CMHC
Cardiometabolic Health Congress

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Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Evaluating Changes in Serum Creatinine While Getting BP Controlled: A Nephrologist's View

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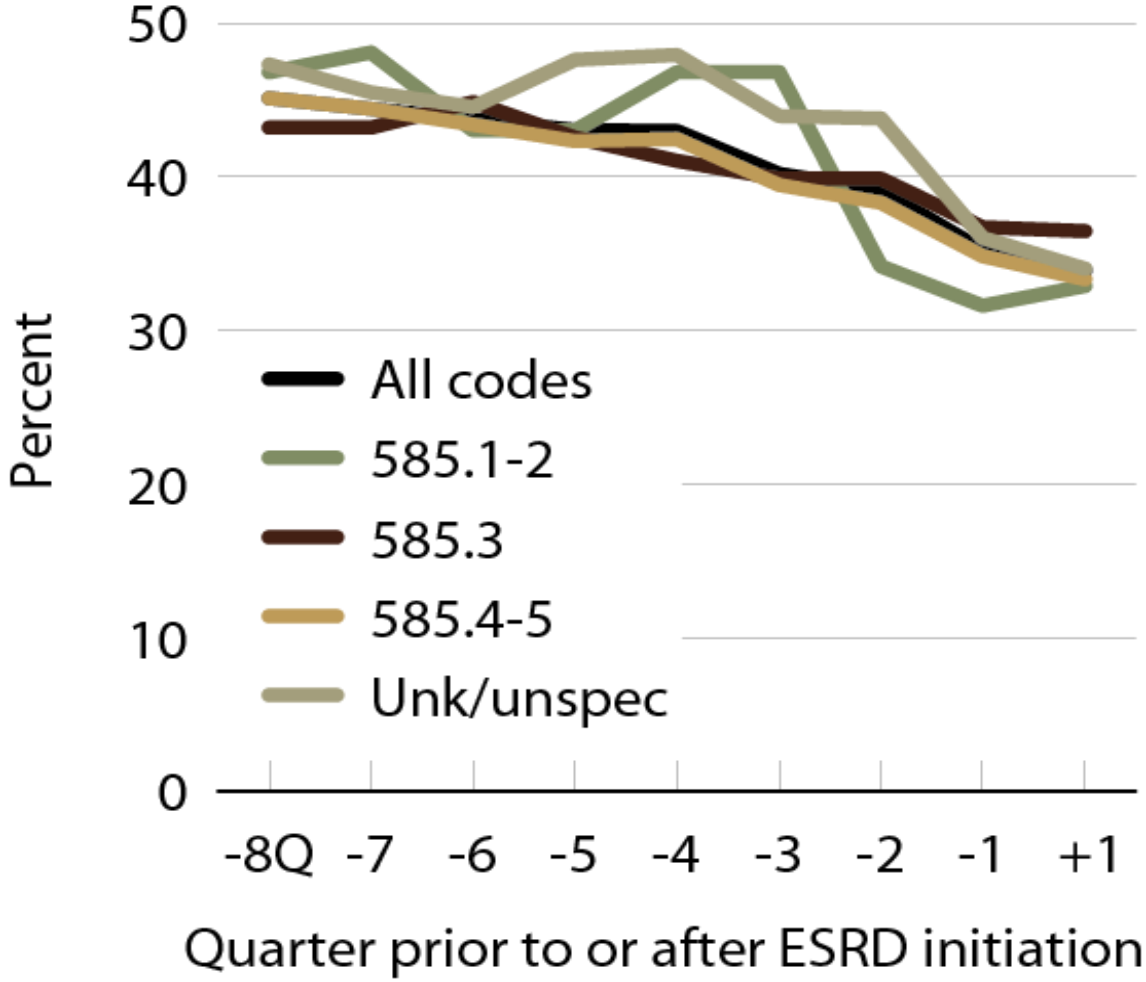
RAASi use falls from 43%–47% 8 quarters before ESRD to 33%–37% in the quarter following initiation of ESRD

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



Point prevalent Medicare CKD patients age 67 and older

ICD-9-CM codes

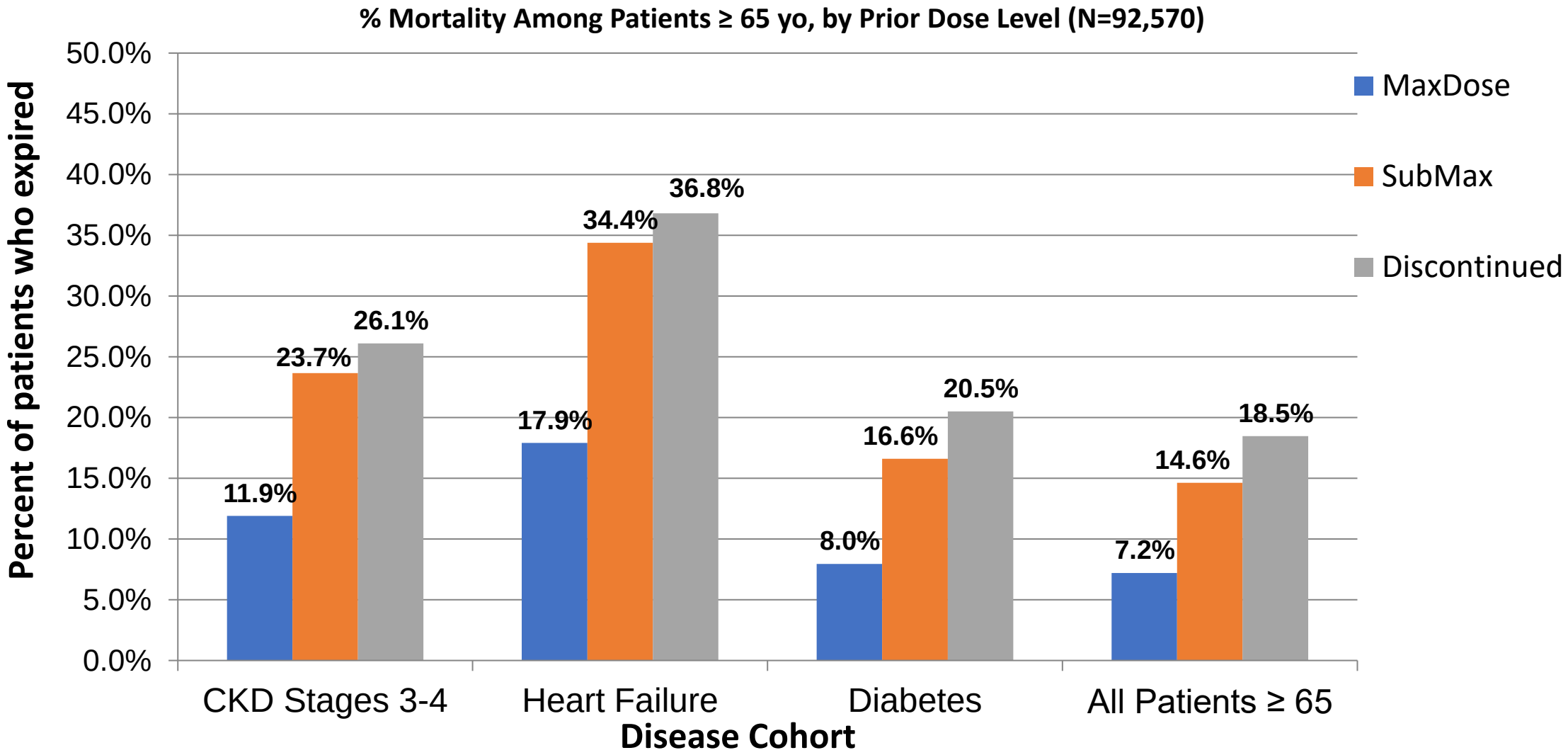
585.1	Chronic kidney disease, Stage 1
585.2	Chronic kidney disease, Stage 2 (mild)
585.3	Chronic kidney disease, Stage 3 (moderate)
585.4	Chronic kidney disease, Stage 4 (severe)
585.5	Chronic kidney disease, Stage 5 (excludes 585.6: Stage 5, requiring chronic dialysis.*)
	Chronic kidney disease, unknown/unspecified

**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.

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.

Higher 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.

CASE

- 58 y/o African American male comes in after he states he wasn't been feeling well and has had periodic headaches. He says he was told he was hypertensive 10 years earlier and was given Rx which he doesn't recall. Also has never checked his BP since then. He comes now figuring his BP may be the cause of the problem. ROS-neg. otherwise
- Pertinent Positives on PE-BP 182/98 mmHg, HR-84 and reg, + S4 on heart exam, 1+ pedal edema

CASE

- Labs: pertinent +-[K+]-3.4 mEq/L, Cr-1.4 mg/dl, urine albumin-423 mg/g.
- After educating the patient on low sodium diet and confirmed that he sleeps well and feels rested after 6-8 hr/night, we started the combination of chlorthalidone 25 mg/d, and amlodipine-olmesartan 5/40 mg/d (single pill). Also told to get an OMRON device and how to check BP in am at least 3 times when awakening over the next week.
- He returns in 5 weeks

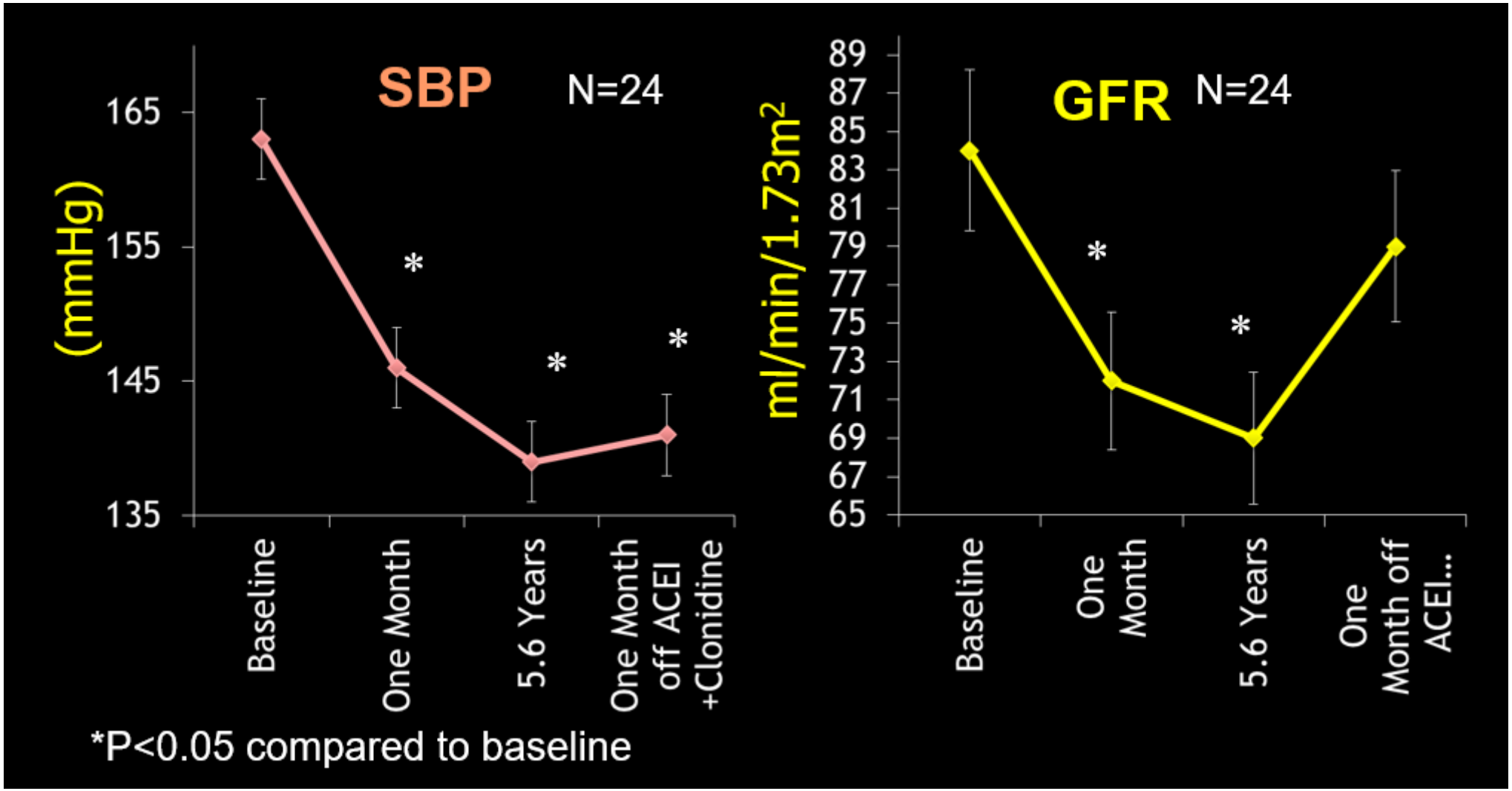
CASE

- BP 146/90 mmHg, HR-76 and reg, no pedal edema
- Labs: pertinent +-[K+]-3.6 mEq/L, Cr-1.72 mg/dl, urine albumin-184 mg/d.
- His home BPs range from 138-146 mmHg systolic and says he feels better and headaches are gone.
- What would you do know-
- We add spironolactone 12.5 mg daily
- Returned in 4 weeks-BP 128/80 mmHg and Cr-1.8 mg/dl

SUMMARY OF CHANGES

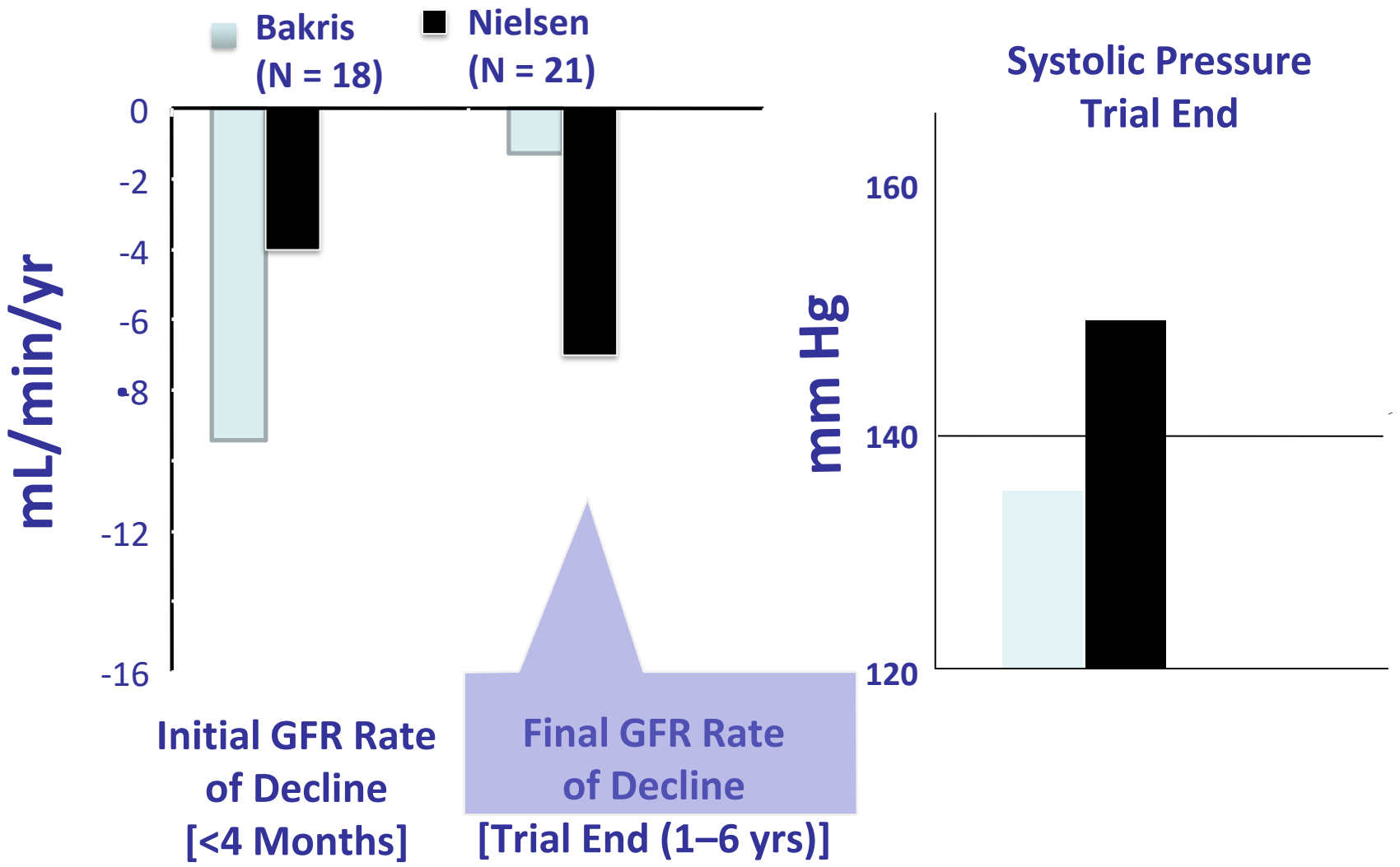
Blood Pressure (mmHg)	182/98	144/90	128/80
Serum Creatinine (mg/dl)	1.43	1.72	1.80

Impact of ACE Inhibition on Blood Pressure and GFR: Acute vs. Chronic Effects



Bakris G and Weir M Arch Intern Med 2000

Effects of lisinopril in untreated hypertensive patients with Type 2 diabetes



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

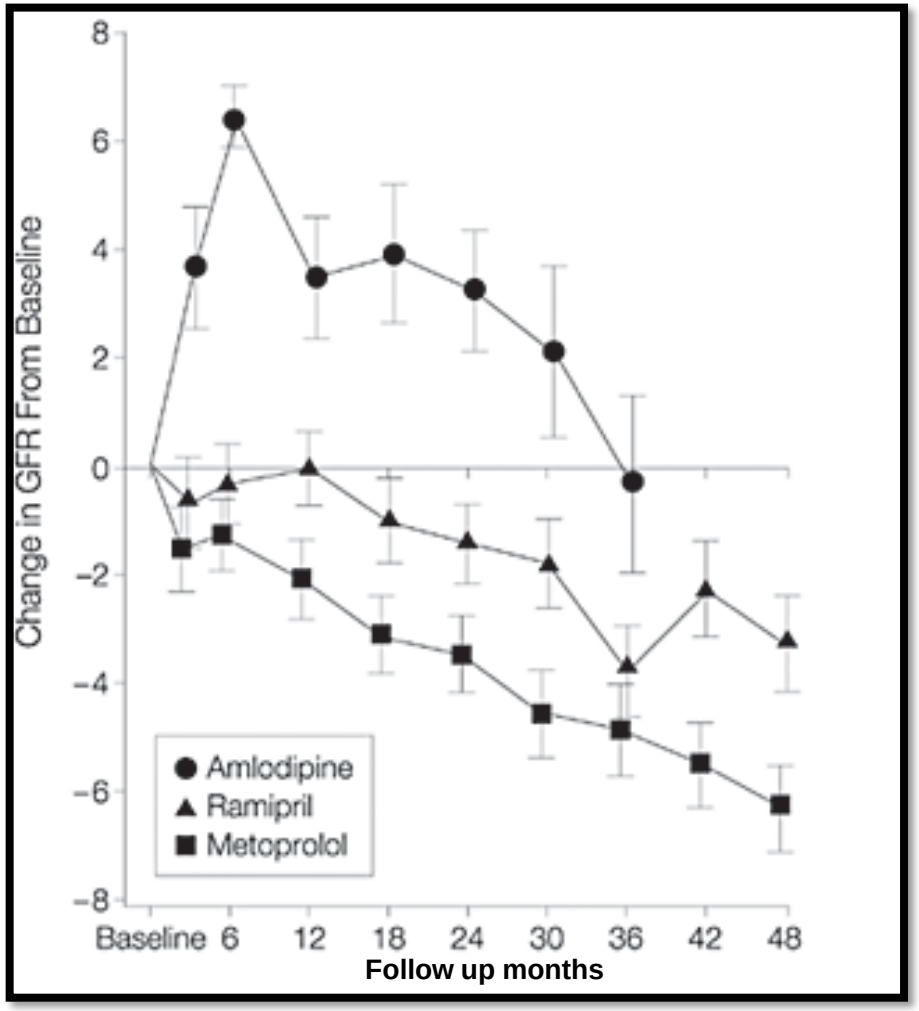
Review of the Literature: Rise in Creatinine and Outcomes

- Angiotensin-Converting Enzyme Inhibitor–Associated Elevations in Serum Creatinine: Is This a Cause for Concern? *Bakris GL and Weir MR, Arch Intern Med. 2000; 160(5): 685-693*
- KDOQI Blood Pressure Guidelines (National Kidney Foundation) *Am J Kidney Disease (Suppl) 2004*
- Tolerating Increases in the Serum Creatinine following Aggressive Treatment of Chronic Kidney Disease, Hypertension and Proteinuria: Pre-Renal Success *Hirsch S et.al. Am J Nephrol 2012;36:430-437*
- Dealing with Renin-Angiotensin Inhibitors, Don't Mind Serum Creatinine *Ruggenenti P and Remuzzi R Am J Nephrol 2012;36:427-429*

Mean change in Glomerular Filtration rate*

Natural History of GFR Change in the AASK

Three randomized groups from AASK trial



Wright JT Jr. et.al., JAMA 2002

*98 months for Amlopidipine and 48 moths for Ramipril and metoprolol

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

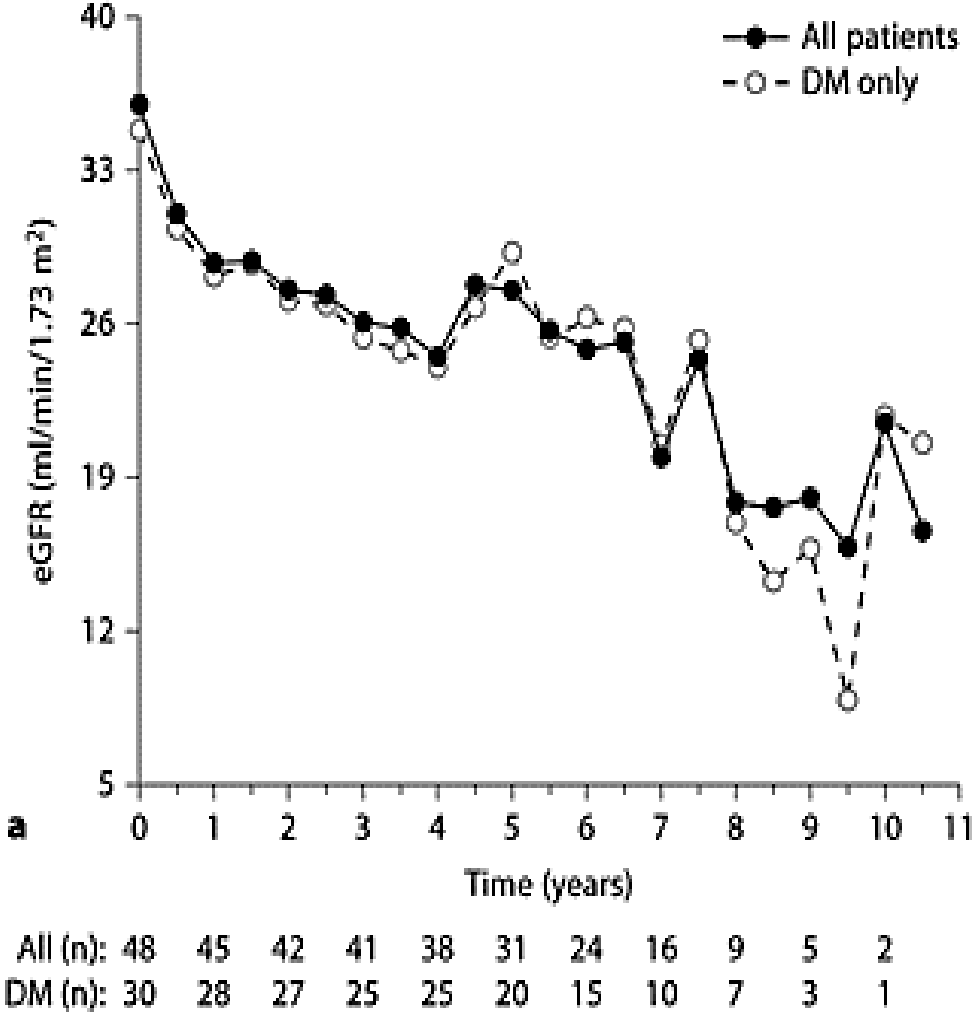
Long Term Follow-up of RAS induced changes in Serum Creatinine

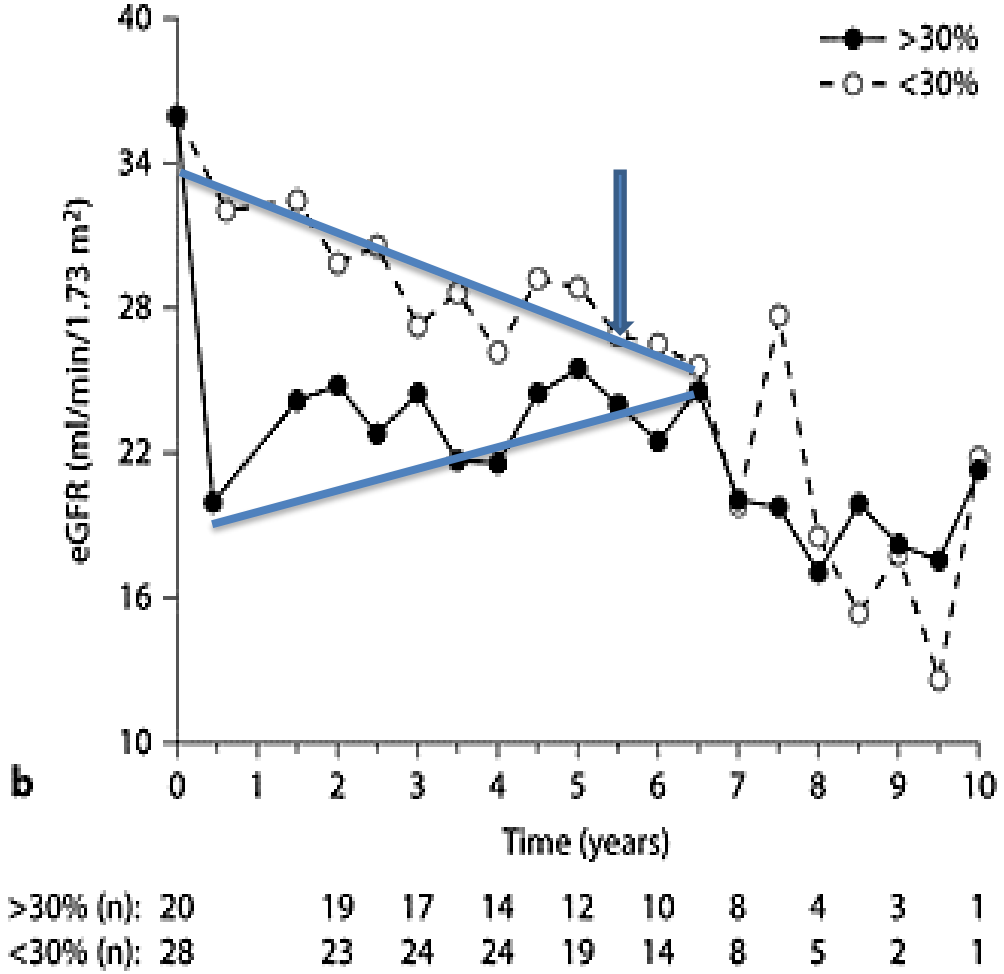
Medication/ timing	>30% (OT) (n = 20)	<30% (UT) (n = 28)	All patients (n = 48)
ACEI, %			
Presentation	60	67.8	64.6
After 1 year	75	82.1	79.2
ARB, %			
Presentation	35	14.3	22.9
After 1 year	65	50	56.3
MRA, %			
Presentation	5	0	2.1
After 1 year	25	25	25
Furosemide, %			
Presentation	70*	28.6	45.8
After 1 year	95	75	83.3
Furosemide dose, mg/day			
Presentation	74.3 ± 46.0	97.5 ± 95.3	82.7 ± 66.8
After 1 year	184.2 ± 143.7	139 ± 156.4	160.5 ± 150.3

* p = 0.04 vs. OT.

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

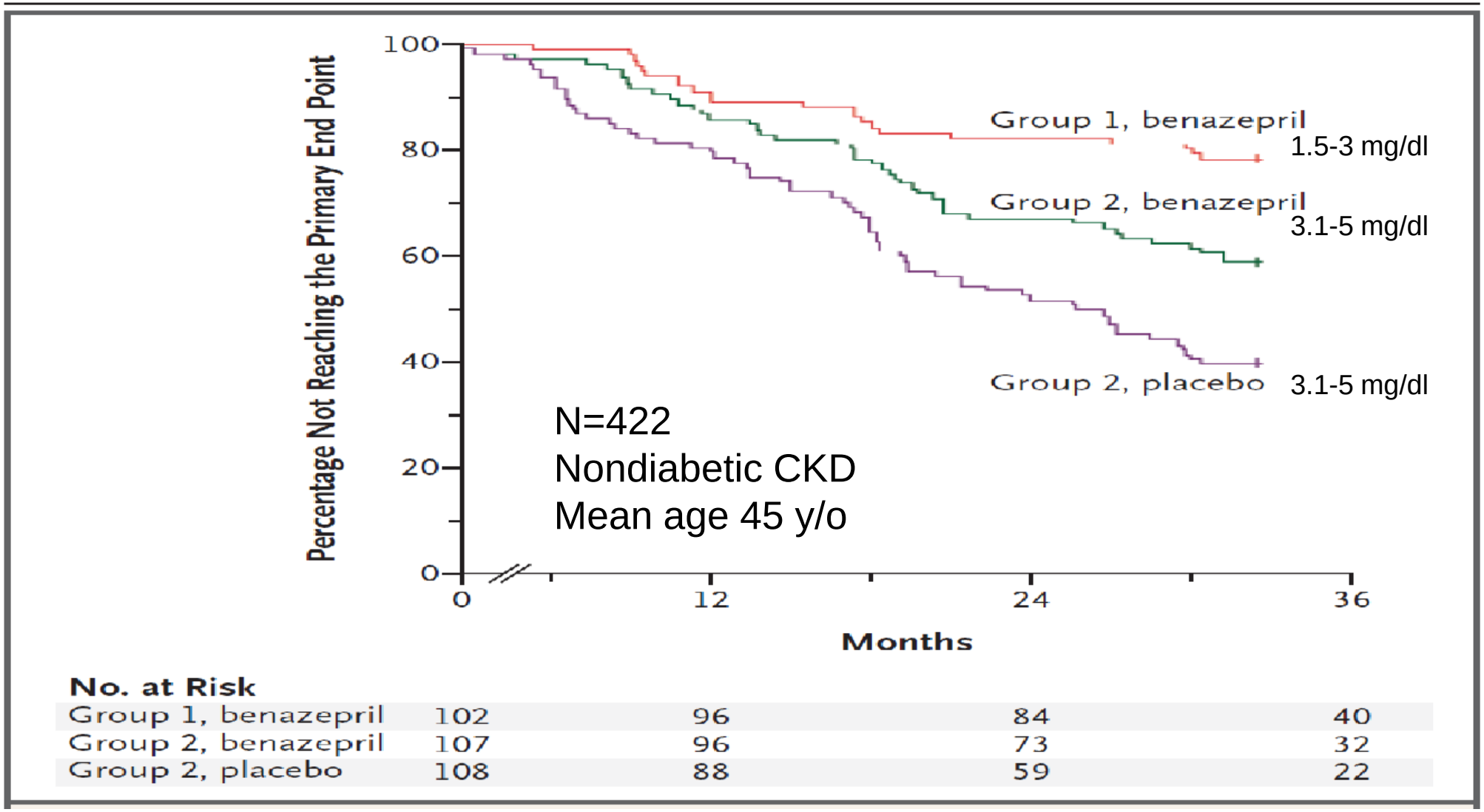
Decline in Kidney Function Over Time in Total Cohort





Hirsch, S et.al. Am.J.Nephrol. 36 (5):430-437, 2012.

Effects of an ACE inhibitors on Progression of Nephropathy



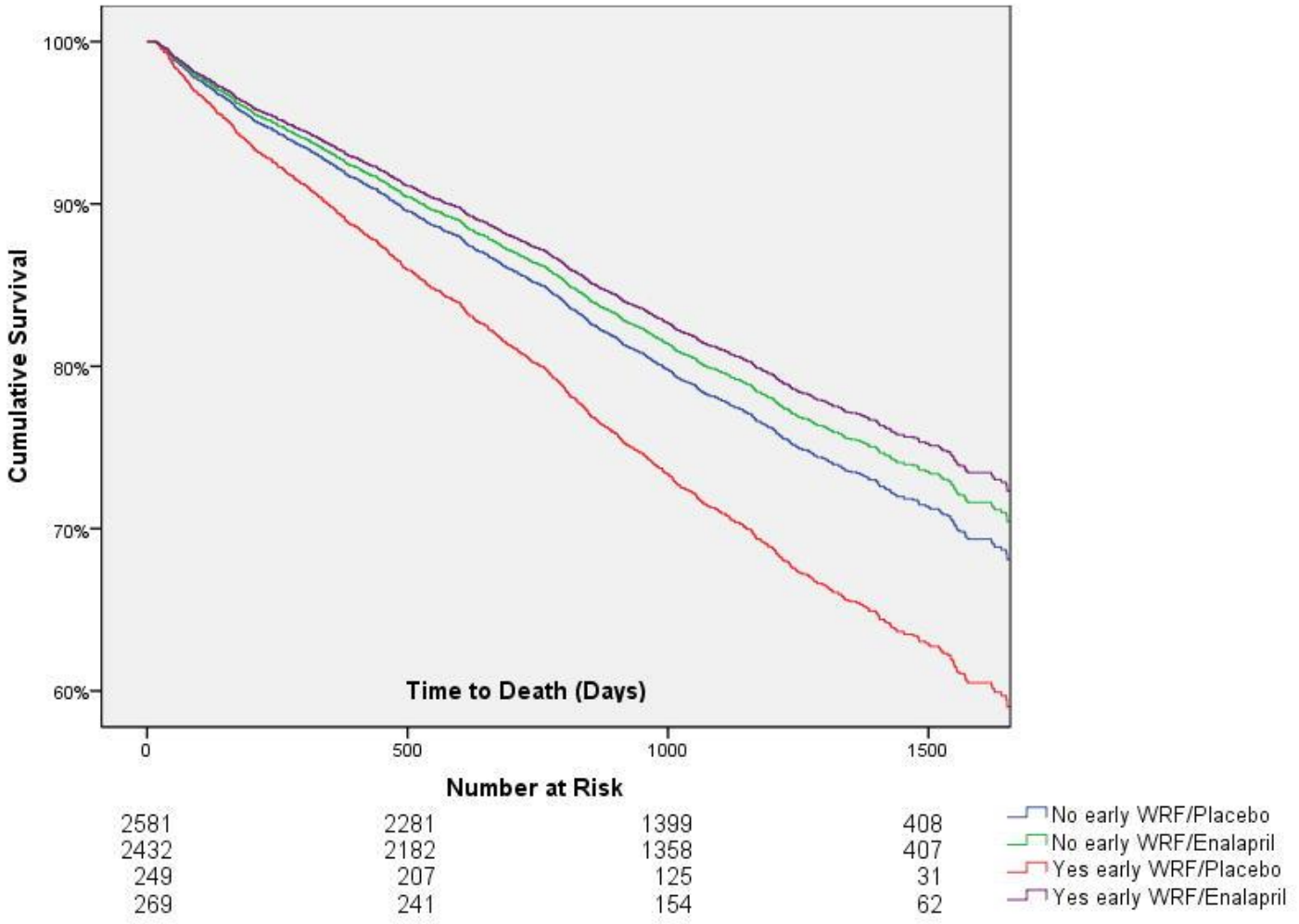
No. at Risk				
Group 1, benazepril	102	96	84	40
Group 2, benazepril	107	96	73	32
Group 2, placebo	108	88	59	22

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

SOLVD Revisited: Δ SCr Response to ACE-I and Survival



WRF defined as 20% drop in GFR in 14 days after starting ACE / placebo

Figure. Adjusted curves grouped by randomization to enalapril or placebo and subsequent early worsening renal function (WRF) status in patients who did not discontinue or dose reduce the study drug in proximity to WRF. Early WRF was defined as a 20% reduction in glomerular filtration rate (GFR) from baseline to 14 days after randomization.
Covariates were adjusted for the following: age; race; ejection fraction; heart rate; diastolic blood pressure; New York Heart Association class; serum sodium level; estimated GFR; history of diabetes, hypertension, stroke, or myocardial infarction; loop diuretic; potassium-sparing diuretic; digoxin; and β-blocker use.

Testani, Coca et al Circ Heart Fail 2011

Neprilysin Inhibition (PARADIGM)

8,442 subject with Class II, III and IV HF (EF < 40%)

Randomized, Double-blind, International (Neprilysin+ARB vs. ACE)

Primary endpoint: CV death or CHF hospitalization

Stopped Early due to overwhelming benefit ….less adverse renal outcomes (p=NS for drop in eGFR or new ESRD/RRT)

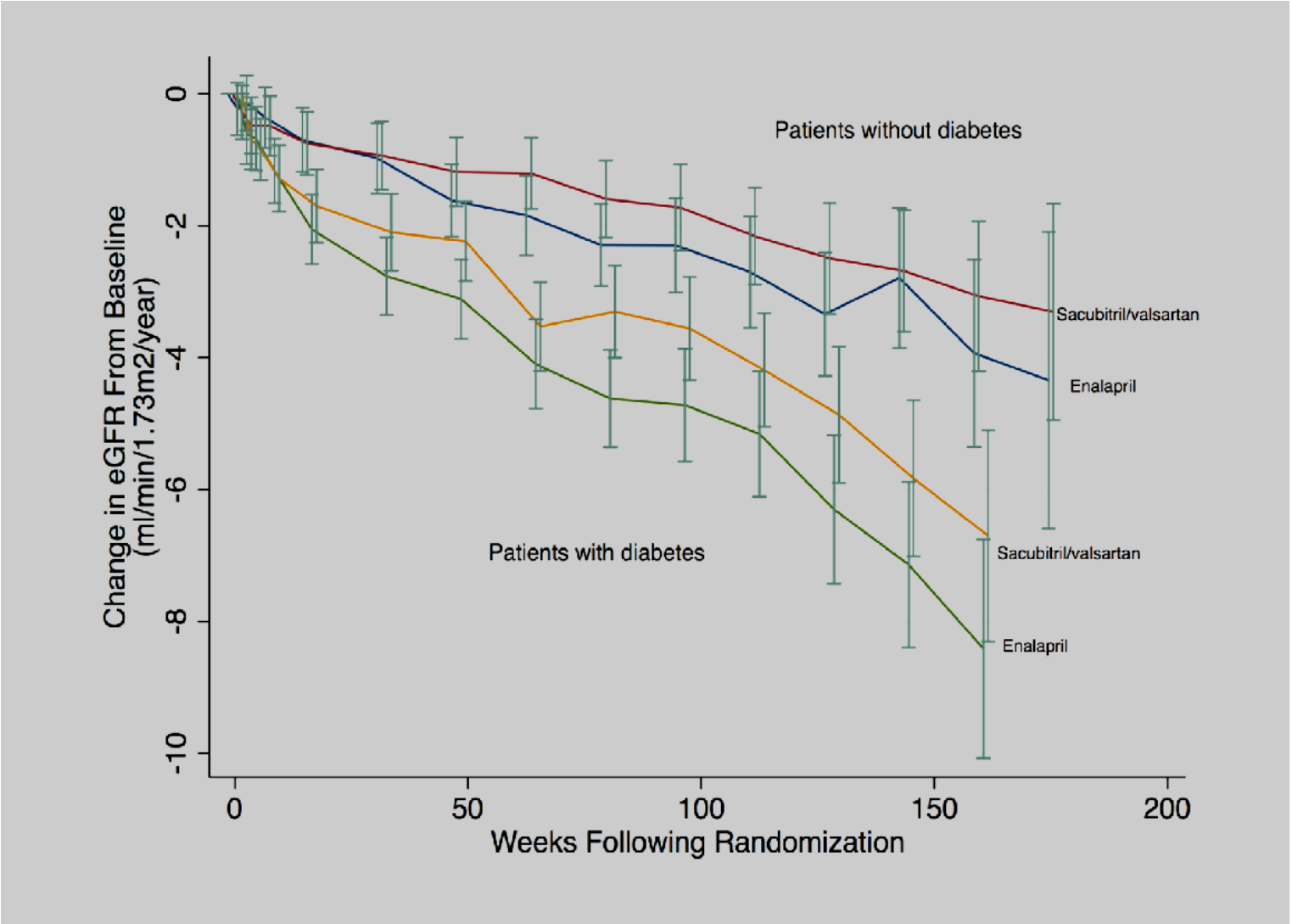
Number needed to treat 35 – to prevent all cause mortality

Table 2. Primary and Secondary Outcomes.*

Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	−2.99±0.36	−4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

McMurray, John JV, et al. N Engl J Med 371 (2014): 993-1004.

Rate of Change of Estimated GFR in Patients With and Without Diabetes Based on Treatment Assignment in PARADIGM



Packer M et.al. Lancet Diabetes and Endo 2018

An outline of current eGFR slope calculation practices and proposed solutions

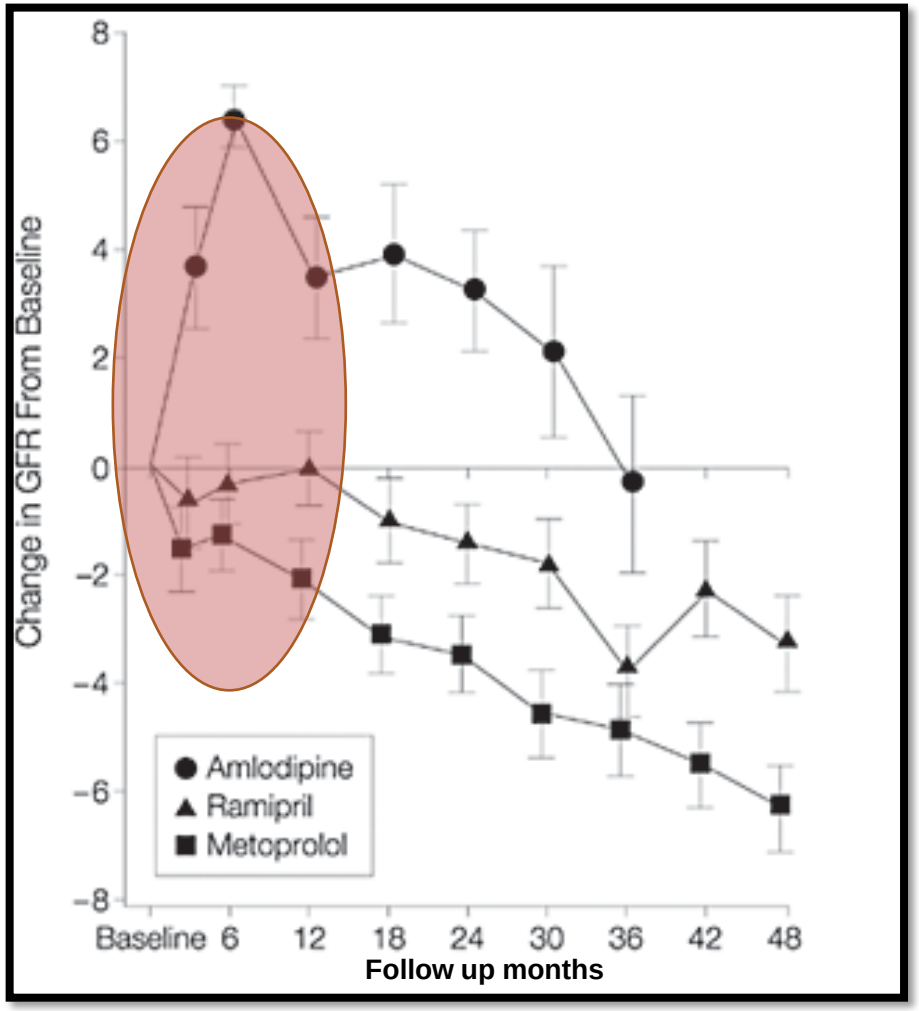
Practice	Pros	Cons	Solutions
eGFR slope as a marker	Can reliably assess CKD progression much earlier in the disease course compared with hard kidney outcomes	Variations with regards to calculation of eGFR values, inclusion of baseline variables, and loss to follow-up owing to long follow-up makes it difficult to compare data across trials; further, the nonlinear trajectory is often not accounted for, which limits its applicability to a population and is not representative of each individual	A framework to minimize current variations in calculation and statistical models used to calculate eGFR slope
Two-slope linear mixed effect model for calculating slope	Accounts for non-linearity and heteroscedasticity associated with earlier models; takes into account all phases of eGFR slope (i.e. short term effect, and total slope (both short and long term)) thereby giving a holistic picture of trajectory of eGFR over time	Variations exist, regarding inclusion or exclusion of initial short-term effect across trials	Need for further analyses to ascertain the most accurate way to compute eGFR slope consistently across trials
Short-term effect (initial decline in eGFR after intervention) in slope calculation	Shows the initial decline or attenuation of eGFR value by the intervention	Differs from the subsequent long term treatment effect and hence is not representative of the effects observed later in the trial	Inclusion of short-term effect is vital to curb confounding bias associated with exclusion of these values
Long-term effect in slope calculation	More representative of the attenuation of eGFR value by the therapeutic; consistently associated as a measure to evaluate kidney disease progression; calculation of only long term slope decreases the risk of false-negative short term effect	Only calculating long-term slope means excluding the values of initial eGFR decline and taking a post randomization value as a baseline to determine eGFR, leading to bias	Although the long-term slope is consistently used as a measure to evaluate kidney disease progression, excluding initial eGFR values associated with short-term effect can lead to bias, confounding results, and yield misleading conclusions
Total slope (short-term and long-term slope)	Gives an accurate analysis of the entire eGFR trajectory without excluding any values and calculating slope from baseline until the require follow-up	Requires greater follow-up, especially if there is an initial large negative short-term effect to minimize type I error	Calculation of total slope with longer follow-up duration to minimize type I error associated with initial negative short-term effect

Khan M et.al. JAMA Cardiol. doi:10.1001/jamacardio.2021.5151

Mean change in Glomerular Filtration rate*

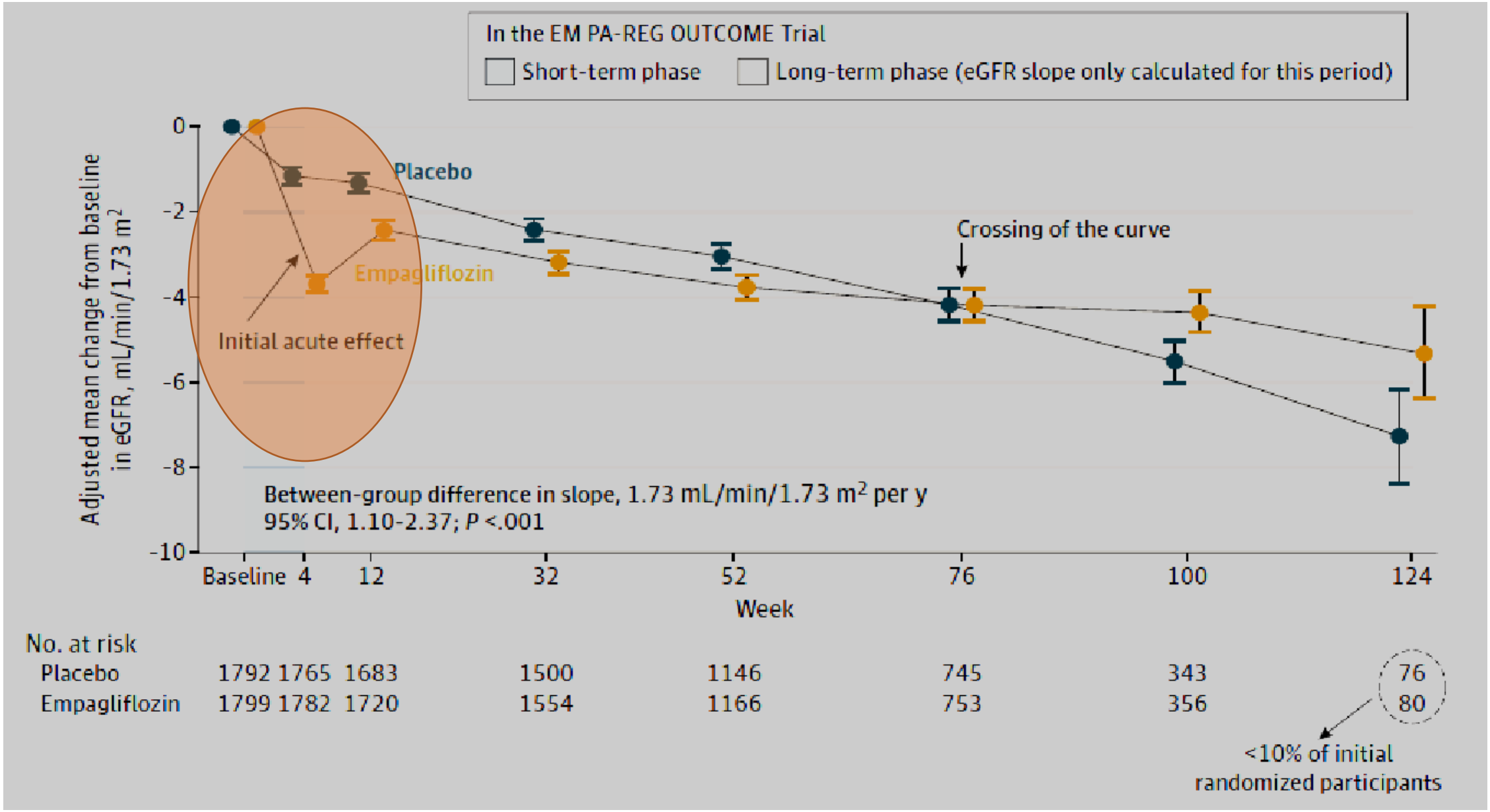
Natural History of GFR Change in the AASK

Three randomized groups from AASK trial



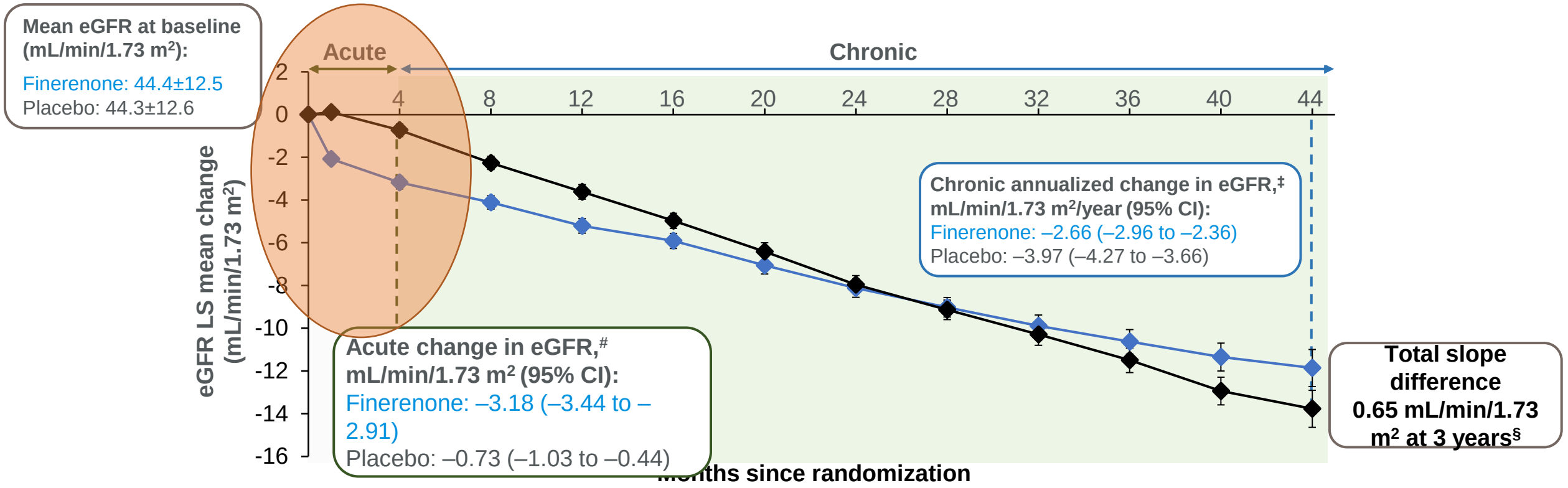
Wright JT Jr. et.al., JAMA 2002

*98 months for Amlopidipine and 48 moths for Ramipril and metoprolol



Khan M et.al. JAMA Cardiol. doi:10.1001/jamacardio.2021.5151

Finerenone also attenuated decline in eGFR* in FIDELIO-DKD



In FIDELIO-DKD, the effects of finerenone on eGFR slope translated into a significant benefit on the 57% eGFR secondary endpoint

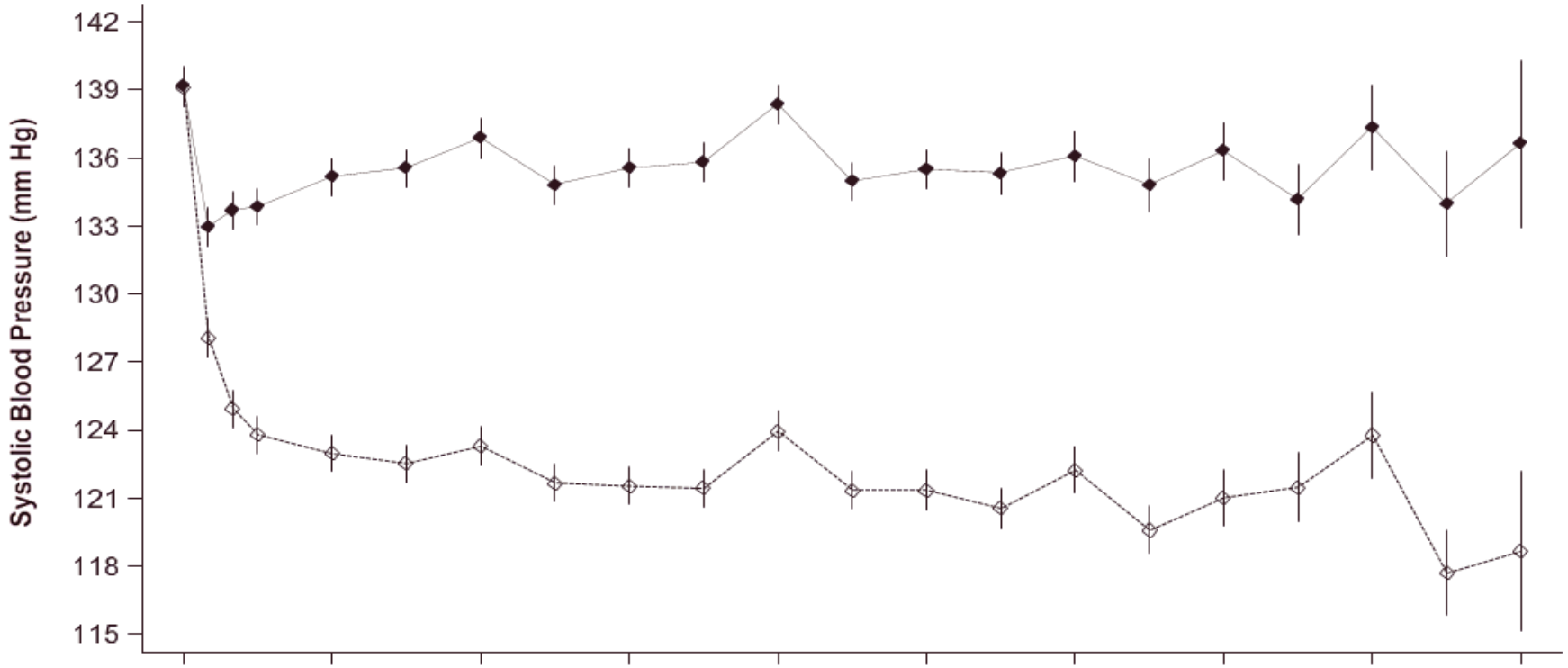
*Mixed model analysis of eGFR over time. Full analysis set; #LS mean change in eGFR slope from baseline to month 4; ‡LS mean change in eGFR slope from month 4 to the permanent discontinuation or end-of-study visit; §total slope data for UACR ≥30 mg/g from Vonesh model calculations
LS, least-squares; UACR, urine albumin-to-creatinine ratio

Bakris GL, et al. N Engl J Med 2020;383:2219–2229

Summary of Study prior to SPRINT evaluating BP on CKD Outcomes

Patients		Achieved mean arterial pressure during follow-up (mm Hg)		Main outcomes (intensified *vs* conventional blood-pressure control)		
		Intensified control	***Conventional control***	***End-stage renal disease***	***ΔGFR***	***Proteinuria***
Comparable ACE-inhibitor therapy in intensified and conventional blood-pressure control arms						
AASK	Non-diabetics	92	102	Similar	Similar	Similar
REIN-2	Non-diabetics	96	100	Similar	Similar	Similar
Intensified ACE-inhibitor therapy in intensified blood-pressure control group						
Captopril Tr.	Type 1 Diabetes	91	97	Similar	Similar	Reduced
MDRD	Non-diabetics	94	100	Reduced	Reduced	Reduced

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

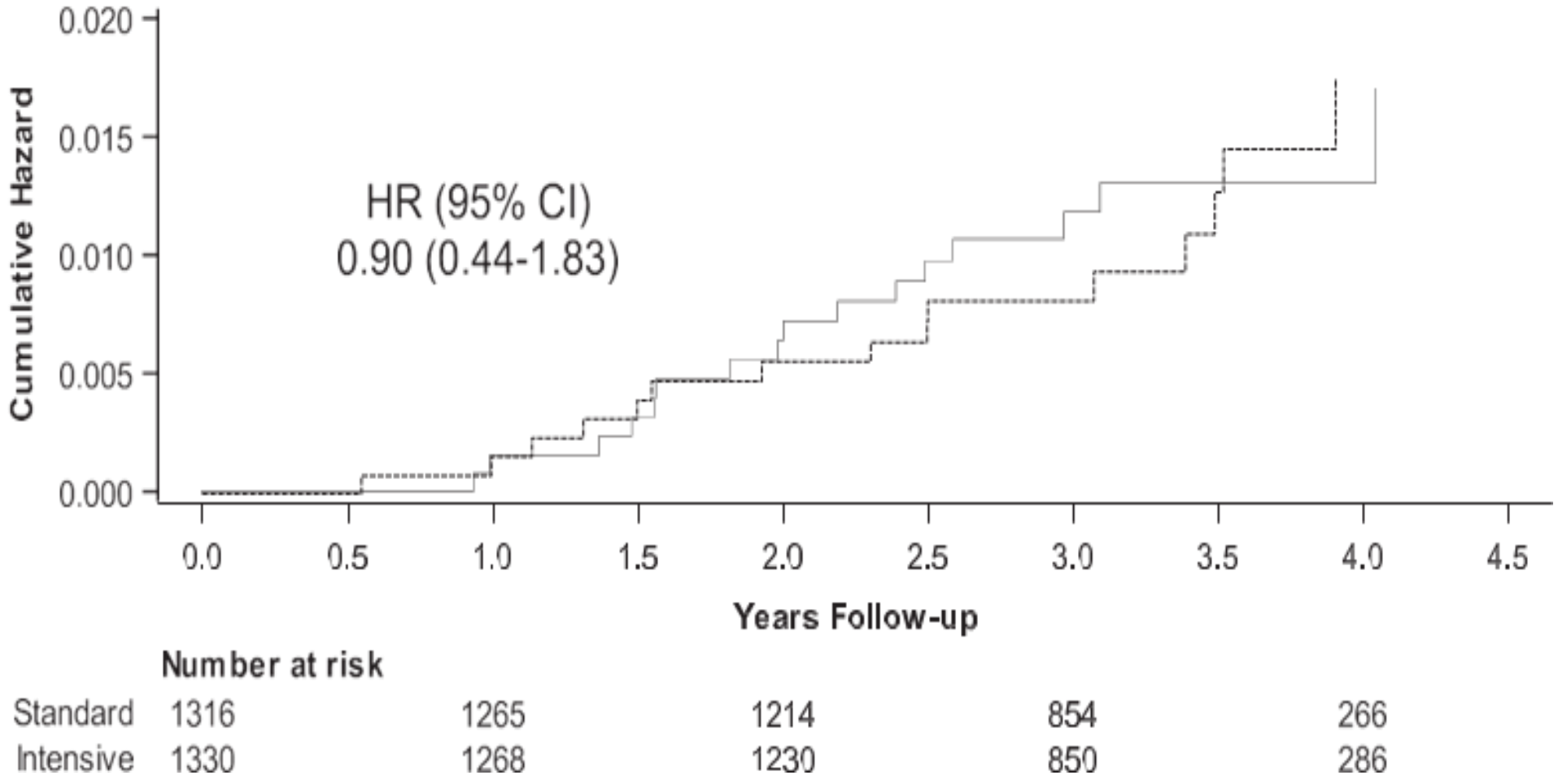


Number With Data										
Standard:	1316	1215	1156	1117	1087	1022	766	480	230	46
Intensive:	1330	1246	1194	1145	1136	1054	804	515	268	58
Mean Number of Meds										
Standard:	2.1	2.0	2.0	2.0	2.1	2.0	2.1	2.1	2.1	2.0
Intensive:	2.1	2.9	3.0	3.0	3.0	3.0	2.9	2.9	3.0	3.1

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



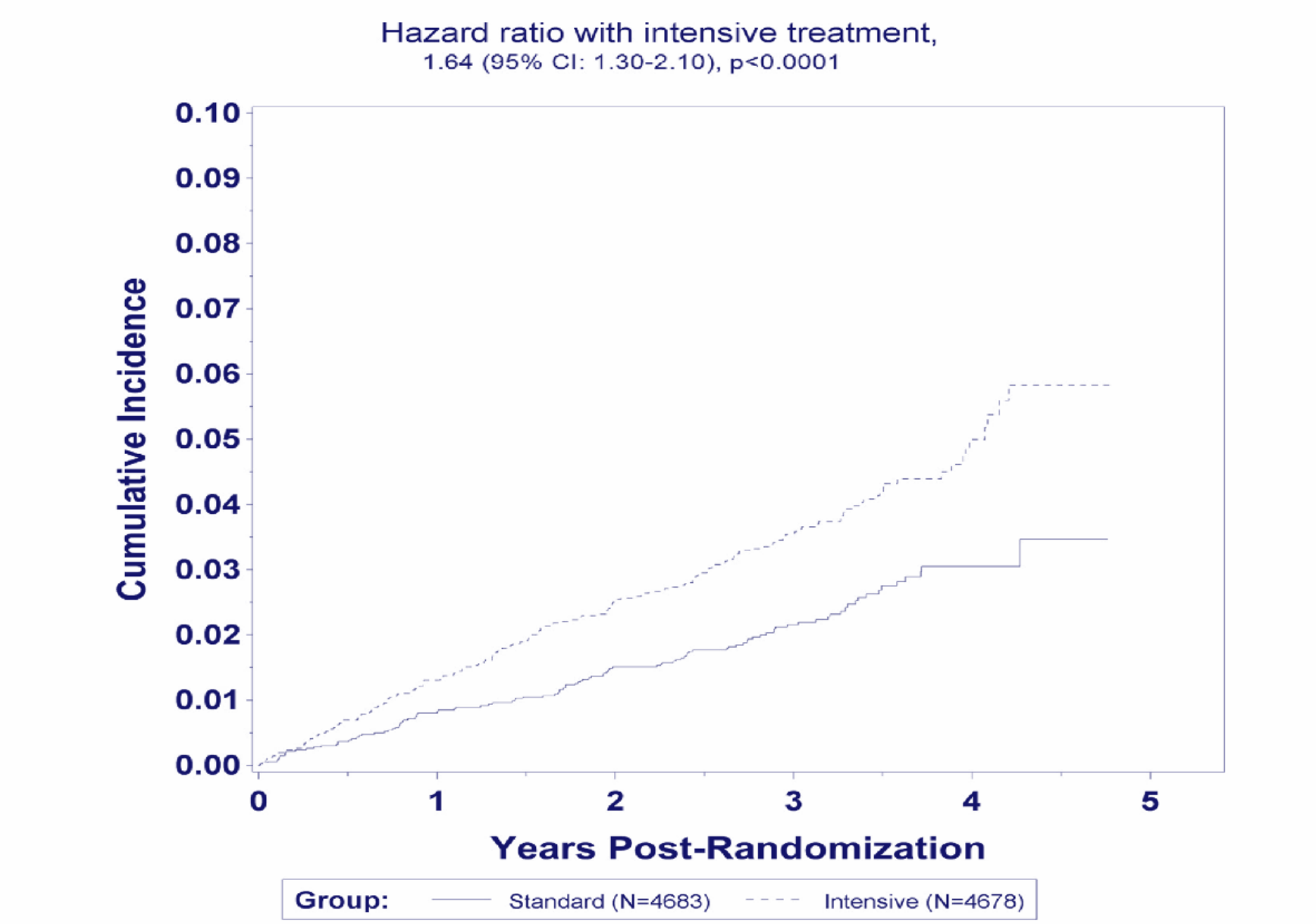
Cheung A et.al. J Am Soc Nephrol 2017

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) Value	*P*
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

Cumulative hazard plot for acute kidney injury.



Rocco, M. V., et al. (2018). Am J Kidney Dis 71(3): 352-361

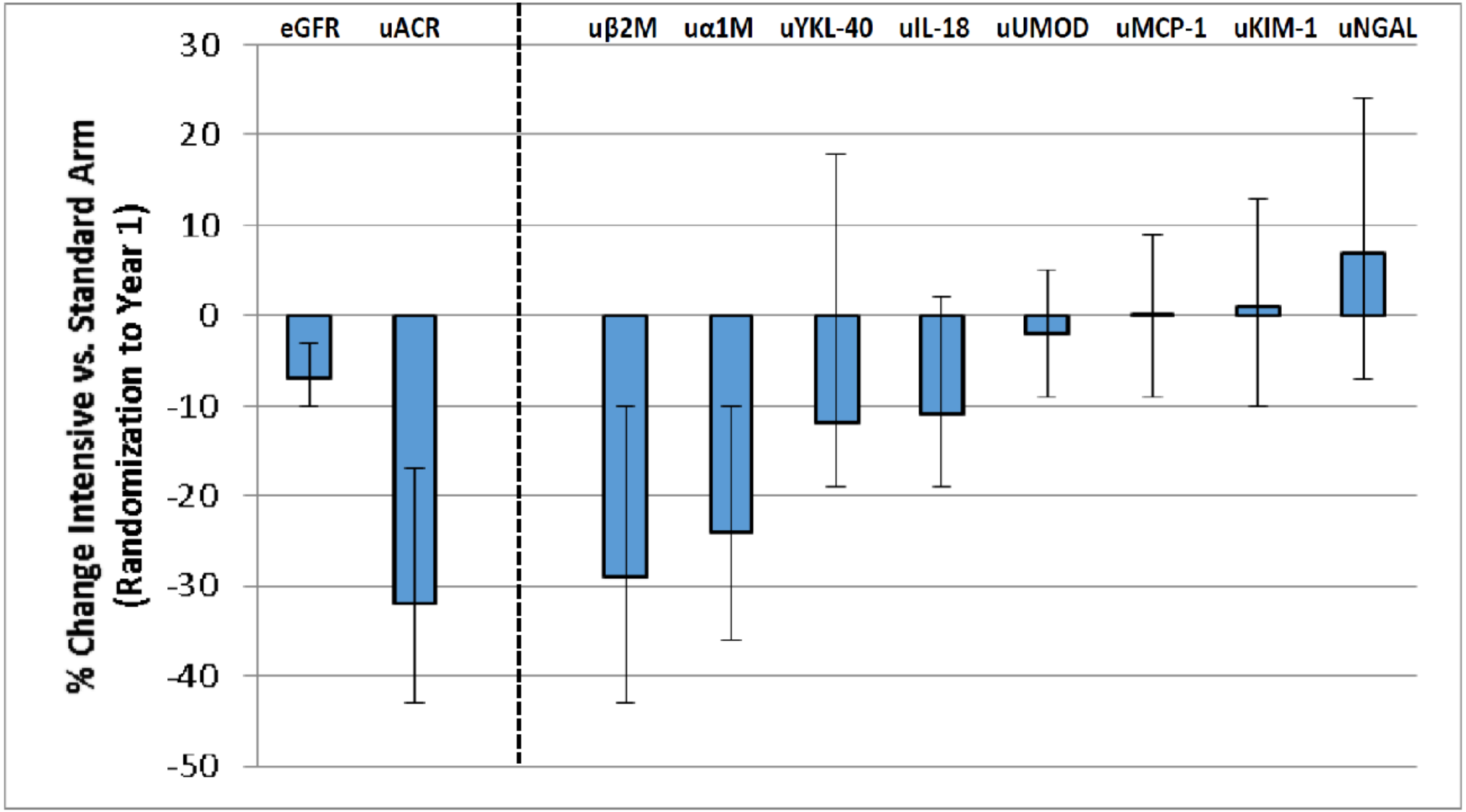
Changes in Kidney Function During and After the AKI Event Among Participants Stratified by Treatment Arm and Presence or Absence of CKD at Baseline

	Intensive Arm			
	Non-CKD (n = 82)	CKD	= 38)	CKD (n = 71)
AKI developed due to dehydration or intravascular volume depletion	60 (61.9%)		(63.6%)	61 (71.8%)
AKI developed due to hypotension		12 (34.4%)	10 (22.7%)	25 (29.4%)
ATN developed or was present during		31 (25.4%)	14 (31.8%)	18 (21.2%)
AKI developed due to medi	25 (25.8%)	37 (30.3%)	10 (22.7%)	17 (2.0%)

Over 85% resolved within 3-6 weeks

Rocco, M. V., et al. (2018). Am J Kidney Dis 71(3): 352-361

Percentage 1-Year Change Between Intensive BP Control vs. Standard Control for eGFR, Albuminuria and Urine Tubular Markers in Participants with CKD in SPRINT



Malhortra R et.al. Am J Kidney Dis 2019

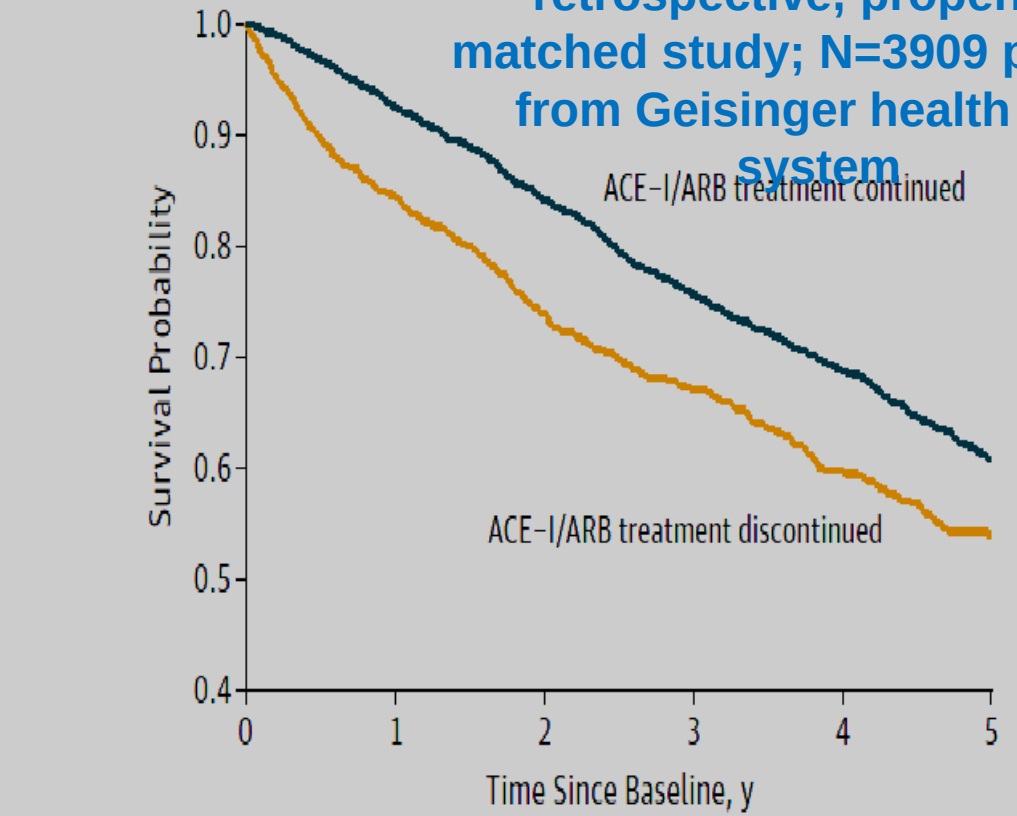
Conclusions of SPRINT BP AKI OUTCOMES

- More intensive BP lowering resulted in more frequent episodes of AKI.
- The majority of cases over 85% were mild Stage 1and most participants had complete recovery of kidney function within 3-6 weeks.

Rocco, M. V., et al. (2018). Am J Kidney Dis 71(3): 352-361

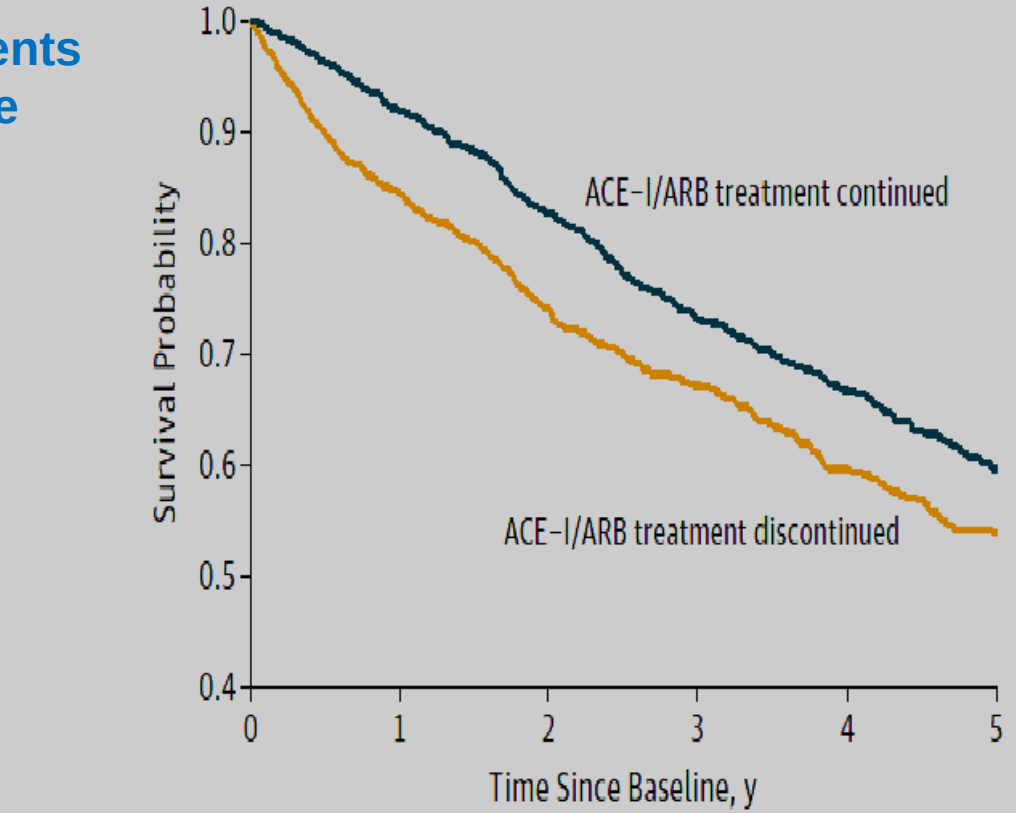
Cumulative Incidence of **All-Cause Mortality** by Angiotensin-Converting Enzyme Inhibitor (ACE-I) and Angiotensin II Receptor Blocker (ARB) Discontinuation Status

retrospective, propensity matched study; N=3909 patients from Geisinger health care system



No. at risk

Continued	2674	2244	1788	1406	1111	837
Discontinued	1235	910	687	524	390	298



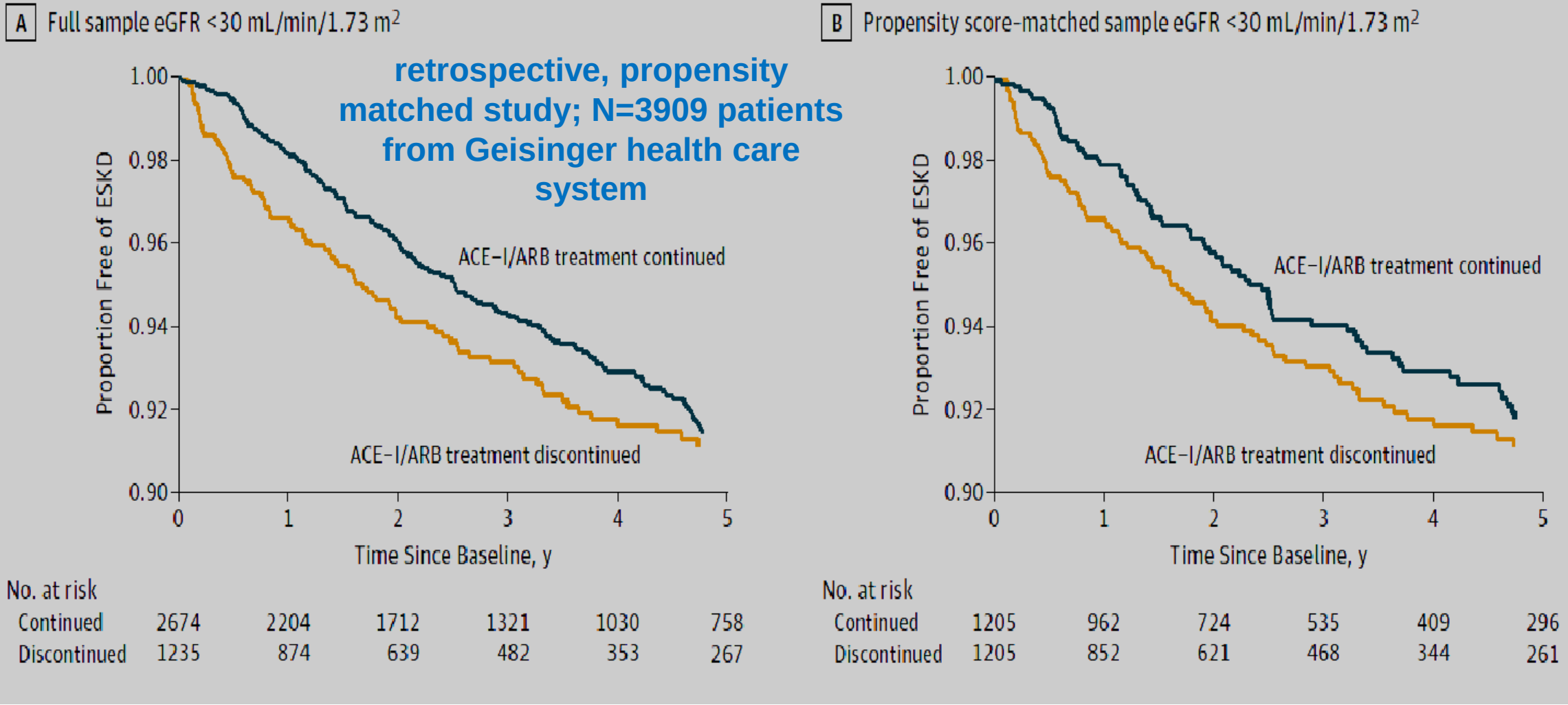
No. at risk

Continued	1205	983	759	574	442	328
Discontinued	1205	888	669	510	380	292

Qiao Y, Shin JI, Chen TK, et al. JAMA Intern Med. May 1 2020;180(5):718-726.

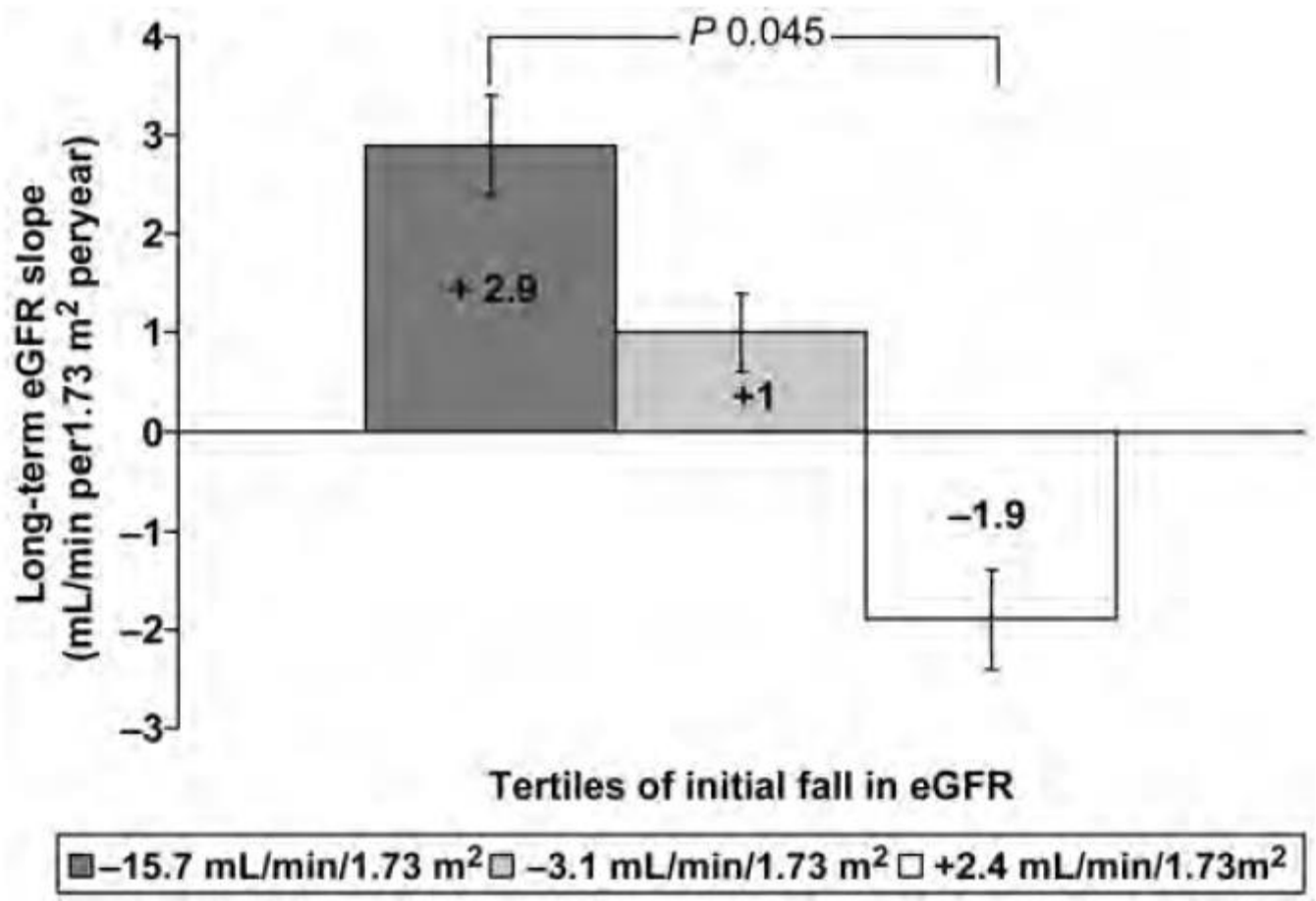
Cumulative Incidence of End-stage Kidney Disease (ESKD) Accounting for the Competing Risk of Death by Angiotensin-Converting Enzyme Inhibitor (ACE-I) and Angiotensin II Receptor Blocker (ARB) Discontinuation Status

retrospective, propensity matched study; N=3909 patients from Geisinger health care system



Qiao Y, Shin JI, Chen TK, et al. JAMA Intern Med. May 1 2020;180(5):718-726.

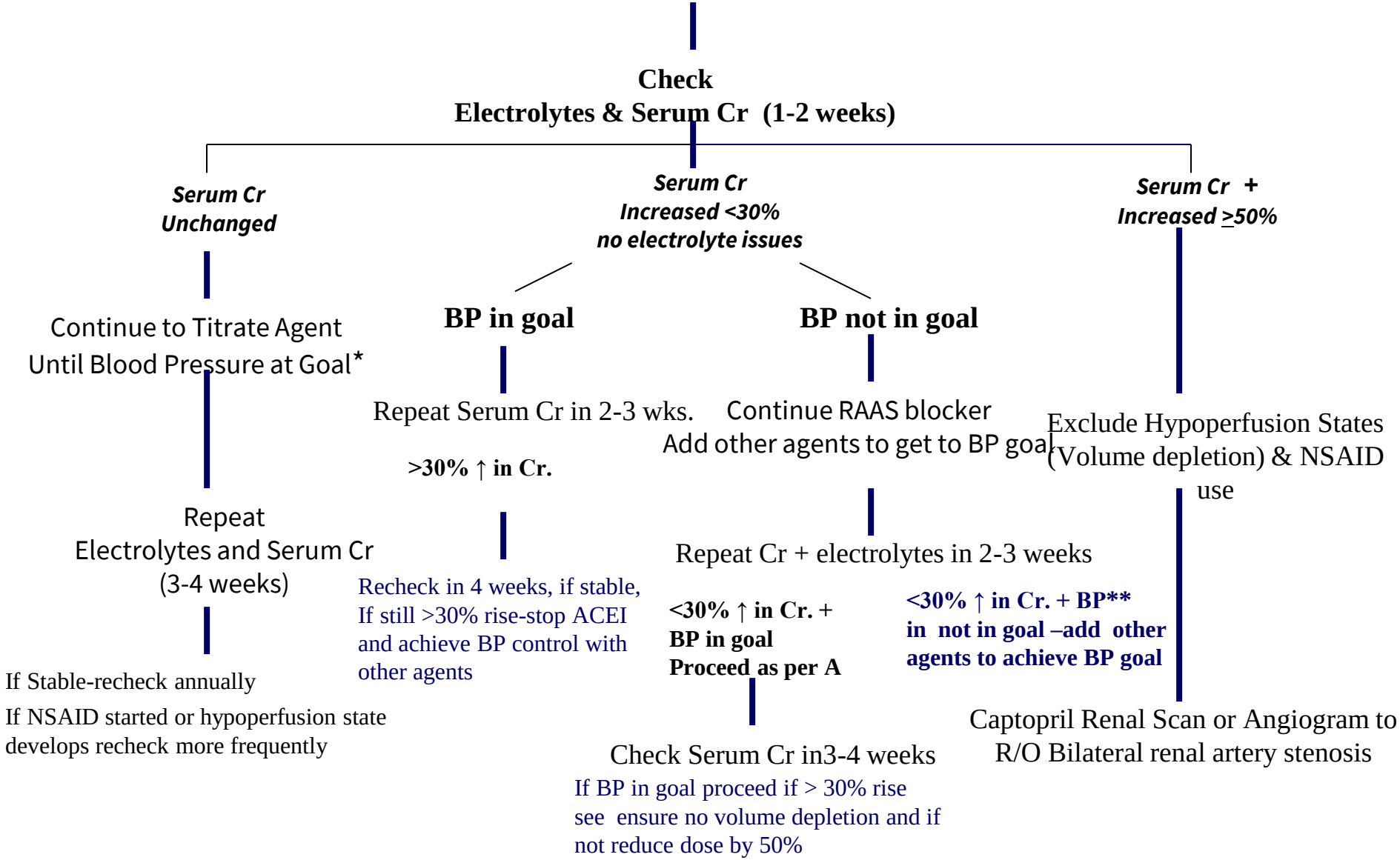
Spironolactone: Similar Effect



- Those with the biggest initial drop in eGFR post-spiro had the best 1 yr eGFRs

Morales, Enrique, et al.." Nephrology Dialysis Transplantation 28.2 (2013): 405-412.

ACE Inhibitor or ARB Started



Bakris G and Weir M Arch Intern Med 2000