Management of Hypertension in 2017

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Goals and Objectives

- Understand JNC 8 guidelines for management of hypertension.
- Review data from recent landmark trials for HTN management
- Projections for JNC 9

Case 1

- 76y male with h/o CKD-II, DM2, HLD, CAD s/p PCI, preserved LV function and HTN. What is the target BP for this patient?

A. <120/80

B. <130/80

C. <140/90

D. <150/90

E. >150/90

Case 2

- 45y African American male with type II non insulin dependent diabetes mellitus, A1C 7.5. BP 160/100 on multiple reads – what is the target BP for this patient?

A. <150/90

B. <140/90

C. <130/80

D. <120/60

BP and CV risk

Figure 9. Ischemic heart disease mortality rate in each decade of age versus usual blood pressure at the start of that decade

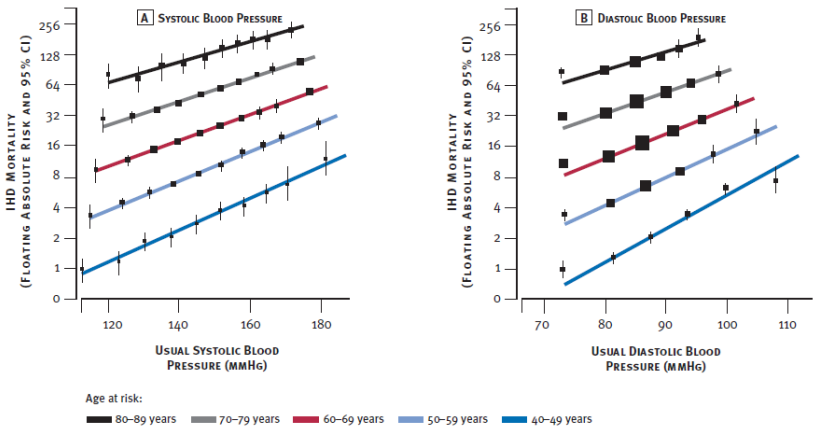


Figure 10. Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade

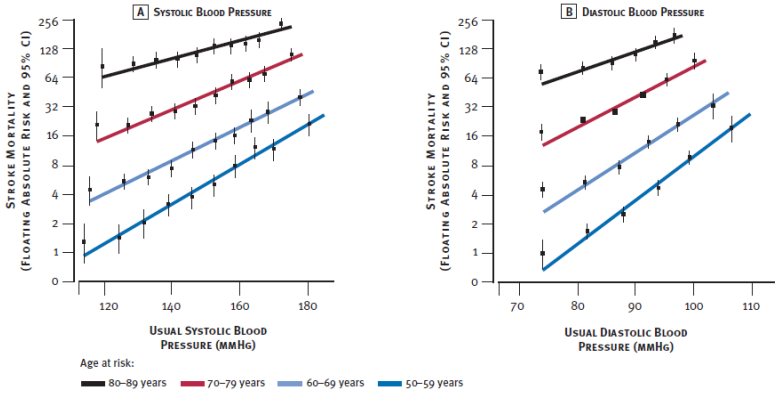
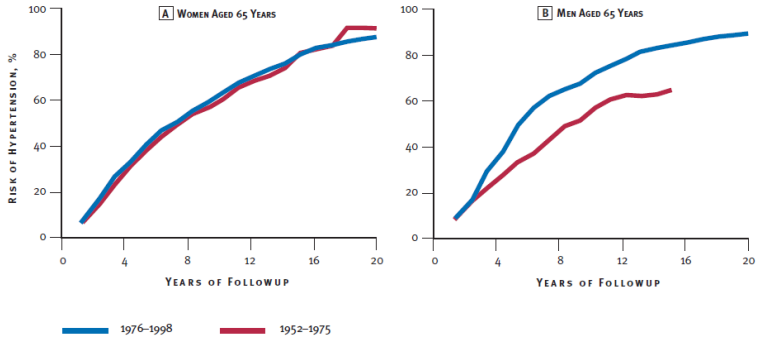


Figure 8. Residual lifetime risk of hypertension in women and men aged 65 years



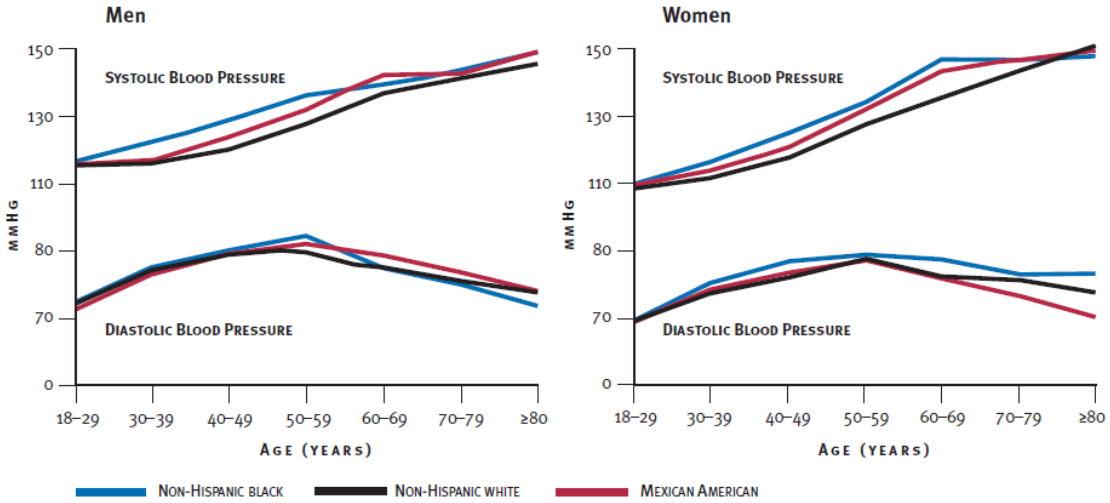
For every 20 mmHg systolic or 10 mmHg diastolic increase in BP, there is a doubling of mortality from both IHD and stroke.

JNC 7 – Reclassification of hypertension stages

Table 2. Changes in blood pressure classification

JNC 6 Category	SBP/DBP	JNC 7 Category
Optimal	<120/80	→ Normal
Normal	120–129/80–84	→ Prehypertension
Borderline	130–139/85–89	
Hypertension	≥140/90	→ Hypertension
Stage 1	140–159/90–99	→ Stage 1
Stage 2	160–179/100–109	→ Stage 2
Stage 3	≥180/110	

What to treat? Systolic or Diastolic



SBP and DBP by age and race or ethnicity for men and women over 18 years of age in the U.S. population. Data from NHANES III, 1988–1991.

Source: Burt VL, et al. Prevelance of hypertension in the U.S. adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension *1995;25 (3):305–13.*

Diastolic hypertension predominates before age 50, either alone or in combination with SBP elevation.

- The prevalence of systolic hypertension increases with age, and above 50 years of age, systolic hypertension represents the most common form of hypertension.
- DBP is a more potent cardiovascular risk factor than SBP until age 50; thereafter, SBP is more important.
- In ALLHAT and CONVINCE trials – diastolic control (<90mmHg) was achieved in >90% patients however, SBP control <140mmHg was achieved only in <60% patients

Doctors surveyed thought diastolic control was more important!!

Lifestyle modifications

Modification	Recommendation	Approximate Systolic BP Reduction, Range
Weight reduction	Maintain normal body weight (BMI, 18.5-24.9)	5-20 mm Hg/10-kg weight loss[23,24]
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8-14 mm Hg[25,26]
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mEq/L (2.4 g sodium or 6 g sodium chloride)	2-8 mm Hg[25-27]
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week)	4-9 mm Hg[28,29]
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks per day (1 oz or 30 mL ethanol [eg, 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey]) in most men and no more than 1 drink per day in women and lighter-weight persons	2-4 mm Hg[30]

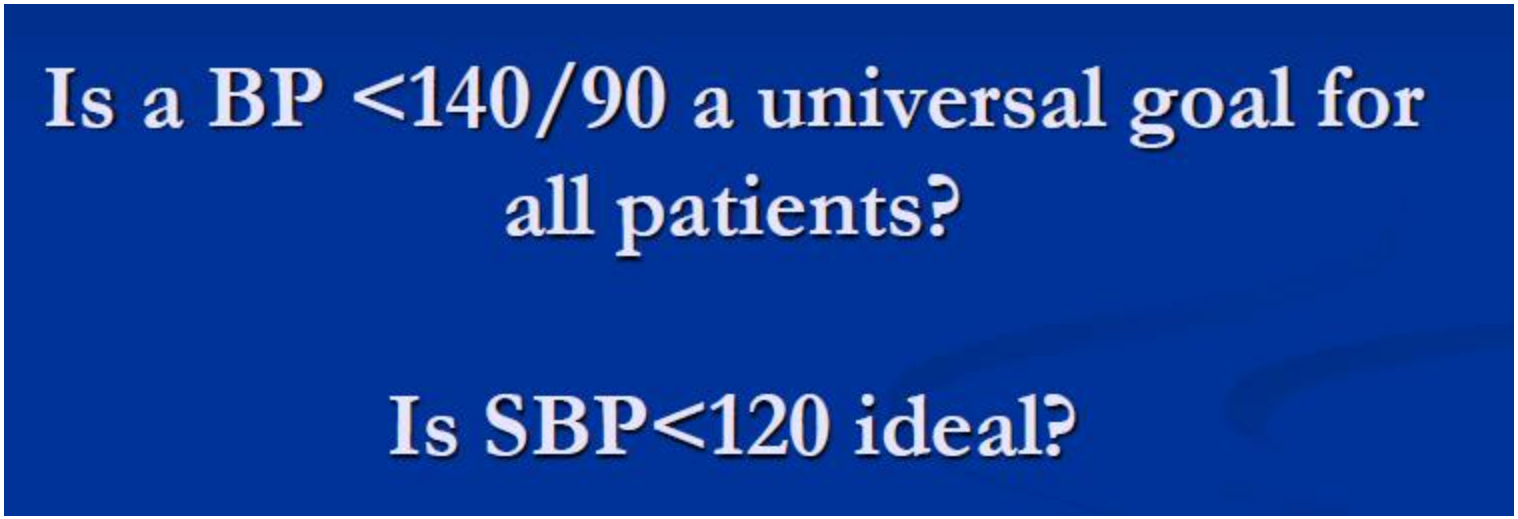
Abbreviations: BMI, body mass index calculated as weight in kilograms divided by the square of height in meters; BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension.

*For overall cardiovascular risk reduction, stop smoking. The effects of implementing these modifications are dose and time dependent and could be higher for some individuals.

Specific drug class recommendations

High-Risk Conditions With Compelling Indication*	Recommended Drugs						Clinical Trial Basis†
	Diuretic	β-Blocker	ACE Inhibitor	ARB	CCB	Aldosterone Antagonist	
Heart failure	•	•	•	•		•	ACC/AHA Heart Failure Guideline,[40] MERIT-HF,[41] COPERNICUS,[42] CIBIS,[43] SOLVD,[44] AIRE,[45] TRACE,[46] ValHEFT,[47] RALES[48]
Post–myocardial infarction		•	•			•	ACC/AHA Post-MI Guideline,[49] BHAT,[50] SAVE,[51] Capricorn,[52] EPHESUS[53]
High coronary disease risk	•	•	•		•		ALLHAT,[33] HOPE,[34] ANBP2,[35] LIFE,[32] CONVINCE[31]
Diabetes	•	•	•	•	•		NKF-ADA Guideline,[21,22] UKPDS,[54] ALLHAT[33]
Chronic kidney disease			•	•			NKF Guideline,[22] Captopril Trial,[55] RENAAL,[56] IDNT,[57] REIN,[58] AASK[59]
Recurrent stroke prevention	•		•				PROGRESS[35]

In 2013


Is a BP <140/90 a universal goal for all patients?
Is SBP<120 ideal?

Antihypertensive therapy trials for Elderly

Table 1. Outcomes of Randomized Placebo-Controlled Clinical Trials Providing Level I Evidence of Antihypertensive Therapy in Elderly People

Source	No. of Participants	Age Range, y	Blood Pressure at Entry, Mean, mm Hg	Intervention Drug	Risk Reduction, %		
					Stroke	CHD	CHF
EWPHE,[22] 1988	840	>60	182/101	Hydrochlorothiazide ± α-methyldopa	36	20	22
Coope and Warrender,[23] 1987	884	60-79	197/100	Atenolol ± bendrofluazide	42[a]	0.03	32
STOP,[24] 1991	1627	70-84	195/102	Atenolol ± hydrochlorothiazide/amiloride	47[a]	13	51[a]
MRC,[25] 1992	4396	65-74	185/91	Hydrochlorothiazide ± amiloride vs atenolol	25[a]	19	
SHEP,[26] 1991	4736	60-80	170/77	Chlorthalidone ± atenolol/reserpine	33[a]	27[a]	55[a]
HDFP,[27] 1979	2376	60-69	170/101	Stepped care: chlorthalidone, reserpine, hydralazine, guanethidine	45[a]	15[a]	
Syst-Eur,[28] 1997	4695	>60	174/86	Nitrendipine ± enalapril/ hydrochlorothiazide	42[a]	30	29
Syst-China,[29] 2000	2394	>60	171/86	Nitrendipine ± captopril/hydrochlorothiazide			
HYVET,[30] 2008	3845	80-105 (Mean, 84)	173/91	Indapamide ± perindopril	39[a,b]	34[a,c]	64[a]

Abbreviations: CHD, coronary heart disease; CHF, congestive heart failure; EWPHE, European Working Party on Hypertension in the Elderly trial; HDFP, Hypertension Detection and Follow-up Program; HYVET, Hypertension in the Very Elderly Trial; MRC, Medical Research Council trial; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients With Hypertension; Syst-China, Systolic Hypertension in China trial; Syst-Eur, Systolic Hypertension European trial.

[a] $P < .05$.

[b] Fatal stroke.

[c] Any cardiovascular event.

JAMA

Antihypertensive therapy for Elderly

Table 2. Targets for Blood Pressure Lowering in Different Groups of Elderly Patients

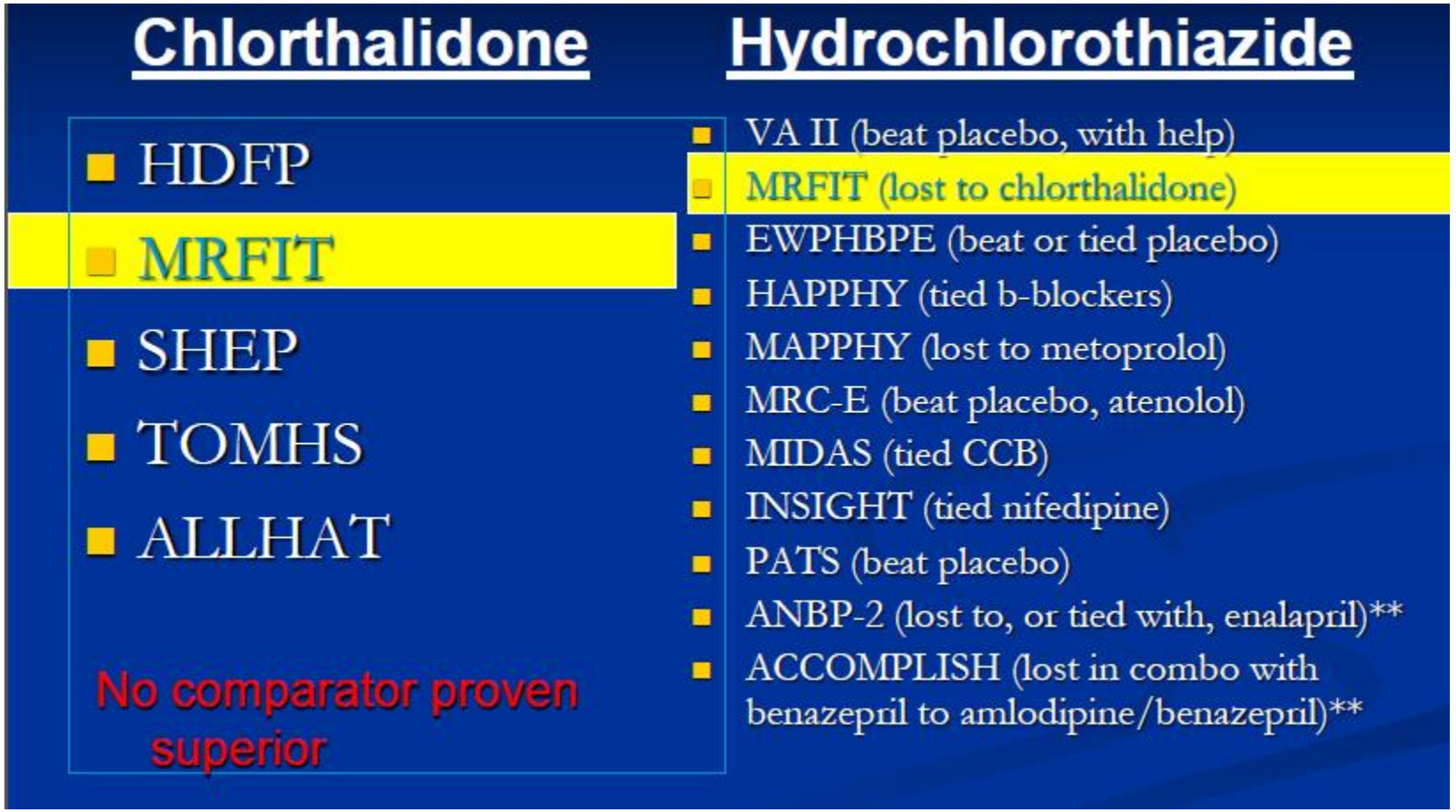
Age Range, y	Health Status	Hypertension Type	Achieved Blood Pressure, mm Hg	Positive Outcomes	Target Blood Pressure, mm Hg	Evidence Source	Evidence Class
65-80	Healthy	Systolic	143/68-151/79	Stroke, CAD, CHF	<150/80	SHEP,[26] Syst-Eur,[28] Syst-China[29]	IA
65-85	Healthy	Mixed	150/80-178/87	Stroke ± CAD, CHF	<150/90	Coope and Warrender,[23] STOP,[24] MRC,[25] HDFP[27]	IA
>80	Healthy	Mixed	144/78	Death, CHF, cardiovascular events	<145/90	HYVET[30]	IB
>85	Disabled	Any	No studies	No studies	<160/90	Expert consensus	IIC

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; HDFP, Hypertension Detection and Follow-up Program; HYVET, Hypertension in the Very Elderly Trial; MRC, Medical Research Council trial; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients With Hypertension; Syst-China, Systolic Hypertension in China trial; Syst-Eur, Systolic Hypertension European trial.

Summary of landmarks trials from 2008-2013

- 2008 HYVET
  - Low risk ≥ 80y/o: SBP<150 is still beneficial
- 2008 ACCOMPLISH
  - High risk 68.4y/o: SBP<130 no better than <140
- 2009 ONTARGET
  - High risk 66.4y/o: SBP =130 is optimal
- 2010 ACCORD BP
  - High risk Diabetics 62.2y/o: SPB<120 no better than <140

2013 questions – Are thiazides better as initial drug and is HCTZ comparable to Chlorthalidone?



What about BB? Case against Atenolol

- Several Meta-analyses have shown that ATENOLOL INCREASES all cause mortality and CV related deaths as compared to other drugs and hence the WARNING not to use atenolol for BP control.

Resistant Hypertension

- Identify and treat secondary causes.
- Centrally acting alpha agonists.
- Direct vasodilators.
- Aldosterone antagonists (ENaC).

JNC 8 or 2014 guidelines

- In contrast to the 2003 JNC 7 guideline recommendation, the 2014 guideline is driven by a systematic review of clinical trial evidence.
- The 2014 guideline offers recommendations for the management of hypertension in:
  - People older or younger than age 60 years
  - People aged ≥18 years with chronic kidney disease
  - People aged ≥18 years with diabetes
  - Black and nonblack populations

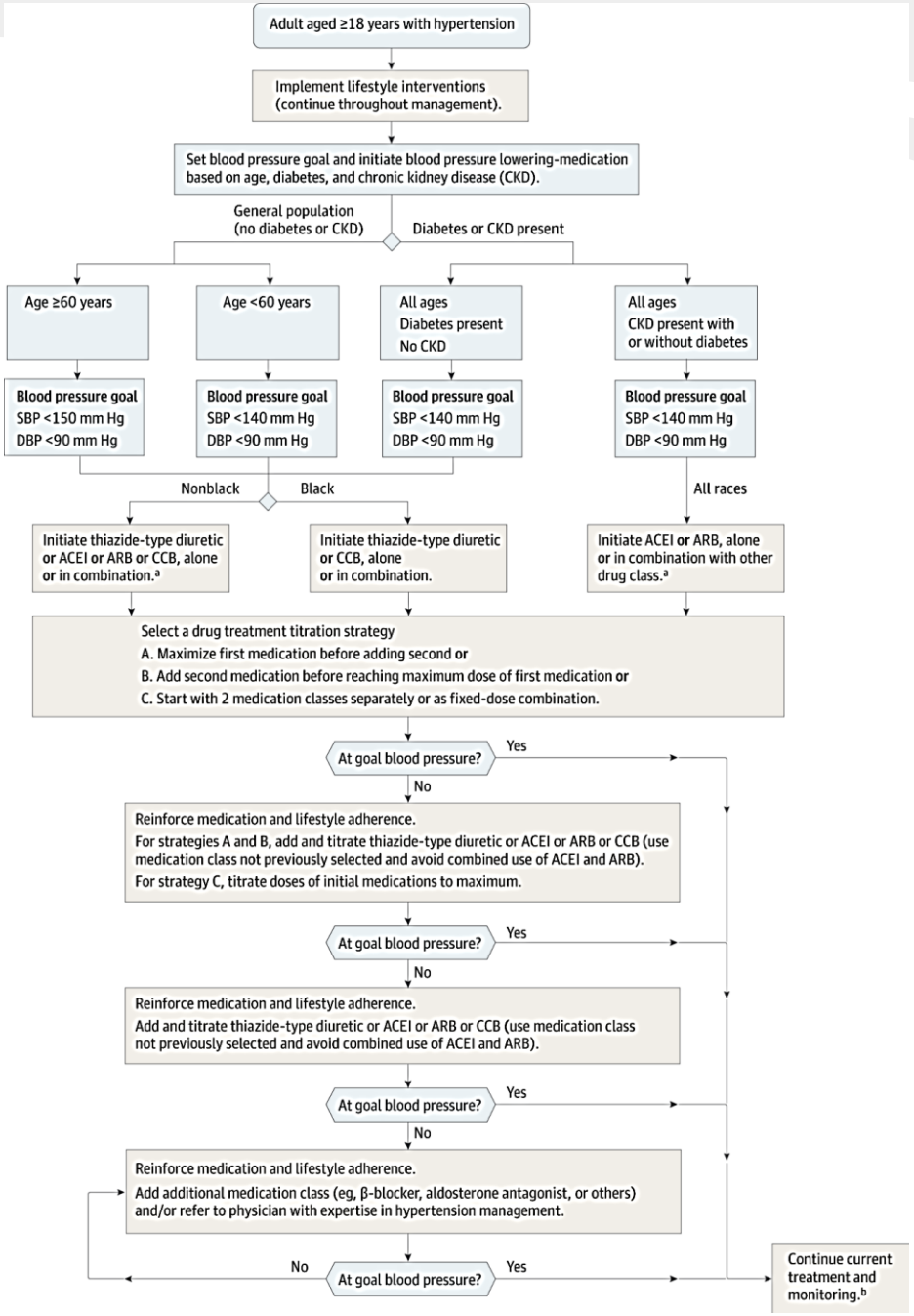
JNC 7 vs JNC 8

Table 1. Comparison of Current Recommendations With JNC 7 Guidelines

Topic	JNC 7	2014 Hypertension Guideline
Methodology	Nonsystematic literature review by expert committee including a range of study designs Recommendations based on consensus	Critical questions and review criteria defined by expert panel with input from methodology team Initial systematic review by methodologists restricted to RCT evidence Subsequent review of RCT evidence and recommendations by the panel according to a standardized protocol
Definitions	Defined hypertension and prehypertension	Definitions of hypertension and prehypertension not addressed, but thresholds for pharmacologic treatment were defined
Treatment goals	Separate treatment goals defined for "uncomplicated" hypertension and for subsets with various comorbid conditions (diabetes and CKD)	Similar treatment goals defined for all hypertensive populations except when evidence review supports different goals for a particular subpopulation
Lifestyle recommendations	Recommended lifestyle modifications based on literature review and expert opinion	Lifestyle modifications recommended by endorsing the evidence-based Recommendations of the Lifestyle Work Group
Drug therapy	Recommended 5 classes to be considered as initial therapy but recommended thiazide-type diuretics as initial therapy for most patients without compelling indication for another class Specified particular antihypertensive medication classes for patients with compelling indications, ie, diabetes, CKD, heart failure, myocardial infarction, stroke, and high CVD risk Included a comprehensive table of oral antihypertensive drugs including names and usual dose ranges	Recommended selection among 4 specific medication classes (ACEI or ARB, CCB or diuretics) and doses based on RCT evidence Recommended specific medication classes based on evidence review for racial, CKD, and diabetic subgroups Panel created a table of drugs and doses used in the outcome trials
Scope of topics	Addressed multiple issues (blood pressure measurement methods, patient evaluation components, secondary hypertension, adherence to regimens, resistant hypertension, and hypertension in special populations) based on literature review and expert opinion	Evidence review of RCTs addressed a limited number of questions, those judged by the panel to be of highest priority.
Review process prior to publication	Reviewed by the National High Blood Pressure Education Program Coordinating Committee, a coalition of 39 major professional, public, and voluntary organizations and 7 federal agencies	Reviewed by experts including those affiliated with professional and public organizations and federal agencies; no official sponsorship by any organization should be inferred

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; JNC, Joint National Committee; RCT, randomized controlled trial

JNC 8 guidelines



Strategies to dose anti-hypertensive drugs

Strategy	Description	Details
A	Start one drug, titrate to maximum dose, and then add a second drug	If goal BP is not achieved with the initial drug, titrate the dose of the initial drug up to the maximum recommended dose to achieve goal BP If goal BP is not achieved with the use of one drug despite titration to the maximum recommended dose, add a second drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB) and titrate up to the maximum recommended dose of the second drug to achieve goal BP If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose to achieve goal BP
B	Start one drug and then add a second drug before achieving maximum dose of the initial drug	Start with one drug then add a second drug before achieving the maximum recommended dose of the initial drug, then titrate both drugs up to the maximum recommended doses of both to achieve goal BP If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose to achieve goal BP
C	Begin with 2 drugs at the same time, either as 2 separate pills or as a single pill combination	Initiate therapy with 2 drugs simultaneously, either as 2 separate drugs or as a single pill combination. Some committee members recommend starting therapy with ≥2 drugs when SBP is >160 mm Hg and/or DBP is >100 mm Hg, or if SBP is >20 mm Hg above goal and/or DBP is >10 mm Hg above goal. If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose.

Abbreviations: ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a]This table is not meant to exclude other agents within the classes of antihypertensive medications that have been recommended but reflects those agents and dosing used in randomized controlled trials that demonstrated improved outcomes.

Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults With Hypertension

Guideline	Population	Goal BP, mm Hg	Initial Drug Treatment Options
2014 Hypertension guideline	General ≥60 y	<150/90	Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB; black: thiazide-type diuretic or CCB
	General <60 y	<140/90	
	Diabetes	<140/90	
	CKD	<140/90	ACEI or ARB
ESH/ESC 2013[37]	General nonelderly	<140/90	Diuretic, β-blocker, CCB, ACEI, or ARB
	General elderly <80 y	<150/90	
	General ≥80 y	<150/90	
	Diabetes	<140/85	ACEI or ARB
	CKD no proteinuria	<140/90	ACEI or ARB
	CKD + proteinuria	<130/90	
CHEP 2013[38]	General <80 y	<140/90	Thiazide, β-blocker (age <60y), ACEI (nonblack), or ARB
	General ≥80 y	<150/90	
	Diabetes	<130/80	ACEI or ARB with additional CVD risk ACEI, ARB, thiazide, or DHPCCB without additional CVD risk
	CKD	<140/90	ACEI or ARB
ADA 2013[39]	Diabetes	<140/80	ACEI or ARB
KDIGO 2012[40]	CKD no proteinuria	≤140/90	ACEI or ARB
	CKD + proteinuria	≤130/80	
NICE 2011[41]	General <80 y	<140/90	<55 y: ACEI or ARB
	General ≥80 y	<150/90	≥55 y or black: CCB
ISHIB 2010[42]	Black, lower risk	<135/85	Diuretic or CCB
	Target organ damage or CVD risk	<130/80	

Hypertension Treatment

Compelling Indications	
Indication	**Treatment Choice**
Heart Failure	ACEI/ARB + BB + diuretic + spironolactone
Post –MI/Clinical CAD	ACEI/ARB AND BB
CAD	ACEI, BB, diuretic, CCB
Diabetes	ACEI/ARB, CCB, diuretic
CKD	ACEI/ARB
Recurrent stroke prevention	ACEI, diuretic
Pregnancy	labetolol (first line), nifedipine, methyldopa

Beta-1 Selective Beta-blockers – possibly safer in patients with COPD, asthma, diabetes, and peripheral vascular disease:

- metoprolol
- bisoprolol
- betaxolol
- acebutolol

Drug Class	Agents of Choice	Comments
Diuretics	HCTZ 12.5-50mg, chlorthalidone 12.5-25mg, indapamide 1.25-2.5mg triamterene 100mg *K+ sparing* – spironolactone 25-50mg, amiloride 5-10mg, triamterene 100mg furosemide 20-80mg twice daily, torsemide 10-40mg	Monitor for hypokalemia Most SE are metabolic in nature Most effective when combined w/ ACEI Stronger clinical evidence w/chlorthalidone Spironolactone - gynecomastia and hyperkalemia Loop diuretics may be needed when GFR <40mL/min
ACEI/ARB	*ACEI:* lisinopril, benazapril, fosinopril and quinapril 10-40mg, ramipril 5-10mg, trandolapril 2-8mg *ARB*: candesartan 8-32mg, valsartan 80-320mg, losartan 50-100mg, olmesartan 20-40mg, telmisartan 20-80mg	SE: Cough (ACEI only), angioedema (more with ACEI), hyperkalemia Losartan lowers uric acid levels; candesartan may prevent migraine headaches
Beta-Blockers	metoprolol succinate 50-100mg and tartrate 50-100mg twice daily, nebivolol 5-10mg, propranolol 40-120mg twice daily, carvedilol 6.25-25mg twice daily, bisoprolol 5-10mg, labetalol 100-300mg twice daily,	Not first line agents – reserve for post-MI/CHF Cause fatigue and decreased heart rate Adversely affect glucose; mask hypoglycemic awareness
Calcium channel blockers	*Dihydropyridines*: amlodipine 5-10mg, nifedipine ER 30-90mg, *Non-dihydropyridines*: diltiazem ER 180-360 mg, verapamil 80-120mg 3 times daily or ER 240-480mg	Cause edema; dihydropyridines may be safely combined w/ B-blocker Non-dihydropyridines reduce heart rate and proteinuria
Vasodilators	hydralazine 25-100mg twice daily, minoxidil 5-10mg terazosin 1-5mg, doxazosin 1-4mg given at bedtime	Hydralazine and minoxidil may cause reflex tachycardia and fluid retention – usually require diuretic + B-blocker Alpha-blockers may cause orthostatic hypotension
Centrally-acting Agents	clonidine 0.1-0.2mg twice daily, methyldopa 250-500mg twice daily guanfacine 1-3mg	Clonidine available in weekly patch formulation for resistant hypertension

2017 shake up

SPRINT , CLARIFY and HOPE 3

ORLANDO HEALTH®

Original Article

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group

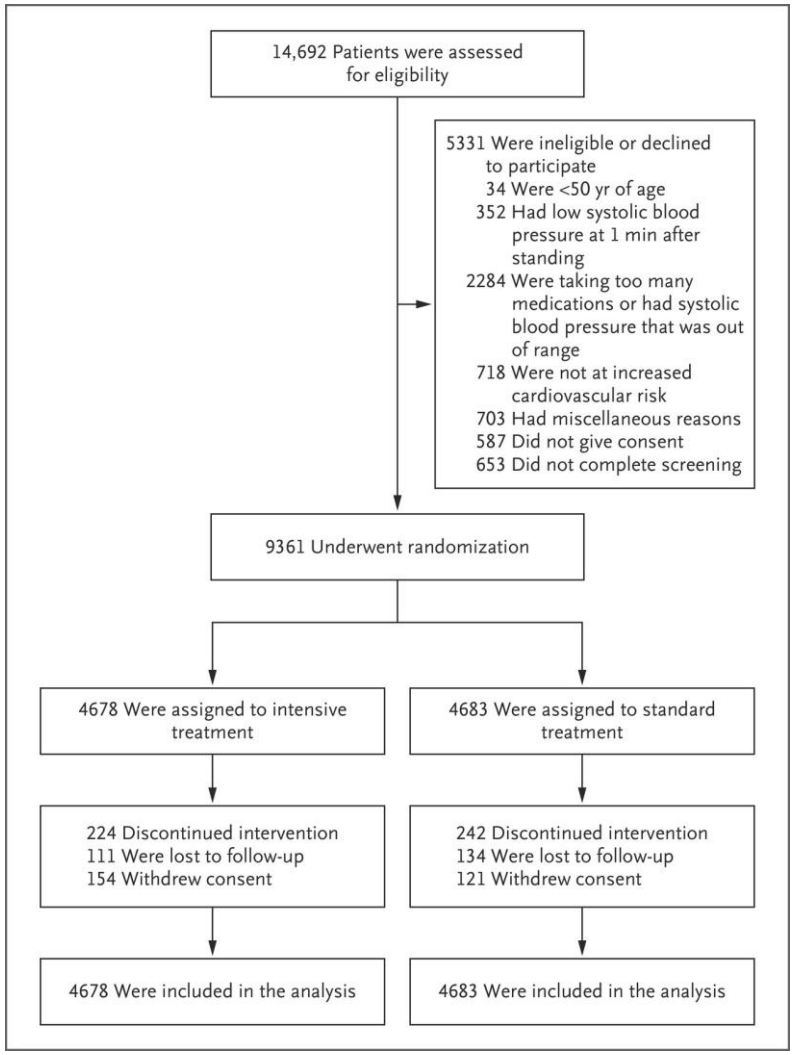
N Engl J Med
Volume 373(22):2103-2116
November 26, 2015

The NEW ENGLAND JOURNAL of MEDICINE

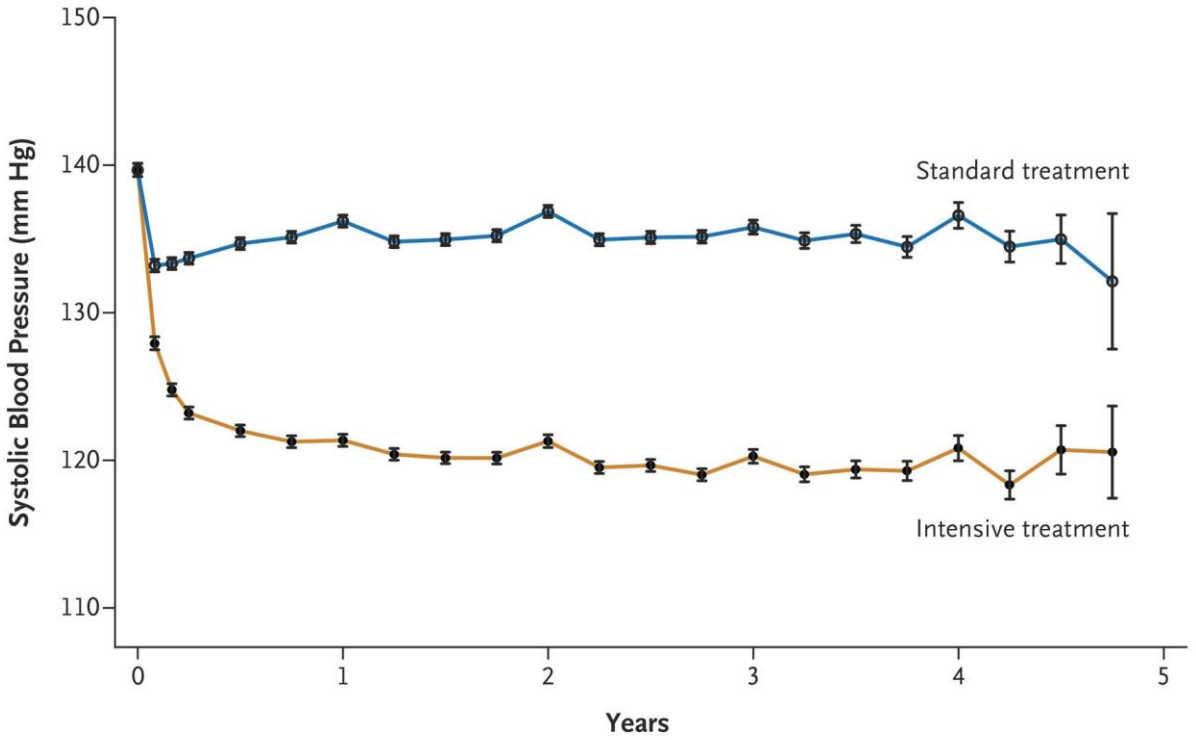
Study Overview

- Patients at increased cardiovascular risk but without diabetes were assigned to intensive treatment of systolic BP (target, <120 mm Hg) or standard treatment (target, <140 mm Hg).
- After a median of 3.26 years, the rate of cardiovascular events was significantly lower with intensive treatment.

Eligibility, Randomization, and Follow-up.

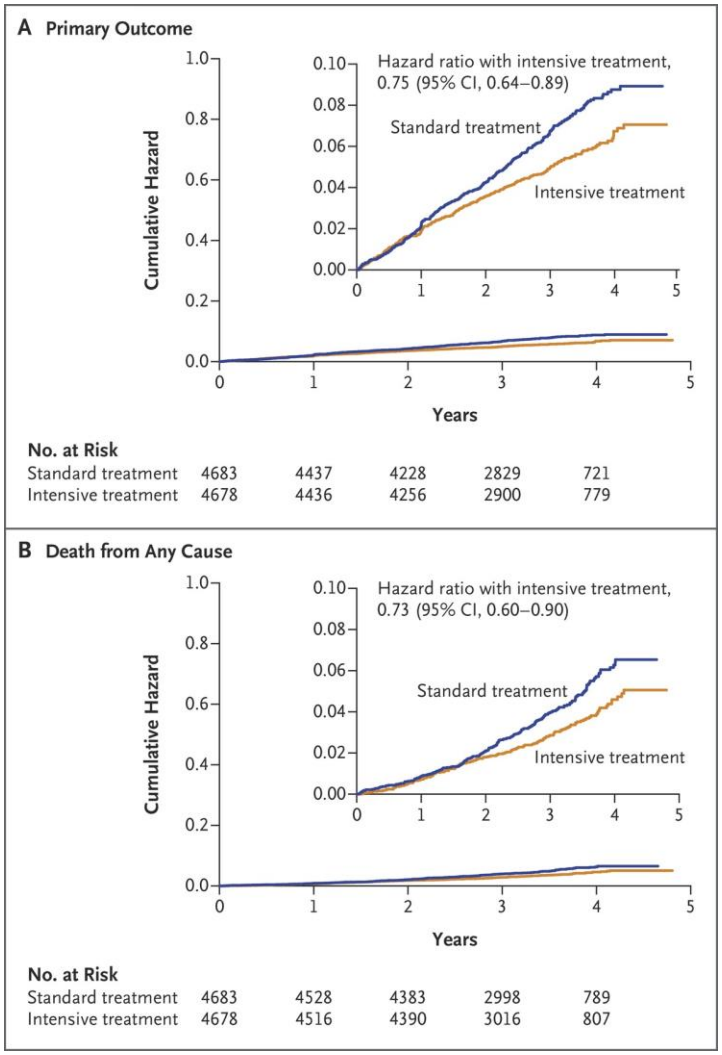


Systolic Blood Pressure in the Two Treatment Groups over the Course of the Trial.



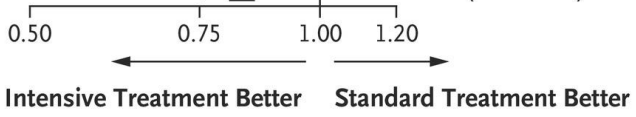
No. with Data										
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286
Mean No. of Medications										
Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8	3.0

Primary Outcome and Death from Any Cause.



Forest Plot of Primary Outcome According to Subgroups.

Subgroup	Intensive Treatment	Standard Treatment	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with primary outcome/total no. (%)			
Overall	243/4678 (5.2)	319/4683 (6.8)	0.75 (0.64–0.89)	
Previous CKD				0.36
No	135/3348 (4.0)	193/3367 (5.7)	0.70 (0.56–0.87)	
Yes	108/1330 (8.1)	126/1316 (9.6)	0.82 (0.63–1.07)	
Age				0.32
<75 yr	142/3361 (4.2)	175/3364 (5.2)	0.80 (0.64–1.00)	
≥75 yr	101/1317 (7.7)	144/1319 (10.9)	0.67 (0.51–0.86)	
Sex				0.45
Female	77/1684 (4.6)	89/1648 (5.4)	0.84 (0.62–1.14)	
Male	166/2994 (5.5)	230/3035 (7.6)	0.72 (0.59–0.88)	
Race				0.83
Black	62/1454 (4.3)	85/1493 (5.7)	0.77 (0.55–1.06)	
Nonblack	181/3224 (5.6)	234/3190 (7.3)	0.74 (0.61–0.90)	
Previous cardiovascular disease				0.39
No	149/3738 (4.0)	208/3746 (5.6)	0.71 (0.57–0.88)	
Yes	94/940 (10.0)	111/937 (11.8)	0.83 (0.62–1.09)	
Systolic blood pressure				0.77
≤132 mm Hg	71/1583 (4.5)	98/1553 (6.3)	0.70 (0.51–0.95)	
>132 to <145 mm Hg	77/1489 (5.2)	106/1549 (6.8)	0.77 (0.57–1.03)	
≥145 mm Hg	95/1606 (5.9)	115/1581 (7.3)	0.83 (0.63–1.09)	



Primary and Secondary Outcomes and Renal Outcomes.

Table 2. Primary and Secondary Outcomes and Renal Outcomes.*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per year*	*no. of patients (%)*	*% per year*		
All participants	**(N=4678)**		**(N=4683)**			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005
Death from any cause	155 (3.3)	1.03	210 (4.5)	1.40	0.73 (0.60–0.90)	0.003
Primary outcome or death	332 (7.1)	2.25	423 (9.0)	2.90	0.78 (0.67–0.90)	<0.001
Participants with CKD at baseline	**(N=1330)**		**(N=1316)**			
Composite renal outcome‡	14 (1.1)	0.33	15 (1.1)	0.36	0.89 (0.42–1.87)	0.76
≥50% reduction in estimated GFR§	10 (0.8)	0.23	11 (0.8)	0.26	0.87 (0.36–2.07)	0.75
Long-term dialysis	6 (0.5)	0.14	10 (0.8)	0.24	0.57 (0.19–1.54)	0.27
Kidney transplantation	0		0			
Incident albuminuria¶	49/526 (9.3)	3.02	59/500 (11.8)	3.90	0.72 (0.48–1.07)	0.11
Participants without CKD at baseline‖	**(N=3332)**		**(N=3345)**			
≥30% reduction in estimated GFR to <60 ml/min/1.73 m^2§	127 (3.8)	1.21	37 (1.1)	0.35	3.49 (2.44–5.10)	<0.001
Incident albuminuria¶	110/1769 (6.2)	2.00	135/1831 (7.4)	2.41	0.81 (0.63–1.04)	0.10

* CI denotes confidence interval, and CKD chronic kidney disease.
† The primary outcome was the first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes.
‡ The composite renal outcome for participants with CKD at baseline was the first occurrence of a reduction in the estimated GFR of 50% or more, long-term dialysis, or kidney transplantation.
§ Reductions in the estimated GFR were confirmed by a second laboratory test at least 90 days later.
¶ Incident albuminuria was defined by a doubling of the ratio of urinary albumin (in milligrams) to creatinine (in grams) from less than 10 at baseline to greater than 10 during follow-up. The denominators for number of patients represent those without albuminuria at baseline.
‖ No long-term dialysis or kidney transplantation was reported among participants without CKD at baseline.

Serious Adverse Events, Conditions of Interest, and Monitored Clinical Events.

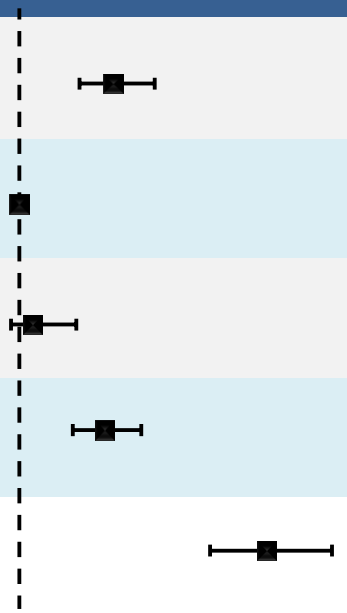
Variable	Intensive Treatment (N=4678)	Standard Treatment (N=4683)	Hazard Ratio	P Value
	no. of patients (%)			
Serious adverse event*	1793 (38.3)	1736 (37.1)	1.04	0.25
Conditions of interest				
Serious adverse event only				
Hypotension	110 (2.4)	66 (1.4)	1.67	0.001
Syncope	107 (2.3)	80 (1.7)	1.33	0.05
Bradycardia	87 (1.9)	73 (1.6)	1.19	0.28
Electrolyte abnormality	144 (3.1)	107 (2.3)	1.35	0.02
Injurious fall†	105 (2.2)	110 (2.3)	0.95	0.71
Acute kidney injury or acute renal failure‡	193 (4.1)	117 (2.5)	1.66	<0.001
Emergency department visit or serious adverse event				
Hypotension	158 (3.4)	93 (2.0)	1.70	<0.001
Syncope	163 (3.5)	113 (2.4)	1.44	0.003
Bradycardia	104 (2.2)	83 (1.8)	1.25	0.13
Electrolyte abnormality	177 (3.8)	129 (2.8)	1.38	0.006
Injurious fall†	334 (7.1)	332 (7.1)	1.00	0.97
Acute kidney injury or acute renal failure‡	204 (4.4)	120 (2.6)	1.71	<0.001
Monitored clinical events				
Adverse laboratory measure§				
Serum sodium <130 mmol/liter	180 (3.8)	100 (2.1)	1.76	<0.001
Serum sodium >150 mmol/liter	6 (0.1)	0		0.02
Serum potassium <3.0 mmol/liter	114 (2.4)	74 (1.6)	1.50	0.006
Serum potassium >5.5 mmol/liter	176 (3.8)	171 (3.7)	1.00	0.97
Orthostatic hypotension¶				
Alone	777 (16.6)	857 (18.3)	0.88	0.01
With dizziness	62 (1.3)	71 (1.5)	0.85	0.35

Conclusions

- Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group.

CLARIFY: Primary Outcome* According to Achieved Systolic BP in Patients with Stable Coronary Disease

Systolic Blood Pressure (BP) Range	Outcome by Blood Pressure Level [n/N (%)]	Hazard Ratio (95% CI)	*p*-Value
<120 mmHg	323/2687 (12.0%)	1.56 (1.36, 1.81)	<0.0001
120-129 mmHg	490/6938 (7.1%)	1.00 (-)	Reference
130-139 mmHg	584/7578 (7.7%)	1.08 (0.95, 1.21)	0.2368
140-149 mmHg	386/3577 (10.8%)	1.51 (1.32, 1.73)	<0.0001
≥150 mmHg	316/1859 (17.0%)	2.48 (2.14, 2.87)	<0.0001



* Primary Outcome = CV death or non-fatal MI or stroke

Vidal-Petiot E, et al. *Lancet.* 2016 Aug 26.

Original Article

Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Eva M. Lonn, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Lisheng Liu, M.D., Prem Pais, M.D., Rafael Diaz, M.D., Denis Xavier, M.D., Karen Sliwa, M.D., Ph.D., Antonio Dans, M.D., Alvaro Avezum, M.D., Ph.D., Leopoldo S. Piegas, M.D., Ph.D., Katalin Keltai, M.D., Ph.D., Matyas Keltai, M.D., Ph.D., Irina Chazova, M.D., Ph.D., Ron J.G. Peters, M.D., Ph.D., Claes Held, M.D., Ph.D., Khalid Yusoff, M.D., Basil S. Lewis, M.D., Petr Jansky, M.D., Alexander Parkhomenko, M.D., Ph.D., Kamlesh Khunti, M.D., Ph.D., William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.Sc., Lawrence A. Leiter, M.D., Dora I. Molina, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D., Joanne Wilkinson, B.A., Hyejung Jung, M.Sc., Gilles Dagenais, M.D., Salim Yusuf, M.B., B.S., D.Phil., for the HOPE-3 Investigators

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Study Overview

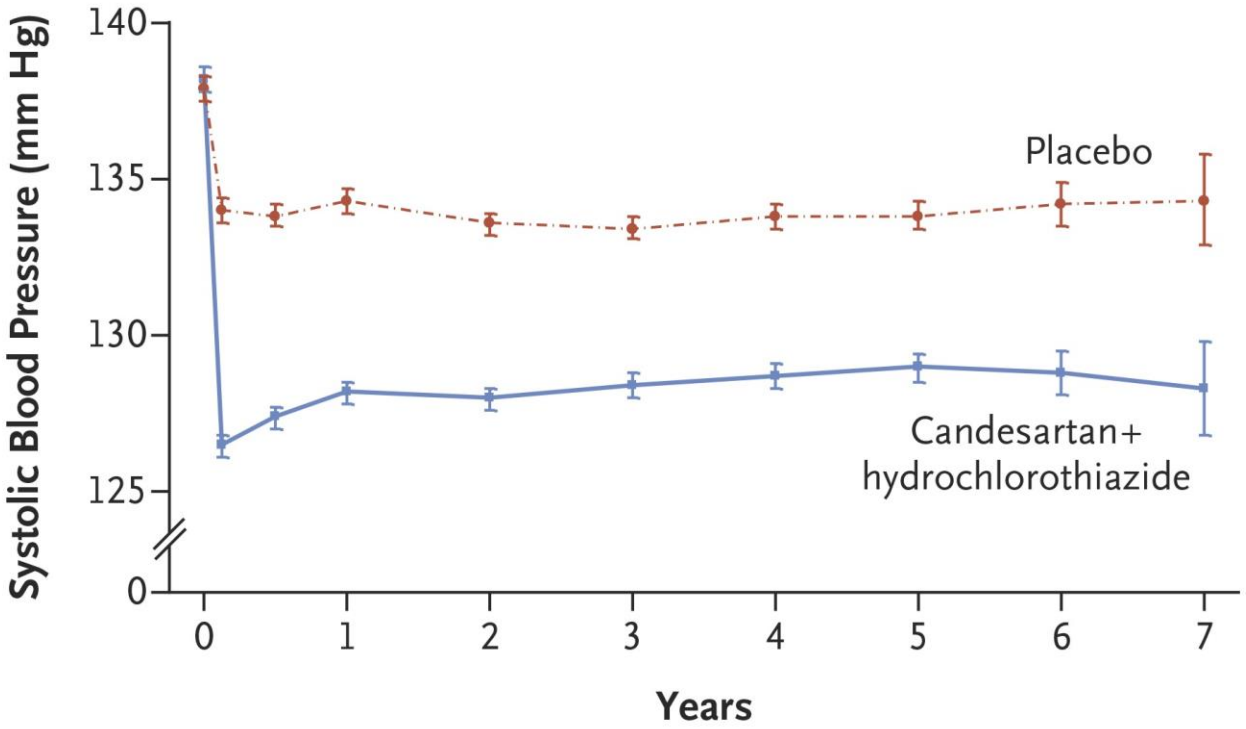
- In one comparison from a 2-by-2 factorial trial, over 12,000 participants with a mean baseline blood pressure of 138/82 mm Hg were assigned to candesartan plus hydrochlorothiazide or to placebo.
- At 5.6 years, there was no between-group difference in the rates of cardiovascular events.

HOPE-3 Patients (Unlike SPRINT, Low CV Risk)

- **Excluded** if previous cardiovascular history
- **Included** if men aged ≥55, women aged ≥65, PLUS at least one of the following:
  - increased waist hip ratio
  - low HDL cholesterol
  - tobacco use (now or previously)
  - dysglycemia
  - family history premature cv disease
  - mild renal dysfunction

NOTE: Hypertension NOT a requirement for study enrollment

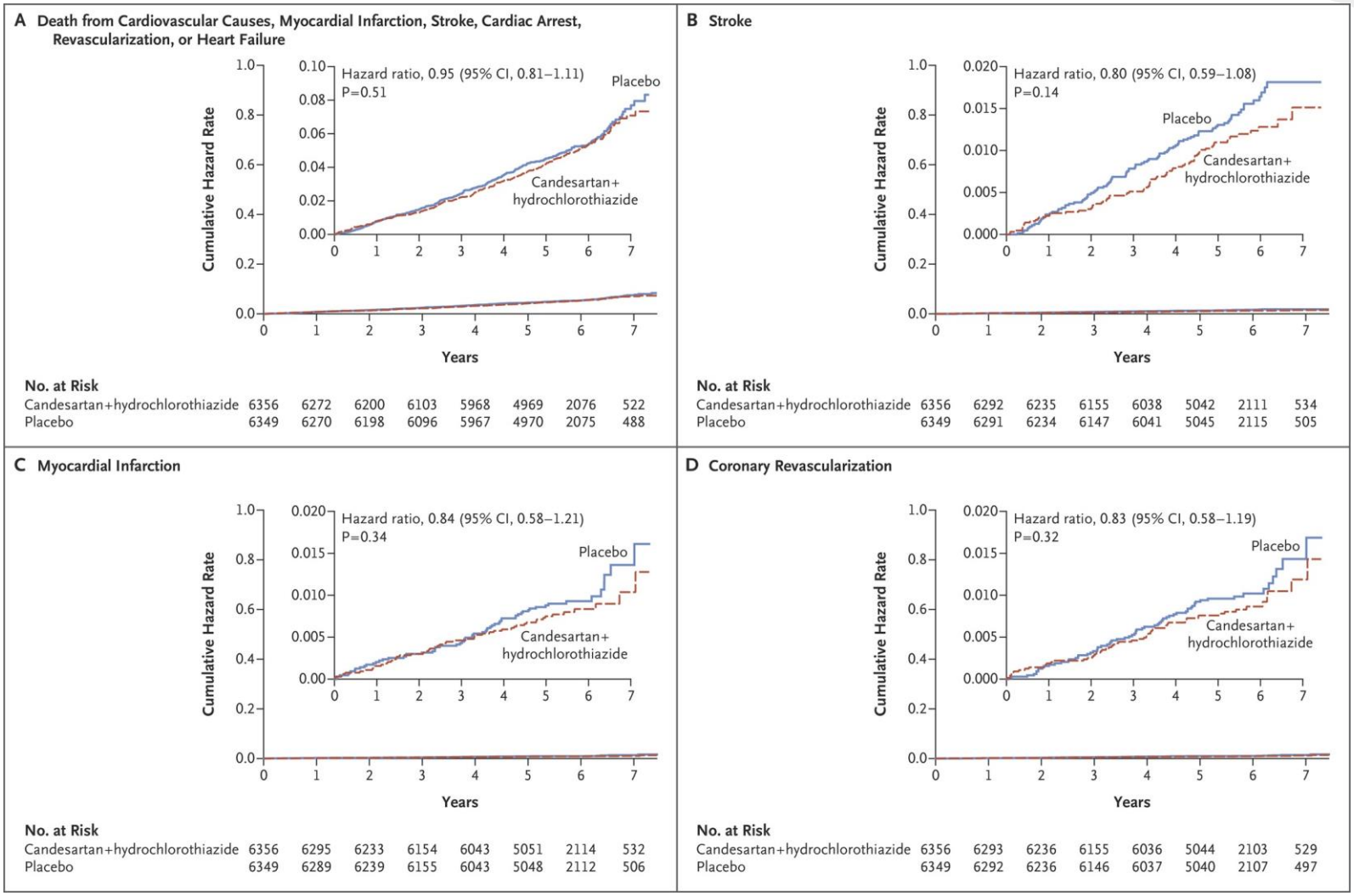
Systolic Blood Pressure over the Course of the Trial, According to Trial Group.



No. at Risk

Candesartan+hydrochlorothiazide	6356	5907	5667	5446	5213	3862	1437	350
Placebo	6347	5879	5623	5442	5186	3822	1424	334

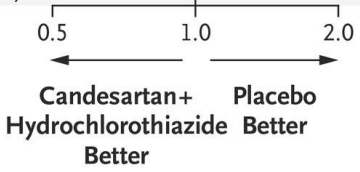
Cumulative Incidence of Major Cardiovascular Events, According to Trial Group.



Forest Plots, According to Subgroup of Systolic Blood Pressure for the Coprimary Outcomes.

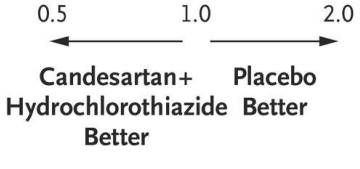
A First Coprimary Outcome

Subgroup	Mean Systolic Blood Pressure	Difference in Blood Pressure	Candesartan+ Hydrochlorothiazide	Placebo	Hazard Ratio (95% CI)	P Value for Trend
	mm Hg		*no. of events/total no. of participants (%)*			
Overall	138.1	6.0/3.0	260/6356 (4.1)	279/6349 (4.4)	0.93 (0.79–1.10)	—
Systolic blood pressure						0.02
≤131.5 mm Hg	122.2	6.1/3.1	70/2080 (3.4)	62/2122 (2.9)	1.16 (0.82–1.63)	
131.6–143.5 mm Hg	137.6	5.6/2.7	87/2120 (4.1)	81/2141 (3.8)	1.08 (0.80–1.46)	
>143.5 mm Hg	154.1	5.8/3.0	103/2156 (4.8)	136/2084 (6.5)	0.73 (0.56–0.94)	



B Second Coprimary Outcome

Subgroup	Mean Systolic Blood Pressure	Difference in Blood Pressure	Candesartan+ Hydrochlorothiazide	Placebo	Hazard Ratio (95% CI)	P Value for Trend
	mm Hg		*no. of events/total no. of participants (%)*			
Overall	138.1	6.0/3.0	312/6356 (4.9)	328/6349 (5.2)	0.95 (0.81–1.11)	—
Systolic blood pressure						0.009
≤131.5 mm Hg	122.2	6.1/3.1	90/2080 (4.3)	74/2122 (3.5)	1.25 (0.92–1.70)	
131.6–143.5 mm Hg	137.6	5.6/2.7	99/2120 (4.7)	98/2141 (4.6)	1.02 (0.77–1.34)	
>143.5 mm Hg	154.1	5.8/3.0	123/2156 (5.7)	156/2084 (7.5)	0.76 (0.60–0.96)	



Conclusions

- Therapy with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day was not associated with a lower rate of major cardiovascular events than placebo among persons at intermediate risk who did not have cardiovascular disease.

2017 Recommendations:

- **NON DIABETICS:** Medium to high CV risk - target should be <130 mmHg. [SPRINT, ACCOMPLISH, VALUE]
  - Note: Includes older patients, but be cautious and monitor renal function [SPRINT].
- **DIABETICS:** the target should be <140 mmHg (OK if close to 130 mmHg). [ACCORD, Brunstrom, ACCOMPLISH]
- **LOW CV RISK PATIENTS:** target is <140 mmHg [HOPE-3]