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Effects of Canagliflozin on Cardiovascular Biomarkers in Older Adults With Type 2 Diabetes

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ABSTRACT

BACKGROUND Sodium glucose co-transporter 2 inhibitors may reduce cardiovascular and heart failure risk in patients with type 2 diabetes mellitus (T2DM).

OBJECTIVES The goal of this study was to examine the effects of canagliflozin on cardiovascular biomarkers in older patients with T2DM.

METHODS In 666 T2DM patients randomized to receive canagliflozin 100 or 300 mg or placebo, the study assessed the median percent change in serum N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin I (hsTnI), soluble (s)ST2, and galectin-3 from baseline to 26, 52, and 104 weeks.

RESULTS Both serum NT-proBNP and serum hsTnI levels increased in placebo recipients, but they remained largely unchanged in those randomized to canagliflozin. Hodges-Lehmann estimates of the difference in median percent change between pooled canagliflozin and placebo were −15.0%, −16.1%, and −26.8% for NT-proBNP, and −8.3%, −11.9%, and −10.0% for hsTnI at weeks 26, 52, and 104, respectively (all $p < 0.05$). Serum sST2 was unchanged with canagliflozin and placebo over 104 weeks. Serum galectin-3 modestly increased from baseline with canagliflozin versus placebo, with significant differences observed at 26 and 52 weeks but not at 104 weeks. These results remained unchanged when only patients with complete samples were assessed.

CONCLUSIONS Compared with placebo, treatment with canagliflozin delayed the rise in serum NT-proBNP and hsTnI for over 2 years in older T2DM patients. These cardiac biomarker data provide support for the beneficial cardiovascular effect of sodium glucose co-transporter 2 inhibitors in T2DM. (A Safety and Efficacy Study of Canagliflozin in Older Patients [55 to 80 Years of Age] With Type 2 Diabetes Mellitus; NCT01106651) (J Am Coll Cardiol 2017;70:704–12) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Sodium glucose co-transporter 2 (SGLT2) inhibitors are a new class of diabetes drugs that lower blood glucose in patients with type 2 diabetes mellitus (T2DM) through increased urinary excretion of glucose (1). SGLT2 inhibitors may have other cardiometabolic benefits; they cause natriuresis, a mild osmotic diuresis, and a net caloric loss that contribute to reductions in body weight and blood pressure (BP) (1). Additionally, increased delivery of sodium to the macula densa helps to restore normal glomerular pressure, which, in turn, results in improved renal function over the longer term (2).

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SGLT2 inhibitors have recently been studied in large cardiovascular outcomes trials for evaluating the cardiovascular effects of newer T2DM agents (3). In the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) study, treatment with empagliflozin resulted in reduction in the risk for major adverse cardiovascular events (3-point MACE: cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction) compared with placebo, driven by a 38% reduction in cardiovascular death; empagliflozin also reduced the risk of hospitalization for heart failure by 35% relative to placebo (4). These effects were apparent early after initiating treatment with empagliflozin, suggesting that acute changes may be at least partially responsible for the observed outcomes (4). Hypotheses regarding the mechanism of cardiovascular benefit for SGLT2 inhibition observed in the EMPA-REG OUTCOME study have focused on the multiple effects beyond glucose lowering, such as diuresis and natriuresis, weight loss, BP lowering, metabolic effects on the myocardium, favorable hemodynamic changes, and attenuation of cardiac remodeling (5–12); each may result in improved cardiovascular outcomes (11).

Biomarkers are useful in prognosis determination and informing the mechanism of benefit provided by therapeutic agents (13). N-terminal pro-B-type natriuretic peptide (NT-proBNP) is recommended for the diagnosis and management of heart failure, with potential utility in the prediction of coronary heart disease and stroke outcomes (14). Similarly, biomarkers of cardiomyocyte injury (e.g., high-sensitivity troponin I [hsTnI]) and those involved in cardiovascular stress/tissue fibrosis (e.g., soluble [s]ST2, galectin-3) may help elucidate prognosis and disease progression, with recent data, in particular, for hsTnI in T2DM (15).

There are very limited data on the effects of SGLT2 inhibitors on cardiovascular biomarkers (16–18). In this study, we sought to assess the longitudinal changes in the concentrations of NT-proBNP, hsTnI, sST2, and galectin-3 in older patients with T2DM randomized to receive canagliflozin or placebo in a 104-week study (19,20) to gain insights into the mechanisms of the potential beneficial cardiovascular effect of SGLT2 inhibitors.

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CI = confidence interval

CV = coefficients of variation

eGFR = estimated glomerular filtration rate

hsTnI = high-sensitivity troponin I

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SGLT2 = sodium glucose co-transporter 2

sST2 = soluble ST2

T2DM = type 2 diabetes mellitus

METHODS

PATIENTS. This post hoc, exploratory analysis was conducted using stored serum samples from a 104-week, randomized, double-blind, placebo-controlled study (NCT01106651) that evaluated the efficacy and safety of canagliflozin 100 and 300 mg in older patients with T2DM. Full study design and key inclusion/exclusion criteria have previously been reported (19,20). Briefly, eligible patients were adults with T2DM who were 55 to 80 years of age, had glycosylated hemoglobin ≥7.0% and ≤10.0% and estimated glomerular filtration rate (eGFR) ≥50 ml/min/1.73 m^2, and were either not on any antihyperglycemic agent or were on a stable regimen of monotherapy or combination therapy. Patients with a history of myocardial infarction, unstable angina, previous coronary revascularization, cerebrovascular accident within 3 months before screening, history of New York Heart Association functional class III to IV symptoms, or uncontrolled hypertension were not eligible to participate. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and followed good clinical practice and applicable regulatory requirements. Approval was obtained from institutional review boards and independent ethics committees for each participating center. Participants provided informed written consent before enrollment in the study.

ENDPOINTS/ASSESSMENTS. Serum samples were collected at baseline and at weeks 26, 52, and 104, and stored at −80°C. NT-proBNP was measured on the cobas e601 immunoanalyzer using the proBNP II electrochemiluminescent immunoassay (Roche Diagnostics, Indianapolis, Indiana), with interassay coefficients of variation (CV) of 2.5% at 137.2 pg/ml (low-quality control concentration) and 2.3% at 4,830 pg/ml (high-quality control concentration). High-sensitivity TnI and galectin-3 were measured on the Architect i2000SR immunoanalyzer using chemiluminescent microparticle immunoassays (Abbott Laboratories, Abbott Park, Illinois). CV were 4.0% at 20.4 ng/l and 3.7% at 15,050 ng/l for hsTnI, and 4.0% at 9.3 ng/ml and 2.9% at 74.4 ng/ml for galectin-3.

TABLE 1 Baseline Demographic and Disease Characteristics Among Patients With Biomarker Assessments

	Placebo (n = 216)	Canagliflozin (n = 450)
Male	133 (62)	248 (55)
Age, yrs	63.2 (6.3)	64.0 (6.3)
55 to <65	136 (63)	269 (60)
≥65	80 (37)	181 (40)
Race		
White	170 (79)	349 (78)
Black or African American	16 (7)	34 (8)
Asian	19 (9)	37 (8)
Other*	11 (5)	30 (7)
HbA_{1c}, %	7.8 ± 0.8	7.7 ± 0.8
BMI, kg/m^2	31.9 ± 4.8	31.4 ± 4.5
T2DM duration, yrs	10.0 (6.0–15.0)	10.3 (6.1–16.0)
eGFR, ml/min/1.73 m^2	76.1 ± 16.5	78.2 ± 16.9
Systolic BP, mm Hg	131.2 ± 12.3	130.8 ± 14.0
History of microvascular disease	55 (25)	145 (32)
History of hypertension	169 (78)	346 (77)
Concomitant medications		
ACE inhibitor/ARB	163 (76)	327 (73)
Beta-blockers	60 (28)	109 (24)
Calcium-channel blockers	48 (22)	103 (23)
Diuretic agents	73 (34)	151 (34)

Values are n (%), mean ± SD, or median (IQR). The population reflects a generally higher-risk cohort of patients with T2DM. *Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, and not reported.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; IQR = interquartile range; T2DM = type 2 diabetes mellitus.

Soluble ST2 was measured using a sandwich monoclonal enzyme-linked immunosorbent assay (Critical Diagnostics, San Diego, California), and the CV were 7.6% at 28.2 ng/ml and 7.5% at 60.0 ng/ml. For each assay, all samples were run in a blinded fashion and in the same period, thereby minimizing interassay variations.

To understand secular trends in biomarkers as a function of treatment allocation, absolute and percent change from baseline in serum levels of NT-proBNP, hsTnI, sST2, galectin-3, eGFR, and hematocrit were analyzed at each time point for patients with data at baseline and at any follow-up time point thereafter. Given the non-normality of these biomarker data including change and percent change from visit to visit, the medians of the change and percent change were analyzed. Data for the 2 canagliflozin doses were pooled after it was determined that there was no dose response observed on any of the biomarkers. A sensitivity analysis was also performed to evaluate absolute and percent change from baseline in biomarkers in the cohort of patients with complete sets of samples (i.e., data available at all visits, including baseline and weeks 26, 52, and 104).

STATISTICAL ANALYSES. Nonparametric Hodges-Lehmann estimates of the difference between canagliflozin and placebo in median change and median percent change from baseline were calculated for each biomarker at each time point. The distribution-free confidence intervals (CIs) and nominal p values for the differences in the median change and median percent change were based on the Wilcoxon rank sum test (21). SE for the median and median percent change at each time point were estimated using the bootstrap technique by simulated repeated samples for each biomarker and treatment group. Spearman correlation coefficients between change from baseline in the specific biomarker and change from baseline in selected clinical parameters (i.e., glycosylated hemoglobin, body weight, systolic BP, hemoglobin, hematocrit, eGFR) were determined within each treatment group at each time point.

RESULTS

PATIENTS. Of 714 patients in the overall study population, 666 patients (93.3%) had serum samples at baseline and ≥1 post-baseline follow-up time point, and these patients were included in this analysis. Among patients included in the biomarker assessments, baseline characteristics were balanced between groups and were generally consistent with the overall study population (Table 1); 77% had a history of hypertension and 30% had a history of microvascular disease (i.e., neuropathy, retinopathy, or nephropathy). The majority of patients (74%) were taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; 25%, 23%, and 34% of patients were on beta-blockers, calcium-channel blockers, and diuretic agents, respectively (Table 1). Of those taking diuretic agents, the majority took thiazides (29.2% in the placebo arm and 28.9% in the canagliflozin arm), whereas loop diuretic agents (4.6% and 3.6%) or mineralocorticoid receptor antagonists (0.5% and 3.1%) were less commonly used. During the course of the study, no changes in electrocardiographic parameters, such as PR interval, QRS interval, QT/QTc, or RR intervals, were noted between treatment groups (data not shown).

BIOMARKER CHANGES. Table 2 summarizes the observed changes in serum NT-proBNP, hsTnI, sST2, galectin-3, eGFR, and hematocrit at all time points. From a baseline median of approximately 47 pg/ml, serum NT-proBNP concentrations increased with placebo, but changed only minimally with canagliflozin over the 2-year study period (Figure 1A).

TABLE 2 Summary of Changes in Serum Concentrations of Cardiovascular Biomarkers, eGFR, and Hematocrit

	Week 26		Week 52		Week 104	
	Placebo	Canagliflozin	Placebo	Canagliflozin	Placebo	Canagliflozin
Serum NT-proBNP	187	402	165	389	155	341
Baseline, pg/ml	48.3 (22.0–110.8)	48.6 (24.2–103.3)	43.6 (22.1–98.2)	48.1 (24.5–103.3)	43.4 (20.8–92.1)	47.4 (23.7–98.1)
Change from baseline, pg/ml*	3.6 ± 3.6	−0.8 ± 4.0	4.3 ± 3.6	−0.3 ± 3.0	12.5 ± 4.5	2.4 ± 3.2
Difference vs. placebo†		−7.2 (−13.5 to −1.0)‡		−8.9 (−16.2 to −2.4)§		−11.8 (−19.9 to −4.3)§
Serum hsTnI	172	344	145	329	140	294
Baseline, pg/ml	3.4 (2.2–5.6)	3.3 (2.2–5.0)	3.3 (2.2–5.1)	3.1 (2.2–5.0)	3.3 (2.2–5.4)	3.2 (2.2–5.0)
Change from baseline, pg/ml*	0.2 ± 0.1	−0.2 ± 0.1	0.2 ± 0.1	−0.2 ± 0.1	0.3 ± 0.1	0.0 ± 0.1
Difference vs. placebo†		−0.3 (−0.5 to −0.1)§		−0.4 (−0.6 to −0.1)§		−0.4 (−0.6 to −0.1)§
Serum sST2	187	409	165	392	155	343
Baseline, ng/ml	28.8 (25.0–35.8)	29.0 (23.9–34.3)	28.8 (25.0–35.8)	29.0 (24.2–34.4)	28.4 (24.7–36.7)	28.9 (23.8–34.2)
Change from baseline, ng/ml*	−0.7 ± 0.5	−1.1 ± 0.4	−0.5 ± 0.5	−0.4 ± 0.5	0.2 ± 0.5	0.3 ± 0.4
Difference vs. placebo†		−0.3 (−1.0 to 0.5)		0.1 (−0.8 to 0.9)		−0.1 (−1.0 to 0.8)
Serum galectin-3	172	343	145	330	140	294
Baseline, ng/ml	17.3 (14.8–20.1)	17.1 (13.7–20.8)	17.4 (15.1–20.4)	16.9 (13.7–20.8)	17.2 (14.6–20.2)	17.0 (13.7–20.8)
Change from baseline, ng/ml*	0.2 ± 0.3	1.1 ± 0.4	−0.1 ± 0.3	0.8 ± 0.3	0.3 ± 0.4	0.8 ± 0.4
Difference vs. placebo†		1.2 (0.7 to 1.7)§		0.9 (0.3 to 1.4)§		0.6 (−0.0 to 1.2)
eGFR	216	450	216	450	216	450
Baseline, ml/min/1.73 m^2	74.0 (64.0–86.0)	77.0 (66.0–89.0)	74.0 (64.0–86.0)	77.0 (66.0–89.0)	74.0 (64.0–86.0)	77.0 (66.0–89.0)
Change from baseline, ml/min/1.73 m^2*	−1.0 ± 0.9	−3.0 ± 1.0	−1.0 ± 1.1	−3.0 ± 1.0	−3.0 ± 1.4	−3.0 ± 1.1
Difference vs. placebo†		−2.0 (−3.0 to 0.0)‡		−1.0 (−2.0 to 1.0)		0.0 (−1.0 to 2.0)
Hematocrit	215	450	215	450	215	450
Baseline, fraction	0.41 (0.39–0.43)	0.41 (0.39–0.43)	0.41 (0.39–0.43)	0.41 (0.39–0.43)	0.41 (0.39–0.43)	0.41 (0.39–0.43)
Change from baseline, fraction*	0.000 ± 0.002	0.020 ± 0.005	0.000 ± 0.002	0.020 ± 0.004	−0.010 ± 0.004	0.020 ± 0.004
Difference vs. placebo†		0.02 (0.02 to 0.03)§		0.02 (0.02 to 0.03)§		0.02 (0.02 to 0.03)§

Values are n, median (IQR), median ± SE, and median (95% CI). Treatment with canagliflozin resulted in prevention of rise in NT-proBNP and hsTnI over a 2-yr period. *The SE for the median was estimated using the bootstrap technique by simulated repeated samples for each biomarker and treatment group. †Data are nonparametric Hodges-Lehmann estimates; 95% CI were estimated based on the Wilcoxon rank sum test. ‡Nominal $p < 0.05$ vs. placebo. §Nominal $p < 0.01$ vs. placebo.

CI = confidence interval; hsTnI = high-sensitivity troponin I; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sST2 = soluble ST2; other abbreviations as in Table 1.

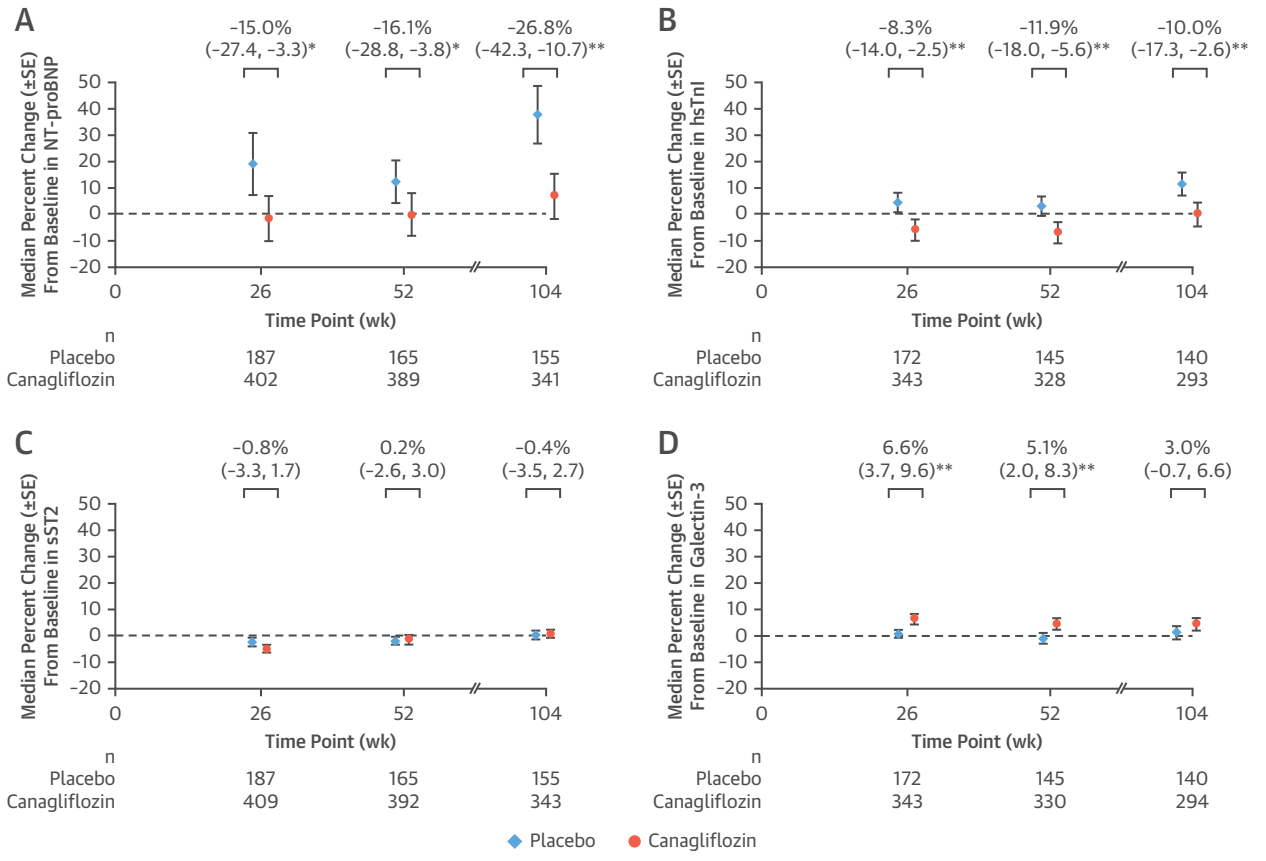
Hodges-Lehmann estimates of the difference in median percent change between canagliflozin and placebo at weeks 26, 52, and 104 were −15.0% (95% CI: −27.4% to −3.3%), −16.1% (95% CI: −28.8% to −3.8%), and −26.8% (95% CI: −42.3% to −10.7%), respectively. A between-group treatment effect was observed at 26 weeks and persisted over 104 weeks (nominal $p < 0.05$ at weeks 26 and 52, nominal $p < 0.01$ at week 104). Considering the relationship between baseline and 104-week concentrations of NT-proBNP (Online Figure 1A), a lower slope from baseline to final measurement was observed in those treated with canagliflozin.

From a baseline median of approximately 3.3 pg/ml, serum hsTnI also gradually increased with placebo at each time point, but was reduced or unchanged with canagliflozin over 104 weeks (**Figure 1B**). Hodges-Lehmann estimates of the difference in median percent change between canagliflozin and placebo at weeks 26, 52, and 104 were −8.3% (95% CI: −14.0% to −2.5%), −11.9% (95% CI: −18.0% to −5.6%), and −10.0% (95% CI: −17.3% to −2.6%), respectively. Differences between canagliflozin and placebo were significant at each time point (nominal $p < 0.01$ for each between-group difference). Considering the correlation between baseline and 104-week concentrations of hsTnI (Online Figure 1B), a lower slope from baseline to final measurement was observed in those treated with canagliflozin.

Baseline serum sST2 concentrations were approximately 29 ng/ml. In contrast to NT-proBNP and hsTnI, median sST2 levels were unchanged in both the canagliflozin and placebo groups at each time point (Hodges-Lehmann estimates of the difference in median percent change of −0.8% [95% CI: −3.3% to 1.7%], 0.2% [95% CI: −2.6% to 3.0%], and −0.4% [95% CI: −3.5% to 2.7%] at weeks 26, 52, and 104, respectively; nominal $p > 0.05$ at each time point) (**Figure 1C**).

Baseline serum galectin-3 concentrations were approximately 17 ng/ml. Small increases from baseline in median galectin-3 levels were observed with canagliflozin relative to placebo at 26 weeks (6.6% [95% CI: 3.7% to 9.6%]; nominal $p < 0.01$) and 52 weeks (5.1% [95% CI: 2.0% to 8.3%]; nominal $p < 0.01$); by 104 weeks, the difference in galectin-3 was still numerically higher in the canagliflozin arm

FIGURE 1 Median Percent Change From Baseline in Cardiac Biomarkers Over 104 Weeks



Treatment with canagliflozin prevented a rise of N-terminal pro-B-type natriuretic peptide (NT-proBNP) **(A)** and high-sensitivity troponin I (hsTnI) **(B)** over a 104-week period, compared with placebo. Soluble ST2 (sST2) concentrations were unchanged **(C)**, whereas galectin-3 concentrations increased modestly **(D)**. *Nominal $p < 0.05$ versus placebo. **Nominal $p < 0.01$ versus placebo.

but not statistically significant (3.0% [95% CI: −0.7% to 6.6%]; nominal $p = 0.11$) (Figure 1D). It is of note that similar trends in eGFR were seen as in the galectin-3 data; modest decreases in eGFR were seen at 26 and 52 weeks with canagliflozin compared with placebo, but by 104 weeks, no difference in change in eGFR was observed between treatment groups.

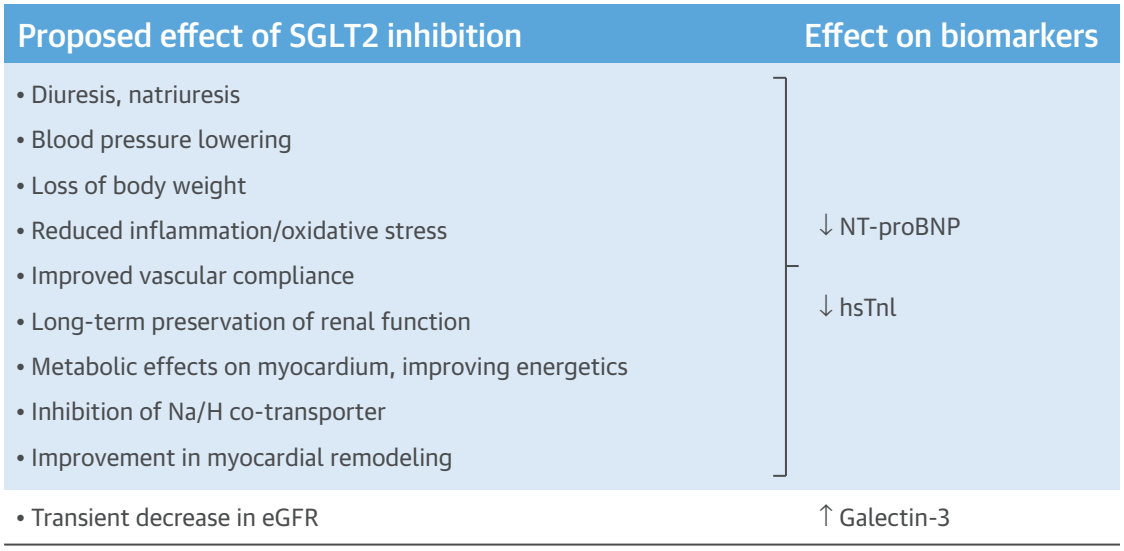
With the exception of a negative correlation between galectin-3 concentrations and eGFR, there were generally no clinically meaningful correlations between change in biomarkers and change in selected physiological parameters at any time point (Online Table 1).

In a sensitivity analysis among patients who had biomarker data at baseline and all 3 time points, changes in cardiovascular biomarkers were consistent with those seen in the primary analysis (Online Figures 2A to 2D).

DISCUSSION

In this randomized trial of older patients with T2DM with biomarker profiles consistent with a generally higher risk for cardiovascular events, we found that serum concentrations of NT-proBNP and hsTnI, biomarkers with proven prognostic value for cardiovascular risk in T2DM (22), rose over a 2-year period in patients allocated to placebo, whereas canagliflozin treatment attenuated their rise. In contrast, we found no obvious effect of treatment with canagliflozin on concentrations of sST2, with a modest, nonpersistent rise in galectin-3. The effects on NT-proBNP and hsTnI seen with canagliflozin versus placebo in this post hoc analysis are compatible with attenuation of cardiovascular risk in those treated with SGLT2 inhibitors (**Central Illustration**). To the extent that it is unclear whether benefits seen in the EMPA-REG

CENTRAL ILLUSTRATION **Proposed Mechanisms of Benefit of Canagliflozin and Effect on Cardiac Biomarkers**



Januzzi, Jr., J.L. et al. J Am Coll Cardiol. 2017;70(6):704–12.

Through its beneficial effects on the heart, canagliflozin prevented a rise in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin I (hsTnI). Possibly through transient reduction in estimated glomerular filtration rate (eGFR), galectin-3 increased modestly. Na/H = sodium/proton; SGLT2 = sodium glucose co-transporter 2.

OUTCOME study could be expected from treatment with all SGLT2 inhibitors, our results provide novel data regarding possible cardiovascular benefits from canagliflozin treatment.

Numerous theories have emerged to explain how SGLT2 inhibitors may reduce cardiovascular risk; however, no consensus exists as to the mechanism of such risk reduction. The early divergence of survival curves seen in the EMPA-REG OUTCOME study suggests an acute effect in particular on heart failure outcomes (4). It has been proposed that sodium and fluid loss, reduction in BP and body weight, attenuation of inflammation and oxidative stress, improvement in arterial stiffness, as well as preservation of renal function may contribute to the observed cardiac benefits (7,10,11,23). Interest has also focused on metabolic effects in the myocardium, including changes in glucagon handling, mitigation of glucotoxicity, and shift to fatty acid metabolism, as well as attenuation of cardiac remodeling (5–9,11). Treatment with SGLT2 inhibitors has been shown to increase levels of ketone bodies, which may be a more favorable energetic substrate for the heart compared with glucose or fatty acids (5,6). Additionally, SGLT2 inhibitors may inhibit the sodium-hydrogen exchanger, leading to reduction of intracellular sodium and calcium in a cariporide-dependent fashion (24), which may foster a cardioprotective effect. Finally, in a basic science model of heart failure, empagliflozin treatment or knockdown of the *SLC5A2* gene (simulating SGLT2 inhibition) created a phenotype with improved cardiac function and reduced BNP expression (25). Our biomarker results help to further the understanding of how SGLT2 inhibition might exert a favorable impact on cardiovascular events.

We lack data on biomarker concentrations during the first 26 weeks of treatment with canagliflozin, making it impossible to determine whether the biomarker changes observed in this analysis are somewhat related to diuretic effects from SGLT2 inhibition; studies suggest there is a 10% reduction in plasma volume after 1 week of treatment with canagliflozin, but the plasma volume nearly returns to baseline by week 12 (26). An alternative or linked possibility is to consider that our findings indicate prevention of rise in NT-proBNP or hsTnI.

Biomarker measurements may help inform the mechanism of benefit in patients treated with novel therapies (13), with change over time frequently imparting greater prognostic information than a single measurement or knowledge of absolute concentration. Our results represent the first larger-scale,

placebo-controlled data regarding cardiac biomarkers in patients treated with SGLT2 inhibition. In a recent study of 66 patients treated with empagliflozin, but without placebo control, serum NT-proBNP concentrations were unchanged after 4 weeks in patients with or without T2DM (16). In another small study of 75 patients with T2DM randomized to dapagliflozin, hydrochlorothiazide, or placebo, no differences in NT-proBNP were seen over 12 weeks of follow-up (17). Thus, our results, gathered in much larger numbers and for a much longer period of time, substantially extend the understanding of how novel drugs for T2DM may exert favorable cardiovascular effects.

Concentrations of each biomarker measured in this exploratory analysis are consistent with those expected for an older patient study group with at least a moderate risk for cardiovascular events (27). Furthermore, over time, placebo-treated patients demonstrated increases in both NT-proBNP and hsTnI; such changes, though modest, may be indicative of increasing risk for cardiovascular events and heart failure (14,27). Our findings indicate that treatment with canagliflozin was associated with a blunting of the rise in NT-proBNP and hsTnI over time. Taken together, these results are compatible with the early and sustained cardiovascular benefits seen in the EMPA-REG OUTCOME study.

Baseline sST2 concentrations in our study participants indicate a generally higher-risk patient population, with a median value near the 90th percentile for a normal healthy population (28). We did not observe any effect on sST2 concentrations with canagliflozin. In contrast, relatively smaller, but significant increases in galectin-3 concentrations were observed at 26 and 52 weeks in patients treated with canagliflozin; by 104 weeks, galectin-3 concentrations were still numerically, but not significantly, higher in the canagliflozin arm. Renal function is a known confounder of galectin-3, and canagliflozin treatment is associated with initial reductions in eGFR that trend back toward baseline with continued treatment (29). Indeed, modest reductions in eGFR paralleled the increase in galectin-3, and there was a correlation between change in galectin-3 and change in eGFR over time: thus, change in renal function may account for the declining between-group difference across time points. It is unknown whether a small early increase in galectin-3 with canagliflozin is clinically relevant.

STUDY LIMITATIONS. Though the current results are the first larger-scale, placebo-controlled assessment of multiple cardiovascular biomarkers in patients with T2DM treated with canagliflozin, there are a few limitations of this study. First, not all patients had samples at every time point; however, a sensitivity analysis using data from patients with samples at all 3 time points showed consistent results. Also, exclusion of patients with eGFR $<$50 ml/min/1.73 m^2 might render our data less generalizable to those with worse renal function; this exclusion criterion was due to use of metformin in an older patient population. However, this minimizes confounding effects of worse renal function on biomarker concentrations. Differences in the concentrations of NT-proBNP and hsTnI between placebo- and canagliflozin-treated patients were relatively modest. However, small changes in both biomarkers may be substantially prognostic, and consistency across multiple time points suggests that these changes for NT-proBNP and hsTnI are more likely to be robust. Lastly, we lack data on other novel biomarkers with prognostic value such as mid-regional pro-adrenomedullin or growth differentiation factor-15. Larger studies should confirm our findings, and, ideally, future outcomes trials should examine links between biomarker changes and long-term cardiovascular disease outcomes.

CONCLUSIONS

Our findings suggest that canagliflozin treatment was associated with attenuation of biomarkers associated with adverse cardiovascular outcomes in this study population of older patients with T2DM. As it is difficult to know for sure whether the benefits seen in the EMPA-REG OUTCOME study related to treatment with empagliflozin can be extrapolated to treatment with canagliflozin, our results are important, and might predict similar risk reduction from canagliflozin treatment. Results from the CANVAS Program, including CANVAS (CANagliflozin cardioVascular Assessment Study [NCT01032629]) and CANVAS-R (CANagliflozin cardioVascular Assessment Study-Renal [NCT01989754]), provide direct evidence on the effects of canagliflozin on cardiovascular outcomes in patients with a history or high risk of cardiovascular disease (30–33).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Elevated levels of NT-proBNP and hsTnI are associated with an increased risk of cardiovascular events, including heart failure and mortality, in older patients with T2DM. SGLT2 inhibitors reduce NT-proBNP and hsTnI concentrations and lower cardiovascular risk in these patients.

TRANSLATIONAL OUTLOOK: Further studies are needed to understand the mechanisms by which SGLT2 inhibitors ameliorate myocardial stress and prevent necrosis in patients with T2DM and to clarify how biomarkers can be optimally utilized to guide therapy.

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APPENDIX For supplemental figures and table, please see the online version of this article.