

# State of the art treatment of hypertension: established and new drugs

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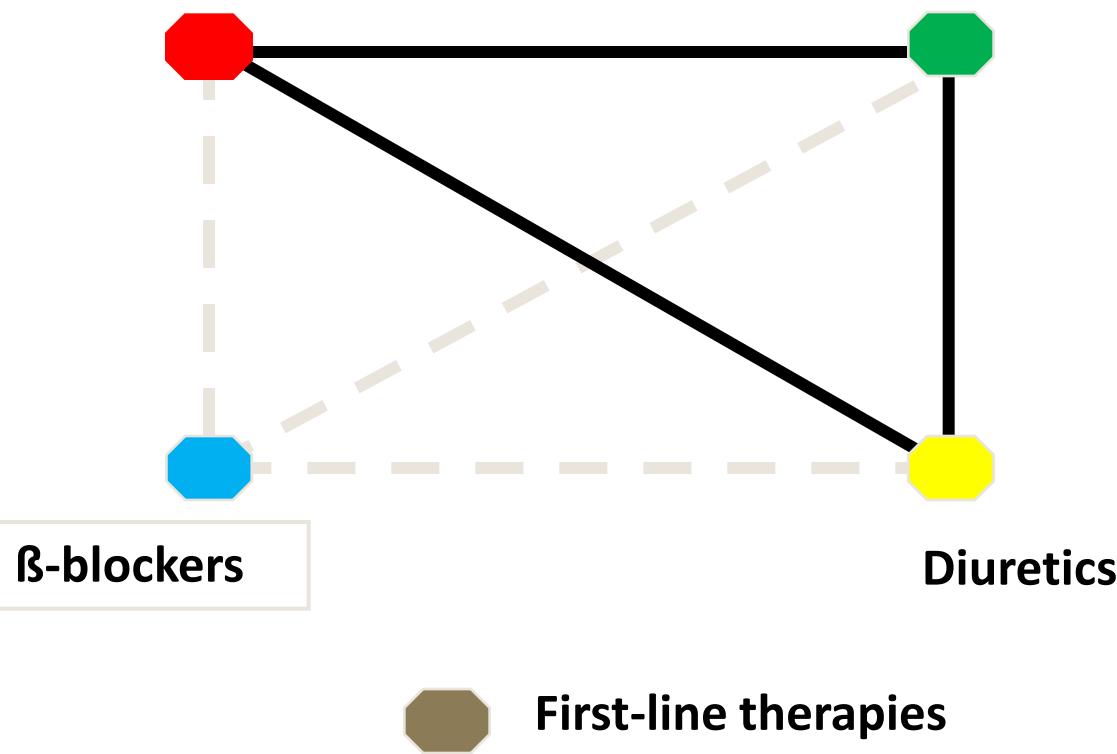


# First line therapies in hypertension

ACE inhibitors

AT<sub>1</sub>-receptor blockers

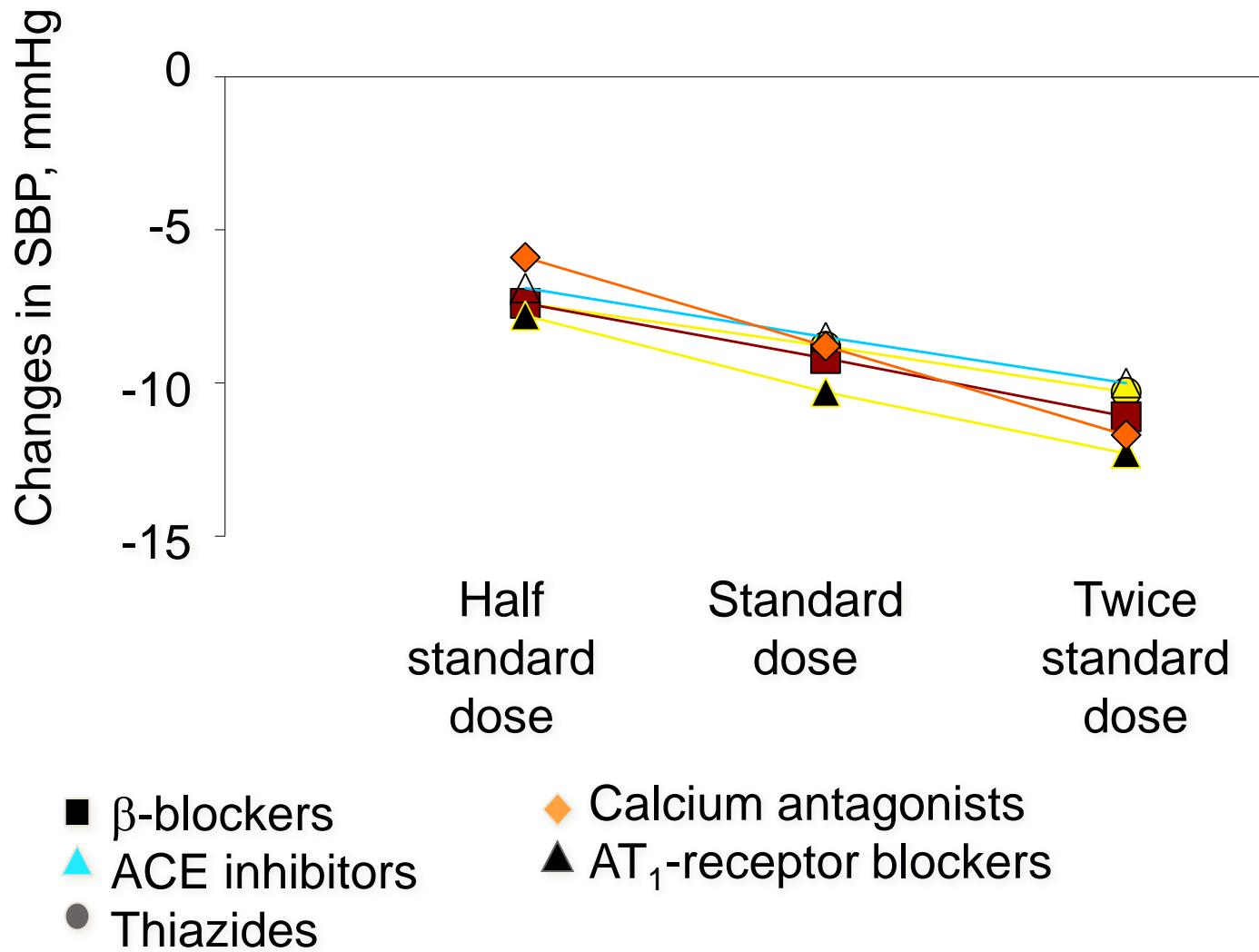
Calcium antagonists

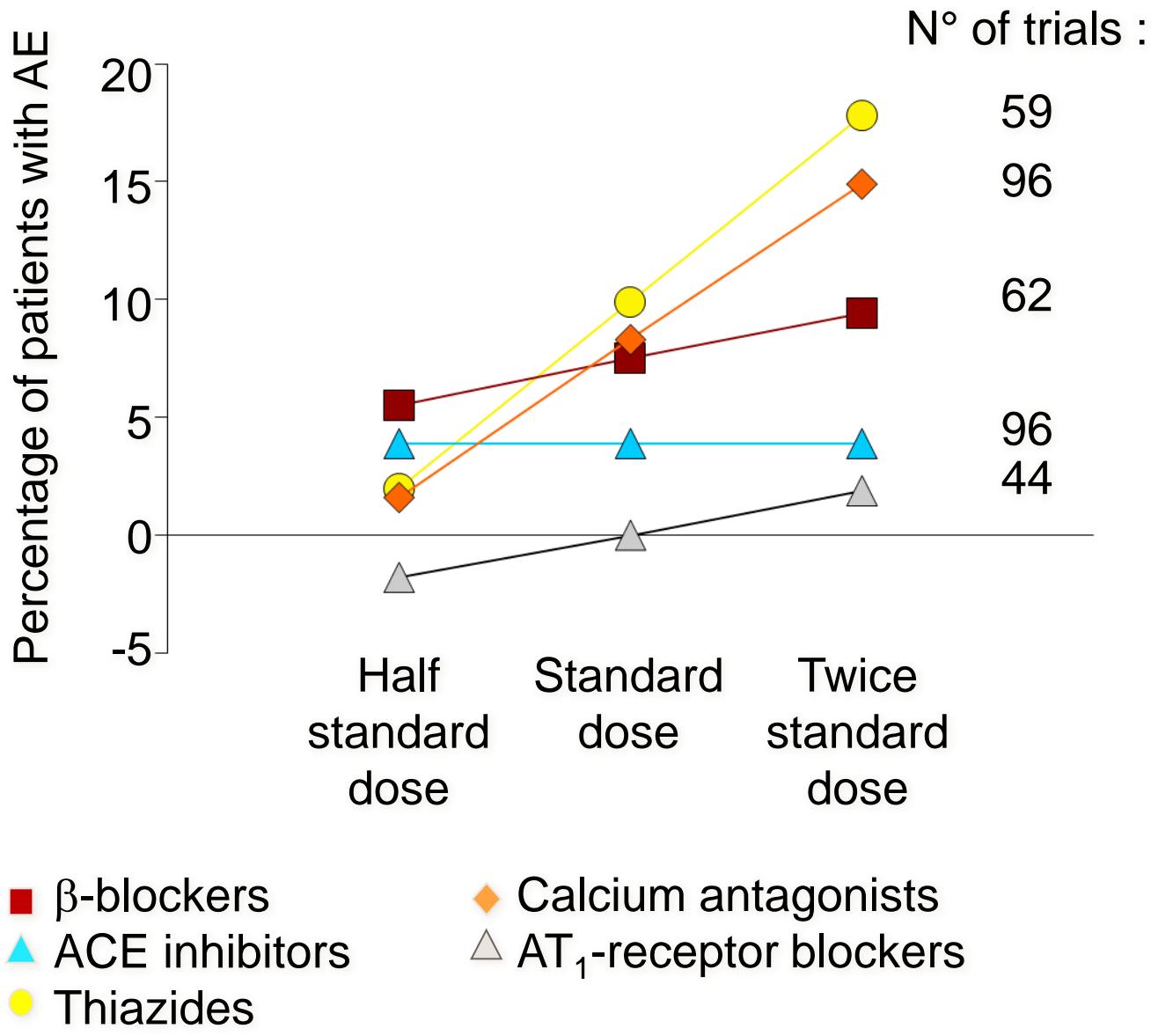


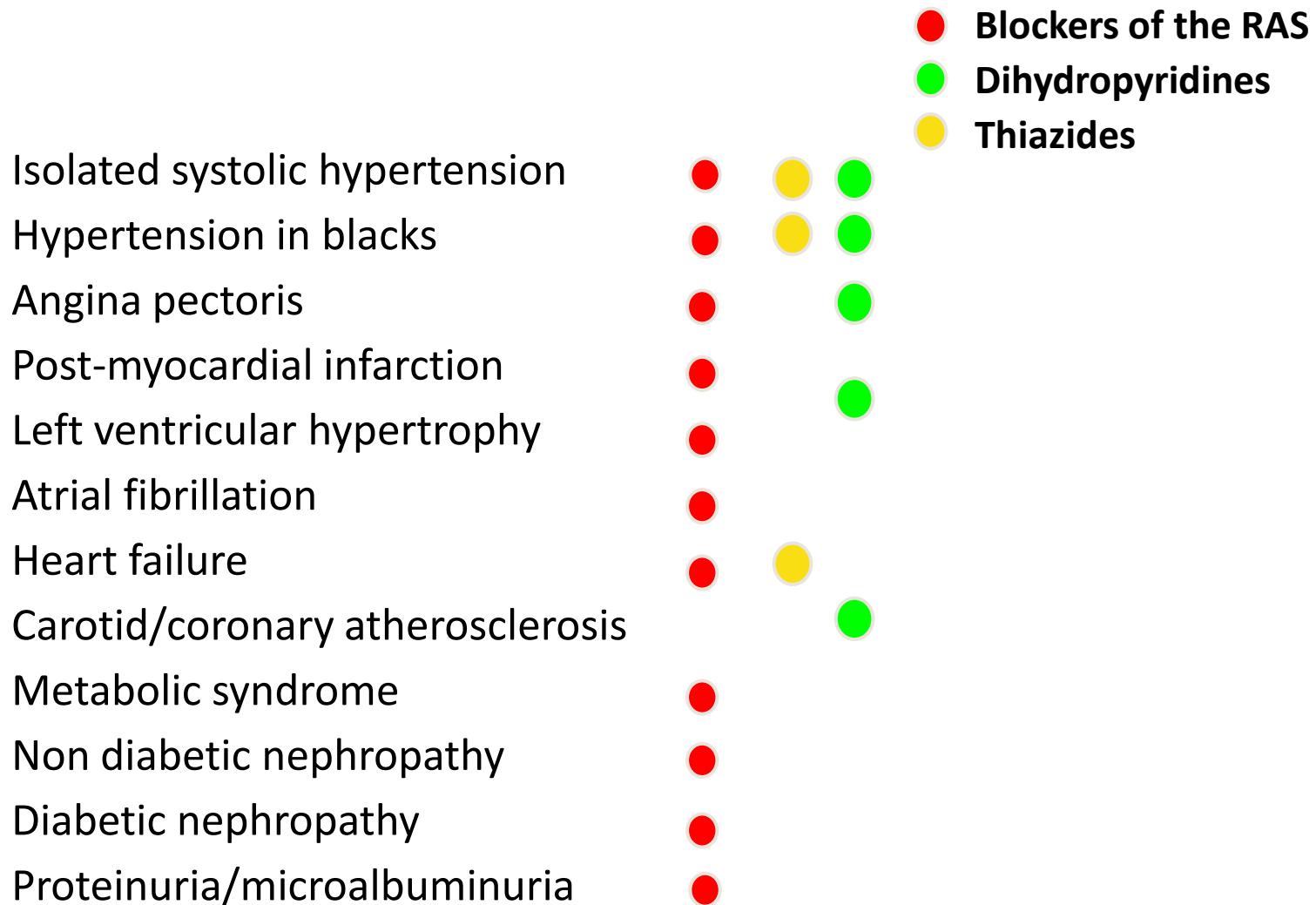
Adapted from the 2009 Reappraisal of ESH/ESC Hypertension Guidelines



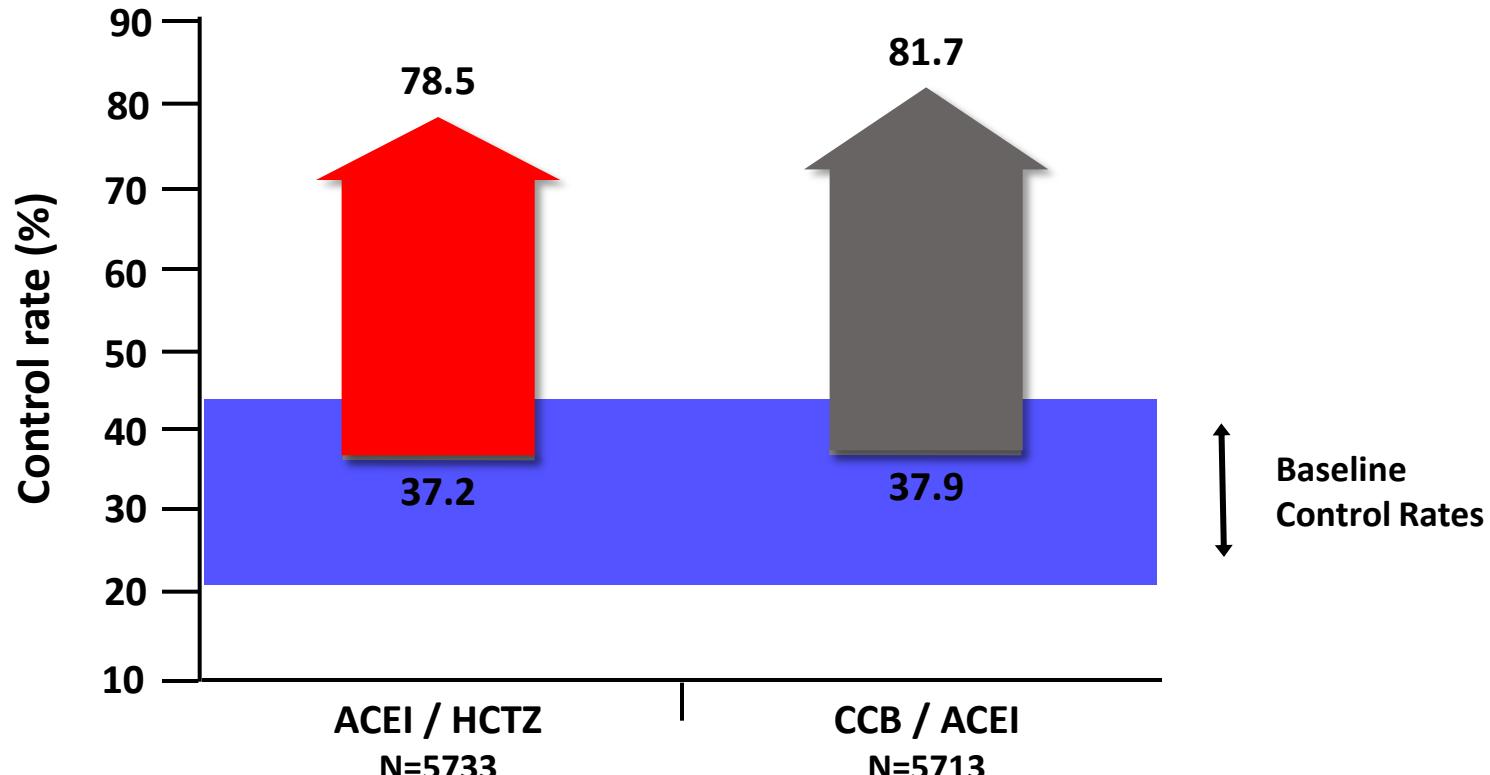
# Placebo-corrected changes in SBP







# ACCOMPLISH: Exceptional Control Rates with Initial Combination Therapy



P<0.001 at 30 months follow-up

Control defined as <140/90 mmHg

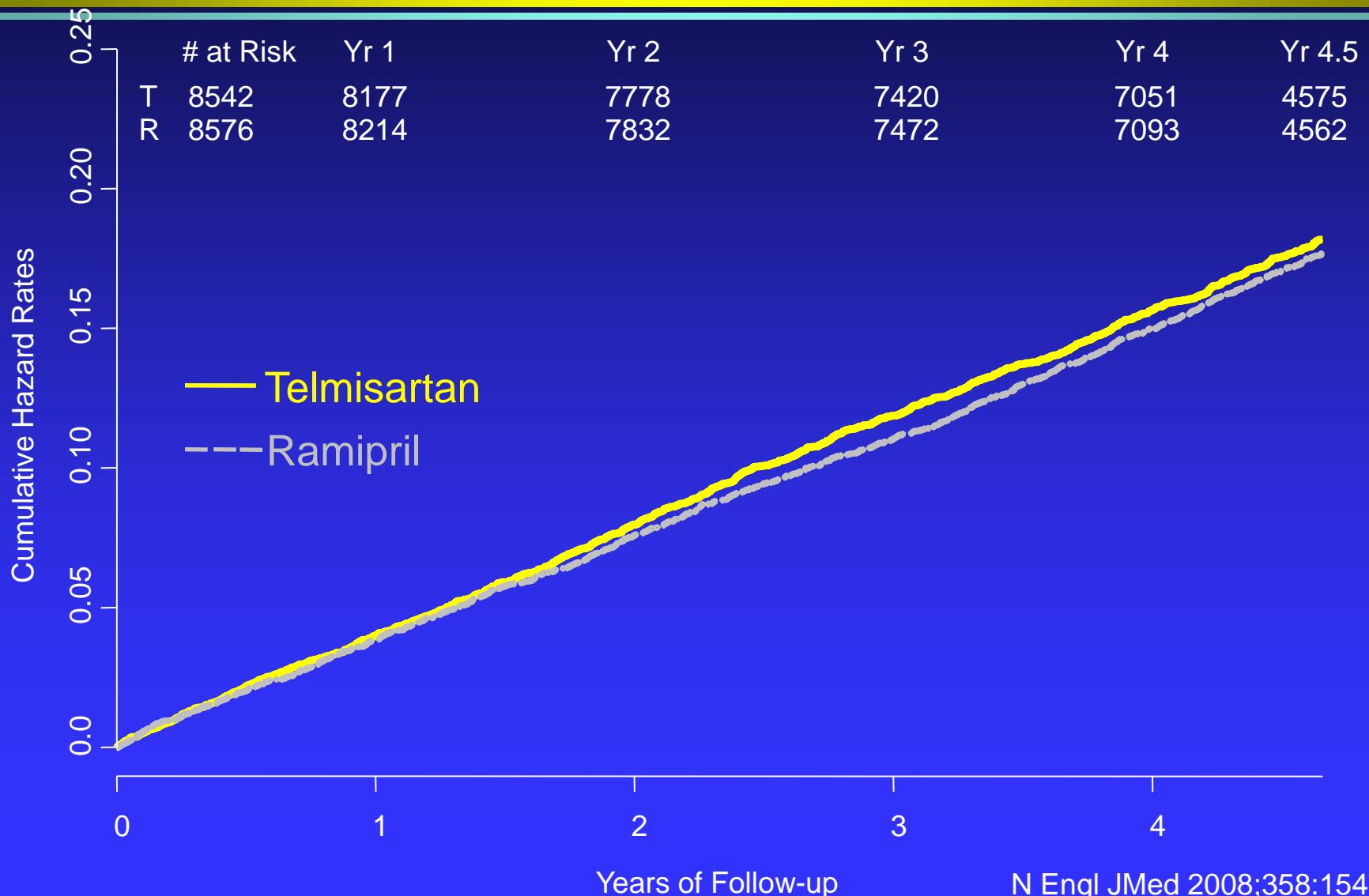
# **One topic of debate: ACEI or ARB ?**

**Arguments regarding:**

Impact on morbidity and mortality

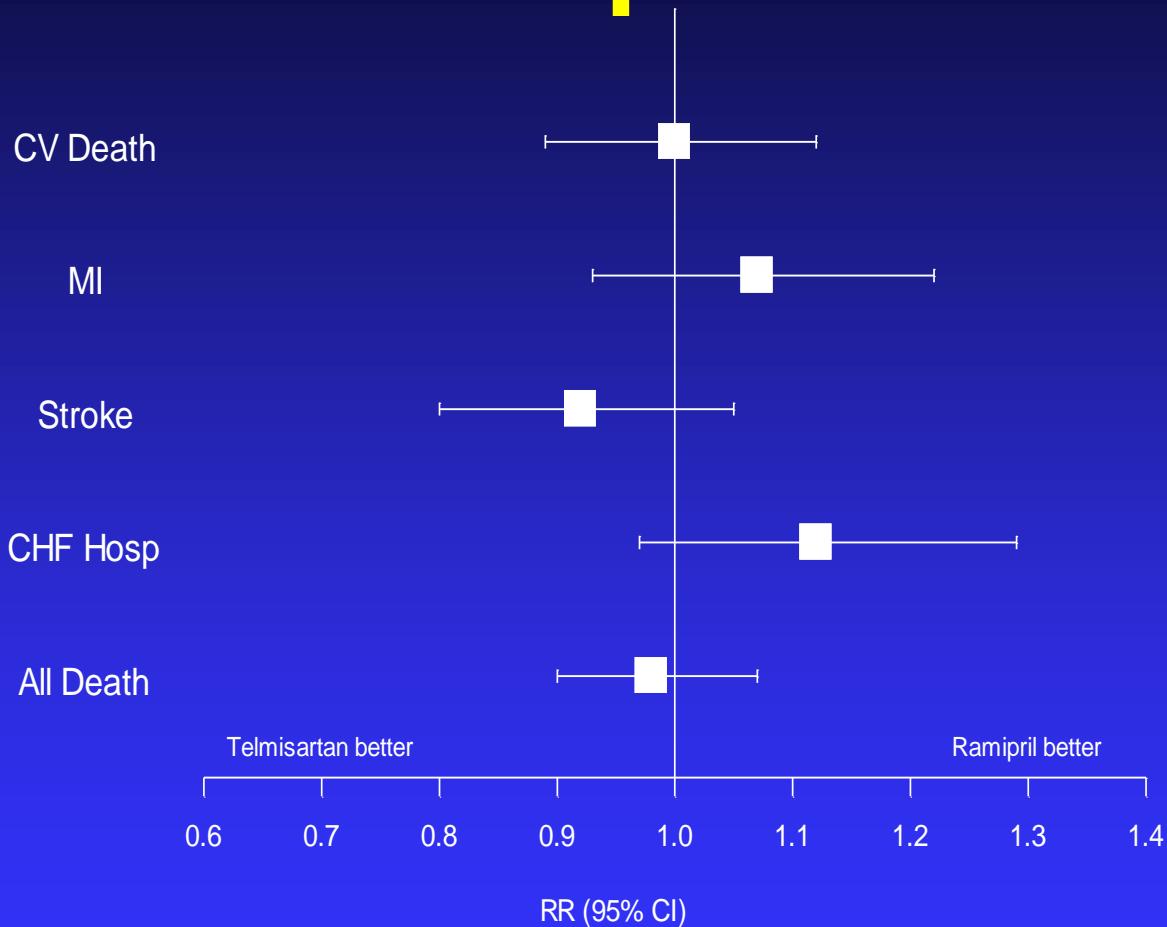
Tolerability profile and risk of SAE

# Ramipril vs Telmisartan Time to Primary Outcome



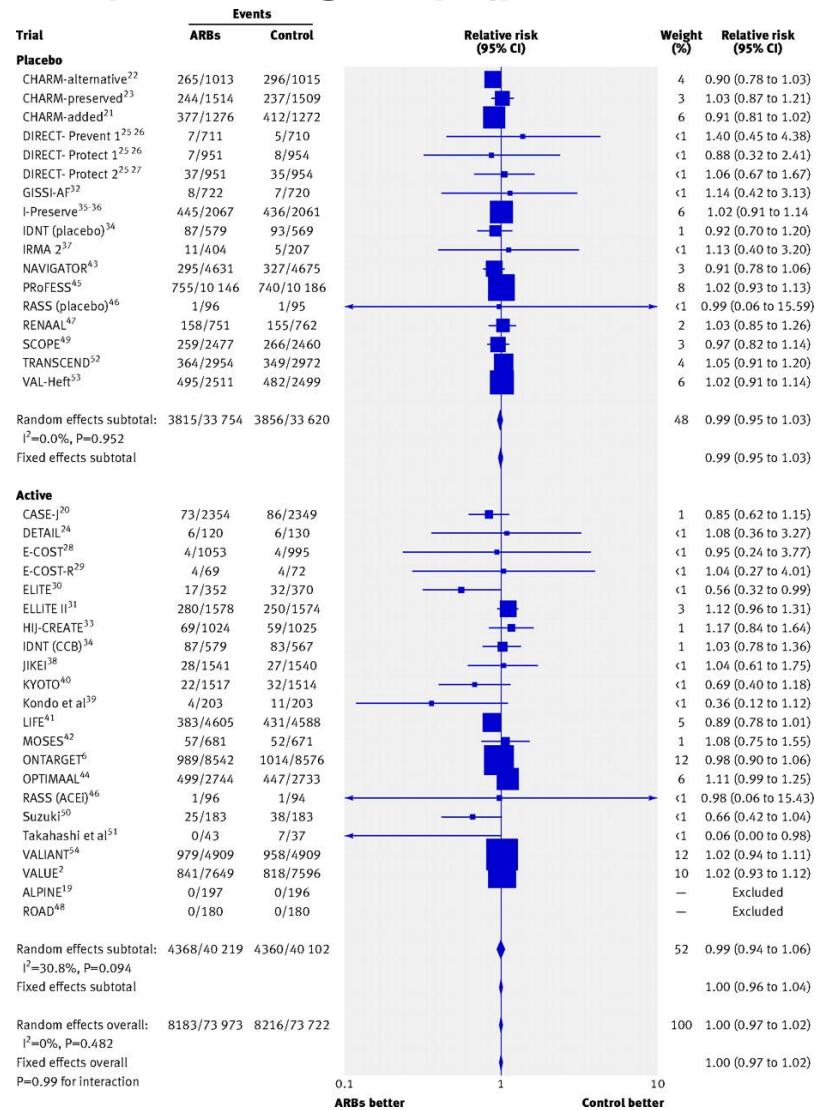
# ONTARGET Non-Inferiority Comparison

ONTARGET



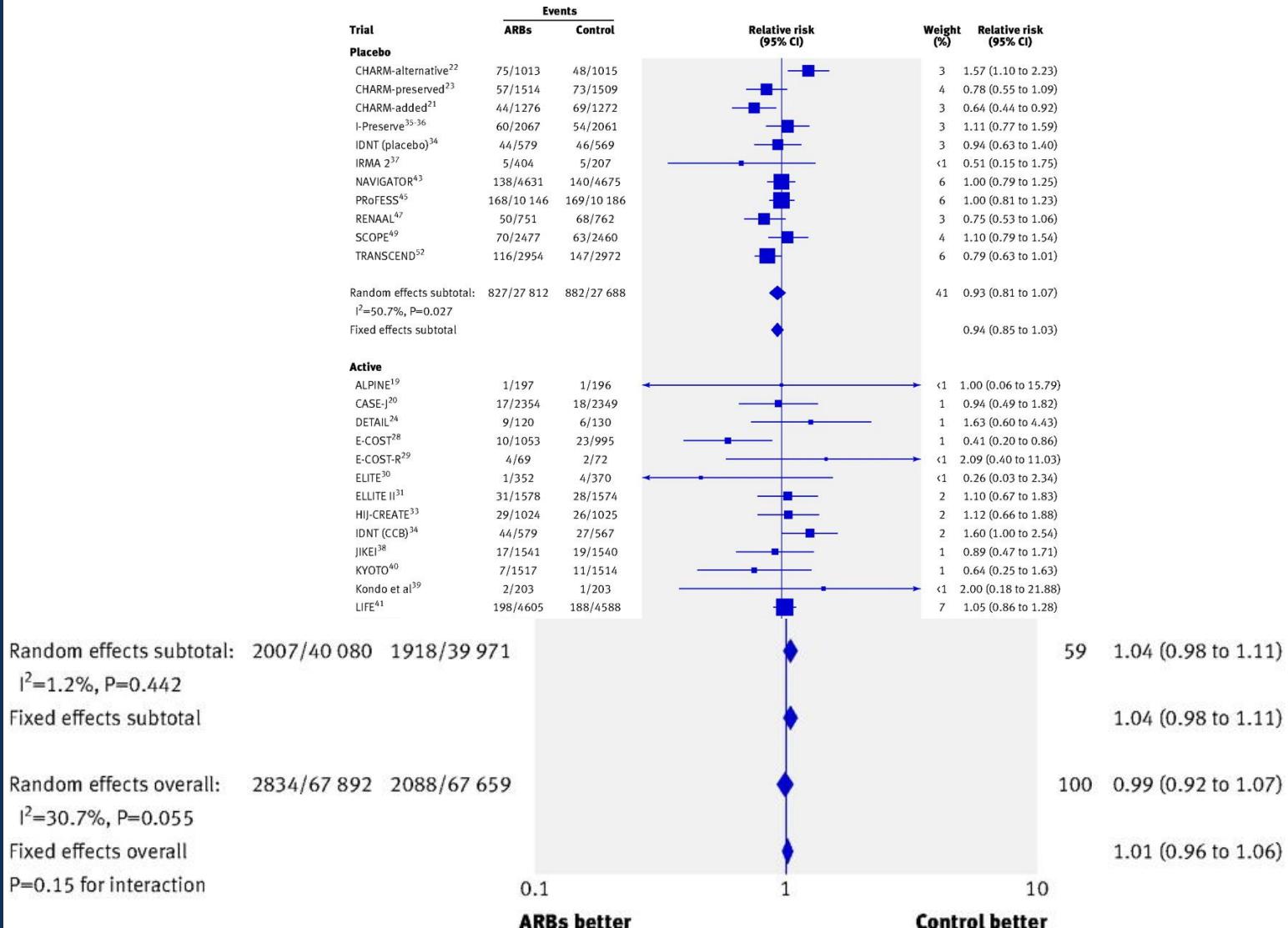
Note that the outcomes are presented as point estimates with confidence intervals. The solid line is the 95% CI representing 1.96 SD for each outcome

# Angiotensin receptor blockers and all cause mortality, stratified by comparison group (placebo v active treatment).

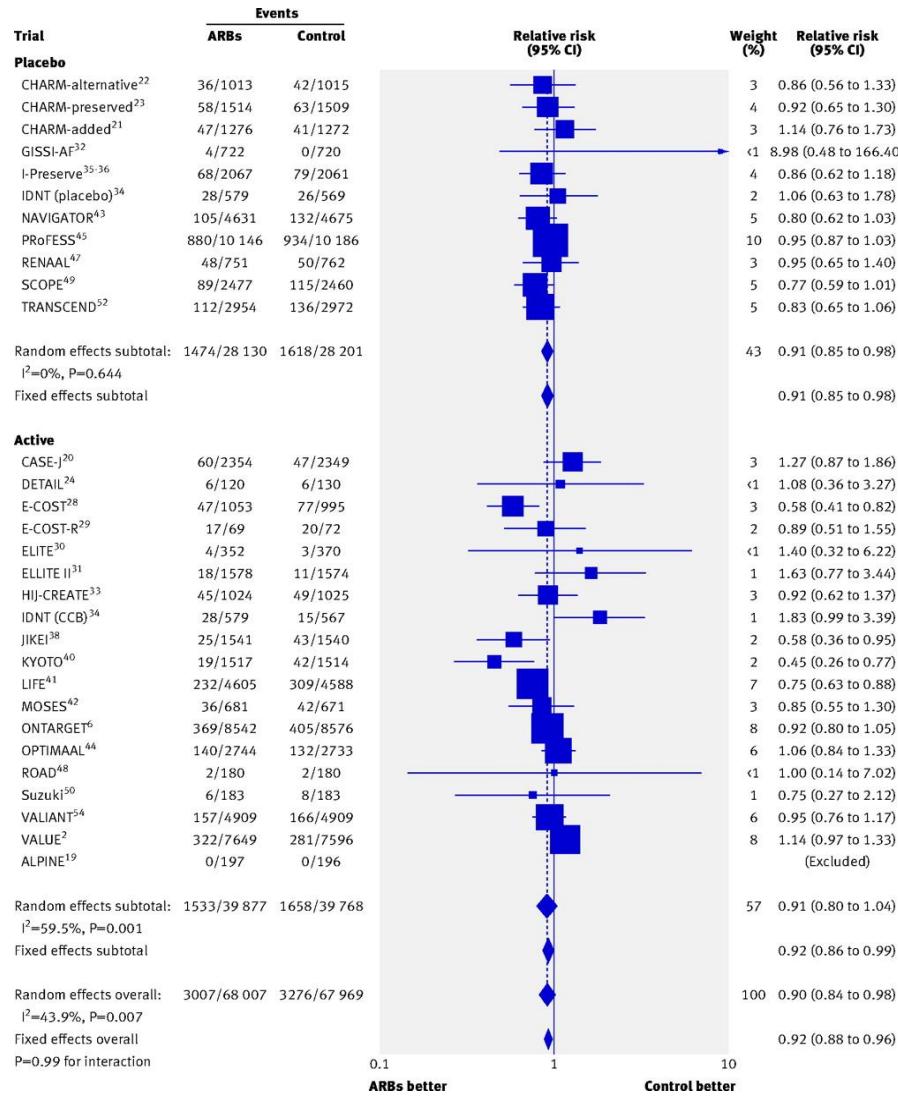


Bangalore S et al. BMJ 2011;342:bmj.d2234

## **Angiotensin receptor blockers and myocardial infarction, stratified by comparison group (placebo v active treatment).**



# Angiotensin receptor blockers and stroke, stratified by comparison group (placebo v active treatment).

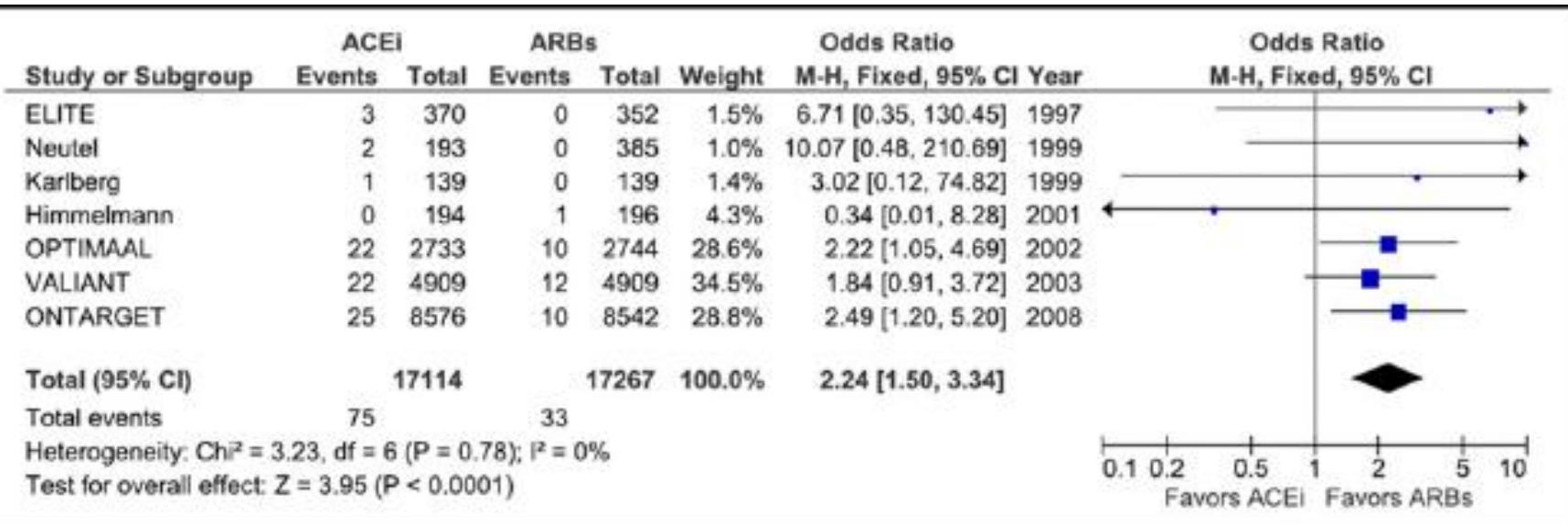


Bangalore S et al. BMJ 2011;342:bmj.d2234

# Reasons for Permanently Stopping Study Medications

	Ram	Tel	Tel vs. Ram	
	N=8576	N=8542	RR	P
Hypotension	149	224	1.51	0.0001
Syncope	15	18	1.20	0.593
Cough	359	93	0.26	<0.0001
Diarrhea	12	19	1.59	0.20
Angioedema	25	10	0.40	0.0115
Renal Impairment	59	68	1.16	0.41
Any Discontinuation	2098	1962	0.94	0.02

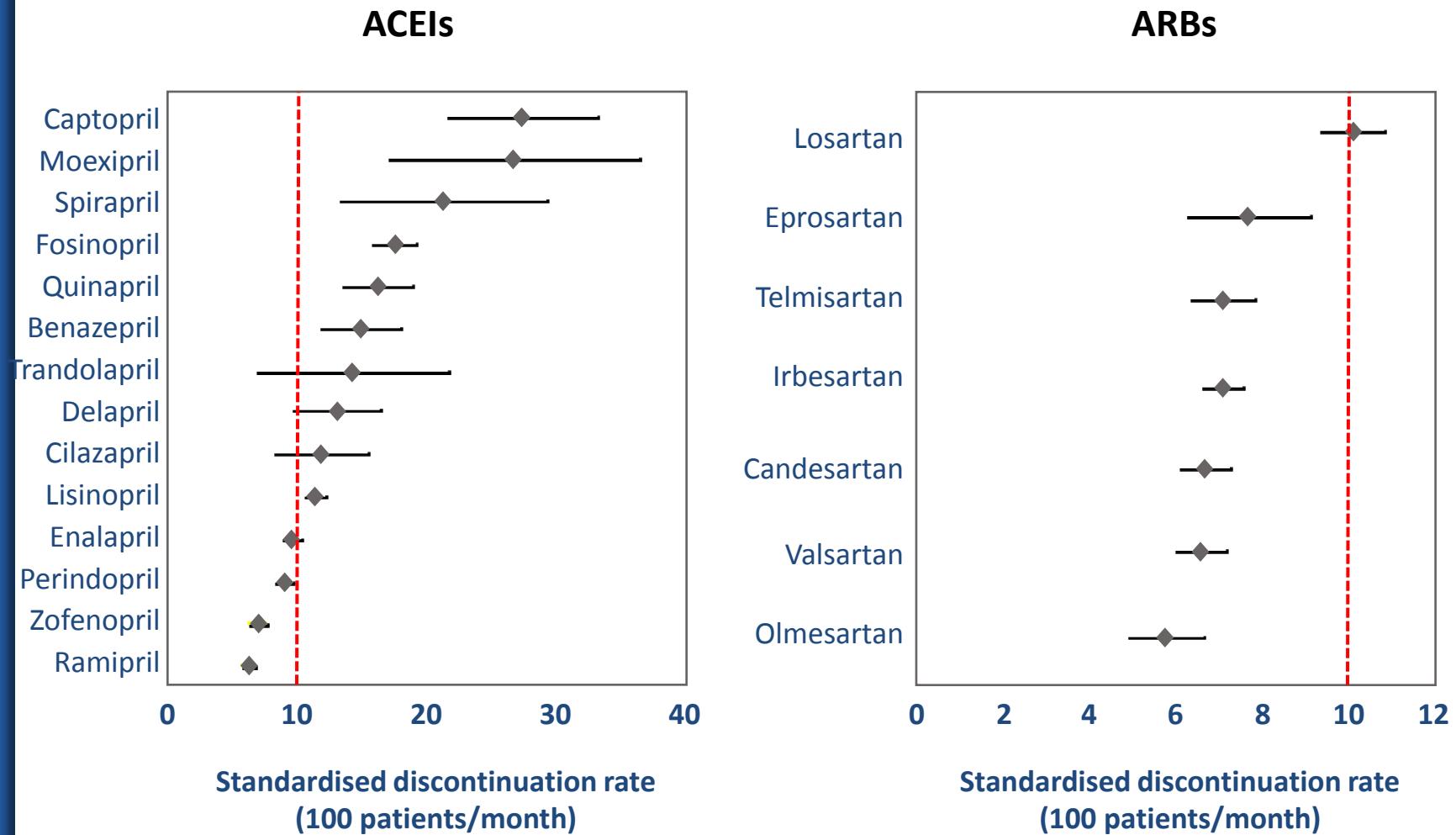
# Risk of angioedema : ARBs vs ACEIs



Incidence of angioedema is higher in patients with heart failure

Makani et al, Am J Cardiol 2012; 110:383

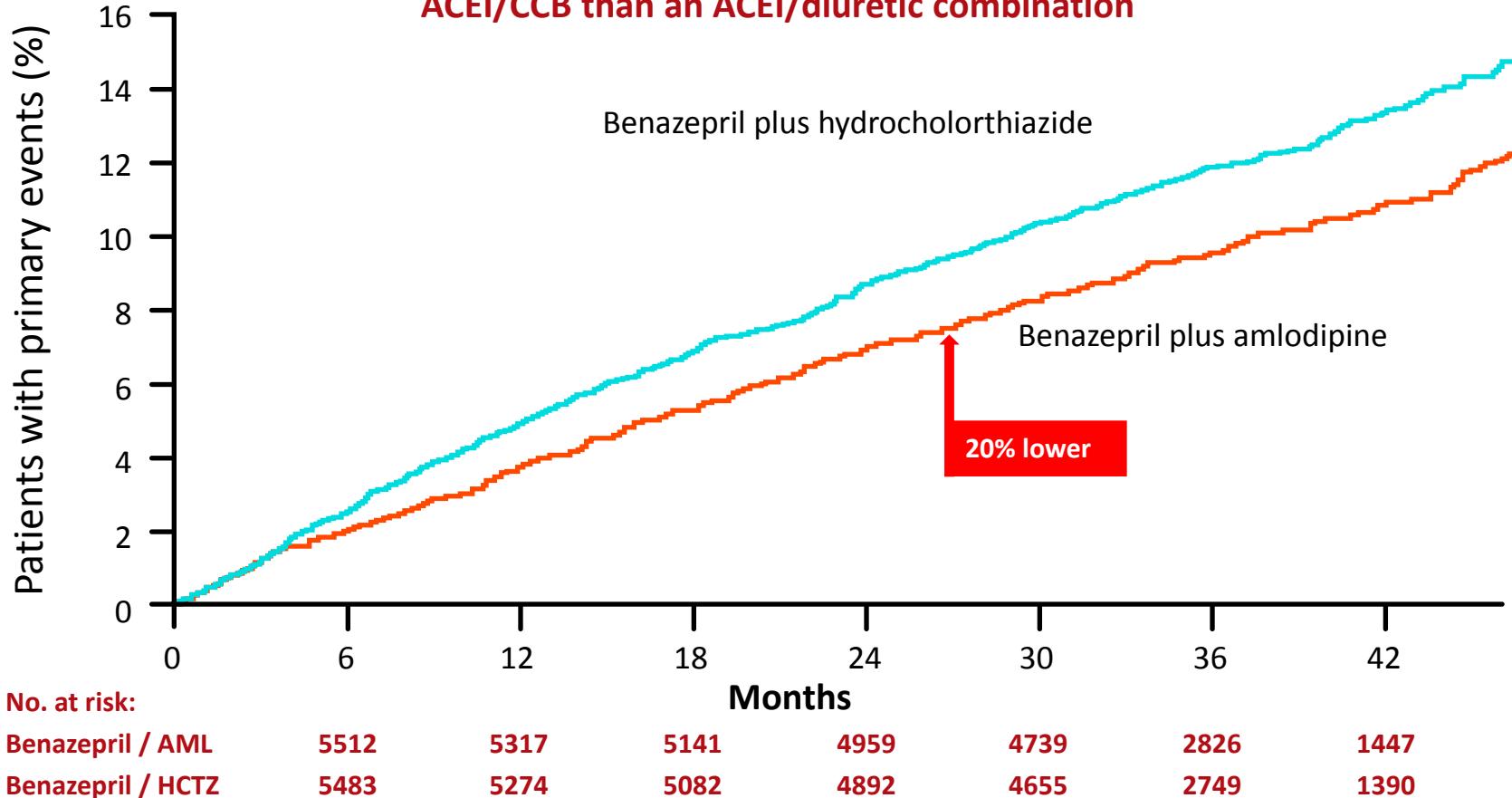
# The importance of tolerability is reflected by within-class differences in discontinuation rates



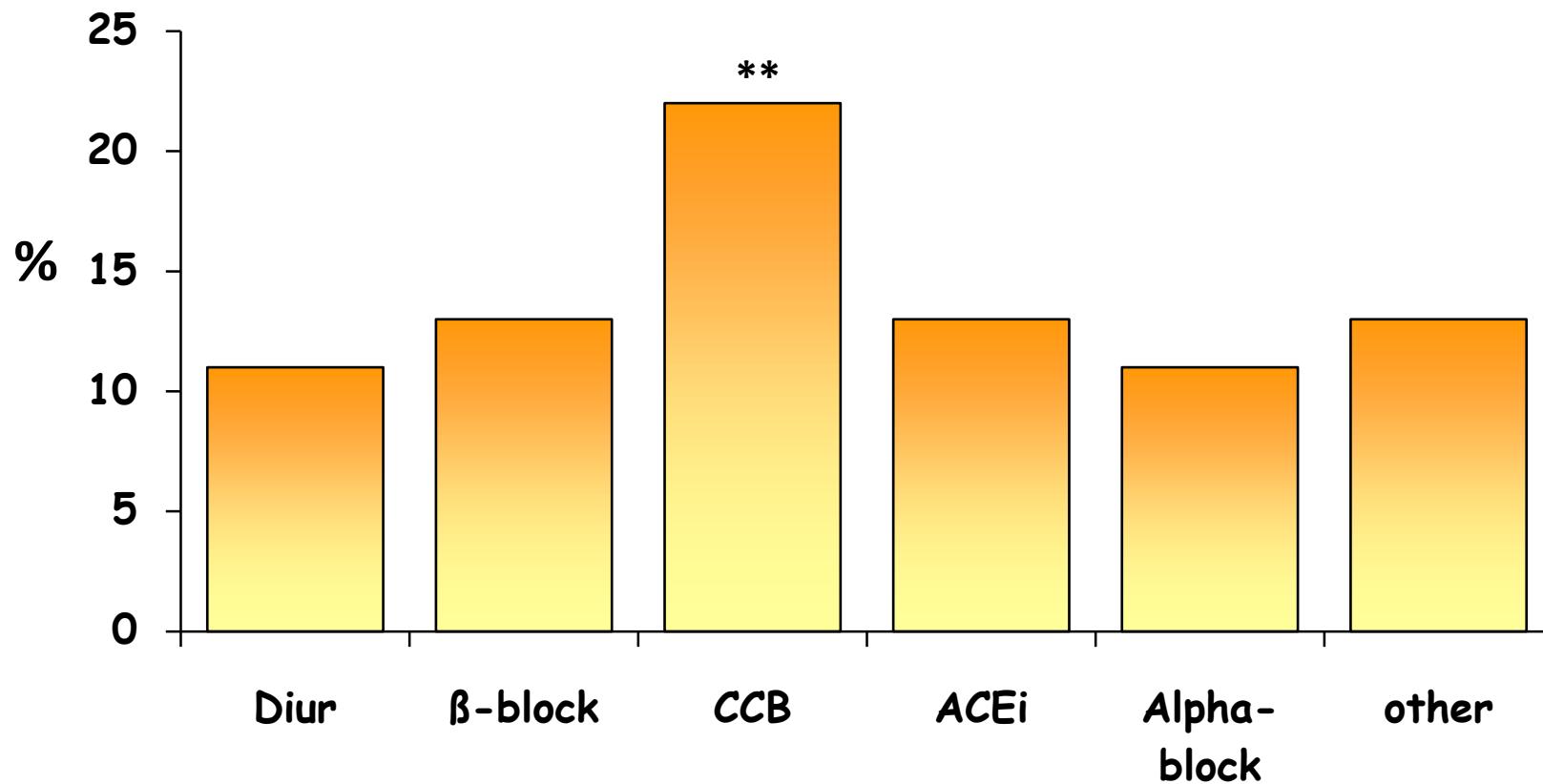
**Another question: which calcium antagonist ?**

# ACCOMPLISH: RAS-blocker/CCB combined therapy offers benefits in higher-risk patients

The primary cardiovascular composite end point was significantly lower with an ACEI/CCB than an ACEI/diuretic combination

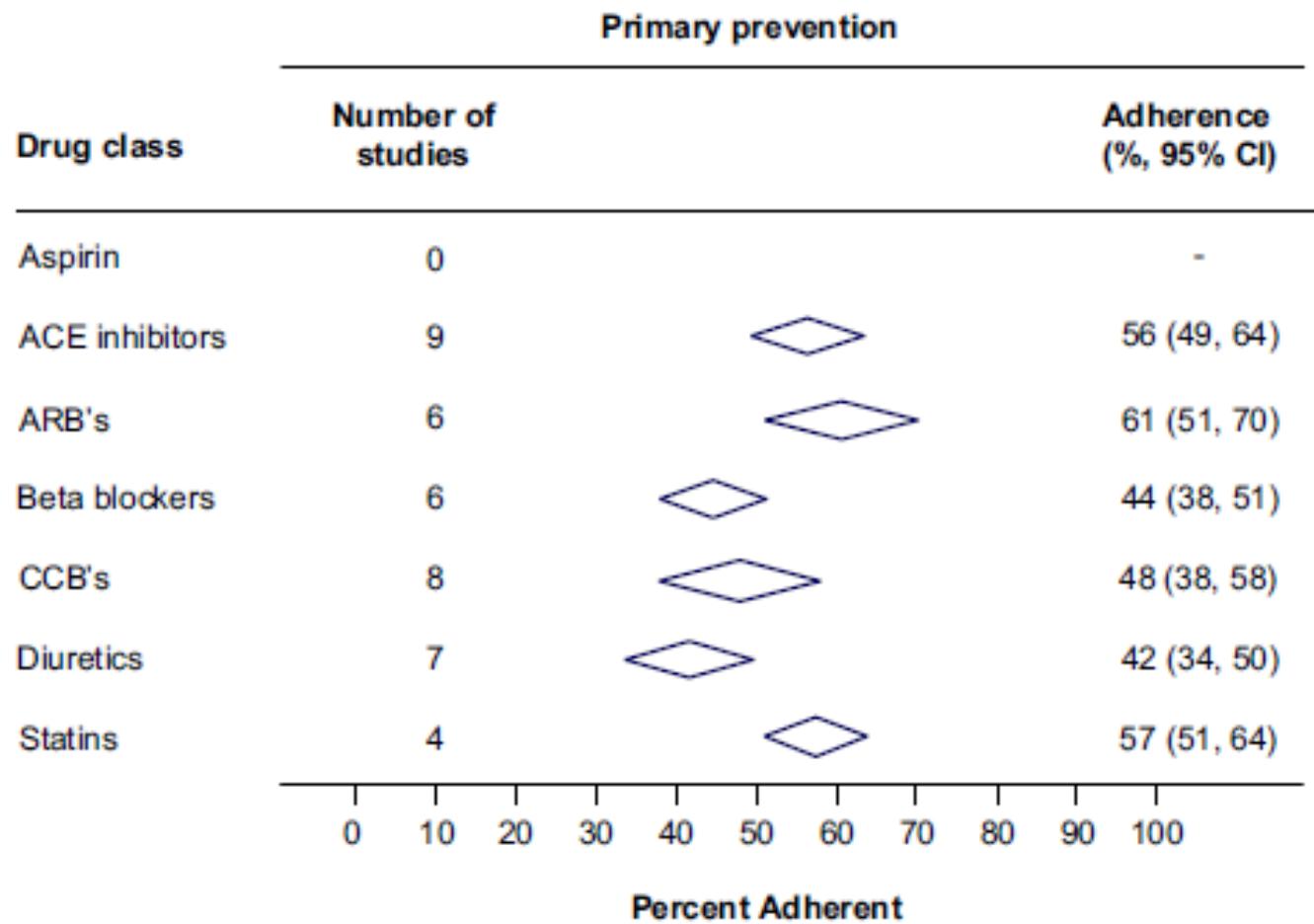


# Incidence of adverse responses to different classes of drugs as reported by physicians



E.Ambrosioni et al, J Hypertens ;18 , 2000

# Adherence to cardiovascular drugs in primary prevention



Naderi et al, *The American Journal of Medicine* (2012) 125, 882-887

## Peripheral edema:



*Don't let  
swollen ankles  
spoil your  
chances!*



# Adverse events in the VALUE trial

	Valsartan (n=7622)	Amlodipine (n=7576)	P
<b>Pre-specified adverse events</b>			
Peripheral edema	1135 (14.9%)	2492 (32.9%)	<0.0001
Dizziness	1257 (16.5%)	1083 (14.3%)	<0.0001
Headache	1120 (14.7%)	947 (12.5%)	<0.0001
Fatigue	739 (9.7%)	674 (8.9%)	0.0750
<b>Additional common adverse events</b>			
Diarrhea*	670 (8.8%)	515 (6.8%)	<0.0001
Edema other*	243 (3.2%)	462 (6.1%)	<0.0001
Hypokaliemia*	266 (3.5%)	469 (6.2%)	<0.0001

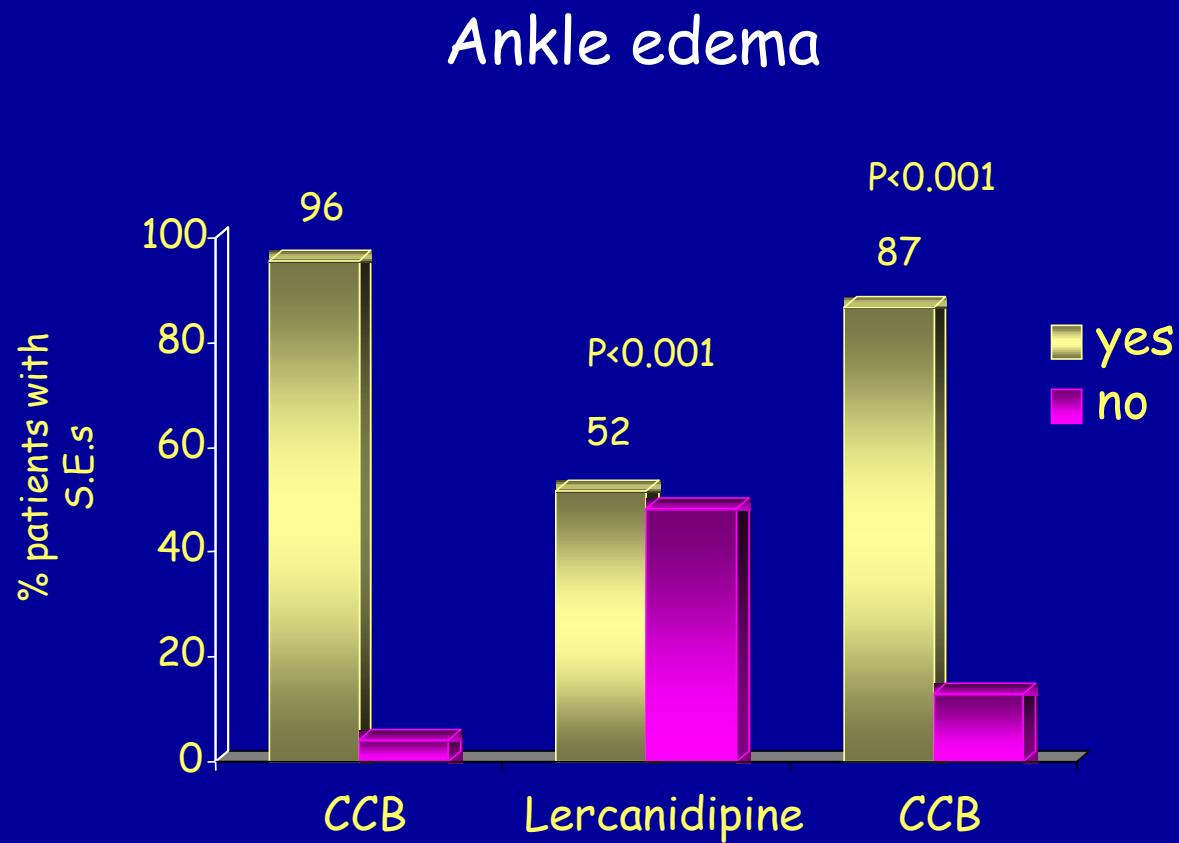
\*With an incidence >3% and a difference between treatment groups >1%  
Julius et al. *Lancet*. 2004;363:2022-2031.

# Adverse events in the ASCOT trial

Adverse event*	Amlodipine ± perindopril n (%)	Atenolol ± thiazide n (%)	p-value
Bradycardia	34 (0.4)	536 (6)	<0.0001
Chest pain	740 (8)	849 (9)	0.0040
Cough	1859 (19)	782 (8)	<0.0001
Diarrhoea	377 (4)	548 (6)	<0.0001
Dizziness	1183 (12)	1555 (16)	<0.0001
Dyspnoea	599 (6)	987 (10)	<0.0001
Eczema	493 (5)	383 (4)	0.0002
Erectile dysfunction	<b>37 % of edema</b>		<0.0001
Fatigue	782 (8)	1556 (16)	<0.0001
Joint swelling	1371 (14)	308 (3)	<0.0001
Lethargy	202 (2)	525 (6)	<0.0001
Oedema peripheral	2188 (23)	588 (6)	<0.0001
Peripheral coldness	81 (1)	579 (6)	<0.0001
Vertigo	642 (7)	745 (8)	0.0039

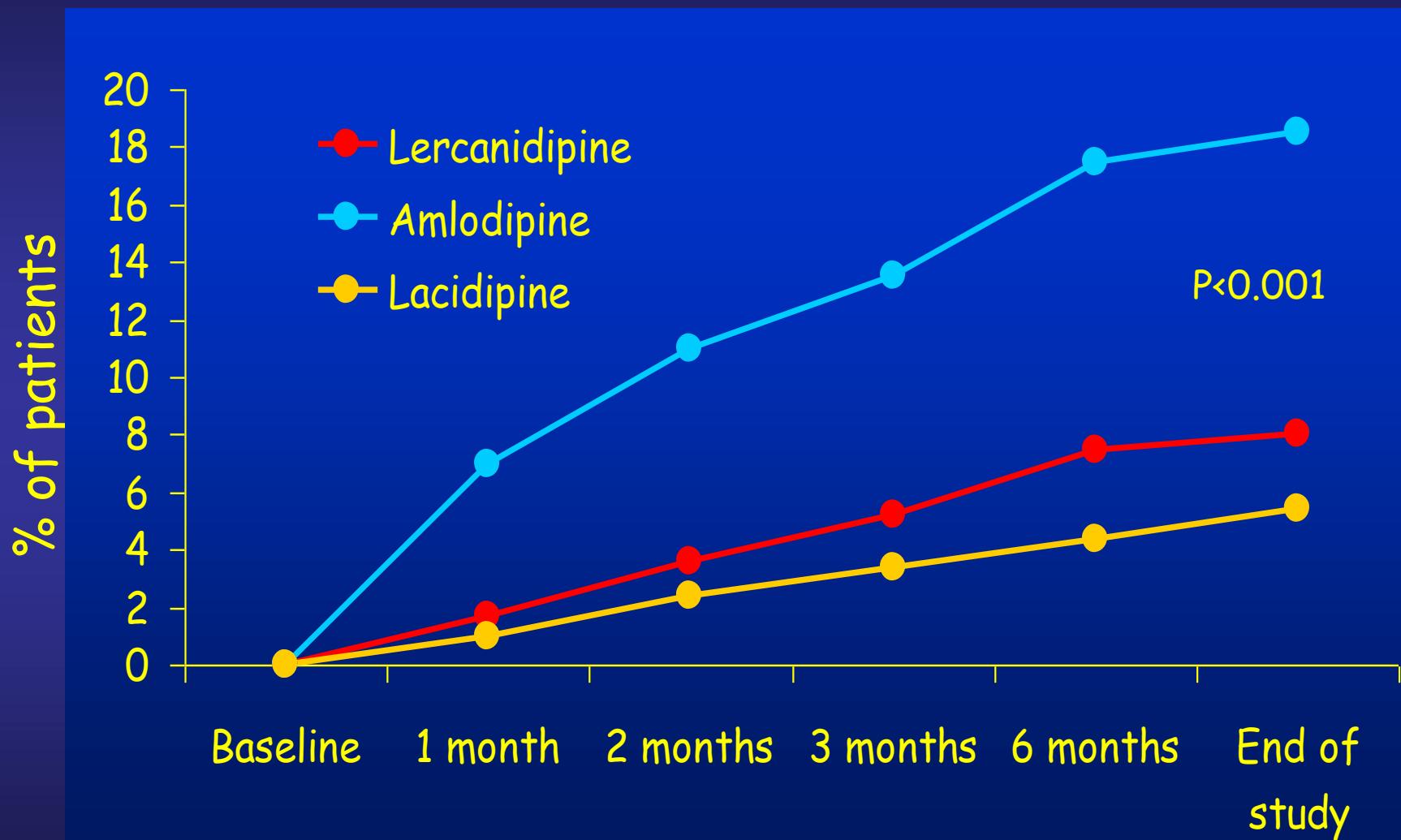
# PREVALENCE OF DRUG-SPECIFIC AE's IN THE LERCANIDIPINE CHALLENGE STUDY.

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Borghi C et al, Blood Pressure, 2003

# % OF PTS WITH ANKLE EDEMA OVER TIME



COHORT Study, Am J Hypertens, 2002

## **Impact of lercanidipine on peripheral edema in 2199 patients followed by GPs in Switzerland**

	<b>Initiation (n=683)</b>	<b>Add-on (n=844)</b>	<b>Substitution (n=672)</b>
<b>Premature treatment interruption due to adverse events</b>	<b>4.4</b>	<b>7.8</b>	<b>8.8</b>
Ankle edema	0.6	1.9	3.0
Headache	0.6	1.1	1.1
Flush	0.4	1.3	0.6
Others	2.8	3.8	4.3

Burnier and Gasser, 2007

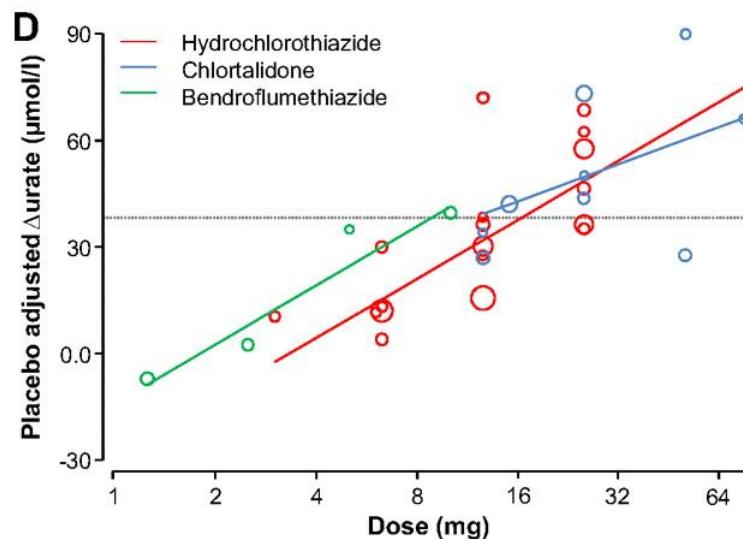
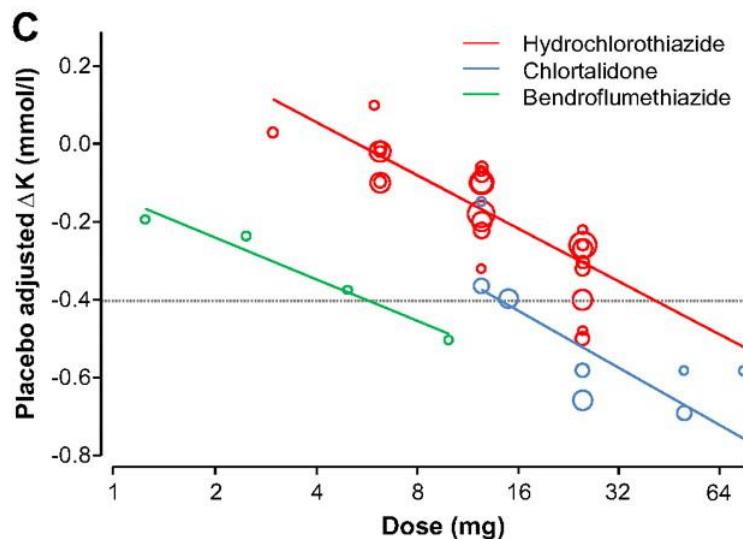
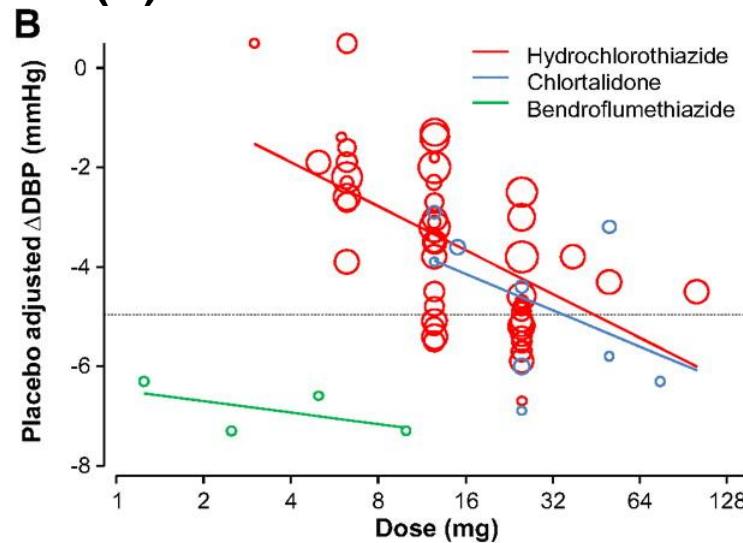
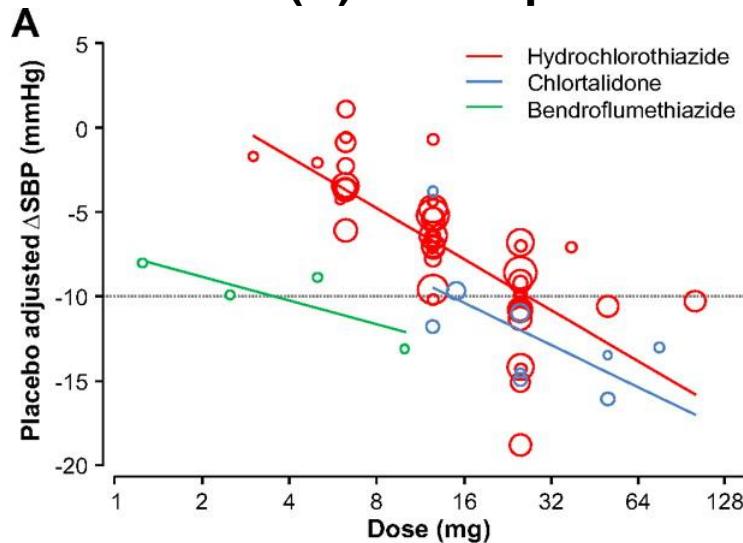
# Last question: which diuretic ?

Hydrochlorothiazide

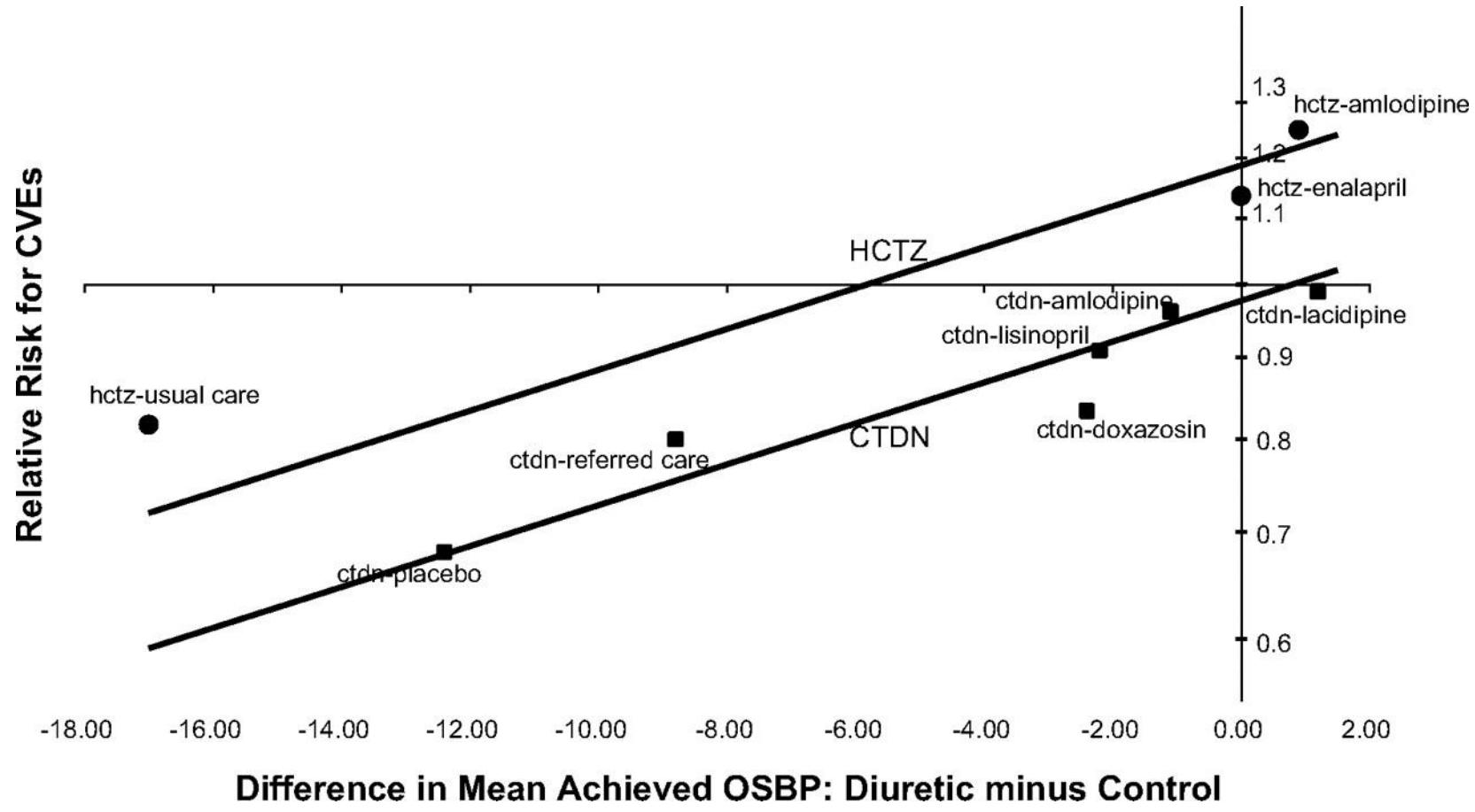
Chlorthalidone

Indapamide

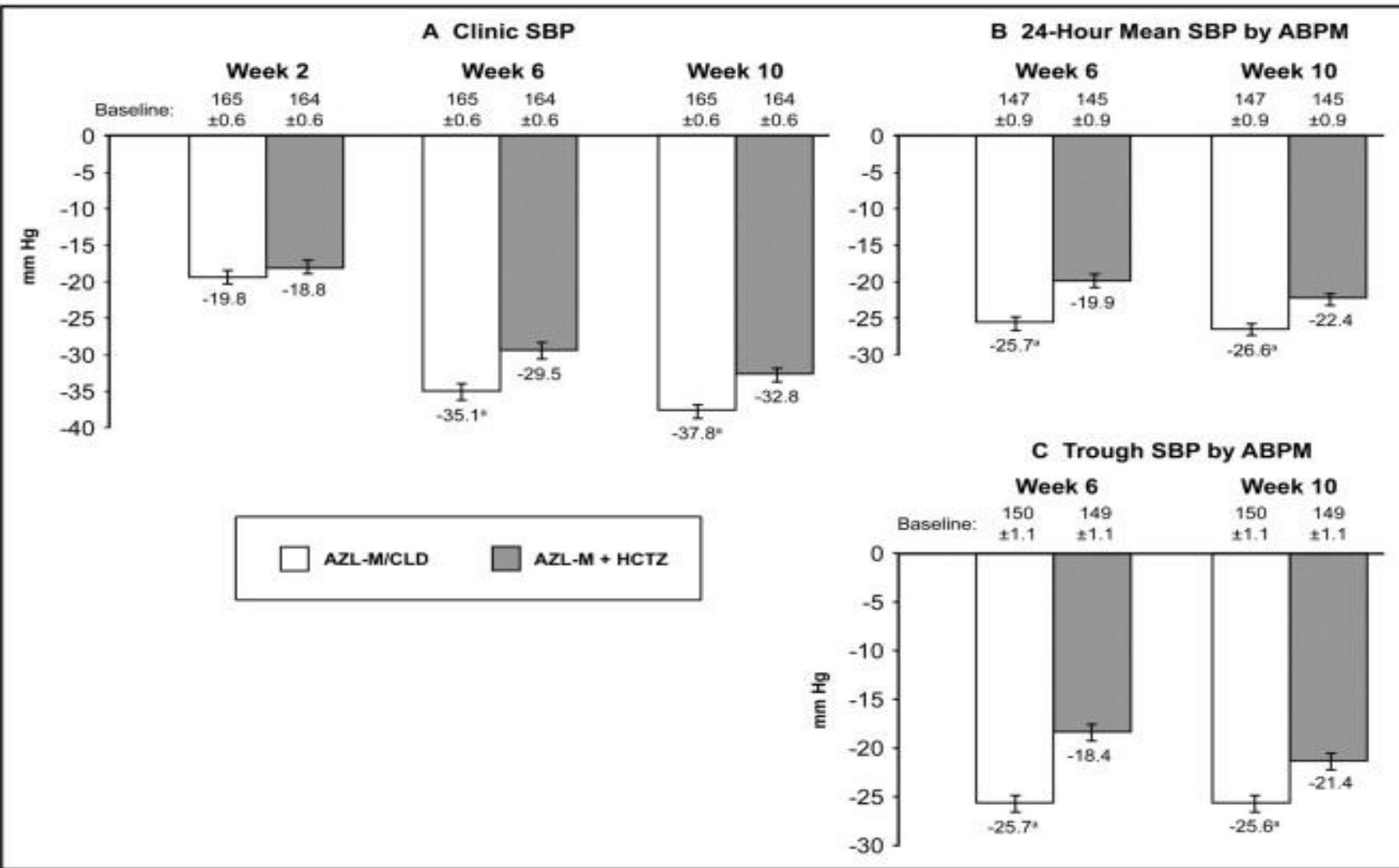
# Dose-response relationships for thiazides vs BP (A and B) (C) serum potassium; and (D) serum urate.



## Risk of cardiovascular events in patients receiving HCTZ or chlorthalidone according to the changes in systolic BP

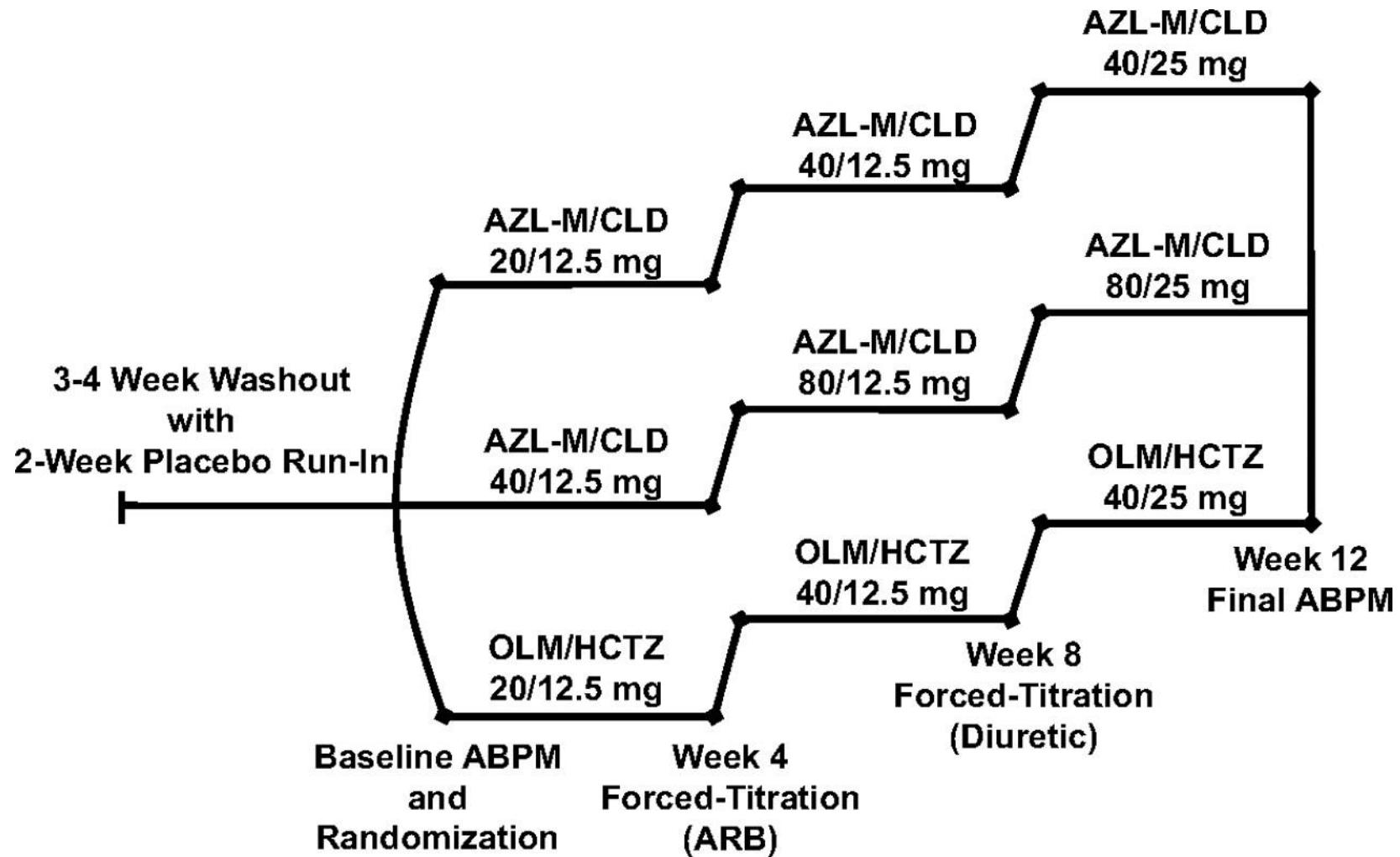


# Antihypertensive Efficacy of Hydrochlorothiazide vs Chlorthalidone Combined with Azilsartan Medoxomil

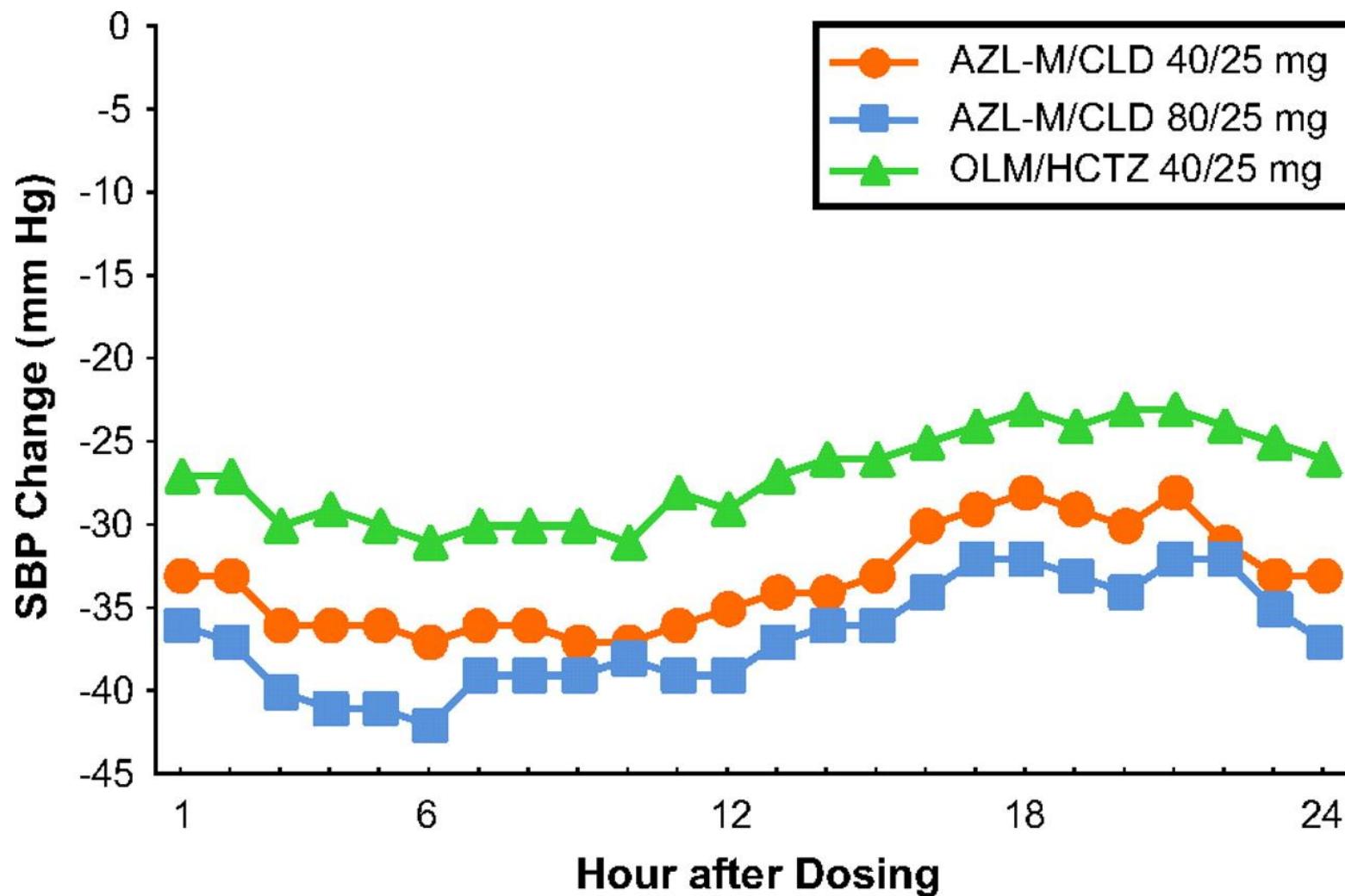


Bakris et al, The American Journal of Medicine 2012, 125; p1229.e1-e10

# Azilsartan + CLD vs olmesartan + HCTZ

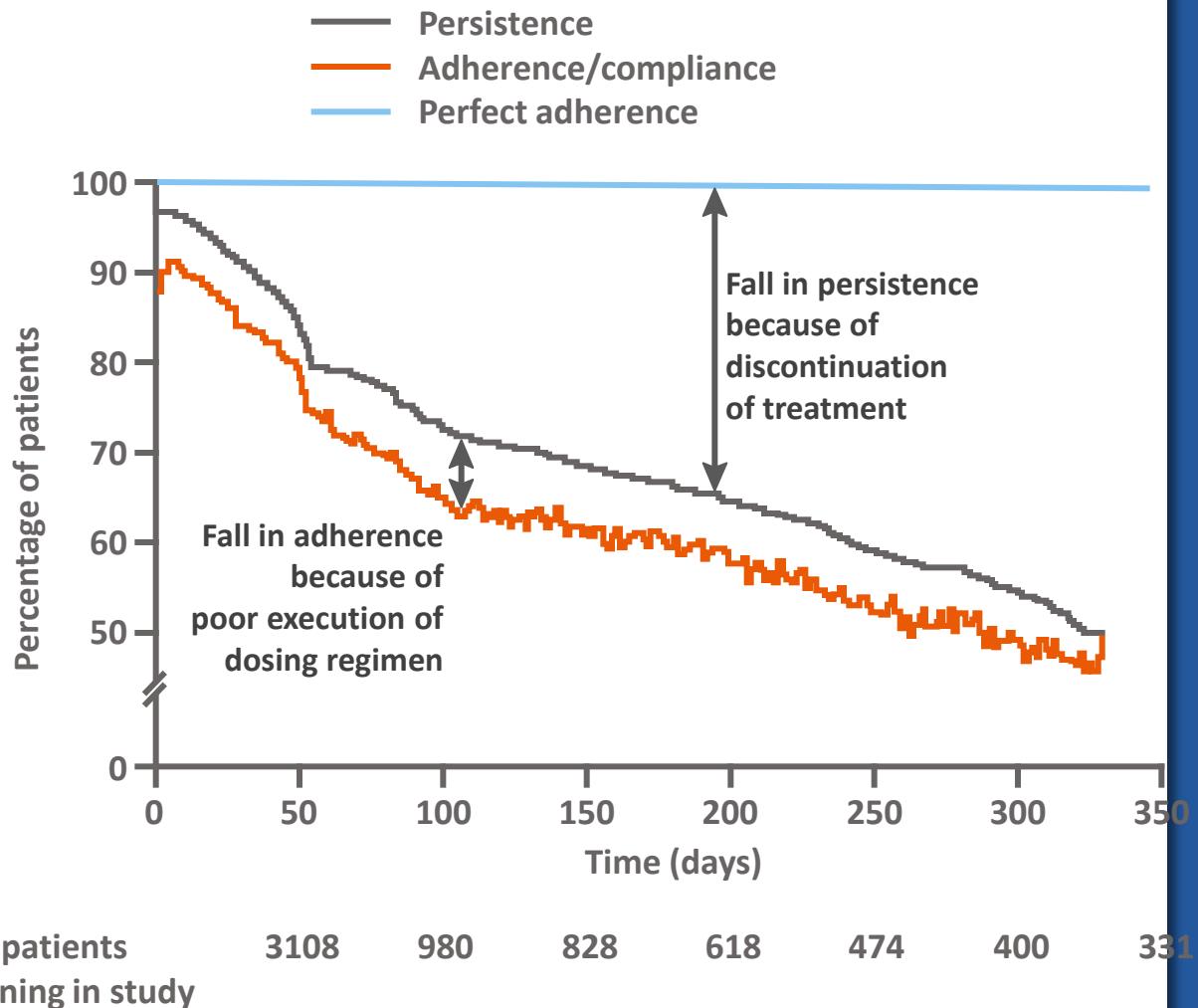


# Change in systolic blood pressure by ABPM at week 12.



# Over one year, compliance and persistence with anti-hypertensive therapy typically falls to <50%

- Study of hypertensive patients in clinical studies
- 4783 patients in 21 Phase IV trials
- Evaluated by medication event monitoring system



# Adherence to cardiovascular drugs

