Hypertension and the Kidney: A perspective in 2017

Matthew R. Weir, MD
Professor and Director
Division of Nephrology
University of Maryland School of Medicine

Disclosure Slide

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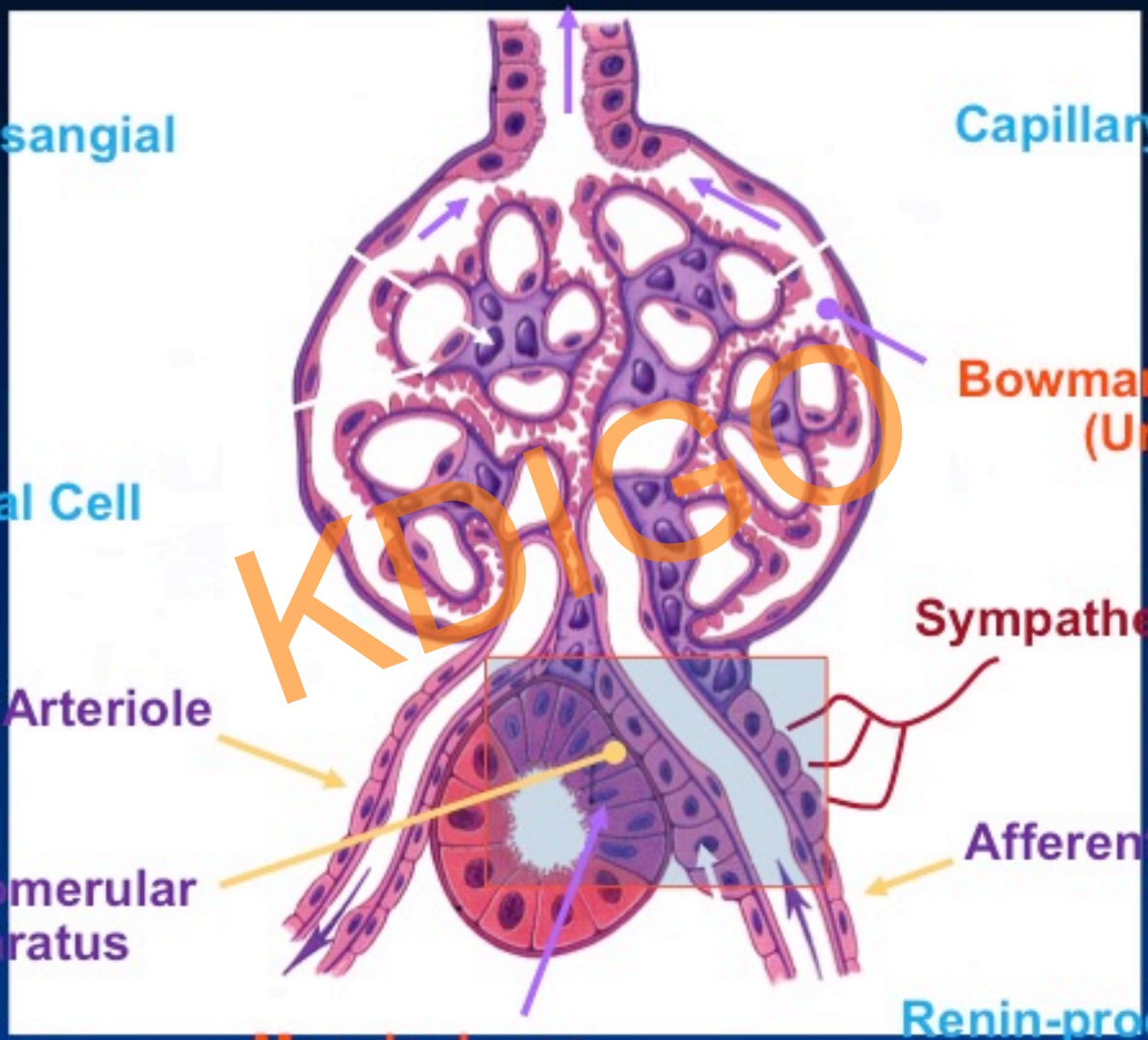
Learning Objectives

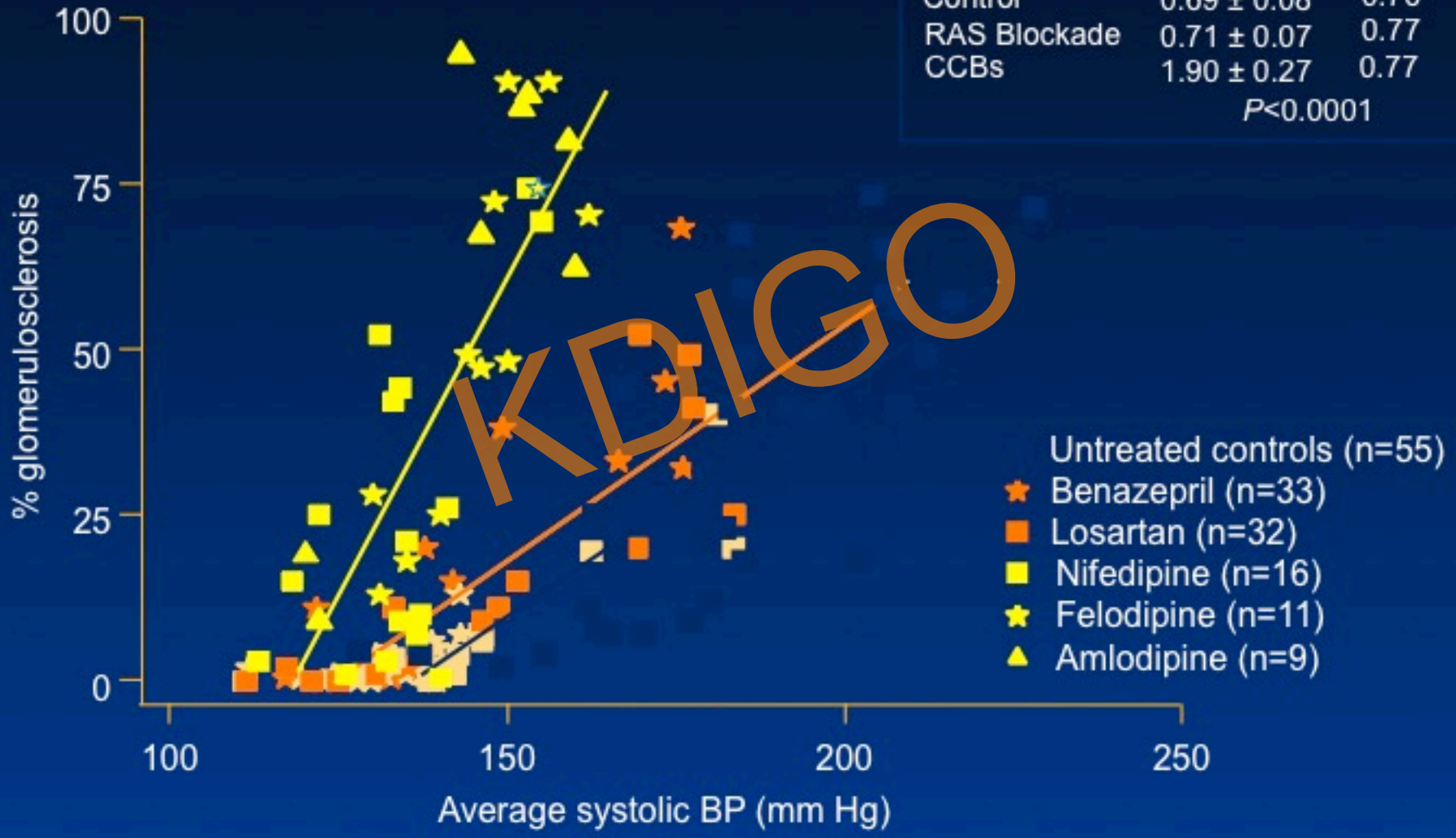
- Perspective
- Experimental Data
- Clinical Data in Non-DM
- Clinical Data in DM
- Summary

Glomerular Structure



Relationship of Renal Damage to BP

	Slopes	r
Control	0.69 ± 0.08	0.76
RAS Blockade	0.71 ± 0.07	0.77
CCBs	1.90 ± 0.27	0.77
	P<0.0001	



Griffin et al, *JCI* 96:793, 1995; *KI* 55: 1849, 1999; *Hypertens* 37: 1268; 2001; Bidani et al, *Kidney Int* 57: 1651, 2000.

Perspective

- All 3 RCT (MDRD, REIN-2, AASK) examining 2 levels of BP goals do not appear to convincingly show the benefit of a lower BP goal. The only exception might be in patients with more proteinuria (more than 1 g/day)

Jafar TH, et al. Ann Intern Med 139; 244-252, 2003.

Diabetic Kidney Disease

- No RCT examining different BP goals on renal outcomes
- No RCT examining the impact of reducing proteinuria, independent of BP, and renal disease progression
- We do have secondary analyses from trials in people with Type 2 DM and CKD

What is Your Definition of "Hypertension"?

- We must delete the word "hypertension"; it has no meaning
- The blood pressure goal should be established for each patient, based on the benefit: risk ratio for the therapeutic intervention

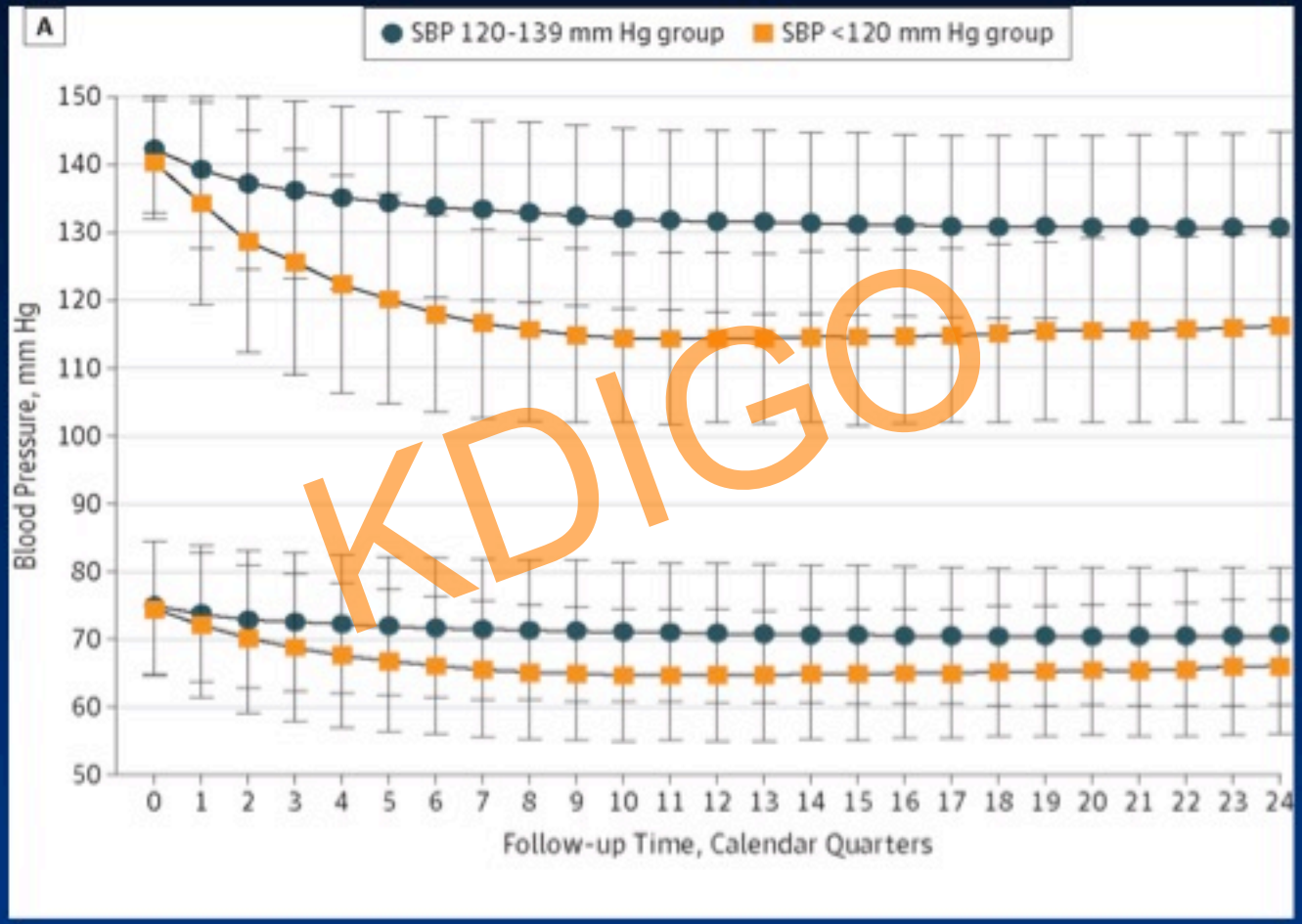
Causal Inference Requires Proof From Observation Evidence!

- Biological plausibility
- Evidence that the reversal of the risk factor is beneficial (interventional trials)

Mounting Evidence that the observational association of SBP with mortality in CKD and ESRD may be qualitatively different from that seen in patients with normal kidney function

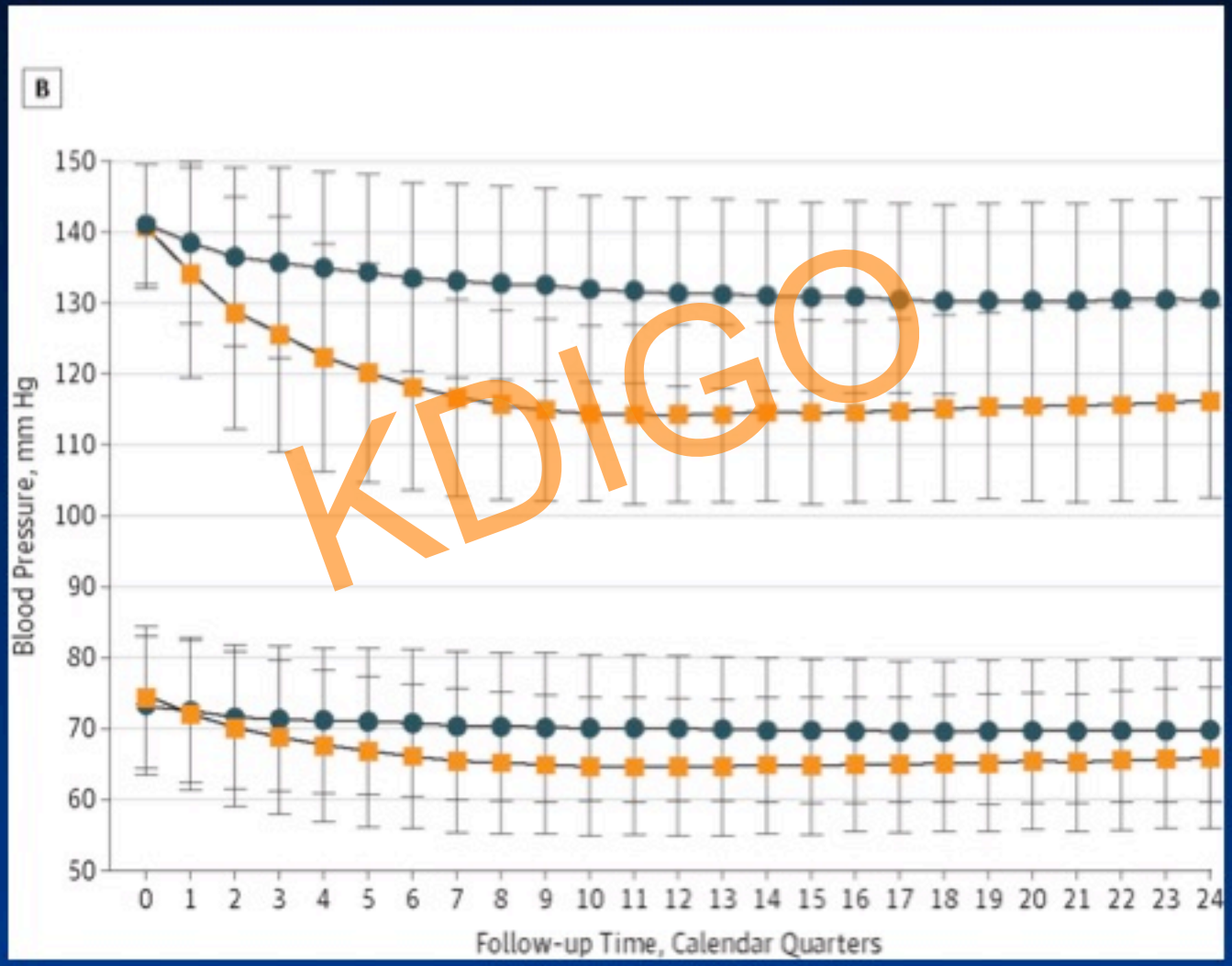
Do people with CKD or ESRD need different BP targets?

Follow-up Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) in Patients With SBP Less Than 120 vs 120 to 139 mmHg from a National VA database with eGFR < 60 ml/min (n=77,765) (overall cohort)



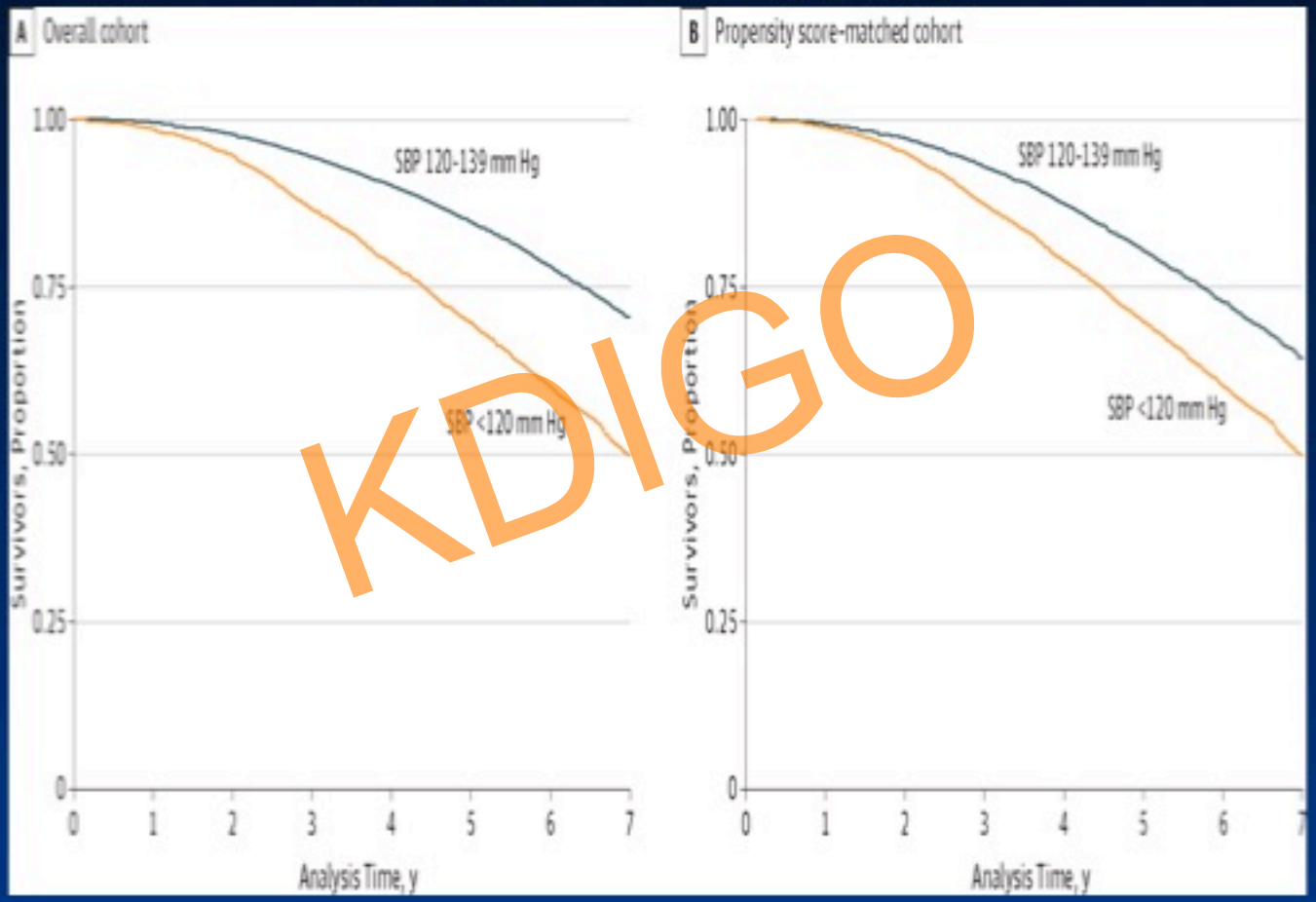
JAMA Intern Med. 2014;174(9):1442-1449. doi:10.1001/jamainternmed.2014.3279

Follow-up Systolic Blood Pressure (SBP) and Diastolic Pressure (DBP) in Patients with SBP Less Than 120 vs 120 to 139 mmHg from a National VA database with eGFR < 60 ml/min (propensity score-matched cohort)



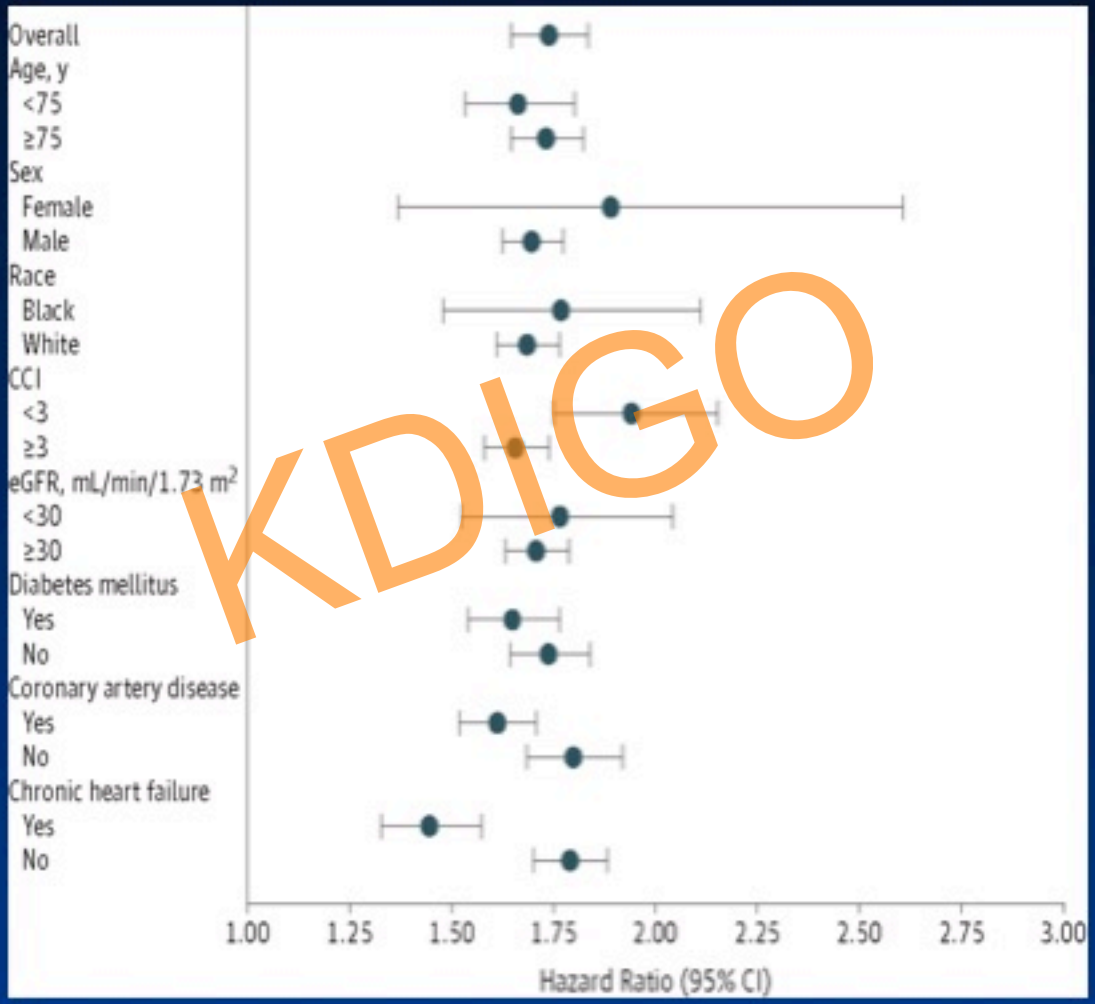
JAMA Intern Med. 2014;174(9):1442-1449. doi:10.1001/jamainternmed.2014.3279

Kaplan-Meier Survival Curves of Patients With Follow-up Systolic Blood Pressure (SBP) Less Than 120 vs 120 to 139 mm Hg



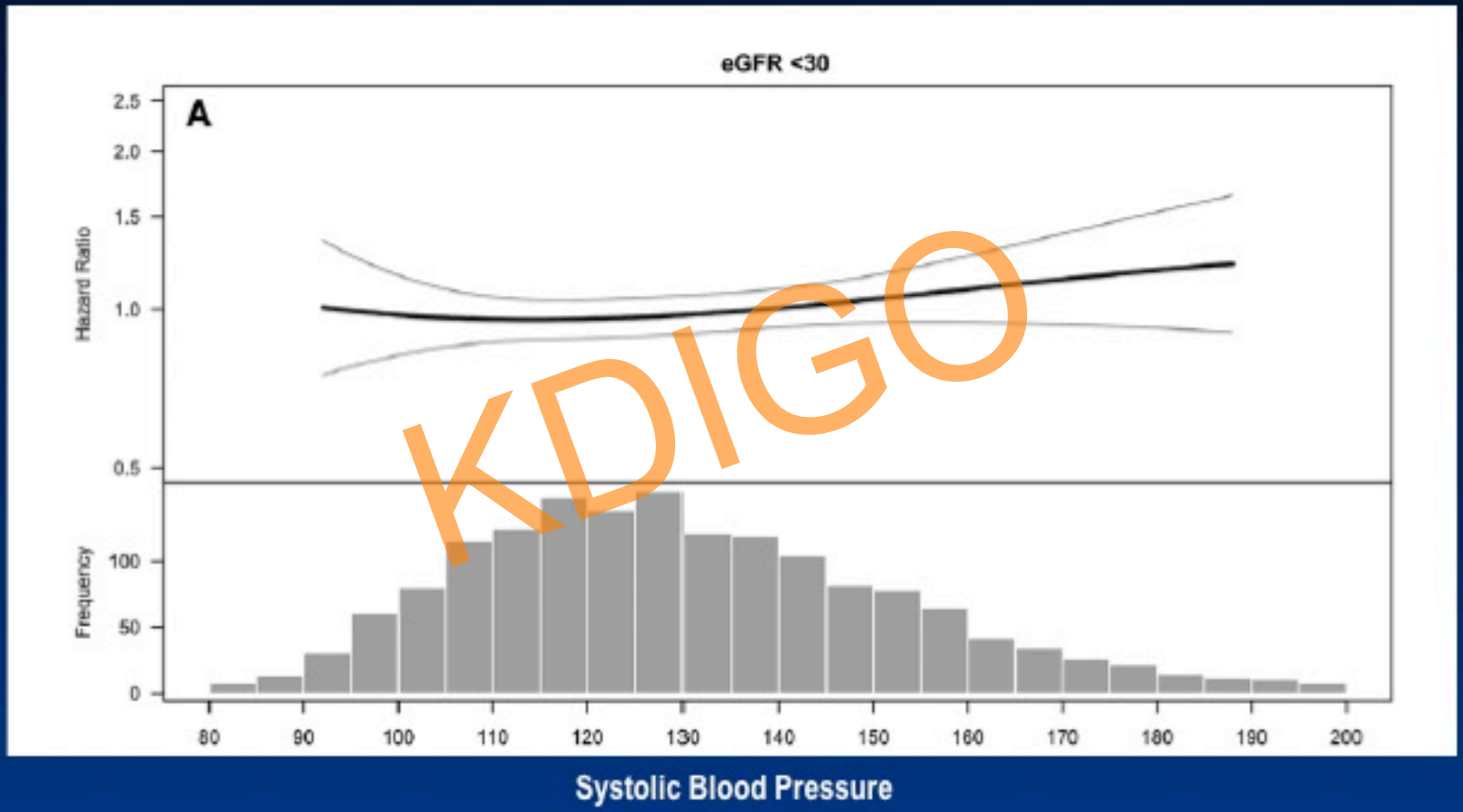
JAMA Intern Med. 2014;174(9):1442-1449. doi:10.1001/jamainternmed.2014.3279

Propensity Score–Adjusted Hazard Ratios of All-Cause Mortality Associated With Systolic Blood Pressure Less Than 120 vs 120 to 139 mmHg in Various Subgroups of Patients in the Overall Cohort



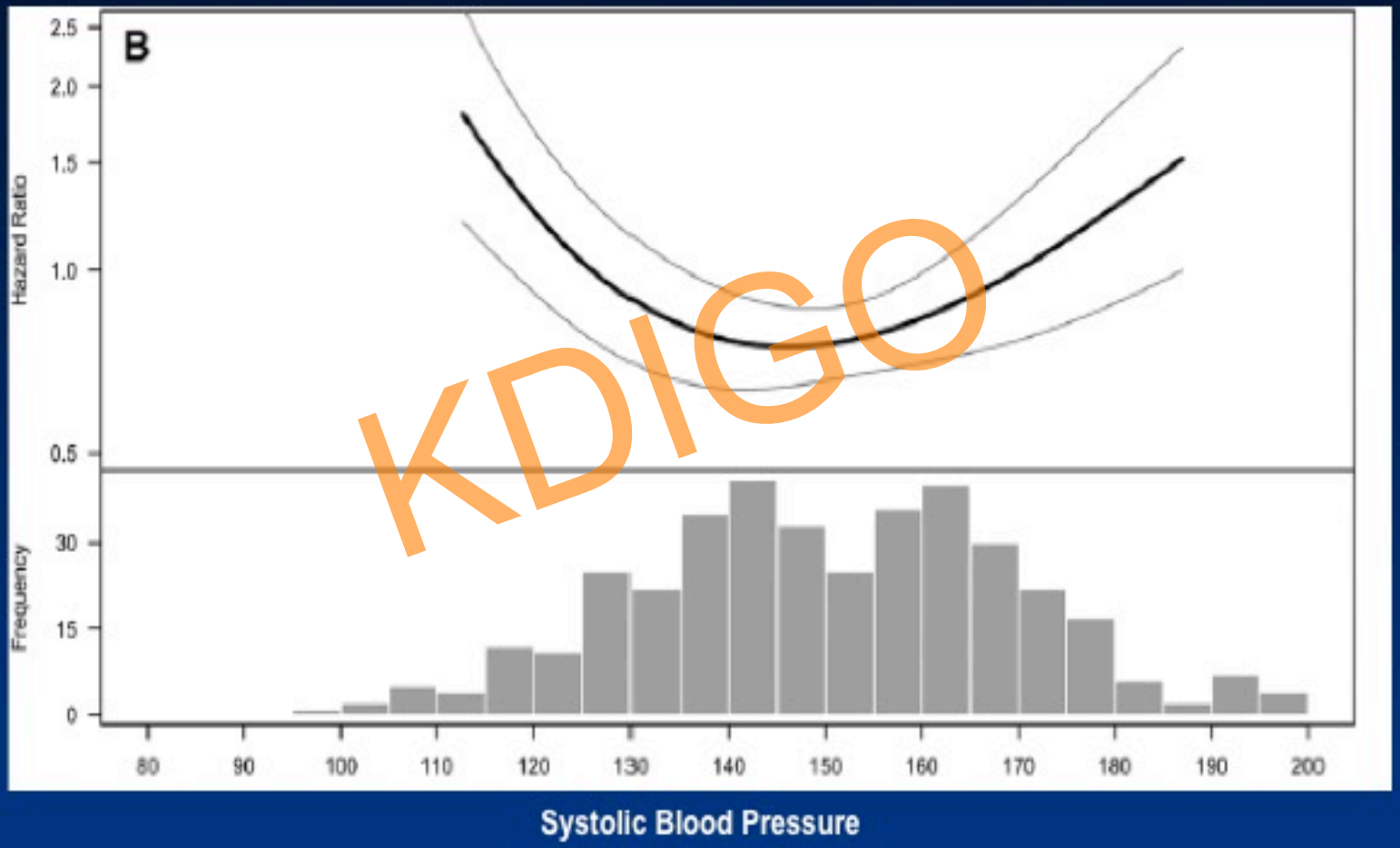
JAMA Intern Med. 2014;174(9):1442-1449. doi:10.1001/jamainternmed.2014.3279

Associations of systolic blood pressure (SBP) with mortality. The smooth spline estimates the hazard ratio of all-cause mortality, according to SBP (mm Hg) in CRIC participants with eGFR <30 ml/min



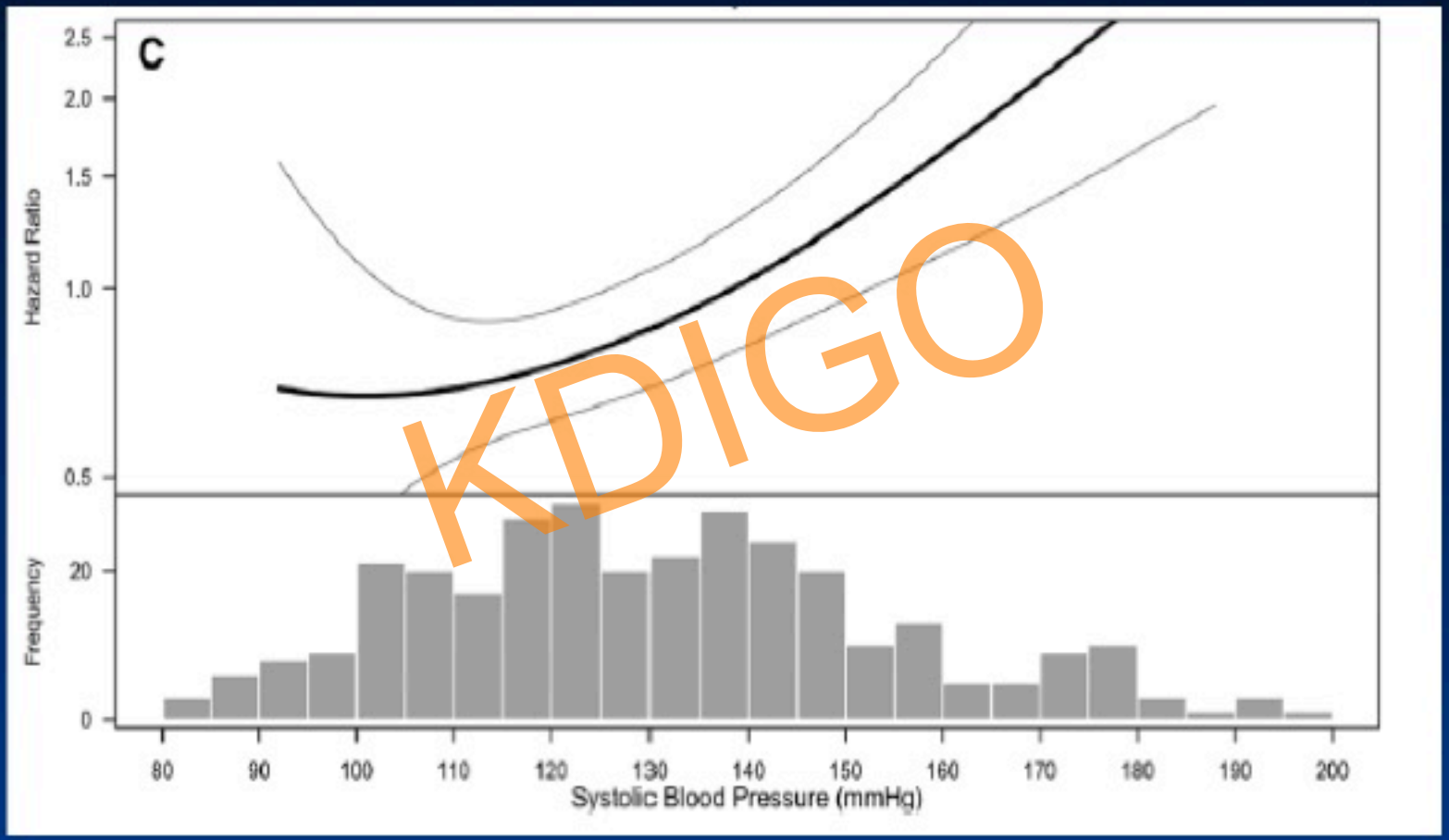
Hypertension 2015; 65:93-100.

Associations of systolic blood pressure (SBP) with mortality. The smooth spline estimates the hazard ratio of all-cause mortality, according to SBP (mm Hg) among CRIC participants with SBP measured in the dialysis unit



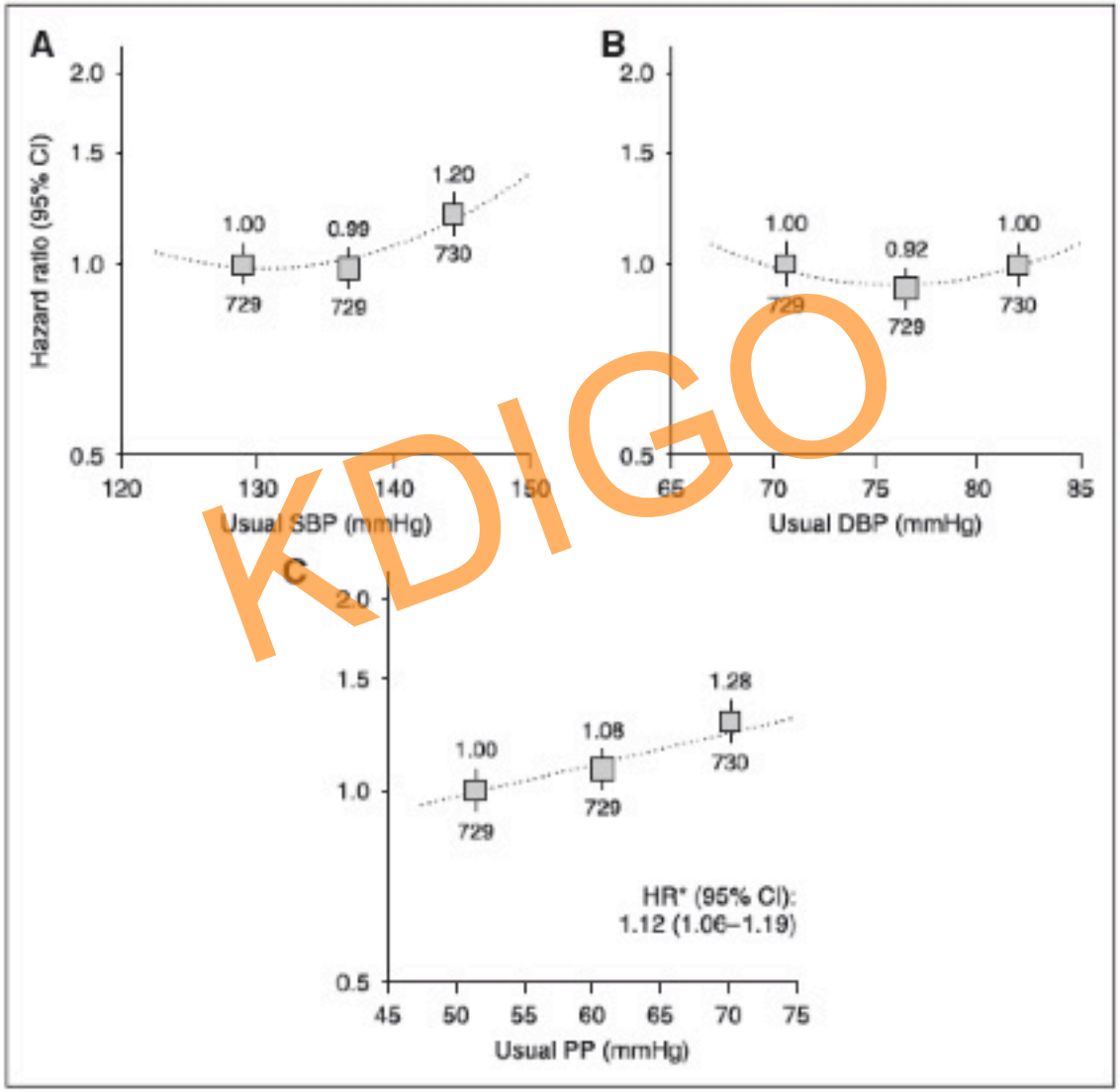
Hypertension 2015; 65:93-100.

Associations of systolic blood pressure (SBP) with mortality. The smooth spline estimates the hazard ratio of all-cause mortality, according to SBP (mm Hg) among CRIC participants with SBP measured out of the dialysis unit



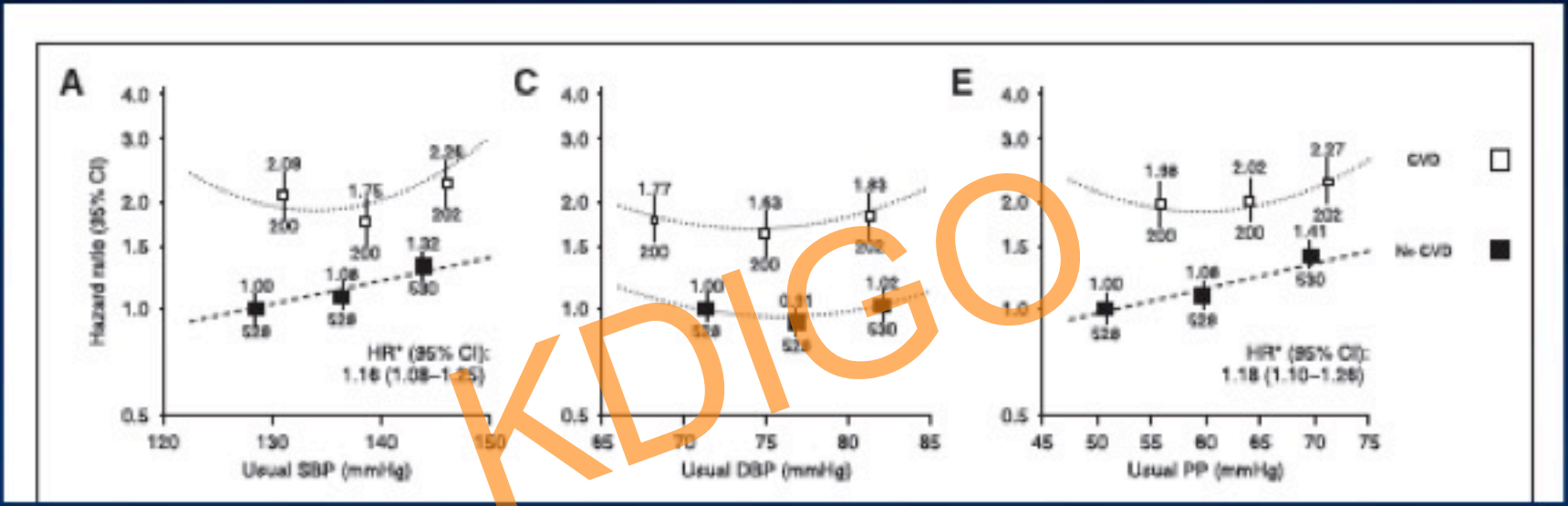
Hypertension 2015; 65:93-100.

Association between (A) systolic blood pressure (SBP), (B) diastolic blood pressure (DBP), and (C) pulse pressure (PP) and cardiovascular events in the SHARP Study (n=9270)



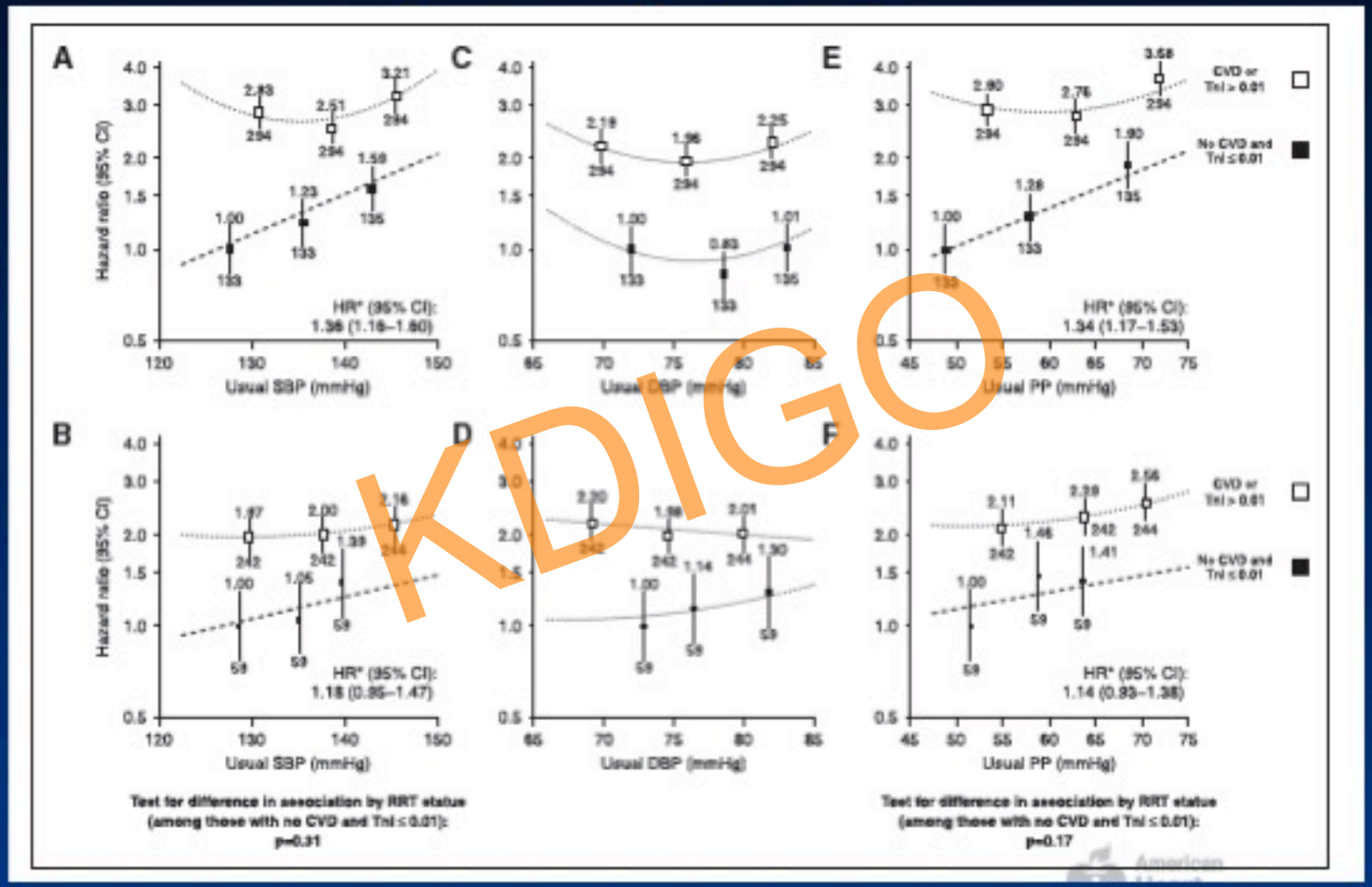
W. Herrington et al. Hypertension. 2017;69:314--322.

Association between systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) and cardiovascular events, subdivided by self-reported history of previous cardiovascular disease (A, C, E)



W. Herrington et al. Hypertension. 2017;69:314--322.

Association between SBP, DBP, and PP and cardiovascular events, subdivided by evidence of previous cardiovascular disease, for those not on dialysis (A, C, E) and on dialysis (B, D, F)



W. Herrington et al. Hypertension. 2017;69:314--322

The presence of a clear positive loglinear relationship between SBP (or PP) and cardiovascular events in patients with CKD at lowest risk of cardiac disease in SHARP suggests that reverse causality is a plausible explanation for previously observed U-shaped associations among patients with moderate-to-advanced CKD.

W. Herrington et al. Hypertension. 2017;69:314--322

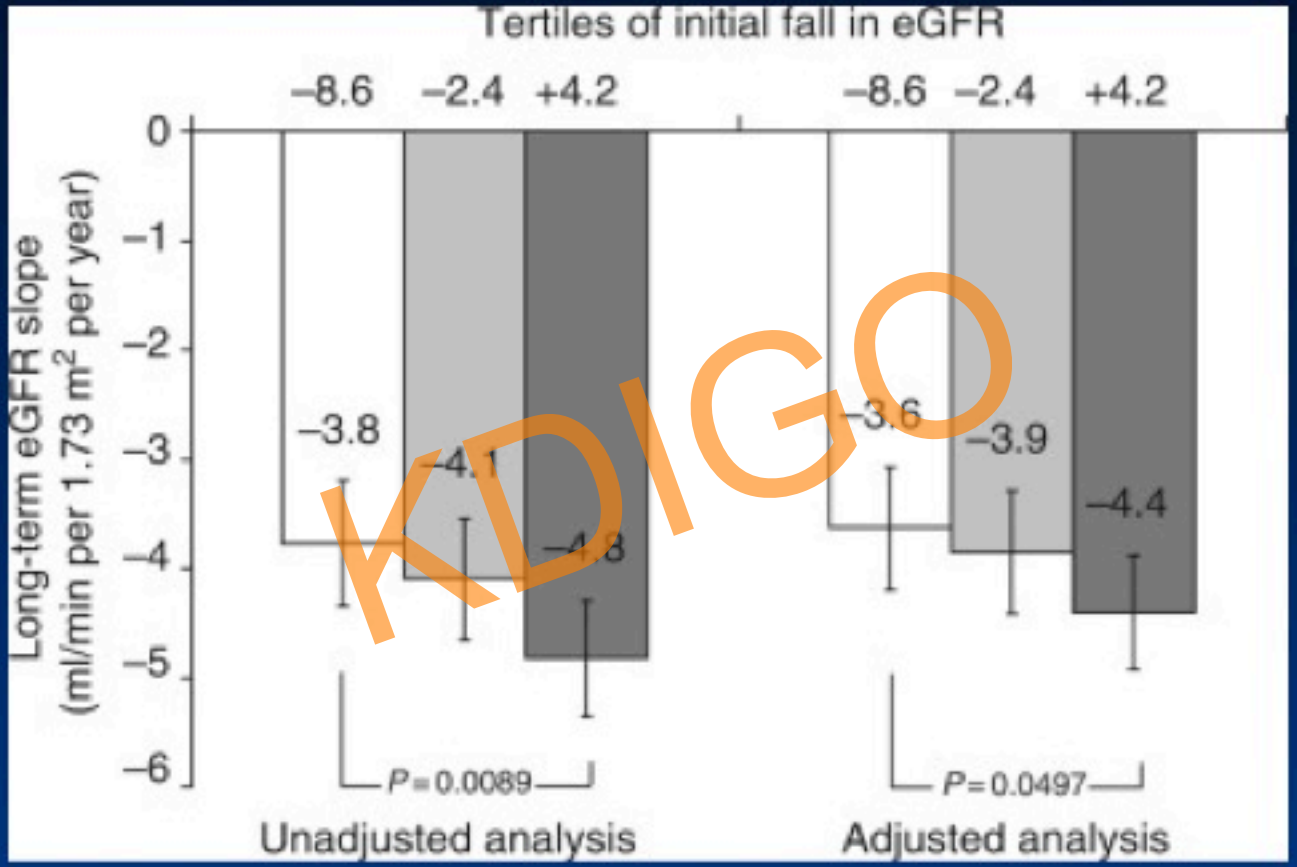
A loglinear relationship between SBP (or PP) and the risk of cardiovascular events was present in both dialysis and nondialysis patients, suggesting that BP remains a cause of cardiovascular disease irrespective of the severity of CKD, and hence that the absolute benefits of lowering BP among dialysis patients may be larger than those achievable at an earlier stage of CKD.

W. Herrington et al. Hypertension. 2017;69:314--322

What about change in eGFR with RAS blockade and BP reduction?

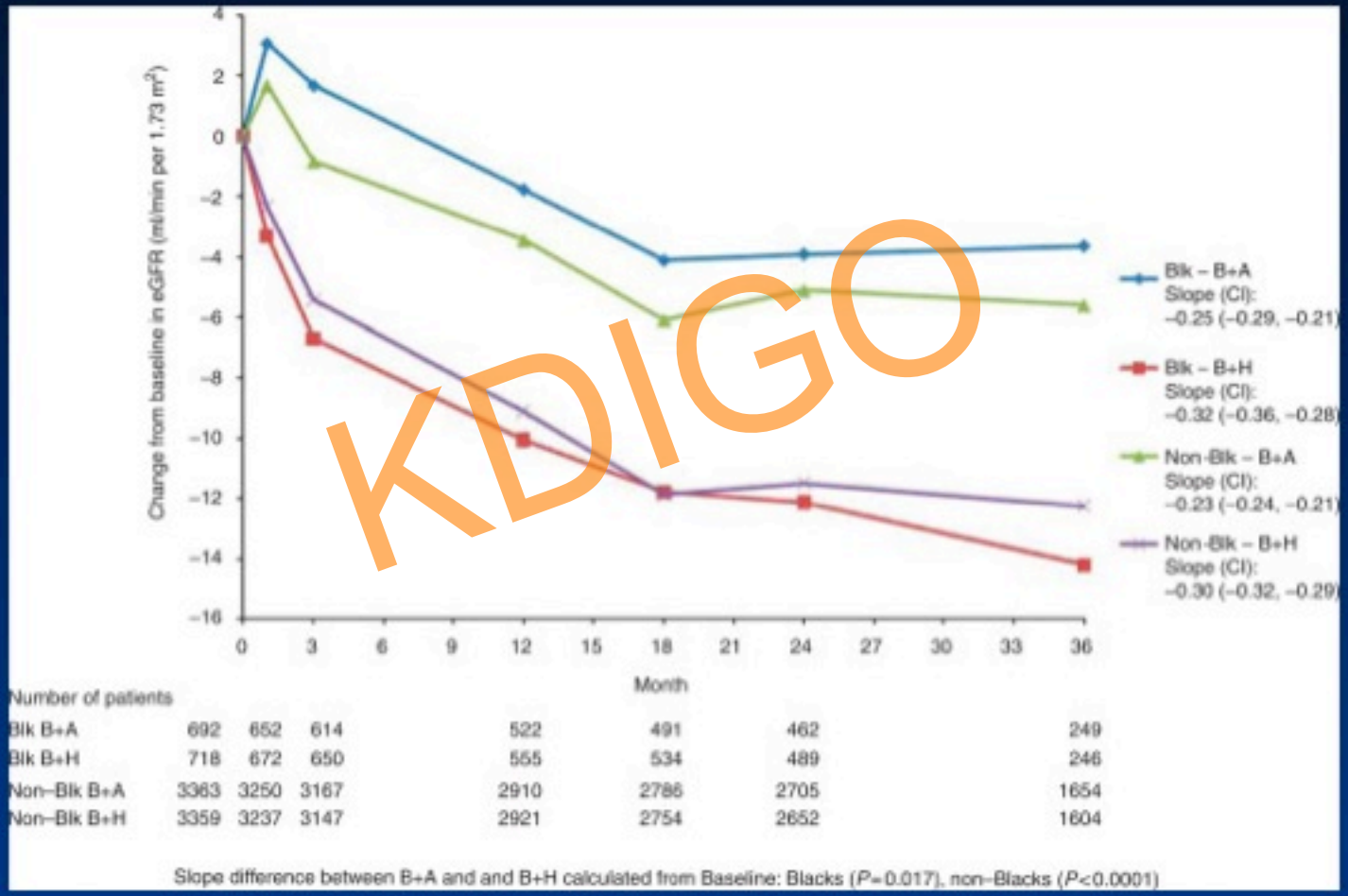
How much is too much?

Long-term estimated glomerular filtration rate (eGFR) slope stratified by acute fall in eGFR in losartan-assigned patients in the RENAAL Study



FA. Holtkamp; Kidney International, Volume 80, Issue 3, 2011, 282–287

Mean change from baseline in estimated glomerular filtration rate (eGFR) by race/ethnicity and treatment groups (US patients); slope difference calculated from baseline between B+A and B+H in Blacks (P<0.02) and non-Blacks (P<0.0001) from the ACCOMPLISH Study



Number of patients							
Blk B+A	692	652	614	522	491	462	249
Blk B+H	718	672	650	555	534	489	246
Non–Blk B+A	3363	3250	3167	2910	2786	2705	1654
Non–Blk B+H	3359	3237	3147	2921	2754	2652	1604

Slope difference between B+A and and B+H calculated from Baseline: Blacks ($P=0.017$), non–Blacks ($P<0.0001$)

MR Weir, Kidney International, Volume 81, Issue 6, 2012, 568–576

Relationship between 2 and 8 week changes in GFR and subsequent renal outcomes in 9340 patients new to RAS blockade in ONTARGET/TRANSCEND

Doubling of creatinine or long-term dialysis, using week 2 (or 8) as the starting point for the calculation of doubling		Doubling of creatinine or long-term dialysis, using week 0 as the starting point for the calculation of doubling	
Quintile (% change in GFR from baseline)	Adjusted HR (95% CI)	Quintile (% change in GFR from baseline)	Adjusted HR (95% CI)
2-week change			
<−12.7	0.55 (0.28–1.11)	<−12.7	2.89 (1.93–4.31)
−12.7 to −5.3	1.60 (0.95–2.68)	−12.7 to −5.3	1.56 (0.98–2.50)
−5.3 to 0	Referent	−5.3 to 0	Referent
0 to 6.2	0.52 (0.21–1.24)	0 to 6.2	0.27 (0.10–0.77)
>6.2	2.84 (1.72–4.68)	>6.2	0.31 (0.13–0.74)
8-week change			
< −14.5	0.91 (0.46–1.81)	< −14.5	4.27 (2.67–6.84)
−14.5 to −6.6	1.04 (0.53–2.01)	−14.5 to −6.6	1.57 (0.89–2.77)
−6.6 to 0	Referent	−6.6 to 0	Referent
0 to 7.2	1.18 (0.57–2.48)	0 to 7.2	0.87 (0.40–1.89)
>7.2	2.71 (1.52–4.85)	>7.2	0.76 (0.34–1.68)

Clase CM et al. Kidney Int 2017;91:683-690

Relationship between 2 and 8 week changes in GFR in subsequent renal and CV outcomes in 9340 patients new to RAS blockade in ONTARGET/TRANSCEND

New micro- or macroalbuminuria		Primary cardiovascular outcome	
Quintile (% change in GFR from baseline)	Adjusted HR (95% CI)	Quintile (% change in GFR from baseline)	Adjusted HR (95% CI)
<−12.3	1.15 (0.94–1.40)	<−12.7	1.36 (1.16–1.59)
−12.3 to −5.1	1.12 (0.92–1.37)	−12.7 to −5.3	1.02 (0.86–1.21)
−5.1 to 0	Referent	−5.3 to 0	Referent
0 to 6.4	1.00 (0.78–1.27)	0 to 6.2	1.03 (0.84–1.26)
>6.4	1.18 (0.96–1.44)	>6.2	1.09 (0.92–1.29)
< −14.0	1.14 (0.93–1.39)	< −14.5	1.17 (0.99–1.38)
−14.0 to −6.2	1.10 (0.90–1.35)	−14.5 to 6.6	1.14 (0.96–1.35)
−6.2 to 0	Referent	−6.6 to 0	Referent
0 to 7.2	1.21 (0.96–1.52)	0 to 7.2	1.06 (0.87–1.30)
>7.2	1.17 (0.95–1.44)	>7.2	1.07 (0.90–1.28)

Clase CM et al. Kidney Int 2017;91:683-690

Conclusions

- Increases and decreases in GFR on initiation of RAS blockade are common
- Changes may be weakly associated with increased risk of CV and renal outcomes
- Changes do not predict benefit of therapy

Association between percent decline in renal function in AASK participants from time of randomization until month 3-4 and risk of ESRD

AASK Trial (N=899)								
Strict BP arm (N=448)					Usual BP arm (N=451)			
Percent renal function decline	N	ESRD incidence* (95% CI)	Unadjusted Hazard ratio (95%CI)	Adjusted Hazard ratio[1] (95%CI)	N	ESRD incidence* (95% CI)	Unadjusted Hazard ratio (95%CI)	Adjusted Hazard ratio[1] (95%CI)
<5%	271	2.9 (2.4-3.6)	1.00 (0.75-1.34)	0.94 (0.70-1.25)	319	2.9 (2.4-3.5)	1.0 (Ref)	1.0 (Ref)
5-<20%	139	3.6 (2.7-4.7)	1.26[a] (0.90-1.76)	1.19[a] (0.84-1.68)	98	6.3 (4.8-8.1)	2.22[a] (1.60-3.09)	1.83[a] (1.30-2.57)
≥20%	38	9.8 (6.7-14.4)	3.58 (2.32-5.52)	3.04 (1.95-4.77)	34	10.4 (6.9-15.7)	3.83 (2.43-6.04)	2.56 (1.60-4.11)

Ku E et al. JASN 2017 (In press)

Association between percent decline in renal function in AASK and MDRD participants from time of randomization until month 3-4 and risk of ESRD

MDRD Trial (N=761)								
Strict BP arm (N=388)					Usual BP arm (N=373)			
Percent renal function decline	N	ESRD incidence* (95% CI)	Unadjusted Hazard ratio (95%CI)	Adjusted Hazard ratio[2] (95%CI)	N	ESRD incidence* (95% CI)	Unadjusted Hazard ratio (95%CI)	Adjusted Hazard ratio[2] (95%CI)
<5%	190	7.1 (6.0-8.5)	0.93 (0.73-1.19)	0.88 (0.68-1.13)	182	7.6 (6.4-9.0)	1.0 (Ref)	1.0 (Ref)
5-<20%	150	9.7 (8.1-11.7)	1.28[§] (0.99-1.64)	1.08[§] (0.84-1.40)	136	12.6 (10.5-15.1)	1.66[§] (1.29-2.13)	1.62[§] (1.25-2.11)
≥20%	48	15.5 (11.5-20.9)	2.03 (1.44-2.87)	1.57 (1.09-2.24)	55	17.3 (13.0-23.7)	2.39 (1.71-3.35)	1.48 (1.04-2.1)

Ku E et al. JASN 2017 (In press)

SPRINT Research Question

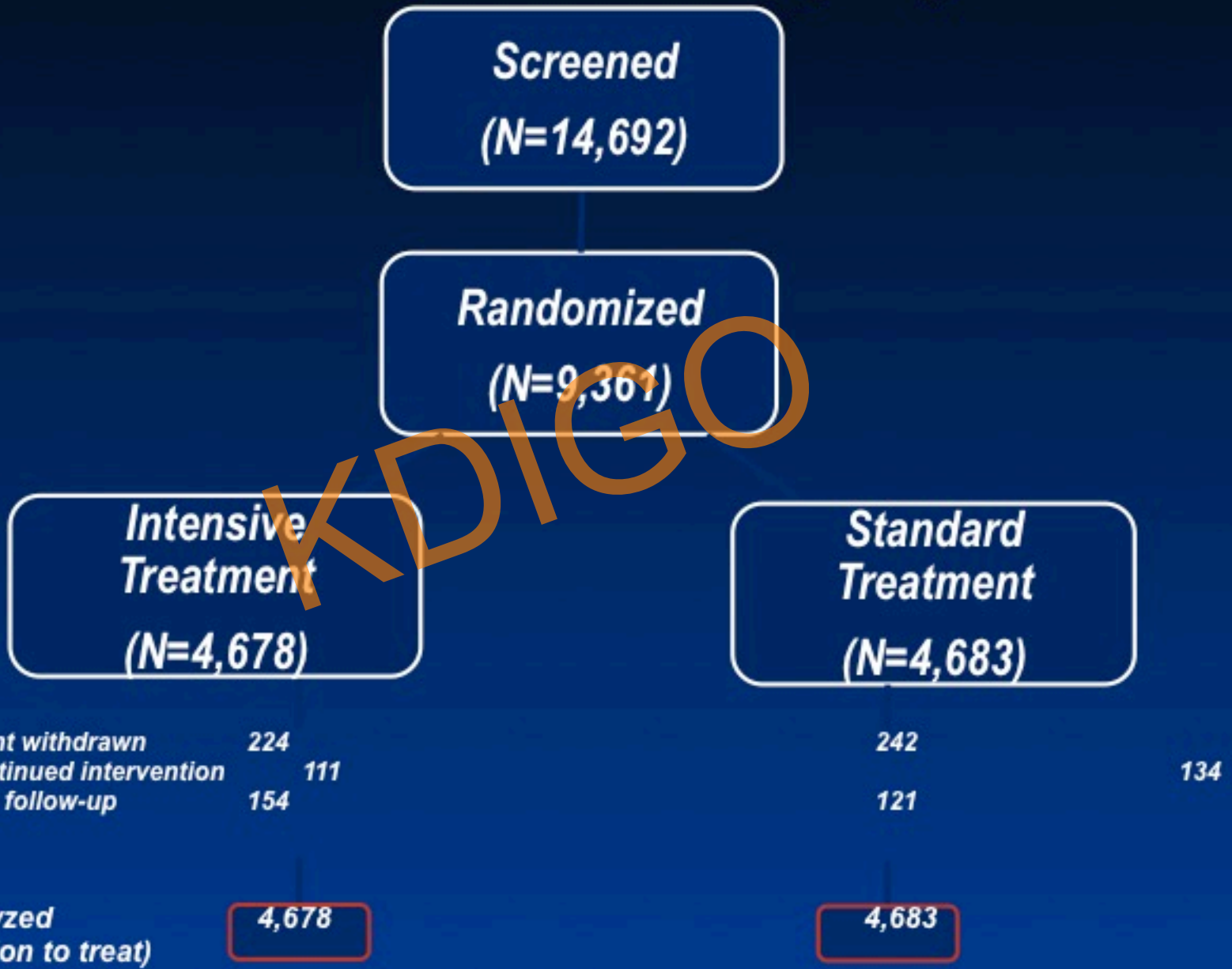
Examine effect of more intensive high blood pressure treatment than is currently recommended

SPRINT design details available at:

ClinicalTrials.gov (NCT01206062)

Ambrosius WT et al. Clin. Trials. 2014;11:532-546.

SPRINT: Enrollment and Follow-up Experience



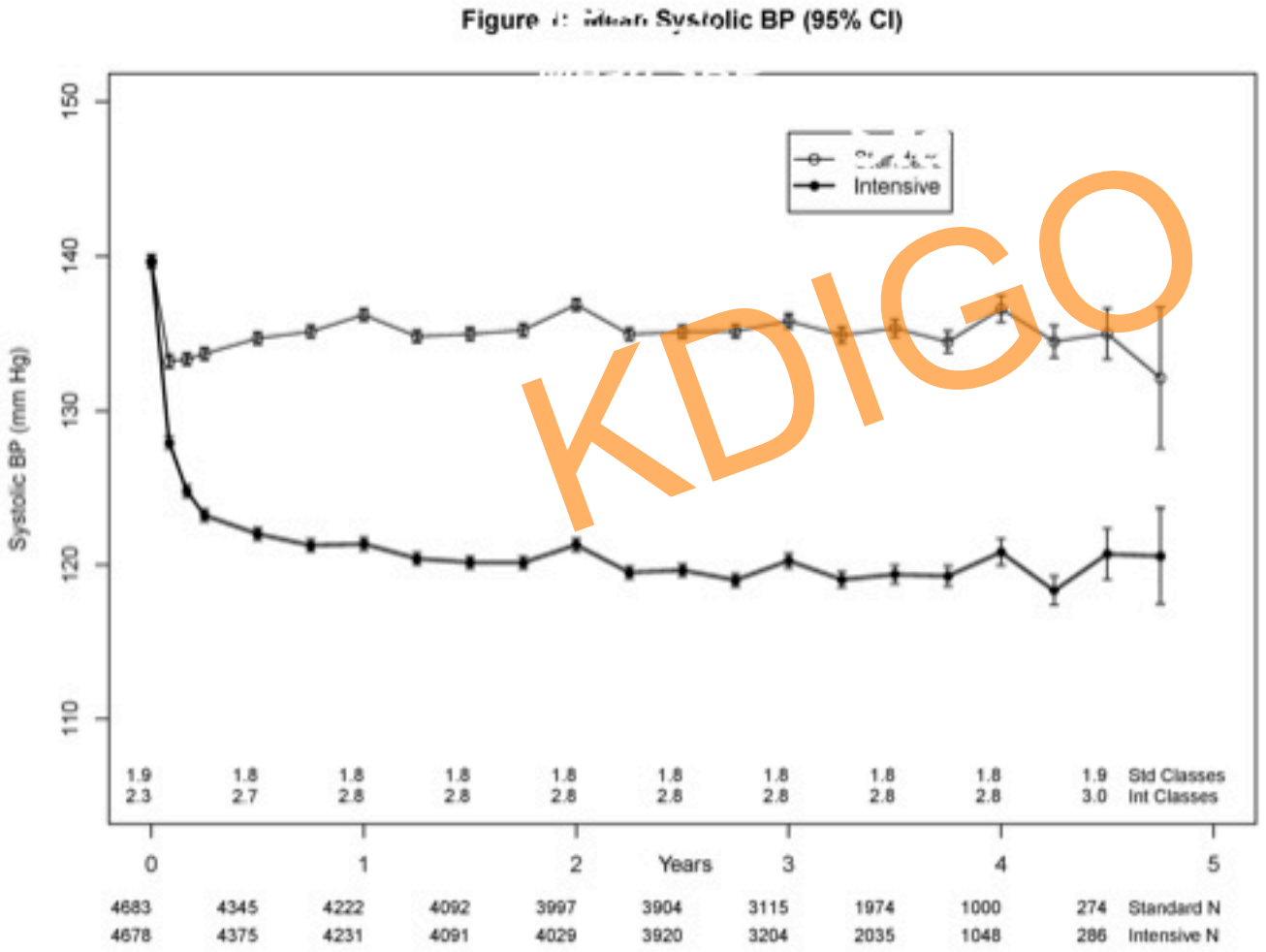
Demographic and Baseline Characteristics

	Total N=9361	Intensive N=4678	Standard N=4683
Mean (SD) age, years	67.9 (9.4)	67.9 (9.4)	67.9 (9.5)
% ≥75 years	28.2%	28.2%	28.2%
Female, %	35.6%	36.0%	35.2%
White, %	57.7%	57.7%	57.7%
African-American, %	29.9%	29.5%	30.4%
Hispanic, %	10.5%	10.8%	10.3%
Prior CVD, %	20.1%	20.1%	20.0%
Mean 10-year Framingham CVD risk, %	20.1%	20.1%	20.1%
Taking antihypertensive meds, %	90.6%	90.8%	90.4%
Mean (SD) number of antihypertensive meds	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)
Mean (SD) Baseline BP, mm Hg			
Systolic	139.7 (15.6)	139.7 (15.8)	139.7 (15.4)
Diastolic	78.1 (11.9)	78.2 (11.9)	78.0 (12.0)

Selected Baseline Laboratory Characteristics

	Total N=9361	Intensive N=4678	Standard N=4683
Mean (SD) eGFR, mL/min/1.73 m^2	71.7 (20.6)	71.8 (20.7)	71.7 (20.5)
% with eGFR<60 mL/min/1.73m^2	28.3	28.4	28.1
Mean (SD) Urine albumin/creatinine, mg/g	42.6 (166.3)	44.1 (178.7)	41.1 (152.9)
Mean (SD) Total cholesterol, mg/dL	190.1 (41.2)	190.2 (41.4)	190.0 (40.9)
Mean (SD) Fasting plasma glucose, mg/dL	98.8 (13.5)	98.8 (13.7)	98.8 (13.4)

Systolic BP During Follow-up



Average SBP
(During Follow-up)

Standard:
134.6 mm Hg

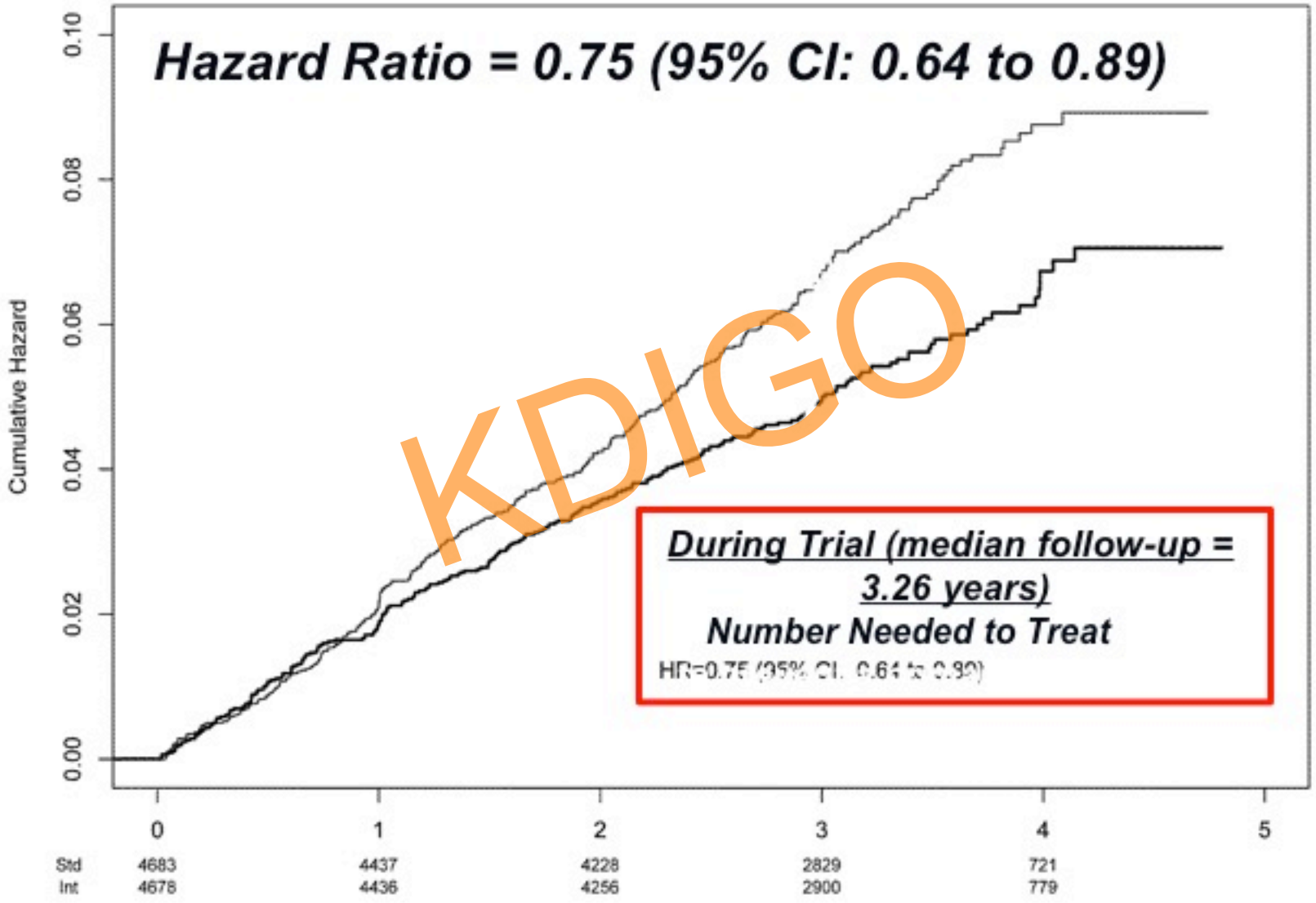
Intensive:
121.5 mm Hg

Average number of antihypertensive medications

Number of participants

SPRINT Primary Outcome

Cumulative Hazard



Renal Disease Outcomes

		Intensive		Standard			
		Events	%/yr	Events	%/yr	HR (95% CI)	P
Participants with CKD at Baseline							
	Primary CKD outcome	**14**	**0.33**	**15**	**0.36**	**0.89 (0.42, 1.87)**	**0.76**
	≥50% reduction in eGFR*	10	0.23	11	0.26	0.87 (0.36, 2.07)	0.75
	Dialysis	6	0.14	10	0.24	0.57 (0.19, 1.54)	0.27
	Kidney transplant	0	-	0	-	-	.
	Secondary CKD Outcome						
	Incident albuminuria**	49	3.02	59	3.90	0.72 (0.48, 1.07)	0.11
Participants without CKD at Baseline							
	Secondary CKD outcomes						
	≥30% reduction in eGFR*	127	1.21	37	0.35	3.48 (2.44, 5.10)	<.0001
	Incident albuminuria**	110	2.00	135	2.41	0.81 (0.63, 1.04)	0.10

*Confirmed on a second occasion ≥90 days apart **Doubling of urinary albumin/creatinine ratio from <10 to >10 mg/g

Individualization of BP goals

- No two patients are alike!
- Is the "right" BP goal that associated with:
  - reduction in proteinuria?
  - reduction in CV risk?
  - slowing of progression of CKD?
- The weight of current evidence suggests that lower BP targets are advantageous for people with CKD or ESRD. Randomized studies are the only ones to control for confounding!