**The Efficacy and Safety of Dapagliflozin in Women and Men**

**with Type 2 Diabetes Mellitus**

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**Abstract**

**Aims/Hypothesis**: Women remain underrepresented in clinical trials and at high risk for cardiovascular events in those with type 2 DM. The sodium-glucose co-transporter-2 (SGLT-2) inhibitor dapagliflozin reduces the risk of CV death or heart failure hospitalizations in type 2 diabetes mellitus; in a pre-specified analysis, we examined whether sex modifies these effects.

**Methods**: The DECLARE-TIMI 58 trial randomized 17,160 patients with type 2 diabetes mellitus with or at risk for atherosclerotic disease to dapagliflozin or placebo (median follow-up 4.2 years). The dual efficacy outcomes were cardiovascular death or heart failure hospitalizations, and cardiovascular death, myocardial infarction, or ischemic stroke. The key renal composite outcome was a sustained ≥40% drop in estimated glomerular filtration rate to <60 ml/min/1.73m2, new end-stage renal disease, or renal death. Cox models were run separately by sex with treatment-by-sex interaction testing for each outcome.

**Results**: At baseline, women (n=6422, 37.4%) had higher glycated hemoglobin, longer type 2 diabetes mellitus duration, and were on fewer antihyperglycemic medications. There was no evidence of effect modification of the effect of dapagliflozin by sex for a) cardiovascular death or heart failure hospitalizations: women (3.8% vs 4.5%; HR 0.84, 95% CI, 0.66-1.07) and men (5.3% vs 6.4%; HR 0.83, 95% CI, 0.71-0.96; Pinteraction=0.90); b) cardiovascular death, myocardial infarction, or ischemic stroke: women (6.3% vs 6.8%; HR 0.93, 95% CI, 0.77-1.12) and men (10.% vs 10.7%; HR 0.93, 95% CI, 0.83-1.05; Pinteraction=0.99); or c) renal-composite: women (1.4% vs 2.8%; HR 0.50, 95% CI, 0.35-0.70) and men (1.5% vs 2.5%; HR 0.55, 95% CI, 0.42-0.73; Pinteraction=0.64). The overall safety profile of dapagliflozin was similar for women and men.

**Conclusions/Interpretation**: Dapagliflozin offers comparable CV and renal benefits and a comparable safety profile in women and men.

**Trial registration:** clinicaltrials.gov NCT NCT01730534

**Keywords:** women, SGLT2 inhibitors, clinical trials, cardiovascular outcomes

**Research in context**

* The sodium-glucose co-transporter-2 (SGLT-2) inhibitor dapagliflozin reduces the risk of CV death or heart failure hospitalizations in type 2 diabetes mellitus
* Is the efficacy and safety of dapagliflozin comparable in women and men?
* Dapagliflozin had similar effects on the relative risk of cardiovascular death or heart failure hospitalization, as well as major adverse cardiovascular events in both women and men.
* Dapagliflozin reduced renal-specific events by 45-50% in both women and men.
* The overall safety profile of dapagliflozin was similar for women and men.
* These findings provide important reassurance that dapagliflozin offers comparable efficacy and safety in both women and men.

**Introduction**

 Sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce the risk of cardiovascular (CV) events, including CV death or heart failure (CV death/HHF), in patients with type 2 diabetes mellitus (T2DM)[[1](#_ENREF_1)], and in patients with HF with reduced ejection fraction independent of T2DM status [[2](#_ENREF_2), [3](#_ENREF_3)]. However, since women remain underrepresented across clinical trials, the efficacy and safety of SGLT2 inhibitors by patient sex remains critical to define. Supporting these concerns, sex disparities already exist in the management and treatment of cardiovascular risk factors in women with T2DM [[4](#_ENREF_4)]. In the presence of a similar burden of risk factors, women are less likely than men to be treated with low-density lipoprotein-cholesterol (LDL-C) lowering therapies or to achieve adequate blood pressure or glycemic control [[4](#_ENREF_4)]. As such, in a pre-specified analysis, we assessed in a large population with robust female representation (n=6422, 37.4%) whether sex modifies the efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with T2DM with or at increased risk of atherosclerotic disease in the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial [[5](#_ENREF_5)].

**Methods**:

Study population and procedures

 The design and results of the DECLARE-TIMI 58 trial have been reported previously [[5](#_ENREF_5), [6](#_ENREF_6)]. In brief, DECLARE-TIMI 58 was a phase 3, multinational, double-blind, placebo-controlled trial that randomized 17,160 patients with T2DM with or at risk for atherosclerotic disease to dapagliflozin versus placebo. Eligible patients were 40 years or older with T2DM, had a creatinine clearance >60ml/min and either multiple risk factors for atherosclerotic CV disease or established atherosclerotic CV disease (ASCVD; coronary artery disease, cerebrovascular disease, or peripheral artery disease). Participants with multiple risk factors were required to be men ≥55 years of age or women ≥60 years of age with at least one additional traditional ASCVD risk factor including hypertension, dyslipidemia or current tobacco use. Following a single-blind placebo run-in period, patients who remained eligible were randomized in a double-blind fashion to dapagliflozin 10mg daily versus matching placebo and followed for a median duration of 4.2 years.

Outcomes

 The dual efficacy outcomes were the composites of a) CV death or HF hospitalization (CV death/HHF) and b) CV death, MI or ischemic stroke (MACE). The pre-specified cardiorenal outcome was the composite of an estimated glomerular filtration rate (eGFR) decrease ≥40% to <60 ml/min/1.73m2, end stage renal disease (ESRD) or cardiovascular or renal death. The pre-specified renal-specific outcome was the composite of a ≥40% drop in eGFR to <60 ml/min/1.73m2, new ESRD or renal death. Safety events collected were adverse events leading to drug discontinuation, adverse events of special interest (AEOSI) or serious adverse events (SAEs). An independent and blinded clinical events committee adjudicated all CV outcomes analyzed.

Statistical analysis

 Baseline characteristics are presented as medians (interquartile ranges) for continuous variables and frequencies for categorical variables. Baseline characteristics were compared with the Wilcoxon rank sum tests for continuous variables and χ2 tests for categorical variables.

Mixed models for repeated measures in HbA1c, weight, systolic blood pressure and diastolic blood pressure were analyzed to produce least-squares mean estimates and 95% CIs by treatment and sex subgroup. Efficacy analyses were conducted with Cox proportional hazards models that included treatment arm, the two randomization stratification factors (presence of established atherosclerotic disease and baseline hematuria) and run separately by patient sex as captured on the electronic case-report form. Effect modification was assessed by including interaction terms in the models. All efficacy analyses were conducted in the intention-to-treat study population and event rates are reported as Kaplan-Meier estimates at 4 years. Safety analyses were performed using the on-treatment analysis set, as previously described, except for amputation, fracture and malignancy outcomes which included all events after first dose in all patients who were randomized and received at least one dose of study drug.[[5](#_ENREF_5), [7](#_ENREF_7)] All tests were two-sided with a P value <0.05 considered to be significant. The TIMI Study Group conducted all analyses. Analyses were performed with use of Stata/SE version 16.1 (Stata Corp., College Station, Texas) or SAS version 9.4 (SAS Institute, Inc, Cary, NC).

**Results**

 Of the 17,160 patients enrolled in the DECLARE-TIMI 58 trial, 6422 (37.4%) were women. The baseline characteristics of the study population by patient sex are summarized in Table 1. Women were treated with fewer non-insulin antihyperglycemic medications than men (Table 2), and these findings were largely consistent across regions (Supplementary Table 1) and by age and/or qualifying disease status (Supplementary Table 2). The use of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide 1 receptor agonists (GLP1-RA) were all significantly lower in women than men (P<0.001). Background use of insulin and sulfonylureas did not differ by sex (Table 2). Crude rates of study drug discontinuation were similar in both women and men (23.6% vs 22.8%, P=0.23), including both the active (21.3% vs 21.0%, P=0.72) and placebo arms (25.8% vs 24.6%, P=0.21).”

Effect of dapagliflozin on cardiovascular risk factors

 Patients randomized to dapagliflozin had a lower HbA1c at month 12 than patients randomized to placebo in both women [least-squares mean (LSM) absolute difference [-0.49%, 95% CI -0.55, -0.43) or (-3.59 mM, 95% CI -4.30, -2.87] and men [-0.55%, 95% CI -0.59, -0.51) or (-3.81 mM, 95% CI -4.36, -3.25); P interaction=0.07]. Similarly, patients treated with dapagliflozin had lower weight at 12 months than placebo-treated patients regardless of sex [12 month LSM absolute difference -1.7 kg, 95% CI -1.9, -1.6) (women); -1.8 kg, 95% CI -2.0, -1.7) (men); P interaction=0.64]. At 12 months, patients treated with dapagliflozin had lower systolic blood pressure than placebo-treated patients for both women [-2.7 mmHg (95% CI -3.4, -2.0)] and men [-3.0 mmHg (95% CI -3.5, -2.5)](P interaction=0.52); similarly, between treatment group differences for diastolic blood pressure was -0.8mmHg (95% CI -1.2, -0.4) in women and -0.9 mmHg (95% CI -1.2, -0.6) in men (P interaction=0.87).

Efficacy outcomes

In the placebo arm, the crude incidence of CV death/HHF was 4.5% in women and 6.4% in men, and for MACE was 6.8% in women and 10.7% in men. All-cause mortality at 4 years was 5.4% in women and 6.3% in men. The incidence for MACE remained lower in women than men for those patients with (13.3% vs 16.2%) or without established ASCVD (4.0% vs 6.2%). Similarly, the incidence of CV death/HHF was lower in women than men in those with (15.2% vs 22.3%) or without a prior HF (3.5% vs 4.6%).

Dapagliflozin reduced the risk of CV death/HHF in women (HR 0.84, 95% CI, 0.66-1.07) and in men (HR 0.83, 95% CI, 0.71-0.96; P interaction=0.90; Figure 1). The effects of dapagliflozin on risk of MACE did not differ between women (HR 0.93, 95% CI, 0.77-1.12) and men (HR 0.93, 95% CI, 0.83-1.05; P interaction=0.99; Table 3). Effects of dapagliflozin on risk of MI also did not differ by sex (women: HR 0.89, 95% CI, 0.67-1.17; men: HR 0.88, 95% CI, 0.75-1.03; P interaction=0.99).

The cardiorenal composite outcome was reduced by dapagliflozin in women (HR 0.68, 95% CI 0.54-0.86) and in men (HR 0.81, 95% CI 0.68-0.96; P interaction=0.26; Table 3). For the renal-specific composite outcome, similar results were observed: women (HR 0.50, 95% CI, 0.35-0.70) and in men (HR 0.55, 95% CI, 0.42-0.73; P interaction=0.64; Figure 2; Supplementary Figure 1).

In patients with established ASCVD, the HR for dapagliflozin versus placebo for risk of MACE was 0.85 (95% CI 0.66-1.09) in women and 0.91 (95% CI 0.79-1.05; P interaction=0.63) in men.

In patients with prior HF, dapagliflozin reduced the risk of CV death/HHF in women (0.78, 95% CI, 0.51-1.20) and in men (HR 0.81, 95% CI, 0.62-1.05; P interaction=0.89). In patients with prior MI, the HR for dapagliflozin versus placebo for risk of MACE was 0.71 (95% CI, 0.50-1.02) in women and 0.88 (95% CI 0.74-1.06; P interaction=0.29) in men. Similarly, the HR for dapagliflozin versus placebo for risk of recurrent MI in patients with prior MI were 0.70 (95% CI, 0.45-1.10) in women and 0.80 (95% CI, 0.63-1.00; P interaction= 0.65) in men.

Safety outcomes

Treatment emergent serious adverse events were less common in dapagliflozin-treated than placebo-treated patients in both women (29.3% vs 31.5%) and men (36.9% vs 39.0%; P interaction=0.78; Table 4). Urinary tract infections (serious adverse events or leading to drug discontinuation) were more frequent in women than men, but were not different in those randomized to dapagliflozin or placebo, irrespective of sex (women: 2.2% vs 2.1%; men: 1.0% vs 1.2%; P interaction=0.30); genital mycotic infections (serious adverse events or leading to drug discontinuation) were more common with dapagliflozin in both women (1.0% vs 0.1%) and men (0.8% vs 0.1%; P interaction=0.93). The incidence of DKA with dapagliflozin versus placebo was 0.5% versus 0.2% in women and 0.2% versus 0.1% in men (P interaction=0.56). The incidence of amputation with dapagliflozin as compared with placebo was not different between women (0.7% vs 0.6%) and men (1.9% vs 1.7%; P interaction=0.87; Table 4).

 **Discussion**

 In patients with T2DM with or at high risk for ASCVD, the SGLT2 inhibitor dapagliflozin demonstrated comparable efficacy and safety in both women and men. Specifically, dapagliflozin significantly reduced the risk of CV death or HF hospitalization by 16-17% irrespective of sex. Dapagliflozin also significantly reduced the risk of renal events including a 45-50% reduction in renal-specific events irrespective of sex.

The current analysis uncovered notable differences at baseline in the management of T2DM in women and men. Although women had slightly higher baseline HbA1c and slightly longer duration of T2DM, women were less likely to be treated with non-insulin antihyperglycemic medications including metformin, DPP-4 inhibitors and GLP-1 receptor agonists. Although not previously well described for antihyperglycemic medications in patients with T2DM, it is well established that women are less likely to be treated with evidence-based therapies across several disease states, including the management of cardiovascular disease [[8](#_ENREF_8)]. Although the reasons for these differences may be multifactorial and need to continue to be elucidated, continued emphasis on the use of appropriate evidence-based therapies in the setting of cardiovascular risk factors in both women and men is of the utmost importance. In the current analysis, it cannot be determined whether the relative underuse of non-insulin antihyperglycemic medications in women was warranted, but may serve as an important avenue for future research.

To date, the efficacy and safety of SGLT2 inhibitors in women compared to men has not been extensively evaluated. In the EMPA-REG OUTCOME trial (n=2004 women), empagliflozin demonstrated comparable benefit toward reducing CV events and slowing worsening nephropathy irrespective of sex, but suggested a possible absolute excess in the risk of genital infections with empagliflozin in women (10.0% vs 2.5%) when compared with men (2.6% vs 1.5%). Other safety outcomes were not specifically reported by sex [[9](#_ENREF_9)]. In the CANVAS program (n=3633 women) [[10](#_ENREF_10)] and CREDENCE trial (n=1494 women)[[11](#_ENREF_11)], canagliflozin similarly had comparable CV and renal protective effects by sex, but safety data by sex were not published. Prior to the completion of DECLARE-TIMI 58, a pooled analysis of phase IIb/III data for dapagliflozin demonstrated that women were more likely than men to experience urinary tract or genital infections irrespective of treatment with dapagliflozin, but did not specifically address the relative risk of these events for women and men treated with the drug owing to relatively fewer events (n=667 women and 3296 men treated with dapagliflozin in 24-week pool).[[12](#_ENREF_12)]

In the present analyses of DECLARE-TIMI 58 (n=6422 women with a median follow-up of 4.2 years), dapagliflozin demonstrated similar CV efficacy and renal protection in both women and men. In DECLARE-TIMI 58, in patients with prior MI, dapagliflozin significantly reduced the risk of recurrent MI by 22% (95% CI 5-27%) in the overall trial with directionally similar effects in women (30% RRR) and men (20% RRR), thereby supporting the concept that the CV benefits of SGLT2 inhibition toward reducing atherosclerotic events may be enhanced in patients with established coronary disease [[1](#_ENREF_1)]. Although dapagliflozin increased the risk of genital mycotic infections (serious adverse events or those leading to drug discontinuation), the relative excess was similar in both women (1.0% vs 0.1%) and men (0.8% vs 0.1%), and urinary tract infections were not increased compared with placebo; however, the patients at highest risk of genitourinary infections may not have been enrolled in the trial. Although infrequent, a numerical excess in DKA cases was also observed with dapagliflozin versus placebo, as has been described with other SGLT2 inhibitors, in both women (0.5% vs 0.2%) and men (0.2% vs 0.1%). Symptoms of volume depletion and amputation risk were not increased with dapagliflozin in patients of either sex.

Limitations to the current analyses include that individual subgroups were underpowered for statistical significance, therefore one cannot definitively exclude that differences in efficacy and safety could emerge by patient sex in a larger study population. Nonetheless, the DECLARE-TIMI 58 trial was the largest of the phase 3 trials of an SGLT2 inhibitor in T2DM.[[10](#_ENREF_10), [13](#_ENREF_13), [14](#_ENREF_14)]

In summary, the use of and interest in SGLT2 inhibitors with regard to CV and kidney effects has continued to expand due to randomized trials that have demonstrated consistent CV and kidney benefit in patients with or without T2DM in the presence of CKD or heart failure with reduced left ventricular ejection fraction. Therefore, the current results provide important reassurance that the efficacy and safety of dapagliflozin are consistent in both women and men.

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**Figure Legend**

**Figure 1**: The cumulative incidence of CV death or HF hospitalization in women and men by randomized treatment arm in DECLARE-TIMI 58.

**Figure 2**: The cumulative incidence of renal-specific events (eGFR decrease ≥40% to <60 ml/min/1.73m2, end-stage renal disease, or renal death) by patient sex and randomized treatment arm. Kaplan-Meier event rates at 4 years are displayed.

**Table 1**: Baseline characteristics for women and men in DECLARE-TIMI 58.

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Men****(N =10,738)** | **Women****(N =6422)** | **P value** |
| Age (years) | 63 (58-68) | 65 (61-69) | <0.01 |
| White (%) | 81.5 | 76.3 | <0.01 |
| BMI (kg/m2), median (IQR) | 31 (28-35) | 32 (28-36) | <0.01 |
| Current tobacco (%) | 16.9 | 10.6 | <0.01 |
| Region (%)North AmericaEuropeLatin AmericaAsia Pacific | 34.543.99.212.3 | 27.445.313.913.4 | <0.01 |
| Established CV disease (%) | 46.8 | 30.3 | <0.01 |
| Prior myocardial infarction (%) | 25.5 | 13.2 | <0.01 |
| HbA1c (mM), median (IQR) | 63.9 (56.3-74.9) | 65.0 (57.4-76.0) | <0.01 |
| HbA1c (%), median (IQR) | 8.0 (7.3-9.0) | 8.1 (7.4-9.1) | <0.01 |
| eGFR (CKD-EPI), median (IQR) (ml/min/1.73m2) | 88 (75-97) | 89 (75-96) | 0.91 |
| UACR, median (IQR) (mg/g) | 14 (6-53) | 12 (7-32) | <0.01 |
| LDL-C, median (IQR) (mg/dl) | 78 (59-102) | 90 (68-117) | <0.01 |
| LV ejection fraction (%) (n=4088) | 56 (49-62) | 60 (55-65) | <0.01 |
| Duration of T2DM, median (IQR) (years) | 10 (6-16) | 11 (6-17) | <0.01 |

Abbreviations: BMI, body mass index; IQR, interquartile range; CV, cardiovascular; UACR, urinary albumin-to-creatinine ratio; T2DM, type 2 diabetes mellitus; LV, left ventricular

**Table 2**: Baseline use of anti-hyperglycemic medication for women and men.

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Men****(N =10,738)** | **Women****(N =6422)** | **P value** |
| Insulin (%) | 41.0 | 40.7 | 0.71 |
| Any non-insulin anti-hyperglycemic medication (%) | 89.7 | 88.7 | 0.028 |
| ≥3 anti-hyperglycemic medications (%) | 20.6 | 16.4 | <0.001 |
| Metformin (%) | 82.8 | 80.6 | <0.001 |
| Sulfonylurea (%) | 42.7 | 42.6 | 0.87 |
| DPP4 inhibitor (%) | 18.0 | 14.9 | <0.001 |
| GLP1 receptor agonist (%) | 4.8 | 3.7 | <0.001 |

Abbreviations: DPP, dipeptidyl peptidase; GLP, glucagon-like peptide

**Table 3**: Efficacy of dapagliflozin versus placebo stratified by patient sex. P interaction reflects the 2-way interaction between treatment arm and sex in a Cox model. Event rates are Kaplan-Meier estimates at 4 years.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Dapagliflozin****N=3171 women****N=5411 men** | **Placebo****N=3251 women****N=5327 men** | **HR (95% CI)** | **P interaction** |
| **Outcome** | **Sex** | Event rate | Event rate |
| CV death or HF hospitalization (%) | Women | 3.8 | 4.5 | 0.84 (0.66-1.07) | 0.90 |
| Men | 5.3 | 6.4 | 0.83 (0.71-0.96) |
| CV death, MI or ischemic stroke (%) | Women | 6.3 | 6.8 | 0.93 (0.77-1.12) | 0.99 |
| Men | 10.0 | 10.7 | 0.93 (0.83-1.05) |
| CV death (%) | Women | 2.1 | 2.4 | 0.93 (0.67-1.27) | 0.69 |
| Men | 3.1 | 3.0 | 1.00 (0.81-1.24) |
| MI (%) | Women | 3.0 | 3.2 | 0.89 (0.67-1.17) | 0.99 |
| Men | 5.5 | 6.2 | 0.88 (0.75-1.03) |
| Stroke (%) | Women | 2.5 | 2.4 | 1.05 (0.77-1.42) | 0.48 |
| Men | 3.1 | 3.5 | 0.92 (0.75-1.13) |
| HF hospitalization (%) | Women | 2.1 | 2.5 | 0.81 (0.59-1.12) | 0.44 |
| Men | 2.7 | 3.9 | 0.70 (0.56-0.86) |
| Sustained eGFR decrease ≥40% to <60ml/min/1.73m2, ESRD or renal or CV death (%) | Women | 3.5 | 5.1 | 0.68 (0.54-0.86) | 0.26 |
| Men | 4.6 | 5.4 | 0.81 (0.68-0.96) |
| Sustained eGFR decrease ≥40% to <60ml/min/1.73m2, ESRD or renal death (%) | Women | 1.4 | 2.8 | 0.50 (0.35-0.70) | 0.64 |
| Men | 1.5 | 2.5 | 0.55 (0.42-0.73) |

**Table 4:** The safety of dapagliflozin versus placebo stratified by patient sex. P interaction reflects the 2-way interaction between treatment arm and sex in a Cox model. Event rates are n/N in the on-treatment analysis set.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Dapagliflozin****N=3169 women****N=5405 men** | **Placebo****N=3246 women****N=5323 men** | **HR (95% CI)** | **P interaction** |
| **Outcome** | **Sex** | Event rate  | Event rate |
| Treatment-emergent SAE (%) | Women | 29.3 | 31.5 | 0.90 (0.82-0.98) | 0.78 |
| Men | 36.9 | 39.0 | 0.91 (0.86-0.97) |
| Major hypoglycemic event (%) | Women | 0.7 | 0.7 | 0.95 (0.54-1.68) | 0.16 |
| Men | 0.6 | 1.1 | 0.57 (0.38-0.87) |
| Diabetic ketoacidosis (%) | Women | 0.5 | 0.2 | 2.64 (1.03-6.74) | 0.56 |
| Men | 0.2 | 0.1 | 1.75 (0.65-4.72) |
| Urinary tract infection (%) | Women | 2.2 | 2.1 | 1.06 (0.76-1.48) | 0.30 |
| Men | 1.0 | 1.2 | 0.81 (0.57-1.15) |
| Genital infection (%) | Women | 1.0 | 0.1 | 8.09 (2.86-22.9) | 0.93 |
| Men | 0.8 | 0.1 | 8.60 (3.41-21.7) |
| Malignancy event (%) | Women | 4.1 | 4.7 | 0.85 (0.67-1.08) | 0.15 |
| Men | 6.5 | 6.2 | 1.04 (0.90-1.21) |
| Acute renal failure (%) | Women | 3.1 | 3.2 | 0.93 (0.70-1.22) | 0.07 |
| Men | 3.6 | 5.1 | 0.69 (0.57-0.82) |
| Symptoms of volume depletion (%) | Women | 1.7 | 1.8 | 0.88 (0.61-1.27) | 0.43 |
| Men | 3.0 | 2.8 | 1.05 (0.84-1.31) |
| Amputation (%) | Women | 0.7 | 0.6 | 1.13 (0.62-2.04) | 0.87 |
| Men | 1.9 | 1.7 | 1.07 (0.80-1.41) |
| Fracture (%) | Women | 7.2 | 6.6 | 1.09 (0.90-1.31) | 0.52 |
| Men | 4.3 | 4.2 | 1.00 (0.83-1.20) |

Abbreviations: SAE, serious adverse event; DAPA, dapagliflozin; HR, hazard ratio; CI, confidence interval

Diabetic ketoacidosis and malignancy events were independently adjudicated. Diabetic ketoacidosis events reported are those adjudicated as definite or probable.

**Figure 1:**



**Figure 2:**

