A Journey of PCSK9 Inhibitors: *From Genetics to Clinics*

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Disclosures

Grant Support/Drugs

- Daiichi-Sankyo

Grant Support/Devices

- Edwards Lifesciences - Abbott Vascular
- Medtronic - Boston Scientific
- CSI - Corvia
- V-Wave Medical - Svelte

Consulting/Advisory Boards

- Medtronic - Edwards Lifesciences
- Janssen Pharmaceuticals - Heartflow

DJC: 4/19

PCSK9 Inhibitors: Background

- LDL cholesterol is well-established as a modifiable risk factor for cardiovascular disease
- Previous trials (mainly using statins) have established the benefits of LDL reduction on reducing the risk of cardiovascular events both in primary and secondary prevention
- Recently, 2 monoclonal antibodies (evolocumab, allorocumab) that inhibit PCSK-9 have been shown to produce marked reductions in LDL levels and other agents are in development
- Until recently, however, the impact of these drugs on cardiovascular outcomes was unknown

3 Questions about PCSK9 Inhibitors

- What are they and how do they work?
- What are the clinical benefits?
- Why has uptake been slow?

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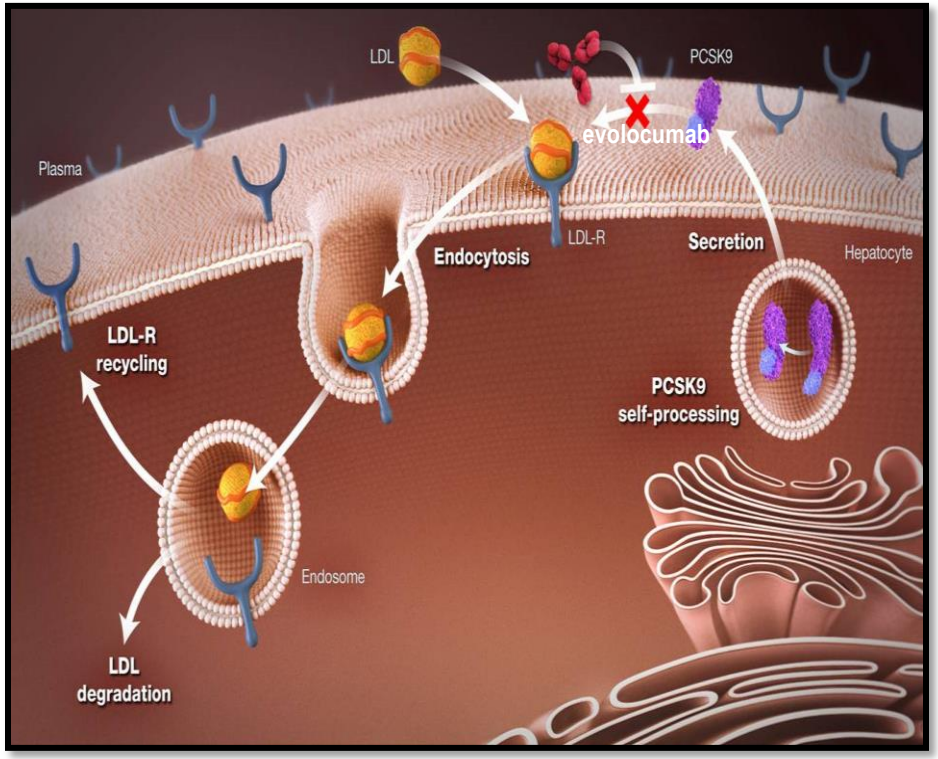
Proprotein convertase subtilisin/kexin type 9 (PCSK9)



Mechanism of PSK9

- Chaperones LDL-receptor to its destruction, leading to increased levels of circulating LDL-C
- Loss-of-function genetic variants lead to ↑'d LDL-R; in these pts, there is marked reduction in circulating LDL-C & ↓'d risk of MI

PCSK9 inhibitors are fully humanized monoclonal antibodies directed against PCSK9 → 60% reduction in LDL in Phase 2 studies

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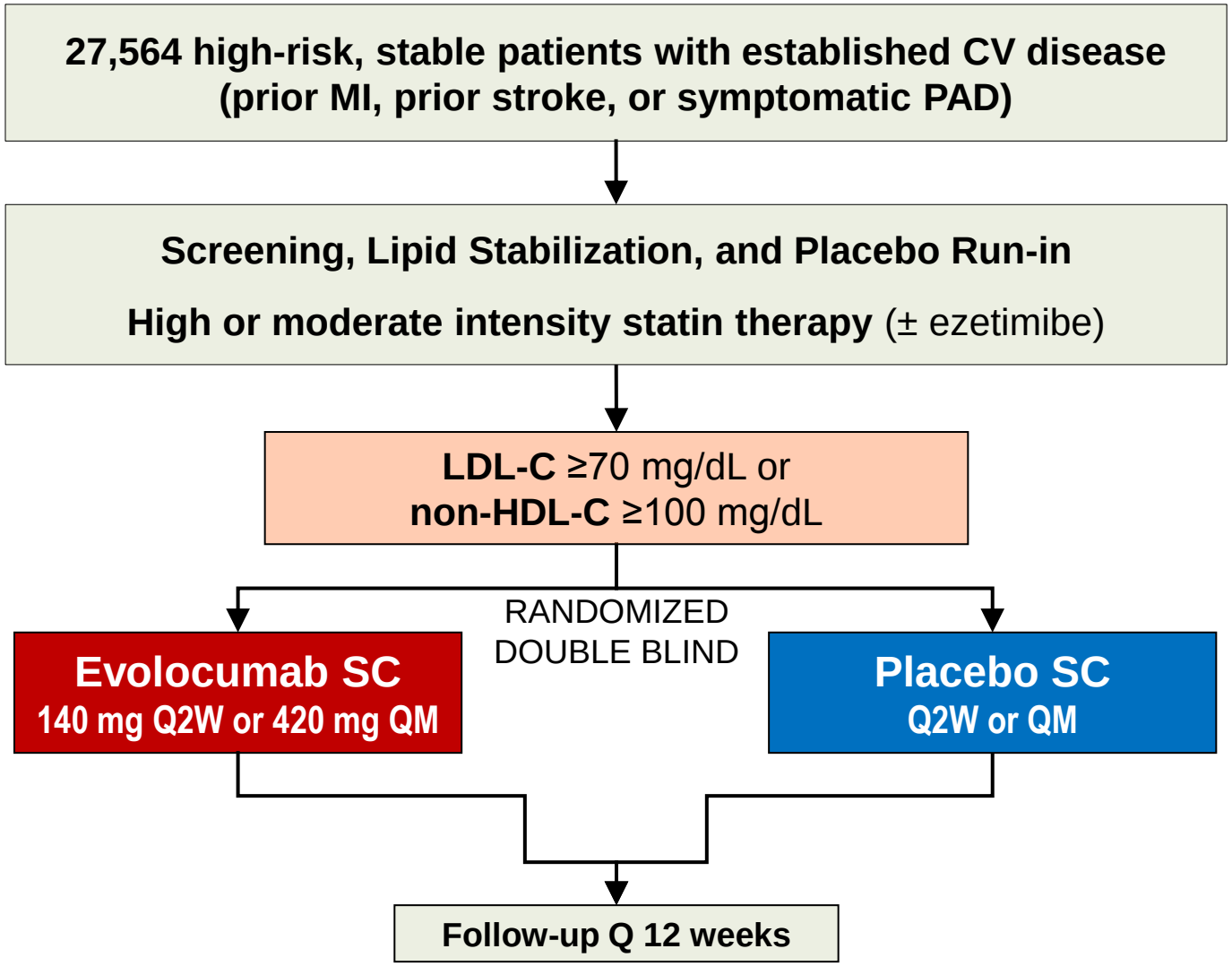
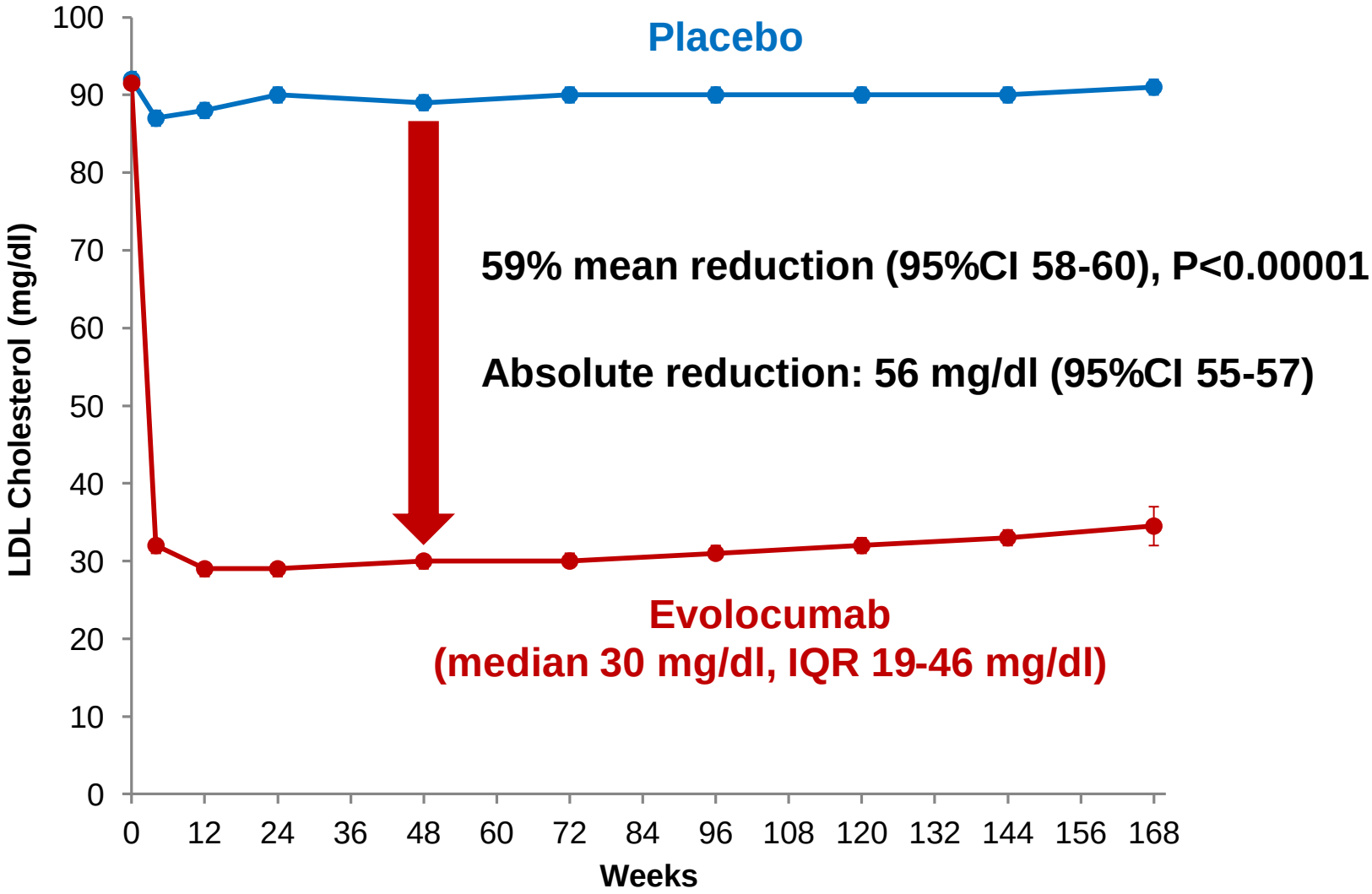
Trial Design

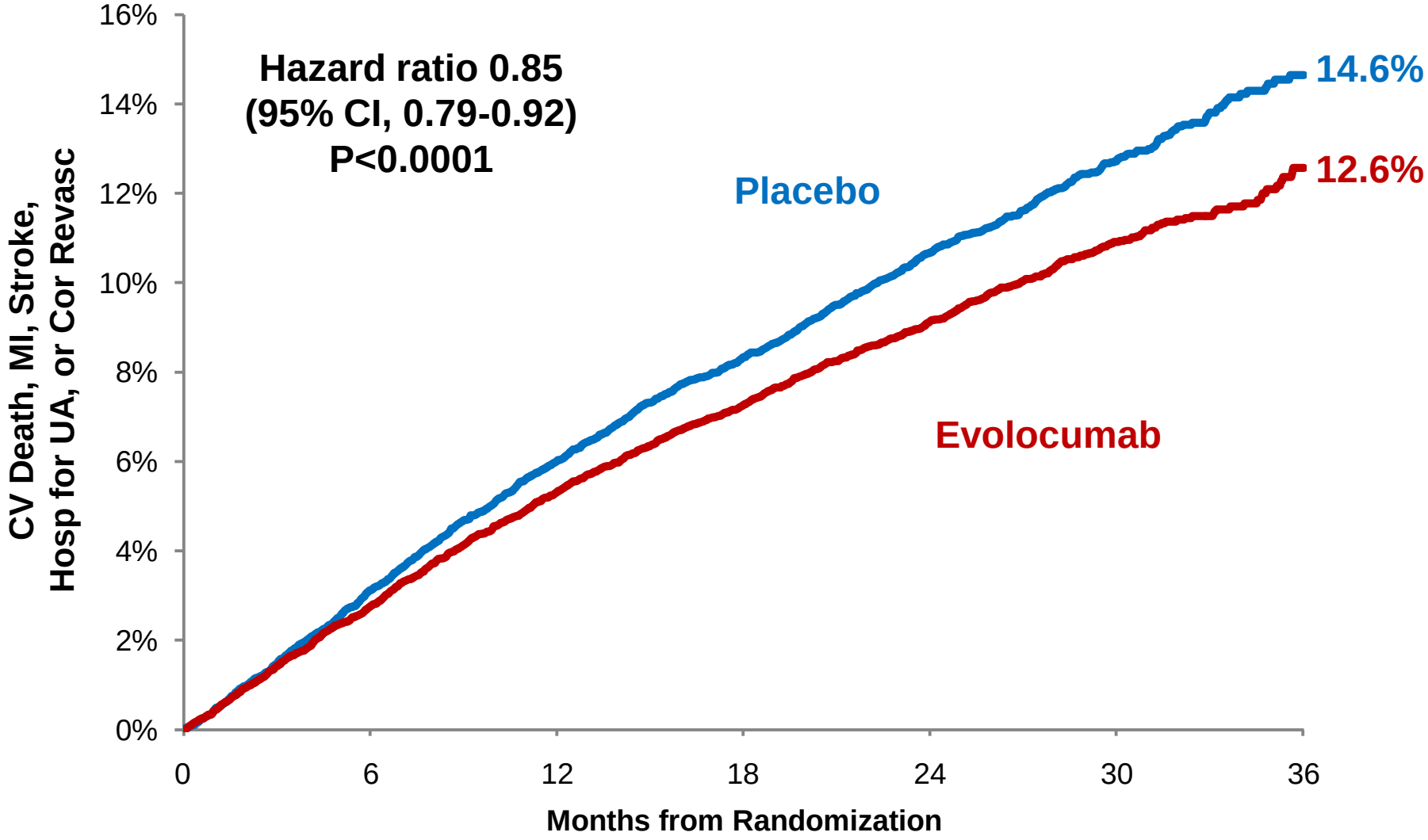


Sabatine MS et al. *Am Heart J* 2016;173:94-101

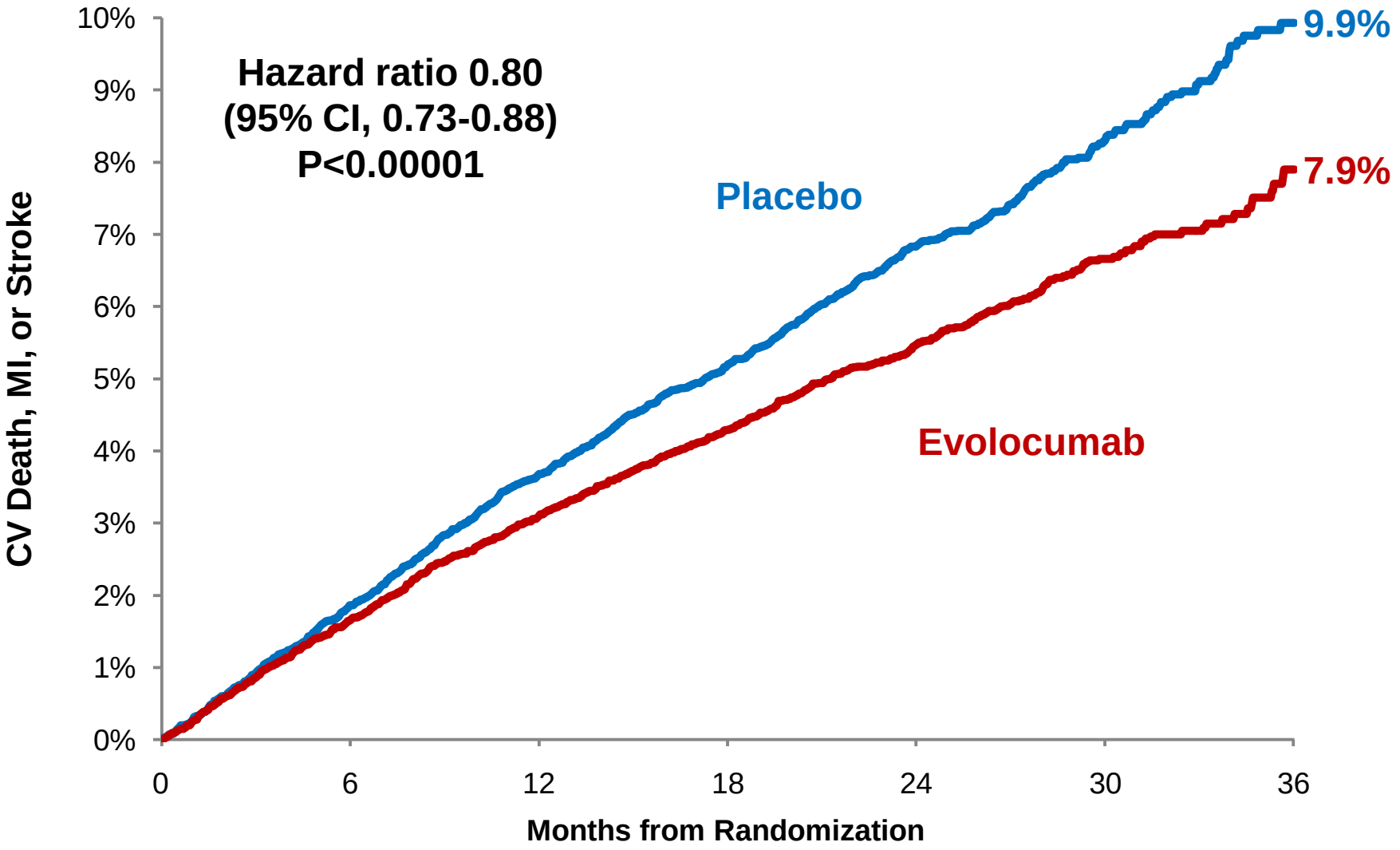
LDL Cholesterol



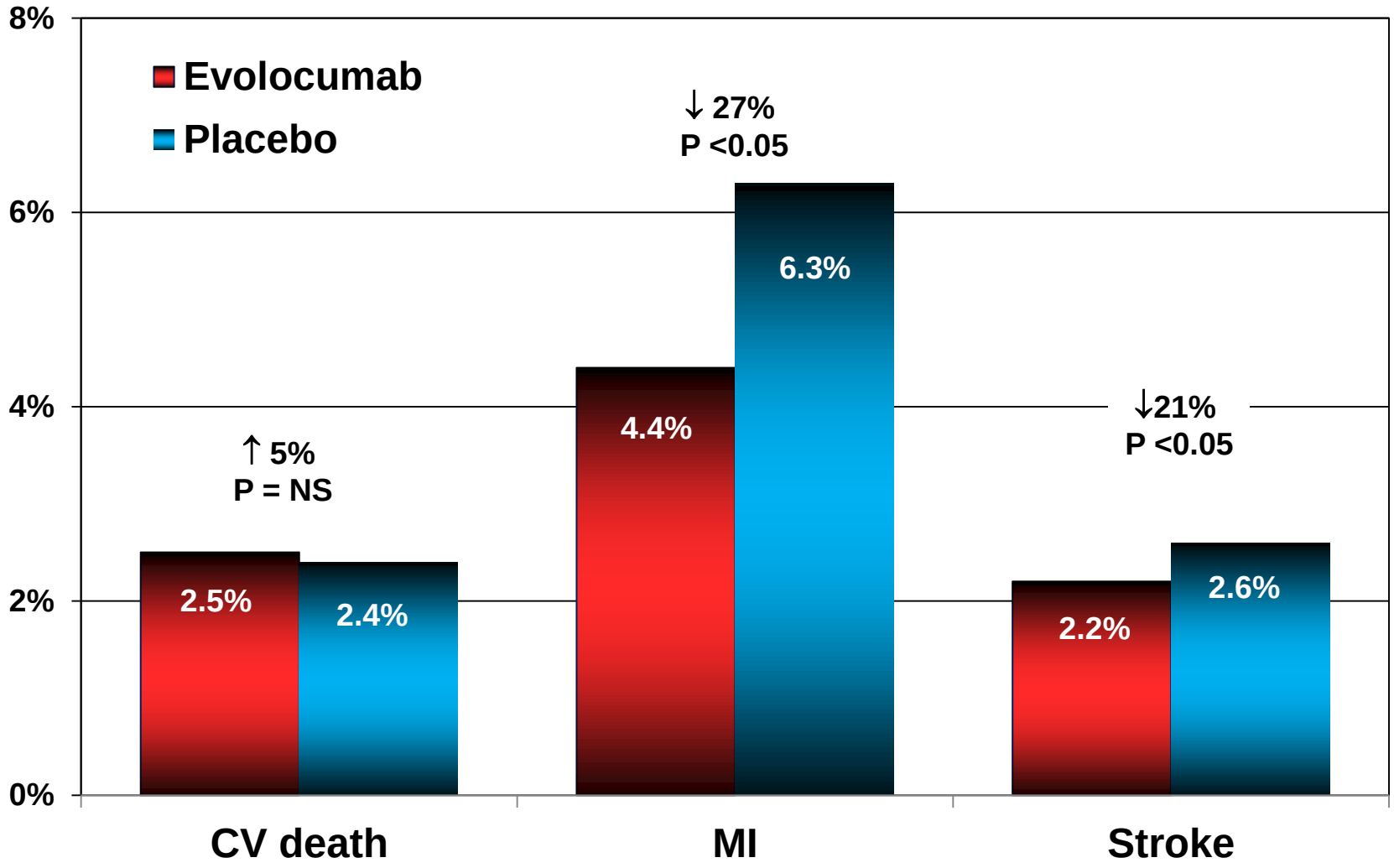
Primary Endpoint



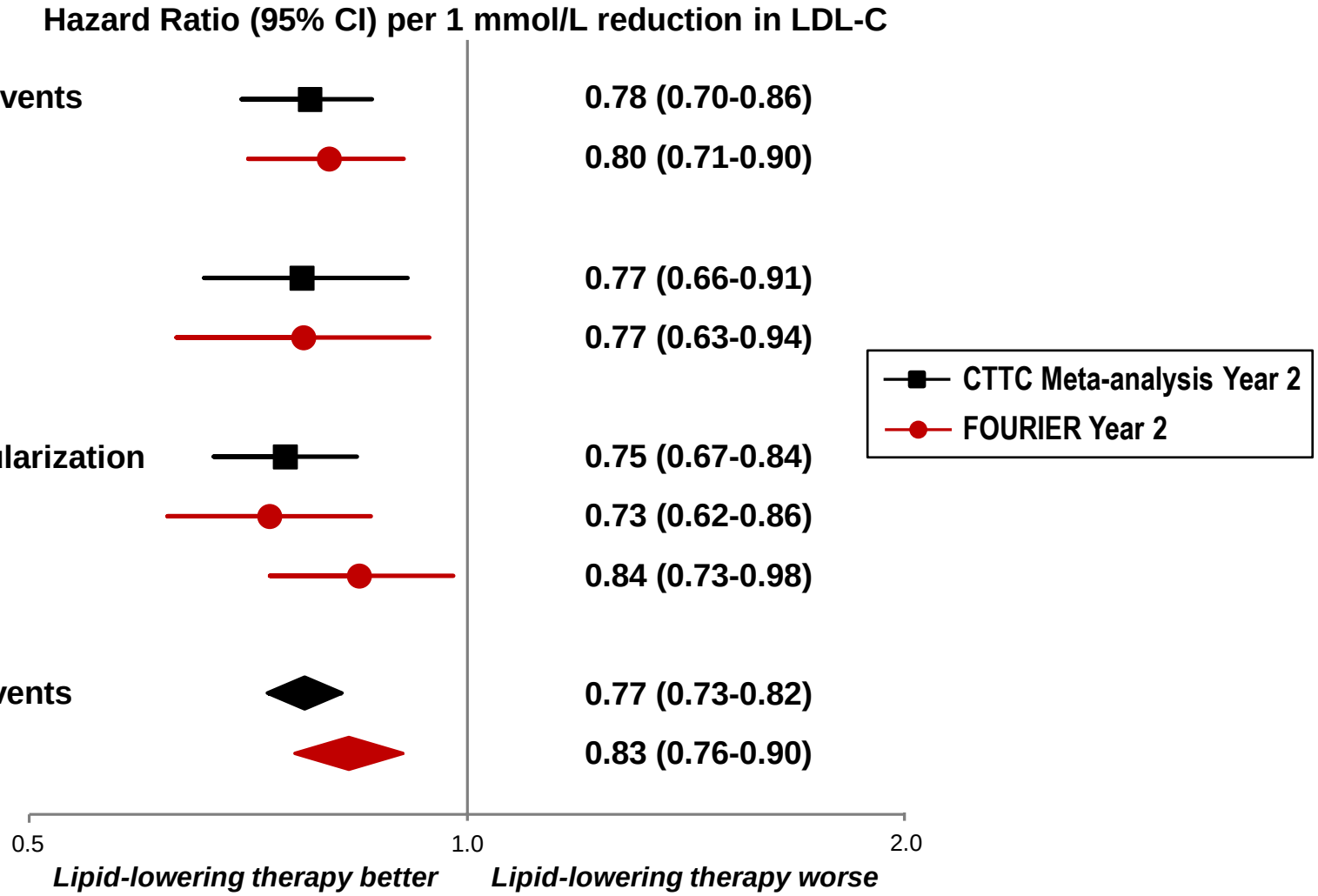
Key Secondary Endpoint



Endpoint Components



Comparison to Cholesterol Treatment Trialists Collaboration



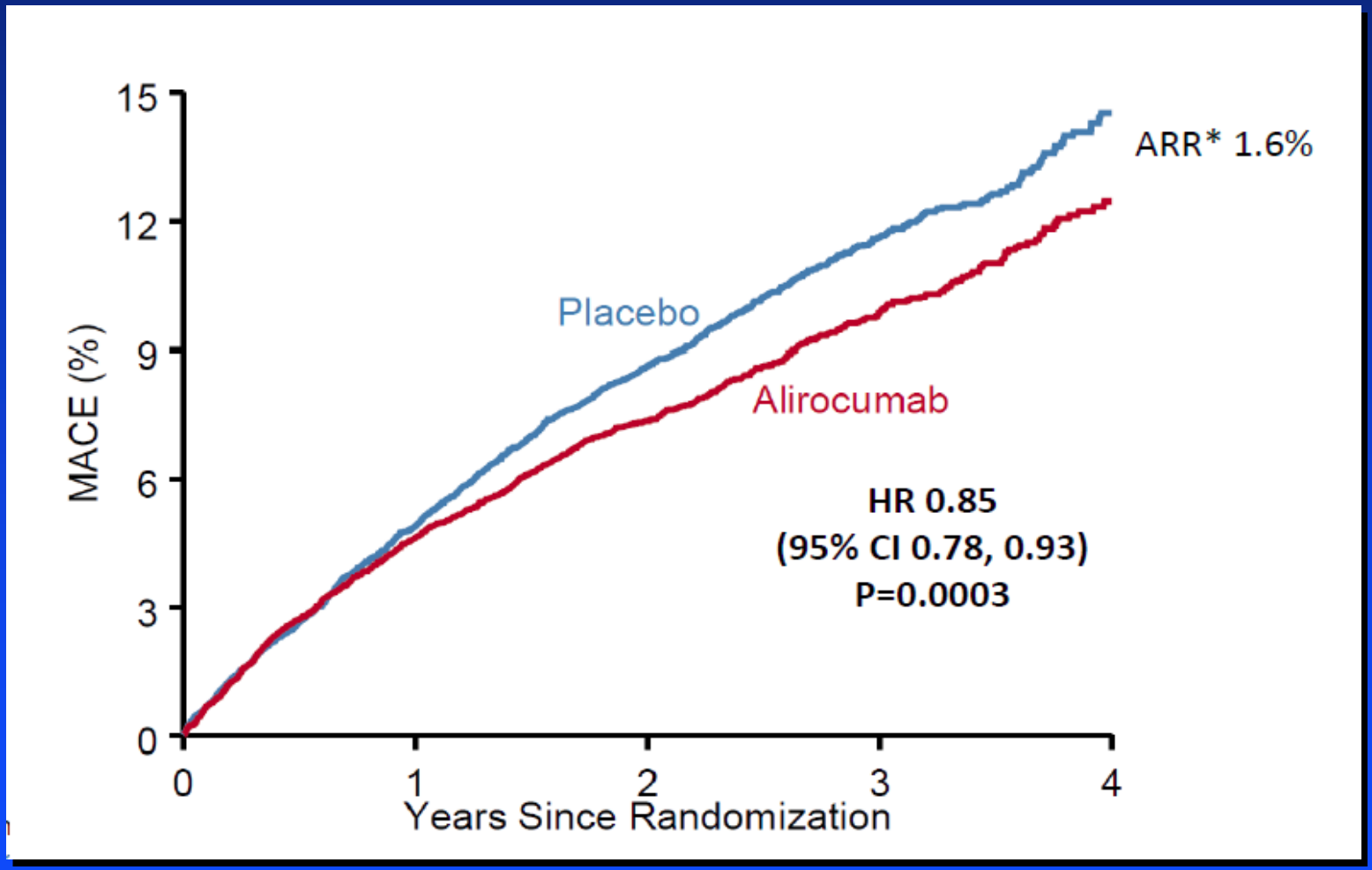
CTTC data from *Lancet* 2010;376:1670-81

Trial Design

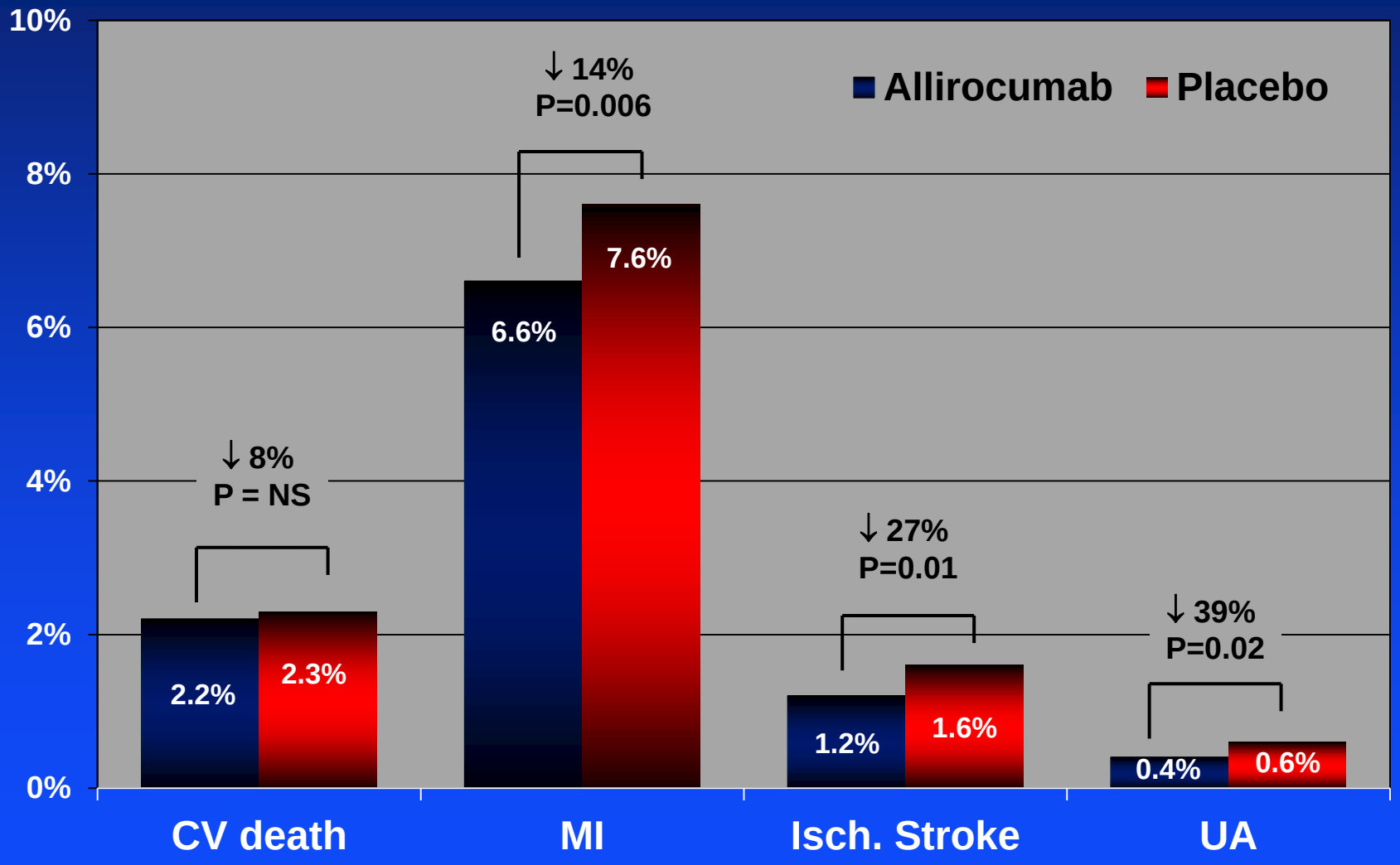
- 18,924 patients with recent ACS and poor lipid control (LDL > 100 on therapy) randomized to:
  - *Allirocumab 75-150 mg SQ Q2wks vs. Placebo*
  - *All patients treated with statin (high intensity, if tolerated)*
  - *Allirocumab dose adjusted to achieve LDL-C 25-50 mg/dL*
- Follow-up for median 2.8 years (44% followed >3 yrs)
- Primary endpoint: CHD death, MI, stroke, or hospitalization for unstable angina

Primary Outcome

CV death, MI, Stroke, or Hosp. for UA

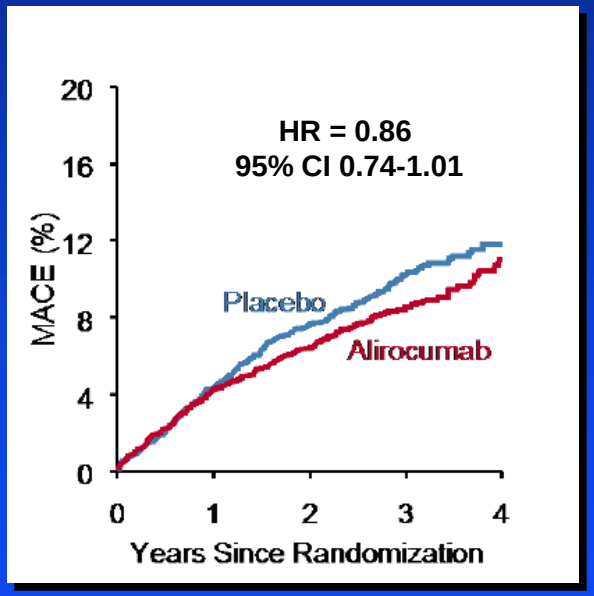


Endpoint Components

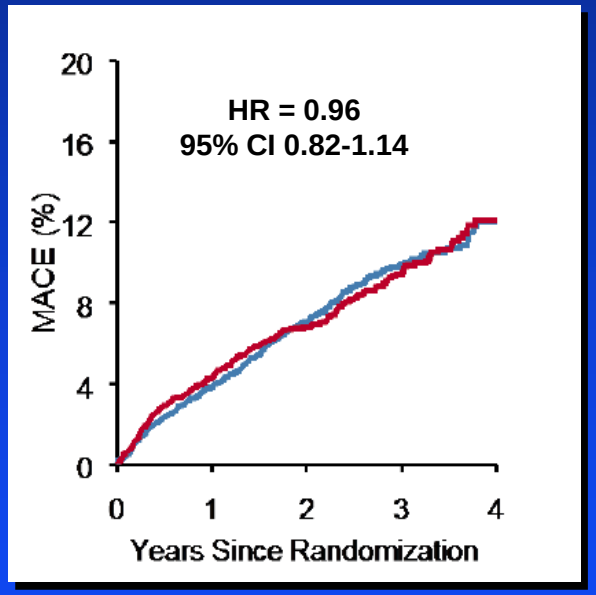


Impact of Baseline LDL on Primary Outcome

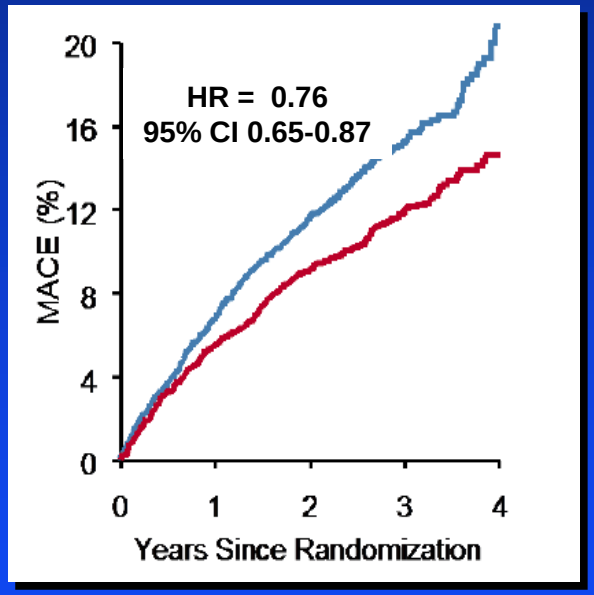
Baseline LDL <80



Baseline LDL 80-100



Baseline LDL ≥100

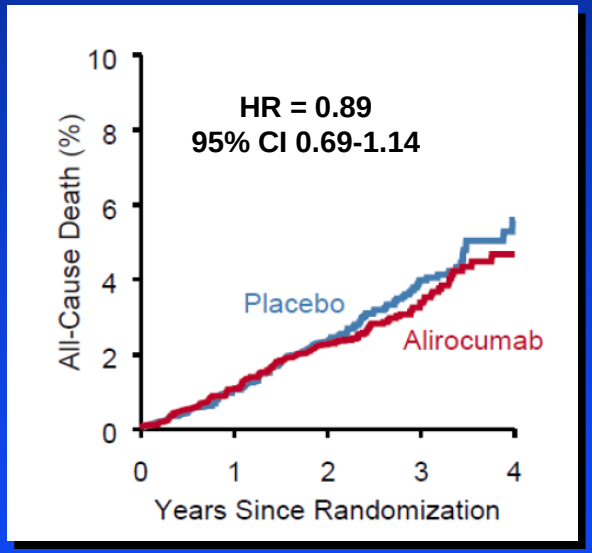


Absolute benefit when baseline LDL ≥100
ARR 3.4% NNT 30

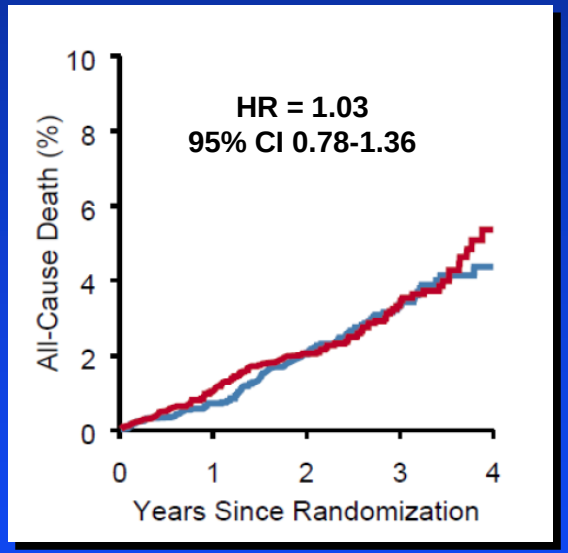
$P_{int} = 0.09$

Impact of Baseline LDL on All-Cause Mortality

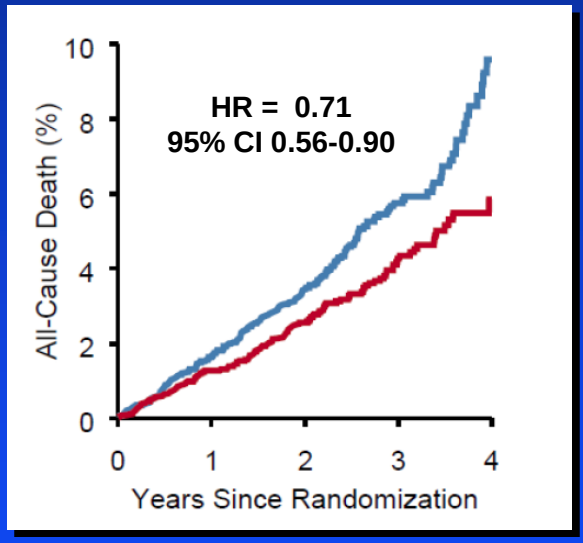
Baseline LDL <80



Baseline LDL 80-100



Baseline LDL ≥100



Mortality benefit when baseline LDL ≥ 100
ARR 1.7% NNT 59

$P_{int} = 0.12$

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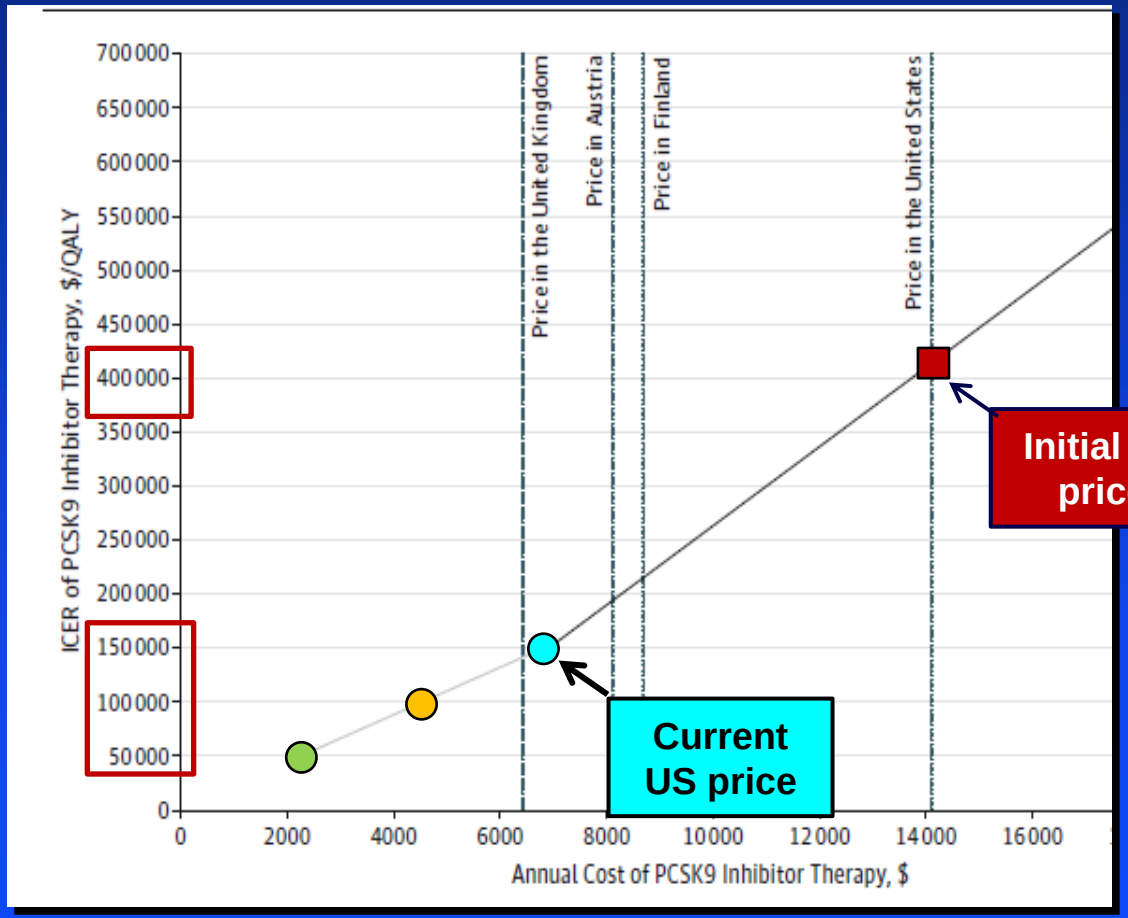
Why aren't PCSK9 inhibitors being used?

How low would the price of PCSK9 inhibitors have to be for the drug to be cost-effective?



- Analysis based on US population with established CAD and LDL-C > 70 mg/dL
- ICER remains >$50,000/QALY gained unless drug cost <$2000/yr
- Cost-effectiveness threshold even lower in other countries given lower event costs

Kazi D, et al. JAMA. 2016;316(7):743-753.

Summary

- PCSK9 inhibitors represent one of the first breakthrough immunologic therapies in cardiovascular prevention
- Randomized trials demonstrate significant reductions in events in patients already treated with high dose statins→ further confirmation of the "LDL hypothesis"
- Trials also confirm safety of extremely low LDL levels → 42% of patients in FOURIER achieved LDL <25 mg/dL
- Cost remains the major barrier to adoption for many countries, although the situation is improving. Targeting specific patient subsets can improve cost-effectiveness
  - *FOURIER: Symptomatic PAD, multiple prior Mis*
  - *ODYSSEY: On-treatment LDL > 100 mg/DL*