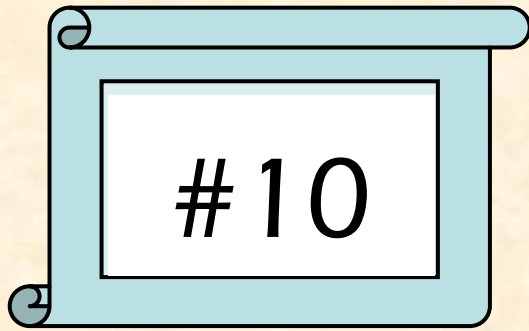


Top Ten Ways to Kill Kidneys

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



Renalism

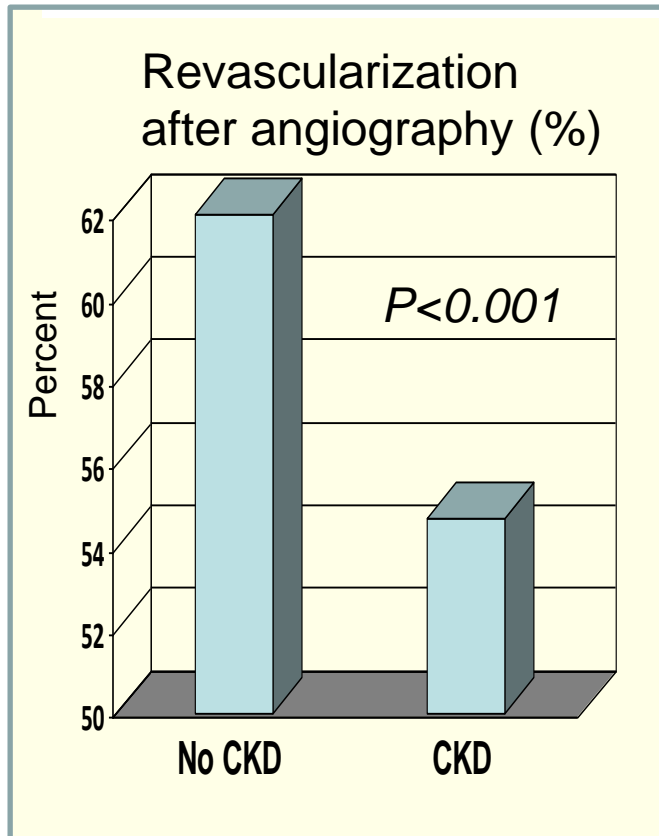
Underutilization of diagnostic and therapeutic interventions in patients with kidney disease out of concern that these interventions are more likely to do harm in this patient group.

“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 other three studies also show lower revascularization rates and higher mortality in CKD patients.

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

Iatrogenic Cardio-Nephrotoxicity after Contrast Associated-AKI in ACS Patients

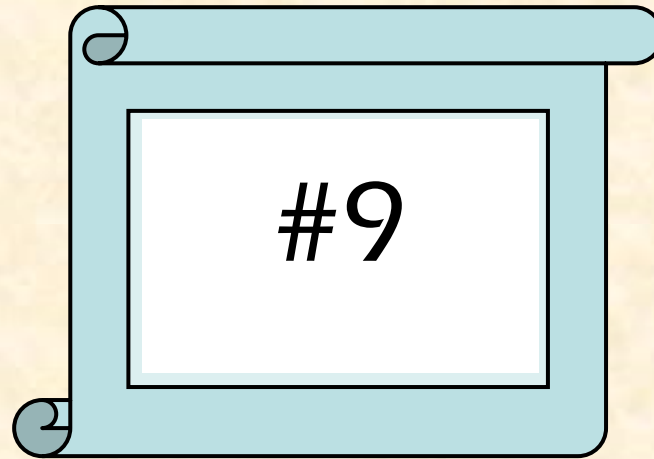
Use of cardiovascular medications after CA-AKI*

	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

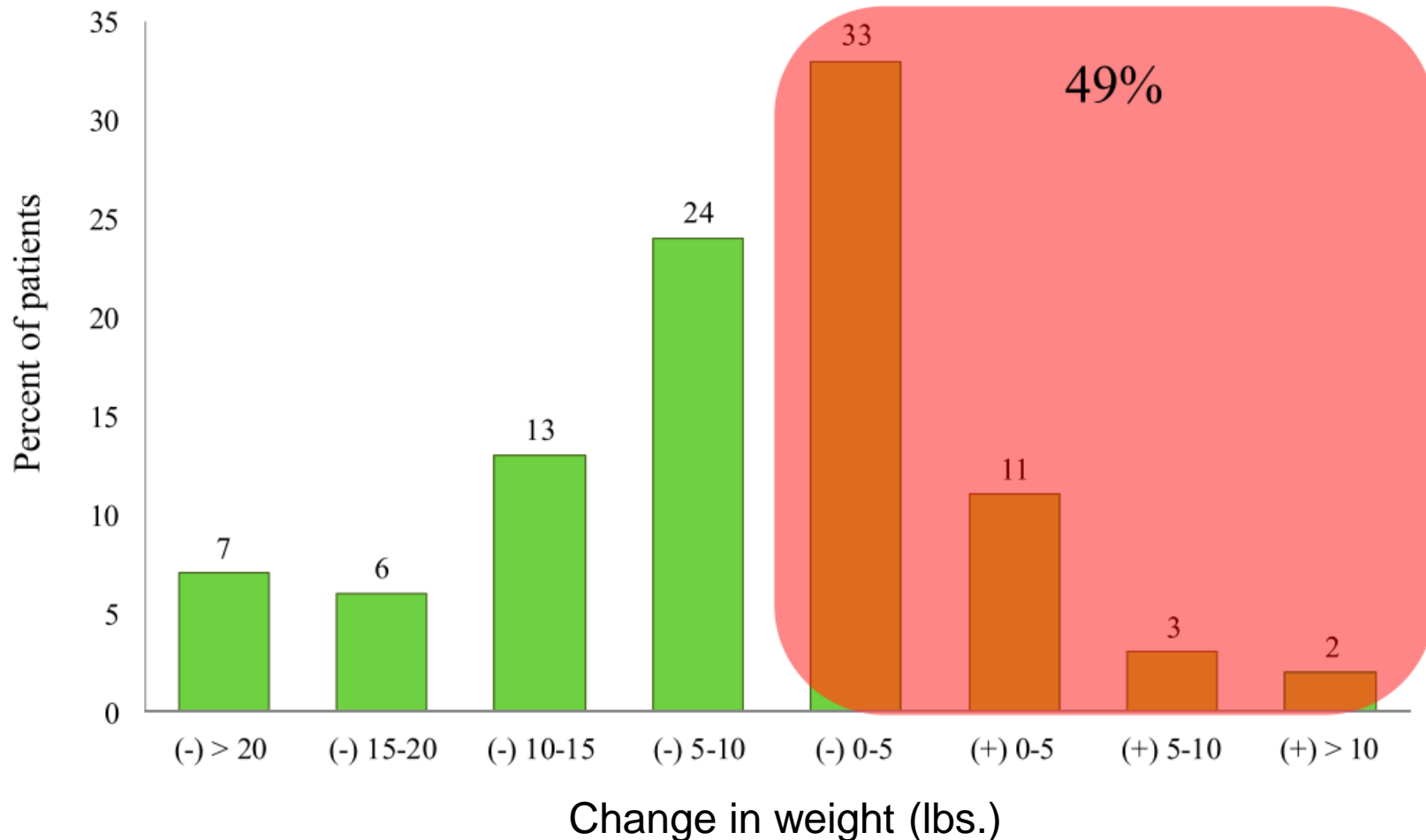
Summary on Death by Renalism

- 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!**



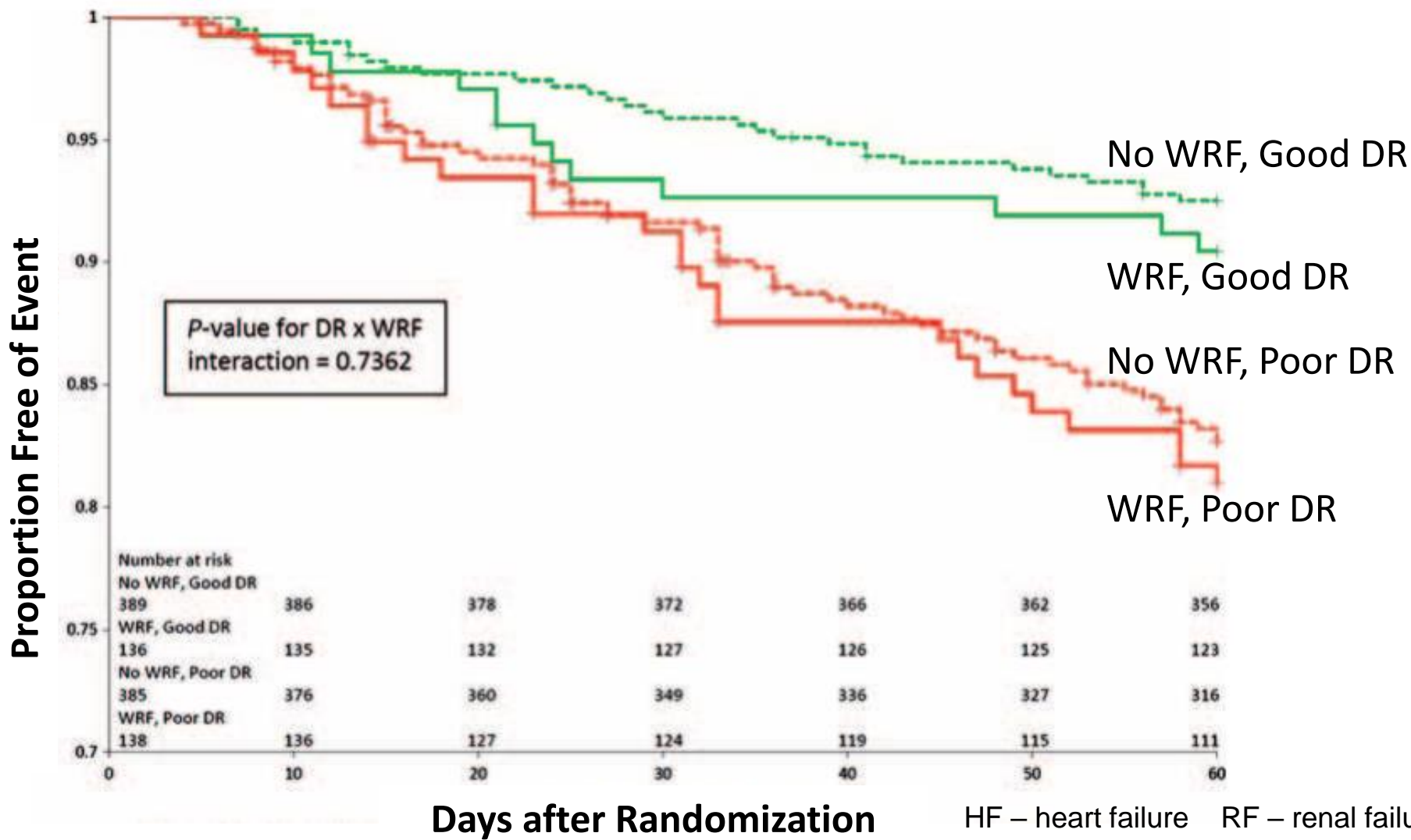
Inappropriate use of diuretics in heart failure
due to fear of worsening renal function

Diuretics in Acute Decompensated Heart Failure (ADHF National Registry)



RELAX-AHF Trial

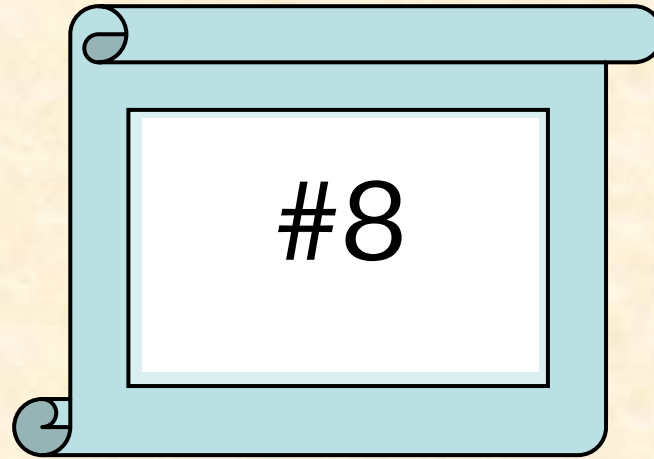
Event: Death or HF/RF readmission through day 60



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

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.**



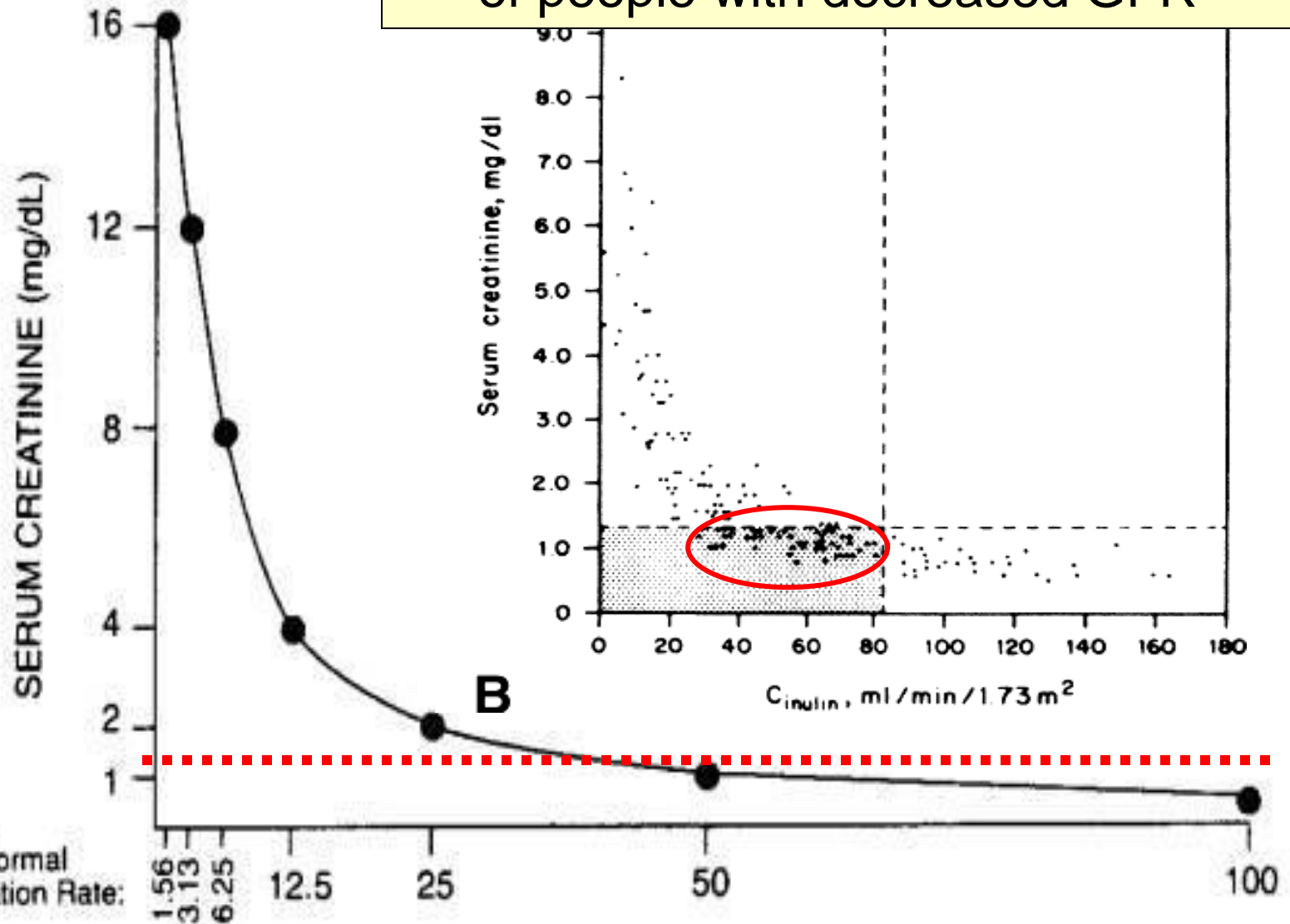
Failure to recognize early CKD due to pitfalls in interpreting tests of renal function



Delayed CKD management

GFR vs. Serum Creatinine

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



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

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

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

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

^aIcahn School of Medicine at Mount Sinai, New York, NY; ^bNational Kidney Foundation, Inc, New York, NY; ^cUniversity of Alabama at Birmingham School of Medicine; ^dUniversity of Texas Health Science Center at San Antonio; ^eJohns Hopkins University School of Medicine, Baltimore, Md; ^fHarvard Medical School, Boston, Mass.

Am J Med 2016;129:153-162

Clinical Advisor

December 9, 2019

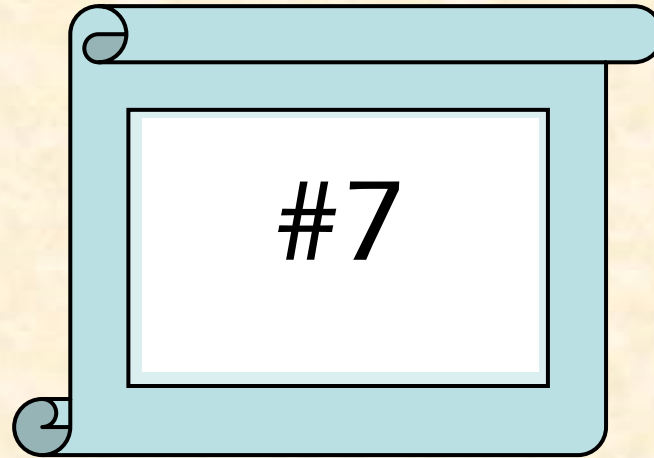
How to Recognize Chronic Kidney Disease in Primary Care



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?

Does contrast-induced nephrotoxicity exist?

- Animal studies support contrast nephrotoxicity
- 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....contrast does have the potential to cause AKI.

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



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

Who should receive prophylaxis for postcontrast acute kidney injury?

Recommendations:

- eGFR ≥ 45 ml/min/1.73 m²
 - Risk negligible: No need for prophylaxis
- **eGFR < 30 ml/min/1.73 m²**
 - **Risk high: Prophylaxis indicated**
- eGFR 30 to 45 ml/min/1.73 m²
 - Risk intermediate, but higher with DM or other risk factors
 - Consider prophylaxis

Who should receive prophylaxis for postcontrast acute kidney injury?

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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

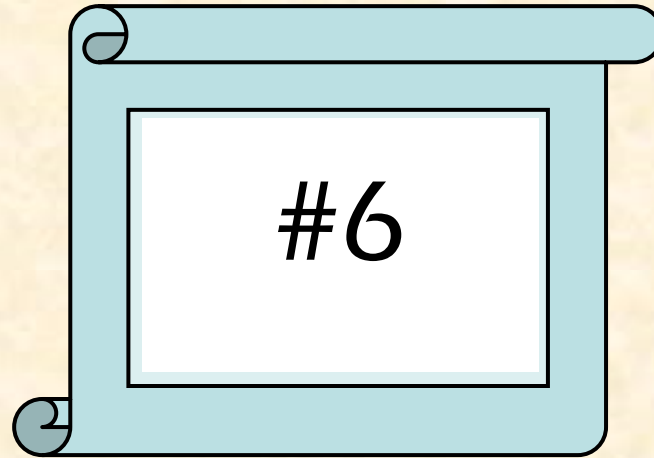
S.D. Weisbord, M. Gallagher, H. Jneid, S. Garcia, A. Cass, S.-S. Thwin, T.A. Conner, G.M. Chertow, D.L. Bhatt, K. Shunk, C.R. Parikh, E.O. McFalls, M. Brophy, R. Ferguson, H. Wu, M. Androsenko, J. Myles, J. Kaufman, and P.M. Palevsky, for the PRESERVE Trial Group*

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 studies, if possible, in high risk patients**
- **Ensure a stable Scr or eGFR before giving contrast**
- **Hydrate your patient**
 - **Normal saline**
 - Outpatients: Oral hydration may be tried
 - 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



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

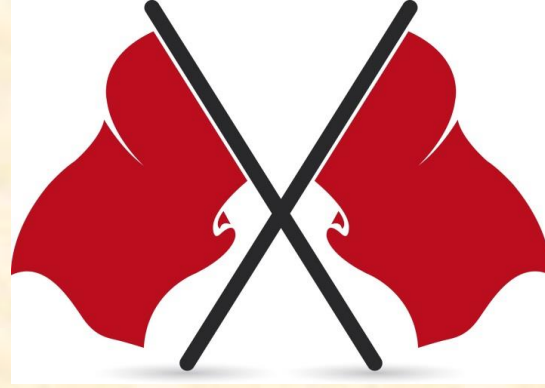
Why is this important?

- ACE inhibitors and ARBs are renoprotective
 - Antiproteinuric
 - Slow down progression of CKD
 - esp. in patients with proteinuria
- **Serum creatinine normally 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**



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





Problematic or uncertain situations

- **Elderly (>70 yo) with nonproteinuric 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



Problematic or uncertain 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

STOP-ACEi Trial – results due December 2022

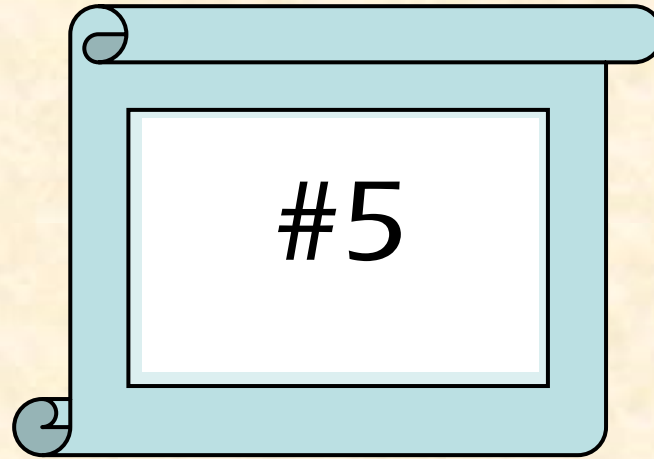
■ Dual RAAS blockade

- 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)

*LORFFAB – Late-onset renal failure from angiotensin blockade

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

Why is this important?

- In general practice, non-traumatic cases predominate
 - alcohol abuse (67%)
 - compression (39%)
 - seizures (24%)
 - drug abuse (15%).
 - AKI is the most serious complication of rhabdomyolysis
 - Prompt diagnosis and treatment can prevent AKI
- Multiple factors often coexist

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)

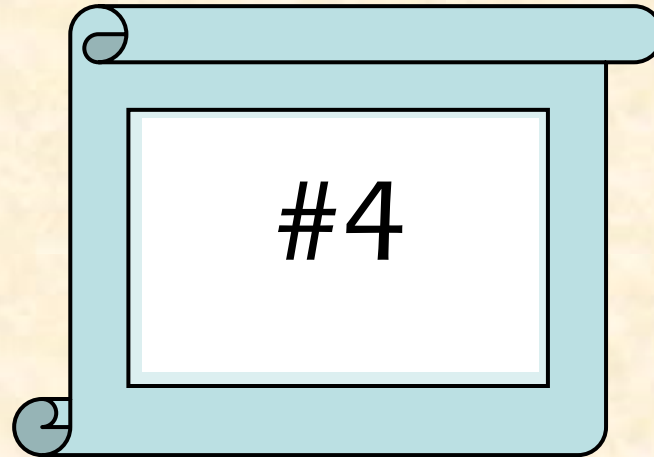
– **envenomations:** snake or spider bite

– **hypothermia**

Diagnosis:

CK: Peaks in 24-36 hours

Urine: Brown, heme + dipstick with few or no RBCs in sediment

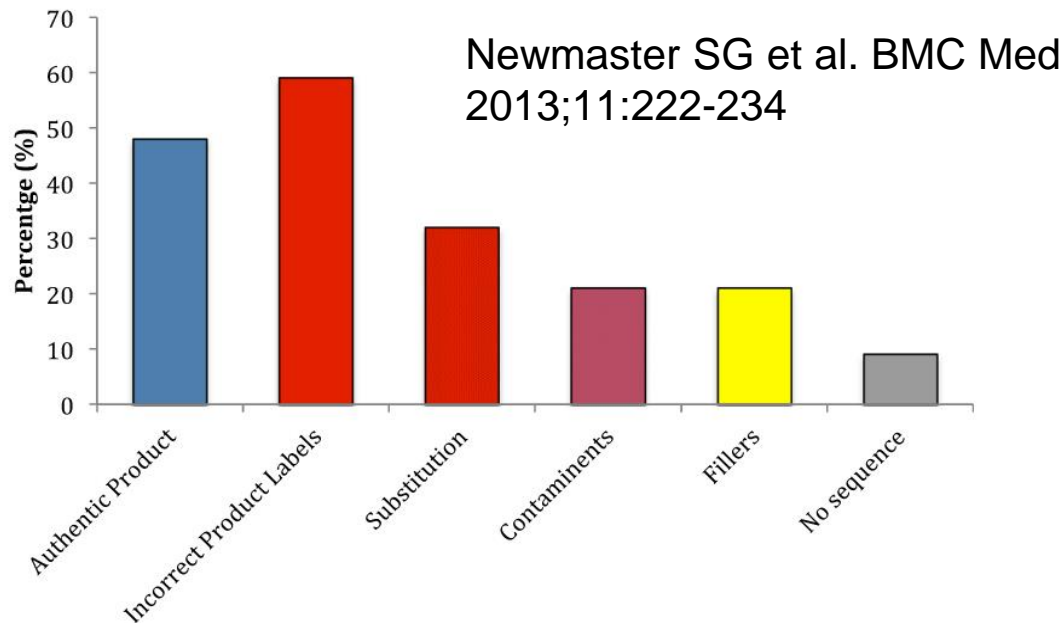


Failure to advise patients about nephrotoxic herbal products

(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 renal 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, dysmenorrhea
	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

NATURAL MEDICINES

COMPREHENSIVE DATABASE

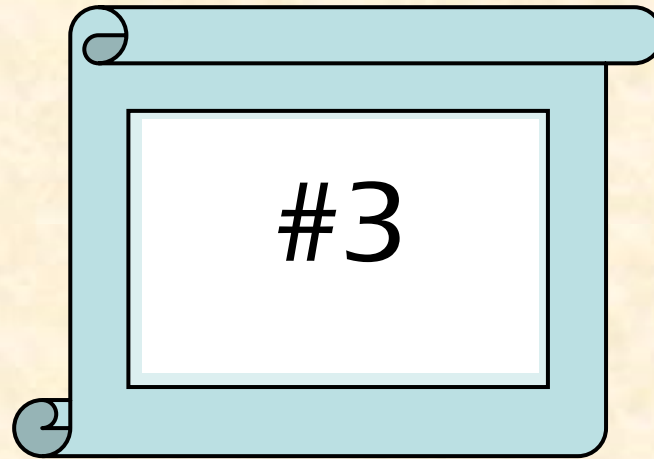


**Scientific Gold Standard for Evidence-Based,
Clinical Information on Natural Medicines**

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

Clinical findings in 21 users with AKI

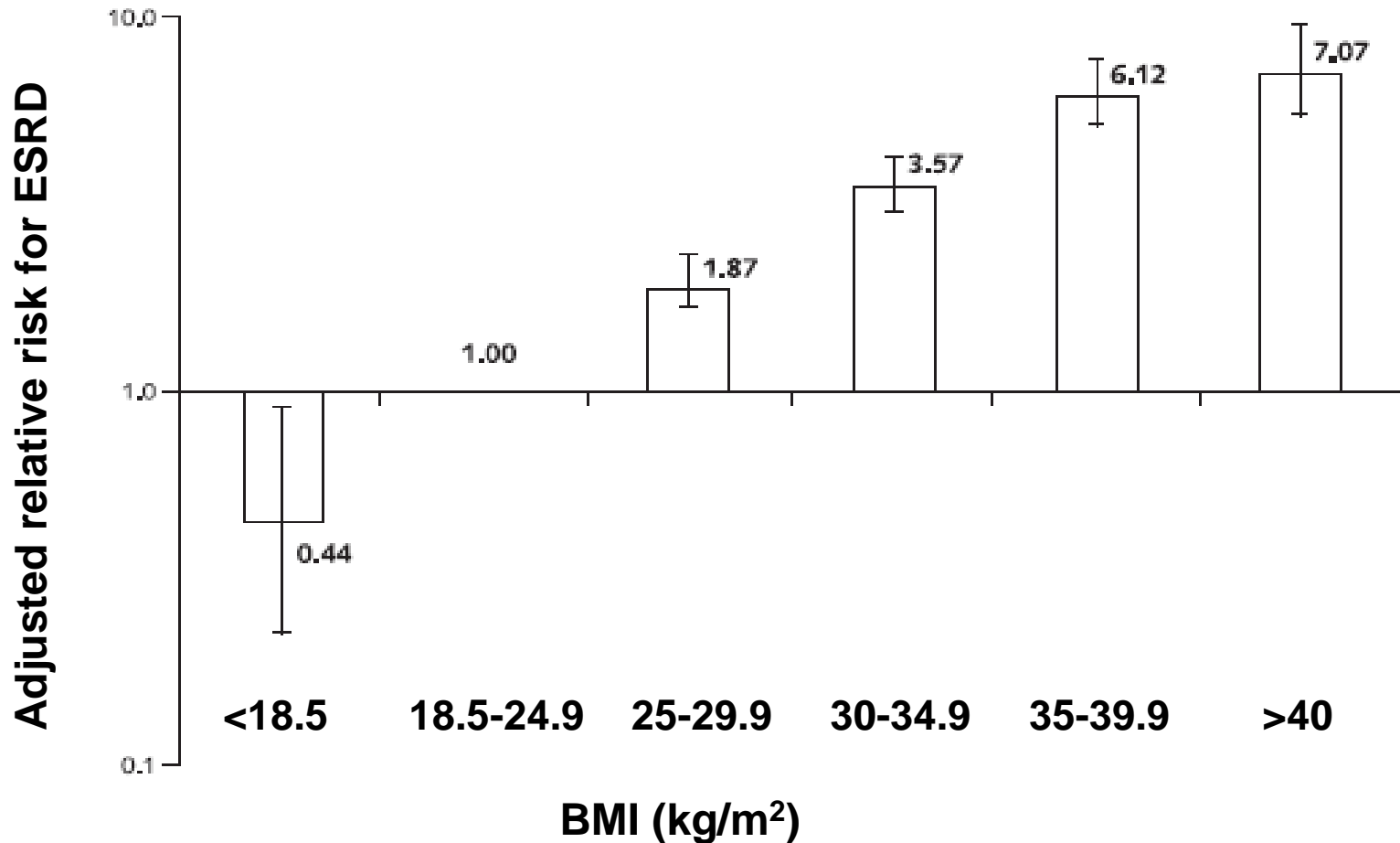
Mean age (years)	20
Male (%)	95
Presenting symptoms (%)	
Nausea and vomiting	100
Abdominal, flank or back pain	71
Mean peak serum creatinine (mg/dL)	7.7
Renal ultrasound (n=17)	
Normal	5
Increased echogenicity	12
Bilateral symmetrical enlargement	1
Renal biopsy findings (n=13)	
Acute tubular necrosis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



Failure to recognize that obesity can cause:
chronic kidney disease
nephrolithiasis
renal cell cancer

Kaiser Permanente Study

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

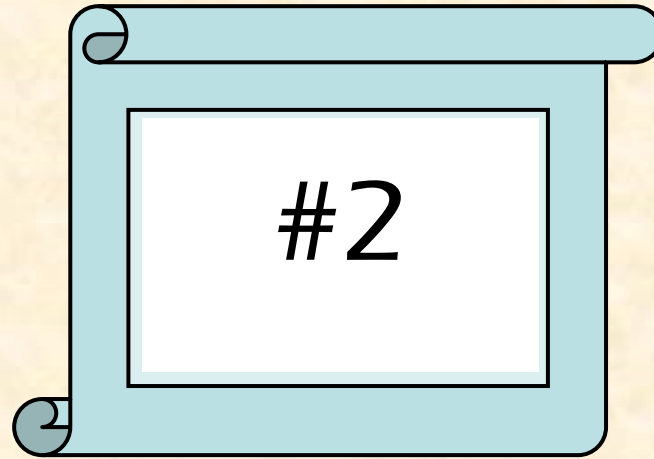


Obesity-Related Factors Contributing to Nephrolithiasis

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

Obesity-Related Cancers

Type of cancer	Relative risk* with BMI of 25–30 kg/m ²	Relative risk* with BMI of ≥ 30 kg/m ²
Colorectal (men)	1.5	2.0
Colorectal (women)	1.2	1.5
Female breast (postmenopausal)	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



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

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

- Half of the hypertensive population has uncontrolled BP
 - Most have a usual source of care
 - Most are insured
 - Most visit a health care professional at least twice per year
- Many are unaware of having hypertension
 - Despite having documented high BP, hypertension is neither diagnosed nor treated

Reasons for therapeutic inertia

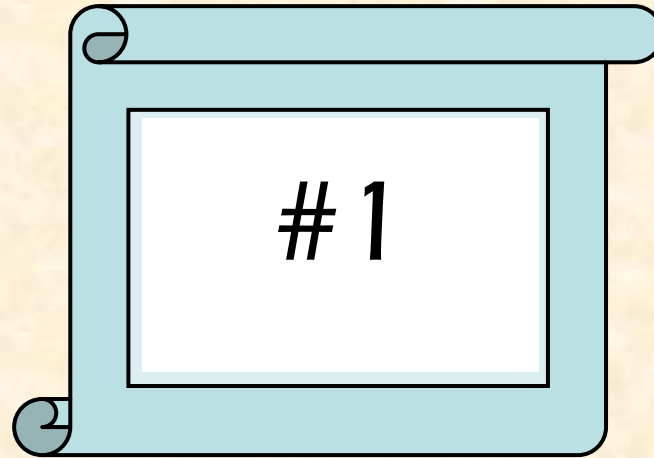
- **Not due to clinician ignorance of BP treatment goals**
 - 97% of physicians know the goals
- Inadequate knowledge of pharmacology of antihypertensive therapy
- **Lack of motivation**
 - “The BP is borderline”; “the target is almost reached”
 - “The patient won’t want to take more medication”
 - “Only 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

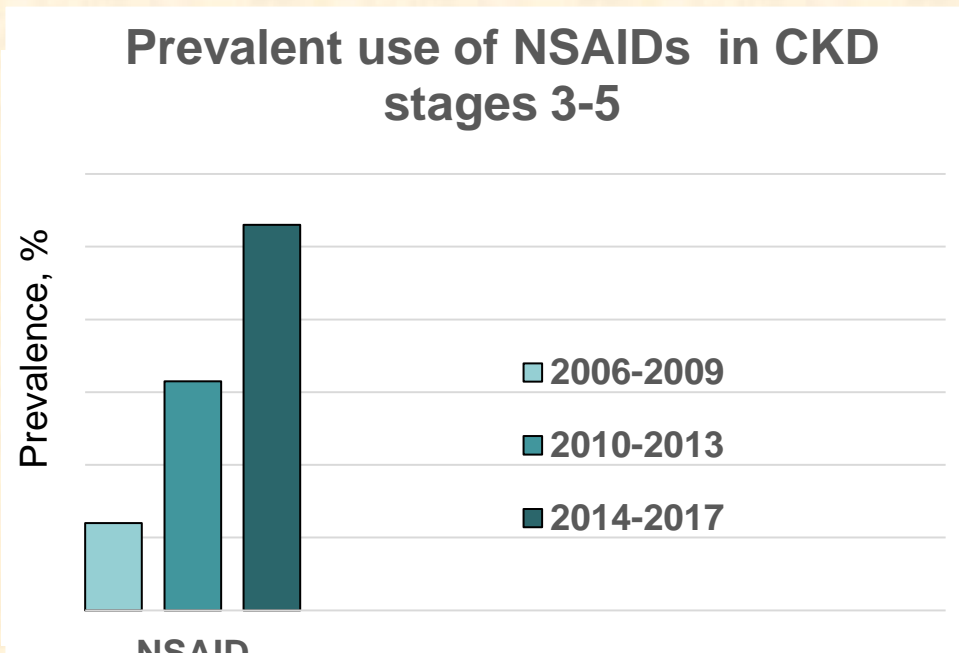
- Inappropriate use of intravenous antihypertensive drugs for a single elevated blood pressure
 - Jacobs ZG et al. J Hosp Med 2019;14:144-50
 - Pasik TS et al. J Hosp Med 2019;14:151-156
- Intensification of antihypertensive medications at hospital discharge, even with controlled BP prior to admission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



Overprescribing NSAIDs and Cox-2 inhibitors

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
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

Before starting a patient on an NSAID.....

- Check blood pressure
 - Avoid in 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.

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