

Low Diastolic Blood Pressure and Progression to Chronic Kidney Disease

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Learning Objectives

1. To review the clinical relevance of low diastolic BP in hypertension
2. To review the relationship between low diastolic BP and adverse outcomes in CKD
3. To review potential approaches to minimize the occurrence of low diastolic BP

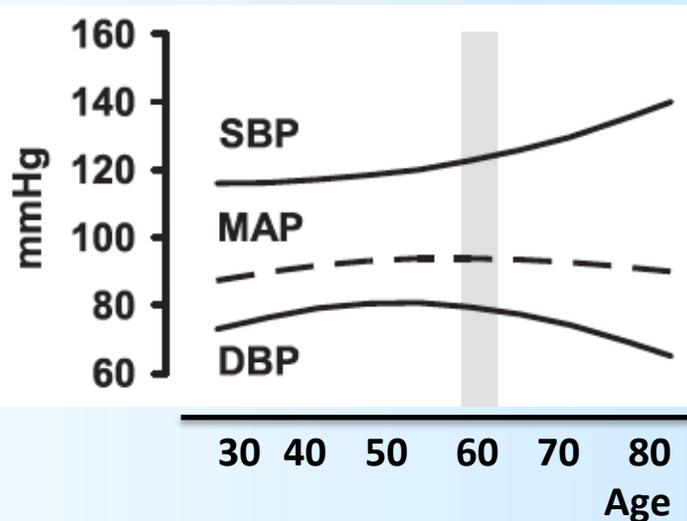
Clinical Questions

Asymptomatic patients with HTN on treatment:

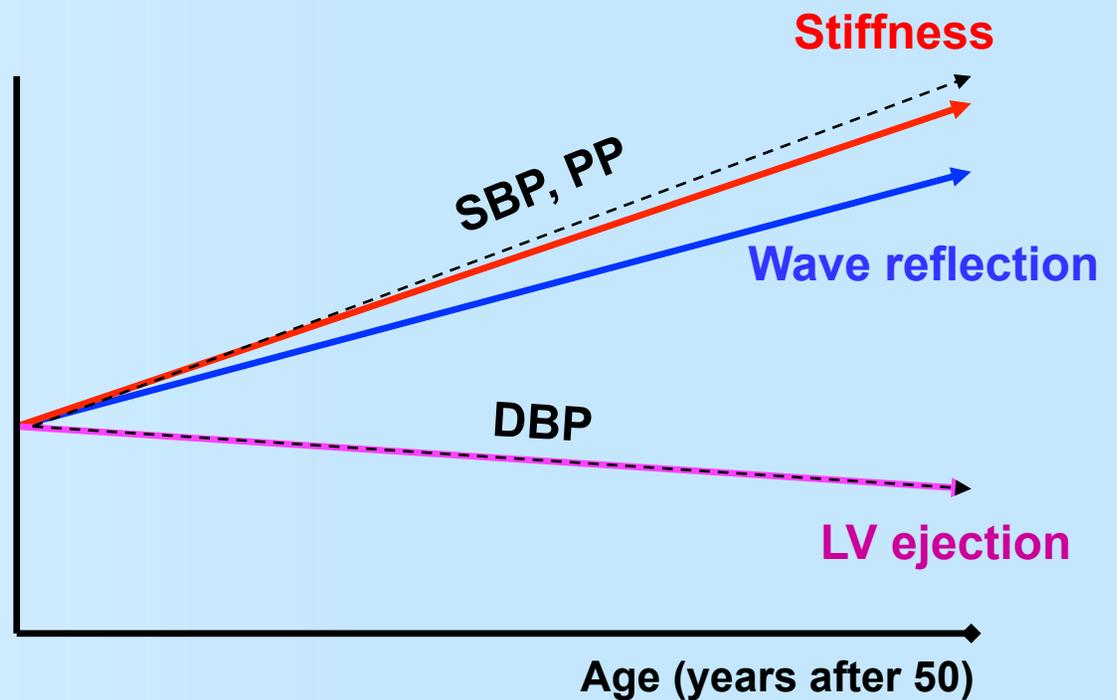
- Age 60, BP = 138/42 (MAP 74) mmHg – do I reduce treatment?
- Age 80, BP = 160/50 (MAP 88) mmHg – do I increase treatment?
- Age 70, BP = 184/54 (MAP 97) mmHg – do I increase treatment?

Low DBP as a Clinical Problem

How does it develop?



Steady BP (MAP) = CO x SVR
 Pulsatile BP (PP) = SV, aortic stiffness, wave reflection



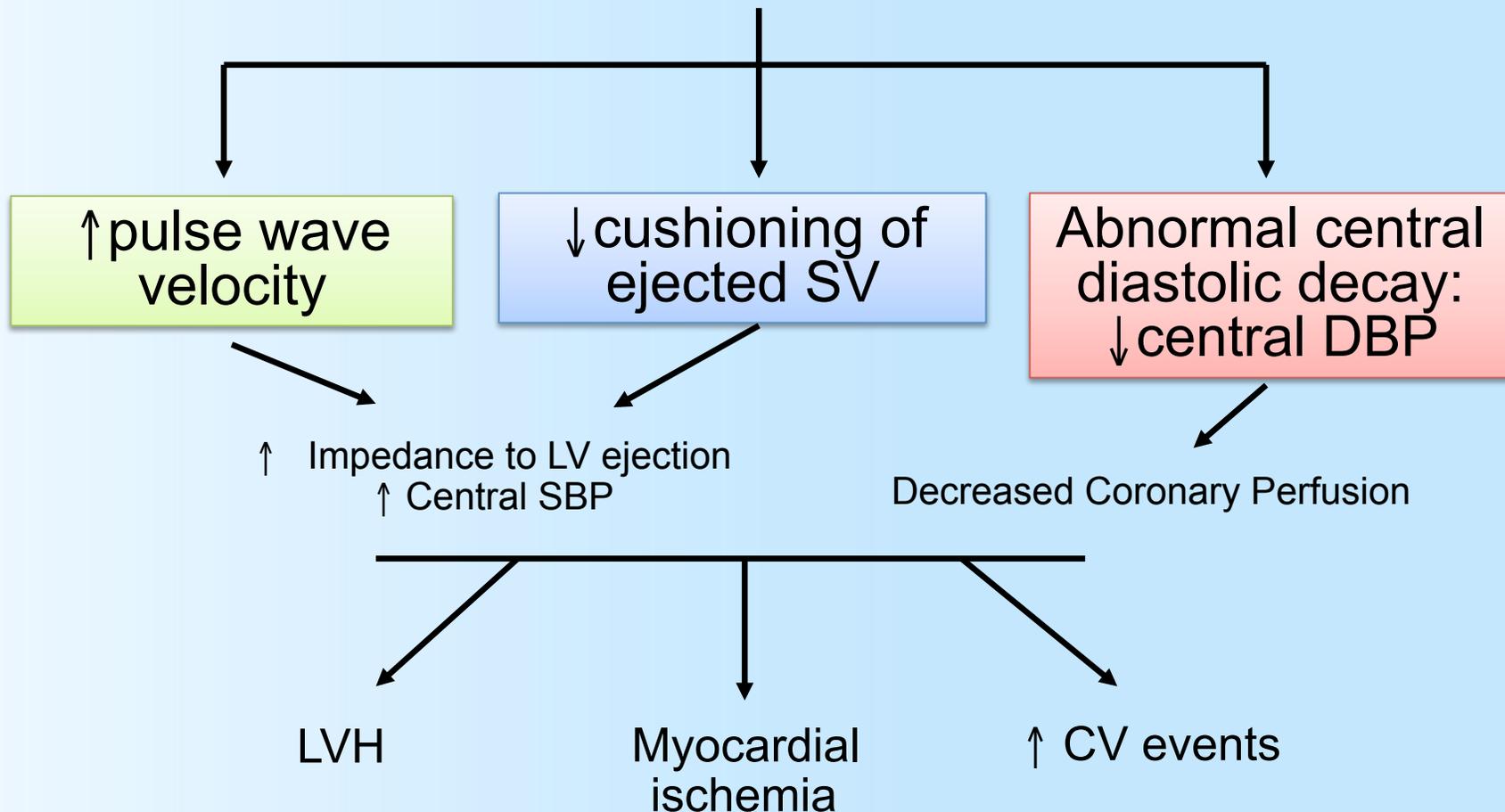
Mitchell. J Appl Physiol 2008; 105: 1652-60

Adapted from Safar. Circulation 2003;107:2864-9.

Low DBP as a Clinical Problem

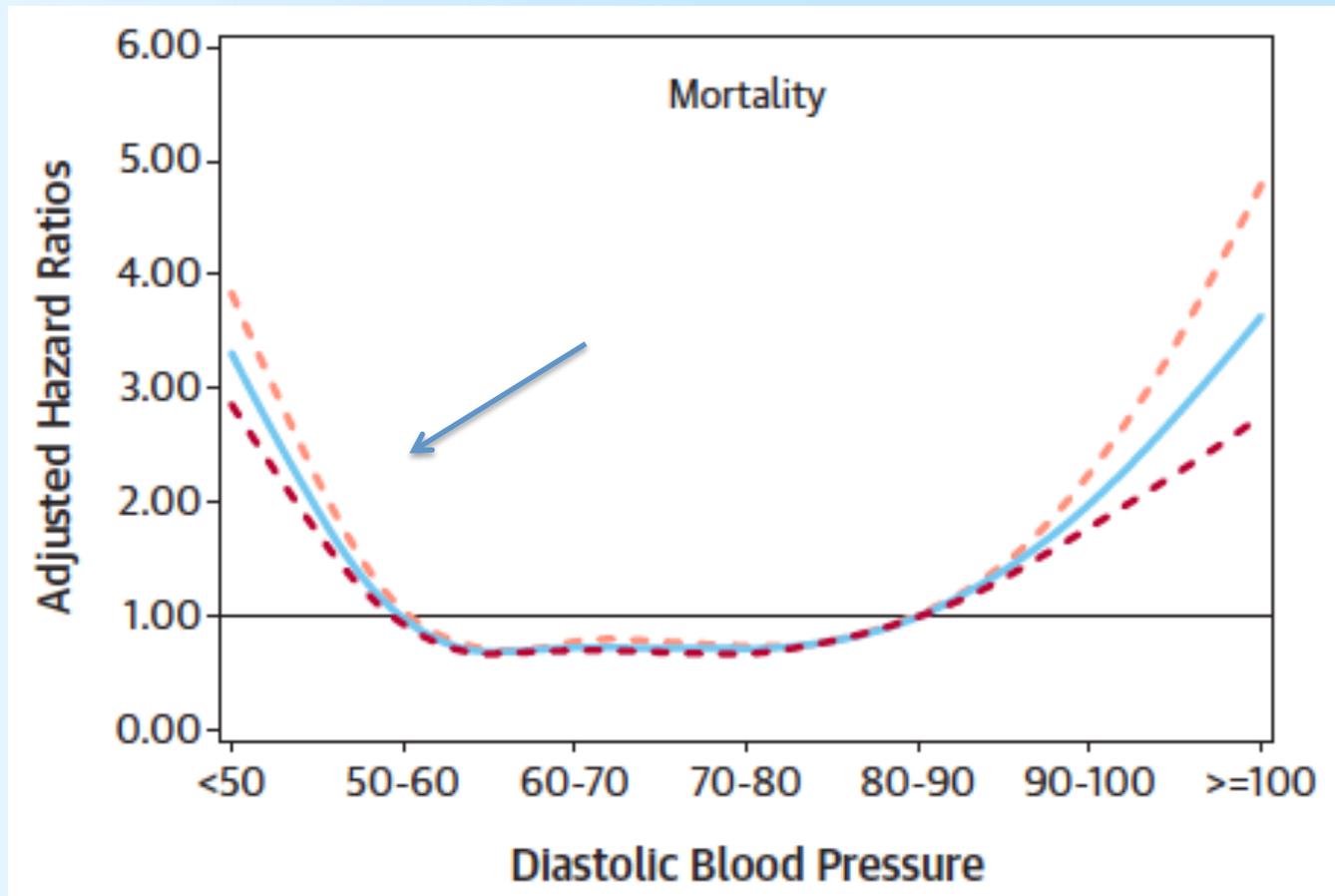
What are its consequences?

Vascular Aging = Arterial stiffening



Low DBP as a Clinical Problem

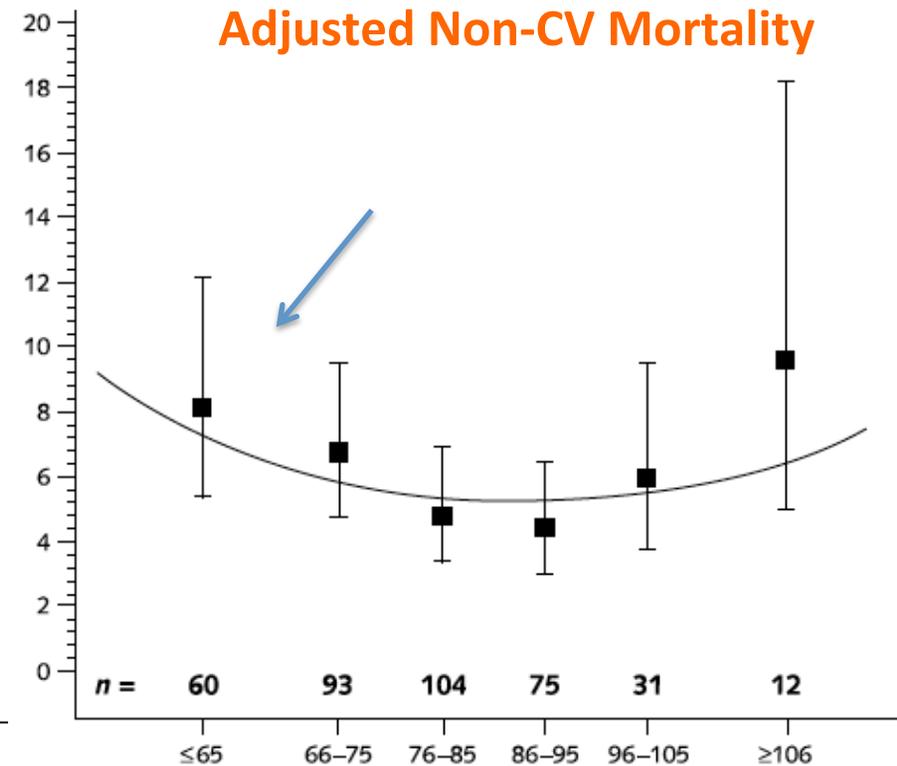
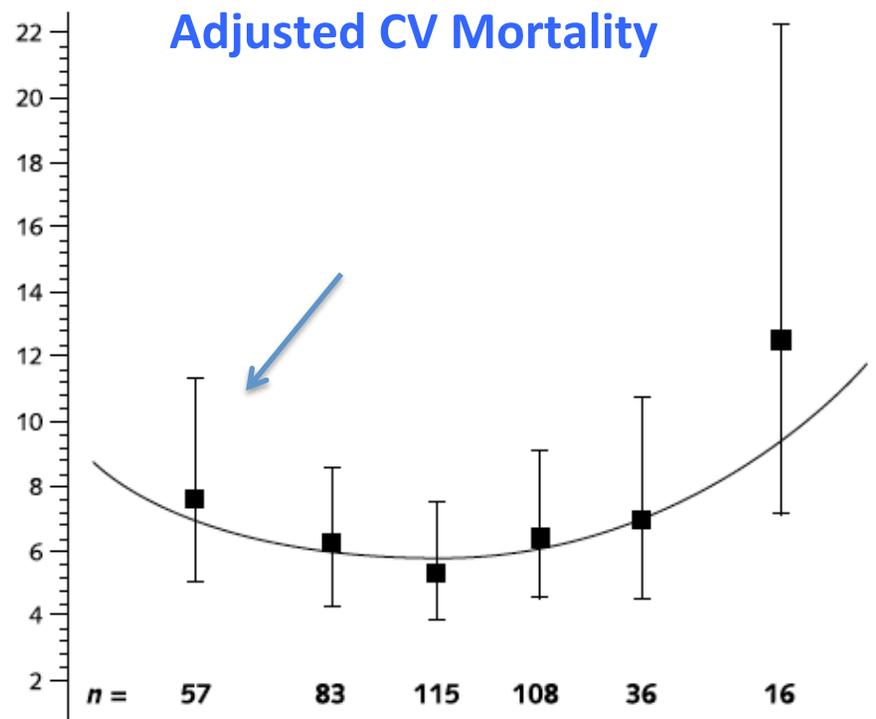
What are its consequences?



Sim et al. J Am Coll Cardiol 2014;64:588-97.

Low DBP as a Clinical Problem

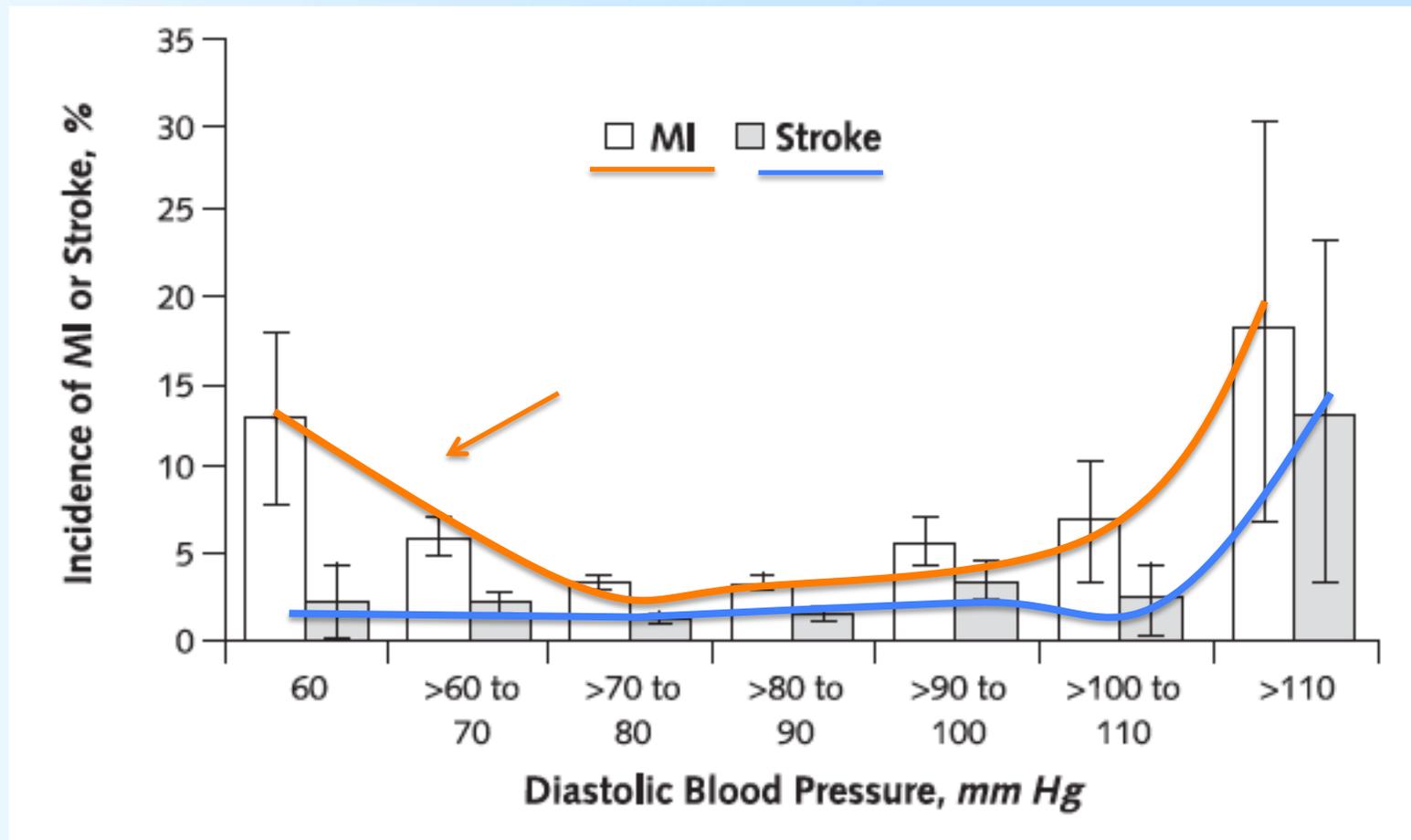
What are its consequences?



Boutitie et al. Ann Intern Med 2002;136:438-48.

Low DBP as a Clinical Problem

What are its consequences?



Messerli et al. Ann Intern Med 2006;144:884-93.

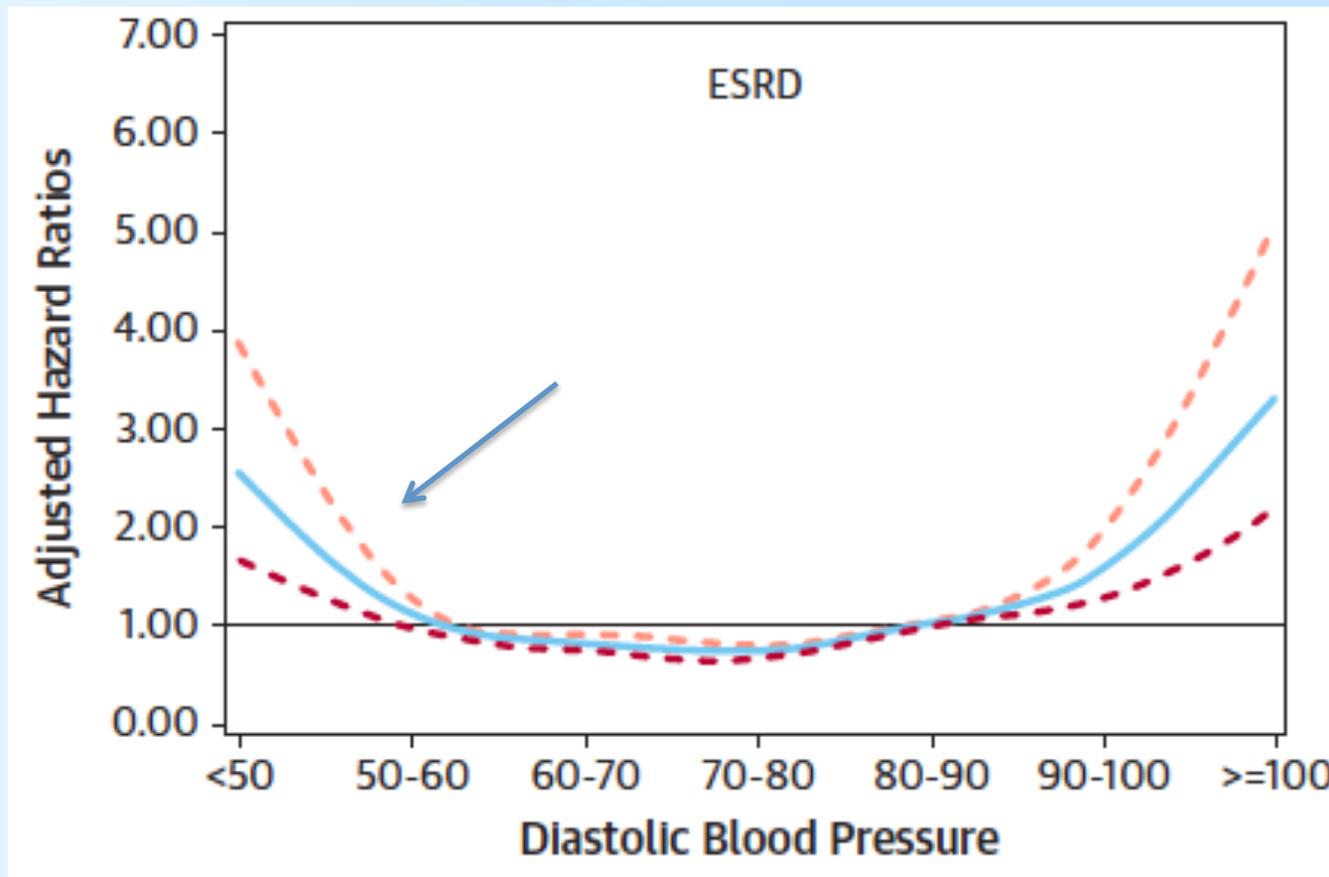
Low DBP in CKD

- CKD is a major cause of accelerated vascular aging
- Markers of arterial stiffness are commonly abnormal in CKD
- Low DBP is common in CKD (20-25% with DBP <60 mmHg)

Clinical Relevance of Low DBP to Kidney Disease Development and Progression

- Does low DBP cause kidney disease?

Diastolic BP and Risk of ESRD in Patients with HTN



Sim et al. J Am Coll Cardiol 2014;64:588-97.

Diastolic BP and ESRD Risk in Chinese Adults Aged 40 and Older

BP Quintile (Range)	Person-Years	No. with ESRD	Age-Standardized Rate per 100,000 Person-Years ^a	Age- and Gender-Adjusted HR (95% CI) ^b	<i>P</i>	Multivariate Adjusted HR (95% CI) ^c	<i>P</i>
DBP (mmHg)							
1 (<68)	247,500	61	21.6	1.0		1.0	
2 (68 to 74)	258,917	47	16.2	0.78 (0.53 to 1.14)	0.203	0.77 (0.53 to 1.13)	0.181
3 (74 to 80)	236,001	73	26.8	1.27 (0.90 to 1.79)	0.175	1.22 (0.86 to 1.72)	0.266
4 (80 to 87)	252,030	74	26.1	1.12 (0.79 to 1.58)	0.531	1.05 (0.74 to 1.50)	0.780
5 (≥87)	241,892	125	45.5	1.81 (1.32 to 2.48)	<0.001	1.58 (1.13 to 2.20)	0.007
<i>P</i> for trend					<0.001		0.001

Reynolds et al. J Am Soc Nephrol 2007;18:1928-35.

Diastolic BP and Risk of Loss of GFR in Elderly Patients

Odds of rapid decline in eGFR (CyC)

DBP range	Odds Ratio	95%CI
<70 mmHg	1.0 (ref)	
70-79 mmHg	1.10	0.93-1.30
80-89 mmHg	1.29	1.02-1.57
>90 mmHg	1.55	1.11-2.15

Rifkin et al. Am J Hypertens 2013;26:1037-44.

Clinical Relevance of Low DBP to Kidney Disease Development and Progression

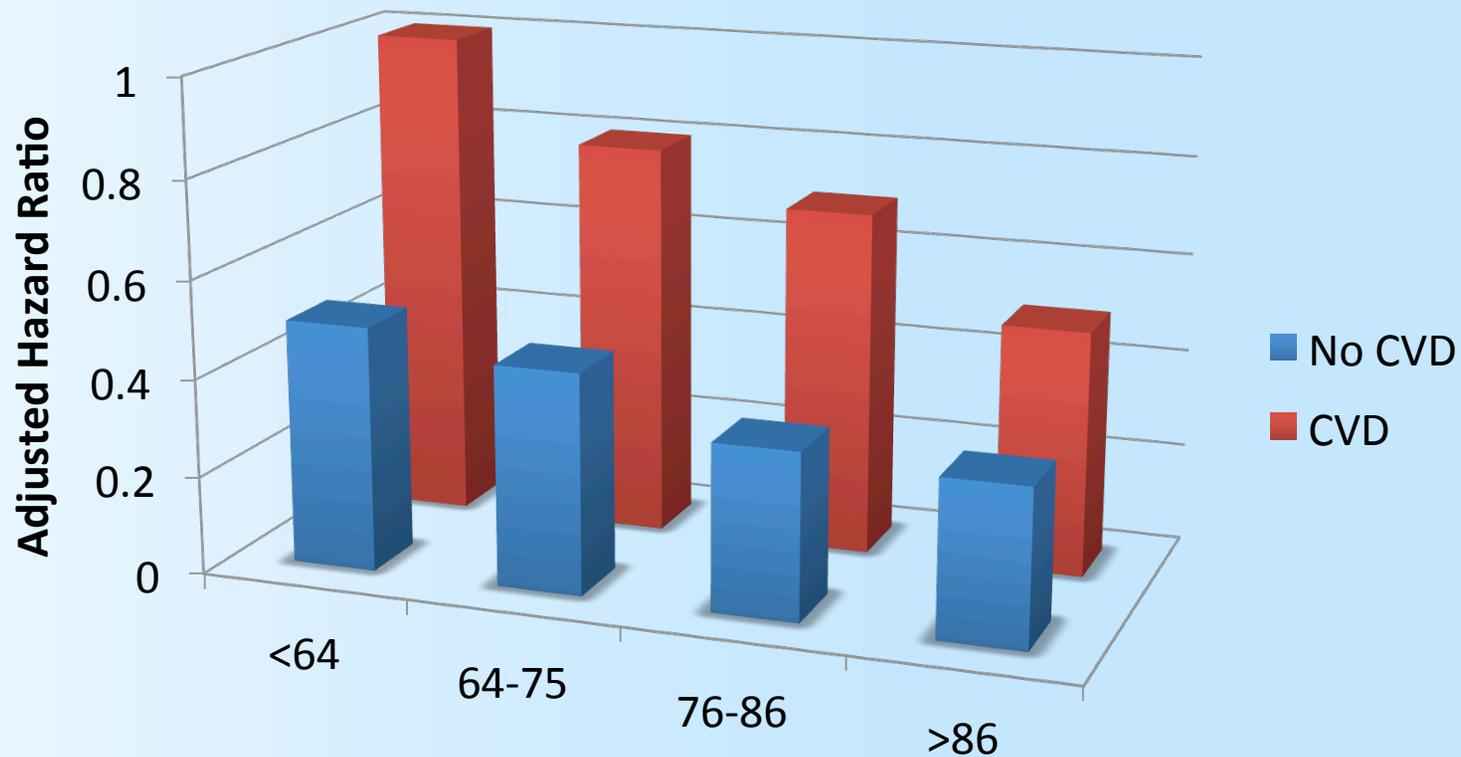
- Is low DBP associated with the development of kidney disease?
- Is low DBP associated with adverse CV outcomes and mortality in patients with CKD?

Impact of Each 10 mmHg Lower Achieved DBP in the Irbesartan Diabetic Nephropathy Trial (IDNT)

Outcome		RR (95% CI)	P Value
All-cause mortality		1.18 (0.98 to 1.42)	0.09
CV death	+	1.11 (0.85 to 1.46)	0.44
MI	-	1.61 (1.28 to 2.02)	<0.0001
CHF		1.15 (0.99 to 1.33)	0.07
Stroke		0.65 (0.48 to 0.88)	0.005

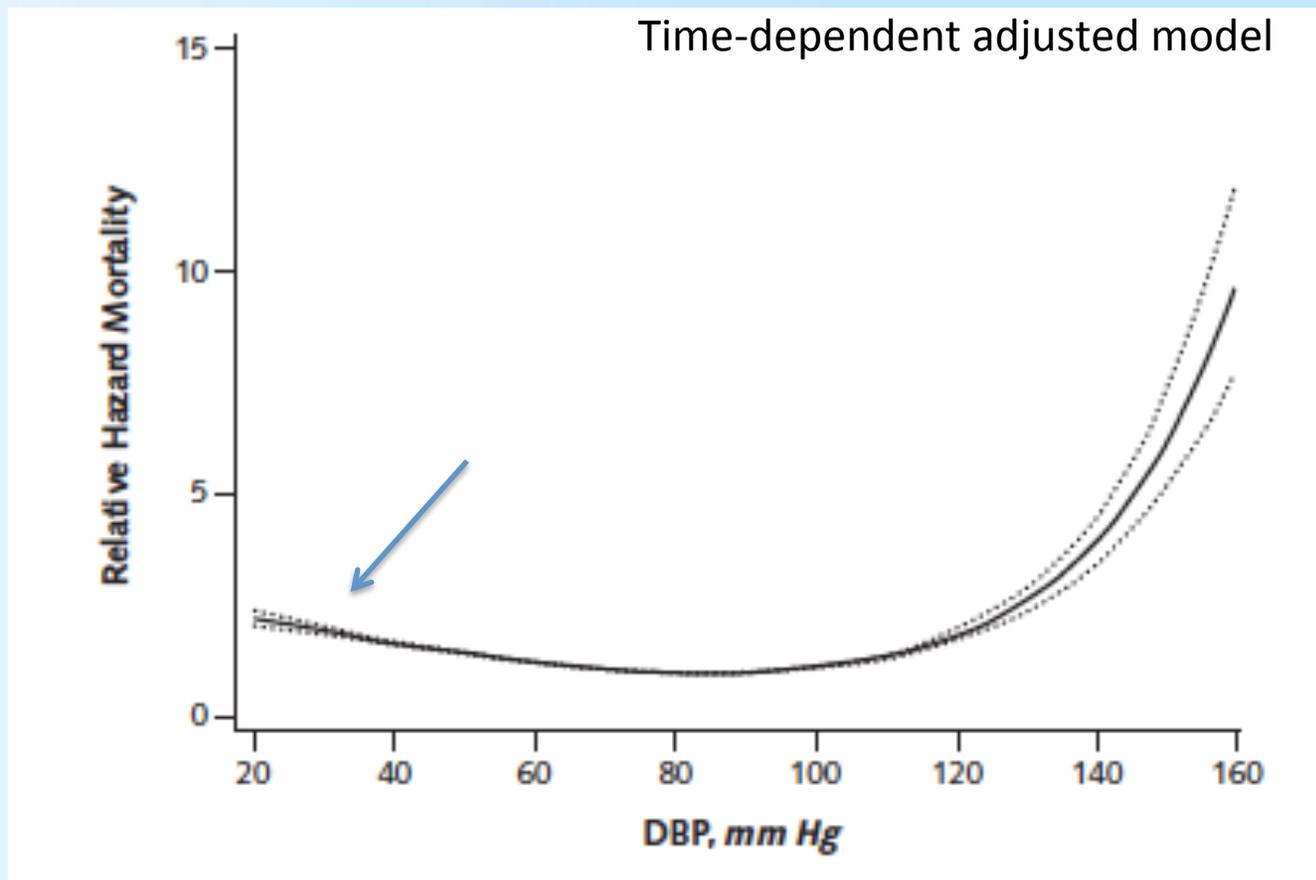
Berl et al. J Am Soc Nephrol 2005;16:2170-9.

Diastolic BP and Total Mortality in CKD



Kovesdy et al. Nephrol Dial Transplant 2006;21:1257-62.

DBP and Risk of Death in CKD



Kovesdy et al. Ann Intern Med 2013;159:233-42.

Integrated Model of SBP and DBP and Risk of Death in CKD

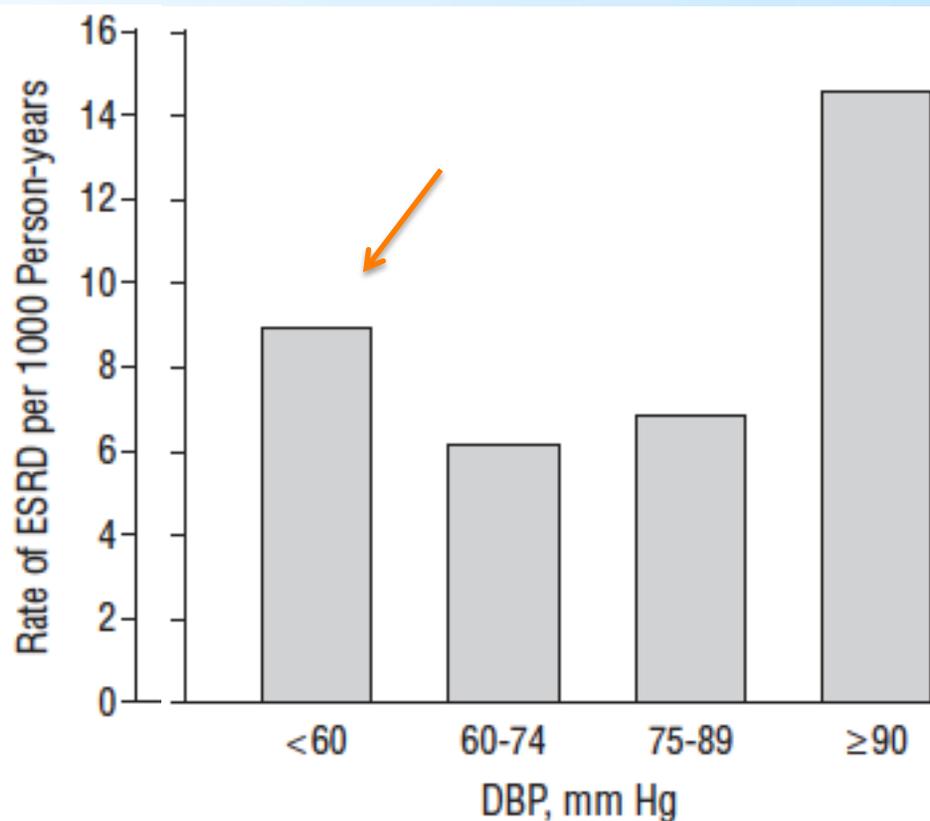
Variable	SBP						
	<80 mm Hg	80–89 mm Hg	90–99 mm Hg	100–109 mm Hg	110–119 mm Hg	120–129 mm Hg	130–139 mm Hg
DBP							
Crude model							
<40 mm Hg	5.88	5.56	5.20	4.19	3.32	3.07	3.07
40–49 mm Hg	6.03	5.32	4.64	3.45	2.87	2.50	2.44
50–59 mm Hg	5.84	4.91	3.84	3.01	2.52	2.10	1.82
60–69 mm Hg		4.72	3.28	2.49	2.07	1.75	1.55
70–79 mm Hg			2.67	1.81	1.41	1.25	1.17
80–89 mm Hg				2.01	1.12	0.94	0.90
90–99 mm Hg					1.75	0.93	0.78
100–109 mm Hg							1.19
110–119 mm Hg							
≥120 mm Hg							
Adjusted model†							
<40 mm Hg	2.56	2.42	2.55	2.15	1.73	1.69	1.91
40–49 mm Hg	2.99	2.69	2.31	1.77	1.58	1.39	1.37
50–59 mm Hg	3.25	2.88	2.24	1.77	1.51	1.27	1.14
60–69 mm Hg		3.11	2.32	1.82	1.48	1.23	1.09
70–79 mm Hg			2.05	1.70	1.34	1.14	1.01
80–89 mm Hg				1.82	1.27	1.08	0.98
90–99 mm Hg					1.57	1.26	1.08
100–109 mm Hg							1.53
110–119 mm Hg							
≥120 mm Hg							

Kovesdy et al. Ann Intern Med 2013;159:233-42.

Clinical Relevance of Low DBP to Kidney Disease Development and Progression

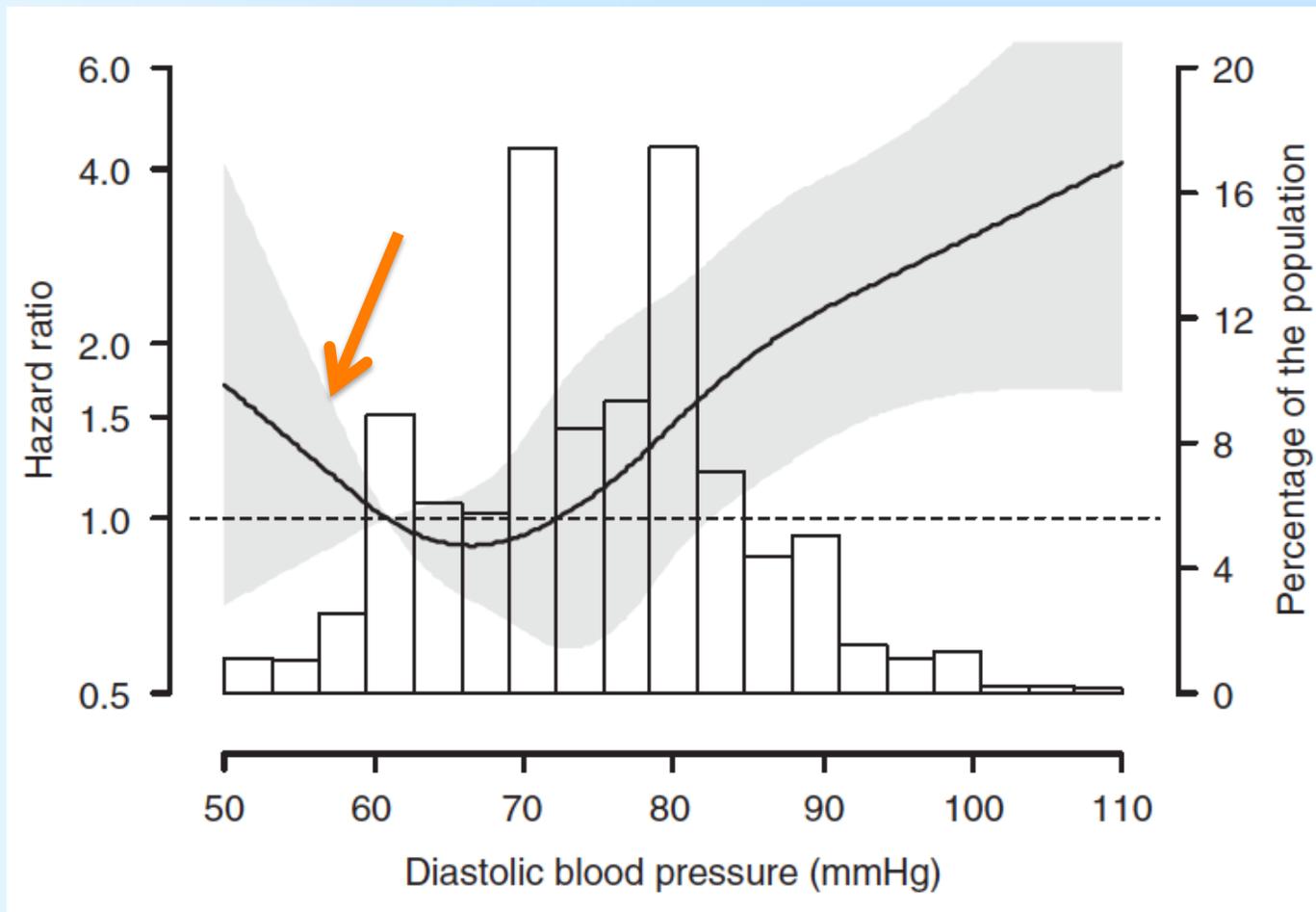
- Is low DBP associated with the development of kidney disease?
- Is low DBP associated with adverse CV outcomes and mortality in patients with CKD?
- Is low DBP associated with faster CKD progression?

DBP and Rate of Development of ESRD in Patients with Early CKD in the Kidney Early Evaluation Program (KEEP)



Diastolic	N	Adjusted HR
<60	692	1.12 (0.65-1.95)
60-74	5207	1 [Reference]
75-89	5716	0.91 (0.69-1.19)
≥90	2039	1.81 (1.33-2.45)

Diastolic BP and Risk of Progression to ESRD in Patients with CKD



Bell et al. Am J Hypertens 2012; 25: 785-96

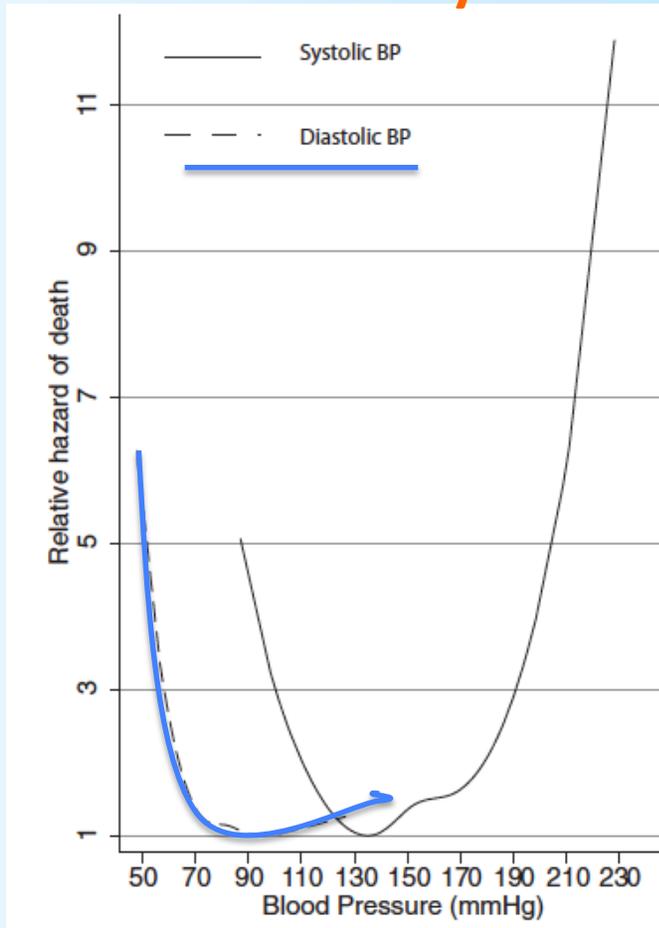
Diastolic BP and Risk of Death or Progression to ESRD in RENAAL

End Point	Event Rate Based on Baseline DBP			
	No. of Patients	Event, No. (%)	HR (95% CI)†	P Value
Primary: DBP, mm Hg				
<70	144	63 (43.8)	1.00 (Reference)	...
70-79	383	160 (41.8)	0.93 (0.69-1.24)	.60
80-89	579	274 (47.3)	1.11 (0.84-1.46)	.48
90-99	326	157 (48.2)	1.15 (0.86-1.55)	.33
≥100	81	32 (39.5)	0.90 (0.59-1.37)	.62
ESRD: DBP, mm Hg				
<70	144	32 (22.2)	1.00 (Reference)	...
70-79	383	77 (20.1)	0.89 (0.59-1.34)	.57
80-89	579	131 (22.6)	1.02 (0.69-1.50)	.94
90-99	326	81 (24.8)	1.14 (0.76-1.71)	.54
≥100	81	20 (24.7)	1.11 (0.64-1.94)	.71
ESRD or death: DBP, mm Hg				
<70	144	52 (36.1)	1.00 (Reference)	...
70-79	383	134 (35.0)	0.95 (0.69-1.31)	.76
80-89	579	213 (36.8)	1.02 (0.75-1.38)	.91
90-99	326	129 (39.6)	1.11 (0.81-1.54)	.51
≥100	81	27 (33.3)	0.93 (0.58-1.47)	.74

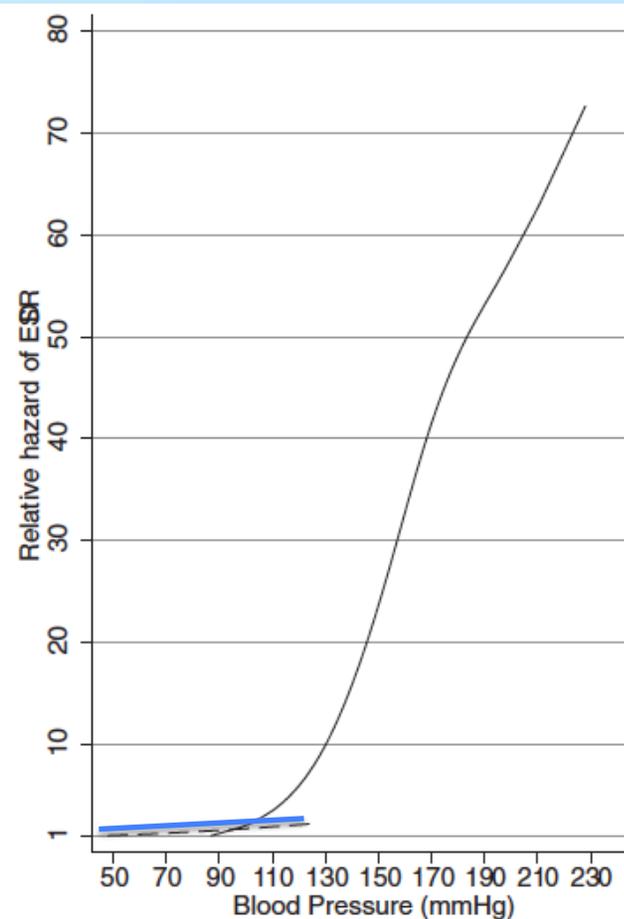
Bakris et al. Arch Intern Med 2003;163:1555-65. RENAAL=Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan

Diastolic BP and Risk of Progression to ESRD in Patients with CKD

Mortality



ESRD



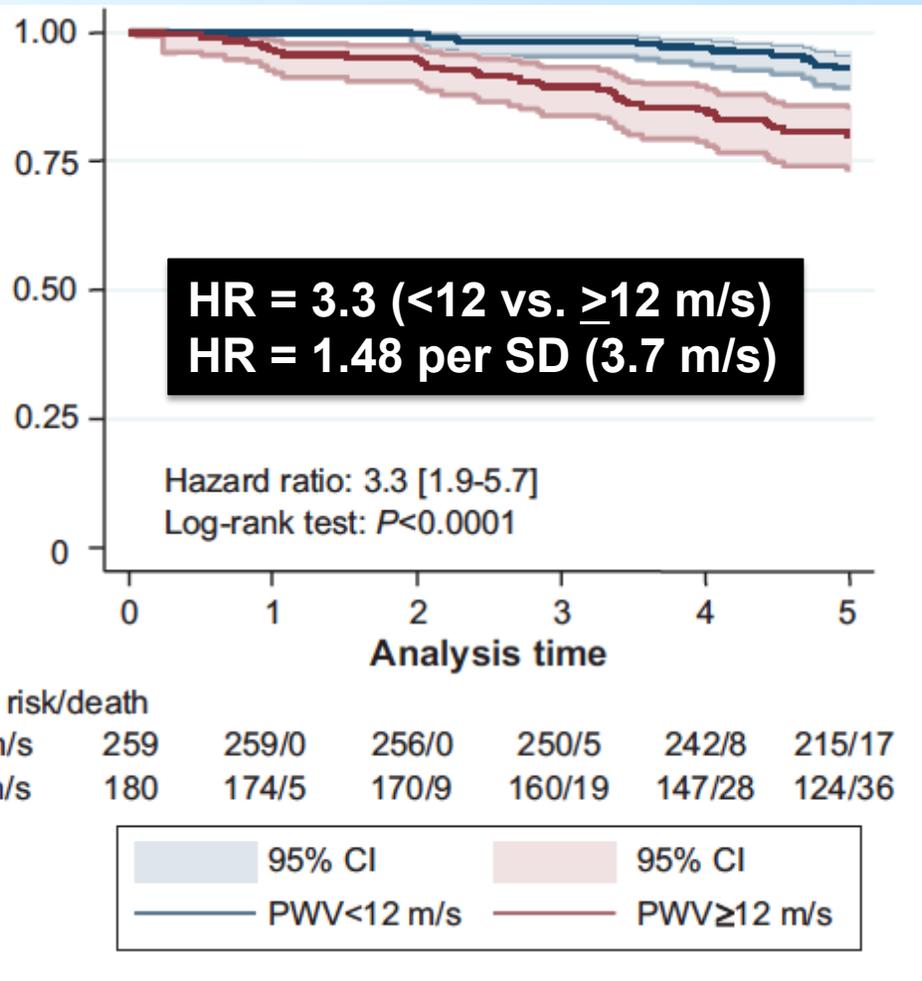
Agarwal. Clin J Am Soc Nephrol 2009;4:830-7.

Low DBP as a Result of Increased Arterial Stiffness

- Can measures of arterial stiffness predict outcomes in CKD better than BP alone?

Aortic PWV is Associated with Increased CV Events and Mortality in CKD 2-5

All-cause death



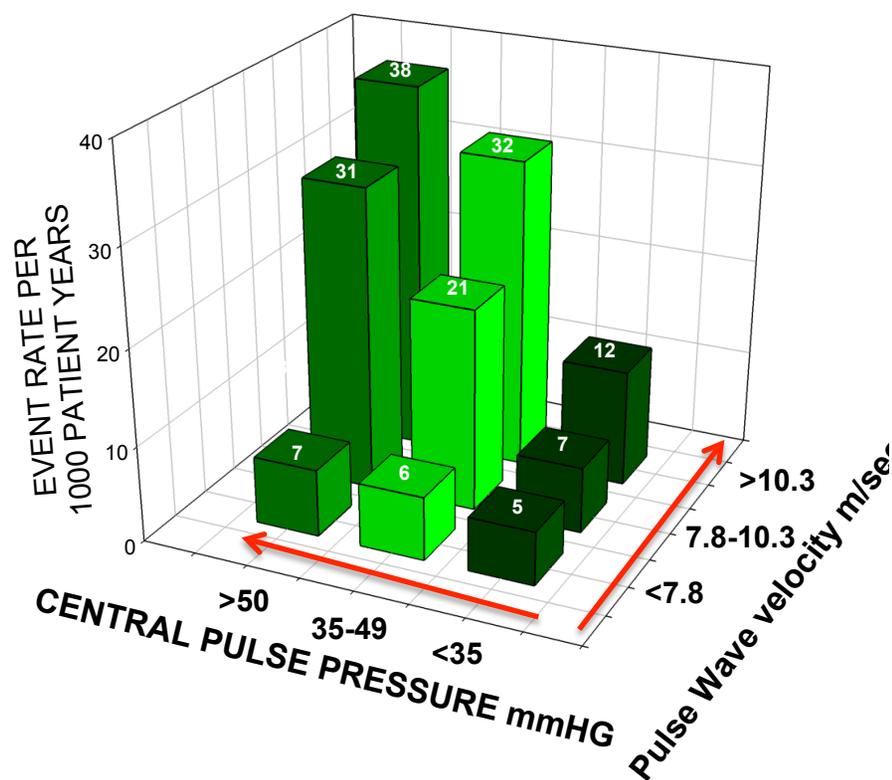
N = 439 CKD 3-5 ND
 Age = 60±14
 GFR = 37±18
 F/U = 4.7 years

PWV stronger than carotid stiffness, brachial PP, carotid PP.

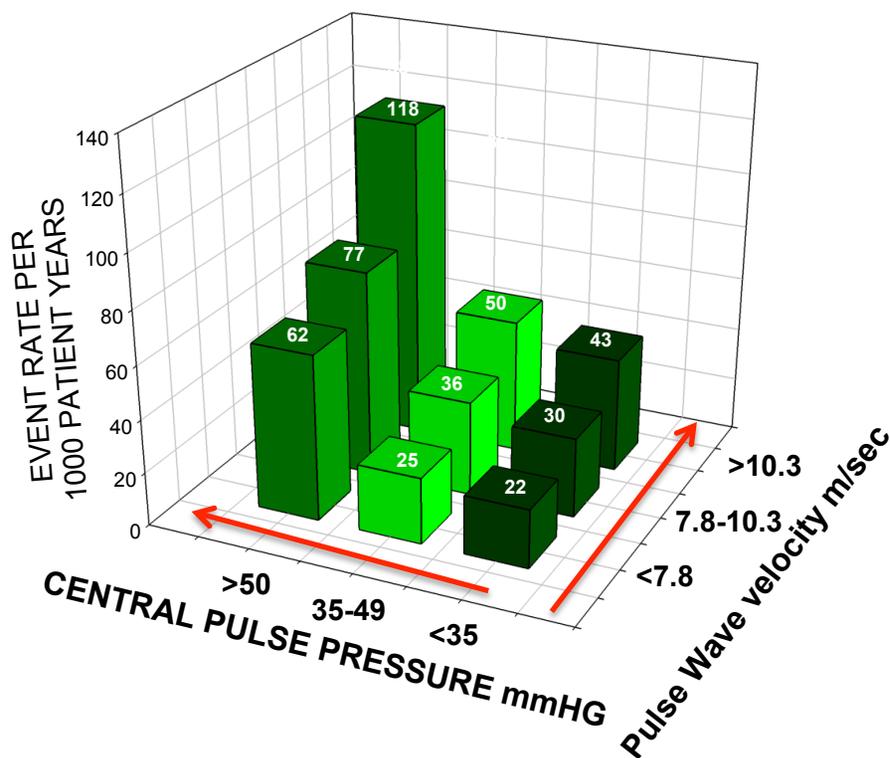
HR for CVE: 1.35 per SD, independent of competing risk (non-CV death)

Measures of Arterial Stiffness and Prediction of Clinical Events in Chronic Renal Insufficiency Cohort (CRIC) Study: Death and Renal Outcomes

DEATH
108 EVENTS



HALVING OF eGFR OR ESKD
244 EVENTS

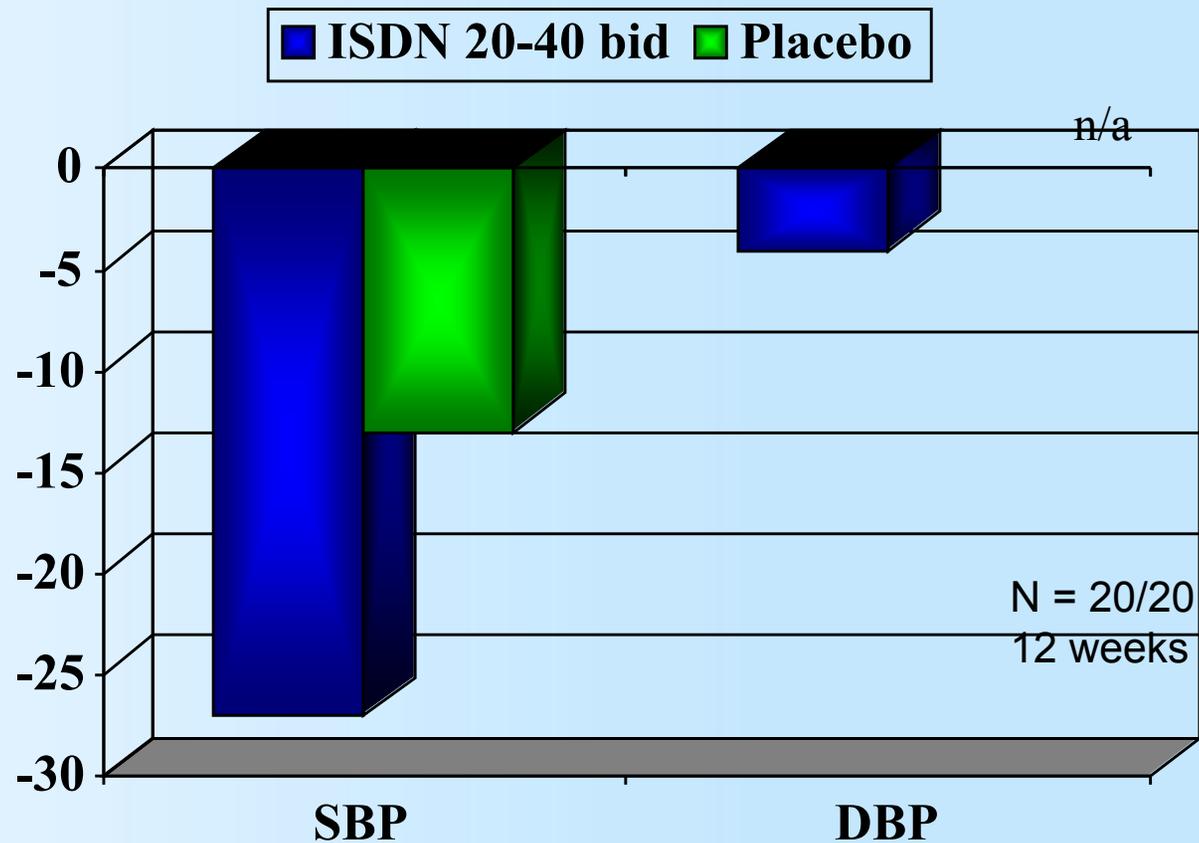


Ray Townsend, MD: Unpublished data.

Treatment Implications of the Available Evidence About Low DBP and Arterial Stiffness

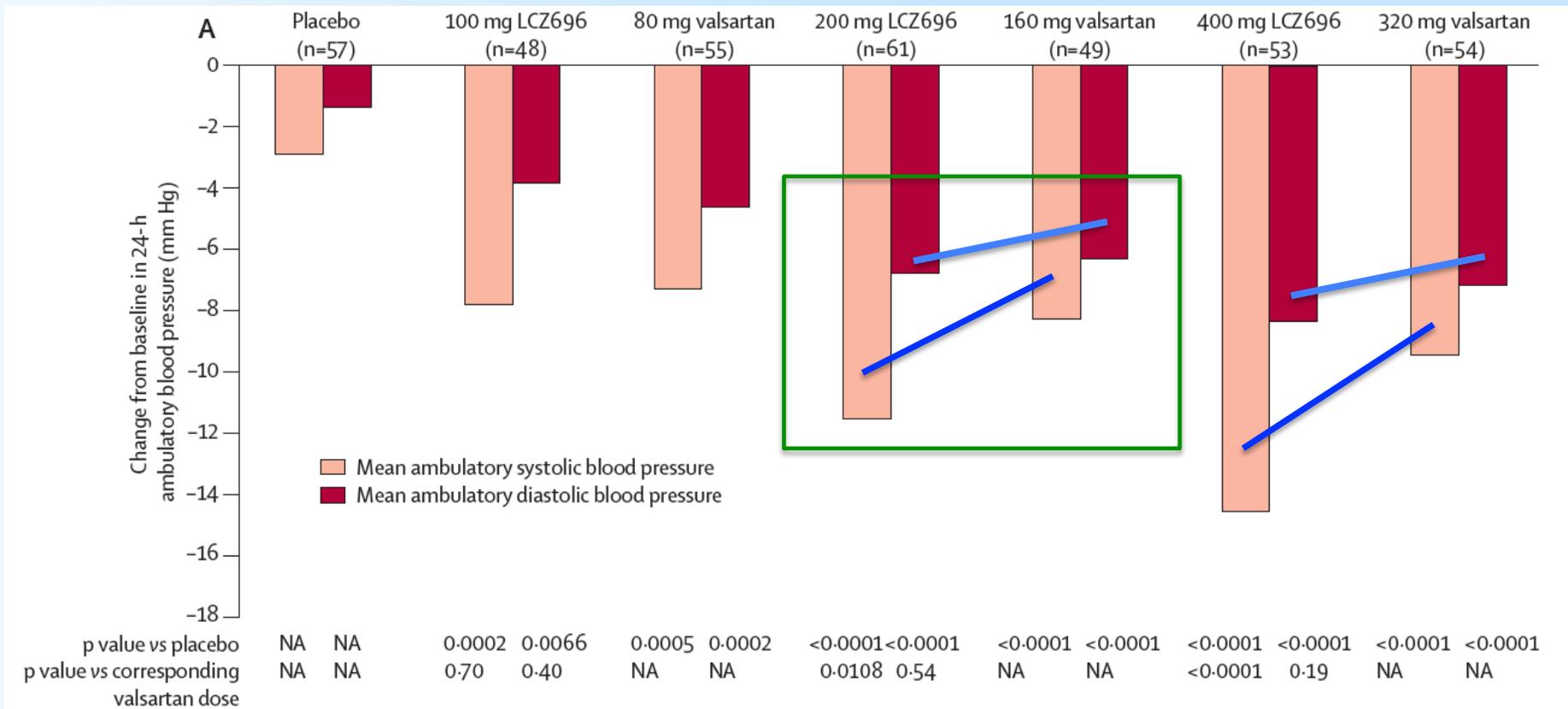
- Most BP drugs improve stiffness.
- Some treatments improve stiffness beyond BP reduction (exercise, Na restriction, RAS blockers, statins, ET1 antagonists).
- “De-stiffening” agents are not yet available.
- Most BP drugs lower both SBP and DBP to similar fractions.
- In short: arterial stiffness is potentially modifiable, low DBP is less so, but...

Nitrates Treat Isolated Systolic HTN in the Elderly with Little Effect on DBP



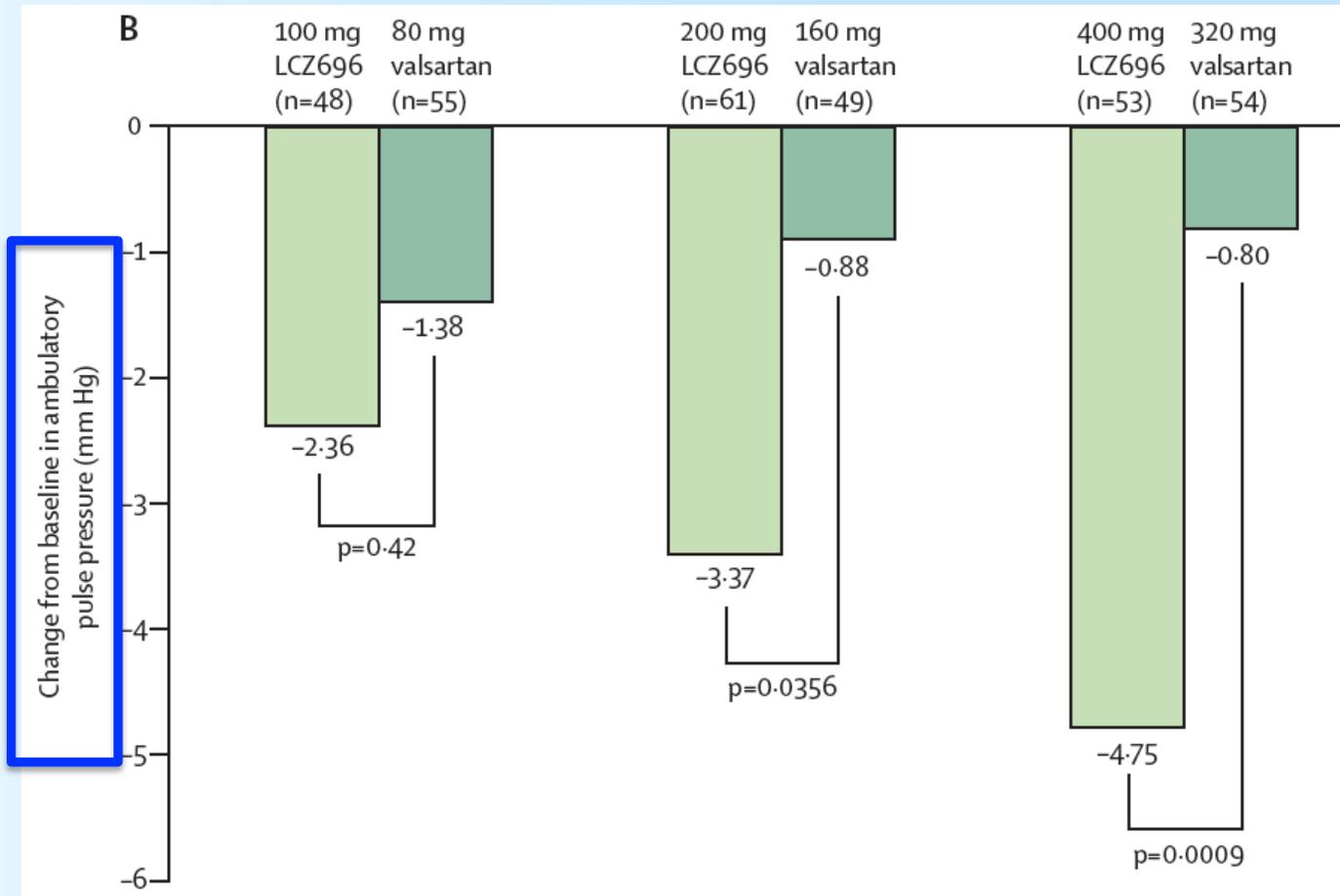
Duchier et al. Am J Cardiol 1987;60:99-102.

LCZ696 vs. Valsartan for 24h SBP/DBP



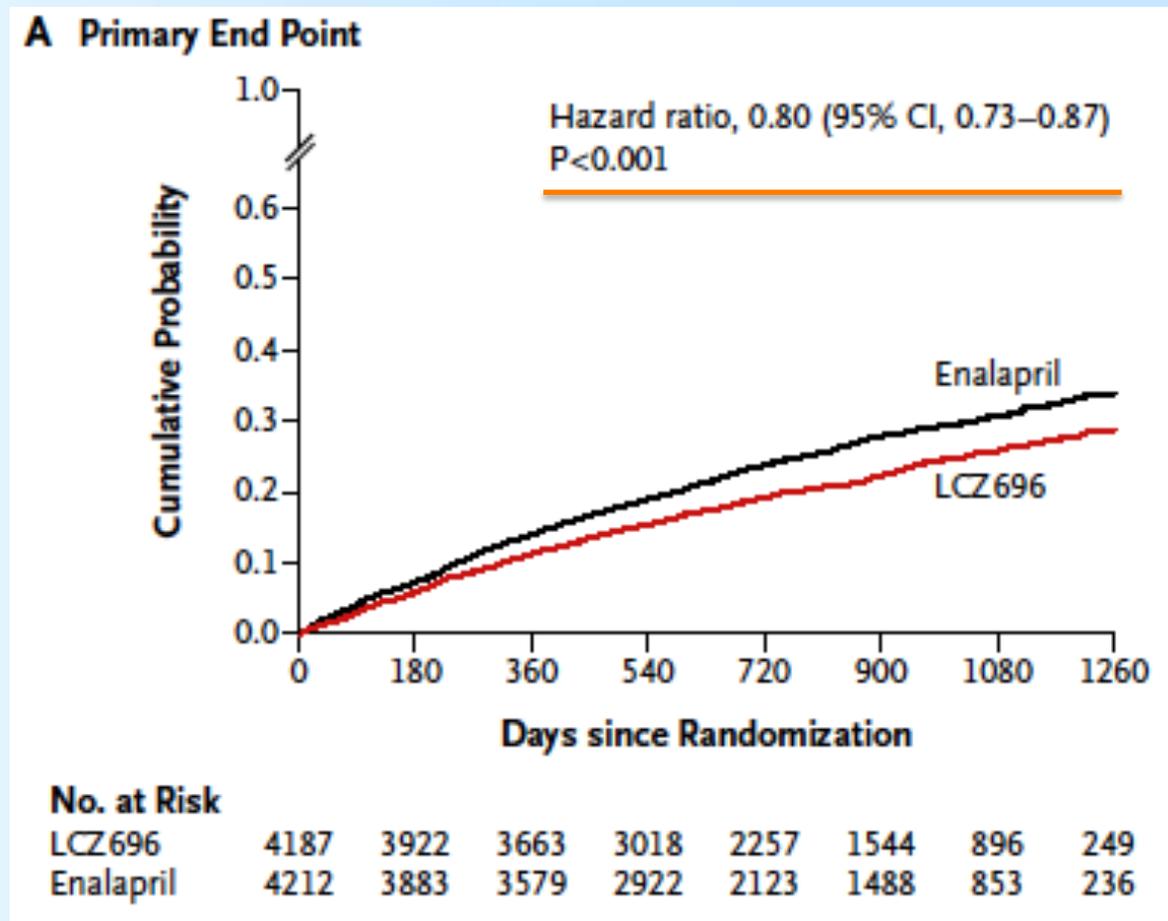
Ruilope et al. Lancet 2010;375:1255-66.

LCZ696 vs. Valsartan for Pulse Pressure



Ruilope et al. Lancet 2010;375:1255-66.

LCZ696 and Prognosis in Systolic HF



McMurray et al. NEJM 2014;371:993-1004.

Back to Our Clinical Questions

Asymptomatic patients with HTN on treatment:

- Age 60, BP = 138/42 (MAP 74) mmHg – do I reduce treatment?
- Age 80, BP = 160/50 (MAP 88) mmHg – do I increase treatment?
- Age 70, BP = 184/54 (MAP 97) mmHg – do I increase treatment?

Summary

- Low DBP results from vascular aging.
- Low DBP is associated with adverse coronary outcomes and mortality, particularly in elderly individuals and those with established CVD.
- Low DBP is associated with increased mortality in CKD.
- It is unclear that low DBP is associated with the development of new CKD or faster CKD progression.
- Treatment of established low DBP is difficult.