

# **Unmet Need in Hypertension and Heart Failure**

-ASPIRE HIGHER: Are there still existing unmet needs?  
What we expect from new antihypertensive treatment

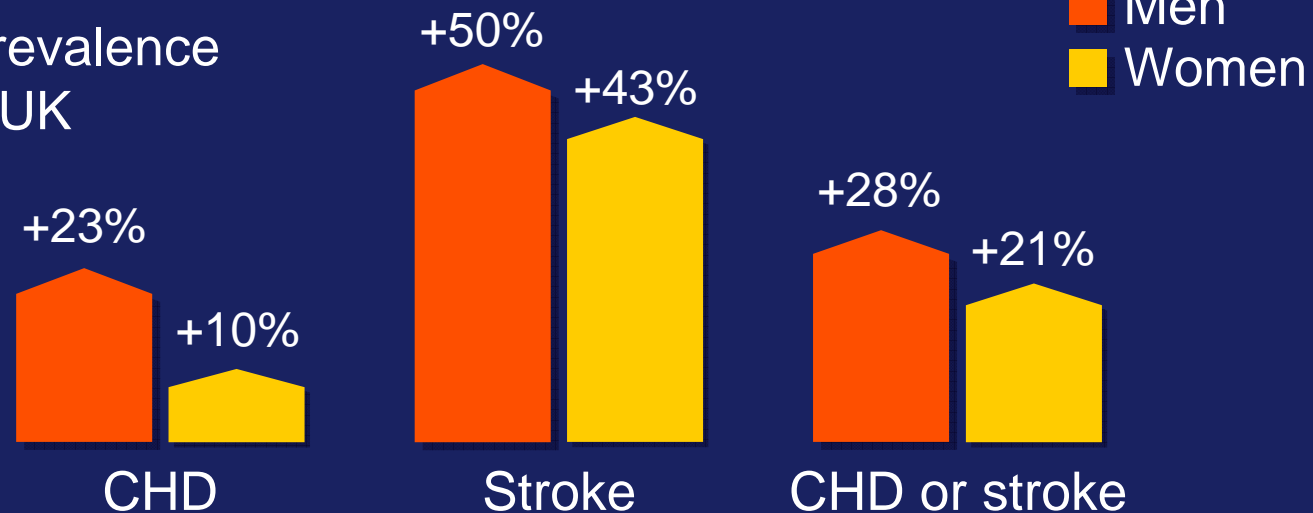
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Seoul, Korea**

# The Prevalence of Cardiovascular Disease is Increasing in Many Countries

- CVD is increasing in prevalence in many regions of the world, particularly in developing countries and eastern Europe<sup>1</sup>
- In countries where mortality rates from coronary heart disease are falling, morbidity rates – particularly in older age groups – appear to be rising<sup>2</sup>

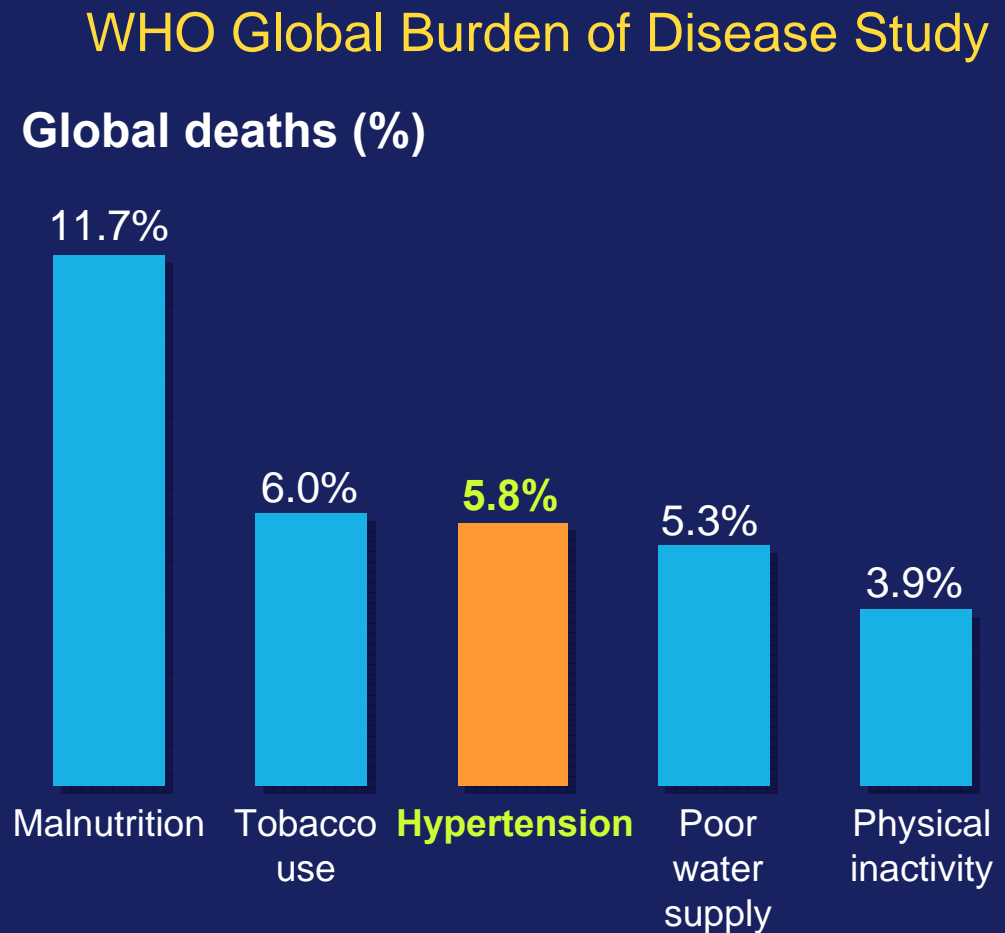
Change in prevalence  
1994–2003, UK



1. Murray CJ, Lopez AD. *Lancet* 1997;349:1436–42  
2. Health Survey for England 2003 (2004)

# Hypertension Usually Has No Symptoms But is A Significant Healthcare Problem

- Hypertension is known as the 'silent killer' because it usually has no symptoms
- Approximately half of those who have hypertension are unaware they have a problem

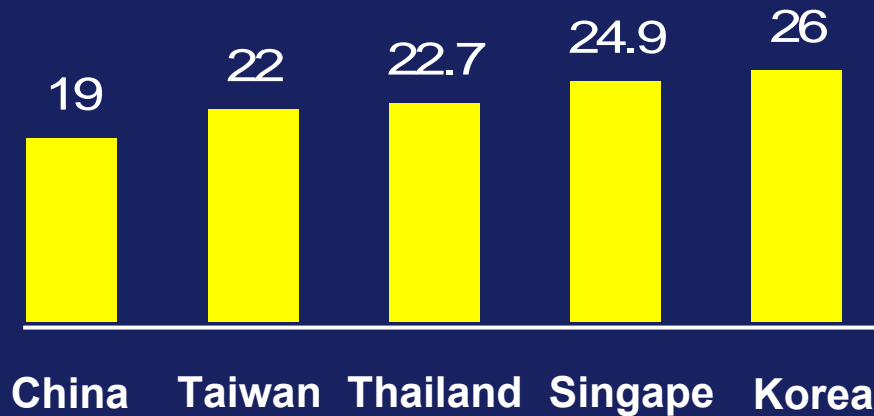


# Asia is Changing

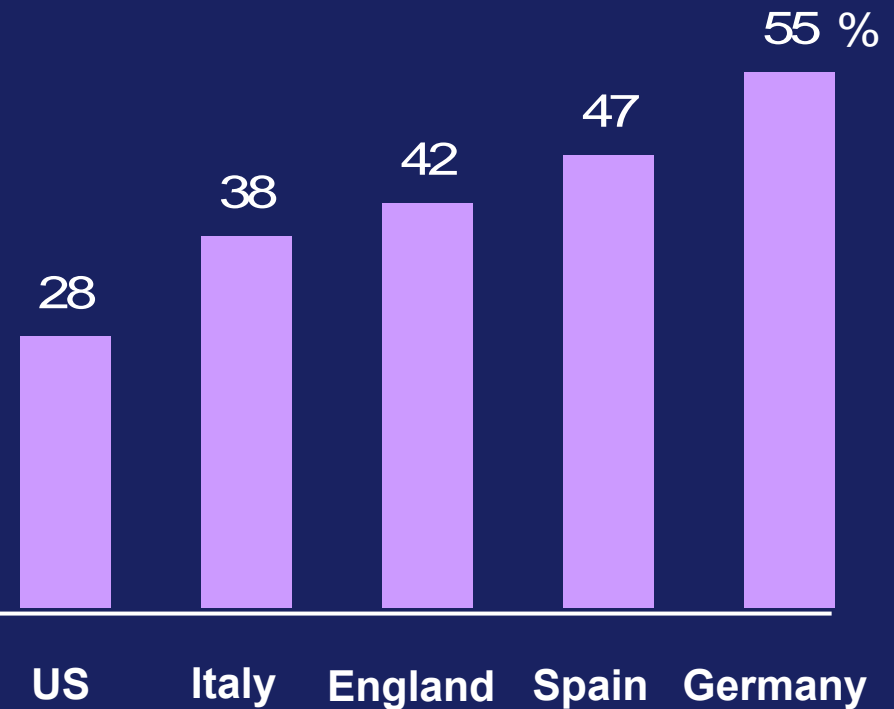
- **Globalization**
  - Exposure to different attitudes and values
  - Changes in lifestyle and interests
  - New role models
- **Demographic changes**
  - Declining fertility; aging population
  - Increased education and work opportunities for both men and women
  - Increased migration and urbanization
- **Rapid changes in technology**

# Prevalence of Hypertension

Lower prevalence but higher growth rate compare to other developed countries

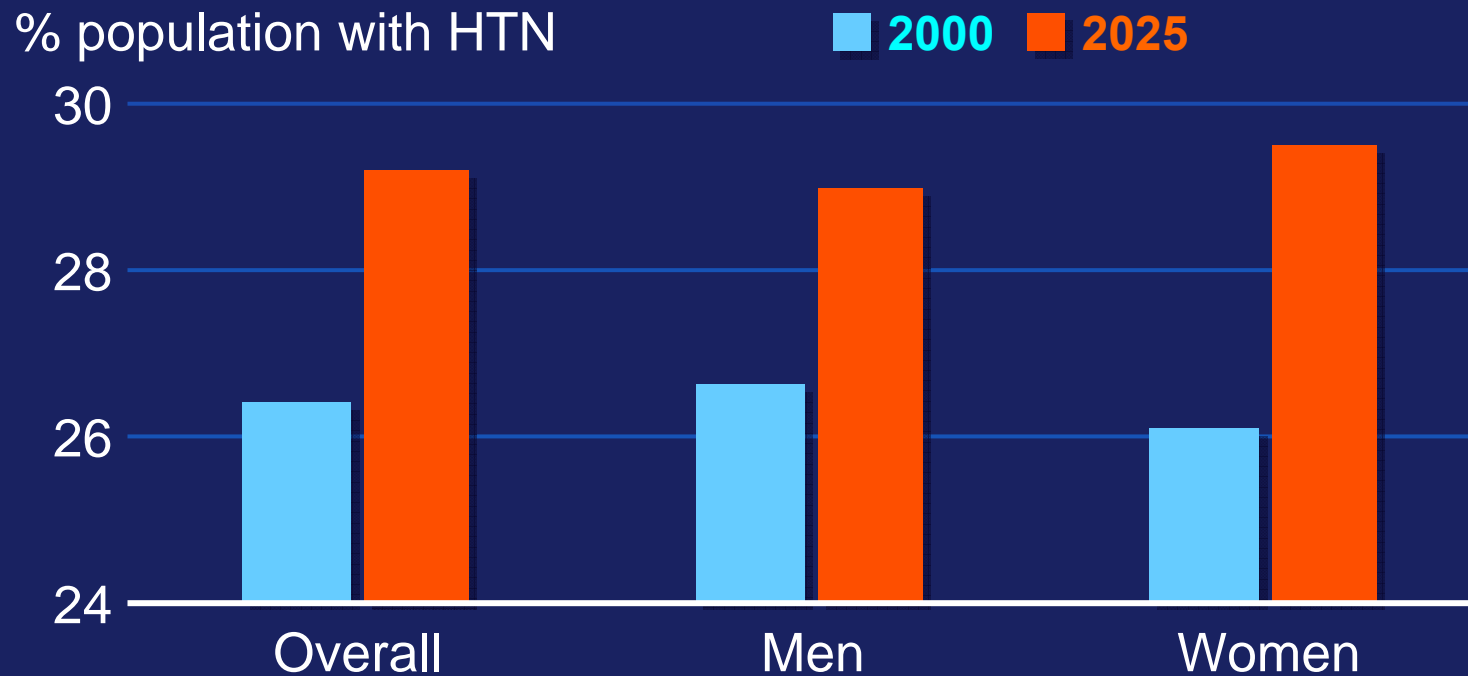


Prevalence of hypertension (%), 35-65 years ( $\geq 140/90$ mmHg)



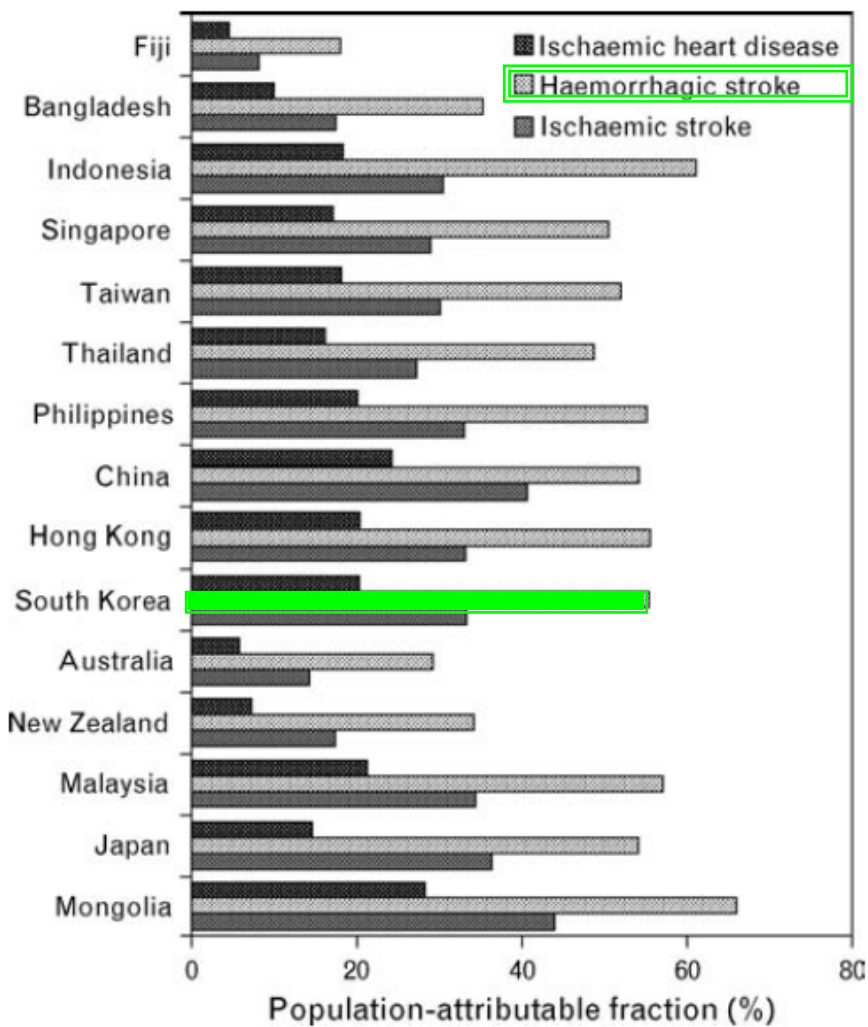
Source: Wolf-Maier K, *et al.* 2003,  
2005 Korea Nutrition & Health Survey, MOHW, June 2006,  
JAMA 2003;289:2363-9  
MOH clinical practice guideline 2

# Global Burden of Hypertension is Predicted to Increase in Spite of Treatment Advances

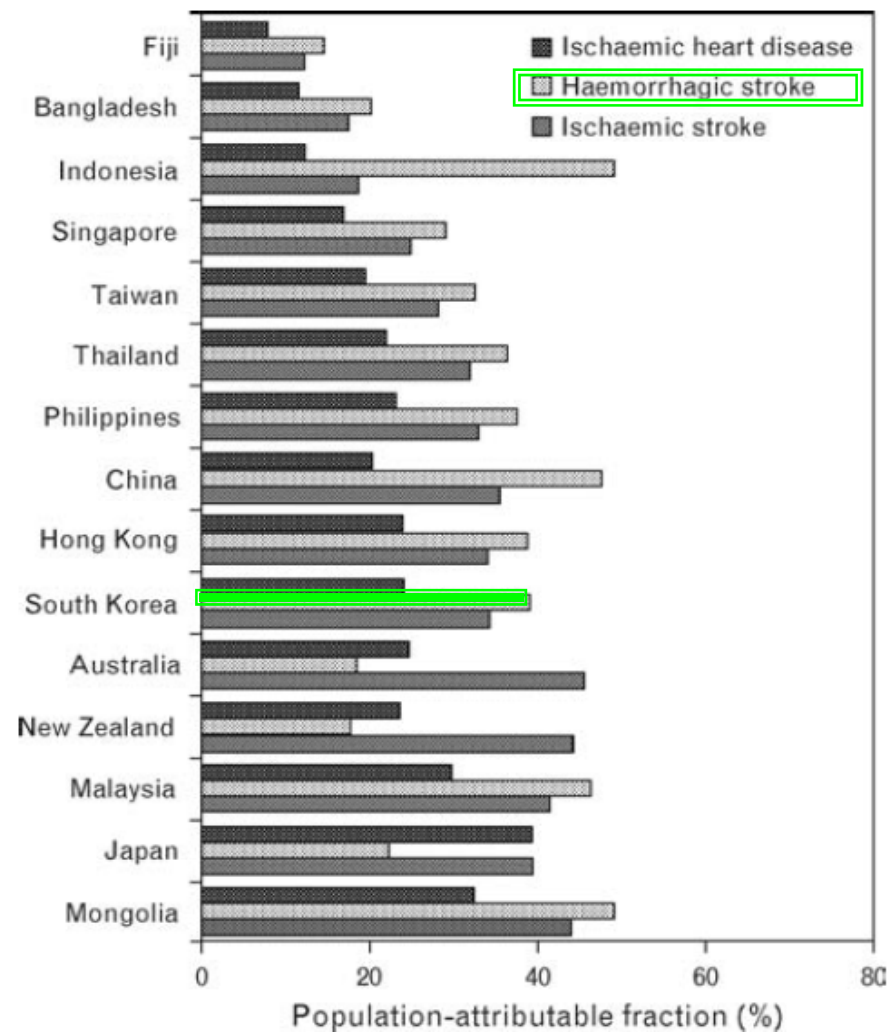


- Pooled data from 30 population-based studies from around the world (Kearney et al. 2005)

# Population-attributable Fractions for Cardiovascular Disease Deaths due to Hypertension



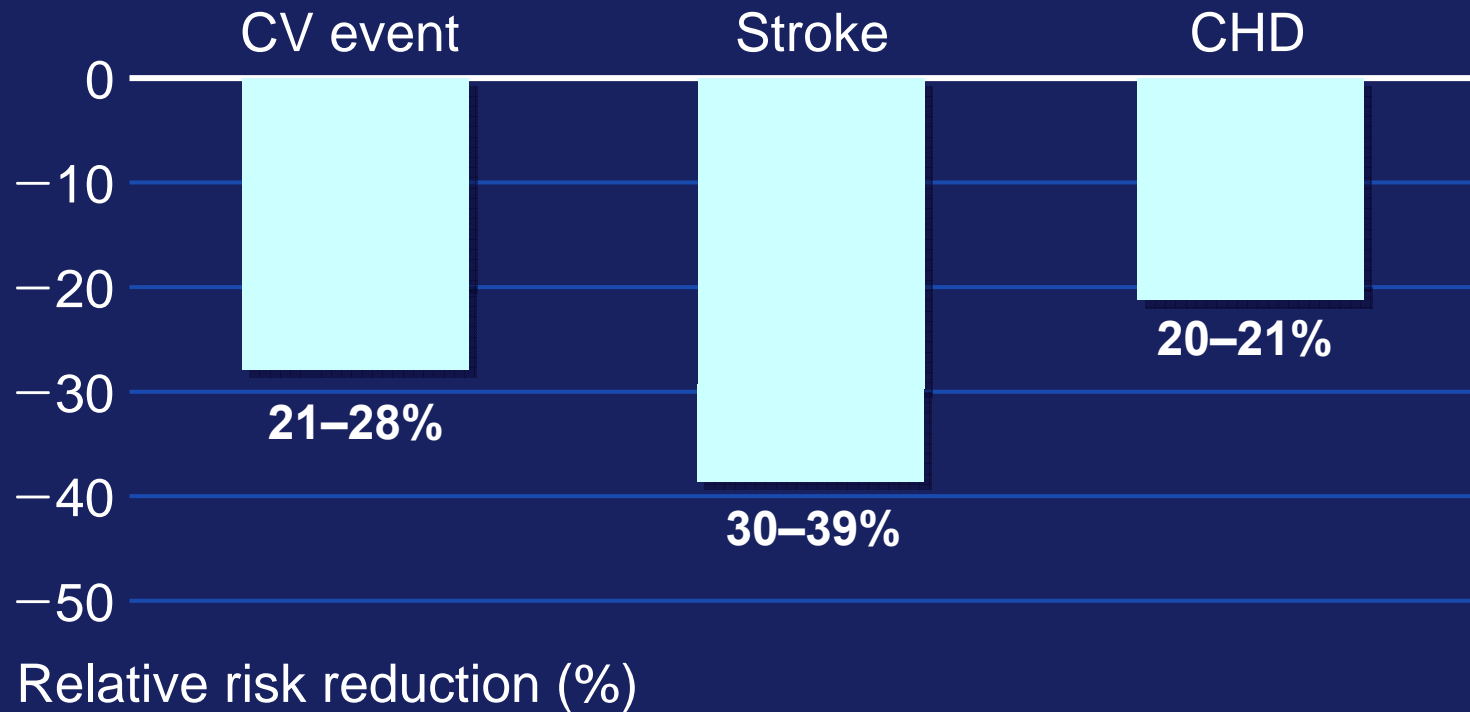
men



women

J Hypertension 2007

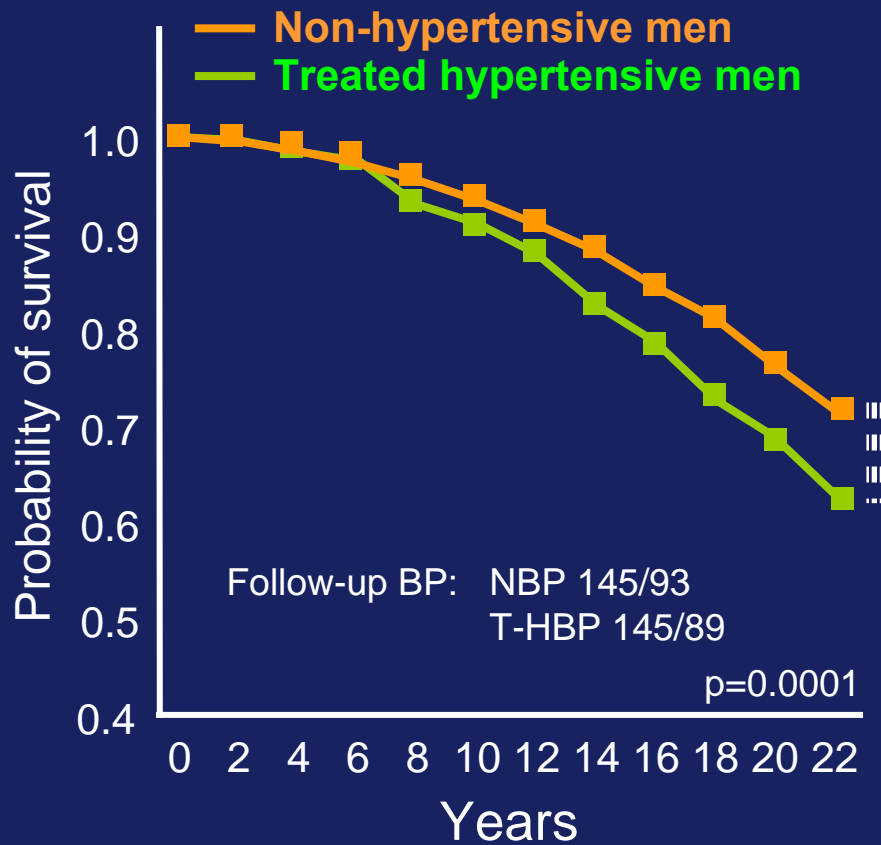
## Long-term Treatment for Hypertension Significantly Reduces CV Events....



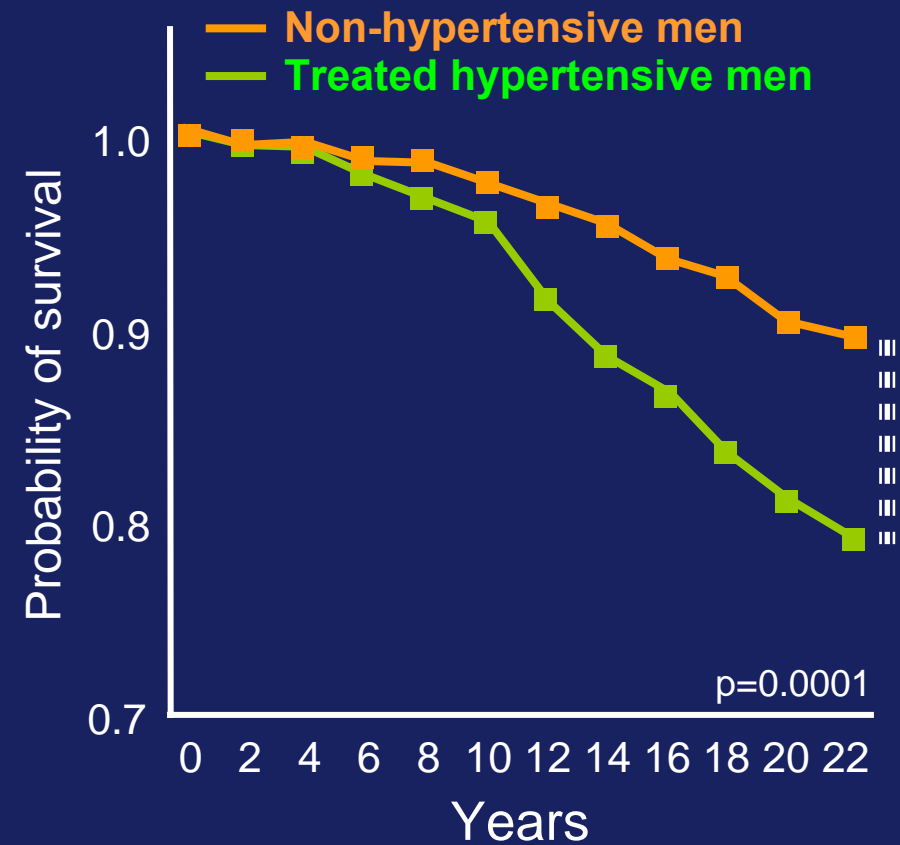


# ... But Even if Hypertension is Controlled Patients are at Increased Risk of Death and Coronary Heart Disease (CHD)

## Overall survival



## CHD deaths



## Increased Risk of Death in Patients with Hypertension Compared with Non-hypertensive Patients is Multifold

- Risk partly irreversible
- Treatment starts too late

Greater protection is afforded by:

Drugs with specific **organ protective** properties

**More aggressive** BP reductions  
<140/90 mmHg

Correction of multi-factorial **risk profile**

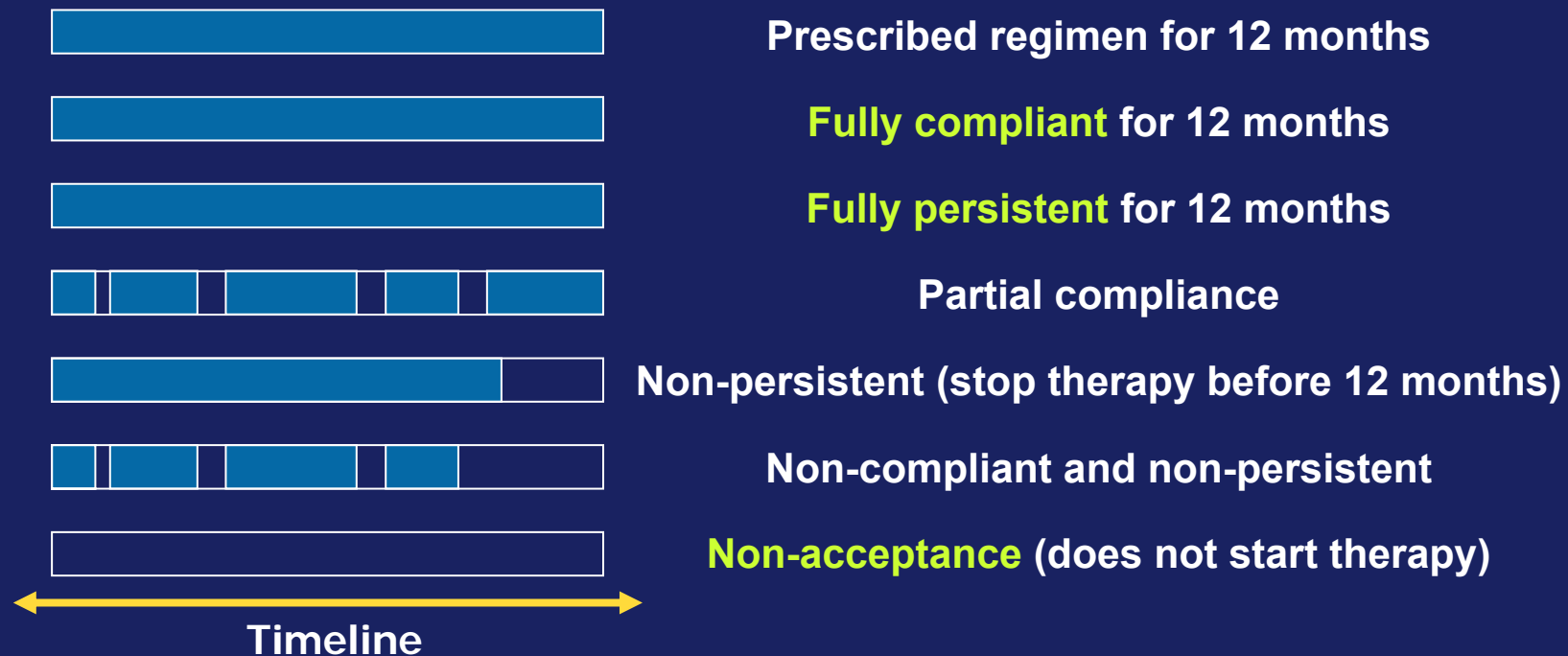
## Hypertension: Problem Setting

- Despite the availability of a range of antihypertensives, the majority of hypertensive patients are **not at goal**
- **Compliance and long-term persistence** with treatment is poor
  - Potentially due to the adverse effects associated with some agents
- Antihypertensive agents need to provide complete **24-hour BP control**
- Patients with hypertension respond differently to the various classes of antihypertensive drugs
  - Most patients require combination therapy to reach goal

## Compliance and Persistence are Central Components of Long-term Drug Therapy

**Compliance:** extent to which a patient acts in accordance with the prescribed interval and dose of dosing regimen (= adherence)

**Persistence:** accumulation of time from initiation to discontinuation of therapy



# Trends in Awareness, Treatment and Control of Hypertension in Korea

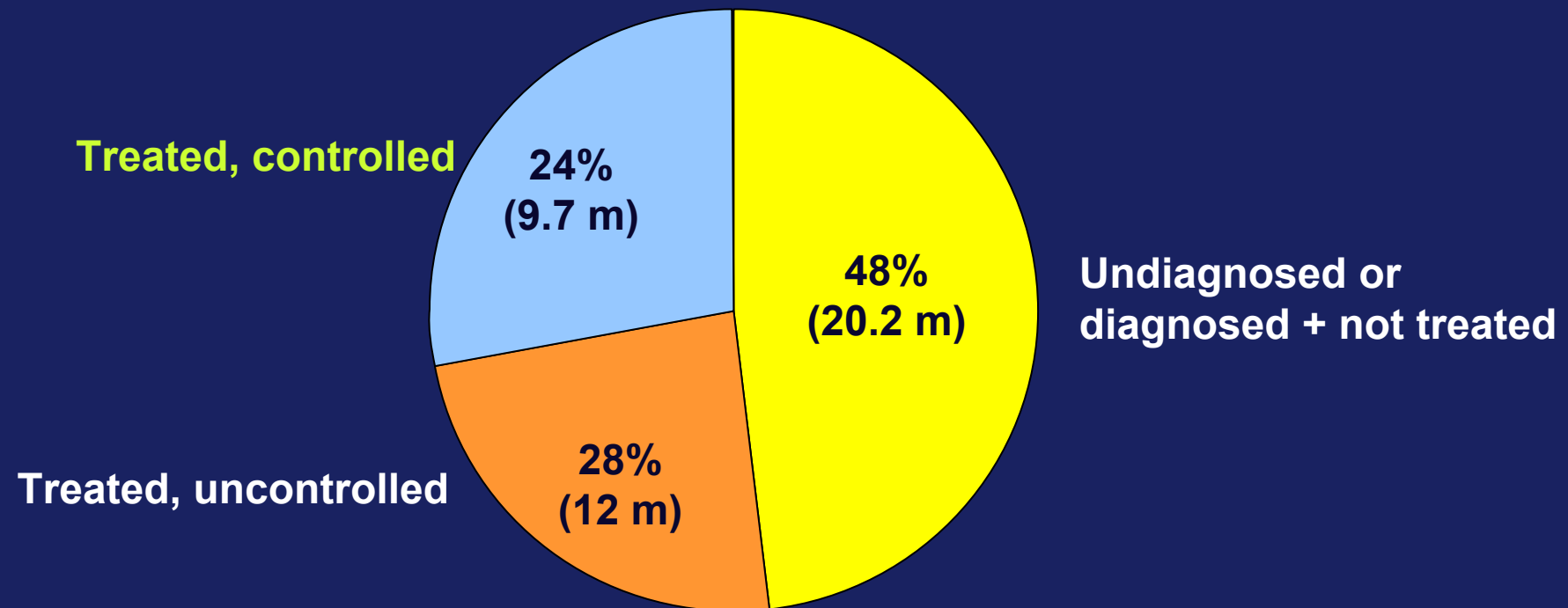
		Korea		US
		2001	2005	1999-2000
<b>Prevalence</b>	m	34.4	30.2	27.1
	f	26.5	25.6	30.1
<b>Awareness</b>	m	-	47.8	66.3
	f	-	65.9	71.2
<b>Treatment</b>	m	25.2	39.2	54.3
	f	39.5	60.0	62.0
<b>Control (All hypertensive pt)</b>	m	7.6	19.9	32.6
	f	16.6	35.0	29.6
<b>Control (All treated pt)</b>	m	30.2	50.7	59.9
	f	42.0	58.4	47.8

%

보건복지부, 한국보건사회연구원, 국민건강영양조사-검진편; 2002 (30세 이상 성인)  
 The Third Korea National Health and Nutrition Examination Survey(KNHANES III), 2005  
 US NHANES 1999-2000, JAMA 2003;290:199 (% of adults aged 18 to 74 years)

# Large Population of Patients Remain Untreated, Undiagnosed, or Diagnosed and Not Treated

Total US hypertension<sup>1</sup> patients: 41.9 m

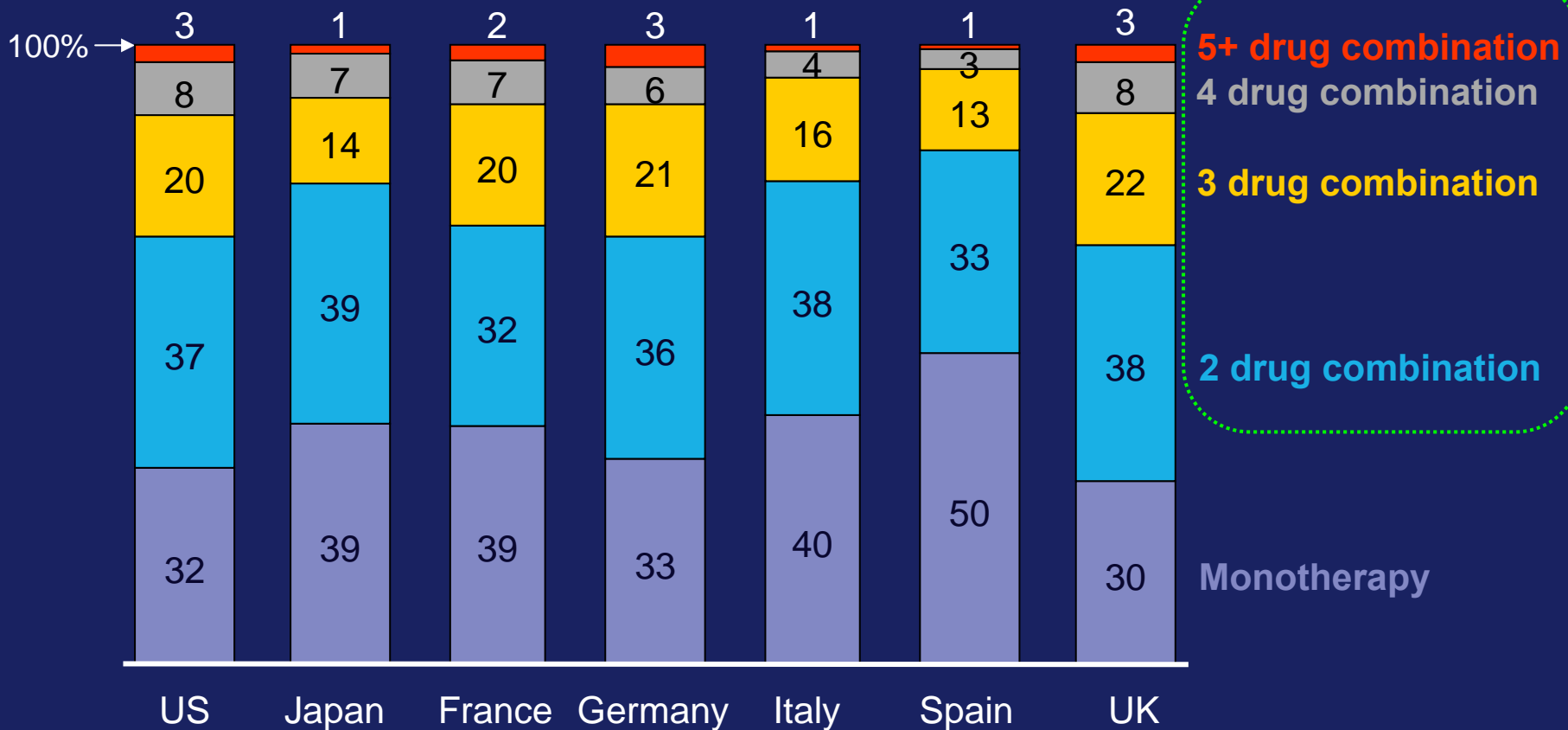


<sup>1</sup> Hypertension defined as: 140/90 mmHg

Source: Epidemiology Database, The Mattson Jack Group, Hypertension, latest Epidata updates; Decision Resources, Decision Base 7, Hypertension Report, Mar 2003; DataMonitor, Treatment Algorithms: Hypertension 3rd edition, Jul 20, 2002

# Over 60% of Treated Hypertensive Patients Require More than One Drug

Proportion of patients (%)



Source: Datamonitor, Treatment algorithms Hypertension, 2003

## Guidelines Recognize Growing Treatment Complexities and Recommend Tighter Control

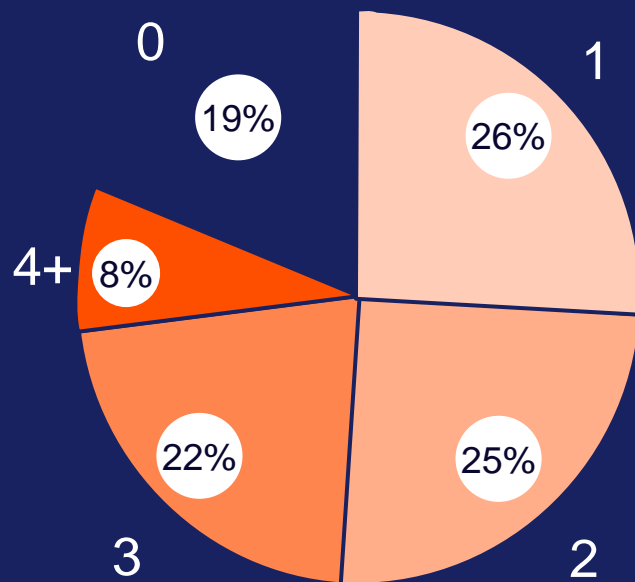
For individuals with hypertension and:		BP goal
JNC VII	Without diabetes or renal disease	<140/90 mmHg
	With diabetes or renal disease	<130/80 mmHg
ESH/ESC	Without diabetes	<140/90 mmHg
	With diabetes or renal disease	<130/80 mmHg
WHO/ISH	Without diabetes	<140/90 mmHg
	With diabetes	<130/80 mmHg

Chobanian AV et al. JAMA. 2003;289:2560-2572. Guidelines Committee. J Hypertens. 2007;25:1105-1187. Guidelines Subcommittee. J Hypertens. 1999; 17: 151-183. World Health Organization, International Society of Hypertension Writing Group. J Hypertens. 2003; 21: 1983-1992.

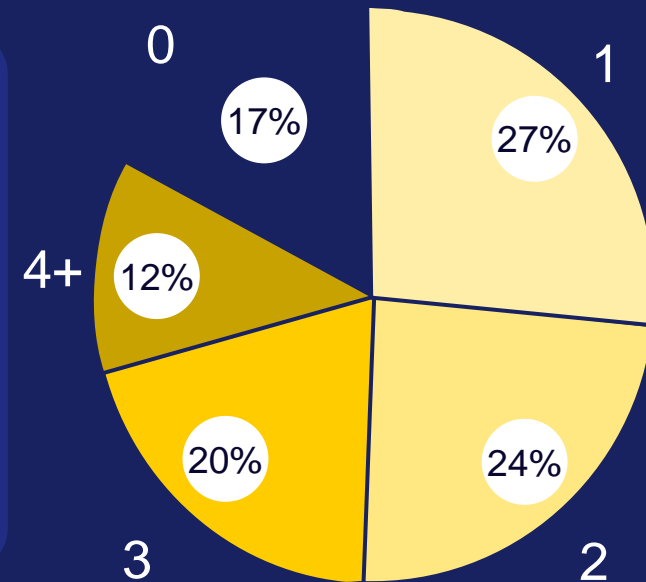


# Hypertension is Complicated by High Prevalence of Metabolic Disorders

Men



Women

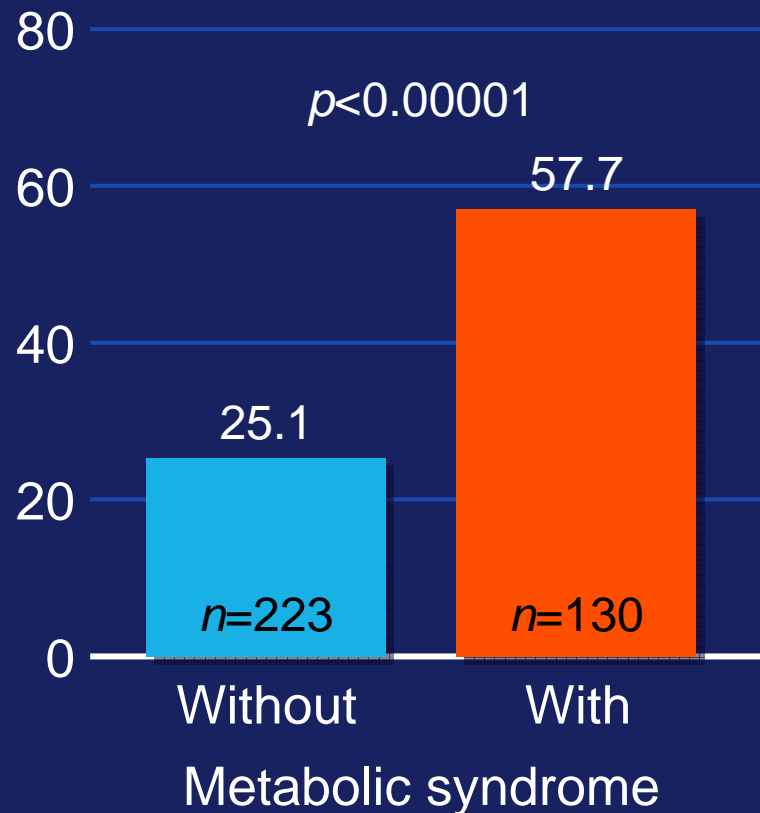


**Obesity**  
**Glucose intolerance**  
**Hyperinsulinaemia**  
**Reduced HDL-C**  
**Elevated LDL-C**  
**Elevated triglycerides**

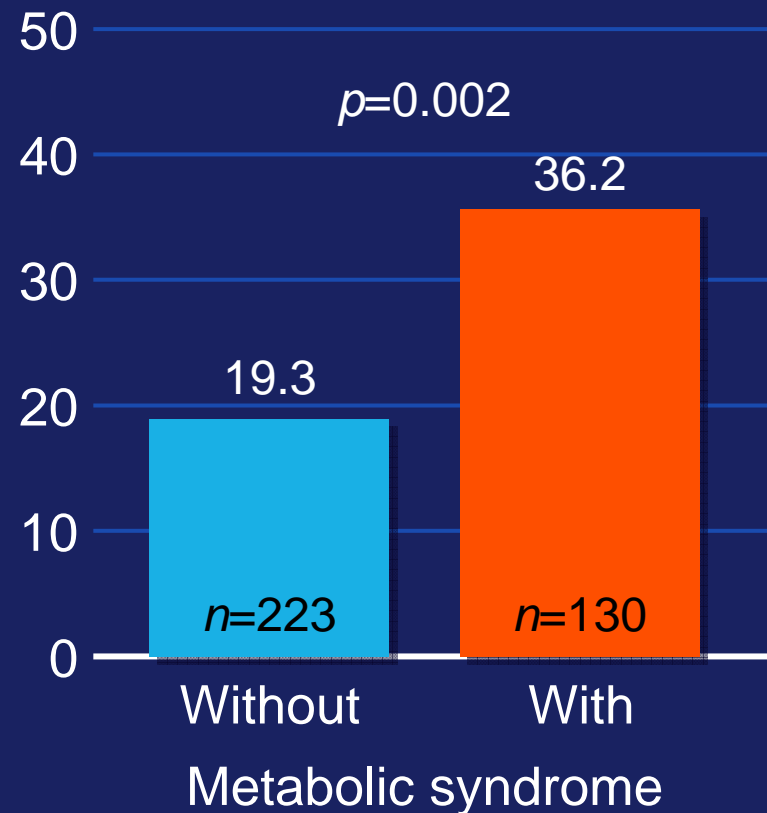
**>50% have two or more comorbidities**

# Hypertensive Patients with Metabolic Syndrome are at a Higher Risk of End-organ Damage

Prevalence of LVH on Echo (%)



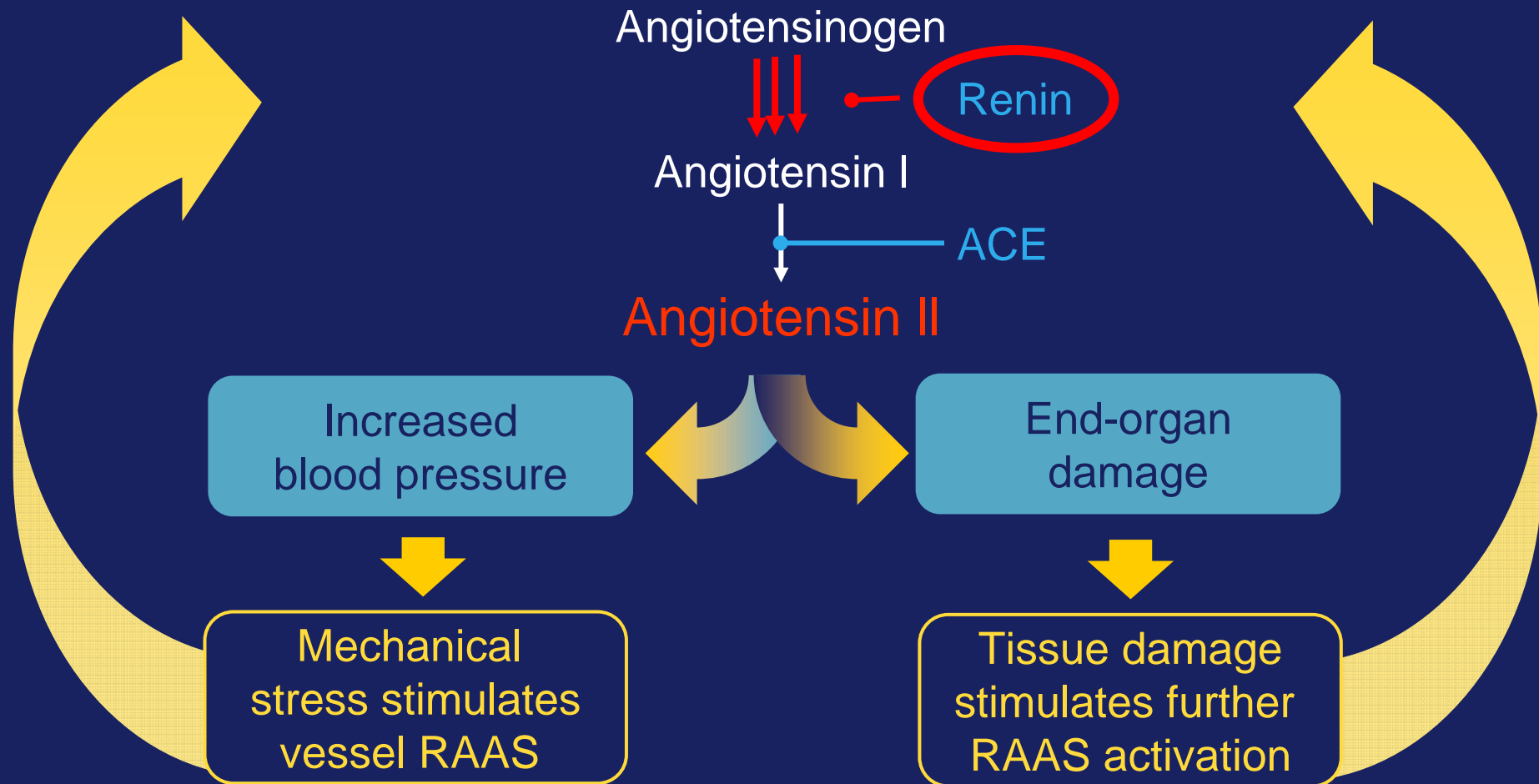
Prevalence of microalbuminuria (%)



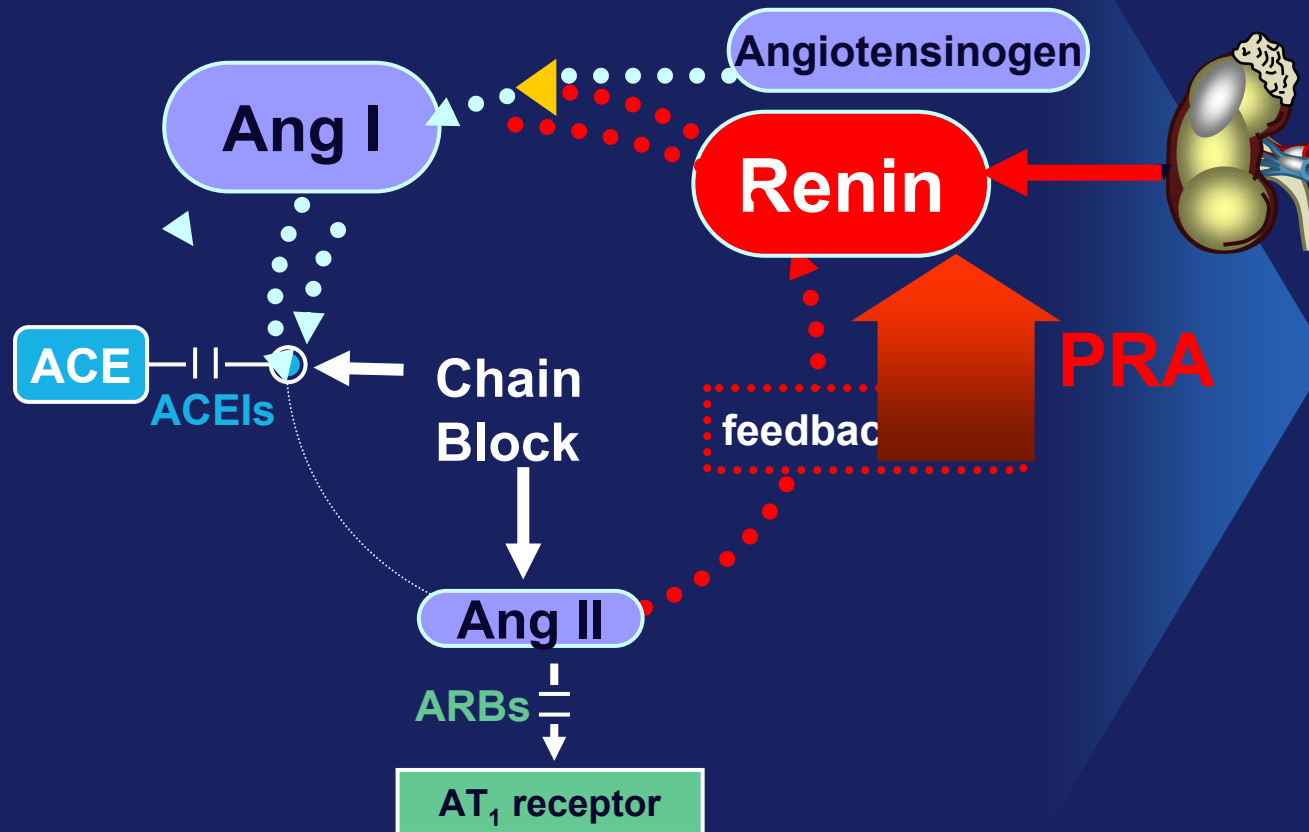
LVH: left ventricular hypertrophy

Mulé *et al.* *J Intern Med* 2005;257:503–513

# The RAAS Key Role in Hypertension and The Chronic Vicious Cycle of RAAS Upregulation



# ACEI and ARB Block Chain Reaction, But Kidneys Try to Overcome Block by Increasing Renin/PRA

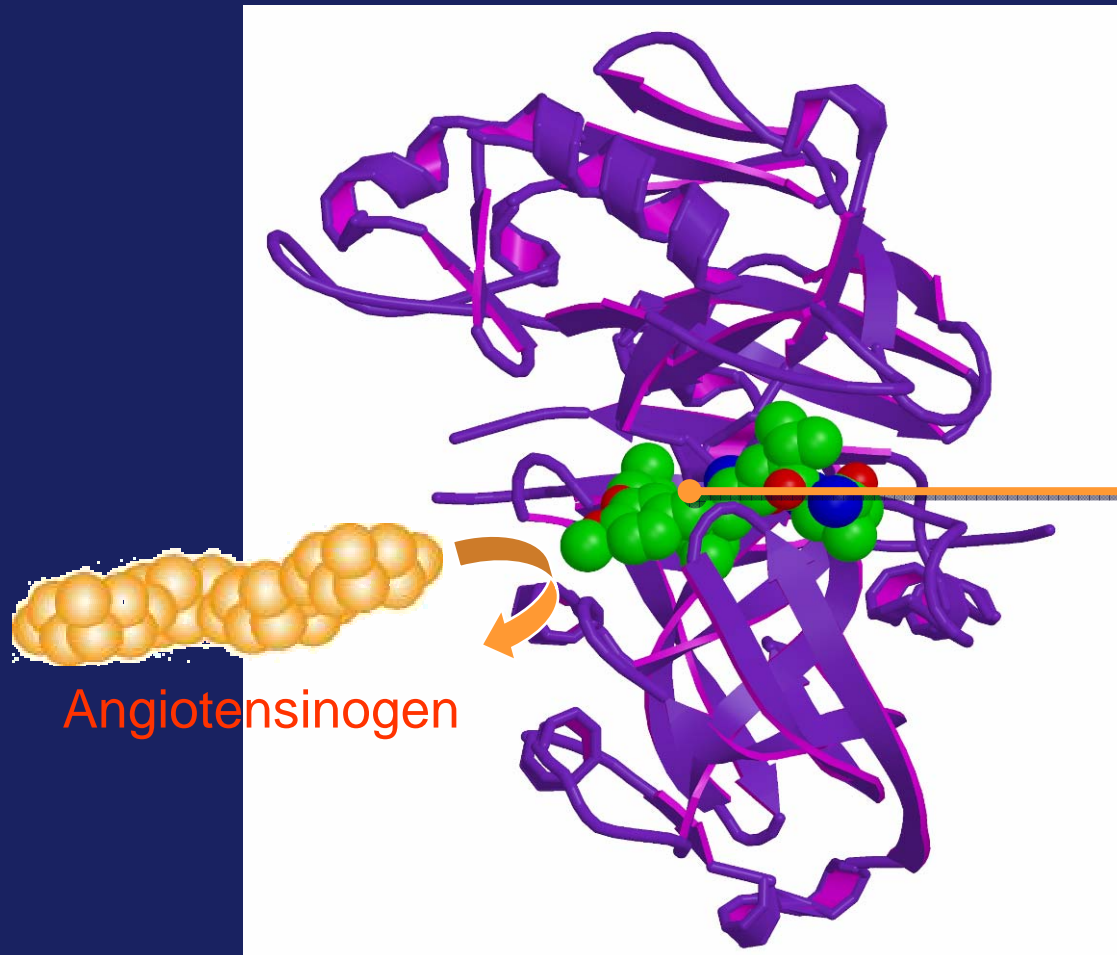


# Crystal Structure of Renin



Adapted from Rahuel J et al. J Struct Biol. 1991;107:227-236.

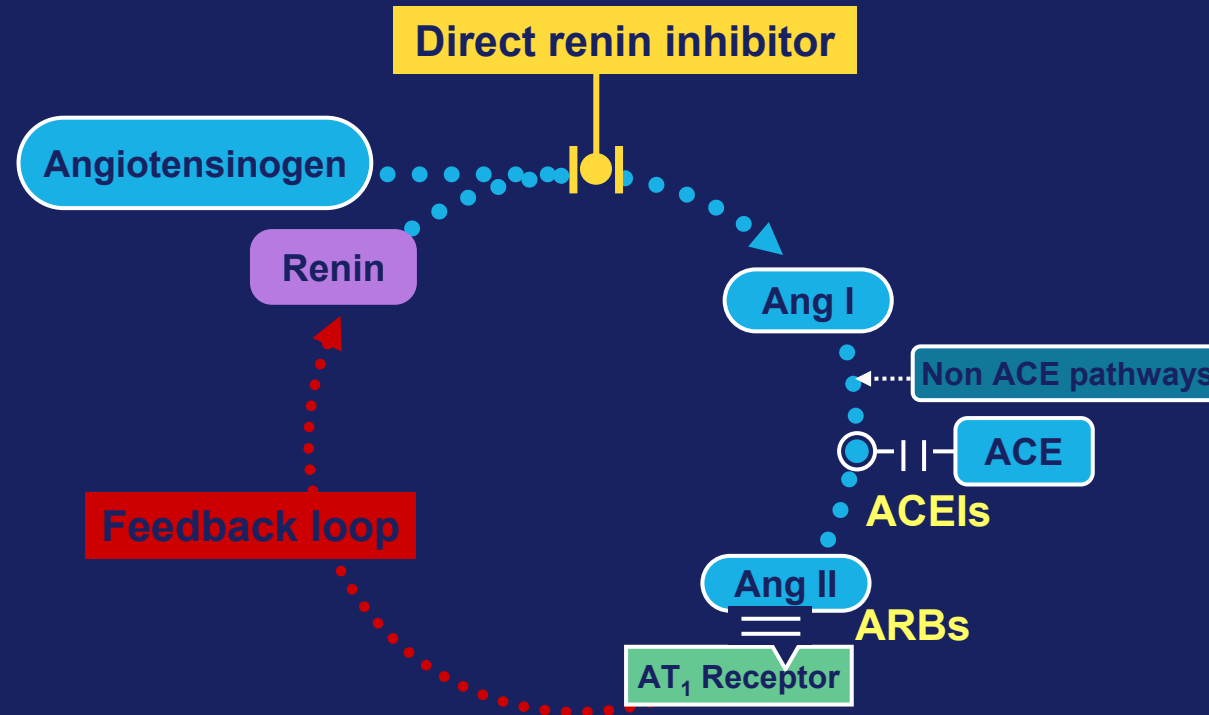
## Direct Renin Inhibitor, Aliskiren, Binds to The Active Site of Renin



**Aliskiren**

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

# Aliskiren Uniquely Lowers PRA



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

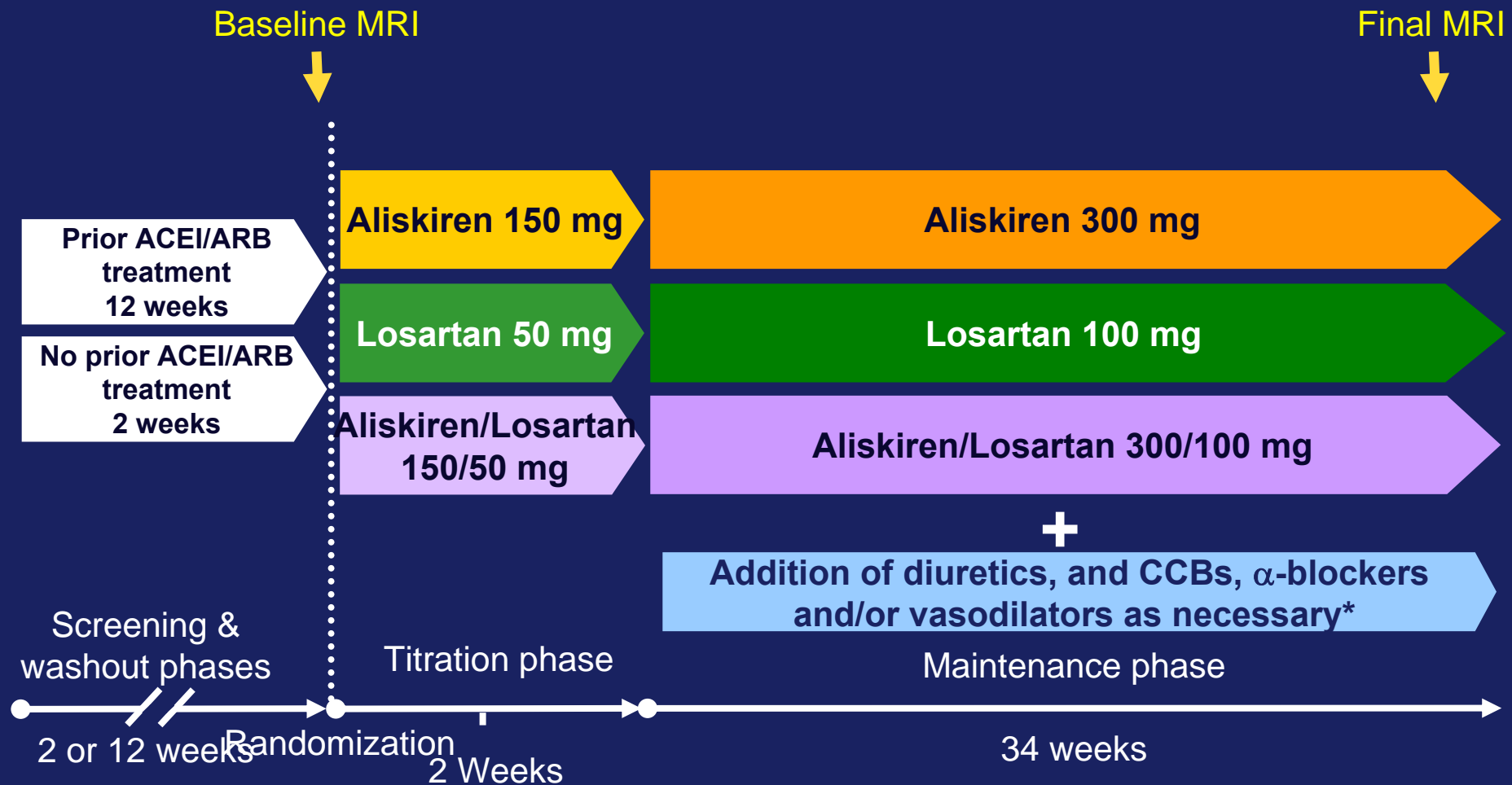
**Effect of the Direct Renin Inhibitor Aliskiren,  
Either Alone or in Combination With Losartan,  
Compared to Losartan, on Left Ventricular Mass  
in Patients With Hypertension and Left  
Ventricular Hypertrophy: The ALiskiren Left  
Ventricular Assessment of HypertrophY (ALLAY)  
Trial**

Scott D. Solomon<sup>1</sup>, Evan Appelbaum<sup>2</sup>, Warren J. Manning<sup>2</sup>,  
Anil Verma<sup>1</sup>, Tommy Berglund<sup>3</sup>, Valentina Lukashevich<sup>4</sup>,  
Cheraz Cherif-Papst<sup>5</sup>, James Carten<sup>4</sup>, Björn Dahlöf<sup>3</sup>

<sup>1</sup>Brigham and Women's Hospital, Boston, MA; <sup>2</sup>Beth Israel Deaconess  
Medical Center, Boston, MA; <sup>3</sup>Sahlgrenska University Hospital/Östra,  
Göteborg, Sweden; <sup>4</sup>Novartis Pharmaceuticals Corp., East Hanover, NJ;  
<sup>5</sup>Novartis Pharma AG, Basel, Switzerland



# A double-blind, randomized, active-controlled trial in overweight patients with hypertension and LV hypertrophy



\*To achieve BP target of < 140/90 mmHg (< 130/80 mmHg for patients with diabetes)

CCBs, calcium channel blocker; LV, left ventricular

77 centers in 9 countries

# CMR for LV mass

BASE

Slice 1

Slice 2

Slice 3

Slice 4

Slice 5

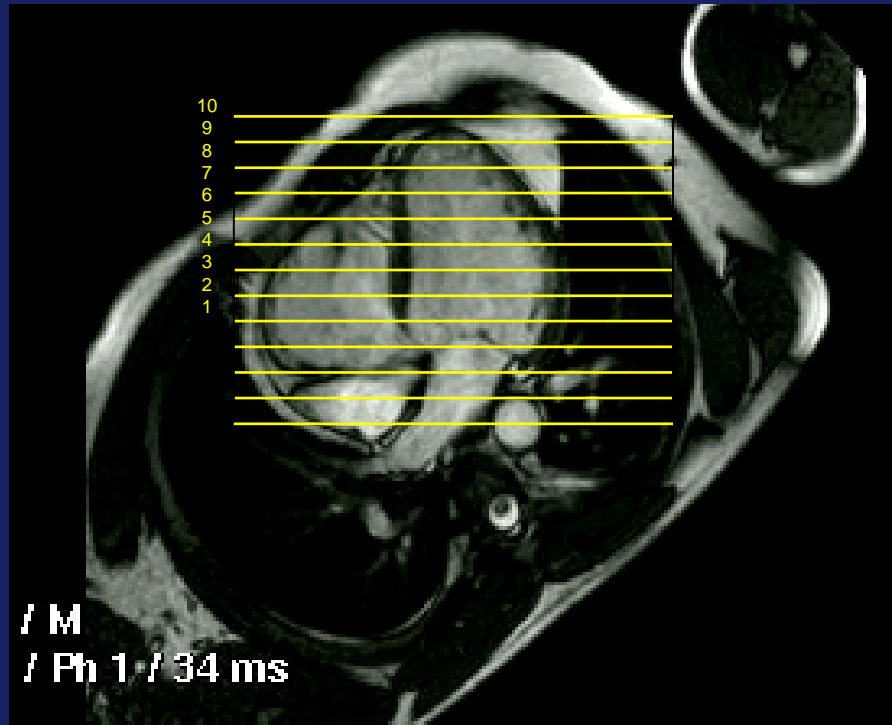
Slice 6

Slice 7

Slice 8

Slice 9

Slice 10



Four-chamber end-diastole (ED)

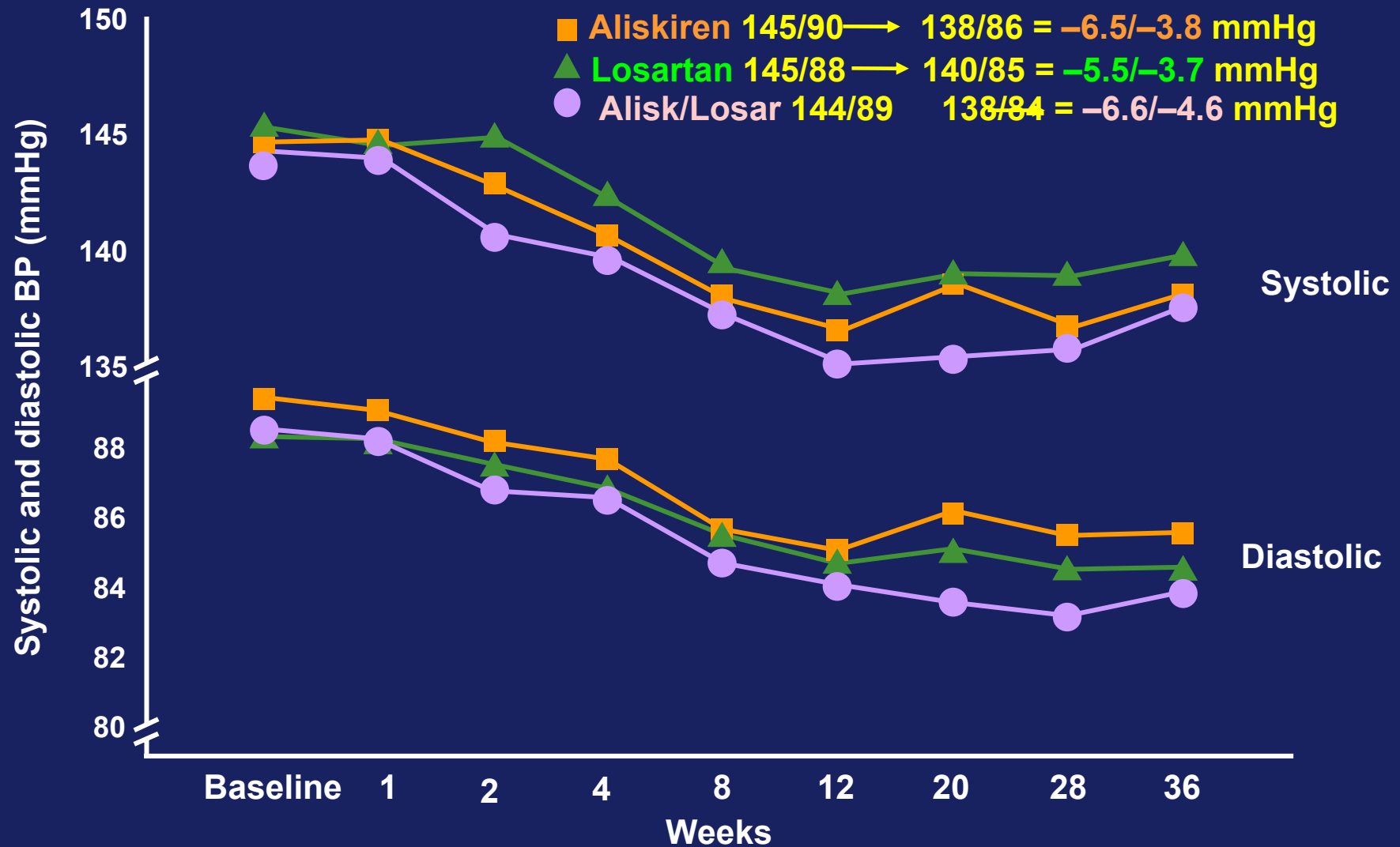
ED short axis stack

slice thickness 10 mm  
spatial resolution 2.0 mm x 2.0 mm  
temporal resolution 30-50ms

APEX

LV, left ventricular; CMR, cardiac magnetic resonance

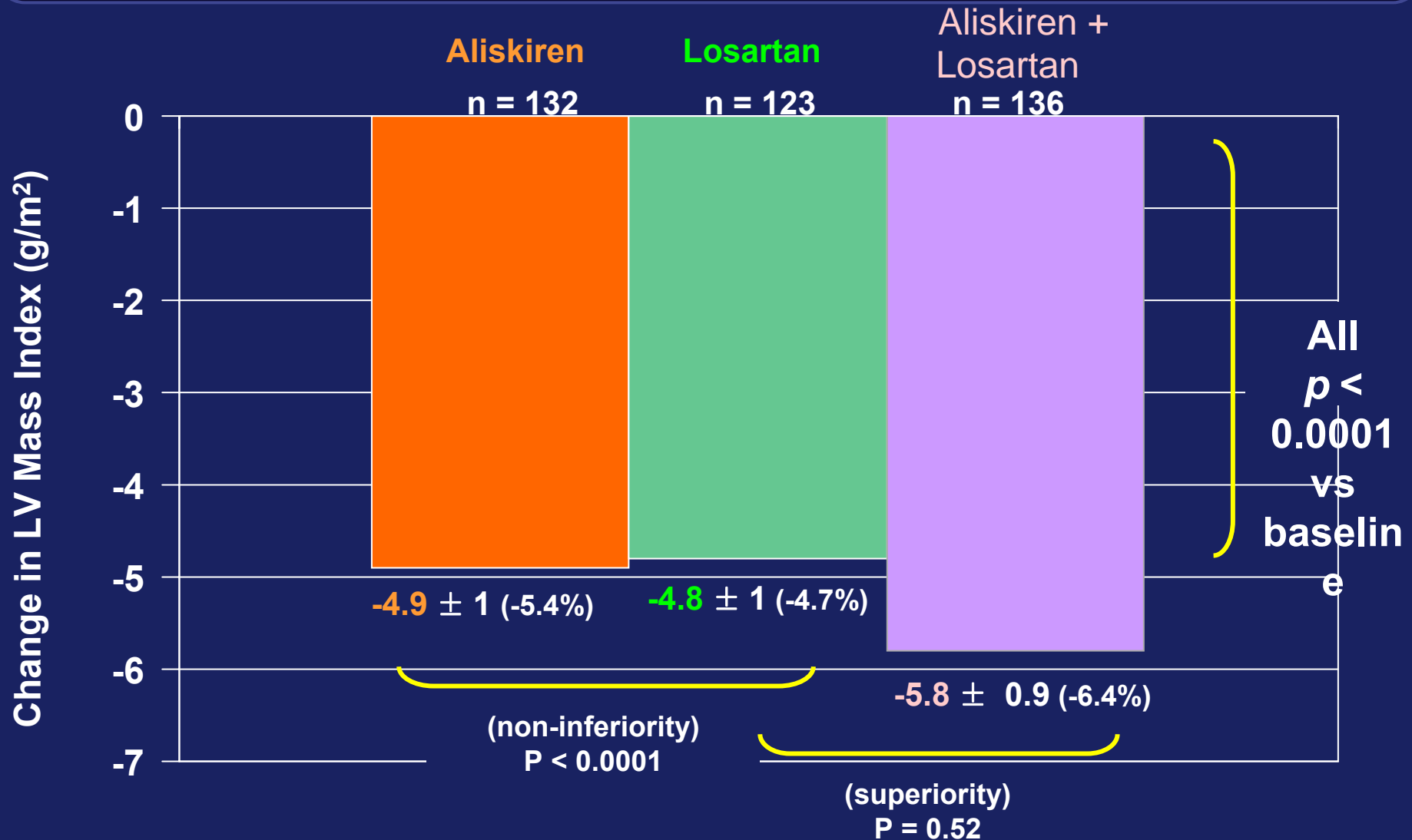
## Effect on Mean Sitting BP of Aliskiren and Losartan Alone or in Combination from Baseline to Week 36



Aliskiren, 300 mg; Losartan, 100 mg; Aliskiren/losartan 300/100 mg

Data are shown as mean (+ SEM) from baseline to Week 36 for the efficacy population

# Effect on LV Mass Index of Aliskiren Alone or in Combination with Losartan from Baseline to Follow-up



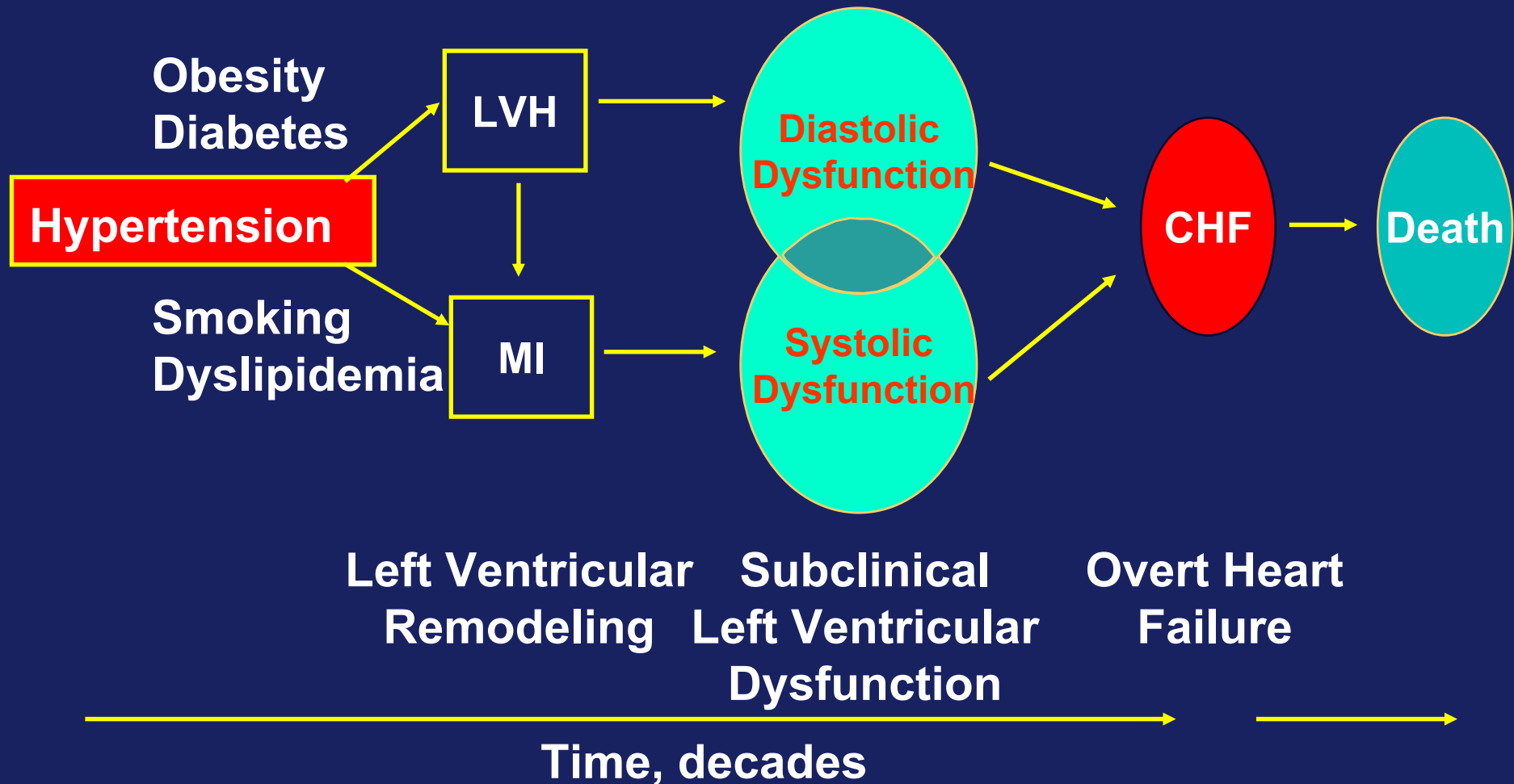
Mean ( $\pm$  SEM) for the efficacy population  
LV, left ventricular

# Hypertension and Heart Failure

- Approximately 5.2 million patients in the US and 10 million patients in Europe have heart failure (HF)<sup>1,2</sup>
- Hypertension precedes HF in approximately 90% of patients with HF<sup>3</sup>
- Despite many proven treatment options being available, **the number of patients experiencing mortality due to HF is high and is increasing:**
  - approximately 50% of patients with HF will die within 4 years of diagnosis<sup>2</sup>
  - from 1994 to 2004, the number of deaths from HF increased by 28%<sup>4</sup>
- Reasons for the increasing number of patients experiencing mortality due to HF include:
  - greater survival of patients with MI<sup>5</sup> (a risk factor for HF)
  - an increasingly elderly population<sup>2,5</sup> (HF is more prevalent in the elderly)
  - an increasing incidence of hypertension<sup>6</sup> (a major risk factor for HF)

1. Himmelmann 1999; 2. Swedberg *et al.* 2005; 3. Chobanian *et al.* 2003;  
4. Rosamond *et al.* 2007; 5. Hunt *et al.* 2005; 6. Kearney *et al.* 2005

# From Hypertension to CHF



## Use of Antihypertensive Agents in Patients with HF

- Elevated systolic and diastolic BP are major risk factors for the development of HF<sup>1,2</sup>
- Consequently, hypertension precedes the development of HF in approximately 90% of patients with HF<sup>3</sup>
- Guidelines recommend that BP should be controlled in patients with **concomitant hypertension and HF**<sup>4</sup>
- Therefore, it is important that antihypertensive therapies can be safely continued in patients initially receiving treatment for hypertension who go on to develop HF
- However, not all antihypertensives are suitable for use in patients with HF

# Not All Antihypertensive Agents are Suitable for Use in Patients with HF

## CCBs

- Most CCBs should be avoided in HF as they have a cardio-depressant effect<sup>1</sup>
- CCBs are associated with increased risk of CV events and can lead to worsening HF<sup>1</sup>
- Only vasoselective CCBs, such as amlodipine, do not adversely affect survival<sup>1</sup>

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## $\beta$ -blockers

- $\beta$ -blockers can initially worsen symptoms of HF<sup>2,3</sup>
- This effect can be minimized if therapy is initiated at low doses and gradually increased until tolerable therapeutic doses are reached<sup>2</sup>
  - $\beta$ -blockers have been shown to significantly reduce mortality in patients with HF and are recommended as standard therapy, unless contraindicated<sup>1</sup>

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## Direct acting vasodilators

- Potent direct acting vasodilators, such as minoxidil, should be avoided as they cause sodium retention<sup>1</sup>

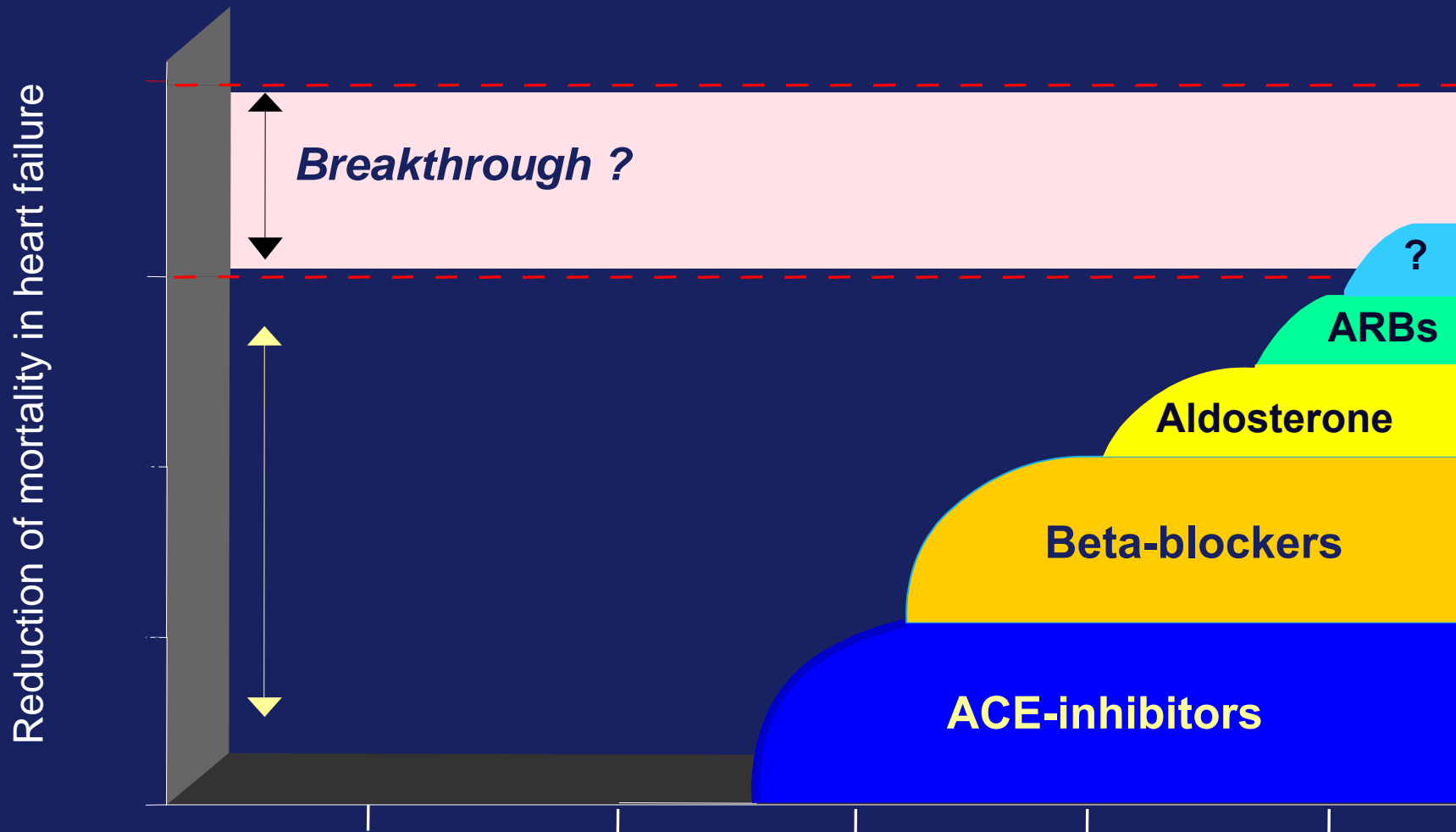
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## $\alpha$ -blockers

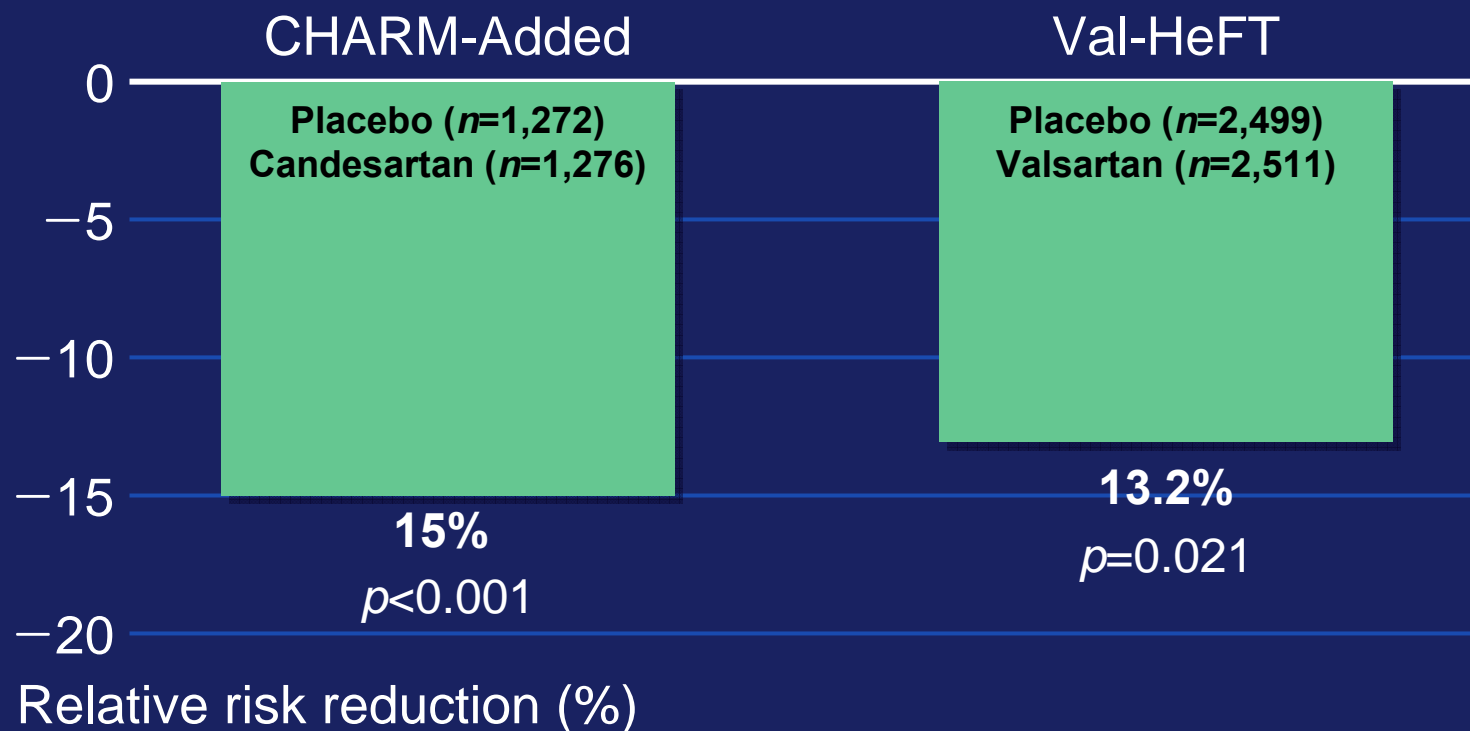
- There is no evidence for the use of  $\alpha$ -blockers in the treatment of HF<sup>4</sup>



# Why We Need Another Agent ?; "Ceiling Benefit" of Neurohumoral Blocking



# ACEI + ARB Combinations Showed CV Benefits Beyond Monotherapy...



CV death or HF hospital admission in patients with HF and LVEF  $\leq$  40% and being treated with an ACEI

CV morbidity and mortality in HF patients, 93% of whom were also taking an ACEI

McMurray JJV *et al. Lancet* 2003;362:767–71  
Pfeffer MA *et al. N Engl J Med* 2003;349:1893–906  
Cohn JN *et al. N Engl J Med* 2001;345:1667–75

## Conclusion

- **End-organ damage** resulting from hypertension is a major public health issue worldwide. Unmet needs in morbidity and mortality remain, despite the success of existing therapies
- Hypertension contributes to major CV outcomes and the global burden of the condition is projected to **increase**
- There is an increased need for **combination therapy**
- Hypertensive patients with metabolic disorders have an even higher risk of end-organ damage
- Further progress is need to effectively **control the RAAS**