

Role of ACE Inhibition in the Cardiovascular Continuum

Abstract

The renin-angiotensin system (RAAS) plays an important role in the pathogenesis of cardiovascular disease. Atherosclerosis and the complications of the disease and adverse remodeling of the damaged myocardium are the most prominent disease processes where RAAS plays an important role. Modulation of RAAS with angiotensin converting enzyme inhibitors has benefits throughout the cardiovascular continuum: extending from the patient with risk factors (diabetes and hypertension) through to the patient with a severely damaged heart. Guidelines for the management of patients with diabetes, hypertension, myocardial infarction and heart failure reflect the important role ACE inhibitors play in the management and prevention of cardiovascular disease.

The role of ACE inhibition for the prevention of vascular events was defined by the HOPE, EUROPA and PEACE trials. Although they enrolled different subjects, the trials confirm the value of ACE inhibition in a range of patients with cardiovascular disease for the reduction of mortality and morbidity endpoints. Despite the PEACE trial being underpowered, the endpoints that compare with HOPE and EUROPA showed a trend towards favourable benefits. This is confirmed by the meta-analysis of ACE inhibitor trials.

Do ACE inhibitors have benefits beyond that of blood pressure lowering ? In the HOPE and EUROPA trials the reduction of vascular events (particularly MI) was greater than the measured BP reduction (HOPE 3/2 mmHg and EUROPA 5/2 mmHg). In hypertension trials analyses have indicated that the reduction of cardiovascular events is greater than expected from BP reduction alone. No such additional benefit was observed with calcium channel blockers. Hence an ACE inhibitor should be considered for antihypertensive treatment for the patient at high risk for coronary or cerebrovascular disease. The success of anti-hypertensive medication depends upon adherence to treatment. Excellent tolerability and simplicity of treatment as achieved by limiting the number of prescribed medications by using combination treatment (such as the ACE inhibitor plus diuretic) helps to improve adherence.

Do Angiotensin receptor blockers (ARBs) have the same role as ACE inhibitors ? Although ARBs prevent the progression and development of heart failure (VALIANT and CHARM) we await the results of the ON-TARGET and TRANSCEND studies to reveal whether the ARBs and ACEi have similar and additive vascular protective properties.

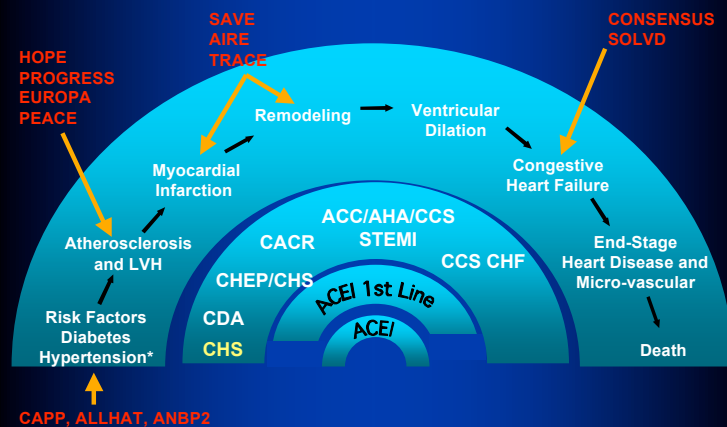
Role of ACE Inhibitor in the Cardiovascular Continuum

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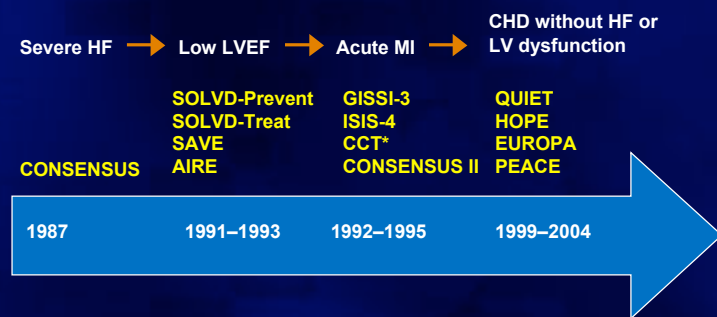
- Lifestyle modifications
 - Smoking cessation
 - Weight loss
 - Exercise
 - Diet
 - Lipid lowering
 - Glycemic control
 - ASA
 - ACE inhibition
 - Blood pressure control
- } For all
- } Selected

Role of ACEI Along the Cardiovascular Continuum: A Reflection of Mortality Benefits and Guidelines



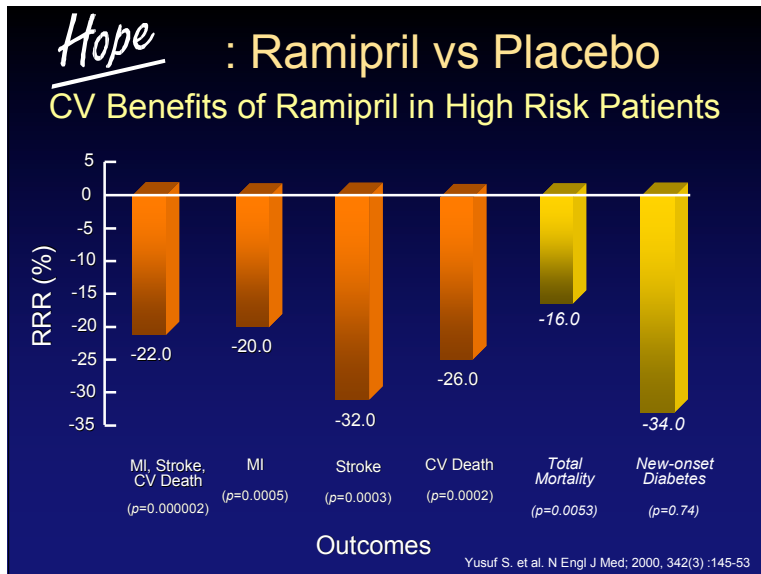
* ISH without compelling indications initial treatment ARB Adapted from Dzau V, Braunwald E. Am Heart J. 1991;121:1244-1263.

Evolution of ACE inhibition for treating patients with CHD



*Chinese Captopril Trial

Adapted from Yusuf S, Lonn E. Eur Heart J. 1998;19(suppl J):J36-44. Lonn EM et al. Circulation. 1994;90:2056-69.



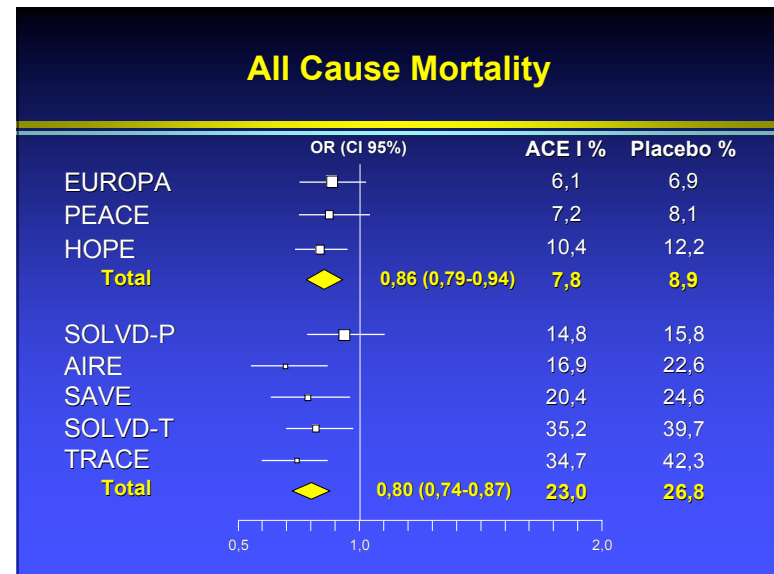
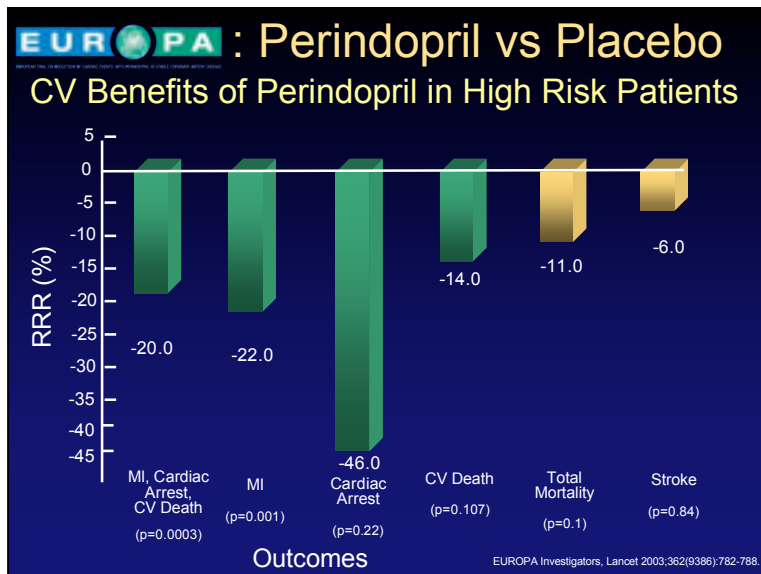
Hope Benefits of Ramipril in a Wide Range of Patient Subsets and Outcomes

Benefit in wide range of clinically relevant patient subsets

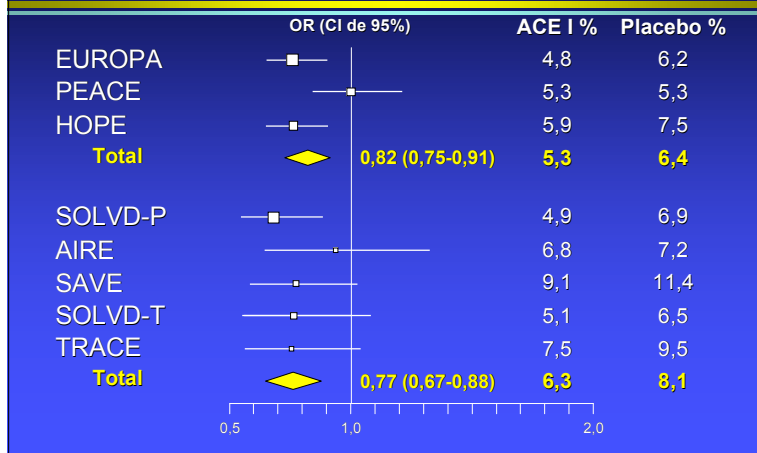
- **Diabetes**
Gerstein H et al Lancet 2000;355:253
- **Peripheral vascular disease**
Ostergreen J et al Eur Ht J 2000
- **Women**
Lonn E et al JACC 2002;40:693
- **Elderly patients**
Probstfield J et al ACC 2002
- **Early renal insufficiency**
Mann J et al Ann Int Med 2001;134:629
- **Microalbuminuria**
Mann J et al Am J Kid Dia 2003;43:936

Benefit in wide range of clinically relevant outcomes

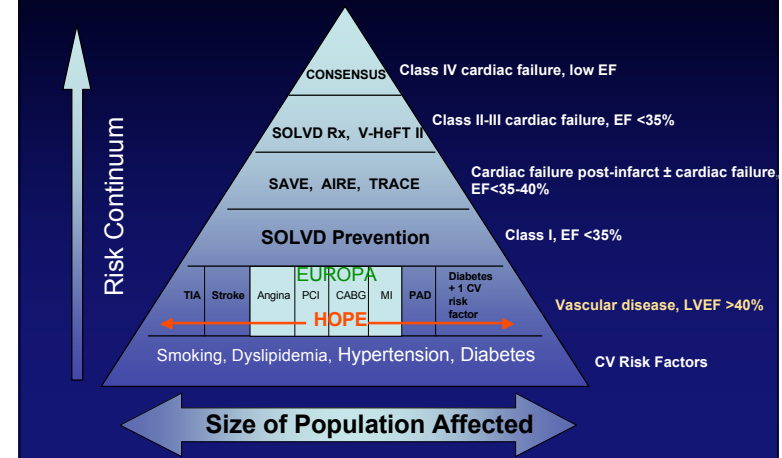
- **Myocardial Infarction**
Dagenais G et al Circ 2001;104
- **Stroke**
Bosch J et al BMJ 2002;324:699
- **Heart failure**
Arnold M et al Circ 2004
- **Sudden cardiac death**
Teo K et al Circ 2004
- **New Diabetes**
Yusuf S et al JAMA 2001;134:



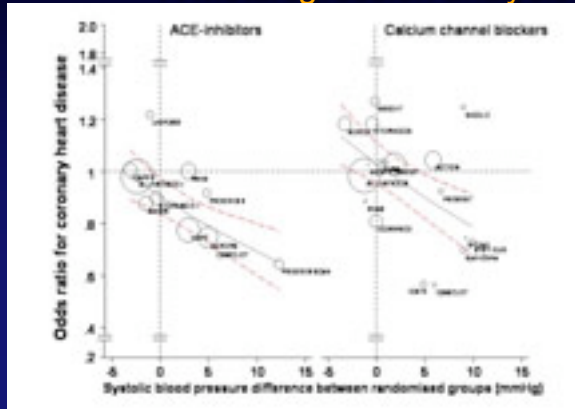
Non Fatal MI



Evolving Role of ACE Inhibitors



At any level of BP reduction, protection from CHD is greater with ACEIs than with CCBs
A Metaregression analysis



Verdecchia P, et al
Hypertension 2005

Rationale for using ACE Inhibitor in Patient with CAD

- BP lowering
- Improved CV hemodynamics (CHF)
- Reduction of LVH
- Improved endothelial function
- Decreased risk of plaque rupture
- Favourable shift anti-thrombotic balance

→ Reduced Athero-thrombosis
Reduced clinical events
→ Reduces LV adverse remodeling
Reduced heart failure

Conclusions

- RCT with tens of thousands of patients show capacity of ACE inhibitor to reduce most CV events in patients with CAD with and without LV dysfunction
- ACE inhibitor should be part of routine treatment for secondary prevention in all patients with CAD