Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease

The STABILITY Investigators*

ABSTRACT

BACKGROUND
Elevated lipoprotein-associated phospholipase A\textsubscript{2} activity promotes the development of vulnerable atherosclerotic plaques, and elevated plasma levels of this enzyme are associated with an increased risk of coronary events. Darapladib is a selective oral inhibitor of lipoprotein-associated phospholipase A\textsubscript{2}.

METHODS
In a double-blind trial, we randomly assigned 15,828 patients with stable coronary heart disease to receive either once-daily darapladib (at a dose of 160 mg) or placebo. The primary end point was a composite of cardiovascular death, myocardial infarction, or stroke. Secondary end points included the components of the primary end point as well as major coronary events (death from coronary heart disease, myocardial infarction, or urgent coronary revascularization for myocardial ischemia) and total coronary events (death from coronary heart disease, myocardial infarction, hospitalization for unstable angina, or any coronary revascularization).

RESULTS
During a median follow-up period of 3.7 years, the primary end point occurred in 769 of 7924 patients (9.7%) in the darapladib group and 819 of 7904 patients (10.4%) in the placebo group (hazard ratio in the darapladib group, 0.94; 95% confidence interval [CI], 0.85 to 1.03; P=0.20). There were also no significant between-group differences in the rates of the individual components of the primary end point or in all-cause mortality. Darapladib, as compared with placebo, reduced the rate of major coronary events (9.3% vs. 10.3%; hazard ratio, 0.90; 95% CI, 0.82 to 1.00; P=0.045) and total coronary events (14.6% vs. 16.1%; hazard ratio, 0.91; 95% CI, 0.84 to 0.98; P=0.02).

CONCLUSIONS
In patients with stable coronary heart disease, darapladib did not significantly reduce the risk of the primary composite end point of cardiovascular death, myocardial infarction, or stroke. (Funded by GlaxoSmithKline; STABILITY ClinicalTrials.gov number, NCT00799903.)
ATHEROSCLEROTIC LESIONS IN HUMANS
— in particular, vulnerable and ruptured plaques—are characterized by inflammatory activity and a high expression of lipoprotein-associated phospholipase A₂. In atherosclerotic plaques, lipoprotein-associated phospholipase A₂ increases the production of proinflammatory and proapoptotic mediators. In a meta-analysis of prospective studies, there was a continuous association between lipoprotein-associated phospholipase A₂ activity and the risk of coronary heart disease, with a relative increase in risk of 1.10 (95% confidence interval [CI], 1.05 to 1.16) for each 1-SD increase in lipoprotein-associated phospholipase A₂ activity, after adjustment for conventional risk factors.

Darapladib is a potent and reversible oral inhibitor of lipoprotein-associated phospholipase A₂. In a swine model of atherosclerosis, darapladib reduced levels of lipoprotein-associated phospholipase A₂ in plaque, reduced the necrotic core area, and inhibited the development of lesions in coronary arteries. Darapladib has also been shown to reduce lipoprotein-associated phospholipase A₂ activity in human carotid plaque. In the Integrated Biomarker and Imaging Study 2 (IBIS-2) involving patients with coronary heart disease, darapladib, as compared with placebo, halted the progression in the volume of the necrotic core of coronary-artery plaques (a secondary end point), as determined by intravascular ultrasonographic virtual histologic analysis during a 12-month period. These findings suggest that darapladib could reduce the risk of events associated with coronary heart disease by altering the composition of atherosclerotic plaques to a less vulnerable state. In the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) trial, we evaluated the clinical efficacy and safety of darapladib in patients with chronic coronary heart disease.

STUDY DESIGN AND OVERSIGHT
The study design has been described previously. The trial was sponsored by GlaxoSmithKline. The executive and steering committees designed the study and supervised its conduct. (A complete list of committee members is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) In each country, the study was approved by national regulatory authorities and by local ethics committees or institutional review boards, according to local regulations.

Data were collected and managed by GlaxoSmithKline. Unblinded interim analyses of the ongoing trial, including four efficacy analyses (two prespecified and two unplanned) and semiannual safety analyses, were conducted at the University of Wisconsin–Madison and reviewed by an independent data and safety monitoring committee. The final analyses of trial data were performed by GlaxoSmithKline. Final statistical analyses of key efficacy and safety measures, including those presented in this article, were independently verified by the Duke Clinical Research Institute.

The first draft of the manuscript was written by the first author. The executive and steering committees contributed to subsequent drafts of the manuscript and approved the submission of the final manuscript for publication. The study's cochairs had full access to all data, verified their accuracy, and vouch for the fidelity of the study to the protocol, available at NEJM.org.

STUDY POPULATION
Patients were eligible to participate in the study if they had coronary heart disease, as documented by at least one of the following: previous myocardial infarction, previous percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG), or multivessel coronary artery disease. In addition, at least one of the following additional predictors of cardiovascular risk was required: an age of 60 years or older, diabetes requiring pharmacotherapy, a high-density lipoprotein (HDL) cholesterol level of less than 40 mg per deciliter (1.03 mmol per liter), status as a smoker of five or more cigarettes per day at study entry or within 3 months before screening, moderate renal dysfunction, or polyvascular arterial disease. Exclusion criteria were planned PCI or CABG or another major surgical procedure, current liver disease, severe renal impairment, a history of nephrectomy or kidney transplantation, current New York Heart Association class III or IV heart failure, or severe asthma that was poorly controlled with standard medical therapy. Details of the inclusion and exclusion criteria are provided in the Supplementary Appendix. All patients provided written informed consent.
STUDY PROCEDURES AND FOLLOW-UP

After baseline assessments were performed, patients were randomly assigned, with the use of an interactive voice-response system, to receive either a once-daily oral dose of darapladib (160 mg) or matching placebo to be taken with food and swallowed whole. The assigned dose of darapladib was expected to lower plasma levels of lipoprotein-associated phospholipase A\(_2\) by approximately 60%.\(^{13}\)

Patients were instructed to return for clinic visits 1, 3, and 6 months after randomization and thereafter every 6 months for the duration of the study. In addition, patients were followed up by telephone beginning at 9 months and then every 6 months thereafter until the end of the study.

Investigators were strongly encouraged to treat patients according to international guidelines for secondary prevention of coronary heart disease. All patients were to receive long-term treatment with platelet-inhibitor therapy and statin therapy unless such therapy was not indicated according to guidelines, was contraindicated, or resulted in unacceptable side effects. Metrics of standard of care were monitored by the study leaders and provided to all investigators every 6 months, which allowed the investigators to compare the standard of care at their sites with national and international standards at other sites participating in this study. In addition, the importance of adherence to standard-of-care medications was reinforced over the duration of the trial and at periodic meetings with investigators.

Patients were instructed to continue taking the study drug until the day before their end-of-treatment visit. Patients who permanently discontinued a study drug before the end of the study were contacted by telephone for an assessment of clinical outcomes. At the end of the study, all patients were asked to return to the clinic within a 3-month period for their final study visit. Final survival status was sought for patients who were lost to follow-up or withdrew consent.

STUDY END POINTS

The primary end point was a composite of cardiovascular death, myocardial infarction, or stroke. Secondary end points included major coronary events (a composite of death from coronary heart disease, myocardial infarction, or urgent coronary revascularization for myocardial ischemia); total coronary events (a composite of death from coronary heart disease, myocardial infarction, hospitalization for unstable angina, or any coronary revascularization procedure); the individual components of the primary end point; a composite of all-cause mortality, myocardial infarction, or stroke; and all-cause mortality. Definitions of the primary and secondary end points are provided in the Supplementary Appendix.

LABORATORY TESTING

All laboratory tests were performed at central laboratories (Quest Diagnostics Clinical Laboratories). The estimated glomerular filtration rate (GFR) was calculated with the use of the Modification of Diet in Renal Disease method.\(^{15}\)

SAFETY MONITORING AND ADJUDICATION

Investigators were responsible for detecting, documenting, and reporting adverse events and serious adverse events. Information on adverse events was collected from the time the randomized regimens were started until 35 days after the last dose of a study drug was taken or at the next follow-up visit, whichever occurred later. Serious adverse events that were assessed as being related to a study drug or related to study participation were recorded up to and including any follow-up contact. The occurrence of cancers and of gastrointestinal polyps or neoplasms was recorded until the end of the study, including during the period after discontinuation of the study drug, since 2-year carcinogenicity studies in rodents had suggested that darapladib was associated with the development of jejunal adenomas or adenocarcinomas in male mice and rats. Other adverse events of special interest included asthma, anaphylaxis, diarrhea, and odor-related events, because in previous studies,\(^{13}\) darapladib had been associated with an unpleasant odor of skin, urine, or feces.

Suspected primary and secondary end points were evaluated by an independent clinical-events committee whose members were unaware of the study-group assignments. Gastrointestinal neoplasms and cancers were adjudicated by a separate committee in a blinded fashion.

STATISTICAL ANALYSIS

We anticipated an annual event rate for the primary end point of 4% in the placebo group. We then estimated that 1500 events would be required for the study to have a power of 90% to
detect a relative-risk reduction of 15.5% in the rate of the primary end point in the darapladib group, as compared with the placebo group.

All patients who underwent randomization were included in the intention-to-treat analyses. Time-to-event analyses were performed with the use of Kaplan–Meier estimates for the primary and secondary end points. Hazard ratios and 95% confidence intervals were estimated with the use of Cox proportional-hazards models. The effect of treatment on the primary end point was estimated with the use of hazard ratios and adjusted 95.1% confidence intervals, with a two-sided P value of 0.049 indicating statistical significance after adjustment for the four interim analyses conducted by the data and safety monitoring committee. For secondary and other end points, no adjustments were made for multiple testing. Nominal significance refers to an unadjusted P value of less than 0.05 in which the type I error was not controlled at the 5% level.

The consistency of effects on efficacy end points was prespecified to be explored in 35 subgroups, without adjustment for multiple comparisons. The analyses of safety data focused on adverse events, laboratory data, and vital signs and included all patients who received at least one dose of a study drug. Baseline and on-treatment lipoprotein-associated phospholipase A2 levels are not yet available and thus are not reported here.

**RESULTS**

**STUDY PATIENTS**

From December 2008 through April 2010, we enrolled 15,828 patients at 663 centers in 39 countries (Fig. 1). A total of 7924 patients were randomly assigned to the darapladib group, and 7904 were assigned to the placebo group. The median age of the patients was 65 years; 81% were men, 78% were white, 20% were current or recent smokers, and 34% had diabetes mellitus requiring pharmacotherapy (Table 1, and Table S1 in the Supplementary Appendix). The median low-density lipoprotein (LDL) cholesterol level at baseline was 79.9 mg per deciliter (2.07 mmol per liter).

**FOLLOW-UP, ADHERENCE, AND BACKGROUND THERAPY**

The median duration of follow-up for the primary end point was 3.7 years (interquartile range, 3.5 to 3.8). The median duration of study-drug exposure was 3.5 years in the darapladib group and 3.6 years in the placebo group. We were able to ascertain vital status for 99.3% of the patients (15,722 of 15,828) and for 99.6% of the total possible follow-up time. For the analysis of the primary end point, complete follow-up was obtained in 96.5% of patients and for 97.7% of total follow-up time (Fig. S1 in the Supplementary Appendix). The percentage of patients with at least 80% adherence to treatment, as determined on the basis of pill counts, was 89.3% in the darapladib group and 91.3% in the placebo group.
The use of guideline-recommended treatments for secondary prevention was high. At trial close-out, 90% of the patients were taking aspirin, 96% statins, 79% beta-blockers, 54% angiotensin-converting–enzyme inhibitors, and 26% angiotensin II–receptor blockers. The median LDL cholesterol level at the end of the study was 78.0 mg per deciliter (2.02 mmol per liter) in the darap-
ladib group and 78.8 mg per deciliter (2.04 mmol per liter) in the placebo group. The mean blood pressure at the end of the study was 132/77 mm Hg in the darapladib group and 131/77 mm Hg in the placebo group.

**Efficacy Outcomes**

**Primary End Point**

The primary end point occurred in 769 of 7924 patients (9.7%) in the darapladib group and in 819 of 7904 patients (10.4%) in the placebo group (hazard ratio in the darapladib group, 0.94; 95% CI, 0.85 to 1.03; P = 0.20) (Table 2 and Fig. 2). There were no significant effects of darapladib on any of the components of the primary end point (cardiovascular death, myocardial infarction, or stroke) or on all-cause mortality. The hazard ratio for the effect of darapladib on myocardial infarction was 0.89 (95% CI, 0.77 to 1.03; P = 0.11). The effects on different types of myocardial infarction are shown in the Table S2 in the Supplementary Appendix.

The treatment effect with respect to the primary end point was consistent in almost all prespecified subgroups. The only interactions below the P=0.10 level were among smokers (P = 0.04).

Table 2. Primary and Secondary Efficacy End Points.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (N=7904)</th>
<th>Darapladib (N=7924)</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with Events</td>
<td>Event Rate</td>
<td>Patients with Events</td>
<td>Event Rate</td>
</tr>
<tr>
<td></td>
<td>no. (%)</td>
<td>no. of events/100 person-yr</td>
<td>no. (%)</td>
<td>no. of events/100 person-yr</td>
</tr>
<tr>
<td>Primary end point</td>
<td>819 (10.4)</td>
<td>3.04</td>
<td>769 (9.7)</td>
<td>2.85</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>315 (4.0)</td>
<td>1.13</td>
<td>308 (3.9)</td>
<td>1.11</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>369 (4.7)</td>
<td>1.36</td>
<td>329 (4.2)</td>
<td>1.21</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>135 (1.7)</td>
<td>0.49</td>
<td>132 (1.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Secondary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major coronary event</td>
<td>814 (10.3)</td>
<td>3.03</td>
<td>737 (9.3)</td>
<td>2.74</td>
</tr>
<tr>
<td>Death from coronary heart disease</td>
<td>303 (3.8)</td>
<td>1.09</td>
<td>284 (3.6)</td>
<td>1.02</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>368 (4.7)</td>
<td>1.36</td>
<td>325 (4.1)</td>
<td>1.20</td>
</tr>
<tr>
<td>Urgent coronary revascularization for myocardial ischemia</td>
<td>143 (1.8)</td>
<td>0.52</td>
<td>128 (1.6)</td>
<td>0.46</td>
</tr>
<tr>
<td>Total coronary events</td>
<td>1269 (16.1)</td>
<td>4.90</td>
<td>1159 (14.6)</td>
<td>4.45</td>
</tr>
<tr>
<td>Death from coronary heart disease</td>
<td>291 (3.7)</td>
<td>1.06</td>
<td>270 (3.4)</td>
<td>0.97</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>320 (4.0)</td>
<td>1.18</td>
<td>281 (3.5)</td>
<td>1.03</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>145 (1.8)</td>
<td>0.53</td>
<td>129 (1.6)</td>
<td>0.47</td>
</tr>
<tr>
<td>Any coronary revascularization procedure</td>
<td>511 (6.5)</td>
<td>1.91</td>
<td>479 (6.0)</td>
<td>1.78</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>373 (4.7)</td>
<td>1.34</td>
<td>359 (4.5)</td>
<td>1.29</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>405 (5.1)</td>
<td>1.49</td>
<td>361 (4.6)</td>
<td>1.33</td>
</tr>
<tr>
<td>Stroke</td>
<td>152 (1.9)</td>
<td>0.55</td>
<td>154 (1.9)</td>
<td>0.56</td>
</tr>
<tr>
<td>All-cause mortality, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>962 (12.2)</td>
<td>3.57</td>
<td>926 (11.7)</td>
<td>3.43</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>458 (5.8)</td>
<td>1.65</td>
<td>465 (5.9)</td>
<td>1.67</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>369 (4.7)</td>
<td>1.36</td>
<td>329 (4.2)</td>
<td>1.21</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>135 (1.7)</td>
<td>0.49</td>
<td>132 (1.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Total all-cause mortality</td>
<td>577 (7.3)</td>
<td>2.00</td>
<td>582 (7.3)</td>
<td>2.02</td>
</tr>
</tbody>
</table>

* The components of each of the composite end points have been summarized as mutually exclusive components without hazard ratios, confidence intervals, or P values. A mutually exclusive component is the first occurrence of any event in the composite. All other categories represent time-to-event end points and are specified as primary or secondary end points in the protocol.

† Hazard ratios are for the darapladib group, as compared with the placebo group.
for interaction) and white patients (P=0.08 for interaction) (Fig. S2 in the Supplementary Appendix).

**Secondary End Points**
Among patients receiving darapladib, there was a nominally significant reduction in the first prespecified secondary end point of a composite of major coronary events, which occurred in 737 patients (9.3%) in the darapladib group and in 814 patients (10.3%) in the placebo group (hazard ratio, 0.90; 95% CI, 0.82 to 1.00; P=0.045) (Table 2, and Fig. S3 in the Supplementary Appendix). Similar effects were observed for the composite of total coronary events (hazard ratio, 0.91; 95% CI, 0.84 to 0.98; P=0.02).

**ADVERSE EVENTS**
More patients in the darapladib group than in the placebo group discontinued the study drug because of diarrhea (3.2% vs. 0.8%), feces odor (2.2% vs. 0.1%), urine odor (1.4% vs. <0.1%), and skin odor (2.2% vs. 0.1%).

There were more serious adverse events of renal failure in the darapladib group than in the placebo group (1.5% vs. 1.1%; hazard ratio, 1.35; 95% CI, 1.03 to 1.78). At 3 months, the mean estimated GFR was lower by 2 ml per minute per 1.73 m² of body-surface area in the darapladib group than in the placebo group, with a similar between-group difference observed during the entire treatment period. There was no significant between-group difference in the subgroup of 2650 patients in whom the estimated GFR was measured approximately 1 month after the end of treatment, with a change from baseline in the estimated GFR in the darapladib group, as compared with the placebo group, of −0.12 ml per minute per 1.73 m² (95% CI, −1.35 to 1.12; P=0.85). No significant between-group difference in the number of overall cancers or gastrointestinal cancers was observed.

**DISCUSSION**
In this large, multicenter, randomized trial involving patients with stable chronic coronary heart
DARAPLIDIB IN STABLE CORONARY HEART DISEASE

There was a nominally significant reduction of approximately 10% in the rate of the prespecified secondary composite end points of major and total coronary events. The effects on these end points were consistent across the components of these composite end points, including death from coronary heart disease, myocardial infarction, coronary revascularization,
and hospitalization for unstable angina, and it is possible that the inhibition of lipoprotein-associated phospholipase A₂ may reduce these measures of coronary disease risk. However, these findings should be considered exploratory and of uncertain importance in light of the lack of effect on the primary end point.

In accordance with previous findings, there was an increase in the rate of diarrhea among patients receiving darapladib, as compared with those receiving placebo, along with increases in the rates of odor (in skin, feces, and urine), an effect that is thought to be related to the sulfhydryl group in the darapladib molecule. Because of the occurrence of these events, there were more study-drug discontinuations in the darapladib group than in the placebo group, with most discontinuations occurring during the first year. The mechanisms and clinical significance of the changes in renal laboratory measures and of the renal serious adverse events are uncertain.

In conclusion, we evaluated a novel mechanism for reducing plaque vulnerability by inhibition of lipoprotein-associated phospholipase A₂ with darapladib in patients with stable coronary heart disease who were receiving guideline-based background medical therapy. Darapladib did not significantly reduce the rate of the primary end point of cardiovascular death, myocardial infarction, or stroke.

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APPENDIX

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