Secretory Phospholipase A_2 Inhibition with Varespladib and Cardiovascular Events in Patients with an Acute Coronary Syndrome: Results of the VISTA-16 Study

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Disclosures

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Residual Risk and Inflammation

- Despite current evidence-based treatment, cardiovascular risk remains high following an acute coronary syndrome (ACS)
- Pathologic studies indicate that inflammation plays a role in atherosclerosis and biomarkers suggest that anti-inflammatory effects may contribute to the benefit of statins.
- However, to date no specific anti-inflammatory agent has been demonstrated to be cardioprotective

Secretory Phospholipase

- Secretory phospholipase A_2 ($sPLA_2$) is a circulating family of enzymes which generates bioactive lipid species implicated in inflammatory pathways
- $sPLA_2$ has been identified in atherosclerotic plaques where it is thought to play a pathogenic role
- Varespladib is a pan-$sPLA_2$ inhibitor that demonstrated favorable effects on lipid and inflammatory markers in phase 2 studies
- The impact of varespladib on cardiovascular outcomes is not known

Objective

To determine the effect of the $sPLA_2$ inhibitor varespladib on cardiovascular outcomes in patients treated for the first 16 weeks following an acute coronary syndrome

VISTA-16

6,500 patients within 96 hours of an ACS

One additional risk factor

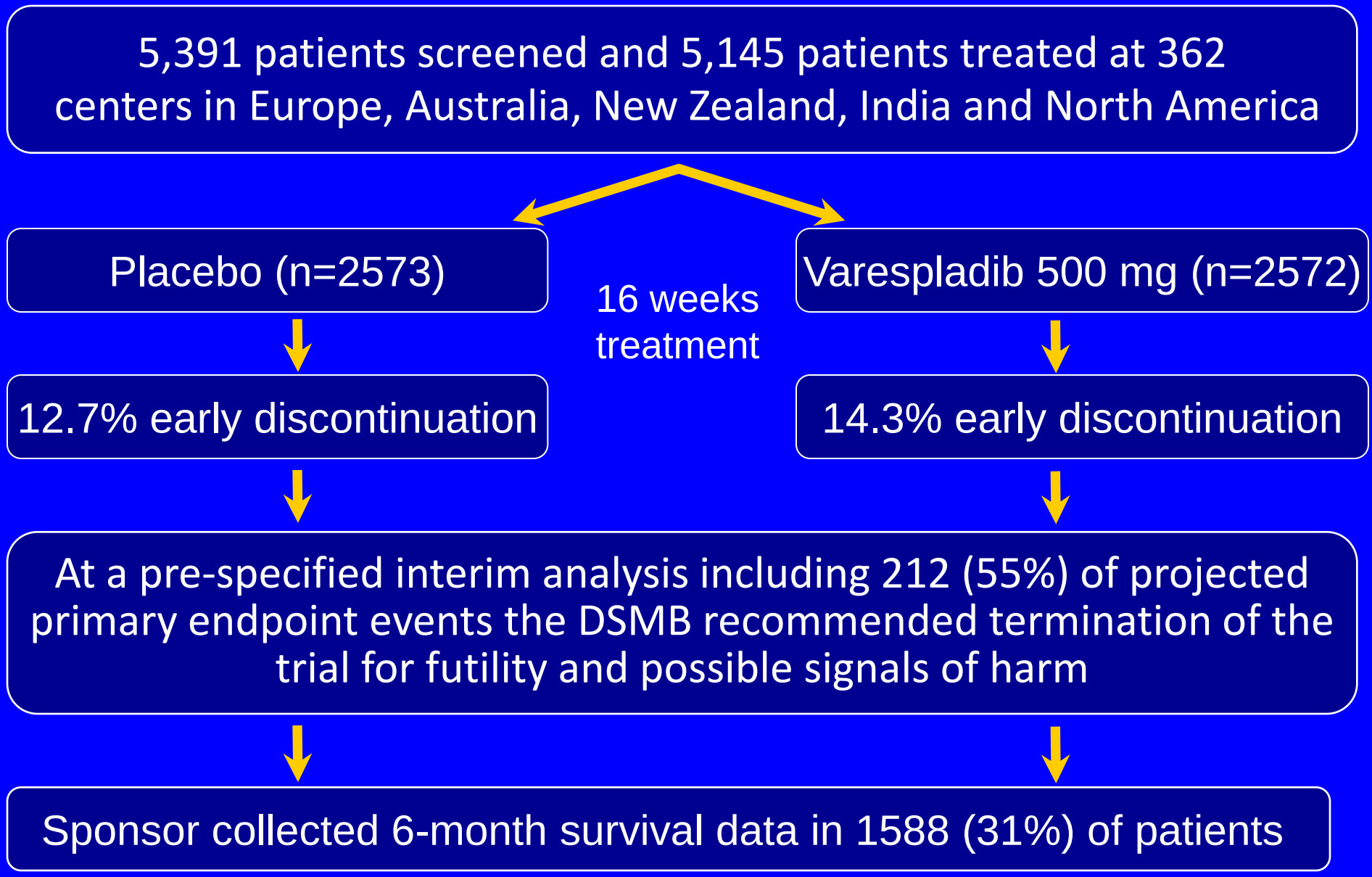
- **Diabetes**
- **Metabolic syndrome**
- **HDL-C <42 mg/dL**
- **eGFR <60 mL/min**
- **Stroke or TIA**
- **Peripheral arterial disease**
- **Myocardial infarction**
- **Coronary revascularization**

Varespladib 500 mg

Placebo

- Treated for 16 weeks in addition to atorvastatin and established medical therapies
- Primary endpoint: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina

VISTA-16 Trial: Flow of Patients



Clinical Characteristics

Parameter	Placebo (n=2573)	Varespladib (n=2572)
Mean age in years	60.7	61.0
Males	74.3%	73.1%
Caucasian	88.5%	88.4%
Mean body mass index	29.6	29.8
History of hypertension	77.8%	75.2%
History of diabetes	31.3%	31.3%
Current smoker	33.6%	33.4%
Prior myocardial infarction	29.6%	30.2%
Prior PCI	18.6%	17.7%
Prior CABG	7.1%	6.3%
Prior lipid modifying therapy	36.5%	35.8%

Baseline Characteristics

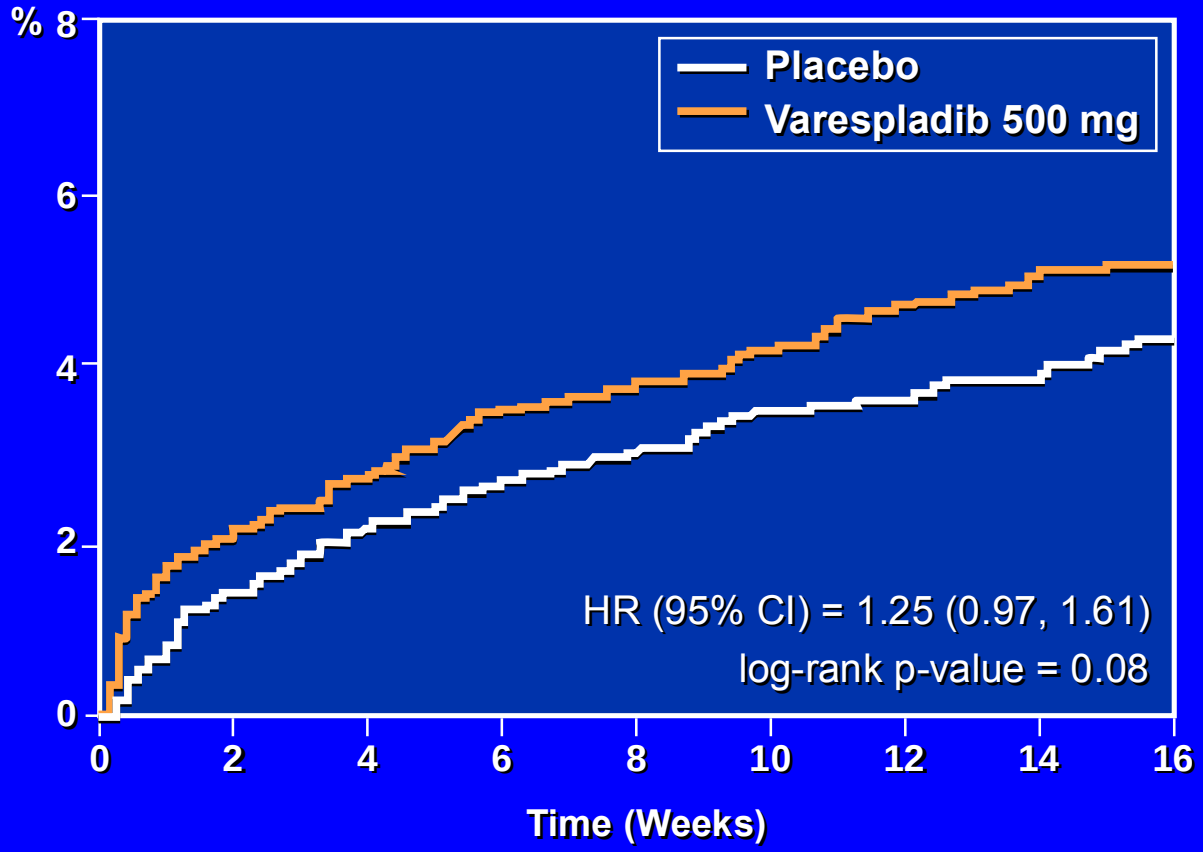
Parameter	Placebo (n=2573)	Varespladib (n=2572)
Index diagnosis		
STEMI	46.9%	47.4%
non-STEMI	38.0%	37.4%
Biomarker negative unstable angina	15.1%	15.3%
Hours to randomization	57.0	57.6
Revascularization for index event	80.3%	82.8%
Concomitant Medications		
Aspirin	91.3%	91.8%
Ticlopidine, clopidogrel, prasugrel	76.2%	76.0%
Beta-blocker	83.9%	82.9%
ACE inhibitor or ARB	82.5%	82.3%

Biochemistry

	Placebo (n=2573)	Varespladib (n=2572)	P Value
Baseline Values			
LDL-C (mg/dL)	105.1	105.0	0.94
HDL-C (mg/dL)	43.2	43.3	0.81
Triglycerides (mg/dL)	153.0	154.0	0.52
CRP (mg/L)	10.4	11.4	0.06
Percentage Change from Baseline			
LDL-C	-25.1%	-28.8%	0.008
HDL-C	5.4%	5.1%	0.77
Triglycerides	-20.3%	-21.7	0.059
CRP	-82.1%	-85.0%	0.008

Primary Efficacy Endpoint

Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina



No. at Risk:

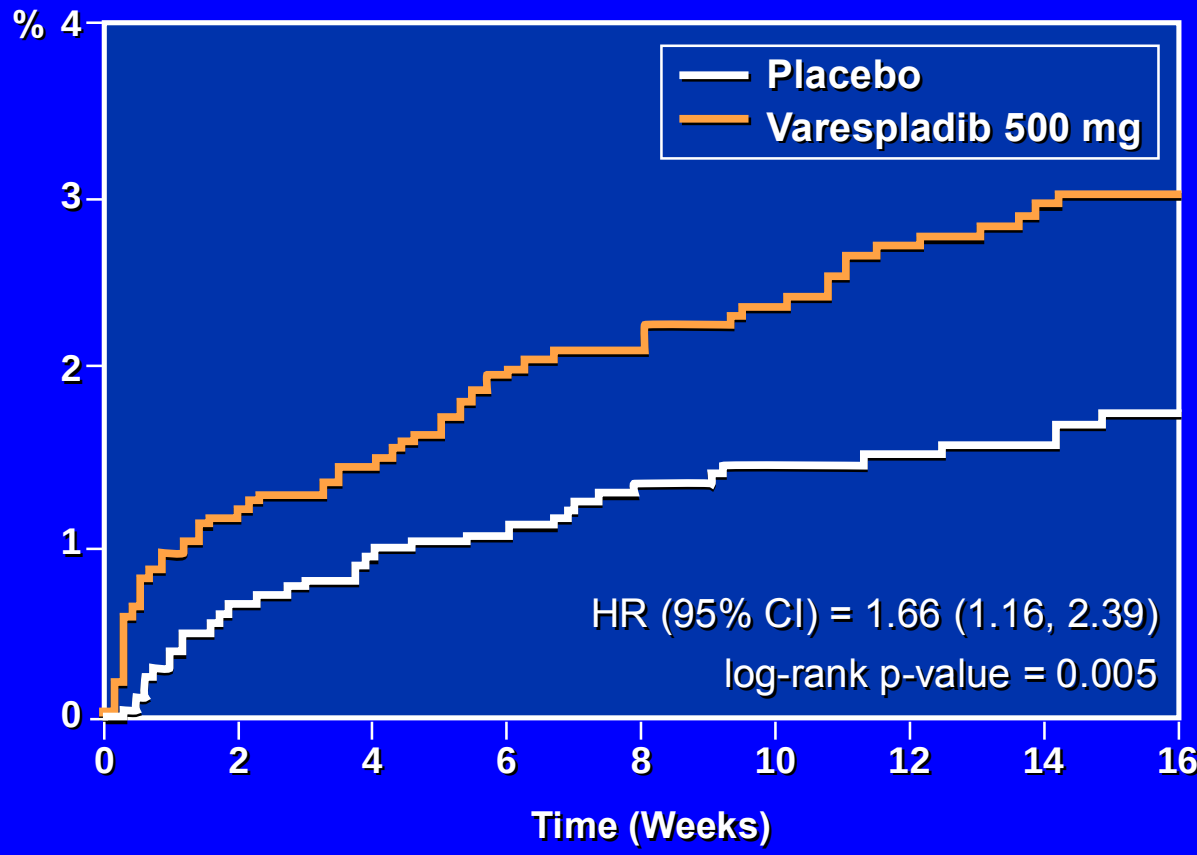
Placebo	2573	2474	2361	2255	2166	2062	2000	1927	1646
Varespladib	2572	2467	2360	2241	2160	2038	1967	1883	1641

Secondary Efficacy Endpoints

	Placebo (n=2573)	Varespladib (n=2572)	P Value
CV death, MI, stroke	3.8%	4.6%	0.04
CV death	1.4%	1.5%	0.54
MI	2.2%	3.4%	0.005
Unstable angina	1.4%	1.9%	0.47
Stroke	0.6%	0.4%	0.81
6-month mortality	2.0%	2.7%	0.15

P values from log rank test. CV: cardiovascular, MI: myocardial infarction

Myocardial Infarction

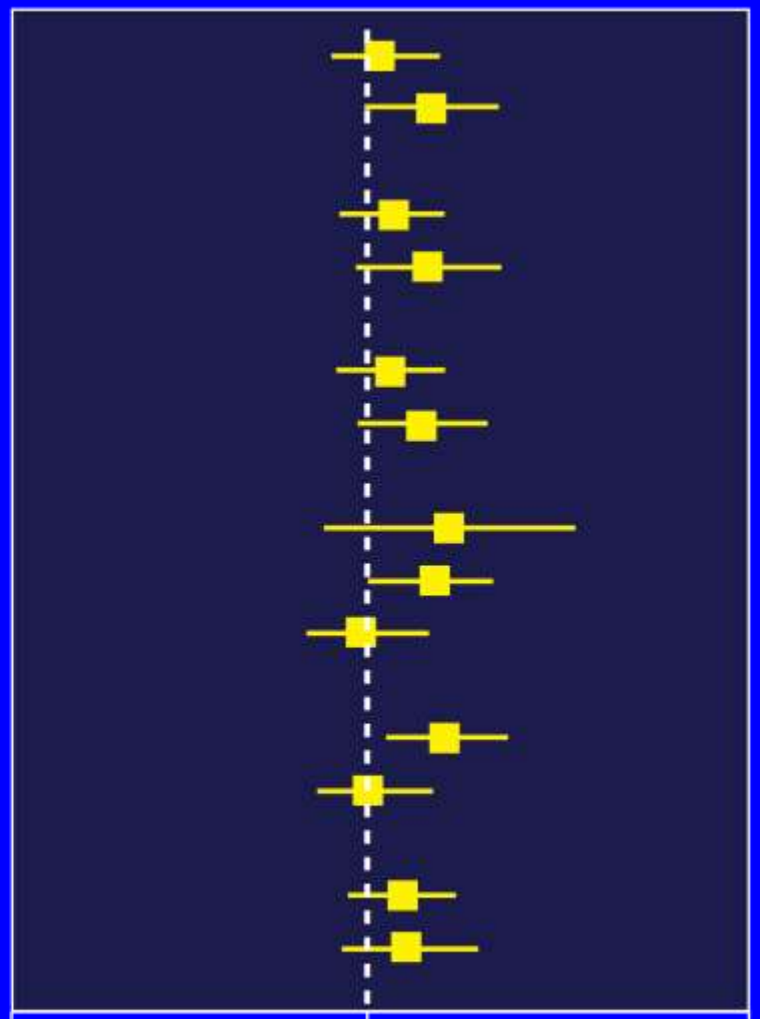


No. at Risk:

Placebo	2573	2487	2379	2277	2189	2090	2030	1957	1672
Varespladib	2572	2477	2376	2258	2180	2059	1991	1909	1662

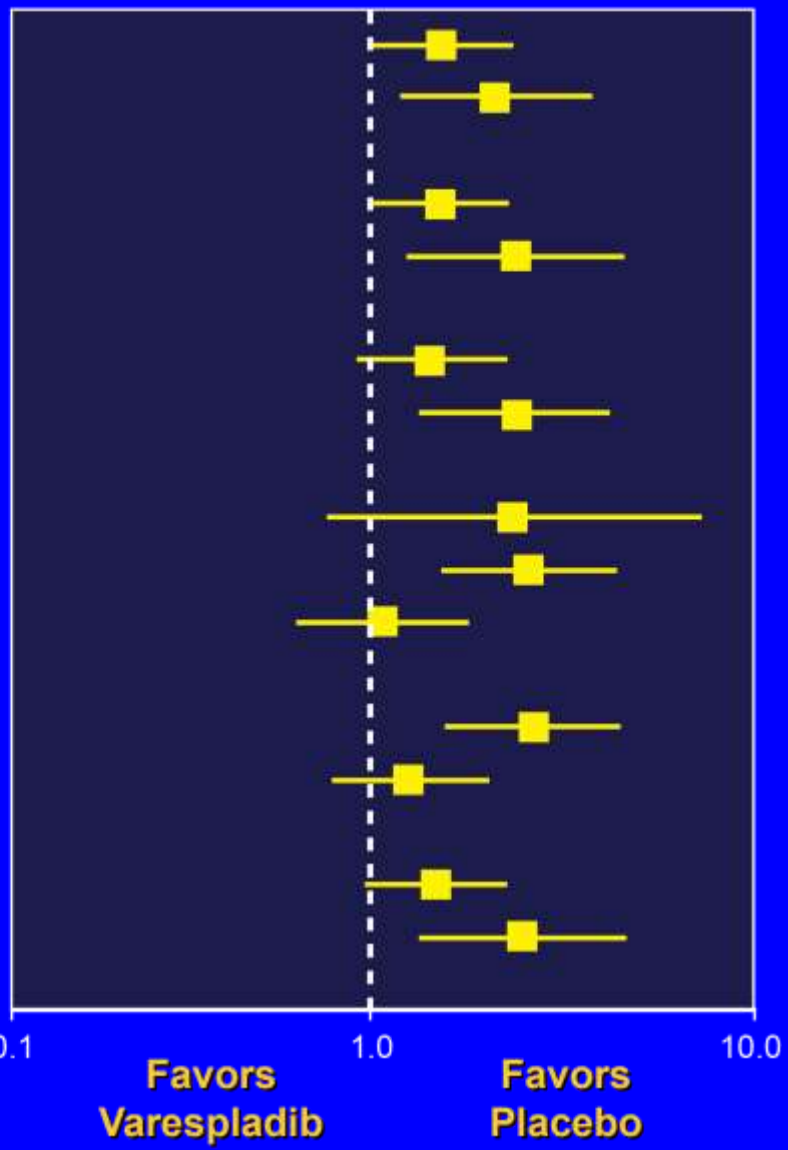
Subgroup Analysis: Primary Endpoint

Patients Characteristics	HR (95% CI)	P Value for Interaction
Age		
≤ 65	1.11 (0.80, 1.54)	0.28
> 65	1.47 (0.99, 2.19)	
Gender		
Male	1.16 (0.85, 1.58)	0.42
Female	1.44 (0.93, 2.23)	
Baseline Lipid Therapy		
No	1.15 (0.83, 1.61)	0.47
Yes	1.39 (0.95, 2.05)	
Primary Indication		
Unstable Angina	1.63 (0.77, 3.45)	0.29
NSTEMI	1.46 (1.00, 2.14)	
STEMI	0.998 (0.68, 1.46)	
PCI Post Index Event		
No PCI	1.60 (1.11, 2.32)	0.09
PCI	1.04 (0.73, 1.46)	
Diabetes at Baseline		
Non-Diabetics	1.23 (0.89, 1.69)	0.84
Diabetics	1.29 (0.86, 1.95)	



Subgroup Analysis: Myocardial Infarction

Patients Characteristics	HR (95% CI)	P Value for Interaction
Age		
≤ 65	1.45 (0.92, 2.28)	0.38
> 65	2.03 (1.12, 3.69)	
Gender		
Male	1.42 (0.93, 2.18)	0.24
Female	2.29 (1.17, 4.51)	
Baseline Lipid Therapy		
No Lipid Therapy	1.34 (0.85, 2.12)	0.17
Lipid Therapy	2.26 (1.25, 4.09)	
Primary Indication		
Unstable Angina	2.24 (0.69, 7.27)	0.06
NSTEMI	2.47 (1.43, 4.28)	
STEMI	0.995 (0.58, 1.71)	
PCI Post Index Event		
No PCI	2.55 (1.46, 4.43)	0.04
PCI	1.19 (0.73, 1.92)	
Diabetes at Baseline		
Non-Diabetics	1.38 (0.89, 2.13)	0.17
Diabetics	2.38 (1.24, 4.56)	



Adverse Clinical and Biochemical Events

Parameter	Placebo (n=2573)	Varespladib (n=2572)
Discontinuation due to adverse events	36	72
ALT/AST >3x ULN	6	38
Bilirubin >2x ULN	4	1
CK >3x ULN	9	6
Creatinine >ULN	84	64

ALT: alanine transaminase; AST: aspartate transaminase; CK: creatine kinase

Conclusions

- Varespladib did not reduce cardiovascular morbidity or mortality after ACS.
- Rather, a harmful effect of varespladib was observed, with an excess rate of myocardial infarction, appearing early during the treatment period.
- Varespladib administration was associated with modest incremental reduction of LDL-C and CRP, but a greater incidence of liver enzyme elevations.
- The findings call into question whether $sPLA_2$ is a valid target of therapy in atherosclerosis.

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

Supplemental content at jama.com

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A Final Thought

- Despite early promising findings in biomarker studies, varespladib proved to be harmful.
- This highlights the importance of ultimately performing outcome trials of novel agents.
- The search for an effective anti-inflammatory therapy for vascular disease continues.