ORIGINAL RESEARCH

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Lipoprotein-Associated Phospholipase A_2 Activity Is a Marker of Risk But Not a Useful Target for Treatment in Patients With Stable Coronary Heart Disease

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***Background*—**We evaluated lipoprotein-associated phospholipase A_2 (Lp-PLA_2) activity in patients with stable coronary heart disease before and during treatment with darapladib, a selective Lp-PLA_2 inhibitor, in relation to outcomes and the effects of darapladib in the STABILITY trial.

***Methods and Results*—**Plasma Lp-PLA_2 activity was determined at baseline (n=14 500); at 1 month (n=13 709); serially (n=100) at 3, 6, and 18 months; and at the end of treatment. Adjusted Cox regression models evaluated associations between Lp-PLA_2 activity levels and outcomes. At baseline, the median Lp-PLA_2 level was 172.4 μmol/min per liter (interquartile range 143.1–204.2 μmol/min per liter). Comparing the highest and lowest Lp-PLA_2 quartile groups, the hazard ratios were 1.50 (95% CI 1.23–1.82) for the primary composite end point (cardiovascular death, myocardial infarction, or stroke), 1.95 (95% CI 1.29–2.93) for hospitalization for heart failure, 1.42 (1.07–1.89) for cardiovascular death, and 1.37 (1.03–1.81) for myocardial infarction after adjustment for baseline characteristics, standard laboratory variables, and other prognostic biomarkers. Treatment with darapladib led to a ≈65% persistent reduction in median Lp-PLA_2 activity. There were no associations between on-treatment Lp-PLA_2 activity or changes of Lp-PLA_2 activity and outcomes, and there were no significant interactions between baseline and on-treatment Lp-PLA_2 activity or changes in Lp-PLA_2 activity levels and the effects of darapladib on outcomes.

***Conclusions*—**Although high Lp-PLA_2 activity was associated with increased risk of cardiovascular events, pharmacological lowering of Lp-PLA_2 activity by ≈65% did not significantly reduce cardiovascular events in patients with stable coronary heart disease, regardless of the baseline level or the magnitude of change of Lp-PLA_2 activity.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT00799903. **(*J Am Heart Assoc*. 2016;5: e003407 doi: 10.1161/JAHA.116.003407)**

Key Words: atherosclerosis • coronary disease • inflammation • lipoprotein • myocardial infarction

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*A complete list of the STABILITY Investigators can be found in the Appendix at the end of the manuscript.

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Inflammatory activity is an integral component of the development of atherosclerosis and its complications.[1] Biomarkers indicating myocardial dysfunction (eg, troponin, natriuretic peptides), renal dysfunction (eg, cystatin C), and inflammatory activity (eg, C-reactive protein) are risk indicators of future cardiovascular events in healthy persons and in patients with established coronary heart disease (CHD).[2–5] Higher levels of lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$) activity have also been associated with an increased risk of coronary events in healthy elderly persons

Table 1. Demographics, Baseline Characteristics, and Biomarker Levels in Relation to Quartile Groups of Baseline Lp-PLA$_2$ Activity

Variables	Baseline Lp-PLA$_2$ Activity				*P* Value	*P* Value for Trend
	Q1 (<143.1) n=3617	Q2 (143.1–172.4) n=3631	Q3 (172.4–204.2) n=3615	Q4 (≥204.2) n=3637		
Lp-PLA$_2$, μmol/min/L	125 (108–135)	158 (151–166)	187 (180–195)	230 (216–253)	<0.0001	<0.0001
Assigned treatment						
Placebo	1817 (50.2)	1766 (48.6)	1779 (49.2)	1859 (51.1)	0.1544	0.4342
Darapladib	1800 (49.8)	1865 (51.4)	1836 (50.8)	1778 (48.9)		
Age, y	65 (60–71)*	65 (60–71)	65 (59–71)	64 (57–71)	<0.0001	<0.0001
Sex, male	2490 (68.8)	2916 (80.3)	3127 (86.5)	3291 (90.5)	<0.0001	<0.0001
Geographic region					<0.0001	<0.0001
Asia–Pacific	821 (22.7)	602 (16.6)	534 (14.8)	609 (16.7)		
Eastern Europe	712 (19.7)	826 (22.7)	922 (25.5)	958 (26.3)		
North America	873 (24.1)	910 (25.1)	961 (26.6)	1061 (29.2)		
South America	207 (5.7)	204 (5.6)	231 (6.4)	226 (6.2)		
Western Europe	1004 (27.8)	1089 (30.0)	967 (26.7)	783 (21.5)		
Weight, kg	79 (68–91)	83 (73–94)	84 (74–95)	85 (74–96)	<0.0001	<0.0001
Current smoker	466 (12.9)	555 (15.3)	677 (18.7)	926 (25.5)	<0.0001	<0.0001
Hypertension	2627 (72.6)	2608 (71.8)	2569 (71.1)	2560 (70.4)	0.1275	0.0311
Diabetes mellitus	1678 (46.4)	1459 (40.2)	1272 (35.2)	1185 (32.6)	<0.0001	<0.0001
Statin at randomization	3575 (98.8)	3577 (98.5)	3508 (97.0)	3439 (94.6)	<0.0001	<0.0001
High-intensity statin	268 (7.4)	270 (7.4)	242 (6.7)	227 (6.2)	0.1271	0.0201
Prior myocardial infarction	2079 (57.5)	2146 (59.1)	2167 (59.9)	2197 (60.4)	0.0583	0.0018
Prior PCI or CABG	2731 (75.5)	2735 (75.3)	2677 (74.1)	2661 (73.2)	0.0715	0.0035
Polyvascular disease	491 (13.6)	535 (14.7)	529 (14.6)	649 (17.8)	<0.0001	<0.0001
LDL cholesterol, mmol/L	1.7 (1.3–2.1)	1.9 (1.6–2.3)	2.2 (1.8–2.7)	2.6 (2.1–3.3)	<0.0001	<0.0001
HDL cholesterol, mmol/L	1.3 (1.1–1.5)	1.2 (1.0–1.4)	1.2 (1.0–1.4)	1.1 (0.9–1.3)	<0.0001	<0.0001
Triglycerides, mmol/L	1.3 (1.0–1.8)	1.5 (1.1–2.0)	1.6 (1.1–2.2)	1.7 (1.3–2.4)	<0.0001	<0.0001
Hemoglobin, g/L	138 (129–146)	142 (133–151)	145 (137–153)	148 (139–156)	<0.0001	<0.0001
eGFR, mL/min†	75 (62–87)	74 (61–86)	74 (62–86)	74 (61–87)	0.5690	0.9025
C-reactive protein, mg/L	2.8 (1.3–3.1)	2.8 (1.4–3.1)	2.8 (1.5–3.2)	3.0 (1.5–3.4)	<0.0001	<0.0001
Interleukin 6, ng/L	1.2 (0.6–2.9)	1.3 (0.6–2.9)	1.3 (0.7–3.1)	1.6 (0.8–3.6)	<0.0001	<0.0001
High-sensitivity troponin T, ng/L	9.0 (5.9–13.6)	9.4 (6.4–14.1)	9.4 (6.3–14.2)	9.4 (6.2–15.0)	<0.0001	<0.0001
NT-proBNP, ng/L	174 (85–372)	181 (87–386)	186 (81–361)	174 (78–402)	0.0762	0.5699
Cystatin C, mg/L	1.0 (0.9–1.2)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	<0.0001	<0.0001
GDF-15, ng/L	1280 (923–1824)	1250 (902–1798)	1216 (905–1746)	1266 (927–1821)	0.0003	0.0913

Categorical variables are shown as number (percentage); continuous variables are presented as median (interquartile range). CABG indicates coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor 15; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp-PLA$_2$, lipoprotein-associated phospholipase A_2; NT-proBNP, N-terminal proB-type natriuretic peptide; PCI, percutaneous coronary intervention; Q, quartile.
†eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula.

Table 2. Multivariable Analysis of Demographics, Baseline Characteristics and Biomarkers Significantly Associated With Baseline Lp-PLA$_2$ Activity

Background Characteristic	Adjusted Difference in Mean*	95% CI*	*P* Value
Western Europe vs North America	−19.81	(−21.58; −18.03)	<0.0001
Eastern Europe vs North America	−17.09	(−18.97; −15.21)	<0.0001
Asia–Pacific vs North America	−16.42	(−18.48; −14.36)	<0.0001
South America vs North America	−14.91	(−17.81; −12.02)	<0.0001
Female vs male	−15.69	(−17.60; −13.77)	<0.0001
Diabetes mellitus	−6.640	(−8.092; −5.188)	<0.0001
HDL cholesterol, 0.1 mmol/L increase	−4.333	(−4.554; −4.113)	<0.0001
Diagnosis of hypertension	−2.066	(−3.503; −0.6295)	0.0048
Body mass index, 1 kg/m^2 increase	−0.218	(−0.361; −0.074)	0.0030
Triglycerides, 0.1 mmol/L increase	−0.071	(−0.139; −0.003)	0.0389
GDF-15, 10% increase	0.401	(0.252; 0.551)	<0.0001
Hemoglobin, 10 g/L increase	0.589	(0.536; 0.641)	<0.0001
Age, 10-year increase	0.908	(0.005; 1.812)	0.0489
Cystatin C, 10% increase	1.159	(0.771; 1.547)	<0.0001
Polyvascular disease	1.919	(0.169; 3.671)	0.0317
Current smoker vs never smoked	2.094	(0.049; 4.139)	0.0447
LDL cholesterol, 0.1 mmol/L increase	3.118	(3.040; 3.196)	<0.0001

GDF-15 indicates growth differentiation factor 15; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$.
*Mean and 95% CI for adjusted difference in mean Lp-PLA$_2$ activity level estimated in relation to the respective change in each background characteristic.

and in patients with stable CHD.[6–9] There is some evidence that Lp-PLA$_2$ might be part of the atherosclerotic process and may contribute to plaque destabilization through inflammatory activity in the atherosclerotic lesions.[10–12] Consequently, it is important to further evaluate the independent prognostic value of Lp-PLA$_2$ activity as a risk marker for individual nonfatal and fatal cardiovascular events in large long-term prospective studies of patients with CHD in addition to considering information provided by other prognostic biomarkers.

Darapladib is a selective Lp-PLA$_2$ inhibitor[13] that reduces Lp-PLA$_2$ activity in plasma[14] and in the atherosclerotic plaque.[15,16] Experiments in hypercholesterolemic diabetic swine[17] and in an angiographic and intravascular ultrasound study in patients[18] showed that darapladib prevented progression of the necrotic core, assumed to be the vulnerable component of atherosclerotic lesions. In the present STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY (STABILITY) trial (ClinicalTrials.gov identifier NCT00799903), darapladib 160 mg daily did not significantly reduce the primary composite end point of cardiovascular death, myocardial infarction (MI), or stroke in patients with stable CHD (hazard ratio [HR] 0.94, 95% CI 0.85–1.03, *P*=0.20) but nominally reduced the rate of the secondary end point, major coronary events (coronary death, MI, or urgent coronary revascularization; HR 0.90, 95% CI 0.82–1.00, *P*=0.045).[19] The present predefined ancillary study evaluated the independent prognostic value of baseline Lp-PLA$_2$ activity concerning cardiovascular events, the reduction of Lp-PLA$_2$ activity by darapladib, and the associations between baseline and changes in Lp-PLA$_2$ activity and clinical outcomes.

Methods

Trial Design, Patients, Treatments, and Follow-up

The STABILITY trial was a prospective double-blind randomized trial evaluating the efficacy and safety of darapladib 160 mg, a specific inhibitor of Lp-PLA$_2$, compared with placebo concerning cardiovascular outcomes in patients with stable CHD.[19] In brief, the study randomized 15 828 patients from 39 countries with stable CHD, defined as prior MI, prior coronary revascularization, or multivessel CHD confirmed by coronary angiography. Patients also had to meet at least 1 of the following cardiovascular risk criteria: age ≥60 years; diabetes mellitus requiring pharmacotherapy; high-density lipoprotein cholesterol <1.03 mmol/L; current or previous smoker, defined as ≥5 cigarettes per day on average; significant renal dysfunction (estimated glomerular filtration rate ≥30 and <60 mL/min per 1.73 m^2 or urine albumin: creatinine ratio of ≥30 mg albumin per gram of creatinine); or polyvascular disease (CHD and cerebrovascular disease or CHD and peripheral arterial disease). The patients were followed with regular outpatient visits for a median of 3.7 years. The primary outcome was the composite of cardiovascular death, nonfatal MI, or nonfatal stroke. Secondary outcomes were the composites of major coronary events (ie, fatal and nonfatal MI, death from CHD, or urgent coronary revascularization for myocardial ischemia) and the

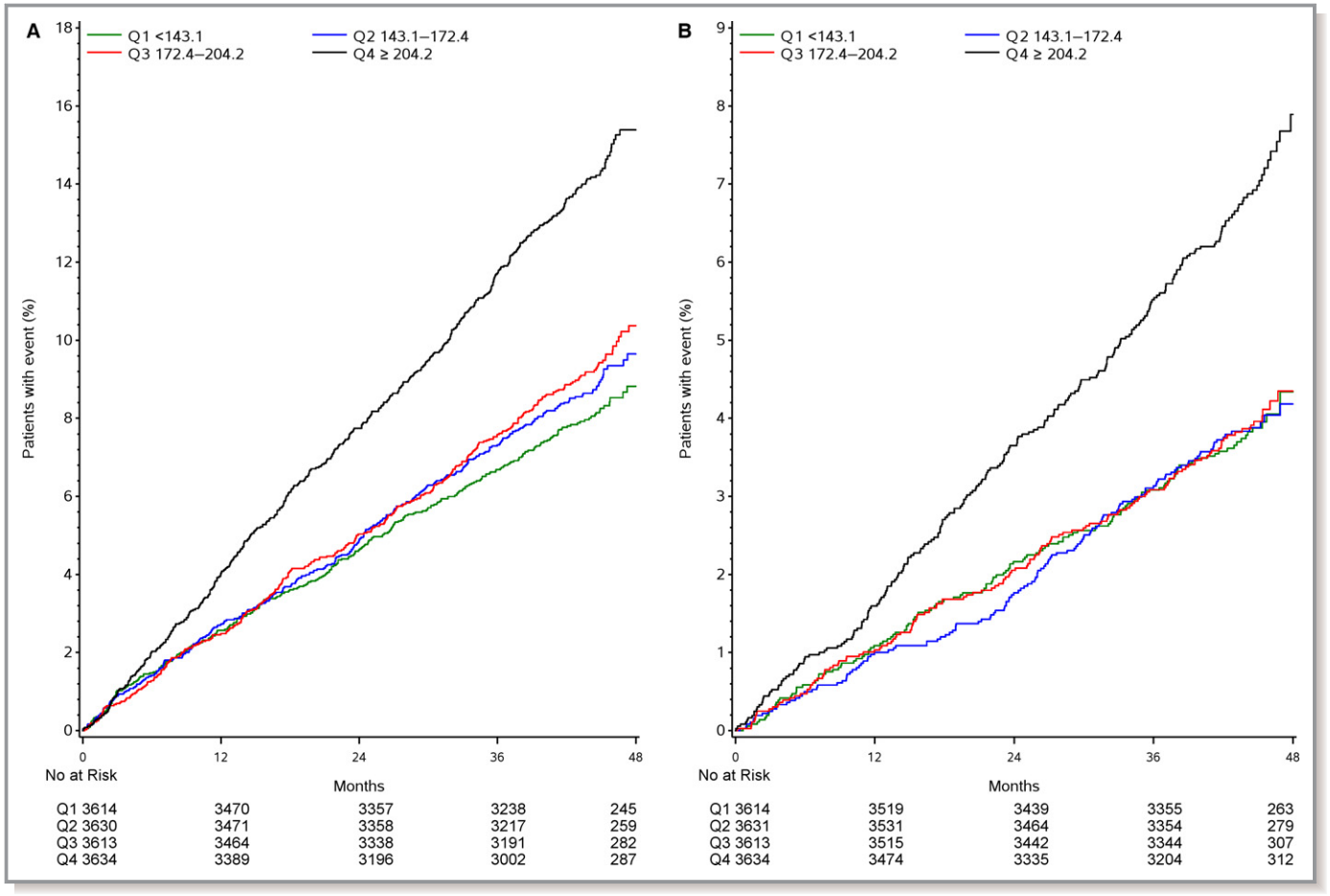


Figure 1. Quartile groups of baseline Lp-PLA$_2$ activity (in μmol/min per liter) in relation to outcomes by Kaplan–Meier analysis. A, Major adverse cardiac events (cardiovascular death, myocardial infarction, or stroke). B, Cardiovascular death. Q indicates quartile; Lp-PLA$_2$; lipoprotein-associated phospholipase A$_2$.

composite of total coronary events, which also included all coronary revascularizations. Additional secondary end points were the individual components of the primary composite end point, hospitalization for heart failure, and all-cause mortality. Components of cardiovascular death included death from unknown cause, fatal MI, fatal stroke, complications of a cardiac procedure, arrhythmia, congestive heart failure or shock, other vascular cause of death, and sudden death. All suspected end points were documented and reported by STABILITY study investigators and were adjudicated by an independent clinical events committee. All participants provided informed consent, and the study was approved by the relevant institutional review committee in each participating country.

Samples and Biochemical Methods

Blood samples were obtained from the majority of patients at baseline and 24±2 hours after the last intake of study drug at months 1, 3, 6, and 18, and at the end of treatment. Plasma aliquots were stored in central repositories at −70°C until biochemical analysis was performed. Measurements of Lp-PLA$_2$ activity and other biomarkers were performed in 14 500 patients at baseline for whom samples were available and suitable for assay. For 13 709 of these patients, Lp-PLA$_2$ activity was also measured after 1 month. In addition, the change in Lp-PLA$_2$ activity over a longer time period was evaluated in a random sample of 100 patients with plasma samples available from all follow-up visits. The sample size of 100 patients was based on the assumption of a mean difference in percentage change from baseline between treatment groups in Lp-PLA$_2$ activity of between 25% and 65%, with a common standard deviation of 25%, a 2-sided type I error rate (α level) of 5% and power of 90%. In total, 100 participants were selected with the goal of having ≈50 participants from each treatment group to describe the long-term inhibition of Lp-PLA$_2$ activity by the randomized treatment.

The Lp-PLA$_2$ activity was measured in an automated enzyme assay system (PLAC Test for Lp-PLA$_2$ Activity;

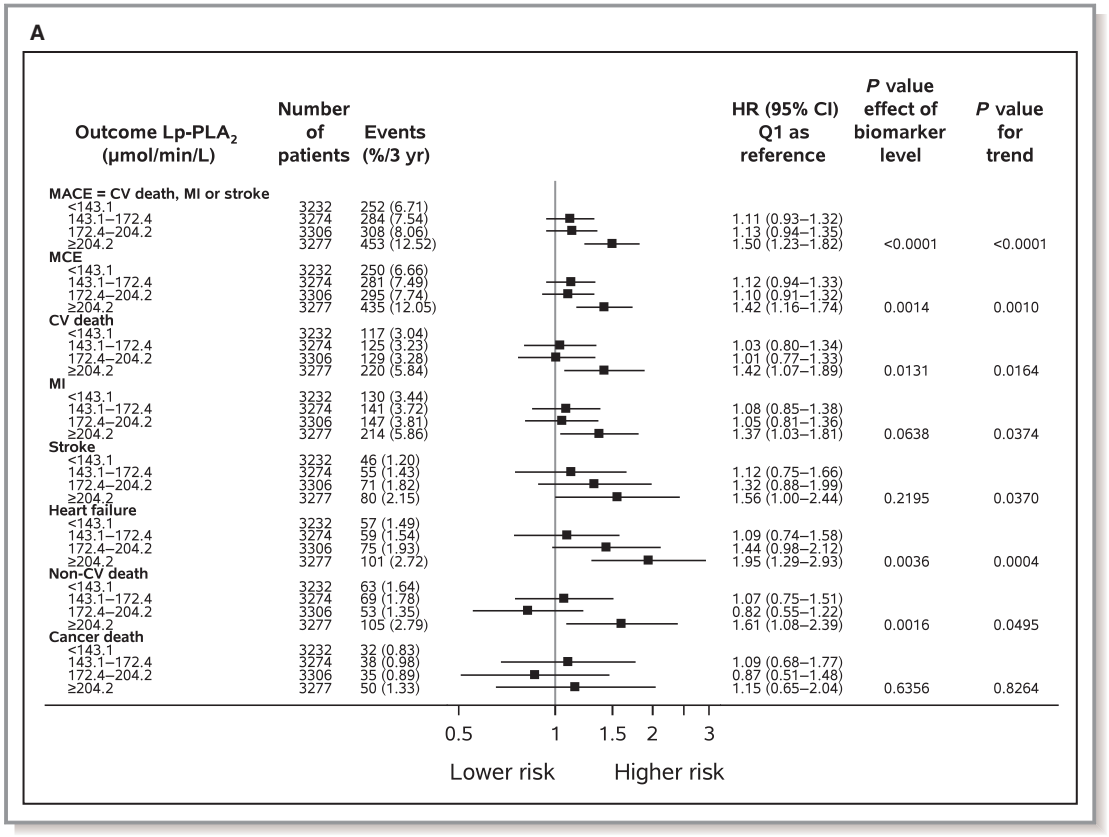
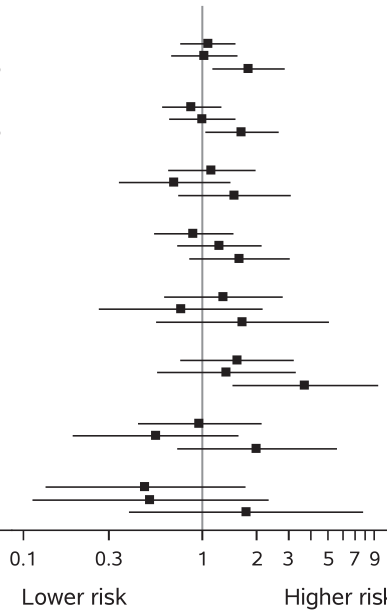


Figure 2. Baseline Lp-PLA$_2$ activity (µmol/min per liter) quartile groups in relation to outcomes in (A) all patients, (B) in women, and (C) in men, adjusted for demographics, baseline characteristics, routine biochemical variables, and prognostic biomarkers. The *x*-axis presents a logarithmic scale. MACE indicates CV death, MI, or stroke; MCE indicates coronary heart disease death, MI, or urgent coronary revascularization. Event rates are Kaplan–Meier rates. Adjustment variables: randomized treatment, geographic region, age, sex, body mass index, current smoking, hypertension, diabetes mellitus, prior MI, prior coronary revascularization, multivessel coronary heart disease, polyvascular disease, significant renal dysfunction, routine biochemical variables (hemoglobin, white blood cell count, estimated glomerular filtration rate [Chronic Kidney Disease Epidemiology Collaboration], low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), and prognostic biomarkers (N-terminal proB-type natriuretic peptide, high-sensitivity cardiac troponin T, cystatin C, high-sensitivity C-reactive protein, and interleukin 6). CV indicates cardiovascular; HR, hazard ratio; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; MACE, major adverse cardiac events; MCE, major coronary events; MI, myocardial infarction; Q, quartile.

Diadexus) with a colorimetric substrate that is converted on hydrolysis by the phospholipase enzyme. The analytical sensitivity (limit of quantitation) of the assay is 10 µmol/min per liter. Within-run and within-laboratory variability were determined by testing 4 human plasma samples and 2 controls with Lp-PLA$_2$ activities ranging from 113 to 315 µmol/min per liter. Samples were assayed in duplicate twice a day over 20 days and with 3 kit lots using 1 instrument. Total precision coefficients of variation for each reagent lot and sample were <3%. Several dilution series were prepared from plasma samples with known high and low Lp-PLA$_2$ activity levels and were tested with 3 kit lots. Linearity with a deviation of ≤10% was demonstrated from 10 to 382 µmol/min per liter, which is considered the measuring range of the assay. The Lp-PLA$_2$ activity measurements were performed by the manufacturer (Diadexus) on samples blinded for study treatment. The levels of high-sensitivity cardiac troponin T, N-terminal proB-type natriuretic peptide, growth differentiation factor 15 (precommercial assay),[20] and cystatin C were determined by electrochemiluminiscence immunoassays using a Cobas Analytics e601 system (Roche Diagnostics), performed at the Uppsala Clinical Research Center Laboratory at Uppsala University in Sweden. High-sensitivity C-reactive protein was analyzed using the CardioPhase high-sensitivity C-reactive protein (Dade Behring) 2-site particle-enhanced immunonephelometry sandwich assay. The routine biochemical analyses and high-sensitivity C-reactive protein assay were performed at a central laboratory with standardized methods (Quest Diagnostics Clinical Laboratories, Inc).

B

Outcome Lp-PLA$_2$ (μmol/min/L)	Number of patients	Events (%/3 yr)	HR (95% CI) Q1 as reference	*P* value effect of biomarker level
MACE = CV death, MI or stroke				
<143.1	1009	83 (7.14)		
143.1–172.4	640	58 (7.95)	1.07 (0.75–1.53)	
172.4–204.2	437	41 (8.14)	1.02 (0.67–1.56)	
≥204.2	311	51 (15.31)	1.80 (1.13–2.88)	0.0348
MCE				
<143.1	1009	80 (6.87)		
143.1–172.4	640	49 (6.74)	0.87 (0.59–1.28)	
172.4–204.2	437	42 (8.39)	0.99 (0.65–1.52)	
≥204.2	311	54 (16.33)	1.65 (1.03–2.65)	0.0266
CV death				
<143.1	1009	30 (2.50)		
143.1–172.4	640	29 (3.86)	1.12 (0.64–1.97)	
172.4–204.2	437	15 (2.90)	0.70 (0.34–1.42)	
≥204.2	311	23 (6.50)	1.50 (0.73–3.09)	0.1815
MI				
<143.1	1009	47 (4.01)		
143.1–172.4	640	26 (3.54)	0.89 (0.53–1.49)	
172.4–204.2	437	28 (5.54)	1.24 (0.72–2.14)	
≥204.2	311	28 (8.31)	1.60 (0.84–3.05)	0.2908
Stroke				
<143.1	1009	17 (1.43)		
143.1–172.4	640	14 (1.88)	1.30 (0.61–2.78)	
172.4–204.2	437	6 (1.16)	0.76 (0.27–2.17)	
≥204.2	311	8 (2.29)	1.67 (0.55–5.06)	0.5122
Heart failure				
<143.1	1009	17 (1.43)		
143.1–172.4	640	17 (2.29)	1.55 (0.75–3.20)	
172.4–204.2	437	11 (2.15)	1.36 (0.56–3.31)	
≥204.2	311	16 (4.62)	3.72 (1.46–9.48)	0.0305
Non-CV death				
<143.1	1009	19 (1.58)		
143.1–172.4	640	13 (1.73)	0.96 (0.44–2.12)	
172.4–204.2	437	5 (0.97)	0.55 (0.19–1.58)	
≥204.2	311	14 (3.96)	2.00 (0.72–5.59)	0.0954
Cancer death				
<143.1	1009	10 (0.83)		
143.1–172.4	640	4 (0.53)	0.48 (0.13–1.74)	
172.4–204.2	437	3 (0.58)	0.51 (0.11–2.33)	
≥204.2	311	7 (1.98)	1.75 (0.39–7.83)	0.2289



C

Outcome Lp-PLA$_2$ (μmol/min/L)	Number of patients	Events (%/3 yr)	HR (95% CI) Q1 as reference	*P* value effect of biomarker level
MACE = CV death, MI or stroke				
<143.1	2223	169 (6.51)		
143.1–172.4	2634	226 (7.44)	1.16 (0.95–1.42)	
172.4–204.2	2869	267 (8.05)	1.18 (0.96–1.46)	
≥204.2	2966	402 (12.24)	1.49 (1.19–1.85)	0.0022
MCE				
<143.1	2223	170 (6.56)		
143.1–172.4	2634	232 (7.67)	1.19 (0.97–1.45)	
172.4–204.2	2869	253 (7.64)	1.12 (0.91–1.39)	
≥204.2	2966	381 (11.61)	1.39 (1.12–1.74)	0.0148
CV death				
<143.1	2223	87 (3.29)		
143.1–172.4	2634	96 (3.08)	1.00 (0.74–1.34)	
172.4–204.2	2869	114 (3.34)	1.06 (0.78–1.44)	
≥204.2	2966	197 (5.78)	1.41 (1.03–1.94)	0.0424
MI				
<143.1	2223	83 (3.19)		
143.1–172.4	2634	115 (3.77)	1.15 (0.87–1.54)	
172.4–204.2	2869	119 (3.55)	1.00 (0.74–1.36)	
≥204.2	2966	186 (5.61)	1.30 (0.95–1.79)	0.1431
Stroke				
<143.1	2223	29 (1.10)		
143.1–172.4	2634	41 (1.32)	1.16 (0.72–1.88)	
172.4–204.2	2869	65 (1.92)	1.56 (0.97–2.51)	
≥204.2	2966	72 (2.13)	1.65 (0.99–2.76)	0.1533
Heart failure				
<143.1	2223	40 (1.52)		
143.1–172.4	2634	42 (1.35)	0.92 (0.58–1.44)	
172.4–204.2	2869	64 (1.89)	1.45 (0.93–2.25)	
≥204.2	2966	85 (2.52)	1.74 (1.09–2.76)	0.0121
Non-CV death				
<143.1	2223	44 (1.66)		
143.1–172.4	2634	56 (1.79)	1.06 (0.71–1.58)	
172.4–204.2	2869	48 (1.41)	0.85 (0.55–1.31)	
≥204.2	2966	91 (2.67)	1.54 (0.99–2.40)	0.0140
Cancer death				
<143.1	2223	22 (0.83)		
143.1–172.4	2634	34 (1.09)	1.26 (0.73–2.17)	
172.4–204.2	2869	32 (0.94)	0.95 (0.52–1.71)	
≥204.2	2966	43 (1.26)	1.14 (0.61–2.16)	0.6508

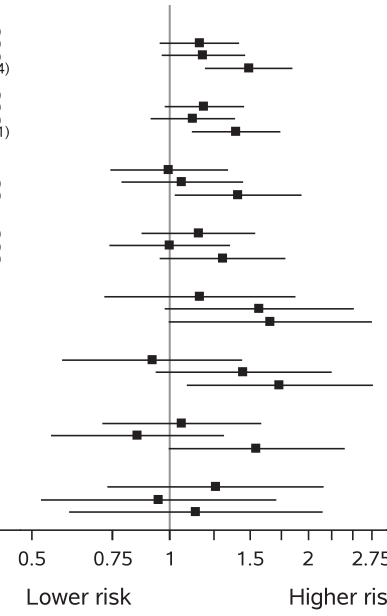


Figure 2. Continued

Table 3. C-Indices and Reclassification Statistics When Adding Information on the Lp-PLA$_2$ Activity Level to the Full Model of Baseline Characteristics and Other Biomarkers

Outcome	C-Index (95% CI) −Lp-PLA$_2$	C-Index (95% CI) +Lp-PLA$_2$	Event NRI	Nonevent NRI	NRI
MACE	0.675 (0.659–0.691)	0.678 (0.662–0.694)	−0.074	0.248	0.175
MCE	0.658 (0.641–0.674)	0.659 (0.643–0.676)	−0.074	0.238	0.164
Cardiovascular death	0.756 (0.733–0.780)	0.757 (0.734–0.781)	−0.046	0.237	0.191
MI	0.665 (0.642–0.687)	0.667 (0.645–0.689)	−0.099	0.239	0.140
Stroke	0.680 (0.646–0.714)	0.686 (0.652–0.720)	0.084	0.050	0.134
Heart failure	0.832 (0.804–0.860)	0.833 (0.805–0.861)	0.167	0.081	0.249
Non-cardiovascular death	0.740 (0.708–0.772)	0.743 (0.711–0.775)	0.051	0.125	0.176
Cancer death	0.757 (0.716–0.798)	0.758 (0.717–0.799)	0.194	−0.029	0.165
Total death	0.732 (0.714–0.751)	0.735 (0.716–0.753)	−0.005	0.207	0.202

The full model contained the following data: randomized treatment, geographic region, age, sex, body mass index, current smoking, hypertension, diabetes mellitus, prior myocardial infarction, prior coronary revascularization, multivessel coronary heart disease, polyvascular disease, significant renal dysfunction, routine biochemical variables (hemoglobin, white blood cell count, estimated glomerular filtration rate [Chronic Kidney Disease Epidemiology Collaboration], low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), and prognostic biomarkers (N-terminal proB-type natriuretic peptide, high-sensitivity cardiac troponin T, cystatin C, high-sensitivity C-reactive protein, and interleukin 6). Lp-PLA$_2$ indicates lipoprotein-associated phospholipase A$_2$; MACE, major adverse cardiac events; MCE, major coronary events; MI, myocardial infarction; NRI, net reclassification index.

Statistics

Lp-PLA$_2$ activity at baseline

Demographics and other baseline characteristics were summarized by quartile group of the baseline Lp-PLA$_2$ activity level. The univariable relationships between Lp-PLA$_2$ activity and background variables were evaluated using the chi-square and Kruskal–Wallis tests for categorical and continuous variables, respectively. Multivariable analyses were used to evaluate the independent associations between baseline Lp-PLA$_2$ activity and other variables, using linear regression models in which continuous variables were included as linear or log-transformed variables, as appropriate. Baseline Lp-PLA$_2$ activity as a predictor of outcomes was evaluated using Kaplan–Meier estimates of the cumulative risk to the first occurrence of an event for the Lp-PLA$_2$ quartile groups. The independent associations between baseline Lp-PLA$_2$ activity levels and outcomes were evaluated using adjusted Cox regression models in which the HR and 95% CI were calculated using the lowest quartile group of Lp-PLA$_2$ activity (quartile 1) as the reference and performing a trend analysis across quartile groups. The predefined adjustment variables for the statistical analyses were randomized treatment, geographic region, age, sex, body mass index, current smoking, hypertension, diabetes mellitus, prior MI, prior coronary revascularization, multivessel CHD, polyvascular disease, significant renal dysfunction, levels of standard biomarkers (hemoglobin, white blood cell count, estimated glomerular filtration rate [Chronic Kidney Disease Epidemiology Collaboration], low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), and levels of prognostic biomarkers (high-sensitivity cardiac troponin T, N-terminal proB-type natriuretic peptide, growth differentiation factor 15, high-sensitivity C-reactive protein, interleukin 6), which were entered as quartiles after log transformation. A Cox proportional hazards model with treatment group (darapladib or placebo), baseline Lp-PLA$_2$ activity categorized by quartile group, and treatment group Lp-PLA$_2$ activity interaction as independent variables was used to test whether the treatment effect differed in relation to Lp-PLA$_2$ activity level. The relevance of the Lp-PLA$_2$ activity interacting with the effect of treatment was evaluated based on the significance of interaction statistics. Data were handled by complete-case analyses with no imputation for missing values. No correction for multiplicity was performed. The analyses of associations between the Lp-PLA$_2$ activity and baseline characteristics, other biomarkers and outcomes, and changes of Lp-PLA$_2$ activity over time were prespecified in the statistical analysis plans.

Lp-PLA$_2$ activity over time

The HRs and *P* values for the association of changes in Lp-PLA$_2$ activity after 1 month and clinical outcomes were estimated using a Cox proportional hazards regression model with baseline Lp-PLA$_2$ activity and change from baseline to month 1 in Lp-PLA$_2$ activity as the covariate, stratified by treatment. In the 100-participant cohort, Lp-PLA$_2$ activity over time was characterized using the generalized estimating equations model with participants fitted as a repeated effect, and it included the following terms: treatment, visit, baseline Lp-PLA$_2$ activity, treatment by visit, and baseline by visit

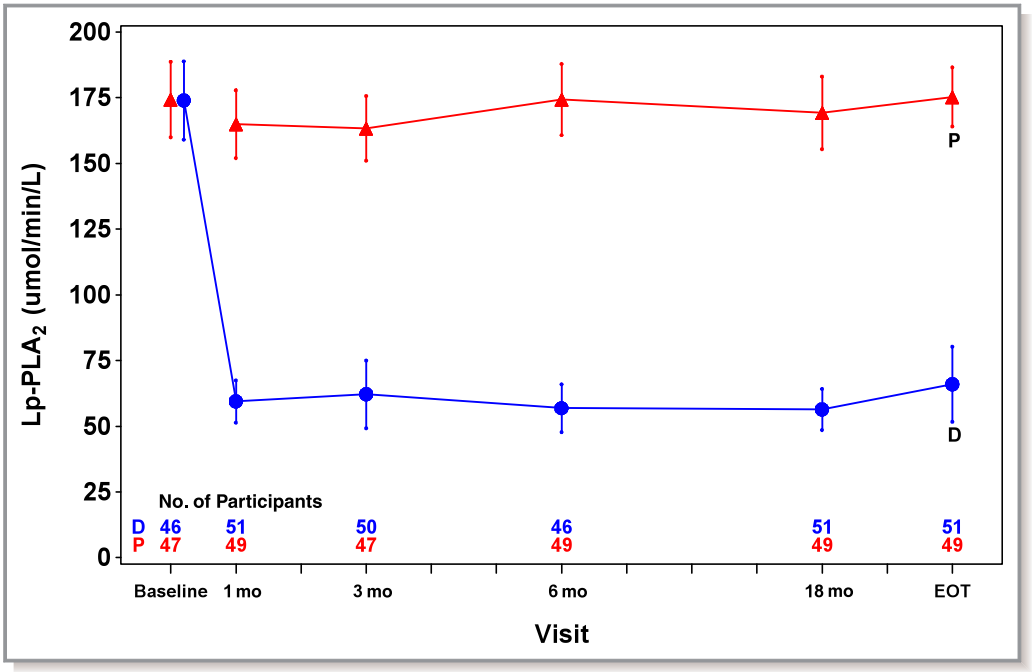


Figure 3. Lp-PLA$_2$ activity (μmol/min per liter) over time during treatment with darapladib and placebo in a subset of 100 patients with available plasma samples for Lp-PLA$_2$ activity measurements until end of follow-up. Symbols illustrate means and CIs for the respective darapladib (blue) and placebo (red) groups at baseline; at follow-up visits at 1, 3, 6, and 18 months; and at the EOT visit. D, darapladib; EOT, end of treatment; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; P, placebo.

interactions. Point estimates, 95% CIs, and *P* values for the mean differences between patients treated with darapladib and placebo at months 1, 3, 6, and 18, and at the end of treatment were calculated using this generalized estimating equations model.

Results

For the 14 500 patients with Lp-PLA$_2$ activity measurements, baseline characteristics were representative of the overall STABILITY population and balanced between the randomized treatment groups (Table 1). There were no differences in rates of outcome events between patients with and without Lp-PLA$_2$ activity measurements. The distribution of the Lp-PLA$_2$ activity levels did not deviate from normality (median 172 μmol/min per liter [interquartile range 143–204 μmol/min per liter]). There were statistically significant differences for the majority of the baseline characteristics and levels of other biomarkers when stratifying patients by baseline Lp-PLA$_2$ quartile groups (Table 1). The following factors showed independent and relevant associations with higher Lp-PLA$_2$ activity in multivariable analyses: male sex, North American origin, current smoking, higher low-density lipoprotein cholesterol level, and lower high-density lipoprotein cholesterol level. Diabetes mellitus was associated with lower Lp-PLA$_2$ activity (Table 2).

In the present cohort, 661 (4.6%) cardiovascular deaths, 695 (4.8%) MIs, and 280 (1.9%) strokes occurred. Of the 661 cardiovascular deaths, 142 deaths of unknown cause were not verified as noncardiovascular and thus were included among the cardiovascular deaths. In total, there were 1444 (10.0%) first primary outcome events and 1404 (9.7%) major coronary events. The outcome events were accrued at a stable rate during follow-up (Figure 1). There was a significant difference in event rates between the highest quartile group of baseline Lp-PLA$_2$ activity in comparison to the lower 3 quartile groups, among which no significant differences in event rates were observed (Figures 1 and 2). The higher event rates in the highest Lp-PLA$_2$ quartile group were observed for all types of events, namely, the primary composite of cardiovascular death, MI, or stroke; the secondary composite of major coronary events; and the individual events cardiovascular death, MI, stroke, hospitalization for heart failure, and cardiovascular and total mortality. The elevated event rates of all of these events in the highest Lp-PLA$_2$ quartile group were maintained after adjusting for baseline characteristics and conventional laboratory tests. In addition, after adjustment for the prognostic biomarkers N-terminal proB-type natriuretic peptide, high-sensitivity cardiac troponin T, growth differentiation factor 15, cystatin C, high-sensitivity C-reactive protein, and interleukin 6, the increased risks of the composite events, hospitalization for heart failure, cardiovascular death, and total death remained,

Table 4. Change in Lipoprotein-Associated Phospholipase A$_2$ Activity After 1 Month by Subgroup in Patients Assigned to Darapladib

Subgroup	Darapladib		
	n	Mean Change	Mean Percentage Inhibition
Prior MI			
Yes	4063	−111.8	63.0
No	2773	−112.9	64.3
Prior coronary revascularization			
Yes	5306	−112.7	64.0
No	1815	−111.1	62.0
Multivessel CHD			
Yes	974	−116.7	65.0
No	5862	−111.5	63.3
Time from CHD event to randomization			
Recent	1628	−110.0	63.1
Remote	5229	−113.0	63.7
Age ≥60 yr			
Yes	5055	−112.5	64.5
No	1781	−111.7	60.7
Diabetes mellitus requiring pharmaceutical management			
Yes	2289	−110.4	65.5
No	4547	−113.2	62.5
HDL-C <40 mg/dL			
Yes	2285	−118.9	63.1
No	4549	−109.0	63.7
Current/previous smoker			
Yes	1344	−113.2	60.1
No	5465	−112.0	64.4
Significant renal dysfunction			
Yes	2068	−117.5	66.3
No	4768	−110.0	62.3
Polyvascular disease			
Yes	1045	−115.3	63.9
No	5791	−111.7	63.4
No. of additional predictors of cardiovascular risk			
1	2376	−108.4	62.0
2	2371	−112.2	63.3
≥3	2066	−117.0	65.5
Race group collapsed			
White	5533	−112.2	62.6
Nonwhite	1303	−112.5	67.2
Region			
North America	1756	−115.6	64.0
Eastern Europe	1632	−109.6	60.4
Western Europe	1833	−110.0	63.7
South America	403	−114.0	62.2
Asia–Pacific	1212	−114.0	67.2
Group in United States			
US	1331	−116.0	63.8
Non-US	5505	−111.4	63.4
Sex			
Male	5623	−114.8	63.1
Female	1213	−100.8	65.4
Blood pressure			
High	3409	−113.8	64.3
Target	3425	−110.8	62.8
eGFR, mL/min/1.73 m^2			
<60	937	−121.0	67.3
≥60	5888	−111.0	62.9
LDL-C, mmol/L			
<1.80	2401	−97.1	63.3
≥1.80 to <2.50	2723	−111.8	63.6
≥2.58	1805	−132.5	63.6
Baseline Lp-PLA$_2$ activity			
Tertile 1	2273	−78.3	61.4
Tertile 2	2342	−110.4	64.0
Tertile 3	2221	−149.0	65.2
High-sensitivity C-reactive protein, mg/L			
<1.0	2516	−108.9	63.9
1.0 to 3.0	2359	−114.4	63.9
>3.0	1667	−115.5	62.9
Family history of CHD			
Yes	1750	−113.4	63.0
No	5069	−111.8	63.7
Body mass index, kg/m^2			
<25	1380	−113.5	66.3
25 to <30	2910	−113.6	63.6
≥30	2536	−110.1	61.9
Waist/hip ratio			
Level 1	851	−110.8	65.3
Level 2	1681	−113.9	64.9
Level 3	4234	−112.1	62.6
Aspirin use			
Yes	6293	−111.7	63.4
No	568	−118.9	64.5
Statin use			
Yes	6657	−111.7	63.5
No	179	−133.9	64.4

Table 4. Continued

Subgroup	Darapladib		
	n	Mean Change	Mean Percentage Inhibition
Beta blocker use			
Yes	5393	−111.6	63.2
No	1443	−114.7	64.8
P2Y12 use			
Yes	2267	−110.4	63.9
No	4569	−113.2	63.3
ACEI/ARB use			
Yes	5291	−112.7	63.9
No	1545	−110.9	62.3

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction.

whereas associations with the individual ischemic events MI or stroke were somewhat attenuated. After complete adjustment, the HRs were 1.50 (95% CI 1.23–1.82) for the primary composite end point, 1.42 (95% CI 1.16–1.74) for major coronary events, 1.95 (95% CI 1.29–2.93) for hospitalization for heart failure, 1.42 (95% CI 1.07–1.89) for cardiovascular death, 1.47 (95% CI 1.17–1.84) for total death, 1.37 (95% CI 1.03–1.81) for MI, and 1.56 (95% CI 1.00–2.44) for stroke when comparing the highest and lowest Lp-PLA$_2$ quartile groups (Figure 2A). These findings were similar in men and women, without any interaction with sex (Figure 2B and 2C). The addition of Lp-PLA$_2$ activity levels to the model including all clinical characteristics, risk factors, and other biomarkers provided no significant change of the c-index and only a modest improvement of the net reclassification index for most events based on better discrimination of patients without increased risk (Table 3).

At 1 month, the Lp-PLA$_2$ activity was reduced from a median of 172 to 57 μmol/min per liter (interquartile range 42–75 μmol/min per liter, mean reduction 112 μmol/min per liter, mean percentage reduction 64%) in the darapladib group compared with a median decrease from 173 to 164 μmol/min per liter (interquartile range 136–196 μmol/min per liter, mean reduction 9 μmol/min per liter, mean percentage reduction 4%) in the placebo group. Darapladib treatment produced a persistent ≈65% relative reduction in Lp-PLA$_2$ activity from the first on-treatment measurement at 1 month until study termination, whereas the placebo group had no significant change in Lp-PLA$_2$ activity (Figure 3). The changes in Lp-PLA$_2$ activity were consistent in all subgroups based on clinical characteristics or biomarkers (Table 4).

In the highest Lp-PLA$_2$ quartile group, there was no significant reduction in the primary composite end point of cardiovascular death, MI, or stroke (HR 0.86, 95% CI 0.72–1.03), whereas the secondary composite end point of major coronary events showed a statistically significant reduction (HR 0.82, 95% CI 0.68–0.98); however, there were no significant interactions between quartile groups of baseline Lp-PLA$_2$ activity and the effects of darapladib (Figures 4 and 5). Finally, there were no significant associations between either the level of Lp-PLA$_2$ activity at 1 month or the reduction in Lp-PLA$_2$ activity and any of the outcome events in the trial (Tables 5 through 8).

Discussion

This prespecified analysis of the STABILITY trial in patients with stable CHD followed for 3.7 years on a background of optimal medical therapy verified that Lp-PLA$_2$ activity is a marker of overall cardiovascular risk and total mortality in patients with stable CHD, in accordance with previous studies.[6–9] Dyslipidemia, male sex, current smoking, and living in the North American region were associated with higher Lp-PLA$_2$ activity, in agreement with other observations.[21] After adjusting for both baseline characteristics and other prognostic biomarkers, Lp-PLA$_2$ activity remained a significant marker of composite cardiovascular events, hospitalization for heart failure, and cardiovascular and total mortality, whereas the associations with new ischemic events such as MI and stroke were attenuated. The finding of an independent association between Lp-PLA$_2$ activity and composite cardiovascular events is in accordance with most [6–9,22–27] although not all[28] previous studies of stable patients at high risk for or with established CHD. The rather weak independent association with a raised risk of cardiovascular events when adjusting for other biomarkers might be a corollary to the lack of association between Lp-PLA$_2$ activity and outcomes in patients with acute coronary syndromes having pronounced elevations of other prognostic biomarkers.[29]

Darapladib treatment persistently reduced Lp-PLA$_2$ activity by ≈65% in all patient groups, consistent with other findings.[16,18,29] Reduction in Lp-PLA$_2$ activity was not associated with any significant effect on the primary composite outcome of cardiovascular death, MI, or stroke in the STABILITY trial overall or with any subgroup based on the Lp-PLA$_2$ activity level at baseline. This lack of effect in the overall trial and in all Lp-PLA$_2$ activity subgroups is in agreement with the findings from the SOLID trial of patients with recent acute coronary syndromes.[29] In addition, in the present study, there were no significant associations between any outcome and the magnitude of reduction in Lp-PLA$_2$ activity level by darapladib treatment. These accumulated experiences show that although high Lp-PLA$_2$ activity was associated with an increased risk of cardiovascular events, pharmacological lowering of Lp-PLA$_2$ activity was not a useful

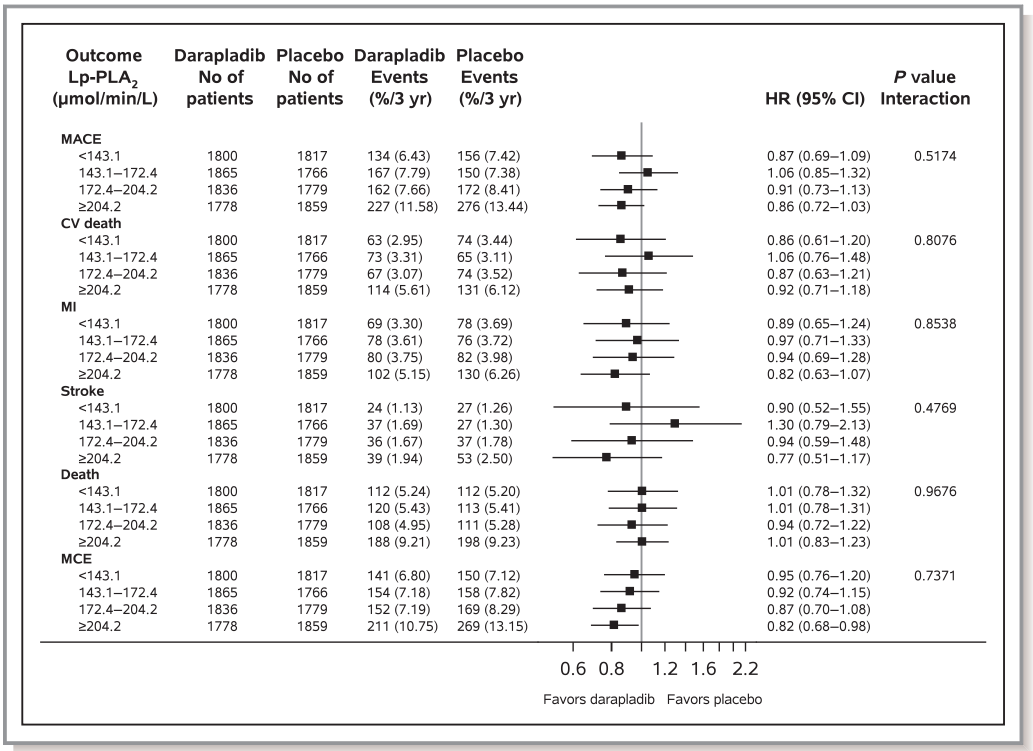


Figure 4. Effect of darapladib compared with placebo in relation to baseline Lp-PLA$_2$ activity (μmol/min per liter) quartile groups concerning all outcomes. MACE specifies CV death, MI, or stroke; MCE specifies coronary heart disease death, MI, or urgent coronary revascularization. Event rates are Kaplan–Meier rates. CV indicates cardiovascular; HR, hazard ratio; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; MACE, major adverse cardiac events; MCE, major coronary events; MI, myocardial infarction.

treatment target for prevention of cardiovascular events in patients with stable CHD.

Prior to the current study, several lines of evidence supported Lp-PLA$_2$ activity as a risk indicator of adverse outcomes both in patients with stable CHD and in the general population in addition to being potentially involved in the development of atherosclerosis and vulnerable plaque at the tissue level.[6–9,22–27] Furthermore, in 2 case–control studies, natural deficiency of Lp-PLA$_2$ activity due to carriage of the V279F-null allele in the Lp-PLA$_2$ gene was associated with a lower risk of developing CHD.[30] In a recent study in European CHD patients, a single-nucleotide polymorphism of the Lp-PLA$_2$ gene was found to be associated with both increased Lp-PLA$_2$ activity in plasma and a raised risk of MI.[31] Lp-PLA$_2$ has also been shown to be highly concentrated in unstable and ruptured atherosclerotic plaques and to be strongly expressed in macrophages in lesions prone to rupture.[16] Direct inhibition of Lp-PLA$_2$ activity prevented progression to advanced coronary atherosclerotic lesions in diabetic and hypercholesterolemic swine.[17] Finally, in a phase II trial, darapladib appeared to stabilize the necrotic core size and plaque burden in coronary atherosclerotic plaques compared with placebo[18]; therefore, it was a logical hypothesis that inhibition of Lp-PLA$_2$ activity with darapladib might lead to clinical benefit, especially in patients with high Lp-PLA$_2$ activity at baseline and/or a pronounced reduction by the treatment.[27] Nevertheless, this current study, based on 3 to 5 years darapladib treatment and Lp-PLA$_2$ activity levels that were available for ≈14 500 patients before and during treatment and with a consistent ≈65% reduction of the Lp-PLA$_2$ activity in all patient groups, showed no associated effects of darapladib on clinical outcomes. This finding clearly refutes any clinically important effects of darapladib for prevention of cardiovascular events in patients with CHD.

The current findings corroborate other studies showing that patients with stable CHD and high Lp-PLA$_2$ activity have a raised risk of cardiovascular events and total mortality. The increase in risk with Lp-PLA$_2$ activity was not linear but was most pronounced in the ≈25% of patients with the highest levels. The increased risk associated with high Lp-PLA$_2$ activity was independent of demographics, clinical characteristics, and conventional biochemical risk indicators such as dyslipidemia, dysglycemia, anemia, and renal dysfunction. When adjusting for cardiac, inflammatory, and renal function biomarkers, the independent associations between Lp-PLA$_2$ activity and cardiovascular and total mortality and

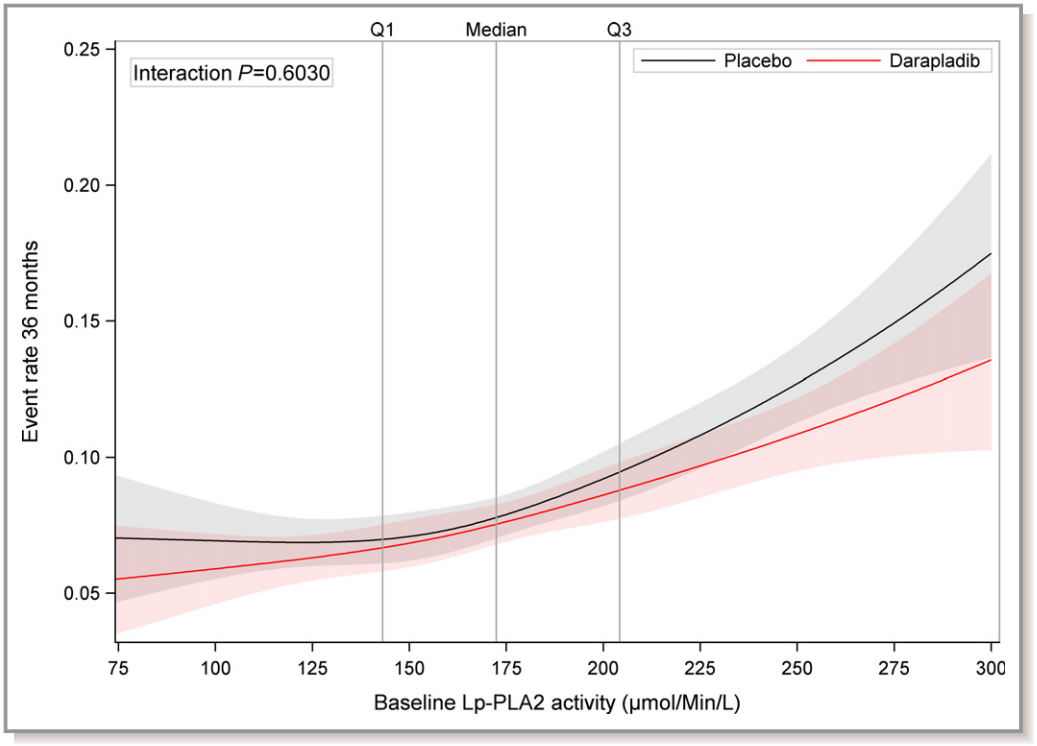


Figure 5. Continuous Lp-PLA$_2$ activity (µmol/min per liter) at baseline in relation to major adverse cardiac events (cardiovascular death, myocardial infarction, or stroke) during treatment with darapladib (red line) and placebo (black line) using restricted cubic splines using a Cox proportional hazards model including treatment group, LpPLA$_2$, and treatment by LpPLA$_2$ interaction as covariates. Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; Q, quartile.

hospitalization for heart failure remained, whereas the associations with ischemic events were attenuated. Similarly, there was no association between Lp-PLA$_2$ activity and cardiovascular outcomes in patients with acute coronary syndromes, in which the majority have elevated cardiac and inflammatory markers.[29] Without an associated indication for a specific treatment, it is unlikely that Lp-PLA$_2$ activity will be used for identification of patients at high risk, considering the competition with other already generally available and more specific prognostic biomarkers. In the present study, as in a previous study,[32] there was an inverse relationship between Lp-PLA$_2$ activity and diabetes mellitus. In that study, diabetes mellitus was associated with a redistribution of Lp-PLA$_2$ activity from low- to high-density lipoprotein particles.[32] These complex interactions among Lp-PLA$_2$ activity, glucose, and lipoprotein metabolism might need to be considered in future studies of the importance of Lp-PLA$_2$ activity for cardiovascular events in different patient populations.

Conclusions

Based on the experiences from 3 to 5 years of darapladib treatment and available Lp-PLA$_2$ activity levels before and during treatment in 14 500 patients with stable CHD, high pretreatment Lp-PLA$_2$ activity was associated with an increased risk of cardiovascular events; however, pharmacological lowering of Lp-PLA$_2$ activity did not significantly reduce cardiovascular events, regardless of the baseline level or degree of reduction of Lp-PLA$_2$ activity.

Appendix

Contributors

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Table 5. Changes in Lp-PLA$_2$ Activity at 1 Month* Compared With Baseline in Relation to Outcomes in the Respective Placebo and Darapladib Groups

		Placebo Change			Darapladib Change			Change From Baseline	
Outcome Events		n	Mean	%	n	Mean	%	HR for 10-U Increase (95% CI)	*P* Value
MACE†	Yes	706	−10.9	5.1	646	−121.7	65.5	0.99 (0.97–1.01)	0.258
	No	6167	−8.5	4.1	6190	−111.3	63.3		
MCE‡	Yes	699	−9.7	4.4	614	−120.4	65.1	1.00 (0.98–1.02)	0.919
	No	6174	−8.7	4.1	6222	−111.5	63.3		
Total coronary events	Yes	1106	−9.1	4.1	976	−117.2	64.3	1.01 (0.99–1.02)	0.451
	No	5767	−8.7	4.2	5860	−111.5	63.4		
Cardiovascular death	Yes	323	−12.0	5.5	291	−122.4	65.4	0.99 (0.96–1.01)	0.335
	No	6550	−8.6	4.1	6545	−111.8	63.4		
Myocardial infarction	Yes	341	−9.1	4.3	311	−121.6	66.0	0.99 (0.97–1.02)	0.571
	No	6532	−8.8	4.2	6525	−111.8	63.4		
Stroke	Yes	136	−13.2	6.3	129	−117.7	64.6	0.99 (0.96–1.03)	0.724
	No	6737	−8.7	4.1	6707	−112.2	63.5		
Hospitalization for heart failure	Yes	160	−10.4	4.5	136	−127.5	66.8	0.97 (0.94–1.01)	0.122
	No	6713	−8.7	4.2	6700	−112.0	63.4		
All-cause mortality	Yes	498	−11.3	5.0	478	−120.9	65.4	0.99 (0.97–1.01)	0.223
	No	6375	−8.6	4.1	6358	−111.6	63.4		

Event rates are Kaplan–Meier rates. Lp-PLA$_2$ indicates lipoprotein-associated phospholipase A$_2$; MACE, major adverse cardiac events; MCE, major coronary events.
*The analyses are adjusted for baseline Lp-PLA$_2$ and stratified by randomized treatment. The changes from baseline results are identical to the Month 1 results as both are adjusted for the baseline value.
†MACE: cardiovascular death, myocardial infarction, or stroke.
‡MCE: coronary heart disease death, myocardial infarction, or urgent coronary revascularization.

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Table 6. Range of Change of Lp-PLA$_2$ Activity Level From Baseline to 1 Month in All Patients With Lp-PLA$_2$ Measurements at 1 Month (Including Both Darapladib and Placebo Groups) Per Decile Group

Decile	Change From Baseline Lp-PLA$_2$ (μmol/min/L)
1	≤−146.1
2	>−146.1 to ≤−121.4
3	>−121.4 to ≤−101.9
4	>−101.9 to ≤−80.9
5	>−80.9 to ≤−46.1
6	>−46.1 to ≤−21.8
7	>−21.8 to ≤−10.9
8	>−10.9 to ≤−2.1
9	>−2.1 to ≤8.6
10	>8.6

Lp-PLA$_2$ indicates lipoprotein-associated phospholipase A$_2$.

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Table 7. Range of Percentage Change of Lp-PLA$_2$ Activity Level at 1 Month Compared With Baseline in All Patients With Lp-PLA$_2$ Measurements at 1 Month (Including Both Darapladib and Placebo Groups) Per Decile Group

Decile	Percentage Inhibition of Lp-PLA$_2$ (μmol/min/L)
1	≤−5.3
2	>−5.3 to ≤1.3
3	>1.3 to ≤6.5
4	>6.5 to ≤12.3
5	>12.3 to ≤25.7
6	>25.7 to ≤55.3
7	>55.3 to ≤63.4
8	>63.4 to ≤69.5
9	>69.5 to ≤76.2
10	>76.2

Lp-PLA$_2$ indicates lipoprotein-associated phospholipase A$_2$.

Table 8. Range of Lp-PLA$_2$ Activity Level at 1 Month in All Patients With Lp-PLA$_2$ Measurements at 1 Month (Including Both Darapladib and Placebo Groups) Per Decile Group

Decile	Levels at 1 Month Lp-PLA$_2$ (μmol/min/L)
1	≤37.9
2	>37.9 to ≤50.9
3	>50.9 to ≤63.3
4	>63.3 to ≤78.5
5	>78.5 to ≤106.9
6	>106.9 to ≤134.7
7	>134.7 to ≤156.4
8	>156.4 to ≤178.1
9	>178.1 to ≤205.6
10	>205.6

Lp-PLA$_2$ indicates lipoprotein-associated phospholipase A$_2$.

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References

1. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420:868–874.
2. Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation*. 2004;109:2818–2825.
3. Omland T, Pfeffer MA, Solomon SD, de Lemos JA, Rosjo H, Saltyte Benth J, Maggioni A, Domanski MJ, Rouleau JL, Sabatine MS, Braunwald E; PEACE Investigators. Prognostic value of cardiac troponin I measured with a highly sensitive assay in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2013;61:1240–1249.
4. Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med*. 2005;352:666–675.
5. Jernberg T, Lindahl B, James S, Larsson A, Hansson LO, Wallentin L. Cystatin C: a novel predictor of outcome in suspected or confirmed non-ST-elevation acute coronary syndrome. *Circulation*. 2004;110:2342–2348.
6. The Lp-PLA2 Studies Collaboration. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet*. 2010;375:1536–1544.
7. Kleber ME, Siekmeier R, Delgado G, Grammer TB, Winkelmann BR, Scharnagl H, Boehm BO, März W. C-reactive protein and lipoprotein-associated phospholipase A2 in smokers and nonsmokers of the Ludwigshafen Risk and Cardiovascular Health study. *Adv Exp Med Biol*. 2015;832:15–23.
8. Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, Thompson A, Butterworth AS, Sarwar N, Wormser D, Saleheen D, Ballantyne CM, Psaty BM, Sundström J, Ridker PM, Nagel D, Gillum RF, Ford I, Ducimetiere P, Kiechl S, Koenig W, Dullaart RP, Assmann G, D'Agostino RB Sr, Dagenais GR, Cooper JA, Kromhout D, Onat A, Tipping RW, Gómez-de-la-Cámara A, Rosengren A, Sutherland SE, Gallacher J, Fowkes FG, Casiglia E, Hofman A, Salomaa V, Barrett-Connor E, Clarke R, Brunner E, Jukema JW, Simons LA, Sandhu M, Wareham NJ, Khaw KT, Kauhanen J, Salonen JT, Howard WJ, Nordestgaard BG, Wood AM, Thompson SG, Boekholdt SM, Sattar N, Packard C, Gudnason V, Danesh J. Lipid-related markers and cardiovascular disease prediction. *JAMA*. 2012;307:2499–2506.
9. Kleber ME, Wolfert RL, De Moissl GD, Grammer TB, Dietz S, Winkelmann BR, Boehm BO, März W. Lipoprotein associated phospholipase A2 concentration predicts total and cardiovascular mortality independently of established risk

factors (The Ludwigshafen Risk and Cardiovascular Health Study). *Clin Lab*. 2011;57:659–667.

10. Mallat Z, Lambeau G, Tedgui A. Lipoprotein-associated and secreted phospholipases A(2) in cardiovascular disease: roles as biological effectors and biomarkers. *Circulation*. 2010;122:2183–2200.
11. Hakkinen T, Luoma JS, Hiltunen MO, Macphee CH, Milliner KJ, Patel L, Rice SQ, Tew DG, Karkola K, Ylä-Herttuala S. Lipoprotein-associated phospholipase A (2), platelet-activating factor acetylhydrolase, is expressed by macrophages in human and rabbit atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 1999;19:2909–2917.
12. Liu J, Wang W, Qi Y, Yong Q, Zhou G, Wang M, Sun J, Liu J, Jia Z, Zhao D. Association between the lipoprotein-associated phospholipase A2 activity and the progression of subclinical atherosclerosis. *J Atheroscler Thromb*. 2014;21:532–542.
13. MacPhee CH, Moores KE, Boyd HF, Dhanak D, Ife RJ, Leach CA, Leake DS, Milliner KJ, Patterson RA, Suckling KE, Tew DG, Hickey DM. Lipoprotein-associated phospholipase A2, platelet-activating factor acetylhydrolase, generates two bioactive products during the oxidation of low-density lipoprotein: use of a novel inhibitor. *Biochem J*. 1999;338(Pt 2):479–487.
14. Mohler ER III, Ballantyne CM, Davidson MH, Hanefeld M, Ruilope LM, Johnson JL, Zalewski A; Darapladib Investigators. The effect of darapladib on plasma lipoprotein-associated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease risk equivalent: the results of a multicenter, randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol*. 2008;51:1632–1641.
15. Johnson JL, Shi Y, Snipes R, Janmohamed S, Rolfe TE, Davis B, Postle A, Macphee CH. Effect of darapladib treatment on endarterectomy carotid plaque lipoprotein-associated phospholipase A2 activity: a randomized, controlled trial. *PLoS One*. 2014;9:e89034.
16. Kolodgie FD, Virmani R, Burke AP, Farb A, Weber DK, Kutys R, Finn AV, Gold HK. Pathologic assessment of the vulnerable human coronary plaque. *Heart*. 2004;90:1385–1391.
17. Wilensky RL, Shi Y, Mohler ER III, Hamamdzic D, Burgert ME, Li J, Postle A, Fenning RS, Bollinger JG, Hoffman BE, Pelchovitz DJ, Yang J, Mirabile RC, Webb CL, Zhang L, Zhang P, Gelb MH, Walker MC, Zalewski A, Macphee CH. Inhibition of lipoprotein-associated phospholipase A2 reduces complex coronary atherosclerotic plaque development. *Nat Med*. 2008;14:1059–1066.
18. Serruys PW, Garcia-Garcia HM, Buszman P, Erne P, Verheye S, Aschermann M, Duckers H, Bleie O, Dudek D, Bøtker HE, von Birgelen C, D'Amico D, Hutchinson T, Zambanini A, Mastik F, van Es GA, van der Steen AF, Vince DG, Ganz P, Hamm CW, Wijns W, Zalewski A; Integrated Biomarker and Imaging Study-2 Investigators. Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation*. 2008;118:1172–1182.
19. White HD, Held C, Stewart R, Tarka E, Brown R, Davies RY, Budaj A, Harrington RA, Steg PG, Ardissino D, Armstrong PW, Avezum A, Aylward PE, Bryce A, Chen H, Chen MF, Corbalan R, Dalby AJ, Danchin N, De Winter RJ, Denchev S, Diaz R, Elisaf M, Flather MD, Goudev AR, Granger CB, Grinfeld L, Hochman JS, Husted S, Kim HS, Koenig W, Linhart A, Lonn E, López-Sendón J, Manolis AJ, Mohler ER III, Nicolau JC, Pais P, Parkhomenko A, Pedersen TR, Pella D, Ramos-Corrales MA, Ruda M, Sereg M, Siddique S, Sinnaeve P, Smith P, Sritara P, Swart HP, Sy RG, Teramoto T, Tse HF, Watson D, Weaver WD, Weiss R, Viigimaa M, Vinereanu D, Zhu J, Cannon CP, Wallentin L. Darapladib for preventing ischemic events in stable coronary heart disease. *N Engl J Med*. 2014;370:1702–1711.
20. Wallentin L, Zethelius B, Berglund L, Eggers KM, Lind L, Lindahl B, Wollert KC, Siegbahn A. GDF-15 for prognostication of cardiovascular and cancer morbidity and mortality in men. *PLoS One*. 2013;8:e78797.
21. Gregson J, Stirnadel-Farrant HA, Doobaree IU, Koro C. Variation of lipoprotein associated phospholipase A2 across demographic characteristics and cardiovascular risk factors: a systematic review of the literature. *Atherosclerosis*. 2012;225:11–21.
22. Koenig W, Twardella D, Brenner H, Rothenbacher D. Lipoprotein-associated phospholipase A2 predicts future cardiovascular events in patients with coronary heart disease independently of traditional risk factors, markers of inflammation, renal function, and hemodynamic stress. *Arterioscler Thromb Vasc Biol*. 2006;26:1586–1593.
23. Corsetti JP, Rainwater DL, Moss AJ, Zareba W, Sparks CE. High lipoprotein-associated phospholipase A2 is a risk factor for recurrent coronary events in postinfarction patients. *Clin Chem*. 2006;52:1331–1338.
24. Sabatine MS, Morrow DA, O'Donoghue M, Jablonksi KA, Rice MM, Solomon S, Rosenberg Y, Domanski MJ, Hsia J; PEACE Investigators. Prognostic utility of lipoprotein-associated phospholipase A2 for cardiovascular outcomes in patients with stable coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2007;27:2463–2469.
25. Ridker PM, MacFadyen JG, Wolfert RL, Koenig W. Relationship of lipoprotein-associated phospholipase A(2) mass and activity with incident vascular events among primary prevention patients allocated to placebo or to statin therapy: an analysis from the JUPITER trial. *Clin Chem*. 2012;58:877–886.
26. O'Donoghue M, Morrow DA, Sabatine MS, Murphy SA, McCabe CH, Cannon CP, Braunwald E. Lipoprotein-associated phospholipase A2 and its association with cardiovascular outcomes in patients with acute coronary syndromes in the PROVE IT-TIMI 22 (PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) trial. *Circulation*. 2006;113:1745–1752.
27. White HD, Simes J, Stewart RA, Blankenberg S, Barnes EH, Marschner IC, Thompson P, West M, Zeller T, Colquhoun DM, Nestel P, Keech AC, Sullivan DR, Hunt D, Tonkin A; LIPID Study Investigators. Changes in lipoprotein-associated phospholipase A2 activity predict coronary events and partly account for the treatment effect of pravastatin: results from the Long-Term Intervention with Pravastatin in Ischemic Disease study. *J Am Heart Assoc*. 2013;2:e000360 doi: 10.1161/JAHA.113.000360.
28. Heart Protection Study Collaborative Group. Lipoprotein-associated phospholipase A(2) activity and mass in relation to vascular disease and nonvascular mortality. *J Intern Med*. 2010;268:348–358.
29. O'Donoghue ML, Braunwald E, White HD, Lukas MA, Tarka E, Steg PG, Hochman JS, Bode C, Maggioni AP, Im K, Shannon JB, Davies RY, Murphy SA, Crugnale SE, Wiviott SD, Bonaca MP, Watson DF, Weaver WD, Serruys PW, Cannon CP; SOLID-TIMI 52 Investigators, Steen DL. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. *JAMA*. 2014;312:1006–1015.
30. Jang Y, Waterworth D, Lee JE, Song K, Kim S, Kim HS, Park KW, Cho HJ, Oh IY, Park JE, Lee BS, Ku HJ, Shin DJ, Lee JH, Jee SH, Han BG, Jang HY, Cho EY, Vallance P, Whittaker J, Cardon L, Mooser V. Carriage of the V279F null allele within the gene encoding Lp-PLA(2) is protective from coronary artery disease in South Korean males. *PLoS One*. 2011;6:e18208.
31. Maiolino G, Pedon L, Cesari M, Frigo AC, Wolfert RL, Barisa M, Pagliani L, Rossitto G, Seccia TM, Zanchetta M, Rossi GP. Lipoprotein-associated phospholipase A2 activity predicts cardiovascular events in high risk coronary artery disease patients. *PLoS One*. 2012;7:e48171.
32. Mayer O Jr, Seidlerova J, Filipovsky J, Timoracka K, Bruthans J, Vanek J, Cerná L, Wohlfahrt P, Renata C, Trefil L. Unexpected inverse relationship between impaired glucose metabolism and lipoprotein-associated phospholipase A2 activity in patients with stable vascular disease. *Eur J Intern Med*. 2014;25:556–560.

Lipoprotein–Associated Phospholipase A_2 Activity Is a Marker of Risk But Not a Useful Target for Treatment in Patients With Stable Coronary Heart Disease

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