**Effects of dapagliflozin on hospitalisations in patients with type 2 diabetes: post hoc analyses of the DECLARE-TIMI 58 trial**

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**Abstract:**

**Background**:

In patients with type 2 diabetes (T2D) at high cardiovascular or kidney risk, sodium-glucose co-transporter 2 (SGLT2) inhibitors consistently reduce the risk of hospitalisations for heart failure. Less is known about their effects on hospitalisation from any-cause, especially in patients with T2D without atherosclerotic cardiovascular disease (ASCVD), comprising most of the global T2D population. We aimed to assess the effect of the SGLT2 inhibitor dapagliflozin on the risks of hospitalizations for any-cause and for specific causes in patients with T2D with and without ASCVD.

**Methods**:

The DECLARE-TIMI 58 trial (NCT01730534) randomised patients with T2D and either risk factors for or established ASCVD to receive oral dapagliflozin 10mg or placebo (1:1) once daily. In post-hoc analyses, the effects of dapagliflozin on risks of first non-elective hospitalisation, both any-cause and cause-specific, were assessed using Cox proportional hazards regression models overall and in the subset of participants without prevalent ASCVD. The risk of total (first plus subsequent) hospitalisations was assessed using Lin-Wei-Ying-Yang model. Investigator-reported System Organ Class terms were used to classify cause-specific hospitalisations.

**Findings**:

A total of 17,160 patients were enrolled, 6974 (40.6%) with established ASCVD and 10,186 (59.4%) with multiple risk factors. Over 4.2 years median follow-up, dapagliflozin was associated with a lower risk of first hospitalisation for any-cause (2779/8582 (32.4%) vs. 3036/8578 (35.4%); HR 0.89 [95% CI 0.85-0.94]) and total hospitalisations (RR 0.92 [0.86-0.97]). The association between dapagliflozin use and the risk of first hospitalisation for any-cause was consistent and significant in subsets of patients with and without ASCVD at baseline (HR 0.92 [95% CI 0.85-0.99)] and 0.87 [0.81-0.94], respectively; p-interaction=0.31). Compared with placebo, patients treated with dapagliflozin had lower risks of first hospitalisations due to cardiac disorders (2153 patients; HR [95% CI] 0.91 [0.84- 0.995]), metabolism and nutrition disorders (408 patients; 0.73 [0.60-0.89]), renal and urinary disorders (311 patients; 0.61 [0.49-0.77]), and due to any other cause (4349 patients; 0.90 [0.85-0.96]).

**Interpretation**:

Dapagliflozin reduced the risk of first and total hospitalisations for any cause in patients with T2D, regardless of the presence of ASCVD, including hospitalisations not directly attributed to cardiac, kidney, or metabolic causes. These findings may have implications on patients’ health-related quality of life and on T2D attributed costs.

**Funding**: AstraZeneca

**Key words:** hospitalisations; dapagliflozin; type 2 diabetes; SGLT2 inhibitors; cardiovascular disease

**Research in context**

**Evidence before this study**

We searched PubMed between January 1, 2000, and October 1, 2022, for trials published in English, using the terms “SGLT2”, “SGLT2 inhibitor”, “type 2 diabetes”, “All cause hospitalisations”, “All cause hospital admissions”, and “randomised controlled clinical trial”.

Hospitalisations are common in patients with type 2 diabetes (T2D). About a third of T2D-attributed expenditure is due to hospitalisations. In randomised controlled trials, sodium–glucose co-transporter 2 inhibitors (SGLT2i) reduced the relative risks of cardiovascular and kidney outcomes in patients with T2D at high cardiovascular risk, as well as in patients with heart failure (HF) or chronic kidney disease with or without T2D. In these trials, SGLT2i consistently reduced the risk of hospitalisations due to heart failure. In patients with T2D and established atherosclerotic cardiovascular disease (ASCVD) or with recent worsening HF, and in patients with chronic kidney disease with or without T2D, SGLT inhibitors have been shown to reduce the risk of hospitalisations from any-cause. However, it is not clear whether SGLT2i affect the risk of hospitalisations from any-cause in patients without ASCVD, comprising the majority of the global population with T2D. Moreover, data on the effect of SGLT2i on cause-specific hospitalisations other than HF is lacking.

The DECLARE-TIMI 58 trial was conducted at 882 sites in 33 countries. It compared dapagliflozin versus placebo (1:1) among 17160 patients with T2D, and creatinine clearance (CrCl)>60 mL/min, 10,186 (59.4%) with risk factors for but without established ASCVD.

**The added value of this study**

In these post-hoc analyses, we assessed the effects of dapagliflozin on the risks for any-cause and cause-specific hospitalisations (excluding elective hospitalisations). Over 4.2 years median follow-up, 2779/8582 (32.4%) and 3036/8578 (35.4%) of the patients treated with dapagliflozin and placebo were hospitalised, respectively (HR 0.89 [95% CI 0.85-0.94]). The number needed to treat to prevent one patient from being hospitalised was 34 during the trial. Compared with placebo, dapagliflozin significantly reduced the risk of hospitalisations for any-cause in patients with and without ASCVD by 8% and 13%, respectively (p-value for interaction=0.31). Dapagliflozin reduces the risk of hospitalisations due to cardiac disorders, metabolism and nutrition disorders, and renal and urinary disorders. It also reduced the risk of hospitalisations due to any reasons other than cardiac, renal and urinary, and metabolism and nutrition disorders.

**Implications of all the available evidence**

SGLT2i reduce the risk of hospitalisations from any cause in patients with T2D at high cardiovascular risk, including patients without evidence of kidney disease or ASCVD. The benefits of SGLT2i in reducing the risk of hospitalisations may extend beyond their direct cardiovascular, kidney, or metabolic benefits.

**Introduction:**

Patients with type 2 diabetes (T2D) are at increased risk for hospitalisation1,2. Hospitalisations reduce patients’ quality of life and impose a significant burden on healthcare systems and payors 1,2 .

In randomised, controlled trials, sodium–glucose co-transporter 2 inhibitors (SGLT2i) have been shown to improve cardiovascular and kidney outcomes in patients with T2D at cardiovascular or kidney risk 3–9. In these trials, SGLT2i robustly and consistently reduced the risk for hospitalisation due to heart failure (HF). However, less is known regarding their effects on the risk of hospitalisation for any cause. Available data, suggesting a reduction for selected SGLT inhibitors, mainly derives from trials of relatively high-risk populations, including patients with T2D and either established atherosclerotic cardiovascular disease (ASCVD) 10 or recent worsening HF 11, or patients with chronic kidney disease (CKD) with or without T2D12. However, 60-70% of the global population of patients with T2D do not have established ASCVD or HF 13,14. Thus, an open question persists whether SGLT2i reduce the risk for hospitalisation for any cause in patients with T2D without evidence of kidney disease or ASCVD. It is also unclear if SGLT2i modify the risk of hospitalisations due to specific causes other than HF.

The DECLARE-TIMI 58 trial assessed the cardiovascular safety and efficacy of dapagliflozin in patients with T2D, with baseline creatinine clearance of >60 mL/min and high risk for or established ASCVD5. The trial results demonstrated the CV safety of dapagliflozin in this population and achieved statistical superiority of dapagliflozin for one of its dual-primary efficacy outcomes (composite of hospitalisation due to HF or CV death), but not the other (composite of CV death, non-fatal myocardial infarction or stroke)5. In the present post-hoc analyses, the effects of dapagliflozin on the risks of any-cause or cause-specific hospitalisations were assessed, focusing on the subgroup of patients without evidence of ASCVD.

**Methods**:

Trial design:

The DECLARE-TIMI 58 trial was a double-blind, multicentre, randomised, placebo-controlled trial that recruited patients with T2D at 882 sites in 33 countries. Participants were required to be ≥40 years old and have evidence of ASCVD or be ≥55 years for men or ≥60 years for women and have multiple risk factors (MRF) for ASCVD. The full trial protocol and the results of the main primary and secondary outcomes have been previously published 5,15.

The trial protocol was approved by ethics committees for all participating centres, and all participants provided written informed consent. The trial was conducted according to the principles of the Declaration of Helsinki and was registered with clinicaltrials.gov (identifier: NCT03036150).

Procedure:

Participants were randomised to receive dapagliflozin 10 mg once daily or a matching placebo (1:1) in addition to the standard of care. Randomisation was stratified on the presence of ASCVD and on the presence of haematuria at baseline 5,16. Participants, treating teams, and trial personnel were blinded to treatment allocation.

Outcomes and subgroups

Hospitalisations were reported by the investigators as part of the trial adverse event monitoring process and were classified as either elective or non-elective. Causes for hospitalisation were classified centrally using the Medical Dictionary for Regulatory Activities (MedDRA; https://www.meddra.org/) System Organ Class nomenclature of adverse event reporting. The risk of non-elective hospitalisations for any cause was the main outcome of the present post-hoc analyses. Other outcomes analysed were elective hospitalisation; a composite of non-elective plus elective hospitalisations; prolonged non-elective hospitalisation (≥3 days or in-hospital death); and very prolonged non-elective hospitalisation (≥7 days or in-hospital death). Hospitalisations durations were defined by the admission and discharge dates (Appendix pxx).

The effect of dapagliflozin on the risk of hospitalisation was determined by baseline characteristics: sex, age (<65 or ≥65 years), race (White or non-White), region (Asia/Pacific, Eastern Europe, Western Europe, Latin America, or North America), presence of ASCVD or MRF, diabetes duration (≤5, >5-≤15, or >15 years), history of hypertension, history of HF, body mass index (<30 or ≥30 kg/m2), glycated haemoglobin (<7, 7-<8, 8-<9, ≥9%), estimated glomerular filtration rate (≥90, 60-90, <60 mL/min/1.73m2 17), urine albumin-to-creatinine ratio (≤15, 15-<30, 30-<300, ≥300 mg/g), subgroups according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification for risk of developing end stage kidney disease (low, moderate, high, or very high) 18, insulin treatment, and use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs). Another subgroup included patients with both low KDIGO risk and no evidence of ASCVD.

Statistical analysis

Categorical variables are reported as frequencies and continuous parameters as median [IQR]. Comparisons of baseline variables among groups of patients defined by the number of non-elective hospitalisations experienced during the trial (0, 1-2, or ≥3 events) were performed using the Cochran Armitage trend test (categorical values) or the Jonckheere-Terpstra test (continuous values).

Analyses of outcomes were performed according to the intention-to-treat principle. Between arm comparison of the cumulative days in hospital of all non-elective hospitalisations was carried out using Mann-Whitney U test. Incidence is reported by the proportion of patients with an event during the trial, and event rates are reported using 4-year Kaplan-Meier estimates. Cox proportional hazards regression models were used for analyses of time to first event. Proportional hazards assumptions were confirmed by checking cumulative sums of martingale residuals. Analyses were performed in the whole trial population and by baseline subgroups. The number of patients needed to treat (NNT) to prevent one event during the trial follow-up was calculated based on the absolute risk reductions using the proportion of patients experiencing an event. Recurrent event analyses were performed using Lin-Wei-Yang-Yin models. The risk of events with dapagliflozin versus placebo by the number of events (for the first six events) were compared using Wei-Lin-Weissfeld model. Cox, Lin-Wei-Yang-Yin, and Wei-Lin-Weissfeld models were adjusted to the trial stratification factors (presence of ASCVD; and the presence of haematuria)5.

These are post-hoc analyses. P-values are reported for descriptive purposes. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

Role of the funding source

The trial sponsor was involved in trial design, data collection and analyses, data interpretation, the writing of the report, and in the decision to submit the paper for publication. The authors had the freedom to make decisions in all aspects of data analyses and manuscript preparation.

**Results**

Baseline characteristics

Overall, 17,160 patients were recruited, 6422 (37.4%) were women, 9253 (53.9%) were younger than 65 years, 10,186 (59.4%) did not have evidence of ASCVD, and 6835 (39.8%) had both no evidence of ASCVD and low KDIGO risk18. During a median follow-up of 4.2 years, there were 14,067 hospitalisations, most (n=11,552 [82.1%]) were non-elective. Of the trial population, 6577 (38.3%) experienced at least one hospitalisation, and 5815 (33.9%) experienced at least one non-elective hospitalisation. Participants who experienced a higher number of non-elective hospitalisations during follow-up were more likely to be men, have a history of ASCVD or HF, or have evidence of kidney disease indicated by lower eGFR or higher albuminuria at baseline (**Appendix Pxx <Supplementary Table S1>**).

Effect of dapagliflozin on non-elective hospitalisations from any-cause

Compared with placebo, dapagliflozin was associated with a lower risk for first non-elective hospitalisation for any cause (HR=0.89 [95% CI 0.85-0.94]; p<0.001; NNT of 34 [95% CI 23-63] patients during the trial) and total (first plus subsequent) non-elective hospitalisations for any cause (RR 0.92 [0.86-0.97]; p=0.0047) (**Figure 1**). Dapagliflozin treatment effects remained significant when assessing the risk of prolonged (≥3 days) or very prolonged (≥7 days) non-elective hospitalisations, and when testing the effect on the composite of non-elective plus elective hospitalisations. No significant between-arm differences were observed in the risk of first or total elective hospitalisations (**Figure 1**). Comparing the risk of hospitalisations by their order, dapagliflozin group had a lower risk of first (HR=0.89 [95% CI 0.85-0.94]), second (0.90 [0.83-0.97]), and third hospitalisations (0.88 [0.79-0.98]), however there was no evidence that it significantly reduced the risk of subsequent hospitalisations (**Appendix Pxx <Supplementary Figure S1>**). The cumulative days in hospital of all non-elective hospitalisations during the trial were 48,175 versus 51,039 days in the dapagliflozin versus placebo arm, respectively (p<0.0001). The respective mean (SD) number of days spent in hospital per patient during the trial were 5.6 (xx) and 6.0 (xx) days.

Effect of dapagliflozin on the risks of hospitalisations by subgroups

Non-elective hospitalisations occurred among 3054/10,186 (43.8%) of the patients with established ASCVD, and in 2,761/6,974 (27.1%) of those with MRF (**Figure 2**). Compared with placebo, dapagliflozin was associated with a lower risk of first non-elective hospitalisation in patients with either established ASCVD (HR 0.92 [95% CI 0.85-0.99]; NNT 35 [95% CI 20-180]) or with MRF but without evidence of ASCVD (0.87 [0.81-0.94]; NNT 34 [22-79]) (p-interaction=0.31) (**Figure 2**). There was no evidence that the effect of dapagliflozin on risk of non-elective hospitalisation varied by other baseline subgroups (p-interaction for the different subgroups ranging between 0.062-0.89) (**Figure 3**). The HRs in patients with baseline diabetes duration ≤5, >5-≤15, or >15 years were 0.98 [0.87-1.10], 0.90 [0.83-0.97], and 0.83 [0.76-0.91], respectively (p-interaction=0.074; p-trend 0.030 when baseline diabetes duration was analysed as a continuous variable). In those with low KDIGO risk and without evidence of ASCVD, the HR for non-elective hospitalisation with dapagliflozin versus placebo was 0.83 ([95% CI 0.76-0.92]) (**Figure 3**).

Effect of dapagliflozin on hospitalisation by System Organ Class aetiology

Compared with placebo, patients treated with dapagliflozin had a reduced risk of first non-elective hospitalisation due to cardiac disorders (HR [95% CI] 0.91 [0.84- 0.995]), infections and infestations (0.86 [0.78-0.96]), metabolism and nutrition disorders (0.73 [0.60-0.89]), musculoskeletal and connective tissue disorders (0.81 [0.67-0.99]) and renal and urinary disorders (0.61 [0.49-0.77]) (**Figure 4**). Dapagliflozin was also associated with a lower risk of non-elective hospitalisations due to any aetiology excluding cardiac, renal and urinary-, and metabolism and nutrition-related disorders (0.90 [0.85-0.96]) (**Figure 4 and Appendix Pxx**). Considering total events (first plus subsequent), patients treated with dapagliflozin had a lower risk of hospitalisations due to renal and urinary-, and metabolism and nutrition-related disorders (**Appendix Pxx <supplementary Figure S2>**).

**Discussion**

Assessment of effects on the outcome of any-cause hospitalisations has not been reported from most cardiovascular outcome trials, although it has significant implications on individual patients’ health-related quality of life and overall burden on healthcare systems and payors. During the DECLARE-TIMI 58 trial’s median follow-up of 4.2 years, non-elective hospitalisations occurred in approximately a third of the participants. Dapagliflozin reduced the risk of non-elective hospitalisations, with effects observed both in patients with established ASCVD and in patients with risk factors but without an established disease. Compared with placebo, those randomised to dapagliflozin had a lower risk for first hospitalisations due to cardiac disorders, renal and urinary disorders, metabolism and nutrition disorders, and from any-cause excluding these three aetiologies.

Six other cardiovascular or kidney outcome trials assessed the effect of SGLT inhibitors on all-cause hospitalisation events in different populations: EMPA-REG OUTCOME 10, EMPA-KIDNEY12, DAPA-CKD , EMPEROR-Preserved19, SOLOIST-WHF11, and the CANVAS trials program 4,20. In some analyses10–12,20,21, but not in others4,19, SGLT inhibition was shown to reduce the risk of any-cause hospitalization22. In patients with chronic kidney disease (CKD) with or without T2D (EMPA-KIDNEY12 and DAPA-CKD21), or with T2D and established ASCVD (EMPA-REG OUTCOME10), SGLT2 inhbitors reduced the risk of first and total (first plus subsequent) non-elective hospitalisations. In patients with T2D and recent worsening of HF (SOLOIST-WHF), sotagliflozin (a dual SGLT 1 and 2 inhibitor) increased the number of days alive and out of hospital by 3% (p=0.027) 11. However, in patients with HF and preserved ejection fraction with or without T2D (EMPEROR-Preserved), empagliflozin did not significantly reduce the risk of total (first plus subsequent) hospitalisations 19. In the CANVAS trials program, which included patients with T2D and high risk for or established ASCVD, canagliflozin was associated with a marginally statistically significant 6% (95% CI, 0-12) reduction in risk of the pre-specified event of first hospitalisation for any cause4. In post hoc analyses, canagliflozin reduced the risk of total (first plus subsequent) non-elective hospitalisations by 8% (95%CI 2-14). This effect was not statistically significant within subgroups of patients with or without evidence of ASCVD at baseline20. Compared with these trials, the DECLARE-TIMI 58 included a larger number of participants followed for a longer period, resulting in more hospitalisations events and increased power. These analyses of the trial demonstrate that dapagliflozin use is associated with a lower risk of non-elective hospitalisation for any cause in patients with T2D in both subsets, with or without ASCVD at baseline. The effects remained significant when considering all (first plus subsequent) hospitalisations, prolonged hospitalisations, or when pooling together elective and non-elective hospitalisations.

Results from the present analyses add novel insights to previously reported data. First, drawbacks of many cardiovascular and kidney outcomes trials are their limited representativeness of the general population and short follow-up. The DECLARE-TIMI 58 trial enrolled a large population of patients with a broad spectrum of baseline cardiovascular and kidney risk, underpinning the generalizability of results to the real-world population of patients with T2D 23. Combining the large trial population with a breadth of clinical risk with a long median follow-up of over four years allowed the demonstration of lower risk for non-elective hospitalisations with dapagliflozin, even in patients with T2D without baseline established ASCVD or kidney disease. Notably, the absolute reduction in risk of hospitalisation for any cause in patients without established ASCVD remained high, with a number needed to treat of 34 patients over 4.2 year median follow-up, highlighting the clinical relevance of these findings.

Secondly, these analyses included a systematic assessment of the risk of hospitalisations by their causes as reported by investigators via the trial adverse event reporting process. As expected by the benefits reported across the SGLT2i class on cardiovascular, kidney, and glycaemic outcomes, dapagliflozin reduced the risk of hospitalisation due to cardiac; renal and urinary; and metabolism and nutrition disorders. The reductions in hospitalizations due to renal, urinary, metabolism, and nutrition disorders were observed despite a modest increase in risk of genital infections and diabetes ketoacidosis with dapagliflozin versus placebo previously reported in the DECLARE-TIMI 585. These finding are in line with data from a recent meta-analysis demonstrating that the absolute benefits of SGLT2i significantly outweigh the small increase in risk of some adverse events 24.

Previous studies were unable to demonstrate reductions in risks of hospitalisations due to causes other than cardiac disorders 20 or HF events 11 with SGLT2i. A recent report from the DAPA-CKD trial found that dapagliflozin reduce the risk of all hospitalisations excluding cardiac disorders in patients with albuminuric CKD 21. The present analyses of DECLARE-TIMI 58 demonstrate that dapagliflozin is associated with a lower risk of non-elective hospitalisation due to any causes, even when excluding cardiac, kidney, and metabolism disorders. This finding may indicate that the benefits of SGLT2i on risk of hospitalisation may extend beyond their already known cardiovascular, kidney, and glycaemic benefits. Possible mechanisms may involve other emerging benefits of SGLT2i such as reduced inflammation 25, increase in haematopoiesis 26,27 among others, deserving further research.

Patients with T2D comprise approximately a quarter of the annual hospitalisations in the United States 2, and about a third of diabetes-attributed expenditure is due to hospitalisations 2. Compared with placebo, dapagliflozin was associated with 11% reduction in the risk of first non-elective hospitalisations and with a lower number of hospitalisations days, in a large, international cohort broadly representative of the general population of patients with T2D. How these findings affect diabetes-attributed costs remains to be investigated.

**Limitations**

This trial has several limitations. These are post hoc analyses and should be considered hypothesis-generating. Hospitalisation events, their aetiology, and durations may greatly fluctuate among healthcare systems, sociodemographic status, differences in treatment protocols, seasons, and pandemics. Hospitalisations, their causes, and their classification as elective or non-elective were not adjudicated and were defined based on investigators reporting and therefore may be affected by intra- and inter-rater variability. The DECLARE-TIMI 58 trial excluded patients with CrCl<60 mL/min at screening, so the generalizability of the present results to patients with reduced kidney function is unknown.

**Conclusions**

In patients with T2D with established ASCVD or with risk factors but without established disease, dapagliflozin was associated with a reduced risk of non-elective hospitalisations for any cause, including hospitalisations not directly attributed to cardiac, kidney, or metabolism causes.

**Data sharing statement**

Data underlying the findings described in this manuscript can be obtained in accordance with AstraZeneca’s data sharing policy, which is available online.

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**Author contribution**

MS, SDW, IR, MSS, and OM conceptualised the analyses and wrote the first draft. ELG had access to the raw data. SAM verified the data. ELG, AR, IY, and SAM performed the analyses. All authors reviewed and revised the manuscript drafts, provided approval of the final version for submission, and accepted responsibility for the accuracy and integrity of the data. MS and OM had final responsibility for the decision to submit for publication.

**Conflict of interests**

**MS** received travel support from AstraZeneca and Novo Nordisk through Hadassah Medical Center.

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**IR** reports advisory board: AstraZeneca, Eli Lilly and Company, Novo Nordisk. Consultant: AstraZeneca, Insuline Medical, Concenter BioPharma, Pluristem. Speaker’s Bureau: AstraZeneca, Eli Lilly and Company, Novo Nordisk, Inc., Sanofi.

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**MF, PAJ, IAMG, AML** are employees at BioPharmaceuticals R&D, Astra-Zeneca, Gothenburg, Sweden.

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**Figure legends:**

**Figure 1:** The effects of dapagliflozin on first and total (first plus subsequent) hospitalisations using different definitions

Kaplan Meier estimates were used to estimate the event rate at 4 years with dapagliflozin or placebo. The risks of the first events with dapagliflozin versus placebo were calculated using Cox proportional hazards regression models. Rates of total (first plus subsequent) hospitalisations were assessed using Lin-Wei-Ying-Yang models. Cox and Lin-Wei-Ying-Yang models were adjusted to the trial stratification factors (presence of ASCVD or the presence of haematuria)

Abbreviations: AE – adverse events; ASCVD – atherosclerotic cardiovascular disease; KM – Kaplan Meier.

**Figure 2:** The effect of dapagliflozin on first non-elective hospitalisations by the presence of ASCVD at baseline

Kaplan Meier estimates were used to estimate the event rate at 4 years with dapagliflozin or placebo. Risks of first non-elective hospitalisation with dapagliflozin versus placebo were calculated using Cox proportional hazards regression models. Cox models were adjusted to the trial stratification factor (presence of haematuria). The number of patients needed to treat (NNT) to prevent one event during the trial follow-up (median of 4.2 years) was calculated based on the absolute risk reduction in the proportion of patients experiencing an event. The number of patients censored for each subgroup by treatment arm: 2003 patients with ASCVD treated with dapagliflozin; 1917patients with ASCVD treated with placebo; 3800 patients with MRF treated with dapagliflozin; 3625 patients with MRF treated with placebo.

Abbreviations: AE – adverse events; ASCVD – atherosclerotic cardiovascular disease; KM – Kaplan Meier; MRF – multiple cardiovascular risk factors.

**Figure 3:** The effect of dapagliflozin on the risk of first non-elective hospitalisation for any cause by baseline subgroups

Kaplan Meier estimates were used to estimate the event rate at 4 years with dapagliflozin or placebo. The risks of first non-elective hospitalisation with dapagliflozin versus placebo were calculated using Cox proportional hazards regression models adjusted to the trial stratification factors (presence of ASCVD; and the presence of haematuria).

Abbreviations: ACEi – angiotensin-converting enzyme inhibitors; AE – adverse events; ARB – angiotensin receptor blockers; ASCVD – atherosclerotic cardiovascular disease; BMI – body mass index; eGFR – estimated glomerular filtration rate; HF – heart failure; HTN – hypertension; KDIGO – Kidney Disease: Improving Global Outcomes; KM – Kaplan Meier; MRF – multiple cardiovascular risk factors; UACR – urine albumin-to-creatinine ratio.

**Figure 4:** The effects of dapagliflozin on first cause-specific non-elective hospitalisations

Non-elective hospitalisations were further classified to their causes based on investigators' reports using the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy, using System Organ Class to classify cause for hospitalisation. Kaplan Meier estimates were used to estimate the event rate at 4 years with dapagliflozin or placebo. The risks of first cause-specific non-elective hospitalisation with dapagliflozin versus placebo were calculated using Cox proportional hazards regression models adjusted to the trial stratification factors (presence of ASCVD; and the presence of haematuria).

Abbreviations: AE – adverse events; ASCVD – atherosclerotic cardiovascular disease; KM – Kaplan Meier.