

Imperial College
London



A clinical view on BET inhibition in targeting residual risk in CVD and Diabetes

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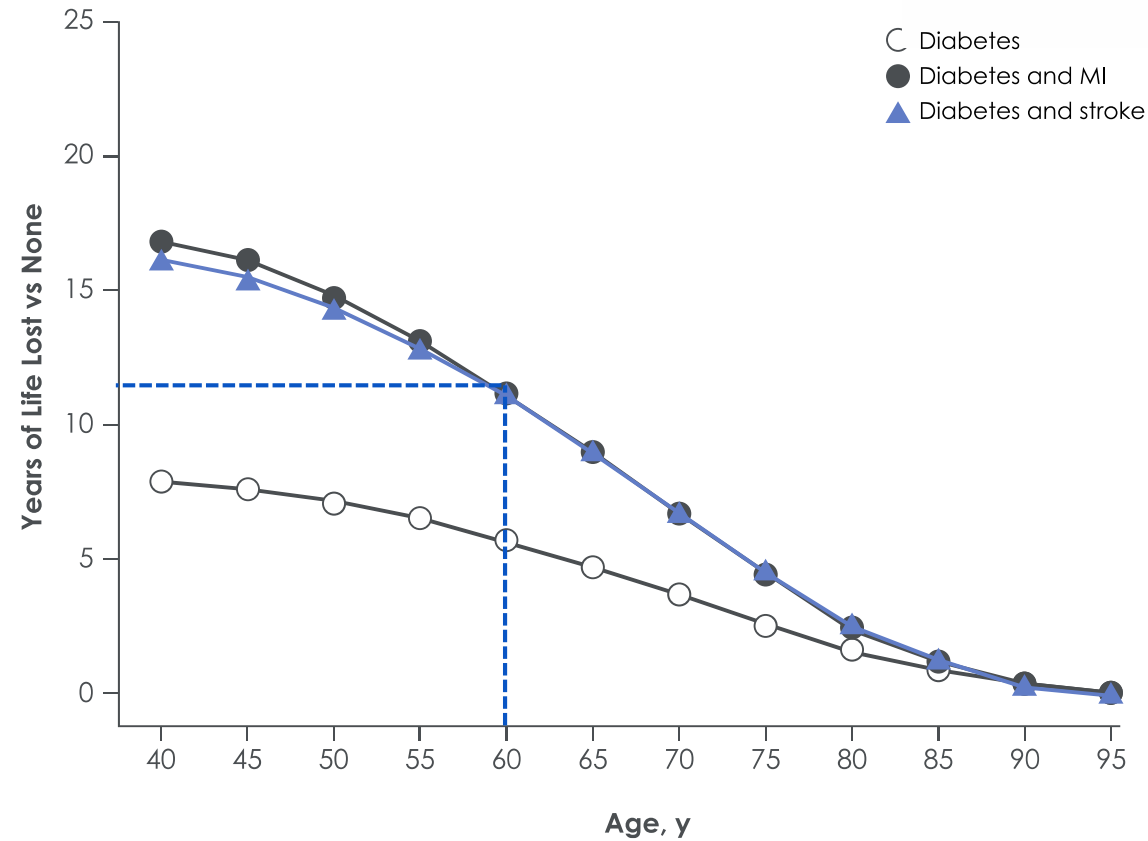
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Disclosures

- **Research grants:** Amgen, Sanofi, Regeneron, MSD, Pfizer
- **Consultancy:** Amgen, Sanofi, Regeneron, MSD, Pfizer, Astra Zeneca, Lilly, Medicines Company, Kowa, IONIS, Takeda, Novo Nordisk, Boehringer Ingelheim, Esperion, Cipla, Algorithm, Abbvie, Resverlogix, Cerenis

Life expectancy is reduced by ~12 years in diabetes patients with previous CVD*

Modelling of Years of Life Lost by Disease Status of Participants at Baseline Compared With Those Free of Diabetes, Stroke, and MI



* male, 60 years of age with history of MI or stroke

Interventions that reduce CVD

Antiplatelet therapies?

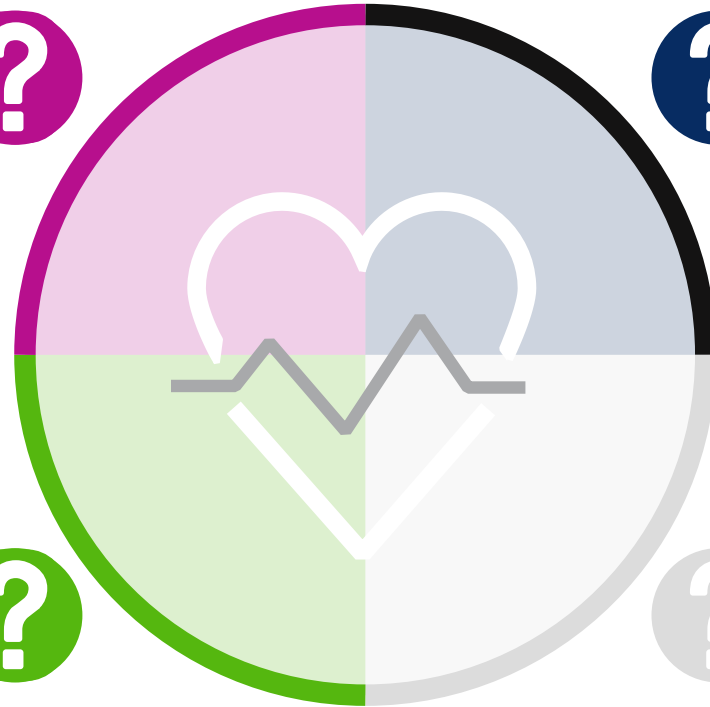


Lipid lowering?

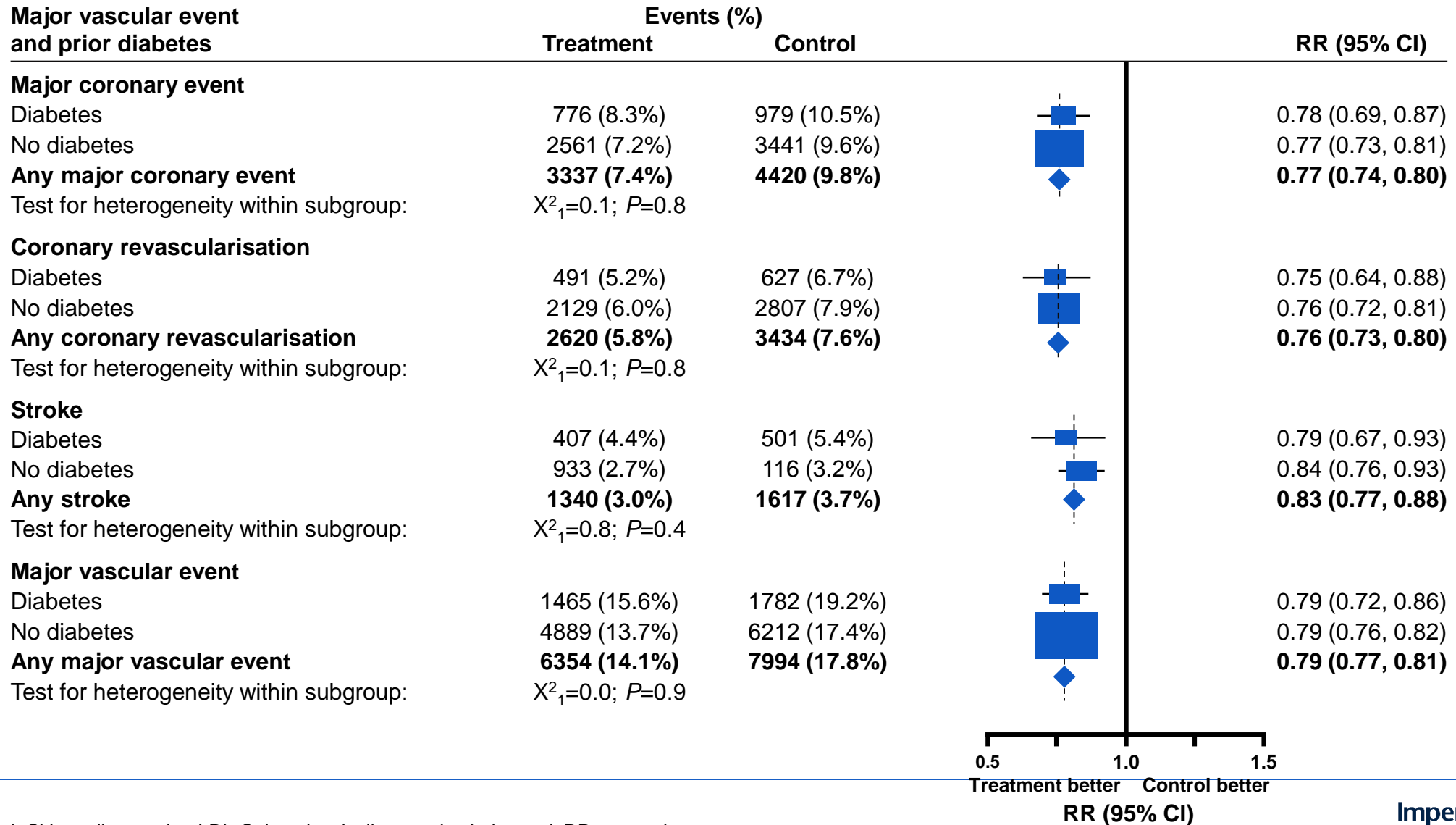
Glucose lowering?



Blood pressure lowering?

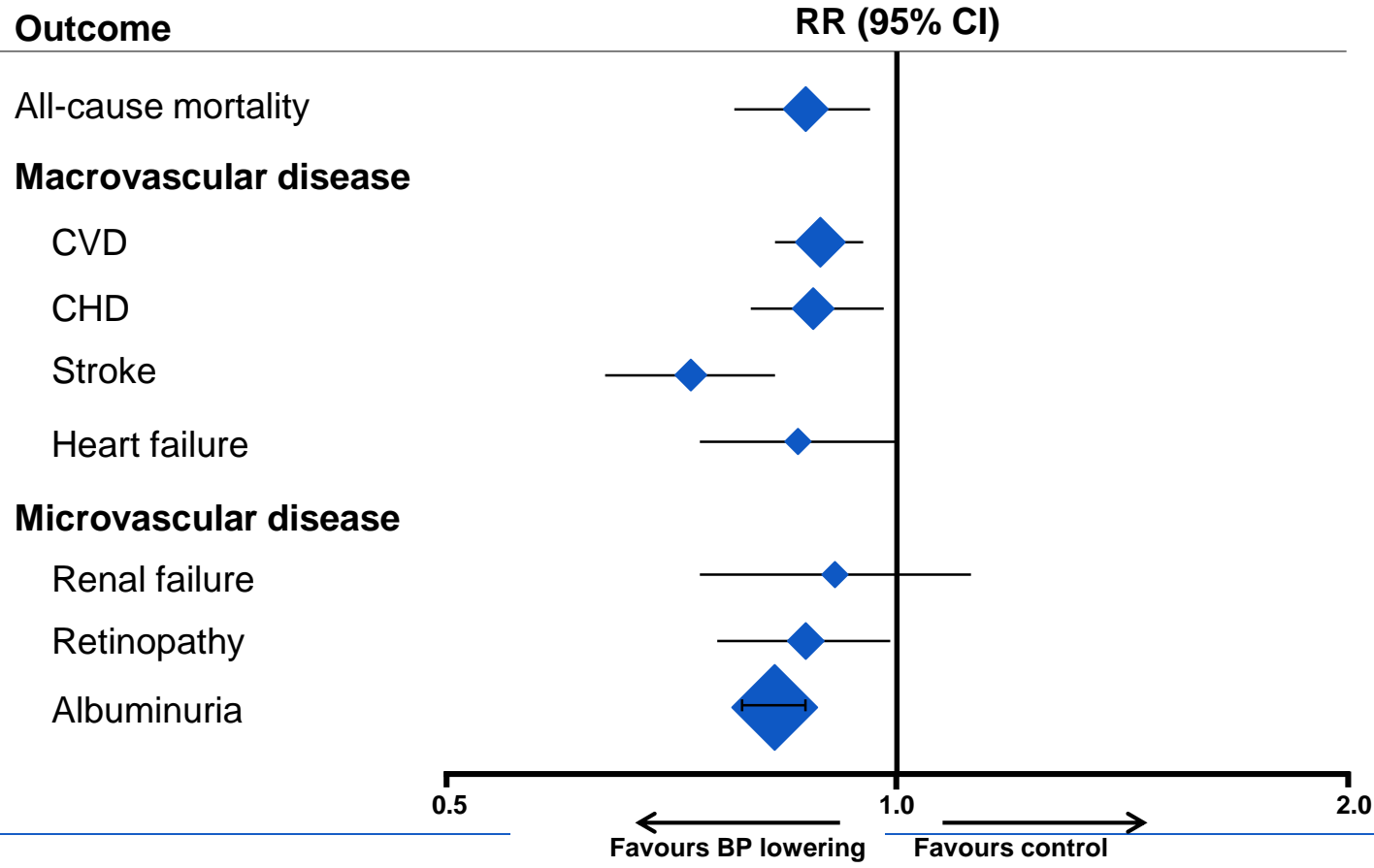


Lipid-lowering therapy with statins consistently reduces CV events (per 39 mg/dL lower LDL-C)



10 mmHg reduction in SBP reduces all-cause mortality and macrovascular and microvascular outcomes in Type 2 diabetes

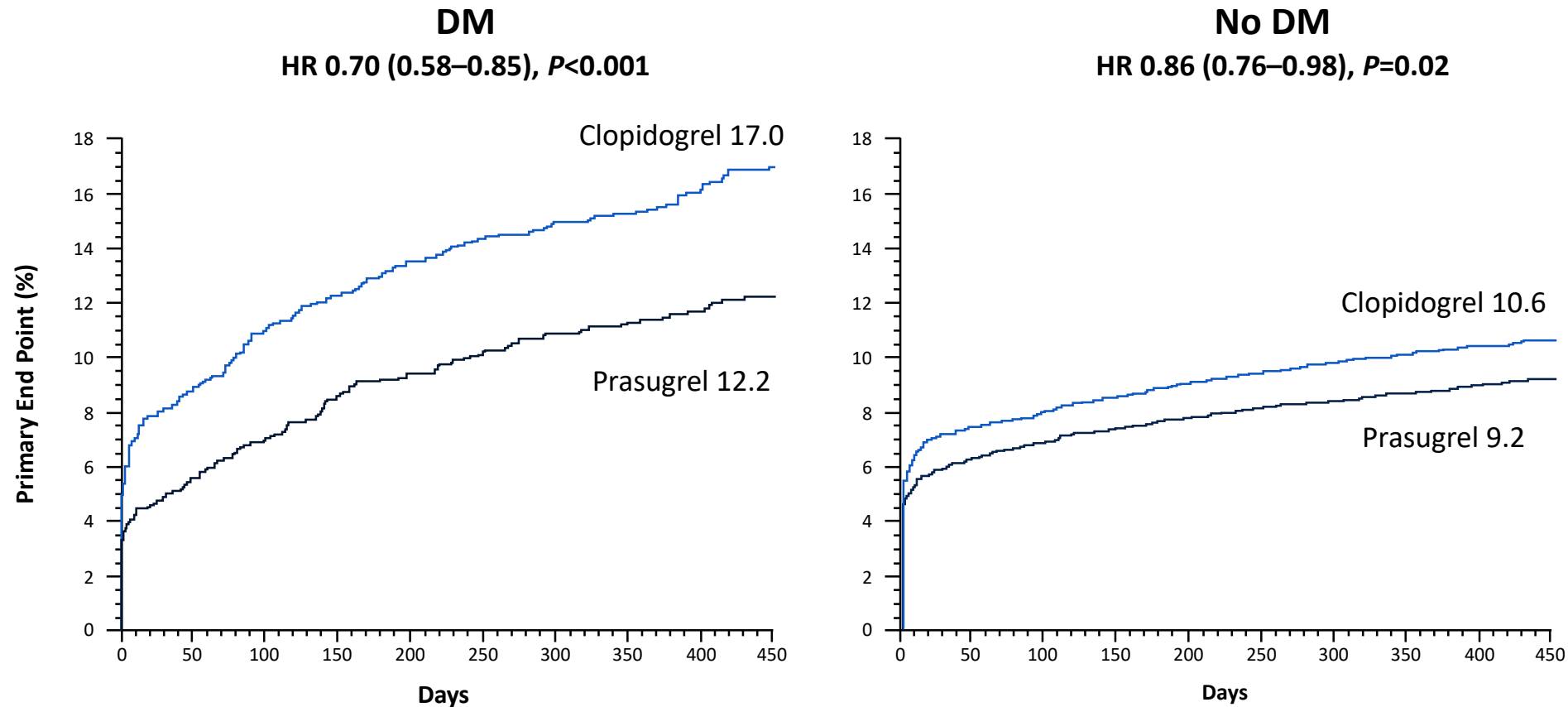
- Meta-analysis of 40 large-scale, randomised, controlled trials of BP-lowering treatment including patients with diabetes (n=100,354 participants)



BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease; RR, relative risk; SBP, systolic blood pressure
Emdin CD, et al. *JAMA* 2015;313:603-615

Effect of antiplatelet therapies on CV death in patients with Type 2 diabetes may be more pronounced than in those without diabetes...

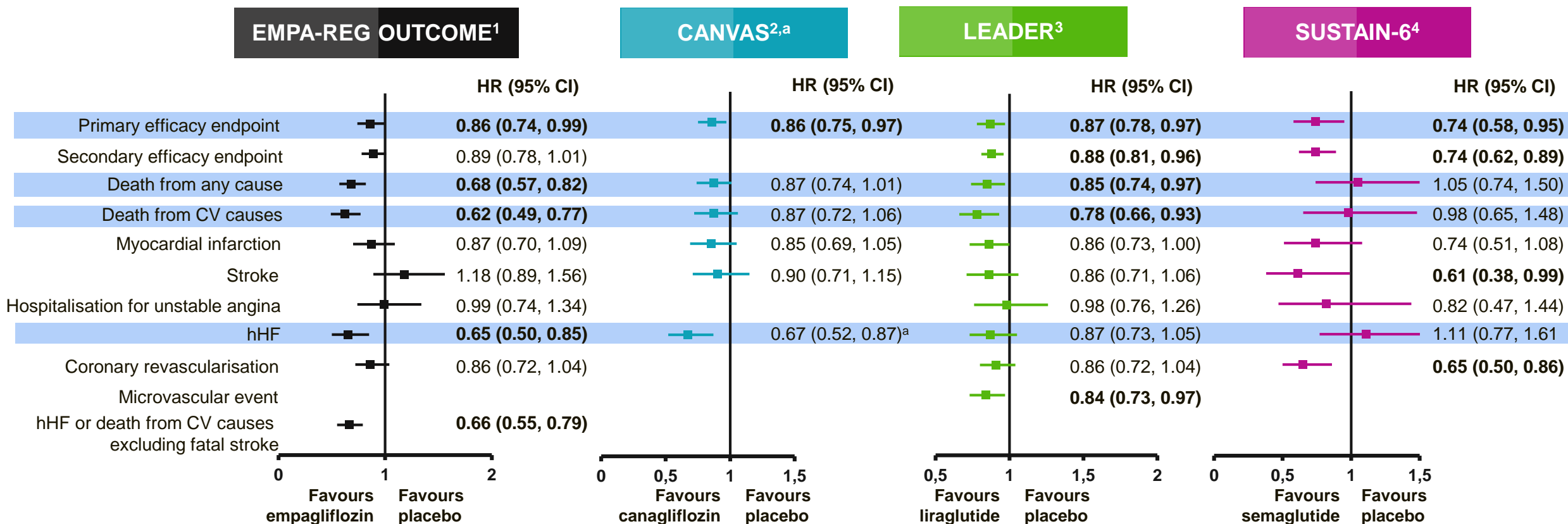
TRITON-TIMI 38: Effects of clopidogrel and prasugrel on CV death, MI, and stroke through 450 days by diabetes status¹



The settings and timeframes differ between TRITON-TIMI 38 and PEGASUS-TIMI 54
CV, cardiovascular; DM, diabetes mellitus; HR, hazard ratio; MI, myocardial infarction
1. Wiviott SD, et al. *Circulation*. 2008;118:1626-1636.

Newer glucose-lowering agents have been shown to improve CV outcomes in patients with Type 2 diabetes and CV disease or CV risk factors

HRs for pre-specified clinical endpoints (95% CI)



^aDifference in hHF was not considered significant due to hierarchical analysis

CI, confidence interval; CV, cardiovascular; hHF, hospitalisation for heart failure; HR, hazard ratio; RCT, randomised controlled trial

1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 2. Neal B, et al. *N Engl J Med* 2017;377:644–657; 3. Marso SP, et al. *N Engl J Med* 2016;375:311–322;

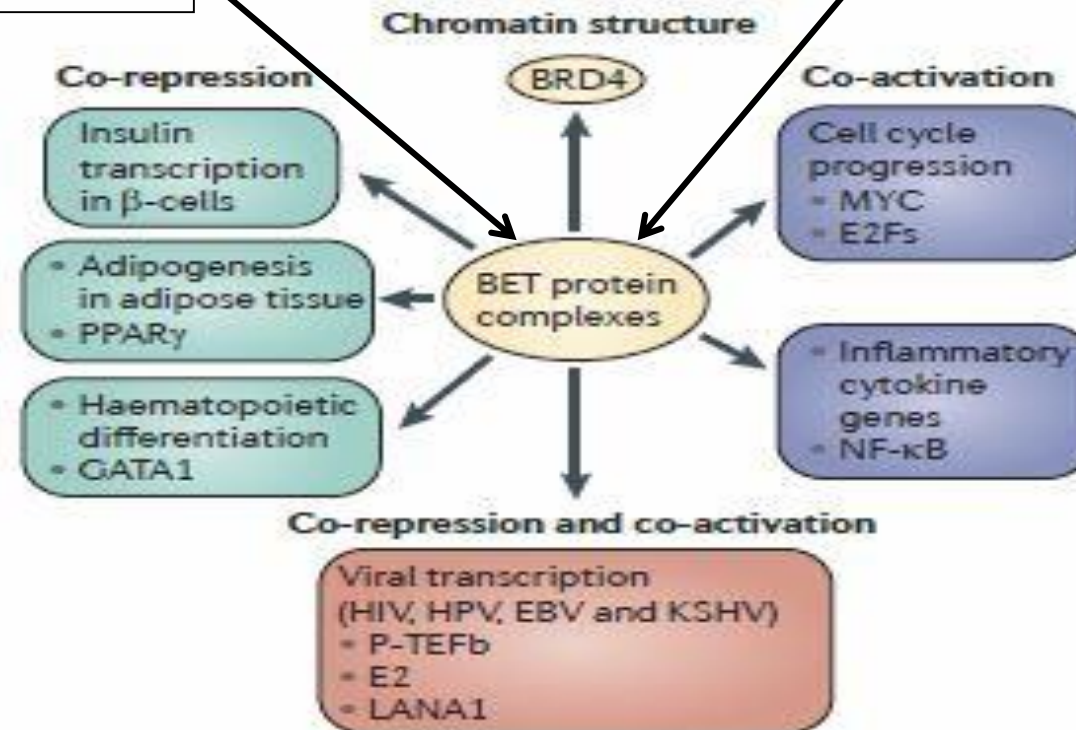
4. Marso SP, et al. *N Engl J Med* 2016;375:1834–1844

BET and BETi

Apabetalone is a selective BET inhibitor

Bromodomain and extra-terminal (BET) proteins have been implicated in a range of pathologic states

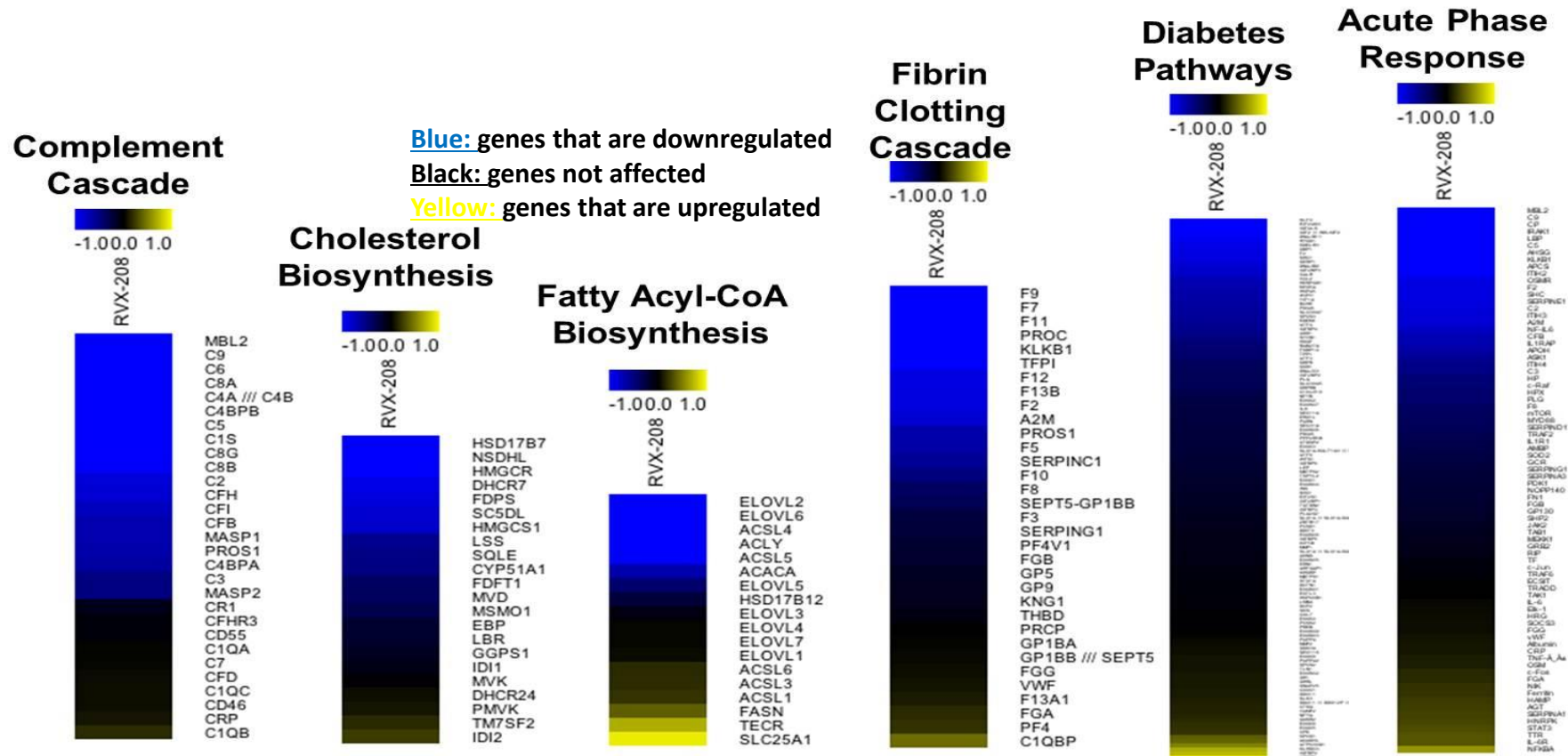
In perturbed states, BET proteins are more abundant



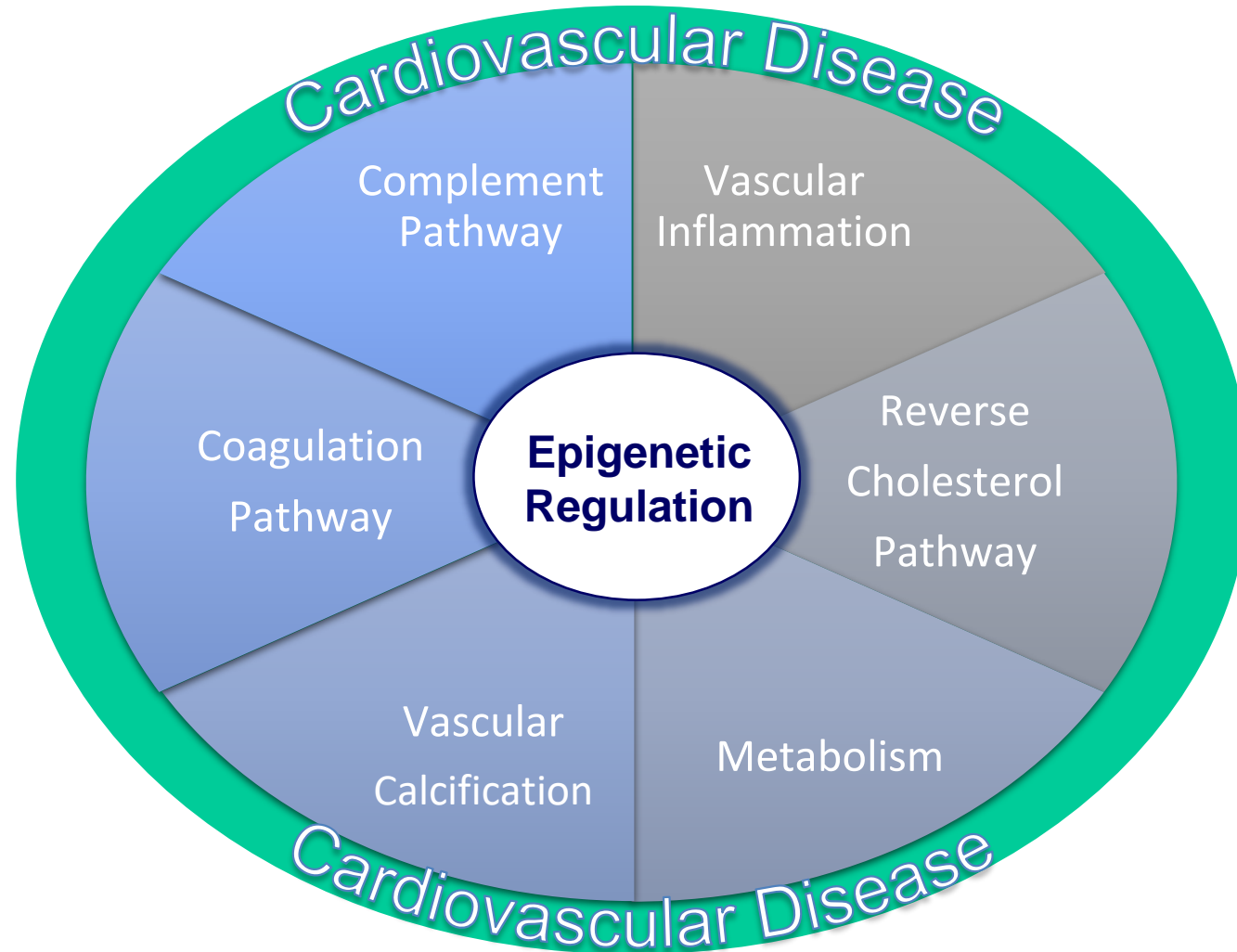
APABETALONE MAY HAVE ACTIONS IN VITRO WHICH SUPPRESS THE EXPRESSION OF MULTIPLE GENES POTENTIALLY INVOLVED IN THE PATHOGENESIS OF ATHEROTHROMBOTIC EVENTS (INTERLEUKIN-6, MCP-1, COMPLEMENT COMPONENT 9, AND THROMBIN.

Downregulation of Pathways Important for Atherosclerotic CV Disease

Microarrays were performed on Primary Human Hepatocytes (PHH) treated with apabetalone at and analyzed for genes (20,000+) and pathways (1,000+) affected.



Potential Mechanistic Effects Linking Apabetalone to CV Risk Reduction



Apabetalone in the Clinic

985 participants in completed trials

706 received treatment with apabetalone, including 576 patients with CAD and/or dyslipidemia on top of standard of care

Three phase 2 studies completed in CAD patients

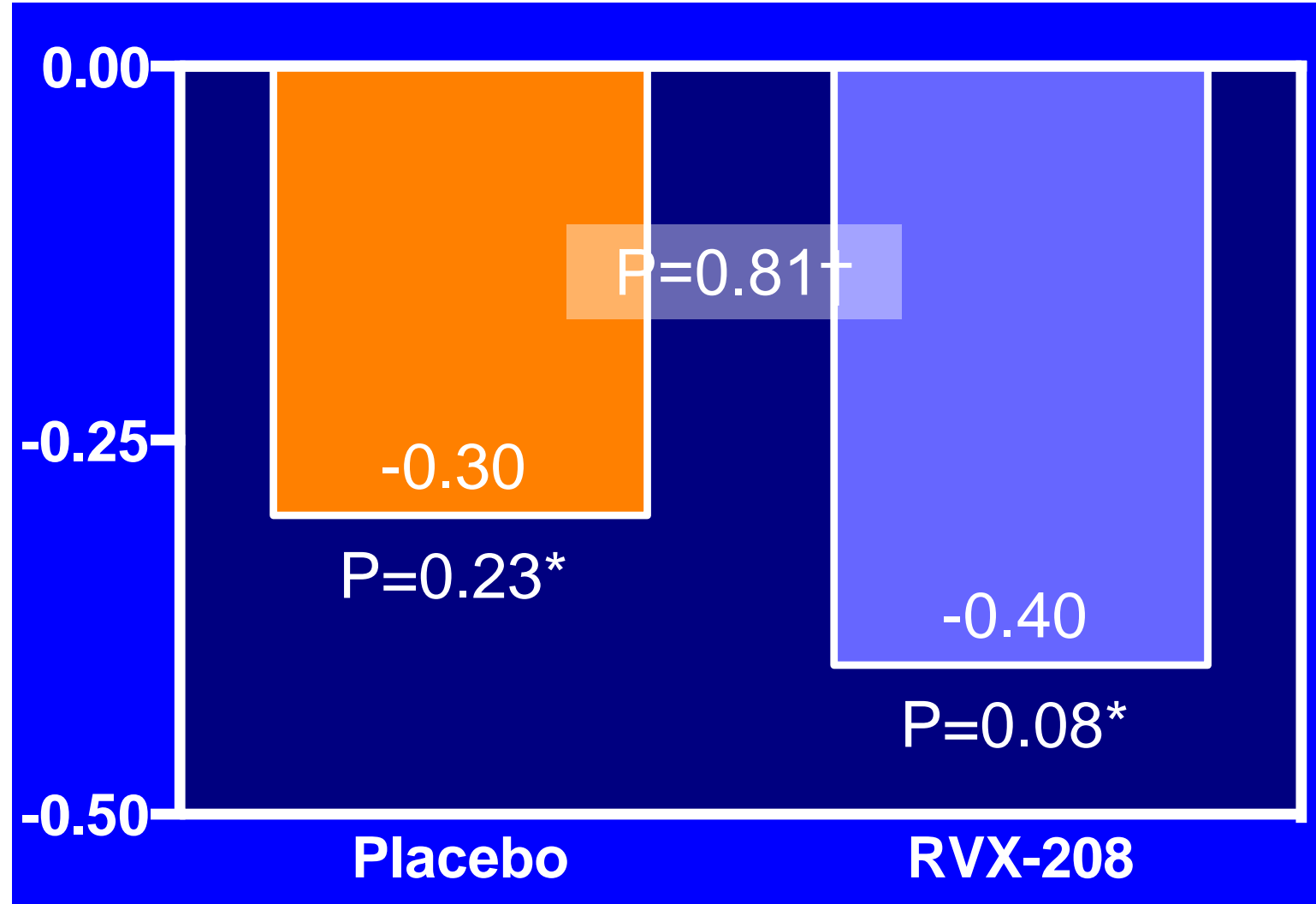
- ASSERT: 12 weeks in 299 patients
- SUSTAIN: 24 weeks in 176 patients
- ASSURE: 26 weeks in 323 patients

Early Effects of Apabetalone in CAD Patients

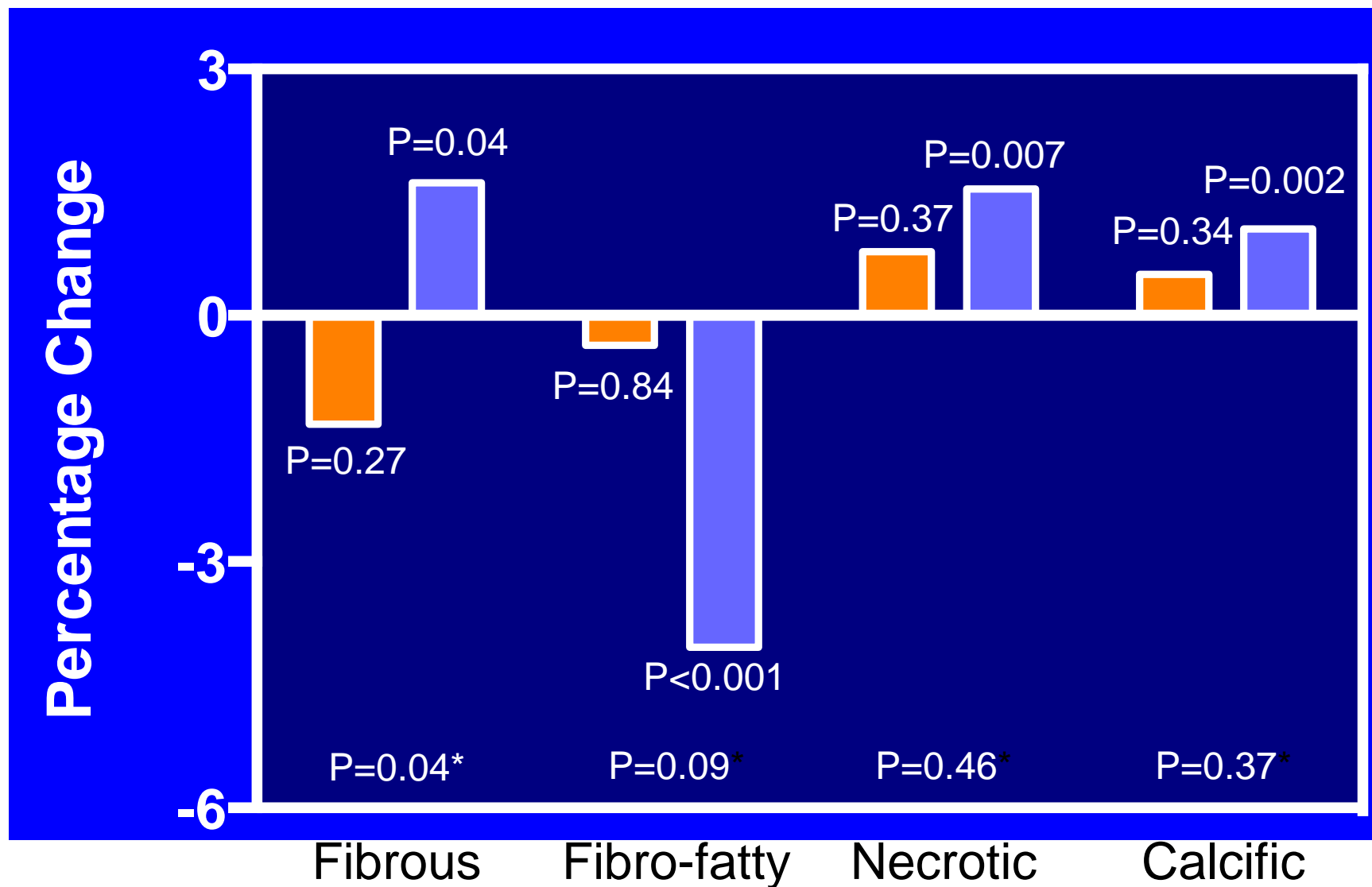
| Parameter | Placebo (n=74) | RVX-208 | | | P Value |
|----------------|-------------------|------------------|------------------|------------------|------------|
| | | 100 mg (n=76) | 200 mg (n=75) | 300 mg (n=74) | |
| ApoA-I | 0.9 | 0.1 | 3.8 | 5.6 | 0.02 |
| HDL-C | 0 | 3.2 | 6.3* | 8.3** | 0.02 |
| Large HDL | -0.5 | 11.1 | 20.2** | 21.1*** | 0.003 |
| Small HDL | 2.6 | -0.4 | -2.6 | -4.0 | 0.07 |
| α 1 HDL | -2.3 | 3.7 | 8.0* | 8.8* | 0.12 |

* P<0.05, ** P<0.01, and *** P<0.001 compared with placebo

ASSURE: Change in Percent Atheroma Volume



ASSURE: VH Measures of Plaque Composition



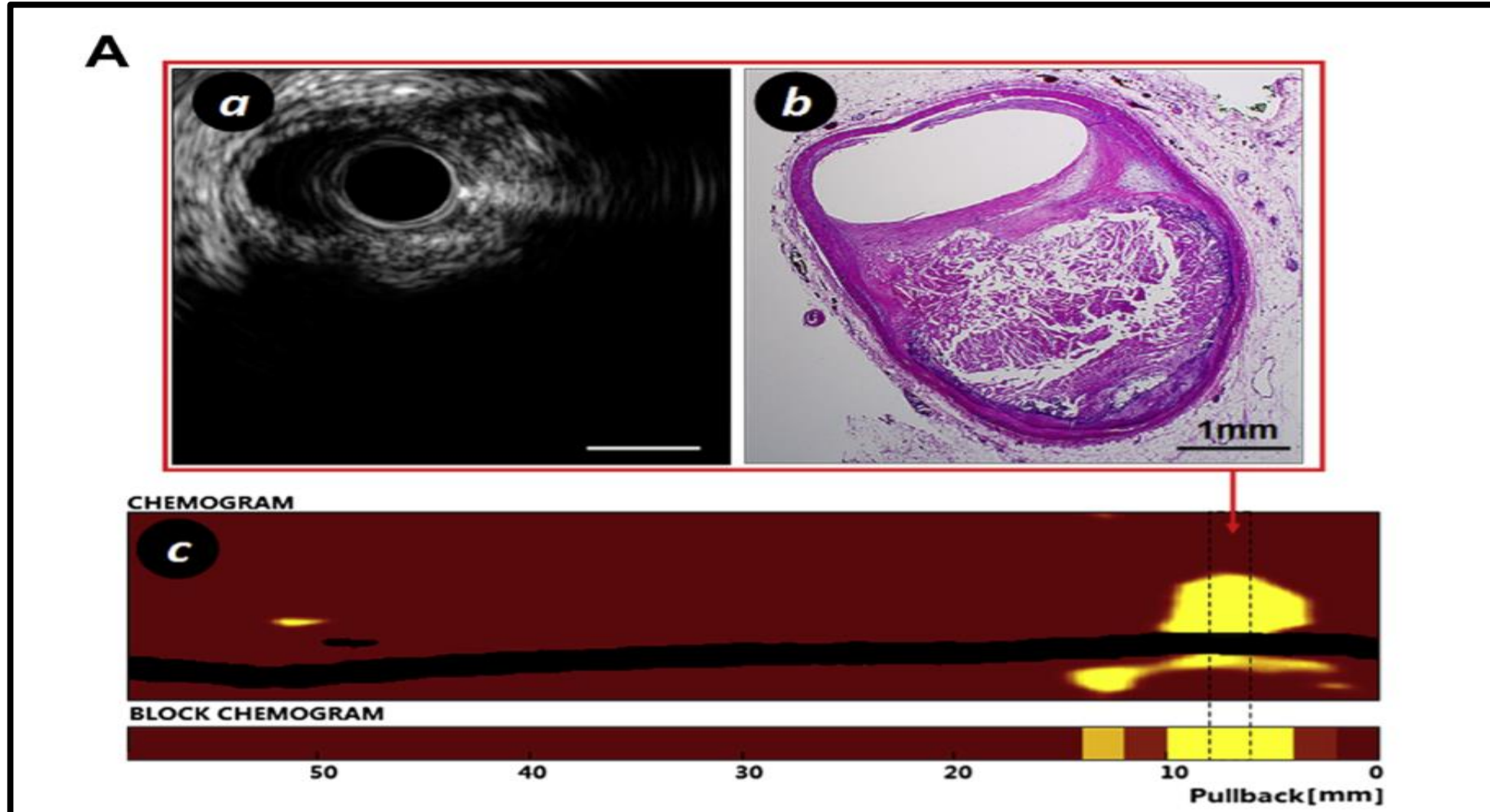
Expressed as LS mean change

P values for comparison with baseline

*P value for comparison with placebo

Placebo RVX-208

Attenuated Plaque as a Measure of Vulnerability



Apabetalone Reduces Levels of Vascular Inflammation Proteins in CVD Patients

ASSERT Clinical Data : anti-inflammatory and plaque-stabilizing effects

| Protein Name | Placebo N=30 | p-value vs baseline | apabetalone 200mg daily N=25 | p-value vs baseline | Δ treated vs. placebo | p-value vs placebo |
|--------------------------|-----------------|------------------------|------------------------------------|------------------------|--------------------------|-----------------------|
| C-reactive protein (CRP) | | * | | | | * |
| RANTES (CCL5) | | * | | | | * |
| sTWEAK (TNFSF12) | | * | | | | * |
| Osteopontin (SPP1) | | * | | | | * |
| PARC (CCL18) | | * | | | | * |
| Epiregulin (EREG) | | * | | | | * |
| TNFSF14 | | * | | | | * |
| Pappalysin-1 (PAPPA) | | | | * | | * |

| Protein Name | Placebo N=30 | p-value vs baseline | apabetalone 200mg daily N=25 | p-value vs baseline | Δ treated vs. placebo | p-value vs placebo |
|---------------------------------------|-----------------|------------------------|------------------------------------|------------------------|--------------------------|-----------------------|
| Metalloproteinase inhibitor 2 (TIMP2) | | * | | * | | * |
| Metalloproteinase inhibitor 1 (TIMP1) | | | | * | | * |

* = p<0.05

†p<0.10

Apabetalone Reduces Levels of Vascular Inflammation Proteins in CVD Patients

ASSURE clinical data: anti-inflammatory and plaque-stabilizing effects

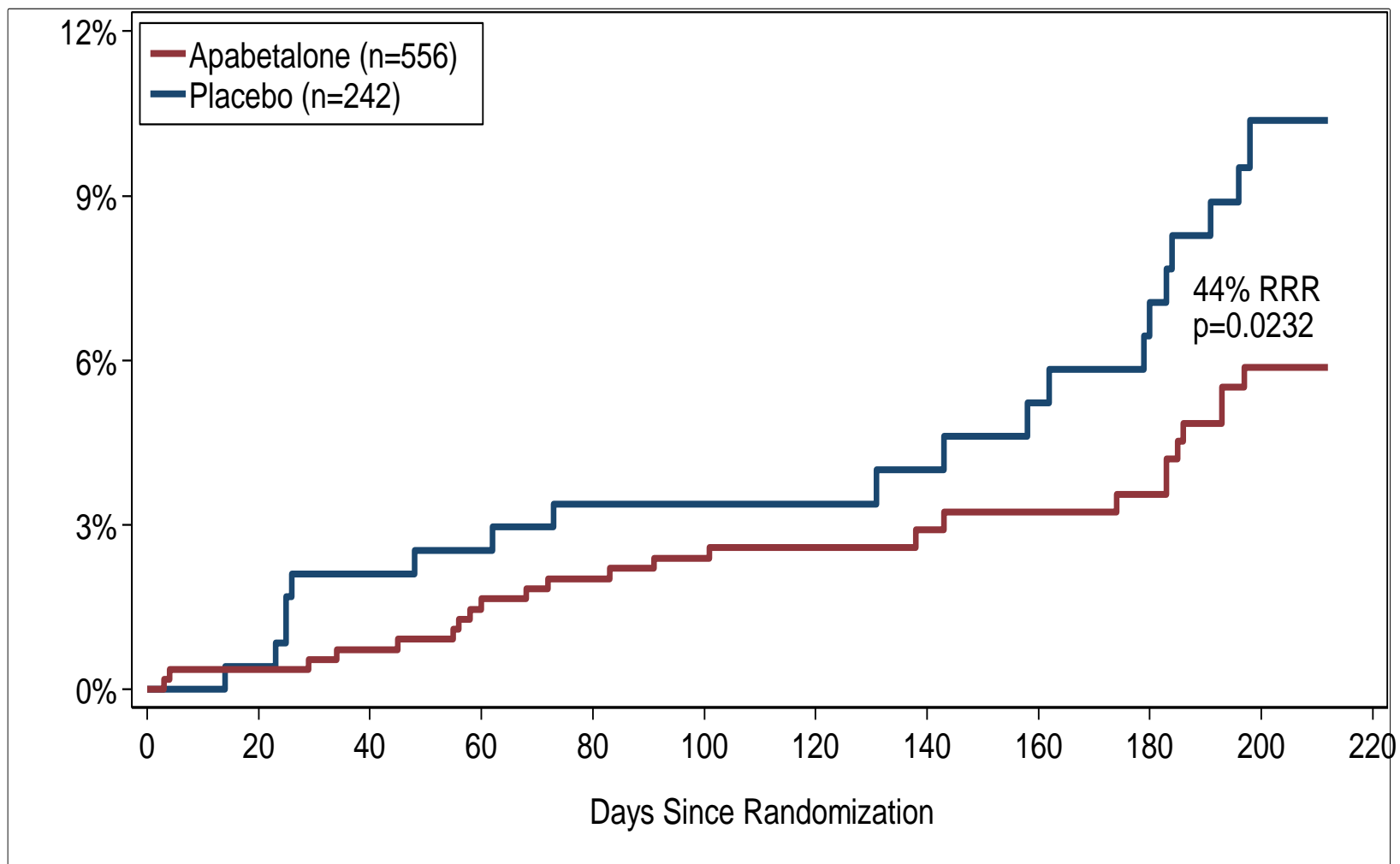
| Protein Name | Placebo N=47 | p-value vs baseline | apabetalone 200mg daily N=47 | p-value vs baseline | Δ treated vs. placebo | p-value vs placebo |
|--|-----------------|------------------------|------------------------------------|------------------------|------------------------------------|-----------------------|
| C-reactive protein (CRP) | | * | | * | | * |
| Pappalysin-1 (PAPPA) | | | | * | | * |
| Vascular cell adhesion protein 1 (VCAM1) | | | | * | | * |
| Serum amyloid P-component (APCS) | | | | * | | * |

| Protein Name | Placebo N=47 | p-value vs baseline | apabetalone 200mg daily N=47 | p-value vs baseline | Δ treated vs. placebo | p-value vs placebo |
|------------------------------------|-----------------|------------------------|------------------------------------|------------------------|------------------------------------|-----------------------|
| Stromelysin-1 (MMP3) | | * | | | | * |
| Macrophage metalloelastase (MMP12) | | | | * | | * |

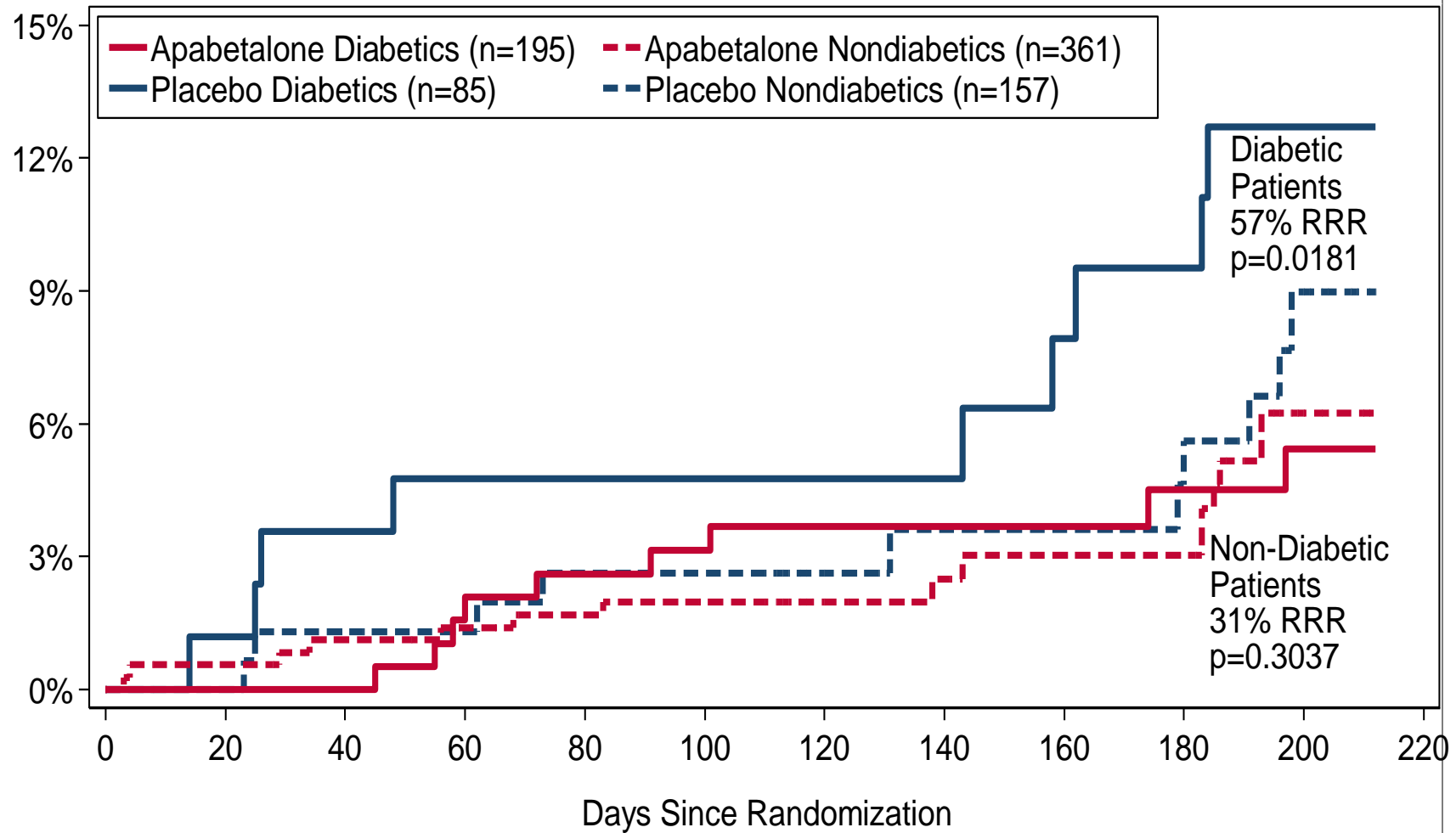
* = p<0.05

†p<0.10

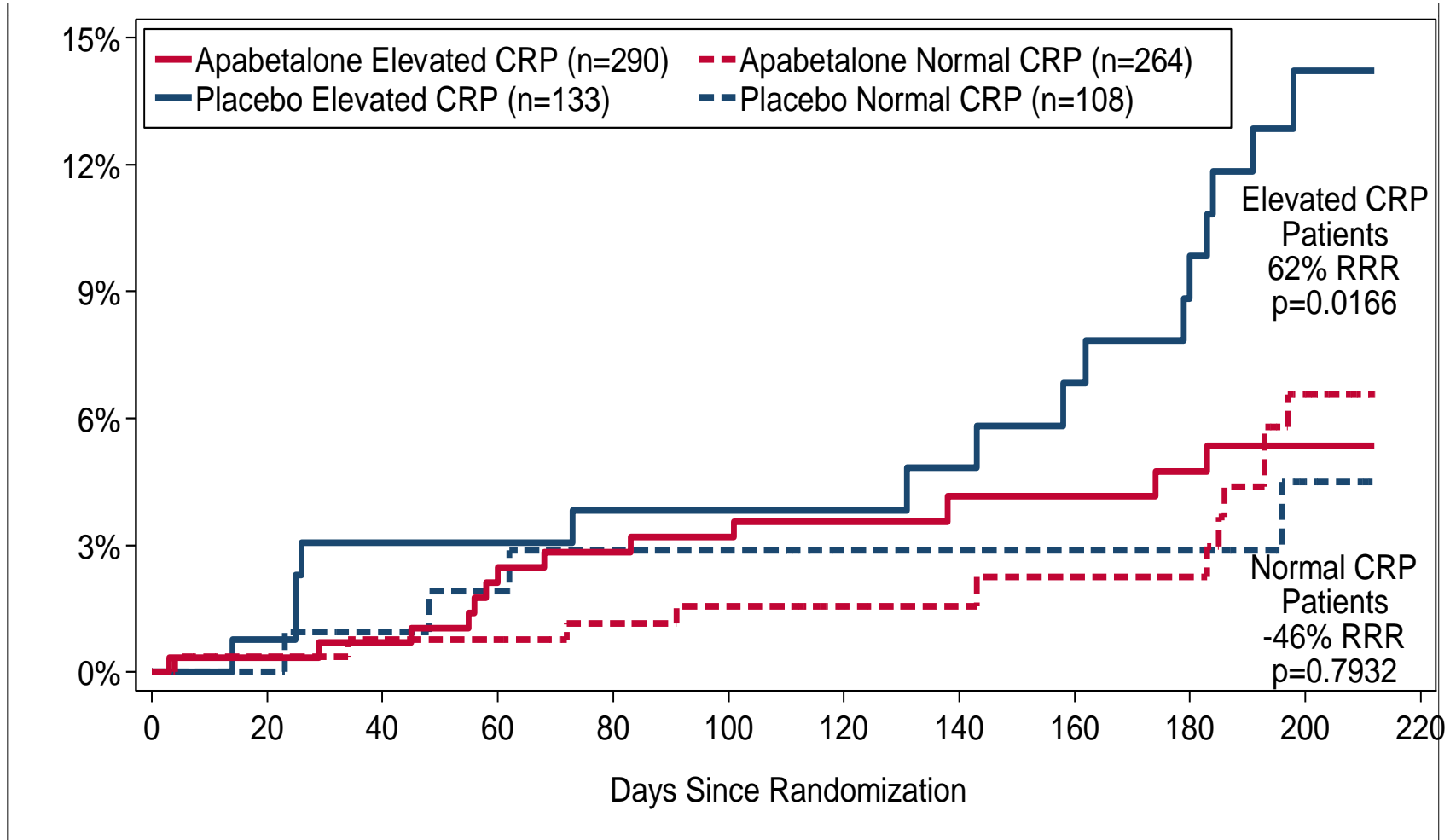
Less CV Events with Apabetalone in Pooled Phase 2 Studies



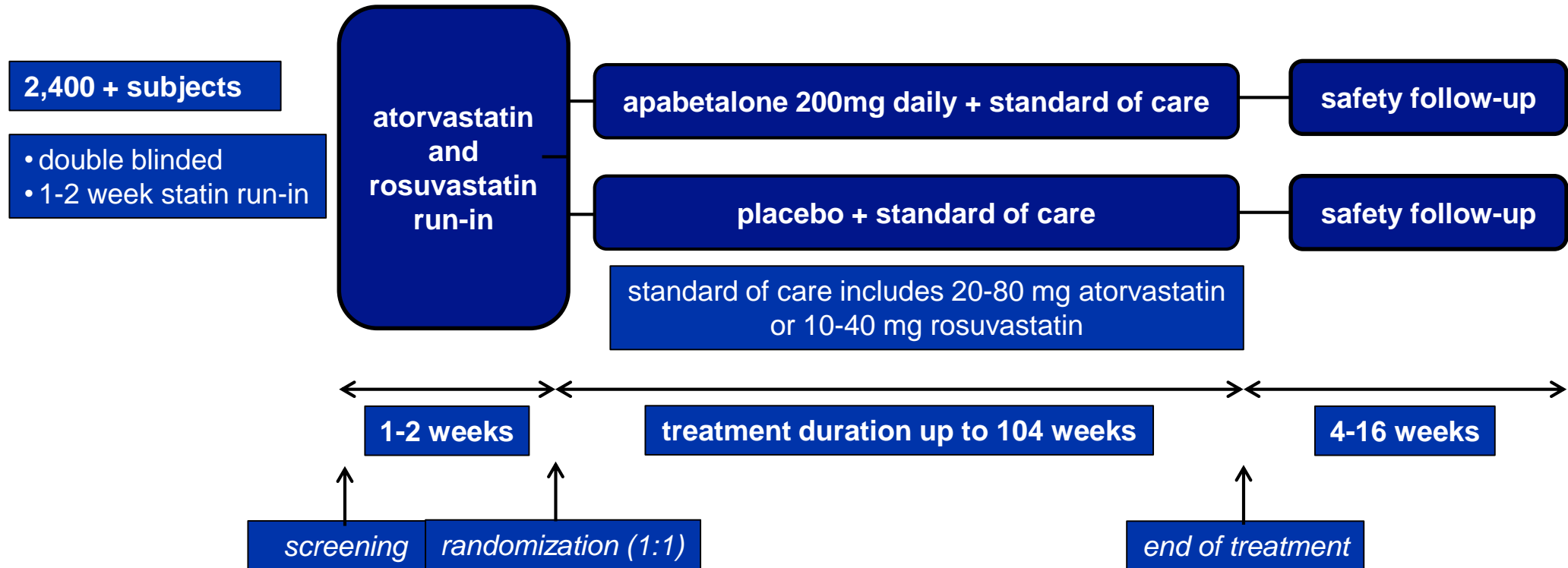
Less CV Events with Apabetalone in Patients with Diabetes



Less CV Events with Apabetalone in Patients with Elevated CRP Levels



BETonMACE



The study is an event-based trial and continues until 250 events have occurred.

BETonMACE CV Outcomes Study

Key inclusion criteria

- T2DM
 - HbA1c > 6.5% or history of diabetes medications
- CAD event 7 days - 90 days prior to Visit 1
 - MI, UA or PCI
- HDL < 1.04 for males and < 1.17 for females

Primary Objective

To evaluate if treatment with apabetalone as compared to placebo increases time to the first occurrence of triple MACE. Triple MACE is defined as a single composite endpoint of CV death or non-fatal MI or stroke.

Primary Endpoint

Time from randomization to the first occurrence of adjudication-confirmed triple MACE defined as a single composite endpoint of CV Death or Non-fatal MI or Stroke.

Secondary Endpoint

Time from randomization to the first occurrence of adjudication-confirmed MACE including revascularization and UA
Changes in apoA-I, apoB, LDL-C, HDL-C, and TG
Changes in HbA1c, fasting glucose, and fasting insulin
Changes in ALP and eGFR

Summary

Apabetalone is a first in class BET-inhibitor that regulates genes and pathways that underlie development of CVD

In phase 2 clinical trials, CVD event reductions were found which were most pronounced in patients with diabetes mellitus or increased inflammation

BETonMACE is an ongoing pivotal phase 3 trial designed to confirm if apabetalone can prevent CVD events in post-ACS patients with T2DM and low HDL cholesterol