Effects of Intensive Glycemic Control on Clinical Outcomes Among Patients With Type 2 Diabetes With Different Levels of Cardiovascular Risk and Hemoglobin A_{1c} in the ADVANCE Trial

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OBJECTIVE

To study whether the effects of intensive glycemic control on major vascular outcomes (a composite of major macrovascular and major microvascular events), all-cause mortality, and severe hypoglycemia events differ among participants with different levels of 10-year risk of atherosclerotic cardiovascular disease (ASCVD) and hemoglobin A_{1c} (HbA_{1c}) at baseline.

RESEARCH DESIGN AND METHODS

We studied the effects of more intensive glycemic control in 11,071 patients with type 2 diabetes (T2D), without missing values, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, using Cox models.

RESULTS

During 5 years' follow-up, intensive glycemic control reduced major vascular events (hazard ratio [HR] 0.90 [95% CI 0.83–0.98]), with the major driver being a reduction in the development of macroalbuminuria. There was no evidence of differences in the effect, regardless of baseline ASCVD risk or HbA_{1c} level (P for interaction = 0.29 and 0.94, respectively). Similarly, the beneficial effects of intensive glycemic control on all-cause mortality were not significantly different across baseline ASCVD risk ($P = 0.15$) or HbA_{1c} levels ($P = 0.87$). The risks of severe hypoglycemic events were higher in the intensive glycemic control group compared with the standard glycemic control group (HR 1.85 [1.41–2.42]), with no significant heterogeneity across subgroups defined by ASCVD risk or HbA_{1c} at baseline ($P = 0.09$ and 0.18, respectively).

CONCLUSIONS

The major benefits for patients with T2D in ADVANCE did not substantially differ across levels of baseline ASCVD risk and HbA_{1c}.

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Hemoglobin A_{1c} (HbA_{1c}) has long been considered the standard for assessing risk from glucose control for development of late organ damage (1). Both the Diabetes Control and Complications Trial (DCCT) (2,3) and the UK Prospective Diabetes Study (UKPDS) trials (4,5) demonstrated that improved glycemic control reduces macrovascular and microvascular complications. A meta-analysis (6) that combined data from the Action to Control Cardiovascular Risk in Diabetes Study (ACCORD) (7), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) (8), UKPDS (5), and Veterans Affairs Diabetes Trial (VADT) (9) showed that more intensive glycemic control affords a modest, but significant, cardiovascular benefit in the short-to-medium term, although with no overall benefit for all-cause or cardiovascular mortality. Thus, the effect of intensive glucose control on macrovascular and microvascular diseases, all-cause mortality, and severe hypoglycemia across various HbA_{1c} categories among patients with type 2 diabetes (T2D) needs to be fully investigated in such clinical trials.

The atherosclerotic cardiovascular disease (ASCVD) risk score is a comprehensive index for evaluation of the risk of future cardiovascular disease (CVD) events (10–12). Compared with individual conventional risk factors, the ASCVD risk score affords better prediction of CVD and is more convenient (13,14). The ASCVD risk score has recently been strongly recommended in major guidelines for use in predicting risk of cardiovascular events in patients with hypertension (15,16) and in those with dyslipidemia (17). Moreover, aggressive management of traditional nonglycemic CVD risk factors, coupled with aggressive glycemic management, is indicated for individuals with type 1 diabetes (3). Cardiovascular risk assessment in patients with diabetes and prediabetes was suggested in the 2019 European Society of Cardiology guidelines on diabetes, prediabetes, and CVDs developed in collaboration with the European Association for the Study of Diabetes. However, so far, no study, to our knowledge, has investigated the role of ASCVD risk stratification for major vascular disease, all-cause mortality, or severe hypoglycemia in relation to glucose control in patients with T2D. Furthermore, because the ASCVD risk score excludes HbA_{1c}, it is of interest to compare the effects of intensive glucose control within strata defined by both markers of risk.

In the current study, we aimed to assess the value, in terms of major vascular outcomes, mortality, and hypoglycemia, of intensive glucose control across levels of the ASCVD risk score and HbA_{1c} at baseline for patients with T2D in the ADVANCE trial.

RESEARCH DESIGN AND METHODS

Study Design and Population

ADVANCE was a double-blind factorial, randomized, controlled, investigator-initiated trial that was designed, conducted, analyzed, and interpreted independently of both sponsors, the National Health and Medical Research Council of Australia and Servier International. A detailed description of the study design has been previously published (18,19). Briefly, the study had a two-by-two factorial design with eligible participants randomly assigned either to an intensive glucose control regimen based on treatment with gliclazide modified release (aiming for an HbA_{1c} level of $\leq$6.5% [48 mmol/mol]) or to a standard glucose control regimen based on the local guidelines of participating countries. Participants were also randomly allocated to either a fixed combination of perindopril and indapamide or matching placebo (20,21).

A total of 11,140 patients who were at least 55 years of age were recruited for the study from 215 centers in 20 countries between June 2001 and March 2003. Eligible patients had received a diagnosis of T2D after 30 years of age and had a history of major macrovascular or microvascular disease or at least one other cardiovascular risk factor. There were no HbA_{1c} or blood pressure criteria for inclusion. Weight, height, blood pressure, and levels of glycated hemoglobin and serum creatinine were measured at baseline, at 4 months, and every 6 months thereafter. Patients were followed up for a median of 5.0 years. Approval for the trial was obtained from each center's institutional review board, and all participants provided written informed consent.

Study Outcomes

The end points considered in the current study were major vascular events (the original primary outcome comprising major microvascular and macrovascular events), all-cause mortality, and severe hypoglycemia. Major macrovascular events included death from cardiovascular causes, myocardial infarction, or stroke, both fatal and nonfatal. Major microvascular events were new or worsening nephropathy (defined as macroalbuminuria, doubling of serum creatinine to $\geq$200 μmol/L, need for renal replacement therapy, or death because of renal disease) or retinopathy (defined as proliferative retinopathy, macular edema, diabetes-related blindness, or retinal photocoagulation therapy). Hypoglycemia was defined as a plasma glucose level of $<$2.8 mmol/L or the presence of typical symptoms and signs of hypoglycemia without another apparent cause, and patients who experienced transient dysfunction of the central nervous system and who required help from another person were considered to have severe hypoglycemia (22). These major vascular events and all-cause mortality outcomes were adjudicated by an independent End Point Adjudication Committee and coded using ICD-10 (23).

The main results from ADVANCE, published in 2008 (8), showed that intensive glucose control was beneficial for the composite end point of major macrovascular and microvascular events. Taking major marovascular disease alone, there was a nonsignificant 6% relative risk reduction; taking major microvascular events alone, there was a significant 14% relative risk reduction, with the major component of this benefit being a reduction in the development of macroalbuminuria.

Statistical Methods

The 10-year risk of ASCVD was estimated using the U.S. Pooled Cohort Risk Equations, as described in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (24,25). It was categorized into three groups: $\leq$20%, 20% to $\leq$40%, and $>$40%. About one-third of ADVANCE participants had a history of CVD at baseline; these were included in the $>$40% group. People for whom any variable that was required to calculate the ASCVD score was missing were excluded from all analyses. Baseline HbA_{1c} levels were categorized as $<$6.5% (42 mmol/mol), 6.5% to $\leq$7% (53 mmol/L), 7% to $\leq$8% (64 mmol/L), and $>$8%. In these definitions, 6 is to be read as 6.0, 7 as 7.0, and 8 as 8.0, as HbA_{1c} was recorded in percentages to one decimal place.

We modeled the association between randomized treatment (intensive control vs. standard control) and major vascular events and all-cause death, stratified by baseline ASCVD categories, HbA_{1c} categories, and combinations of ASCVD and HbA_{1c} categories using Cox proportional hazards models. We also analyzed the association between treatment and severe hypoglycemia stratified by baseline ASCVD categories and HbA_{1c} categories by Cox proportional model. Tests for interaction between the stratification variable and treatment were performed by adding interaction terms to the relevant model. Analyses were carried out using the SAS Enterprise Guide, version 7.11. We considered a two-sided $P < 0.05$ as statistically significant.

RESULTS

Comparisons Between ASCVD Risk and HbA_{1c} Categories at Baseline

After excluding 69 patients because of missing variables, 11,071 ADVANCE patients were included in analyses. Characteristics of participants according to ASCVD and HbA_{1c} categories at baseline are presented in Table 1. Participants in the ASCVD >40% risk group were more likely to be male, be older, and have higher systolic blood pressure and creatinine.

Major Vascular Events (Major Macrovascular or Microvascular Events) and All-Cause Death Across Baseline Categories of ASCVD Risk and HbA_{1c}

Over a mean 5 years' follow-up, there were 2,114 major vascular events (1,006 intensive control and 1,108 standard control) and 1,023 deaths (493 intensive control and 530 standard control). Intensive glycemic control reduced major vascular events (hazard ratio [HR] 0.90 [95% CI 0.83–0.98]), with a nonsignificant reduction in all-cause mortality (HR 0.93 [95% CI 0.82–1.05]) (Figs. 1 and 2).

Compared with the standard glucose control group, the risks of the primary outcome (major macrovascular or microvascular disease) and of all-cause mortality were lower in the intensive glucose control group in the 20% < ASCVD risk ≤ 40% subgroup, with HRs (95% CIs) of 0.80 (0.68–0.95) and 0.75 (0.58–0.98), respectively. However, the effects of intensive glycemic control were not significantly different across ASCVD risk subgroups for major vascular events (P for interaction = 0.29), major macrovascular events (P for interaction = 0.28), major microvascular events (P for interaction = 0.66), or all-cause mortality (P for interaction = 0.15) (Fig. 1).

As shown in Fig. 2, there was also no evidence of heterogeneity in the treatment effects across HbA_{1c} subgroups for major vascular events (major macrovascular or microvascular events) or all-cause mortality (P for interaction = 0.94 and 0.87, respectively) or when we considered combinations of categories of HbA_{1c} and ASCVD (Supplementary Fig. 4).

Severe Hypoglycemia Across Baseline ASCVD Risk and HbA_{1c} Categories

The risks of severe hypoglycemic events during follow-up (150 in the intensive control group and 81 in the standard control group) were higher in the intensive glycemic control group compared with those in the standard glycemic control group (HR 1.85 [95% CI 1.41–2.42]) (Fig. 3). There was no statistically significant heterogeneity in the effects across subgroups defined by HbA_{1c} ($P = 0.09$) or ASCVD ($P = 0.18$) (Fig. 3).

Sex Differences in Associations

Repeating the analyses of Figs. 1–3 for women and men separately showed no evidence of any sex differences (Supplementary Figs. 1–3).

CONCLUSIONS

We found there were no significant differences in the treatment effects of intensive glucose control on major vascular events (major macrovascular or microvascular events) and all-cause mortality across various ASCVD risk and/or

Table 1—Characteristics of participants according to the ASCVD and HbA_{1c} categories at baseline

	ASCVD risk ≤20%		20% < ASCVD risk ≤ 40%		ASCVD risk >40%	
Variable	HbA_{1c} ≤7%	HbA_{1c} >7%	HbA_{1c} ≤7%	HbA_{1c} >7%	HbA_{1c} ≤7%	HbA_{1c} >7%
N	1,008	1,308	1,425	1,757	2,574	2,999
Age (years)	61.3 ± 4.5	60.9 ± 4.4	66.0 ± 4.7	65.4 ± 4.9	68.2 ± 6.8	67.5 ± 6.8
Female	765 (75.9)	1,002 (76.6)	523 (36.7)	710 (40.4)	764 (29.7)	931 (31.0)
Glucose (mmol/L)	7.2 ± 1.7	9.9 ± 3.2	7.2 ± 1.7	9.7 ± 3.0	7.1 ± 1.7	9.4 ± 2.9
HbA_{1c} (%)	6.3 ± 0.6	8.7 ± 1.5	6.3 ± 0.5	8.5 ± 1.4	6.3 ± 0.5	8.4 ± 1.4
SBP (mmHg)	133 ± 17	134 ± 18	143 ± 18	146 ± 19	150 ± 22	150 ± 23
BMI (kg/m^2)	28.2 ± 5.5	27.9 ± 5.8	28.4 ± 5.3	28.6 ± 5.4	28.3 ± 4.8	28.4 ± 4.8
Waist (cm)	94.8 ± 13.2	94.4 ± 13.4	98.5 ± 13.1	99.6 ± 13.4	99.5 ± 12.3	100.1 ± 12.8
Waist-to-hip ratio	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
Total cholesterol (mmol/L)	5.3 ± 1.2	5.4 ± 1.2	5.2 ± 1.2	5.3 ± 1.1	5.0 ± 1.1	5.2 ± 1.2
Triglycerides (mmol/L)	1.5 (1.1–2.1)	1.7 (1.2–2.4)	1.5 (1.1–2.2)	1.7 (1.2–2.5)	1.5 (1.1–2.1)	1.8 (1.3–2.5)
HDL cholesterol (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3
LDL cholesterol (mmol/L)	3.2 ± 1.0	3.2 ± 1.0	3.1 ± 1.0	3.2 ± 1.0	3.0 ± 1.0	3.1 ± 1.1
Creatinine (μmol/L)	76.7 ± 18.8	75.5 ± 27.8	86.1 ± 21.8	86.1 ± 23.0	91.7 ± 27.2	90.9 ± 25.0
Current smoker	91 (9.0)	107 (8.2)	237 (16.6)	353 (20.1)	325 (12.6)	429 (14.3)
Current drinker	227 (22.5)	195 (14.9)	513 (36.0)	495 (28.2)	970 (37.7)	974 (32.5)

Data are means ± SD, *n* (%), or median (interquartile range) unless otherwise indicated. A 7% HbA_{1c} converts to 53 mmol/mol. SBP, systolic blood pressure.

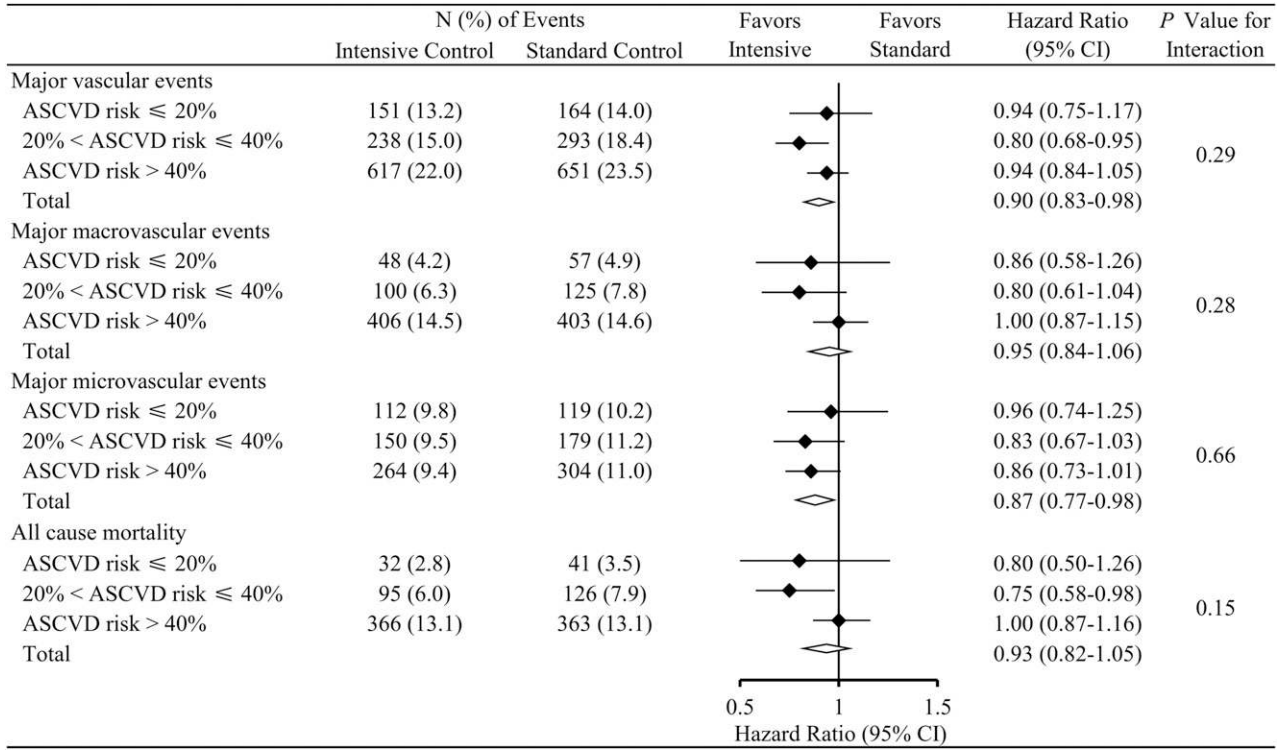

Figure 1—HRs for intensive vs. standard glycemic control for major vascular events (major macrovascular or microvascular events) and all-cause mortality at different ASCVD risk levels.

HbA_{1c} levels. However, the risks of severe hypoglycemic events were higher in the intensive glycemic control group compared with the standard glycemic control group, with no significant heterogeneity across subgroups defined by ASCVD risk or HbA_{1c} at baseline.

Cardiovascular risk stratification is widely used for evaluating the risk of hypertension-related CVD events, for guidance for the initiation of antihypertensive treatment, as well as for setting the blood pressure targets for treatment (15,16). The recent ACC/AHA guideline on hypertension (16) recommended ASCVD risk assessment for all adults with hypertension, including adults with diabetes. The American Association of Clinical Endocrinologists/American College of Endocrinology guidelines for management of dyslipidemia and prevention of CVD suggest that LDL cholesterol treatment goals should be determined by detailed ASCVD risk assessment using the Framingham risk assessment tool (17). However, neither previous observational studies nor the current interventional studies examined the role of baseline cardiovascular risk assessment in the management of patients with T2D. This is, to our knowledge, the first study to examine the effects of intensive glycemic control on major vascular outcomes and all-cause mortality and on severe hypoglycemia using baseline ASCVD risk in the context of a large clinical trial. We found that over a mean 5-year follow-up, the effects of intensive glycemic control were not significantly different across ASCVD risk subgroups for major vascular events (major macrovascular or microvascular events) or all-cause mortality.

Because the ASCVD score using the U.S. Pooled Cohort Risk Equations does not take account of blood glucose in determining risk, one of the purposes of our study was to compare these two methods of stratifying the risk of complications in patients with T2D: one using the traditional CVD risk method using blood pressure, lipids, smoking, and such parameters and the other using HbA_{1c}, a glucose-specific method. The current study is, as far as we are aware, the first to explore whether the effects of intensive glycemic control on major vascular outcomes, all-cause mortality, and severe hypoglycemia differ after comparing these two methods of stratifying risk of complications in diabetes using a traditional CVD risk assessment method or a glucose-specific method. We found that there was no evidence of significant heterogeneity in the treatment effects across HbA_{1c} subgroups for major vascular events (major macrovascular or microvascular events) or all-cause mortality. Furthermore, there was no evidence of heterogeneity in the treatment effects for major vascular events or all-cause mortality across subgroups expressing the full range of combinations of categories of HbA_{1c} and ASCVD.

The intensive glucose control regimen in ADVANCE had the most effect on macroalbuminuria (8). Hence, as a post hoc analysis, we investigated the effect of removing macroalbuminuria from our definition of vascular events. While this attentuated the overall estimate of effect, it left our conclusion of lack of evidence of heterogeneity intact (Supplementary Table 1).

Intensive glucose control is also associated with an increased risk of severe hypoglycemia, depending on the glucose-lowering treatment being received (22). In the ADVANCE trial, patients who were randomly assigned to undergo intensive glucose control were all initially given gliclazide modified release (30–120 mg daily) and required to discontinue

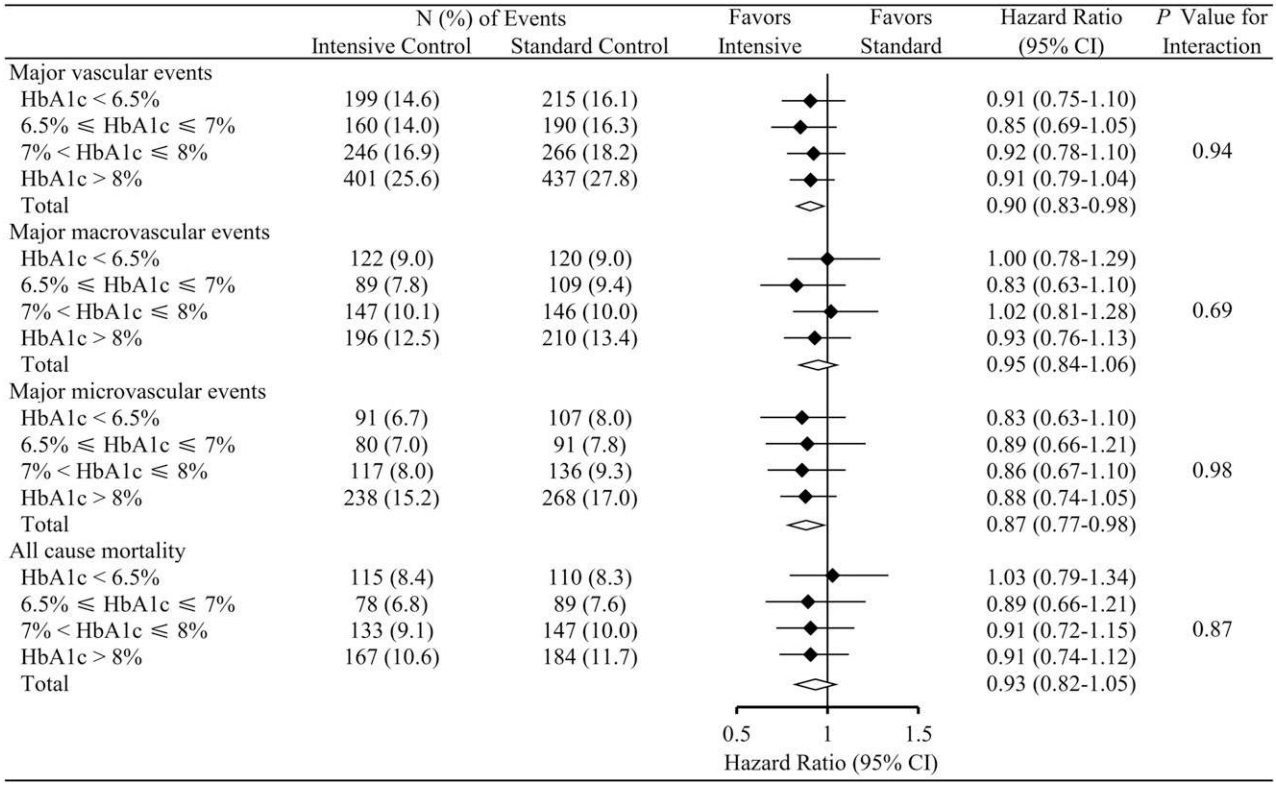

Figure 2—HRs for intensive vs. standard glycemic control for major vascular events (major macrovascular or microvascular events) and all-cause mortality at different HbA_{1c} levels.

any other sulfonylurea. If the glycated hemoglobin level remained above the target of 6.5% (48 mmol/mol) at the follow-up visits, the protocol advised increasing the dose of gliclazide modified release (to the maximum of 120 mg), with the sequential addition or increase in dose of other therapies, including metformin, thiazolidinediones, acarbose, or insulin. Supplementary Table 2 shows that patients in the intensive control group with HbA_{1c} >8% (64 mmol/L) generally took more drugs than those with HbA_{1c} <6.5% (48 mmol/mol). Patients in the standard control group were, by definition, not so differentially treated, and the corresponding contrast in drug use was considerably weaker. This issue may explain the nonsignificant higher relative risk of severe hypoglycemia in those with HbA_{1c} >8% (64 mmol/mol) (HR 2.97) than in those with HbA_{1c} <6.5% (48 mmol/mol) (HR 1.11).

Although severe hypoglycemia events were more frequently present in the intensive control group than in the standard control group, there was no statistically significant heterogeneity in the effects across subgroups defined by ASCVD risk or HbA_{1c} level in this study. To determine the optimal glycemic target, the importance of individualization according to patient characteristics is currently emphasized (26,27), in which less stringent control is recommended for patients with established vascular complications. However, taken together with the present findings on vascular outcomes as well as severe hypoglycemia,

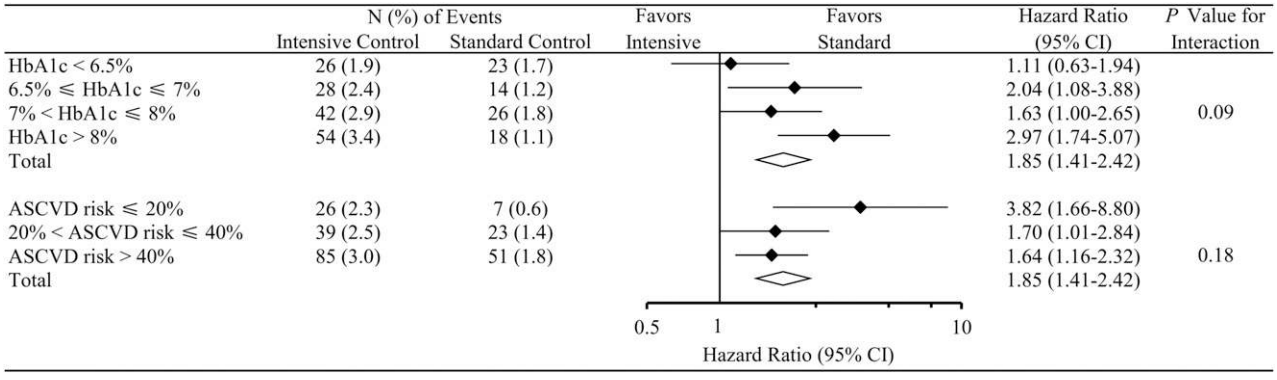

Figure 3—HRs for intensive vs. standard glycemic control for severe hypoglycemic events at different HbA_{1c} or ASCVD risk levels.

intensive glucose control may provide benefits in terms of prevention of vascular events as long as close attention is paid to hypoglycemia.

It is important to note that our results are relative risks, comparing intensive to standard glucose control, within subgroups. Absence of heterogeneity in relative risk within subgroups of expected risk does not suggest absence of heterogeneity in risk across the subgroups. Indeed, the risk of a major vascular event should increase as the level of expected CVD risk increases, whether or not relative risks of treatment effect differ. Also, lack of heterogeneity does not imply homogeneity, but may simply reflect lack of sufficient evidence.

Recent studies showed that sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide 1 agonists reduce CVD events in patients with diabetes and CVD or in those who are at very high/high CVD risk. However, the mechanisms through which some of these glucagon-like peptide receptor antagonists reduced CVD outcomes have not been established, and the cardiovascular benefits of sodium–glucose cotransporter 2 inhibitors are mostly unrelated to the extent of glucose lowering and occur too early to be the result of weight reduction.

Our findings should be interpreted in light of the strengths and limitations of the study. Strengths include use of data derived from a large cohort of ethnically diverse patients with T2D who took part in a randomized clinical trial, with high-quality data, including independent ratification of outcomes. Another strength is the novelty of comparing two methods for stratifying the risks of complications—one a glucose-specific method and the other a traditional risk factor method that takes no account of blood glucose. The analyses also have limitations. Because of the post hoc nature of the analysis and the selected study population of patients at high risk of CVD, the results will not necessarily be applicable to patients with T2D at lower ASCVD risk. However, we have previously reported that the ADVANCE population is not very different from community populations with diabetes (28). The most recent ACC/AHA guideline for hypertension recommends pharmacological therapy for a 10-year ASCVD risk of $\geq$10%, and the American Association of Clinical Endocrinologists/American College of Endocrinology guideline for LDL cholesterol treatment goals among individuals with T2D defined a 10-year ASCVD risk $<$10% as moderate risk. However, due to the small number of individuals with a 10-year ASCVD risk of $<$10% in our study, which would therefore result in inadequate power, we chose a lower cutoff of 20% (23). This preempts our ability to comment on whether there would be any different effect of intensive glucose therapy between individuals with $<$10% and $\geq$10% ASCVD risk.

In conclusion, the effects of intensive glycemic control on major vascular outcomes (with the major advantage expressed through a reduction in the development of macroalbuminuria) and all-cause mortality and on severe hypoglycemia were similar across various baseline ASCVD risk and HbA_{1c} levels. Patients with T2D in ADVANCE were able to benefit from intensive glucose control across different baseline ASCVD risk and HbA_{1c} levels.

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