Clinical Outcomes in Patients With Type 2 Diabetes Mellitus and Peripheral Artery Disease

Results From the EXSCEL Trial

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BACKGROUND: Recent trials have identified anti–diabetes mellitus agents that lower major adverse cardiovascular event (MACE) rates, although some increase rates of lower-extremity amputation (LEA). Patients with peripheral artery disease (PAD) have greater incidence of diabetes mellitus and risk for LEA, prompting this investigation of clinical outcomes in patients with diabetes mellitus and PAD in the EXSCEL trial (Exenatide Study of Cardiovascular Event Lowering).

METHODS: EXSCEL evaluated the effects of once-weekly exenatide (a GLP-1 [glucagon-like peptide-1] receptor agonist) versus placebo on the rates of the primary composite MACE end point (cardiovascular death, myocardial infarction, or stroke) among patients with type 2 diabetes mellitus. In this post hoc analysis, we assessed the association of baseline PAD with rates of MACE, LEA, and the effects of exenatide versus placebo in patients with and without PAD.

RESULTS: EXSCEL included 2800 patients with PAD (19% of the trial population). These individuals had higher unadjusted and adjusted rates of MACE compared with patients without PAD (13.6% versus 11.4%, respectively) as well as a higher adjusted hazard ratio (adjusted hazard ratio, 1.13 [95% CI, 1.00–1.27]; P=0.047). Patients with PAD had higher all-cause mortality (adjusted hazard ratio 1.38 [95% CI, 1.20–1.60]; P<0.001) and more frequent LEA (adjusted hazard ratio 5.48 [95% CI, 4.16–7.22]; P<0.001). Patients treated with exenatide or placebo had similar rates of MACE and LEA, regardless of PAD status.

CONCLUSIONS: EXSCEL participants with PAD had higher rates of all-cause mortality and LEA compared with those without PAD. There were no differences in MACE or LEA rates with exenatide versus placebo.

VISUAL OVERVIEW: A visual overview is available for this article.

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Key Words: amputation ■ exenatide ■ diabetes mellitus ■ lower extremity ■ myocardial infarction

Large randomized controlled trials in patients with diabetes mellitus (DM) have identified agents that confer cardiovascular benefits, but data for their effect on patients with peripheral artery disease (PAD) remain limited. Lower-extremity PAD affects ≈8.5 million Americans over the age of 40 years and 202 million people worldwide; many of these patients also have DM.[1] Lower rates of major adverse cardiovascular events (MACE; cardiovascular mortality, nonfatal myocardial infarction (MI), and nonfatal stroke) were seen with 3 GLP-1 (glucagon-like peptide-1) receptor agonists—liraglutide, semaglutide, and albiglutide—in the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), SUSTAIN-6

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For Sources of Funding and Disclosures, see page 8.

WHAT IS KNOWN

- Large randomized controlled trials have identified various GLP-1 (glucagon-like peptide-1) agonists and SGLT2 (sodium-glucose cotransporter-2) inhibitors that improve glycemic control, and many are associated with a reduction in major adverse cardiovascular events rates, but there are concerns for some off-target effects, such as canagliflozin's association with higher rates of lower-extremity amputations.
- EXSCEL (Exenatide Study of Cardiovascular Event Lowering) studied the cardiovascular effects of adding once a week exenatide to usual care in diabetic patients and showed that the primary end point of major adverse cardiovascular event occurred in 11.4% of patients in the exenatide group and 12.2% of patients in the placebo group (hazard ratio, 0.91 [95% CI 0.83–1.00]).

WHAT THE STUDY ADDS

- Describes the baseline characteristics and cardiovascular risk factors for EXSCEL participants with and without peripheral artery disease (PAD) and shows that patients with PAD were less likely to be on optimal medical therapy for secondary prevention of cardiovascular disease.
- Describes the association of PAD with major adverse cardiovascular events, all-cause mortality, and lower-limb events.
- Examines the treatment effect of exenatide versus placebo by PAD status on major adverse cardiovascular events, all-cause death, and lower-limb events, and shows that exenatide was not associated with lower-extremity amputations in diabetic patients with or without PAD.

Nonstandard Abbreviations and Acronyms

CANVAS	Canagliflozin Cardiovascular Assessment
DECLARE-TIMI-58	Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58
DM	diabetes mellitus
EMPA-REG OUTCOME	BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
EXSCEL	Exenatide Study of Cardiovascular Event Lowering
GLP-1	glucagon-like peptide-1
HR	hazard ratio
HR_{adj}	adjusted hazard ratio
LEA	lower-extremity amputation
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MACE	major adverse cardiovascular event
MI	myocardial infarction
PAD	peripheral artery disease
SGLT2	sodium-glucose cotransporter-2
SUSTAIN-6	Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes

(Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes), and Harmony Outcomes trial, respectively.[2–4] Although lixenatide and exenatide did not reduce MACE compared to placebo, pooled data from major randomized controlled trials studying GLP-1 receptor agonists demonstrated a 10% relative risk reduction in MACE with this class of agents (hazard ratio [HR] 0.90 [95% CI, 0.82–0.99]; P=0.03).[5–7] Additionally, 2 SGLT2 (sodium-glucose cotransporter-2) inhibitors, canagliflozin, and empagliflozin, both reduced rates of MACE.[8,9] However, canagliflozin led to a near doubling of lower-extremity amputation (LEA) rates when compared with placebo (HR, 1.97 [95% CI, 1.41–2.75]), with a majority of amputations occurring at the level of the toe or metatarsal.[8] To offer safe and effective medications to patients, it is important to study how these new agents affect patients with concurrent PAD and DM.

In this analysis of the Exenatide Study of Cardiovascular Event Lowering trial (EXSCEL), we aimed to (1) describe differences in baseline clinical characteristics and cardiovascular risk factors in patients with and without PAD; (2) examine the association between PAD and cardiovascular and lower-limb events; and (3) assess the effect of exenatide on cardiovascular and lower-limb adverse events in the PAD population.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. EXSCEL was a double-blind, randomized controlled trial that studied the cardiovascular effects of adding once-weekly exenatide to usual care by randomizing 14 752 patients with type 2 DM to receive subcutaneous injection of either 2 mg of exenatide or matched placebo. Patients were followed for an average of 3.2 years. The study design and rationale have been described.[10] The trial's primary composite end point of cardiovascular death, nonfatal MI, and nonfatal stroke occurred in 11.4% of patients in the exenatide group and 12.2% of patients in the placebo group (HR, 0.91 [95% CI, 0.83–1.00]).[7]

Adults with type 2 DM, defined as glycated hemoglobin level of 6.5% to 10%, were eligible to enroll in the trial, and

73% of enrolled patients had previous cardiovascular disease defined as coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic PAD. PAD was defined as including prior nontraumatic amputation due to history of vascular disease, current symptoms of intermittent claudication, confirmation by an ankle-brachial index <0.90, or history of surgical or percutaneous lower-extremity revascularization procedure.

Key exclusion criteria comprised the following: >2 episodes of severe hypoglycemia requiring third-party assistance in the preceding year, end-stage renal disease, or an estimated glomerular filtration rate <30 mL/(min·1.73 m^2) of body surface area, previous treatment with a GLP-1 receptor agonist, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, and a baseline calcitonin level >40 ng/L. The trial was designed and overseen by a steering committee, and an independent data and safety monitoring committee performed regular safety surveillance. Patients were monitored for adverse events over the course of the trial and a 90-day post-trial follow-up period. The site investigator collected information on adverse events, including amputations, and captured them on the case report form. All patients provided written informed consent. Institutional review board approval was required at all participating institutions.

Outcomes

The primary efficacy outcome was the first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. Secondary efficacy outcomes were all-cause mortality, the individual components of the primary outcome, and hospitalizations for acute coronary syndrome or heart failure. An independent clinical events classification committee, whose members were unaware of group assignments, adjudicated the primary and secondary efficacy outcomes. Additionally, postrandomization data for prespecified events of clinical interest were collected on specific clinical events pages. Lower-extremity end points, including the first occurrence of nontraumatic LEA, gangrene, and endovascular or surgical lower-extremity revascularization were ascertained at each visit by EXSCEL investigators, but these events were not adjudicated.

Statistical Analysis

This study is a post hoc subgroup analysis of the EXSCEL trial. Cox hazards regression models were used to examine the association between PAD and efficacy and safety outcomes, specifically cardiovascular and lower-limb events, and to assess the effect of exenatide as compared to placebo on cardiovascular and lower-limb events in the subgroup of patients with PAD.

For each outcome of interest, we used proportional hazards models to estimate the unadjusted HR comparing patients with a history of a PAD event at baseline versus patients who did not have a history of PAD. To estimate adjusted HRs, the following adjustment covariates (all significant at the level of $P<0.05$ in univariate analysis) were added to the models: age, sex, race, DM duration, glycated hemoglobin group, smoking status, and prior cardiovascular event at baseline, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, aspirin, β-blocker, clopidogrel, other antiplatelet agents, and statin. These intrinsic patient-level variables were selected based off previously published risk models and thought to be independently associated with outcomes.[11]

Additionally, because 73% of participants in the original trial had established prior cardiovascular disease, we repeated the above analyses comparing subjects with PAD to those without PAD but with prior cardiovascular events.

To assess whether there was a differential effect of exenatide on each outcome by PAD status, models were constructed, including an interaction term between treatment and PAD status. The *P* value of the test of the interaction term was used to determine whether an interactive effect existed. Additionally, unadjusted models were fitted within the baseline PAD status subgroups to estimate HRs comparing exenatide versus placebo. We repeated this analysis in all subjects with prior cardiovascular disease to detect differences from the overall trial population. The Kaplan-Meier method was used to calculate event rates. Analyses were conducted using SAS software version 9.4 (SAS Institute).

RESULTS

Patient Characteristics

The trial was designed such that ≈70% of enrolled patients would have had previous cardiovascular events, including a manifestation of coronary artery disease, ischemic cerebrovascular disease, or PAD. Of the 14 752 patients enrolled in EXSCEL, 2800 (18.9%) had documented PAD. Of these, 345 had a prior endovascular or surgical revascularization procedure, and 546 had a nontraumatic amputation at the time of randomization. Baseline patient demographics and clinical characteristics by the presence or absence of PAD are shown in Table 1. Patients with PAD were more likely to be black (10.6% versus 4.9%), had lower incidence of coronary artery disease (35.8% versus 56.8%), and were less likely to have had a prior MI (20% versus 34.5%) when compared with patients without PAD. Patients with PAD were more likely to be on insulin (54.8% versus 44.4%) and less likely to be on a statin (65.8% versus 75.3%), a β-blocker (45.4% versus 58.1%), an angiotensin-converting enzyme inhibitor (45.2% versus 49.5%), or aspirin (57.3% versus 65.0%), when compared with those without PAD. Of the 11 951 participants without PAD, there were 8045 (67%) who also had previous cardiovascular disease (as defined by coronary artery disease, MI, or cerebrovascular disease).

Clinical Outcomes (MACE and Limb Outcomes)

MACE occurred more frequently in patients with PAD compared with those without (13.6% versus 11.4%, respectively; unadjusted HR, 1.36 [95% CI, 1.21–1.52]; $P<0.001$; Table 2). This difference persisted after adjustment for patient characteristics and medications (adjusted hazard ratio [HR_{adj}], 1.13 [95% CI, 1.00–1.27]; $P=0.047$). Patients with PAD did have higher adjusted rates of cardiovascular death when compared with patients without PAD (6.5% versus 4.5%; HR_{adj}, 1.34 [95% CI, 1.14–1.62]; $P=0.001$). All-cause mortality was

Table 1. Baseline Demographics and Patient Characteristics by History of PAD

	PAD; N=2800	No PAD; N=11 951	All Participants; N=14 751
Age, y	62.4 (9.1)	61.8 (9.5)	61.9 (9.4)
Female sex (%)	40.7	37.3	38.0
Race			
White	2108/2798 (75.3)	9066/11 948 (75.9)	11 174/14 746 (75.8)
Black	297/2798 (10.6)	581/11 948 (4.9)	878/14 746 (6.0)
Asian	136/2798 (4.9)	1316/11 948 (11.0)	1452/14 746 (9.8)
Hispanic	244/2798 (8.7)	890/11 948 (7.4)	1134/14 746 (7.7)
Body mass index, kg/m^2	31.8 (5.9)	32.9 (6.5)	32.7 (6.4)
Duration of DM, y	13.9 (8.7)	12.9 (8.2)	13.1 (8.3)
HbA1c, %	8.2 (1.0)	8.1 (1.0)	8.1 (1.0)
eGFR, mL/min/1.73m^2	75.5 (23.8)	79.0 (24.2)	78.4 (24.1)
Cigarette smoking status			
Current	380/2800 (13.6)	1341/11 944 (11.2)	1721/14 744 (11.7)
Never	1225/2800 (43.8)	6008/11 944 (50.3)	7233/14 744 (49.1)
Prior history			
Coronary artery disease	1001/2800 (35.8)	6792/11 951 (56.8)	7793/14 751 (52.8)
Cerebrovascular disease	459/2800 (16.4)	2050/11 950 (17.2)	2509/14 750 (17.0)
Prior myocardial infarction	559/2800 (20.0)	4120/11 951 (34.5)	4679/14 751 (31.7)
Antihyperglycemic agents			
Biguanides	2018/2800 (72.1)	9276/11 951 (77.6)	11 294/14 751 (76.6)
Sulfonylurea	985/2800 (35.2)	4415/11 951 (36.9)	5400/14 751 (36.6)
Thiazolidinedione	74/2800 (2.6)	504/11 951 (4.2)	578/14 751 (3.9)
Insulin	1533/2800 (54.8)	5303/11 951 (44.4)	6836/14 751 (46.3)
DPP-4 inhibitors	303/2800 (10.8)	1900/11 951 (15.9)	2203/14 751 (14.9)
SGLT2 inhibitors	19/1869 (1.0)	58/6671 (0.9)	77/8540 (0.9)
Antihypertensive, antianginal, and other cardiovascular medications			
ACE inhibitor	1266/2800 (45.2)	5915/11 951 (49.5)	7181/14 751 (48.7)
Angiotensin receptor blocker	879/2800 (31.4)	3727/11 951 (31.2)	4606/14 751 (31.2)
β-blocker	1270/2800 (45.4)	6940/11 951 (58.1)	8210/14 751 (55.7)
Aspirin	1605/2800 (57.3)	7774/11 951 (65.0)	9379/14 751 (63.6)
Clopidogrel/ticlopidine	492/2800 (17.6)	2032/11 951 (17.0)	2524/14 751 (17.1)
Lipid-lowering medication	1951/2800 (69.7)	9418/11 951 (78.8)	11 369/14 751 (77.1)
Statin	1843/2800 (65.8)	9001/11 951 (75.3)	10 844/14 751 (73.5)

Values shown are mean (SD) or n/N (%), except where indicated otherwise. ACE indicates angiotensin-converting enzyme; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; PAD, peripheral artery disease; and SGLT2, sodium-glucose cotransporter-2.

higher in patients with PAD (10.0%) when compared with patients without PAD (6.8%; HR_{adj}, 1.38 [95% CI, 1.20–1.60]; $P<0.001$). Additionally, rates of first occurrence of fatal or nonfatal stroke were higher in patients with PAD (3.5%) when compared with patients without PAD (2.6%; HR_{adj}, 1.29 [95% CI, 1.01–1.65]; $P=0.044$). When compared with patients without PAD, patients with PAD had higher unadjusted and adjusted rates of nontraumatic amputations, gangrene, endovascular revascularization, and surgical revascularization (Table 2).

MACE occurred at a rate of 13.6% in patients with PAD and 14.4% in those without PAD but with previous cardiovascular disease (HR_{adj}, 1.12 [95% CI, 0.99–1.27]; $P=0.062$), changing to nonsignificance largely due to a reduction in population. After adjustment, there were no significant differences in all other outcomes, including all-cause mortality and lower-limb events, between the population with previous cardiovascular disease compared with the overall population.

Treatment Effects of Exenatide

There was no significant difference in MACE in patients with PAD who received Exenatide or placebo (exenatide 12.8% versus placebo 14.5%; HR, 0.85 [95% CI, 0.69–1.04]) and in those without PAD (exenatide 11.1%

Table 2. Association Between Baseline PAD and Outcomes

Outcomes	PAD N=2800	No PAD N=11 951	Unadjusted Model HR (95% CI)	*P* Value	Adjusted Model* HR (95% CI)	*P* Value
Primary end point						
MACE	382 (13.6%)	1362 (11.4%)	1.36 (1.21–1.52)	<0.001	1.13 (1.00–1.27)	0.047
Cardiovascular death	182 (6.5%)	541 (4.5%)	1.70 (1.44–2.02)	<0.001	1.36 (1.14–1.62)	0.001
Nonfatal MI	184 (6.6%)	762 (6.4%)	1.16 (0.98–1.36)	0.077	0.95 (0.80–1.12)	0.522
Nonfatal stroke	86 (3.1%)	276 (2.3%)	1.50 (1.18–1.91)	0.001	1.28 (0.98–1.66)	0.066
Secondary end points						
All-cause death	280 (10.0%)	811 (6.8%)	1.77 (1.55–2.03)	<0.001	1.38 (1.20–1.60)	<0.001
First occurrence of nonfatal or fatal MI	195 (7.0%)	781 (6.5%)	1.20 (1.02–1.40)	0.026	0.98 (0.83–1.15)	0.793
First occurrence of nonfatal or fatal stroke	97 (3.5%)	308 (2.6%)	1.51 (1.20–1.90)	<0.001	1.29 (1.01–1.65)	0.044
Hospitalization for ACS	217 (7.8%)	955 (8.0%)	1.07 (0.92–1.24)	0.363	0.89 (0.76–1.03)	0.122
Hospitalization for heart failure	102 (3.6%)	348 (2.9%)	1.44 (1.15–1.80)	0.001	1.16 (0.92–1.46)	0.219
Limb events						
Lower-limb composite event	290 (10.4%)	233 (2.0%)	6.14 (5.17–7.31)	<0.001	5.53 (4.58–6.66)	<0.001
Amputation (nontraumatic)	139 (5.0%)	108 (0.9%)	6.12 (4.75–7.87)	<0.001	5.48 (4.16–7.22)	<0.001
Gangrene	96 (3.4%)	71 (0.6%)	6.44 (4.73–8.76)	<0.001	6.03 (4.29–8.48)	<0.001
Lower-extremity endovascular revascularization	126 (4.5%)	92 (0.8%)	6.69 (5.10–8.76)	<0.001	5.27 (3.96–7.00)	<0.001
Lower-extremity surgical revascularization	69 (2.5%)	36 (0.3%)	9.19 (6.12–13.80)	<0.001	8.35 (5.44–12.82)	<0.001

Values shown are n (%), except where indicated otherwise. ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; HR, hazard ratio; MACE, major adverse cardiac event; MI, myocardial infarction; and PAD, peripheral artery disease.

*Adjusted model includes PAD status, age, sex, race, diabetes mellitus duration, hemoglobin A1c status, smoking status, prior cardiovascular event, ACE inhibitor or angiotensin receptor blocker, aspirin, β-blocker, clopidogrel, other antiplatelet agents, statin.

versus placebo 11.7%; HR, 0.94 [95% CI, 0.84–1.04] interaction *P*=0.42; Table 3 and Figure 1). There was no treatment interaction associated with exenatide for the individual components of MACE, regardless of PAD status (all *P*>0.05).

Finally, there was no differential treatment effect on rates of lower-limb composite events, nontraumatic amputations, gangrene, and endovascular/surgical revascularization procedures in all participants (Figure 2). Specifically, treatment with exenatide or placebo had similar rates of nontraumatic amputations in those with PAD (5.0% in exenatide versus 4.9% in placebo; HR, 0.99 [95% CI, 0.71–1.38]) and in those without PAD (0.9% in exenatide versus 0.9% in placebo; HR, 0.96 [95% CI, 0.66–1.41] interaction *P*=0.92).

Lastly, the treatment effects of exenatide based on PAD status in participants with prior cardiovascular disease mirrored those of the overall population (see Table 4). There was also no differential treatment effect of exenatide in participants with prior cardiovascular disease.

DISCUSSION

This analysis of patients with PAD in EXSCEL has 4 key findings. First, PAD was included as a risk enrichment factor for the overall trial, but, surprisingly, patients with PAD were treated less aggressively for cardiovascular risk reduction with aspirin, statin, angiotensin-converting enzyme inhibitors, and β-blockers. Second, patients with PAD had higher unadjusted and adjusted rates of MACE and LEA when compared with patients without PAD. Third, there was no treatment interaction based on PAD status for MACE, key secondary end points, and lower-limb events. Fourth, exenatide was not associated with LEA in patients with DM with and without baseline PAD.

PAD is up to 4×more frequent in patients with DM than the general population.[12] The UK Prospective Diabetes Study showed that PAD prevalence increases with DM duration.[13] Additionally, the degree of glycemic control is an independent risk factor for PAD; with every 1% increase in glycated hemoglobin, there is a 28% greater risk of development of PAD.[13] Moreover, patients with DM and PAD were 5× more likely to have an amputation, had higher rates of cerebrovascular and cardiovascular disease, and had higher rates of cardiovascular and all-cause mortality than nondiabetic patients with PAD.[14,15] Hence, it is imperative to thoroughly study novel antidiabetic agents to prevent adverse limb outcomes in this inherently sick population.

Although many randomized controlled trials have been designed to determine the cardiovascular safety and efficacy of new antidiabetic agents, few trials before the CANVAS (Canagliflozin Cardiovascular Assessment) investigated LEA risks in detail.[8] For instance, trials comparing dipeptidyl peptidase-4 inhibitors with placebo demonstrated similar rates of MACE with either intervention in patients with DM, but no information was reported on adverse limb events.[16–18] Similarly, some GLP-1 receptor

Table 3. Treatment Effect of Exenatide by PAD Status

Outcomes	No PAD			PAD			Interaction *P* Value
	Exenatide; N=5955	Placebo N=5996	HR (95% CI)	Exenatide N=1400	Placebo N=1400	HR (95% CI)	
Primary end point							
MACE	660 (11.1%)	702 (11.7%)	0.94 (0.84–1.04)	179 (12.8%)	203 (14.5%)	0.85 (0.69–1.04)	0.417
Cardiovascular death	256 (4.3%)	285 (4.8%)	0.90 (0.76–1.07)	84 (6.0%)	98 (7.0%)	0.83 (0.62–1.11)	0.66
Nonfatal MI	378 (6.4%)	384 (6.4%)	0.99 (0.86–1.14)	88 (6.3%)	96 (6.9%)	0.89 (0.66–1.19)	0.522
Nonfatal stroke	124 (2.1%)	152 (2.5%)	0.81 (0.64–1.03)	45 (3.2%)	41 (2.9%)	1.06 (0.69–1.61)	0.271
Secondary end points							
All-cause death	383 (6.4%)	428 (7.1%)	0.90 (0.78–1.03)	124 (8.9%)	156 (11.1%)	0.77 (0.61–0.98)	0.288
First occurrence of nonfatal or fatal MI	388 (6.5%)	393 (6.6%)	0.99 (0.86–1.14)	95 (6.8%)	100 (7.1%)	0.92 (0.69–1.22)	0.65
First occurrence of nonfatal or fatal stroke	138 (2.3%)	170 (2.8%)	0.81 (0.65–1.01)	49 (3.5%)	48 (3.4%)	0.98 (0.66–1.47)	0.38
Hospitalization for ACS	495 (8.3%)	460 (7.7%)	1.08 (0.95–1.23)	107 (7.6%)	110 (7.9%)	0.95 (0.72–1.23)	0.369
Hospitalization for heart failure	178 (3.0%)	170 (2.8%)	1.05 (0.85–1.29)	41 (2.9%)	61 (4.4%)	0.65 (0.44–0.96)	0.035
Limb events							
Lower-limb composite event	114 (1.9%)	119 (2.0%)	0.96 (0.74–1.24)	134 (9.6%)	156 (11.1%)	0.83 (0.66–1.04)	0.4
Amputation (nontraumatic)	53 (0.9%)	55 (0.9%)	0.96 (0.66–1.41)	70 (5.0%)	69 (4.9%)	0.99 (0.71–1.38)	0.923
Gangrene	33 (0.6%)	38 (0.6%)	0.87 (0.55–1.38)	44 (3.1%)	52 (3.7%)	0.83 (0.55–1.23)	0.863
Lower-extremity endovascular revascularization	48 (0.8%)	44 (0.7%)	1.09 (0.72–1.64)	51 (3.6%)	75 (5.4%)	0.65 (0.46–0.93)	0.062
Lower-extremity surgical revascularization	13 (0.2%)	23 (0.4%)	0.57 (0.29–1.11)	37 (2.6%)	32 (2.3%)	1.11 (0.69–1.78)	0.105

Values shown are n (%), except where indicated otherwise. ACS indicates acute coronary syndrome; HR, hazard ratio; MACE, major adverse cardiac event; MI myocardial infarction; and PAD, peripheral artery disease.

agonists (liraglutide, semaglutide, albiglutide) have been shown to have cardiovascular benefits, whereas others agents (lixisenatide and exenatide) demonstrated non-inferiority on cardiovascular end points when compared with placebo.[2–4,6,7] Nonetheless, effects of these agents on lower-extremity PAD were not fully examined. A recent post hoc analysis of LEADER showed that patients with DM treated with liraglutide had similar rates of developing

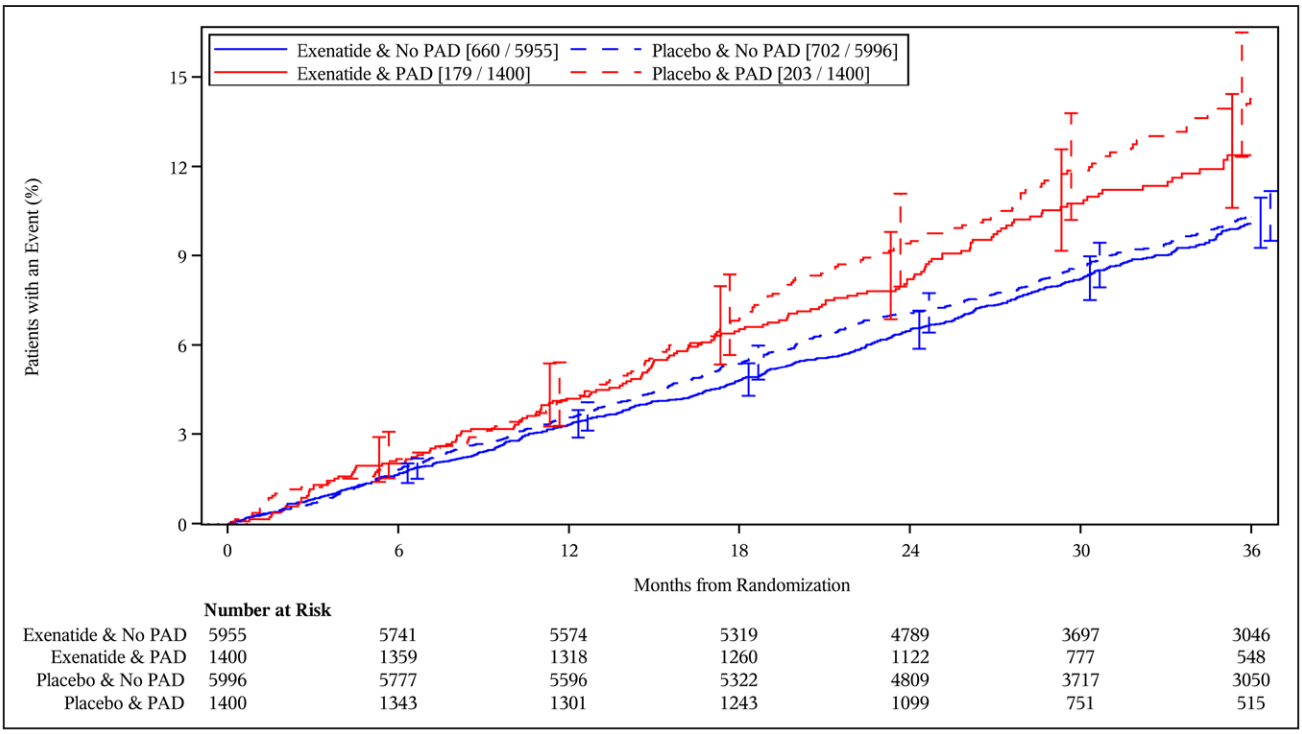

Figure 1. Kaplan-Meier curves for time to major adverse cardiac event composite event by treatment and baseline peripheral artery disease (PAD) status.

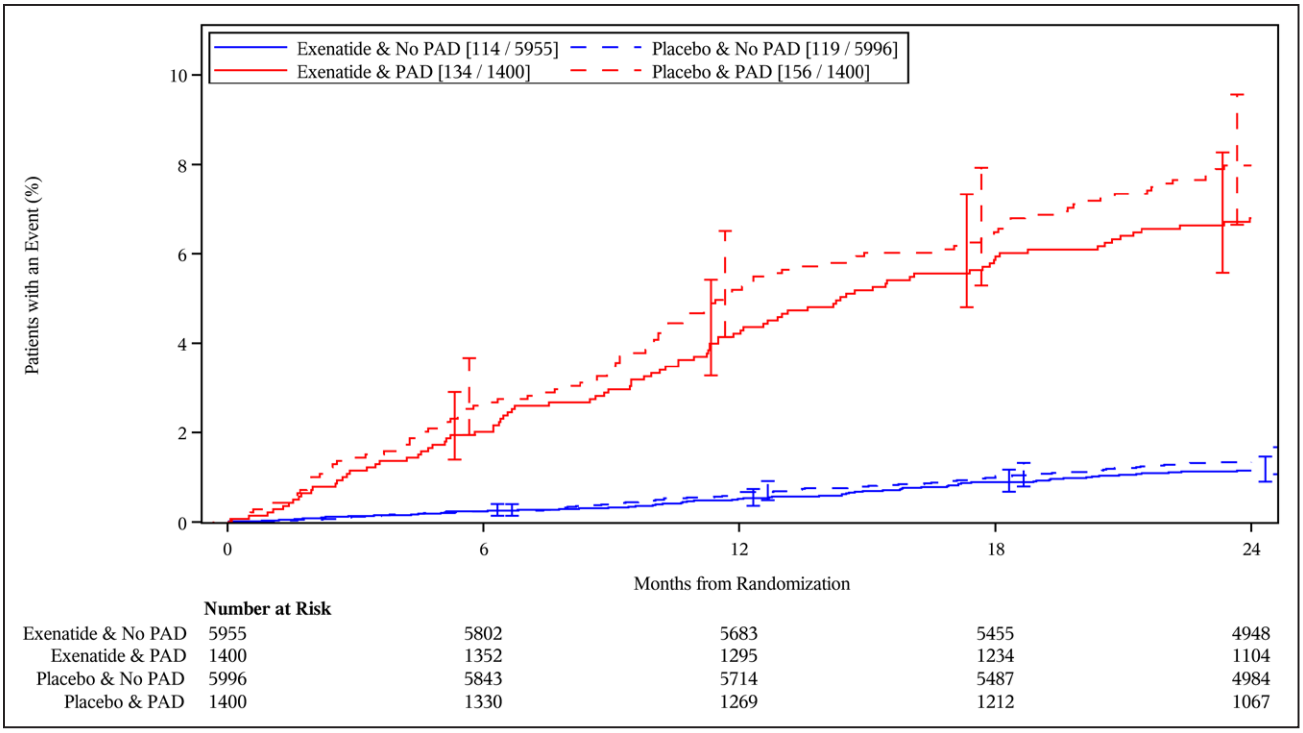

Figure 2. Kaplan-Meier curves for time to lower-limb composite event by treatment and baseline peripheral artery disease (PAD) status.

diabetic foot ulcers as those receiving placebo (3.8% with liraglutide versus 4.1% with placebo; HR, 0.90 [95% CI, 0.75–1.13]) and lower rates of diabetic foot ulcer-related amputations (0.9% with liraglutide versus 1.4% with placebo; HR, 0.65 [95% CI, 0.45–0.95]).[19] However, a prior diagnosis of PAD was not reported, and due to methods of data collection, only amputations associated with known diabetic foot ulcers were analyzed.

The SGLT2 inhibitor canagliflozin was found to decrease MACE in patients with DM; however, it was associated with a near 2-fold increase in LEAs as reported in CANVAS and CANVAS-Renal studies.[8] The pathophysiologic mechanism to explain the increased LEAs remains unknown, as does whether the class of SGLT2 inhibitors is associated with amputations. A post hoc analysis of the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), where lower-limb amputations were manually identified from searches of severe adverse events narratives, reported that empagliflozin and placebo had similar rates of LEAs (HR, 1.00 [95% CI, 0.70–1.44]).[20] As this study preceded CANVAS, there was no concern for amputation, and it was not a listed adverse event on the case report form. In contrast, a large retrospective cohort study of commercially insured patients found that new use of SGLT2 inhibitors was associated with a statistically significant increased risk of LEA compared with use of metformin, sulfonylureas, or thiazolidinediones (HR, 2.12 [95% CI, 1.19–3.77]). Among this SGLT2 inhibitor cohort, 70% were taking canagliflozin, with the remainder taking dapagliflozin or empagliflozin.[21] Lastly, the DECLARE-TIMI-58 trial (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) showed no difference in rates of amputation between patients treated with dapagliflozin or placebo (HR, 1.09 [95% CI, 0.84–1.40]).[22] Of note, however, only 6% of enrolled patients had PAD.

This analysis from EXSCEL included a large cohort of patients with PAD with DM and directly compared the clinical characteristics, rates of MACE and LEA, and treatment effect of the GLP-1 receptor agonist exenatide according to PAD status. Our study provides evidence that exenatide is not associated with LEA and can be safely used in patients with DM with and without PAD who are inherently at higher risk for LEA.

Limitations

This was a post hoc analysis of the EXSCEL trial, which was powered to study MACE and not LEA. There were differences between the PAD and no PAD groups based on inclusion criteria (eg, 70% of patients had established cardiovascular disease, and since PAD counted as an inclusion criterion, those patients without baseline PAD were, by definition, more likely to have other forms of cardiovascular disease at study entry). Additionally, although we used multivariable models to attempt to adjust for known confounders between patients with and without PAD, we were not able to control for unknown confounders. Moreover, although site investigators identified

Table 4. Treatment Effect of Exenatide Based on PAD Status in Subjects With Prior Cardiovascular Disease

Outcomes	No PAD			PAD			Interaction P Value
	Exenatide N=4026	Placebo N=4019	HR (95% CI)	Exenatide N=1367	Placebo N=1369	HR (95% CI)	
Primary end point							
MACE	544 (13.5%)	589 (14.7%)	0.91 (0.81–1.02)	178 (13.0%)	197 (14.4%)	0.88 (0.72–1.08)	0.78
Cardiovascular death	213 (5.3%)	233 (5.8%)	0.91 (0.76–1.10)	84 (6.1%)	97 (7.1%)	0.85 (0.64–1.14)	0.697
Nonfatal MI	319 (7.9%)	337 (8.4%)	0.94 (0.81–1.09)	88 (6.4%)	93 (6.8%)	0.92 (0.69–1.23)	0.909
Nonfatal stroke	95 (2.4%)	122 (3.0%)	0.77 (0.59–1.01)	44 (3.2%)	39 (2.9%)	1.10 (0.72–1.69)	0.166
Secondary end points							
All-cause death	315 (7.8%)	337 (8.4%)	0.93 (0.80–1.09)	121 (8.9%)	154 (11.3%)	0.77 (0.61–0.98)	0.192
First occurrence of nonfatal or fatal MI	329 (8.2%)	343 (8.5%)	0.95 (0.82–1.11)	95 (7.0%)	97 (7.1%)	0.95 (0.72–1.26)	0.991
First occurrence of nonfatal or fatal stroke	107 (2.7%)	139 (3.5%)	0.76 (0.59–0.98)	48 (3.5%)	46 (3.4%)	1.02 (0.68–1.53)	0.229
Hospitalization for ACS	424 (10.5%)	405 (10.1%)	1.04 (0.91–1.20)	107 (7.8%)	107 (7.8%)	0.98 (0.75–1.28)	0.672
Hospitalization for heart failure	153 (3.8%)	141 (3.5%)	1.08 (0.86–1.35)	41 (3.0%)	60 (4.4%)	0.66 (0.44–0.98)	0.036
Limb events							
Lower-limb composite event	90 (2.2%)	100 (2.5%)	0.89 (0.67–1.19)	128 (9.4%)	156 (11.4%)	0.79 (0.63–1.00)	0.521
Amputation (nontraumatic)	39 (1.0%)	47 (1.2%)	0.82 (0.54–1.26)	66 (4.8%)	69 (5.0%)	0.94 (0.67–1.31)	0.644
Gangrene	26 (0.7%)	30 (0.8%)	0.86 (0.51–1.46)	41 (3.0%)	52 (3.8%)	0.77 (0.51–1.16)	0.744
Lower-extremity endovascular revascularization	41 (1.0%)	41 (1.0%)	0.99 (0.64–1.53)	49 (3.6%)	75 (5.5%)	0.63 (0.44–0.90)	0.111
Lower-extremity surgical revascularization	11 (0.3%)	19 (0.5%)	0.57 (0.27–1.21)	35 (2.6%)	32 (2.3%)	1.06 (0.66–1.71)	0.174

Values shown are n (%), except where indicated otherwise. ACS indicates acute coronary syndrome; HR, hazard ratio; MACE, major adverse cardiac event; MI myocardial infarction; and PAD, peripheral artery disease.

patients with PAD by both objective and subjective measures, the severity of PAD, composition of PAD subset, and exact ankle-brachial index values were not captured on the case report forms. Additionally, although gangrene was differentiated from amputation, no information was available for diabetic foot ulcers, and thus, we cannot account for amputations that were a result of diabetic foot ulcers. Lastly, a major limitation of the EXSCEL trial is the high rate of premature discontinuation (≈40%) of treatment assignment, which was primarily driven by patient decision.

Conclusions

This post hoc analysis of the EXSCEL trial studying patients with DM and PAD showed that those with PAD were less likely to be on optimal medical therapy for secondary prevention of cardiovascular disease. Patients with PAD had similar adjusted rates of MACE when compared with patients without PAD, although patients with PAD had higher rates of cardiovascular and all-cause mortality, and higher adverse lower-limb events, including LEA and limb revascularization. Lastly, exenatide was not associated with LEA in patients with or without PAD and was associated with lower all-cause mortality in patients with DM and PAD.

ARTICLE INFORMATION

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