The Latest in Hypertension :

Simplifying the treatment

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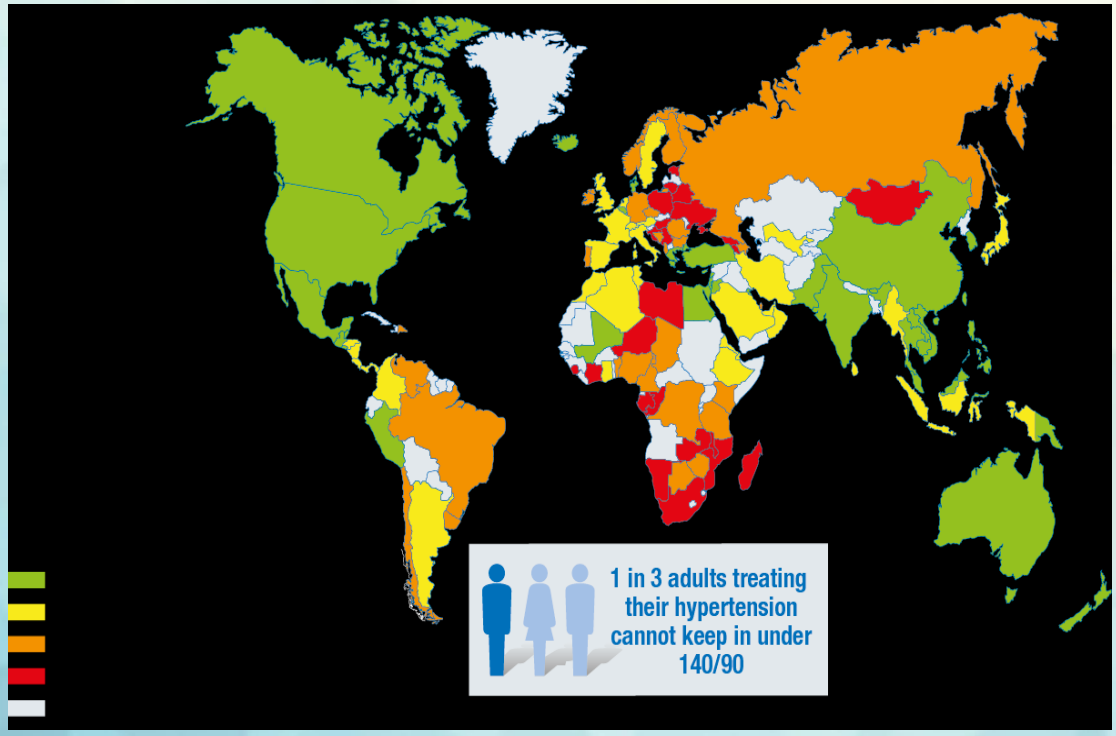
1.13 billion hypertensive patients worldwide[1*]



Globally

- Prevalence - 1 in every 3 individuals
- Deaths - 7.6 million / year (13.5% of total)

HTN is responsible for

- 45% of deaths due to heart disease
- 51% of deaths due to stroke

*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.

Arnett KD et al, Circulation 2014Lim SS et al, The Lancet 2013:380: 2224 – 2260; US Renal Data System ,2015

WORLD DIABETES FOUNDATION

WHO

National Survey on Diabetes Mellitus and Risk Factors for Non-communicable Diseases (NCDs) in Myanmar 2014

European Heart Journal Advance Access published June 14, 2013

European Heart Journal
doi:10.1093/eurheartj/eht151

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The Latest in Hypertension :

Simplifying the treatment

lood Pressure Clinical Practice Guideline

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2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

NHS National Institute for Health and Clinical Excellence

BHS British Hypertension Society

MMA Central Annual Conference
2018 (YGN)

American Heart Association
life is why™

Categories of BP in Adults*

BP Category	SBP		DBP
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.

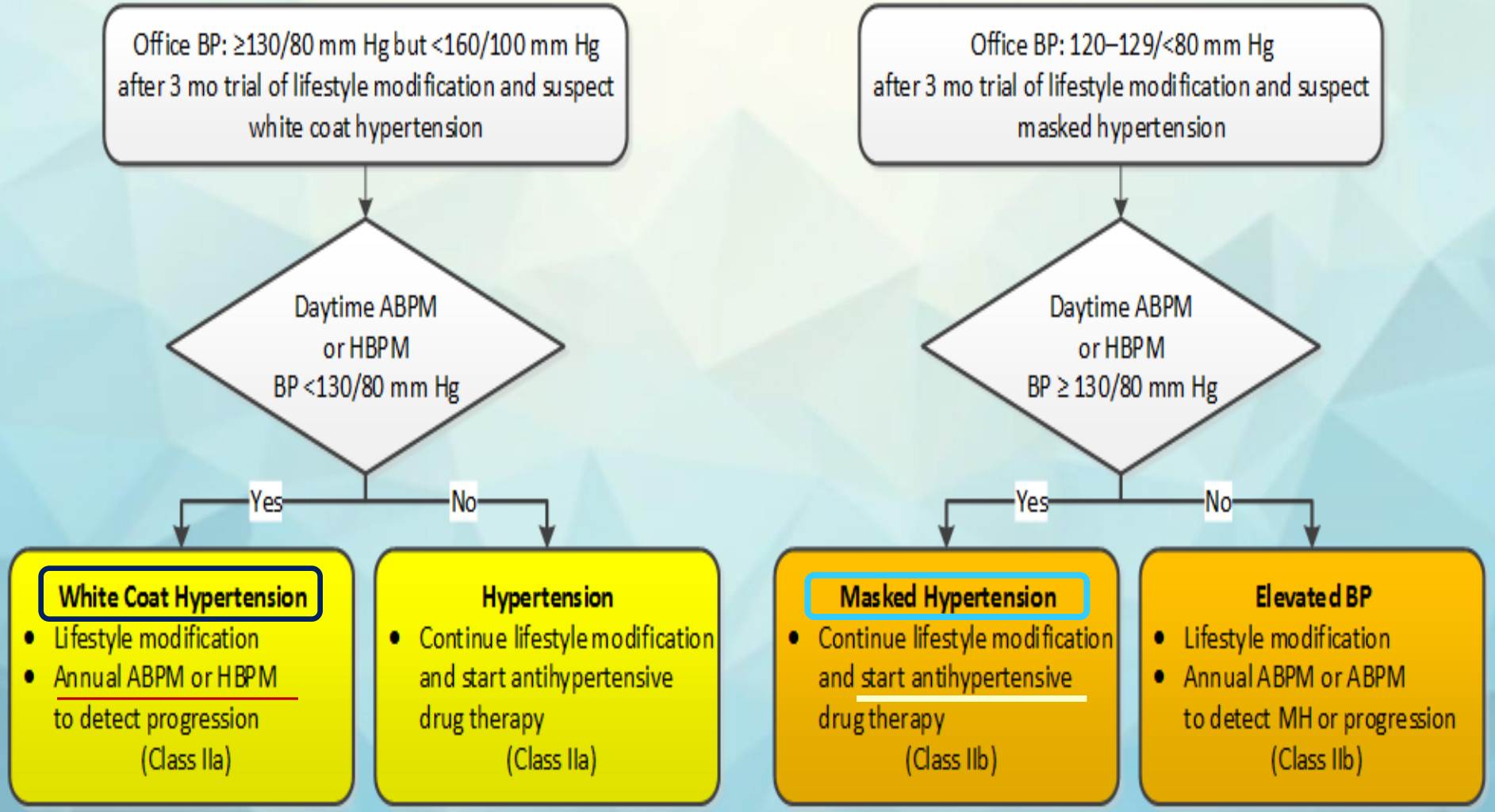
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.

BP Patterns Based on Office and Out-of-Office Measurements

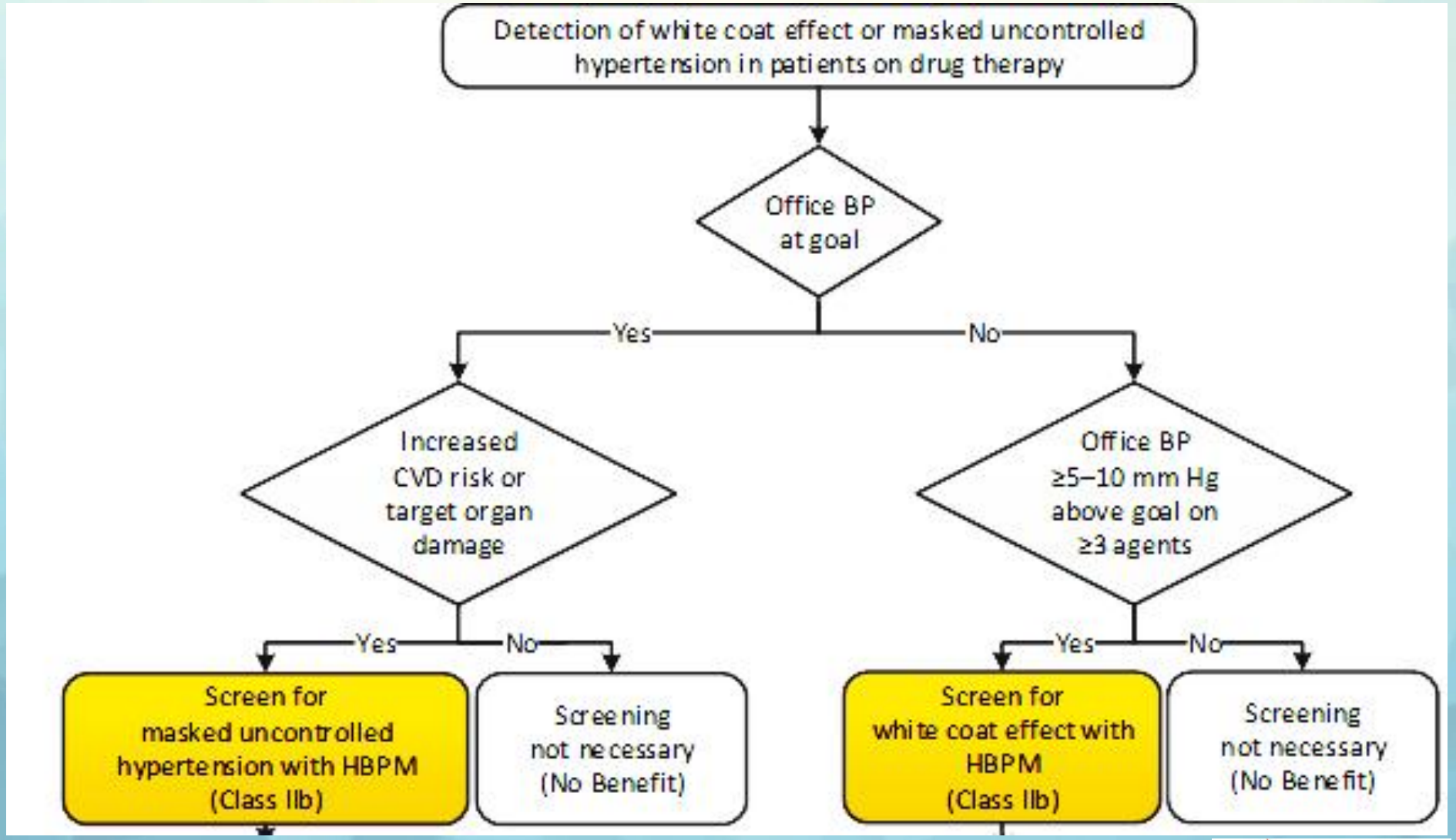
	Office/Clinic/Healthcare Setting	Home/Nonhealthcare/ ABPM Setting
Normotensive	No hypertension	No hypertension
Sustained hypertension	Hypertension	Hypertension
Masked hypertension	No hypertension	Hypertension
White coat hypertension	Hypertension	No hypertension

ABPM indicates ambulatory blood pressure monitoring; and BP, blood pressure.

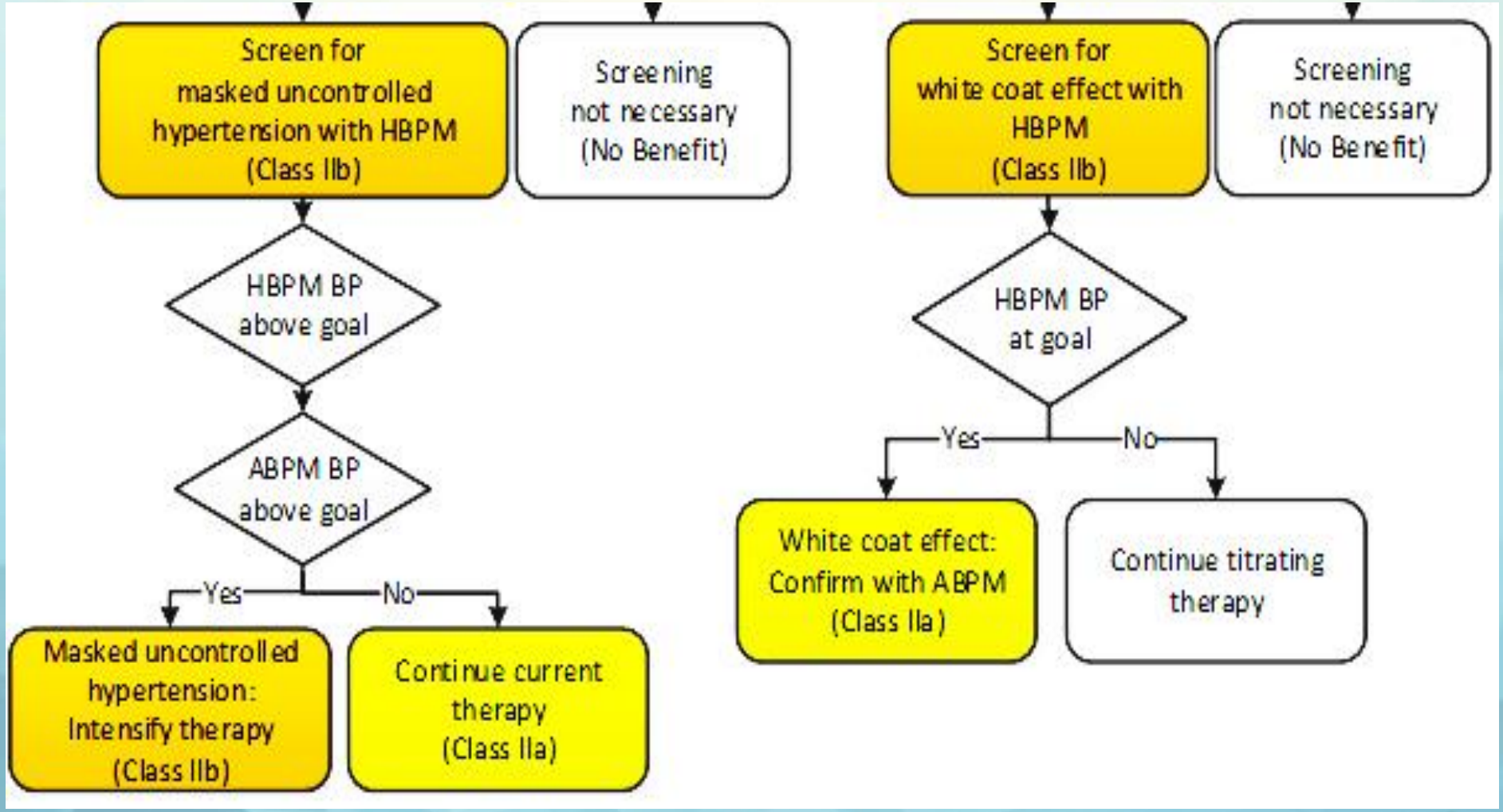
Detection of White Coat Hypertension or Masked Hypertension in Patients Not on Drug Therapy



Detection of White Coat Effect or Masked Uncontrolled Hypertension in Patients on Drug Therapy



Detection of White Coat Effect or Masked Uncontrolled Hypertension in Patients on Drug Therapy



BP Treatment Threshold and the Use of CVD Risk Estimation to Guide Drug Treatment of Hypertension

COR	LOE	Recommendations for BP Treatment Threshold and Use of Risk Estimation* to Guide Drug Treatment of Hypertension
I	SBP: A DBP: C-EO	Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher, and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average SBP 130 mm Hg or higher or an average DBP 80 mm Hg or higher.
I	C-LD	Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher.

*ACC/AHA Pooled Cohort Equations (http://tools.acc.org/ASCVD-Risk-Estimator/) to estimate 10-year risk of atherosclerotic CVD.

BP Treatment Threshold

BP-lowering medications is recommended for

- **secondary prevention** – clinical CVD + SBP ≥ 130 mmHg or DBP ≥ 80 mmHg
- **primary prevention**
  - estimated 10-year ASCVD risk ≥ 10% + SBP ≥ 130 mmHg or DBP ≥ 80 mmHg
  - estimated 10-year ASCVD risk <10% + SBP ≥ 140 mmHg or DBP ≥ 90 mmHg

*ACC/AHA Pooled Cohort Equations (http://tools.acc.org/ASCVD-Risk-Estimator/) to estimate 10-year risk of atherosclerotic CVD.

ESC / ESH Guideline (2013)

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
1–2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
≥3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

Guideline for the diagnosis and management of hypertension in adults

2016

Heart Foundation | hbprca | Kidney Health | strokefoundation

Recommendations for treatment strategies and treatment targets for patients with hypertension

Recommendations for treatment strategies and treatment targets for patients with hypertension	Grade of recommendation	Level of evidence
to identify treatment related adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury.		
g. In patients with uncomplicated hypertension ACE inhibitors or ARBs, calcium channel blockers, and thiazide diuretics are all suitable first-line antihypertensive drugs, either as monotherapy or in some combinations unless contraindicated.	Strong	I
h. The balance between efficacy and safety is less favourable for beta-blockers than other first-line antihypertensive drugs. Thus beta-blockers should not be offered as a first-line drug therapy for patients with hypertension not complicated by other conditions.	Strong	I
i. ACE inhibitors and ARBs are not recommended in combination due to the increased risk of adverse effects.	Strong	I

Anti –hypertensive therapy should be started for patients with

- Moderate CVD risk (10-15% 5-year-risk) - ≥ 140/90
- Low CVD risk (<10% 5-year-risk) - ≥ 160/100

BP Goal

COR	LOE	Recommendations for BP Goal for Patients With Hypertension
I	SBP:B-R[SR]	For adults with confirmed hypertension and known CVD or 10-year ASCVD event risk of 10% or higher a BP target of less than 130/80 mm Hg is recommended.
	DBP: C-EO	
IIb	SBP:B-NR	For adults with confirmed hypertension, without additional markers of increased CVD risk, a BP target of less than 130/80 mm Hg may be reasonable.
	DBP: C-EO	

ACC/AHA (2017)

- ❑ **Recommended**
  - < 130/80 mm Hg - known CVD **or** 10-year ASCVD risk ≥ 10%
- ❑ **Reasonable**
  - < 130/80 mm Hg - without additional markers of ↑ CVD risk

JNC 8 (2014)

- ❑ **<140/90 - <60 yr**
- ❑ **<150/90 - >60 yr**

2017 Hypertension Clinical Practice Guidelines

BP and CVD Risk

COR	LOE	Recommendation for Coexistence of Hypertension and Related Chronic Conditions
I	B-NR	Screening for and management of other modifiable CVD risk factors are recommended in adults with hypertension.

CVD Risk Factors Common in Patients With Hypertension

Modifiable Risk Factors*	Relatively Fixed Risk Factors†
• Current cigarette smoking, secondhand smoking • Diabetes mellitus • Dyslipidemia/hypercholesterolemia • Overweight/obesity • Physical inactivity/low fitness • Unhealthy diet	• 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.

Patient Evaluation

Basic testing	Fasting blood glucose*
	Complete blood count
	Lipid profile
	Serum creatinine with eGFR*
	Serum sodium, potassium, calcium*
	Thyroid-stimulating hormone
	Urinalysis
	Electrocardiogram
Optional testing	Echocardiogram
	Uric acid
	Urinary albumin to creatinine ratio

*May be included in a comprehensive metabolic panel.
eGFR indicates estimated glomerular filtration rate.

Nonpharmacological Interventions

COR	LOE	Recommendations for Nonpharmacological Interventions
I	A	Weight loss is recommended to reduce BP in adults with elevated BP or hypertension who are overweight or obese.
I	A	A heart-healthy diet, such as the DASH (Dietary Approaches to Stop Hypertension) diet, that facilitates achieving a desirable weight is recommended for adults with elevated BP or hypertension.
I	A	Sodium reduction is recommended for adults with elevated BP or hypertension.
I	A	Potassium supplementation, preferably in dietary modification, is recommended for adults with elevated BP or hypertension, unless contraindicated by the presence of CKD or use of drugs that reduce potassium excretion.

Nonpharmacological Interventions (cont.)

COR	LOE	Recommendations for Nonpharmacological Interventions
I	A	Increased physical activity with a structured exercise program is recommended for adults with elevated BP or hypertension.
I	A	Adult men and women with elevated BP or hypertension who currently consume alcohol should be advised to drink no more than 2 and 1 standard drinks* per day, respectively.

*In the United States, 1 “standard” drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol).

Nonpharmacological Interventions

- Diet – heart healthy diet (eg- DASH – Dietary Approach to Stop Hypertension)
- Sodium ↓
- Potassium supplementation (in dietary modification) - unless contraindicated (eg- CKD or drug reducing K^+ excretion)
- Moderation of alcohol – 2 Standard drinks/day for men and 1 for women

- ↑ Physical Activity
- Weight reduction – if wt ↑

*In the United States, 1 “standard” drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol).

General Principles of Drug Therapy

COR	LOE	Recommendation for General Principle of Drug Therapy
III: Harm	A	Simultaneous use of an ACE inhibitor, ARB, and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension.

Choice of Initial Medication

COR	LOE	Recommendation for Choice of Initial Medication
I	A^{SR}	For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs.

SR indicates systematic review.

Choice of Initial Monotherapy Versus Initial Combination Drug Therapy

COR	LOE	Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy*
I	C-EO	Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target.
IIa	C-EO	Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target.

Pharmacological Therapy

- Simultaneous use of an **ACEI + ARB**, and/or **renin inhibitor** → **not recommended**
- **first-line agents** → thiazide diuretics, CCBs, and ACEIs / ARBs.
- **Initiation with a single drug** → stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target.
- **Initiation with 2 first-line agents** → stage 2 hypertension and an average BP >20/10 mm Hg above their BP target

Hypertension in Patients With Comorbidities

Hypertension in Patients With Comorbidities

	Target	Initial (first-line)	Addition
Stable IHD	<130/80	GDMT* beta blockers, ACEI or ARBs	dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists

*GDMT beta blockers - carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol. Avoid beta blockers with intrinsic sympathomimetic activity. The beta blocker atenolol should not be used because it is less effective than placebo in reducing cardiovascular events.

Hypertension in Patients With Comorbidities

	Target	Initial (first-line)
CKD	<130/80	ACEI If ACEIs are not tolerated – change to ARBs

American Diabetes Association®

ADA 2018

MANAGEMENT OF BP in DM

Goals

- **DM + HTN** → **<140/90 mmHg**
- **DM + HTN + high risk of CVD** → **<130/80 or <120/80 mmHg**
  (if they can be achieved without undue treatment burden)
- **DM + HTN + Pregnancy** → **<120–160/ 80–105 mmHg**
  (in 2016 ADA - BP targets - 110–129/65–79 mmHg)

Pharmacologic interventions	▪ Indication → **≥140/90** ▪ **≥160/100 → initiate with 2 drugs or single-pill combination**

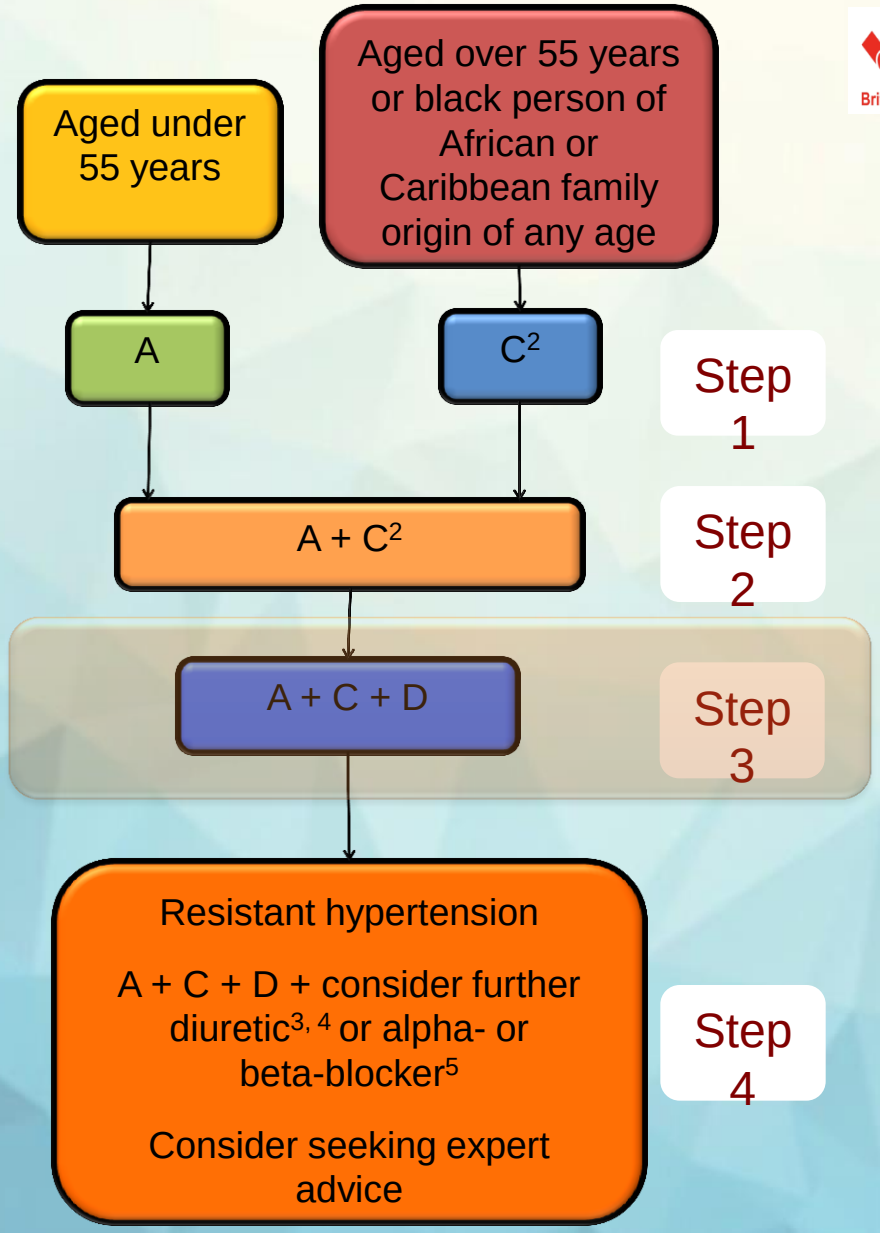
Drug choices

- **ACEI, ARB, thiazide-like diuretics, dihydropyridine CCB**
- **Generally – multiple drug therapy is required**
- **NOT recommend – ACEI + ARB or ACEI + ARB + direct Renin Inhibitor**
- **DM + HTN + UACR ≥300 mg/g or 30-299 mg/g → ACEI or ARB**
- **Resistant Hypertension –** mineralocorticoid receptor antagonist therapy

Hypertension in Patients With Comorbidities

	Target	Initial (first-line)
AF		

How can we start in Hypertension with no special consideration



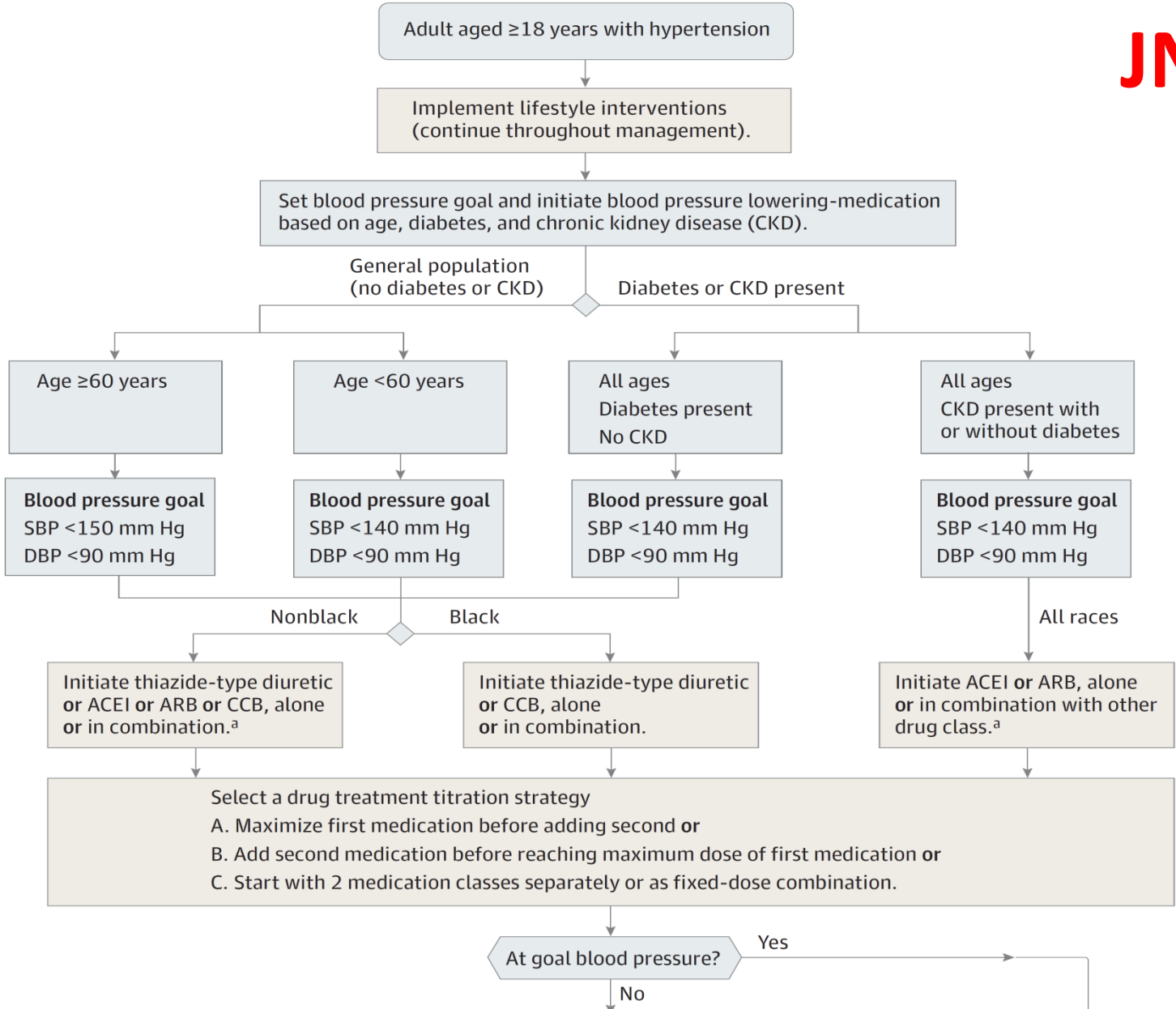
BHS British Hypertension Society

NHS National Institute for Health and Clinical Excellence

Summary of antihypertensive drug treatment

Key
A – ACE inhibitor or low-cost angiotensin II receptor blocker (ARB)[1]
C – Calcium-channel blocker (CCB)
D – Thiazide-like diuretic

Figure. 2014 Hypertension Guideline Management Algorithm



The A,B,C,D drug classes

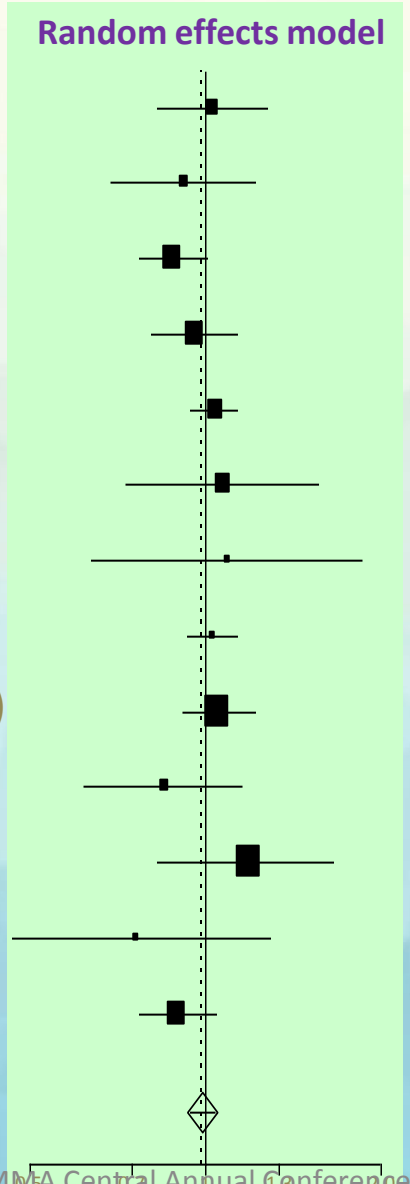
- **A** Angiotensin-converting enzyme inhibitors
- **A** Angiotensin receptor blockers
- **B** Beta-blockers
- **C** Calcium channel blockers
- **D** Diuretics

ACEI ? OR ARB?

ACEI –CVD and High CVD risk

ARB -Nephropathy

All-cause mortality: effect of ARBs

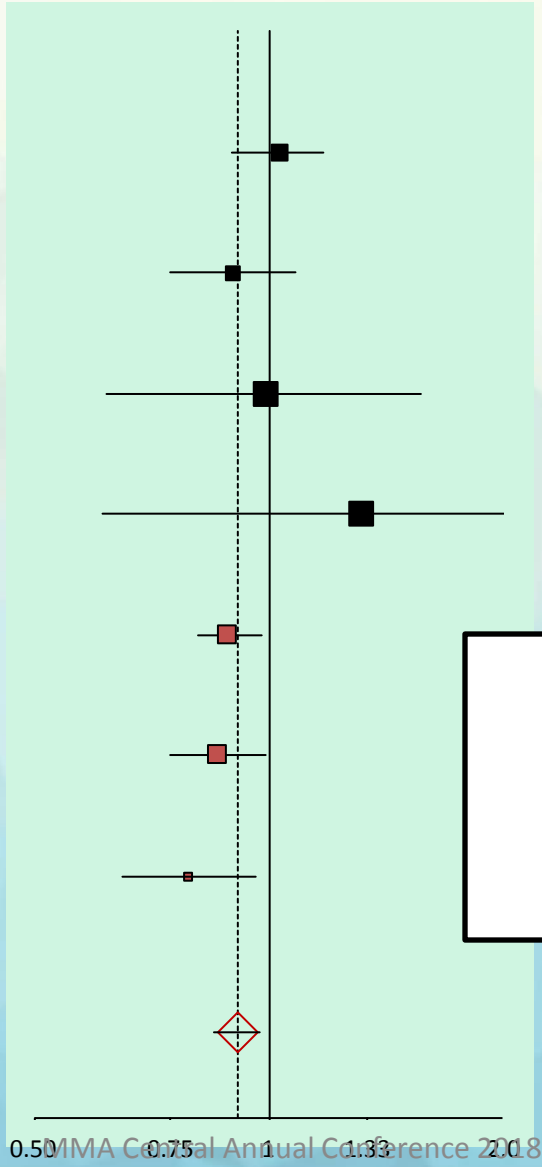


	HR (95% CI)	P
RENAAL (losartan)	1.03 (0.83-1.29)	
IDNT (irbesartan)	0.92 (0.69-1.23)	
LIFE (losartan)	0.88 (0.77-1.01)	
SCOPE (candesartan)	0.96 (0.81-1.14)	
VALUE (valsartan)	1.04 (0.94-1.14)	
MOSES (eprosartan)	1.07 (0.73-1.57)	
JIKEI HEART (valsartan)	1.09 (0.64-1.85)	
PRoFESS (telmisartan)	1.03 (0.93-1.14)	
TRANSCEND (telmisartan)	1.05 (0.91-1.22)	
CASE-J (candesartan)	0.85 (0.62-1.16)	
HIJ-CREATE (candesartan)	1.18 (0.83-1.67)	
KYOTO HEART (valsartan)	0.76 (0.40-1.30)	
NAVIGATOR (valsartan)	0.90 (0.77-1.05)	
Overall	0.99 (0.94-1.04)	0.683

N=82 383

Van Vark LC, Bertrand M, Fox K, Mourad JJ, Boersma E, et al. *Eur Heart J 2012;* published online April 17

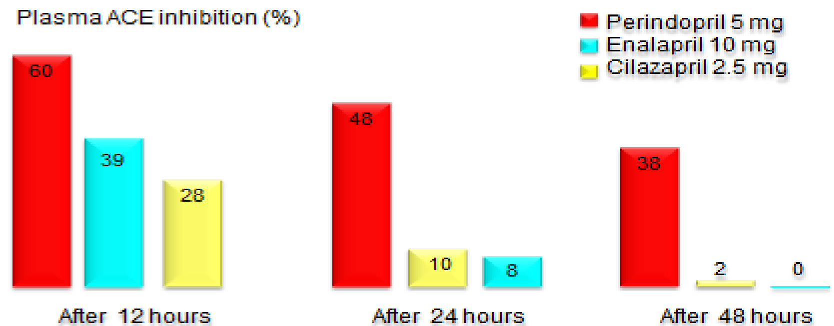
All-cause mortality: effect of ACEI



Van Vark LC, Bertrand M, Fox K, Mourad JJ, Boersma E, et al. *Eur Heart J 2012;* published online April 17.

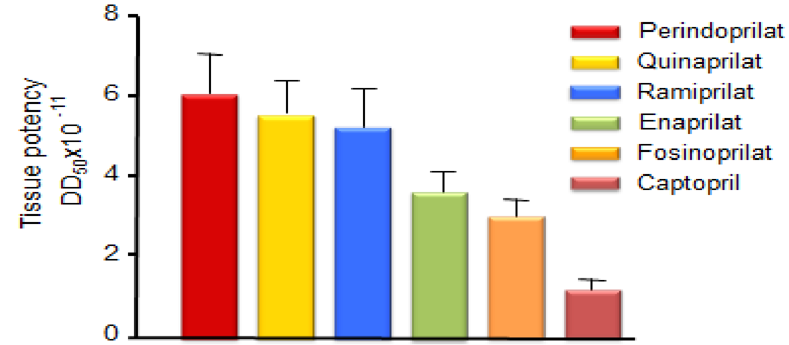
Are all ACEIs the same?

Pharmacokinetic and pharmacodynamic profiles of perindopril, enalapril and cilazapril



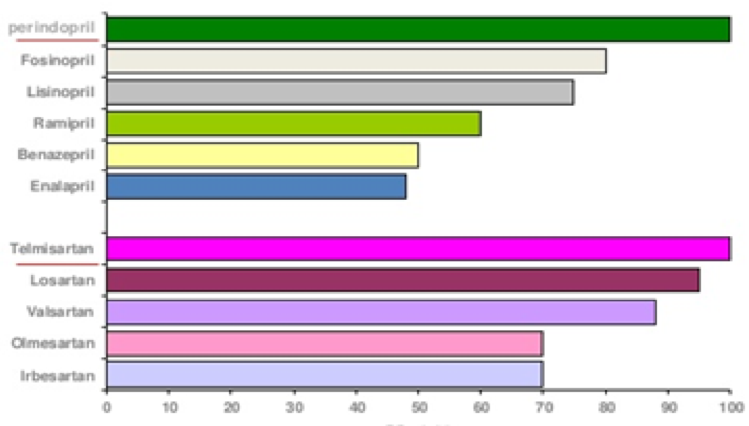
Louis et al. *Clin Exp Pharmacol Physiol.* 1992;19:55-60

ACE-inhibitors: Differential affinity for tissue ACE



Ferrari R. ***Dialogues Cardiovasc Med*** **2004;9:71-92.**

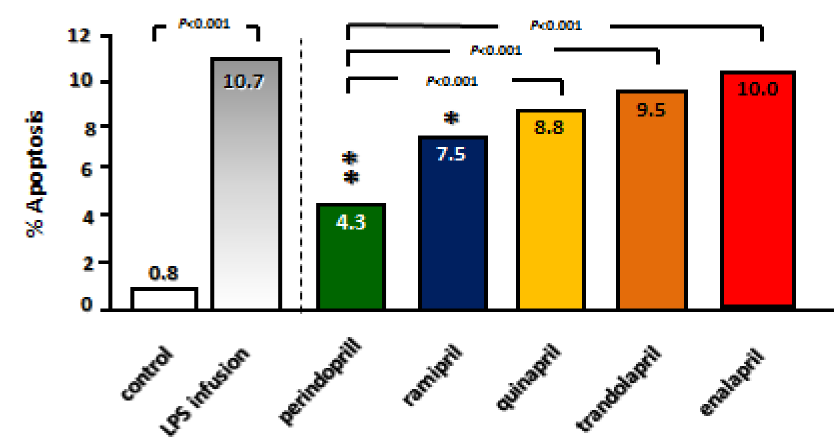
24 hour antihypertensive efficacy: trough-to-peak ratio



1. Physicians Desk Reference. NJ: Medical Economics Company; 2008. 2. Diamant H and Vincent HH. Lisin... evaluation of trough:peak ratio by ambulatory blood pressure monitoring. *J Hum Hypertens.* 1999;13:405-412. 3. Martell M, Gill B, ... of once-daily lisinopril and twice-daily captopril in patients with essential hypertension. *J Hum Hypertens.* 1998;12:69-72. 4. Hermida RC, Calvo C, Ayala DE, et al. Administration time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. *Hypertension.* 2000;42:282-290.

ACEi and apoptosis: a class effect?

(after 1 week's treatment)



* $P<0.001$ vs LPS

Ceconi C et al. *Cardiovasc Drugs Ther.* 2007;21:423-429.

Are all ACEIs the same?

Table 3. Clinical Trials of ACE Inhibitors in Patients With CHD

ACE Inhibitor	Trial	Results
Perindopril	EUROPA[21]	Positive 20% relative risk reduction on the primary endpoint (CV death, MI, or cardiac arrest) (95% CI 9–29, $P = 0.0003$) with perindopril versus placebo.
Ramipril	HOPE[37]	Positive 22% reduction in the primary outcome (MI, stroke or CV death) (relative risk 0.78: 95% CI: 0.70–0.86, $P < 0.001$).
Trandolapril	PEACE[39]	Negative No difference in the primary endpoint (CV death, nonfatal MI, CABG, PCI) between trandolapril (21.9%) and placebo (22.5%) (HR 0.96, 95% CI: 0.88–1.08, $P = 0.43$).
Quinapril	QUIET[40]	Negative The rates of CV mortality, overall mortality, and nonfatal AMI were similar between patients treated with quinapril and those given placebo (1.4% vs 1.5%; 3.1% vs 3.2%; and 4.1% vs 4.6%, respectively; P = NS for each endpoint).
Enalapril	CAMELOT[43]	Negative No significant reduction in CV eventswith enalapril versus placebo (20.2% vs 23.1%), (HR, 0.85; 95% CI, 0.67–1.07; $P = 0.16$).

- PERINDOPRIL
- ENALAPRIL
- RAMIPRIL
- QUINALAPRIL
- TRANDOLAPRIL

PERINDOPRIL OR RAMIPRIL?

Evidence of risk reduction

Perindopril

- in stable CAD patients - EUROPA trial
- In High risk CAD patients - ASCOT-BPLA

Ramipril

- in high risk CAD patients - HOPE trial

- **other evidence for Perindopril**
  - ADVANCE, PROGRESS, HYVET

Beta blocker

Propranolol,Atenolol,metoprolol XL,Carvidolol,Bisoprolol,Nevivolol

Beta Blockers

- less appealing as first-line agents for patients with diabetes mellitus (grade A).

- the major adverse effects of BBs may be mediated by peripheral vasoconstriction and increasing insulin resistance
- the use of the new third-generation BBs (such as Nebivolol) or drugs that block both a and b receptors (such as Carvedilol) may prove to be particularly beneficial (grade A).
- These agents cause vasodilatation and an increase in insulin sensitivity.

American Association of Clinical Endocrinologist, 2006

- BBs - not recommended for patients age 60+ without another compelling indication. *CHEP 2008*

Calcium Channel Blockers

Dihydropyridine –Amlodipine,Nifedipine,Felodipine,clinidipine

Non dihydropyridine - diltiazen,verepamil

- **MOA** - Block movement of calcium into cells → vasodilation → ↓ BP
- **Side effects -** Bradycardia, heart block

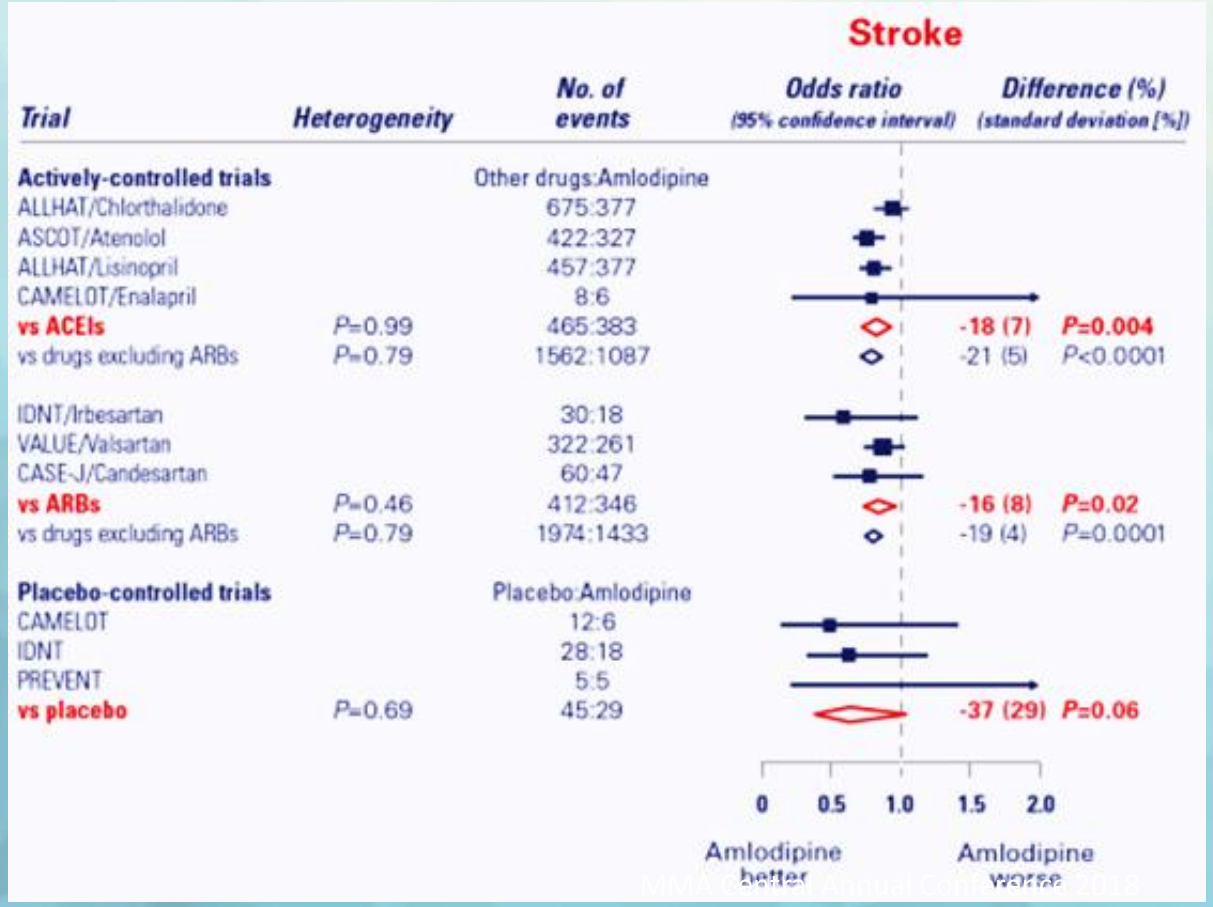
Amlodipine provides effective protection against stroke

Protection against stroke with amlodipine vs placebo, ARBs, or ACEIs

Wang meta-analysis (2007)[1]

Protection against stroke (n=94 338)

	vs Placebo	vs ARBs	vs ACE inhibitors
Amlodipine	-37% *P*=0.06	-16% *P*=0.02	-18% *P*=0.004



Effects of antihypertensive treatment on stroke in trials comparing amlodipine with placebo or other classes of antihypertensive drugs, including angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors.

(YGN)

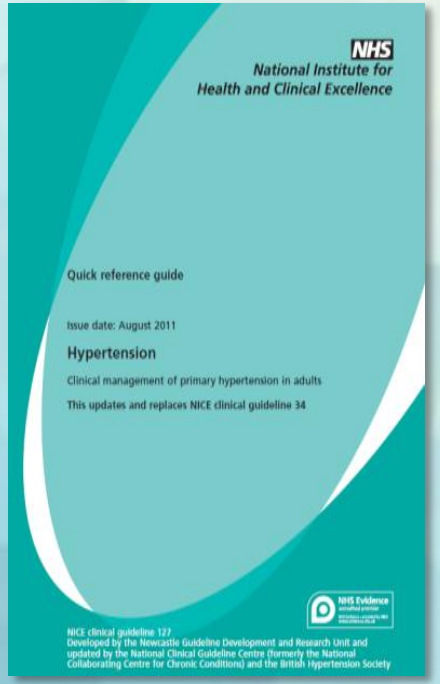
1. Wang et al. *Hypertension*. 2007;50:181-188.

Diuretics

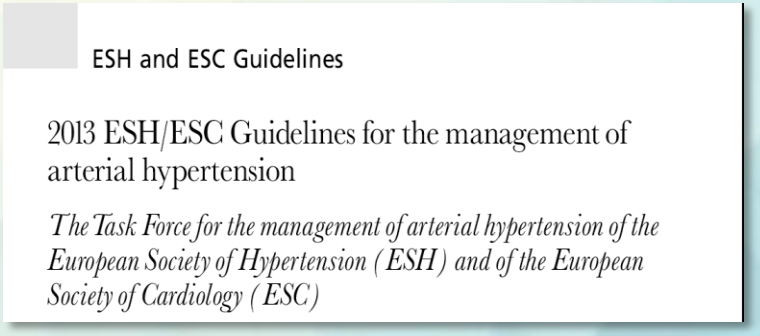
- Thiazide – Hydrochlorthiazide
- Thiazide-like Diuretics - Chlortalidone, Indapamide SR
- Loop diuretics - Frusemide, torsemide, Metolazone

- If GFR<30 - Frusemide
- If GFR >30 - any diuretics
- **Side effects:**
  - Electrolyte imbalances: ↓ Na, ↓ Cl, ↓ K** (advise K rich foods)
  - Fluid volume depletion (monitor for orthostatic hypotension)
  - Impotence, decreased libido
  - new onset DM, lipid abnormalities

Debate of preferred thiazide-like diuretics since NICE 2011



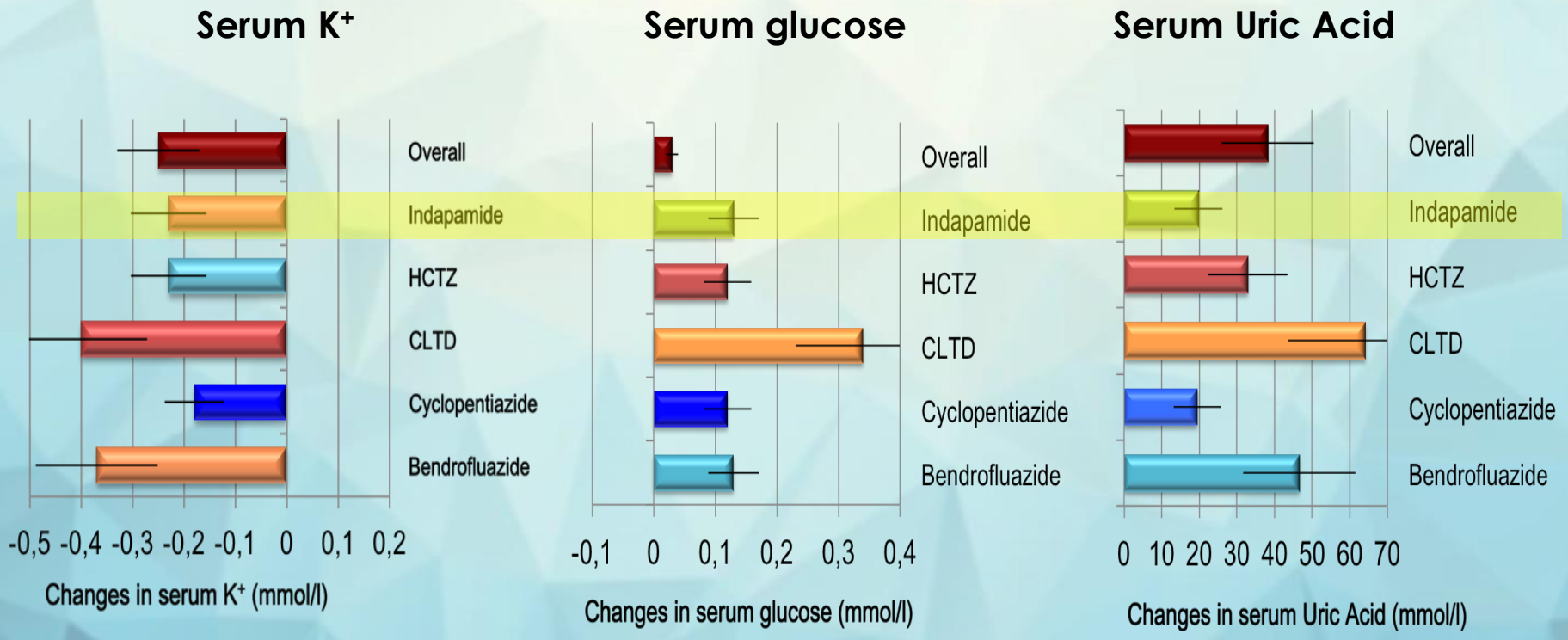
***…D: Thiazide-like Diuretics like Chlortalidone** (12.5-25 mg once daily) or **Indapamide** (2.5 or 1.5 SR mg once daily) rather than thiazide diuretics such as Bendroflumethiazide or Hydrocholorothiazide.*



…Diuretics have remained the cornerstone of antihypertensive treatment...
*…It has also been argued that diuretics **such as chlorthalidone or indapamide should be used in preference to conventional thiazide diuretics**, such as hydrochlorothiazide [271].*

Effects of different diuretics on metabolic profile.

Cochrane metanalysis of RCT[1]



1. Musini VM et al. *Cochrane Coll Library*. 2014;29;(5):CD003824

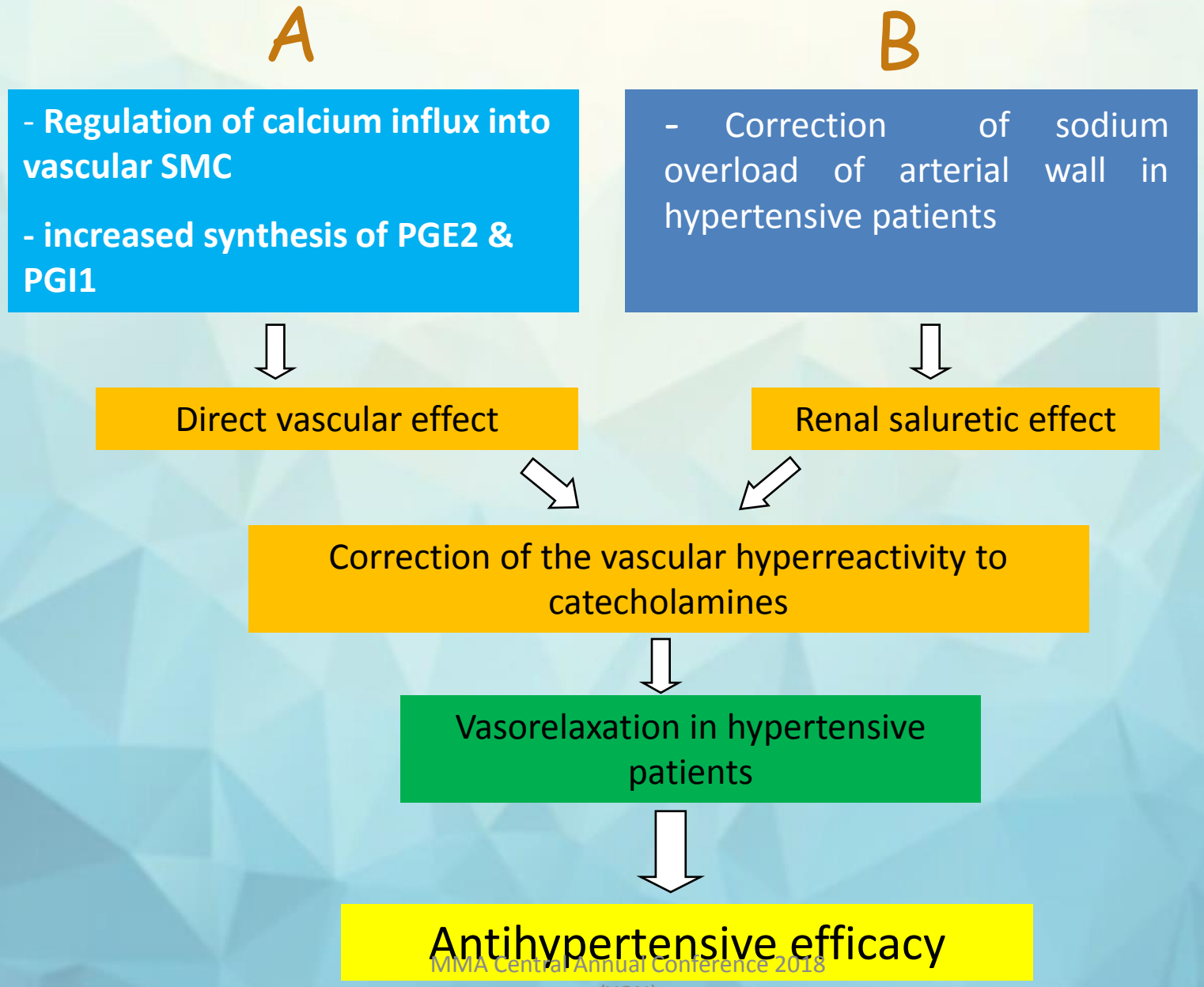
Are all Diuretics the same ?

	Indapamide	Chlortalidone	HCTZ*
BP-lowering efficacy	+++	++	+
24-hour BP control	☑	☑	-
Metabolic neutrality	☑	-	-
Cardiovascular protection	☑	☑	-
Renal protection	☑	-	-
Total mortality reduction	☑	-	-

* Hydrochlorothiazide, doses ranging 12.5 – 25 mg/day

1. Roush et al. *Hypertension*. 2015;65:1041-1046. 2. London G, Schmieder R, Calvo C, Asmar R. *Am J Hypertens*. 2006;19:113-121. 3. Messerli FH, Makani H, Benjo A, Romero J, Alviar C, Bangalore S. *J Am Coll Cardiol*. 2011;57:590-600. 4. Ambrosioni E, Safar M, Degaute J-P, et al. *J Hypertens*. 1998;16:1677-1684. 5. Akram J, Sheikh UE, Mahmood M, Donnelly R. *Curr Med Res Opin*. 2007;23:2929-2936. 6. Gaciong Z, Symonides B. *Expert Opin Pharmacother*. 2010;11:2579-2597. 7. Beckett NS, Peters R, Fletcher AE, et al. *N Engl J Med*. 2008;358:1887-1898. 8. Gosse P, Sheridan DJ, Zannad F, et al. *J Hypertens*. 2000;18:1465-1475. 9. Marre M, Garcia J, Kokot F, et al. *J Hypertens*. 2004;22:1613-1622. 10. Roush GR, Sica DA. Diuretics for Hypertension: A Review and Update. *Am J Hypertens*. 2016;29(10):1130-7 .

Indapamide SR: Unique mode of action



Summary of evidence from large-scale clinical trials with Indapamide

Study	Agent	End point(s)	Key findings
HYVET	**Indapamide ±** Perindopril vs. Placebo	**Primary:** Fatal or non fatal stroke **Secondary:** death from any cause death from CV causes, death from cardiac causes, death from stroke	**30% reduction in fatal or nonfatal Stroke** **39% reduction in death from Stroke** **64% reduction in heart failure** **21% reduction in death from any cause** **23% reduction in death from cardiovascular causes**
ADVANCE	**Indapamide +** Perindopril vs. Placebo	Composite of macrovascular (CV death, nonfatal MI, nonfatal stroke) and microvascular (new or worsening nephropaty or retinopathy) events	**9% reduction in primary end point** **18% reduction in CV death** **14% reduction in all cause mortality** **21% reduction in total renal events**
PROGRESS	**Indapamide +** Perindopril vs. Placebo	Fatal or non fatal stroke	**43% reduction in stroke** **40% reduction in major CV events**
PATS	**Indapamide** vs. Placebo	Fatal or non fatal stroke	**29% reduction in stroke**

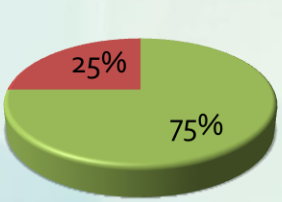
Are all Diuretics the same ?

	Indapamide	Chlortalidone	HCTZ*
NICE (2011)	++	++	-
ESC-ESH (2013)	+	+	+
ACC-AHA (2017)	[+] [post stroke]	++	-
ADA (2017)	++	++	-

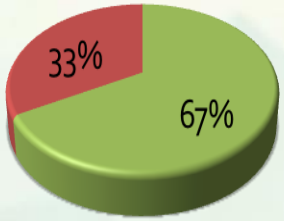
1.

* Hydrochlorothiazide

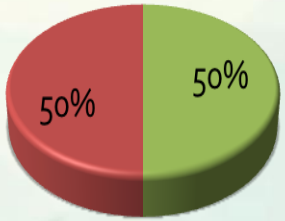
Percentage of positive outcome studies with different combinations of antihypertensive drugs



ACE-I's & CCB's (4)



ACE-I's & Diuretics (6)

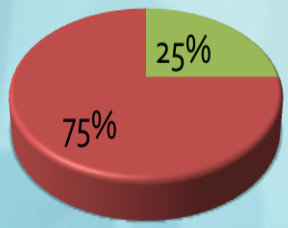


ARB's & Diuretics (2)

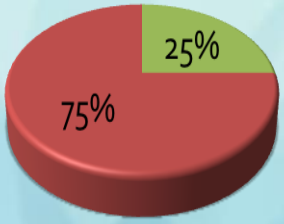
Positive studies

Neutral or negative studies

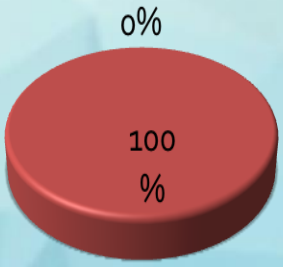
ARB's & CCB's



CCB's & Diuretics (4)



BB's & Diuretics (12)



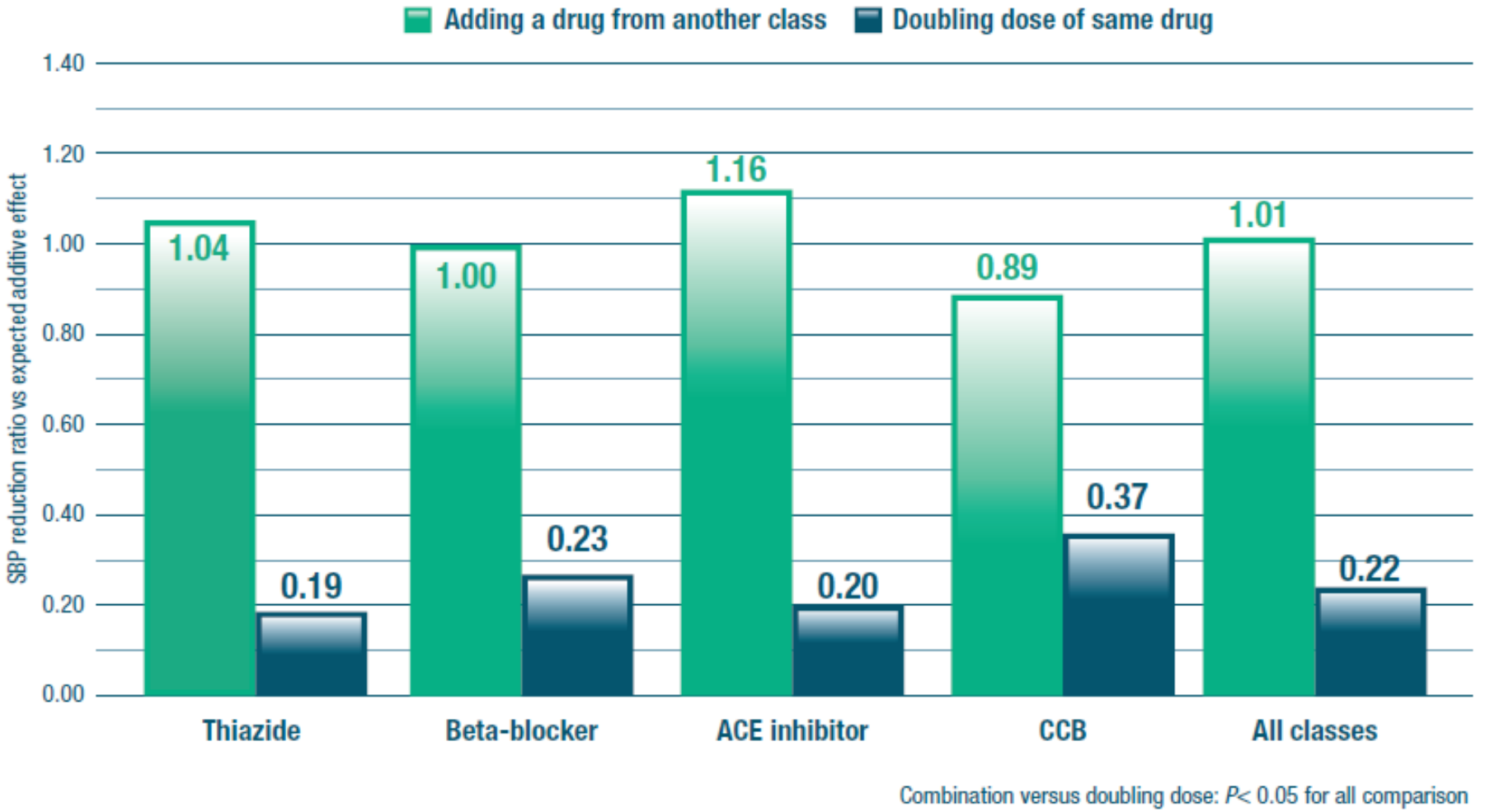
Two RAS-inhibitors (2)

From: Mancia G et al, J Hypertens 2013 (ESH)

JNC 8 Recommendation 9: Strategies to Dose of Antihypertensive Drugs To Achieve Goal BP

James PA et al. *JAMA* 2014;311:507-20.

Combining 2 classes of drug is 5 times more effective than doubling the dose of 1 drug



Combination versus doubling dose: $P < 0.05$ for all comparison

Recommended 2-drug combinations of antihypertensive drugs

NICE	ESH ESC	ASH-ISH	'JNC8'
All	**All**	**Non-black**	**Non-black**
A† + C§	A + C	A + C	A + C
	A + D*	A + D	A + D
	C + D		C + D
		Black	**Black**
		A + C	
		A + D	
		C + D	C + D

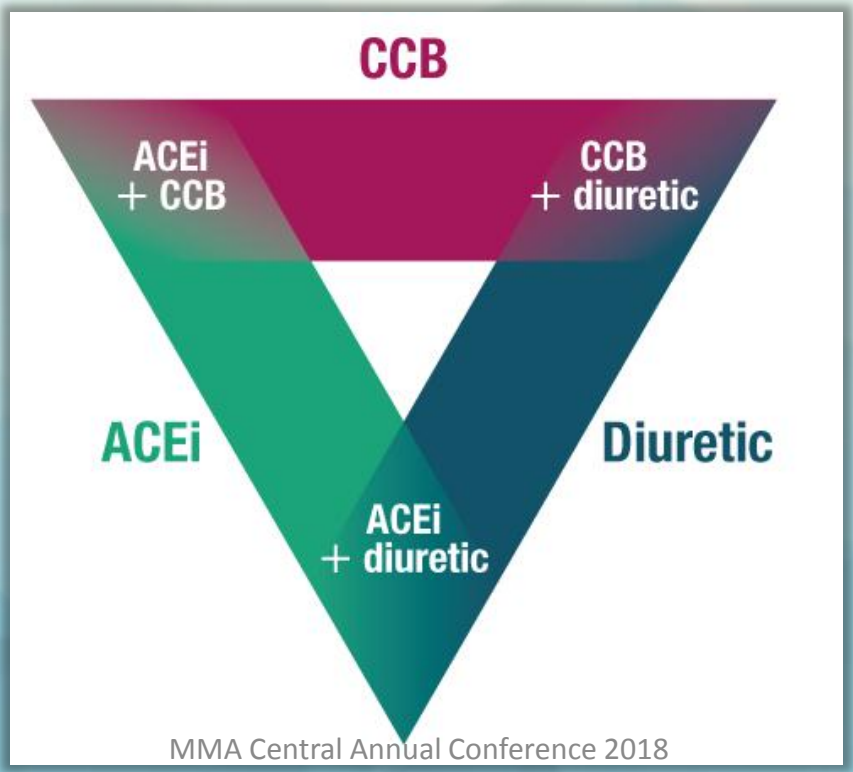
ACCEPTABLE COMBINATIONS FROM RECENT GUIDELINES

- A+C
- A+D
- C+D

†: A = ACE-inhibitor or angiotensin receptor blocker
§: C = Calcium channel blocker
*: D = Diuretic (including thiazides or thiazide-like/type)

The most rational combination: ACE inhibitor + diuretic + CCB

- Among the large number of randomized clinical trials, only 3 fixed-dose combinations demonstrated effective reductions in CV outcomes



Mancia G et al. *Eur Heart J.* 2013;28:1462-1536.

Drug combinations in hypertension: Recommendations of ASH

Preferred 2-drug combinations	Acceptable 2-drug combinations	Unacceptable 2-drug combinations
ACEI/diuretic*	B-B/diuretic*	ACE inhibitor/ARB
ARB/diuretic*	CCB/diuretic	BB and • ACE inhibitor/ • ARB/ • CCB (nonhydropyridine)/ • Centrally acting agent/
ACEI/CCB*	Renin inhibitor/diuretic	
ARB/CCB*	Thiazide diuretic/ potassium-sparing diuretic	

*Single-pill combinations available in the US
CCB=calcium-channel blocker
ARB=angiotensin-receptor blocker

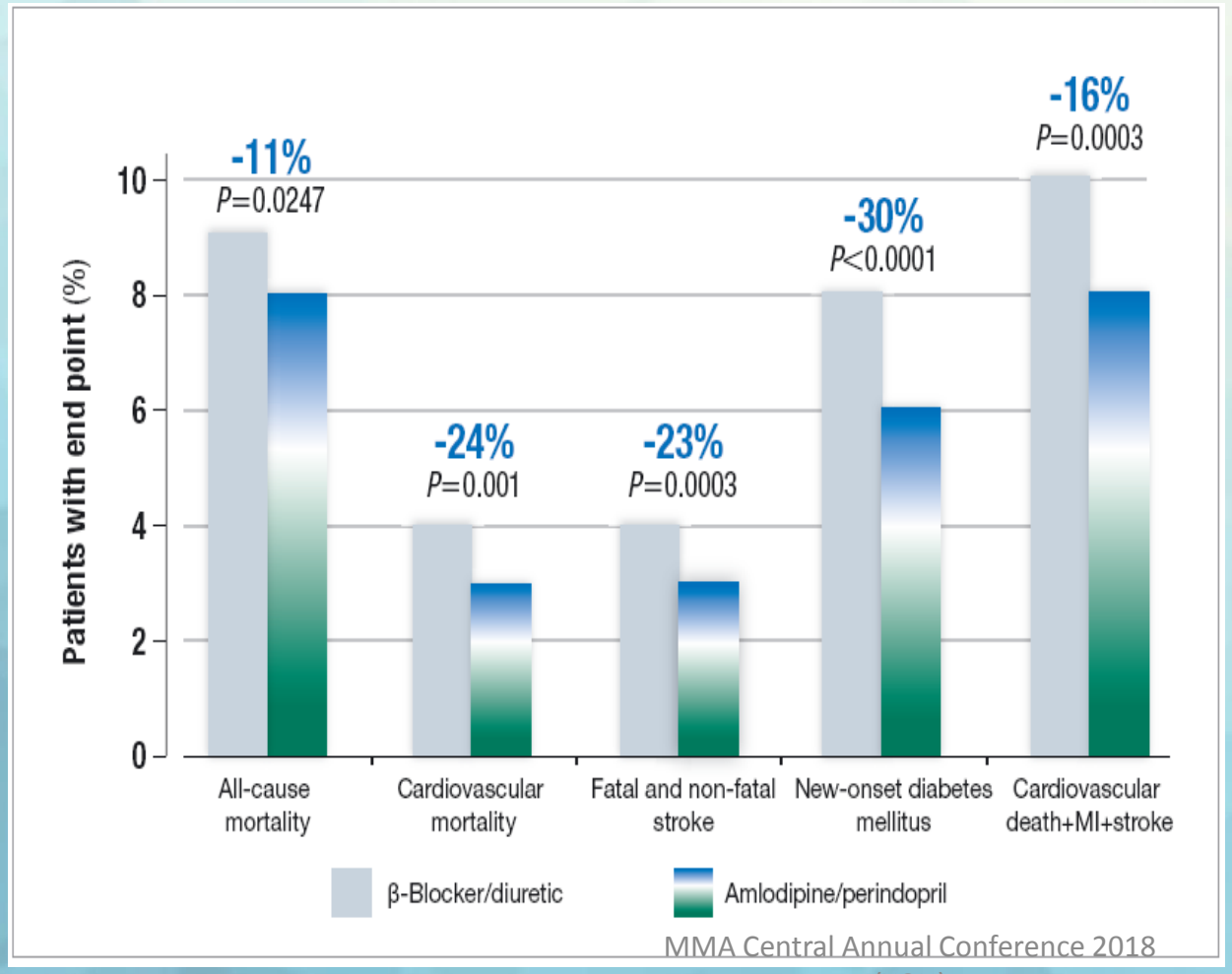
Gradman AH et al. *J Am Soc Hypertension* 2010; 4:42-50., 90-98.

Anglo-Scandinavian ascot Cardiac Outcomes Trial

A + C

Significant benefits of **Perindopril + Amlodipine**

Hypertensive patients (n=19,257)



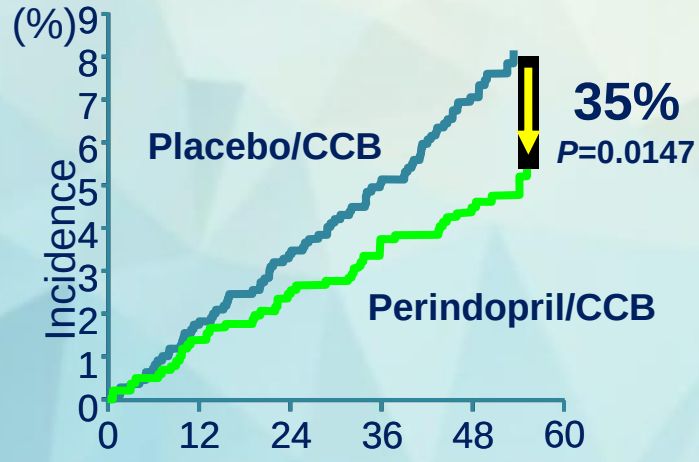
- **Amlodipine + perindopril based therapy confers an advantage over atenolol + thiazide based therapy on all major CV end points, all-cause mortality and new-onset diabetes**

Dahlöf B et al. Lancet. 2005;366(9489):895-906.

A + C

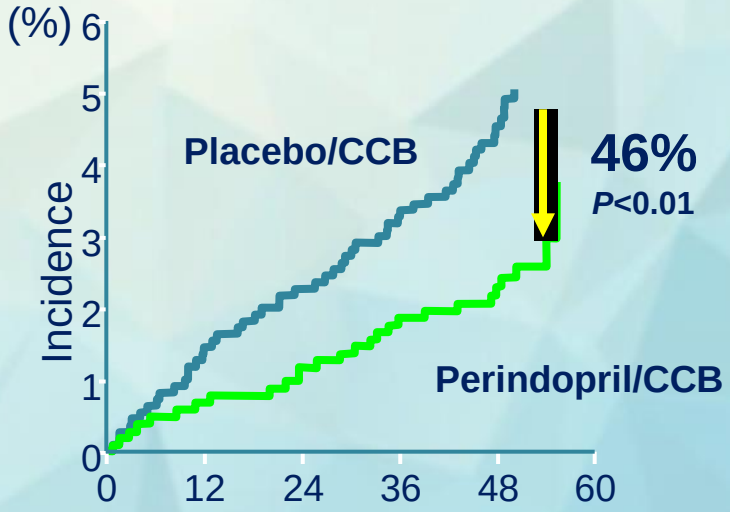
Reduction in total mortality and major cardiac events with perindopril/CCB

Primary end point
(CV death, MI, resuscitated cardiac arrest)



Patients at risk						
Pl/CCB	1100	1076	1055	1029	762	16
Per/CCB	1122	1005	992	974	746	9

Total mortality



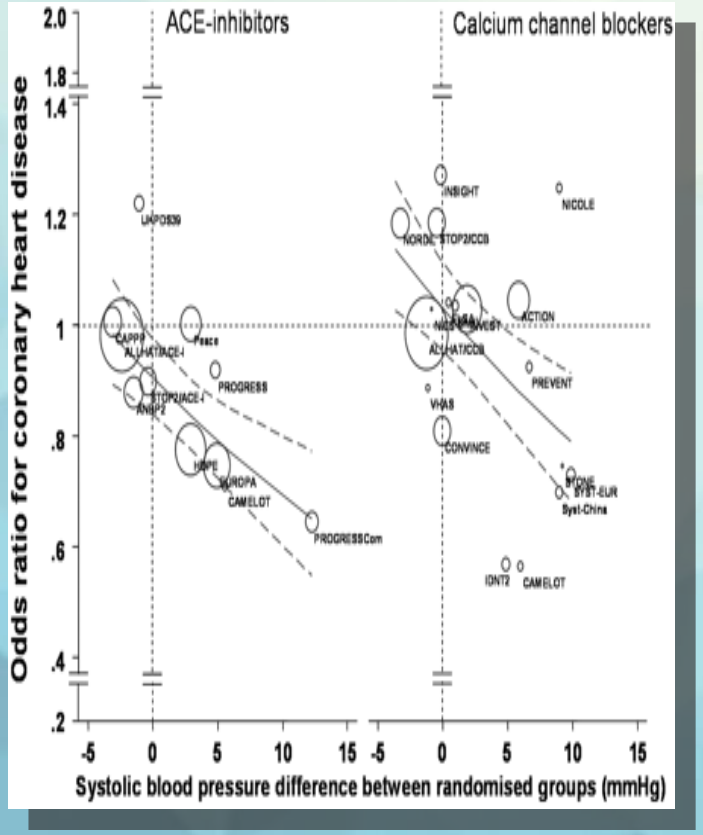
Patients at risk						
Pl/CCB	1100	1084	1075	1059	801	16
Perl/CCB	1122	1015	1010	1000	770	8

Bertrand ME, *et al. Am Heart J.* 2010;159:795-802.

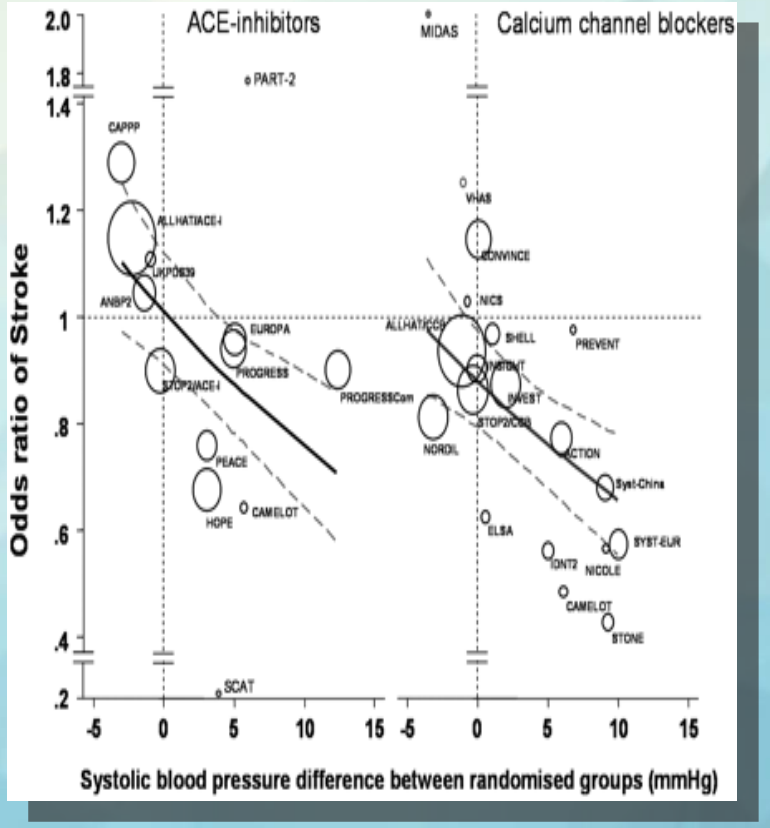
ACEi reduce risk of CHD

CCBs reduce risk of stroke

Coronary artery disease



Stroke



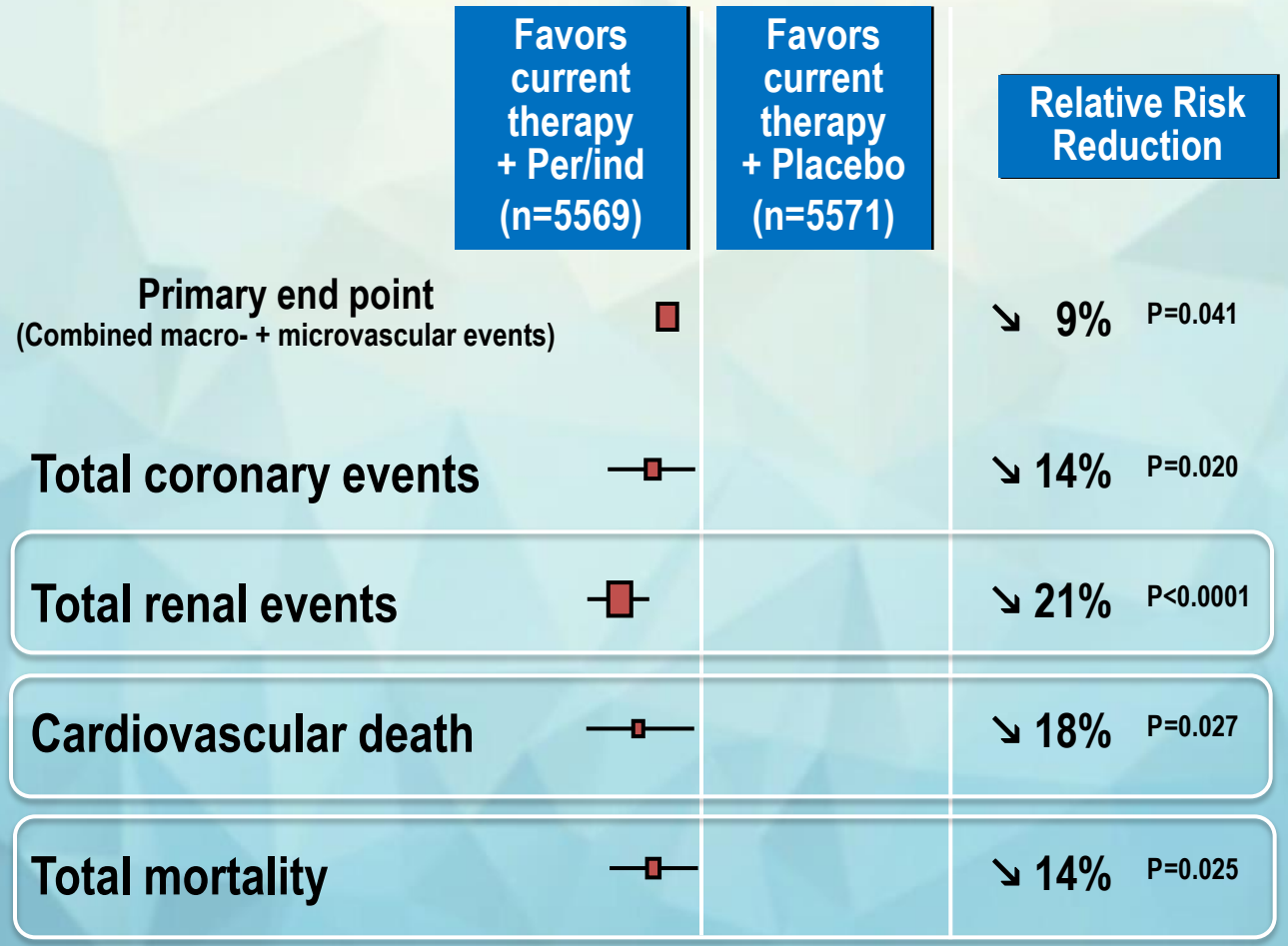
28 trials > 175.000P

Verdecchia P et Al., Hypertension 2005;46:386-392

ADVANCE
ACTION IN DIABETES AND VASCULAR DISEASE: PRETERAX AND DIAMICRON MR CONTROLLED EVALUATION

A + D

Significant benefit of Perindopril + Indapamide

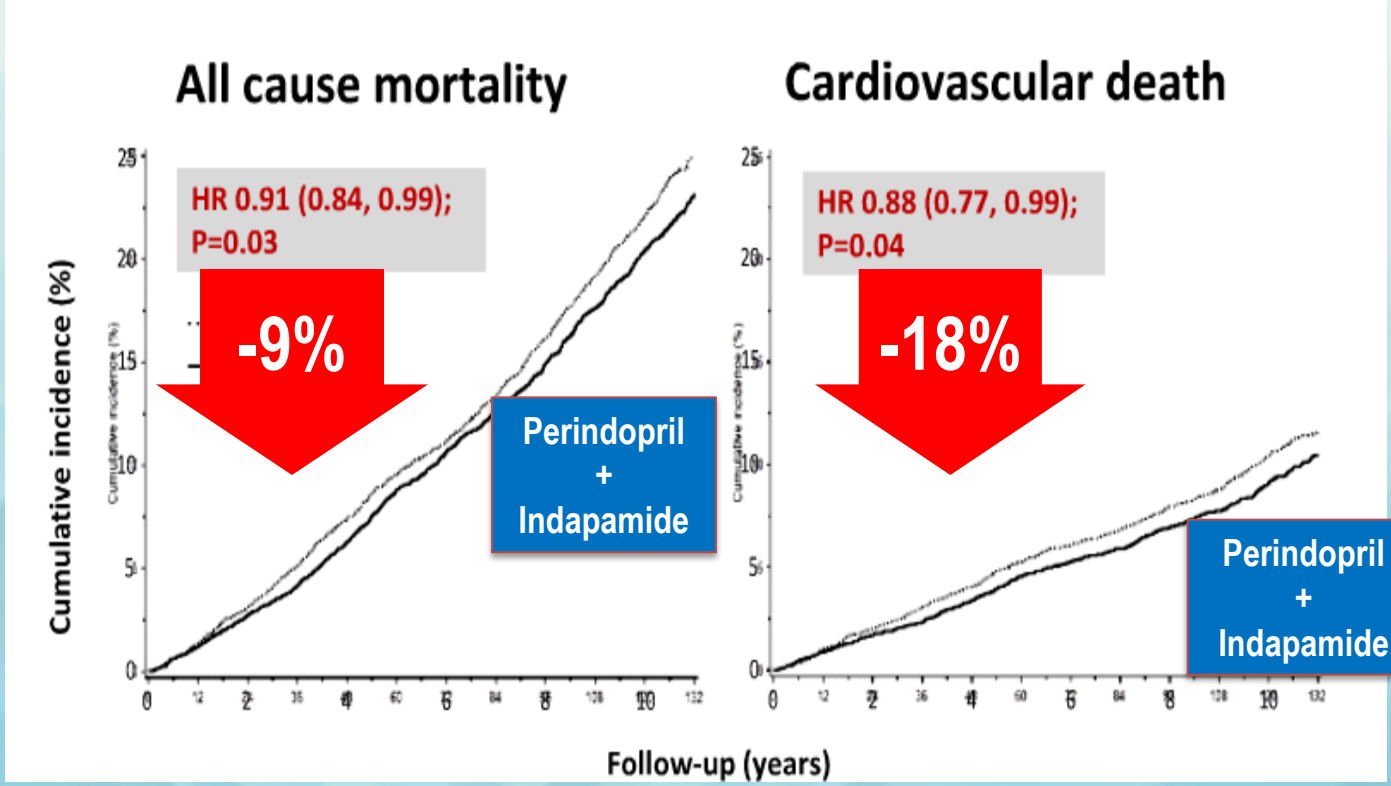


ADVANCE Collaborative group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007; 370:829-840

ADVANCE-ON
ACTION IN DIABETES AND VASCULAR DISEASE: PRETERAX AND DIAMICRON MR CONTROLLED EVALUATION POST-TRIAL OBSERVATIONAL STUDY

A + D

But mortality benefits maintained for 10 years…



Difference in the blood pressure is lost…

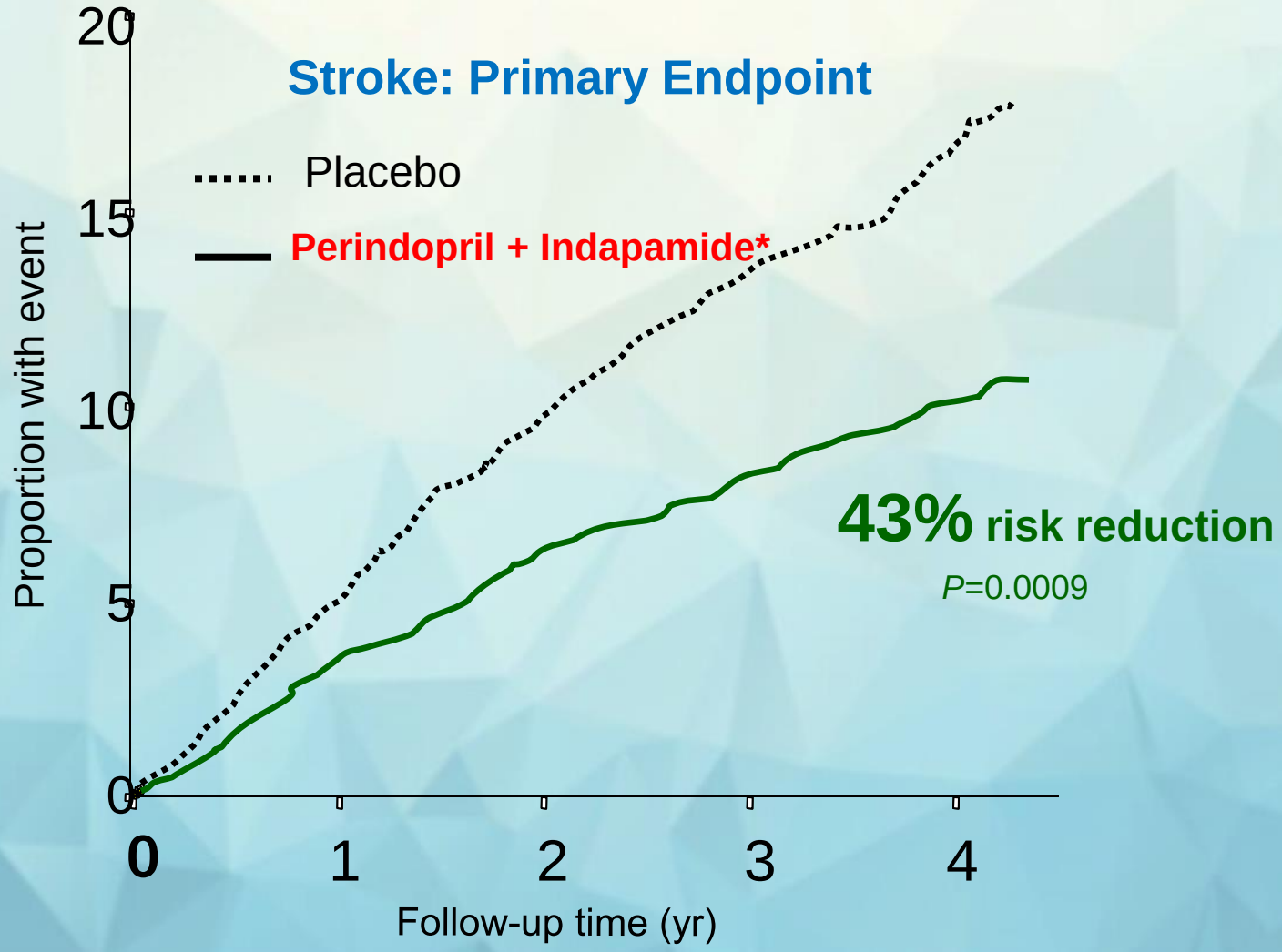
But Proven legacy effect

ADVANCE-ON Collaborative Group. *N Engl J Med.2014;371:1392-1406*

PROGRESS
PERINDOPRIL PROTECTION AGAINST RECURRENT STROKE STUDY

A + D

Perindopril + Indapamide Combination

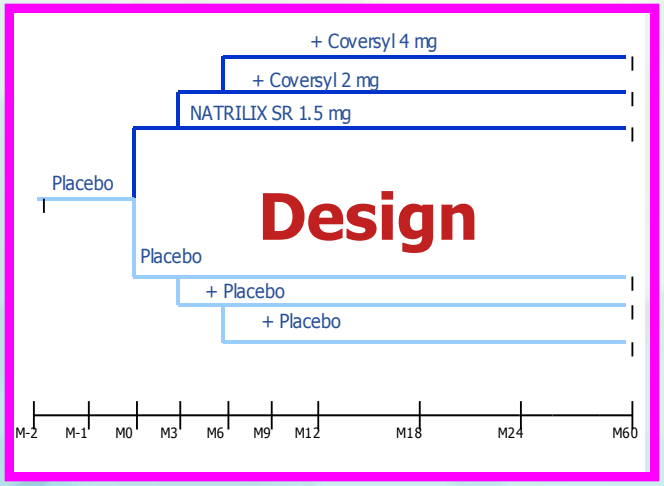


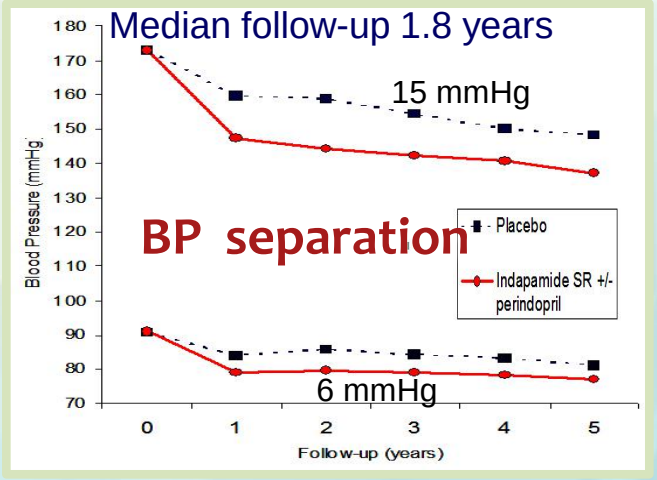
THELANCET • Vol 358 • September 29, 20011033

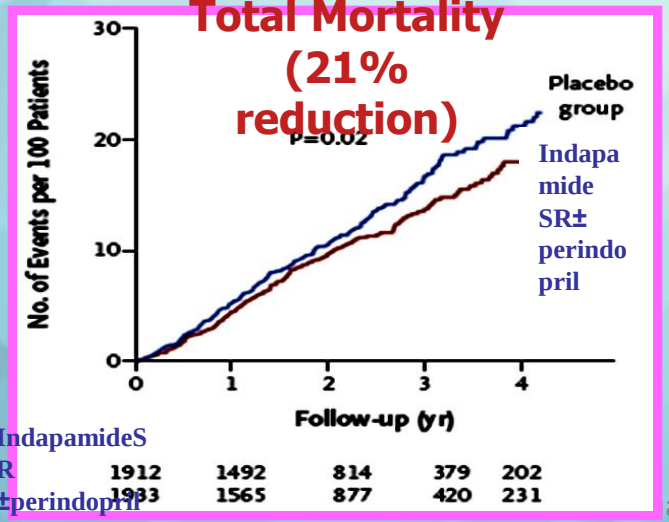
HYVET
HYPERTENSION IN THE VERY ELDERLY TRIAL

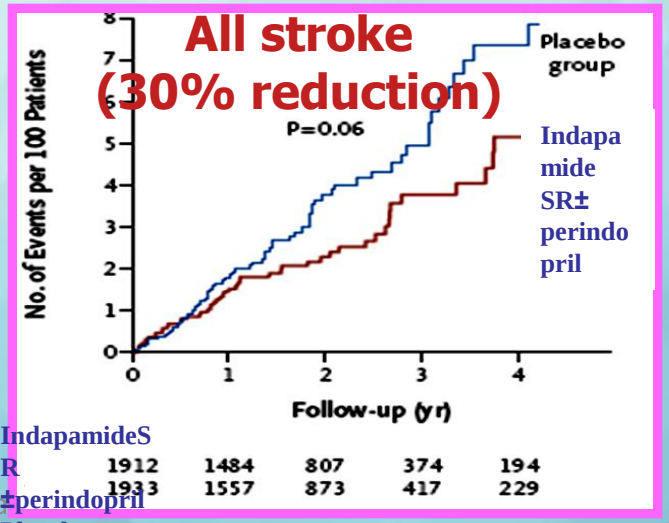
D + A

The HYpertension in the Very Elderly Trial



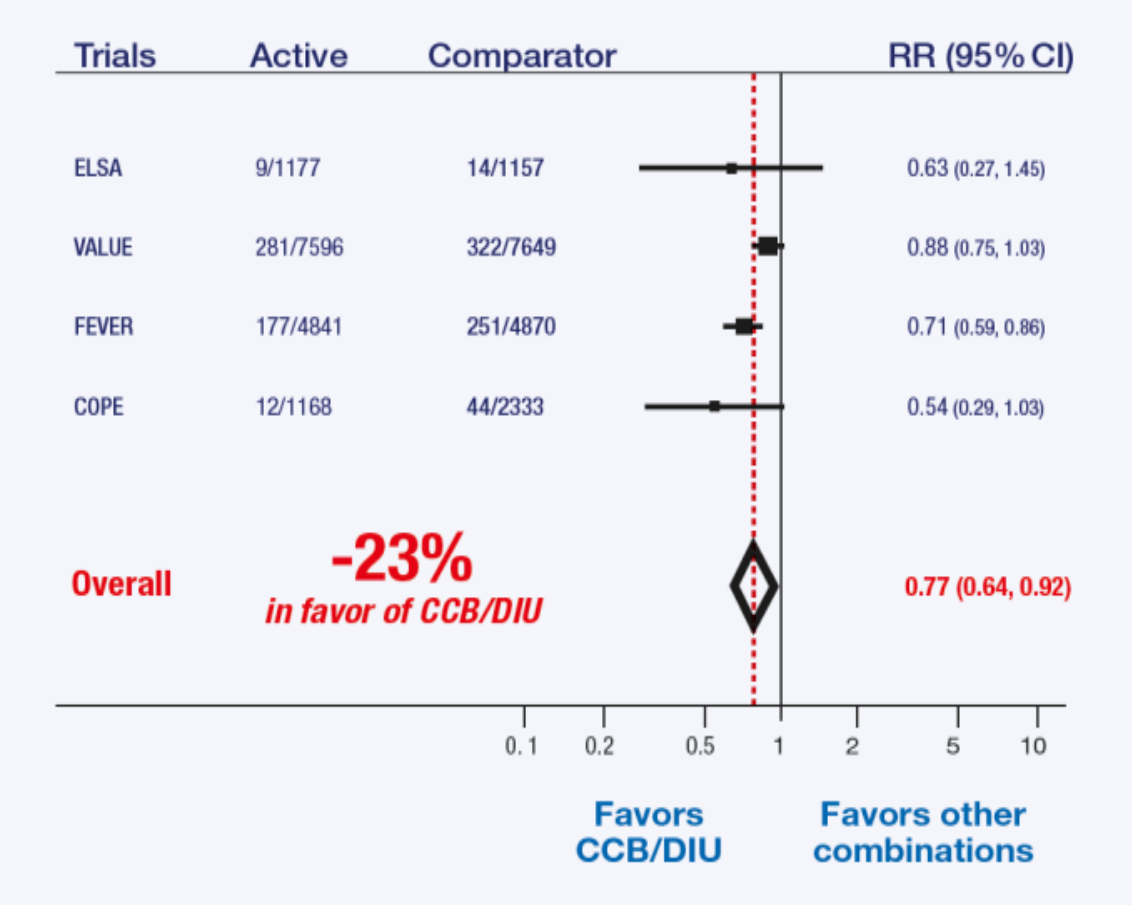






C + D

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



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

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

A + C +D

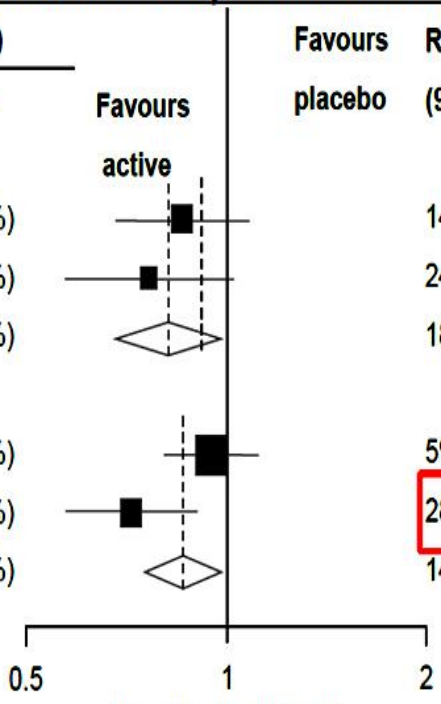
Evidence ?

The ADVANCE CCB Study

ADVANCE Substudy: Perindopril/Amlodipine/CCB

Effects on CV death and total death by baseline use of CCB

	Events (annual rate) Active	Placebo	Favours active / Favours placebo	Risk reduction (95% CI)	P homog
CV death					
No baseline CCB	134 (0.8%)	152 (0.9%)		14% (-8 to 32%)	0.21
Baseline CCB	77 (1.1%)	105 (1.4%)		24% (-2 to 43%)	
TOTAL	211 (0.9%)	257 (1.1%)		18% (2 to 32%)	
Total death					
No baseline CCB	283 (1.7%)	290 (1.8%)		5% (-12 to 20%)	0.02
Baseline CCB	125 (1.7%)	181 (2.4%)		28% (10 to 43%)	
TOTAL	408 (1.7%)	471 (2.0%)		14% (2 to 25%)	



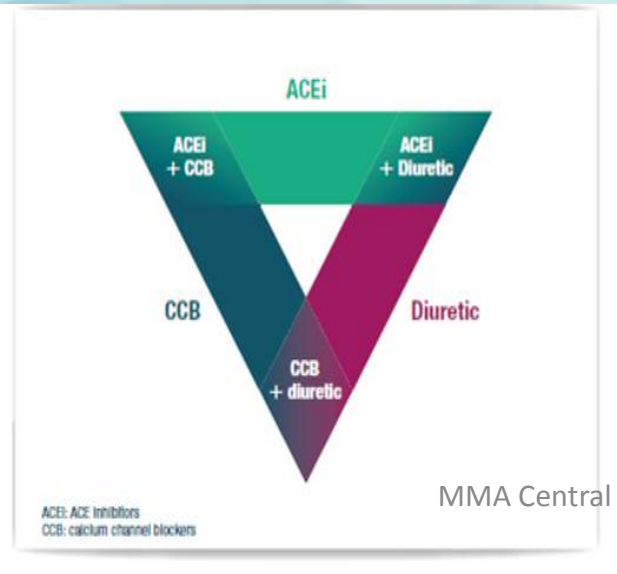
ADVANCE

John Chalmers et al. *Hypertension*. 2014;63:259-264

Tòth K, on behalf of PIANIST Investigators. *Am J Cardiovasc Drugs*. 2014;14:137-145.

Triple Therapy: Guideline Recommendation

Guideline	Drugs
NICE/BHS	A + C + D 1
ASH/ISH	A + C + D 2
'JNC 8'	A + C + D 3
ESC – ESH	D + any 2 of A, B, C



Key

A – ACE inhibitor or angiotensin II receptor blocker

C – Calcium-channel blocker (CCB)

D – Diuretic

1 =Thiazide-like (excluding thiazides)

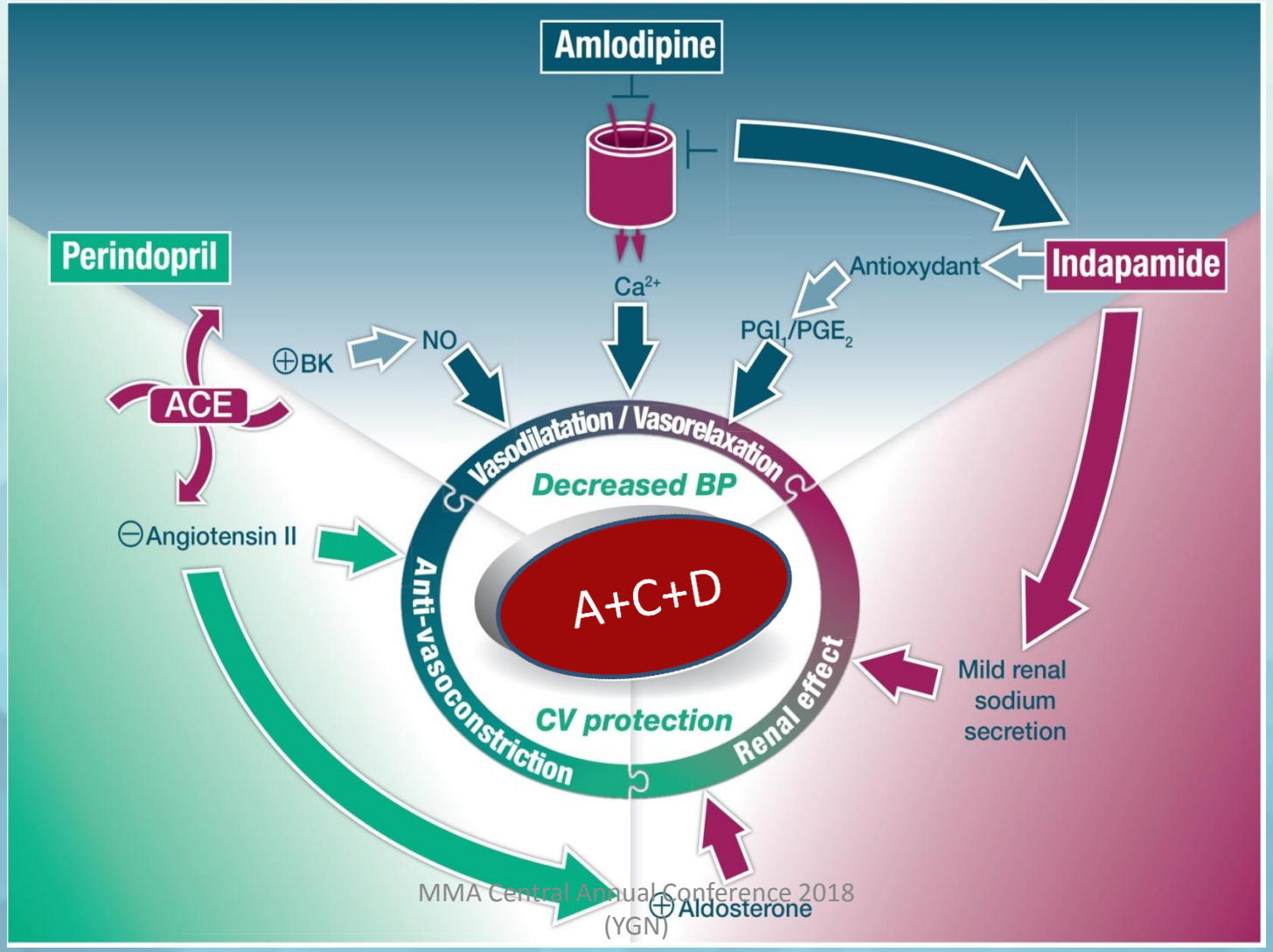
2 =Thiazide (including thiazide-like)

3 =Thiazide-like (including thiazide)

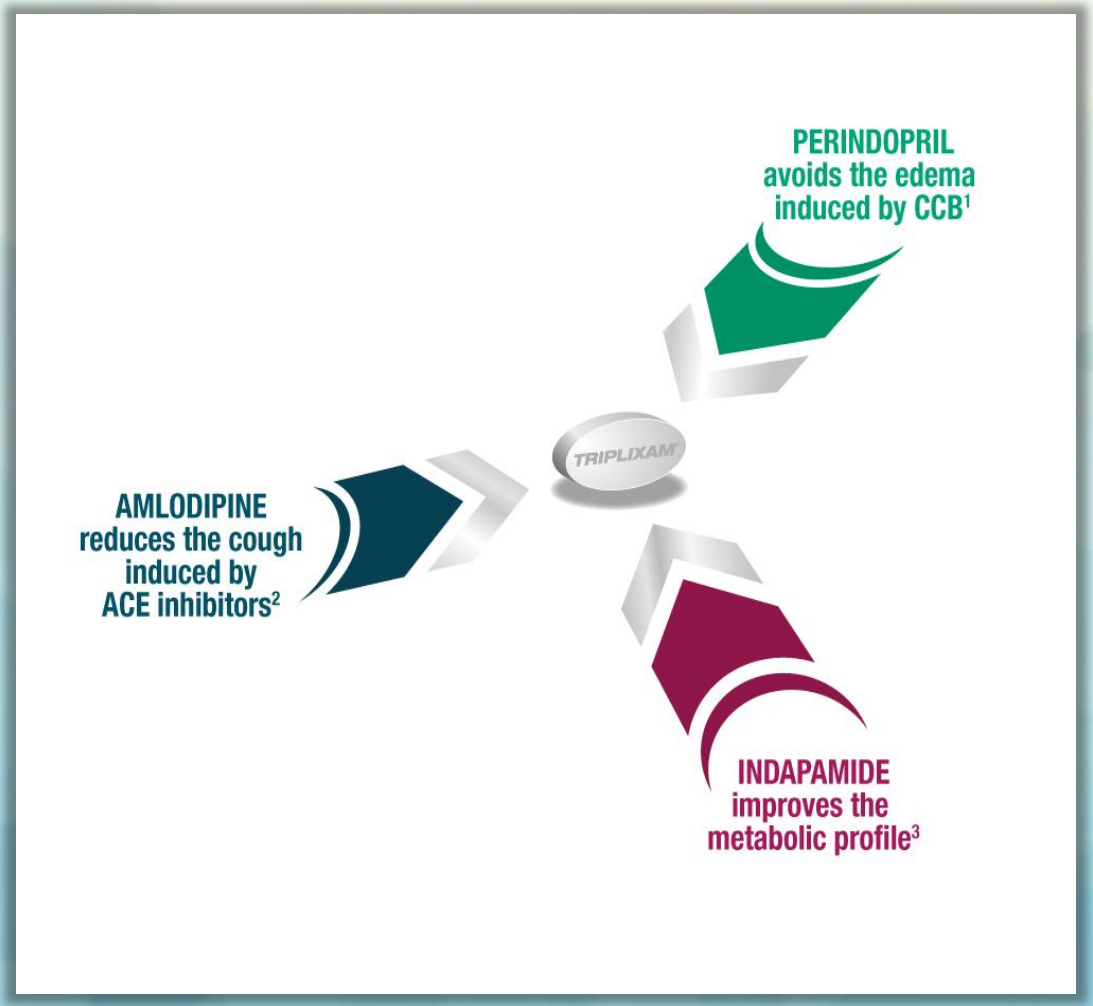
B – β- Blocker

Hypothetical reason

Three complementary mode of action



Three complementary compounds for optimized tolerability



1. Makani H et al. *Am J Med*. 2011;124:128-135.
2. Fogari R et al. *Curr Ther Res Clin Exp*. 1999;60:121-128.
3. Tòth K et al; PIANIST Investigators. *Am J Cardiovasc Drugs*. 2014;14:137–145.

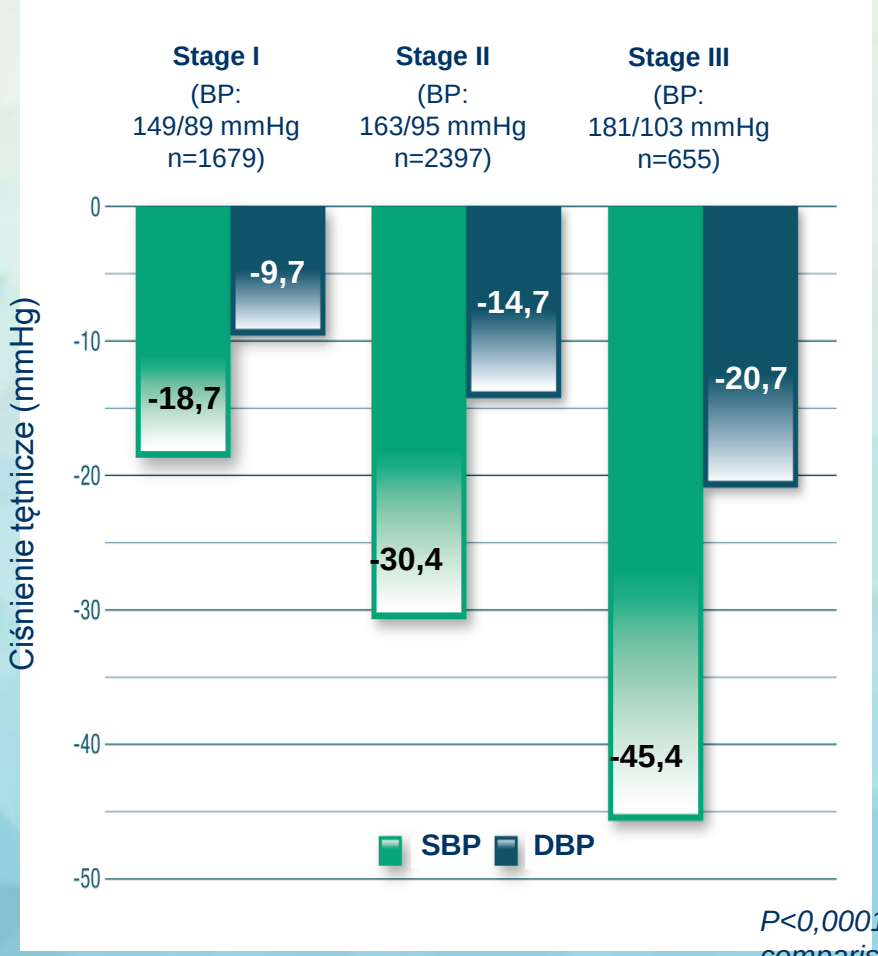
ADVANCE CCB

A + C +D

Any Evidence ?

Perindopril/Indapamide/Amlodipine combination

is efficient in all stages of hypertension



P<0,0001 for all comparisons

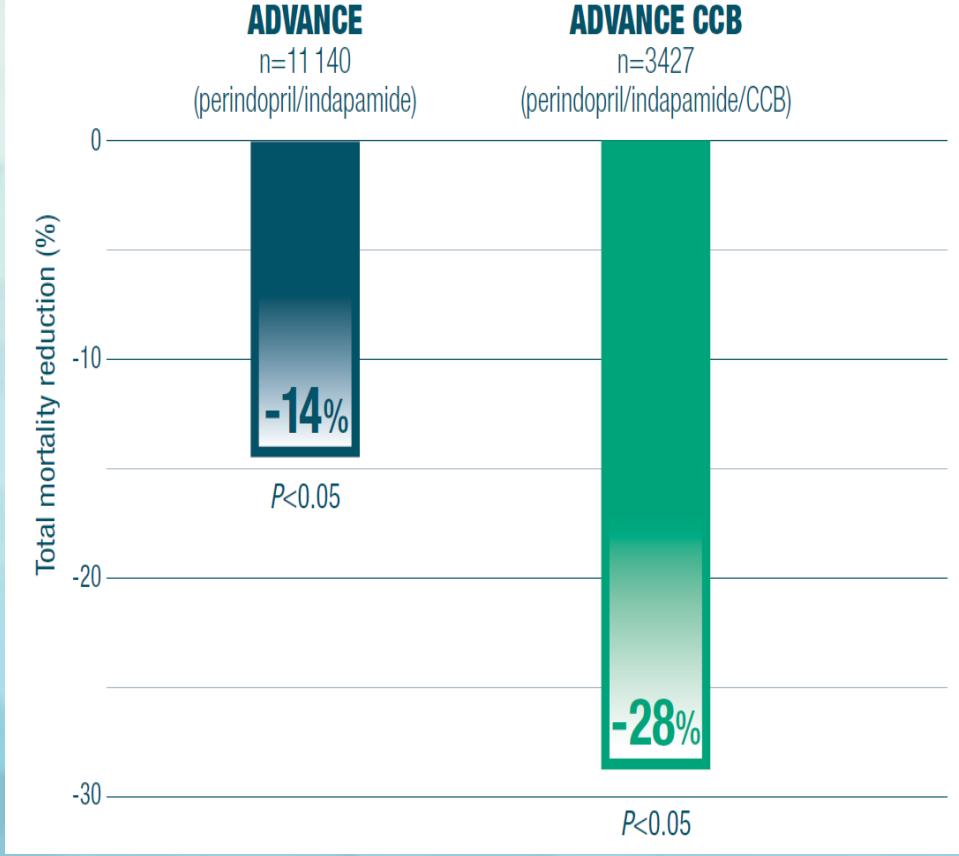
Tòth K et al. PIANIST study *Am J Cardiovasc Drugs*. 2014; 14(2):137-145

Mortality benefits with

Perindopril/Indapamide/Amlodipine combination

ADVANCE CCB

Total mortality reduction



Chalmers J, Arima H, Woodward M, et al. Hypertension. 2013;63:259-264.

Evolution of guidelines on fixed-dose combinations

1999 WHO/ISH	"The use of fixed-dose combinations **may be advantageous**…"
2003 WHO/ISH	"Where they are no more expensive, such formulations may be preferable since **they have advantages in terms of compliance**"
2003 JNC 7	"When BP is more than 20/10 mm Hg above goal, **consideration should be given** to initiating therapy with two drugs, either in separate prescriptions or in fixed-dose combinations"
2003 ESH/ESC	Fixed-dose combinations… allow administration of two agents within a single tablet, thus **optimizing compliance**"
2007 ESH/ESC	"Fixed-dose combinations reduce the number of tablets to be taken, and this **has some advantages on compliance**"
2009 ESH/ESC	"**Whenever possible**, use of single-tablet combinations should be preferred, because simplification of treatment causes advantages for compliance to treatment"
2013 ESH/ESC	"The guidelines **favor the use** of combinations of two antihypertensive drugs at fixed doses in a single tablet, because… **improves adherence**… and **increases the rate of BP control**"

45

Clinician's Sequential Flow Chart for the Management of Hypertension

Clinician's Sequential Flow Chart for the Management of Hypertension
Measure office BP accurately
Detect white coat hypertension or masked hypertension by using ABPM and HBPM
Evaluate for secondary hypertension
Identify target organ damage
Introduce lifestyle interventions
Identify and discuss treatment goals
Use ASCVD risk estimation to guide BP threshold for drug therapy
Align treatment options with comorbidities
Account for age, race, ethnicity, sex, and special circumstances in antihypertensive treatment
Initiate antihypertensive pharmacological therapy
Insure appropriate follow-up
Use team-based care
Connect patient to clinician via telehealth
Detect and reverse nonadherence
Detect white coat effect or masked uncontrolled hypertension
Use health information technology for remote monitoring and self-monitoring of BP

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.

BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.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MSEM


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Internal Medicine Society

Thank You


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