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Peripheral arterial disease and type 2 diabetes: Older patients still exhibit a survival benefit from glucose control

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Abstract

Objective: To investigate a possible beneficial effect of strict glycaemic control on all-cause mortality in patients with peripheral arterial disease and type 2 diabetes mellitus.

Methods: A total of 367 mainly older peripheral arterial disease patients [age: 69 (62–78) years, 34% women, Fontaine stage I–II] were categorized according to glycaemic control, that is, (a) no type 2 diabetes mellitus, (b) strict glucose control (HbA1c $<$ 53 mmol/mol) and (c) lenient glucose control (HbA1c $\geqslant$ 53 mmol/mol) at inclusion and by mean HbA1c over the first study year. Mortality was analysed using Kaplan–Meier and Cox-regression analyses after 7 years.

Results: The combination of type 2 diabetes mellitus and peripheral arterial disease reduced survival from 78.8% to 68.9% in comparison to patients without type 2 diabetes mellitus ($p = 0.023$). Patients with strict glucose control (75%) were associated with increased survival in comparison to patients with lenient glucose control (58.9%) stratified by mean HbA1c ($p = 0.042$). Baseline cardiovascular risk factors were similar in those type 2 diabetes mellitus patients. In this peripheral arterial disease cohort HbA1c (hazard ratio: 1.3, 1.04–1.63), age (hazard ratio: 1.7, 1.3–2.3) and C-reactive protein (hazard ratio: 1.5, 1.2–2.0) remained independent associates for mortality adjusted for cardiovascular risk factors and diabetes duration.

Conclusion: Older patients with peripheral arterial disease and type 2 diabetes mellitus still benefit from strict glucose control in a cohort of patients with similar distribution of cardiovascular risk factors.

Keywords

Peripheral arterial disease, atherosclerosis, type 2 diabetes mellitus, mortality

Introduction

The combination of peripheral arterial disease (PAD) and type 2 diabetes mellitus (T2D) is still hazardous. PAD is the most common cause for amputation in patients with T2D.[1] Even T2D patients with healed foot ulcers show an increased mortality rate compared to patients without foot ulceration within 2 years (22.8% vs 12.1%).[2] The progression of severe PAD and T2D increases mortality profoundly.[3] However, the underlying aetiology is unknown. It has been speculated that T2D or even prediabetes increase vascular inflammation.[4] This highlights the importance to screen for T2D or eventually even prediabetes in patients with PAD. Screening for T2D in PAD patients results in a higher yield of patients with disturbed glucose metabolism compared to screening for coronary artery disease (CAD) patients.[5]

European and US guidelines have propagated cardiovascular risk factors modification in PAD patients. Multimodal guideline-based pharmacotherapy should be implemented including antiplatelet therapy, statins and treatment of all additional risk factors as T2D or hypertension. However,

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publications from the last decade[6,7] indicate poor risk factor control even though guidelines for cardiovascular risk factor prevention were published in 2003 in Europe.[8] The Reduction of Atherothrombosis for Continued Health (REACH) registry indicates that PAD patients without additional clinical manifestation of CAD or cerebrovascular disease (3067 subjects) are treated less intensively compared to patients with additional manifestations of cerebro-cardiovascular disease (4844 subjects).[7] The usage of cardio-protective medication in PAD 'only' was 76.3% versus 84.6% for antiplatelet medication, 50.2% versus 73% for statins, 33% versus 49.4% for angiotensin-converting enzyme (ACE)-inhibitors or 34.5% versus 42.8% for anti-diabetic medication.[7] In a large Swedish T2D cohort study ($n=271,174$), excellent risk factor control decreased the risk of death, myocardial inflation or stroke to the risk of the general population within 5.7 years.[9]

Increased mortality rates of PAD patients with T2D (58%) compared to those without (19%) have been reported over 10 years.[10] The objective of the present study was to investigate whether a strict glycaemic control has a potential beneficial effect on all-cause mortality in patients with T2D and PAD in comparison to PAD patients without T2D in the context of strict secondary preventive pharmacotherapy according to current guidelines.

Methods

Study population

Patients with established PAD were recruited at the outpatient department of the division of Angiology of Vienna General Hospital, a tertiary care centre in Austria, during routine clinical follow-up visits. All patients included into this observational study exhibited stable PAD [Fontaine stage I–II, age: 69 (interquartile range (IQR): 62–78) years] and were recruited between 2006 and 2011 for the Vascular Medicine Center (VMC) cohort in Vienna, Austria.[11] Women of childbearing age were not included into this study. Patients with critical limb ischaemia and/or ulceration were not eligible for this study. Patients were observed three times in the first study year and thereafter every 6–12 months at the VMC as medically needed. Inclusion criteria were age up to 90 years and stable PAD. Exclusion criteria were known cancer, serum creatinine $>229\,\mu mol/L$ (3 mg/dL), connective tissue disease, hormone replacement therapy, critical illness within the last 6 months. The study was approved by the institutional ethics committee and complies with the Declaration of Helsinki. All subjects gave written informed consent before inclusion into the study.

Definition of cardiovascular co-morbidities

Baseline demographic and clinical characteristics were recorded. Hypertension was defined as documentation of a systolic blood pressure of ≥ 140 mmHg and/or a diastolic blood pressure of ≥ 90 mmHg in at least two measurements[12] or active use of any antihypertensive medication. Smoking was defined as current smoking. Former smoking was defined as previous smoking of at least 100 cigarettes. Body mass index (BMI) was calculated as body weight in kilogram divided by squared body height in metres (kg/m^2). Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology (CKD-EPI) equation.[13]

Vascular assessments

Presence of PAD was detected by non-invasive ultrasound measurements (ELCAT VL5000, Wolfratshausen, Germany) by trained technicians and calculation of ankle-brachial index (ABI). Systolic blood pressure was measured in both arms (brachial arteries) and both ankles (dorsal pedal arteries and posterior tibial arteries). ABI was calculated according to the TASC criteria[14] by dividing of the higher ankle pressure by the highest brachial pressure. In case of incompressible ankle arteries ($ABI > 1.4$), patients were classified as Moenckeberg's mediasclerosis. PAD was classified after the Fontaine classification by the self-reported pain-free walking distance (50.4% Fontaine stage I, 49.3% Fontaine stage II, one patient not classified due to orthopaedic immobility).

Definition of diabetes

T2D was defined as a fasting plasma glucose level over 7.0 mmol/L, glucose level over 11.1 mmol/L after standardized oral glucose tolerance test (oGTT),[15] glycated haemoglobin (HbA1c) of at least 6.5% (48 mmol/mol) or current use of an anti-diabetic agent. Prediabetes was defined by either a fasting glucose of 5.55–6.94 mmol/L, a 2-h glucose level of 7.77–11.05 mmol/L or an HbA1c of 5.7%–6.4% (39–46 mmol/mol). Fasting C-peptide levels were only available in 87% of patients. Newly detected T2D was primarily treated with metformin. Duration of previously known T2D was assessed by questionnaire at inclusion into the study and verified by hospital records. All patients with T2D were checked for prevalence of autoimmune antibodies (tyrosine phosphatase IA2, glutamate decarboxylase) to rule out late onset autoimmune diabetes in the adult.

Medical investigation

Fasting blood samples were drawn at baseline for glucose, HbA1c, cholesterol, liver and renal function parameter monitoring. Standardized oGTTs were performed at every patient visit in those without known T2D.[15] Mortality was assessed by central death registry queries (Statistik Austria) and was censored for every individual patient at 7 years.

In case of survival, patients were additionally contacted by phone to ensure data quality. International Classification of Diseases (ICD)-10 codes were retrieved from the central death registry and verified by hospital or autopsy reports as available to quantify cardiovascular mortality. Cardiovascular mortality was defined by the ICD-10 diseases of the circulatory system (I00–I99 code). During the study period, 94 patients died within a follow-up of 7 (6.3; 7) years. Survival status was available for all patients in the study cohort. ICD-10 mortality codes were classified as 57 cardiovascular, 17 oncology and 20 other causes of death (including sepsis, pneumonia, suicide and trauma/cerebral bleeding). In addition, the occurrence of the first major cardiovascular event (MACE) including non-fatal stroke, non-fatal myocardial infarction and all-cause death was available for the first five study years. MACE events included 13 non-fatal myocardial infarctions, 11 non-fatal stroke and 43 deaths.

Medical therapy

Patients were treated with acetylsalicylic acid or clopidogrel for PAD. Patients routinely received ACE-inhibitors or angiotensin receptor blocker unless otherwise contraindicated, statins for hyperlipidaemia, and metformin, gliclazide and basal insulin for T2D. Therapeutic goal for diabetes mellitus treatment was an HbA1c below 7 rel. % (<53 mmol/mol). Diabetes pharmacotherapy was adapted to avoid hypoglycaemia if needed.

Statistics

Data are presented as mean ± standard deviation (SD) or median (25; 75 percentile). Student's unpaired t-test, as well as χ^2-test were used as appropriate. Survival curves were calculated by the Kaplan–Meier method and compared using the log-rank test. Cox-regression analysis was performed to estimate effect size and to allow for multivariable adjustment. Three patients were omitted during multivariable adjustment due to missing covariates. Multivariable interaction was defined as beta change over 10%.[16] Effect size for continuous parameters is given as hazard ratio (HR) per 1 SD. A two-sided alpha-level of $p < 0.05$ was considered statistically significant. All statistical analyses were performed with the statistical software package SPSS 24 (IBM, Chicago, IL, United States). The shown figures were generated by GraphPad Prism 6.0h (GraphPad Software Inc., La Jolla, CA, United States).

Results

This study included 367 mainly older PAD patients [age: 69 (62; 78) years, 34% women] of the VMC Vienna patient cohort as depicted in Supplemental Figure 1S. At baseline, before the oGTT, there were 229 patients with presumed absence of glucose disturbance and 138 patients with known T2D. Initial intensified screening (oGTT, HbA1c) revealed 26 patients unaware of having type T2D. Further screening at 6 and 12 months added 13 additional patients with the diagnosis T2D. The diagnosis T2D was based on pathological oGTT in 25 patients and according to HbA1c criteria in 14 patients.

Glycaemic control

Patients were stratified into three groups according to glycaemic control, that is, (a) no T2D (control, $n = 203$), (b) HbA1c < 7% (53 mmol/mol, strict glycaemic control, $n = 100$) and (c) HbA1c ⩾ 7% (53 mmol/mol, lenient glycaemic control, $n = 64$) at inclusion as depicted in Table 1. Across the all patient groups, patient age, gender, renal function measured by eGFR and C-reactive protein showed a similar distribution pattern. Patient with T2D exhibited increased BMI ($p < 0.001$) and triglyceride levels ($p = 0.043$), while showing lower high density lipoprotein cholesterol (HDL-C) ($p < 0.001$) and low density lipoprotein cholesterol (LDL-C) ($p < 0.001$) levels. In comparison of patients with strict glycaemic control and lenient glycaemic control, no significant differences for baseline laboratory parameters or BMI levels were observed. Patients with lenient glycaemic control exhibited an increased use of anti-diabetic combination therapy and insulin use (41.1% vs 21.9%) as depicted in Supplemental Figure 2S. Diabetes duration was 4.5 (1; 13.5) years in patients with strict glycaemic control and 15 (9; 24) years in patients with lenient glycaemic control.

Cardiovascular and all-cause mortality

The diagnosis T2D reduced all-cause survival from 78.8% to 68.9% over 7 years in PAD patients ($p = 0.023$) as depicted in Figure 1(a). Survival was already numerically reduced in the prediabetic phase (76.8%) in comparison with normal glucose tolerance on baseline oral glucose tolerance testing (82.6%) [Figure 1(b)]. Cardiovascular survival was statistically equal in patients without T2D (85.7%) and T2D patients (79.3%) [Figure 1(d)]. Patient cardiovascular survival was similar in patients with prediabetes (85.1%) and normal glucose tolerance (89.1%) ($p = 0.521$) [Figure 1(e)].

Influence of glycaemic control on cardiovascular and all-cause mortality

Patients were stratified by mean HbA1c levels over the first study year into the following groups: (a) no T2D ($n = 186$), (b) newly detected T2D ($n = 39$), (c) T2D – strict glycaemic control [HbA1c < 7% (53 mmol/mol), $n = 80$] and (d) T2D – lenient glycaemic control [HbA1c ⩾ 7% (53 mmol/mol), $n = 56$]. Patients without T2D (81.7%) are

Table 1. Baseline characteristics according to diagnosis of type 2 diabetes mellitus at the beginning of the study.

	Control	Type 2 diabetes mellitus			*p*-value (all)
		Strict control	Lenient control	*p*-value*	
n	203	100	64		
Age (years)	68 ± 11	70 ± 10	71 ± 10	0.565	0.210
Female, *n* (%)	33 (33)	14 (21.9)	76 (37.4)	0.124	0.070
Body mass index (kg/m^2)	27 ± 4	28 ± 4	29 ± 4	0.066	<0.001
HbA_{1c} (mmol/mol)	40 (37, 42)	45 (42, 49)	62 (55, 66)	<0.001	<0.001
Diabetes duration (years)	–	4.5 (1, 13.5)	15 (9, 24)		
Triglycerides (mmol/L)	1.5 (1.1, 2.2)	1.6 (1.1, 2.4)	1.9 (1.3, 2.6)	0.151	0.043
HDL-C (mmol/L)	1.4 (1.2, 1.7)	1.3 (1.1, 1.5)	1.2 (1.1, 1.3)	0.083	<0.001
LDL-C (mmol/L)	2.8 (2.3, 3.5)	2.4 (2.0, 2.9)	2.5 (2.0, 3.2)	0.705	<0.001
C-reactive protein (nmol/L)	25.7 (14.3, 45.7)	28.6 (13.3, 62.9)	31.4 (15.2, 58.1)	0.735	0.854
eGFR (mL/min/1.73 m^2)	70.2 ± 19	66.3 ± 20.2	64.8 ± 18.3	0.632	0.112
Hypertension, *n* (%)	180 (88.7)	96 (96)	62 (96.9)	0.771	0.025
RAAS blockage, *n* (%)	129 (63.5)	79 (79)	56 (87.5)	0.164	<0.001
Statin use, *n* (%)	159 (78.3)	79 (79)	54 (84.4)	0.391	0.571
Smoking – active, *n* (%)	82 (40.4)	26 (26)	18 (28.1)	0.946	0.070
Quit, *n* (%)	80 (39.4)	54 (54)	33 (51.6)		
Never, *n* (%)	41 (20.2)	26 (26)	13 (20.3)		
PAD – Fontaine stage I	105 (51.7)	51 (51)	29 (46)	0.537	0.728
Fontaine stage II	98 (48.3)	49 (49)	34 (54)		
Carotid artery disease, *n* (%)	73 (36)	44 (44)	28 (43.8)	0.975	0.302
Stroke, *n* (%)	19 (9.4)	10 (10)	10 (15.6)	0.283	0.356
Coronary artery disease, *n* (%)	55 (27.1)	37 (37)	25 (39.1)	0.790	0.088
Myocardial infarction, *n* (%)	30 (14.8)	19 (19)	11 (17.2)	0.770	0.634

HbA_{1c}: glycated haemoglobin A_{1c}; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate according to CKD-EPI equation; RAAS: renin–angiotensin–aldosterone system; PAD: peripheral arterial disease.
Data are mean ± SD or median (25, 75 percentile) or *n* (%). Control: patients without type 2 diabetes mellitus; type 2 diabetes mellitus: strict control – HbA1c < 7% (53 mmol/mol), lenient control – HbA1c ⩾ 7% (53 mmol/mol).
Differences were analysed by Students' t-test, ANOVA, chi-square test or Kruskal–Wallis test as appropriate. An alpha-level of $p < 0.05$ (two-tailed) was considered statistically significant.
*p-value for type 2 diabetes mellitus subgroup.

associated with increased survival in comparison to newly detected T2D (71.8%), strict glycaemic control patients (75%) and lenient glycaemic control patients (58.9%) as depicted in Figure 1(c) ($p = 0.002$). The all-cause survival difference between patients without T2D and strict glycaemic control ($p = 0.164$) and newly detected T2D ($p = 0.156$) did not reach statistical significance [Figure 1(c)]. However, patients with lenient glycaemic control are associated with increased mortality in comparison to patients with strict glycaemic control ($p = 0.042$) [Figure 1(c)]. Furthermore, similar mortality patterns were seen for cardiovascular mortality with a survival ranging from no T2D (88.7%) to newly detected T2D (84.6%) and strict glycaemic control (87.5%) with a declined survival in lenient glycaemic control patients (64.3%) ($p < 0.001$) [Figure 1(f)]. Women were equally distributed among the patient subgroups ($p = 0.224$). Omission of patients with recently diagnosed T2D within 1 year before and during the study ($n = 58$) revealed similar all-cause survival differences between patients without T2D (81.7%), strict glycaemic control (72.6%) and lenient glycaemic control (60%) ($p = 0.001$). Baseline characteristics of these patients are depicted in Supplemental Table 1S. Patients with lenient glycaemic control at baseline showed increased MACE events in comparison to patients with strict glycaemic control and those without T2D after 5 years of observation ($p = 0.002$, Supplemental Figure 3S).

Influence of modifiable cardiovascular risk factors on cardiovascular and all-cause mortality

The achievement of treatment targets for modifiable cardiovascular risk factors within the first study year is depicted in Figure 2. Prescription of renin–angiotensin–aldosterone system blockage in the study cohort was 71.9% at inclusion and increased to 76.8% over the first study year. Statin prescription was 79.6% at inclusion and increased to 88.5% over the first study year. Survival benefits were only seen in patients with strict glycaemic control ($p = 0.042$) [Figure 2(a)] while the achievement of an LDL-C target below 2.6 mmol/L or normalization of blood

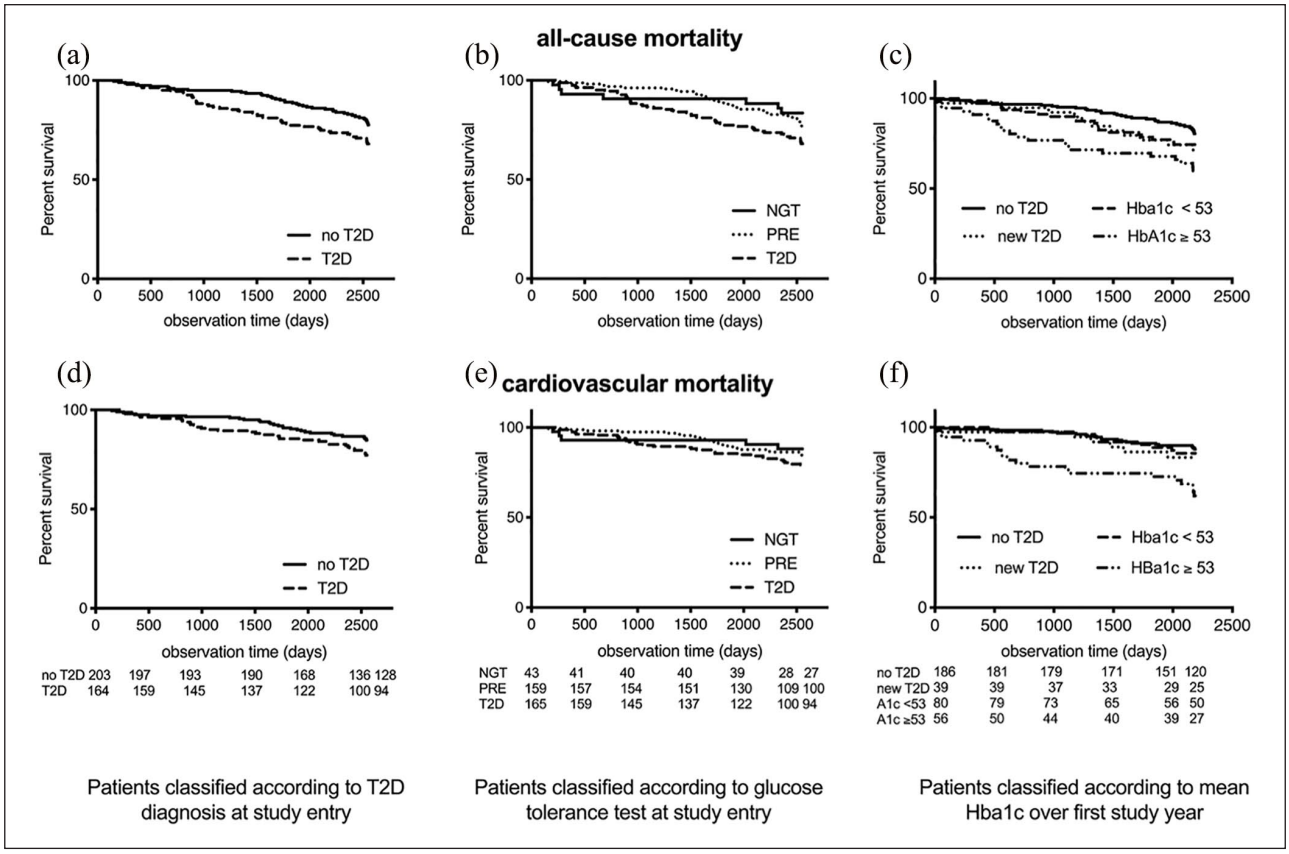

Figure 1. All-cause and cardiovascular survival according to glucose metabolism disturbances. Kaplan–Meier curves for the prediction of all-cause mortality according to (a) diagnosis of diabetes, (b) glucose tolerance or (c) mean HbA1c levels over the first study year are displayed. Kaplan–Meier curves for the prediction of cardiovascular mortality according to the same categories are displayed in (d) to (f).
HbA1c: glycated haemoglobin A1c in mmol/mol; NGT: normal glucose tolerance; PRE: prediabetes; T2D: type 2 diabetes mellitus.

pressure to below 140 mmHg systolic was not associated with a reduction in all-cause [Figure 2(b) and (c)] or cardiovascular mortality in this patient cohort over 7 years. Furthermore, changes in mean LDL-C ($p=0.688$), systolic blood pressure ($p=0.601$), BMI ($p=0.536$) and eGFR ($p=0.508$) over the first study year were equal between diabetic patients with lenient glycaemic control and strict glycaemic control in the same time period.

Multivariable adjustment of patient mortality

Multivariable adjustment for typical cardiovascular risk factors revealed patients' baseline HbA1c (HR: 1.3, 1.04–1.63), age (HR: 1.7, 1.3–2.3) and C-reactive protein (HR: 1.5, 1.2–2.0) as significant independent associates for all-cause mortality while patients' gender, LDL-C, systolic blood pressure, eGFR and diabetes duration were not independent predictors in the whole study cohort. The associations of all-cause mortality with patients' HbA1c (HR: 1.44, 1.20–1.73), age (HR: 1.8, 1.46–2.31) and C-reactive protein (HR: 1.55, 1.19–2.02) were unchanged by further adjustment for PAD severity (Fontaine stage). In addition, patients HbA1c (HR: 1.4, 1.1–1.8) and age (HR: 2.0, 1.4–2.9) were significantly linked to cardiovascular death after adjustment for gender, LDL-C, systolic blood pressure, C-reactive protein, eGFR and diabetes duration.

Discussion

In this study, we found that strict glycaemic control in older type 2 diabetes PAD patients ameliorates the excessive mortality risk in comparison to PAD patients without T2D. The survival characteristics of patients with newly diagnosed T2D mimics those of PAD patients with strict glycaemic control. Landmark studies [Action to Control Cardiovascular Risk in Diabetes (ACCORD),[17] Action in Diabetes and Vascular Disease – Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),[18] Veterans Affairs Diabetes Trial (VADT)[19]] evaluating the effect of intensive glycaemic control on cardiovascular outcomes did not report outcomes of patients with T2D and PAD. A metanalysis[20] of those studies demonstrated a benefit of intensive glucose control on myocardial infarction, but not on all-cause mortality. In contrast, a large

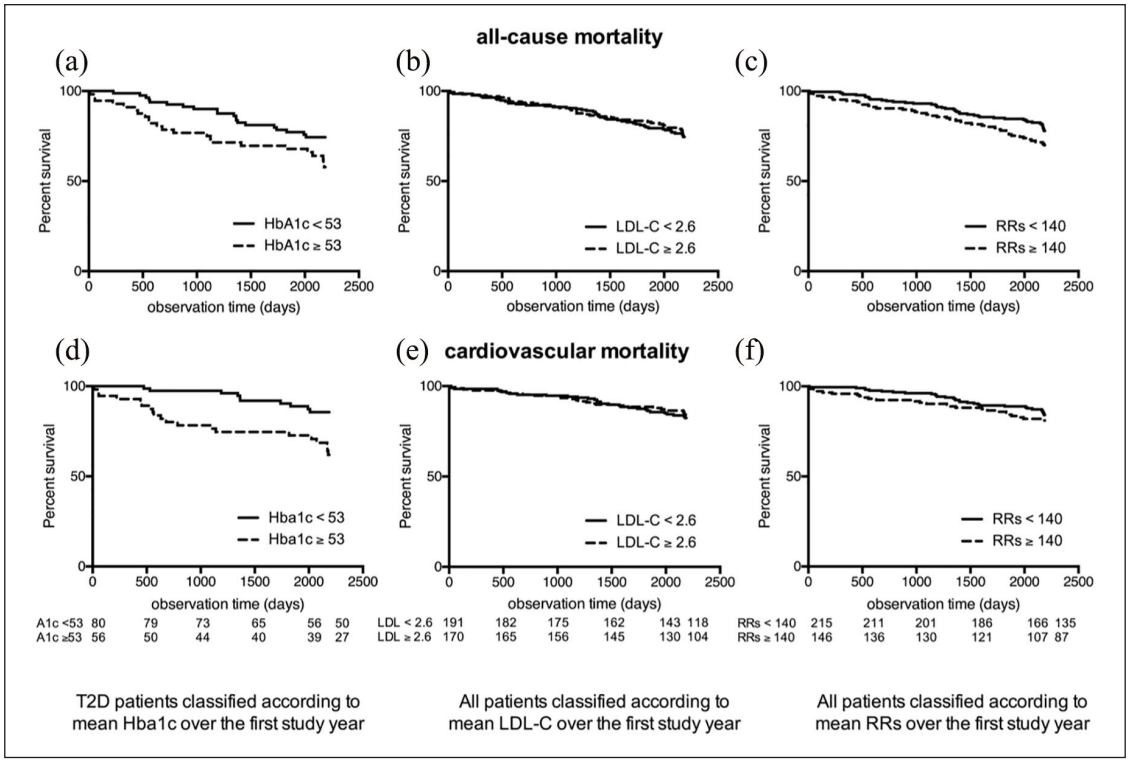

Figure 2. All-cause and cardiovascular survival according to modifiable risk factors. Kaplan–Meier curves for the prediction of all-cause mortality according to (a) mean HbA1c levels in mmol/mol, (b) mean LDL-cholesterol levels (LDL-C) in mmol/L and (c) mean systolic blood pressure (RRs) in mmHg over the first study year. Kaplan–Meier curves for the prediction of cardiovascular mortality according to the same categories are displayed in (d) to (f).
T2D: type 2 diabetes mellitus.

observational Swedish study[9] demonstrated that good glycaemic control (HbA1c < 53 mmol/mol) was one of the key risk factors among 18 tested risk factors for predicting death from any cause, acute myocardial infarction, stroke and hospitalization for heart failure among T2D patients with or without preexisting conditions.

This study delineates a survival benefit for strict glycaemic control in comparison to patients with lenient glycaemic control. Current diabetes guidelines emphasize strict glycaemic control with a possibility to individualize to higher target values in elderly people with long-standing or more complicated disease.[21] The increased use of combination therapy and insulin treatment in patients with lenient glycaemic control in this study reflects this population. However, the exclusion of recently diagnosed T2D patients before the study begin did not change the survival characteristics of patients with strict glycaemic control. Long-standing T2D was more pronounced in patients with lenient glycaemic control [16 (10–28) years] in comparison to strict glycaemic control [8 (2–15.5) years]. Furthermore, C-peptide levels were significantly lower in patients with lenient glycaemic control (3.59 ± 1.7 vs 2.83 ± 1.93 ng/mL, $p = 0.025$).

Possible explanations for the mortality difference in our study are various: first, the sustained strict glycaemic control itself over time (mean HbA1c), as recently demonstrated by Roussel et al.[22] Second, patients with a longer diabetes duration and reduced C-peptide levels reflect patients with higher glucose exposure over years due to an increased beta cell loss. Third, PAD patients exhibit already more frequently insulin resistance/prediabetes in comparison to other manifestation of atherosclerosis.[5,23] It is most likely that patients with a longer diabetes duration exhibit higher insulin resistance, unfortunately no mechanistic clamp studies were performed in this study. Forth, patients with longer diabetes duration (median: 16 years) received insulin treatment more frequently.

Patients were recruited between 2006 and 2011 for this study resulting in patients mainly treated with metformin, sulfonylureas or insulin-based therapy. The introduction of sodium-glucose cotransporter-2 inhibitors[24] or glucagon-like peptide 1 analogues[25] into diabetes treatment in recent years might benefit all T2D patients with PAD and ameliorate the increased mortality rates in patients with lenient glycaemic control. The novel armamentarium to treat T2D might increase safety from adverse hypoglycaemic events in these older patients; however, both drug classes were still in development at onset of our study.

Achievement of antihypertensive or lipid modifying therapy goal showed no additional benefit in this study. However, it has to be considered that the treatment goal for

systolic blood pressure was only accomplished in 60% of these patients within 1 year. Similarly obtaining LDL-C treatment goal increased continuously over 5 years reflecting necessary treatment intensification in the VMC Vienna cohort.[11] In addition, current PAD guidelines emphasize an even stricter LDL-C target below 1.8 mmol/L[26] or even below 1.4 mmol/L for extreme risk patients.[27] The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial elucidated a reduction of cardiovascular events with even lower LDL-C levels (0.78 mmol/L) in patients with cardiovascular disease by treatment with statins and an additional proprotein convertase subtilisin–kexin type 9 inhibitor (PCSK9i).[28] It is thus expected to result in a further mortality benefit by stronger LDL-C reduction in PAD patients. However, such a strong reduction at study recruitment below 1.8 mmol/L was not feasible, since PCSK9i were not available and treatment guidelines did not advocate for such strict goals.

The association of C-reactive protein and all-cause mortality has been revisited in the recent Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) study.[29] However, we cannot analyse the significance of C-reactive protein for cancer mortality in 17 cancer deaths.

The effects of patient age and glucose control on all-cause and cardiovascular mortality are independent in the whole study cohort. However, in the T2D subgroup, significant interaction between patient age and HbA1c is present. In elderly patients, the effect of glucose control on mortality has been challenged.[30] In our cohort, glucose control still exhibited a significant age-adjusted effect on all-cause (HR: 1.43, 1.14–1.79) and cardiovascular (HR: 1.76, 1.38–2.25) mortality in the type 2 diabetes subgroup.

Study limitations

Several limitations have to be considered. First, this study is of observational nature and represents a single centre experience in a limited number of stable PAD cohort and is thus only hypothesis generating. In addition, due to the limited patients sample, only limited adjustment for potential confounders was possible. Further evaluation of PAD patients including the current anti-diabetic therapy options and updated treatment guidelines in a larger study has to be performed. Second, PAD patients with critical limb ischaemia have been excluded limiting the findings to stable PAD patients. Third, patients suffering from other forms of diabetes apart of T2D were excluded from participation of this study. Fourth, historic HbA1c levels before inclusion into the study were not available due to a lack of electronic medical records.

Conclusion

The results of the ACCORD and VADT study may have translated into reduced glucose control in older patients with cardiovascular disease by the treating cardiovascular community. Admittedly, even in countries with a universal health care system, the majority of patients with T2D are not at treatment target. Our data suggest that older patients reaching treatment target benefit in increased survival. Verification of this finding could only be performed in a randomized controlled trail with different treatment targets on the basis of hypoglycaemia-avoiding treatment choices. However, whenever hypoglycaemia-avoiding treatment is available, doctors and patients would always prioritize a lower HbA1c, resulting in a regression to the mean rendering such a study unlikely.

Author contributions

C.H. performed the literature search, study design, conducted the statistical analyses, interpretation of the results and drafted the manuscript. C.T.H. revised the statistical analyses, interpretation of the results and contributed to the manuscript draft. T.W. contributed to data collection, data coordination and data management. R.K. participated in the interpretation of the results and revised the manuscript. G.-H.S. designed the VMC study cohort, supervised the statistical analyses, interpretation of the results and revised the manuscript.

Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval

This study was performed with the approval of the ethics committee of the Medical University of Vienna in accordance with the principles of the Helsinki Declaration of 1964 and its further amendments. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

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Supplemental material

Supplemental material for this article is available online.

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