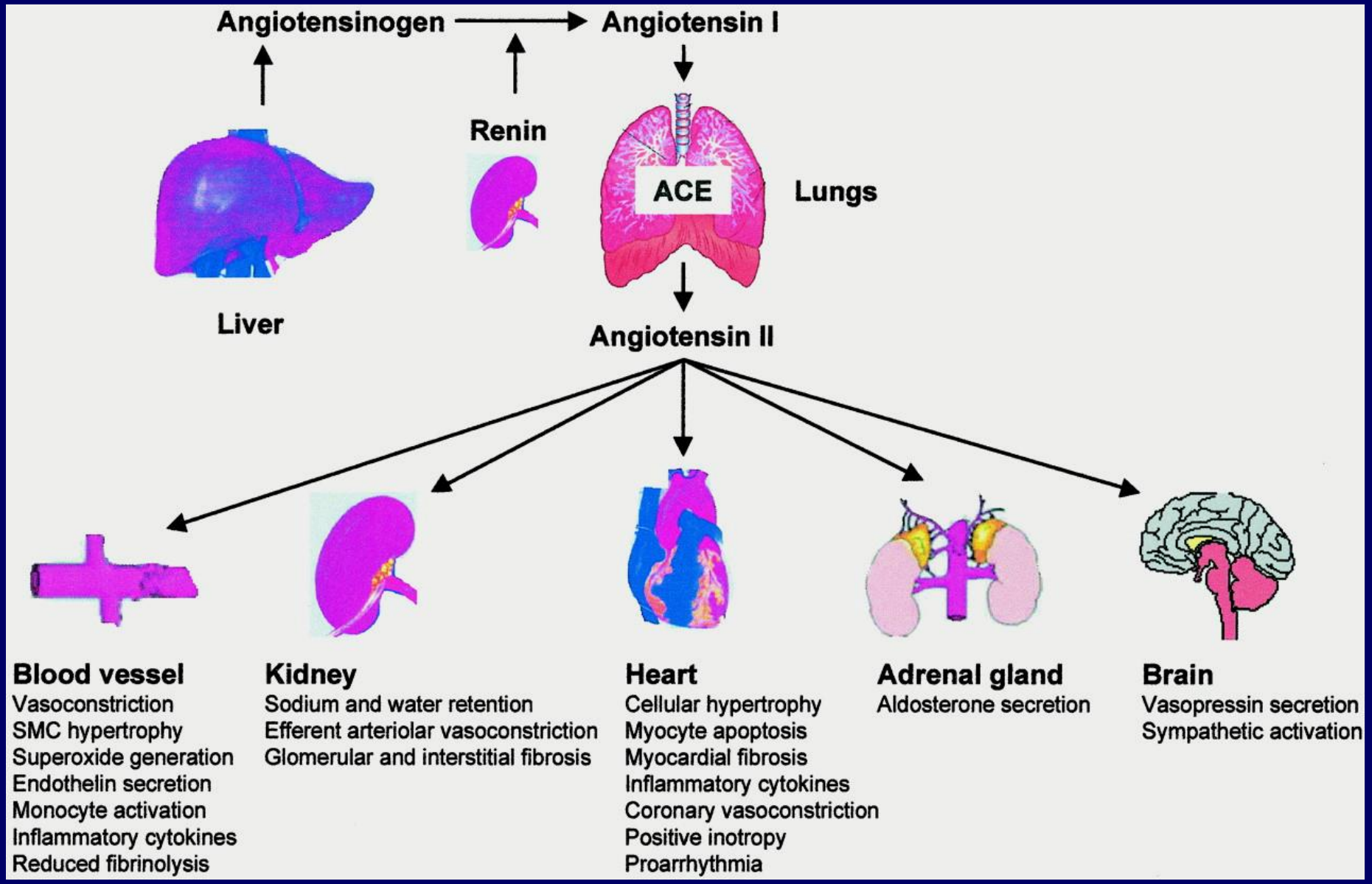
INIBITORI DEL SRA NEL TRATTAMENTO IMA


Angiotensinogen
Angiotensin I
Renin
ACE
Lungs
Liver
Angiotensin II
Blood vessel
Vasoconstriction
SMC hypertrophy
Superoxide generation
Endothelin secretion
Monocyte activation
Inflammatory cytokines
Reduced fibrinolysis
Kidney
Sodium and water retention
Efferent arteriolar vasoconstriction
Glomerular and interstitial fibrosis
Heart
Cellular hypertrophy
Myocyte apoptosis
Myocardial fibrosis
Inflammatory cytokines
Coronary vasoconstriction
Positive inotropy
Proarrhythmia
Adrenal gland
Aldosterone secretion
Brain
Vasopressin secretion
Sympathetic activation

Meccanismi di controllo del rilascio della renina

Fattori stimolanti

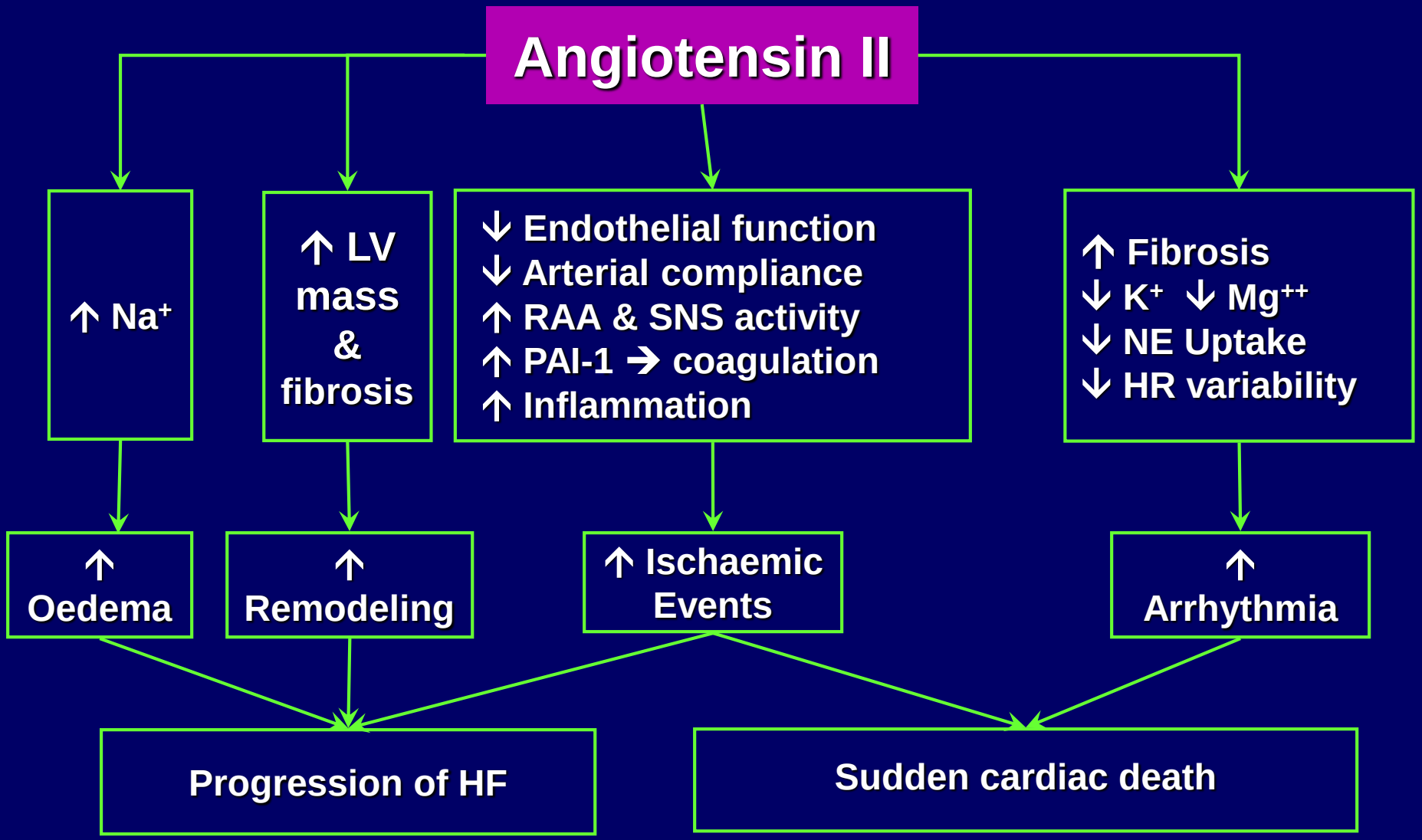
- **Bassi livelli di NaCl**

- **Ridotta pressione nell'arteriola efferente**
- **Attivazione recettori beta-1 c. iuxtaglomerulari**

Fattori inibenti

- **Feedback negativo dell' AII**
- **ANF**
- **Ossido nitrico**
- **Chinine**

Angiotensin II and Cardiovascular Damage



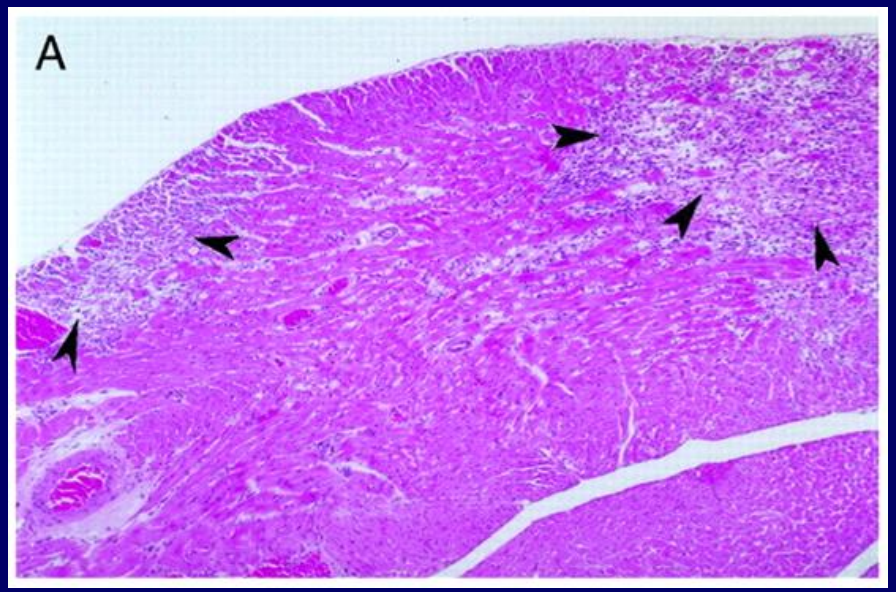
Biological Responses Mediated by AT Receptors in the Human Cardiovascular System

Biological response	Receptor mediation
Vasoconstriction	AT_1
Smooth muscle proliferation	AT_1
Norepinephrine release	AT_1
Aldosterone release	AT_1
Mild positive inotropic effect	AT_1
Cardiac myocyte growth	AT_1
Fibroblast proliferation	AT_1
Myocyte apoptosis	AT_1, AT_2
Cardiac myocyte toxicity	β-AR via NE release

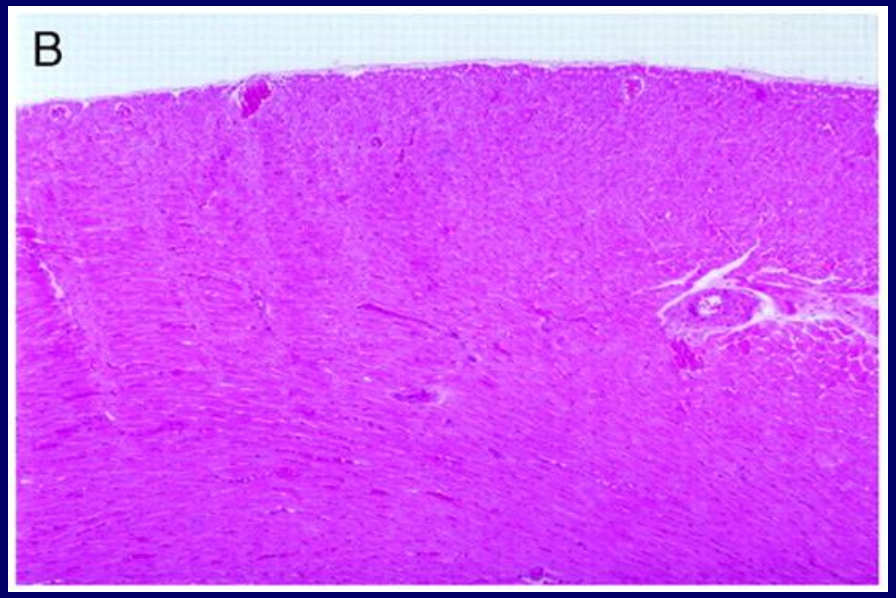
(from Braunwald E, Heart Disease 6th Edition, 582)

Aldosterone is a Mediator of Myocardial Necrosis: Results in a Rat Model of Cardiac Injury

L-NAME/AngII/NaCl treatment
Multiple necrotic lesions



L-NAME/AngII/NaCl + Eplerenone
Absence of necrotic lesions



Rocha et al. Endocrinology 2000; 141:3871

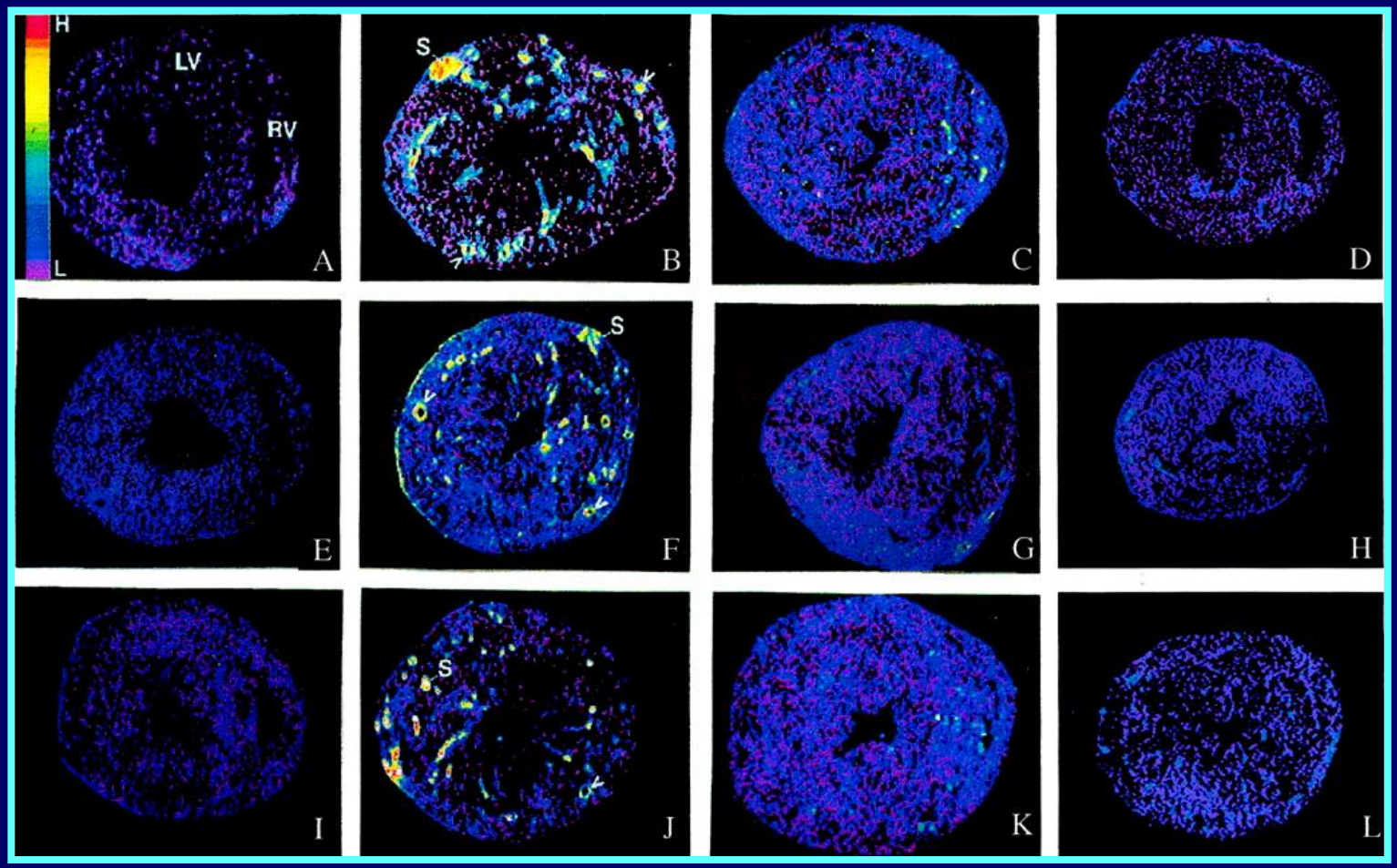
Aldosterone Causes the Expression of Inflammatory Factors in the Rat Myocardium

Normal | ALD/Salt | PTDC (antioxidant) | Spiro (antiald.)

ICAM-I

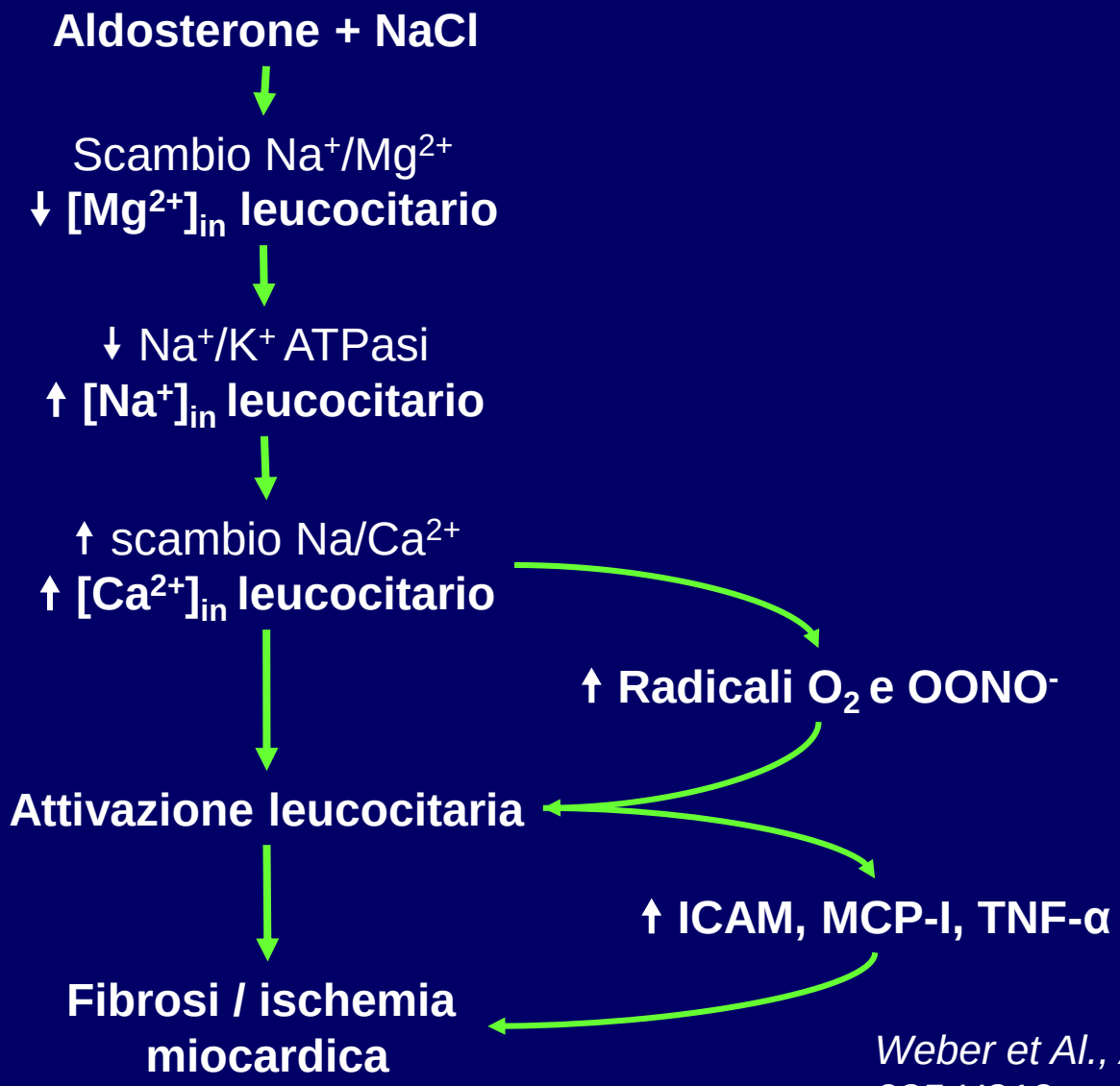
MCP-I

TNF-α



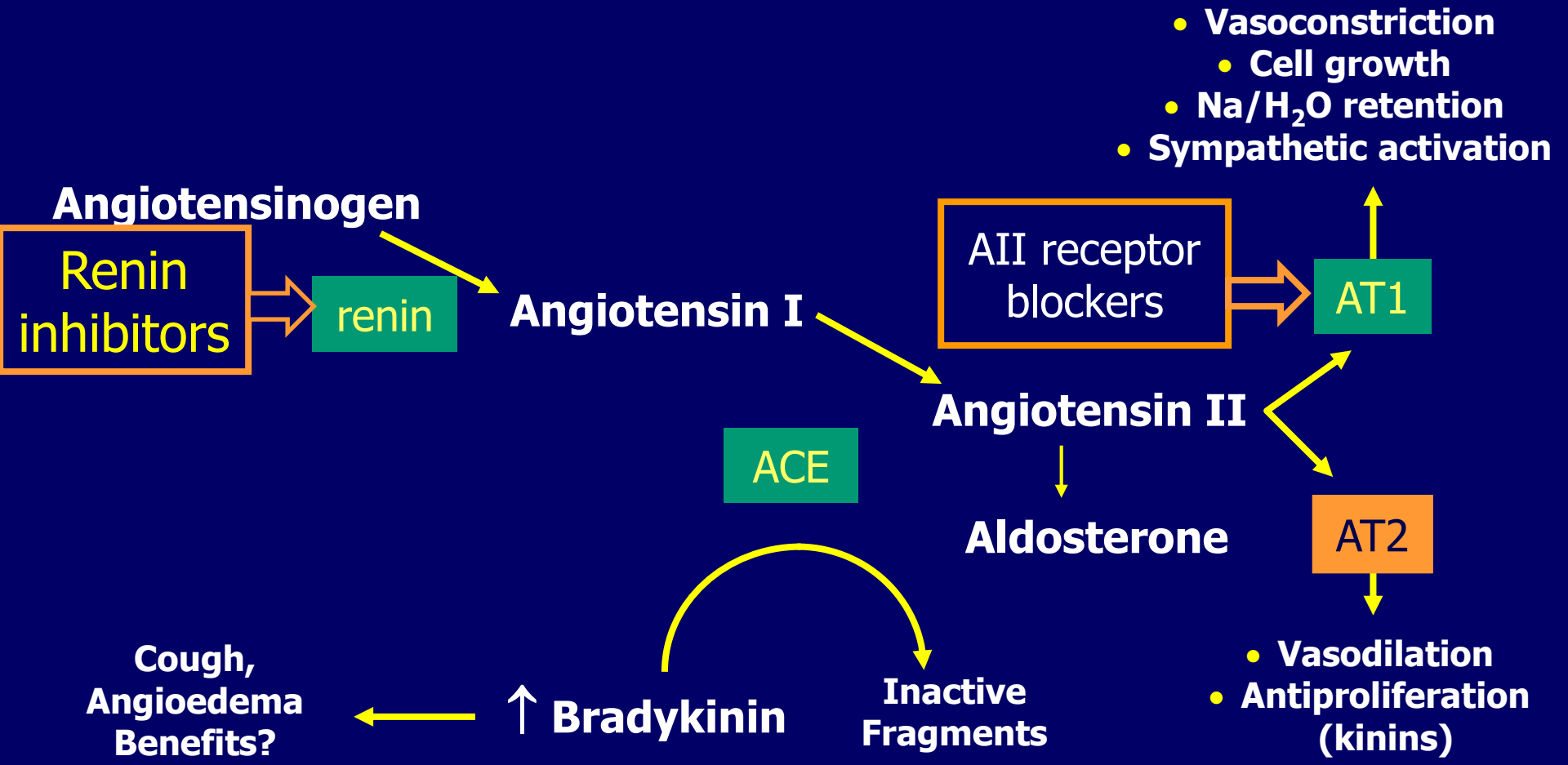
Sun et al. Am J Pathol 2002; 161:1773

Aldosterone, Stimolazione Immunitaria e Danno Cardiovascolare



Weber et Al., Am J Physiol 2003, 285:H813. modificata

Pharmacologic modulation of the Renin-Angiotensin System



Guidelines for the management of AMI

ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC)

Authors/Task Force Members: Ph. Gabriel Steg (Chairperson) (France)*, Stefan K. James (Chairperson) (Sweden)*, Dan Atar (Norway), Luigi P. Badano (Italy), Carina Blömstrom-Lundqvist (Sweden), Michael A. Borger (Germany), Carlo Di Mario (United Kingdom), Kenneth Dickstein (Norway), Gregory Ducrocq (France), Francisco Fernandez-Aviles (Spain), Anthony H. Gershlick (United Kingdom), Pantaleo Giannuzzi (Italy), Sigrun Halvorsen (Norway), Kurt Huber (Austria), Peter Juni (Switzerland), Adnan Kastrati (Germany), Juhani Knuuti

ACE inhibitors: mechanisms of action

Infarction expansion and remodeling

ACE inhibitors therapy started within 24 hours in all patients with an AMI.

ARBs are recommended in patients who are intolerant of ACE inhibitors

Combination of ACE inhibitors and ARBs is not recommendate

Rodrigues et al Am J Med 2003; 115: 473

ACE inhibitors: Contraindications

Allergy, history of bilateral renal artery stenosis

Hypotension(SBP≤ 100 mmHg, SBP≥30 mmHg baseline)

Shock, prior worsening renal function with ACE inhibitor

Recommendations of ACC/AHA

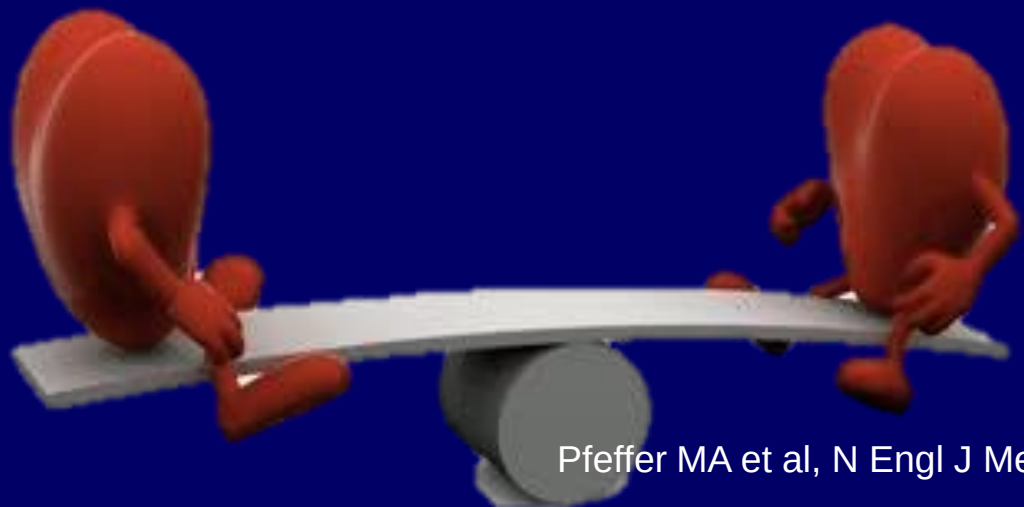
- Dosing oral administration at low doses monitoring of the blood pressure (↓nitroglycerin and diuretic) continuing indefinite time
- The concomitant use of betablocker can reduce blood pressure

Recommendations of ACC/AHA

- ACE vs ARBs

VALIANT (Valsartan in Acute Myocardial Infarction) Captopril vs Valsartan non significant trend toward lower mortality at 2,7 years captopril vs losartan (16.4 vs18.2% RR 0.88,95% CI 0,78-1.01)

- VALIANT no difference in the primary end point of all cause of mortality 20 % however adverse events increase in the combination therapy



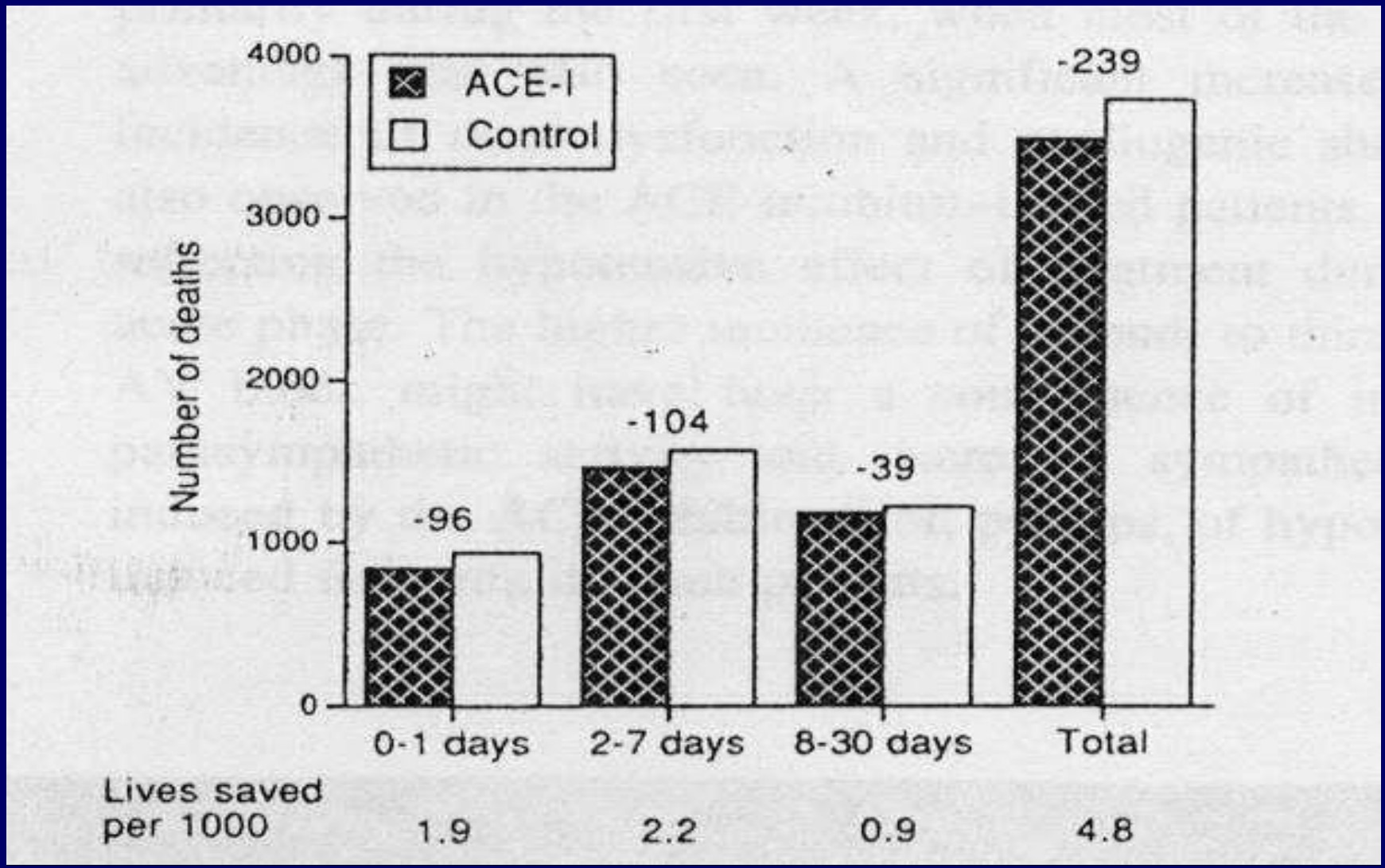
Pfeffer MA et al, N Engl J Med 2003 ; 349 : 1893-1906

EPHESUS (Eplerenone post-AMI Heart Failure Efficacy and Survival Study

- I pazienti sono stati randomizzati a ricevere Eplerenone (25mg/die, fino ad un massimo di 50 mg/die; n pazienti=3.313) o placebo (n pazienti= 3.319), oltre alla terapia standard.
- follow-up di 16 mesi, ci sono state 478 morti nel gruppo Eplerenone e 554 morti nel gruppo placebo (rischio relativo: 0,85; p=0.008).
- incidenza di gravi iperpotassiemie è stata del 5,5% nel gruppo Eplerenone e 3,9% nel gruppo placebo (p=0.02) mentre la percentuale di ipopotassiemia è stata dell'8,4% nel gruppo Eplerenone e del 13% nel gruppo placebo (p<0.001)

Pitt B et al, N Engl J Med 2003; 348:1309-1321

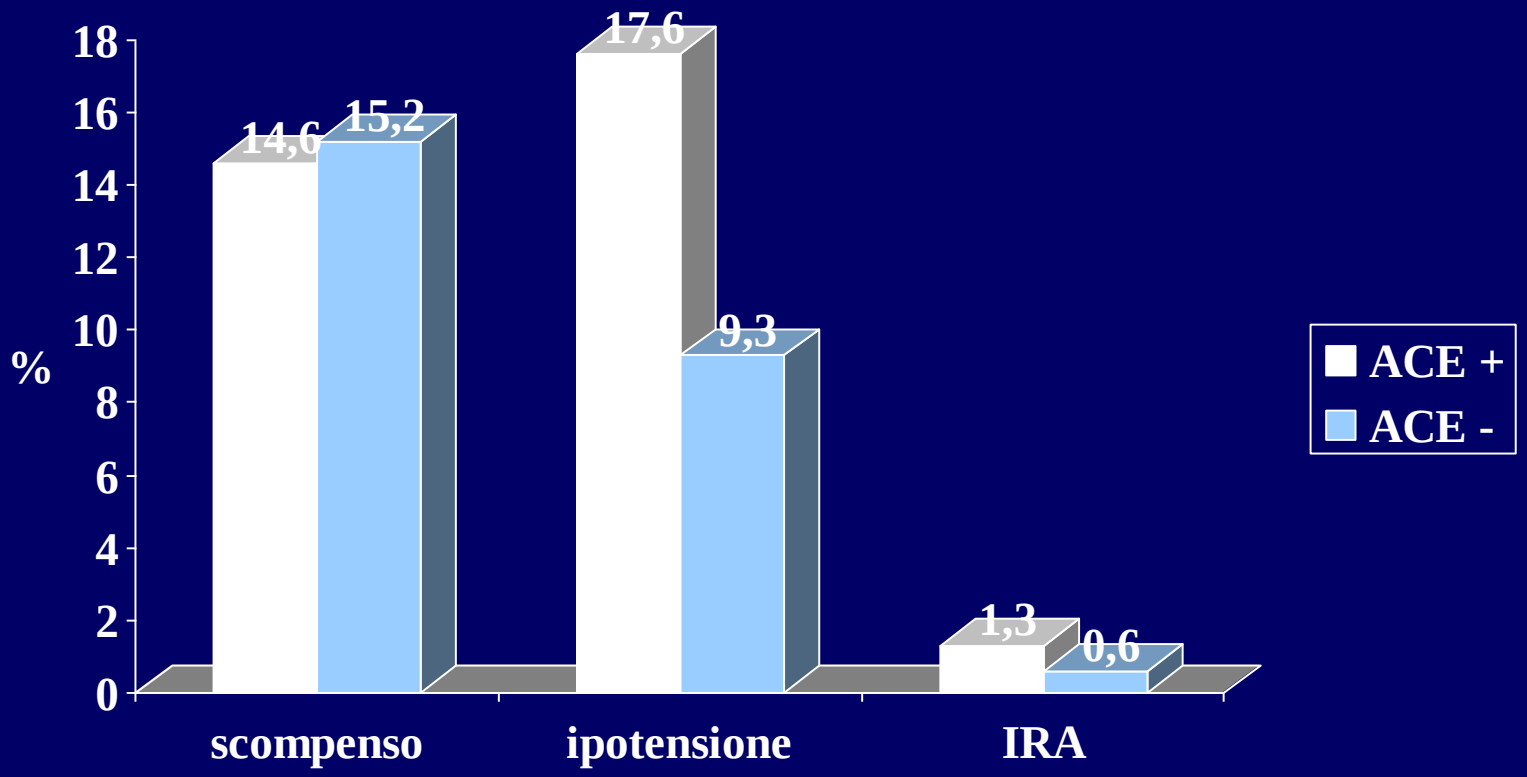
SHORT TERM TRIALS (98.496 paz)
mortalità 1 mese: 7.1% vs 7.6% (-7%)



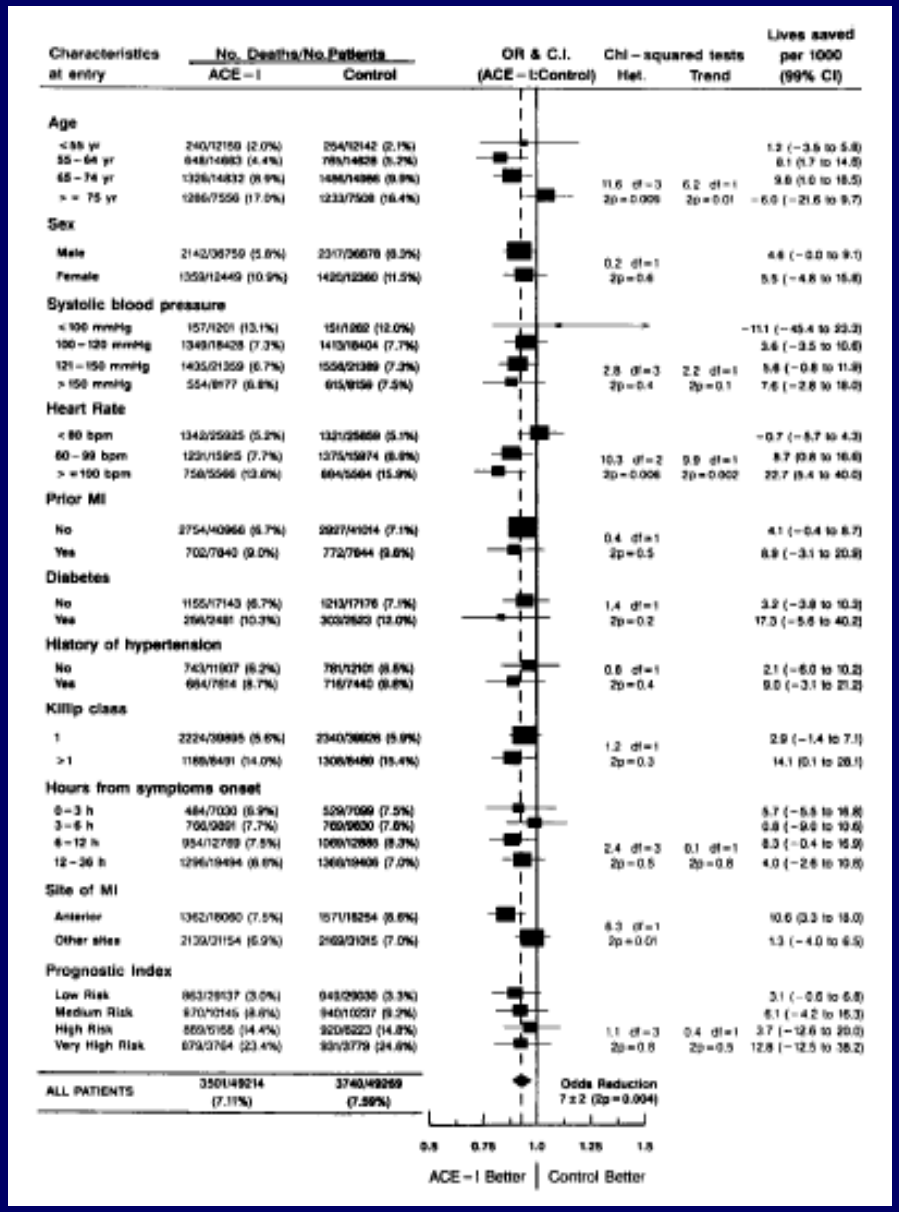
(ACE Inhibitor Myocardial Infarction Collaborative Group. 1998)

SHORT TERM TRIALS

- 6 eventi per 1000paz



SHORT TERM TRIALS
ANALISI SOTTOGRUPPI

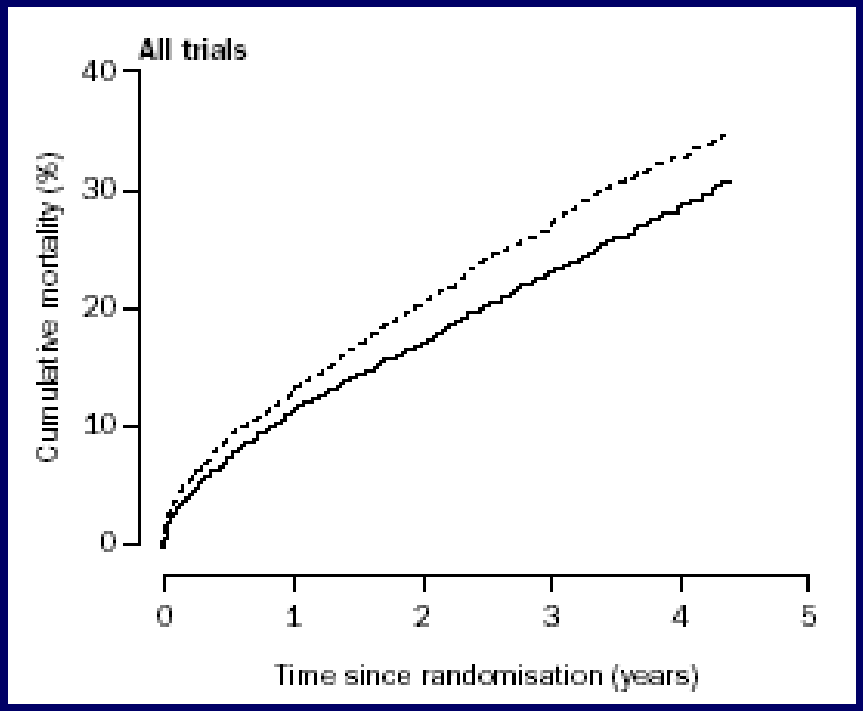


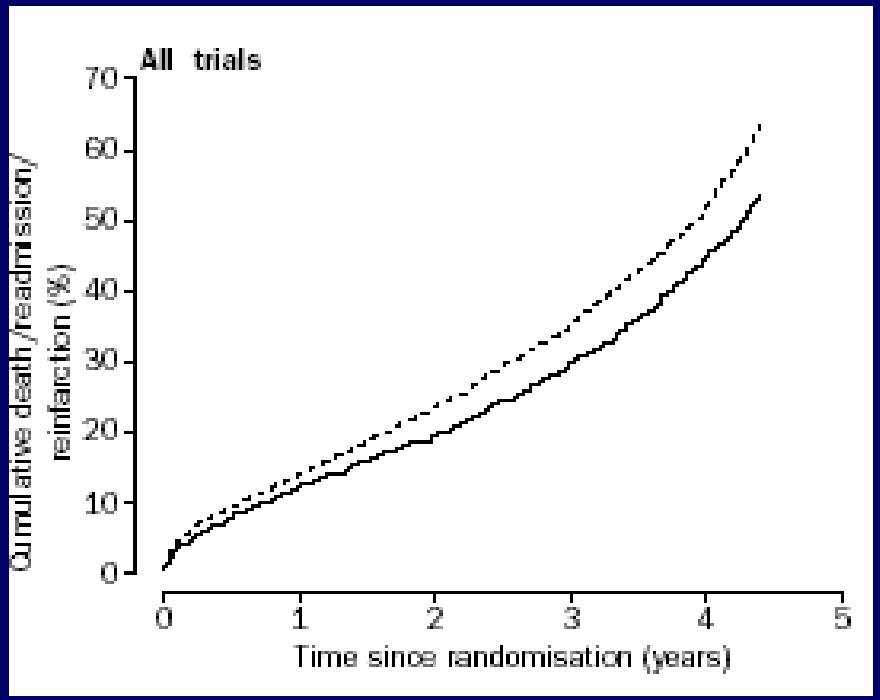
LONG TERM TRIALS (> 1 anno)

ACE –

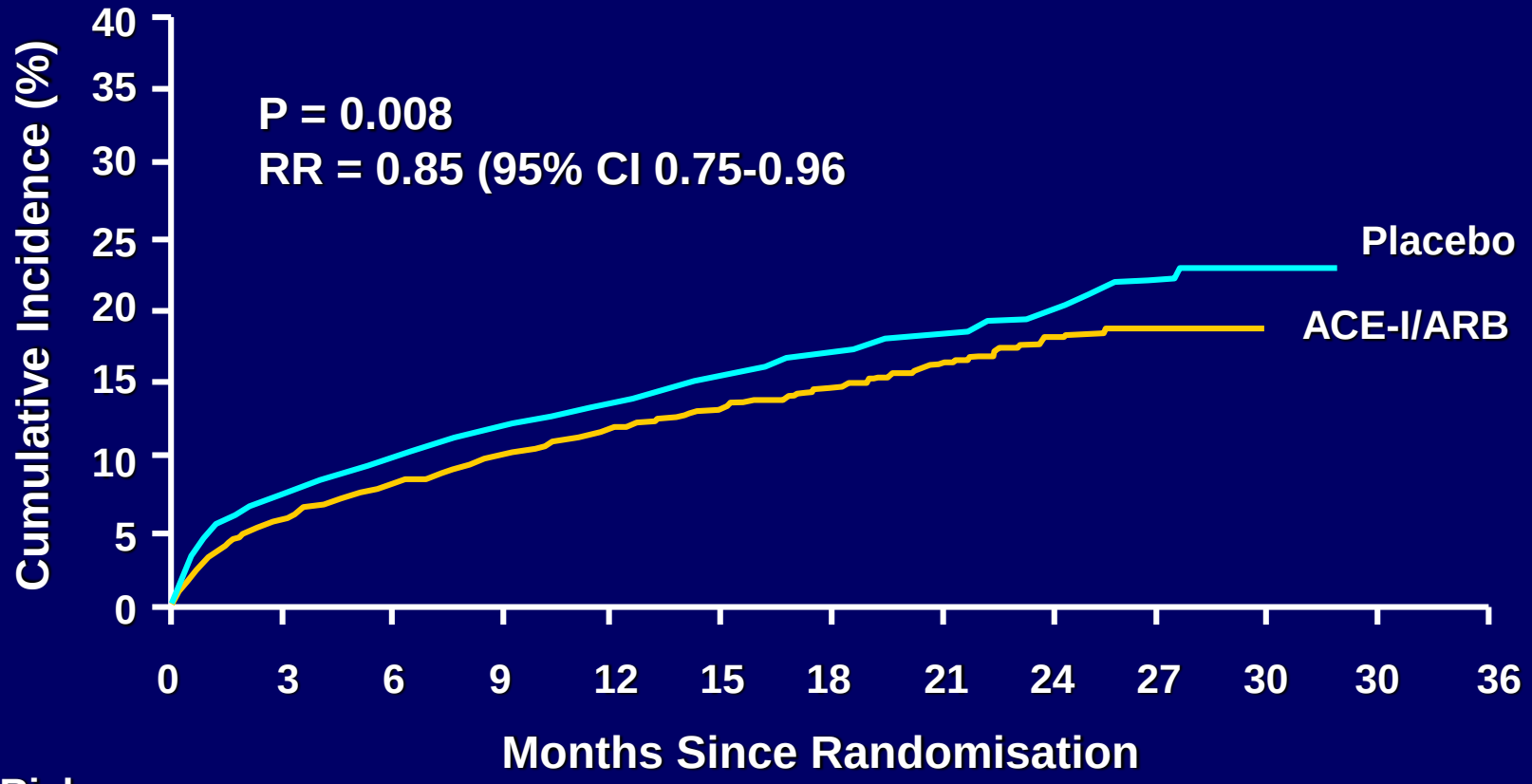
Controllo . . .

- 28%





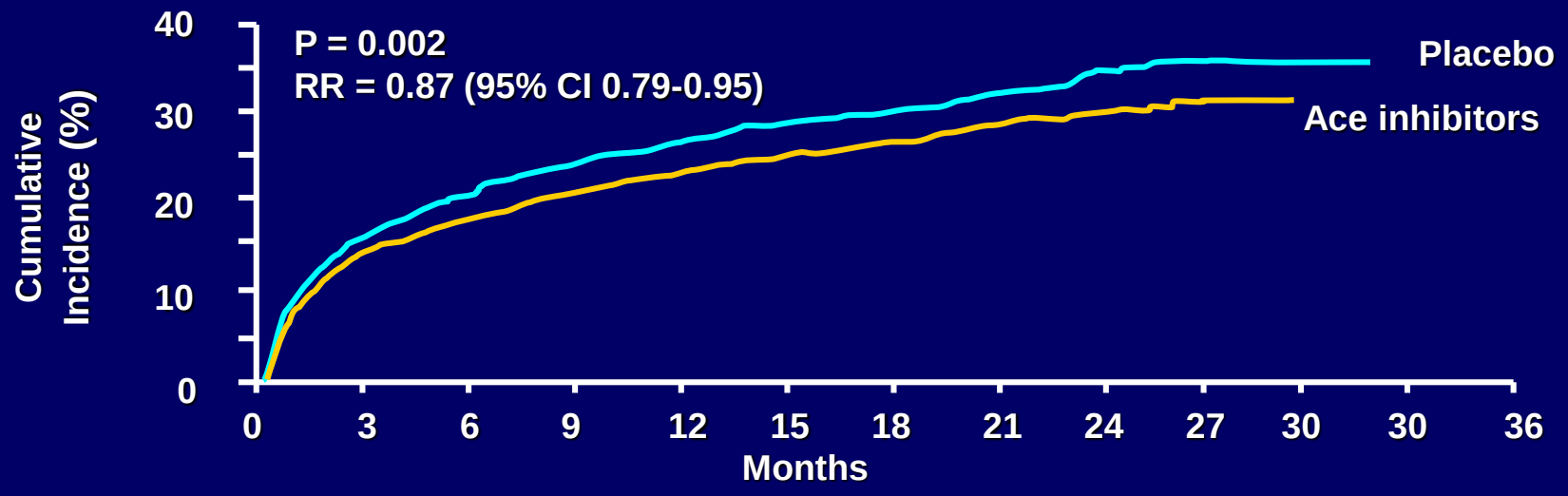
Effetti di bloccante del SRA dopo IMA



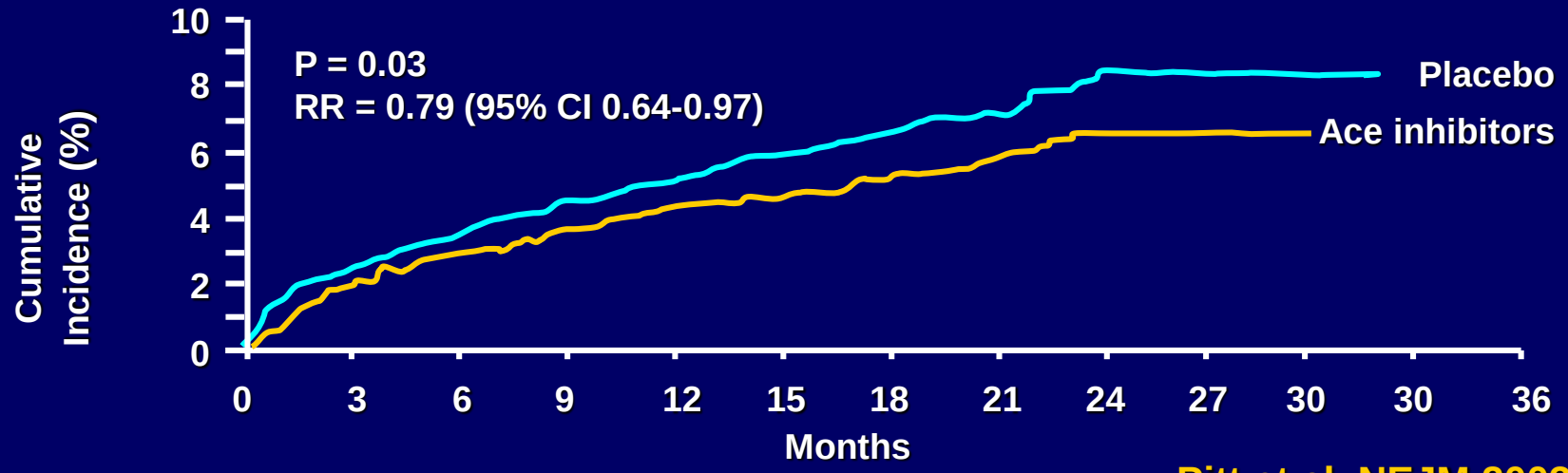
No. at Risk													
Placebo	3313	3064	2983	2830	2148	1801	1213	709	323	99	2	0	0
ACE-I/ARB	3319	3125	3044	2896	2463	1857	1260	728	336	110	0	0	0

Pitt et al. NEJM April 2003

Death or Hospitalisation from Cardiovascular Causes



Sudden Death from Cardiac Causes



Pitt et al. NEJM 2003

STRATEGIE IMPIEGO ACE - I

- Inizio precoce in tutti i paz con IMA che non presentino controindicazioni e rivalutazione alla dimissione o dopo alcune setttimane

- Utilizzo a lungo termine solo in categorie particolari di paz quali gli IMA anteriori e paz ad alto rischio (presenza di tachicardia, scompenso cardiaco, diabete mellito)