STABILITY

Stabilization of **A**therosclerotic plaque **B**y Initiation of darap**L**ad**I**b **T**herap**Y**

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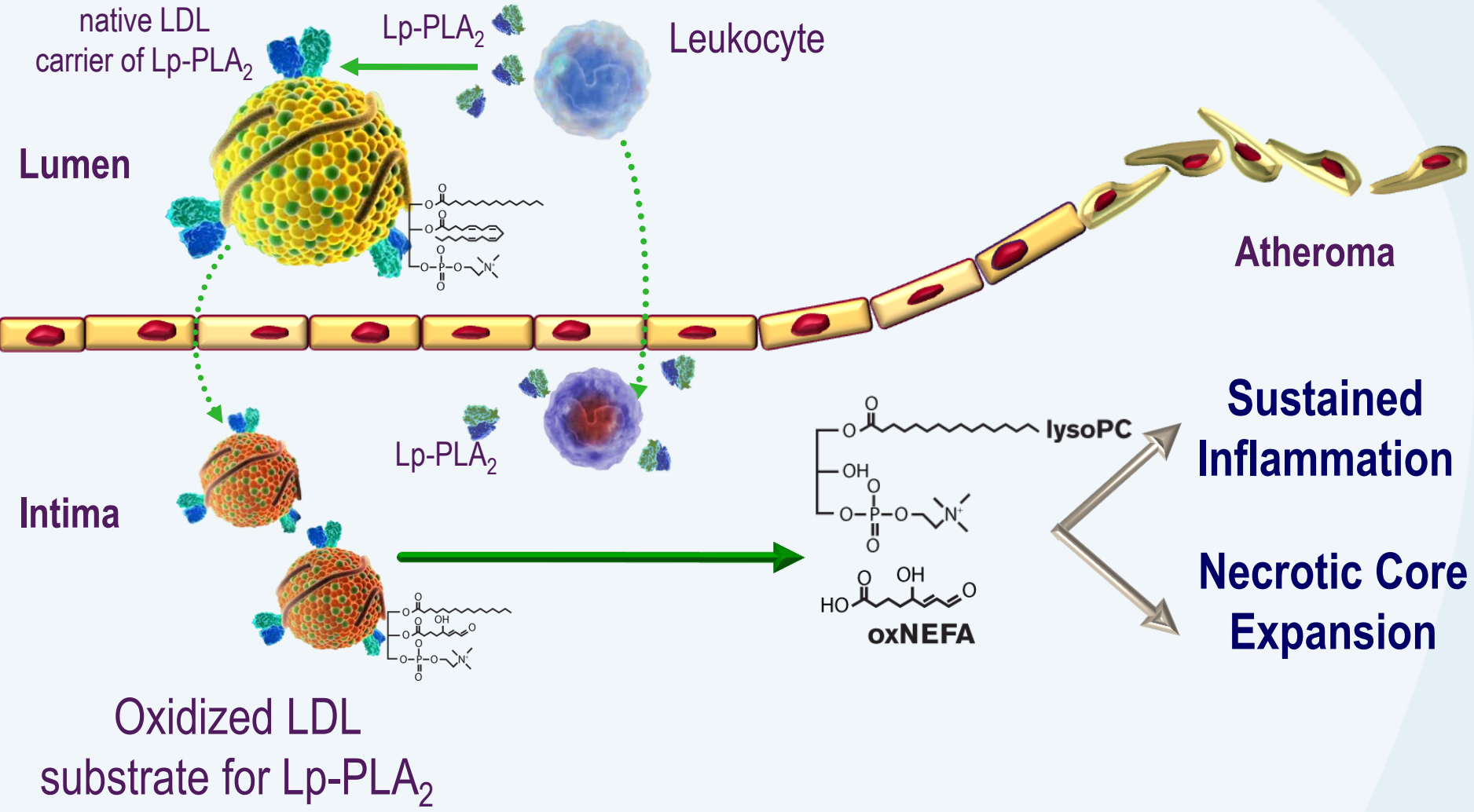
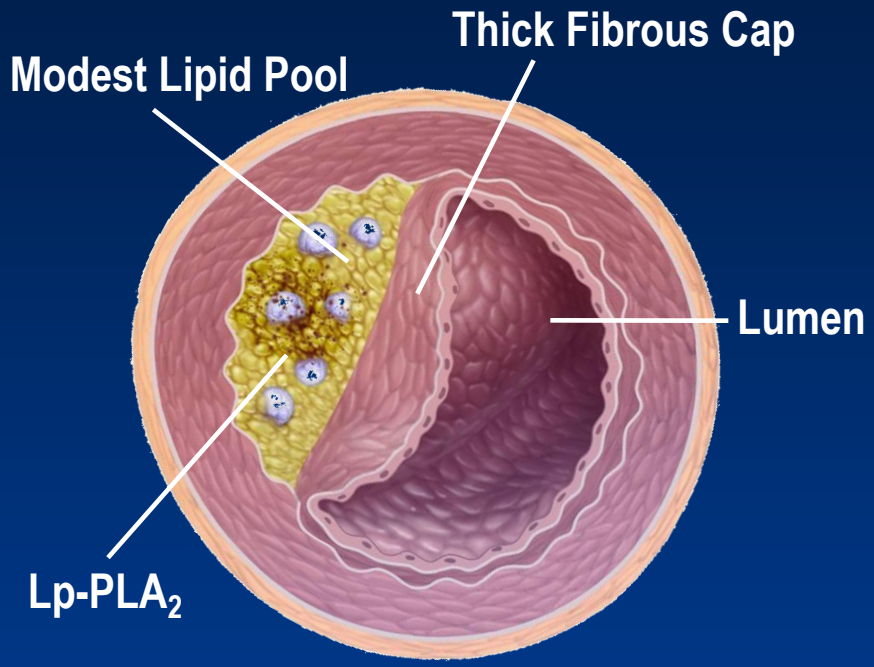
on behalf of
The STABILITY Investigators

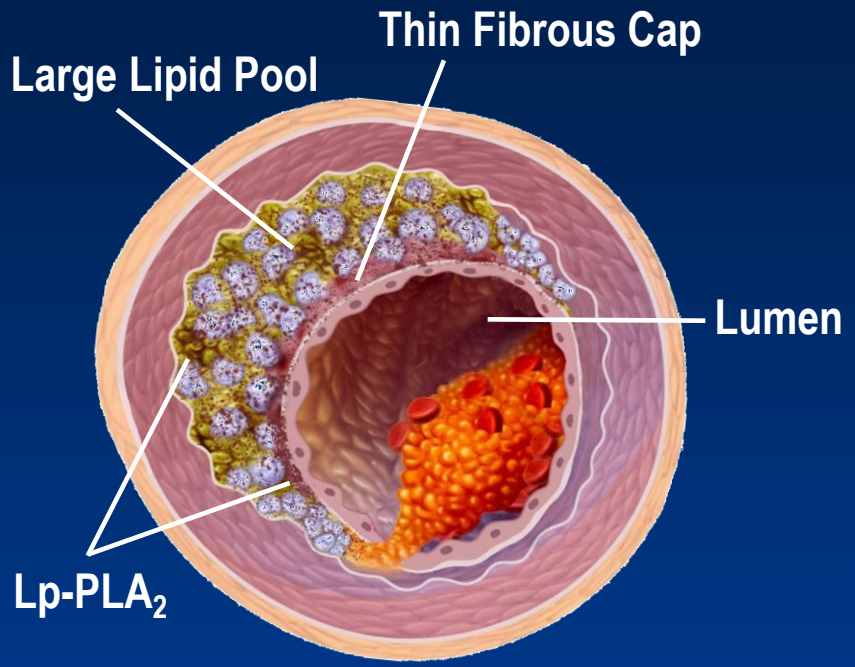
Lipoprotein- associated Phospholipase A_2 (Lp-PLA_2) activity: Background



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

Contrasting histopathological characteristics of a stable versus a vulnerable or ruptured plaque





Stable Plaque

- ✓ Low Lp-PLA_2 content (dark staining)
- ✓ May have significant stenosis
- ✓ Thick fibrous cap / high collagen content
- ✓ Modest lipid pool
- ✓ Few inflammatory cells

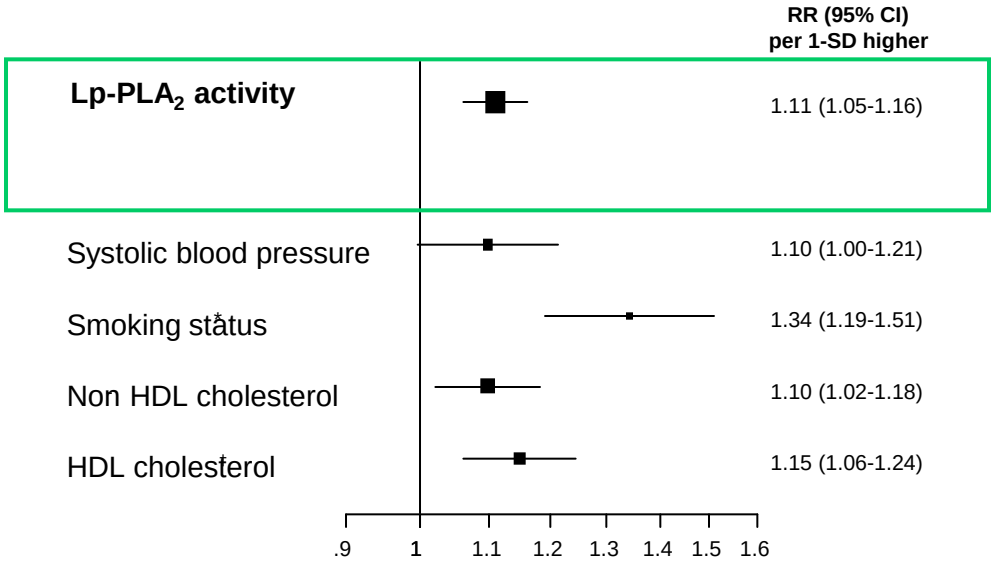
Vulnerable or ruptured Plaque

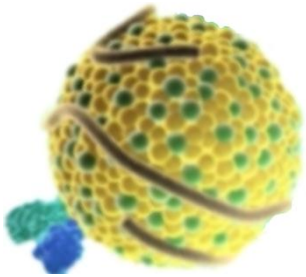
- ✓ High Lp-PLA_2 content (dark staining)
- ✓ May have minimal stenosis
- ✓ Thin fibrous cap / low collagen content
- ✓ Large lipid pool
- ✓ Many inflammatory cells

Corson et al. Am J Card 2008;101(Suppl):41F-50F

Lp-PLA$_2$ and CHD risk: The Lp-PLA$_2$ Studies Collaboration; compared with conventional risk factors

79,036 participants from 32 prospective studies





Adjusted for non-lipid and lipid conventional risk factors

LSC *Lancet* 2010; 375:1536

STABILITY: Background

Association studies

EPIDEMIOLOGY

Higher Lp-PLA_2 levels predict CV events

GENETICS

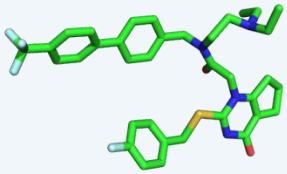
Deficiency in Lp-PLA_2 due to null allele results in decreased CHD

PATHOLOGY

Up-regulation of Lp-PLA_2 in vulnerable plaques

STABILITY

Darapladib is a selective oral inhibitor that decreases Lp-PLA_2 by 60%



Intervention with darapladib

PRECLINICAL

Reduces Lp-PLA_2 in plaque and necrotic core area (pig)

HUMAN ATHEROMA

Reduces carotid plaque Lp-PLA_2 activity

CORONARY IMAGING

IBIS-2

Halts progression of coronary artery necrotic plaque core volume

STABILITY Trial

Stabilization of **A**therosclerotic plaque **B**y Initiation of darap**L**ad**I**b **T**herap**Y**

Patients with chronic CHD
(prior MI >1 mth, prior coronary revascularization, multivessel CAD)

Enrichment criteria: ≥60 years of age, diabetes mellitus, low HDL, current smoking, significant renal dysfunction, polyvascular disease

15,828 patients randomized

Darapladib 160mg

Placebo

Optimized guideline-mandated treatment

median follow-up 3.7 years , 1588 events

Primary endpoint: composite of CV death, MI, stroke
Secondary endpoints: major coronary events, total coronary events

Key Exclusion Criteria

- Planned coronary revascularization
- Current liver disease or severe renal impairment
- Current severe heart failure
- Poorly controlled hypertension
- Severe asthma that is poorly controlled
- History of anaphylaxis, anaphylactoid reactions, or severe allergic responses
- Concomitant cytochrome P-450 inhibitor use
- Lp-PLA_2 activity ≤20.0 nmol/min/mL

Recruitment into STABILITY Trial (N=15,828)

North America (25%)

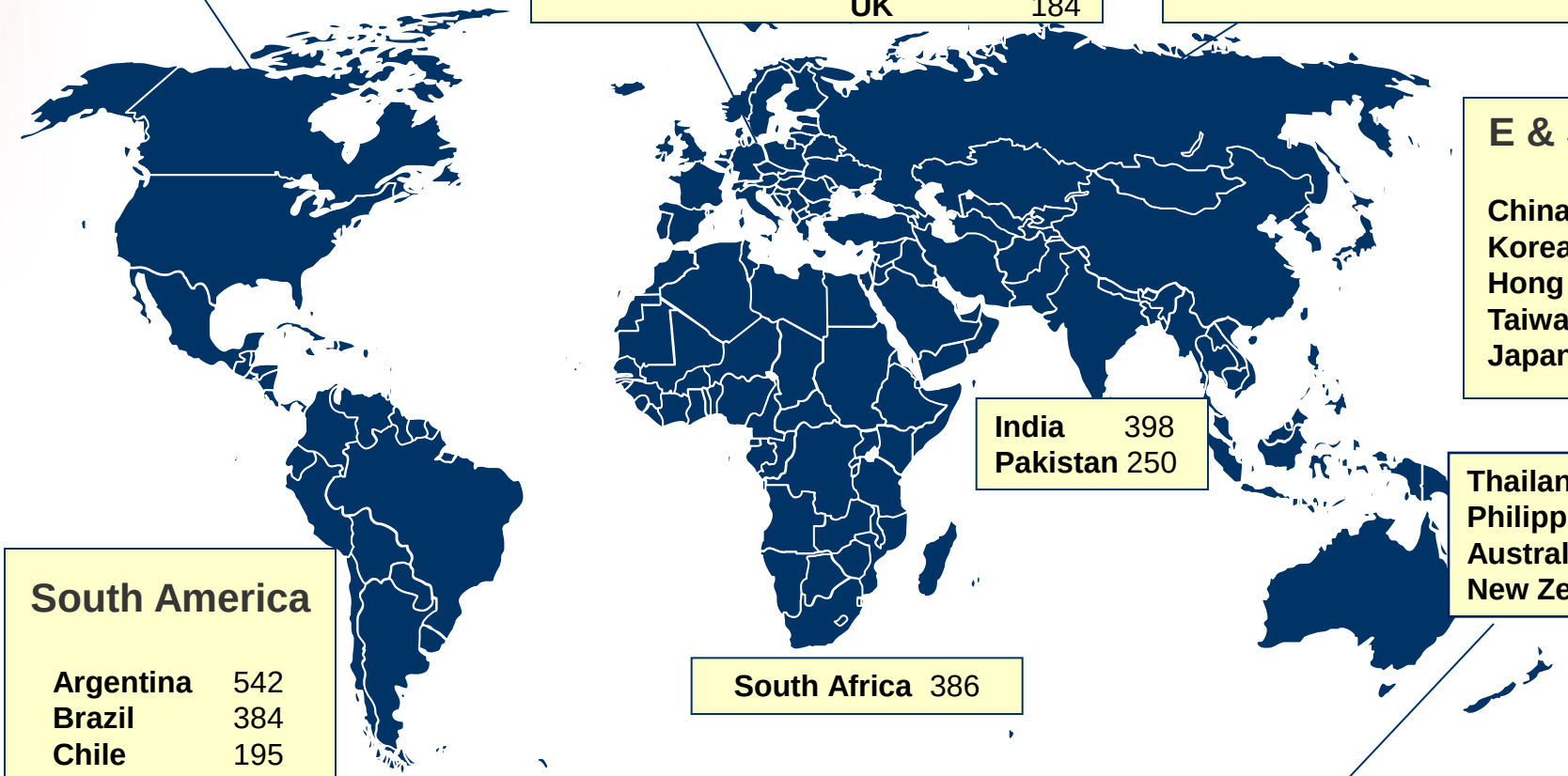
USA	3102
Canada	780
Mexico	141

Western Europe (22%)

Belgium	202	**Italy**	256
Denmark	102	**Netherlands**	444
France	250	**Norway**	113
Greece	187	**Spain**	474
Germany	1089	**Sweden**	299
		UK	184

Eastern Europe (22%)

Bulgaria	222	**Poland**	510
Cz Republic	774	**Romania**	411
Estonia	77	**Russia**	654
Hungary	410	**Slovakia**	120
		Ukraine	353



E & SE Asia

China	369
Korea	503
Hong Kong	117
Taiwan	200
Japan	318

India	398
Pakistan	250

Thailand	207
Philippines	219
Australia	306
New Zealand	202

South America

Argentina	542
Brazil	384
Chile	195
Peru	78

South Africa	386

Asia-Pacific/Latina (31%)

Demographics

	Placebo (N=7904)	Darapladib (N=7924)
Age: Median in years	65.0	65.0
<65 years (%)	49%	48%
65-74 years (%)	37%	38%
>=75 years (%)	14%	14%
Female (%)	19%	18%
Race or Ethnic Group (%)		
White	78%	79%
Black	2%	2%
Central/South/South East Asian	8%	7%
East Asian/Japanese	10%	10%
Other	2%	2%

Chronic Coronary Heart Disease Qualifying Diagnosis

	Placebo (N=7904)	Darapladib (N=7924)
Prior MI	59%	59%
Coronary revascularization	75%	75%
PCI	50%	50%
CABG	33%	33%
Multi-vessel CAD	15%	15%

Enrichment Criteria

	Placebo (N=7904)	Darapladib (N=7924)
Age ≥ 60 years	73%	73%
Diabetes req. pharmacotherapy	34%	34%
HDL < 40 mg/dL (1.03 mmol/L)	35%	33%
Current smoker or former smoker within 3 months (≥5 cigs/day)	21%	20%
Significant renal dysfunction (eGFR 30 to 59 mL/min/1.73 m^2 or urine ACR ≥3 mg albumin/g creatinine)	30%	30%
Polyvascular disease (cerebrovascular disease or peripheral arterial disease)	15%	15%

Baseline LDL

	Placebo (N=7904)	Darapladib (N=7924)
LDL-C (mg/dL)		
Median (Interquartile range)	80 (63 – 101)	80 (63 – 101)
<70 (<1.8mmol/L)	36%	35%
70 – 100 (1.8-2.6 mmol/L)	38%	39%
≥100 (≥2.6 mmol/L)	26%	26%

Concomitant Medication Usage

	Time Point	Placebo (N=7904)	Darapladib (N=7924)
Aspirin	Baseline Study end	93% 91%	92% 90%
Statins	Baseline Study end	97% 96%	97% 96%
Beta-Blockers	Baseline Study end	79% 79%	79% 78%
P2Y12 Inhibitors	Baseline Study end	34% 27%	34% 27%
ACE inhibitor	Baseline Study end	56% 54%	57% 54%
Angiotensin II receptor blocker	Baseline Study end	23% 27%	22% 26%

Standard of Care Measures

	Time Point	Placebo (N=7890)	Darapladib (N=7912)
LDL-Cholesterol (mg/dL)			
Median (Interquartile range)	Baseline Study end	80 (63 – 101) 79 (62 – 100)	80 (63 – 101) 78 (61 – 99)
Blood Pressure (mmHg)			
Mean	Baseline Study end	132/79 mmHg 131/77 mmHg	132/79 mmHg 132/77 mmHg

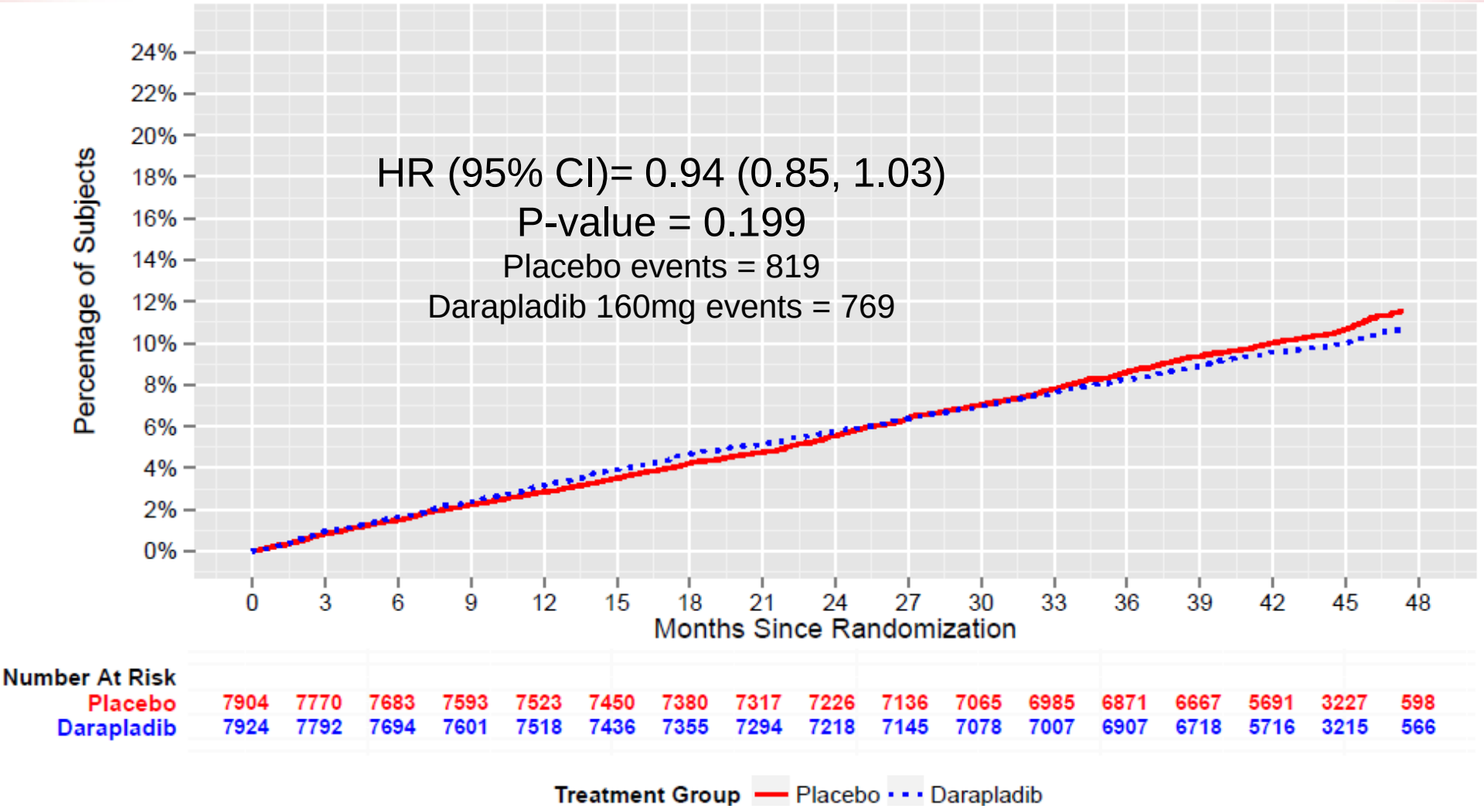
Subject Status Overview

	Placebo (N=7904)	Darapladib (N=7924)
IP Discontinuation	26.8%	32.7%
Study Withdrawal	273 (3.5%)	278 (3.5%)
Complete CV Endpoint Follow-up	7628 (96.5%)	7641 (96.4%)
Complete Vital Status Follow-up	7845 (99.3%)	7877 (99.4%)

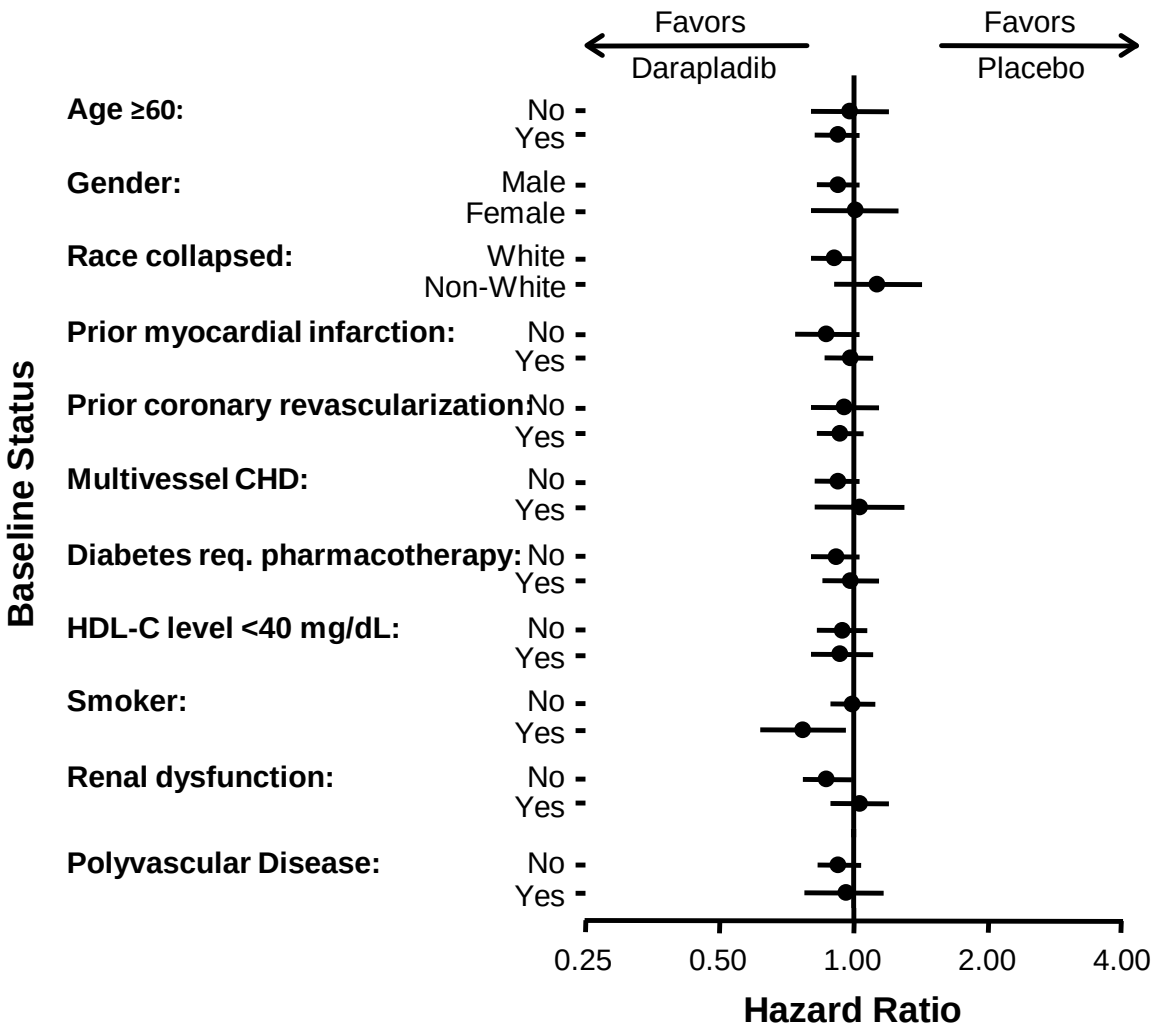
Median follow-up time was 3.7 years for both treatment groups

Adherence (≥ 80%) was 91.3% for placebo and 89.3% for darapladib

Primary Endpoint:
Time to First Occurrence CV Death, MI, Stroke

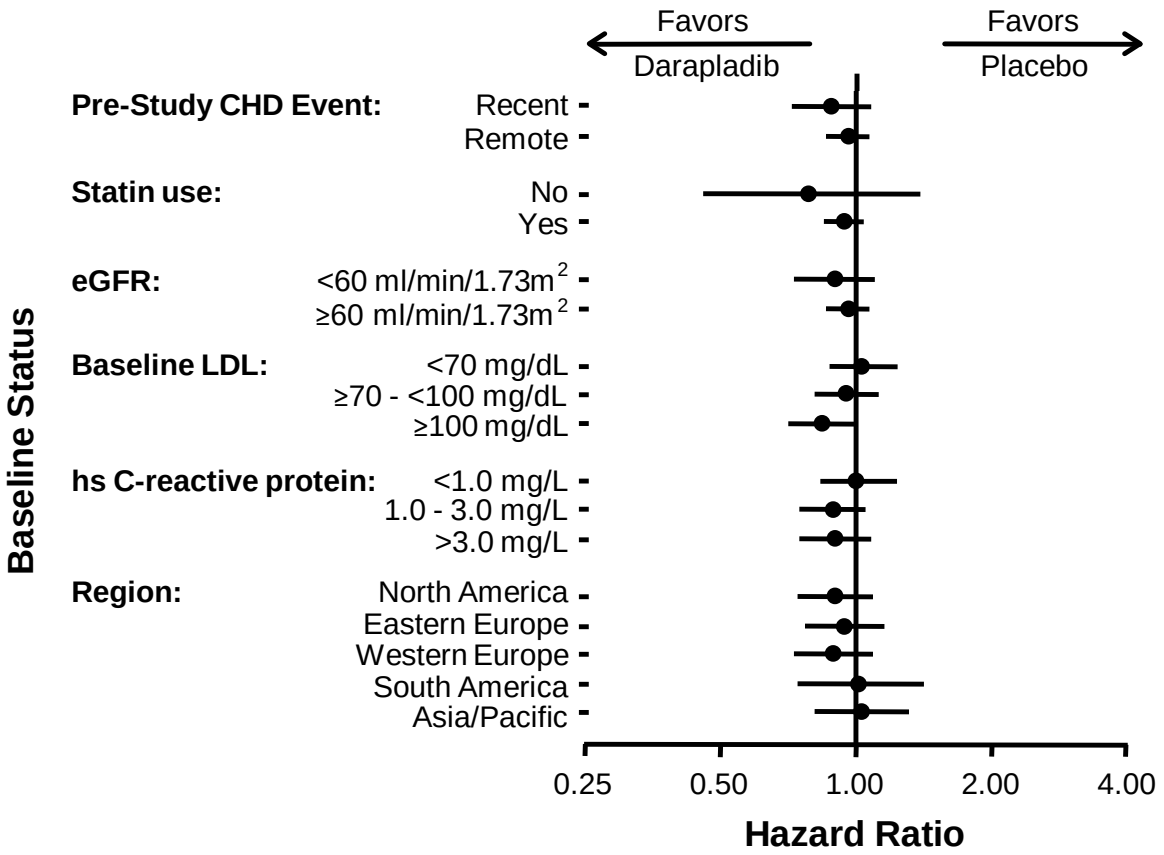


Subgroup Analyses for CV Death, MI, Stroke



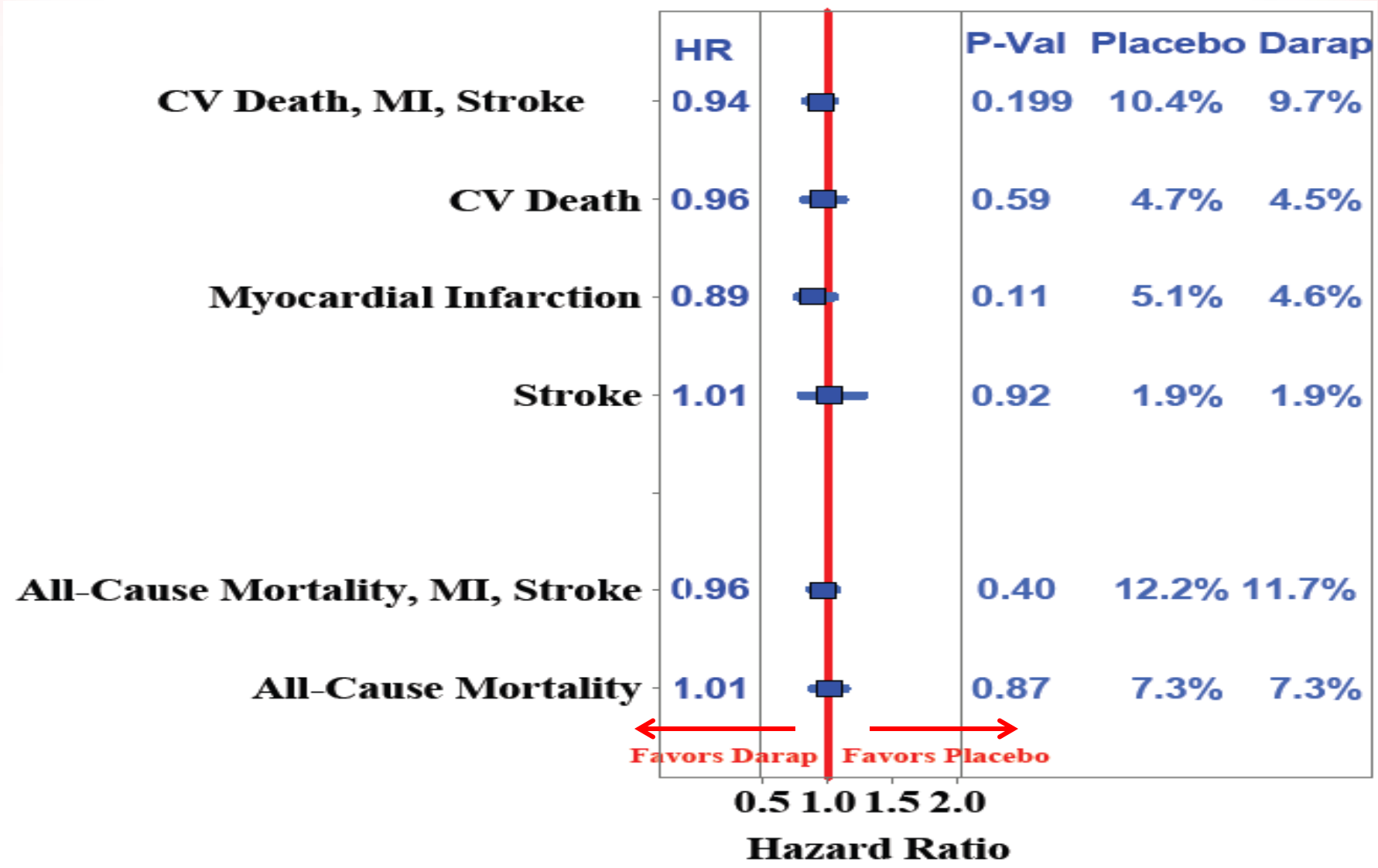
	HR (95% CI)	Interaction P-value	Number of Events (%) Placebo	Darapladib
Age ≥60:				
No	0.98 (0.80, 1.20)	0.613	191 (8.8%)	182 (8.6%)
Yes	0.92 (0.82, 1.03)		628 (10.9%)	587 (10.1%)
Gender:				
Male	0.92 (0.83, 1.03)	0.500	670 (10.5%)	624 (9.7%)
Female	1.01 (0.80, 1.26)		149 (9.9%)	145 (9.9%)
Race collapsed:				
White	0.90 (0.80, 1.00)	0.077	675 (10.9%)	610 (9.8%)
Non-White	1.13 (0.90, 1.41)		144 (8.3%)	159 (9.4%)
Prior myocardial infarction:				
No	0.87 (0.74, 1.03)	0.295	314 (9.6%)	274 (8.4%)
Yes	0.98 (0.86, 1.10)		505 (10.9%)	495 (10.6%)
Prior coronary revascularization:				
No	0.95 (0.80, 1.14)	0.837	244 (12.2%)	229 (11.6%)
Yes	0.93 (0.83, 1.05)		575 (9.7%)	540 (9.1%)
Multivessel CHD:				
No	0.92 (0.82, 1.03)	0.395	672 (10.0%)	620 (9.2%)
Yes	1.03 (0.82, 1.29)		147 (12.3%)	149 (12.4%)
Diabetes req. pharmacotherapy:				
No	0.91 (0.80, 1.03)	0.422	477 (9.1%)	435 (8.3%)
Yes	0.98 (0.85, 1.14)		342 (12.7%)	334 (12.5%)
HDL-C level <40 mg/dL:				
No	0.94 (0.83, 1.07)	0.951	502 (9.8%)	486 (9.2%)
Yes	0.93 (0.80, 1.10)		316 (11.3%)	281 (10.6%)
Smoker:				
No	0.99 (0.89, 1.11)	0.044	619 (10.0%)	625 (9.9%)
Yes	0.77 (0.62, 0.96)		192 (11.6%)	140 (8.9%)
Renal dysfunction:				
No	0.87 (0.77, 0.99)	0.104	482 (8.7%)	420 (7.6%)
Yes	1.03 (0.89, 1.19)		337 (14.2%)	349 (14.5%)
Polyvascular Disease:				
No	0.93 (0.83, 1.04)	0.796	626 (9.3%)	584 (8.7%)
Yes	0.96 (0.78, 1.17)		193 (16.3%)	185 (15.6%)

Subgroup Analyses for CV Death, MI, Stroke

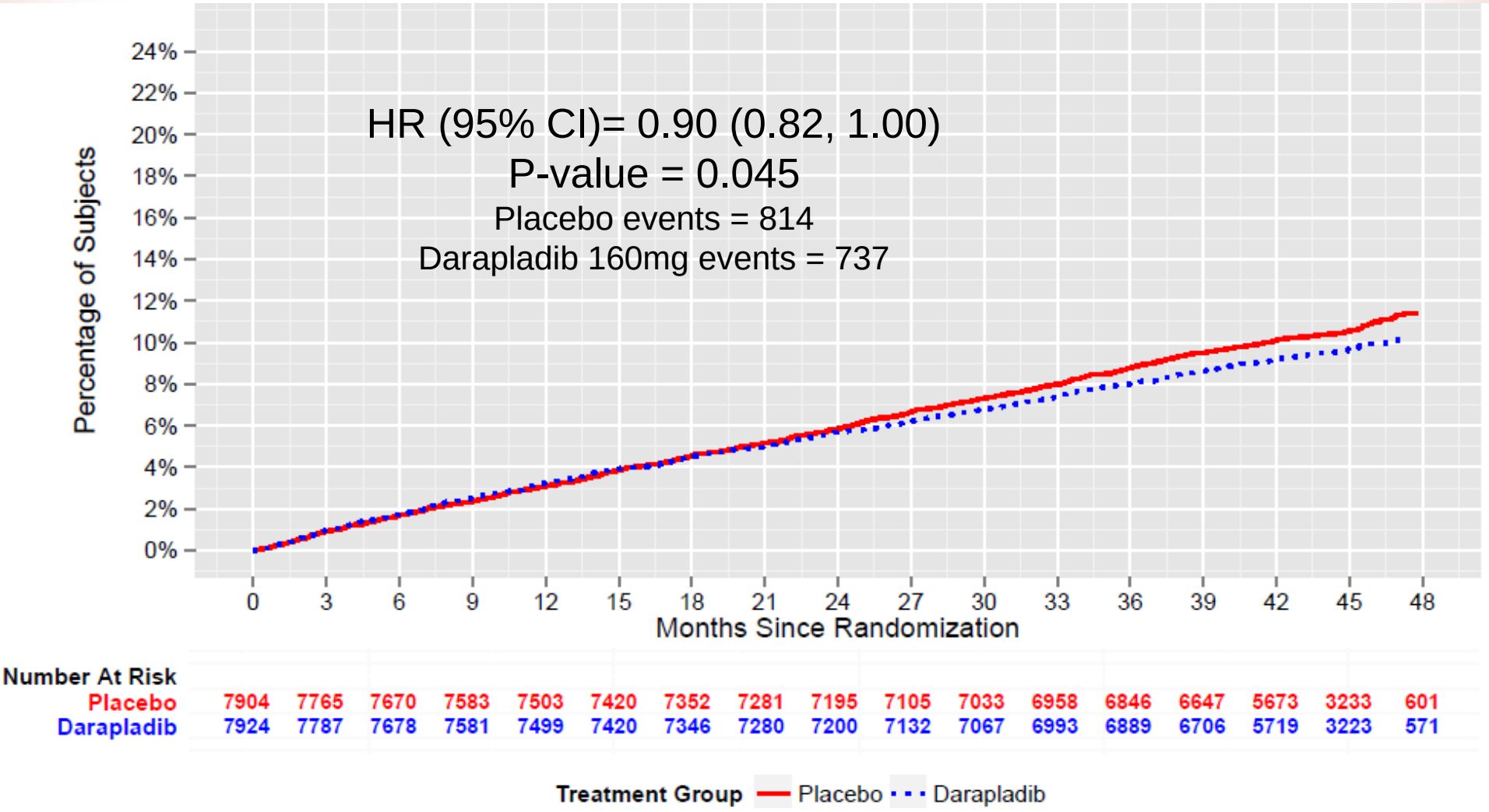


	HR (95% CI)	Interaction P-value	Number of Events (%) Placebo	Darapladib
Pre-Study CHD Event:				
Recent	0.88 (0.72, 1.08)	0.481	194 (10.2%)	173 (9.1%)
Remote	0.96 (0.86, 1.07)		623 (10.4%)	596 (9.9%)
Statin use:				
No	0.79 (0.46, 1.38)	0.544	29 (13.0%)	22 (10.7%)
Yes	0.94 (0.85, 1.04)		790 (10.3%)	747 (9.7%)
eGFR:				
<60 ml/min/1.73m^2	0.90 (0.73, 1.10)	0.575	191 (17.0%)	165 (15.2%)
≥60 ml/min/1.73m^2	0.96 (0.86, 1.07)		625 (9.2%)	604 (8.9%)
Baseline LDL:				
<70 mg/dL	1.03 (0.87, 1.23)	0.238	245 (8.7%)	251 (9.0%)
≥70 - <100 mg/dL	0.95 (0.81, 1.12)		291 (9.6%)	278 (9.1%)
≥100 mg/dL	0.84 (0.71, 1.00)		281 (13.7%)	240 (11.6%)
hs C-reactive protein:				
<1.0 mg/L	1.00 (0.83, 1.22)	0.604	209 (7.6%)	209 (7.6%)
1.0 - 3.0 mg/L	0.89 (0.75, 1.05)		283 (10.8%)	253 (9.7%)
>3.0 mg/L	0.90 (0.75, 1.08)		249 (13.6%)	225 (12.2%)
Region:				
North America	0.90 (0.74, 1.09)	0.863	213 (10.6%)	190 (9.5%)
Eastern Europe	0.94 (0.77, 1.15)		193 (10.9%)	181 (10.2%)
Western Europe	0.89 (0.73, 1.09)		207 (10.5%)	187 (9.3%)
South America	1.02 (0.74, 1.41)		73 (12.2%)	74 (12.3%)
Asia/Pacific	1.03 (0.81, 1.31)		133 (8.6%)	137 (8.9%)

Cardiovascular and Mortality Endpoints

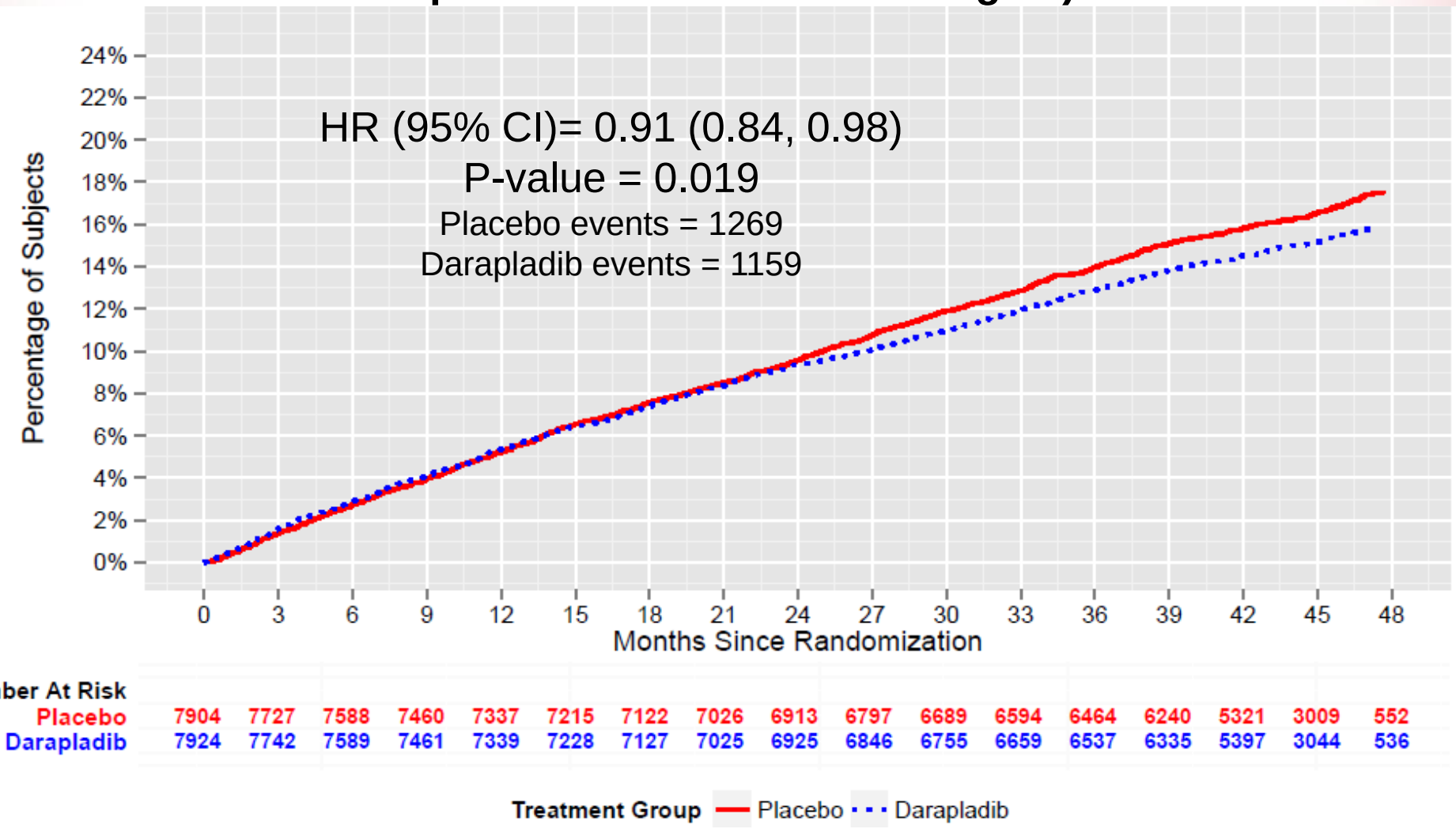


Time to First Occurrence Major Coronary Events
(CHD Death, MI, Urgent Coronary Revascularization)

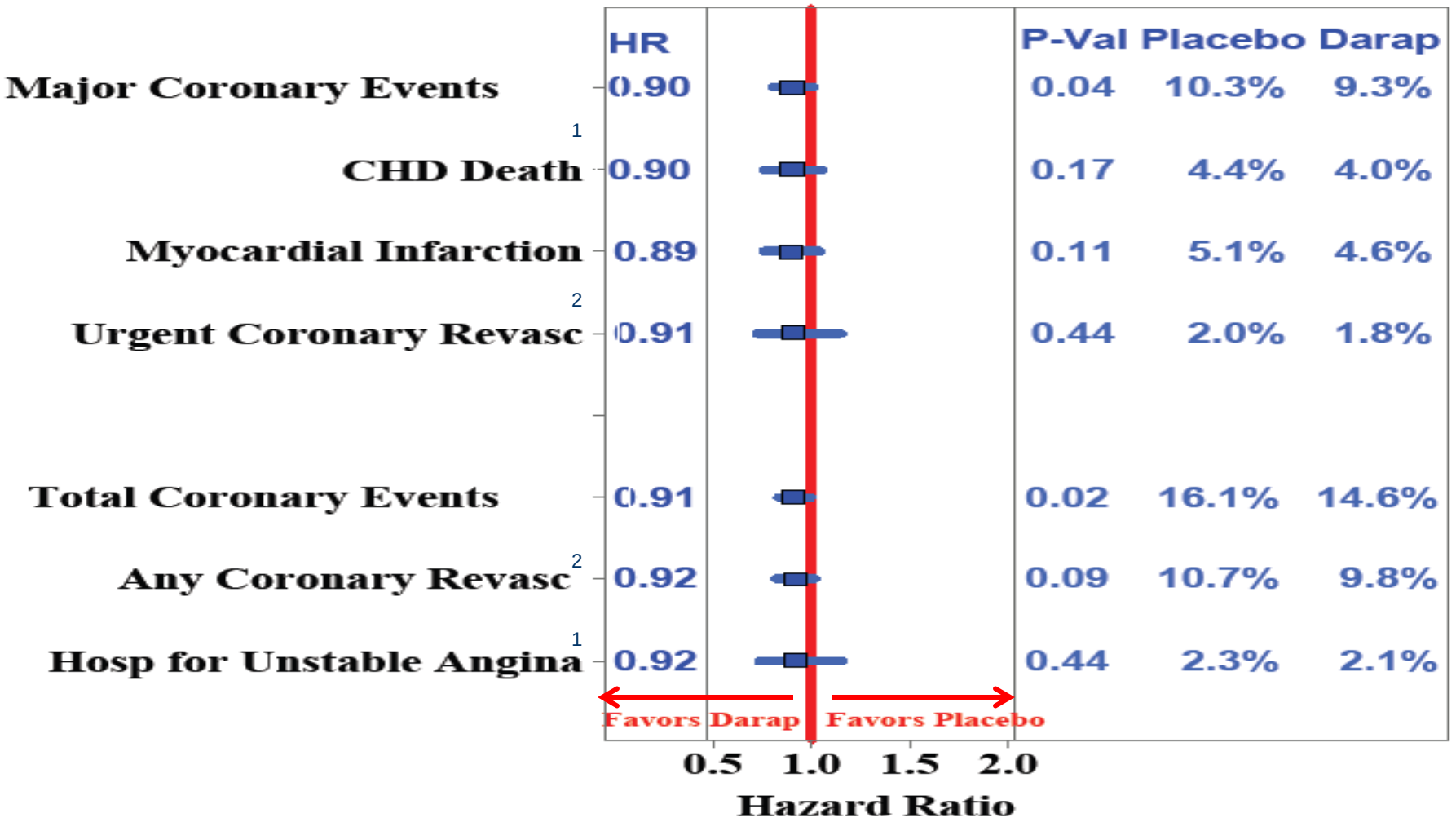


Time to First Occurrence Total Coronary Events

(CHD Death, MI, Any Coronary Revascularization, Hospitalization for Unstable Angina)



Coronary-Specific Endpoints



1 - Component of pre-specified composite, but not a pre-specified endpoint
2 - Component of pre-specified composite, pre-specified as an endpoint of interest

Diarrhea/Odor Adverse Events Leading to Study Drug Discontinuation

	Placebo (N=7890)		Darapladib (N=7912)	
	n (%)	Rate per 100 PY	n (%)	Rate per 100 PY
Diarrhea	60 (0.8%)	0.21	254 (3%)	0.92
Abnormal feces	5 (<0.1%)	0.02	177 (2%)	0.64
Abnormal skin odor	4 (<0.1%)	0.01	174 (2%)	0.63
Abnormal urine odor	1 (<0.1%)	<0.01	113 (1%)	0.40

Adverse Events

	Placebo (N=7890)		Darapladib (N=7912)	
	n (%)	Rate per 100 PY	n (%)	Rate per 100 PY
Any serious adverse event	3448 (44%)	16.02	3369 (43%)	15.53
Any adverse event leading to study drug discontinuation	1067 (14%)	3.98	1569 (20%)	6.25
Asthma	64 (0.8%)	0.23	43 (0.5%)	0.15
Renal Effects				
Renal failure	89 (1.1%)	0.32	120 (1.5%)	0.43
eGFR (ml/min/1.73m^2): Mean (SD) change from baseline at end of treatment period	1.7 (14.4)		-0.8 (14.1)	
Treatment difference (95% CI)	-2.5 (-3.0, -2.1)			
Cancer				
New cancer	529 (6.7%)		508 (6.4%)	
Adjudicated new GI cancer	105 (1.3%)		102 (1.3%)	
Liver Events	52 (0.7%)		54 (0.7%)	
Anaphylaxis	7 (<0.1%)		9 (0.1%)	

Conclusions

Darapladib in patients with stable CHD followed for 3.7 years on a background of optimal medical therapy

- Did not significantly reduce the incidence of the primary composite endpoint of CV death, MI or stroke
- There was no effect on stroke or total mortality
- Reduced the prespecified coronary-specific secondary endpoints of major coronary events (1% absolute) and total coronary events (1.5% absolute) with nominal significance ($p<0.05$)

Implications

The STABILITY trial is the first large scale randomized global trial to test a novel mechanism of inhibition of inflammation in the atherosclerotic plaque

- Further analyses of the trial results in subgroups based on biomarkers, including Lp-PLA_2 levels, and genetics will explore if darapladib might be useful in specific patient subsets
- The STABILITY trial results indicate that darapladib warrants further evaluation in other clinical settings

Study Acknowledgements

We would like to acknowledge all the study investigators, research staff and study patients, without whom this study would not be possible

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