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Original article

Diuretics and risk of major adverse limb events in patients with type-2 diabetes: An observational retrospective study

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ABSTRACT

Aim: In patients with type-2 diabetes mellitus (T2DM), sodium-glucose co-transporter 2 inhibitors are suspected to increase the risk of amputation. "Traditional" diuretics may increase major adverse limb events (MALEs), but the evidence is weak. We studied the association between common diuretics (i.e. thiazides, loop- and potassium-sparing diuretics) and MALEs/amputations in patients with T2DM.

Methods: Consecutive T2DM patients without cardiovascular history referred to our center for cardiovascular check-ups were retrospectively studied. Follow-up data on MALEs were collected. We used Cox models to assess the association between diuretics and MALEs, or amputation alone. A propensity score with inverse probability of diuretic treatment weighting (IPTW) analysis was performed.

Results: We studied 1309 patients, (59.5 ± 10.7 years, 51 % females) with diabetes duration of 9.1 ± 8.5 years, among whom 402 (30 %) were taking diuretics. During a follow-up of 3.8 ± 1.64 years, 121 (9.1 %) had MALEs, including 19 (1.4 %) amputations. Death occurred in 111 patients and the proportion of death was significantly different between groups: patients with diuretics $n = 49$, 44.1% vs patients without diuretics $n = 62$, 55.9 %, $P = 0.001$. Diuretics, in multivariable analysis, were associated with MALEs (aHR[95 %CI] 1.96[1.32;2.91] $P = 0.001$), even after adjustment on propensity score (aHR 1.66[1.08;2.56] $P = 0.02$) and IPTW analysis (aHR 1.76 [1.67;1.84] $P < 0.0001$). This risk was particularly increased in case of an abnormal ankle-brachial index (aHR 2.29[1.32;3.96], $P = 0.003$) at baseline. Looking at diuretic classes separately, the adjusted risk was increased with loop diuretics (aHR 2.56[1.16;5.64] $P = 0.020$), thiazides (aHR 2.21[1.37;3.57] $P = 0.001$) or potassium sparing diuretics (aHR 2.56[1.16;5.64] $P = 0.020$).

Conclusion: Diuretic treatment weighting may be associated with increased risk of MALEs. We identified several markers of increased risk of limb events where the use of diuretics should be considered with caution.

Introduction

Peripheral artery disease (PAD) is one of the most devastating complications of diabetes, with an increased risk of disability and major adverse limb events (MALEs) including limb loss [1,2]. These consequences are not only related to the increased risk of PAD in the presence of diabetes, but also the coexistence of other complications such as microvascular disease (MVD) and neuropathy. Recently, sodium-glucose co-transporter 2 inhibitors (SGLT2is), one of the newer classes of antiglycemic agents approved for the management of patients with T2DM, were reported to possibly increase amputation risk, according to one trial with canagliflozin [3]. This risk excess has also been reported in observations issued from large health claims data [4]. Some studies also suggested that they could contribute to ischemic and lower limb events in general including MALEs [5–7]. However studies with other SGLT2is have not found such risk and even the results of other studies with canaglifozin are contradictory [8,9].

While this risk is still debated, one possible reason might be related

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to the diuretic effect and increased blood concentration [10,11]. Other studies suggest a similar risk with regular diuretics, but confounding factors regarding reasons for their prescription must be considered.

We aimed to assess the long-term risk of MALEs treated by traditional diuretics in patients with type-2 diabetes (T2DM) free of any clinical cardiovascular disease. Our secondary aim was to identify risk factors for MALEs in these patients, and to assess whether the use of diuretics in the presence of these risk factors would be more specifically associated with increased risk of such events.

Materials and methods

Design and framework

This single-center study was conducted in Dupuytren University Hospital of Limoges. The patients were included from January 2007 to December 2016, and follow-up was performed until April 30th, 2021. The adult patients were referred for a cardiovascular check-up according to local protocol of follow-up of patients with T2DM. Only patients free of any atherosclerotic CVD history were retrospectively included in this study. Patients with highly suspect cardiovascular symptoms during the cardiovascular check-up (e.g., typical angina or intermittent claudication) were excluded.

Baseline data

Sociodemographic anthropometric data (age, sex, waist, height, and weight to calculate body mass index [BMI]) were collected, along with cardiovascular risk factors (smoking status, dyslipidemia defined according to history and/or blood tests, hypertension according to resting blood pressure equal or >140/90 mmHg or use of anti-hypertensive treatment, and family history of premature cardiovascular diseases), microvascular disease (MVD, a composite of any of the three following T2DM-related end-target damage reported in medical charts: retinopathy, nephropathy or neuropathy) and other comorbidities. For each leg, ankle-brachial index (ABI) was determined by taking the highest pressure between posterior tibial and dorsalis pedis arteries, divided by the highest brachial arterial systolic pressure [10]. We determined patient's ABI by the lowest value between the left and right legs and defined abnormal ABI when $\leq$ 0.90 and $\geq$ 1.40 [12]. Treatments of interest collected were: antidiabetic agents including insulin therapy, and cardiovascular therapies including diuretics classified into *i*) loop diuretics; *ii*) thiazide diuretics; and *iii*) potassium sparing diuretics. Of note, SGLT2is were not available on the French market during the study.

Outcomes

The patients were followed up until May 1st, 2021, by checking the medical charts in our tertiary care hospital as well as by making phone contacts with patients' family physicians. The primary outcome was the occurrence of MALEs, a composite of hospitalization for PAD, lower-extremity revascularization, and/or amputation. The secondary outcome was the occurrence of any amputation, irrespective of its extent. None of the reported amputations was traumatic.

Statistical analysis

The distribution of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables were reported with mean ± standard deviation. Categorical variables were reported with number and percentages (%). Chi-square tests with Yates and Fisher corrections were performed to compare qualitative variables and Mann-Whitney tests to compare quantitative variables according to the use of diuretics or not (Table 1).

The determinants of diuretic use were identified by univariate logistic regression among the 24 variables shown in Table 2. Variables with $P < 0.25$ were entered into a multivariable model. to provide a propensity score, the probability of a patient being treated with diuretics.

The survival and MALEs-free survival was assessed using Kaplan-Meier curves and comparison between groups obtained with log-rank tests. Follow-up time was defined as the period between the date of the screening visit and the date of last news (up to June 2021) for living patients without event, or the date of the event for living patients who

Table 1
Characteristics of people with type 2 diabetes mellitus according to treatment with diuretics. A follow-up study of major adverse limb events in 1309 people from Dupuytren university hospital, Limoges, France.

Variables	n	With diuretics (*n* = 402, 30.2 %)	Without diuretics (*n* = 907, 68.1 %)	*P*-values
Men	1309	196 (49)	449 (51)	.80
Age, years	1309	63 ± 10	58 ± 11	<0.001
Body mass index, kg m^{-12}	1300	**35 ± 8**	**32 ± 7**	<0.001
Waist, cm	1220	**115 ± 16**	**109 ± 15**	<0.001
Smoking	1299			
Current Smokers		58 (15)	208 (24)	.002
Past smokers		137 (35)	277 (31)	
Non-smokers		203 (51)	416 (46)	
Diabetes duration, years	1234	10.5 ± 9.2	8.6 ± 8.2	<0.001
Dyslipidemia	1291	280 (70)	583 (65)	.074
Hypertension	1305	366 (91)	455 (50)	<0.001
Family cardiovascular disease history	1298	101 (25)	215 (24)	.56
Retinopathy	1309	65 (16.2)	113 (13)	.071
Nephropathy	1309	110 (46.4)	126 (53)	<0.001
Neuropathy	1309	28 (7.0)	72 (7.9)	.54
Microvascular disease	1309	167 (40.4)	243 (59)	<0.001
Atrial fibrillation	1309	24 (6.0)	28 (3.1)	.014
Obstructive sleep apnea syndrome	1309	108 (26.9)	173 (19)	.002
Heart rate, beats/min	1244	79 ± 13	81 ± 13	.009
Hb_{A1C}, %	1105	**7.9 ± 1.7**	**8.0 ± 2.0**	.87
Total cholesterol, mmol/l	1032	180 ± 49	180 ± 43	.49
High density lipoprotein-cholesterol, mmol/l	1085	**0.4 ± 0.1**	**0.5 ± 0.1**	.99
Low density lipoprotein-cholesterol, mmol/l	1051	**1.0 ± 0.4**	**1.0 ± 0.3**	.048
Triglycerides, mmol/l	1085	**1.7 ± 1.0**	**1.7 ± 1.1**	.074
Diabetes treatments				
Insulin	1299	141 (35)	271 (30)	.068
metformin (Glucophage)	1301	292 (73)	685 (76)	.20
Other antidiabetic	1301	262 (65)	605 (67)	.50
Antiplatelets	1301	113 (38)	188 (62)	.004
Antihypertension treatment				
Betablockers	1302	113 (28)	125 (14)	<0.001
Angiotensin conversion enzyme inhibitors	1302	107 (27)	121 (13)	<0.001
Angiotensin receptor blockers	1302	255 (63)	291 (32)	<0.001
Calcium channel blockers	1302	154 (38)	141 (16)	<0.001
Diuretics				
Loop diuretics	1309	62 (15)	0 (0.0)	<0.001
Thiazide diuretics	1309	303 (75)	0 (0.0)	<0.001
Potassium sparing diuretics	1309	50 (12)	0 (0.0)	<0.001
Statins	1302	250 (62)	492 (55)	.009
Ankle-brachial index	1236	**1.1 ± 0.2**	**1.1 ± 0.2**	.82
Abnormal ankle-brachial index*	1236	71 (25)	133 (64)	.12
Outcomes composite of MALEs:				
Amputation	1309	7 (1.7)	12 (1.3)	.56
Lower-extremity revascularization	1309	48 (11.9)	14 (1.5)	<0.001
Hospitalization for PAD	1309	22 (5.4)	18 (2.0)	<0.001

Data are means (percentages) or means ± SDs (standard deviations). Hb_{A1C}: glycated hemoglobin; *abnormal ABI: ABI <0.90 or >1.40.

Table 2
Factors predictive of diuretic use in people with type 2 diabetes mellitus from Dupuytren University Hospital, Limoges, France, using univariate logistic regression models; odds ratios from a multivariable logistic regression for variables with $P < 0.25$ in the univariate analysis, selected for the propensity score, $n = 1126$.

		Univariable			Multivariable	
Variables	OR	95 %CI	*P*	OR	95 %CI	*P*
Age (yr)	1.03	1.01;1.06	.006	1.03	1.01;1.05	< 0.001
BMI (kg m^{-12})	1.07	1.01;1.12	.02	1.07	1.04;1.09	< 0.001
Waist, cm	0.99	0.97;1.02	.89	;	;	–
Smoking	1.16	1.69;1.94	.05	0.95	0.63;1.41	.80
Diabetes duration (yr)	1.00	1.00;1.02	.09	1.01	0.98;1.03	.45
Dyslipidemia	1.25	1.18;1.94	.03	0.87	0.62;1.20	.39
Hypertension	7.21	7.12;10.37	< 0.001	8.82	5.76;13.49	< 0.001
Retinopathy	1.13	0.55;2.33	.74	;	;	–
Nephropathy	1.19	0.57;2.47	.65	;	;	–
Microvascular disease	1.70	1.29;3.66	.17	1.50	1.10;2.05	.01
Atrial fibrillation	1.41	1.05;3.94	.05	0.68	0.32;1.41	.30
OSAS	0.33	0.22;0.53	.23	0.96	0.67;1.38	.82
Heart rate, beats/min	0.99	0.98;1.01	.75	;	;	–
Low density Lipoprotein-cholesterol, mmol/l	0.93	0.55;1.58	.80	;	;	–
Triglycerides, mmol/l	1.27	0.97;1.64	.77	;	;	–
Insulin	1.96	1.75;2.03	.24	1.05	0.75;1.46	.77
metformin (Glucophage)	0.97	0.60;1.55	.72	;	;	–
Antiplatelets	0.83	0.54;1.27	.40	;	;	–
Betablockers	0.69	0.44;1.10	.28	;	;	–
Angiotensin conversion enzyme inhibitors	0.36	0.21;0.62	.48	;	;	–
Angiotensin receptor blockers	0.30	0.19;0.49	.51	;	;	–
Calcium channel blockers	0.52	0.35;0.79	.30	;	;	–
Statins	1.06	0.70;1.59	.78	;	;	–
Abnormal ABI*	1.29	1.19;2.11	.12	1.17	0.79;1.70	.82

All data are OR: odds ratios and 95 %CI: 95 % confidence interval. ABI: ankle-brachial index; BMI: body mass index; OSAS: obstructive sleep apnea syndrome. *abnormal ABI: ABI < 0.90 or >1.40, $n = 1$ 126.
Age, BMI, hypertension and microvascular disease were included in the propensity score.

had an event, or the date of death. A secondary outcome amputation, studied diuretic users and non-users using Kaplan Meier curves and the log rank test.

Cox proportional hazard univariate model was used thereafter to identify variables associated with MALEs. We selected variables with a *P*-value < 0.10 and added them into a multivariable stepwise regression Cox proportional hazard model. We then picked out those that had $p < 0.05$ in the multivariable model from those selected in the univariate Cox model, considered as statistically significant. To assess the association between diuretics and MALEs, we also performed a multivariable stepwise regression Cox proportional hazard model adjusted on propensity score. To estimate the strength of those associations, hazard ratios (HRs) and 95 % confidence interval (95 %CI) were calculated.

Variables associated with outcomes from the above analyses were used to adjust the HRs of MALEs for diuretic use; in a secondary analysis, the propensity score was also used to adjust the HR.

Finally, inverse probability weighting with the propensity score was used in multivariable models to create a pseudo population to balance baseline patient characteristics in the diuretic user and non-user groups [13]. We analyzed variable by variable whether there were any interactions between the variables predictive of MALEs and diuretic use.

Data were analyzed with IBM SPSS 21.0 software package for Windows.

Ethics

All data retrieved and analyzed were non-experimental, and consent was therefore not necessary according to the national law during the assessment period.

Results

From 2007 to 2016, 1331 T2DM patients free from clinical atherosclerotic CVD had a cardiovascular check-up. Among them 1309 (742 women and 567 men) were finally included in this study. The flowchart of patient selection is shown in the supplemental data.

Population characteristics

Main characteristics of the population and their comparison according to diuretic use are presented in Table 1. The mean age was 60 ±11 years, with an average diabetes duration of 9.1 ± 8.5 years. Among them, 412 (31 %) patients were on insulin. Four-hundred and two patients were tking diuretics, of whom 366 (91 %) were hypertensive. Patients under diuretics were older, with a longer diabetes duration and a higher proportion of cardiovascular risk factors. Thiazide diuretics were more frequently used (75 %), followed by loop diuretics (15 %) and potassium sparing diuretics (12 %). The indications were mostly hypertension. <1 % had a combination of two diuretics. Determinants of diuretic use included in the propensity score were: age, BMI, hypertension, and microvascular disease (Table 2). Of note, the average ABI value was not significantly different at baseline between the two groups.

Outcomes and MALES

During an average follow-up period of 7 years, death was reported in 111 patients and occurred more frequently in patients without diuretics (patients with diuretics ($n = 49$), 44.1% vs ($n = 62$), 55.9 % patients without diuretics, $P = 0.001$).

During the follow-up period, 121 (9.1 %) patients experienced MALEs, including 19 (1.4 %) amputations. As compared to their counterparts, patients under diuretics at baseline experienced more often MALEs, (Fig. 1, **panel A***P* < 0.0001). In univariate analysis, the use of diuretics was associated with increased risk of MALEs (HR[95 %CI] 2.41 [1.68;3.46] $P < 0.001$). Regarding diuretics classes, similar trends were observed for the three diuretic drug groups, although the results were only significant for loop and thiazide diuretics but not with potassium sparing diuretics (Fig. 2**, panels B, C, D**). As a secondary outcome, the occurrence of amputation was studied according to the diuretic use at baseline (**Figures S1 and S2; see Y figures associated with this article on line**). We found no statistical difference between the two groups according to the diuretic status.

Diuretics, in multivariable analysis, were associated with incident

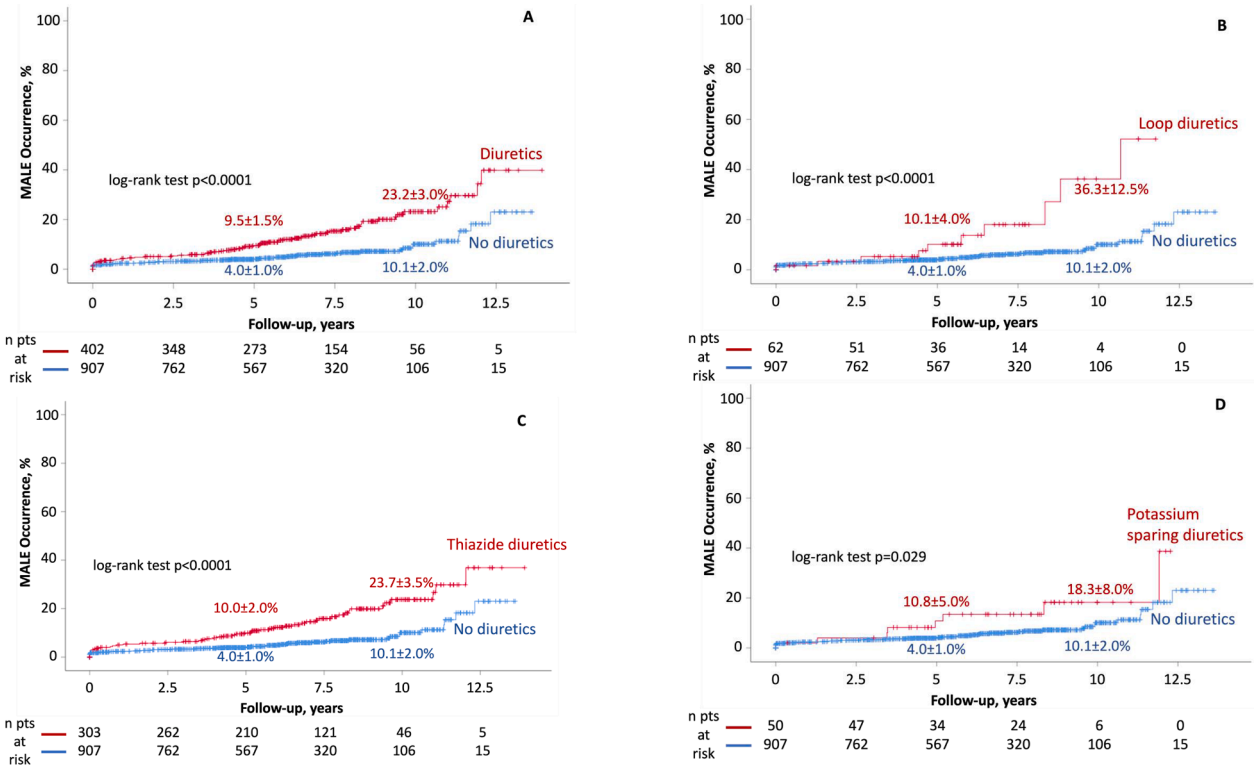

Fig. 1. Kaplan Meier curves and percentages with MALE according to A: all diuretics vs no diuretics, B: loop vs no diuretics, C: thiazide vs no diuretics, D: potassium sparing vs no diuretics, For 1309 people with type 2 diabetes from Dupuytren University Hospital, Limoges, France. MALE incidence at 5 and 10 years by diuretic use is reported on each figure.

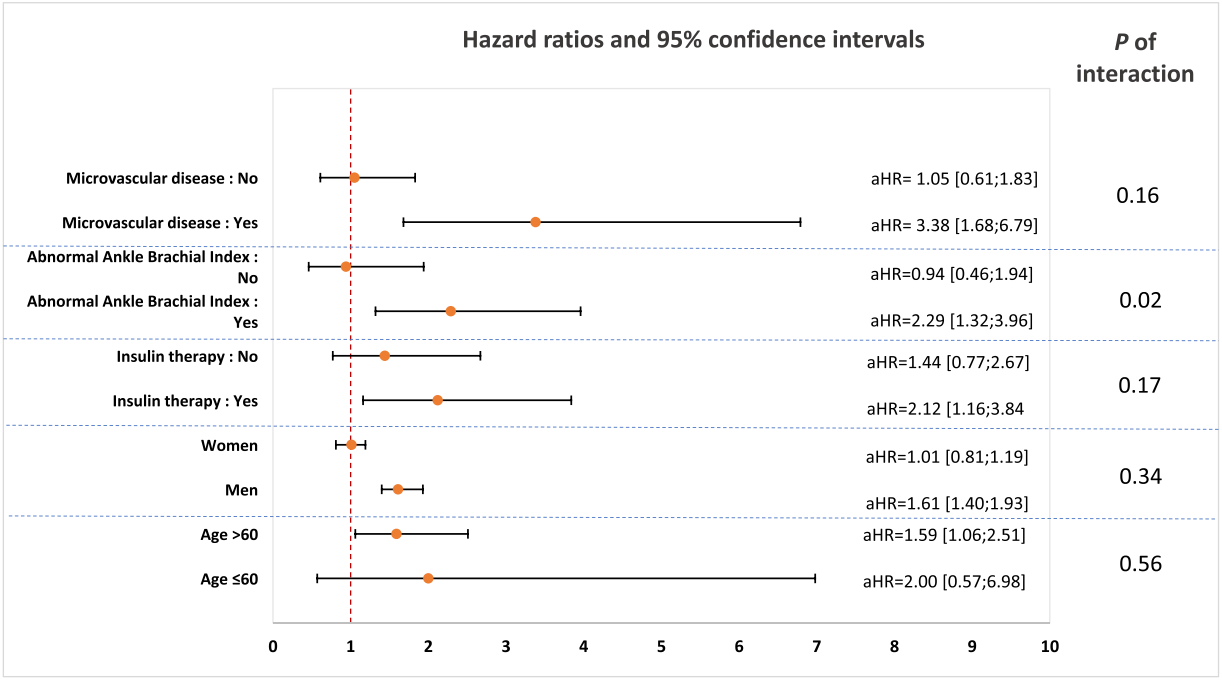

Fig. 2. Forest plot of stratified analysis evaluating diuretics effects on MALEs between different sub-groups of co-variables studied and interaction test. *ABI : ankle-brachial index. MVD : microvascular disease.*

MALEs, after adjustment for propensity score (aHR 2.38[1.54;3.71] $P < 0.0001$). This was also significant in those under loop diuretics (aHR 2.56[1.16;5.64] $p = 0.020$), thiazides (aHR 2.21[1.37;3.57] $P = 0.001$) or potassium sparing diuretics (aHR=2.56[1.16;5.64] $P = 0.020$). Results after adjustment for the propensity score are presented in Table 3.

In multivariable analysis, independent statistically significant determinants of MALEs were: age, male sex, MVD, insulin use, and abnormal ABI (Table 4).

We then stratified the association between diuretics and MALEs according to the presence or absence of predictors for these events (Fig. 2).

Table 3
Risk of MALEs under diuretics in multivariable analysis and after adjustment on propensity score, $n = 1126$.

Variables	aHR	95 % CI	*P*-value
Diuretics	2.38	1.54;3.71	< 0.001
Loop diuretics	2.56	1.16;5.64	0.020
Thiazide diuretics	2.21	1.37;3.57	0.001
Potassium sparing diuretics	2.56	1.16;5.64	0.020

Variables used for adjustment on propensity score: age, body mass index, hypertension, and microvascular disease.

We found a high risk in patients with abnormal ABI (aHR 2.29 [1.32;3.96] $P = 0.003$). We found no significant interaction for the determinants of outcome according to the use of diuretics, except for ABI groups: the association of diuretics with incident MALEs was significantly higher in case of abnormal ABI (aHR 2.29[1.32;3.96] $P = 0.001$ vs. normal ABI (aHR 0.94[0.46;1.94] $P = 0.31$, P for interaction = 0.02).

Propensity score with IPTW analysis

The propensity score was calculated in 1126 patients. Using the IPTW analysis, Cox proportional hazard model showed diuretics remaining significantly associated with MALEs: aHR 1.76[1.67;1.84] $P < 0.0001$.

Discussion

Our study confirms the hypothesis that in patients with T2DM, the use of diuretics appears associated with incident MALEs, even after adjustment for the propensity score and significant confounding factors. Using IPTW analysis, the Cox proportional hazard model showed that diuretics remained significantly associated with MALEs: aHR 1.76 [1.67;1.84] $P < 0.0001$. While some other studies suggested such association [5,11], this is to our knowledge the most bias-controlled report in a large cohort of T2DM without clinical history of cardiovascular disease. In addition, our study found that patients with abnormal ABI ($\leq$ 0.90 or $\geq$ 1.40) were at high risk of MALEs where the use of diuretics might be more detrimental.

We found that age, male sex, MVD, insulin therapy and abnormal ABI were significantly associated with MALEs. The lack of a significant association between duration of diabetes and MALEs, while the association with insulin treatment was significant, could be explained by a collinearity bias between insulin treatment and diabetes duration. Indeed, Yusof *et al.* previously reported that the risk of MALEs with diuretics was particularly increased in case of diabetic duration >10 years [14].

Several studies have shown that microvascular complications of diabetes are associated with increased risk of amputation and other lower extremity artery disease (LEAD) events [15–17]. In the ADVANCE clinical trial, the highest risk of LEAD was observed in patients with microalbuminuria or retinal photocoagulation therapy, as proxies for MVD in diabetes [17].

In our study, the incidence of MALEs was higher in diuretic users than non-users. Similar results were found by Potier *et al.* in a French prospective cohort study [6]. Previous studies have already suggested a similar association in diabetic and non-diabetic patients [18,19]. In our study, we found an increased incidence of MALEs regardless of drug class. One previous study showed that the use of loop diuretics could increase lower-limb events (odds ratio, OR 1.5 [95 % CI 1.1;2.1], $P = 0.010$) [20], while another one found an increased risk under thiazide diuretics (OR 6.11 [1.32;28.27]) [19]. However, in those studies, no information was reported regarding all diuretics in general. Hypovolemia and dehydration could affect blood rheology by increasing blood viscosity with potential effect on limb perfusion, especially when this is also hampered by other macro- or microvascular disease. Previous studies suspected diuretics as responsible of leg and/or mesenteric ischemia due to extracellular volume deficit [21,22]. Kim *et al.* showed that isovolemic dilution treatment of critical limb ischemia patients reduced the rate of limb events and even increased amputation-free survival [10]. Recently, it has been suggested that intermittent claudication and rest pain can be reduced by hyper-hydration [23,24]. It has

Table 4
Cox regression model of association between patient characteristics and MALEs.

		Univariable			Multivariable ($n = 950$)		
Variables	n	HR	95 % CI	*P*-values	HR	95 % CI	*P* -values
Men	1331	1.88	1.30;2.73	.001	1.92	1.26;2.93	.002
Age, years	1331	1.05	1.03;1.07	< 0.001	1.04	1.02;1.06	< 0.001
Body mass index, kg m^{-12}	1322	0.99	0.97;1.02	.91	–	–	–
Waist, cm	1242	1.00	0.99;1.01	.35	–	–	–
Current Smokers	1320	1.45	1.10;1.62	.007	–	–	–
Diabetes duration, years	1255	1.02	1.01;1.04	.032	–	–	–
Dyslipidemia	1311	1.16	0.78;1.73	.45	–	–	–
Hypertension	1327	2.29	1.47;3.59	< 0.001	–	–	–
Family cardiovascular history	1320	0.61	0.37;1.98	.043	–	–	–
Microvascular disease	1331	2.85	1.98;4.09	< 0.001	1.93	1.28;2.92	.002
Atrial fibrillation	1331	2.03	1.03;4.01	.041	–	–	–
Obstructive sleep apnea syndrome	1331	0.95	0.62;1.45	.82	–	–	–
Heart rate, beats/min	1263	0.99	0.97;1.00	.43	–	–	–
Hb_{A1C}, %	1114	1.09	0.99;1.20	.077	–	–	–
Total cholesterol, mmol/l	1045	1.28	0.83;1.95	.26	–	–	–
High density lipoprotein cholesterol, mmol/l	1098	1.41	0.39;5.02	.59	–	–	–
Low density lipoprotein cholesterol, mmol/l	1065	1.16	0.66;2.05	.59	–	–	–
Triglycerides, mmol/l	1098	1.11	0.93;1.32	.24	–	–	–
Insulin	1299	1.89	1.32;2.72	< 0.001	1.53	1.03;2.28	.033
metformin (Glucophage)	1301	0.58	0.40;0.85	.005	–	–	–
Other antidiabetic	1301	0.85	0.58;1.24	.39	–	–	–
Antiplatelets	1301	1.84	1.26;2.67	.001	–	–	–
Betablockers	1302	1.34	0.87;2.05	.18	–	–	–
Angiotensin conversion enzyme inhibitor	1302	1.68	1.12;2.54	.011	–	–	–
Angiotensin receptor blocker	1302	1.44	1.00;2.06	.048	–	–	–
Calcium channel blocker	1302	1.56	1.05;2.29	.024	–	–	–
Statin	1302	1.44	0.99;2.11	.056	–	–	–
Abnormal ABI	1257	3.03	2.05;4.48	< 0.001	2.11	1.39;3.21	< 0.001

The data shown are hazard ratio (HR) (95 % CI). Hb_{A1C}: glycated hemoglobin; *abnormal ABI: ABI ⟨ 0.90 or ⟩ 1.40.

also been shown that increased hematocrit or copeptin, both markers of blood volume, were significantly associated with incident LEAD and MALEs in T2DM patients [11,25]. Data on hematocrit were lacking in our cohort study. Also, a recent systematic review and meta-analysis showed an increased risk of amputation in patients with or at risk of LEAD under diuretics (OR 1.75[1.53;1.99] $P < 0.001$) mostly in the presence of other comorbidities, including diabetes [26]. Regarding our results as compared to another study performed in France some time ago [6], our study showed lower rates of amputation because our population was at lower risk. Indeed, we focused our study on patients without any clinical cardiovascular disease, while Potier *et al.* included a mix of patients with (30 %) or without (70 %) CVD history. We confirmed that in a population at lower cardiovascular risk, diuretic use was associated with MALE.

Lastly, propensity scores were used, allowing to minimize confounders effects between patients with and without diuretics. The use of propensity scores maintained the association between diuretics and MALEs.

Study limitations

This was a retrospective observational study so by its design and lack of randomization, some confounding bias may affect our conclusions. However, we did our best to control for confusion bias, especially by using propensity scores and IPTW analysis, although the indication for the use of diuretics could not be systematically ascertained, some patients had been taking these treatments for a long while. Also, we analyzed the use of diuretics at baseline, and therefore could not assess the potential effect of prescription of diuretics over time. In addition, we did not have information on different diuretic drugs within each of the three diuretic classes. We were also unable to test different doses or duration of use of diuretics. The information on the level of amputation was not always available so we could not provide this information precisely. The proportion of death was significantly different between the groups. The risk of death was particularly low in these asymptomatic patients in primary prevention. Indeed, death occurred in 111 patients, statistically more frequently in patients not receiving diuretics. This result suggests that there is no competing risk in patients treated with diuretics.

Importantly, we have studied here only patients with T2DM without clinical CVD, so the extrapolation of our data to those with CVD requires further studies. However, the relatively large size of the cohort managed homogeneously in a same center, non- use of SGLT2is which may interact via their effects on MALEs, and the focus on atherosclerotic CVD-free asymptomatic patients at baseline can be considered as strengths of our study.

Conclusion

In this population of T2DM patients without clinical CVD, we consolidate and extend previous findings on the risk of occurrence of major adverse limb events with diuretics. The risk of MALEs particularly increased in subclinical PAD (abnormal ABI).

Until we have more data, the prescription of diuretics should be considered with caution, especially in the presence of an abnormal ABI. Further analyses in larger databases along with assessment of rheologic and vascular markers are required to confirm and better understand related mechanisms.

Appendix supplementary material

Supplementary materials (Figures S1 - S2) associated with this article can be found at http://www.scincedirect.com at doi …

Figures S1 and S2.

Flowchart of patients' selection. *MALEs : Major Adverse Lower Limb Events*

Kaplan Meier curve and percentages with amputation according to all diuretics. Incidence of amputation at 5 and 10 years by diuretic use is reported on the figure.

CRediT authorship contribution statement

Khadija Ba: Writing – original draft, Formal analysis. **Laurence Salle:** Writing – original draft, Formal analysis. **Laudy Serhal:** Writing – review & editing, Investigation. **Mamadou Adama Sow:** Writing – review & editing. **Julien Magne:** Writing – review & editing, Methodology. **Philippe Lacroix:** Writing – review & editing, Investigation. **Lucie Chastaingt:** Writing – review & editing, Investigation. **Victor Aboyans:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

J Magne - Servier, AstraZeneca

V Aboyans - Amarin, AstraZeneca, Bayer, BMS/Pfizer alliance, Boehringer-Ingelheim, NovoNordisk, Vifor.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2024.101582.

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