The Differentiated Clinical Values of Valsartan for CV Disease Management

성균관의대 삼성서울병원 내과

박 승 우

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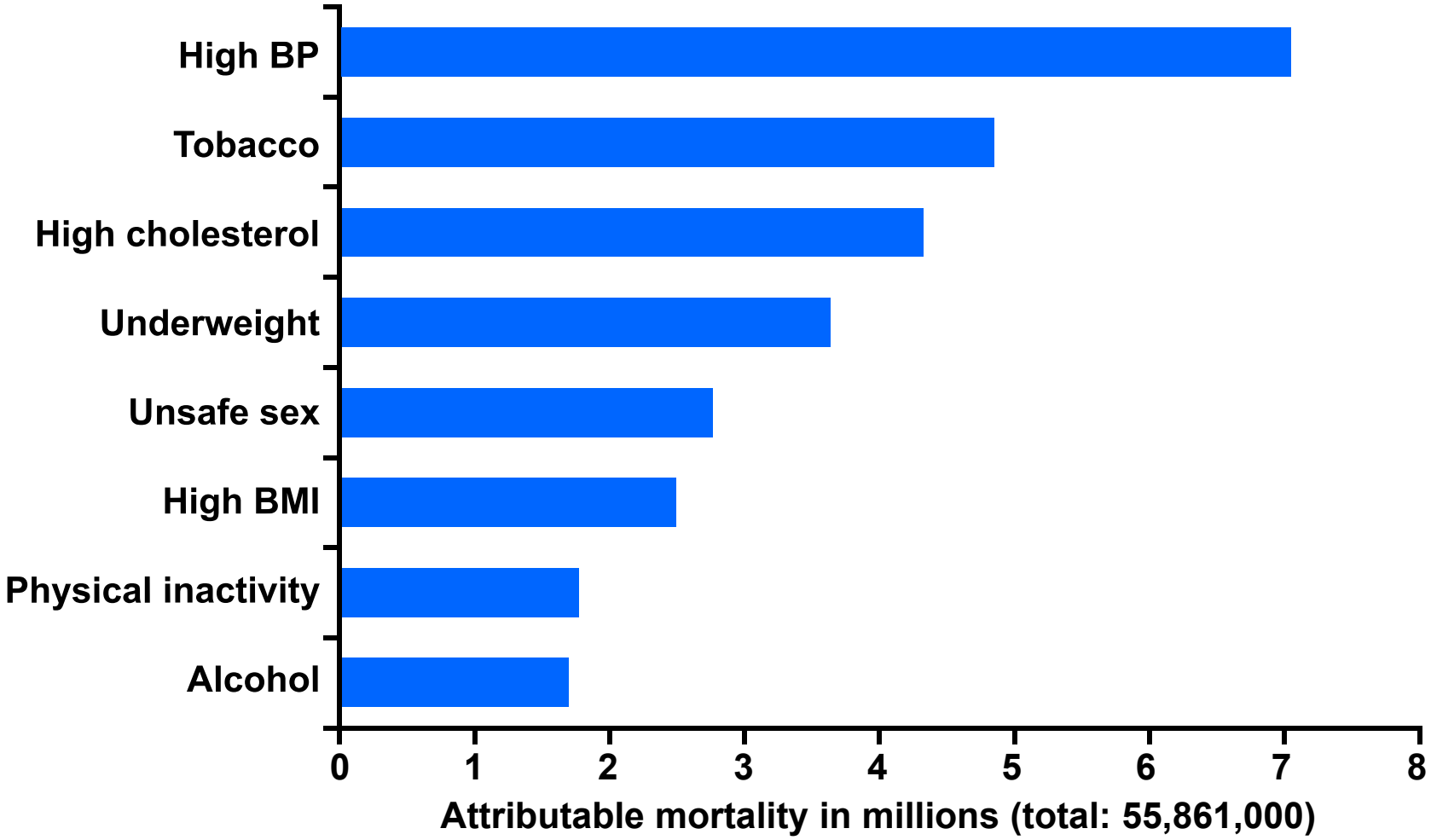
- The aim of Hypertensive Therapy
- Management of Hypertension
- The Wealth of Clinical outcome ARB : Diovan
- The efficacy of High dose Diovan

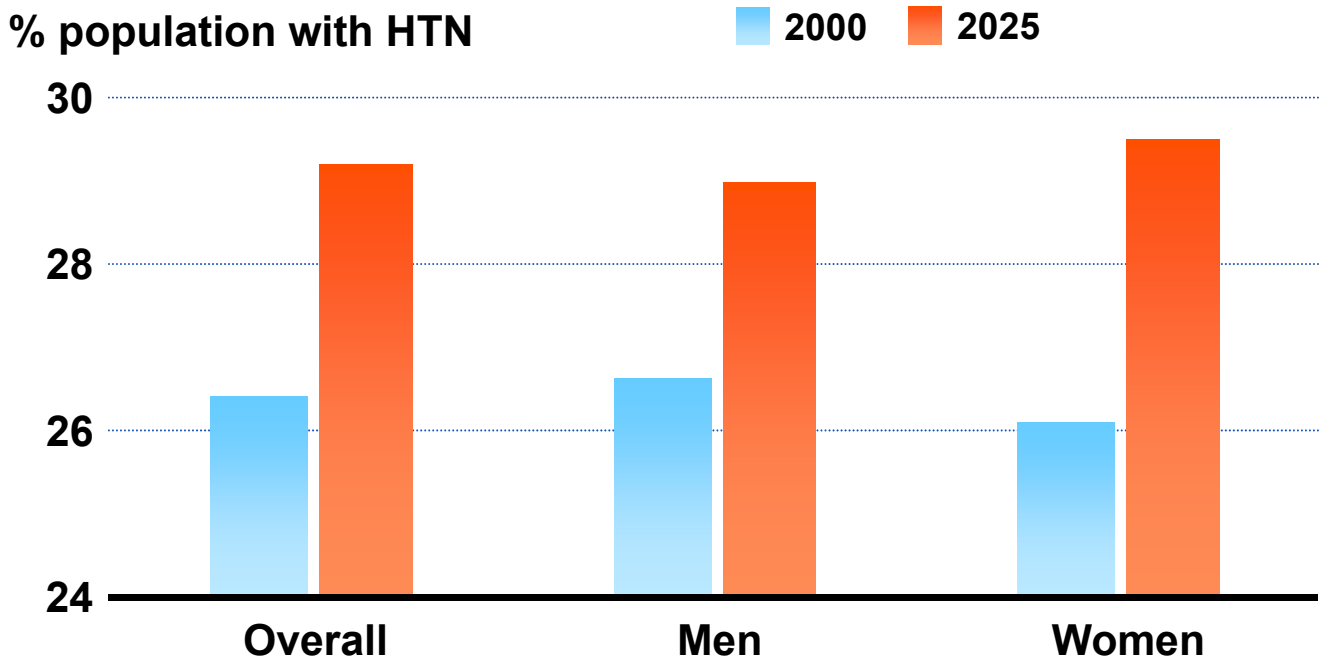
The aim of Hypertensive Therapy

Hypertension is the Number One Risk Factor for Global Mortality



Ezzati et al. Lancet 2002;360:1347–60

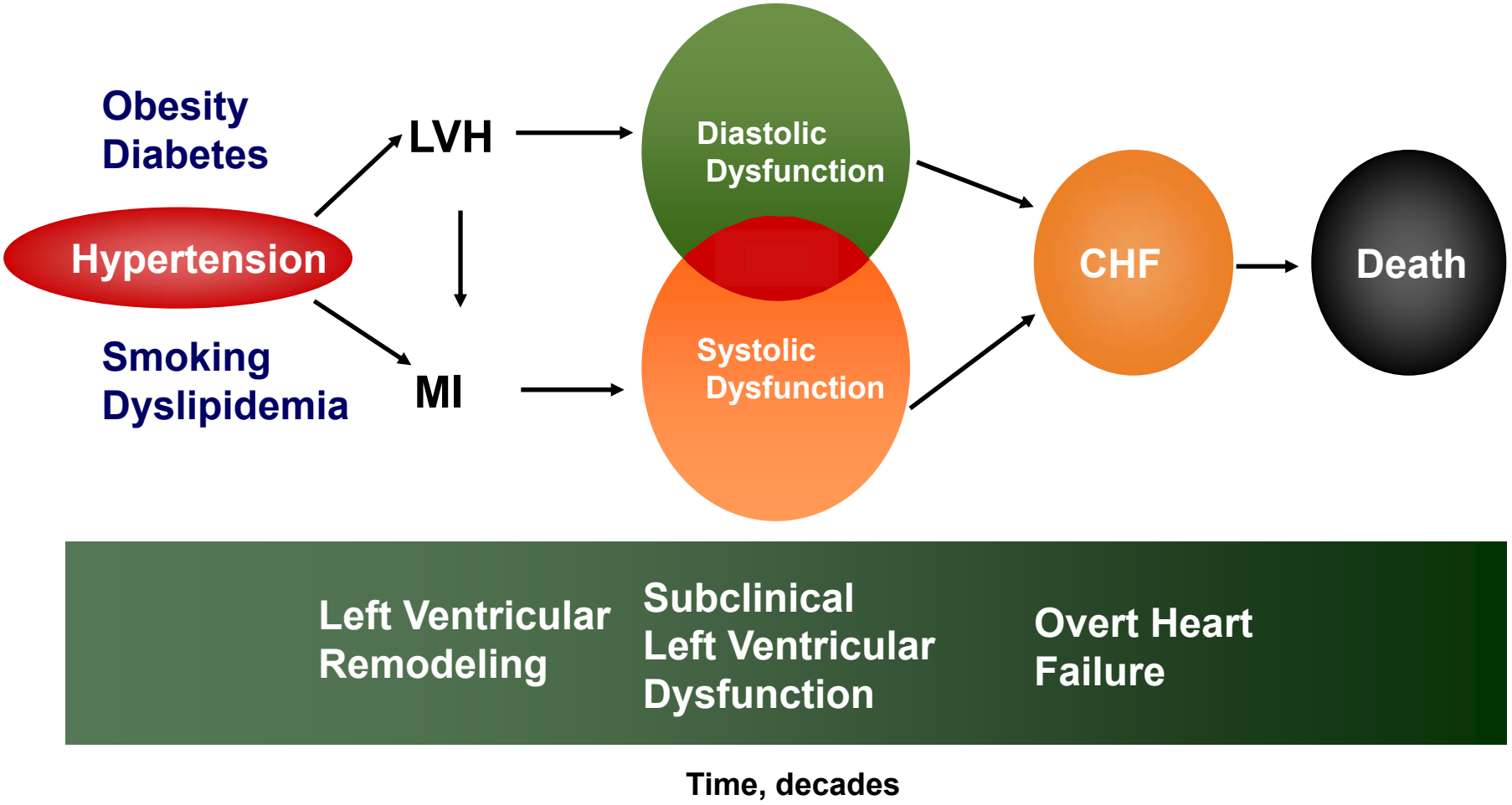
Global Burden of Hypertension is Predicted to Increase In Spite of Treatment Advances



Pooled data from 30 population-based studies from around the world

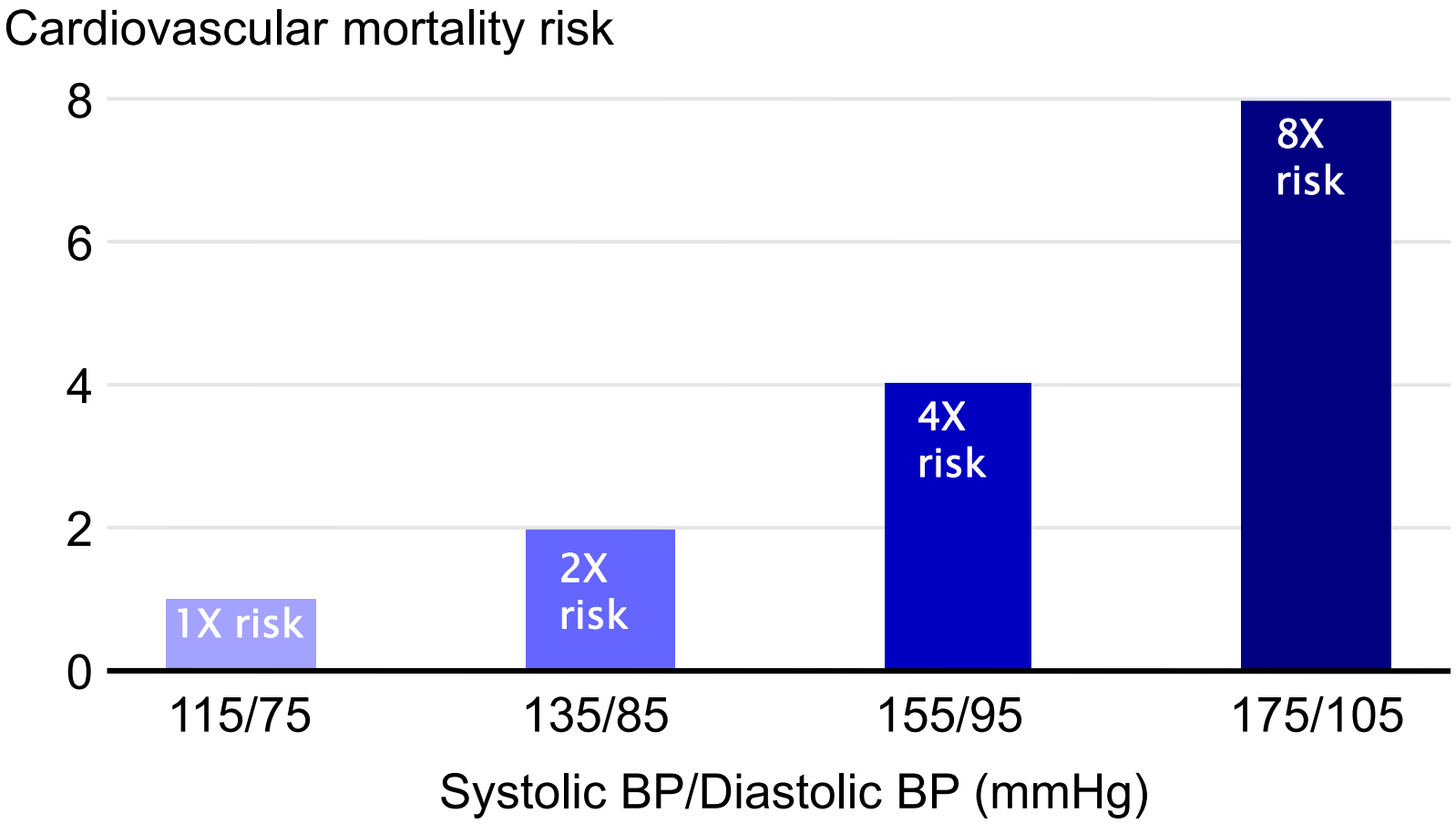
Kearney et al. Lancet 2005;365:217–23

From Hypertension to CHF and Death



Vasan RS, Levy D. Arch Intern Med. 1996;156:1789-1796.

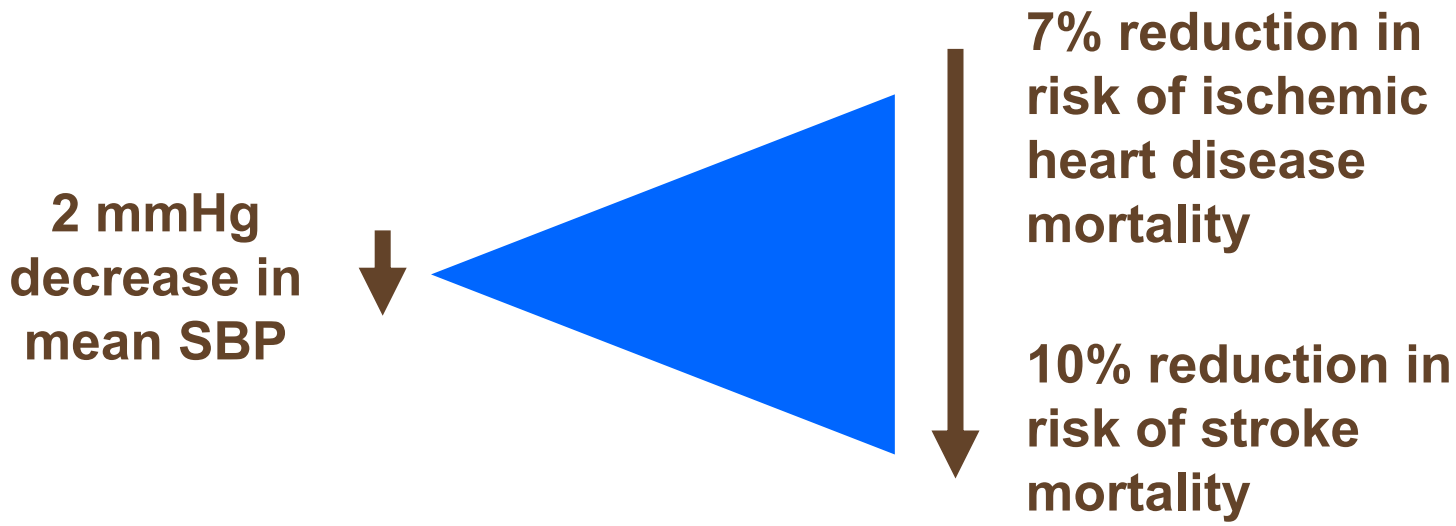
Cardiovascular Mortality Risk Doubles With each 20/10 mmHg BP Increment*



*Individuals aged 40–69 years

Lewington et al. Lancet 2002;360:1903–13

Blood Pressure Reduction of 2 mmHg Decreases the Risk of Cardiovascular Events by 7–10%



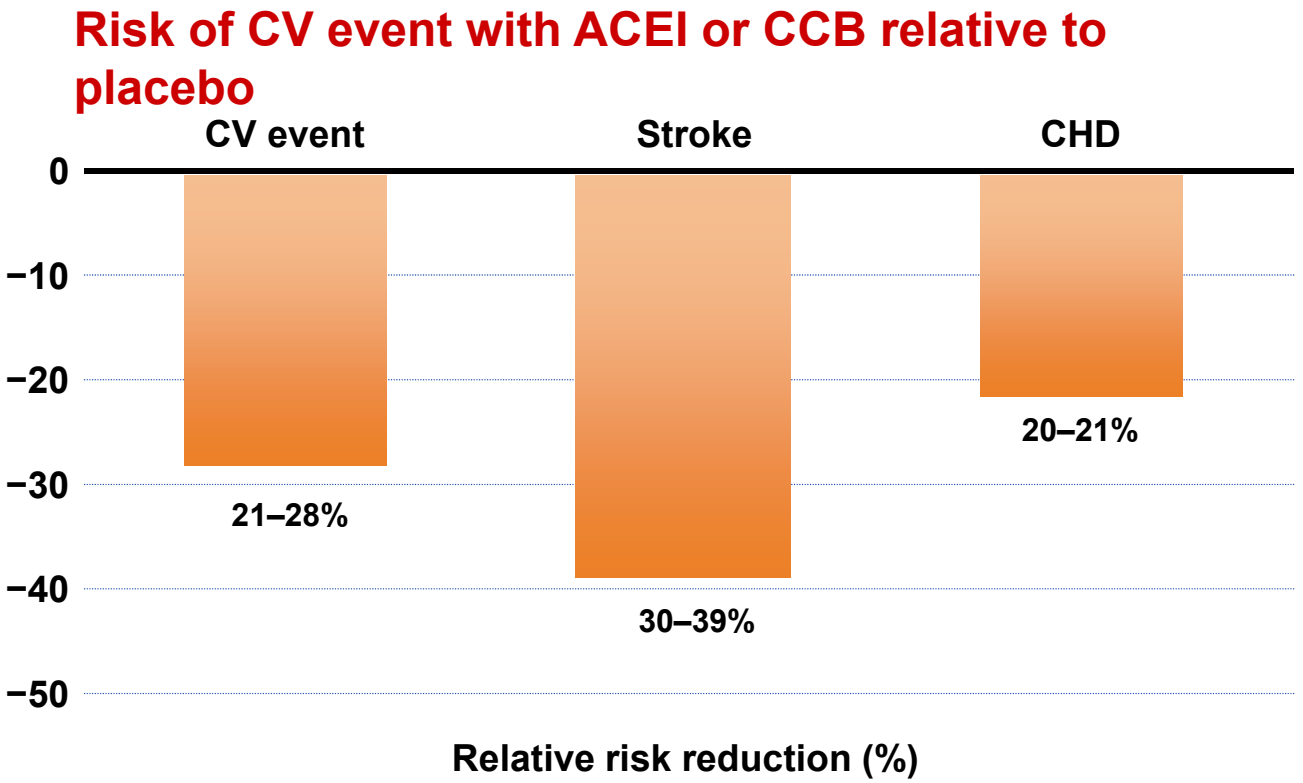
- Meta-analysis of 61 prospective, observational studies
- 1 million adults
- 12.7 million person-years

Lewington et al. Lancet 2002;360:1903–13

Cardiovascular Risk of Hypertension is related to

- **Level of Blood pressure**
- **Associated Cardiovascular risk factors**

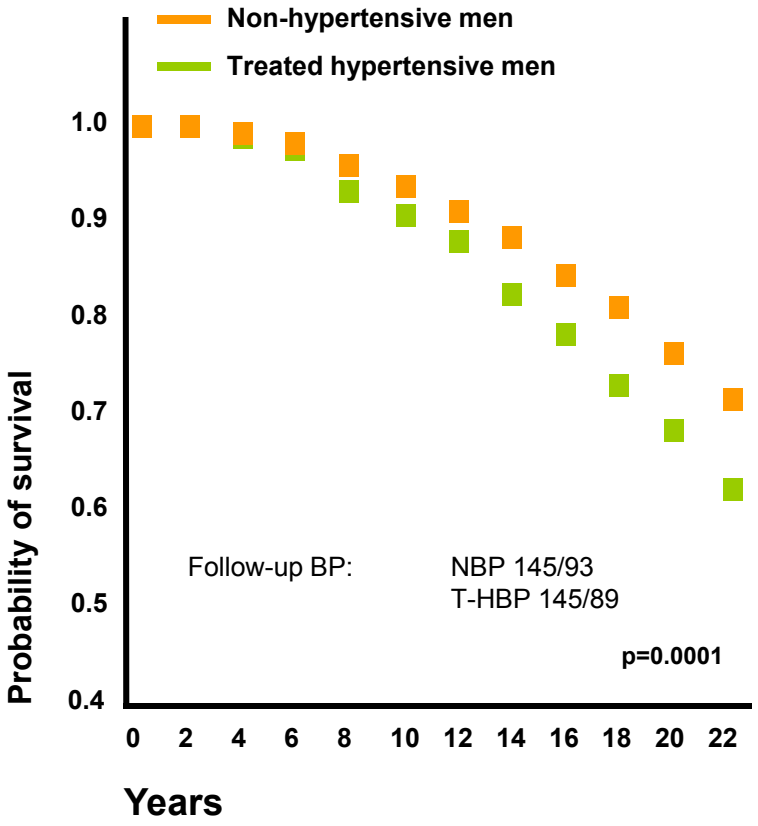
Long-term treatment for hypertension significantly reduces CV events….



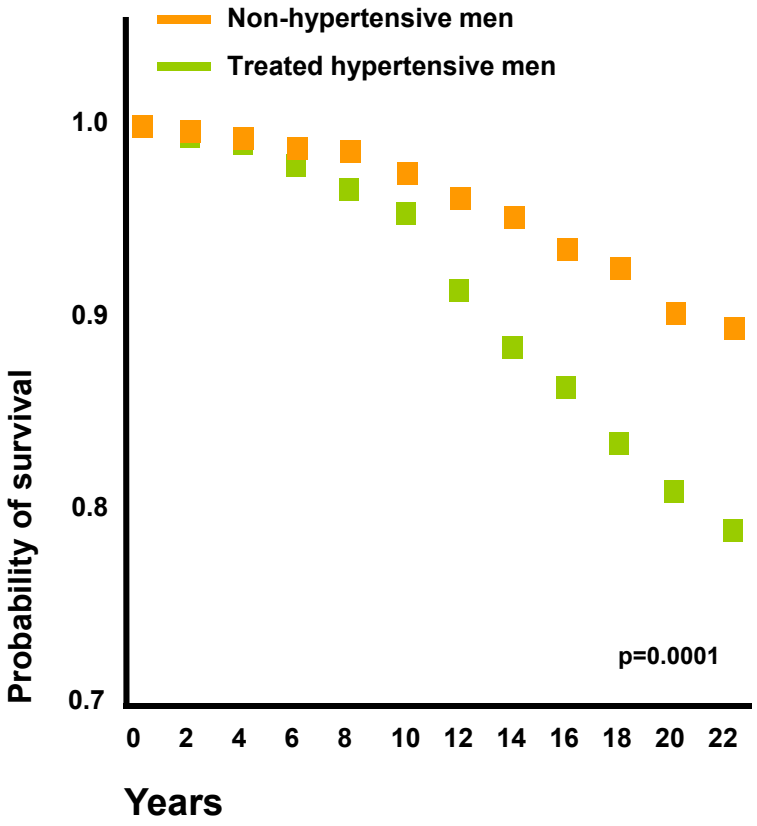
Neal B, et al. 2000

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

Overall survival

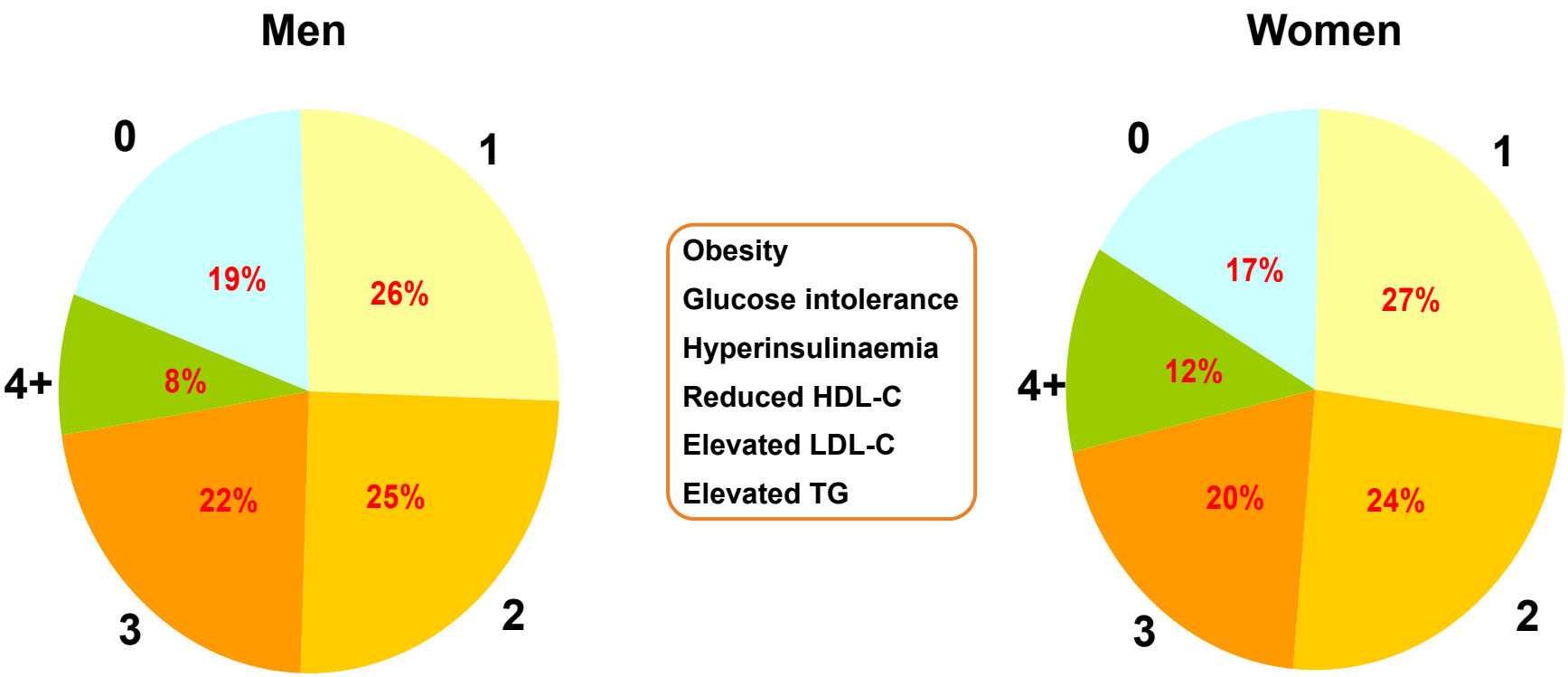


CHD deaths



Andersson OK et al., 1998

Hypertension is complicated by high prevalence of metabolic disorders



>50% have two or more comorbidities

Kannel WB *Am J Hypertens* 2000:13:3S–10S

Aims of Hypertensive Therapy

- **Reduce cardiovascular morbidity and mortality**
  - ✓ **Cardiac**
  - ✓ **Cerebrovascular**
- **Prevent or delay target-organ damage**
  - ✓ **Heart**
  - ✓ **Brain**
  - ✓ **Kidney**

Management of Hypertension

ESH–ESC and JNC 7 Guidelines Recommendations for BP Goals

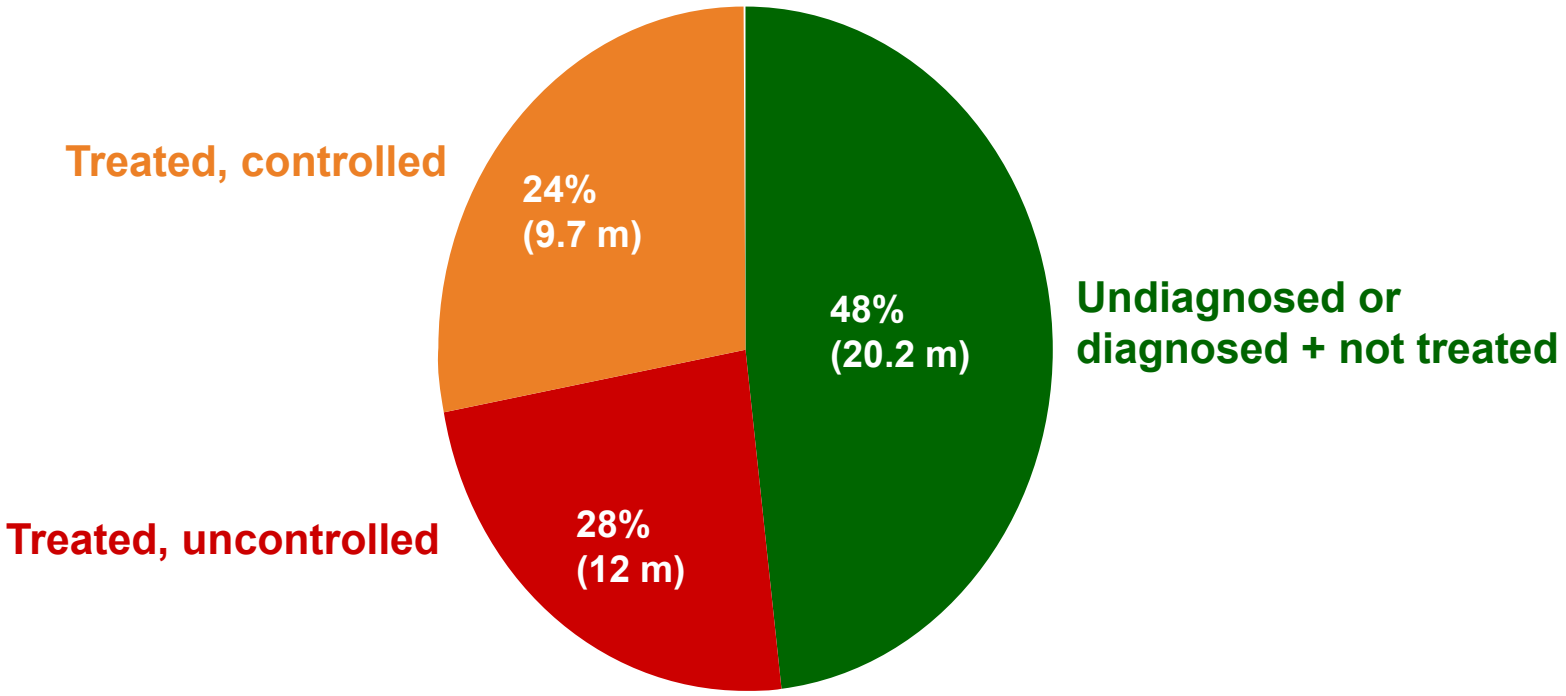
Type of hypertension	JNC 7[1] BP goal (mmHg)	ESH-ESC[2] BP goal (mmHg)
Uncomplicated	**<140/90**	**130–139/80–85**
Complicated		
Diabetes mellitus	**<130/80**	**130–139/80–85**
Kidney disease	**<130/80***	**130–139/80–85**
Other high risk (stroke, myocardial infarction)	**<130/80**	**130–139/80–85**

*Lower if proteinuria is >1 g/day

1. Chobanian et al. Hypertension 2003;42:1206–52
2. Mancia et al. Blood Pressure 2009;18:308–47

Large Population of Patients Remain…

Undiagnosed, Diagnosed and not treated, Treated but uncontrolled



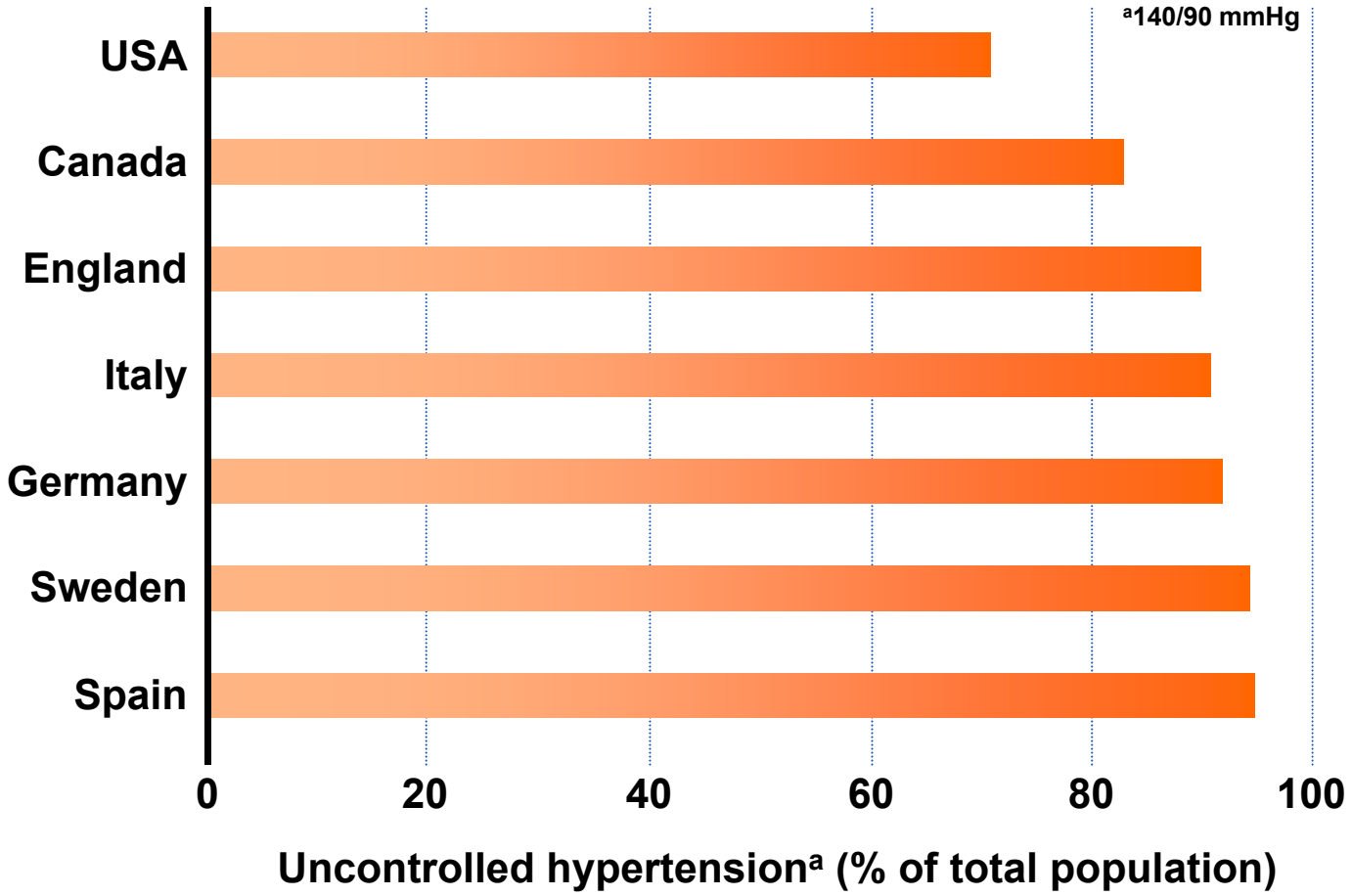
Total US hypertension[1] patients: 41.9 m

[1] Hypertension defined as 140/90 mmHg

Sources

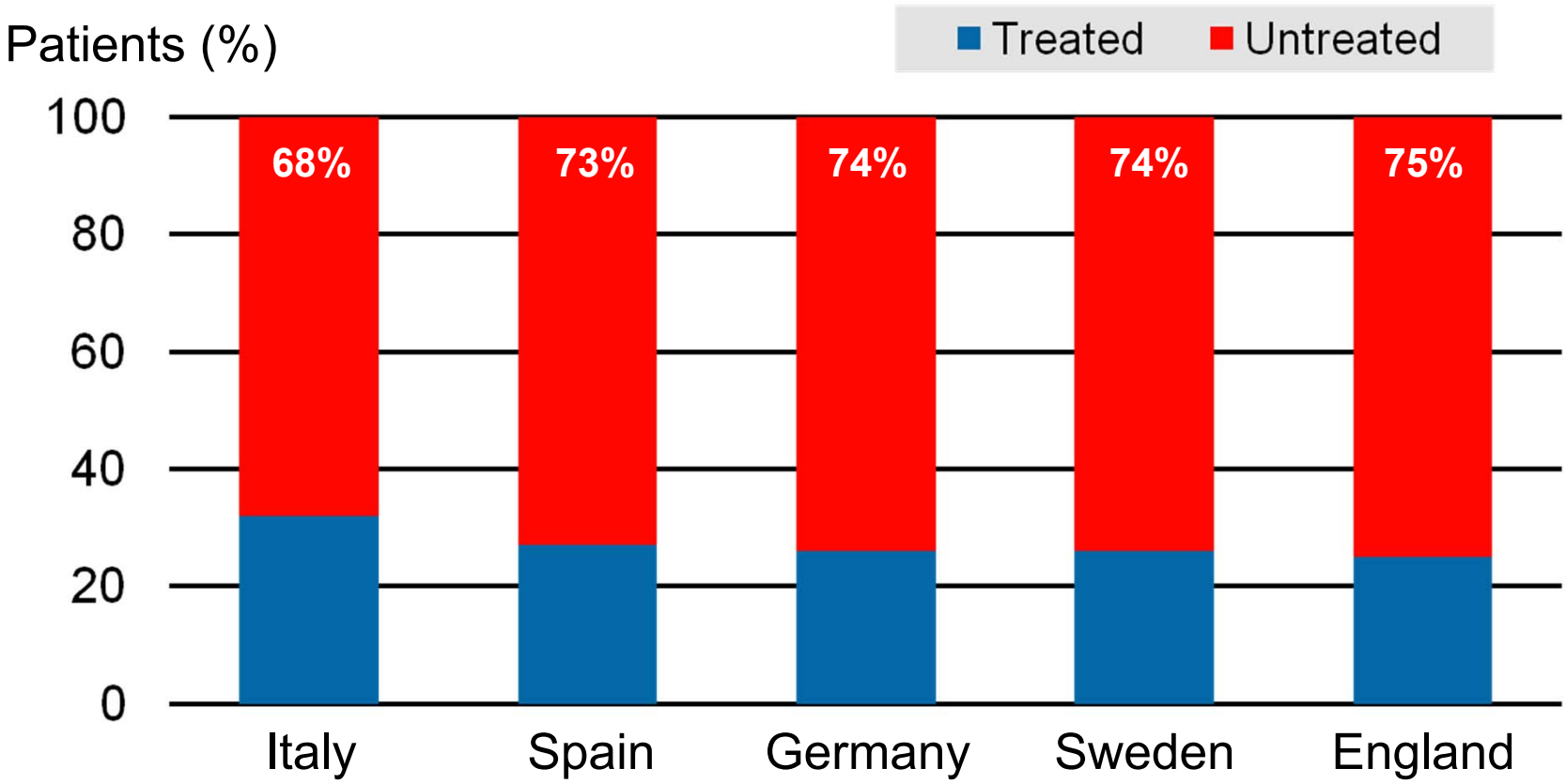
Epidemiology Database, The Mattson Jack Group, Hypertension, latest Epidata updates
Decision Resources, Decision Base 7, Hypertension Report, Mar 2003
DataMonitor,Treatment Algorithms
Hypertension 3rd edition, Jul 20, 2002

BP is poorly controlled in Europe and North America



Wolf-Maier K et al. Hypertension 2004;43:10–7

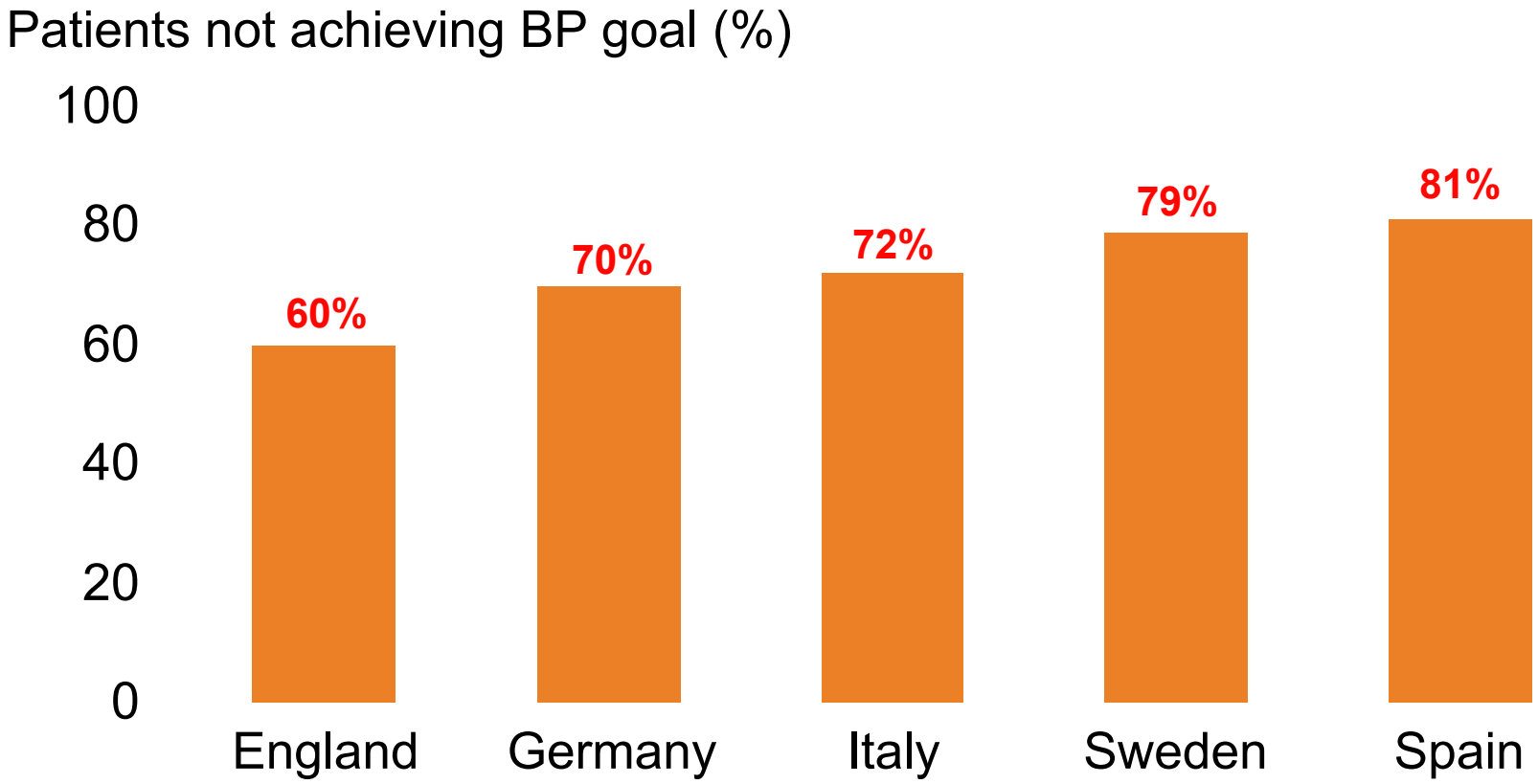
The Majority of Patients* with Hypertension in Europe Remain Untreated



*Age adjusted; patients aged 35–64 years
Hypertension = 140/90 mmHg threshold

Wolf-Maier et al. Hypertension 2004;43:10–17

Approximately 70% of Patients* in Europe Who Receive Treatment Do Not Reach BP Goal#

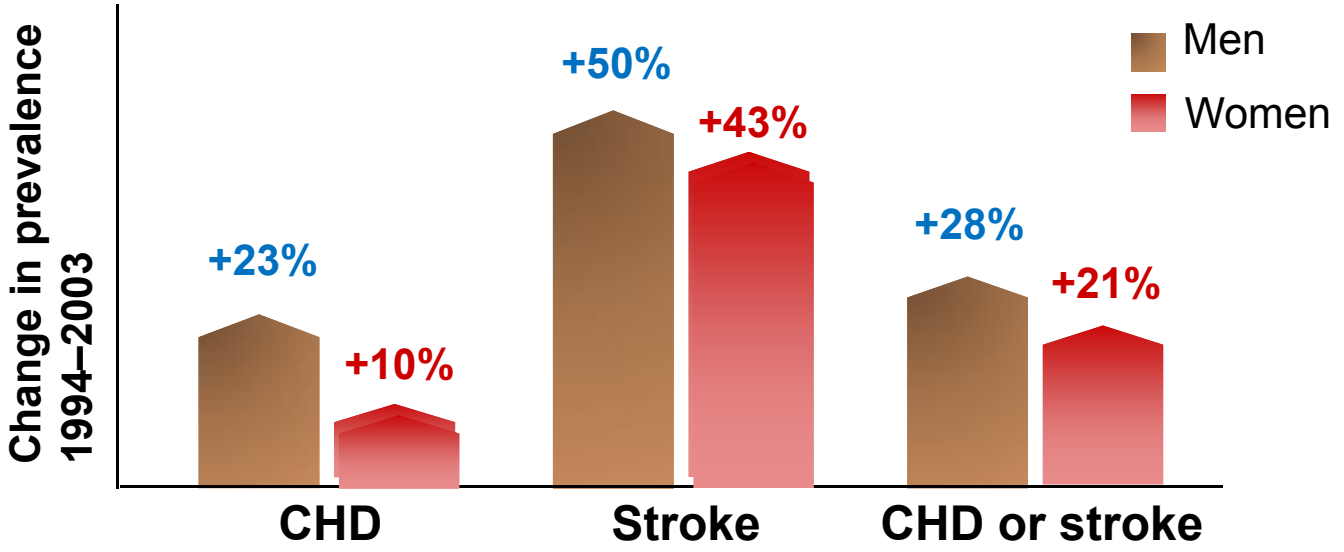


*Treated for hypertension
#BP goal <140/90 mmHg

Wolf-Maier et al. Hypertension 2004;43:10–17

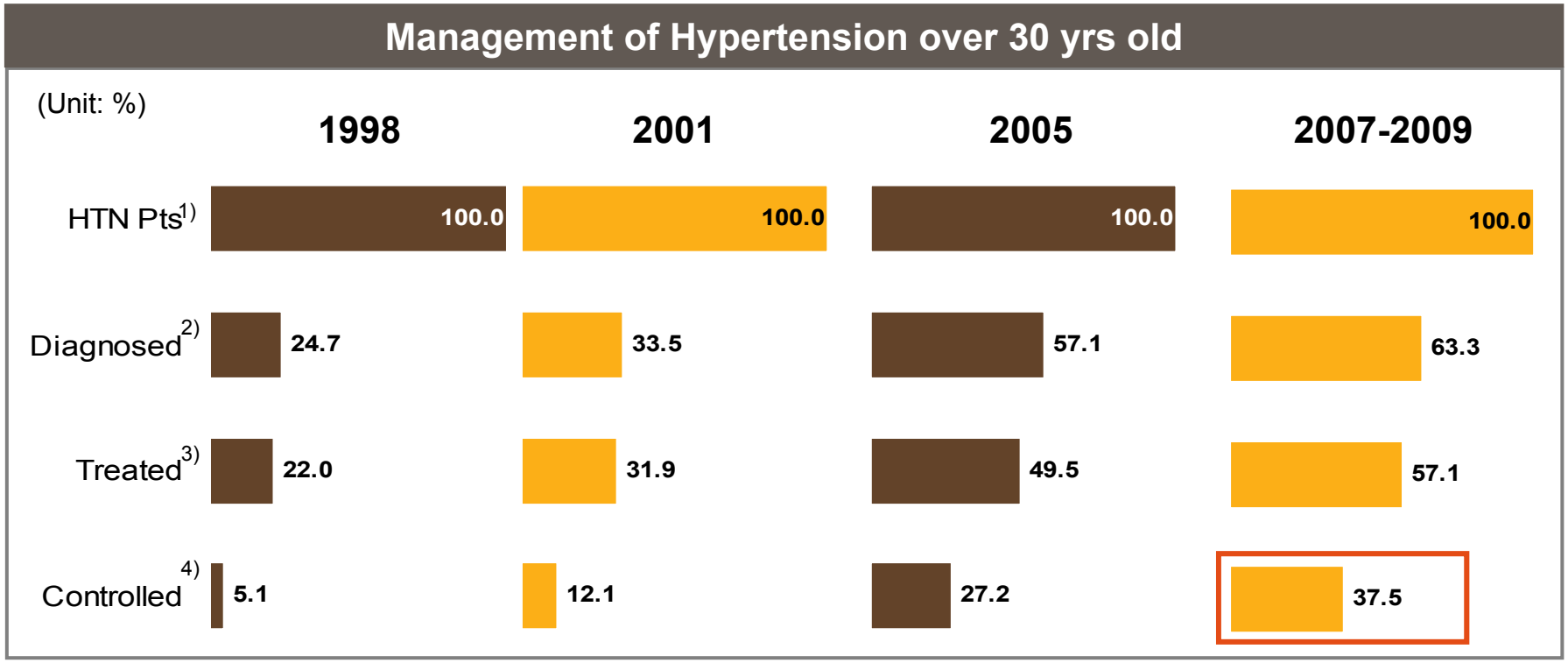
Prevalence of CVD is increasing in many countries

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



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

Approximately 62% of Hypertensive Patients have not been controlled in Korea

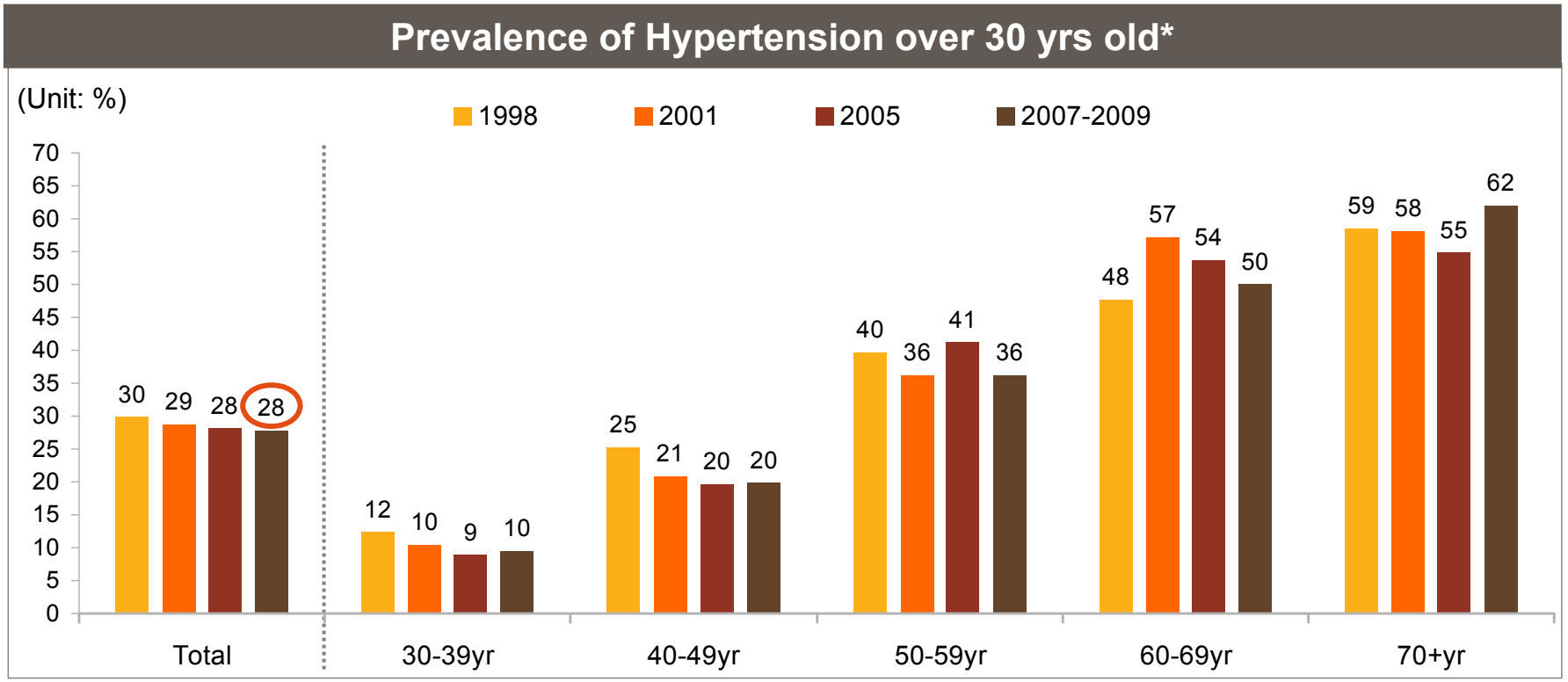


1) Definition of Hypertension: BP over 140 / 90mmHg, or taking anti-hypertensive, Over 30 yrs old
2) Diagnosis rate : Rate of having been diagnosed by medical doctors
3) Treatment rate: Ratio of taking Anti-Hypertensive everyday or more than 20 days per month
4) Control rate: Ratio of blood pressure below 140 / 90mmHg

2009 Korea National Health & Nutrition Survey

Prevalence of Hypertension in Korea

One third of those who are over 30 have a HTN and the prevalence of hypertension looks steadily decreasing over 10 years



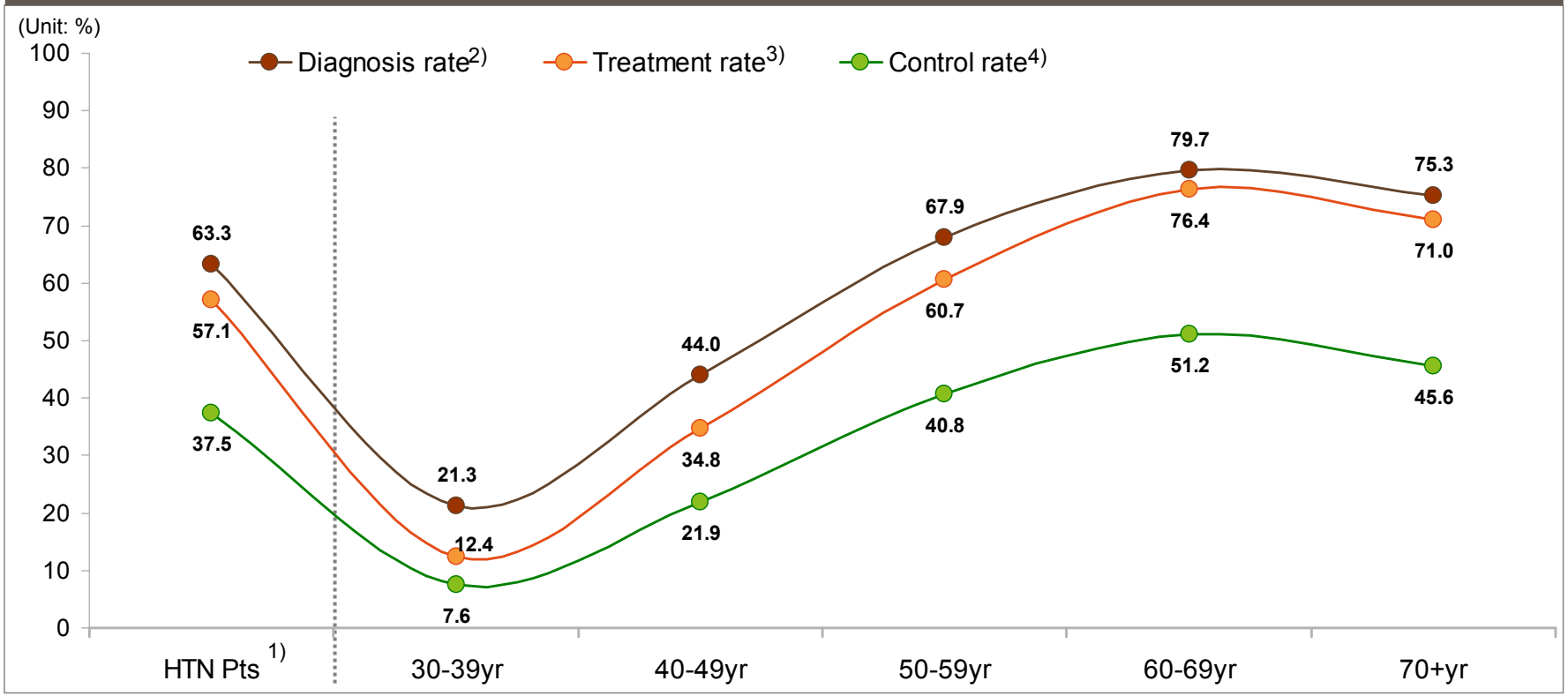
Definition of Hypertension: BP over 140 / 90 mmHg, or taking anti-hypertensive, Over 30 yrs old*

2009 Korea National Health & Nutrition Survey

Management of Hypertension

The younger HTN patients are, the poorer management of hypertension is shown

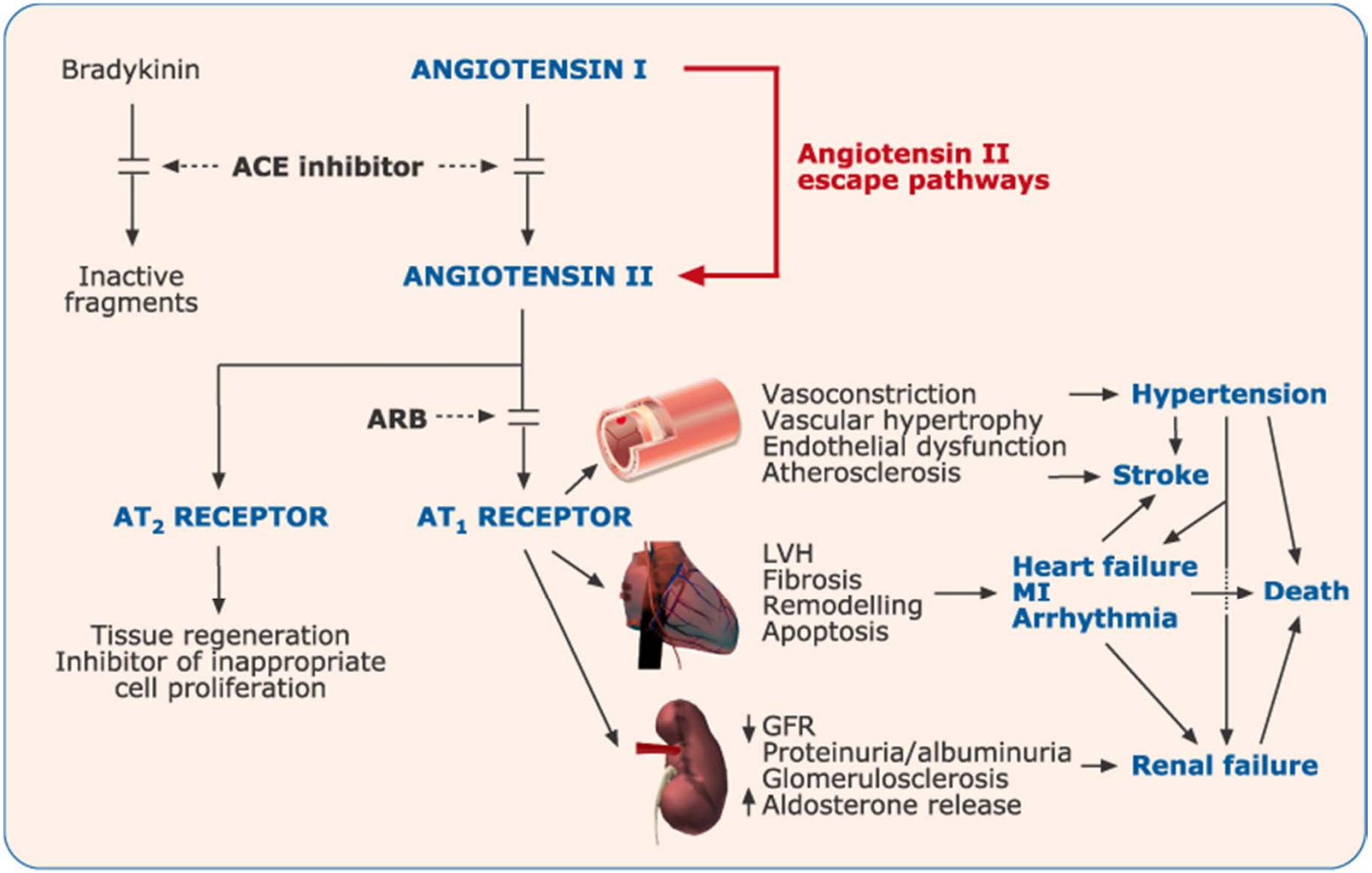
Management of Hypertension among HTN patients



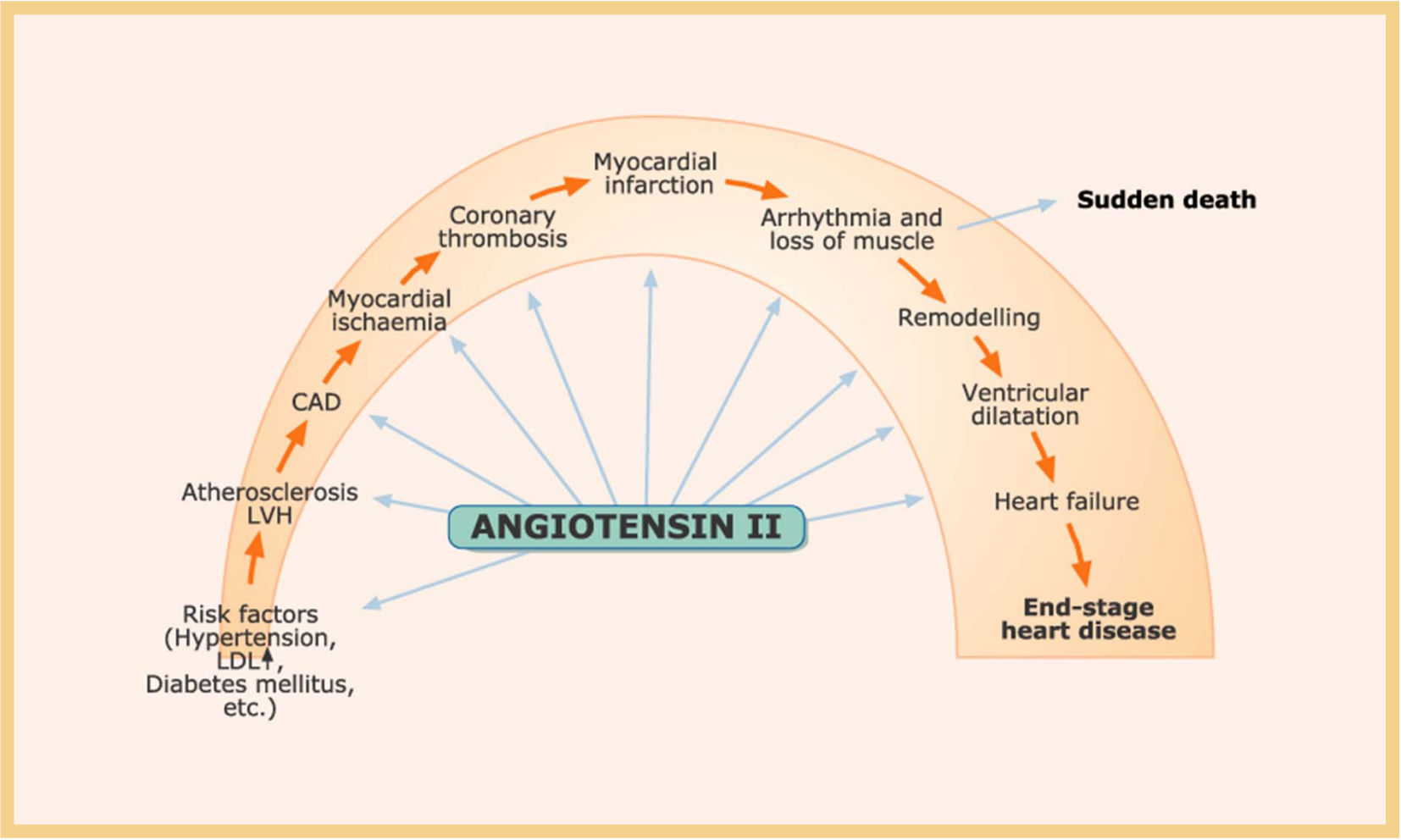
1) Definition of Hypertension: BP over 140 / 90mmHg, or taking anti-hypertensive, Over 30 yrs old
2) Diagnosis rate : Rate of having been diagnosed by medical doctors
3) Treatment rate: Ratio of taking Anti-Hypertensive everyday or more than 20 days per month
4) Control rate: Ratio of blood pressure below 140 / 90mmHg

What is the Valsartan?

ARB: Mechanism of Action



Cardiovascular Disease



ARB: How Does it Work?

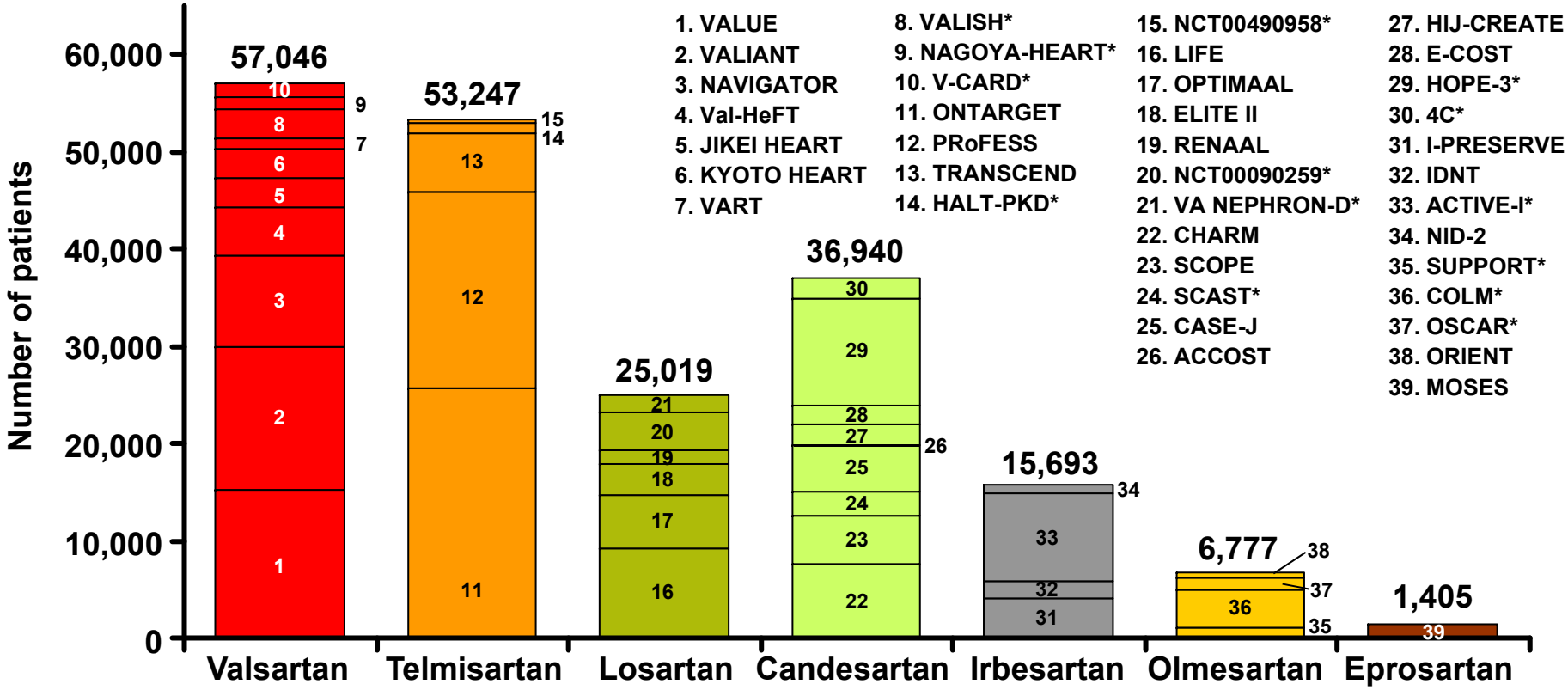
- By binding to the AT_1 receptor, ARB prevents the binding of angiotensin II produced by the renin-angiotensin-aldosterone system (RAAS) thereby blocking:
  - Sodium reabsorption
  - Aldosterone release
  - Vasoconstriction
  - Activation of the sympathetic nervous system

  all of which can increase blood pressure (BP)

ARB: Further Benefits

- ARB allows continued activation of the angiotensin II type 2 (AT_2) receptor, which is thought to counteract AT_1 receptor-mediated actions
- ARB can inhibit the effects of circulating and tissue angiotensin II, resulting in more complete RAAS blockade than that seen with ACE inhibitors (ACE-Is)
- ARB is not associated with the dry cough seen with ACE inhibition because it does not interfere with the breakdown of bradykinin

Angiotensin Receptor Blockers Have a Wealth of Outcomes Data



*Expected enrolment

‡Ongoing and completed randomized controlled trials with death or hard CV events as or part of the primary endpoint

¶Valid as of December 2009

1. Julius et al. 2004; 2. Pfeffer et al. 2003; 3. Califf et al 2008; 4. Cohn et al. 2001; 5. Mochizuki et al. 2007; 6. Sawada et al 2009; 7. Narumi et al. 2009 [abstract at ESC]; 8. http://clinicaltrials.gov (NCT00151229); 9. http://clinicaltrials.gov (NCT00129233); 10. http://clinicaltrials.gov (NCT00140790); 11. ONTARGET Investigators 2008; 12. Yusuf et al 2008; 13. TRANSCEND Investigators 2008; 14. http://clinicaltrials.gov (NCT00283686); 15. http://clinicaltrials.gov (NCT00490958); 16. Dahlöf et al. 2002; 17. Dickstein et al. 2002; 18. Pitt et al. 2000; 19. Brenner et al. 2001; 20. http://clinicaltrials.gov (NCT00090259); 21. Fried et al 2009; 22. Pfeffer et al 2003; 23. Papademetriou et al. 2004; 24. http://clinicaltrials.gov (NCT00120003); 25. Ogihara et al. 2008; 26. http://clinicaltrials.gov (NCT00108706); 27. Laufs et al. 2008; 28. Suzuki et al. 2005; 29. http://clinicaltrials.gov (NCT00468923); 30. http://clinicaltrials.gov (NCT00139386); 31. Massie et al 2008; 32. Lewis et al. 2001; 33. http://clinicaltrials.gov (NCT00249795); 34. http://clinicaltrials.gov (NCT00535925); 35. http://clinicaltrials.gov (NCT00417222); 36. Ogihara et al 2009; 37. Ogawa et al 2009; 38. Imai et al. 2009 (Abstract F-FC313 at ASN 2009); 39. Schrader et al. 2005

Valsartan has a Wealth of CV Outcomes Data

VALUE[1] **15,245 high-risk patients with hypertension; Double-blind, randomized study vs. amlodipine**	**No difference in composite of cardiac mortality and morbidity (primary)** **23% ↓ new-onset diabetes**
VALIANT[2] **14,703 post-myocardial infarction patients; Double- blind, randomized study vs. captopril and vs. captopril + Diovan**	**No difference vs. captopril in all-cause mortality (primary)** **(Diovan is as effective as standard of care)**
Val-HeFT[3–5] **5,010 heart failure II–IV patients; Double-blind, randomized study vs. placebo**	**13% ↓ morbidity and mortality (primary)** **↓ left ventricular remodeling** **37% ↓ atrial fibrillation occurrence** **↓ heart failure signs/symptoms** **28% ↓ heart failure hospitalization**
MARVAL[6] 332 patients with T2D + microalbuminuria ± HTN: Multicenter, randomized, double-blind, active-controlled study vs. amlodipine (Primary endpoint: % change in urinary albumin excretion rate (UAER) over 6 months)	**44% ↓ in UAER vs. baseline with Diovan vs. 8% with amlodipine** **15.4% between-group difference favoring Diovan in patients returning to normoalbuminuria**

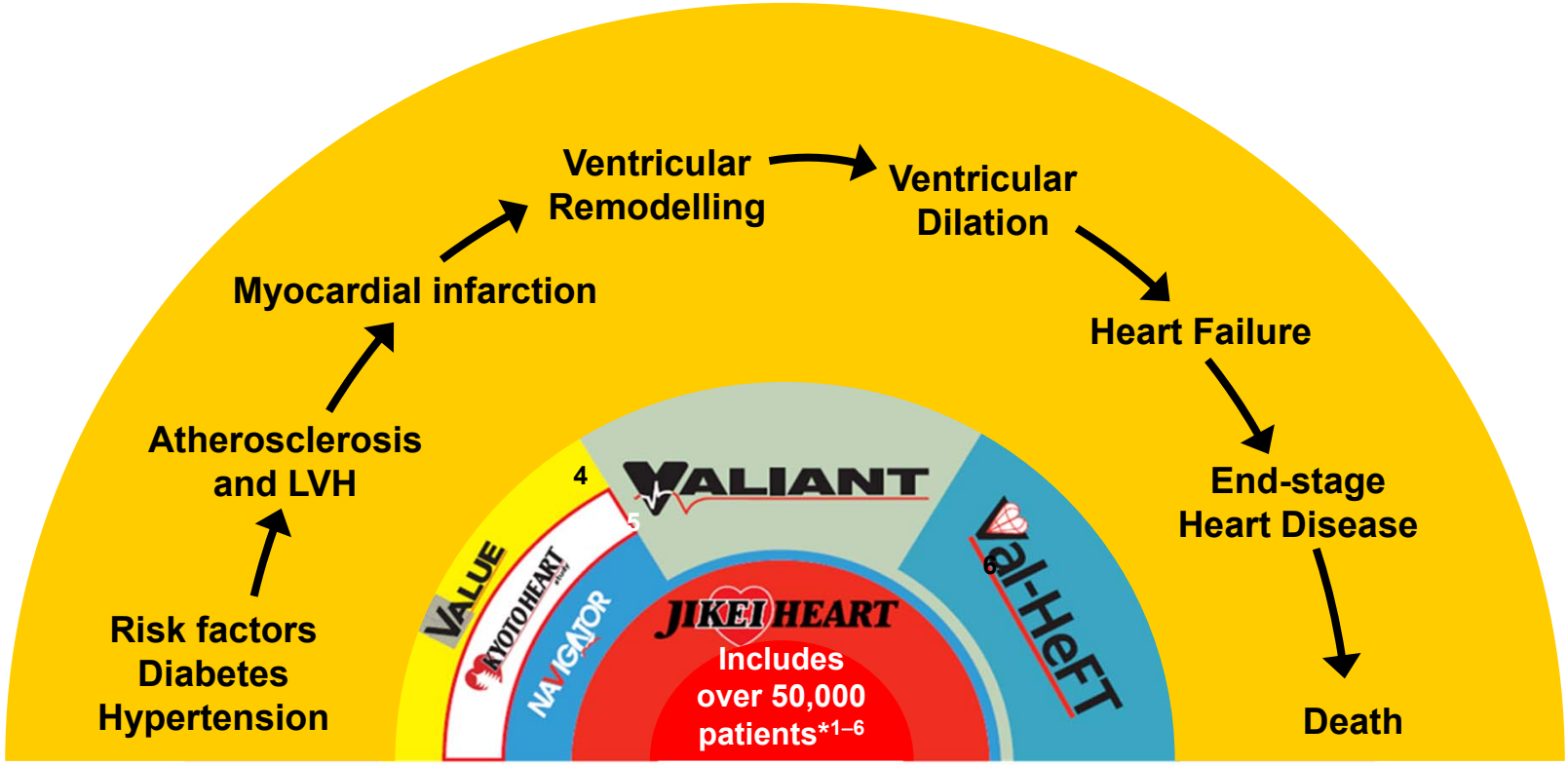
1. Julius et al. Lancet 2004;363:2022–31;
2. Pfeffer et al. N Engl J Med 2003;349:1893–906;
3. Maggioni et al. Am Heart J 2005;149:548–57;
4. Wong et al. J Am Coll Cardiol 2002;40:970–5;
5. Cohn et al. N Engl J Med 2001;345:1667–7;
6. Viberti et al. Circulation 2002;106:672–8

Valsartan has a Wealth of CV Outcomes Data

JIKEI HEART[7] **3,081 Japanese patients on conventional treatment for hypertension, coronary heart disease, heart failure or combination of these; Multicenter, randomized, controlled trial comparing addition of Diovan vs. non-ARB to conventional treatment**	**39% ↓ composite CV mortality and morbidity** **40% ↓ Stroke/transient ischemic attack** **47% ↓ Hospitalization for heart failure** **65% ↓ Hospitalization for angina**
KYOTO HEART[8] **3,031 Japanese patients on conventional treatment for hypertension and high CV risk; Multicentre PROBE trial comparing addition of Diovan vs non-ARB to conventional treatment**	**45% ↓ Composite CV mortality and morbidity** **45% ↓ Stroke/transient ischemic attack (TIA)** **49% ↓ Angina pectoris** **33% ↓ New-onset diabetes**
NAGOYA study[9] **1,150 Japanese patients with T2DM or IGT(Impaired Glucose Tolerance); Multicentre PROBE trial comparing addition of Diovan vs Amlodipine to conventioal treatment**	**No difference in composite of cardiac mortality and morbidity (primary)** **33% ↓ congestive heart failure**

7. Mochizuki et al. Lancet 2007;369:1431–9;
8. Sawada et al. Eur Heart J 2009;30:2461–69
9. Kunihiri M. et al NAGOYA HEART study : Apr. 2011 ACC

Valsartan: Extensively Studied Across the CV Continuum



1. Julius et al. Lancet 2004; 363:2022–31; 2. Pfeffer et al. N Engl J Med 2003;349:1893–906
3. Cohn et al. N Engl J Med 2001; 345:1667–75; 4. Sawada et al. Eur Heart J 2009;30:2461–69
5. Califf et al. Am Heart J 2008;156:623–32; 6. Mochizuki et al. Lancet 2007;369:1431–9

ARBs in CHF

	ELITE II	Val-HeFT	CHARM
	Losartan 50 OD vs Captopril 25 tid	Valsartan 40-160 BID add on Standard Tx vs Standard Tx	Candesartan 8-32 OD add on Stardard Tx vs Standard Tx
N	3,152	5,010	7,601
Primary endpoint	All-cause mortality: NS **"No Approved Indication"**	All-cause mortality: NS All-cause M/M: - Overall population : ACEI+ARB = -13.2% - Subgroup w/o ACEI: ARB = -44.5% **" Approved Indication"**	All-cause mortality: NS CV death or HF hospitalization: - CHARM Added: ACEI+ARB = -15% - CHARM Alternative: ARB = -30% - CHARM Preserved: NS **" Approved Indication"**

ARBs in Post MI

	OPTIMAAL	VALIANT
	Captopril vs. Losartan	Captopril vs. Valsartan vs. Combination
N	5,477	14,703
Primary endpoint: **All-cause mortality**	**Captopril vs. Losartan** **RR 1.13** (95% CI; 0.99 – 1.28) ***p* = 0.069**	**Valsartan vs. Captopril:** **HR = 1.00; P = 0.982** **Valsartan + Captopril vs. Captopril:** **HR = 0.98; P = 0.726**
Conclusion	**Study revealed that losartan was not superior to captopril, and *losartan was not shown to be equivalent to captopril*** **"No Approved Indication"**	**Valsartan is *as effective as* a proven dose of captopril in reducing the risk of:** **- Death** **- CV death or nonfatal MI or heart failure admission** **"Approved Indication"**

Valsartan(Diovan®): Who is it Intended For?*

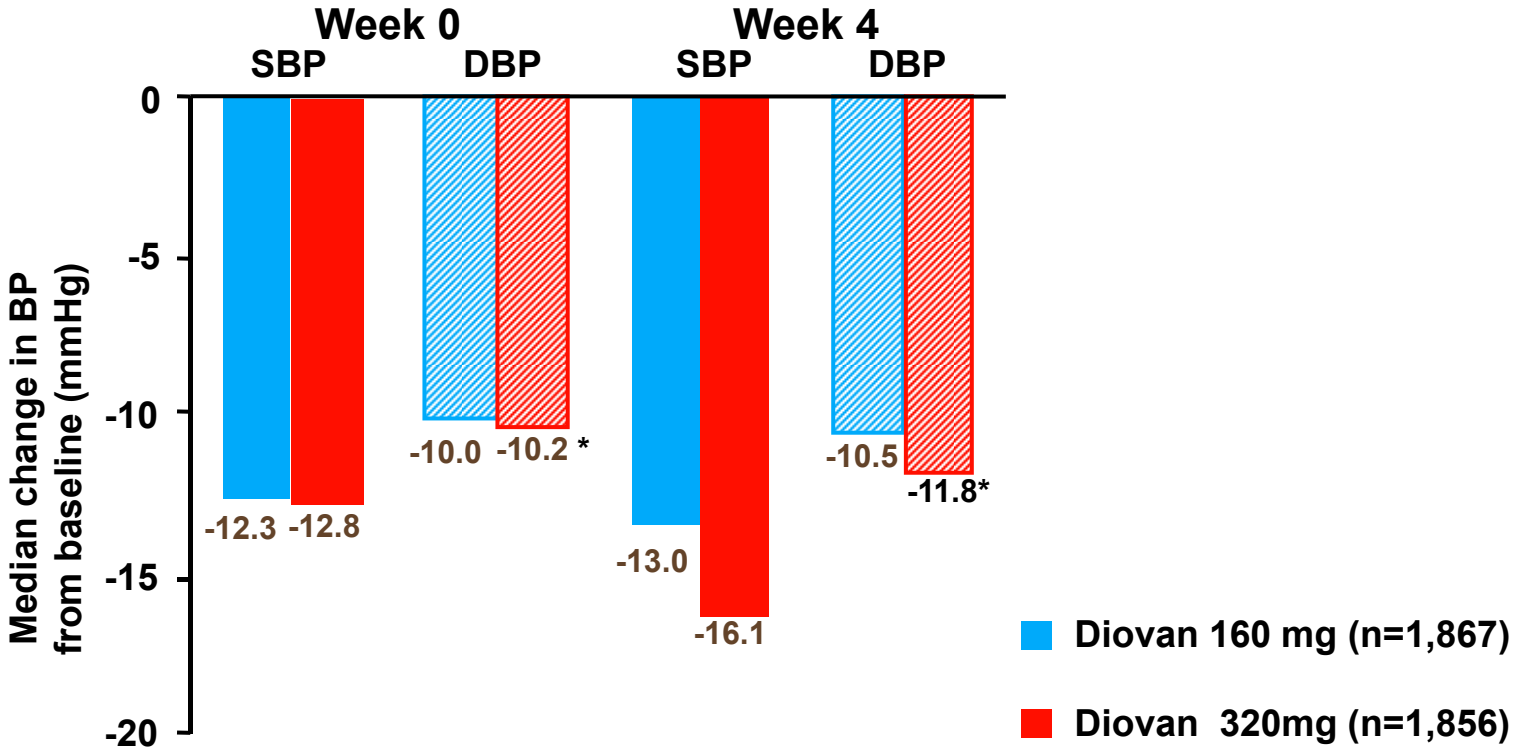
- Valsartan is indicated for use in patients with:
  - Hypertension (with or without other antihypertensive agents)
  - Post-myocardial infarction (MI) (to improve survival after MI in clinically stable patients with signs, symptoms or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction [LVSD])
  - Heart failure (HF) (patients receiving usual therapy such as diuretics, digitalis and either ACE-Is or beta-blockers but not both)
- Co-Diovan (Diovan + hydrochlorothiazide [HCTZ]) is indicated for use in:
  - Hypertension (with inadequate BP control by monotherapy) as second-line therapy

***Licensed indications**

The efficacy of High-dose Valsartan

High dose of valsartan provides more BP reduction in mild-to-moderate Hypertensive patients

Results from a 8-week study in 3776 patients with mild-to-moderate HTN patients (**ValTop study**)

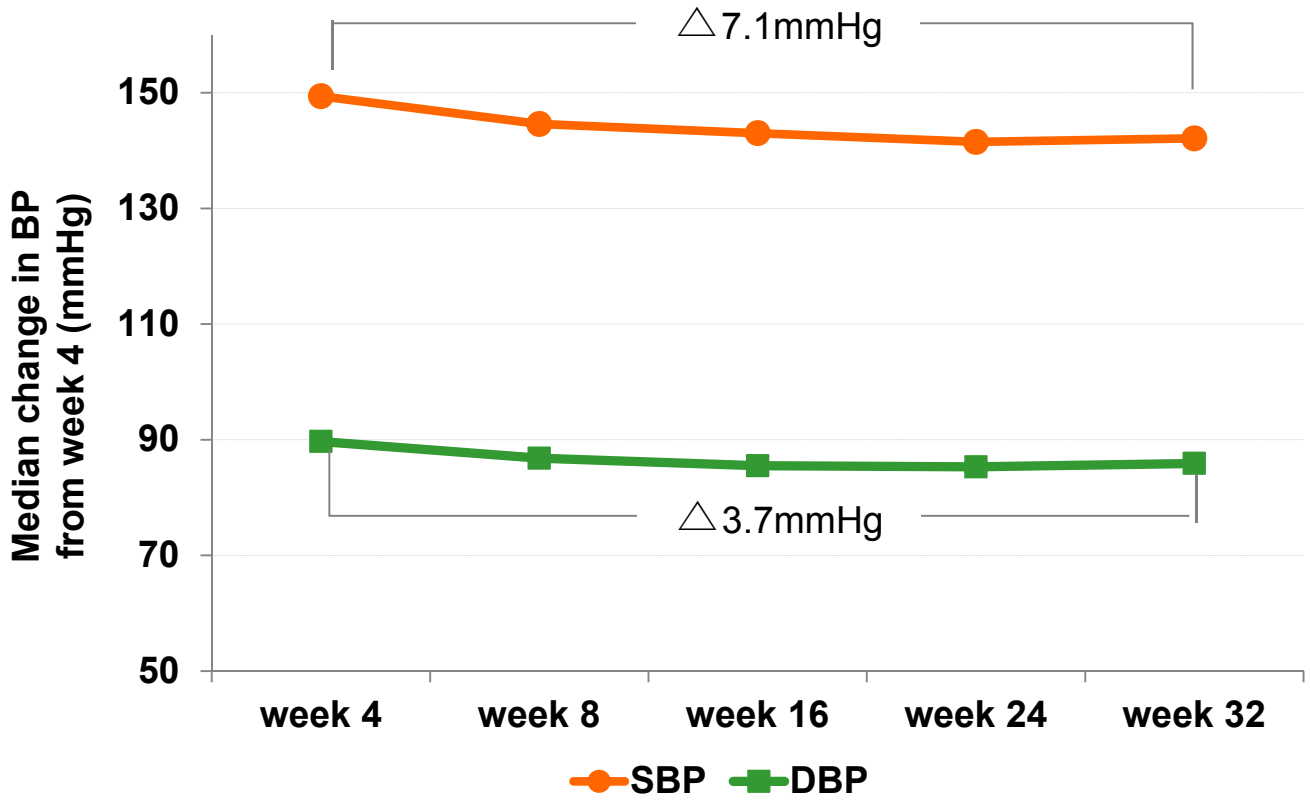


-4~0-week open-label treatment with Diovan 160mg.(MSDBP : 90~109mmHg)
0~4-week double-blind treatment with either 160 or 320mg Diovan.
#ITT population, *p<0.0001 vs. Diovan 160mg group

Parati et al. *Hypertension reseach* 2010;33:986-994

High-dose valsartan in Monotherapy is both safe and effective in mild-to-moderate uncomplicated hypertensive patients over relatively long periods of time

Results from an 28-week extension study in 642 patients with valsartan 320mg (**ValTop study**)

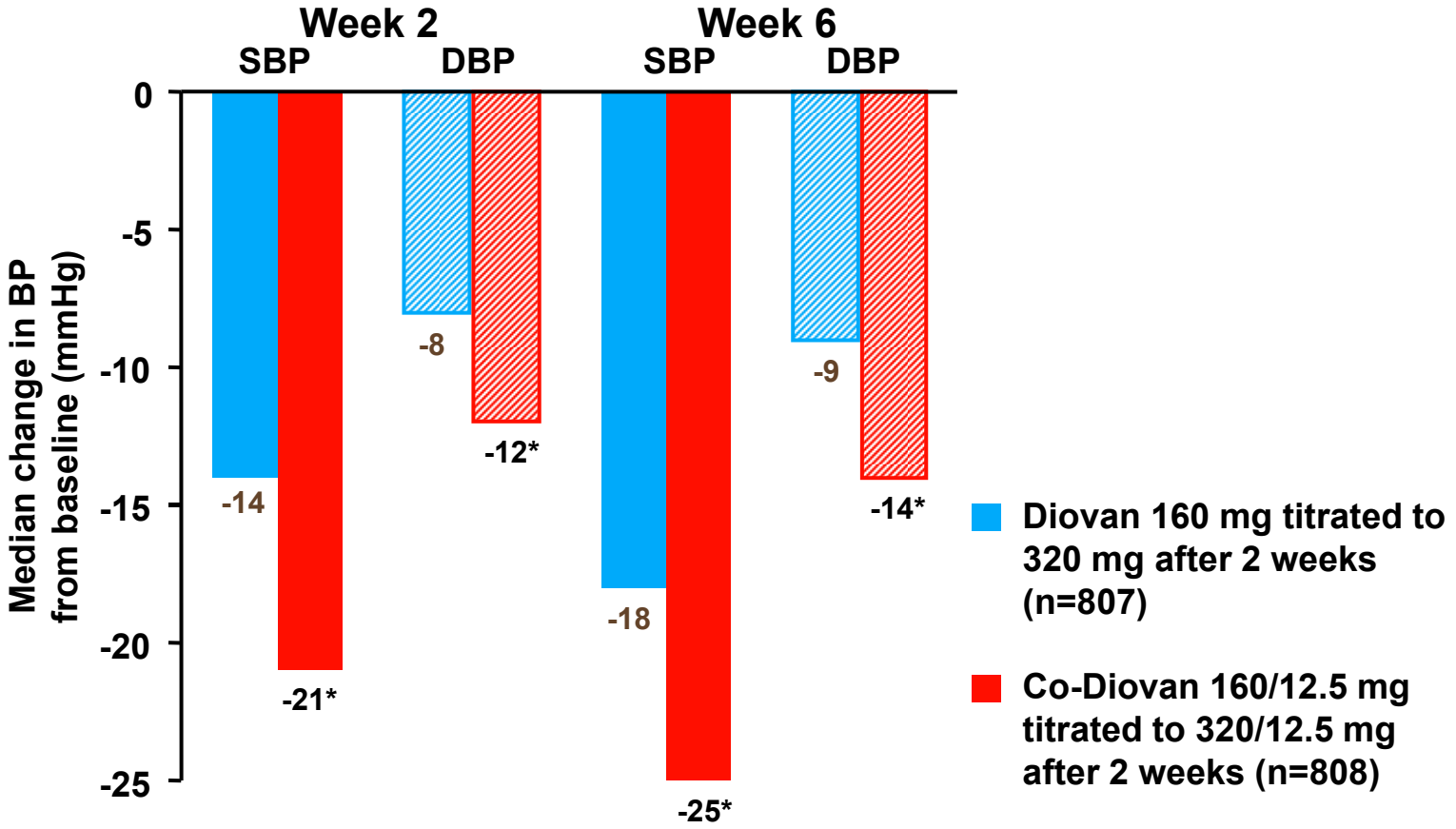


Extension study : 28-week open-label treatment with Diovan 320mg after core trial(total 8-week; 4-week open-label Diovan 160mg, 4-week double -blind 160mg vs 320mg treatment)

Parati et al. *Hypertension reseach* 2010;33:986-994

Diovan and Co-Diovan Provide Rapid and Powerful Median BP Reductions

Results from a 12-week study in 1615 patients with stage 2 hypertension[#]
(**Val-MARC study**)

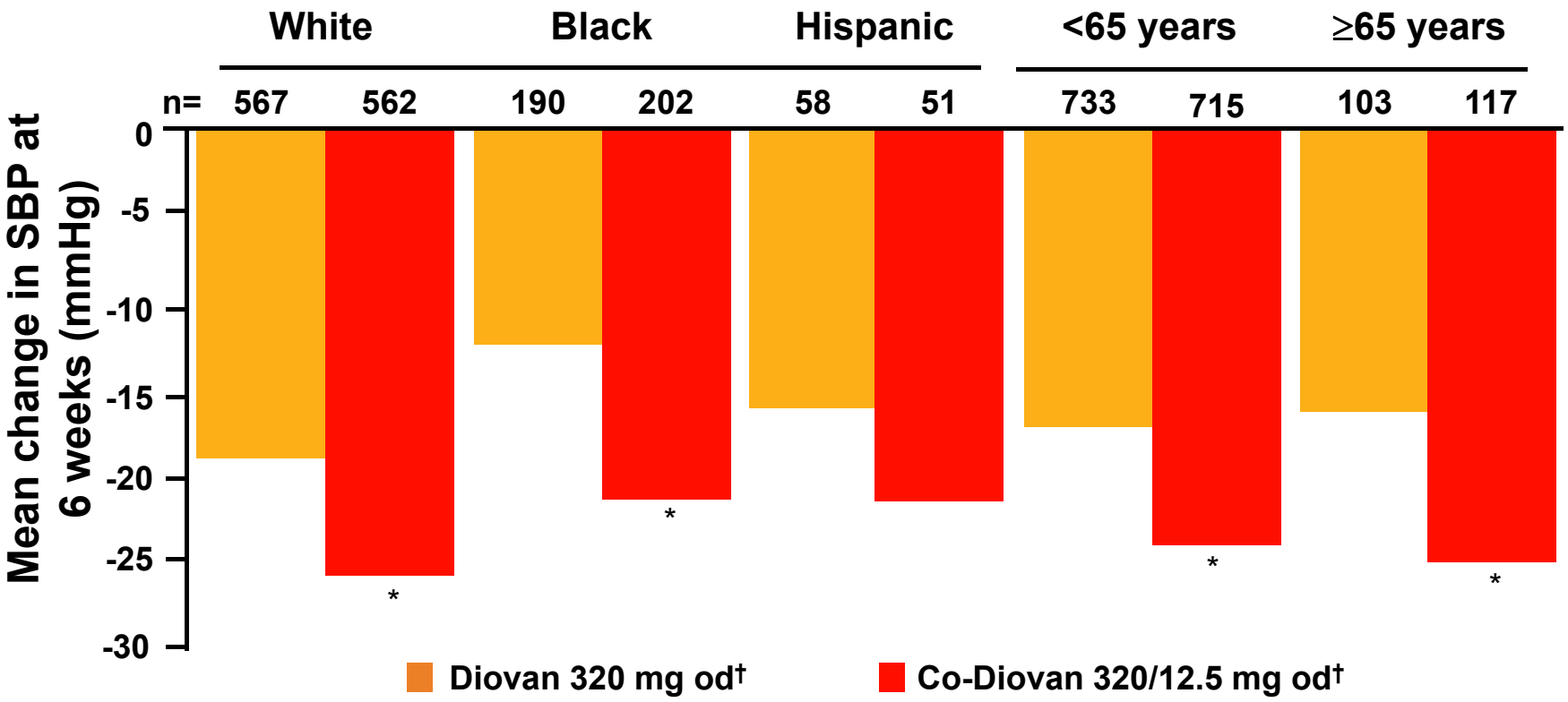


[#]ITT population, SBP/DBP ≥160/100 and BP >185/109 mmHg were excluded; *p<0.001 vs. monotherapy

Ridker et al. *Hypertension* 2006;48(1):73-79

Diovan and Co-Diovan as Initial Therapy Effectively Reduces SBP Across Age and Race

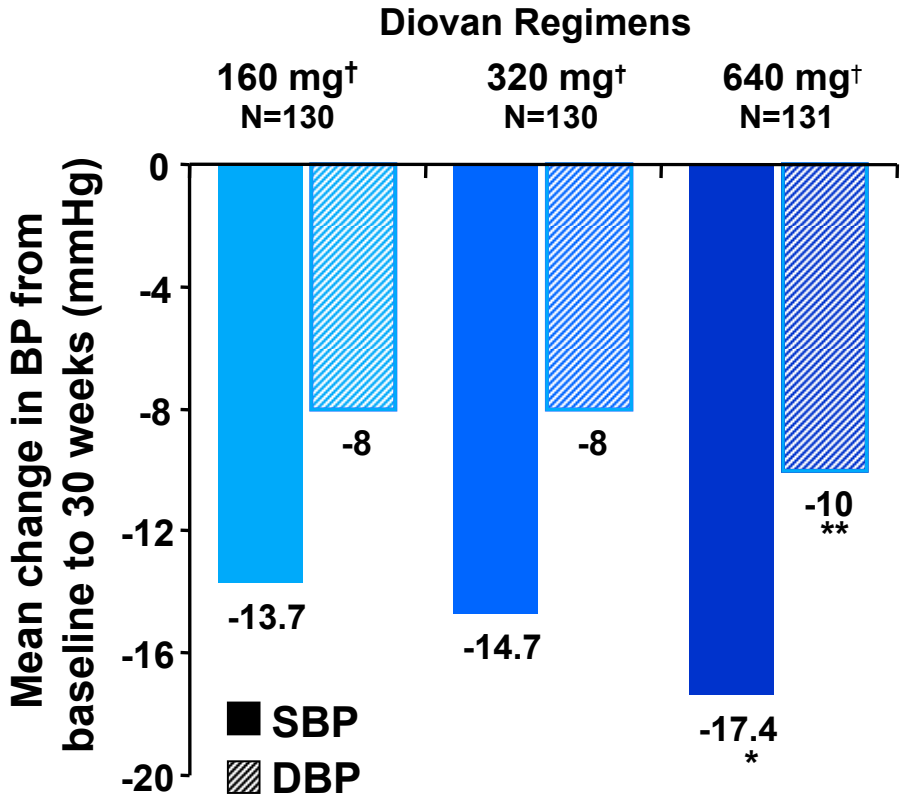
Results from a 12-week study (6-week subgroup analysis) in patients with stage 2 HTN[#] (**Val-MARC study subgroup analysis**)

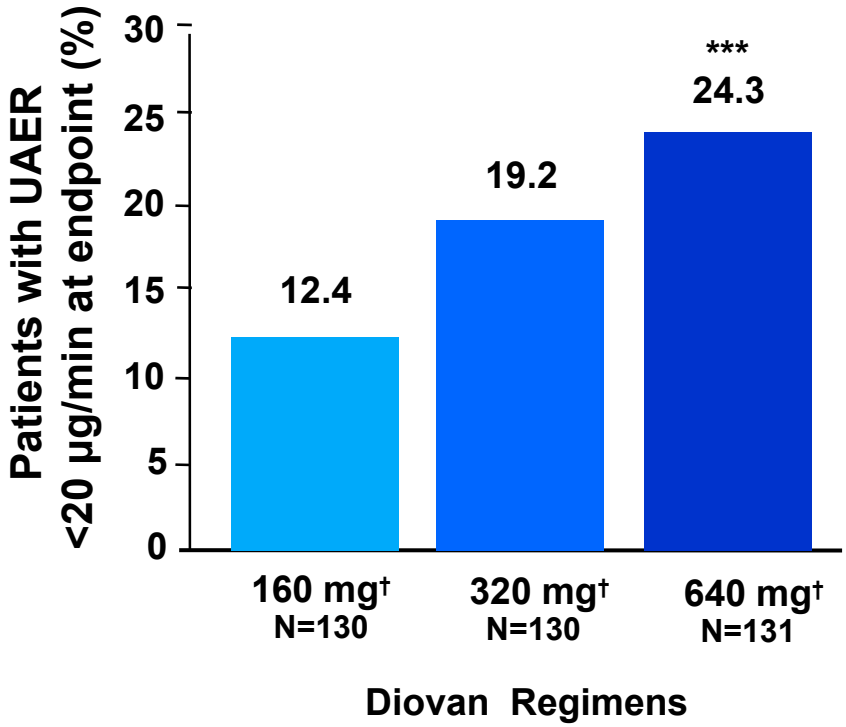


[#]1668 patients with SBP ≥160 mmHg and/or DBP ≥100 mmHg; †Diovan 160 mg od or Co-Diovan 160/12.5 mg; force-titrated to 320 mg or 320/12.5 mg od after 2 weeks; HCTZ 12.5 mg add-on to either regimen after 6 weeks for further BP control; *p≤0.01 vs. Diovan; HTN=Hypertension; SBP=Systolic blood pressure; Everett et al. *Clin Ther* 2008;30:661-72

High-dose Valsartan Produces Additional BP Control and Renal Protection

Results from a 30-week study in 391 patients with hypertension[#], proteinuria and type 2 diabetes mellitus (**DROP study**)



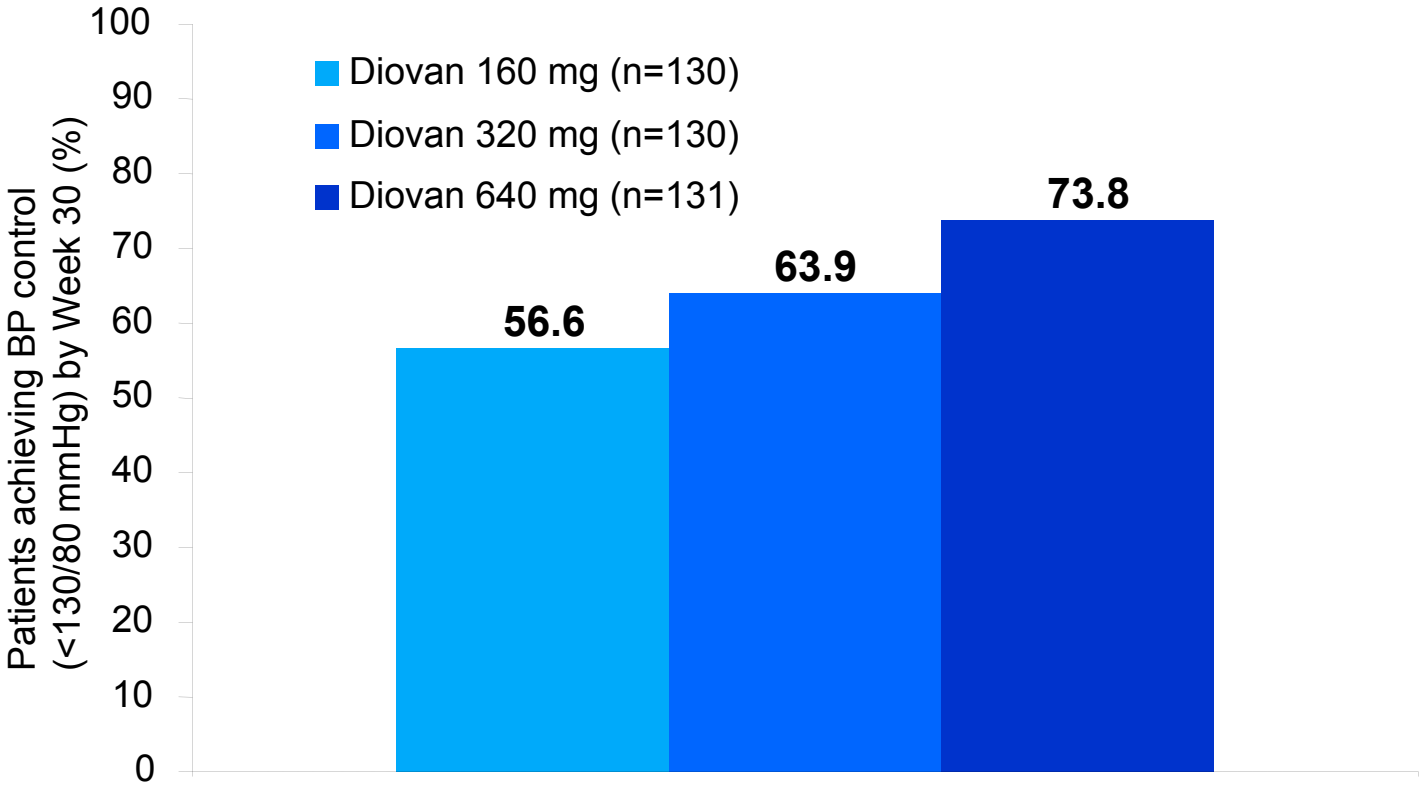


[#]Mean SBP/DBP>150/85 mmHg; †Additional antihypertensive therapy allowed at 6 weeks (excluding ACEi, aldosterone blockers or other ARBs); *p=0.07 vs. 160, p=0.08 vs. 320; **p=0.05 vs. 160 p=0.045 vs. 320; ***p<0.05 vs. 160 mg

Hollenberg et al. presented at American Heart Association Meeting 2006

Proportion of Patients who Achieved BP Goal of <130/80 mmHg by Week 30

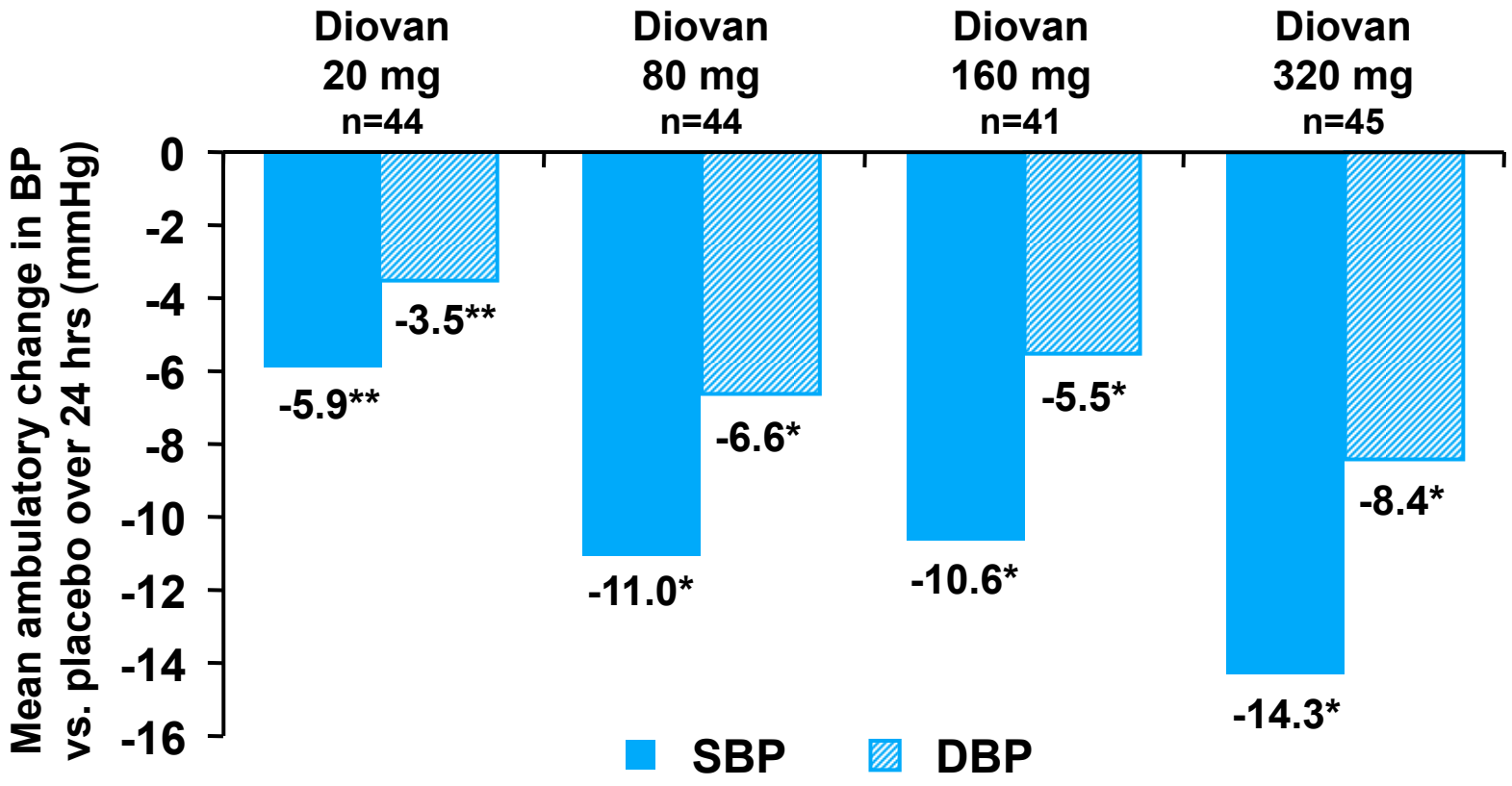
Results from a 30-week study in 391 patients with hypertension#, proteinuria and type 2 diabetes mellitus (**DROP study**)



Hollenberg et al. presented at American Heart Association Meeting 2006

Valsartan doses provide effective SBP/DBP control over 24 Hours

Results from a 8-week study in 216 outpatients† with uncomplicated hypertension#

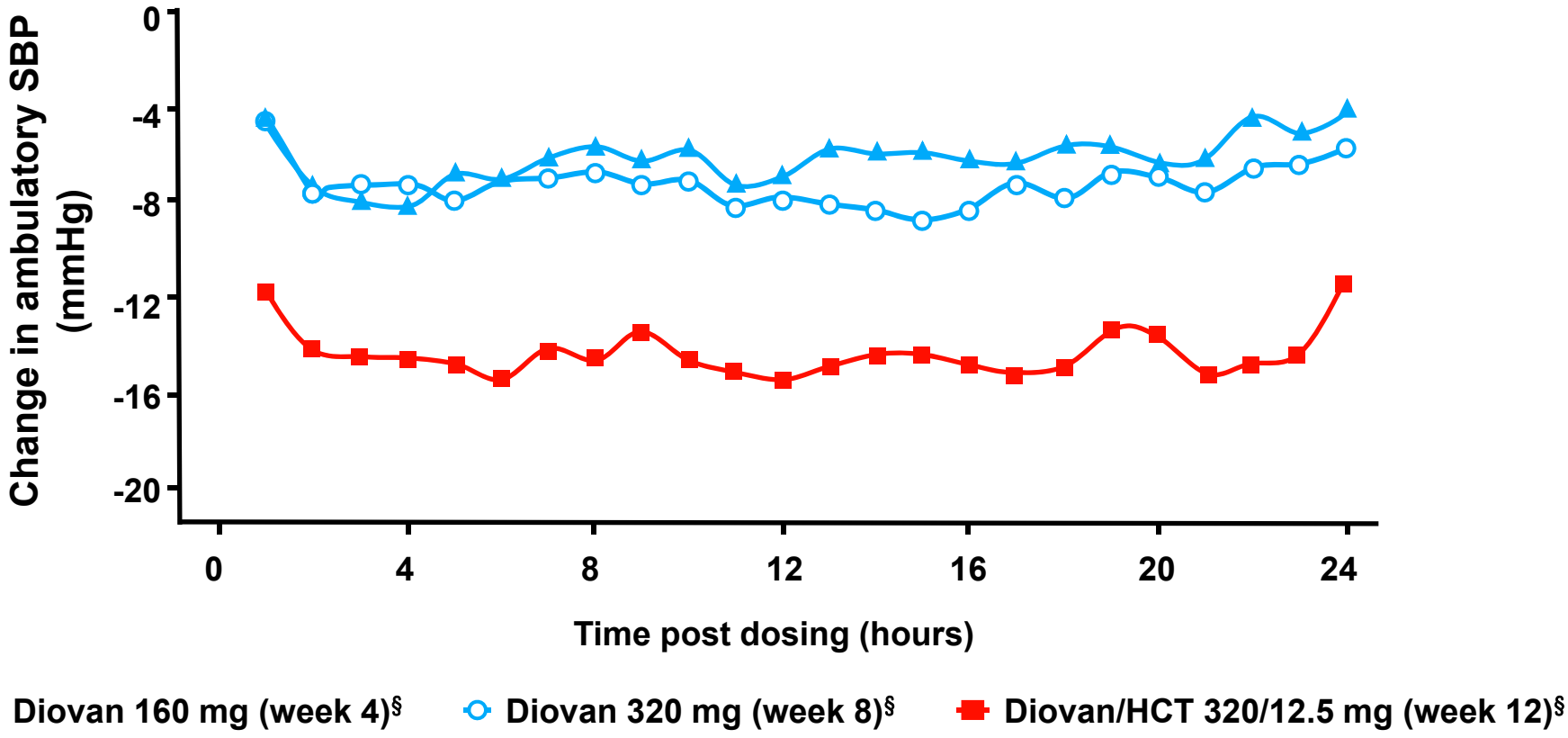


†ITT population; #DBP ≥95 and ≤115 mmHg; *p<0.001 vs. placebo; **p=0.010 for DBP, p=0.008 for SBP vs. placebo

Neutel et al. *Clin Ther* 1997;19(3):447-458

Diovan and Co-Diovan Provide Powerful 24-Hour BP Control in Patients with HTN

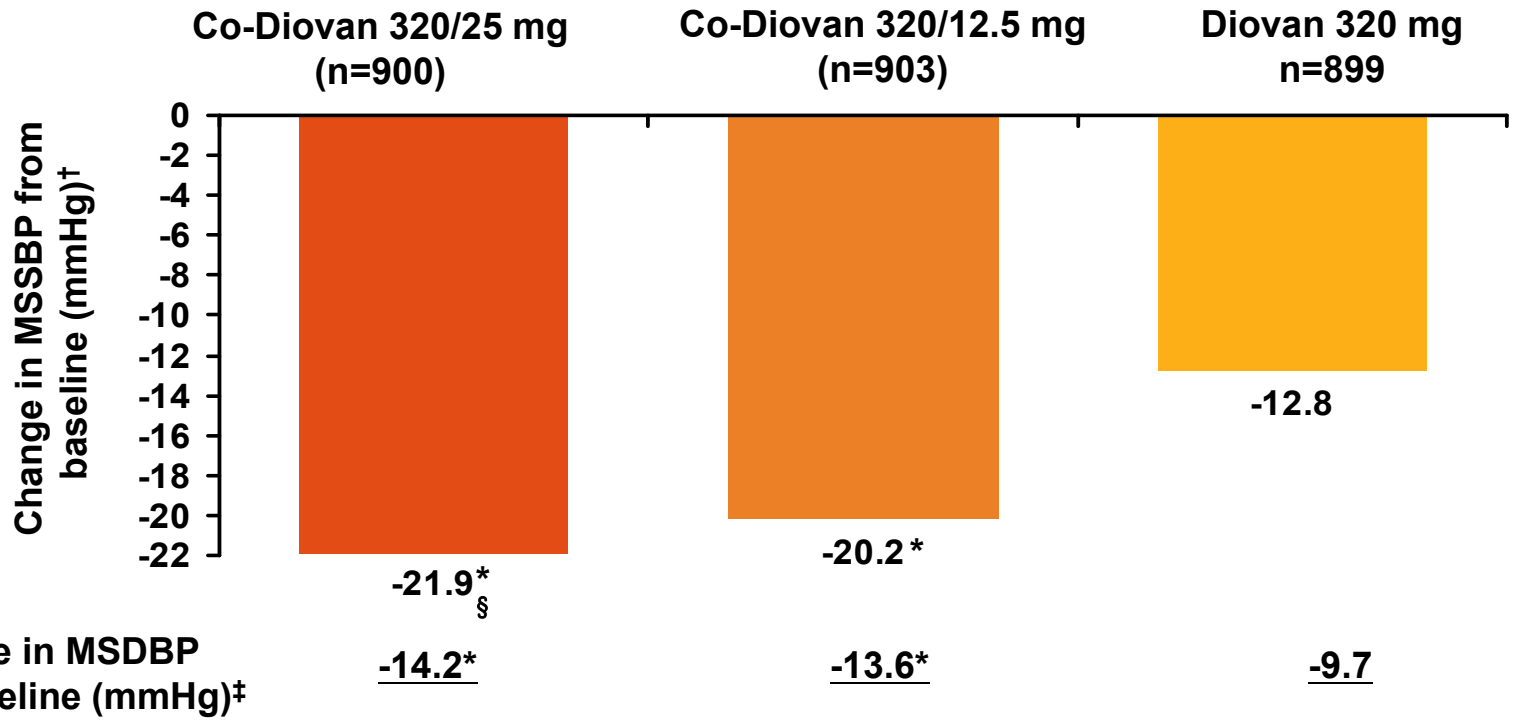
Results from a 12-week ABPM study in patients with mild-to moderate HTN[#]



[#]329 patients with DBP ≥95 mmHg and <110 mmHg; [§]Diovan 160 mg; force-titrated after 4 weeks to Diovan 320 mg and to Co-Diovan 320/12.5 mg after 8 weeks; ABPM=Ambulatory blood pressure monitoring; BP=Blood pressure; DBP=Diastolic blood pressure; HTN=Hypertension; SBP=Systolic blood pressure; Zappe et al. *ESH* 2007 (Poster)

Co-Diovan provides effective BP reductions in Non-responders to Diovan monotherapy

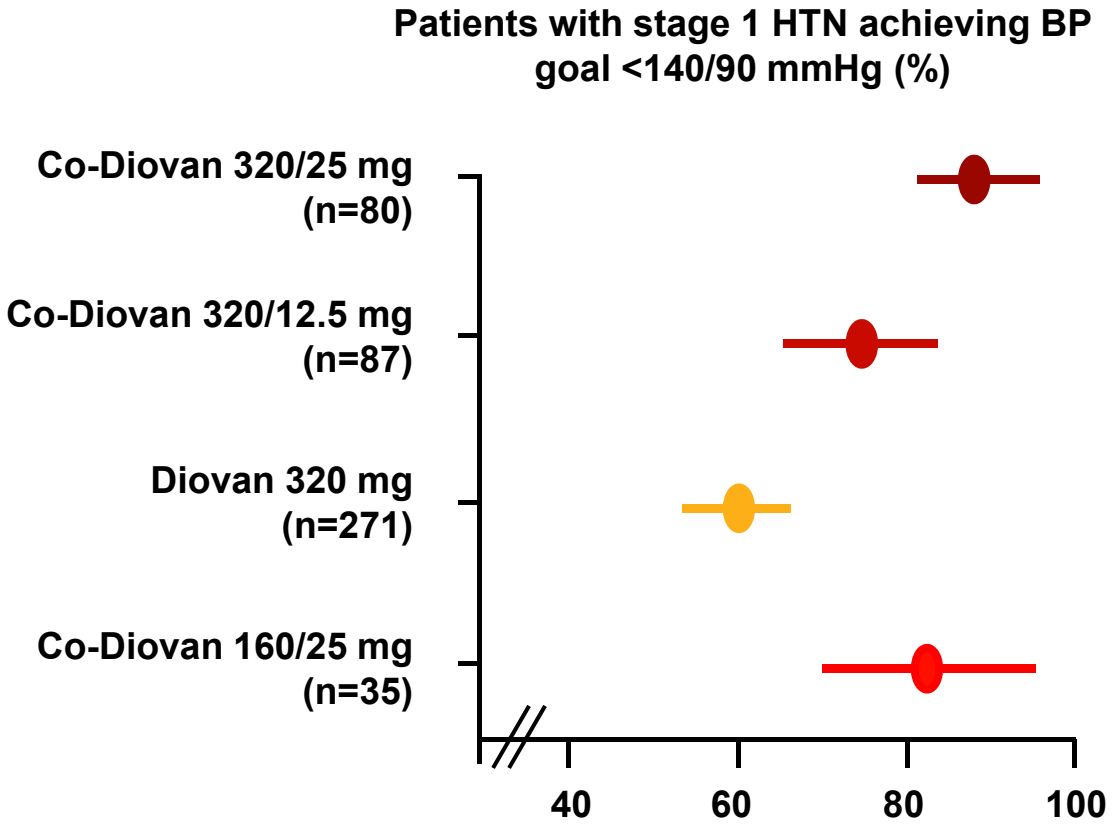
Results from a 12-week study in patients with untreated mild-to-moderate essential HTN[#]



[#]3805 patients with MSDBP ≥90 and <110 mmHg; [†]Baseline MSSBP=159.9 mmHg in Co-Diovan 320/25 group, 160.0 mmHg in Co-Diovan 320/12.5 group and 159.4 mmHg in Diovan group; [‡]Baseline MSDBP=100.3 mmHg in Co-Diovan 320/25 group, 100.6 mmHg in Co-Diovan 320/12.5 group and 100.5 mmHg in Diovan group; *p<0.0001 vs. Diovan 320 mg; [§]p<0.05 vs. Co-Diovan 320/12.5 mg; HTN=Hypertension; MSDBP=Mean sitting diastolic blood pressure; MSSBP=Mean sitting systolic blood pressure; Tuomilehto et al. Blood Pressure 2008;17:15-23

Co-Diovan 320/25 mg achieves BP goal in up to 9 out of 10 patients with stage 1 HTN

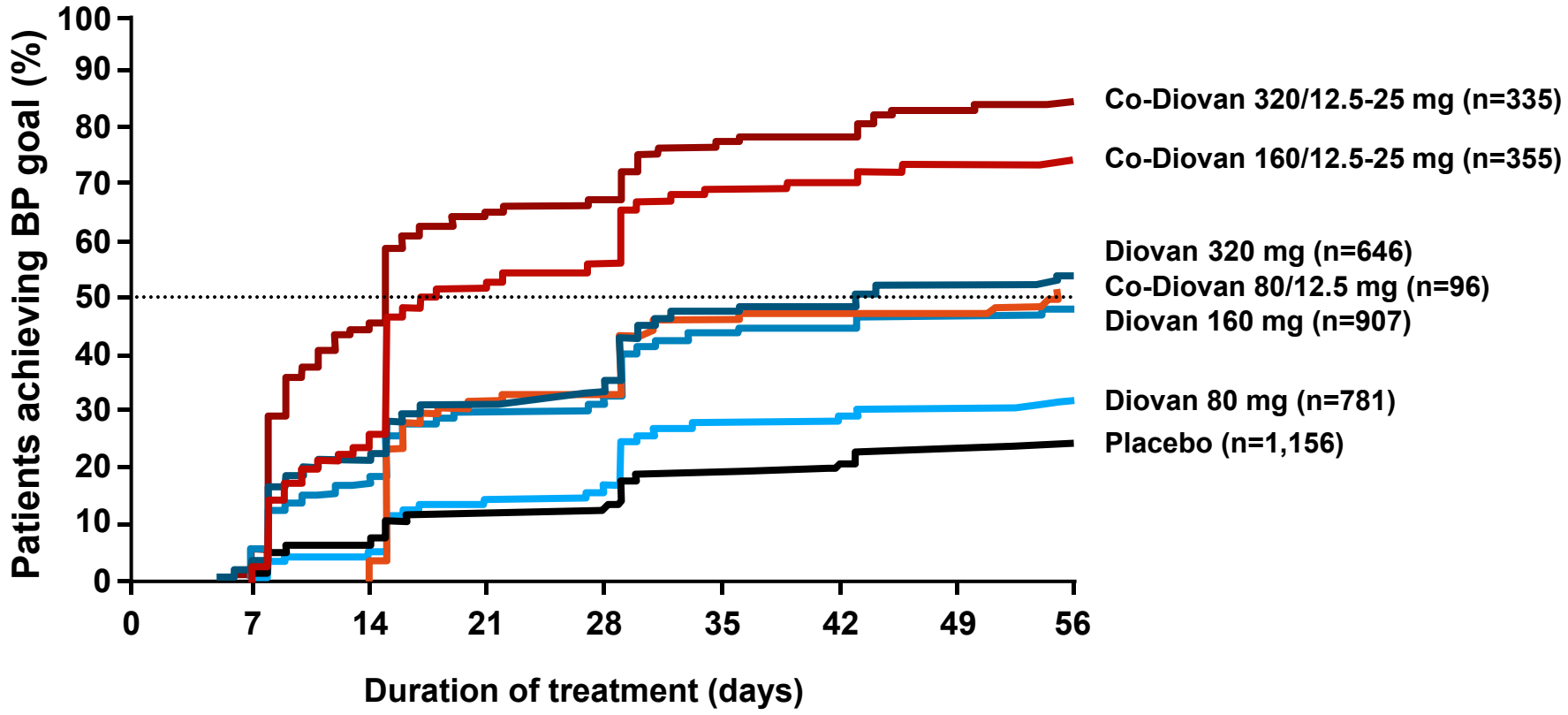
Results from a pooled analysis of 9 randomized trials[#] in patients with HTN[§]



[#]Pooled analysis of 9 double-blind, randomized, placebo-controlled studies of 4-8–week duration with 2-4–week placebo run-in periods, the analysis included a placebo arm, Diovan 80 and 160 mg arms, and Co-Diovan 80/12.5 and 120/12.5 mg arms (data not shown); [§]4278 patients with DBP ≥95 and ≤115 mmHg; BP=Blood pressure; DBP=Diastolic blood pressure; HTN=Hypertension; Weir et al. *J Clin Hypertens* 2007;9:103-112

Diovan and Co-Diovan high doses rapidly achieve BP Goal in more patients

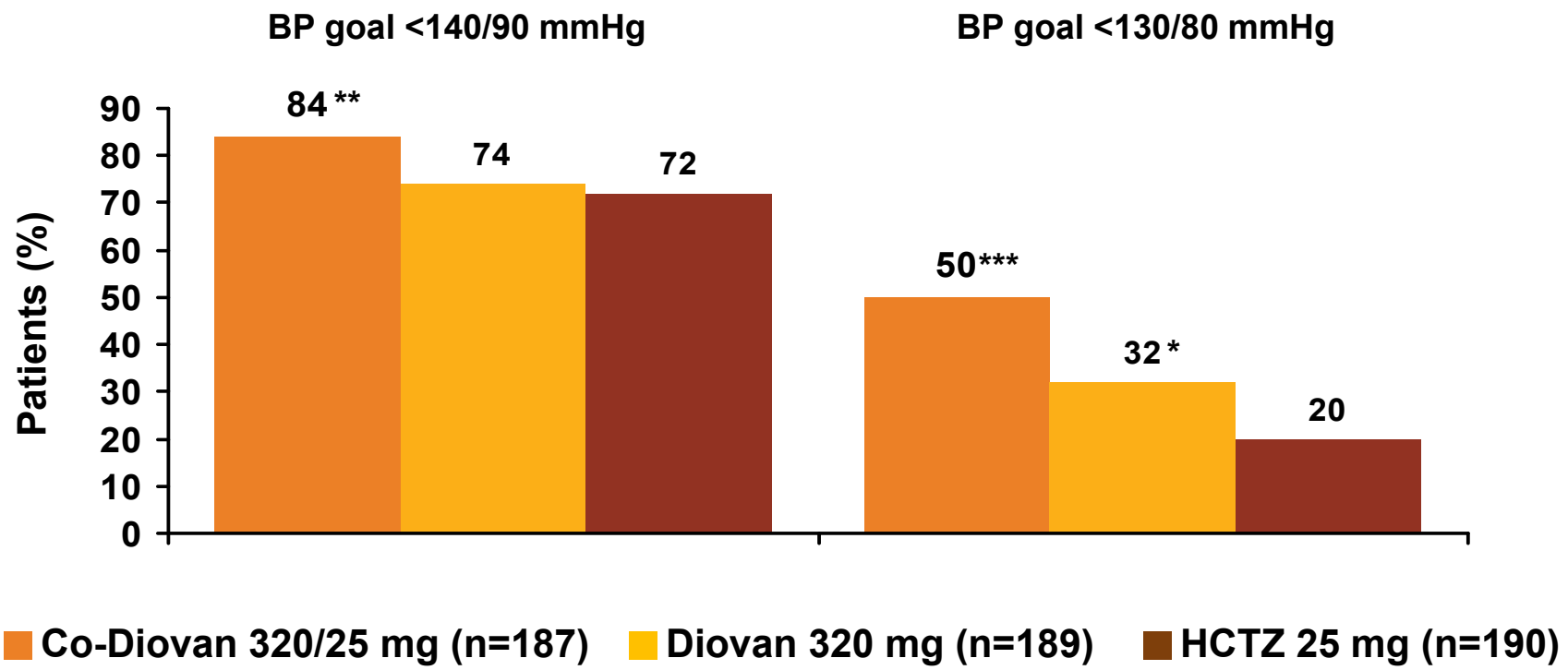
Results from a pooled analysis of 9 randomized trials[#] in patients with HTN[§]



[#]Pooled analysis of 9 double-blind, randomized, placebo-controlled studies of 4-8–week duration with 2-4–week placebo run-in periods; [§]4278 patients with DBP ≥95 and ≤115 mmHg; BP=Blood pressure; DBP=Diastolic blood pressure; HTN=Hypertension;
Weir et al. *Am J Hypertens* 2007;20:807-15

Co-Diovan provides high control rates in patients with metabolic syndrome

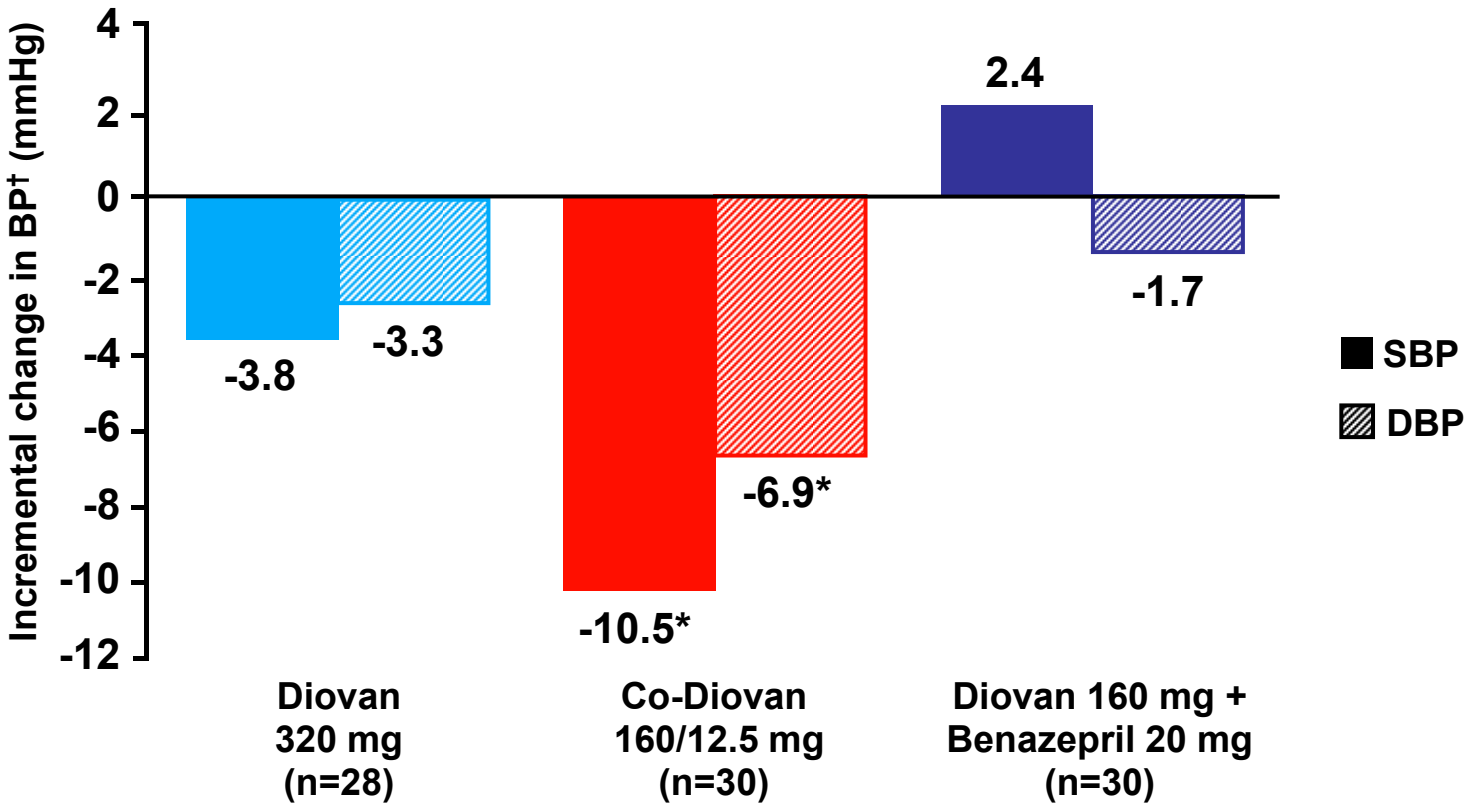
Results from a 16-week study in pre-diabetic patients with HTN, obesity and metabolic syndrome[#] (**MADE-ITT study**)



[#]566 patients with HTN (MSSBP ≥130 and ≤160 mmHg, MSDBP ≥85 and ≤100 mmHg), obesity (waist circumference >40 inches for males and >35 inches for females) and metabolic syndrome (fasting plasma glucose 100-125 mg/dL, or serum triglycerides >150 mg/dL, or serum HDL cholesterol <40 mg/dL in males or <50 mg/dL in females); *p=0.0017, **p=0.002 and ***p<0.0001 vs. HCTZ; BP=Blood pressure; HTN=Hypertension; MSDBP=Mean sitting diastolic blood pressure; MSSBP=Mean sitting systolic blood pressure; Zappe et al. *J Clin Hypertens* 2008;10:894-903

Co-Diovan provides incremental BP reductions in African Americans on high salt diet

Results from a 16-week study in 88 African Americans with hypertension[#]

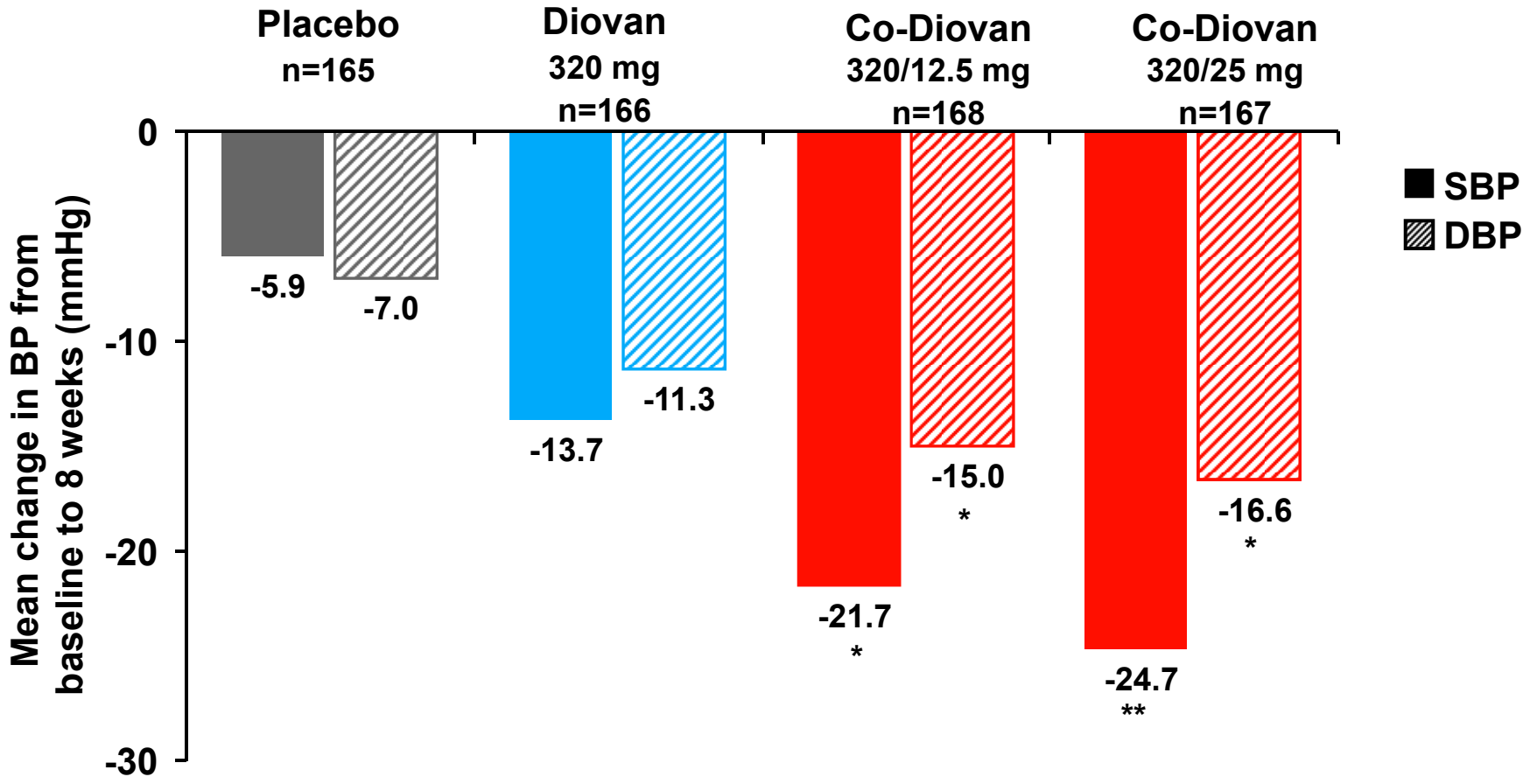


[#]DBP 95-114 mmHg; †Incremental to 4-weeks Diovan 160 and 200 mEq Na+/day; *p<0.05 vs. Diovan 160 mg +
Na+ 200 mEq/day (high salt diet)

Weir et al. *Am J Hypertens* 2001;14:665-671

Co-Diovan 320/25 produces additional BP reductions compared to lower doses of Diovan(/HCTZ)

Results from an 8-week study in 1346 patients with essential hypertension#



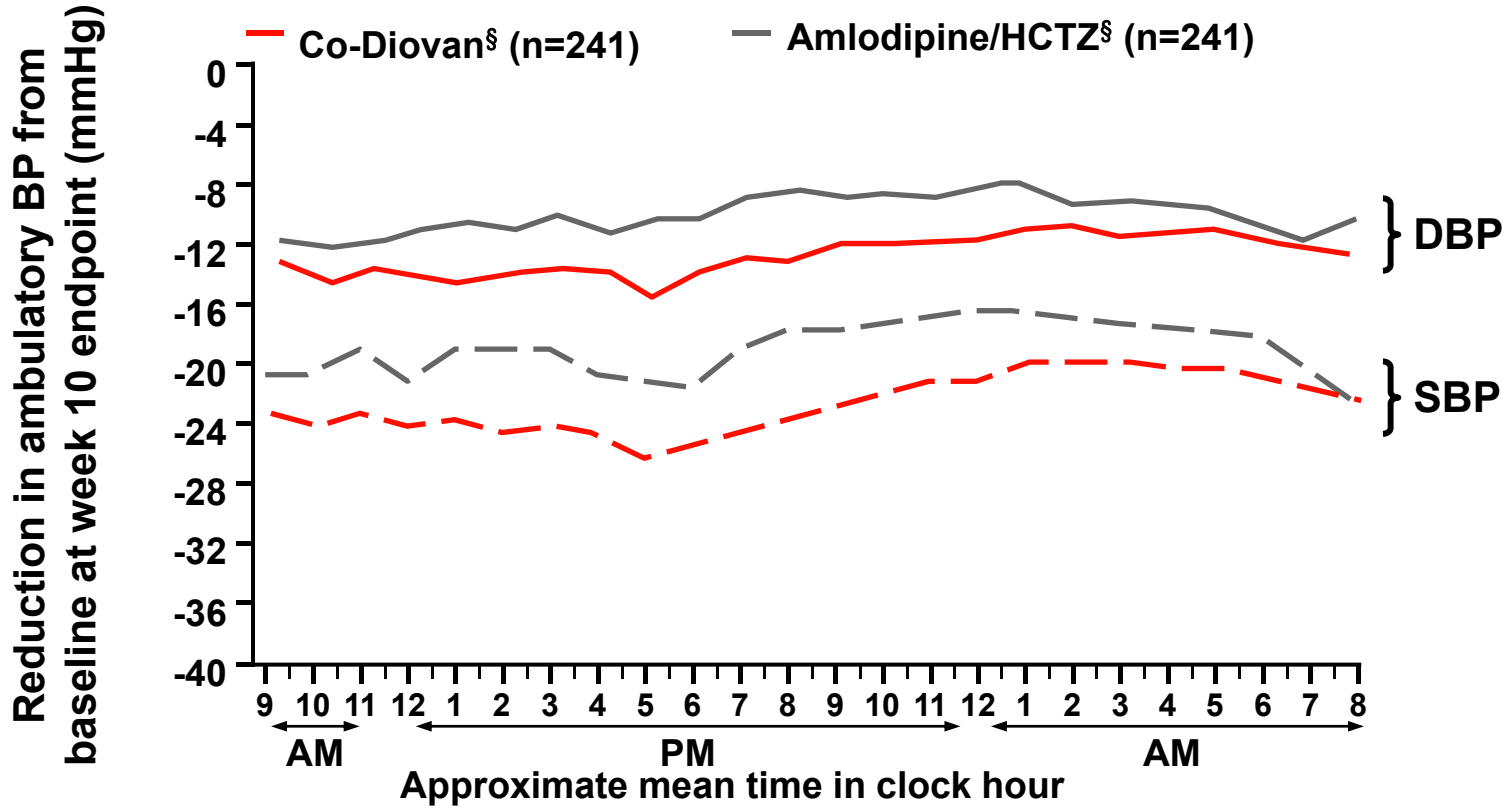
#Mean sitting DBP ≥95 and <110 mmHg; *p<0.0001 compared with placebo and respective monotherapy component; **p=0.0017 vs. 160/12.5 mg

Pool et al. *J Clin Hypertens* 2006;8(5, Supplement A):A81

Co-Diovan reduces 24-Hour ambulatory BP more effectively than Amlodipine/HCTZ

Results from a 10-week study in patients with stage 2 HTN[#] (**EVALUATE study**)

Ambulatory BP over 24 hours: reductions from baseline at week 10 endpoint



[#]482 patients with MSSBP ≥160 mmHg and <200 mmHg; MSDBP <120 mmHg; [§]Diovan 160 mg or amlodipine 5 mg; force-titrated after 2 weeks to Co-Diovan 160/12.5 mg or amlodipine 10 mg and after 4 weeks to Co-Diovan 320/25 mg or amlodipine/HCTZ 10/25 mg; BP=Blood pressure; DBP=Diastolic blood pressure; HTN=Hypertension; SBP=Systolic blood pressure;

Lacourciere et al. *ESH* 2008 (Poster)

Summary

- **Valsartan has a wealth of CV outcomes data across the Cardiovascular Continuum [1-6]**
- **Valsartan is indicated for use in patients with hypertension, Post-myocardial infarction (MI), Heart failure (HF) [7]**
- **High-dose Valsartan in monotherapy is both safe and effective in mild-to-moderate uncomplicated hypertensive patients over relatively long periods of time [8]**
- **High-dose Valsartan provide not only rapid and powerful median BP reductions but also additional BP control and renal protection [9-11]**
- **Valsartan doses provide effective SBP/DBP control over 24 Hours[12]**

1. Julius et al. Lancet 2004; 363:2022–31; 2. Pfeffer et al. N Engl J Med 2003;349:1893–906 , 3. Cohn et al. N Engl J Med 2001; 345:1667–75; 4. Sawada et al. Eur Heart J 2009;30:2461–69 , 5. Califf et al. Am Heart J 2008;156:623–32; 6. Mochizuki et al. Lancet 2007;369:1431–9 7. **Licensed indications 8.** Parati et al. *Hypertension reseach* 2010;33:986-994 9. Weir et al. *Am J Hypertens* 2007;20:807-15 10. Zappe et al. *ESH* 2007, 11. Hollenberg et al. presented at American Heart Association Meeting 2006 , 12.Neutel et al. *Clin Ther* 1997;19(3):447-458

경청해주셔서 감사합니다.