Original Investigation

Varespladib and Cardiovascular Events in Patients With an Acute Coronary Syndrome
The VISTA-16 Randomized Clinical Trial

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IMPORTANCE Secretory phospholipase A_2 ($sPLA_2$) generates bioactive phospholipid products implicated in atherosclerosis. The $sPLA_2$ inhibitor varespladib has favorable effects on lipid and inflammatory markers; however, its effect on cardiovascular outcomes is unknown.

OBJECTIVE To determine the effects of $sPLA_2$ inhibition with varespladib on cardiovascular outcomes.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, randomized, multicenter trial at 362 academic and community hospitals in Europe, Australia, New Zealand, India, and North America of 5145 patients randomized within 96 hours of presentation of an acute coronary syndrome (ACS) to either varespladib (n = 2572) or placebo (n = 2573) with enrollment between June 1, 2010, and March 7, 2012 (study termination on March 9, 2012).

INTERVENTIONS Participants were randomized to receive varespladib (500 mg) or placebo daily for 16 weeks, in addition to atorvastatin and other established therapies.

MAIN OUTCOMES AND MEASURES The primary efficacy measure was a composite of cardiovascular mortality, nonfatal myocardial infarction (MI), nonfatal stroke, or unstable angina with evidence of ischemia requiring hospitalization at 16 weeks. Six-month survival status was also evaluated.

RESULTS At a prespecified interim analysis, including 212 primary end point events, the independent data and safety monitoring board recommended termination of the trial for futility and possible harm. The primary end point occurred in 136 patients (6.1%) treated with varespladib compared with 109 patients (5.1%) treated with placebo (hazard ratio [HR], 1.25; 95% CI, 0.97-1.61; log-rank P = .08). Varespladib was associated with a greater risk of MI (78 [3.4%] vs 47 [2.2%]; HR, 1.66; 95% CI, 1.16-2.39; log-rank P = .005). The composite secondary end point of cardiovascular mortality, MI, and stroke was observed in 107 patients (4.6%) in the varespladib group and 79 patients (3.8%) in the placebo group (HR, 1.36; 95% CI, 1.02-1.82; P = .04).

CONCLUSIONS AND RELEVANCE In patients with recent ACS, varespladib did not reduce the risk of recurrent cardiovascular events and significantly increased the risk of MI. The $sPLA_2$ inhibition with varespladib may be harmful and is not a useful strategy to reduce adverse cardiovascular outcomes after ACS.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01130246

JAMA. 2014;311(3):252-262. doi:10.1001/jama.2013.282836
Published online November 18, 2013.

Supplemental content at jama.com

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Despite a high rate of use of contemporary therapies, patients with acute coronary syndrome (ACS) face a substantial risk of early, recurrent adverse cardiovascular events.[1] Increasing evidence supports a potential role of inflammation in the progression and clinical instability of coronary heart disease.[2] Necropsy studies show inflammatory cells within atherosclerotic plaques,[3] and clinical outcomes trials show an association between systemic inflammatory markers and cardiovascular risk.[4] Conversely, reductions in inflammatory markers associate with reductions in cardiovascular events in clinical trials and may contribute to the benefit of statins.[4] These observations provide a rationale to test novel agents that target specific inflammatory factors implicated in atherosclerosis to determine if it reduces cardiovascular risk.[5]

The secretory phospholipase A_2 ($sPLA_2$) family of enzymes hydrolyze fatty acids of glycophospholipids, generating bioactive lipid species involved in inflammation.[6] However, although some $sPLA_2$ isoforms are proatherogenic (groups IIA and V), other isoforms are protective (group X).[7] Considerable evidence implicates a potential role for groups IIA and V $sPLA_2$ in cardiovascular disease. Higher circulating levels of $sPLA_2$-IIA concentration and activity associate with cardiovascular risk in asymptomatic individuals and patients with established coronary disease.[8] Pathologic studies demonstrate the presence of $sPLA_2$ isoforms groups IIA, III, V, and X in atherosclerotic lesions and myocardial regions that have sustained ischemic injury.[6,9,10] These observations have stimulated interest in the potential value of $sPLA_2$ inhibition as a cardioprotective strategy.[5]

Varespladib methyl is a nonspecific pan-$sPLA_2$ inhibitor with favorable effects on atherosclerotic lesions in animal studies.[11] Initial studies demonstrated that varespladib reduced levels of $sPLA_2$-IIA by more than 90%, in addition to lowering low-density lipoprotein cholesterol (LDL-C) and C-reactive protein (CRP) in patients with stable coronary disease and ACS.[12-14] The Vascular Inflammation Suppression to Treat Acute Coronary Syndrome for 16 Weeks (VISTA-16) study was designed to evaluate the effects of varespladib on cardiovascular risk in patients with ACS.[15]

Methods

Study Population

Details of the study design and study protocol have been published previously.[15] Patients aged 40 years or older hospitalized with an ACS who provided written, informed consent were eligible to participate. Documentation of ACS required either (1) elevation of biomarkers accompanied by symptoms of acute myocardial ischemia and/or new or presumed new ischemic electrocardiographic abnormalities or (2) symptoms in combination with new or presumed new electrocardiographic changes in patients without elevated biomarkers. Patients were also required to have 1 additional risk factor for recurrent events, including diabetes, metabolic syndrome, a high-density lipoprotein cholesterol (HDL-C) level of less than 42 mg/dL (to convert to millimoles per liter, multiply by 0.0259), calculated glomerular filtration rate of less than 60 mL/min, peripheral vascular disease, prior history of ischemic stroke, or transient ischemic attack, myocardial infarction (MI), or coronary revascularization. Patients were excluded from enrollment if LDL-C measured before the index ACS event was not at target levels according to local guidelines, despite current treatment with the maximum labeled dose of a statin. Other key exclusion criteria included advanced congestive heart failure, glycated hemoglobin value of at least 11% (to convert to proportion of total hemoglobin, multiply by 0.01), malignancy, severe liver or renal disease, malignancy, statin intolerance, and fasting triglyceride levels of at least 400 mg/dL (to convert to millimoles per liter, multiply by 0.0113).

Study Procedures

The protocol specified that enrolled patients be treated with individualized, evidence-based management of ACSs, including diet and atorvastatin at a dose of at least 20 mg. Patients who met all inclusion criteria were randomized within 96 hours of presentation of the index event in a 1:1 ratio to treatment with varespladib (500 mg/d) or matching placebo, stratified by use of any lipid-modifying therapy before the index event and the type of qualifying index event (ST-elevation MI [STEMI], non–ST-elevation MI, or unstable angina). Any clinically indicated coronary revascularization during the index event was performed before randomization. Patients reported for study visits at weeks 1, 2, 4, 8, and 16 during the treatment phase. Patients with an LDL-C level of at least 100 mg/dL (to convert to millimoles per liter, multiply by 0.0259) at week 8 underwent atorvastatin dose escalation. Telephone follow-up to ascertain vital status was scheduled to occur 6 months following cessation of study drug.

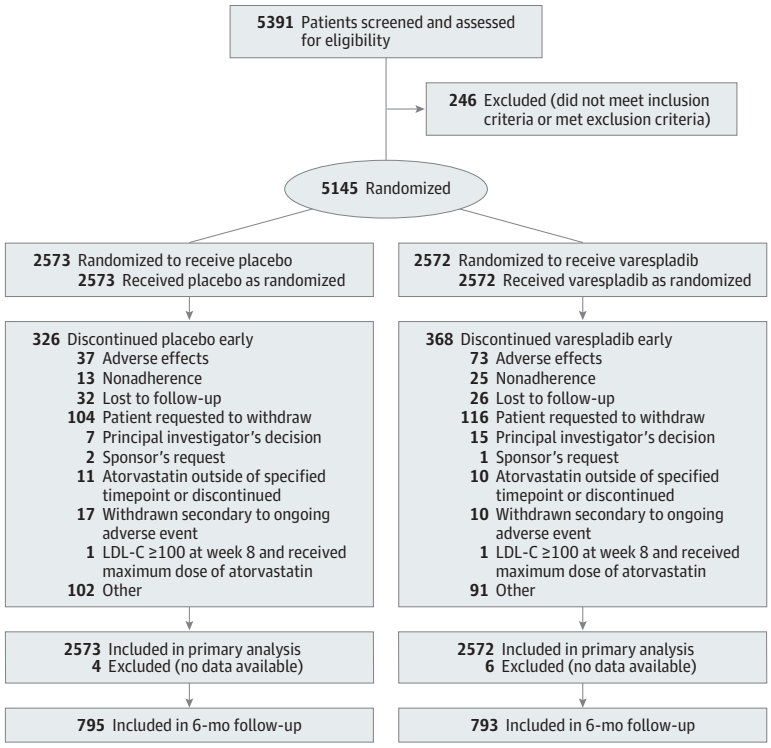
Study Outcomes

The primary efficacy outcome was a composite of cardiovascular mortality, nonfatal MI, nonfatal stroke, or unstable angina with evidence of ischemia requiring hospitalization. Secondary efficacy outcomes included the composite of cardiovascular mortality, nonfatal MI, and nonfatal stroke; each component of the primary outcome; total mortality; and changes in circulating lipid and inflammatory markers. All investigator-reported outcomes were adjudicated by a central committee at the Cleveland Clinic Coordinating Center for Clinical Research (C5Research).

Statistical Analysis

Primary efficacy analysis was based on time to first occurrence of any positively adjudicated primary end point event by intention-to-treat, including all events in all patients from randomization to trial termination. The trial was designed to enroll 6500 patients, assuming an 8.5% primary end point event rate in the placebo group, with 80% power to detect a 25% reduction in the relative risk of the varespladib group, necessitating the adjudication of 385 primary end point events. An interim end point analysis for futility was specified at approximately 50% of the required primary end point events. Estimates of hazard ratios (HRs) and 95% CIs for varespladib compared with placebo were calculated by Cox proportional hazards regression models. Continuous data are presented as

Figure 1. Flow of Patients Through the Trial



LDL-C indicates low-density lipoprotein cholesterol.

mean (SD), unless otherwise indicated. Race/ethnicity was self-reported by participants. Significance testing was performed using 2-sided tests (α = .05) using SAS version 9.2 (SAS Institute). Additional analytical methods are described in the previously published study protocol.[15]

Results

Study Population

A total of 5145 patients were enrolled at 362 sites in 17 countries between June 1, 2010, and March 7, 2012, and entered into the intention-to-treat analysis. The patient disposition during the study is shown in **Figure 1**. The qualifying ACS event was biomarker positive in 85% of the patients. The median (interquartile range [IQR]) time from presentation with the index event to randomization and first study drug administration was 57 (39-76) hours. Baseline characteristics of patients at randomization were well matched in the 2 treatment groups (**Table 1**). A high rate of cardiovascular risk factors and established atherosclerotic disease was observed in both groups. Before the index ACS event, 36% of patients had been treated with a lipid-modifying agent. At randomization, patients were well treated in both groups with a high rate of use of antiplatelet agents, statins, β-blockers, angiotensin-converting enzyme inhibitors, or receptor blockers (see eTable 1 in the Supplement). Coronary revascularization in response to the index event was performed in 80% of the patients. At randomization, mean LDL-C was 105 mg/dL and HDL-C was 43 mg/dL. Median (IQR) CRP was 10.4 (4.0-28.7) mg/L in the placebo group and 11.4 (4.5-33.0) mg/L in the varespladib group. (To convert CRP to nmol/L, multiply by 9.524.)

On March 9, 2012, at the prespecified interim analysis, when 212 primary outcomes had been recorded in 5012 randomized patients, the independent data and safety monitoring board recommended termination of the trial for futility according to predetermined criteria. The executive steering committee and sponsor (Anthera Pharmaceuticals) accepted this recommendation and terminated the trial on this date, with median (IQR) patient follow-up of 16.1 (13.4-16.4) weeks. Patients were treated for a mean (SD) of 13.4 (4.4) weeks. The mean (SD) follow-up of patients for the treatment period was 13.5 (4.6) weeks. All 5145 patients were included in the 16-week analysis. Time to event was calculated from randomization date to the date of the event, or censored at the last known follow-up for each patient if no event occurred. Only 1588 patients were contacted for the 6-month assessment.

Before study termination, premature discontinuation of treatment for reasons other than death occurred in 11.0% of the patients receiving varespladib and 10.4% of the patients receiving placebo. During treatment, 96% of patients in both groups remained at least 80% adherent with prescribed study drug doses. In the varespladib and placebo groups, 4.2% and 3.7%, respectively, of patients withdrew consent and an additional 0.8% and 1.1%, respectively, were lost to follow-up with unknown final vital status.

Biochemical Parameters

Changes in biochemical parameters during the course of the study are shown in **Figure 2**. Per protocol, atorvastatin was used

in nearly all patients, with a median dosage of 40 mg/d. Slightly fewer than 20% of patients received 80 mg/d. Between randomization and week 16 of the study, LDL-C decreased by 28.8% in the varespladib group and 25.1% in the placebo group (P = .008). At week 16, the mean LDL-C was 69.1 mg/dL in the varespladib group and 73.8 mg/dL in the placebo group. During assigned treatment, levels of triglycerides and HDL-C did not differ between groups. The CRP levels were initially very

Table 1. Clinical Baseline Characteristics of Patients Treated With Placebo or Varespladib

Characteristics[a]	Placebo (n = 2573)	Varespladib (n = 2572)
Age, mean (SD), y	60.7 (9.8)	61.0 (10.0)
Female sex	660 (25.7)	691 (26.9)
Race/ethnicity		
White	2277 (88.5)	2274 (88.4)
Asian	226 (8.8)	221 (8.6)
Black	30 (1.2)	433 (16.8)
Other[b]	41 (1.6)	33 (1.3)
Region of enrollment		
North America	528 (20.8)	535 (20.8)
Western Europe and Lebanon	315 (12.2)	323 (12.6)
Eastern Europe	1422 (55.3)	1388 (54.0)
Asia	215 (8.4)	213 (8.3)
Australia and New Zealand	93 (3.6)	113 (4.4)
Cardiovascular risk factors		
Hypertension	1977 (77.8)	1911 (75.2)
Diabetes	803 (31.3)	801 (31.3)
Hypercholesterolemia	1292 (50.9)	1255 (49.3)
Present smoker[c]	860 (33.6)	854 (33.4)
Metabolic syndrome	1587 (64.3)	1589 (64.2)
Cardiovascular disease history		
Myocardial infarction	743 (29.6)	769 (30.2)
PCI	476 (18.6)	453 (17.7)
CABG surgery	182 (7.1)	161 (6.3)
Stroke	123 (4.8)	128 (5.0)
Peripheral arterial disease	177 (6.9)	179 (7.0)
Body mass index, mean (SD)[d]	29.6 (5.1)	29.8 (5.4)
Prior lipid-modifying therapy	934 (36.5)	917 (35.8)
Index diagnosis		
STEMI	1207 (46.9)	1216 (47.4)
NSTEMI	976 (38.0)	960 (37.4)
Unstable angina (biomarker negative)	388 (15.1)	392 (15.3)
Index event to randomization, median (IQR), h	57.0 (39.1-75.6)	57.6 (38.7-76.7)
PCI or CABG surgery for index event	1573 (80.3)	1656 (82.8)
Medications at randomization		
Aspirin	2348 (91.3)	2362 (91.8)
Clopidogrel, ticlopidine, or prasugrel	1960 (76.2)	1956 (76.0)
β-Blocker	2158 (83.9)	2131 (82.9)
ACE inhibitor or ARB	2124 (82.5)	2116 (82.3)
Biochemical parameters at randomization, mean (SD), mg/dL		
LDL-C	105.1 (43.1)	105.0 (43.3)
HDL-C	43.2 (10.9)	43.3 (11.2)
Triglycerides	153.0 (115.0-213.0)	154.0 (115.0-207.0)
C-reactive protein, median (IQR), mg/L	10.4 (4.0-28.7)	11.4 (4.5-33.0)
Concomitant atorvastatin dose, mg		
20	1217 (47.9)	1192 (46.8)
40	827 (32.6)	916 (36.0)
80	495 (19.5)	438 (17.2)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

SI conversions: To convert HDL-C and LDL-C to mmol/L, multiply by 0.0259. To convert triglycerides to mmol/L, multiply by 0.0113. To convert C-reactive protein to nmol/L, multiply by 9.524.

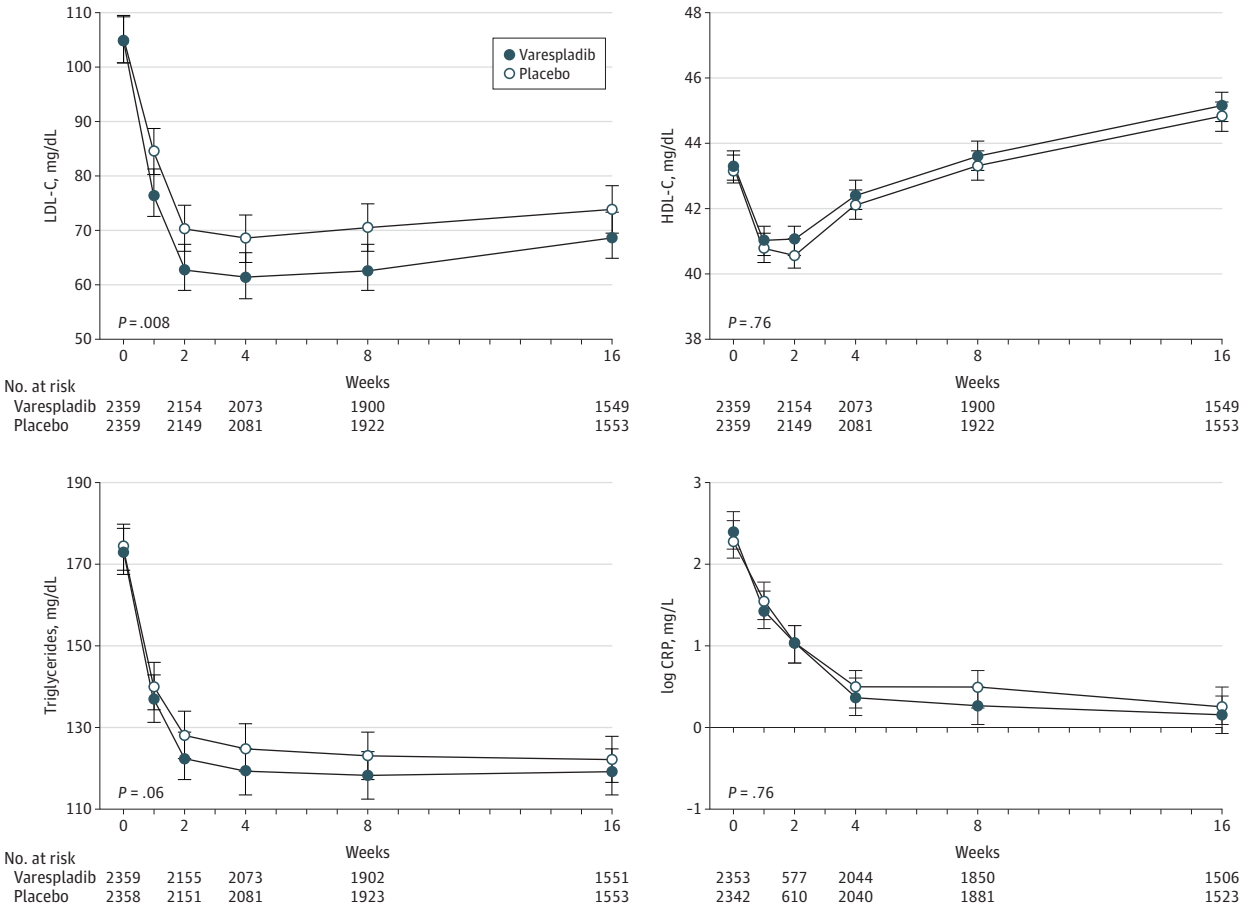
[a] Data are presented as No. (%) unless otherwise specified.

[b] Other included those individuals who did not identify themselves as white, Asian, or black.

[c] Indicates smokes currently.

[d] Calculated as weight in kilograms divided by height in meters squared.

Figure 2. Median Levels of Lipid Parameters and Log CRP in Patients Treated With Placebo and Varespladib



CRP indicates C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein. Error bars for LDL-C and HDL-C represent standard errors. Error bars for triglycerides and log CRP represent interquartile ranges. *P* values for LDL-C, HDL-C, and CRP are by *t* test. *P* value for triglycerides is by Wilcoxon rank sum test for percentage change.

high in both groups due to the index ACS event. Between randomization and week 16, CRP decreased by 85.0% in the varespladib group and 82.1% in the placebo group (*P* = .008). At week 16, median CRP was 1.4 mg/L in the varespladib group and 1.5 mg/L in the placebo group.

Clinical Outcomes

The primary outcome of cardiovascular mortality, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization occurred in 6.1% of patients treated with varespladib and 5.1% of patients treated with placebo (HR, 1.25; 95% CI, 0.97-1.61; log-rank *P* = .08) (**Table 2**). The composite secondary outcome of cardiovascular mortality, MI, and stroke occurred in 4.6% of patients in the varespladib group and 3.8% of patients in the placebo group (HR, 1.36; 95% CI, 1.02-1.82; *P* = .04). This was due primarily to a greater incidence of MI in the varespladib group compared with the placebo group (3.4% vs 2.2%; HR, 1.66; 95% CI, 1.16-2.39; *P* = .005) (**Figure 3**). Cardiovascular mortality at the end of the randomized treatment period was nonsignificantly greater in the varespladib group (1.5% vs 1.4%; *P* = .54), although risks of stroke (0.4% vs 0.6%; *P* = .81) and hospitalization for unstable angina (1.9% vs 1.4%; *P* = .47) were similar in both groups. There was no subgroup in which varespladib reduced risk. However, greater rates of MI with varespladib were observed in patients who did not undergo percutaneous coronary intervention, meeting statistical significance for heterogeneity (*P* = .04). Furthermore, there was a higher rate of MI associated with varespladib among patients whose index event was not a STEMI, although this did not reach statistical significance (*P* = .06 for heterogeneity) (**Figure 4**). At 6 months after discontinuation of study treatment, all-cause mortality in those patients whose survival status was established was 2.7% in the varespladib group and 2.0% in the placebo group (*P* = .15).

Safety

Numbers of adverse events and serious adverse events are reported in eTable 2 in the Supplement. Discontinuation of study treatment for adverse events occurred in 2.8% of patients in the varespladib group and 1.4% of patients in the placebo group. There was an excess of alanine transaminase elevations more than 3 times the upper limit of normal during the treatment

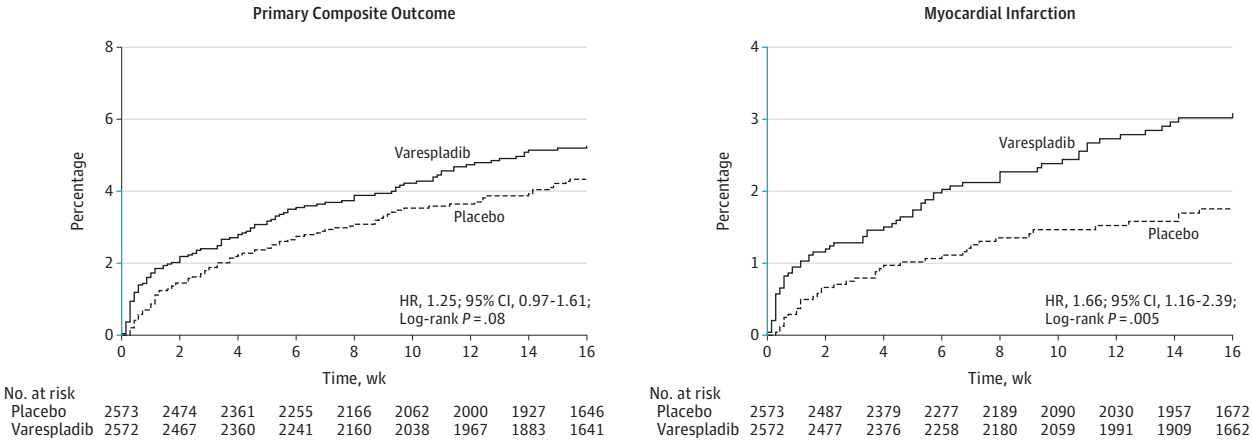
Table 2. Cardiovascular Outcomes in Patients Treated With Placebo or Varespladib

Outcomes	Placebo (n = 2573)	Varespladib (n = 2572)	Hazard Ratio (95% CI)	*P* Value
Primary outcome[a]	109 (5.1)	136 (6.1)	1.25 (0.97-1.61)	.08
All-cause mortality, myocardial infarction, stroke, unstable angina with evidence of ischemia requiring hospitalization	110 (5.1)	140 (6.3)	1.28 (0.996-1.64)	.05
Cardiovascular mortality, myocardial infarction, and stroke	79 (3.8)	107 (4.6)	1.36 (1.02-1.82)	.04
All-cause mortality	33 (1.5)	41 (1.7)	1.25 (0.79-1.98)	.35
Cardiovascular mortality	32 (1.4)	37 (1.5)	1.16 (0.73-1.87)	.54
Myocardial infarction	47 (2.2)	78 (3.4)	1.66 (1.16-2.39)	.005
Unstable angina with evidence of ischemia requiring hospitalization	32 (1.4)	38 (1.9)	1.20 (0.75-1.92)	.47
Stroke	9 (0.6)	8 (0.4)	0.89 (0.34-2.31)	.81
All-cause mortality at 6 mo[b]	41 (2.0)	55 (2.7)	1.35 (0.90-2.02)	.15

[a] A composite of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, and unstable angina with evidence of ischemia requiring hospitalization at 16 weeks.

[b] Total number of patients included in the 6-mo outcome was 795 for placebo and 793 for varespladib.

Figure 3. Kaplan-Meier Survival Curves for the Primary Composite Outcome and Myocardial Infarction in Patients Treated With Placebo and Varespladib



The primary efficacy outcome was a composite of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, and unstable angina with evidence of ischemia requiring hospitalization at 16 weeks. Patients were randomized to receive either varespladib (500 mg/d) or placebo for 16 weeks. HR indicates hazard ratio. Y-axis scale shown in blue indicates range from 0% to 4%.

phase with varespladib (38 patients) compared with placebo (6 patients), with no evidence of concomitant bilirubin elevations. Varespladib had no effect on renal function or on creatine kinase levels.

Discussion

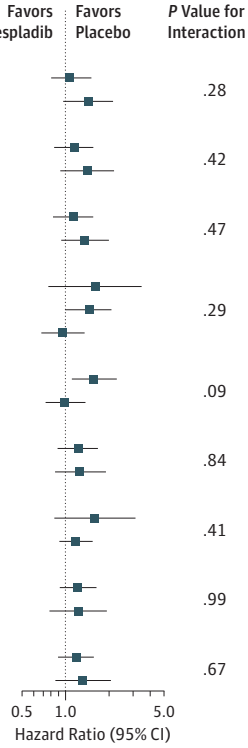
Despite experimental and observational clinical data suggesting that pan-inhibition of $sPLA_2$ would exert beneficial cardiovascular effect, the VISTA-16 trial provides evidence to the contrary. Despite lower achieved levels of LDL-C and CRP, there was no evidence of a beneficial reduction in the primary cardiovascular outcome. In contrast, treatment with varespladib caused an excess of MI and the composite of cardiovascular mortality, MI, and stroke. Consequently, these findings suggest that short-term $sPLA_2$ inhibition with varespladib is harmful following ACS.

The lack of any indication of cardiovascular benefit with varespladib contradicts the favorable effects on cardiovascular biomarkers in patients with ACS. Initial clinical experience with varespladib consistently demonstrated beneficial effects on lipid and inflammatory biomarkers, which theoretically should have translated to a lower propensity to plaque rupture.[12-14] We conducted the VISTA-16 trial because of the established link between $sPLA_2$ and vascular inflammation, as well as preclinical evidence for benefit in ischemia reperfusion injury.[5] Favorable effects of varespladib on LDL-C and CRP were again demonstrated in the present trial, suggesting that other unfavorable consequences of $sPLA_2$ inhibition or other unmeasured effects of varespladib influenced the clinical outcomes of treatment. Possible explanations for the unfavorable outcomes include potentially inadequate penetration of varespladib into vascular cells to inhibit pro-inflammatory intracellular mediators. Alternatively, varespladib may have abrogated the effects of both pro-atherogenic (IIA and V) and antiatherogenic $sPLA_2$

Figure 4. Comparison of the Effects of Varespladib and Placebo on the Incidence of Primary Composite Outcome and Myocardial Infarction in Prespecified Subgroup Patient Characteristics

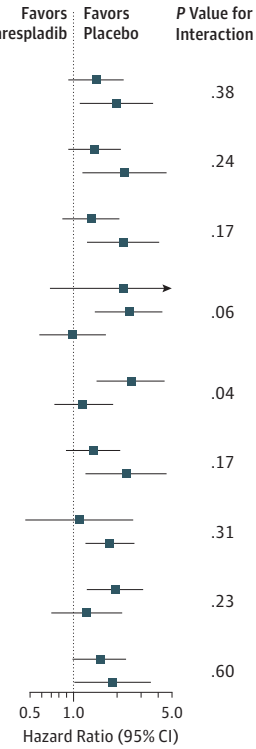
A Primary Composite Outcome

Patient Characteristics	No. of Patients		No. of Events		Hazard Ratio (95% CI)	P Value for Interaction
	Placebo	Varespladib	Placebo	Varespladib		
Age, y						
≤65	1742	1715	69	76	1.11 (0.80-1.54)	.28
>65	827	851	41	61	1.47 (0.99-2.19)	
Sex						
Male	1908	1878	76	87	1.16 (0.85-1.58)	.42
Female	660	688	34	50	1.44 (0.93-2.23)	
Baseline lipid therapy						
No	1622	1639	65	75	1.15 (0.83-1.61)	.47
Yes	932	915	45	61	1.39 (0.95-2.05)	
Primary indication						
Unstable angina	388	392	11	18	1.63 (0.77-3.45)	.29
NSTEMI	975	959	45	65	1.46 (1.00-2.14)	
STEMI	1204	1212	54	54	0.998 (0.68-1.46)	
PCI Postindex event						
No	953	887	48	69	1.60 (1.11-2.32)	.09
Yes	1616	1679	62	68	1.04 (0.73-1.46)	
Diabetes at baseline						
No	1757	1759	69	85	1.23 (0.89-1.69)	.84
Yes	801	799	41	52	1.29 (0.86-1.95)	
Hypertension at baseline						
No	562	629	14	25	1.63 (0.85-3.13)	.41
Yes	1975	1907	95	111	1.21 (0.92-1.59)	
Smoking history						
Nonsmoker	1697	1705	77	96	1.25 (0.93-1.69)	.99
Current smoker	858	851	33	41	1.25 (0.79-1.79)	
Congestive heart failure						
No	2085	2096	78	94	1.20 (0.89-1.63)	.67
Yes	461	455	32	43	1.36 (0.86-2.15)	



B Myocardial Infarction

Patient Characteristics	No. of Patients		No. of Events		Hazard Ratio (95% CI)	P Value for Interaction
	Placebo	Varespladib	Placebo	Varespladib		
Age, y						
≤65	1742	1715	32	46	1.45 (0.92-2.28)	.38
>65	827	851	16	33	2.03 (1.12-3.69)	
Sex						
Male	1908	1878	36	51	1.42 (0.93-2.18)	.24
Female	660	688	12	28	2.29 (1.17-4.51)	
Baseline lipid therapy						
No	1622	1639	32	43	1.34 (0.85-2.12)	.17
Yes	932	915	16	35	2.26 (1.25-4.09)	
Primary indication						
Unstable angina	388	392	4	9	2.24 (0.69-7.27)	.06
NSTEMI	975	959	18	44	2.47 (1.43-4.28)	
STEMI	1204	1212	26	26	0.995 (0.58-1.71)	
PCI Postindex event						
No	953	887	18	41	2.55 (1.46-4.43)	.04
Yes	1616	1679	30	38	1.19 (0.73-1.92)	
Diabetes at baseline						
No	1757	1759	35	49	1.38 (0.89-2.13)	.17
Yes	801	799	13	30	2.38 (1.24-4.56)	
Hypertension at baseline						
No	562	629	9	11	1.10 (0.46-2.66)	.31
Yes	1975	1907	38	67	1.82 (1.22-2.71)	
Smoking history						
Nonsmoker	1697	1705	27	53	1.96 (1.23-3.12)	.23
Current smoker	858	851	21	26	1.25 (0.70-2.21)	
Congestive heart failure						
No	2085	2096	33	51	1.53 (0.99-2.38)	.60
Yes	461	455	15	28	1.89 (1.08-3.54)	



The primary efficacy outcome was a composite of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, and unstable angina with evidence of ischemia requiring hospitalization at 16 weeks. Patients were randomized to receive either varespladib (500 mg/d) or placebo for 16 weeks. Non-STEMI indicates non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction. Because of missing data, number of patients in the subgroups do not sum to total number of patients randomized to receive placebo or varespladib.

isoforms.[6,7] Our findings with $sPLA_2$ inhibition reemphasize that identification of a circulating marker of cardiovascular risk does not necessarily imply that pharmacologic suppression or inhibition of the marker will reduce risk. The failure to demonstrate any benefit is supported by a recent report from Mendialian randomization studies concluding that $sPLA_2$ does not play a causative role in coronary disease[16]; however, such studies cannot necessarily predict the result of a pharmacologic intervention in patients with established coronary disease. Ultimately, most therapies must be tested using careful human randomized clinical trials.

The precise mechanism underlying the adverse effect on the rate of MI with varespladib remains unknown. Recurrent MI in patients with a recent ACS often results from ongoing episodes of plaque rupture and thrombosis, often at sites remote from the lesion responsible for the initial event. The increased rate of MI observed early in the trial might also suggest that the drug may have induced a prothrombotic state. However, we observed no excess rate of early stent thrombosis in the varespladib group. In fact, we observed less harm for MI with varespladib in patients who had undergone percutaneous coronary intervention for the index ACS event and in patients whose initial presentation was with STEMI. There currently exists no external information regarding potential interactions between either $sPLA_2$ activity or varespladib and factors that influence the coagulation cascade or platelet function. Given that other therapies that modulate prostaglandin metabolites have been reported to be associated with an excess rate of MI,[17] the potential effect of the varespladib molecule and $sPLA_2$ inhibition on thrombotic and fibrinolytic pathways, in addition to plaque stability, require further investigation.

The findings may have implications for targeting other inflammatory pathways as strategies to reduce cardiovascular risk. Although the role of vascular inflammation in atherosclerosis is widely accepted, there is at present no evidence to our knowledge that targeting any specific inflammatory factor will attenuate cardiovascular risk. The complexity and redundancy of inflammatory pathways may confound such efforts.[8] Evidence by other studies indicates that interventions targeting prostaglandin inflammatory pathways, such as rofecoxib, are harmful rather than protective against coronary heart disease.[17] Nevertheless, other anti-inflammatory agents, including inhibitors of lipoprotein-associated phospholipase A_2, are undergoing evaluation in large clinical trials.[18-20]

A number of limitations should be noted with regard to our study. Survival status at 6 months was not established in a majority of patients. Accordingly, we cannot exclude that the increased rate of MI with varespladib did not ultimately result in an excess mortality rate. Given that varespladib is a pan-$sPLA_2$ inhibitor, it is unknown whether a more selective agent would be beneficial. Patients were not selected for randomization on the basis of their underlying $sPLA_2$ concentration or activity. The VISTA-16 trial was an evaluation of the effect of $sPLA_2$ inhibition with varespladib in the first few months following an ACS. It is unknown whether such a strategy would be more likely to be protective in a more chronic stage of the disease. However, the finding of an excess risk of MI with varespladib makes it unlikely that this will be investigated.

The administrative actions of the sponsor and the timelines involved with the dissemination of data from this clinical trial require further comment. The sponsor took the appropriate scientific and ethical course of action to accept the recommendation by the data and safety monitoring board and prematurely stop the study for futility on March 9, 2012.[21] Although the study protocol stipulated that survival status would be determined for all patients who participated in the study, data were collected by the sponsor for only 1588 of the 5145 enrolled patients. In addition, the study steering committee and the investigators did not receive the full database for analysis until May 10, 2013, approximately 1 month after the sponsor's compound license expired and was returned to the original developer of the compound.

Conclusions

In conclusion, $sPLA_2$ inhibition with varespladib administration did not reduce cardiovascular ischemic complications and resulted in an excess rate of MI and the composite of cardiovascular mortality, MI, and stroke in patients with ACS. Whether this represents an adverse effect of the varespladib molecule or a consequence of pan-$sPLA_2$ inhibition remains to be determined.

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Published Online: November 18, 2013. doi:10.1001/jama.2013.282836.

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Obtained funding: Menon.
Administrative, technical, or material support: Bash, Rosenson, Cavender, Wright, Menon, Lincoff, Nissen, Nicholls.
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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Nicholls reported having received research support

from Anthera, AstraZeneca, Cerenis, Eli Lilly, InfraReDx, Roche, Resverlogix, Novartis, Amgen, and LipoScience; and consulting fees from AstraZeneca, Abbott, Atheronova, Esperion, Merck, Takeda, Roche, Amgen, LipoScience, Novartis, Omthera, CSL Behring, Boehringer Ingelheim, and Pfizer. Dr Kastelein reported serving as a consultant to and receiving honoraria from Anthera, MSD, Eli Lilly, The Medicines Company, CSL Behring, AstraZeneca, Resverlogix, Boehringer Ingelheim, Cerenis, Novartis, and Catabasis. Dr Schwartz, through his institution, reported receiving research grants from Anthera, Resverlogix, Roche, and sanofi. Dr Rosenson reported receiving consulting fees from Aegerion, Abbott, Amgen Roche, LipoScience, Pfizer, Regeneron, and sanofi; receiving research support from AstraZeneca, Amgen, and sanofi; owning stock in LipoScience and The Medicines Company; and receiving royalties from UpToDate. Dr Koenig reported receiving consulting fees from Roche, BioInvent, diaDexus, Cerenis, Novartis, Servier, Amgen, The Medicines Company, Genzyme, Aegerion, and AstraZeneca; receiving honoraria for lectures from Roche, Novartis, and Merck; and receiving research support from Roche. Dr Jukema reported receiving research grants from and speaking on (CME accredited) meetings sponsored by Astellas, Anthera, Astra-Zeneca, Bayer, Biotronik, Boston Scientific, Daiichi Sankyo, Lilly, Genzyme, Medtronic, Merck-Schering-Plough, Pfizer, Orbus Neich, Novartis, Roche, Servier, sanofi aventis, the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Community Framework KP7 Programme. Dr Wright reported having received consulting fees from Roche, Genentech, and sanofi. Dr Nissen reported that the Cleveland Clinic Center for Clinical Research receives funding performing clinical trials from AstraZeneca, Anthera, Amgen, Pfizer, The Medicines Company, Novartis, Takeda, Resverlogix, Ethicon, Orexigen, Vivus, and Eli Lilly. Dr Nissen is involved in these clinical trials, but receives no personal remuneration for his participation. He also consults for many pharmaceutical companies, but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction. Drs Cavender, Nambi, Menon, and Lincoff and Mss Bash and Brennan reported no disclosures.

Funding/Support: The study was funded by Anthera Pharmaceuticals.

Role of the Sponsors: Anthera Pharmaceuticals participated actively in designing the study, developing the protocol, and provided logistical support during the trial. The protocol was developed by members of the independent academic Executive Steering Committee, in conjunction with Anthera Pharmaceuticals. The study design was approved by responsible regulatory agencies and ethics committees. Collecting the data and monitoring of the study was performed by WorldWide Clinical Trials (Los Angeles, California). Anthera Pharmaceuticals maintained the trial database. Although the executive steering committee and coordinating center had confidentiality agreements with the sponsor, the study contract specified that a copy of the study database be provided to the coordinating center for independent analysis and granted the academic authors the unrestricted rights to publish the results. After completion of the trial, as specified in the study contract, a complete copy of the database was transferred to the Cleveland Clinic Coordinating Center for Clinical Research (C5Research), where statistical analyses were performed by an independent statistician, Danielle Brennan, MPH. The results reported in the manuscript are the results of the analyses performed by Ms Brennan. The manuscript was prepared by the corresponding author and modified after consultation with coauthors. The final decision on content was exclusively retained by the academic authors.

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Correction: The forest plots in both panels of Figure 4 were corrected on December 20, 2013.

REFERENCES

1. Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350(15):1495-1504.

2. Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med*. 1999;340(2):115-126.

3. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. *Eur Heart J*. 2013;34(10):719-728.

4. Ridker PM, Cannon CP, Morrow D, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med*. 2005;352(1):20-28.

5. Rosenson RS. Future role for selective phospholipase A2 inhibitors in the prevention of atherosclerotic cardiovascular disease. *Cardiovasc Drugs Ther*. 2009;23(1):93-101.

6. Rosenson RS, Hurt-Camejo E. Phospholipase A2 enzymes and the risk of atherosclerosis. *Eur Heart J*. 2012;33(23):2899-2909.

7. Ait-Oufella H, Herbin O, Lahoute C, et al. Group X secreted phospholipase A2 limits the development of atherosclerosis in LDL receptor-null mice. *Arterioscler Thromb Vasc Biol*. 2013;33(3):466-473.

8. Koenig W, Khuseyinova N. Lipoprotein-associated and secretory phospholipase A2 in cardiovascular disease: the epidemiological evidence. *Cardiovasc Drugs Ther*. 2009;23(1):85-92.

9. Ivandic B, Castellani LW, Wang XP, et al. Role of group II secretory phospholipase A2 in atherosclerosis, 1: increased atherogenesis and altered lipoproteins in transgenic mice expressing group IIa phospholipase A2. *Arterioscler Thromb Vasc Biol*. 1999;19(5):1284-1290.

10. Menschikowski M, Kasper M, Lattke P, et al. Secretory group II phospholipase A2 in human atherosclerotic plaques. *Atherosclerosis*. 1995;118(2):173-181.

11. Shaposhnik Z, Wang X, Trias J, Fraser H, Lusis AJ. The synergistic inhibition of atherogenesis in apoE−/− mice between pravastatin and the $sPLA_2$ inhibitor varespladib (A-002). *J Lipid Res*. 2009;50(4):623-629.

12. Rosenson RS, Hislop C, McConnell D, et al; PLASMA Investigators. Effects of 1-H-indole-3-glyoxamide (A-002) on concentration of secretory phospholipase A_2 (PLASMA study): a phase II double-blind, randomised, placebo-controlled trial. *Lancet*. 2009;373(9664):649-658.

13. Rosenson RS, Hislop C, Elliott M, Stasiv Y, Goulder M, Waters D. Effects of varespladib methyl on biomarkers and major cardiovascular events in acute coronary syndrome patients. *J Am Coll Cardiol*. 2010;56(14):1079-1088.

14. Rosenson RS, Elliott M, Stasiv Y, Hislop C; PLASMA II Investigators. Randomized trial of an inhibitor of secretory phospholipase A2 on atherogenic lipoprotein subclasses in statin-treated patients with coronary heart disease. *Eur Heart J*. 2011;32(8):999-1005.

15. Nicholls SJ, Cavender MA, Kastelein JJ, et al. Inhibition of secretory phospholipase A(2) in patients with acute coronary syndromes: rationale and design of the vascular inflammation suppression to treat acute coronary syndrome for 16 weeks (VISTA-16) trial. *Cardiovasc Drugs Ther*. 2012;26(1):71-75.

16. Holmes MV, Simon T, Exeter HJ, et al. Secretory phospholipase A2-IIA and cardiovascular disease: a Mendelian randomization study [published online July 19, 2013]. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.06.044.

17. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*. 2001;286(8):954-959.

18. White H, Held C, Stewart R, et al. Study design and rationale for the clinical outcomes of the STABILITY Trial (STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY) comparing darapladib versus placebo in patients with coronary heart disease. *Am Heart J*. 2010;160(4):655-661.

19. O'Donoghue ML, Braunwald E, White HD, et al. Study design and rationale for the Stabilization of pLaques usIng Darapladib-Thrombolysis in Myocardial Infarction (SOLID-TIMI 52) trial in patients after an acute coronary syndrome. *Am Heart J*. 2011;162(4):613-619.

20. Ridker PM, Thuren T, Zalewski A, Libby P. Interleukin-1β inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). *Am Heart J*. 2011;162(4):597-605.

21. Anthera halts VISTA-16 clinical study due to lack of efficacy following recommendation by the independent data safety monitoring board [press release]. Anthera Pharmaceuticals Inc; March 9, 2012.