

Amlodipine/Valsartan (Exforge[®]) Changing the Landscape of BP Management

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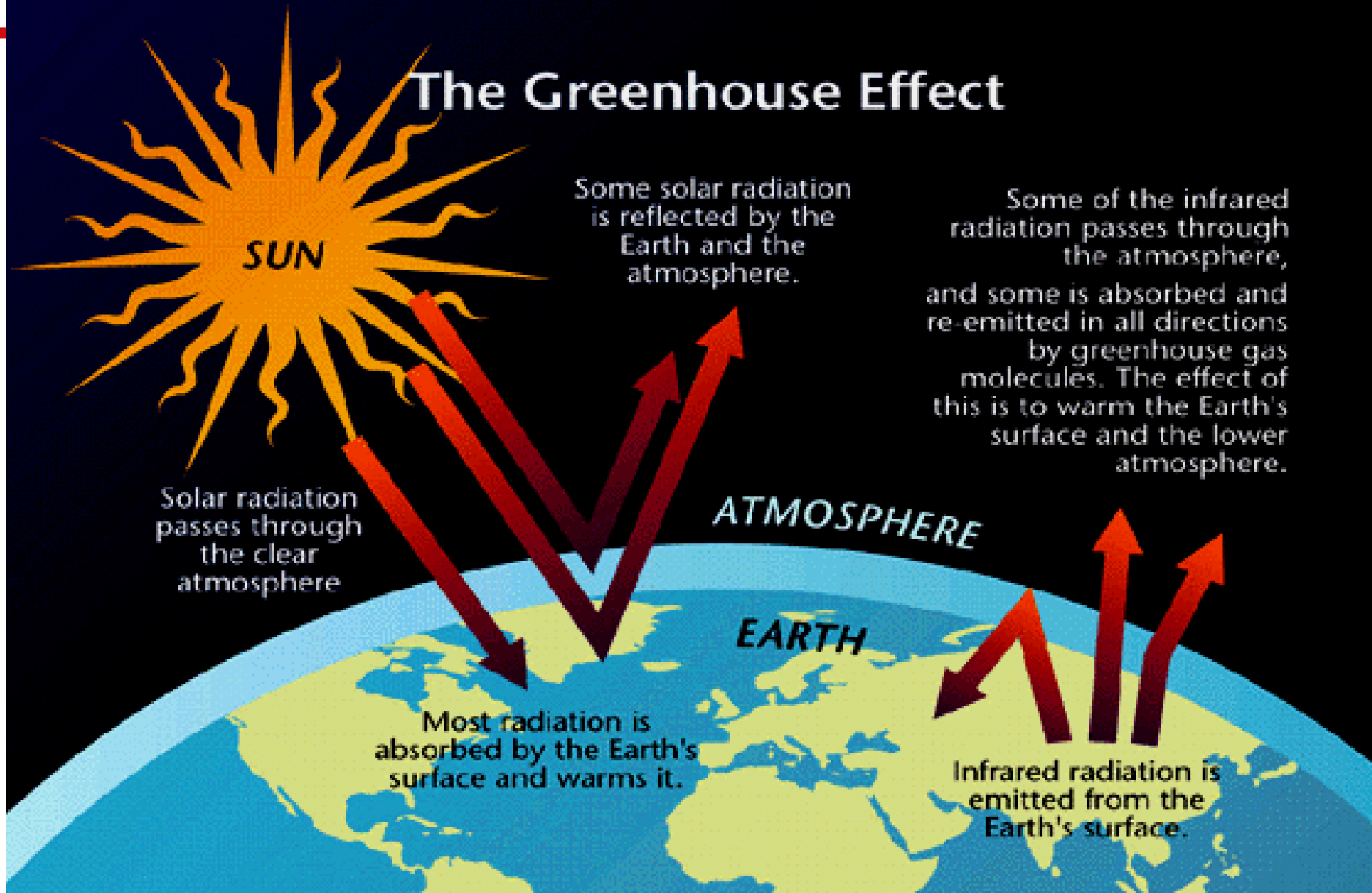
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EXFORGE[®]
amlodipine besylate/valsartan

GREAT DROPS JUST GOT BETTER



The Greenhouse Effect



Rationale for Multiple-Mechanism Therapy

- Inadequacy of agents with a single mechanism of action
- Advantages of multiple-mechanism therapy
- Recommendations for multiple agent therapy
- Benefits of fixed-dose combinations vs. free combinations

Fixed Combinations of Antihypertensives

“Notable Absentee”

■ Angiotensin-converting enzyme (ACE) inhibitor and CCB

- Benazepril + amlodipine (Lotrel)
- Trandolapril + verapamil (Tarka)
- Ramipril + felodipine (Unimax)

■ ACE inhibitor and diuretic

- Benazepril + HCTZ (Lotensin HCTZ)
- Captopril + HCTZ (Capozide)

■ ARB and diuretic

- Valsartan + HCTZ (Diovan HCTZ/Co-Diovan)
- Candesartan + HCTZ (Atacand plus)
- Losartan + HCTZ (Cozaar plus)

■ β -blocker and diuretic

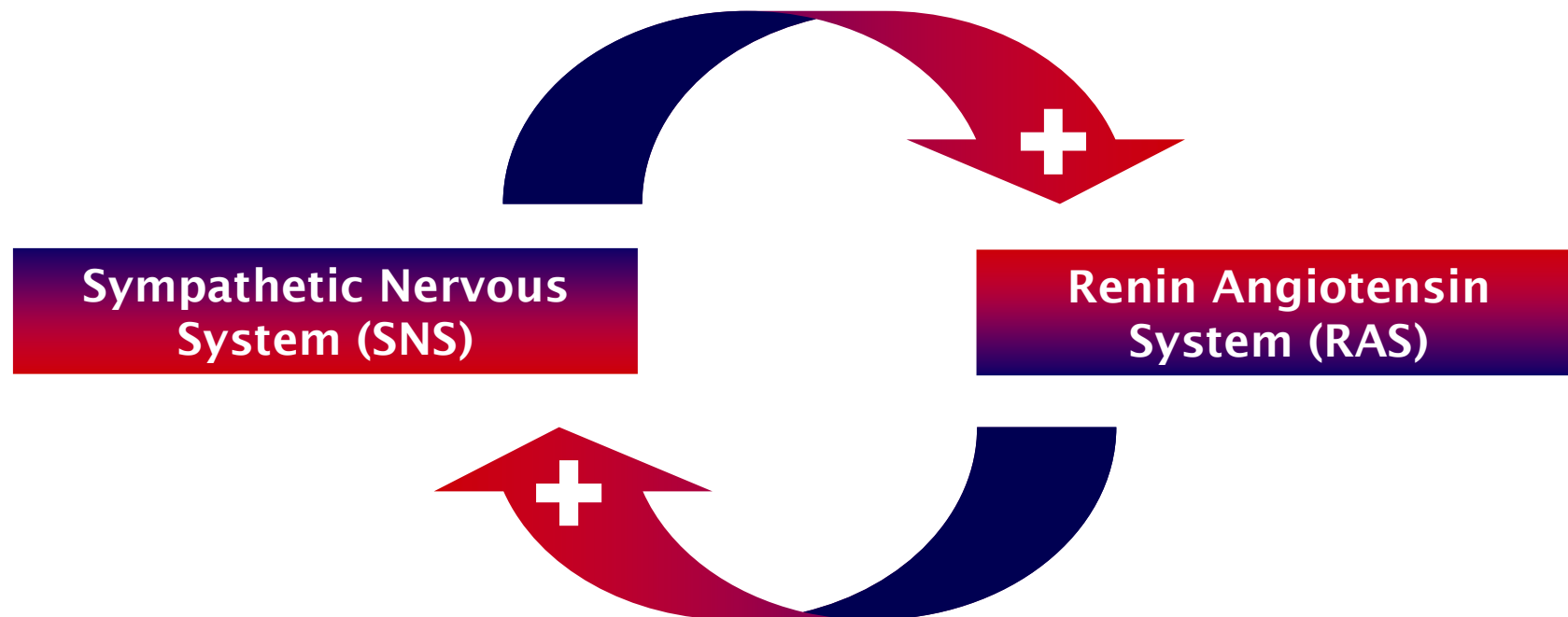
- Atenolol + chlorthalidone (Tenoretic)
- Metoprolol + HCTZ (Lopressor HCT)

■ β -blocker and CCB

- Metoprolol + felodipine (Logimax)
- Atenolol + nifedipine (Nif-Ten)

Notable absentee

Two Key Systems in BP Regulation



“Mutually reinforcing actions combine to regulate BP”

Grassi. J Hypertens 2001;19:1713-6

CCB-ARB: 2 Key BP Effector Pathways On Sympathetic Nervous System

- Adrenergic receptors on vascular smooth muscle > Vasoconstriction¹
- ↑SNS also stimulates renin secretion from the kidney, thereby activating the renin angiotensin system²
- CCBs inhibit SNS-induced vasoconstriction by blocking influx of Ca⁺⁺ (needed for contraction) through voltage-gated Ca⁺⁺ channels > Vasodilation^{3,4}
- Other effects of CCBs: natriuresis; Inhibition of aldosterone release; interference with angiotensin II-mediated vasoconstriction⁴

¹Grassi. *J Hypertens* 2001;19:1713-16

²Mancia and Grassi. <http://www.sns-web.org/pages/advances/11/article.asp>

³Robertson & Robertson. In: Hardman JG, Limbard JG. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. 1996. : Oparil S, Weber MA, editors. *Hypertension: Companion to Brenner & Rector's The Kidney*. 2nd ed. 2005. p. 683-704

CCB-ARB: 2 Key BP Effector Pathways

On Renin-Angiotensin-Aldosterone System

- Release of renin catalyzes conversion of angiotensinogen into angiotensin I, which is converted by ACE to angiotensin II:
 - Vasoconstriction: \uparrow Aldosterone and Na^+ /water retention $>$ \uparrow SNS
- ARBs block the effects of angiotensin II by binding to AT_1 receptors
 - Arterial and venous dilation
 - \downarrow SNS activity
 - \downarrow Secretion of aldosterone and \uparrow secretion of Na^+ / water

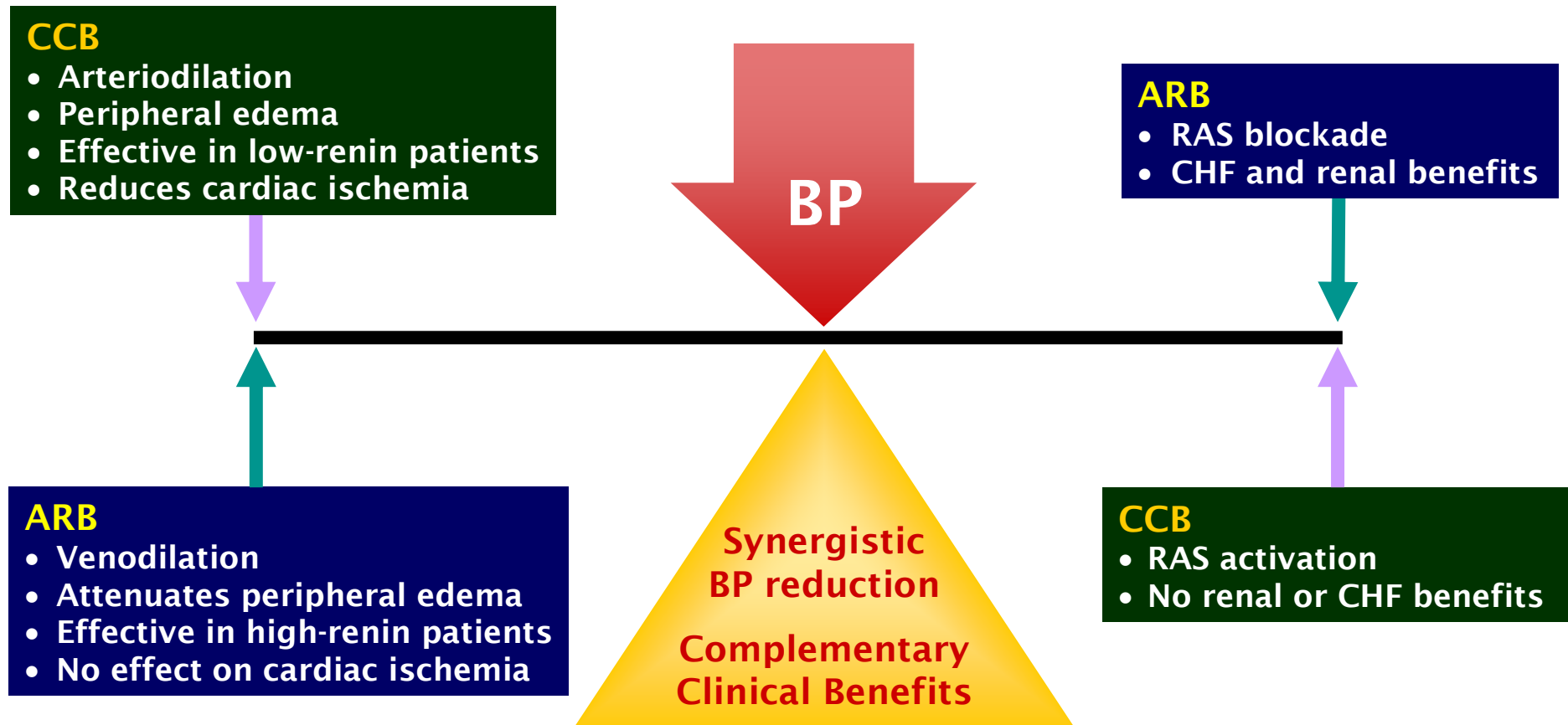
Neutralizing Counter-regulatory Mechanisms to Minimize Elevations in Blood Pressure

- CCBs will variably activate the SNS; the SNS, in turn activates the RAS^{1,2}
 - Overall effect is to blunt BP-lowering efficacy
 - Through the effects of RAS blockade, ARBs can counteract such effects, thereby maintaining potent BP-lowering effects of CCBs
- In addition, CCBs possess diuretic and natriuretic properties and thereby induce a state of negative sodium balance^{1,2}
 - This further reinforces the antihypertensive effect of the ARB

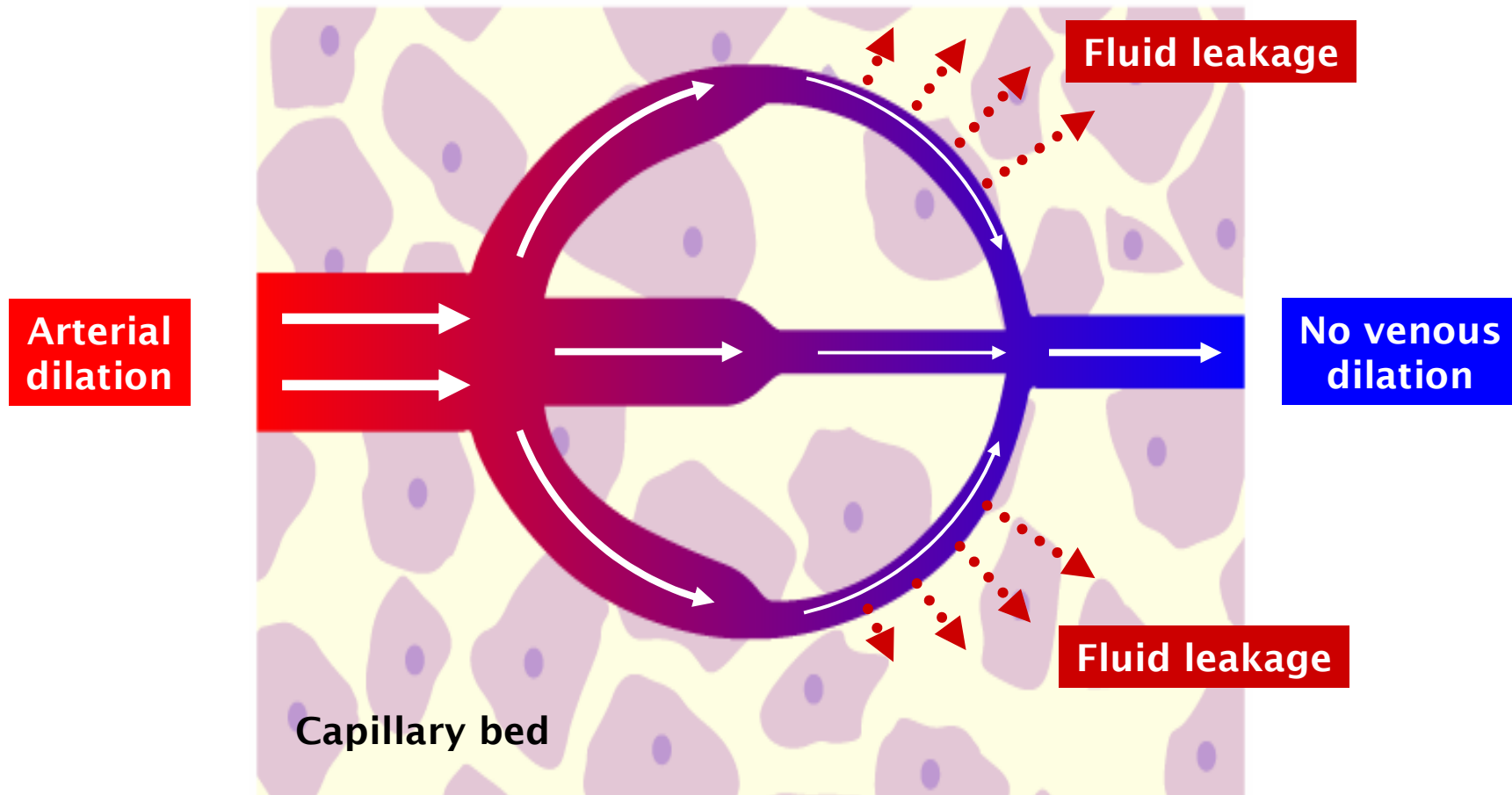
¹Sica. *Drugs* 2002;62:443–62

²Quan et al. *Am J Cardiovasc Drugs* 2006;6:103–13

CCB-ARB: Synergy of Counter-regulation



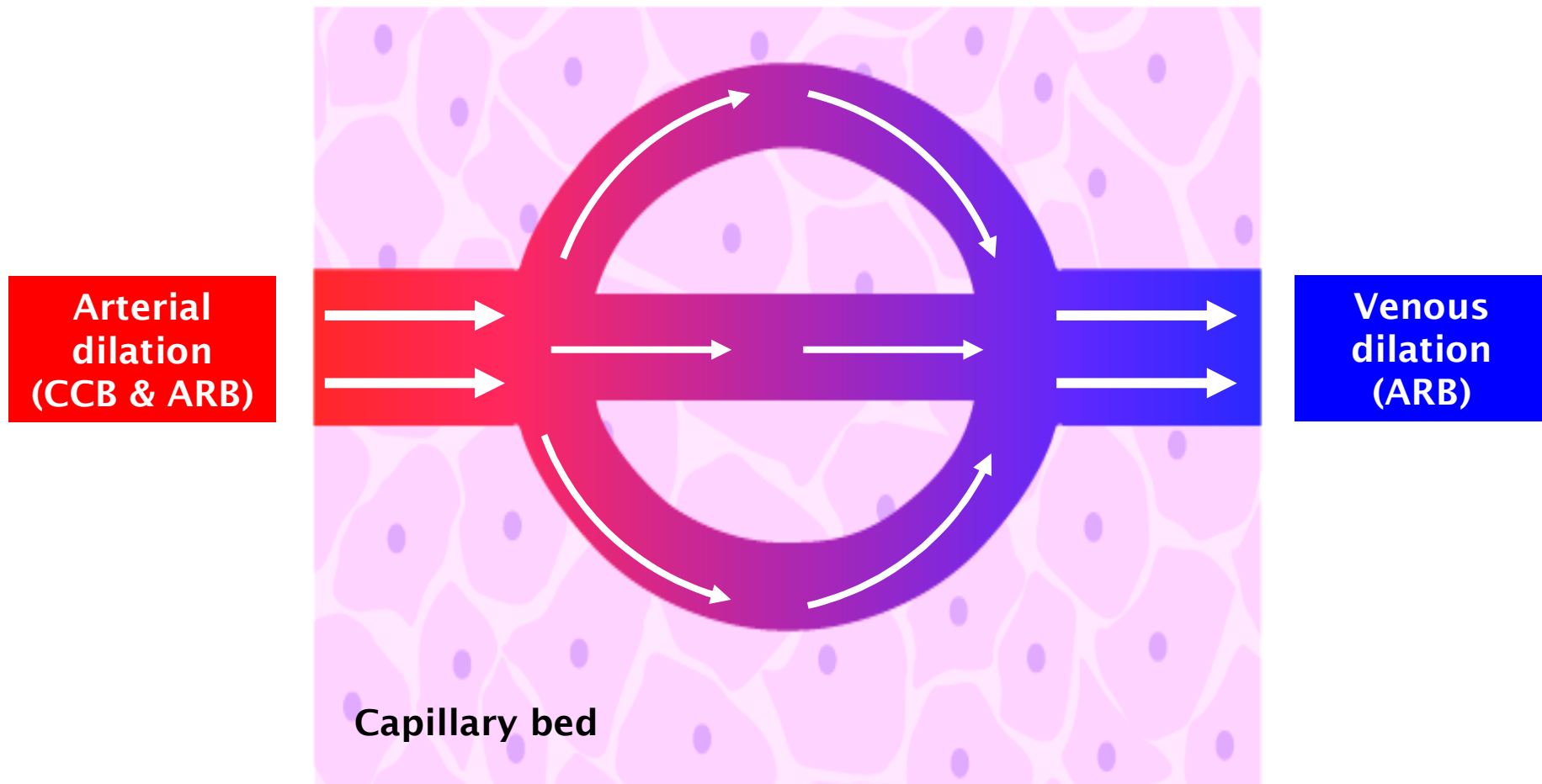
Peripheral Edema Associated with CCBs



Opie et al. In: Opie LH, editor. Drugs for the Heart. 3rd ed. 1991:42-73
White et al. Clin Pharmacol Ther 1986;39:43-8
Gustaffson. J Cardiovasc Pharmacol 1987;10(Suppl 1):S121-31

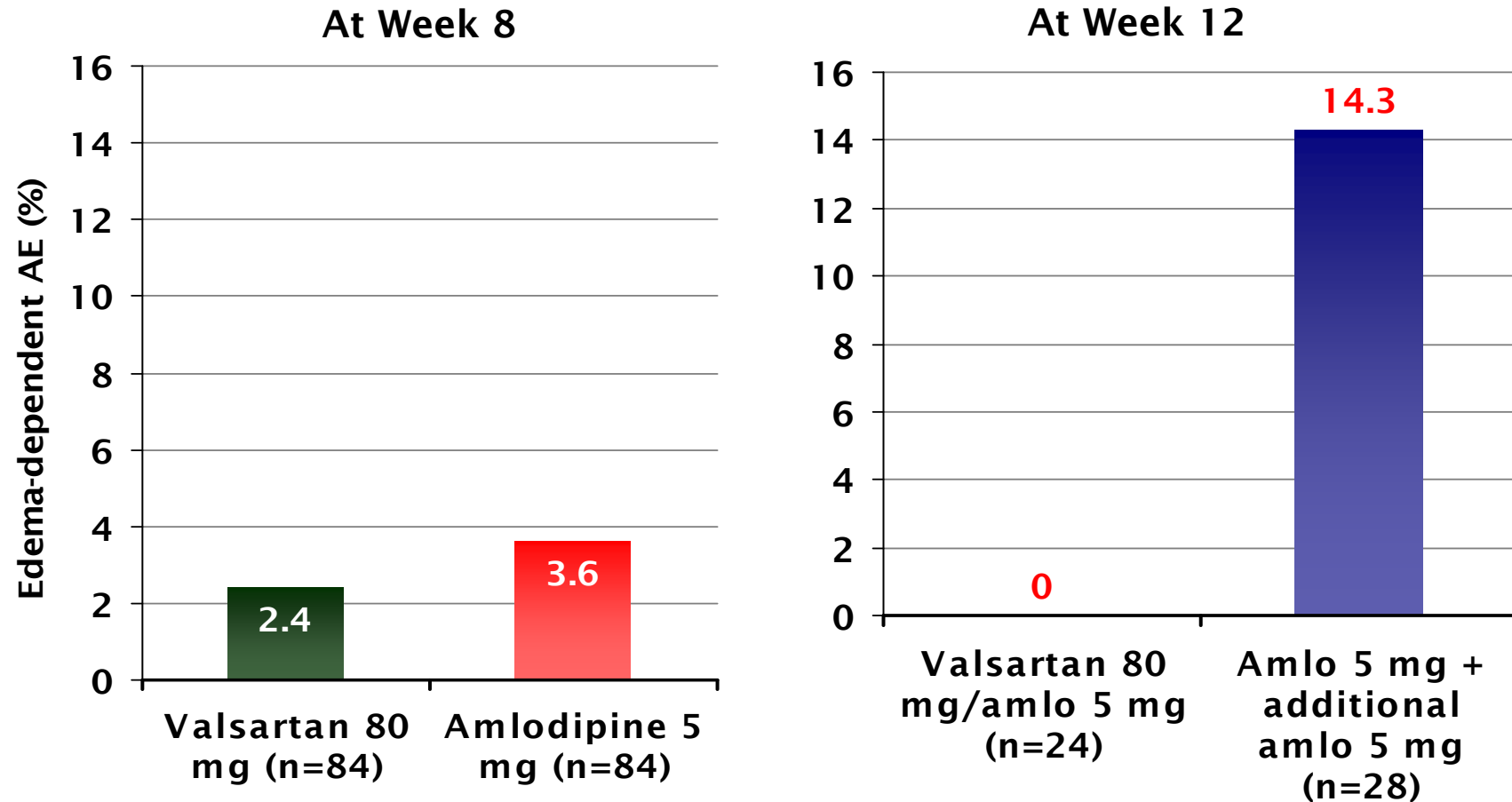
Complementary Effects of CCB/ARB

Reduction of CCB-associated Edema



Opie et al. In: Opie LH, editor. Drugs for the Heart. 3rd ed. 1991:42-73
White et al. Clin Pharmacol Ther 1986;39:43-8
Gustaffson. J Cardiovasc Pharmacol 1987;10(Suppl 1):S121-31

Edema-dependent Adverse Events with Increasing Doses of Amlodipine



After 8 weeks of therapy, amlodipine 5 mg added to initial therapy in patients not at goal (sitting DBP >95 mmHg)

Amlodipine: Wealth of CV Outcome Data

PREVENT¹

825 CAD patients ($\geq 30\%$): Multicenter, randomized, placebo controlled

Primary outcome: No difference in mean 3 yr coronary angiographic changes vs. placebo

- 35% ↓ hospitalization for heart failure + angina
- 33% ↓ revascularization procedures

CAMELOT²

1,991 CAD patients ($> 20\%$): Double-blind, randomized study vs. placebo and enalapril 20 mg

Primary outcome: 31% ↓ in CV events vs. placebo

- 41% ↓ hospitalization for angina
- 27% ↓ coronary revascularization

ASCOT-BPLA/CAFE^{3,4}

19,257 HTN patients: Multicenter, randomized, prospective study vs. atenolol

Primary outcome: 10% ↓ in non-fatal MI & fatal CHD

- 16% ↓ total CV events and procedures
- 30% ↓ new-onset diabetes
- 27% ↓ stroke
- 11% ↓ all-cause mortality
- ↓ central aortic pressure by 4.3 mmHg

ALLHAT⁵

18,102 HTN patients: Randomized, prospective study vs. lisinopril

Primary outcome: No difference in composite of fatal CHD + non-fatal MI vs. lisinopril

- 6% ↓ combined CVD
- 23% ↓ stroke

Valsartan: Wealth of CV Outcomes Data

VALUE¹

15,245 high-risk HTN patients: Double-blind, randomized, active-controlled study vs. amlodipine

Primary outcome: No difference in composite of cardiac mortality and morbidity

23% ↓ new-onset diabetes

VALIANT²

14,703 post-myocardial infarction patients: Double-blind, randomized study vs. captopril and vs captopril + valsartan

Primary outcome: No difference vs. captopril in all-cause mortality

(Valsartan is as effective as standard of care)

Val-HeFT³⁻⁵

5,010 heart failure II-IV patients: Double-blind, randomized study vs placebo

Primary endpoints: Mortality and combined endpoint of mortality and morbidity

13% ↓ mortality and morbidity

↓ left ventricular remodeling

37% ↓ atrial fibrillation occurrence

↓ heart failure signs/symptoms

28% ↓ heart failure hospitalization

¹Julius et al. *Lancet* 2004;363:2022-31; ²Pfeffer et al. *N Engl J Med* 2003;349:1893-906

³Maggioni et al. *Am Heart J* 2005;149:548-57; ⁴Wong et al. *J Am Coll Cardiol* 2002;40:970-5; ⁵Cohn et al. *N Engl J Med* 2001;345:1667-75

Valsartan: Wealth of CV Protection Data

MARVAL¹

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 valsartan vs. 8% with
amlodipine

15.4% between-group difference favoring valsartan in
patients returning to normoalbuminuria

Val-MARC²

1,668 stage 2 HTN patients: Multicenter, open-label, ra
ndomized study vs valsartan/HCTZ

Primary endpoints: change in systolic BP and in high-
sensitivity C-reactive protein (hsCRP) between
randomization and Week 6

Drop in systolic BP was greater with the combination

13% ↓ hsCRP vs. valsartan/HCTZ

¹Viberti et al. *Circulation* 2002;106:672-8

²Ridker et al. *Hypertension* 2006;48:73-9

Rationale for CCB/ARB Therapy

- **Notable absence of available dual-mechanism therapies**
- **Complementary mode of action**
- **CCB-induced edema is minimized by ARB**
- **Wealth of CV Outcomes Data for Amlodipine and Valsartan**

Clinical Evidence with Amlodipine/Valsartan

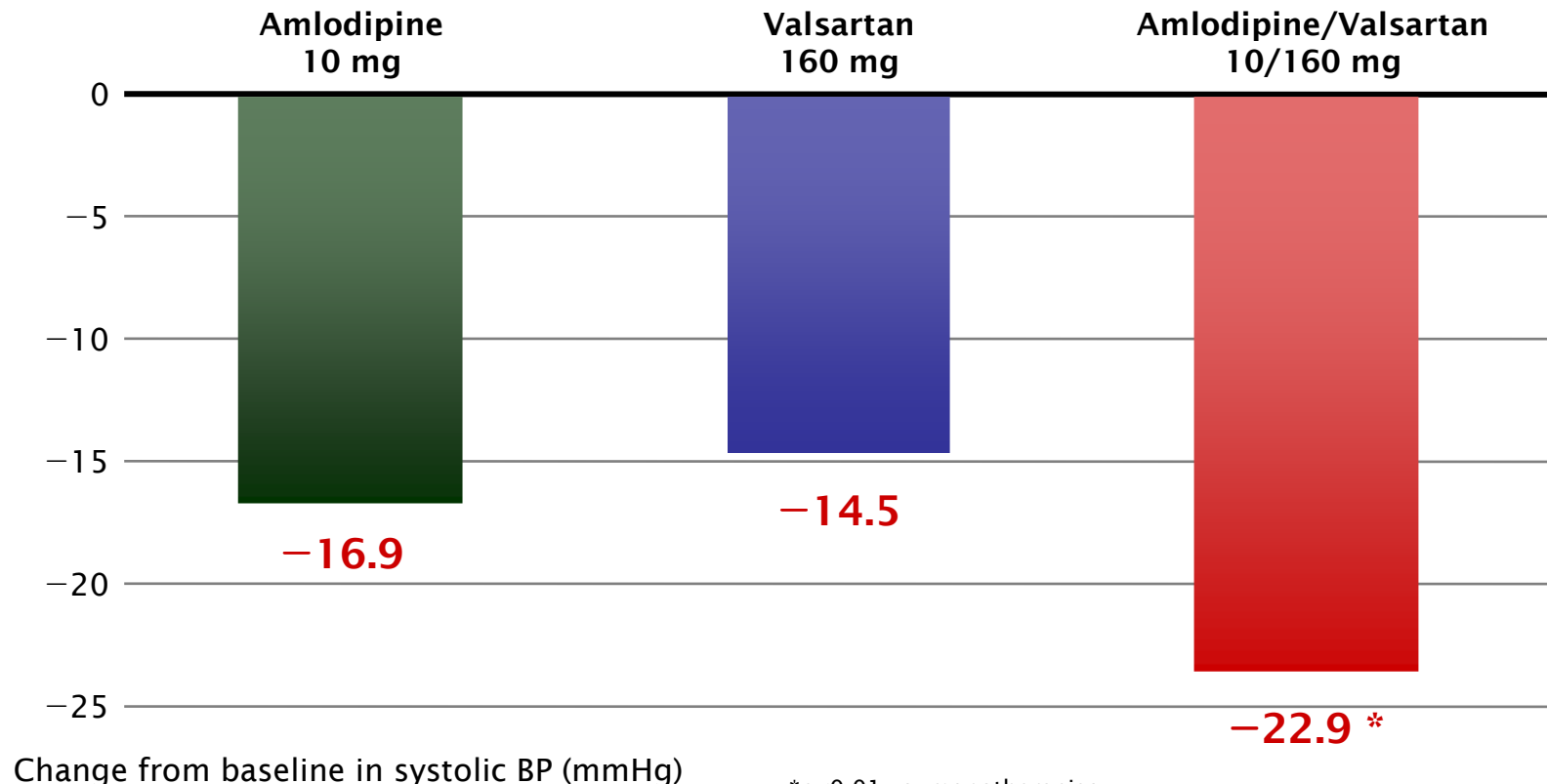
- **BP-lowering Efficacy and Get to Goal Rates**
- **Efficacy in Non-responders to Monotherapy**
- **Efficacy in Non-responders to Combination Therapy**
- **Efficacy Across Different Grades of Hypertension**
- **Safety and Tolerability**

Amlodipine/Valsartan

BP-lowering efficacy and get to goal rates



Superior BP-lowering efficacy compared with monotherapies in patients with mild-to-moderate hypertension



*p<0.01 vs. monotherapies
Mild-to-moderate hypertension = diastolic BP >90 and <110 mmHg
N=80

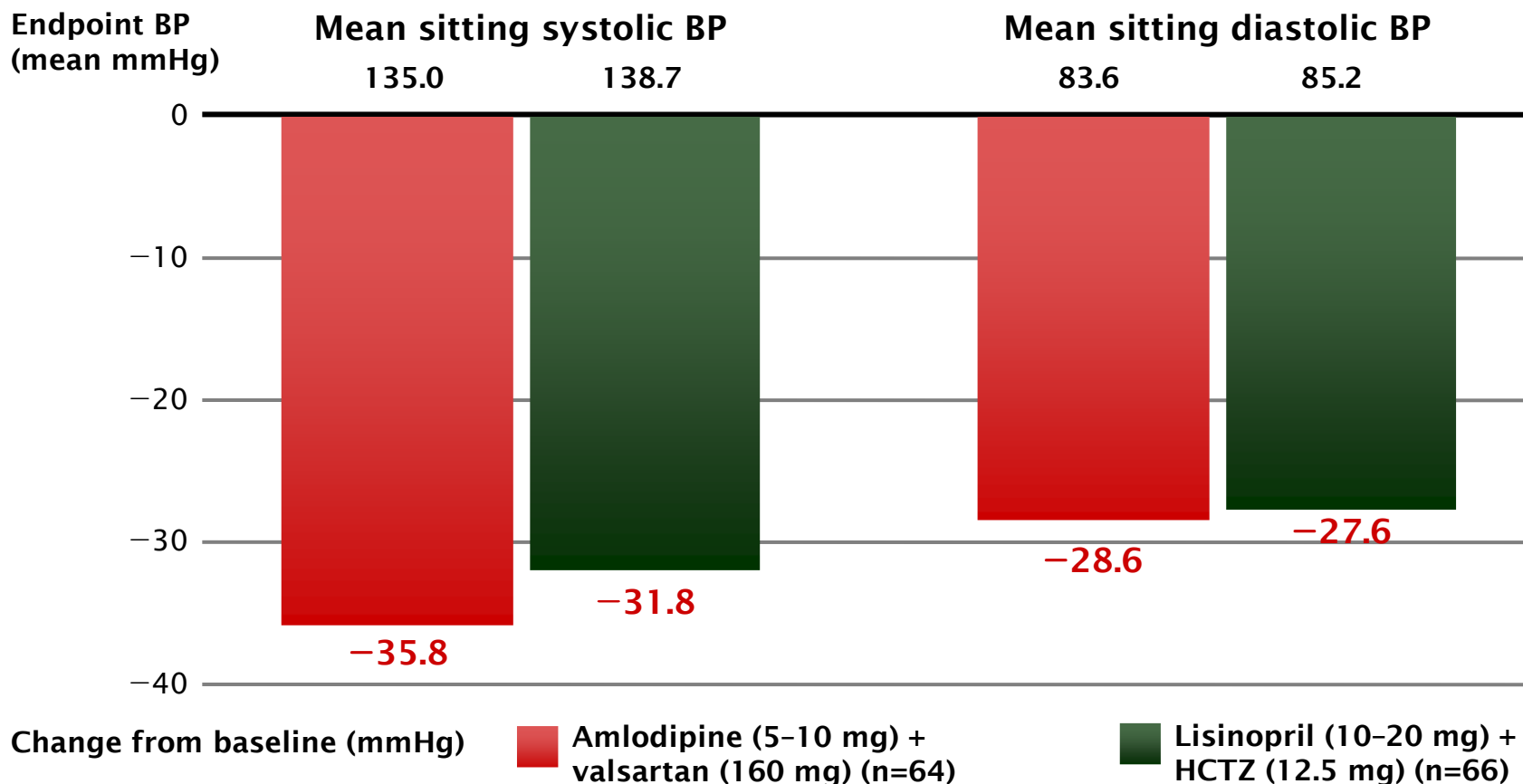
Fogari et al. J Hum Hypertens 2007;21:220-4

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BP-lowering efficacy and get to goal rates



BP-lowering efficacy in patients with stage 2 hypertension



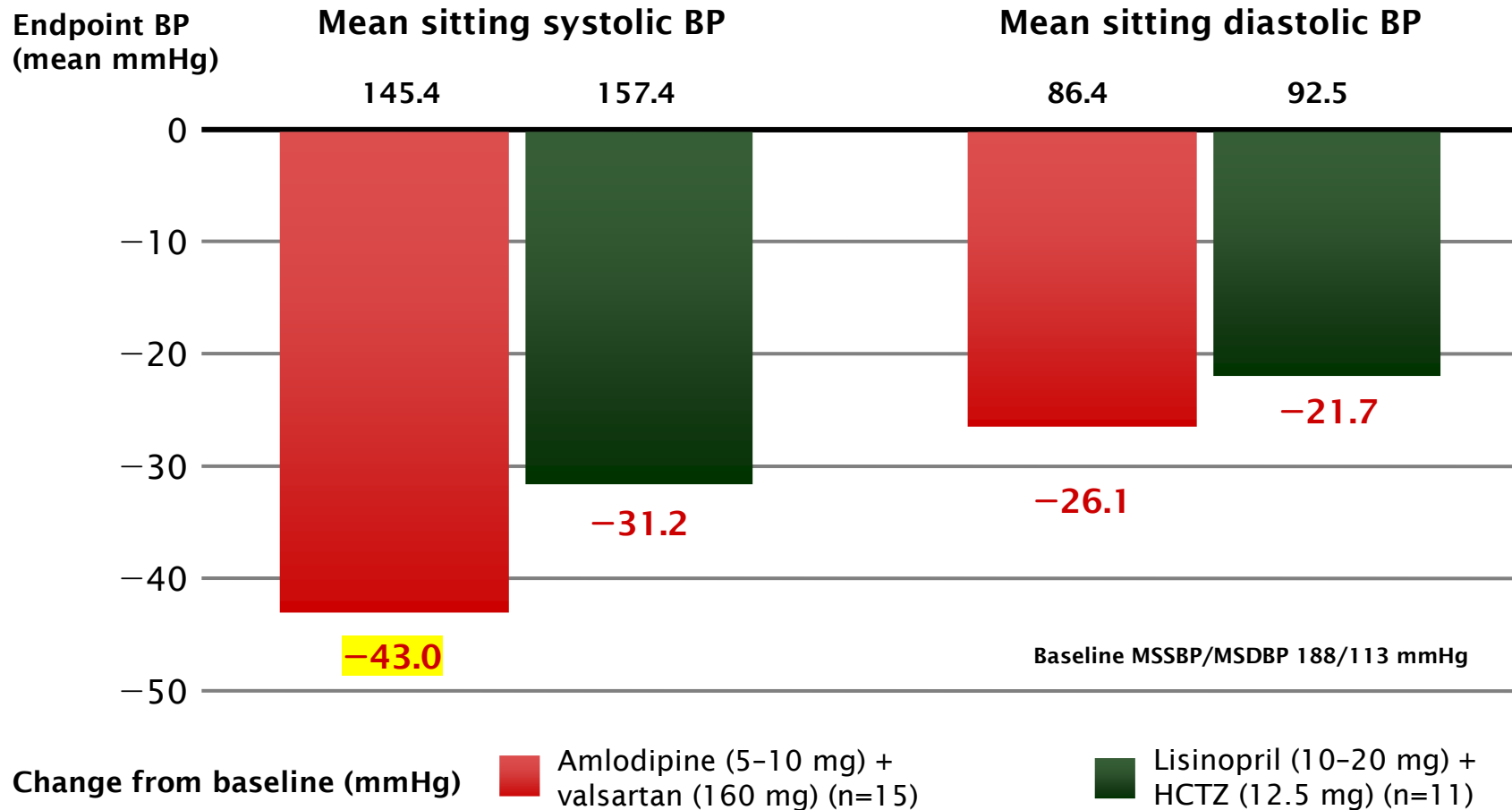
Poldermans et al. J Clin Hypertens 2006;8(5, Suppl. A)
Poldermans et al. J Hypertens 2006;24(Suppl. 4):S20

Amlodipine/Valsartan

BP-lowering efficacy and get to goal rates



↓43 mmHg in MSSBP in patients with baseline MSSBP ≥180 mmHg



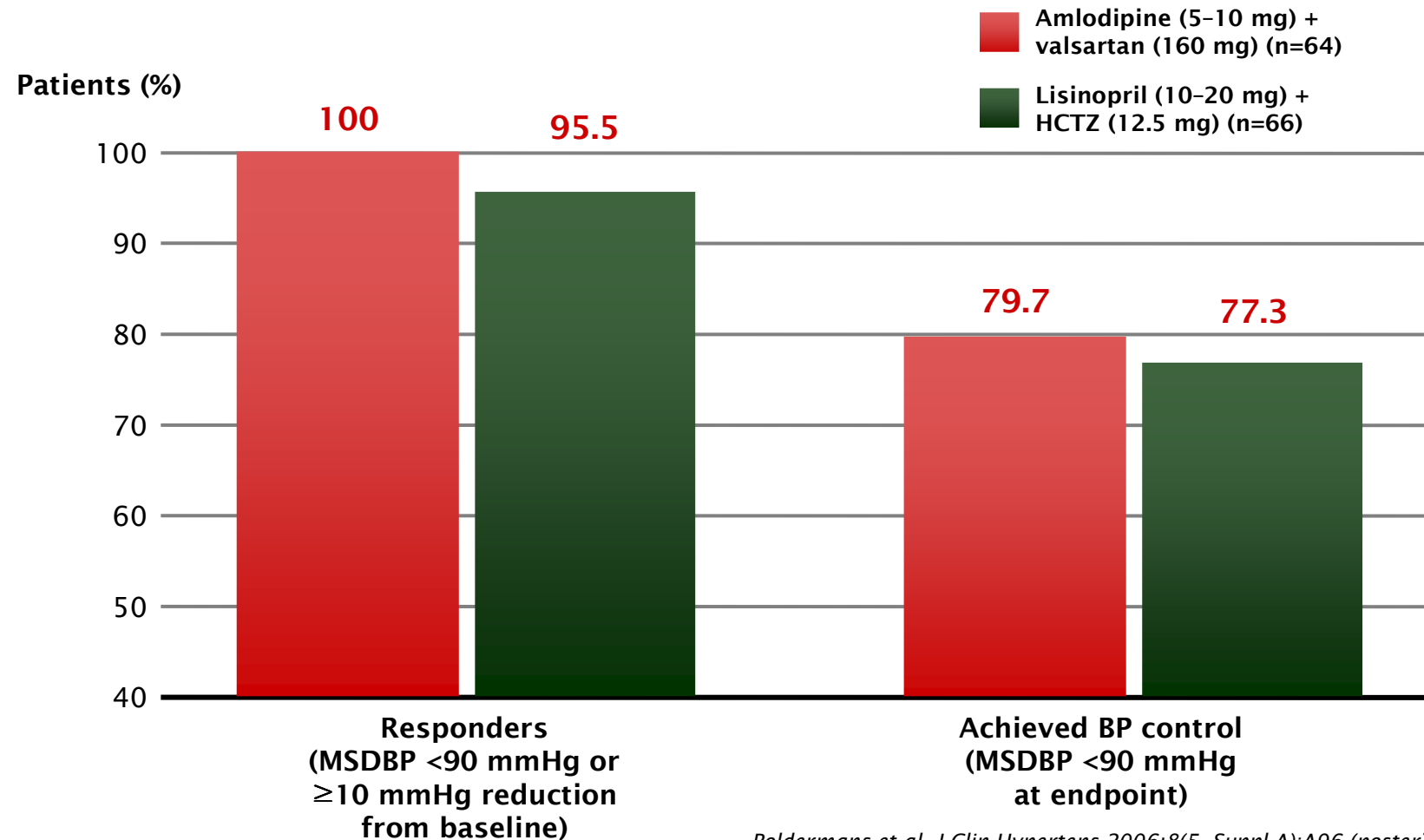
Poldermans et al. J Clin Hypertens 2006;8(5, Suppl. A):A96
Poldermans et al. J Hypertens 2006;24(Suppl. 4):S20

Amlodipine/Valsartan

BP-lowering efficacy and get to goal rates



Responder & control rates in patients with stage 2 hypertension



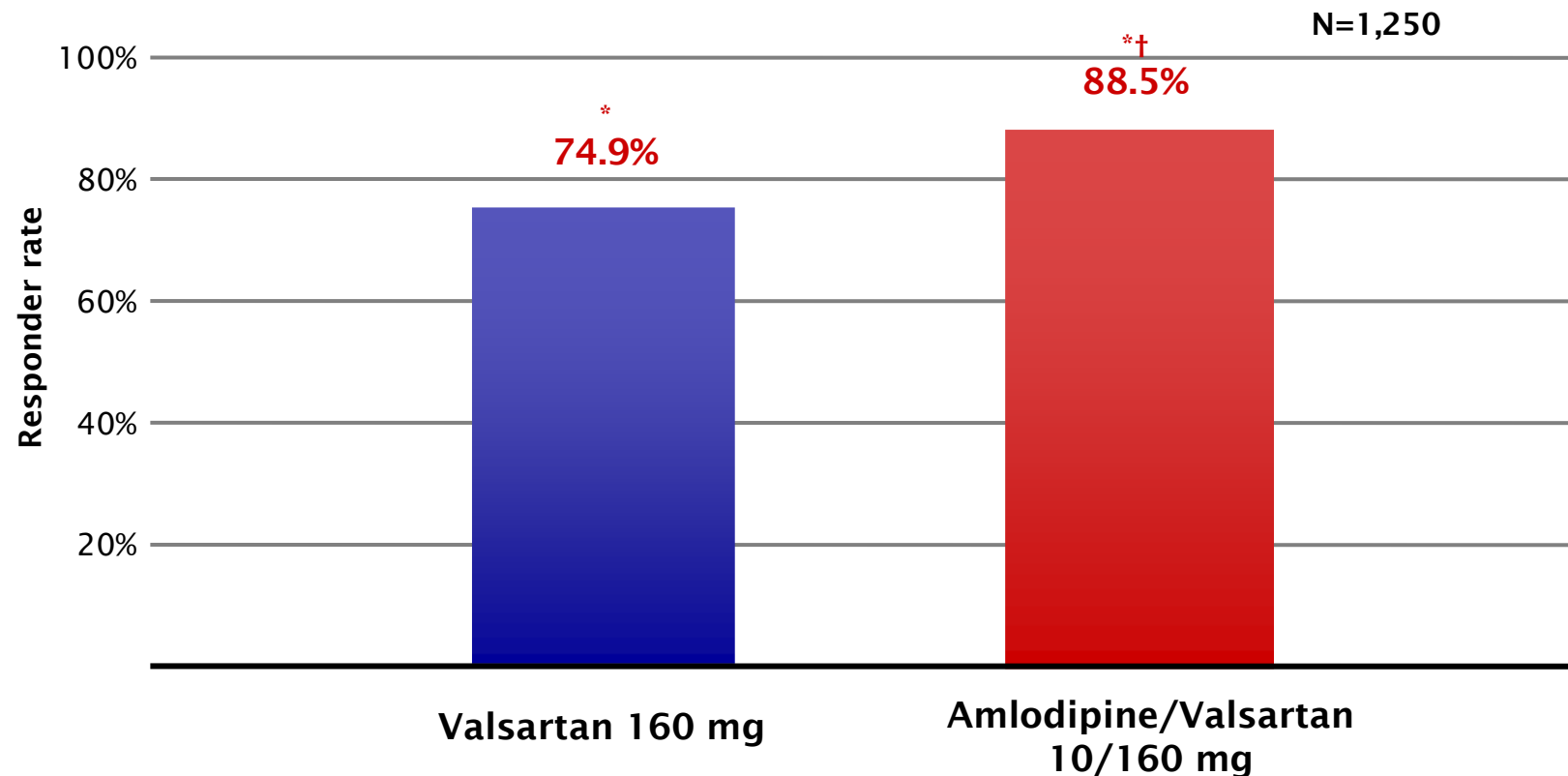
Poldermans et al. J Clin Hypertens 2006;8(5, Suppl A):A96 (poster)
Poldermans et al. J Hypertens 2006;24(Suppl 4):S20 (poster)

Amlodipine/Valsartan

BP-lowering efficacy and get to goal rates



Response rates in mild-to-moderate hypertension



*p<0.05 vs placebo; †p<0.05 vs valsartan

Mean sitting diastolic BP ≥ 95 mmHg and < 110 mmHg at study entry or randomization

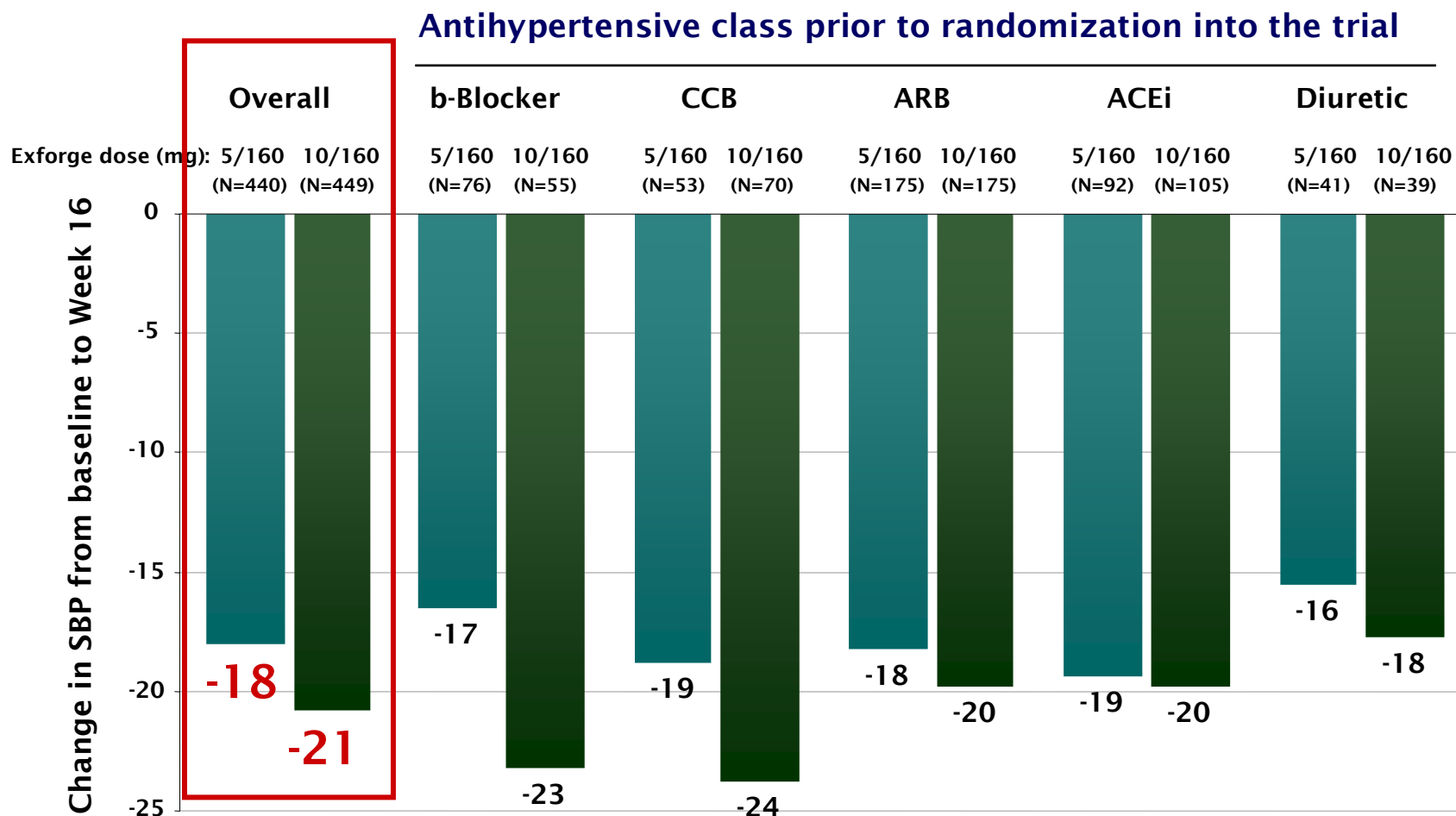
Response rate = MSDBP < 90 mmHg or ≥ 10 mmHg decrease vs baseline

Amlodipine/Valsartan

Efficacy on Non-Responders to Monotherapy



Antihypertensive efficacy of Exforge® in patients previously uncontrolled on monotherapy



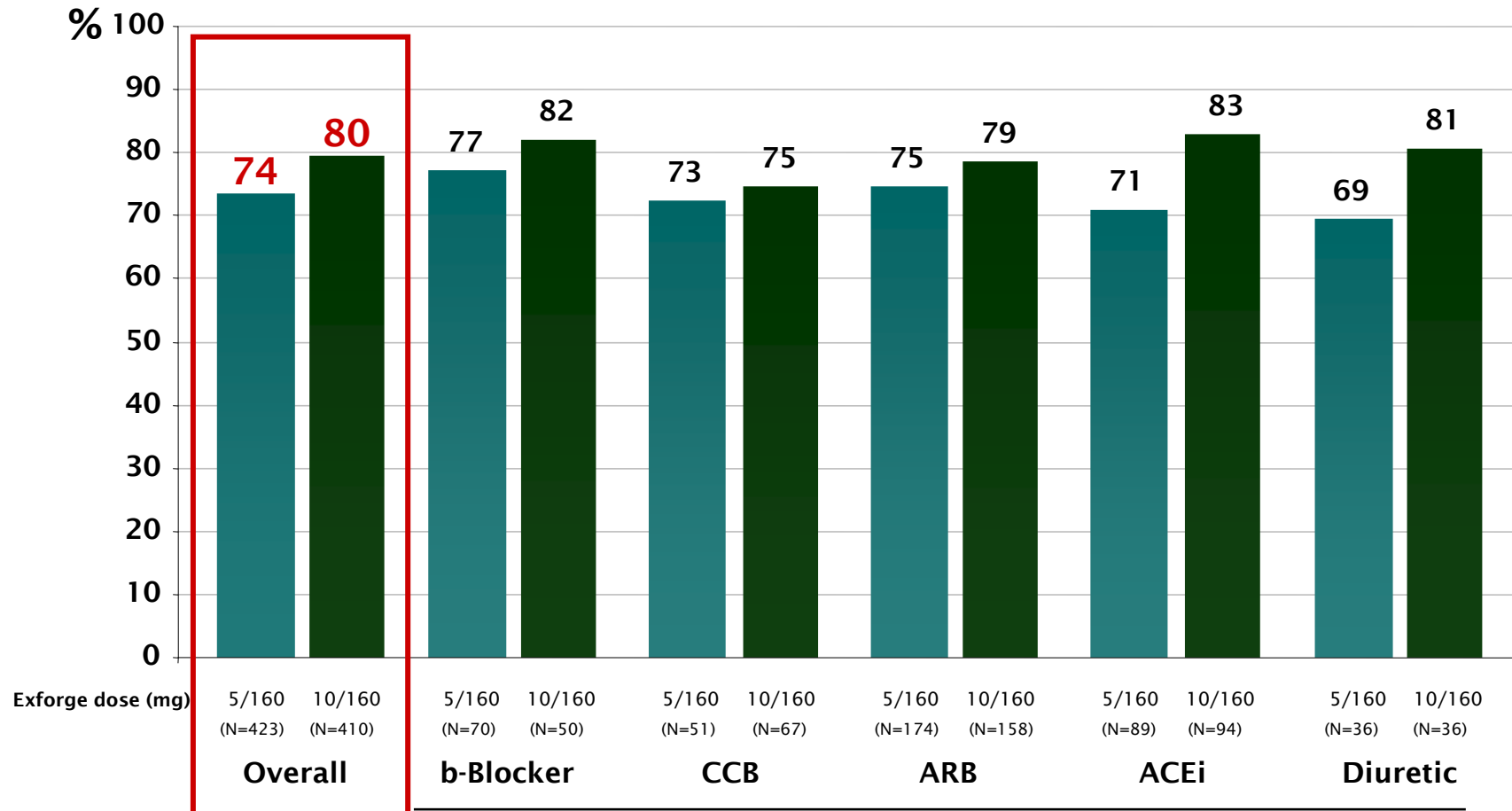
Presented in 2007 ASH

Amlodipine/Valsartan

Efficacy on Non-Responders to Monotherapy



BP Control Rates at Week 8* according to Prior BP Medication



Antihypertensive class prior to randomization into the trial

Control rate defined as BP <140/90 mmHg for non-diabetic and <130/80 mmHg for diabetic patients

* No HCTZ add-on was allowed until after week 8

Presented in 2007 ASH

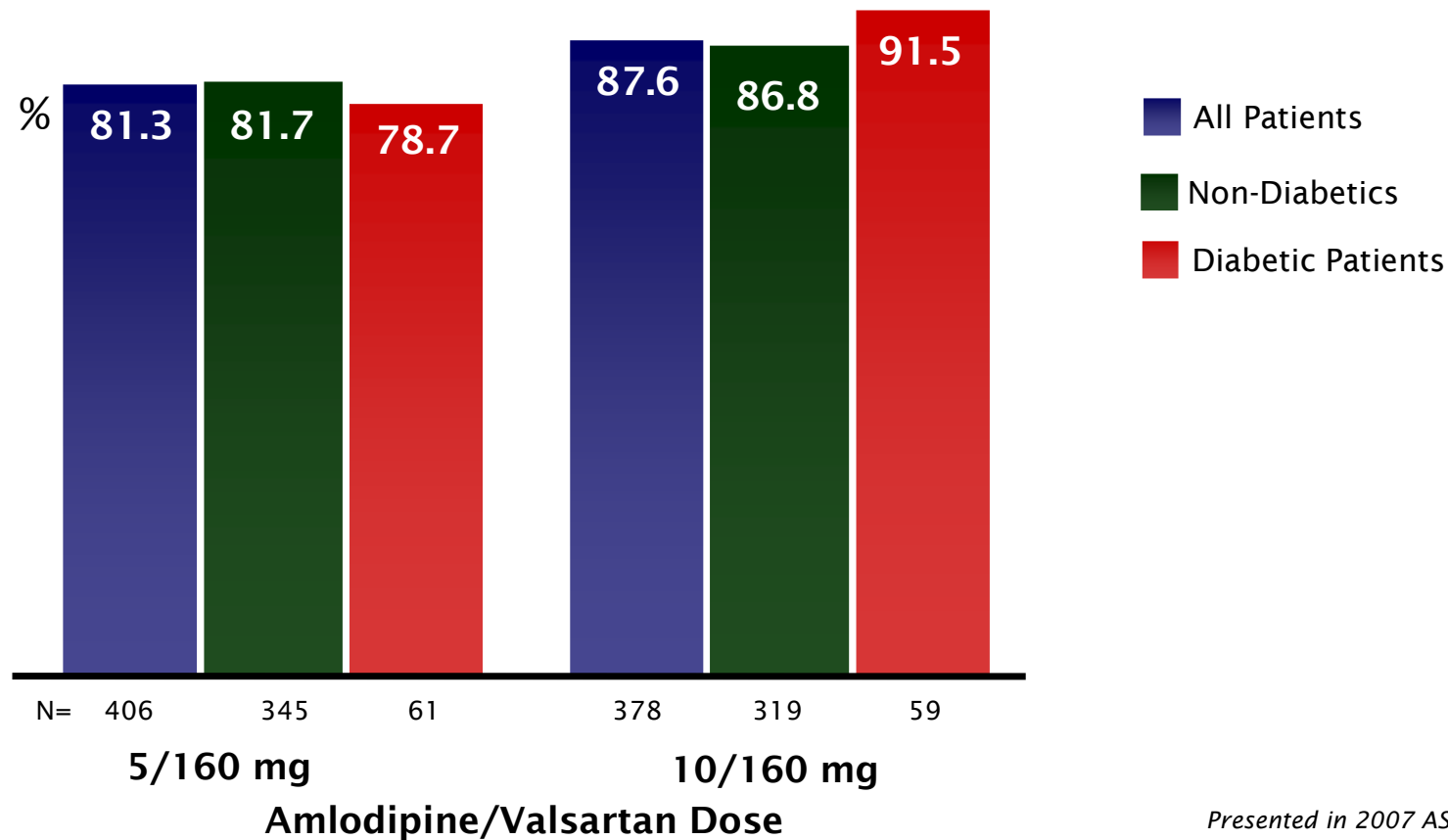
Amlodipine/Valsartan

Efficacy on Non-Responders to Monotherapy



% Patients achieving BP <140/90 mmHg at Week 16 by DM Status

Diabetic Patients with BP<130/80 at Week 16 were 45.9% & 40.7% for 5/160 & 10/160 mg doses, respectively.



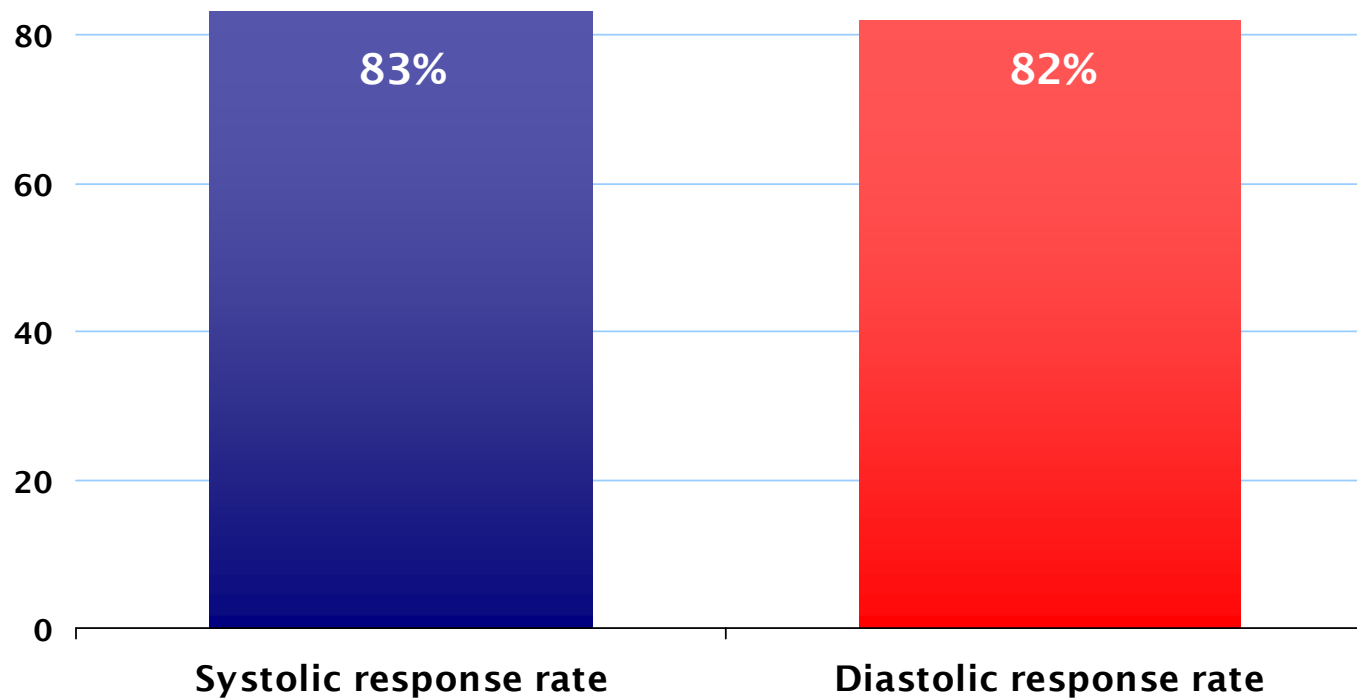
Presented in 2007 ASH

Amlodipine/Valsartan



Efficacy on Non-Responders to Combination Therapy “ExPress-C”

Systolic/diastolic responder rates with amlodipine/valsartan 10/160 mg among non-responders to ramipril/felodipine 5/5 mg



Systolic response: SBP <140 mmHg or ≥ 20 mmHg decrease compared to Visit 4*
Diastolic response: DBP <90 mmHg or ≥ 10 mmHg decrease compared to Visit 4*

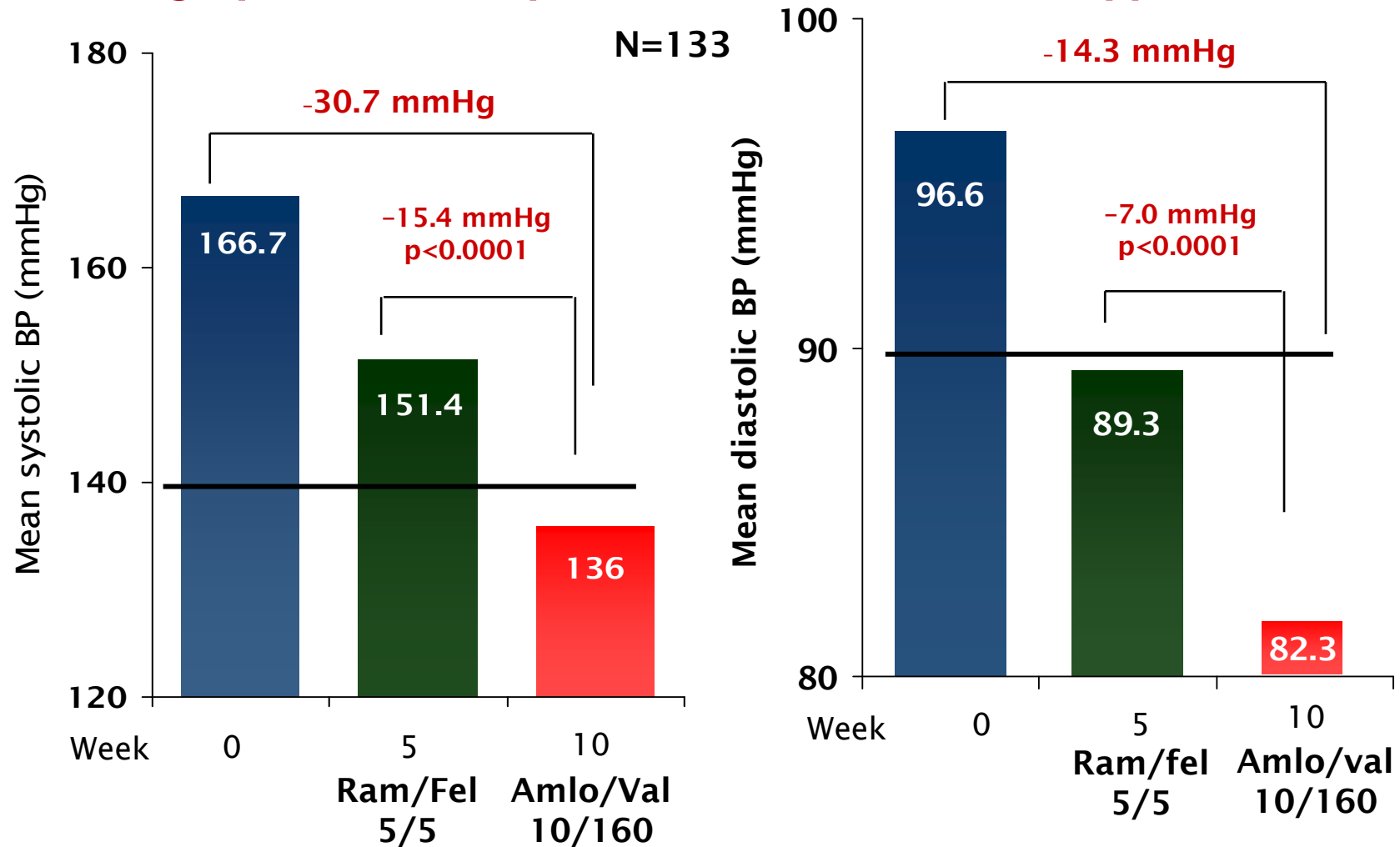
*Visit 4 occurred at the end of ramipril/felodipine therapy

Trenkwalder et al. DMW 2006;131:S164

Amlodipine/Valsartan

Efficacy on Non-Responders to Combination Therapy “ExPress-C”

↓ 31 mmHg Systolic BP in patients with moderate hypertension



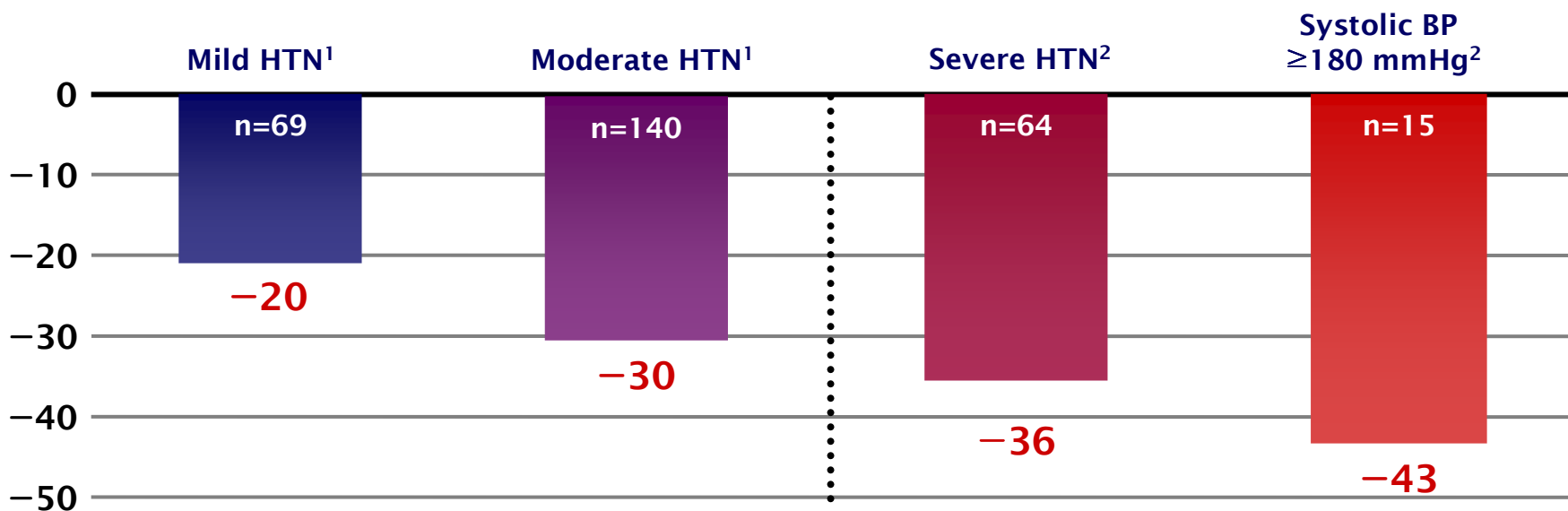
Amlodipine/Valsartan

Efficacy across Different Grades of Hypertension



BP lowering across all grades of hypertension

Mean change in mean sitting SBP from baseline (mmHg)



DBP Reduction (mmHg)	-17	-18	-29	-26
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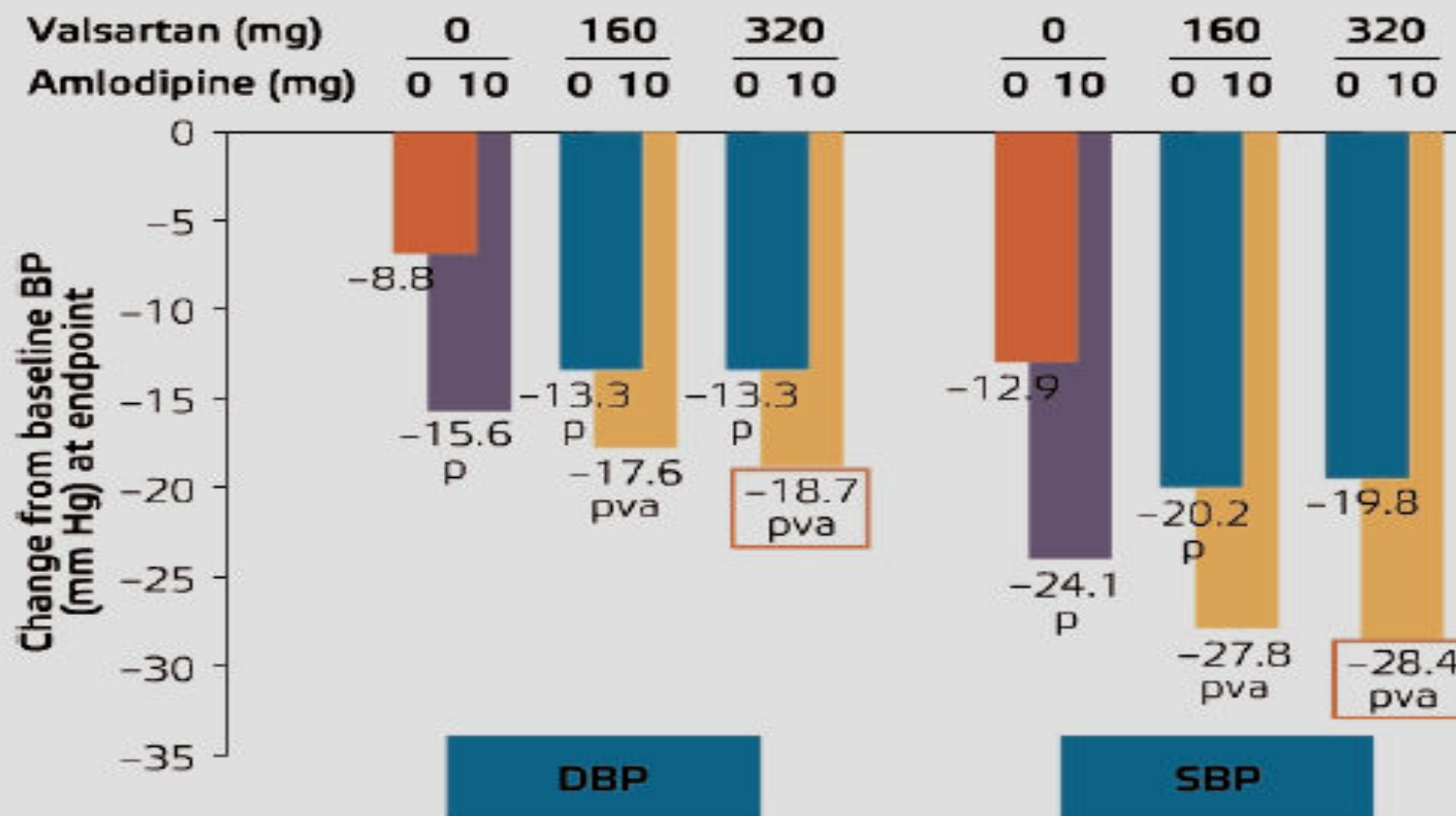
¹Novartis data on file: Dose 10/160 mg

²Data from Poldermans et al. J Hypertens 2006;24(Suppl 4):S20 (poster): Dose 5-10/160 mg

Amlodipine/Valsartan

Efficacy in All Doses

Figure 2. Study 2307: Decreases in Absolute BP Are Competitive

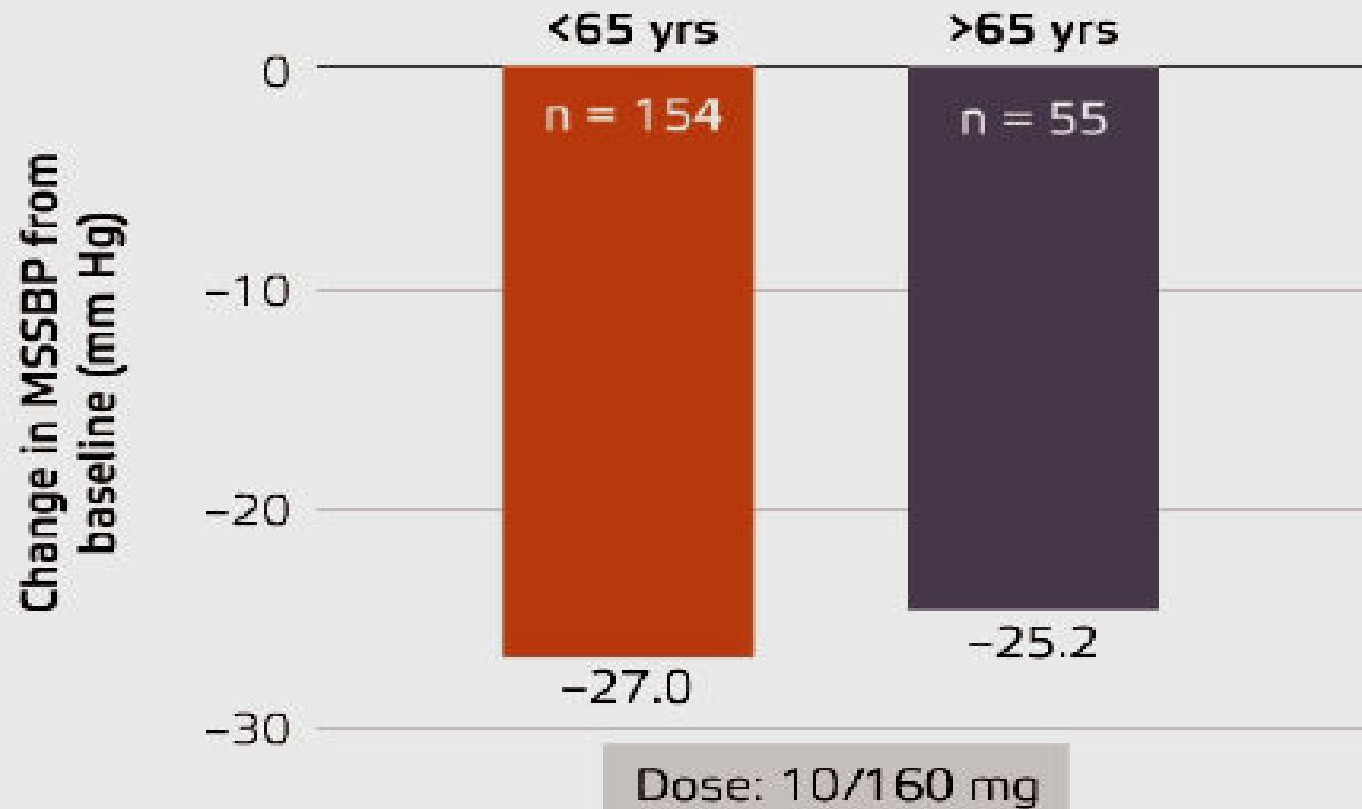


p = Statistically significant vs placebo ($P < 0.05$)
 v = Statistically significant vs valsartan ($P < 0.05$)
 a = Statistically significant vs amlodipine ($P < 0.05$)

Amlodipine/Valsartan

Efficacy across All Ages

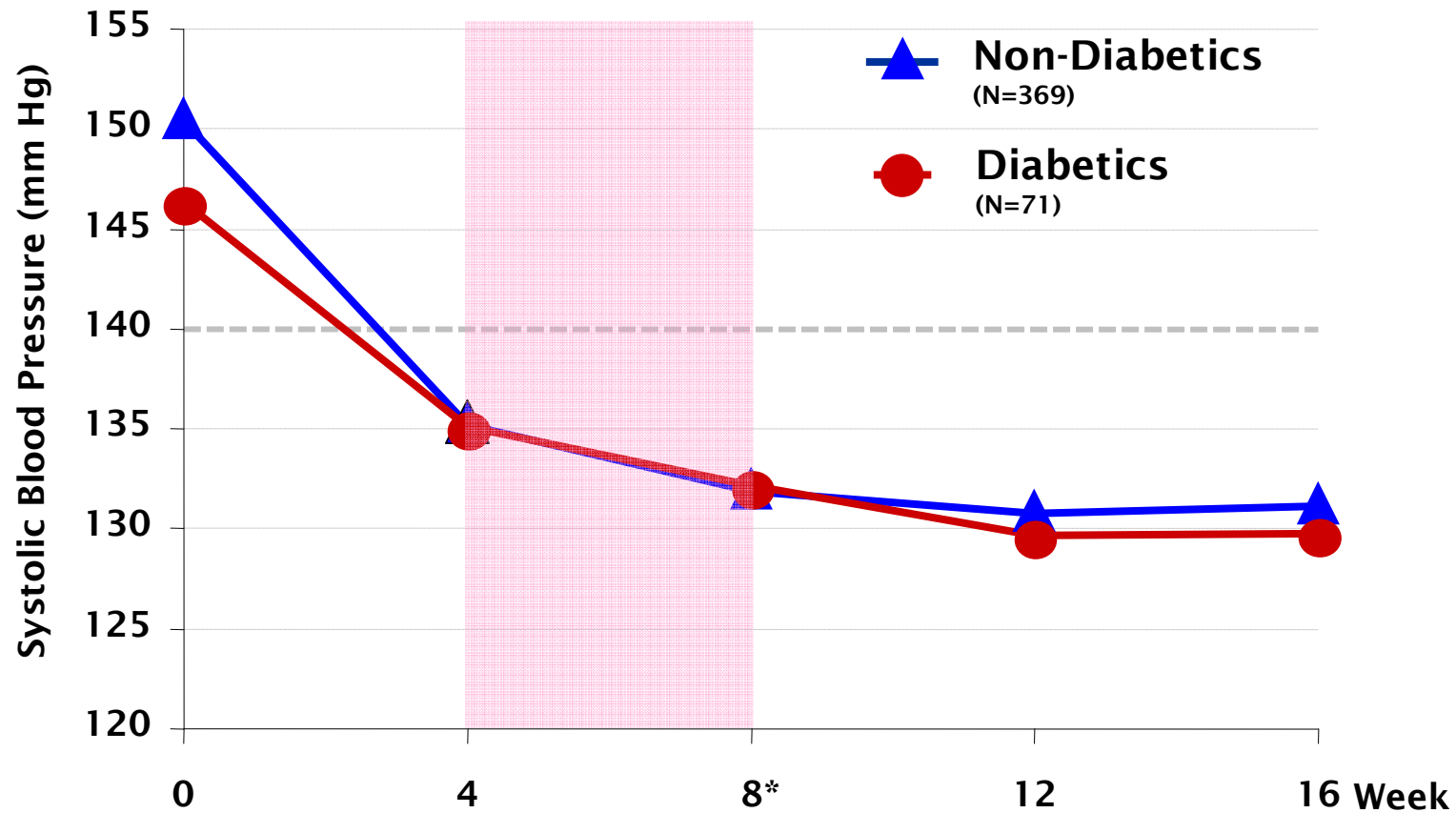
Figure 4. Efficacy of EXFORGE Across All Ages



Baseline BP: ≥ 95 and < 100 mm Hg
Patients with stage 3 (DBP > 110 mm Hg or SBP ≥ 180 mm Hg) were excluded.

Amlodipine/Valsartan

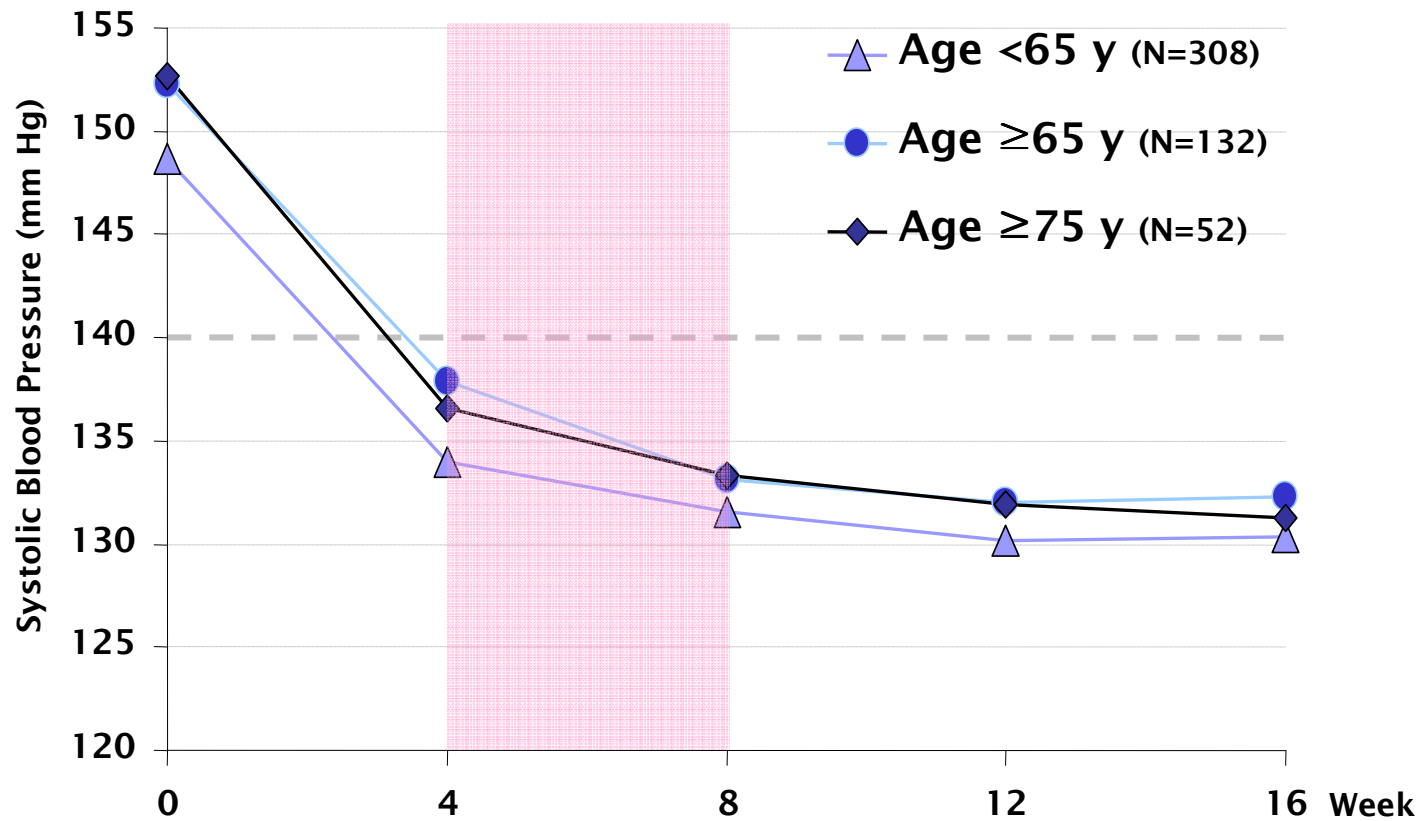
Rapid Control of BP: Non-DM vs. DM



Change from baseline in SBP was **-18.5 mmHg** for the Non-Diabetics and **-14.9 mmHg** for Diabetic Patients.
*Patients not at BP goal had the option to receive HCTZ add-on starting at 8 weeks

Amlodipine/Valsartan

Rapid Control of BP across All Ages



Change from baseline to Endpoint in SBP (ITT population) was **-17.9 mmHg** for Patients <65 y, **-18.2 mmHg** for Patients >65 y and **-19.7 mmHg** for Patients >75 y

*Patients not at BP goal had the option to receive HCTZ add-on starting at 8 weeks

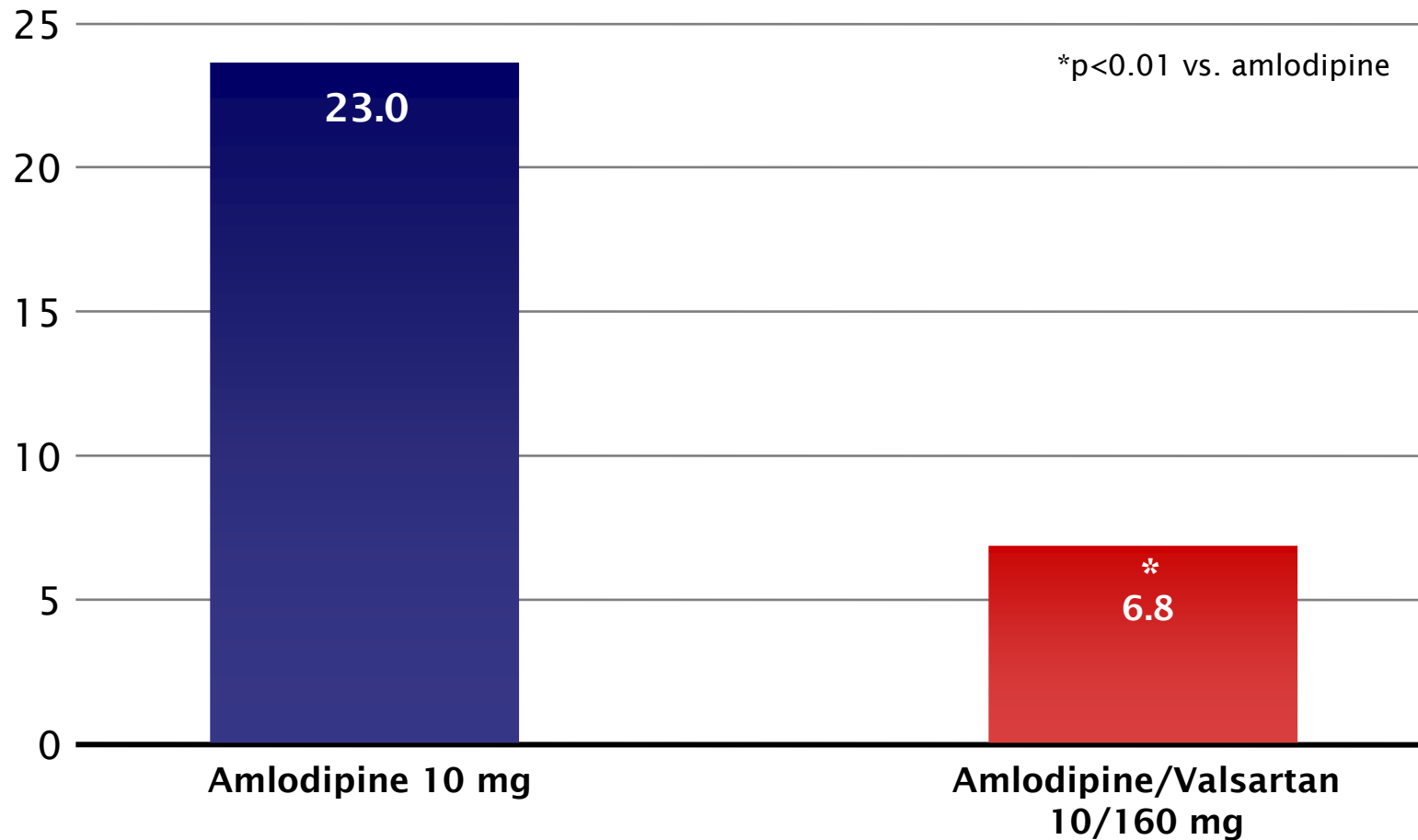
Amlodipine/Valsartan

Safety and Tolerability



↓ Fluid retention with amlo/val compared with amlo monotherapy

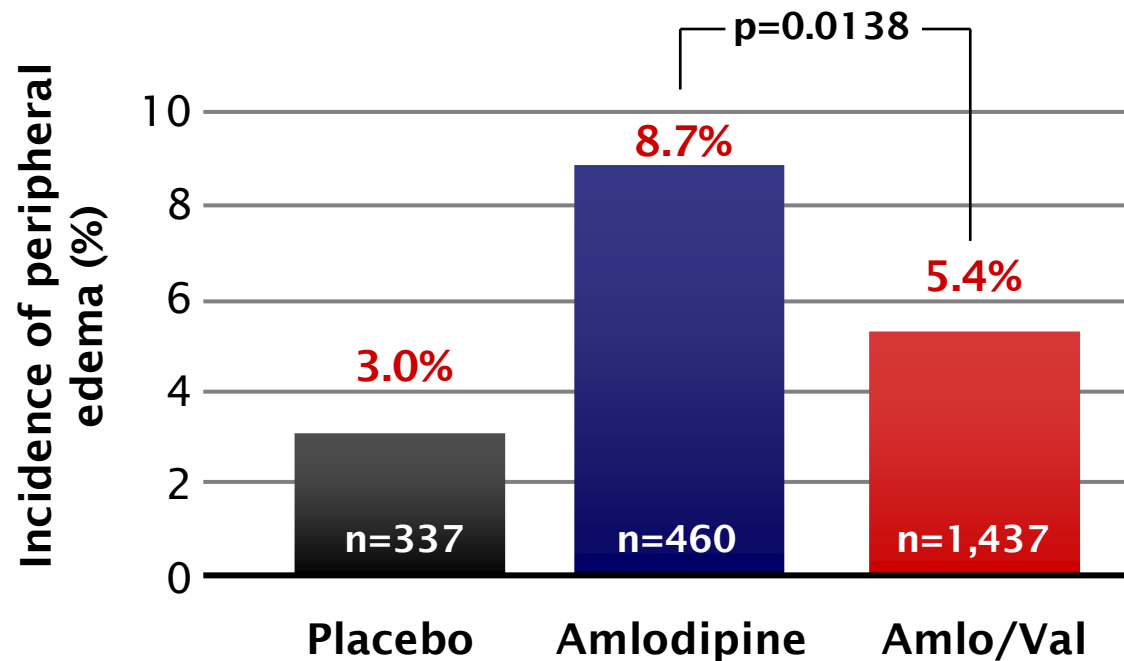
Ankle-foot volume increase (%)



Amlodipine/Valsartan

Safety and Tolerability

Effect on amlodipine-induced peripheral edema



Pooled data from two trials at doses of Amlo/Val up to 10/320 mg and Amlo up to 10 mg

Novartis data on file

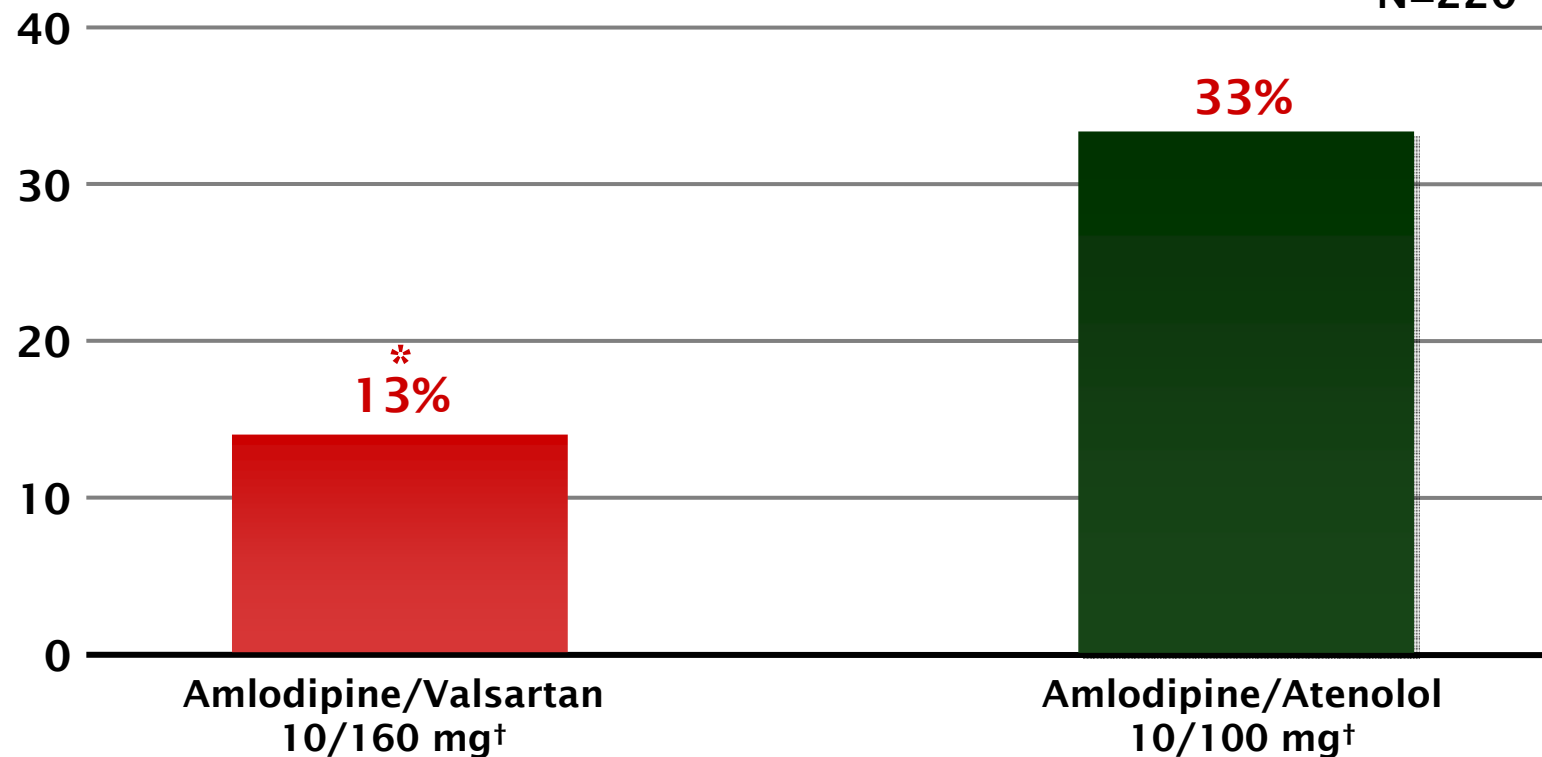
Amlodipine/Valsartan

Safety and Tolerability

Recurrence of atrial fibrillation with Amlodipine/Valsartan compared with Amlodipine/Atenolol during a 1-year follow-up

Patients with at least one symptomatic or non-symptomatic ECG-documented episode of atrial fibrillation (% incidence)

N=220



*p<0.01 vs amlodipine/atenolol

[†]Titration to maximum dose of amlodipine

Mugellini et al. J Hypertens 2006;24(Suppl. 4):S5

Take-away Messages

Exforge[®] shows...

- **Big SBP reduction**
- **Superior efficacy across all the grades of HiBP**
- **Additional BP lowering in any mono uncontrolled**
- **Additional BP lowering in combination uncontrolled**
- **Wealth in safety and tolerability evidence**



Ex(tra)+Forge



Safely

“√ Big Drop of BP”