The Relation Between HbA_{1c} and Cardiovascular Events in Patients With Type 2 Diabetes With and Without Vascular Disease

Guido Kranenburg,[1] Yolanda van der Graaf,[2] Joep van der Leeuw,[1] Hendrik M.W. Nathoe,[3] Gert Jan de Borst,[4] L. Jaap Kappelle,[5] Frank L.J. Visseren,[1] and Jan Westerink,[1] on behalf of the SMART Study Group

Diabetes Care 2015;38:1930–1936 | DOI: 10.2337/dc15-0493

OBJECTIVE

Poor glycemic control is related to vascular events in patients with type 2 diabetes, but the presence of vascular disease might influence this relation. We evaluated the relation between glycemic control (HbA_{1c} level) and new cardiovascular events and mortality in patients with type 2 diabetes, with and without vascular disease.

RESEARCH DESIGN AND METHODS

In a cohort of 1,687 patients with type 2 diabetes enrolled in the Second Manifestations of Arterial Disease (SMART) study, the continuous relation between HbA_{1c} and cardiovascular events (composite of myocardial infarction, stroke, and vascular mortality) and all-cause mortality was evaluated with Cox proportional hazard analyses stratified for the presence of vascular disease.

RESULTS

During a median follow-up time of 6.1 years (interquartile range 3.1–9.5 years), a new cardiovascular event developed in 293 patients and 340 patients died. In all patients, the hazard ratio (HR) of the relation between HbA_{1c} level and cardiovascular events was 1.06 (95% CI 0.97–1.17). A 1 percentage point higher HbA_{1c} level was related to a 27% higher risk of a cardiovascular event in patients with type 2 diabetes without vascular disease (HR 1.27 [95% CI 1.06–1.51]), but not in patients with vascular disease (HR 1.03 [95% CI 0.93–1.15], *P* for interaction = 0.195). A 1 percentage point higher HbA_{1c} level was related to a 16% higher risk of death (HR 1.16 [95% CI 1.06–1.28]) in patients with vascular disease and a nonsignificant 13% higher risk of all-cause mortality (HR 1.13 [95% CI 0.97–1.31]) in patients without vascular disease.

CONCLUSIONS

In patients with type 2 diabetes, there is a modest, but not statistically significant, relation between HbA_{1c} level and cardiovascular events, and, as there was no statistically significant interaction, this relation was not different for patients with or without clinical manifestation of vascular disease.

Strict glycemic control has been proposed as an important means to lower the risk of both microvascular and macrovascular complications of type 2 diabetes. A strong relation between glycemic control and microvascular complications (nephropathy, retinopathy, and neuropathy) and macrovascular complications is observed in patients

[1]Department of Vascular Medicine, University Medical Centre Utrecht, Utrecht, the Netherlands
[2]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands
[3]Department of Cardiology, University Medical Centre Utrecht, Utrecht, the Netherlands
[4]Department of Vascular Surgery, University Medical Centre Utrecht, Utrecht, the Netherlands
[5]Department of Neurology, University Medical Centre Utrecht, Utrecht, the Netherlands

Corresponding author: Jan Westerink, j.westerink-3@umcutrecht.nl.

Received 8 March 2015 and accepted 4 July 2015.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-0493/-/DC1.

with type 2 diabetes (1–4). However, most of the cohort studies (3,5) conducted with patients having type 2 diabetes have investigated the relation between glycemic control and cardiovascular disease in patients without vascular disease at baseline.

As prolonged exposure to hyperglycemia results in vascular damage, it seems feasible that strict glycemic control will be associated with a decrease in cardiovascular risk (6). Although cohort studies (7–9) have indeed found a relation between glycemic control and the incidence of cardiovascular disease, the cardiovascular risk in patients with type 2 diabetes does not seem to further decrease with intensive glycemic control beyond an HbA_{1c} level of 7%. Identifying those patients with type 2 diabetes who would benefit from intensive glycemic control might be an opportunity for improving treatment. Existing guidelines on the treatment of diabetes are based on this principle and thus stress the importance of identifying the characteristics for determining the optimal HbA_{1c} target in individual patients. Guidelines do address which patient groups are more likely to profit or suffer from strict glycemic control. Unfortunately, as studies (10,11) in specific patient groups are lacking, setting practical treatment goals in different patient groups is still difficult.

Post hoc analyses from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) (9); the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) (8); the UK Prospective Diabetes Study (UKPDS) (12); and the Veterans Affairs Diabetes Trial (VADT) (7) suggested that the presence of vascular disease is an important patient characteristic to determine an individual glycemic goal, since a different effect of glycemic control was found in patients with and without vascular disease (13). The goal of the current study is to investigate the relation between HbA_{1c} level and cardiovascular events and all-cause mortality in patients with type 2 diabetes with and without clinical manifestations of vascular disease.

RESEARCH DESIGN AND METHODS

Study Population

For this study, data from 1,687 participants with type 2 diabetes who were enrolled in the Second Manifestations of Arterial Disease (SMART) study before 1 March 2013 were used. Diabetes was defined as a referral diagnosis of type 2 diabetes, self-reported type 2 diabetes, a fasting serum glucose concentration of $\geq$7.0 mmol/L at study inclusion with the initiation of glucose-lowering treatment within 1 year, or the use of oral antihyperglycemic agents or insulin at baseline. Participants with known type 1 diabetes were excluded for this analysis. The SMART study is an ongoing prospective, single-center, cohort study in patients with manifest vascular disease and/or cardiovascular risk factors. Starting from September 1996, consecutive patients, who were 18–80 years of age and had been referred to the University Medical Centre Utrecht (UMCU), the Netherlands, with manifest vascular disease or a cardiovascular risk factor underwent a vascular screening. Written informed consent was obtained from all participants. The study was approved by the Medical Ethics Committee of the UMCU.

Follow-up

Patients were biannually asked to fill out a questionnaire. Events of interest for the current study were the occurrence of vascular death, stroke, myocardial infarction, and the composite of these vascular events. In addition, we were interested in mortality and nonvascular death. Definitions have been described previously (14) and are included in Supplementary Table 1. When a possible event was recorded by the participant, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. With this information, all events were audited by three members of the SMART study End Point Committee, comprising physicians from different departments.

HbA_{1c} Measurement

HbA_{1c} level was measured at baseline in all patients who were enrolled in the SMART study after 2006. In patients who were enrolled in the SMART study before 2006, HbA_{1c} level was determined using available stored blood samples.

Data Analyses

Missing data for HbA_{1c} (n = 128; 7.6%) were singly imputed by weighted probability matching on the basis of multivariable regression using covariate and outcome data.

Baseline data are presented as the mean $\pm$ SD or median with interquartile range in the case of a skewed distribution.

Cox proportional hazards analyses were performed to estimate hazard ratios (HRs) and 95% CIs for the relation between HbA_{1c} and the occurrence of cardiovascular events, defined as a composite of nonfatal and fatal myocardial infarction, nonfatal and fatal stroke, or vascular mortality. If a patient had multiple events, the first event was used in the analyses. The proportional hazards assumption was satisfied based on a Schoenfeld residual plot.

To estimate the relation between HbA_{1c} level and cardiovascular events and mortality, we built three models. First, the unadjusted relation between HbA_{1c} level and cardiovascular events was estimated. In model II, age and sex were added. In model III, the model was additionally adjusted for current smoking status, systolic blood pressure, diabetes duration, non–HDL cholesterol level, and modification of diet in renal disease (MDRD). The variables mentioned in the models were a set of previously chosen confounders of the relation between HbA_{1c} level and cardiovascular events and mortality (age, sex, current smoking, and diabetes duration), and a set of previously chosen traditional cardiovascular risk factors (systolic blood pressure, non–HDL cholesterol, and MDRD).

To investigate the possible modifying effect of the presence of vascular disease at baseline, we stratified the population accordingly and performed separate analyses in the different strata. In addition, we performed standard multiplicative interaction analyses by adding the cross-product to the Cox proportional hazards models. Using a similar methodology, we investigated whether vascular disease duration was an effect modifier in the relation between plasma HbA_{1c} level and new cardiovascular events, since a differential effect with vascular disease of longer duration might be plausible from a pathophysiological perspective. Also, the relation between HbA_{1c} level and all-cause mortality, nonvascular mortality, and separate end points (vascular mortality, myocardial infarction, and stroke) was studied in the strata of patients with and without previous vascular disease. Finally, the relation between HbA_{1c} level and cardiovascular events and mortality was assessed in strata of HbA_{1c} tertiles, and in a continuous way using plots of restricted cubic splines. The P values of

the nonlinear effect of baseline HbA_{1c} level on cardiovascular events and mortality was based on the χ^2 statistic.

Sensitivity analyses were performed after excluding patients with the 1% highest and 1% lowest HbA_{1c} levels to eliminate the effect of outliers. As it is possible that the relation of interest differed in the number of years of follow-up, for instance because of better risk management over time, the year of study inclusion was added to the Cox models. As differences in the use of thrombocyte aggregation inhibitors and anticoagulants were expected between patients with and without vascular disease, it was investigated in the same manner whether addition of the use of these medications changed the direction or magnitude of the relation. Also, the use of glucose-lowering medication, blood pressure–lowering treatment, and statins was included in the models as a sensitivity analysis. Finally, sensitivity analyses were performed investigating whether the relation was similar when analyses were performed separately in patients with cerebrovascular, peripheral artery, coronary artery, or vascular disease on various locations at baseline. The level of significance was set at $P < 0.05$ for all analyses. As the analyses were prespecified, no correction for multiple comparisons was performed. All statistical analyses were performed using SPSS version 21 and R version 3.1.0.

RESULTS

Baseline characteristics are presented in Table 1. The mean age was 60.2 years (SD 10.2 years), and 30% of participants were female. During a median follow-up time of 6.1 years (range 3.1–9.5 years), 293 patients experienced a new cardiovascular event (event rate 17.3%). Of those 293 patients, 189 died of a vascular cause, while 340 patients died of all causes (event rate 20.1%). In total, 6.9% of the patients were lost to follow-up (8.5% in patients without vascular disease and 6.2% in patients with vascular disease).

Relation of HbA_{1c} With Cardiovascular Events and Mortality in Patients With and Without Vascular Disease

Cardiovascular Events

In all patients with type 2 diabetes, higher levels of HbA_{1c} were nonsignificantly related to cardiovascular events (HR 1.06 [95% CI 0.97–1.17]). In patients with type 2 diabetes and vascular disease at baseline, no relation between HbA_{1c} level and new cardiovascular events was found (HR 1.03 [95% CI 0.93–1.15]) (Table 2). Results were similar when performed separately in patients with cerebrovascular, peripheral artery, coronary artery, or vascular disease on various locations at baseline (Supplementary Table 2). On the other hand, in patients without vascular disease, a strong relation between HbA_{1c} level and cardiovascular events was observed (HR 1.27 [95% CI 1.06–1.51]). Additional sensitivity analyses (the exclusion of patients with the 1% highest and lowest levels of HbA_{1c}; and adjustment for the year of study inclusion or use of platelet inhibitors, anticoagulants, glucose-lowering medication, blood pressure–lowering treatment, and statins) did not change the direction and magnitude of the relation (data not shown). Analyses in tertiles of HbA_{1c} (data not shown) and cubic splines describing the relation of HbA_{1c} level with new cardiovascular events and mortality did not indicate the presence of nonlinearity in patients both with and without vascular disease (Supplementary Fig. 1). The *P* value for the cross-product of HbA_{1c} level and the presence of vascular disease was 0.195, indicating no significant interaction.

The relation between HbA_{1c} and separate events (vascular mortality and the occurrence of coronary ischemic disease or ischemic stroke) in patients with and without vascular disease is shown in Table 3. Though the numbers of events are small, HbA_{1c} level was significantly associated with the occurrence of ischemic stroke in patients without vascular disease (HR 1.40 [95% CI 1.01–1.94]), while no relation was found in patients with vascular disease (HR 1.03 [95% CI 0.81–1.31]).

The *P* value for the cross-product of vascular disease duration and new cardiovascular events was 0.490, indicating no statistical interaction by the duration of vascular disease. In all different groups of patients based on the duration of vascular disease, no significant relations were found between HbA_{1c} level and new cardiovascular events (Table 4).

Mortality

Patients with type 2 diabetes and manifest vascular disease had a 16% higher risk of all-cause mortality per 1 percentage point increase in HbA_{1c} (HR 1.16 [95% CI 1.06–1.28]), while a similar, albeit nonsignificant, relation was found in patients without vascular disease (HR 1.13 [95% CI: 0.97–1.31]). The *P* value for the cross-product of HbA_{1c} level and the presence of vascular disease in the relation with all-cause mortality was 0.749. The relation between HbA_{1c} level and all-cause mortality in patients with vascular disease was found specifically in patients with coronary disease or cerebrovascular disease at baseline (Supplementary Table 2).

When investigating the relation between HbA_{1c} and all-cause mortality in tertiles of vascular disease duration, differential relations were found between the groups (*P* value of cross-product = 0.044). Interestingly, a significant relation of HbA_{1c} level and all-cause mortality (HR 1.25 [95% CI 1.07–1.46]) was found in patients with the longest vascular disease duration (6–51 years). No significant relations were found between HbA_{1c} level and nonvascular mortality in all subgroups. The effect of baseline HbA_{1c} level on all-cause mortality was of similar magnitude in patients with and without vascular disease, although the relation was not statistically significant in patients without vascular disease.

CONCLUSIONS

The current study shows that in patients with type 2 diabetes there is a modest, but not statistically significant, relation between HbA_{1c} level and cardiovascular events, and as there was no statistically significant interaction, this relation was not different for patients with or without clinical manifestation of vascular disease. The effect of baseline HbA_{1c} level on all-cause mortality was of similar magnitude in patients with and without vascular disease, although the relation was not statistically significant in patients without vascular disease.

To the best of our knowledge, this is the first prospective cohort study to investigate the relation between HbA_{1c} level and new cardiovascular events in patients with and without vascular disease. Interestingly, a different relation between glycemic control and cardiovascular outcomes was suggested in a meta-analysis (13) of randomized controlled trials that investigated the effect of intensive versus standard glycemic control (interaction *P* = 0.04). Although

Table 1—Baseline characteristics of 1,687 patients with type 2 diabetes

	T2D and vascular disease present (*n* = 1,156)	T2D and no vascular disease present (*n* = 531)	*P* value
Age, years	62.7 ± 8.9	54.7 ± 11.0	<0.001
Female sex	25 (288)	41 (216)	<0.001
Time since diagnosis of diabetes, median (IQR), years	4 (1–10)	3 (0–7)	<0.001
Oral glucose-lowering treatment	67.9 (745)	77 (411)	0.335
Use of insulin	24 (273)	22 (119)	0.586
Both oral treatment and insulin	10 (116)	9 (50)	0.692
Only lifestyle/diet treatment for diabetes	22 (254)	20 (107)	0.397
HbA_{1c}			
%	7.5 ± 1.5	7.0 ± 1.2	<0.001
mmol/mol	58 ± 16	52 ± 13	<0.001
Fasting blood glucose, mmol/L	8.5 ± 2.7	9.3 ± 3.3	<0.001
Total cholesterol, mmol/L	4.6 ± 1.2	5.3 ± 1.7	<0.001
HDL cholesterol, mmol/L	1.1 ± 0.3	1.2 ± 0.4	0.003
LDL cholesterol, mmol/L	2.7 ± 1.0	3.1 ± 1.1	<0.001
Triglycerides, mmol/L	1.6 (1.2–2.4)	1.8 (1.2–2.7)	<0.001
Non–HDL cholesterol, mmol/L	4.1 ± 1.7	3.5 ± 1.2	<0.001
Creatinine, μmol/L	96 ± 43	84 ± 25	<0.001
eGFR (MDRD)	75 ± 20	84 ± 22	<0.001
Platelet inhibitor	77 (886)	14 (75)	<0.001
Oral anticoagulants	14 (160)	4 (23)	<0.001
Statins	60 (695)	32 (171)	<0.001
Blood pressure–lowering medication	83 (957)	63 (333)	<0.001
Systolic blood pressure, mmHg	145 ± 20	146 ± 21	0.298
Diastolic blood pressure, mmHg	81 ± 11	86 ± 12	<0.001
Weight, kg	86 ± 15	91 ± 20	<0.001
BMI, kg/m^2	30.1 ± 6.1	28.4 ± 4.3	<0.001
Waist circumference, cm	101 ± 12	101 ± 15	0.156
Current smoking	26.0 (300)	23.2 (123)	0.220
Vascular disease	100	0	
Coronary disease	66 (766)	0	
Cerebrovascular disease	29 (333)	0	
Peripheral arterial disease	22 (253)	0	
Abdominal aortic aneurysm	7 (82)	0	
Duration of vascular disease, median (IQR), years	1 (0–9)	NA	

Data are reported as the mean ± SD or % (*n*), unless otherwise indicated. *P* values for differences in baseline characteristics between patients with and without vascular disease are given. Differences were evaluated with the independent samples *t* test for continuous variables with a normal distribution and with the Mann-Whitney *U* test for continuous variables without a normal distribution. For categorical variables, the Pearson χ^2 test was used. eGFR, estimated glomerular filtration rate; IQR, interquartile range; NA, not applicable; T2D, type 2 diabetes.

the point estimates and CIs of the HRs are different in direction between the groups, no significant interaction *P* value (*P* = 0.195) for multiplicative interaction was found. Since we observed no statistical interaction, we cannot conclude that the relation between HbA_{1c} level and cardiovascular events is really different depending on the presence or absence of vascular disease. However, the results of this study are mainly important for hypothesis generation. Further research is warranted to specifically investigate this potential difference in effect.

Our findings in patients with type 2 diabetes (with and without vascular disease) are in line with those of other cohort studies (3,5) that studied the relation between HbA_{1c} level and macrovascular complications in patients with type 2 diabetes. Some cohort studies (15–17) have suggested the presence of a U-shaped relation between HbA_{1c} level and cardiovascular events. In this study, we did not find a U-shaped curve between HbA_{1c} level and macrovascular complications in patients with type 2 diabetes, and thus proceeded to analyze the data in a linear fashion. The explanation for the difference between our findings and those of earlier studies is probably to be found in the difference in study population, comprising younger patients and patients with diverse types of vascular disease in the current study versus only patients with coronary artery disease in most other studies.

The findings of cohort studies (18–22) investigating the relation between HbA_{1c} level and new cardiovascular events in patients with and without type 2 diabetes after cardiac interventions for coronary artery disease are in line with our findings. In these studies

Table 2—Relation between HbA_{1c} level and new cardiovascular events and all-cause mortality

		New cardiovascular events*		All-cause mortality‡	
	Model	HR (95% CI)†	*P* value for interaction	HR (95% CI)†	*P* value for interaction
T2D with vascular disease (*n* = 1,156)	I	1.03 (0.93–1.14)		1.12 (1.02–1.22)	
	II	1.07 (0.96–1.18)		1.19 (1.09–1.31)	
	III	1.03 (0.93–1.15)		1.16 (1.06–1.28)	
			0.195		0.749
T2D without vascular disease (*n* = 531)	I	1.16 (0.99–1.35)		1.11 (0.96–1.27)	
	II	1.24 (1.03–1.43)		1.15 (1.00–1.32)	
	III	1.27 (1.06–1.51)		1.13 (0.97–1.31)	

Model I, crude; Model II, sex and age; Model III, Model II plus current smoking, systolic blood pressure, diabetes duration, non–HDL cholesterol level, and MDRD; T2D, type 2 diabetes. *T2D patients with vascular disease and new cardiovascular events, *n* = 240; T2D patients without vascular disease and new cardiovascular events, *n* = 53. †HR per 1 percentage point increase in HbA_{1c} level. For example, in patients with T2D without vascular disease a 1% higher HbA_{1c} level is associated with a 1.27-fold higher risk of vascular events. *P* value for interaction between HbA_{1c} level and new cardiovascular events is 0.195, and for all-cause mortality 0.749. ‡T2D patients with vascular disease and all-cause mortality, *n* = 264; T2D patients without vascular disease and all-cause mortality, *n* = 73.

(19–21), no relation was found between HbA_{1c} level and cardiovascular events in patients with established type 2 diabetes after cardiac interventions. In patients without established type 2 diabetes, this relation did exist (18,21,22). In the current study, we expand on these findings by showing a consistent relation across different types of vascular disease.

Several explanations can be given for the different relation between HbA_{1c} level and new cardiovascular events in patients with type 2 diabetes with and without vascular disease. Although we could not support this hypothesis in this study, it is possible that the relation between HbA_{1c} level and cardiovascular events is more U shaped in patients with vascular disease compared with the relation in patients without vascular disease. Such a U-shaped relation between HbA_{1c} level and vascular events and mortality in the total diabetic population was indeed suggested in several cohort studies (15–17). As hypoglycemia is associated with severe cardiovascular events and arrhythmia (23), the left arm of this U shape might be caused by the occurrence of hypoglycemia. Analyses of the data from the ADVANCE trial (8) suggested that the increased all-cause mortality in the intensive treatment group could be associated with the occurrence of hypoglycemia, although the causality of this observation is uncertain. An explanation for the different relation in patients with and without vascular disease could thus be that patients with established vascular disease might be more susceptible to the detrimental effects of hypoglycemia. However, analyses in the current study did not indicate the presence of a U-shaped relation between HbA_{1c} level and new cardiovascular events. Our findings probably differ from earlier cohort studies because of the inclusion of patients without vascular disease and with different types of vascular disease besides coronary artery disease.

Another explanation for the different relation between HbA_{1c} level and new cardiovascular events in patients with type 2 diabetes with and without vascular disease could be that in patients with established vascular disease, hyperglycemia is not the key factor for progressive vascular damage. Factors such as hypertension (24,25) and dyslipidemia (26,27) have been shown to be strongly related to new cardiovascular events in patients with type 2 diabetes and in patients with already established vascular disease. Thus, if hypertension and dyslipidemia are important modifiable risk factors contributing to the pathogenesis of cardiovascular events in patients with type 2 diabetes in general, these risk factors may be even more important in patients with type 2 diabetes in whom a cardiovascular event developed before inclusion in our study. In patients with diabetes, the pathogenesis of vascular disease is at least in part intrinsically different from that of vascular disease in patients without diabetes, as medial vascular calcification or Mönckeberg medial sclerosis is often found in patients with diabetes (28). This difference in pathogenesis could therefore translate into a difference in the most important risk factors for new cardiovascular disease.

The interpretation of the strong relation between HbA_{1c} level and all-cause mortality in patients with type 2 diabetes with long-term vascular disease and the absence of this relation in patients with short-term vascular disease is not

Table 3—Relation of HbA_{1c} level with different events

	T2D and vascular disease (*n* = 1,156)		T2D without vascular disease (*n* = 531)	
	HR (95% CI)*	Events (*n*)	HR (95% CI)*	Events (*n*)
Vascular mortality	1.11 (0.97–1.26)	161	1.25 (0.99–1.60)	28
Nonvascular mortality	1.16 (0.98–1.38)	87	1.01 (0.81–1.25)	39
Myocardial infarction	0.90 (0.75–1.09)	77	1.32 (0.98–1.78)	46
Ischemic stroke†	1.03 (0.81–1.31)	49	1.40 (1.01–1.94)	13
Peripheral arterial disease	1.10 (0.95–1.28)	119	1.13 (0.80–1.61)	18

T2D, type 2 diabetes. *HR per 1 percentage point increase in HbA_{1c} level for vascular events adjusted for sex, age, current smoking, systolic blood pressure, diabetes duration, non–HDL cholesterol level, and MDRD. For example, in patients without vascular disease a 1% higher HbA_{1c} level is related to a 1.40-fold increased risk of ischemic stroke. †Ischemic stroke does not include hemorrhagic stroke.

Table 4—Relation of HbA_{1c} level with vascular events and all-cause mortality in different groups of vascular disease duration

Vascular disease duration (n = 1,151)	Model*	New cardiovascular events		All-cause mortality	
		HR (95% CI)†	P value	HR (95% CI)†	P value
0 years (n = 545, 93 events, 100 died)	I	0.98 (0.83–1.16)	0.800	1.04 (0.89–1.21)	0.634
	II	1.01 (0.85–1.21)	0.873	1.10 (0.94–1.29)	0.243
	III	0.97 (0.81–1.16)	0.723	1.02 (0.86–1.21)	0.787
0–6 years (n = 220, 44 events, 57 died)	I	0.85 (0.65–1.12)	0.249	1.07 (0.88–1.30)	0.492
	II	0.88 (0.67–1.16)	0.351	1.13 (0.92–1.39)	0.257
	III	0.84 (0.62–1.13)	0.247	1.11 (0.88–1.41)	0.356
6–51 years (n = 386, 99 events, 107 died)	I	1.11 (0.94–1.31)	0.207	1.18 (1.02–1.37)	0.029
	II	1.14 (0.97–1.34)	0.103	1.26 (1.08–1.46)	0.003
	III	1.12 (0.95–1.33)	0.179	1.25 (1.07–1.46)	0.006

*Model I, crude model; Model II, model I with sex and age; Model III, Model II with current smoking, systolic blood pressure, diabetes duration, non–HDL cholesterol level, and MDRD. †HR per 1 percentage point increase in HbA_{1c} level.

obvious. An explanation might be that HbA_{1c}, as a marker of glycemic regulation, is a proxy of overall condition or frailty and therefore singles out the patients with the poorest health status, especially in those patients with a longer duration of vascular disease.

The chief strengths of this study include the prospective design and large number of participants, both with and without cardiovascular disease. Because of the substantial follow-up period and large cohort size, there was a relatively high number of events. Furthermore, the risk of bias in this study was reduced because of the completeness of the data.

Several limitations of this study need to be addressed. As the SMART study is a single-center cohort study in an academic hospital, it may be questioned whether this cohort is a representation of the total population of patients with type 2 diabetes. It should be noted that the current cohort contains a broad scope of patients with type 2 diabetes with and without vascular disease representing clinical practice. Despite the relatively large number of participants in this cohort, a small number of end points in some groups could have resulted in insufficient power. This is most likely the case in the patients with type 2 diabetes without vascular disease at baseline because of the small number (n = 531) in this group. Furthermore, only baseline HbA_{1c} level was used for the analyses in the current study, while the median duration of follow-up in this study was 6 years. While a possible variation in HbA_{1c} level during follow-up could theoretically change the relations, this is not taken into account in the current study. The lack of statistically significant interaction of the presence of vascular disease at baseline needs to be taken into account when interpreting these results. Although the point estimates are clearly different between the two groups, no significant interaction was observed. The difference in point estimates may, of course, be due to chance, but we think that, in light of the relatively wide CIs, the absence of statistically significant interaction could very well be due to insufficient power in this study. Further studies are needed to support our hypothesis of a differential effect of HbA_{1c} level on cardiovascular events between patients with and without vascular disease.

As we only studied patients with type 2 diabetes, our findings cannot be extrapolated to patients with type 1 diabetes, a population in which strict control has been shown to be associated with fewer cardiovascular events (2,29). Last, our study only takes into account macrovascular complications of type 2 diabetes. As HbA_{1c} level has been shown to be strongly related to microvascular complications (2,12,29,30), the importance of strict glycemic control should not be devaluated completely in patients with type 2 diabetes and vascular disease. Microvascular complications should be taken into account when setting individualized therapeutic targets in patients with type 2 diabetes, including those with vascular disease. Nevertheless, our findings are important for generating hypotheses that may eventually lead to more tailored treatment in this very high-risk population. Further studies are therefore needed to establish whether the presence of vascular disease influences the relation between HbA_{1c} level and cardiovascular events.

HbA_{1c} level is related to cardiovascular events, and no interaction of the presence or absence of vascular disease on this relation was observed. The effect of baseline HbA_{1c} level on all-cause mortality was of similar magnitude in patients with and without vascular disease, although the relation was not statistically significant in patients without vascular disease.

Acknowledgments. For their contribution, the authors thank the SMART research nurses; R. van Petersen (data manager); H. Pijl (vascular manager); and the following members of the SMART Study Group: P.A. Doevendans, Department of Cardiology; A. Algra, Y. van der Graaf, D.E. Grobbee, and G.E.H.M. Rutten, Julius Center for Health Sciences and Primary Care; L.J. Kappelle, Department of Neurology; T. Leiner, Department of Radiology; F.L. Moll, Department of Vascular Surgery; and F.L.J. Visseren, Department of Vascular Medicine.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. G.K. researched the data and wrote the manuscript. Y.v.d.G., J.v.d. L., and F.L.J.V. contributed to the methodology and reviewed and edited the manuscript. H.M.W.N., G.J.d.B., and L.J.K. reviewed and edited the manuscript. J.W. wrote, reviewed, and edited the manuscript. J.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Hemmingsen B, Lund SS, Gluud C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database Syst Rev 2013;11:CD008143

2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment

of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
3. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:421–431
4. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
5. Zhang Y, Hu G, Yuan Z, Chen L. Glycosylated hemoglobin in relationship to cardiovascular outcomes and death in patients with type 2 diabetes: a systematic review and meta-analysis. PLoS One 2012;7:e42551
6. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Eur Heart J 2013;34:2436–2443
7. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
8. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
9. Gerstein HC, Miller ME, Genuth S, et al.; ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011;364:818–828
10. Rydén L, Grant PJ, Anker SD, et al.; Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); Document Reviewers. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013;34:3035–3087
11. American Diabetes Association. Standards of medical care in diabetes-2015 abridged for primary care providers. Clin Diabetes 2015;33:97–111
12. 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;352:837–853
13. Turnbull FM, Abraira C, Anderson RJ, et al.; Control Group. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288–2298
14. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol 1999;15:773–781
15. Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481–489
16. Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. Diabetes Care 2011;34:1329–1336
17. Nichols GA, Joshua-Gotlib S, Parasuraman S. Glycemic control and risk of cardiovascular disease hospitalization and all-cause mortality. J Am Coll Cardiol 2013;62:121–127
18. Liu Y, Yang YM, Zhu J, Tan HQ, Liang Y, Li JD. Prognostic significance of hemoglobin A1c level in patients hospitalized with coronary artery disease. A systematic review and meta-analysis. Cardiovasc Diabetol 2011;10:98
19. Kassaian SE, Goodarzynejad H, Boroumand MA, et alet al. Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting. Cardiovasc Diabetol 2012;11:82
20. Singla A, Orshaw P, Boura J, Harjai KJ. Glycosylated hemoglobin and outcomes in diabetic patients with acute myocardial infarction after successful revascularization with stent placement: findings from the guthrie health off-label stent (GHOST) investigators. J Interv Cardiol 2012;25:262–269
21. Lemesle G, Bonello L, de Labriolle A, et al. Prognostic value of hemoglobin A1C levels in patients with diabetes mellitus undergoing percutaneous coronary intervention with stent implantation. Am J Cardiol 2009;104:41–45
22. Halkos ME, Lattouf OM, Puskas JD, et al. Elevated preoperative hemoglobin A1c level is associated with reduced long-term survival after coronary artery bypass surgery. Ann Thorac Surg 2008;86:1431–1437
23. Chow E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 2014;63:1738–1747
24. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–713
25. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585
26. Scott R, O'Brien R, Fulcher G, et al.; Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study Investigators. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetes Care 2009;32:493–498
27. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–1574
28. Lanzer P, Boehm M, Sorribas V, et al. Medial vascular calcification revisited: review and perspectives. Eur Heart J 2014;35:1515–1525
29. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381–389
30. 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;359:1577–1589