Circulation

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Dapagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Previous Myocardial Infarction

Subanalysis From the DECLARE-TIMI 58 Trial

Editorial, see p 2537

BACKGROUND: Sodium glucose transporter-2 inhibitors reduce the risk of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus and a history of atherosclerotic cardiovascular disease. Because of their baseline risk, patients with previous myocardial infarction (MI) may derive even greater benefit from sodium glucose transporter-2 inhibitor therapy.

METHODS: DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) randomized 17 160 patients with type 2 diabetes mellitus and either established atherosclerotic cardiovascular disease (n=6974) or multiple risk factors (n=10 186) to dapagliflozin versus placebo. The 2 primary end points were composite of MACE (cardiovascular death, MI, or ischemic stroke) and the composite of cardiovascular death or hospitalization for heart failure. Those with previous MI (n=3584) made up a prespecified subgroup of interest.

RESULTS: In patients with previous MI (n=3584), dapagliflozin reduced the relative risk of MACE by 16% and the absolute risk by 2.6% (15.2% versus 17.8%; hazard ratio [HR], 0.84; 95% CI, 0.72–0.99; *P*=0.039), whereas there was no effect in patients without previous MI (7.1% versus 7.1%; HR, 1.00; 95% CI, 0.88–1.13; *P*=0.97; *P* for interaction for relative difference=0.11; *P* for interaction for absolute risk difference=0.048), including in patients with established atherosclerotic cardiovascular disease but no history of MI (12.6% versus 12.8%; HR, 0.98; 95% CI, 0.81–1.19). There seemed to be a greater benefit for MACE within 2 years after the last acute event (*P* for interaction trend=0.007). The relative risk reductions in cardiovascular death/hospitalization for heart failure were more similar, but the absolute risk reductions tended to be greater: 1.9% (8.6% versus 10.5%; HR, 0.81; 95% CI, 0.65–1.00; *P*=0.046) and 0.6% (3.9% versus 4.5%; HR, 0.85; 95% CI, 0.72–1.00; *P*=0.055) in patients with and without previous MI, respectively (*P* interaction for relative difference=0.69; *P* interaction for absolute risk difference=0.010).

CONCLUSIONS: Patients with type 2 diabetes mellitus and previous MI are at high risk of MACE and cardiovascular death/hospitalization for heart failure. Dapagliflozin appears to robustly reduce the risk of both composite outcomes in these patients. Future studies should aim to confirm the large clinical benefits with sodium glucose transporter-2 inhibitors we observed in patients with previous MI.

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Remo H.M. Furtado, MD, PhD
Marc P. Bonaca, MD, MPH
Itamar Raz, MD
Thomas A. Zelniker, MD, MSc
Ofri Mosenzon, MD, MSc
Avivit Cahn, MD
Julia Kuder, MA
Sabina A. Murphy, MPH
Deepak L. Bhatt, MD, MPH
Lawrence A. Leiter, MD
Darren K. McGuire, MD, MHSc
John P.H. Wilding, MD
Christian T. Ruff, MD, MPH
Jose C. Nicolau, MD, PhD
Ingrid A.M. Gause-Nilsson, MD, PhD
Martin Fredriksson, MD, PhD
Anna Maria Langkilde, MD, PhD
Marc S. Sabatine, MD, MPH*
Stephen D. Wiviott, MD*

*Drs Sabatine and Wiviott contributed equally.

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Clinical Perspective

What Is New?

- Our results demonstrated that, in the DECLARE-TIMI 58 trial (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58), dapagliflozin appeared to reduce both major adverse cardiovascular events and cardiovascular death or heart failure hospitalization in patients with type 2 diabetes mellitus and previous myocardial infarction (MI) with greater absolute benefit compared with patients without a history of MI.
- There was a robust decrease in type 2 MIs, that is, those caused by mismatch between myocardial oxygen supply and demand rather than plaque rupture and atherothrombosis.

What Are the Clinical Implications?

- These results bring new important data for the selection of therapies for treating type 2 diabetes mellitus aimed not only at glycemic control but also at cardiovascular events reduction.
- Whether this benefit could be expanded to the acute phase of MI or to patients with previous MI even if they do not have type 2 diabetes mellitus should be addressed in future studies.
- The potential mechanisms that explain the CV benefits with sodium glucose transporter-2 inhibitors are not completely understood and should be a matter of intense research in the future, including possible myocardium-protective effects.

Type 2 diabetes mellitus (T2DM) is a global epidemic, with the number of affected individuals projected to be ≈640 million in 2040.[1] Moreover, T2DM is strongly and independently associated with incident cardiovascular ischemic events and hospitalization for heart failure (HHF).[2–4] Among patients with previous myocardial infarction (MI), those with T2DM make up a higher-risk subgroup.[5] Even with contemporary standard-of-care treatment, residual risk is so heightened in this population that patients with T2DM derived a robust benefit in terms of major adverse cardiovascular event (MACE) reduction with more advanced secondary prevention therapies in the post-MI setting such as prolonged dual antiplatelet therapy[6] and more aggressive lipid-lowering therapy.[7,8] In addition, patients with previous MI present with a higher risk of incident heart failure (HF) and subsequent lower survival in the long term.[9] Therefore, preventing both MACE and HHF in patients with T2DM and history of MI remains an unmet clinical need.

Sodium-glucose transporter 2 inhibitors (SGLT2is) are a class of antihyperglycemic drugs with proven efficacy for reducing cardiovascular events in patients with T2DM.[10–12] Moreover, in a pooled analysis from SGLT2i cardiovascular outcomes trials, there was a reduction in MACE (the composite of cardiovascular death, MI, or stroke) only in patients with previous established atherosclerotic cardiovascular disease (ASCVD), whereas there was a decrease in the composite of cardiovascular death or HHF regardless of the presence of clinical HF or established ASCVD.[13] Although the mechanism of action for such benefit is not completely understood,[14–16] SGLT2is are now being recommended not only for glycemic control but also for cardiovascular protection in patients with T2DM and established ASCVD.[17–19]

The DECLARE-TIMI 58 trial (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) demonstrated that the SGLT2i dapagliflozin decreased the composite of cardiovascular death or HHF in patients with T2DM, both in those with established ASCVD and in those with only multiple risk factors (MRF), whereas a potential signal of benefit for MACE was apparent only in patients with ASCVD.[12] Considering the increased residual risk in patients with T2DM and previous MI, we anticipated that this subgroup could derive potentially greater benefit from dapagliflozin. Therefore, we conducted this prespecified subgroup analysis from the DECLARE-TIMI 58 trial in patients with T2DM and a history of MI at baseline.

METHODS

Population and End Point Selection

The DECLARE-TIMI 58 trial design, baseline characteristics, and main results were previously published.[12,20,21] Briefly, patients with history of T2DM were randomly assigned to dapagliflozin 10 mg once daily or matching placebo, stratified according to the presence of ASCVD or only MRF, on top of standard-of-care medical therapy for T2DM and concomitant diseases. Patients with established ASCVD had as enrollment criteria age ≥40 years plus previous ischemic heart disease (defined as previous MI, coronary revascularization, or evidence of significant stenosis in at least 2 coronary artery territories), cerebrovascular disease (defined as previous ischemic stroke, carotid stenting, or endarterectomy), or peripheral arterial disease (defined as previous peripheral revascularization, lower extremity amputation, or intermittent claudication with ankle-brachial index <0.9). In the cohort with MRF, enrollment criteria were age ≥55 years for men or ≥60 years for women plus at least one of the following: dyslipidemia, hypertension, or current tobacco use. Patients with creatinine clearance (estimated by the Cockcroft-Gault equation) <60 mL/min at enrollment were excluded. In addition, eligible patients were at least 8 weeks from their most recent ischemic event (either MI or stroke) at the time of enrollment. We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

History of previous MI was a prespecified subgroup of interest and collected at enrollment in patients with previous ASCVD, including information on the date of the last MI and concomitant medications. The 2 trial primary efficacy end

points were MACE (the composite of cardiovascular death, MI, or ischemic stroke) and the composite of cardiovascular death and HHF. In the main trial, α was split between the 2 primary efficacy end points, with both end points tested at a final significance level of 0.023, taking into account also adjustment for the interim analyses. If either end point was met, then α could be recycled to test the other end point at a significance level of 0.046.[12,20] Secondary outcomes were the individual components of the coprimary end points, as well as all-cause mortality and the renal composite of sustained estimated glomerular filtration rate (calculated by the Chronic Kidney Disease Epidemiology Collaboration equation)[22] decrease by at least 40%, end-stage renal disease (renal replacement therapy for ≥90 days, kidney transplantation, or sustained glomerular filtration rate of ≤15 mL·min^{-1}·1.73 m^{-2}), or cardiovascular or renal death. As exploratory end points, we also analyzed deaths caused by coronary heart disease (which includes all deaths due to MI, sudden cardiac deaths, and deaths related to coronary procedures) and the composite of coronary heart disease death or nonfatal MI. All component events were adjudicated with the use of previously published definitions[20] by an independent clinical events committee blinded to the assigned treatment. The same committee also classified positively adjudicated MI end points according to the third universal MI definition.[23]

Statistical Analysis

Categorical variables were compared with the χ^2 test and are described as absolute numbers and percentages. Continuous variables are described as medians and interquartile ranges and were compared with the 2-sample Wilcoxon test.

A Cox proportional hazards model was used to derive hazard ratios (HRs) and 95% CIs. A model was developed to compare the risk of aforementioned outcomes in patients with and without previous MI within the placebo arm, with adjustment for the following independent variables: age ≥65 years versus <65 years, sex, race, weight ≥89 kg versus <89 kg (median), T2DM duration >10 years versus ≤10 years, region, baseline insulin, history of HF, history of dyslipidemia, history of hypertension, smoking, history of ischemic stroke, and history of peripheral artery disease. These were the clinical characteristics that were associated with the outcomes of interest on the basis of previous scientific knowledge or were significantly imbalanced between the 2 groups of interest (ie, previous MI versus no previous MI).

A Cox proportional hazards model was used to compare randomized treatment within the subgroups of subjects with and without a previous MI. Heterogeneity across previous MI versus no previous MI subgroups was analyzed with a test for treatment-by-subgroup interaction. Qualitative interaction tests for the absolute risk reduction (ARR) according to previous MI versus no previous MI subgroups were analyzed with a 1-sided Gail-Simon test. This test evaluates the likelihood that the treatment has the same directional effects when stratified by subgroups. A value of $P<0.05$ means that there is little evidence that the subgroups have the same directional ARR.[24]

All efficacy analyses included the intention-to-treat population. Safety assessments were performed in a safety analysis population, which consisted of patients who received at least 1 dose of dapagliflozin or placebo. The proportions of patients with events of interest are presented. For survival analysis of the 2 efficacy primary end points, the Kaplan–Meier method was used to create the corresponding graphs. The primary analysis of interest was to evaluate the effect of dapagliflozin versus placebo stratified according to history of MI versus no

Table 1. Baseline Characteristics According to Presence of Previous MI or Not at Baseline (n=17 160)

Characteristics	Previous MI (n=3584)	No Previous MI (n=13 576)	*P* Value
Age, median (IQR), y	62 (57–68)	64 (60–68)	<0.001
Female sex, n (%)	845 (23.6)	5577 (41.1)	<0.001
Race, n (%)			
White	2925 (81.6)	10 728 (79.0)	0.001
Black	94 (2.6)	509 (3.7)	
Asian	451 (12.6)	1852 (13.6)	
Other	114 (3.2)	487 (3.6)	
Region, n (%)			
North America	1167 (32.6)	4301 (31.7)	<0.001
Europe	1784 (49.8)	5845 (43.1)	
Latin America	238 (6.6)	1639 (12.1)	
Asia-Pacific	395 (11.0)	1791 (13.2)	
Weight, median (IQR), kg	91 (79–105)	88 (76–102)	<0.001
Duration of T2DM, median (IQR), y	10 (5–16)	11 (6–16)	<0.001
HbA_{1c}, median (IQR), %	8.0 (7.3–9.2)	8.0 (7.4–9.0)	0.060
eGFR, median (IQR), mL·min^{-1}·1.73	88 (73–97)	89 (75–96)	0.10
Hypertension, n (%)	3130 (87.3)	12 297 (90.6)	<0.001
Dyslipidemia, n (%)	3340 (93.2)	10 456 (77.0)	<0.001
Current smoker, n (%)	554 (15.5)	1944 (14.3)	0.086
History of heart failure, n (%)	770 (21.5)	954 (7.0)	<0.001
Previous CAD, n (%)	3584 (100)	2074 (15.3)	<0.001
Previous PCI, n (%)	2274 (63.4)	1381 (10.2)	<0.001
Previous CABG, n (%)	855 (23.9)	824 (6.1)	<0.001
Previous ischemic stroke, n (%)	218 (6.1)	895 (6.6)	0.27
Previous PAD, n (%)	281 (7.8)	744 (5.5)	<0.001
Antihyperglycemic medications, n (%)			
Insulin at baseline	1644 (45.9)	5369 (39.5)	<0.001
Metformin	2760 (77.0)	11 308 (83.3)	<0.001
Sulfonylurea	1395 (38.9)	5927 (43.7)	<0.001
Cardiovascular medications, n (%)			
Dual antiplatelet therapy	956 (26.7)	706 (5.2)	<0.001
ACE inhibitor/ARB	3014 (84.1)	10 936 (80.6)	<0.001
β-Blocker	2946 (82.2)	6084 (44.8)	<0.001
Statin or ezetimibe	3266 (91.1)	9602 (70.7)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycohemoglobin; IQR, interquartile range; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; and T2DM, type 2 diabetes mellitus.

previous MI at baseline. In a sensitivity analysis, we also stratified patients into 3 groups: previous MI, no previous MI but with ASCVD, and MRF alone.

Unless otherwise stated, all tests are 2 sided, and a value of $P<0.05$ was considered statistically significant. No adjustment for multiplicity was performed. The statistical programs used for the analysis were SAS version 9.4 (SAS Institute Inc, Cary, NC) and Stata version 14.2 (StataCorp, College Station, TX).

Compliance With Ethics Standards

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

RESULTS

Descriptive Statistics

From the overall trial population, 3584 patients (20.9% of the overall trial population and 51.4% of the cohort with established ASCVD) had a history of MI at baseline, whereas 13 576 did not (of those, 3390 patients had established ASCVD and 10 186 had only MRF). Compared with patients without previous MI, patients with previous MI were younger, more likely to be male and

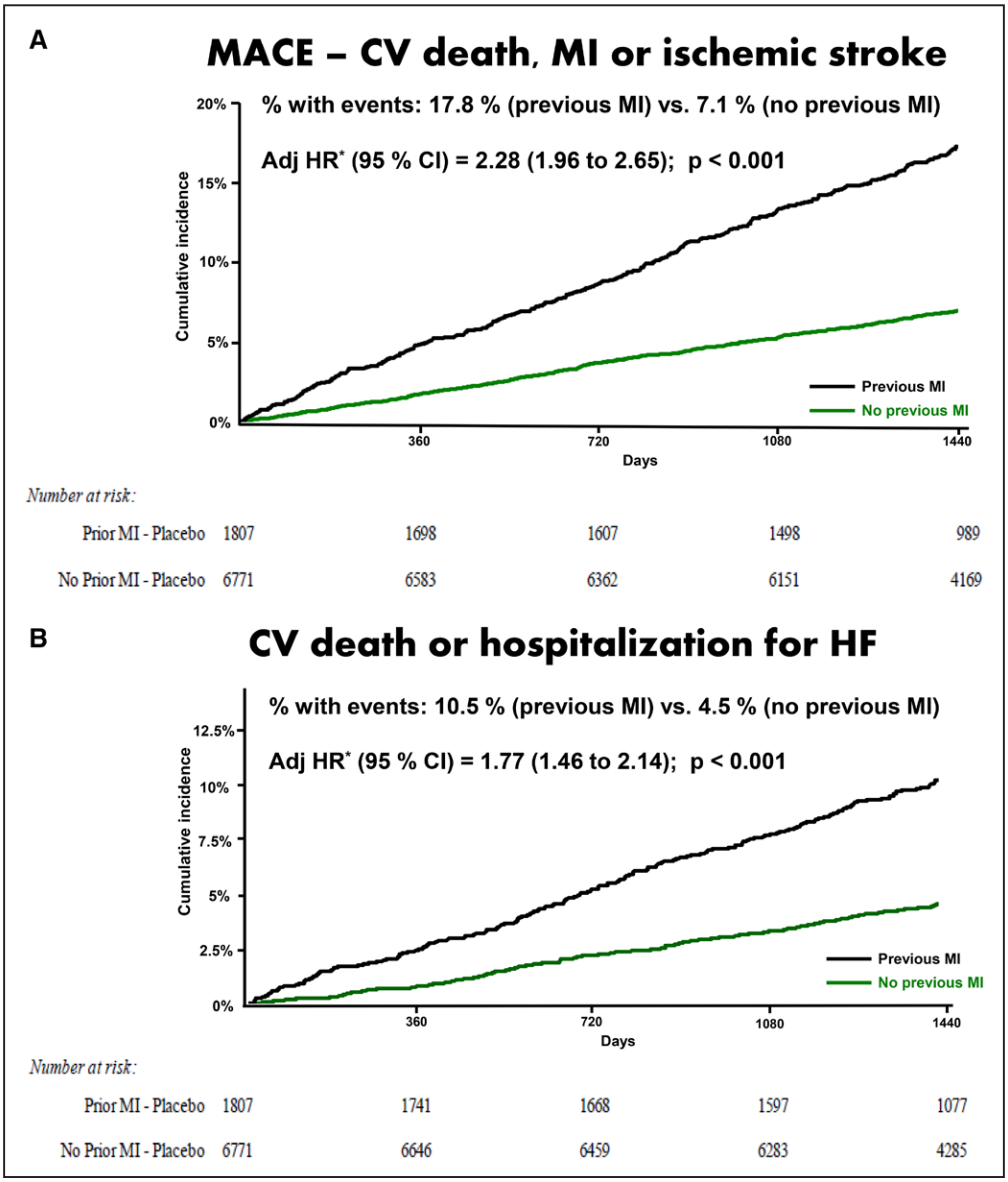

Figure 1. Cumulative incidence at 4 years within the placebo group for patients with (n = 1807) vs without (n = 6771) a history of myocardial infarction (MI) at baseline.

A, Major adverse cardiovascular events (composite of cardiovascular [CV] death, MI, or ischemic stroke). **B**, CV death or hospitalization for heart failure (HHF). *Adjusted for age ≥65 vs <65 years, sex, race, weight ≥89 kg vs <89 kg, diabetes mellitus duration >10 years vs ≤10 years, region, baseline insulin, history of heart failure, history of dyslipidemia, history of hypertension, smoking, history of ischemic stroke, and history of peripheral artery disease. Adj HR indicates adjusted hazard ratio.

white, and more likely to have dyslipidemia at baseline. Despite a slightly shorter duration of T2DM, patients with previous MI were more likely to be on insulin. Patients with previous MI were more likely to have a history of HF and, as expected, were more commonly taking cardiovascular medications at baseline (Table 1). When patients with previous MI were compared with patients without MI but with established ASCVD, the same differences were present, except that the proportion of patients on insulin at baseline was the same (Table I in the online-only Data Supplement). As expected, baseline characteristics were similar between randomized arms (dapagliflozin versus placebo) in patients with previous MI (Table II in the online-only Data Supplement).

Event Rates for Previous MI Versus No Previous MI Within the Placebo Arm

Within the placebo arm, patients with previous MI had higher event rates compared with patients without a history of MI for MACE (17.8% versus 7.1% with events, respectively; adjusted HR, 2.28; 95% CI, 1.96–2.65; *P*<0.001), cardiovascular death or HHF (10.5% versus 4.5%, respectively; adjusted HR, 1.77; 95% CI, 1.46–2.14; *P*<0.001), and particularly for recurrent MI (11.7% versus 3.4%, respectively; adjusted HR, 3.05; 95% CI, 2.50–3.71, *P*<0.001). The cumulative incidence curves for MACE and cardiovascular death/HHF are depicted in Figure 1. Table 2 shows the event rates and HRs for other primary and secondary end points.

Effect of Dapagliflozin on MACE Stratified According to History of MI

In the overall trial, the HR for MACE with dapagliflozin was 0.93 (95% CI, 0.84–1.03; *P*=0.17). In patients with previous MI, 15.2% of patients in the dapagliflozin arm versus 17.8% in the placebo arm experienced MACE, yielding a relative risk reduction of 16% (HR, 0.84; 95% CI, 0.72–0.99; *P*=0.039) and an ARR of 2.6% (95% CI, 0.1–5.0). This ARR translates into a number needed to treat over 4 years of 39. In contrast, there was no effect in patients without previous MI (7.1% versus 7.1%; HR, 1.00; 95% CI, 0.88–1.13; *P*=0.97; ARR, 0.0%; 95% CI, −0.9 to 0.8; relative *P* for interaction=0.11; ARR *P* for interaction=0.048). This was also true in patients with no previous MI but with established ASCVD (12.6% versus 12.8%; HR, 0.98; 95% CI, 0.81–1.19; *P*=0.85; ARR, 0.2%; 95% CI, −2.0 to 2.4) and in patients only with MRF (5.3% versus 5.2%; HR, 1.01; 95% CI, 0.86–1.20; *P*=0.87; ARR, −0.1%; 95% CI, −1.0 to 0.8). Cumulative incidence curves are shown in Figures 2 and 3.

Lower rates of MACE in patients with previous MI were driven mainly by lower rates of recurrent MI (HR, 0.78; 95% CI, 0.63–0.95), both type 1 (HR, 0.80; 95% CI, 0.63–1.02) and type 2 (HR, 0.64; 95% CI, 0.42–0.97) MIs. In addition, we observed lower rates of the exploratory composite outcome of coronary heart disease death or nonfatal MI with dapagliflozin (HR, 0.81; 95% CI, 0.67–0.97). For coronary heart disease death, the HR was 0.84 (95% CI, 0.60–1.19); for cardiovascular death, it was 0.92 (95% CI, 0.69–1.23); and for all-cause mortality, it was 0.83 (95% CI, 0.67–1.03). The HR for ischemic stroke was 0.93 (95% CI, 0.66–1.30). Figure 4 shows the array of cardiovascular outcomes according to previous MI versus no previous MI, and Figure I in the online-only Data Supplement shows the same outcomes stratified according to the spectrum of patients with previous MI, no previous MI with established ASCVD, and only MRF.

Table 2. Study End Points in Patients With Versus Without Previous MI Within Placebo Group

	Previous MI (n=1807), n (% with event)	No Previous MI (n=6771), n (% with event)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*P* Value
MACE (cardiovascular death, MI, or ischemic stroke)	321 (17.8)	482 (7.1)	2.65 (2.30–3.05)	2.28 (1.96–2.65)	<0.001
Cardiovascular death/HHF	190 (10.5)	306 (4.5)	2.40 (2.01–2.88)	1.77 (1.46–2.14)	<0.001
Renal composite*	152 (8.4)	328 (4.8)	1.77 (1.46–2.15)	1.53 (1.25–1.89)	<0.001
All-cause death	187 (10.3)	383 (5.7)	1.86 (1.56–2.22)	1.65 (1.37–1.99)	<0.001
MI	211 (11.7)	230 (3.4)	3.64 (3.02–4.38)	3.05 (2.50–3.71)	<0.001
Type 1	150 (8.3)	157 (2.3)	3.73 (2.99–4.67)	3.33 (2.63–4.22)	<0.001
Type 2	57 (3.2)	58 (0.9)	3.79 (2.63–5.46)	2.82 (1.92–4.15)	<0.001
Ischemic stroke	71 (3.9)	160 (2.4)	1.70 (1.28–2.24)	1.58 (1.17–2.12)	0.002
Cardiovascular death	96 (5.3)	153 (2.3)	2.39 (1.85–3.09)	1.90 (1.45–2.51)	<0.001
CHD death	71 (3.9)	113 (1.7)	2.39 (1.78–3.22)	1.87 (1.36–2.58)	<0.001

CHD indicates coronary heart disease; HHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; and MI, myocardial infarction.

*Renal composite is persistent ≥40% decrease in estimated glomerular filtration rate, end-stage renal disease, or cardiovascular/renal death.

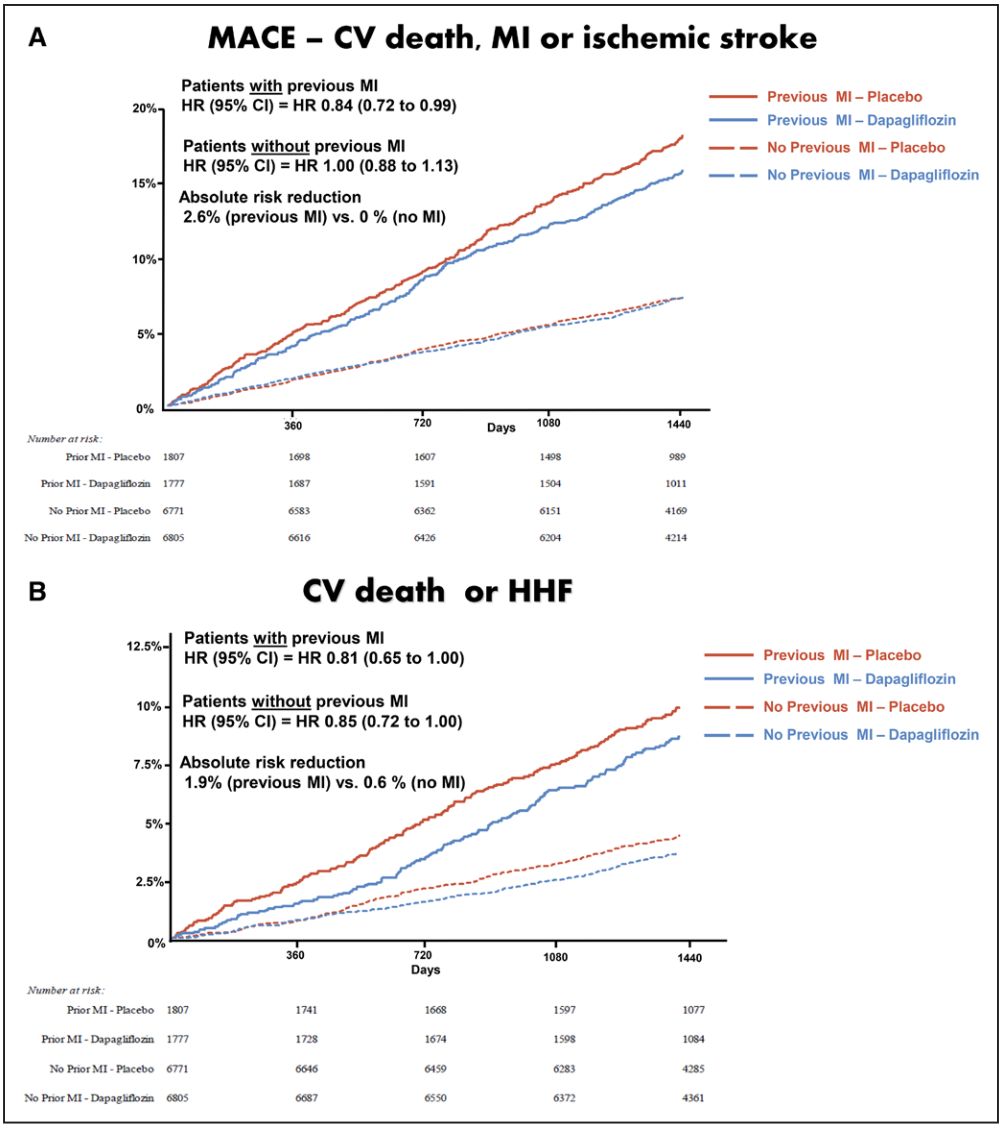

Figure 2. Cumulative incidence at 4 years for dapagliflozin vs placebo stratified by previous myocardial infarction (MI) status.
A, Major adverse cardiovascular events (composite of cardiovascular [CV] death, MI, or ischemic stroke): hazard ratio (HR), 0.84 (95% CI, 0.72–0.99) for patients with vs 1.00 (95% CI, 0.88–1.13) for patients without previous MI (relative *P* for interaction=0.11; absolute risk reduction [ARR] *P* for interaction=0.048). **B**, CV death or hospitalization for heart failure (HHF). HR is 0.81 (95% CI, 0.65–1.00) for patients with vs 0.85 (95% CI, 0.72–1.00) for patients without previous MI (relative *P* for interaction=0.69; ARR *P* for interaction=0.010).

Effect of Dapagliflozin on Cardiovascular Death or HHF Stratified According to History of MI

In the overall trial, the HR for cardiovascular death or HHF with dapagliflozin was 0.83 (95% CI, 0.73–0.95; *P*=0.005). Dapagliflozin had consistent relative risk reductions in the composite of cardiovascular death or HHF in patients with and without previous MI, with an HR of 0.81 (95% CI, 0.65–1.00) and 0.85 (95% CI, 0.72–1.00), respectively (relative *P* for interaction=0.69). However, because of their higher baseline risk, patients with previous MI tended to derive higher ARRs with dapagliflozin (8.6% versus 10.5% for patients with events; ARR, 1.9%; 95% CI, 0.0–3.8) compared with patients without MI (3.9% versus 4.5%; ARR, 0.6%; 95% CI, 0.0–1.3; ARR *P* for interaction=0.010; Figure 2). This ARR for patients with previous MI translated into a number needed to treat over 4 years of 53. Cumulative incidence curves are depicted in Figures 2 and 3.

Outcomes With Dapagliflozin According to Time From Last MI

In patients with previous MI, the median time from the last event was 5.4 years (interquartile range, 2.1–10.9 years) at baseline. The rate of MACE tended to be higher the closer patients were to their qualifying MI. Likewise, the benefit of dapagliflozin in reducing the risk of MACE was greater the closer patients were to their qualifying MI (*P* for interaction trend=0.007). Figure 5 provides further details.

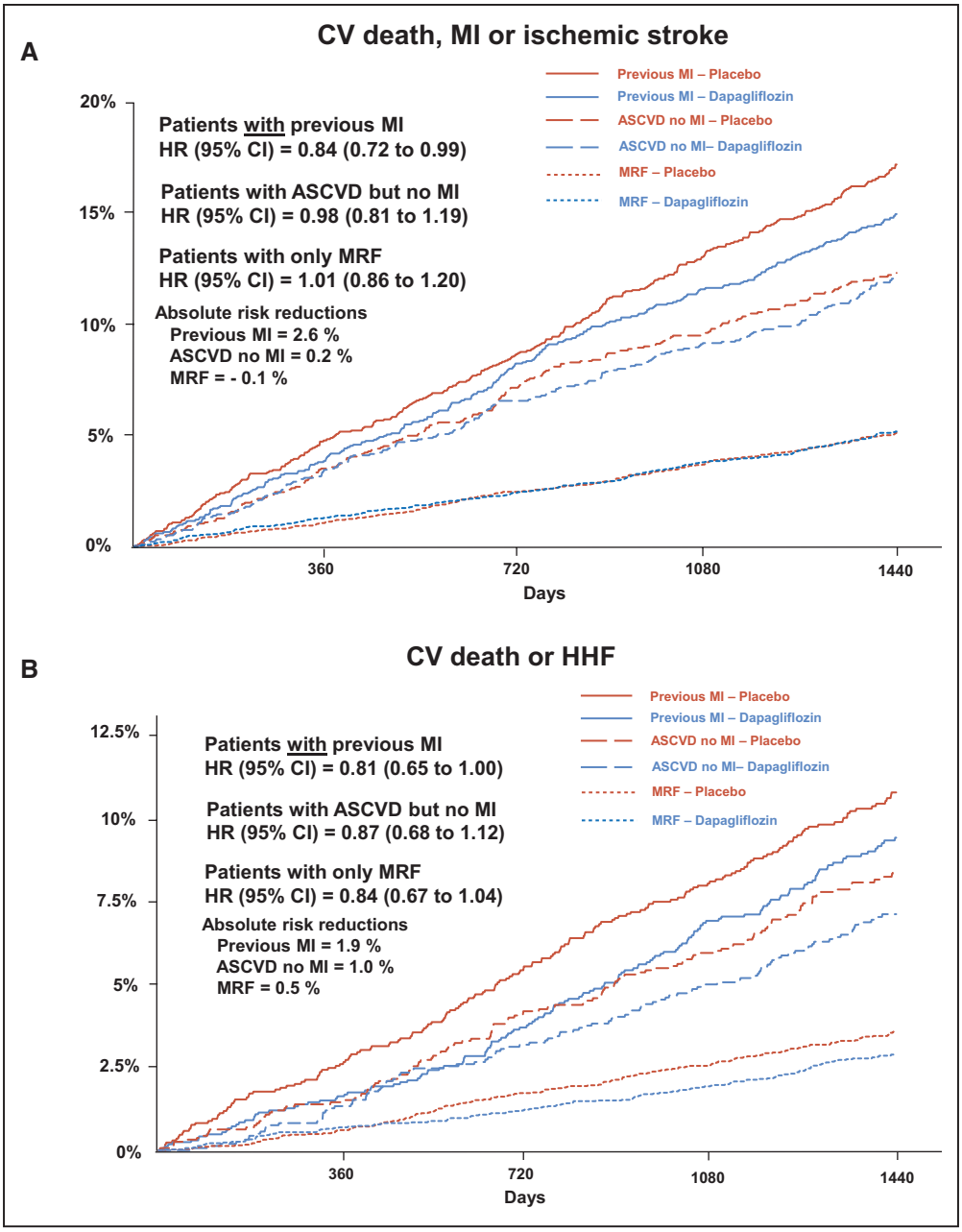

Figure 3. Cumulative incidence at 4 years for dapagliflozin vs placebo stratified across subgroups with previous myocardial infarction (MI), no previous MI but with established atherosclerotic cardiovascular disease (ASCVD), and no previous MI with only multiple risk factors (MRF).
A, Major adverse cardiovascular events (composite of cardiovascular [CV] death, MI, or ischemic stroke). **B**, CV death or hospitalization for heart failure (HHF). HR indicates hazard ratio.

Safety Outcomes

Adverse events of special interest from the main trial stratified according to history of MI are given in Table III in the online-only Data Supplement.

DISCUSSION

In this analysis from the DECLARE-TIMI 58 trial, patients with T2DM and previous MI were at increased risk for both MACE and HF events. This risk persisted even after adjustment for baseline differences and is in accordance with previous reports.[2,4,5] We observed lower rates of MACE with dapagliflozin in patients with previous MI, whereas there was no apparent reduction in either patients with established ASCVD but no previous MI or patients with MRF alone. In patients with previous MI, dapagliflozin consistently reduced the composite of cardiovascular death or HHF with a higher ARR compared with patients without previous MI. These findings build on current guidelines recommendations and highlight that patients with T2DM and MI should strongly be considered for SGLT2i therapy to reduce cardiovascular risk.[17–19]

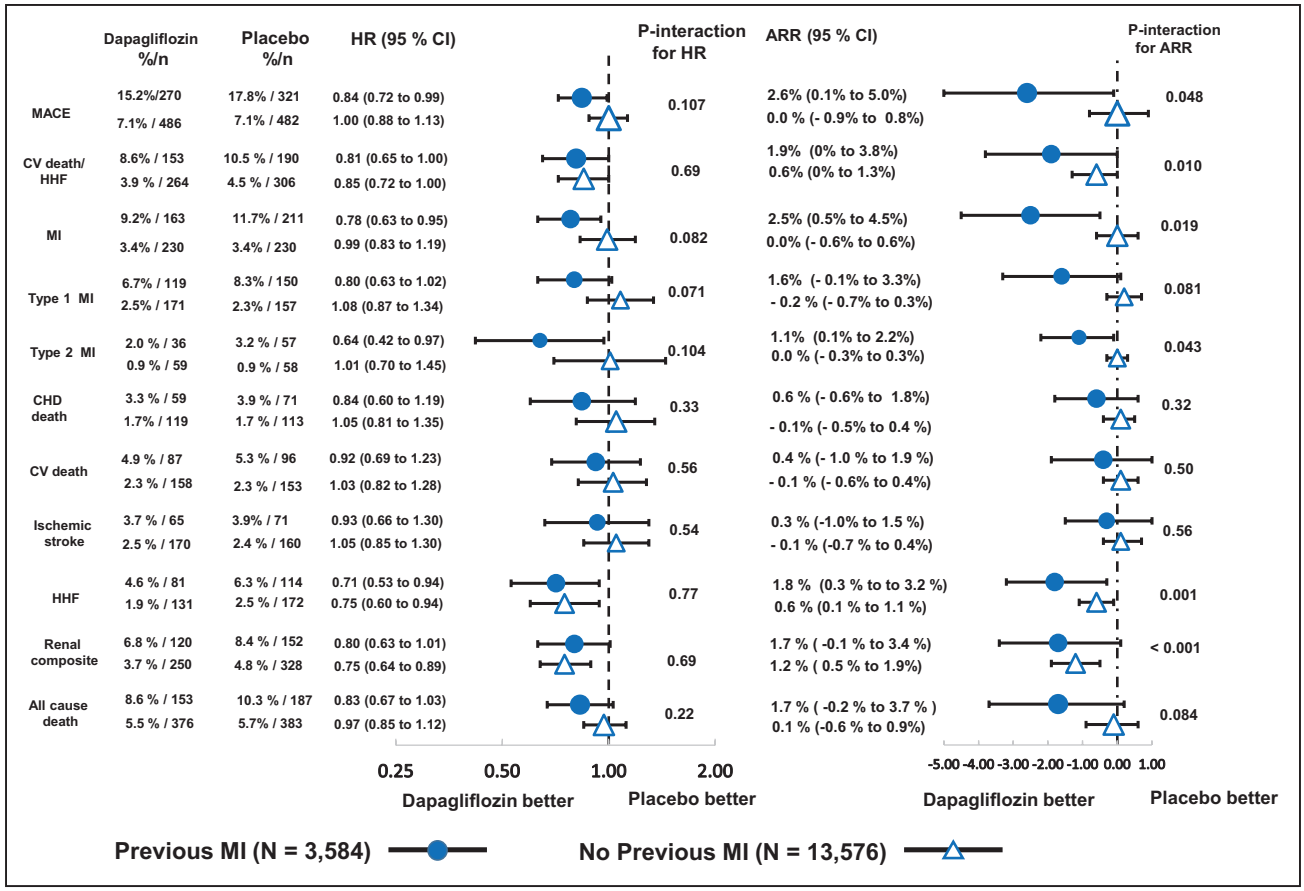

Figure 4. Study end points for dapagliflozin vs placebo stratified according to previous myocardial infarction (MI) at baseline.
Major adverse cardiovascular event (MACE) is the composite of cardiovascular (CV) death, MI, or ischemic stroke. Renal composite is the composite of estimated glomerular filtration rate decrease by at least 40%, end-stage renal disease, cardiovascular death, or renal death. ARR indicates absolute risk reduction; CHD, coronary heart disease; HHF, hospitalization for heart failure; and HR, hazard ratio.

We have recently shown in a meta-analysis that SGLT2is reduced the risk of MACE in patients with ASCVD but not in those with only MRF. Moreover, there was a reduction in MI that was consistent across the 3 trials..[13] Limited data from other trials examine the broad subgroup of patients with ASCVD with greater granularity. Recently, a subanalysis from EMPA REG OUTCOMES trial [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], which enrolled only patients with established ASCVD, examined the clinical benefit of empagliflozin in patients with versus those without previous MI or stroke.[25] As expected, patients in the former subgroup were at higher risk for MACE and for cardiovascular death or HHF. The efficacy with empagliflozin for these outcomes was numerically greater in magnitude among those with previous MI or stroke, but there was no statistical evidence for heterogeneity of efficacy by previous MI or stroke status. However, the ARRs with empagliflozin among those with previous MI or stroke were about twice as high compared with those without previous MI or stroke, congruent with the pattern observed in DECLARE-TIMI 58. In our data, the observations that there was no apparent MACE reduction in patients with previous ASCVD but no history of MI and that, among those with previous MI, the benefit might be higher the closer they were to the acute event reinforce the notion that the higher the risk is, the higher the cardiovascular benefit with SGLT2is is.

In terms of glucagon-like peptide 1 receptor agonists, another class of antihyperglycemic drugs with proven efficacy at reducing cardiovascular events, in the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), which enrolled 9340 individuals with T2DM and either established ASCVD (72.5% of total) or MRF (27.5% of total), liraglutide reduced MACE in the former subgroup, whereas there was no apparent benefit in the latter. The benefit in patients with ASCVD seemed to be consistent regardless of the presence of previous MI or stroke. No data on patients with only previous MI were reported from this trial.[26] Potentially different mechanisms underpinning the cardiovascular risk reduction with glucagon-like peptide 1 receptor agonists versus SGLT2is limit any head-to-head comparison of our results and those from the LEADER trial subanalysis.

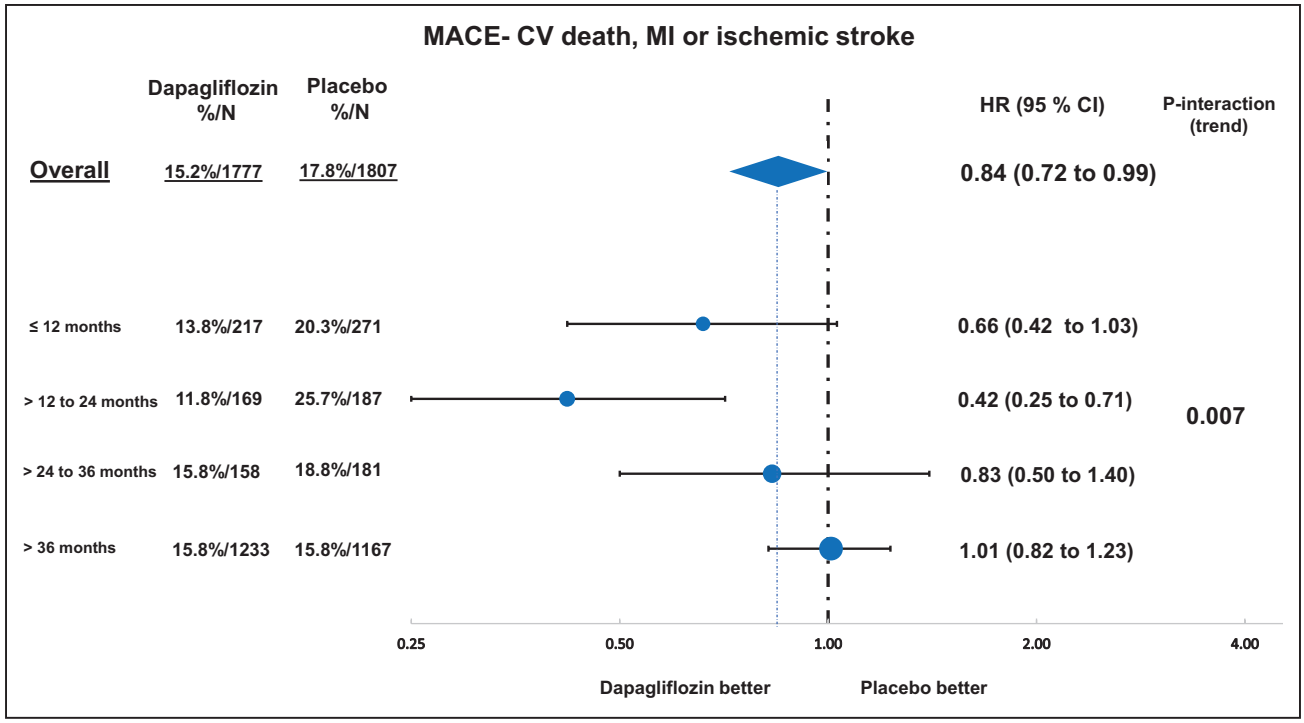

Figure 5. Major adverse cardiovascular (CV) events (MACE; the composite of cardiovascular death, myocardial infarction [MI] or ischemic stroke) for dapagliflozin vs placebo in patients with previous MI, stratified by time from last coronary event at baseline, in months.
HR indicates hazard ratio.

The magnitude of relative risk reduction in recurrent MI in our study is comparable to what has been demonstrated for other therapies aimed at secondary prevention in post-MI patients such as lipid-lowering[27,28] and antiplatelet agents.[29] Moreover, we found a robust decrease in type 2 MI (ie, related to mismatch between myocardial oxygen supply and demand instead of plaque rupture and atherothrombosis), a finding different from what might be expected for MI reduction with antithrombotic therapies.[30] Few therapies have been reported to decrease type 2 MIs, and achieving such a reduction is an unmet clinical need.[31]

The precise pharmacological mechanisms of action that could potentially explain the cardiovascular benefits with SGLT2is are still unclear. Some hypotheses that have been proposed include restoration of tubulo-glomerular feedback and resultant attenuation of the renin-angiotensin-aldosterone system and sympathetic nervous system activation[14]; osmotic diuresis with a decrease in ventricular overload[32]; inhibition of the sodium-hydrogen exchanger pump, resulting in a decrease in myocardial calcium overload[33]; improvement in heart fuel energetics[34]; and increased hematocrit resulting from hemoconcentration or an increase in red cell mass.[35] The last hypothesis could help to explain a reduction of MIs caused by supply-demand mismatch (type 2 MI). Those possible mechanisms could lead to myocardial protection, which would account for the benefits in terms of not only HHF but also cardiovascular death. The mechanisms underlying the reduction in risk of MI are less clear but also may be related to myocardial cytoprotective effects. In agreement with that, evidence from an animal model has suggested a reduction in myocardial oxidative stress, interstitial fibrosis, and macrophage infiltration with empagliflozin.[36] Moreover, canagliflozin attenuated the rise in cardiac biomarkers (both troponin and NT-proBNP [N-terminal pro-B natriuretic peptide]) after 2 years in patients with T2DM.[37] Finally, the recently completed EMPA-HEART trial (Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes; NCT02998970) has demonstrated that empagliflozin decreased left ventricular mass (assessed by cardiac magnetic resonance) after 6 months in patients with T2DM and either previous coronary revascularization or history of MI, thus suggesting that SGLT2is may lead to improvement in left ventricular remodeling after MI and secondarily decrease supply-demand mismatch ischemia.

Study Limitations

First, as is generally the case for subgroup analyses, the trial was not powered to detect all possible event reductions and treatment-by-subgroup interactions. Moreover, the MACE end point was not significantly reduced with dapagliflozin in the overall trial, and the interaction for the relative risk reduction by previous MI status was not significant, but the interaction for ARR was. Moreover, the previous MI subgroup was prespecified, and the observed benefit for MACE in patients with previous MI is consistent with findings from a meta-analysis of car-

diovascular outcomes trials with SGLT2is.[13] Second, the exclusion of patients with previous MI within the first 8 weeks after the index event does not allow understanding of the effects of SGLT2is in patients with MI during the acute phase, who may have other competing risks (eg, stent thrombosis and recurrent plaque rupture).

Conclusions

Patients with T2DM and previous MI are at high risk of MACE and cardiovascular death/HHF. Dapagliflozin appears to robustly reduce the risk of both events in these patients. Future studies should aim to confirm the large clinical benefits with SGLT2is that we observed in patients with previous MI.

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Correspondence

Stephen D. Wiviott, MD, 60 Fenwood Rd, Ste 7022, Boston, MA 02115. Email swiviott@bwh.harvard.edu

Affiliations

Thrombolysis in Myocardial Infarction (TIMI) Study Group–Brigham and Women's Hospital, Boston, MA (R.H.M.F., T.A.Z., J.K., S.A.M., D.L.B., C.T.R., M.S.S., S.D.W.). CPC Clinical Research and Vascular Research Unity, University of Colorado, Denver (M.P.B.). Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Hebrew University of Jerusalem, Faculty of Medicine, Jerusalem, Israel (I.R., O.M., A.C.). Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Ontario, Canada (L.A.L.). Division of Cardiology, University of Texas Southwestern Medical Center, Dallas (D.K.M.). Institute of Ageing and Chronic Disease, University of Liverpool, UK (J.P.H.W.). Instituto do Coracao (InCor), Hospital das Clinicas da Faculdade de Medicina, Universidade de Sao Paulo, Brazil (R.H.M.F., J.C.N.). AstraZeneca Gothenburg, Mölndal, Sweden (I.A.M.G.-N., M.F., A.M.L.).

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