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

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TIMI

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Disclosures

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Background

- Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is believed to contribute to atherosclerosis (plaque build-up) through pathways of inflammation
- Epidemiologic studies have shown that higher levels of Lp-PLA_2 are associated with an increased risk of cardiovascular events
- Darapladib is an oral, direct inhibitor of the Lp-PLA_2 enzyme that reduces Lp-PLA_2 activity in the circulation and in plaque.
- In phase II testing, darapladib did not modify atheroma volume, but halted necrotic core progression vs placebo on a background of statin therapy*

*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*

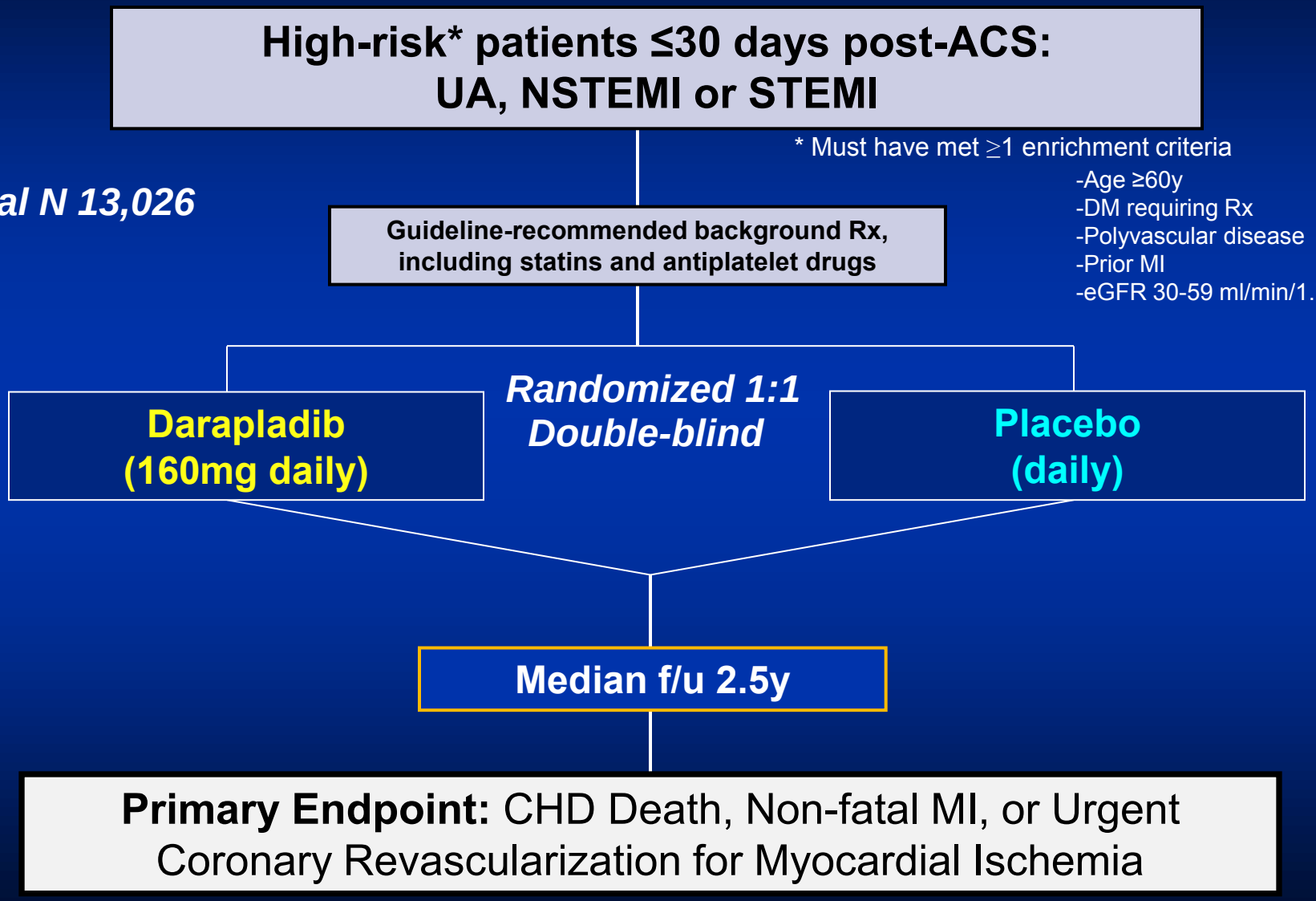
Randomization ≤30 days from hospitalization with ACS

Randomization to Darapladib or Placebo

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

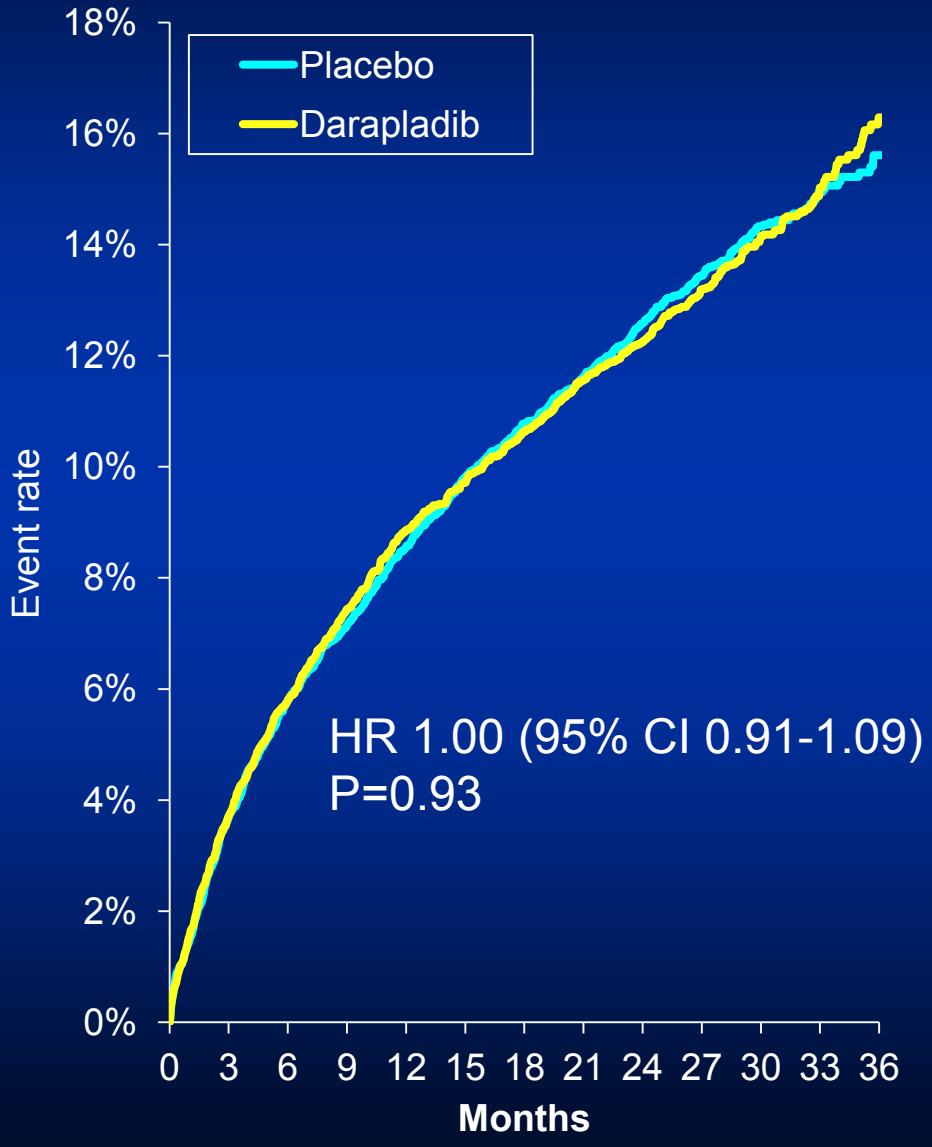
* High-risk criteria (≥1 of the following): age ≥60 years, diabetes mellitus requiring Rx, eGFR 30-59 ml/min/1.73 m^2, polyvascular disease, HDL <40 mg/dl (STABILITY only), tobacco use (STABILITY only), or prior MI (SOLID-TIMI 52 only)

SOLID-TIMI 52 Study Design

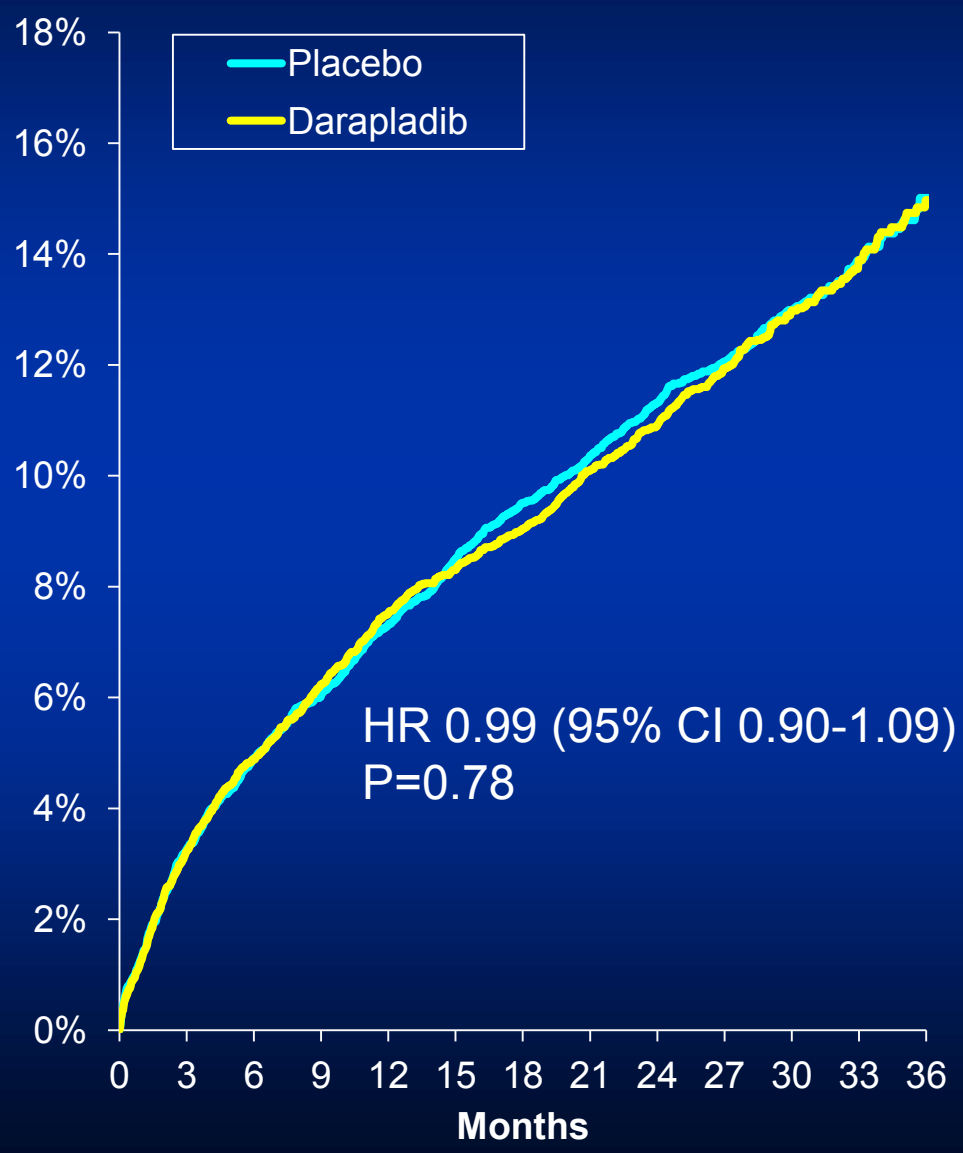


SOLID TIMI 52

Primary Endpoint: CHD death, MI or urgent coronary revascularization



Secondary Endpoint: CV death, MI or stroke



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

Summary

- 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.
- These findings do not support a role for Lp-PLA$_2$ inhibition in patients after ACS.
- Evidence continues to support a central role for inflammation in atherosclerosis. However, reliable surrogate endpoints are lacking to gain insight into drug efficacy prior to phase 3 testing.


Research

Original Investigation

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

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