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Risk Factors for Heart Failure in Patients With Type 2 Diabetes Mellitus and Stage 4 Chronic Kidney Disease Treated With Bardoxolone Methyl

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ABSTRACT

Background: A phase 3 randomized clinical trial was designed to test whether bardoxolone methyl, a nuclear factor erythroid-2—related factor 2 (Nrf2) activator, slows progression to end-stage renal disease in patients with stage 4 chronic kidney disease and type 2 diabetes mellitus. The trial was terminated because of an increase in heart failure in the bardoxolone methyl group; many of the events were clinically associated with fluid retention.

Methods and Results: We randomized 2,185 patients with type 2 diabetes mellitus (T2DM) and stage 4 chronic kidney disease (CKD) (estimated glomerular filtration rate 15 to $30 \text{ mL min}^{-1} \text{ m}^{-2}$) to once-daily bardoxolone methyl (20 mg) or placebo. We used classification and regression tree analysis to identify baseline factors predictive of heart failure or fluid overload events. Elevated baseline B-type natriuretic peptide and previous hospitalization for heart failure were identified as predictors of heart failure events; bardoxolone methyl increased the risk of heart failure by 60% in patients with these risk factors. For patients without these baseline characteristics, the risk for heart failure events among bardoxolone methyl—and placebo-treated patients was similar (2%). The same risk factors were also identified as predictors of fluid overload and appeared to be related to other serious adverse events.

Conclusions: Bardoxolone methyl contributed to events related to heart failure and/or fluid overload in a subpopulation of susceptible patients with an increased risk for heart failure at baseline. Careful selection of participants and vigilant monitoring of the study drug will be required in any future trials of bardoxolone methyl to mitigate the risk of heart failure and other serious adverse events. (J Cardiac Fail 2014;20:953–958)

Key Words: Bardoxolone methyl, B-type natriuretic peptide, chronic kidney disease, randomized controlled trial.

Bardoxolone methyl and its analogues are oleanolic acid–derived synthetic triterpenoid compounds that potently induce the nuclear factor erythroid-2—related factor 2 (Nrf2)—Keap1 pathway.1,2 Through interaction with the Nrf2 repressor molecule, Keap1, bardoxolone methyl promotes translocation of Nrf2 to the nucleus, where it binds to antioxidant response elements in the promoter region of its target genes, leading to induction of many antioxidant and cytoprotective enzymes and related proteins.3 Bardoxolone methyl is also a potent inhibitor of the nuclear factor κB inflammatory pathway through both direct (ie, inhibition of IKKβ kinase activity) and indirect (ie, detoxification of reactive oxygen species) mechanisms.3 Because of this dual mechanism of action, bardoxolone methyl is hypothesized to have therapeutic potential in a variety of disease settings involving oxidative stress and inflammation.
Preclinical studies have shown that bardoxolone methyl and close analogues have activity in animal models of kidney disease, including amelioration of murine ischemic acute kidney injury, attenuation of renal interstitial inflammation and fibrosis in mice with proteinuria induced by protein overload, and protection against fibrosis in a 5/6 nephrectomy model of chronic kidney disease (CKD). Several phase 2 clinical trials have demonstrated that bardoxolone methyl lowers serum creatinine concentration, along with other markers of kidney function (eg, urea nitrogen, uric acid). A phase 2, double-blind, randomized, placebo-controlled trial enrolling patients with type 2 diabetes mellitus (T2DM) and mild to moderate CKD showed these effects to be sustained for 52 weeks.

On the basis of these data, we initiated a multinational, randomized, double-blind, placebo-controlled phase 3 outcomes trial in patients with T2DM and stage 4 CKD: Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes: The Occurrence of Renal Events (BEACON).

The BEACON trial was terminated for safety concerns; the primary reason for study termination was an excess in heart failure events, many occurring soon after bardoxolone methyl treatment was started. We conducted a series of post hoc analyses attempting to identify risk factors for heart failure and fluid overload in the BEACON population.

Materials and Methods

Previous publications have described the BEACON trial design, patient demographics, and baseline characteristics. Briefly, 2,185 patients with T2DM and stage 4 CKD were randomized 1:1 to once-daily administration of bardoxolone methyl (20 mg) or placebo. The primary efficacy outcome was the time to first event in the composite outcome defined as end-stage renal disease (ESRD; need for chronic dialysis, renal transplantation, or renal death) or cardiovascular death. The study had 3 secondary efficacy outcomes: 1) change in estimated glomerular filtration rate; 2) time-to-first hospitalization for heart failure or death due to heart failure; and 3) time to first event in the composite outcome consisting of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or cardiovascular death.

An independent Events Adjudication Committee (EAC), blinded to study treatment assignment, evaluated whether ESRD events, cardiovascular events, strokes, and fatalities met prespecified definitions of primary and secondary end points, as described in the EAC charter. The study (ClinicalTrials.gov identifier NCT01351675) was approved by Institutional Review Boards at participating study sites and was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

We used classification and regression tree (CART) analysis to identify baseline factors predictive of adjudicated hospitalization or death due to heart failure. We selected CART as the method of choice because we did not want to limit the form of interaction terms to those easily defined by logistic or similar regression models. We constructed separate classification trees for patients randomized to the placebo and bardoxolone methyl groups. We evaluated the following baseline characteristics as potential risk factors: urine albumin-to-creatinine ratio, serum creatinine, B-type natriuretic peptide (BNP), age, prescription of inhibitors of the renin-angiotensin-aldosterone system, and previous hospitalization for heart failure. We used a 10-fold cross-validation testing method and Gini splitting rule in tree development and selected the best tree on the basis of minimum cost, regardless of tree size and complexity. We handled missing values of BNP by substituting surrogate splitters.

In reviewing heart failure case reports (eg, hospital admission notes) we observed that evidence of fluid overload often preceded heart failure events. Because some fluid overload events might have progressed to heart failure, we viewed fluid overload events as potential predictors of a patient’s being hospitalized for heart failure. Therefore, we also performed CART analyses to explore baseline factors predictive of EAC-adjudicated heart failure events or potential fluid overload events. The latter were not EAC confirmed.

Fluid overload events were not collected on specific case report forms; rather, they were collected on the general adverse event forms. We identified preferred terms potentially related to fluid overload with the use of terms in the standardized MedDRA (v15.1) query (SMQ) of “cardiac failure” and several other key words (detailed in the Appendix). From this list of potential fluid overload events, we determined which preferred terms were most likely to lead to an EAC-confirmed heart failure event by calculating the probability that a patient would report an identified preferred term as a serious adverse event that started after the 1st dose of study drug and that preceded or occurred on the same day as an EAC-confirmed heart failure event (Table 2). To assess the sensitivity and specificity of the preferred terms used to define fluid overload, we generated 4 definitions that included preferred terms with probabilities reported of ≥80%, ≥70%, ≥50%, and ≥30% of being followed by an EAC-confirmed heart failure event. We used the 80% cutoff to maximize specificity and therefore considered patients to have had a fluid overload event if they reported a preferred term in the 80% fluid overload definition as a post-treatment adverse event (serious or nonserious). For example, 5 of the 6 patients (83%) who reported a serious adverse event of acute pulmonary edema also reported an EAC-confirmed heart failure event that started after or before the serious adverse event; however, in our analyses we consider all 9 patients who reported acute pulmonary edema (serious or nonserious) to have had a fluid overload event.

We also used logistic regression as another method for identifying risk factors. This approach led to the same risk factors identified by CART; however, diagnostics showed that the models were poor fits to the data, probably because they were unable to capture the nature of the interaction among the risk factors.

We used the software package CART v7 (Salford Systems, San Diego, California) to perform the analyses and SAS v9.2 to perform logistic regression.

Results

Overview of BEACON Results

An increase in heart failure events was the major finding that led to the termination of BEACON: 96/1,088 patients (8.8%) randomized to bardoxolone methyl versus 55/1,097 patients (5.0%) randomized to placebo, corresponding to a hazard ratio (HR) of 1.83 (95% confidence interval
Table 1. Primary and Secondary Outcomes and All-Cause Mortality for Bardoxolone Methyl (BARD) Versus Placebo (PBO) Patients in BEACON Stratified by Baseline BNP Level and Earlier Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>Event</th>
<th>All Patients</th>
<th>PBO (n = 1,097)</th>
<th>BARD (n = 1,088)</th>
<th>BNP ≤200 pg/mL, No Previous HF Hospitalization</th>
<th>PBO (n = 557)</th>
<th>BARD (n = 519)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite*</td>
<td></td>
<td>69 (6)</td>
<td>69 (6)</td>
<td>25 (5)</td>
<td>15 (3)</td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td></td>
<td>51 (5)</td>
<td>43 (4)</td>
<td>20 (4)</td>
<td>8 (2)</td>
<td></td>
</tr>
<tr>
<td>Any cardiovascular death</td>
<td></td>
<td>19 (2)</td>
<td>27 (2)</td>
<td>6 (1)</td>
<td>7 (1)</td>
<td></td>
</tr>
<tr>
<td>Secondary composite†</td>
<td></td>
<td>86 (8)</td>
<td>139 (13)</td>
<td>23 (4)</td>
<td>27 (5)</td>
<td></td>
</tr>
<tr>
<td>Heart failure†</td>
<td></td>
<td>55 (5)</td>
<td>96 (9)</td>
<td>10 (2)</td>
<td>12 (2)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td></td>
<td>16 (1)</td>
<td>19 (2)</td>
<td>6 (1)</td>
<td>6 (1)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td></td>
<td>11 (1)</td>
<td>14 (1)</td>
<td>5 (1)</td>
<td>2 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>All-cause death†</td>
<td></td>
<td>31 (3)</td>
<td>44 (4)</td>
<td>8 (1)</td>
<td>11 (2)</td>
<td></td>
</tr>
</tbody>
</table>

Serious adverse events by primary system organ class†

- **Blood and lymphatic system disorders**: 11 (1) vs 20 (2) vs 3 (1) vs 6 (1)
- **Cardiac disorders**: 84 (8) vs 124 (11) vs 25 (4) vs 36 (2)
- **Ear and labyrinth disorders**: 1 (<1) vs 3 (<1) vs 1 (<1) vs 1 (<1)
- **Eye disorders**: 2 (<1) vs 3 (<1) vs 1 (<1) vs 1 (<1)
- **Gastrointestinal disorders**: 39 (4) vs 46 (4) vs 22 (4) vs 17 (3)
- **General disorders and administration site conditions**: 20 (2) vs 29 (3) vs 6 (1) vs 5 (1)
- **Hepatobiliary disorders**: 8 (1) vs 4 (<1) vs 0 vs 1 (<1)
- **Immune system disorders**: 0 vs 2 (<1) vs 0 vs 0
- **Infections and infestations**: 63 (6) vs 79 (7) vs 29 (5) vs 22 (4)
- **Injury, poisoning, and procedural complications**: 17 (2) vs 19 (2) vs 2 (<1) vs 6 (1)
- **Investigations**: 2 (<1) vs 3 (<1) vs 1 (<1) vs 1 (<1)
- **Metabolism and nutrition disorders**: 42 (4) vs 51 (5) vs 18 (3) vs 12 (2)
- **Musculoskeletal and connective tissue disorders**: 13 (1) vs 21 (2) vs 7 (1) vs 12 (2)
- **Neoplasms benign, malignant and unspecified**: 10 (1) vs 11 (1) vs 5 (1) vs 3 (1)
- **Nervous system disorders**: 35 (3) vs 37 (3) vs 19 (3) vs 10 (2)
- **Psychiatric disorders**: 3 (<1) vs 5 (<1) vs 2 (<1) vs 2 (<1)
- **Renal and urinary disorders**: 71 (6) vs 52 (5) vs 27 (5) vs 11 (2)
- **Reproductive system and breast disorders**: 3 (<1) vs 2 (<1) vs 2 (<1) vs 0
- **Respiratory, thoracic, and mediastinal disorders**: 32 (3) vs 43 (4) vs 13 (2) vs 12 (2)
- **Skin and subcutaneous tissue disorders**: 1 (<1) vs 4 (<1) vs 0 vs 3 (1)
- **Surgical and medical procedures**: 0 vs 2 (<1) vs 0 vs 1 (<1)
- **Vascular disorders**: 18 (2) vs 20 (2) vs 10 (2) vs 8 (2)

Observed totals for number (%) of patients (intention-to-treat population) with Events Adjudication Committee—confirmed primary or secondary events and serious adverse events occurring through the study drug termination date (October 18, 2012).

*Number of patients with a primary event (time to first event in the composite end point of end-stage renal disease or cardiovascular death).
†Number of patients with a secondary event (time to first event in the composite end point of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or cardiovascular death).

Includes hospitalizations or deaths due to heart failure.

/3 Total events include only serious adverse events (SAEs) with onset dates ≤30 days after a patient’s last dose of the study drug. Patients with multiple SAEs are represented only once within each primary system organ class.

[CI] 1.32–2.55). The excess in heart failure events observed in the bardoxolone methyl group occurred within the 1st 4 weeks after randomization. After this initial period, the Kaplan-Meier time-to-event curves for both treatment groups remained roughly parallel.

From randomization to the end of follow-up, 44 patients (4.0%) in the bardoxolone methyl group and 31 (2.8%) in the placebo group died (HR 1.47, 95% CI 0.93–2.32; P = .11). Approximately two-thirds of the deaths (49 of 75 deaths) were cardiovascular in nature (29 bardoxolone methyl versus 20 placebo; HR 1.44, 95% CI 0.80–2.59; P = .23). Of the 49 cardiovascular deaths, the EAC classified 5 deaths in the bardoxolone methyl group and 1 in the placebo group as due to heart failure.

Risk Factors Associated With Adjudicated Heart Failure and Fluid Overload Events

Baseline BNP and previous hospitalization for heart failure were identified as the only baseline factors associated with EAC-confirmed heart failure events in bardoxolone methyl— and placebo-treated patients. Among patients with previous hospitalization for heart failure or BNP > ~200 pg/mL, treatment with bardoxolone methyl increased the risk of heart failure by 60% (Fig. 1). Conversely, among patients with no previous heart failure hospitalizations or a baseline BNP level < ~200 pg/mL, the risk of heart failure was relatively low and similar (2.0%) in the bardoxolone methyl and placebo groups.
Consistently with these findings, CART analyses that included a composite of heart failure and fluid overload events also identified elevated baseline BNP and previous hospitalization for heart failure as predictors. More specifically, for patients who had previous hospitalizations for heart failure or a BNP level $\leq 200$ pg/mL, treatment with bardoxolone methyl increased the risk of heart failure or fluid overload by 50% (Fig. 2).

Post hoc exclusion of patients with these risk factors yielded a population (519 bardoxolone methyl and 557 placebo patients) in which there would have been little difference between treatment groups for serious adverse events and adjudicated primary and secondary end point events (Table 1).

To investigate whether exposure to bardoxolone methyl was associated with heart failure events, we used a pharmacokinetic model based on several earlier studies conducted with bardoxolone methyl. We obtained population pharmacokinetic sampling in 995/1,088 (91%) bardoxolone methyl treated patients. No significant difference in exposure (based on serum concentrations of bardoxolone methyl) was noted in patients who experienced heart failure and those who did not (Fig. 3; $P = .12$).

### Table 2. Fluid Overload Serious Adverse Events (SAEs) That Are Potentially Predictive of Heart Failure (HF) Events

<table>
<thead>
<tr>
<th>Investigator-Reported Events Classified by MedDRA Preferred Term</th>
<th>Patients (n = 2,185) Reporting SAEs, n (%)</th>
<th>Proportion Whose Event Preceded or Occurred on day of EAC HF, *n/N (%)</th>
<th>Patients (n = 2,185) Reporting Event (SAE or Non-SAE), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricular failure $\dagger$</td>
<td>2 2 (&lt;1)</td>
<td>2/2 (100)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Cardiogenic shock $\dagger$</td>
<td>1 1 (&lt;1)</td>
<td>1/1 (100)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Cardiomegaly $\dagger$</td>
<td>1 1 (&lt;1)</td>
<td>1/1 (100)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Hypervolemia $\dagger$</td>
<td>1 1 (&lt;1)</td>
<td>1/1 (100)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Left ventricular failure $\dagger$</td>
<td>1 1 (&lt;1)</td>
<td>1/1 (100)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Cardiac failure congestive $\dagger$</td>
<td>128 99 (5)</td>
<td>85/99 (86)</td>
<td>139 (6)</td>
</tr>
<tr>
<td>Acute pulmonary edema $\dagger$</td>
<td>6 6 (&lt;1)</td>
<td>5/6 (83)</td>
<td>9 (&lt;1)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>15 13 (1)</td>
<td>10/13 (77)</td>
<td>18 (1)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>13 11 (1)</td>
<td>8/11 (73)</td>
<td>406 (19)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>8 8 (&lt;1)</td>
<td>5/8 (63)</td>
<td>19 (1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21 20 (1)</td>
<td>12/20 (60)</td>
<td>220 (10)</td>
</tr>
<tr>
<td>Cardiac failure chronic</td>
<td>5 5 (&lt;1)</td>
<td>3/5 (60)</td>
<td>6 (&lt;1)</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>16 14 (1)</td>
<td>8/14 (57)</td>
<td>48 (2)</td>
</tr>
<tr>
<td>Cardiac failure acute</td>
<td>2 2 (&lt;1)</td>
<td>1/2 (50)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>2 2 (&lt;1)</td>
<td>1/2 (50)</td>
<td>7 (&lt;1)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>2 2 (&lt;1)</td>
<td>1/2 (50)</td>
<td>6 (&lt;1)</td>
</tr>
<tr>
<td>Generalized edema</td>
<td>4 3 (&lt;1)</td>
<td>1/3 (33)</td>
<td>21 (1)</td>
</tr>
<tr>
<td>Pneumonia (not known to be infectious)</td>
<td>39 35 (2)</td>
<td>10/35 (29)</td>
<td>68 (3)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>7 6 (&lt;1)</td>
<td>1/6 (17)</td>
<td>18 (1)</td>
</tr>
<tr>
<td>Angioedema</td>
<td>4 4 (&lt;1)</td>
<td>0/4</td>
<td>6 (&lt;1)</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>1 1 (&lt;1)</td>
<td>0/1</td>
<td>6 (&lt;1)</td>
</tr>
<tr>
<td>Lobar pneumonia</td>
<td>1 1 (&lt;1)</td>
<td>0/1</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Pulmonary congestion</td>
<td>1 1 (&lt;1)</td>
<td>0/1</td>
<td>13 (1)</td>
</tr>
<tr>
<td>Scan myocardial perfusion abnormal</td>
<td>1 1 (&lt;1)</td>
<td>0/1</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

EAC, Events Adjudication Committee—confirmed.

*Proportion of patients whose fluid overload event preceded or occurred on the same day as an Events Adjudication Committee—confirmed heart failure event out of the total number of patients reporting the fluid overload event.

$\dagger$Included in the 80% cutoff fluid overload definition.

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**Fig. 1.** Classification tree for heart failure (HF) events in the BEACON trial. Analyses include only hospitalizations or deaths due to HF that were confirmed by the Event Adjudication Committee (EAC). Classification trees were constructed for all randomized patients receiving bardoxolone methyl (left) or placebo (right) and used the following baseline characteristics as potential risk factors: randomized treatment assignment, baseline urine albumin-to-creatinine ratio, 1/serum creatinine, B-type natriuretic peptide (BNP), age, concomitant angiotensin-converting enzyme or angiotensin receptor blocker use, and previous hospitalization for HF.
Discussion

The phase 3 randomized placebo-controlled trial of bardoxolone methyl in patients with T2DM and stage 4 CKD showed a significantly increased risk of heart failure events. No increased risk of heart failure or fluid retention with bardoxolone methyl had been observed in previous phase 1 and phase 2 trials, but those trials were much smaller than BEACON. Moreover, whereas most of the patients in previous trials had stage 3 CKD, BEACON limited enrollment to patients with T2DM and stage 4 CKD, a population known to be at higher risk for cardiovascular events.

Two major risk factors were shown to predict heart failure events in BEACON: baseline BNP > 200 pg/mL and previous hospitalization for heart failure, both recognized risk factors for heart failure hospitalization and death in other populations. BNP had not been assessed in any previous trial conducted with bardoxolone methyl. CART analyses that included a composite of heart failure and fluid overload events identified the same risk factors. These results suggest that bardoxolone methyl increased the risk of heart failure principally in an identifiable subpopulation of patients.

Area under the receiver operating characteristic curve concentrations of bardoxolone methyl did not distinguish bardoxolone methyl-treated patients who experienced heart failure from those who did not, suggesting that the dose, formulation, and frequency of administration did not materially contribute to the observed increase in risk. Additionally, in the BEACON substudy, bardoxolone methyl—treated patients had a meaningful reduction in urine volume and sodium excretion at week 4 relative to baseline, and preclinical studies had demonstrated that bardoxolone methyl modulates endothelin expression in the kidneys. These data suggest that through modulation of the endothelin pathway, bardoxolone methyl may pharmacologically promote acute sodium and volume retention. Thus, retention of fluid from bardoxolone methyl treatment may have translated to frank fluid overload and heart failure in susceptible patients with recognized risk factors at baseline. Notably, in patients without these baseline risk factors for heart failure, bardoxolone methyl did not increase the occurrence of heart failure or fluid overload compared with placebo.

Although the primary intention of the analyses was to identify risk factors associated with heart failure and fluid overload, these same risk factors may have contributed to other safety-related imbalances observed in BEACON. Events such as lower respiratory tract infection, edema, and anemia can be associated with (or mistaken for) fluid overload and heart failure. Whether these findings reflect...
the uncertainties associated with adverse event reporting (noncardiovascular, renal, or neurologic events that were not adjudicated) or a true susceptibility to other adverse outcomes is unknown. Although patients with normal or near normal BNP and no history of heart failure did not experience an increased risk of adverse events, these characteristics are common in patients with T2DM and stage 4 CKD. Had we excluded patients on the basis of either of these characteristics, the BEACON population would have been reduced by roughly one-half.

The CART and pharmacokinetic analyses presented here cannot fully explain the findings observed in BEACON. Nevertheless, post—clinical trial “forensics” can help us design better, smarter clinical trials in the future. Any future trials of bardoxolone methyl in other patient populations will require careful selection of study patients to mitigate the risk of heart failure and other serious adverse events.

Disclosures

G.L.B. was a member of the BEACON Steering Committee and is a consultant for Abbvie and Reata. G.M.C. was the chair of the BEACON Steering Committee and has received research support from Reata. D.d.Z. was the chair of the BEACON Steering Committee and is a consultant for and has received honoraria from Abbvie and Reata. P.A.M. was the chair of the BEACON Independent Data Monitoring Committee and is a consultant for Reata. J.J.M. was a member of the BEACON Steering Committee and is a consultant for and has received honoraria from Reata. Her company, Statistics Collaborative, served as the statistical group for the BEACON study. D.W. is employed by Statistics Collaborative. M.P.C., A.G., and C.J.M. are employed by and have a financial interest in Reata. P.G.L. is employed by and has a financial interest in Abbvie.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cardfail.2014.10.001

References


