An update on the management of isolated systolic hypertension

Krzysztof Narkiewicz

Research on hypertension and development of effective and well-tolerated antihypertensive therapies have been among the greatest successes of medicine in the second half of the 20th century

Alberto Zanchetti

Progress in hypertension management

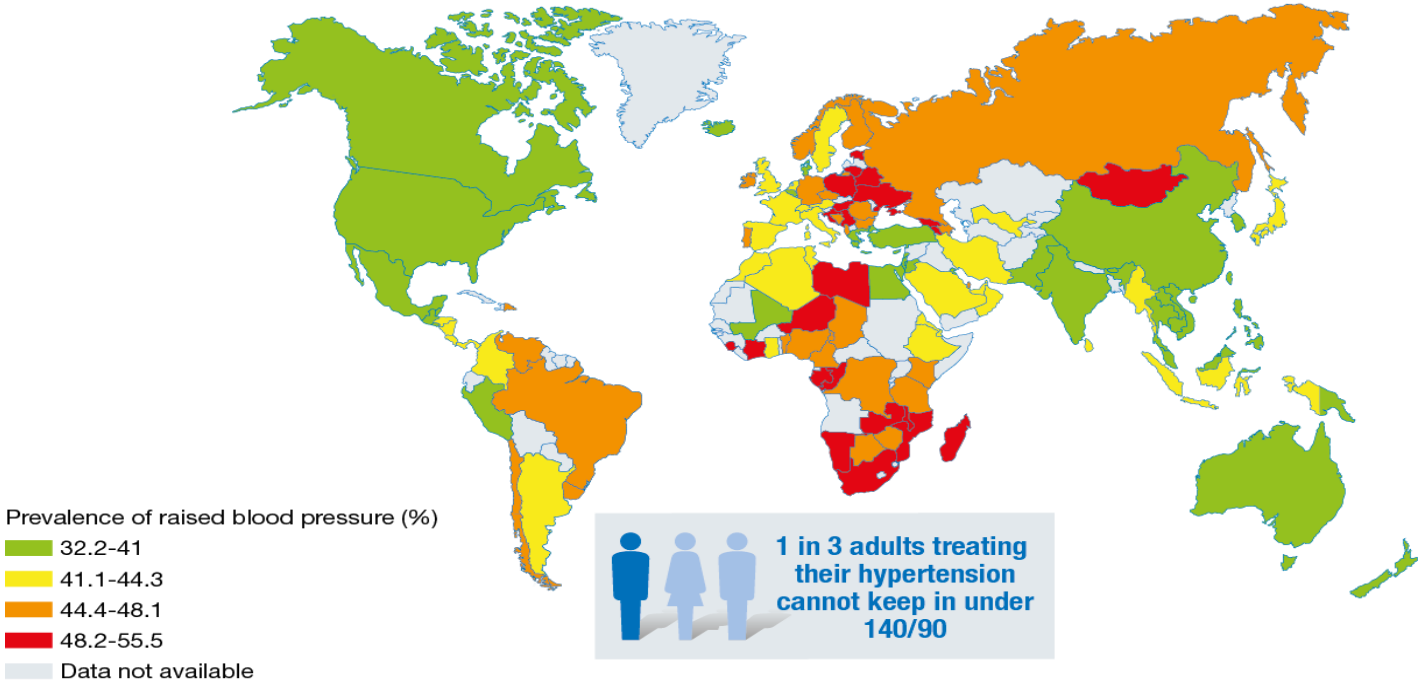
1970s

- Malignant hypertension
- Reserpine
- First diuretics
- First randomized trials
- No guidelines

2019

- Non-existing
- Well-tolerated treatment
- Several drug classes
- Landmark clinical trials
- EBM-driven guidelines

1.13 billion hypertensive patients worldwide[1*]



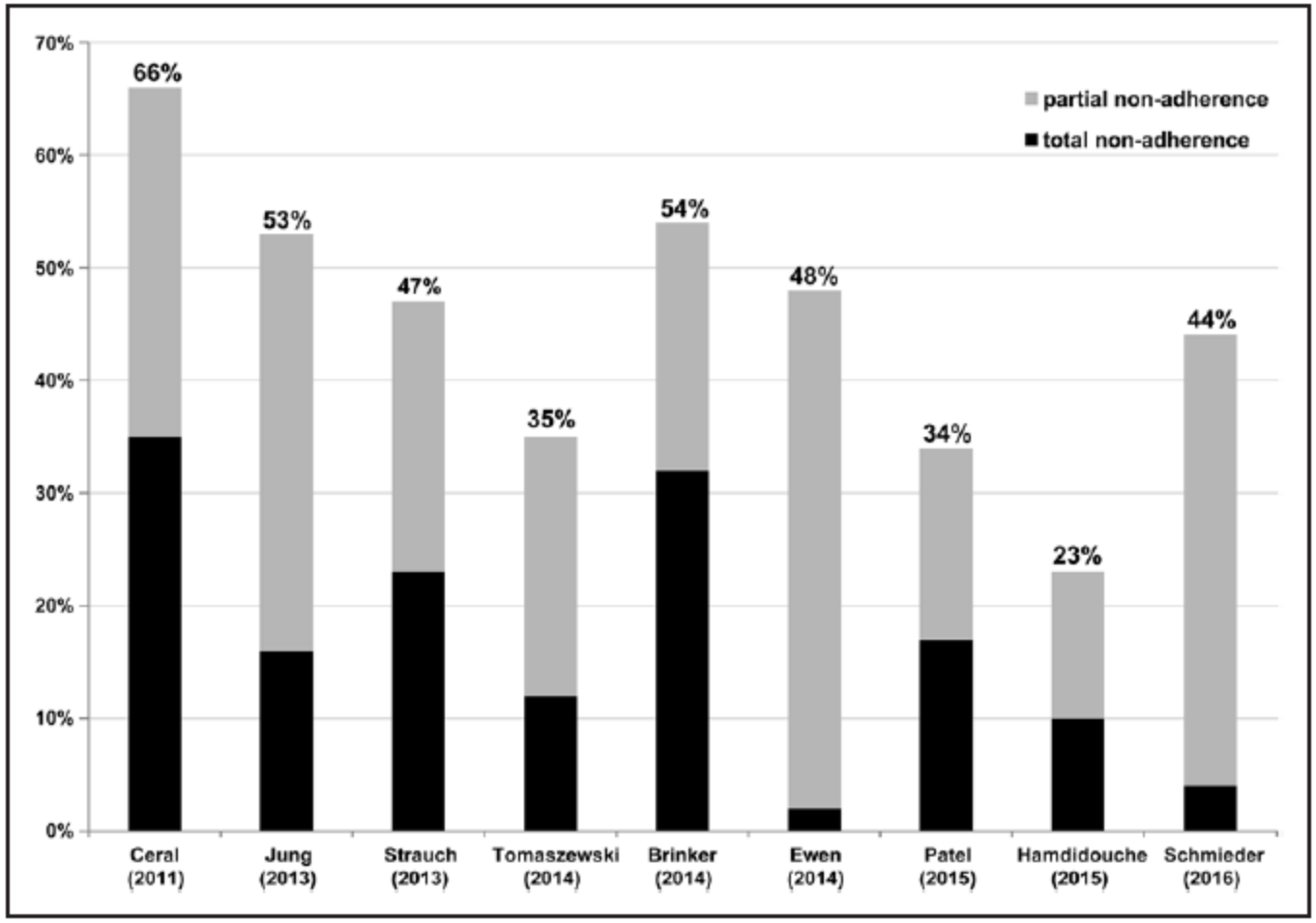
*Data from 2015, 200 countries, pooled analysis of 19.1 million adults (1479 studies)

1. NCD-RisC. *Lancet*. 2017;389:37-55. 2. World Health Organization. Global status report on noncommunicable diseases 2010. Geneva. WHO. 2010.

Hypertension is still the first contributor to global burden of disease and mortality[1]

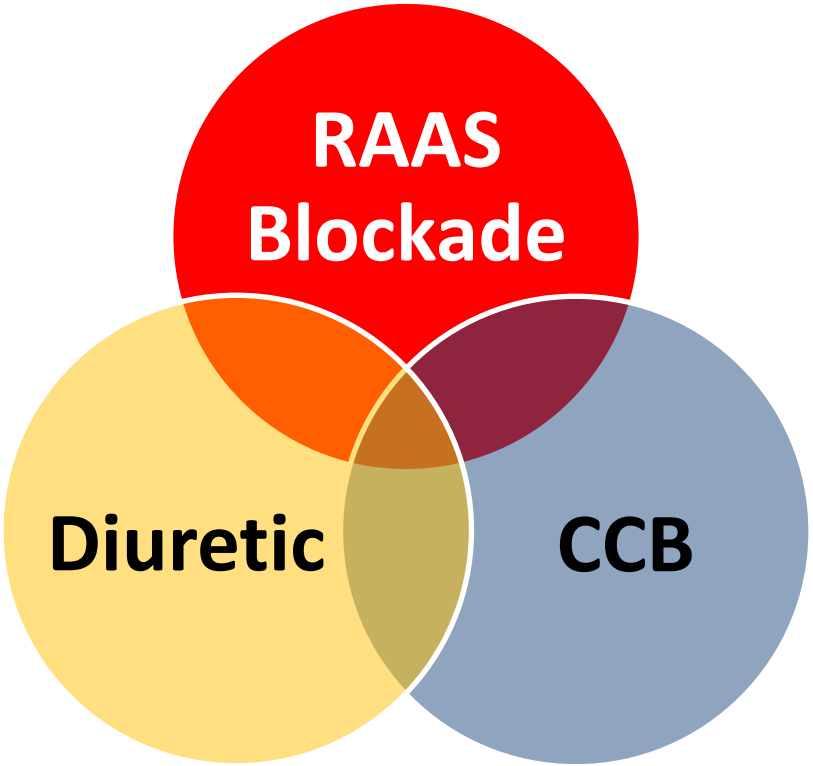
1. World Heart Organization. Global atlas on cardiovascular disease prevention and control. WHO Press 2011

- Appropriate treatment
- Adherent patient

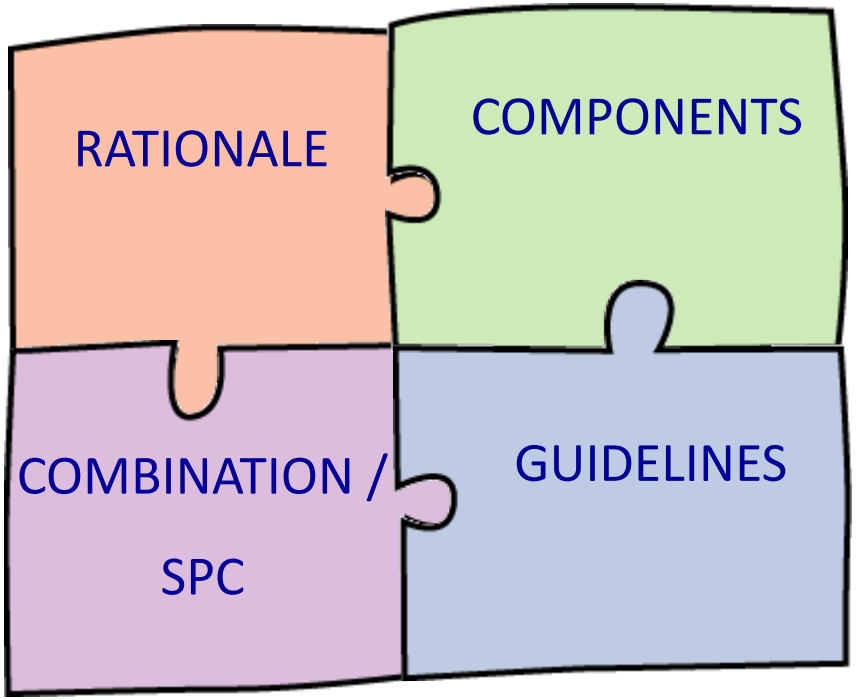


Hypertension. 2016;68:297-306.

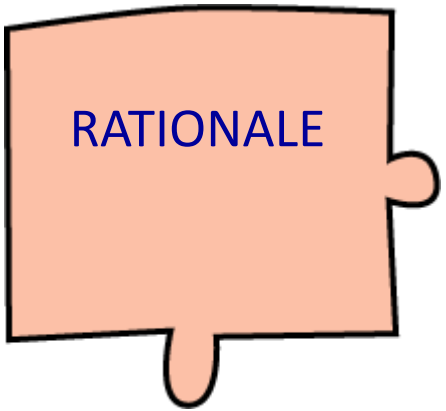
Simplifying Combination Therapy



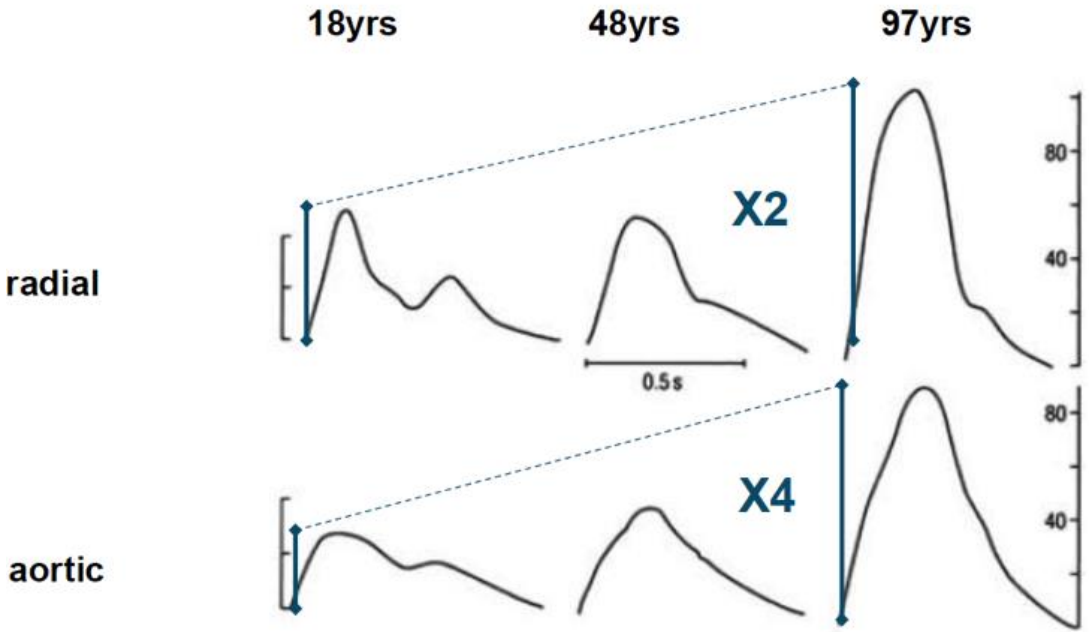
Combination of CCB / diuretics



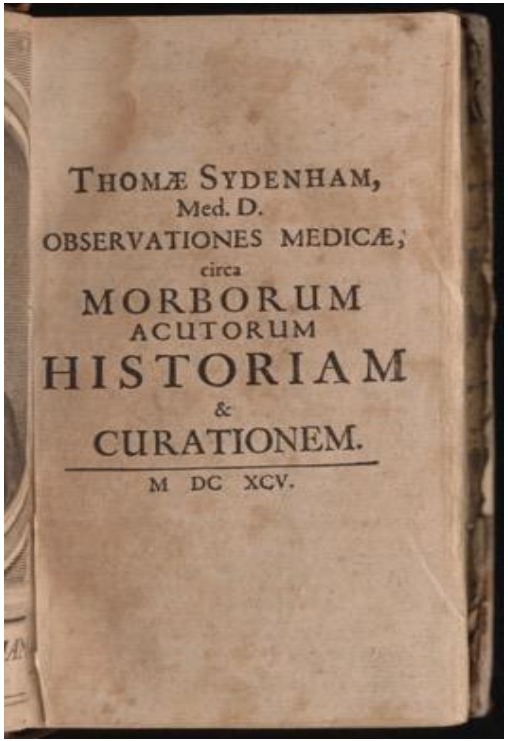
Combination of CCB / diuretics



Effects of Ageing on Peripheral and Central Systolic and Pulse Pressure

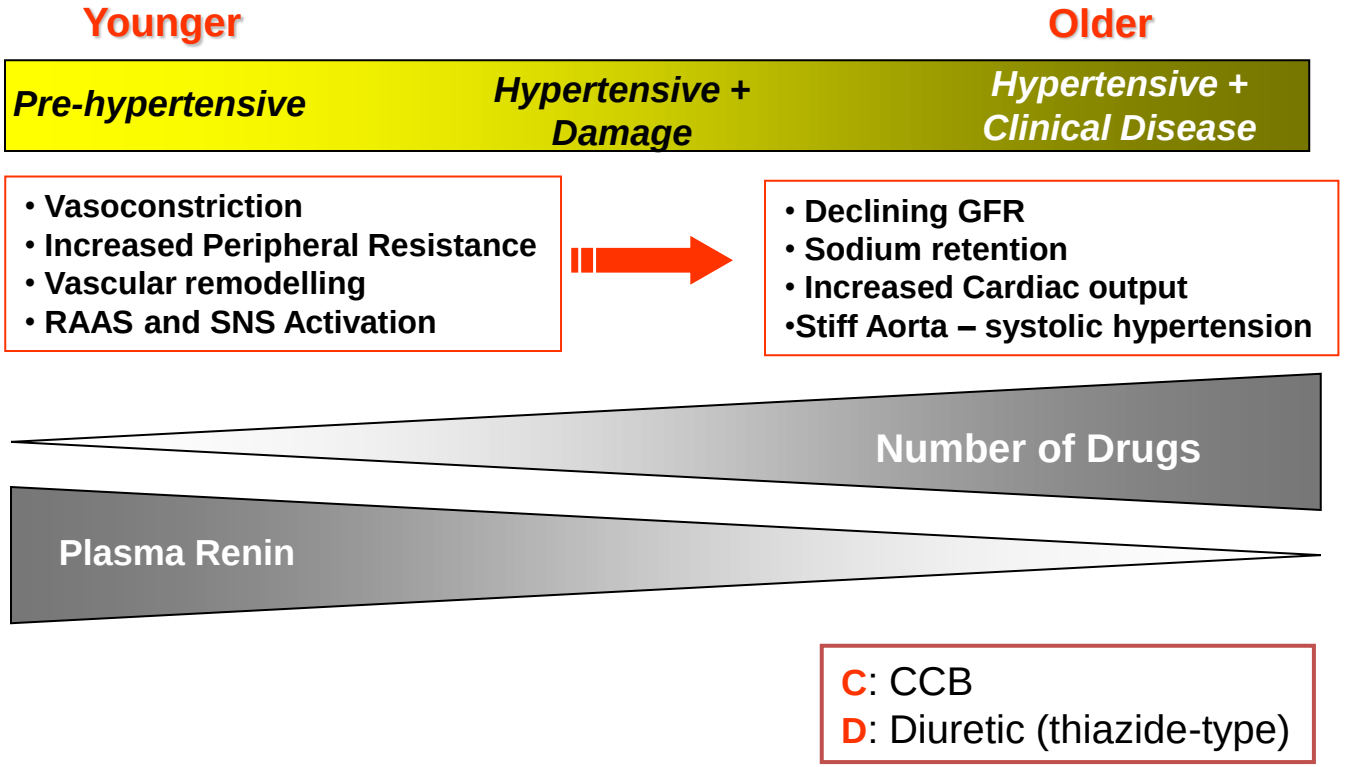


”A man is as old as his arteries”


THOMÆ SYDENHAM,
Med. D.
OBSERVATIONES MEDICÆ;
circa
MORBORUM
ACUTORUM
HISTORIAM
&
CURATIONEM.
M DC XCV.

Thomas Sydenham 1624-1689
The English Hippocrates

Evolution of Hypertension



B. Williams. 2007

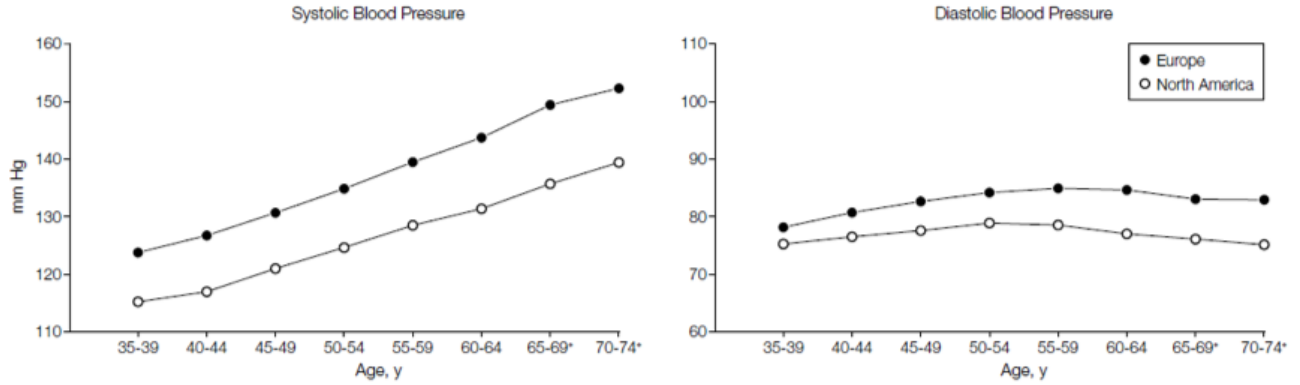
Hypertension Prevalence and Blood Pressure Levels in 6 European Countries, Canada, and the United States

Katharina Wolf-Maier, MD
Richard S. Cooper, MD
José R. Banegas, MD
Simona Giampaoli, MD

Context Geographic variations in cardiovascular disease (CVD) and associated risk factors have been recognized worldwide. However, little attention has been directed to potential differences in hypertension between Europe and North America.

Objective To determine whether higher blood pressure (BP) levels and hyperten-

Figure 2. Mean Systolic and Diastolic Blood Pressures in 6 European and 2 North American Countries, Men and Women Combined, by Age



projects, most notably the World Health

veys that include rigorous measurement of cardiovascular risk status. Considerable epidemiologic research has

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For editorial comment see p 2420.

JAMA, May 14,2003 – vol 289, №18, 2363 - 2369

Systolic pressure is all that matters

Lancet 2008

Bryan Williams, Lars H Lindholm, Peter Sever

Blood pressure is usually expressed as two components—diastolic and systolic pressures. Systolic hypertension is much more common than diastolic hypertension, and systolic blood pressure contributes more of the huge global disease burden attributable to hypertension than does diastolic pressure.[1–3] However, there has undoubtedly been confusion about the relative pressure with age, accompanied by a fall in diastolic pressure and a widening in pulse pressure. Increased pulse pressure is therefore indicative of large artery disease and is also associated with increased cardiovascular risk. However, assessment of systolic pressure is sufficient to capture this component of risk, since there is hardly ever a situation in which pulse

Published Online
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DOI:10.1016/S0140-6736(08)60804-1

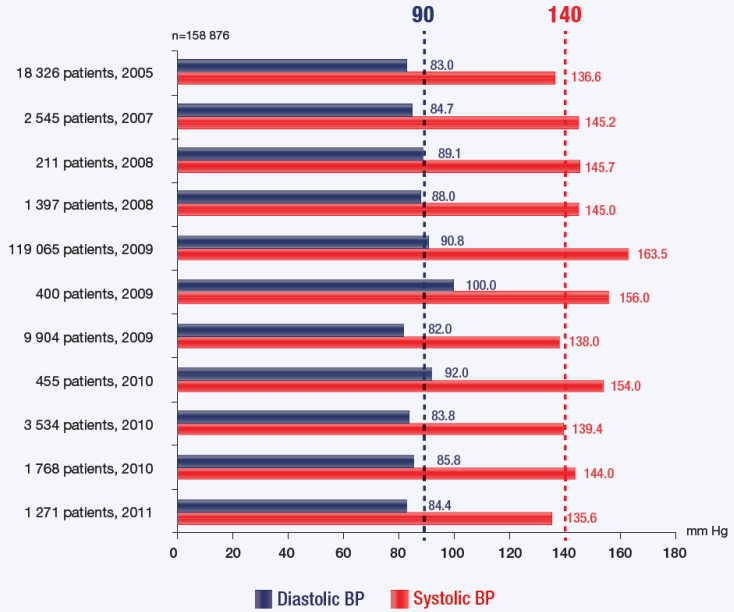
Department of Cardiovascular Sciences, University of Leicester, Leicester, UK (Prof B Williams FRCP);

- SBP accounts for hypertension
- SBP accounts for uncontrolled hypertension
- SBP accounts for morbidity and mortality.

Lancet. 2008

Systolic blood pressure
is the most difficult BP parameter to control

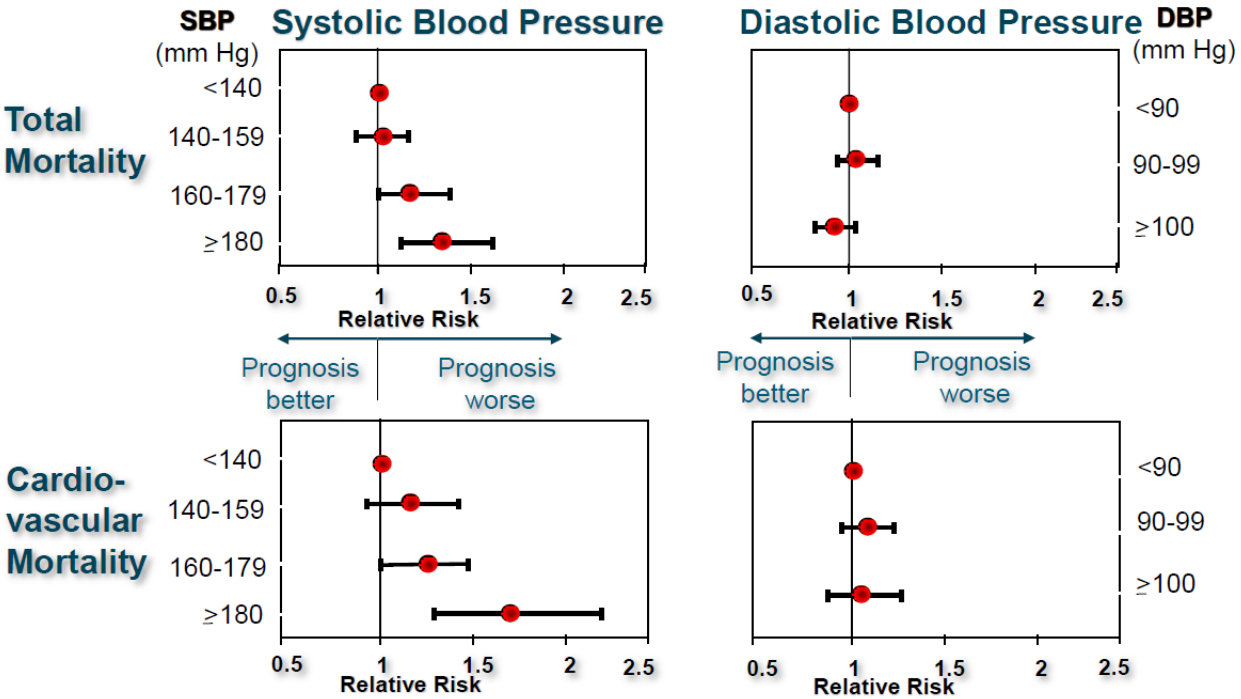
Mean BP results for 158 876 treated patients[1]



Clinic blood pressure levels in hypertensive patients included in observational studies or clinical surveys on hypertension between 2005 and 2011 in Italy.
Histograms represent average systolic BP and diastolic BP levels in each study included in the analysis.
Data are expressed as mean standard deviation.

1. Tocci G et al. *J Hypertens*. 2012;30:1065-1074.

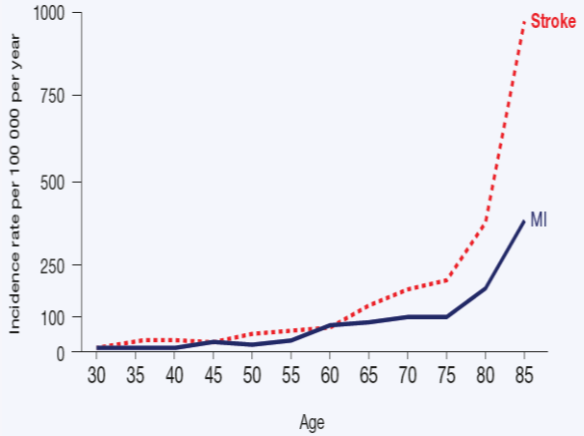
Predictive Power of SBP on overall cardiovascular risk



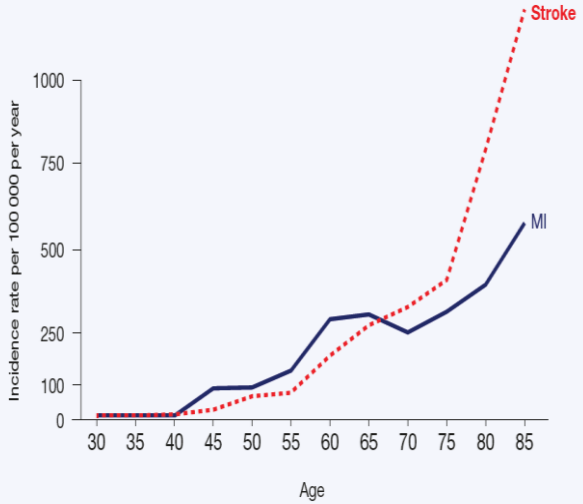
Alli C et al. Arch Intern Med. 1999;159:1205-1212.

Stroke is the most devastating complication for older hypertensive patients

Age-specific incidence rates of stroke and acute myocardial infarction (MI) in women[1]



Age-specific incidence rates of stroke and acute myocardial infarction (MI) in men[1]

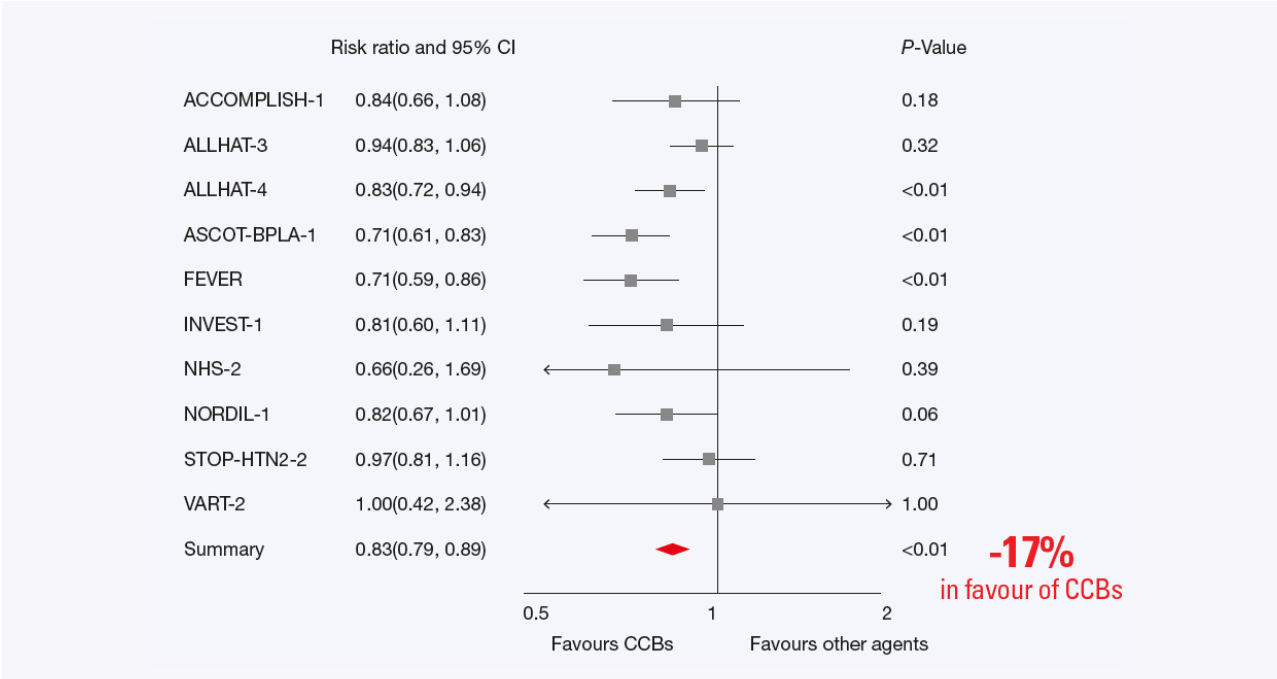


1. Gentil A et al. *J Neurol Neurosurg Psychiatry*. 2009;80:1006-1010.)

CCBs are still one of the best classes for reducing strokes

Mukete meta-analysis (2015)[1]

Risk ratios for stroke comparing treatment with calcium channel blockers versus other antihypertensive agents(ACE) inhibitors

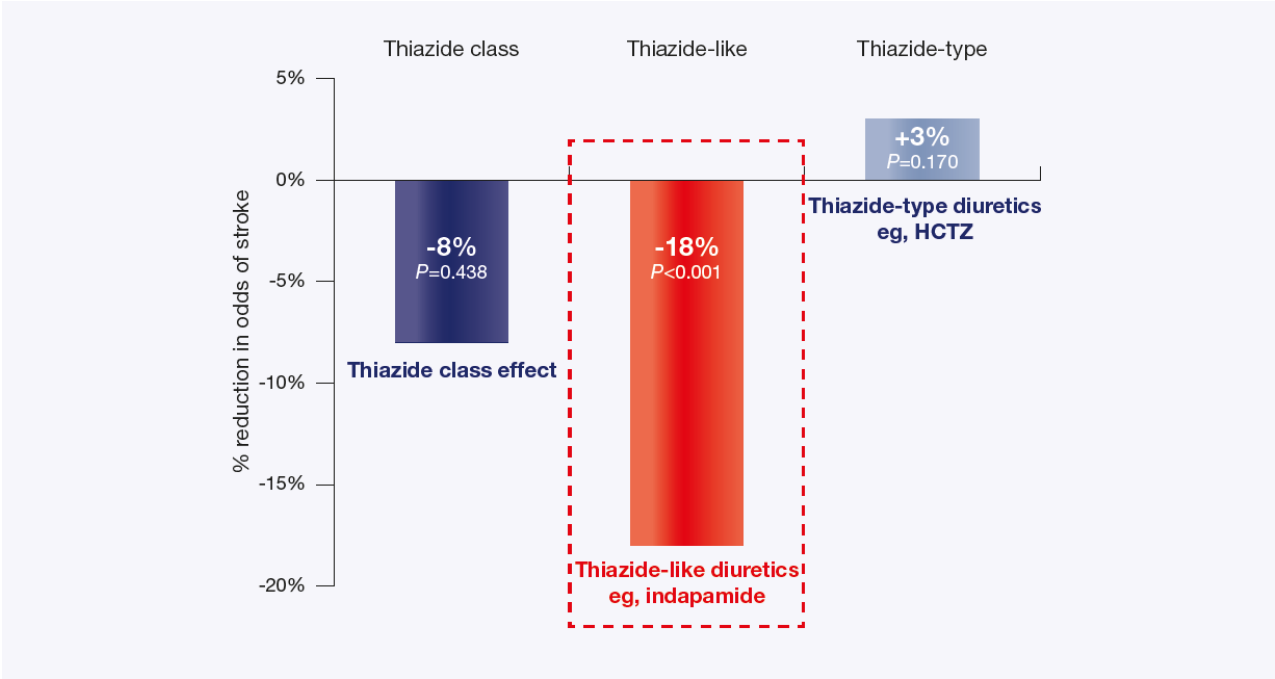


1. Mukete B et al. *Am J Cardiovasc Drugs*. 2015;15:243-257.

Thiazide-like diuretics are better than thiazide-type diuretics in reducing stroke

Chen meta-analysis (2007)[1]

Stroke reduction with thiazide diuretics is mainly driven by thiazide-like diuretics and not thiazide-type diuretics

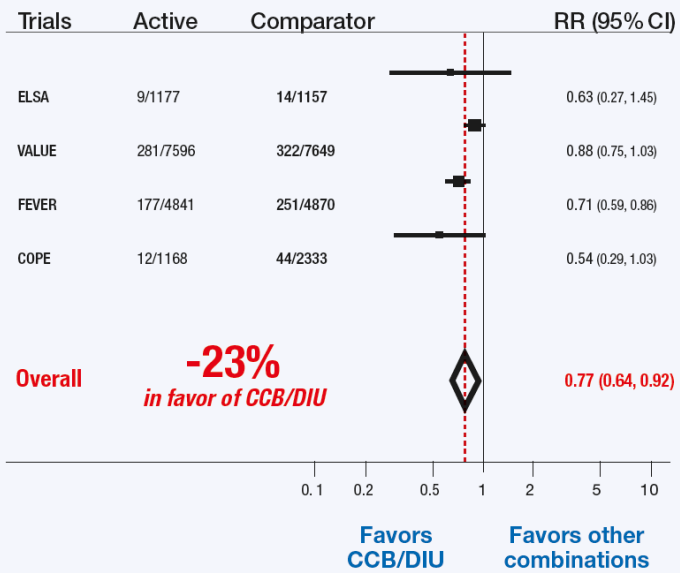


1. Chen P et al. *Am J Hypertension*. 2015;28:1453-1463.

CCB/thiazide-like diuretic combinations are more effective at reducing stroke than other combinations

Rimoldi meta-analysis (2015)[1]

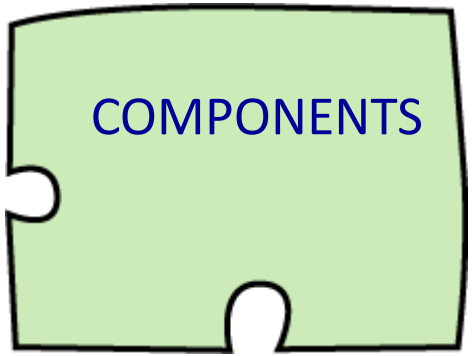
Risk ratios for stroke comparing treatment with combination CCB/thiazide-like diuretic vs other combinations



CCB, calcium channel blocker; CI, confidence interval, Diu, diuretic; RR, risk ratio.

1. Rimoldi SF et al. *J Clin Hypertens*. 2015;17:193-199.

Combination of CCB / diuretics

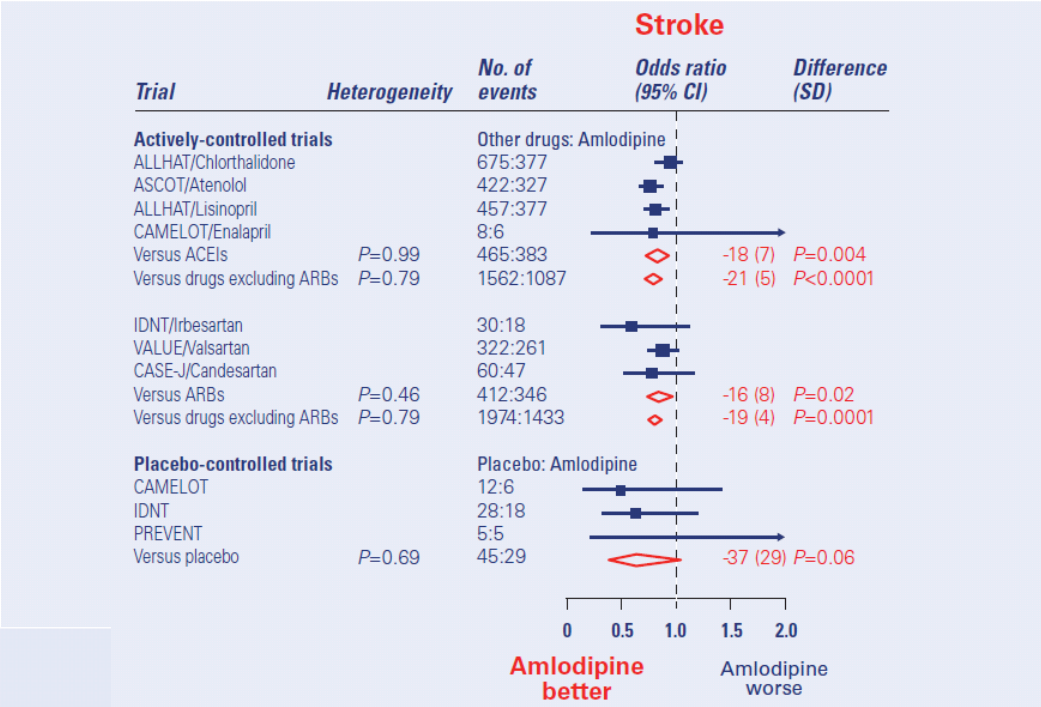


CCBs: evidence with amlodipine

ACCOMPLISH[1] 11 506 hypertensive patients amlodipine/benazepril vs HCTZ/benazepril	Primary outcome: 20% ↓ in CV events vs. placebo 22% ↓ myocardial infarction (0.04)
ALLHAT[2] 18 102 hypertensive patients: amlodipine vs lisinopril vs chlorthalidone	Primary outcome: No difference in composite of fatal CHD + non-fatal MI vs. lisinopril 6% ↓ combined CVD 23% ↓ stroke
VALUE[3] 15 245 hypertensive patients: amlodipine +/- HCTZ vs valsartan +/- HCTZ	Primary outcome: No difference in composite of fatal CHD + non-fatal MI vs valsartan 19% ↓ myocardial infarction

1 ACCOMPLISH Investigators. *N Engl J Med.* 2008;359:2417-2428; 2 ALLHAT Research Group. *JAMA.* 2002;288:2981-2997.
3 Julius S, Kjeldsen SE, Weber M, et al. *Lancet.* 2004;363:2022-2031.

Amlodipine: evidence-based protection against Stroke



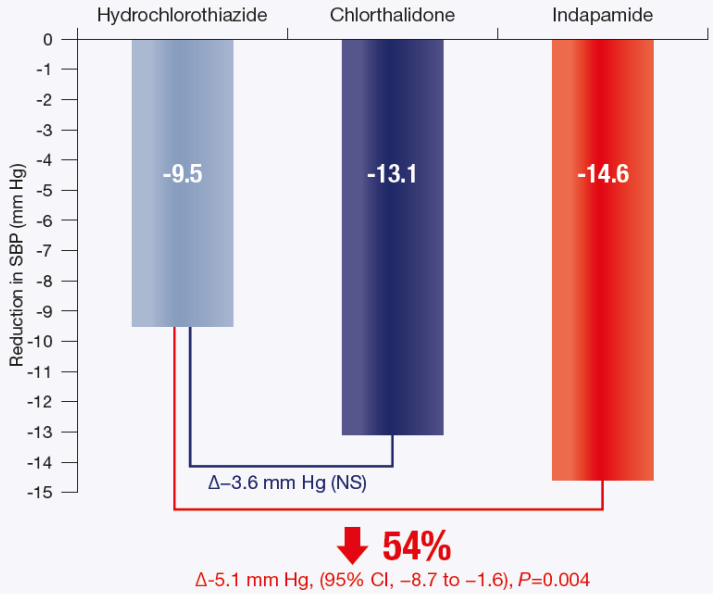
amlodipine provided more protection against stroke and myocardial infarction than other antihypertensive drugs, including angiotensin receptor blockers (−19%, $P<0.0001$ and −7%, $P=0.03$) and placebo (−37%, $P=0.06$ and −29%, $P=0.04$).

Wang J-G, et al. *Hypertension*. 2007;50:181-188.

Indapamide is more potent than HCTZ at reducing systolic blood pressure

Roush meta-analysis (2015)[1]

Indapamide is significantly more potent than HCTZ at reducing systolic blood pressure, which is not the case with chlorthalidone



Systematic review and meta-analysis; head-to-head RCTs comparing HCTZ vs indapamide (10 RCTS, n=813) and HCTZ vs chlorthalidone (3 RCTS, n=70).

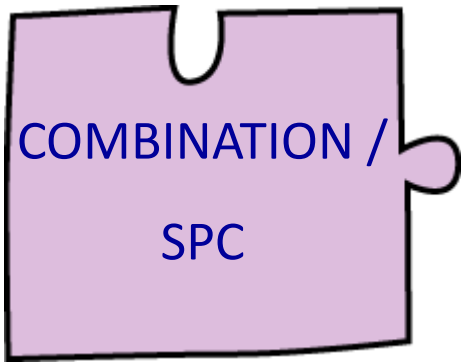
1. Roush et al. *Hypertension*. 2015;65:1041-1046.

Diuretics: evidence with indapamide

HYVET[1] 3845 elderly hypertensive patients indapamide SR vs placebo	Primary outcome: 30% ↓ in stroke vs placebo 64% ↓ heart failure 34% ↓ cardiovascular events (fatal and non-fatal) 21% ↓ all death
PROGRESS[2] 6105 patients with cerebrovascular disease: perindopril +/- indapamide vs placebo	Primary outcome: 28% ↓ in stroke vs placebo 38% ↓ non-fatal MI 26% ↓ major coronary events 26% ↓ congestive heart failure
ADVANCE[3] 11 140 HT patients with type 2 diabetes perindopril + indapamide vs placebo	Primary outcome: 9% ↓ Combined macrovascular + microvascular 14% ↓ coronary events 21% ↓ renal events 18% ↓ cardiovascular mortality 14% ↓ all death

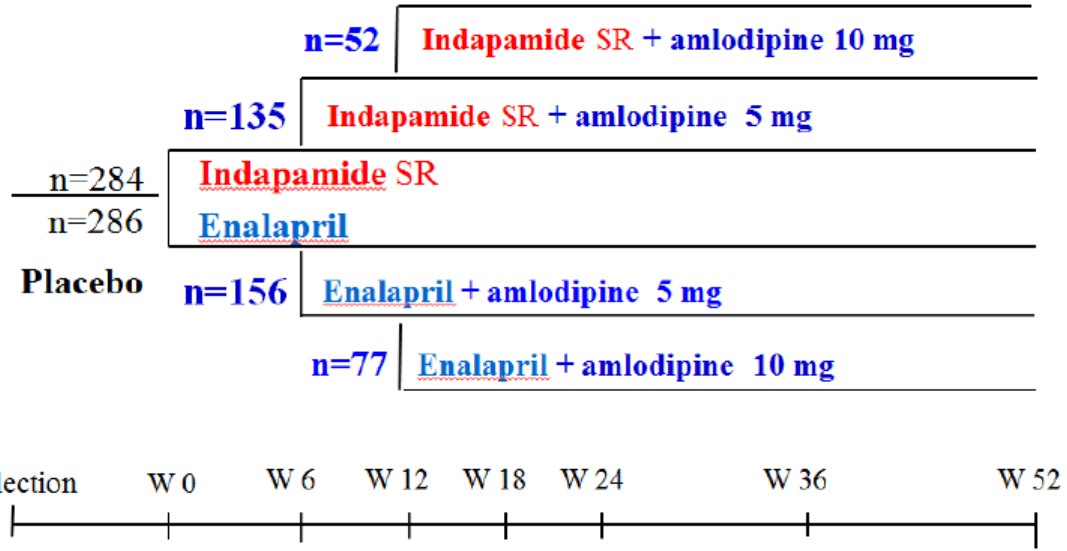
1. Beckett NS, Peters R, Fletcher AE, et al. *N Engl J Med.* 2008;358:1887-1898. 2. PROGRESS Collaborative Group. *Lancet*. 2001;358:1033-1041. 3. Patel A, Group AC, MacMahon S, et al. *Lancet.* 2007;370:829-840.

Combination of CCB / diuretics



NESTOR-CCB trial: Results of adding amlodipine 5/10 mg to indapamide1.5 mg

Hypertensive patients with type 2 diabetes (1-year follow-up)



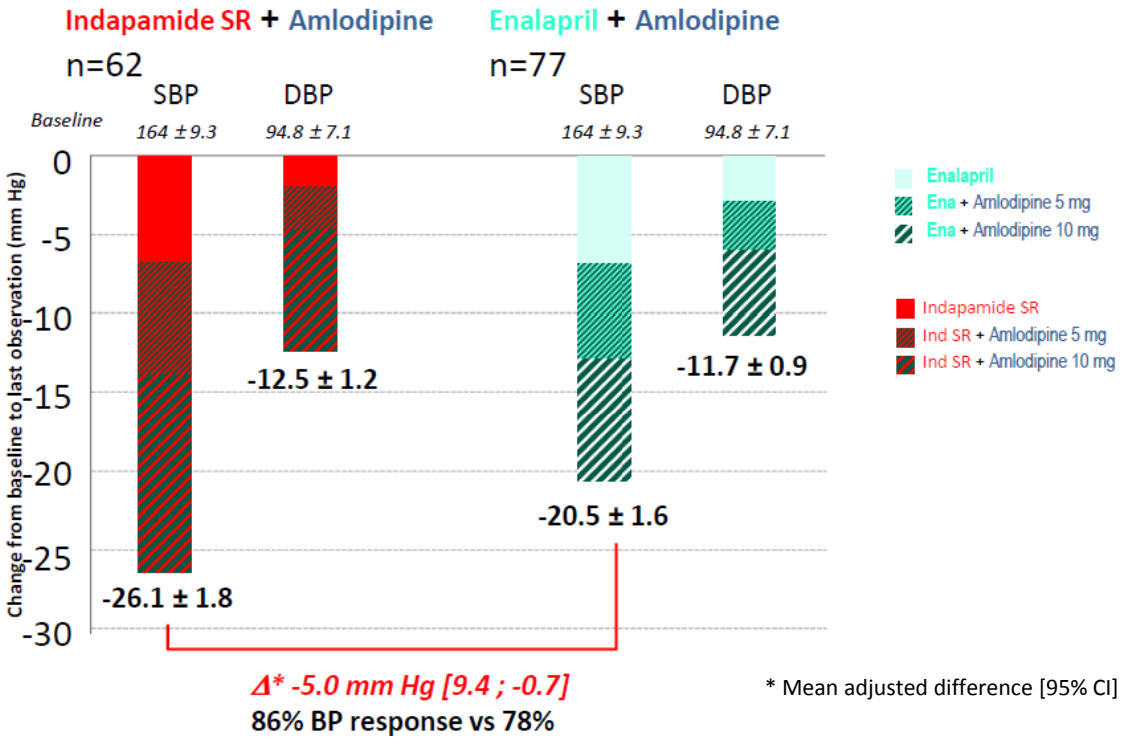
Randomised double-blind controlled trial over 1 year (n=570)

- **Indapamide 1.5 mg SR vs enalapril based therapy**
- **291 hypertensive patients uncontrolled on monotherapy**

Hanon O, Asmar R et al. Oral presentation, ESH Milan 2013

NESTOR-CCB trial: Results of adding amlodipine 5/10 mg to indapamide 1.5 mg

Changes in BP after adding Amlodipine 5 and 10 mg



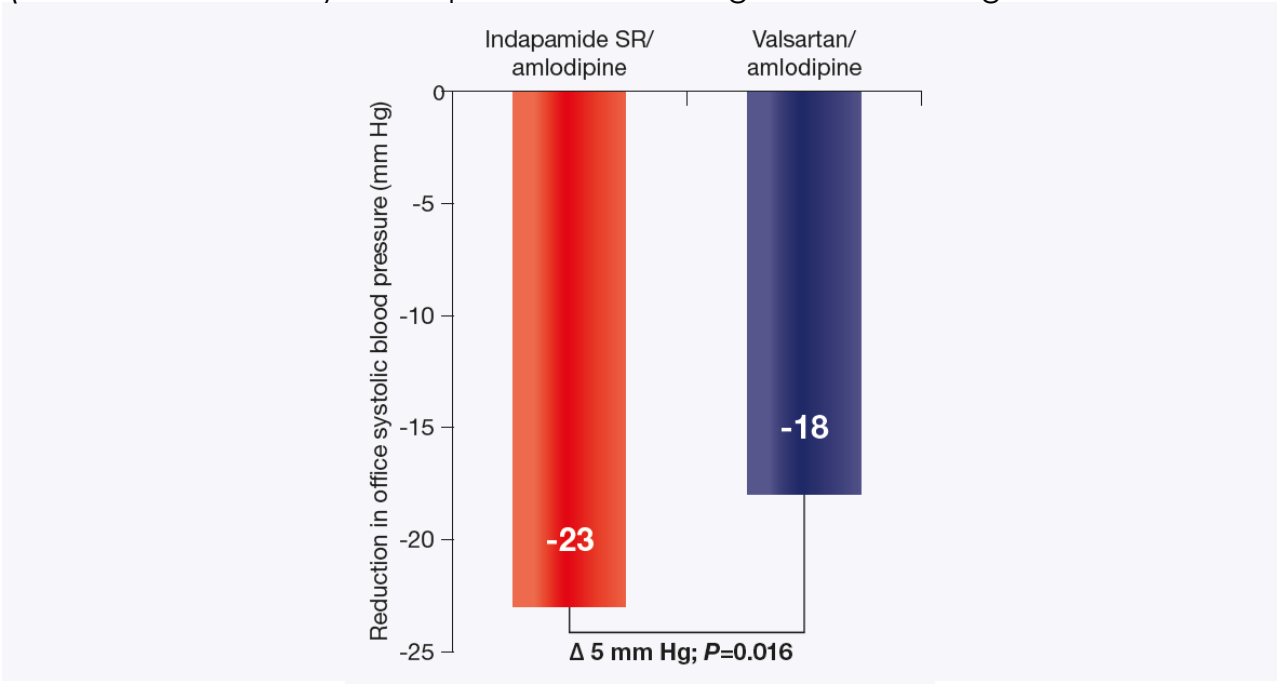
* Mean adjusted difference [95% CI]

Hanon O, Asmar R et al. Oral presentation, ESH Milan 2013

Indapamide SR/CCB further reduces SBP versus ARB/CCB combinations

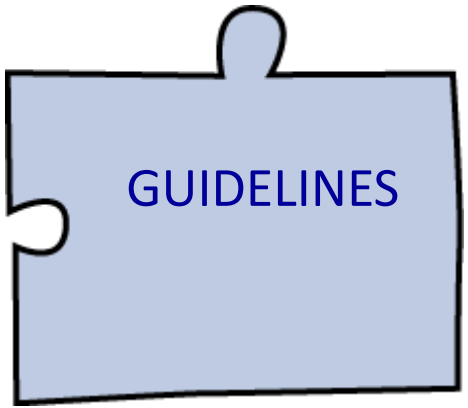
006 study (2016)[1]

Reduction in office SBP at week 12 in 216 patients with sustained hypertension (baseline ambulatory blood pressure monitoring >130/80 mm Hg.

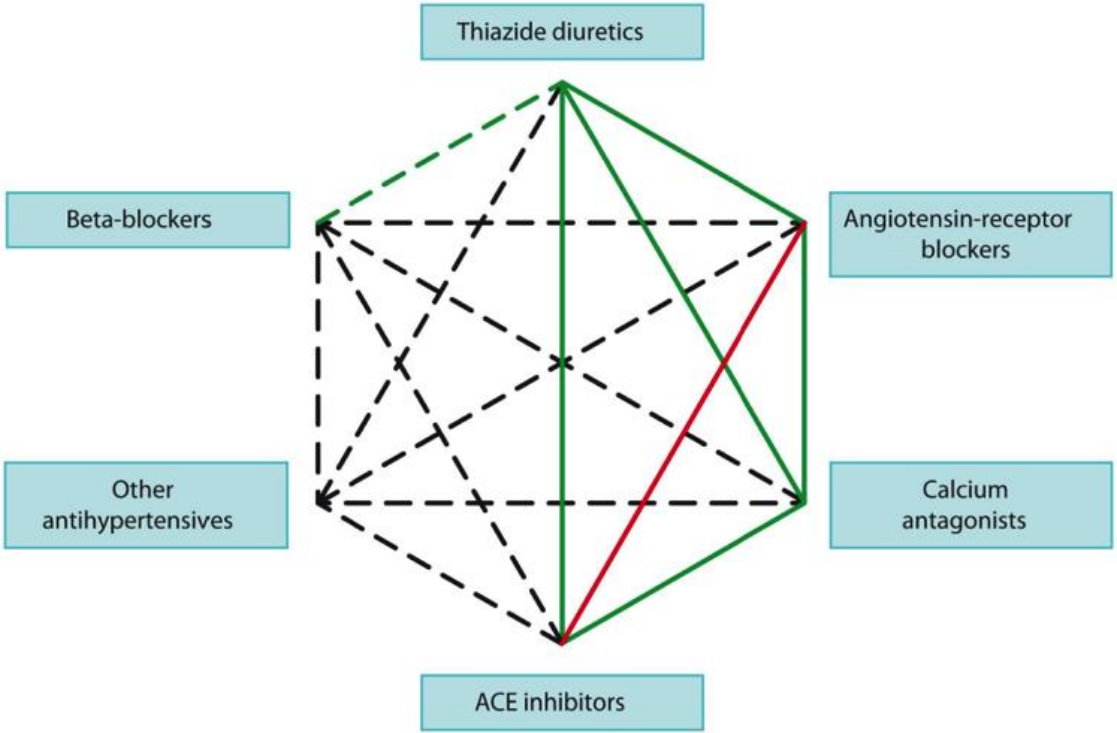


1. Dominiczak A, Asmar R et al. *ESH Abstract 2016.*

Combination of CCB / diuretics



2013 ESH/ESC Guidelines



Mancia et al. J Hypertens 2013

2013 ESH/ESC Guidelines

Condition	Drug
Asymptomatic organ damage	
LVH	ACE inhibitor, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB
Clinical CV event	
Previous stroke	Any agent effectively lowering BP
Previous myocardial infarction	BB, ACE inhibitor, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists
Aortic aneurysm	BB
Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist
Atrial fibrillation, ventricular rate control	BB, non-dihydropyridine calcium antagonist
ESRD/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, calcium antagonist
Other	
ISH (elderly)	Diuretic, calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

Mancia et al. J Hypertens 2013

2018 ESC-ESH Guidelines for the Management of Arterial Hypertension

Combination of CCB / diuretics