

Overview of large randomized trials of ACE inhibitors in patients with stable vascular disease without left ventricular systolic dysfunction or heart failure in the context of previous large trials

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Potential conflicts of interest regarding this study,

- GR Dagenais and S Yusuf received honoraria for lectures and research grants from Hoechst-Marion Roussel, AstraZeneca, and King Pharmaceuticals, and
- K Fox and ML Simoons received honoraria and research grants from Servier

Background

ACE inhibitors reduce CV mortality and morbidity in patients with heart failure or left ventricular systolic dysfunction (LVSD).

Three large trials, HOPE, EUROPA and PEACE, have assessed the impact of ACE inhibitors in stable patients without these conditions but with atherosclerosis.

Objectives

We undertook a systematic review of these 3 studies as well as of 5 trials in patients with heart failure or LVSD, to answer 2 questions:

1. Is there a consistency with which ACE inhibitors reduce total mortality, and fatal and non-fatal CV events?
2. Do benefits vary between patients with varying levels of risks or by ancillary treatments?

Data Collection and Outcomes

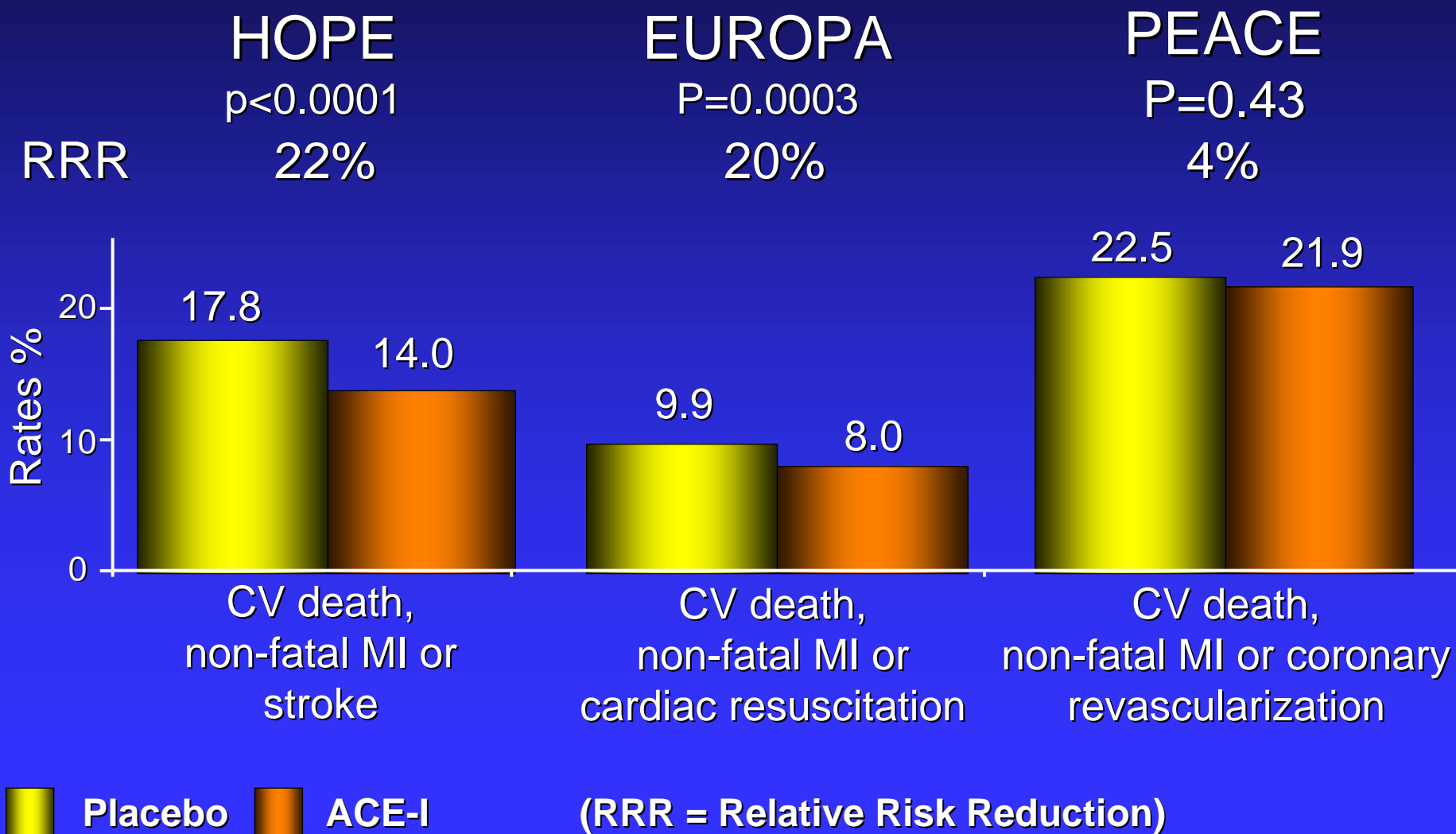
- For HOPE, EUROPA, and PEACE, data were obtained from published reports, and additional data were made available from EUROPA and HOPE but not from the PEACE trial.
- For the 5 trials, SOLVD-T & SOLVD-P, SAVE, AIRE and TRACE data were obtained from published reports and database.
- The outcomes assessed were based on those available from the PEACE study.

Main Baseline Characteristics

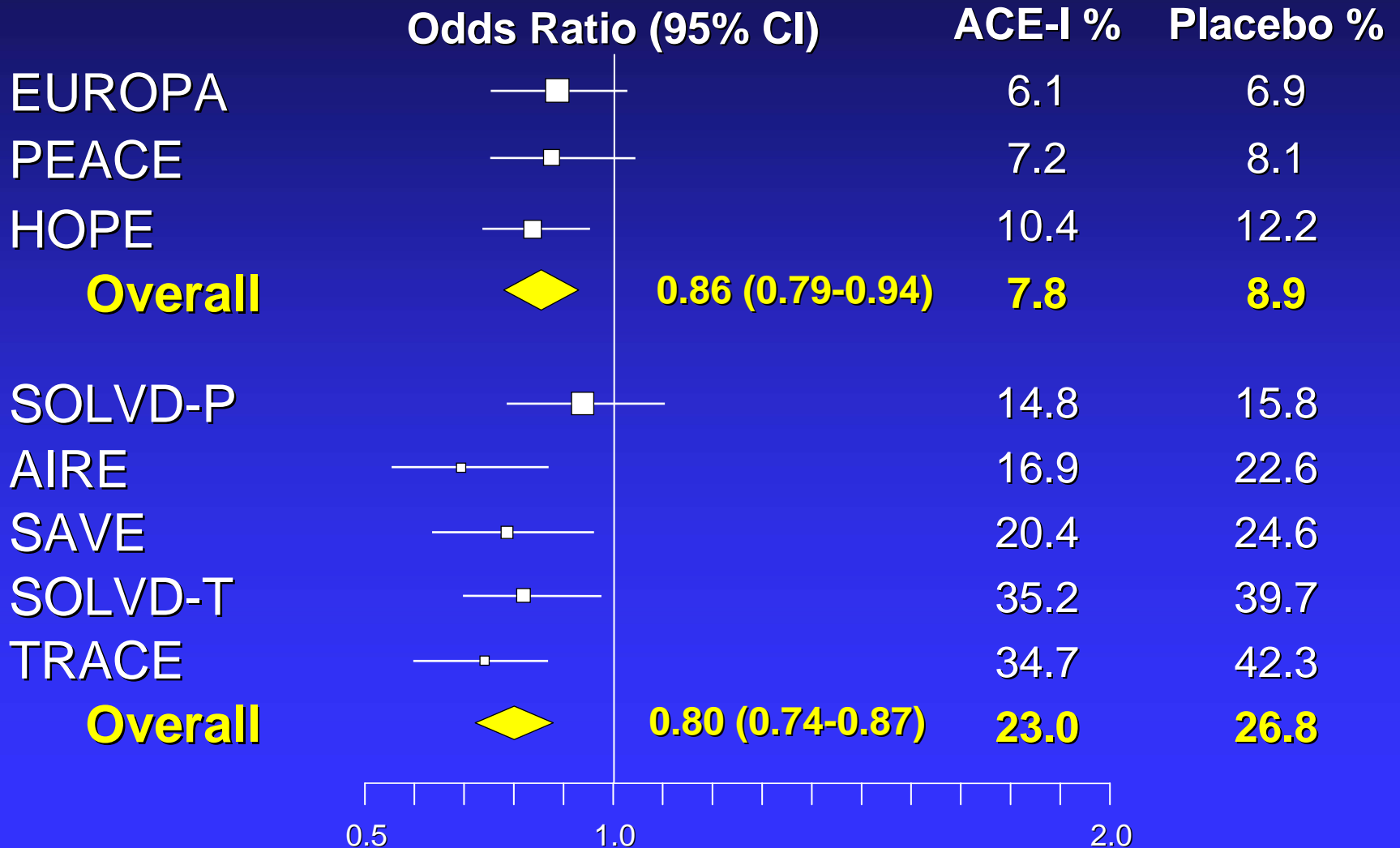
HOPE, EUROPA and PEACE Participants

Characteristics	HOPE n = 9 297	EUROPA n = 12 218	PEACE n = 8 290
Age (mean) (years)	66	60	64
Previous MI %	53	65	55
Diabetes %	38	12	17
PCI or CABG %	40	55	72
LVEF (mean) %	N.d.	N.d.	58
BP (mm Hg)	139/79	137/82	133/78
Antiplatelet agents %	76	92	91
Lipid lowering agents%	29	58	70
Beta blockers %	40	62	60

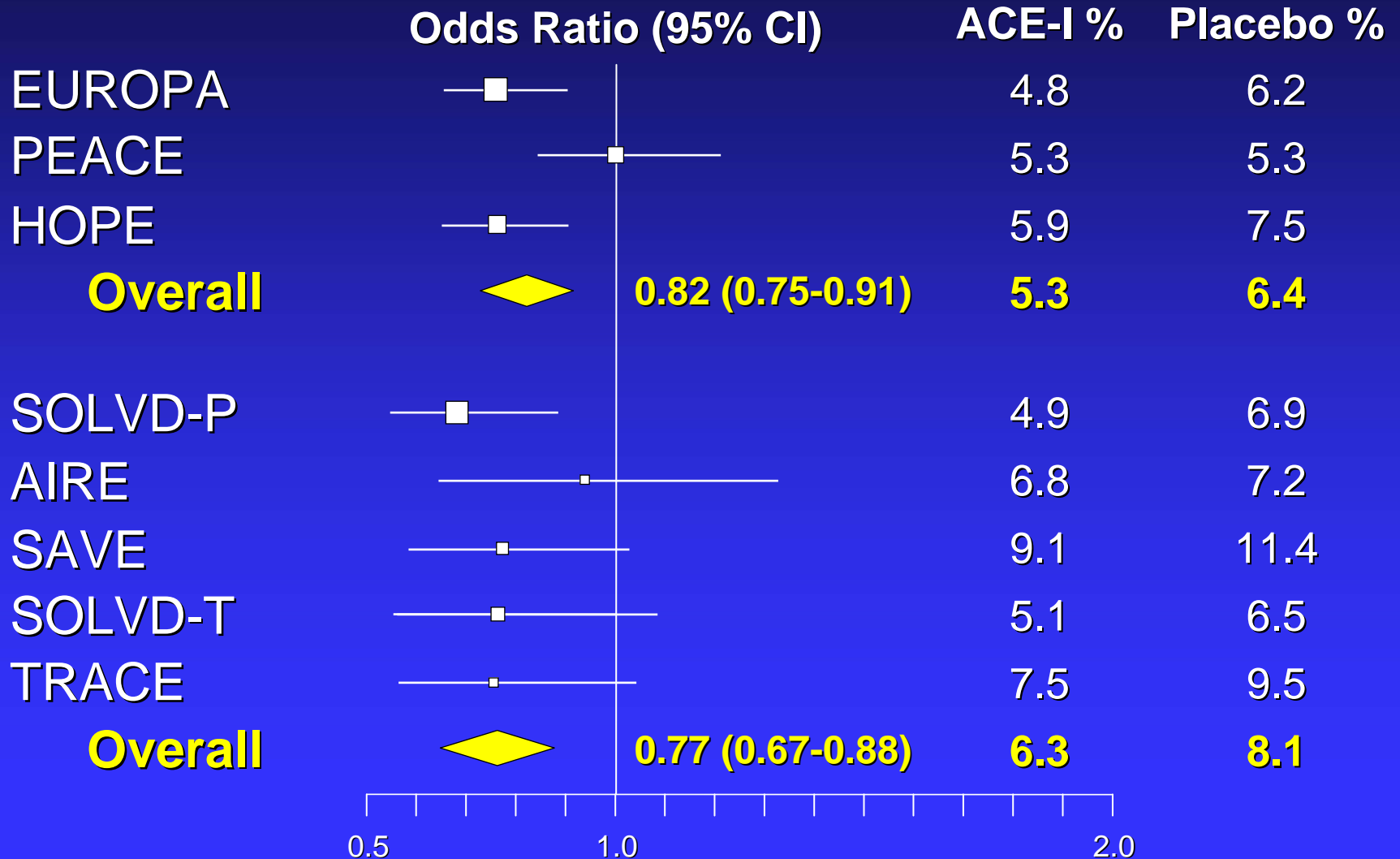
Primary Outcomes



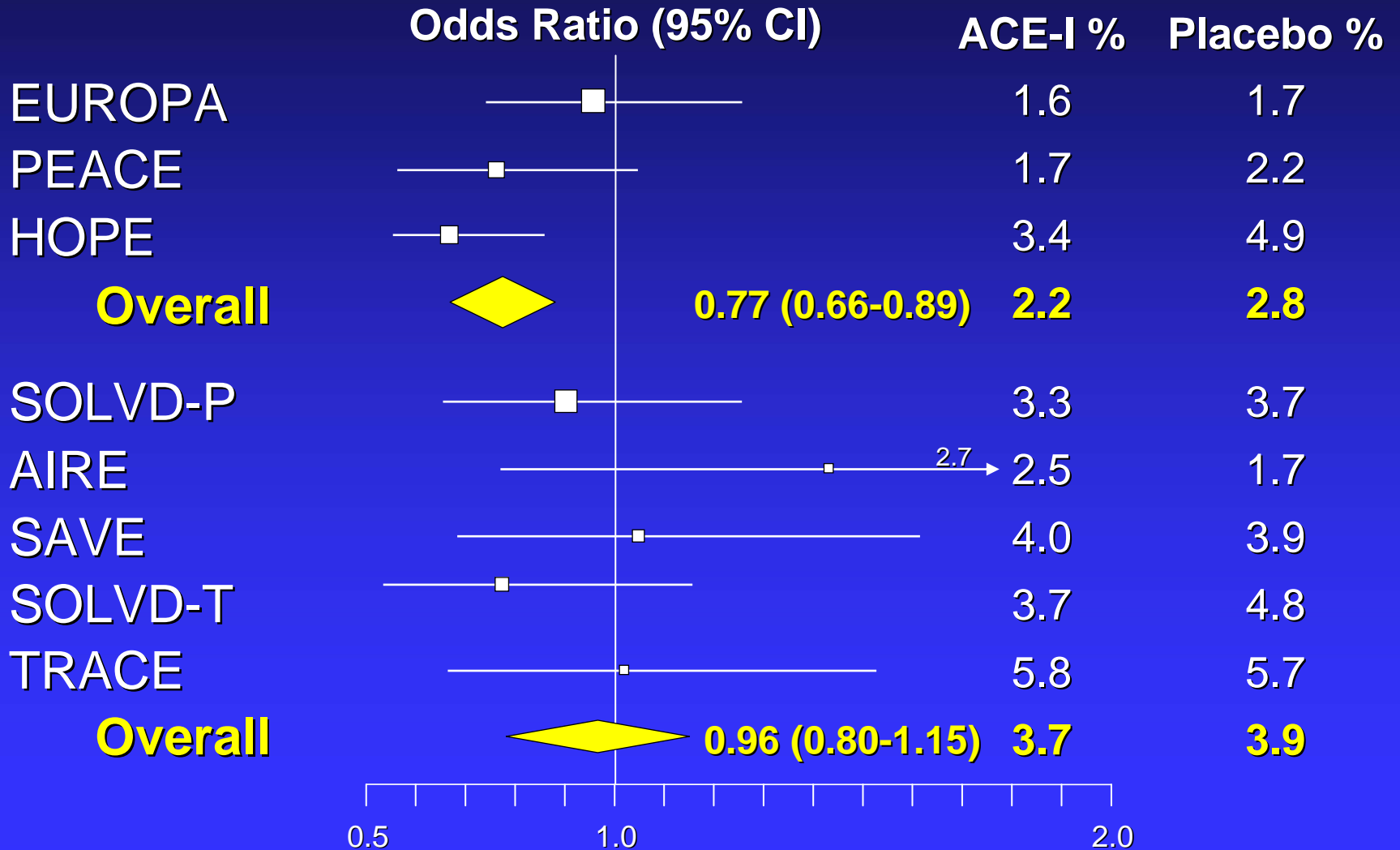
All Cause Mortality



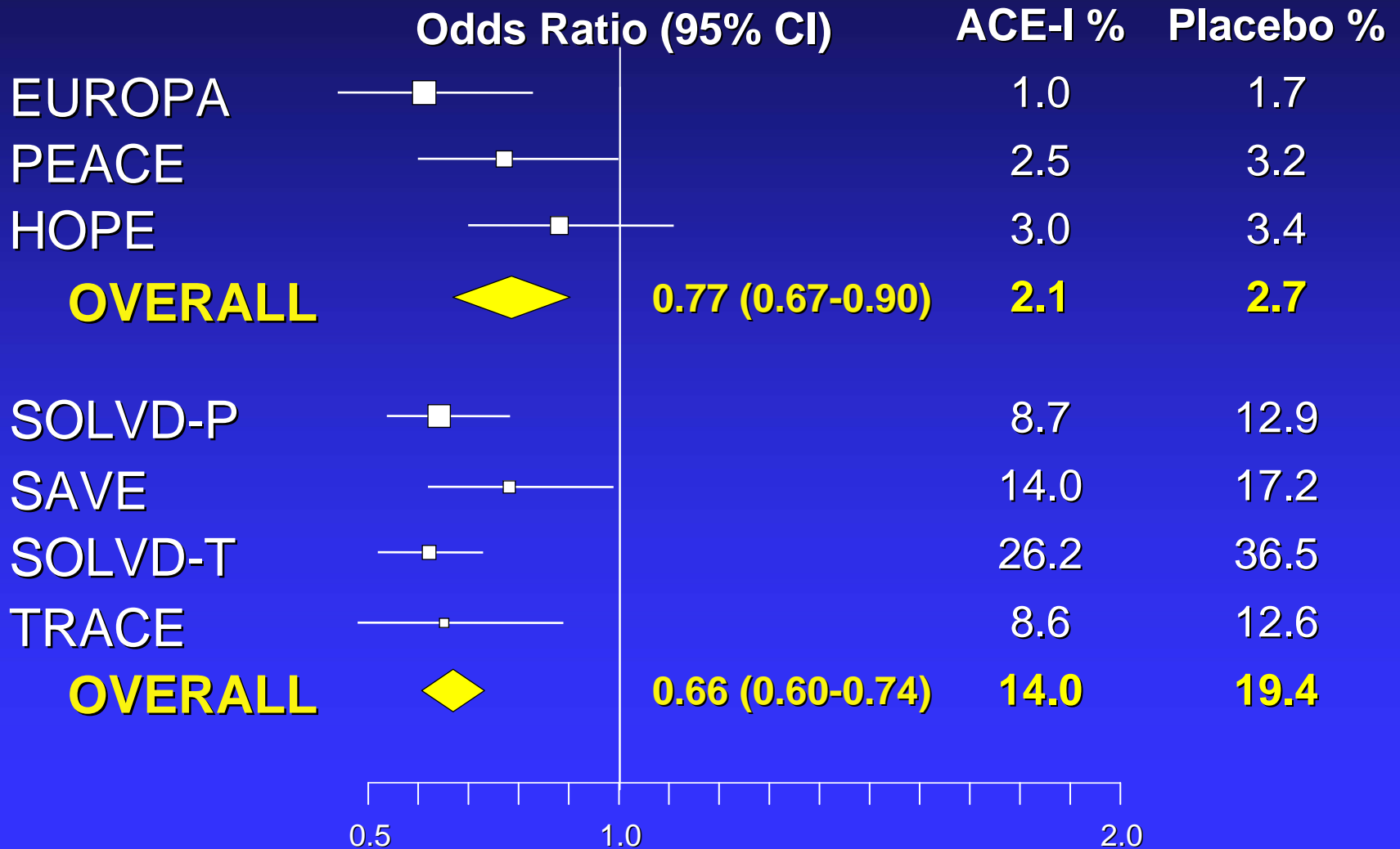
Non-fatal Myocardial Infarction



Fatal and Non-fatal Stroke



Hospitalization for Heart Failure



Coronary Revascularization in EUROPA, PEACE and HOPE

Coronary artery bypass graft

ACE-I % Placebo %

EUROPA

4.5

4.7

PEACE

6.5

7.1

HOPE

7.6

9.4

OVERALL



0.87 (0.79-0.96)

6.0

6.9

Percutaneous coronary interventions

EUROPA

5.4

5.6

PEACE

12.4

12.0

HOPE

5.6

6.3

OVERALL



0.97 (0.89-1.06)

7.4

7.6

0.5

1.0

2.0

1. Is there a consistency with which ACE inhibitors reduce total mortality, and fatal and non-fatal CV events?

- *The review in these 30,000 patients without known HF or LVSD demonstrates consistency and clear benefits of ACE-I on different outcomes.*
- *In the 12,000 patients with HF or LVSD, there is consistency of treatment benefits across a broad range of about 4 fold risk for major outcomes except stroke.*

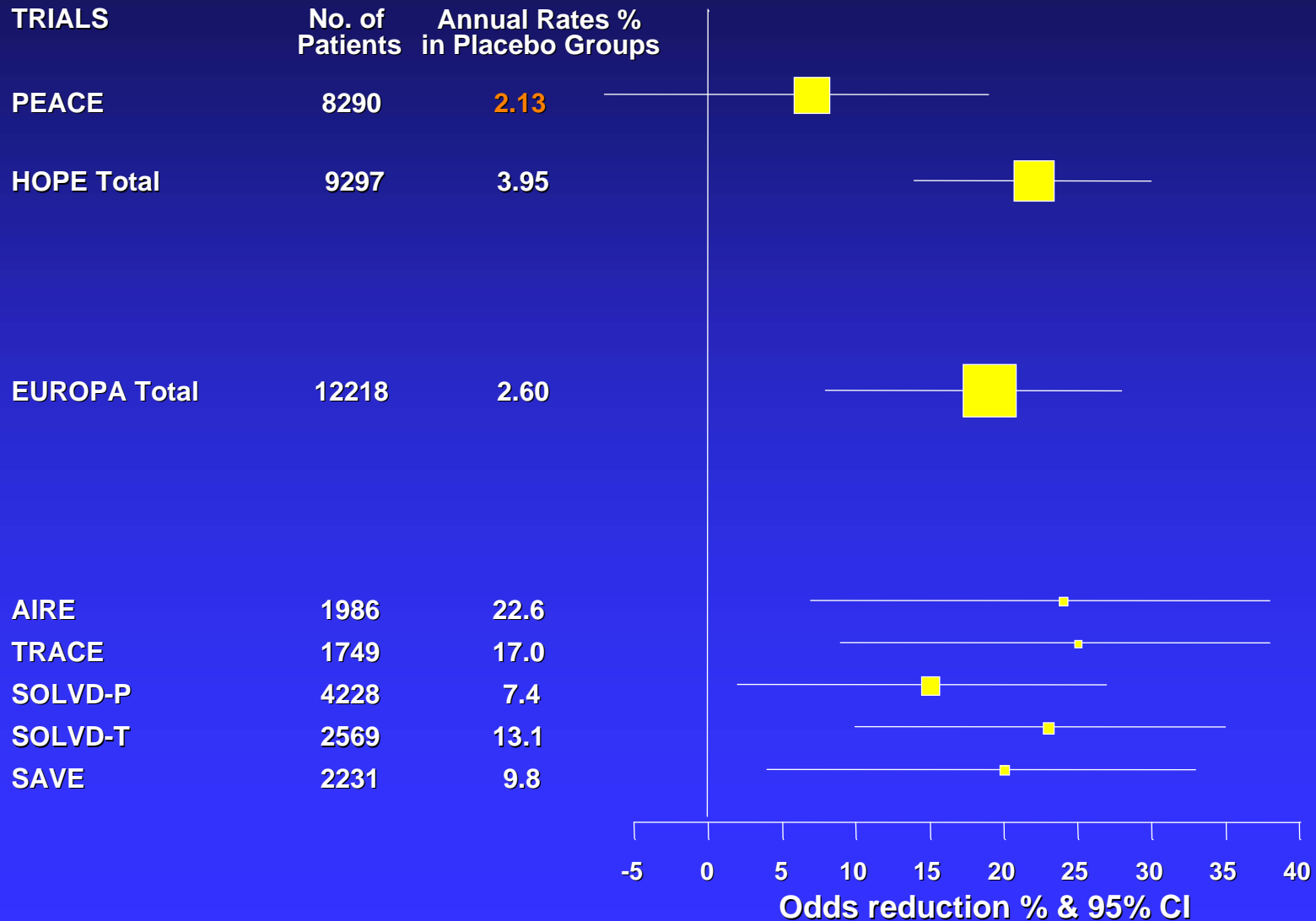
2. Do benefits vary between patients with varying levels of risks or by ancillary treatments?

Considerations on PEACE results

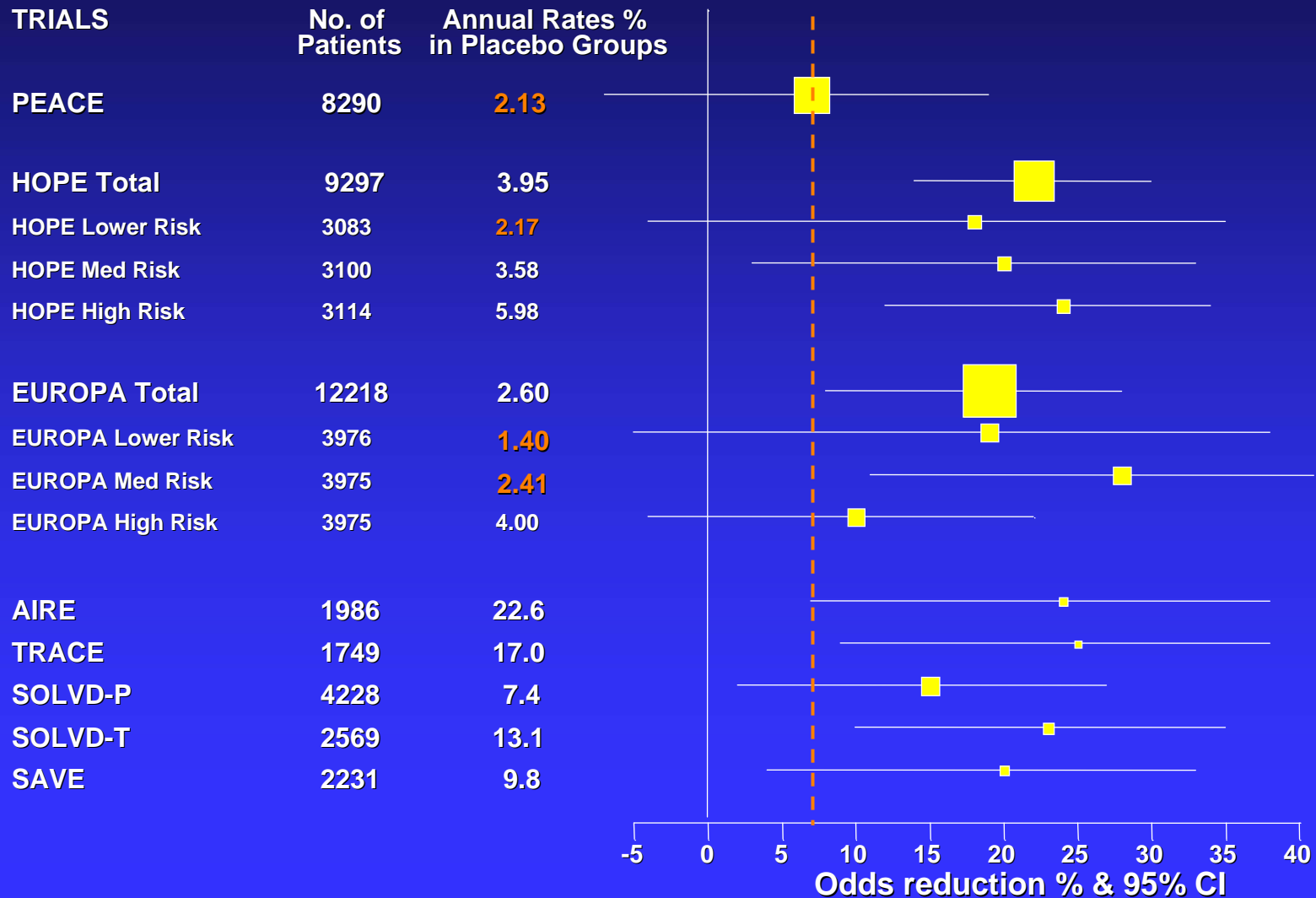
- Different patient risk?
- Different concomitant therapy?
- Different outcomes?
- Power?

(other factors: different ACE-I, appropriate dose)

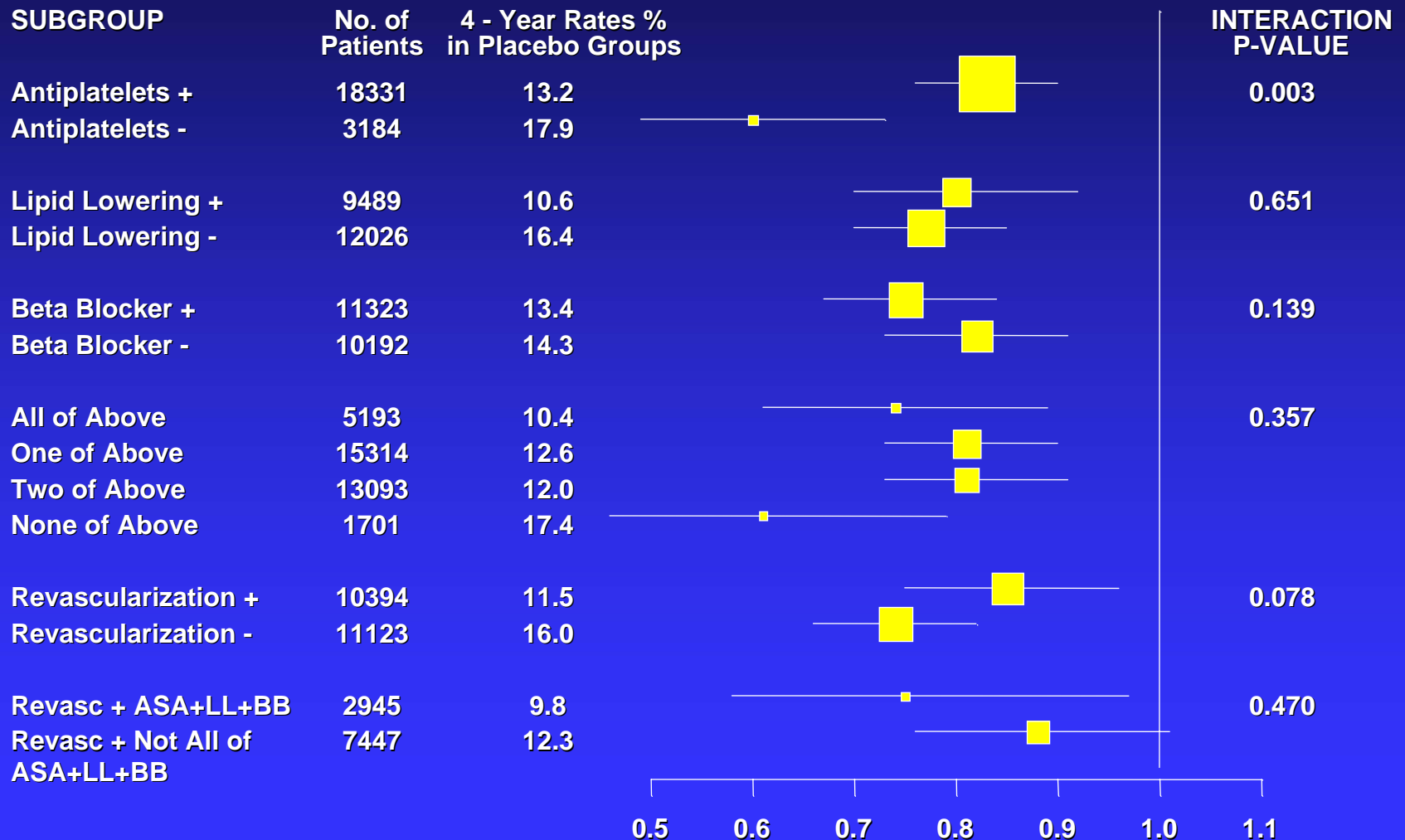
Impact of ACE-I on CV Death, Non-fatal MI or Stroke at Different Annual Risks



Impact of ACE-I on CV Death, Non-fatal MI or Stroke at Different Annual Risks



Different Concomitant Therapies on the Effects of ACE-I on CV Death, Non-fatal MI or Stroke



Different Outcomes Between the 3 Trials

- HOPE: CV death, non-fatal MI or **stroke**
- EUROPA: CV death, non-fatal MI or **cardiac arrest resuscitation**
- PEACE: CV death, non-fatal MI or **coronary revascularization**

PCI and CABG accounted for nearly 60% in PEACE. Such outcome depends on medical practice decision and is a soft endpoint compared to CV death and non-fatal MI.

Conclusion

1. There is consistency in different outcomes in HOPE, EUROPA and PEACE.
2. In patients with CAD, it is unlikely that the benefits of ACE-I vary between patients with varying levels of risks or by ancillary treatments.

PEACE results appear to differ from the other trials most likely because PEACE is underpowered and used one soft endpoint.

ACE-I should be broadly considered in patients with any evidence of vascular atherosclerotic disease as long as they can tolerate these agents and the absolute benefits are judged to be worthy.