Adverse Effects from Intensive BP Lowering on Kidney Function

George L. Bakris, MD
Professor of Medicine
Director, ASH Comprehensive Hypertension Center
University of Chicago Medicine

Disclosure of Interests

Consultant: Bayer, Janssen, Merck, AbbVie, Vascular Dynamics, Medtronic, GSK, Elcelyx Therapeutics

ORIGINAL CONTRIBUTION

(Reprinted) JAMA, November 20, 2002—Vol 288, No. 19 **2421**

Effect of Blood Pressure Lowering and Antihypertensive Drug Class on Progression of Hypertensive Kidney Disease

Results From the AASK Trial

Jackson T. Wright, Jr., MD, PhD
George Bakris, MD
Tom Greene, PhD
Larry Y. Agodoa, MD
Lawrence J. Appel, MD, MPH
Jeanne Charleston, RN
DeAnna Cheek, MD
Janice G. Douglas-Baltimore, MD
Jennifer Gassman, PhD
Richard Glassock, MD
Lee Hebert, MD
Kenneth Jamerson, MD
Julia Lewis, MD
Robert A. Phillips, MD, PhD
Robert D. Toto, MD
John P. Middleton, MD
Stephen G. Rostand, MD
for the African American Study of Kidney Disease and Hypertension Study Group

The New England Journal of Medicine

Volume 330 MARCH 31, 1994 Number 13

THE EFFECTS OF DIETARY PROTEIN RESTRICTION AND BLOOD-PRESSURE CONTROL ON THE PROGRESSION OF CHRONIC RENAL DISEASE

SAULO KLAHR, M.D., ANDREW S. LEVEY, M.D., GERALD J. BECK, PH.D., ARLENE W. CAGGIULA, PH.D., LAWRENCE HUNSICKER, M.D., JOHN W. KUSEK, PH.D., AND GARY STRIKER, M.D., FOR THE MODIFICATION OF DIET IN RENAL DISEASE STUDY GROUP*

Lancet. 2005 Mar 12-18;365(9463):939-46.

Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial.

Ruggenenti P[1], Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, Lesti M, Perticucci E, Chakarski IN, Leonardis D, Garini G, Sessa A, Basile C, Alpa M, Scanziani R, Sorba G, Zoccali C, Remuzzi G; REIN-2 Study Group.

Effects of Intensive BP Control in CKD

Alfred K. Cheung,*† Mahboob Rahman,‡§ David M. Reboussin,| Timothy E. Craven,| Tom Greene,¶ Paul L. Kimmel,** William C. Cushman,†† Amret T. Hawfield,‡‡ Karen C. Johnson,§§ Cora E. Lewis,|| Suzanne Oparil,¶¶ Michael V. Rocco,‡‡ Kaycee M. Sink,*** Paul K. Whelton,††† Jackson T. Wright Jr.,‡ Jan Basile,‡‡‡§§§ Srinivasan Beddhu,*† Udayan Bhatt,||| Tara I. Chang,¶¶¶ Glenn M. Chertow,¶¶¶ Michel Chonchol,**** Barry I. Freedman,‡‡ William Haley,†††† Joachim H. Ix,‡‡‡‡ Lois A. Katz,§§§§|||| Anthony A. Killeen,¶¶¶¶ Vasilios Papademetriou,***** Ana C. Ricardo,†††‡ Karen Servilla,‡‡‡‡ Barry Wall,§§§§§||||| Dawn Wolfgram,¶¶¶¶¶ and Jerry Yee,****** for the SPRINT Research Group

J Am Soc Nephrol 28: ccc–ccc, 2017. doi: https://doi.org/10.1681/ASN.2017020148

Adverse Renal and Hemodynamic Events from MDRD Trial

- The major of deaths were due to Cardiovascular events or Cancer (23 total events)

Events to Stop Study participation

- Rapid decline in GFR- 10% of participants
- Hypotension-in low BP group but BP was increased so as NOT to stop the study
- BP randomization did NOT influence this adverse event rate

Klahr S et.al. N Eng J Med 1994;330:877-884

AASK Trial:Percent of Patients Reporting Symptoms By Drug Group

Symptom	Ramipril	Amlodipine	Metoprolol
Hyperkalemia	0.7	0	0.2
Angioedema	6.4[1,2]	2.3	2.7
Shortness of Breath	43.0	44.4	45.8
Syncope	6.7[2]	2.3[1]	6.3
Dizziness	50.1	46.7	47.8
Lightheadedness	49.2	48.1	47.8

[1] Significantly different from Metoprolol group ($p < 0.05$)
[2] Significantly different between Ramipril and Amlodipine groups ($p < 0.05$)

Wright JT Jr. et.al. JAMA 2002;288:2421-2431

Table 3. Event Rates for Primary and Secondary Outcomes, According to Study Phase and Proteinuria Status at Baseline.*

Variable	Intensive Control		Standard Control		Hazard Ratio (95% CI)	P Value
	no./total no.	*rate per 100 person-yr*	*no./total no.*	*rate per 100 person-yr*		
All patients						
Doubling of serum creatinine level, ESRD, or death						
Trial phase	159/540	7.0	169/554	7.3	0.88 (0.71–1.09)	0.24
Cohort phase	123/377	7.9	116/382	7.7	0.95 (0.74–1.23)	0.70
Both phases	282/540	7.3	285/554	7.5	0.91 (0.77–1.08)	0.27
Doubling of serum creatinine level or ESRD						
Trial phase	121/540	5.3	125/554	5.4	0.91 (0.71–1.18)	0.49
Cohort phase	92/377	5.9	84/382	5.5	0.99 (0.73–1.33)	0.95
Both phases	213/540	5.5	209/554	5.5	0.95 (0.78–1.15)	0.59
ESRD or death						
Trial phase	124/540	5.3	140/554	5.9	0.84 (0.66–1.07)	0.16
Cohort phase	114/412	6.4	116/411	6.9	0.86 (0.67–1.12)	0.27
Both phases	238/540	5.8	256/554	6.3	0.85 (0.71–1.02)	0.08
Patients with baseline urinary protein-to-creatinine ratio ≤0.22						
Doubling of serum creatinine level, ESRD, or death						
Trial phase	64/357	4.0	61/376	3.6	1.14 (0.80–1.63)	0.46
Cohort phase	81/290	6.5	74/312	5.6	1.21 (0.88–1.66)	0.24
Both phases	145/357	5.1	135/376	4.5	1.18 (0.93–1.50)	0.16
Doubling of serum creatinine level or ESRD						
Trial phase	42/357	2.6	34/376	2.0	1.44 (0.91–2.26)	0.12
Cohort phase	56/290	4.5	49/312	3.7	1.36 (0.92–2.00)	0.12
Both phases	98/357	3.4	83/376	2.7	1.39 (1.04–1.87)	0.03
ESRD or death						
Trial phase	47/357	2.9	50/376	2.9	0.98 (0.66–1.47)	0.94
Cohort phase	72/307	5.2	62/323	4.3	1.22 (0.87–1.72)	0.25
Both phases	119/357	3.9	112/376	3.6	1.12 (0.87–1.45)	0.39

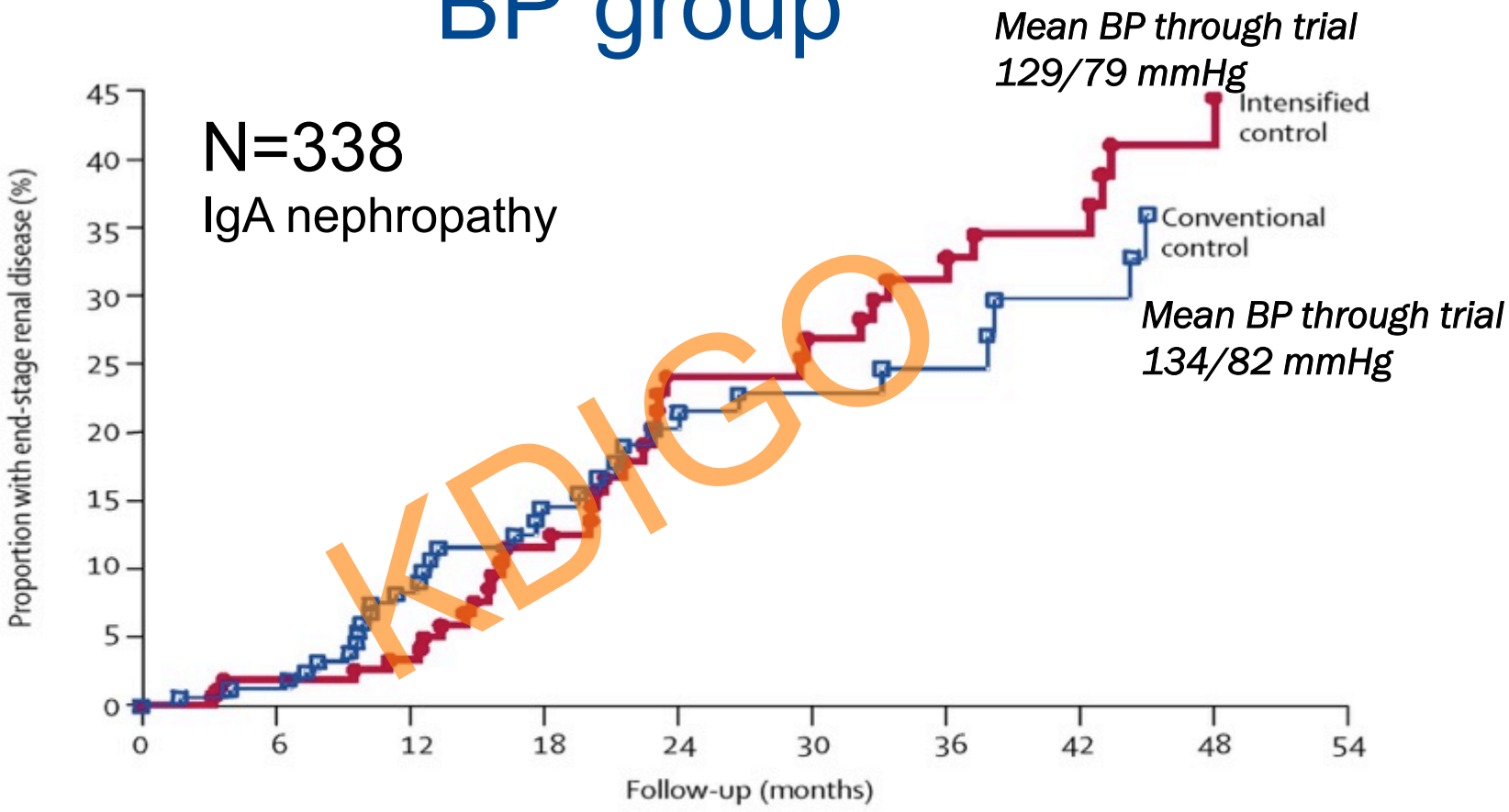
Appel L et.al. N Engl J Med 2010:363:918-29

Table 3. (Continued.) Events Rates for Primary and Secondary Endpoints

Variable	Intensive Control *rate per 100 person-yr*		Standard Control *rate per 100 person-yr*		Hazard Ratio (95% CI)	P Value
	no./total no.		*no./total no.*			
Patients with baseline urinary protein-to-creatinine ratio >0.22						
Doubling of serum creatinine level, ESRD, or death						
Trial phase	94/181	13.9	108/176	18.3	0.74 (0.56–0.99)	0.04
Cohort phase	42/86	13.7	41/68	21.1	0.66 (0.43–1.03)	0.07
Both phases	136/181	13.8	149/176	19.0	0.73 (0.58–0.93)	0.01
Doubling of serum creatinine level or ESRD						
Trial phase	78/181	11.5	91/176	15.4	0.76 (0.55–1.04)	0.08
Cohort phase	36/86	11.8	35/68	18.0	0.68 (0.43–1.09)	0.11
Both phases	114/181	11.6	126/176	16.1	0.76 (0.58–0.99)	0.04
ESRD or death						
Trial phase	76/181	10.6	90/176	14.3	0.76 (0.56–1.04)	0.09
Cohort phase	42/104	11.0	53/86	20.3	0.55 (0.37–0.84)	0.005
Both phases	118/181	10.8	143/176	16.1	0.67 (0.52–0.87)	0.002

Appel L et.al. N Engl J Med 2010;363:918-29

ESRD Outcomes from REIN-2 by BP group



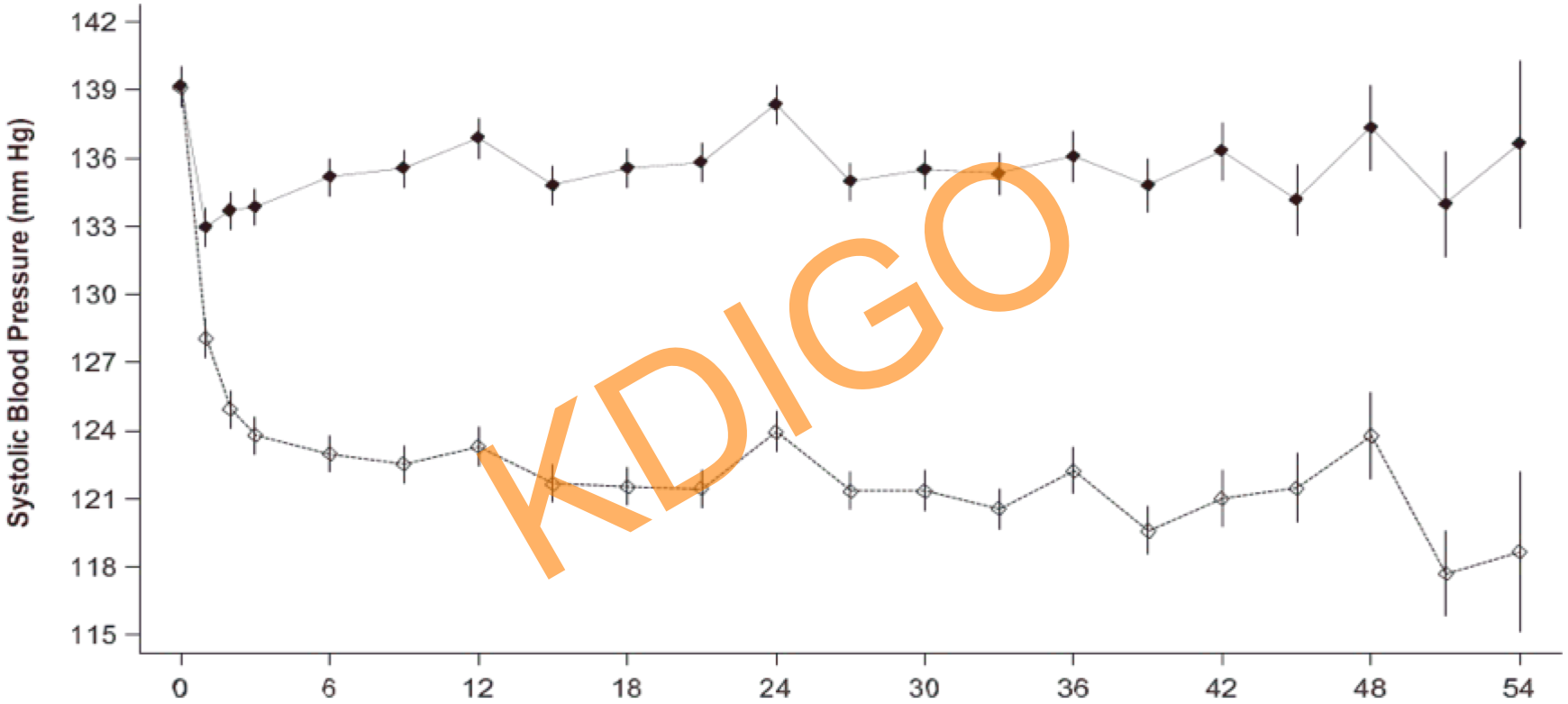
Number at risk										
Conventional control	168	158	121	84	64	50	34	24	13	2
Intensified control	167	155	126	88	59	51	43	31	17	0

Ruggenenti P et.al. Lancet 2005;365;939-946

REIN-2 Adverse Events

- Five patients died, 3 in conventional and 2 in the intensified-BP group.
- 25 non-fatal serious adverse events conventional group (*including myocardial infarction, congestive heart failure, stroke, and cancer*) and 37 in intensified group (including myocardial infarction, acute coronary syndrome, acute congestive heart failure, stroke, transient ischemic attack, and cancer).
- No case of severe hyperkalemia (K>6 mEq/L) was reported.

BP levels between the two intervention groups in the SPRINT participants with CKD

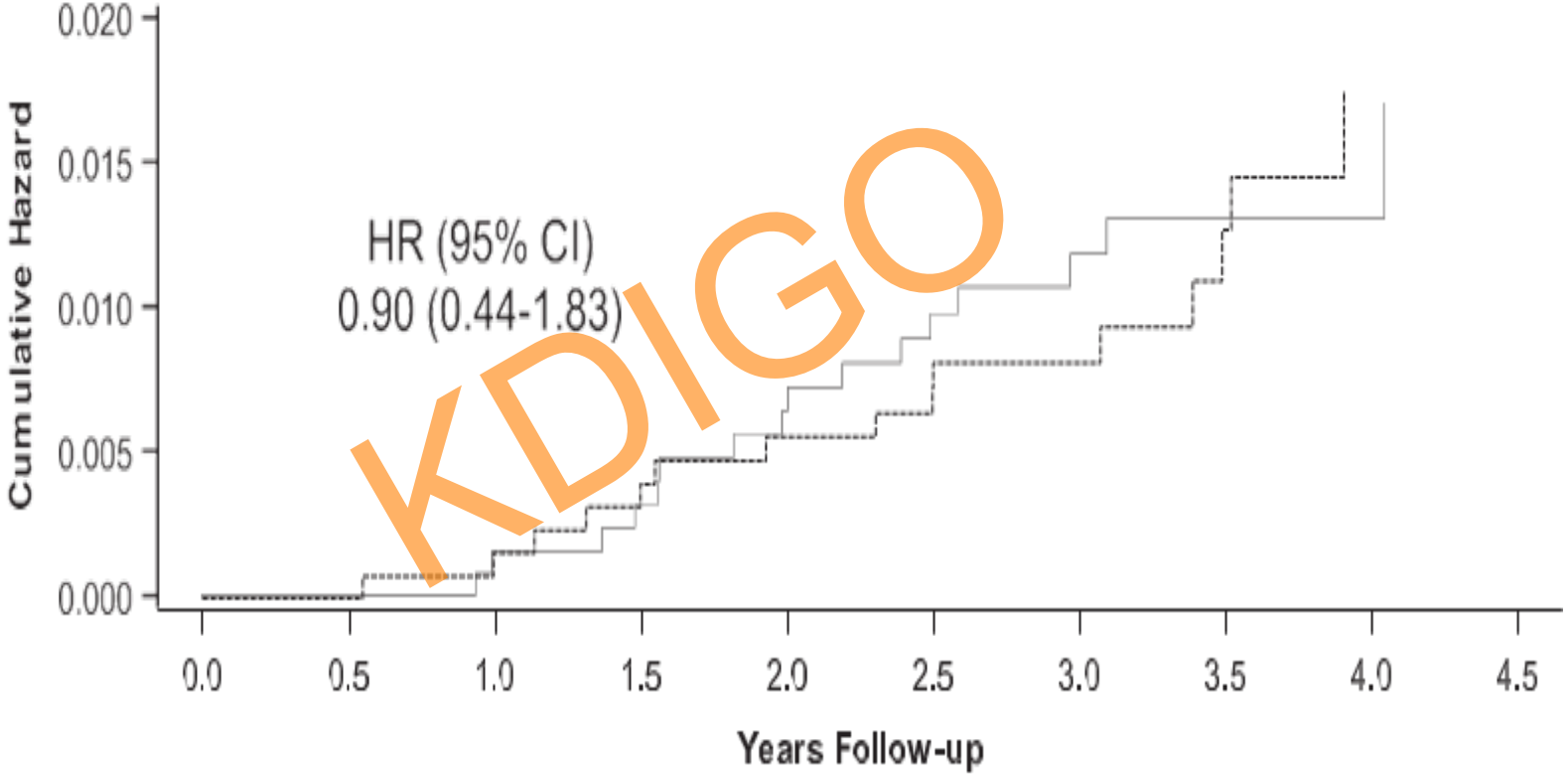


Number With Data										
Standard:	1316	1215	1156	1117	1087	1022	766	480	230	46
Intensive:	1330	1246	1194	1145	1136	1054	804	515	268	58
Mean Number of Meds										
Standard:	2.1	2.0	2.0	2.0	2.1	2.0	2.1	2.1	2.1	2.0
Intensive:	2.1	2.9	3.0	3.0	3.0	3.0	2.9	2.9	3.0	3.1

Cheung A et.al. J Am Soc Nephrol 2017-online

Pre-specified outcomes in SPRINT participants with CKD

main kidney outcome, defined as the composite of a decrease in eGFR of >50% from baseline (confirmed by repeat testing 90 days later) or the development of ESRD



Number at risk					
Standard	1316	1265	1214	854	266
Intensive	1330	1268	1230	850	286

Cheung A et.al. J Am Soc Nephrol 2017-online

SAEs, conditions of interest, and monitored clinical events in RENAL SPRINT

Events	No. of Events (% per 1 yr)		Intensive Treatment Versus Standard Treatment	
	Intensive Treatment, *n*=133	Standard Treatment, *n*=1316	HR (95% CI)	*P* Value
Total SAEs[a]	627 (19.8)	640 (20.2)	0.98 (0.87 to 1.09)	0.67
Conditions of interest (ER visits or SAEs)				
Hypotension	51 (1.2)	38 (0.9)	1.34 (0.88 to 2.04)	0.17
Syncope	54 (1.3)	42 (1.0)	1.28 (0.86 to 1.92)	0.22
Bradycardia	37 (0.9)	40 (1.0)	0.92 (0.59 to 1.44)	0.71
Electrolyte abnormalities	69 (1.7)	51 (1.2)	1.35 (0.94 to 1.94)	0.10
Injurious fall	125 (3.1)	138 (3.4)	0.90 (0.71 to 1.15)	0.40
ARF[b]	114 (2.8)	78 (1.9)	1.46 (1.10 to 1.95)	0.01
Monitored clinical events				
Adverse clinical measures				
Serum sodium 130 mmol/L	49 (2.7)	35 (0.9)	1.39 (0.90 to 2.15)	0.13
Serum sodium 150 mmol/L	3 (0.1)	0 (0)	—	.0.99
Serum potassium ,3.0 mmol/L	30 (0.7)	16 (0.4)	1.87 (1.02 to 3.43)	0.04
Serum potassium .5.5 mmol/L	106 (2.7)	78 (2.0)	1.36 (1.01 to 1.82)	0.04
Orthostatic hypotension				
Without dizziness	301 (8.5)	302 (8.5)	0.99 (0.85 to 1.17)	0.94
With dizziness	24 (0.6)	23 (0.6)	1.04 (0.59 to 1.84)	0.89

Cheung A et.al. J Am Soc Nephrol 2017-online

Summary of key adverse effects from randomized BP trials

- Lower BP associated with:

a) higher incidence of hyperkalemia

PERSPECTIVE:

❖ Data from Clinical Trials can't always be extrapolated to bedside

❖ Results of studies should be put in context of group studied.

renal outcome or CV outcome

✓ Does change in albuminuria affect outcomes in these circumstances

Hyperkalemia Rates in RAASi-Treated Patients in Randomized Trials

Patient Population	# of Patients	Definition	Rate
AASK[1]: non-diabetic CKD	417	≥5.5	7.2%
J-LIGHT[2]: HTN-CKD	58	>5.1 ≤6.9	5.2%
RENAAL[3]: diabetic nephropathy	751	≥5.5	10.8%
IDNT[4]: diabetic nephropathy	579	>6	18.6

1. Weinberg JM, et al. *Arch Intern Med*. 2009;169(17):1587-1594. **2.** Iino Y, et al. *Hypertens Res*. 2004;27(1):21-30. **3.** Miao Y, et al. *Diabetologia*. 2011;54(1):44-50. **4.** Avapro [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC. 2012.

Impact of RAS Therapy on Hyperkalemia in Stages 3 and 4 CKD

Trials	Hyperkalemia (>5.5 mEq/L)			
	ACEI or ARB (n)	%	Non-RAAS Treatment (n)	%
AIPRI	5/300	1.7	3/283	1
REIN	1/78	1.3	1/88	1.1
Captopril Trial	3/207	1.4	0/202	0
ALTITUDE	1670/4274 (Combo)	39.1	No such group	-
	1244/4274 (V)	29		
VA NEPHRON D	72/724 (Combo)	9.9	Non such group	-
	32/724 (ACEI alone)	4.4		

Lazich I and Bakris G. Sem Nephrol 2014;34:333-339

Predictors of Hyperkalemia Before Starting Therapy

- eGFR <45 ml/min/1.73m^2

(HR:2.9 fold)

- Starting serum potassium of >4.5 mEq/L on appropriate diuretics

(HR:3.7 fold)

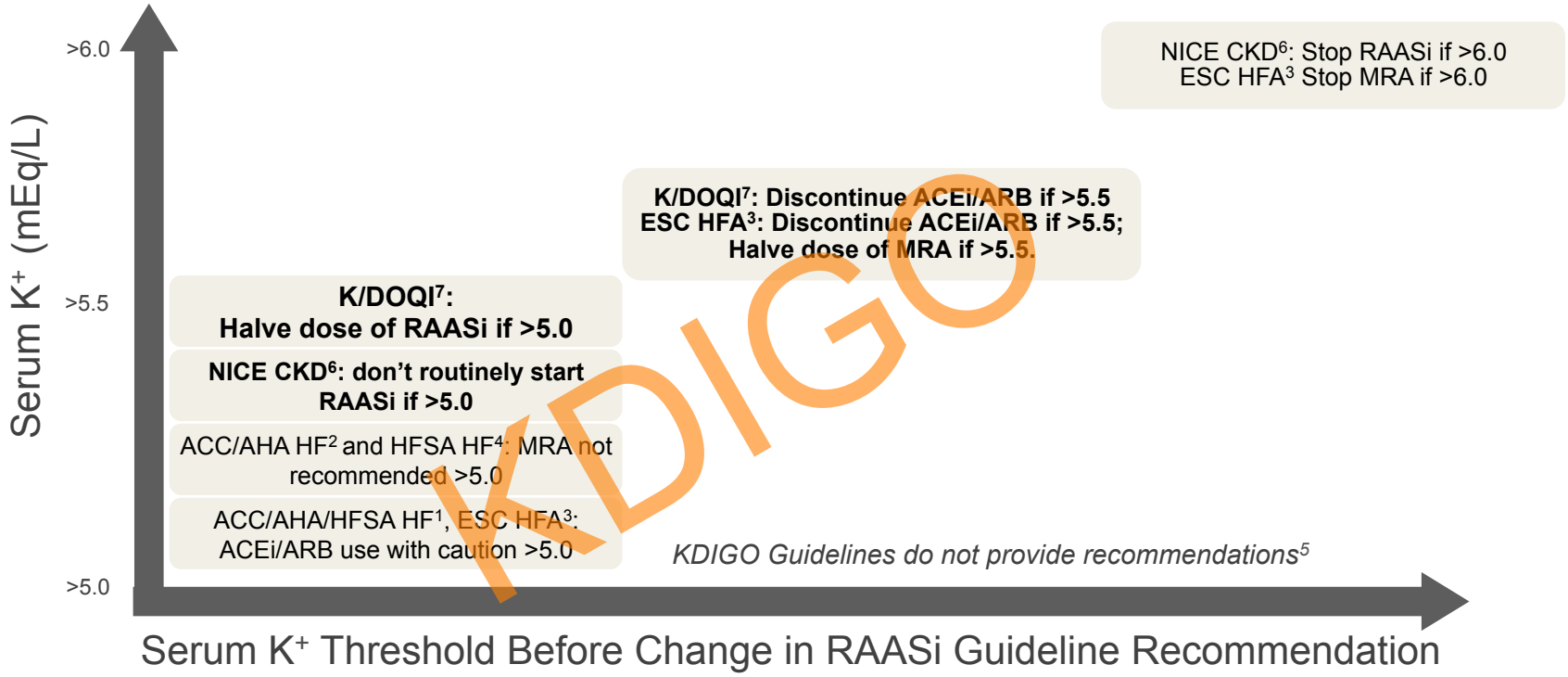
- eGFR <45 ml/min/1.73m^2 +

serum [K+] >4.5 mEq/L (***HIGHEST PREDICTOR***)

(HR:8.7 fold)

Lazich I and Bakris G. Sem Nephrol 2014;34:333-339; Khosla N et.al. Am J Nephrol 2009;30:418-423; Weinberg JM, et al. *Arch Intern Med*. 2009;169(17):1587-1594

Guidelines Recommend RAASi Dose Modifications With Increasing Serum K^+



RAASi: renin-angiotensin-aldosterone system inhibitor

Yancy CW, et al., *Circulation.* 2016;134:[Epub ahead of print]. 2. Yancy CW, et al. J Am Coll Cardiol. 2017 Apr 21. pii: S0735-1097(17)37087-0. doi: 10.1016/j.jacc.2017.04.025. [Epub ahead of print]. 3. Ponikowski P., et al., *European Heart Journal.* 2016 May 20. pii: ehw128. [Epub ahead of print] 4. Heart Failure Society of America, Lindenfeld J, et al. *J Card Fail.* 2010;16(6):475-539. 5. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl.* 2013;3(1). 6. National Institute for Health and Clinical Excellence (NICE) [UK]. Chronic kidney disease (partial update): Early identification and management of chronic kidney disease in adults in primary and secondary care. 2014. https://www.nice.org.uk/guidance/cg182/evidence/update-full-guideline-191905165. 7. National Kidney Foundation. Guideline 11. http://www2.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm. Accessed February 17, 2015. 8. Epstein M., et al., Am J Manag Care. 2015;21:S212-S220

KDIGO 2012 Guidance if K is Elevated

Standard advice to avoid drugs that can raise K like NSAIDs and COX-2 inhibitors

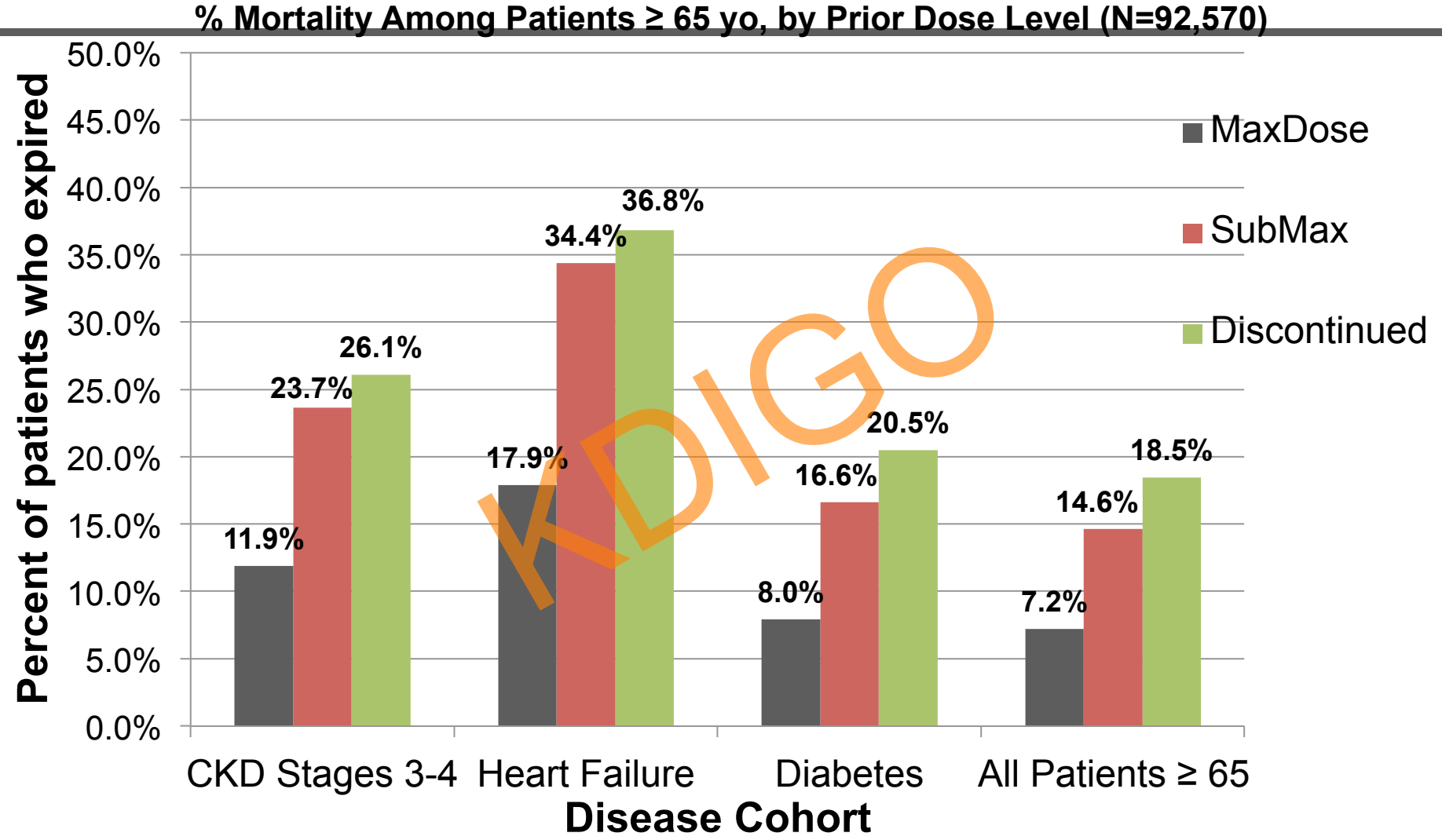
"If hyperkalemia occurs in CKD patients taking a renal excreted ACE-I, possible interventions include dietary advice, reducing the dose, switching to fosinopril or trandolapril, or adding a potassium-losing diuretic.

Lower Doses of ACEi/ARB Have Not Been Shown Effective in Slowing CKD Progression

TRIAL	N	OUTCOME (vs placebo)
RENAAL[1] T2DM with HTN + macroalbuminuria + mean eGFR ~ 43	1513	Losartan 100 mg (~ 80 % of active patients): 25% ↓RR doubling of SC 28% ↓RR in progression to ESRD **Losartan 50 mg (~ 20 % of active patients):** **No proven renoprotective effect**
IDNT[2] T2DM with HTN + macroalbuminuria + mean eGFR ~ 41	1715	Irbesartan 300 mg: 33% ↓RR doubling of SC 28% ↓RR in progression to ESRD
IRMA 2[3] T2DM with HTN, microalbuminuria (20-200 ug/min UAE rate); <1.5 mg/dl SC	611	Irbesartan 300 mg: 70 % ↓RR of progression to macroalbuminuria **Irbesartan 150 mg:** **No statistically significant effect in ↓RR of progression to macroalbuminuria**

1) Brenner_2001_Losartan_DN_RENAAL (Brenner, B. M., M. E. Cooper, et al. (2001). N.Engl.J Med 345(12): 861-869)
2) Lewis_2001_IDNT_CKD (Lewis, E. J., L. G. Hunsicker, et al. (2001). N.Engl.J Med 345(12): 851-860.)
3) Parving_2001_NEJM (Parving, H. H., H. Lehnert, et al. (2001). N Engl J Med 345(12): 870-878.)

Mortality Among Patients Discontinued or Lower-Dose RAASi Compared to Those Prescribed RAASi at Maximum Dose

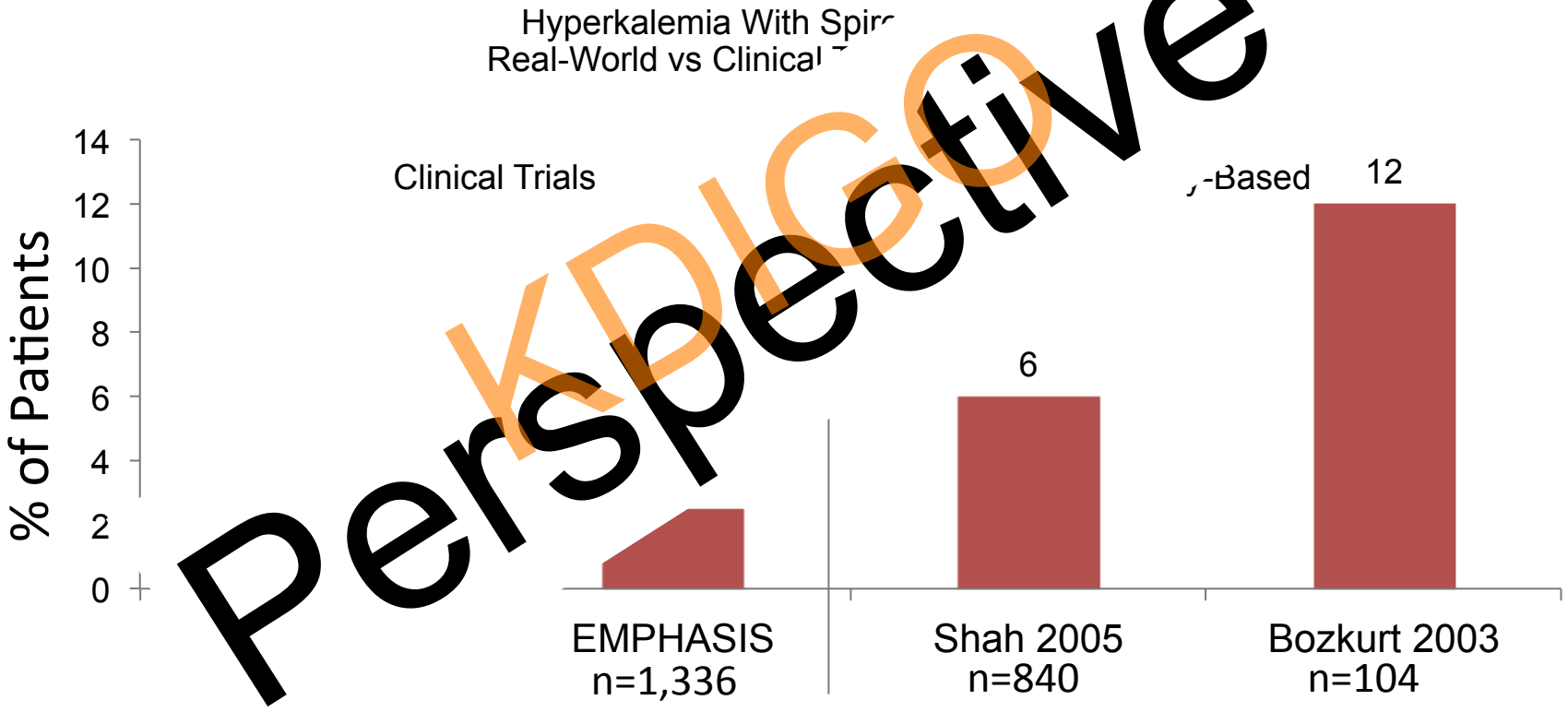


Excluding patients with ESRD. RAASi dose classified at end of outcome period.
Adverse Outcome = ESRD initiation, CKD progression, stroke, acute myocardial infarction, or cardiac revascularization by CABG or PCI.
Data not shown for persons on above-maximum doses of RAASi (< 0.5% of population).

Epstein, M., et al. *Am J Manag Care 2015; 21(11 Suppl): S212-220.*

Heart Failure: Rates of Hyperkalemia (≥6.0 mEq/L) in HF Patients on Mineralocorticoid Receptor Antagonists (MRA)

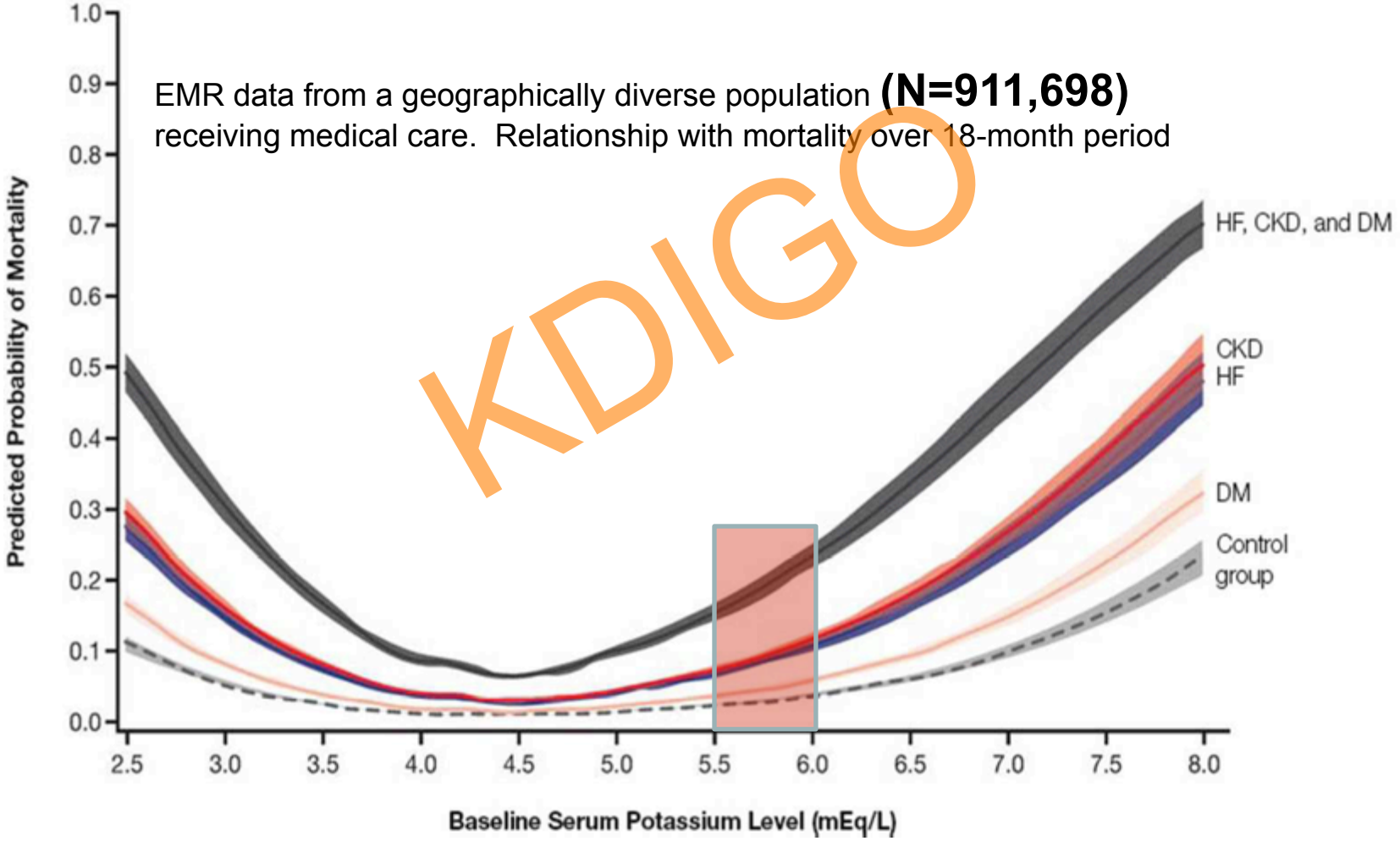
- RAAS clinical trials populations are carefully selected to exclude patients at high risk for hyperkalemia[1]
- Incidence of hyperkalemia in community-based practice far ex[illegible] observed in clinical trials[1]



1. Desai AS. *Curr Heart Failu[illegible] Rep*. 2009;6(4):272-280.
2. Pitt B, Zannad F, Remme WJ, et al. *N Engl J Med*. 1999;341(10):709-717.
3. Bozkurt B, Agoston I, Knowlton AA. *J Am Coll Cardiol*. 2003;41(2):211-214.
4. Shah KB, Rao K, Sawyer R, et al. *J Am Coll Cardiol.* 2005;46(5)845-849.

Spline analysis adjusted for covariates, showing serum potassium as a continuous variable with all-cause mortality over the distribution of potassium values (2.5–8.0 mEq/L) in HF, CKD, DM, and combined cohort compared to controls.

EMR data from a geographically diverse population **(N=911,698)** receiving medical care. Relationship with mortality over 18-month period



Collins A et.al. Am J Nephrol , 2017 in press

Humedica database, Cambridge, MA.

Summary of key adverse effects from randomized BP trials

- Lower BP associated with:

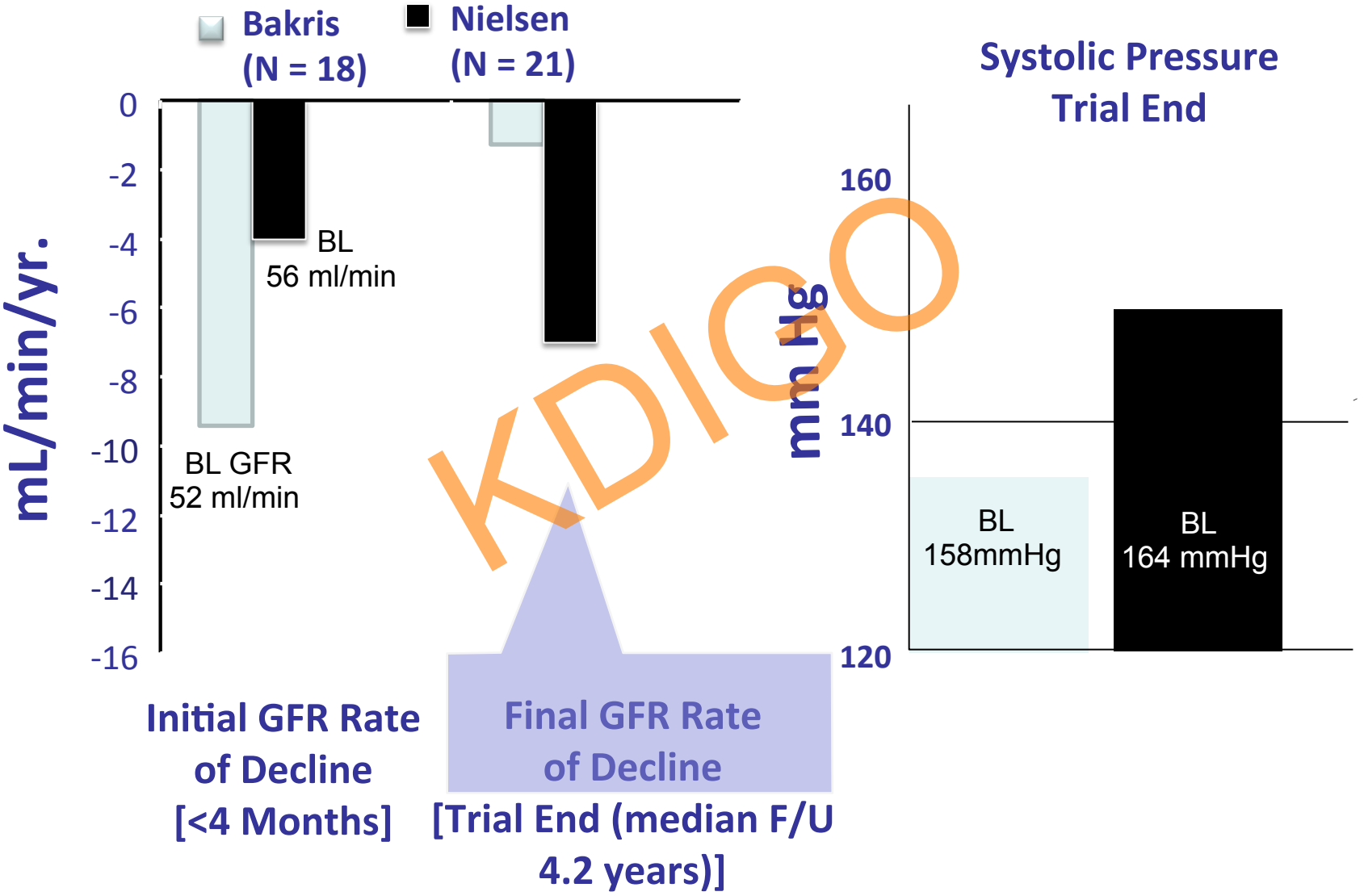
a) higher incidence of hyperkalemia

b) higher acute rise in serum creatinine

Unanswered QUESTIONS

- ✓ Does the magnitude of change in creatinine predict the change in serum potassium
- ✓ Does a greater rise in creatinine portend a worse renal outcome or CV outcome
- ✓ Does change in albuminuria affect outcomes in these circumstances

Effects of lisinopril in untreated hypertensive patients with Type 2 diabetes



Bakris GL & Weir M Arch Intern Med. 2000:160:685-693

Long Term Follow-up of RAS induced changes in Serum Creatinine

	All patients	Diabetics only	Cr↑>30%	Cr↑<30%
Age, years	64.2±11.5	66.5±8.2	65.3±11.8	63.4±11.4
Patients	48	30	20	28
Male, %	58.3	46.7	35*	75
Diabetes, %	62.5	100	65.0	60.7
SBP, mm Hg	151.7±23.6	151.4±22.7	159.75±26.8+	145.9±19.6
eGFR, ml/min/1.73 m^2	36.0±14.3	34.9±12.3	35.9±13.1	36.2±15.2
Urine protein ≤30 mg/dl, %	41.7	46.7	50	35.6
Black, %	93.8	96.7	95	92.9

Values are means ± SD. * p = 0.008 vs. <30% ↑; + p = 0.044 vs. <30% ↑.

Hirsch S et.al. Am J Nephrol 2012;36:430-437

Long Term Follow-up of RAS induced changes in Serum Creatinine

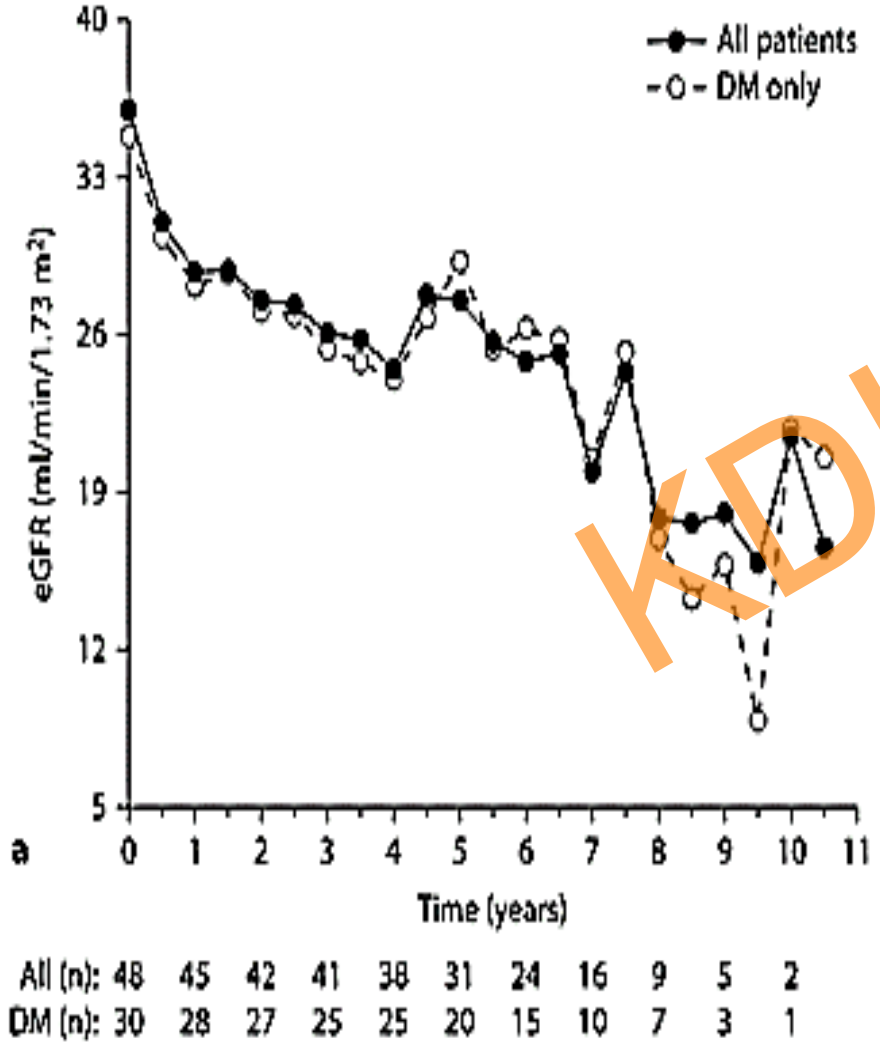
- 2.1% had episode of hyperkalemia-defined as ≥ 6 mEq/L over the entire trial,
- Three hospitalizations

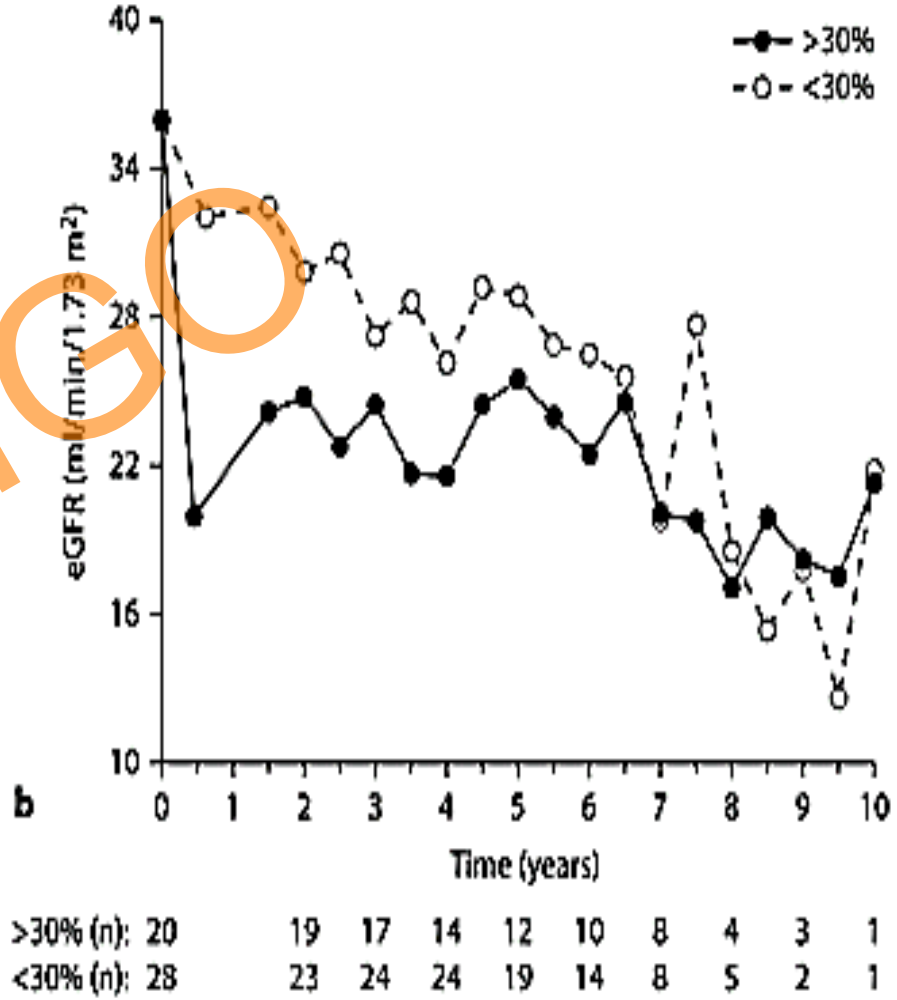
2-Hypotension

1-Hyperkalemia

Hirsch S et.al. Am J Nephrol 2012;36:430-437

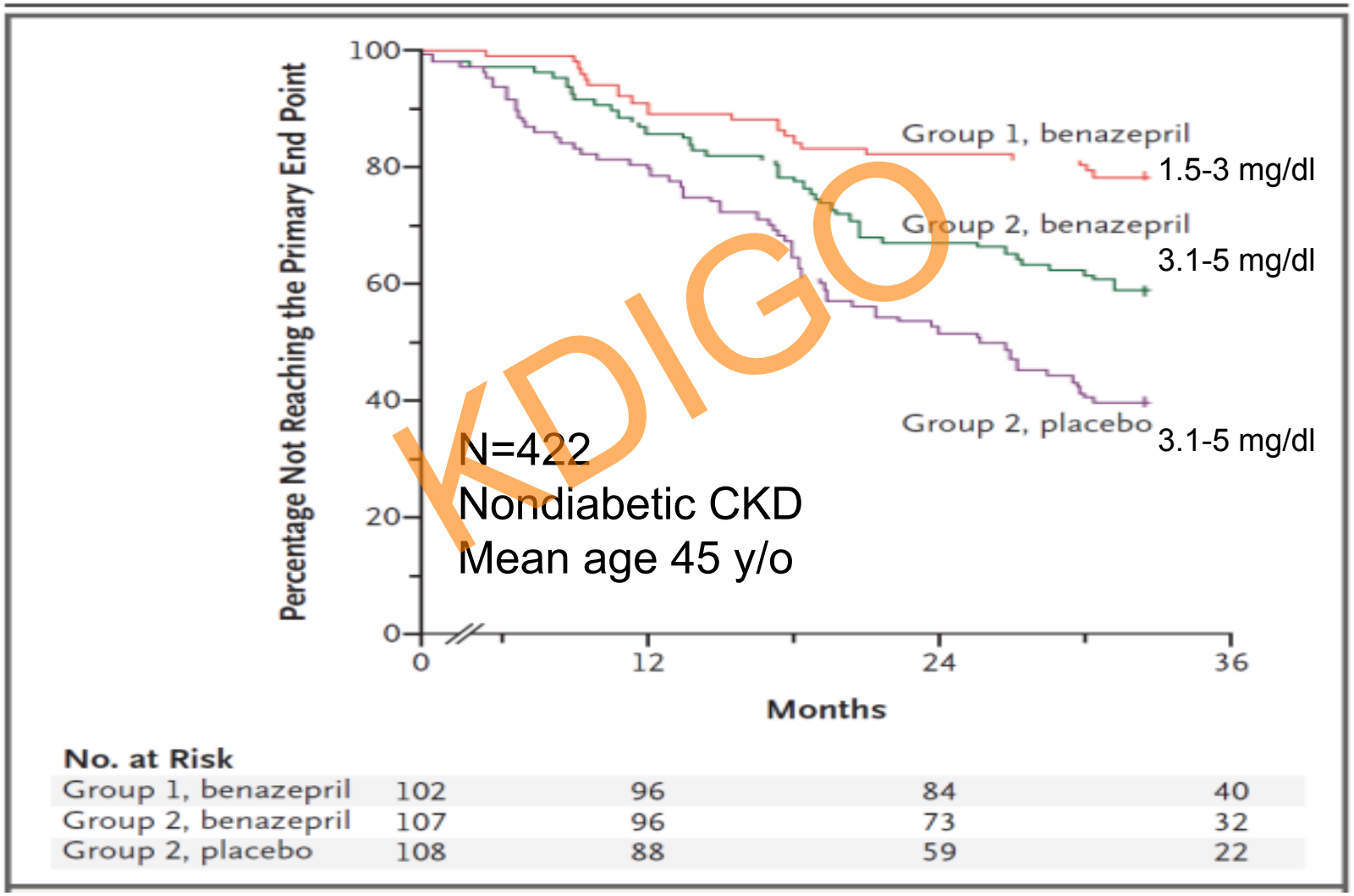
Long Term Follow-up of RAS induced changes in Serum Creatinine





Hirsch S et.al. Am J Nephrol 2012;36:430-437

Effects of an ACE inhibitors on Progression of Nephropathy



No. at Risk				
Group 1, benazepril	102	96	84	40
Group 2, benazepril	107	96	73	32
Group 2, placebo	108	88	59	22

Hou FF et.al. N Eng J Med 2006;354:131-40

Table 3. Adverse Events after Randomization.*

Adverse Event	Group 1 (N=104)	Group 2	
		Benazepril (N=112)	Placebo (N=112)
		no. of events	
Death	0	1	0
Nonfatal cardiovascular event			
Myocardial infarction	3	5	8
Heart failure	1	3	5
Stroke	1	2	3
Other adverse events			
Hyperkalemia†	2	6	5
Acute decline in renal function	1	1	1
Dry cough	0	1	0
Hypotension‡	1	0	0
Total	9	19	22

Hou FF et.al. N Eng J Med 2006;354:131-40

Conditions Associated with Marked early elevations in serum creatinine when BP is Treated

- Volume Depletion (Over aggressive diuresis) secondary to diuretic over use

PERSPECTIVE: Some but not all of these factors have been examined post hoc in trials and can't be in epidemiological studies

- [illegible] weeks
- Bilateral Renal Artery Stenosis

ACE Inhibitor or ARB Started

Check
Electrolytes & Serum Cr (1-2 weeks)

Serum Cr Unchanged

Continue to Titrate Agent
Until Blood Pressure at Goal*

Repeat
Electrolytes and Serum Cr
(3-4 weeks)

If Stable-recheck annually

If NSAID started or hypoperfusion state develops recheck more frequently

Serum Cr Increased <30% no electrolyte issues

BP in goal

Repeat Serum Cr in 2-3 wks.

>30% ↑ in Cr.

Recheck in 4 weeks, if stable,
If still >30% rise-stop ACEI and achieve BP control with other agents

BP not in goal

Continue RAAS blocker
Add other agents to get to BP goal

Repeat Cr + electrolytes in 2-3 weeks

<30% ↑ in Cr. + BP in goal Proceed as per A

Check Serum Cr in3-4 weeks

If BP in goal proceed if > 30% rise see ensure no volume depletion and if not reduce dose by 50%

<30% ↑ in Cr. + BP in not in goal –add other agents to achieve BP goal**

Serum Cr **+** *Increased ≥50%*

Exclude Hypoperfusion States
(Volume depletion) & NSAID use

Captopril Renal Scan or Angiogram to R/O Bilateral renal artery stenosis

Bakris G and Weir M Arch Intern Med 2000;160:685-693

Staging of AKI for adults

AKI stage	Serum Creatinine Criteria: KDIGO	Serum Creatinine Criteria: AKIN	Serum Creatinine Criteria: RIFLE	Urine volume criteria: KDIGO/AKIN/RIFLE
1 (R)	1.5–1.9 times baseline or ≥0.3 mg/dl (≥26 µmol/l) Increase within 48h	Increase ≥0.3 mg/dl (26.5 µmol/l) or≥1.5- to 2-fold from baseline	Increase×1.5 baseline or GFR decrease >25%	<0.5ml/kg/h for 6–12 h
2 (I)	2.0–2.9 times baseline	Increase >2- to 3-fold from baseline	Increase×2 from baseline or GFR decreased >50%	<0.5ml/kg/h for 12 h
3 (F)	3.0 times baseline or increase in serum creatinine to≥4.0 mg/dl (354 µmol/l) or initiation of renal replacement therapy or, in patients <18 years, decrease in eGFR to <35ml/min per 1.73 m^2	Increased >300% (>3-fold) from baseline, or ≥4.0 mg/dl (354mmol/l) with an acute increase of ≥0.5 mg/ dl (44 µmol/l) or on renal replacement therapy	Increase × 3 from baseline, or serum creatinine >4mg/dl (>354 µmol/l) with an acute rise >0.5mg/dl (>44 µmol/l) or GFR decreased >75%	<0.3ml/kg/h for 24 h or anuria for 12 h

Okusa, M. D. and A. Davenport Kidney Int 2014;85(1): 39-48

The story of worsening renal function

(i.e. change in serum creatinine ≥ 0.3mg/dl)

Correlates and Impact on Outcomes of Worsening Renal Function in Patients ≥65 Years of Age With Heart Failure*

Harlan M. Krumholz, MD, Ya-Ting Chen, PhD, Viola Vaccarino, MD, PhD, Yun Wang, MS, Martha J. Radford, MD, W. David Bradford, PhD, and Ralph I. Horwitz, MD

TABLE III Impact of Worsening Renal Function (WRF) on Patient Clinical Outcomes and Resource Consumption

Outcomes	Total	WRF Absent	WRF Present	Adjusted Estimate*
In-hospital mortality	68 (4%)	36 (3%)	32 (7%)	2.72 (1.62–4.58)
30-d mortality	123 (7%)	76 (6%)	47 (10%)	1.87 (1.25–2.80)
30-d readmission, all-cause	296 (18%)	201 (17%)	95 (20%)	1.29 (0.98–1.71)
30-d readmission, heart failure related	118 (7%)	80 (7%)	38 (8%)	1.17 (0.77–1.77)
6-month mortality	354 (21%)	235 (19%)	119 (25%)	1.56 (1.19–2.05)
6-month readmission, all-cause	790 (47%)	555 (46%)	235 (50%)	1.16 (0.93–1.44)
6-month readmission, heart failure related	380 (23%)	264 (22%)	116 (25%)	1.07 (0.82–1.39)
Length of hospital stay, mean (SD) (d)	7.55 (4.70)	6.93 (3.92)	9.14 (6.01)	2.28 (0.25)†
Hospital cost, mean (SD)	$6,823 ($5,175)	$6,327 ($4,874)	$8,085 ($5,665)	$1,758 ($287.2)†

*Estimates were odds ratios and 95% confidence intervals for mortality and readmission outcomes, and regression coefficients and their standard errors for length of hospital stay and hospital cost outcomes; estimates adjusted for sex, age, diabetes, hypertension, rales, pulse, baseline creatinine, systolic blood pressure, and left ventricular ejection fraction.

†$p < 0.0001$.

Krumholz H et.al. Am J Cardiol 2000; **85**(9): 1110-1113.

Aggrastat to Zocor trial and CVD outcomes based on creatinine change

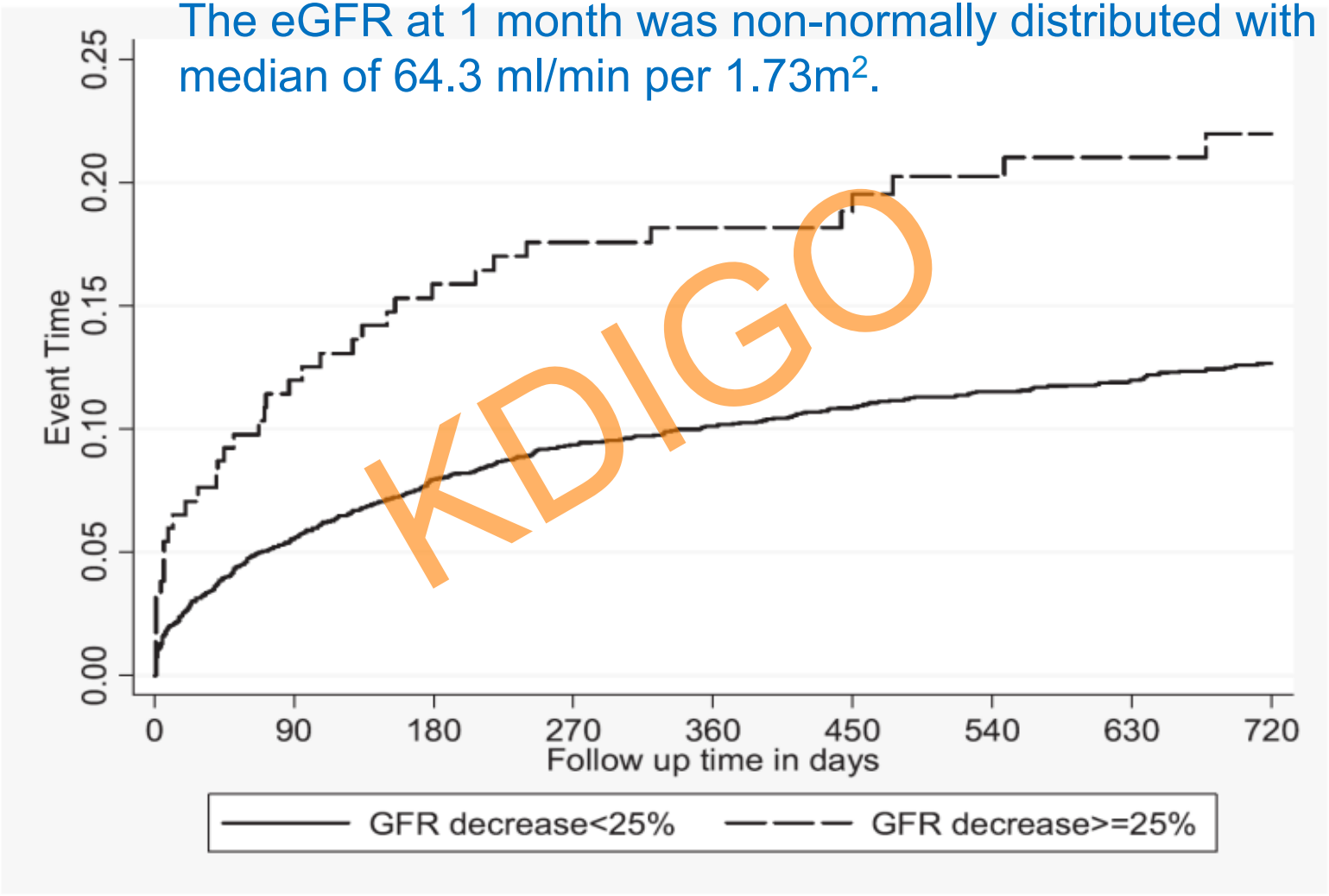
Table 1. Baseline clinical characteristics of population based on an early decline in renal function (decline in GFR of ≥25% over 1 mo)

Characteristic	eGFR Decrease <25% (n = 3611)	eGFR Decrease ≥25% (n = 184)	P
Age (yr; mean ± SD)	60.2 + 10.6	60.8 + 10.4	0.4
Female sex (%)	23.2	38.6	<0.001
Diuretic use within 7 days (%)	22.7	32.1	0.01
Lytics (%)	21.7	22.8	0.7
Clinical or echo evidence LV dysfunction (%)	11.2	16.9	0.02

Mielniczuk, LM et.al. Clin J Am Soc Nephrol 2009;4: 1811–1817

Kaplan-Meier estimates of death rates from any cause and CV composite (CV death, recurrent MI, CHF, or stroke) endpoint *according to a significant change in estimated GFR over 1 month*

The eGFR at 1 month was non-normally distributed with a median of 64.3 ml/min per 1.73m^2.



Post hoc data from the Aggrastat to Zocor trial and CVD outcomes based on creatinine change

Mielniczuk, LM et.al. Clin J Am Soc Nephrol 2009;4: 1811–1817

Many reasonable studies uniformly show that significant sustained increases in serum creatinine of > 25% following cardiac procedures or CV events are associated with higher CV mortality

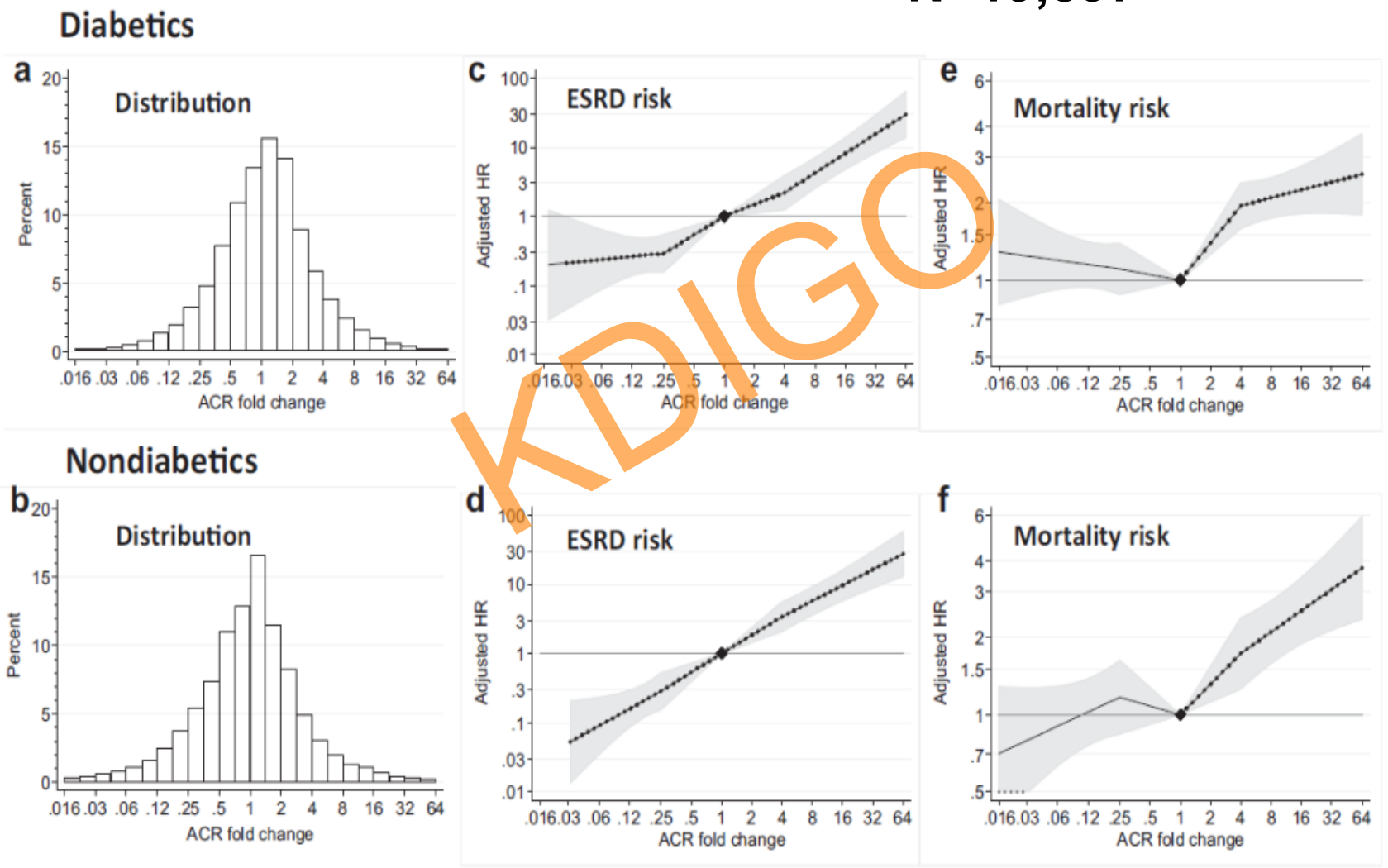
- Schneider, C., et al. (2016). "Doubling of serum creatinine and the risk of cardiovascular outcomes in patients with chronic kidney

NOTE: All studies showing this relationship between increased creatinine and mortality are in hospitalized patients that have a had major morbid CV event.

The changes in creatinine related to BP treatment in the outpatient setting have not been shown to have adverse CV outcomes have not been studied.

Distribution of 2-year albumin-to-creatinine ratio changes

N=19,897



Carrero JJ et.al. Kidney Int 2017;91:244-251

Summary

- Aggressive reduction in BP over the first month or two results in reductions in GFR especially if using RAS blockers.
- Resultant hyperkalemia, acute kidney injury (*def. dependent*) and postural hypotension may also occur especially if BP is <130/80 mmHg and achieved quickly i.e. within 1-2 months.
- It is difficult to tease out the true contribution of lower BP versus the multiple agents needed to lower BP on some adverse effects
- Acute elevation of serum creatinine ≤ 30% are not associated with faster declines in nephropathy or higher CV risk in the outpatient setting