 versus 7.9 percent) on the complications of diabetes in **newly diagnosed** patients [5]. The UKPDS post-interventional study showed a benefit of initial intensive glycemic control (to achieve an A1C of 7 percent) on CVD in these individuals [6]. During the entire follow-up period (approximately 17 years), there were fewer overall deaths (RRs 0.87 [95% CI 0.79-0.96] and 0.73 [95% CI 0.59-0.89]), diabetes-related deaths (RRs 0.83 [95% CI 0.73-0.96] and 0.70 [95% CI 0.53-0.92]), and myocardial infarction (RRs 0.85 [95% CI 0.74-0.97] and 0.67 [95% CI 0.51-0.89]) in patients who were initially assigned to intensive treatment with sulfonylurea-insulin or metformin, respectively, compared with those assigned to conventional therapy [6]. In the UKPDS, the use of nonglycemic interventions recognized to reduce CVD was less frequent, and follow-up was longer than in the other trials. In a subsequent trial (metformin versus placebo added to insulin therapy) with achieved mean glucose control similar to the UKPDS (achieved mean A1C 7.5 versus 7.9 percent), there was also a decrease in the risk of the secondary macrovascular endpoint, which was a composite of 13 vascular events including myocardial infarction, heart failure, stroke, amputation, and sudden death (event rates 15 versus 18 percent, adjusted HR 0.6 [95% CI 0.4-0.9]) [37].

In meta-analyses including UKPDS, VADT, ACCORD, ADVANCE, there was a reduction in the risk for coronary heart disease (eg, RR 0.89 [95% CI 0.81-0.96]) and nonfatal myocardial infarction (RR 0.84 [95% CI 0.75-0.94]) with intensive glucose-lowering versus standard treatment [38-40]. However, intensive treatment did not significantly affect stroke, all-cause, or cardiovascular mortality [18,38-40]. These findings differ from the results of the individual trials (VADT, ACCORD, ADVANCE) and are likely related to differences in study design, including choice of pharmacologic therapy, baseline glycemic control, and frequency of hypoglycemia (table 3). As an example, in the intensively treated arm of the ACCORD trial, more than 90 percent of participants were treated with rosiglitazone and 77 percent were taking insulin, whereas in the ADVANCE trial, all patients in the intensive-treatment cohort were assigned to a sulfonylurea, and thiazolidinediones and insulin were used in only 16 and 40 percent, respectively. In VADT, insulin use (90 and 74 percent, respectively) and rosiglitazone use (72 and 62 percent, respectively) were common in both the intensive and standard groups. Metformin use was high among all patients in both ACCORD and ADVANCE (94 and 73 percent, respectively, in intensively treated patients).

Median baseline A1C was higher in VADT than in ACCORD and ADVANCE (9.4, 8.1, and 7.2 percent, respectively). A1C values were rapidly lowered during the first four months of the ACCORD trial, and there was a greater difference between the intensive and standard groups with regards to hypoglycemic events and weight gain.

Risks

Hypoglycemia and weight gain — Intensive treatment of blood glucose is associated with an increased risk of hypoglycemia [18], as well as accompanying burdens of polypharmacy, additional side effects, and cost (see "Hypoglycemia in adults with diabetes mellitus", section on 'Magnitude of the problem'). Depending on the agents prescribed, weight gain may also be an adverse effect of intensive treatment (table 3). In UKPDS, patients in the intensive therapy group had more weight gain; weight gain was greater in those receiving insulin (4.0 kg) than in those receiving chlorpropamide (2.6 kg) or glibenclamide (1.7 kg) [5].

MULTIFACTORIAL RISK REDUCTION

The most effective approach for prevention of macrovascular complications appears to be

multifactorial risk factor reduction (glycemic control, stopping smoking, aggressive blood pressure control, treatment of dyslipidemia, and, for secondary prevention, daily aspirin) (see "Overview of general medical care in nonpregnant adults with diabetes mellitus", section on 'Multifactorial risk factor reduction'). In addition, for patients with CVD, the actual type of glucose-lowering medication used has a more substantive effect on CVD risk (and, in some circumstances, renal risk) than might be expect from the degree of glucose lowering itself. Specifically, the sodium-glucose co-transporter 2 (SGLT2) inhibitors and the glucagon-like peptide 1 (GLP-1) receptor agonists, and, perhaps to a lesser extent, the thiazolidinedione pioglitazone, have been associated with reduced incidence of major adverse cardiovascular events, mainly in individuals with preexisting CVD. The SGLT2 inhibitors also appear to reduce adverse heart failure outcomes and the progression of chronic kidney disease, and this benefit applies to both those with and without CVD. In contrast, pioglitazone increases heart failure risk. Importantly, these effects appear to be independent of the effect of these agents on A1C. (See "Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus", section on 'Cardiovascular effects' and "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Cardiovascular effects' and "Thiazolidinediones in the treatment of type 2 diabetes mellitus", section on 'Cardiovascular effects'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diabetes mellitus in adults" and "Society guideline links: Diabetes mellitus in children".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are

comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: The ABCs of diabetes (The Basics)" and "Patient education: Type 2 diabetes (The Basics)")
- Beyond the Basics topics (see "Patient education: Type 2 diabetes: Overview (Beyond the Basics)" and "Patient education: Glucose monitoring in diabetes (Beyond the Basics)" and "Patient education: Preventing complications from diabetes (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Glycemic targets** – Glycated hemoglobin (A1C) goals in patients with type 2 diabetes should be tailored to the individual, balancing the improvement in microvascular complications with the risk of hypoglycemia. A reasonable goal of therapy might be an A1C value of ≤7 percent for most patients (using an assay in which the upper limit of normal is 6 percent). Glycemic targets are generally set somewhat higher (eg, <8 percent or higher) for patients with a history of severe hypoglycemia, patients with limited life expectancy, very young children or older adults, and individuals with comorbid conditions. (See 'Choosing a glycemic target' above.)
- **Microvascular disease** – Improved glycemic control improves the risk of microvascular complications in patients with type 2 diabetes (table 2). (See 'Microvascular disease' above.)
- **Macrovascular disease** – Randomized clinical trials have not demonstrated a beneficial effect of intensive therapy on macrovascular outcomes in patients with **longstanding** type 2 diabetes (table 3). In contrast, the results of the United Kingdom Prospective Diabetes Study (UKPDS) post-trial, observational follow-up study suggest that initial intensive control (A1C 7 percent) in individuals with **newly diagnosed** diabetes may have long-term benefit in decreasing the risk of myocardial infarction, diabetes-related death, and overall death. (See 'Macrovascular disease'

above.)

- **Hypoglycemia risk** – Intensive treatment of blood glucose is associated with an increased risk of hypoglycemia, as well as accompanying burdens of polypharmacy, additional side effects, and cost. Depending on the agents prescribed, weight gain may also occur with intensive treatment. (See 'Hypoglycemia and weight gain' above.)

- **Multifactorial risk factor reduction** – The most effective approach for prevention of macrovascular complications appears to be multifactorial risk factor reduction (glycemic control, stopping smoking, aggressive blood pressure control, treatment of dyslipidemia, and, for secondary prevention, daily aspirin). In addition, for patients with cardiovascular disease (CVD), the actual type of glucose-lowering medication used has a more substantive effect on CVD risk (and, in some circumstances, renal risk) than might be expect from the degree of glucose lowering itself. (See 'Multifactorial risk reduction' above and "Overview of general medical care in nonpregnant adults with diabetes mellitus", section on 'Multifactorial risk factor reduction'.)

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Topic 1760 Version 41.0

GRAPHICS

Average glucose levels before and after meals for specified A1C levels

	A1C percentage (mmol/mol)				
	5.5-6.49 (37-47)	**6.5-6.99 (48-52)**	**7.0-7.49 (52-58)**	**7.5-7.99 (58-64)**	**8.0-8.5 (64-69)**
	Estimated average glucose as mg/dL (95% CI)				
	111-139	**140-153**	**154-168**	**169-182**	**183-197**
Pre-breakfast	122 (117-127)	142 (135-150)	152 (143-162)	167 (157-177)	178 (164-192)
Pre-lunch	113 (108-117)*	127 (121-133)*	147 (139-155)	140 (132-149)*	167 (151-182)
Pre-supper	119 (115-123)	145 (138-152)	155 (148-162)	163 (153-173)	186 (168-205)
Post-breakfast	150 (144-157)¶	177 (170-184)¶	192 (181-203)¶	206 (193-219)¶	219 (204-234)Δ
Post-lunch	140 (135-145)	158 (151-164)	172 (164-180)	181 (170-191)	194 (178-209)
Post-supper	142 (136-146)	159 (152-166)	169 (162-177)	182 (171-193)	211 (195-227)

A1C: glycated hemoglobin.
* p<0.05 comparing mean pre-lunch glucose with pre-breakfast and pre-supper.
¶ p<0.05 comparing mean post-breakfast glucose with post-lunch and post-supper.
Δ p<0.05 comparing mean post-breakfast glucose with post-lunch.

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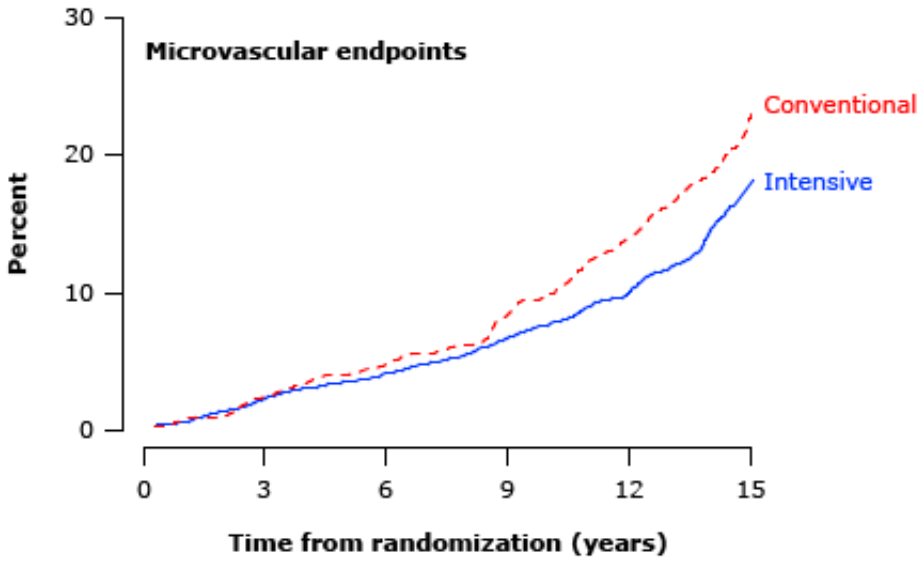
Graphic 121967 Version 2.0

Intensive glycemic control prevents severe microvascular disease in patients with type 2 diabetes



Kaplan-Meier plots of aggregate endpoints of microvascular disease in patients with type 2 diabetes mellitus in the United Kingdom Prospective Diabetes Study who were randomly assigned to receive either intensive therapy with a sulfonylurea or insulin, or to conventional treatment with diet; drugs were added if the patients had hyperglycemic symptoms or fasting blood glucose concentrations greater than 270 mg/dL (15 mmol/L). Intensive therapy was associated with a 25% reduction (p = 0.01) in the development of microvascular disease, which was defined as renal failure, death from renal failure, retinal photocoagulation, or vitreous hemorrhage.

Data from: Intensive blood-glucose control with sulphonylureas 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 1998; 352:837.

Graphic 52273 Version 4.0

Effect of intensive versus standard blood glucose control on major microvascular outcomes in type 2 diabetes

Study	Kumamoto study	UKPDS 33	UKPDS 80 (post-UKPDS 33)	ACCORD	ADVAN
Population	110	4209	3277	10,251	11,140
Age (years)	47-52	53		62	66
BMI (kg/m^2)	19-21	28		32	28
Complications	–/+	–/+		++	++
Disease duration (years)	6-10	0		10	8
Baseline A1C (%)	8.9-9.4	7.1		8.3	7.5
Post-trial A1C (intensive versus standard; %)	7.1 versus 9.4	7.0 versus 7.9		6.3 versus 7.5	6.5 versu 7.3
Microvascular endpoints					
Retinopathy	0.31 (0.13-0.76) ≥2-step cumulative change	0.75 (0.60-0.98) Any microvascular outcome	0.76 (0.64-0.89) Any microvascular outcome	0.67 (0.51-0.87)* 3-step progression	0.72 (0.44-1.17 3-step progressi
Nephropathy	0.30 (0.11-0.86) New or worsening nephropathy			0.72 (0.61-0.84) Incident macroalbuminuria	0.79 (0.66 0.93) New or worsenin nephropa
Neuropathy				0.92 (0.86-0.99) Neuropathy (MNSI>2)	

UKPDS: United Kingdom Prospective Diabetes Study; ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and Vascular Disease; VADT: Veterans Affairs Diabetes Trial; BMI: body mass index; A1C: glycated hemoglobin; MNSI: Michigan Neuropathy Screening Instrument.
* Data are relative risk (95% confidence interval) or odds ratio.

Graphic 126680 Version 1.0

Comparison of the three trials of intensive glycemic control and CVD outcomes

	ACCORD	ADVANCE	VADT
Participant characteristics			
n	10,251	11,140	1791
Mean age (years)	62	66	60
Duration of diabetes (years)	10	8	11.5
History of CVD (%)	35	32	40
Median baseline A1C (%)	8.1	7.2	9.4
On insulin at baseline (%)	35	1.5	52
Protocol characteristics			
A1C goals (%; I versus S)*	<6.0 versus 7.0-7.9	≤6.5 versus "based on local guidelines"	<6.0 (action if >6.5) versus planned separation of 1.5
Protocol for glycemic control (I versus S)*	Multiple drugs in both arms	Multiple drugs added to gliclizide versus multiple drugs with no gliclizide	Multiple drugs in both arms
Management of other risk factors	Embedded blood pressure and lipid trials	Embedded blood pressure trial	Protocol for intensive treatment in both arms
On-study characteristics			
Achieved median A1C (%; I versus S)	6.4 versus 7.5	6.3 versus 7.0	6.9 versus 8.5
On insulin at study end (%) (I versus S)*	77 versus 55*	40 versus 24	89 versus 74
Weight changes (kg)			
Intensive glycemic control arm	+3.5	–0.1	+7.8

Standard glycemic control arm	+0.4	–1.0	+3.4
Severe hypoglycemia (participants with one or more episodes during study; %)			
▪ Intensive glycemic control arm	16.2	2.7	21.2
▪ Standard glycemic control arm	5.1	1.5	9.9
Outcomes			
Definition of primary outcome	Nonfatal MI, nonfatal stroke, CVD death	Microvascular plus macrovascular (nonfatal MI, nonfatal stroke, CVD death) outcomes	Nonfatal MI, nonfatal stroke, CVD death, hospitalization for heart failure, revascularization
HR for primary outcome (95% CI)	0.90 (0.78-1.04)	0.9 (0.82-0.98); macrovascular 0.94 (0.84-1.06)	0.88 (0.74-1.05)
HR for mortality findings (95% CI)	1.22 (1.01-1.46)	0.93 (0.83-1.06)	1.07 (0.81-1.42)

CVD: cardiovascular disease; ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and Vascular Disease; VADT: Veterans Affairs Diabetes Trial; A1C: glycated hemoglobin; I: intensive glycemic control; S: standard glycemic control; MI: myocardial infarction; HR: hazard ratio.
* Insulin rates for ACCORD are for any use during the study.

Graphic 126681 Version 1.0

Contributor Disclosures

Silvio E Inzucchi, MD Consultant/Advisory Boards: AstraZeneca [Type 2 diabetes]; Bayer [Chronic kidney disease]; Boehringer Ingelheim [Type 2 diabetes]; Merck [Type 2 diabetes]; Novo Nordisk [Type 2 diabetes]; Pfizer [Type 2 diabetes]. All of the relevant financial relationships listed have been mitigated. **Beatrice Lupsa, MD** No relevant financial relationship(s) with ineligible companies to disclose. **David M Nathan, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Katya Rubinow, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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Conflict of interest policy

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