University of Groningen

Cardiorenal outcomes with dapagliflozin by baseline glucose-lowering agents

Cahn, Avivit; Wiviott, Stephen D.; Mosenzon, Ofri; Murphy, Sabina A.; Goodrich, Erica L.; Yanuv, Ilan; Rozenberg, Aliza; Wilding, John P. H.; Leiter, Lawrence A.; Bhatt, Deepak L.

Published in:
Diabetes obesity & metabolism

DOI:
[10.1111/dom.14179](https://doi.org/10.1111/dom.14179)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Cahn, A., Wiviott, S. D., Mosenzon, O., Murphy, S. A., Goodrich, E. L., Yanuv, I., Rozenberg, A., Wilding, J. P. H., Leiter, L. A., Bhatt, D. L., McGuire, D. K., Litwak, L., Kooy, A., Gause-Nilsson, I. A. M., Fredriksson, M., Langkilde, A. M., Sabatine, M. S., & Raz, I. (2021). Cardiorenal outcomes with dapagliflozin by baseline glucose-lowering agents: Post hoc analyses from DECLARE-TIMI58. *Diabetes obesity & metabolism*, 23(1), 29-38. <https://doi.org/10.1111/dom.14179>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

ORIGINAL ARTICLE

WILEY

Cardiorenal outcomes with dapagliflozin by baseline glucose-lowering agents: Post hoc analyses from DECLARE-TIMI 58

Avivit Cahn MD^{1,2} | Stephen D. Wiviott MD³ | Ofri Mosenzon MD^{1,2} |
 Sabina A. Murphy MPH³ | Erica L. Goodrich MS³ | Ilan Yanuv MSc¹ |
 Aliza Rozenberg MA¹ | John P. H. Wilding MD⁴ | Lawrence A. Leiter MD⁵ |
 Deepak L. Bhatt MD³ | Darren K. McGuire MD⁶ | Leon Litwak MD⁷ |
 Adriaan Kooy MD⁸ | Ingrid A. M. Gause-Nilsson MD⁹ | Martin Fredriksson MD⁹ |
 Anna Maria Langkilde MD⁹ | Marc S. Sabatine MD³ | Itamar Raz MD^{1,2}

¹Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel

²Faculty of Medicine, Hebrew University of Jerusalem, Israel

³Division of Cardiovascular Medicine, TIMI Study Group, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

⁴Department of Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK

⁵Department of Medicine, Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Canada

⁶Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, and Parkland Health and Hospital System, Dallas, Texas

⁷Endocrinology Unit, Diabetes Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

⁸University Medical Center Groningen and Bethesda Diabetes Research Center, Groningen, the Netherlands

⁹BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

Correspondence

Avivit Cahn, Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Hebrew University Hospital, PO Box 12000, Jerusalem 91120, Israel.
 Email: avivit@hadassah.org.il

Funding information

The sponsor of the DECLARE-TIMI 58 study was initially AstraZeneca and Bristol-Myers Squibb and AstraZeneca later became the sole sponsor of the study, Grant/Award Number: 14151181

Abstract

Aim: To assess the associations between baseline glucose-lowering agents (GLAs) and cardiorenal outcomes with dapagliflozin versus placebo in the DECLARE-TIMI 58 study.

Materials and methods: DECLARE-TIMI 58 assessed the cardiorenal outcomes of dapagliflozin versus placebo in patients with type 2 diabetes. This post hoc analysis elaborates the efficacy and safety outcomes by baseline GLA for treatment effect and GLA-based treatment interaction.

Results: At baseline, 14 068 patients (82.0%) used metformin, 7322 (42.7%) sulphonylureas, 2888 (16.8%) dipeptidyl peptidase-4 inhibitors, 750 (4.4%) glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and 7013 (40.9%) insulin. Dapagliflozin reduced the composite of cardiovascular death (CVD) and hospitalization for heart failure (HHF) versus placebo regardless of baseline GLA, with greater benefit in the small group of patients with baseline use of GLP-1 RAs (HR [95% CI] 0.37 [0.18, 0.78] vs. 0.86 [0.75, 0.98] in GLP-1 RA users vs. non-users, $P_{\text{interaction}} = .03$). The overall HR for major adverse cardiovascular events (CVD, myocardial infarction or ischaemic stroke) was 0.93 (95% CI 0.84, 1.03) with dapagliflozin versus placebo, with no interaction by baseline GLA ($P_{\text{interaction}} > .05$). The renal-specific outcome was reduced with dapagliflozin versus placebo in the overall cohort (HR [95%CI] 0.53 [0.43-0.66]), with no interaction by baseline GLA ($P_{\text{interaction}} > .05$). All of these outcomes were similar in those with versus those without baseline metformin use.

Conclusions: The effects of dapagliflozin on cardiorenal outcomes were generally consistent regardless of baseline GLA, with consistent benefits regardless of baseline metformin use. The potential clinical benefit of combining sodium-glucose co-transporter-2 inhibitors with GLP-1 RAs, given some evidence of cardiovascular risk reduction with both classes, should be explored further.

KEYWORDS

cardiovascular disease, dapagliflozin, GLP-1 analogue, heart failure, insulin therapy, metformin

1 | INTRODUCTION

Global prevalence of type 2 diabetes (T2D) is steadily increasing and the number of people living with diabetes in 2019 was estimated to be 463 million.¹ The last 2 decades have seen marked advancements in diabetes care with the inclusion of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), dipeptidyl-peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter-2 (SGLT-2) inhibitors in the treatment armamentarium of T2D.² In contrast to sulphonylureas or insulin, these agents do not lead to hypoglycaemia or weight gain, and SGLT-2 inhibitors and GLP-1 RAs in fact lead to weight loss.² Cardiovascular outcome trials (CVOTs) with DPP-4 inhibitors showed no cardiovascular benefit, however, more recent trials of SGLT-2 inhibitors and GLP-1 RAs showed marked cardiovascular and renal benefits, albeit with some heterogeneity within each class.^{3–7} Moreover, while a recent meta analysis indicated the magnitude of benefit on major adverse cardiovascular events (MACE) was overall similar with GLP-1 RAs and SGLT-2 inhibitors (HR 0.88, 95% CI 0.82–0.94 for both drug classes), effects on hospitalization for heart failure (HHF) and adverse renal outcomes differed markedly, with a more pronounced reduction observed with SGLT-2 inhibitors.⁵ Whether combining these two drug classes yields additive or synergistic cardiorenal outcomes is currently unclear and has been the focus of several observational and post hoc analyses.^{8–11}

The vast majority of patients included in the CVOTs conducted over the last decade were not treatment-naïve and had been taking at least one glucose-lowering agent (GLA) at baseline. In the earlier trials, these consisted mostly of metformin, sulphonylureas and insulin, whereas in the more recent Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 trial, incretin-based therapies (DPP-4 inhibitors and GLP-1 RAs) were also used.^{12,13} While metformin is generally positioned as standard of care first line treatment for patients with T2D, recent guidelines have challenged its status, because of a lower quality of evidence supporting its cardio-protective role.¹⁴ The high prevalence of baseline metformin users in CVOTs of GLP-1 RAs or SGLT-2 inhibitors argues against this approach, as the benefits observed were in a population with high background metformin use. Thus, it is clearly of interest to assess cardiorenal outcomes in patients with versus those without baseline metformin use.^{15,16}

In these post hoc analyses of the DECLARE-TIMI 58 trial (clinical trial registration [<https://clinicaltrials.gov>] unique identifier: NCT01730534), we assessed the associations between baseline GLA and cardiorenal outcomes.

2 | MATERIALS AND METHODS

2.1 | Study overview

In the DECLARE-TIMI 58 trial, a total of 17 160 patients, including 6974 with established atherosclerotic cardiovascular disease (ASCVD) and 10 186 with multiple risk factors (MRFs) but without ASCVD, were

randomly assigned to receive dapagliflozin 10 mg daily or placebo and followed for a median of 4.2 years. All patients were treated according to regional standards of care for cardiovascular risk factors: blood pressure, lipids, antithrombotic treatment and HbA1c. The design, baseline characteristics and principal results of this study have been published.^{12,13,17}

2.2 | Assessment of outcomes

The dual composite efficacy endpoints were cardiovascular death (CVD) or HHF and MACE (the composite of CVD, myocardial infarction [MI] or ischaemic stroke). Additional prespecified efficacy outcomes included a renal-specific composite outcome (a sustained decrease of 40% or more in estimated glomerular filtration rate [eGFR] to less than 60 mL/min/1.73m², new end-stage renal disease or death from renal causes), and the individual components of the primary endpoints. New onset confirmed sustained albuminuria was defined as the development of micro- or macro-albuminuria in people with normoalbuminuria at baseline that was observed over two consecutive visits at least 4 weeks apart.

2.3 | Statistical analysis

Baseline characteristics are reported as frequencies and percentages for categorical variables and as mean and standard deviation, or median and interquartile range for continuous variables. Analyses were performed on an intention-to-treat basis. Within each subgroup, we calculated the effect of dapagliflozin on the incidence of the efficacy outcome using Cox regression models.

To test for heterogeneity of efficacy, hazard ratios (HRs) and 95% confidence intervals (CIs) were determined from Cox regression models with stratification factor (ASCVD or MRF status and baseline haematuria) as strata in models comparing treatment in baseline GLA groups with formal statistical testing for interaction. Of note, because of a numerical imbalance in the early development programme of dapagliflozin regarding bladder cancer events, all patients were screened for haematuria at trial entry, and patients in whom bladder cancer could not be ruled out were excluded from the study.

To increase the robustness of our findings, multivariate analyses were conducted for each outcome and baseline GLA adjusting for baseline differences between users and non-users of each GLA. The baseline insulin subgroup was adjusted for baseline body mass index (BMI), eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]), diabetes duration, HbA1c, ASCVD versus MRF, history of heart failure, history of MI and all other baseline GLAs. The baseline metformin subgroup was adjusted for baseline age, sex, baseline BMI, eGFR (CKD-EPI), ASCVD versus MRF, diabetes duration, HbA1c, history of heart failure, history of MI and all other baseline GLAs. The baseline sulphonylureas subgroup was adjusted for baseline BMI, eGFR (CKD-EPI), diabetes duration, ASCVD versus MRF, history of

MI and all other baseline GLAs. The baseline DPP-4 inhibitors subgroup was adjusted for sex, baseline BMI, urinary albumin creatinine ratio (UACR), eGFR (CKD-EPI), diabetes duration, HbA1c, history of heart failure, history of MI and all other baseline GLAs. The baseline GLP-1 RA subgroup was adjusted for baseline BMI, age, sex, diabetes duration, history of heart failure and all other baseline GLAs.

As a sensitivity analysis, we considered all outcomes by the use of each GLA at any time during the trial (defined as 'ever' vs. 'never' users).

Mixed models for repeated measures in HbA1c, weight, systolic blood pressure (SBP), eGFR and UACR were analysed to produce LS mean estimates and 95% CIs in each treatment and baseline GLA group. Three-way interactions were calculated assessing the interaction of baseline GLA status, visit and treatment allocation to dapagliflozin versus placebo.

This study should be considered as hypothesis-generating, and there was no statistical adjustment for multiple comparisons. A *P*-value of less than .05 was considered statistically significant.

All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA) and Stata version 14.2 (College Station, TX, USA).

3 | RESULTS

3.1 | Baseline characteristics

In the DECLARE-TIMI 58 trial, metformin was used by 14 068 (82.0%), sulphonylureas by 7322 (42.7%), DPP-4 inhibitors by 2888

FIGURE 1 A, CVD/HHF with dapagliflozin versus placebo by baseline glucose-lowering agents. B, HHF with dapagliflozin versus placebo by baseline glucose-lowering agents

(16.8%), GLP-1 RAs by 750 (4.4%) and insulin by 7013 (40.9%) of the patients at baseline. Baseline characteristics of patients by medication use are shown in Table S1A-E. As expected, multiple differences were noted when comparing baseline users versus non-users of each drug class. Briefly, patients using metformin or GLP-1 RAs were younger than non-users. HbA1c levels were higher with baseline insulin or sulphonylurea use versus non-use whereas metformin or DPP-4 inhibitors were associated with lower baseline HbA1c levels compared with non-users. BMI was markedly higher in patients with baseline use of GLP-1 RAs ($35.4 \pm 6.8 \text{ kg/m}^2$) versus those without GLP-1 RA use at baseline ($31.9 \pm 5.9 \text{ kg/m}^2$). Baseline eGFR levels were lower in insulin users yet higher in metformin or sulphonylurea users. Use versus non-use of DPP-4 inhibitors was associated with lower levels of UACR and insulin users had higher levels of UACR compared with non-users. Patients with baseline insulin use had a longer disease duration and a higher prevalence of established cardiovascular disease or prior MI compared with non-users, while the opposite trends were observed with baseline use of metformin or sulphonylureas.

3.2 | Cardiovascular outcomes

Dapagliflozin reduced the composite of CVD/HHF (HR [95% CI] 0.83 [0.73, 0.95]) regardless of baseline GLA ($P_{\text{interaction}} > .05$), although the effect appeared to be particularly large in the small group of patients with baseline use of GLP-1 RAs ($P_{\text{interaction}} .03$; Figure 1A). This was driven by a marked reduction in HHF in patients with baseline use of GLP-1 RAs (HR 0.2 [95% CI 0.07, 0.60]; Figure 1B). These effects were not observed in analysis by use of GLP-1 RAs at any time during the study, whereby the HRs for CVD/HHF and for HHF in GLP-1 RA users were in line with those seen in the overall study population, and

no interaction was observed between use or non-use of GLP-1 RAs during the trial and reduction in CVD/HHF and in HHF with dapagliflozin versus placebo ($P_{\text{interaction}} > .05$; Figure S1A,B).

The overall HR for MACE was 0.93 (95% CI 0.84, 1.03) with dapagliflozin versus placebo, and this was consistent regardless of the different GLA used at baseline (Figure 2). A tendency toward greater benefit with dapagliflozin was observed in baseline insulin users ($P_{\text{interaction}} .06$), yet not in those using insulin at any time during the study ($P_{\text{interaction}} .28$; Figure S1C).

The individual components of MACE (CVD, MI, ischaemic stroke) and all-cause mortality with dapagliflozin versus placebo are shown in Figures S2A-H for baseline GLA use and by use of GLAs at any time during the trial. Generally, these outcomes were balanced in the overall study population and consistently by GLA subgroups.

Adjustment of all outcomes for baseline characteristics maintained these results (Table S2A-G). Moreover, the baseline number of GLAs used revealed consistent outcomes as in the overall population (i.e. reduction of CVD/HHF and HHF with dapagliflozin vs. placebo and balanced for MACE and its components; Table S3).

3.3 | Renal outcomes

The prespecified composite renal-specific outcome was reduced with dapagliflozin versus placebo in the overall study population (HR [95% CI] 0.53 [0.43, 0.66]) with no interaction by baseline GLA ($P_{\text{interaction}} > .05$; Figure 3). New onset albuminuria (confirmed sustained) in patients without albuminuria at baseline was reduced with dapagliflozin versus placebo (HR [95% CI] 0.79 [0.72, 0.87]) regardless of baseline GLA ($P_{\text{interaction}} > .05$; Figure 4). Adjustment of these two outcomes for baseline characteristics maintained

FIGURE 2 Major adverse cardiovascular events with dapagliflozin versus placebo by baseline glucose-lowering agents

FIGURE 3 Renal-specific outcome with dapagliflozin versus placebo by baseline glucose-lowering agents. The renal-specific outcome was a composite of sustained decrease of 40% or more in eGFR to less than 60 mL/min/1.73m², new end-stage renal disease or death from renal causes

FIGURE 4 New onset albuminuria with dapagliflozin versus placebo by baseline glucose-lowering agents. New onset, sustained, albuminuria (micro or macro) in patients with normoalbuminuria at baseline

these results (Table S2H-I). These observations were consistent regardless of the number of baseline GLAs used ($P_{\text{interaction}} > .05$; Table S3).

The overall pattern of eGFR changes with dapagliflozin versus placebo throughout the trial was consistent across all baseline GLAs. There was no interaction between treatment, visit and use or non-use of each GLA at baseline ($P_{\text{interaction}} > .05$ for all GLAs). An initial decline in eGFR was observed with dapagliflozin versus placebo with subsequent stabilization of levels, and final eGFR levels at month 48 were generally higher with dapagliflozin versus placebo (Table 1, Figure S3A).

UACR levels were also generally lower after 48 months with dapagliflozin versus placebo across the different GLA categories (Table 1).

3.4 | Cardiometabolic efficacy

There was greater decline in HbA1c, weight and SBP with dapagliflozin versus placebo across all subgroups of GLA with all variables significantly lower with dapagliflozin at month 48 (Table 1, Figure S3B-D).

TABLE 1 Metabolic variables at 48 months with dapagliflozin and placebo by baseline glucose-lowering agent

Baseline glucose-lowering agent		HbA1c (%)		Weight (kg)		SBP (mmHg)		eGFR		UACR	
		DAPA	PBO	DAPA	PBO	DAPA	PBO	DAPA	PBO	DAPA	PBO
Metformin	YES	7.83 ± 0.02 [*]	8.08 ± 0.02	86.73 ± 0.08 [*]	88.77 ± 0.08	132.51 ± 0.21 [*]	135.03 ± 0.21	77.61 ± 0.18 [*]	75.80 ± 0.18	128.74 ± 6.33 [*]	185.42 ± 6.42
	NO	7.95 ± 0.04 ⁺	8.14 ± 0.04	88.17 ± 0.20 [*]	89.58 ± 0.21	132.26 ± 0.47 ⁺	133.97 ± 0.49	73.45 ± 0.40	72.67 ± 0.41	170.99 ± 16.38	195.12 ± 16.77
SUR	YES	7.90 ± 0.03 [*]	8.17 ± 0.03	84.36 ± 0.11 [*]	86.46 ± 0.11	131.67 ± 0.29 [*]	134.71 ± 0.29	78.01 ± 0.25 [*]	76.38 ± 0.25	111.37 ± 8.45 [*]	161.41 ± 8.49
	NO	7.82 ± 0.02 [*]	8.03 ± 0.02	88.96 ± 0.11 [*]	90.77 ± 0.11	133.06 ± 0.26 [*]	134.94 ± 0.26	76.03 ± 0.22 [*]	74.39 ± 0.23	153.23 ± 7.22 [*]	200.25 ± 7.39
DPP-4 i	YES	7.84 ± 0.04 ⁺	8.02 ± 0.04	85.65 ± 0.15 [*]	88.14 ± 0.15	130.36 ± 0.45 [*]	133.57 ± 0.46	77.87 ± 0.38 [*]	75.75 ± 0.38	101.89 ± 10.01	126.81 ± 10.08
	NO	7.86 ± 0.02 [*]	8.11 ± 0.02	87.22 ± 0.07 [*]	89.07 ± 0.07	132.91 ± 0.21 [*]	135.11 ± 0.22	76.69 ± 0.18 [*]	75.15 ± 0.19	140.49 ± 6.73 [*]	195.71 ± 6.87
GLP-1 RA	YES	7.93 ± 0.08 [¶]	8.19 ± 0.09	99.44 ± 0.46 [¶]	100.97 ± 0.50	131.11 ± 0.87 [¶]	133.72 ± 0.94	78.04 ± 0.76	76.14 ± 0.82	106.00 ± 23.16 [¶]	178.02 ± 25.08
	NO	7.85 ± 0.02 [*]	8.09 ± 0.02	86.39 ± 0.07 [*]	88.36 ± 0.07	132.54 ± 0.19 [*]	134.90 ± 0.20	76.83 ± 0.17 [*]	75.22 ± 0.17	138.63 ± 13.84 [¶]	181.79 ± 13.92
Insulin	YES	8.07 ± 0.03 [*]	8.35 ± 0.03	90.89 ± 0.13 [*]	92.85 ± 0.14	133.10 ± 0.31 [*]	135.50 ± 0.32	74.44 ± 0.26 [*]	72.81 ± 0.27	162.97 ± 31.28	232.56 ± 32.04
	NO	7.70 ± 0.02 [*]	7.92 ± 0.02	84.33 ± 0.08 [*]	86.25 ± 0.08	132.04 ± 0.24 [*]	134.41 ± 0.24	78.54 ± 0.21 [*]	76.88 ± 0.21	111.37 ± 6.93 ⁺	145.17 ± 6.97

Abbreviations: eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SUR, sulphonylureas; UACR, urinary albumin creatinine ratio.

Note: Values are LS mean ± SE. ^{*} *P* < .0001, ⁺ *P* < .01, [¶] *P* < .05 for dapagliflozin vs placebo.

4 | DISCUSSION

The current analyses of the DECLARE-TIMI 58 trial show overall consistent cardiovascular, renal and metabolic benefits with dapagliflozin versus placebo regardless of the type of GLA or the number of baseline GLAs used. Cardiorenal outcomes did not differ irrespective of baseline use of metformin. CVD/HHF was more prominently reduced with dapagliflozin versus placebo in the small subset of patients who used GLP-1 RAs at baseline compared with those who did not, yet the magnitude of CVD/HHF reduction with dapagliflozin was similar when comparing those using versus those not using GLP-1 RAs at any time during the study. Adverse renal outcomes were less frequent with dapagliflozin versus placebo regardless of baseline GLA; moreover, new onset albuminuria was less frequent with dapagliflozin consistently across all of the subgroups assessed.

In our study, 3092 patients were not using metformin at baseline. This population was older, with longstanding diabetes and a higher prevalence of cardiovascular disease, congestive heart failure and chronic kidney disease compared with metformin users. Nevertheless, the impact of dapagliflozin on the cardiovascular, renal and metabolic outcomes of this cohort did not significantly differ from its effect in patients who had been using metformin at baseline. This observation persisted after adjusting for baseline characteristics. These data support the notion that the beneficial effect of dapagliflozin is consistent irrespective of baseline metformin use. Notably, analysis of data from the EMPA-REG OUTCOME trial also did not reveal heterogeneity of cardiovascular outcomes by baseline use versus non-use of metformin.¹⁸ Thus, the role of metformin as first line treatment is further challenged, whereas early treatment with an SGLT-2 inhibitor may be a better therapeutic choice for many patients.

Current treatment algorithms promote the early use of SGLT-2 inhibitors or GLP-1 RAs for patients with T2D either with or at high risk of ASCVD.^{2,14} The cardiometabolic benefits of combining GLP-1 RAs and SGLT-2 inhibitors have been assessed in several trials showing further improvement in cardiometabolic variables when intensifying therapy with one class in addition to the other.^{19–24} Post hoc analysis of the CANVAS programme revealed a greater reduction of HbA1c, SBP and body weight with canagliflozin versus placebo in patients with baseline use of GLP-1 RAs compared with those without.²⁴

Combined use of GLP-1 RAs and SGLT-2 inhibitors is advocated in patients at high CV risk, if HbA1c remains above target, but the cardiorenal outcomes of this combination require further study.^{9,10} Post hoc analysis of the CANVAS programme noted a similar effect of canagliflozin on the primary cardiovascular outcome and the composite adverse renal outcome in those with versus those without baseline use of GLP-1 RAs.²⁴ Observational real-world data analysis with propensity score matching of patients using GLP-1 RAs who added SGLT-2 inhibitors versus sulphonylureas showed reduced cardiovascular events and HHF in those adding SGLT-2 inhibitors.⁸ Our study randomized a significant number of patients with baseline use of incretin based therapies to the addition of an SGLT2 inhibitors versus

placebo, and thus enables analyses of the cardiorenal outcomes of this treatment combination.

All DPP-4 inhibitors have been neutral with respect to MACE, while a reduction in MACE has been shown with most GLP-1 RAs (liraglutide, semaglutide, albiglutide and dulaglutide); within the SGLT-2 inhibitors class this has been shown for canagliflozin and empagliflozin but did not reach statistical significance with dapagliflozin or ertugliflozin.^{5,25} In our study, treatment with dapagliflozin versus placebo did not significantly reduce MACE irrespective of baseline use of DPP-4 inhibitors or GLP-1 RAs.

Most DPP-4 inhibitors are neutral with respect to HHF, although a significant increased risk has been observed with saxagliptin.³ GLP-1 RAs have been shown to have a modest benefit on reducing HHF, with an HR of 0.91 (0.84–1.00) in a recently published meta analysis, albeit reduced HHF was not observed in the individual studies.⁵ On the contrary, SGLT-2 inhibitors have an established benefit in reducing HHF, and current guidelines and consensus society recommendations, as well as drug product labelling, promote the use of dapagliflozin for the prevention of HHF in patients with T2D either with risk factors for or established ASCVD.^{2,6,14,26} Results from the current analyses suggest greater benefit with the combined use of a GLP-1 RA and dapagliflozin regarding CVD/HHF, implying a possible synergistic effect. However, the number of evaluable events is small (only 34 events of CVD/HHF among baseline GLP-1 RA users), CIs are wide, and this observation did not persist when analysing by use of GLP-1 RAs at any time during the trial, implying that this may be a chance observation.

Our analyses further clarify the long-term renal outcomes of combining SGLT-2 inhibitors—a class with established robust renal benefits—with incretin-based therapies, which have also shown some favourable renal outcomes. DPP-4 inhibitors have been shown to reduce albuminuria in most (but not all) studies, with no effect on eGFR.^{27–30} GLP-1 RAs have shown a larger and more consistent effect on albuminuria compared with DPP-4 inhibitors, and a slowing of eGFR decline has been shown with dulaglutide and liraglutide in patients with an eGFR of less than 60 mL/min/1.73m².^{31,32} Dulaglutide has also shown reduced rates of eGFR decline by 40% or more, or by 50% or more, compared with placebo.³³ The renal benefits observed with incretin-based therapies, particularly GLP-1 RAs, have been attributed to anti-inflammatory effects, alteration of renal haemodynamics because of inhibition of sodium reabsorption, as well as effects secondary to weight loss, improved glycaemic control and reduced blood pressure.¹⁰ SGLT-2 inhibitors convey renal protection by multiple mechanisms, including alteration of renal haemodynamics and restoration of tubulo-glomerular feedback, reduction in tubular workload and metabolic stress, and reduced blood pressure, weight, glucose and vascular stiffness.^{34–36} Many of the reno-protective effects of incretin-based therapies and SGLT-2 inhibitors are probably complementary and therefore an added benefit of dapagliflozin on top of these agents may be expected.¹⁰

In our cohort, patients using DPP-4 inhibitors at baseline had lower levels of albuminuria compared with non-users. Whether this is reflective of other baseline characteristics or of the drug itself cannot

be determined from these analyses. Nevertheless, the renal benefits of dapagliflozin occurred irrespective of baseline DPP-4 inhibitor use, indicating an added renal benefit of prescribing dapagliflozin on top of DPP-4 inhibitors, although probably not a synergistic effect. Adding dapagliflozin to patients using a GLP-1 RA maintained the renal benefits observed in the overall DECLARE-TIMI 58 study population, with lower rates of the renal-specific endpoint and of new onset albuminuria, and lower UACR at month 48. Although differences in the renal outcomes did not reach statistical significance in the small group of GLP-1 RA users, the trends were similar with no heterogeneity by GLP-1 RA use. Thus, the benefit of dapagliflozin was not altered by baseline GLP-1 RA use, promoting their combined use in renal protection.

Patients using insulin at baseline experienced lower rates of MACE with dapagliflozin versus placebo (HR [95% CI] 0.84 [0.74, 0.97]), yet this was not observed in patients not using insulin at baseline (interaction *P*-value .06). Notably, insulin users were more probable to have prior MI and longer disease duration, both of which we have previously shown to be associated with reduced rates of MACE with dapagliflozin versus placebo.^{37,38} Thus, it may be possible that patient characteristics, and not insulin use in itself, underlie this observation. Moreover, analysis by use of insulin at any time during the trial did not show a differential effect on MACE of dapagliflozin versus placebo by insulin use.

Dapagliflozin led to a greater decline in HbA1c, weight and SBP compared with placebo. These changes were largely unaffected by baseline GLA in line with previously published data, further supporting the favourable metabolic impact of adding dapagliflozin to any prevailing glucose-lowering regimen.³⁹ The addition of dapagliflozin to patients with versus those without baseline use of an incretin-based GLA led to comparable HbA1c reductions (Table 1, Figure S3B), in line with data from most studies showing the glycaemic efficacy of this combination.^{19–23}

Some limitations of our analyses should be noted. First, while analyses by baseline GLA were generally prespecified, the specific analytical plan as well as analysis of the metabolic outcomes were largely post hoc. Second, baseline use or non-use of a particular GLA may have been determined by local guidelines, cost, availability of treatment or patient preference, and not by true biological variation, and the results should thus be interpreted in this context. Moreover, the impact of this confounder is even more substantial in the sensitivity analyses by medication use at any time during the study. This post-randomization analysis may be affected by treatment allocation as well and thus is more subject to potential bias than the primary one by baseline medications. Third, we did not account for the particular agents used within each class or for drug dosages. Finally, no correction for multiplicity was performed, thus although some of the interaction *P*-values were indeed less than .05, these must be considered as hypothesis-generating alone.

In conclusion, in this study, the cardiovascular and renal benefits of dapagliflozin were observed regardless of baseline GLA. Benefit is maintained when combining classes of cardiovascular and renal-protecting agents, and there is no evidence to support a role of metformin in mediating the observed benefits of dapagliflozin.

ACKNOWLEDGMENTS

The sponsor of the DECLARE-TIMI 58 study was initially AstraZeneca and Bristol-Myers Squibb and AstraZeneca later became the sole sponsor of the study. The DECLARE-TIMI 58 trial was a collaboration between the funder and two academic research organizations (the 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 performed by the academic TIMI Study Group, which has access to the complete study database, allowing independent analyses of the results; any discrepancies were resolved by discussion. The DECLARE-TIMI 58 publication committee made the decision to submit for publication.

CONFLICT OF INTEREST

A.C. reports grants and personal fees from AstraZeneca and Novo Nordisk and personal fees from Abbott, Eli Lilly, Sanofi, Boehringer Ingelheim, Merck Sharp & Dohme, Medial Early-Sign and GlucoMe. S.D.W. discloses grants from AstraZeneca, Bristol-Myers Squibb, Sanofi Aventis and Amgen; grants and personal fees from Arena, Daiichi Sankyo, Eisai, Eli Lilly and Janssen; grants and consulting fees from Merck (additionally his spouse is employed by Merck); and personal fees from Aegerion, Allergan, AngelMed, Boehringer Ingelheim, Boston Clinical Research Institute, Icon Clinical, Lexicon, St Jude Medical, Xoma, Servier, AstraZeneca and Bristol-Myers Squibb. O.M. reports grants and personal fees from AstraZeneca, Bristol-Myers Squibb and Novo Nordisk, and personal fees from Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, Johnson & Johnson and Novartis. S.A.M. and E.L.G. report research grant support through Brigham and Women's Hospital from Abbott, Amgen, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company and Zora Biosciences. I.Y. and A.R. declare no competing interests. J.P.H.W., outside the submitted work, has grants, personal fees for lectures and consultancy fees (paid to his institution) from AstraZeneca and Novo Nordisk; personal fees for lectures and consultancy fees (paid to his institution) from Boehringer Ingelheim, Janssen, Lilly, Mundipharma, Napp, Sanofi and Takeda; and consultancy fees (paid to his institution) from Rhythm Pharmaceuticals and Wilmington Healthcare. L.A.L. reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk and Sanofi; personal fees from Merck and Servier; and grants from GlaxoSmithKline and Lexicon. D.L.B. discloses the following relationships – advisory board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, PhaseBio, PLx Pharma and Regado Biosciences; board of directors: Boston VA Research Institute, Society of Cardiovascular Patient Care and TobeSoft; chair: American Heart Association Quality Oversight Committee; data monitoring committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute;

honorary: American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), Level Ex, MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer) and WebMD (CME steering committees); other: *Clinical Cardiology* (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); research funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, and Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic and The Medicines Company; royalties: Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); site co-investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; trustee: American College of Cardiology; and unfunded research: FlowCo, Merck, Novo Nordisk and Takeda. D.K.M. discloses the following relationships: personal fees for clinical trial leadership from GlaxoSmithKline, Janssen, Lexicon AstraZeneca, Sanofi Aventis, Boehringer Ingelheim, Merck & Co, Pfizer, Novo Nordisk, Eisai Inc., Esperion and Lilly USA; and personal fees for consultancy from AstraZeneca, Lilly USA, Boehringer Ingelheim, Merck & Co, Novo Nordisk, Metavant, Applied Therapeutics, Sanofi Aventis and Afimmune. L.L. is a member of the following advisory boards: Eli Lilly, AstraZeneca, Boehringer Ingelheim, Novo Nordisk and Sanofi. A.K. reports grants and fees from AstraZeneca, Merck Sharp & Dohme, Novo Nordisk and Sanofi; and fees from Boehringer Ingelheim, Eli Lilly and Mundipharma. I.A.M.G.-N., M.F. and A.M.L. are employees of AstraZeneca. M.S.S. reports grants and consulting fees from Amgen, consulting fees from Anthos Therapeutics, grants and consulting fees from AstraZeneca, grants from Bayer, consulting fees from Bristol-Myers Squibb, consulting fees from CVS Caremark, grants from Daiichi-Sankyo, consulting fees from DaiCor, consulting fees from Dynamix, grants from Eisai, consulting fees from Esperion, grants from GlaxoSmithKline, consulting fees from IFM Therapeutics, grants and consulting fees from Intarcia, consulting fees from Ionis, grants and consulting fees from Janssen Research and Development, grants and consulting fees from Medicines Company, grants and consulting fees from MedImmune, grants and consulting fees from Merck, grants and consulting fees from Novartis, grants from Pfizer, grants from Poxel, grants from Quark Pharmaceuticals, grants from Takeda, and is a member of the TIMI Study Group, which has also received institutional research grant support through

Brigham and Women's Hospital from: Abbott, Aralez, Roche and Zora Biosciences. I.R. reports personal fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Concenter BioPharma and Silkim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Orgenesis, Pfizer, Sanofi, SmartZyme Innovation, Panaxia, FuturRx, Insuline Medical, Medial EarlySign, CameraEyes, Exscopia, Dermal Biomics, Johnson & Johnson, Novartis, Teva, GlucoMe and DarioHealth.

AUTHOR CONTRIBUTIONS

AC, SDW, SAM, IAMG-N, MF, AML, MSS, and IR contributed to the study design. AC, SDW, SAM, ELG, IAMG-N, MF, AML, MSS, and IR contributed to data collection. AC, SDW, OM, ELG, SAM, AR, IY, DLB, LAL, DKM, JPHW, LL, AK, IAMG-N, MF, AML, MSS, and IR contributed to data analysis. AC, SDW, OM, SAM, ELG, AR, IY, DLB, LAL, DKM, JPHW, LL, AK, IAMG-N, MF, AML, MSS, and IR contributed to the writing of the report and approved the final submitted version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Avivit Cahn <https://orcid.org/0000-0002-7830-9994>

Ofri Mosenzon <https://orcid.org/0000-0002-5702-7584>

John P. H. Wilding <https://orcid.org/0000-0003-2839-8404>

Lawrence A. Leiter <https://orcid.org/0000-0002-1040-6229>

Deepak L. Bhatt <https://orcid.org/0000-0002-1278-6245>

Adriaan Kooy <https://orcid.org/0000-0002-8853-0019>

Marc S. Sabatine <https://orcid.org/0000-0002-0691-3359>

Itamar Raz <https://orcid.org/0000-0003-0209-4453>

REFERENCES

- IDF Diabetes Atlas. 9th ed. https://diabetesatlas.org/upload/resources/2019/IDF_Atlas_9th_Edition_2019.pdf. Accessed February 10, 2020.
- American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43(suppl 1):S98-S110.
- Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317-1326.
- Alfayez OM, Almutairi AR, Aldosari A, Al Yami MS. Update on cardiovascular safety of incretin-based therapy in adults with type 2 diabetes mellitus: a meta-analysis of cardiovascular outcome trials. *Can J Diabetes*. 2019;43(7):538-545.
- Ghosh-Swaby OR, Goodman SG, Leiter LA, et al. Glucose-lowering drugs or strategies, atherosclerotic cardiovascular events, and heart failure in people with or at risk of type 2 diabetes: an updated systematic review and meta-analysis of randomised cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2020;8(5):418-435.
- Bhatt DL, Verma S, Braunwald E. The DAPA-HF trial: a momentous victory in the war against heart failure. *Cell Metab*. 2019;30(5):847-849.
- Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation*. 2019;139(17):2022-2031.
- Dave CV, Kim SC, Goldfine A, Glynn R, Paterno E. 35-OR: risk of cardiovascular outcomes in diabetes patients following the addition of SGLT2i inhibitors vs. sulfonylureas to baseline GLP-1RA therapy. *Diabetes*. 2020;69(suppl 1). <https://doi.org/10.2337/db20-35-OR>.
- Packer M. Should we be combining GLP-1 receptor agonists and SGLT2 inhibitors in treating diabetes? *Am J Med*. 2018;131(5):461-463.
- DeFronzo RA. Combination therapy with GLP-1 receptor agonist and SGLT2 inhibitor. *Diabetes Obes Metab*. 2017;19(10):1353-1362.
- Clegg LE, Penland RC, Bachina S, et al. Effects of exenatide and open-label SGLT2 inhibitor treatment, given in parallel or sequentially, on mortality and cardiovascular and renal outcomes in type 2 diabetes: insights from the EXSCEL trial. *Cardiovasc Diabetol*. 2019;18(1):138.
- Wiviott SD, Raz I, Bonaca MP, et al. The design and rationale for the dapagliflozin effect on cardiovascular events (DECLARE)-TIMI 58 trial. *Am Heart J*. 2018;200:83-89.
- Raz I, Mosenzon O, Bonaca MP, et al. DECLARE-TIMI 58: participants' baseline characteristics. *Diabetes Obes Metab*. 2018;20(5):1102-1110.
- Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41(2):255-323.
- Inzucchi SE, Fonseca V. Dethroning the king?: the future of metformin as first line therapy in type 2 diabetes. *J Diabetes Complications*. 2019;33(6):462-464.
- Scherthner G, Scherthner GH. The right place for metformin today. *Diabetes Res Clin Pract*. 2020;159:107946.
- Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.
- Inzucchi SE, Fitchett D, Jurišić-Eržen D, et al. Are the cardiovascular and kidney benefits of empagliflozin influenced by baseline glucose-lowering therapy? *Diabetes Obes Metab*. 2020;22(4):631-639.
- Zinman B, Bhosekar V, Busch R, et al. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2019;7(5):356-367.
- Ludvik B, Frías JP, Tinahones FJ, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2018;6(5):370-381.
- Frías JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2016;4(12):1004-1016.
- Blonde L, Belousova L, Fainberg U, et al. Liraglutide as add-on to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes: LIRA-ADD2SGLT2i, a 26-week, randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2020;22:929-937.
- Ali AM, Martinez R, Al-Jobori H, et al. Combination therapy with canagliflozin plus liraglutide exerts additive effect on weight loss, but not on HbA(1c), in patients with type 2 diabetes. *Diabetes Care*. 2020;43:1234-1241.
- Arnott C, Neuen BL, Heerspink HJL, Figtree GA, Kosiborod M, Lam CS, Cannon CP, Rosenthal N, Shaw W, Mahaffey KW, Jardine MJ, Perkovic V, Neal B. The effects of combination canagliflozin and glucagon-like peptide-1 receptor agonist therapy on intermediate markers of cardiovascular risk in the CANVAS program. *International Journal of Cardiology*. 2020. <http://dx.doi.org/10.1016/j.ijcard.2020.06.011>.
- Christopher PC. The VERTIS CV Trial. <https://www.acc.org/~media/Clinical/PDF-Files/Approved-PDFs/2020/05/15/12/18/ADA20-Presentation-Slides-VERTIS-CV.pdf>. Accessed August 9, 2020.

26. Farxiga, prescribing information, last update 2.3.2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s022lbl.pdf. Accessed February 10, 2020.
27. Mosenson O, Leibowitz G, Bhatt DL, et al. Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 trial. *Diabetes Care*. 2017;40(1):69-76.
28. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA*. 2019;321(1):69-79.
29. Groop PH, Cooper ME, Perkovic V, et al. Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial. *Diabetes Obes Metab*. 2017;19(11):1610-1619.
30. Coppolino G, Leporini C, Rivoli L, et al. Exploring the effects of DPP-4 inhibitors on the kidney from the bench to clinical trials. *Pharmacol Res*. 2018;129:274-294.
31. Muskiet MHA, Tonneijck L, Smits MM, et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. *Nat Rev Nephrol*. 2017;13(10):605-628.
32. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol*. 2018;6(8):605-617.
33. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet*. 2019;394(10193):131-138.
34. DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. *Nat Rev Nephrol*. 2017;13(1):11-26.
35. Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZL. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. *Kidney Int*. 2018;94(1):26-39.
36. 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.
37. Furtado RHM, Bonaca MP, Raz I, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes and prior myocardial infarction: a sub-analysis from DECLARE TIMI-58 trial. *Circulation*. 2019;139(22):2516-2527.
38. Bajaj HS, Wiviott SD, Mosenson O, et al. Cardiovascular and renal benefits of dapagliflozin as a function of diabetes duration: analyses from DECLARE-TIMI-58. *Diabetes Obes Metab*. 2020;22(7):1122-1131.
39. Jabbour S. Durability of response to dapagliflozin: a review of long-term efficacy and safety. *Curr Med Res Opin*. 2017;33(9):1685-1696.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Cahn A, Wiviott SD, Mosenson O, et al. Cardiorenal outcomes with dapagliflozin by baseline glucose-lowering agents: Post hoc analyses from DECLARE-TIMI 58. *Diabetes Obes Metab*. 2021;23:29-38. <https://doi.org/10.1111/dom.14179>