Changing the Landscape of CKD Progression

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Conflicts of Interest

- National Clinical Trial Principal Investigator Studies -
- Bayer, Relypsa (direct funding to University of Chicago)
- Consultant/Advisor -Takeda, AbbVie, CVRx, Janssen, Eli Lilly/Boeringher-Ingelheim, Medtronic, Novartis, GSK, Bayer
- Editor, Am J Nephrology ; Editor in Chief, Hypertension-UpToDate
- Special Government Employee-FDA and CMS

Biggest Causes of End Stage Kidney Disease in the World

- Diabetes
- Hypertension
- IgA Nephropathy
- Polycystic Kidney Disease

Global Burden of Hypertension* 2025 Projection

Year 2000

- 26.4% of world adult population had hypertension
- Total of 972 million adults
- Highest prevalence is in established market economies (eg, North America, Europe)

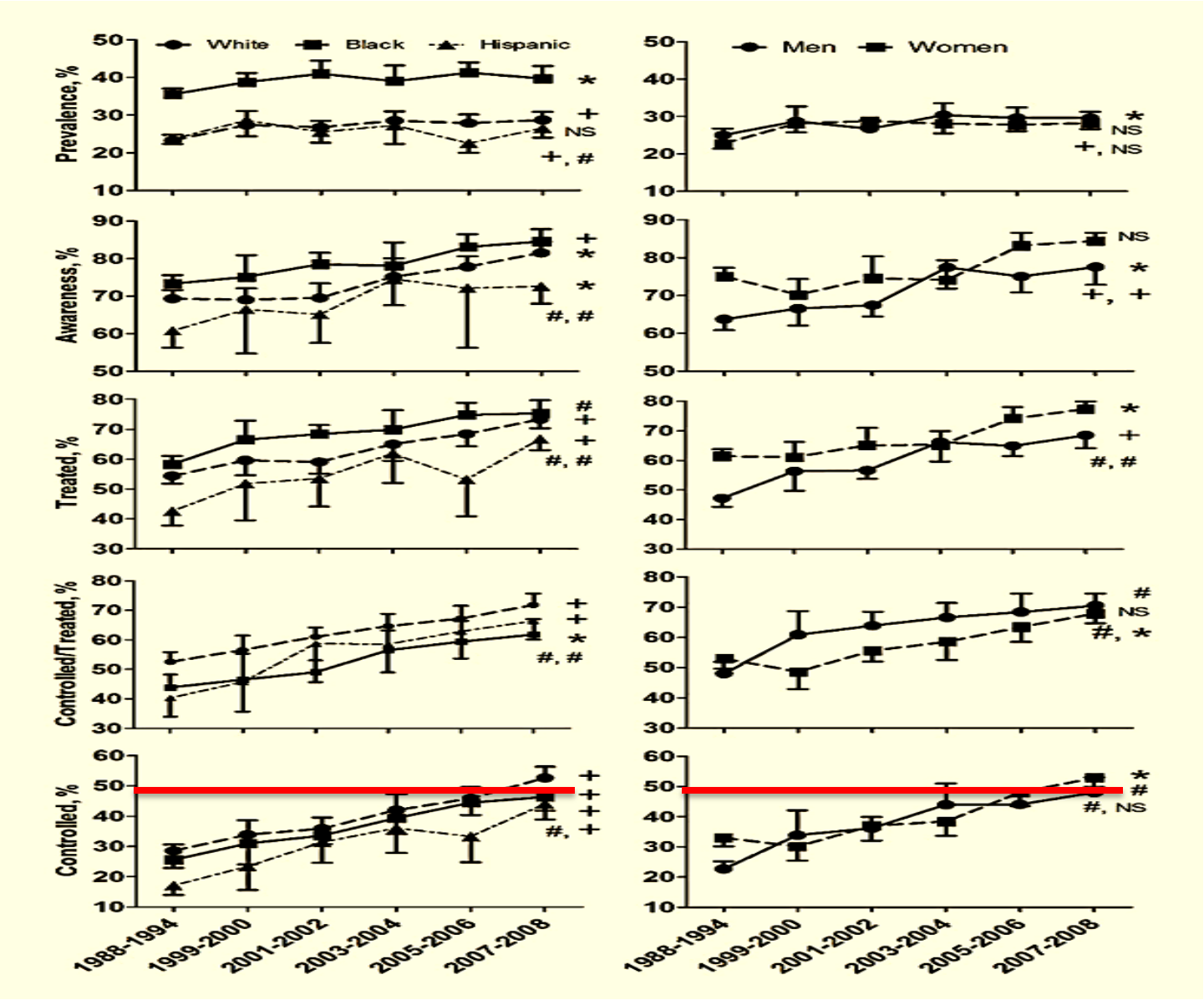
Year 2025

- 29.2% of world adult population will have hypertension
- Total of 1.56 billion adults (60% ↑ overall; 24% ↑ in developed nations, 80% ↑ in developing nations)
- Highest prevalence will be in economically developing continents (e.g., Asia, Africa) will account for 75% of world's hypertensive patients

**defined by a BP>140/90 mm Hg; >130/80 mm Hg in diabetes and renal impairment*

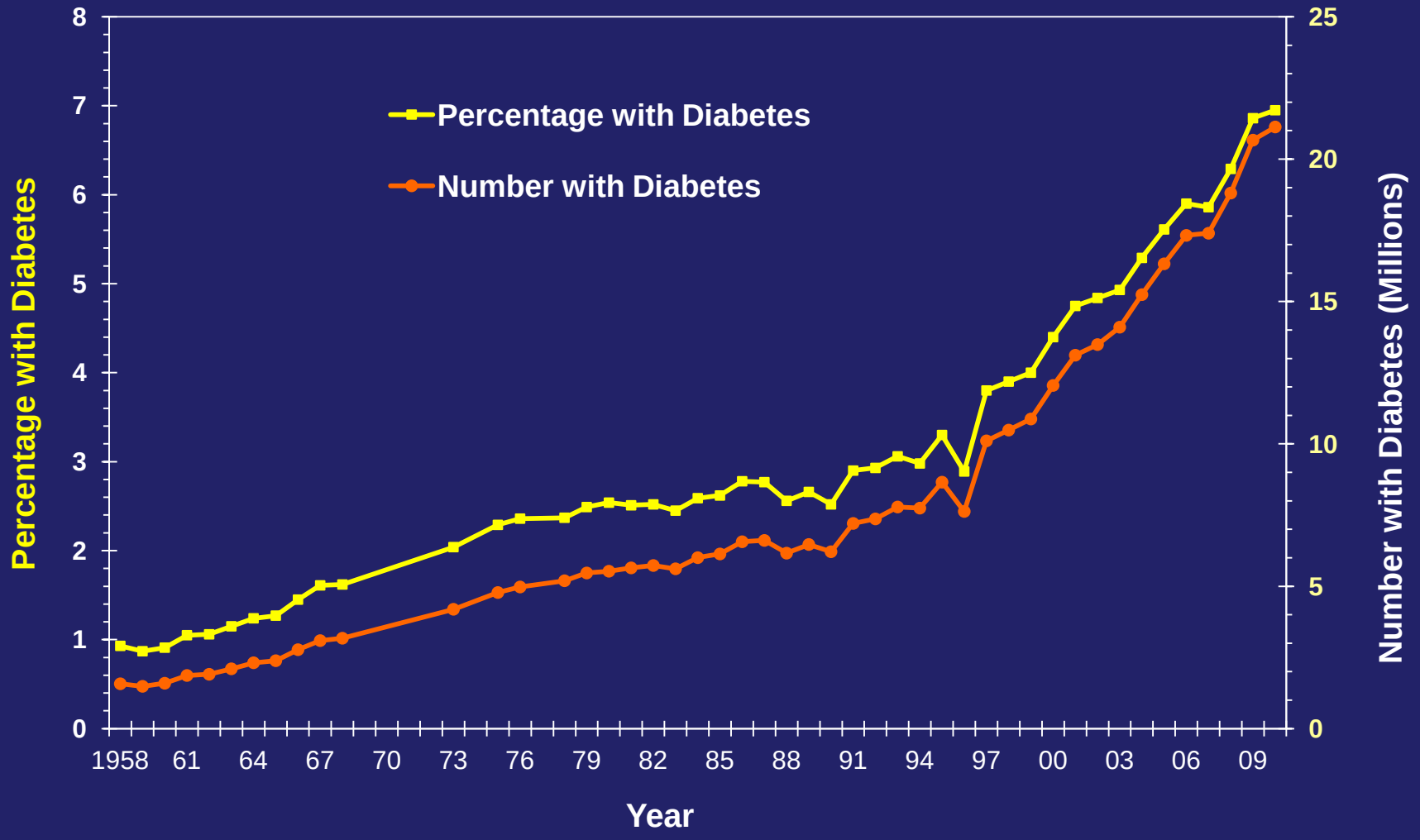
Kearney PM et al. Lancet. 2005;365:217-223.

Prevalence, Awareness, Treatment, for 1988–1994 & and Control 1999–2008



Egan B et.al. JAMA 2010;303:2043-2050

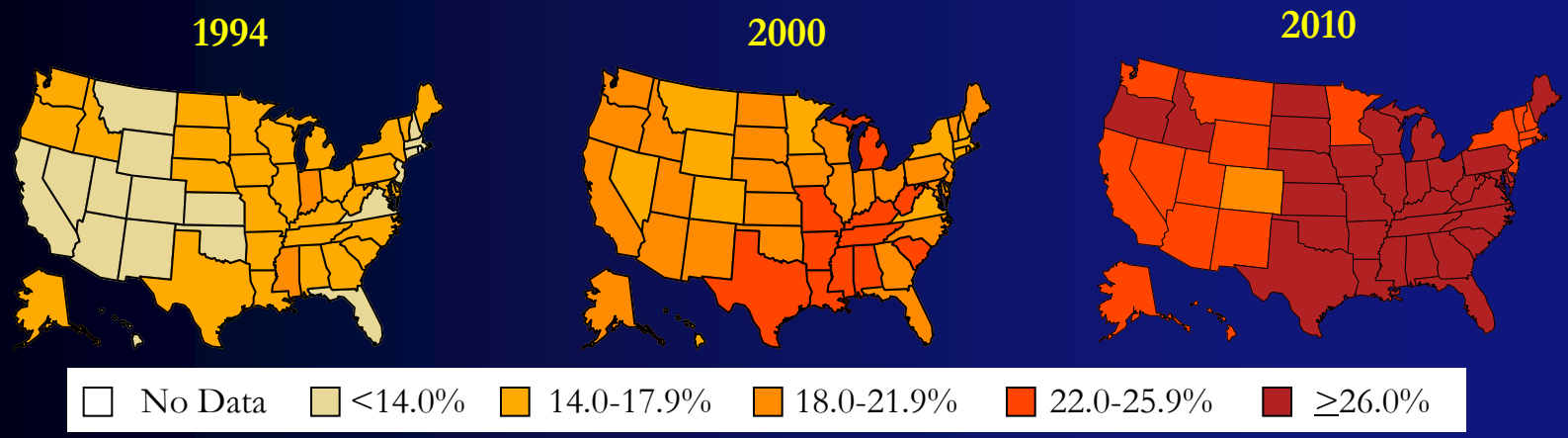
Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958–2010



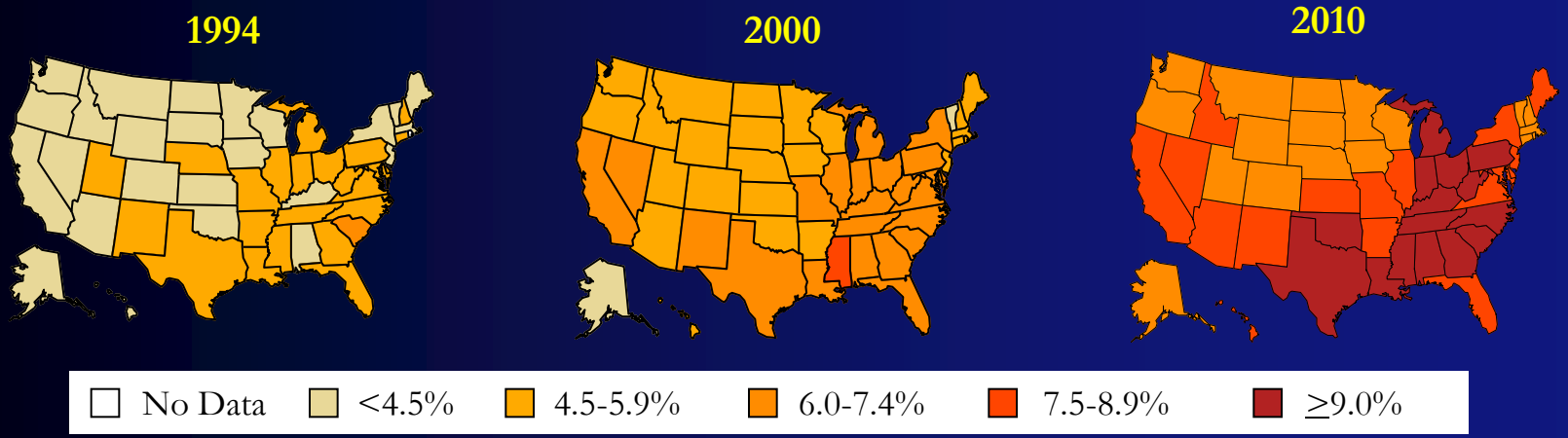
CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics- accessed 8/2014

Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults Aged 18 Years or older

Obesity (BMI ≥30 kg/m^2)

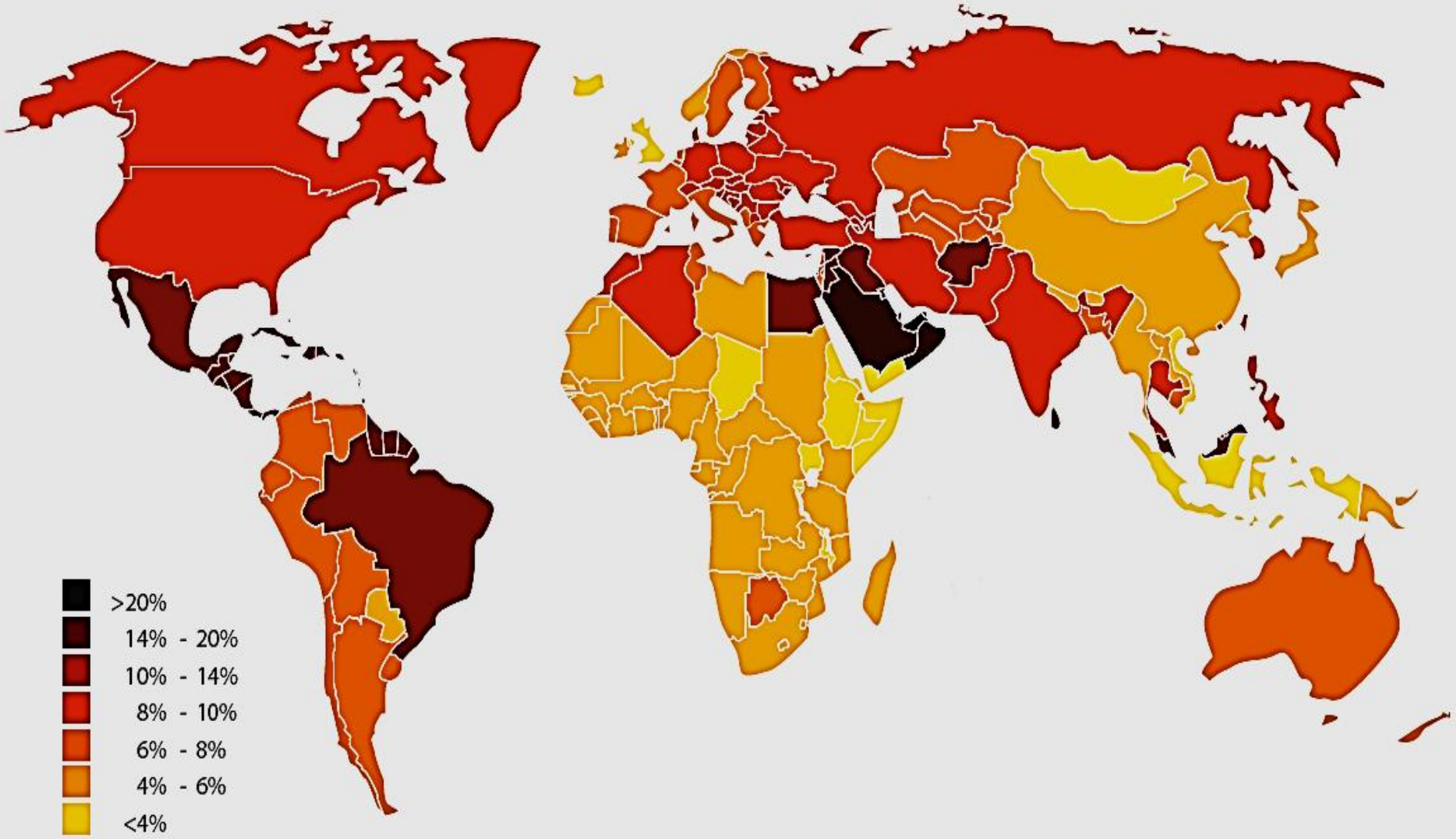


Diabetes



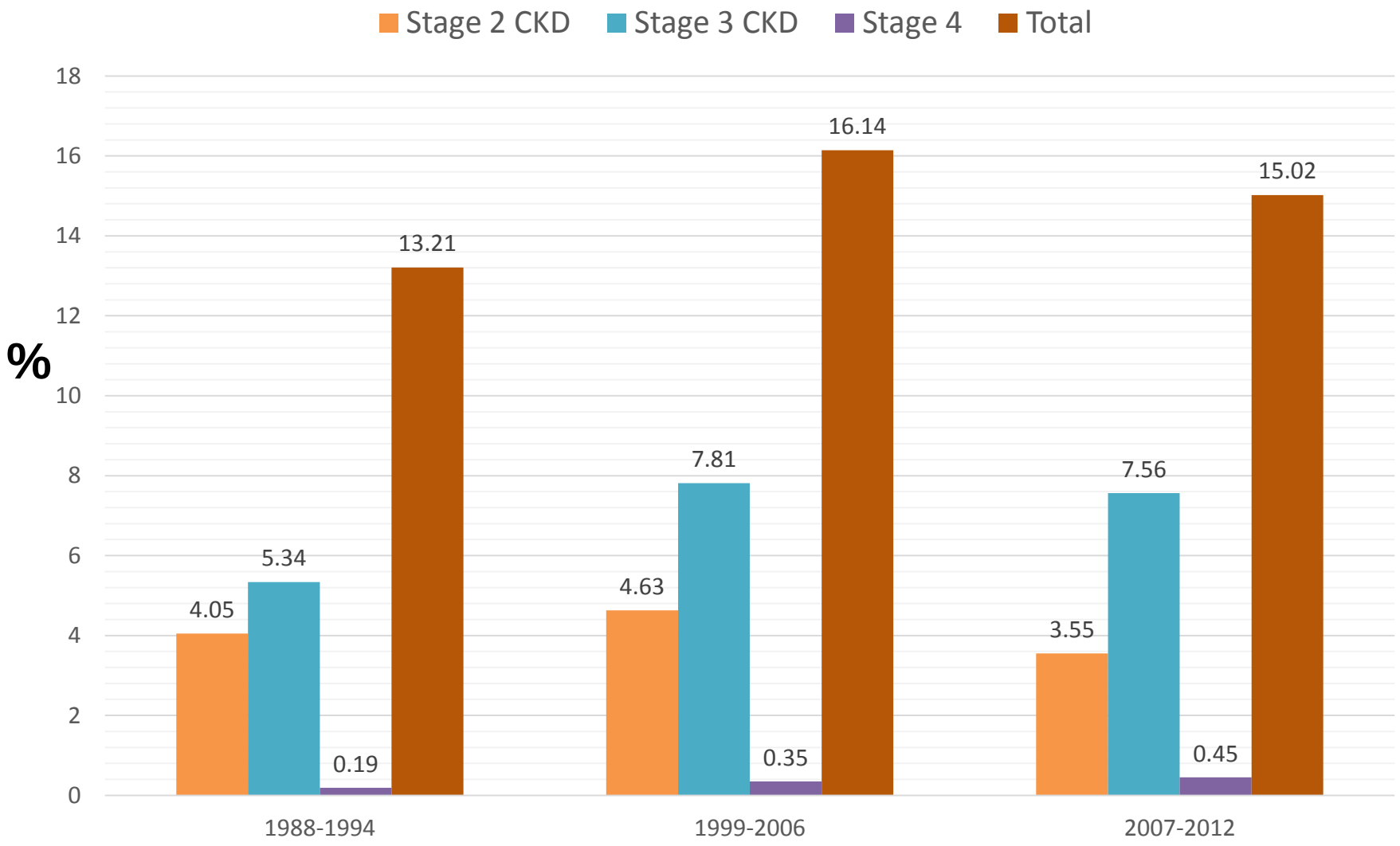
CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics accessed 8-2014

Prevalence estimates of diabetes, 2025



SOURCE: *DIABETES ATLAS THIRD EDITION*, © INTERNATIONAL DIABETES FEDERATION, 2006

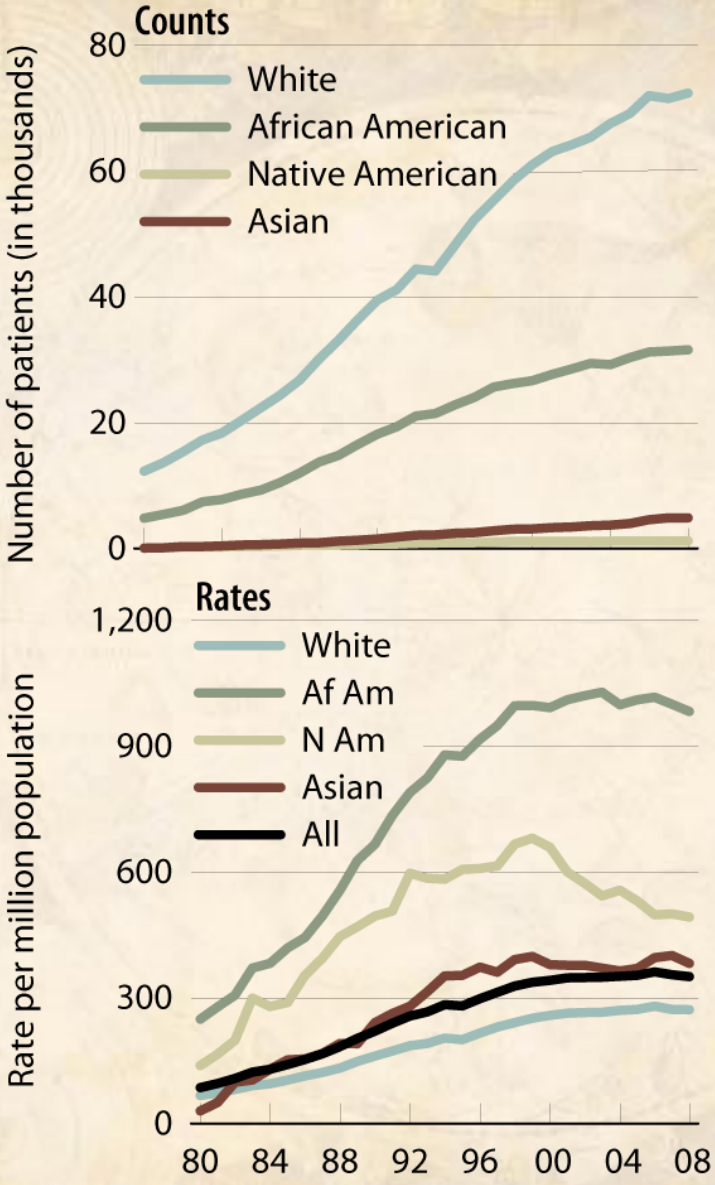
Prevalence of CKD Stages, 1988-1994 vs. 1999-2006 vs. 2007-2012 by Stage and Year



Centers for Disease Control and Prevention. Chronic Kidney Disease Surveillance System—United States. Web site. http://nccd.cdc.gov/CKD.

Incident counts & adjusted rates, by race

Figure 2.5 (Volume 2)



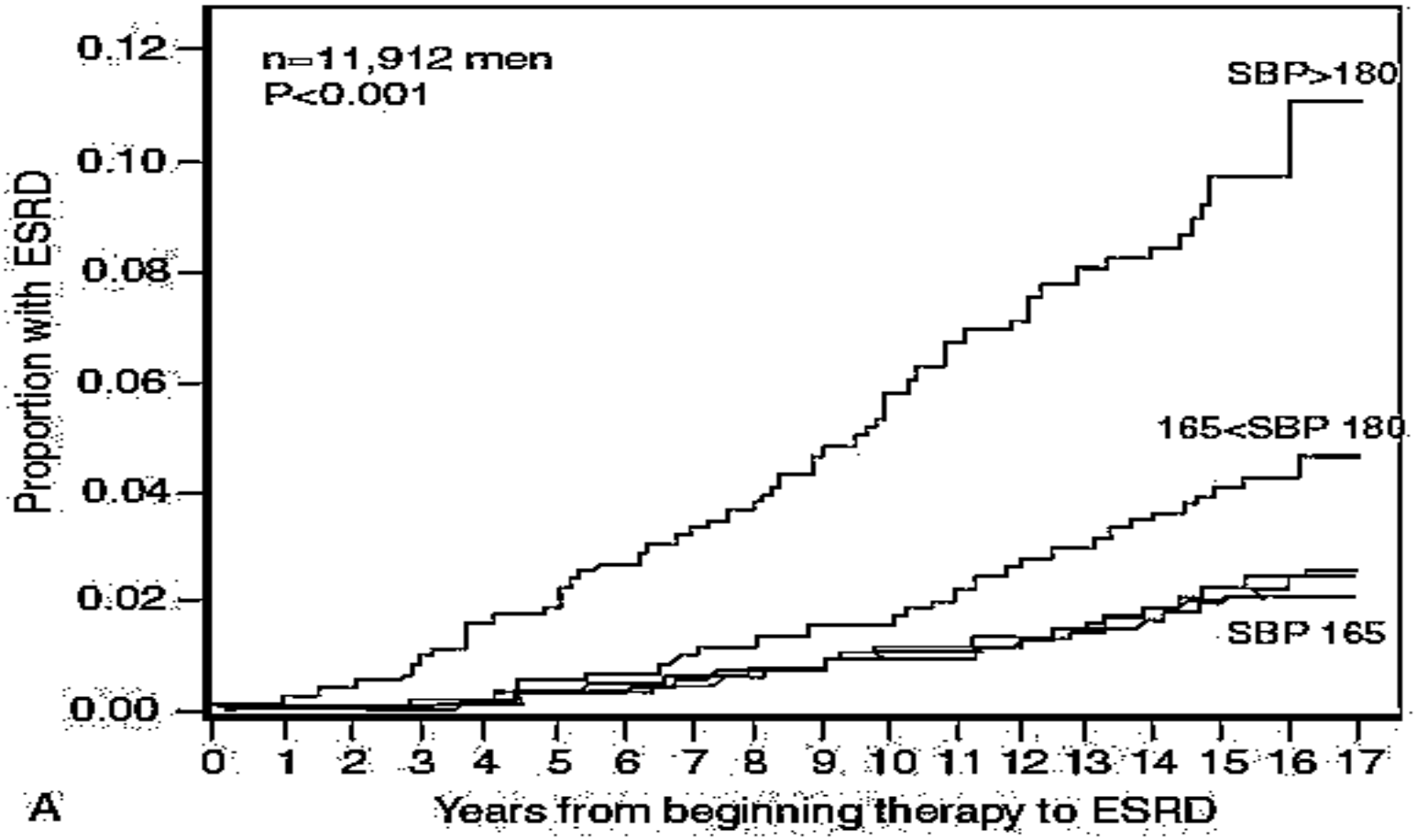
Incident ESRD patients; rates adjusted for age & gender.

USRDS 2010 ADR

USRDS

What Do We Know About Nephropathy Progression

17 Year Follow-Up from VA Hypertension Clinics on ESRD



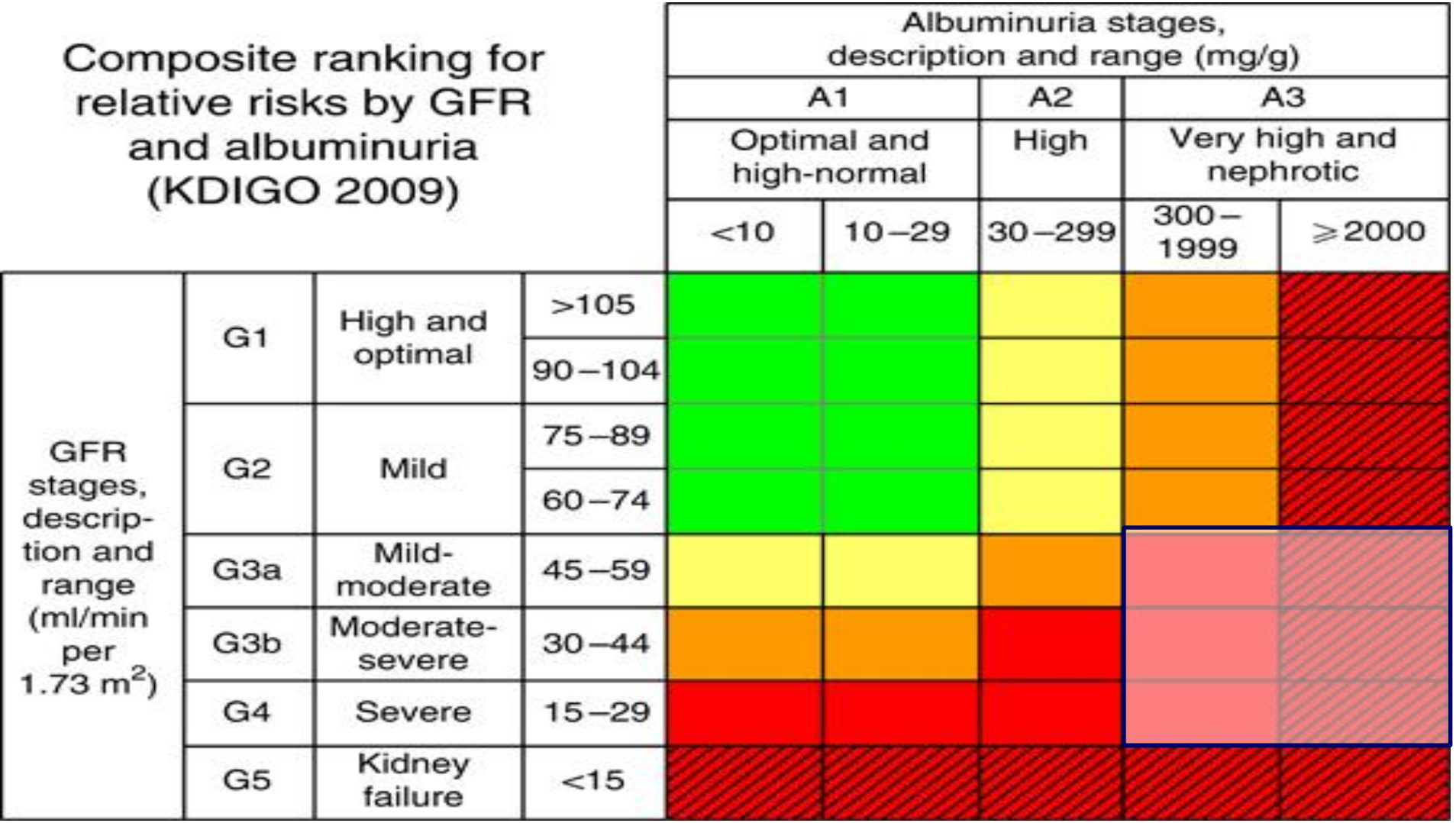
H. M. Perry, Jr., et.al Hypertension 25 (4 Pt 1):587-594, 1995.

Studies With Primary Renal Endpoints That Show Differences in Outcome: min=2.5 year F/U

Nondiabetic	Baseline GFR
• MDRD, N Engl J Med, 1993	40*
• AIPRI, N Engl J Med, 1996	52
• REIN, Lancet,1997	56*
• AASK, JAMA, 2002	46*
• Hou, NEJM, 2006	27
Diabetes	
• Captopril Trial, N Engl J Med, 1993	68
• Hannadouche et.al B Med J, 1994	51
• Bakris et.al Kidney Int., 1996	59
• Bakris et.al Hypertension, 1997	62
• IDNT, N Engl J Med, 2001	51
• RENAAL, N Engl J Med, 2001	49
• ALTITUDE, N Engl J Med, 2012	57
• VA NEPHRON D, N Engl J Med, 2013	54
• *ABCD, Diabetes Care (Suppl), 2000*	*87*

*** Signifies GFR measured using iothalamate or iohexol**

Composite Ranking for Relative Risks by glomerular filtration rate (GFR) and Albuminuria (Kidney Disease: Improving Global Outcomes (KDIGO) 2009



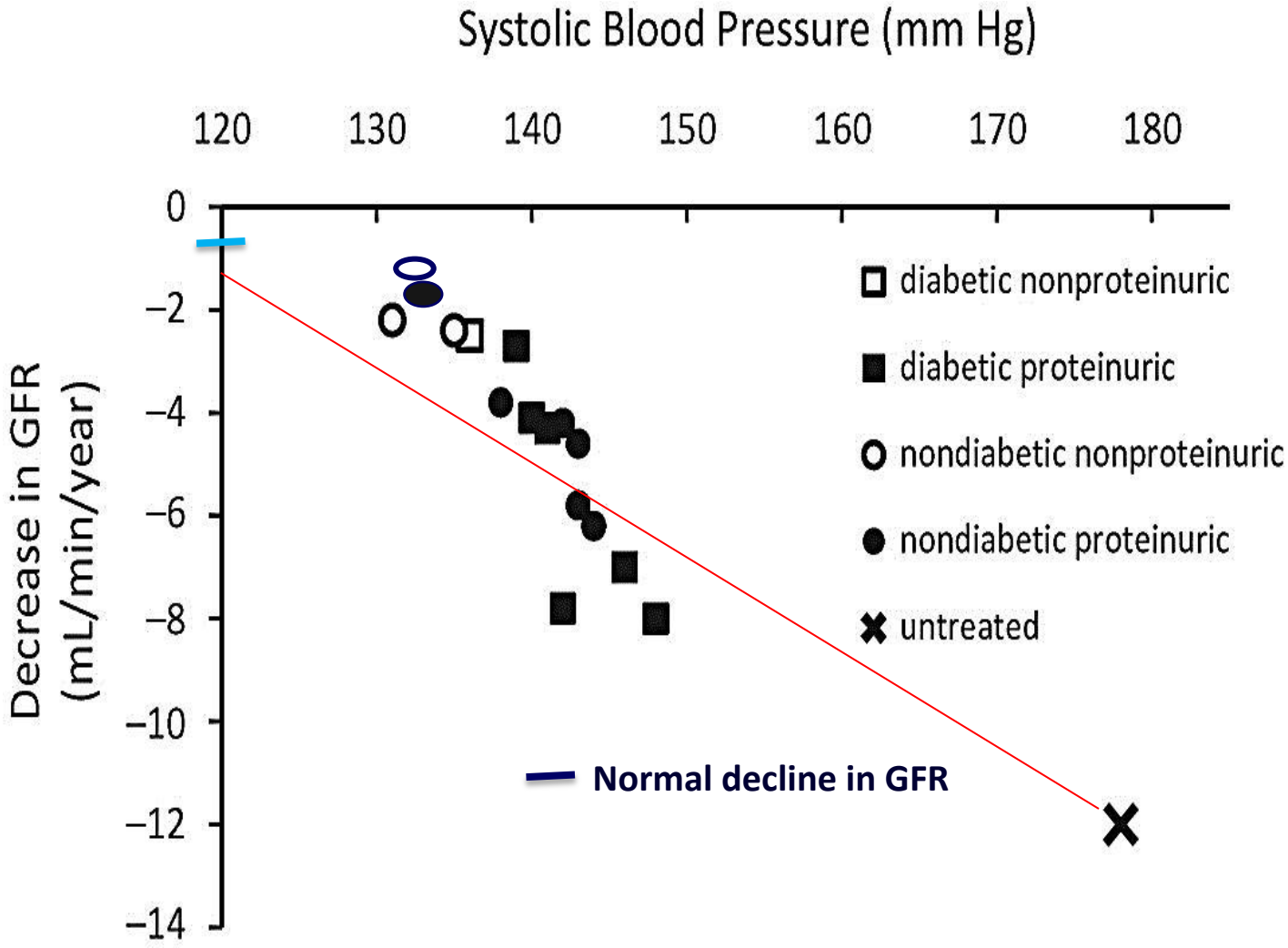
Levey AS et.al. Kidney Int 2010; doi: 10.1038/ki.2010.483

Relationship Between Achieved BP and Decline in Kidney Function from Primary Renal Endpoint Trials

Nondiabetes

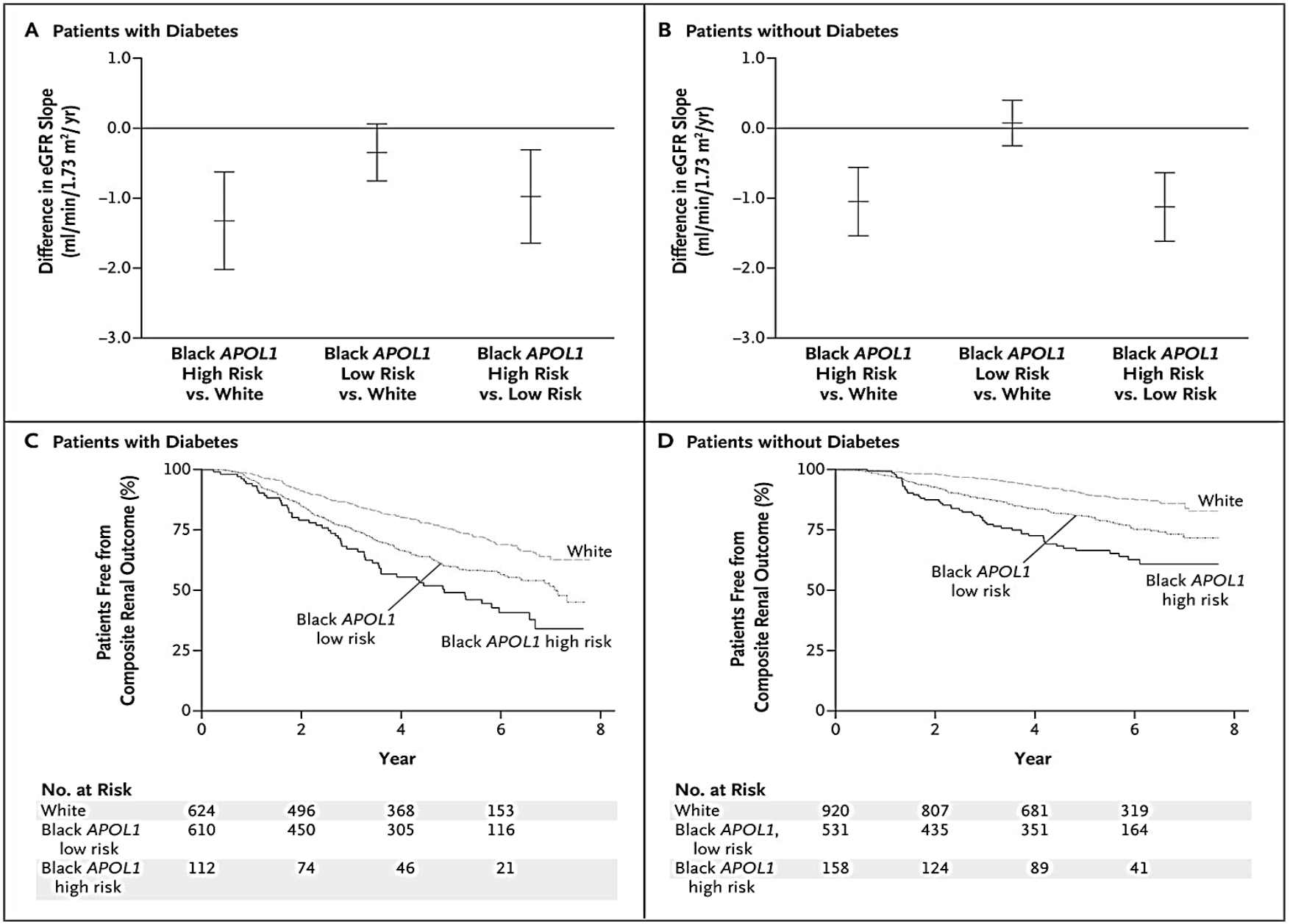
MDRD. *N Engl J Med.* 1993
AIPRI. *N Engl J Med.* 1996
REIN. *Lancet.* 1997
AASK. *JAMA.* 2002
Hou FF, et al. *N Engl J Med.* 2006
Parsa A et.al. NEJM 2013

Diabetes
Captopril Trial. *N Engl J Med.* 1993
Hannadouche T, et al. *BMJ.* 1994
Bakris G, et al. *Kidney Int.* 1996
Bakris G, et al. *Hypertension.* 1997
IDNT. *NEJM*. 2001
RENAAL. *NEJM.* 2001
ABCD. *Diabetes Care (Suppl).* 2000

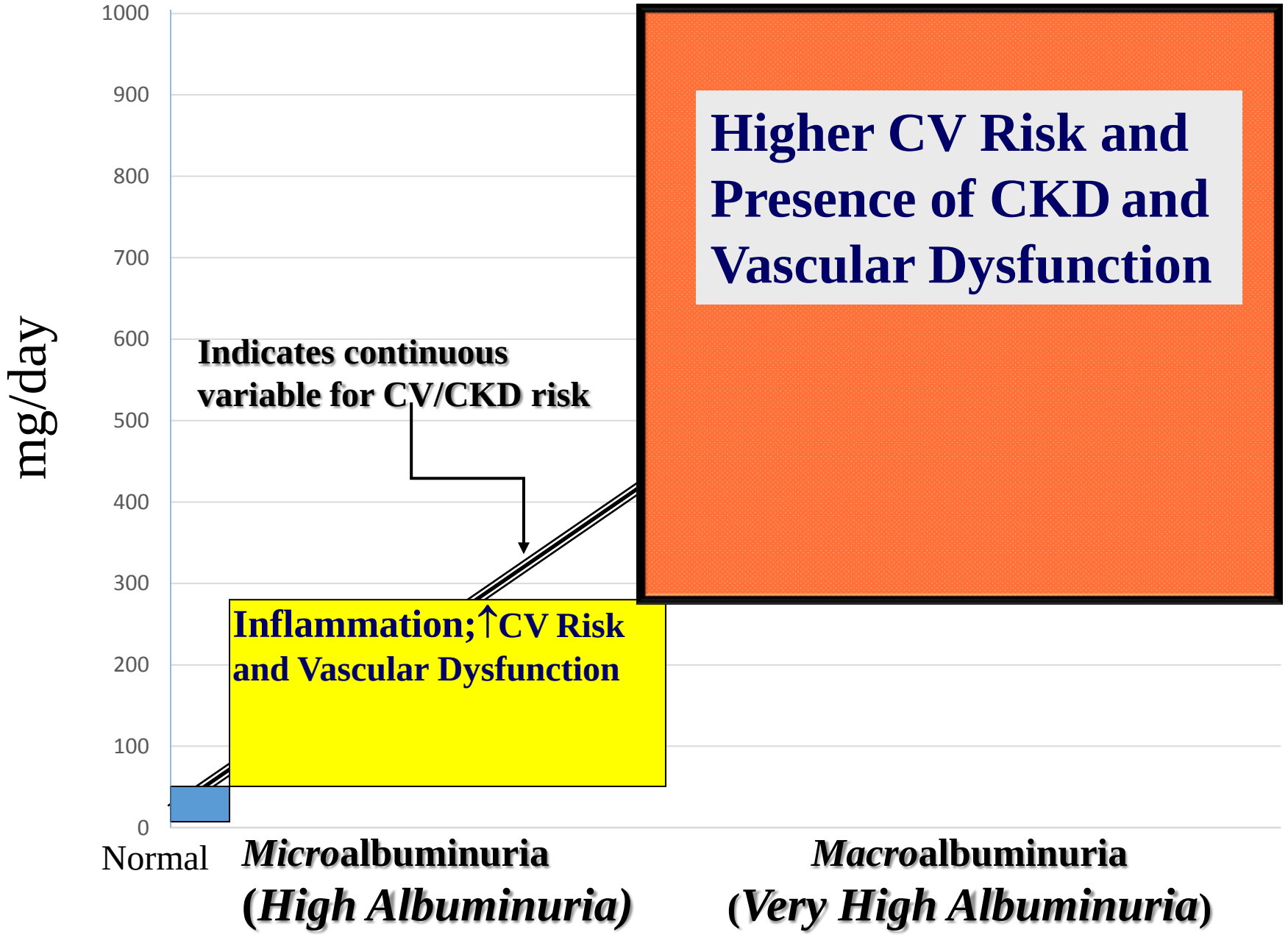


Update from Kalaitzidis R and Bakris GL In: ***Handbook of Chronic Kidney Disease*** *Daugirdas J (Ed.) 2011*

Between-Group Comparisons of the eGFR Slope and Proportion of Patients Free from a Primary Outcome Event in the CRIC Study



Parsa A et al. N Engl J Med 2013;369:2183-2196.


mg/day
1000
900
800
700
600
500
400
300
200
100
0
Higher CV Risk and Presence of CKD and Vascular Dysfunction
Indicates continuous variable for CV/CKD risk
Inflammation;↑CV Risk and Vascular Dysfunction
Normal
Microalbuminuria (High Albuminuria)
Macroalbuminuria (Very High Albuminuria)

Clinical Trials and Renal Outcomes Based on Proteinuria Reduction (Retrospective Analysis)

Increased Time to Dialysis

- (30-35% proteinuria reduction)
- Captopril NEJM, 1993
- AASK Trial-JAMA, 2001
- RENAAL- NEJM, 2001
- IDNT- NEJM, 2001

No Change in Time to Dialysis

- (NO proteinuria reduction)
- DHPCCB arm-IDNT
- DHPCCB arm-AASK

Hart P & Bakris GL Managing Hypertension in the Diabetic Patient.
IN: Egan BM, Basile JN, and Lackland DT (eds.) ***Hot Topics in Hypertension***
Hanley and Belfus, Philadelphia, 2004, pp.249-252.

Prospective Trials Demonstrating Further Significant Reductions in Proteinuria Translating into Worse Renal Outcomes

- VA NEPHRON-D
- ALTITUDE

What is the Goal BP and Initial Therapy in Kidney Disease or Diabetes to Reduce CV Risk?

Group	Goal BP (mmHg)	Initial Therapy
ADA (2015)	<140/90	ACE Inhibitor/ARB*
KDIGO/KDOQI (NKF) (2012)	<140/90	ACE Inhibitor/ARB
2014 Expert Panel	<140/90	ACE Inhibitor/ARB*
KDOQI (NKF) (2004)	<130/80	ACE Inhibitor/ARB*
JNC 7 (2003)	<130/80	ACE Inhibitor/ARB*
Am. Diabetes Assoc (2003)	<130/80	ACE Inhibitor/ARB*
Canadian HTN Soc. (2002)	<130/80	ACE Inhibitor/ARB*
Am. Diabetes Assoc (2002)	<130/80	ACE Inhibitor/ARB*
Natl. Kidney Foundation (2000)	<130/80	ACE Inhibitor*
British HTN Soc. (1999)	<140/80	ACE Inhibitor
WHO/ISH (1999)	<130/85	ACE Inhibitor
JNC VI (1997)	<130/85	ACE Inhibitor

Three Randomized Trials of BP Control on CKD Progression In Non-Diabetic CKD

- MDRD (Modification of Dietary Protein in Renal Disease)
- REIN-2 (Ramipril Efficacy in Nephropathy)
- AASK (African American Study of Kidney Disease)
- None support BP <130/80 mmHg

Does Hyperkalemia Limit the Use of RAAS Inhibitor Therapy?

Hyperkalemia Rates in IDNT and RENAAL

IDNT

Hyperkalemia: In IDNT (proteinuria ≥900 mg/day, and serum creatinine ranging from 1.0-3.0 mg/dL), the percent of patients with hyperkalemia (>6 mEq/L) was 18.6% in the irbesartan group versus 6.0% in the placebo group.

RENAAL

Results at month 6, 22.8% patients in the losartan group and 5.1% patients in the placebo group had serum potassium ≥5.5 mmol/l, ($p<0.001$).

Lewis, E. J.,et al. (2001). N.Engl.J Med **345(12): 851-860.;** Miao, Y. et al. (2011). Diabetologia **54(1): 44-50.**

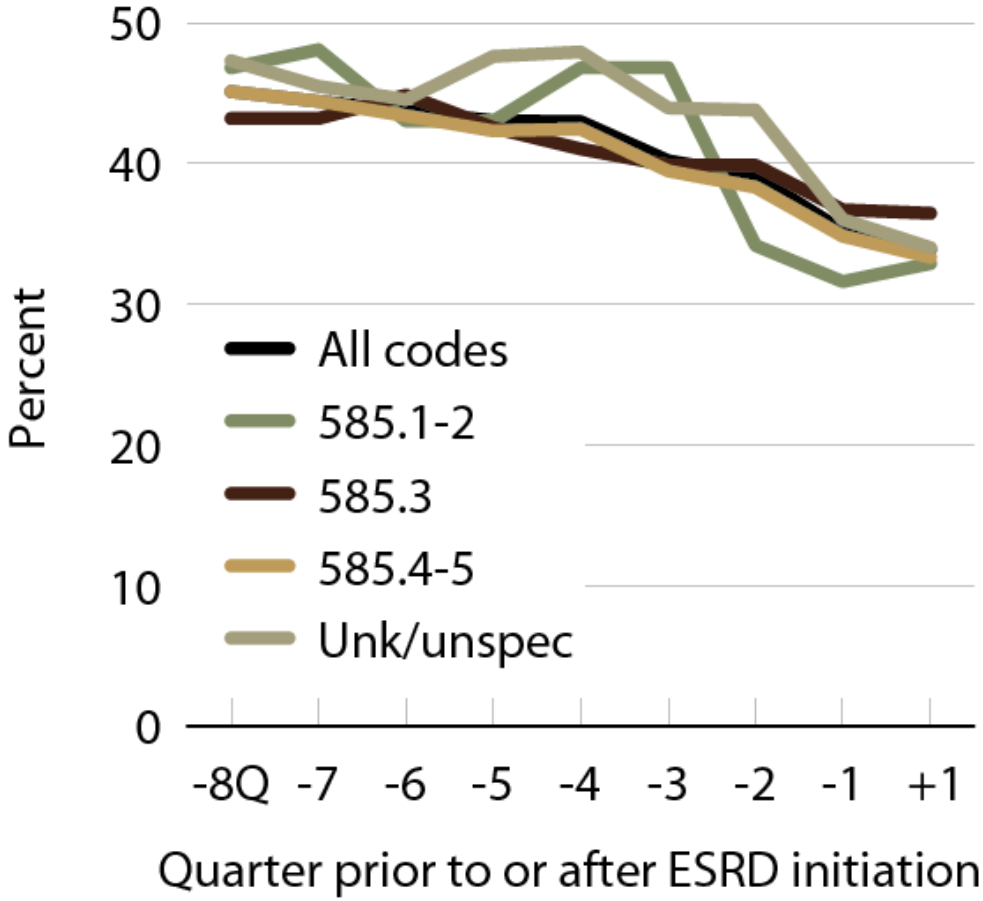
Lower Doses of ACEi/ARB Are NOT Effective in Slowing CKD Progression

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.)

RAASi Use Falls From 43%–47% 8 Quarters Before ESRD to 33%–37% in the Quarter Following Initiation of ESRD

ACEi/ARB/renin inhibitor use in Part D enrollees in the transition to ESRD, 2011



ICD-9-CM codes

585.1	Chronic kidney disease, Stage 1
585.2	Chronic kidney disease, Stage 2 (mild)
585.3	Chronic kidney disease, Stage 3 (moderate)
585.4	Chronic kidney disease, Stage 4 (severe)
585.5	Chronic kidney disease, Stage 5 (excludes 585.6: Stage 5, requiring chronic dialysis.*)

Chronic kidney disease, unknown/unspecified

**In USRDS analyses, patients with ICD-9-CM code 585.6 & with no ESRD 2728 form or other indication of ESRD are considered to have code 585.5; see Appendix A for details.*

CKD stage estimates are from a single measurement. For clinical case definition, abnormalities should be present ≥ 3 months.

Point prevalent Medicare CKD patients age 67 and older

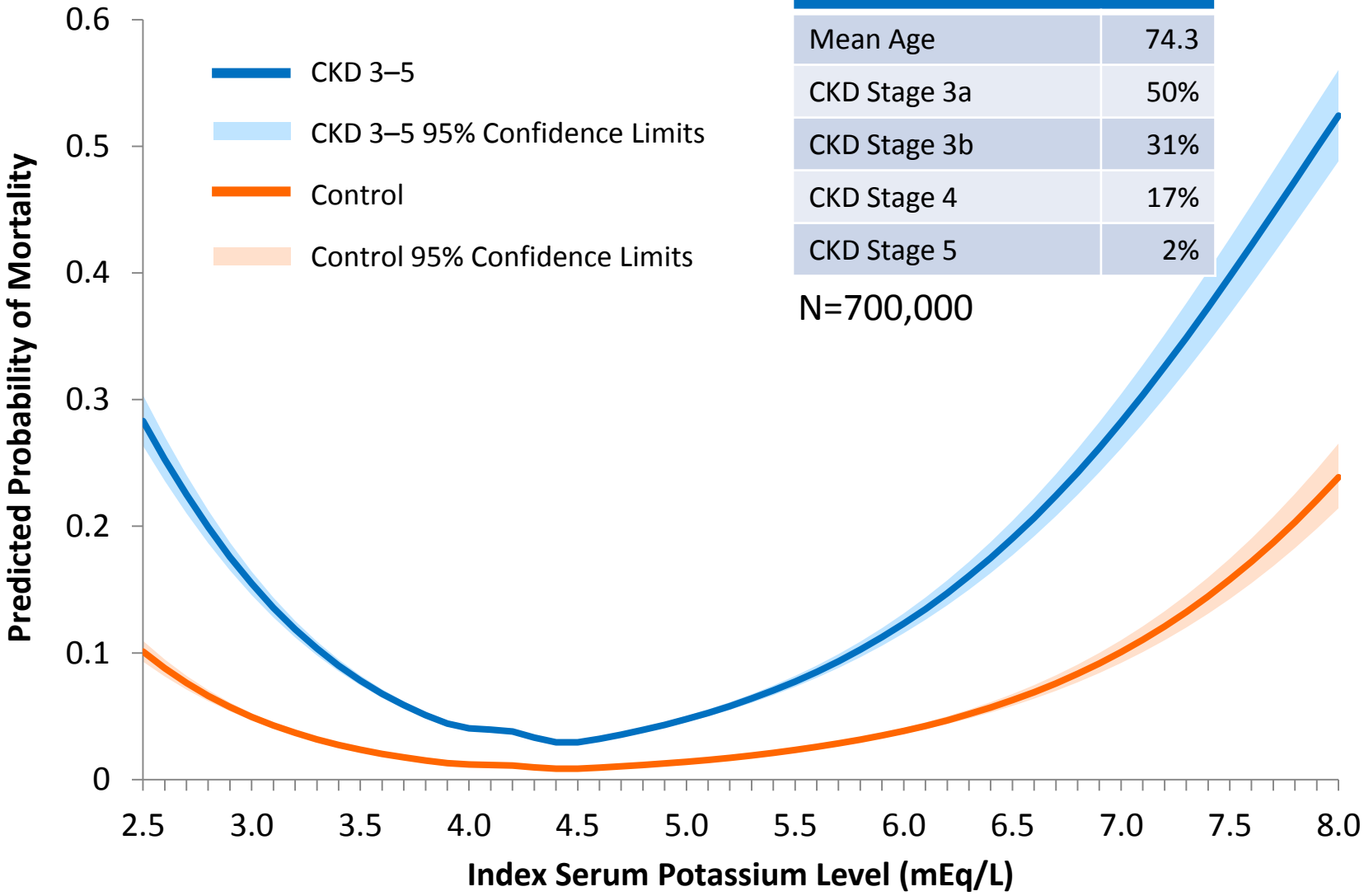
U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD, 2013.

Odd Ratio of Hyperkalemia Development following Aldosterone Antagonism in Nephropathy

Variable	Odds Ratio	P value
Baseline eGFR $\leq$45 ml/min/1.73m^2 + serum potassium >4.5 mEq/L	8.71 (2.89-24.8)	<0.0001
Baseline eGFR $\leq$45 ml/min/1.73m^2 + >30% reduction in eGFR	7.76 (2.13-29.8)	<0.0001
Baseline eGFR $\leq$45 ml/min/1.73m^2	2.97 (1.14-21.3)	<0.001
Baseline eGFR $\leq$45 ml/min/1.73m^2 + >15 mmHg in systolic BP	3.98 (0.89-27.1)	0.09

Khosla N et.al. Am J Nephrol 2009;30:418 ; Lazich I et.al. Sem in Nephrol 2014

Adjusted Mortality in Patients with CKD 3-5 vs Controls



Baseline Characteristics	
Mean Age	74.3
CKD Stage 3a	50%
CKD Stage 3b	31%
CKD Stage 4	17%
CKD Stage 5	2%

N=700,000

Collins A, et al. *ASN*. 2014.

Management of Hyperkalemia

- Low Potassium Diet
- Polystrene Binding resins
- Newer compounds

Systematic Review of Necrosis Case Reports of SPS-Related GI Adverse Events

- Review included search of Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), bibliographies of identified articles, and websites of relevant drug agencies and professional associations

- 58 cases were identified in 30 reports
  - Necrosis was reported in patients given Kayexalate with (n=41) and without sorbitol (n=17)

- Mortality due to gastrointestinal injury was reported in 33% of these cases

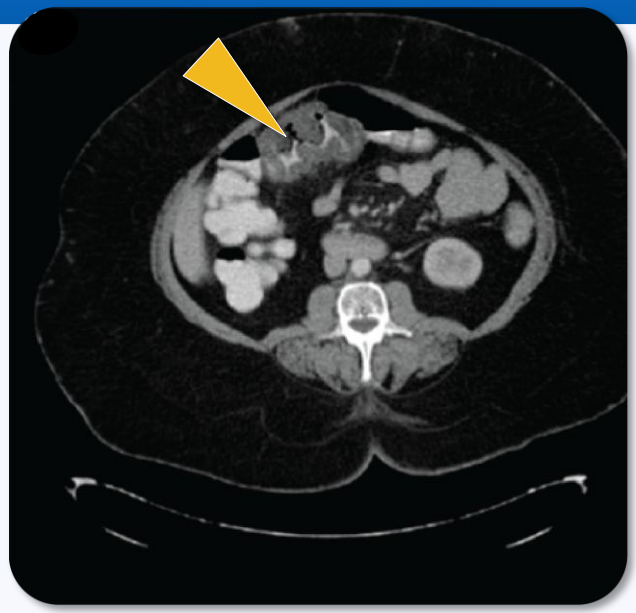
- Cases of necrosis treated without sorbitol were more likely to be receiving chronic SPS (41%) than cases without (0%)

Harel Z, et al. *Am J Med*. 2013;126(3):264.e9-24.

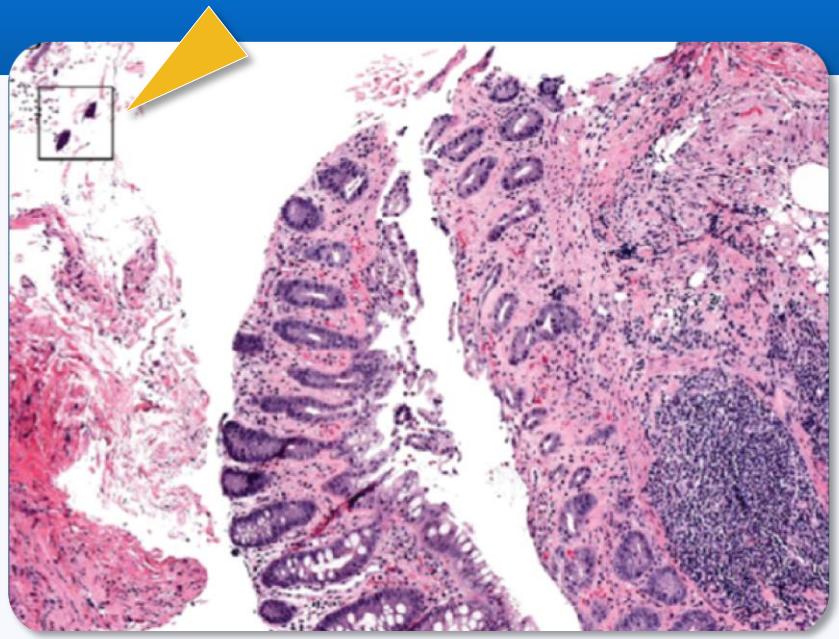
Histopathology of SPS-Related GI Injury

Necrosis (62%), Ulceration (48%), Perforation (9%), and SPS Crystals (90%)[1]

Circumferential wall thickening and pericolonic stranding on CT scan[2]*



Angulated basophilic crystals, a typical appearance of Kayexalate[2]

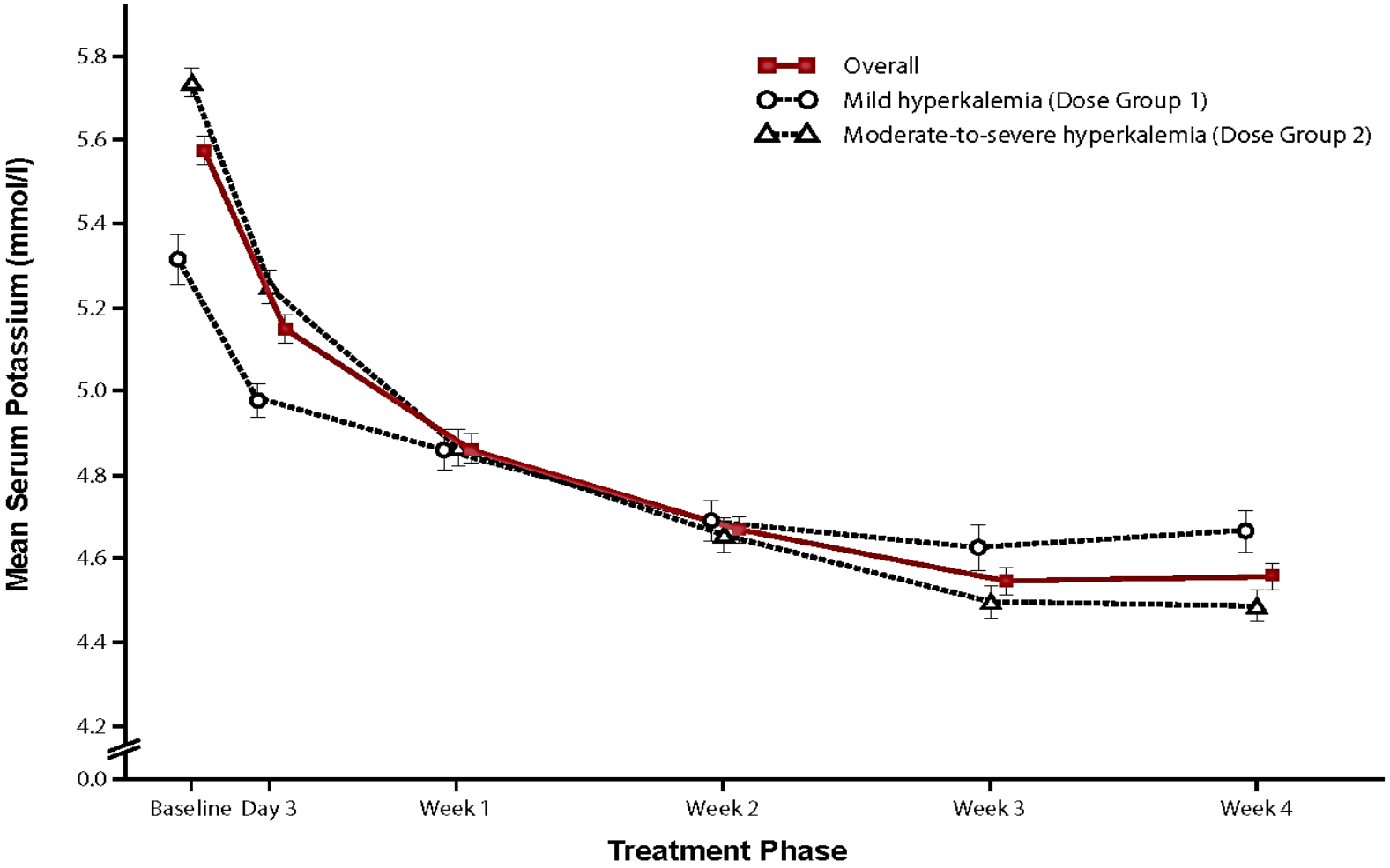


Fragments of colonic mucosa have miniaturized crypts with leakage of RBCs and fibrin into the surrounding lamina propria[2] **

* IV and oral contrast, a focal region of large bowel in the proximal transverse colon, near the hepatic flexure.
** a few normal-sized crypts are present at the bottom center for comparison.

1. Harel Z, et al. *Am J Med*. 2013;126(3):264.e9-24. **2.** Bomback AS, et al. *Am J Emerg Med*. 2009 Jul;27(6):753.e1-2.

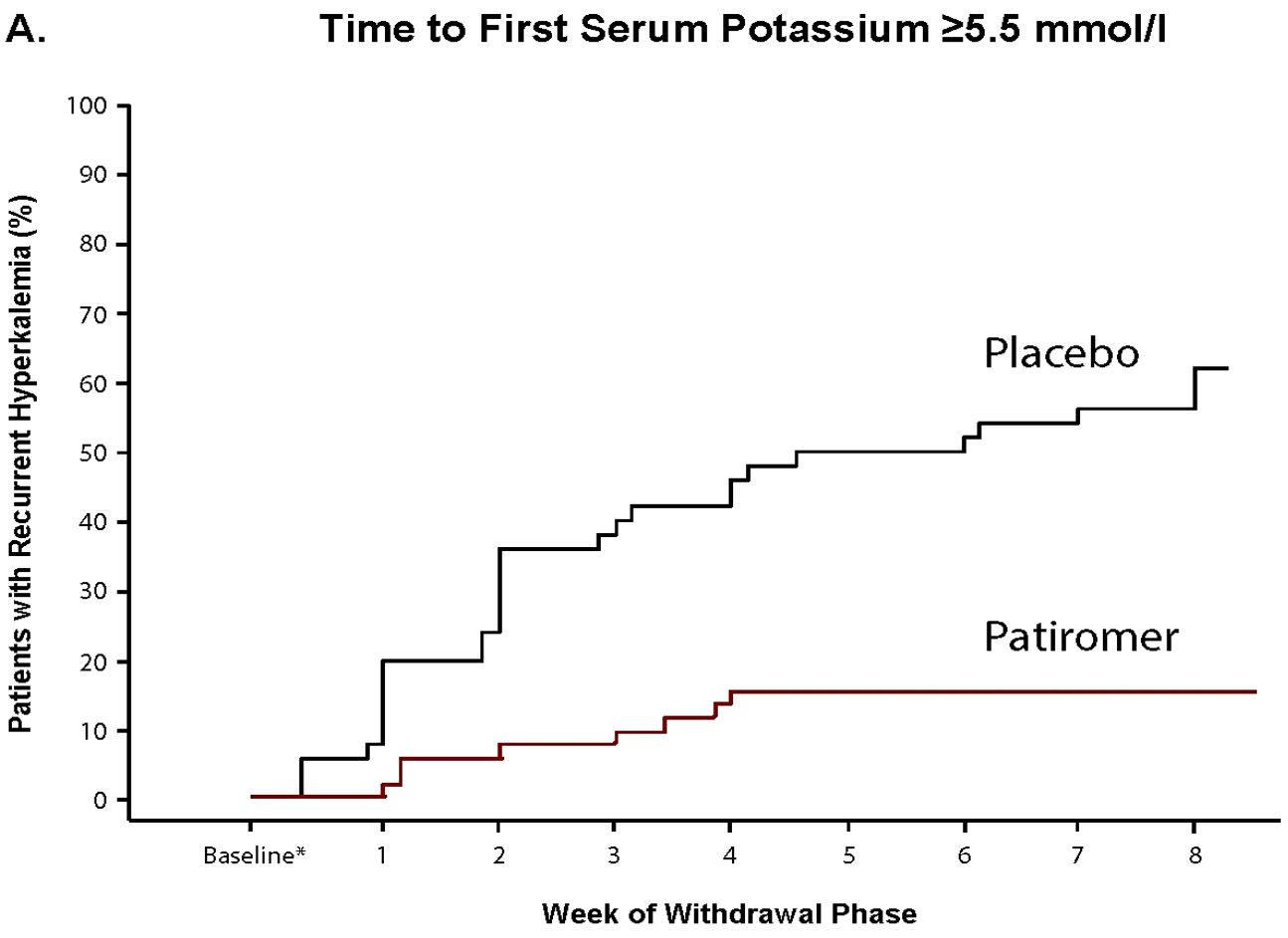
Serum Potassium Over Time: Treatment Phase. Values are observed mean from central laboratory. I bars indicate standard errors.



No. of Patients						
Overall	243	217	237	228	221	219
Dose Group 1	92	80	90	87	85	85
Dose Group 2	151	137	147	141	136	134

Weir M et.al. NEJM Jan 2015

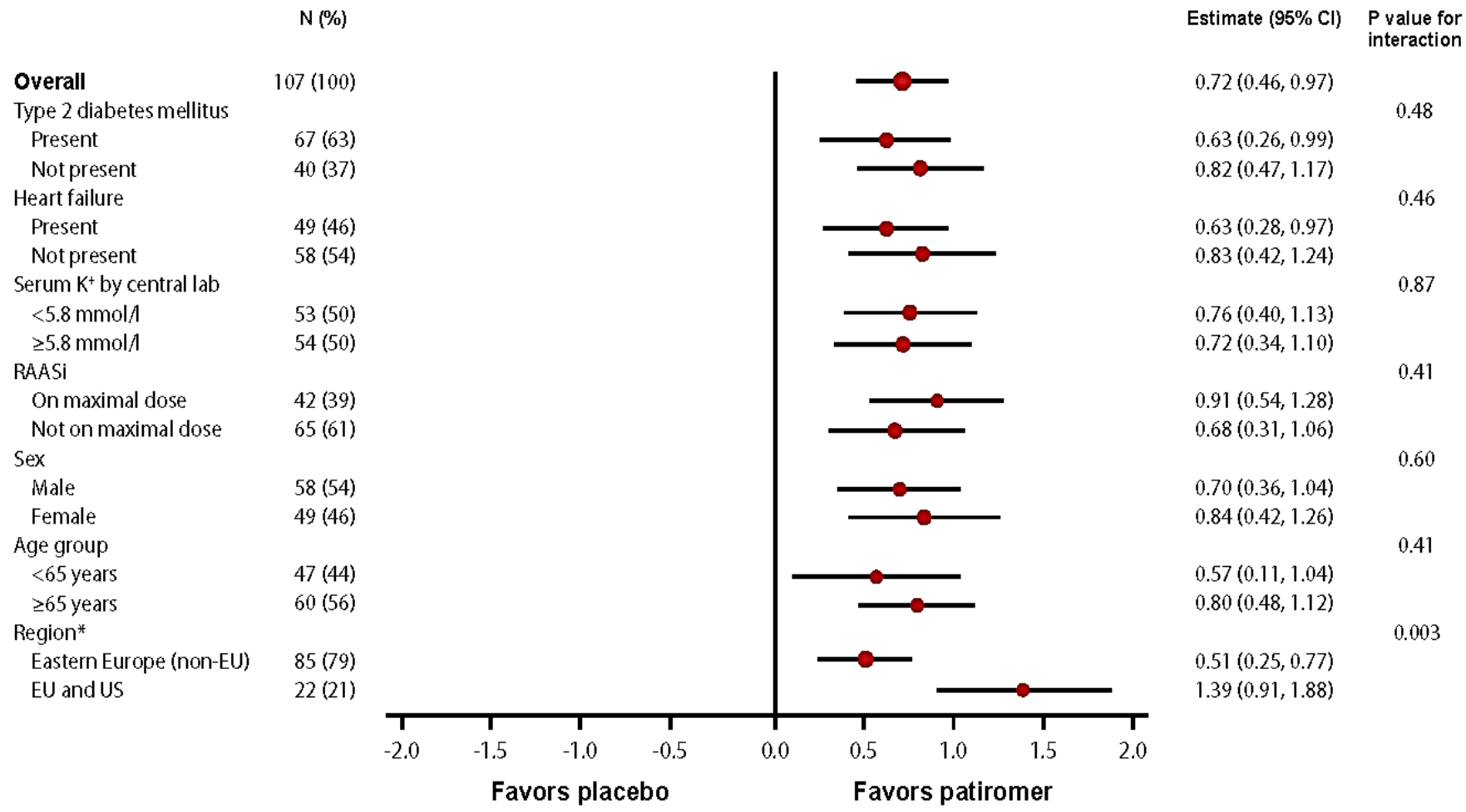
Time to First Recurrent Hyperkalemia: Withdrawal Phase



No. of Patients									
Placebo	52	46	38	31	29	25	25	23	15
Patiromer	55	53	49	48	45	43	42	42	32

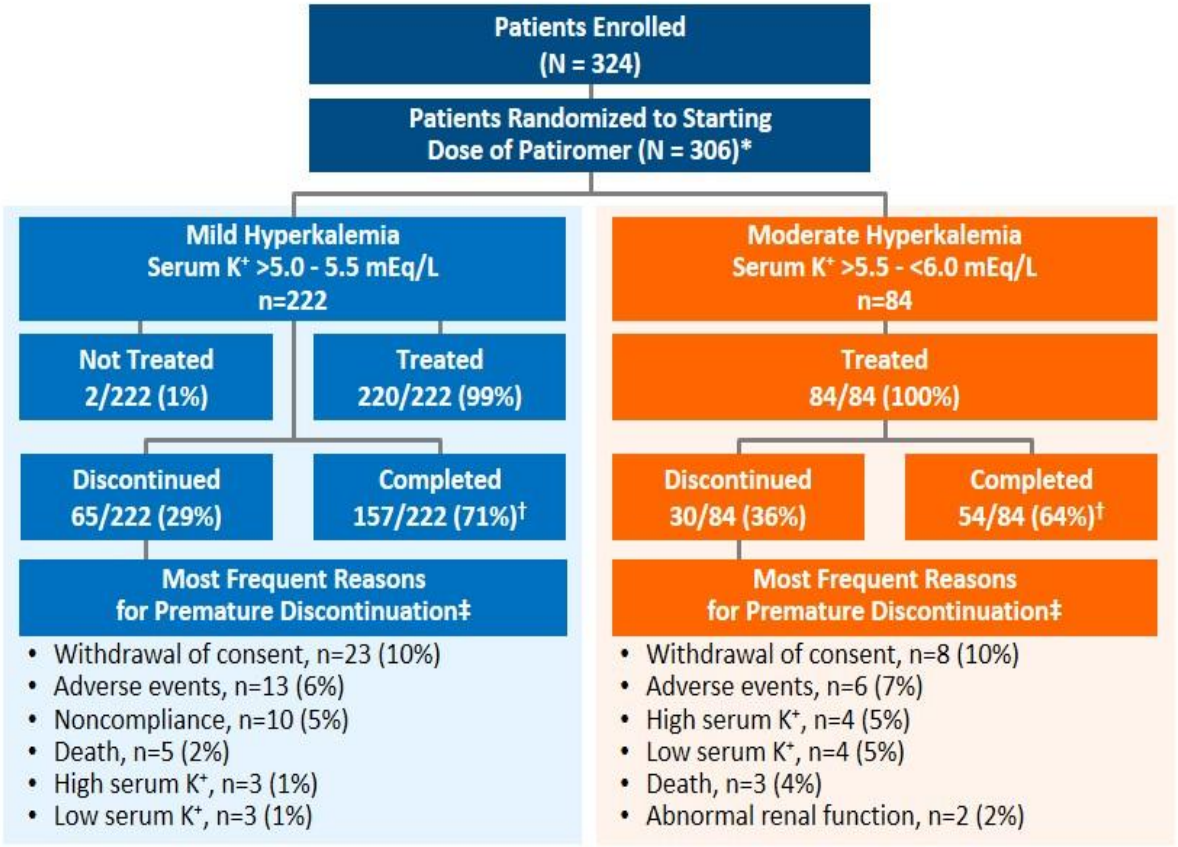
Weir M et.al. NEJM Jan 2015

Forest Plot of the Primary Efficacy End Point by Subgroups: Withdrawal Phase. Difference between placebo and Patiromer in median change in serum potassium from the start of the Withdrawal to Week 4 of the Withdrawal Phase.



Weir M et.al. NEJM Jan 2015

Patient Disposition by Assigned Strata (Mild or Moderate Hyperkalemia) Over 52 Weeks



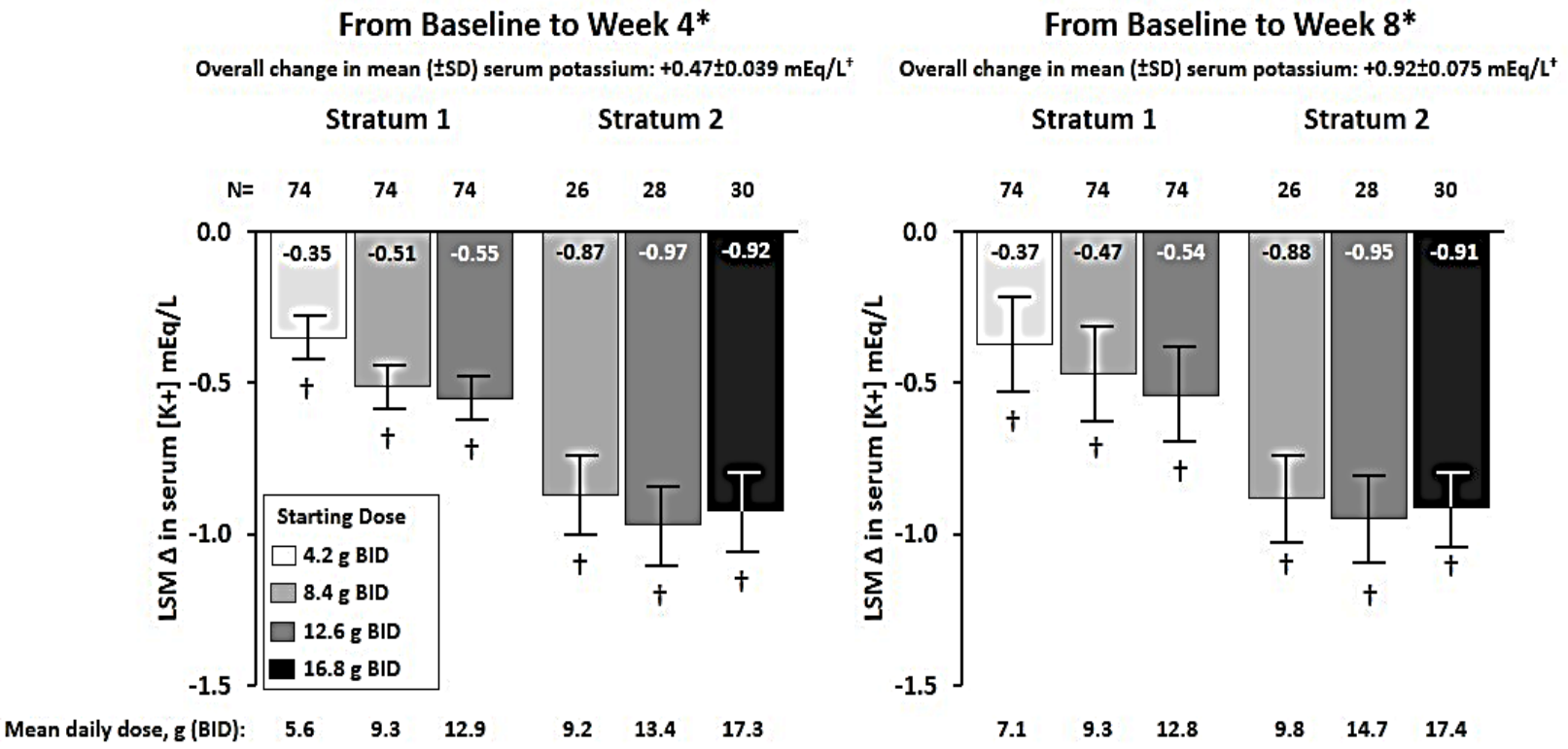
*Eighteen patients from Cohorts 1 and 2 who were enrolled in the trial failed the run-in and were not eligible for randomization.

†Ten patients with mild hyperkalemia and 4 patients with moderate hyperkalemia completed the 8-wk Treatment Phase before the protocol amendment that added the 44-wk Maintenance Phase.

‡Reasons were assigned by study investigators; in the adverse event category, events leading to discontinuations in 5 patients were fatal adverse events.

Bakris GL. et.al. .JAMA in review

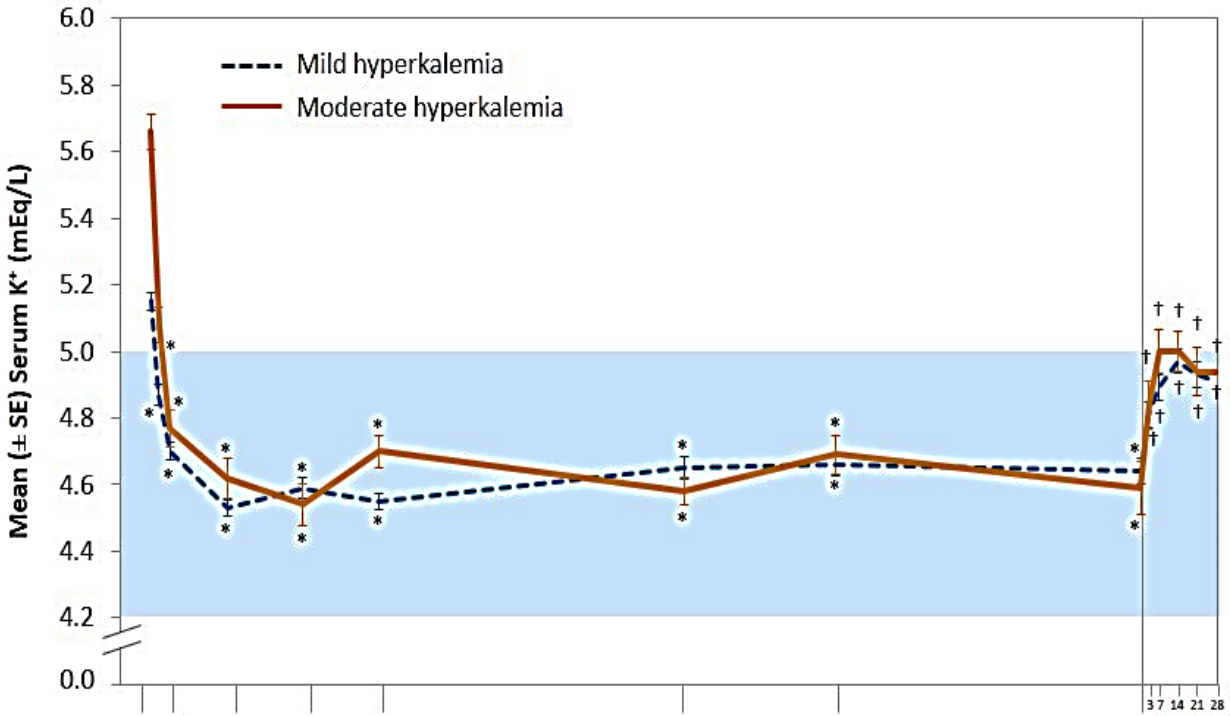
Mean Patiromer Dose and LSM (±SD) Change from Baseline in Serum Potassium by Starting Dose at Weeks 4 and 8 .



* Allowing for titration.
†*P*<0.001 versus baseline
Stratum 1, mild hyperkalemia (serum potassium >5.0 to 5.5 mEq/L). Stratum 2, moderate hyperkalemia (serum potassium >5.5 to <6.0 mEq/L

Bakris GL. et.al. .JAMA in review

Change from Baseline in Mean (±SE) Serum Potassium (mEq/L) to Week-52 (Treatment and Maintenance Phases) and Post-Treatment Follow-up Period in Patients with Mild or Moderate Hyperkalemia



All serum potassium analyses are based on central laboratory values; 3 patients (2 with mild hyperkalemia and one with moderate hyperkalemia) did not have a central laboratory serum potassium value at baseline and therefore are not included in the analysis at this timepoint.
*p<0.0001 by t-test for change from baseline. †p≤0.001 by t-test for change from Week 52 (or from the last dose of patiromer received during the study). BL, baseline; F/Up, follow-up; HK, hyperkalemia.

Bakris GL. et.al. .JAMA in review

Most Common Adverse Effects

Adverse Event*	Mild hyperkalemia n=220	Moderate hyperkalemia n=84	Overall N=304
Worsening of CKD	14 (6.4%)	14 (16.7%)	28 (9.2%)
Hypomagnesemia†	15 (6.8%)	11 (13.1%)	26 (8.6%)
Worsening of HTN	14 (6.4%)	10 (11.9%)	24 (7.9%)
Constipation	11 (5.0%)	8 (9.5%)	19 (6.3%)
Diarrhea	12 (5.5%)	5 (6.0%)	17 (5.6%)
Hypoglycemia†	4 (1.8%)	6 (7.1%)	10 (3.3%)

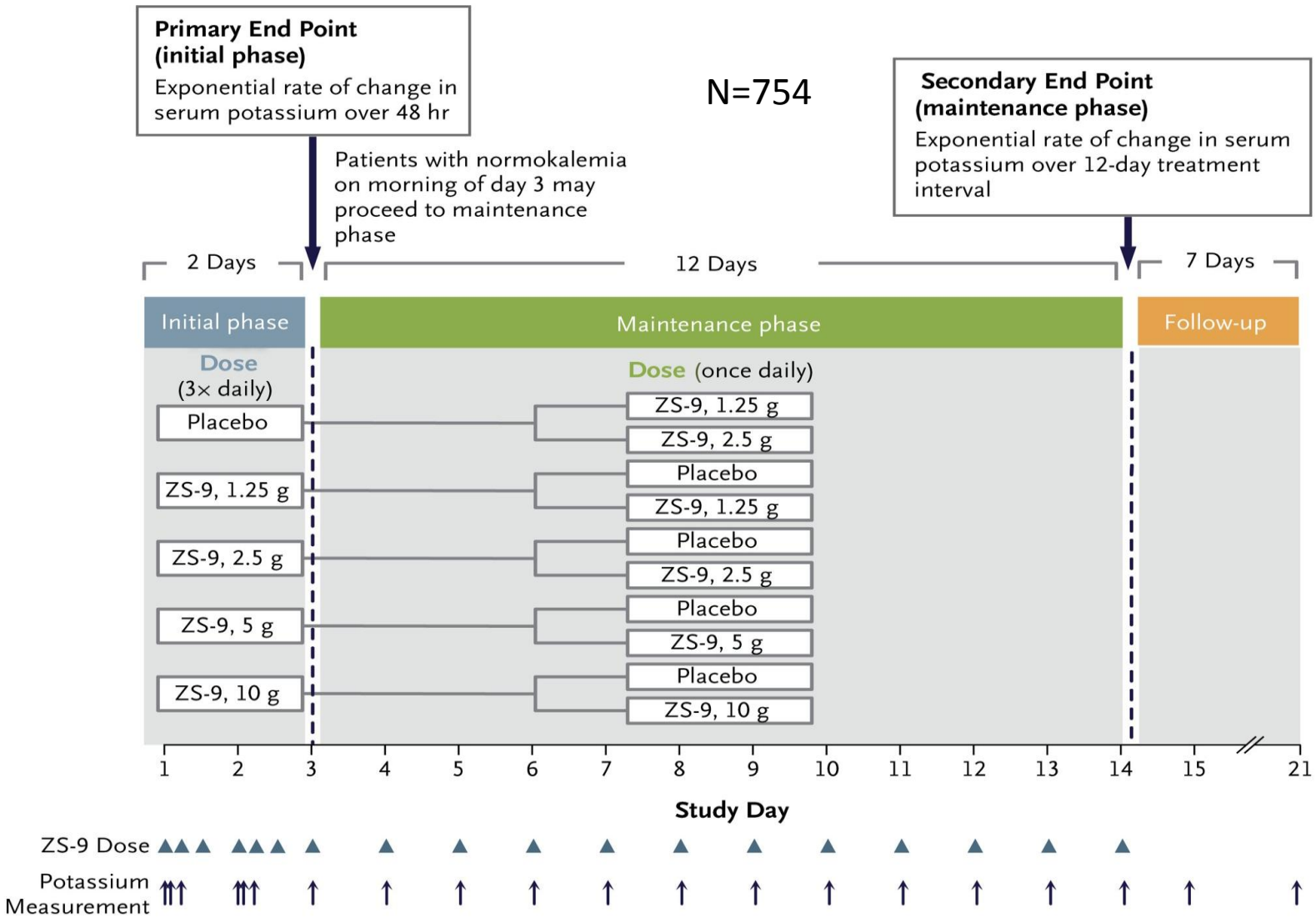
Bakris GL. et.al. .JAMA in review

Sodium Zirconium Cyclosilicate in Hyperkalemia

David K. Packham, M.B., B.S., M.D., Henrik S. Rasmussen, M.D., Ph.D., Philip T. Lavin, Ph.D., Mohamed A. El-Shahawy, M.D., M.P.H., Simon D. Roger, M.D., Geoffrey Block, M.D., Wajeh Qunibi, M.D., Pablo Pergola, M.D., Ph.D., and Bhupinder Singh, M.D.

N Engl J Med
Volume 372(3):222-231
January 15, 2015

Study Design.



Packham DK et al. N Engl J Med 2015;372:222-231

Characteristics of the Patients at Baseline.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=158)	ZS-9			
		1.25 g (N=154)	2.5 g (N=141)	5 g (N=157)	10 g (N=143)
Age — yr	65.6±12.2	65.4±13.1	65.9±11.7	65.2±11.9	66.2±12.2
Male sex — no. (%)	98 (62.0)	83 (53.9)	91 (64.5)	96 (61.1)	80 (55.9)
Race — no. (%)†					
White	136 (86.1)	131 (85.1)	125 (88.7)	132 (84.1)	120 (83.9)
Black	17 (10.8)	20 (13.0)	11 (7.8)	20 (12.7)	19 (13.3)
Baseline serum potassium — no. (%)					
5.0–5.3 mmol/liter	95 (60.1)	76 (49.4)	72 (51.1)	90 (57.3)	94 (65.7)
5.4–5.5 mmol/liter	22 (13.9)	38 (24.7)	29 (20.6)	36 (22.9)	27 (18.9)
5.6–6.5 mmol/liter	41 (25.9)	40 (26.0)	40 (28.4)	31 (19.7)	22 (15.4)
Medical history — no. (%)					
Chronic kidney disease	96 (60.8)	102 (66.2)	89 (63.1)	93 (59.2)	83 (58.0)
Heart failure	66 (41.8)	57 (37.0)	54 (38.3)	64 (40.8)	59 (41.3)
Diabetes mellitus	96 (60.8)	94 (61.0)	84 (59.6)	96 (61.1)	81 (56.6)
Use of RAAS inhibitor — no. (%)	101 (63.9)	109 (70.8)	97 (68.8)	99 (63.1)	96 (67.1)

* Plus–minus values are means ±SD. There were no significant differences among the groups at baseline, except for the serum potassium level (P=0.03 for the overall comparison among the five study groups). RAAS denotes renin–angiotensin–aldosterone system.
† Race was self-reported.

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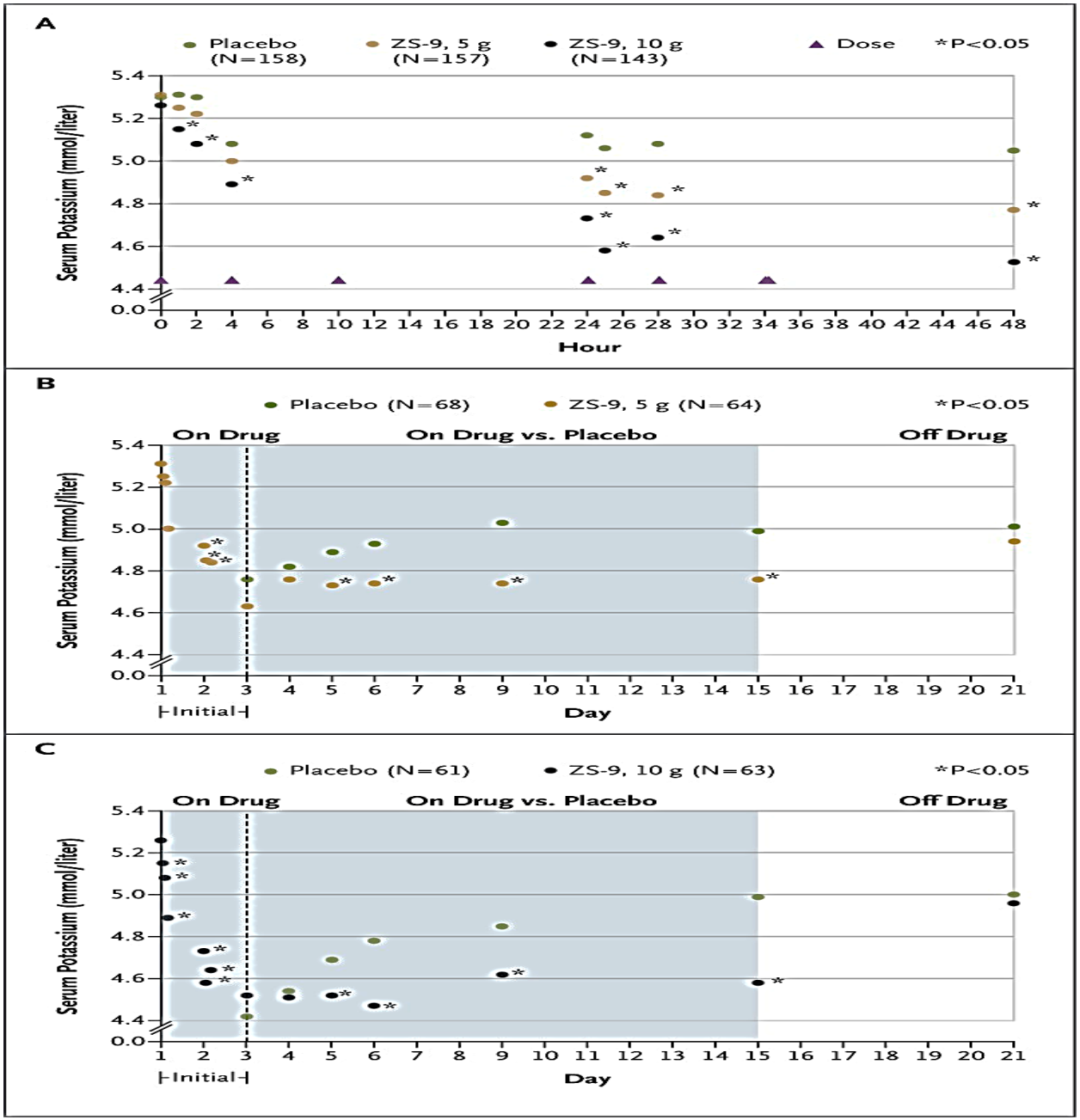
Potassium Levels during the Study.



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Adverse Events during Initial Phase and Maintenance Phase.

Table 2. Adverse Events during Initial Phase and Maintenance Phase.*

Adverse Events in Initial Phase	Placebo	ZS-9, 1.25 g	ZS-9, 2.5 g	ZS-9, 5 g	ZS-9, 10 g
No. of patients	158	154	141	157	143
Adverse event — no. (%)					
Any	17 (10.8)	25 (16.2)	13 (9.2)	22 (14.0)	17 (11.9)
Gastrointestinal disorder†	8 (5.1)	7 (4.5)	3 (2.1)	6 (3.8)	5 (3.5)
Cardiac disorder‡	0	1 (0.6)	0	3 (1.9)	2 (1.4)
Urinary tract infection	0	3 (1.9)	0	1 (0.6)	0

Adverse Events in Maintenance Phase	ZS-9, 1.25 g	ZS-9, 2.5 g	Placebo	ZS-9, 1.25 g	Placebo	ZS-9, 2.5 g	Placebo	ZS-9, 5 g	Placebo	ZS-9, 10 g
No. of patients	46	50	41	49	46	54	68	65	61	63
Adverse event — no. (%)										
Any	10 (21.7)	12 (24.0)	13 (31.7)	14 (28.6)	9 (19.6)	11 (20.4)	16 (23.5)	14 (21.5)	15 (24.6)	21 (33.3)
Gastrointestinal disorder†	4 (8.7)	2 (4.0)	1 (2.4)	0	2 (4.3)	4 (7.4)	5 (7.4)	5 (7.7)	0	3 (4.8)
Cardiac disorder‡	0	0	0	0	0	1 (1.9)	1 (1.5)	2 (3.1)	1 (1.6)	2 (3.2)
Urinary tract infection	2 (4.3)	1 (2.0)	2 (4.9)	1 (2.0)	0	1 (1.9)	1 (1.5)	3 (4.6)	0	1 (1.6)

* Patients in the ZS-9 group who had a serum potassium level of 3.5 to 4.9 mmol per liter at 48 hours during the initial phase of the study were randomly assigned to receive either their original ZS-9 dose or placebo once daily before breakfast on days 3 to 14 during the maintenance phase. Patients in the placebo group in the initial phase were randomly assigned to receive either 1.25 g or 2.5 g of ZS-9 in the maintenance phase.

† Gastrointestinal disorders included diarrhea, constipation, nausea, vomiting, abdominal pain, abdominal distention, dyspepsia, flatulence, gastric ulcers, gastritis, and frequent bowel movements.

‡ Cardiac disorders included atrial fibrillation, atrial flutter, bradycardia, palpitations, sinus tachycardia, ventricular extrasystole, left-sided bundle-branch block, congestive cardiac failure, cardiovascular disorder, diastolic dysfunction, and the long-QT syndrome.

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Summary

- No data supporting additional benefit on CKD outcomes, regardless of strategy in patients with normo or microalbuminuria-over BP control and in normotensive patients apart maybe from glycemic control
- No data to support advantage on CKD outcome in elderly without proteinuria.
- Only place where there is definitive data for RAAS to slow diabetic nephropathy is in advanced proteinuric disease

Summary

- New therapies to reduce serum potassium in stage 3b and higher CKD will provide opportunities for better patient management and testing of hypotheses regarding RAS therapy and CKD outcomes.