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Contribution of type 2 diabetes to major adverse cardiovascular events (MACE) in a long-term observational study with different stages of atherosclerosis

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The impact of diabetes on incident cardiovascular disease in relation to the extent of atherosclerotic disease remains unclear. We aimed to investigate major adverse cardiovascular events (MACE) in patients with or without type 2 diabetes (T2DM) presenting with two extremes of atherosclerotic disease, those with angiographically documented minor coronary atherosclerotic lesions and those with symptomatic peripheral artery disease. We included 1238 patients from two prospective, long-term cohort studies. Patients underwent coronary angiography and/or sonography in order to assess the grade of atherosclerosis and were defined as having no signs of Atherosclerosis ($n = 332$; Group I), minor atherosclerosis ($n = 425$; Group II) and major atherosclerosis ($n = 481$; Group III). Cardiovascular events were recorded over a median follow-up period of 7.1 years (Q1 = 3.6 years, Q2 = 7.1 years, Q3 = 11.3 years), covering a total of 9533 patient years. We tested the hypothesis that T2DM infers the same relative risk increase irrespective of the atherosclerosis stage, considering 3-point MACE as the primary endpoint. Incident MACE was reported in 681 patients (51%). MACE occurred more frequently in patients with T2DM than in patients without T2DM ($p < 0.001$). Further, MACE occurred more frequently in group III (58.1%), than group II (34.1%) or group I (19.1%) (group I vs. group II vs. group III, $p < 0.001$). In a cox-regression-model, T2DM was a significant predictor of MACE in univariate analyses (HR = 2.43 [1.88–3.14], $p < 0.001$) and after multivariate adjustment for cardiovascular risk factors, as well as the different grades of atherosclerosis (HR = 1.37 [1.02–1.84], $p = 0.034$). Also, atherosclerosis grades predicted MACE (HR = 3.19 [2.75–3.70], $p < 0.001$) in univariate analyses, and also after multivariate adjustment for known cardiovascular risk factors, including T2DM (HR = 1.61 [1.31–1.98], $p < 0.001$). Finally, when testing for interactions between T2DM and stages of atherosclerosis on MACE we could not find any significant interaction (HR = 1.14 [0.86–1.52], $p = 0.364$). We conclude that T2DM infers an increased risk for MACE across anatomically and morphologically distinct stages of atherosclerosis.

Keywords Diabetes mellitus type 2, Imaging, Prospective study, Major adverse cardiovascular events, Lower extremity artery disease, Coronary heart disease, Vascular bed, Atherosclerosis

Abbreviations

T2DM	type 2 diabetes mellitus
ASCVD	atherosclerotic cardiovascular disease

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CAD	coronary artery disease
noAS	no atherosclerosis
minAS	minor atherosclerosis
majAS	major atherosclerosis
PAD	peripheral artery disease
HR	hazard ratio
aHR	adjusted hazard ratio
MACE	major adverse cardiovascular event

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in patients with type 2 diabetes (T2DM), although therapeutic advances have been achieved over the recent years. Ever since the Finnish EAST-WEST-study[1] which reported risk equivalence between T2DM and myocardial infarction (MI), there is a matter of debate to what extent T2DM affects outcome at different stages of atherosclerosis. The risk equivalence concept has been challenged later on, mainly because the atherothrombotic event of an MI turned out more relevant than the simple presence of T2DM without a characterization of the arterial state[2–6].

Previously, we have shown that T2DM as well as the presence of peripheral artery disease (PAD) or coronary artery disease (CAD) are predictors of major adverse cardiovascular events (MACE), independent of each other. Patients with both PAD and T2DM are at an exceedingly high risk of cardiovascular events[7]. Based on these data, we aimed to investigate incident MACE in patients with or without T2DM presenting with two extremes of atherosclerotic disease, namely those with angiographically documented minor coronary atherosclerotic lesions (Group II) and those with a severe manifestation of atherosclerosis, i.e. symptomatic peripheral artery disease (PAD; Group III). Imaging studies were performed in a large, prospective observational study. We tested the hypothesis that T2DM infers the same relative risk increase irrespective of the atherosclerosis stage, considering 3-point MACE as the primary endpoint.

Methods

Study design

We investigated patients from two prospective, long-term cohort studies including (i) patients who underwent coronary angiography for the evaluation of established or suspected stable CAD and (ii) patients with clinically and sonographically proven peripheral artery disease (PAD). Patients with normal coronary angiograms and absence of clinical signs of PAD served as a control group. The study design has been described in detail previously[8,9]. The primary endpoint of the present study was a composite of cardiovascular death, myocardial infarction, or ischemic stroke (3-point MACE).

Patient populations and group allocation

Patients, all Caucasian ethnicity, were recruited at the Academic Teaching Hospital Feldkirch, Austria, a central European tertiary care center and at the Inselspital, University of Bern, Switzerland.

According to the aim of the study we generated three groups of atherosclerotic disease-stages. Two of our three groups (Group I and II) were referred for evaluation of CAD based on clinical criteria. Coronary angiography was performed with the Judkins technique, as described previously[10]. Atherosclerotic lesion severity was defined according to the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization[11]. Subjects without any signs of coronary atherosclerosis in coronary angiography were allocated to group I and served as control group. Patients with signs of atherosclerosis but without relevant lumen obliteration over > 50% of any coronary vessel were allocated to Group II. Groupe III was conducted of patients with symptomatic PAD Fontain-Stage IIa, IIb and III, according to "2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)"[12]. In all patients PAD was sonographically verified.

Excluded from analyses were patients with a relevant CAD (angiographically revealed > 50% lumen narrowing) of any vessel and PAD patients Fontain-Stage I and patients with media-sclerosis, diagnosed with ABI (ancel-brachial index)[13].

In total, data from 1,238 patients were analyzed. Group I consisted of 332 subjects, Group II of 425 patients, and Group III of 481 patients. The inclusion criteria and group allocation is shown in Fig. 1. The follow-up period is reported as the median with interquartile range (IQR), where Q1 represents the 25th percentile, Q2 the median (50th percentile), and Q3 the 75th percentile.

Study procedures

Baseline analyses included height and weight as well as waist and hip circumferences. Common cardiovascular risk factors were recorded (history of smoking and current smoking, hypertension, established T2DM) from a standardized interview. Systolic and diastolic blood pressures were measured by Riva-Rocci method under resting conditions in sitting position at the day of hospital admission. Hypertension was defined according to the 2023 European Society of Cardiology (ESC)/ESH guidelines[14]. T2DM was diagnosed according to ADA clinical practice recommendations[15]. The study was designed as a two-center (Feldkirch, A; Bern, CH), prospective cohort study. During the follow-up period, we recorded cardiovascular events and all-cause death. Date and cause of death were collected annually using a national register (Statistik Austria, Vienna, Austria) and the Insel Data Science Center (Bern, Switzerland), hospital registries and telephone contacts. Standardized interviews were performed at 2-year intervals to assess non-fatal events. Cardiovascular death (fatal myocardial infarction, sudden cardiac death, mortality from congestive heart failure due to CAD, and fatal ischemic stroke), non-fatal myocardial infarction, non-fatal ischemic stroke and limb amputation were recorded.

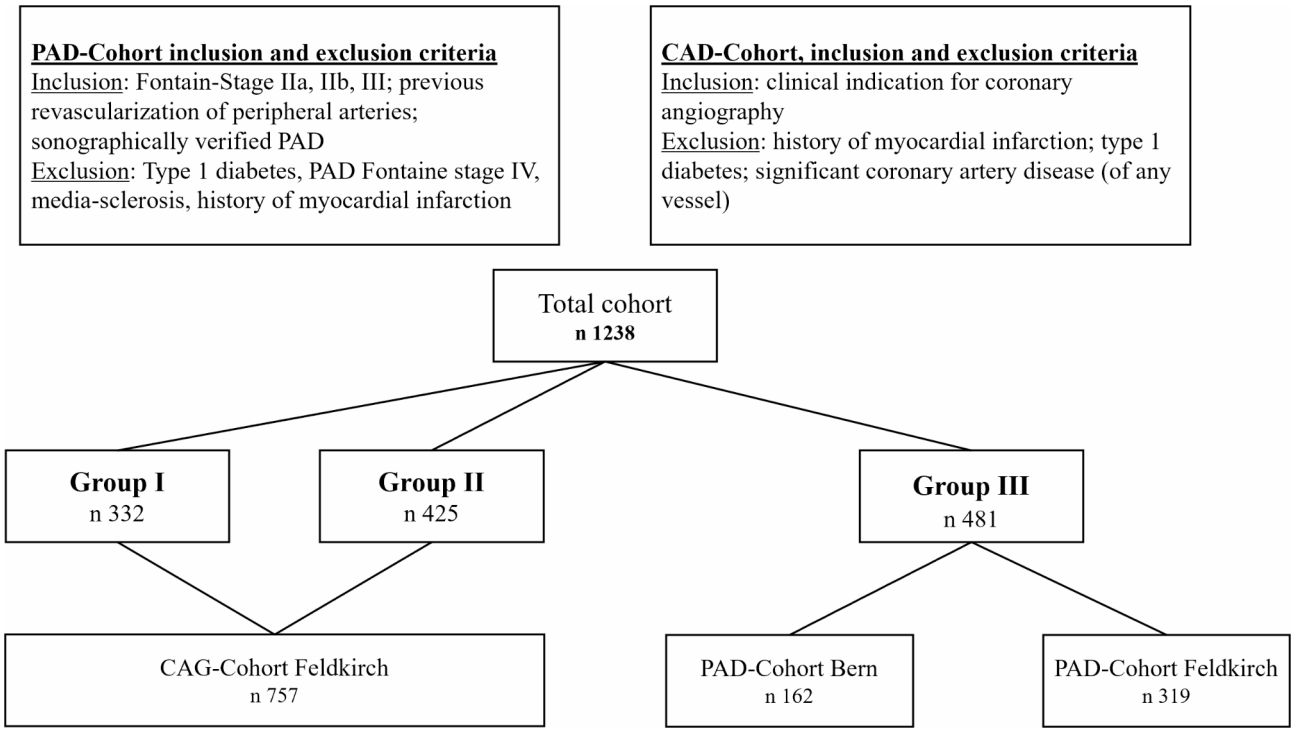

Fig. 1. Study population including inclusion and exclusion criteria, as well as group allocation. *PAD* peripheral artery disease, *CAG* coronary angiography, *ABI* ancle brachial index.

Laboratory analyses

Laboratory measurements were performed from fresh serum samples, as described previously[8,16]. Serum levels of C reactive protein, plasma glucose triglycerides, total cholesterol, low density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol were measured with a Cobas Integra 800 (Roche, Basel, Switzerland). Hemoglobin A1c (HbA1c) was determined on a Menarini-Arkray KDK HA 8160 (Arkray KDK, Kyoto, Japan) by high-performance liquid chromatography. Creatinine was measured by a kinetic Jaffe method (Roche, Switzerland) using a Hitachi 717 or 911 or a Cobas Integra 800 (Roche). The Chronic Kidney Disease Epidemiology Collaboration creatinine equation was applied to estimate the glomerular filtration rate (eGFR)[17].

Statistical analyses

Analyses were performed considering prevalent atherosclerosis status within the three groups (Group I, Group II, Group III) overall, and stratified by diabetes status (T2DM; NoT2DM). Between group differences of baseline data were tested for statistical significance with $\chi 2$ and Mann-Whitney U tests for categorical and continuous variables as appropriate. Event-free survival was estimated by an actuarial approach. Pairwise comparisons of event-free survival between patient groups were done with the Wilcoxon-Gehan statistic. HRs for the incidence of first cardiovascular events were derived from Cox regression analysis. Results from Cox regression analysis were obtained both univariately and after multivariate adjustment for covariates that may potentially affect cardiovascular outcomes. As such, we included age, sex, smoking, (including history of smoking and current smoking), arterial hypertension, LDL cholesterol, HDL cholesterol and body-mass-index (BMI). Potential interactions between T2DM and stages of atherosclerosis were tested for statistical significance by including interaction terms T2DM x atherosclerosis stage into the regression models. Results are given as mean (SD) if not denoted otherwise. All statistical analyses were performed with the software package IBM SPSS Statistics Version 28.0.0.0 for Windows (SPSS).

Results

Baseline data (Tables 1 and 2)

At baseline 332 patients were included into Group I, 425 patients to Group II and 481 patients to Group III. Mean age of Group I was 60.5 years, 65.3 years in the Group II and 67.2 years in Group III ($p < 0{,}001$). The prevalence of T2DM significantly increased ($p < 0.001$) from those in Group I (20.5%) over those in Group II (24.2%) to those in Group III (44.5%). Patients in Group III were more likely to have a history of smoking ($n = 371$, $p < 0.001$) and a large majority of the patients had a history of hypertension ($n = 432$ (89.8%), $p < 0.001$). Body mass index (BMI) was highest in group I (28 kg/m^2, $p = 0.002$).

	Group I	Group II	Group III	*p*
n	332	425	481	
Male sex (%)	39	63	72	< 0.001
Age (years) ± SD	61 ± 11	64 ± 10	67 ± 10	< 0.001
Smoking (%)	46	54	80	< 0.001
Hypertension (%)	52	65	83	< 0.001
T2DM (%)	21	24	45	< 0.001
HbA1C (%) ± SD	5.9 ± 1.1	6.0 ± 0.9	6.3 ± 1.2	< 0.001
LDL (mg/dl) ± SD	131 ± 37	132 ± 39	104 ± 39	< 0.001
HDL (mg/dl) ± SD	58 ± 19	56 ± 16	52 ± 17	< 0.001
TG (mg/dl) ± SD	137 ± 88	147 ± 101	157 ± 110	0.023
BMI (kg/m²) ± SD	28 ± 5	27 ± 4	27 ± 4	0.002

Table 1. Baseline characteristics of the study populations. Data are shown for Group I, Group II and Group III as means ± SD if not denoted otherwise. *HbA1c* hemoglobin A1c, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *T2DM* type 2 diabetes mellitus. P-values for trend are given using Jonckhere Terpstra and Chi-squared tests for trend for continuous and categorical variables, respectively. To convert values for triglycerides to mmol/L multiply by 0.0113 and to convert values for total cholesterol, LDL cholesterol or HDL cholesterol to mmol multiply by 0.0259.

	Group I nT2DM *N* = 264	Group I T2DM *n* = 68	Group II nT2DM *N* = 322	Group II T2DM *n* = 103	Group III nT2DM *n* = 267	Group III T2DM *n* = 214
Age, years	60 ± 11	60 ± 12	64 ± 10	65 ± 10	67 ± 10	67 ± 10
Male sex (%)	39	32	62	65	70	75
T2DM duration (years)	N/A	5 ± 4	N/A	8 ± 10	N/A	11 ± 8
Hypertension (%)	48	68	62	78	80	91
Smoking (%)	46	47	52	61	84	78
Body mass index (kg/m²)	27 ± 4	31 ± 6	27 ± 4	29 ± 5	26 ± 4	28 ± 4
HbA1c (%)	5.6 ± 0.4	7.1 ± 1.7	5.7 ± 0.3	7.2 ± 1.1	5.6 ± 0.4	7.1 ± 1.3
Triglycerides (mg/dl)	131 ± 78	166 ± 119	136 ± 85	182 ± 134	140 ± 86	180 ± 132
Total cholesterol (mg/dl)	213 ± 44	198 ± 47	210 ± 44	200 ± 45	185 ± 42	173 ± 49
LDL-cholesterol (mg/dl)	135 ± 36	119 ± 38	135 ± 38	124 ± 38	109 ± 35	98 ± 43
HDL-cholesterol (mg/dl)	60 ± 19	52 ± 16	57 ± 16	50 ± 14	56 ± 18	48 ± 16
Systolic blood pressure (mm Hg)	133 ± 19	139 ± 21	137 ± 19	140 ± 21	139 ± 22	142 ± 26
Diastolic blood pressure (mm Hg)	81 ± 10	84 ± 11	82 ± 10	82 ± 12	79 ± 11	79 ± 13
Statin use (%)	25	35	38	47	66	75
ACE inhibitors / AT II RBA (%)	26	47	39	51	46	70
Beta receptor blocking agents (%)	37	58	51	48	36	47
Aspirin or clopidogrel (%)	63	55	64	74	85	85
eGFR-EPI (ml/min/1.73m2)	83	80	74	68	72	68
CKD (%) (EPI eGFR < 60 ml/min/1.73 m²)	13	25	14	26	14	22

Table 2. Baseline characteristics of the study populations stratified by diabetes status. Data are shown for Group I, Group II and Group III as means ± SD if not denoted otherwise. *ACE* angiotensin converting enzyme, *ATII RBA* angiotensin II receptor blocking agents, *HbA1c* hemoglobin A1c, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *T2DM* type 2 diabetes mellitus, *prior MI* prior myocardial infarction, *GFR-EPI* glomerular filtration rate according to Chronic Kidney Disease Epidemiology Collaboration formula; *CKD* chronic kidney disease. To convert values for triglycerides to mmol/L multiply by 0.0113 and to convert values for total cholesterol, LDL cholesterol or HDL cholesterol to mmol multiply by 0.0259.

Primary endpoint (Fig. 2a,b)

The endpoint of MACE was reported in 681 (51%) patients over a median follow-up period of 7.1 years (Q1 = 3.6 years, Q2 = 7.1 years, Q3 = 11.3 years). The study thus covered a total of 9533 patient years. Figure 2 shows the incidence of MACE in a Kaplan-Meier survival analysis. MACE occurred more frequently in patients with diabetes than in patients without diabetes (Fig. 2a; $p < 0.001$). Also, MACE occurred more frequently in Group III (58.1%), than in those in Group II (34.1%) or group I (19.1%), with statistically significant differences between the 3 groups (Group I vs. Group II vs. Group III, $p < 0.001$; Fig. 2b).

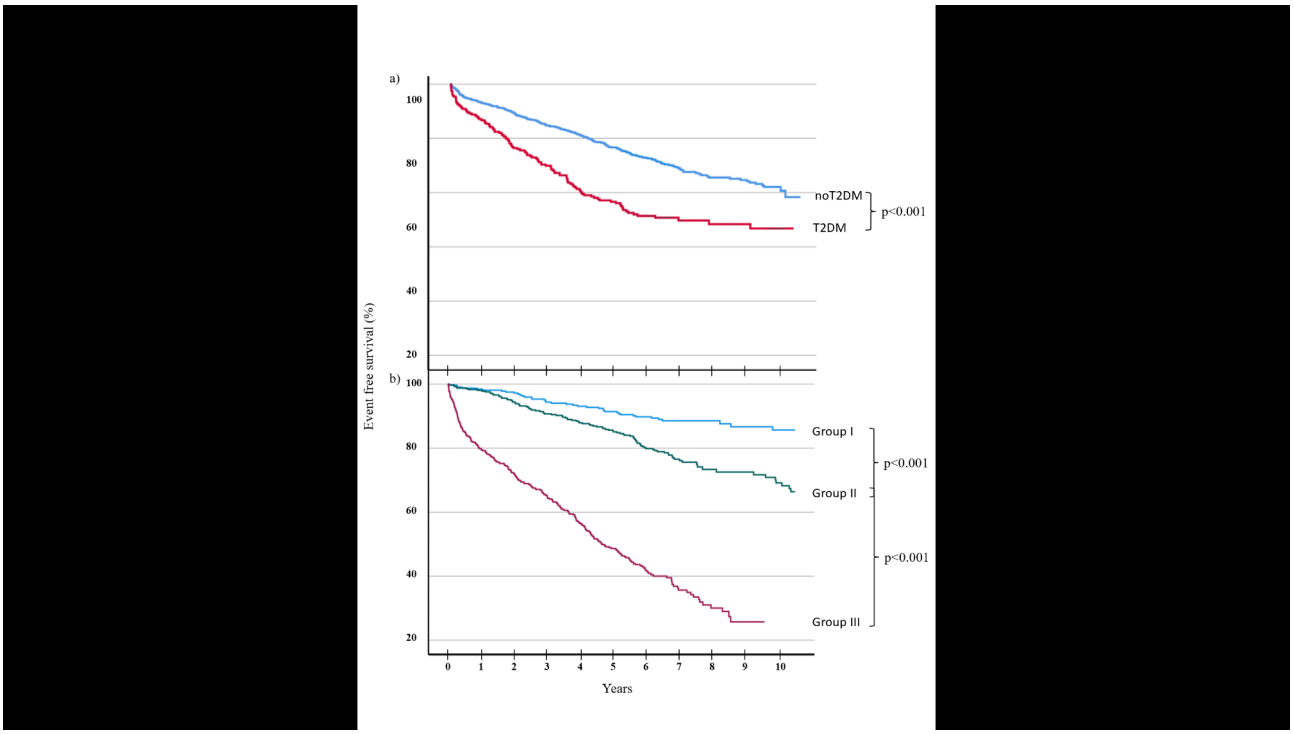

Fig. 2. Incidence of MACE shown in a Kaplan-Meier-Survival analysis, (**a**) according to diabetes-state and (**b**) according to the atherosclerotic grade (Group I-Group III). *noT2DM* no type-2-diabetes, *T2DM* type-2-diabetes, *MACE* major cardiovascular event.

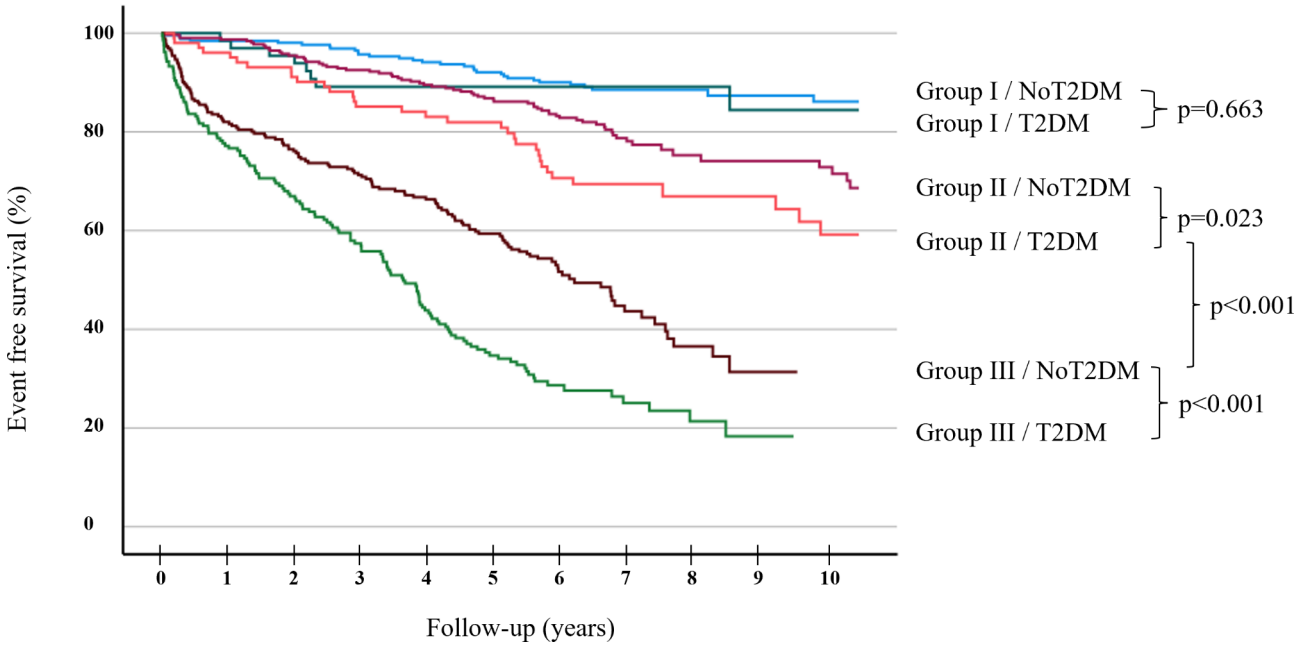

Fig. 3. Incidence of MACE in a Kaplan-Meier-Survival analysis. Comparing Group I, Group II and Group III according to the diabetes state; *T2DM* type 2 diabetes mellitus, *nT2DM* non-type 2 diabetes mellitus, *MACE* major adverse cardiovascular event.

Analyses considering both diabetes status as well as grades of atherosclerosis (Figs. 3, 4 and 5)

T2DM significantly increased the risk of MACE both among patients in Group I (78.0% vs. 67.6%; $p = 0.023$) and Group III (49.4% vs. 32.9%; $p < 0.001$); in Group I the risk of MACE did not differ between those with T2DM and

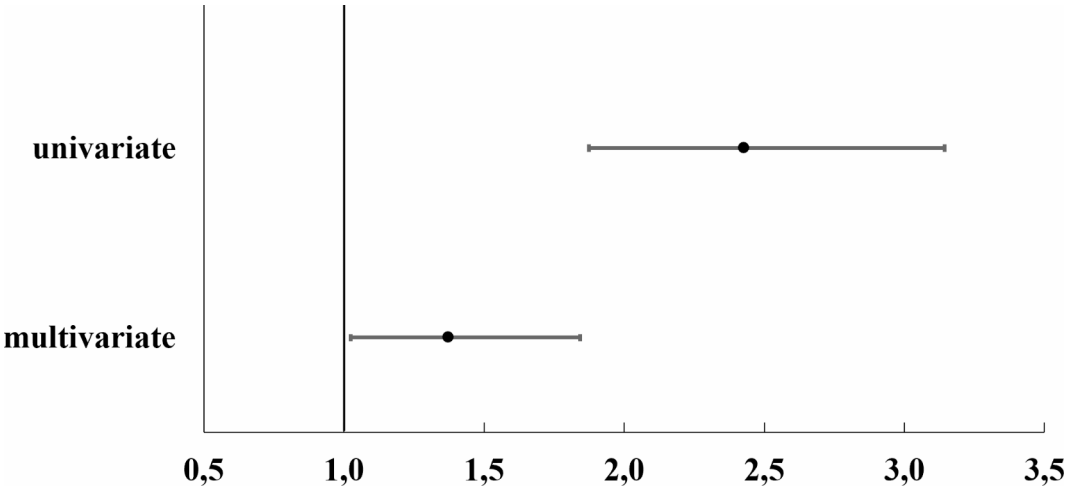

Fig. 4. Hazard ratios (HRs) for diabetes impacting major adverse cardiac events (MACE) within the entire study cohort are presented as follows: in a univariate analysis, HR = 2.43 [95% CI 1.88–3.14], $p < 0.001$; and after adjustment for multiple variables including age, sex, LDL, HDL, BMI, smoking status, hypertension, and the degree of atherosclerosis (Group I, Group II and Group III) in a multivariate analysis, HR = 1.37 [95% CI 1.02–1.84], $p = 0.034$.

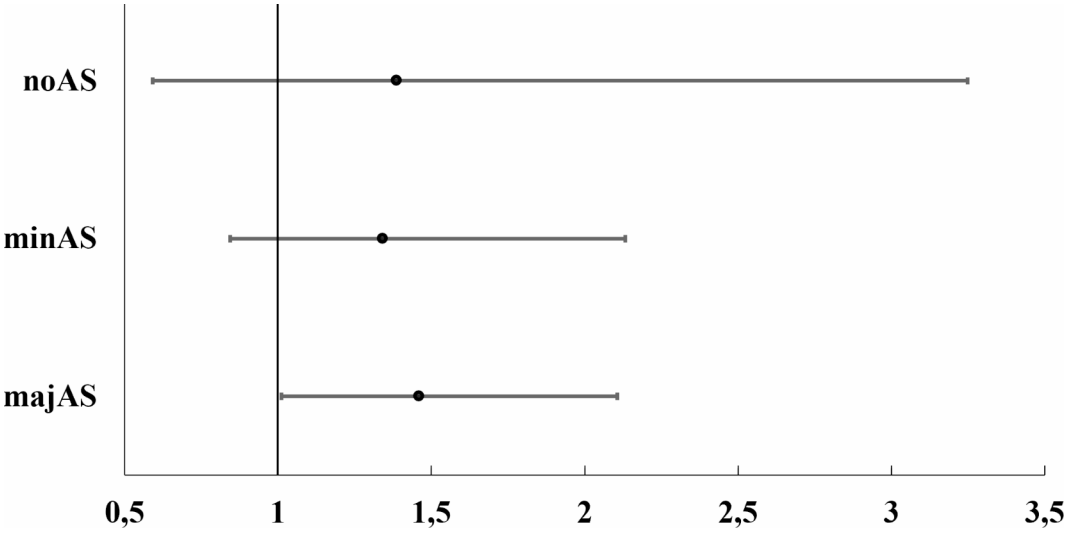

Fig. 5. Univariate hazard ratios for diabetes on MACE across Group I-Group III: Group I HR = 1.39 [95% CI: 0.59–3.25, $p = 0.451$], Group II HR = 1.34 [95% CI: 0.84–2.13, $p = 0.214$], and Group III HR = 1.46 [95% CI: 1.01–2.11, $p = 0.043$].

those who did not have T2DM (88.0% vs. 87.9%; $p = 0.663$). In patients in Group III who did not have T2DM, the risk of MACE was higher than that of T2DM patients in Group II ($p < 0.001$) (Fig. 3).

In a cox-regression-model, T2DM was a significant predictor of MACE in univariate analyses (HR = 2.43 [1.88–3.14], $p < 0.001$) and also after multivariate adjustment for cardiovascular-risk-factors (age, sex, hypertension, smoking, low density lipoprotein (LDL), high density lipoprotein, body-mass-index) and as well after adjustment for the three stages of atherosclerotic disease (Group I, Group II and Group III) (HR = 1.37 [1.02–1.84], $p = 0.034$) (Fig. 4). Further, we found that our defined atherosclerotic stages predicted MACE (HR = 3.19 [2.75–3.70], $p < 0.001$) in a univariate analysis, and also after multivariate adjustment for known cardiovascular-risk-factors including T2DM (age, sex, hypertension, smoking, low density lipoprotein (LDL), high density lipoprotein, body-mass-index and the diabetes-state) (HR = 1.61 [1.31–1.98], $p < 0.001$).

In a cox-regression-model for MACE (Fig. 5) stratified by the three groups, T2DM was no significant predictor for MACE in Group I and Group II univariately (Group I: HR = 1.39 [0.59–3.25], $p = 0.451$; Group II: HR = 1.34 [0.84–2.13], $p = 0.214$), and there was a borderline significance in patients Group III (HR = 1.46 [1.01–2.11], $p = 0.043$, respectively). However, there was a similar trend for risk increase by T2DM along the three grades of atherosclerosis, indicated by respective comparable point estimates of between 1.34 and 1.46 (Fig. 5).

After multivariate adjustment for common cardiovascular risk-factors (age, sex, smoking state, hypertension, low density lipoprotein cholesterol (LDL-C) and high-density-lipoprotein cholesterol, HDL-C and body-mass-index (BMI)) there was no correlation in Group I (aHR = 1.17 [0.48–2.87], $p = 0.733$) and Group II (aHR = 1.13 [0.70–1.83], $p = 0.609$), but a trend in patients Group III (aHR = 1.47 [0.99–2.18], $p = 0.55$), respectively.

When testing for interactions between T2DM and stages of atherosclerosis on MACE we could not find any significant interaction (HR = 1.14 [0.86–1.52], $p = 0.364$).

Discussion

The present prospective, observational study over a median follow-up period of 7.1 years yielded several new clinically important findings.

First, our data indicate that both prevalent T2DM, as well as prevalent atherosclerosis are mutually independent prognostic factors for incident MACE. Also, we were able to demonstrate that the presence of diabetes remained a significant contributor to the risk of MACE, independent of underlying atherosclerosis-stage. Although the effect of diabetes on MACE was numerically more pronounced in Group I and Group II, as compared to Group III (Fig. 3). Corresponding multivariate analyses (Fig. 5), as well as interaction analyses suggest an independent effect of T2DM. This indicates that the risk of experiencing a MACE is inevitably higher once diabetes is diagnosed, regardless of underlying atherosclerosis-stage. This finding is new, and further prospective studies including morphological data should be encouraged.

Second, we found that patients with prevalent atherosclerosis represent a very high-risk population, which is particularly pronounced in patients with advanced PAD. This is in line with previous findings and has also been reflected in several clinical practice recommendations[18–21]. In our study as many as around 60% of patients with PAD Fountain stages 2 or 3 at baseline reached the primary endpoint of MACE during follow-up. Previously we have shown that PAD is a stronger risk factor for future cardiovascular events than T2DM, and that T2DM accelerates atherothrombotic disease and dramatically increases the incidence of cardiovascular events in PAD patients[22,23]. This confirms a clear need for intensive risk factor management in these patients.

Third, both T2DM as well as the grade of atherosclerosis at baseline predicted MACE. This has been shown previously in populations at various stages of atherosclerosis and different stages of diabetes, such as in a large post-hoc analyses of the EXSCEL trial[24] demonstrating increased risk in patients with T2DM depending on the amount of vascular bed involvement[25]. Results from large clinical trials (e.g. SAVOR-TIMI 53[26]; LEADER[27], IMPROVE-IT[28]) indicate that diabetes should not be seen as a precursor for atherosclerotic disease, rather that diabetes confers additive cardiovascular risk[25]. Remarkably, the higher incidence of MACE in patients with T2DM was observed despite of glycaemic control being close to an HbA1c target of 7% at baseline. The prognostic importance of glycaemic control for cardiovascular outcomes has been confirmed by a recent interesting study in diabetic patients following stent-supported angioplasty. The optimally controlled T2DM in this cohort was associated with a favourable cardiovascular outcome, even in patients with advanced atherosclerotic lesions in renal arteries causing renovascular hypertension[29].

Our study has several important strengths and limitations. Major strengths are the large sample size, the comprehensive clinical and demographic characterization of study subjects, and a long follow-up period. Also, we used imaging techniques in order to quantify atherosclerosis, rather than solely relying on clinical data. A limitation is that our study is restricted to only two study sites, and therefore our findings may be less applicable to other populations. The diabetes therapy of the study patients was in the hands of the physicians referring patients to our two centers. It represents a limitation of our protocol in that we cannot provide data of glycaemic control. Furthermore, populations of our study differ in terms of site (PAD, CAD) as well as stages of atherosclerosis. However, both atherosclerosis entities are morphologically well defined, minor CAD by angiography and PAD by ultrasonography[30–33].

Conclusions

In summary, we would like to conclude that T2DM infers an increased risk for incident MACE across anatomically and morphologically distinct stages of atherosclerosis.

Data availability

The datasets generated during the current study are available in the VIVIT-Institute repository and from the corresponding author on reasonable request.

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A.M.: data evaluation and statistical analysis, drafting of the manuscriptD.H.: data evaluation and statistical analysisB.L.: data evaluation, drafting of the manuscriptJ.D.: data evaluation, revision of the manuscript for intellectually important contentC. S.: data evaluation, revision of the manuscript for intellectually important C.H.: statistical analysisP.A.: revision of the manuscript for intellectually important contentM.S.: data evaluation and statistical analysisA.F.: data evaluation, revision of the manuscript for intellectually important H.D. conception and design of the study, drafting of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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