2011. 4. 15-16 춘계심장학회

Combination of antihypertensive therapy for high risk patients

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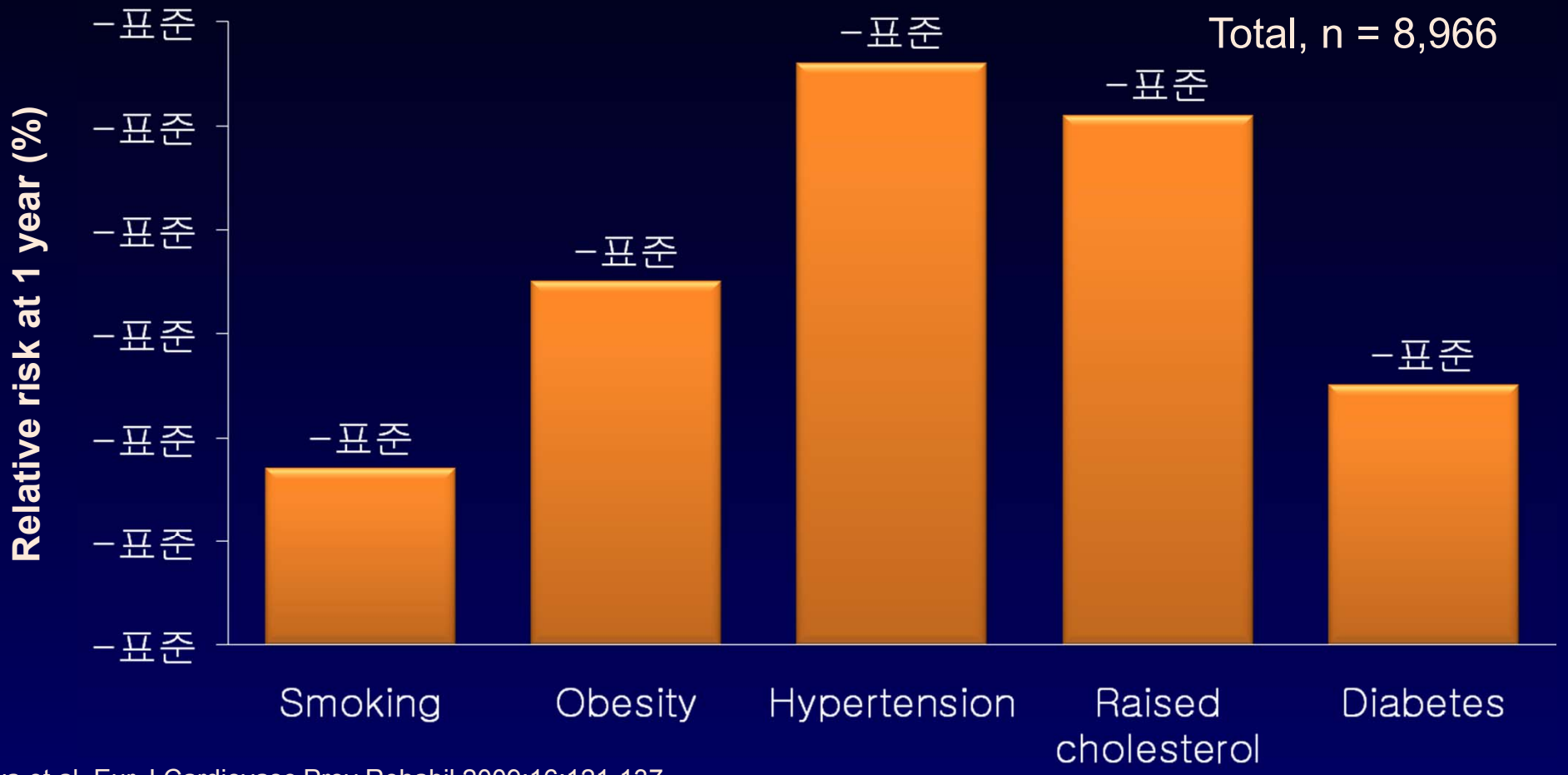
목차:

- High risk patients
- Combination of antihypertensive drug
  - Background
  - Mechanism
  - Evidence
  - Future

High risk patients in hypertension

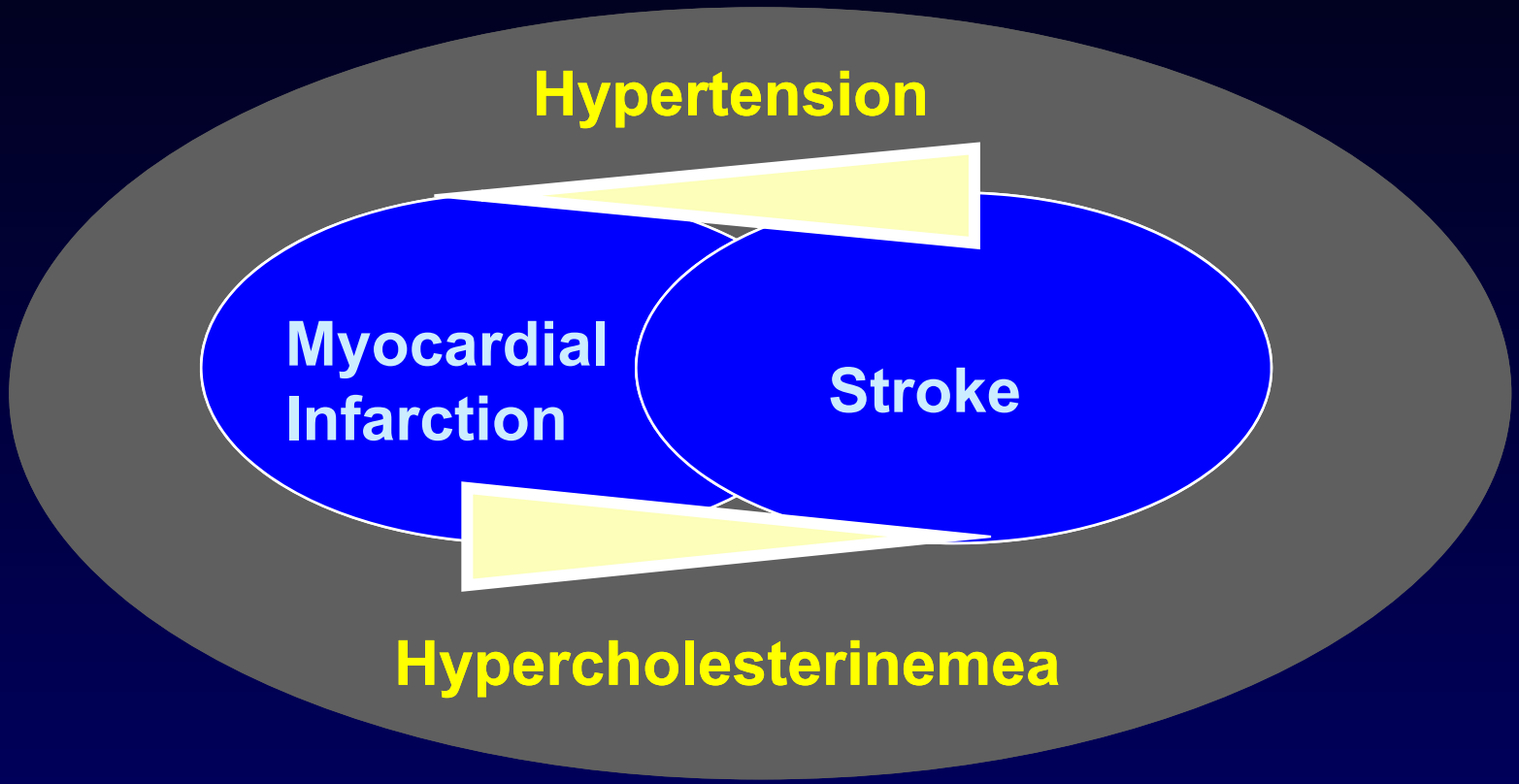
Identification of patients' individual CV risk is central

EUROASPIRE III



Kotseva et al, Eur J Cardiovasc Prev Rehabil 2009;16:121-137.

Interaction in-between Risks

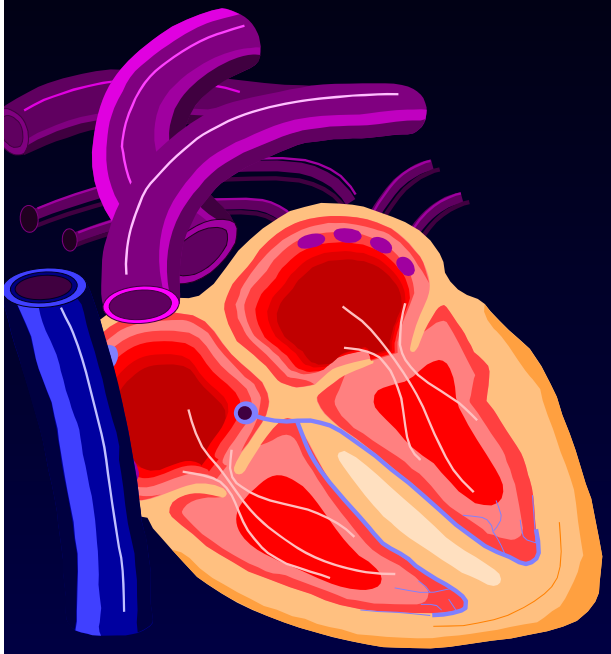


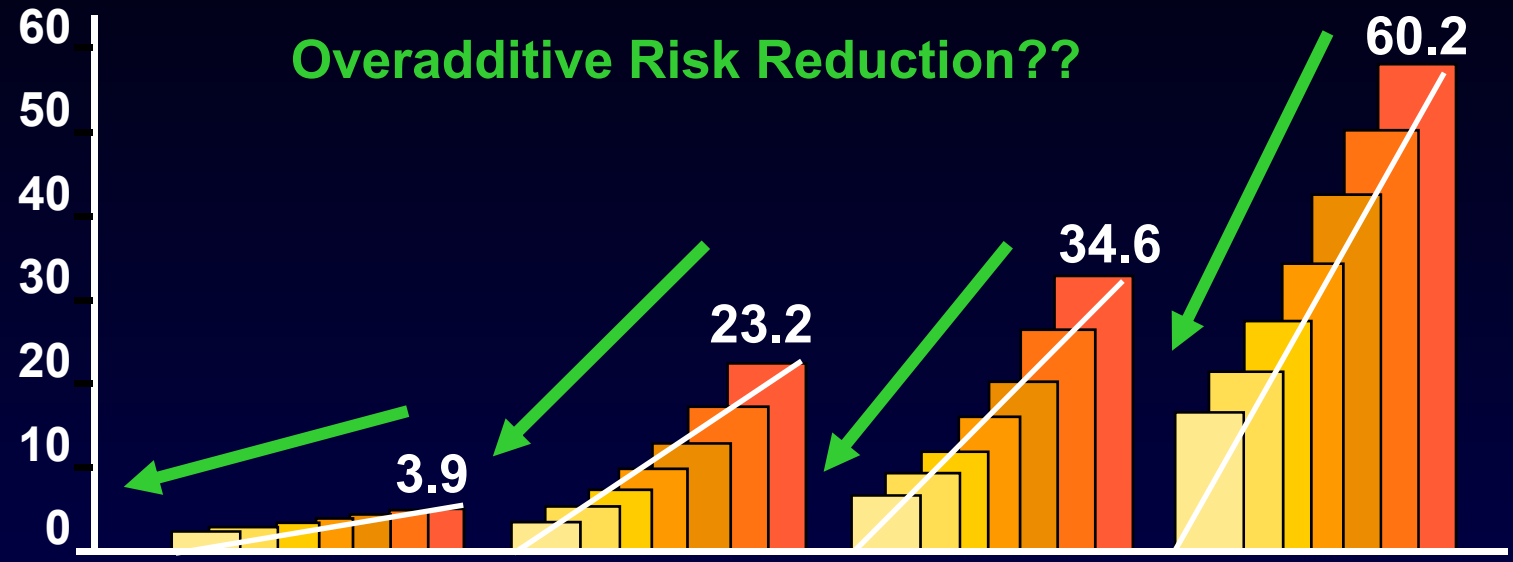
Treatment of common CV risk factors is well established and reduces CV events

Encourage lifestyle changes	Use drugs proven to reduce the risk of devastating CV events
• Improve diet • Increase physical activity • Quit smoking	• Statins • Antiplatelets • Hypoglycaemics • Antihypertensives • Beta-blockers • RAS blockade

Bakris et al. Clin Res Cardiol. 2008;97:713-725.

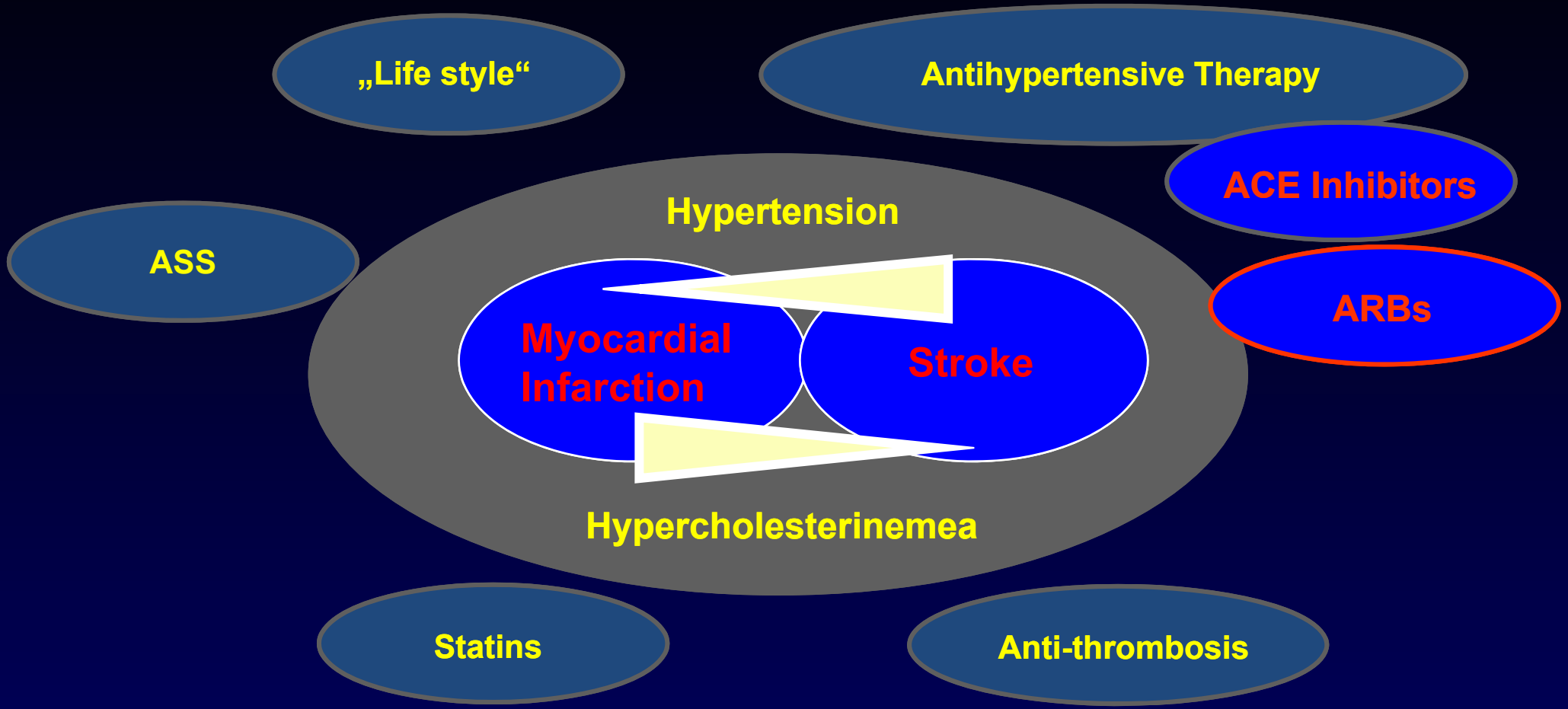
Mechanisms: What Do We Need: Improved Treatment of CV Global Risk





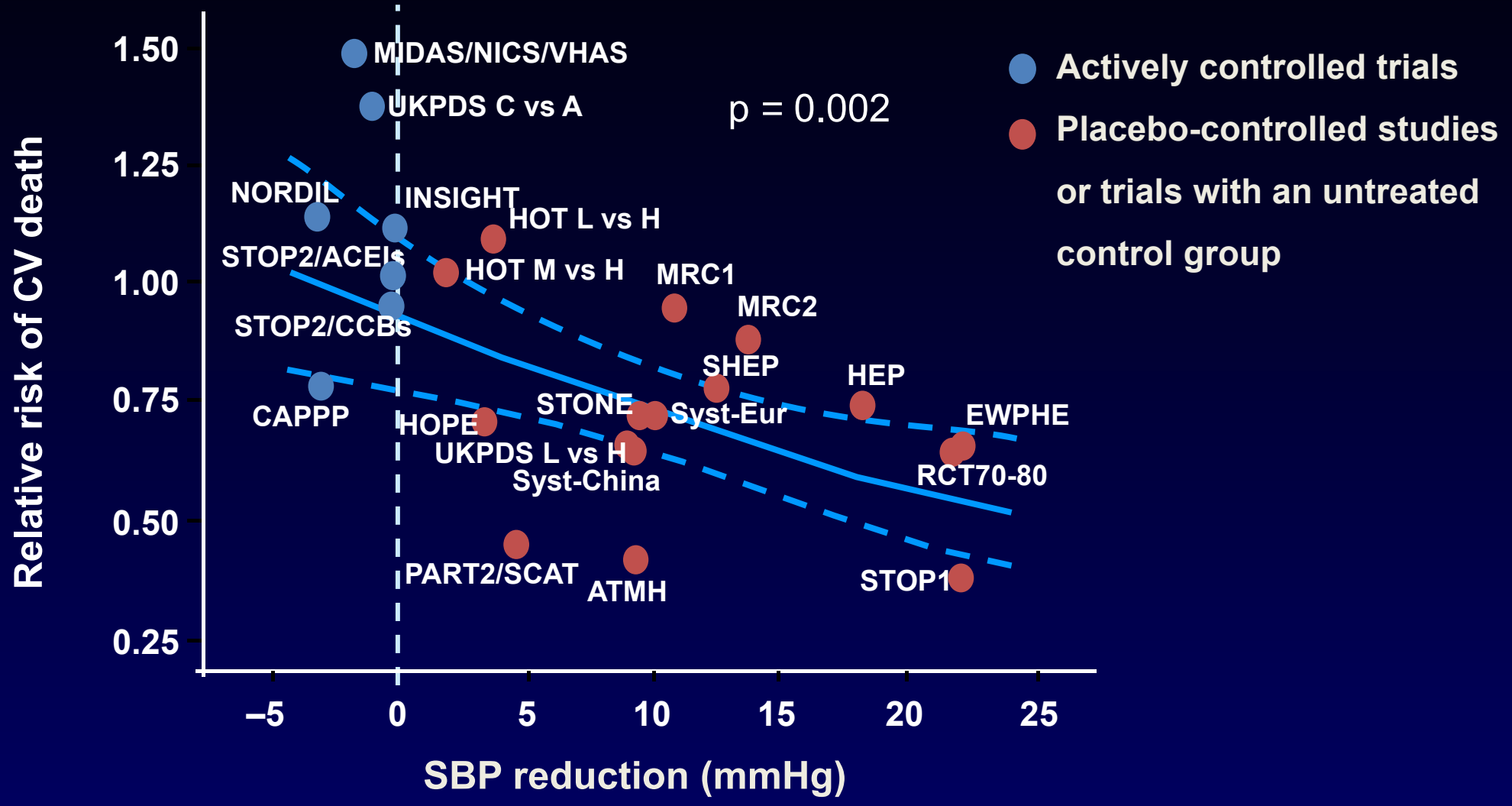
Cholesterol, mg/dL (mmol/L)	185↔335 (4.8↔8.7)	185↔335 (4.8↔8.7)	185↔335 (4.8↔8.7)	185↔335 (4.8↔8.7)
Glucose intolerance	0	+	+	+
Systolic BP, mm Hg	105	195	195	195
Cigarettes	0	0	+	+
LVH on ECG	0	0	0	+

Interaction between Risk and Therapy



RAS-Inhibition – CV Global Protection?

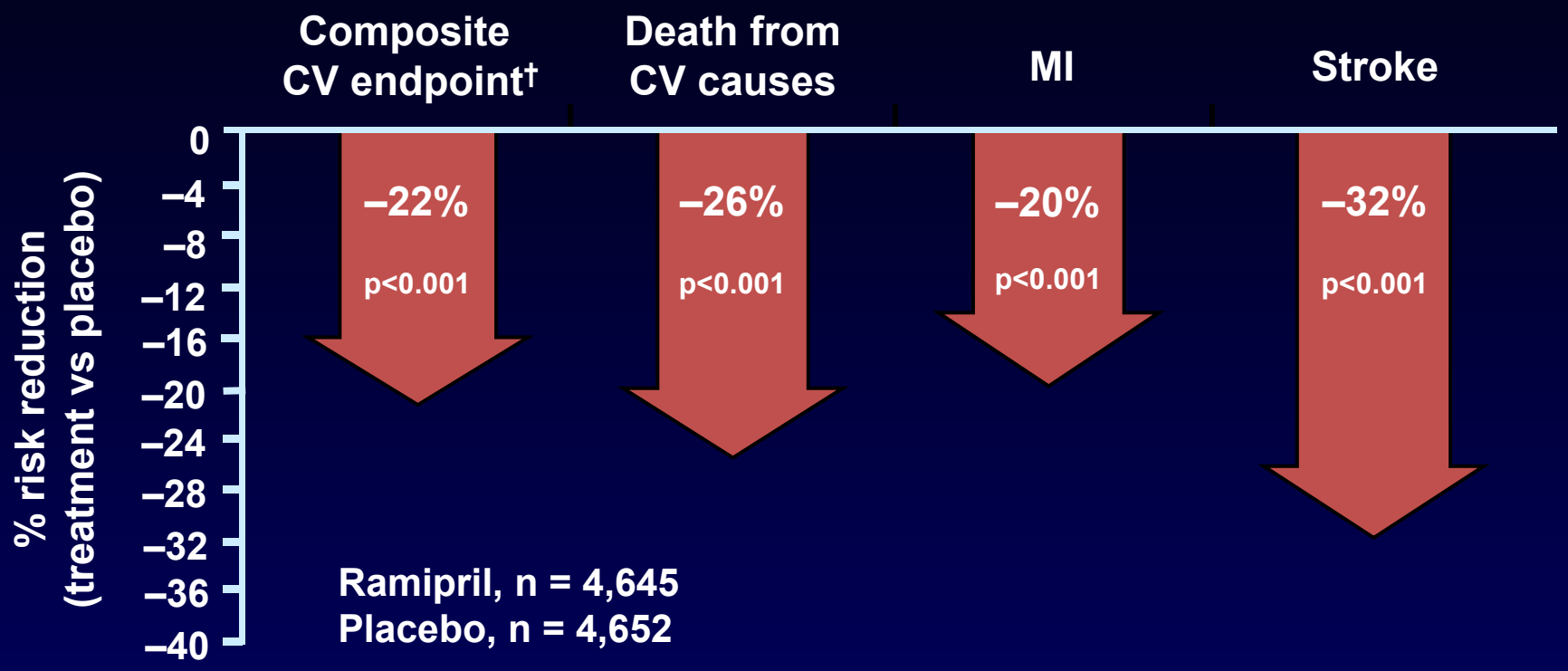
BP reduction reduces CV risk



Staessen et al. Hypertens Res. 2005;28:385-407.

The ACEi ramipril reduces CV mortality and morbidity in CV high-risk patients

HOPE: CV high-risk patients; mean baseline SBP/DBP 139/79 mmHg



Ramipril, n = 4,645
Placebo, n = 4,652

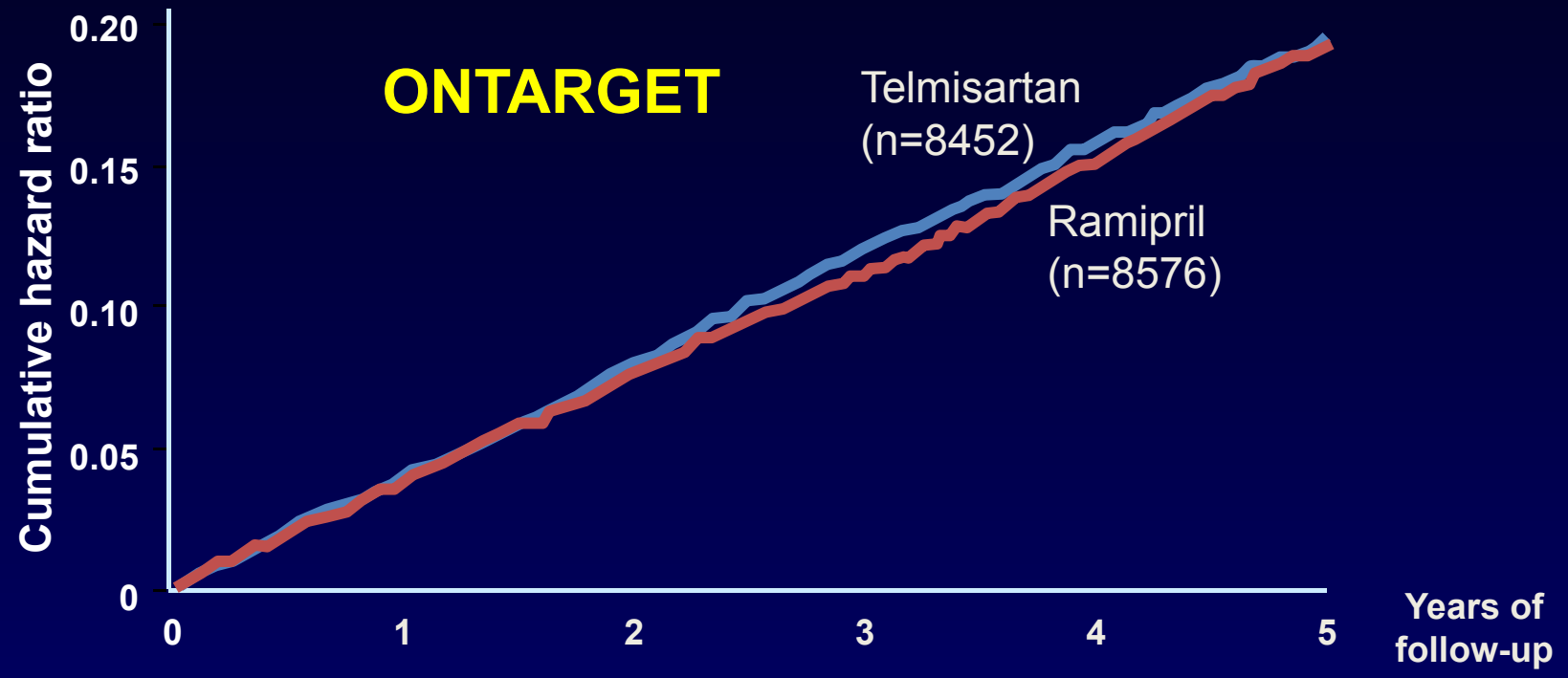
† Composite CV endpoint = death from CV causes + MI + stroke
HOPE = Heart Outcomes Prevention Evaluation

Yusuf et al. N Engl J Med 2000;342:145

The ARB telmisartan is similarly effective to ramipril in preventing CV events in CV high-risk patients

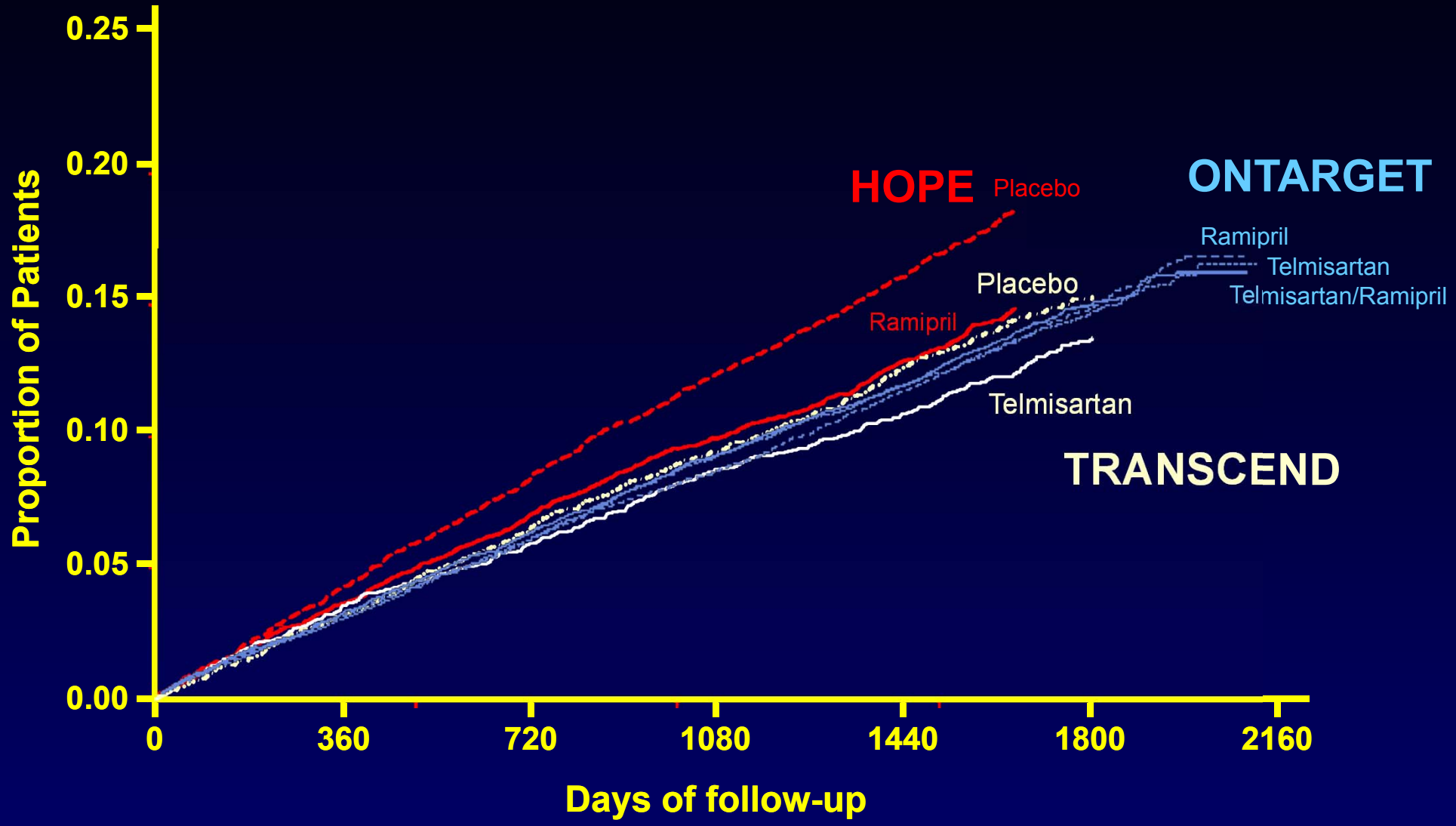
Reduction in composite CV risk

(Primary endpoint: CV mortality, non-fatal MI, hospitalisation for CHF, non-fatal stroke)



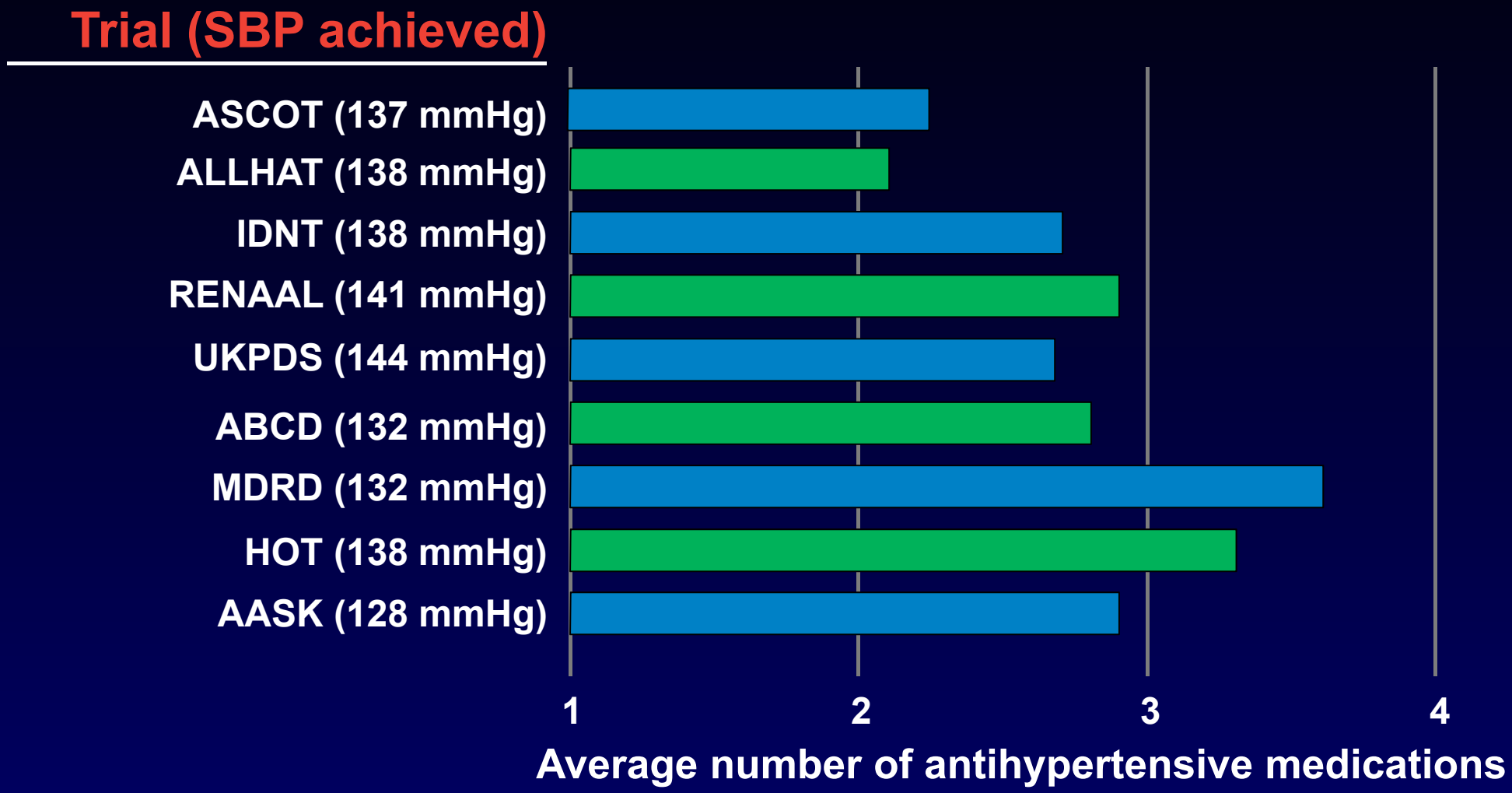
The ONTARGET Investigators. N Engl J Med 2008;358:1547-1559.

Major Studies in RAS-Inhibition (HOPE Composite) Global Protection



Combination of antihypertensive drug in high-risk hypertension

The Majority of Hypertensive Patients Need Combination Therapy to Achieve BP Goals



Bakris et al. *Am J Med.* 2004;116:30S; Dahlöf et al. *Lancet.* 2005;366:895.

Treating Blood Pressure to Target
"the rule of 1/3rds"

- ≥ 2/3rds require two or more drugs
- Combination therapy is the norm
  - especially for patients at high risk

ESC/ESH: Algorithm for Treatment of Hypertension

Consider: **BP level before treatment /absence or presence of target organ damage and risk factors**

- **Mild BP elevation**
- **Low/moderate CV risk**
- **Conventional BP target**

Low-dose single agent

Full dose of single agent

Switch to different agent at low dose

Two/three-drug combination at full dose

Full-dose single agent

Not at BP goal

Not at BP goal

- **Marked BP elevation**
- **High/very high CV risk**
- **Lower BP target**

Low-dose two-drug combination

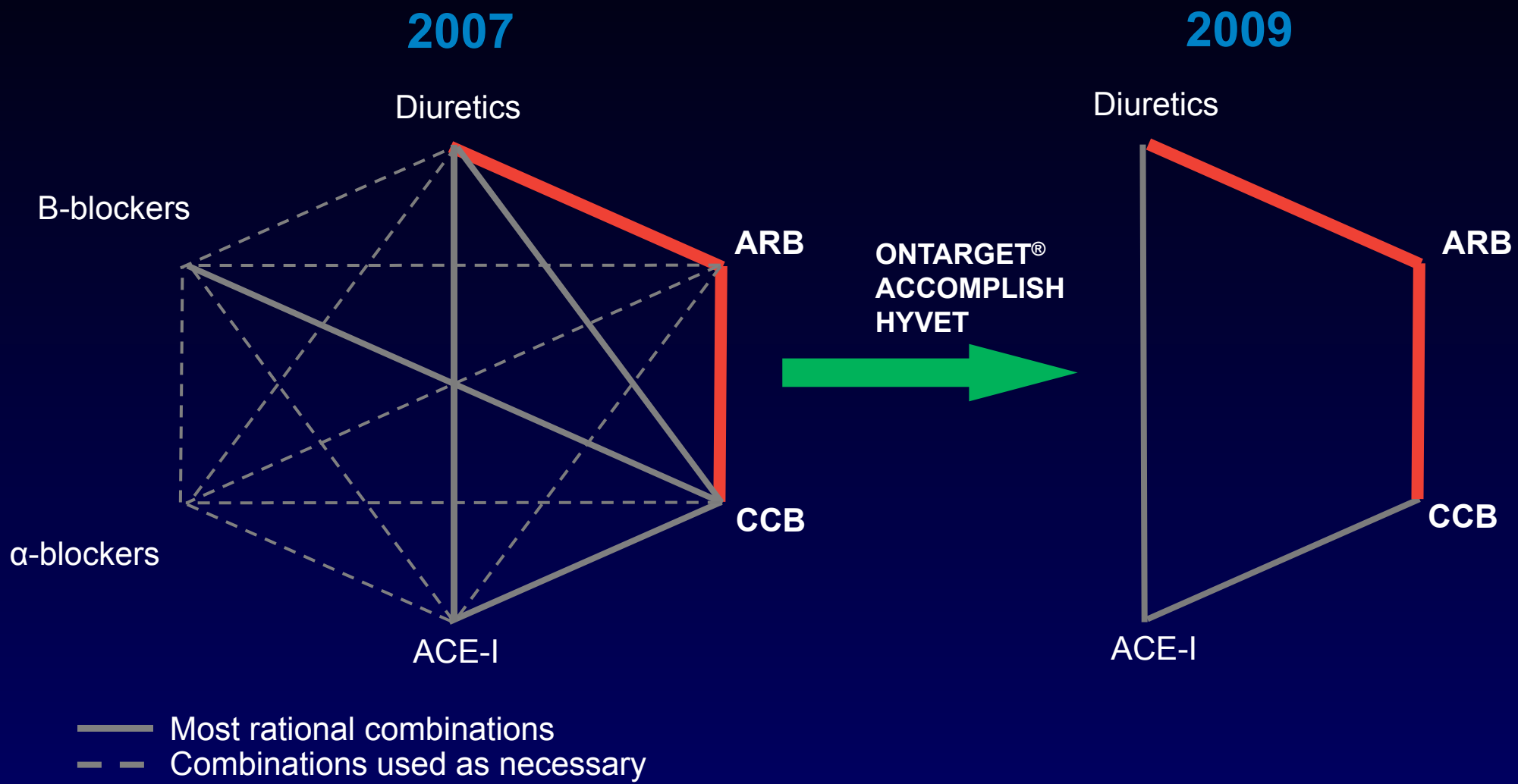
Full dose of two-drug combination

Add a third drug at low dose

Full doses of two/three-drug combination

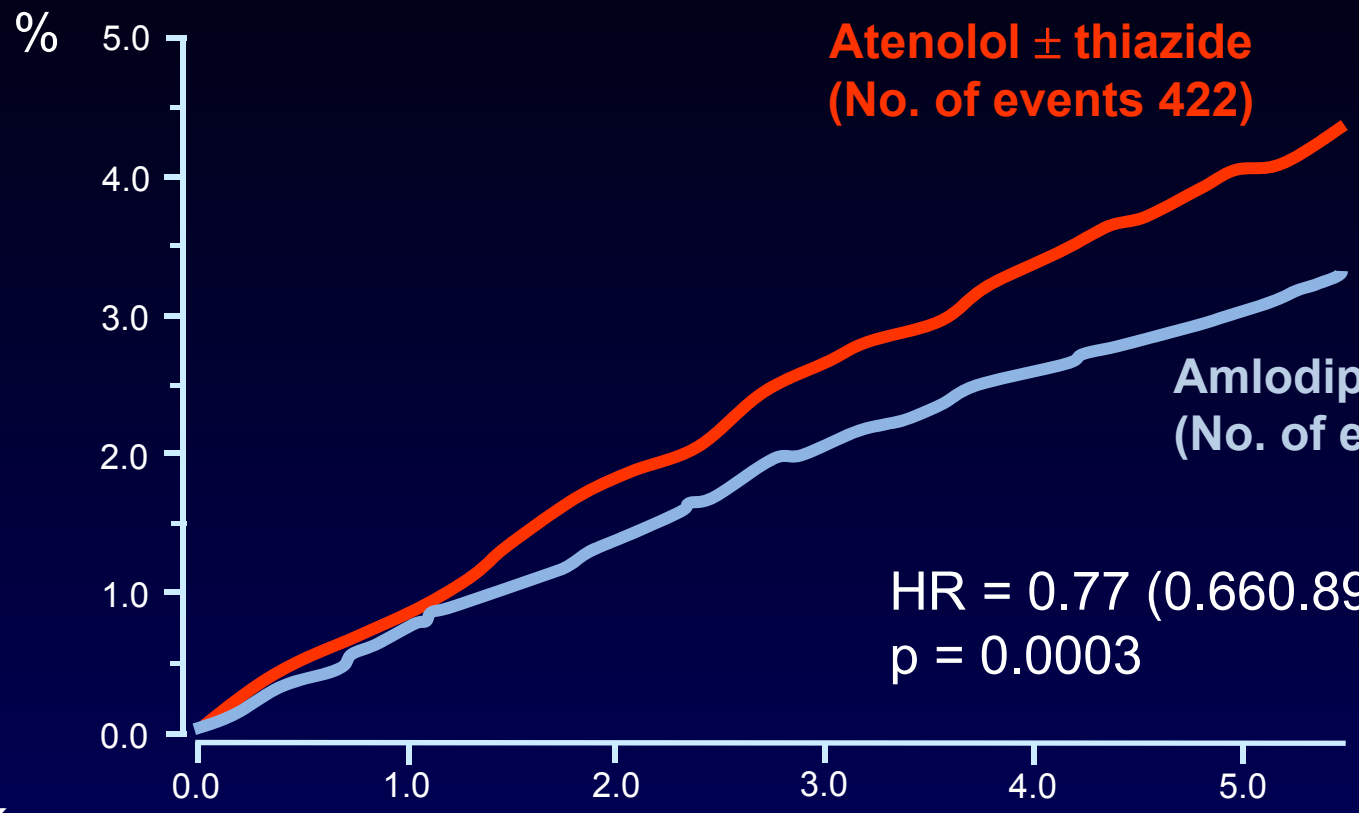
Mancia et al. *Eur Heart J.* 2007;28:1462.

Reappraisal of ESH/ESC Guidelines Suggests Four Preferred Antihypertensive Drug Classes



Mancia et al. *Eur Heart J.* 2007;28:1462; Mancia et al. *J Hypertens.* 2009;27:2121

ASCOT: Fatal & Nonfatal Stroke

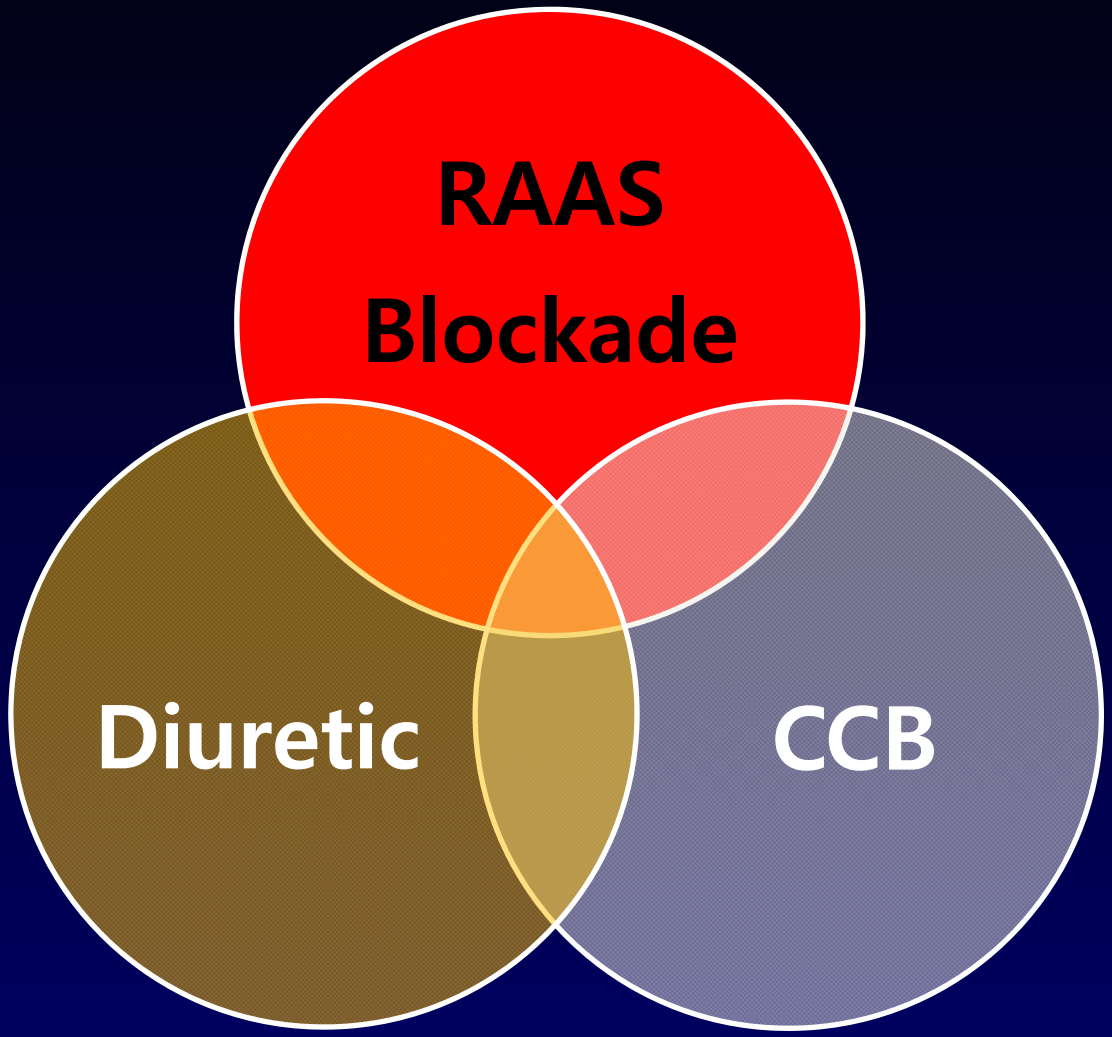


Number at risk

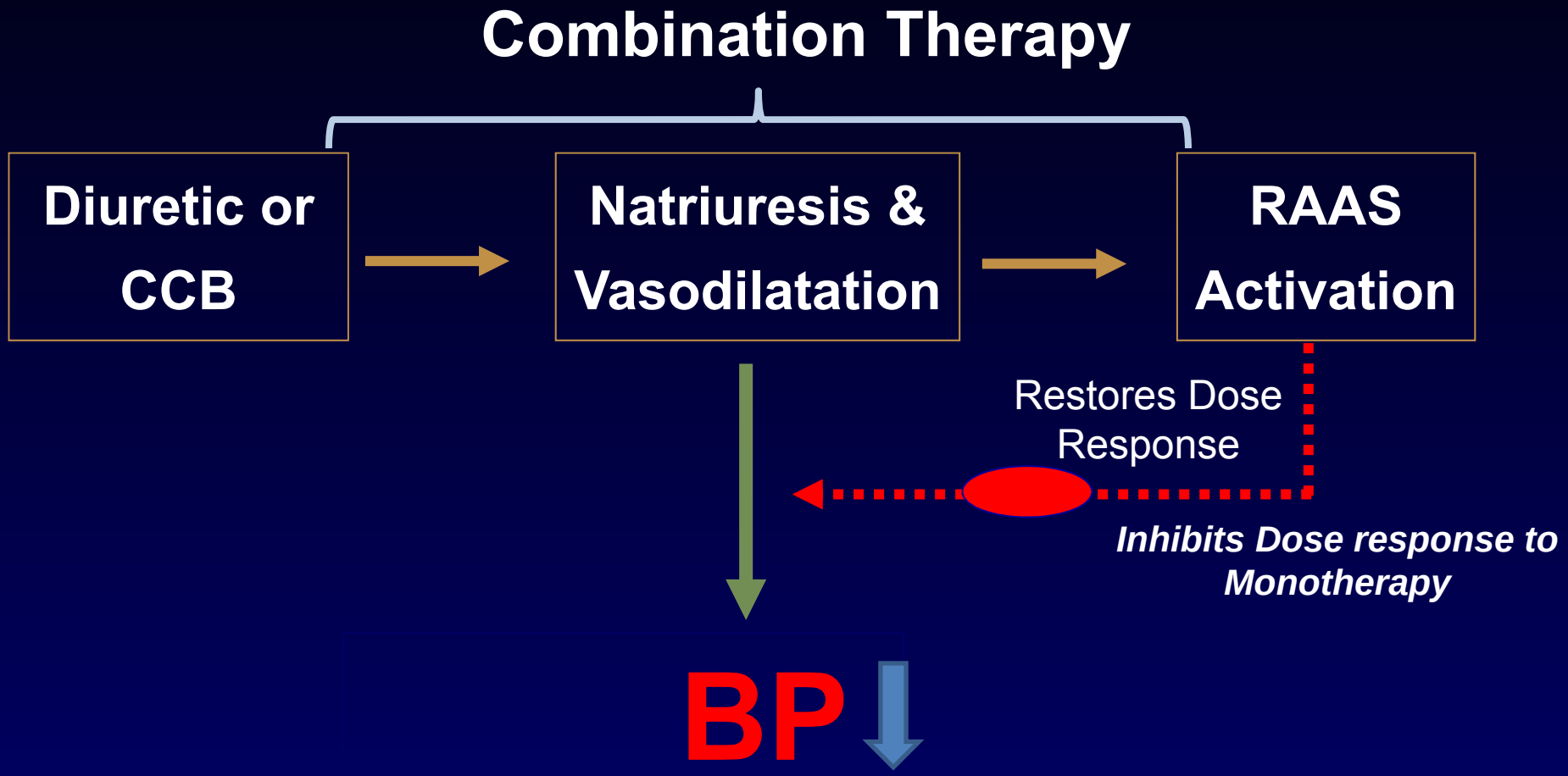
Amlodipine ± perindopril	9639	9483	9331	9156	8972	7863
Atenolol ± thiazide	9618	9461	9274	9059	8843	7720

Dahlöf et al. *Lancet* 2005;366:895-906

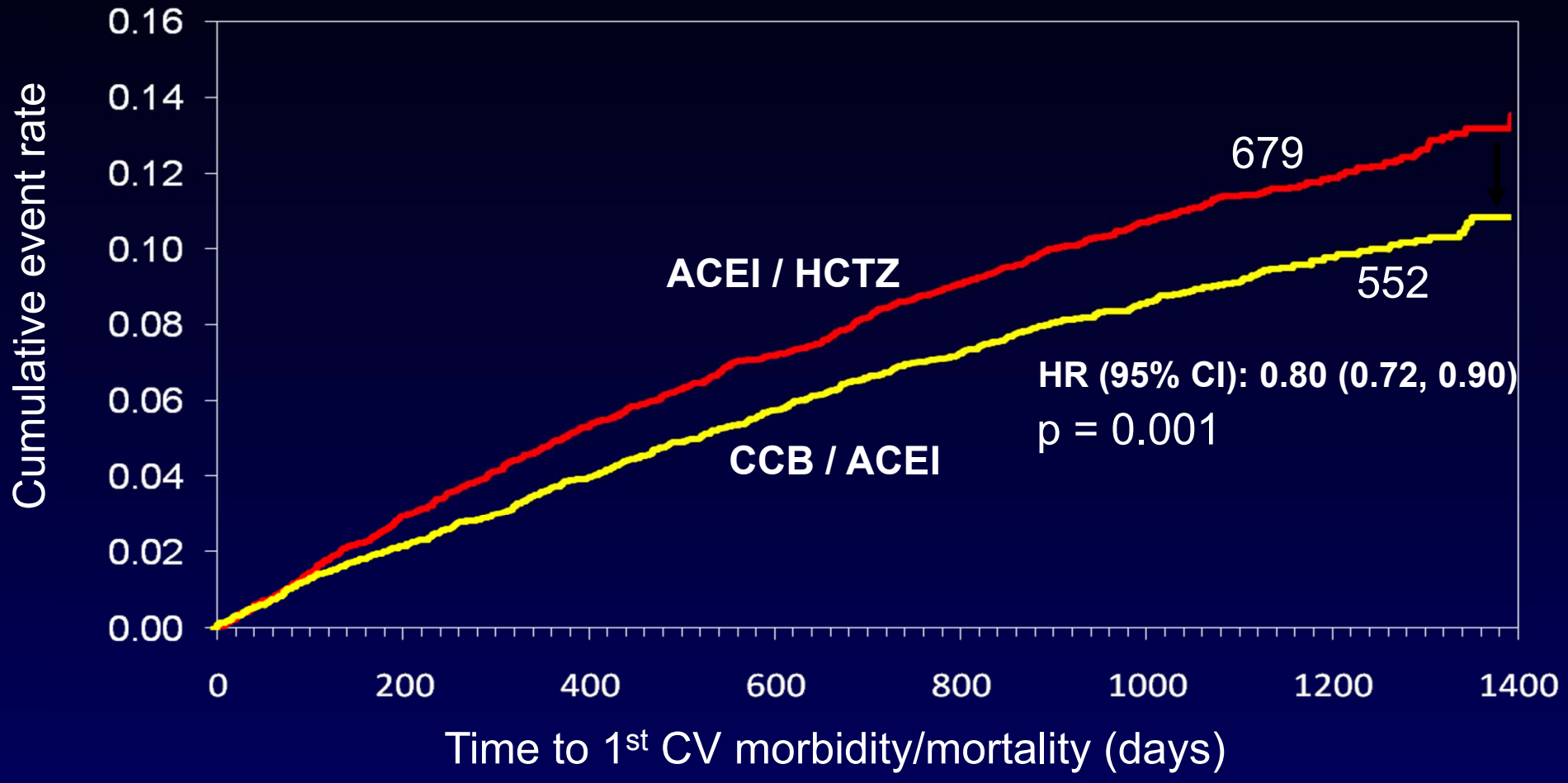
Simplifying Combination Therapy



Combination Therapy Restores Dose Response



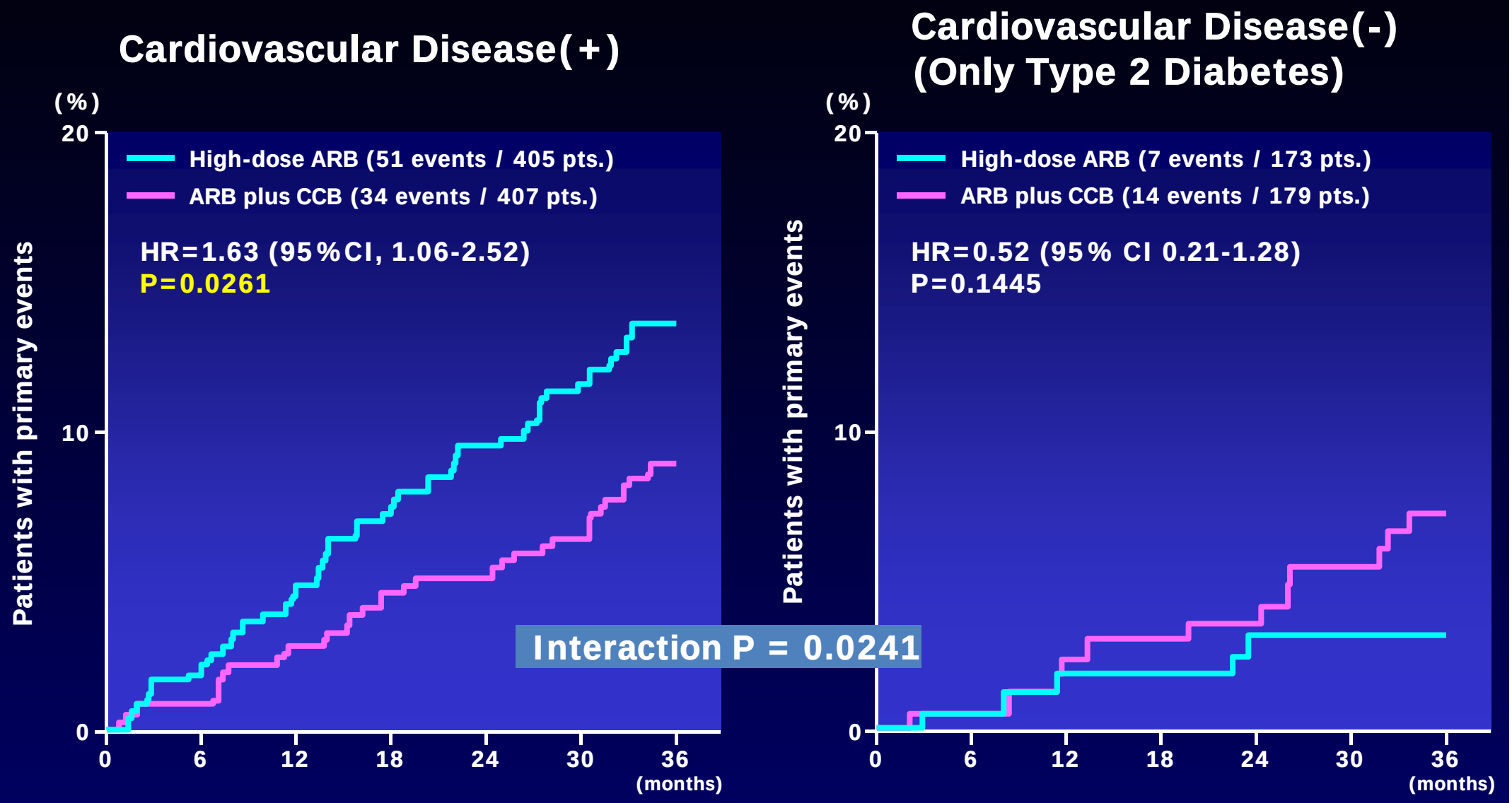
ACCOMPLISH: Morbidity/mortality



Jamerson et al. NEJM. 2008; 359(23); 2417-2428.

Primary Composite Endpoint in Subgroup of Patients with CVD or only Type 2 DM

OSCAR Study™



Late-breaking clinical trial ACC 60th Annual Scientific session, April 5, 2011, in New Orleans

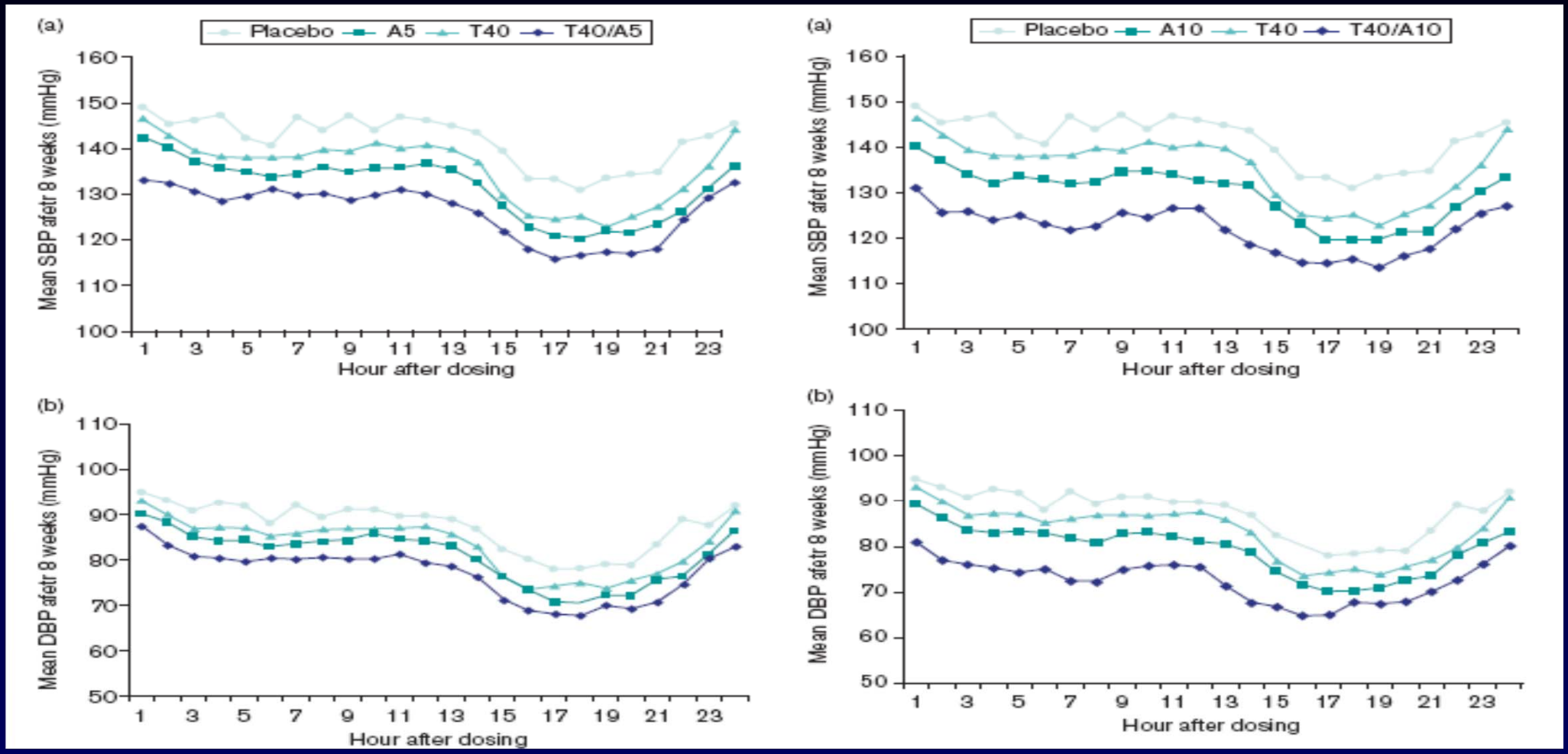
Not getting the added protection that we are relying on, could result in

unexpected,

unpleasant

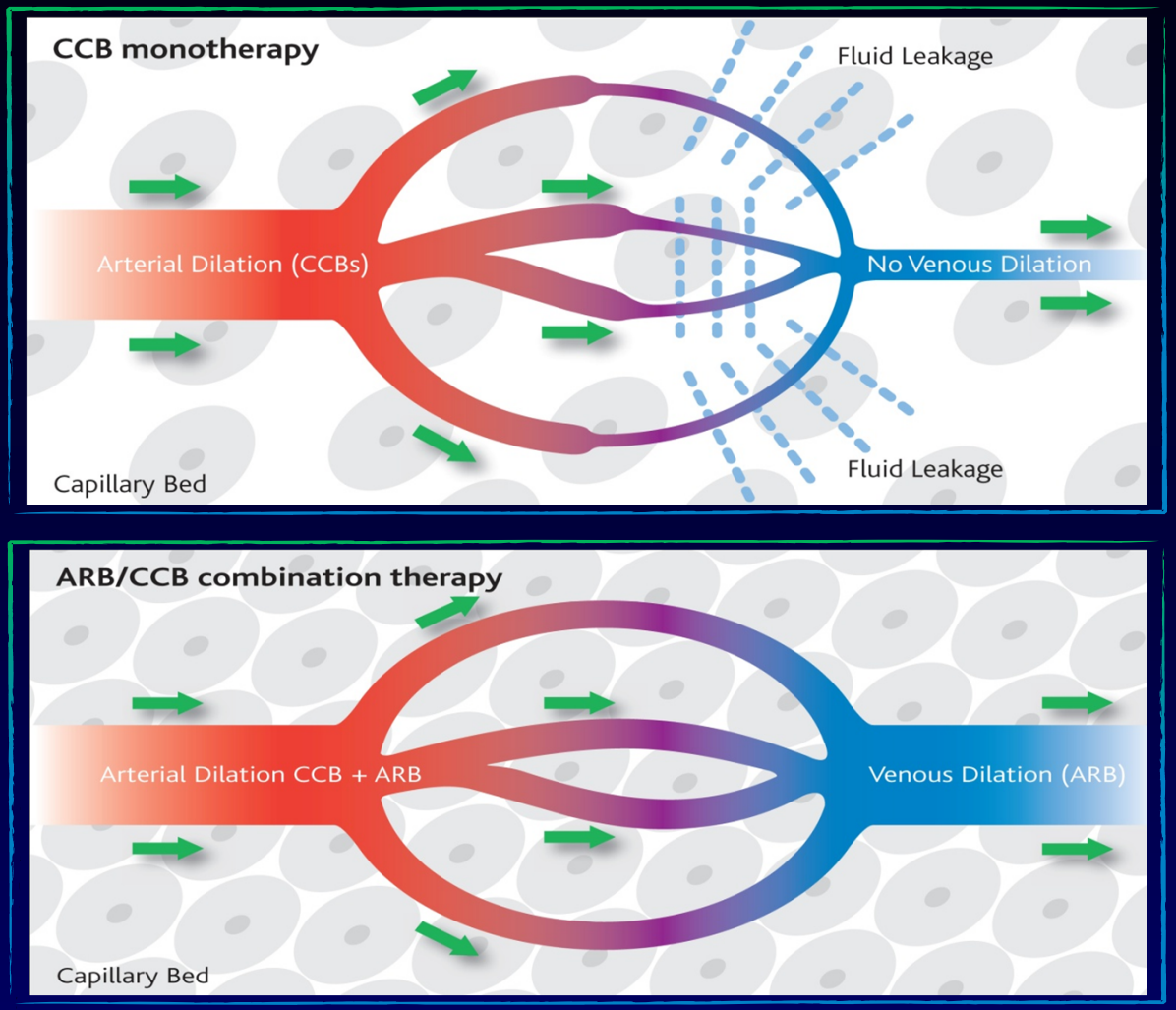
side effects

ARB+CCB combination vs. ARB or CCB alone in 24h BP reductions



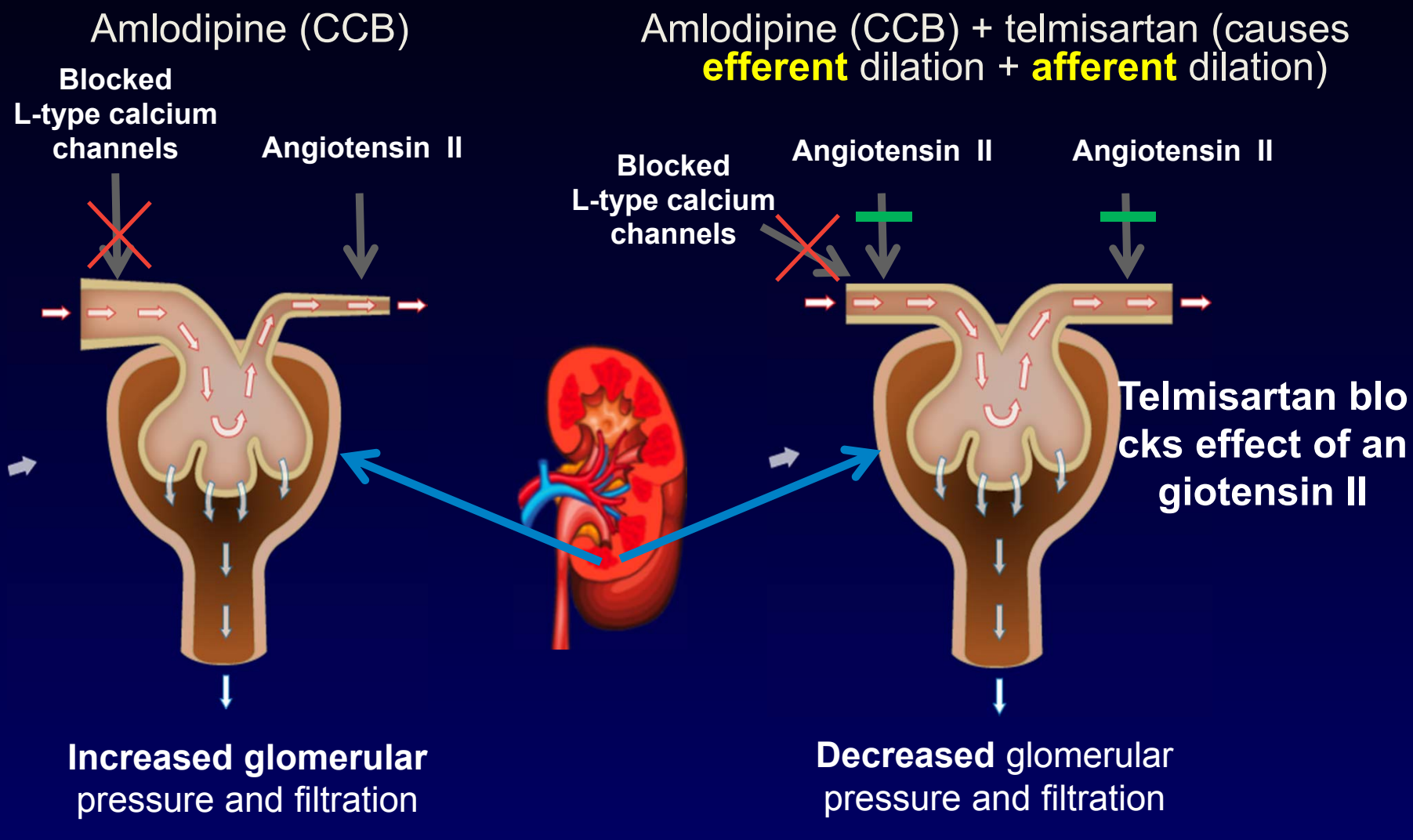
Blood pressure Monitoring 2010, 15:205-212

Venous fluid leakage induced by CCBs … gets reduced by co-administration of ARBs



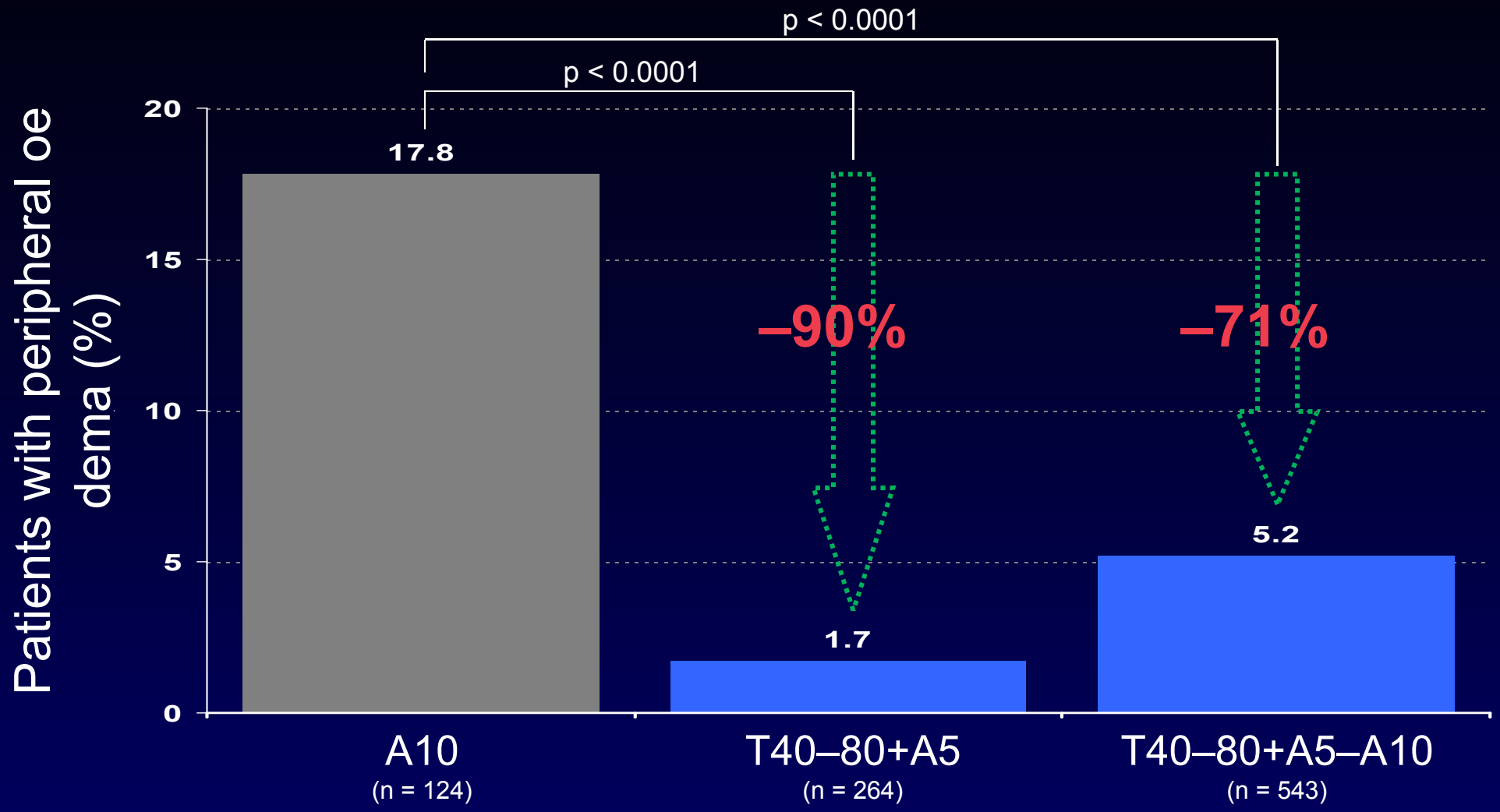
Opie et al. In: Opie LH, editor. *Drugs for the Heart*. 3rd ed. 1991:42–73; White et al. *Clin Pharmacol Ther.* 1986;39:43–48; Gustaffson. *J Cardiovasc Pharmacol.* 1987;10:S121–S131; Messerli et al. *Am J Cardiol.* 2000;86:1182–1187.

In a preclinical model, renal hyperfiltration induced by a CCB is reduced by an ARB



Peti-Peterdi; Abstract ESC 2010.

Telmisartan+Amlodipine is Associated With Less Peri-pheral Oedema Compared With Amlodipine 10mg



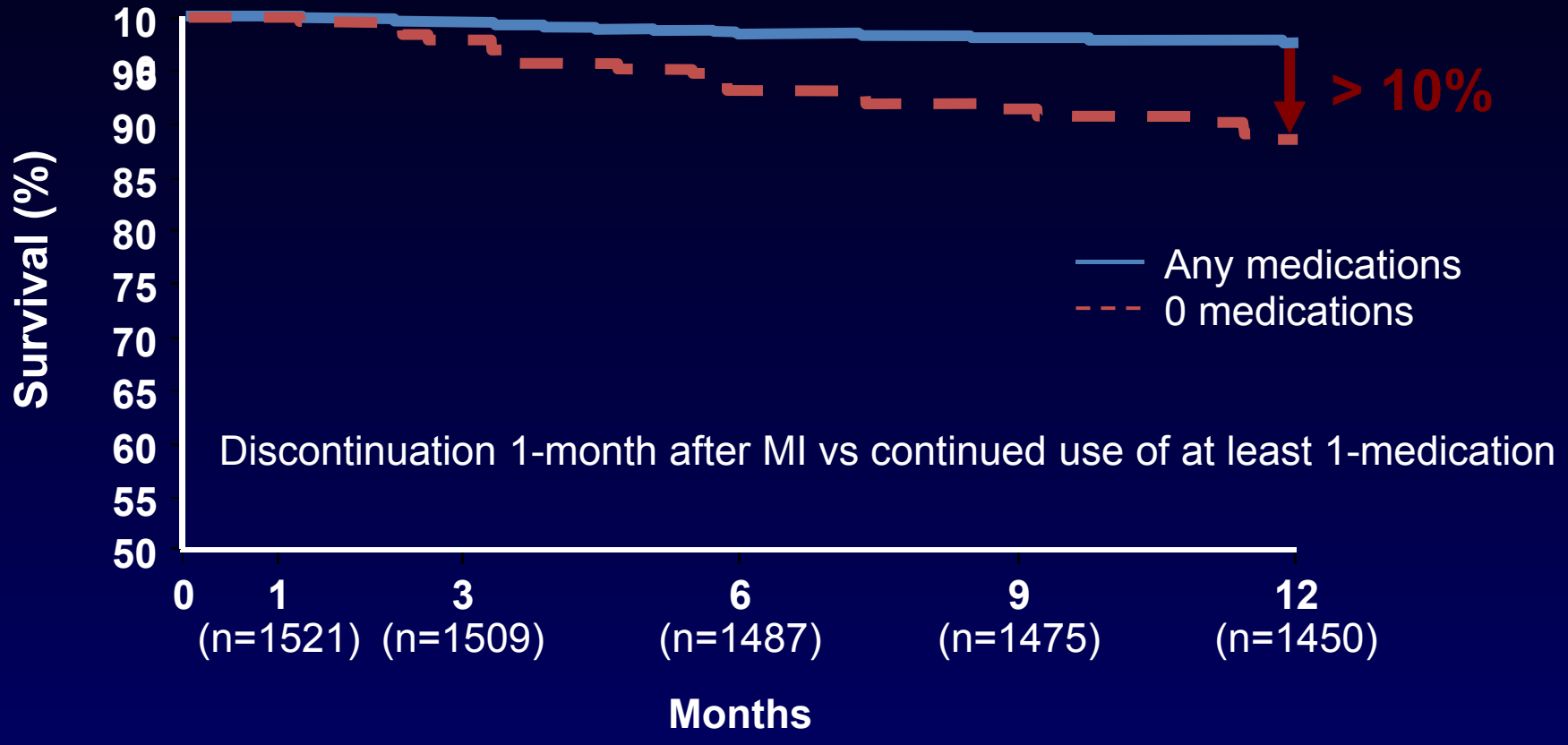
Littlejohn et al. *J Clin Hypertens.* 2009;11:207–213.

“Drugs Don’t Work in Patients who Don’t Take Them”

C. Everett Koop, MD, US Surgeon General (1982 to 1989)

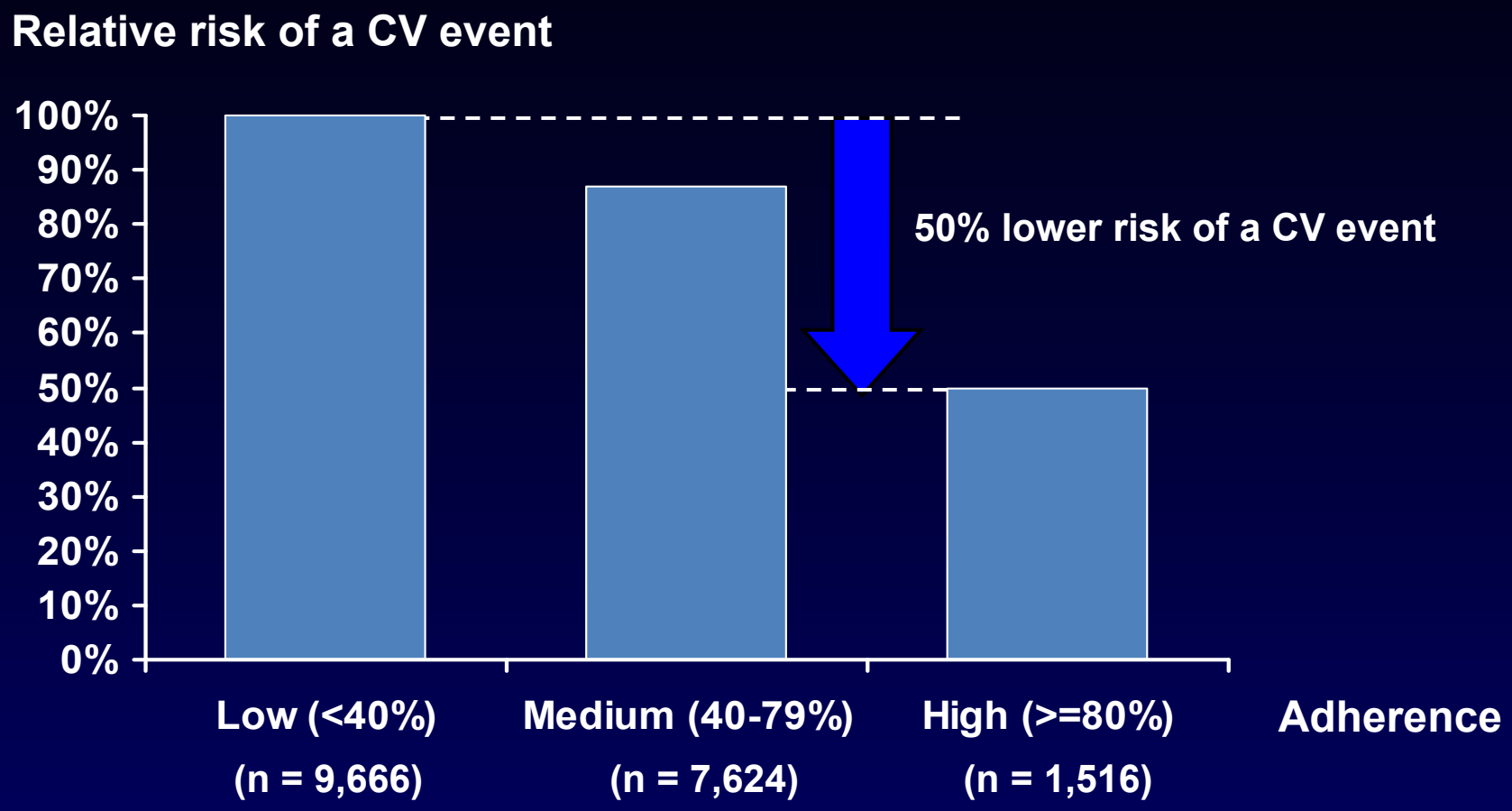
Treatment adherence is important

Impact of medication therapy discontinuation on mortality



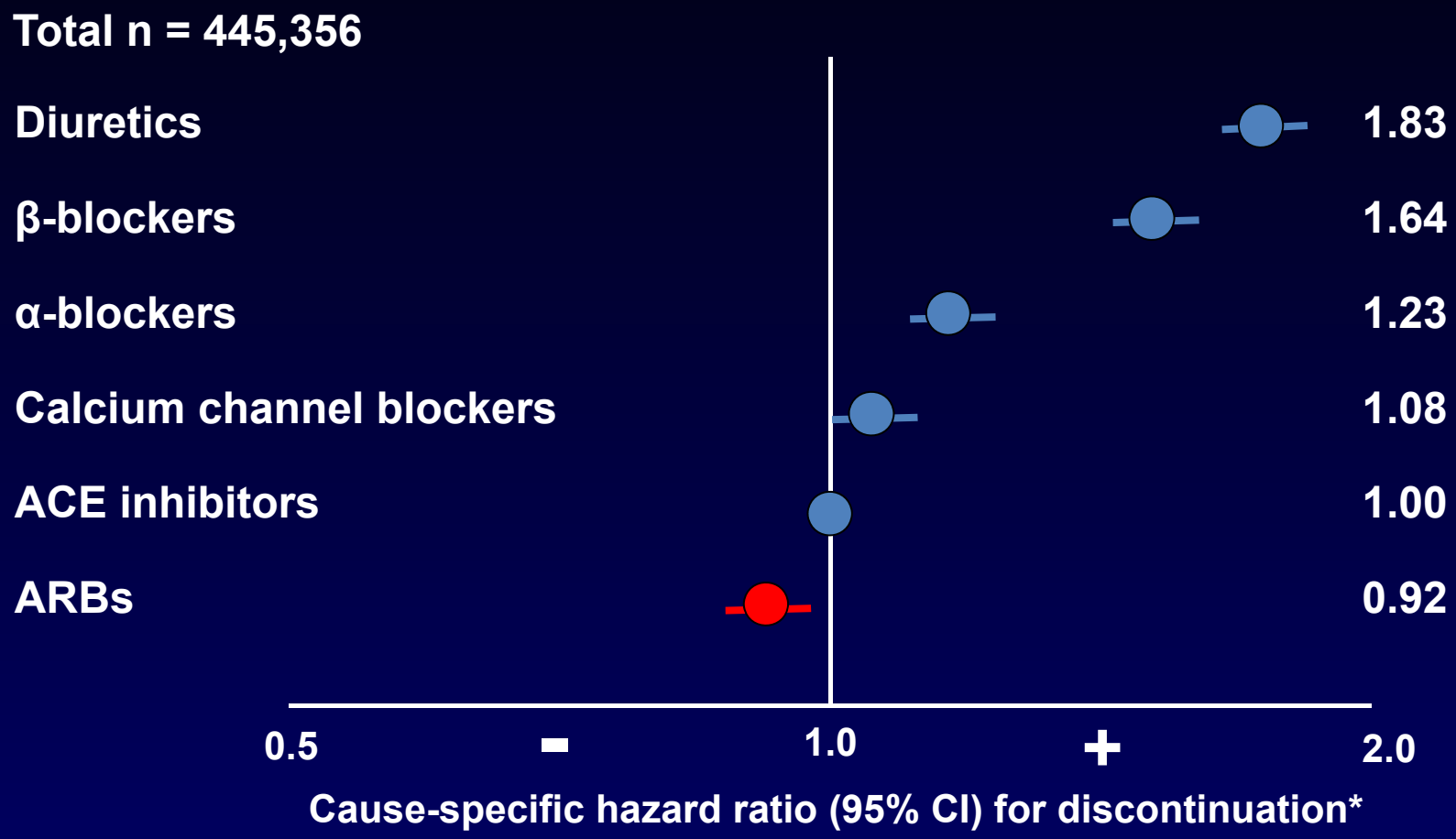
Ho et al. Arch Intern Med 2006;166:1842-1847.

Patients who are adherent are at lower CV risk



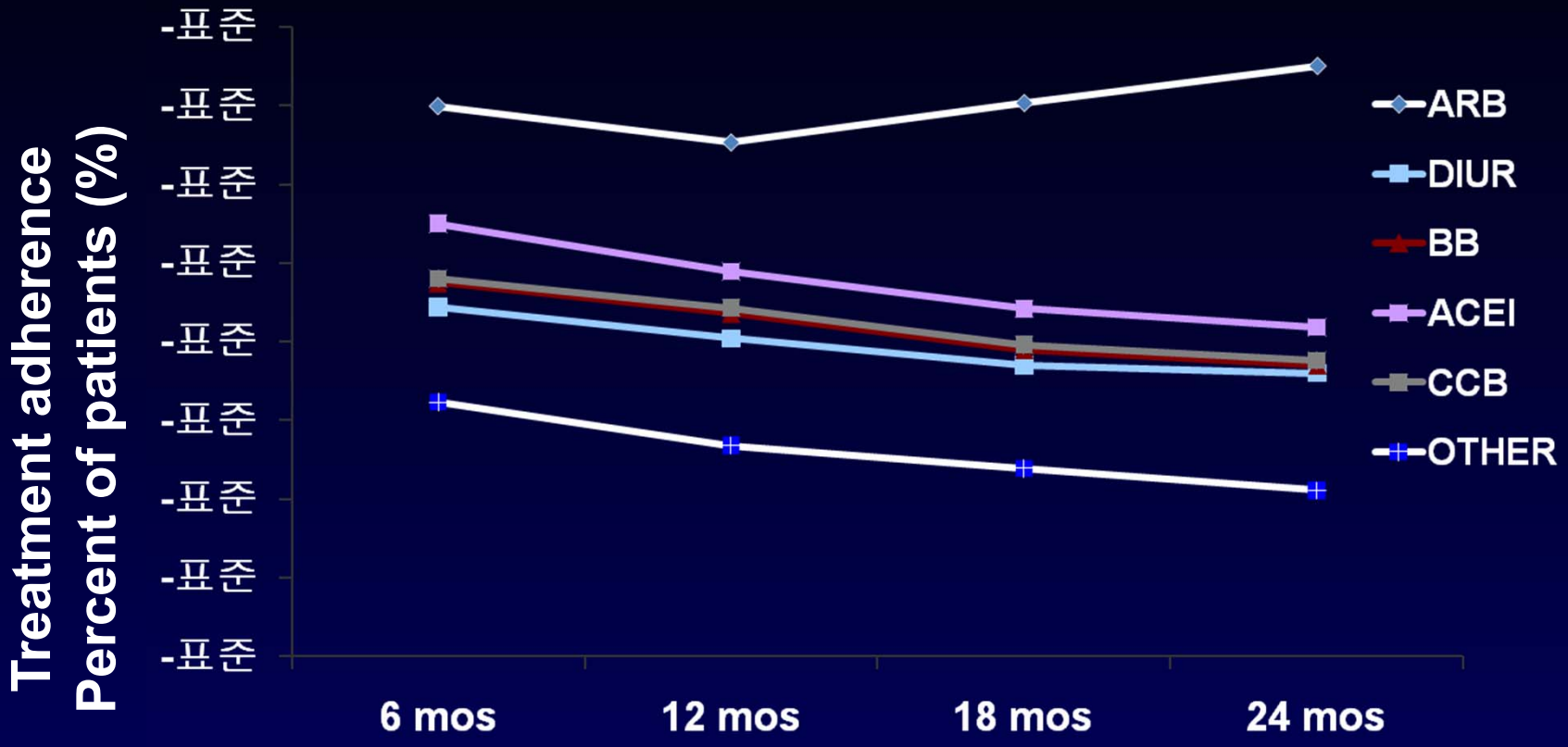
Mazzaglia et al. Circulation 2009;120:1598-1605

Treatment adherence is highest with ARBs at 1 year



Corrao et al. J Hypertens 2008;26:819-24.

ARBs are considered to have the best treatment adherence over time



	6 mos	12 mos	18 mos	24 mos
P value*	<0.001	<0.001	<0.001	0.060

* ARB p value vs each of the other classes (Chi-Square)
Chaput AJ. Can J Cardiol 2000;16(suppl F):194A.

Persistence with ARBs over 4 years

15,175 patients

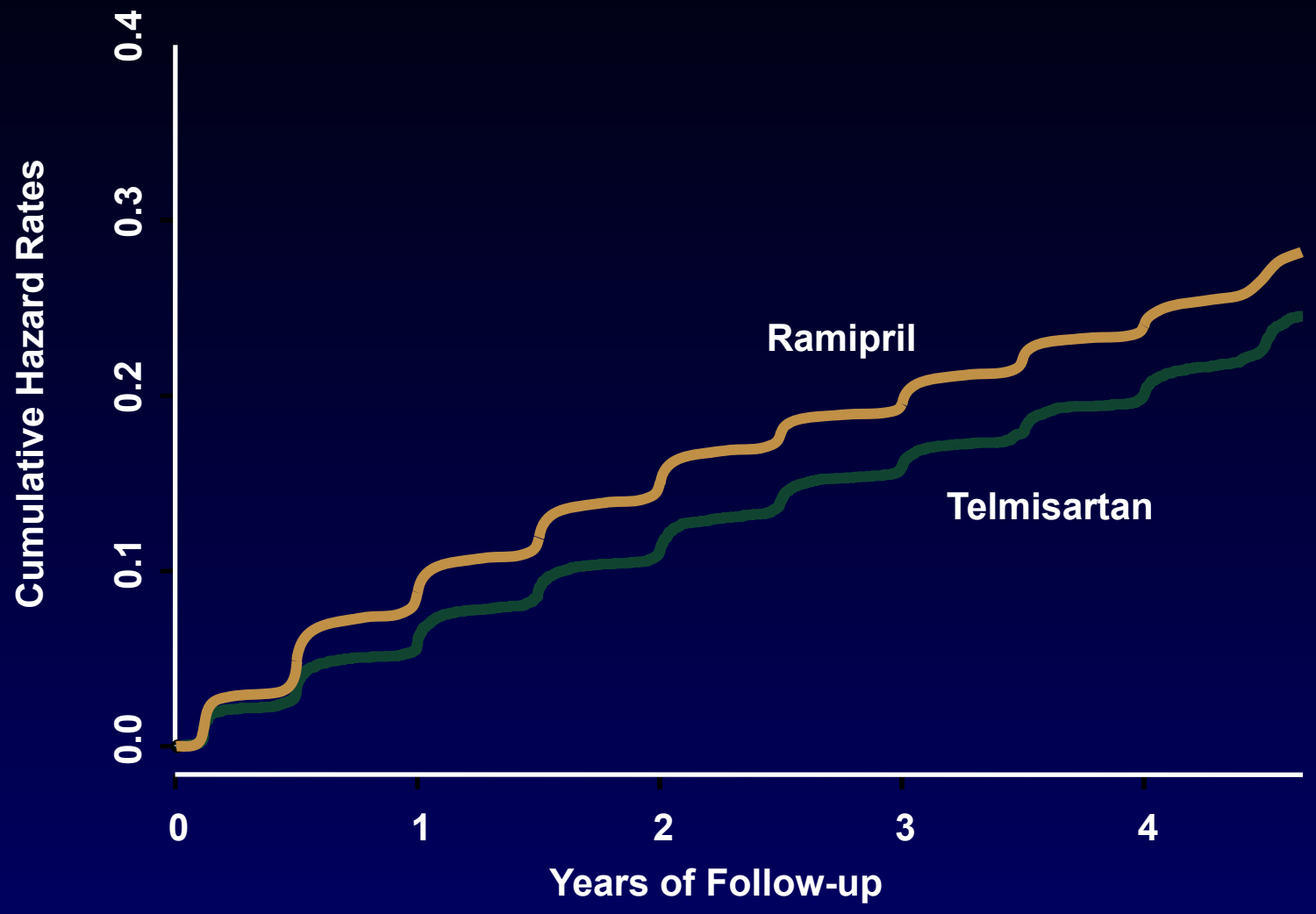
Persistence in the ARB class > ACE-I, CCB, BB and Diuretic:

- **12 months (p=0.05)**
- **24 months (p<0.007)**
- **36 months (p<0.01)**
- **48 months versus CCB, BB and Diuretic (p<0.03) with a statistical trend for ACE (p=0.095)**
- **HALF of patients in the beta blocker and diuretic class were**

NOT BEING TREATED AT ALL by 4 years

Boccuzzi SJ et al. *Am J Hypertens* 2001;14:10A

ONTARGET: Time to Permanent Discontinuation of Study Medication



ONTARGET Investigators

ONTARGET: Reasons for Permanently Stopping Study Medications

	Ram N=8576	Tel N=8542	Tel vs. Ram RR	P
Hypotension	149	229	1.54	0.0001
Syncope	15	19	1.27	0.4850
Cough	360	93	0.26	<0.0001
Diarrhea	12	19	1.59	0.20
Angioedema	25	10	0.40	0.0115
Renal Impairment	60	68	1.14	0.46
Any Discontinuation	2099	1962	0.94	0.02

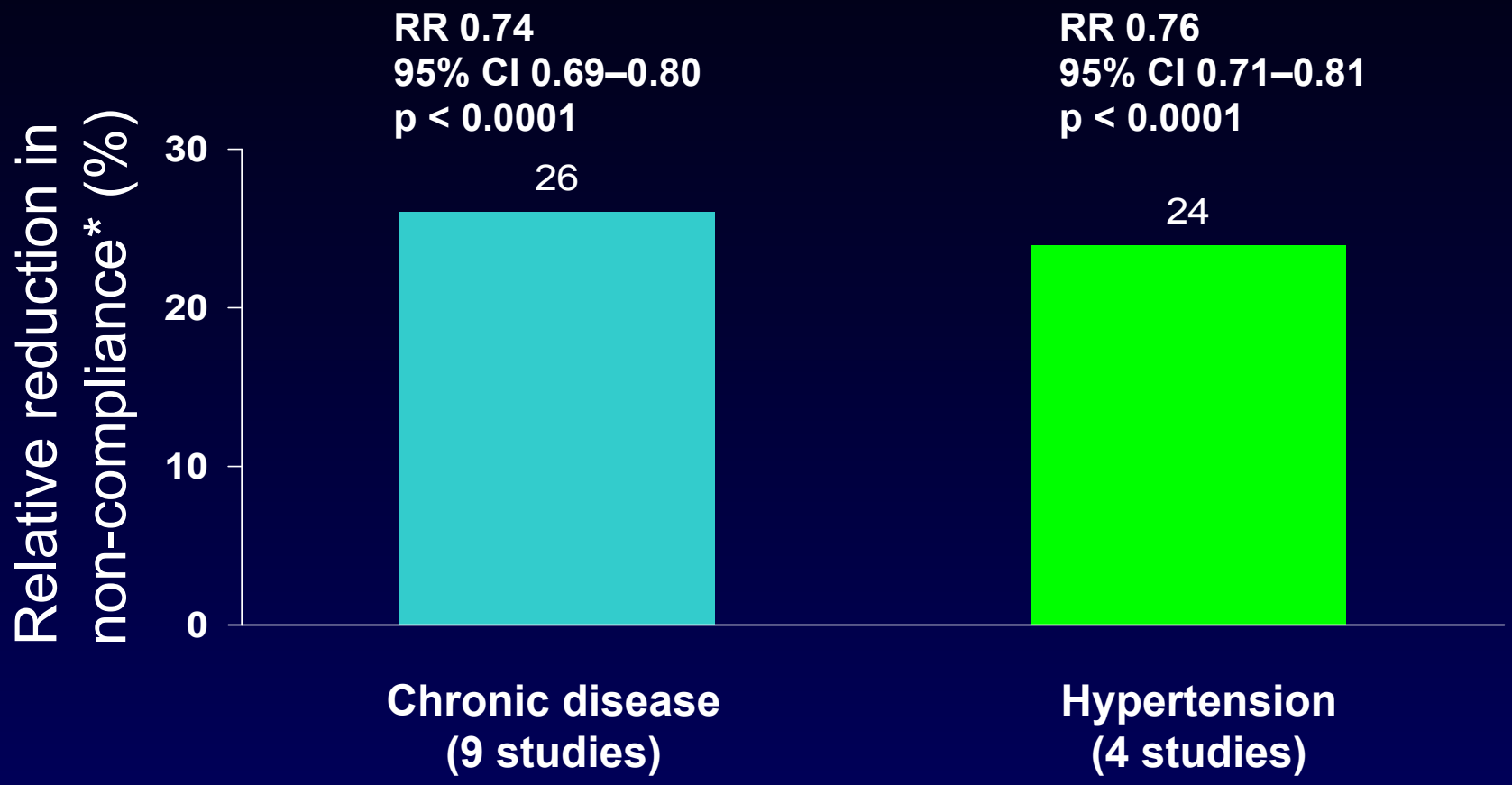
Simpler Regimens Improve BP Control

Cross-sectional assessment of 161,697 Kaiser Permanente Northern California diabetes patients

- **Using once daily dosing decreases SBP by 6 mmHg**
- **Fixed-dose combination tablets increased adherence up to 10-20%**

Schmittdiel JA et al. J Gen Int Med 2008;23:588

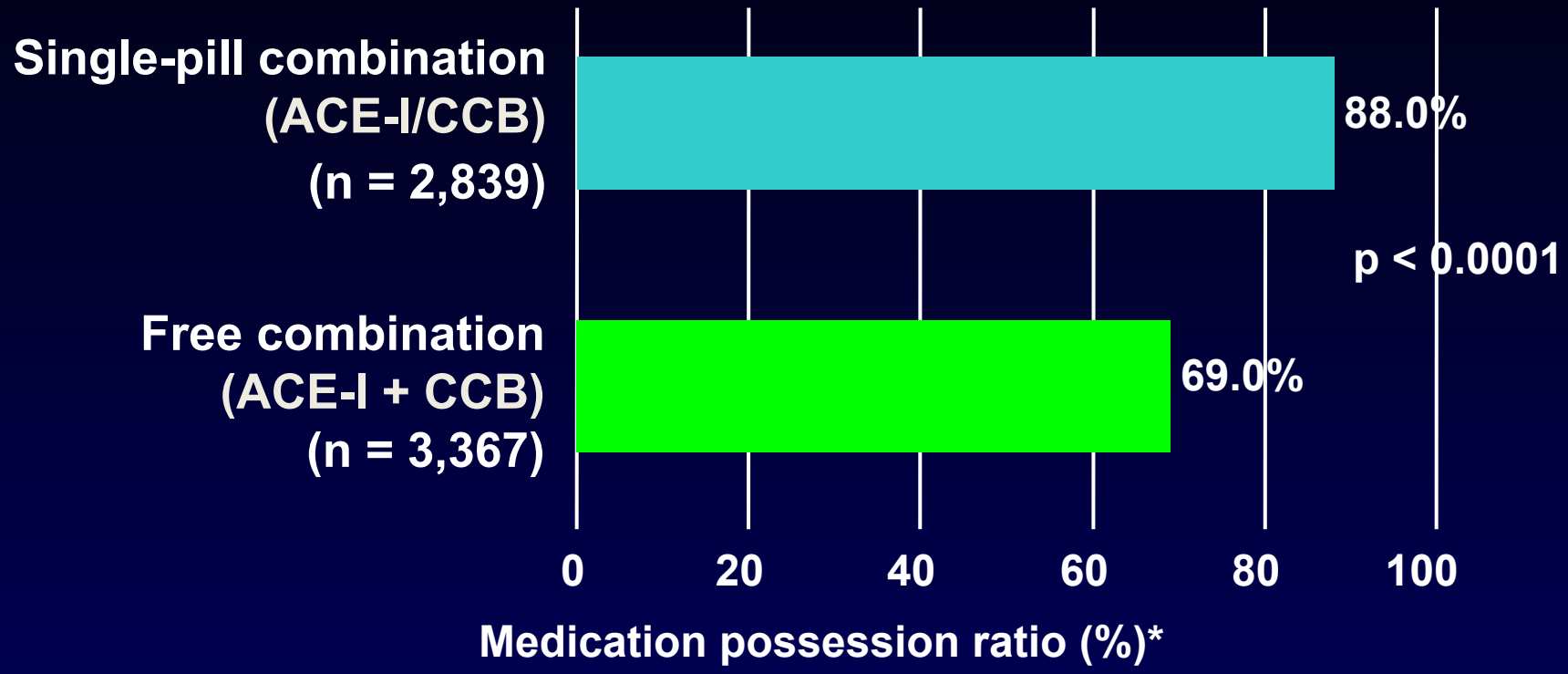
Single-Pill Combinations Improve Treatment Compliance



*With single-pill combination therapy vs free-drug regimens

Bangalore *et al*. *Am J Med.* 2007;120:713–719.

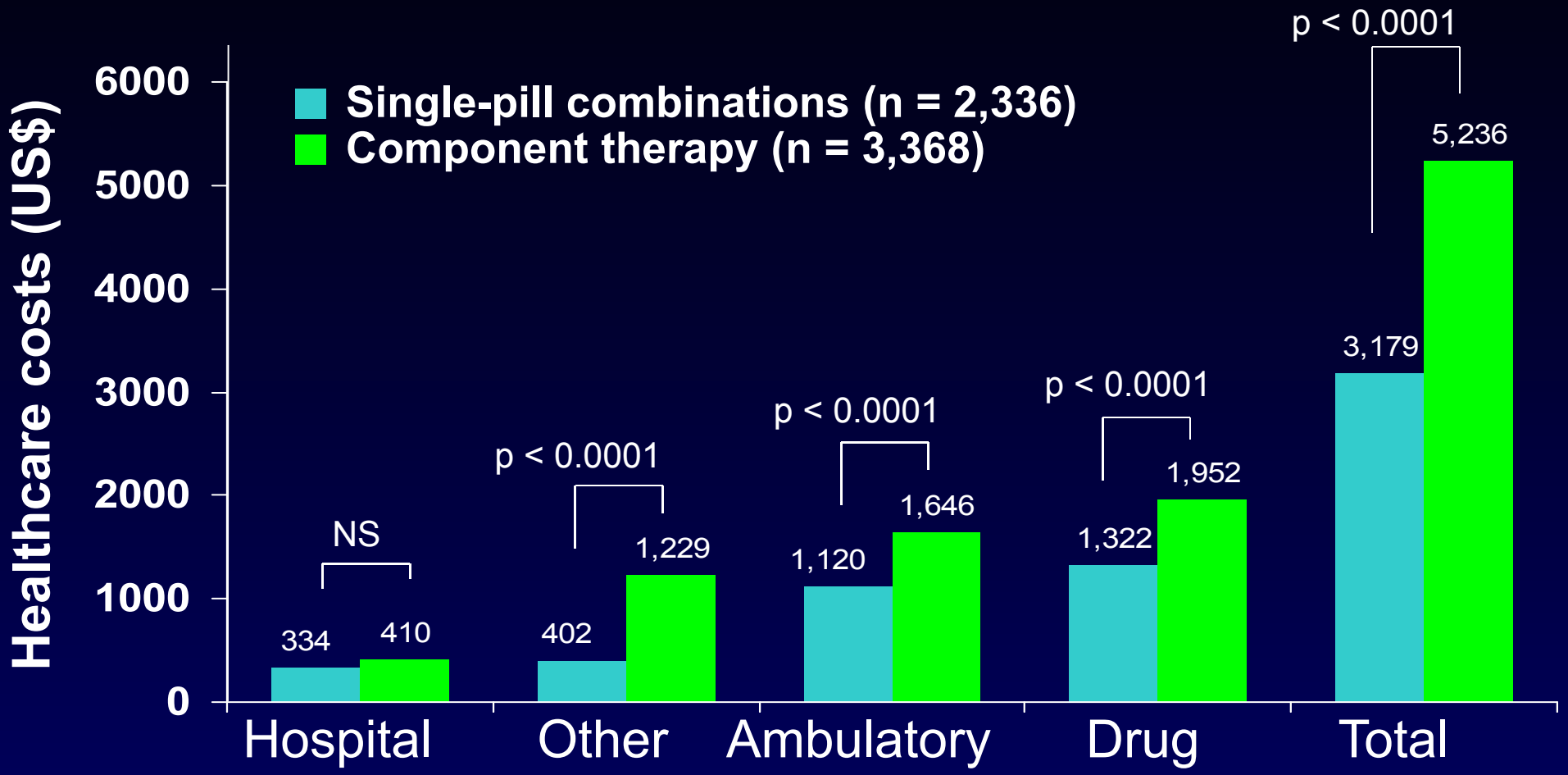
Single-Pill Combinations of ACE-I and CCB Improve Treatment Compliance



* Defined as the total number of days of therapy for medication dispensed/365 days of study follow-up

Gerbino and Shoheiber. *Am J Health System Pharm.* 2007;64:1279–1283.

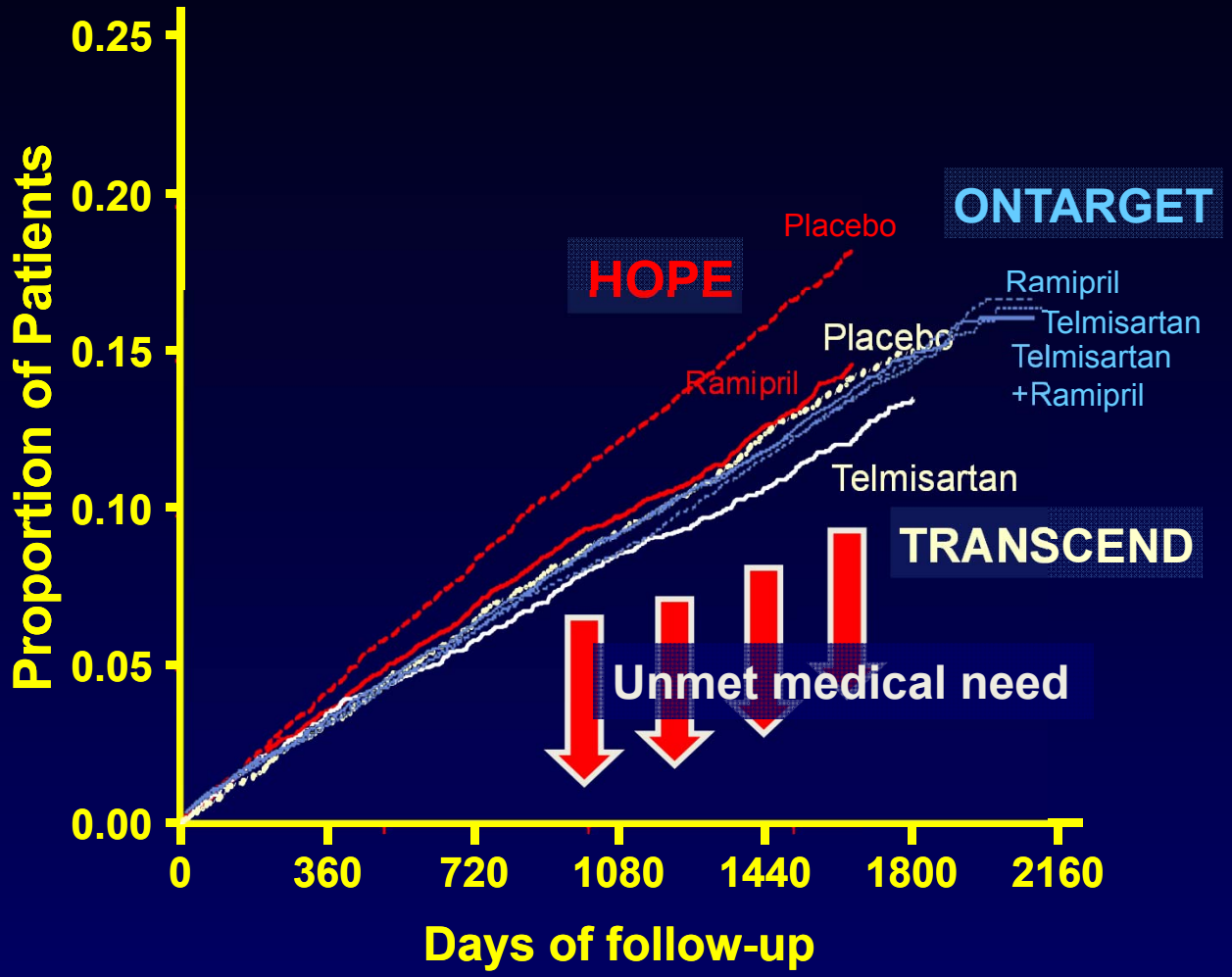
Single-Pill Combinations Reduce Resource Utilization



NS = not significant

Dickson and Plauschinat. *Am J Cardiovasc Drugs.* 2008;8:45–50.

Future Best Practice
In High Risk Hypertension



- RAS inhibition– Key role
- Unmet Medical Need
- Single Pill-Combination
  - Better BP reduction
  - Less SE
  - Better Adherence
- How?
  - RAS blocker+CCB
  - +/-Diuretic
- What else?
  - 3-drug single-pill
  - Dose combination
  - Renin inhibition?