**Dapagliflozin and Cardiac, Kidney and Limb Outcomes in Patients With and Without Peripheral Artery Disease in DECLARE-TIMI 58**

Short Title: Limb and Cardiac Risk in Patients with Diabetes and PAD

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**ABSTRACT**

**Background:** Patients with peripheral artery disease (PAD) are at heightened risk of cardiovascular complications. The SGLT2 inhibitor (SGLT2i) dapagliflozin reduces the risk for hospitalization for heart failure (HHF) and kidney events in patients with type 2 diabetes mellitus (T2DM). An increased risk of amputation has been observed with canagliflozin in one prior trial. We examined cardiovascular and kidney efficacy and the risk of limb related events in patients with and without peripheral artery disease (PAD) in an exploratory analysis.

**Methods:** 17,160 patients with T2DM, including 1,025 (6%) with PAD, were randomized. Key efficacy outcomes were MACE (CV Death, MI, stroke), CV Death/HHF, and progression of kidney disease. Amputations, peripheral revascularization and limb ischemic adverse events were site reported and categorized by a blinded reviewer.

**Results:** Patients in the placebo arm with PAD versus those without tended to have higher adjusted risk of MACE (Adj HR 1.23, 95% CI 0.97 – 1.56, p=0.094) and significantly higher adjusted risk of CV Death/HHF (Adj HR 1.60, 95% CI 1.21 – 2.12, p=0.0010) and progression of kidney disease (Adj HR 1.51, 95% CI 1.13 – 2.03, p=0.0058). The relative risk reductions with dapagliflozin for CV Death/HHF (HR 0.86 PAD, HR 0.82 no PAD, p-interaction 0.79) and progression of kidney disease (HR 0.78 PAD, HR 0.76 no PAD, p-interaction 0.84) were consistent regardless of PAD. There were 560 patients who had at least one limb ischemic event, 454 patients with at least one peripheral revascularization, and 236 patients with at least one amputation with a total of 407 amputations reported. Overall, there were no significant differences in any limb outcome with dapagliflozin vs. placebo including limb ischemic adverse events (HR 1.07, 95% CI 0.90 – 1.26) and amputation (HR 1.09, 95% CI 0.84 – 1.40), with no significant interactions by a history of PAD vs. not (P interactions 0.30 and 0.093 respectively).

**Conclusion:** Patients with versus without PAD are at higher risk of MACE, CV Death/HHF and kidney outcomes, and have consistent benefits for CV Death/HHF and progression of kidney disease with dapagliflozin. Patients with PAD had higher risk of limb events, with no consistent pattern of incremental risk observed with dapagliflozin.

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Abbreviations

ABI – ankle brachial index

AKA – above the knee amputation

ALI – acute limb ischemia

ARR – absolute risk reduction

BKA – below the knee amputation

BMI – body mass index

CLI – chronic critical limb ischemia

HR – hazard ratio

IQR – intraquartile range

MACE – major adverse cardiovascular events

NNT – number needed to treat

PAD – peripheral artery disease

PCI – percutaneous coronary intervention

SGLT2i – sodium-glucose cotransporter 2 inhibitor

T2DM – Type 2 Diabetes Mellitus

**Introduction**

Patients with symptomatic lower extremity peripheral artery disease (PAD) are at heightened risk of cardiovascular complications including MI and stroke, even in the absence of symptomatic disease in the coronary or cerebral vasculature, with a magnitude of risk similar to that faced by patients who have symptomatic coronary disease or prior stroke.1 In addition, recent observational studies report a heightened risk of heart failure (HF) in patients with PAD versus those without even after adjusting for other risk factors.2 The most notable manifestations of disease that differentiates this population from others with atherosclerosis are those of limb morbidity including peripheral revascularization procedures, chronic critical limb ischemia (CLI), acute limb ischemia (ALI) and amputation; often referred to as major adverse limb events (MALE).3 In stable PAD populations, the incidence of amputation and acute limb ischemia (ALI), events associated with severe morbidity and tissue loss, are as high or exceed the incidence of myocardial infarction and stroke.4-6

Type 2 diabetes mellitus (T2DM) is one of the strongest risk factors for developing PAD.7 In addition, patients with both PAD and T2DM suffer further heightened risk of MACE, HF and limb complications relative to those with either condition alone.8 Amputation is a severe morbidity associated with T2DM with an associated 10-20 fold risk of amputation compared with those without diabetes.7 Risk factors for amputation are complex and include microvascular disease (e.g. small vessel arteriopathy and neuropathy) as well as obstructive macrovascular PAD (e.g. claudication and/or an abnormal ankle-brachial index, ABI).9 The combination of both macrovascular PAD and microvascular disease in the setting of T2DM leads to very high risk of amputation beyond either disease state alone and with a complex and multifactorial pathobiology including trophic injury from neuropathy, impaired wound healing, and limb ischemia.8

The sodium-glucose cotransporter 2 inhibitors (SGLTi) have been shown to reduce hospitalization for heart failure (HHF) and kidney complications in broad populations with T2DM.10-12 In the canagliflozin cardiovascular assessment study (CANVAS) trials program with canagliflozin, however, a 2-fold risk of amputation for canagliflozin versus placebo was seen.10 Results from the subsequent evaluation of the effects of canagliflozin on renal and cardiovascular outcomes in participants with diabetic nephropathy (CREDENCE) trial, also evaluating canagliflozin versus placebo, did not show an increased risk of amputation13 Therefore, whether there is an adverse effect of SGLT2i across the spectrum of MALE and the balance of efficacy and safety for patients with T2DM with or without PAD remain important clinical questions.

The Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58) Trial provides an opportunity to further examine the effect on dapagliflozin in a broad population of patients with T2DM with and without PAD. 14 The effect of dapagliflozin was evaluated in a pre-specified exploratory analysis of MALE as well as its overall efficacy and safety in patients with and without PAD.

**METHODS**

**Study Population**

The DECLARE-TIMI 58 trial design and primary results have been previously published.11, 14 The study was approved by institutional review committees for each participating site and all participants provided written informed consent. Patients with T2DM qualified if they had either evidence of atherosclerotic vascular disease (ASCVD) or multiple ASCVD risk factors (MRF). Patients were characterized has having baseline PAD if they had symptoms of claudication and an ABI < 0.90 documented in the 12 months prior to enrollment or history of lower extremity revascularization or amputation for PAD. Patients with PAD were further stratified by whether there was a concomitatnt history of myocardial infarction or stroke (PAD Polyvascular) or no history of either event (PAD only). It should be noted that due to the patients enrolled, “polyvascular” generally refers to PAD and CAD in the current trial. Baselinesymptoms were classified according to the Fontaine Classification (Stage I – asymptomatic, Stage IIa – intermittent claudication with onset at ≥ 200 meters of walking, Stage IIb – intermittent claudication with onset at < 200 meters of walking, Stage IV – ischemic ulcers or gangrene).15 In order to qualify for trial participation, patients had to be aged ≥40 for patients with ASCVD or ≥55 years men or ≥60 years for women with MRF, have a glycated hemoglobin (HbA1c) of 6.5%-12% inclusive, and have a creatinine clearance of at least 60 ml per minute.

The data, analytical methods, and study materials will not be made universally available to other researchers for purposes of reproducing the results or replicating the procedure. However, we encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

**Outcomes**

The primary safety outcome for non-inferiority analysis was the composite of cardiovascular death (CVD), myocardial infarction (MI) or ischemic stroke (MACE). The dual primary efficacy outcomes for superiority were MACE and the composite of CV Death or HHF. A secondary prespecified cardiorenal composite outcome was defined as the composite of a sustained decrease of 40% or more in estimated glomerulal filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) to < 60 ml/min/1.73m2, new end-stage kidney disease, or kidney-related or CV death. Additional efficacy outcomes included coronary and non-coronary (peripheral) revascularization procedures, overall and stratified by urgent and elective revascularizations. All efficacy outcomes were adjudicated by a blinded independent clinical events committee (CEC).

Limb outcomes included amputations, limb ischemic events, and limb infections. Limb ischemic adverse events (AEs) were determined through site reported safety events and defined by specific Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT) prior to database lock. Amputation events prior to March 2017 were identified from the database retrospectively and prospectively thereafter by sites on a dedicated case report form page including date, site of amputation, primary etiology and contributing factors and were reviewed by a vascular medicine specialist blinded to treatment allocation. In addition to the primary or dominant cause of amputation, sites were also to capture contributing factors (e.g. primary infection, neuropathy contributing). Major amputation was defined as BKA or AKA with minor limited to the foot. Other limb outcomes were prospectively ascertained through investigator reporting on adverse event forms and reviewed by a blinded vascular medicine specialist using both verbatim terms and narrative reviews. Outcomes included acute limb ischemia (ALI), chronic critical limb ischemia (CLI), and limb infections. The composite of major adverse limb events (MALE) included the composite of ALI, CLI, amputation for ischemia, or urgent revascualrizatoin for ischemia. Subtypes of infections (e.g. diabetic foot ulcer, osteomyelitis) are also reported.

**Statistical Considerations**

As part of prespecified analyses, patients were stratified into those with or without symptomatic lower extremity PAD at baseline as described above. Baseline characteristics of the subgroups were compared using Wilcoxon rank sum tests for continuous data and χ2 tests for categorical data. All efficacy analyses of dapaglifozin versus placebo were done on an intention-to-treat basis. Safety analyses included all patients who received at least one dose of study treatment (safety cohort) and included all events and follow up. Hazard ratios (HRs),95% CIs and p-values for the effect of dapagliflozin versus placebo were generated by use of Cox proportional hazards models. The proportional hazards assumption were assessed using the sums of martingale residuals to test visually and numerically.16 For the analysis of natural history evaluating the risk of outcomes comparing patients with and without PAD a multivariable-adjusted HR was obtained from a Cox model that included age, sex, race, BMI, hypertension, dyslipidemia, smoking, diabetes duration, HbA1c, eGFR (CKD-EPI), history of CAD, cerebrovascular disease. These natural history analyses were restricted to the placebo population as treatment impacted key outcomes including heart failure and renal outcomes. The p-interaction for subgroup analysis uses history of PAD and treatment in the model. The HR are reported stratified by history of PAD and no history of PAD. Clinical predictors of amputation were evaluated in the overall population, and within the subgroup of patients with a history of PAD at baseline by creating logistic regression models using backwards selection models. P values below 0.05 were regarded as significant without adjustment for multiple comparisons. SAS version 9.4 (SAS Institute, Cary, NC) was used for all statistical analyses.

**RESULTS**

Of the 17,160 patients randomized, 1,025 (6%) had a history of symptomatic lower extremity PAD at baseline and of those, 491 patients (48.0%) had a history of prior peripheral revascularization or amputation, 618 (60.4%) had claudication at baseline with the majority (453) having mild (Fontaine Class IIa) symptoms. There were 106 (10.3%) with prior amputation and 22 (2.4%) and 31 (3.3%) with rest pain or ulceration/gangrene present at baseline, respectively (Table 1). Patients with PAD were younger, more frequently male, had a greater prevalence of risk factors, and had longer standing diabetes and higher hemoglobin A1C at baseline relative to patients without PAD (Table 1). Of the PAD subgroup, 475 patients (46.3%) had a history of ischemic heart disease including 281 (27.4%) with prior MI and 150 (14.6%) had a history of cerebrovascular disease (Table 1). At baseline, 81% were taking antiplatelet therapy, 80% ACE inhibitors or ARBs, and 78% LDL-C lowering therapy defined as statin and or ezetimibe.

**Cardiac and Kidney Risk in Placebo Patients with and without PAD**

Among patients in the placebo arm, patients with PAD versus those without had higher incidence of MACE (n/N: 15.9% vs 9.0%), CV death/HF (12.1% vs 5.4%) and progression of kidney disease (10.9% vs 5.3%, Figure 1a). Patients with PAD also had higher incidence of coronary or peripheral revascularization (29.0% vs 8.2%) including urgent (11.5% vs 3.7%), elective (21.7% vs 4.6%), coronary (14.3% vs 7.1%) and non-coronary revascularization (19.1% vs 1.5%, Table 3). Within the subgroup with PAD, those with PAD and polyvascular disease had higher risk. of cardiovascular and kidney complications than those without PAD and those with PAD only (Figure 1b). After adjusting for baseline differences, patients with PAD vs those without remained at significantly higher risk of CVD/HHF (Adj. HR 1.60, 95% CI 1.21 – 2.12, p=0.001), kidney complications (Adj. HR 1.51, 95% CI 1.13 -2.03, p<0.01, Figure 1, Table 2) but not MACE (Adj. HR 1.23, 95% CI 0.97 – 1.56, p=0.094, Table 2). The pattern was similar in those with PAD and polyvascular disease overall but in contrast, this group also had a significantly higher risk of MACE compared with those without PAD (Adj. HR 1.38, 95% CI 1.01 – 1.89, p=0.0402); however, there was no excess risk of MACE in PAD only (Adj HR 1.06, 95% CI 0.74 – 1.52, p=0.7418, Figure 1b)

**Major Adverse Limb Events in Patients with and without Peripheral Artery Disease**

During the trial, there were 1,694 limb ischemic adverse events occurring in 560 patients including 225 patients with MALE. There were 97 with at least 1 urgent revascularization, 56 patients with at least 1 ALI event and 120 patients with at least one CLI event. There were 407 amputations in 236 patients with 86 patients having 2 or more amputations during and 21 with for or more during follow up. The primary etiology of amputation was most often infection (315, 77%), followed by CLI (63, 15%) and ALI (26, 6%), with only 3 (1%) traumatic amputations reported. Critical limb ischemia was the most frequent secondary contributing factor to amputation (101, 25%), followed by neuropathy (87, 21%), ALI (17, 4%) and infection (15, 4%). There were 87 major (21%) major amputations and 310 (76%) minor amputations. Of the major amputations, the majority (57, 66%) were due to infection followed by CLI (19, 22%) and ALI (11, 13%). Minor amputations followed a similar pattern with the majority, 252 (81%) due to infection followed by 43 (14%) due to CLI followed by 15 (5%) due to ALI.

In the placebo group, the incidence of any limb adverse event was higher in those with PAD versus those without (20.3% vs 2.1%, Adj. HR 8.37, 95% CI 6.45 – 10.87, p<0.001) with ~13 fold higher risk and ~20 fold higher risk of CLI and ALI, respectively (Table 3, Figure 2a). The risk of amputation for any reason was higher in those with versus without PAD (5.6% vs 1.1%, Adj. HR 4.47, 95% CI 2.86 – 7.00, p<0.001), as was the risk of any limb infection (8.2% vs. 3.3%, Adj. HR 2.13, 95% CI 1.51 – 3.00, p<0.001, Figure 2a). In contrast to other cardiovascular events, the risk of amputation did not differ by the presence or absence of polyvascular disease (5.5% for PAD only vs. 5.6% for PAD polyvascular, Figure 1b). The most frequent primary etiology leading to amputation was infection both in patients with (69%) and without (82%) PAD. However, a greater proportion of amputations were driven by CLI (21% vs 13%) as well as ALI (10% vs. 5%) in those with versus without PAD (Figure 2b).

Overall predictors of amputation included PAD, longer duration of diabetes, male sex, history of HF, white versus non-white race, higher HgbA1C at baseline, and non-use of statin and/or ezetimibe (Supplemental Table 1, Table 4). Within the subgroup of patients with known PAD, predictors included history of amputation or peripheral revascularization, male sex, longer duration of T2DM and HgbA1C at baseline (Table 4). The indepedent predictors with greatest magnitude of association with future amputation were the presence of symptomatic PAD (OR 6.24, 95% CI 4.66 – 8.36, p<0.001) in the overall population and within the subgroup with PAD, a history of amputation (OR 4.74, 95% CI 2.63 – 8.56, p<0.001, Table 4).

**Cardiac and Kidney Efficacy of Dapagliflozin in Patients with and without PAD**

Consistent with the overall trial results, there was no significant effect on MACE for dapagliflozin versus placebo in the subgroup of patients with PAD (HR 1.05, 95% CI 0.77 – 1.42, p-interaction 0.4215, Table 2, Figure 3). The benefit of dapagliflozin for CV Death/HHF was consistent regardless of PAD status (PAD, HR 0.86, 95% CI 0.60 – 1.24; no PAD HR 0.82, 95% CI 0.72 – 0.95, p-interaction 0.7877, Table 2, Figure 3) with an absolute risk reduction in those with and without PAD of 1.4% and 0.9%, respectively, translating into a number needed to treat (NNT) of 72 for patients with PAD and 111 for patients without PAD (Table 2, Figure 3). Similarly, benefits for reductions in kidney complications with dapagliflozin versus placebo were consistent regardless of PAD status, with absolute risk reductions in those with versus without PAD of 2.1% and 1.3% respectively (Table 2, Figure 3).

**Limb Outcomes with Dapagliflozin in All Patients**

Overall, there was no significant imbalance in limb outcomes with dapagliflozin vs. placebo, including any limb ischemic AE (HR 1.07, 95% CI 0.90 – 1.26, p=0.45) ALI (HR 1.00, 95% CI 0.59 – 1.69, p=0.99), CLI (HR 1.40, 95% CI 0.97 – 2.01, p=0.069), amputation (HR 1.09, 0.84 – 1.40, p=0.53) or lower extremity revascularizations (HR 1.00, 95% CI 0.81 – 1.24, p=0.98, Figure 4a, Figure 4b). In addition, there was no pattern suggesting time-dependent risk of amputation overall or within randomized groups. (Supplemental Figure 1). There was also was no imbalance for amputation by randomized treatment when subtyped by etiology, including ALI (HR 0.99), CLI (HR 1.18) or infection (1.14, Figure 4b). Similarly, when considering limb infections, there was no imbalance with dapagliflozin vs. placebo (HR 0.93, 95% CI 0.79 – 1.09, p=0.36), including diabetic foot ulcer (HR 0.95, 95% CI 0.73 – 1.24), osteomyelitis (HR 0.83, 95% CI 0.54 – 1.26, p=0.38), wet gangrene (HR 0.72, 95% CI 0.44 – 1.16, p=0.18) and fungal infections (HR 0.63, 95% CI 0.34 – 1.15, p=0.13).

When stratifying by PAD at baseline, there was similarly no statistically significant difference in limb ischemic AEs (HR 0.93, 95% CI 0.71 – 1.23) or subtypes including ALI (HR 0.84, 95% CI 0.42 – 1.69), CLI (HR 1.12, 95% CI 0.66 – 0.91) or amputation (HR 1.51, 95% CI 0.94 – 2.42, Table 3, Supplemental Figure 2). When examining the risk of amputation among subgroups at higher risk including older age, longer duration of diabetes, kidney dysfunction or HbA1c at baseline, there was no significant heterogeneity for the risk of amputation, although due to the small number of events, confidence intervals tended to be broad (Figure 5).

**Discussion**

The results of the present analyses describe four key observations regarding the risks associated with PAD and T2DM as well as the risks and benefits of long-term dapagliflozin treatment. First, patients with T2DM and prevalent PAD are at heightened risk of cardiovascular complications, with PAD remaining an indendent predictor of HHF and progression of kidney disease even after adjusting for baseline differences. Secondly, the benefit of dapagliflozin for the composite outcomes of CV Death/HHF and kidney complications is consistent in those with and without PAD. However, by nature of their higher risk, the absolute benefits in those with PAD are greater. Third, although it is intuitive that rates of MALE would be higher in those with versus without PAD, those with PAD are also at higher risk of limb infections and the dominant primary etiology leading to amputation is infection even in those with PAD. Finally, there was no significant imbalance in limb ischemic AEs, subtypes of MALE or amputation overall or in any high-risk subgroup in those treated with dapagliflozin vs. placebo.

Several clinical trial subgroup analyses and observational analyses have described MACE risk in patients with PAD and noted higher risk relative to those without, even if they have other forms of symptomatic atherosclerosis.1, 4, 8 The results from the present analyses adds to these observations by broadening the associated risk profile to HHF and kidney complications. The reason for the heightened risk of these complications may the greater prevalence of risk factors beyond that adjusted for in the analyses. There may also be, however, features specific to the disease state in PAD that contribute to this risk profile including diffuse occlusive disease in other peripheral conduit arteries (e.g. renal artery disease), broader abnormalities in vascular compliance, and obstructions in outflow which may alter hemodynamic measures such as augmentation index and pulse wave velocity. Further research investigating the complex relationship between PAD, HF and kidney disease will further elucidate this complex pathobiology. Regardless, the observation that patients with PAD are at higher risk may help clinicians and researchers selecting patients at higher risk for more intensive therapies. In this light, the observations regarding the benefits of dapagliflozin in this population may be helpful as clinicians work to identify patients who will derive the greatest benefits from therapy.

The risks of MALE in patients with PAD observed in the full DECLARE-TIMI 58 population further extend those of analyses in broad populations with PAD to patients with both PAD and T2DM.1, 4, 17, 18 Although outcomes such all-cause amputation are often described in this population, there are few robustly sized analyses that have systematically categorized MALE events by subtypes, including amputation, as well as by etiology. The findings of the present analyses demonstrate that the incidence of amputation and limb infection are roughly two-fold higher than those of acute limb ischemia, which contrasts with observations in broader PAD populations where amputations are uncommon relative to atherothrombotically mediated events such as ALI.1, 4, 17, 18 In addition, the observation that the dominant primary etiology leading to amputation, even in those with PAD, is infection, underscores the importance of appropriate education, foot hygiene and other measures to prevent and treat foot wounds relative to measures to reduce ischemic risk. While both may be efficacious, the impact of the former is likely as great or greater than therapies that reduce thrombotic limb complications. These observations also highlight the importance of pathology beyond conduit artery disease in patients with diabetes, supporting recent observations regarding the independent role of microvascular disease in limb loss in patients with diabetes.9

Finally, the present analyses add important information regarding the safety of dapagliflozin in patients with T2DM at heightened CVD risk.19 When evaluating limb ischemia AEs, amputations, and foot infections, there was no statistical excess with dapagliflozin in the overall population. In addition, in evalulations of high-risk subgroups including those with PAD, there was no consistent pattern of excess risk for limb events. Although there were numerically more amputations, the difference between groups was small (44 vs 28 events) and not statistically significant and there was no pattern among limb ischemic events that would suggest an adverse vascular effect. These results are reassuring with regard to the safety of dapagliflozin overall and in patients with PAD. They are also in line with both data from the dapagliflozin development program and the DAPA-HF study20, where no indication of imbalance of amputation has been seen Whether any incremental risk for amputation is present with canagliflozin remains a subject of debate. Although there was a 2-fold higher risk for amputation in the CANVAS trial program, the subsequent CREDENCE trial did not show such risk.10, 13 Of note, patients at high risk of amputation were excluded from CREDENCE, and investigators were recommended to stop canagliflozin if there was a wound or other finding that was associated with increased amputation risk. It is unclear how these differences in population and trial conduct may have contributed to the different findings in CANVAS and CREDENCE. In addition, results from studies in animal models have shown that canagliflozin improves blood flow in models of limb ischemia.21 These observations raise the question that, if there is a true risk of amputation with canagliflozin, whether a non-vascular mechanism might be at play. Future studies will continue to evaluate this outcome and the safety of individual agents as well as the class.

There are several limitations to the present analyses. When evaluating risk of outcomes in patients with and without PAD, analyses were adjusted for differences in baseline characteristics; however, there remains the possibility of unmeasured confounders impacting the observed differences rather than PAD itself. Nonetheless, the observation that patients with PAD are at heightened risk of HHF, kidney complications and adverse limb outcomes, regardless of the independent predictors, may be useful to clinicians selecting higher risk patients for more intensive therapies. Secondly, although amputations were categorized according to primary etiology, many were multifactorial. In fact, it is intuitive that conduit artery disease and impaired limb perfusion may predispose to non-healing infections. There were, however, few amputations for infection in which true ALI was a secondary etiology suggesting that the majority of patients had stable occlusive disease that would not have led to amputation based on ischemia alone. In addition, substudy data evaluating microvascular function and the role it may play particularly in infectious amputation was not available and warrants consideration in future studies of limb outcomes in patients with diabetes. Amputations and other limb outcomes were prospectively captured as adverse events of special interest and through a dedicated adverse event reporting page for such events, relevant data and clinical annotations were submitted for centralized blinded review and categorization. Finally, DECLARE-TIMI 58 was not powered to evaluate limb safety in individual subgroups such as those with and without PAD, therefore, these analyses do not exclude any possible risk even one of small magnitude. Finally, DECLARE-TIMI 58 was not powered to evaluate limb safety in individual subgroups such as those with and without PAD, therefore, these analyses do not exclude any possible risk even one of small magnitude. The observation that there was no significant excess in such a large trial and with follow up beyond 4 years is nonetheless reassuring that a large hazard is not present. Specifically, with 236 amputations captured, the trial had >90% power to detect a 2-fold or greater relative hazard in amputation similar to what was seen in the CANVAS trials program; within the PAD subgroup, there were 72 events providing 79% power to detect such a difference.

**Conclusions**

Patients with PAD and T2DM are a heightened risk of HHF and kidney complications as well as adverse limb events. In the overall population as well as in those with PAD, limb complications are predominantly driven by infection as opposed to ALI or CLI without infection. Dapagliflozin reduces the risk of HHF and kidney complications consistently in those with and without PAD; however, due to their higher absolute risk, patients with PAD have greater absolute benefits. There was no statistically significant excess risk of limb ischemic adverse events, subtypes including ALI or CLI, amputations or limb infections with dapagliflozin overall and there was no consistent pattern of risk for any of these complications in high risk subgroups.

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**Figure Legends**

Figure 1a – Risk of major adverse cardiovascular events (MACE), cardiovascular death or hospitalization for heart failure (CVD/HF) and kidney complications in patients randomized to placebo with and without peripheral artery disease. Model adjusted by age, sex, race, BMI, hypertension, dyslipidemia, smoking, diabetes duration, HbA1c, eGFR (CKD-EPI), history of CAD, cerebrovascular disease

Figure 1b – Risk of major adverse cardiovascular events (MACE), cardiovascular death or hospitalization for heart failure (CVD/HHF), kidney complications, and amputations in patients with no peripheral artery disease (PAD), PAD and no history of stroke or myocardial infarction, and PAD with prior history of myocardial infarction or stroke (PAD Polyvascular). Model adjusted by age, sex, race, BMI, hypertension, dyslipidemia, smoking, diabetes duration, HbA1c, eGFR (CKD-EPI), history of CAD, cerebrovascular disease. For amputation, denominator is the safety population with 8067 no PAD, 325 PAD and no polyvascular, and 177 PAD with polyvascular disease.

Figure 2a – Adverse limb events in patients randomized to placebo. Model adjusted by age (continuous), sex, race(4 groups), BMI(continuous), Hx of Hypertension, Hx of Dyslipidemia,Current Smoker(vs. Not), DM Duration (years, continuous), HbA1c (continuous), eGFR(CKD-EPI, continuous), Hx CAD, Hx Cerebrovascular disease

Figure 2b – The primary etiology of non-traumatic amputation in patients with and without PAD

Figure 3 – Dapagliflozin versus placebo for major adverse cardiovascular events (MACE), cardiovascular death or hospitalization for heart failure (CVD/HF) and kidney complications in patients with and without peripheral artery disease

Figure 4a – Adverse limb events with dapagliflozin vs. placebo in all patients randomized in DECLARE-TIMI 58 included in the safety population. Revascularization endpoints were analyzed as efficacy endpoints and the denominators are 8,578 randomized to placebo and 8,582 for dapagliflozin

Figure 4b – Amputation risk with dapagliflozin vs. placebo overall and by primary etiology

Figure 5 – The risk of amputation with dapagliflozin versus placebo in high risk subgroups

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PAD**  **N=1,025** | **No PAD**  **N=16,135** | **p-value** |
| Age, median (IQR) | 62.0 (57.0, 68.0) | 64.0 (60.0, 68.0) | <0.0001 |
| Female sex, n (%) | 324 (31.6) | 6098 (37.8) | <0.0001 |
| Body Mass Index, median (IQR) | 30.8/1023  (27.8, 34.7) | 31.3/16128 (27.8, 35.5) | 0.0256 |
| Caucasian, n (%) | 861 (84.0) | 12792 (79.3) | <0.0003 |
| History Hypertension, n (%) | 869 (84.8) | 14558 (90.2) | <0.0001 |
| History Hyperlipidemia, n (%) | 840 (82.0) | 12956 (80.3) | 0.1959 |
| Current Smoker, n (%) | 234 (22.8) | 2264 (14.0) | <0.0001 |
| Duration of Diabetes (yrs), median (IQR) | 12.0 (7.0, 18.0) | 10.016133  (6.0, 16.0) | <0.0001 |
| Hemoglobin A1C (%) | 8.3 (7.5, 9.2) | 8.0 (7.3, 9.0) | <0.0001 |
| Estimated GFR (CKD-EPI) < 60 mL/min/1.73m2, n (%) | 115 (11.2) | 1150/16134 (7.1) | <0.0001 |
| History of Ischemic Heart Disease, n (%) | 475 (46.3) | 5183 (32.1) | <0.0001 |
| History of Myocardial Infarction, n (%) | 281 (27.4) | 3303 (20.5) | <0.0001 |
| History of Cerebrovascular Disease, n (%) | 150 (14.6) | 1151 (7.1) | <0.0001 |
| History of CHF, n (%) | 147 (14.3) | 1577 (9.8) | <0.0001 |
| ***Peripheral Artery Disease History*** |  |  |  |
| Prior peripheral revascularization (endovascular or surgical), n (%) | 415 (40.5) |  |  |
| Prior endovascular revascularization, n (%) | 271 (26.4) |  |  |
| Prior amputation, n (%) | 106 (10.3) |  |  |
| **Fontaine Classification at Randomization** | | | |
| Stage I: Asymptomatic, n (%) | 232/933 (24.9) |  |  |
| Stage IIa: Mild claudication, n (%) | 453/933 (48.6) |  |  |
| Stage IIb: Moderate-severe claud., n (%) | 195/933 (20.9) |  |  |
| Stage III: Ischemia rest pain, n (%) | 22/933 (2.4) |  |  |
| Stage IV: Ulceration or gangrene, n (%) | 31/933 (3.3) |  |  |
| **Ankle Brachial Index Category** | | | |
| < 0.5, N (%) | 18/331 (5.4) |  |  |
| 0.5-<0.9, N (%) | 308/331 (93.1) |  |  |
| 0.9-<1.4, N (%) | 5/331 (1.5) |  |  |
| ***Medications at Baseline*** |  |  |  |
| Insulin, n (%) | 530 (51.7) | 6483 (40.2) | <0.0001 |
| Metformin, n (%) | 783 (76.4) | 13285 (82.3) | <0.0001 |
| Statin and/or ezetimibe, n (%) | 800 (78.0) | 12068 (74.8) | 0.0196 |
| Antiplatelet or Anticoagulant, n (%) | 877 (85.6) | 10347 (64.1) | <0.0001 |
| ACE-I or ARB use at baseline, n (%) | 817 (79.7) | 13133 (81.4) | 0.1792 |
| Cilostazol | 63 (6.1) | 84 (0.5) | <0.0001 |

**Table 1 Baseline Characteristics by presence of prior PAD**

**Table 2 Cardiac and Kidney Outcomes with Dapagliflozin in Patients with and without Peripheral Artery Disease**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***Efficacy Outcomes*** |  | **PAD** | |  | **No PAD** | | | |
|  | **Adjusted HR**  **(95% CI)**  **P-Value**  **PAD vs. no PAD (placebo arm)** | **Placebo**  **N=503**  **(n/N%)** | **Dapagliflozin**  **N=522**  **(n/N%)** | **Hazard Ratio**  **(95% CI)** | **Placebo**  **N=8075**  **(n/N%)** | **Dapagliflozin**  **N=8060**  **(n/N%)** | **Hazard Ratio**  **(95% CI)** | **p-Interaction** |
| **CV Death, MI, Stroke** | **1.23**  **(0.97 – 1.56)**  **0.094** | **80, (15.9%)** | **88, (16.9%)** | **1.05**  **(0.77 – 1.42)** | **723, (9.0%)** | **668 (8.3%)** | **0.92**  **(0.83 – 1.02)** | **0.4215** |
| **CV Death, Heart Failure** | **1.60**  **(1.21 – 2.12)**  **0.0010** | **61, (12.1%)** | **56, (10.7%)** | **0.86**  **(0.60 – 1.24)** | **435, (5.4%)** | **361, (4.5%)** | **0.82**  **(0.72 – 0.95)** | **0.7877** |
| *CVD* | 1.55  (1.05 – 2.29)  0.027 | 32, (6.4%) | 29. (5.6%) | 0.84  (0.51 – 1.40) | 217, (2.7%) | 216, (2.7%) | 1.00  (0.82 – 1.20) | 0.6039 |
| *Hosp. for HF* | 1.74  (1.21 – 2.50)  0.0027 | 37, (7.4%) | 35, (6.7%) | 0.89  (0.56 – 1.41) | 249, (3.1%) | 177, (2.2%) | 0.71  (0.58 – 0.86) | 0.3621 |
| **Progression of** kidney **Disease\*** | 1.51  (1.13 – 2.03)  0.0058 | **55, (10.9%)** | **46, (8.8%)** | **0.78**  **(0.53 – 1.16)** | **425, (5.3%)** | **324, (4.0%)** | **0.76**  **(0.66 – 0.88)** | **0.8384** |
| *\*increase in estimated glomerulo-filtration rate (CKD-EPI) of 40% or more to below 60 mL/min/1.73m2, n (%), progression to end-stage kidney disease, kidney-related death or cardiovascular death*  *\*\** *the adjusted HR are from Model adjusted by age (continuous), sex, race(4 groups), BMI(continuous), Hx of Hypertension, Hx of Dyslipidemia,Current Smoker(vs. Not), T2DM Duration (years, continuous), HbA1c (continuous), eGFR(CKD-EPI, continuous), Hx CAD, Hx Cerebrovascular disease* | | | | | | | | |

**Table 3 Adverse Limb Outcomes with Dapagliflozin in Patients with and without Peripheral Artery Disease**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ***Outcomes*** | **PAD** | |  | **No PAD** | | | |
|  | **Placebo**  **N=502**  **(n/N%)** | **Dapagliflozin**  **N=521**  **(n/N%)** | **Hazard Ratio**  **(95% CI)** | **Placebo**  **N=8067**  **(n/N%)** | **Dapagliflozin**  **N=8053**  **(n/N%)** | **Hazard Ratio**  **(95% CI)** | **p-Interaction** |
| **Limb Ischemic Adverse Event** | **102, (20.3%)** | **101, (19.4%)** | **0.93**  **(0.71 – 1.23)** | **169, 2.1%** | **188, 2.3%** | **1.11**  **(0.90 – 1.37)** | **0.3046** |
| *Acute limb ischemia (ALI)* | 17, (3.4%) | 15, (2.9%) | 0.84  (0.42 – 1.69) | 11, (0.1%) | 13, (0.2%) | 1.19  (0.53 – 2.65) | 0.4997 |
| *Critical limb ischemia (CLI)* | 25, (5.0%) | 30, (5.8%) | 1.12  (0.66 – 1.91) | 25, (0.3%) | 40, (0.5%) | 1.60  (0.97 – 2.64) | 0.3412 |
| *Other Limb Ischemic AE* | 72, (14.3%) | 57, (10.9%) | 0.75  (0.53 – 1.06) | 99, (1.2%) | 114, (1.4%) | 1.15  (0.88 – 1.51) | 0.0447 |
| **Non-coronary Revascularizatoin** | 96, (19.1%) | 88, (16.9%) | 0.86  (0.65 – 1.15) | 120, (1.5%) | 150, (1.9%) | 1.25  (0.99 – 1.59) | 0.0443 |
| **Amputation** | **28, (5.6%)** | **44, (8.4%)** | **1.51**  **(0.94 – 2.42)** | **85, (1.1%)** | **79, (1.0%)** | **0.93**  **(0.68 – 1.26)** | **0.0926** |
| **Limb Infection** | **41, (8.2%)** | **50, (9.6%)** | **1.15**  **(0.76 – 1.74)** | **265, (3.3%)** | **235, (2.9%)** | **0.88**  **(0.74 – 1.05)** | **0.2203** |
| *Outcomes analyzed in safety population/censoring with the exception of non-coronary revascularization which was prespecified and analyzed as an efficacy outcome* | | | | | | | |

**Table 4 Predictors of Amputation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **Odds Ratio** | **95% CI** | **P-Value** | **Chi Square** |
| **All Patients** |  |  |  |  |
| History of PAD | 6.24 | 4.66 – 8.36 | <0.001 | 150.77 |
| T2DM duration > 15 yrs (ref≤5 yrs)a | 2.77 | 1.87 – 4.10 | <0.001 | 25.91 |
| Male | 2.69 | 1.92 – 3.76 | <0.001 | 33.29 |
| History of CHF | 1.75 | 1.24 – 2.48 | 0.0014 | 10.22 |
| White vs. non-White | 1.62 | 1.09 – 2.40 | 0.016 | 5.78 |
| HgbA1C (%) at baseline (per unit) | 1.38 | 1.25 – 1.53 | <0.001 | 40.82 |
| Statin and/or ezetimibe at baseline | 0.70 | 0.52 – 0.94 | 0.017 | 5.67 |
| **Patients with PAD** |  |  |  |  |
| History of amputation | 4.74 | 2.63 – 8.56 | <0.001 | 26.65 |
| Prior peripheral revascularization | 2.71 | 1.61 – 4.56 | <0.001 | 14.01 |
| Male | 2.35 | 1.17 – 4.72 | 0.016 | 5.79 |
| HgbA1C (%) at baseline (per unit) | 1.29 | 1.06 – 1.56 | 0.0102 | 6.60 |

a. Additional categorical levels of duration of type 2 diabetes included in modeling, but were not to be statistically significant with a p-value < 0.05. These categories include >5-<=10 years and >10-<=15 years with <=5 years as reference.

Figure 1a



Figure 1b



Figure 2a



Figure 2b



Figure 3



Figure 4a



Figure 4b



**Figure 5**



**Online Supplement**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Amputation**  **N=236** | **No Amputation**  **N=16,907** | **p-value** |
| Age, median (IQR) | 63.0 (58.5, 67.0) | 64.0 (60.0, 68.0) | 0.017 |
| Female sex, n (%) | 44 (18.6) | 6371 (37.7) | <0.0001 |
| Body Mass Index, median (IQR) | 31.1  (27.5, 35.6) | 31.3/16898 (27.8, 35.4) | 0.8361 |
| Caucasian, n (%) | 206 (87.3) | 13433 (79.5) | 0.0030 |
| History Hypertension, n (%) | 214 (90.7) | 15198 (89.9) | 0.6906 |
| History Hyperlipidemia, n (%) | 183 (77.5) | 13599 (80.4) | 0.2665 |
| Current Smoker, n (%) | 38 (16.1) | 2495 (14.5) | 0.5006 |
| Duration of Diabetes (yrs), median (IQR) | 15.0  (9.0, 20.0) | 10.0/16906  (6.0, 16.0) | <0.0001 |
| Hemoglobin A1C (%) | 8.8 (7.8, 9.9) | 8.0 (7.3, 9.0) | <0.0001 |
| Estimated GFR (CKD-EPI) < 60 mL/min/1.73m2, n (%) | 26 (11.0) | 1236 (7.3) | 0.0304 |
| History of Ischemic Heart Disease, n (%) | 97 (41.1) | 5556 (32.9) | 0.0075 |
| History of Myocardial Infarction, n (%) | 62 (26.3) | 3520 (20.8) | 0.0408 |
| History of Cerebrovascular Disease, n (%) | 27 (11.4) | 1269 (7.5) | 0.0232 |
| History of CHF, n (%) | 44 (18.6) | 1679 (9.9) | <0.0001 |
| History of Peripheral artery disease, n (%) | 72 (30.5) | 951 (5.6) | <0.0001 |
| ***Peripheral Artery Disease History*** |  |  |  |
| Prior peripheral revascularization (endovascular or surgical), n (%) | 43 (18.2) | 370 (2.2) | <0.0001 |
| Prior endovascular revascularization, n (%) | 35 (14.8) | 236 (1.4) | <0.0001 |
| Prior surgical revascularization, n (%) | 24 (10.2) | 189 (1.1) | <0.0001 |
| Prior amputation, n (%) | 21 (8.9) | 84 (0.5) | <0.0001 |
| **Fontaine Classification at Randomization** <0.0001 | | | |
| Stage I: Asymptomatic, n (%) | 19/60 (31.7) | 213/871 (24.5) |  |
| Stage IIa: Mild claudication, n (%) | 15/60 (25.0) | 437/871 (50.2) |  |
| Stage IIb: Moderate-severe claud., n (%) | 15/60 (25.0) | 179/871 (20.6) |  |
| Stage III: Ischemia rest pain, n (%) | 3/60 (5.0) | 19/871 (2.2) |  |
| Stage IV: Ulceration or gangrene, n (%) | 8/60 (13.3) | 23/871 (2.6) |  |
| **Ankle Brachial Index Category** 0.2466 | | | |
| < 0.5, N (%) | 2/13 (15.4) | 16/320 (5.0) |  |
| 0.5-<0.9, N (%) | 11/13 (84.6) | 299/320 (93.4) |  |
| 0.9-<1.4, N (%) | 0/13 (0.0) | 5/320 (1.6) |  |
| ***Medications at Baseline*** |  |  |  |
| Insulin, n (%) | 148 (62.7) | 6855 (40.5) | <0.0001 |
| Metformin, n (%) | 181 (76.7) | 13875 (82.1) | 0.0329 |
| GLP-1 agonist, N (%) | 8 (3.4) | 741 (4.4) | 0.4586 |
| Statin and/or ezetimibe, n (%) | 170 (72.0) | 12685 (75.0) | 0.2915 |
| Antiplatelet or Anticoagulant, n (%) | 177 (75.0) | 11035 (65.3) | 0.0018 |
| ACE-I or ARB use at baseline, n (%) | 188 (79.7) | 13749 (81.3) | 0.5159 |
| Diuretic, n (%) | 115 (48.7) | 6844 (40.5) | 0.0104 |

**Supplemental Table 1 Baseline Characteristics by Amputation during Follow-up**

**Supplemental Figure 1 – Any Amputation by Treatment**



**Supplemental Figure 2**

