Angiotensin receptor blocker/CBC combincation:A rational approach for such an antihypertensive strategy

Getz pharma

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Hypertension

- It is defined as:
  - A sustained SBP > 130 mm Hg

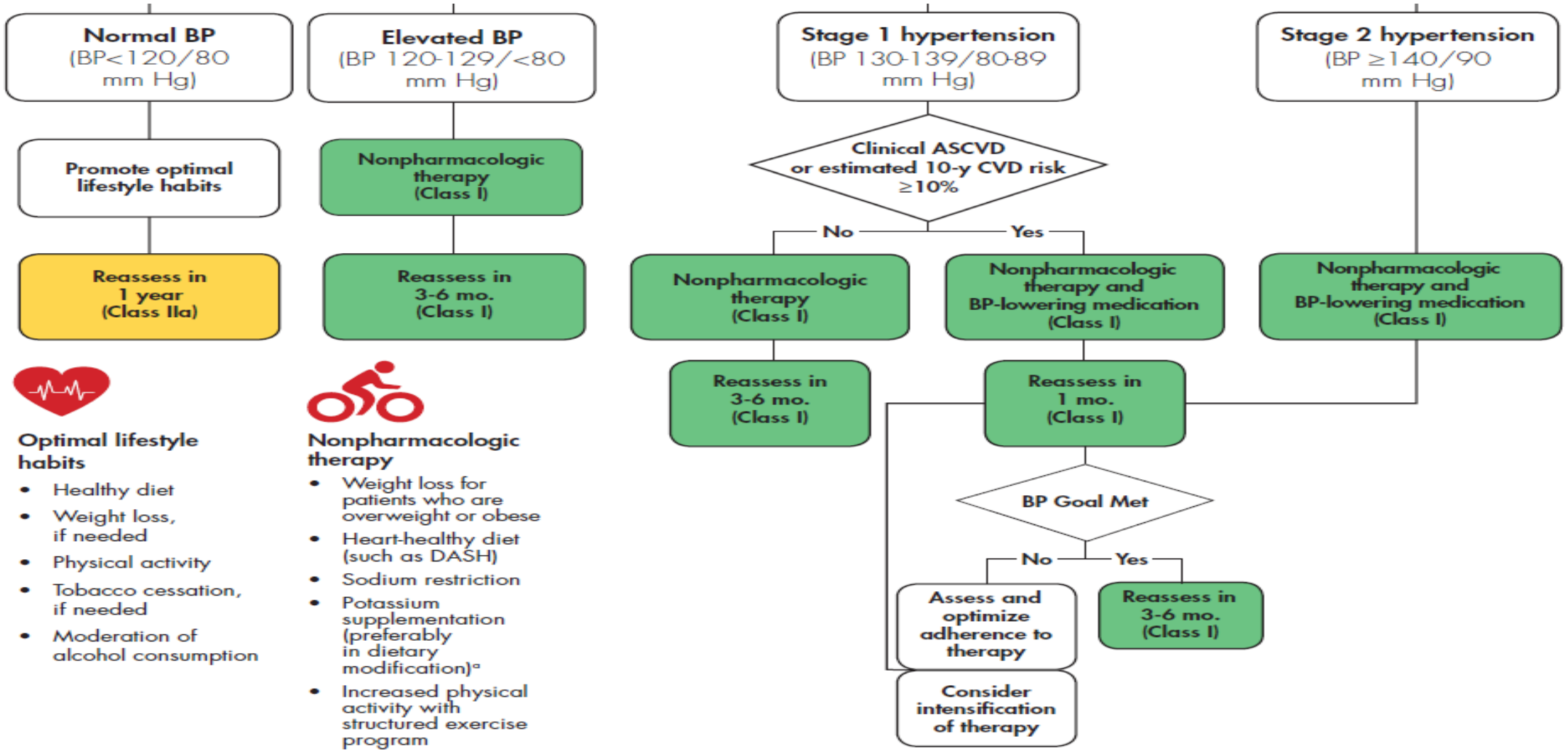
    OR
  - A sustained DBP > 90 mm Hg
- The protocol of reading include:
  - Average of two or more readings
  - In seated condition
  - On each of two or more visits.

HTN DEFINITION AHA/ACA 2017

BP Category	BP Category		BP Category
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.



Optimal lifestyle habits

- Healthy diet
- Weight loss, if needed
- Physical activity
- Tobacco cessation, if needed
- Moderation of alcohol consumption

Nonpharmacologic therapy

- Weight loss for patients who are overweight or obese
- Heart-healthy diet (such as DASH)
- Sodium restriction
- Potassium supplementation (preferably in dietary modification)[a]
- Increased physical activity with structured exercise program
- Limitation of alcohol to 1 (women) or 2 (men) standard drinks per day[b]

[a] Unless contraindicated by the presence of chronic kidney disease or use of drugs that reduce potassium excretion.
[b] In the United States, one standard drink is equivalent to 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), or 1.5 oz of distilled spirits (usually about 40% alcohol).

Classification of hypertension stages according to BP levels, presence of CV risk factors, HMOD, or comorbidities

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High-normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥ 180 DBP ≥ 110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥ 3 risk factors	Low to moderate risk	Moderate to high risk	High risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥ 4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

Williams, Mancia et al., J Hypertens 2018;36:1953-2041 and Eur Heart J 2018;39:3021-3104

CVD RISK FACTORS COMMON IN PATIENTS WITH HYPERTENSION

Modifiable Risk Factors*

- Current cigarette smoking, secondhand smoking
- Diabetes mellitus
- Dyslipidemia/hypercholesterolemia
- Overweight/obesity
- Physical inactivity/low fitness
- Unhealthy diet

Relatively Fixed Risk Factors†

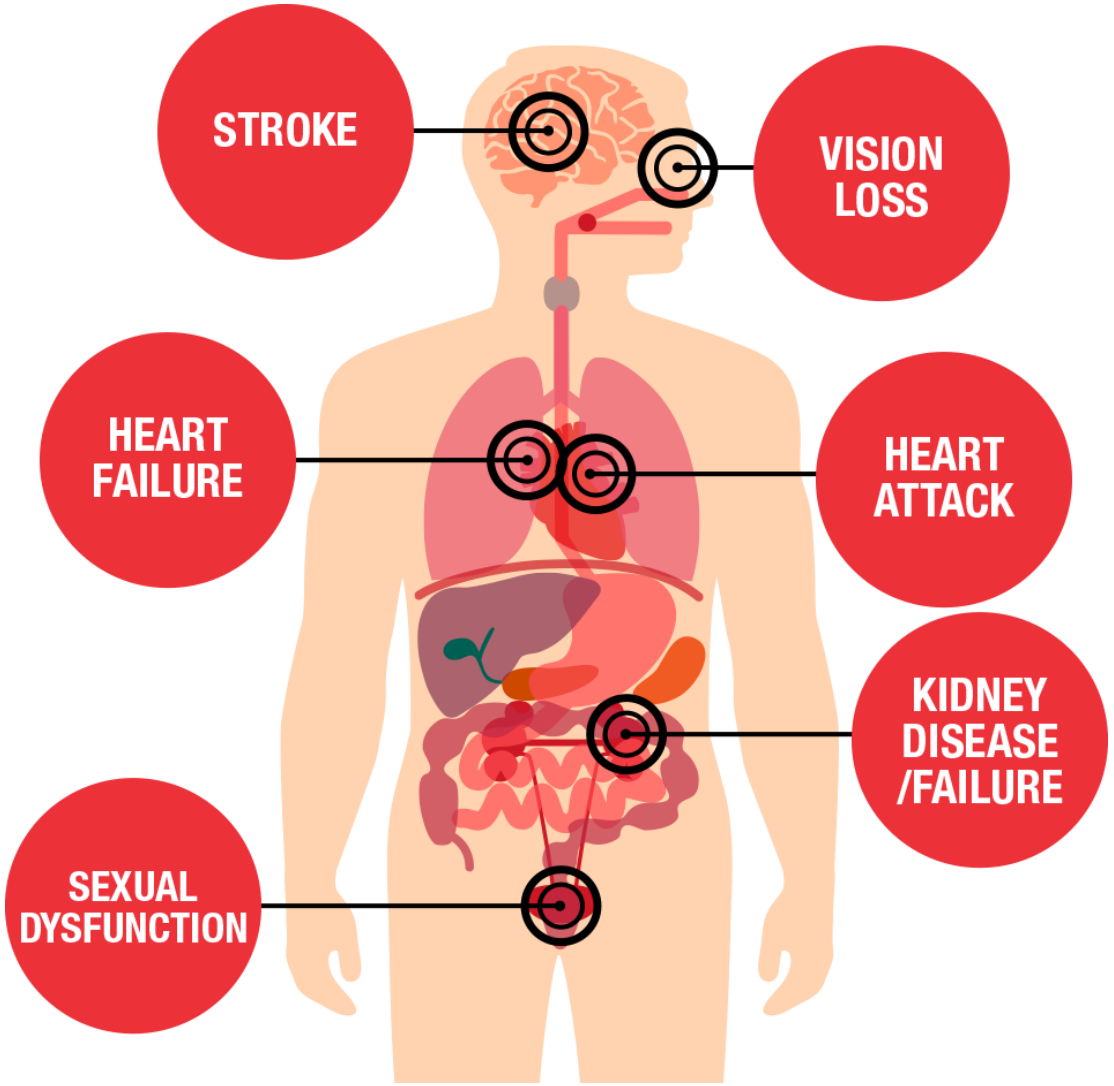
- CKD
- Family history
- Increased age
- Low socioeconomic/educational status
- Male sex
- Obstructive sleep apnea
- Psychosocial stress

*Factors that can be changed and, if changed, may reduce CVD risk.

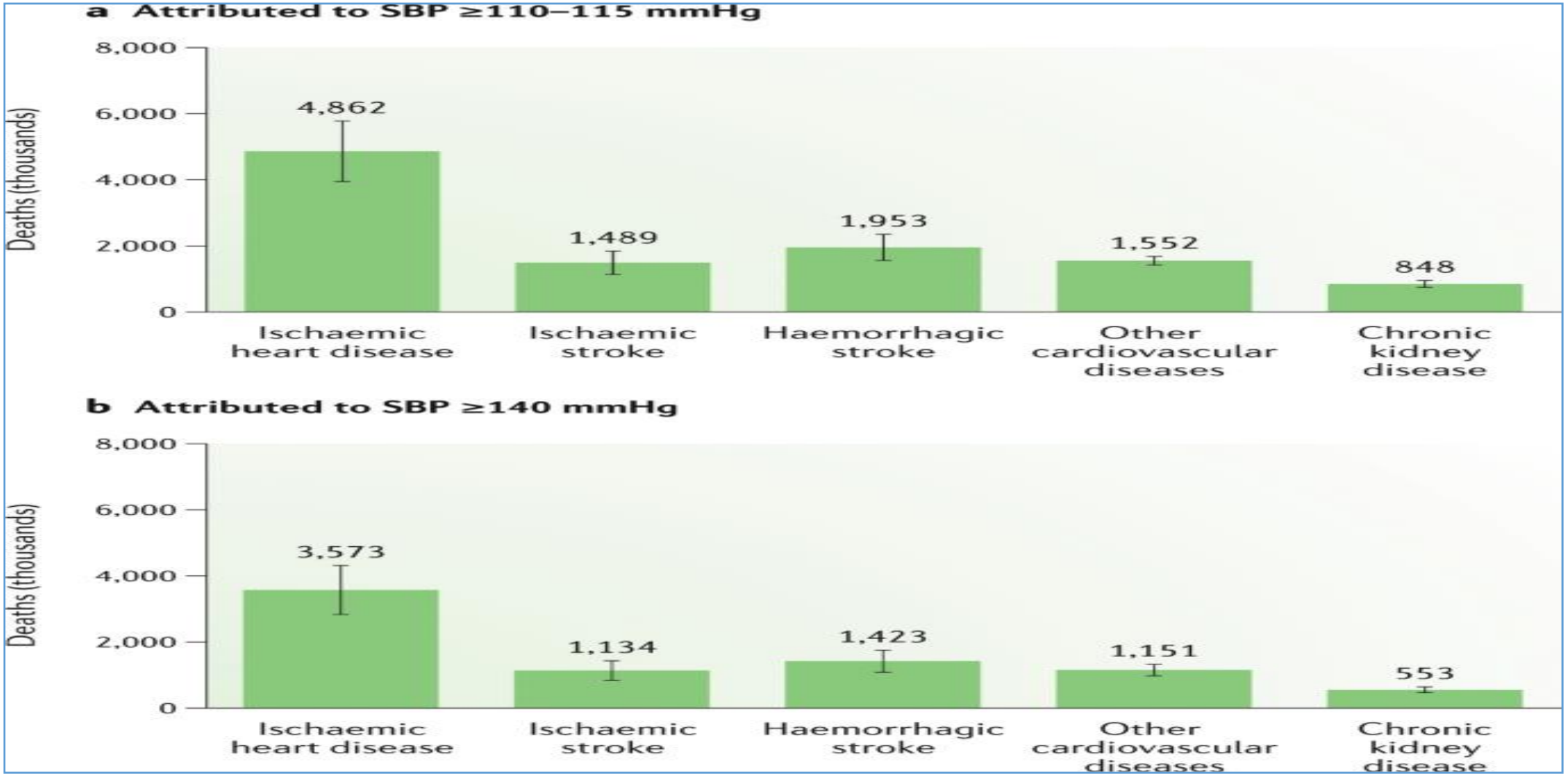
†Factors that are difficult to change (CKD, low socioeconomic/educational status, obstructive sleep apnea, cannot be changed (family history, increased age, male sex), or, if changed through the use of current intervention techniques, may not reduce CVD risk (psychosocial stress).

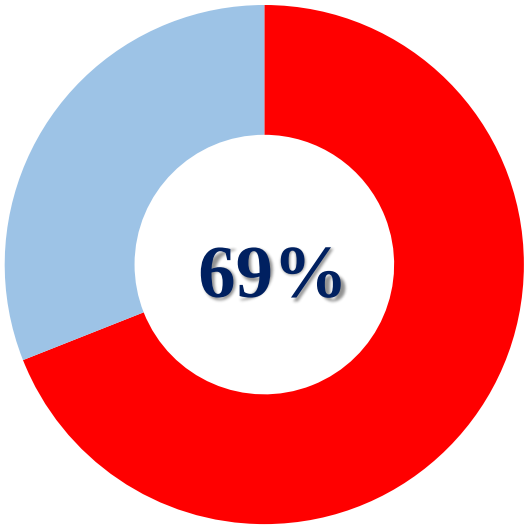
CKD indicates chronic kidney disease; and CVD, cardiovascular disease.

Hypertension-Associated Target-Organ Damage

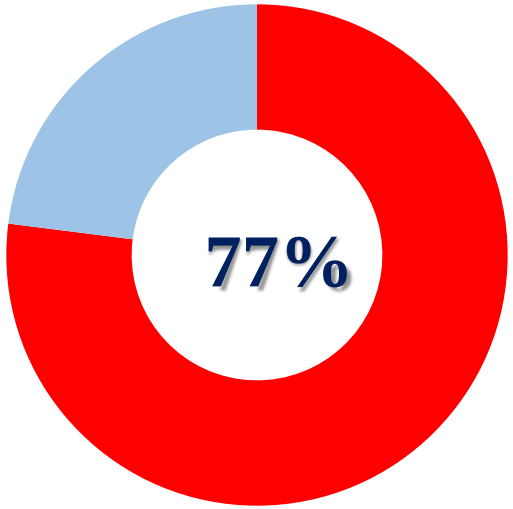


Hypertension remains a major cause of premature death worldwide

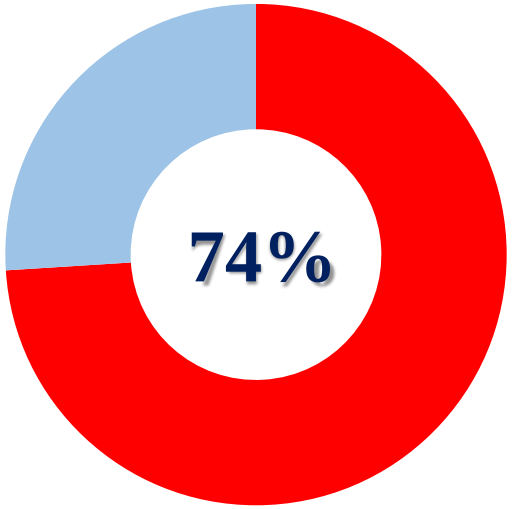




Of people who have a first heart attack.



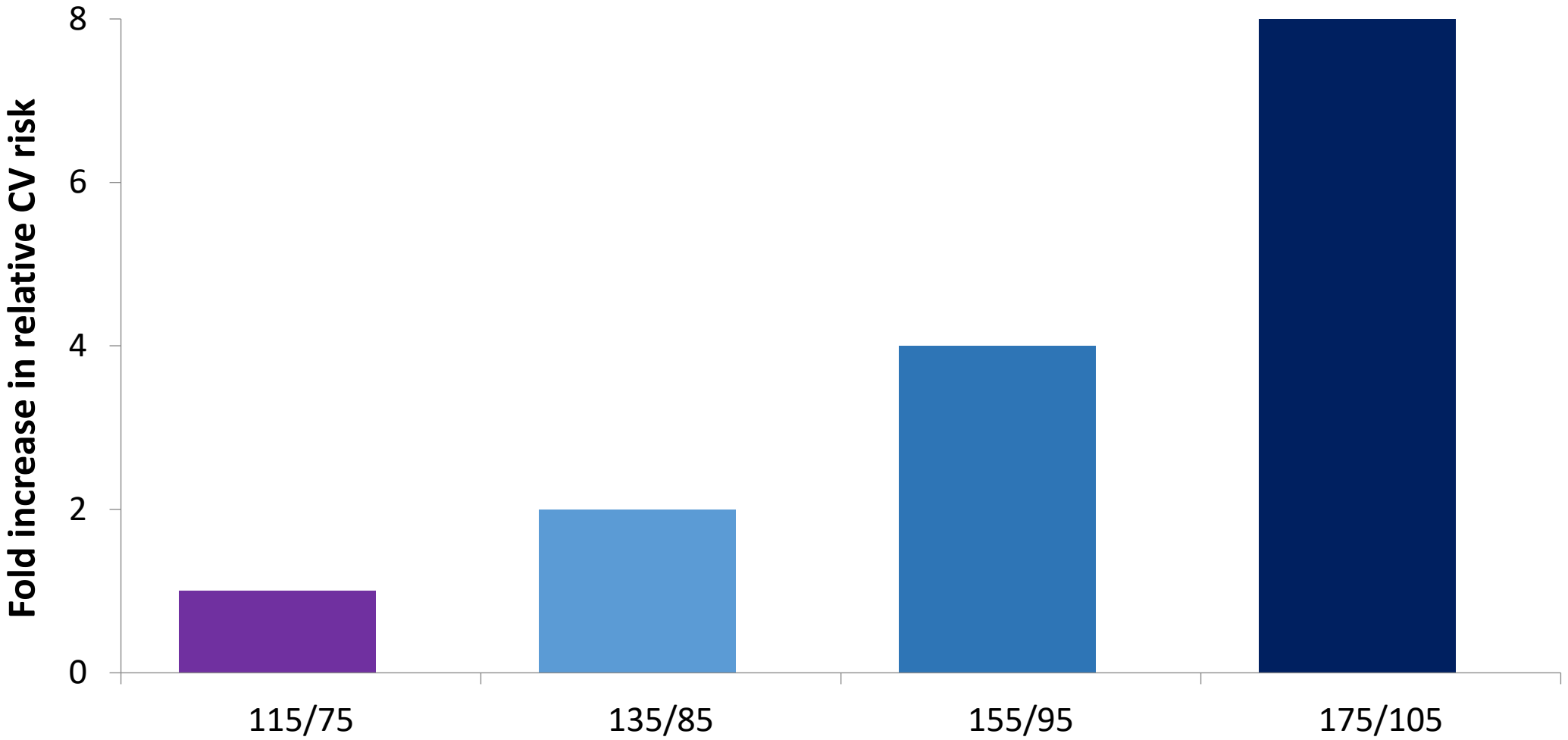
Of people who have a first stroke.



Of people with a chronic heart failure.

Have high blood pressure

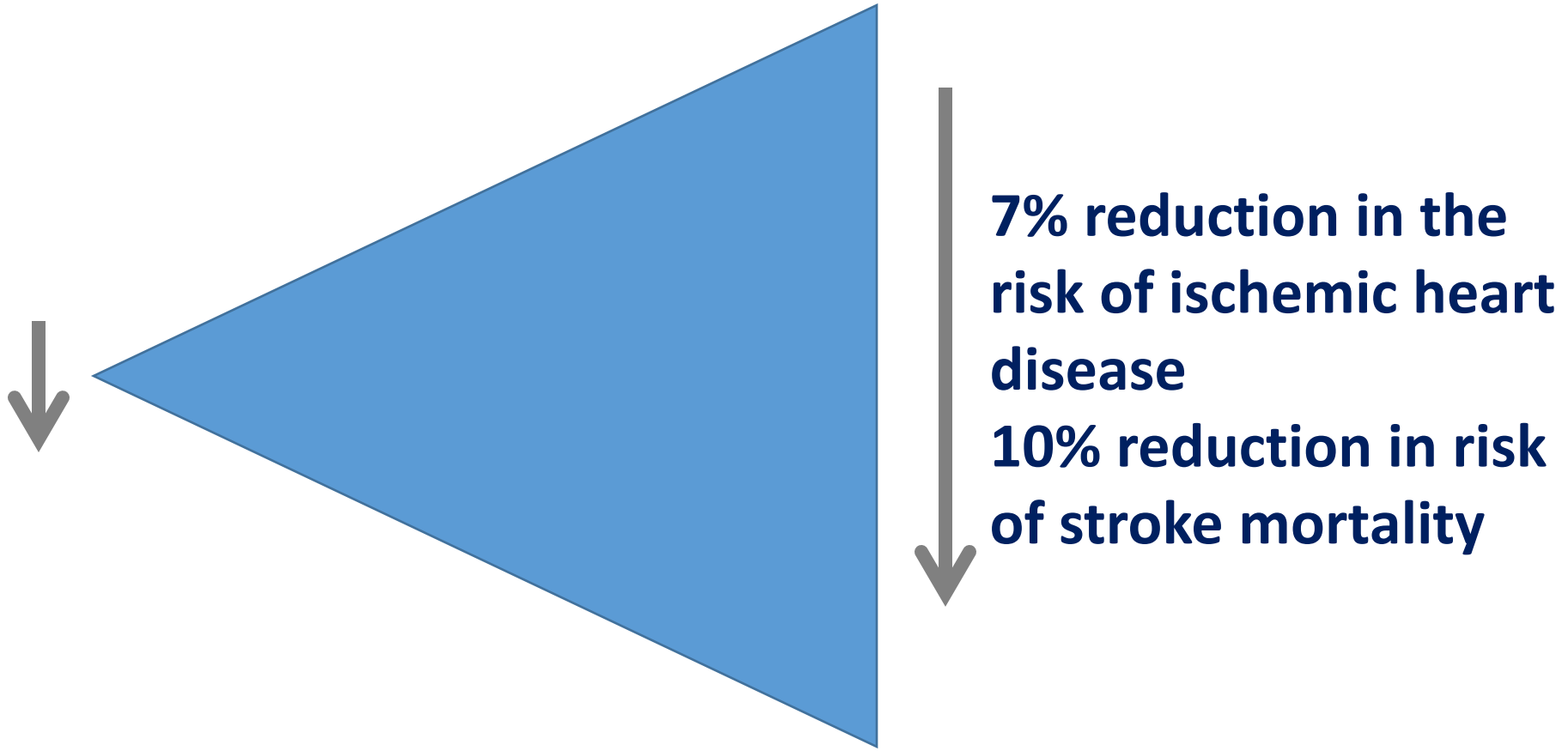
Cardiovascular mortality risk doubles with each 20/10 mmHg increment in systolic diastolic BP



lewington et al lancet 2002;360:1903-13

BP reduction of 2 mmHg decrease the risk of CV events by 7-10%

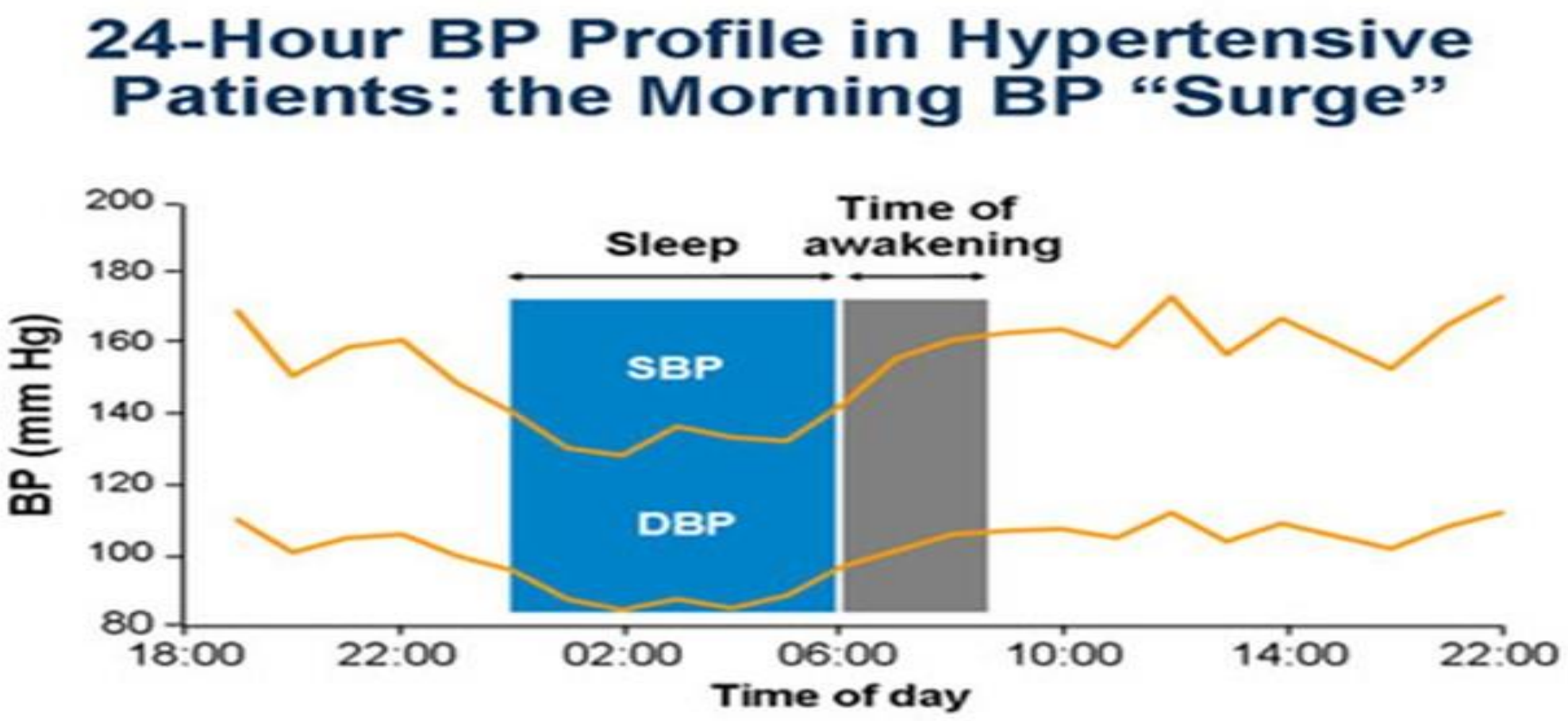
2 mmHg reduction in mean SBP



7% reduction in the risk of ischemic heart disease
10% reduction in risk of stroke mortality

lewington et al lancet 2002;360:1903-13

Morning surge increase in BP



Millar-Craig MW et al. *Lancet* 1978;795-797.

Morning surge increase in BP

- Epidemiologic studies have also shown that there is a substantial increase in the rate of :

1. acute myocardial infarction
2. ischemic stroke

- and sudden death in the early morning period—especially during the first 4 to 6 h after awakening.

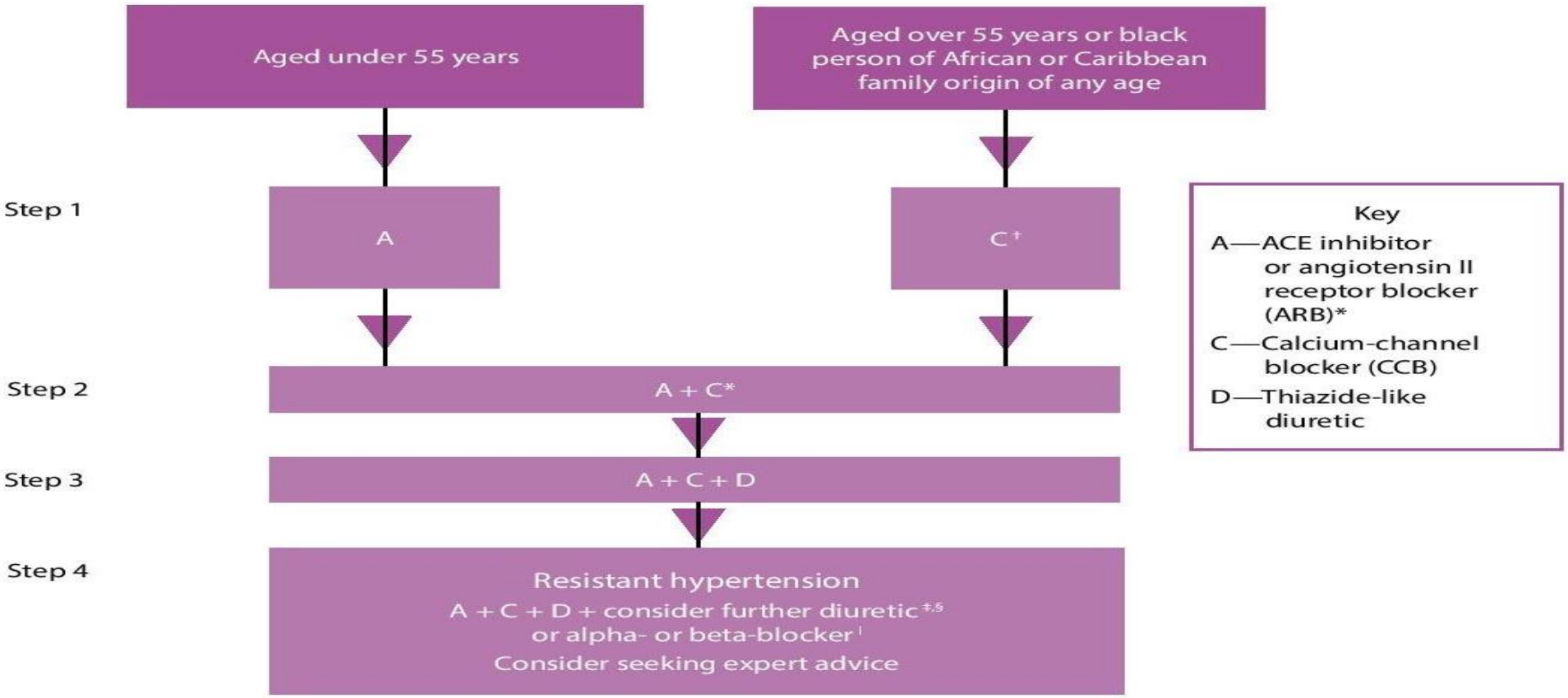
Hypertension management

- Non pharmacological :
  - Lifestyle Modifications
  - WEIGHT REDUCTION
  - DASH EATING PLAN
  - DIETARY SODIUM RESTRICTION
  - PHYSICAL ACTIVITY

JNC VIII Guidelines for Treatment of HTN

* non black population JAMA. Doi:10.1001/jama.2013.284427
Published online December 18, 2013.

Updated NICE guideline for hypertension



* Choose a low-cost ARB.

† A CCB is preferred but consider a thiazide-like diuretic if a CCB is not tolerated or the person has oedema, evidence of heart failure or a high risk of heart failure.

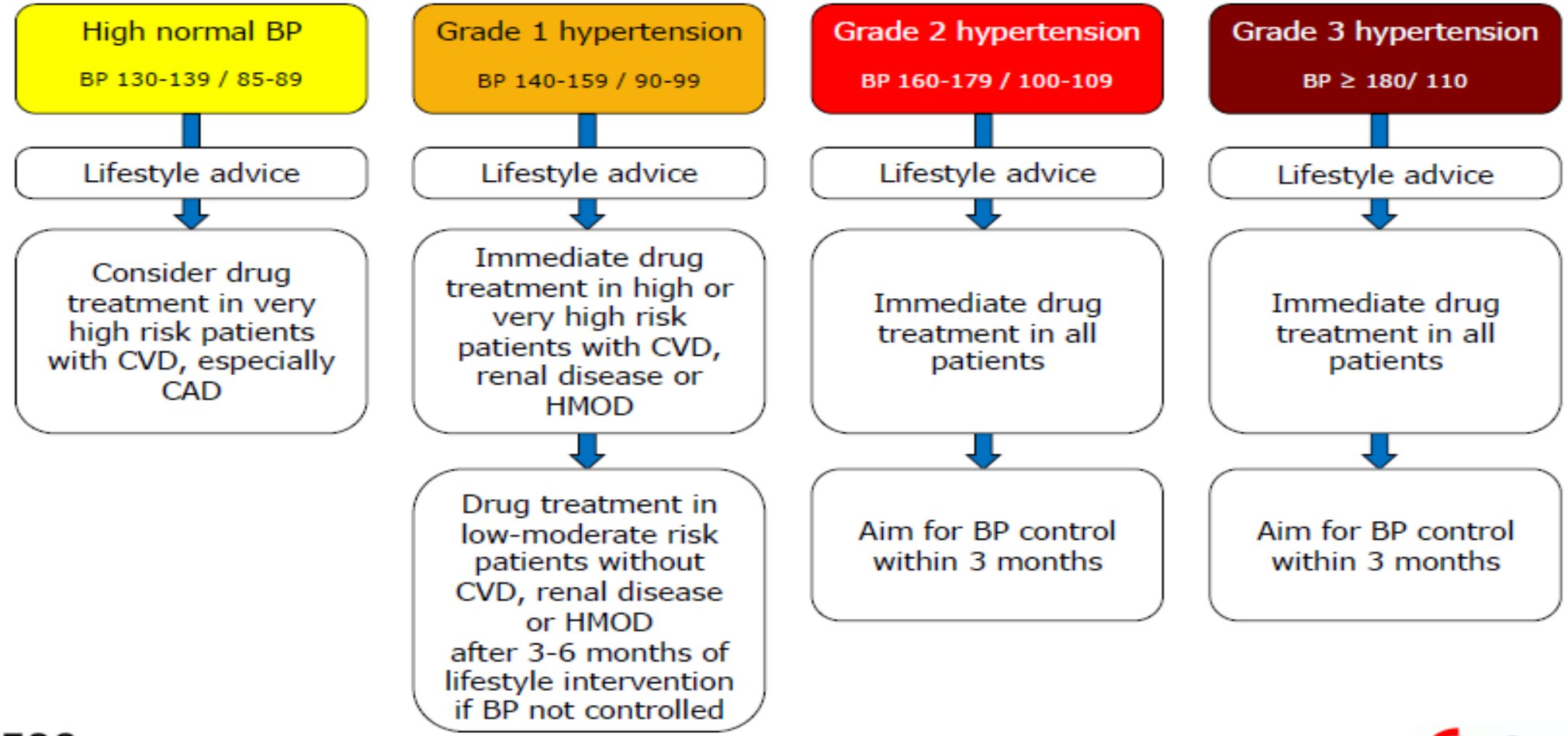
‡ Consider a low dose of spironolactone§ or higher doses of a thiazide-like diuretic.

§ At the time of publication (August 2011), spironolactone did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented.

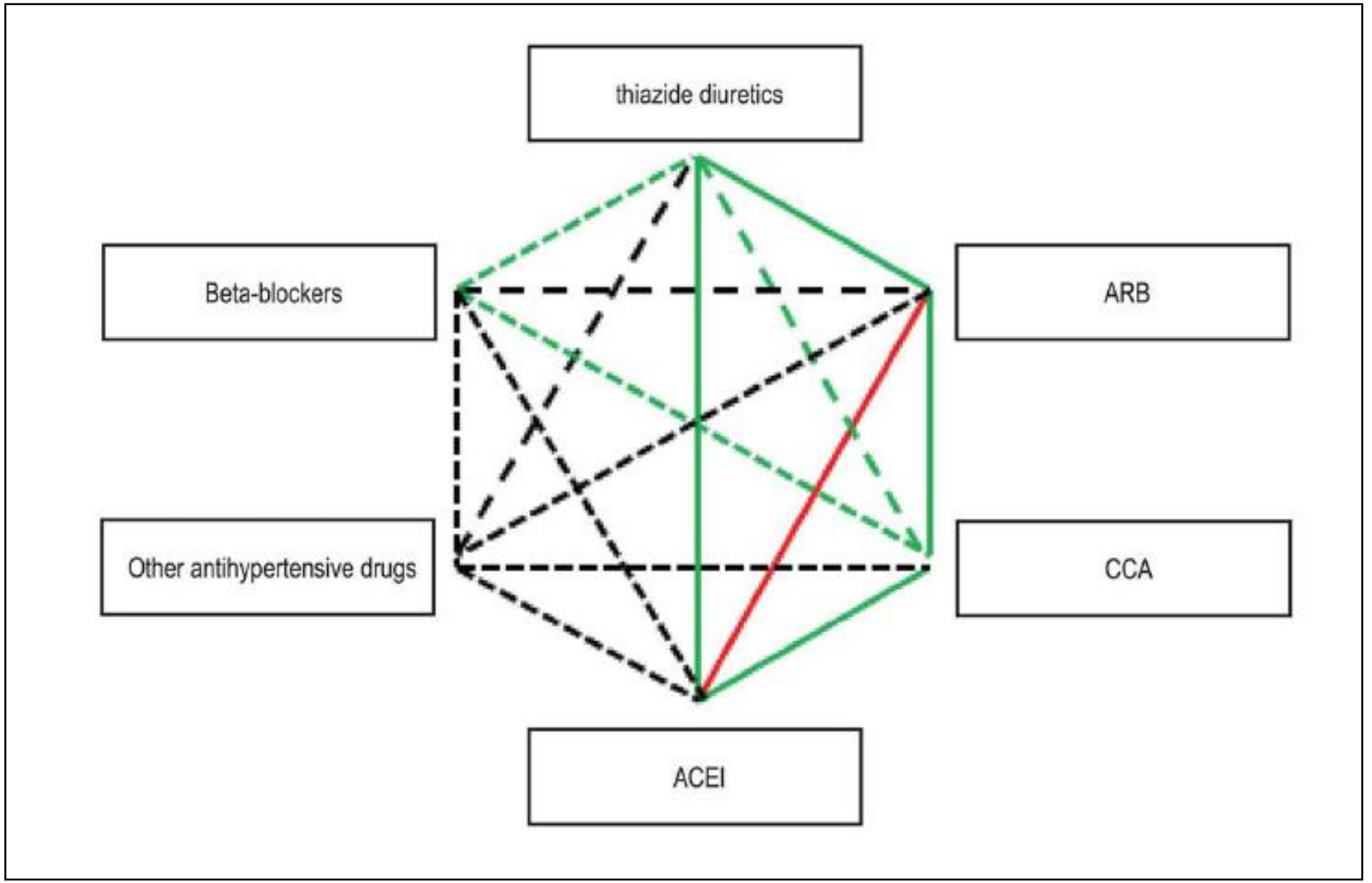
‖ Consider an alpha or beta blocker if further diuretic therapy is not tolerated, or is contraindicated or ineffective.

ESH and ESC Guideline of Hypertension

Initiation of BP-lowering treatment (lifestyle changes and medication) at different initial office BP levels



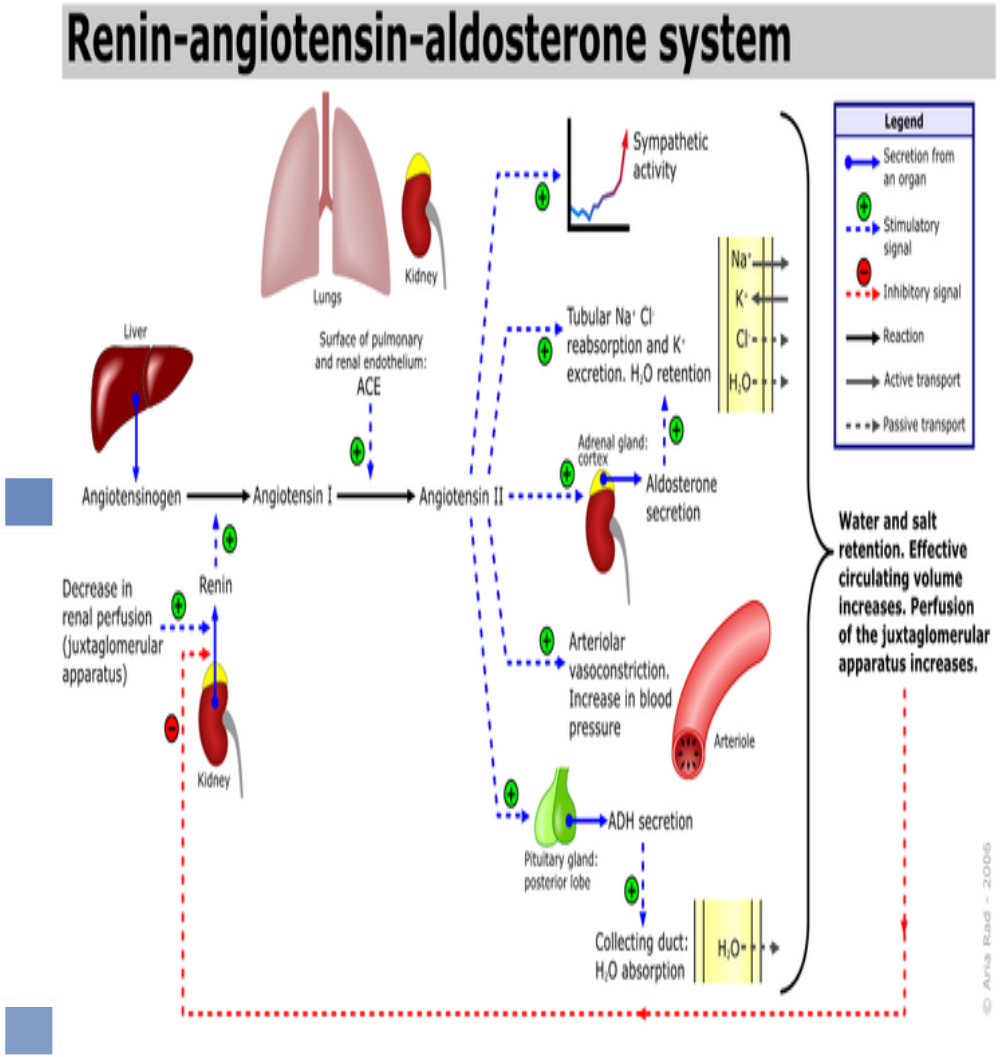
Williams, Mancia et al., J Hypertens 2018;36:1953-2041 and Eur Heart J 2018;39:3021-3104


thiazide diuretics
Beta-blockers
ARB
Other antihypertensive drugs
CCA
ACEI

Angiotensin receptor blockers

ARBs selectively competes with angiotensin II for the binding of the **angiotensin II receptor subtype 1 (AT1)** in **vascular smooth muscle**, blocking angiotensin II-mediated vasoconstriction and inducing **vasodilatation**.

In addition, antagonism of AT1 in the adrenal gland inhibits **angiotensin II-stimulated aldosterone synthesis** and secretion by the adrenal cortex; **sodium and water excretion increase**, followed by a **reduction in plasma volume** and blood pressure.



Are all ARBs the same?

Telmisartan is the only ARB indicated in CV high-risk patients – representing the majority of the patients typically seen in clinical practice

	Lo-sartan	Epro-sartan	Irbe-sartan	Olme-sartan	Val-sartan	Cande-sartan	Telmi-sartan
Hypertension	●	●	●	●	●	●	●
Renal disease with hypertension and T2DM	•		•				
Prevention of stroke in hypertensive patients with LVH	•						
CV High-Risk							●
Type 2 diabetes with target organ damage							●
Coronary Heart Disease							●
Peripheral Vascular Disease							●
Stroke							●
Heart Failure (or LV dysfunction)	●				●	●	

Telmisartan indicated for reduction of CV morbidity

ONTARGET trial

Aim :to evaluate whether the ARB telmisartan was not inferior to the ACE inhibitor ramipril and whether a combination of the two drugs was superior to ramipril alone as a treatment to prevent vascular events.

Design :patients at high risk for cv events, without HF were randomized to take either telmisartan or ramipril or combination of them(median follow up 56 months)

Results

- **The primary outcome occurred in 1412 patients (16.5%) in the ramipril group, in 1423 patients (16.7%) in the telmisartan group, and in 1386 patients (16.3%) in the combination-therapy group.**

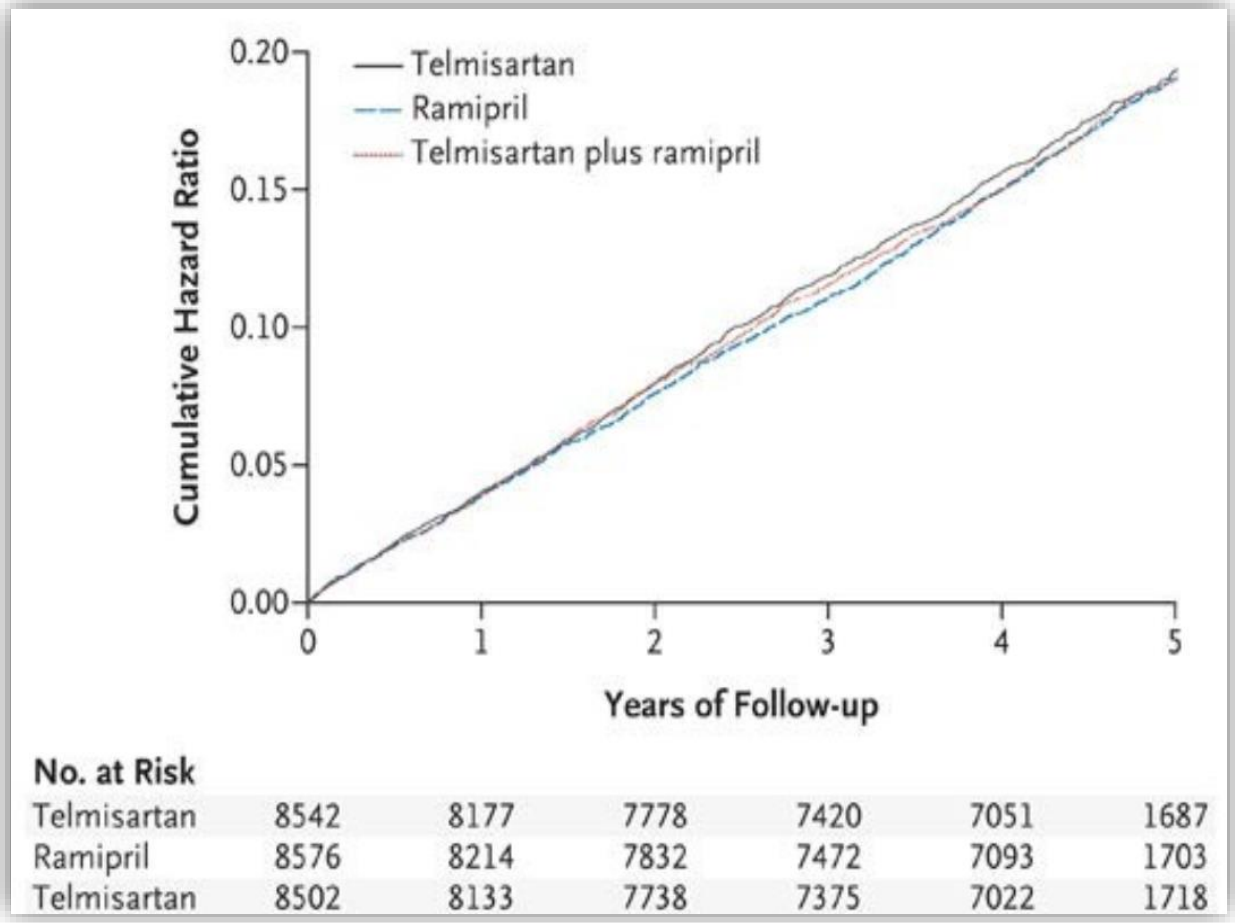
***Primary endpoint(cv death,stroke,MI,HF)**

conclusion

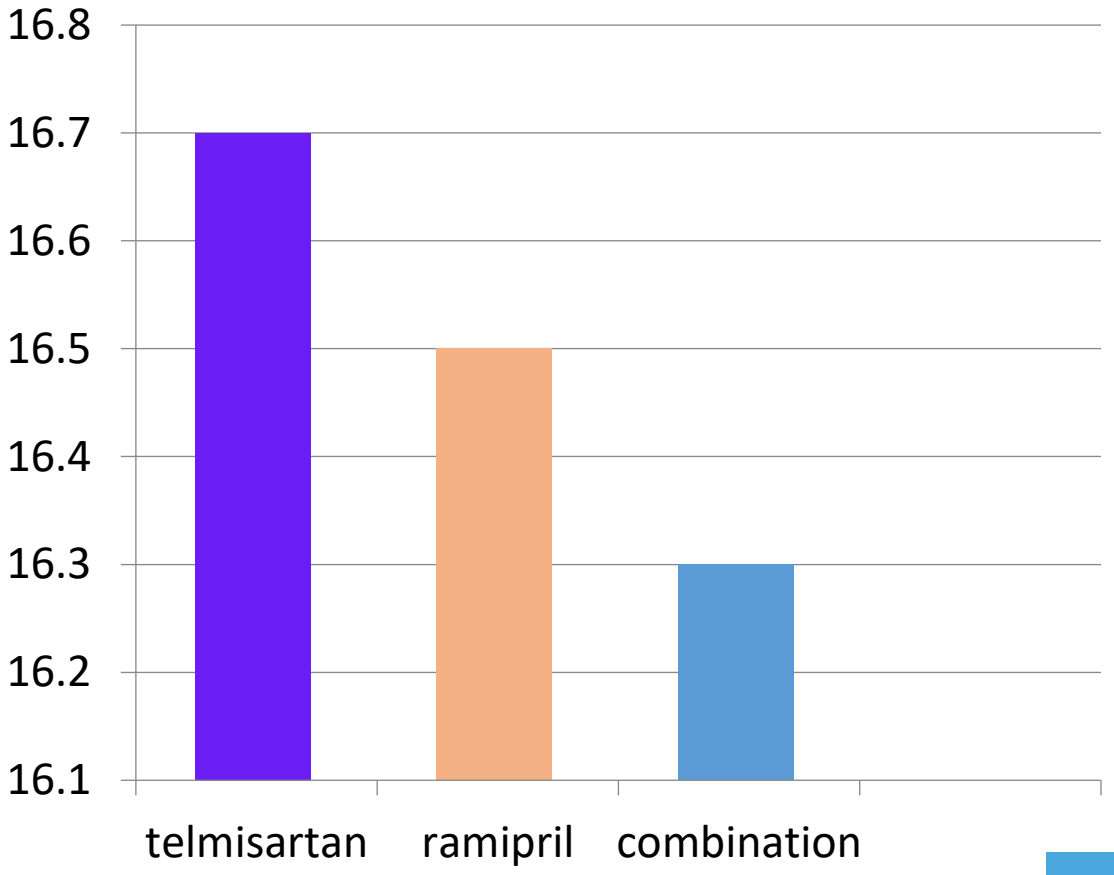
- **in patients who have vascular disease or high-risk diabetes but do not have heart failure, telmisartan is an equally effective alternative to ramipril and is less likely to cause angioedema.**
- **There is no additional advantage (and there is some harm) from the combination**

ONTARGET trial

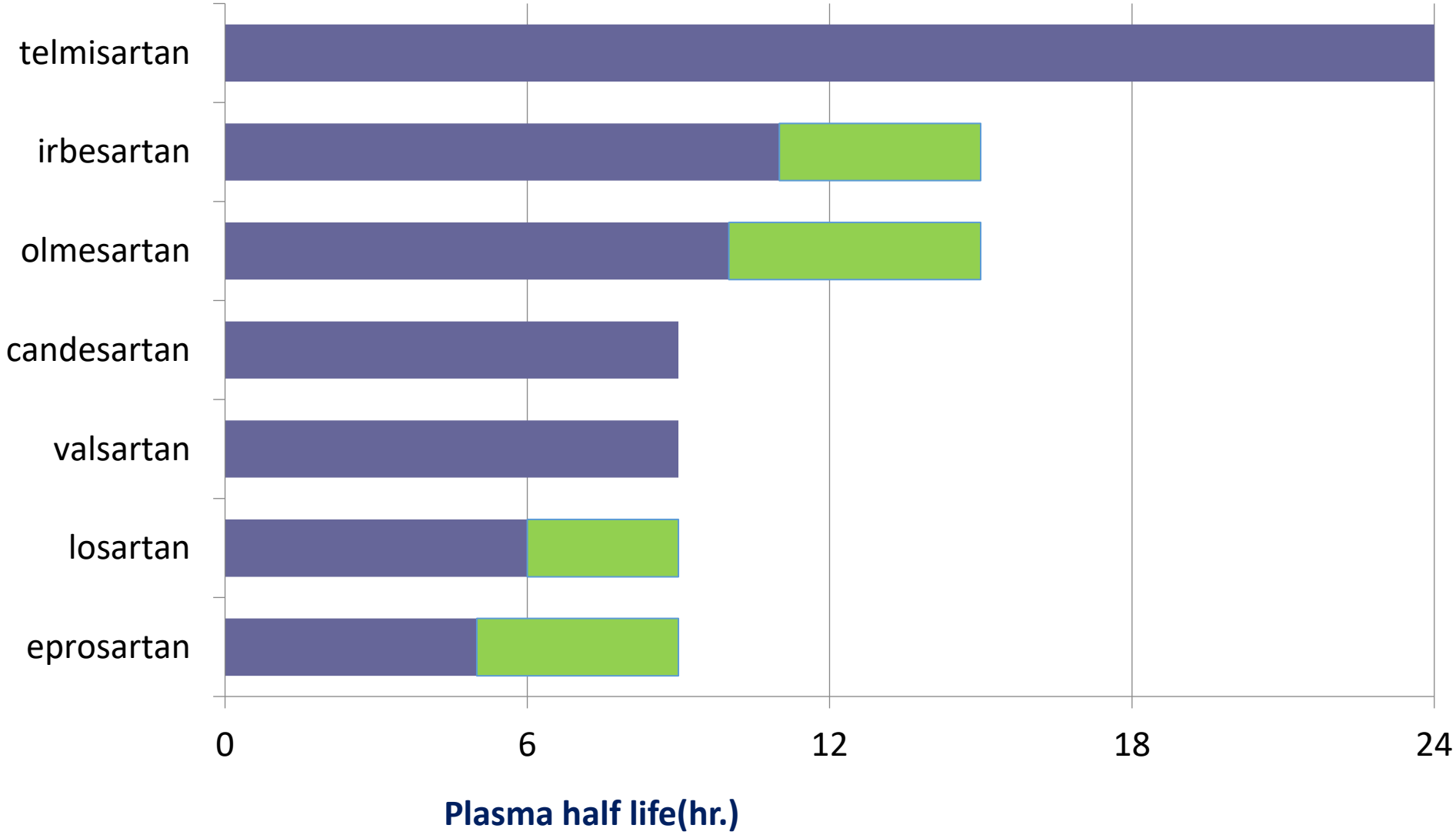
Primary endpoint



No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan	8502	8133	7738	7375	7022	1718



Telmisartan has the longest half life of all clinically available ARBs



Lipophilicity

Telmisartan is 5 times more lipophilic than Losartan

ARBs	Partition coefficient
Telmisartan	3.20
Irbesartan	1.48
Valsartan	-0.95
Losartan (active metabolite)	-2.45

Highest partition coefficient

Highest lipophilicity

Maximum tissue penetration

Drugs 2001, 61(10), 1501-1529

Receptor antagonism

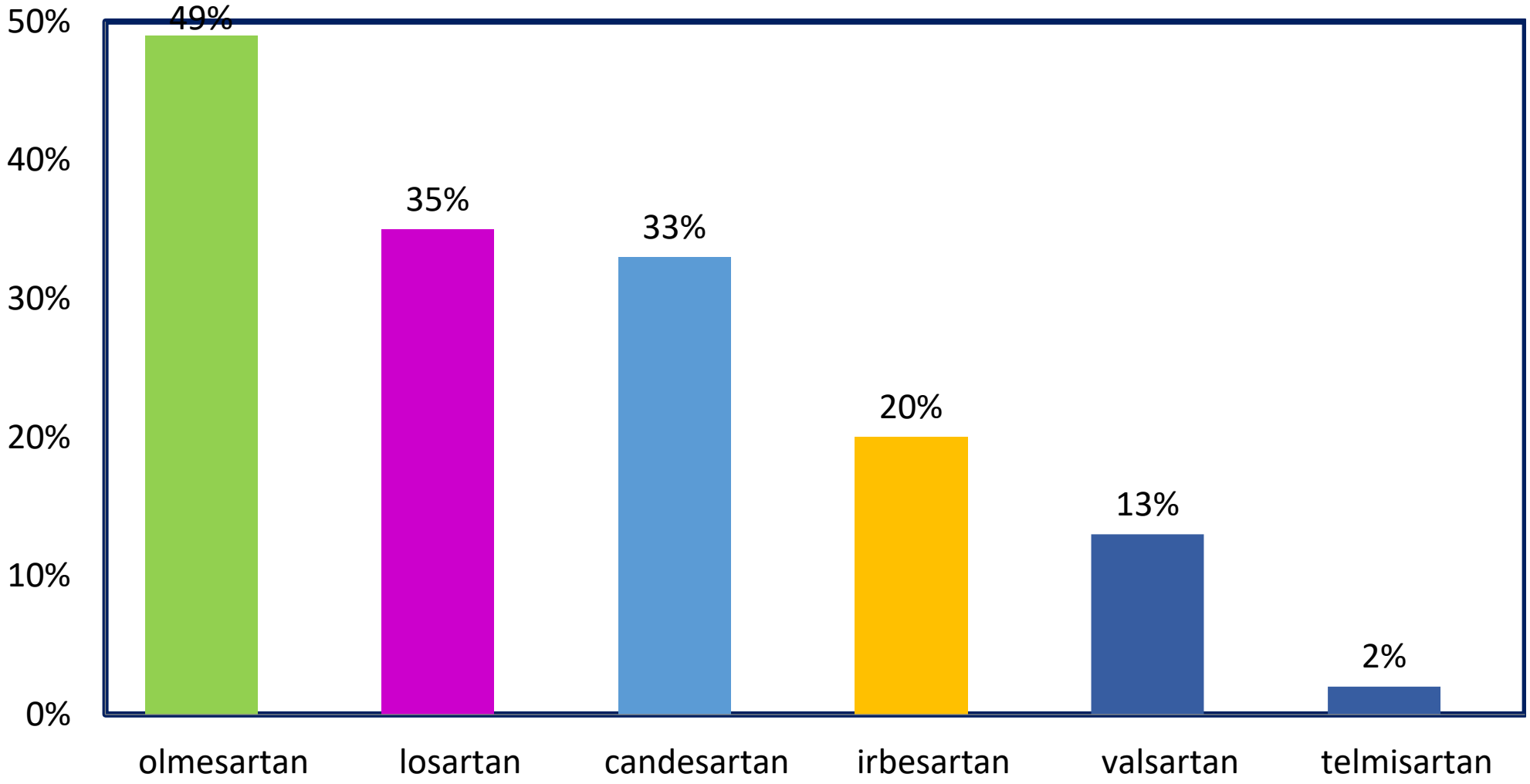
Telmisartan has 35 times higher dissociation half-life than Losartan

ARBs	Dissociation half-life
Telmisartan	87 min
Losartan	2.5 min
Angiotensin II	12 min

Telmisartan has 7 times higher dissociation half-life than Angiotensin II which confirms the insurmountable antagonism

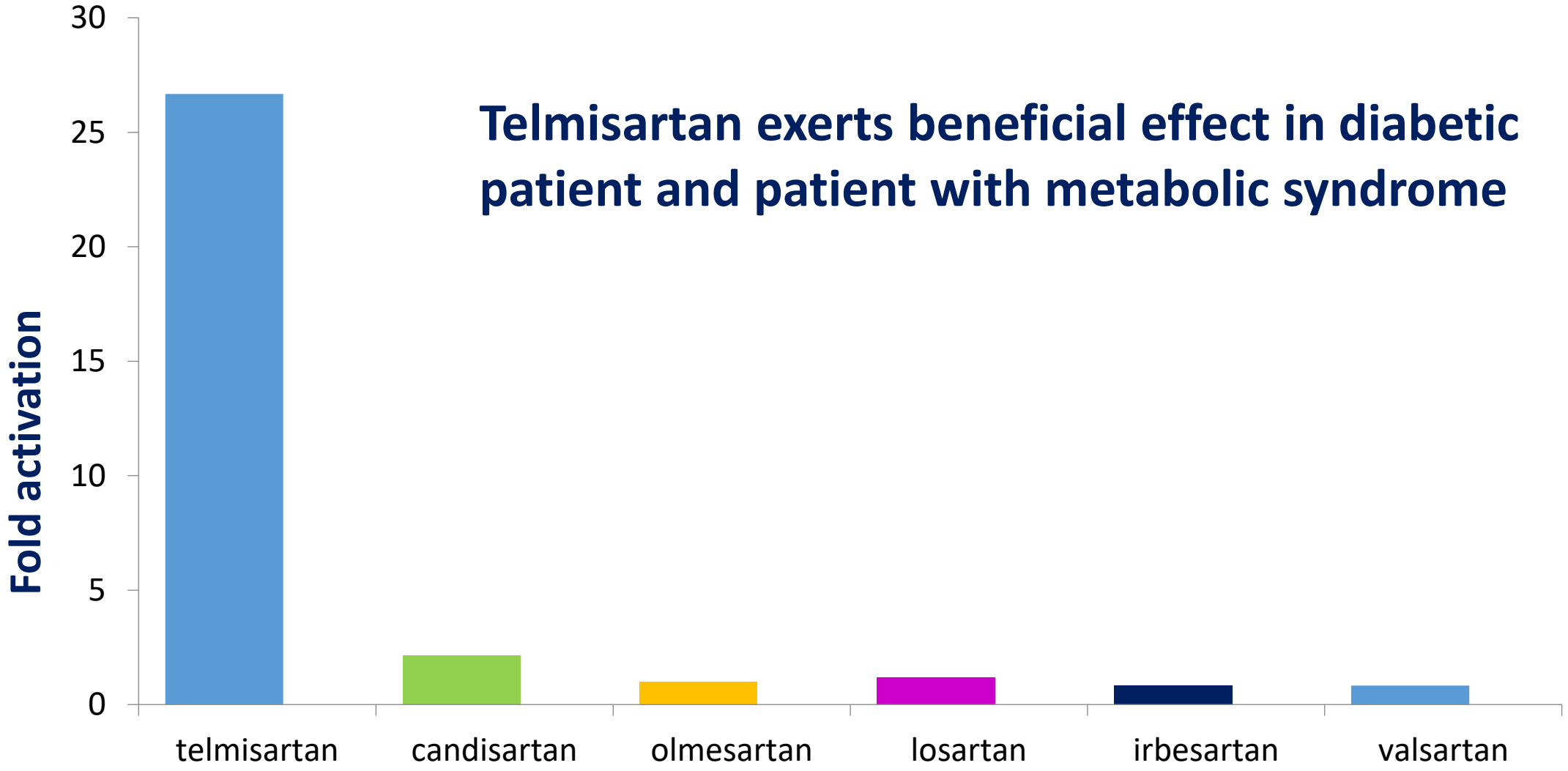
Am J Cardiol, 1999, 84: 9S-15S

Telmisartan has the lowest renal excretion of Clinically available ARABs



Journal of International Medical Research 2009 37: 1662 Telmisartan: A Different Angiotensin II Receptor Blocker Protecting a Different population.

Telmisartan has a PPAR gama agonist activity



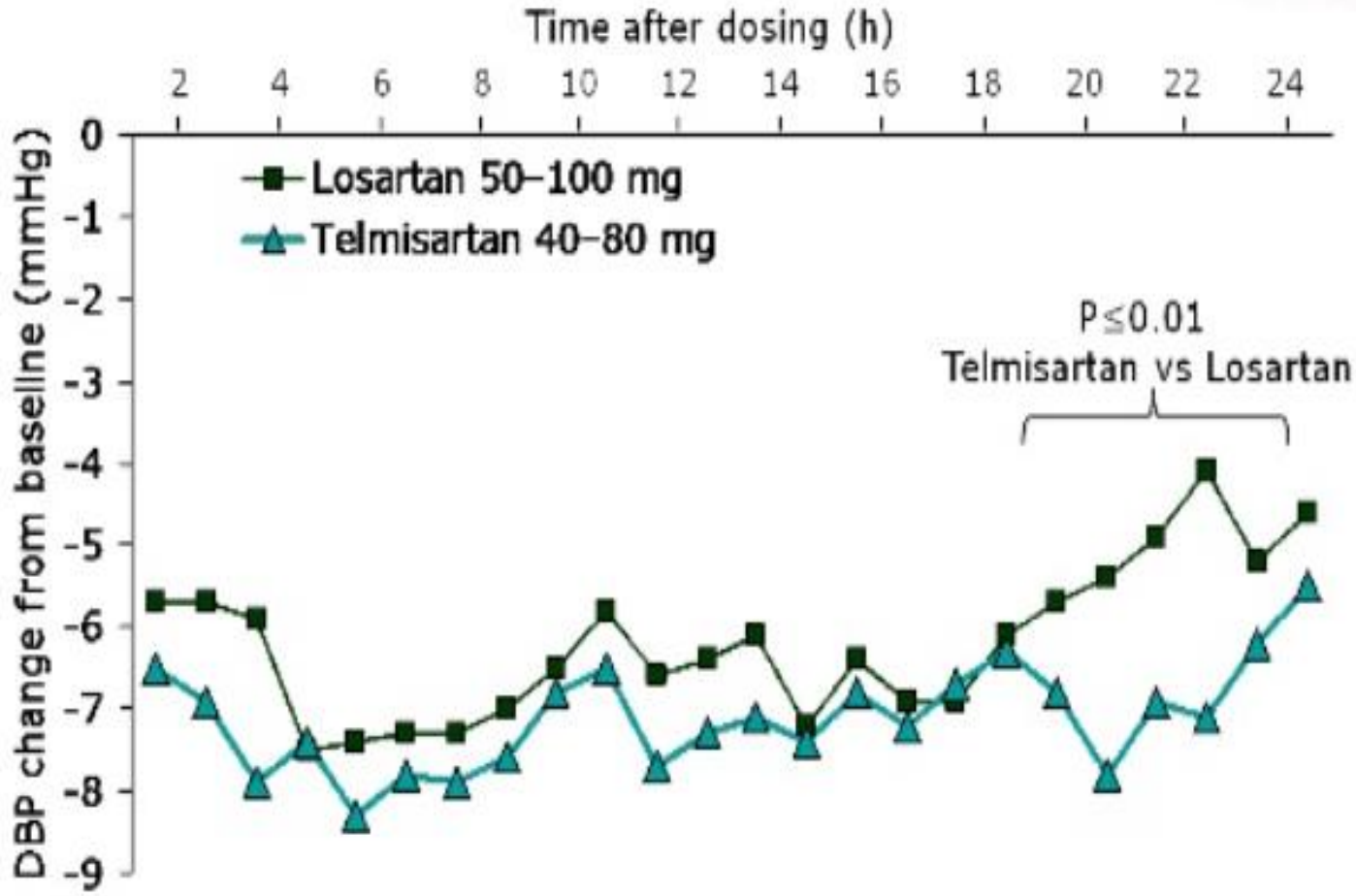
Telmisartan exerts beneficial effect in diabetic patient and patient with metabolic syndrome

benson et al hypertension 2004;43:993-1002

PPARγ agonist properties of telmisartan

- Telmisartan is a partial agonist of peroxisome proliferator-activated receptor γ (PPARγ).
- Its high lipophilicity allows it to penetrate into the nucleus where the PPARγ receptor is located.
- The ATHLETE study also showed that in obese patients with hypertension and IR, telmisartan significantly improved the hyperinsulin response to glucose loading.
- Telmisartan treatment was further associated with improvement of vascular inflammation, reductions in visceral fat and serum TNF-a

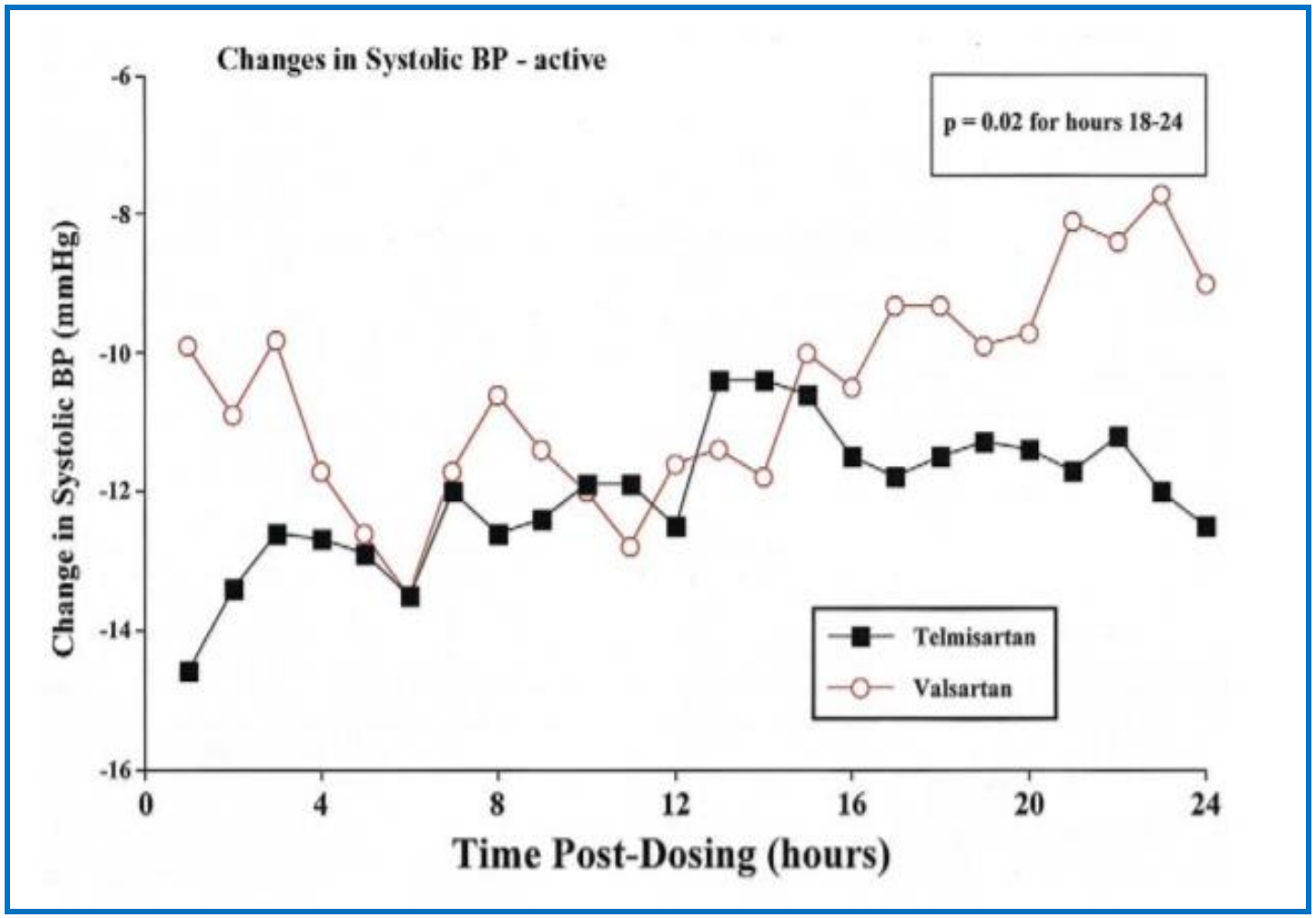
Telmisartan vs. losartan



Some ARBs loose their efficacy at the end of dosing interval.

telmisartan-induced reductions in DBP during the last 6 h of the dosing interval were greater than those with losartan

Telmisartan vs. valsartan

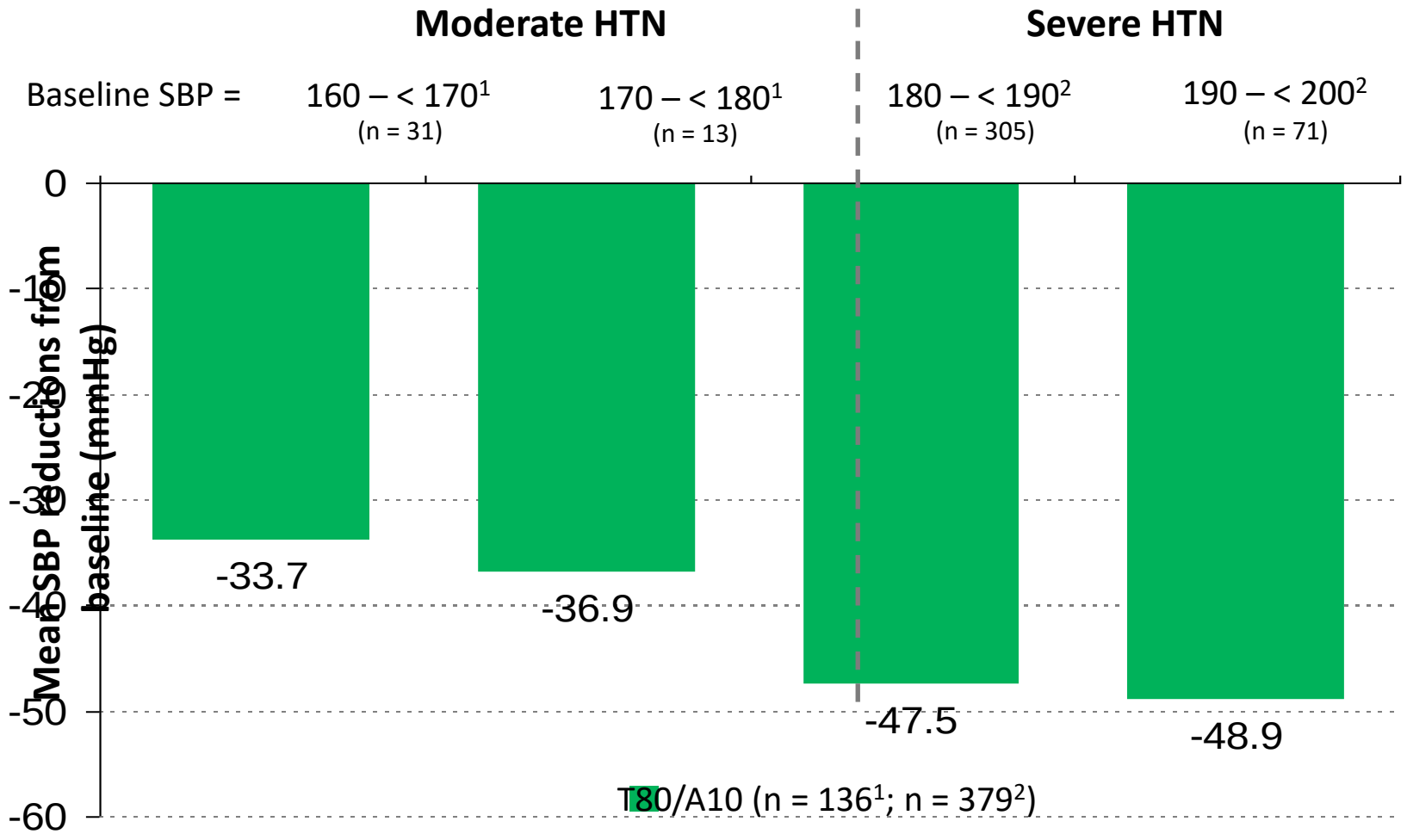


Telmisartan reduced SBP/DBP during the last 6 h of the dosing period by 11/7.6 mmHg, compared with 8.7/5.8 mmHg with valsartan

White WB, et al. Effects of the angiotensin II receptor blockers telmisartan versus valsartan on the circadian variation of blood pressure. Am J Hypertens 2004; 17: 347–353.

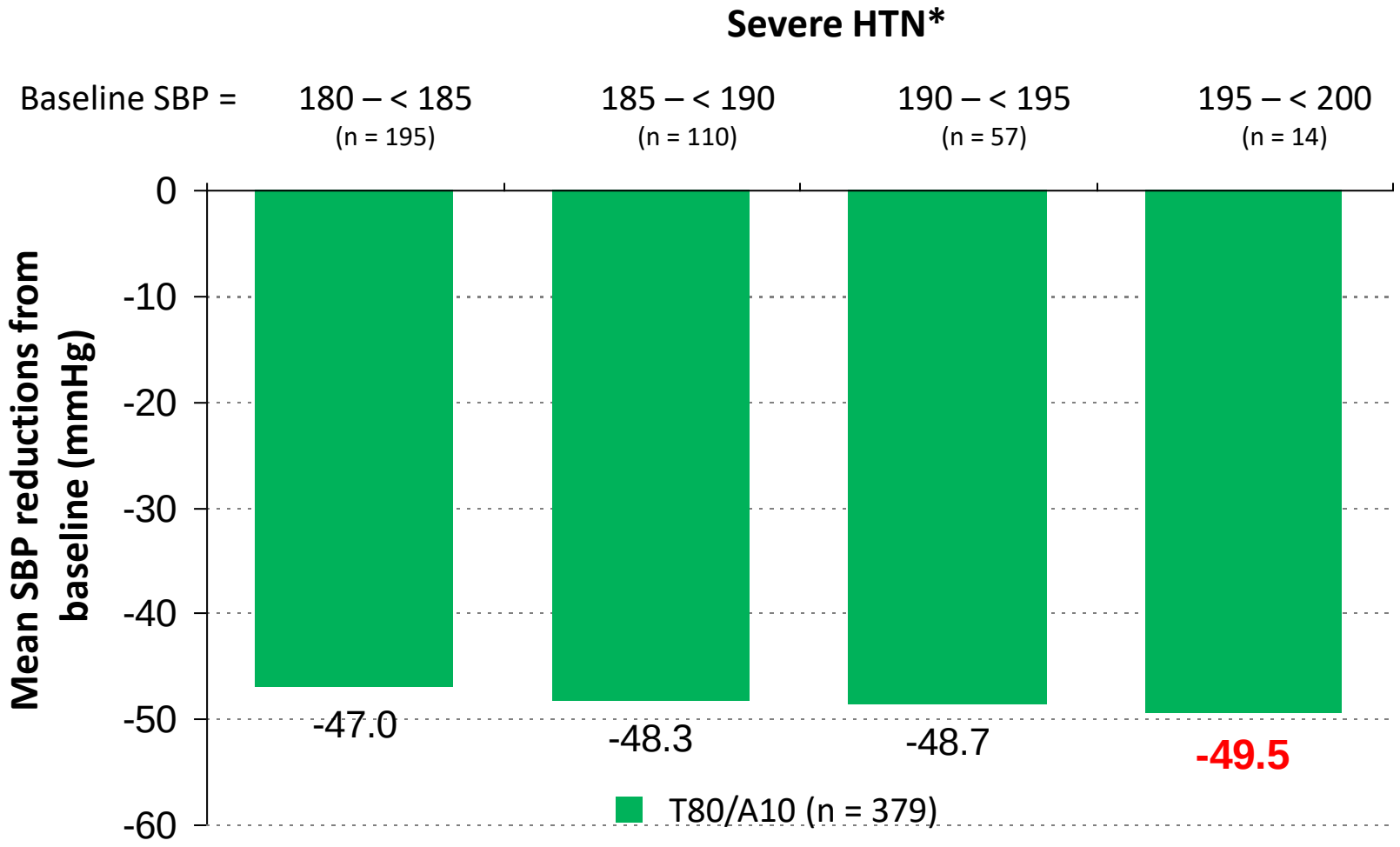
Combination with amlodipine

Telmisartan Plus Amlodipine Provides Consistent BP Reductions Across HTN Severities



1. Littlejohn et al. *J Clin Hypertens.* 2009;11:207–213; 2. Neutel et al. *J Clin Hypertens.* 2010: In press; ASH 2010 poster presentation (LB-PO-10) & data on file

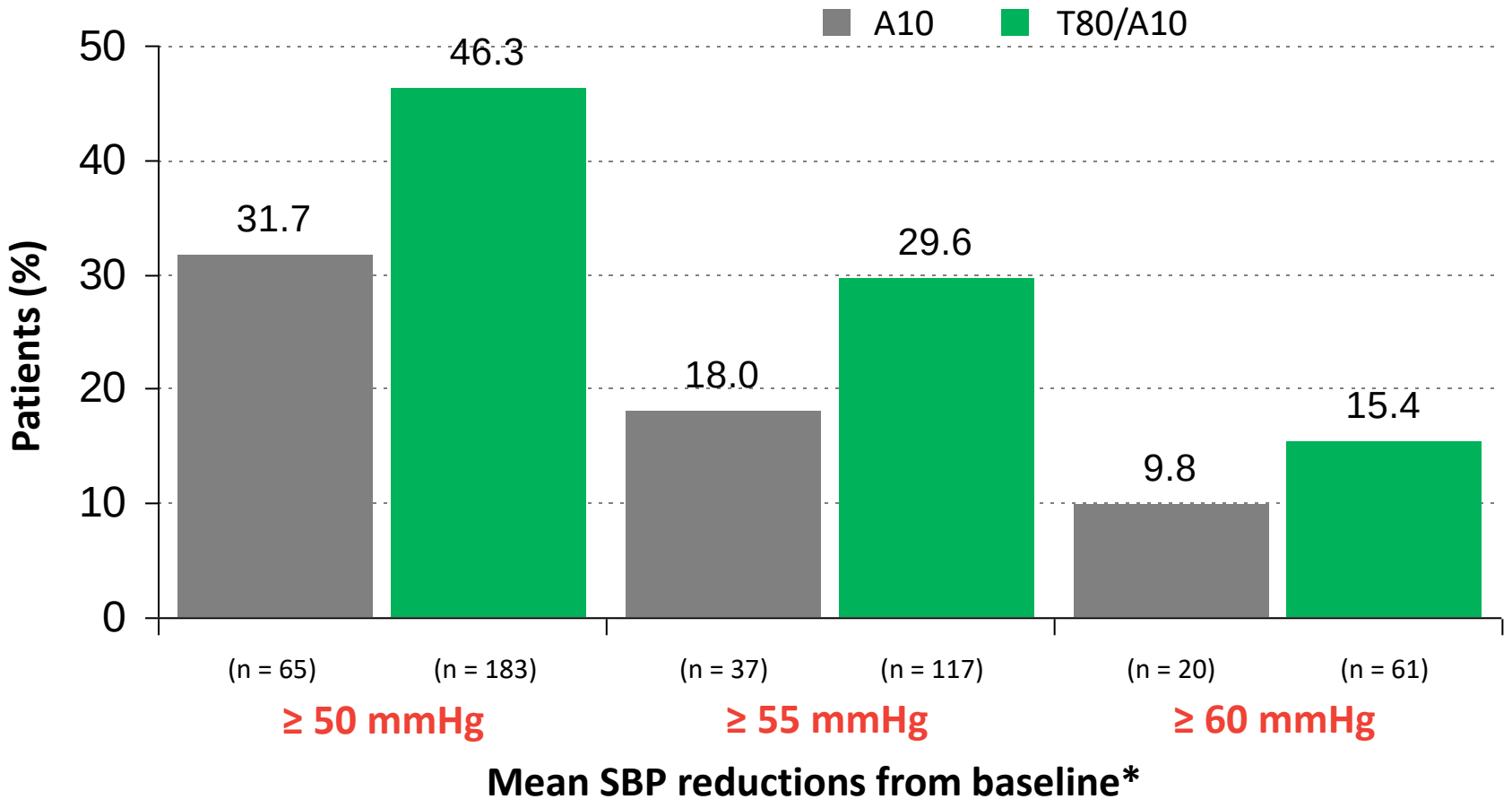
Telmisartan Plus Amlodipine Provides BP Reductions of Almost 50 mmHg



* SBP ≥ 180 – < 200 mmHg; mean baseline BP = 185.4/103.2 mmHg

Neutel et al. *J Clin Hypertens.* 2010: In press; ASH 2010 poster presentation (LB-PO-10).

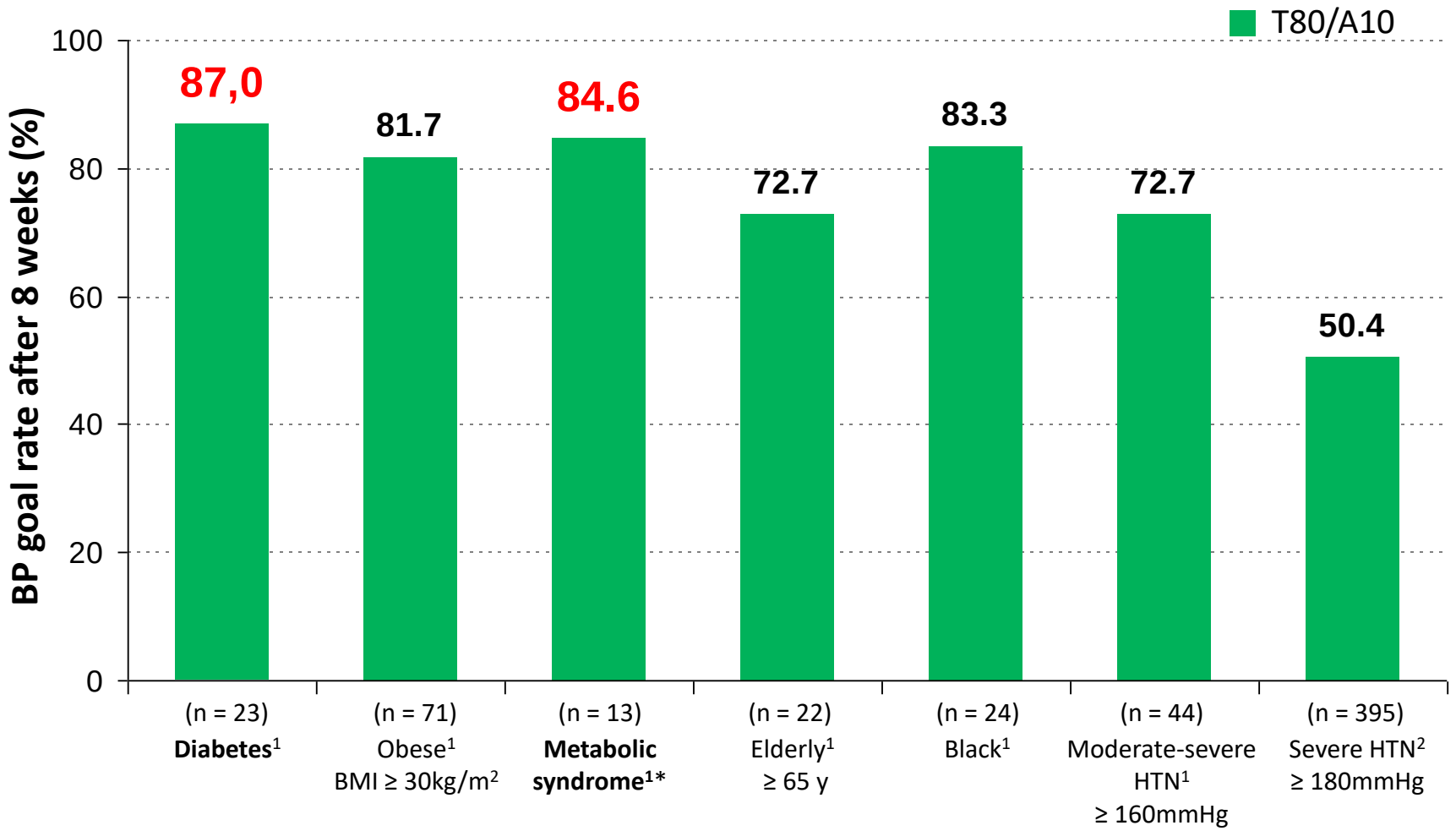
Telmisartan Plus Amlodipine Provides BP Reductions of ≥ 50 mmHg in Almost 50% of Patients With Severe HTN*



* Mean baseline BP = 185.4/103.2 mmHg

Neutel et al. *J Clin Hypertens.* 2010: In press; ASH 2010 poster presentation (LB-PO-10).

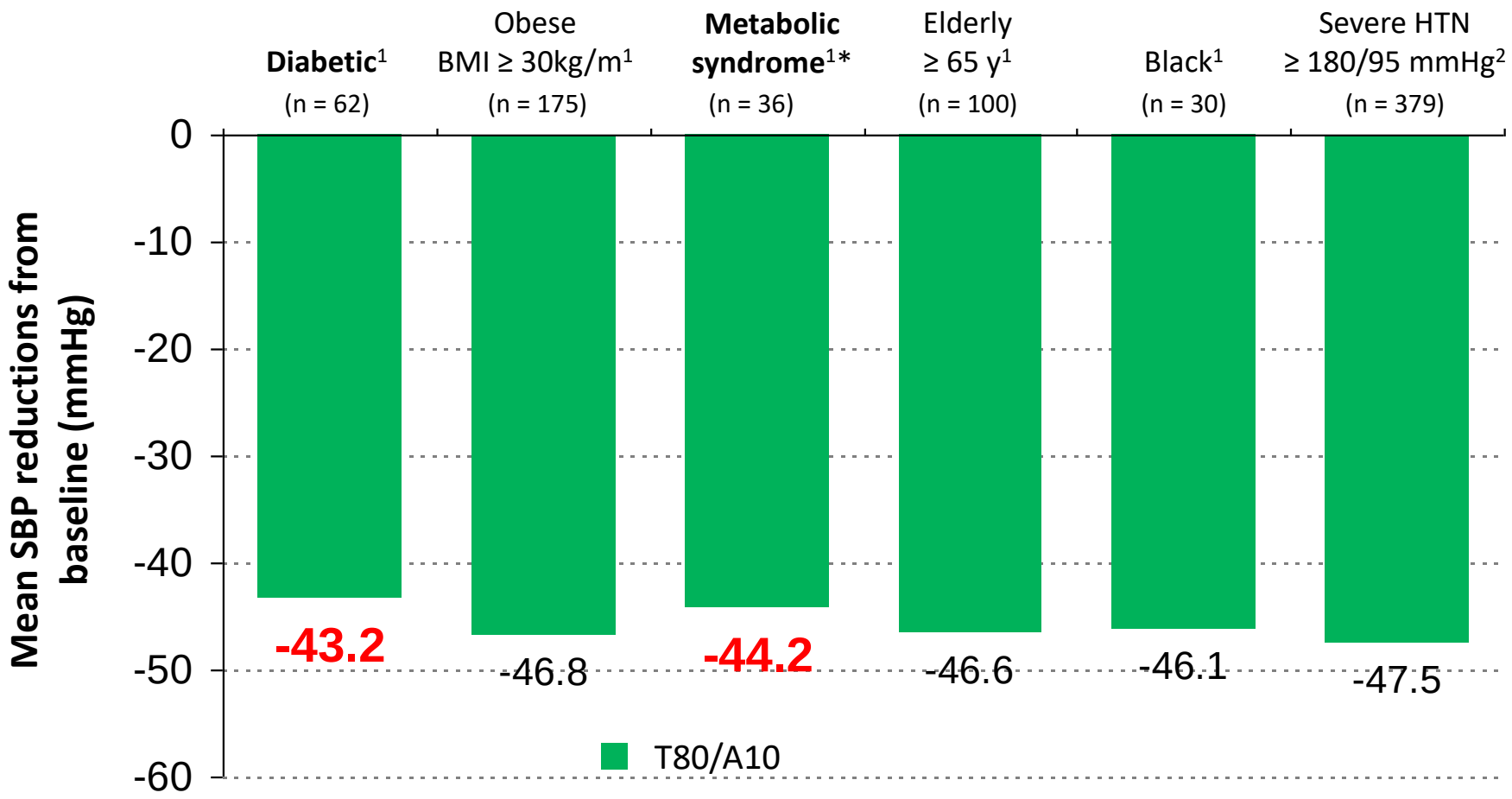
Telmisartan/Amlodipine Provides High BP Goal Rates (< 140/90 mmHg) in HTN at-Risk Patients



* Presence of diabetes, obesity (BMI ≥ 30kg/m²), and HTN

1. Factorial design study (data on file; Boehringer Ingelheim Pharmaceuticals, Inc);
2. Neutel et al. *J Clin Hypertens.* 2010: In press; ASH 2010 poster presentation (LB-PO-10).

Telmisartan Plus Amlodipine Provides Consistently High BP Reductions in Hypertensive at-Risk Patients



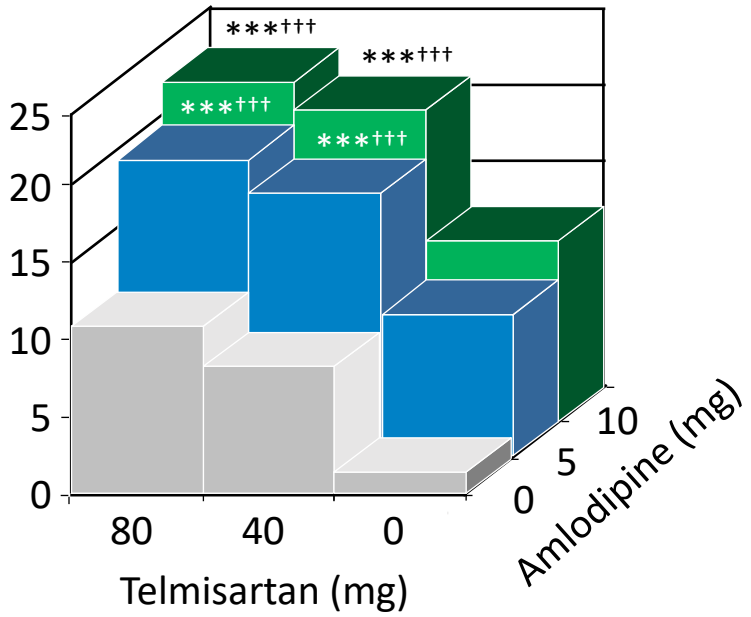
Mean baseline BP = 185.4/103.2 mmHg

* Diabetes, obesity (BMI ≥ 30kg/m^2), and HTN

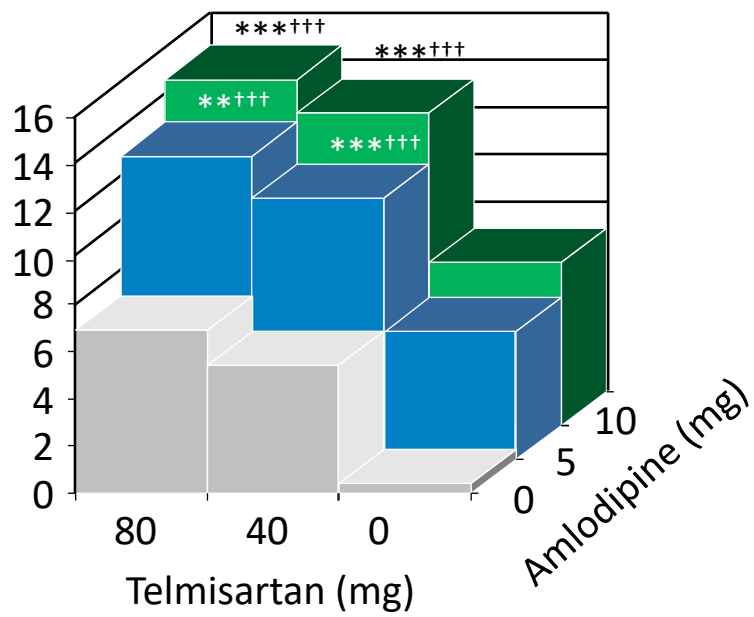
1. TEAMSTA Severe HTN study (data on file; Boehringer Ingelheim Pharmaceuticals, Inc);
2. Neutel et al. *J Clin Hypertens*. 2010: In press; ASH 2010 poster presentation (LB-PO-10).

Telmisartan Plus Amlodipine Provides Consistent 24-h ABPM Dose Response

24-h mean SBP reduction (mmHg)

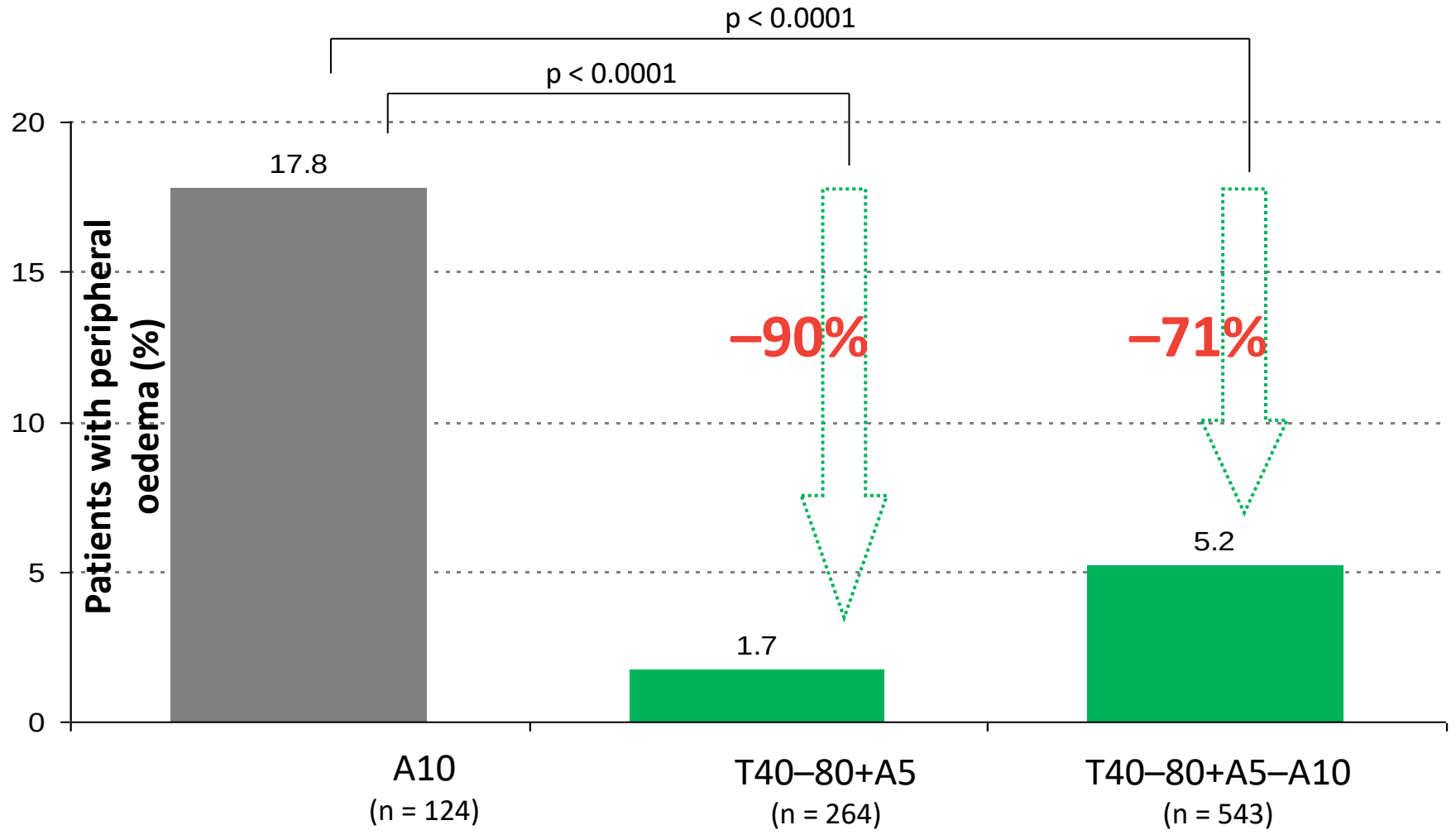


24-h mean DBP reduction (mmHg)



** p < 0.001; *** p < 0.0001 vs Telmisartan alone; ††† p < 0.0001 vs Amlodipine alone; n = 562

Telmisartan Plus Amlodipine is Associated With Less Peripheral Oedema Compared With Amlodipine 10 mg



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

AMTAS

Amlodipine Plus Telmisartan