**Efficacy and Safety of Dapagliflozin in Type 2 Diabetes according to Baseline Blood Pressure: Observations From DECLARE-TIMI 58 Trial**

**Dapagliflozin and blood pressure in T2DM**

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**ABSTRACT**

**Background:** Dapagliflozin improved heart failure and kidney outcomes in patients with type 2 diabetes mellitus (T2DM) with or at high risk for cardiovascular disease in the DECLARE-TIMI 58 trial. Here, the aim was to analyze efficacy and safety of dapagliflozin stratified according to baseline systolic blood pressure (SBP).

**Methods:** The DECLARE-TIMI 58 trial randomized patients with T2DM and either prior atherosclerotic cardiovascular disease (ASCVD) or ASCVD risk factors to dapagliflozin or placebo. Patients were categorized by baseline SBP levels: < 120, 120-129, 130-139, 140-159 and ≥ 160 mmHg (respectively, normal, elevated, stage 1, stage 2 and severe hypertension). Efficacy outcomes of interest were hospitalization for heart failure (HHF) and a renal-specific composite outcome (sustained decrease in estimated glomerular filtration rate by 40%, progression to end-stage renal disease or renal death). Safety outcomes included symptoms of volume depletion, lower extremity amputations and acute kidney injury.

**Results:** The trial comprised 17,160 patients; mean age of 64.0 ± 6.8 years ; 37.4% women; median duration of T2DM 11 years; 40.6% with prevalent CVD. Overall,dapagliflozin reduced SBP by 2.4 mmHg (95% CI 1.9-2.9; p < 0.0001) compared with placebo at 48 months. The beneficial effects of dapagliflozin on HHF and renal outcomes were consistent across all baseline SBP categories, with no evidence of modification of treatment effect (p-interactions = 0.28 and 0.52, respectively). Among normotensive patients, the HR´s were 0.66 (95% CI 0.42-1.05) and 0.39 (95% CI 0.19-0.78), respectively for HHF and the renal specific outcome. Events of volume depletion, amputation and acute kidney injury did not differ with dapagliflozin overall or within any baseline SBP group.

**Conclusions:** In patients with T2DM with or at high ASCVD risk, dapagliflozin reduced risk for HHF and renal outcomes regardless of baseline systolic blood pressure, with no difference in adverse events of interest at any level of baseline SBP. These results indicate that dapagliflozin provides important cardiorenal benefit in patients with T2DM at high ASCVD risk, independent of baseline blood pressure.

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**Keywords:** SGLT2 inhibitors; dapagliflozin; blood pressure; type 2 diabetes mellitus; renal outcomes; heart failure

**Clinical Perspective**

**What is new?**

* The present results suggest that efficacy of dapagliflozin for reducing cardiorenal events in patients with type 2 diabetes is not dependent on baseline blood pressure, with no difference in benefit for reduction in HHF and renal outcomes among patients with blood pressure from the normal range to severe hypertension;
* Moreover, there appeared to be no difference in adverse events of volume depletion, acute kidney injury or amputations across the levels of baseline blood pressure.

**What are the clinical implications?**

* Among patients with type 2 diabetes mellitus at high ASCVD risk, the cardiorenal benefits of dapagliflozin are evident across the spectrum of baseline blood pressure, from the normal range to the most severely hypertensive;
* Blood pressure should not influence prescription of dapagliflozin for patients with type 2 diabetes mellitus who have an indication for an SGLT2 inhibitor.

**INTRODUCTION**

Hypertension and type 2 diabetes mellitus (T2DM) are two diseases that often co-exist, and the risks of micro and macrovascular complications from T2DM are magnified in the presence of high blood pressure (BP). In the United Kingdom Prospective Diabetes Study (UKPDS), every 10 mmHg higher systolic blood pressure (SBP) was associated with a 12% higher risk of T2DM-related complications, including incident heart failure (HF) and all-cause death (1). On the other hand, even those patients with T2DM and normal BP may experience a substantial residual risk of cardiovascular and renal events, that is not completely mitigated by intensive SBP management (2).

Sodium glucose co-transporter 2 inhibitors (SGLT2i) are glucose-lowering agents that confer substantial reduction in hospitalization for HF and progression of diabetic nephropathy in patients with T2DM, regardless of the presence of prior cardiovascular (CV) or renal disease (3,4). Among other actions, these medications have salutary effects on weight, uric acid, blood pressure, intravascular volume, and attenuation of renin-angiotensin-aldosterone system and sympathetic nervous system activation-all of which may contribute to the clinical benefits observed for cardio-renal outcomes (5,6,7). However, on average, SGLT2i decrease SBP and diastolic blood pressure (DBP) by only 3.8 and 1.4 mmHg, respectively (8). Furthermore, concerns remain about the safety of SGLT2i in patients with low to normal SBP. In theory, some adverse events could be potentially worsened by BP lowering, such as acute kidney injury, symptoms of volume depletion/dehydration, falls/fractures and lower limb amputations (9,10).

For all those reasons, using data from the DECLARETIMI 58 (Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58) trial, it was investigated whether the benefit of the SGLT2i dapagliflozin for cardio-renal protection among patients with T2DM is seen across all levels of baseline SBP (including those patients with baseline blood pressure in the normal range), as well as to whether it is safe to treat patients with normal to near normal blood pressure with dapagliflozin.

**METHODS**

**Population and outcomes selection**

The DECLARE-TIMI 58 trial design and overall results have been published previously (11,12). In brief, 17,160 patients aged ≥ 40 years with diagnosis of T2DM, a glycated hemoglobin between 6.5% and 12%, and established atherosclerotic cardiovascular disease (ASCVD) or multiple ASCVD risk factors were randomly assigned to dapagliflozin 10 mg once daily versus matching placebo. Median follow-up time was 48 months, and patients were to be seen at scheduled in person study visits at randomization and every 6 months thereafter (with phone calls in between regular visits), up to the end of follow-up. Use of BP lowering medications during the trial was left to the discretion of the treating provider. Patients with screening SBP > 180 mmHg or DBP > 100 mmHg were not eligible to participate, with no minimum threshold of SBP or DBP for enrolment.

All patients had BP routinely measured using standardized methods at baseline and at every study visit, as described in the study protocol (11). SBP in mmHg was reported as the average of three measures. Baseline medications, including BP lowering ones, were also collected at each study visit.

For the present analyses, categories of baseline SBP were defined as follows: < 120, 120-129, 130-139, 140-159 and ≥160 mmHg (respectively, normal, elevated, stage 1, stage 2, and severe hypertension). Those levels were chosen according to the most recent hypertension guidelines (13).

In the main trial, the two primary efficacy outcomes were: major adverse cardiovascular events (MACE), which was the composite of CV death, myocardial infarction (MI) or ischemic stroke, and the composite of CV death or HHF. The present sub-analyses focused on HHF and the kidney specific outcomes, since those two outcomes were significantly reduced with dapagliflozin in the overall trial population (12). The renal specific outcome was the composite of sustained decrease in estimated glomerular filtration rate (eGFR) by at least 40%, progression to end-stage renal disease (ESRD) (meaning sustained eGFR <15 ml/min/1.73 m2, need for renal replacement therapy for more than 90 days, or renal transplantation), or renal death. Other prespecified outcomes in the trial included the individual components of the aforementioned outcomes; and the cardiorenal outcome, which included all components of the renal-specific outcome plus CV death; and all-cause mortality. CV efficacy outcomes were reviewed by a central adjudication committee blinded to randomized arm, whereas renal outcomes were based on central laboratory measurements and adverse events reports.

Safety outcomes included overall serious adverse events, volume depletion events, acute kidney injury, and lower extremity non-traumatic amputations. All those safety events have been defined previously and were collected throughout the trial with specific adverse event data reporting. Lower limb amputations were collected in dedicated forms from study CRF and blindly reviewed by a vascular specialist, as described previously (14).

**Statistical analysis**

We encourage parties interested in collaboration and data sharing to contact the corresponding author directly. Baseline characteristics are reported stratified by categories of baseline SBP (i.e., normal: SBP < 120 mmHg; elevated: SBP 120-129; stage 1: SBP 130-139; stage 2: SBP 140-159; and severe hypertension: SBP ≥160 mmHg), per the 2017 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines (13). Categorical variables across categories of baseline SBP were compared with the χ2 test. Continuous variables were compared with the Kruskal-Wallis test.

Comparison of serial SBP across time between placebo and dapagliflozin was done with a mixed linear effects model, which includes baseline SBP, randomized treatment group, visit and the interaction of treatment and visit. The least-squares mean and the difference between the two randomized groups was reported, with corresponding 95% confidence intervals (CI). Furthermore, those differences were explored stratified according to the following subgroups: prior atherosclerotic disease versus not; age ≥ 65 years versus < 65 years; males versus females; race (white, black/African), use of angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) or Angiotensin Receptor-Neprilysin Inhibitor (ARNI) at baseline versus not; use of diuretic at baseline versus not.

In the placebo arm, the association between each category of baseline SBP and study CV and renal outcomes was explored. Models were adjusted for the following co-variates: DBP, history of CAD, history of ischemic stroke, history of PAD, history of dyslipidemia, history of hypertension, history of HF, eGFR < 60 ml/min/1.73 m2, urinary albumin:creatinine ratio >300 mg/g, age white race, BMI, DM duration >10 years, region, and smoking. Multivariable Cox proportional hazards models were developed and hazard ratios (HR) and 95% CI generated. The reference group was assumed as that one with the lowest cumulative incidence rate at 4 years for the outcome of interest. Those co-variates were selected because they had imbalances (p < 0.05 or standardized mean difference > 0.10) among the groups of interest of baseline BP.

Proportional hazards models using restricted cubic splines were developed to explore the association between probability of each efficacy outcome of interest and SBP as continuous variable and depicted graphically. Models were selected with 3, 4 and 5 knots, with final model chosen as the one with the lowest AIC (Akaike information criterion).

Efficacy and safety of dapagliflozin versus placebo for each outcome and adverse events of interest were assessed by a Cox Proportional-Hazards models for subgroups of SBP. Prior ASCVD and baseline hematuria status were used as stratification factors within these models. Treatment by subgroup interaction were tested with interactions terms in each model. In a sensitivity analysis, a model was done analyzing efficacy of dapagliflozin versus placebo including changes in SBP from baseline as a time-varying co-variate.

All tests are two sided and a p-value < 0.05 was considered as statistically significant. No adjustment for multiplicity was performed. The statistical program used for the analysis was SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

**Compliance with ethical standards**

This trial conformed to the recommendations of the Declaration of Helsinki and International Council on Harmonization norms on medical research in humans. The trial protocol was approved by all institutional review boards of participating sites before starting enrollment. All patients provided written informed consent before participation.

**RESULTS**

**Descriptive statistics**

From the overall trial population, 2557, 3686, 4385, 5501 and 1031 patients were categorized by baseline SBP as normal, elevated, stage 1, stage 2 and severe hypertension, respectively. Patients with severe hypertension were older, less likely to have established ASCVD and had higher BMI. They also had higher UACR and longer diabetes duration. Use of diuretics, ACE inhibitors/ARBs and beta blockers was also more commonly observed among patients with severe hypertension (Table 1).

**BP effect lowering of dapagliflozin**

Overall, compared with placebo, effects of dapagliflozin on SBP were apparent as early as at the first 6 months trial assessment (least means square difference -3.1 mmHg; 95% CI -3.5 to -2.7; p < 0.0001). Reductions in SBP with dapagliflozin remained sustained at 48 months follow-up (least means square difference -2.4 mmHg; 95% CI -2.9 to -1.9; p < 0.0001). SBP lowering effects of dapagliflozin were observed regardless of baseline SBP (although absolute change appears to be higher in categories of higher baseline SBP), and regardless of concomitant use of ACE inhibitors/ARBs/ARNIs or diuretics. (Supplemental Tables 1-2).

**Cardiovascular and renal outcomes according to categories of baseline blood pressure in the placebo arm**

In the placebo arm, unadjusted incidence of HHF and renal outcomes were higher among patients with severe hypertension and reached a nadir in patients with elevated blood pressure (SBP 120-129 mmHg). Those findings are presented in Table 2.

After adjustment for baseline differences, patients with severe hypertension experienced 3-fold higher frequency of HHF (adjusted HR 3.01; 95% CI 1.88-4.82; p < 0.0001) and more than 4-fold higher frequency of the renal-specific composite outcome (adjusted HR 4.23; 95% CI 2.52-7.12; < 0.0001). Those results are summarized in Table 3. Figure 1 shows association between HHF and kidney-specific outcomes with continuous levels of a restricted cubic spline of SBP in the placebo and dapagliflozin arms. Supplement Figure 1 shows similar analyses for MACE, CV death or HHF and CV death.

**Efficacy of dapagliflozin stratified according to baseline blood pressure**

Dapagliflozin consistently reduced the risk of HHF regardless of baseline SBP (p-interaction = 0.28), when SBP at baseline was modeled as a continuous variable (Figure 2A). Similarly, dapagliflozin reduced the risk of the renal specific composite outcome with no evidence of heterogeneity across levels of baseline SBP (p for interaction = 0.52; Figure 2B). Of note, patients with SBP in the optimal range (<120 mmHg) experienced consistent benefit with dapagliflozin with HR of 0.66 (95% CI 0.42-1.05) and 0.39 (95% CI 0.19-0.78), respectively for HHF and the renal specific outcome (Figures 2C and 2D).

**Effects of dapagliflozin in heart failure and renal endpoints according to change in SBP from baseline**

Effects of dapagliflozin versus placebo in the overall population over HHF and renal endpoints did not materially change in a sensitivity analysis including SBP change from baseline to follow-up as a time-varying co-variate in the model (HR 0.72; 95% CI 0.61-0.87; p =0.0004 for HHF and HR 0.53; 95% CI 0.43-0.66; p <0.0001 for the renal specific endpoint; Supplement Table 3). Supplemental Figure 2 shows association between probabilities of event in the dapagliflozin arm versus change in SBP from baseline to 6 months. **Safety of dapagliflozin stratified according to baseline blood pressure**

Overall, there was no difference in adverse events of lower limb amputation, symptoms of volume depletion or acute kidney injury at any level of SBP with dapagliflozin. Of note, patients with baseline SBP < 120 mmHg experienced no significant harm from dapagliflozin regarding those events, with HR = 1.18 (95% CI 0.62-2.22) for amputation; HR = 0.29 (95% CI 0.14-0.61) for acute kidney injury, and HR = 0.96 (95% CI 0.61-1.51) for symptoms of volume depletion (Figure 3).

**DISCUSSION**

SGLT2 inhibitors are cornerstone therapies in the treatment of patients with T2DM due to their positive impact on CV and renal outcomes in, in addition to their salutary effects on blood glucose (without hypoglycemia), body weight, BP, and favorable safety profile. Results from the present sub-analyses from the DECLARE-TIMI 58 trial suggest that benefits of dapagliflozin at reducing HF and renal events are observed across all ranges of baseline SBP. Moreover, dapagliflozin did not increase acute kidney injury, amputations, or volume depletion events within any category of baseline SBP.

To put the present findings into context, results from a sub-analysis from the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial), which evaluated the effect of dapagliflozin versus placebo in patients with heart failure with reduced ejection fraction (HFrEF) independent of diabetes status (15), suggested that dapagliflozin reduced CV death or worsening HF regardless of baseline SBP, and regardless of a BP lowering effect (16). Results from another similar sub-analysis were published from the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial (which randomized patients with T2DM and chronic albuminuric kidney disease), suggesting that reductions in renal events (the composite of decrease in GFR of 40% or more, ESRD or renal death) with canagliflozin was observed regardless of baseline SBP (17). In the EMPEROR REDUCED (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) trial, patients with HFrEF also experienced a reduction in CV death or worsening HF, as well as renal outcomes, regardless of baseline SBP (18). Observations from the present study expand those findings, since DECLARE – TIMI 58 enrolled a broader range of patients with T2DM, with nearly two thirds having no history of ASCVD and less than a tenth having history of prior HF or chronic kidney disease. Of note, in DECLARE-TIMI 58, nearly 2,600 patients had T2DM with SBP in the optimal range, where consistent reductions in HHF and renal events were observed, thus reinforcing that SGLT2i might be considered even among patients with well controlled hypertension. Moreover, in the present study, due to the larger sample size and longer term follow-up compared with the aforementioned studies, data for many patient-years could be more rigorously assessed (19), thus providing reassurance of the safety of dapagliflozin, regardless of baseline BP, among patients with T2DM .

There has been much discussion about the mechanisms of action that may explain the cardio-renal effects from SGLT2i. BP lowering has been hypothesized as one possible explanation. This hypothesis is reinforced by findings from studies suggesting decrease in LV mass with SGLT2i among patients with T2DM, assessed by cardiac magnetic resonance imaging, although it remains uncertain whether mechanisms other than BP lowering (e.g., reduction of volume overload) could have affected those findings. (20,21). However, the present results demonstrate consistency of benefits, in terms of HF and renal events, among patients with SBP in the optimal range (< 120 mmHg) in whom there were only small decreases in SBP (<2 mmHg). This finding contrasts with a meta-analysis of BP lowering therapies in patients with T2DM suggesting that other anti-hypertensive medications have lesser impact in cardio-renal outcomes among those patients with SBP < 140 mmHg (22).

In some previous studies, SGLT2i have been associated with potential increase in amputations, acute kidney injury or volume depletion adverse events (9,10), although later data have not confirmed those increased risks (and have actually shown a decreased risk for acute kidney injury) ( 14,23,24). Since BP lowering could be a potential mechanism for those adverse events, the present findings are reassuring, thus reinforcing the safety of SGLT2i among patients with SBP < 120 mmHg.

Some limitations of the current study merit consideration. First of all, despite the sub-analysis being pre-specified, the SBP levels categories were not. However, those levels are in accordance with those ones established by current hypertension guidelines (13,25, 26). Second, DECLARE-TIMI 58 trial was not designed and powered to assess events within specific subgroups, especially small ones such as SBP categories. Third, despite the findings of benefit in patients with normal BP, this study was not designed specifically to test the hypothesis of whether SGLT2i exert their CV and renal protective effects by a BP lowering mechanism. It is possible that a combination of, rather than a single isolated mechanism, is responsible for explaining CV and renal outcomes reductions observed with SGLT2i.

**Conclusion**

Among patients with type 2 diabetes, clinical efficacy of dapagliflozin for reducing the risk of HF and renal outcomes was not affected by baseline systolic blood pressure. Moreover, dapagliflozin appeared to be safe, with no increase in acute renal injury, symptoms of volume depletion, or lower limb amputation, in any level of baseline systolic blood pressure.

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**REFERENCES**

1. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;3 21(7258): 412-9.
2. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010; 362: 1575-85.
3. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. SGLT2 Inhibitors for Primary and Secondary Prevention of Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Cardiovascular Outcomes Trials. Lancet. 2019; 393: 31-39.
4. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, Gantz I, Terra SG, Masiukiewicz U, Cannon CP. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol. 2021; 6(2):148-158.
5. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020; 75(4): 422-434.
6. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes: Cardiovascular and Kidney Effects, Potential Mechanisms and Clinical Applications. Circulation. 2016; 134: 752-772.
7. Lopaschuk GD, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC Basic Transl Sci. 2020; 5: 632-644.
8. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, WhiteWB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. J Am Soc Hypertens. 2014 ;8(4):262–75.e9.
9. Chang HY, Singh S, Mansour O, Baksh S, Alexander GC. Association between sodium-glucose cotransporter 2 inhibitors and lower extremity amputation among patients with type 2 diabetes. JAMA Intern Med. 2018; 178:1190-1198.
10. Perlman A, Heyman SN, Matok I, Stokar J, Muszkat M, Szalat A. Acute renal failure with sodium-glucose-cotransporter-2 inhibitors: analysis of the FDA adverse event report system database. Nutr Metab Cardiovas Dis. 2017;27:1108-1113.
11. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Bansilal S, Bhatt DL, Leiter LA, McGuire DK, Wilding JP, Gause-Nilsson IA, Langkilde AM, Johansson PA, Sabatine MS. The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. Am Heart J. 2018; 200: 83-89.
12. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019; 380: 347-357.
13. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018; 138: e426-e483.
14. Bonaca MP, Wiviott SD, Zelniker TA, Mosenzon O, Bhatt DL, Leiter LA, McGuire DK, Goodrich EL, Furtado RHM, Wilding JPH, Cahn A, Gause-Nilsson IAM, Johanson P, Fredriksson M, Johansson PA, Langkilde AM, Raz I, Sabatine MS. Dapagliflozin and Cardiac, Kidney, and Limb Outcomes in Patients With and Without Peripheral Artery Disease in DECLARE-TIMI 58. Circulation. 2020; 142: 734-747.
15. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019; 381(21):1995-2008.
16. Serenelli M, Böhm M, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Solomon SD, DeMets DL, Bengtsson O, Sjöstrand M, Langkilde AM, Anand IS, Chiang CE, Chopra VK, de Boer RA, Diez M, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Verma S, Docherty KF, Jhund PS, McMurray JJV. Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF). Eur Heart J 2020; 41: 3402-3418.
17. Ye N, Jardine MJ, Oshima M, Hockham C, Heerspink HJL, Agarawal R,Bakris G, Schutte AE, Arnott C, Chang TI, et al. Blood pressure effects of canagliflozin and clinical outcomes in type 2 diabetes and chronic kidney disease: insights from the CREDENCE trial. Circulation. 2021; 143:1735–1749.
18. Böhm M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Mahfoud F, Brueckmann M, Jamal W, Ofstad AP, Schüler E, Ponikowski P, Wanner C, Zannad F, Packer M; EMPEROR-Reduced Trial Committees and Investigators. Empagliflozin Improves Cardiovascular and Renal Outcomes in Heart Failure Irrespective of Systolic Blood Pressure. J Am Coll Cardiol. 2021; 78(13):1337-1348.
19. Cahn A, Raz I, Bonaca M, Mosenzon O, Murphy SA, Yanuv I, Rozenberg A, Wilding JPH, Bhatt DL, McGuire DK, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Jermendy G, Hadjadj S, Langkilde AM, Sabatine MS, Wiviott SD, Leiter LA. Safety of dapagliflozin in a broad population of patients with type 2 diabetes: Analyses from the DECLARE-TIMI 58 study. Diabetes Obes Metab; 22(8):1357-1368.
20. Verma S, Mazer CD, Yan AT, Mason T, Garg V, Teoh H, Zuo F, Quan A, Farkouh ME, Fitchett DH, Goodman SG, Goldenberg RM, Al-Omran M, Gilbert RE, Bhatt DL, Leiter LA, Jüni P, Zinman B, Connelly KA. Effect of Empagliflozin on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease: The EMPA-HEART CardioLink-6 Randomized Clinical Trial. Circulation 2019; 140: 1693-1702.
21. Brown AJM, Gandy S, McCrimmon R, Houston JG, Struthers AD, Lang CC. A randomized controlled trial of dapagliflozin on left ventricular hypertrophy in people with type two diabetes: the DAPA-LVH trial. Eur Heart J. 2020; 41: 3421-3432.
22. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015; 313: 603-15.
23. Udell JA, Yuan Z, Rush T, Sicignano NM, Galitz M, Rosenthal N. Cardiovascular Outcomes and Risks After Initiation of a Sodium Glucose Cotransporter 2 Inhibitor: Results From the EASEL Population-Based Cohort Study (Evidence for Cardiovascular Outcomes With Sodium Glucose Cotransporter 2 Inhibitors in the Real World). Circulation 2018; 137: 1450-1459.
24. Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, Mahaffey KW, Charytan DM, Wheeler DC, Arnott C, Bompoint S, Levin A, Jardine MJ. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019; 7: 845-854.
25. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39: 3021-3104.
26. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, Wainford RD, Williams B, Schutte AE. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020; 75(6): 1334-1357.

**Table 1 – Baseline characteristics according to systolic blood pressure (SBP) categories**

| **Characteristics** | **SBP < 120**  **(N=2557)** | **SBP 120-129**  **(N=3686)** | **SBP 130-139**  **(N=4385)** | **SBP 140-159**  **(N=** **5501)** | **SBP ≥ 160**  **(N= 1031)** | **P-value** |
| --- | --- | --- | --- | --- | --- | --- |
| Age in years, Median (IQR) | 63 (59, 68) | 63 (59, 68) | 64 (60., 68) | 64 (60, 69) | 65 (61, 70) | <0.0001 |
| Male sex, N (%) | 1588 (62.1) | 2313 (62.8) | 2777 (63.3) | 3426 (62.3) | 634 (61.5) | 0.72 |
| White race, N (%) | 1830 (71.6) | 2869 (77.8) | 3579 (81.6) | 4531 (82.4) | 844 (81.9) | <0.0001 |
| Region | | | | | | |
| North America | 1194 (46.7) | 1451 (39.4) | 1334 (30.4) | 1256 (22.8) | 233 (22.6) | <0.0001 |
| Latin America | 341 (13.3) | 368 (10.0) | 488 (11.1) | 570 (10.4) | 110 (10.7) | 0.0004 |
| Europe | 620 (24.2) | 1383 (37.5) | 2051 (46.8) | 2978 (54.1) | 597 (57.9) | <0.0001 |
| Asia/Pacific | 402 (15.7) | 484 (13.1) | 512 (11.7) | 697 (12.7) | 91 (8.8) | <0.0001 |
| Duration of diabetes > 10 years, N (%) | 1298 (50.8) | 1774 (48.1) | 2141 (48.8) | 2816 (51.2) | 562 (54.5) | 0.0006 |
| Current smoker, N(%) | 445 (17.4) | 576 (15.6) | 648 (14.8) | 733 (13.3) | 96 (9.3) | <0.0001 |
| Dyslipidemia, N(%) | 2189 (85.6) | 3033 (82.3) | 3481 (79.4) | 4308 (78.3) | 785 (76.1) | <0.0001 |
| Established ASCVD, N (%) | 1186 (46.4) | 1541 (41.8) | 1731 (39.5) | 2121 (38.6) | 395 (38.3) | <0.0001 |
| Prior MI, N(%) | 645 (25.2) | 791 (21.5) | 920 (21.0) | 1031 (18.7) | 197 (19.1) | <0.0001 |
| Prior ischemic stroke, N(%) | 162 (6.3) | 224 (6.1) | 274 (6.2) | 373 (6.8) | 80 (7.8) | 0.28 |
| Prior PAD, N(%) | 162 (6.3) | 205 (5.6) | 241 (5.5) | 349 (6.3) | 68 (6.6) | 0.24 |
| Prior HF, N(%) | 273 (10.7) | 353 (9.6) | 475 (10.8) | 536 (9.7) | 87 (8.4) | 0.074 |
| BMI in kg/m2, Median (IQR) | 30.3 (26.7, 34.6) | 30.9 (27.5,  35.1) | 31.4 (27.9,  35.4) | 31.8 (28.4,  35.7) | 32.2 (28.4,  36.3) | <0.0001 |
| DBP in mmHg, Median (IQR) | 70.0 (64.5, 74.5) | 75.5 (70.0, 80.0) | 79.5 (73.0, 83.5) | 82.5 (77.0, 88.0) | 86.5 (80.0, 92.0) | <0.0001 |
| Pulse pressure in mmHg, Median (IQR) | 42.0 (37.5, 47.0) | 49.0 (44.0, 54.0) | 55.5 (50.0, 61.0) | 64.5 (59.0, 71.0) | 80.0 (73.0, 87.5) | <0.0001 |
| HR in bpm, Median (IQR) | 72.0 (66.0, 79.5) | 72.0 (66.0, 79.0) | 72.0 (66.0, 79.0) | 72.5 (66.0, 80.0) | 73.0 (64.5, 81.5) | 0.15 |
| eGFR in ml/min/1.73 m2, median (IQR) | 88.0 (73.0, 97.0) | 89.0 (75.0,  97.0) | 89.0 (75.0, 97.0) | 89.0 (76.0, 96.0) | 87.0 (74.0, 96.0) | 0.0128 |
| UACR in mg/g, median (IQR) | 9.9 (4.8,  26.6) | 10.5 (5.4,  30.3) | 12.2 (5.9,  37.2) | 16.5 (7.0,  62.9) | 29.6 (9.6,  141.9) | <0.0001 |
| HbA1c in %, median (IQR) | 8.1 (7.3, 9.1) | 8.0 (7.3, 9.0) | 8.0 (7.3, 8.9) | 8.0 (7.4, 9.0) | 8.1 (7.4, 9.1) | 0.17 |
| Concomitant medications | | | | | | |
| Metformin | 2037 (79.7) | 3050 (82.7) | 3588 (81.8) | 4568 (83.0) | 825 (80.0) | 0.0014 |
| ACE inhibitors/ARBs | 1911 (74.7) | 2928 (79.4) | 3589 (81.8) | 4640 (84.3) | 882 (85.5) | <0.0001 |
| Beta blockers | 1304 (51.0) | 1868 (50.7) | 2260 (51.5) | 2973 (54.0) | 625 (60.6) | <0.0001 |
| Thiazides | 477 (18.7) | 744 (20.2) | 973 (22.2) | 1313 (23.9) | 266 (25.8) | <0.0001 |
| Calcium channel blockers | 592 (23.2) | 1052 (28.5) | 1495 (34.1) | 2338 (42.5) | 516 (50.0) | <0.0001 |

**Table 2 – Cardiovascular and renal outcomes in the placebo arm by categories of baseline systolic blood pressure (SBP), with SBP 120-129 as reference group for the comparisons.**

| **Outcome** | **SBP < 120**  **(N=1312)** | | **SBP 120-129**  **(N=1843)** | **SBP 130-139**  **(N=2165)** | | **SBP 140-159**  **(N=** **2758 )** | | **SBP ≥ 160**  **(N= 500)** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **n (%)** | **P-value** | **n (%)** | **n (%)** | **P-value** | **n (%)** | **P-value** | **n (%)** | **P-value** |
| HHF | 46 (3.5%) | 0.0308 | 42 (2.3%) | 67 (3.1%) | 0.1106 | 92 (3.3%) | 0.0340 | 39 (7.8%) | <0.0001 |
| Renal-specific outcome\* | 29 (2.2%) | 0.19 | 30 (1.6%) | 62 (2.9%) | 0.0096 | 76 (2.8%) | 0.0127 | 41 (8.2%) | <0.0001 |
| CV death/HHF | 84 (6.4%) | 0.0167 | 84 (4.6%) | 116 (5.4%) | 0.24 | 156 (5.7%) | 0.0896 | 56 (11.2%) | <0.0001 |
| Cardiorenal outcome\*\* | 72 (5.5%) | 0.1067 | 80 (4.3%) | 113 (5.2%) | 0.19 | 152 (5.5%) | 0.0700 | 63 (12.6%) | <0.0001 |
| MACE\*\*\* | 129 (9.8%) | 0.0427 | 146 (7.9%) | 187 (8.6%) | 0.39 | 266 (9.6%) | 0.0382 | 75 (15.0%) | <0.0001 |
| CV death | 44 (3.4%) | 0.31 | 51 (2.8%) | 53 (2.4%) | 0.54 | 79 (2.9%) | 0.79 | 22 (4.4%) | 0.0480 |
| MI | 71 (5.4%) | 0.0267 | 71 (3.9%) | 106 (4.9%) | 0.1051 | 150 (5.4%) | 0.0125 | 43 (8.6%) | <0.0001 |
| Ischemic stroke | 31 (2.4%) | 0.67 | 49 (2.7%) | 50 (2.3%) | 0.50 | 76 (2.8%) | 0.79 | 25 (5.0%) | 0.0048 |
| All cause death | 94 (7.2%) | 0.16 | 110 (6.0%) | 123 (5.7%) | 0.75 | 183 (6.6%) | 0.29 | 60 (12.0%) | <0.0001 |

\*Renal-specific outcome is the composite of sustained decrease in eGFR of 40% or more, end-stage renal disease, or renal death

\*\* Cardio-renal outcome is the composite of sustained decrease in eGFR of 40% or more, end-stage renal disease, CV death or renal death;

\*\*\* MACE is the composite of CV death, MI, or ischemic stroke

HHF = hospitalization for heart failure; HR = hazard ratio; MACE = major adverse cardiovascular events (denotes the composite of CV death, MI or ischemic stroke); MI = myocardial infarction;

**Table 3 – Adjusted risk of cardiovascular and renal outcomes in the placebo arm by categories of baseline systolic blood pressure (SBP), with SBP 120-129 as reference group.**

| **Outcome** | **SBP < 120**  **(N=1312)** | | **SBP 130-139**  **(N=2165)** | | **SBP 140-159**  **(N=** **2758 )** | | **SBP ≥ 160**  **(N= 500)** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Adjusted HR (95% CI)** | **P-value** | **Adjusted**  **HR (95% CI)** | **P-value** | **Adjusted**  **HR (95% CI)** | **P-value** | **Adjusted**  **HR (95% CI)** | **P-value** |
| HHF | 1.39 (0.90-2.13) | 0.14 | 1.45 (0.97-2.16) | 0.0672 | 1.48 (1.00-2.18) | 0.0479 | 3.01 (1.88-4.82) | <0.0001 |
| Renal-specific outcome\* | 1.40 (0.83-2.35) | 0.21 | 1.73 (1.11-2.71) | 0.0162 | 1.45 (0.92-2.26) | 0.1076 | 4.23 (2.52-7.12) | <0.0001 |
| CV death/HHF | 1.31 (0.96-1.78) | 0.0921 | 1.18 (0.88-1.57) | 0.26 | 1.18 (0.89-1.57) | 0.24 | 2.23 (1.55-3.21) | <0.0001 |
| Cardiorenal outcome\*\* | 1.28 (0.92-1.77) | 0.14 | 1.17 (0.87-1.57) | 0.29 | 1.12 (0.84-1.50) | 0.44 | 2.59 (1.80-3.72) | <0.0001 |
| MACE\*\*\* | 1.18 (0.93-1.51) | 0.18 | 1.09 (0.88-1.37) | 0.42 | 1.17 (0.94-1.45) | 0.16 | 1.81 (1.34-2.44) | 0.0001 |
| CV death | 1.18 (0.78-1.79) | 0.43 | 0.83 (0.56-1.24) | 0.37 | 0.94 (0.65-1.37) | 0.75 | 1.45 (0.85-2.48) | 0.17 |
| MI | 1.25 (0.89-1.75) | 0.19 | 1.30 (0.96-1.77) | 0.0901 | 1.41 (1.04-1.91) | 0.0251 | 2.19 (1.45-3.30) | 0.0002 |
| Ischemic stroke | 0.97 (0.61-1.55) | 0.91 | 0.89 (0.59-1.33) | 0.56 | 0.97 (0.66-1.44) | 0.90 | 1.73 (1.02-2.92) | 0.0412 |
| All-cause death | 1.12 (0.84-1.48) | 0.45 | 0.91 (0.70-1.19) | 0.49 | 1.00 (0.78-1.29) | 0.99 | 1.72 (1.22-2.41) | 0.0019 |

Model adjusted for: DBP, history of CAD, history of ischemic stroke, history of PAD, history of dyslipidemia, history of hypertension, history of HF, eGFR < 60 ml/min/1.73 m2, urinary albumin:creatinine ratio >300 mg/g, age white race, BMI, DM duration >10 years, region, and smoking.

\*Renal-specific outcome = composite of sustained decrease in eGFR of 40% or more, end-stage renal disease, or renal death

\*\* Cardio-renal outcome = composite of sustained decrease in eGFR of 40% or more, end-stage renal disease, CV death or renal death;

\*\*\* MACE is the composite of CV death, MI, or ischemic stroke

HHF = hospitalization for heart failure; HR = hazard ratio; MACE = major adverse cardiovascular events (denotes the composite of CV death, MI or ischemic stroke); MI = myocardial infarction;

**Figure 1– Effects of dapagliflozin over systolic blood pressure (SBP).** The least-squares mean and the difference between the two randomized groups was reported, with corresponding 95% confidence intervals (CI).

Gráfico, Gráfico de linhas

Descrição gerada automaticamente

**Figure 2 – Spline models showing the association between probability of event across the continuum of baseline SBP in the placebo and dapagliflozin arms. A.** Hospitalization for heart failure (HHF). **B.** Renal specific composite of sustained decrease in eGFR of 40% or more, end-stage renal disease (ESRD) or renal death.

\*Adjusted hazard ratios (HR) with 95% confidence intervals (CI) represent comparisons within the placebo arm. Model adjusted for: DBP, history of CAD, history of ischemic stroke, history of PAD, history of dyslipidemia, history of hypertension, history of HF, eGFR < 60 ml/min/1.73 m2, urinary albumin:creatinine ratio >300 mg/g, age white race, BMI, DM duration >10 years, region, and smoking.

**Diagrama

Descrição gerada automaticamente**

**Tabela

Descrição gerada automaticamente**

**Figure 3 - Hazard ratio for dapagliflozin, compared with placebo across baseline systolic blood pressure (SBP) A.** Hospitalization for heart failure (HHF) across baseline SBP modelled as a continuous spline variable. **B.** Renal-specific (the composite of sustained decrease in eGFR of 40% or more, end-stage renal disease or renal death) across baseline SBP modelled as a continuous spline variable. **C.** HHF across baseline SBP modelled as a categorical variable. **D.** Renal-specific across baseline SBP modelled as a categorical variable.

**Gráfico, Gráfico de linhas

Descrição gerada automaticamente**

**Gráfico

Descrição gerada automaticamente**

**Gráfico, Gráfico de caixa estreita

Descrição gerada automaticamenteGráfico, Gráfico de caixa estreita

Descrição gerada automaticamente**

**Figure 4 – Safety of dapagliflozin stratified according to baseline systolic blood pressure (SBP). A.** Symptoms of volume depletion. **B.** Lower extremity amputation. **C.** Acute kidney injury.







**ONLINE SUPPLEMENT**

**Supplement Table 1 – Effects of dapagliflozin over systolic blood pressure (SBP) according to SBP at baseline in mmHg.** LSM = least square mean

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **6 months** | **48 months** |
| **Overall** | **Placebo** | 135.3 | 134.9 |
|  | **Dapagliflozin** | 132.2 | 132.5 |
|  | **LSM (95% CI)** | - 3.1 (-3.5 to -2.7) | -2.4 (-2.9 to -1.9) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **< 120** | **Placebo** | 121.3 | 124.0 |
|  | **Dapagliflozin** | 119.3 | 122.6 |
|  | **LSM (95% CI)** | - 1.9 (-2.9 to -0.9) | - 1.5 (-2.7 to -0.2) |
|  | **p-value** | 0.0002 | 0.0262 |
| **120 – 129** | **Placebo** | 129.2 | 130.4 |
|  | **Dapagliflozin** | 125.7 | 128.1 |
|  | **LSM (95% CI)** | - 3.5 (-4.3 to -2.7) | -2.3 (-3.3 to -1.3) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **130 – 139** | **Placebo** | 135.2 | 134.9 |
|  | **Dapagliflozin** | 132.1 | 132.1 |
|  | **LSM (95% CI)** | - 3.1 (- 3.8 to -2.3) | -2.8 (-3.7 to -1.9) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **140 – 159** | **Placebo** | 142.4 | 140.2 |
|  | **Dapagliflozin** | 139.6 | 137.8 |
|  | **LSM (95% CI)** | -2.9 (-3.6 to -2.2) | -2.5 (-3.3 to -1.6) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **≥160** | **Placebo** | 154.4 | 148.2 |
|  | **Dapagliflozin** | 148.4 | 145.7 |
|  | **LSM (95% CI)** | - 6.0 (-8.1 to -4.0) | -2.5 (-4.9 to -0.1) |
|  | **p-value** | < 0.0001 | 0.0456 |

**Supplement Table 2 – Effects of dapagliflozin over systolic blood pressure (SBP) according to subgroups.** ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; LSM = least square mean

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **6 months** | **48 months** |
| **Overall** | **Placebo** | 135.3 | 134.9 |
|  | **Dapagliflozin** | 132.2 | 132.5 |
|  | **LSM (95% CI)** | - 3.1 (-3.5 to – 2.7) | -2.4 (-2.9 to -1.9) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **ASCVD** | **Placebo** | 135.2 | 134.7 |
|  | **Dapagliflozin** | 132.0 | 132.4 |
|  | **LSM (95% CI)** | -3.2 (-3.9 to -2.6) | -2.4 (-3.2 to -1.5) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **MRF** | **Placebo** | 135.9 | 135.3 |
|  | **Dapagliflozin** | 132.8 | 133.0 |
|  | **LSM (95% CI)** | -3.0 (-3.5 to -2.5) | -2.4 (-2.9 to -1.8) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **Age ≥ 65 years** | **Placebo** | 136.7 | 136.1 |
|  | **Dapagliflozin** | 133.3 | 133.1 |
|  | **LSM (95% CI)** | -3.4 (-4.0 to -2.8) | -3.0 (-3.7 to -2.3) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **Age < 65 years** | **Placebo** | 134.2 | 133.8 |
|  | **Dapagliflozin** | 131.3 | 131.9 |
|  | **LSM (95% CI)** | -2.8 (-3.3 to -2.3) | -1.9 (-2.5 to -1.2) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **Male** | **Placebo** | 135.4 | 134.7 |
|  | **Dapagliflozin** | 132.2 | 132.5 |
|  | **LSM (95% CI)** | -3.2 (-3.7 to -2.7) | -2.2 (-2.8 to -1.6) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **Female** | **Placebo** | 135.3 | 135.2 |
|  | **Dapagliflozin** | 132.4 | 132.5 |
|  | **LSM (95% CI)** | -2.9 (-3.6 to -2.3) | -2.7 (-3.5 to -1.9) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **White race** | **Placebo** | 135.9 | 135.4 |
|  | **Dapagliflozin** | 132.7 | 133.2 |
|  | **LSM (95% CI)** | -3.1 (-3.6 to -2.7) | -2.2 (-2.8 to -1.7) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **Black race** | **Placebo** | 136.3 | 135.8 |
|  | **Dapagliflozin** | 131.6 | 132.6 |
|  | **LSM (95% CI)** | -4.7 (-7.1 to -2.3) | -3.2 (-6.6 to 0.25) |
|  | **p-value** | 0.0002 | 0.0695 |
| **ACEI/ARB/ARNI** | **Placebo** | 135.9 | 135.5 |
|  | **Dapagliflozin** | 132.9 | 133.0 |
|  | **LSM (95% CI)** | -3.0 (-3.5 to -2.6) | -2.4 (-3.0 to -1.9) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **No ACEI/ARB/ARNI** | **Placebo** | 132.8 | 132.1 |
|  | **Dapagliflozin** | 129.5 | 130.0 |
|  | **LSM (95% CI)** | -3.3 (-4.2 to -2.5) | -2.1 (-3.2 to -1.0) |
|  | **p-value** | < 0.0001 | 0.0002 |
| **Diuretics** | **Placebo** | 136.6 | 135.9 |
|  | **Dapagliflozin** | 133.5 | 133.6 |
|  | **LSM (95% CI)** | -3.2 (-3.8 to -2.5) | -2.3 (-3.1 to -1.5) |
|  | **p-value** | < 0.0001 | < 0.0001 |
| **No diuretics** | **Placebo** | 134.5 | 134.1 |
|  | **Dapagliflozin** | 131.4 | 131.7 |
|  | **LSM (95% CI)** | -3.1 (-3.6 to -2.6) | -2.4 (-3.1 to -1.8) |
|  | **p-value** | < 0.0001 | < 0.0001 |

ASCVD = atherosclerotic cardiovascular disease; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor blocker-neprylisin inhibitor; LSM = least mean square; MRF = multiple risk factors

**Supplement Table 3 – Events event reduction with dapagliflozin versus placebo considering systolic blood pressure (SBP) lowering after baseline as a time-varying co-variate.** Placebo group is used as reference. Models include treatment arm, baseline SBP, and SBP change as time-varying covariate and were stratified according to baseline atherosclerotic cardiovascular disease category (established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease) and the presence or absence of hematuria at baseline. Renal specific outcome is the composite of sustained decrease in eGFR of 40% or more, end-stage renal disease or renal death. CI = confidence interval; HHF = hospitalization for heart failure; HR = hazard ratio.

| **Endpoint** | **HR (95% CI)** | **P-Value** |
| --- | --- | --- |
| HHF | 0.72 (0.61-0.87) | 0.0004 |
| Renal Specific outcome | 0.53 (0.43-0.66) | <0.0001 |

**Supplement Figure 1 – Spline models showing the association between probability of event across the continuum of baseline SBP in the placebo arm. A.** Major adverse cardiovascular events (MACE), the composite of CV death, MI or ischemic stroke.  **B.** Cardiovascular (CV) death or hospitalization for heart failure. **C.** CV death.



**A**



**B**



**C**

**Supplement Figure 2. Spline models showing the association between probability of event in the dapagliflozin arm versus change in systolic blood pressure (SBP) from baseline to 6 months. A.** Hospitalization for heart failure (HHF) **B.** Renal specific outcome (the composite of sustained decrease in estimated glomerular filtration rate of 40% or more, end-stage renal disease or renal death).CI = confidence interval.

Gráfico, Gráfico de linhas

Descrição gerada automaticamente

**Gráfico, Gráfico de linhas

Descrição gerada automaticamente**