Renin Angiotensin System
Current and Potential Targets

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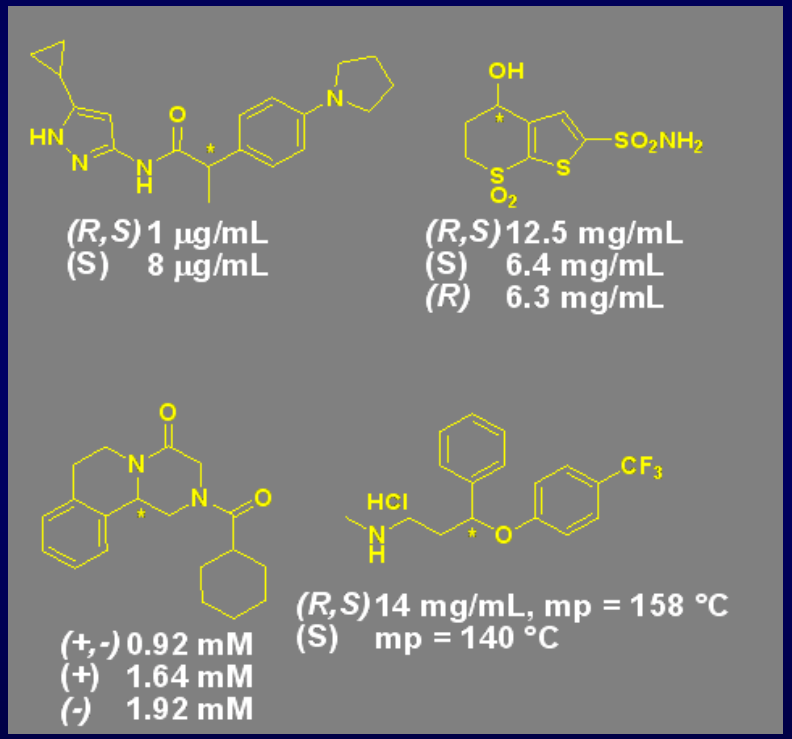
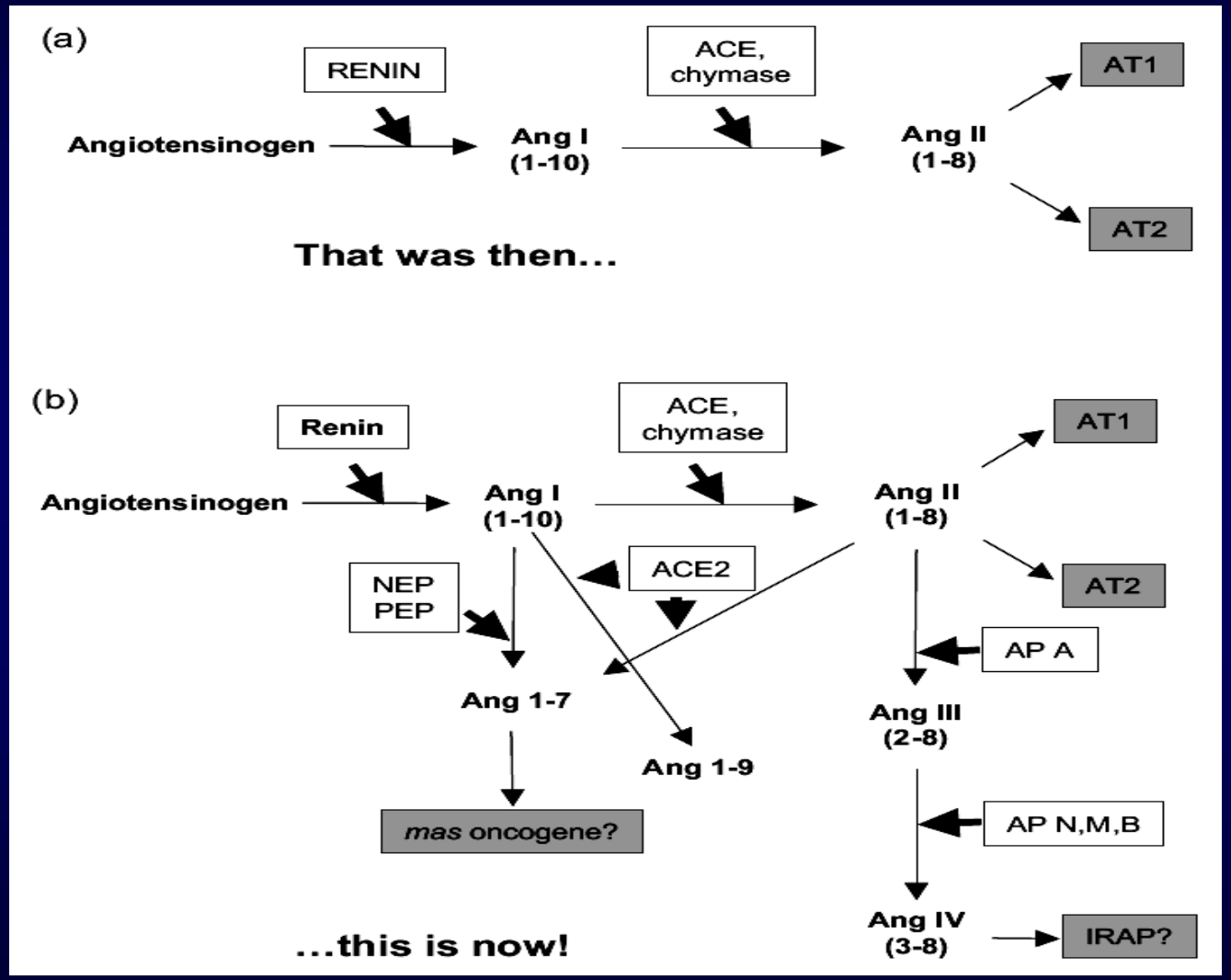
Renin – The First Component of RAS
More Than 100 Years of History



Robert Tigerstedt, the Finnish physiologist

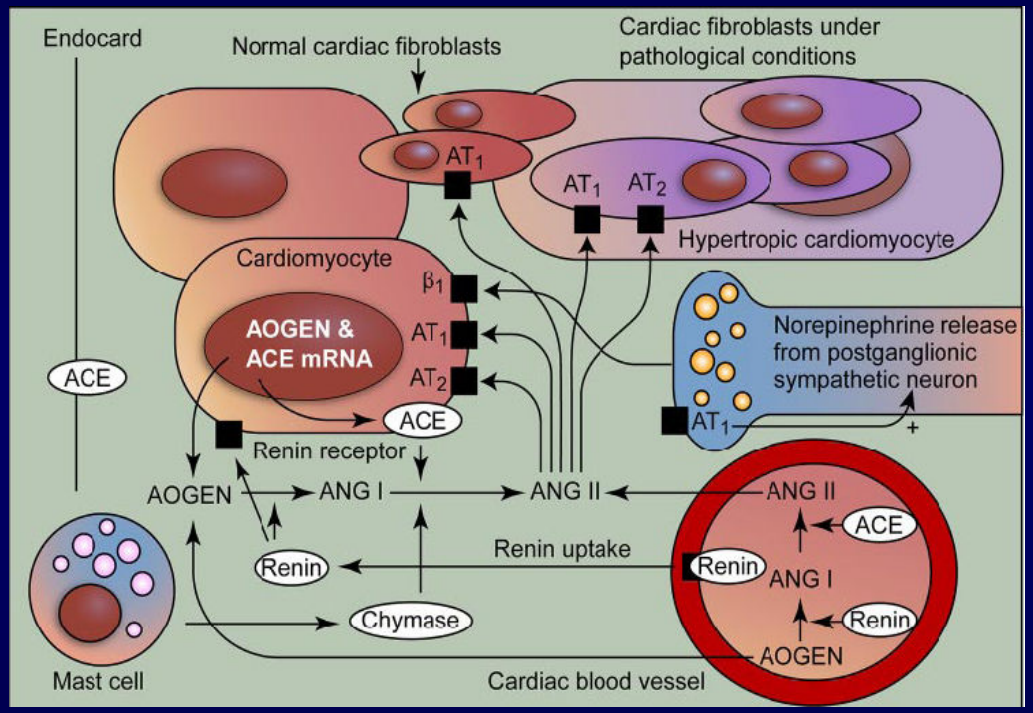
- *The first discoverer of renin*

The Renin-Angiotensin System - Then and Now



Reudelhuber. Curr Opin Nephrol Hypertens 2005;14:155-159

Local RAS Exists Everywhere



- Local RAS exists in heart, kidney, brain, vasculature, adipose tissue, testis, ovary and intestine.
- Most cardiac Ang II results from the conversion of local, rather than circulatory Ang I.
- The cardiac RAS can regulate Ang II within the heart independently of the systemic RAS.

Paul et al, Physiol Rev 2006;86:747-803

MacKenzie et al, JRAAS 2002;**3**:214-21

Effects of A II at AT_1 and AT_2 Receptors

AT_1

Sensitive to blockade by ARBs

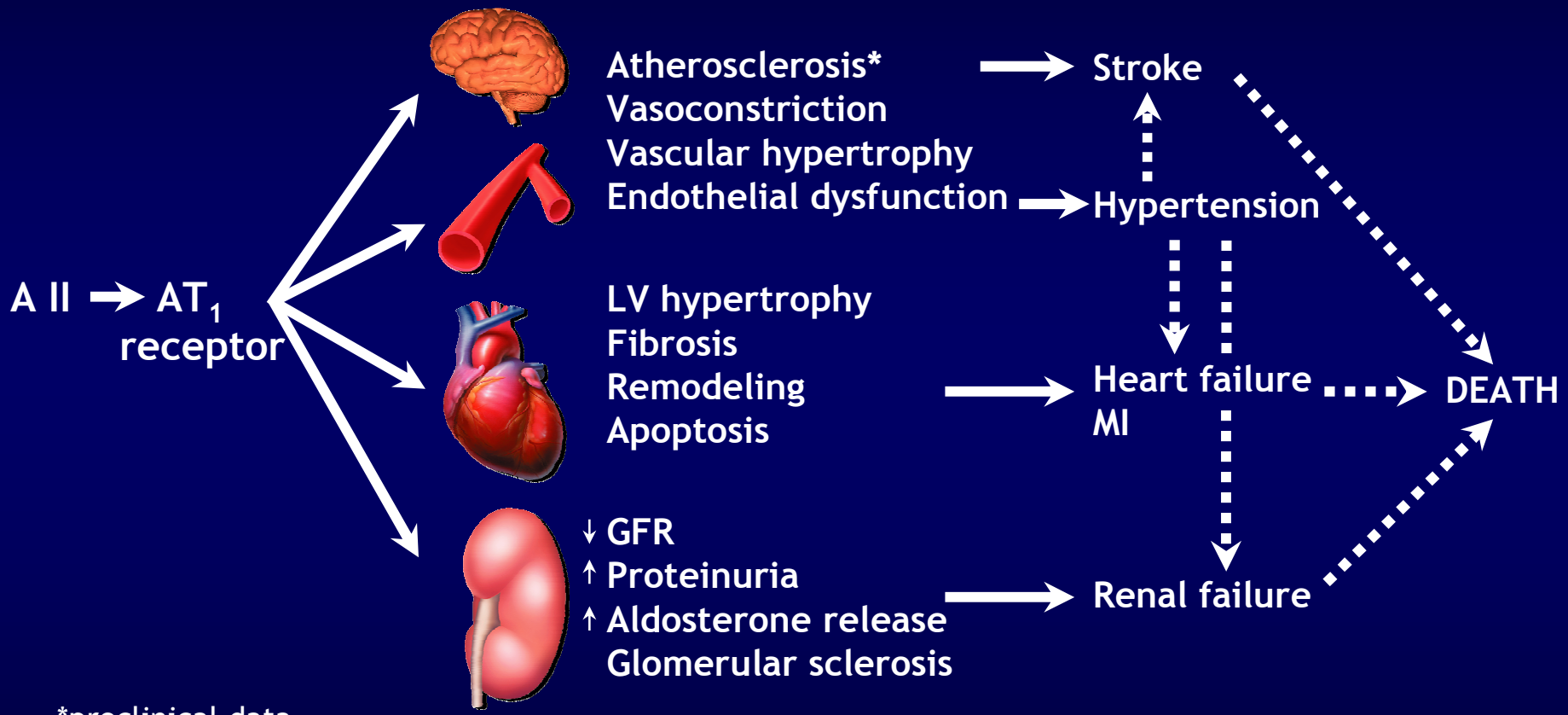
- Vasoconstriction
- Aldosterone release
- Oxidative stress
- Vasopressin release
- SNS activation
- Inhibits renin release
- Renal Na^+ & H_2O reabsorption
- Cell growth & proliferation

AT_2

- Vasodilation
- Antiproliferation
- Apoptosis
- Antidiuresis/antinatriuresis
- Bradykinin production
- NO release

Siragy H. Am J Cardiol. 1999;84:3S-8S.

Angiotensin II Plays a Central Role in Organ Damage



*preclinical data
LV = left ventricular; MI = myocardial infarction; GFR = glomerular filtration rate

Adapted from Willenheimer R et al Eur Heart J 1999; 20(14): 997–1008, Dahlöf B J Hum Hypertens 1995; 9(suppl 5): S37–S44, Daugherty A et al J Clin Invest 2000; 105(11): 1605–1612, Fyhrquist F et al J Hum Hypertens 1995; 9(suppl 5): S19–S24, Booz GW, Baker KM Heart Fail Rev 1998; 3: 125–130, Beers MH, Berkow R, eds. The Merck Manual of Diagnosis and Therapy. 17th ed. Whitehouse Station, NJ: Merck Research Laboratories 1999: 1682–1704, Anderson S Exp Nephrol 1996; 4(suppl 1): 34–40, Fogo AB Am J Kidney Dis 2000; 35(2):179–188

Involvement of RAS in Cardiovascular and Renovascular Diseases as Evidenced by Utilizing AIIAs

- Vascular remodeling/Atherosclerosis
  - ↓ Vascular hypertrophy (intima-media thickness)
  - Inhibition of LDL oxidation, Ox-LDL receptor expression, and Ox-LDL uptake
  - ↓ Fatty streaks (non-human primates)
  - Inhibition of inflammation (NF-κB activation, macrophage binding to endothelial cells, MCP-1 expression
  - ↓ COX-2 mRNA expression and COX-2-dependent TxA_2 and PGF_{2a} generation in human endothelial cells (via losartan metabolite EXP-3179)

Ferrario CM JRAAS 2006;7:3-14

Involvement of RAS in Cardiovascular and Renovascular Diseases as Evidenced by Utilizing AIIAs

- Cardiac remodeling
  - ↓ Left ventricular mass
  - ↓ Myocardial fibrosis
  - ↓ Collagen synthesis
- Arrythmogenicity
  - ↓ New onset atrial fibrillation
  - ↓ QT dispersion
  - ↓ Risk of stroke in hypertensive patients with LVH and atrial fibrillation
- Endothelial dysfunction
  - Improve endothelial function
  - ↑Extracellular superoxide dismutase in arterial wall, increasing the bioavailability of NO
  - Improve vasomotor function
  - ↓ Intercellular adhesion mulecule (ICAM-1) expression in endothelial cells

Ferrario CM JRAAS 2006;7:3-14

Involvement of RAS in Cardiovascular and Renovascular Diseases as Evidenced by Utilizing AIIAs

- Thrombus formation and platelet aggregation
  - ↓ Platelet aggregation
  - ↓ Platelet shape change (early phase of platelet activation) induced by Ang II and TxA_2 analogue
  - ↓ PAI-1
  - ↓ Tissue factor (initiates coagulation via factor VII)
- Impact on risk factors
  - ↓ New onset diabetes mellitus
  - ↓ Albuminuria

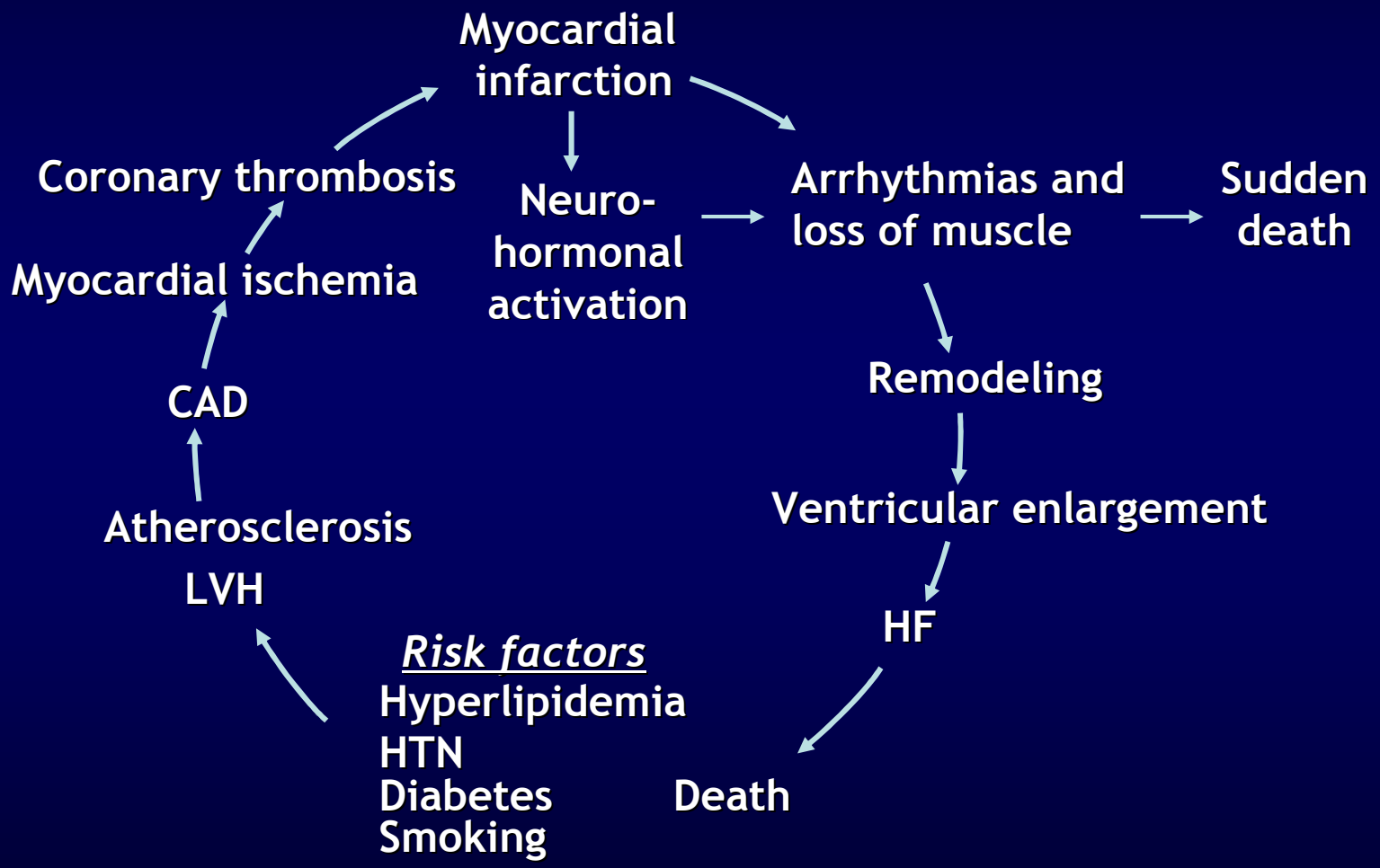
Ferrario CM JRAAS 2006;7:3-14

Involvement of RAS in Cardiovascular and Renovascular Diseases as Evidenced by Utilizing AIIAs

- Renal effects
  - ↓ Proteinuria in type 2 diabetes and non-diabetic nephropathy
  - ↓ TGF-β in type 2 diabetes mellitus and chronic allograft nephropathy
  - ↓ Oxidative stress and proinflammatory state of the kidney
  - Preservation of glomerular and tubulointerstitial structure (rats)
  - ↓ Pore size of glomerular membrane

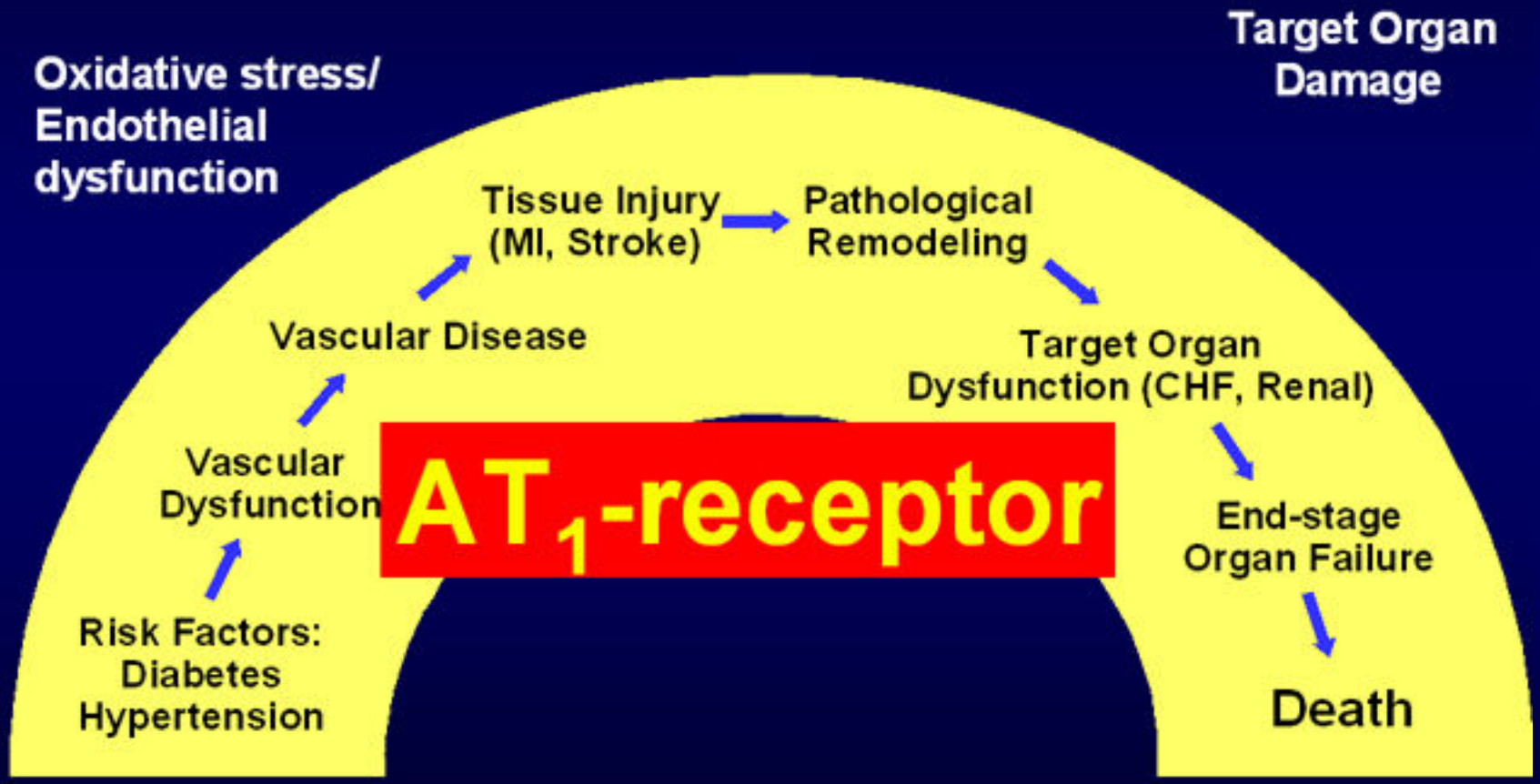
Ferrario CM JRAAS 2006;7:3-14

The Cardiovascular Continuum



Dzau V, Braunwald E. Am Heart J. 1991;121:1244-163.

The Cardiovascular Continuum:

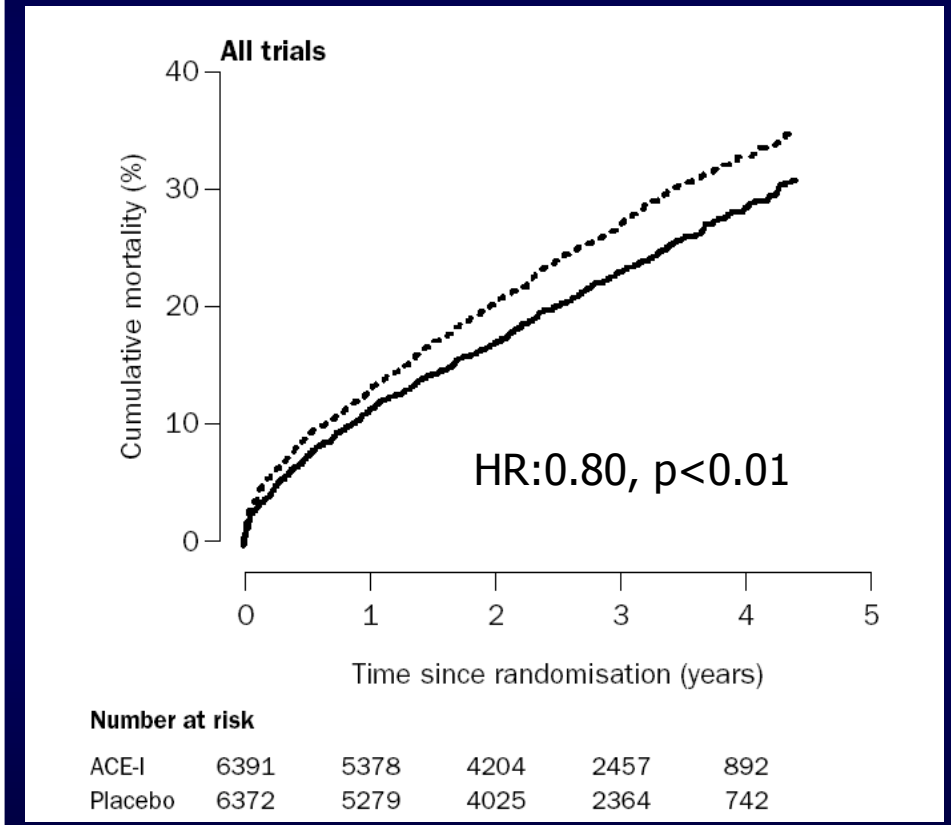


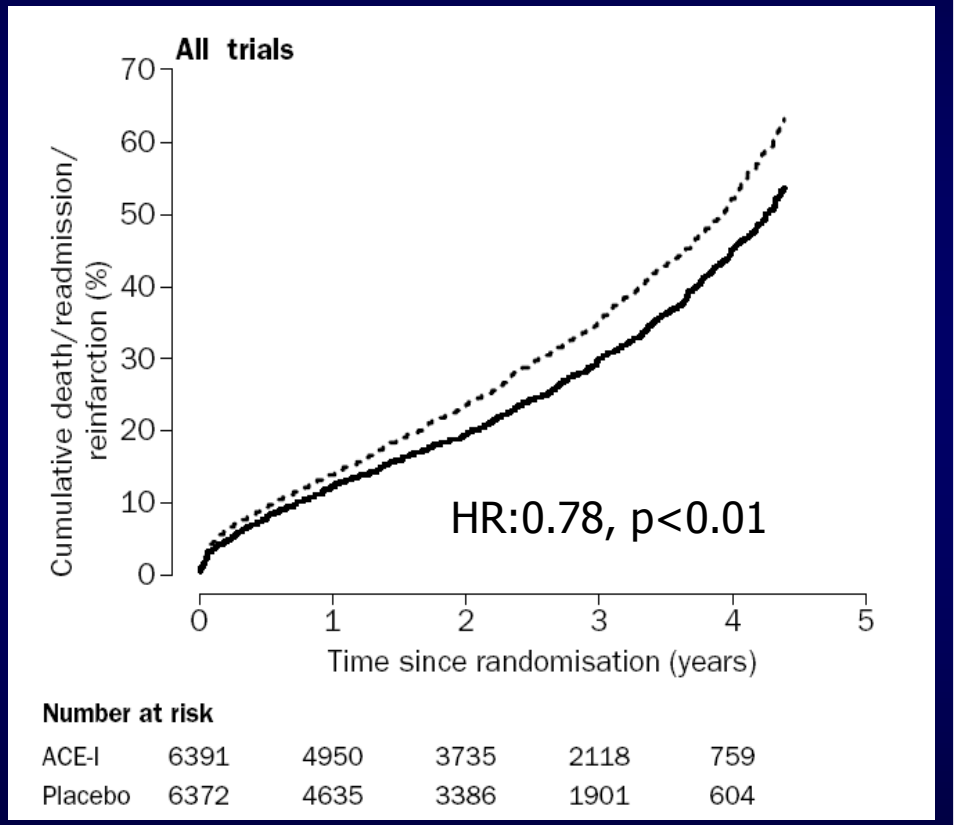
Adapted from Dzau V, Braunwald E. Am Heart J 1991;121:1244-163

Therapeutic Implication of RAS Blockade

- Target Organ Protection -

ACE Inhibitors Lower Rates of Adverse Outcomes in Patients with Heart Failure

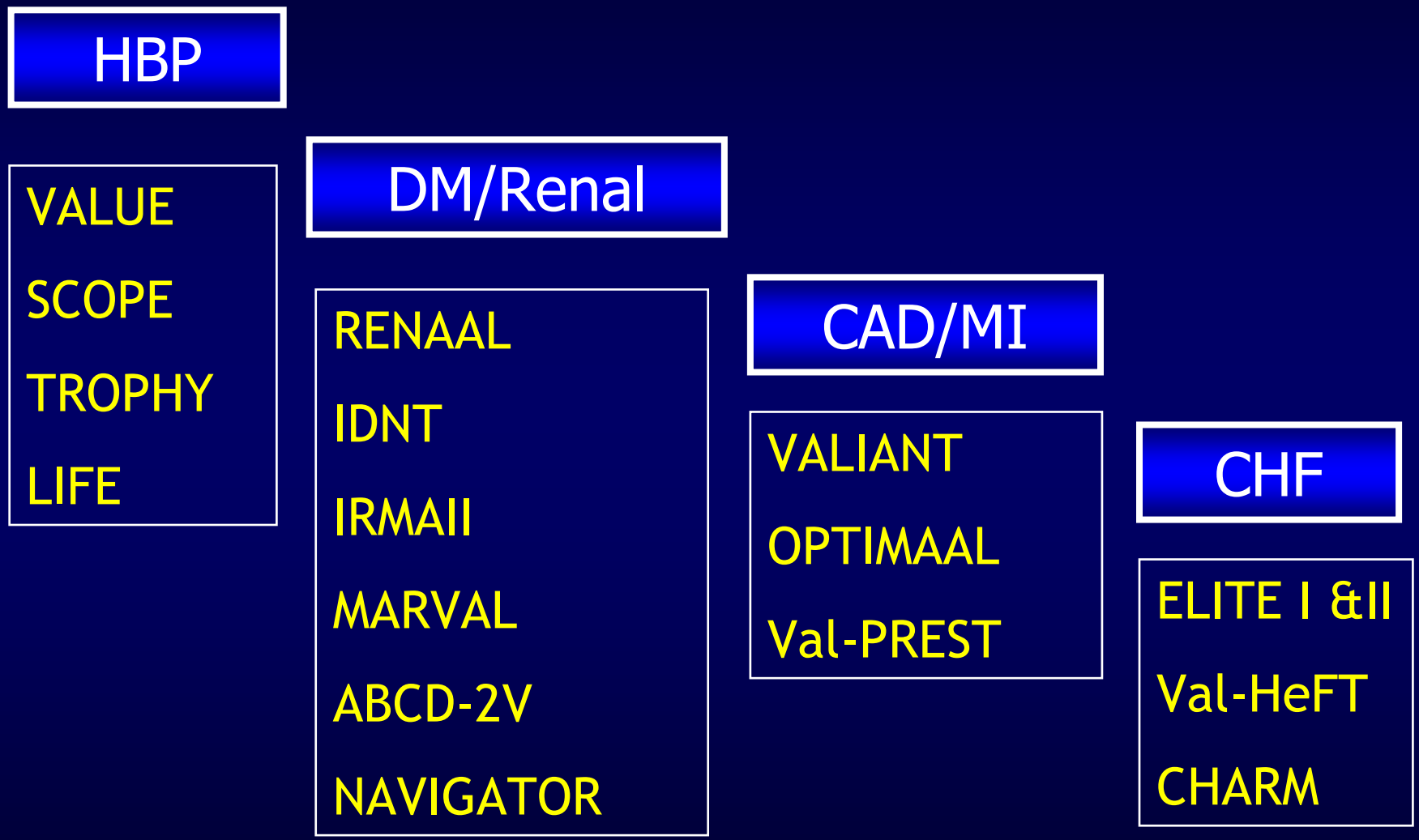




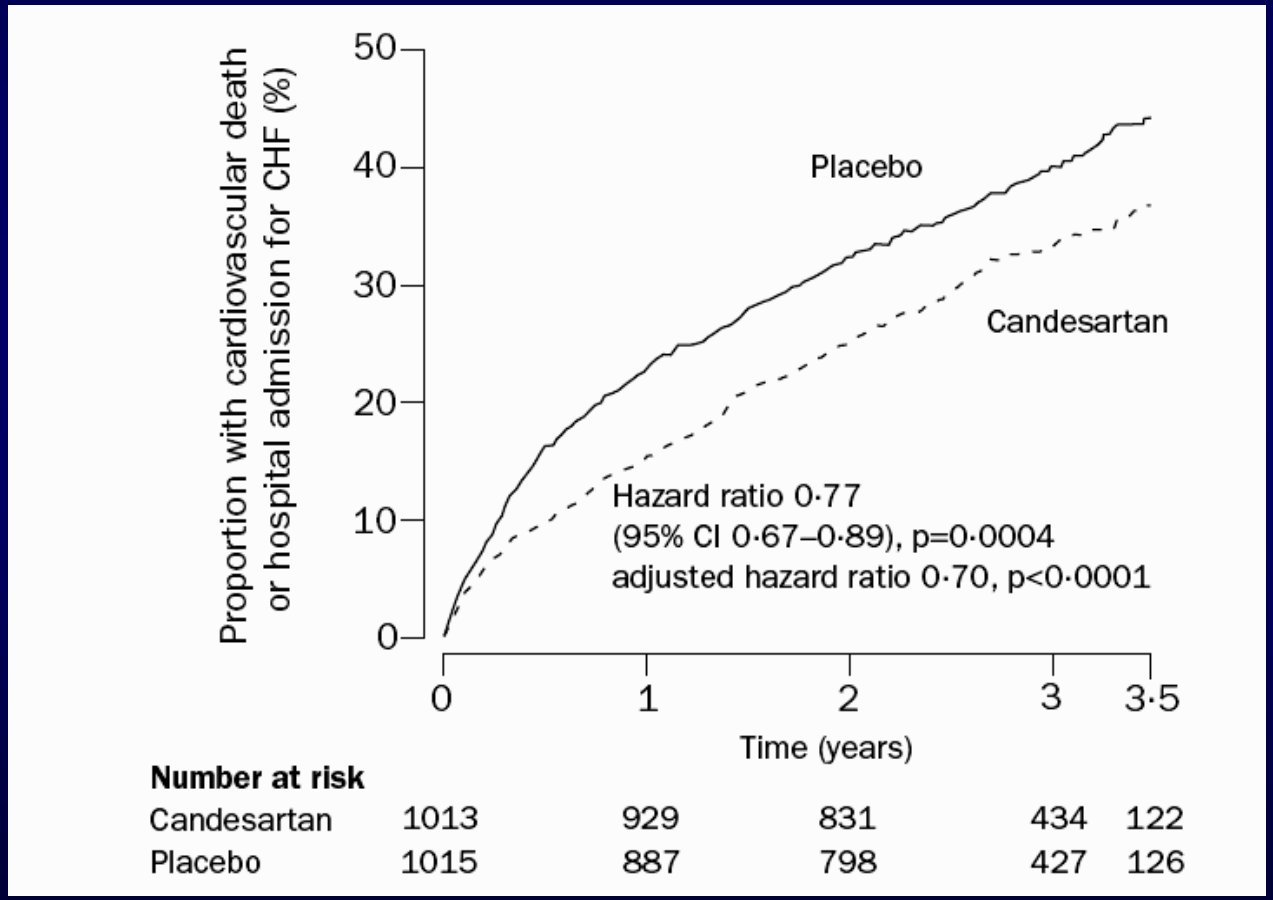
***All trials: SAVE, AIRE, TRACE, SOLVD**

Flather et al, Lancet 2000;355:1575-81

ARB Clinical Trials CV Diseases

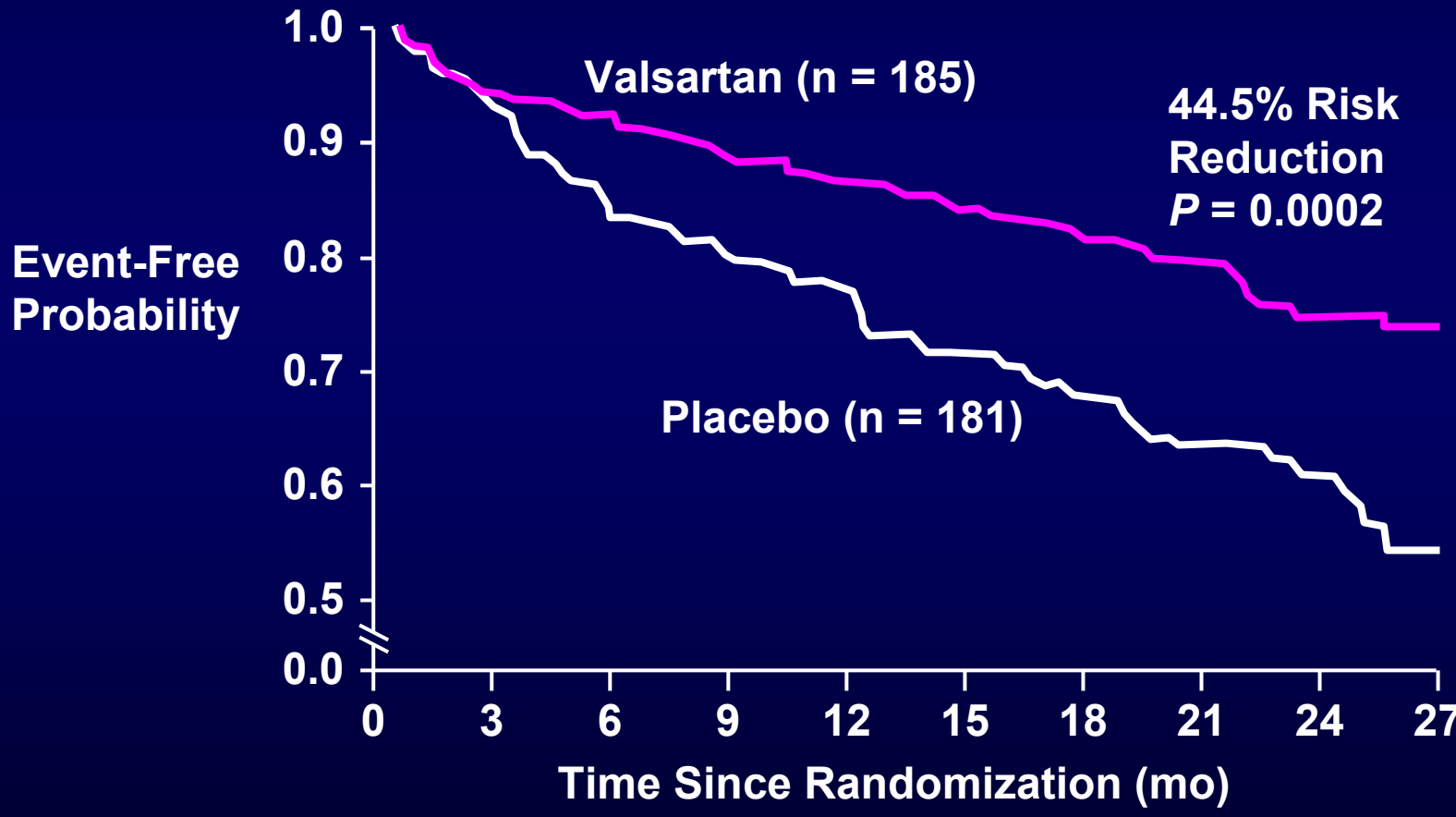


Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Alternative



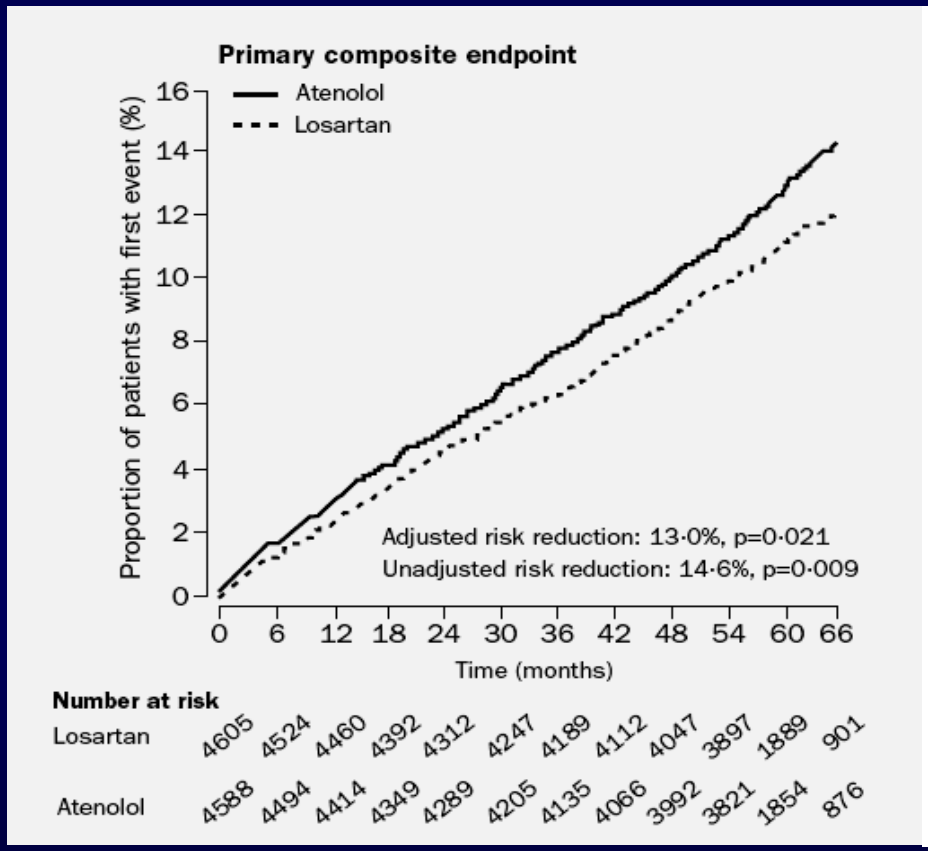
Granger et al, Lancet 2003; 362: 772-776

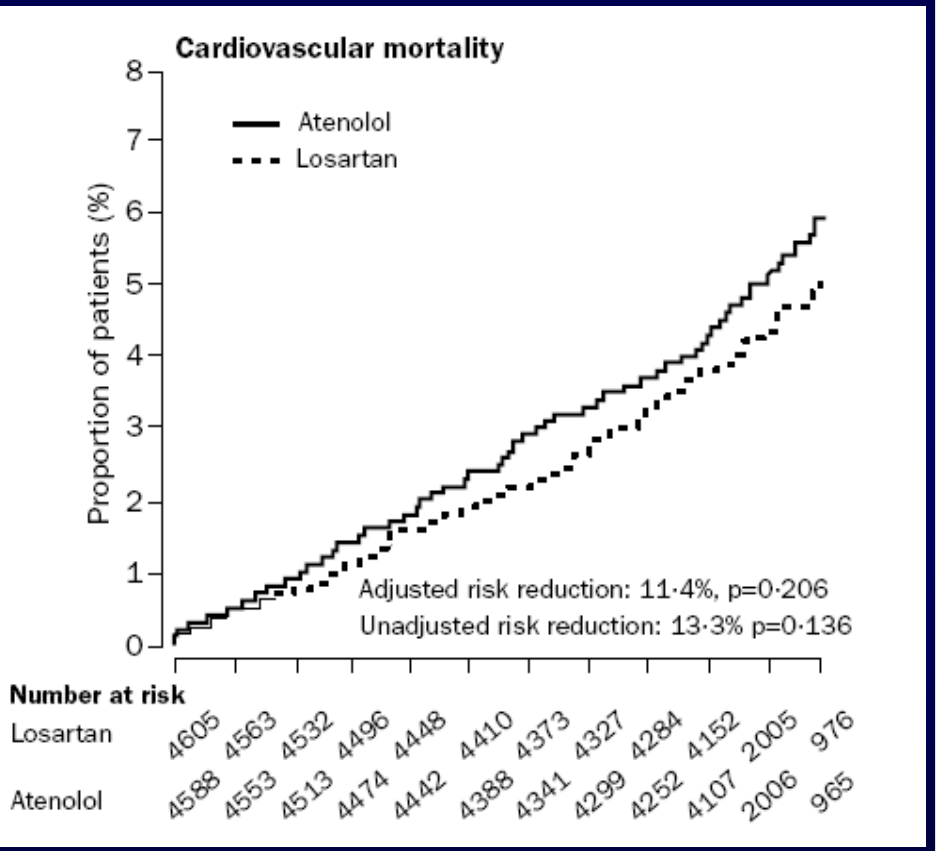
Val-HeFT: Combined All-Cause Mortality and Morbidity — Subgroup Without ACEI Background Therapy



Cohn JN. Oral presentation. AHA 2000.

Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE)



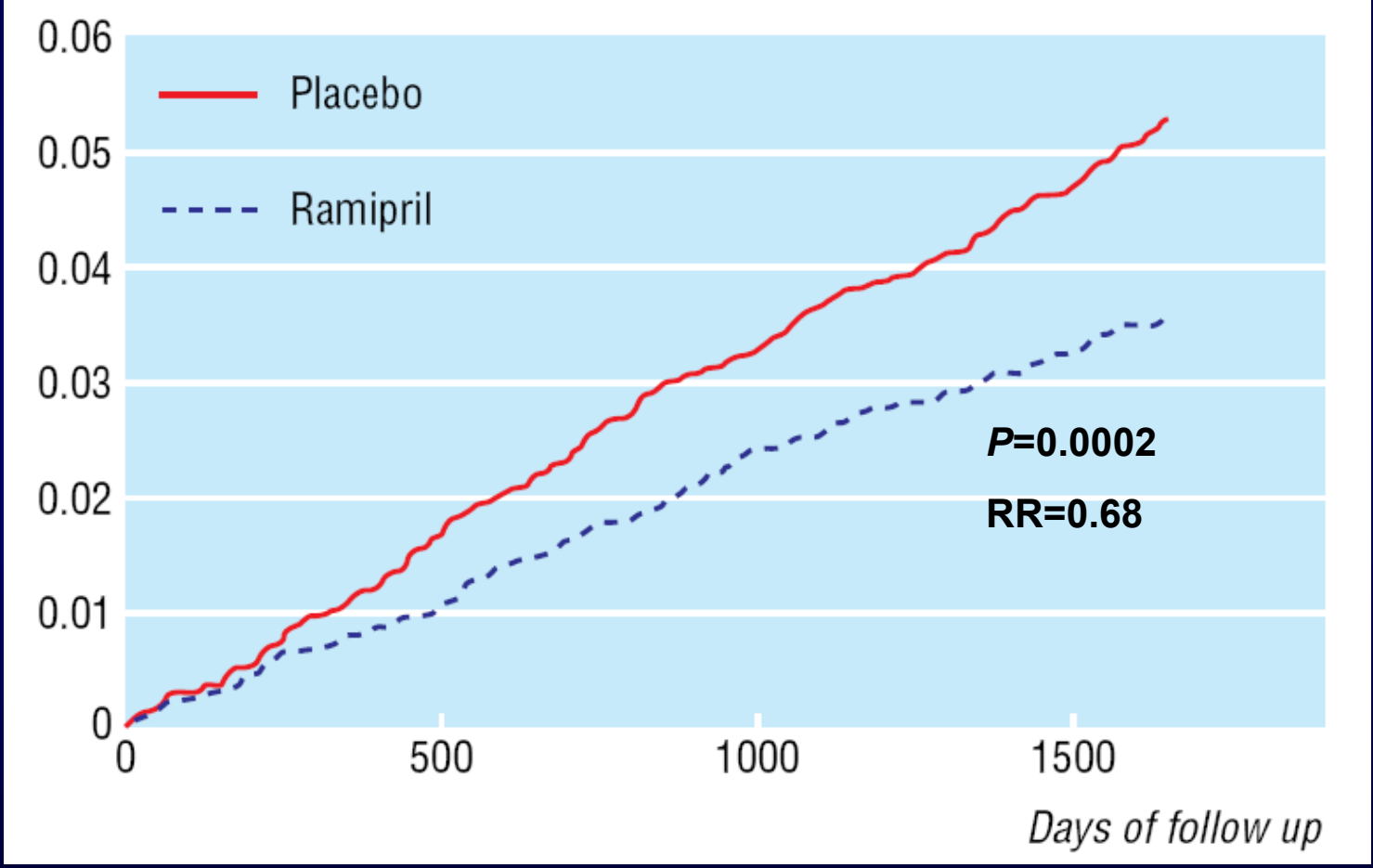


Dahlof et al, Lancet 2002;359:995-1003

Clinical Trials of RAS Blockade - Stroke

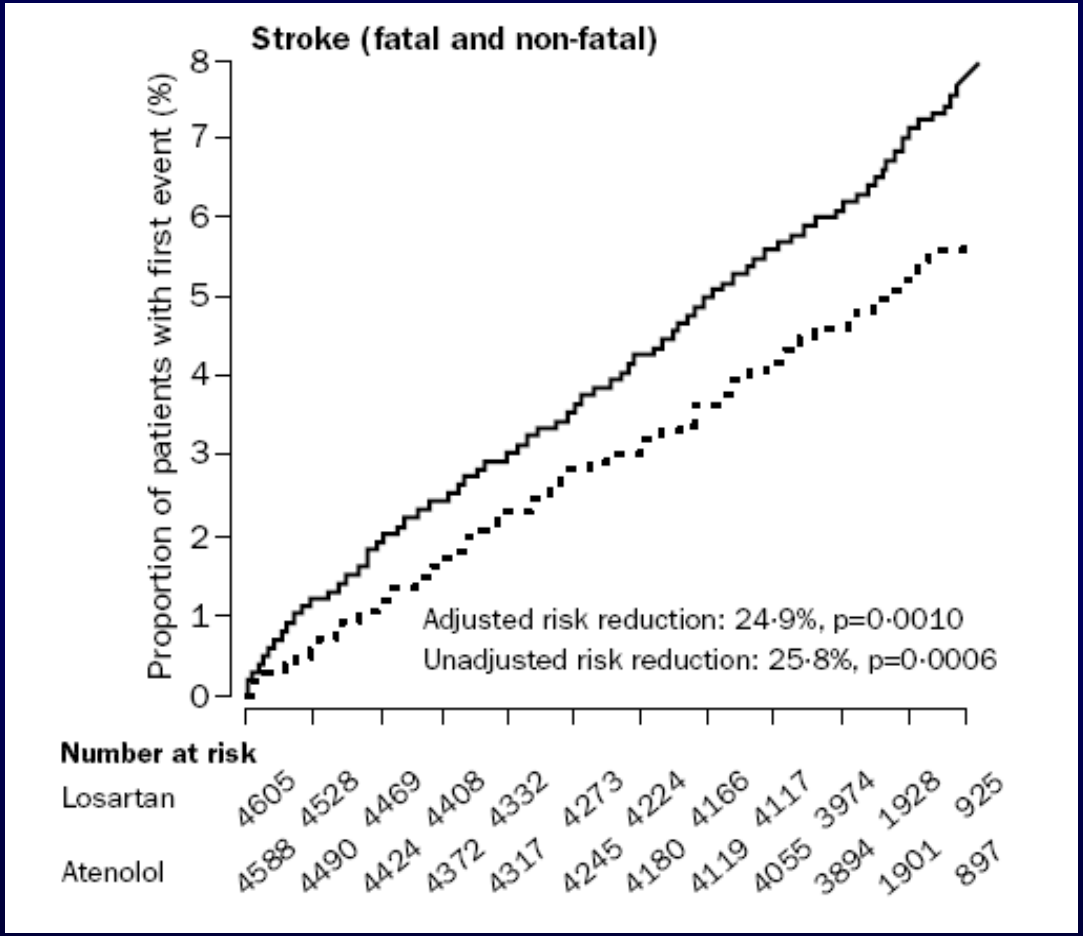
Trial	Study population	Randomization	Primary Endpoint	F/U
HOPE (2000)	n=9,297 >55-yrs old, High risk of CV events	Ramipril vs. Placebo	composite: CV mortality, stroke, MI	4.5 yrs
LIFE (2002)	n=9,193 Hypertensives with LVH	Losartan vs. Atenolol	Composite: CV mortality, stroke, MI	4.7 yrs
SCOPE (2004)	n=4,964 Elderly Hypertensives	Candersartan vs. Placebo	Composite: CV mortaility, non-fatal MI and stroke	3.6 yrs

Use of Ramipril in Preventing Stroke: Double Blind Randomized Trial (HOPE)



Bosch et al, BMJ 2002;324:1-5

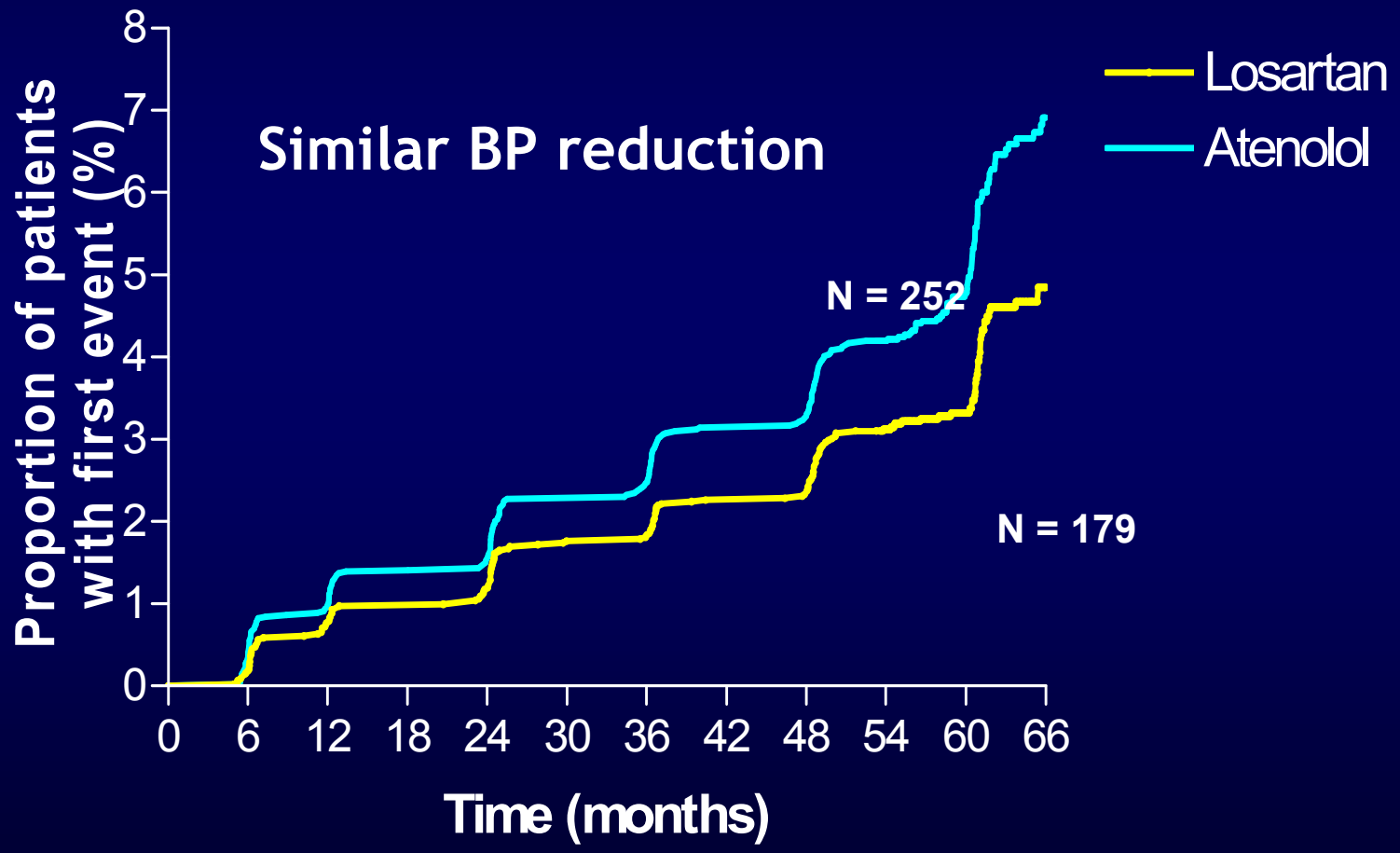
The Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE)



Dahlof et al, Lancet 2002;359:995-1003

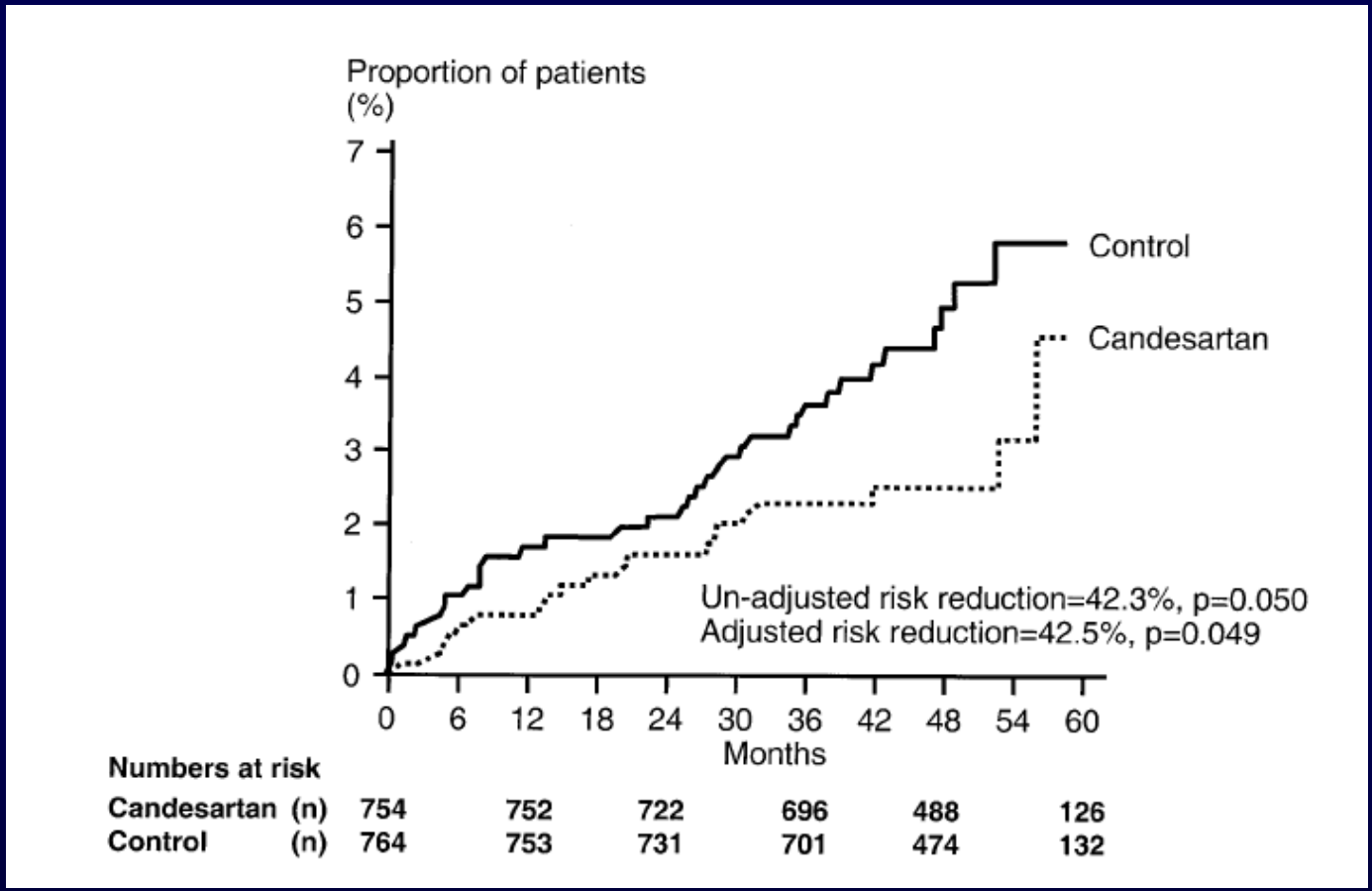
LIFE: New Onset Atrial Fibrillation - by Treatment Group

RR: 0.70 [95% CI: 0.58-0.85], p<0.001.
Adj. RR: 0.72 [95% CI: 0.59-0.89], p<0.001.



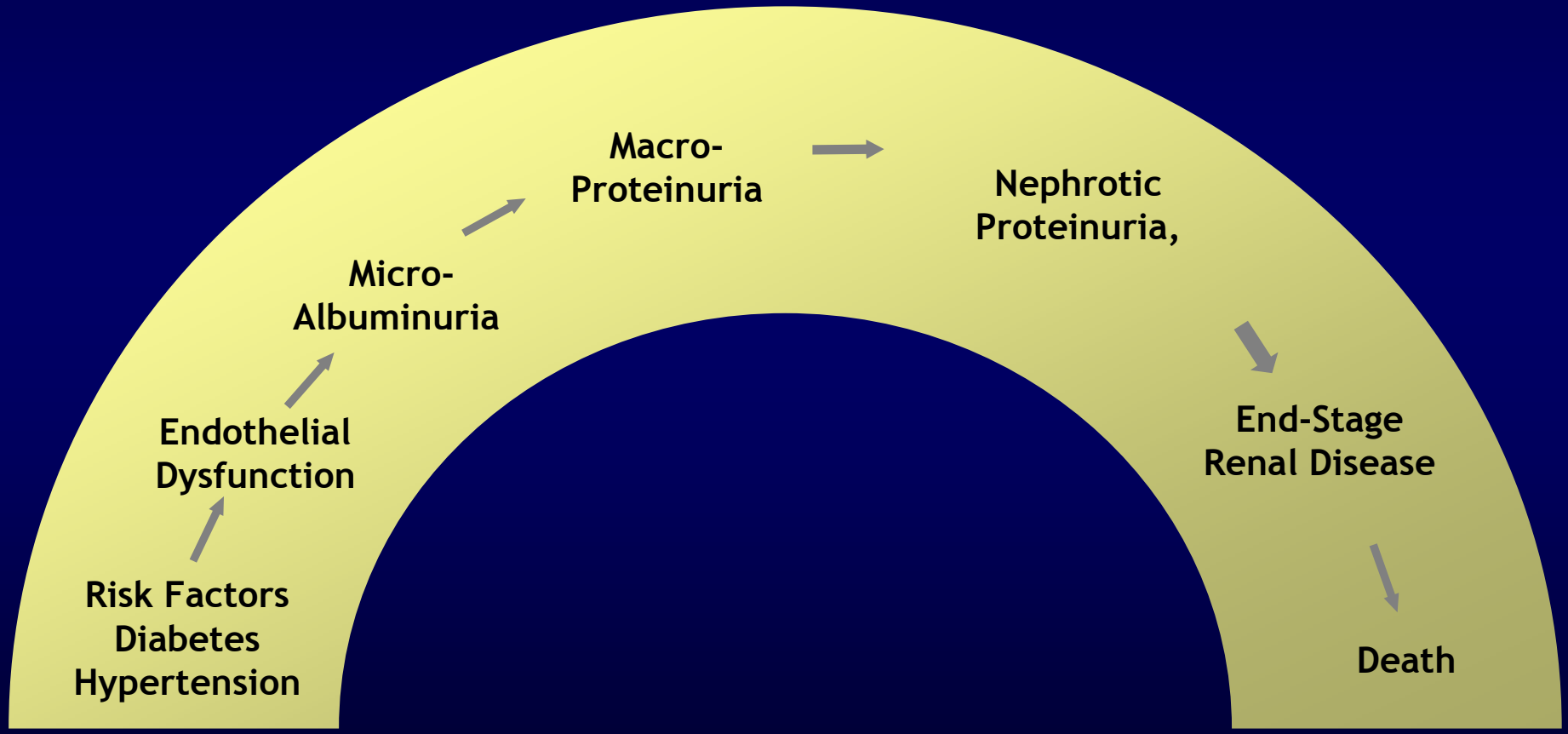
Wachtell K et al. J Am Coll Cardiol 2005:45;712-719

The Study on COgnition and Prognosis in the Elderly (SCOPE)



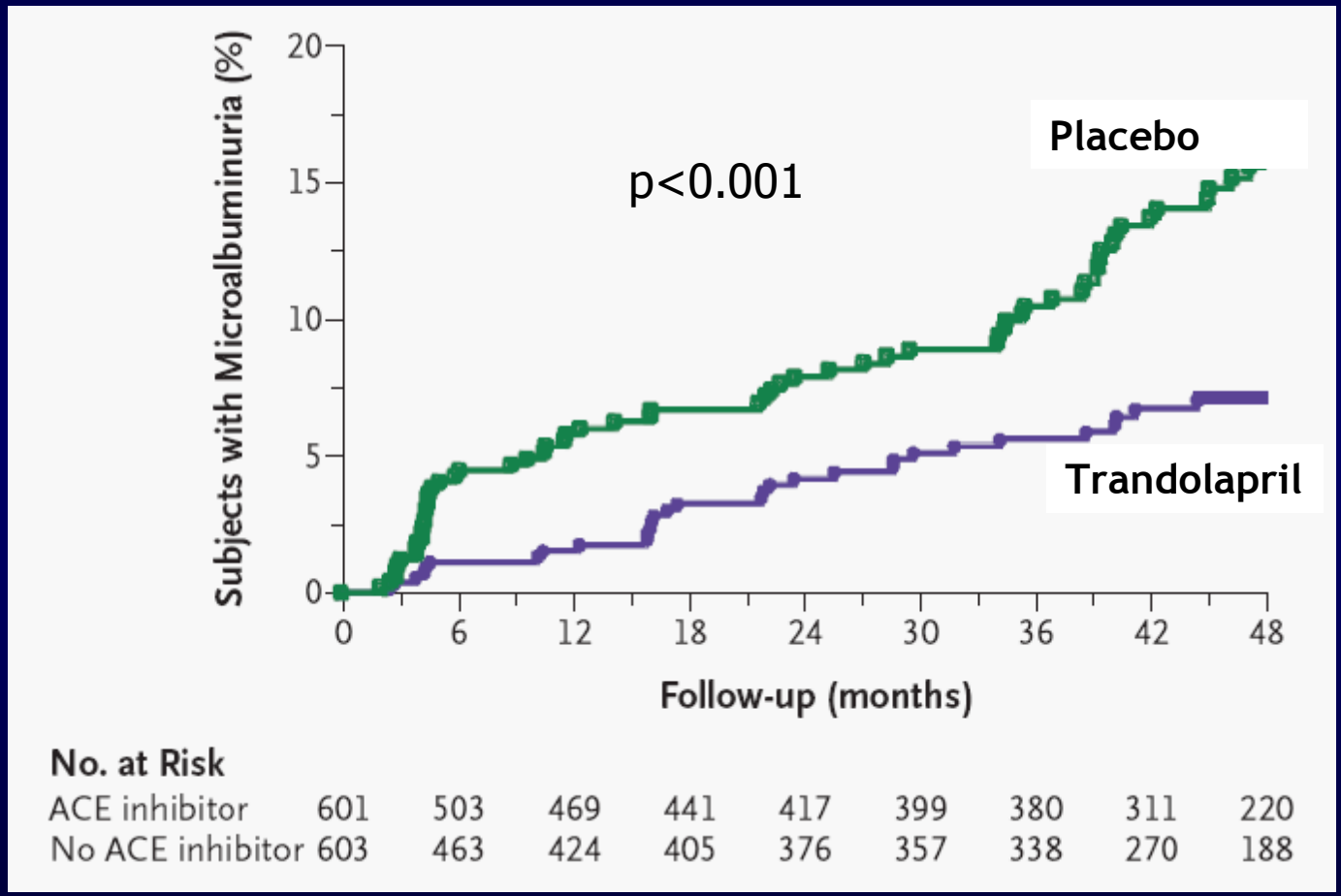
Papademetriou et al, J Am Coll Cardiol 2004;44:1175-80

Morbidity and Mortality Along the Renal Continuum



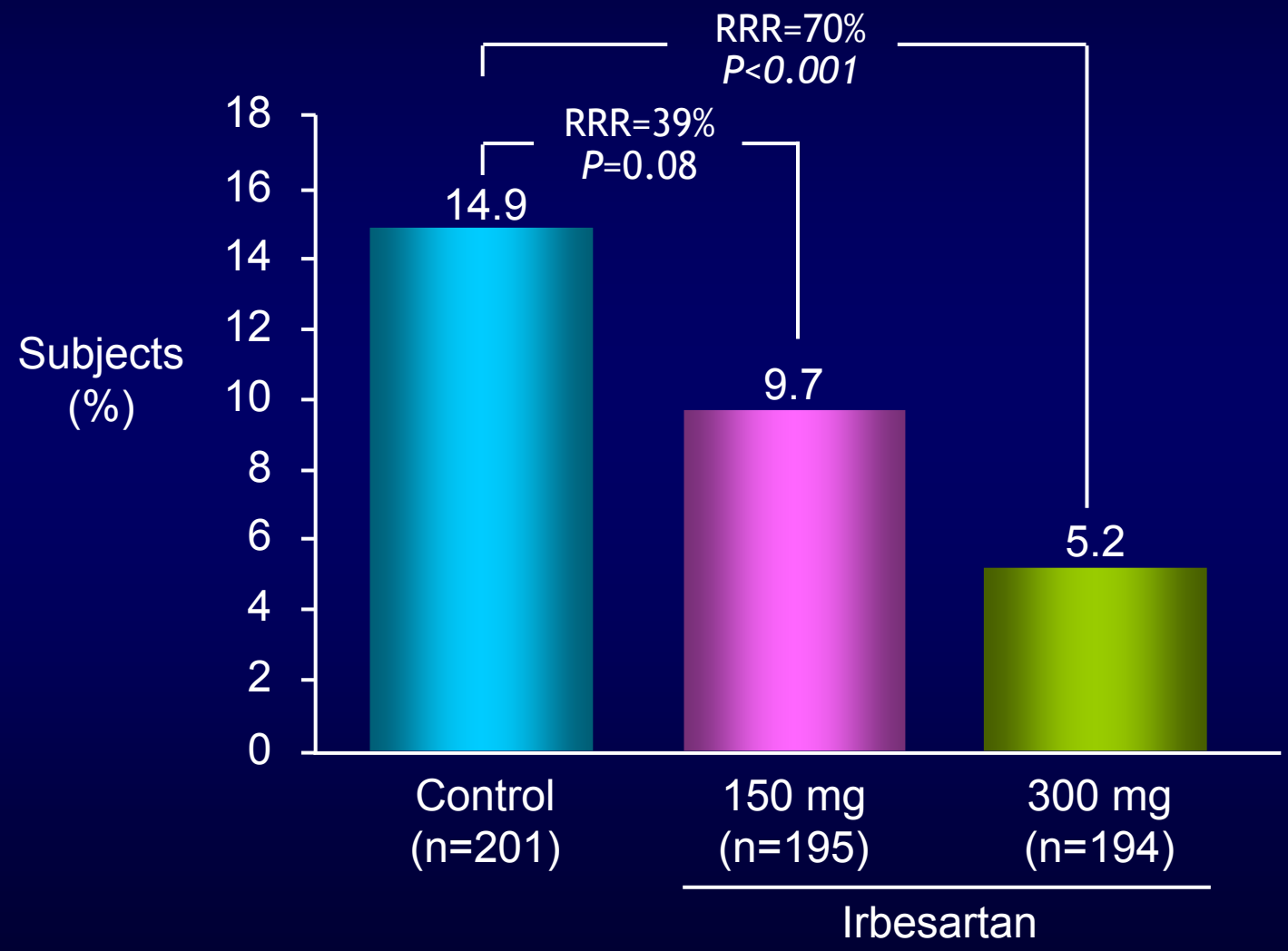
Adapted from Burgess

RAS Blockade Can Prevent the New-Onset Microalbuminuria (BENEDICT study)



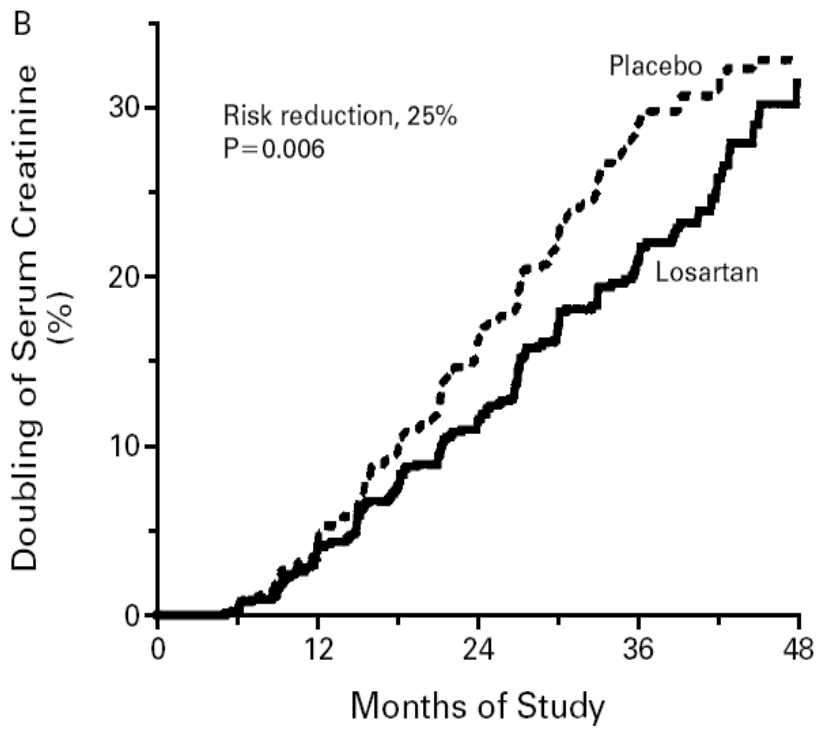
Ruggenenti et al, N Engl J Med 2004;351:1941-51

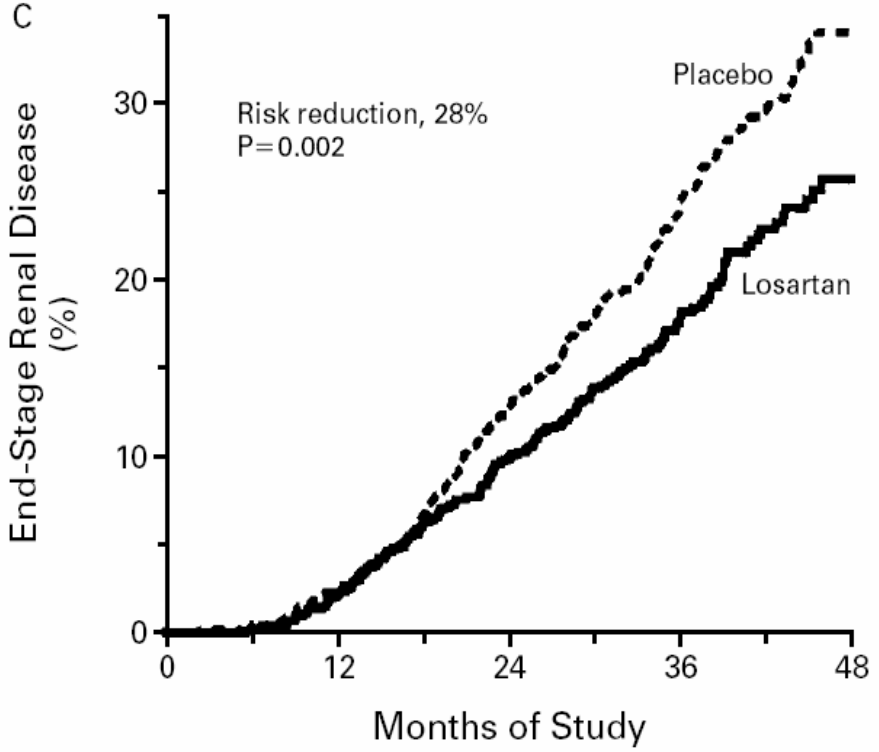
IRMA 2 Primary Endpoint
Development of Overt Proteinuria



Parving H-H, et al. N Engl J Med 2001;345:870-878.

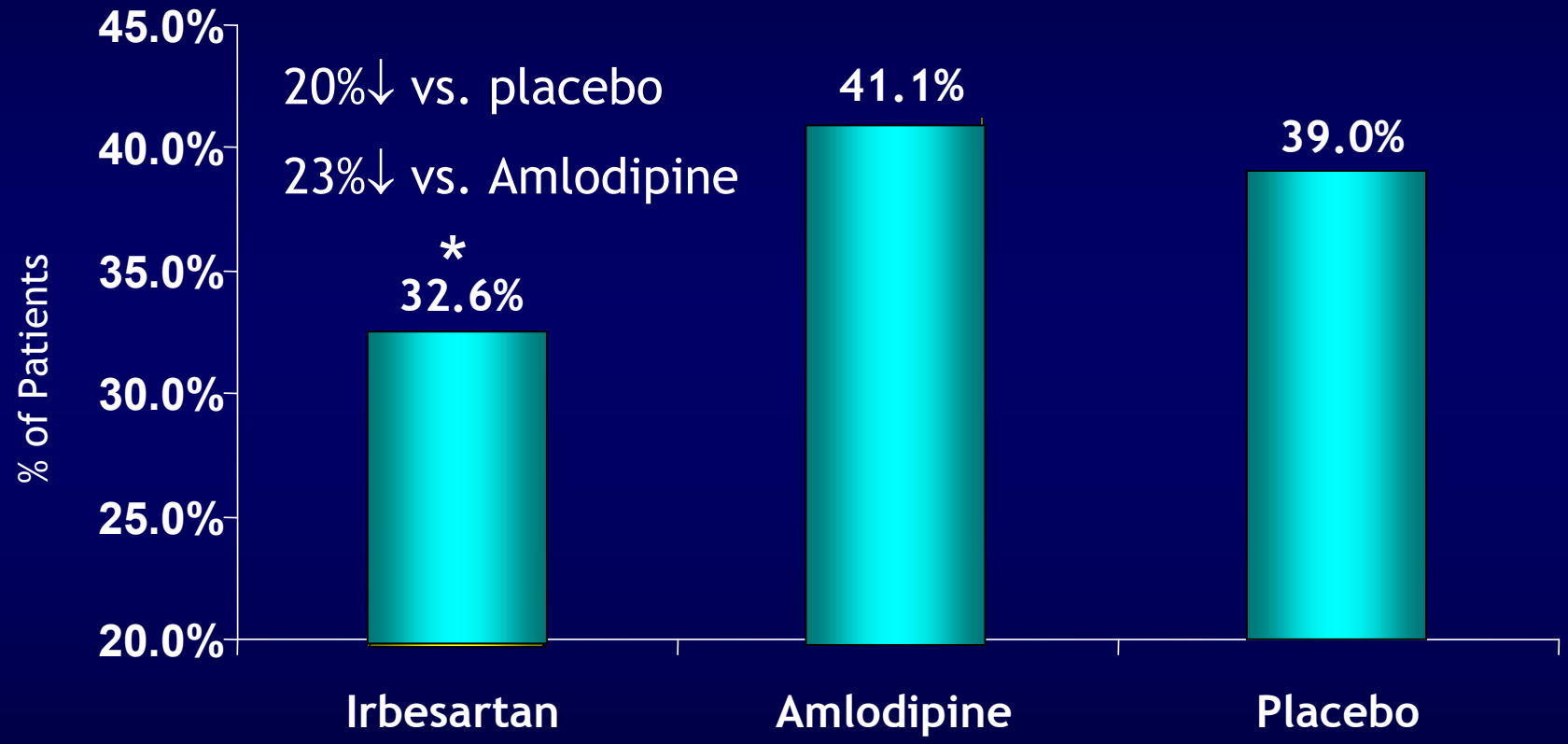
Reduction of Endpoints in NIDDM with Angiotensin II Antagonist with Lorsartan (RENAAL) Study





Brenner et al, N Engl J Med 2001;345:861-9

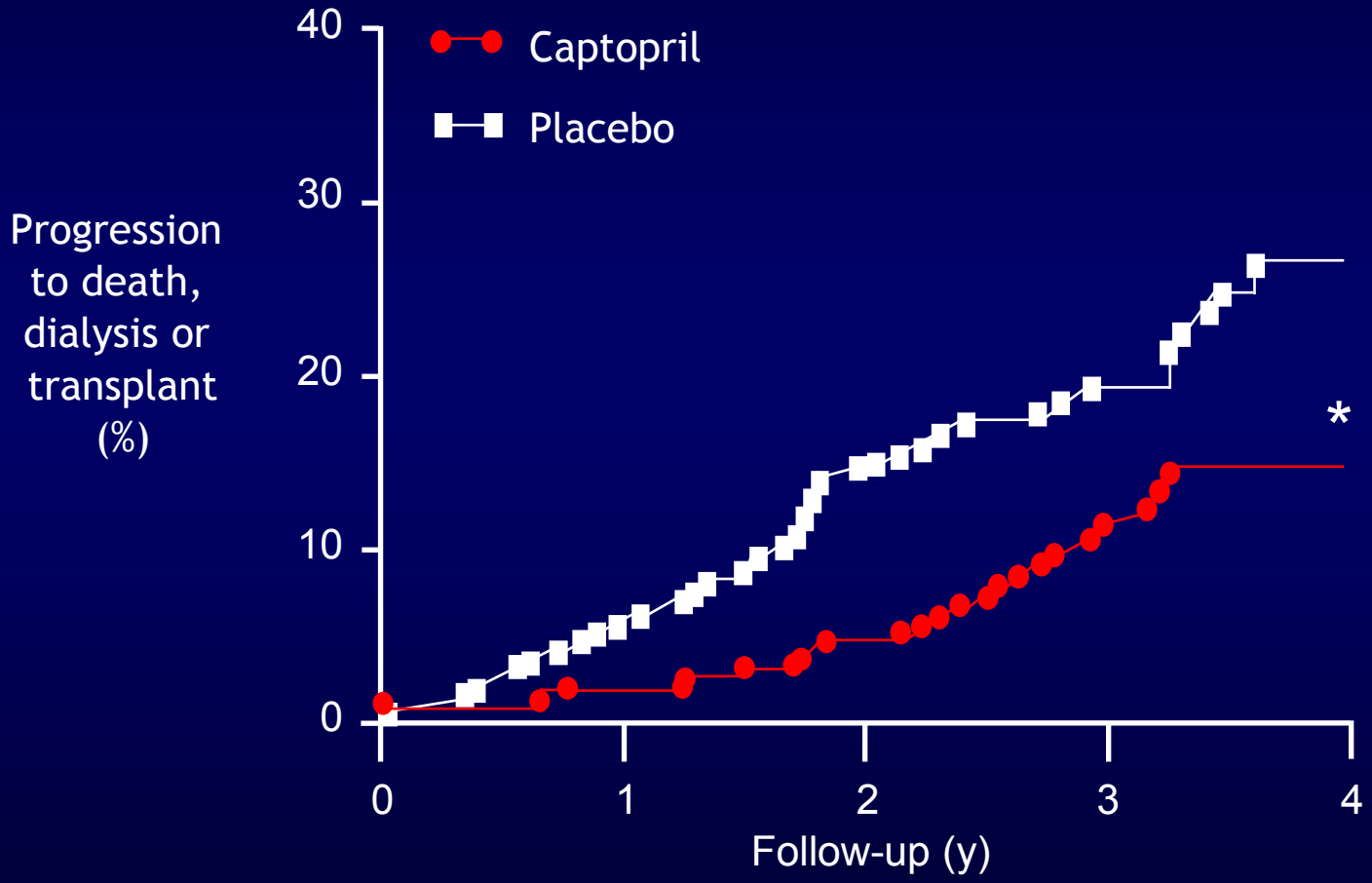
IDNT: Primary Composite Endpoint
- Doubling of Serum Creatinine, ESRD, and/or Death



* *P*=0.02 vs. Placebo and P=0.006 vs. Amlodipine

Lewis EJ. et al. N Engl J Med 2001;345:851-860.

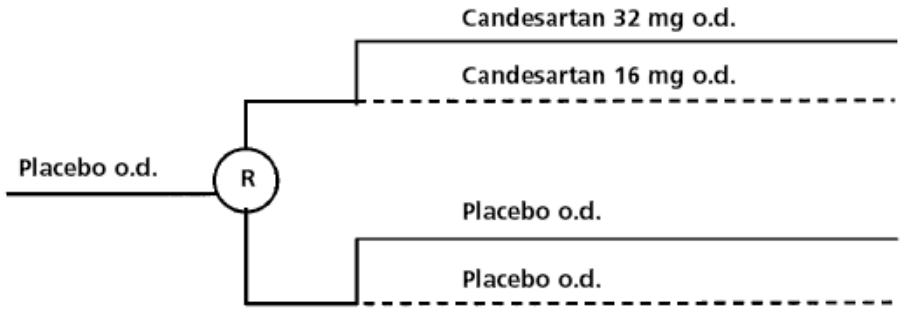
Effect of ACE Inhibition on Nephropathy in Patients with Type 1 Diabetes



Collaborative Study Group
* p = 0.006 vs placebo.

Lewis EJ et al. N Engl J Med 1993;329:1456-1462.

Ongoing Trial - The DIabetic REtinopathy Candesartan Trials (DIRECT)



Months	-2	0	1	2	6	12	every 6 m	36 m follow-up
Visit	V1	V2	V3	V4	V5	V6	V7-11	V12

Month	-2	0	1	2	6	12	18	24	30	36	every 6m	final
BP	x	x	x	x	x	x	x	x	x	x	x	x
UAER	x					x		x		x		x
HbA_{1c}	x					x		x		x		x
Retinal Photographs	x				(x)	x		x		x		x

(x) only secondary prevention studies
UAER = Urinary albumin excretion rate
BP = blood pressure

Metabolic Benefits of RAS Blockade

- Anti-diabetic

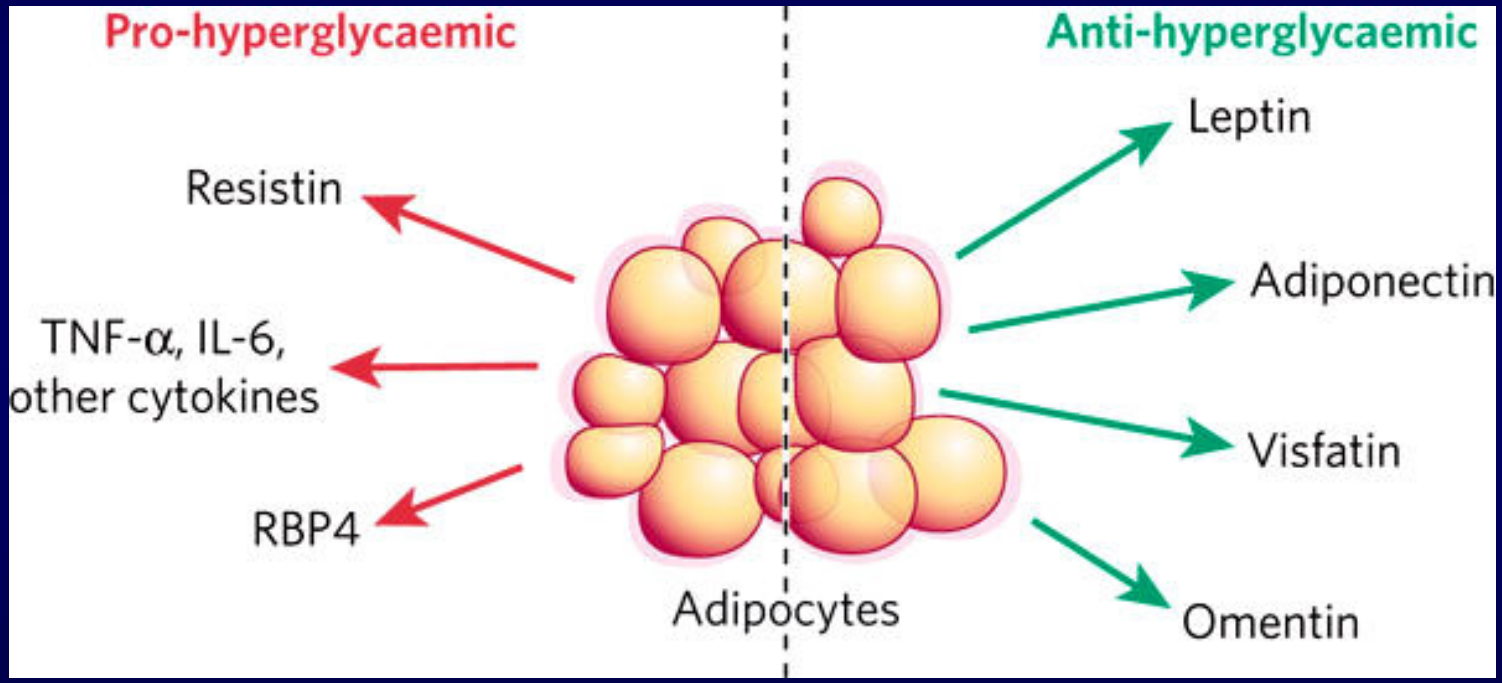
  * Proposed mechanisms

  - lowers aldosterone and prevents potassium wasting, which could preserve β-cell responsiveness
  - increase islet blood flow
  - reduces insulin resistance in skeletal muscle
  - increase insulin-mediated glucose disposal
  - has PPAR-γ activity

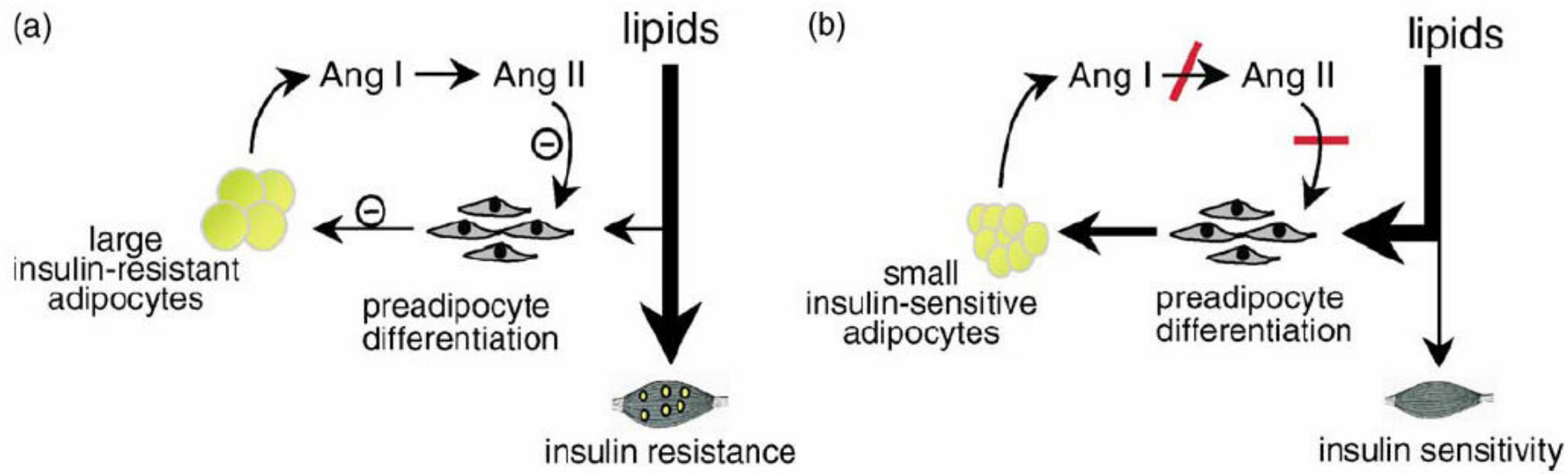
- Decreased uric acid level

  - decreased reabsorption of uric acid in proximal tubules

Adipocytes Secrete Proteins with Varied Effects on Glucose Homeostasis

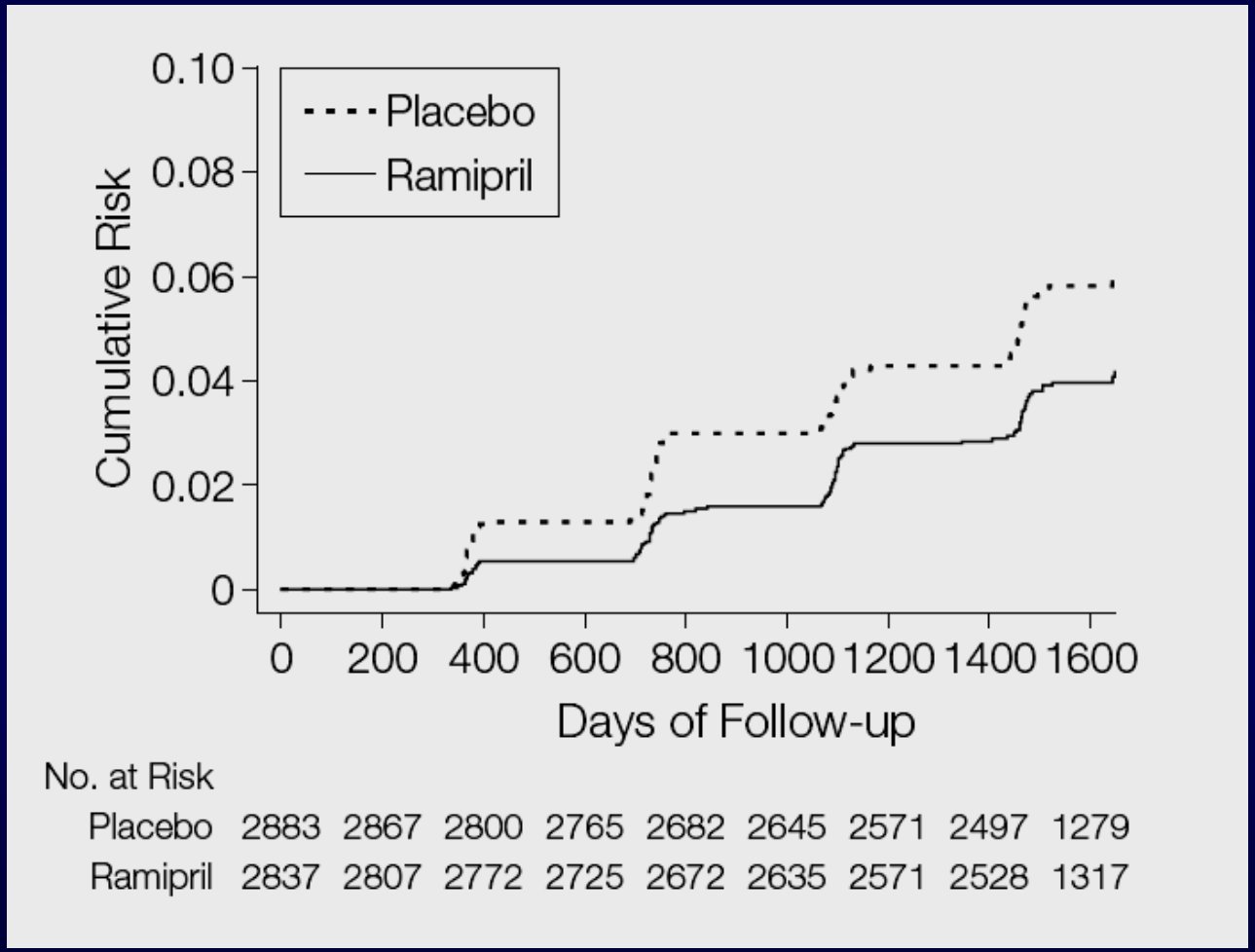


RAS Blockade Improves Insulin Sensitivity in Adipose Tissue



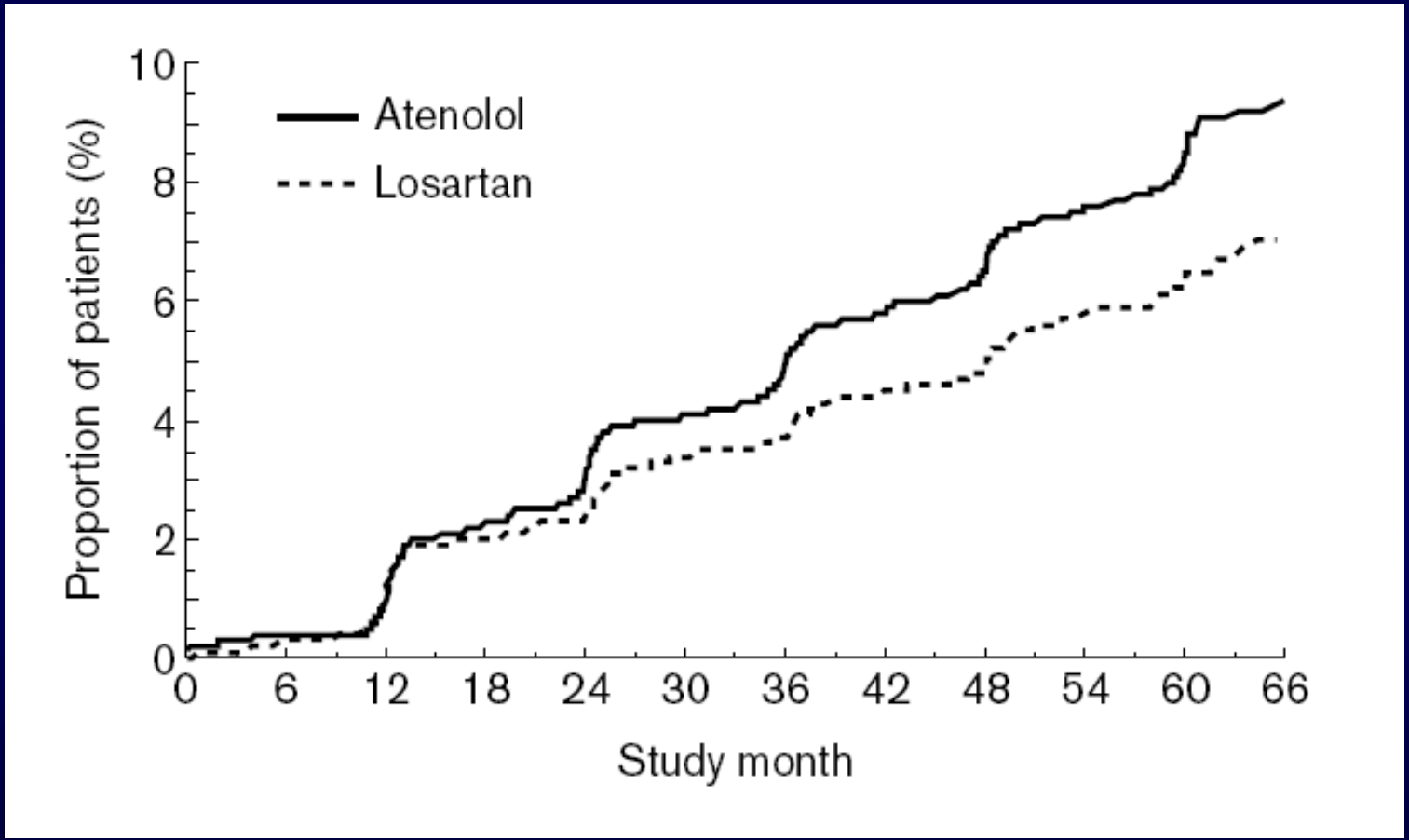
Engeli et al, Int J Biochem Cell Biol 2003;35:807-25

Ramipril Decreased the Development of New-onset DM (HOPE Trial)



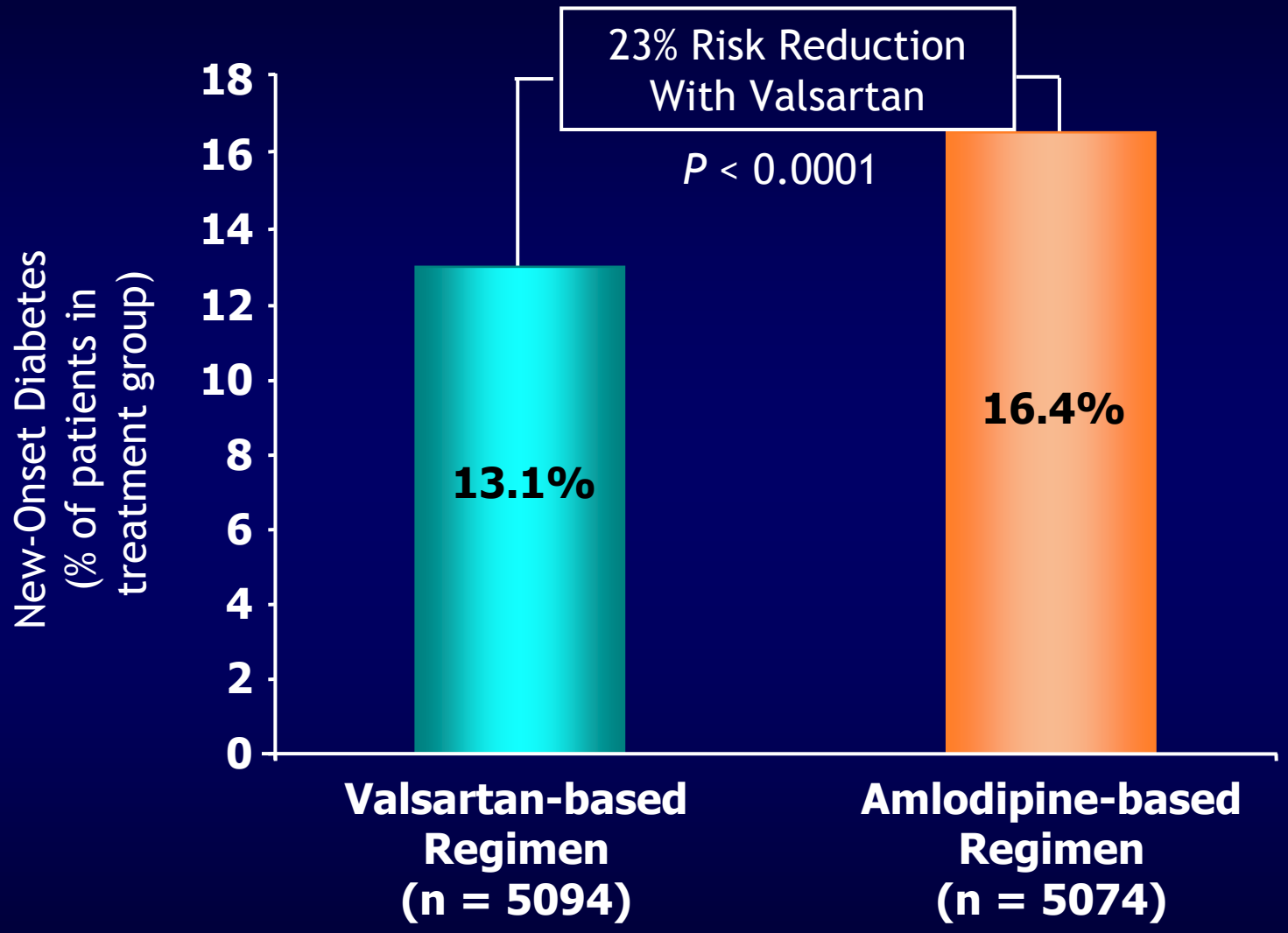
Yusuf et al, JAMA 20012;86:1882-85

Losartan Decreased the Development of New-onset DM (LIFE Study)



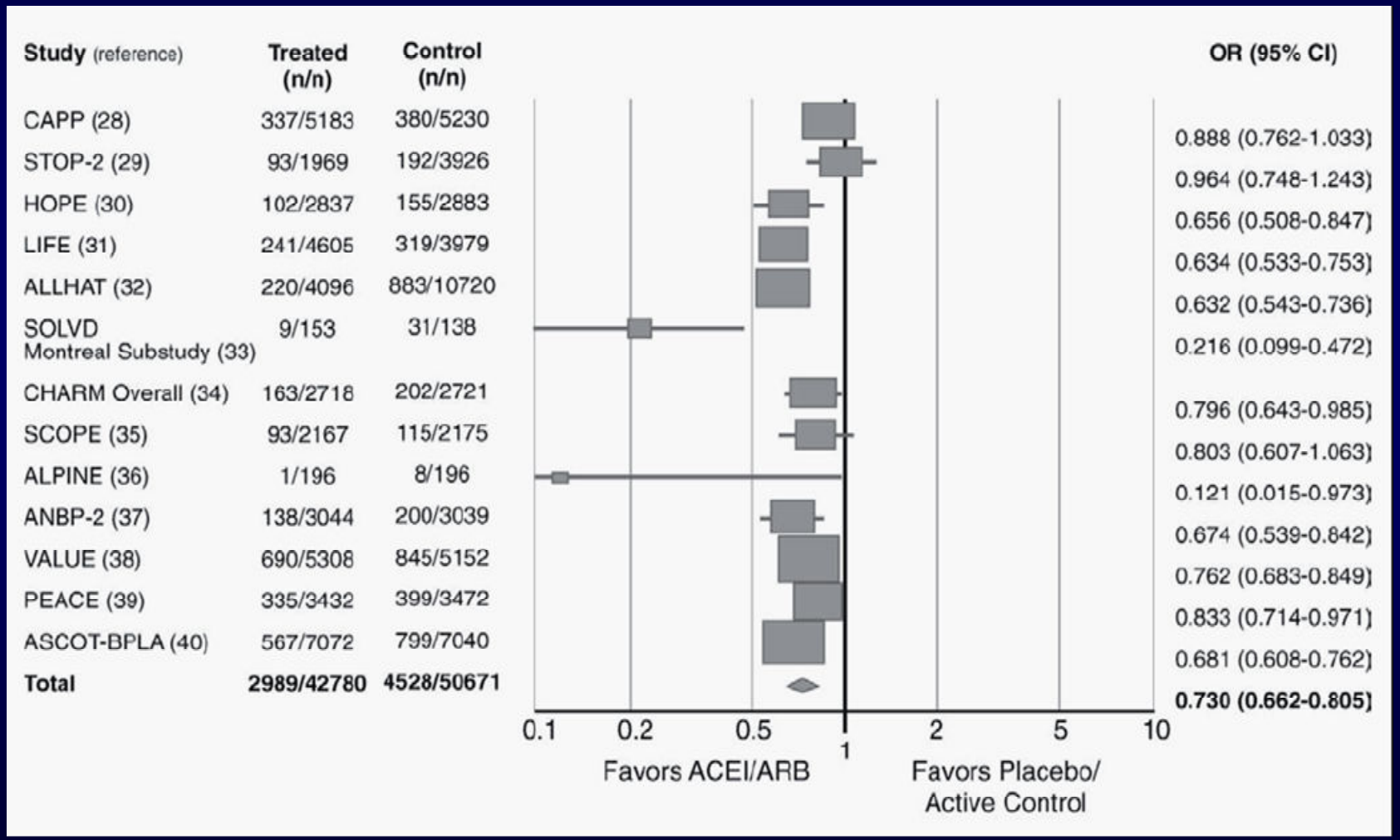
Lindholm et al, J Hypertens 2002;20:1879-86

VALUE: Incidence of New-Onset Diabetes



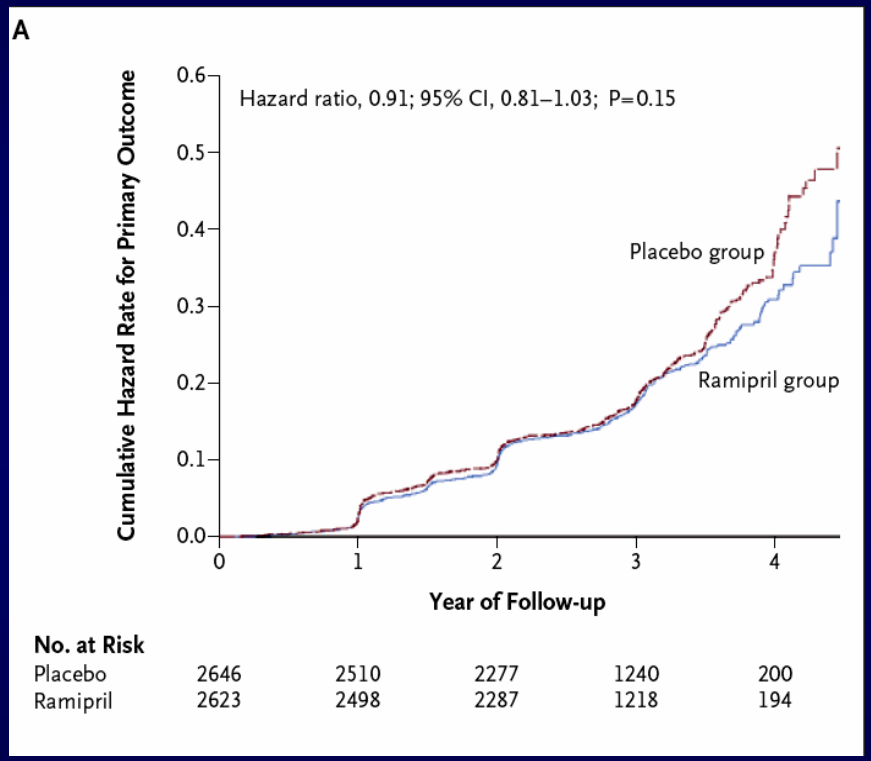
Julius S et al. Lancet. June 2004;363.

The Effect of RAS Blockade on the Development of New-onset DM

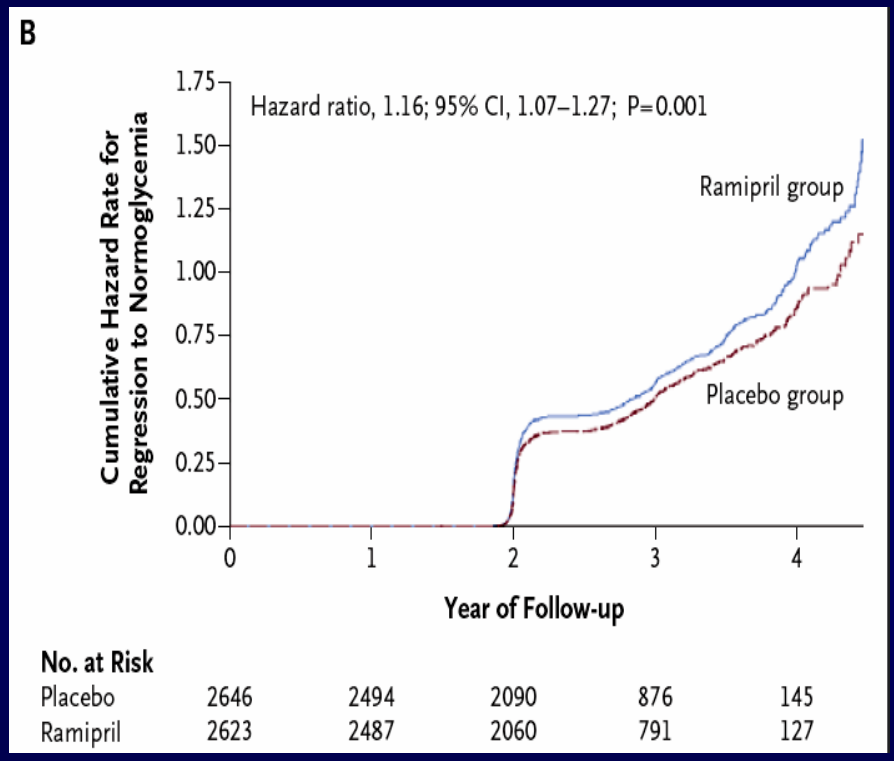


Andraws et al, Am J Cardiol 2007;99:1006 -12

Effect of Ramipril on the Incidence of Diabetes – The DREAM Trial



New-onset DM or death



Regression to normoglycemia

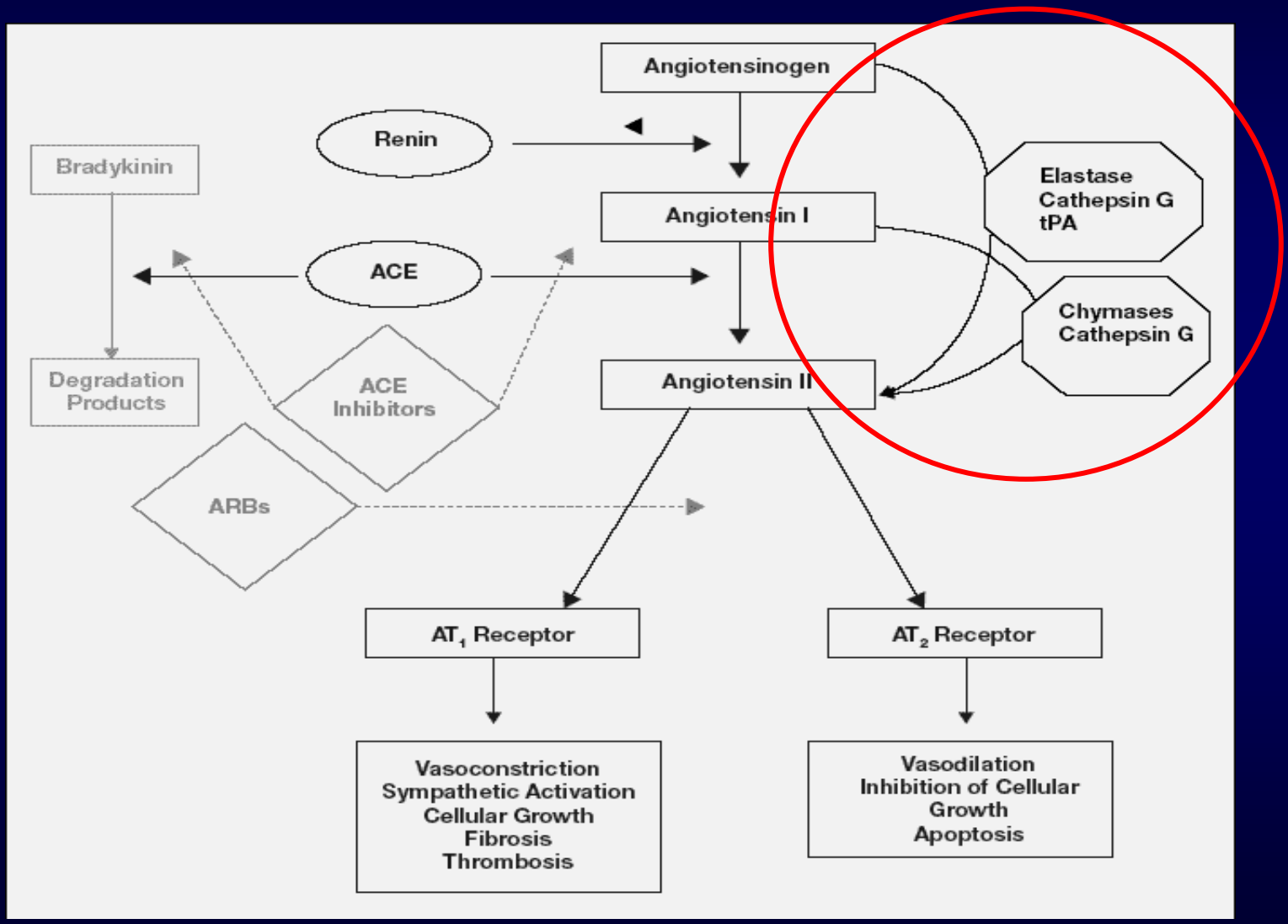
The DREAM Trial Investigators, New Engl J Med 2006;355:1551-62

Two Ongoing Trials

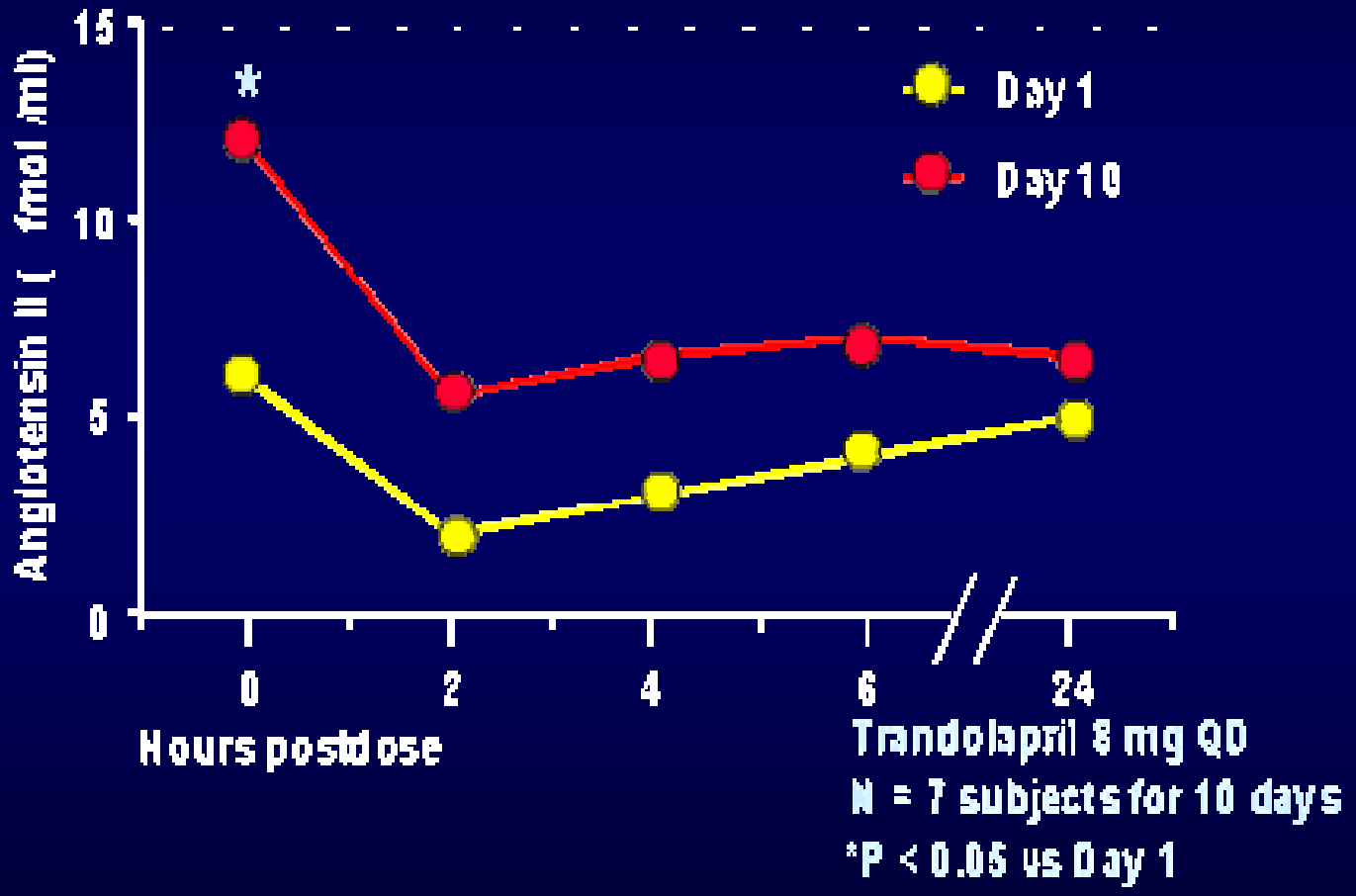
Study	No. of patients	Randomization	F/U	Outcome
NAVIGATOR	7,500	Nateglinide vs. Valsartan	3 yrs	Metabolic effects (New-onset DM)
ONTARGET/ TRANSCEND	ONTARGET 22,500 TRANSCEND 5,000	ONTARGET Telmisartan vs. Ramipril vs. Both TRASCEND Telmisartan vs. Placebo	5.5 yrs	Primary: CV death, MI, stroke, hospitalization for HF Secondary: New-onset DM

Is ACE inhibitor or Angiotensin Receptor Blocker Alone Enough to Stop Disease Progression?

Non-ACE Pathway in RAS



Chronic ACE-Inhibition Incompletely Suppresses Angiotensin II



Mooser V et al, J Cardiovasc Pharmacol 1990;15:276-282

Higher Doses are Required to Effectively Block the Intrarenal RAS

- A number of studies have suggested that blockade of the intrarenal RAS requires higher doses than those needed to reduce BP

  - Elevated local RAS activity

  - Reduced AT1 receptor expression

  - Tissue penetration within intrarenal compartment

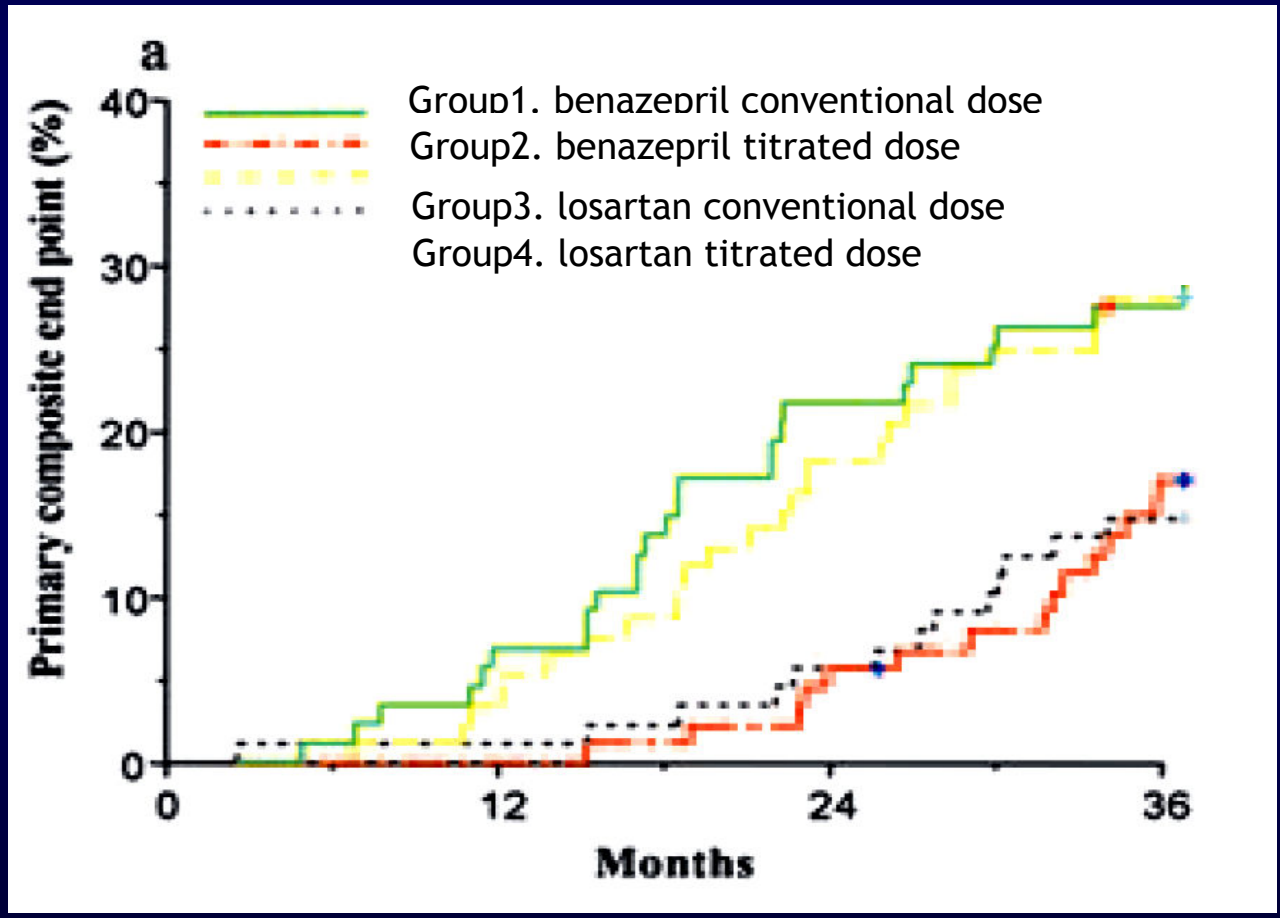
Wang-CT et al, JASN 1997;8:535
Rakugi-H et al, Circulation 1994;90(1):449-455
Wagner-J et al, JASN 1999;10:545

Clinical Trial to Examine the Efficacy of High-dose ARB Treatment in Reducing Proteinuria in Patients with Renal Disease

- **S**uper **M**aximal **A**tacand **R**enal **T**rial **(SMART)**
  - designed to determine the optimal dose for candesartan cilexetil (up to 128 mg/day) for maximum reduction of proteinuria

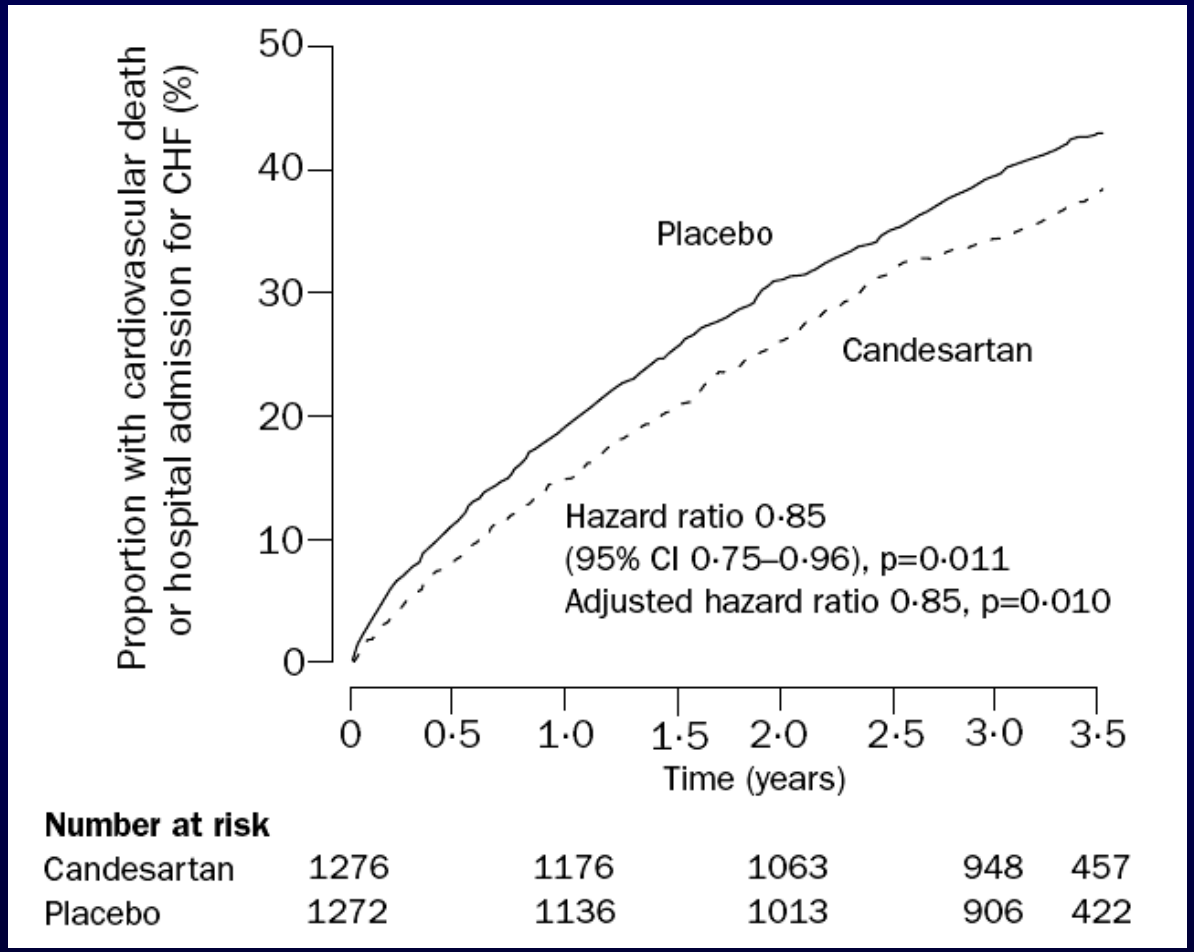
- **D**iovan **R**eduction of **P**roteinuria **S**tudy **(DROP)**
  - use of valsartan, up to 640 mg/day, in patients with type 2 diabetes

Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: A Randomized Controlled Study of Benazepril and Losartan in CKD



Hou et al, J Am Soc Nephrol 2007;18:1889-98

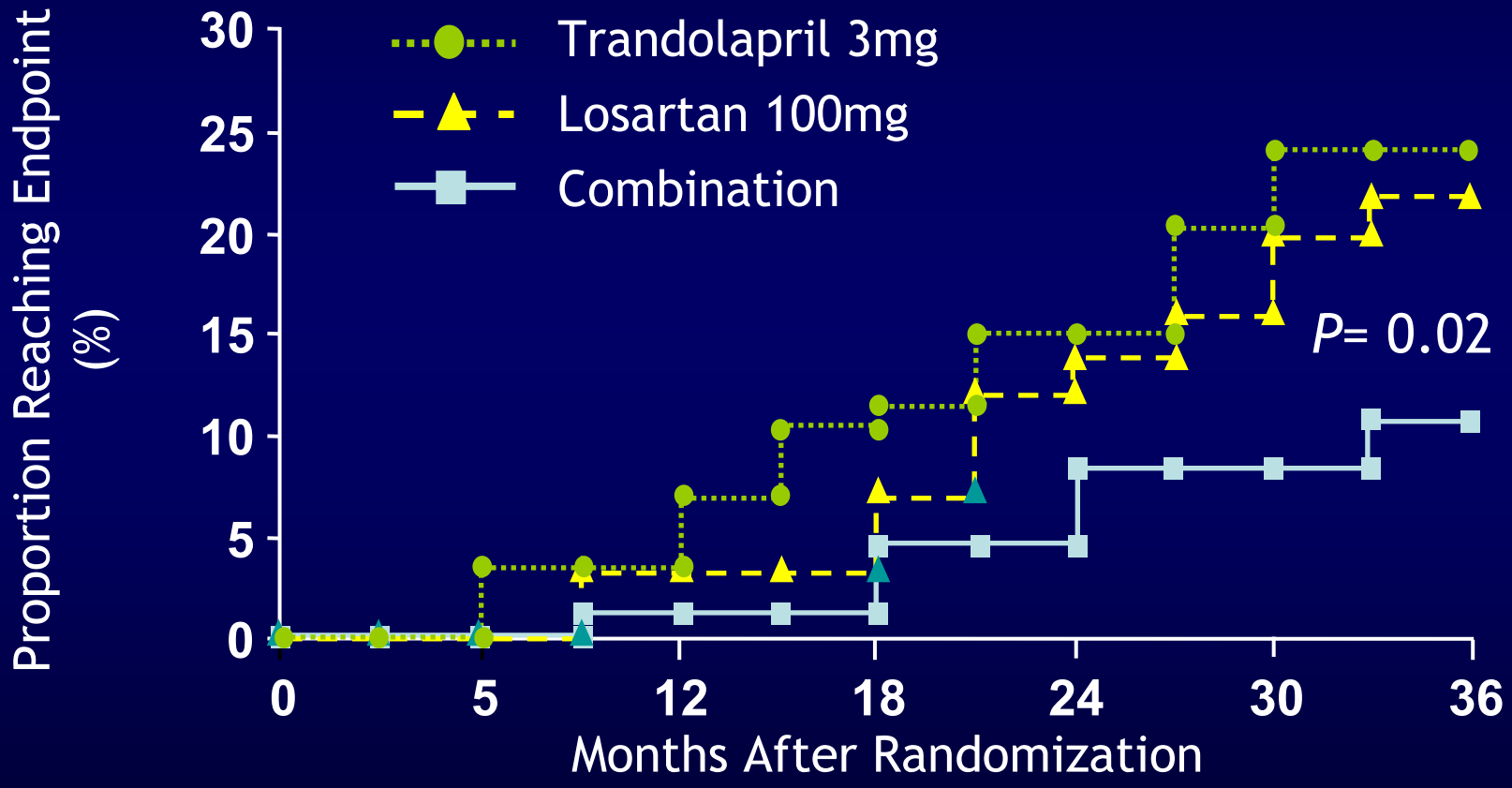
Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Added



McMurray et al, Lancet 2003; 362: 767-71

COOPERATE: Primary Endpoint

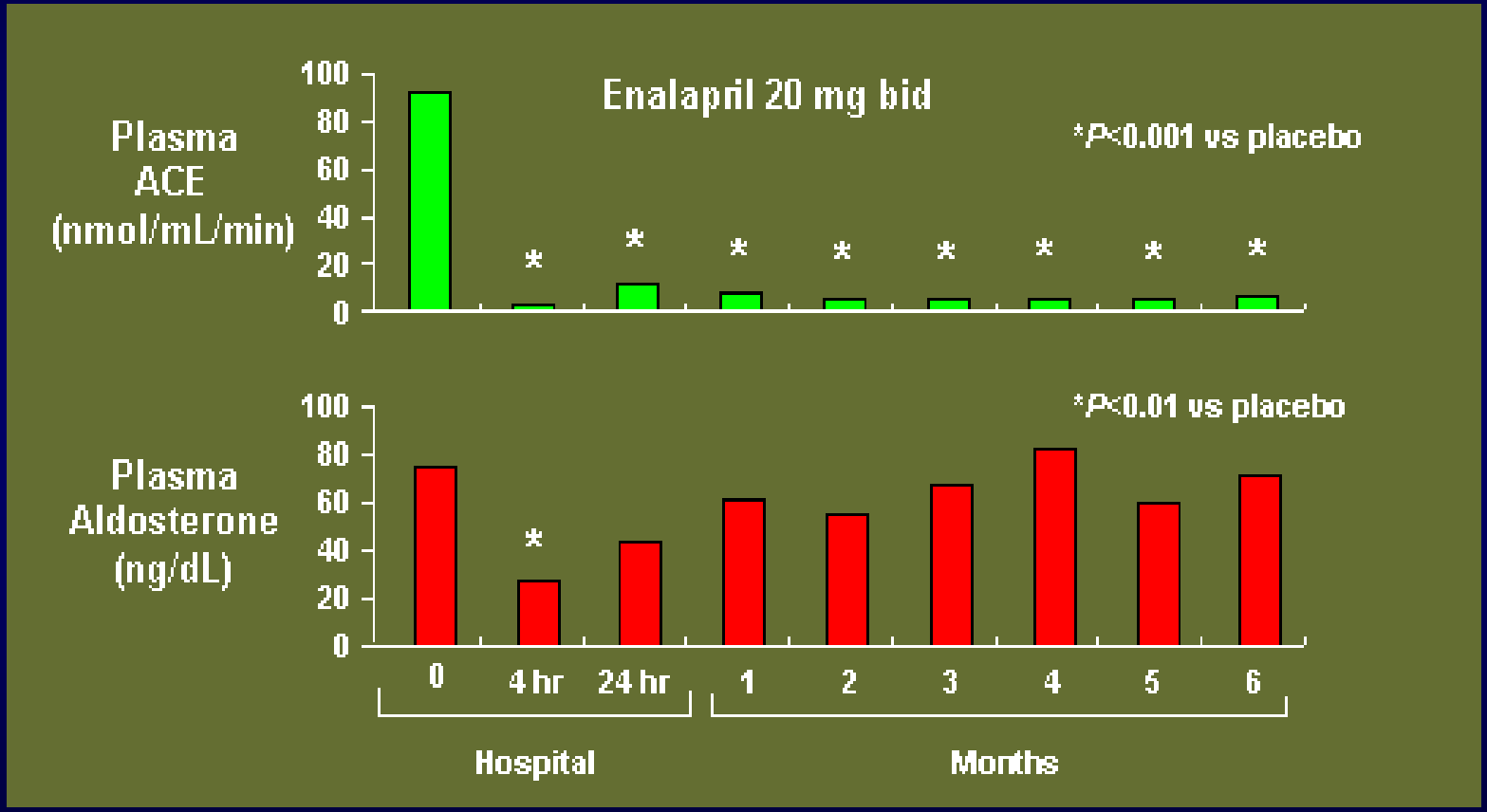
Doubling of Serum Creatinine or Progression to ESRD



Randomized double-blind trial

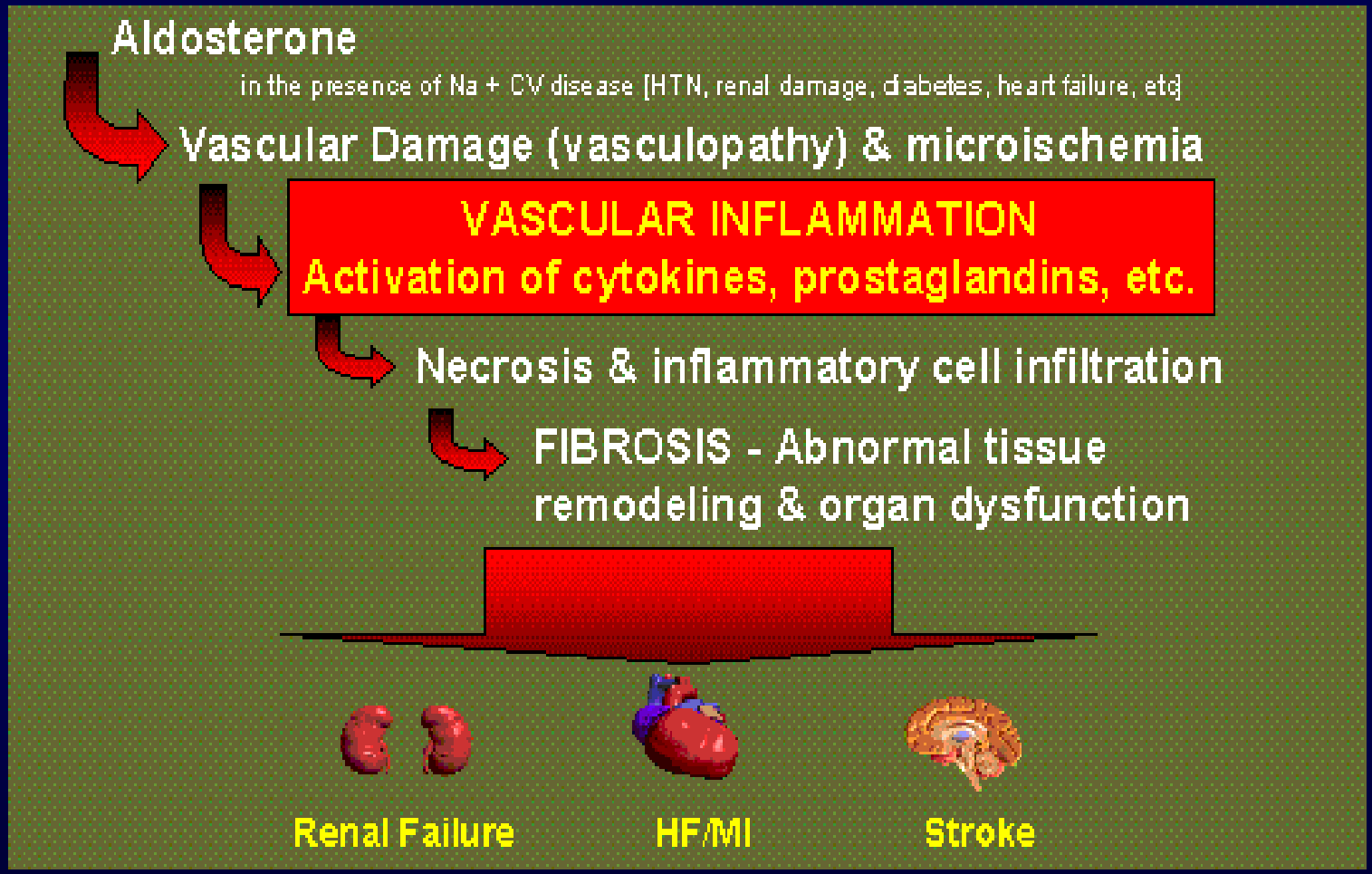
Nakao N et al, Lancet 2003;361:117-124

Aldosterone Not Adquately Suppressed by ACE inhibition

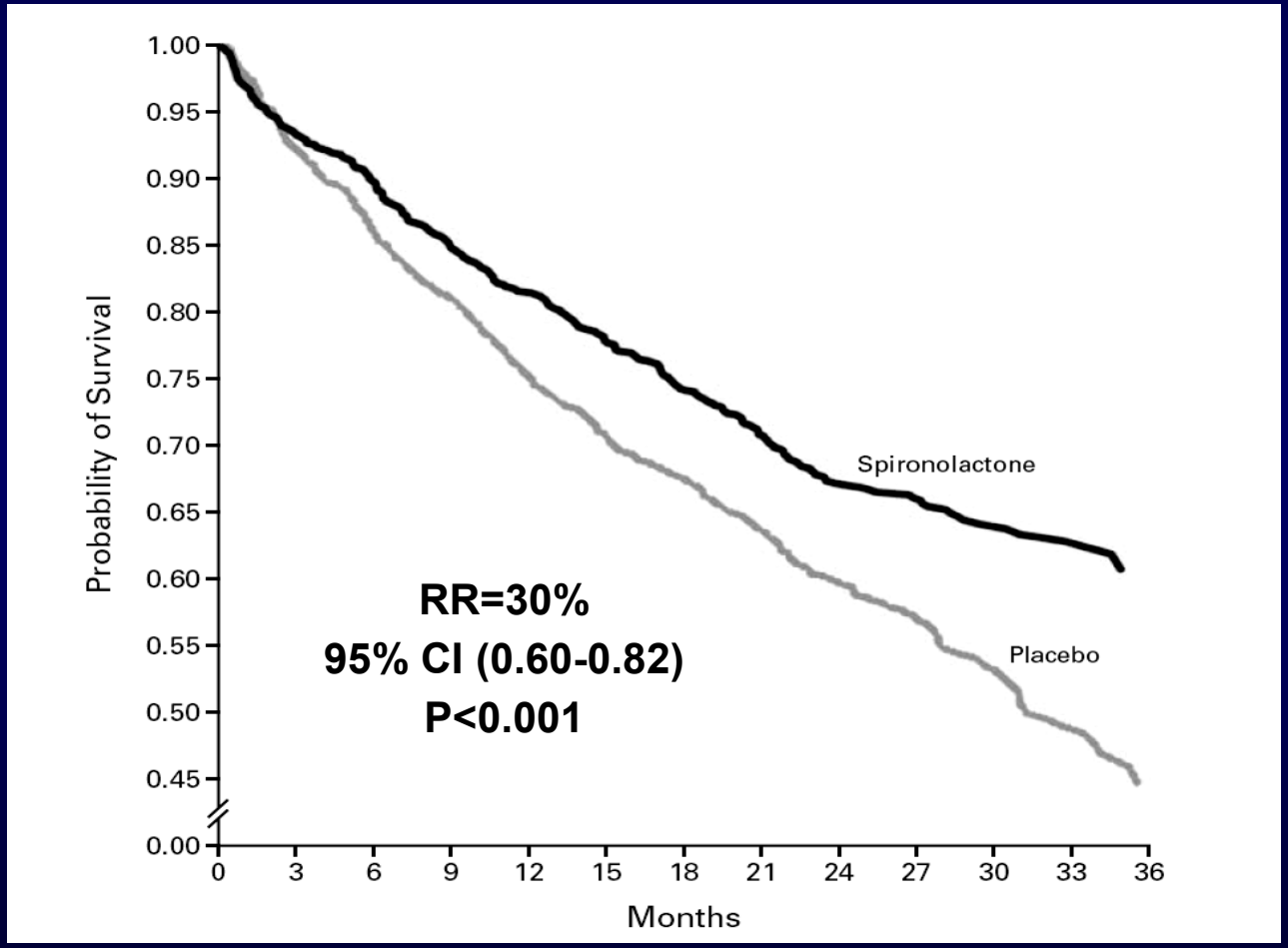


Biollaz et al, J Cardiovasc Pharmacol 1982;4(6):966-972

Proposed Mechanisms for Aldosterone-induced Injury

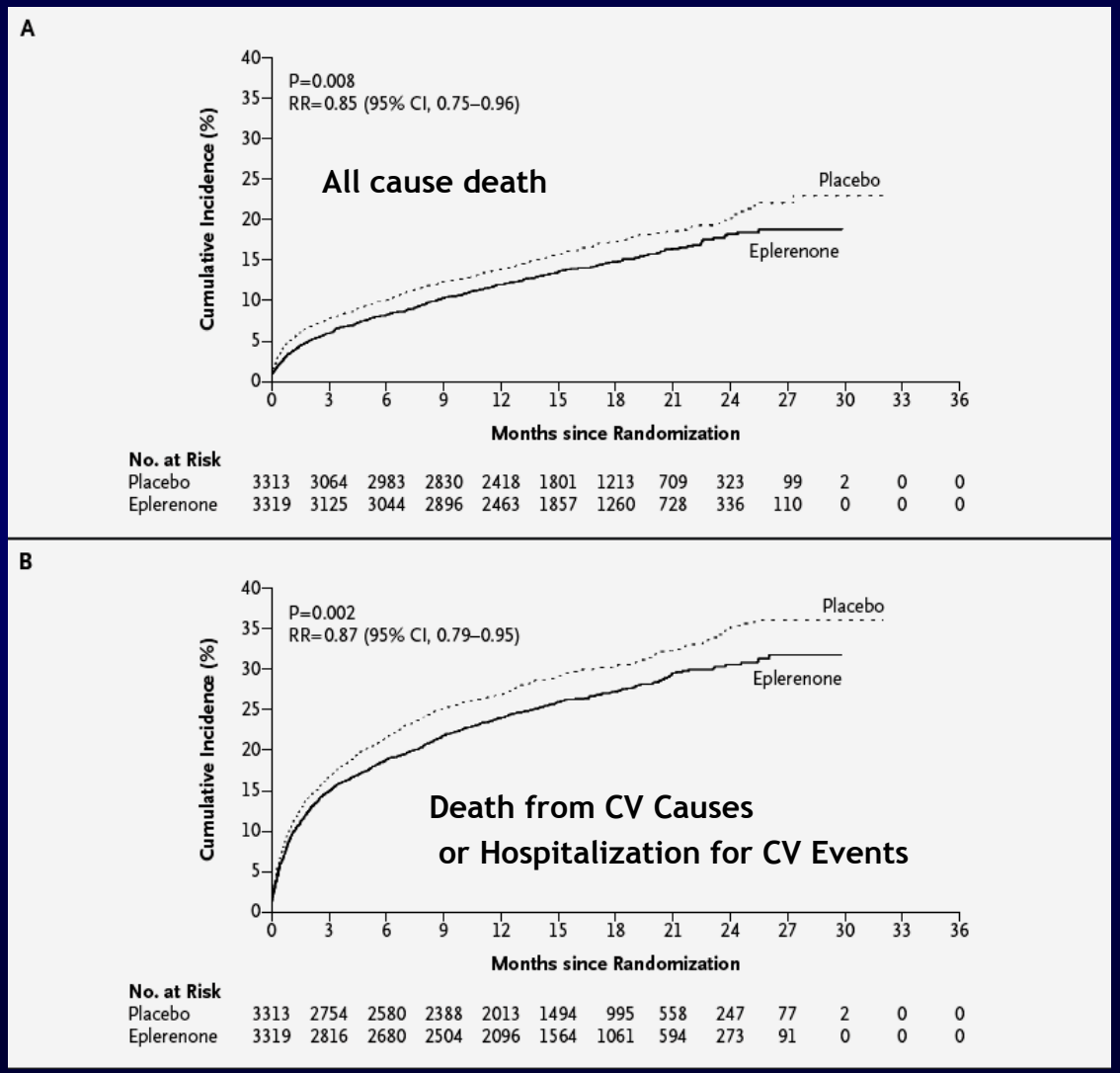


Aldosterone Blockade Reduces Mortality in Patients with Severe Heart Failure (RALES)



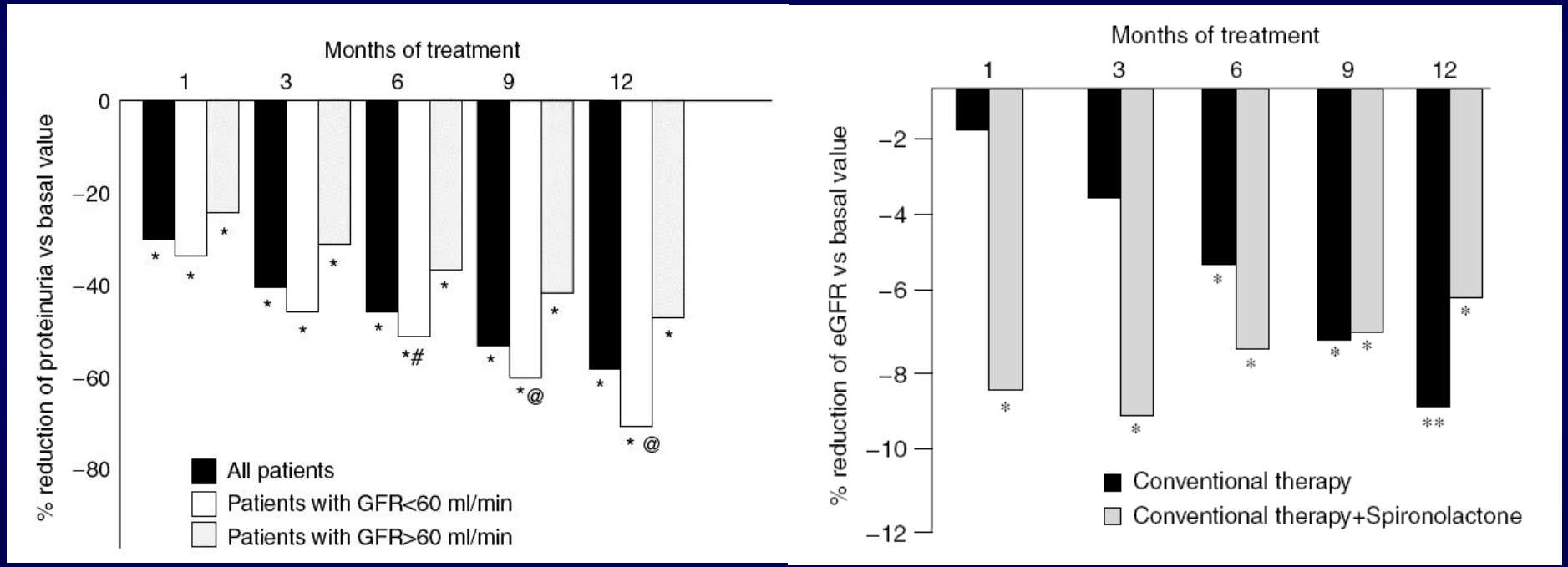
Pitt B, et al N Engl J Med 1999;341:709-717

Eplerenone in Patients with Left Ventricular Dysfunction after Myocardial Infarction



Pitt et al, the EPHESUS group, N Engl J Med 2003;348:1309-21

Long-term Effects of Spironolactone on Proteinuria and Kidney Function in Patients with CKD



Bianchi et al, Kidney Int. 2006;70:2116-23

What is the Future of RAS?

Special Commentary

Renin Inhibition: What Are the Therapeutic Opportunities?

Naomi D.L. Fisher and Norman K. Hollenberg

Departments of Medicine and Radiology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Blockade of the renin-angiotensin system with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers has become a crucial element in cardiovascular and renal medicine. This review evaluates the potential of renin inhibition as an adjunct to therapies that depend on renin system interruption.

J Am Soc Nephrol 16: 592–599, 2005. doi: 10.1681/ASN.2004100874

J Am Soc Nephrol 2005;16:1889-98

Mini-Review

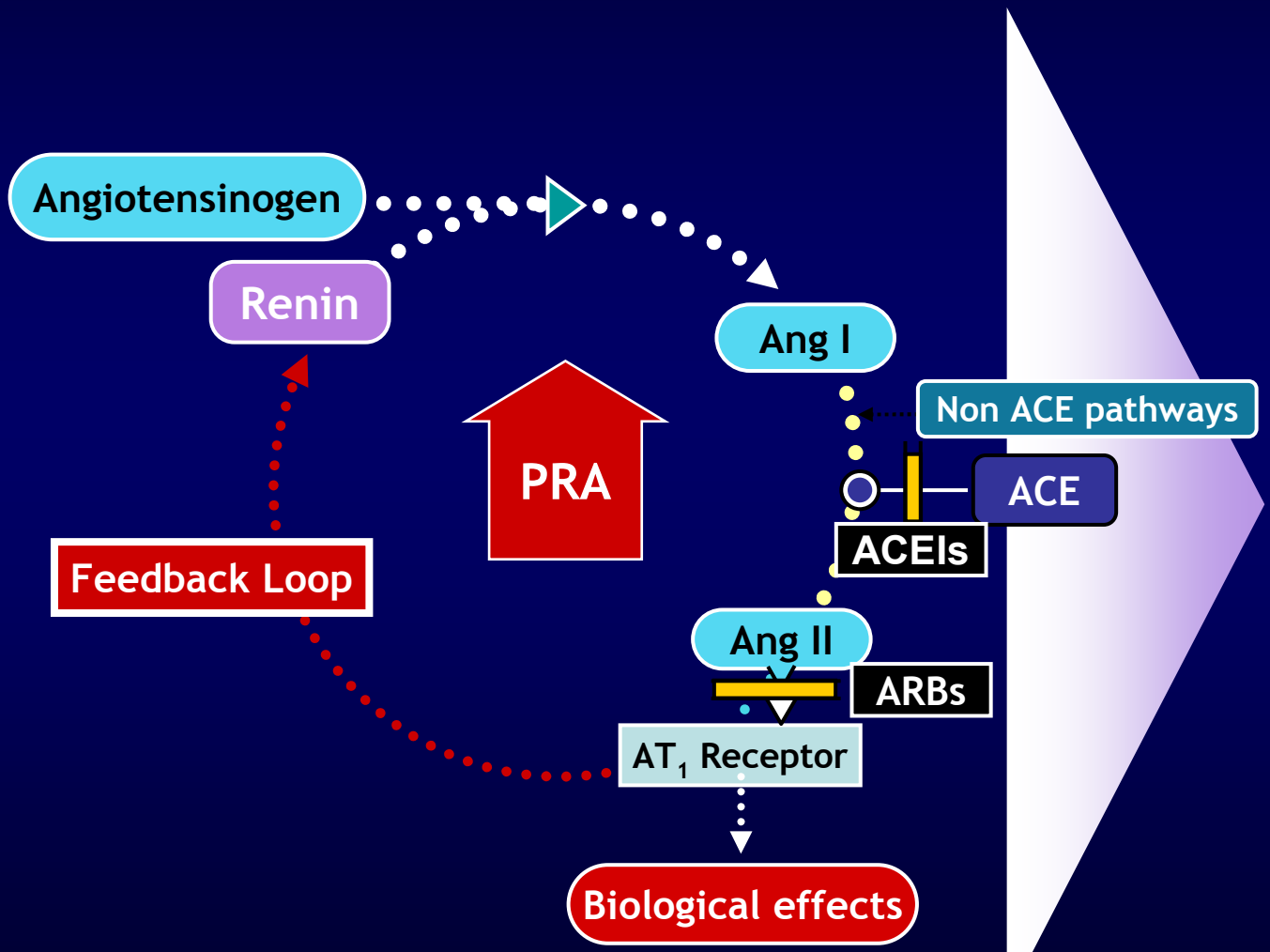
Direct Renin Inhibition with Aliskiren in Hypertension and Target Organ Damage

Dominik N. Müller and Friedrich C. Luft

Medical Faculty of the Charité, Max Delbrück Center for Molecular Medicine, Franz Volhard Clinic, HELIOS Klinikum-Berlin, Berlin, Germany

Clin J Am Soc Nephrol 2006;1:221-228

ACEIs and ARBs Cause Compensatory Rises in PRA



Kidney
- Glomerular vasoconstriction
- Inflammation
- Fibrosis

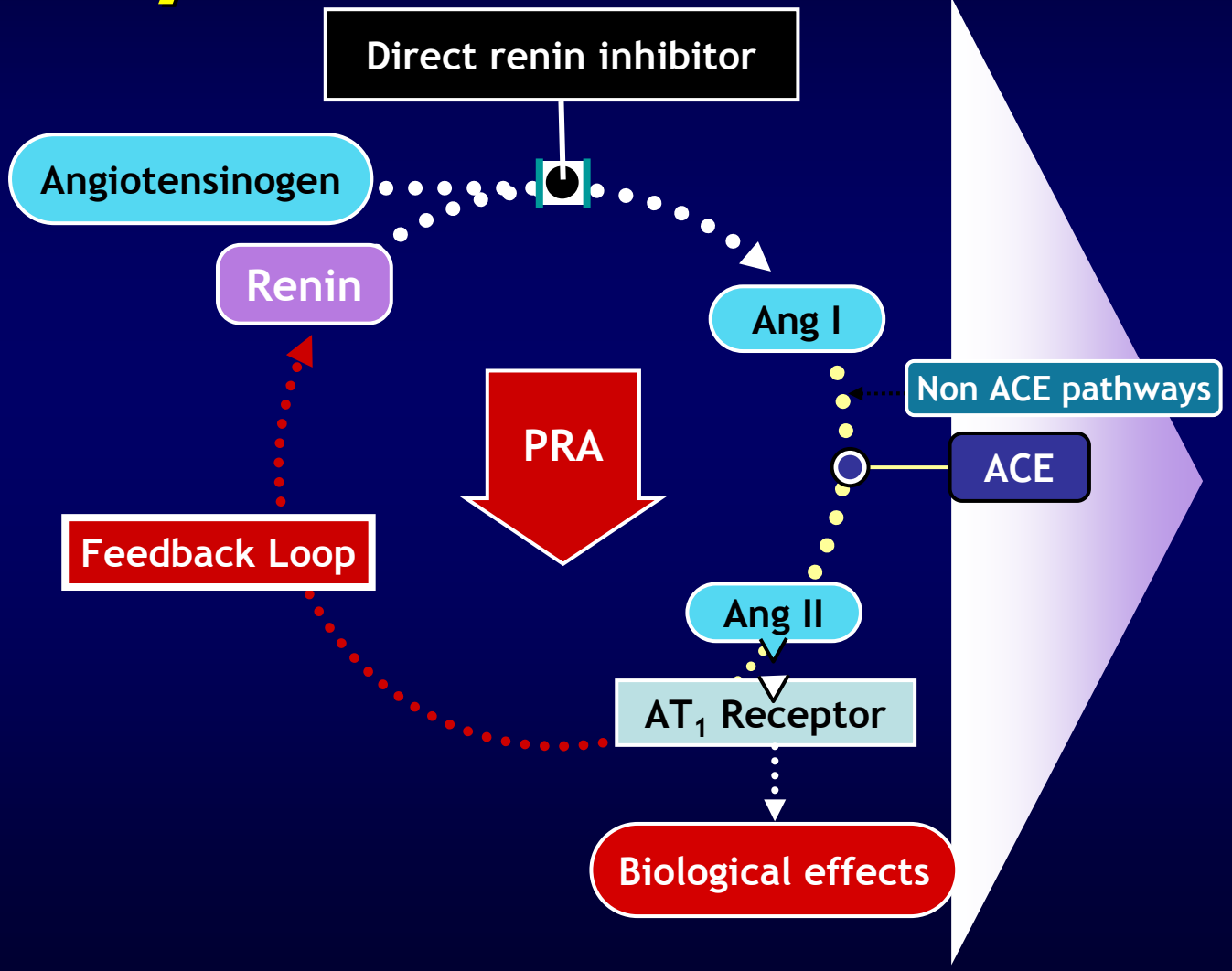
Heart
- Hypertrophy
- Fibrosis
- Vasoconstriction

Vessels
- Hyperplasia hypertrophy
- Inflammation
- Oxidation
- Fibrosis

Brain
- Vasoconstriction

Adapted from: Müller DN & Luft FC. 2006

Direct Renin Inhibition Acts at The Point of Activation of The Renin System and Neutralizes The PRA Rise



Kidney
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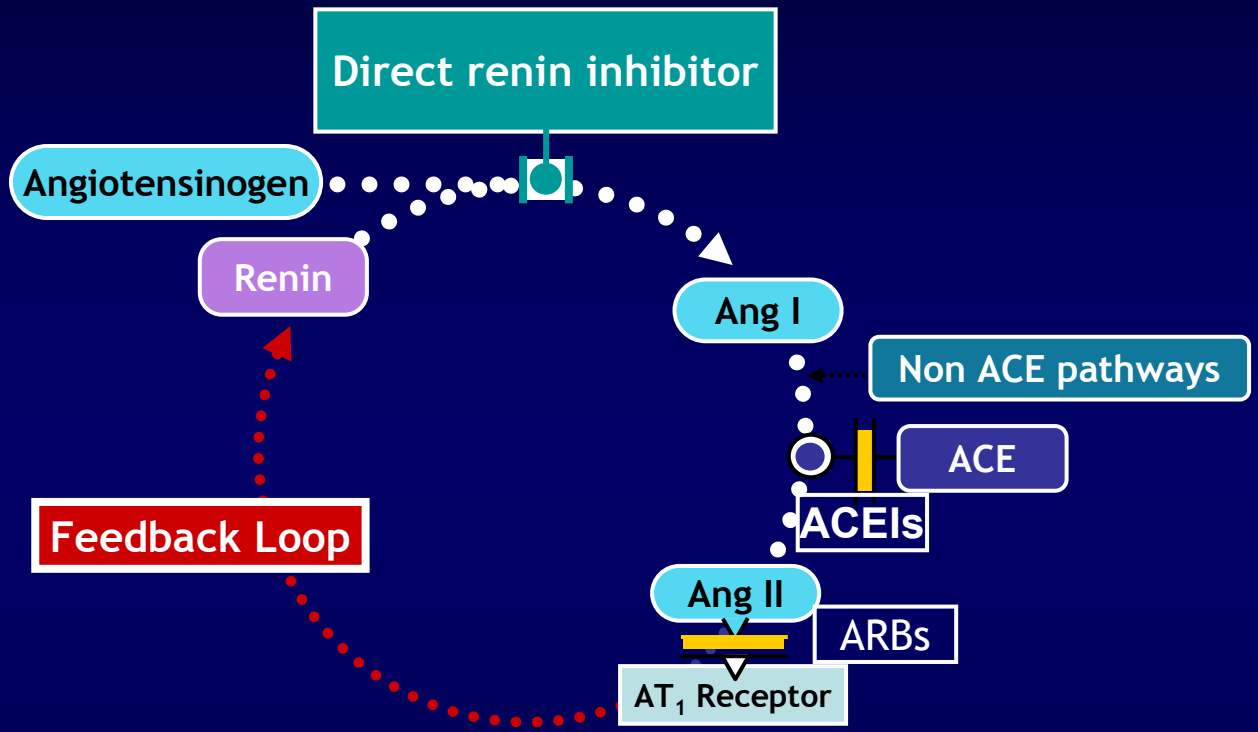
Brain
- Vasoconstriction

Adapted from: Müller DN & Luft FC. 2006

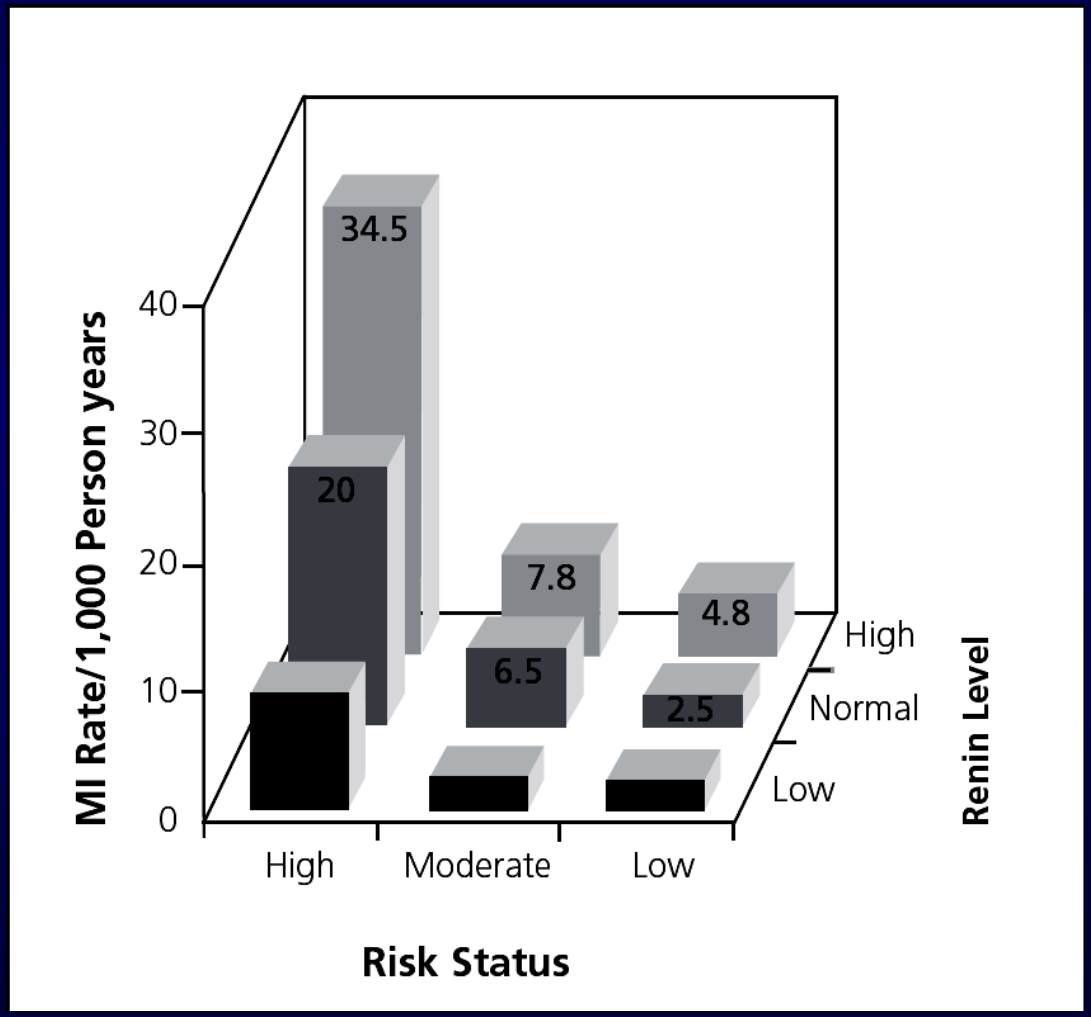
Unlike ACEIs and ARBs, Aliskiren Reduces Ang I, Ang II and PRA



	Ang I	Ang II	Renin	PRA
ACEI	↑	↓	↑	↑
ARB	↑	↑	↑	↑
Aliskiren	↓	↓	↑	↓

Azizi M *et al.* 2006

Relationship between Renin Activity and Risk of Myocardial Infarction in Patients with Hypertension



Alderman MH et al. Am J Hypertens 1997;10:1-8

Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin

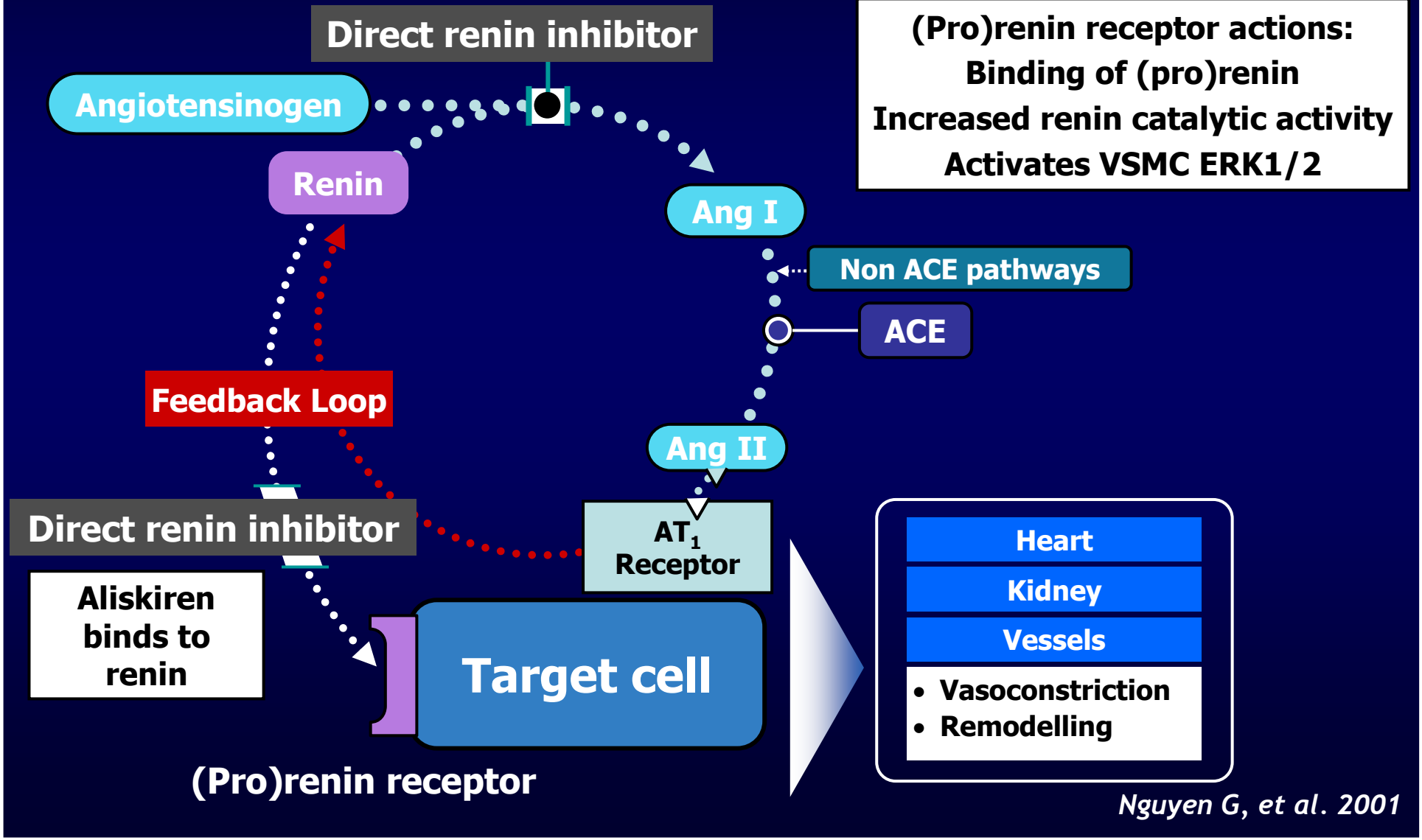
Genevieve Nguyen,[1] Françoise Delarue,[1] Céline Burcklé,[1] Latifa Bouzhir,[1] Thomas Giller,[2] and Jean-Daniel Sraer[1]

[1]Institut National de la Santé et de la Recherche Médicale (INSERM) U489, and Association Claude Bernard, Hopital Tenon, Paris, France
[2]Hoffman–La Roche Ltd., Basel, Switzerland

- This receptor is localized primarily in the mesangium of glomeruli but also in the subendothelium of arteries of the heart and kidney

J Clin Invest 2002;109:1417-1427

(Pro)renin Receptor May Play an Important Role In Cardiovascular Disease



Nguyen G, et al. 2001

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Plasma Prorenin Activity and Complications in Children with Insulin-Dependent Diabetes Mellitus

- Prospective observational study
- Plasma prorenin activity was measured in 135 children and adolescents with type I DM
- Increased plasma prorenin activity indentifies a group of young patients with diabetes who are at risk for retinopathy or nephropathy

Wilson DM et al, New Engl J Med 1990;323:1101-1106

Editorial

ACE2: A New Target for Prevention of Diabetic Nephropathy?

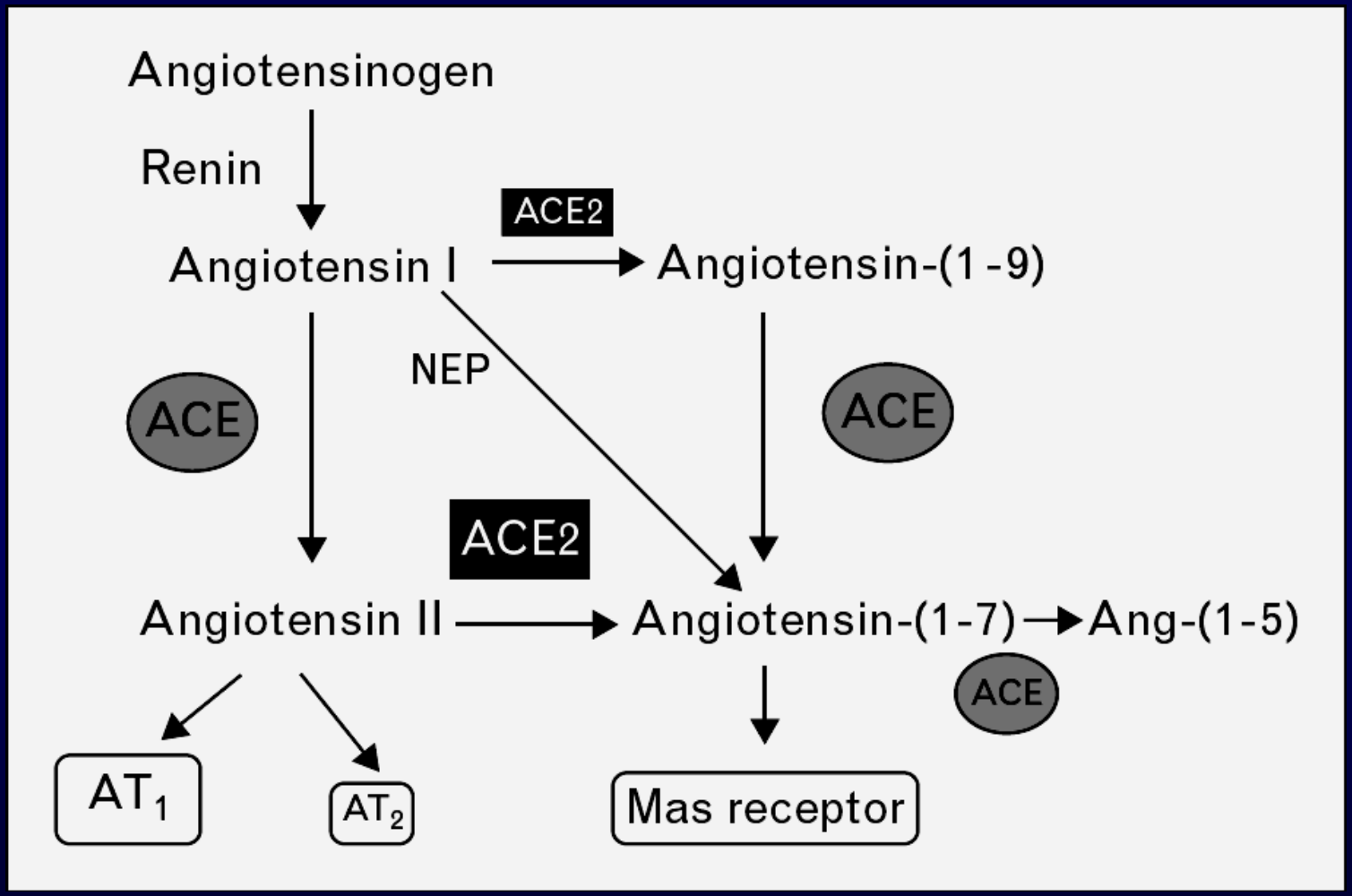
Julie R. Ingelfinger

Professor of Pediatrics, Harvard Medical School, Senior Consultant, Pediatric Nephrology, MassGeneral Hospital for Children at Massachusetts General Hospital, Boston, Massachusetts

J Am Soc Nephrol 17: 2957–2959, 2006. doi: 10.1681/ASN.2006090986

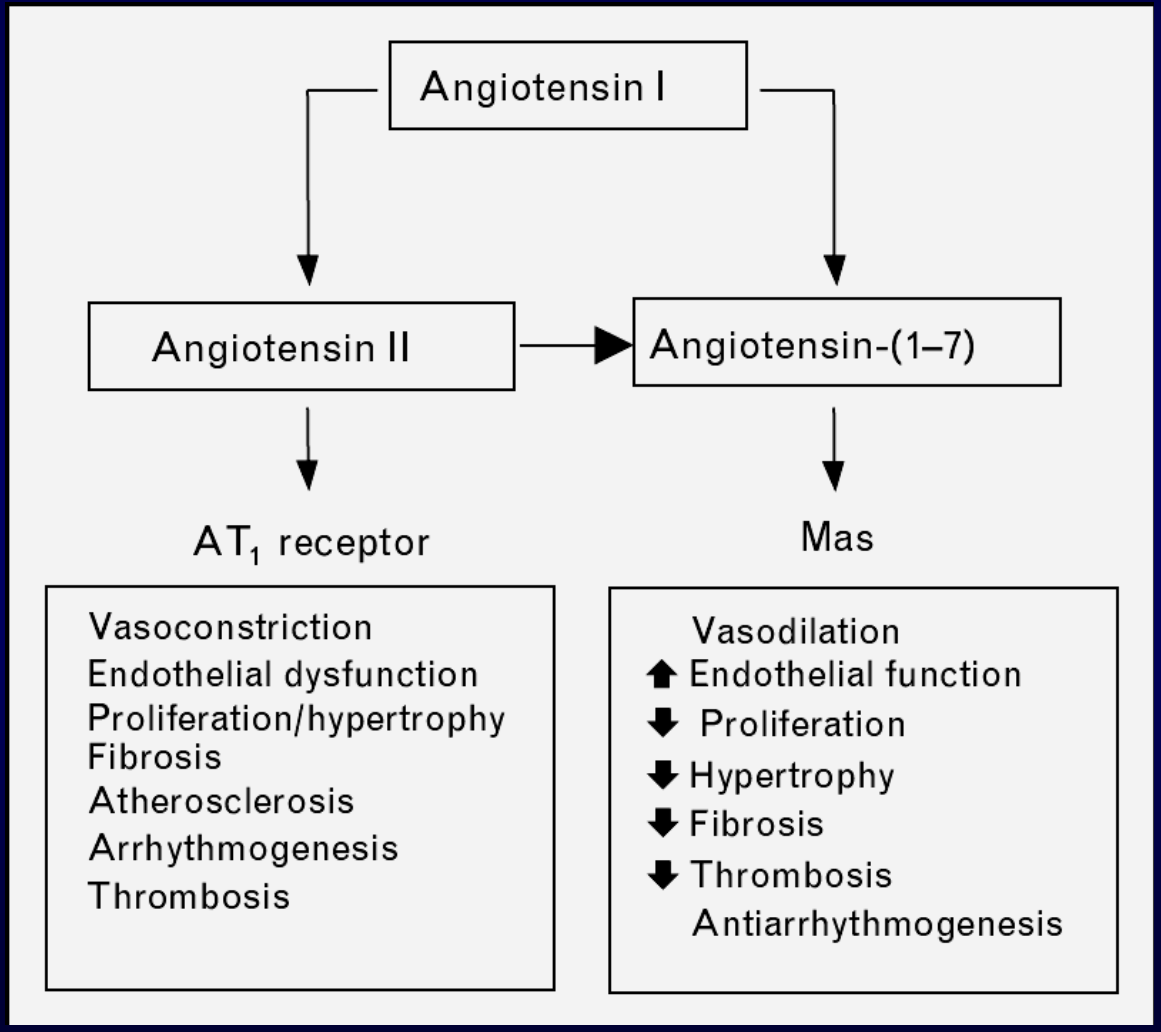
J Am Soc Nephol 2006;17:2957-2959

Role of Angiotensin-Converting Enzyme-2 in The Renin-Angiotensin System



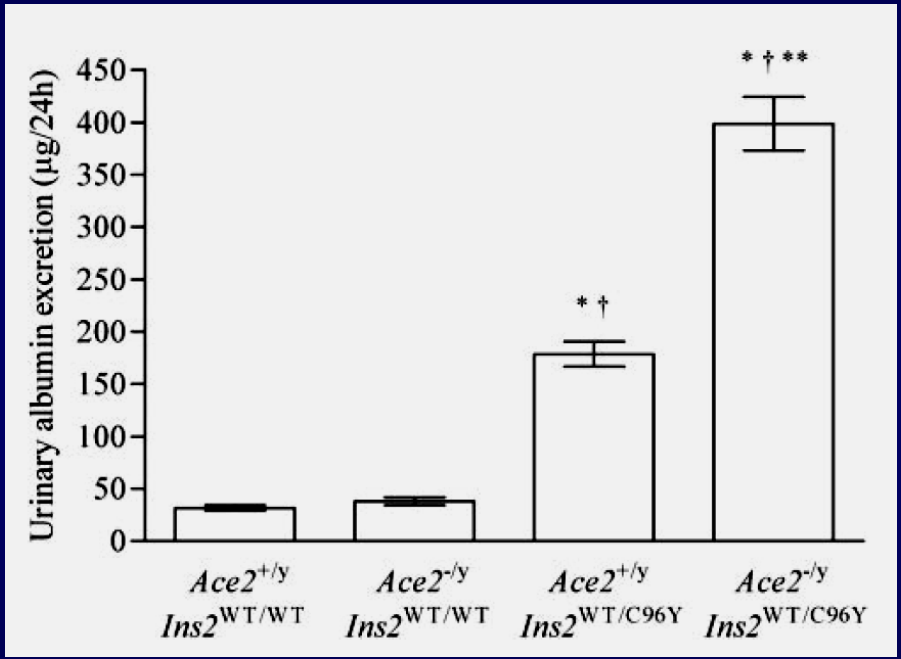
Burns KD. Curr Opin Nephrol Hypertens 2007;16:116-121

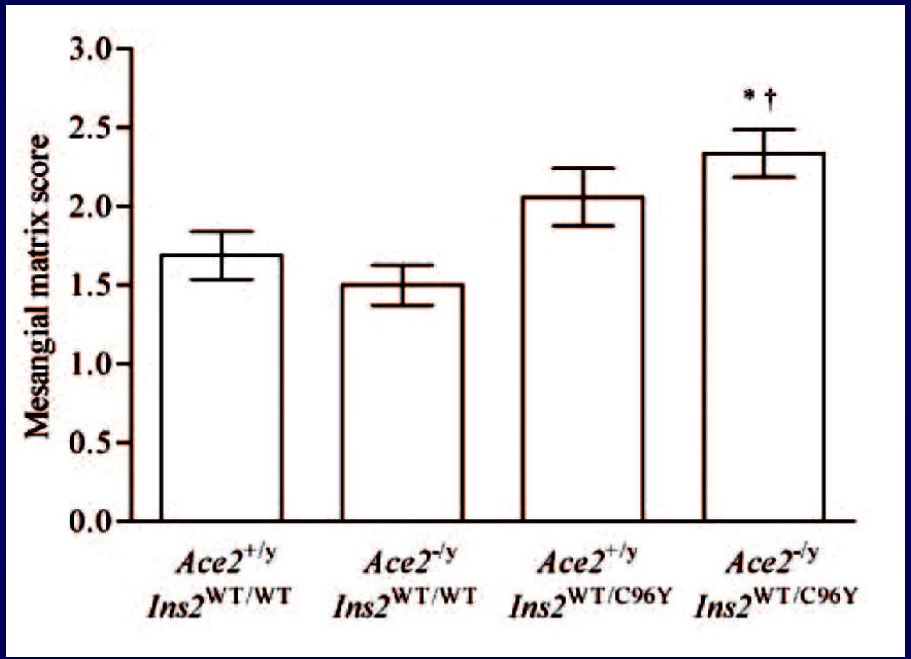
Opposing Cardiovascular Effects of The Counter Regulatory Arms of The Renin-Angiotensin System



Santos RAS et al. Curr Opin Nephrol Hypertens 2007;16:122-128

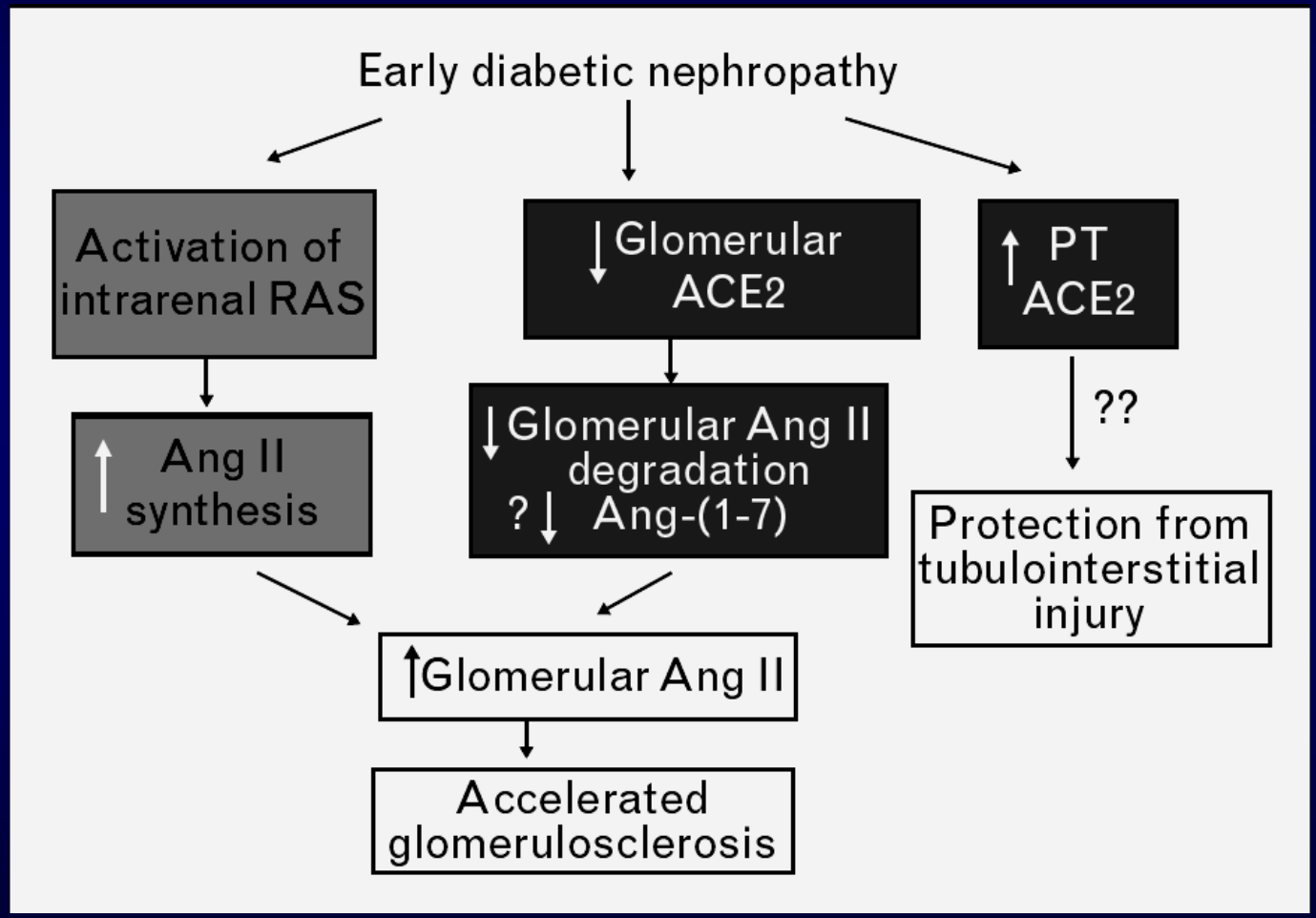
Loss of ACE-2 Accelerates Diabetic Kidney Injury in ACE-2 Null Mice





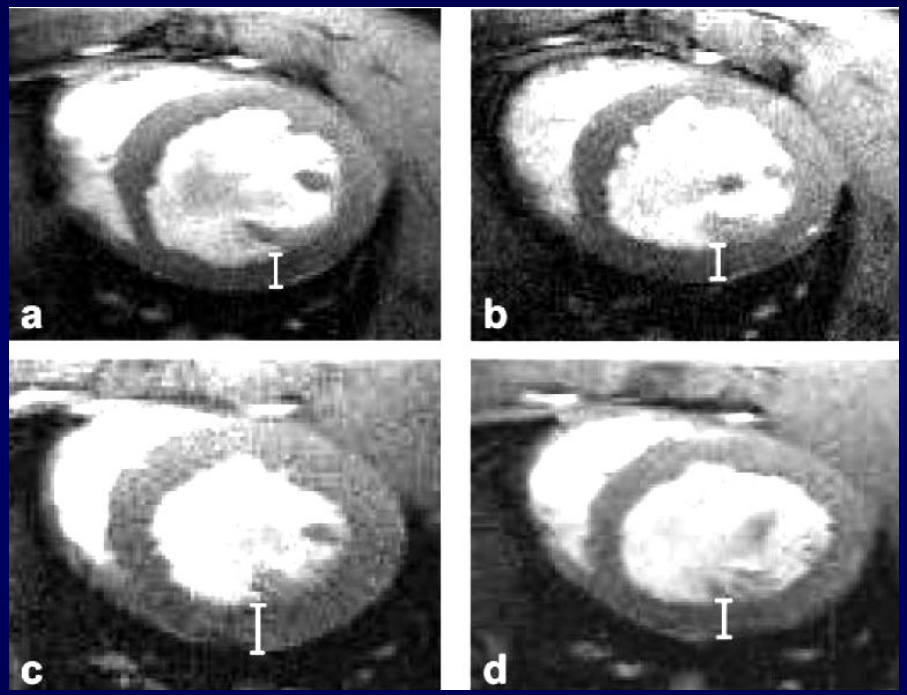
Wong DW et al. Am J Pathol 2007;171:428-451

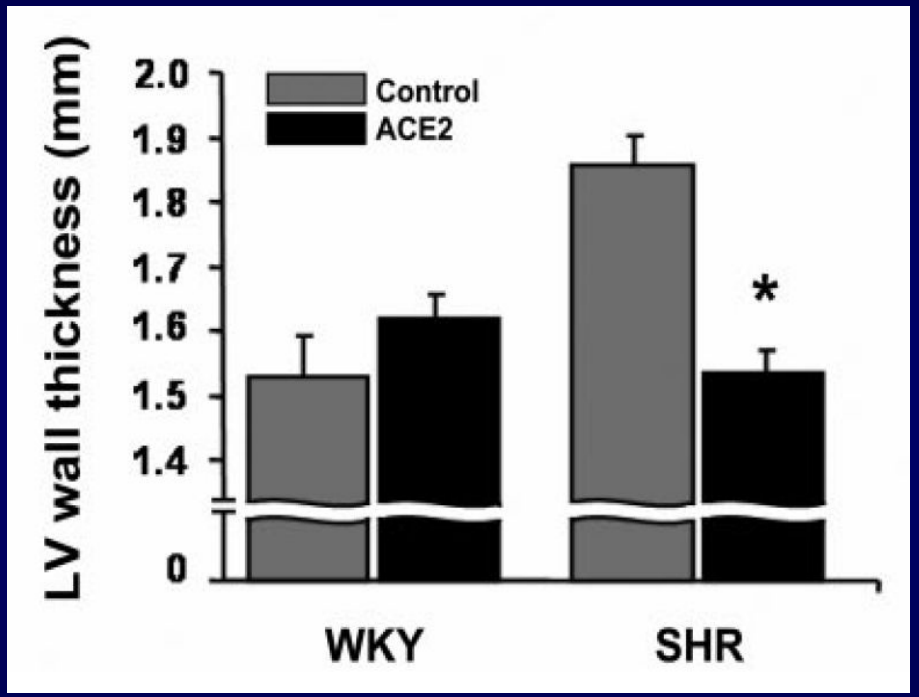
Proposed Role of Angiotensin-Converting Enzyme-2 in Early Diabetic Nephropathy



Burns KD. Curr Opin Nephrol Hypertens 2007;16:116-121

Overexpression of ACE-2 Attenuated Cardiac Hypertrophy in SHR





(a) WKY rat treated with lenti-EGFP

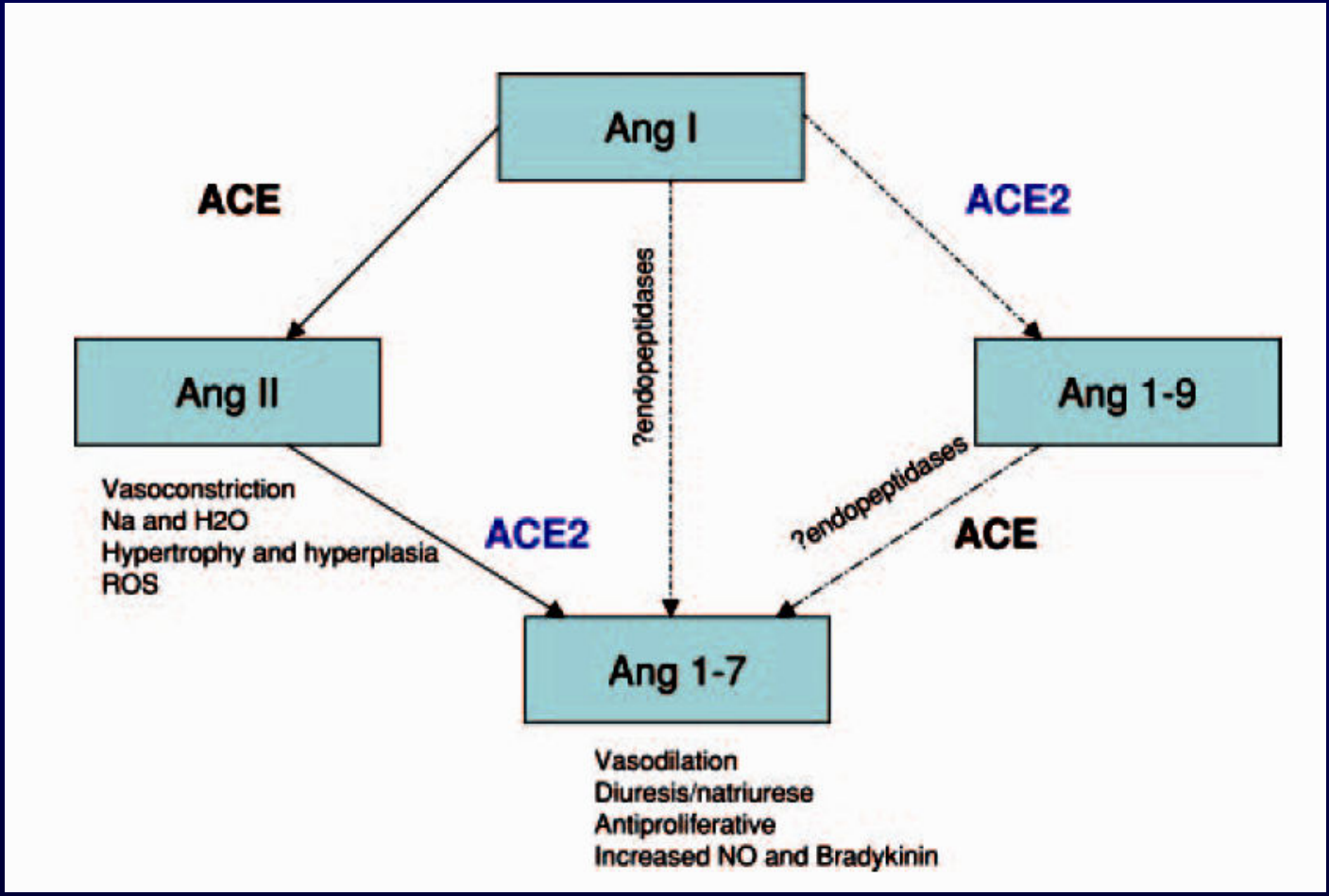
(b) WKY rat treated with lenti-ACE2

(c) SHR treated with lenti-EGFP

(d) SHR treated with lenti-ACE2

Diez-Freire C et al. Physiol Genomics 2006;27:12-19

ACE2 and Its Product Ang (1-7) Future Therapeutic Target



Angiotensin II Type 2 (AT2) Receptor

- In fetal tissues, the AT2-R is the dominating receptor subtype.
- In the adult, AT2-Rs are re-expressed under pathophysiological conditions such as mechanical injury or ischemia.
- The function role of AT2-Rs is uncertain. However, it is supposed to counteract AT1-Rs.

Cardiovascular and Renal Effects of Targeted Deletions of the AT2 Receptor Gene

Cardiac

- ↑ cardiac AT1-R expression
- ↑ cardiac hypertrophy after MI
- ↓ survival and increased left ventricular dilatation after MI

- Renal

- ↓ urine Na excretion/flow rate during chronic Ang II infusion
- ↓ pressure natriuresis
- ↑ renal AT1-R expression
- ↓ bradykinin and cGMP response after dietary sodium restriction or chronic Ang II infusion
- ↑ interstitial fibrosis and less apoptotic cells after UUO