Body mass index and cardiorenal outcomes in the EMPEROR-Preserved trial: Principal findings and meta-analysis with the DELIVER trial


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Received 20 October 2023; revised 13 March 2024; accepted 14 March 2024; online publish-ahead-of-print 1 April 2024

Aims
Both low and high body mass index (BMI) are associated with poor heart failure outcomes. Whether BMI modifies benefits of sodium–glucose cotransporter 2 inhibitors (SGLT2i) in heart failure with preserved ejection fraction (HFP EF) requires further investigation.

Methods and results
Using EMPEROR-Preserved data, the effects of empagliflozin versus placebo on the risks for the primary outcome (hospitalization for heart failure [HHF] or cardiovascular [CV] death), change in estimated glomerular filtration rate (eGFR) slopes, change in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), and secondary outcomes across baseline BMI categories (<25 kg/m², 25 to <30 kg/m², 30 to <35 kg/m², 35 to <40 kg/m², and ≥40 kg/m²) were examined, and a meta-analysis conducted with DELIVER. Forty-five percent had a BMI of ≥30 kg/m². For the primary outcome, there was a consistent treatment effect of empagliflozin versus placebo across the BMI categories with no formal interaction (p trend = 0.19) by BMI categories. There was also no difference in the effects on secondary outcomes including total HHF (p trend = 0.19), CV death (p trend = 0.20), or eGFR slope with slower declines with empagliflozin regardless of BMI (range 1.12–1.71 ml/min/1.73 m² relative to placebo, p trend = 0.85 for interaction), though there was no overall impact on the composite renal endpoint. The difference in weight change between empagliflozin and placebo was −0.59, −1.48, −1.54, −0.87, and −2.67 kg in the lowest weight change group.
BMI and cardiorenal outcomes in EMPEROR-Preserved

Conclusions

Empagliflozin treatment resulted in broadly consistent cardiac effects across the range of BMI in patients with HfPpEF. SGLT2i treatment yields benefit in patients with HfPpEF regardless of baseline BMI.

Graphical Abstract

Question: Does BMI modify the benefit of empagliflozin in HfPpEF in EMPEROR-Preserved?

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Wt Δ (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>-0.59</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>-1.48</td>
</tr>
<tr>
<td>30 to &lt;35</td>
<td>-1.54</td>
</tr>
<tr>
<td>35 to &lt;40</td>
<td>-0.87</td>
</tr>
<tr>
<td>≥40</td>
<td>-2.67</td>
</tr>
</tbody>
</table>

No BMI interactions with:

1° end-point (p=0.19)
Total HHF (p=0.19)
CV Death (p=0.20)
eGFR slope (p=0.85)
+ Trend towards greater KCCQ-CSS benefit at higher BMIs

Conclusion: SGLT2i treatment yields benefit in patients with HfPpEF regardless of baseline BMI

Introduction

Excess adiposity (overweight or obesity) is a risk factor for heart failure (HF), and represents a potentially distinct phenotype in HF with preserved ejection fraction (HfPpEF); of course, lower body mass index (BMI) levels also predict adverse outcomes in prevalent HF. Obesity (defined as BMI ≥30 kg/m²) is highly prevalent in trials of patients with HfPpEF (e.g. 45% in EMPEROR-Preserved,3 49% in PARAGON-HF,4 55% in TOPCAT,5 41% in I-PRESERVE6). With rising numbers of individuals living with excess adiposity (and HfPpEF),6 understanding the impact of baseline BMI on treatment outcomes in HfPpEF is important information. Since patients with HfPpEF with comorbid obesity have reported lower quality of life than those with normal BMI, the impact of therapies on these patient-reported outcomes for patients with higher BMI is of particular importance.7

Recently, DELIVER, investigating dapagliflozin versus placebo in patients with HF and left ventricular ejection fraction (LVEF) >40%, showed around 45% of patients with HfPpEF recruited had a BMI of 30 kg/m² or more at baseline.8 The authors reported that whilst there was no difference in the effect of dapagliflozin on outcomes by five different BMI categories, there were greater absolute
reductions in weight and increases in Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (TSS) in the highest BMI category group. Given this is the only trial to examine this important issue, we considered it important to test whether the benefits of empagliflozin in EMPEROR-Preserved varied by baseline BMI. Such work would usefully validate and extend relevant results reported in DELIVER. Of relevance to this study, at visit 1 more powerful aggregated result across two trials.

Methods

Study design

EMPEROR-Preserved was an international, phase III, double-blind, parallel-group, placebo-controlled trial that enrolled 5988 patients with symptomatic HF, an LVEF >40%, elevated natriuretic peptide levels and evidence of structural cardiac changes or documented prior hospitalization for HF (HHF). Patients were randomized to empagliflozin 10 mg daily or placebo. The design and results of this trial have been published previously. Of relevance to this study, at visit 1 (screening) BMI had to be <45 kg/m² and eGFR ≥20 ml/min/1.73 m². The trial was approved by the ethics committee at each study site, and all patients provided written informed consent.

Trial endpoints

The primary endpoint was the time to first HHF or cardiovascular (CV) death. The key secondary endpoints included first and recurrent HHFs and the rate of decline in the eGFR during double-blind treatment (eGFR slope). Other secondary endpoints included time to first HHF, CV death, and all-cause death and the change in KCCQ clinical summary score (CSS) from baseline to week 52. In addition, we analysed time to a first composite renal endpoint defined as time to first occurrence of (1) chronic dialysis; (2) renal transplantation; (3) sustained reduction of ≥40% in eGFR; or (4) sustained eGFR <15 ml/min/1.73 m² for patients with baseline eGFR ≥30 ml/min/1.73 m² or <10 ml/min/1.73 m² for patients with baseline eGFR <30 ml/min/1.73 m².

For the current analyses patients were categorized according to their BMI at baseline in the following categories: <25, 25 to <30, 30 to <35, 35 to <40, and ≥40 kg/m², according to the World Health Organization classification of obesity. We chose BMI 25 kg/m² as the lower cut-off and 40 kg/m² as the higher cut-off due to limited sample size below BMI 25 kg/m² and above 40 kg/m². These subgroups also permitted a pooled comparison of BMI groups for the primary endpoint in DELIVER which conducted relevant analyses in 6203 patients.

Statistical analyses

For time-to-first-event analyses, differences between the placebo and empagliflozin groups for the primary endpoint across the various BMI categories were assessed for statistical significance using a Cox proportional hazards model, with pre-specified covariates of age, gender, geographical region, diabetes status at baseline, LVEF, and eGFR at baseline. These analyses were performed according to the intention-to-treat principle for all randomized patients and included data up to the end of the planned treatment period. Event rates per 100 patient-years and adjusted hazard ratios are reported for each BMI category. For the analysis of total (first and repeated) events, between-group differences were assessed using a joint frailty model, with CV death as a competing risk. For the analysis of changes in eGFR, weight and KCCQ, treatment effects were assessed based on changes from baseline using a mixed model for repeated measures (MMRM) adjusting for the covariates age, gender, geographical region, diabetes status, LVEF and eGFR, and in addition for weight at baseline for weight changes, and KCCQ at baseline for KCCQ changes. Between-group differences in the slope of change during the treatment period in eGFR were analysed using a random intercept, random slope model in the treated set. The MMRM, the slope model and the joint frailty model included the same covariates as the Cox model. To assess the consistency of effects across subgroups, subgroup-by-treatment interaction terms were added in the models. Analyses for safety were performed including all the patients who had received at least one dose of empagliflozin or placebo. Fixed-effect meta-analysis (inverse variance method) was performed for each outcome and for individual subgroups to generate pooled estimates for the effect of sodium–glucose cotransporter 2 inhibitors (SGLT2i) compared with placebo. Hazard ratios and 95% confidence intervals were used. Between-trial heterogeneity of treatment effect was assessed using the I² index and Cochran’s Q-test. We tested treatment-by-subgroup heterogeneity of effect using Cochran’s Q-test. Meta-analysis calculations were done using STATA (version 17.0).

All analyses (except the meta-analysis) were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). All p-values reported are two-sided, and p < 0.05 was considered as statistically significant in all cases. No adjustments for multiple testing were made.

Results

Of the 5988 patients randomized, 1310 (21.9%) had BMI <25 kg/m², 1986 (33.2%) had BMI 25 to <30 kg/m², 1533 (25.9%) had BMI 30 to <35 kg/m², 771 (12.9%) had BMI 35 to <40 kg/m², and 368 (6.1%) had BMI ≥40 kg/m² at baseline. Thus, 45% were in the obese category at baseline.

Patients with higher BMIs were more likely to be younger, female, and White. Patients in higher BMI categories also tended to have worse New York Heart Association (NYHA) class, worse/lower KCCQ-CSS scores, higher rates of atrial fibrillation and diabetes mellitus, and higher LVEF and lower N-terminal pro-B-type natriuretic peptide concentrations (Table 1).

Empagliflozin consistently reduced the primary composite outcome of time to first HHF or CV death across baseline BMI categories, with no formal interaction (p trend = 0.19) (Figure 1). There were 148 patients with a baseline BMI <20 kg/m² and analyses of treatment effect on the primary endpoint by BMI as a continuous variable suggested consistent effects also in these lower ranges of BMI (data not shown). The effect of empagliflozin on eGFR slope was also consistent across BMI categories (p trend = 0.85; Figure 2), although there was no benefit on the composite renal endpoint, overall or in BMI subgroups (online
Table 1 Baseline characteristics by body mass index categories

<table>
<thead>
<tr>
<th>BMI category</th>
<th>&lt;25 kg/m² (n = 1130)</th>
<th>25 to &lt;30 kg/m² (n = 1986)</th>
<th>30 to &lt;35 kg/m² (n = 1553)</th>
<th>35 to &lt;40 kg/m² (n = 771)</th>
<th>≥40 kg/m² (n = 346)</th>
<th>p-value trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>73.5 ± 10.1</td>
<td>72.9 ± 9.1</td>
<td>71.4 ± 8.9</td>
<td>69.8 ± 8.8</td>
<td>67.0 ± 9.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.5 ± 1.93</td>
<td>27.52 ± 1.43</td>
<td>32.78 ± 1.44</td>
<td>37.20 ± 1.40</td>
<td>42.61 ± 1.46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>554 (42.3)</td>
<td>815 (41.0)</td>
<td>699 (45.0)</td>
<td>393 (31.0)</td>
<td>213 (38.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>722 (55.2)</td>
<td>1512 (76.1)</td>
<td>1307 (84.2)</td>
<td>684 (88.7)</td>
<td>316 (95.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White</td>
<td>52 (40)</td>
<td>68 (3.4)</td>
<td>79 (5.1)</td>
<td>34 (4.4)</td>
<td>25 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>447 (34.1)</td>
<td>272 (13.7)</td>
<td>81 (5.2)</td>
<td>18 (2.3)</td>
<td>6 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Other including mixed races</td>
<td>87 (6.6)</td>
<td>133 (6.7)</td>
<td>86 (5.5)</td>
<td>35 (4.5)</td>
<td>21 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td>1125 (85.9)</td>
<td>1689 (85.0)</td>
<td>1247 (80.3)</td>
<td>577 (74.8)</td>
<td>245 (66.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>II</td>
<td>178 (13.6)</td>
<td>293 (14.8)</td>
<td>303 (19.5)</td>
<td>189 (24.5)</td>
<td>130 (20.6)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>5 (0.4)</td>
<td>3 (0.2)</td>
<td>3 (0.2)</td>
<td>5 (0.6)</td>
<td>2 (0.5)</td>
<td></td>
</tr>
<tr>
<td>KCCQ-CSS</td>
<td>76.94 ± 19.35</td>
<td>72.56 ± 20.09</td>
<td>68.77 ± 20.27</td>
<td>62.60 ± 22.23</td>
<td>59.19 ± 23.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>KCCQ-CSS, median (IQR)</td>
<td>81.35 (64.58, 93.23)</td>
<td>76.04 (59.38, 89.58)</td>
<td>70.83 (54.17, 85.42)</td>
<td>64.38 (45.31, 80.89)</td>
<td>61.98 (41.15, 77.34)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>130.2 ± 15.9</td>
<td>131.3 ± 15.5</td>
<td>132.5 ± 15.3</td>
<td>133.2 ± 15.7</td>
<td>132.5 ± 15.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60.7 ± 9.4</td>
<td>75.7 ± 9.9</td>
<td>89.4 ± 11.9</td>
<td>102.2 ± 13.5</td>
<td>115.6 ± 16.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>54.2 ± 9.0</td>
<td>53.9 ± 8.9</td>
<td>54.3 ± 8.7</td>
<td>55.1 ± 8.3</td>
<td>55.5 ± 8.5</td>
<td>0.0030</td>
</tr>
<tr>
<td>NT-proBNP, pg/ml, median (IQR)</td>
<td>1170 (601, 2111)</td>
<td>993 (506, 1773)</td>
<td>898 (467, 1608)</td>
<td>900 (427, 1334)</td>
<td>784 (438, 1356)</td>
<td>&lt;0.0001 (based on log-transformed results)</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation unless stated otherwise.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
*Defined as atrial fibrillation in any electrocardiogram before treatment intake or history of atrial fibrillation reported in medical history.

Collectively, these data suggest that empagliflozin may be initiated (n = 5988) and DELIVER (n = 6203) trials thereby lending more power, revealed point estimates below one (thus favouring SGLT2i) for all five categories (Figure 5). There was a low degree of heterogeneity in the meta-analysed estimates by BMI category (I² = 26.0%, p = 0.248).

Discussion
In EMPEROR-Preserved, there was no significant interaction of BMI on the hazards of primary outcome of CV death or HFH, or on the secondary endpoints of total HHFs, CV death, first HFH, first renal composite, or all-cause death with empagliflozin versus placebo in patients with HFpEF. The robustness of this conclusion was also supported by a meta-analysis of the primary outcome data with the DELIVER trial. In addition, no effect modification of BMI on eGFR slope was noted, though the relevance of this remains uncertain given eGFR slopes can be confounded, and there was no benefit on the composite renal outcome. There were no new safety findings and no clear evidence of different safety concerns by BMI categories. Weight loss with empagliflozin was also very modest (mean ± 0.41 kg) in those in the lowest baseline BMI category. Collectively, these data suggest that empagliflozin may be initiated in patients with HFpEF irrespective of BMI (Graphical Abstract).
Consistent with prior research, we noted that patients with higher BMI and HFpEF were significantly younger and more likely to be female.9,10 In addition, patients with higher BMIs were also significantly more likely to have a higher NYHA class and significantly worse KCCQ score, findings similar to what has been reported elsewhere.9 Also, patients randomized to empagliflozin who were overweight or obese had statistically more weight loss than patients randomized to placebo. Such results lend external validity to these new observations. Though absolute differences in weight were modest at \( \sim 1.3 \) kg, any effort to help support weight loss is likely to be meaningful to patients. Our results also suggest that absolute amount of weight lost was greatest for those in higher BMI categories, where weight loss is most likely to provide clinical benefit, and lowest in the lower BMI categories.

Visually, greatest benefit across many of the outcomes appeared to be for those with either normal (lowest) BMI category or severe obesity, but this is fundamentally confounded by extremely varying sample sizes and uneven power. The insignificant interaction \( p \)-value observed for each of these outcomes should reassure both providers and patients that the benefits of empagliflozin are preserved across the spectrum of BMI. Furthermore, we find that this visual pattern is attenuated by the larger sample size achieved in a meta-analysis combining results from EMPEROR-Preserved with DELIVER across BMI category.

We did observe a trend toward larger improvements in KCCQ-CSS score with higher BMI at 32 weeks, with a \( p \)-value for trend = 0.080. These data are broadly consistent with the DELIVER data where a significant interaction (\( p = 0.03 \)) was noted at 8 months for a similar analysis with KCCQ-TSS.8 They also accord with a recent paper examining predictors of health status in EMPEROR-Preserved.11 Thus, it appears patients with higher BMIs likely derive a larger absolute benefit in terms of KCCQ improvement. Prior literature12 suggests patients living with both HFpEF and obesity and starting dapagliflozin experience meaningful improvements in KCCQ-CSS and KCCQ-TSS within 12 weeks: given the higher symptom burden experienced by those at higher BMIs, these observed improvements in KCCQ may be particularly relevant.
Figure 3 (A–E) Change from baseline in body weight by baseline body mass index (BMI) categories. Point estimates and 95% confidence intervals (CI) given at each time point as per the x-axis, as well as number of patients with data at each visit. Adjusted mean weight change in kg by treatment groups from baseline to week 52 (from lowest to highest BMI category) were as follows: 0.18 (P) and −0.41 (E), 0.29 (P) and −1.20 (E), −0.13 (P) and −1.67 (E), −1.50 (P) and −2.36 (E), −0.23 (P) and −2.90 (E). E, empagliflozin; P, placebo; SE, standard error.

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Figure 4 (A–E) Change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS) by baseline body mass index (BMI) categories. Point estimates and 95% confidence intervals (CI) given at each time point as per the x-axis, as well as number of patients with data at each visit. SE, standard error.
BMI and cardiorenal outcomes in EMPEROR-Preserved

Notably, in a meta-analysis of results across BMI category from both EMPEROR-Preserved and DELIVER, we find that the meta-analysed hazards of a composite of CV death or HHF is broadly consistent across BMI categories ($I^2 = 26.0\%, p = 0.248$; Figure 5). EMPEROR-Preserved also adds data on the consistent slowing of eGFR slopes across all BMI categories, though the relevance of this is uncertain given that there was no overall benefit on the first renal composite outcome in the trial, nor in subgroups. Even so, these BMI analyses in the two HfPcEF trials suggest patients with either BMI $<25$ kg/m$^2$ or $\geq 40$ kg/m$^2$ benefit from SGLT2i just as well as do patients with BMI between these limits, with some evidence for greater absolute symptomatic benefits at higher BMI levels. This latter finding is interesting given recent notable symptomatic (KCCQ) benefits seen with semaglutide in the STEP-HfPcEF trial$^{13}$ where mean weight loss levels at 10.7% relative to placebo were greater than seen with SGLT2i in DELIVER or EMPEROR-Preserved, speculatively suggesting complementary mechanisms of action.

There are limitations to our analysis. EMPEROR-Preserved excluded patients with a BMI of $\geq 45$ kg/m$^2$, limiting any evaluation of more extreme degrees of obesity. Similarly, very few underweight (BMI $<18.5$ kg/m$^2$) were enrolled. Perhaps most importantly, BMI is an incomplete measure of body composition, and our analysis may therefore not capture the true impact of increasing degrees of adiposity on outcomes in this patient population. Nevertheless, BMI remains the most clinically used measure and as such these results do have clinical translation.

In conclusion, these data from EMPEROR-Preserved suggest that the SGLT2i empagliflozin is safe and effective across the

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**Figure 5** Meta-analysis of the primary outcome in EMPEROR-Preserved and DELIVER by baseline body mass index (BMI) categories. Point estimates and 95% confidence intervals (CI) with the meta-analysed estimate in the blue diamond. Subgroup interaction $p = 0.25$. HR, hazard ratio; SGLT2i, sodium–glucose cotransporter 2 inhibitor.
**Supplementary Information**

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

**Acknowledgements**

The authors thank Liz Coyle, University of Glasgow, for her excellent assistance in the preparation of this article.

**Funding**

The EMPEROR-Preserved trial (ClinicalTrials.gov: NCT03057951) was funded by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance. Graphical support was provided by 7.4 Limited and Elevate Scientific Solutions and supported financially by Boehringer Ingelheim. N.S. acknowledges funding support from the British Heart Foundation Research Excellence Award (RE/18/6/34217). The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version.

**Conflict of interest:** N.S. reports personal fees from Abbott Laboratories, Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Haini Pharmaceuticals, Janssen, Menarini-Ricerche, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and Sanofi; and grants to his university from AstraZeneca, Boehringer Ingelheim, Novartis and Roche Diagnostics. J.B. reports consulting fees from Boehringer Ingelheim, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivanaNova, Luipoldt, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave Ltd.; and Vifor. M.M.L. reports grants to his university from AstraZeneca, Boehringer Ingelheim and Roche Diagnostics; and committee member contributions in trials sponsored by Bayer and Cytokinetics. J.H. completed work for this while on T32 grant T32HL067949. A.S. is supported by CIHR grant # 451301, Fonds de Recherche Santé Quebec (FRSQ) Junior 1 clinician scholars program, Roche Diagnostics, Boehringer Ingelheim, Novartis, AstraZeneca, Novo Nordisk, Boston Scientific, BMS-Pfizer, Akcea, Janssen, Takeda, AREA19 (as advisor). F.Z. reports steering committee or advisory board fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cardior, CVRx, Janssen, LivianaNova, Merck, Mundipharma, Novartis, Novo Nordisk, and Vifor Fresenius. G.F. reports lecture fees and/or committee member contributions in trials sponsored by Bayer, Medtronic, Vifor, Servier, Novartis, Amgen, and Boehringer Ingelheim; and research support from the European Union. S.V. holds a Tier 1 Canada Research Chair in Cardiovascular Surgery; and reports receiving research grants and/or speaking honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Canadian Medical and Surgical Knowledge Translation Research Group, Eli Lilly, HLS Therapeutics, Janssen, Novartis, Novo Nordisk, Pfizer, PhaseBio, S & L Solutions Event Management Inc, and Sanofi; is the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. J.L.J. is a Trustee of the American College of Cardiology, is a Director at Imbria Pharmaceuticals, an Advisor at Jana Care; has received grant support from Abbott, Applied Therapeutics, HeartFlow Inc, Innolife and Roche Diagnostics, consulting income from Abbott, Janssen, Novartis, Merck, and Roche Diagnostics, and participates in clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Bayer, CVRx, Intercept, Pfizer and Takeda. J.P.F. reports consulting fees from Boehringer Ingelheim; and is a Trial Executive Committee member of the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). S.J.P. reports consulting fees and payment or honoraria for lectures, presentations, speakers’ bureaus, manuscript writing, or educational events from Boehringer Ingelheim; and is a Trial Executive Committee member of Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). E.P., A.P.O., and M.B. are employees of Boehringer Ingelheim. M.P. reports consulting fees from Abbvie, Actavis, Amgen, Amarin, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Casana, CSL Behring, Cytokinetics, Johnson & Johnson, ELC, Moderna, Novartis, ParatusRx, Pfizer, Relypsa, Salamandra, Synthetic Biologics, and Theravance; and is a Trial Executive Committee member of the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). S.D.A. reports grants and personal fees from Vifor and Abbott Vascular, and personal fees for consultations, trial committee work and/or lectures from Actimed, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bioventrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Cytokinetics, Edwards, Farraday Pharmaceuticals, GSK, HeartKinetics, Impulse Dynamics, Novartis, Oclutech, Pfizer, Repairon, Sensible Medical, Servier, Vectorious, and V-Wave; named co-inventor of two patent applications regarding MR-proANP (DE 20100710834 & DE 20100722367); but he does not benefit personally from the related issued patents.

**References**


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