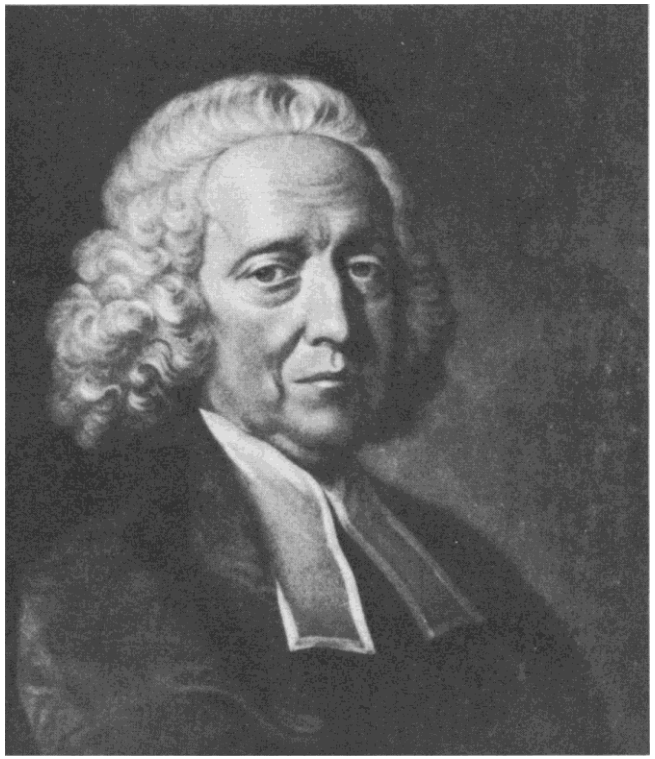
Hypertension in CKD: A Clinician's Guide to Treatment Targets

Csaba P Kovesdy, MD

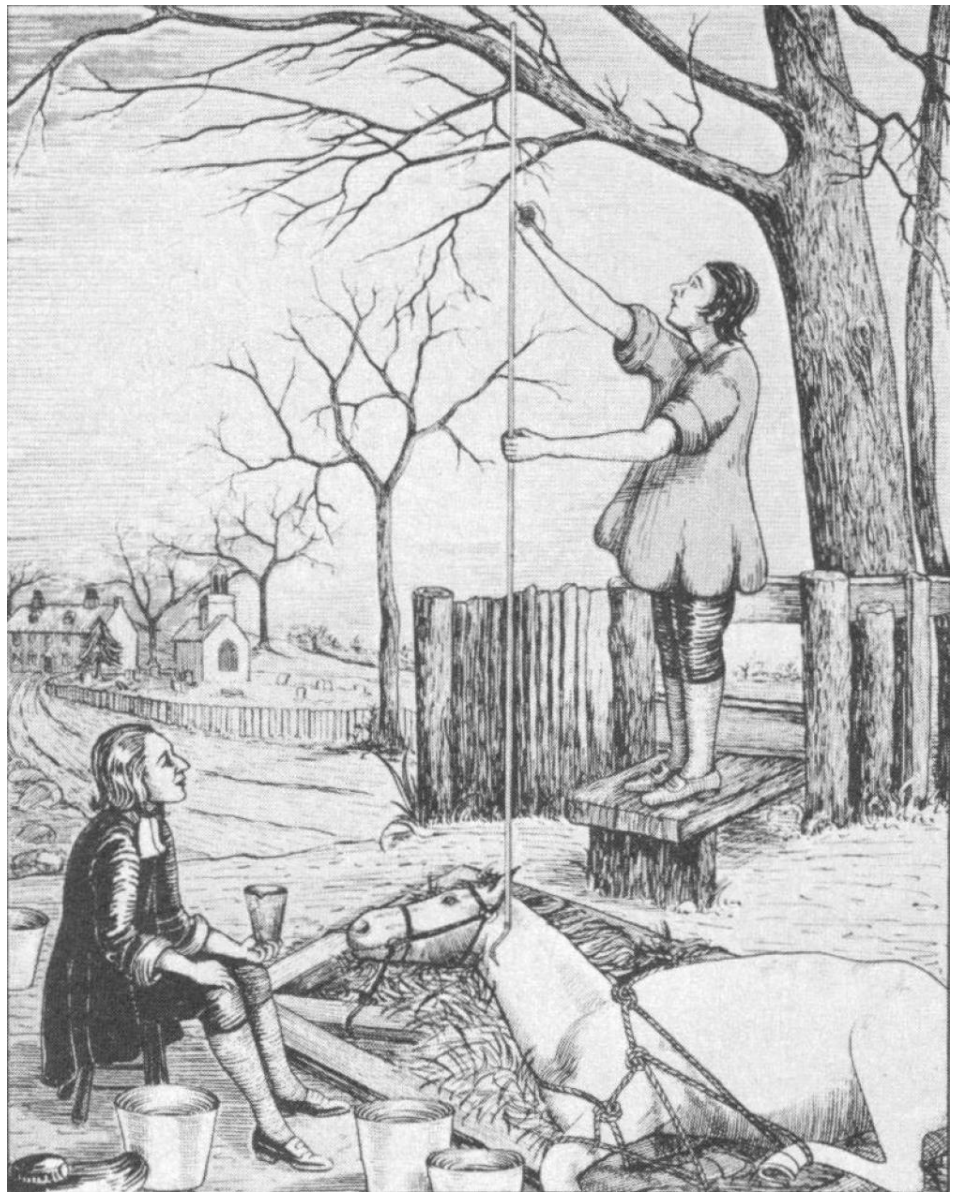
University of Tennessee Health Science Center, Memphis TN

Objectives

- Describe the prevalence and consequences of hypertension in the general population and in patients with chronic kidney disease
- Review the physiology and pathophysiology underlying the differences in hypertension characteristics in patients with and without chronic kidney disease
- Examine practical questions regarding hypertension treatment targets in patients with chronic kidney disease

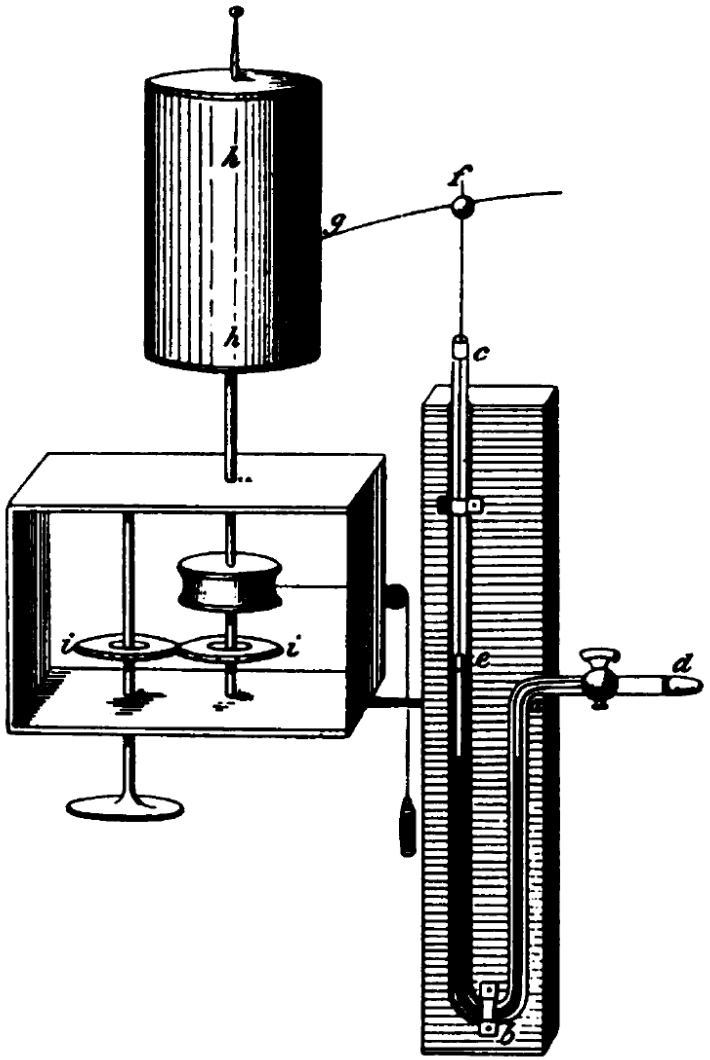


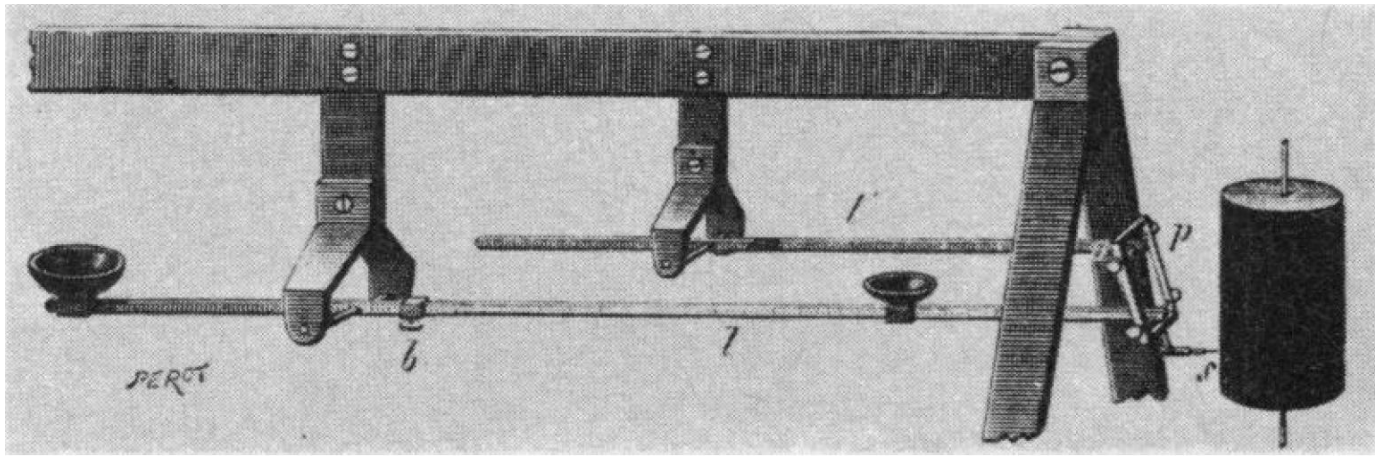
Stephen Hales (1677-1761)



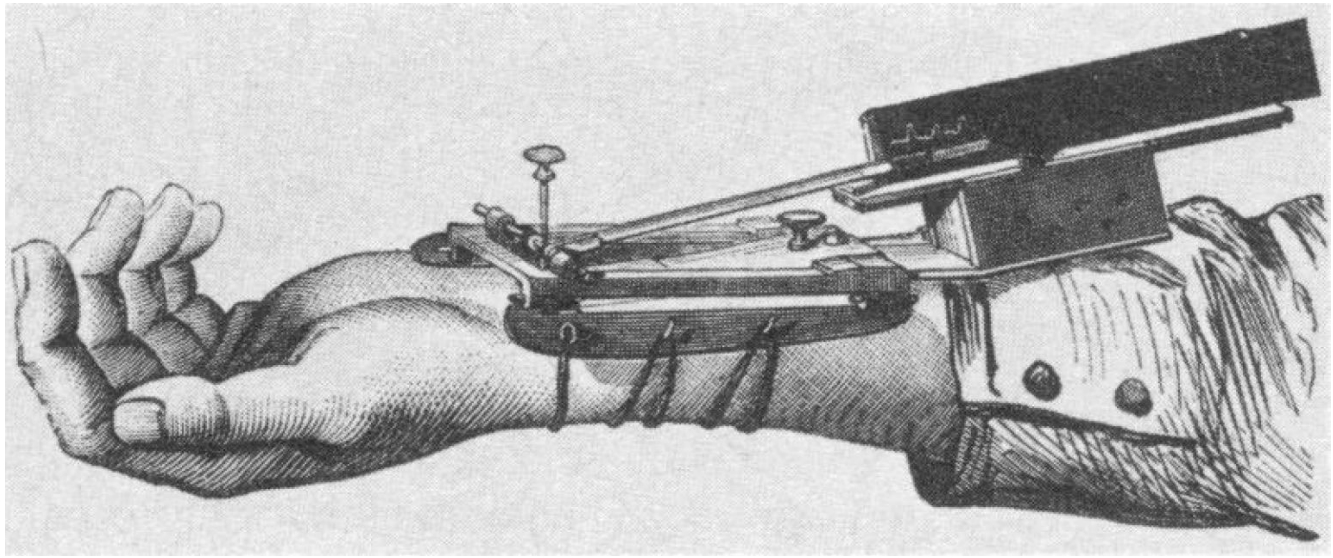
Booth J. *Proc Roy Soc Med*. 1977;70:793-799

Ludwig’s kymograph (1847)





Vierordt’s sphygmograph (1852)



Direct sphygmograph (Marey, cca 1881)

Booth J. *Proc Roy Soc Med*. 1977;70:793-799

History of BP measurement

- Scipione Riva-Rocci: Introduction of modern circumferential BP cuff (1896)
- Friedrich von Recklinghausen: Started using larger size cuff (1901)
- Nikolai Korotkov: Introduction of the auscultatory technique (1905)

Nikolai Sergeyevich Korotkov (1874-1920)

Booth J. *Proc Roy Soc Med*. 1977;70:793-799

'CAME OUT OF CLEAR SKY,' SAYS PRESIDENT'S PHYSICIAN

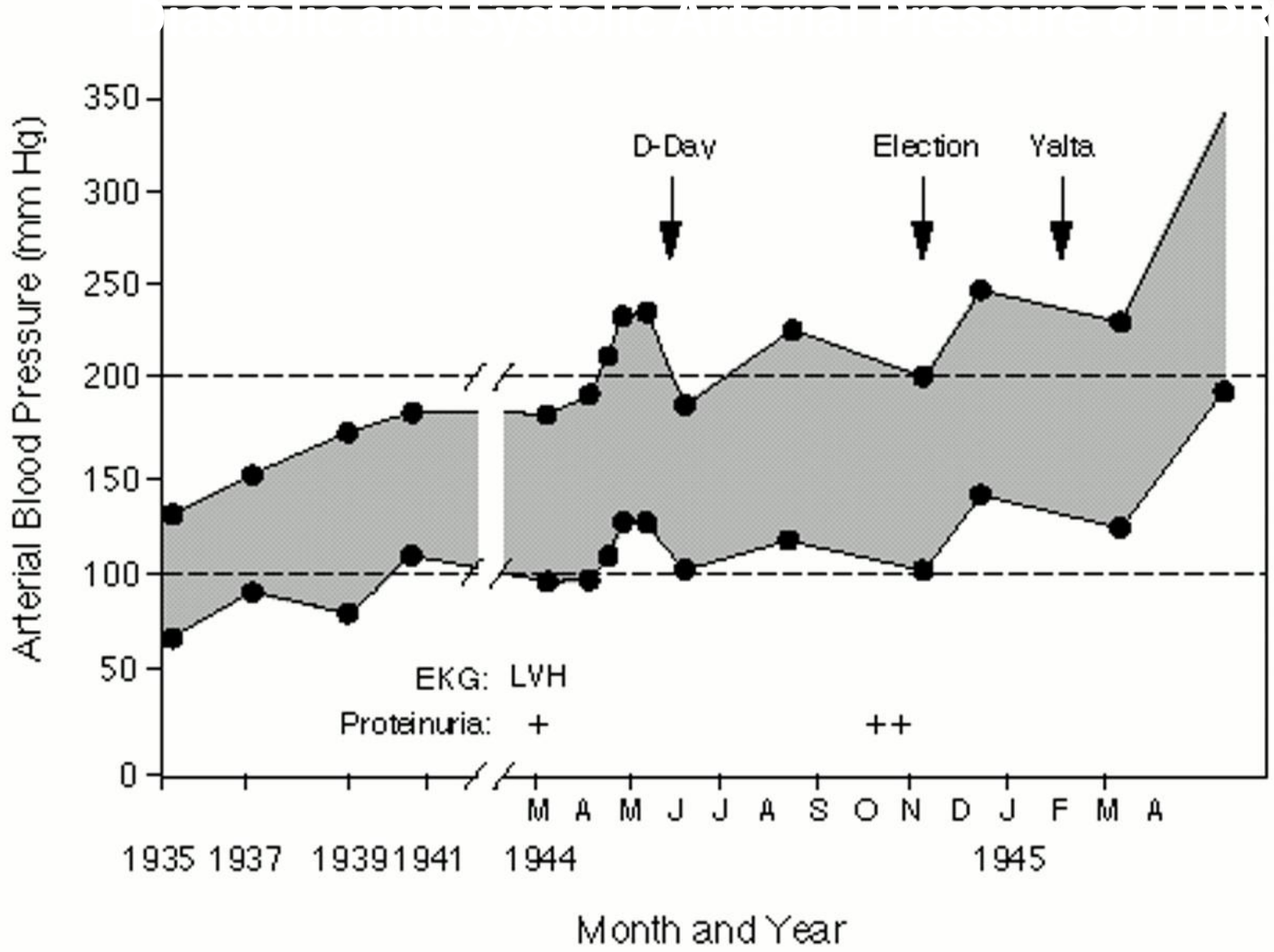
Adm. Ross T. McIntire Asserts There Was No Indication of Imminent Danger.

By CHARLES G. ROSS

DEATH DUE TO CEREBRAL HEMORRHAGE --- BLOOD VESSEL IN BRAIN BROKE

WASHINGTON, April 13 (AP). PRESIDENT ROOSEVELT died from what doctors call a cerebral hemorrhage, which means a sudden exten-

Messerli F. *N Engl J Med* 1995;332:1038-1039



Messerli F. *N Engl J Med* 1995;332:1038-1039

Age	Blood pressure (mm Hg)	Reduction in life expectancy (years)	
		Man	Woman
35 years	130/90	4	-
	140/95	9	-
	150/100	16.5	-
45 years	130/90	3	1.5
	140/95	6	5
	150/100	11.5	8.5
55 years	130/90	1	0.5
	140/95	4	3
	150/100	6	4

METROPOLITAN LIFE INSURANCE COMPANY. "Blood pressure: insurance experience and its implications". New York: Metropolitan Life Insurance Company; 1961.

Hypertension in Medicine: Key Moments

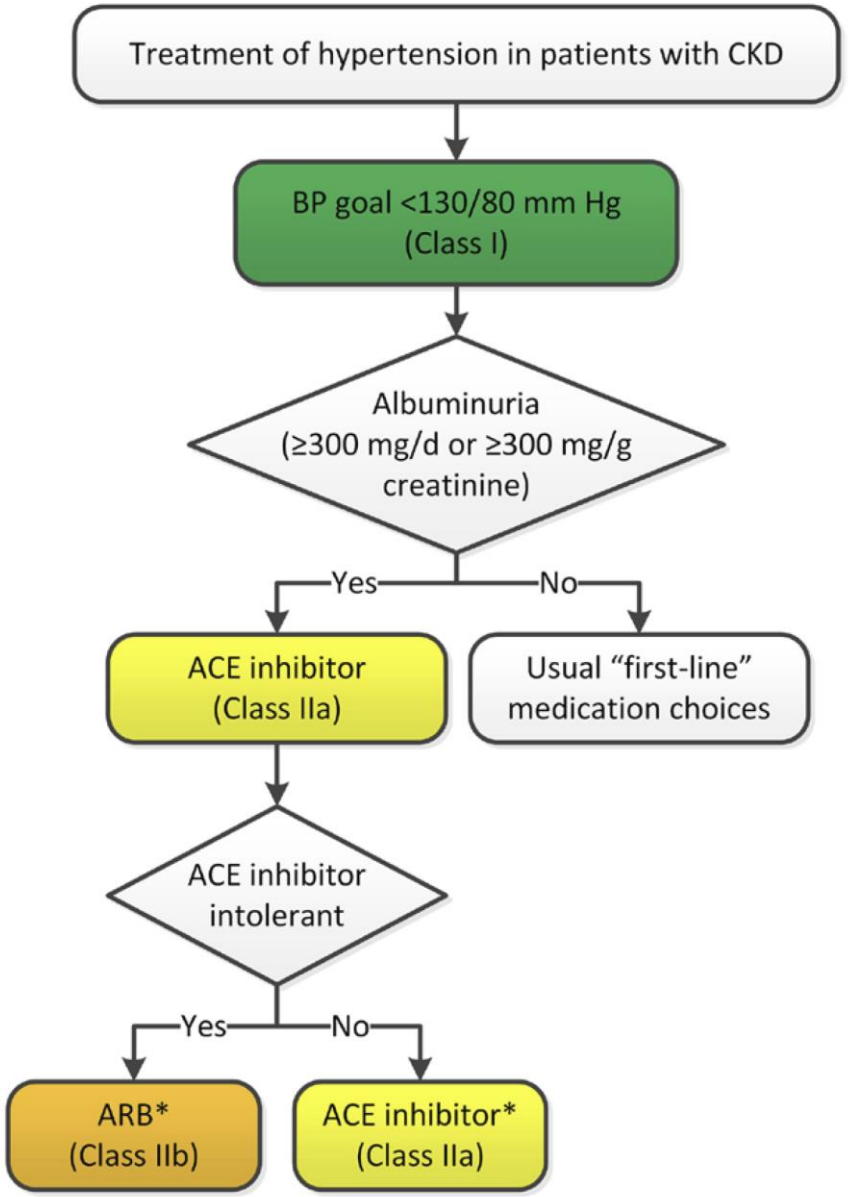
- Framingham Study: Kannel et al, Ann Intern Med. 1961 Jul;55:33-50
- First clinical trials of BP lowering
  - Hamilton M, Thompson EN: The role of blood pressure control in preventing complications of hypertension. *Lancet* 1964; 1:235-239
  - VA Cooperative Study Group: Effects of treatment on morbidity of hypertension. *JAMA* 1967; 202:1028-1033

- Relationship of BP with CV risk is “strong, continuous, independent, predictive and etiologically significant.”

JNC 6, *Arch Intern Med*. 1997;157:2413-46.

New 2017 AHA/ACC Hypertension Guidelines

BP Category	Systolic BP		Diastolic BP	Treatment or Follow-up
Normal	<120 mm Hg	**and**	<80 mm Hg	Evaluate yearly; encourage healthy lifestyle changes to maintain normal BP
Elevated	120-129 mm Hg	**and**	<80 mm Hg	Recommend healthy lifestyle changes and reassess in 3-6 months
Hypertension: stage 1	130-139 mm Hg	**or**	80-89 mm Hg	Assess the 10-year risk for heart disease and stroke using the atherosclerotic cardiovascular disease (ASCVD) risk calculator • If risk is less than 10%, start with healthy lifestyle recommendations and reassess in 3-6 months • If risk is greater than 10% or the patient has known clinical cardiovascular disease (CVD), diabetes mellitus, or chronic kidney disease, recommend lifestyle changes and BP-lowering medication (1 medication); reassess in 1 month for effectiveness of medication therapy – If goal is met after 1 month, reassess in 3-6 months – If goal is not met after 1 month, consider different medication or titration – Continue monthly follow-up until control is achieved
Hypertension: stage 2	≥140 mm Hg	**or**	≥90 mm Hg	Recommend healthy lifestyle changes and BP-lowering medication (2 medications of different classes); reassess in 1 month for effectiveness • If goal is met after 1 month, reassess in 3-6 months • If goal is not met after 1 month, consider different medications or titration • Continue monthly follow-up until control is achieved



Recommendations for Treatment of Hypertension in Patients With CKD

References that support recommendations are summarized in Online Data Supplements 37 and 38 and Systematic Review Report.

COR	LOE	Recommendations
I	SBP: B-R[SR] DBP: C-EO	1. Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mm Hg.[S9.3-1–S9.3-6]
IIa	B-R	2. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void]), treatment with an ACE inhibitor is reasonable to slow kidney disease progression.[S9.3-3,S9.3-7–S9.3-12]
IIb	C-EO	3. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio in the first morning void]) (S9.3-7,S9.3-8), treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated.

Hypertension. 2018;71:e13-e115.

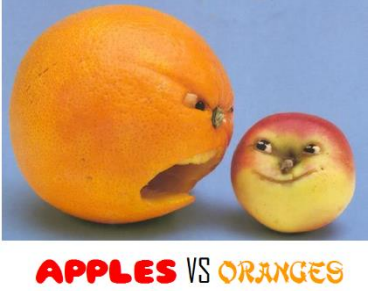
BP goal in CKD

- Recommendation 3.1.1: We suggest that adults with high BP and CKD be treated with a **target systolic blood pressure (SBP) of <120 mm Hg**, when tolerated, using standardized office BP measurement (**2B**).
  - Practice Point 3.1.1: It is potentially hazardous to apply the recommended SBP target of <120 mm Hg to BP measurements obtained in a non-standardized manner.
  - Practice Point 3.1.2: Clinicians can reasonably offer less intensive BP-lowering therapy in patients with very limited life expectancy or symptomatic postural hypotension.

KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD

BP treatment goals in CKD: What is the level of evidence?

- Paucity of conclusive clinical trials, trials with contradictory results
  - Extrapolation from other populations
  - Secondary analyses of trials examining different end points
  - Newer clinical trials that are relevant: SPRINT, ACCORD



US General population

- N=324,227,000 (Aug 13 2016)
- Median age: 36.8 years
- Ethnic composition
  - White 72.4%
  - Black 12.6%
  - Hispanic 16.3%
- Life expectancy at age 65: 19.1 years

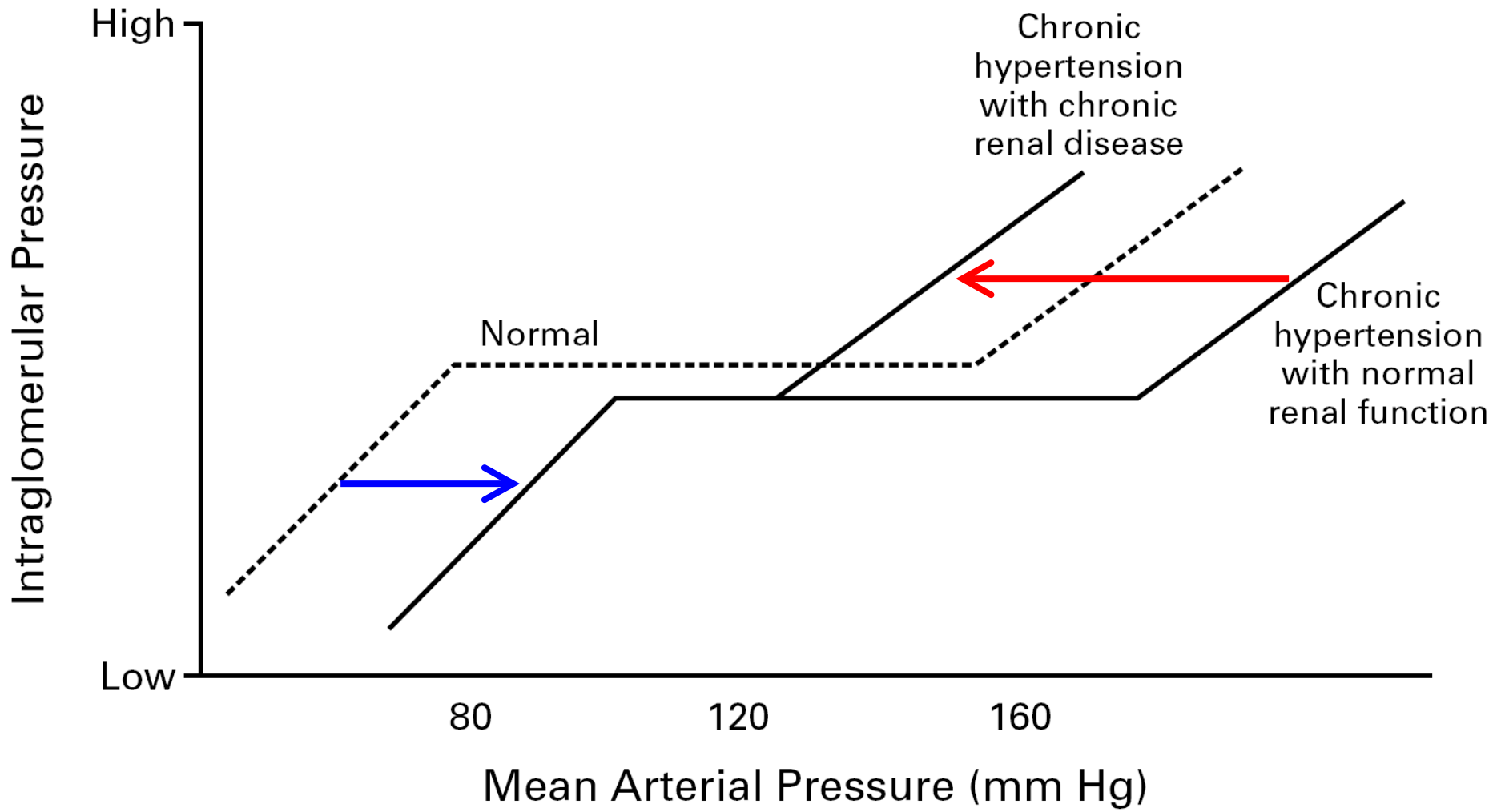
US Dialysis

- N= 466,607 (December 31, 2013)
- Median age: **59.1 years**
- Ethnic composition
  - White 57.8%
  - Black **35.3%**
  - Hispanic 17.9%
- Expected remaining life time at age 65: **4.7 years**

https://www.census.gov/quickfacts/table/PST045215/00
https://en.wikipedia.org/wiki/Demography_of_the_United_States
https://www.usrds.org/2015/download/vol2_06_Mortality_15.pdf

	General population	CKD
Mean SBP	135.9 (135.0 to 136.9)	141.3 (139.7 to 142.9)
Mean DBP	76.1 (75.4 to 76.8)	67.5 (66.1 to 68.9)
Mean pulse pressure	59.8 (58.9 to 60.7)	73.8 (71.6 to 75.9)
On antihypertensive medications (%)	37.2 (34.9 to 39.7)	66.4 (63.7 to 69.0)

Plantinga et al, *Hypertension* 2009;54:47-56



Palmer BF, *N Engl J Med* 2002; 347(16):1256-1261

Changes in renal vasculature

- Afferent arteriolar endothelial dysfunction leading to impaired vasodilatation
- Hyaline arteriosclerosis
- Myointimal hyperplasia

- Result is impaired autoregulatory capacity
- Intraglomerular pressure begins to vary directly with changes in systemic pressure

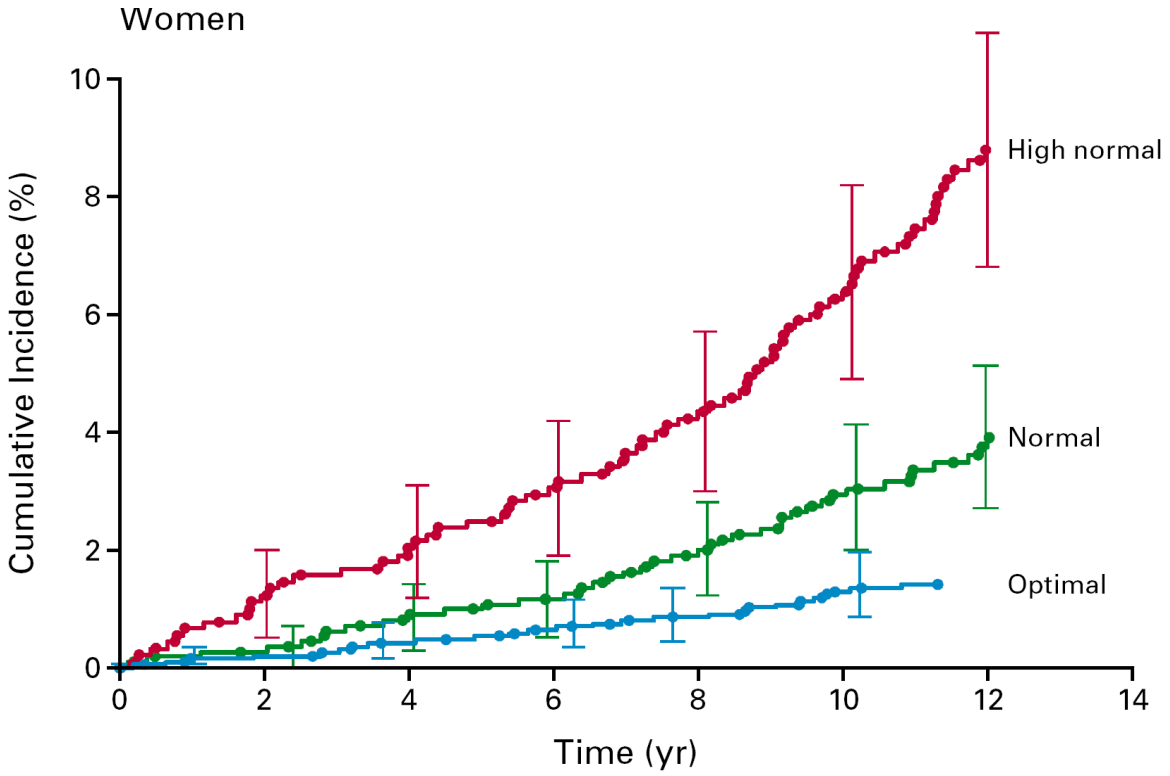
Ditscherlein G, *Hypertension* 1985;7:II-29–II-32.
Bidani et al, *Hypertension* 1994;24:309-16.
Pelayo and Westcott, *J Clin Invest* 1991;88:101-5.
Hayashi et al, *J Hypertens* 1996;14:1387-401.
Palmer BF, *Am J Med Sci* 2001;321:388-400.

Table 1. Factors Increasing Susceptibility to Renal Hypoperfusion.

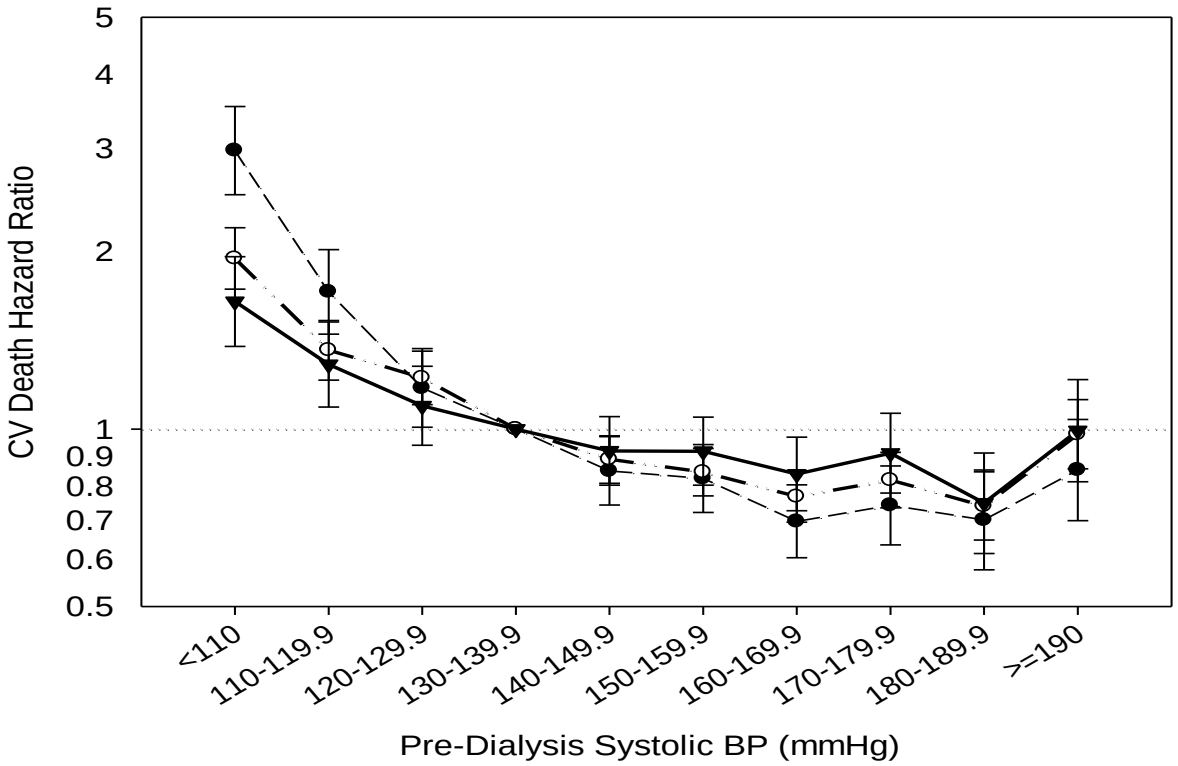
Failure to decrease arteriolar resistance
Structural changes in renal arterioles and small arteries
Old age
Atherosclerosis
Chronic hypertension
Chronic kidney disease
Malignant or accelerated hypertension
Reduction in vasodilatory prostaglandins
Nonsteroidal antiinflammatory drugs
Cyclooxygenase-2 inhibitors
Afferent glomerular arteriolar vasoconstriction
Sepsis
Hypercalcemia
Hepatorenal syndrome
Cyclosporine or tacrolimus
Radiocontrast agents
Failure to increase efferent arteriolar resistance
Angiotensin-converting–enzyme inhibitors
Angiotensin-receptor blockers
Renal-artery stenosis

Abuelo JG, N
Engl J Med 2007;357:797-805.

APPLES VS ORANGES



Vasan et al, *N Engl J Med* 2001;345:1291-7



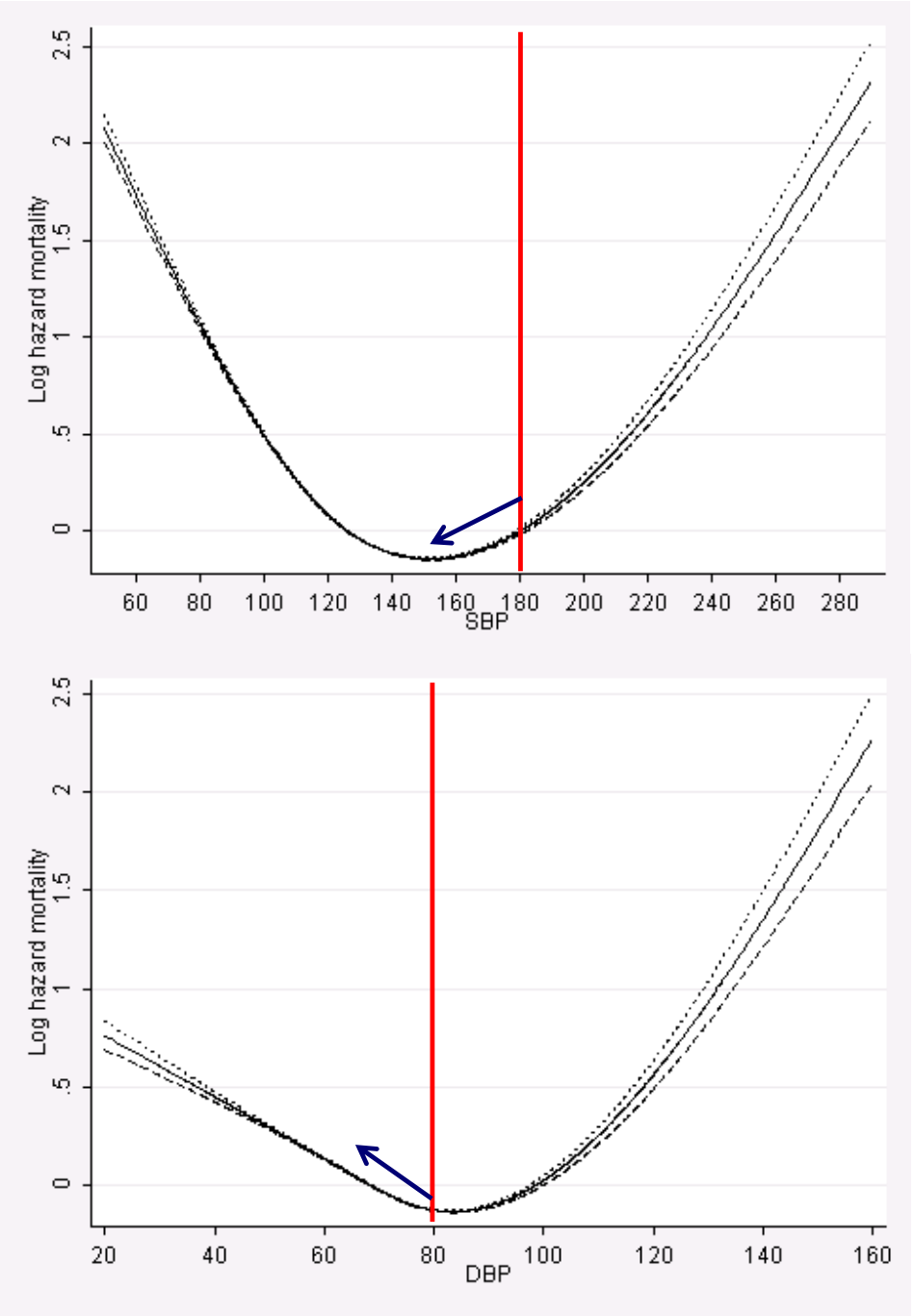
Kalantar-Zadeh et al, *Hypertension* 2005;45:811-7

BP and mortality in US veterans

- From 4,381,049 patients with an eGFR between October 1, 2004 and September 30, 2006 we analyzed 651,749 patients with non-dialysis dependent CKD.

Kovesdy et al, *Ann Intern Med* 2013;159(4):233-42

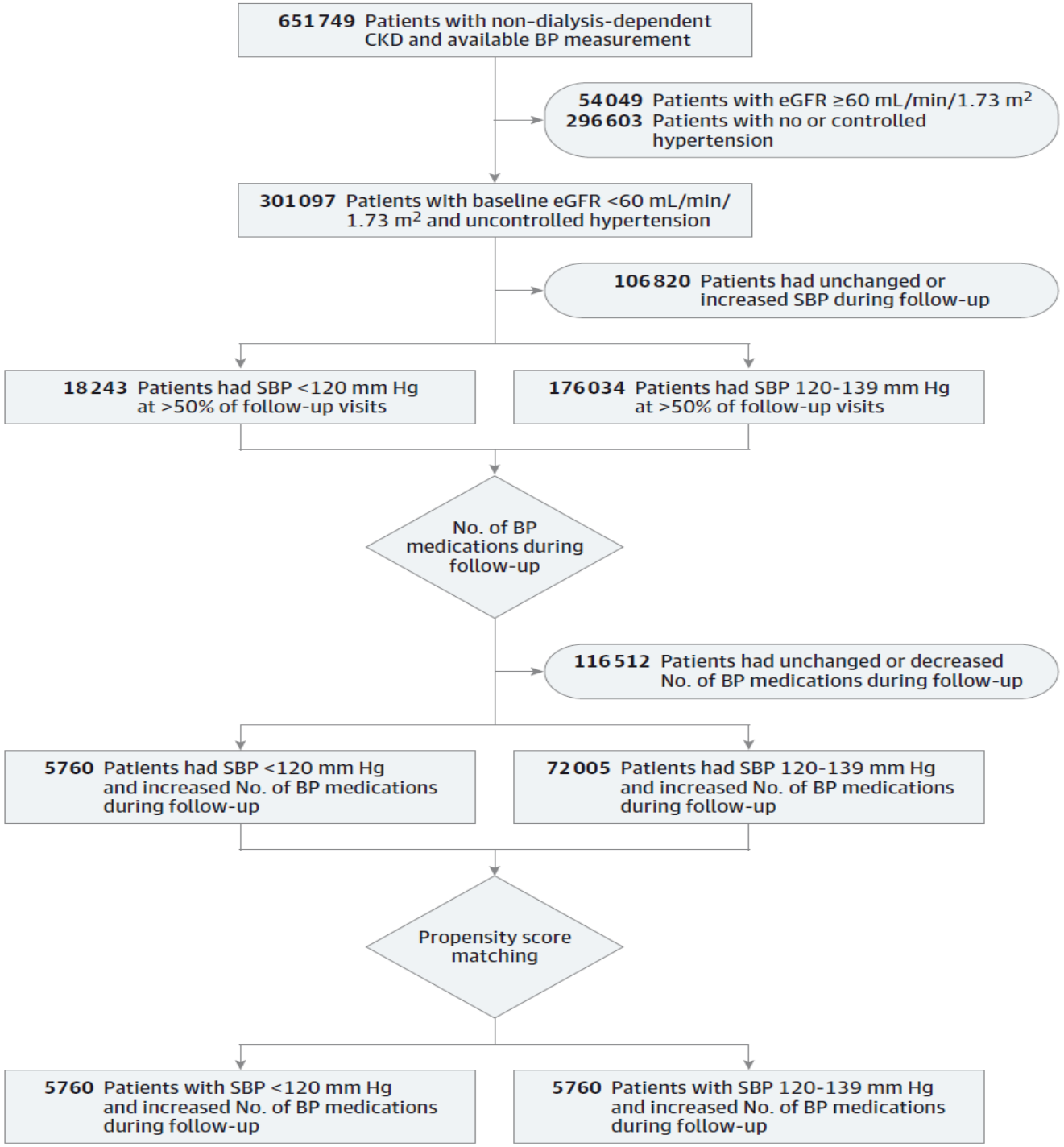
- The dilemma of BP lowering on the J-curve:
  - Lowering SBP
  - Also lowers DBP



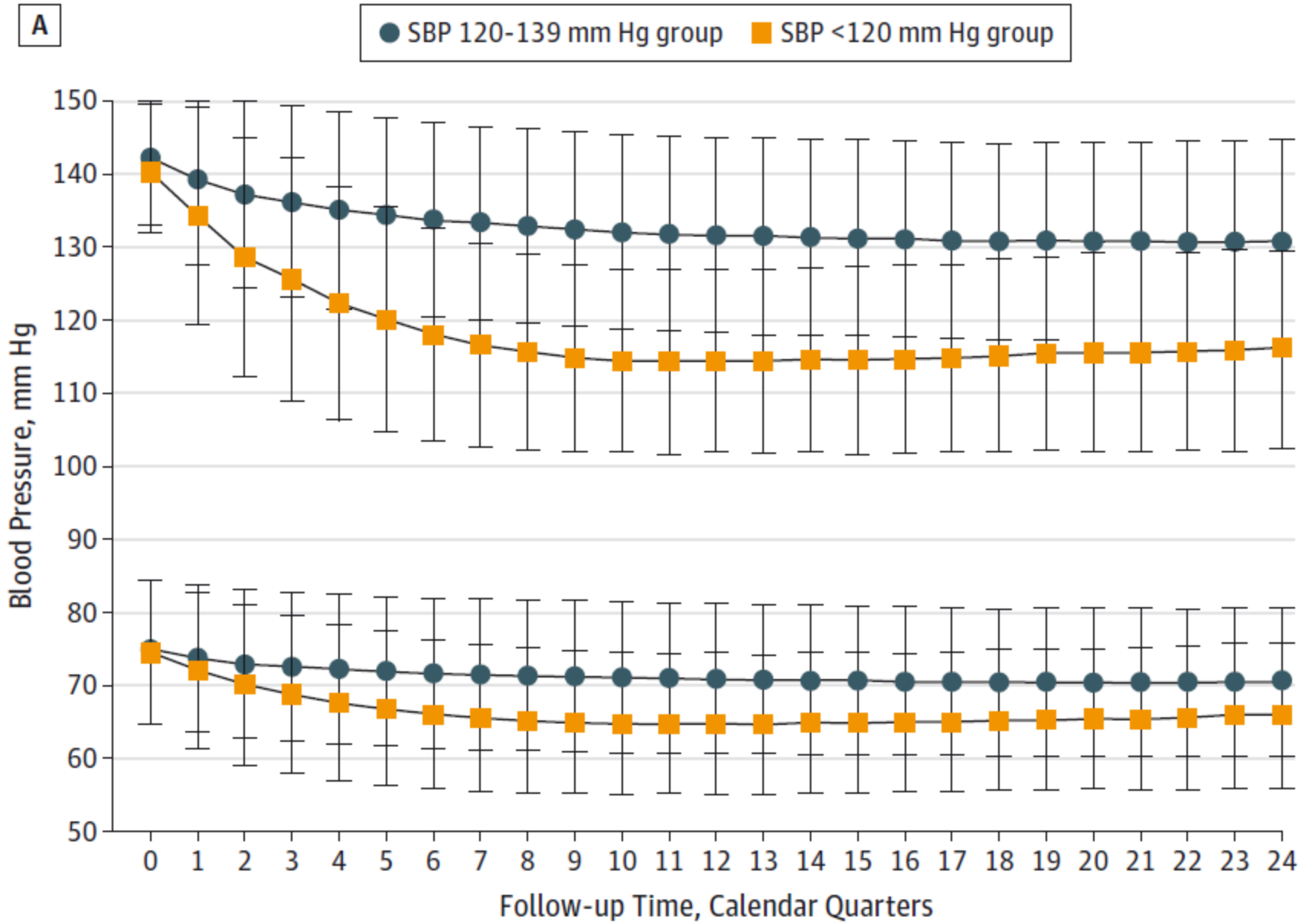
Kovesdy et al, *Ann Intern Med* 2013;159(4):233-42

		SBP (mmHg)													
		<80	80-89	90-99	100-109	110-119	120-129	130-139	140-149	150-159	160-169	170-179	180-189	190-199	200-210	≥210
DBP (mmHg)	<40	2.56	2.42	2.55	2.15	1.73	1.69	1.91								
	40-49	2.99	2.69	2.31	1.77	1.58	1.39	1.37	1.30	1.50	1.83					
	50-59	3.25	2.88	2.24	1.77	1.51	1.27	1.14	1.17	1.27	1.32	1.63	1.20			
	60-69		3.11	2.32	1.82	1.48	1.23	1.09	1.09	1.12	1.13	1.28	1.36	1.00		
	70-79			2.05	1.70	1.34	1.14	1.01	1.01	1.04	1.07	1.12	1.19	1.11	1.17	1.26
	80-89				1.82	1.27	1.08	0.98	Ref.	1.01	1.07	1.13	1.22	1.43	1.25	1.35
	90-99					1.57	1.26	1.08	1.10	1.15	1.18	1.25	1.23	1.16	1.38	1.04
	100-109							1.53	1.16	1.31	1.33	1.37	1.30	1.62	1.40	1.42
	110-119									1.11	1.28	1.81	1.35	1.89	1.85	1.71
	≥120											1.62			2.44	2.06

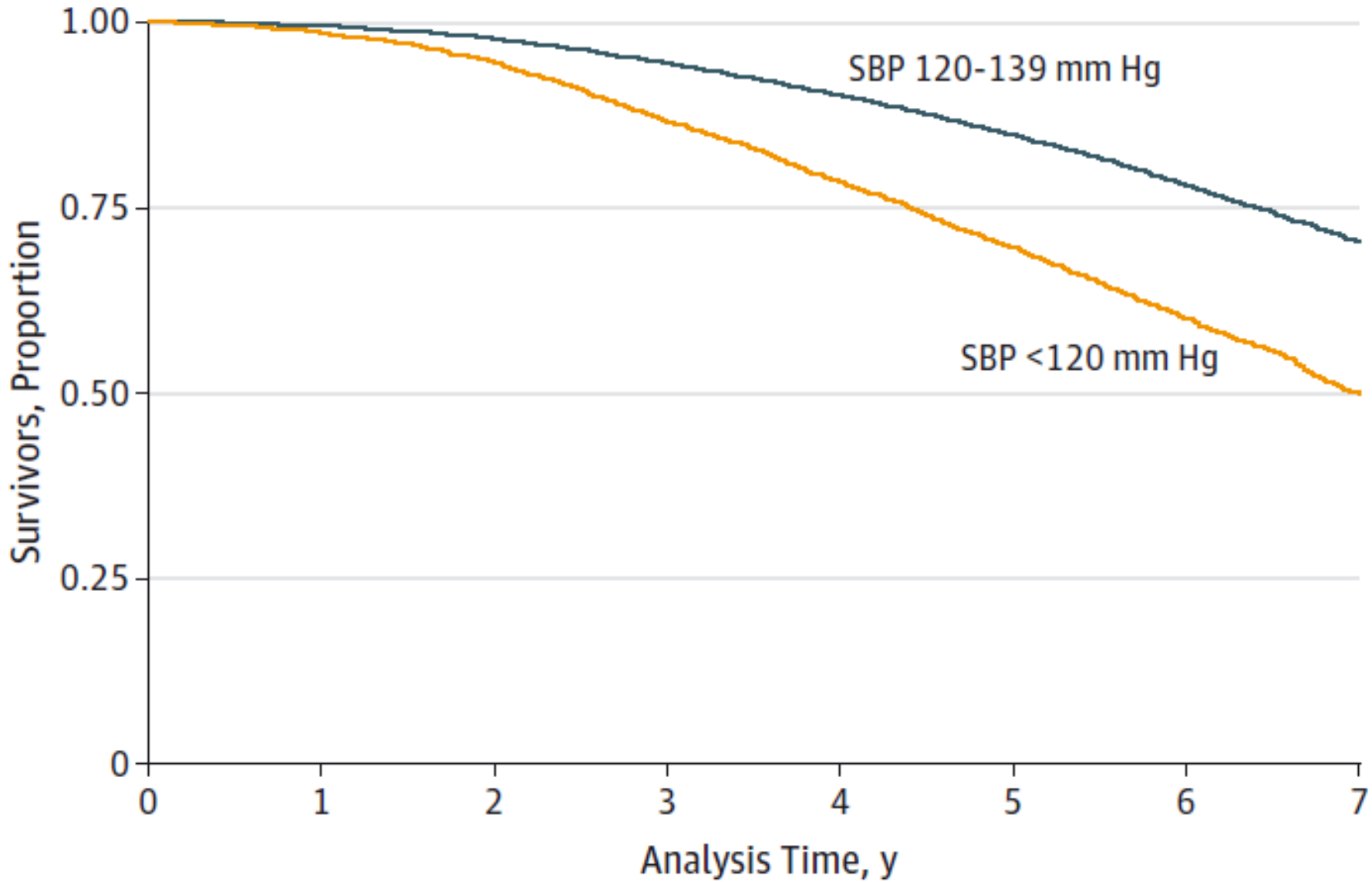
Kovesdy et al, *Ann Intern Med* 2013;159(4):233-42



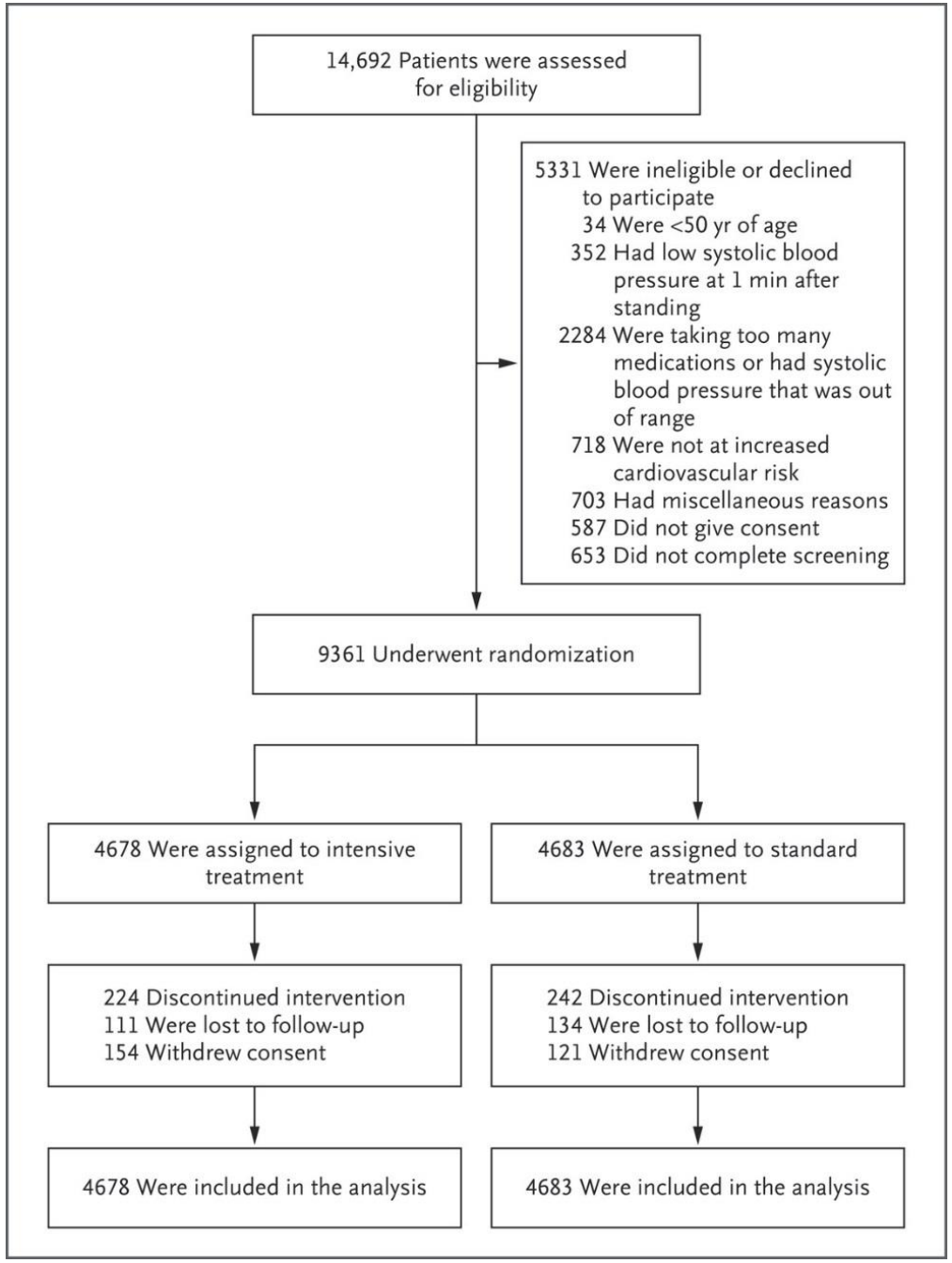
Kovesdy CP et al, JAMA Intern Med 2014



Kovesdy CP et al, JAMA Intern Med 2014



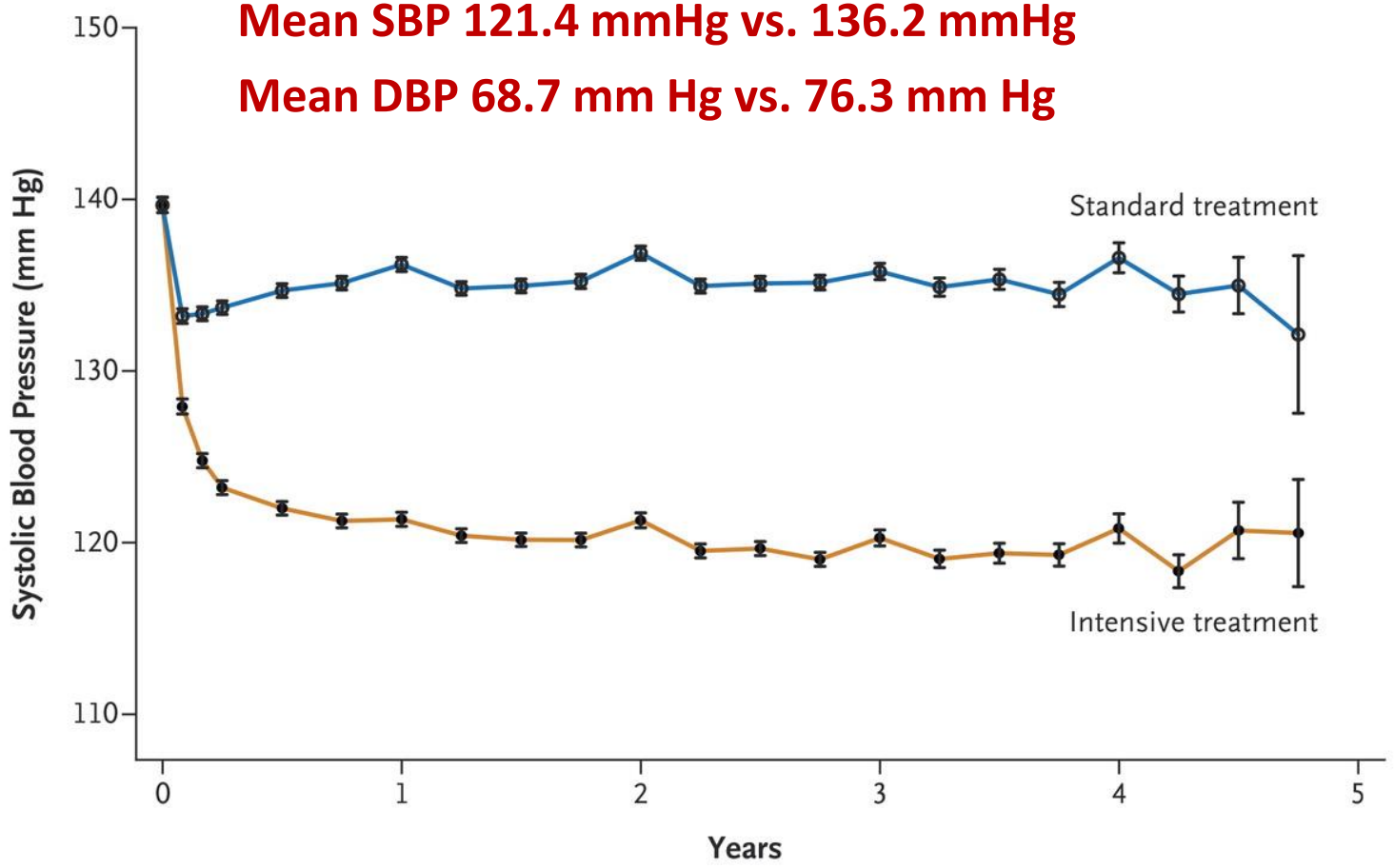
Kovesdy CP et al, JAMA Intern Med 2014



The SPRINT Research Group. N Engl J Med 2015. DOI: 10.1056/NEJMoa1511939

Mean SBP 121.4 mmHg vs. 136.2 mmHg

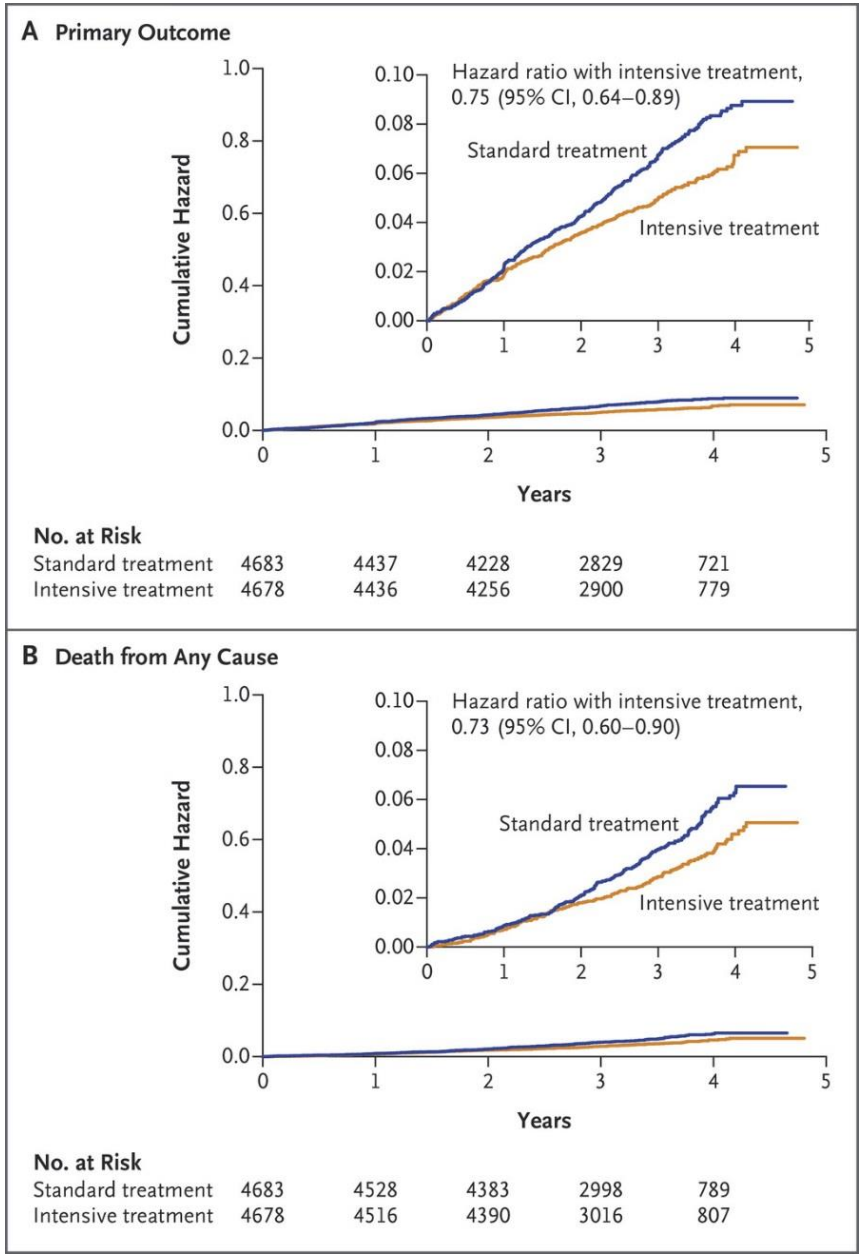
Mean DBP 68.7 mm Hg vs. 76.3 mm Hg



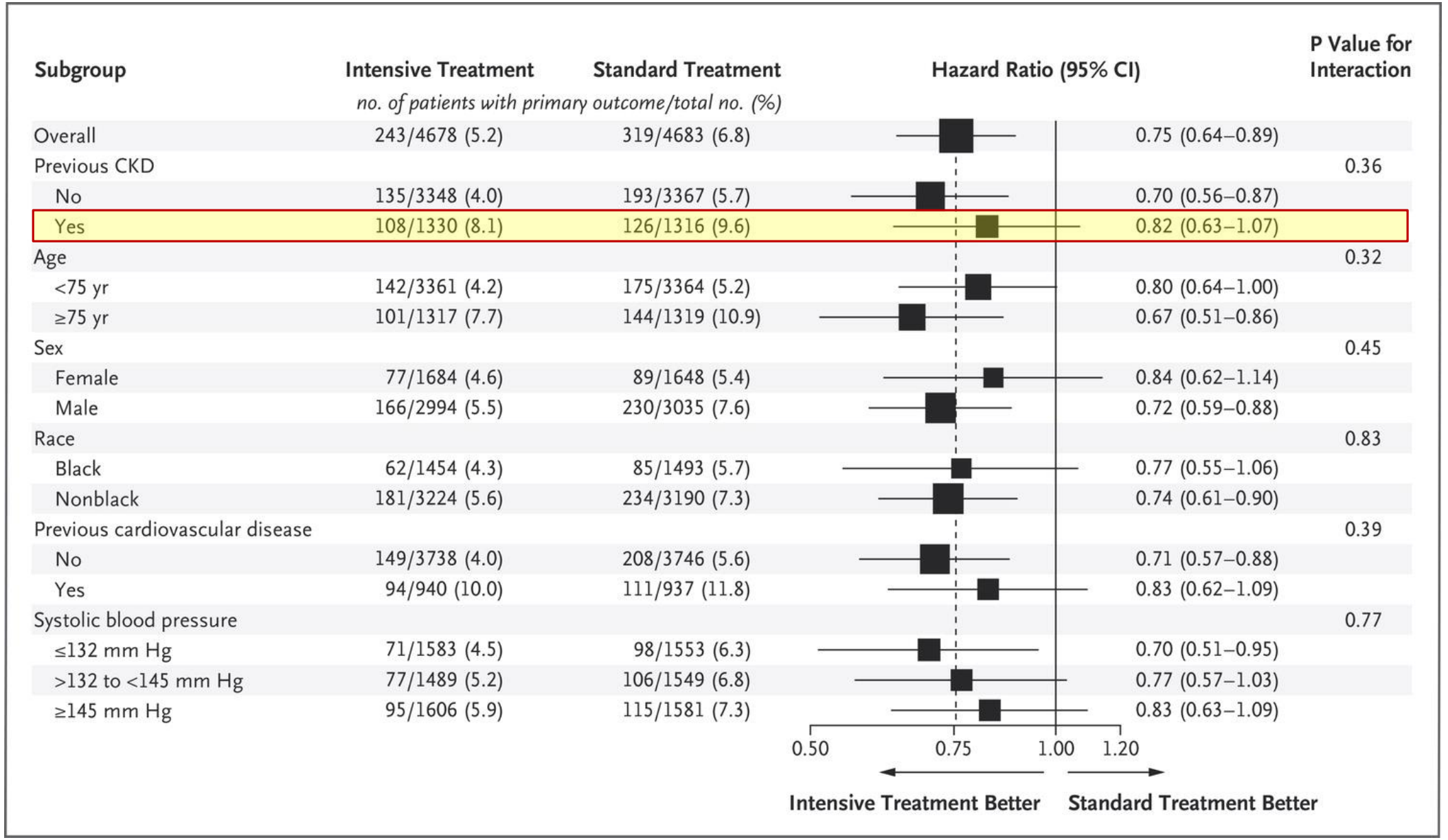
No. with Data										
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286
Mean No. of Medications										
Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8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

SPRINT Research Group. N Engl J Med 2015;26;373(22):2103-16

- Median follow-up of 3.26 years
- Significantly lower rate of the primary composite outcome in the intensive-treatment group
  - 1.65% per year vs. 2.19% per year
  - Hazard ratio 0.75; 95% CI 0.64 to 0.89; P<0.001
- All-cause mortality hazard ratio 0.73; 95% CI, 0.60 to 0.90; P=0.003



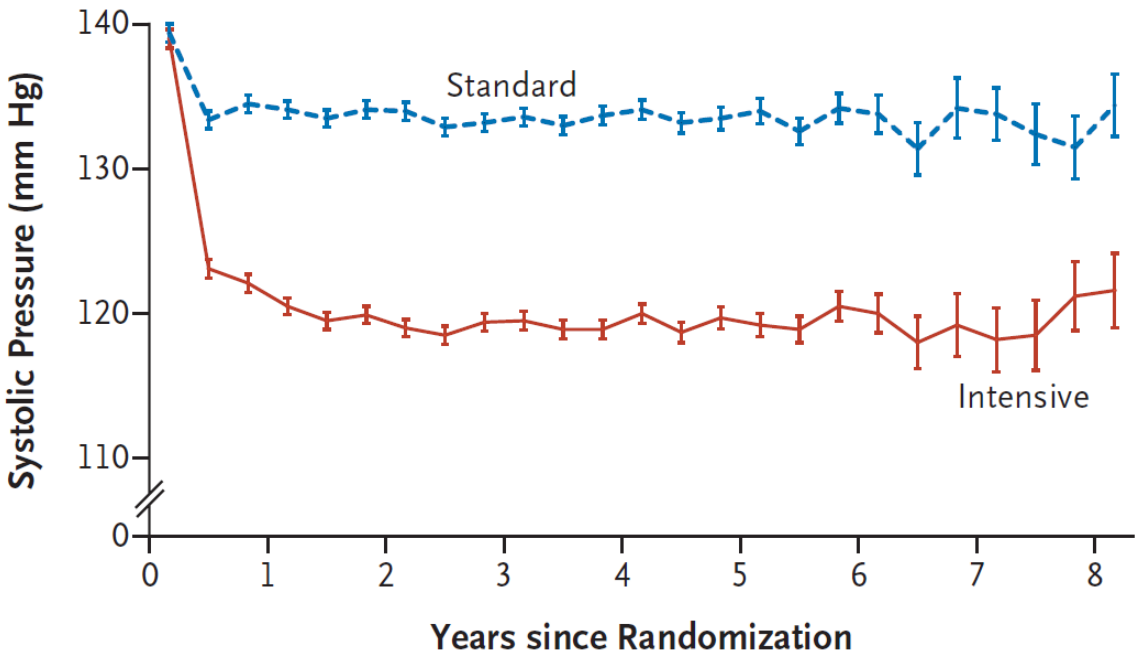
SPRINT Research Group. N Engl J Med 2015;26;373(22):2103-16



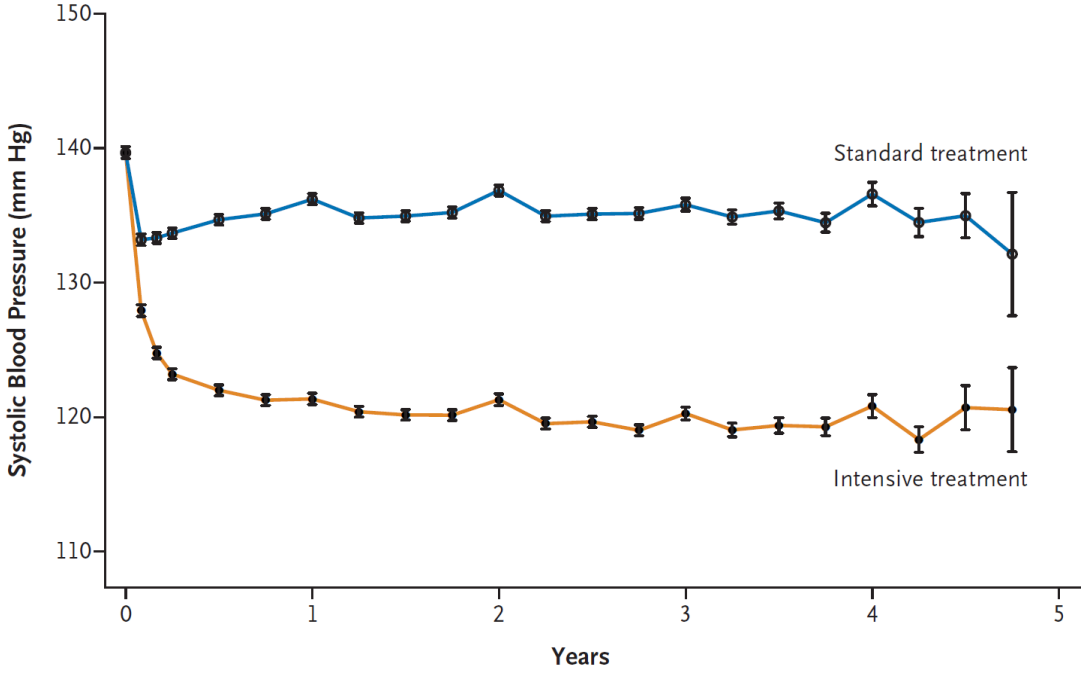
SPRINT Research Group. N Engl J Med 2015;26;373(22):2103-16

Are differences in results a result of biases inherent of observational studies?

ACCORD BP



SPRINT



The ACCORD Study Group. N Engl J Med 2010;362:1575-85
The SPRINT Research Group. N Engl J Med 2015. DOI: 10.1056/NEJMoa1511939

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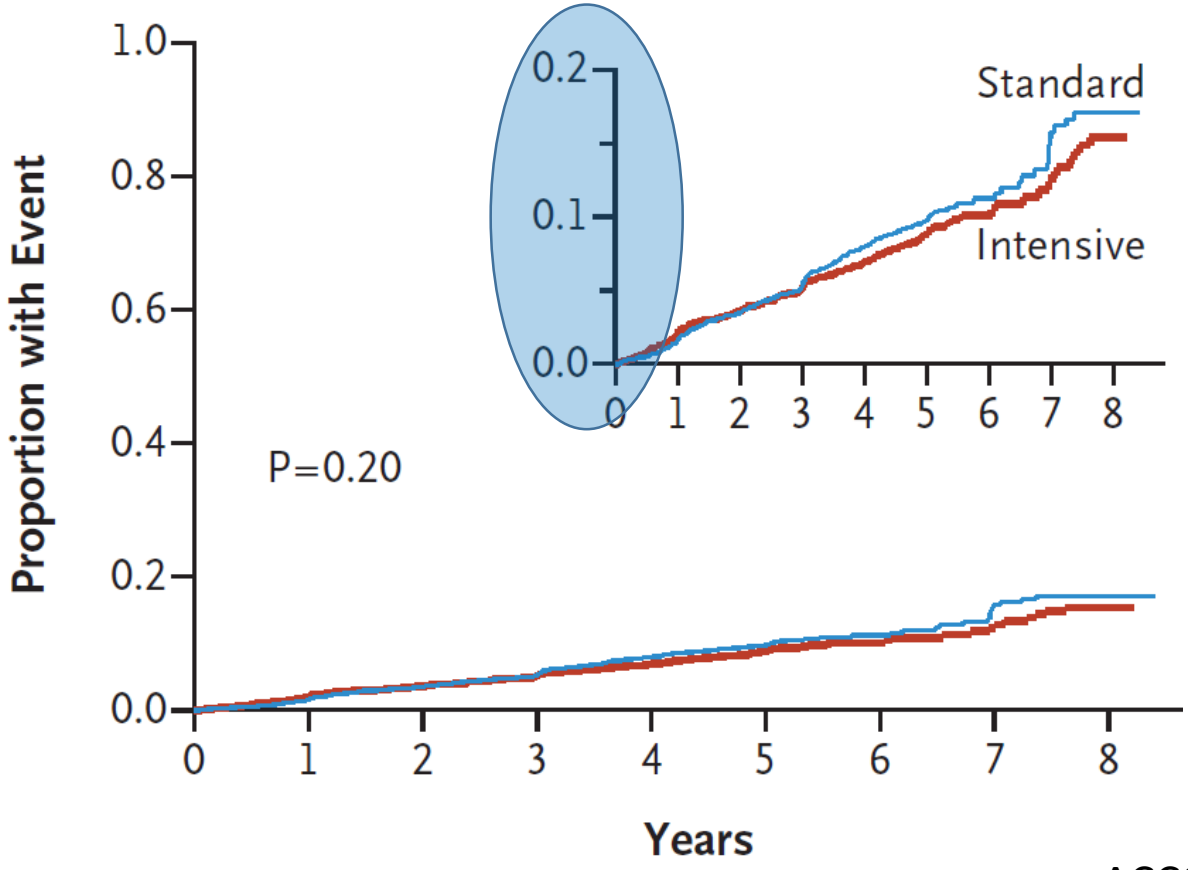
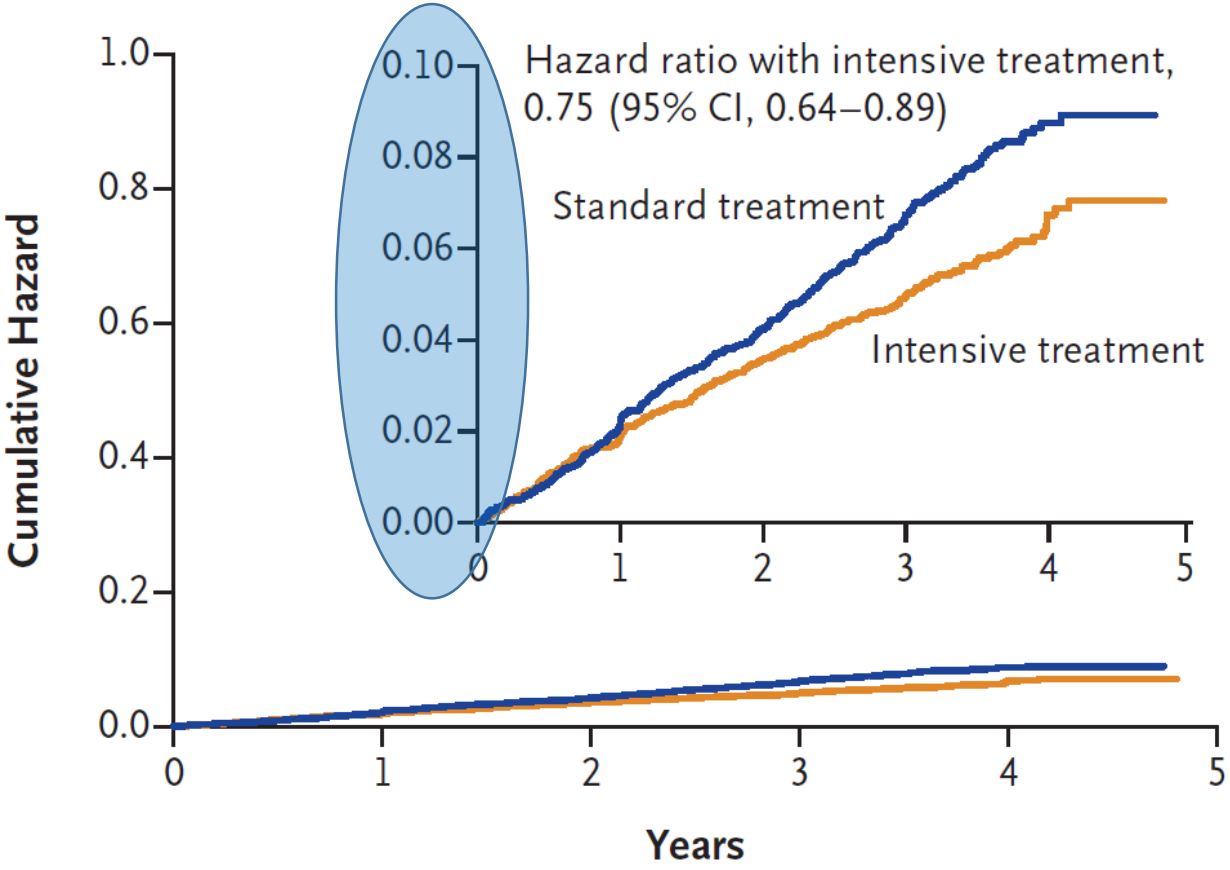
ACCORD VS. SPRINT

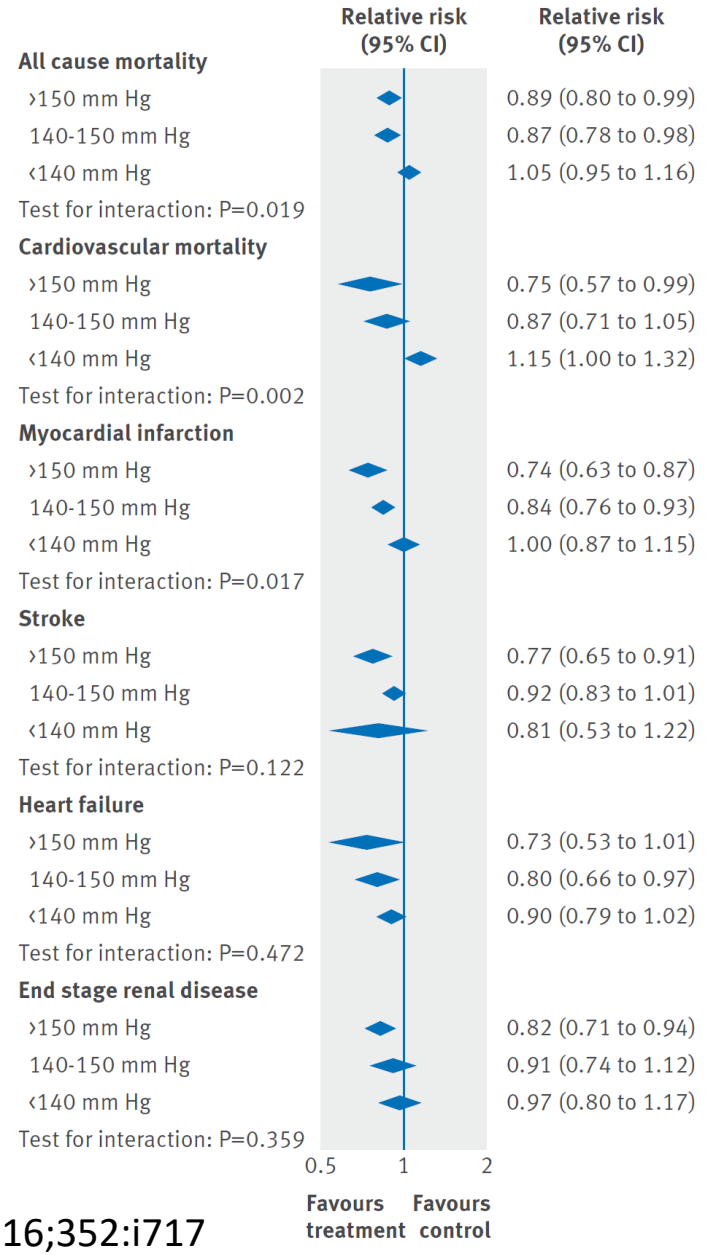




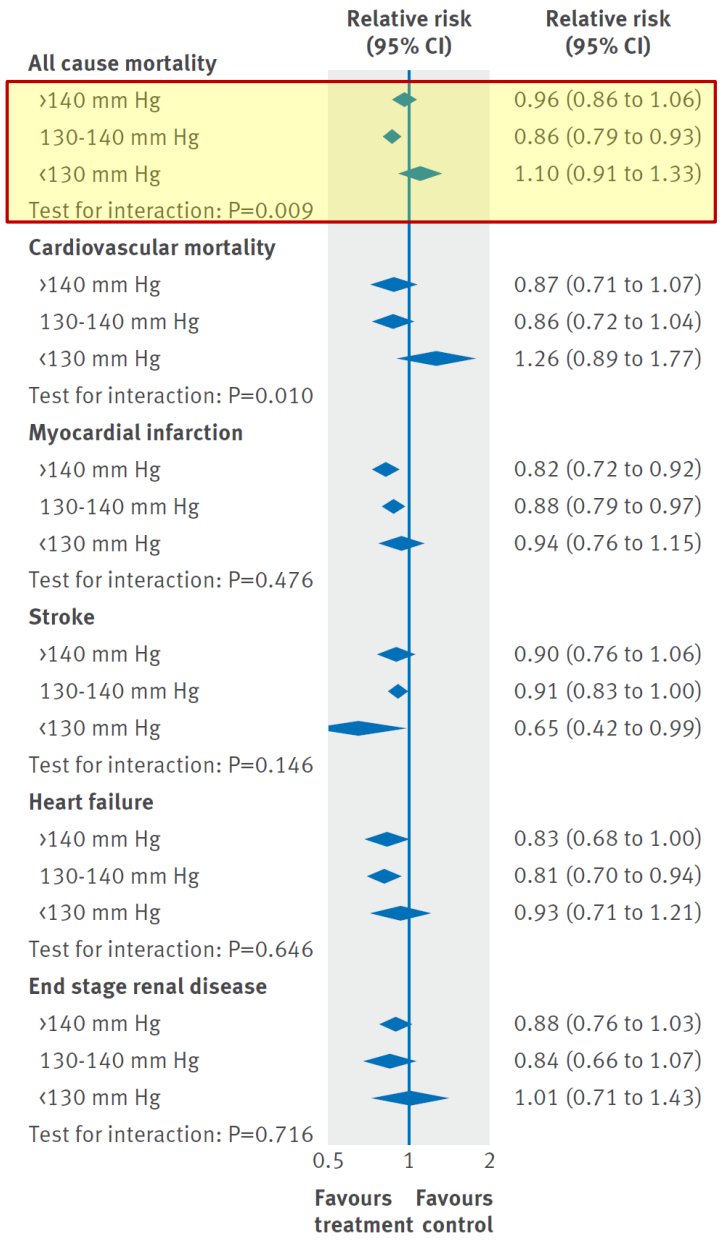
ACCORD Study Group. N Engl J Med 2010;362:1575-85
SPRINT Research Group. N Engl J Med 2015;26;373(22):2103-16

Strict BP targets in DM

Baseline SBP



Treated SBP



Brunstrom and Carlberg, BMJ 2016;352:i717

SBP target in SPRINT: Possible explanations for discrepant results?

- "Strict" vs. "conventional" SBP target
  - Achieved SBP of 121 vs 136 mmHg
  - Achieved DBP of 69 vs 76 mmHg
- BP measurement method
  - Examiner left the room and an automated device measured the patients' BP after several minutes
- This method can result in measured BP levels that are ~5-20 mmHg lower compared to methods applied in clinical practice
  - Achieved SBP may have been equivalent to levels associated with ideal outcomes in observational studies and in DM trials (SBP ~130-140 mmHg)

Kjeldsen et al., *Hypertension* 2016; 67: 808-812
Kovesdy CP, *Nephrol Dial Transplant* 2016

SPRINT vs. all-comers

- SPRINT
  - N=2,646 (CKD subgroup)
  - Age 68 years (overall)
  - Black race 31% (overall)
  - Baseline SBP 140 mmHg
  - eGFR 48 ml/min/1.73m^2 (CKD)
  - Baseline number of AHD 1.8±1
  - Deaths 6.2% (2% per year) (CKD)
- VA-CKD observational modeling
  - N=77,765
  - Age 74 years
  - Black race 7%
  - Baseline SBP 142 mmHg
  - eGFR 49 ml/min/1.73m^2
  - Baseline number of AHD 2 (1-2)
  - Deaths 25% (4.4% per year)

SPRINT Research Group. N Engl J Med 2015;26;373(22):2103-16
Kovesdy CP et al, JAMA Intern Med 2014;174(9):1442-1449
Kovesdy CP et al., Adv Chronic Kidney Dis. 2012 Jan;19(1):11-8.

Relative effect (i.e., hazard ratio) of intensive BP control may vary across CKD stages.

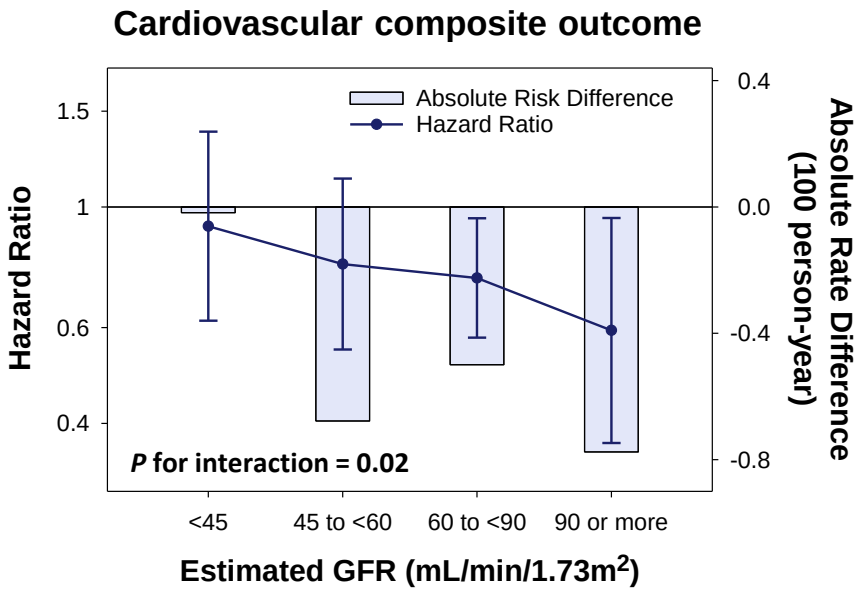
(Original report)

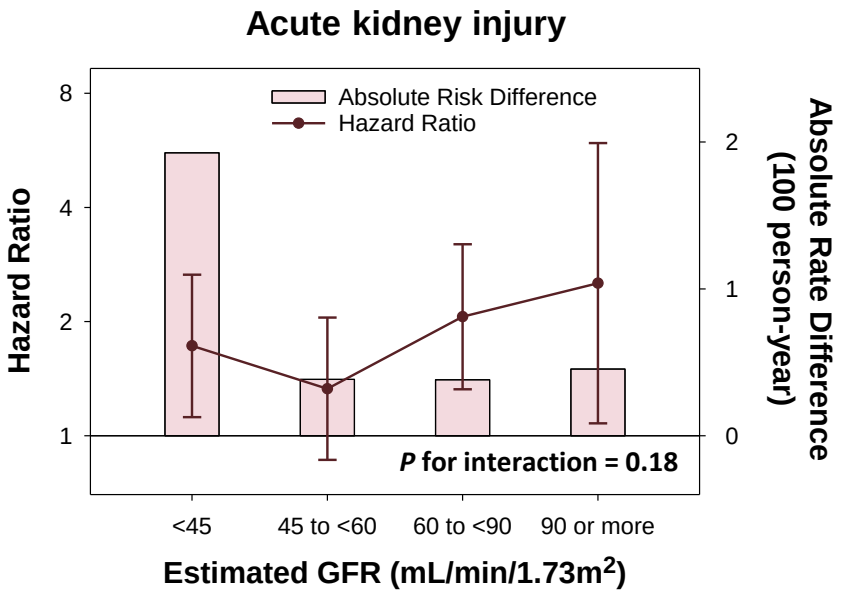
But what if …

Additionally, there were no information on AKI risk in CKD vs. non-CKD.

Obi et al, J Intern Med. 2018 Mar;283(3):314-327.

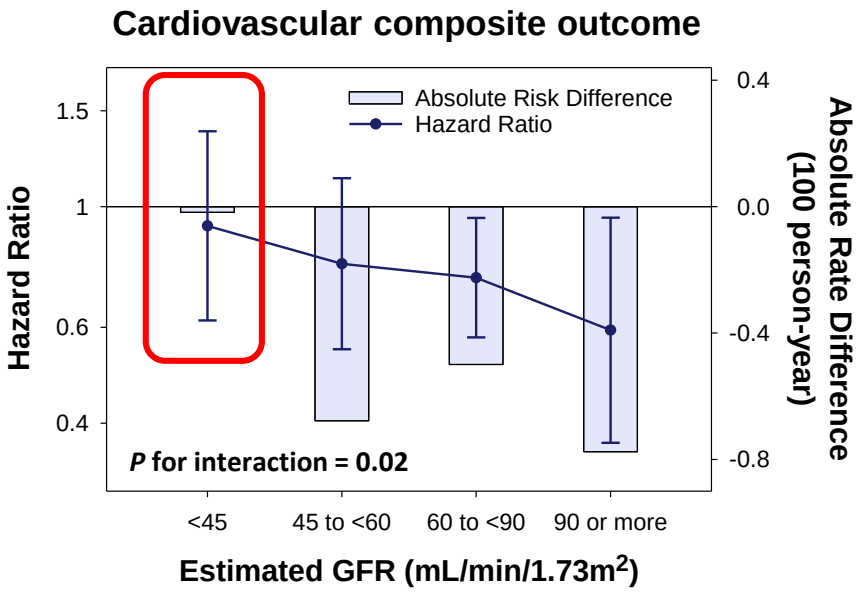
Intensive BP control may provide little benefit but potential harm among patients with advanced CKD
- Secondary analysis of the SPRINT study -

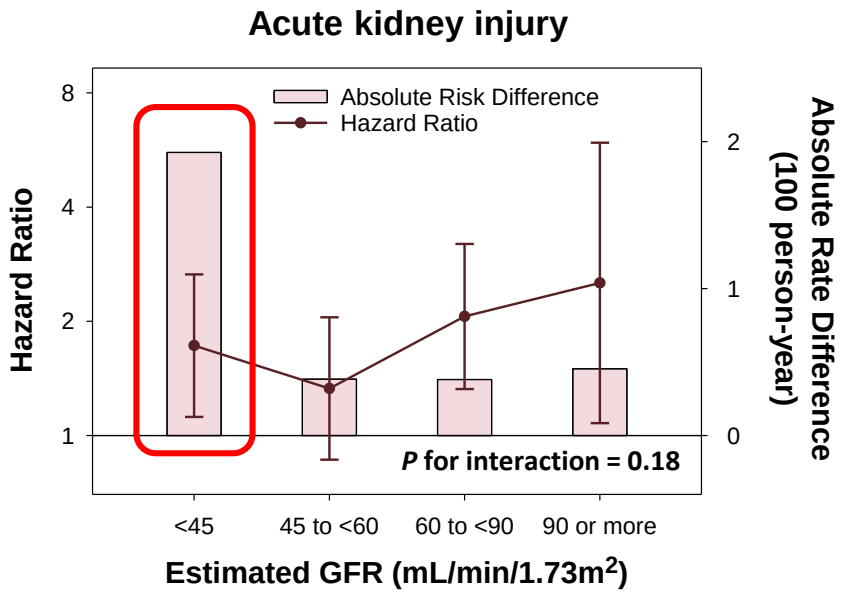




Obi et al, J Intern Med. 2018 Mar;283(3):314-327.

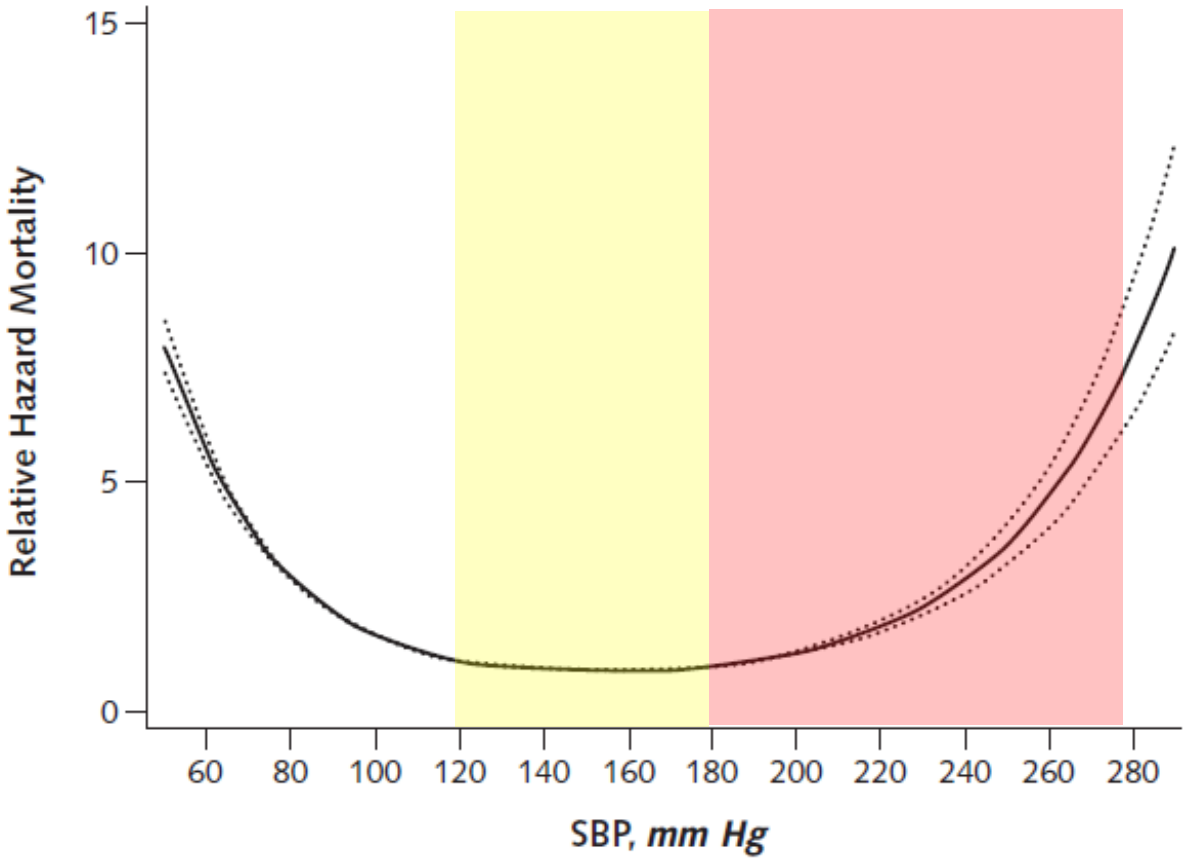
Intensive BP control may provide little benefit but potential harm among patients with advanced CKD - Secondary analysis of the SPRINT study -

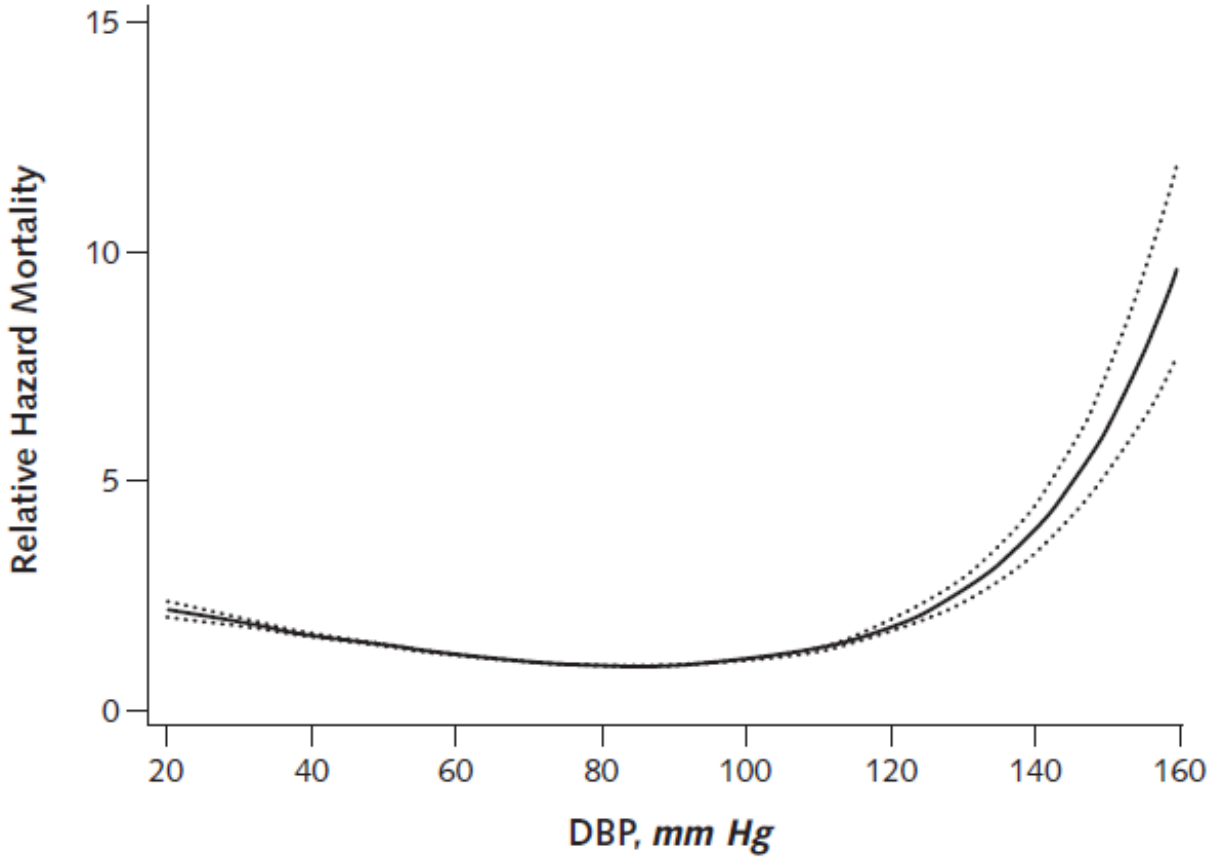




Obi et al, J Intern Med. 2018 Mar;283(3):314-327.

Multivariable-adjusted relative hazards (hazard ratios [95% CIs]) of all-cause mortality associated with SBP and DBP





Kovesdy et al, *Ann Intern Med* 2013;159(4):233-42

Treating BP in CKD: Magnitude of benefit

- Baseline BP: 186/121 mmHg
  - Reduction in SBP: 43 mmHg
  - Reduction in DBP: 30 mmHg

  - NNT to prevent 1 AE: 2.8
  - NNT to prevent 1 death: 17.5

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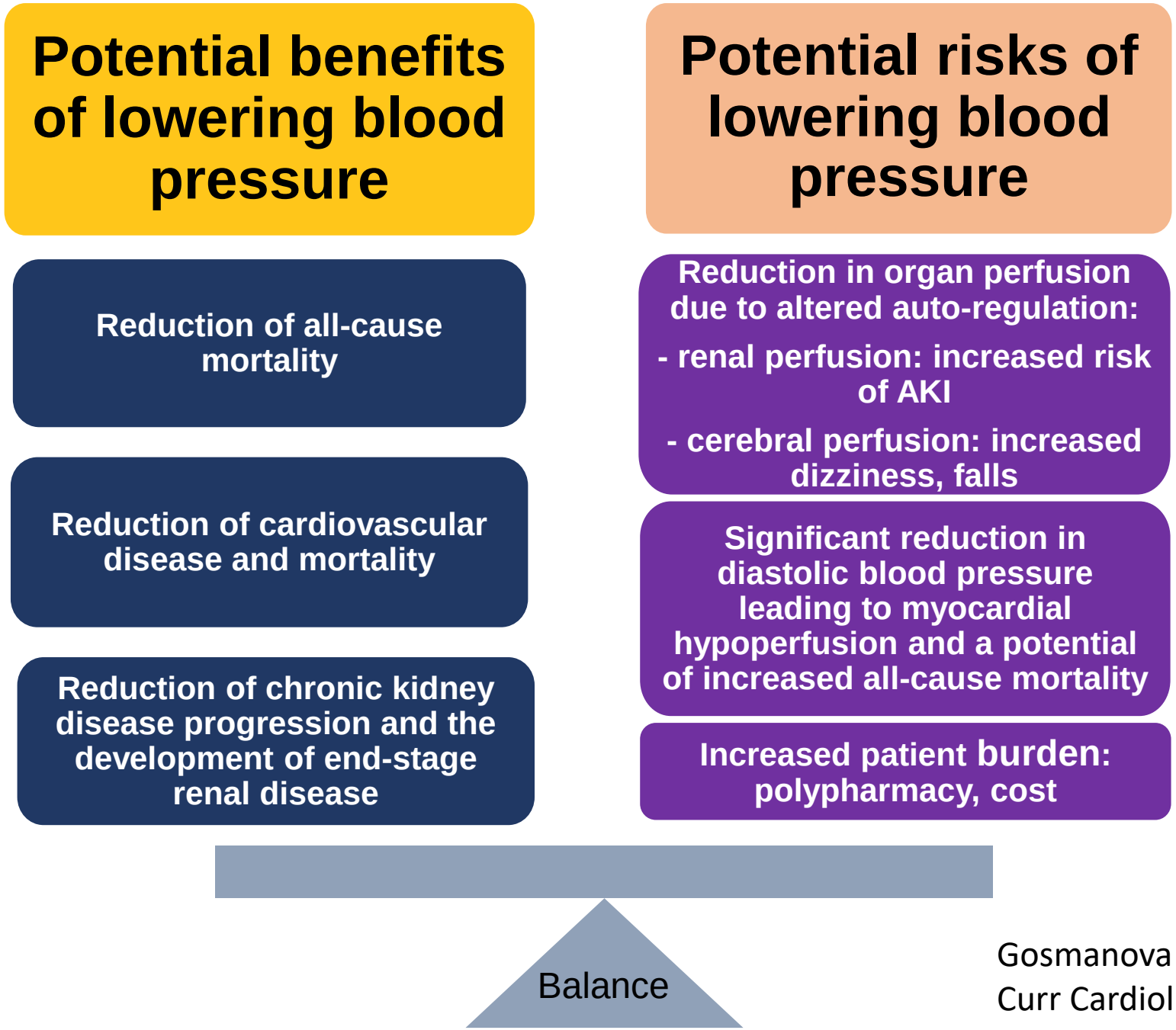
Kovesdy CP, JAMA Intern Med. 2017 Oct 1;177(10):1506-1507
VA Cooperative Study Group, JAMA. 1967;202(11):1028-1034
Malhotra R et al., JAMA Intern Med. 2017 Oct 1;177(10):1498-1505
Lv et al., CMAJ 2017 Oct 1;177(10):1498-1505



Gosmanova EO & Kovesdy CP
Curr Cardiol Rep. 2016 Sep;18(9):88.

Conclusions

- Elevated BP is associated with adverse outcomes in patients with CKD
- Several aspects of BP control in CKD may need special consideration
  - Age – the elderly may derive less benefit from BP lowering and may experience more complications from strict BP control
  - Morbidity/frailty – patients with short life expectancy may derive less benefit from BP lowering and may experience more complications from strict BP control
- Ideal BP target in patients with CKD
  - Stricter control in non-diabetic CKD patients based on SPRINT
    - SBP <120 only applies if using standardized BP measurement!
  - No similar statement can be made for diabetic CKD patients
  - Benefit in patients with advanced CKD and ESKD remains questionable
  - Individual patient tolerance has to be considered, due to potential limited external validity of SPRINT
  - **Most bang for the buck: focus on those with the highest BP**

SPECIAL ARTICLE www.jasn.org

Managing Hypertension in Patients with CKD: A Marathon, Not a SPRINT

Glenn M. Chertow,* Srinivasan Beddhu,† Julia B. Lewis,‡ Robert D. Toto,§ and Alfred K. Cheung†

*Division of Nephrology, Department of Medicine, Stanford University, Stanford, California; †Division of Nephrology, Internal Medicine School of Medicine, University of Utah, Salt Lake City, Utah; ‡Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University, Nashville, Tennessee; and §Department of Clinical Science, University of Texas Southwestern, Dallas, Texas

Questions?