ACEi/ARB for everyone?

Professor John D Horowitz
Director, Cardiology Unit
The Queen Elizabeth Hospital
The University of Adelaide

A threatened management acronym?

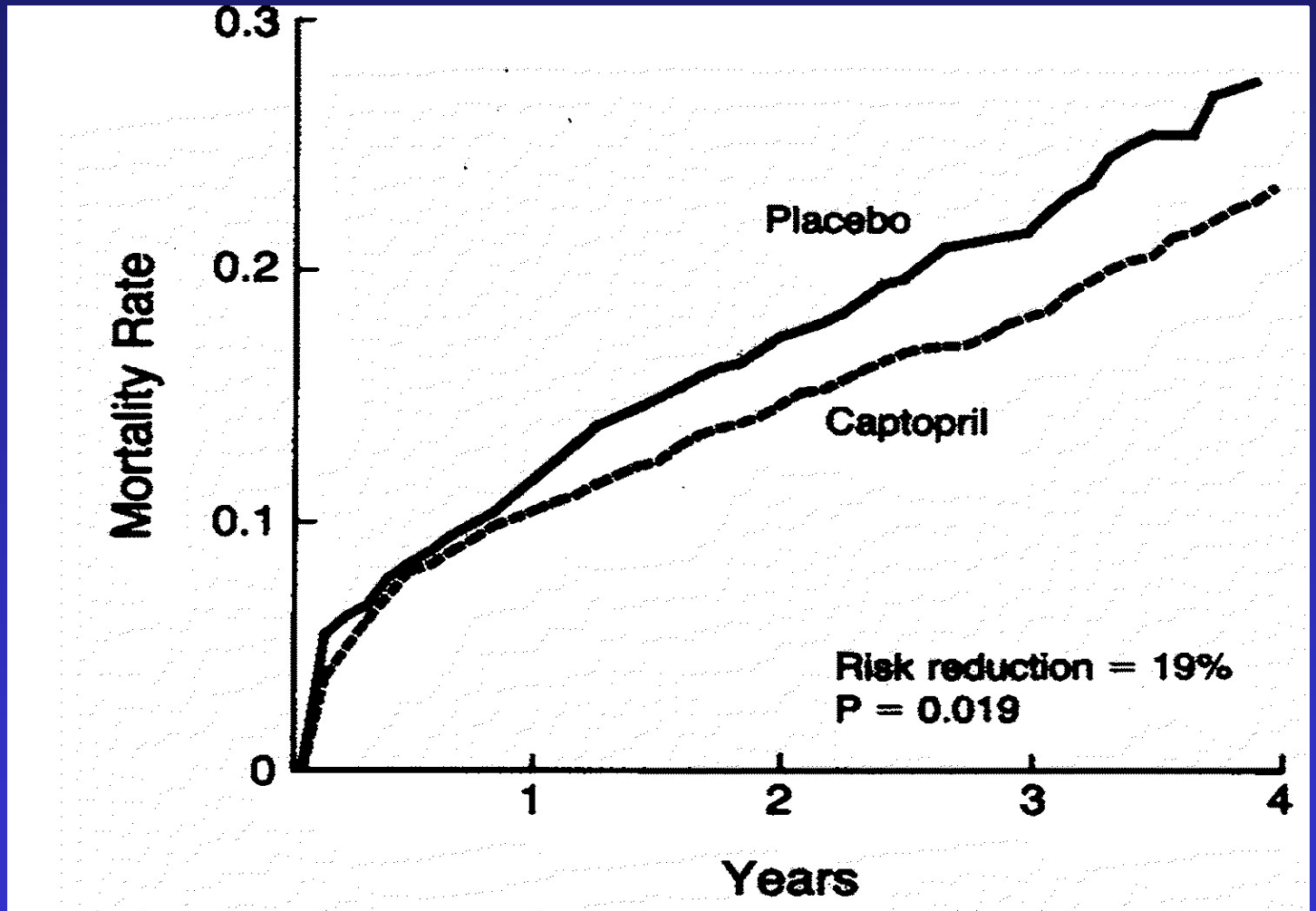
Routine post-infarct management: Swedish-style

- **S**tatin
- **A**spirin
- **A**ce Inhibitor
- **B**eta Blocker

ACEi Post STEMI: the original idea (M/J Pfeffer,1980)

- Captopril therapy post coronary ligation in rats
- Moderate/large infarcts led to progressive ventricular dilatation and reduced CO
- Captopril limited this deleterious”remodelling”

Application of principle: SAVE



Placebo	1116	987	915	609	262
Captopril	1115	1000	938	614	288

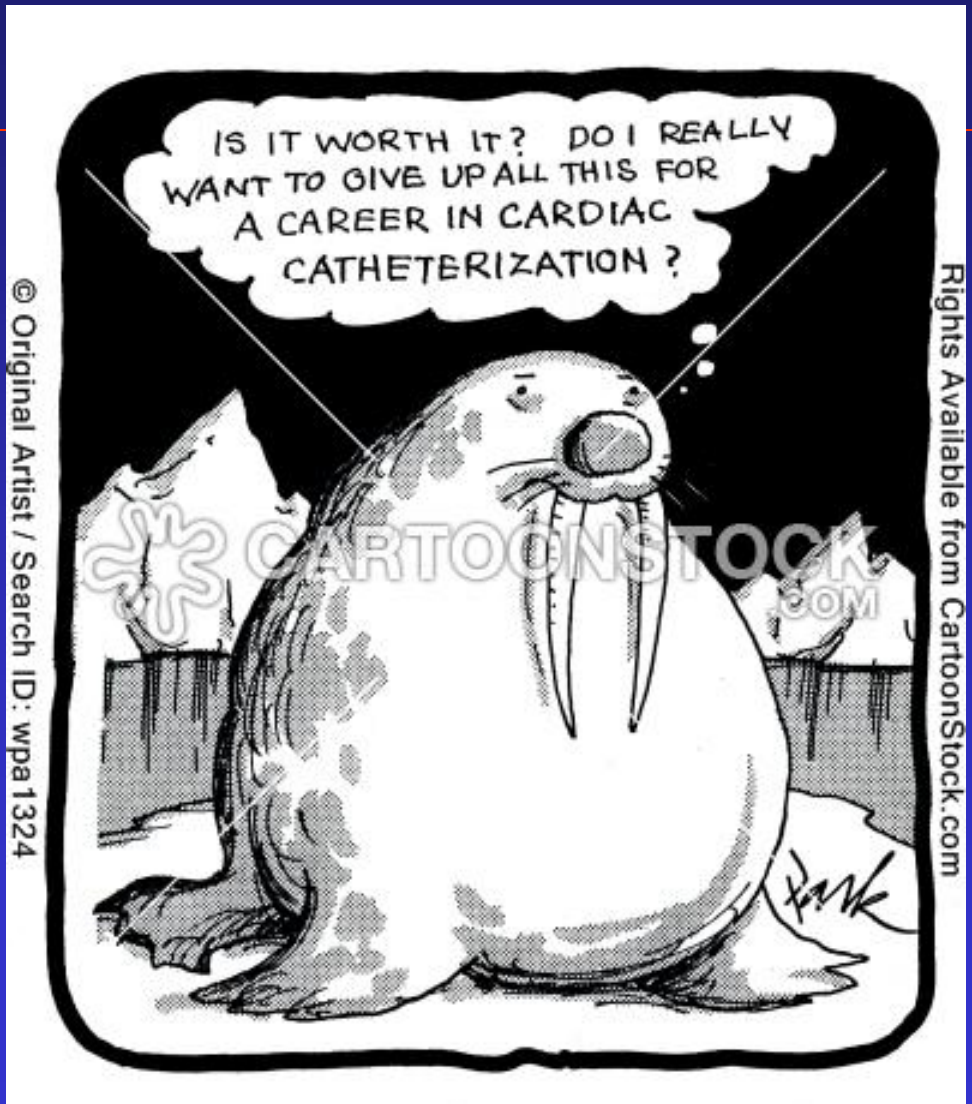
But what if the infarct is small?

- Remodelling is not really a clinically relevant issue
- Key outcomes relate to RECURRENT ISCHAEMIA
- Therefore there are 2 further issues:-

  (a) Are there any patients with no ischaemic risk

  (b) Are ACE inhibitors effective in prevention of recurrent ischaemia/infarction

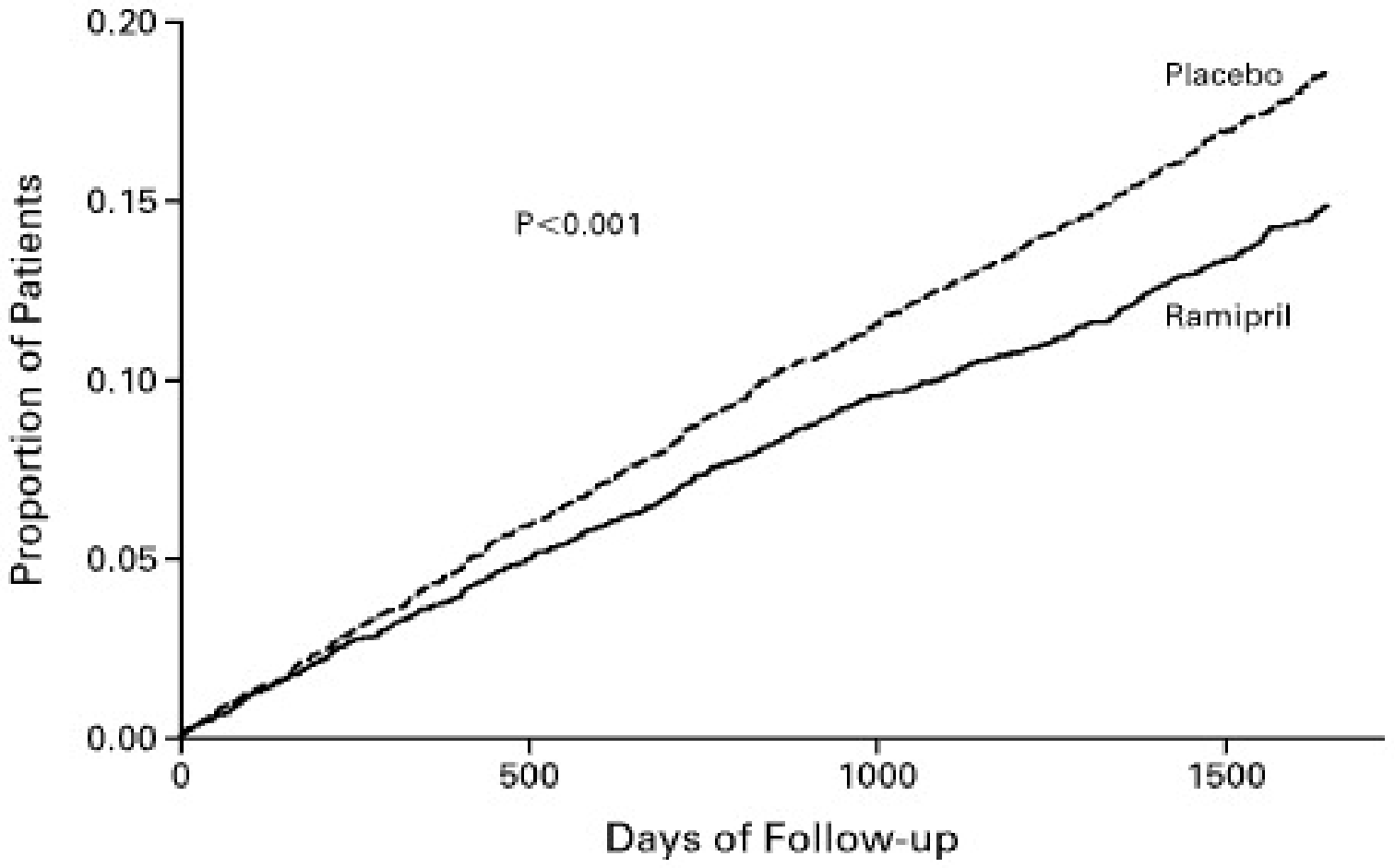
"NO FURTHER RISK" patients



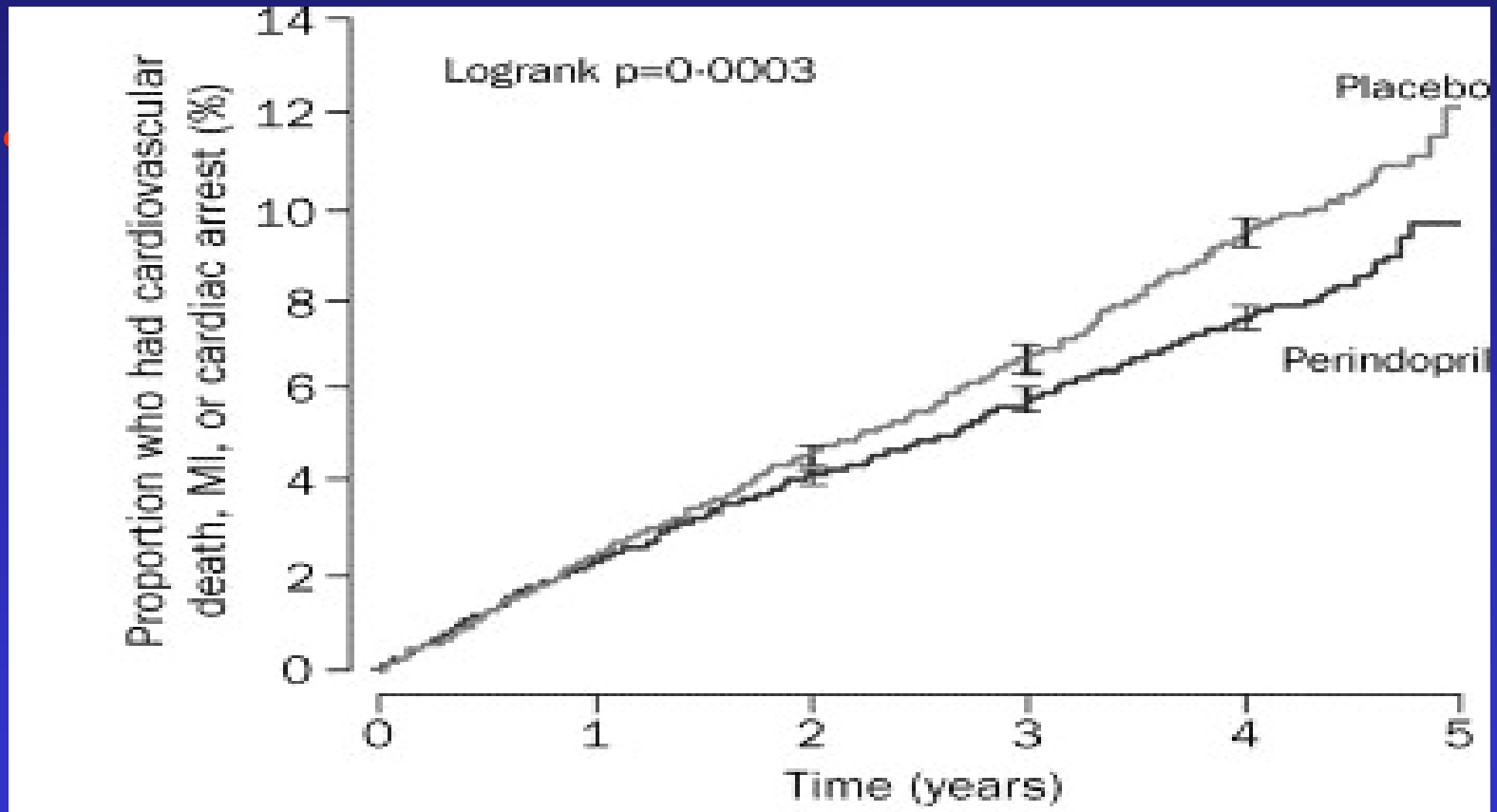
Is there evidence that ACE inhibitors Prevent Infarction?

- **HOPE Trial: Ramipril 10mg: 9297 patients with ischaemia and/or diabetes, not CHF**
- **EUROPA Trial: Perindopril 10mg: 13655 patients with ischaemia and no CHF**
- **PEACE Trial: Trandolapril 4mg: 8290 patients: stable CAD, "normal" LVEF**

Outcomes: HOPE: AMI/CVA/death (Yusuf et al,2000)



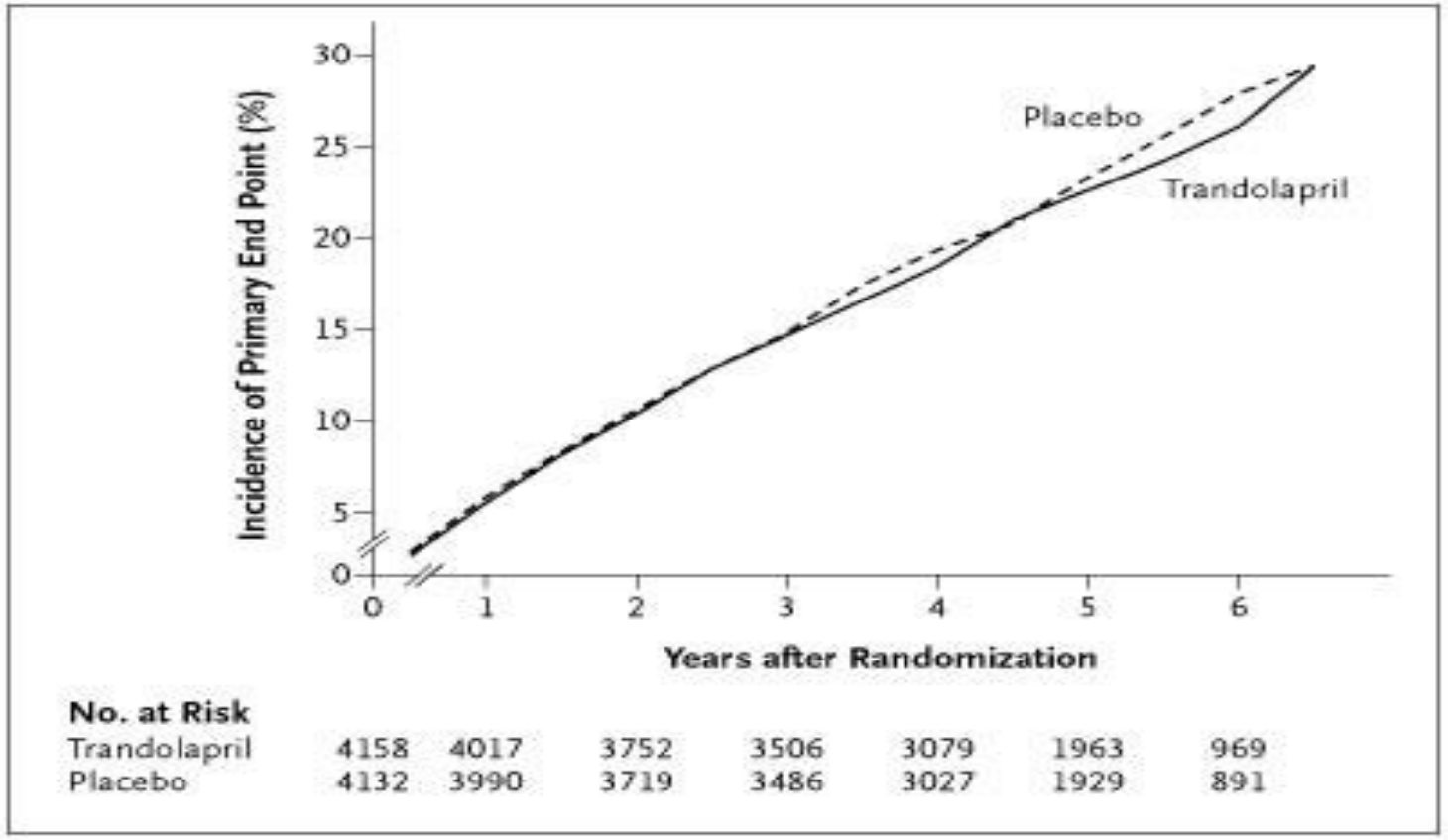
Outcomes: EUROPA: cardiovascular death or AMI (Fox et al,2003)



Patients at risk

Placebo	6108	5943	5781	5598	4450	71
Perindopril	6110	5957	5812	5653	4515	64

Outcomes: PEACE: Death/AMI/Revasc (Braunwald et al,2004)



Why was PEACE negative?

- "Very low risk cohort"

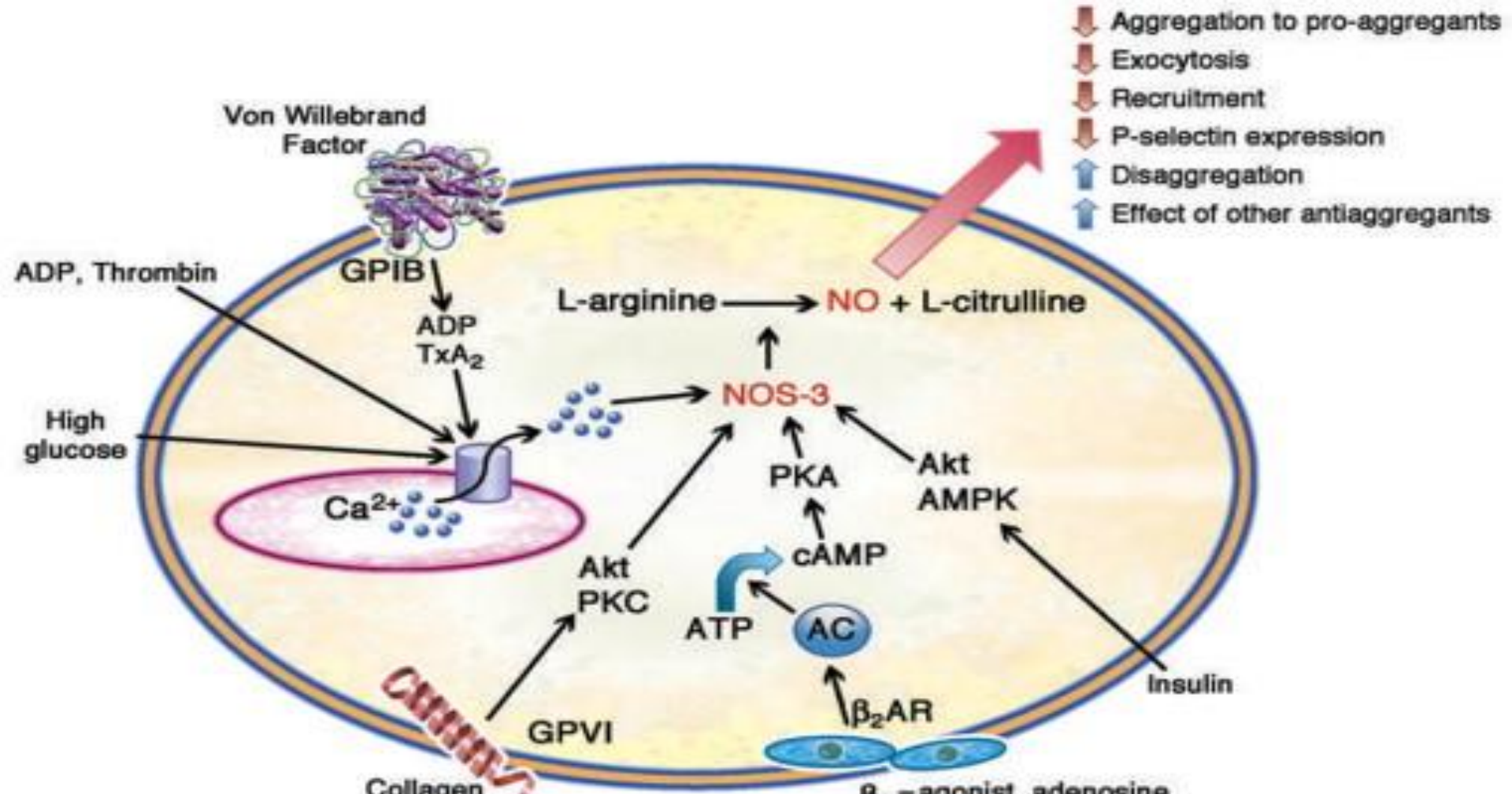
OR

- Under-powered study: (revised) end-point driven by revascularisation

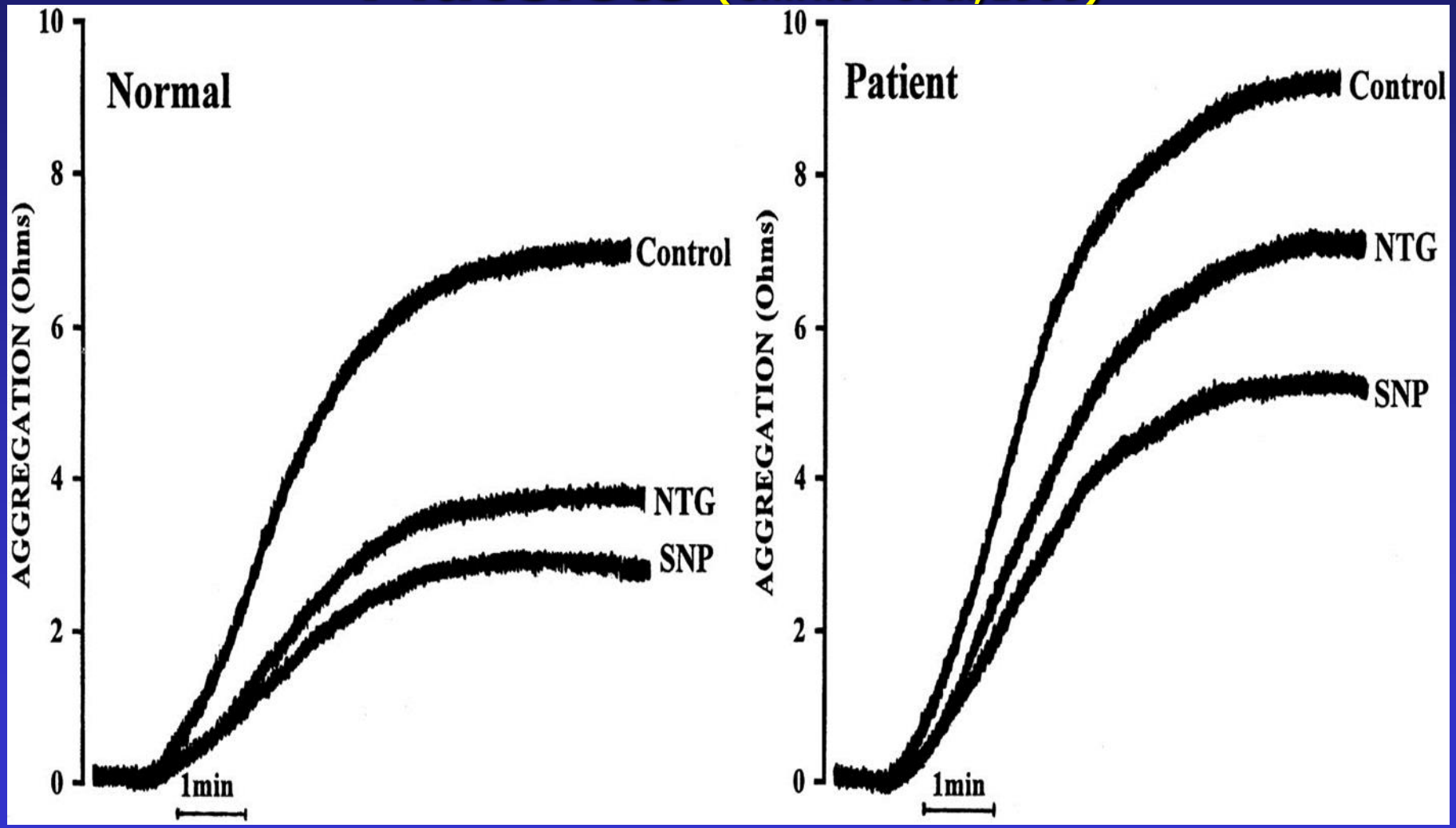
Are there known mechanisms of protection for ACE inhibitors?

- Prevention of redox stress
- Anti-inflammatory effects: TxNIP suppression
- Resultant improvement in:-
  - (a) Vascular endothelial function
  - (b) Platelet response to nitric oxide

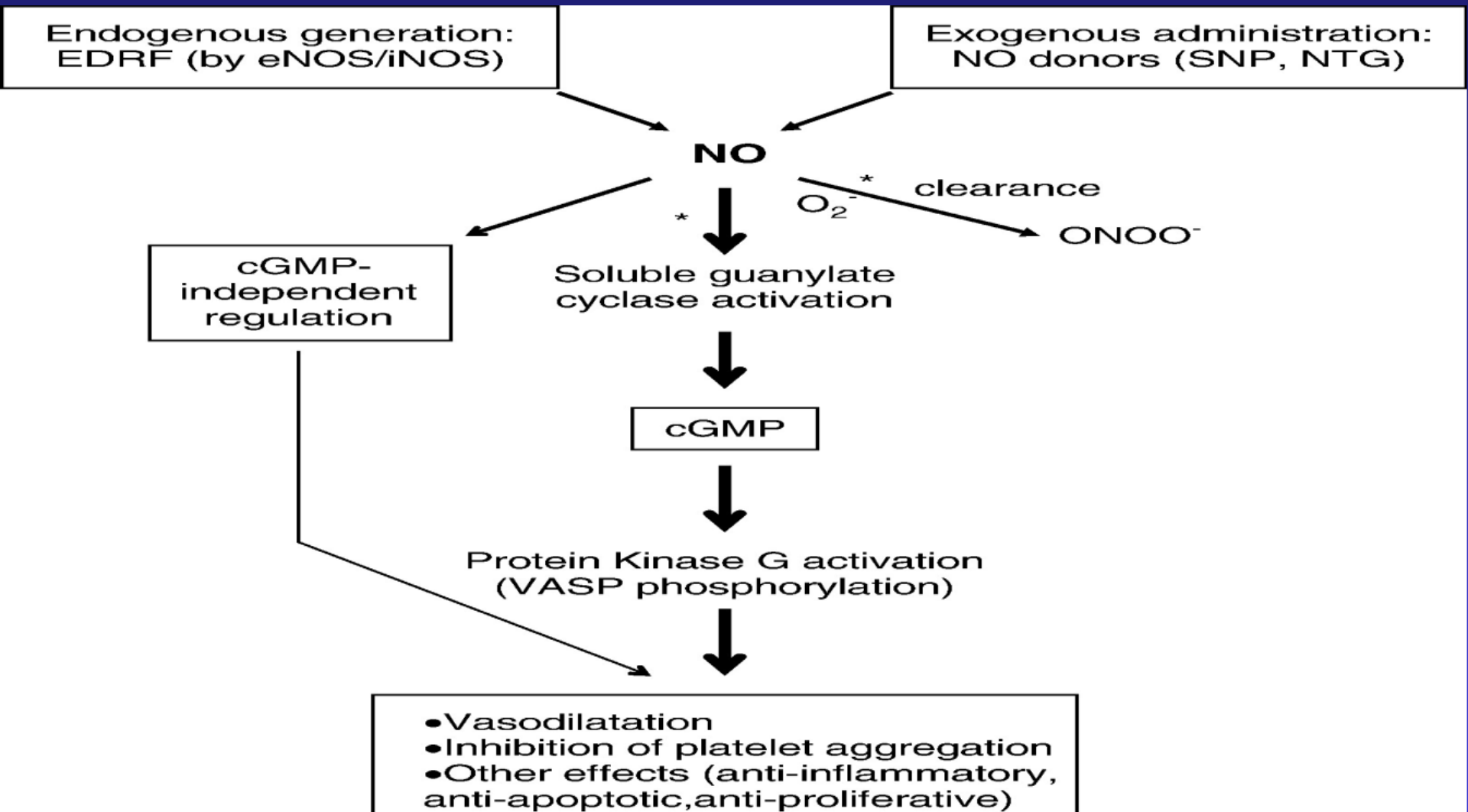
Nitric Oxide and platelet homeostasis (Angiolillo, Capodanno 2012)



Nitric Oxide Resistance in Platelets (Chirkov et al,1999)

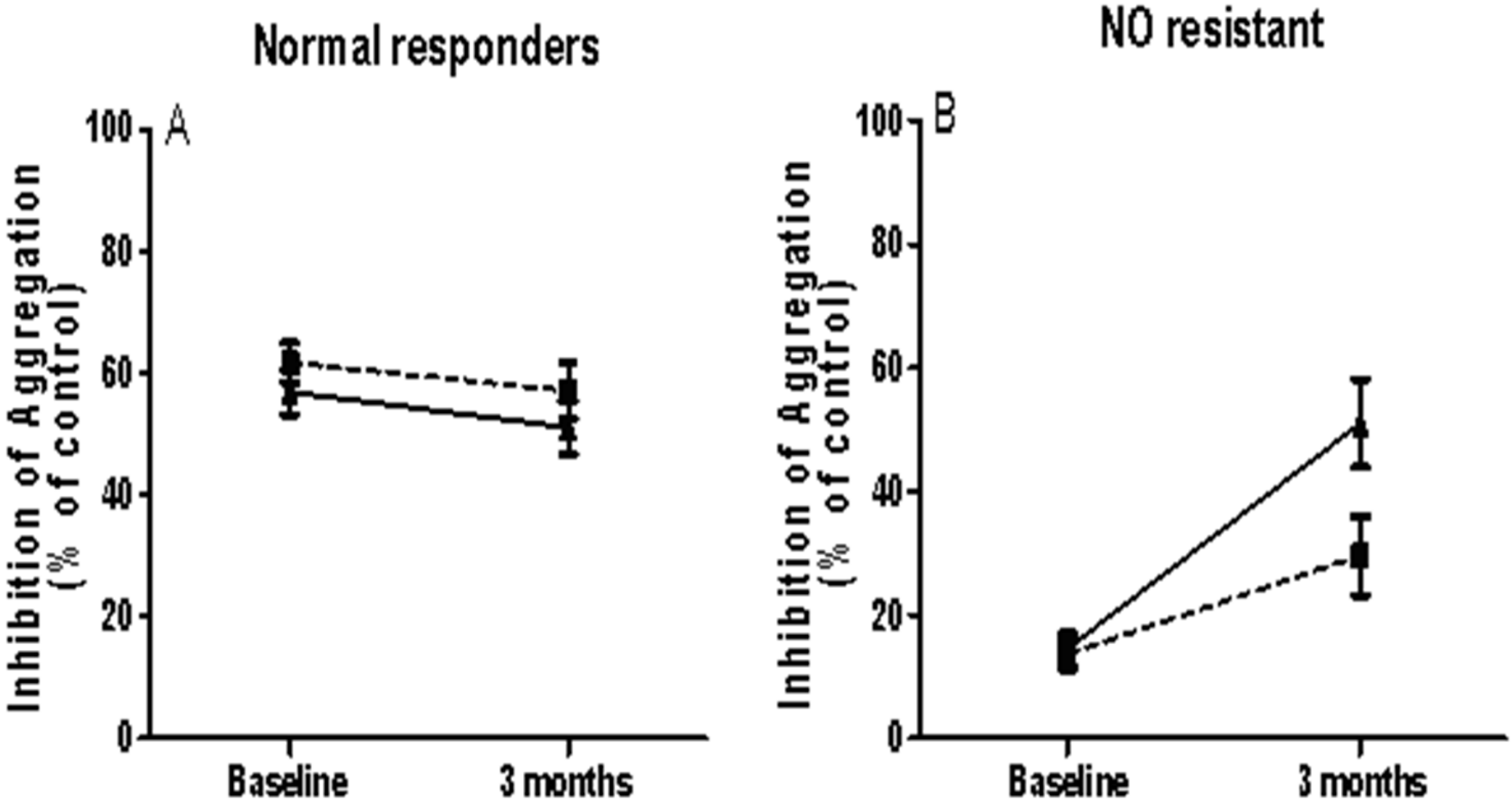


Mechanisms of NO resistance

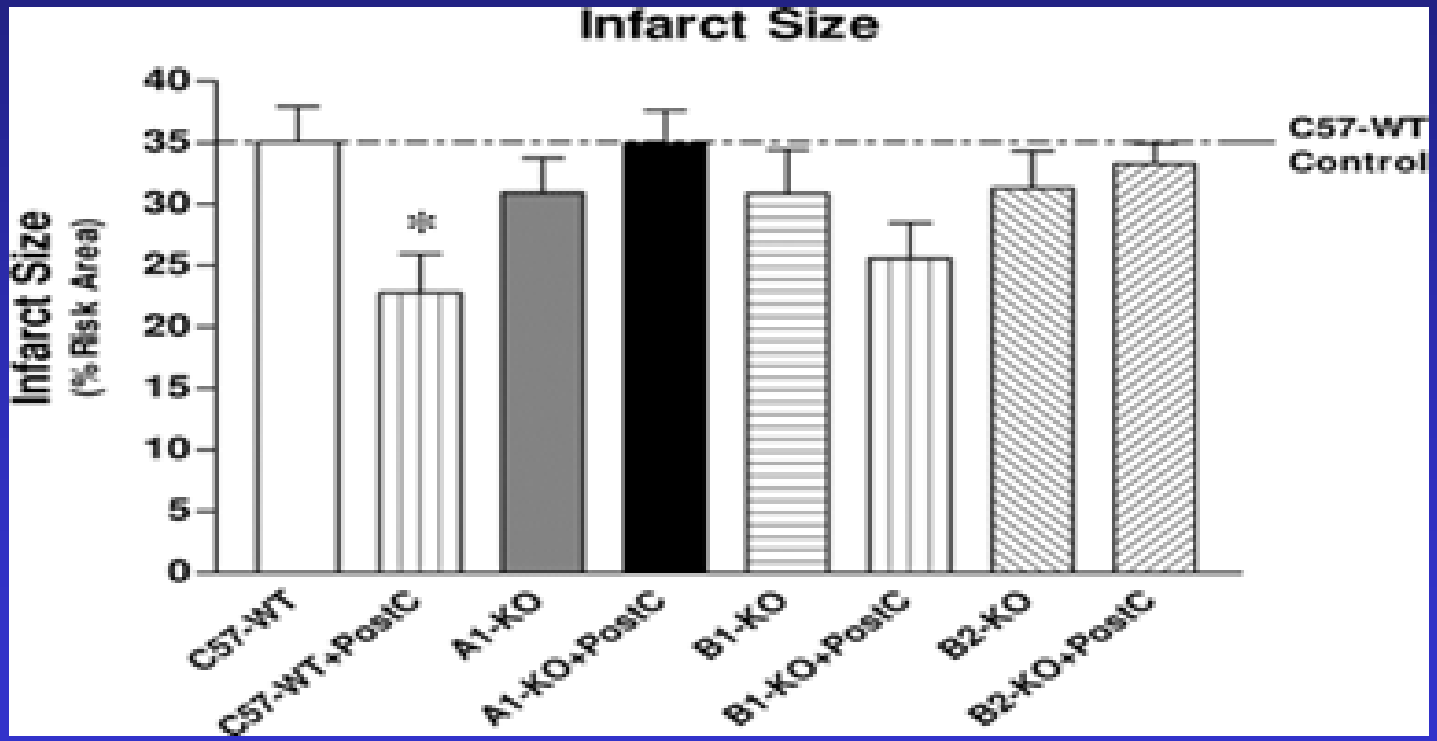


Ramipril Reverses NO resistance

(Willoughby et al,2012)



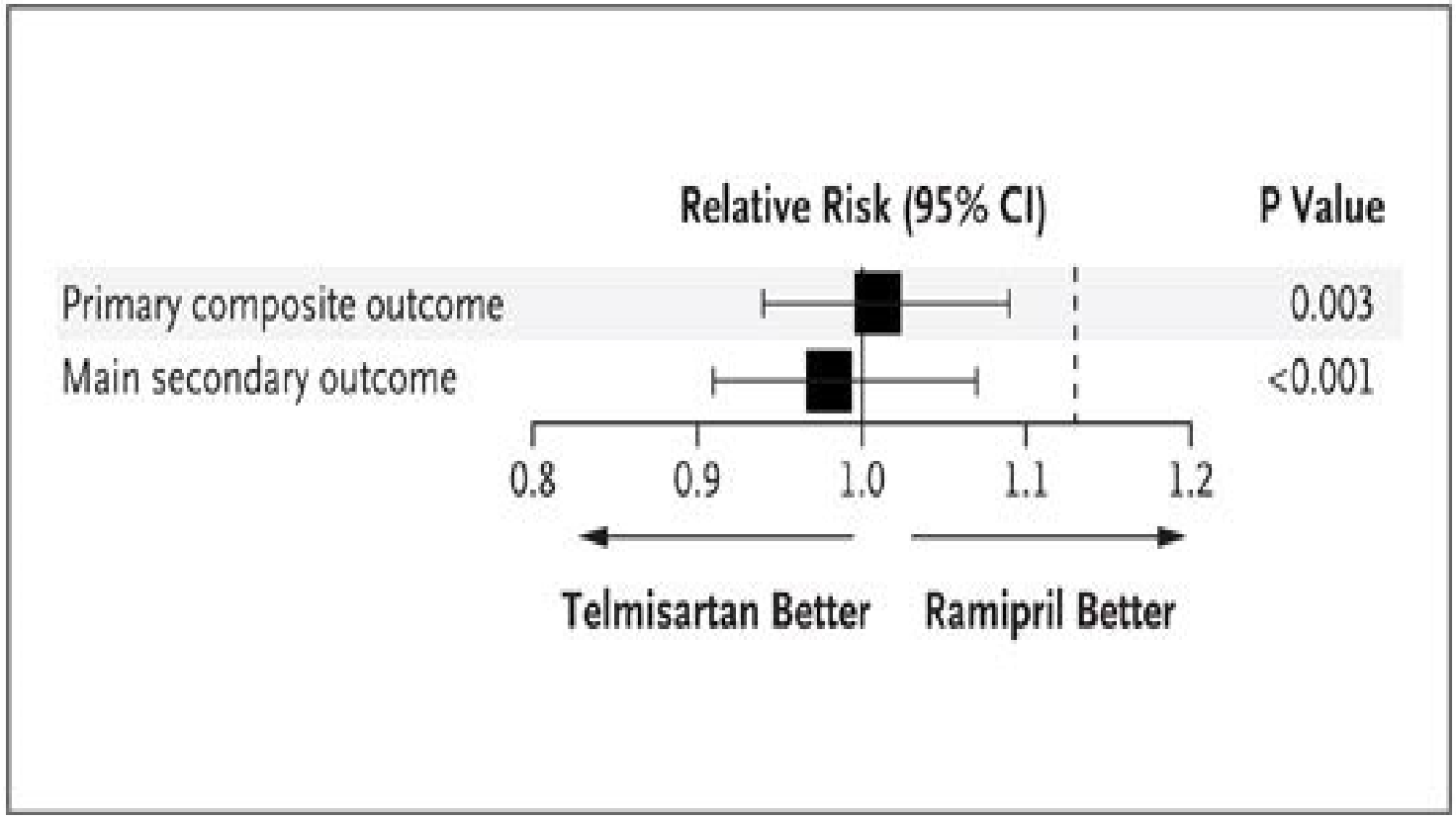
BK2 receptor knock-out mice lack post-conditioning



What about ARBs? ONTARGET (Yusuf et al,2008)

- Comparison of telmisartan, ramipril or both
- Entry criteria as for HOPE
- End-point: CVS death/AMI/CVA/CHF
- >25000 patients followed for 56 months

Outcomes: ONTARGET



SO, where do we stand after all these trials?

- Ramipril and perindopril reduce risk of cardiac events in high risk patients with good LV function
- Telmisartan appears to be equi-effective with ramipril
- This is despite the theoretical role of bradykinin in cardioprotection

Might there be some fringe benefits?

- Aortic stenosis: ACEi slows progression in rabbits
  : ACEi/ARB reduces early disease
  : ACEi/ARB reduces mortality
- Diabetes : new onset diabetes incidence reduced
- Renal protection

Is this orthodox opinion?

"…ACE inhibitors or ARBs should be part of the standard treatment for patients at risk of CV events"

Volpe,M QJMed 2012

But maybe the problem will just go away..

- Inser