RECENT HYPERTENSION GUIDELINES CONSOLIDATING THE EVIDENCE

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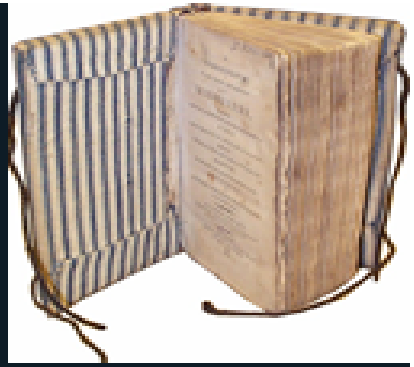
1946 Textbook - Diseases of the Heart, Friedberg



"People with mild benign hypertension with levels up to 210/110 mmHg need not be treated"

"There is a psychopathologic personality associated with hypertension"

February 1945, Yalta

Blood pressure goals for hypertension control, JNC 1–JNC 7

Report number (year of publication)	Committee chair	BP Goal (mm Hg)
1 (1977)	Marvin Moser	DBP <90
2 (1980)	Iqbal Krishan	a. DBP <90 b. DBP 90–100 for individuals with moderate or severe hypertension
3 (1984)	Harriet Dustan	DBP <90
4 (1988)	Aram Chobanian	BP <140/90
5 (1993)	Ray Gifford	BP <140/90
6 (1997)	Sheldon Sheps	BP <140/90 and "lower if tolerated"
7 (2003)	Aram Chobanian	a. BP <140/90 b. <130/80 in patients with diabetes or renal disease

JNC 2 classification of hypertension

Classification	Diastolic blood pressure (mmHg)
Stratum 1 (mild)	90–104
Stratum 2 (moderate)	105–114
Stratum 3 (severe)	≥115

JNC 3 and JNC 4 classification of hypertension

Classification	BP Range (mm Hg)
Diastolic	
Normal BP	<85
High normal BP	85–89
Mild hypertension	90–104
Moderate hypertension	105–114
Severe hypertension	≥115
Systolic, when diastolic BP <90	
Normal BP	<140
Borderline isolated systolic hypertension	140–159
Isolated systolic hypertension	≥160

JNC 5 classification of hypertension

Classification	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Normal	<130	<85
High normal	130–139	86–89
Hypertension		
Stage 1 (mild)	140–159	90–99
Stage 2 (moderate)	160–179	100–109
Stage 3 (severe)	180–209	110–119
Stage 4 (very severe)	≥210	≥120

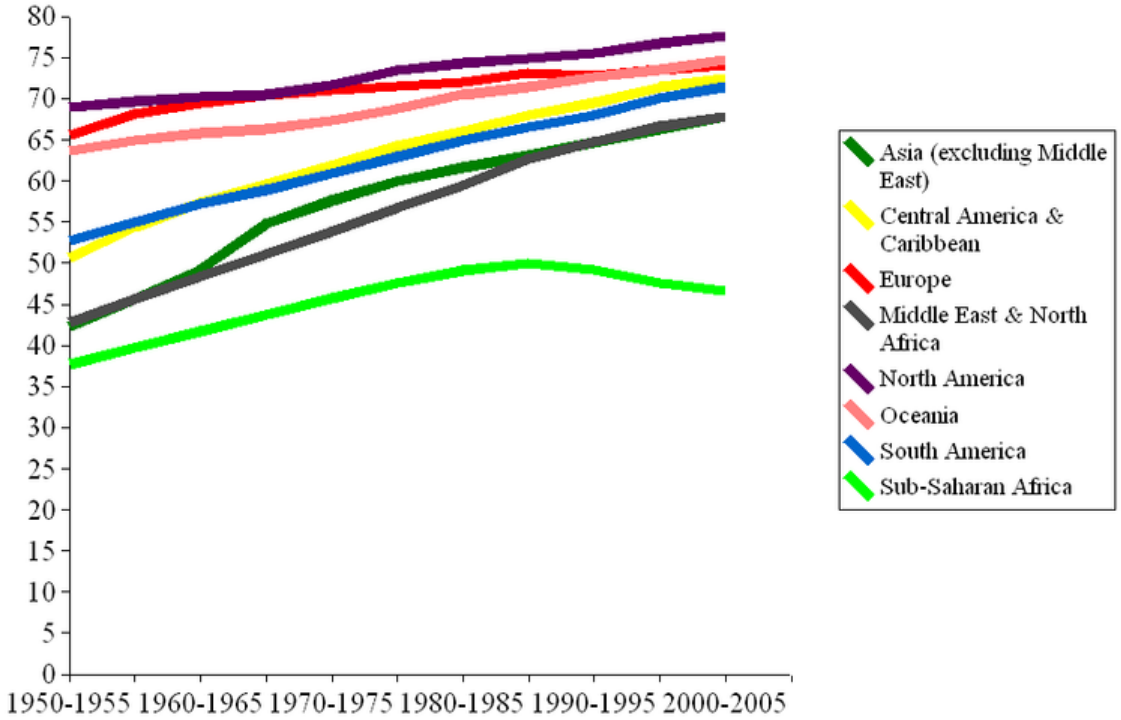
Table 5. JNC 6 classification of hypertension

Classification	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
Optimal	<120	AND	<80
Normal	<130	AND	<85
High normal	130–139	OR	80–89
Hypertension			
Stage 1	140–159	OR	90–99
Stage 2	160–179	OR	100–109
Stage 3	≥180	OR	≥110

Table 6. JNC 7 classification of hypertension

Classification	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
Normal	<120	AND	<80
Prehypertension	120–139	OR	80–89
Stage 1 hypertension	140–159	OR	90–99
Stage 2 hypertension	≥160	OR	≥100

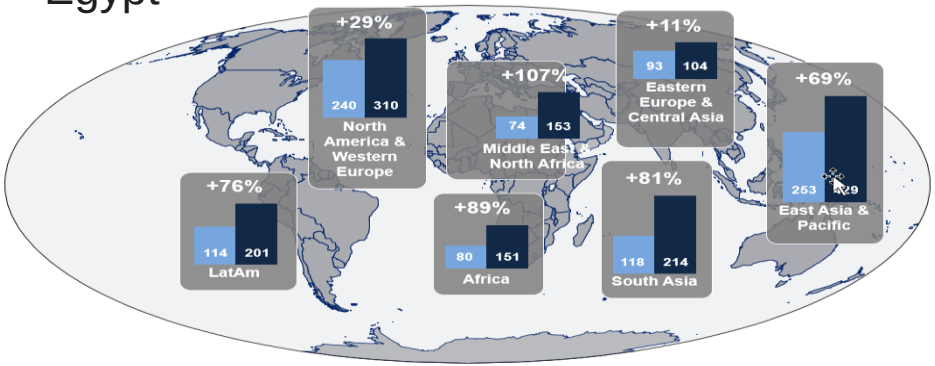
Increased life expectancy across the globe 1950-2005



Hypertension prevalence and blood pressure control rates

Worldwide prevalence of hypertension is high and is expected to increase to 1.56 billion by 2025

Hypertension is a serious health problem with prevalence rate of **26.3%** in year 2000 in Egypt



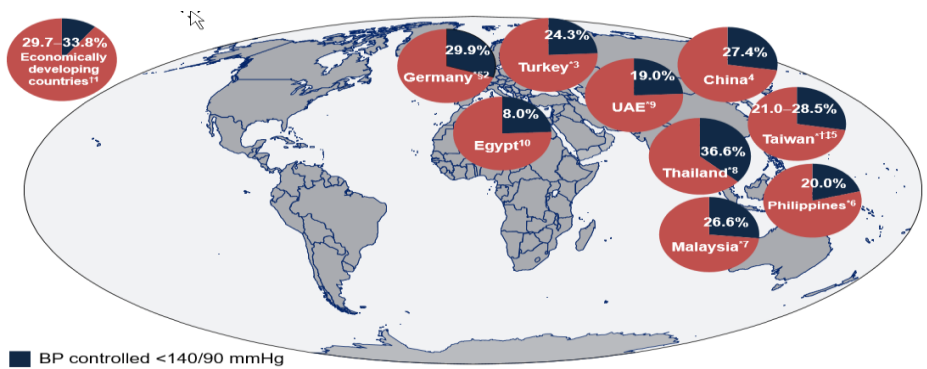
Number of adults with hypertension in 2000: 972 million
Estimated number of adults with hypertension in 2025: 1.56 billion (~60%)

Number of people aged ≥20 years with hypertension (in millions) for the years 2000 (light blue bar) and 2025 (dark blue bar)

Kearney et al. Lancet 2005;365:217–23

Blood pressure control rates in patients with hypertension remain low across different regions

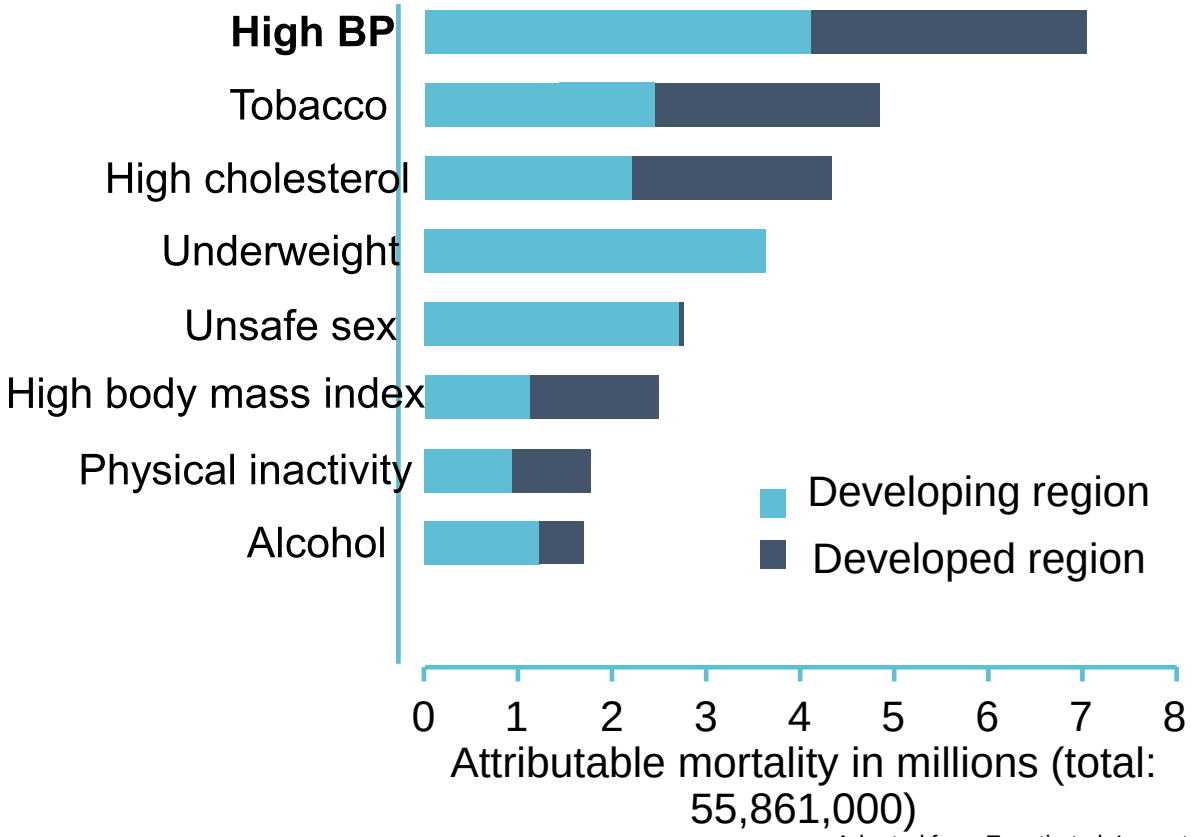
Only 8% of Egyptian patients with hypertension have their BP controlled*



† Control rate shown in males % – females %; *Treated population; §patients age 35–64 years; ‡ adults aged ≥19 to 44 years; BP control levels not defined for China data

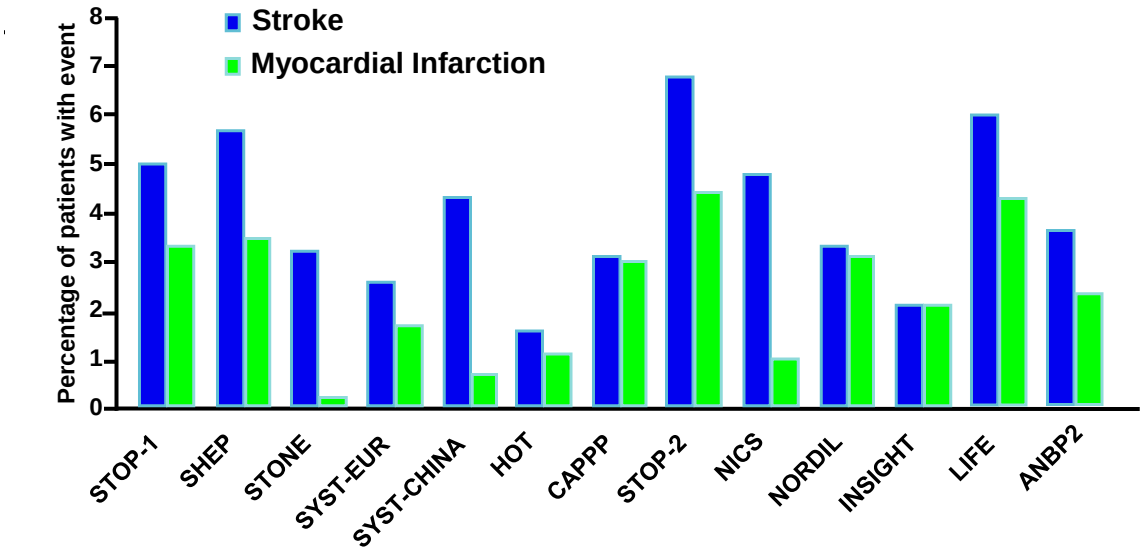
1. Pereira M et al. J Hypertens 2009; 27: 963–975; 2. Wolf-Maier et al. Hypertension 2004;43:10–17; 3. Erem et al. J Public Health 2009;31:47–58; 4. Wang et al. Chin J Epidemiol 2012;33:903–6; 5. Su et al. J Hypertens. 2008;26:600–06; 6. Sison et al. PJC 2007;35:1–9; 7. Rampal et al. Public Health 2008;122:11–18; 8. Aekplakorn et al. J Hypertens 2008;26:191–8; 9. Ibrahim et al. Saudi J Kidney Dis Transplant 1999;10:376–81; 10. Ibrahim & Damasceno. Lancet 2012;380:611–19

Hypertension is the Number One Risk Factor for Global Mortality



Adapted from Ezzati et al. Lancet 2002;360:1347–60

Stroke and MI in Hypertension Trials[1-3]



Percentage of fatal and nonfatal strokes, and fatal and nonfatal MIs reported in large, prospective hypertension trials published after 1990.

1. Kjeldsen SE et al. *Blood Pressure* 2001;10:190-192. **2.** Dalhöf B et al. *Lancet* 2002;359:995-1003. **3.** Wing LMH et al. *N Engl J Med* 2003;348:583-592.

The 140/90 mmHg dogma

SPRINT trial

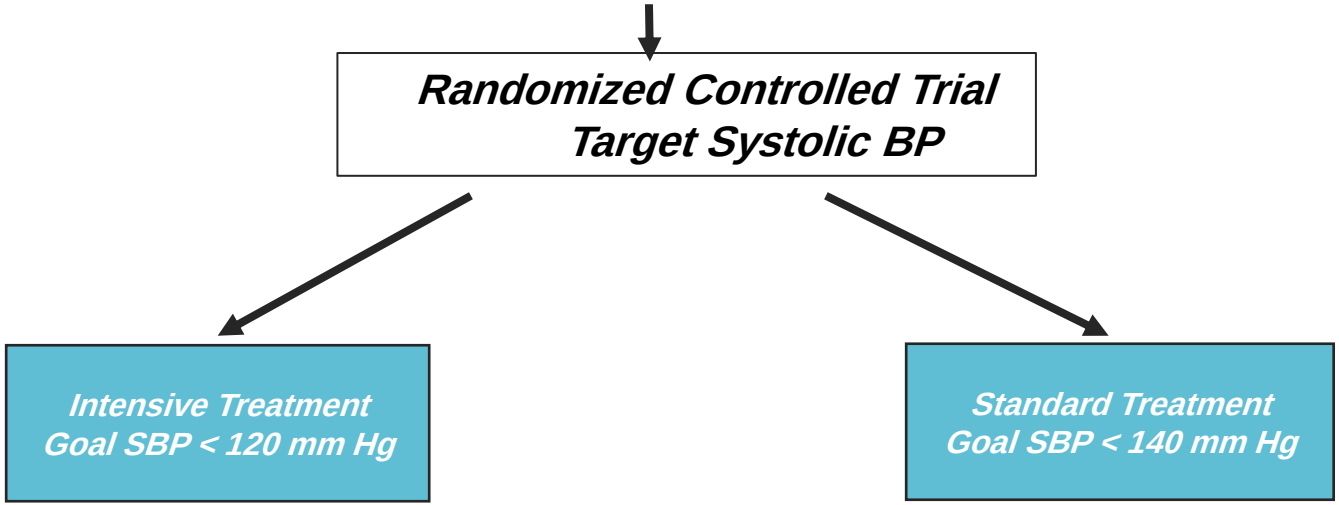
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2015 VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

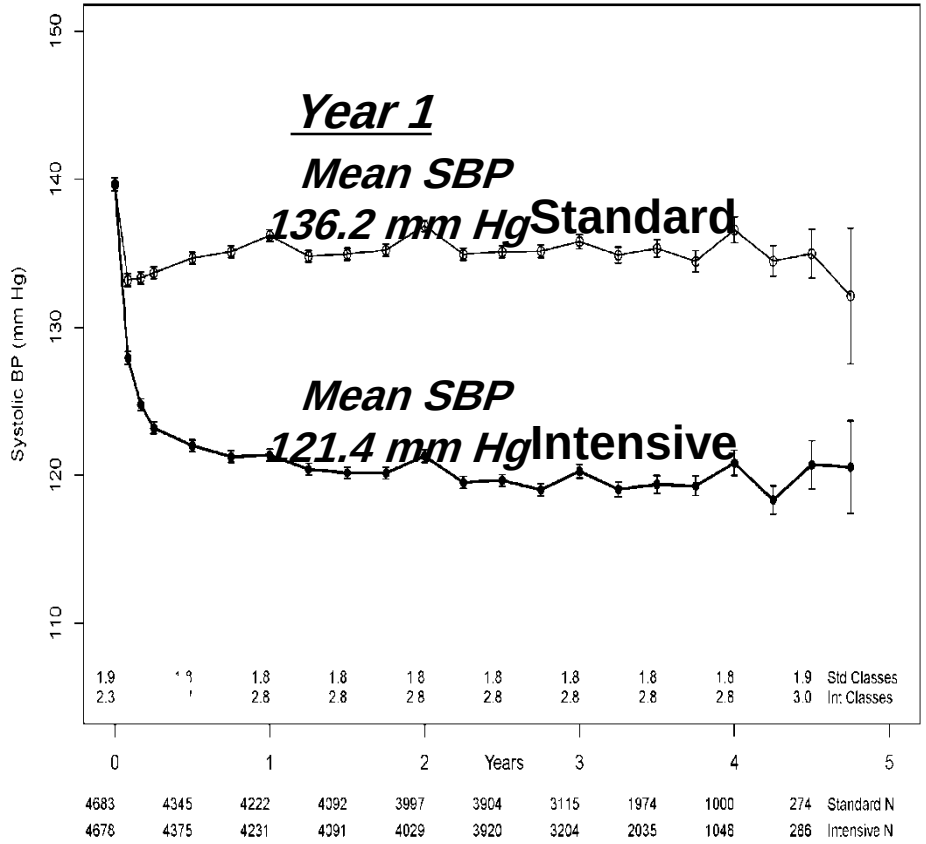
The SPRINT Research Group*

Examine effect of more intensive high blood pressure treatment than is currently recommended



SPRINT
Systolic Blood Pressure Intervention Trial

Systolic BP During Follow-up



Average SBP
(During Follow-up)

Standard: 134.6 mm Hg

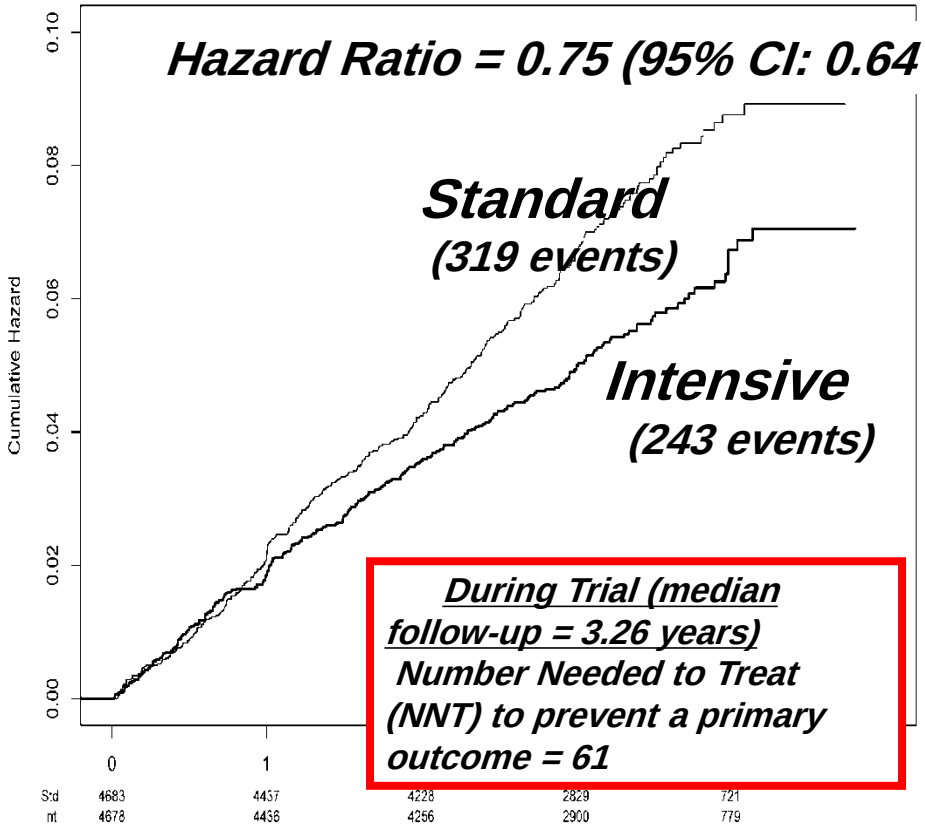
Intensive: 121.5 mm Hg

Average number of antihypertensive medications

Number of participants

SPRINT Primary Outcome

Cumulative Hazard



During Trial (median follow-up = 3.26 years)
Number Needed to Treat (NNT) to prevent a primary outcome = 61

SPRINT
Systolic Blood Pressure Intervention Trial

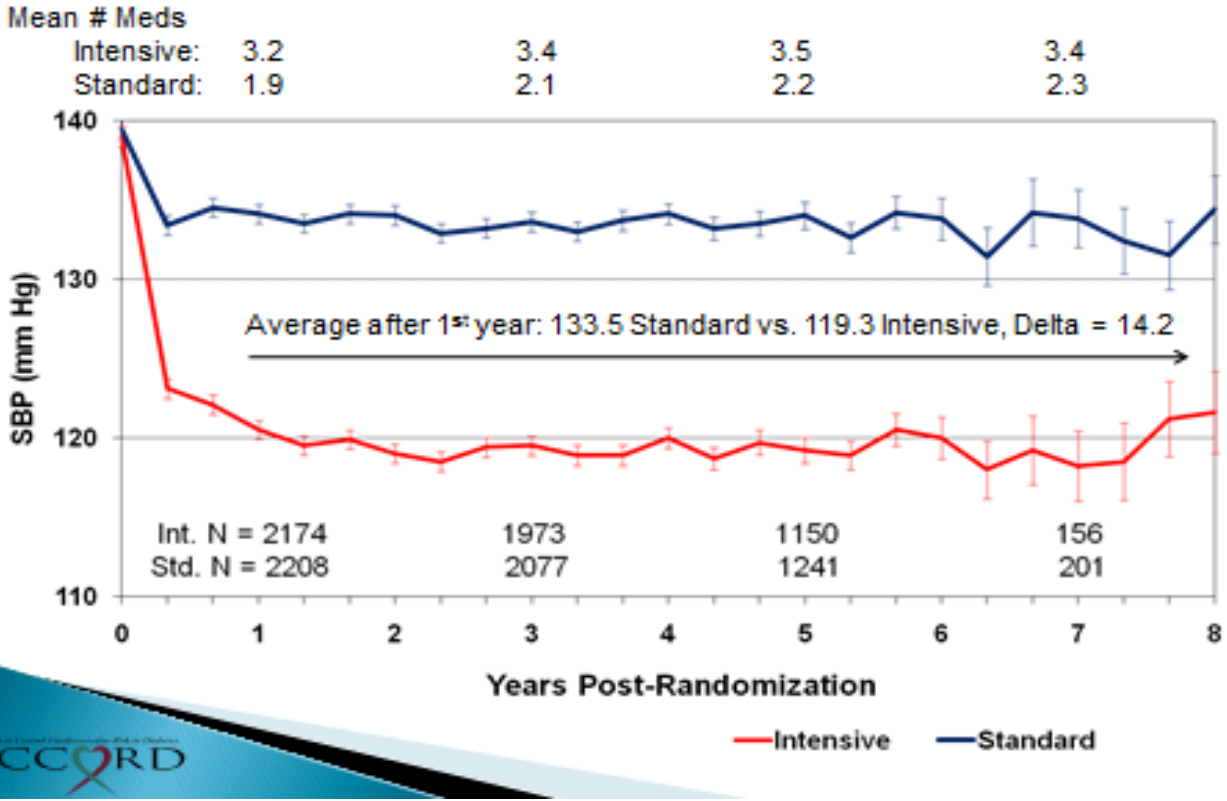
The NEW ENGLAND JOURNAL of MEDICINE

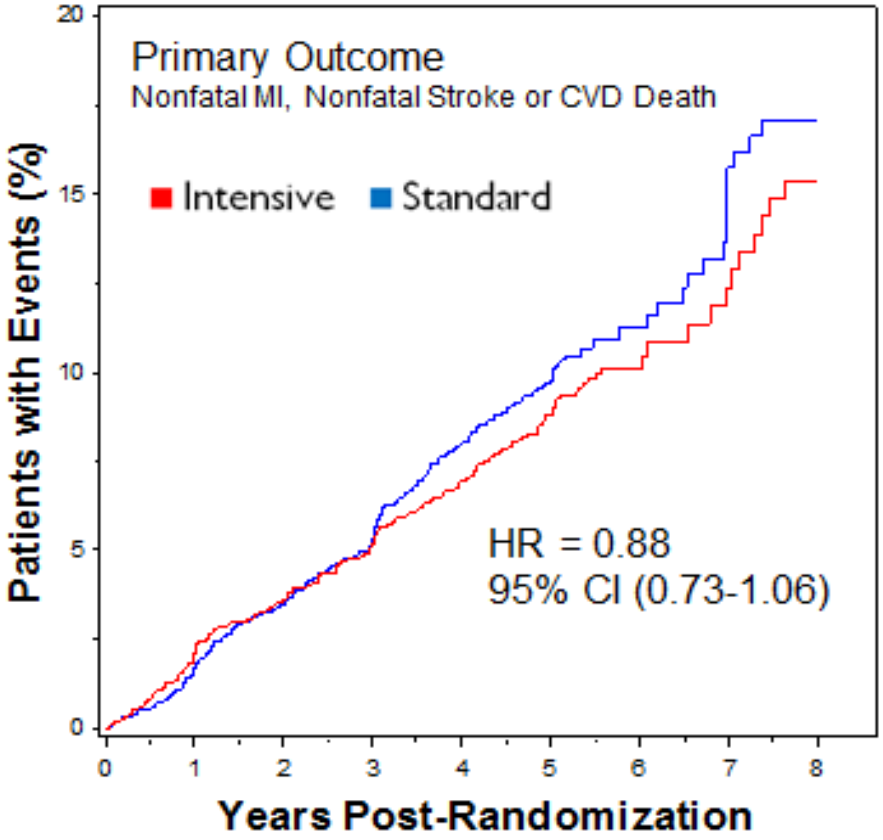
ORIGINAL ARTICLE

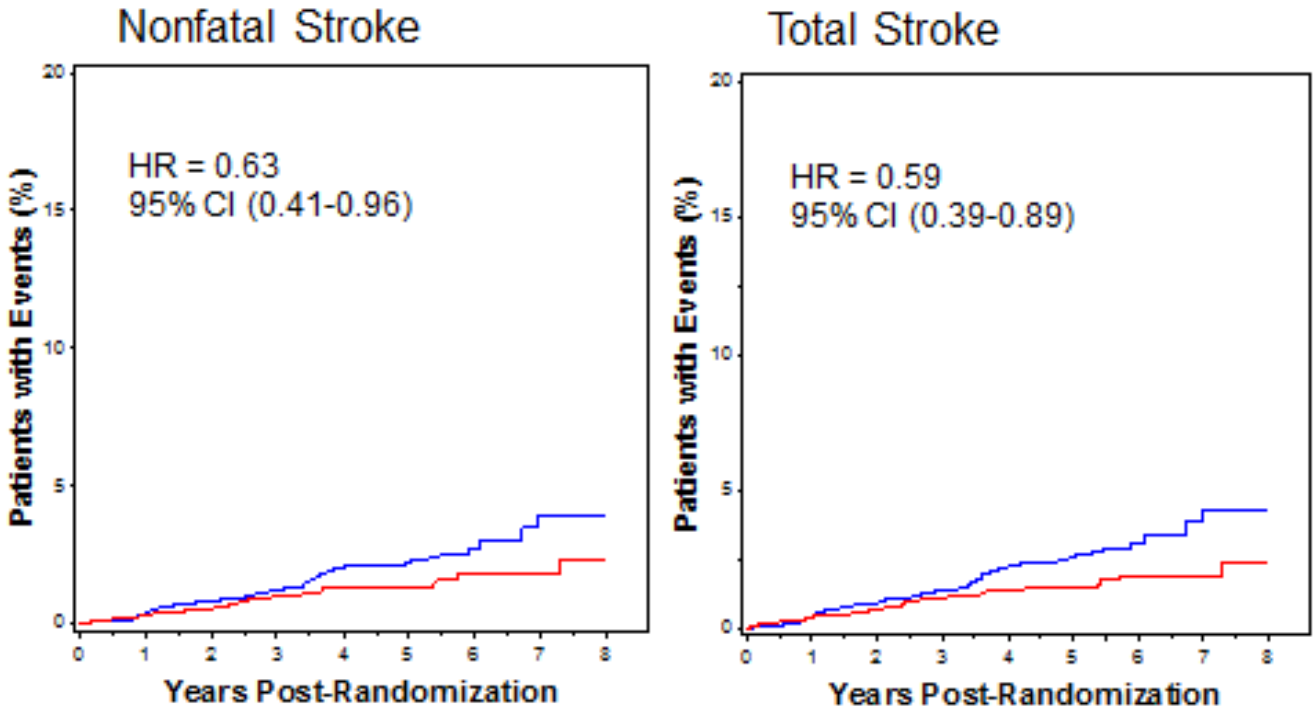
Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

Systolic Pressures (mean ± 95% CI)




Primary Outcome
Nonfatal MI, Nonfatal Stroke or CVD Death
Intensive
Standard
HR = 0.88
95% CI (0.73-1.06)
Patients with Events (%)
Years Post-Randomization
0
5
10
15
20
0
1
2
3
4
5
6
7
8


Nonfatal Stroke
HR = 0.63
95% CI (0.41-0.96)
Patients with Events (%)
Years Post-Randomization
Total Stroke
HR = 0.59
95% CI (0.39-0.89)
Patients with Events (%)
Years Post-Randomization
Intensive
Standard
ACCORD

Implications for the GUIDELINES?

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

Whelton PK, et al.

2017 High Blood Pressure Clinical Practice Guideline

Recommendation for Definition of High BP

COR	LOE	Recommendation
I	B-NR	1. BP should be categorized as normal, elevated, or stage 1 or 2 hypertension to prevent and treat high BP (Table 6) (1-20).

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

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	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.
	DBP: C-EO	
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.

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.

AMERICAN COLLEGE of CARDIOLOGY

American Heart Association.
life is why™

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.

2018 ESC-ESH Guidelines for the Management of Arterial Hypertension

ESC European Society of Cardiology

ESH European Society of Hypertension

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

Classification of office BP and definitions of hypertension grade

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	< 120	and	< 80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	and	< 90

Summary of office BP thresholds for treatment

Age group	Office SBP treatment threshold (mmHg)					Office DBP treatment threshold (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18–65 years	≥ 140	≥ 140	≥ 140	≥ 140	≥ 140	≥ 90
65–79 years	≥ 140	≥ 140	≥ 140	≥ 140	≥ 140	≥ 90
≥ 80 years	≥ 160	≥ 160	≥ 160	≥ 160	≥ 160	≥ 90
Office DBP treatment threshold (mmHg)	≥ 90	≥ 90	≥ 90	≥ 90	≥ 90	

Office BP treatment target range

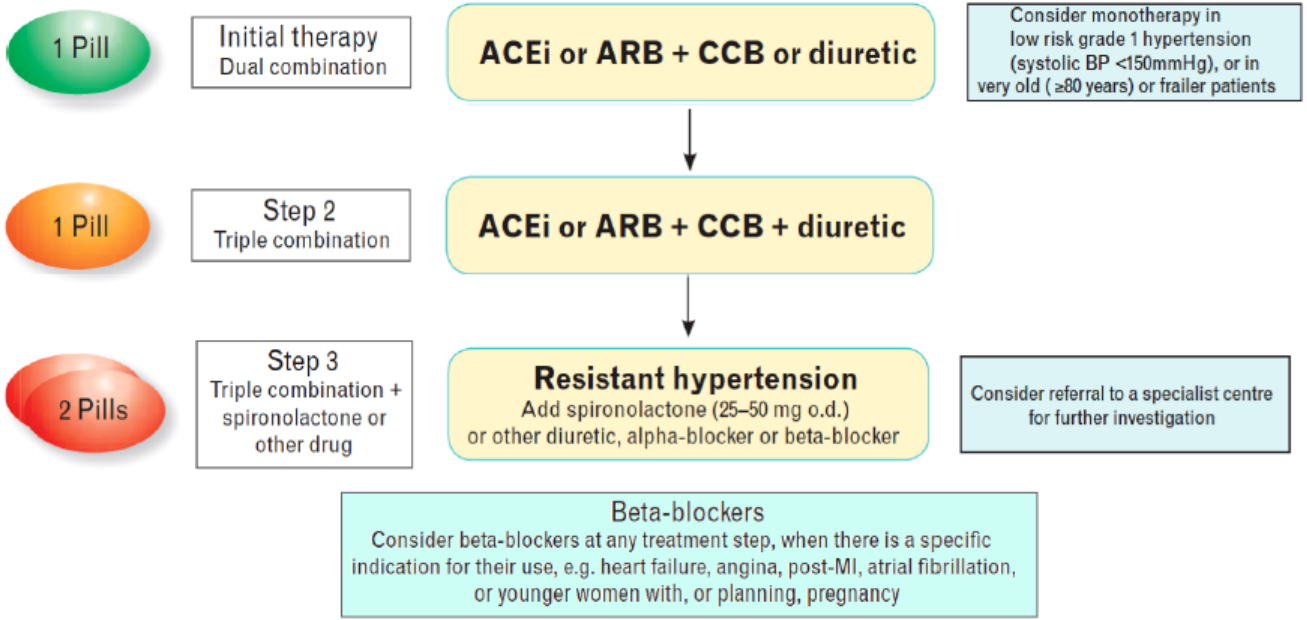
Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18–65 years	**Target to 130** *or lower if tolerated* Not < 120	**Target to 130** *or lower if tolerated* Not < 120	**Target to < 140 to 130** *if tolerated*	**Target to 130** *or lower if tolerated* Not < 120	**Target to 130** *or lower if tolerated* Not < 120	70-79
65–79 years	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	70-79
≥ 80 years	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	70-79
Office DBP treatment target range(mmHg)	70-79	70-79	70-79	70-79	70-79	

ESC European Society of Cardiology

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

ESH European Society of Hypertension

Core drug-treatment strategy for uncomplicated hypertension



The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD

Drug treatment strategy for hypertension - 1

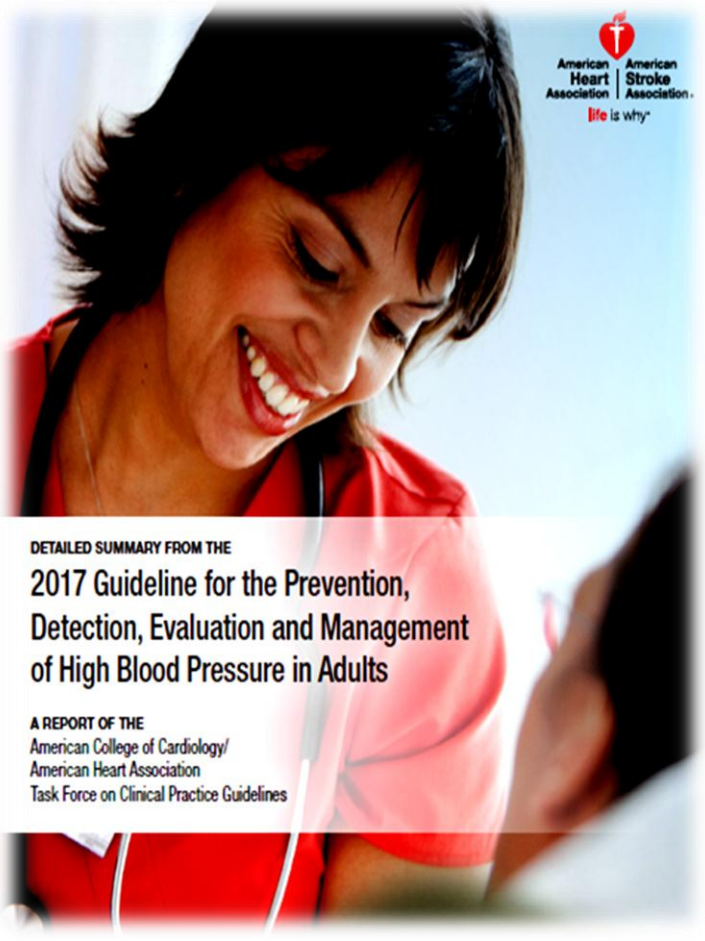
Recommendations	Class	Level
Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies.	I	A
Combination treatment is recommended for most hypertensive patients, as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used.	I	A
It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-myocardial infarction, heart failure, or heart-rate control.	I	A

Drug treatment strategy for hypertension - 2

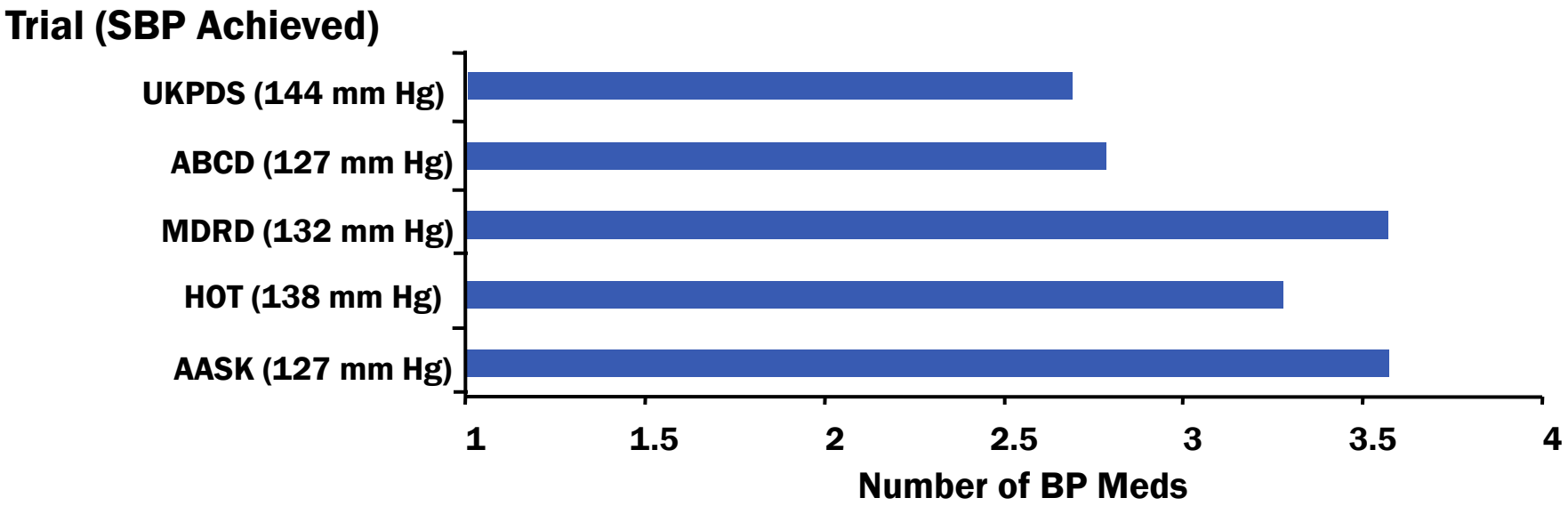
Recommendations	Class	Level
It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in a SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is < 150 mmHg).	I	B
It is recommended that if BP is not controlled with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker + CCB + thiazide/thiazide-like diuretic, preferably as an SPC.	I	A
It is recommended that if BP is not controlled with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker.	I	B
The combination of two RAS blockers is not recommended.	III	A

Why combination therapy in hypertension?


The definition of hypertension has changed.
Are you ready?
SYS
mmHg
130
135
80
85
PULSE
/min


American Heart Association | American Stroke Association
life is why
DETAILED SUMMARY FROM THE
2017 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

High Blood Pressure Evidence: Number of Medications Needed



AASK=African American Study of Kidney Disease and Hypertension, ABCD=Appropriate Blood Pressure Control in Diabetes, BP=Blood pressure, HOT=Hypertension Optimal Treatment, MDRD=Modification of Dietary Protein in Renal Disease, SBP=Systolic blood pressure, UKPDS=UK Prospective Diabetes Study

Source: Abbott K et al. *J Clin Pharmacology* 2004;44:431-438

Choice of Initial Monotherapy Versus Initial Combination Drug Therapy

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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.

Racial and Ethnic Differences in Treatment

COR	LOE	Recommendations for Race and Ethnicity
I	B-R	In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.
I	C-LD	Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension.

Antihypertensive Medication Adherence Strategies

COR	LOE	Recommendations for Antihypertensive Medication Adherence Strategies
I	B-R	In adults with hypertension, dosing of antihypertensive medication once daily rather than multiple times daily is beneficial to improve adherence.
IIa	B-NR	Use of combination pills rather than free individual components can be useful to improve adherence to antihypertensive therapy.

Rationale for initial 2 drug combination therapy for most patients

1. The combination of medications targeting multiple mechanisms, reduces the variability of the BP response
2. Initial combination therapy is more effective at BP lowering than monotherapy
3. Initial combination therapy shows higher Early prevention of CV events than Monotherapy
4. 2 drug combinations as initial therapy have been shown to be safe and well tolerated (even when given to patients with grade 1 hypertension)

Rationale for initial 2 drug combination therapy for most patients

5. compared with patients on initial monotherapy those who start treatment with a 2 drug combination exhibit more frequent BP control after 1 year.
6. Studies show that initial combination treatment results in reduced treatment discontinuation than initial monotherapy :

Non-adherence was usually <10% with a single pill,
Non-adherence was usually 20% with two pills,
Non-adherence was usually 40% with three pills

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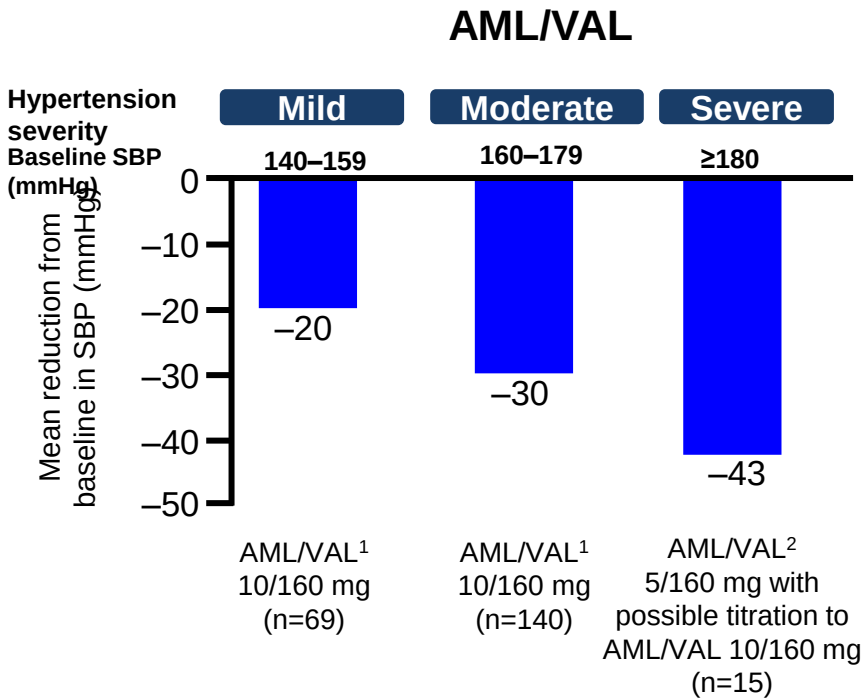
- Non-adherence was usually <10% with a single pill,
- Non-adherence was usually 20% with two pills,
- Non-adherence was usually 40% with three pills

What evidence do we have for Valsartan/Amlodipine combination?

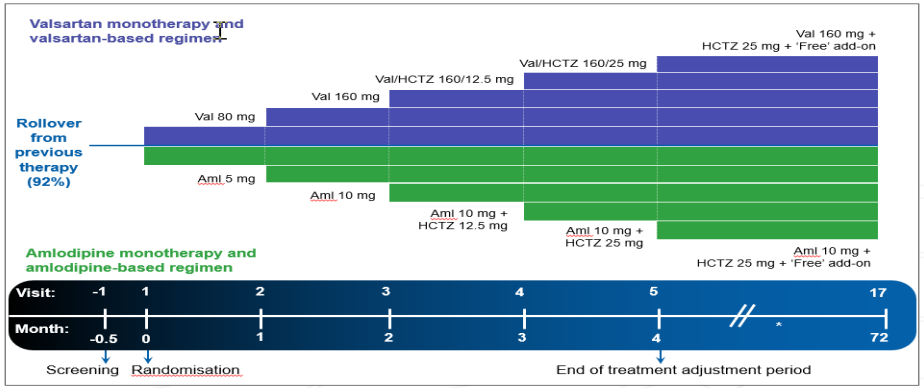
AML/VAL systolic blood pressure reductions across hypertension severities

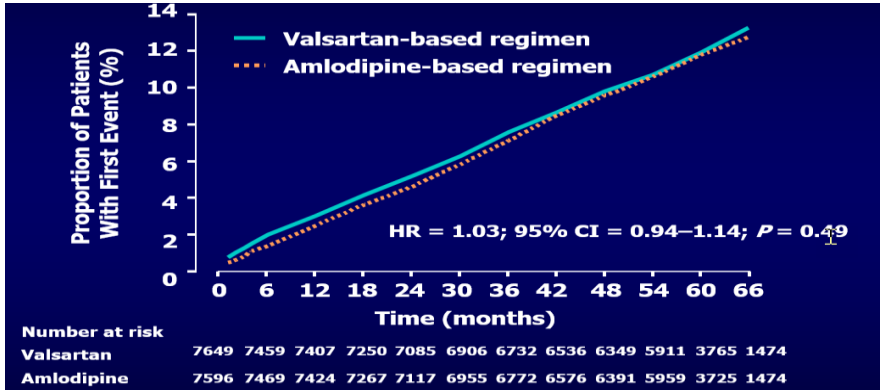


AML/VAL: amlodipine+valsartan combination;
AML/VAL/HCT: amlodipine+valsartan+hydrochlorothiazide combination;
BP: blood pressure; RCT: randomized controlled trial ; SBP = Systolic Blood Pressure

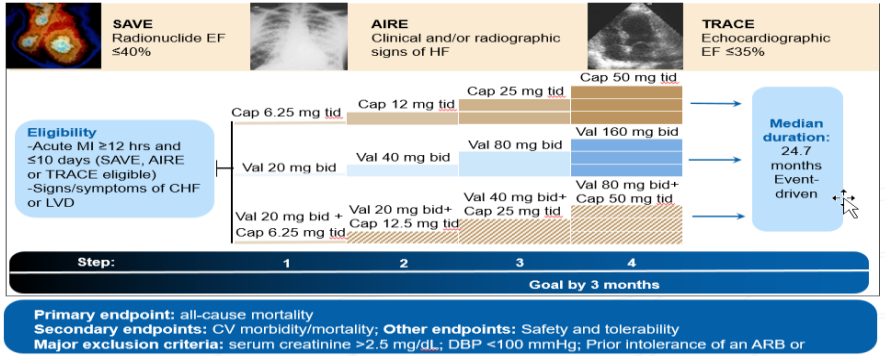
Cardio protection

VALUE

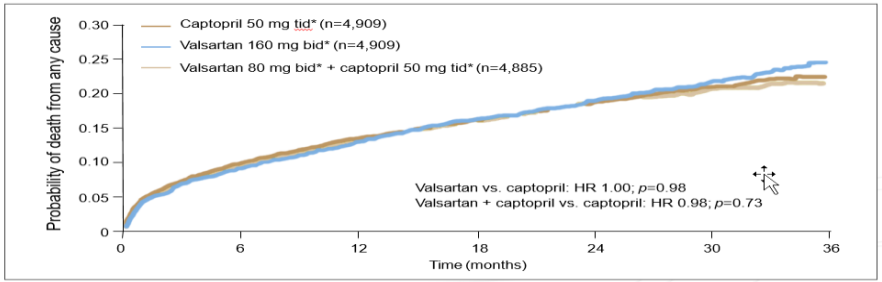




VALIANT



Primary endpoint: all-cause mortality
Secondary endpoints: CV morbidity/mortality; **Other endpoints:** Safety and tolerability
Major exclusion criteria: serum creatinine >2.5 mg/dL; DBP <100 mmHg; Prior intolerance of an ARB or

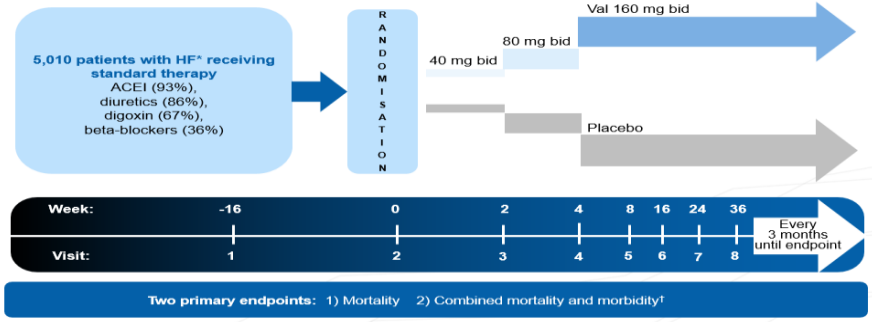


Number at risk

Captopril	4,909	4,428	4,241	4,018	2,635	1,432	364
Valsartan	4,909	4,464	4,272	4,007	2,648	1,437	357
Val + Cap	4,885	4,414	4,265	3,994	2,648	1,435	382

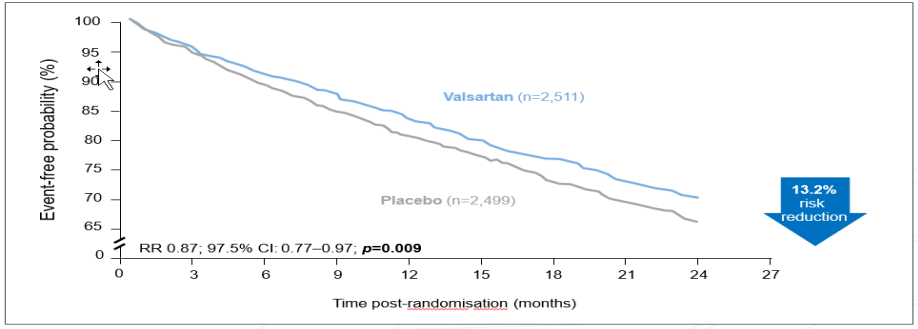
Cardioprotection and its effect on glucose metabolism

Val-HeFT



* ≥18 years; EF <40%; NYHA II–IV; LVIDd >2.9 cm/m². † defined as cardiac arrest with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for four hours or more without hospitalization.
ACEI = angiotensin-converting enzyme inhibitor; bid = twice daily; EF = ejection fraction; NYHA = New York Heart Association; LVIDd = left-ventricular internal diastolic diameter; Val = valsartan; Val-HeFT = Valsartan Heart Failure Trial.
121. Cohn JN, Valsartan Heart Failure Trial Investigators. N Engl J Med. 2001;345:1667–75.

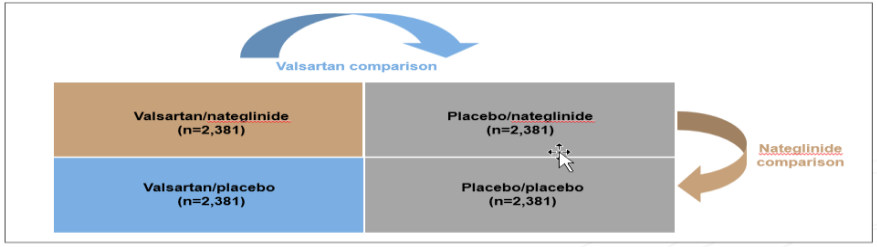
NOVARTIS



* Combined primary endpoint: all-cause mortality, cardiac arrest with resuscitation, hospitalization for worsening heart failure, or therapy with intravenous inotropes or vasodilators.
CI = confidence interval; RR = relative risk; Val-HeFT = Valsartan Heart Failure Trial.
121. Cohn JN, Valsartan Heart Failure Trial Investigators. N Engl J Med. 2001;345:1667–75.

NOVARTIS

NAVIGATOR

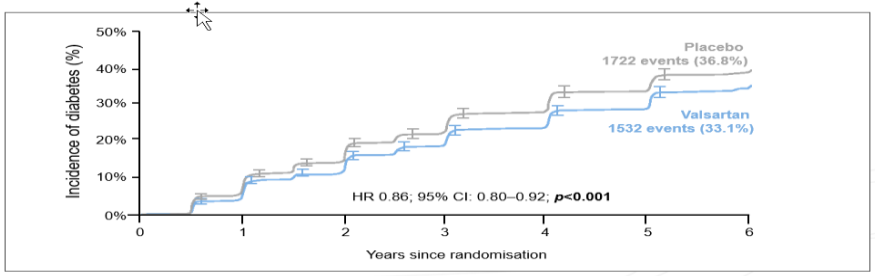


Dosages
- Nateglinide 60 mg tid before meals
- Valsartan 160 mg od

All subjects had impaired glucose tolerance
- FPG ≥5.3 mmol/L and <7.0 mmol/L
- 2-hour glucose ≥7.8 mmol/L but <11.1 mmol/L during oral glucose tolerance test
- All subjects received a lifestyle advice programme

FPG = fasting plasma glucose; NAVIGATOR = Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research; od = once daily; tid = three-times daily.
127. Califf RM, NAVIGATOR Study Group. Am Heart J 2008;156:623-32.

NOVARTIS



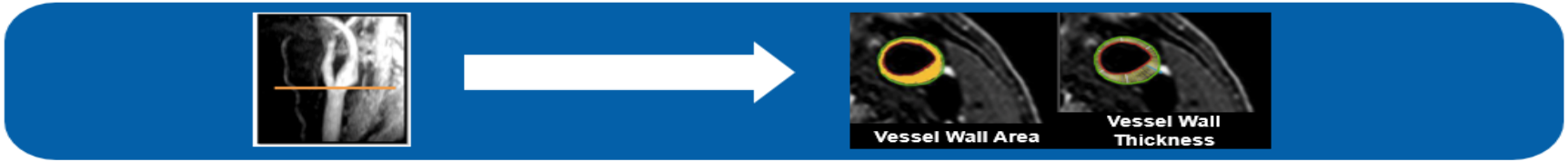
Number at risk

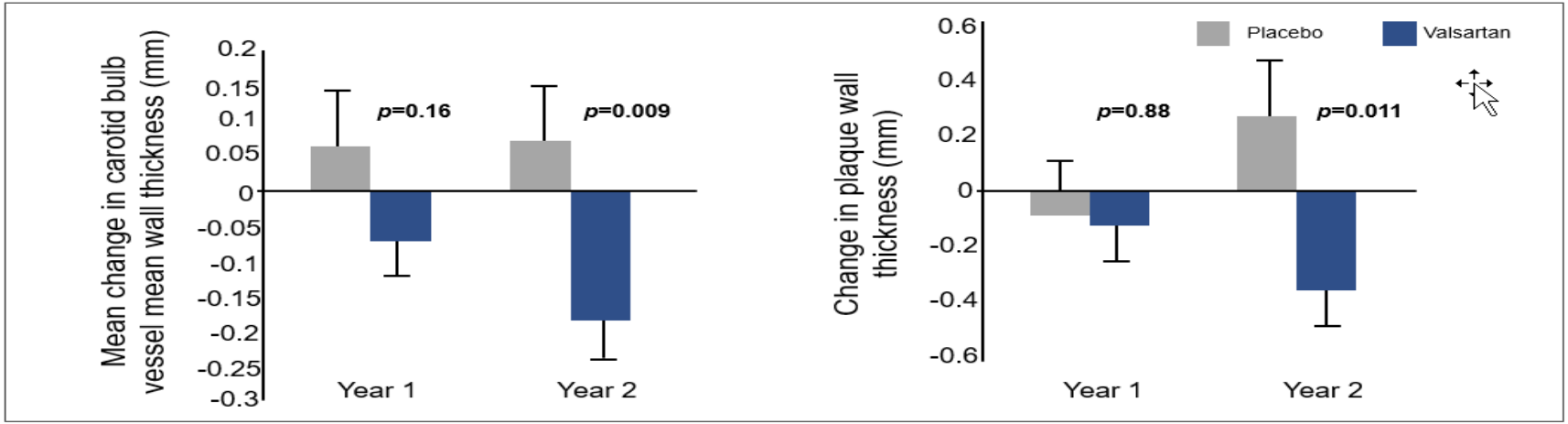
Valsartan	4,631	3,784	3,335	2,857	2,511	2,208	1,533
Placebo	4,675	3,743	3,248	2,717	2,366	2,070	1,403

* Only data from valsartan and placebo groups are shown on this slide.
CI = confidence interval; CV = cardiovascular; HR = hazard ratio; NAVIGATOR = Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research. 126. NAVIGATOR Study Group. N Engl J Med. 2010;362:1477-90.

NOVARTIS

Regression of vessel wall area and thickness with valsartan (EFFERVESCENT)



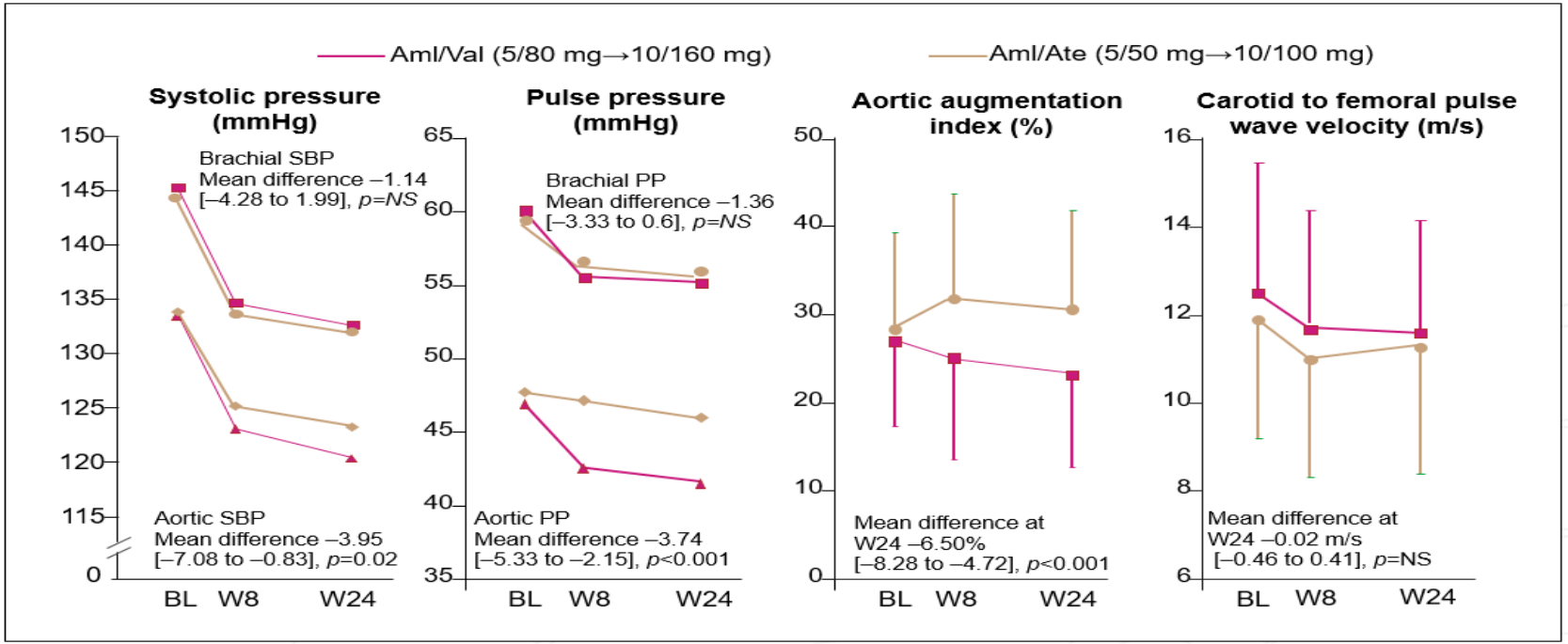


- In addition, there was no difference in BP, cholesterol and statin therapy between treatment groups

BP = blood pressure; EFFERVESCENT = EFFect of angiotEnsin II type I Receptor blockade with Valsartan on carotid artEry atheroSClerosis: a double blind randomizEd cliNical Trial comparing valsartan and placebo.

131. Ramadan R, et al. Am Heart J. 2016;174:68-79.

Effect of amlodipine/valsartan on systolic and pulse pressure, augmentation index and pulse wave velocity with AML/VAL in comparison to AML/ATE (EXPLOR study)



AI = augmentation index; Aml = amlodipine; Ate = atenolol; NS = not significant; PP = pulse pressure; SBP = systolic blood pressure; W = week; Val = valsartan.

160. Boutouyrie P, EXPLOR Trialist Group. Hypertension. 2010;55(6):1314-22.

Efficacy (RCTs) and effectiveness (RWEs)
Summary of AML/VAL and AML/VAL/HCTZ data

Randomized-controlled trials

- Evaluates safety and efficacy of a product[1]
- Rigorous experimental design, randomization, blinding, high internal validity ensures that changes in the dependent variables can be confidently attributed to the experimental treatment and not to other factors, less likelihood of bias[3]

Efficacy>Effectiveness

Enrolment → Randomization → Treatment / Control

Real-world evidence

- Evaluates real-world effectiveness of a launched product[1,2]
- Routine practice setting, realistic therapy adherence, economical (vs RCTs), large sample size and more representative of population (with confounding factors), longer follow-up[3,4]

Efficacy=Effectiveness

Prescribed with → Treatment → Enrolment / Comparator → Enrolment

Cumulative Aml/Val patient exposure: 20.8 million PTY

13 RWE studies with Aml/Val in >60,000 patients with hypertension and additional risk factors (e.g., diabetes, metabolic risk, renal insufficiency)

Study Details
- Duration: 8 weeks to 2.93 years
- Mean age range: 52-64 years
- Baseline BP: 147-169/85-99 mmHg

Outcomes
- Aml/Val provided significant BP reductions with mean reduction in SBP/DBP at study end: -12.5-40.1/-4.1-19.6 mmHg, dependent on respective baseline BP
- Common AEs (frequency ≥1% in real world studies with Aml/Val): headache, dizziness, and weakness/malaise

* Middle East: Bahrain, Egypt, Kuwait, Lebanon, Oman, Qatar, and United Arab Emirates; Asia: Indonesia, Hong Kong, Pakistan, Philippines, South Korea, and Taiwan.

AEs = adverse events; Aml = amlodipine; BP = blood pressure; RWE = real word evidence; Val = valsartan.

201. Sison J, et al. Curr Med Res Opin. 2014;30(10):1937-1945; 202. Assaad-Khalil SH, et al. Vasc Health Risk Manag. 2015;11:71-78; 203. Khan W, et al. Ther Adv Cardiovasc Dis. 2014;8(2):45-55; 204. Sison JA, Francisco SG. Philippine J Int Med. 2014;52(4):1-7; 205. Setiawati A, et al. Acta Med Indones. 2015;47(3):223-233; 206. Kizilirmak P, et al. Turk Kardiyol Dern Ars. 2013;41(5):406-417; 207. Ito D, et al. Adv Ther. 2014;31(7):762-775; 208. Ge B, et al. J Cardiovasc Pharmacol. 2015;66(5):497-503; 209. Eckert S, et al. Blood Press. 2013; 22 Suppl 1:11-21; 210. Tung YC, et al. J Clin Hypertens (Greenwich). 2015;17(1):51-58; 211. Chazova IE, Martynyuk TV, Ter Arkh. 2013;85(9):35-212. Cheng SM, et al. Blood Press. 2012;21 Suppl 1:11-19; 213. Vilela GC, Villanueva AT, Philippine J Int Med. 2010;50:-46; 214. Karpov Y, et al. Adv Ther. 2012;29(2):134-147; 215. Linz R, et al. Ann Pharmacother. 2011;45(6):727-739.

Cumulative Aml/Val/HCTZ patient exposure: 5 million PTY

2 RWE studies with Aml/Val/HCTZ from 13 countries in >8,000 patients with hypertension

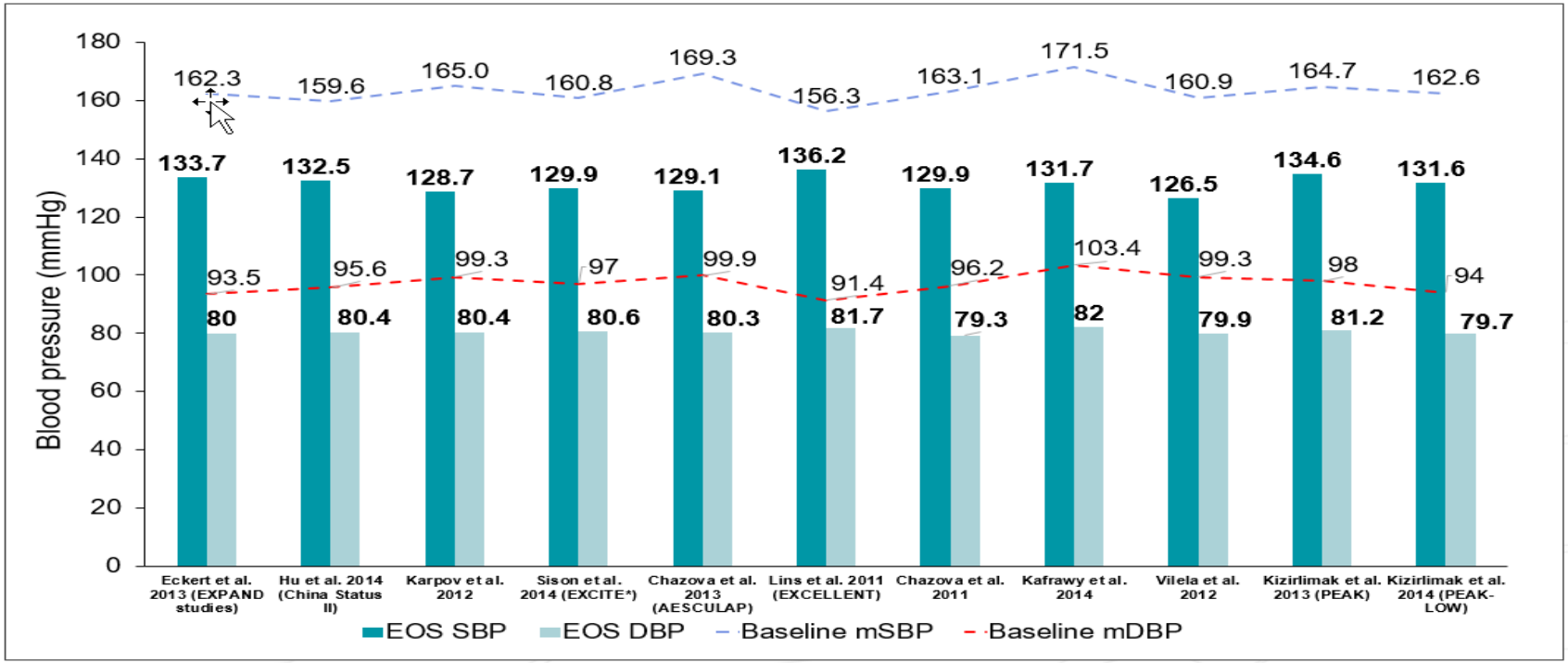
Study Details[201-204,221,222]
- Duration: : 12-26 weeks
- Mean age: 56-64 years
- Baseline BP: 158-171/91-99 mmHg

Outcomes[201-204,221,222]
- Aml/Val/HCTZ provided significant BP reductions with mean reduction in SBP/DBP at study end: 23.7-43.9/5.9-21.9 mmHg, dependent on respective baseline BP
- Common AEs (frequency ≥1%) in RWE studies with Aml/Val/HCTZ: peripheral edema, edema, and dizziness

AEs = adverse events; Aml = amlodipine; BP = blood pressure; HCTZ = hydrochlorothiazide; RWE = real world evidence; Val = valsartan.

201. Sison J, et al. Curr Med Res Opin. 2014;30(10):1937-1945; 202. Assaad-Khalil SH, et al. Vasc Health Risk Manag. 2015;11:71-78; 203. Khan W, et al. Ther Adv Cardiovasc Dis. 2014;8(2):45-55; 204. Sison JA, Francisco SG. Philippine J Int Med. 2014;52(4):1-7;

Blood pressure reduction with AML/VAL across real world evidence studies



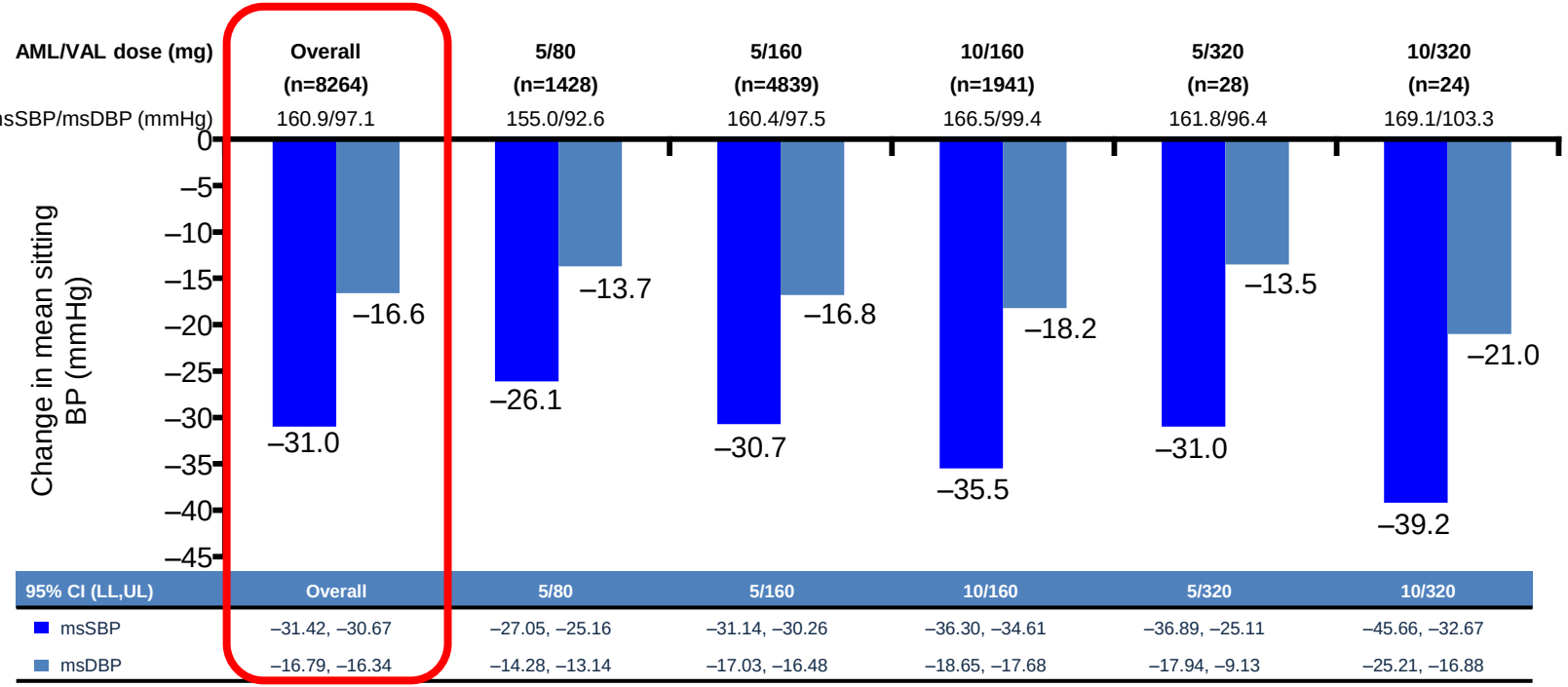
* Data for Val/Aml presented here.
# Cheng et al. 2012 and Schroeder et al. 2008 did not report absolute values.
Aml = amlodipine; EOS = end of study; mDBP = mean diastolic BP; mSBP = mean systolic BP; Val = valsartan.

Tolerability profile of patients treated with AML/VAL across real world evidence studies

Study title	AEs (%)	SAEs (%)	Common AEs	AEs leading to discontinuation (%)
Eckert et al. 2013 (EXPAND studies)	2.4	0.5	Edema (0.2), peripheral edema (0.9), dizziness (0.1), headache (0.1)	NR
Hu et al. 2014 (China Status II)	1.4	<0.1	Headache (0.2), dizziness (0.2), edema (0.2)	0.2
Karpov et al. 2012	5.3	NR	Edema (3.2), headache (0.7), dizziness (0.4), hypotension (0.2)	NR
Sison et al. 2014 (EXCITE*)	11.2	0.6	Edema (2.0), peripheral edema (1.2)	0.7
Chazov et al. 2013 (AESCULAP)	3.1	NR	Peripheral edema (1.4)	0.5
Schrader et al. 2008	2.9	NR	Peripheral edema (0.9), edema (0.2), dizziness (0.2)	NR
Lins et al. 2011 (EXCELLENT)	NR	NR	NR	NR
Chazova et al. 2011	8.8	NR	Edema (2.3), dizziness (1.4), headache (1.1)	0.3
Kafrawy et al. 2014	4.4	0.1	Edema (3.6), headache (0.7), gastrointestinal disorder (0.3)	NR
Vilela et al. 2012	5.5	0.2	Headache (0.9), dizziness/light-headedness without hypotension (0.8)	NR
Kizirlimak et al. 2013 (PEAK)	12.7	0.4	Edema (10.8), headache (0.4), dizziness (0.3)	NR
Cheng et al. 2012	12.1	1.7	Dizziness (2.6), cough (1.0)	1.3
Kizirlimak et al. 2014 (PEAK-LOW)	3.2	NR	Edema (1.3), pruritus (0.5)	NR

* Data for Val/Aml presented here. Data represents % of patients experiencing AEs.
AEs = adverse events; Aml = amlodipine; NR, not reported; SAE = serious adverse event; Val = valsartan

Blood pressure reductions across all treatment dosages with AML/VAL in the EXCITE real-world evidence study



95% CI (LL,UL)	Overall	5/80	5/160	10/160	5/320	10/320
msSBP	–31.42, –30.67	–27.05, –25.16	–31.14, –30.26	–36.30, –34.61	–36.89, –25.11	–45.66, –32.67
msDBP	–16.79, –16.34	–14.28, –13.14	–17.03, –16.48	–18.65, –17.68	–17.94, –9.13	–25.21, –16.88

n: number of patients from which change in BP was calculated, (full analysis set: all patients with at least one baseline and post-baseline BP assessment, last observation carried forward)
AML/VALamlodipine+valsartan combination; BP: blood pressure; BL msSBP/msDBP: mean sitting systolic / mean sitting diastolic blood pressure at baseline; CI: confidence interval; LL; lower limit; UL: upper limit

Sison et al. Abstract102 presented at the 5th International Conference on Fixed Combination in the Treatment of Hypertension, Dyslipidemia and Diabetes Mellitus, Bangkok, Thailand, 21–24 November 2013

AML/VAL and AML/VAL/HCT tolerability in the EXCITE real-world evidence study

Adverse events (AEs) by preferred term*	AML/VAL N=8603 n (%)	AML/VAL/HCT N=1191 n (%)	Total N=9794 n (%)
Total AEs	**963 (11.2)**	**73 (6.1)**	**1036 (10.6)**
Oedema	173 (2.0)	39 (3.3)	212 (2.2)
Peripheral oedema	99 (1.2)	9 (0.8)	108 (1.1)
Headache	87 (1.0)	2 (0.2)	89 (0.9)
Cough	52 (0.6)	3 (0.3)	55 (0.6)
Nausea	41 (0.5)	2 (0.2)	43 (0.4)

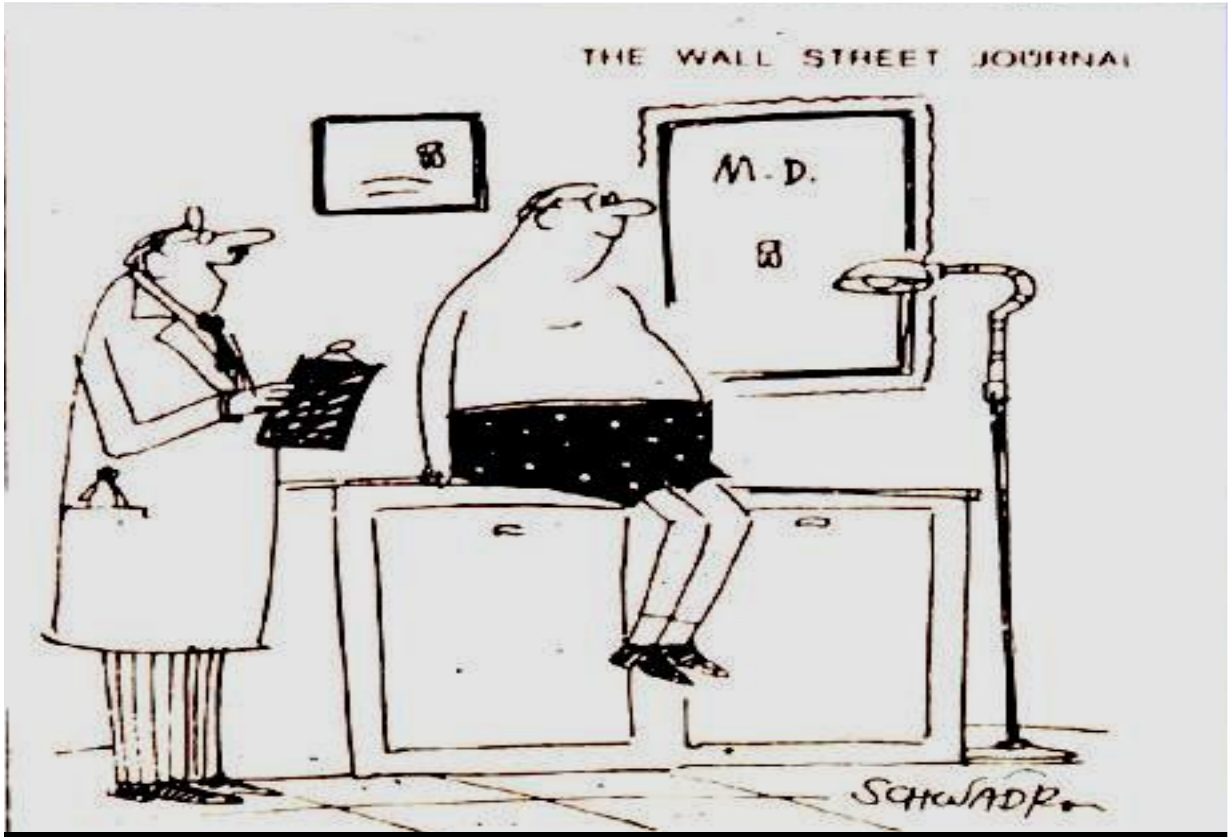
- SAEs were reported in a total of 50 (0.5%) patients [AML/VAL: 49 (0.6%) and AML/VAL/HCT: 1 (0.1%)]. Most of the AEs and SAEs were assessed by the study investigators as being unrelated to the medication of interest.
- A total of 13 deaths (AML/VAL:12 and AML/VAL/HCT: 1) were reported during the study, none were considered to be related to the medication of interest by the study investigator

*Events occurring in ≥0.5% of any treatment group safety set.
Serious adverse events (SAEs)
AML/VAL: Amlodipine+Valsartan combination;
AML/VAL/HCT: Amlodipine+Valsartan+Hydrochlorothiazide combination

Sison et al. Abstracts 102 and 109 presented at the 5th International Conference on Fixed Combination in the Treatment of Hypertension, Dyslipidemia and Diabetes Mellitus, Bangkok, Thailand, 21–24 November 2013; Novartis Data on File, 2013

Conclusion

- Hypertension prevalence continues to grow and control rates are still not satisfactory.
- Fixed dose combination therapies can help addressing this serious health care issue by improving treatment compliance.
- In addition targeting different mechanisms of action augments the efficacy and can improve organ protection and clinical outcomes.
- Valsartan & Amlodipine have demonstrated cardio protection in a large number of morbidity-mortality landmark studies.
- Valsartan and Amlodipine have been extensively studies in observational studies which confirmed effectiveness and tolerability in various patient sub-types including those at high risk.



I have some bad news for you. While your blood pressure has remained the same, the research findings have changed.

Thank you