Long-term Benefit of High-Density Lipoprotein Cholesterol–Raising Therapy With Bezafibrate

16-Year Mortality Follow-up of the Bezafibrate Infarction Prevention Trial

Ilan Goldenberg, MD; Valentina Boyko, MA; Alexander Tennenbaum, MD, PhD; David Tanne, MD; Solomon Behar, MD; Victor Guetta, MD

Background: Major randomized trials of fibrate therapy demonstrate an inverse relationship between on-treatment high-density lipoprotein cholesterol (HDL-C) increments and clinical outcome. We hypothesized that the degree of HDL-C response to bezafibrate is independently associated with subsequent long-term mortality.

Methods: The risk of death at 16 years of follow-up among 3026 patients with coronary heart disease allocated to the original bezafibrate (n=1509) and placebo (n=1517) arms of the Bezafibrate Infarction Prevention (BIP) trial was related to HDL-C response to bezafibrate therapy, categorized as upper-tertile (>8 mg/dL) or lower-tertile (≤8 mg/dL) on-treatment HDL-C change.

Results: Multivariate analysis demonstrated that patients allocated to bezafibrate therapy experienced a significant 11% reduction (P=.06) in the risk of long-term mortality compared with placebo-allocated patients. Mortality reduction among bezafibrate-allocated patients was related to a significant 22% (P=.008) reduction in the risk of death in patients with an upper-tertile HDL-C response to therapy, whereas among patients with a lower HDL-C response, the risk of death was similar to that of the placebo group (hazard ratio, 0.95; P=.43). Accordingly, the cumulative probability of death at 16 years was significantly lower among bezafibrate-allocated patients with an upper-tertile HDL-C response (32.1%) compared with the placebo group (37.9%; P=.02), whereas patients with a lower HDL-C response to treatment displayed a mortality rate (36.8%) similar to the placebo group (P=.57).

Conclusion: Our findings suggest that HDL-C level-raising therapy with bezafibrate is associated with long-term mortality reduction that may be related to the degree of HDL-C response to treatment.

Arch Intern Med. 2009;169(5):508-514

Previous studies have consistently identified an inverse correlation between high-density lipoprotein cholesterol (HDL-C) levels and cardiovascular risk among patients with normal or elevated low-density lipoprotein cholesterol (LDL-C) levels. Accordingly, the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATP III) guidelines indicate that a low HDL-C level is an important determinant of the Framingham risk score and should be regarded as a major risk factor for coronary heart disease (CHD). Despite these recommendations, however, recent data demonstrate that low HDL-C levels occur in a substantial proportion of patients with CHD who are currently treated with statin therapy and lifestyle modification.

The Bezafibrate Infarction Prevention (BIP) trial was designed to assess the effect of raising HDL-C levels and reducing triglyceride levels on cardiac risk in patients with established CHD who exhibited total serum cholesterol in the normal or slightly elevated range. Treatment with bezafibrate in the BIP trial was associated with a reduction in the rate of nonfatal myocardial infarction (MI). However, mortality rates in the 2 treatment groups were similar, resulting in a relatively small and statistically nonsignificant reduction in the combined end point comprising fatal and nonfatal cardiac events during the original course of the trial. Notably, post hoc extended analyses of the BIP trial demonstrated enhanced benefit of the study medication 2 years after trial closure and more pronounced reduction in the risk of cardiac death during this time period among patients who exhibited upper-tertile HDL-C response to bezafibrate (>8-mg/dL increase). (To convert HDL-C to millimoles per liter, multiply by 0.0259.)
We have recently acquired 16-year mortality records for all participants in the BIP trial. These data were assessed in the current study. We hypothesized that (1) the reduction in nonfatal MI among bezafibrate-allocated patients during the original course of the trial would translate into a more meaningful effect on subsequent long-term mortality and (2) the degree of HDL-C and triglyceride modification with the study medication is independently associated with long-term survival.

METHODS

STUDY PATIENTS

The BIP trial was a multicenter, prospective, randomized trial that studied the effect of bezafibrate therapy on major coronary events and mortality in patients with CHD. Details of the study design have been published. Briefly, 3122 male and female patients 45 to 74 years of age with a history of MI and/or angina and a lipid profile of serum total cholesterol level of 180 to 250 mg/dL, a low-density lipoprotein cholesterol (LDL-C) level 180 mg/dL or lower (≥160 mg/dL for patients <50 years), an HDL-C level of 45 mg/dL or lower, and a triglyceride level of 300 mg/dL or lower were randomized to bezafibrate, 400 mg/d, or placebo. (To convert LDL-C and total cholesterol to milligrams per liter, multiply by 0.0113.) Of the 3122 randomized patients, 32 patients did not commence study medication, and information on changes in serum HDL-C levels during follow-up was unavailable for 64 patients. These 96 patients were equally distributed between the placebo and bezafibrate treatment groups and were excluded from the present study. Thus, the current study comprises 3026 patients. The median follow-up period of the original double-blind phase of the study was 6.2 years (interquartile range [IQR], 5.3-6.8 years). After discontinuation of study medication, patients were observed for medical therapies and cardiac events for an additional mean of 2 years. For the current study, long-term mortality data for all participants in the BIP trial. These data were assessed using a log-rank test. Multivariate analysis of mortality as a function of (1) the total bezafibrate treatment group, (2) the LDL-C response subgroups, and (3) the triglyceride response subgroups, compared with the placebo group, was performed using Cox proportional hazards regression models. A test based on a defined time-dependent covariate was used for assessing the proportionality of hazards. The following covariates were included in each model: age; sex; smoking status (present or past smokers compared with never smokers); New York Heart Association functional class of II or higher; angina pectoris functional class of II or higher (according to the Canadian Cardiovascular Society Classification System); history of diabetes mellitus, MI, cerebrovascular accident, chronic obstructive pulmonary disease, or hypertension; the presence of peripheral vascular disease; systolic blood pressure; body mass index (BMI; calculated as weight in kilograms divided by height in meters squared); heart rate; and baseline total cholesterol, HDL-C, and triglyceride levels. The effect of nonfatal MI during the original course of the trial (in-trial nonfatal MI) on the risk of long-term mortality was evaluated in a time-dependent manner.

In a secondary analysis, the long-term benefit of bezafibrate therapy was also assessed within prespecified subgroups, stratified by the presence or absence of diabetes mellitus, triglyceride levels of 200 mg/dL or higher, BMI higher than 27, and by sex. In these analyses, the prespecified covariate × treatment interaction term was included in the multivariate model.

We used SAS statistical software (version 8.12; SAS Institute Inc, Cary, North Carolina) for the analyses. A 2-sided P = .05 significance level was used for hypothesis testing.

LABORATORY ASSESSMENT

Lipids were measured in fasting serum obtained at randomization, at 4 months, and annually thereafter until the end of the double-blind phase of the study. Laboratory measurements were performed using standard automated procedures with commercially available kits (Roche Diagnostics, Indianapolis, Indiana). Levels of HDL-C were measured by precipitation, and LDL-C was estimated using the equation of Friedewald et al. Changes in laboratory parameters were calculated as the difference between the baseline value (measured before administration of the study medication) and the mean of all values measured during the study in the annual laboratory examinations.

CATEGORIZATION OF HDL-C AND TRIGLYCERIDE RESPONSE AND OUTCOME MEASURES

In the primary analysis of the current study, we assessed the relationship between on-treatment changes in HDL-C levels during the double-blind phase of the study and the risk of all-cause mortality at 16 years of follow-up. Based on our prior data, HDL-C response to bezafibrate was categorized as an upper-tertile (eg, on-treatment HDL-C rise in the third-tertile range [T3]) or lower-tertile (eg, on-treatment HDL-C change in the first- or second-tertile range [T1 and T2]) HDL-C change.

Event rates in these subgroups were compared with those in the placebo group. The consistency of the results in the 2 separate tertiles (T1 and T2) that constitute the subgroup of lower-HDL-C responders was also assessed. Changes in HDL-C levels in the 2 prespecified response subgroups were as follows: among patients with an upper-tertile response (n = 495), HDL-C levels increased from more than 8 mg/dL to 34 mg/dL, whereas among patients with a lower response (n = 1014), HDL-C change ranged from −12 to 8 mg/dL. Within the latter subgroup, the lowest tertile of HDL-C response (T1) comprised 497 patients with an HDL-C change ranging from −12 to 3 mg/dL; and the intermediate tertile of HDL-C response (T2) comprised 517 patients with HDL-C increases ranging from more than 3 to 8 mg/dL. Similar analyses were performed to evaluate the effect of triglyceride reduction with the study medication on long-term mortality. Upper-tertile (T3) triglyceride response comprised patients with triglyceride reduction of more than 43 mg/dL (n = 496); intermediate response (T2) was a 10- to 43-mg/dL reduction (n = 513); and the lower tertile (T1) comprised those with a less than a 10-mg/dL reduction (n = 497).

STATISTICAL ANALYSIS

Baseline characteristics among the HDL-C response subgroups and the placebo group were compared using the χ² test for categorical parameters and analysis of variance for continuous variables. Survival curves were constructed by the Kaplan-Meier method, and the significance of the variation between them was assessed using a log-rank test. Multivariate analysis of mortality as a function of (1) the total bezafibrate treatment group, (2) the LDL-C response subgroups, and (3) the triglyceride response subgroups, compared with the placebo group, was performed using Cox proportional hazards regression models. A test based on a defined time-dependent covariate was used for assessing the proportionality of hazards. The following covariates were included in each model: age; sex; smoking status (present or past smokers compared with never smokers); New York Heart Association functional class of II or higher; angina pectoris functional class of II or higher (according to the Canadian Cardiovascular Society Classification System); history of diabetes mellitus, MI, cerebrovascular accident, chronic obstructive pulmonary disease, or hypertension; the presence of peripheral vascular disease; systolic blood pressure; body mass index (BMI; calculated as weight in kilograms divided by height in meters squared); heart rate; and baseline total cholesterol, HDL-C, and triglyceride levels. The effect of nonfatal MI during the original course of the trial (in-trial nonfatal MI) on the risk of long-term mortality was evaluated in a time-dependent manner.

Baseline characteristics and lipid profiles by HDL-C response in the bezafibrate group and in the placebo group are shown in Table 1. Patients with an upper-tertile
HDL-C response to treatment displayed clinical characteristics similar to those of patients who exhibited a lower response and to the placebo group, with the exception of sex (Table 1). Similarly, within the lower-tertiles HDL-C response subgroup there were no statistically significant differences (P > .10) in baseline characteristics between patients in T1 and T2 (data not shown). Baseline total cholesterol, LDL-C, and HDL-C levels were similar among the comparison subgroups (Table 1), whereas baseline triglyceride levels were higher among patients in the bezafibrate group with an upper-tertile HDL-C response compared with the placebo group and those with a lower-tertile HDL-C response to therapy (mean [SD] levels: T1, 138 [51] mg/dL; T2, 146 [52] mg/dL).

During the double-blind phase of the trial a greater proportion of placebo-allocated patients received other lipid-lowering drugs (LLDs), comprising mainly statins (Table 1). Subsequently, during the 2-year period after termination of the trial, in which open-label medical therapies were followed up, fibrates were used in 10% of placebo-allocated patients and in 9% of bezafibrate-allocated patients (T1 HDL-C response, 7%; T1 and T2 HDL-C response, 10%), whereas other LLDs were administered to 54% of placebo-allocated patients and to 51% of bezafibrate-allocated patients (T3 HDL-C response, 53%; T1 and T2 HDL-C response, 49%).

LONG-TERM MORTALITY IN THE 2 ORIGINAL TREATMENT GROUPS

Among the 1517 patients allocated to the original placebo group of the study, 566 (37.3%) died during a median follow-up period of 15.7 years, whereas 525 patients (34.8%) among the 1509 patients who were allocated to bezafibrate therapy died during the same time period. The respective cumulative probabilities of death at 16 years were 37.9% and 35.3%, representing a 7% reduction in the rate of death at 16 years among patients allocated to the original bezafibrate group (P = .12). The difference in mortality between the 2 groups appeared at 7 years of follow-up and persisted thereafter (Figure 1). Consistently, multivariate analysis demonstrated that patients allocated to the original bezafibrate group experienced an 11% reduction (P = .06) in the risk of long-term mortality compared with patients allocated to the original placebo group (Table 2). No statistically significant differences in bezafibrate efficacy were shown within prespecified risk subgroups (see Table 2 for P values). However, the long-term benefit of the study medication was more prominent among women (27% reduction in the risk of long-term mortality), patients with elevated baseline triglyceride levels (27% reduction in risk of long-term mortality), and those with increased BMI (21% reduction in the risk of long-term mortality).

HDL-C AND TRIGLYCERIDE RESPONSE TO BEZAFIBRATE AND LONG-TERM MORTALITY

When event rates were assessed by HDL-C response to bezafibrate therapy (Figure 2), cumulative mortality rates were shown to be significantly lower among patients with upper-tertile HDL-C response to treatment (32.1%) compared with the placebo group (37.9%; P = .02), whereas the cumulative probability of death was similar between patients who exhibited a lower HDL-C response (36.8%) and the placebo response. (Table 1). Subsequently, during the 2-year period after termination of the trial, in which open-label medical therapies were followed up, fibrates were used in 10% of placebo-allocated patients and in 9% of bezafibrate-allocated patients (T1 HDL-C response, 7%; T1 and T2 HDL-C response, 10%), whereas other LLDs were administered to 54% of placebo-allocated patients and to 51% of bezafibrate-allocated patients (T3 HDL-C response, 53%; T1 and T2 HDL-C response, 49%).

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During the double-blind phase of the BIP trial, 161 patients (10.6%) and 127 patients (8.4%) experienced nonfatal MIs in the placebo and bezafibrate groups, respectively (P = .04). Multivariate analysis demonstrated that the occurrence of in-trial nonfatal MI was the most powerful predictor of long-term outcome and was associated with nearly a 2-fold increase in the risk of 16-year mortality (HR, 1.97 [95% CI, 1.66-2.34]; P < .001). Notably, the rate of long-term mortality was 16% lower among bezafibrate-allocated patients who experienced in-trial nonfatals MIs compared with the corresponding patients in the placebo group (Figure 3), whereas among patients who did not experience in-trial nonfatals MIs, mortality rates were substantially lower and similar, in the 2 allocation groups (Figure 3).

Table 2. Bezafibrate- vs Placebo-Adjusted Risk for Long-term Mortality: Overall Effect and Effects Within Prespecified Subgroups

<table>
<thead>
<tr>
<th>Analysis Group</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall effect</td>
<td>0.89 (0.79-1.01)</td>
<td>.06</td>
</tr>
<tr>
<td>Effect by risk subgroup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n=260)</td>
<td>0.73 (0.48-1.10)</td>
<td>.32</td>
</tr>
<tr>
<td>Male (n=2764)</td>
<td>0.91 (0.80-1.03)</td>
<td></td>
</tr>
<tr>
<td>Triglyceride level ≥200 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=452)</td>
<td>0.73 (0.53-0.99)</td>
<td>.17</td>
</tr>
<tr>
<td>No (n=2572)</td>
<td>0.92 (0.81-1.05)</td>
<td></td>
</tr>
<tr>
<td>BMI &gt; 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=1268)</td>
<td>0.79 (0.66-0.95)</td>
<td>.08</td>
</tr>
<tr>
<td>No (n=1756)</td>
<td>0.98 (0.84-1.16)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=302)</td>
<td>0.96 (0.70-1.32)</td>
<td>.62</td>
</tr>
<tr>
<td>No (n=2722)</td>
<td>0.88 (0.77-1.00)</td>
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</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; HR, hazard ratio.

SI conversion factor: To convert triglycerides to millimoles per liter, multiply by 0.0113.

a Multivariate analysis was performed using Cox proportional hazards regression models; see the “Statistical Analysis” subsection in the “Methods” section for a complete list of additional covariates that were evaluated by including a covariate x treatment group interaction term in the multivariate model.

b P value for interaction.

The cumulative probability of 16-year mortality was nonsignificantly lower among bezafibrate-allocated subjects who exhibited an upper-tertile triglyceride response to treatment (33.5%) compared with those with a lower response (36.2%) and the placebo group (37.9%; P = .21). Consistently, patients who exhibited an upper-tertile triglyceride response to treatment exhibited an 18% reduction in the risk of long-term mortality (P = .03) compared with the placebo group, whereas those with a lower triglyceride response had a mortality risk similar to that of placebo-allocated patients (HR, 0.93; P = .28) (Table 3). The results were consistent in the 2 separate tertiles that constitute the lower triglyceride response subgroup (T1 vs placebo: HR, 0.97 [95% CI, 0.82-1.16]; P = .77; and T2 vs placebo: HR, 0.89 [95% CI, 0.75-1.14]; P = .17).

**RELATION OF IN-TRIAL NONFATAL MI TO LONG-TERM MORTALITY**

In this long-term mortality follow-up study based on the intention-to-treat principle, we compared mortalities in the 2 original treatment groups of the BIP trial. Our data indicate that early therapy with bezafibrate was associated with a nonsignificant 11% reduction in the risk of 16-year mortality (P = .06) that reflected a significant 22% reduction in the risk of long-term mortality (P = .008) among patients who exhibited upper-tertile on-treatment HDL-C increase (>8 mg/dL). These findings suggest that HDL-C–raising therapy with bezafibrate has important long-term clinical implications that may extend for many years after termination of active treatment with the drug.
Table 3. Adjusted Risk for Long-term Mortality by HDL-C and Triglyceride Response to Bezafibrate for Bezafibrate-Allocated vs Placebo-Allocated Patients

<table>
<thead>
<tr>
<th>Response Subgroup</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C response a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper tertile, &gt;8 mg/dL increase vs placebo</td>
<td>0.78 (0.65-0.94)</td>
<td>.008</td>
</tr>
<tr>
<td>Lower tertile, &lt;8 mg/dL increase vs placebo</td>
<td>0.95 (0.83-1.08)</td>
<td>.43</td>
</tr>
<tr>
<td>Triglyceride response c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper tertile, &gt;43 mg/dL reduction vs placebo</td>
<td>0.82 (0.68-0.99)</td>
<td>.03</td>
</tr>
<tr>
<td>Lower tertile, &lt;43 mg/dL reduction vs placebo</td>
<td>0.93 (0.81-1.06)</td>
<td>.28</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio.

SI conversion factors: To convert HDL-C to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.

a Multivariate analysis was performed using Cox proportional hazards regression models; see the “Statistical Analysis” subsection in the “Methods” section for a complete list of additional covariates that were included in all models.

b Adjusted risk when the lower tertiles of the HDL-C response subgroup were used as a reference group; upper tertile vs lower tertiles: HR, 0.83 (95% CI, 0.69-0.99); P = .04; for placebo vs lower tertiles: HR, 1.06 (95% CI, 0.92-1.21); P = .42.

c Adjusted risk when the lower tertiles of the triglyceride response subgroup were used as a reference group: upper tertile vs lower tertiles: HR, 0.88 (95% CI, 0.72-1.09); P = .24; for placebo vs lower tertiles: HR, 1.08 (95% CI, 0.94-1.24); P = .28.

Early trials of fibrate therapy raised concerns about the effect of these lipid-modifying drugs on overall mortality. The relatively small studies from Scotland and Newcastle Upon Tyne, England, yielded contrasting results on the effect of clofibrate on all-cause mortality, and the primary prevention World Health Organization cooperative trial17,18 reported a higher overall and cancer mortality rate in the clofibrate group. Our data suggest that the observed late benefit of the study medication may be related to a possible modification of the early favorable effect of bezafibrate in decreasing nonfatal MI, during the course of the study, into a subsequent 11% reduction (P = .06) in the risk of long-term mortality, 10 years after termination of the trial. We have shown that the occurrence of in-trial nonfatal MI was the most powerful predictor of long-term mortality in the BIP population. Furthermore, the reduction in long-term mortality related to the study medication was observed mostly among patients who experienced in-trial nonfatal MI. A similar long-term mortality reduction associated with HDL-C level–raising therapy was shown in a 15-year follow-up of the Coronary Drug Project. During the original course of the trial, treatment with niacin showed modest benefit in decreasing definite nonfatal recurrent MI but did not decrease total mortality, whereas nearly 9 years after termination of the trial, mortality in the niacin group was 11% lower than in the placebo group.

The results of randomized controlled trials of lipid-modifying therapies suggest that HDL-C increments during fibrate therapy are inversely correlated with cardiovascular risk. Analysis of data from the Helsinki Heart Study estimated that a 1% incremental rise in HDL-C levels with gemfibrozil was independently associated with a 3% reduction in the risk of major CHD events and that risk reduction with HDL-C exceeded that achieved with an equivalent magnitude of decrement in LDL-C (−2%) or triglyceride (0%) levels. Similarly, the VA-HIT showed that a 6% incremental rise in HDL-C levels, achieved with the use of gemfibrozil, decreased CHD death and nonfatal MI by 22%. Consistent with the results from the Helsinki Heart Study and the VA-HIT, we have recently shown in a post hoc analysis of the BIP trial that increasing increments of on-treatment HDL-C change were independently associated with reduced cardiac mortality over a median follow-up period of 7.9 years, whereas LDL-C reductions in the study were relatively small and did not contribute to outcome. The present study extends these observations, and demonstrates that pa-
tients with an early favorable HDL-C response to bezafibrate experienced a significant 22% reduction in the risk of mortality at 16 years of follow-up (P = .008). Importantly, mortality reduction among patients who exhibited an upper-tertile HDL-C response to bezafibrate appeared 2 years after the onset of the trial and persisted for 10 years after discontinuation of treatment with the study drug and was independent of baseline lipid levels. Similar trends, although more modest, were also seen for the benefit associated with on-treatment triglyceride level reduction. It should also be noted that the models that assessed the independent effect of on-treatment changes in serum levels of HDL-C and triglycerides on long-term mortality included a further adjustment for baseline serum lipids (ie, baseline total cholesterol, HDL-C, and triglycerides were included as additional covariates in both models). Thus, it seems that favorable modification of HDL-C and triglyceride levels by fibrate therapy has important long-term prognostic implications that are independent of baseline levels of serum lipids.

Previous post hoc analyses of the BIP trial suggested that the benefit of fibrate therapy is more prominent among patients with baseline triglyceride levels of 200 mg/dl or higher11 and those with components of the metabolic syndrome.23 Our data indicate consistent long-term mortality among patients allocated to the original bezafibrate group among patients allocated to the original placebo group and to a similar proportion of the 2 HDL-C response groups among bezafibrate-allocated patients. These data further suggest that the difference in long-term outcome between the 2 original treatment groups of the BIP trial was the result of the effect of the study drug during the original course of the trial.

Recent studies have shown that low HDL-C levels are associated with adverse outcome even in patients with very low LDL-C levels,25,26 further stressing the importance of identifying clinically effective HDL-C level raising therapies. Our study demonstrates the long-term beneficial effects of raising HDL-C levels and reducing triglyceride levels with bezafibrate and suggests that monitoring short-term lipid response to fibrate therapy may be important in identifying a substantial subset of treated patients in whom long-term survival is substantially improved even after termination of active treatment with the drug.

Accepted for Publication: September 12, 2008.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Goldenberg, Behar, and Guetta. Acquisition of data: Goldenberg and Tanne. Analysis and interpretation of data: Goldenberg, Boyko, Tennenbaum, Tanne, and Behar. Drafting of the manuscript: Goldenberg and Guetta. Critical revision of the manuscript for important intellectual content: Goldenberg, Boyko, Tennenbaum, Tanne, and Behar. Statistical analysis: Goldenberg and Boyko. Study supervision: Goldenberg, Tennenbaum, Behar, and Guetta.

Financial Disclosure: None reported.

REFERENCES


