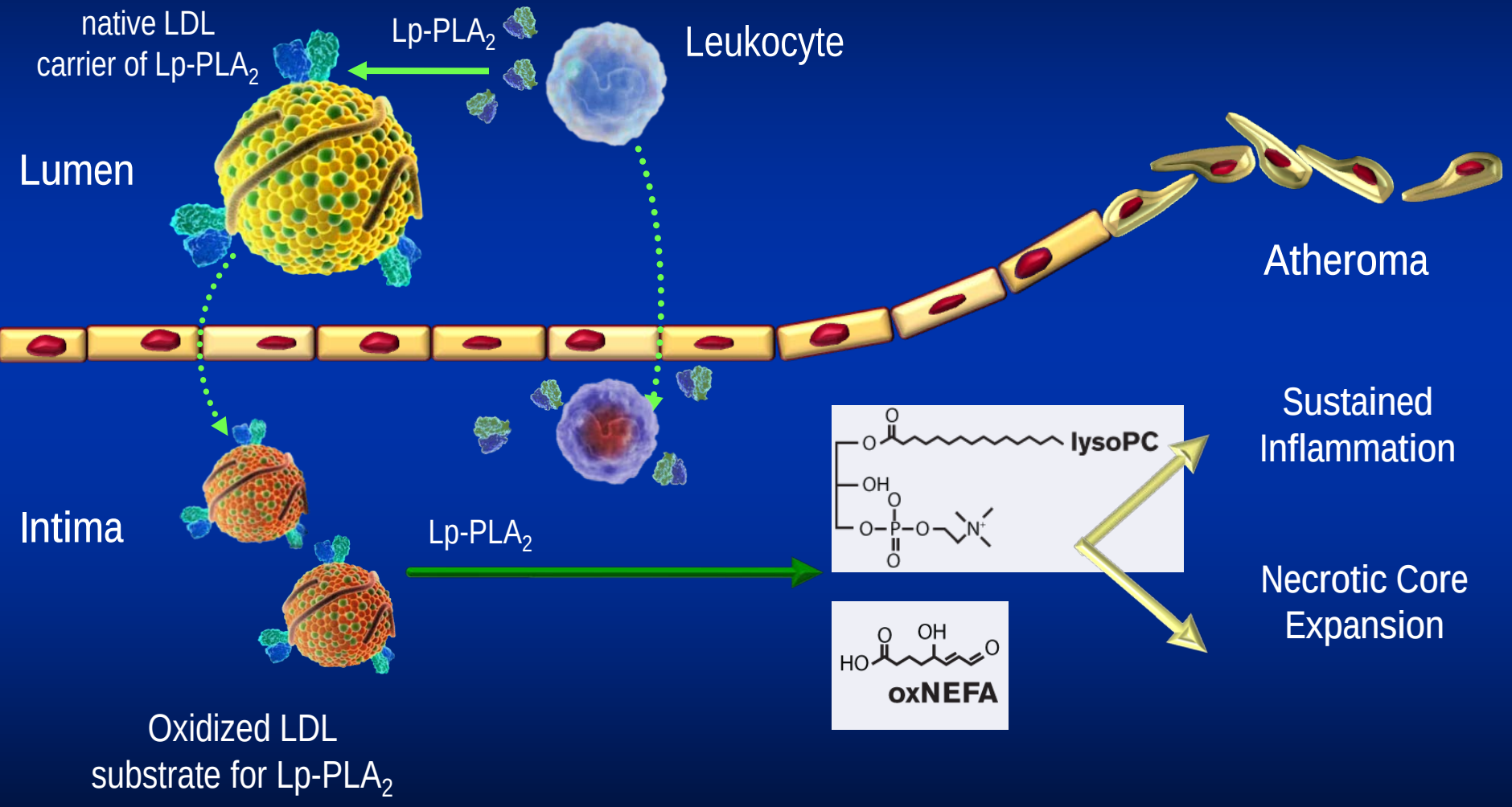
The Stabilization Of pLaques usIng Darapladib (SOLID)-TIMI 52 trial: Primary Results

Michelle L. O'Donoghue MD MPH, on behalf of the SOLID-TIMI 52 investigators

European Society of Cardiology Congress
Barcelona, Spain
Sunday August 31, 2014

BRIGHAM AND WOMEN'S HOSPITAL
Heart & Vascular Center

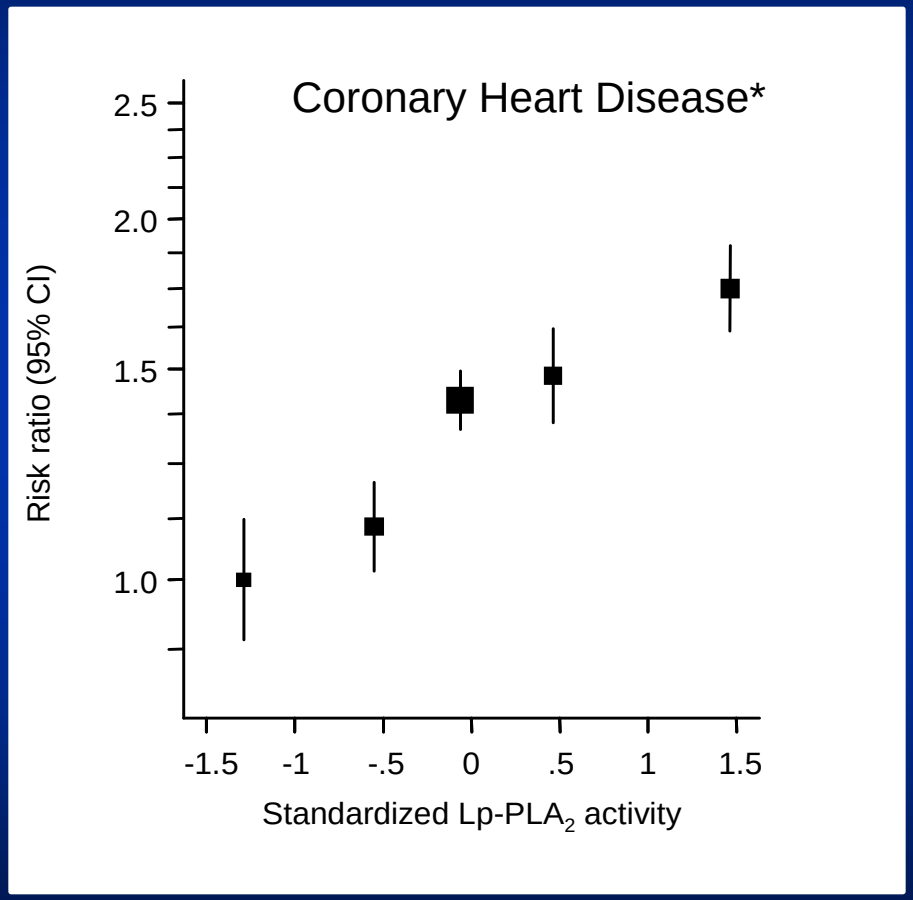
Lipoprotein- associated Phospholipase A_2 ($Lp\text{-}PLA_2$) activity: Background

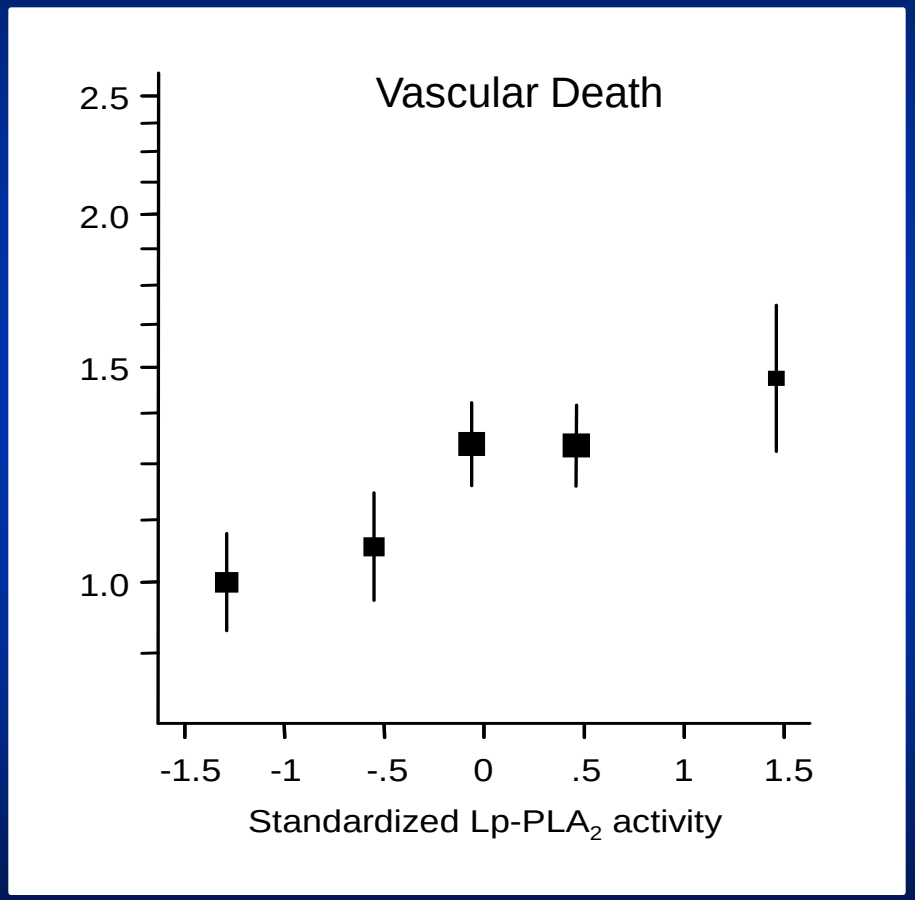


Macphee, *Biochem J* 1999; Zalewski and Macphee, *ATVB* 2005; Shi *Atherosclerosis* 2007; Kolodgie, *ATVB* 2006

Lp-PLA$_2$ activity and risk of CV outcomes

79,036 participants, 32 prospective studies





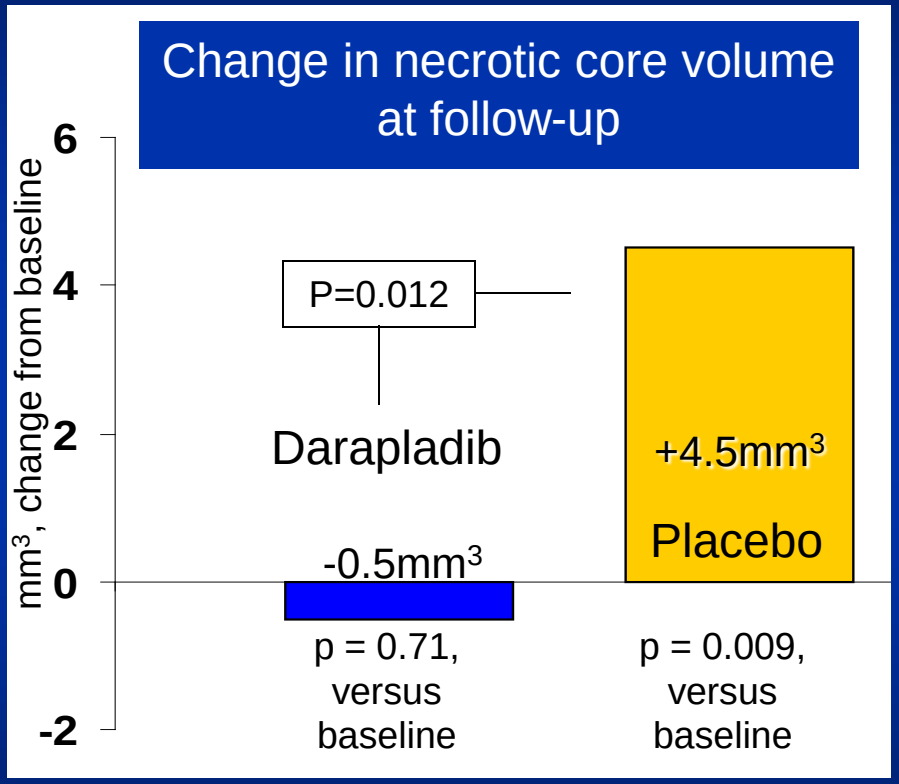
Adjusted for age, sex, diabetes and baseline history of vascular disease

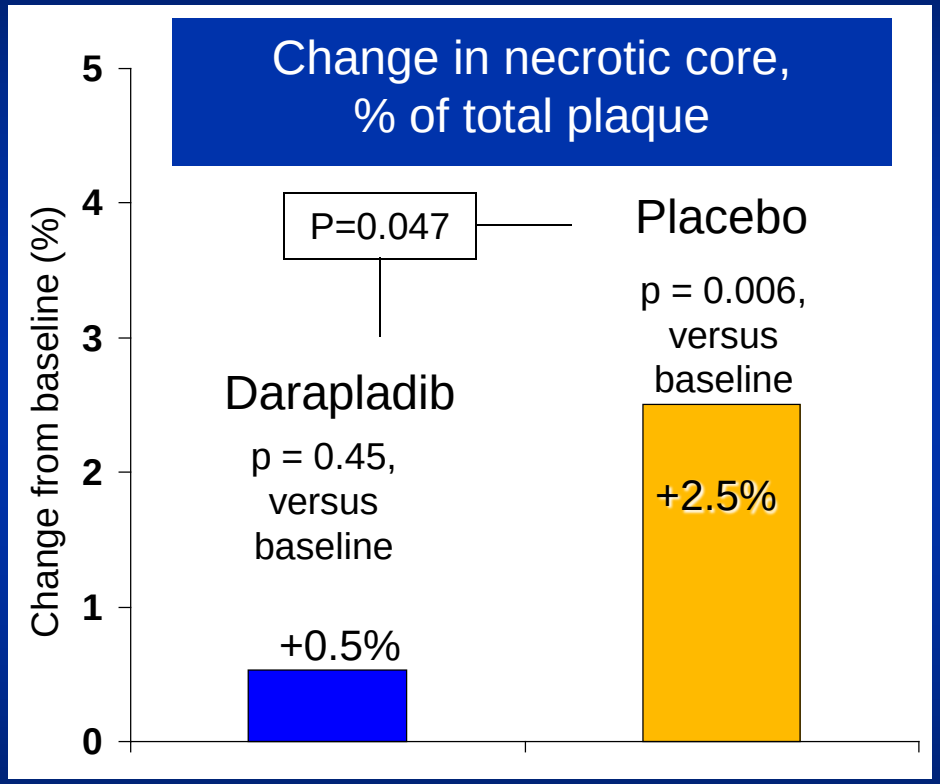
Lp-PLA$_2$ Studies Collaboration. *Lancet* 2010;375:1536-44

Darapladib – Phase 2 Results

IBIS-2 Trial

330 patients with angiographic CAD





- **No significant change in:**
  - **Plaque deformability**
  - **C-reactive protein**
  - **Atheroma volume**

} Primary endpoint

Serruys et al., *Circulation* 2008;118:1172-1182.

Darapladib Phase III Clinical Program

Chronic CHD patients with high-risk features*

Randomization to Darapladib or Placebo

n= 15,898
(3.7 year median follow-up)

ACS patients (NSTE- or STE-ACS) with high-risk features*

Randomization ≤30 days from hospitalization with ACS

Randomization to Darapladib or Placebo

n= 13,026
(2.5 year median follow-up)

* High-risk criteria (≥1 of the following): age ≥60 years, diabetes mellitus requiring Rx, eGFR 30-59 ml/min/1.73 m^2, polyvascular disease, HDL <40 mg/dl (STABILITY only), tobacco use (STABILITY only), or prior MI (SOLID-TIMI 52 only)

STABILITY Trial

15,828 patients with stable CHD randomized to darapladib 160mg QD vs placebo

Primary Endpoint

CV death, MI or stroke

HR (95% CI)
0.94 (0.85-1.03)
P=0.20

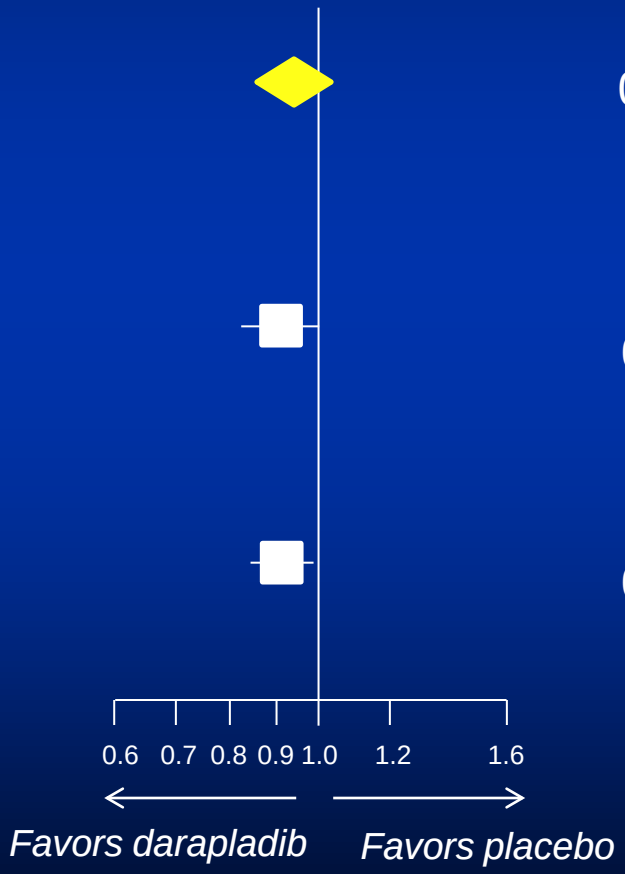
Selected Secondary Endpoints

Major Coronary Events:
(CHD death, MI or urgent coronary revascularization for myocardial ischemia)

0.90 (0.82-1.00)
P=0.045

Total Coronary Events:
(CHD death, MI, hospitalization for UA or any coronary revascularization)

0.91 (0.84-0.98)
P=0.02



White et al., *N Engl J Med* 2014; 370:1702-11.

SOLID-TIMI 52
Primary Trial Objective

To demonstrate that the addition of darapladib to a background of optimal medical therapy would significantly reduce the risk of major coronary events in patients after ACS.

Trial Organization

TIMI Study Group

Eugene Braunwald (Chair)
Christopher P. Cannon (Global PI)
Michelle L. O'Donoghue (Co-PI)
Dylan P. Steen (Co-Investigator)
Sharon Crugnale (Senior Project Director)
Suzanne Morin (Director of Operations)
Sabina A. Murphy (Statistics)
Kyungah Im (Statistics)
Stephen D. Wiviott (CEC Chair)
Marc P. Bonaca (SAE Chair)

Executive Committee

Eugene Braunwald
Christopher P. Cannon
P. Gabriel Steg
Aldo P. Maggioni
Harvey D. White
Christoph Bode
Judith S. Hochman
Patrick W. Serruys
W. Douglas Weaver

Sponsor (GlaxoSmithKline)

Elizabeth Tarka
Mary Ann Lukas
David F. Watson
Shruti Daga
Richard Y. Davies
Jennifer B. Shannon
Katharine Edmonds

Independent Data Monitoring Committee

Rory Collins (Chair)
Jeffrey Anderson
Peter Ganz
David DeMets
Peter Sandercock
Michael Weber

National Lead Investigators

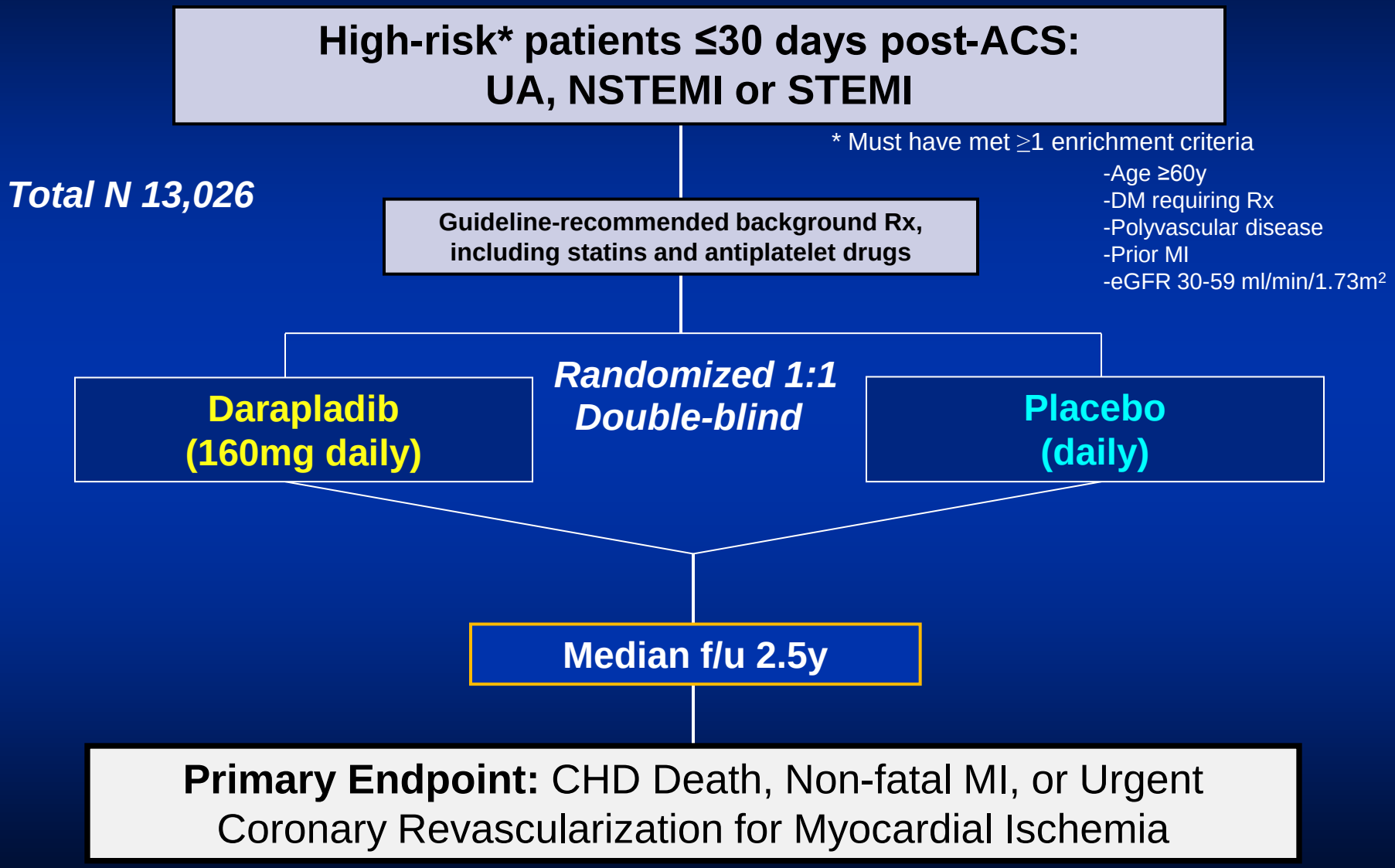
ARGENTINA (159)
Ernesto Paolasso
AUSTRALIA (210)
Phil Aylward
BELGIUM (139)
William Wijns
BRAZIL (415)
Jose Carlos Nicolau
BULGARIA (284)
Assen Goudev
CANADA (327)
Pierre Theroux
G.B. John Mancini
CHILE (155)
Ramon Corbalan
CHINA (444)
Runlin Gao
COLOMBIA (173)
Daniel Isaza
CZECH REPUBLIC (443)
Jindrich Spinar
DENMARK (442)
Steen Husted
ESTONIA
Juri Voitk
FRANCE (270)
Gilles Montalescot

GERMANY (510)
Christian Hamm
GREECE
John Lekakis
HUNGARY (350)
Robert Kiss
INDIA (348)
Atul Mathur/Krishna Reddy/
Sanjay Mittal/B. Soma Raju
ISRAEL (690)
Basil Lewis
ITALY(229)
Diego Ardissino
JAPAN (211)
Takeshi Kimura
KOREA (119)
Ki-Bae Seung
MEXICO
Guillermo Llamas Esperon
NETHERLANDS (622)
Ton Oude-Ophuis/R.J. DeWinter
NEW ZEALAND (120)
Harvey White
PHILIPPINES (110)
Noe Babilonia
POLAND (1056)
Andrzej Budaj

ROMANIA (246)
Maria Dorobantu
RUSSIA (876)
Nikolay Gratsiansky
SLOVAKIA (203)
Tibor Duris
SOUTH AFRICA (297)
Anthony Dalby
SPAIN (165)
Jose Lopez-Sendon
SWEDEN (157)
Mikael Dellborg
TAIWAN (132)
Shih-Ann Chen
THAILAND (114)
Piyamatr Sritara
TURKEY(9)
Sema Guneri
UNITED KINGDOM (167)
Kausik Ray
UKRAINE (306)
Alexander Parkhomenko
UNITED STATES (2476)
Christopher P. Cannon

36 Countries 868 Sites

SOLID-TIMI 52 Study Design



Baseline Characteristics

Characteristic	Placebo (n=6522)	Darapladib (n=6504)
Age (median, IQR)	64 (59-71)	64 (59-70)
Female	26%	25%
White race	84%	84%
BMI (kg/m^2, median, IQR)	28 (25-31)	28 (25-31)
Current smoker	19%	19%
Diabetes mellitus requiring Rx	30%	30%
Prior MI	31%	31%
Index event STEMI NSTEMI UA	44% 44% 12%	46% 42% 12%
Catheterization for qualifying event	86%	86%
PCI performed for qualifying event	77%	77%
Days from qualifying event to rando (median, IQR)	14 (6-23)	15 (6-23)

BMI=body mass index; IQR= interquartile range; PCI= percutaneous coronary intervention

Baseline Data

Characteristic	Placebo (n=6522)	Darapladib (n=6504)
LDL cholesterol (mg/dl, median, IQR)	75 (57-97) [1.9 (1.5-2.5) mM]	75 (57-97) [1.9 (1.5-2.5) mM]
HDL cholesterol (mg/dl, median, IQR)	42 (36-50) [1.1 (0.9-1.3) mM]	42 (36-50) [1.1 (0.9-1.3) mM]
Triglycerides (mg/dl, median, IQR)	134 (100-183) [1.5 (1.1-2.1) mM]	135 (101-182) [1.5 (1.1-2.1) mM]
Baseline medications		
Aspirin	96%	96%
Statin	95%	94%
Beta blocker	87%	87%
$P2Y_{12}$ inhibitor	88%	88%
ACE inhibitor or ARB	82%	83%

IQR=interquartile range

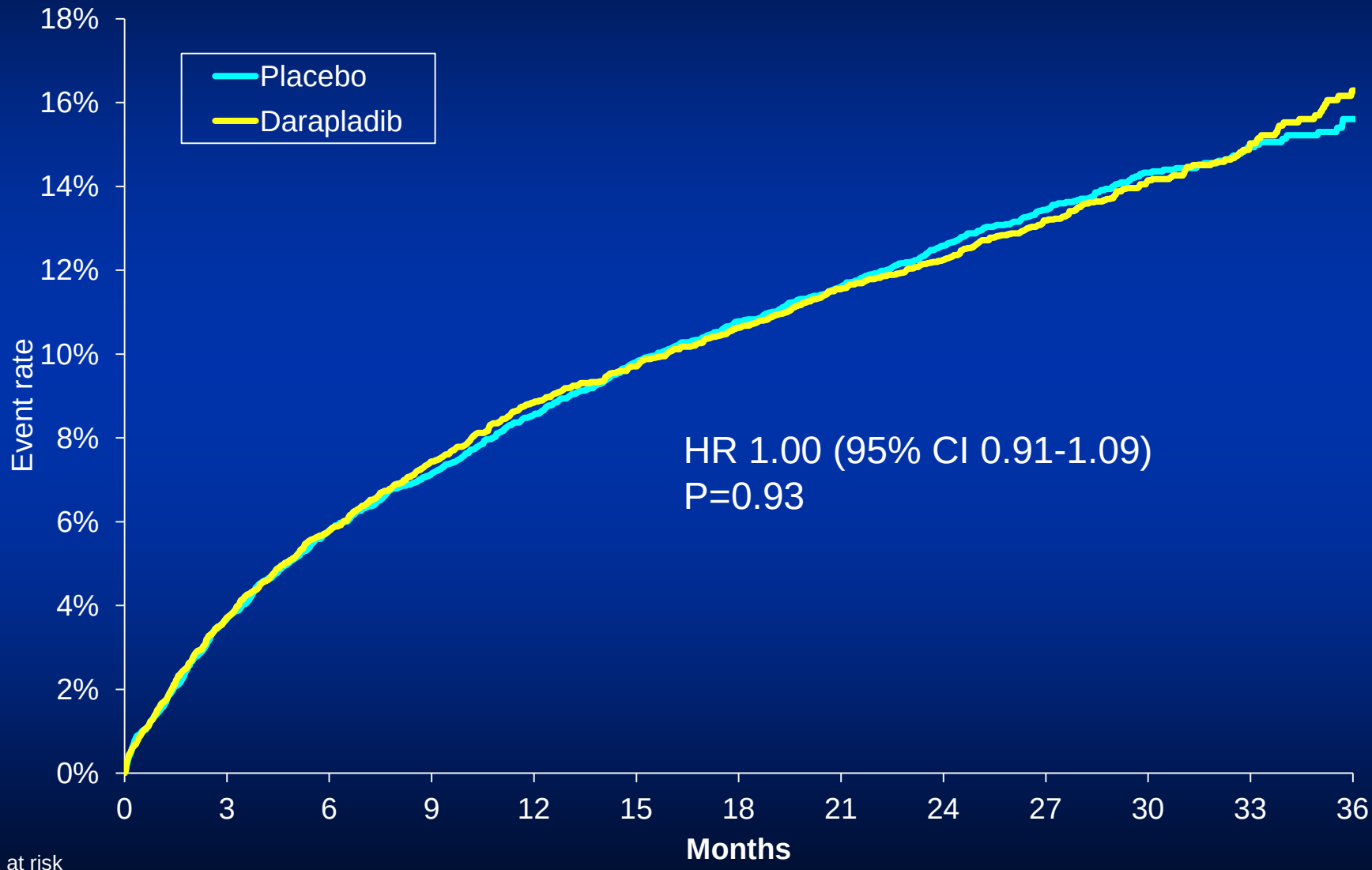
Trial Retention Metrics

	Placebo (n=6,522)	Darapladib (n=6,504)	Overall (n=13,026)
Premature study drug discontinuation	1546 (9.5% per yr)	1854 (11.4% per yr)	3400 (10.4% per yr)
Withdrawn consent	111 (1.7%)	109 (1.7%)	220 (1.7%)
VS known	96	90	186
VS unknown	15	19	34
Lost to Follow Up			
VS known	34	37	71
VS unknown	7	6	13

Vital status at end of study was known in 99.6% of subjects.
There were 31,167 total patient-years of follow-up.

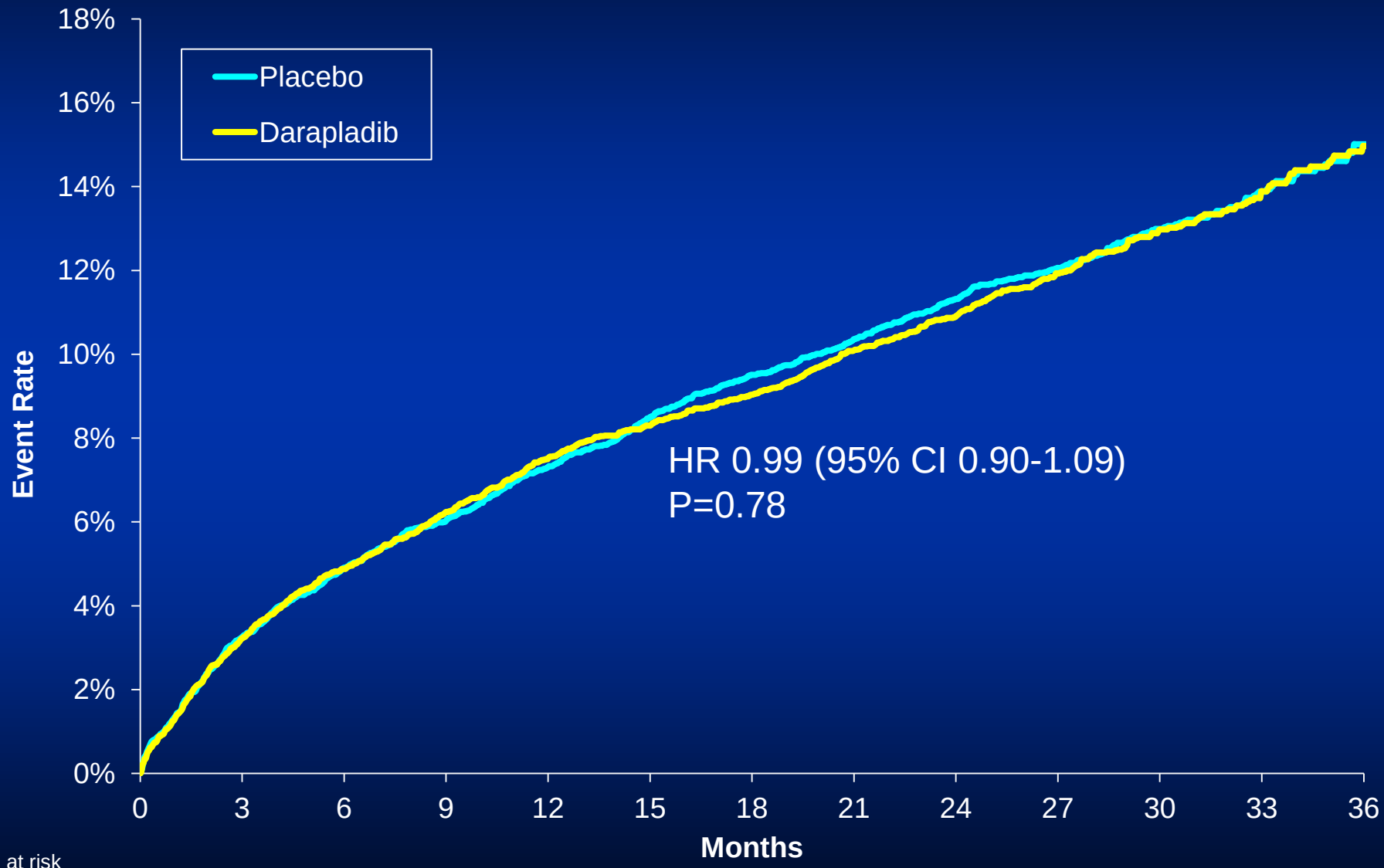
VS=vital status

Primary Endpoint: CHD death, MI or urgent coronary revascularization



No. at risk													
Placebo	6522	6219	6060	5945	5825	5726	5638	5544	5046	3942	2684	1550	669
Darapladib	6504	6201	6038	5902	5787	5708	5636	5534	5061	3955	2673	1558	634

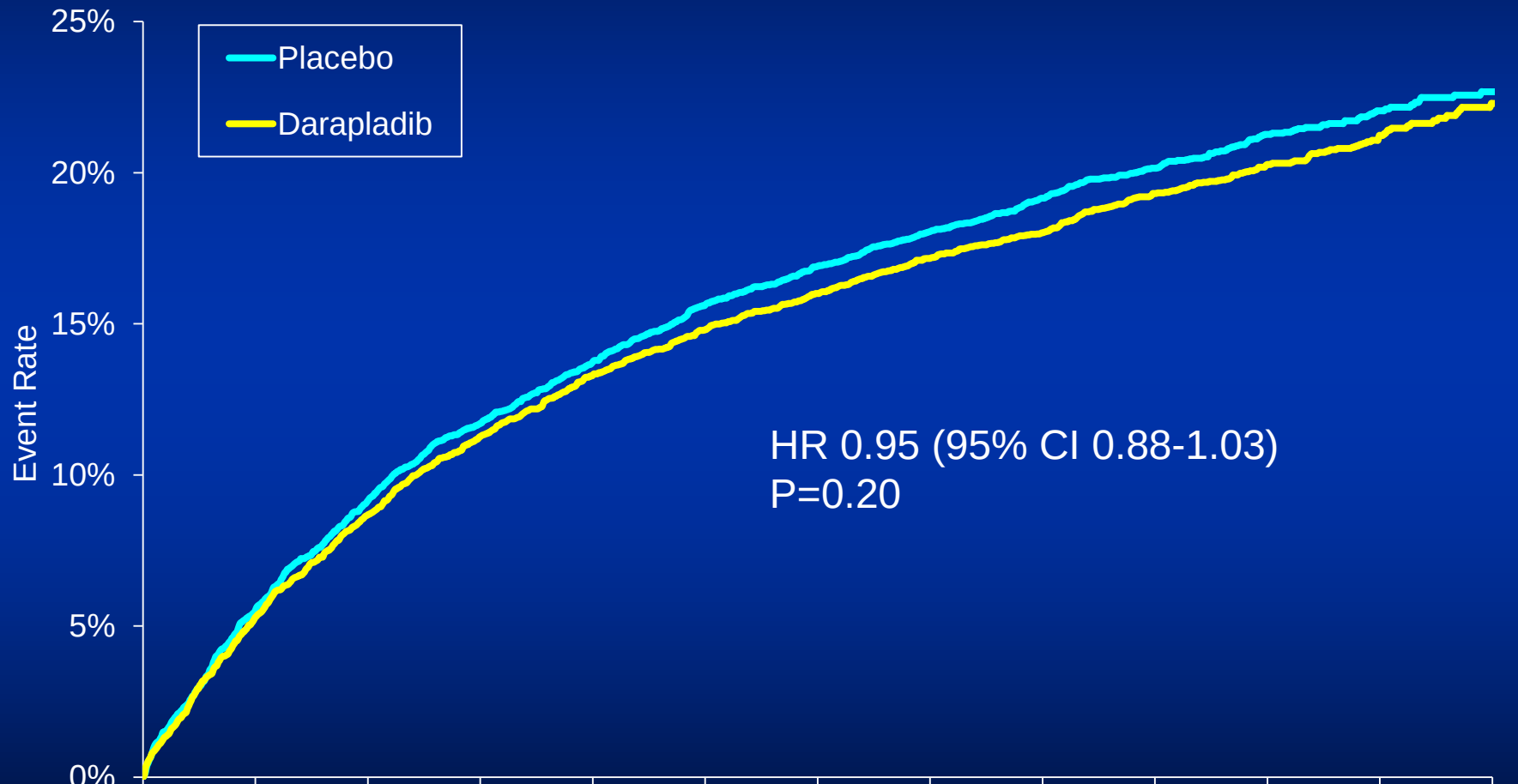
CV death, MI or stroke



No. at risk													
Placebo	6522	6249	6118	6021	5911	5818	5732	5640	5142	4031	2747	1587	678
Darapladib	6504	6238	6100	5987	5881	5805	5746	5636	5152	4018	2723	1584	644

Total coronary events

(CHD death, MI, UA or any coronary revascularization)



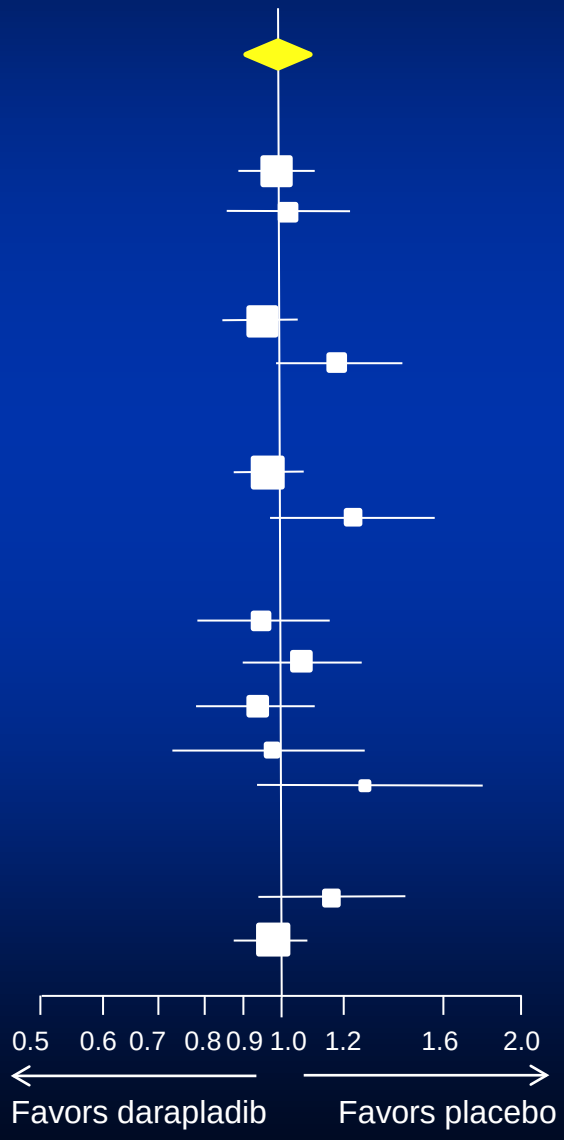
No. at risk													
Placebo	6504	6100	5852	5657	5504	5384	5294	5180	4729	3678	2485	1444	584
Darapladib	6522	6102	5846	5654	5495	5356	5249	5137	4666	3637	2467	1418	606

Components of Primary Endpoint

Outcome	HR (95% CI)	P value
Primary endpoint: Major coronary events (CHD death, MI or urgent coronary revascularization for myocardial ischemia)	**1.00 (0.91-1.09)**	**0.93**
CHD death	0.88 (0.73-1.05)	0.16
MI (fatal and non-fatal)	0.97 (0.86-1.09)	0.63
Urgent coronary revascularization for myocardial ischemia	1.09 (0.91-1.31)	0.36

Subgroup Analyses

Subgroup	Total #	CHD death, MI or urgent revascularization	Hazard Ratio (95% CI)	P value for interaction
Overall	13,026		1.00 (0.91-1.09)	
Age				
Age ≥60 years	9,661		0.99 (0.89-1.10)	0.79
Age <60 years	3,365		1.02 (0.85-1.21)	
Sex				
Men	9,700		0.94 (0.84-1.05)	0.04
Women	3,326		1.17 (0.98-1.40)	
White race				
Yes	10,921		0.96 (0.87-1.06)	0.07
No	2,105		1.22 (0.96-1.54)	
Region				
North America	2,806		0.94 (0.78-1.14)	0.45
Eastern Europe	3,773		1.06 (0.89-1.26)	
Western Europe	3,688		0.93 (0.78-1.10)	
Asia Pacific	1,804		0.97 (0.73-1.27)	
South America	955		1.28 (0.92-1.78)	
Current smoker				
Yes	2,472		1.15 (0.93-1.42)	0.13
No	10,542		0.96 (0.87-1.07)	



Subgroup Analyses (2)

Subgroup	Total #	CHD death, MI or urgent revascularization	Hazard Ratio (95% CI)	P value for interaction
Overall	13,026		1.00 (0.91-1.09)	
Diabetes mellitus				
Yes	4,502		0.96 (0.84-1.11)	0.55
No	8,524		1.02 (0.90-1.15)	
Index diagnosis				
STEMI	5,883		1.06 (0.91-1.24)	0.46
NSTEMI	5,559		1.00 (0.88-1.14)	
Unstable angina	1,584		0.88 (0.67-1.14)	
Statin use >8 weeks prior to randomization				
Yes	5,676		0.97 (0.86-1.10)	0.39
No	6,641		1.06 (0.91-1.22)	
Baseline LDL-C				
<70mg/dl	5,495		0.91 (0.79-1.06)	0.17
70-<100mg/dl	4,315		0.95 (0.81-1.11)	
≥100mg/dl	2,946		1.13 (0.94-1.35)	
Baseline Lp-PLA$_2$ activity (nmol/min/ml)				
≤154.3	4,034		0.96 (0.81-1.14)	0.98
154.3-≤195.2	4,030		0.99 (0.83-1.17)	
>195.2	4,027		0.97 (0.83-1.14)	

Additional Secondary and Exploratory Endpoints

Outcome	HR (95% CI)	P value
CHD death or MI	0.97 (0.87-1.07)	0.55
CV death	0.91 (0.76-1.08)	0.27
All-cause death	0.94 (0.82-1.08)	0.40
Stroke (fatal and non-fatal)	1.12 (0.88-1.42)	0.35
Any coronary revascularization	0.96 (0.87-1.05)	0.33
Heart failure requiring hospitalization	0.97 (0.81-1.16)	0.75

Safety Data

Event	Placebo (n=6465)	Darapladib (n=6452)
Any serious adverse event (SAE)	46.6%	45.5%
Any adverse event leading to study drug discontinuation	12.0%	17.0%
Any odor-related complaint*	2.5%	11.5%
Diarrhea	5.6%	10.6%
Renal failure (SAE)	1.0%	1.2%
Renal failure (SAE or non-serious AE)	2.5%	2.5%
Any reported cancer	4.5%	4.6%
Any gastrointestinal cancer (adjudicated)	0.93%	0.88%

* Including odor of feces, urine and skin , as well as dysgeusia

Conclusion

In patients after ACS, direct inhibition of Lp-PLA$_2$ with darapladib on a background of optimal medical therapy did not reduce the risk of coronary events through 2.5 years of follow-up.

Research

Original Investigation

Effect of Darapladib on Major Coronary Events After an Acute Coronary Syndrome
The SOLID-TIMI 52 Randomized Clinical Trial

Michelle L. O'Donoghue, MD, MPH; Eugene Braunwald, MD; Harvey D. White, MBChB, DSc; Dylan P. Steen, MD; Mary Ann Lukas, MD; Elizabeth Tarka, MD; P. Gabriel Steg, MD; Judith S. Hochman, MD; Christoph Bode, MD; Aldo P. Maggioni, MD; KyungAh Im, PhD; Jennifer B. Shannon, MS; Richard Y. Davies, MS; Sabina A. Murphy, MPH; Sharon E. Crugnale, MS; Stephen D. Wiviott, MD; Marc P. Bonaca, MD, MPH; David F. Watson, MSc; W. Douglas Weaver, MD; Patrick W. Serruys, MD, PhD; Christopher P. Cannon, MD; for the SOLID-TIMI 52 Investigators

IMPORTANCE Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) has been hypothesized to be involved in atherogenesis through pathways related to inflammation. Darapladib is an oral, selective inhibitor of the Lp-PLA_2 enzyme.

OBJECTIVE To evaluate the efficacy and safety of darapladib in patients after an acute coronary syndrome (ACS) event.

DESIGN, SETTING, AND PARTICIPANTS SOLID-TIMI 52 was a multinational, double-blind, placebo-controlled trial that randomized 13 026 participants within 30 days of hospitalization with an ACS (non–ST-elevation or ST-elevation myocardial infarction [MI]) at 868 sites in 36 countries.

INTERVENTIONS Patients were randomized to either once-daily darapladib (160 mg) or placebo on a background of guideline-recommended therapy. Patients were followed up for a median of 2.5 years between December 7, 2009, and December 6, 2013.

MAIN OUTCOMES AND MEASURES The primary end point (major coronary events) was the composite of coronary heart disease (CHD) death, MI, or urgent coronary revascularization for myocardial ischemia. Kaplan-Meier event rates are reported at 3 years.

RESULTS During a median duration of 2.5 years, the primary end point occurred in 903 patients in the darapladib group and 910 in the placebo group (16.3% vs 15.6% at 3 years; hazard ratio [HR], 1.00 [95% CI, 0.91-1.09]; $P = .93$). The composite of cardiovascular death, MI, or stroke occurred in 824 in the darapladib group and 838 in the placebo group (15.0% vs 15.0% at 3 years; HR, 0.99 [95% CI, 0.90-1.09]; $P = .78$). There were no differences between the treatment groups for additional secondary end points, for individual components of the primary end point, or in all-cause mortality (371 events in the darapladib group and 395 in the placebo group [7.3% vs 7.1% at 3 years; HR, 0.94 [95% CI, 0.82-1.08]; $P = .40$). Patients were more likely to report an odor-related concern in the darapladib group vs the placebo group (11.5% vs 2.5%) and also more likely to report diarrhea (10.6% vs 5.6%).

CONCLUSIONS AND RELEVANCE In patients who experienced an ACS event, direct inhibition of Lp-PLA_2 with darapladib added to optimal medical therapy and initiated within 30 days of hospitalization did not reduce the risk of major coronary events.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01000727

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A list of the SOLID-TIMI 52 Investigators is included in Supplement 1.

Corresponding Author: Michelle L. O'Donoghue, MD, MPH, TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, 350 Longwood Ave, First Floor, Boston, MA 02115 (modonoghue@partners.org).

JAMA. doi:10.1001/jama.2014.11061
Published online August 31, 2014.

JAMA®
The Journal of the American Medical Association

M. L. O'Donoghue and coauthors

Effect of Darapladib on Major Coronary Events After an Acute Coronary Syndrome: The SOLID-TIMI 52 Randomized Clinical Trial

Published online August 31, 2014

Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com

JN The JAMA Network