JNC 8 Hypertension Guidelines and the Blood Pressure Limbo

How ~~Low~~ High Should You Go? LOW

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Disclosures: none

UCSF

Question #1

A 55 yo white woman with a history of HTN and CAD presents to your clinic for the first time. Her blood pressure is 157/95. You start her on HCTZ 25 mg qd and ask that she return in 1 week for a BP check.

What is her BP goal?

A) 150/90
B) 140/90
C) 130/85
D) 120/80

Question #2

An 84 yo man without a past medical history returns to your clinic with a recurrent BP of 142/94, confirmed on several checks. He is not taking any medications.

How many would start him on BP medication?

A) Yes
B) No

Question #3

A 66 yo black man with HTN presents to your office for the first time. His BP is 174/99.

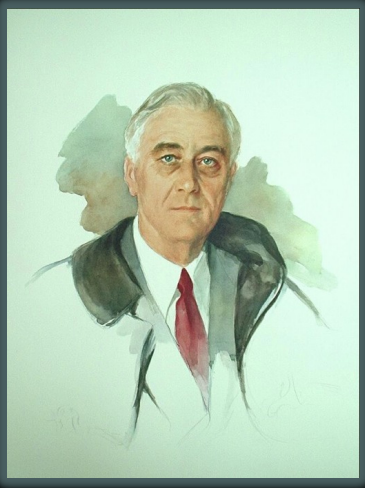
Which of the following regimen is the least preferred option to start?

A) HCTZ 25 mg qd
B) Chlorthalidone 25 mg qd
C) Amlodipine 10 mg qd
D) Lisinopril 20 mg qd

Outline

- Review historical controversy in the treatment of hypertension
- Discuss JNC 8 guidelines and the evidence used to construct recommendations
- Assess impact of recent clinical trial data on JNC 8 and hypertension management

Historical controversy in treatment of hypertension



April 12, 1945 300/190

Historical controversy in treatment of hypertension

"The greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try to reduce it."

– J.H. Hay, British Med J, 1931

"Hypertension may be an important compensatory mechanism which should not be tampered with, even were it certain that we could control it."

– Paul Dudley White, 1937

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

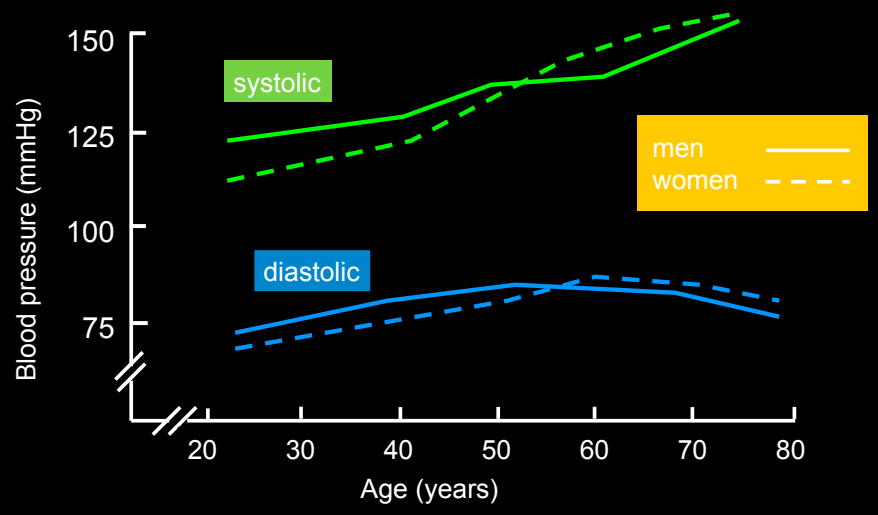
– Friedberg, Disease of the Heart, 1946

Current health burden of hypertension

- 70 million Americans and more than 1 billion people world wide have hypertension
- 7 million deaths per year attributed to HTN
- Uncontrolled HTN is the greatest contributor to stroke and ischemic heart disease
- Number one reason listed for office visits

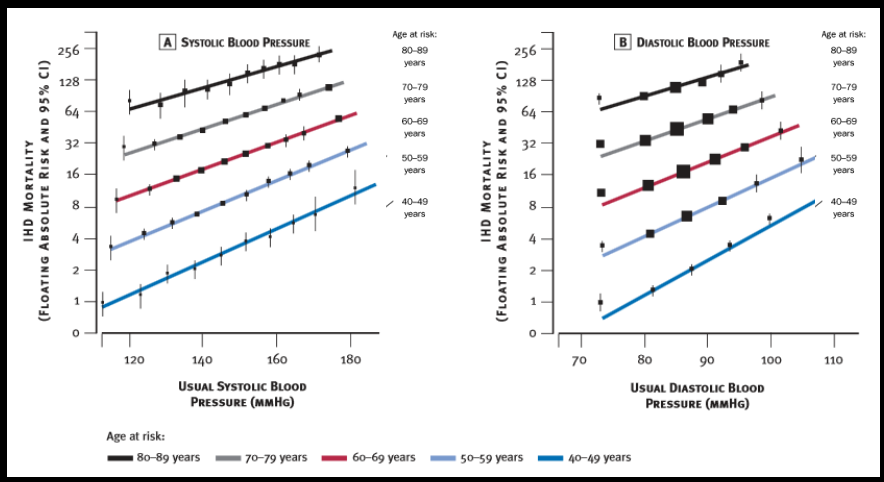
Hajjar et al. JAMA 2003. World Health Report WHO 2002. Burt el al. Hypertension 1995.

Age related changes in blood pressure



Burt el al. Hypertension 1995.

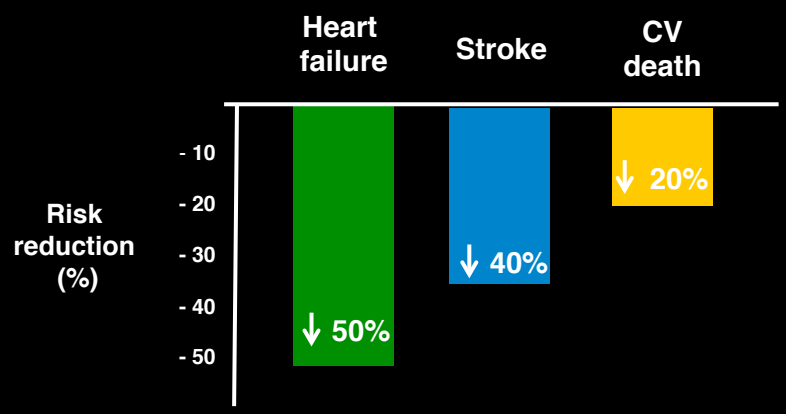
Blood pressure predicts CV mortality



Meta-analysis of 61 population studies including 958,074 adults.

Prospective Studies Collaboration. Lancet 2002.

CV benefits of treating HTN from RCTs



Hebert et al. Archives Int Med 1993.

2003 JNC 7 HTN treatment algorithm

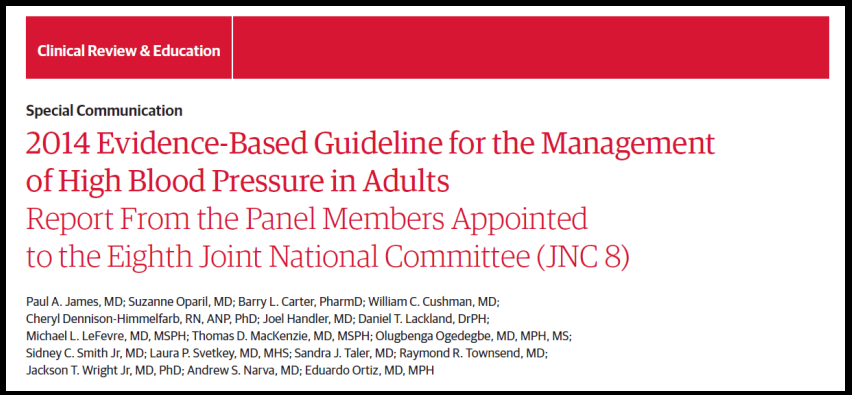
Lifestyle modifications		
Goal blood pressure < 140/90 mmHg <130/80 mmHg with diabetes or CKD		
Initial drug choices		
Without compelling indications		With compelling indications
Stage 1 HTN SBP 140-159 DBP 90-99	Stage 2 HTN SBP > 160 DBP > 100	Drug(s) for compelling indications
Diuretics; consider ACEi, ARB, BB, CCB	2 drug combo diuretic, ACEi, ARB, BB, CCB	Diuretics, ACE-I, ARB, BB, CCB as needed

JNC 7. JAMA 2003.

Evolution of classification of hypertension

	SBP (mmHg)	DBP (mmHg)
JNC 1, 2 (1977, 1980)		≥ 105
JNC 3 (1984)	≥ 160	90-104 mild 105-114 moderate ≥ 115 severe
JNC 6 (1997)	140-159 stage I 160-179 stage II ≥ 180 stage III	90-99 stage I 100-109 stage II ≥ 109 stage III
JNC 7 (2003)	120-140 pre-HTN 140-159 stage I ≥ 160 stage II	90-99 stage I ≥ 100 stage II

JNC 8



James et al. JAMA 2014.

JNC 8 restricted to answering 3 questions

- Does starting drugs at specific BP thresholds improve outcomes?
- Does titrating drugs to a specific BP goal improve outcome?
- Do various BP drugs or drug classes differ in benefits and harms on specific outcome?

9 evidence-based recommendations

James et al. JAMA 2014.

Strength of the 9 JNC 8 recommendations

Grade	Strength of recommendation	JNC 8
A	Strong Recommendation - high certainty that benefit is substantial	2
B	Moderate Recommendation - moderate certainty benefit is moderate to substantial or there is high certainty that benefit is moderate	2
C	Weak Recommendation - moderate certainty that there is a small benefit	1
D	Recommendation against - No benefit or that risks/harms outweigh benefits	0
E	Expert Opinion	4
N	No Recommendation for or against	0

James et al. JAMA 2014.

Recommendation #1: patients ≥ 60 years old

Group	Start	Goal	Level of evidence
≥ 60 years old	≥ 150/90 mmHg	< 150/90 mmHg	Strong evidence Grade A

HYVET trial: benefit of target < 150/90 in very elderly

ORIGINAL ARTICLE

Treatment of Hypertension in Patients 80 Years of Age or Older

Nigel S. Beckett, M.B., Ch.B., Ruth Peters, Ph.D., Astrid E. Fletcher, Ph.D., Jan A. Staessen, M.D., Ph.D., Lisheng Liu, M.D., Dan Dumitrascu, M.D., Vassil Stoyanovsky, M.D., Riitta L. Antikainen, M.D., Ph.D., Yuri Nikitin, M.D., Craig Anderson, M.D., Ph.D., Alli Belhani, M.D., Françoise Forette, M.D., Chakravarthi Rajkumar, M.D., Ph.D., Lutgarde Thijs, M.Sc., Winston Banya, M.Sc., and Christopher J. Bulpitt, M.D. for the HYVET Study Group

3,845 patients ≥ 80 years with SBP ≥ 160 mmHg

Indapamide diuretic 1.5 mg daily ± perindopril 2-4 mg daily as needed

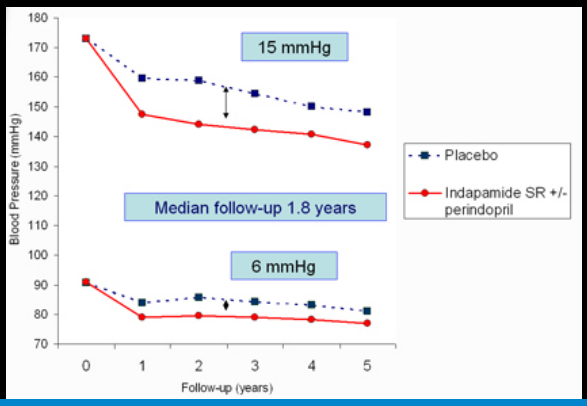
Placebo

Target blood pressure: 150/80

Primary endpoint: fatal and non-fatal strokes

Beckett et al. NEJM 2008

HYVET trial: benefit of HTN rx in the very elderly



OUTCOME: ↓ 34% CV events, 39% stroke death, 21% total mortality

Beckett et al. NEJM 2008

VALISH trial: no benefit of target < 140/90 in elderly

Target Blood Pressure for Treatment of Isolated Systolic Hypertension in the Elderly

Valsartan in Elderly Isolated Systolic Hypertension Study

3,260 patients 70-84 years old with SBP ≥ 160 mmHg

Strict Control	Moderate Control
SBP < 140 mmHg	SBP 140-150 mmHg

Rx: Valsartan + diuretic, CCB as needed

No difference in primary outcome of sudden death, CVA, MI, cardiac death, renal dysfunction

Ogihara et al. Hypertension 2010.

Recommendation #2, #3: patients < 60 years old

Group	Start	Goal	Level of evidence
< 60 years old	DBP ≥ 90 mmHg	< 90 mmHg	Strong evidence Grade A
< 60 years old	SBP ≥ 140 mmHg	< 140 mmHg	Expert opinion Grade E

James et al. JAMA 2014.

Recommendation #2, #3: patients < 60 years old

Effects of Treatment on Morbidity in Hypertension

II. Results in Patients With Diastolic Blood Pressure Averaging 90 Through 114 mm Hg

	Placebo N = 194	Active Rx N = 186
Stroke	20	5
Total coronary event	13	11
Fatal coronary event	11	6
CHF	11	0
Renal damage	3	0
Deaths	19	8

Active rx: HCTZ 50 mg/reserpine 0.1 mg bid, hydralazine 35-50 mg tid

VA Coop Study Group on Antihypertensive Agents. JAMA 1970.

Recommendation #4, #5: patients with CKD or DM

Group	Start	Goal	Level of evidence
CKD or DM	≥ 140/90 mmHg	< 140/90 mmHg	Expert opinion Grade E

JNC 7 recommended goal of < 130/80 for adults with CKD or DM

James et al. JAMA 2014.

MDRD trial: HTN rx in CKD

ORIGINAL ARTICLE

The Effects of Dietary Protein Restriction and Blood-Pressure Control on the Progression of Chronic Renal Disease

Saulo Klahr, Andrew S. Levey, Gerald J. Beck, Arlene W. Caggiula, Lawrence Hunsicker, John W. Kusek, and Gary Striker for the Modification of Diet in Renal Disease Study Group

1,585 patients with GFR 25-55

Low blood pressure
Goal MAP 92 (120/80)

Usual blood pressure
Goal MAP 107 (140/90)

Rx: ACEi plus diuretic or CCB as needed

Outcome: no difference in renal disease progression or cardiovascular mortality

Klahr et al. NEJM 1994

ACCORD Trial: HTN rx in DM


ORIGINAL ARTICLE

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

The ACCORD Study Group

4,773 patients with DM

Target SBP < 120 mmHg	Target SBP < 140 mmHg
Rx: all major classes of HTN therapies	
Mean SBP 119 mmHg	Mean SBP 133.5 mmHg

No difference in composite primary outcome: nonfatal MI, nonfatal stroke, or CV death

ACCORD Study Group. NEJM 2010

Recommendation #6: Rx in nonblack population

Group	Recommended treatment	Level of evidence
General nonblack population	Thiazide-type diuretic, CCB, ACEi, ARB	Moderate recommendation Grade B

James et al. JAMA 2014.

ALLHAT: Comparison of HTN regimens

Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic
The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) FREE

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group

33,357 patients with HTN and 1 other CVD risk factors

chlorthalidone 12.5 to 25 mg/d	amlodipine 2.5 to 10 mg/d	lisinopril 10 to 40 mg/d

Goal BP < 140/90

No difference in primary outcome combined fatal CHD or nonfatal MI

ALLHAT Study Group. JAMA 2002.

Recommendation #7: Rx in black population

Group	Recommended treatment	Level of evidence
Black population	Thiazide-type diuretic or CCB	Moderate recommendation Grade B

James et al. JAMA 2014.

ALLHAT: Increased risk of stroke and combined CVD events in Black subjects taking lisinopril*

Outcome	RR (95% CI) Black: Amlodipine	Black: Lisinopril	Nonblack: Amlodipine	Nonblack: Lisinopril
CHD	0.99 (0.82-1.19)	1.07 (0.90-1.28)	0.95 (0.85-1.08)	0.93 (0.83-1.05)
Mortality	0.97 (0.85-1.10)	1.07 (0.94-1.21)	0.93 (0.83-1.02)	0.96 (0.87-1.06)
Stroke	0.91 (0.72-1.15)	1.36 (1.10-1.68)	0.91 (0.76-1.10)	0.97 (0.81-1.17)
Combined CVD	1.03 (0.93-1.15)	1.17 (1.05-1.29)	1.01 (0.94-1.08)	1.04 (0.97-1.12)
Heart failure*				
First year	2.85 (1.75-4.66)	2.47 (1.49-4.10)	2.49 (1.68-3.68)	2.14 (1.43-3.20)
Beyond first year	1.23 (0.99-1.52)	1.13 (0.90-1.41)	1.16 (1.00-1.35)	1.01 (0.87-1.19)

Abbreviations: CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; RR, relative risk.
*The proportional hazards assumption was violated for the heart failure outcome.

**Amlodipine or lisinopril treatment compared to chlorthalidone.*

Wright et al. JAMA 2005

Recommendation #8: Rx in CKD

Group	Recommended treatment	Level of evidence
CKD	ACEi, ARB	Moderate recommendation Grade B

Applies to all CKD patients regardless of race or DM status

James et al. JAMA 2014.

Recommendation #8: Rx in CKD

Study	Pts	Design	RR CKD progression
Maschio et al. 1996	583	Benazapril vs. placebo	53%
Gisen et a. 1997	166	Ramampril vs. placebo	48%
Brenner et al. 2001	1513	Losartan vs. placebo	22%
Hou et al. 2006	224	Benazapril vs. placebo	43%

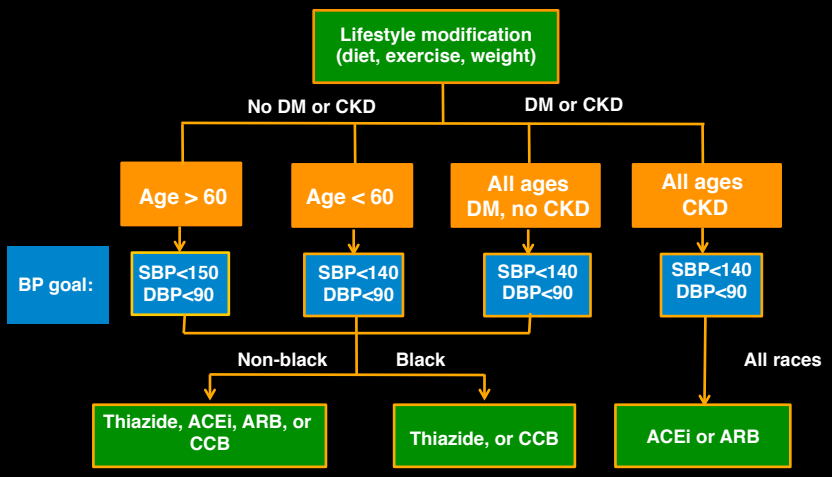
Observed benefit of ACE-i/ARB in reducing progression of renal dysfunction in patients with CKD with and without HTN.

Recommendation #9: Approach to HTN

Group	Recommended treatment	Level of evidence
ALL	If BP is not reached within a month, increase the dose or add a drug from one of the classes (thiazide-type diuretic, CCB, ACEI, or ARB). Do not use an ACEI and an ARB together. If goal BP cannot be reached using the recommended drugs, drugs from other classes can be used. Referral to a specialist may be indicated for patients in whom goal BP cannot be attained or for the complicated patient.	**Expert opinion Grade E**

James et al. JAMA 2014.

JNC 8 HTN treatment algorithm



James et al. JAMA 2014.

Important differences between guidelines

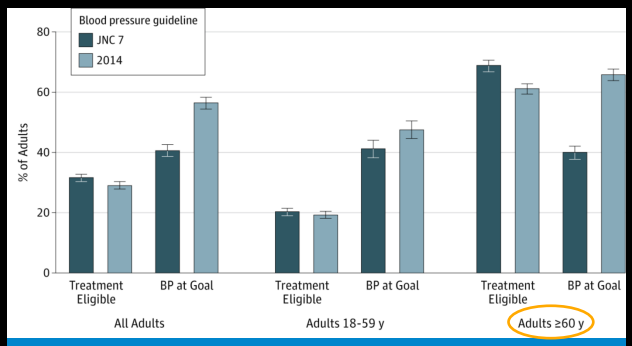
	JNC 7	JNC 8
Was it is evidence based?	Yes multiple sources, study designs	Yes only RCT data
Did it define HTN?	Yes	No
Did it provide treatment goals?	Separate goals for subsets with co-morbid conditions	Similar goals for all HTN populations; unless stated by evidence
What were the drug recommendations?	Thiazide as initial therapy; particular drug for compelling reasons	4 specific med classes based on RCT; specific meds based on race, CKD, DM
Were other topics addressed?	Yes measuring BP, resistant HTN, secondary HTN, compliance	No
Who reviewed the guidelines?	NHLBI, 39 professional societies	Expert reviewers; no official sponsorship by any organization

Comparing current HTN guidelines

	2014 JNC8	2014 ASH	2013 ESH/ESC
General BP goal	140/90	140/90	140/90
BP goal (elderly)	150/90 (>60 yrs)	150/90 (> 80 yrs)	150/90 (> 80 yrs)
BP goal DM	140/90		
BP goal CKD	140/90	140/90 130/90 w/ proteinuria	140/90 130/90 w/ proteinuria
Initial drug choice	Thiazide, ACEi/ ARB, CCB	ACEi/ARB > 60 yrs, CCB or thiazide > 60 yrs	Thiazide, ACEi/ARB, CCB, BB
BP rx – Blacks	CCB or thiazide	CCB or thiazide	

James et al. JAMA 2014.

Implications of 2014 JNC 8 in US



Decrease in number of treatment eligible adults and increases in those meeting BP goals under JNC 8

62% increase in adults ≥ 60 yo at BP goals

Navar-Boggan et al. JAMA 2014.

JNC 8 controversy

Annals of Internal Medicine | SPECIAL ARTICLE

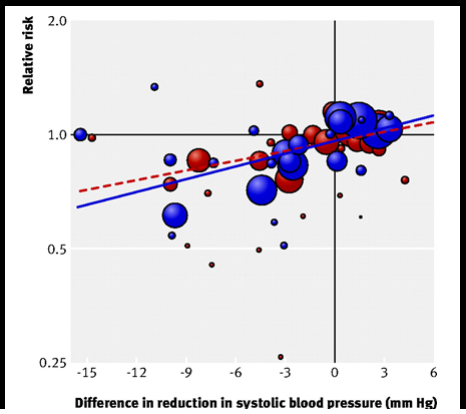
Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in Patients Aged 60 Years or Older: The Minority View

Jackson T. Wright Jr., MD, PhD; Lawrence J. Fine, MD, DrPH; Daniel T. Lackland, DrPH; Gbenga Ogedegbe, MD, MPH, MS; and Cheryl R. Dennison Himmelfarb, PhD, RN, ANP

guideline development (3). Although there was almost unanimous agreement on nearly all recommendations, a minority of the panel (the authors of this commentary) disagreed with the recommendation to increase the target systolic blood pressure (SBP) from 140 to 150 mm Hg in persons aged 60 years or older without diabetes mellitus (DM) or chronic kidney disease (CKD). This target

Wright et al. Ann Int Med 2014

Similar CV risk reduction with BP lowering in elderly



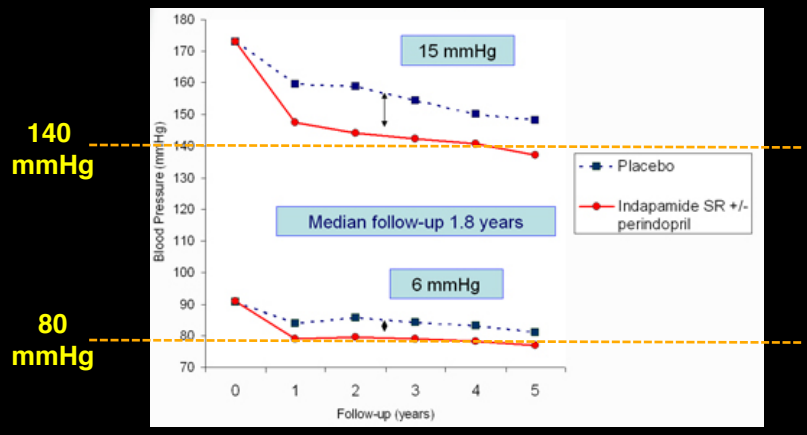
Reduction in risk for each 5 mm Hg reduction in systolic blood pressure:
Age <65: 11.9% (5.3% to 18.0%)
Age ≥65: 9.1% (3.6% to 14.3%)
P for heterogeneity of slopes = 0.38

Blood Pressure Lowering Treatment Trialists' Collaboration

- Meta-analysis of 31 trials with190,606 participants
- No difference in effects of lowering BP on CV events between age groups

Turnbull et al. BMJ 2008

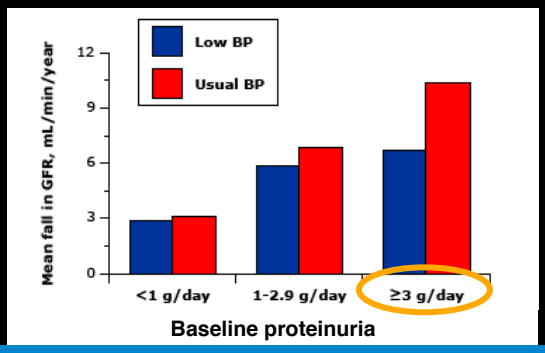
HYVET trial: benefit of HTN rx in the very elderly



In patients older than 80 years:
CV benefit seen with diuretic ± ACEi was seen with lowering BP to < 140/90

Beckett et al. NEJM 2008

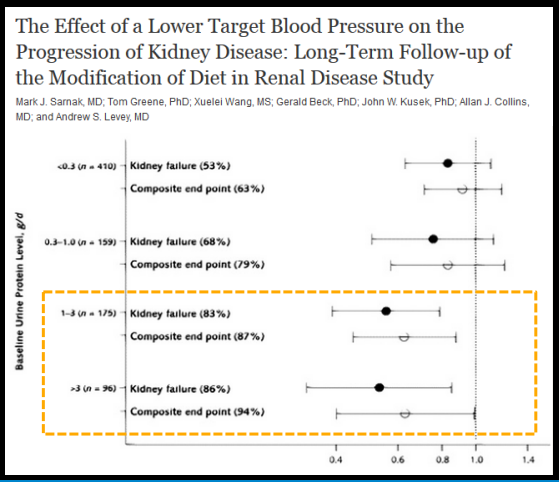
MDRD trial: benefit of aggressive BP rx in advanced CKD



Aggressive BP control (goal < 130/80) significantly reduced decline in GFR in patients with greater baseline proteinuria (> 3 g/d).

Khlar et al. NEJM 1994

MDRD trial: long-term benefit of aggressive BP rx in CKD



7 year follow-up: low BP group had significant reductions in progression to kidney failure in those with elevated levels of urine protein

Sarnak et al. Annals Int Medicine 2003.

SPRINT trial: benefit with more aggressive BP goal

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group

9,361 adults ≥ 50 years with SBP 130-180 mmHg and increased CVD risk*

- * ASCVD, CKD, Framingham > 15%, age > 75 yo
- Excluded: adults with prior CVA or DM

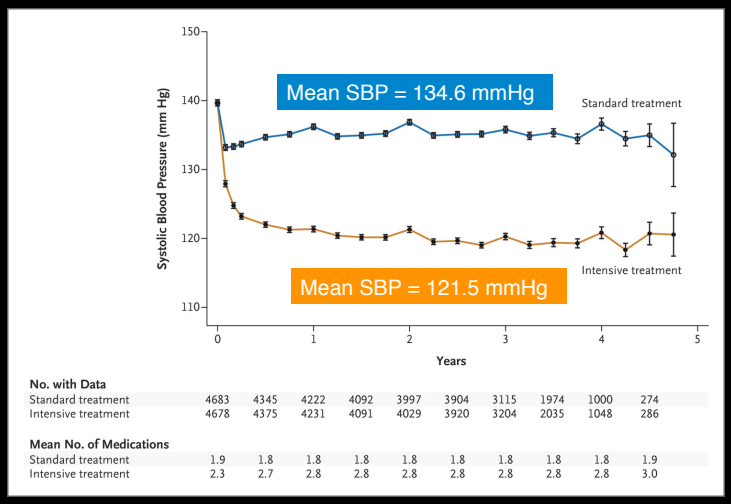
Intensive treatment	Standard treatment
SBP < 120 mmHg	SBP < 140 mmHg

Rx: Thiazide diuretic, ACEi, ARB, CCB

Endpoint: Nonfatal MI, stroke, or HF, and CV death

SPRINT Research Group. NEJM 2015

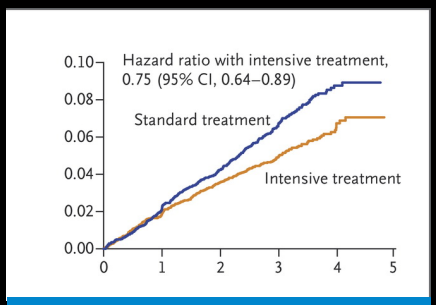
SPRINT trial: benefit with more aggressive BP goal



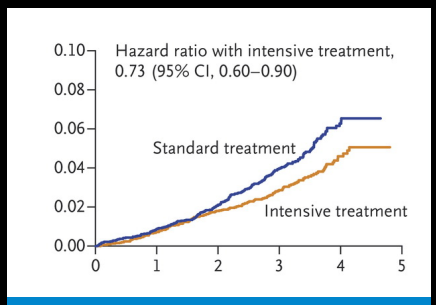
No. with Data										
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286
Mean No. of Medications										
Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8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

SPRINT Research Group. NEJM 2015

SPRINT trial: benefit with more aggressive BP goal



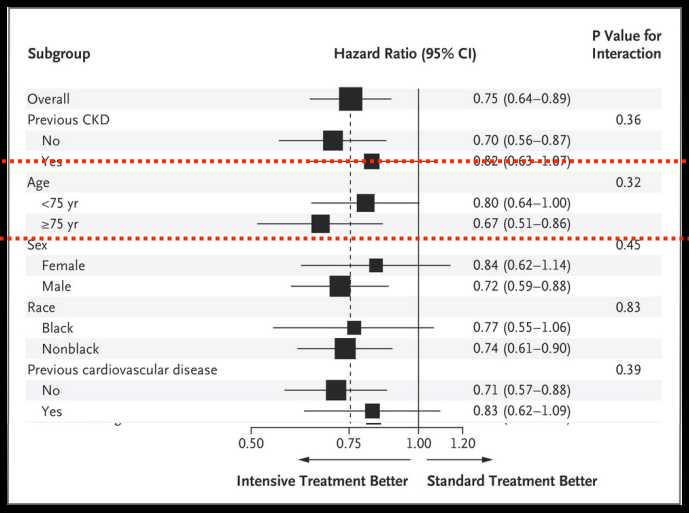
↓ 25% Primary outcome:
MI, ACS, CVA, HF, CV death
NNT = 61



↓ 27% all cause mortality
NNT = 90

SPRINT Research Group. NEJM 2015

SPRINT trial: benefit with more aggressive BP goal

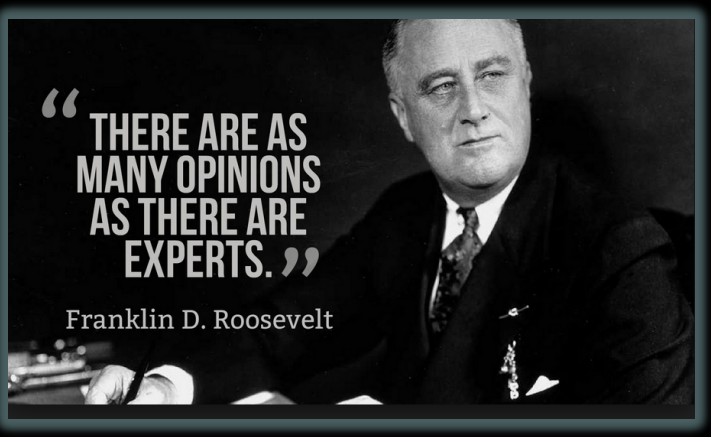


SPRINT Research Group. NEJM 2015

My take home points on HTN management

- Consider BP goal of < 140/90 for all adults, including those > 60 years old
- In those adults with increased CVD risk or advanced CKD, consider lower BP goal
- Thiazide diuretics, ACE-i/ARB, and CCB are equally effective in lowering BP and reducing CV risk in the general non-black population
- Tailor HTN treatment based upon proven therapies for specific comorbidities

Thank you.


“THERE ARE AS MANY OPINIONS AS THERE ARE EXPERTS.”
Franklin D. Roosevelt