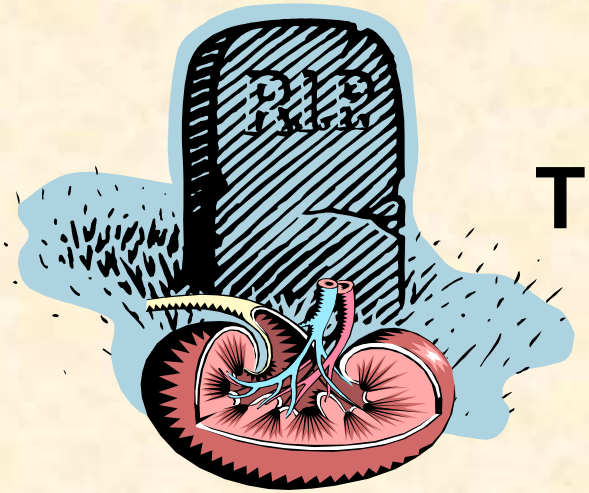
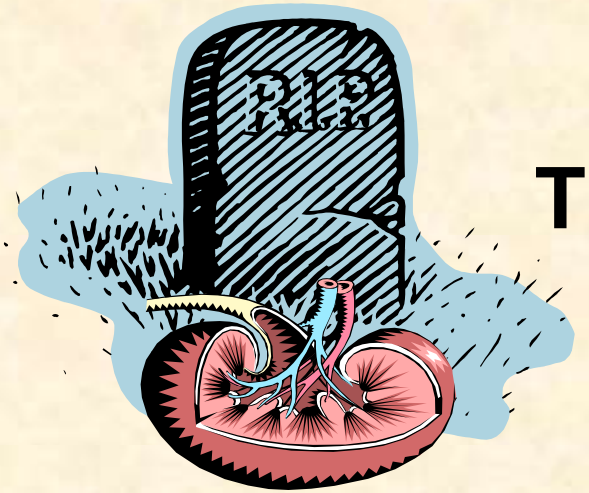


Top Ten Ways to Kill Kidneys

Harvey Feldman, MD, FCP, FASN
Professor, Physician Assistant Program
Nova Southeastern University
Ft. Lauderdale, FL



Top Ten Ways to Kill Kidneys

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Learning Objectives

1. Recognize the risks from fearful underutilization of cardiorenal protective interventions in patients with kidney disease.
2. Recognize pitfalls in diagnosing and shortcomings in managing chronic kidney disease early enough to prevent progression.
3. Avoid therapeutic inertia in the treatment of hypertension, especially with respect to the new BP targets.
4. Avoid mishandling of diuretics in the treatment of heart failure and RAAS blockers (ACEIs, ARBs) in patients with acute and chronic kidney disease.
5. Identify and avoid commonly encountered endogenous and exogenous nephrotoxins.

Which of the following cardiac patients would not benefit from an initial interventional strategy (coronary angiography and revascularization)?

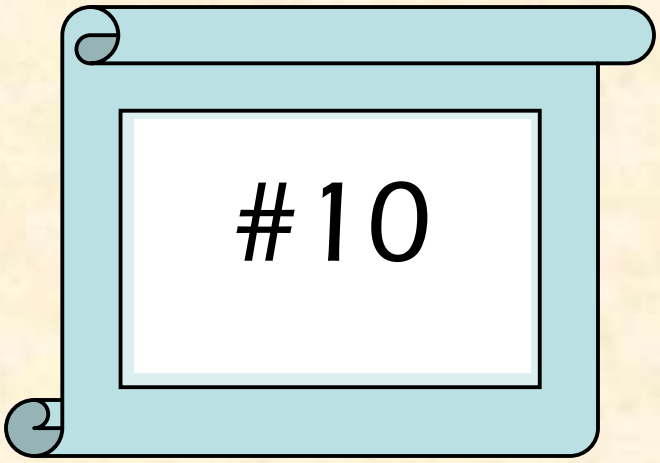
A. Acute ST-elevation myocardial infarction, stage 4 chronic kidney disease (eGFR 15-29 ml/min)
B. Non-ST-elevation acute coronary syndrome, stage 4 chronic kidney disease
C. Stable coronary artery disease with severe ischemia on a stress test, stage 4 chronic kidney disease
D. All of the above

True or False: A 65-year-old male with eGFR 50 ml/min undergoing contrast CT scan of the abdomen should receive prophylaxis against contrast-associated acute kidney injury.

A. True
B. False

Which of the following is a risk factor for renal cell cancer?

A. Diabetes
B. Hypertension
C. Obesity
D. Nephrolithiasis



Death by Renalism

Renalism

Underutilization of diagnostic and therapeutic interventions in patients with kidney disease out of concern that these interventions are more likely to do harm in this patient group.

Chertow GM et al. J Am Soc Nephrol 2004;15:2462-2468

Lower Use of Coronary Angiography in CKD

Authors	Presentation	Patients (*N*)	Angiography ± PCI (%) CKD vs. No CKD	
Chertow 2004	MI	57,284	25.2	46.8
Han 2006	NSTE ACS	45,343	47.6	73.8
Goldenberg 2010	NSTE ACS	13,141	49.9	67.8
Summer 2010	MI	57,477	33.2	58.4

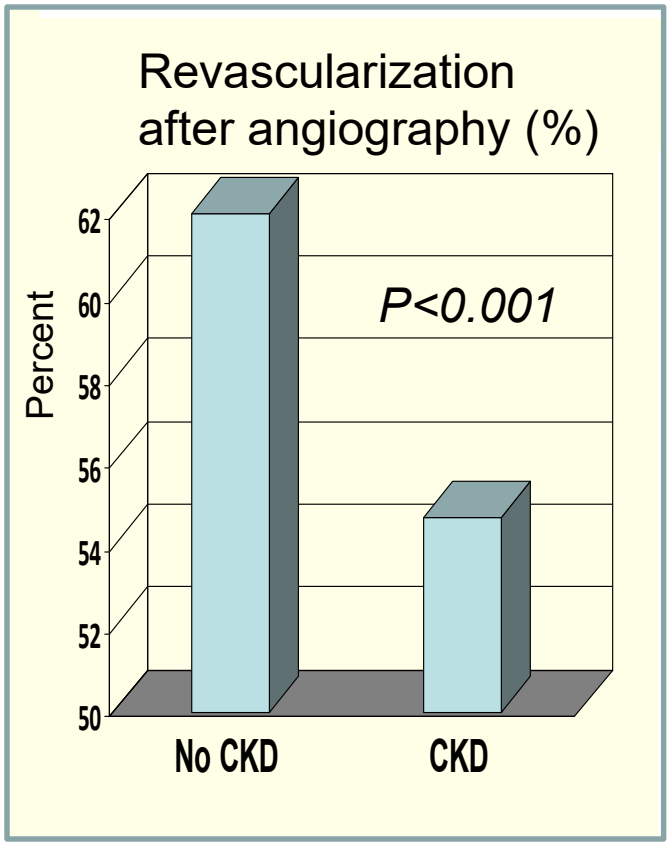
MI, myocardial infarction; NSTE ACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; NS, not specified

Chertow GM et al. J Am Soc Nephrol 2004;15:2462-2468
Weisbord SD. Clin J Am Soc Nephrol 2014;9:1823-1825

"Renalism": Inappropriately Low Rates of Coronary Angiography in Elderly Individuals with Renal Insufficiency

GLENN M. CHERTOW,* SHARON-LISE T. NORMAND,†‡ and BARBARA J. MCNEIL‡
*Division of Nephrology, Departments of Medicine, Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California; †Department of Health Care Policy, Harvard Medical School, Boston, Massachusetts; and ‡Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts

J Am Soc Nephrol 2004;15:2462-2468



1-year Mortality in CKD Patients (%)

	Overall	CABG	PTCA	PTCA + CABG
Angiography	26.7	23.4	14.3	29.8
No angiography	47.4	——	———	———

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

ISCHEMIA-CKD Trial

Management of Coronary Disease in Patients with Advanced Kidney Disease

and

Health Status after Invasive or Conservative Care in Coronary and Advanced Kidney Disease

N Engl J Med 2020; 382:1608-18. N Engl J Med 2020;382:1619-28.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Bangalore at the New York University Grossman School of Medicine, 550 First Ave., New York, NY 10016, or at sripalbangalore@gmail.com.

*A list of the members of the ISCHEMIA-CKD Research Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 30, 2020, at NEJM.org.

N Engl J Med 2020;382:1608-18.
DOI: 10.1056/NEJMoa1915925

ABSTRACT

PURPOSE

Assess the effect of revascularization vs. conservative medical management of patients with advanced chronic kidney disease and stable coronary disease with moderate to severe ischemia on stress testing.

CONCLUSION

There were no significant differences in death, myocardial infarction, or angina-related health status with an initially invasive strategy vs. a conservative strategy.

Lower Rates of Cardiorenal Protective Interventions Post-acute myocardial infarction in CKD Patients

Discharge Medications and Recommendations			
	CKD (%)	No CKD (%)	Adj. Odds Ratio
Beta blockers	84.7	83.8	1.01
Dietary modifications	69.8	73.5	0.94
Lipid-lowering drugs	79.1	80.6	0.93
Aspirin	86.9	90.7	0.82
Clopidogrel	46.5	56.9	0.87
Cardiac rehab referral	31.6	42.7	0.84
ACE inhibitor	59.8	61.1	0.76
Smoking cessation counseling	48.4	66.6	0.70

Han JH et al. Am J Med 2006;119:248-254

Contrast-Associated AKI and Use of Cardiovascular Medications after Acute Coronary Syndrome

Kelvin C.W. Leung, Neesh Pannu,† Zhi Tan,‡ William A. Ghali,*‡ Merril L. Knudtson,* Brenda R. Hemmelgarn,*‡ Marcello Tonelli,* and Matthew T. James*‡ for the APPROACH and AKDN Investigators*
Clin J Am Soc Nephrol 2014;9:1840–1848

Objective: Study relationship between contrast-associated AKI and subsequent use of prognosis-modifying cardiovascular medications (ACEIs/ARBs, beta blockers, and statins) 120 days after hospital discharge

Iatrogenic Cardio-Nephrocide after CA-AKI in ACS Patients

Use of cardiovascular medications after CA-AKI*			
	Statins Odds Ratio	**Beta-blockers** Odds Ratio	**ACEI/ARB** Odds Ratio
All participants			
No CA-AKI	Reference	Reference	Reference
CA-AKI Stage 2/3	0.44	0.46	0.34 (Stg 1: 0.65)
Prior medicine use			
No CA-AKI	Reference	Reference	Reference
CA-AKI Stage 2/3	0.30	0.41	0.32

*Use within 120 days following hospital discharge

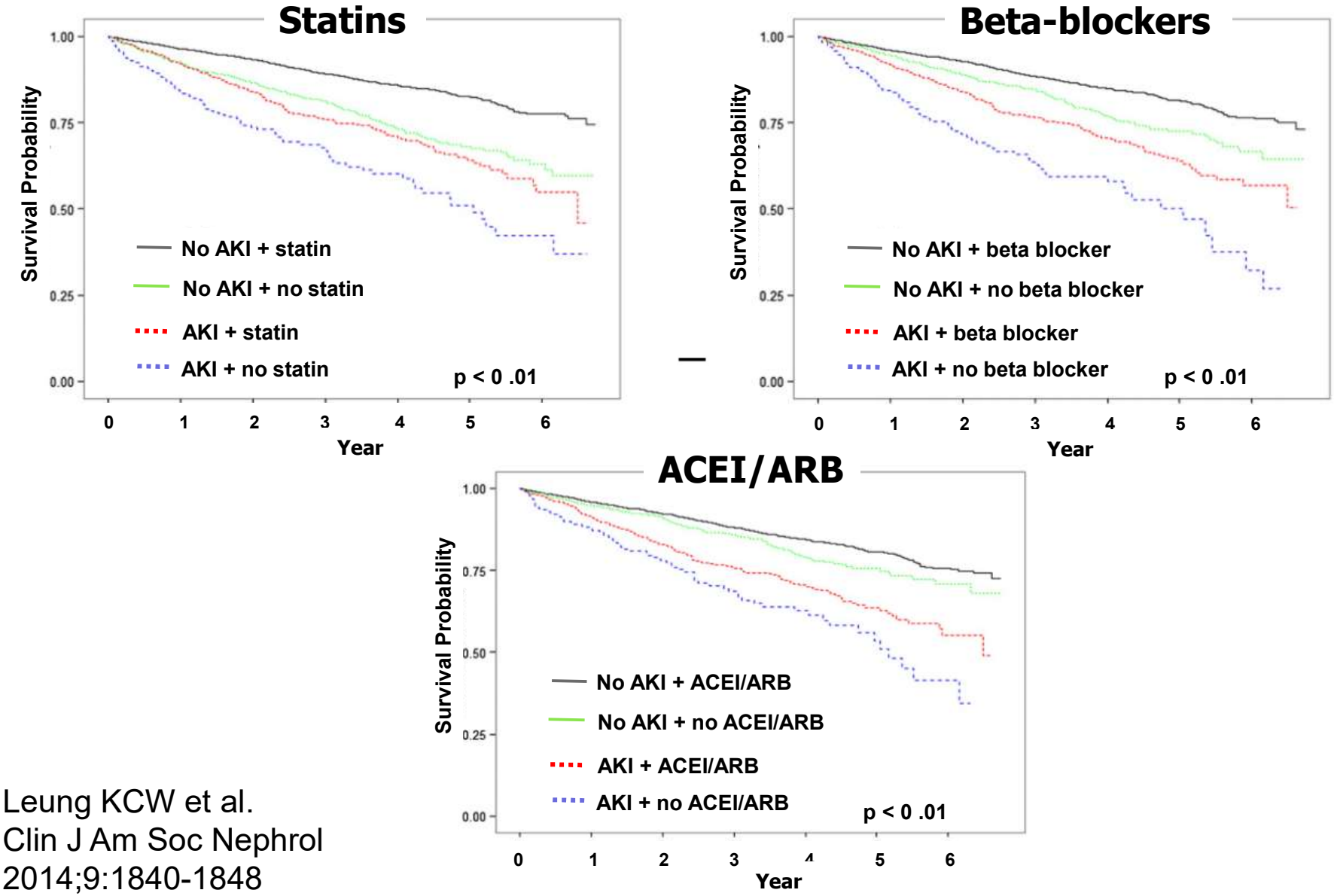
Leung KCW et al. Clin J Am Soc Nephrol 2014;9(Nov):1840-1848

Iatrogenic Nephrocide in Proteinuric Patients with CA-AKI

Use of ACEIs or ARBs after CA-AKI	
	ACEI/ARB Odds Ratio
No AKI	Reference
AKI Stage 1	0.62
AKI Stage 2/3	**0.20**

Leung KCW et al. Clin J Am Soc Nephrol 2014;9(Nov):1840-1848

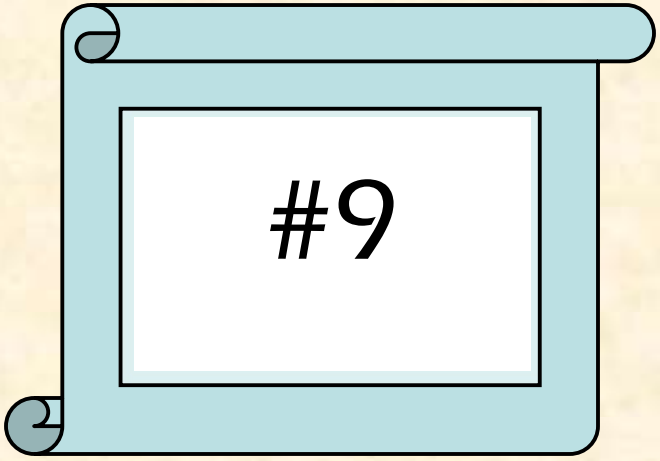
Iatrogenic Homicide after CA-AKI in ACS Patients



Leung KCW et al.
Clin J Am Soc Nephrol
2014;9:1840-1848

Summary on Death by Renalism

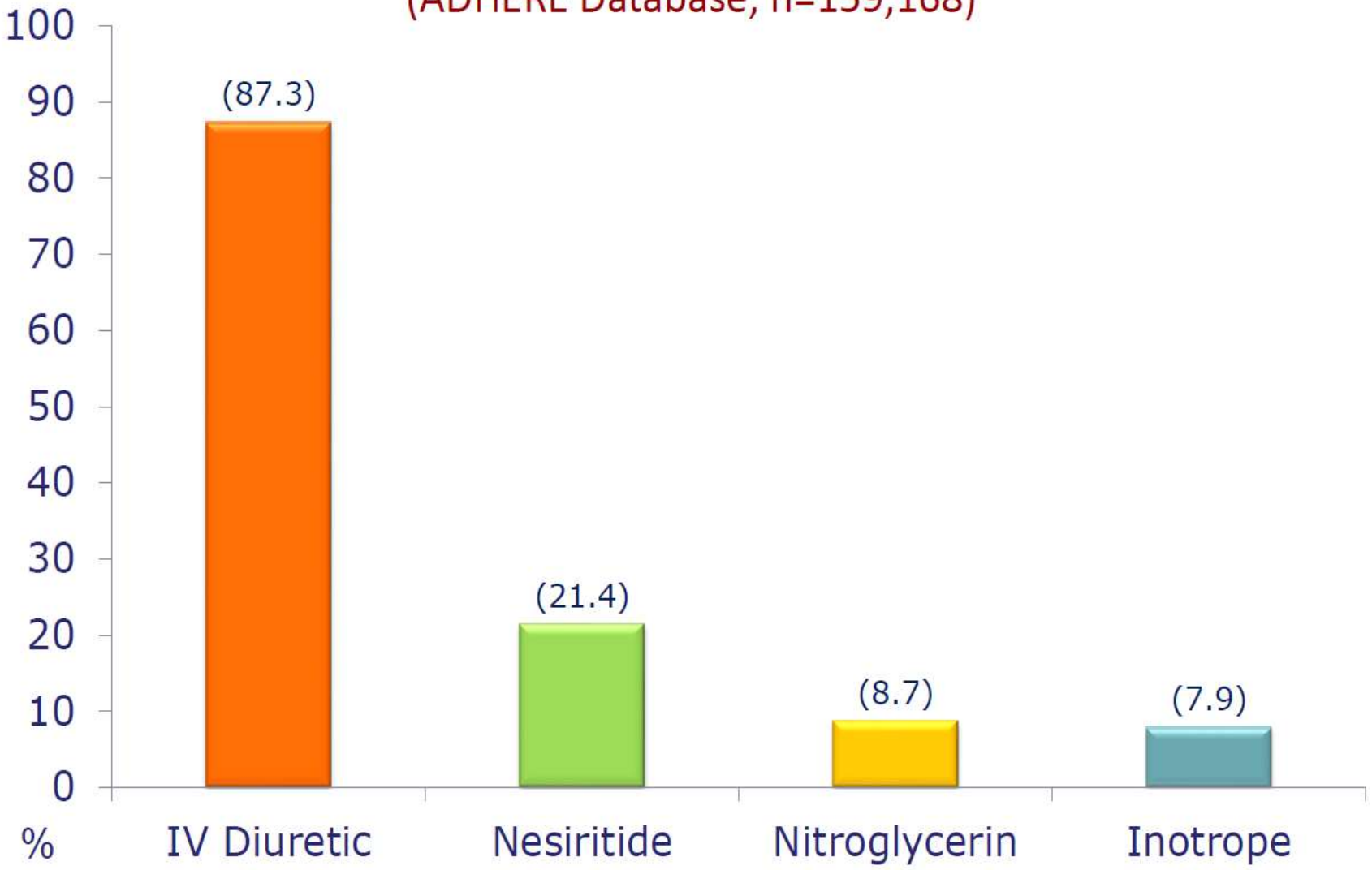
- Clinicians are underutilizing cardiac and renal-protective interventions in patients with both chronic and acute kidney disease
- Underutilization is misguided
  - KD patients are at highest risk and would benefit the most from these interventions
- **Renalism must die before your patients do!**



Inappropriate use of diuretics in heart failure due to fear of worsening renal function

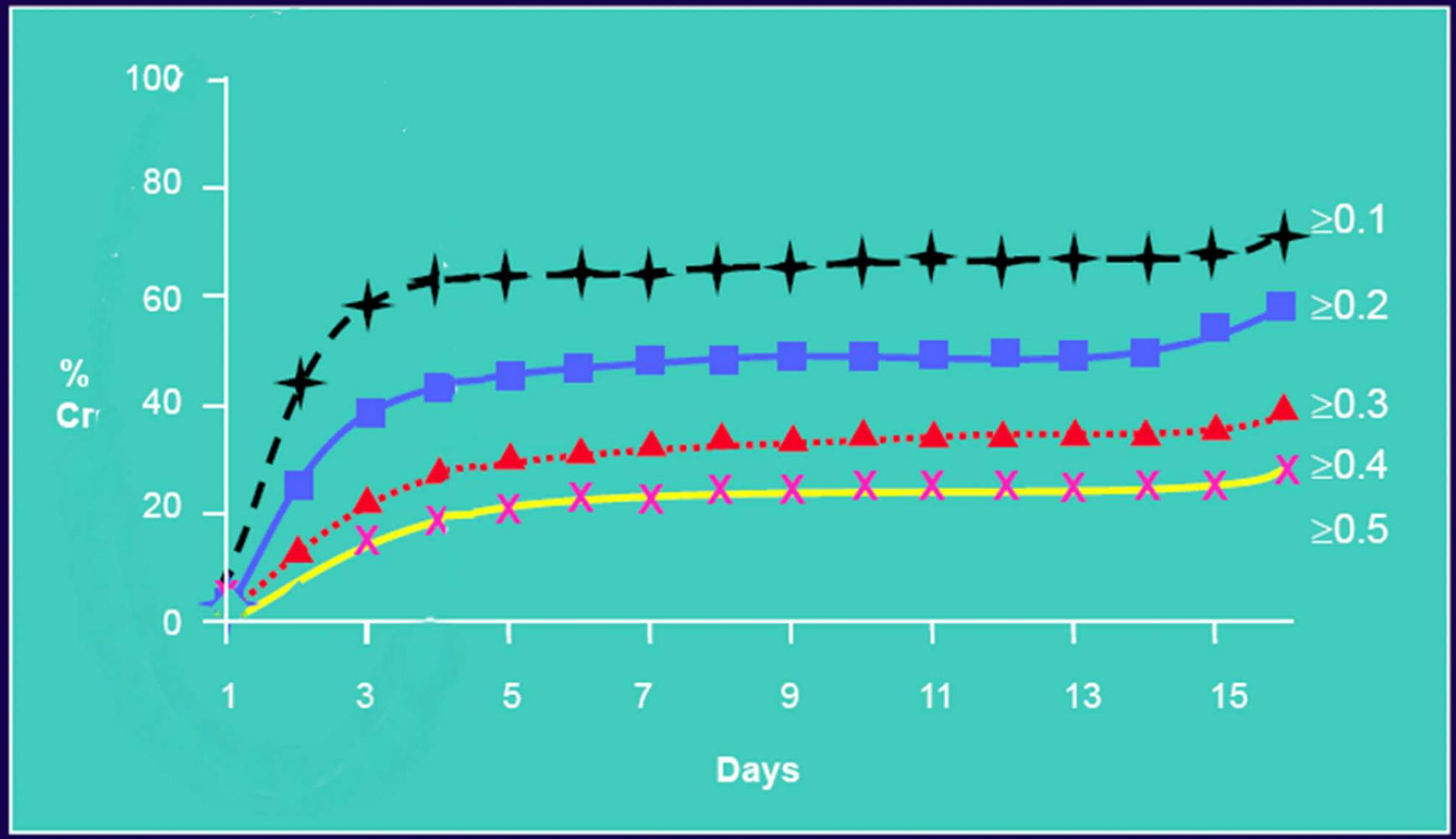
Contemporary Treatment of ADHF

(ADHERE Database, n=159,168)



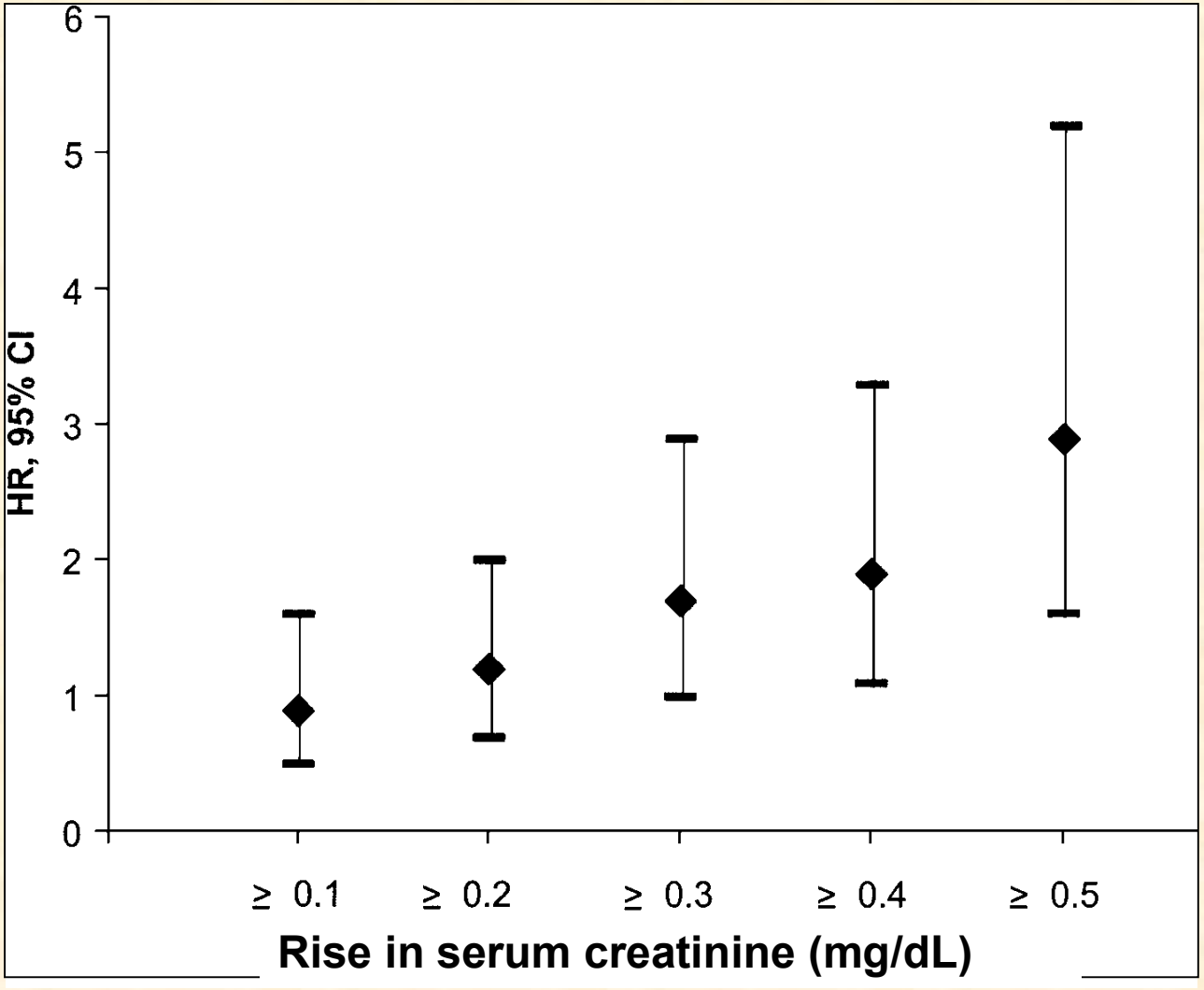
Fonarow GC et al (ADHERE Registry). Am Heart J 2007;153:1021-8

Time Course of Development of Increasing Creatinine in Hospitalized HF Patients



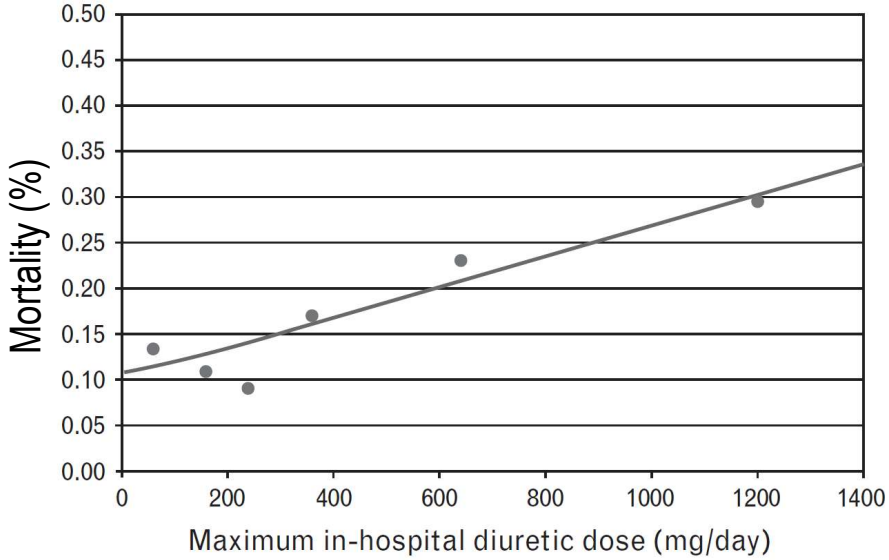
Cr, serum creatinine. Gottlieb SS et al. J Card Fail. 2002;8:136. Smith G, J Card Fail. 2003 Feb;9(1):13-25

Mortality Risk of Acute Kidney Injury in Acute Decompensated Heart Failure

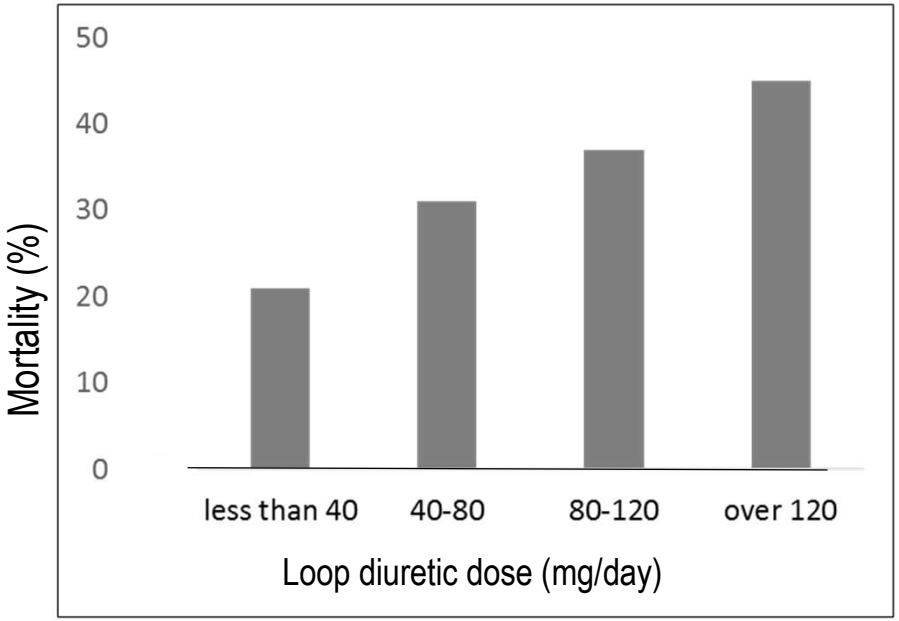


Smith GL et al. J Card Fail 2003;9(1):13-25

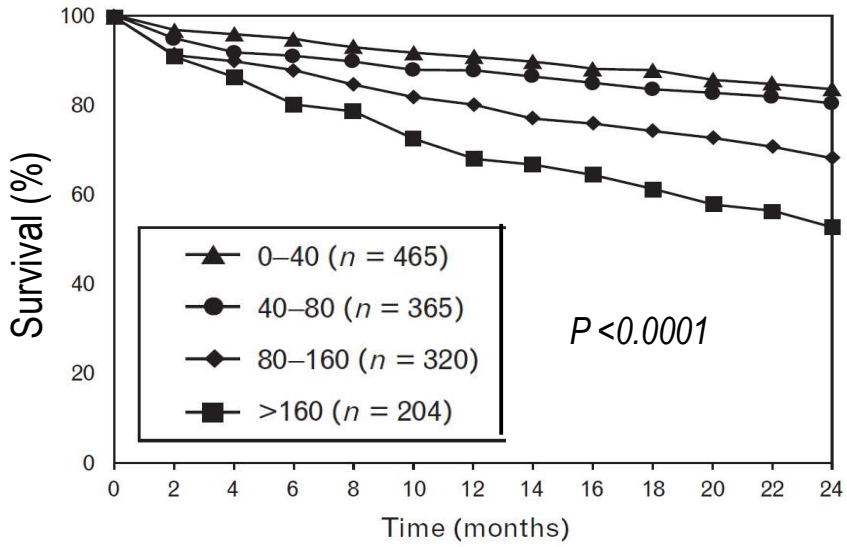
Loop diuretic dose directly associates with increased mortality in heart failure.



Hasselblad V et al. Eur J Heart Fail 2007;9:1064–69.



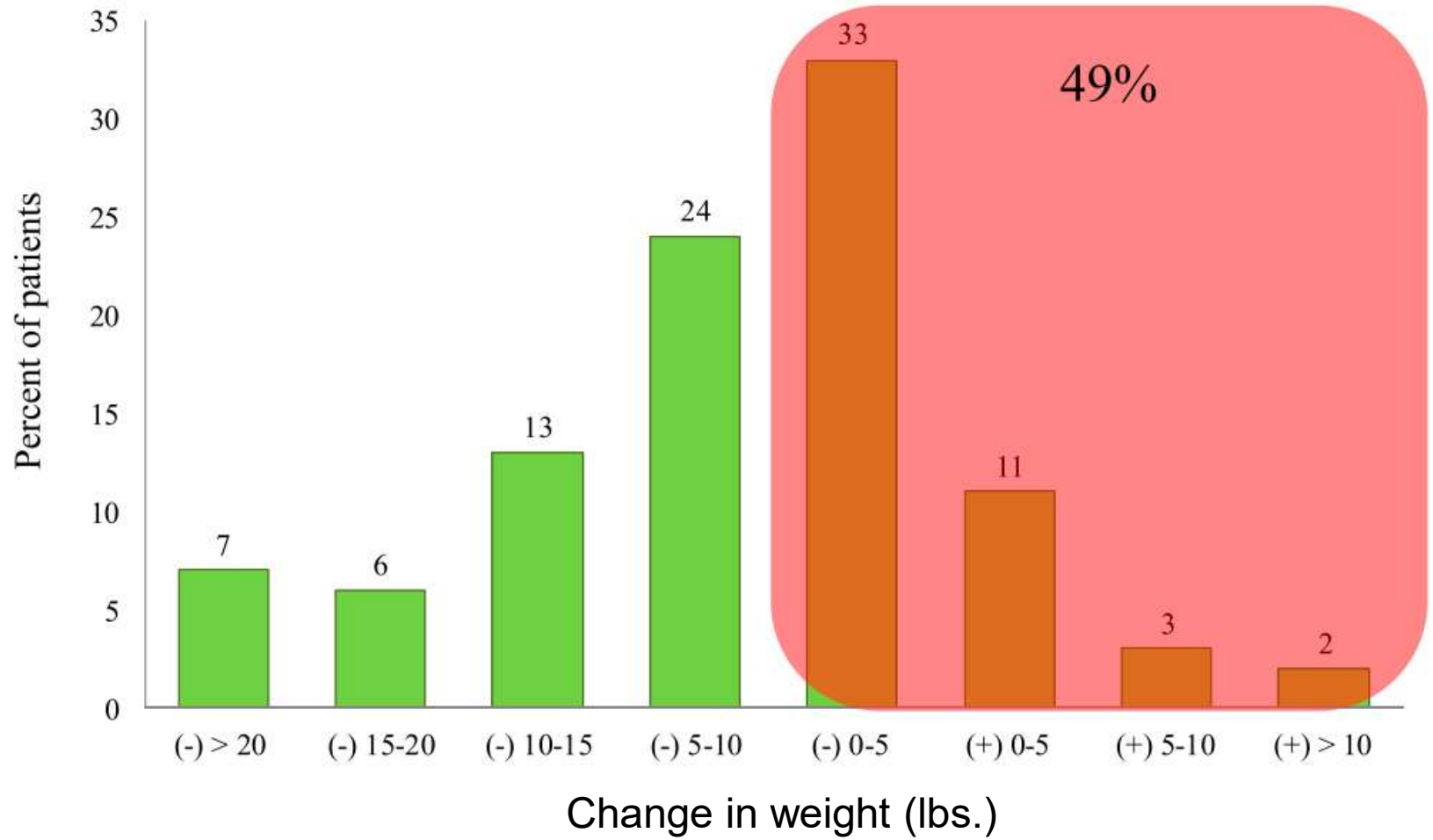
Neuberg GW et al. Am Heart J 2002;31-38



Eshaghian S at al. Am J Cardiol 2006; 97:1759–1764.


Aggressive Diuretic Use
in Acute Decompensated
Heart Failure is BAD!!

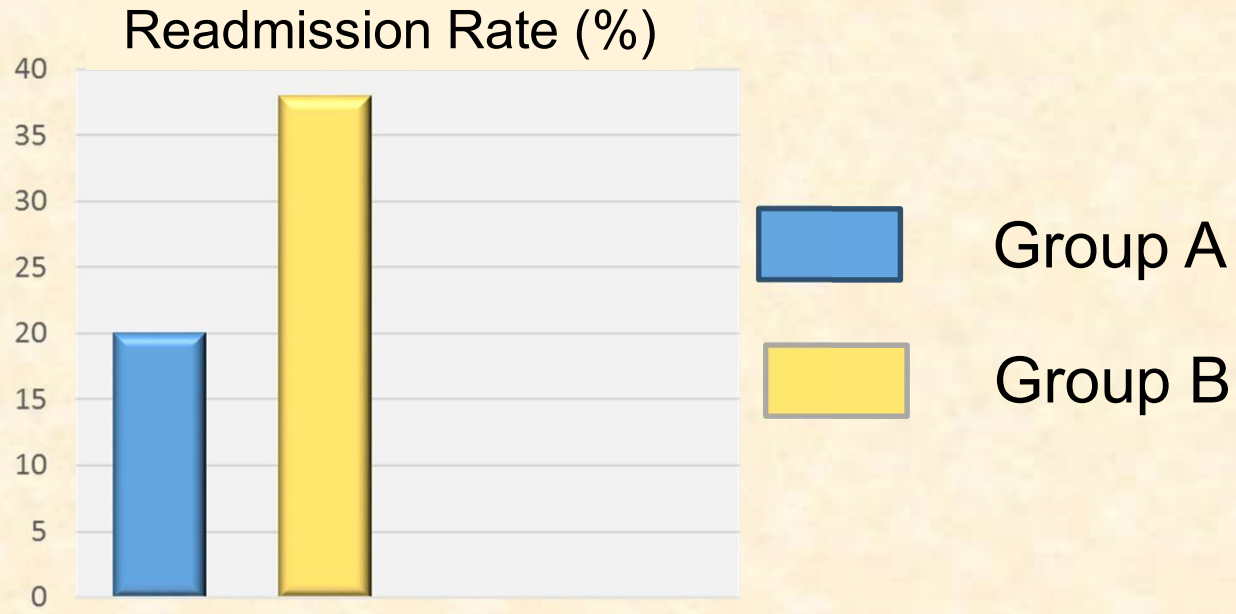
Diuretics in Acute Decompensated Heart Failure (ADHF National Registry)



Kazory A. Clin J Am Soc Nephrol 2013;8:1816-1828.

Discharge Diuretic Dose and 30-day Readmission Rate in ADHF

- Multicenter retrospective cohort study
- 131 patients with discharge dx of HFrEF
  - All were on chronic loop diuretics prior to admission
  - 50 discharged with increased loop diuretic dose (group A)
  - 81 discharged with no change or decreased dose (group B)



Woodruff AE et al. Ann Pharmacother 2016;50:437-45

Diuretics – the double-edged sword in the treatment of heart failure

Reduced pulmonary congestion

↓

Improved CO and renal function

Volume contraction

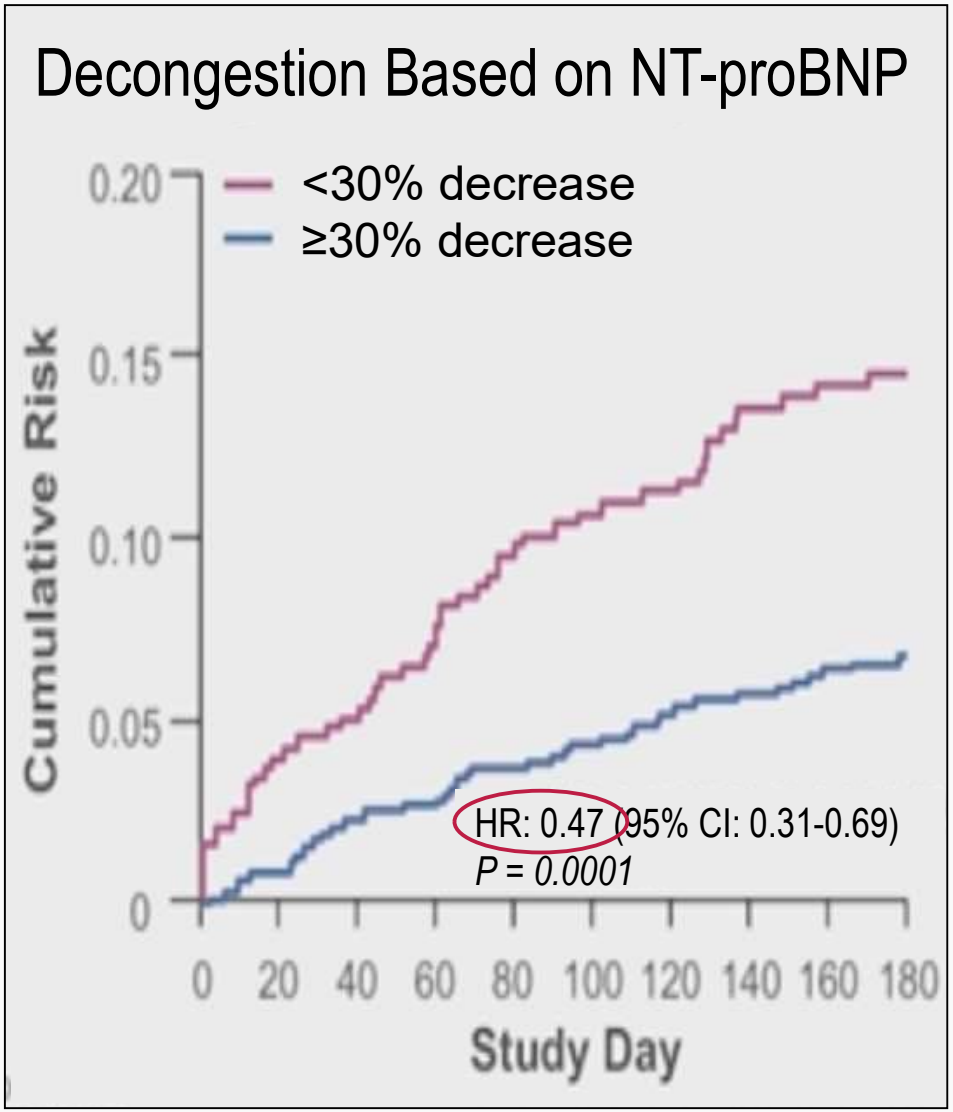
↓

Electrolyte imbalance

+

Worsening renal function

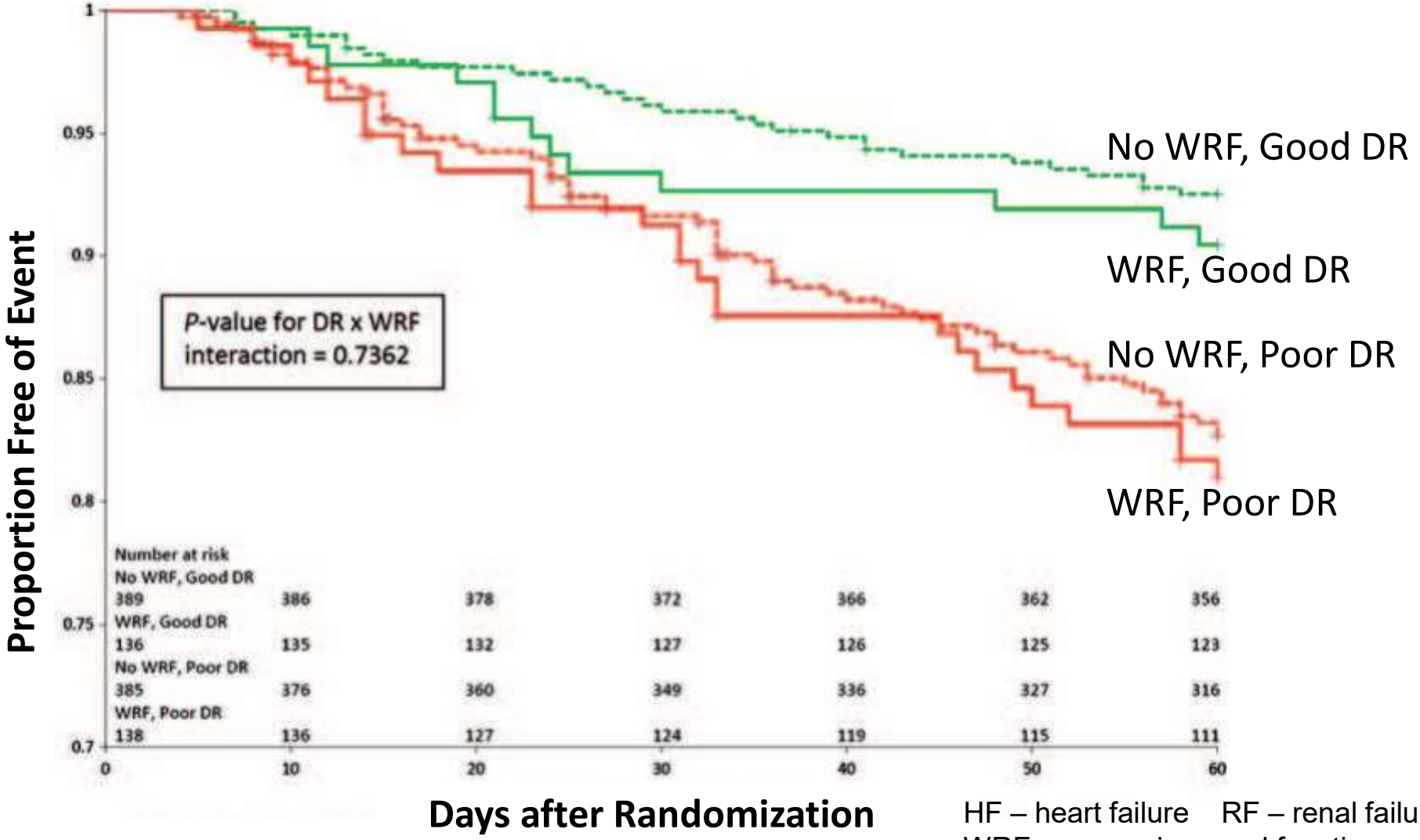
Failure to Decongest in ADHF Increases Risk of All-Cause Mortality through Day 180



Metra M et al. RELAX-AHF Trial. J Am Col Cardiol 2013;61:196-206

RELAX-AHF Trial

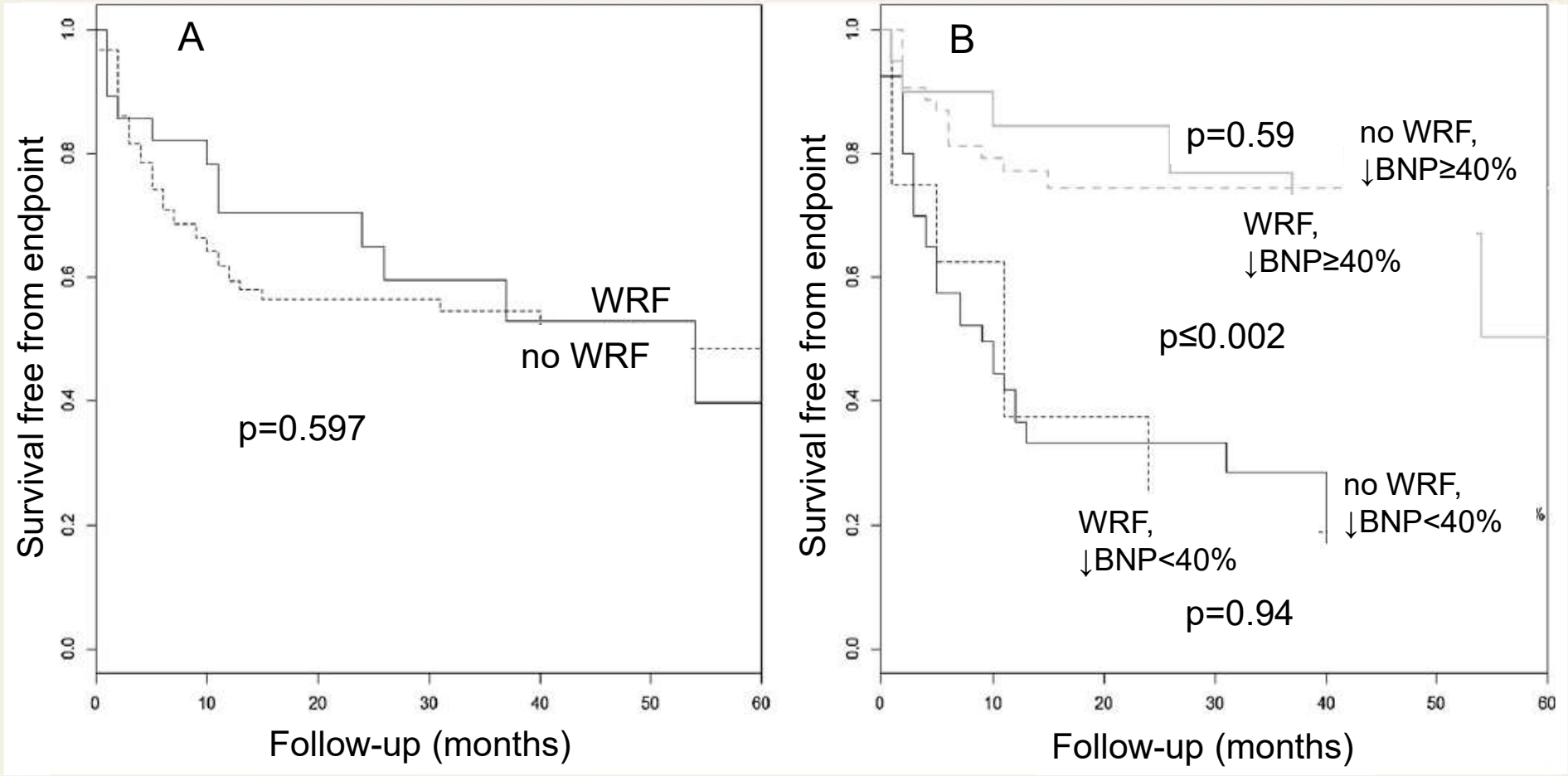
Event: Death or HF/RF readmission through day 60



HF – heart failure RF – renal failure
WRF – worsening renal function
DR – diuretic response

Voors AA et al. Eur J Heart Fail 2014;16:1230-40

Prognostic Impact of BNP in Patients with ADHF with and without In-Hospital Worsening Renal Function



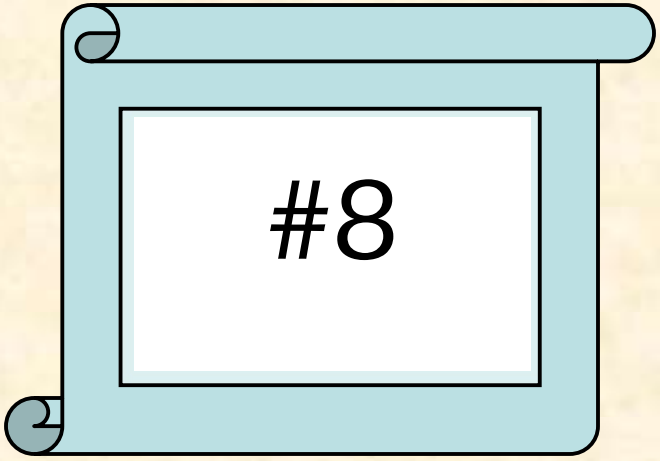
Endpoint: Combination of death/urgent heart transplantation and re-hospitalization for ADHF

A. Survival free from combined endpoint according to worsening renal function (WRF)
B. Survival free from combined endpoint according to change (Δ) in BNP and WRF

Stolfo D et al. Heart Lung Circ 2017;26:226-

American College of Cardiology/American Heart Association Heart Failure Guideline

- The goal of diuretic therapy is to eliminate clinical evidence of fluid retention (↑JVD, edema) even if this leads to asymptomatic reduction in renal function.

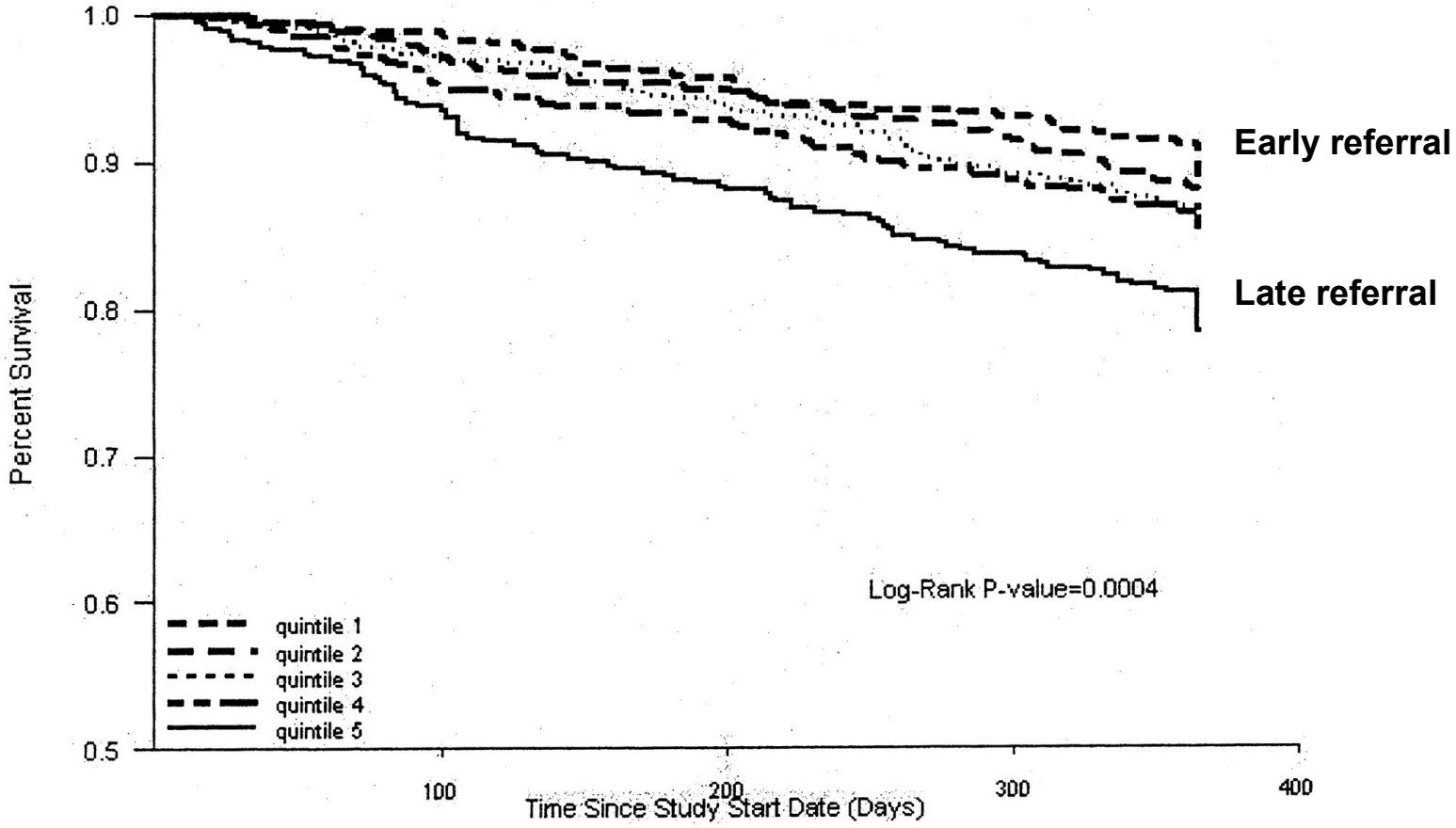


Failure to recognize early CKD due to pitfalls in interpreting tests of renal function

↓

Delayed CKD management

Kaplan-Meier curve comparing percentage survival among quintiles of PS



Kazmi, W. H. et al. Nephrol. Dial. Transplant. 2004 19:1808-1814;

CKD is often not recognized by patients or their clinicians

- 90% of people with CKD are unaware they have it
- 48% of people with **severely** reduced kidney function are unaware they have CKD

Primary care clinicians are not diagnosing chronic kidney disease!

Kidney disease undiagnosed in majority of type 2 diabetics

- NKF cross-sectional study: “Awareness, Detection and Drug Therapy in Type 2 Diabetes Mellitus and CKD”
  - 9,307 patients in 466 primary care practices in the U.S.
- **Main finding: Only 12.1% of the 5,036 patients with CKD were diagnosed by their primary care practitioner!**
  - 1.1% in Stage 1 CKD
  - 4.9% in Stage 2 CKD
  - 18.0% in Stage 3 CKD
  - 52.9% in Stage 4 CKD
  - 58.8% in Stage 5 CKD

Szczech LA et al. PLoS One 2014;9(11):e110535; doi:10.1371

JAMA Network | Open 2019;2(12):e1918169

Original Investigation | Nephrology

Clinical Characteristics of and Risk Factors for Chronic Kidney Disease Among Adults and Children

An Analysis of the CURE-CKD Registry

Katherine R. Tuttle, MD; Radica Z. Alicic, MD; O. Kenrik Duru, MD; Cami R. Jones, PhD; Kenn B. Daratha, PhD; Susanne B. Nicholas, MD, MPH, PhD; Sterling M. McPherson, PhD; Joshua J. Neumiller, PharmD; Douglas S. Bell, MD; Carol M. Mangione, MD; Keith C. Norris, MD, PhD

- 2.6 million adults and children with CKD or at risk of CKD (i.e., prediabetes, diabetes, HTN)

Albuminuria or proteinuria tested	ACEi or ARB prescribed	NSAID or PPI prescribed
12%	20%	**33%**

Tell your primary care colleagues to…….

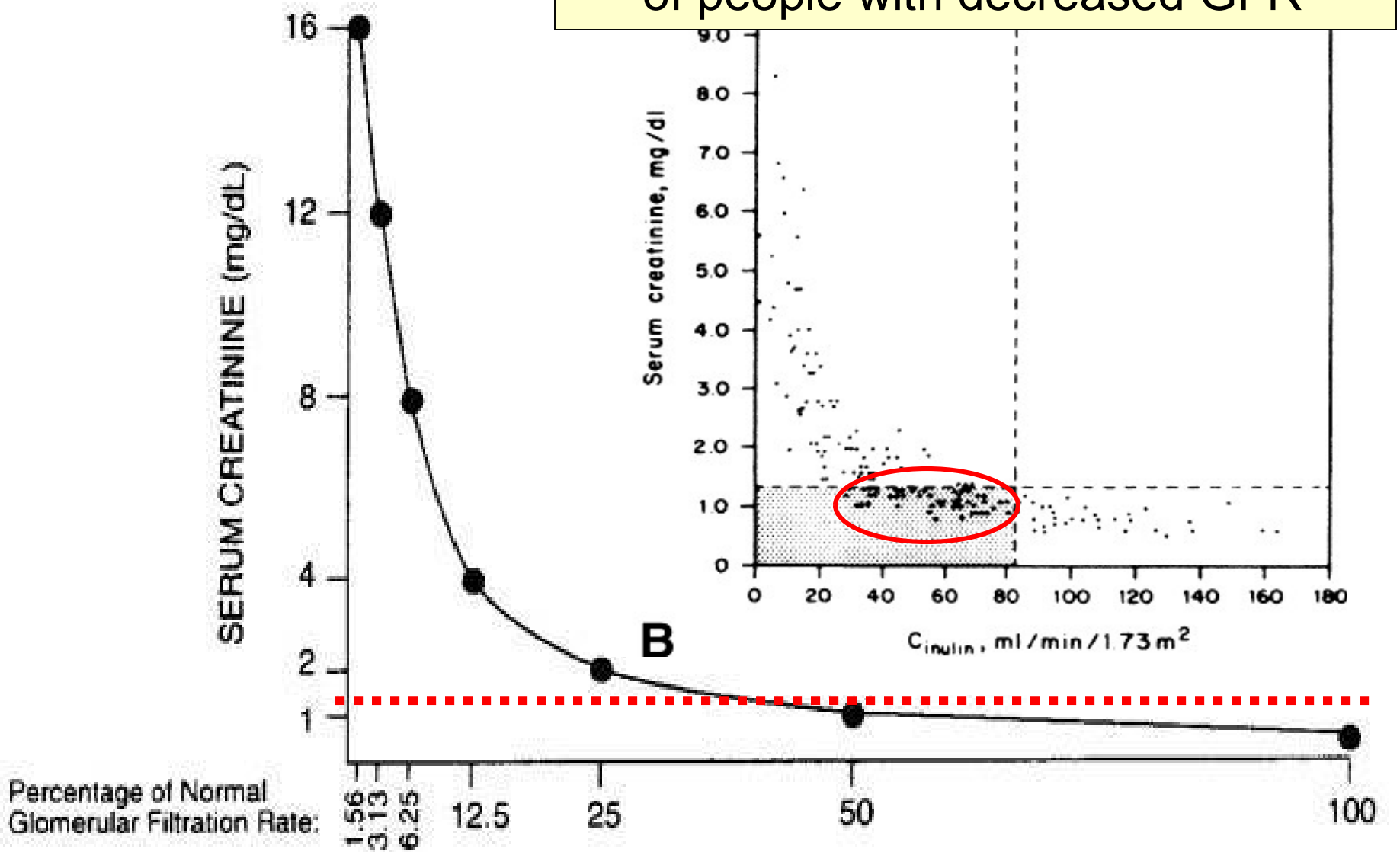
- **Periodically assess renal function in patients with or at risk of CKD:**
  - Diabetes
  - Hypertension
  - Cardiac disease, esp. with abnormal LV function
  - Peripheral vascular disease
  - Dyslipidemias
  - Nephrotoxic drug use
  - Serum phosphorus in upper half of normal range
  - Mild normochromic normocytic anemia

Why isn't CKD being diagnosed by primary care clinicians?

Overreliance on serum creatinine

GFR vs. Serum Creatinine

Serum creatinine is WNL in 40% of people with decreased GFR



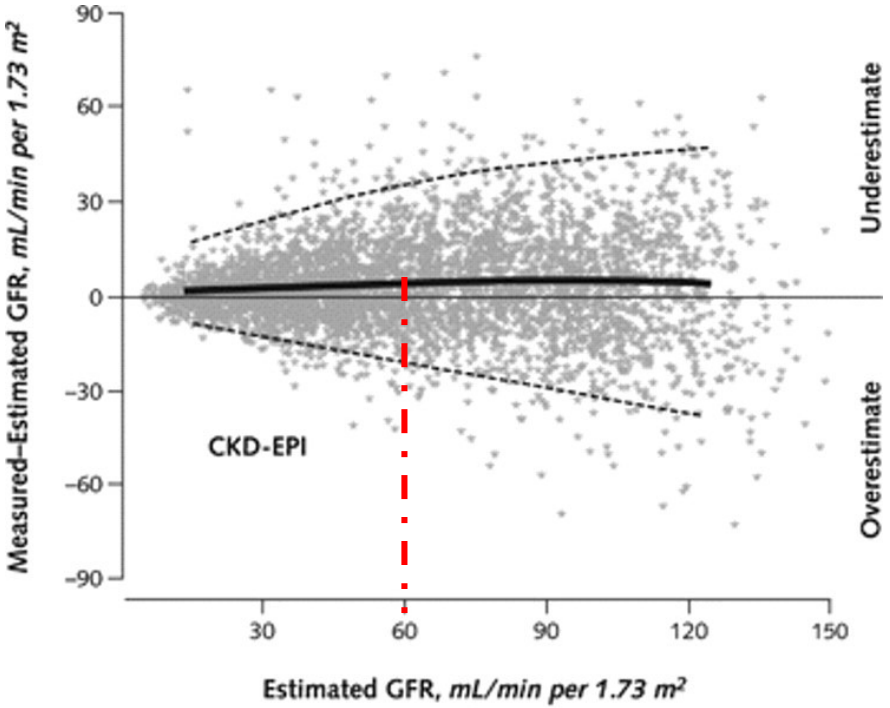
Pitfalls with using serum creatinine to estimate GFR

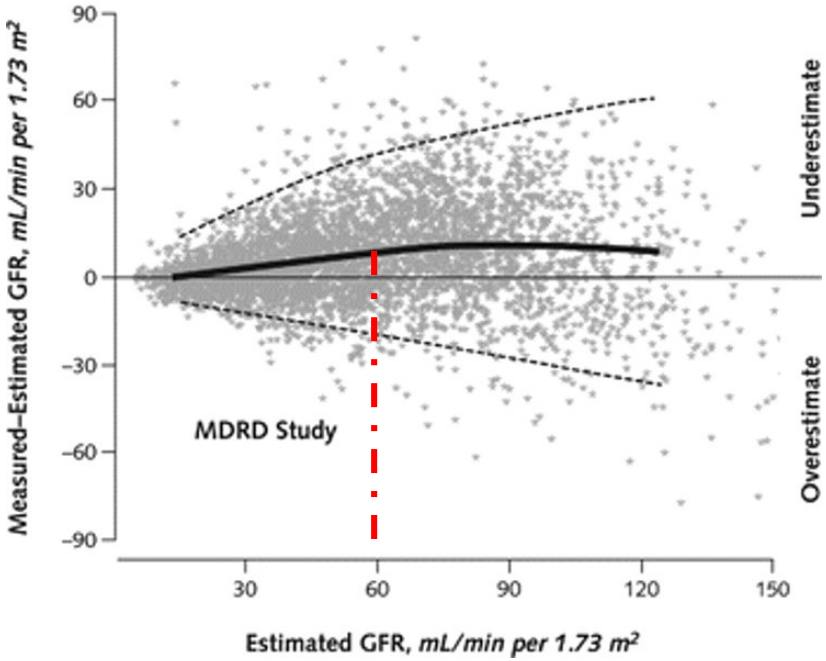
- Affected by muscle mass, age, gender, and race
- Affected by meat intake
- Affected by physical activity
- Increased by some drugs
  - trimethoprim and cimetidine block renal tubular secretion

Pitfalls of the MDRD Equation (estimated GFR)

- Creatinine-based
  - affected by nonrenal factors influencing serum creatinine
- Not reliable in:
  - Patients with GFR $>$ 60 ml/min/1.73 m^2 (normal renal function or stage 1-2 CKD)

Performance of the CKD-EPI$_{creat}$ vs. MDRD Equations in estimating measured GFR.





Levey A S et al. Ann Intern Med 2009;150:604-612

Cystatin C versus Creatinine in Determining Risk Based on Kidney Function

- **eGFRcys correlates better than eGFRcr with risk for:**
  - all-cause mortality
  - cardiovascular mortality
  - end-stage renal disease
- **Use eGFRcys equation when:**
  - Screatinine is low (↓muscle mass, low protein diet)
  - eGFRcr and eGFRcys differ by >40%

Shlipak MG. NEJM 2013;369:932-943

eGFR calculators are available online:

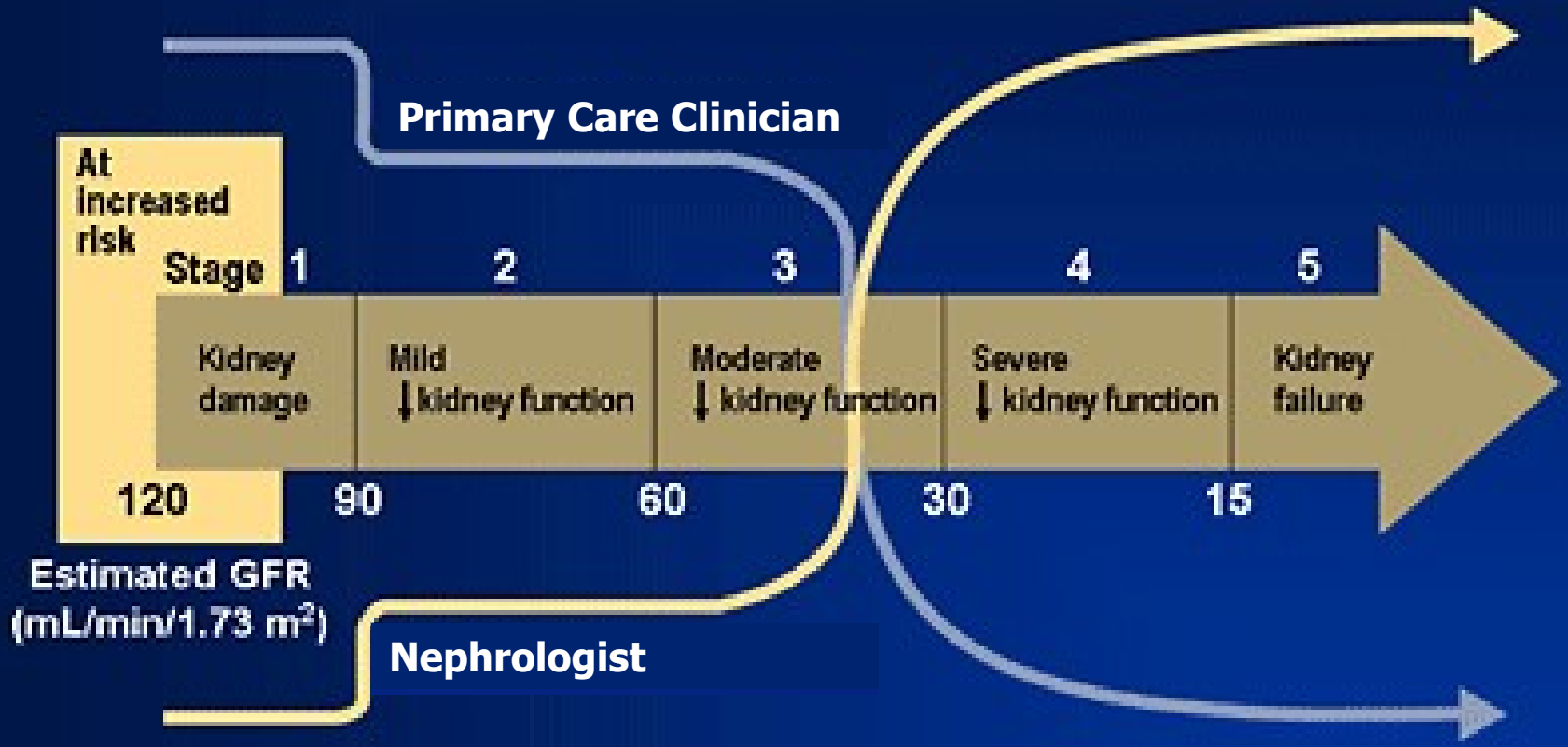
Serum Creatinine:	1.2	◉ mg/dL ○ µmol/L
Serum Cystatin C:	0.9	mg/L
Age:	30	Years
Gender:	◉ Male	○ Female
Race:	◉ Black	○ Other
Standardized Assays:	◉ Yes	○ No ○ Not Sure
Remove body surface adjustment:	○ Yes	◉ No ○ Not Sure

Results

CKD-EPI creatinine equation (2009)	93	mL/min/1.73m^2
CKD-EPI creatinine-cystatin equation (2012)	97	mL/min/1.73m^2
CKD-EPI cystatin C equation (2012)	101	mL/min/1.73m^2
MDRD study equation	86	mL/min/1.73m^2

https://www.kidney.org/professionals/kdoqi/gfr_calculator

Continuum of CKD Care: Interaction of PCP and Nephrologist



Refer for: eGFR ~30-45 ml/min and/or
severe albuminuria (alb:creat ratio ≥300 mg/g)

When to refer to a nephrologist

- CKD with eGFR <45 ml/min (stage 3b)
- Urine albumin-to-creatinine ratio ≥300 mg/g
- Hematuria not due to urologic conditions
- Unexplained eGFR decline of >30% in less than 4 months
- CKD complications (e.g., anemia requiring erythropoietin or need for phosphorus binders or vitamin D preparations)
- Serum potassium > 5.5 mEq/L
- Difficult-to-manage drug complications
- Resistant hypertension
- Recurrent or extensive nephrolithiasis
- Confirmed or presumed hereditary kidney disease (eg, polycystic kidney disease, Alport syndrome)

Practical Approach to Detection and Management of Chronic Kidney Disease for the Primary Care Clinician

Joseph A. Vassalotti, MD,[a,b] Robert Centor, MD,[c] Barbara J. Turner, MD, MSED,[d] Raquel C. Greer, MD, MHS,[e] Michael Choi, MD,[e] Thomas D. Sequist, MD, MPH,[f] National Kidney Foundation Kidney Disease Outcomes Quality Initiative

[a]Icahn School of Medicine at Mount Sinai, New York, NY; [b]National Kidney Foundation, Inc, New York, NY; [c]University of Alabama at Birmingham School of Medicine; [d]University of Texas Health Science Center at San Antonio; [e]Johns Hopkins University School of Medicine, Baltimore, Md; [f]Harvard Medical School, Boston, Mass.

Am J Med 2016;129:153-162

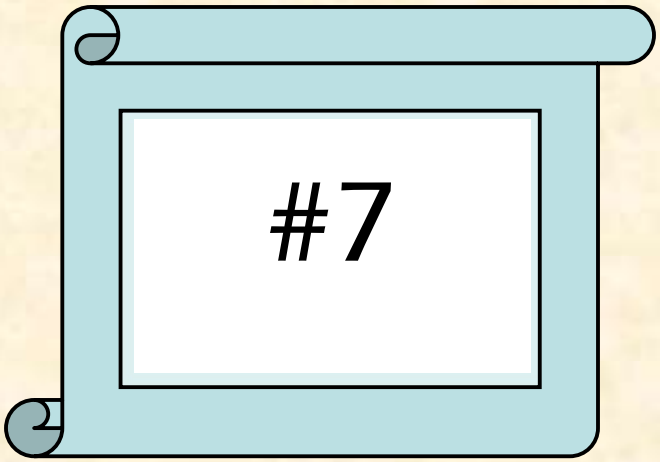
Clinical Advisor

December 9, 2019

How to Recognize Chronic Kidney Disease in Primary Care

Natalie Wynn, PA-S

E. Rachel Fink, MPA, PA-C



Unfamiliarity with contrast-induced nephropathy: Does it exist, who is at risk and how to prevent it?

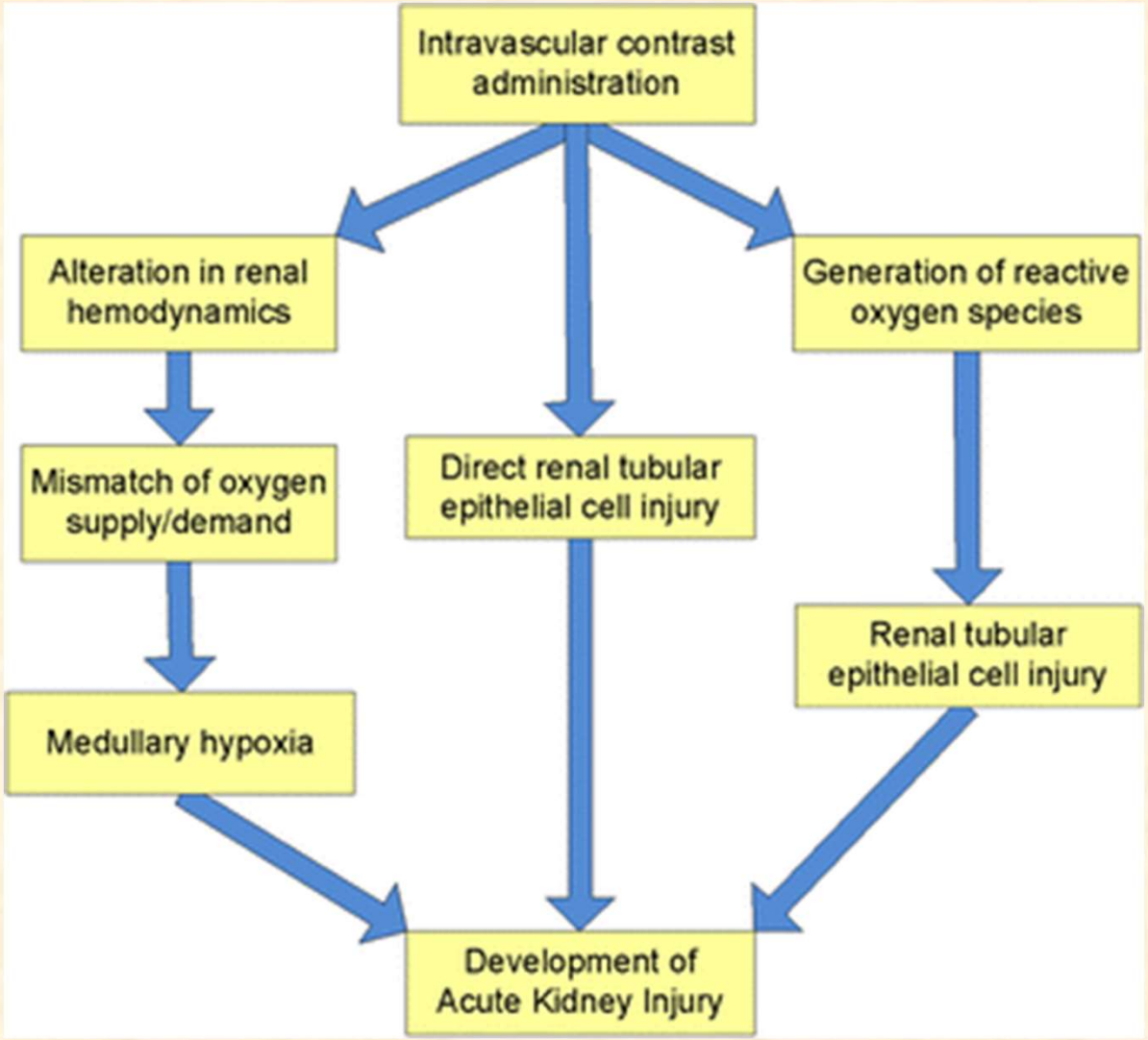
Why are questions about contrast nephrotoxicity important?

40 to 50 million contrast procedures are done each year!

- If we **overestimate** contrast nephrotoxicity:
  - Deprive patients of a beneficial study
  - Order unnecessary preventive measures
- If we **underestimate** contrast nephrotoxicity:
  - Cause AKI
  - AKI may progress to CKD and/or late mortality

Does contrast-induced nephrotoxicity exist?

- Animal/in-vitro studies support contrast nephrotoxicity



Does contrast-induced nephrotoxicity exist?

- BUT…..In humans: NO RCTs
- Observational studies with propensity score matching
  - With normal or mildly reduced renal function: No difference in AKI with contrast CT vs. non-contrast CT
  - With worse baseline GFR and/or DM: Higher rates of AKI with contrast
  - The **causal** role of contrast is **uncertain** due to confounders and selection bias

Suggested new terminology

~~Contrast-induced nephropathy (CIN)~~
~~Contrast-induced acute kidney injury (CI-AKI)~~

Contrast-associated acute kidney injury (CA-AKI)
Postcontrast acute kidney injury (PC-AKI)

BUT….whether causally related or not,
AKI can occur following contrast administration.

Therefore, preventive measures are appropriate for patients deemed to be at high risk:

- **Moderate to severe kidney disease**
- Proteinuria
- Diabetes
- Heart failure
- Hypovolemia
- Intra-arterial contrast administration

Who should receive prophylaxis for postcontrast acute kidney injury?

Recommendations:

- eGFR ≥ 45 ml/min/1.73 m^2
  - Risk negligible: No need for prophylaxis
- **eGFR <30 ml/min/1.73 m^2**
  - **Risk high: Prophylaxis indicated**
- eGFR 30 to 44 ml/min/1.73 m^2 (stage 3b)
  - Risk intermediate, but higher with other risk factors
  - Consider prophylaxis

Rudnick MR et al. Am J Kidney Dis 2020;75(1):105-113
Davenport MS et al. Radiology 2020;294:660-668

Pharmacologic Prevention of CA-AKI

- Volume expansion
  - NS vs. $NaHCO_3$
- Antioxidants (free radical scavengers)
  - N-acetylcysteine (NAC)
  - Ascorbic acid
- Antioxidant, antiinflammatory, antithrombotic
  - High-dose statins
- Inhibition of renal vasoconstriction
  - Dopamine/fenoldopam
  - Theophylline
  - Calcium channel blockers
  - Endothelin receptor antagonists
  - Atrial natriuretic peptide
- Remove contrast agent
  - Prophylactic hemodialysis and hemofiltration

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 15, 2018 VOL. 378 NO. 7

Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine

S.D. Weisbord, M. Gallagher, H. Jneid, S. Garcia, A. Cass, S.-S. Thwin, T.A. Conner, G.M. Chertow, D.L. Bhatt, K. Shunk, C.R. Parikh, E.O. McFalls, M. Brophy, R. Ferguson, H. Wu, M. Androsenko, J. Myles, J. Kaufman, and P.M. Palevsky, for the PRESERVE Trial Group*

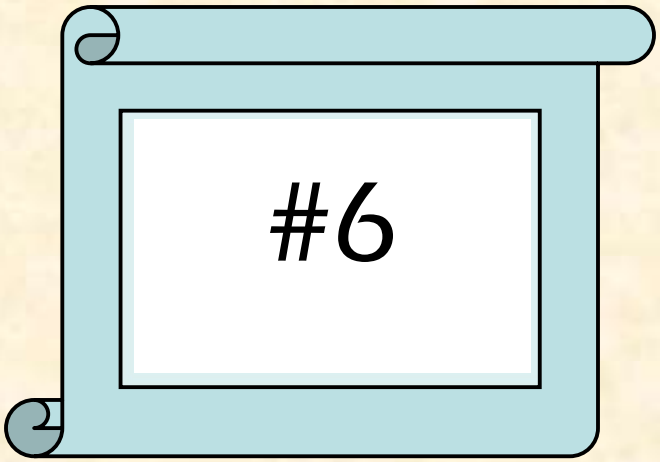
CONCLUSIONS: Among patients at high risk for renal complications who were undergoing angiography, there was no benefit of intravenous sodium bicarbonate over sodium chloride or of oral acetylcysteine over placebo for the prevention of death, need for dialysis, or persistent decline in kidney function at 90 days or for the prevention of contrast-associated acute kidney injury.

Conclusions Regarding Prevention of CA-AKI

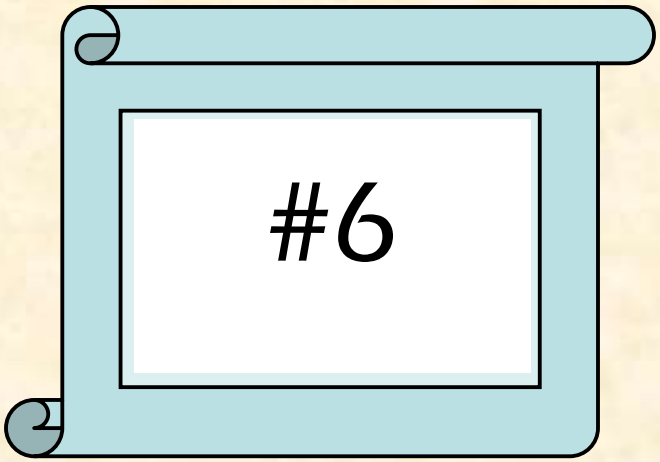
- **Identify patients at risk of AKI**
- **Avoid contrast, if possible, in high-risk patients**
- **Ensure a stable Scr or eGFR before giving contrast**
- **Discontinue nephrotoxic drugs**
- **Minimize dose of contrast; isosmotic agent preferred**
- **Hydrate your patient**
  - **Normal saline or balanced crystalloid solution**
  - No standard hydration regimen

Use of Intravenous Iodinated Contrast Media in Patients With Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation

Radiology 2020; 00:1–9 • https://doi.org/10.1148/radiol.2019192094



Stopping ACEIs or ARBs prematurely because of an initial increase of up to 20-30% in serum creatinine

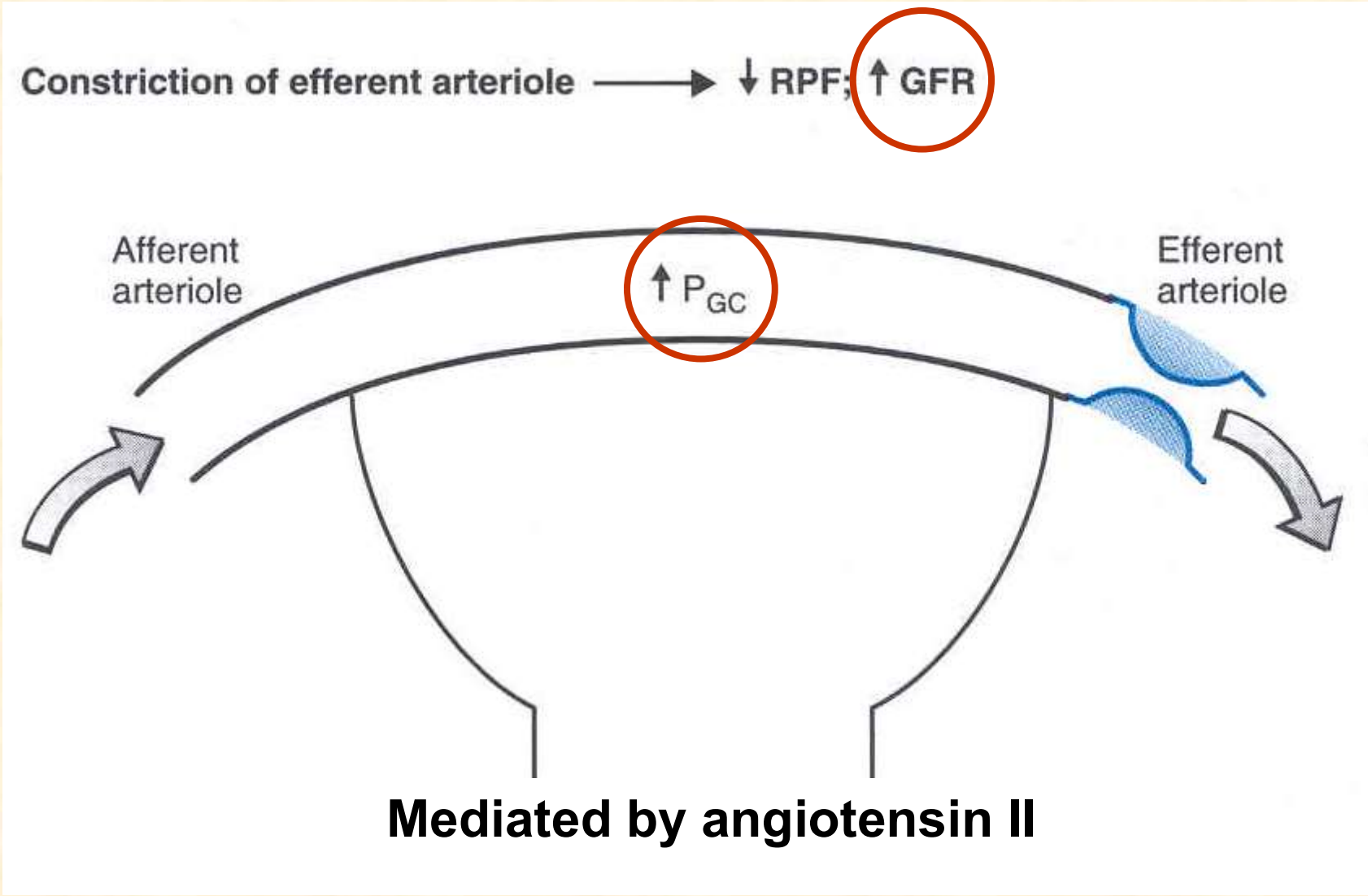


Stopping ACEIs or ARBs prematurely because of an initial increase of up to 30% in serum creatinine

Why is this important?

- ACE inhibitors and ARBs are renoprotective
  - Antiproteinuric
  - Slow down progression of CKD
    - esp. in patients with proteinuria
- **Serum creatinine <u>normally</u> increases 20-30% after starting ACEIs and ARBs**
- Prematurely stopping treatment may accelerate the decline in renal function in patients with CKD
- **Don't be afraid to continue ACEs and ARBs**

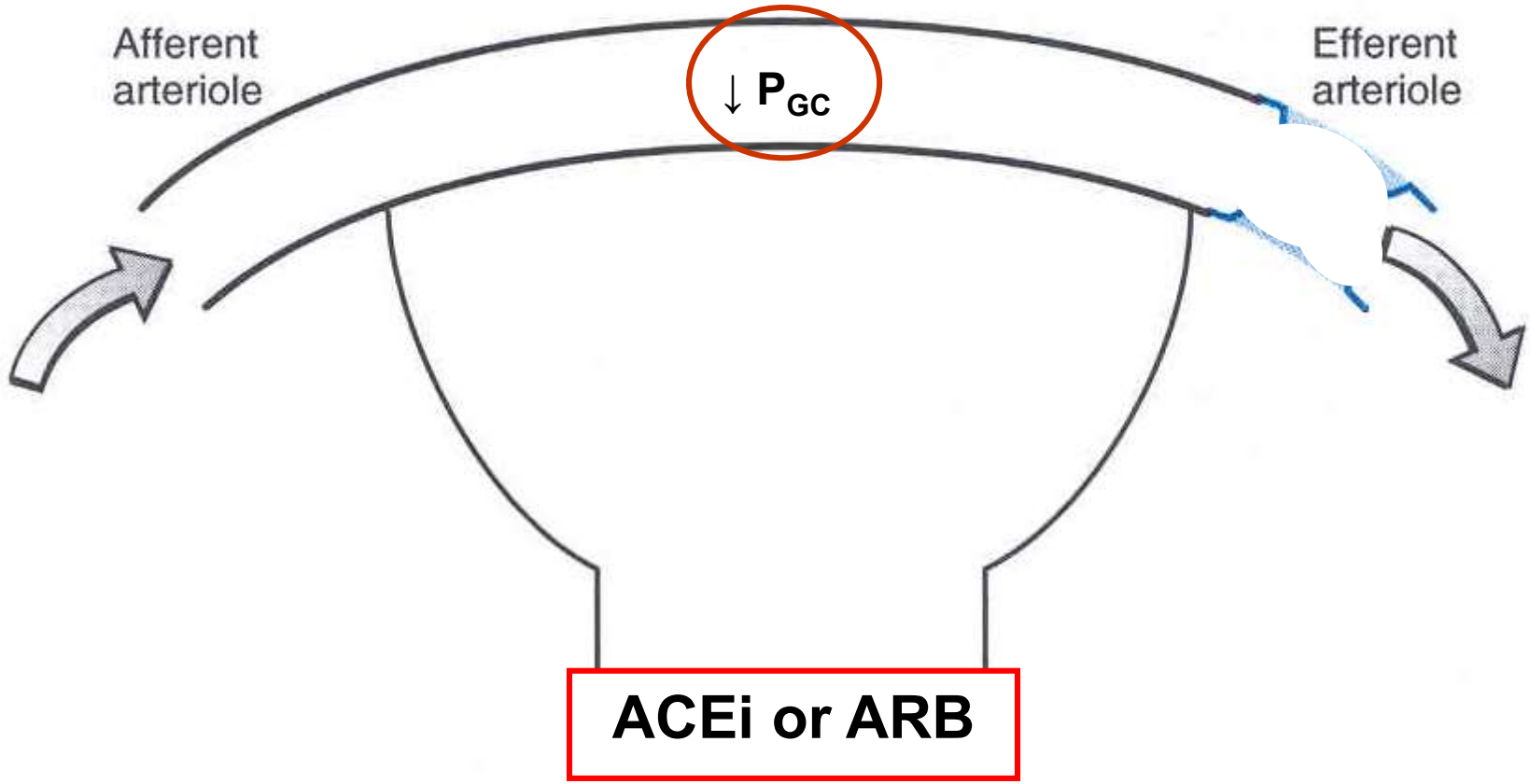
Effect of angiotensin II on glomerular hemodynamics



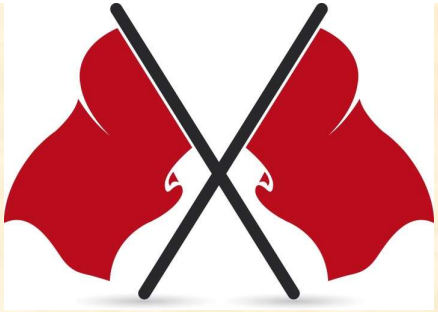
Mediated by angiotensin II

Effect of ACEIs and ARBs on glomerular hemodynamics

Dilation of efferent arteriole → ↑ RPF; ↓ GFR

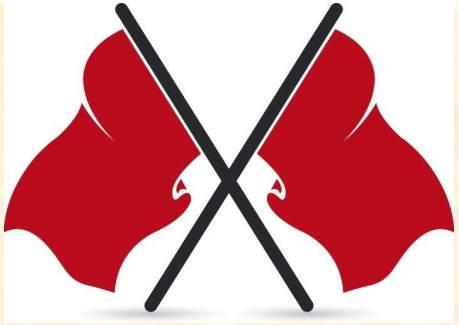


BUT…. Are RAAS Blockers a Two-Edged Sword?



Uncertain situations

- **Elderly (>70 yo) with <u>nonproteinuric</u> CKD**
  - Weiss JW et al. Curr Opin Nephrol Hypertens 2010; 19:413–419
  - O'Hare AM et al. Ann Intern Med. 2009;150:717-24
  - Fang g et al. Pharmacotherapy 2018;38:29-41
- **AKI (e.g., peri-operative, pre-contrast, post-AKI)**
  - Rim MY et al. Am J Kid Dis 2012;60:576-582
  - Yacoub R et al. Am J Kidney Dis. 2013;62(6):1077-1086
  - Alpern RJ et al. JAMA Intern med 2018;178:1690-92
  - Hsu CY et al. Clin J Am Soc Nephrol 2020;15:26-34

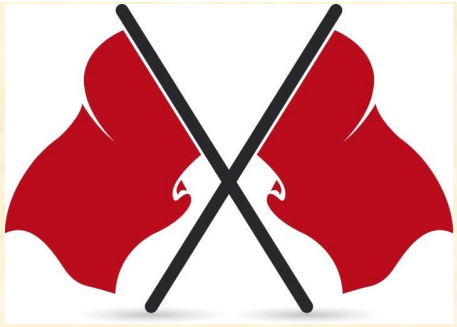


Uncertain or problematic situations

- **Stage 4-5 CKD (?LORFFAB)***
  - Goncalves AR et al. Nephron Clin Pract 2011;119:c348–c354
  - Hsu T-W et al. JAMA Intern Med 2014;174:347-54
  - Molnar MZ et al. J Am Coll Cardiol 2014;63:650-58
  - Ahmed A et al. Nephron 2016;133:147-58
  - Onuigbo MA. Int J Clin Pract 2017;71:e12916
  - Fu EL et al. JASN 2020(12);doi.org/10.1681/ASN.2020050682
    - 10,000+ patients with eGFR <30 ml/min, followed x 5 years
    - Continuing RAAS blockers → ↓ mortality and ↓ MACE; ↑ KRT

STOP-ACEi Trial – results due December 2022

*LORFFAB – Late-onset renal failure from angiotensin blockade



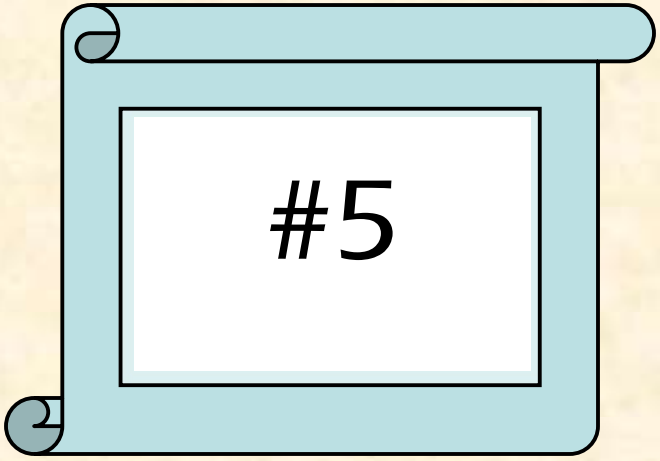
Problematic situation

- **Dual RAAS blockade**
  - Yusuf s et al. N Engl J Med 2008;358:1547-59 (ONTARGET)
  - Parving H-H et al. N Engl J Med 2012;367:2204-13 (ALTITUDE)
  - Fried LF et al. N Engl J Med 2013;369:1892-903 (NEPHRON-D)

Increased risk of hypotension, hyperkalemia and acute kidney injury

Conclusions and Recommendations

- **Don’t stop a RAAS blocker unless the rise in creatinine exceeds 30% or progresses within the first two months**
  - Temporarily decreasing or stopping diuretic may allow for continuing the RAAS blocker
- **Dual RAAS blockade in CKD should be avoided**
- **Uncertainties**
  - Should we stop RAAS blockers when AKI risk exists?
  - Should we continue RAAS blockers in advanced CKD?



Failure to recognize non-traumatic rhabdomyolysis

The New York Times

January 13, 2010

Fierce Quake Devastates Haitian Capital – Worst Is Feared

The New York Times

March 12, 2011

Powerful Quake and Tsunami Devastate Northern Japan

Why is this important?

- In general practice, non-traumatic cases predominate
  - alcohol abuse (67%)
  - compression (39%)
  - seizures (24%)
  - drug abuse (15%).

  Multiple factors often coexist
- AKI is the most serious complication of rhabdomyolysis
- Prompt diagnosis and treatment can prevent AKI

Non-traumatic Causes of Rhabdomyolysis

- **COMPRESSION BY BODY PARTS**
  - **Coma:** drug intoxications, diabetic coma
- **EXERTIONAL CAUSES**
  - **Voluntary exertion**

    excessive exercise, esp. in unconditioned persons

    sickle cell trait

    hypothyroidism

    genetic disorders of muscle metabolism (e.g., McArdle syndrome)
  - **Involuntary "exertion"**

    seizures: cocaine; amphetamines; alcohol (delirium tremens), ecstasy

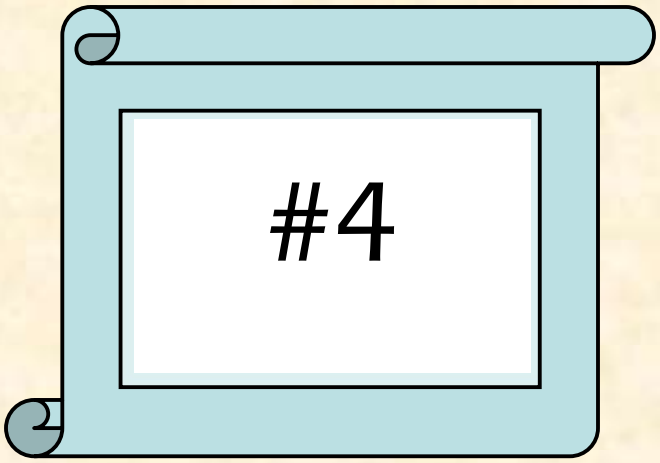
    hyperthermic conditions: malignant neuroleptic syndrome

    electrical current

Non-traumatic Causes of Rhabdomyolysis

- **NONEXERTIONAL CAUSES**
  - **medications**
    lipid lowering drugs (statin + gemfibrozil combination)
    drugs causing hypokalemia (diuretics; laxatives; amphotericin B)
  - **electrolyte abnormalities**
    hypokalemia; hypophosphatemia; hypomagnesemia
  - **infections**:
    viral (Influenza; Coxsackie virus; HIV)
    bacterial (Legionella; Streptococcus; Staphylococcus; Salmonella)
  - **envenomations**: snake or spider bite
  - **hypothermia**

Diagnosis:
CK: Peaks in 24-36 hours
Urine: Brown, heme +++ dipstick with few or no RBCs in sediment

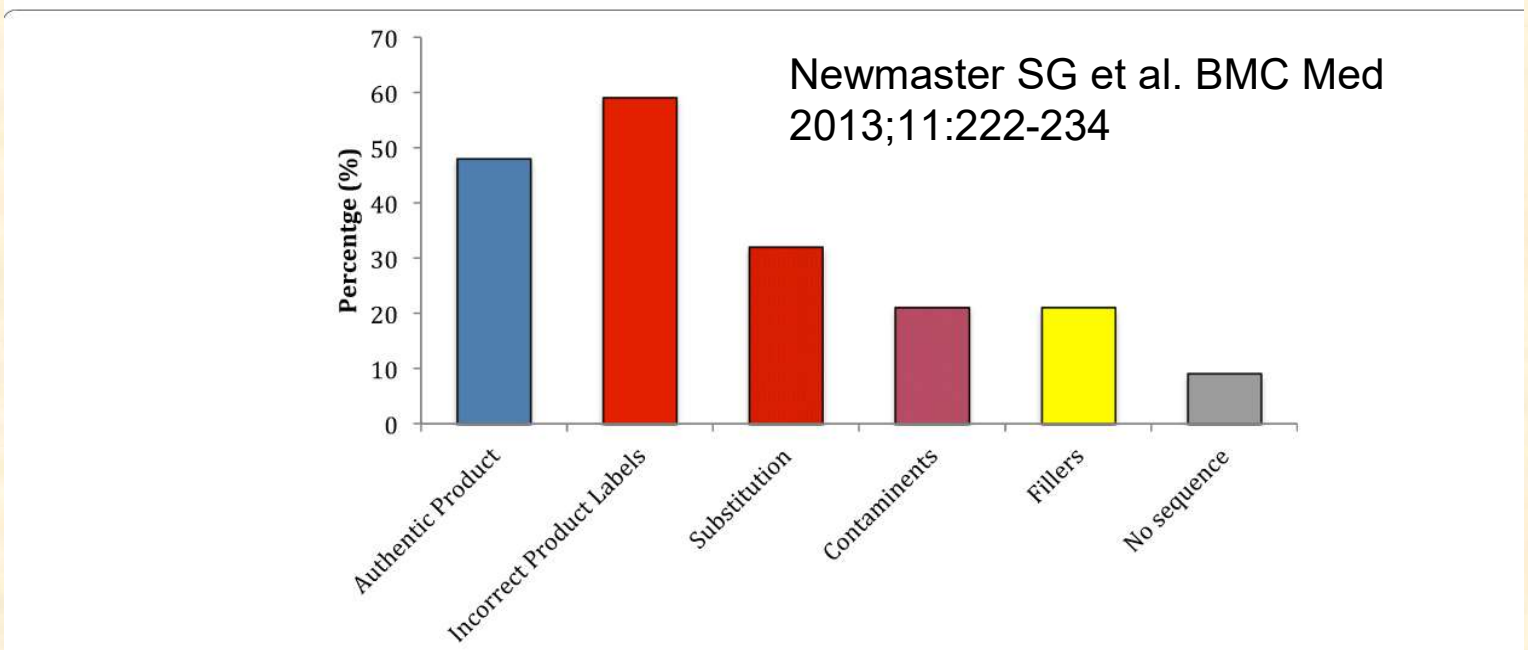


Failure to advise patients about nephrotoxic herbal products

(i.e., what your patients are taking..…that you did not prescribe)

Herbal Remedies

- Alternative medicines are a 30+ billion-dollar industry
- Used by over 60% of surveyed adults
- **Government testing and regulation are lacking**



DNA barcoding of 44 medicinal herbal products from 12 companies

- NKF lists 37 herbs that are nephrotoxic or can harm CKD patients (Grubbs V et al. Am J Kidney Dis 2013;61:739-747)

Herbal remedies and renal injury

Type of injury	Product	Marketed for:
Acute kidney failure	Autumn crocus	arthritis, gout
	Cape aloe	Laxative, antiinflammatory
	Periwinkle	"Brain health", ↑BP, diarrhea
	Horse chestnut	varicose veins, phlebitis. hemorrhoids, BPH
	White willow bark (salicin) (mimics NSAID toxicity)	Arthritis, headache, fever, dysmennorhea
	Aristolochia species	Weight loss supplement
Chronic nephropathy (interstitial fibrosis)	Chinese herbs (incl. Aristolochia species)	Weight loss supplement
Uroepithelial cancer	Chinese herbs (incl. Aristolochia species)	Weight loss supplement

Ifudu O and Friedman E. Dial & Transplan April 2009, pp124-127

NKF lists 37 herbs that are nephrotoxic or can harm CKD patients

http://www.kidney.org/atoz/content/herbalsupp.cfm

Grubbs V et al. Am J Kidney Dis 2013;61:739-747

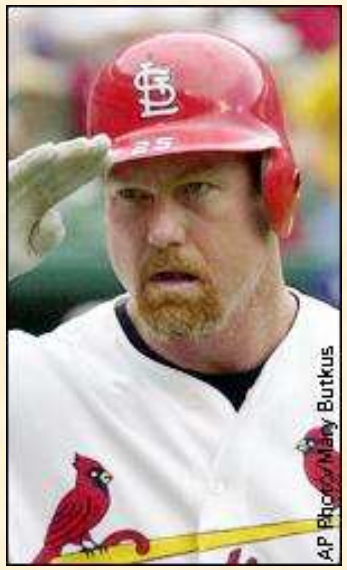
Herbal remedies that cause hyperkalemia in patients with chronic kidney disease

Herbal product	Mechanism for hyperkalemia
Lily-of-the-valley, Siberian ginseng, Hawthorn berries, dried toad skin	Digitalis-like effect (inhibition of Na^+/K^+- ATPase blocks K^+ entry into cells)
Noni juice, alfalfa, dandelion, horsetail, nettle	High potassium content

What do these guys have in common?

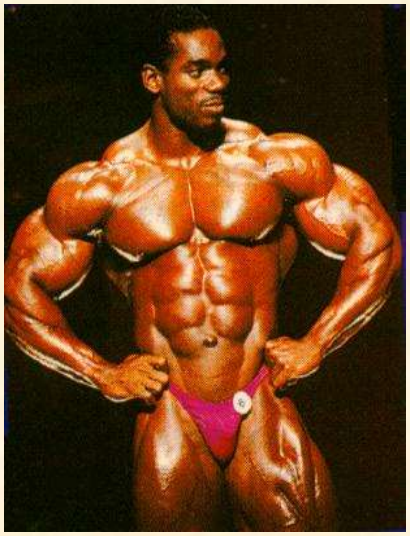
Sammy Sosa

Alex Rodriguez



Mark McGuire

Kenneth Wheeler



Barry Bonds

BODYBUILDING WITH STEROIDS DAMAGES KIDNEYS

Bulking up with Steroids Harms Kidneys More than Obesity

Development of FSGS Following Anabolic Steroid Use in Bodybuilders

Leal C. Herlitz, Glen S. Markowitz, Alton B. Farris, et al.
Dept. of Pathol, Columbia University Medical Center, NY

JASN 2010; 21:163-172

10 bodybuilders with long-term anabolic androgenic steroid abuse
BMI: 27-43 kg/m^2 (mean 34.7 kg/m^2)
Proteinuria: range 1.3-26.3 g/day (mean 10.1 g/day)
Renal insufficiency: serum creatinine range 1.3-7.8 mg/dl (mean 3.0 mg/dL)
Renal biopsy: **FSGS, glomerulomegaly**, tubulointerstitial scarring
Cessation of steroids, ↓ exercise and weight loss → stabilization or improvement in renal function and proteinuria

SYNTHETIC CANNABINOIDS (aka “Spice” or “K2”) CAUSE ACUTE KIDNEY INJURY

Clinical findings in 21 users with AKI

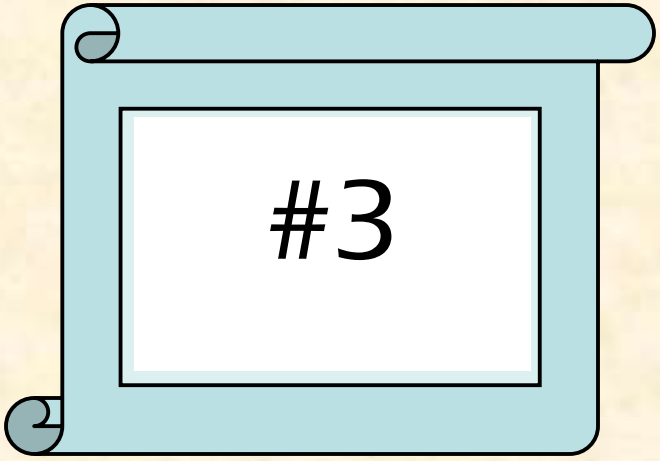
Mean age (years)	20
Male (%)	95
Presenting symptoms (%)	
Nausea and vomiting	100
Abdominal, flank or back pain	71
Mean peak serum creatinine (mg/dL)	7.7
Renal ultrasound (n=17)	
Normal	5
Increased echogenicity	12
Bilateral symmetrical enlargement	1
Renal biopsy findings (n=13)	
Acute tubular necrosis	10
Acute interstitial nephritis	3

Synthetic cannabinoids are NOT detected on standard toxicology screens.

Pendergraft, III WF et al. Clin J Am Soc Nephrol 2014;9:1996-2005

Conclusion

- Always ask your patients about medicinal products that you did NOT prescribe.



Failure to recognize that obesity can cause:

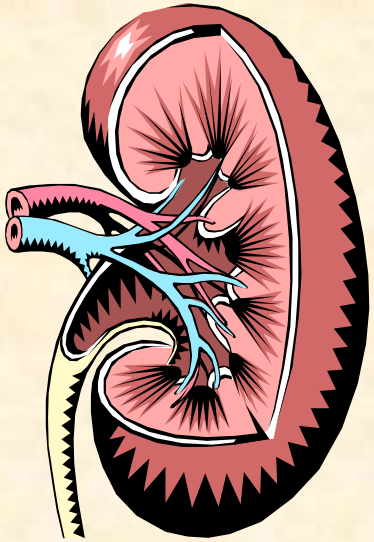
chronic kidney disease

nephrolithiasis

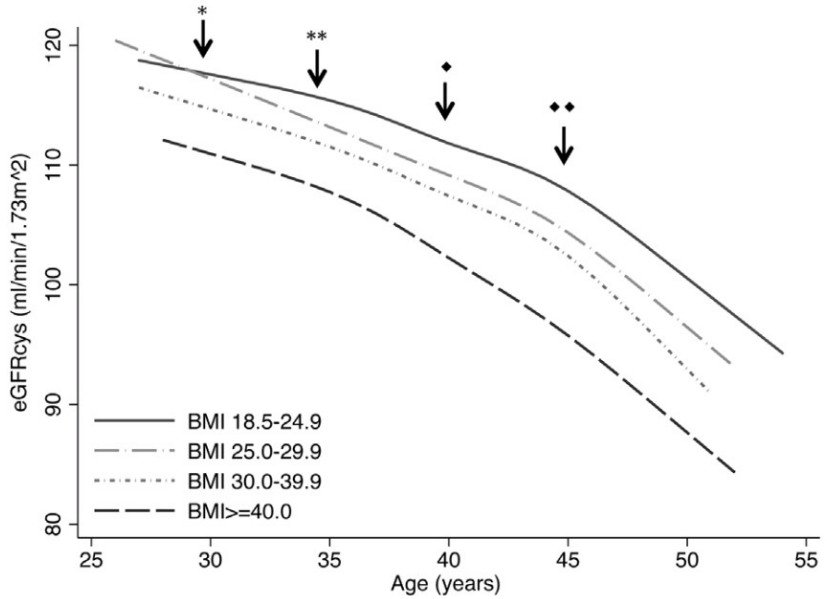
renal cell cancer

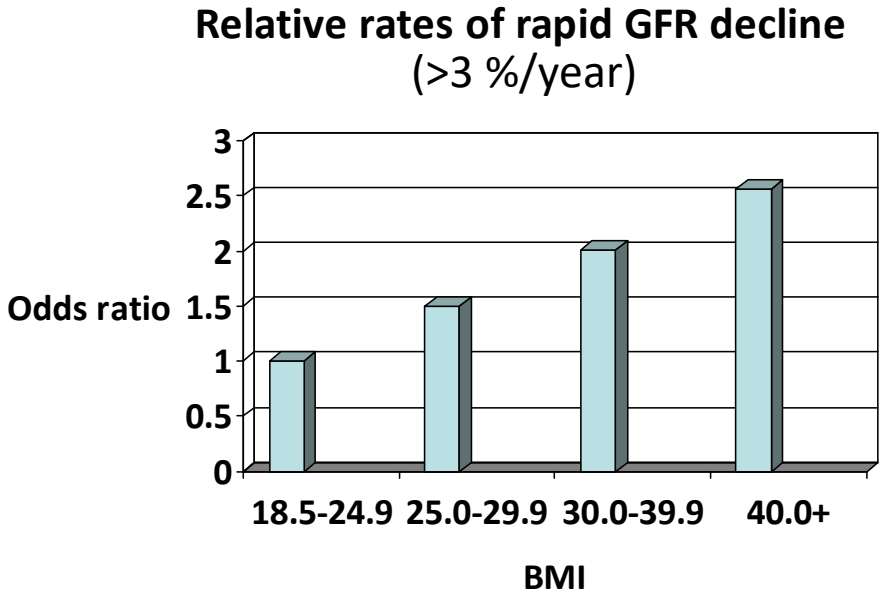
Diseases commonly associated with obesity

- Diabetes
- Hypertension
- Hyperlipidemia
- Atherosclerotic cardiovascular disease
- Gout
- Gallstones
- Nonalcoholic fatty liver
- GERD
- Obstructive sleep apnea
- Degenerative joint disease



Higher BMI associates with greater decline in kidney function



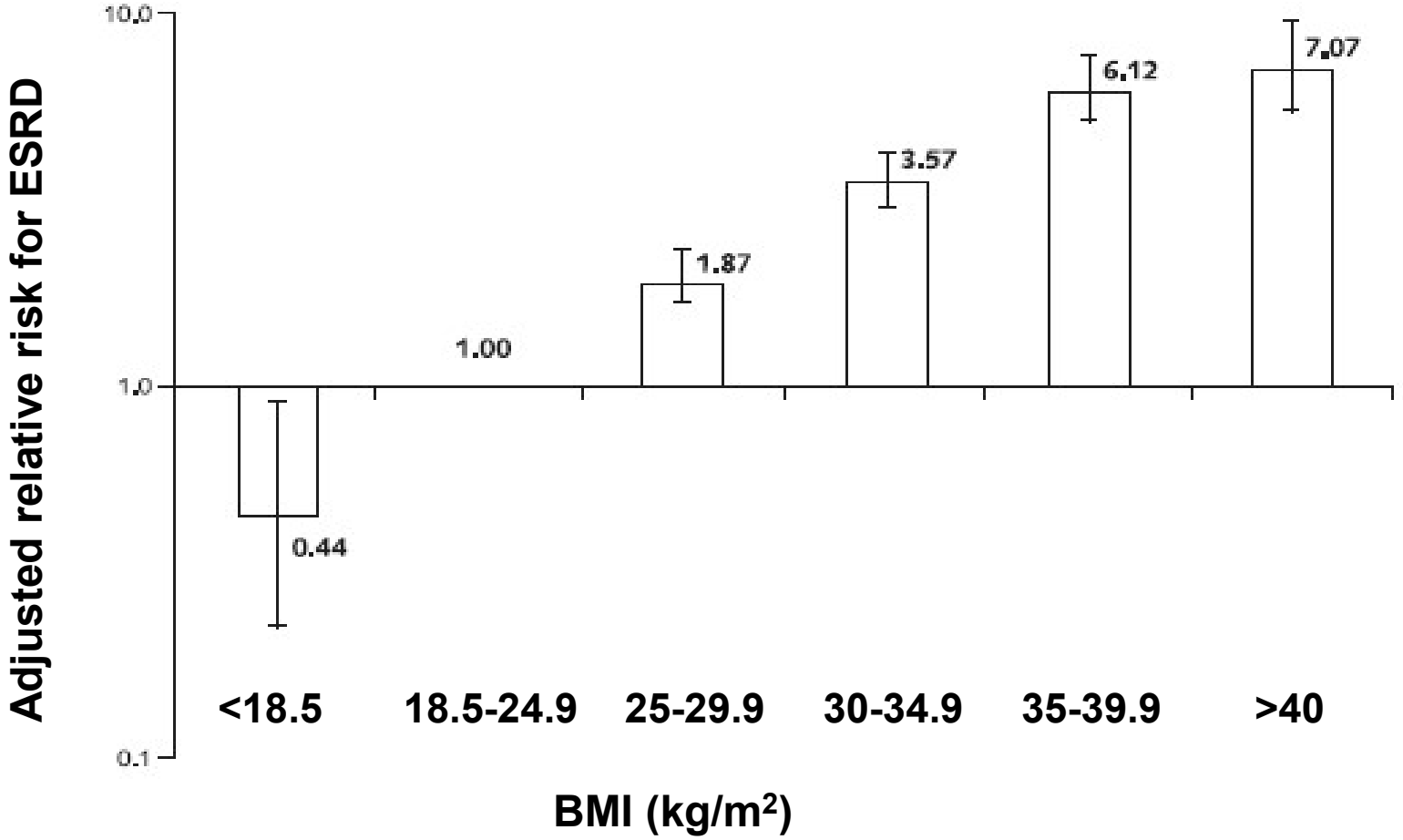


Analysis of CARDIA (Coronary Artery Risk Development in Young Adults) Cohort
25-year longitudinal study of adults ages 18-30 at baseline.
2,839 participants followed from year 10 to year 20 with eGFRcys

Grubbs V et al. Am J Kidney Dis 2014;63:590-597

Kaiser Permanente Study

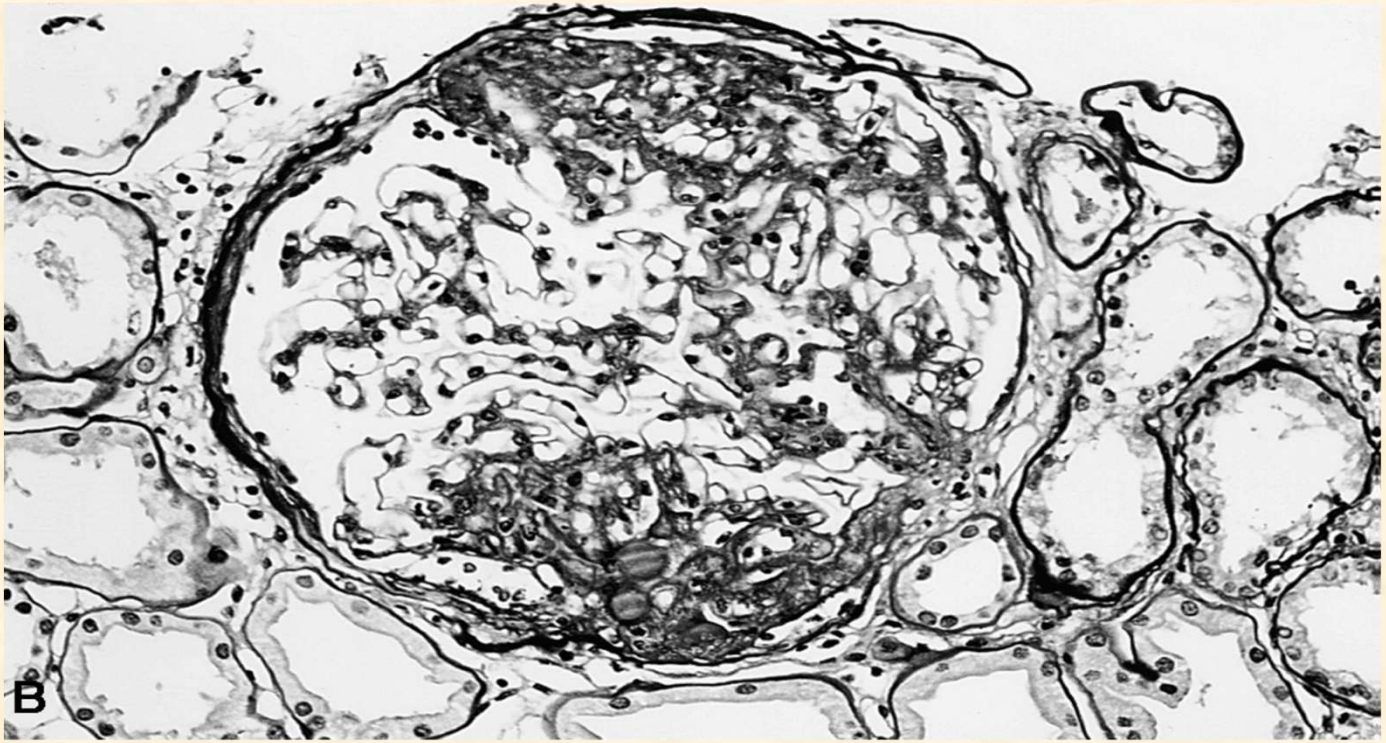
- 320,252 patients followed from 1964-1985
- 1471 cases of ESRD occurred



Hsu CY et al. Ann Intern Med 2006;144:21-28

Obesity-related glomerulopathy: An emerging epidemic

- Renal biopsy series of obesity-related glomerulopathy
  - Focal segmental glomerulosclerosis
  - Glomerulomegaly
  - Mean BMI 41.7 kg/m^2 (range 30.9-62.7 kg/m^2)



Kambham N et al. Kidney Int 2001;59:1498-1509

Obesity, Weight Gain, and the Risk of Kidney Stones

Eric N. Taylor, MD
Meir J. Stampfer, MD, DrPH
Gary C. Curhan, MD, ScD

Context Larger body size may result in increased urinary excretion of calcium, oxalate, and uric acid, thereby increasing the risk for calcium-containing kidney stones. It is unclear if obesity increases the risk of stone formation, and it is not known if weight gain influences risk.

Objective To determine if weight, weight gain, body mass index (BMI), and waist circumference are associated with kidney stone formation.

Design, Setting, and Participants A prospective study of 3 large cohorts: the Health Professionals Follow-up Study (N=45 988 men; age range at baseline, 40-75 years), the Nurses' Health Study I (N=93 758 older women; age range at baseline, 34-59 years), and the Nurses' Health Study II (N=101 877 younger women; age range at baseline, 27-44 years).

Main Outcome Measures Incidence of symptomatic kidney stones.

Results We documented 4827 incident kidney stones over a combined 46 years of follow-up. After adjusting for age, dietary factors, fluid intake, and thiazide use, the relative risk (RR) for stone formation in men weighing more than 220 lb (100.0 kg) vs men less than 150 lb (68.2 kg) was 1.44 (95% confidence interval [CI], 1.11-1.86; $P=.002$ for trend). In older and younger women, RRs for these weight categories were 1.89 (95% CI, 1.52-2.36; $P<.001$ for trend) and 1.92 (95% CI, 1.59-2.31; $P<.001$ for trend), respectively. The RR in men who gained more than 35 lb (15.9 kg) since age 21 years vs men whose weight did not change was 1.39 (95% CI, 1.14-1.70; $P=.001$ for trend). Corresponding RRs for the same categories of weight gain since age 18 years in older and younger women were 1.70 (95% CI, 1.40-2.05; $P<.001$ for trend) and 1.82 (95% CI, 1.50-2.21; $P<.001$ for trend). Body mass index was associated with the risk of kidney stone formation: the RR for men with a BMI of 30 or greater vs those with a BMI of 21 to 22.9 was 1.33 (95% CI, 1.08-1.63; $P<.001$ for trend). Corresponding RRs for the same categories of BMI in older and younger women were 1.90 (95% CI, 1.61-2.25; $P<.001$ for trend) and 2.09 (95% CI, 1.77-2.48; $P<.001$ for trend). Waist circumference was also positively associated with risk in men ($P=.002$ for trend) and in older and younger women ($P<.001$ for trend for both).

Conclusions Obesity and weight gain increase the risk of kidney stone formation. The magnitude of the increased risk may be greater in women than in men.

JAMA. 2005;293:455-462 www.jama.com

JAMA, January 26, 2005---Vol. 293, No. 4, pp. 455-462

KIDNEY STONES ARE A MAJOR cause of morbidity. The lifetime prevalence of symptomatic nephrolithiasis is approximately 10% in men and 5% in women,[1-3] and more than $2 billion is spent on treatment each year.[4,5] About 80% of kidney stones contain calcium, and the majority of calcium stones consist primarily of calcium oxalate.[6,7] The identification of common, modifiable risk factors for kidney stones may result in new approaches to treatment and prevention.

Obesity is associated with insulin resistance and compensatory hyperinsulinemia, metabolic derangements that may lead to the formation of calcium-containing kidney stones. A recent metabolic trial demonstrated that insulin resistance was associated with defects in renal ammonium production,[8] and an examination of more than 4500 patients with a history of kidney stones showed that urinary pH was inversely related to body weight.[9] A defect in renal acid excretion could lead to hypocitraturia, an important risk factor for calcium nephrolithiasis.[6,10] Hyperinsulinemia

oxalate kidney stones.[14-16] In one study of nearly 6000 individuals with nephrolithiasis, men weighing more than 120 kg excreted 37% more uric acid than men who weighed less than 100 kg.[17] Similar results were seen in women

cium salts, prospective data on the relation between body size and the risk of kidney stone formation are limited. We have previously reported on the association between higher body mass index (BMI) and an increased risk of in-

lor and Curhan), Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass; and Departments of Nutrition and Epidemiology, Harvard School of Public Health (Drs Stampfer and Curhan).
Corresponding Author: Eric N. Taylor, MD, Channing Laboratory, Third Floor, Brigham and Women's Hospital, 181 Longwood Ave, Boston, MA 02115 (entaylor@partners.org).

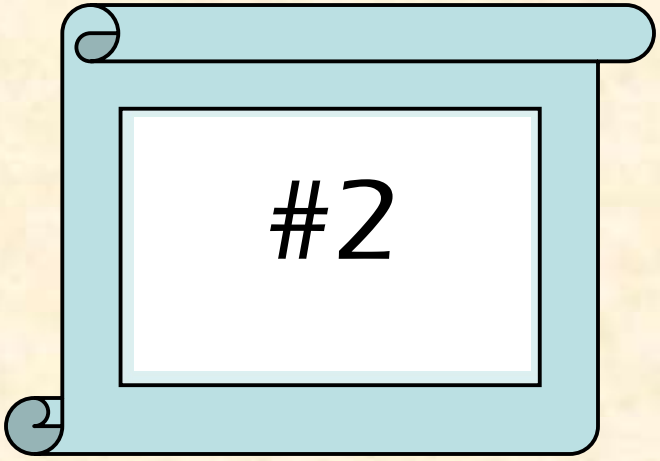
Obesity-Related Factors Contributing to Nephrolithiasis

- Low urine pH
- Increased urine uric acid
- Low urine citrate
- Increased urine oxalate
- Increased urine calcium

Obesity-Related Cancers

Type of cancer	Relative risk* with BMI of 25–30 kg/m²	Relative risk* with BMI of ≥ 30 kg/m²
Colorectal (men)	1.5	2.0
Colorectal (women)	1.2	1.5
Female breast (postmenonopausal)	1.3	1.5
Endometrial	2.0	3.5
Kidney (renal-cell)	1.5	2.5
Oesophageal (adenocarcinoma)	2.0	3.0
Pancreatic	1.3	1.7
Liver	ND	1.5–4.0
Gallbladder	1.5	2.0
Gastric cardia (adenocarcinoma)	1.5	2.0

Calle EE et al. Nature Rev:Cancer 2004;4:579-591



Therapeutic inertia in treating
office hypertension
and
Overtreatment of elevated BP in stable
hospitalized patients

What is Therapeutic Inertia?

- The failure of healthcare providers to:

  initiate therapy or intensify therapy when goal BP is not reached

What is the extent of therapeutic inertia in the U.S.?

- Half of the hypertensive population has uncontrolled BP
- Many are unaware of having hypertension
- **Despite having documented high BP, hypertension is neither diagnosed nor treated**

Morb Mortal Wkly Rep (CDC data). 2012;61:703-709

Reasons for therapeutic inertia

- **Not due to clinician ignorance of BP treatment goals**
  - 97% of physicians know the goals
- Inadequate knowledge of pharmacology of antihypertensive therapy
- **Lack of motivation**
  - “The BP is borderline”; ”the target is almost reached”
  - “The patient won’t want to take more medication”
  - “Only the systolic BP is high”
  - “Waiting for full drug effect; time is too short”
  - “The patient says his/her BP is good outside of the clinic”

Flip side of coin

Overtreatment of asymptomatic elevated BP in stable hospitalized patients

- Inappropriate use of intravenous antihypertensive drugs for a single elevated blood pressure
  - Jacobs ZG et al. J Hosp Med 2019:14:144-50
  - Pasik TS et al. J Hosp Med 2019:14:151-156
- Intensification of antihypertensive medications at hospital discharge, even with controlled BP prior to admission
  - Anderson TS et al. JAMA Intern Med 2019;179:1528-1536
  - Anderson TS et al. BMJ Open Access 2018;362;k3503

REVIEW

Am J Med 2020;133:165-169

THE AMERICAN JOURNAL of MEDICINE®

An Evidence-Based Review of Elevated Blood Pressure for the Inpatient

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ABSTRACT

There is no data that elevated blood pressure leads to end-organ damage or hypertensive emergency in asymptomatic hospitalized patients.

Available literature suggests possible harm and little to no benefit in treating asymptomatic elevated blood pressure in these patients.

BACKGROUND

Elevated blood pressure is a common dilemma encountered by emergency department and inpatient physicians, but there are no guidelines or recommendations to direct medical providers for the care of patients who are hospitalized

This review will describe medical terminology related to elevated blood pressure, survey the available literature related to its management, and make recommendations to guide providers' approach to elevated blood pressure in the inpatient setting

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Treatment and Outcomes of Inpatient Hypertension Among Adults With Noncardiac Admissions

Radhika Rastogi, MD, MPH; Megan M. Sheehan, BS; Bo Hu, PhD; Victoria Shaker, BA; Lisa Kojima, BSE; Michael B. Rothberg, MD, MPH

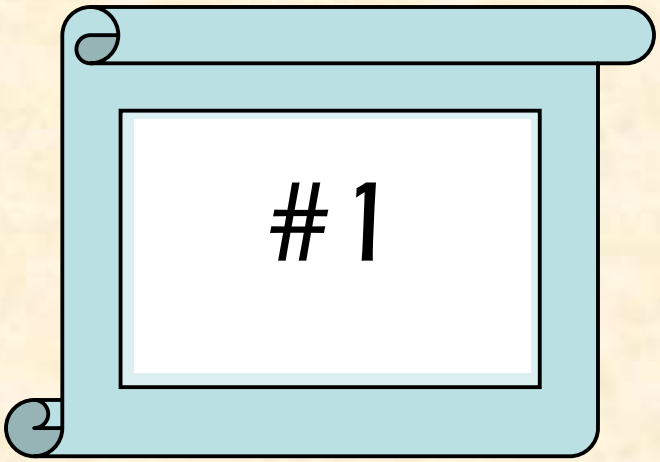
JAMA Intern Med. doi:10.1001/jamainternmed.2020.7501. Published online December 28, 2020.

22,834 adults hospitalized for noncardiac diagnoses, mean age 65 yrs.

- 78% had at least 1 hypertensive episode during hospital stay.
- 33% were treated with oral (66%) or IV (34%) medication.
- 9% were discharged on an intensified antihypertensive regimen.

RESULTS: **Treated patients had higher rates of acute kidney injury and myocardial injury.**

BP at one year no better in treated vs. untreated patients.

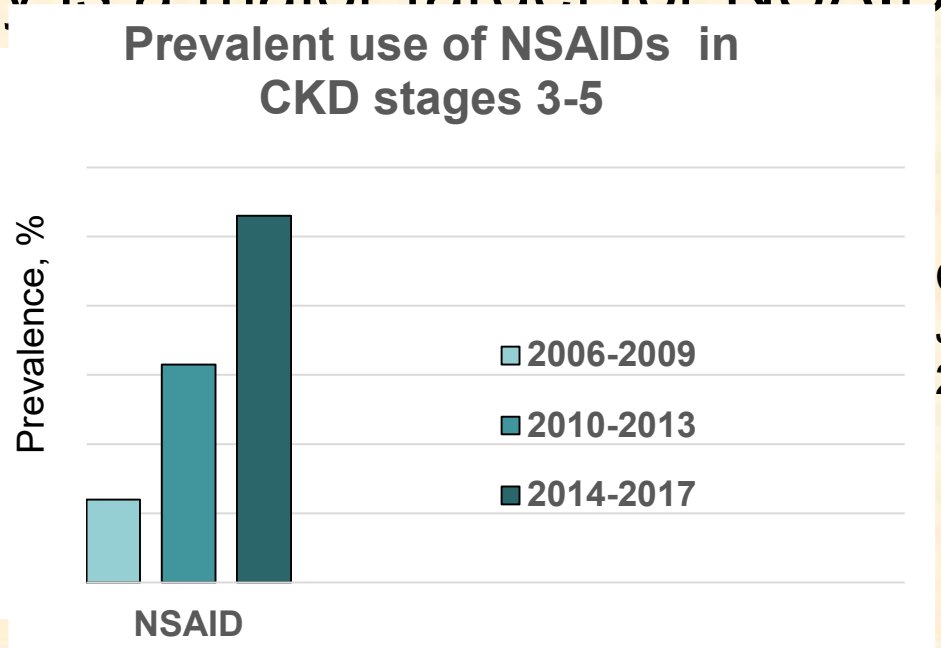


Overprescribing NSAIDs and Cox-2 inhibitors

Be Aware of and Beware of…….
The many evil faces of NSAIDS!!

Overview of NSAID Toxicity

- More than 17 million Americans use NSAIDs on a daily basis
- Elderly people are at increased risk of toxicity
- NSAIDs are responsible for ~30% of hospital admissions for adverse drug events
- The kidney is a major target for NSAID-related injury

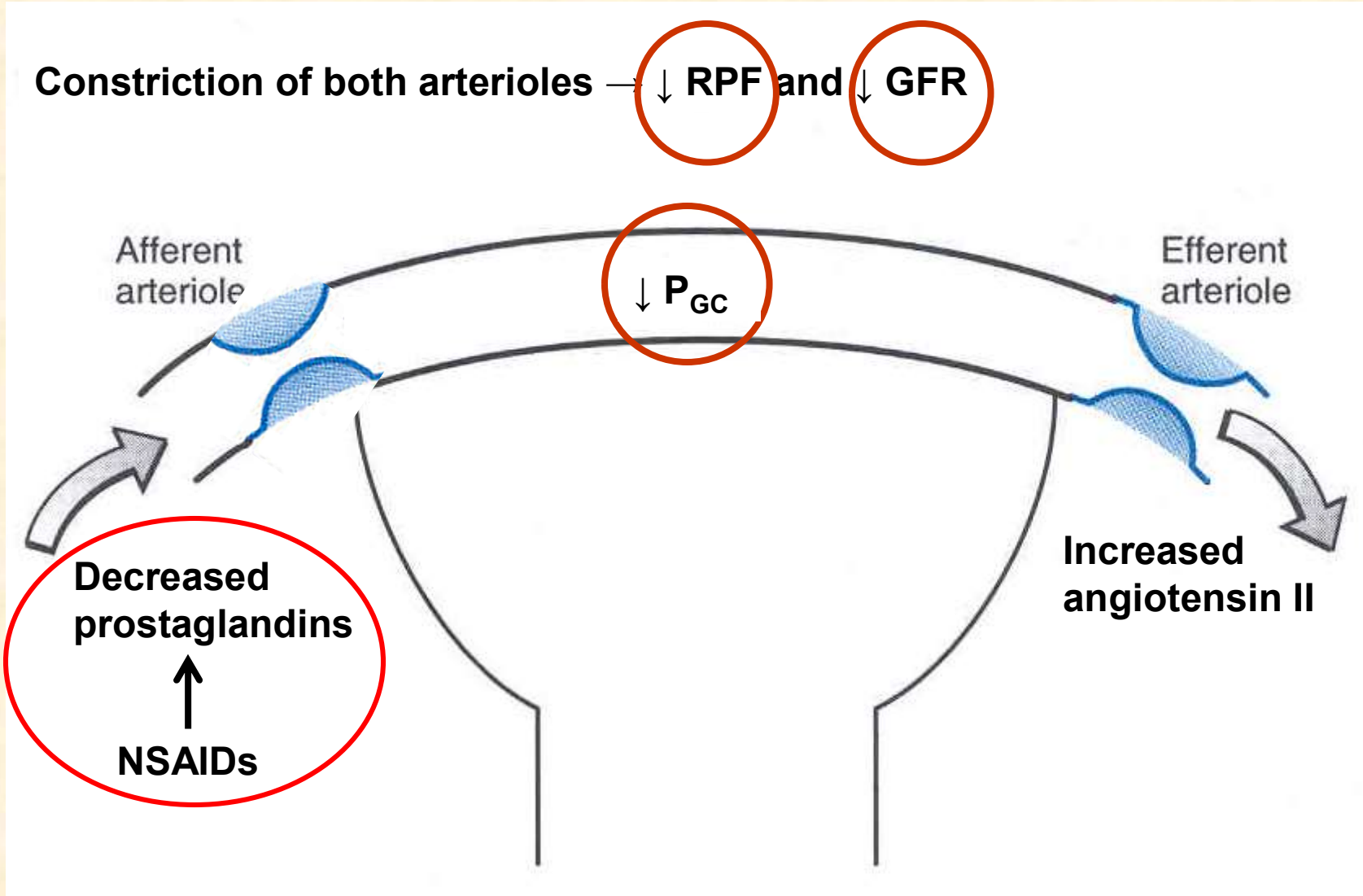


CURE-CKD Registry
JAMA Network Open
2019;2(12):e1918169

Renal actions of the prostaglandins and associated complications with NSAIDs

Physiologic effects of prostaglandins	**Adverse consequences of blocking prostaglandins with NSAIDs**
Maintain RBF and GFR (dilate afferent arteriole)	**Acute kidney injury** in states of increased renal vasoconstriction or CKD

Effect of NSAIDs on glomerular hemodynamics in states of renal hypoperfusion



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Maintain RBF and GFR (dilate afferent arteriole)	**Acute kidney injury** in states of increased renal vasoconstriction or CKD
Oppose systemic vasoconstriction	**Hypertension**
Increase renin secretion	**Hyperkalemia**, esp. in CKD patients (hyporeninemic hypoaldosteronism)
Oppose action of ADH	**Hyponatremia (SIADH)**
Increase sodium excretion	**Sodium retention** → edema, impaired response to diuretics, CHF

NSAID-related Acute Interstitial Nephritis

- T-cell mediated
- Sxs: hematuria, pyuria, WBC casts, proteinuria, acute renal failure
- Usually absent: fever, rash, eosinophilia and eosinophiluria
- Reversible within weeks to months after stopping NSAID

NSAID-related Glomerulopathies

- Minimal change disease
  - Usually accompanies acute interstitial nephritis
- Membranous nephropathy
  - Reversible within weeks to months after stopping NSAID

NSAID-induced Chronic Kidney Disease

- Prolonged use of large quantities of NSAIDs
  - Incidence is low relative to # or Rxs written
  - Pathology similar to other analgesic nephropathy (e.g., with acetaminophen)
    - Papillary necrosis/sclerosis
    - Chronic interstitial nephritis

Cardiovascular risk of nonsteroidal anti-inflammatory drugs in dialysis patients: a nationwide population-based study

Hyung Ah Jo, Dong Ki Kim, Seokwoo Park, Yaerim Kim, Seung Seok Han, Bo Ram Yang, So-Hyun Choi, Mi-Sook Kim, Joongyub Lee, Hajeong Lee ... Show more

Nephrology Dialysis Transplantation, gfz276, https://doi.org/10.1093/ndt/gfz276
Published: 14 January 2020

Results

	Odds ratio
Major cardiovascular and cerebrovascular events:	1.37
Mortality:	1.29

Risks did not increase in a dose-dependent manner.
Incidence of adverse events greater with more recent exposure.

Before starting a patient on an NSAID…..

- Check blood pressure
  - Avoid in uncontrolled or resistant hypertension
- Check kidney function
  - Avoid if eGFR <30
  - Avoid if eGFR 30-59 and on a RAASi or diuretic
- Check electrolytes (Na+, K+)
- Assess cardiovascular risk
  - Avoid in patients at high risk

Reassess while on NSAID therapy

Non-steroidal anti-inflammatory drug (NSAID) therapy in patients with hypertension, cardiovascular, renal or gastrointestinal comorbidities: joint APAGE/APLAR/APSDE/APSH/APSN/PoA recommendations.

Szeto CC et al. Gut 2020; Jan 14. pii: gutjnl-2019-319300. doi: 10.1136/gutjnl-2019-319300.

Take Home Points

- Follow this list of DO NOTS:
  - Avoid interventional strategies in kidney disease patients with acute coronary syndromes
  - Underutilize diuretics in acute decompensated heart failure because of a rise in creatinine
  - Discontinue RAAS blockers due to an initial 20-30% rise in creatinine
  - Undertreat chronic hypertension or overtreat asymptomatic transient BP rises in hospitalized patients
  - Prescribe NSAIDs for CKD patients or let them use OTC nephrotoxic herbal products or anabolic steroids

Top Ten Ways to Kill Kidneys (in order of presentation)

1. Underutilizing cardiorenal protective interventions in patients with kidney disease (death by renalism)
2. Inappropriate use of diuretics in heart failure
3. Failure to recognize early CKD
4. Not knowing when and how to prevent CIN
5. Stopping ACEIs or ARBs prematurely in CKD
6. Failure to recognize non-traumatic rhabdomyolysis
7. Failure to inquire and advise patients about nephrotoxic herbal products
8. Failure to recognize obesity-related nephrotoxicities
9. Therapeutic inertia and overtreatment of hypertension
10. Overprescribing of NSAIDs and Cox-2 inhibitors

Which of the following cardiac patients would not benefit from an initial interventional strategy (coronary angiography and revascularization)?

A. Acute ST-elevation myocardial infarction, stage 4 chronic kidney disease (eGFR 15-29 ml/min)
B. Non-ST-elevation acute coronary syndrome, stage 4 chronic kidney disease
C. Stable coronary artery disease with severe ischemia on a stress test, stage 4 chronic kidney disease 
D. All of the above

True or False: A 65-year-old male with eGFR 50 ml/min undergoing contrast CT scan of the abdomen should receive prophylaxis against contrast-associated acute kidney injury.

A. True

B. False 

Which of the following is a risk factor for renal cell cancer?

A. Diabetes

B. Hypertension

C. Obesity 

D. Nephrolithiasis

Selected References from this Presentation

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Questions…..

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