ORIGINAL ARTICLE

Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease

The STABILITY Investigators*

ABSTRACT

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BACKGROUND

Elevated lipoprotein-associated phospholipase A_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_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[1] and ruptured plaques — are characterized by inflammatory activity and a high expression of lipoprotein-associated phospholipase A_2.[2,3] In atherosclerotic plaques, lipoprotein-associated phospholipase A_2 increases the production of proinflammatory and proapoptotic mediators.[4-8] In a meta-analysis of individual records from 79,036 participants in 32 prospective studies, there was a continuous association between lipoprotein-associated phospholipase A_2 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 A_2 activity, after adjustment for conventional risk factors.[9]

Darapladib is a potent and reversible oral inhibitor of lipoprotein-associated phospholipase A_2.[10] In a swine model of atherosclerosis, darapladib reduced levels of lipoprotein-associated phospholipase A_2 in plaque, reduced the necrotic core area, and inhibited the development of lesions in coronary arteries.[11] Darapladib has also been shown to reduce lipoprotein-associated phospholipase A_2 activity in human carotid plaque.[12] 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.[13] 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.[1] 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.

METHODS

STUDY DESIGN AND OVERSIGHT

The study design has been described previously.[14] 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 Glaxo-SmithKline. 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 A$_2$ 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.
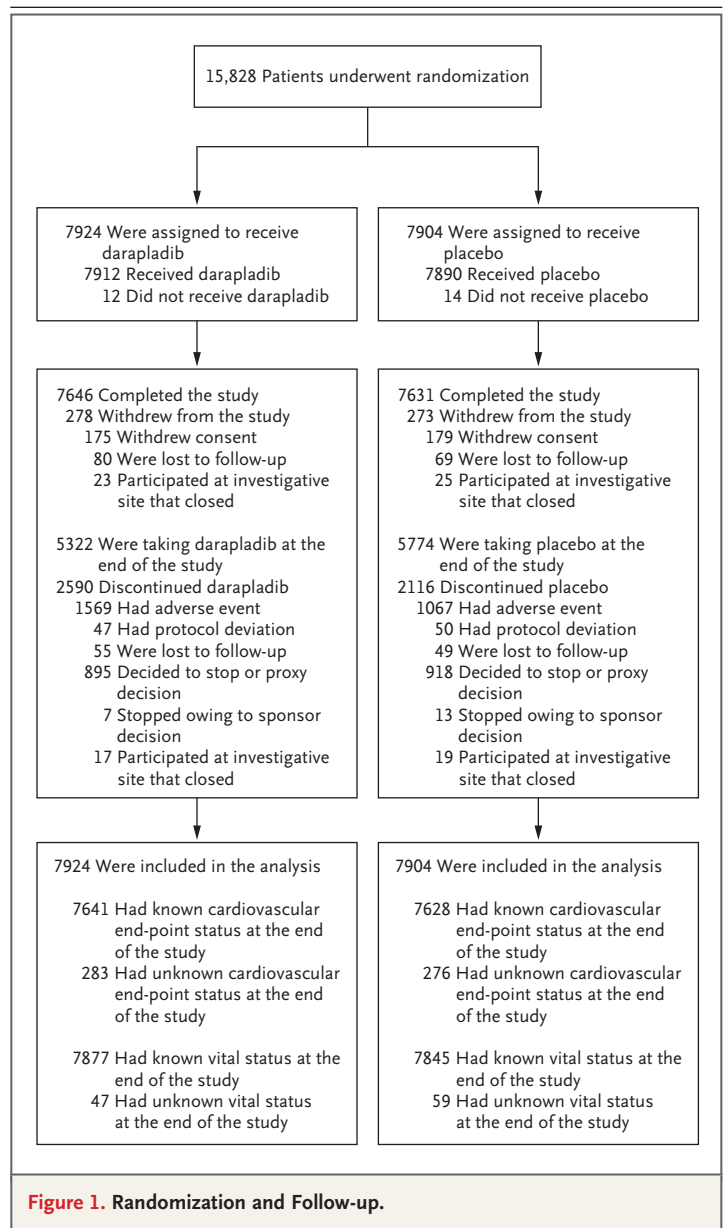

Figure 1. Randomization and Follow-up.

Table 1. Characteristics of the Patients at Baseline.*		
Characteristic	Placebo (N=7904)	Darapladib (N=7924)
Age		
Median (IQR) — yr	65.0 (59.0–71.0)	65.0 (59.0–71.0)
<65 yr — no. (%)	3893 (49.3)	3808 (48.1)
65–74 yr — no. (%)	2938 (37.2)	3022 (38.1)
≥75 yr — no. (%)	1073 (13.6)	1094 (13.8)
Female sex — no. (%)	1506 (19.1)	1461 (18.4)
Race or ethnic group — no. (%)†		
White	6174 (78.1)	6232 (78.6)
Black	191 (2.4)	175 (2.2)
Central, South, or Southeast Asian	598 (7.6)	592 (7.5)
East Asian or Japanese	766 (9.7)	758 (9.6)
Other	175 (2.2)	167 (2.1)
Region of enrollment — no. (%)		
North America		
All	2016 (25.5)	2007 (25.3)
United States	1555 (19.7)	1547 (19.5)
South America	597 (7.6)	602 (7.6)
Western Europe	1980 (25.1)	2006 (25.3)
Eastern Europe	1764 (22.3)	1767 (22.3)
Asia or Pacific Rim	1547 (19.6)	1542 (19.5)
Cardiovascular risk factors		
Diabetes requiring pharmacotherapy — no. (%)	2687 (34.0)	2664 (33.6)
High-density lipoprotein cholesterol		
Median (IQR) — mg/dl	44.4 (38.6–52.9)	44.8 (38.6–53.7)
<40 mg/dl — no. (%)	2786 (35.2)	2646 (33.4)
Smoker — no. (%)‡	1656 (21.0)	1572 (19.8)
Renal dysfunction — no. (%)§	2374 (30.0)	2410 (30.4)
Polyvascular disease — no. (%)	1187 (15.0)	1185 (15.0)
Qualifying diagnosis of coronary heart disease — no. (%)		
Previous myocardial infarction	4642 (58.7)	4681 (59.1)
Previous coronary revascularization	5911 (74.8)	5952 (75.1)
Percutaneous coronary intervention	3978 (50.3)	3987 (50.3)
Coronary-artery bypass grafting	2592 (32.8)	2644 (33.4)
Multivessel disease	1191 (15.1)	1199 (15.1)

* There was no significant difference between the two groups, except among patients who had a high-density lipoprotein cholesterol level of less than 40 mg per deciliter (P=0.01). Percentages may not total 100 because of rounding. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. IQR denotes interquartile range.

† Race or ethnic group was self-reported.

‡ Smokers included both current smokers of five or more cigarettes per day and those who were smokers within 3 months before screening.

§ Renal dysfunction was defined as an estimated glomerular filtration rate of 30 to 59 ml per minute per 1.73 m² of body-surface area (moderate kidney disease) or a urine albumin-to-creatinine ratio of 30 or more (as measured in milligrams of albumin and grams of creatinine).

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.*

End Point	Placebo (N=7904)		Darapladib (N=7924)		Hazard Ratio (95% CI)†	P Value
	Patients with Events	Event Rate	Patients with Events	Event Rate		
	no. (%)	*no. of events/ 100 person-yr*	*no. (%)*	*no. of events/ 100 person-yr*		
Primary end point	819 (10.4)	3.04	769 (9.7)	2.85	0.94 (0.85–1.03)	0.20
Cardiovascular death	315 (4.0)	1.13	308 (3.9)	1.11		
Nonfatal myocardial infarction	369 (4.7)	1.36	329 (4.2)	1.21		
Nonfatal stroke	135 (1.7)	0.49	132 (1.7)	0.48		
Secondary end point						
Major coronary event	814 (10.3)	3.03	737 (9.3)	2.74	0.90 (0.82–1.00)	0.045
Death from coronary heart disease	303 (3.8)	1.09	284 (3.6)	1.02		
Nonfatal myocardial infarction	368 (4.7)	1.36	325 (4.1)	1.20		
Urgent coronary revascularization for myocardial ischemia	143 (1.8)	0.52	128 (1.6)	0.46		
Total coronary events	1269 (16.1)	4.90	1159 (14.6)	4.45	0.91 (0.84–0.98)	0.02
Death from coronary heart disease	293 (3.7)	1.06	270 (3.4)	0.97		
Nonfatal myocardial infarction	320 (4.0)	1.18	281 (3.5)	1.03		
Hospitalization for unstable angina	145 (1.8)	0.53	129 (1.6)	0.47		
Any coronary revascularization procedure	511 (6.5)	1.91	479 (6.0)	1.78		
Cardiovascular death	373 (4.7)	1.34	359 (4.5)	1.29	0.96 (0.83–1.11)	0.59
Myocardial infarction	405 (5.1)	1.49	361 (4.6)	1.33	0.89 (0.77–1.03)	0.11
Stroke	152 (1.9)	0.55	154 (1.9)	0.56	1.01 (0.81–1.27)	0.92
All-cause mortality, nonfatal myocardial infarction, or nonfatal stroke	962 (12.2)	3.57	926 (11.7)	3.43	0.96 (0.88–1.05)	0.40
All-cause mortality	458 (5.8)	1.65	465 (5.9)	1.67		
Nonfatal myocardial infarction	369 (4.7)	1.36	329 (4.2)	1.21		
Nonfatal stroke	135 (1.7)	0.49	132 (1.7)	0.48		
Total all-cause mortality	577 (7.3)	2.00	582 (7.3)	2.02	1.01 (0.90–1.13)	0.87

* 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.
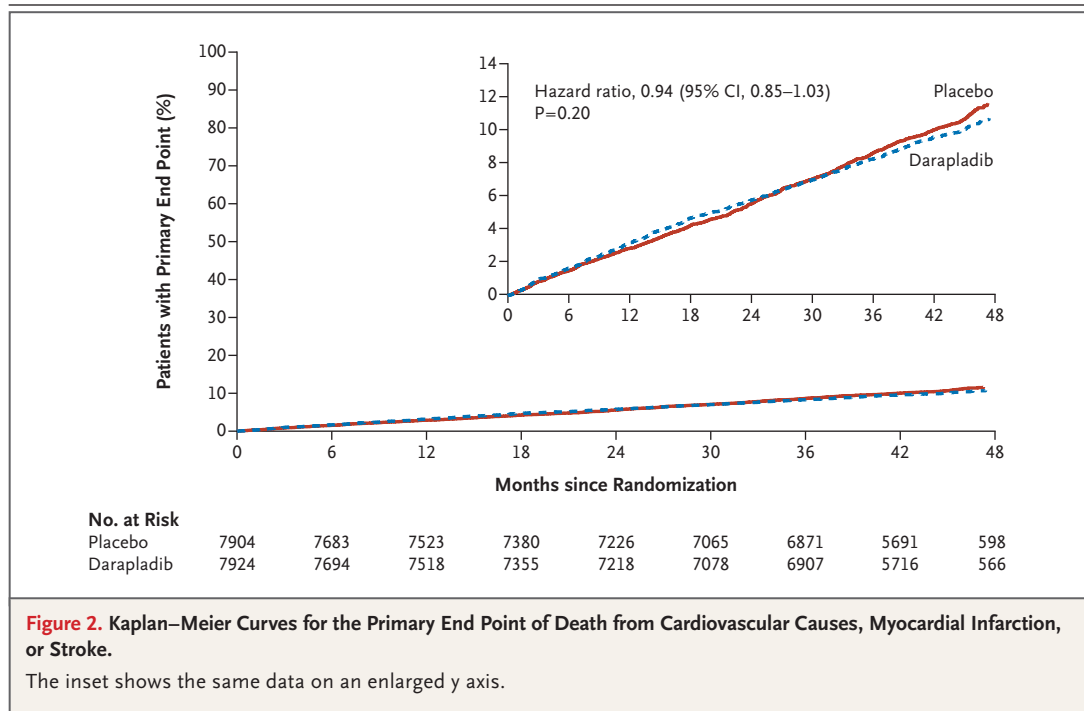† Hazard ratios are for the darapladib group, as compared with the placebo group.

Figure 2. Kaplan–Meier Curves for the Primary End Point of Death from Cardiovascular Causes, Myocardial Infarction, or Stroke.

The inset shows the same data on an enlarged y axis.

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 (32.7% vs. 26.8%; hazard ratio, 1.29; 95% CI, 1.22 to 1.37) (Fig. S4 in the Supplementary Appendix). Any adverse event leading to discontinuation of a study drug occurred in 19.8% of the patients in the darapladib group and in 13.5% of those in the placebo group (hazard ratio, 1.55; 95% CI, 1.43 to 1.67) (Table 3). More patients in the darapladib group than in the pla-

cebo 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

disease who were followed for a median of 3.7 years, darapladib did not significantly reduce the incidence of the primary end point of cardiovascular death, myocardial infarction, or stroke. There were no significant reductions in the incidence of the components of the primary end point, as assessed individually, or in the rate of all-cause mortality. There was a nominally significant reduction in the secondary end points of major and total coronary events, which is a signal of possible efficacy. The lack of effect of the administered dose of darapladib on the primary end point may relate to a smaller effect on vulnerable coronary plaque than was anticipated on the basis of previous studies.[12,13]

It is possible that the coronary risk among patients in our study may already have been minimized by concurrent therapy. The trial was designed to test the incremental effect of a new treatment administered in patients who were receiving a high level of standard of care for secondary prevention at baseline. Thus, more than a third of the patients had an LDL cholesterol level of less than 70 mg per deciliter (1.81 mmol per liter) at baseline, and revascularization had been performed in 75% of the patients before randomization. High rates of the use of evidence-based medications were maintained throughout the trial. These standards of care are consistently higher than those that were observed in patients with stable chronic coronary heart disease who were included in previous large international registries.[16-18] These factors probably reduced event rates in the two study groups and may have reduced the proportion of events that were modifiable.

Another consideration is that 96% of the patients at trial closeout were taking statins, which have been shown to reduce levels of lipoprotein-associated phospholipase A_2 by up to 35%.[19-21] In addition, in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study, among patients with stable chronic coronary heart disease, more than half the treatment effect of pravastatin in reducing rates of death from coronary heart disease or myocardial infarction was estimated to be due to an association with a reduction in levels of lipoprotein-associated phospholipase A_2.[22] Incremental benefits of inhibiting lipoprotein-associated phospholipase A_2 activity, if present, could be less in patients treated with statins.

Table 3. Adverse Events.

Event	Placebo (N=7890)	Darapladib (N=7912)
	no. of patients (%)	
Any serious adverse event*	3448 (43.7)	3369 (42.6)
Any adverse event leading to study-drug discontinuation	1067 (13.5)	1569 (19.8)
Diarrhea		
Any	495 (6.3)	965 (12.2)
Leading to study-drug discontinuation	60 (0.8)	254 (3.2)
Abnormal feces odor		
Any	63 (0.8)	728 (9.2)
Leading to study-drug discontinuation	5 (0.1)	177 (2.2)
Abnormal skin odor		
Any	34 (0.4)	383 (4.8)
Leading to study-drug discontinuation	4 (0.1)	174 (2.2)
Abnormal urine odor		
Any	81 (1.0)	473 (6.0)
Leading to study-drug discontinuation	1 (<0.1)	113 (1.4)
Asthma	64 (0.8)	43 (0.5)
Renal failure†	89 (1.1)	120 (1.5)
Newly diagnosed cancer		
Any	529 (6.7)	508 (6.4)
Adjudicated gastrointestinal	105 (1.3)	102 (1.3)
Liver events‡	52 (0.7)	54 (0.7)
Anaphylaxis‡	7 (0.1)	9 (0.1)

* Serious adverse events include cardiovascular events. A complete list of adverse events according to system organ class is provided in Table S3 in the Supplementary Appendix.
† Patients listed in this category include all those with serious renal adverse events according to the *Medical Dictionary for Regulatory Activities* preferred terms of acute renal failure, renal failure, and chronic renal failure. The mean (±SD) change from baseline in the estimated glomerular filtration rate at the end of the treatment period was a reduction of 0.8±14.1 ml per minute per 1.73 m² among 7322 patients who were evaluated in the darapladib group and an increase of 1.7±14.4 ml per minute per 1.73 m² among 7498 patients who were evaluated in the placebo group, for a between-group difference (darapladib group minus placebo group) of −2.5 ml per minute per 1.73 m² (95% confidence interval, −3.0 to −2.1).
‡ All the patients included in this category met the criteria for discontinuing the study on the basis of these events, as specified in the protocol.

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 A$_2$ 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 A$_2$ 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.

APPENDIX

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