The Road to Renin System Optimization: Renin Inhibitor

A New Perspective on the Renin-Angiotensin System (RAS)

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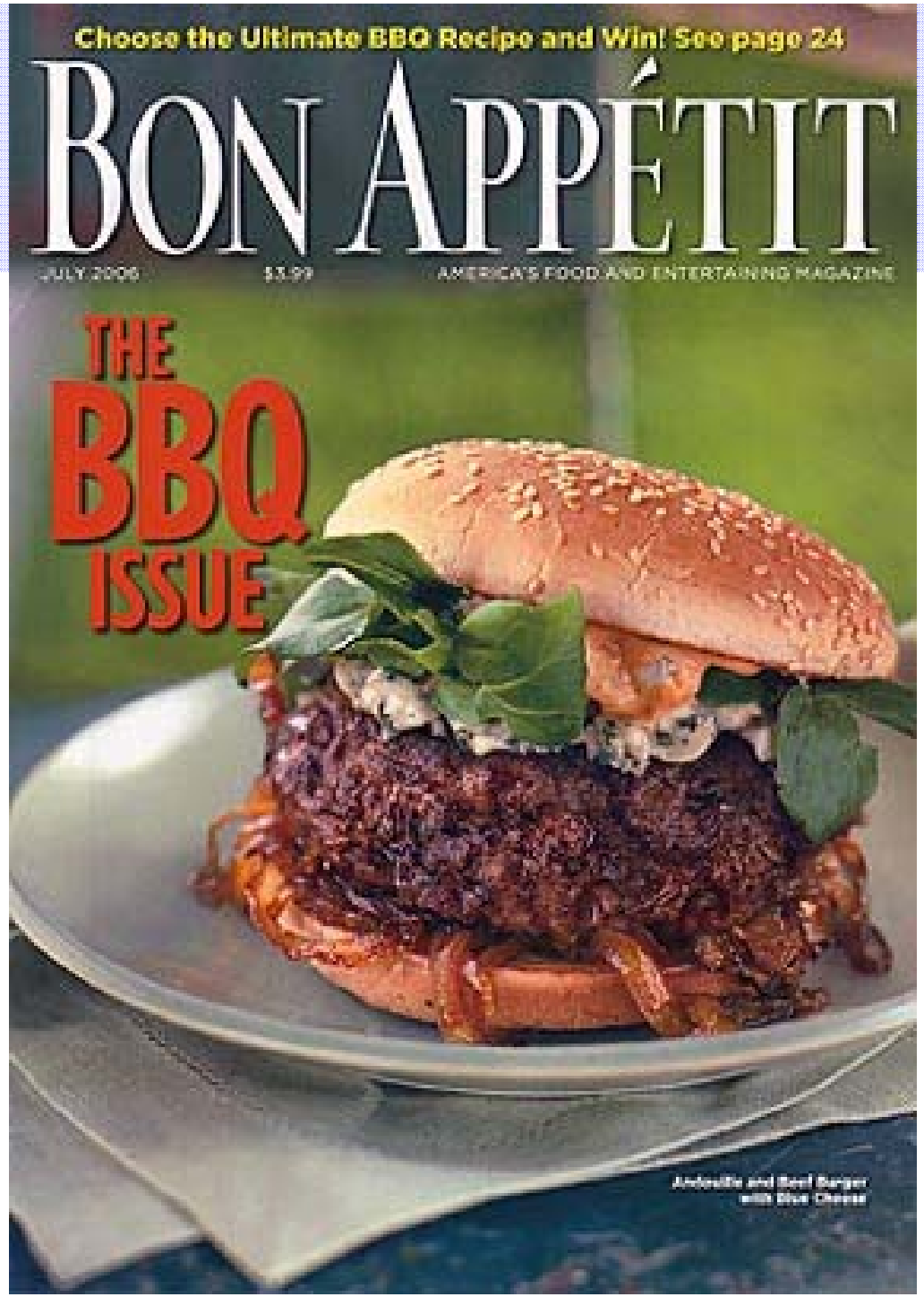
Seoul National University Hospital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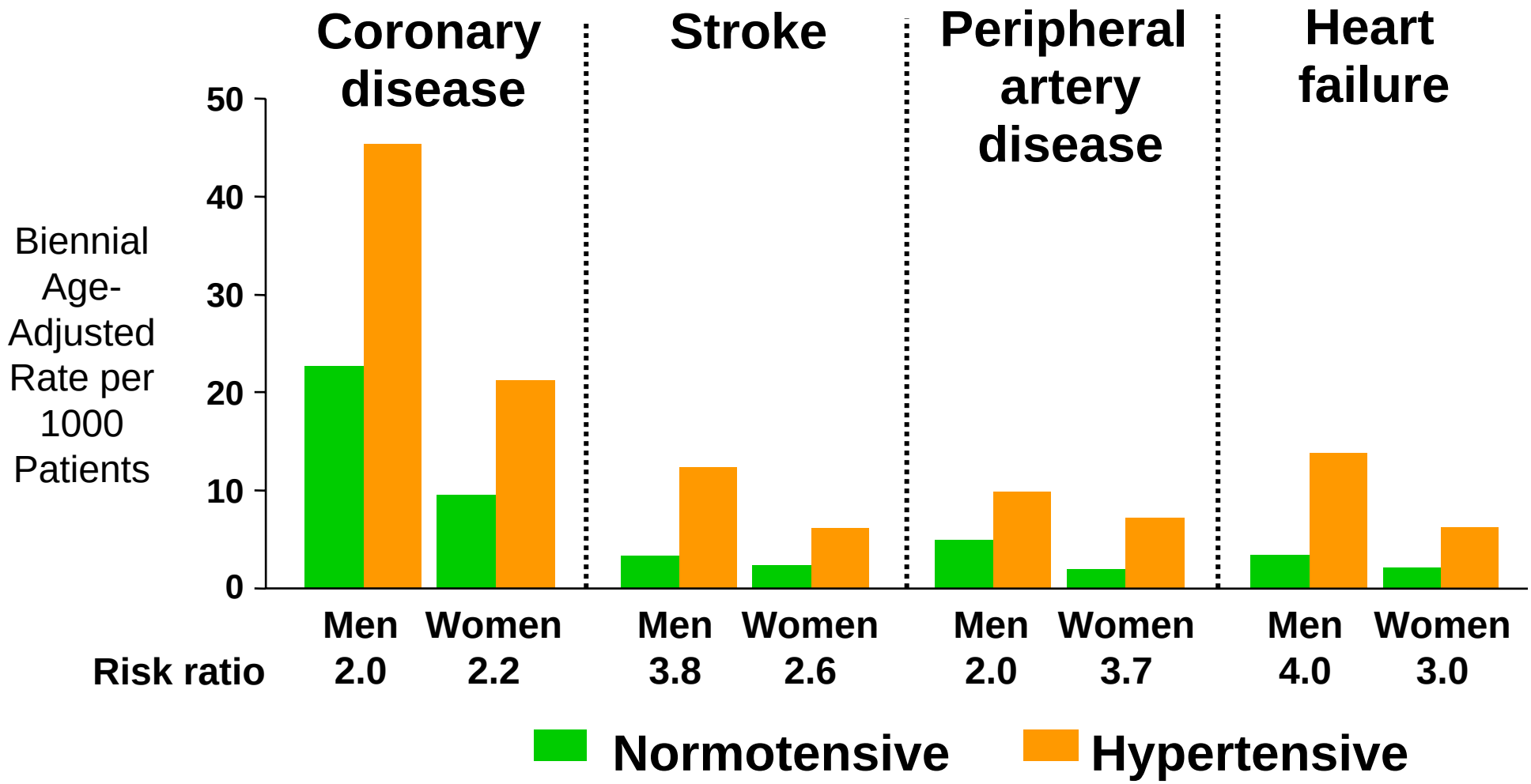
THE BBQ ISSUE
Andouille and Beef Burger with Blue Cheese

Human and Economic Costs of Hypertension (HT)

- **Single-most common cause of physician visits**
- **1/3 of American adults have HT**
- **Major multiplicative factor for cardiovascular disease**
- **Total costs of HT: $64 billion annually**

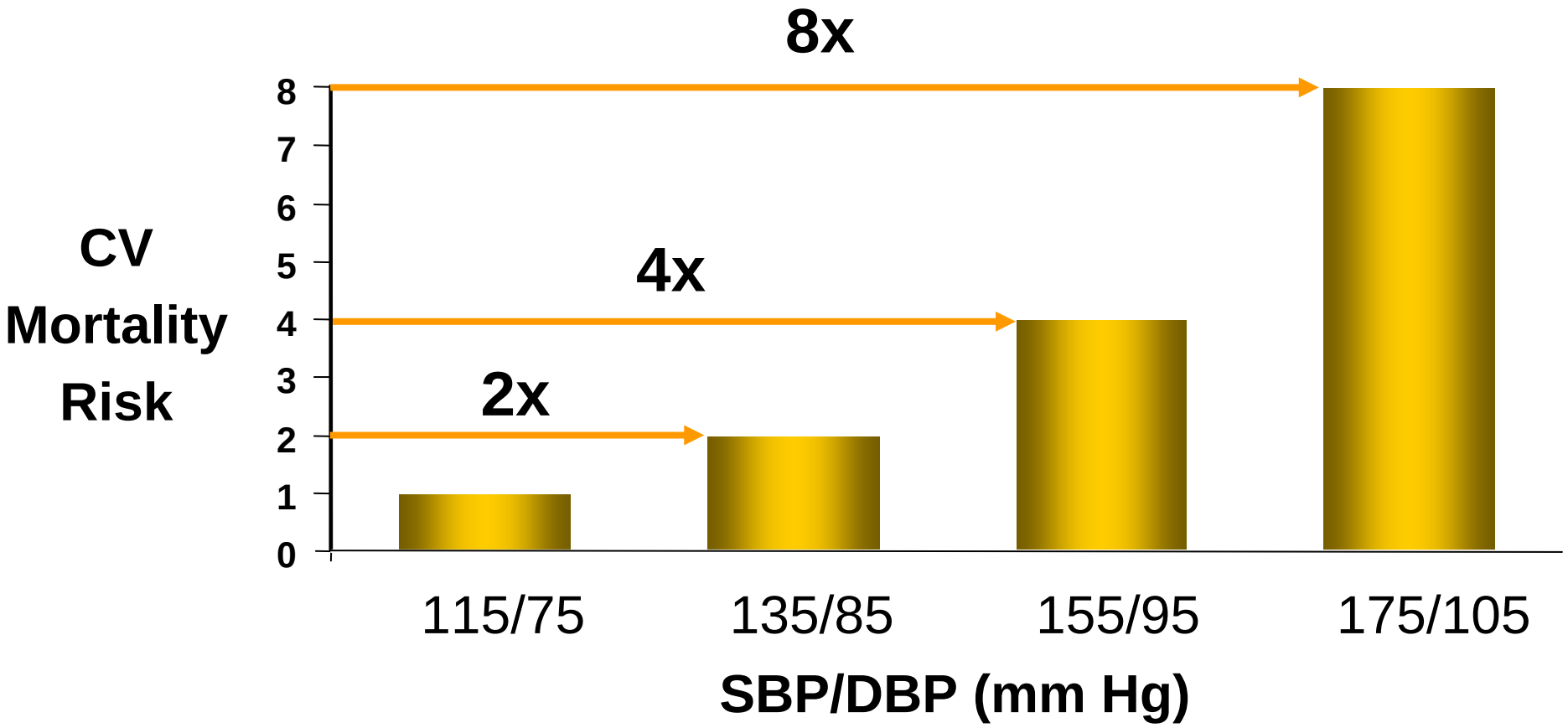
American Heart Association. *Heart Disease and Stroke Statistics-2006 Update.* Dallas, Tex: American Heart Association; 2006.

Hypertension:
A Risk Factor for CV Disease



Kannel WB. *JAMA.* 1996;275:1571-1576.

CV Mortality Risk Doubles With Each 20 and/or 10 mm Hg BP Increment*



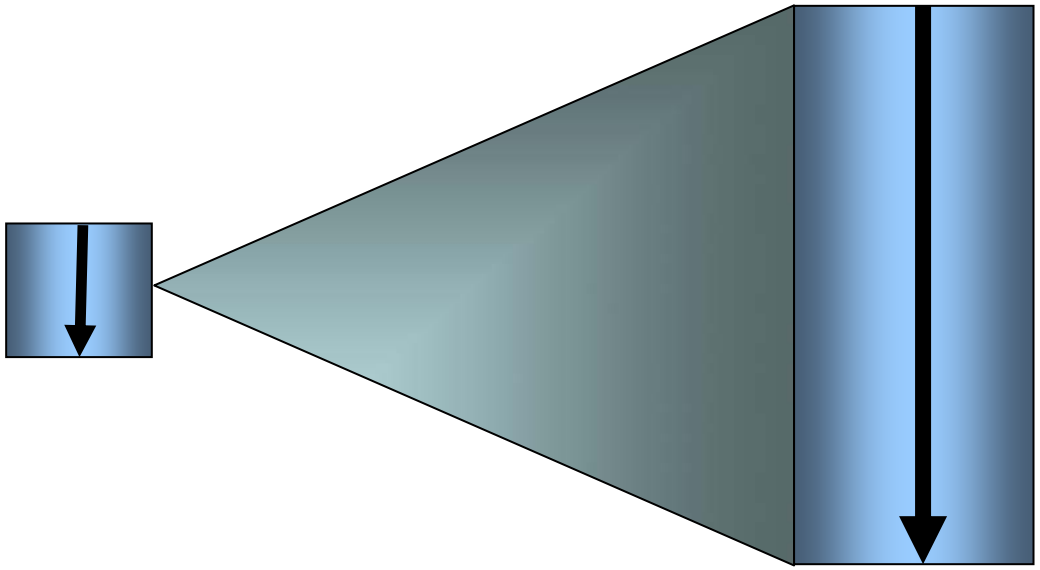
*Individuals aged 40 to 69 years, starting at blood pressure 115/75 mm Hg

Chobanian AV et al. *JAMA*. 2003;289:2560-2572. Lewington S et al. *Lancet*. 2002;360:1903-1913.

A Small Difference in BP Produces a Difference in Risk of CV Events

- **Meta-analysis of 61 observational studies**
- **1 million adults**

For every 2 mm Hg decrease in mean SBP



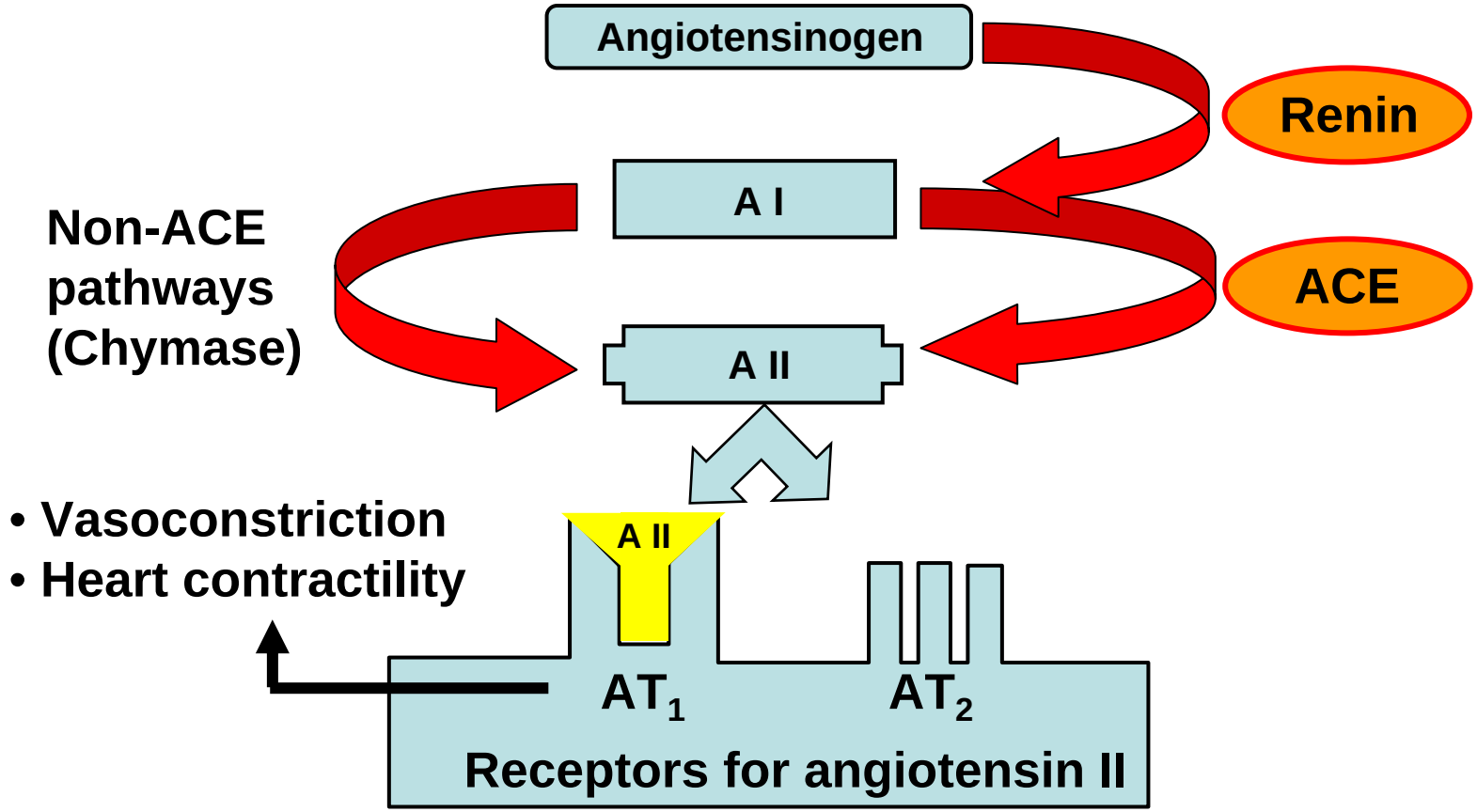
There is a:

- **7% reduction in risk of CHD mortality**
- **10% reduction in risk of stroke mortality**

Lewington S et al. *Lancet.* 2002;360:1903-1913.

RAS Activation/A II Formation in Regulating BP

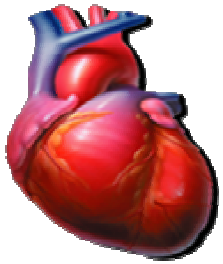
Cascade Model of the RAS



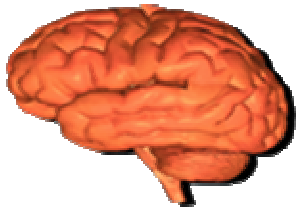
A I = angiotensin I; A II = angiotensin II; ACE = angiotensin-converting enzyme.

RAS Activation/A II Formation in Target Organ Damage

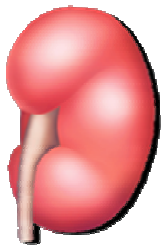
Angiotensin II



Heart



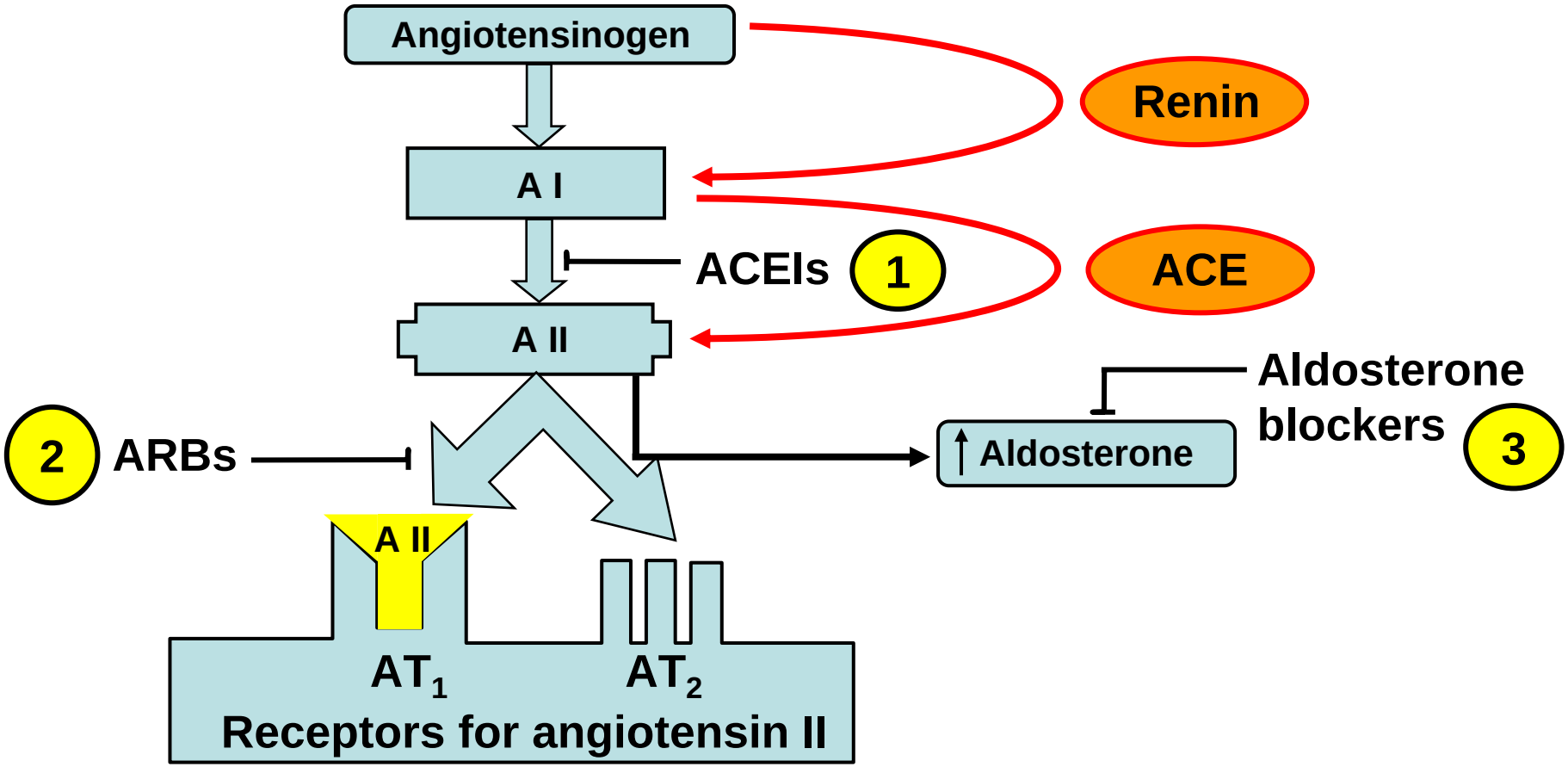
Brain



Kidney

Blood Vessel

Current Pharmacologic Interventions of the RAS



PROs: RAS Blockade Via ACEIs or ARBs

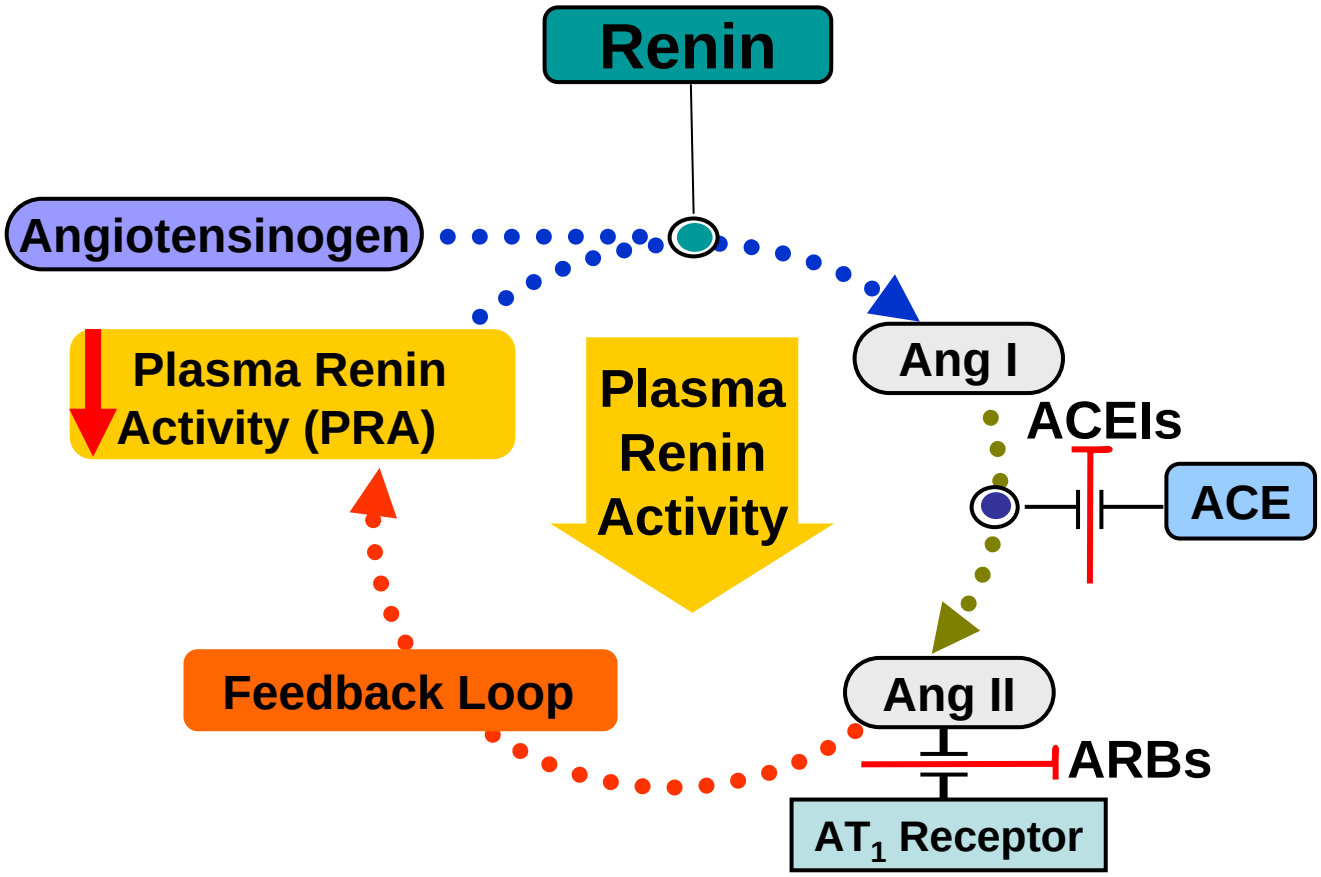
ACEI and ARBs

- Highly effective
- Well tolerated
- Benefits in addition to lowering BP
  - Chronic kidney disease
  - Diabetes
  - Heart failure
  - Recurrent stroke prevention*
  - Post-MI

*Only ACEIs have an indication for recurrent stroke prevention.

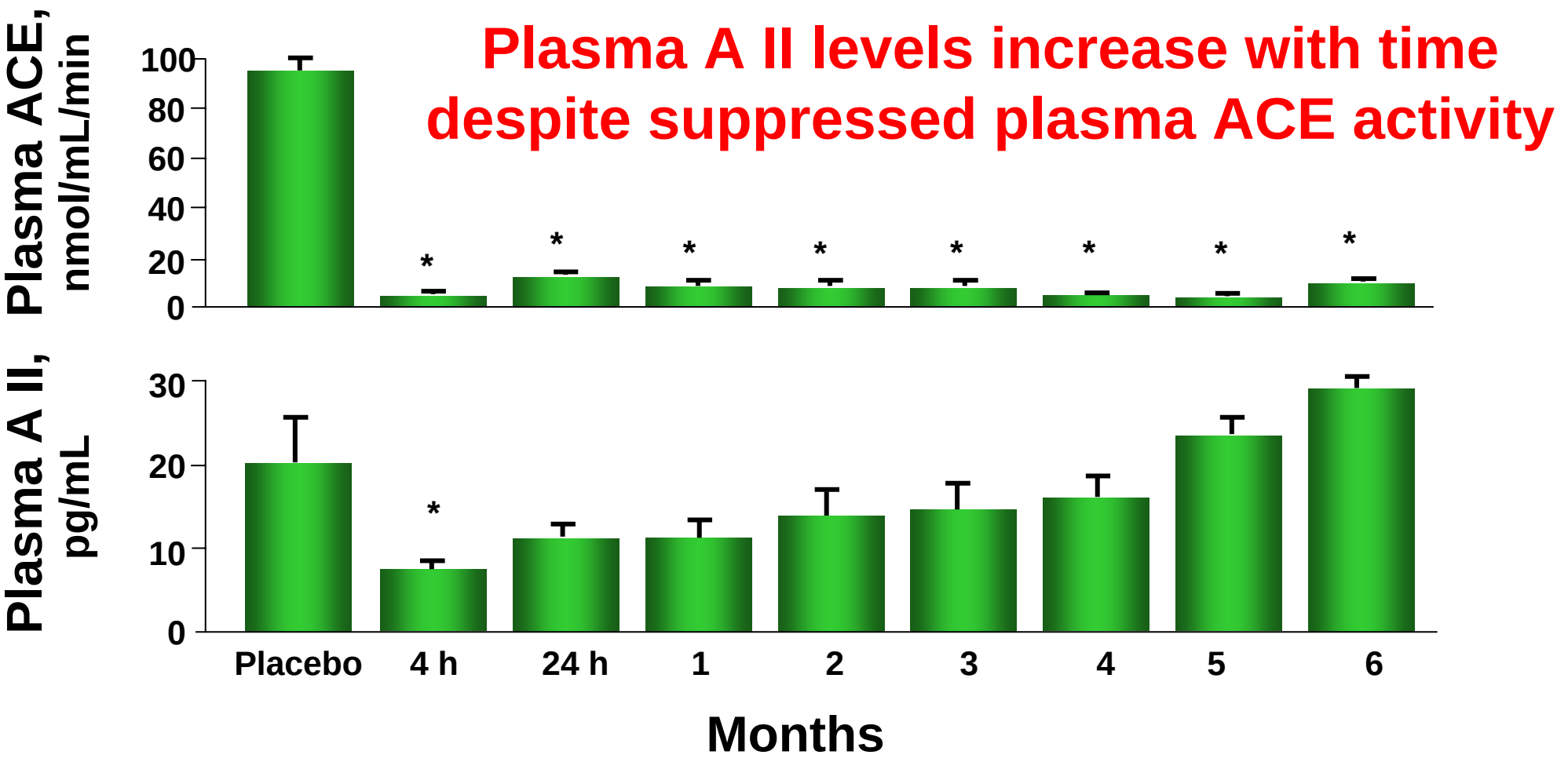
Chobanian AV et al. *JAMA*. 2003;289:2560-2572.

Current RAS-Blocking Agents Interrupt the RAS Negative-Feedback Loop



ACEIs & ARBs increase PRA through compensatory feedback mechanisms

Angiotensin II Escape With Long-Term ACEI Therapy



*P <0.001 vs placebo.

Adapted from Biollaz J et al. *J Cardiovasc Pharmacol.* 1982;4:966-972.

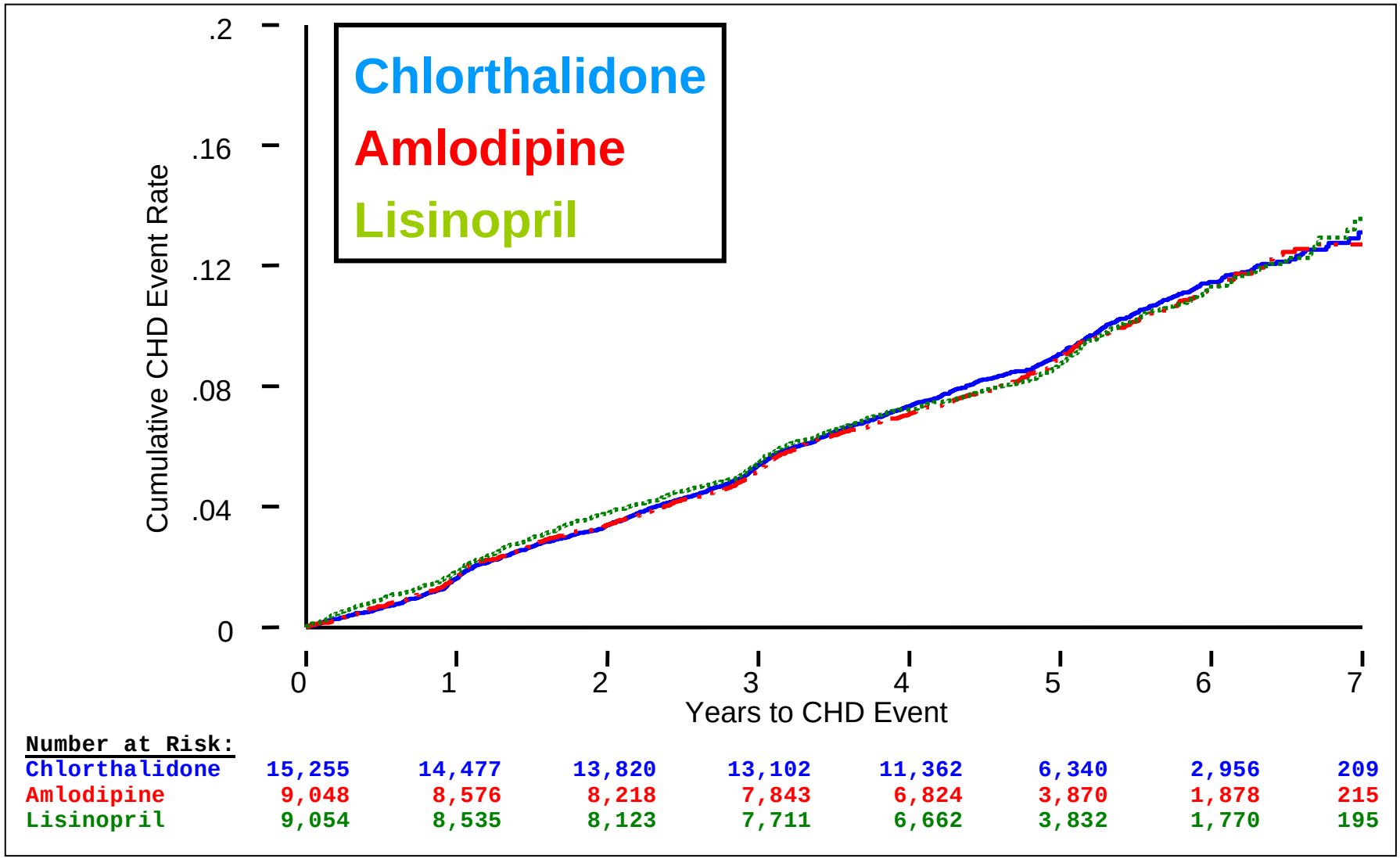
CONs: RAS Blockade Via ACEIs or ARBs

ACEI and ARBs

- ACEIs & ARBs:
  - Renin, Ang I and Ang II elevations
  - May prevent full BP-lowering potential
- ACEIs: incomplete RAS suppression d/t “A II escape phenomenon”
- ACEIs: cough, rash and angioedema

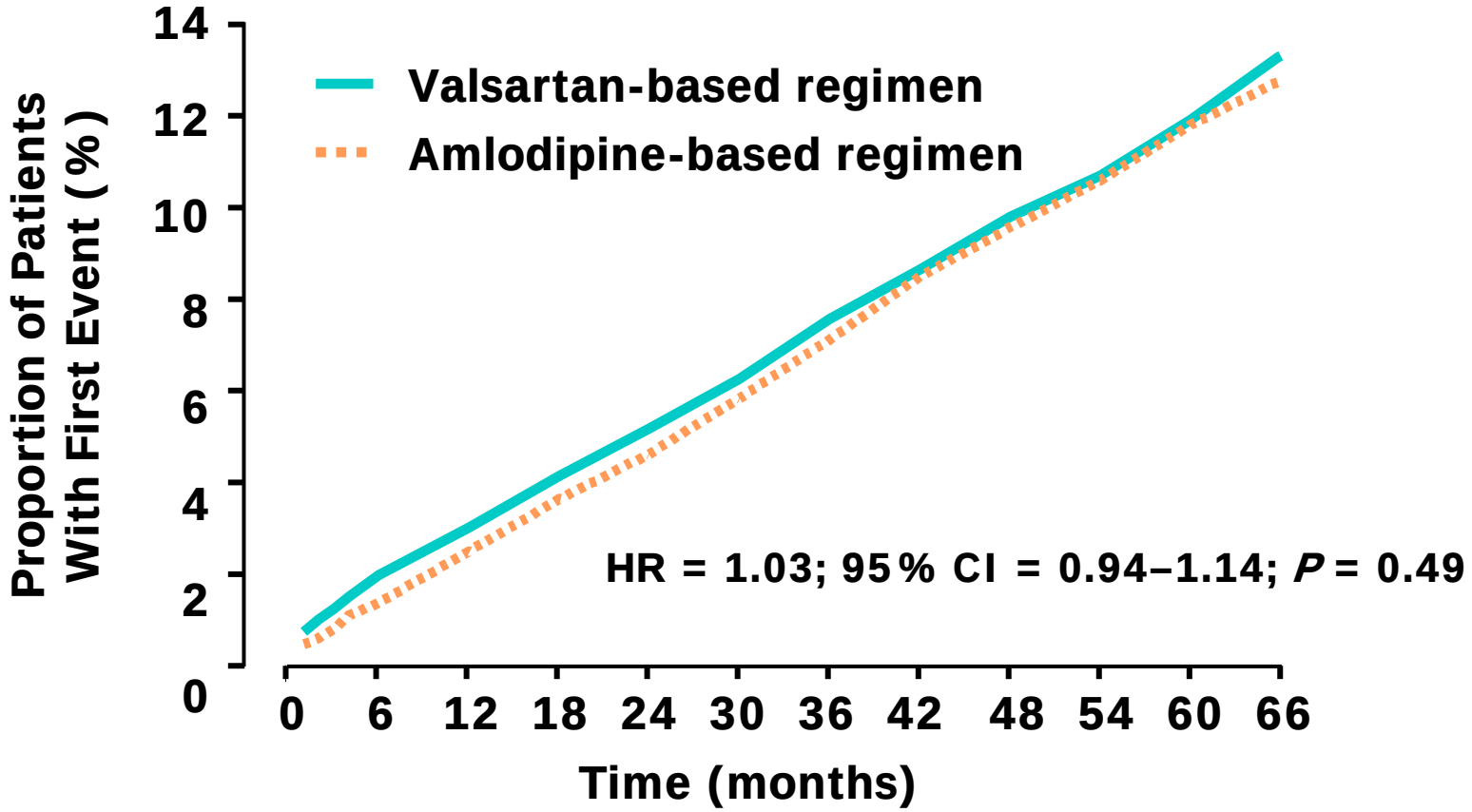
Chobanian AV et al. *JAMA*. 2003;289:2560-2572.

ALLHAT: Primary Composite Endpoints



Number at Risk:								
Chlorthalidone	15,255	14,477	13,820	13,102	11,362	6,340	2,956	209
Amlodipine	9,048	8,576	8,218	7,843	6,824	3,870	1,878	215
Lisinopril	9,054	8,535	8,123	7,711	6,662	3,832	1,770	195

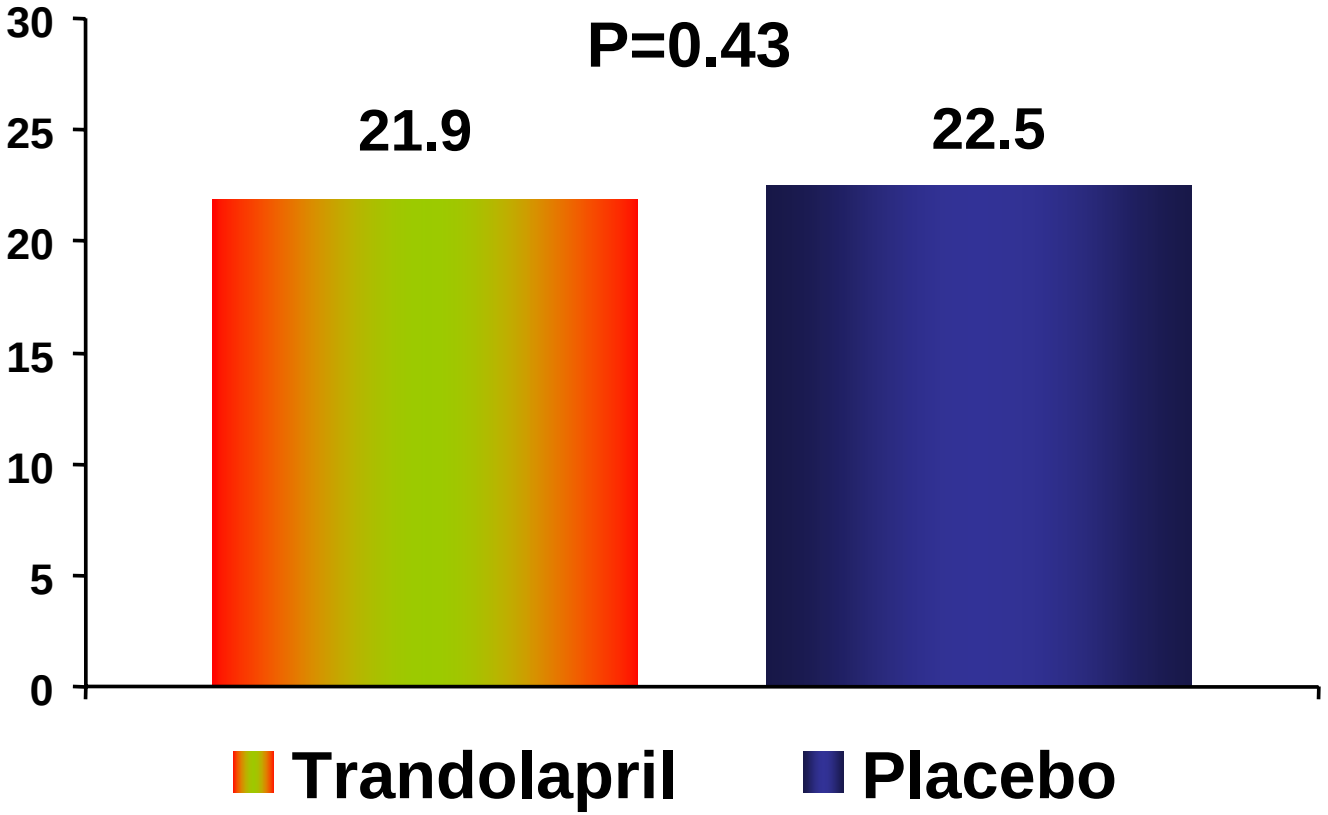
VALUE: Composite Cardiac Endpoints



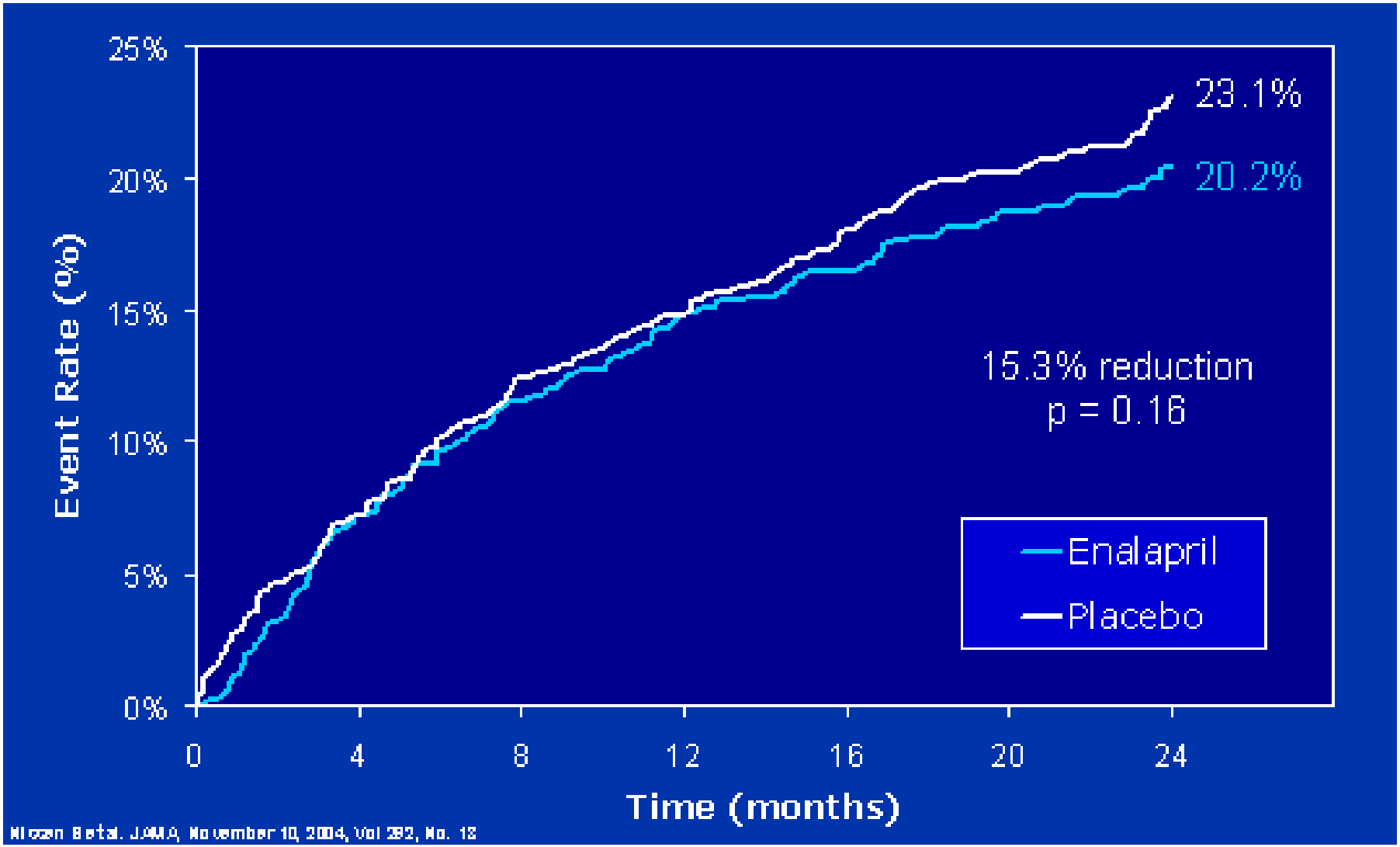
Julius S et al. *Lancet*. June 2004;363:2022 .

PEACE trial

CV death, nonfatal MI, coronary revascularization



CAMELOT:
CV events Enalapril vs Placebo



How Do We Improve RAS Inhibition?

- **Optimal Dosing of RAS blockers:**
  - **Ongoing clinical trials with Valsartan 640mg, Candesartan 128mg, and Irbesartan 900mg**
- **Combining RAS (ACEI + ARB) blockers:**
  - **May reduce the Ang II escape seen with ACEIs**
  - **Benefits in heart failure (CHARM-Added)**
  - **May reduce proteinuria (COOPERATE)**

How Do We Improve RAS Inhibition?

- **Target renin:**
  - **Renin's high specificity for its only known substrate, angiotensinogen:**
    - specific RAS inhibition without other metabolic effects
  - **Potential to block the RAS at its initial point of activation**

Gradman AH et al. *Circulation*. 2005;111:1012-1018.

How Do We Improve RAS Inhibition?

- **Target Renin:**
  - **Counteract feedback by ACEI/ARB**
  - **Proximal blockade prevents both A I and A II**
    - may be more efficacious than distal RAS inhibition via ACEIs and ARBs
    - a possible therapeutic profile distinct from those of both ACEIs and ARBs

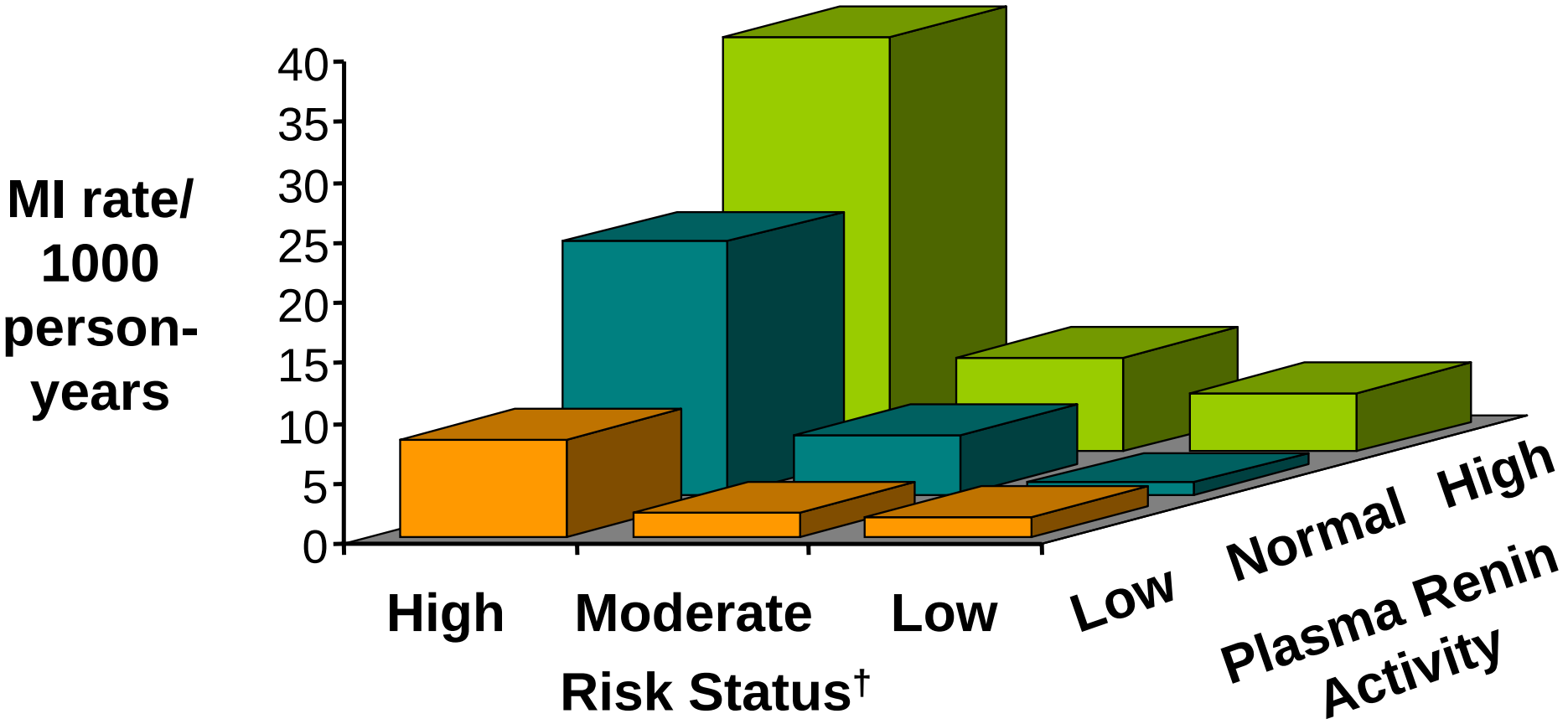
Gradman AH et al. *Circulation*. 2005;111:1012-1018.

How Do We Improve RAS Inhibition?

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

Azizi M *et al*. 2006

Plasma Renin Activity Predicts the Incidence of Myocardial Infarction



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†Risk status: high, ≥2 risk factors (smoking, cholesterol, LVH); moderate, 1 risk factor; low, no risk factors.
PRA, plasma renin activity.

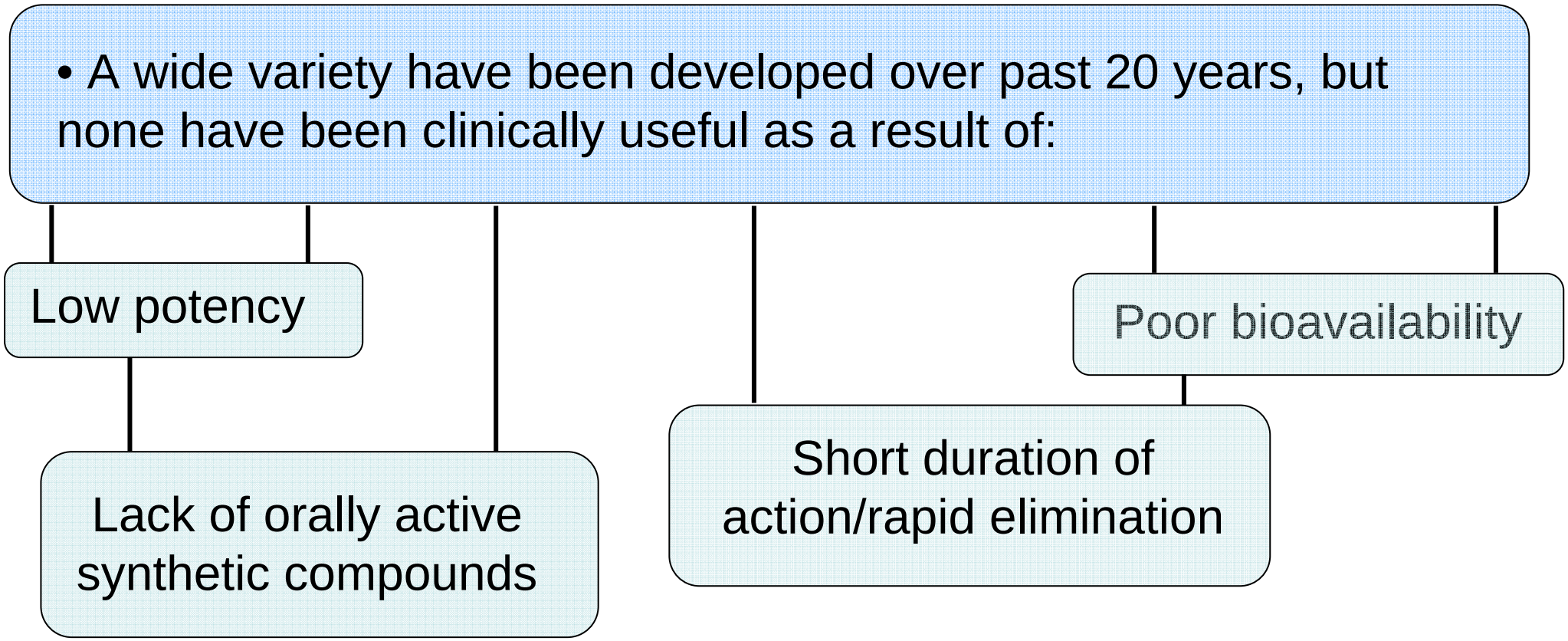
Alderman MH et al. *Am J Hypertens*. 1997;10:1-8.

PRA Is the Strongest Predictor of Mortality in Chronic Heart Failure

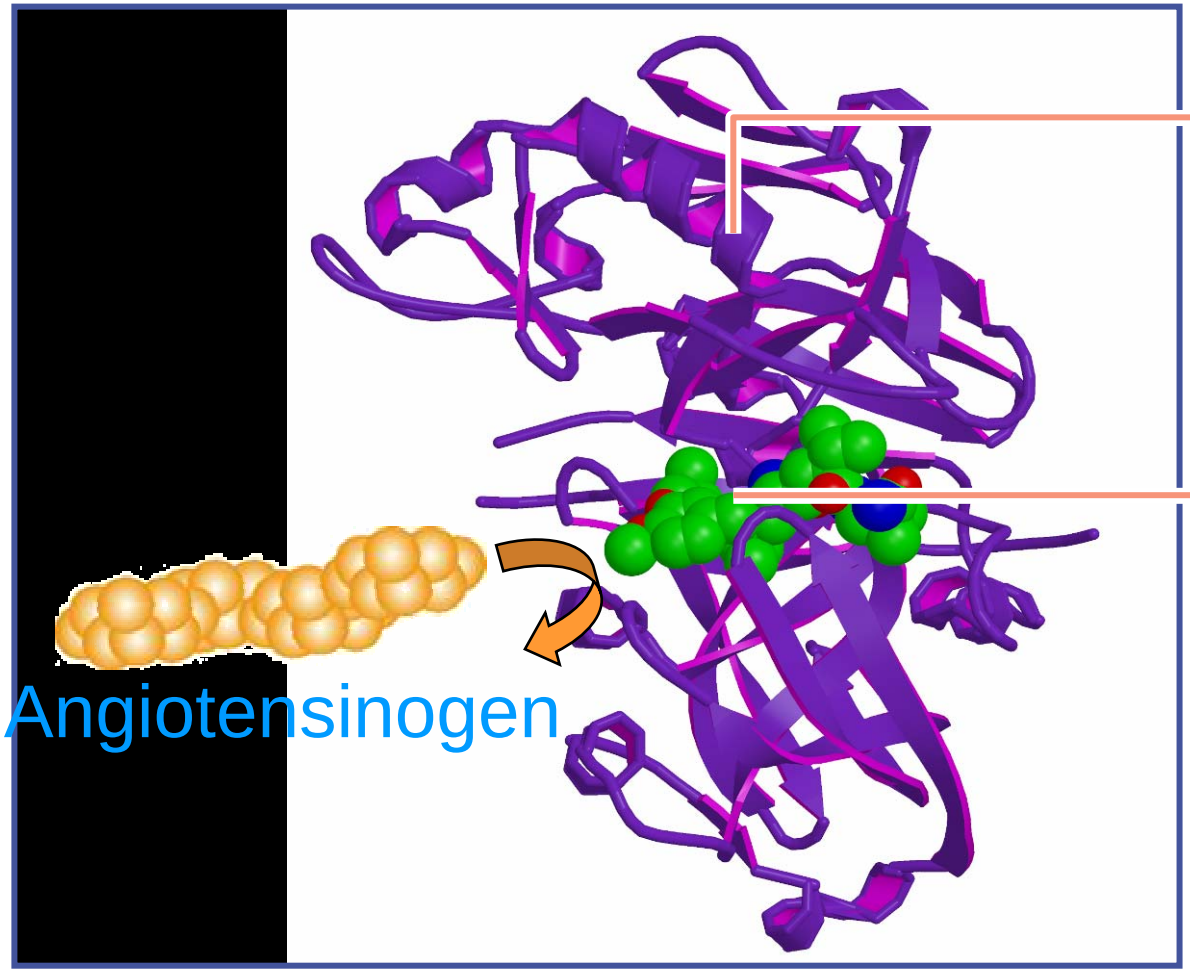
Variables	*P value*
Renin activity	**<0.001**
LV stroke work index	**<0.001**
Serum Cr concentration	**<0.004**
Other vasodilators	**<0.02**
Functional class	**<0.001**
Blood urea nitrogen	**<0.001**
Other vasodilators	**<0.02**

Rockman HA et al. *Am J Cardiol*. 1989;64:1344-1348.

History of Renin Inhibitor Development



Renin Inhibitor: Aliskiren



Renin

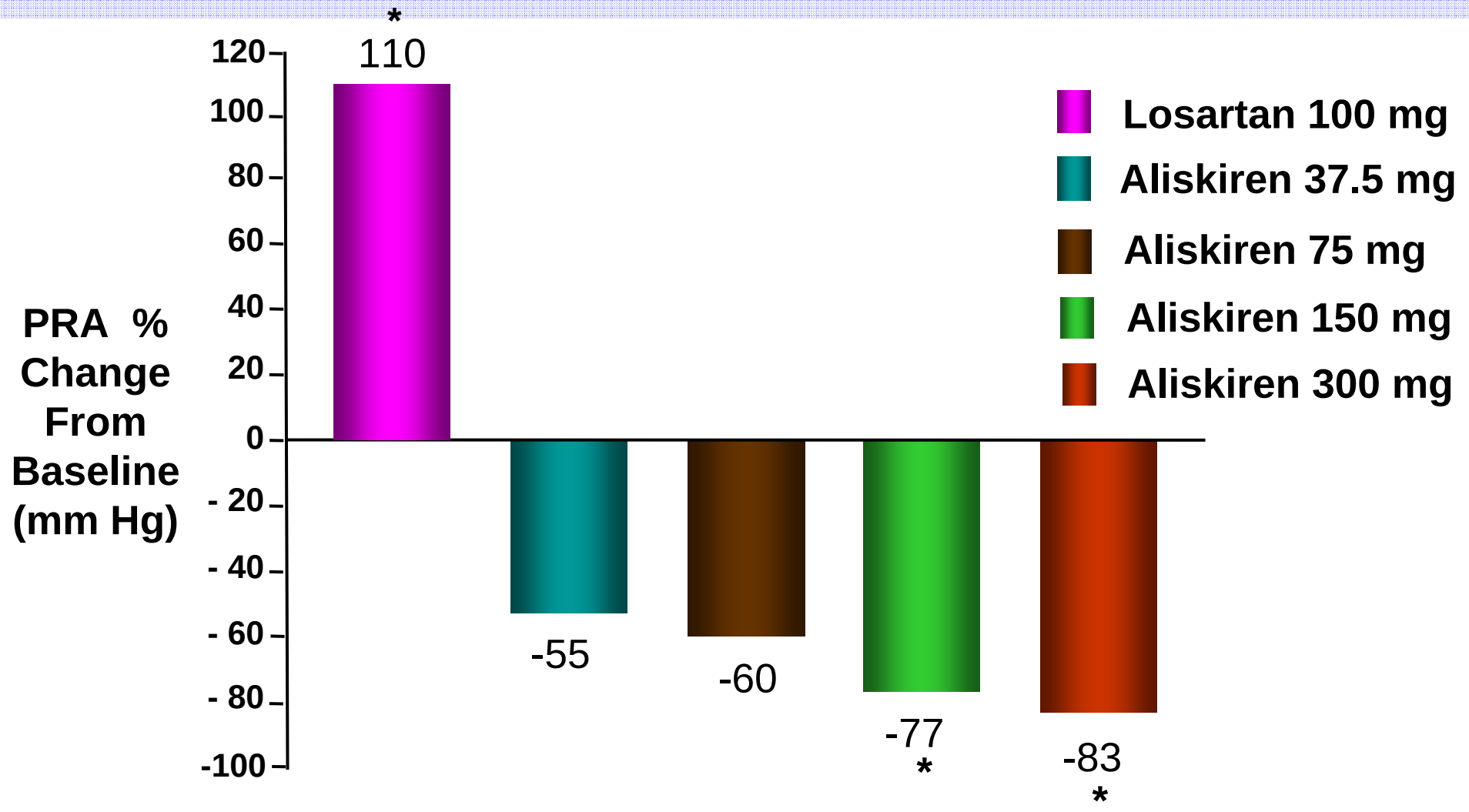
Aliskiren

binds to a pocket in the renin molecule, blocking cleavage of angiotensinogen to angiotensin I

Adapted from Wood JM, *et al.* 2003

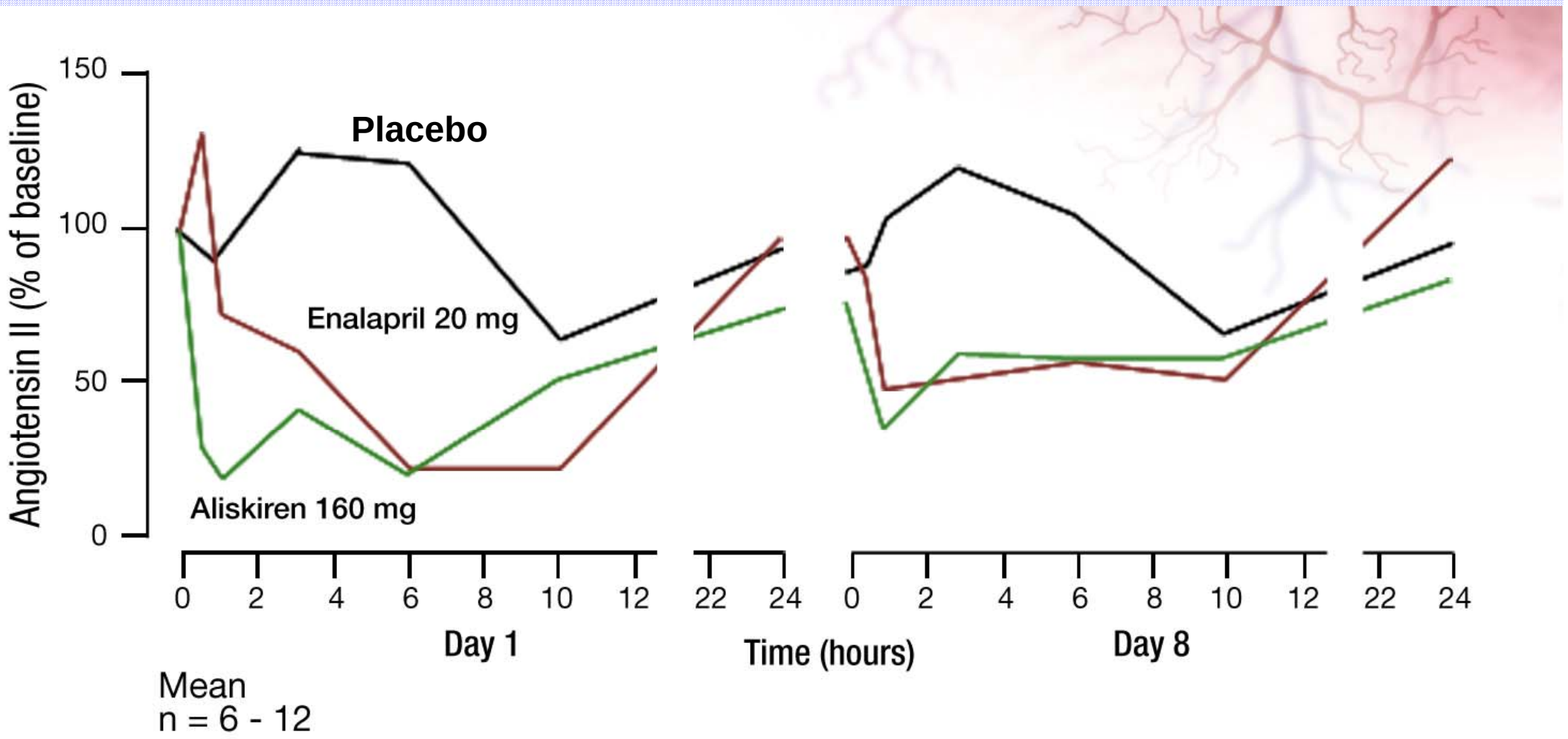
Clinical Data of Aliskiren

Reductions in PRA: Aliskiren vs Losartan



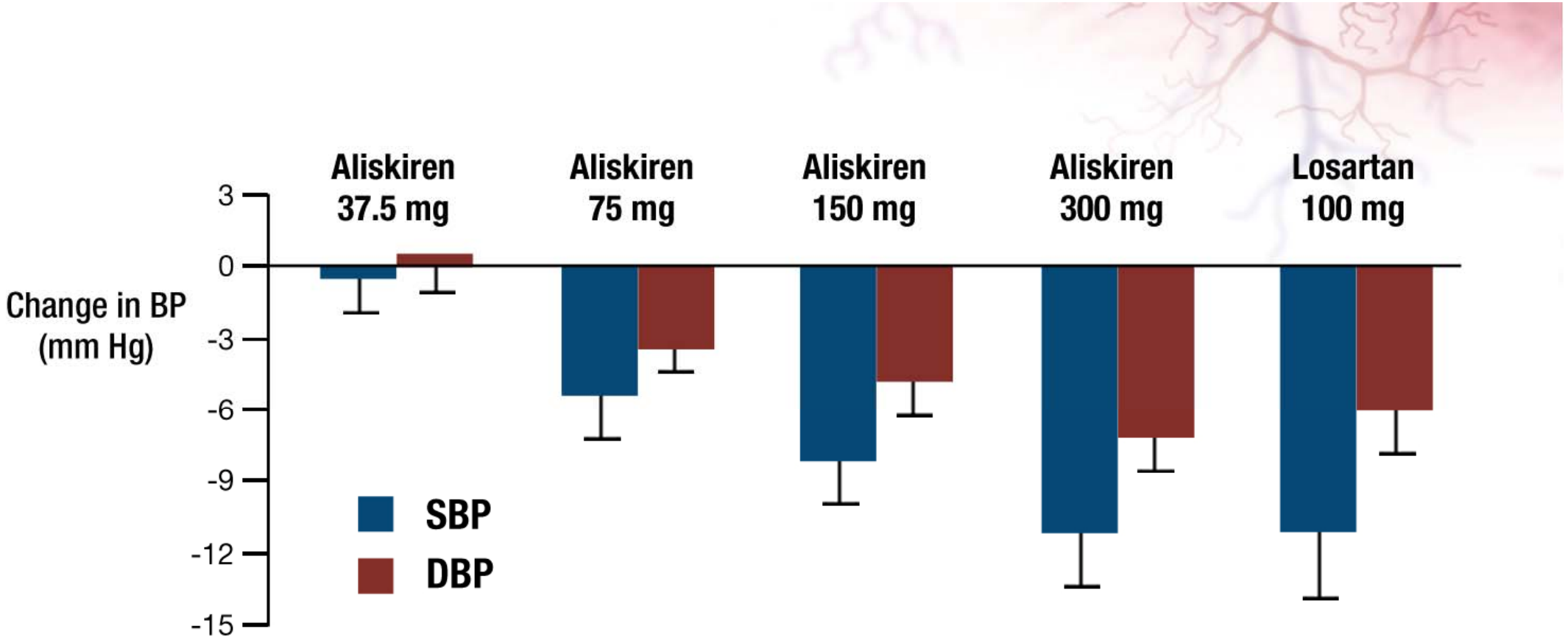
Stanton A et al. *Hypertension.* 2003;42:1137-1143.

Plasma A I I Suppression in Humans: Aliskiren vs Enalapril



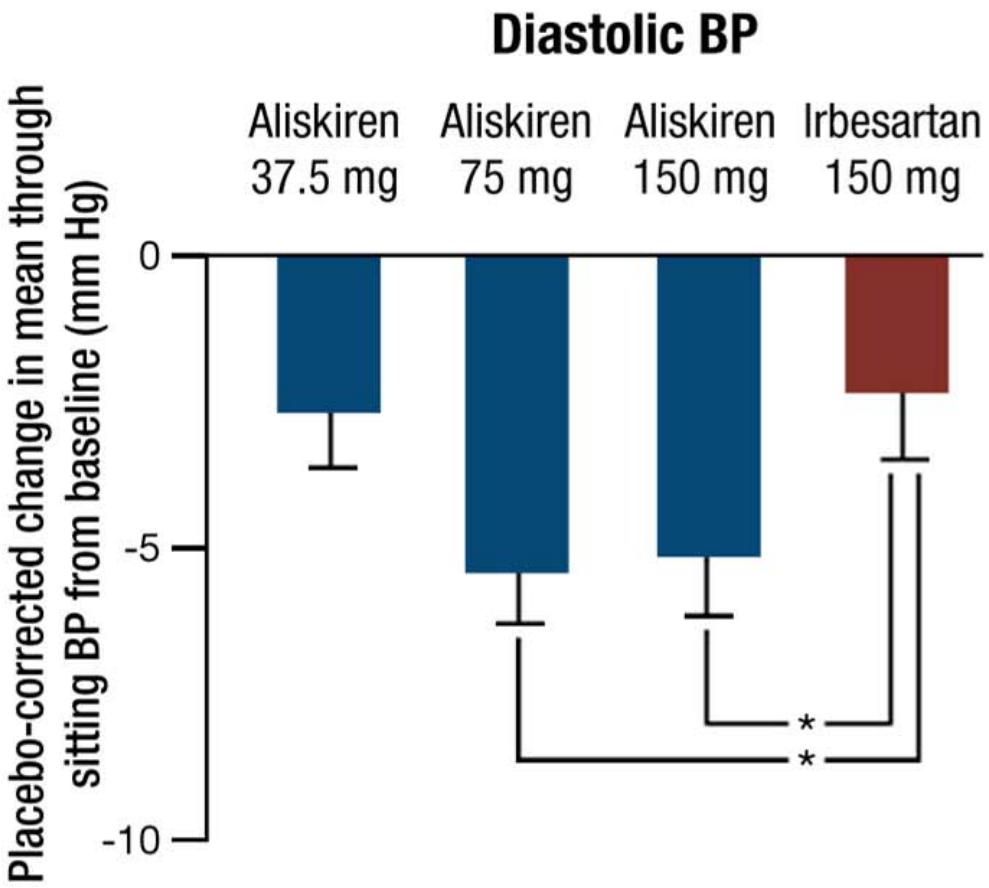
Nussberger J et al. Hypertension. 2002;39:e1-e8.

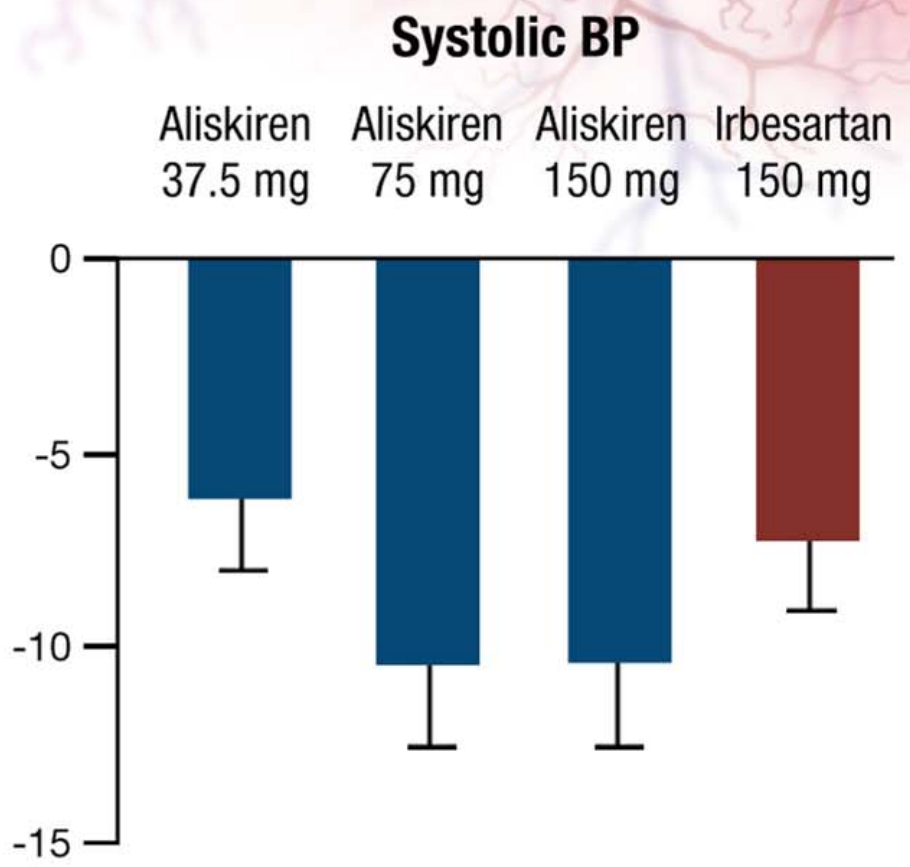
Ambulatory BP Reductions: Aliskiren vs Losartan



Stanton A et al. *Hypertension.* 2003;42:1137-1143.

Diastolic & Systolic BP Reductions: Aliskiren vs Irbesartan

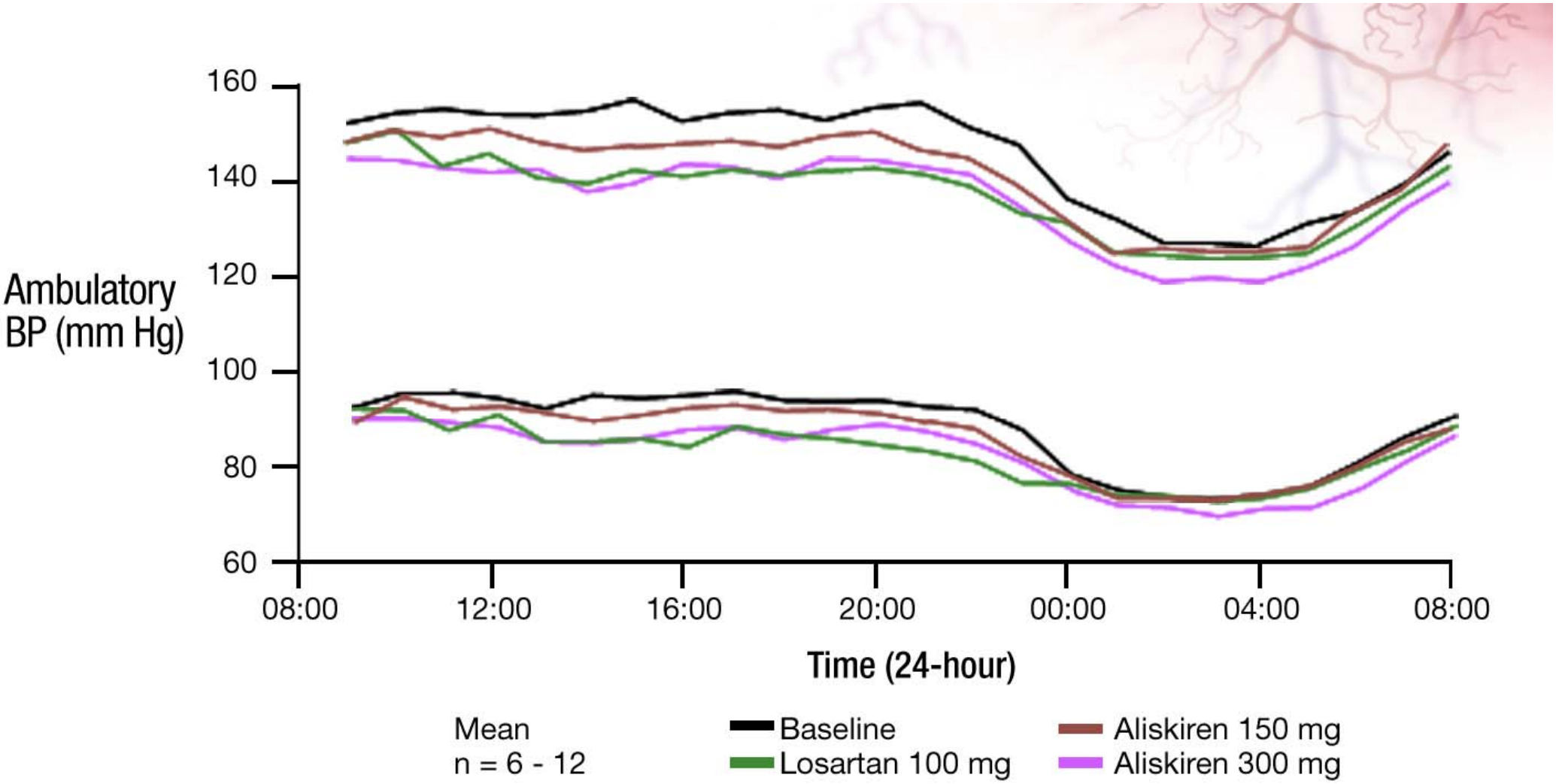




*$P<0.05$ vs irbesartan 150 mg.

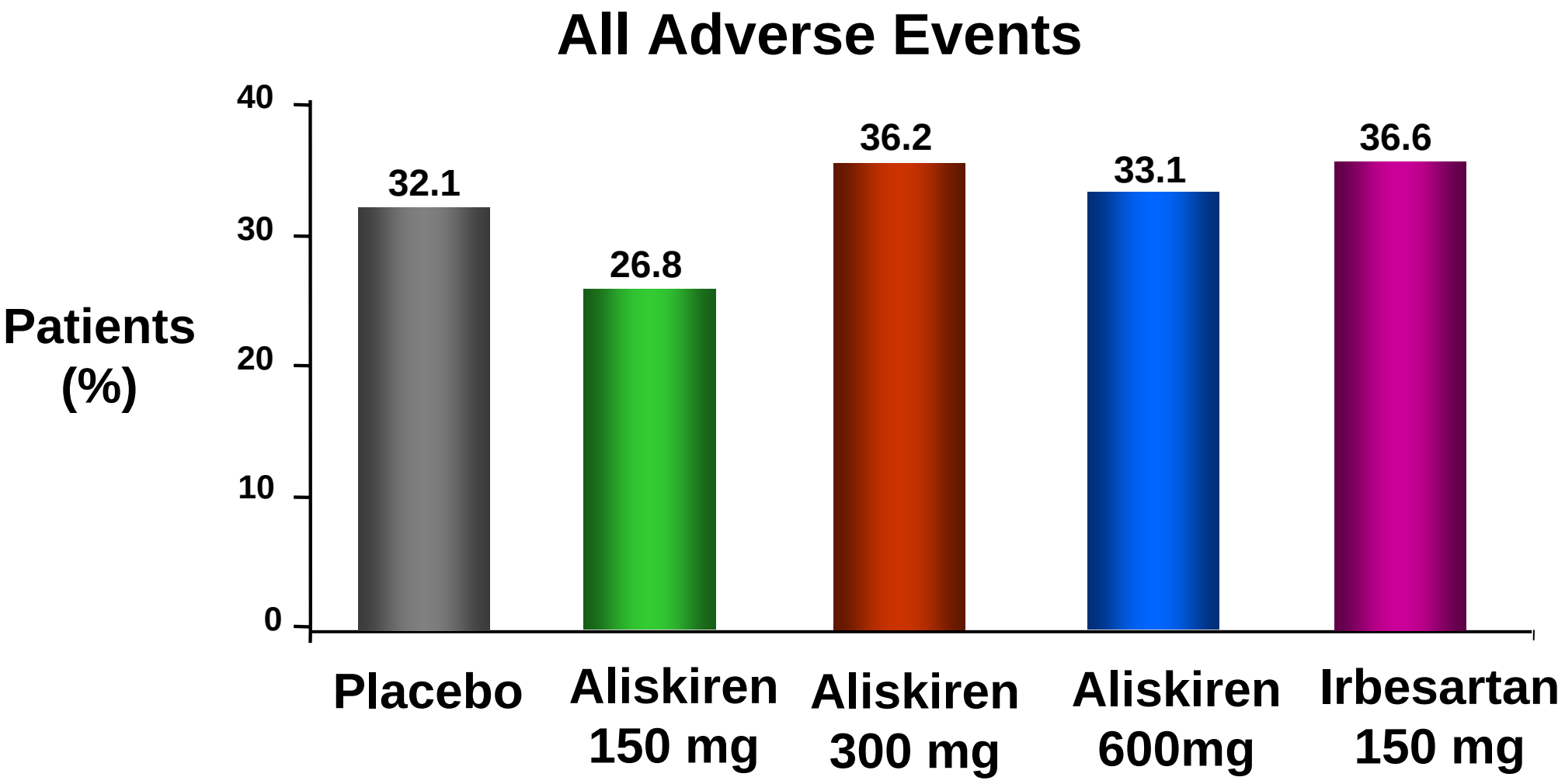
Gradman AH et al. *Circulation.* 2005;111:1012-1018.

24-hour BP Profiles: Aliskiren vs Losartan



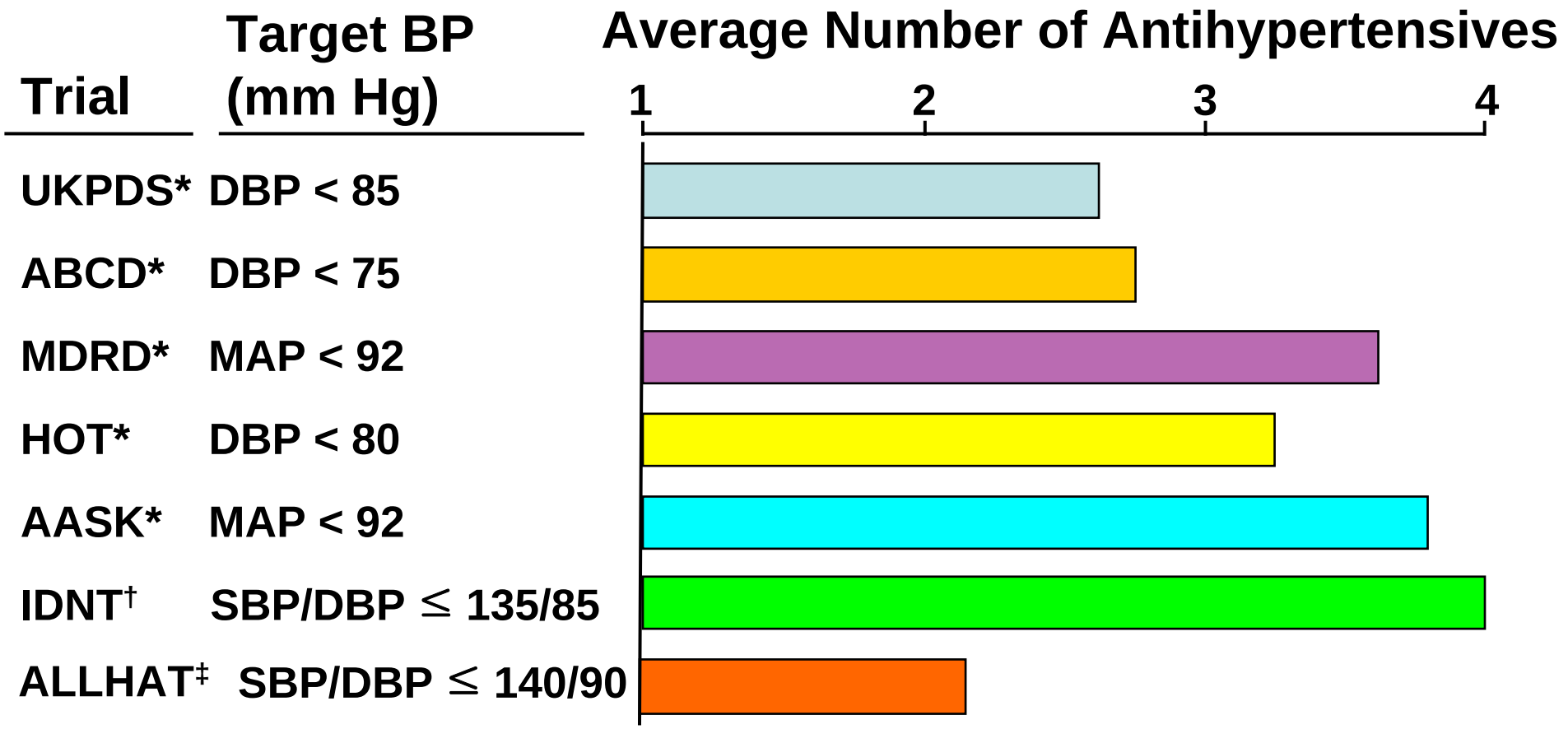
Stanton A et al. *Hypertension.* 2003;42:1137-1143.

Safety and Tolerability: Aliskiren vs Irbesartan



Aliskiren as a Combination Therapy in Hypertension

Clinical Trials Illustrate a Need for Multiple Antihypertensive Agents

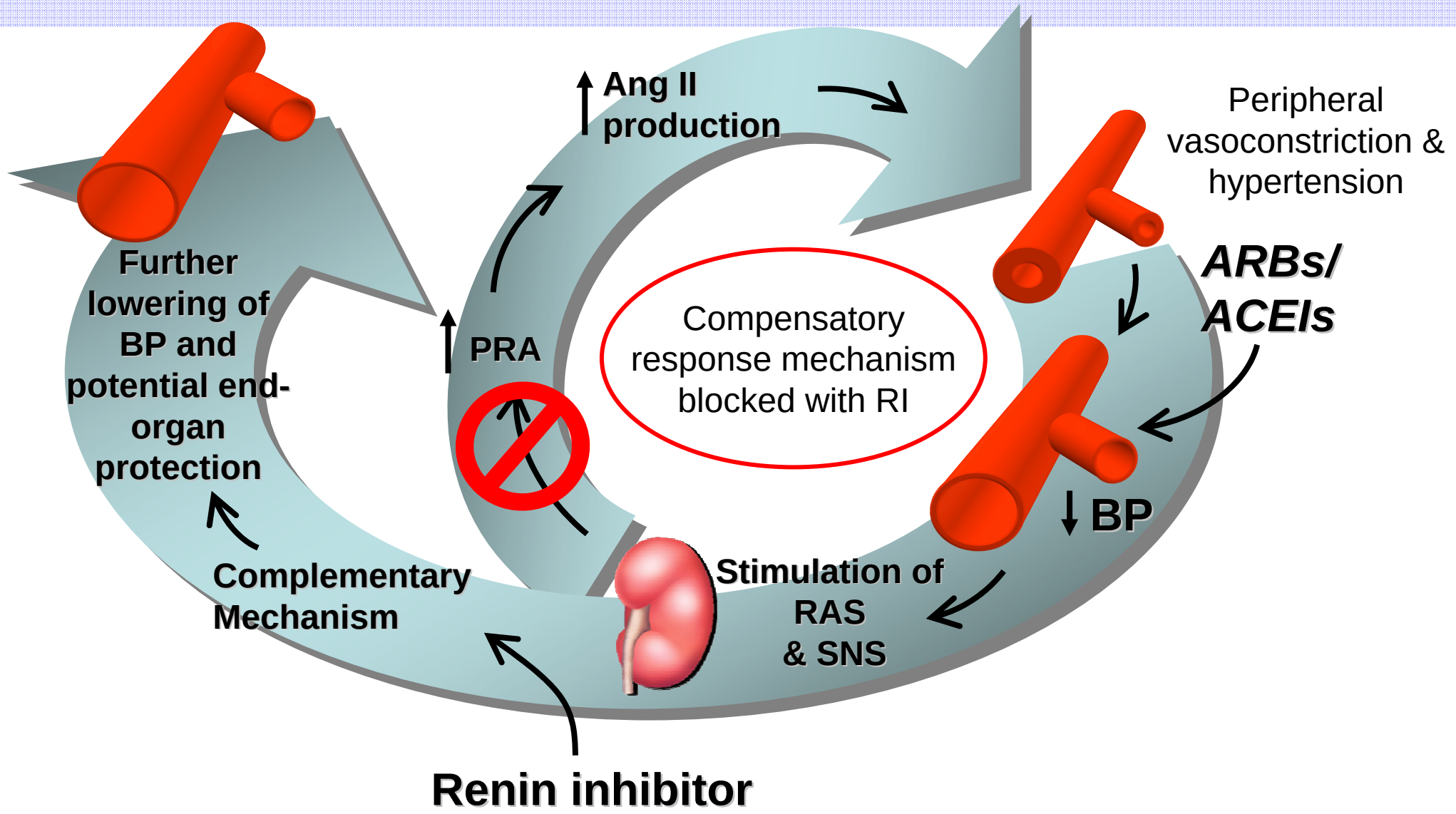


*Bakris GL et al. *Am J Kidney Dis*. 2000;36:646-661; †Lewis EJ et al. *N Engl J Med*. 2001;345:851-860. ‡Cushman WC et al. *J Clin Hypertens*. 2002;4:393-404.

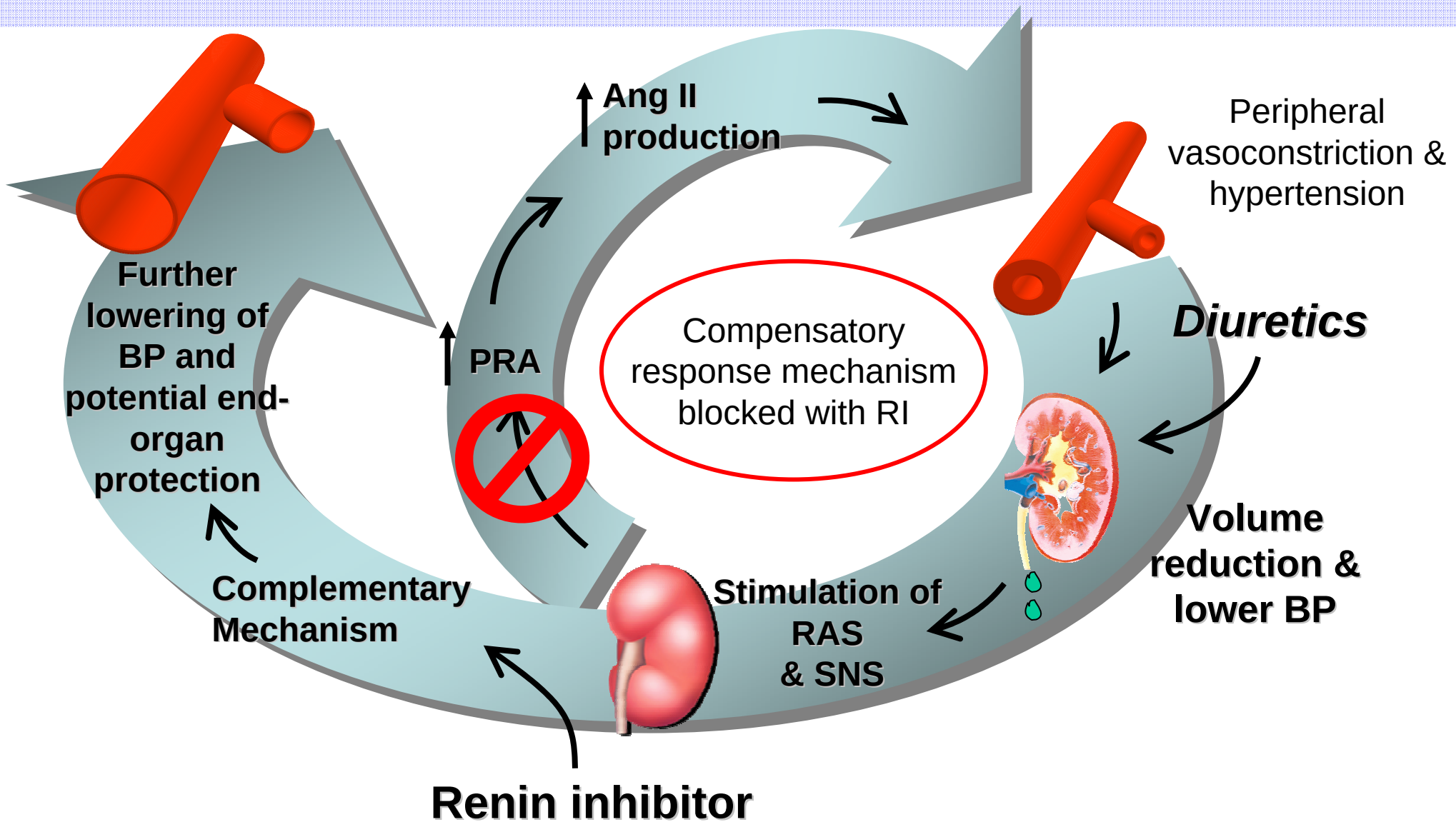
Best Combinations Offer……

- Long durations of action
- Complementary mechanisms of action
- Components with the potential to provide benefits beyond BP reduction
- Reductions in drug-related adverse events

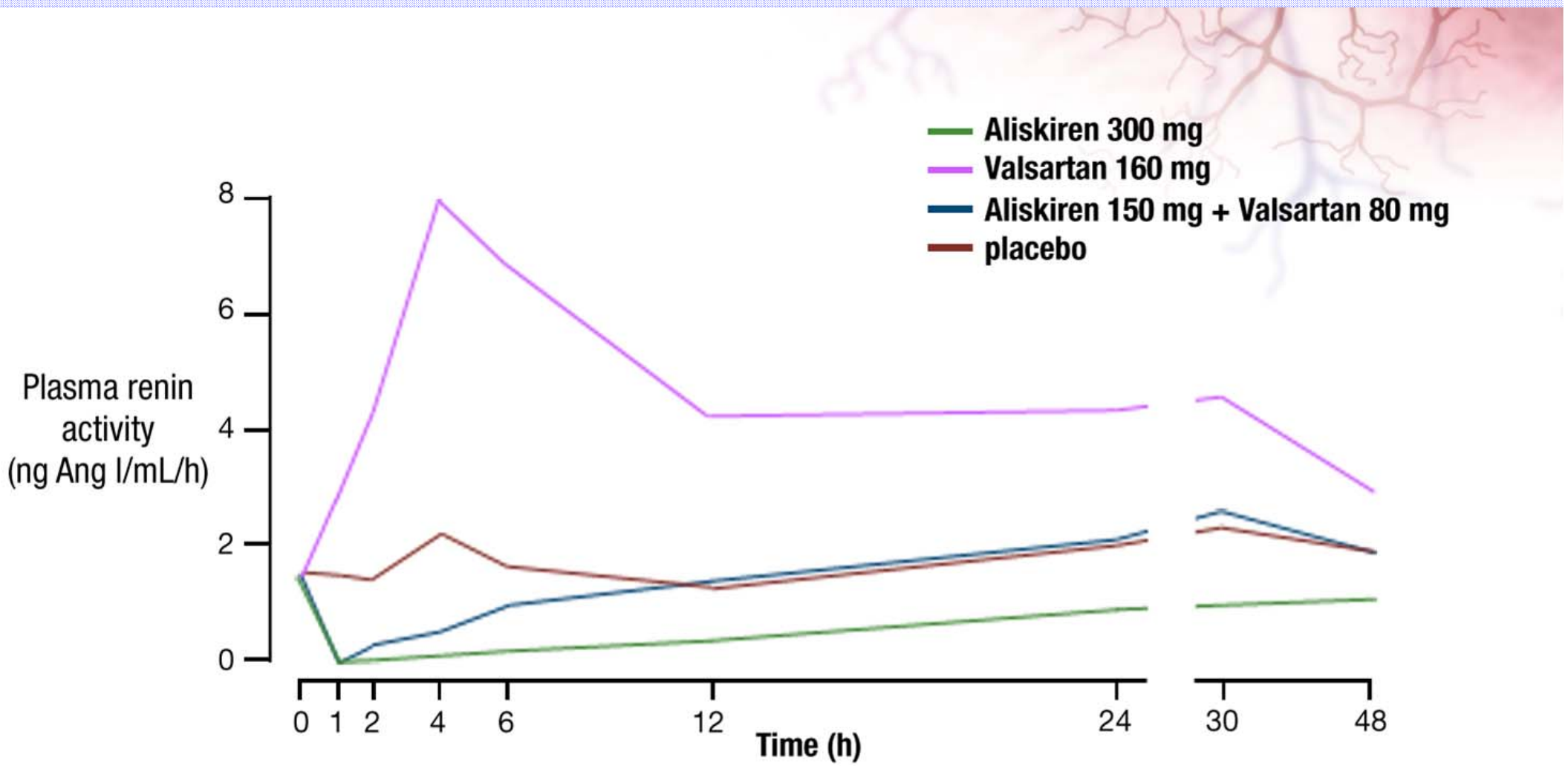
Rationale for ARB/ACEI + Renin Inhibitor Combinations



Rationale for Diuretic + Renin Inhibitor Combinations

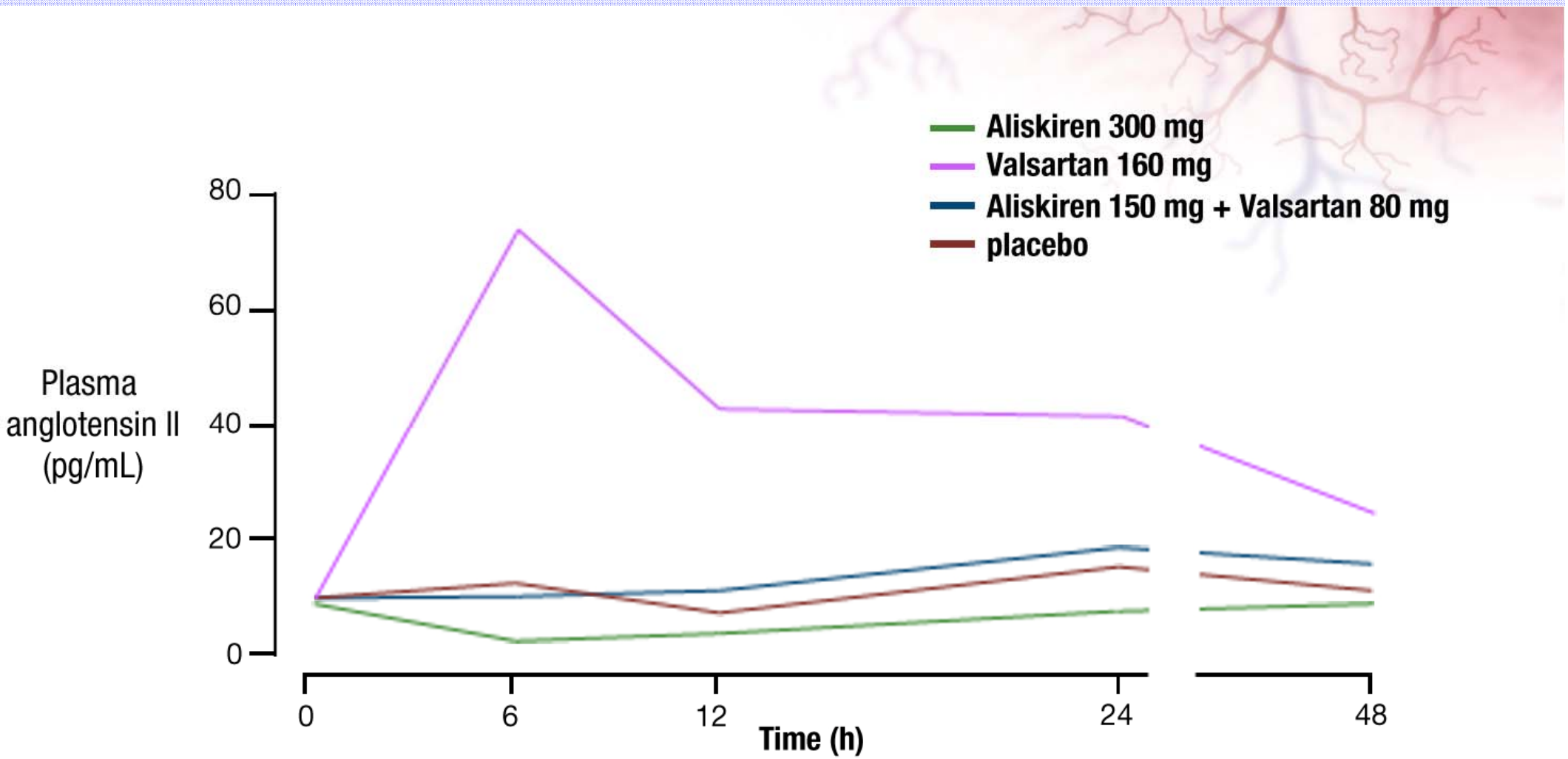


Effects of Aliskiren + Valsartan on Plasma Renin Activity



Azizi M et al. J AM Soc Nephrol. 2004;15:3126-3133.

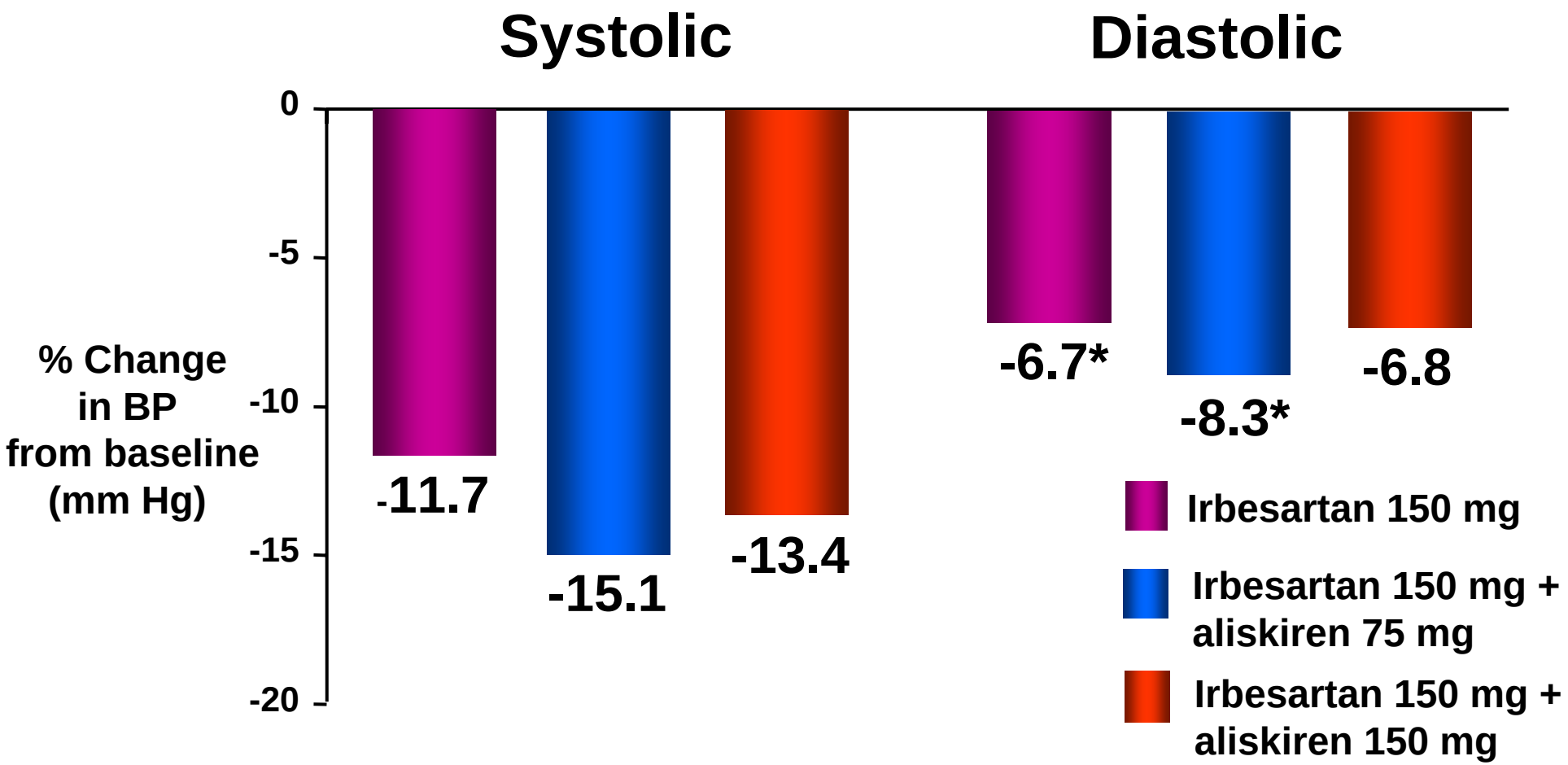
Effects of Aliskiren + Valsartan on Angiotensin I I Levels



trations. —○—, A300; —◆—, V160; —●—, A150+V80; —▼—, placebo. Data are geometric means.

Azizi M et al. J AM Soc Nephrol. 2004;15:3126-3133.

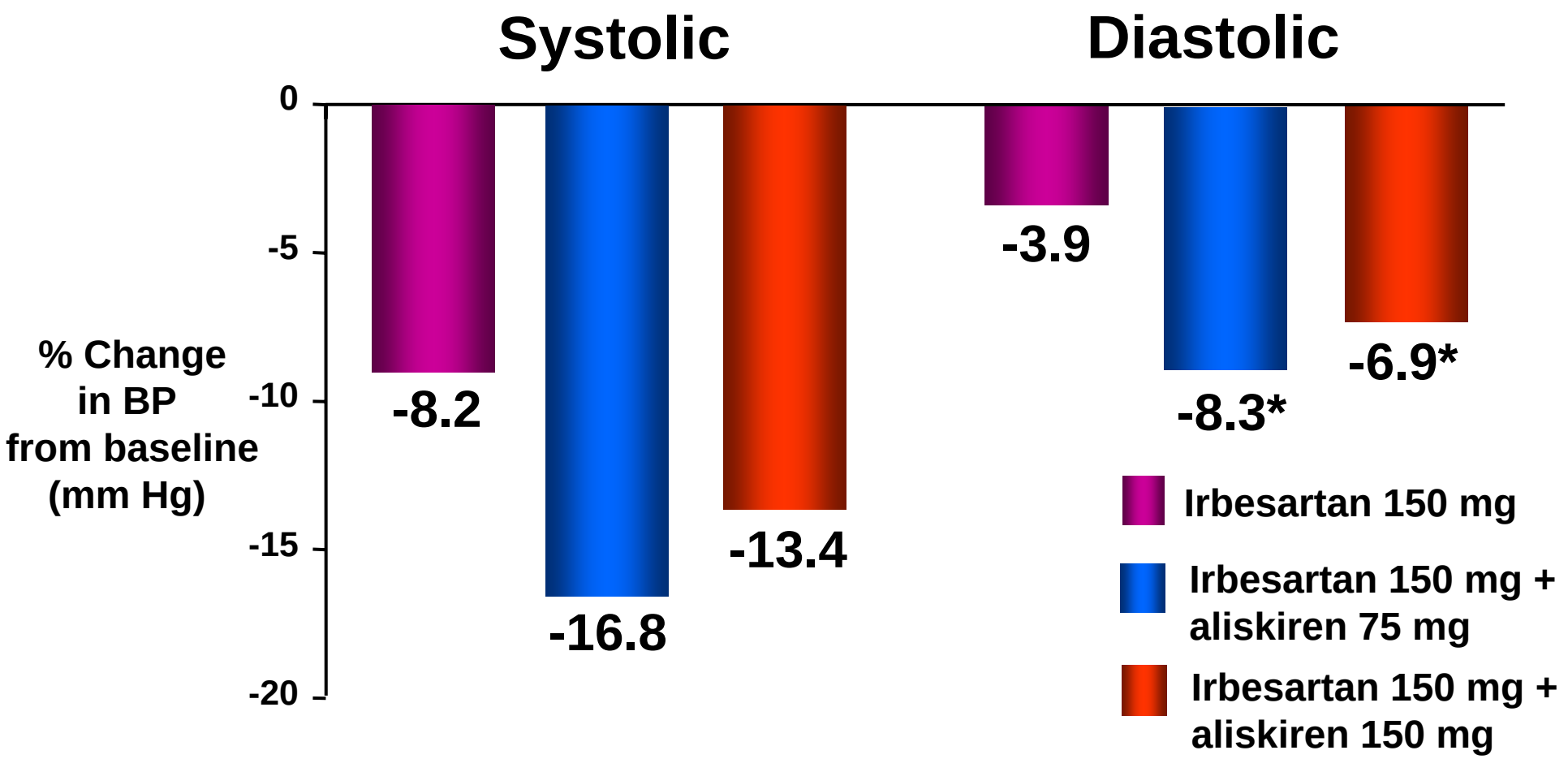
Changes in Daytime ABP: With Aliskiren Plus Irbesartan



*P<0.05 compared with irbesartan 150 mg

O'Brien et al. Presented at American Heart Association Scientific Sessions 2005. Poster # 2224.

Changes in Nighttime ABP: With Aliskiren Plus Irbesartan

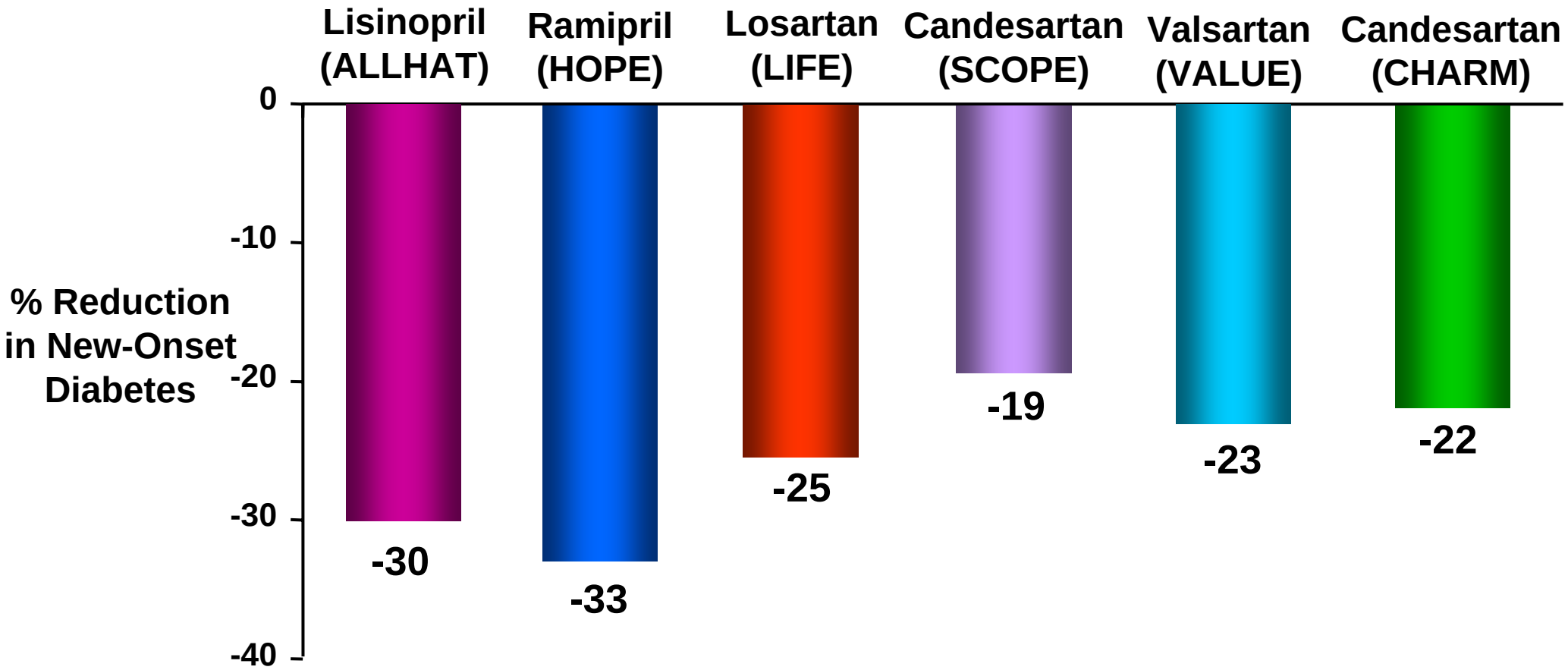


*P<0.05 compared with irbesartan 150 mg

O'Brien et al. Presented at American Heart Association Scientific Sessions 2005. Poster # 2224.

Benefits of Aliskiren Incremental to BP lowering

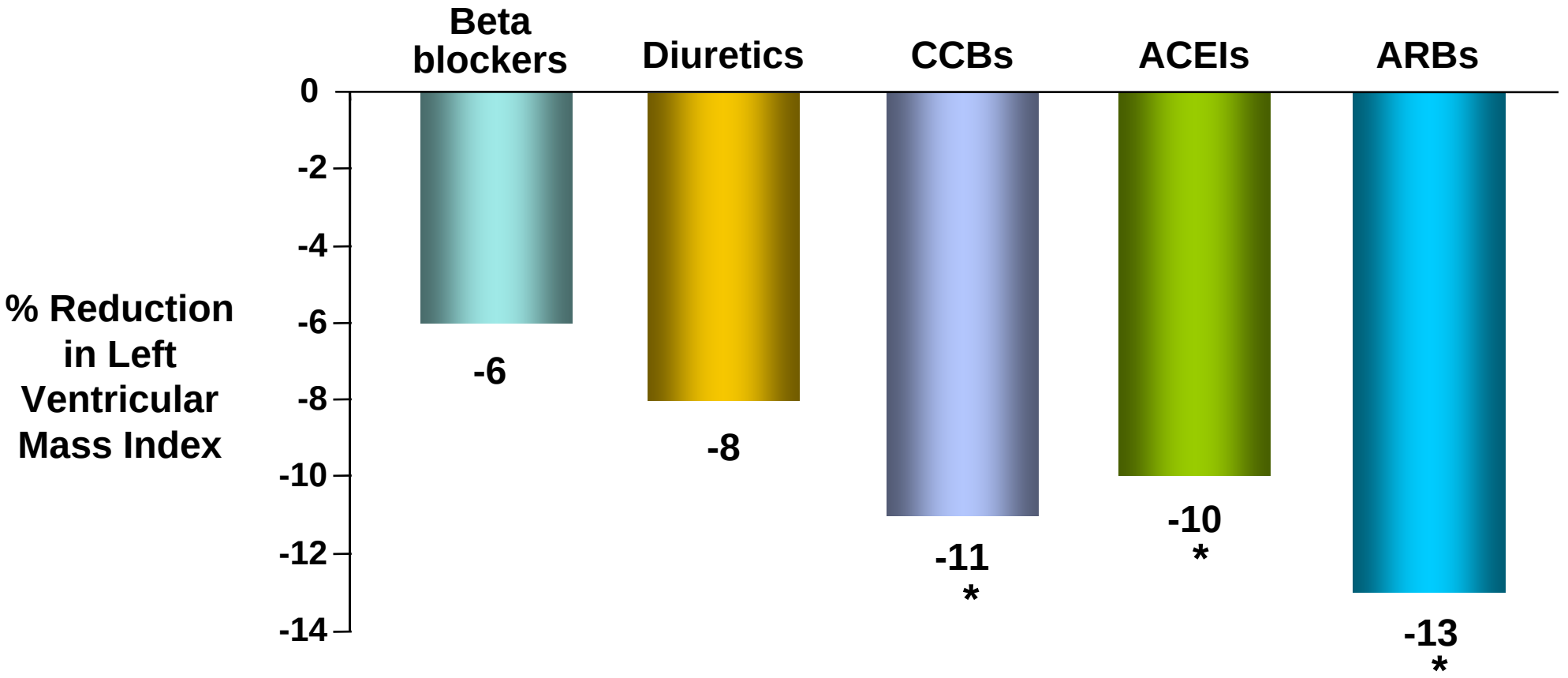
Reduction of New-Onset Diabetes With RAS Blockade



ALLHAT Officers and Collaborators. *JAMA*. 2002;288:2981-2997. Yusuf S et al. *JAMA*. 2001;286:1882-1885. Dähloff B et al. *Lancet*. 2002;359:995-1003. Lithell H et al. *J Hypertens*. 2003;21:875-886. Julius S et al. *Lancet*. 2004;363:2022-2031. Pfeffer MA et al. *Lancet.* 2003;362:759-766.

Regression of Left Ventricular Hypertrophy

Meta-Analysis of 80 Studies Involving 3767 Patients With Equivalent Blood Pressure Lowering



*P<0.05 vs beta-blockers.

Klingbeil AU et al. *Am J Med.* 2003;115:41-46.

JNC 7: Compelling Indications for Specific Antihypertensive Agents

Based on Favorable Outcome Data From Clinical Trials

	Diuretic	BB	ACEI	ARB	CCB	AA
CHF	✓	✓	✓	✓		✓
Post-MI		✓	✓	✓		✓
CAD risk	✓	✓	✓		✓	
Diabetes mellitus	✓	✓	✓	✓	✓	
Renal disease			✓	✓		
Recurrent stroke prevention	✓		✓			

Adapted from Chobanian AV et al. *Hypertension*. 2003;42:1206-1252.
Valsartan prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2005.

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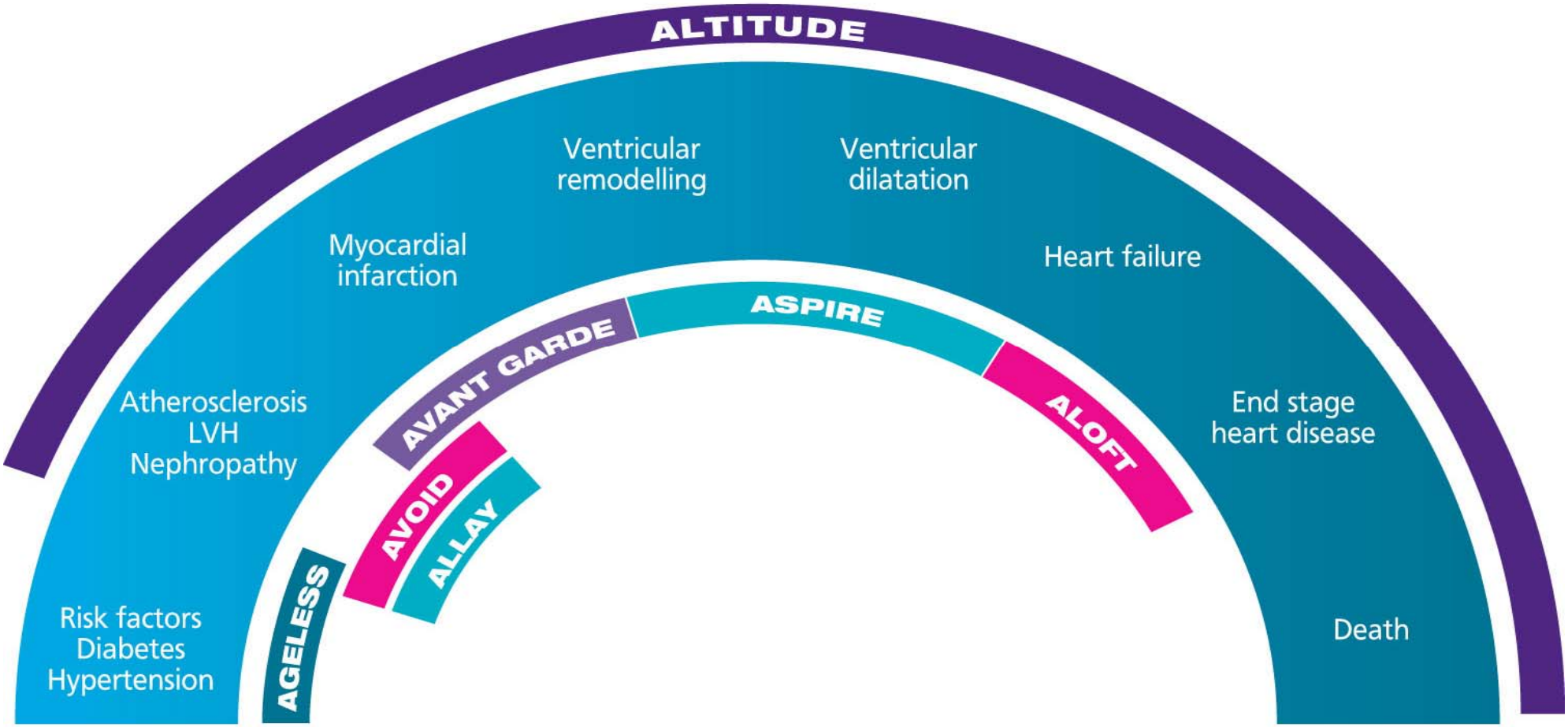
ASPIRE HIGHER: a morbidity and mortality trial programme for aliskiren



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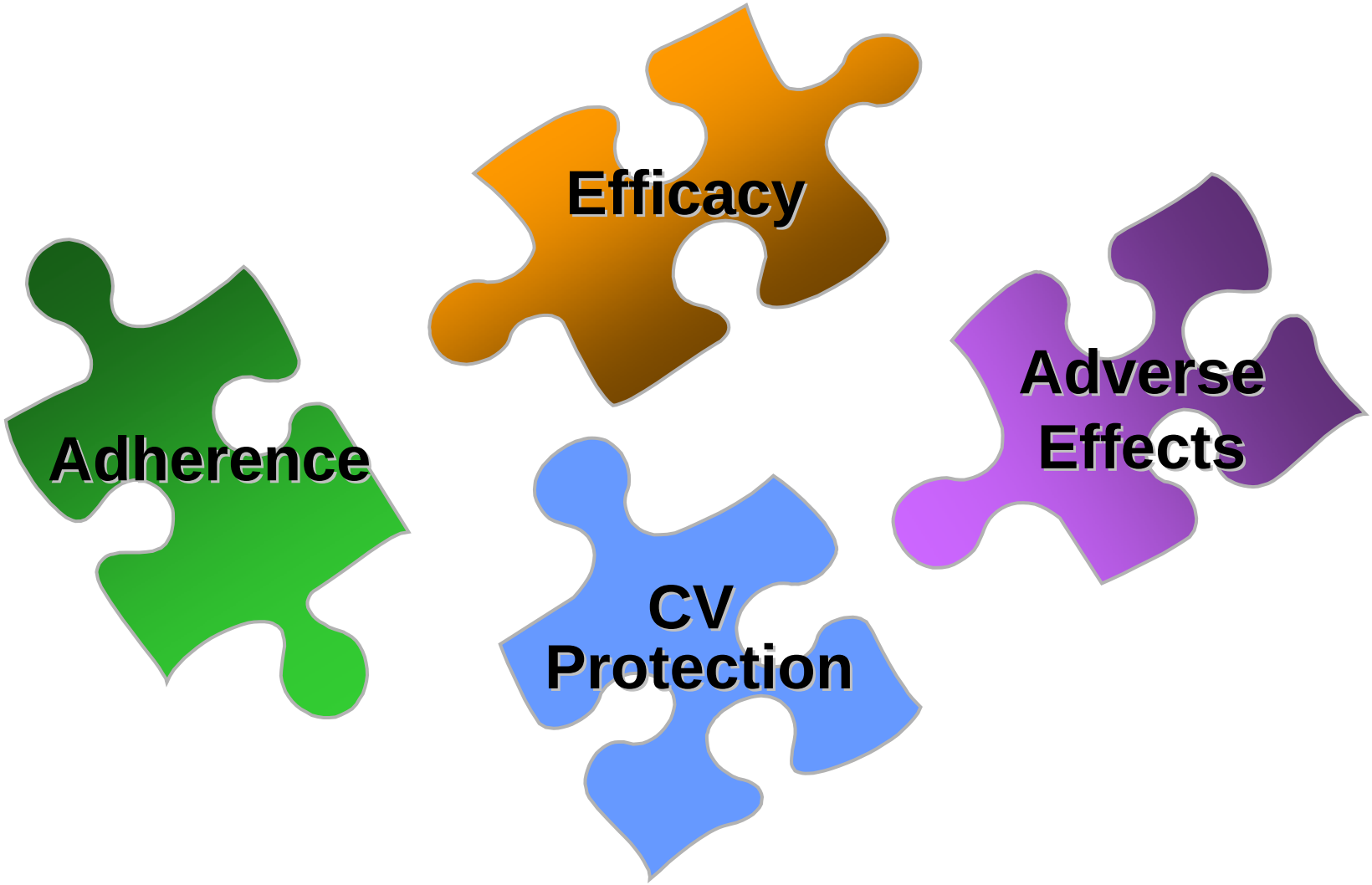
marmont_n, 2007-03-12

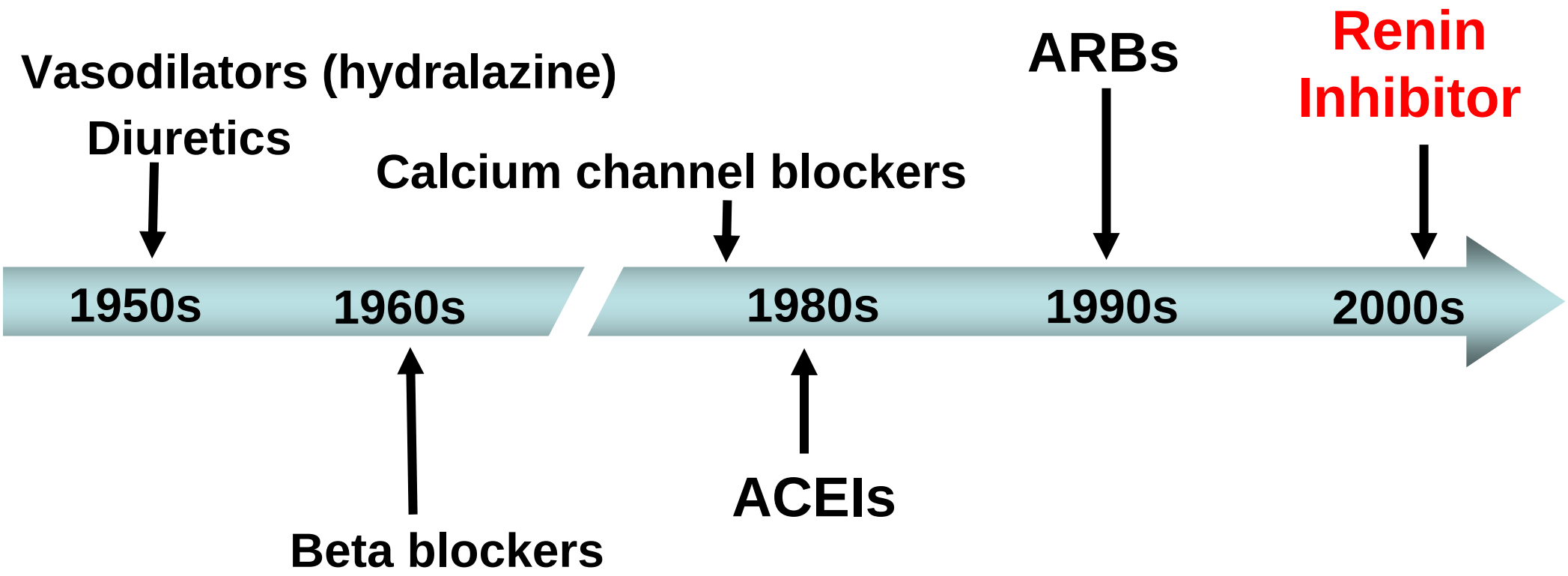
Summary

- **Direct renin inhibition with aliskiren suppresses the entire renin-angiotensin system, providing effective BP lowering and the potential for organ protection**

Multiple Factors for the Choice of Pharmacotherapy



Antihypertensive Therapies Have Evolved Over the Past 50 Years



Moser M. *Am J Hypertens.* 1997;10:2S-8S.

Aliskiren profiling programme
Ongoing intermediate clinical endpoint studies

AVOID
Aliskiren in the EValuation of PrOteinuria in Diabetes

- Diabetic Nephropathy
- Aliskiren vs Placebo in addition to Losartan 100mg
- UACR Endpoint
- FIR May 2007
- Publication planned in ACC / AHA / EASD

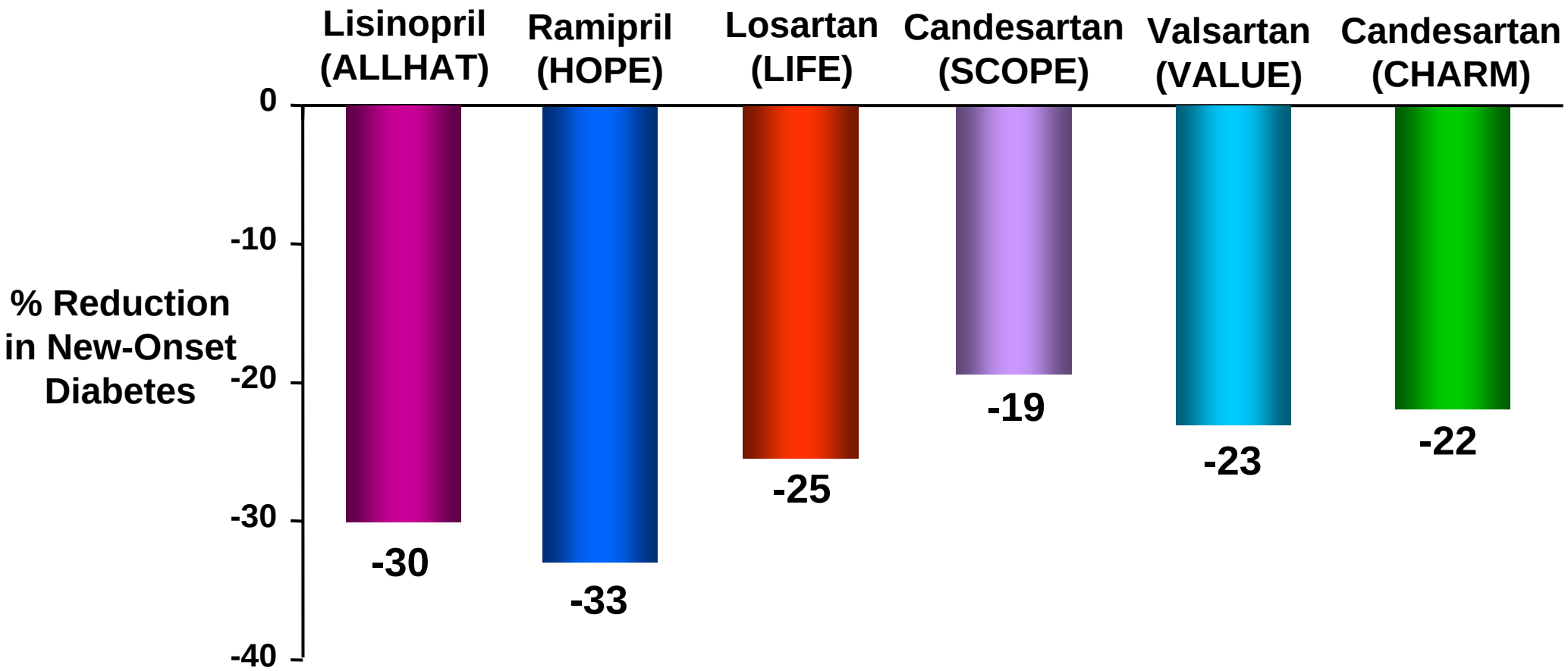
ALOFT
ALiskiren Observation of Heart Failure Treatment

- Heart Failure
- Aliskiren vs Placebo on top of standard HF therapy
- Safety and Tolerability Endpoint
- FIR May 2007
- Publication planned in ACC / AHA

ALLAY
ALiskiren in Left VentriculAr HypertrophY

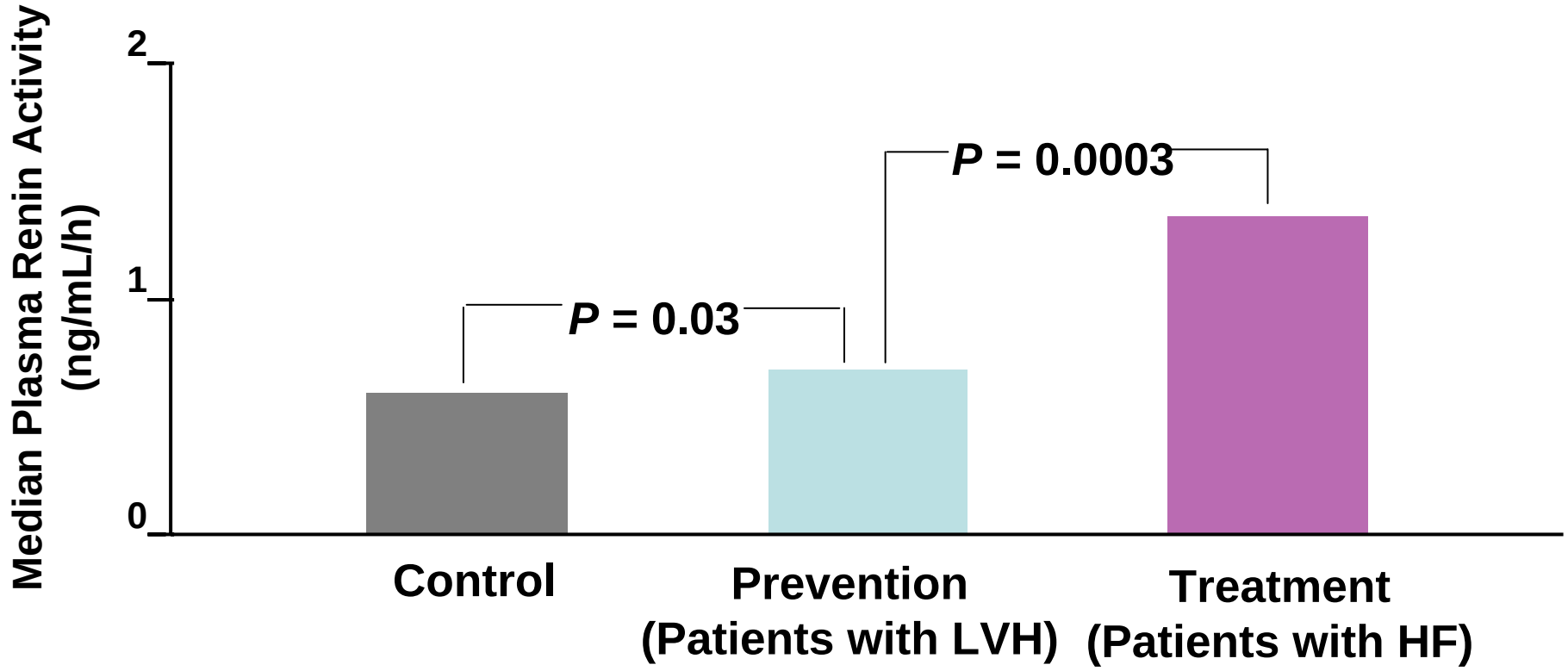
- LVH
- Aliskiren vs Losartan vs Combination
- LVH Regression Endpoint
- FIR December 2007
- Publication planned in ESC

Reduction of New-Onset Diabetes With RAS Blockade



ALLHAT Officers and Collaborators. *JAMA*. 2002;288:2981-2997. Yusuf S et al. *JAMA*. 2001;286:1882-1885. Dähloff B et al. *Lancet*. 2002;359:995-1003. Lithell H et al. *J Hypertens*. 2003;21:875-886. Julius S et al. *Lancet*. 2004;363:2022-2031. Pfeffer MA et al. *Lancet.* 2003;362:759-766.

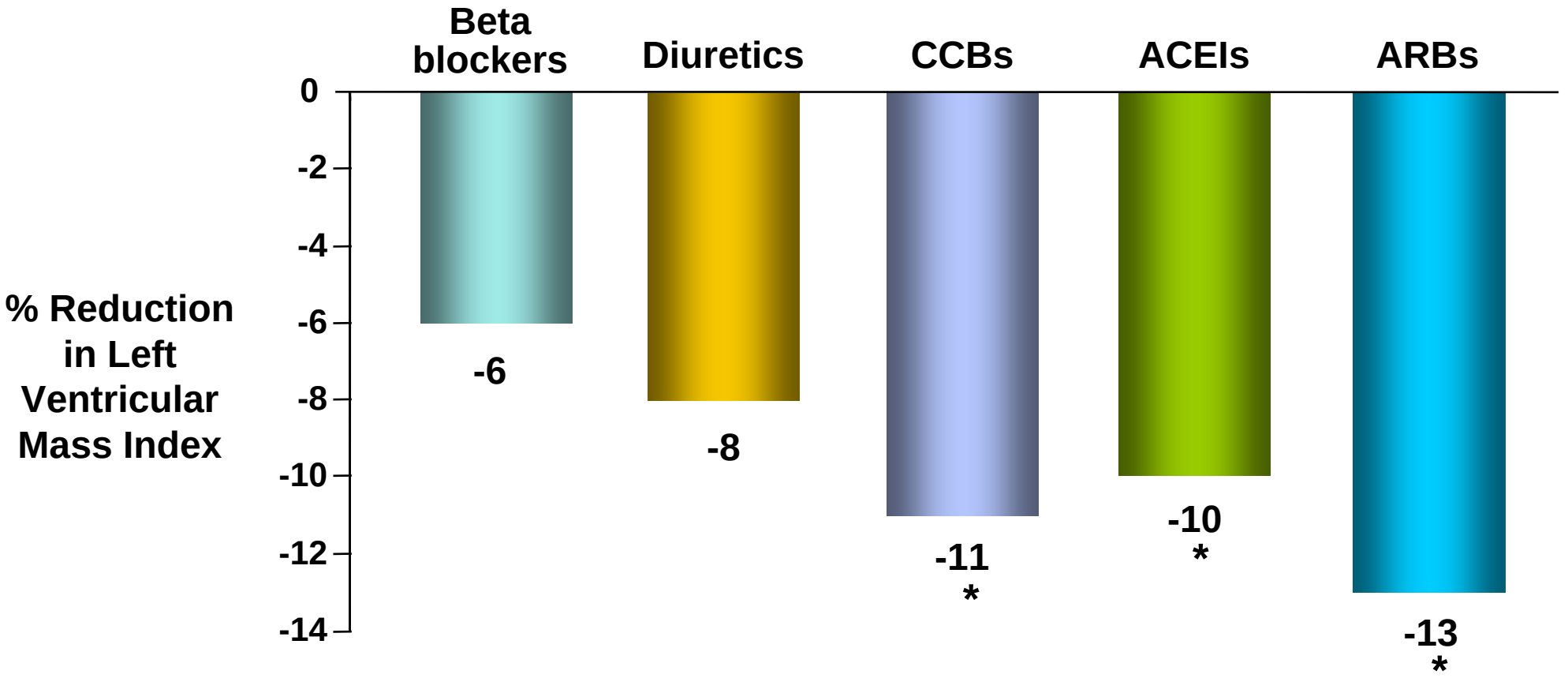
Patients with LV Dysfunction ± CHF Have Increased PRA Levels



Adapted from Francis GS et al. *Circulation*. 1990;82:1724-1729.

Regression of Left Ventricular Hypertrophy

Meta-Analysis of 80 Studies Involving 3767 Patients With Equivalent Blood Pressure Lowering



*P<0.05 vs beta-blockers.

Klingbeil AU et al. *Am J Med.* 2003;115:41-46.

Recent Study Shows High PRA Predicts MI in Both Controlled and Uncontrolled Hypertensive Patients

- An increase of 2 ng/mL/h in plasma renin levels was associated with a 23% increase in MI and revascularization procedures after controlling for other variables
- Men with high plasma renin levels had twice the risk of MI or a revascularization procedure versus those with lower renin rates, even though BP was treated successfully

Hailpern SM et al. Presented at ASH 20th Annual Scientific Meeting and Exposition; Oral Abstract 3. May 15, 2005.

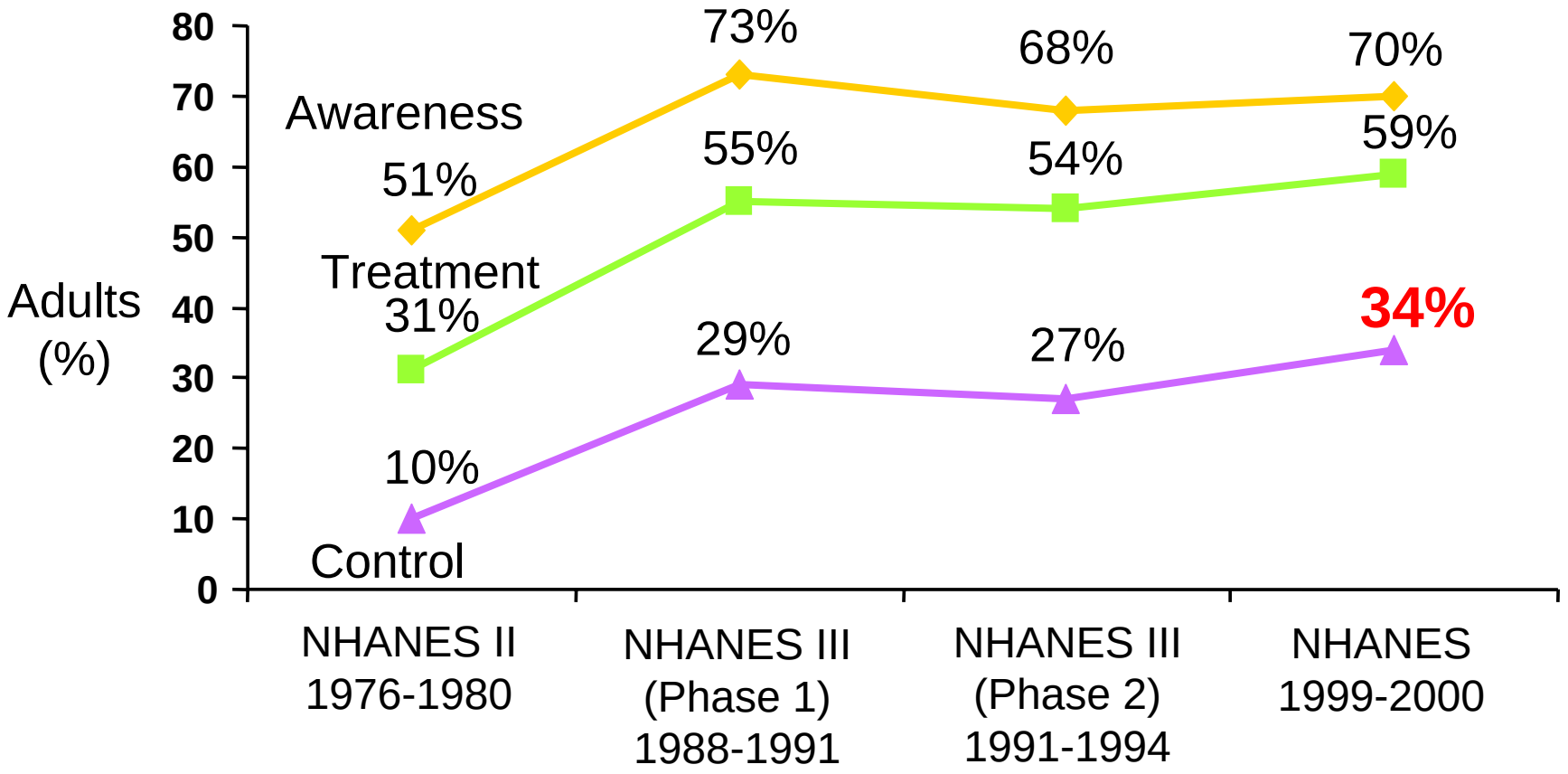
Can RIs Be More Effective Than Other RAS Inhibitors in Reducing End-organ Damage?

- Early studies indicate RIs are very effective for reducing blood pressure
- Reducing target end-organ damage
  - The organ-protective benefits of ACEIs and ARBs might be synergistically enhanced by addressing the incomplete RAS suppression/compensatory feedback loop associated with these agents
- More proximal blockade may prove to be important in limiting changes in structure and function of vascular beds and target organs and limit long-term injury

Conclusions

- Getting BP to below 140/90 mm Hg as quickly as possible is a priority for maintaining excellent CV health
  - Using a RAS blocker may provide additional protective benefits
- Proximal RAS blockade with renin inhibitors may provide more opportunistic chances in controlling BP and reducing CV events
- Combining a renin inhibitor with other RAS modulators may provide incremental BP-lowering effects

Despite Increasing Treatment, 2/3 of Patients are Still Uncontrolled



NHANES = National Health and Nutrition Examination Survey.

Adapted from Chobanian AV et al. *JAMA.* 2003;289:2560-2572; Hajjar I, Kotchen TA. *JAMA.* 2003;290:199-206.

Summary

- Optimal Renin System suppression
  - aliskiren inhibits all key Renin System components alone and in combination
- Highly effective as monotherapy
  - aliskiren monotherapy has demonstrated robust BP reductions
- Strength in combination therapy
  - adding aliskiren provides an additional 30–50% reduction in BP
- Smooth, sustained BP control **beyond** 24 hours
  - due to 40-hour half-life
  - BP reductions return gradually to baseline after stopping aliskiren treatment
- Safety and tolerability
  - placebo-like, low potential for DDIs, no dosage adjustments required
- Organ protection potential
  - proven in preclinical data; clinical studies underway