ORIGINAL ARTICLE

Follow-up of Glycemic Control and Cardiovascular Outcomes in Type 2 Diabetes

Rodney A. Hayward, M.D., Peter D. Reaven, M.D., Wyndy L. Wiitala, Ph.D.,
Gideon D. Bahn, Ph.D., Domenic J. Reda, Ph.D., Ling Ge, M.S.,
Madeline McCarren, Ph.D., William C. Duckworth, M.D.,
and Nicholas V. Emanuele, M.D., for the VADT Investigators*

ABSTRACT

BACKGROUND

The Veterans Affairs Diabetes Trial previously showed that intensive glucose lowering, as compared with standard therapy, did not significantly reduce the rate of major cardiovascular events among 1791 military veterans (median follow-up, 5.6 years). We report the extended follow-up of the study participants.

METHODS

After the conclusion of the clinical trial, we followed participants, using central databases to identify procedures, hospitalizations, and deaths (complete cohort, with follow-up data for 92.4% of participants). Most participants agreed to additional data collection by means of annual surveys and periodic chart reviews (survey cohort, with 77.7% follow-up). The primary outcome was the time to the first major cardiovascular event (heart attack, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or cardiovascular-related death). Secondary outcomes were cardiovascular mortality and all-cause mortality.

RESULTS

The difference in glycated hemoglobin levels between the intensive-therapy group and the standard-therapy group averaged 1.5 percentage points during the trial (median level, 6.9% vs. 8.4%) and declined to 0.2 to 0.3 percentage points by 3 years after the trial ended. Over a median follow-up of 9.8 years, the intensive-therapy group had a significantly lower risk of the primary outcome than did the standard-therapy group (hazard ratio, 0.83; 95% confidence interval [CI], 0.70 to 0.99; P=0.04), with an absolute reduction in risk of 8.6 major cardiovascular events per 1000 person-years, but did not have reduced cardiovascular mortality (hazard ratio, 0.88; 95% CI, 0.64 to 1.20; P=0.42). No reduction in total mortality was evident (hazard ratio in the intensive-therapy group, 1.05; 95% CI, 0.89 to 1.25; P=0.54; median follow-up, 11.8 years).

CONCLUSIONS

After nearly 10 years of follow-up, patients with type 2 diabetes who had been randomly assigned to intensive glucose control for 5.6 years had 8.6 fewer major cardiovascular events per 1000 person-years than those assigned to standard therapy, but no improvement was seen in the rate of overall survival. (Funded by the VA Cooperative Studies Program and others; VADT ClinicalTrials.gov number, NCT00032487.)

PATIENTS WITH TYPE 2 DIABETES HAVE A greatly increased risk of cardiovascular events.[1] Although end-stage microvascular events (such as end-stage renal disease and blindness) represent important complications of diabetes, the morbidity and mortality related to cardiovascular events are an order of magnitude greater than that related to microvascular events.[2] Therefore, whether improved glucose control reduces the rate of cardiovascular events is an important clinical question.

Most observational studies have shown an association between glucose control and cardiovascular disease.[3-6] Among the four large, randomized, controlled trials of improved glucose control in patients with type 2 diabetes — the United Kingdom Prospective Diabetes Study (UKPDS), the Veteran Affairs Diabetes Trial (VADT), the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[7-12] — the most evidence for a reduction in the rate of cardiovascular events with intensive glucose control came from the UKPDS. The fact that the UKPDS had a more extended follow-up than the other trials could potentially explain its positive results. Alternatively, the more favorable outcomes in the UKPDS could be related to interventions in a younger, healthier group of patients with newly diagnosed type 2 diabetes or could be related to the fact that the UKPDS used a less intensive glucose treatment protocol than that used in the other trials.

The ACCORD trial also recently showed a significant reduction in the rate of nonfatal cardiovascular events in a follow-up of its study population,[13] but that benefit was offset by an increase in mortality in the original trial.[12] In contrast, no reduction in the rate of cardiovascular events or in mortality was found in a follow-up of the ADVANCE trial.[14] Consequently, one of the most important questions facing clinicians who care for patients with type 2 diabetes remains unanswered — what benefits and risks are conferred by tight glucose control in patients with diabetes who receive modern combination glycemic therapy?

We report cardiovascular outcomes after an extended follow-up period of the VADT,[10] a multisite, randomized, controlled trial of intensive versus standard glucose control in U.S. military veterans with type 2 diabetes, in which patients were followed for up to 7.5 years (median, 5.6 years). At the end of the VADT, the primary outcome of major cardiovascular events was nonsignificantly lower in the intensive-therapy group than in the standard-therapy group (hazard ratio, 0.88; 95% confidence interval [CI], 0.74 to 1.05; P=0.14). At the conclusion of the trial, all the participants were returned to usual care with no further clinical intervention by the research team. The current prespecified analysis includes approximately 5 additional years of observational follow-up of the study cohort.
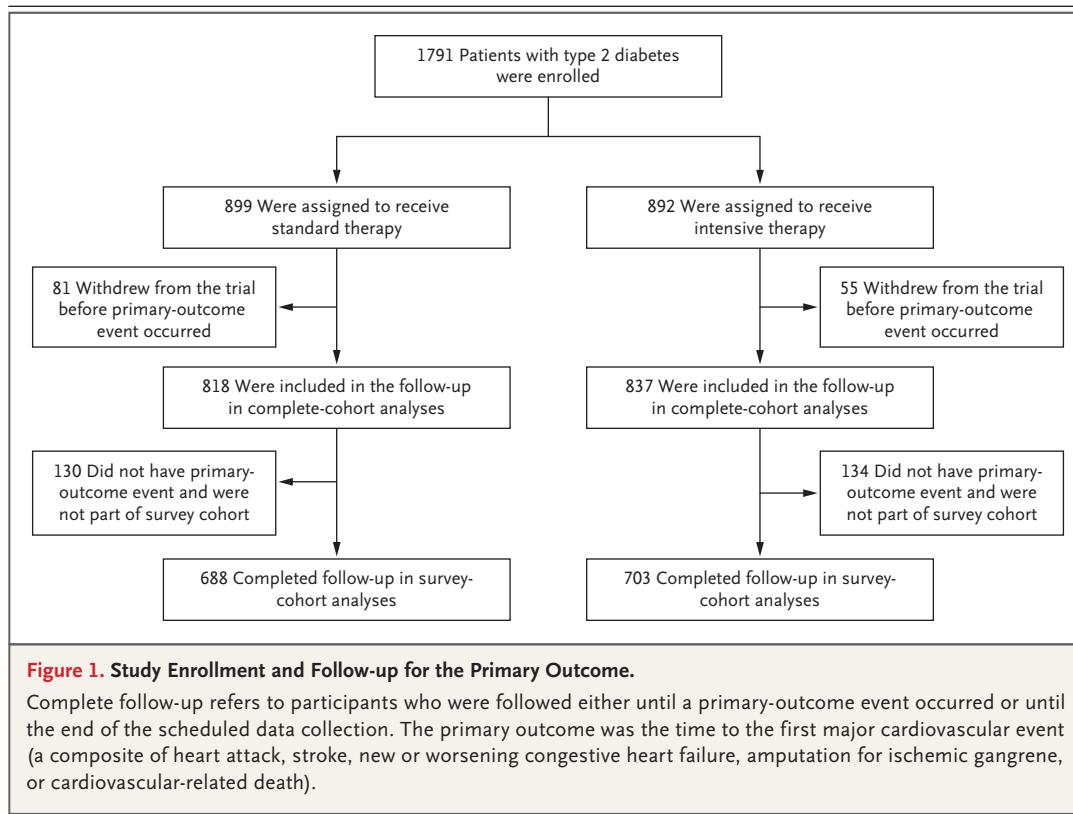
METHODS

STUDY DESIGN

The design of the active portion of our study and the main results were published previously.[10] Briefly, the original study included 1791 military veterans with type 2 diabetes who were randomly assigned to receive either intensive or standard glucose control. The interventional component of the study ended on May 29, 2008 (median follow-up, 5.6 years).

As approved by the institutional research board at the Central Database Collection Center (VA Ann Arbor), all the participants who were alive and enrolled at the conclusion of the study are being followed through a national data registry (a description of the complete cohort is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). Some patients (the survey cohort) provided written informed consent for additional data collection, including a yearly survey and chart reviews to detect outcomes that were not easily obtained from central data registries (Fig. 1). The coordinating sites in Hines, Illinois, and Ann Arbor, Michigan, collected all the data for this follow-up study.

The third and fourth authors vouch for the data and analyses. The manuscript was written by the first author, with all the coauthors approving the final version. The timing of this report and the statistical analysis plan were prespecified by the lead investigators of the study (the first, second, and last authors). At the time that the statistical analysis plan was finalized, the lead investigators were unaware of all the results and had no access to the data set. No agreements concerning the confidentiality of the

Figure 1. Study Enrollment and Follow-up for the Primary Outcome.

Complete follow-up refers to participants who were followed either until a primary-outcome event occurred or until the end of the scheduled data collection. The primary outcome was the time to the first major cardiovascular event (a composite of heart attack, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or cardiovascular-related death).

data were made between the sponsors and the authors or the institutions listed in the Supplementary Appendix, other than those required to protect the confidentiality of study participants. The protocol, available at NEJM.org, has ongoing approval and oversight by the institutional review boards at the Hines and Ann Arbor VA health systems. The study is reviewed annually by a data monitoring committee.

DATA SOURCES

Four national data registries are being used to collect follow-up data on patients — the central VA medical information files, the Centers for Medicare and Medicaid Services (CMS) Medicare claims files, the VA death files, and the National Death Index (NDI) (Tables S1 and S2 in the Supplementary Appendix). The survey cohort receives an annual self-administered survey that asks, among other questions, whether major events (e.g., heart attacks and strokes) occurred during the previous year. Patients who report having had a heart attack, stroke, or amputation in the past year are asked whether they received care for the event within the VA system or from an outside provider. For participants younger than 65 years of age (for whom CMS data are not available), those reporting an event outside the VA system are asked to provide written informed consent to allow review of their hospital records; medical records were successfully received and reviewed for 15 of 18 reports (83%). The adjudication process is described in the Supplementary Appendix.

The present interim report includes all the follow-up data that were available through December 2013. For most study outcomes, we obtained a median of 11.8 years of follow-up data. However, two of the central data registries — NDI (the source for data on deaths from cardiovascular causes) and CMS (used to detect events occurring outside the VA system in participants 65 years of age or older) — have a lag time in data availability of approximately 2 years. We decided a priori that our primary analysis of the time to the first major cardiovascular event would be limited to the period in which we have complete capture of data on primary-outcome events (median follow-up, 9.8 years), and we included a sensitivity analysis that used available outcome data for the full 11.8-year period.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was the time to the first major cardiovascular event (a composite of heart attack, stroke, new or worsening congestive heart failure, death from cardiovascular causes, or amputation for ischemic gangrene). This composite outcome was selected a priori and differs slightly from the outcome used in the original VADT, which also included selected cardiac procedures and the occurrence of new peripheral vascular disease. The former was excluded from the composite outcome because of a desire to focus on hard outcomes, and the latter was excluded because of the lack of reliable methods for identification of these events with the use of central data collection. Since these changes in the primary outcome make direct comparisons with the original VADT results difficult, we also separately show our results obtained during the original VADT and during observational follow-up in Table S6 in the Supplementary Appendix.

Events during the interventional part of the study were evaluated with the use of the original outcome-assessment method (adjudication by a committee whose members were unaware of the study-group assignments), although data regarding a few major cardiovascular events and deaths in patients who missed their final study visit during the last 6 months of the intervention were captured from central databases (see the Additional Details on End Points section in the Supplementary Appendix). During the observational follow-up period, heart attacks, strokes, and new or worsening congestive heart failure were identified by means of the primary discharge diagnosis in VA or CMS registry files (which have been shown previously to have excellent positive predictive value)[15,16] or by review of outside records in the case of participants younger than 65 years of age who reported an event on their survey, as described above. New or worsening congestive heart failure was identified by means of the primary discharge diagnosis in the CMS or VA data registry or by an ejection fraction of less than 40% as observed on echocardiography (see the Additional Details on End Points section in the Supplementary Appendix).

The two prespecified secondary outcomes were cardiovascular mortality and total mortality.[17] Both of these secondary outcomes were assessed in the complete cohort.

SENSITIVITY ANALYSIS

To assess for potential sample-selection bias (i.e., the possibility that the survey cohort was not representative of the original study population), we sought and were granted a Health Insurance Portability and Accountability Act waiver to examine our primary and secondary outcomes in the complete cohort (see the Supplementary Appendix). In the case of patients who were not in the survey cohort and who had not had an event during the interventional phase of the study, we estimate that only approximately 6% of cardiovascular outcomes were missing from registry data (specifically, amputations for ischemic gangrene [events that require adjudication] and strokes and heart attacks in participants younger than 65 years of age at non-VA facilities [since persons younger than 65 years of age are not included in CMS files]).

STATISTICAL ANALYSIS

The main analysis was performed according to the intention-to-treat principle, and Kaplan–Meier survival curves were generated by means of the product-limit method. Cox proportional-hazards modeling was used to estimate hazard ratios. Data were censored when the participants had a primary-outcome event, died, or withdrew from the study or at the end of the follow-up period for this report.

Differences in attributes between the two treatment groups were assessed with the use of the chi-square test for proportions and Student's t-test or analysis of variance for continuous variables. We prespecified three variables to examine heterogeneity of treatment effects, following the approach proposed by Kent and colleagues[18] — baseline cardiovascular risk (with the use of the baseline UKPDS score or the Framingham risk score),[18,19] history of cardiovascular disease, and the baseline glycated hemoglobin level.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Figure 1 shows the enrollment and follow-up of the patients in the VADT.[20] For the primary outcome (time to the first major cardiovascular event), complete follow-up data were available for 92.4% of the complete cohort and for 77.7% of the survey cohort. At baseline, study partici-

pants were on average older (60.5 years of age in the complete cohort) and had had diabetes for many years (mean, 11.5 years), and more than 40.0% had had a previous cardiovascular event or had a history of microvascular disease (Table 1). The characteristics at baseline were similar in the intensive-therapy group and the standard-therapy group in the two cohorts.

The difference in the glycated hemoglobin level between the intensive-therapy group and the standard-therapy group averaged 1.5 percentage points during the interventional component of the trial (median level, 6.9% vs. 8.4%), but for unclear reasons the difference declined to a level closer to 1.0 percentage point in the last 6 months of the intervention. The difference in the glycated hemoglobin level declined to 0.5 percentage points 1 year after the end of the trial (7.8% in the intensive-therapy group vs. 8.3% in the standard-therapy group) and remained at 0.2 to 0.3 percentage points from 3 years after the end of the trial until the end of follow-up for this interim analysis (Fig. 2). No significant differences were observed between the standard-therapy group and the intensive-therapy group in blood-pressure or lipid levels either during the interventional phase of the trial or after the conclusion of that phase (Figs. S1, S2, and S3 in the Supplementary Appendix).

PRIMARY OUTCOME AND SECONDARY OUTCOMES

Figure 3A shows the time to the first major cardiovascular event in the two treatment groups. At 9.8 years of follow-up, 288 major cardiovascular events had occurred in the standard-therapy group, as compared with 253 in the intensive-therapy group. These results indicate a significant increase in the time to a first major cardiovascular event in the intensive-therapy group (hazard ratio, 0.83; 95% CI, 0.70 to 0.99; P=0.04). This finding represents 8.6 major cardiovascular events prevented per 1000 person-years (or 1 event prevented per 116 person-years) (Fig. 3 and Table 2). Results for the individual components of the primary outcome are shown in Tables S4 and S5 in the Supplementary Appendix.

Results regarding mortality are shown in Figure 3 and Table 2. No significant between-group differences were observed in either cardiovascular mortality (hazard ratio in the inten-sive-therapy group, 0.88; 95% CI, 0.64 to 1.20; P=0.42) or all-cause mortality (hazard ratio, 1.05; 95% CI, 0.89 to 1.25; P=0.54).

HETEROGENEITY OF TREATMENT EFFECTS

The effect of intensive glucose control did not differ significantly between patients with lower overall cardiovascular risk and those with higher overall cardiovascular risk, as assessed by means of the UKPDS score or the Framingham risk score (P>0.20 for both comparisons) (Table S7 in the Supplementary Appendix). There was also no evidence of heterogeneity in treatment effect according to status with respect to a prior cardiovascular event or according to baseline glycated hemoglobin level.

SENSITIVITY ANALYSIS

We found no evidence of sample-selection bias. The results of the analyses that used available data regarding major cardiovascular events from the complete cohort were similar to those that used data from the survey cohort.

DISCUSSION

The leading cause of complications and death in patients with type 2 diabetes is cardiovascular disease.[1-3] This extended follow-up study of the VADT showed that a current multidrug glycemic treatment regimen can be associated with a significant reduction in major cardiovascular events among older patients who have had diabetes for many years. However, there was no evidence of an improved rate of overall survival after almost 12 years of follow-up.

When our results are combined with those of the three other major clinical trials of glycemic control in type 2 diabetes,[7-12] a clearer picture of the effect of improved glycemic control seems to be emerging. We found a 17% relative reduction in the rate of cardiovascular events with intensive therapy, as compared with standard therapy, which is similar to that observed in the follow-up studies of the ACCORD trial[13] and the UKPDS, after accounting for the greater reduction in glycated hemoglobin level observed in the VADT.[8,9] However, we found no evidence of a reduction in total mortality even after almost 12 years of follow-up, which was similar to the results of the ADVANCE study.[11,14] In contrast, the

Table 1. Baseline Characteristics of the Patients Included in the Study Follow-up.*

Characteristic	Complete Cohort (N=1655)			Survey Cohort (N=1391)		
	Standard Therapy (N=818)	Intensive Therapy (N=837)	P Value	Standard Therapy (N=688)	Intensive Therapy (N=703)	P Value
Age — yr	60.5±8.6	60.5±8.8	0.85	61.1±8.6	61.1±8.8	0.99
Sex — no. (%)			0.82			0.36
Male	794 (97.1)	814 (97.3)		672 (97.7)	681 (96.9)	
Female	24 (2.9)	23 (2.7)		16 (2.3)	22 (3.1)	
Time since diabetes diagnosis — yr	11.5±7.2	11.6±7.9	0.81	11.6±7.2	12.0±8.2	0.36
Previous cardiovascular event — no. (%)	338 (41.3)	335 (40.0)	0.59	297 (43.2)	298 (42.4)	0.77
Hypertension — no./total no. (%)†	593/816 (72.7)	604/836 (72.2)	0.85	510/687 (74.2)	504/702 (71.8)	0.31
Race or ethnic group — no. (%)‡			0.51			0.52
Non-Hispanic white	517 (63.2)	507 (60.6)		446 (64.8)	440 (62.6)	
Hispanic white	121 (14.8)	144 (17.2)		100 (14.5)	122 (17.4)	
Black	141 (17.2)	141 (16.8)		112 (16.3)	108 (15.4)	
Other	39 (4.8)	45 (5.4)		30 (4.4)	33 (4.7)	
Glycated hemoglobin level — %	9.5±1.6	9.4±1.5	0.45	9.4±1.6	9.4±1.4	0.44
Weight — kg	97.2±16.4	97.2±16.2	0.98	97.3±16.4	97.4±15.9	0.93
Body-mass index§	31.1±4.4	31.3±4.4	0.61	31.1±4.4	31.3±4.3	0.49
Blood pressure — mm Hg						
Systolic	132±17	132±17	0.72	132±17	132±16	0.59
Diastolic	76±10	76±10	0.75	76±10	76±10	0.57
Cholesterol — mg/dl						
Total	184±54	182±40	0.29	183±47	181±40	0.35
Low-density lipoprotein	108±34	107±31	0.72	107±33	106±30	0.56
High-density lipoprotein	36±11	36±10	0.69	35±10	36±10	0.20
Estimated GFR¶	82±21	82±23	0.98	81±21	81±23	0.62
Tobacco smoking status — no./total no. (%)			0.60			0.72
Current	126/816 (15.4)	144/837 (17.2)		100/686 (14.6)	110/703 (15.6)	
Past	465/816 (57.0)	468/837 (55.9)		394/686 (57.4)	397/703 (56.5)	
Never	225/816 (27.6)	225/837 (26.9)		192/686 (28.0)	196/703 (27.9)	
Estimated 10-yr cardiovascular risk‖	0.37±0.21	0.36±0.20	0.45	0.38±0.21	0.37±0.20	0.25

* Plus–minus values are means ±SD. Data are baseline values before randomization. The group numbers are participants who have complete follow-up data in the analyses (i.e., who were followed until the end of December 2013, had a primary-outcome event, or died during active follow-up). The complete cohort included follow-up data for 92.4% of participants in the original trial. The survey cohort included participants who agreed to additional data collection by means of annual surveys and periodic chart reviews, with follow-up data for 77.7% of trial participants. The P values are for the comparisons of the standard-therapy group with the intensive-therapy group. There were no significant differences between the complete cohort and survey cohort in any of the above characteristics. To convert the values for weight to pounds, multiply by 2.2. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
† Hypertension was defined as current treatment for hypertension or a blood pressure of 140/90 mm Hg or more.
‡ Race or ethnic group was self-reported.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ The estimated glomerular filtration rate (GFR) was calculated with the use of the Modification of Diet in Renal Disease equation.
‖ The estimated 10-year cardiovascular risk was calculated with the use of the United Kingdom Prospective Diabetes Study Risk Engine.[19]

follow-up study of the UKPDS showed a significant reduction in mortality,[21] whereas the AC-CORD trial showed a significant increase in mortality.[12]

The four major clinical trials of glycemic control to date have potentially important clinical heterogeneity. The VADT participants were more similar to the participants in the ACCORD trial (mean age, 62 years; mean duration of diabetes, 10 years) than to those in the UKPDS (mean age, 53 years; newly diagnosed diabetes), and the intensity of the intervention in the VADT was intermediate between these two studies. Unlike the UKPDS, in which most participants received monotherapy, the VADT added multiple glycemic medications to reduce the glycated hemoglobin level to less than 7.0%, but the intensive therapeutic algorithm in the VADT was less aggressive than that used in the ACCORD trial, in which investigators tried to normalize the glycated hemoglobin level. Unfortunately, it is not possible to know whether this clinical heterogeneity explains the increased mortality observed in the ACCORD trial, the lack of a treatment effect on mortality in our study, and the reduced mortality shown in the UKPDS.

In the observational follow-up of the UKPDS, the rates of microvascular and cardiovascular events remained lower in the intervention group than in the control group after the trial ended. Because glucose control had equalized in the intervention group and the control group, a legacy effect (sometimes referred to as metabolic memory) was postulated.[20] It would be incorrect, however, to suggest that our results support evidence of a legacy effect. First, a substantive difference in the glycated hemoglobin level persisted for 2 years after the trial ended and never completely reached zero, and second, the statistical power of the study at present is insufficient to fully assess this issue. Ongoing follow-up of this cohort may help address this question.

Our results should not be interpreted as supporting a performance measure for evaluating the quality of care provided by clinicians and health systems that uses the proportion of patients who reach a glycated hemoglobin level of less than 7.0%.[21-23] Even with the support of a dedicated research team, only approximately half the participants had a glycated hemoglobin level of less than 7.0%. In addition, in the ab-
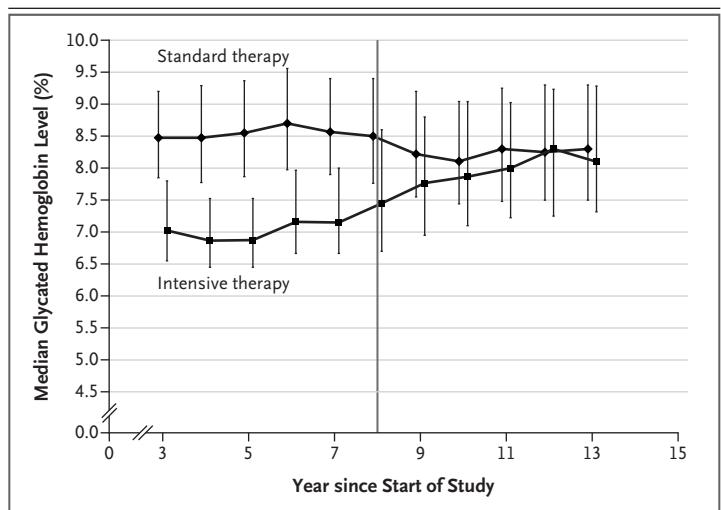

Figure 2. Changes in Median Glycated Hemoglobin Level, According to Year since the Start of the Study.

Data are shown starting at year 3 because that was the point at which all the participants had been enrolled and had been in the study for at least 3 months. The I bars (slightly offset for better visibility) represent interquartile ranges. The vertical line represents the end of the interventional component of the trial and the beginning of the follow-up study period. The reason for the slight decline in the difference in glycated hemoglobin levels between the two groups that was observed in the last 6 months of the trial is unclear.

sence of a reduction in total mortality, a small-to-moderate reduction in the rate of cardiovascular events needs to be weighed against potential harm due to overly aggressive care and the burden, long-term safety profile, and side effects of treatment, including weight gain and hypoglycemia.

For example, Vijan and colleagues examined the net benefit of glucose lowering, assuming a 15% reduction in the rate of nonfatal cardiovascular events for every reduction of 1 percentage point in the glycated hemoglobin level (a slightly greater reduction per 1-percentage-point reduction in the glycated hemoglobin level than that found in our study).[24] They found that once patients began taking metformin and their glycated hemoglobin level was less than 8.5%, the preferences of the patients were a critically important factor in determining whether further glycemic treatment resulted in net benefit or net harm, especially in patients older than 55 years of age. Their results suggested that the risk–benefit ratio of intensive glycemic control might be better in younger patients but that the attitudes of patients regarding the burden and adverse ef-
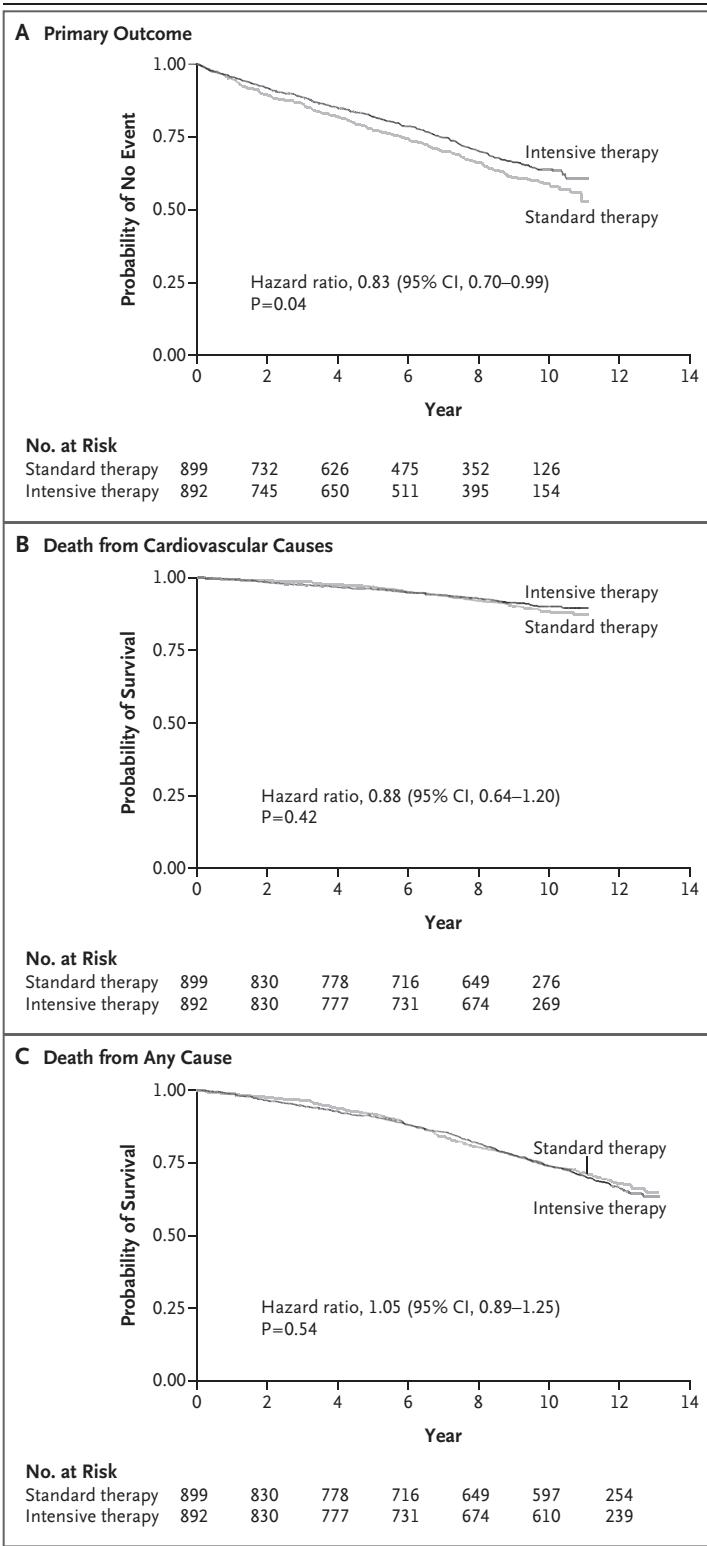
Figure 3. Probability Curves for Time to the First Major Cardiovascular Event and for Cardiovascular Mortality and Total Mortality.

The primary outcome was the time to the first major cardiovascular event (a composite of heart attack, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular causes).

fects of the treatment are very relevant in all age groups once the glycated hemoglobin is less than 9.0%.[24] Our results provide further evidence that improved glycemic control can reduce the rate of major cardiovascular events. This potential benefit may be considered in conversations with patients and balanced with the burdens and side-effect profile of the specific glucose-lowering treatment being considered.

Our study has several limitations. First, it is an observational follow-up of an unblinded, randomized, controlled trial. The possibility that there were differences between the two groups other than the difference in glycated hemoglobin levels, either during or after the trial, cannot be completely excluded. However, we found no evidence of a differential treatment effect in the follow-up period with respect to blood-pressure and lipid levels — two major modifiable cardiovascular risk factors. Second, the survey cohort is a subgroup of the full study population and the findings in that cohort may not fully represent findings for the whole cohort. However, we found no evidence of sample-selection bias. The intensive-therapy group and the standard-therapy group did not differ significantly with respect to any baseline characteristics, and a sensitivity analysis that used data from the complete cohort showed results very similar to the results of analyses that used data from the survey cohort. Finally, we had limited power to assess cardiovascular mortality, although our power to assess overall mortality was similar to that for the primary outcome.

In conclusion, we found that among patients who had been randomly assigned to intensive glucose control or standard therapy for a median of 5.6 years, the intensive-therapy group had a significant 17% relative reduction in major car-

Table 2. Effect of Intensive Glucose Control on the Rate of Major Cardiovascular Events and Mortality.*

Outcome	Standard Therapy		Intensive Therapy		Hazard Ratio (95% CI)	P Value
	Events	Rate	Events	Rate		
	no. of participants/ total no.	*per 1000 person-yr*	*no. of participants/ total no.*	*per 1000 person-yr*		
Primary outcome: major cardiovascular event	288/688	52.7	253/703	44.1	0.83 (0.70–0.99)	0.04
Secondary outcomes						
Death from cardiovascular causes	83/818	11.3	74/837	10.0	0.88 (0.64–1.20)	0.42
Death from any cause	258/818	30.3	275/837	32.0	1.05 (0.89–1.25)	0.54

* The primary outcome was the time to the first major cardiovascular event (a composite of heart attack, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular causes) and was analyzed in the survey cohort. Mortality outcomes were analyzed in the complete cohort.

diovascular events, as compared with the standard-therapy group, after almost 10 years of total follow-up; this relative reduction represented 8.6 major cardiovascular events prevented per 1000 person-years. As compared with standard therapy, intensive glucose control was not associated with a significant decrease in all-cause mortality after almost 12 years of follow-up.

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs (VA) or the U.S. government.

REFERENCES

1. Fox CS, Coady S, Sorlie PD, et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007;115:1544-50.
2. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34.
3. Duckworth WC, McCarren M, Abraira C. Glucose control and cardiovascular complications: the VA Diabetes Trial. Diabetes Care 2001;24:942-5.
4. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med 2004;141:413-20.
5. Kirkman MS, McCarren M, Shah J, Duckworth W, Abraira C. The association between metabolic control and prevalent macrovascular disease in type 2 diabetes:

the VA Cooperative Study in diabetes. J Diabetes Complications 2006;20:75-80.
6. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004; 141:421-31.
7. Control Group, Turnbull FM, Abraira C, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288-98.
8. UK Prospective Diabetes Study (UKPDS) Group. 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; 352:837-53.
9. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352: 854-65.

10. 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.
11. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.
12. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358: 2545-59.
13. Gerstein HC, Miller ME, Ismail-Beigi F, et al. Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. Lancet 2014;384:1936-41.
14. Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392-406.
15. Petersen LA, Wright S, Normand SL, Daley J. Positive predictive value of the diagnosis of acute myocardial infarction in

an administrative database. J Gen Intern Med1999;14:555-8.

16. Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. Am Heart J 2004;148:99-104.

17. Pocock SJ. Clinical trials with multiple outcomes: a statistical perspective on their design, analysis, and interpretation. Control Clin Trials 1997;18:530-45.

18. Kent DM, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials 2010;11:85.

19. University of Oxford Diabetes Trials Unit. UKPDS risk engine (https://www .dtu.ox.ac.uk/riskengine).

20. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.

21. Hayward RA, Hofer TP, Kerr EA, Krein SL. Quality improvement initiatives: issues in moving from diabetes guidelines to policy. Diabetes Care 2004; 27:Suppl 2:B54-B60.

22. Pogach LM, Rajan M, Aron DC. Comparison of weighted performance measurement and dichotomous thresholds for glycemic control in the Veterans Health Administration. Diabetes Care 2006;29:241-6.

23. Hayward RA. All-or-nothing treatment targets make bad performance measures. Am J Manag Care 2007;13:126-8.

24. Vijan S, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. JAMA Intern Med 2014;174:1227-34.

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