CHOICES OF AGENTS AND INTERVENTIONAL THERAPIES FOR HTN IN CKD

Robert D. Toto, M.D.
Professor of Medicine
Assoc. Dean Clinical and Translational Research
UT Southwestern Medical Center
Dallas, Texas

Disclosure of Interests

- Akebia-Consultant
- Amgen-Consultant
- Astra-Zeneca-Consultant
- Boehringer-Ingelheim-Consultant
- Novo Nordisk-Consultant
- Relypsa-Consultant
- ZS Pharma-Consultant\

Take Home: Management of Hypertension in Chronic Kidney Disease

- RAAS blockade-based drug regimens
  - Vs placebo and other comparators improve renal outcomes especially in those with proteinuria
  - Systematic review: reduce mortality in DM
- Combined RAAS blockade based drug regimens compared to single RAAS blockade
  - do not improve renal or cardiovascular or all-cause mortality
- Tight vs Standard BP target: similar improvement in CV Disease and slightly lower all-cause mortality (SPRINT)
- Dietary intervention and Devices not tested/proven to improve renal or CV outcomes or all cause mortality
- Role of SGLT-2 and K binding agents on renal and CV outcomes unknown-stay tuned

Pathophysiologic Basis of Treatment of Hypertensive Kidney Disease

↑ Na Reabsorption

- Angiotensin II
- Sympathetic nerves
- NOS inhibitors
- Impaired pressure natriuresis
- ↓ Glomerular surface area
- Decreased PGs

Volume Expansion

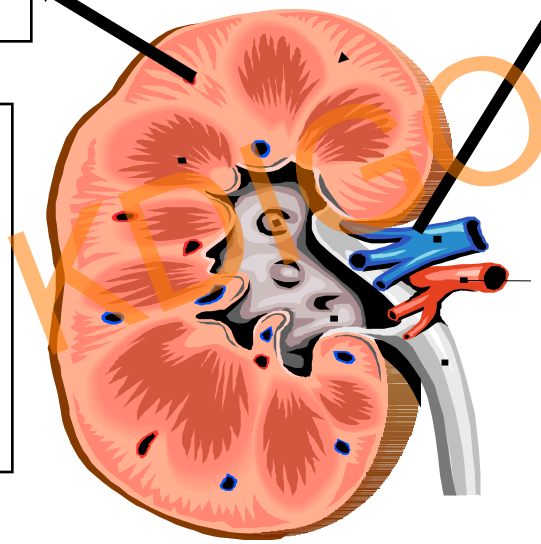
Diuretic

Vasoconstrictors

- Angiotensin II
- Endothelin
- Sympathetic Nerves
- NOS inhibitors
- Decreased PGs
- Digoxin- like factors

↑ Peripheral Resistance

Vasodilator



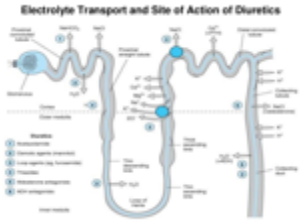
HYPERTENSION

Approaches to Lowering BP in Hypertensive Patients with CKD

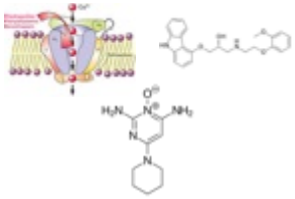
RAAS blockade

Non-RAAS Antihypertensives

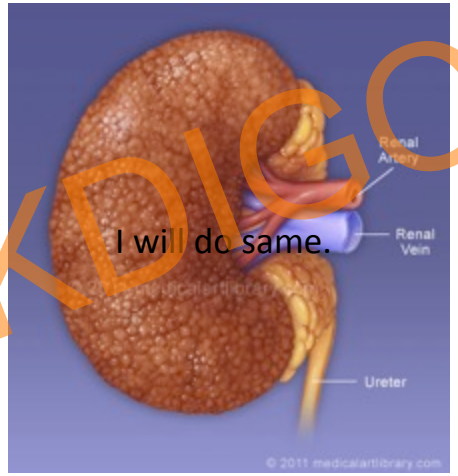
Diuretics



Other: CCB, BB, Vasodilators, etc.



Lifestyle
Dietary Sodium Restriction
Weight Loss



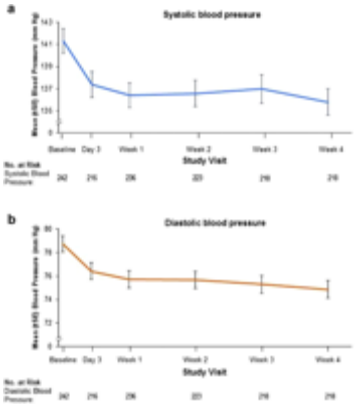
Devices

Renal Denervation

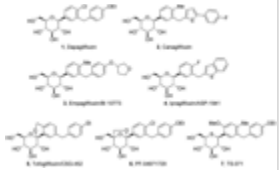
Baroreceptor Activation

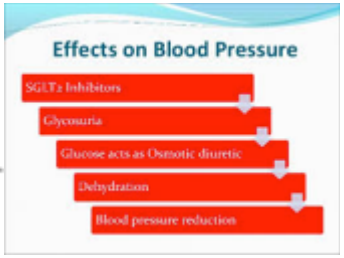
Novel Agents

K lowering agents



SGLT-2 Inhibition

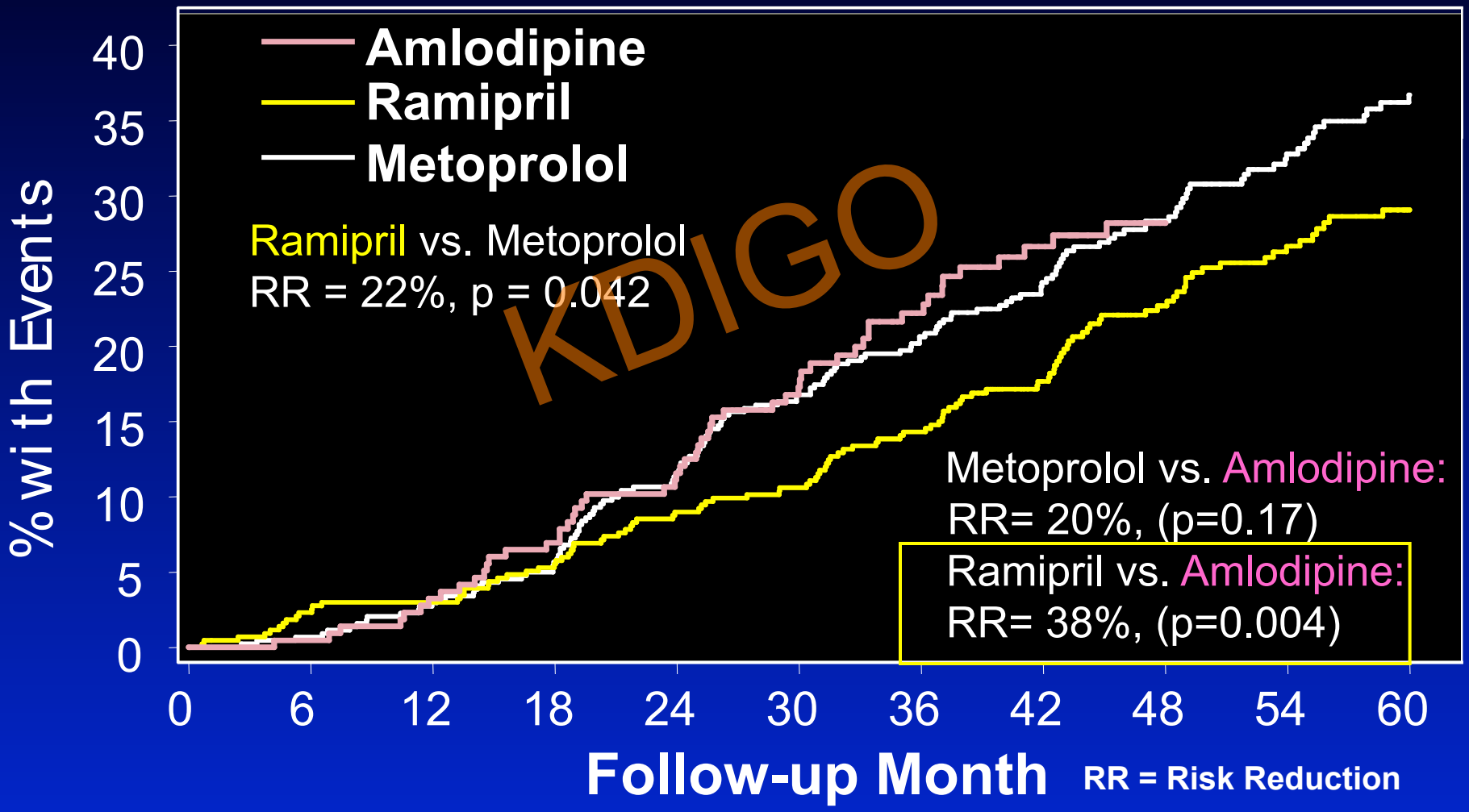




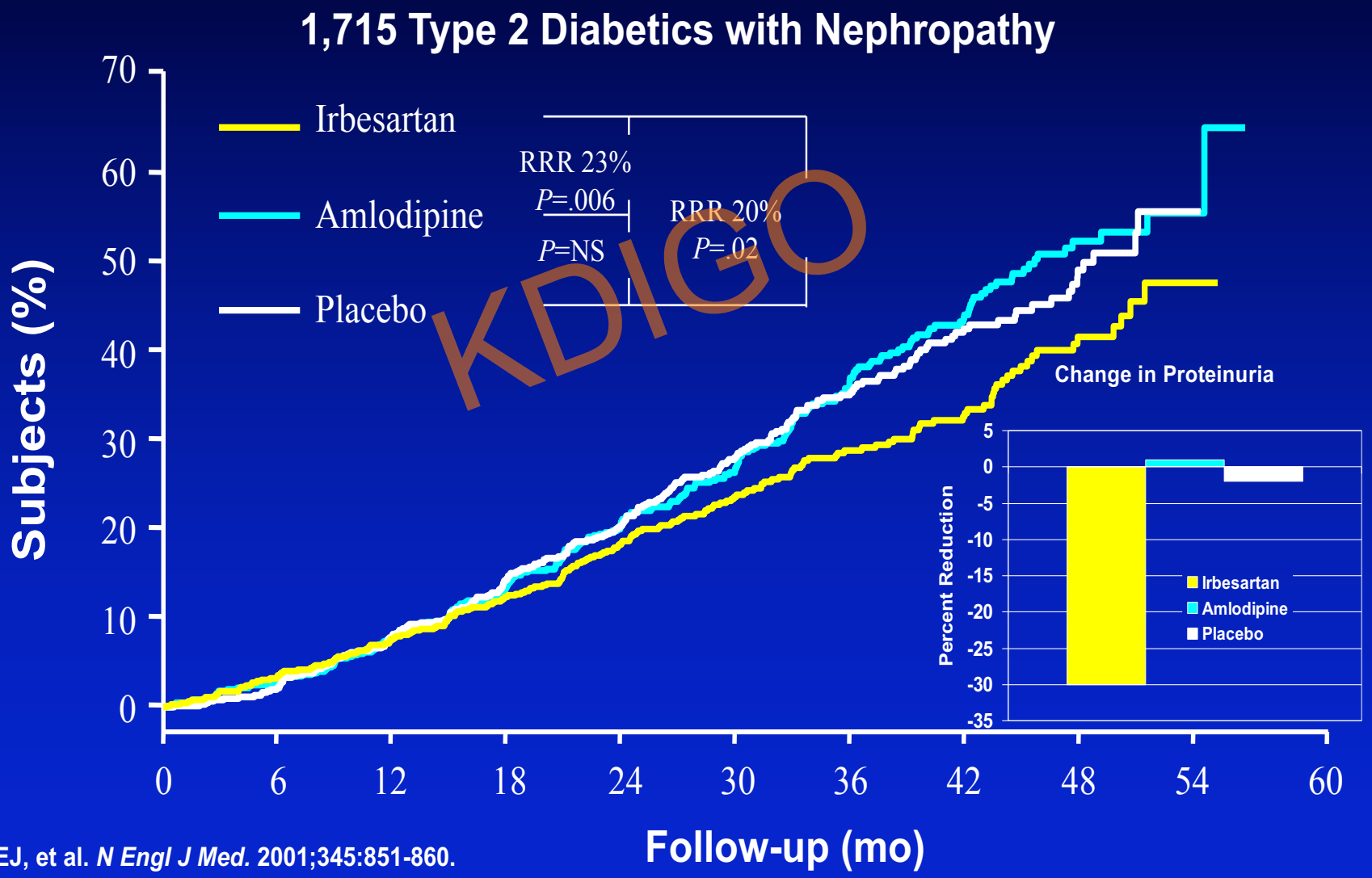
Some Randomized Placebo/Comparator Outcomes Trials using RAAS blockade in CKD

Trial	Year Journal	Drug	Outcome	Benefit	Potential Harm
CSG Group	1993 NEJM	Captopril	DScr, ESRD Death	Yes	No
RENAAL/IDNT	2001 NEJM	Losartan /Irbesartan	DScr, ESRD Death	Yes	No
ALTITUDE	2012 NEJM	Aliskerin+ ACEi/ARB	CV and Renal ESRD Death	No	Yes
VA NEPHRON D	2014 NEJM	Lisinopril + ARB	DScr, ESRD Death	No	Yes
AASK	2002 JAMA	Ramipril Metoprolol Amlodipine	50% decline GFR, ESRD, Death	Yes	No
Hou et al	2006 NEJM	Benazepril	DScr, ESRD	Yes	No
HALT-PKD	2014 NEJM	Lisinopril + Telmisartan	eGFR Decline	No	No
SPRINT	2015 NEJM	Various ACEi/ ARB	DScr, 30% decline in eGFR, ESRD	No	No

AASK: Composite Clinical Events: Declining GFR Event, ESRD or Death by Drug Group



Irbesartan in Diabetic Nephropathy Trial: Time to Doubling of Serum Creatinine, ESRD, or Death



Lewis EJ, et al. *N Engl J Med.* 2001;345:851-860.

RAAS Blockade in non DM CKD: 3 Cochrane Systematic Reviews

- **Effectiveness of ACEi or ARBs in patients with early CKD**
  - ACEi had little or no effect on all-cause mortality, cardiovascular events and end-stage kidney disease in people with stage 3 CKD.
- **Effectiveness of MRAs with or without ACEi or ARB in patients with CKD**
  - Decrease proteinuria and lower blood pressure.
  - insufficient data on mortality, ESKD and cardiovascular events
- **Effectiveness of of ACEi or ARB in patients with IgA nephropathy**
  - reduced proteinuria
  - no evidence that treatment with decreased mortality, cardiovascular events or adverse renal outcomes

RAAS blockade in CKD with DM: Cochrane Systematic Review (26 trials, N=61,264)

- ACEi vs placebo reduced
  - risk of mortality (6 studies, 11,350): RR 0.84,
  - new onset of micro and macroalbuminuria, (8 studies, N=11,906) RR 0.71.
- ACEi vs CCB, reduced onset of micro and macroalbumuria (5 studies, N=1,253): RR 0.60.
- ARB vs placebo no difference
  - mortality (5 studies, N=7,653: RR 1.12, 95%CI 0.88 to 1.41)
  - onset of microalbuminuria, macroalbuminuria or both (5 studies, N=7,653): RR 0.90.
- Combination of ACEi and ARB vs ACEi alone no difference in onset of micro or macroalbuminuria (2 studies, N=4171): RR 0.88.

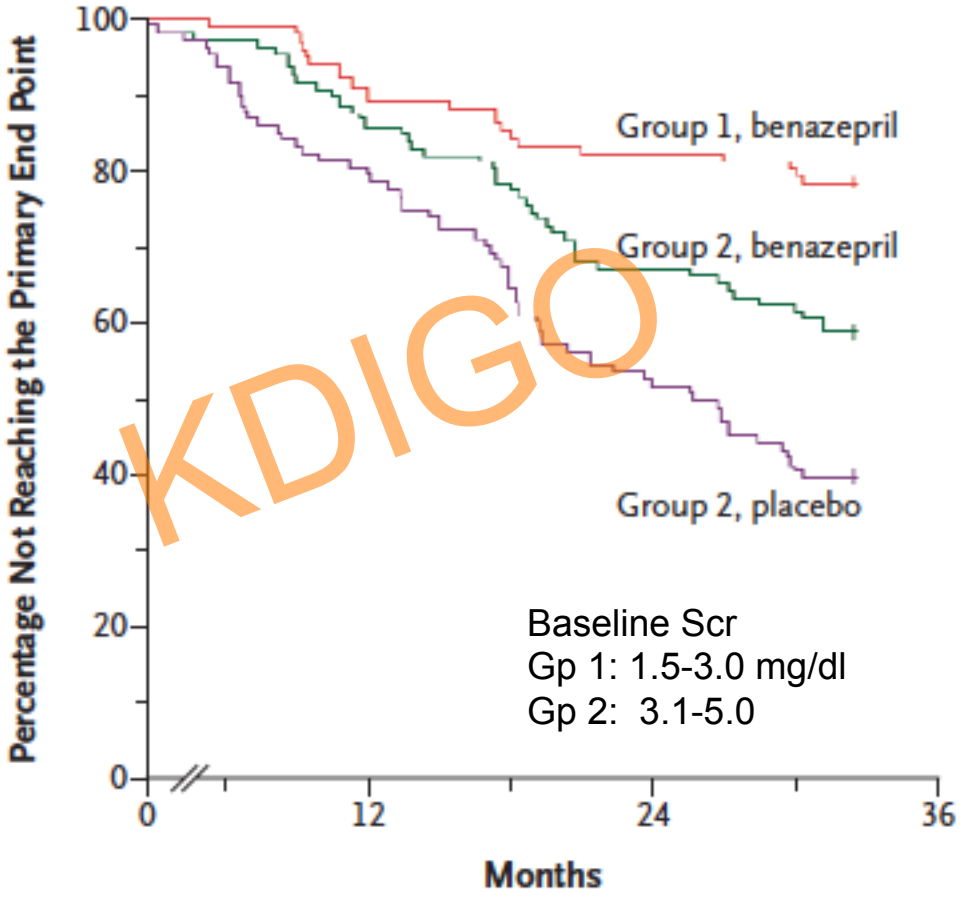
Conclusion

ACE inhibitors or Angiotensin Receptor Blockers should be first line agents in patients with hypertensive CKD

WHEN IS the GFR TOO LOW TO SEE BENEFIT OF ACEi in CKD?

Controversy

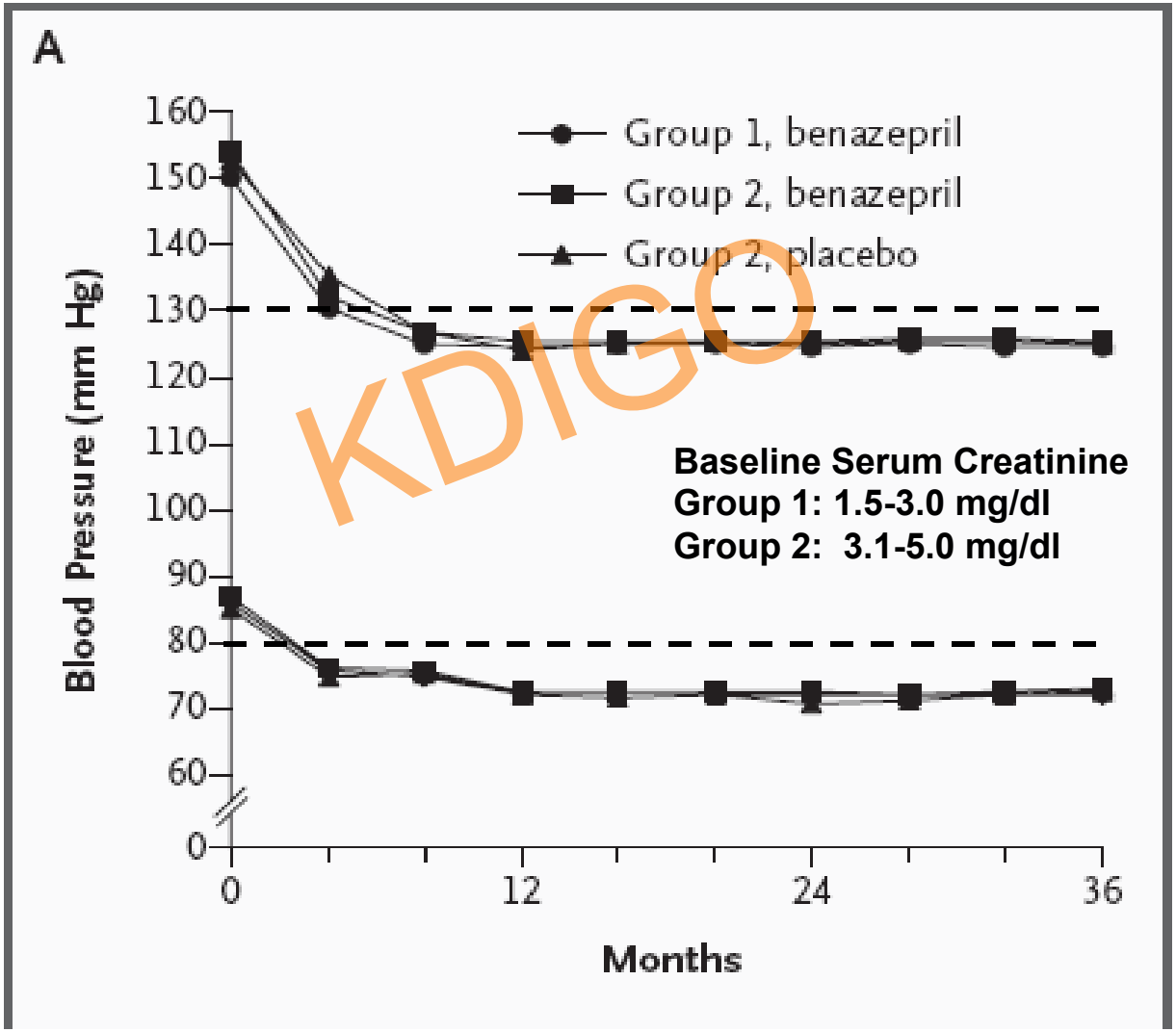
ACE inhibition in Non-Diabetic Nephropathy (N = 317)



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 et al. N Engl J Med 354;2:131-140, 2006

BP Control in Non-Diabetic Nephropathy (N = 317)

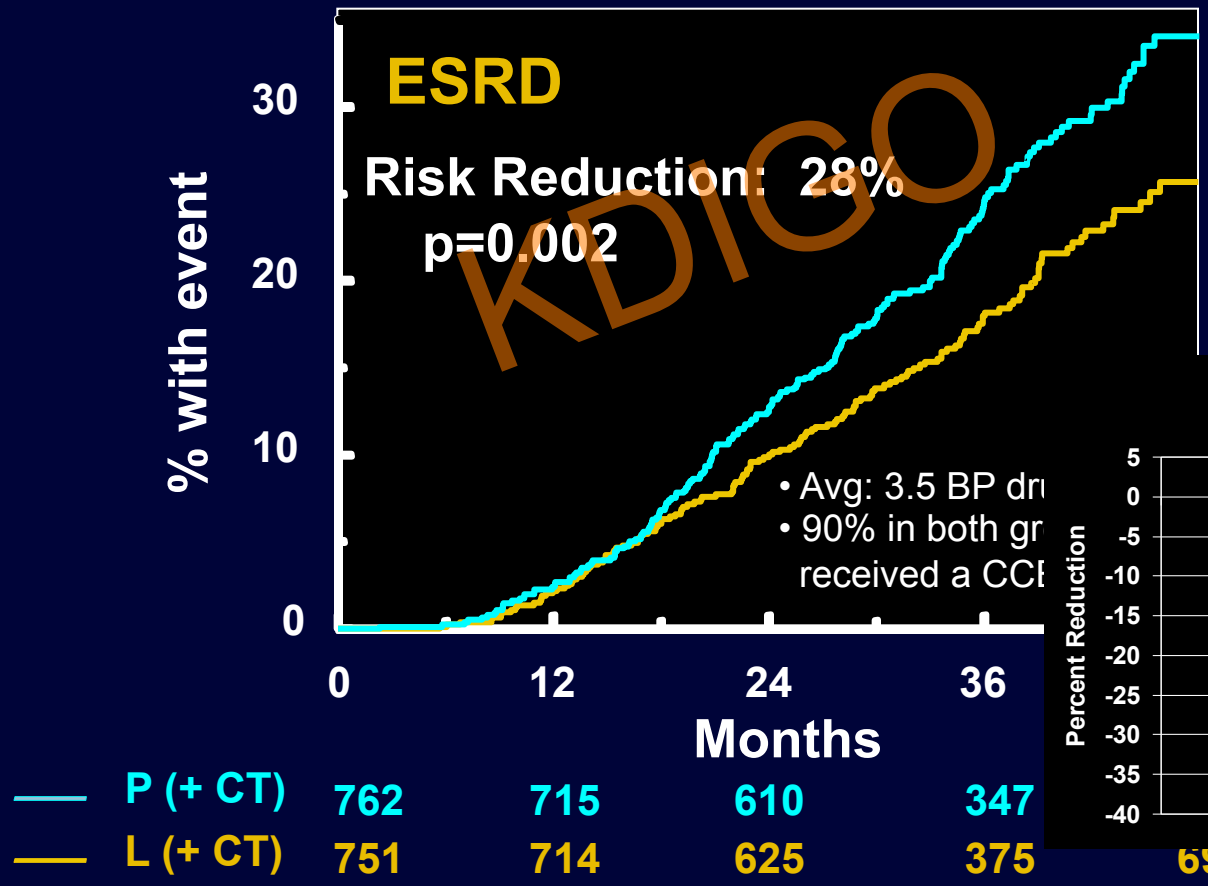


Hou et al. N Engl J Med 354;2:131-140, 2006

WHAT IS EFFECT OF PROTEINURIA ON RENAL OUTCOME?

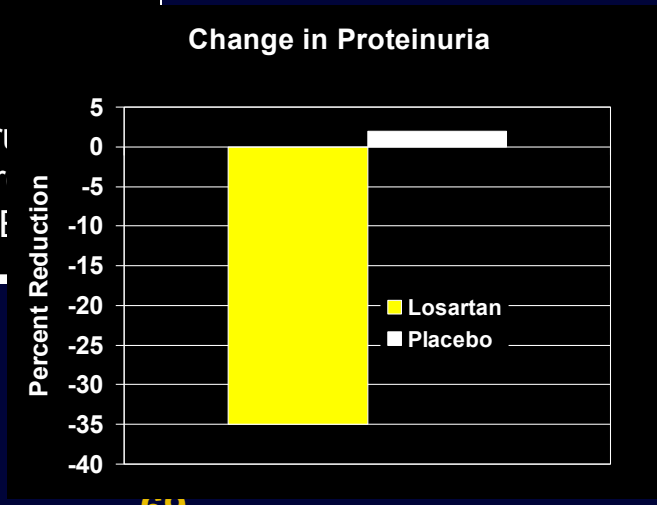
ARB (losartan) Reduces Risk of ESRD in Diabetic Nephropathy

Reduction in Endpoints in NIDDM with Angiotensin Antagonist Losartan (RENAAL) Trial: 1513 type 2 Diabetics with Nephropathy



Placebo
BP 142 / 74

Losartan
BP 140 / 74



Brenner et al. *New Engl J. Med* Sept 20 2001

Meta-Analysis Non-Diabetic CKD

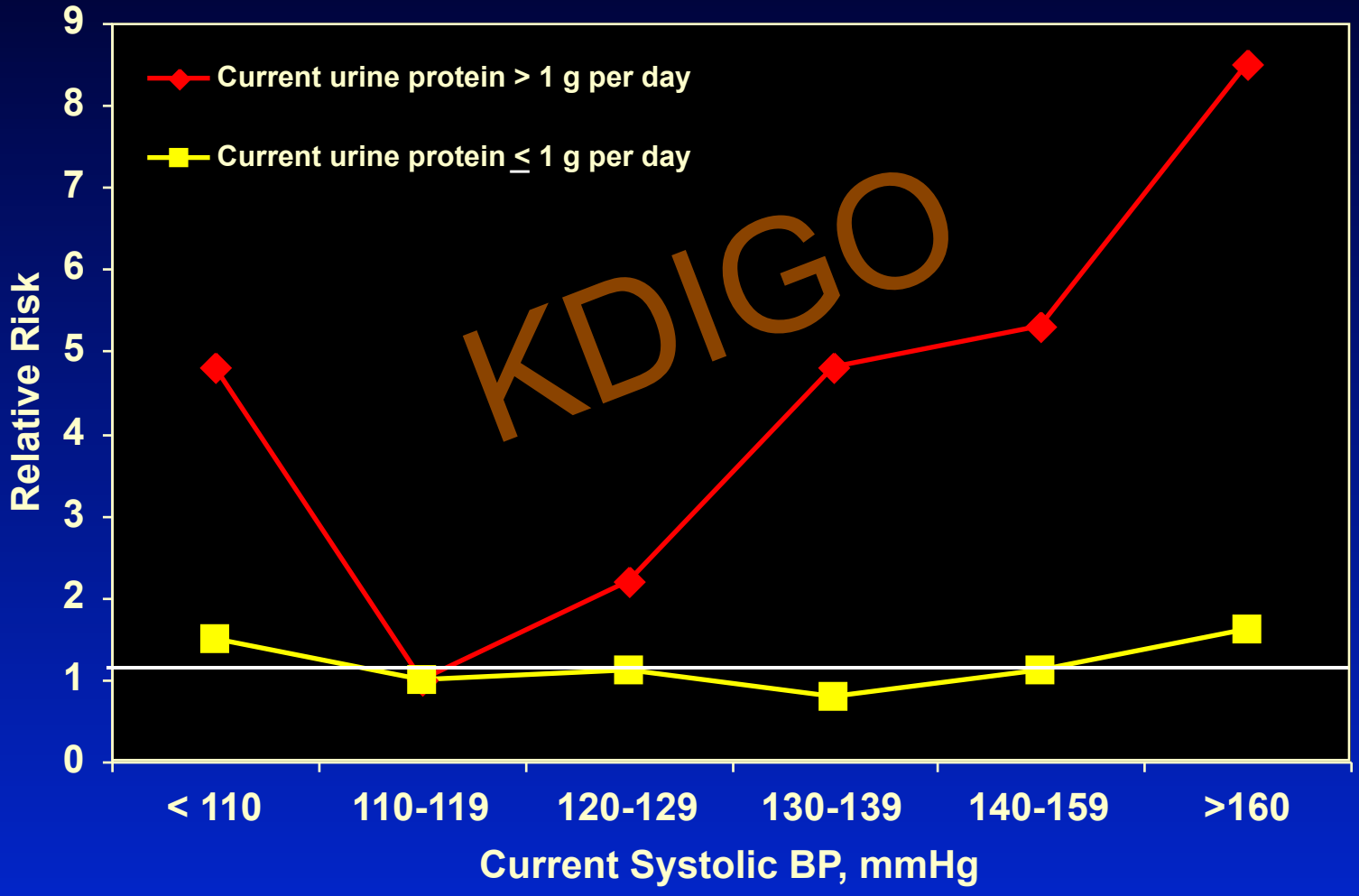
- 1860 patients from 11 RCTS with non-diabetic kidney disease
  - Anti-hypertensive regimens with ACE inhibitors vs. regimens without ACE inhibitors on progression of kidney disease.
    - Minimum follow-up of one year
- Objectives:

1) Determine whether antihypertensive regimens with ACE inhibitors are superior to those without ACE inhibitors

2) Assess the relationship of BP with progression of kidney disease across a wide range of urine protein excretion

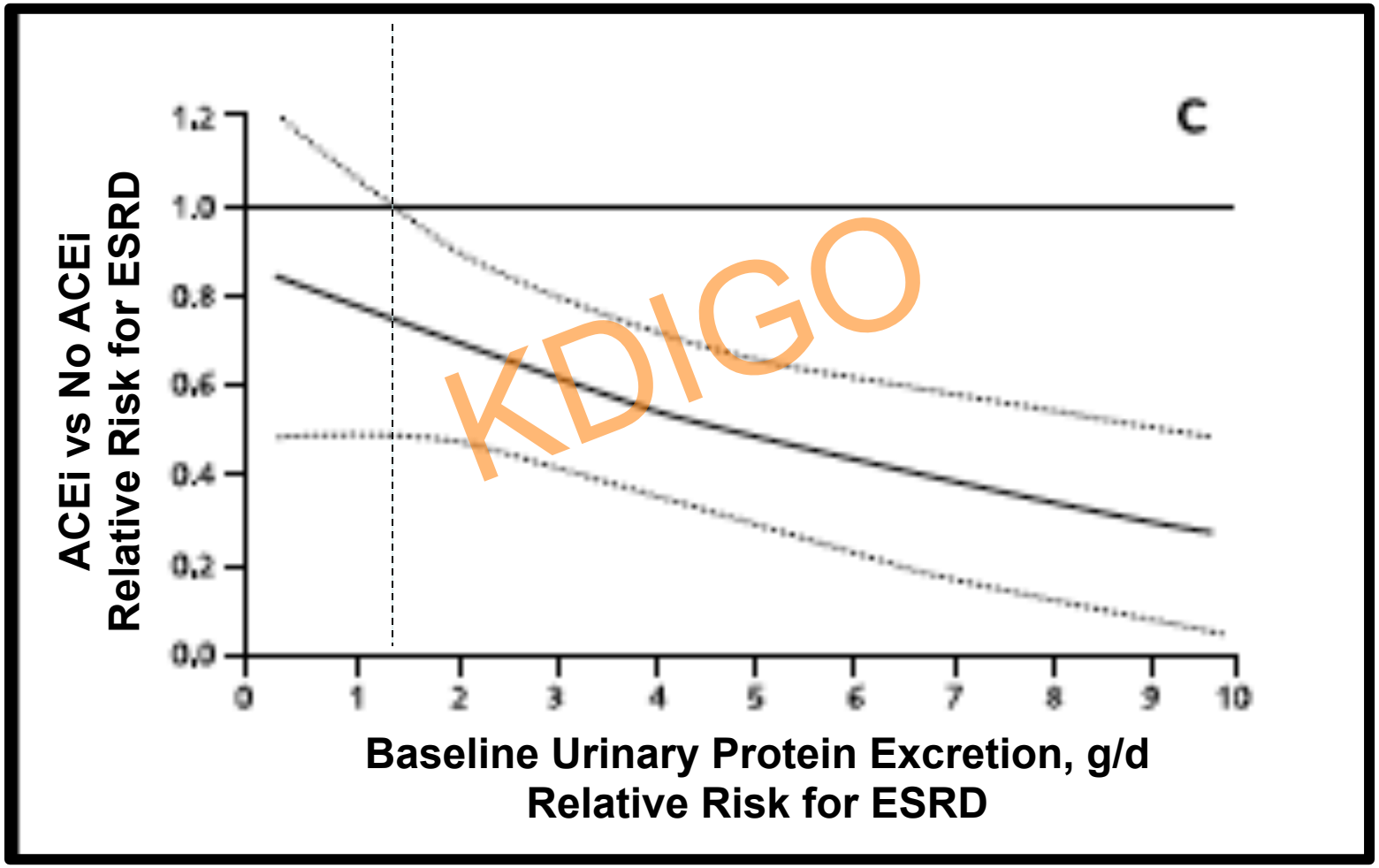
(Jafar, T. et. al. *Ann Intern Med 2001)*

Relative Risk for Kidney Disease Progression with ACEi vs. non-ACE based regimen in Non-Diabetic Nephropathies



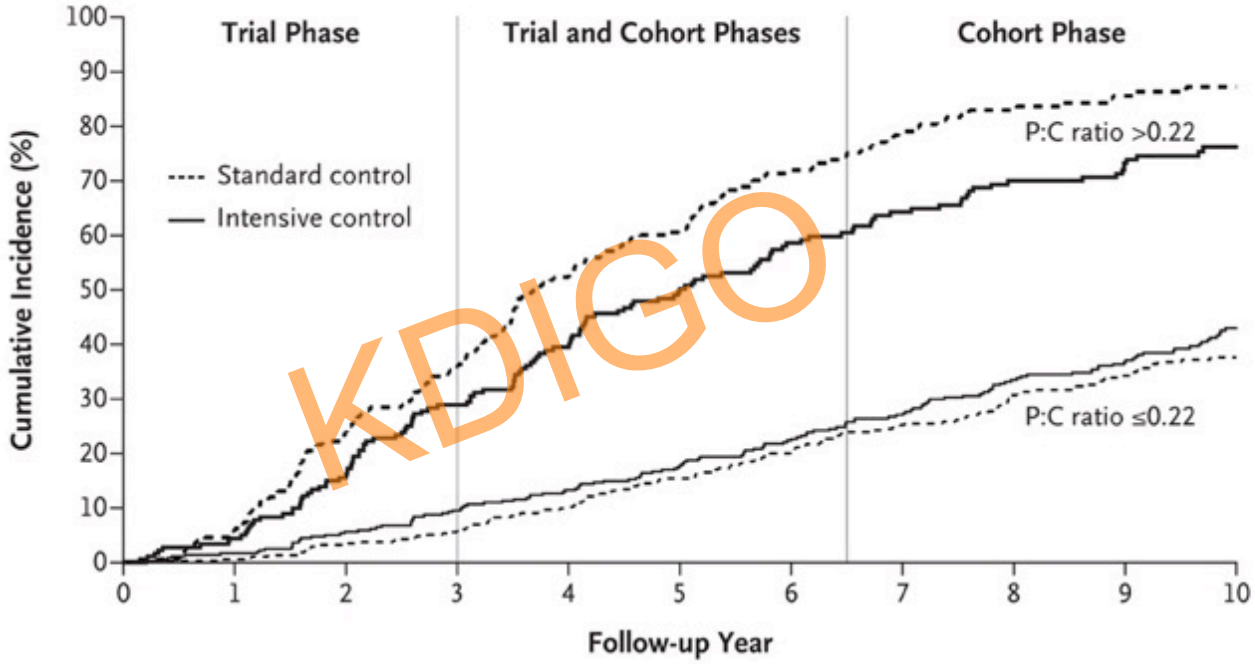
Jafar et al. *Ann. Int. Med.* 124(4)244-253, 2003

Relative Risk for ESRD: ACEi vs No ACEi in Non-Diabetic CKD (N=1860)



(Jafar, T. et. al. *Ann Intern Med 2001)*

AASK: Cumulative Incidence of the Composite Primary Outcome, According to Baseline Proteinuria Status.



P:C Ratio >0.22											
Standard control	176	165	134	113	81	66	45	32	26	22	13
Intensive control	181	172	151	128	109	87	67	56	47	40	25
P:C Ratio ≤0.22											
Standard control	376	373	362	353	332	302	267	234	214	196	128
Intensive control	357	350	335	321	306	282	254	228	206	189	128

Appel LJ et al. N Engl J Med 2010;363:918-929.

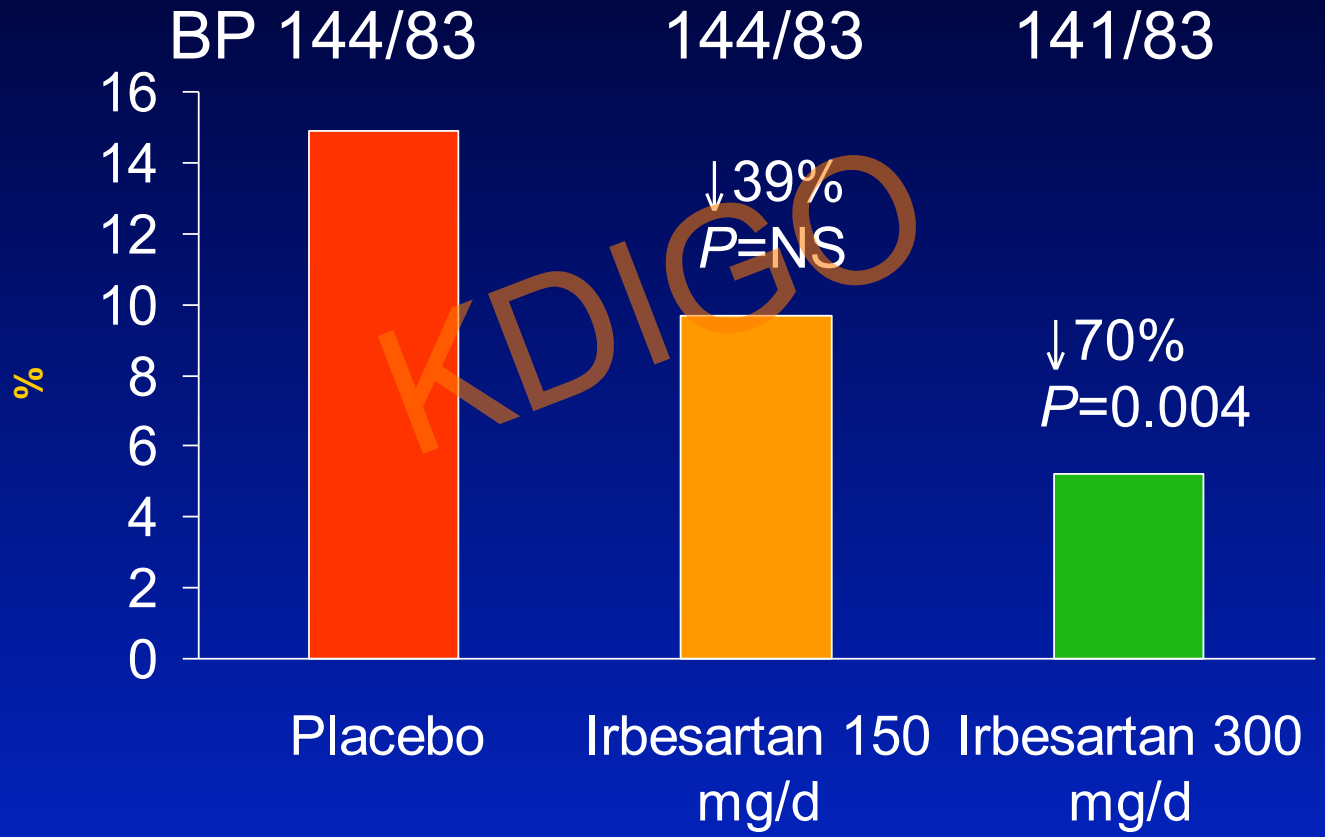
Conclusion

Proteinuria modulates the effect of blood pressure lowering in hypertensive patients with CKD

ARE ACEi and ARB SUPERIOR TO NON-ACEI/ ARB IN CKD WITH MICROALBUMINURIA?

Controversy

Irbesartan in Microalbuminuria (IRMA 2): Development of Overt Nephropathy



NNT: 10 patients over 2 years to prevent 1 case of overt nephropathy

Parving et al. *New. Engl. J. Med* Sept 20, 2001

Conclusion

No long-term Outcomes Trials of Renal or Cardiovascular Endpoints

WHEN SHOULD YOU CONSIDER STOPPING ACEI/ARB IN CKD?

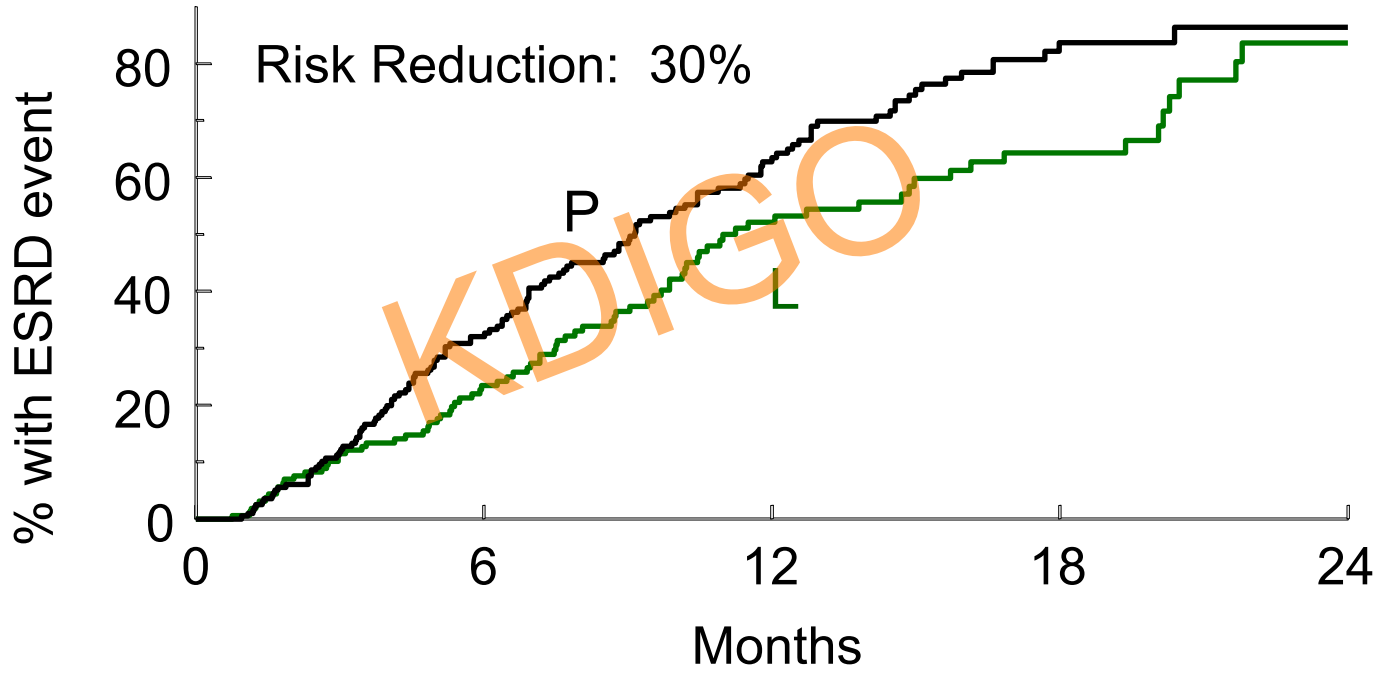
Controversy

When to Stop RAAS blockade in CKD

- Hyperkalemia

- When the GFR is low?
- In my opinion NO

Continuation of Losartan After Serum Creatinine Doubles AND Incident ESRD



P (+CT)	198	111	48	11	4
L (+CT)	162	104	43	19	3

Brenner et al. *New Engl J. Med* Sept 20 2001

Basis for Discontinuing ACEi in Advanced CKD: Observational Study

- 52 patients (1/2 DM) stages 4 and 5 CKD observed year before and year after stopping ACEi/ARB mean eGFR ~ 16

- 12 months after discontinuation
  - eGFR increased about 10 ml and decline in the eGFR slope was reversed +0.48 ± 0.1 (p = 0.0001).
  - BP increased about 5 mmHg

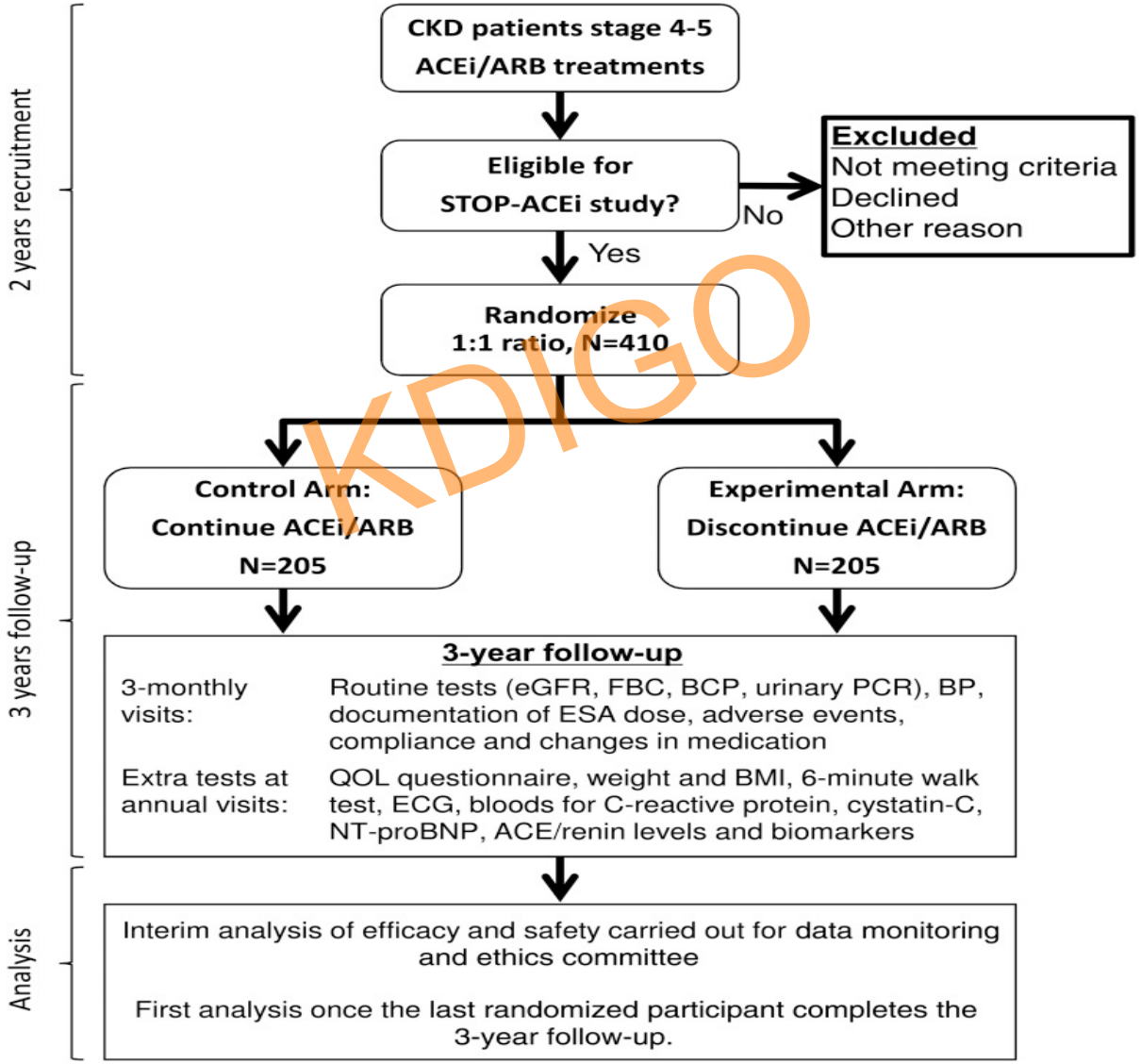
- Discontinuation of ACEi/ARB delayed the onset of RRT

Ahmed et al. Nephrol Dial Transplant (2010) 25: 3977–3982

Conclusion

We do not yet know whether stopping RAAS blockade in stage 4 or 5 CKD improves outcomes, so...

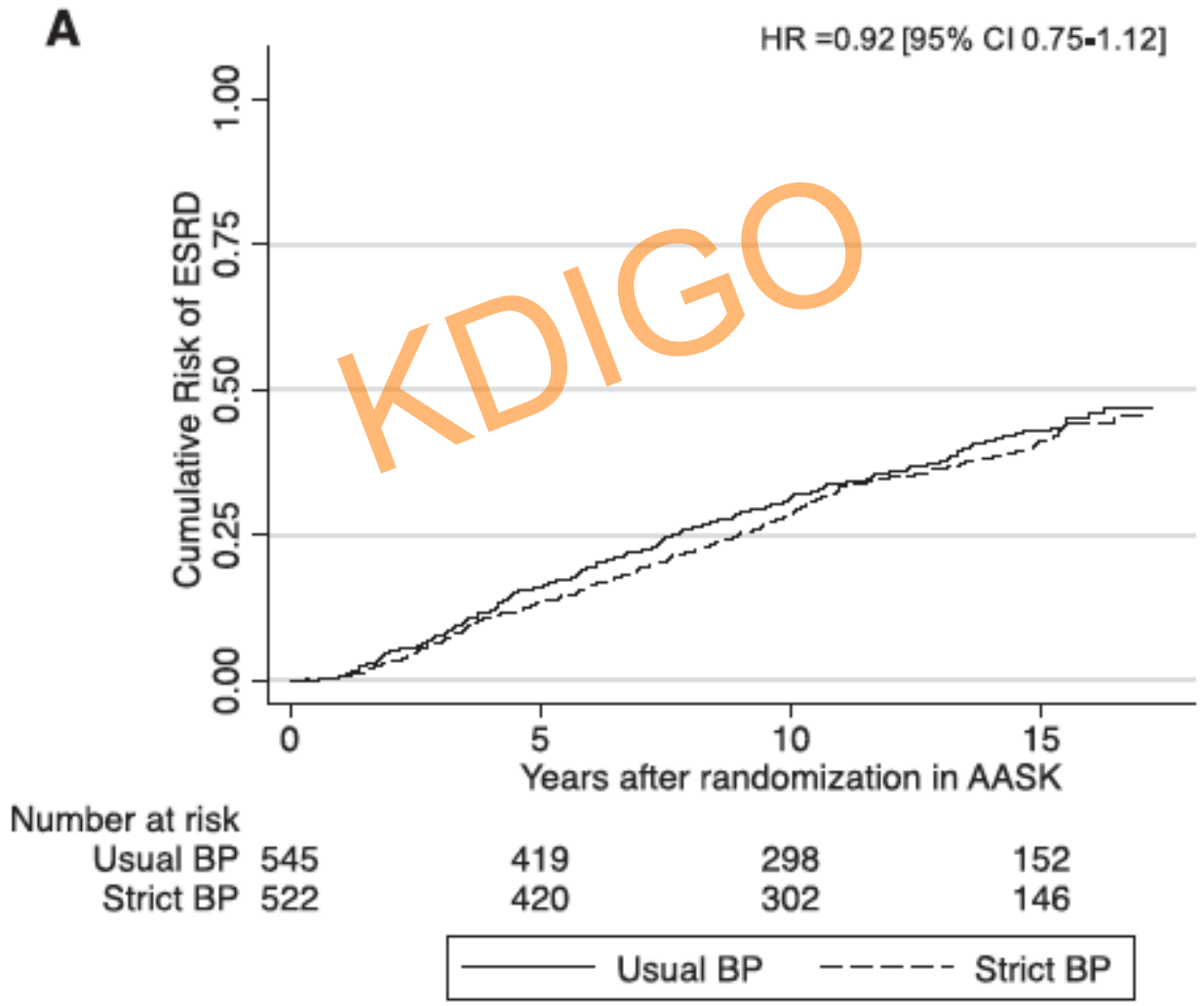
STOP ACEi Trial



Bhandari et al. Nephrol Dial Transplant (2016) 31: 255–261

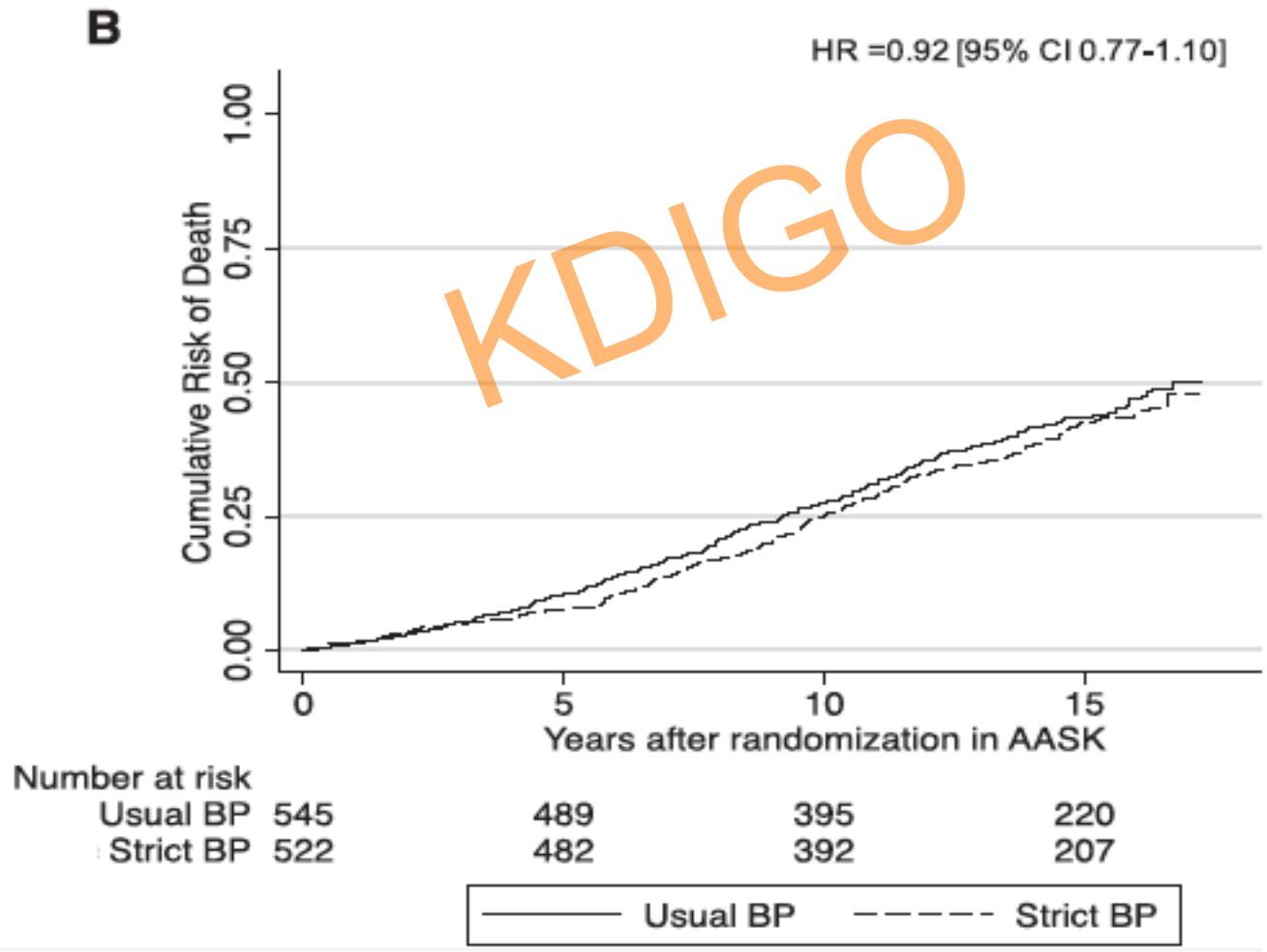
A LITTLE BIT ABOUT BP CONTROL LEVEL

Long-term risk of ESRD in AASK: Strict vs Usual BP Control



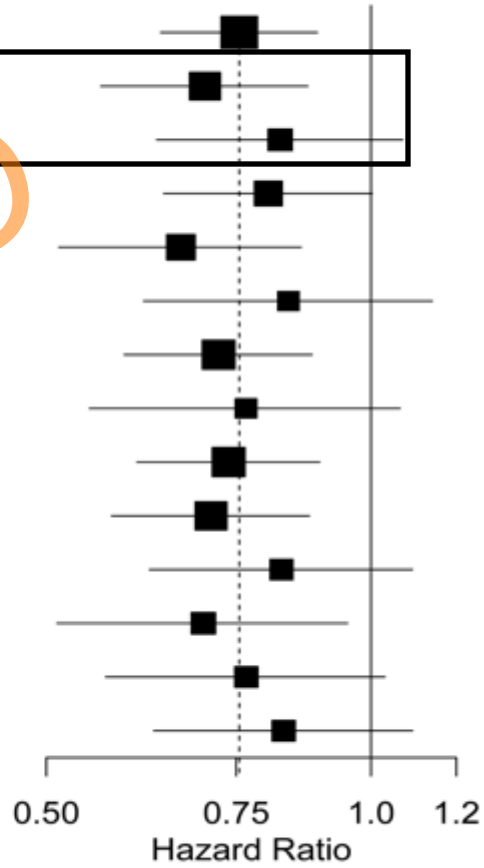
Ku et al. *Kid. Int.* 2016

Long-term risk of All Cause Mortality in AASK: Strict vs Usual BP Control



SPRINT: Primary Outcome Experience in 6 Pre-specified Subgroups

Subgroup	HR	P*
Overall	0.75 (0.64,0.89)	
No Prior CKD	0.70 (0.56,0.87)	0.36
Prior CKD	0.82 (0.63,1.07)	
Age < 75	0.80 (0.64,1.00)	0.32
Age ≥ 75	0.67 (0.51,0.86)	
Female	0.84 (0.62,1.14)	0.45
Male	0.72 (0.59,0.88)	
African−American	0.77 (0.55,1.06)	0.83
Non African−American	0.74 (0.61,0.90)	
No Prior CVD	0.71 (0.57,0.88)	0.39
Prior CVD	0.83 (0.62,1.09)	
SBP ≤ 132	0.70 (0.51,0.95)	0.77
132 < SBP < 145	0.77 (0.57,1.03)	
SBP ≥ 145	0.83 (0.63,1.09)	

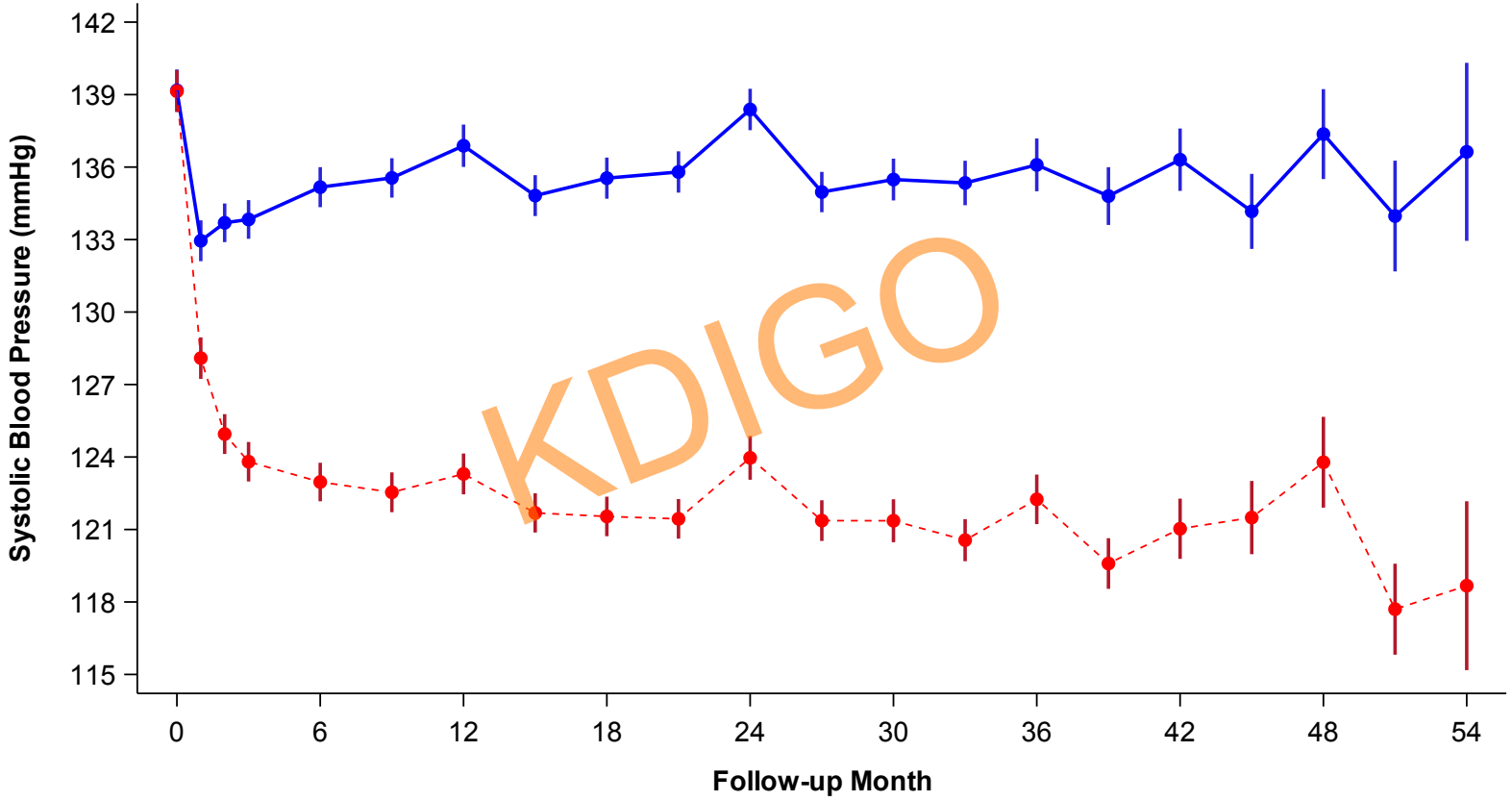


*Unadjusted for multiplicity

*Treatment by subgroup interaction

SPRINT Research Group: *N Engl J Med.* Volume 373(22):2103-2116, 2015

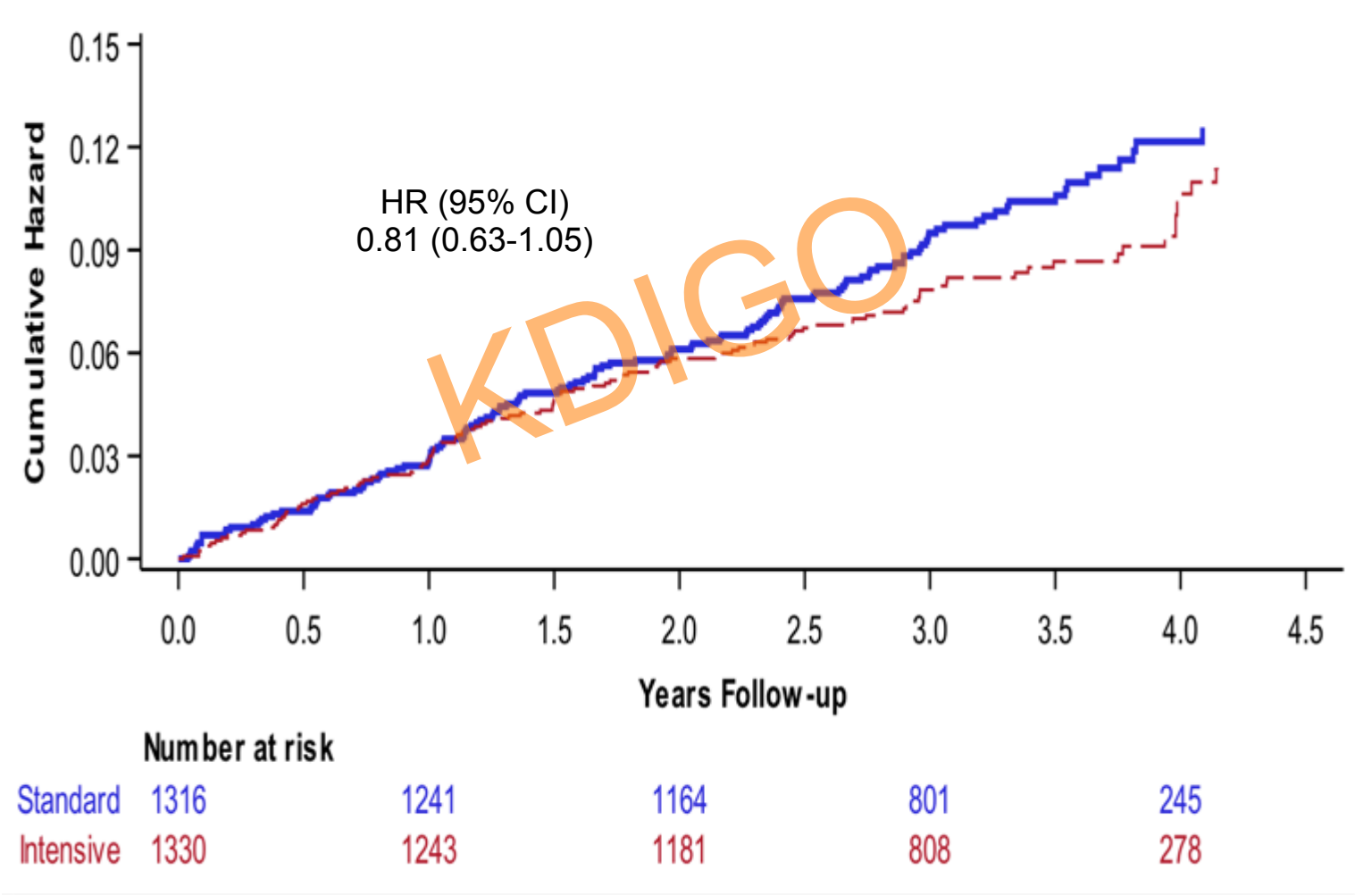
SPRINT CKD (baseline eGFR < 60) Cohort: Blood Pressure Control



	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

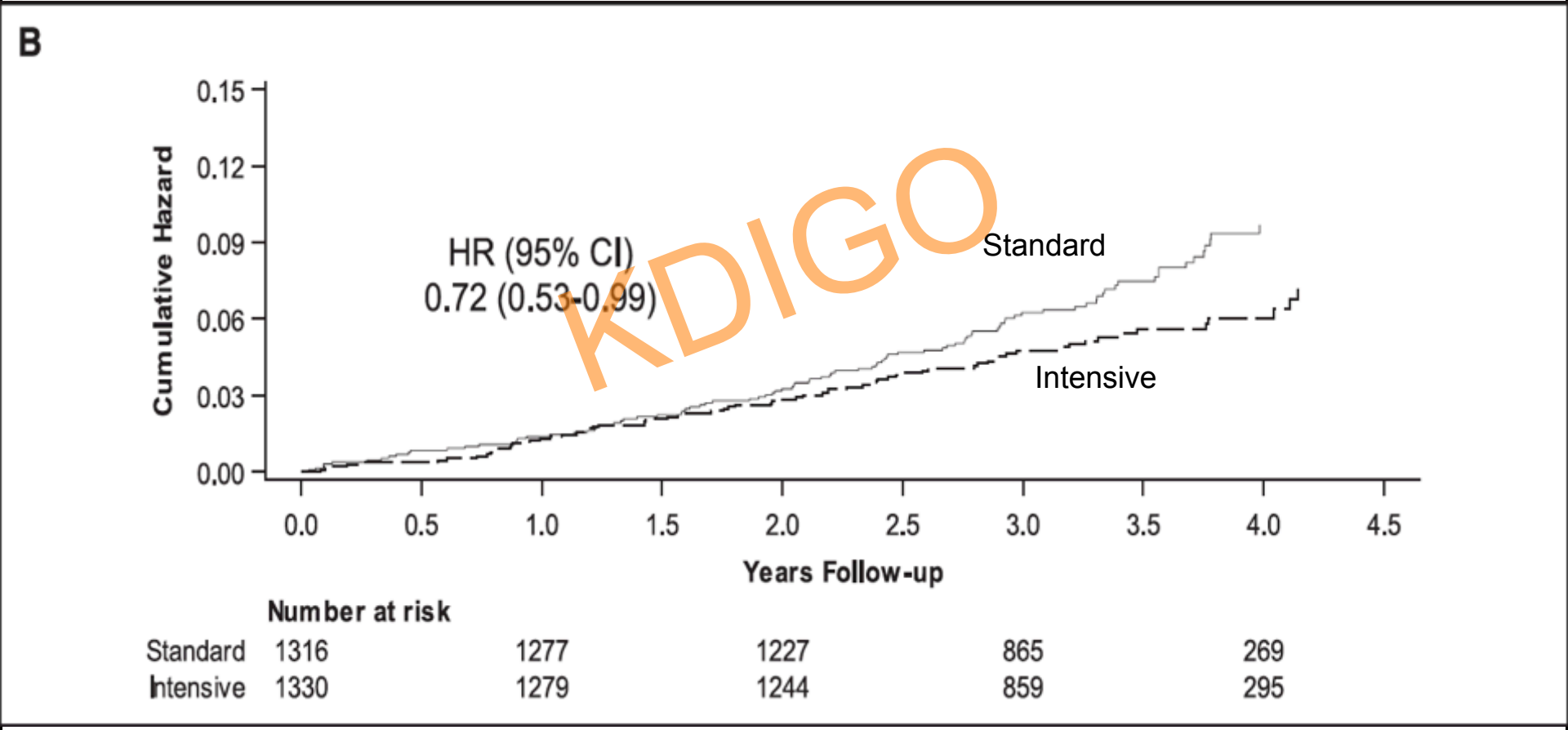
Cheung et al. *J Am Soc Nephrol* Jun 22 2017

Renal Outcome Decrease in eGFR > 50% or ESRD in SPRINT Participants with CKD at Baseline



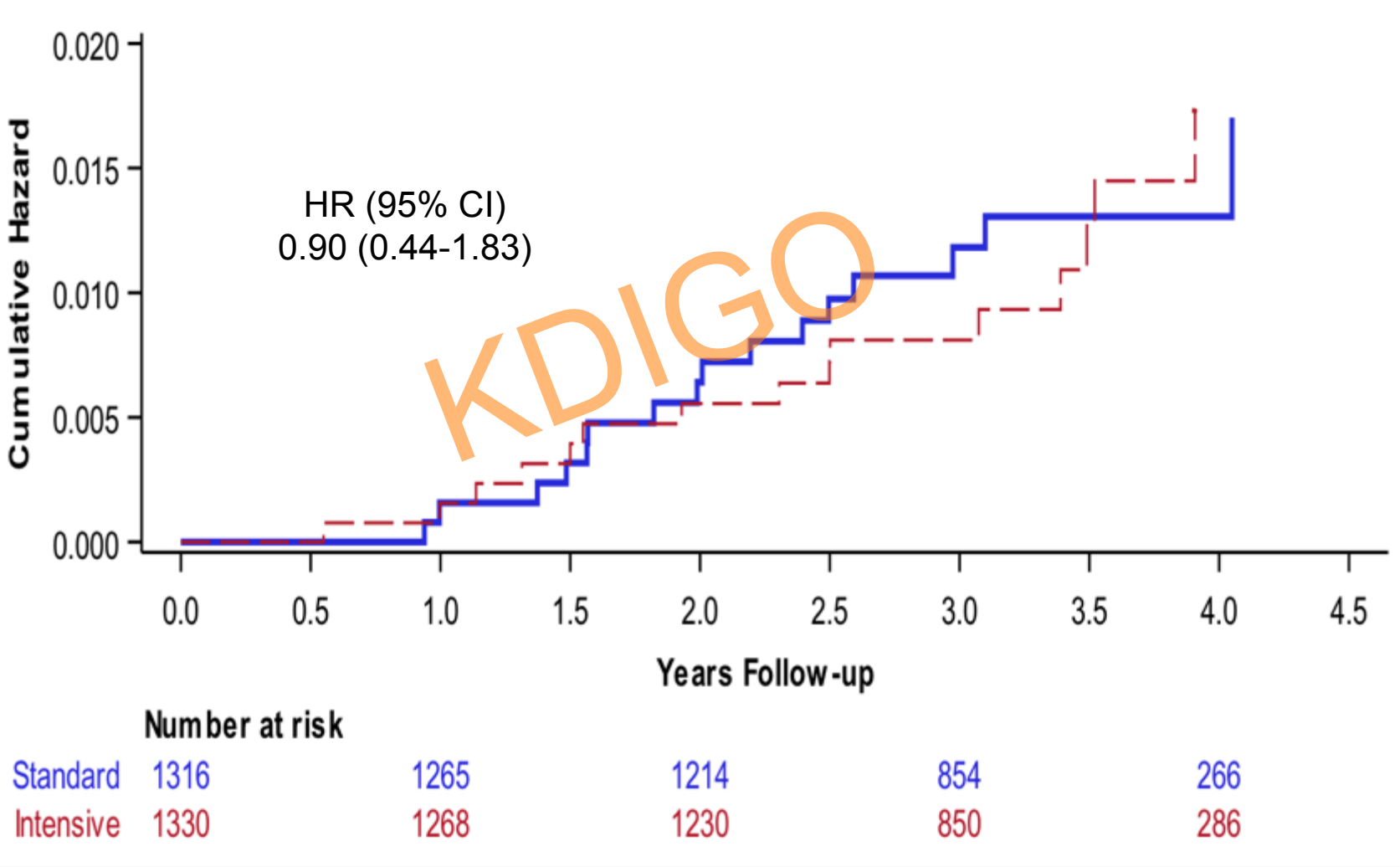
Cheung et al. *J Am Soc Nephrol* Jun 22 2017

All Cause Mortality in SPRINT Participants with CKD at Baseline



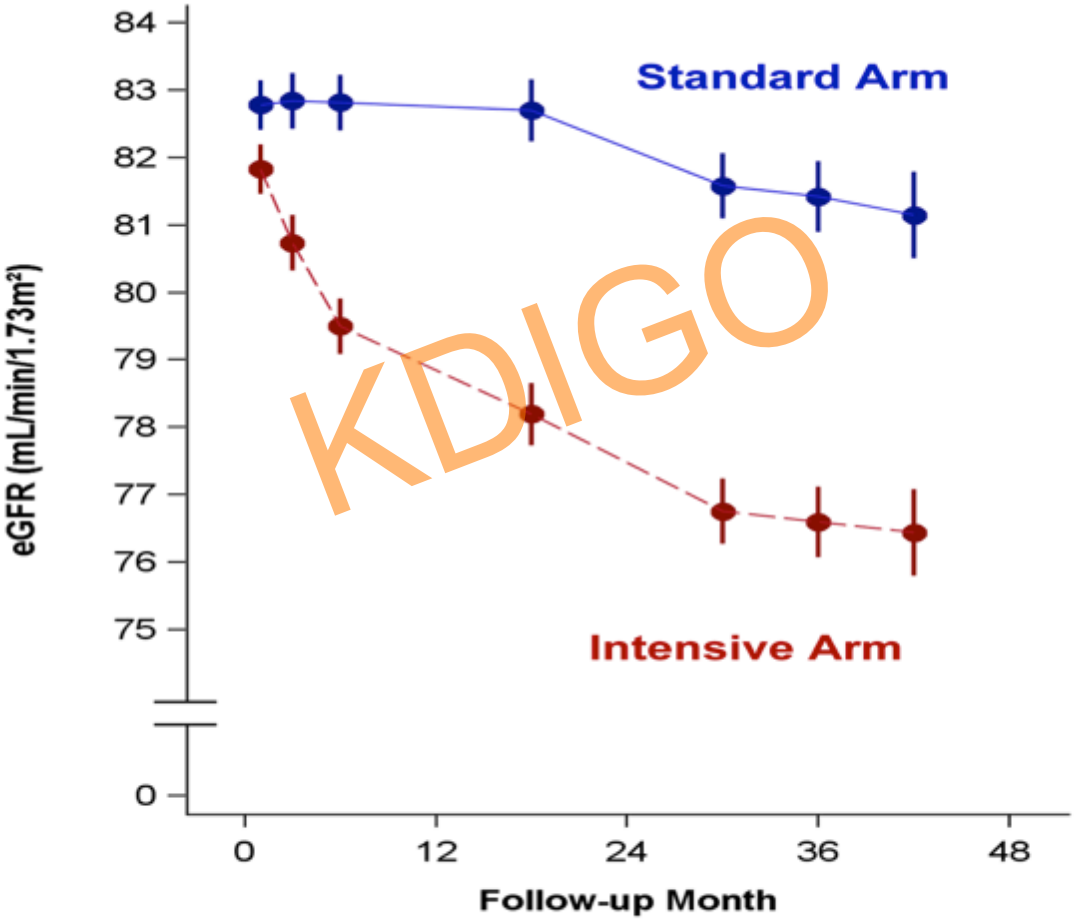
Cheung et al. *J Am Soc Nephrol* Jun 22 2017

Cardiovascular Outcome in SPRINT Participants with CKD at Baseline (eGFR < 60 ml/min/1.73 m^2)



Cheung et al. *J Am Soc Nephrol* Jun 22 2017

Change in eGFR in non-CKD (eGFR ≥ 60) in SPRINT Participants (N=6405)

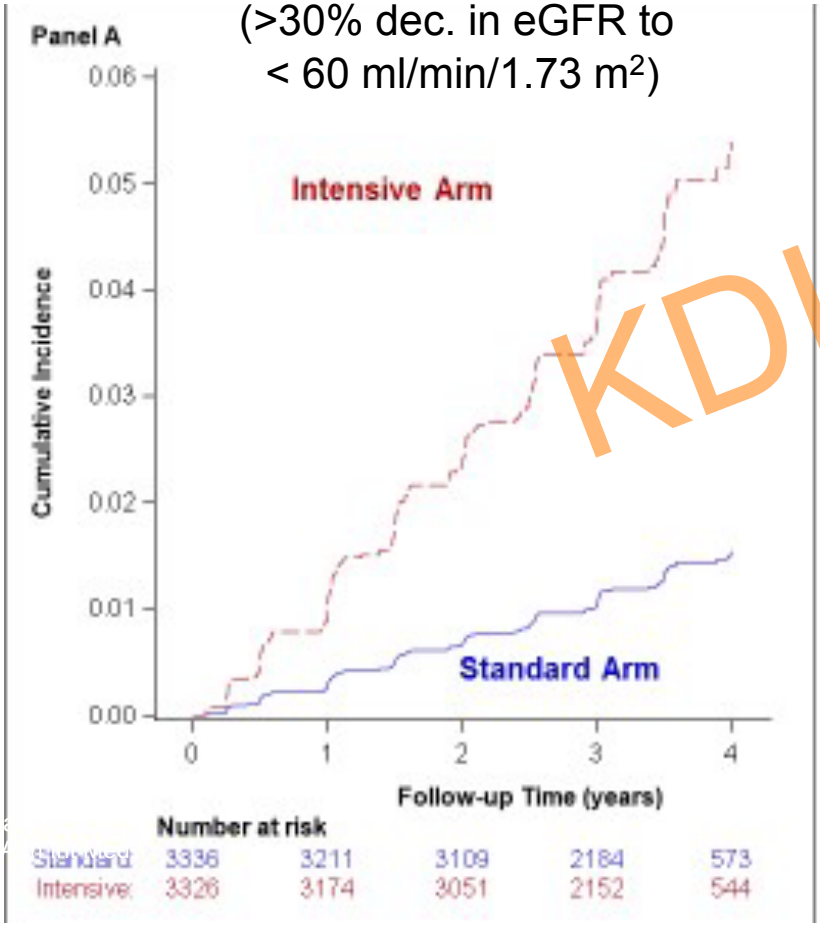


Beddhu et al. *Annals of Internal Medicine* Sept 2017

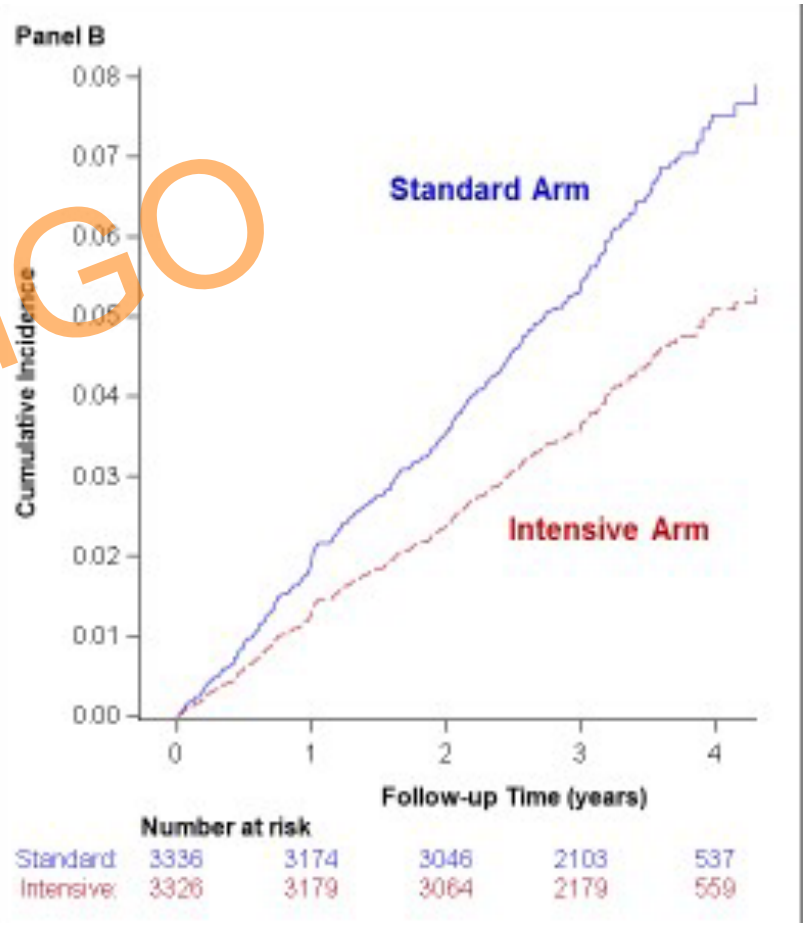
Outcomes in SPRINT Participants without Baseline CKD

Incident CKD

(>30% dec. in eGFR to < 60 ml/min/1.73 m^2)

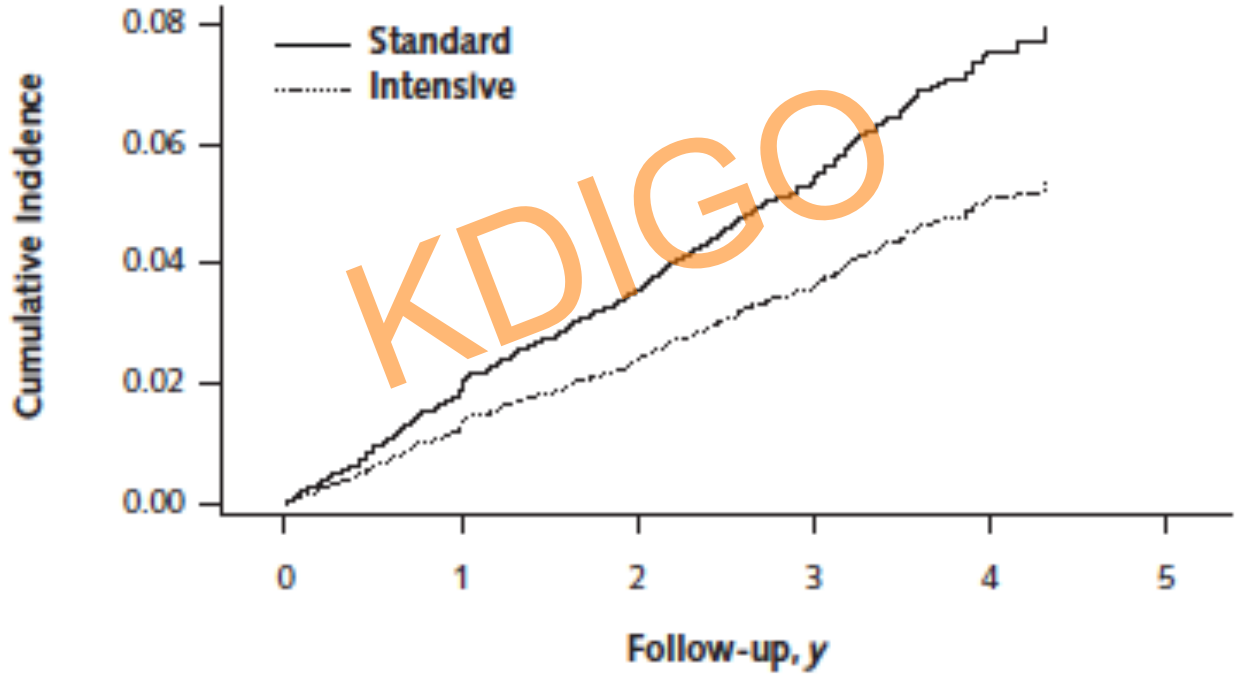


Incident CVD



Beddhu et al. *Annals of Internal Medicine* Sept 2017

All Cause Mortality in SPRINT Participants without Baseline CKD



Beddhu et al. *Annals of Internal Medicine* Sept 2017

Conclusions

AASK

- Strict BP control strategy may lead to a mortality benefit consistent with SPRINT.

SPRINT

- Targeting an SBP of120 compared with140 reduced rates of MACE and all-cause death without evidence of effect modifications by CKD or deleterious effect on the main kidney outcome.
- Intensive SBP lowering increased risk for incident CKD, but this was outweighed by cardiovascular and all cause mortality benefits

KDIGO

DIETARY INTERVENTIONS

Dietary Interventions in CKD: Systematic Review (17 studies, N=1639)

- 3 enrolled dialysis pt, 4 enrolled transplant recipients, and 10 enrolled CKD stages 1 to 5.
- Follow up median of 12 months (range 1 to 46.8).
- Conclusions:
  - uncertain effects on mortality, cardiovascular events and ESKD (rarely reported).
  - may increase HRQOL, eGFR, serum albumin, and reduce blood pressure and cholesterol levels.
  - large-scale pragmatic RCTs to test the effects of dietary interventions on patient outcomes are required.

MANAGING HYPERTENSION IN CKD

MY RECIPE

How I do get Blood Pressure to 120 - 130 / 70 - 80 mmHg?: Part 1

- Dietary sodium restriction
- Once Daily ACE Inhibitor or ARB
- Diuretic
  - eGFR $\geq$ 50 ml/min thiazide or chlorthalidone
  - eGFR < 50 ml/min loop diuretic, or chlorthalidone

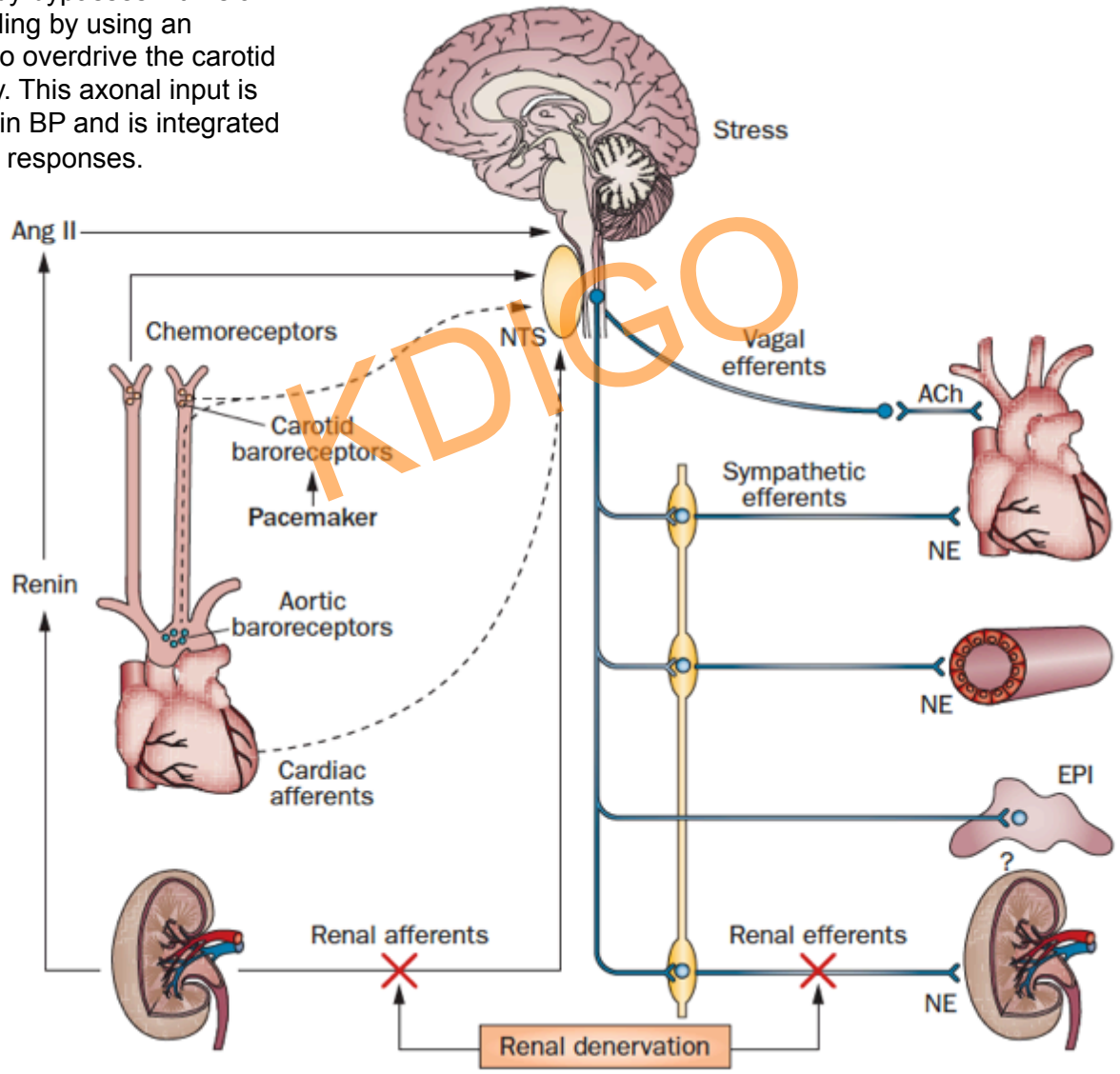
How I do get Blood Pressure to 120 - 130 / 70 - 80 mmHg?: Part 2

- α,β-blocker, e.g. carvedilol
- Long-Acting CCB, e.g. Amlodipine
- Spironolactone
- Minoxidil/ Clonidine

Baroreceptor Activation and Renal Denervation

Sympathetic Neural Mechanisms of Blood Pressure Regulation and Treatment Targets

Baroreflex activation therapy bypasses intrinsic mechanical-electrical coupling by using an extrinsic electrical current to overdrive the carotid baroreceptor axons directly. This axonal input is interpreted as an increase in BP and is integrated centrally to elicit baroreflex responses.



Resistant Hypertension

Sustained Reduction of Blood Pressure With Baroreceptor Activation Therapy

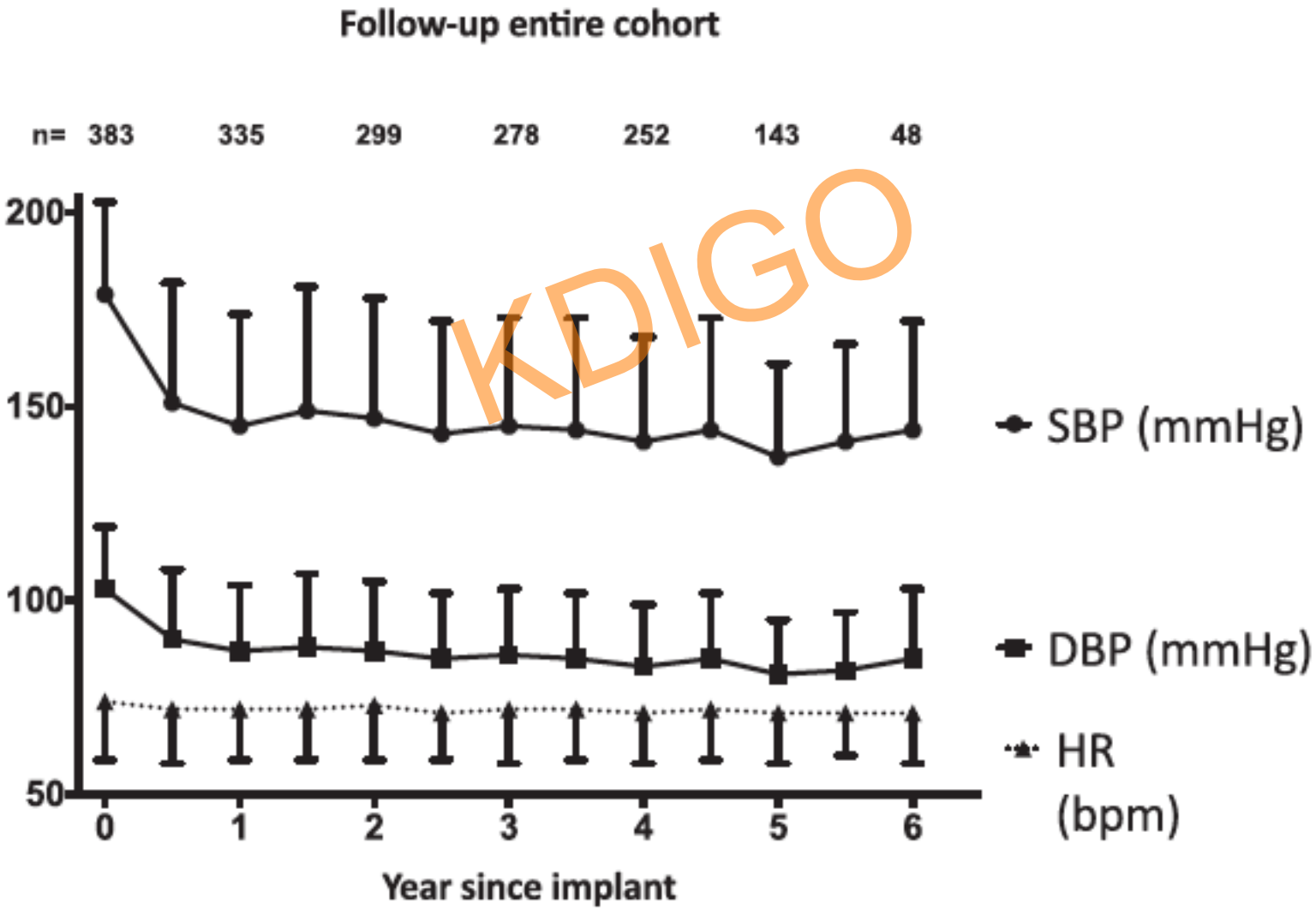
Results of the 6-Year Open Follow-Up

Peter W. de Leeuw, John D. Bisognano, George L. Bakris, Mitra K. Nadim, Hermann Haller, Abraham A. Kroon; on behalf of the DEBuT-HT and Rheos Trial Investigators

Long-term follow-up data were analyzed from all patients who had been included in 1 of the 3 trials that focused on treatment-resistant hypertensive patients

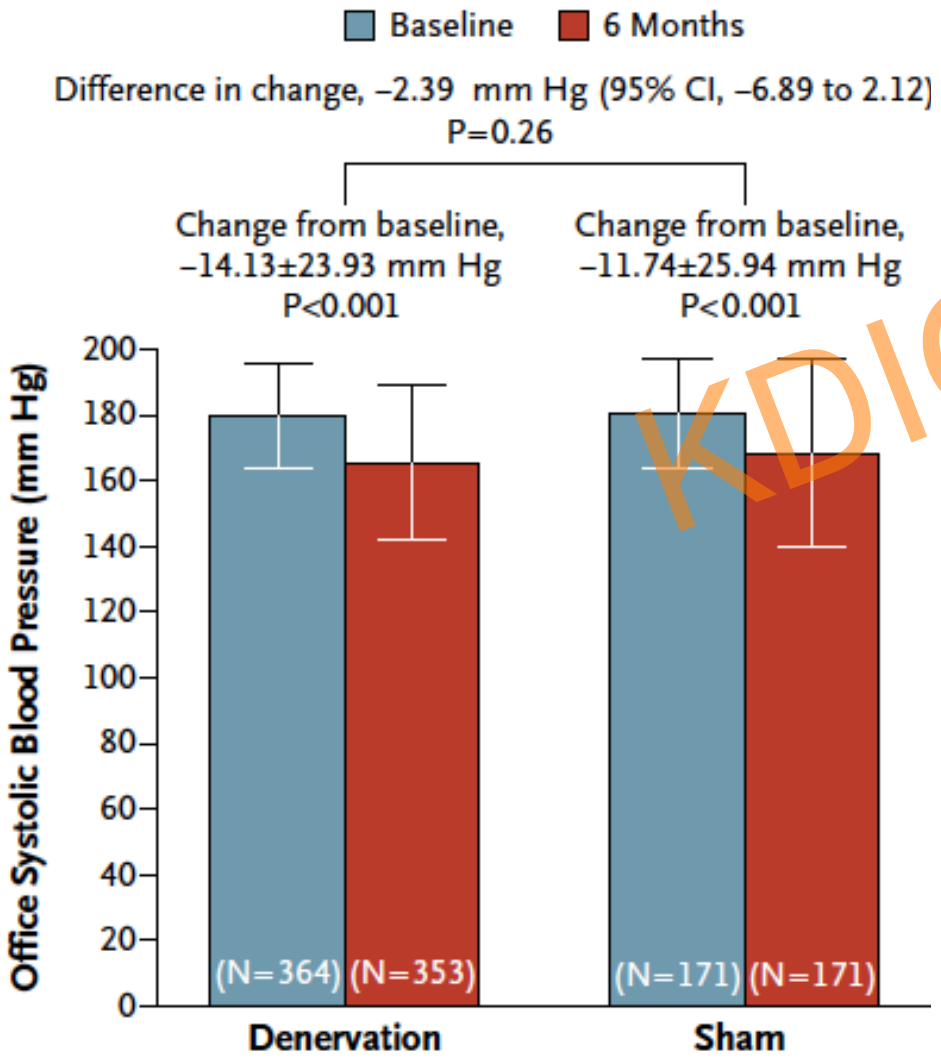
De Leeuw et al. Hypertension. 2017;69:836-843

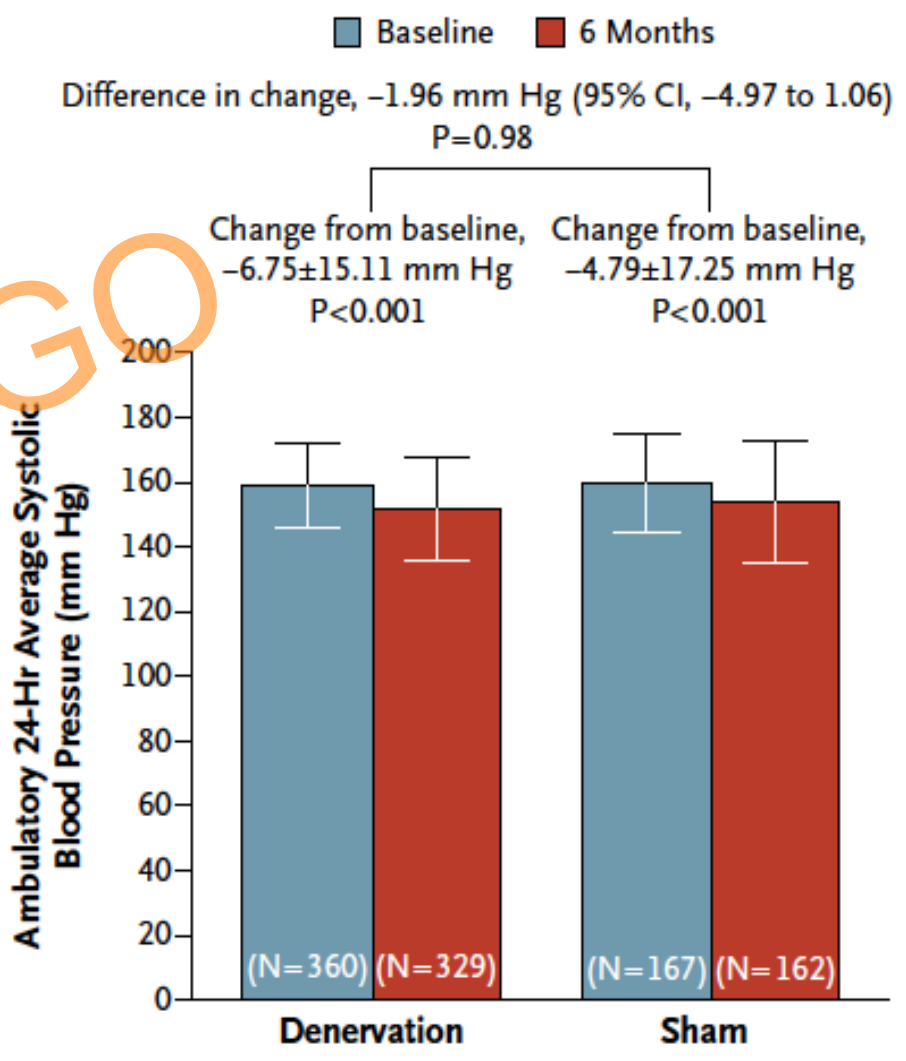
Time course of blood pressure and heart rate after implantation



De Leeuw et al. Hypertension. 2017;69:836-843

Renal denervation in Resistant Hypertension





Bhatt et al. *N Engl J Med* April 10, 2014

Effect of Renal Denervation in CKD

- 30 patients stage 2-4 CKD underwent Renal Denervation with ”standard procedure” by single operator
- Office BP at baseline 185/107 Hg
- 24-month follow-up 131/87 mm Hg
- Mean eGFR increased from 61.9 to
- 88.0 mL/min/1.73 m2 (P<.0001).
- UACR decreased from 99.8 mg/g to 11.0 mg/g
- CKD Stage decreased

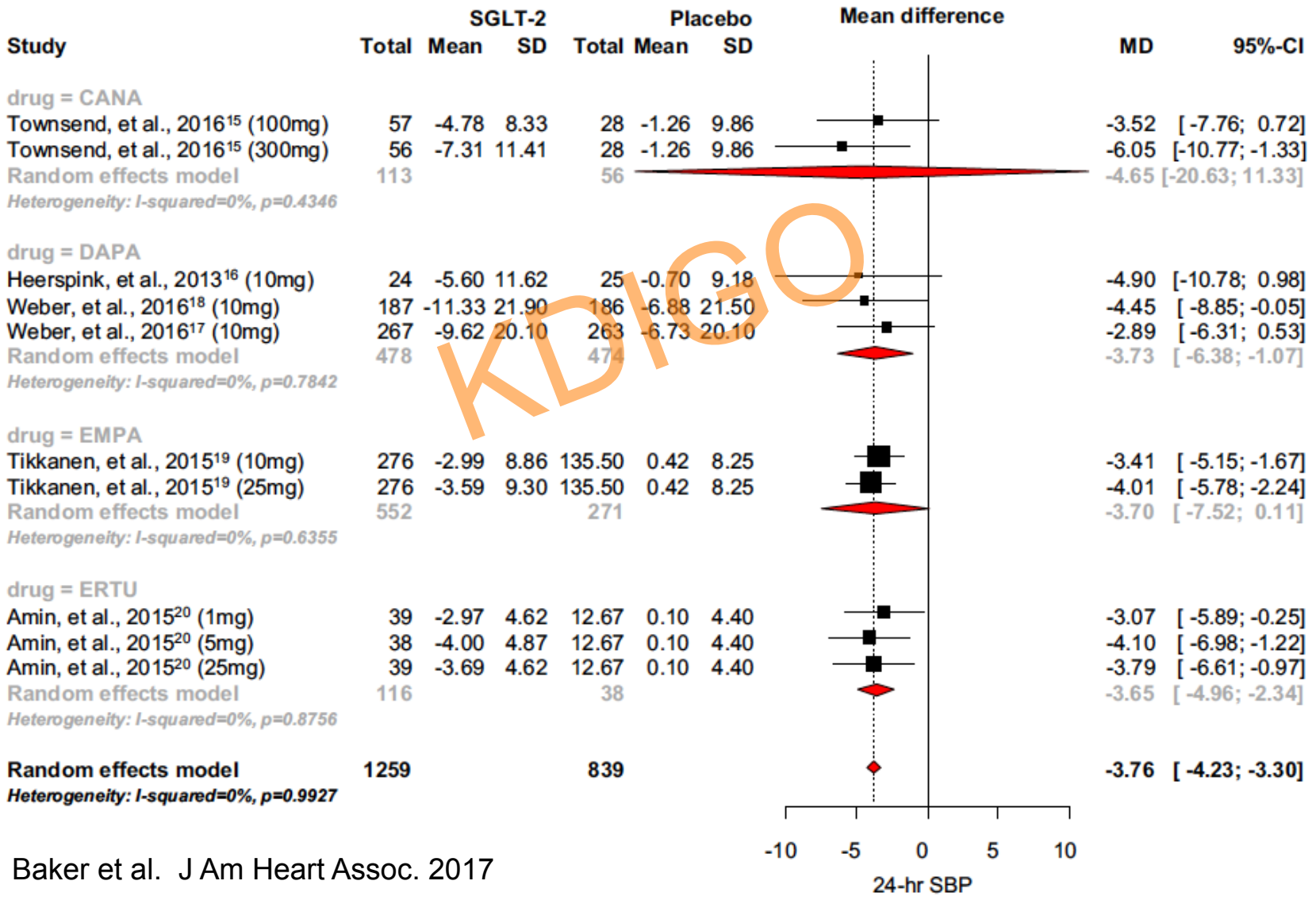
Galindo et al. The Journal of Clinical Hypertension Vol 18 | No 3 | March 2016

Conclusion

BAT and Renal Denervation hold promise for management of HTN in CKD. Long-term larger scale studies with CV and Renal Outcomes-Stay tuned

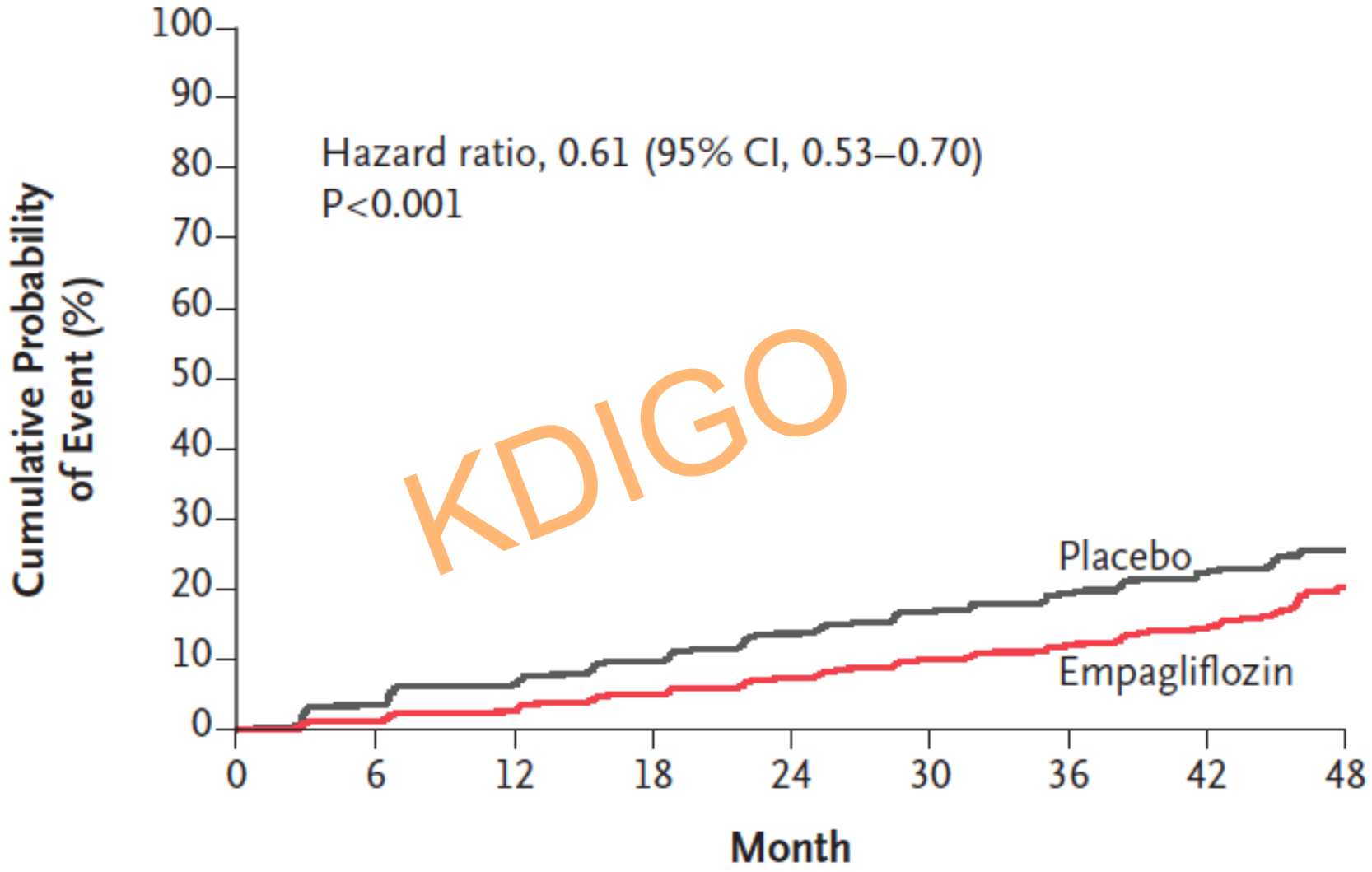
SGLT-2 INHIBITORS and Potassium Binders

Effect of SGLT2 inhibitors on daytime diastolic blood pressure.



Baker et al. J Am Heart Assoc. 2017

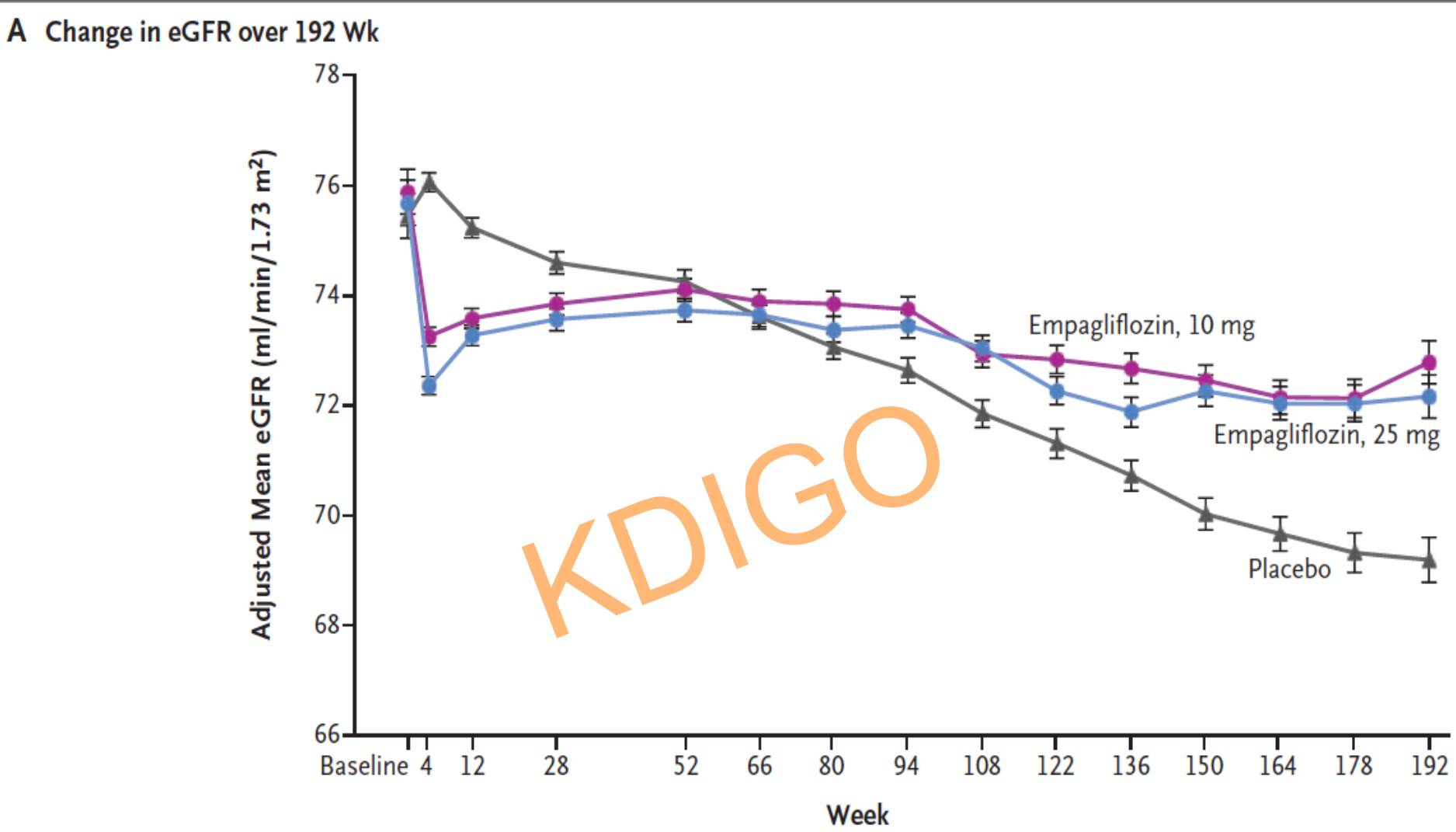
A Incident or Worsening Nephropathy



No. at Risk

Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

Wanner et al.N Engl. Med 375;4: 323-334, July 28, 2016

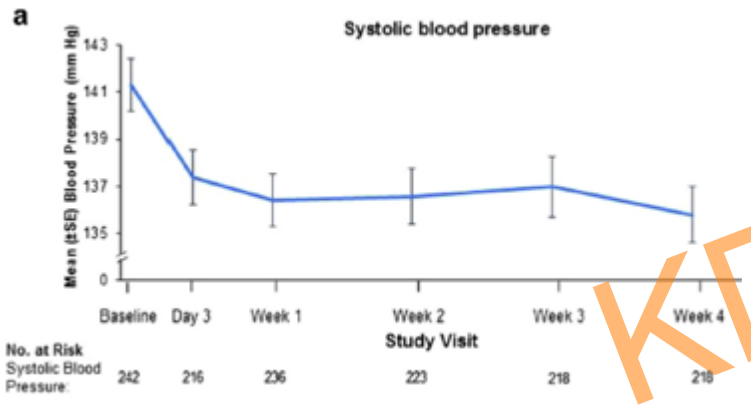


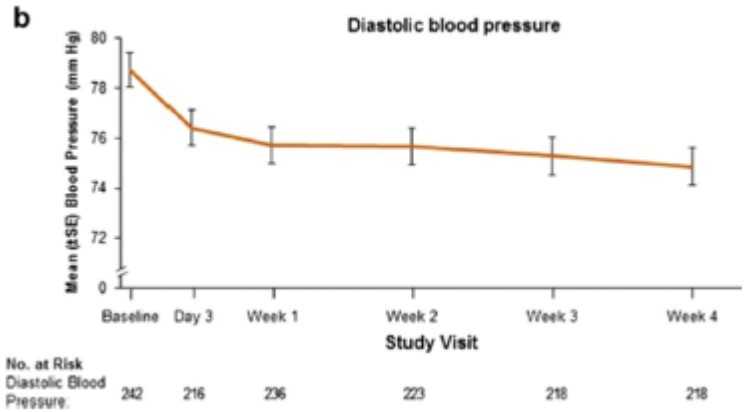
No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

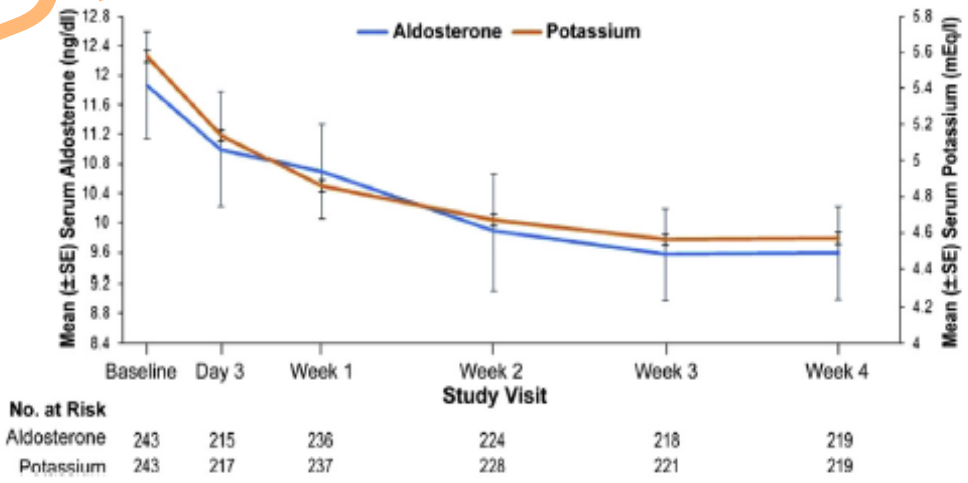
Wanner et al.N Engl. Med 375;4: 323-334, July 28, 2016

Patiromer, Aldosterone Potassium and Blood Pressure in CKD

Randomized Placebo Controlled Trial
Patiromer N =242 Type 2 DM and CKD On ACEi or ARB at baseline
Hyperkalemia







Weir et. al. *Kidney International* (2016) 90, 696–704

Take Home: Management of Hypertension in Chronic Kidney Disease

- RAAS blockade-based drug regimens
  - Vs placebo and other comparators improve renal outcomes
  - Systematic review: reduce mortality in DM
- Combined RAAS blockade based drug regimens compared to single RAAS blockade
  - do not improve renal or cardiovascular or all-cause mortality
- Tight vs Standard BP control does not increase CV morbidity or mortality (SPRINT)
- Dietary intervention and Devices not tested/proven to improve renal or CV outcomes or all cause mortality
- Role of SGLT-2 and K binding agents on renal and CV outcomes unknown-stay tuned