Cardiovascular, Renal, and Metabolic Outcomes of Dapagliflozin Versus Placebo in a Primary Cardiovascular Prevention Cohort: Analyses From DECLARE-TIMI 58

Avivit Cahn,[1] Itamar Raz,[1] Lawrence A. Leiter,[2] Ofri Mosenzon,[1] Sabina A. Murphy,[3] Erica L. Goodrich,[3] Ilan Yanuv,[1] Aliza Rozenberg,[1] Deepak L. Bhatt,[4] Darren K. McGuire,[5,6] John P.H. Wilding,[7] Ingrid A.M. Gause-Nilsson,[8] Anna Maria Langkilde,[8] Marc S. Sabatine,[3] and Stephen D. Wiviott[3]

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OBJECTIVE

International guidelines propose prescribing sodium–glucose cotransporter 2 (SGLT2) 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 with multiple risk factors (MRF) for ASCVD. The current analyses expand on the cardiovascular renal and metabolic effects of SGLT2 inhibitors in MRF patients.

RESEARCH DESIGN AND METHODS

In DECLARE-TIMI 58, 17,160 patients with T2D and MRF (59.4%) or established ASCVD (40.6%) were randomized to dapagliflozin versus placebo; patients were 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 cardiovascular death or hospitalization for heart failure (CVD/HHF) (hazard ratio [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 that for patients with ASCVD ($P_{interaction}$ 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 directionally consistent across clinically relevant subgroups. At 48 months, HbA_{1c}, weight, systolic blood pressure, and urinary albumin–to–creatinine ratio were lower with dapagliflozin versus placebo and estimated glomerular filtration rate was higher ($P < 0.001$).

CONCLUSIONS

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 for important outcomes in a broad primary prevention population.

[1]*Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, and The Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel*
[2]*Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Canada*
[3]*TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA*
[4]*Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA*
[5]*Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX*
[6]*Parkland Health and Hospital System, Dallas, TX*
[7]*Department of Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, U.K.*
[8]*BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden*

Corresponding author: Avivit Cahn, avivit@hadassah.org.il

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been approved for the treatment of type 2 diabetes (T2D) 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 Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), 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) and cardiovascular death or hospitalization for heart failure (CVD/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 and 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 CVOT Dapagliflozin Effect on Cardiovascular Events trial (DECLARE-TIMI 58) with dapagliflozin versus 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 CVD/HHF (hazard ratio [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 ($P_{interaction} > 0.05$) (6). In the current analysis, we focus on the MRF cohort, aiming to better characterize the cardiovascular, renal, and metabolic benefits of dapagliflozin for a broad population with varying demographic, clinical, and metabolic features.

RESEARCH DESIGN AND METHODS

Study Overview

In DECLARE-TIMI 58, 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 HbA_{1c} of 6.5% to <12.0% and creatinine clearance of ≥60 mL/min 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 HbA_{1c}. 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 previously been published (6,10,12).

Table 1—Baseline characteristics of the MRF population

	Dapagliflozin	Placebo	*P*
N	5,108	5,078	
Age, years, mean (SD)	64.8 (5.7)	64.8 (5.6)	0.697
Male sex, *N* (%)	2,874 (56.3)	2,839 (55.9)	0.717
BMI (kg/m^2), mean (SD)	32.0 (5.9)	32.0 (6.1)	0.958
White, *N* (%)	4,056 (79.4)	4,013 (79.0)	0.639
Diabetes duration, years, mean (SD)	11.8 (7.4)	11.7 (7.7)	0.316
HbA_{1c} (%), mean (SD)	8.3 (1.2)	8.3 (1.2)	0.818
SBP (mmHg), mean (SD)	135.7 (15.0)	135.5 (15.2)	0.704
DBP (mmHg), mean (SD)	78.4 (8.9)	78.4 (8.8)	0.550
eGFR (CKD-EPI) (mL/min/1.73 m^2), mean (SD)	85.4 (15.2)	85.8 (14.8)	0.522
<60	325 (6.4)	297 (5.8)	0.445
60 to <90	2,281 (44.7)	2,313 (45.5)	
≥90	2,501 (49.0)	2,468 (48.6)	
UACR (mg/g), median (IQR)	12.2 (5.9–35.9)	12.1 (5.8–36.7)	0.835
<30	3,602 (71.6)	3,590 (71.8)	0.769
30–300	1,123 (22.3)	1,121 (22.4)	
>300	305 (6.1)	286 (5.7)	
LDL-C (mg/dL), mean (SD)	91.4 (34.9)	91.5 (35.4)	0.832
Number of additional risk factors, *N* (%)			
One	1,440 (28.2)	1,422 (28.0)	0.770
Two	3,257 (63.8)	3,263 (64.3)	
Three	406 (8.0)	386 (7.6)	
History of heart failure, *N* (%)	268 (5.2)	300 (5.9)	0.146
Dyslipidemia, *N* (%)	3,745 (73.3)	3,782 (74.5)	0.182
Hypertension, *N* (%)	4,692 (91.9)	4,595 (90.5)	0.015
Current tobacco use, *N* (%)	735 (14.4)	729 (14.4)	0.962
Baseline medications			
Insulin, *N* (%)	1,948 (38.1)	1,873 (36.9)	0.192
Antiplatelet, *N* (%)	2,221 (43.5)	2,231 (43.9)	0.644
ACE/ARB, *N* (%)	4,123 (80.7)	4,092 (80.6)	0.864
MRA, *N* (%)	123 (2.4)	145 (2.9)	0.158
β-Blocker, *N* (%)	1,969 (38.5)	1,992 (39.2)	0.481
Statin or ezetimibe, *N* (%)	3,395 (66.5)	3,414 (67.2)	0.411

ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; IQR, interquartile range; LDL-C, LDL cholesterol; MRA, mineralocorticoid receptor agonists.

Assessment of Outcomes

The dual primary composite efficacy outcomes were CVD/HHF and MACE (the composite of cardiovascular death, myocardial infarction, and ischemic stroke). A renal-specific composite outcome included a sustained decrease of 40% or more in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2, end-stage renal disease, 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 SD or median (interquartile range) for continuous variables. Baseline and efficacy analyses were performed on an intention-to-treat basis. Safety analyses were performed with use of 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 HRs and 95% CIs. To test for heterogeneity of effect, we included an interaction term in the Cox regression model.

The least squares (LS) mean ± SE values of HbA_{1c}, weight, systolic blood pressure (SBP), diastolic blood pressure, eGFR, and urinary albumin–to–creatinine ratio (UACR) with dapagliflozin versus placebo during the trial in the MRF group are graphically shown. Mixed models for repeated measures were analyzed for comparison of change from baseline by treatment group at month 48. All urine albumin values <7.0 mg/L were imputed to a value of 7 mg/g UACR, which was the lowest detectable level of the assay used in the latter part of the trial. Since UACR did not follow a normal distribution, UACR data were log transformed before analysis. LS means and SE were back transformed to the original scale.

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

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

RESULTS

Baseline Characteristics

A total of 10,186 MRF patients were included in these analyses. Their baseline characteristics are shown in Table 1. There were 5,713 (56.1%) males, and the mean ± SD age was 64.8 ± 5.6 years, BMI 32.0 ± 6.0 kg/m^2, and baseline HbA_{1c} 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 m^2.

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 ($P_{interaction}$ 0.99). The effect on CVD/HHF was entirely driven by a reduction in HHF (HR 0.64, 95% CI 0.46–0.88) (Fig. 1*A*). HHF was reduced with dapagliflozin versus placebo in MRF patients, with no heterogeneity across subgroups assessed ($P_{interaction}$ > 0.05) (Fig. 2*A*). MACE was balanced with dapagliflozin versus placebo in the MRF patients (HR 1.01, 95% CI 0.86–1.20), consistent with

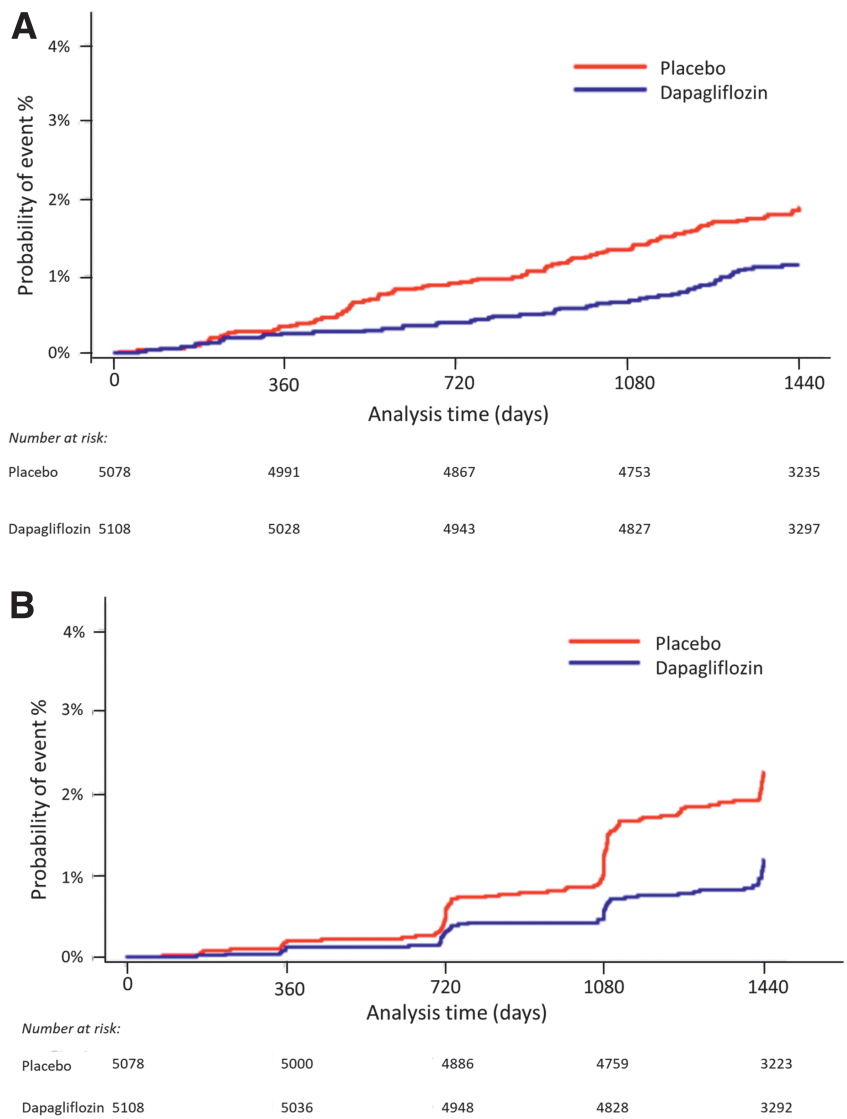

Figure 1—*A:* Hospitalization for heart failure in the MRF cohort with dapagliflozin versus placebo. *B*: The renal-specific outcome in the MRF cohort with dapagliflozin versus placebo.

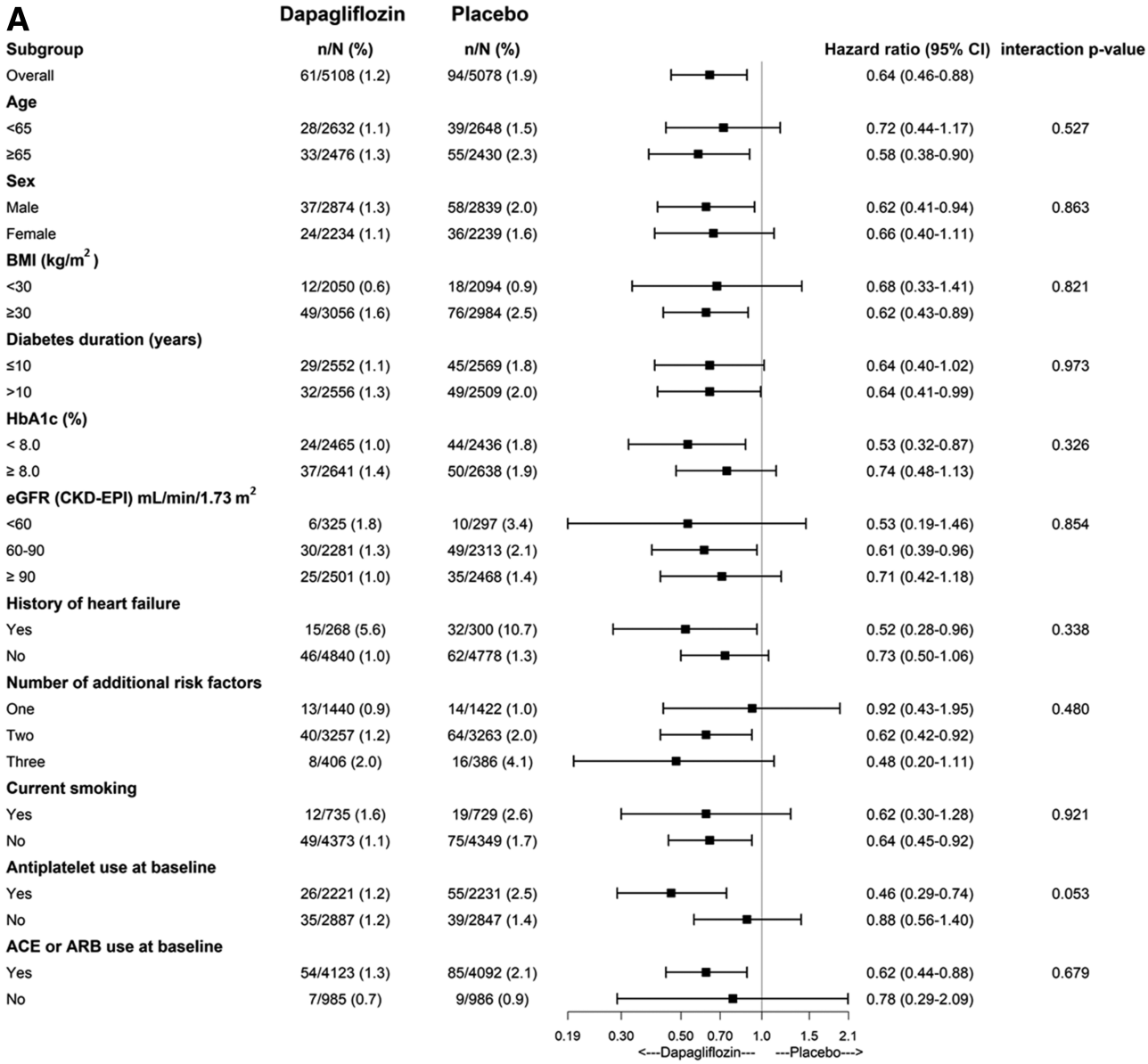

Figure 2—*A*: Hospitalization for heart failure in the MRF cohort by subgroups. *B*: Renal-specific outcome in the MRF cohort by subgroups. Age is presented in years. ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

observations in the established ASCVD cohort ($P_{interaction}$ 0.25).

The risk of the renal-specific outcome was reduced with dapagliflozin versus placebo in the MRF group (HR 0.51, 95% CI 0.37–0.69) (Fig. 1*B*) and the magnitude of the risk reduction did not differ from that in patients with ASCVD ($P_{interaction}$ 0.72). This observed reduction was consistent across all subgroups assessed (Fig. 2*B*), with a nominally greater benefit of dapagliflozin observed in current smokers versus nonsmokers, but note that the subgroup of current smokers and, hence, the number of events were very small.

Metabolic Outcomes

At 48 months, LS mean ± SE for patients randomized to dapagliflozin versus placebo was lower for HbA_{1c} (7.79 ± 0.04 vs. 8.03 ± 0.04%), weight (85.76 ± 0.14 vs. 87.86 ± 0.14 kg), SBP (132.96 ± 0.37 vs. 135.32 ± 0.37 mmHg), and UACR (22.53 ± 1.03 vs. 27.42 ± 1.03 mg/g) and higher for eGFR (77.21 ± 0.31 vs. 75.62 ± 0.31 mL/min/1.73 m^2). There was a significant difference in change from baseline for dapagliflozin versus placebo for all measurements ($P < 0.001$) (Fig. 3).

Safety Outcomes

In the MRF group, there were fewer patients with a serious adverse event or with major hypoglycemia with dapagliflozin versus 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 versus placebo (Supplementary Table 1).

CONCLUSIONS

This post hoc analysis of the large primary prevention cohort (MRF) in DECLARE-TIMI 58 delineates the benefits of dapagliflozin in patients without

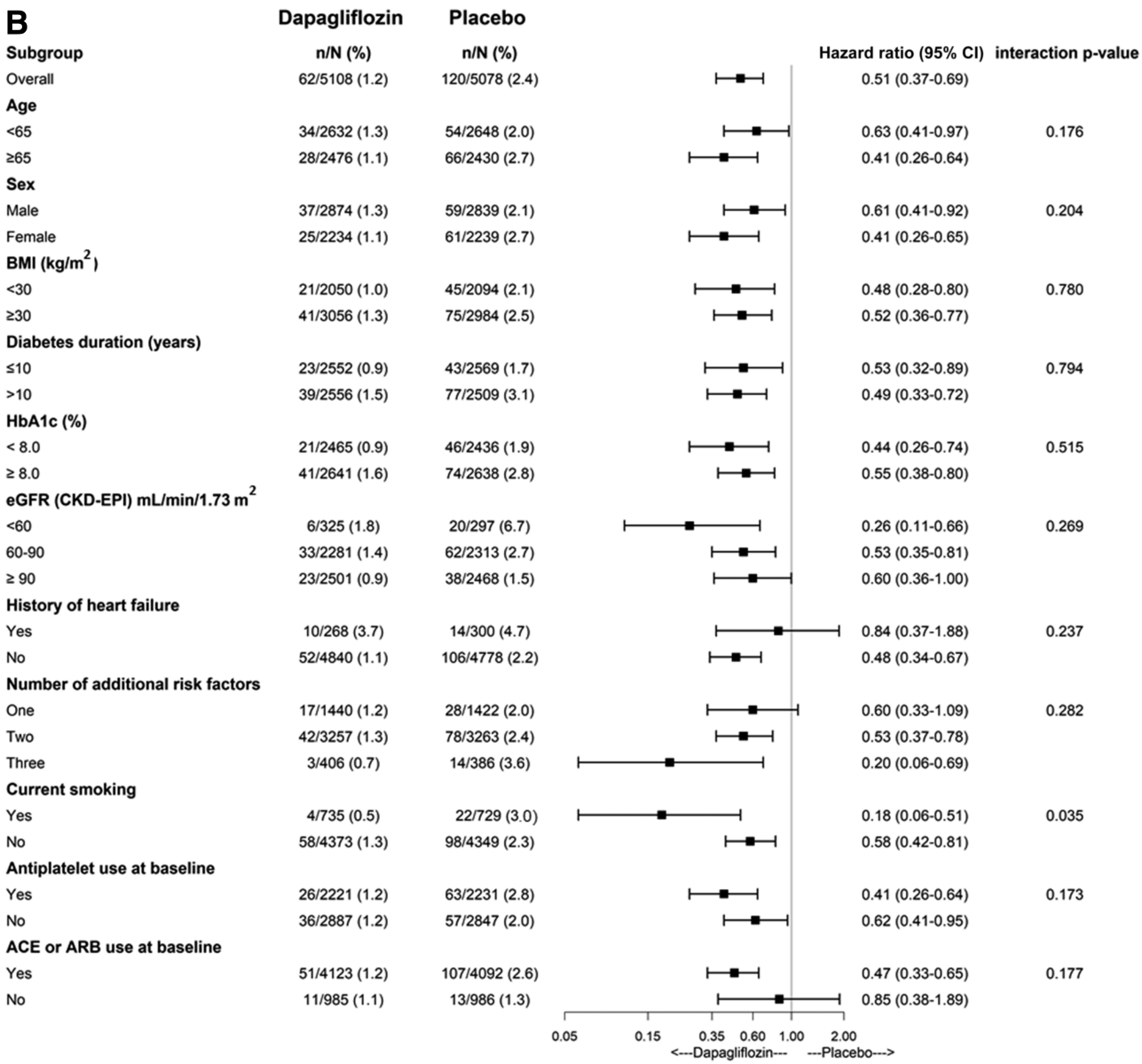

Figure 2—Continued

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, current smoking, HbA_{1c}, eGFR, history of heart failure, number of additional cardiovascular risk factors, and baseline medications. 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 SGLT2 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 HbA_{1c}, 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 DECLARE-TIMI 58 has enabled closer scrutiny of the benefits of dapagliflozin in this patient cohort.

In determination of the treatment regimen for patients with T2D, particularly in the case of lower risk patients without established ASCVD, several factors should be considered. T2D 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. Our analyses of the large primary prevention population in the trial demonstrate a sustained benefit of dapagliflozin versus placebo added to standard of care in reducing HbA_{1c},

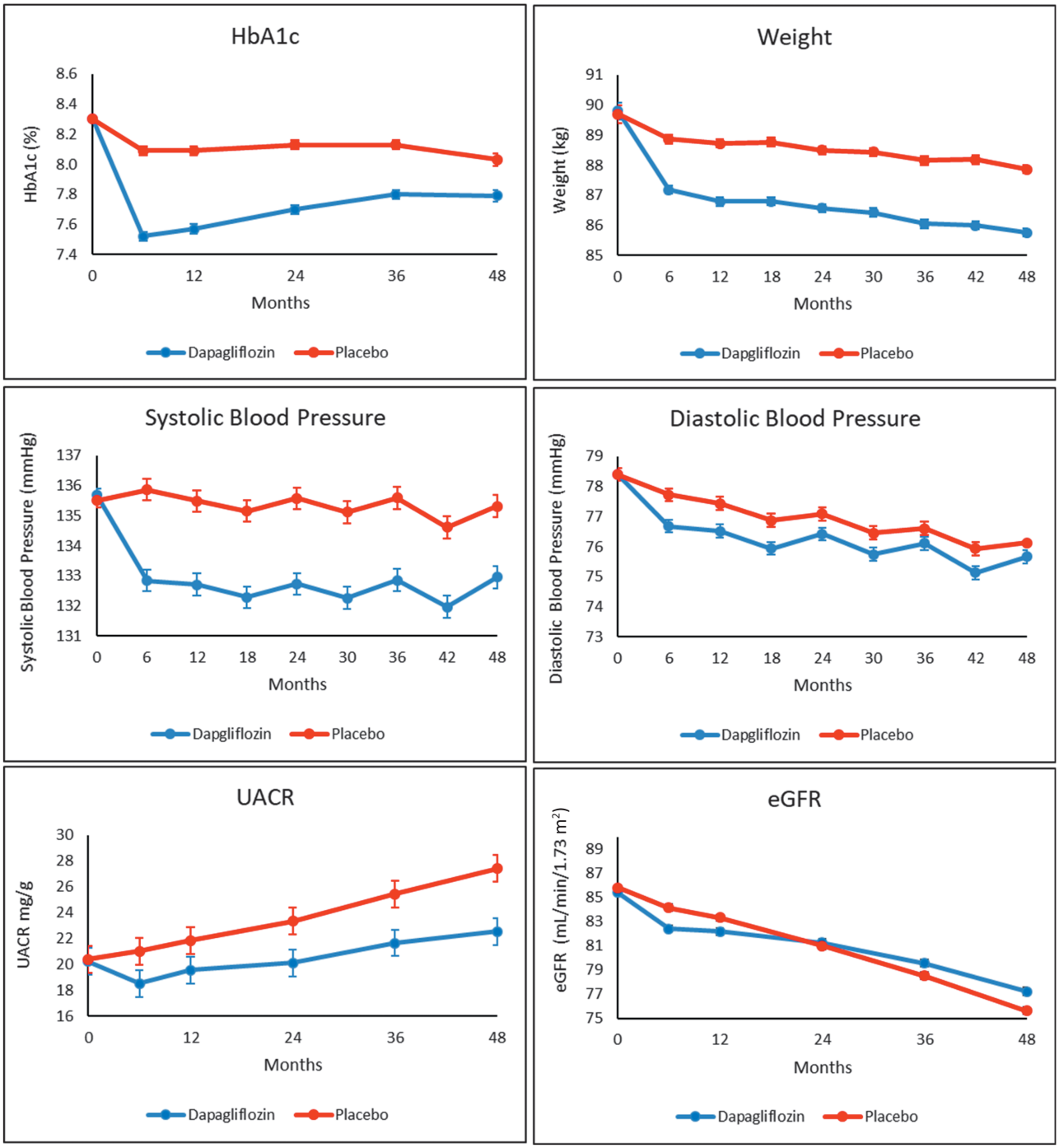

Figure 3—Metabolic outcomes in the MRF cohort. Data shown are LS mean ± SE. eGFR, estimated glomerular filtration rate; UACR, urinary albumin creatinine ratio.

weight, and blood pressure. Long-term benefits can be expected in slowing of diabetes progression by maintenance of HbA_{1c} reduction and 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 and 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 preexisting albuminuria and reduced conversion from normo- to micro- or macroalbuminuria. 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).

In the current analysis, adverse renal outcomes have been markedly reduced with dapagliflozin, along with a marked decline in albuminuria. The renal-specific outcome was reduced 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 in the present analyses—also in lower-risk patients with no heterogeneity based on age, sex, smoking, BMI, diabetes duration, HbA_{1c}, eGFR, history of heart failure, baseline medications, 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 American Diabetes Association 2021 *Standards of Medical Care in Diabetes* propose prescribing SGLT2 inhibitors with evidence of reducing heart failure and/or CKD progression, independently of HbA_{1c} levels and use of metformin, to patients in whom heart failure or CKD predominates (14). Yet, these benefits were observed in our study irrespective of preexisting heart failure or CKD, and consistently across risk categories, suggesting that these recommendations may be expanded to a broader population with T2D.

The European Society of Cardiology 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 proposes initiating SGLT2 inhibitors or glucagon like peptide-1 receptor agonists in patients with T2D and additional cardiovascular risk factors (15). This definition is reflective of the broad inclusion criteria of DECLARE-TIMI 58.

The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial which included patients with type 2 diabetes and albuminuric chronic kidney disease showed no evidence of heterogeneity on the effects of MACE in patients with and without ASCVD (8). Notably, MACE reduction was noted for glucagon like peptide-1 receptor agonists as well, with no heterogeneity in primary versus secondary prevention populations (28,29). These results were mainly driven by data from the CVOT of dulaglutide Researching Cardiovascular Events With a Weekly INcretin in Diabetes (REWIND), 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 we extensively reviewed in our previous analysis, was consistently observed in the MRF population, providing further reassurance regarding 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 Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF) trial demonstrated a reduction in HHF in patients with heart failure and reduced ejection fraction with or without diabetes (32). Notably, a reduction in HHF in patients with heart failure and reduced ejection fraction 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 CKD has been shown in the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) study, and the benefit was observed irrespective of preexisting diabetes (34).

The strengths of our analyses are the inclusion of a large, broad population of patients with T2D at high risk for cardiovascular disease. Our study further expands on different levels of risk within this population as defined by clinically relevant subgroups. However, several limitations to our analyses should be considered. First, as is generally noted in subgroup analyses, the trial was not powered to detect all possible event reductions and treatment-by-subgroup interactions. Furthermore, although the comparison of results in ASCVD vs. MRF patients was pre-specified, the analyses of subgroups within the MRF patients are post hoc and no adjustment was made for multiple comparisons; thus, these data should be considered as hypothesis generating. Finally, creatinine clearance $<$60 mL/min was an exclusion criterion in the study, limiting our ability to draw conclusions on this specific high-risk, primary prevention population.

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.

Duality of Interest. The sponsor of DECLARE-TIMI 58 was initially AstraZeneca and Bristol-Myers Squibb, and AstraZeneca later became the sole sponsor of the study. DECLARE-TIMI 58 was a collaboration between the funder and two academic research organizations (TIMI Study Group and Hadassah Medical Organization). The funder was involved in the study design, data collection, data analysis, interpretation, and writing of this report. Data analyses were done by the academic TIMI Study Group, which has access to the complete study database, allowing independent analyses of the results, and any discrepancies were resolved by discussion. The DECLARE-TIMI 58 publication committee made the decision to submit for publication.

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