**Cardiovascular, renal and metabolic outcomes of dapagliflozin vs. placebo in a primary cardiovascular prevention cohort. Analyses from the DECLARE-TIMI 58 study**

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Running head: DECLARE TIMI-58 outcomes in the MRF cohort

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**Abstract**

**Aims:** International guidelines propose prescribing SGLT-2 inhibitors to patients with type-2 diabetes (T2D) as secondary prevention in patients with established atherosclerotic cardiovascular disease (ASCVD) or for primary prevention of cardiovascular events in high-risk patients. The current analyses expand on the cardiovascular and renal effects of SGLT-2 inhibitors in high-risk populations with multiple risk factors (MRF) for ASCVD.

**Methods:** The DECLARE-TIMI 58 trial randomized 17,160 patients with T2D and MRF (59.4%) or established ASCVD (40.6%) to dapagliflozin vs. placebo, followed for a median of 4.2 years. The cardiovascular and renal outcomes in the MRF cohort were studied across clinically relevant subgroups for treatment effect and subgroup-based treatment interaction.

**Results:** Among patients with MRF, the reduction with dapagliflozin in risk of CVD/HHF (HR 0.84, 95% CI 0.67-1.04) and the renal-specific outcome (HR 0.51, 95% CI 0.37-0.69) did not differ from patients with ASCVD (Pinteraction 0.99 and 0.72 respectively). The effect on CVD/HHF was entirely driven by a reduction in HHF (HR 0.64, 95% CI 0.46-0.88). The benefits of dapagliflozin on HHF and on the renal-specific outcome, among the subset with MRF, were consistent across all subgroups assessed (Pinteraction >0.05 for all). At 48 months, HbA1c, weight, systolic blood pressure and urinary albumin:creatinine ratio were lower with dapagliflozin vs. placebo and eGFR was higher (p<0.05).

**Conclusion:** In patients with T2D and MRF, dapagliflozin reduced the risk of HHF and adverse renal outcomes regardless of baseline characteristics. These analyses support the benefit of dapagliflozin on important outcomes in a broad primary prevention population.

**introduction**

Sodium glucose cotransporter 2 (SGLT2) inhibitors have been approved for the treatment of T2DM since 2012. Early clinical trials with these agents demonstrated their capacity not only for lowering glucose but also for reducing weight and blood pressure, thus addressing several important components of the metabolic syndrome (1). The EMPA-REG OUTCOME trial, the first published cardiovascular outcome trial (CVOT) of a drug in the class, revolutionized our view of management of T2D by demonstrating significant reduction in risk for major adverse cardiovascular events (MACE), cardiovascular death, hospitalization for heart failure (HHF), as well as significant reduction in the occurrence of adverse renal outcomes (2, 3). Subsequently, published CVOTs demonstrated some heterogeneity with respect to SGLT2 inhibitor effects on MACE and cardiovascular death, yet the effects on HHF and renal outcomes were largely consistent (4-7). Still, all patients included in the studies of empagliflozin, ertugliflozin and most of the patients included in the canagliflozin program had established atherosclerotic cardiovascular disease (ASCVD), thus limiting our ability to extrapolate the effects of these drugs on populations without established ASCVD, which include the majority of patients with T2D (8-9).

In the DECLARE-TIMI 58 CVOT of dapagliflozin vs. placebo, 59.4% of the patients had multiple risk factors (MRF) but not established ASCVD. This large primary prevention cohort (N=10,146) represents a broad T2D population with respect to the number of cardiovascular risk factors, age, disease duration and renal function. Thus, this trial affords a unique opportunity to assess the effects of an SGLT2 inhibitor in a population with T2D without prevalent ASCVD. (6, 10).

In the overall trial, dapagliflozin demonstrated a reduction in one of the dual primary composite outcomes of hospitalization for heart failure / cardiovascular death (HHF/CVD; HR 0.83, 95% CI 0.73-0.95), driven by a reduction in HHF, and also met the prespecified criterion for noninferiority but did not achieve statistically significant superiority with respect to the second dual primary outcome of MACE (HR 0.93, 95% CI 0.84-1.03) (6). The renal-specific outcome was significantly reduced with dapagliflozin (HR 0.53, 95% CI 0.43-0.66) (11). All outcomes were directionally consistent in the established ASCVD and the MRF groups (Pinteraction >0.05) (6). In the current analysis, we focus on the MRF cohort aiming to better characterize the cardiovascular, renal and metabolic benefits of dapagliflozin on a broad population with varying demographic, clinical and metabolic features.

**Materials and Methods**

***Study overview***

In the DECLARE - TIMI 58 trial, a total of 17,160 patients were randomly assigned to receive dapagliflozin 10 mg daily or placebo and followed for a median of 4.2 years. The trial included 6,974 patients with established ASCVD and 10,186 with MRF but without ASCVD. MRF participants were men aged ≥55 and women aged ≥60 years with at least one additional cardiovascular risk factor including dyslipidemia, hypertension, or current tobacco use. Patients with a HbA1c of 6.5 - <12.0% and a creatinine clearance of ≥60 ml/min/1.73 m2 were eligible for inclusion. All patients were treated according to guidelines and regional standards of care for cardiovascular risk factors - blood pressure, lipids, antithrombotic treatment and HbA1c. The trial protocol was approved by the institutional review board at each participating site, and all participants provided written informed consent. The design, baseline characteristics and principal results of this study have been previously published (6, 10, 12).

***Assessment of outcomes***

The dual primary composite efficacy outcomes were cardiovascular death or hospitalization for heart failure (CVD/HHF) and major adverse cardiovascular events (MACE; the composite of cardiovascular death, myocardial infarction or ischemic stroke). A renal-specific composite outcome included a sustained decrease of 40% or more in eGFR to <60 ml/min/1.73 m2, end stage renal disease (ESRD) or death from renal cause. Additional outcomes included the components of the primary outcomes and all-cause mortality.

***Statistical analysis***

Baseline characteristics are reported as frequencies and percentages for categorical variables and as mean and standard deviation (SD) or median (IQR) for continuous variables. Baseline and efficacy analyses were performed on an intention-to-treat basis. 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.

We calculated the effect of dapagliflozin on the incidence of the efficacy outcome within each subgroup using Cox regression models that included the randomization stratification factor of baseline hematuria, and we report the hazard ratios (HRs) and 95% confidence intervals (CI). To test for heterogeneity of effect, an interaction term was included in the Cox regression model.

The mean ± SD values of HbA1c, weight, systolic blood pressure (SBP), eGFR and urinary albumin creatinine ratio (UACR) with dapagliflozin vs. placebo during the trial in the MRF group are shown. Mixed models for repeated measures were analyzed to compare change from baseline by treatment group at month 48. Undetectable UACR values were imputed to be 7.0 mg/g which was the lowest detectable level of the assay used in the latter part of the trial.

There was no statistical adjustment for multiple comparisons. A p-value <0.05 was considered statistically significant.

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 16.1 (College Station, TX, USA).

**Results**

***Baseline characteristics***

10,186 MRF patients were included in these analyses. Their baseline characteristics are shown in table 1. There were 5713 (56.1%) males, the mean ± SD age was 64.8±5.6 years, BMI 32.0±6.0 kg/m2 and baseline HbA1c was 8.3±1.2%. Heart failure at baseline was noted in 568 (5.6%) patients and 622 (6.1%) had an eGFR <60 mL/min/1.73 m2.

***Cardiovascular and renal outcomes***

Among patients with MRF, the reduction with dapagliflozin in risk of CVD/HHF (HR 0.84, 95% CI 0.67-1.04) did not differ from that seen in patients with ASCVD (Pinteraction 0.99). The effect on CVD/HHF was entirely driven by a reduction in HHF (HR 0.64, 95% CI 0.46-0.88, figure 1A). HHF was reduced with dapagliflozin vs. placebo in MRF patients with no heterogeneity across subgroups assessed (Pinteraction >0.05, figure 2A). MACE was balanced with dapagliflozin vs. placebo in the MRF patients (HR 1.01, 95% CI 0.86-1.20), in line with that observed in the established ASCVD cohort (Pinteraction 0.25).

The renal-specific outcome was reduced with dapagliflozin vs. placebo in the MRF group (HR 0.51, 95% CI 0.37-0.69, figure 1B) and did not differ from those with ASCVD (Pinteraction 0.72). This observed reduction was consistent across all subgroups assessed (Pinteraction >0.05, figure 2B).

***Metabolic outcomes***

At 48 months, patients randomized to dapagliflozin vs. placebo had lower HbA1c (7.8±1.2 vs. 8.0±1.4%), weight (86.8±19.7 vs. 88.4±20.4 kg), systolic blood pressure (132.8±14.6 vs. 135.1±15.0 mmHg), and urinary albumin creatinine ratio (93.0±437.4 vs. 130.2±483.6 mg/g), and had higher eGFR (77.7±16.8 vs. 76.8±17.3 mL/min/1.73m2; p<0.05 for difference in change from baseline for dapagliflozin vs. placebo for all parameters; Figure 3).

***Safety outcomes***

In the MRF group, there were fewer patients with a serious adverse event or with major hypoglycemia with dapagliflozin vs. placebo. Genital infections and diabetic ketoacidosis were increased consistent with the known safety profile of the class. Additional safety outcomes including amputations, fractures, volume depletion, acute kidney injury, urinary tract infection and cancer were balanced with dapagliflozin vs. placebo (supplementary table 1).

**Discussion**

This post-hoc analysis of the large primary prevention cohort (MRF) in the DECLARE-TIMI 58 trial delineates the benefits of dapagliflozin in patients without established ASCVD. The reduction in HHF and in adverse renal outcomes that was observed in the overall study population was consistently observed in the MRF group irrespective of age, sex, diabetes duration, HbA1c, eGFR, history of heart failure or number of additional cardiovascular risk factors. Moreover, in line with the overall study data, no new safety signals emerged in this cohort, and the metabolic benefits known for the class were observed as well.

In recent years, with accumulating data from cardiovascular and renal outcome trials of SGLT-2 inhibitors, the position of these agents in the treatment algorithm of patients with T2D has been under extensive discussion (13-15). Trials of SGLT2 inhibitors have demonstrated consistent metabolic benefits in patients with T2D with clinically significant reductions in HbA1c, blood pressure and weight, irrespective of baseline cardiovascular risk. The cardiovascular and renal benefits of the class were initially assessed in a mostly secondary prevention population, however, the large primary prevention population in the DECLARE-TIMI 58 trial has enabled closer scrutiny of the benefits of dapagliflozin in this patient cohort.

When determining the treatment regimen for patients with T2D, particularly in the case of lower risk patients without established ASCVD, several factors should be considered. Type 2 diabetes usually occurs in the constellation of the metabolic syndrome with obesity, hypertension and dyslipidemia being important comorbidities. Multifactorial intervention targeting several cardiovascular risk factors, particularly when implemented in the early stages of T2D, is thus of paramount importance (16). The unique mode of action of SGLT2 inhibitors, which is insulin independent, yields metabolic advantages in early as well as progressive T2D when endogenous insulin reserves may have diminished. Long-term benefits can be expected in slowing diabetes progression by maintaining HbA1c reduction, reducing microvascular complications as well as decreasing cardiovascular complications (17-20).

Besides control of the “standard” cardiovascular risk factors (obesity, hypertension, dyslipidemia, dysglycemia), the clinical relevance of the cardio-renal axis is becoming increasing apparent (21). Reduced eGFR as well as increased albuminuria lead to a synergistic increase in the risk of cardiovascular events (22, 23). SGLT2 inhibitors have consistently demonstrated improvements in renal outcomes. These include both reversal of pre-existing albuminuria, as well as reduced conversion from normo- to micro- or macro-albuminuria. Moreover, SGLT2 inhibitors have been shown to slow the decline in eGFR and lead to a significant reduction in end stage renal disease (3, 9, 11, 24, 25). These benefits have been observed in those with and without baseline chronic kidney disease (CKD), and regardless of established ASCVD (5).

Adverse renal outcomes have been markedly reduced with dapagliflozin. A reduction in adverse renal outcomes, as well as a marked decline in albuminuria, were observed irrespective of baseline cardiovascular or renal risk, and consistently across all risk categories in the MRF population. These data further support the role of dapagliflozin in early, primary prevention, of adverse renal outcomes (11).

HHF was also significantly reduced with dapagliflozin, and in the present analyses – also in lower risk patients with no heterogeneity based on age, sex, BMI, diabetes duration, HbA1c, eGFR, history of heart failure or number of additional risk factors. The pivotal role of heart failure in the prognosis of patients with diabetes is becoming increasingly apparent, and the role of dapagliflozin in the primary prevention of HHF in patients with T2DM is of utmost importance (26, 27).

The ADA 2020 Standards of Medical Care propose prescribing SGLT2 inhibitors with evidence of reducing heart failure and / or CKD progression, independently of HbA1c levels, to patients in whom heart failure or CKD predominate (14). Yet, these benefits were observed in our study irrespective of pre-existing heart failure or CKD, and consistently across risk categories – suggesting these recommendations may be expanded to a broader population of T2D.

The ESC 2019 guidelines propose prescribing SGLT2 inhibitors to patients with T2D and cardiovascular disease, or at high or very high cardiovascular risk (13). Additionally, the 2019 American College of Cardiology/American Heart Association Guideline on the primary prevention of cardiovascular disease propose initiating SGLT2 inhibitors or glucagon like peptide-1 receptor agonists (GLP-1 RA) in patients with T2D and additional cardiovascular risk factors (15). This definition is reflective of the broad inclusion criteria of the DECLARE-TIMI 58 study.

A meta-analysis of SGLT2 inhibitors CVOTs – showed no evidence of heterogeneity on the effects on MACE in patients with and without ASCVD, supporting the use of SGLT-2 inhibitors in primary prevention populations as well (8). Notably, MACE reduction was noted for GLP-1 RA as well, with no heterogeneity in primary vs. secondary prevention populations (28, 29). These results were mainly driven by data from the REWIND CVOT of dulaglutide, which included a large primary prevention population (30). However, though relative risk reduction was consistent in both classes in primary and secondary prevention populations, absolute risk reduction was smaller in the lower risk populations, and individualized decision making is recommended.

Safety is an important consideration for a drug intended for use early in the disease, as long-term exposure is expected. In that respect, the safety profile of dapagliflozin, which had been extensively reviewed in our previous analysis, was consistently observed in the MRF population, providing further reassurance to the early use of this agent (31).

Recent data have expanded the role of dapagliflozin from the prevention of HHF and adverse renal outcomes to the treatment of these conditions once established. The DAPA-HF trial demonstrated a reduction in HHF in patients with heart failure and reduced ejection fracture with or without diabetes (32). Notably, a reduction in HHF in patients with heart failure and reduced ejection fracture was also observed with empagliflozin, and was likewise unrelated to baseline diabetes status (33). Moreover, a reduction in adverse renal outcomes with dapagliflozin in patients with established chronic kidney disease has been shown in the DAPA-CKD study, and the benefit was observed irrespective of pre-existing diabetes (34).

In conclusion, extensive early clinical data show the beneficial glucose, weight and blood pressure lowering effects of dapagliflozin in patients at all stages of T2D. The current analyses highlight the benefits of dapagliflozin in the prevention of HHF and adverse renal outcomes across a broad risk continuum of a primary prevention population with T2D. Expected outcomes of dapagliflozin treatment include – long term metabolic benefits (glucose, weight, blood pressure and albuminuria) as well as primary prevention of HHF and adverse renal outcomes. Moreover, dapagliflozin’s overall favorable safety profile places it as an appropriate option early in the disease for patients with T2D.

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**conflict of interest**

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**Legends to figures**

Figure 1A – Hospitalization for heart failure in the MRF cohort with dapagliflozin vs. placebo

Figure 1B – The renal specific outcome in the MRF cohort with dapagliflozin vs. placebo

Figure 2A – Hospitalization for heart failure in the MRF cohort by subgroups

Figure 2B – Renal-specific outcome in the MRF cohort by subgroups

Figure 3 - Metabolic outcomes in the MRF cohort

Legend: Data shown are mean ±SE. SBP – systolic blood pressure, UACR – urinary albumin creatinine ratio, eGFR – estimated glomerular filtration rate

Table 1 – Baseline characteristics of the Multiple Risk Factor population

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Dapagliflozin**  **N=5108** | **Placebo**  **N=5078** | **p-value** |
| Age, Mean (SD) | 64.8 (5.7) | 64.8 (5.6) | 0.697 |
| Male Sex, N (%) | 2874 (56.3%) | 2839 (55.9%) | 0.717 |
| BMI (kg/m2), Mean (SD), N | 32.0 (5.9) | 32.0 (6.1) | 0.958 |
| White N (%) | 4056 (79.4%) | 4013 (79.0%) | 0.639 |
| Diabetes duration, Mean (SD) | 11.8 (7.4) | 11.7 (7.7) | 0.316 |
| HbA1c (%) | 8.3 (1.2) | 8.3 (1.2) | 0.818 |
| Systolic BP (mmHg), Mean (SD) | 135.7 (15.0) | 135.5 (15.2) | 0.704 |
| eGFR (CKD-EPI), Mean (SD) | 85.4 (15.2) | 85.8 (14.8) | 0.522 |
| <60 mL/min/1.73m2 | 325 (6.4%) | 297 (5.8%) | 0.445 |
| 60 to <90 mL/min/1.73m2 | 2281 (44.7%) | 2313 (45.5%) |
| ≥90 mL/min/1.73m2 | 2501 (49.0%) | 2468 (48.6%) |
| UACR mg/g, Median (IQR), N | 12.2 (5.9, 35.9) | 12.1 (5.8, 36.7) | 0.835 |
| <30 mg/g | 3602 (71.6%) | 3590 (71.8%) | 0.769 |
| 30 - 300 mg/g | 1123 (22.3%) | 1121 (22.4%) |
| > 300 mg/g | 305 (6.1%) | 286 (5.7%) |
| LDL-C (mg/dL), Mean (SD), N | 91.4 (34.9) | 91.5 (35.4) | 0.832 |
| Number of Additional Risk Factors |  |  |  |
| One | 1440 (28.2%) | 1422 (28.0%) | 0.770 |
| Two | 3257 (63.8%) | 3263 (64.3%) |
| Three | 406 (8.0%) | 386 (7.6%) |
| History of HF, N (%) | 268 (5.2%) | 300 (5.9%) | 0.146 |
| Dyslipidemia, N (%) | 3745 (73.3%) | 3782 (74.5%) | 0.182 |
| Hypertension, N (%) | 4692 (91.9%) | 4595 (90.5%) | 0.015 |
| Current tobacco use, N (%) | 735 (14.4%) | 729 (14.4%) | 0.962 |
| Baseline medications |  |  |  |
| Insulin, N (%) | 1948 (38.1%) | 1873 (36.9%) | 0.192 |
| Antiplatelet, N (%) | 2221 (43.5%) | 2231 (43.9%) | 0.644 |
| ACE/ARB, N (%) | 4123 (80.7%) | 4092 (80.6%) | 0.864 |
| Beta-blocker, N (%) | 1969 (38.5%) | 1992 (39.2%) | 0.481 |
| Statin or Ezetimibe, N (%) | 3395 (66.5%) | 3414 (67.2%) | 0.411 |

Figure 1A – Hospitalization for heart failure in the MRF cohort with dapagliflozin vs. placebo

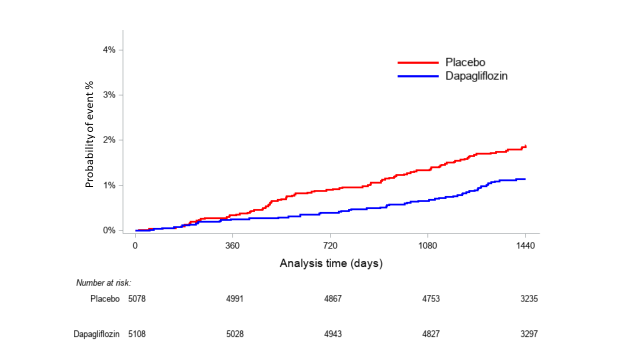
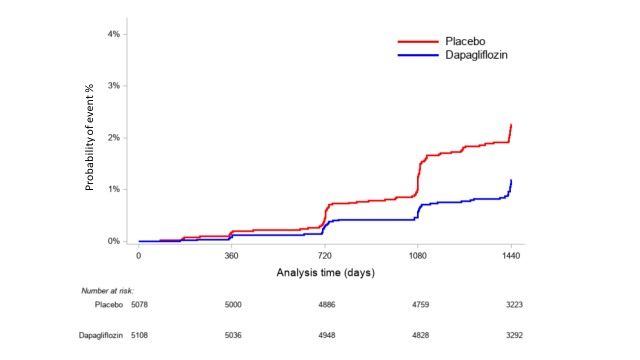
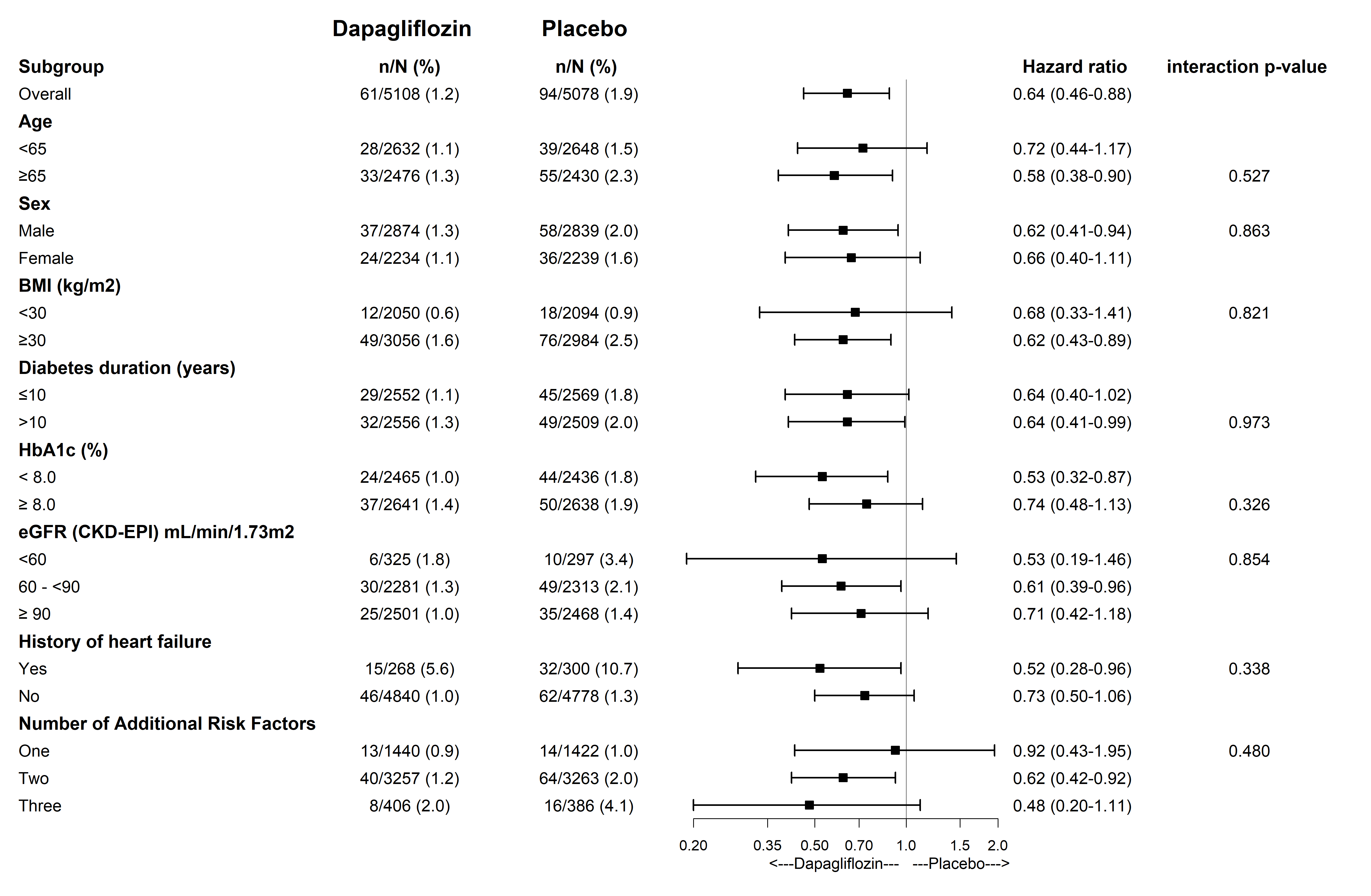
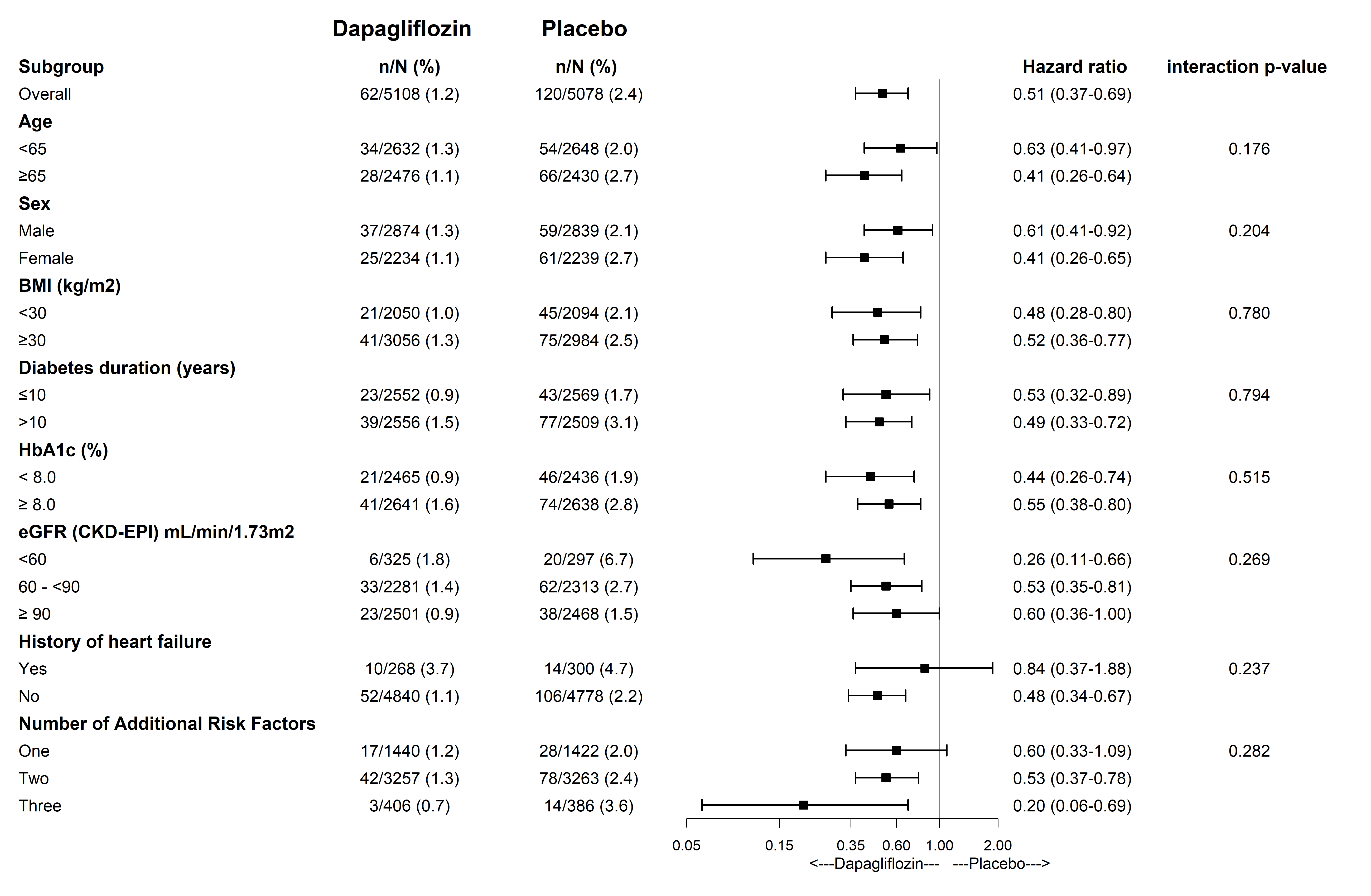
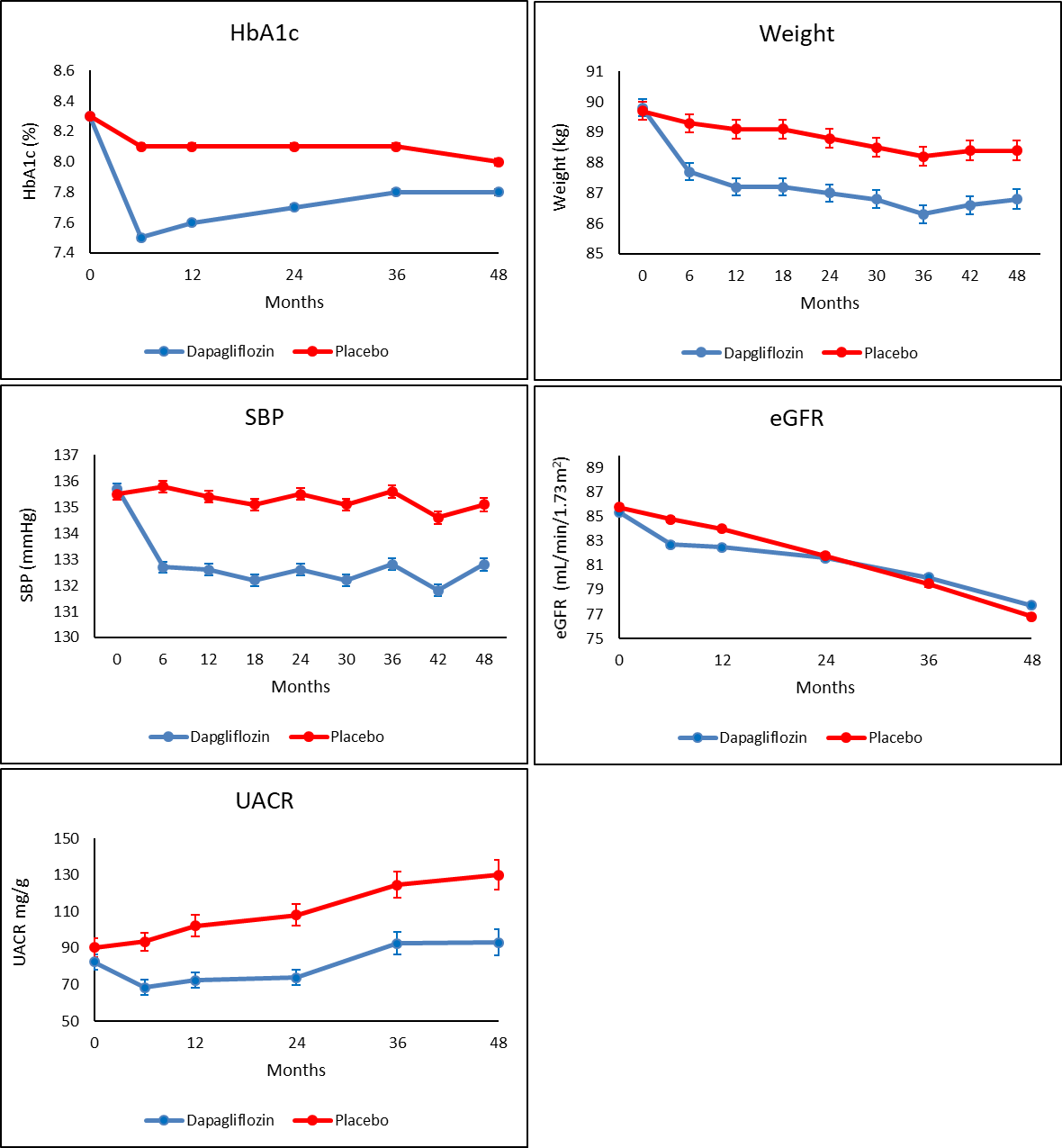


Figure 1B – The renal specific outcome in the MRF cohort with dapagliflozin vs. placebo



Figure 2A – Hospitalization for heart failure in the MRF cohort by subgroups

 Figure 2B – Renal-specific outcome in the MRF cohort by subgroups

Figure 3 - Metabolic outcomes in the MRF cohort

Legend: Data shown are mean ±SE. SBP – systolic blood pressure, UACR – urinary albumin creatinine ratio, eGFR – estimated glomerular filtration rate

Supplementary table 1 – Safety outcomes in the MRF cohort

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Dapagliflozin**  **N=5104** | | **Placebo**  **N=5073** | |  |  |
| **Outcome** | **n** | **%** | **n** | **%** | **HR (95% CI)** | **Cox p-value** |
| Major hypoglycemic event | 24 | 0.5% | 44 | 0.9% | 0.53 (0.32-0.87) | 0.011 |
| Diabetic Ketoacidosis Definite or Probable | 16 | 0.3% | 6 | 0.1% | 2.56 (1.00-6.54) | 0.050 |
| Amputation | 42 | 0.8% | 54 | 1.1% | 0.77 (0.51-1.15) | 0.200 |
| Fracture | 262 | 5.1% | 227 | 4.5% | 1.15 (0.96-1.37) | 0.128 |
| Symptoms of volume depletion | 82 | 1.6% | 78 | 1.5% | 1.02 (0.75-1.39) | 0.921 |
| Genital infections | 51 | 1.0% | 3 | 0.1% | 16.72 (5.22-53.56) | <0.001 |
| Urinary tract infection | 70 | 1.4% | 80 | 1.6% | 0.84 (0.61-1.16) | 0.301 |
| Cancer | 294 | 5.8% | 281 | 5.5% | 1.04 (0.88-1.22) | 0.668 |
| Acute kidney injury | 59 | 1.2% | 64 | 1.3% | 0.89 (0.62-1.26) | 0.505 |

Legend: Genital and urinary infections considered were either serious (2 in each arm) or led to discontinuation of study drug.