Effect of Type 2 Diabetes on Recurrent Major Cardiovascular Events for Patients With Symptomatic Vascular Disease at Different Locations

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OBJECTIVE

Our aim is to compare the effect of type 2 diabetes on recurrent major cardiovascular events (MCVE) for patients with symptomatic vascular disease at different locations.

RESEARCH DESIGN AND METHODS

A total of 6,841 patients from the single-center, prospective Second Manifestations of ARTerial disease (SMART) cohort study from Utrecht, the Netherlands, with clinically manifest vascular disease with (*n* = 1,155) and without (*n* = 5,686) type 2 diabetes were monitored between 1996 and 2013. The effect of type 2 diabetes on recurrent MCVE was analyzed with Cox proportional hazards models, stratified for disease location (cerebrovascular disease, peripheral artery disease, abdominal aortic aneurysm, coronary artery disease, or polyvascular disease, defined as ≥2 vascular locations).

RESULTS

Five-year risks for recurrent MCVE were 9% in cerebrovascular disease, 9% in peripheral artery disease, 20% in those with an abdominal aortic aneurysm, 7% in coronary artery disease, and 21% in polyvascular disease. Type 2 diabetes increased the risk of recurrent MCVE in coronary artery disease (hazard ratio [HR] 1.67; 95% CI 1.25–2.21) and seemed to increase the risk in cerebrovascular disease (HR 1.36; 95% CI 0.90–2.07), while being no risk factor in polyvascular disease (HR 1.12; 95% CI 0.83–1.50). Results for patients with peripheral artery disease (HR 1.42; 95% CI 0.79–2.56) or an abdominal aortic aneurysm (HR 0.93; 95% CI 0.23–3.68) were inconclusive.

CONCLUSIONS

Type 2 diabetes increased the risk of recurrent MCVE in patients with coronary artery disease, but there is no convincing evidence that it is a major risk factor for subsequent MCVE in all patients with symptomatic vascular disease.

Type 2 diabetes has a significant effect on a patient's life expectancy, with a recently estimated loss of 6 life-years (1). Reduced life expectancy in these patients is mainly attributable to a higher incidence of vascular disease and heart failure (2–4). Type 2 diabetes increases the risk of cerebrovascular disease (CeVD) by 35% and peripheral

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artery disease (PAD) by 70% (5,6). The risk of coronary artery disease (CAD) is two to three times higher in patients with type 2 diabetes compared with patients without type 2 diabetes, particularly in women (7–9).

Type 2 diabetes is assumed to be a major risk factor for the occurrence of vascular events in patients with established vascular disease as well. Although the incidence of major cardiovascular events (MCVE) among patients without diabetes with vascular disease is ~5% in 3 years (10), the incidence in patients with diabetes with vascular disease is approximately three times higher (11). However, it is unknown and questionable whether the risk increase caused by type 2 diabetes is equal for various locations of vascular disease. Subsequent vascular events occur far more often in patients with PAD and CeVD than in patients with CAD, and the risk profiles of these patients differ (12,13). Therefore, the risk increase for MCVE caused by type 2 diabetes may depend on the site of the vascular disease.

Furthermore, because atherosclerosis is a systemic disease, many patients have symptomatic vascular disease at multiple locations. It is interesting to evaluate whether type 2 diabetes still has an influence on the processes leading to new vascular events in those with advanced, widespread vascular disease. If we were able to identify patients in whom diabetes induces a relevant increase in MCVE risk, we could be more cautious for signs of recurrent vascular disease in these patients and offer them strict vascular preventive strategies.

We therefore primarily aimed to quantify and compare the effect of type 2 diabetes on recurrent MCVE for patients with symptomatic vascular disease at different locations. Furthermore, we evaluated the effect of type 2 diabetes on subsequent MCVE risk in patients with symptomatic vascular disease at multiple sites versus a single site.

RESEARCH DESIGN AND METHODS

Study Population

Patients originated from the ongoing, single-center prospective SMART (Second Manifestations of ARTerial disease) cohort study conducted at the University Medical Center (UMC) Utrecht in the Netherlands. Patients with clinically manifest vascular disease or risk factors for vascular disease from various areas of the Netherlands are referred to this tertiary care hospital (14). The quality and complexity of care given at the UMC Utrecht is to a great extent comparable to a secondary care hospital. Patients with rare and complex disorders are also treated in this hospital. Patients were asked to participate after referral to the UMC Utrecht because of a (recent) clinical manifestation of vascular disease or a major risk factor for vascular disease such as hyperlipidemia, hypertension, or type 2 diabetes. Nine-year follow-up data were used from patients with clinically manifest vascular disease enrolled and monitored between 1996 and 2013. Clinically evident vascular disease included a history or recent diagnosis of symptomatic CeVD, PAD, abdominal aortic aneurysm (AAA), or CAD.

CAD was defined as a prior myocardial infarction, symptoms of myocardial ischemia with >50% stenosis in at least one of three major coronary arteries on coronary angiography, or symptoms of myocardial ischemia for which a percutaneous coronary intervention or coronary artery bypass graft was performed. Patients were classified as having CeVD when they had experienced a transient ischemic attack or cerebral infarction as diagnosed by a neurologist. Patients had an AAA if they were known to have an aortic diameter ≥3.0 cm or a distal-to-proximal diameter ratio ≥1.5 as diagnosed by a vascular surgeon before inclusion or had a history of surgical or endovascular aneurysm repair. PAD was defined as a diagnosis made by the vascular surgeon because a patient had intermittent claudication or rest pain with an ankle-brachial pressure index (ABPI) ≤0.90 at rest, a postexercise deterioration in ABPI of 20% or more in at least one leg, a documented obstruction in one or more arteries, or because a patient had gangrene or ulcers (15). The UMC Utrecht Medical Ethics Committee approved the study, and all participants gave their written informed consent.

Data Collection and Follow-up

A thorough medical assessment was performed at baseline to acquire information on the vascular health of these patients. Study participants received a standardized questionnaire on medical history, medication use, and patient characteristics associated with vascular disease. Furthermore, information was gained by a physical examination and a wide spectrum of laboratory measurements, including specific measures of glucose regulation such as fasting plasma glucose, glycated hemoglobin (HbA_{1c}) and insulin levels. HbA_{1c} levels had only been assessed since 2006 and were therefore not available for all study participants.

During the follow-up period, patients completed a standardized questionnaire on hospital admission and outpatient clinic visits for new vascular events twice a year. If an event was reported, discharge letters and laboratory and radiology examinations were collected and evaluated. Death and cause of death were reported by the study participant's family members, the general practitioner, or the medical specialist.

The end point committee consisted of three physicians from different medical fields who independently judged reported events. The primary outcome was a composite of myocardial infarction, hemorrhagic, and nonhemorrhagic stroke and vascular mortality (detailed outcome definitions are presented in Supplementary Data). Secondary outcomes were vascular mortality and all-cause mortality.

Study Definitions

The diagnostic criteria for type 2 diabetes were a patient-reported history of type 2 diabetes, use of oral glucose-lowering therapy or insulin, or a fasting plasma glucose ≥7.0 mmol/L with the start of diabetes treatment (dietary advice, weight reduction, or medication) within 1 year from inclusion. Patients with vascular disease at a single site were classified according to their location of disease (e.g., CeVD, PAD, AAA, or CAD). Patients with symptomatic vascular disease at more than one of four major locations were categorized as having polyvascular disease (PVD). Smoking was defined as current or past nicotine addiction. Current use of insulin and glucose-lowering, blood pressure-lowering, antiplatelet, anticoagulant, or lipid-lowering agents was self-reported by the study participant at baseline. Blood pressure was measured twice, manually at the left and right upper

arm using the correct cuff size. The mean of the two measurements was taken as the blood pressure. Waist circumference was measured halfway between the lowest rib and the iliac crest with the patient standing. BMI was defined as weight (kg) divided by squared height (m^2). Fasting plasma glucose, triglycerides, and total cholesterol were measured using commercial enzymatic dry chemistry kits (Johnson & Johnson), and HDL-cholesterol was measured using a commercial enzymatic kit (Boehringer Mannheim). LDL-cholesterol was estimated with the Friedewald formula up to a plasma triglyceride level of 9 mmol/L (16). HOMA, a method for assessing β-cell function and insulin resistance, was calculated as fasting plasma insulin (mU/L) * fasting plasma glucose (mmol/L)/22.5 (17). The glomerular filtration rate was assessed using the Modification of Diet in Renal Disease formula (18). Albuminuria was defined as a urinary albumin-to-creatinine ratio (mg/mmol) of >2.5 in men and >3.5 in women (2).

Data Analysis

Cox regression models for 9-year follow-up were fitted to estimate hazard ratios (HR) for type 2 diabetes as a risk factor for vascular disease and mortality. For the combined end point, the date at which the first event occurred was set as the primary outcome date. Analyses were stratified for location of symptomatic vascular disease and for number of locations of vascular disease. Prespecified confounders in the association between type 2 diabetes and recurrent MCVE were sex, age, smoking, systolic blood pressure, BMI, LDL-cholesterol, and duration of clinically manifest vascular disease.

Results are displayed as HR and 95% CI. We checked the Cox proportional hazards assumption with plots of the Schoenfeld residuals and tested nonproportionality. If nonproportionality was observed for a particular covariate, the model was extended with a time-dependent covariate (19). Missing values were single imputed by weighted probability matching using multivariate regression because complete case analysis results in loss of power and possibly in bias. Risk factors for vascular disease, other patient characteristics, and outcomes were included in the imputation model. Missing values were imputed for the variables smoking (n = 42 [0.61%]), BMI (n = 14 [0.20%]), systolic blood pressure (n = 47 [0.69%]), LDL-cholesterol (n = 302 [4.4%]), and duration of clinically manifest vascular disease (n = 24 [0.35%]). Imputed values were only used for multivariable analysis.

We tested effect modification on a multiplicative scale by adding a "type 2 diabetes * location of vascular disease" term to the nonstratified model. We compared models with and without the interaction term with the likelihood ratio test, and a P value < 0.05 indicated a significant interaction. The same was done for the interaction between type 2 diabetes and mono- versus polyvascular disease.

Analyses were performed with R 3.0.3 statistical software and the add-on packages foreign, survival, Hmisc, rms, and xlsx.

RESULTS

Baseline Characteristics

The study population consisted of 6,841 patients with clinically manifest vascular disease, of whom 1,115 (16.9%) had type 2 diabetes. Baseline patient characteristics are reported in Table 1. Patients with type 2 diabetes were slightly older and more intensively treated with antihypertensive, lipid-lowering, and antiplatelet agents than control subjects without diabetes. Patients with diabetes had higher systolic blood pressure, BMI, and waist circumference. Furthermore, triglyceride levels were higher, whereas HDL- and LDL-cholesterol were both lower. Albuminuria was much more frequent in patients with diabetes than in those without.

The prevalence of type 2 diabetes was 13% in patients with CeVD, 15% in those with PAD, 11% in those with AAA, 18% in those with CAD, and 22% in patients with PVD. Mean duration of diabetes was 5.9 (SD 6.9) years for patients with CeVD, 7.3 (SD 8.7) years for patients with PAD, 8.6 (SD 8.6) years for patients with AAA, 7.8 (SD 7.3) years for patients with CAD, and 8.8 (SD 8.3) years for those with PVD. Patients with type 2 diabetes and PAD had the poorest glycemic control, with the highest fasting plasma glucose (9.5 [SD 3.3] mmol/L) and HbA_{1c} levels (7.3 [SD 1.4] %; 56 [SD 16] mmol/mol).

Type 2 Diabetes as a Risk Factor for Recurrence of Vascular Events According to Vascular Disease Location

Five-year risks for recurrent vascular events were 9% in CeVD, 9% in PAD, 20% in AAA, 7% in CAD, and 21% in PVD. The adjusted Cox 9-year MCVE incidence curves for patients in different strata of location of vascular disease are shown in Fig. 1. These Cox survival curves are derived from the fully adjusted model. The same differences in incidence of recurrent MCVE between locations of vascular disease were observed for vascular mortality and for all-cause mortality.

Because the Schoenfeld residuals and test showed nonproportionality for age, a time-dependent age-covariate (age*log[follow-up time]) was added to all Cox models. Patients with CAD and type 2 diabetes had a 67% higher risk for the combined vascular end point compared with patients with CAD without diabetes (HR 1.67; 95% CI 1.25–2.21; Table 2). Type 2 diabetes seemed to confer a higher risk in patients with cerebrovascular artery disease (HR 1.36; 95% CI 0.90–2.07), whereas there was no increased risk for patients with PAD (HR 1.42; 95% CI 0.79–2.56) or PVD (HR 1.12; 95% CI 0.83–1.50) (P = 0.28 for interaction type 2 diabetes and location of vascular disease).

Type 2 diabetes increased risk of vascular mortality in patients with CAD (HR 1.55; 95% CI 1.00–2.41) and seemed to increase risk of vascular mortality in patients with CeVD (HR 1.57; 95% CI 0.91–2.70) (P = 0.057 for interaction type 2 diabetes and location of vascular disease). Type 2 diabetes increased risk of all-cause mortality in patients with PAD (HR 1.64; 95% CI 1.01–2.68) and seemed to increase the risk of all-cause mortality in CeVD (HR 1.34; 95% CI 0.90–1.98) and CAD (HR 1.29; 95% CI 0.95–1.75) (P = 0.057 for interaction of type 2 diabetes and location of vascular disease).

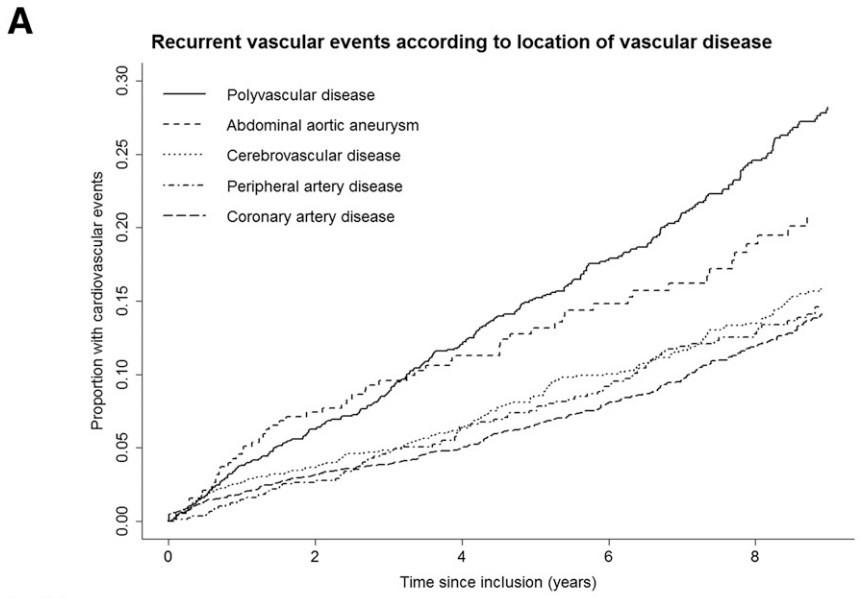
Type 2 Diabetes as a Risk Factor for Recurrence of Vascular Events According to the Number of Locations of Vascular Disease

Of 935 patients with PVD at two locations, 306 (33%) had CAD and CeVD, 267 (28%) had CAD and PAD, 171 (18%) had CAD with an AAA, 101 (11%)

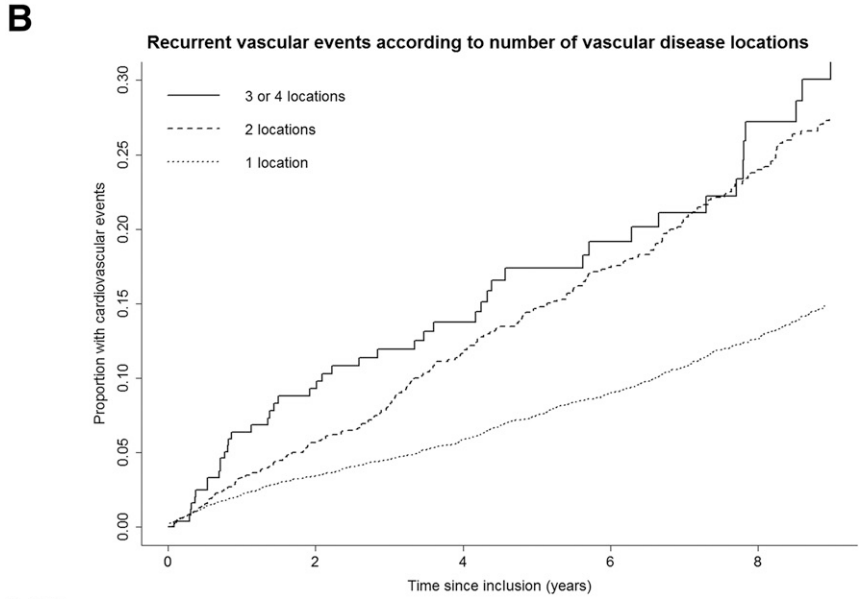
Table 1—Baseline characteristics of patients with symptomatic vascular disease with and without diabetes

	Diabetes					No diabetes				
	CeVD *n* = 188	PAD *n* = 121	AAA *n* = 28	CAD *n* = 577	PVD* *n* = 241	CeVD *n* = 1,286	PAD *n* = 666	AAA *n* = 219	CAD *n* = 2,681	PVD* *n* = 834
Patient characteristics										
Male sex, *n* (%)	123 (65)	83 (69)	22 (79)	447 (77)	192 (80)	736 (57)	404 (61)	191 (87)	2,193 (82)	657 (79)
Age (years)	62 (10)	61 (9)	63 (10)	62 (8)	65 (8)	58 (12)	57 (11)	66 (9)	59 (10)	63 (10)
Age at first clinical manifestation of vascular disease (years)	60 (11)	60 (10)	58 (12)	57 (11)	54 (11)	57 (12)	56 (11)	64 (11)	57 (10)	53 (12)
Smoking current/past, *n* (%)	142 (76)	100 (85)	23 (82)	431 (75)	213 (88)	956 (75)	603 (92)	192 (88)	2,015 (76)	738 (89)
Diabetes duration (years)	5.9 (6.9)	7.3 (8.7)	8.6 (8.6)	7.8 (7.3)	8.8 (8.3)					
Oral glucose-lowering agents, *n* (%)	125 (66)	70 (58)	18 (64)	388 (67)	143 (59)					
Insulin use, *n* (%)	26 (14)	24 (20)	4 (14)	146 (25)	73 (30)					
Blood pressure-lowering agents, *n* (%)	129 (69)	69 (57)	17 (61)	543 (94)	198 (82)	636 (49)	233 (35)	108 (49)	2,427 (91)	661 (79)
Antiplatelet/oral anticoagulant agents, *n* (%)	153 (81)	66 (55)	8 (29)	539 (93)	226 (94)	1,005 (78)	345 (52)	88 (40)	2,473 (92)	739 (89)
Lipid-lowering agents, *n* (%)	103 (55)	46 (38)	12 (43)	488 (85)	185 (77)	669 (52)	235 (35)	66 (30)	2,151 (80)	554 (66)
Medical history, *n* (%)										
CeVD	188 (100)	0 (0)	0 (0)	0 (0)	145 (60)	1,286 (100)	0 (0)	0 (0)	0 (0)	397 (48)
PAD	0 (0)	121 (100)	0 (0)	0 (0)	131 (54)	0 (0)	666 (100)	0 (0)	0 (0)	402 (48)
AAA	0 (0)	0 (0)	28 (100)	0 (0)	54 (22)	0 (0)	0 (0)	219 (100)	0 (0)	293 (35)
CAD	0 (0)	0 (0)	0 (0)	577 (100)	189 (78)	0 (0)	0 (0)	0 (0)	2,681 (100)	667 (80)
Physical examination										
Blood pressure (mmHg)										
Systolic	150 (23)	150 (23)	146 (17)	142 (19)	148 (21)	141 (21)	145 (21)	144 (20)	136 (20)	144 (22)
Diastolic	84 (12)	82 (11)	86 (15)	81 (11)	79 (11)	83 (12)	82 (11)	85 (11)	80 (11)	81 (12)
BMI (kg/m^2)	27.9 (4.7)	27.9 (5.1)	29.5 (3.7)	28.8 (4.1)	28.0 (3.8)	26.2 (4.0)	25.7 (4.2)	25.6 (3.4)	27.1 (3.6)	26.4 (3.8)
Waist circumference (cm)	99 (13)	100 (13)	105 (10)	101 (12)	102 (11)	91 (12)	92 (12)	96 (11)	96 (11)	96 (12)
Laboratory measurements										
Triglycerides (mmol/L)†	1.5 (1.0–2.2)	2.0 (1.3–2.6)	1.7 (1.4–2.6)	1.6 (1.1–2.3)	1.7 (1.3–2.6)	1.2 (0.9–1.8)	1.5 (1.1–2.1)	1.3 (1.1–2.0)	1.3 (1.0–1.9)	1.5 (1.1–2.1)
HDL-cholesterol (mmol/L)†	1.2 (0.4)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.4 (0.4)	1.3 (0.4)	1.2 (0.4)	1.2 (0.3)	1.2 (0.4)
LDL-cholesterol (mmol/L)†	2.8 (1.2)	3.2 (1.0)	2.9 (1.1)	2.5 (0.9)	2.7 (1.0)	3.0 (1.1)	3.6 (1.1)	3.5 (1.1)	2.7 (0.9)	3.0 (1.0)
Plasma glucose (mmol/L)†	8.4 (2.7)	9.5 (3.3)	8.8 (2.7)	8.4 (2.6)	8.4 (2.7)	5.6 (0.6)	5.8 (0.9)	5.8 (0.8)	5.8 (0.7)	5.8 (0.8)
HbA_{1c} (%)	6.9 (1.1)	7.3 (1.4)	7.0 (1.6)	6.9 (1.1)	7.0 (1.2)	5.6 (0.3)	5.7 (0.4)	5.7 (0.4)	5.6 (0.4)	5.7 (0.4)
HbA_{1c} (mmol/mol)	52 (12)	56 (16)	53 (17)	52 (12)	53 (13)	38 (3)	39 (4)	39 (4)	38 (3)	39 (4)
HOMA-IR	3.7 (2.0–5.6)	3.6 (1.6–5.7)	4.0 (1.8–6.6)	3.8 (2.0–7.1)	4.3 (2.5–7.7)	1.8 (1.0–2.8)	2.0 (1.1–3.2)	1.7 (1.2–2.7)	2.1 (1.2–3.4)	2.3 (1.2–3.4)
Creatinine (μmol/L)	93 (31)	94 (61)	95 (33)	94 (32)	102 (30)	87 (22)	87 (23)	102 (46)	92 (23)	102 (46)
MDRD GFR (mL/min/1.73 m^2)	75 (20)	80 (23)	77 (24)	76 (20)	70 (20)	78 (17)	79 (18)	73 (20)	77 (16)	71 (19)
High urinary albumin-to-creatinine ratio, *n* (%)	44 (56)	37 (64)	10 (56)	114 (47)	74 (60)	137 (34)	90 (41)	43 (51)	211 (30)	167 (51)
CRP (mg/L)	4.9 (7.0)	8.0 (13.5)	6.9 (9.5)	4.3 (9.2)	5.8 (8.9)	3.8 (7.6)	5.7 (10.1)	6.5 (8.5)	3.5 (7.9)	6.3 (14.3)

Nonimputed data are displayed as mean (SD), median (interquartile range), or *n* (%). GFR, glomerular filtration rate; IR, insulin resistance; MDRD, Modification of Diet in Renal Disease. *Indicates vascular disease at more than one of the four sites (CeVD, PAD, AAA, CAD). †Fasting laboratory measurements.



N at risk					
PVD	1075	862	657	480	331
AAA	247	197	161	123	91
CeVD	1474	1214	949	749	504
PAD	787	696	582	469	362
CAD	3258	2780	2238	1643	1059



N at risk					
1 location	5766	4887	3930	2984	2016
2 locations	935	758	580	428	298
3 or 4 locations	140	104	77	52	33

Figure 1—*A*: Incidence of recurrent vascular events according to location of symptomatic vascular disease. *B*: Incidence of recurrent vascular events according to number of vascular disease locations. Cox survival graphs are adjusted for type 2 diabetes, sex, age, smoking, systolic blood pressure, BMI, LDL-cholesterol, and duration of clinically manifest vascular disease. *N* at risk, number of patients at risk for the outcome at a certain time point.

had CeVD and PAD, 38 (4%) had CeVD with an AAA, and 52 (6%) had PAD with an AAA.

Type 2 diabetes was a risk factor for recurrence of vascular events in patients with symptomatic vascular disease at one location (HR 1.51; 95% CI 1.23–1.86) (Table 3) but not at two locations (HR 1.16; 95% CI 0.84–1.61) or three locations (HR 1.30; 95% 0.58–2.91) (P = 0.11 for interaction of type 2 diabetes and mono- vs. polyvascular disease). Results for vascular and all-cause mortality were comparable with those for the combined vascular end point (P = 0.053 and P = 0.022 for interaction of type 2 diabetes and mono- vs. polyvascular disease, respectively).

CONCLUSIONS

In the present cohort study in patients with clinically manifest vascular disease, type 2 diabetes was related to a 67% increased risk of recurrent MCVE in patients with CAD and a 36% increased risk of recurrent MCVE in patients with CeVD. Type 2 diabetes was not a risk factor for recurrent MCVE in patients with vascular disease at multiple locations.

The association between type 2 diabetes and vascular disease in general is quite well understood. Insulin resistance is likely to be the main pathophysiological mechanism underlying the increased vascular risk in patients with type 2 diabetes. Insulin resistance leads to formation of advance glycation end products, oxidative stress, and endothelial dysfunction, resulting in accelerated atherogenesis with intimal and medial calcifications (20–22). Other processes induced by insulin resistance that increase vascular risk are vascular inflammation due to proinflammatory cytokines secreted by adipose tissue, elevated blood pressure, and dyslipidemia with high triglyceride and concordant low HDL-cholesterol plasma levels (23,24). We found that the strength of the association between type 2 diabetes and vascular disease with these underlying pathophysiologic mechanisms depends on the location of vascular disease.

Results of the current study indicate that in patients with CAD, those with type 2 diabetes have higher risk of recurrent vascular events than those without diabetes. An explanation may be that patients with type 2 diabetes have higher risk of late complications after coronary interventions than patients without diabetes, including more recurrent myocardial infarctions and target lesion revascularizations (25,26). Half of the recurrent events in patients with CAD in the current study were myocardial infarctions, compared with 10–25% in patients with vascular

Table 2—Type 2 diabetes as a risk factor for recurrent cardiovascular events stratified for location of vessel disease

	N patients	*N* events	5-year event risk (%)	Model 1: HR (95% CI)	Model 2: HR (95% CI)
Combined end point					
Total cohort	6,841	901	10.2	1.37 (1.17–1.61)	1.41 (1.20–1.67)
CeVD	1,474	161	8.8	1.53 (1.02–2.29)	1.36 (0.90–2.07)
PAD	787	97	8.5	1.13 (0.64–1.99)	1.42 (0.79–2.56)
AAA	247	59	19.8	0.50 (0.15–1.68)	0.93 (0.23–3.68)
CAD	3,258	301	6.9	1.70 (1.29–2.22)	1.67 (1.25–2.21)
PVD	1,075	283	21.3	1.08 (0.81–1.43)	1.12 (0.83–1.50)
Vascular mortality					
Total cohort	6,841	502	5.3		
CeVD	1,474	80	4.1	1.96 (1.19–3.24)	1.57 (0.91–2.70)
PAD	787	58	4.7	1.37 (0.69–2.72)	1.87 (0.90–3.90)
AAA	247	46	13.9	0.53 (0.14–1.99)	1.23 (0.26–5.79)
CAD	3,258	112	2.3	1.72 (1.13–2.62)	1.55 (1.00–2.41)
PVD	1,075	206	14.2	1.02 (0.73–1.43)	1.08 (0.76–1.54)
All-cause mortality					
Total cohort	6,841	919	9.1		
CeVD	1,474	166	7.4	1.51 (1.05–2.19)	1.34 (0.90–1.98)
PAD	787	126	9.1	1.22 (0.76–1.96)	1.64 (1.01–2.68)
AAA	247	76	19.7	0.75 (0.30–1.91)	1.16 (0.40–3.39)
CAD	3,258	242	5.2	1.37 (1.03–2.14)	1.29 (0.95–1.75)
PVD	1,075	309	20.6	0.90 (0.68–1.19)	0.96 (0.72–1.29)

Model 1: HRs adjusted for sex, age, and age*log(follow-up time). Model 2: HRs adjusted for sex, age, smoking, systolic blood pressure, BMI, LDL-cholesterol, duration of clinically manifest vascular disease, and age*log(follow-up time).

disease at another location. The reason for rethrombosis could be an increased proinflammatory state in patients with diabetes, possibly combined with impaired re-endothelialization (27). Moreover, platelets are in an activated state, and platelet adhesiveness and aggregation is enhanced in patients with diabetes (28). A second explanation might be that patients with diabetes have a higher prevalence of heart failure and left ventricular dysfunction (29). This could result in death caused by heart failure or sudden death because of an arrhythmia in patients with established CAD (30). Prior studies found that in patients with a myocardial infarction or a percutaneous coronary intervention, diabetes increases the risk of recurrent MCVE 1.5 to 2.0 times (31–33). These studies assessed the recurrence of myocardial infarction or death but not a composite of vascular events as in the current study. Also, a substantial number of patients in these studies had concomitant symptomatic vascular disease at other locations, whereas we assessed the risk increase by type 2 diabetes for patients with vascular disease restricted to a single location, such as the coronary arteries.

A large worldwide cohort from the REduction of Atherothrombosis for Continued Health (REACH) investigators found type 2 diabetes was related to an increased risk of recurrent MCVE in patients with CeVD (HR 1.32; 95% CI

Table 3—Type 2 diabetes as a risk factor for recurrent events stratified for the number of locations of vessel disease

	N patients	*N* events	5-year event risk (%)	Model 1: HR (95% CI)	Model 2: HR (95% CI)
Combined end point					
Total cohort	6,841	901	10.2	1.37 (1.17–1.61)	1.41 (1.20–1.67)
1 location	5,766	618	8.2	1.44 (1.19–1.76)	1.51 (1.23–1.86)
2 locations	935	237	20.3	1.12 (0.82–1.54)	1.16 (0.84–1.61)
≥3 locations	140	46	27.9	1.36 (0.63–2.94)	1.30 (0.58–2.91)
Vascular mortality					
Total cohort	6,841	502	5.3		
1 location	5,766	296	3.6	1.48 (1.13–1.94)	1.47 (1.11–1.95)
2 locations	935	169	13.1	1.10 (0.76–1.61)	1.14 (0.78–1.68)
≥3 locations	140	37	22.1	1.06 (0.42–2.65)	0.89 (0.33–2.44)
All-cause mortality					
Total cohort	6,841	919	9.1		
1 location	5,766	610	6.9	1.29 (1.06–1.56)	1.35 (1.11–1.66)
2 locations	935	255	18.9	0.94 (0.69–1.30)	0.99 (0.71–1.37)
≥3 locations	140	54	32.4	1.05 (0.49–2.23)	1.04 (0.47–2.34)

Model 1: HRs adjusted for sex, age, and age*log(follow-up time). Model 2: HRs adjusted for sex, age, smoking, systolic blood pressure, BMI, LDL-cholesterol, duration of clinically manifest vascular disease, and age*log(follow-up time).

1.20–1.45) (34). Median follow-up in the REACH study was only 2 years, and patients originated from a primary care setting in contrast to the tertiary care setting in the current study. Yet, findings in patients with CeVD from the SMART population are comparable with those from the REACH population and make it likely that type 2 diabetes increases risk of recurrent MCVE in patients with CeVD.

The results in the current study for patients with PAD or an AAA were inconclusive, most likely due to a lack of power. Because the prevalence of coexisting atherosclerotic disease in patients with PAD is high (35–37), the number of patients in SMART with symptomatic vascular disease only in the leg arteries is small. The number of patients with clinically manifest vascular disease restricted to an AAA is even smaller. Furthermore, this was a selected population of AAA patients at very high risk of recurrent MCVE because half of them had a vascular intervention planned at the date of inclusion, and 19% had a history of surgical aneurysm repair.

Interestingly, type 2 diabetes seemed to be most detrimental for patients with clinically manifest vascular disease limited to one part of the vascular tree, such as CAD. There was no increased vascular risk for type 2 diabetes in patients with PVD. Our hypothesis is that patients with symptomatic vascular disease at multiple locations are in a strong proatherogenic state with increased inflammation and coagulation as shown by a very high MCVE recurrence rate of 21% in 5 years. In such an advanced disease state, the additional influence of diabetes on vascular risk processes is no longer relevant. The duration of type 2 diabetes might also play a role. Patients with PVD had a longer duration of diabetes than patients with monovascular disease. The influence of type 2 diabetes on recurrent vascular events might diminish with longer duration of diabetes, because patients with a diagnosis of diabetes of several years' duration may have more stable glucose levels and may have been treated according to the guidelines for more years than patients with a recent diagnosis of diabetes.

Because type 2 diabetes increases recurrent MCVE risk in patients with CAD and CeVD, physicians should be more vigilant for signs of recurrent vascular disease in patients with type 2 diabetes and pay special attention to preventive strategies in those individuals. Even though patients with atherosclerotic disease limited to the coronary arteries were in general adequately treated in the current study, it could be hypothesized that those with diabetes might benefit from targeting toward lower LDL-cholesterol levels. Part of the vascular risk reduction in patients with CeVD might be achieved by consistently treating patients with lipid-lowering agents. More comprehensive therapy to lower blood pressure could also be beneficial in these patients. Aggressive management of risk factors may be beneficial in patients with PVD because their risk of recurrent vascular disease is very high.

A strength of our study is the large and well-phenotyped cohort of patients with symptomatic vascular disease who were monitored for a long period. Medical care was given according to current international guidelines and thereby reflected current clinical practice. Also, the SMART cohort is representative for patients with symptomatic vascular disease in Western countries because it comprises patients from a large catchment area in the Netherlands. The prevalence of type 2 diabetes in patients with various manifestations of vascular disease in this cohort is equal to the prevalence of type 2 diabetes in patients with vascular disease in the country. Furthermore, type 2 diabetes and various types of clinically manifest vascular disease were clearly defined and reported in a standardized manner. Because of the large sample size, it was possible to make a distinction between various groups of patients with and without type 2 diabetes according to their location of symptomatic vascular disease and to adequately adjust for possible confounders.

Study limitations also need to be considered. Patient characteristics were only measured at baseline. This also accounts for measures of diabetes regulation such as fasting plasma glucose and HbA_{1c} values. We had no information about diabetes regulation during follow-up. Therefore, the relation between glycemic control and recurrent vascular events could not be studied. Moreover, the intensity of management of patients with and without diabetes was different according to the location of the vascular disease. To adjust for potential confounding factors, we added major vascular risk factors that are influenced by medical therapy (i.e., systolic blood pressure and LDL-cholesterol) to the Cox models. A sensitivity analysis in which we also adjusted for antiplatelet and oral anticoagulant therapy did not change the effect estimates.

In conclusion, type 2 diabetes increased the risk of recurrent MCVE and mortality in patients with CAD but was not a risk factor in patients with PVD. There is no convincing evidence that type 2 diabetes is a major risk factor for subsequent MCVE in all patients with clinically manifest vascular disease.

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