Top Ten Ways to Kill Kidneys

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

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Death by Renalism

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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

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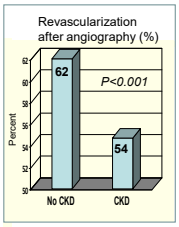
"Renalism": Inappropriately Low Rates of Coronary Angiography in Elderly Individuals with Renal Insufficiency

GLENN M. CHERTOW,* SHARON-LISE T. NORMAND,†‡ and BARBARA J. MCNEIL‡



Angiography in eligible patients (%)		
CKD	25.7	Odds Ratio 0.47
No CKD	46.8	

1-year Mortality in CKD Patients (%)				
	Overall	CABG	PTCA	PTCA + CABG
Angiography	26.7	23.4	14.3	29.8
No angiography	47.4	——	——	——

1-year Mortality (%)	
CKD	52.6
No CKD	26.4

J Am Soc Nephrol 2004;15:2462-2468

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KI REPORTS — CLINICAL RESEARCH
KIReports.org

Cardiovascular Drug Use After Acute Kidney Injury Among Hospitalized Patients With a History of Myocardial Infarction

Alejandro Y. Meraz-Muñoz[1], Nivethika Jeyakumar[2], Bin Luo[2], William Beaubien-Souligny[3], Rahul Chanchlani[2,4,5], Edward G. Clark[6], Ziv Harel[1,2], Abhijat Kitchlu[2,7], Javier A. Neyra[8], Michael Zappitelli[9], Glenn M. Chertow[10], Amit X. Garg[2,11], Ron Wald[1,2] and Samuel A. Silver[2,12]

Kidney Int Rep 2023;8:294-304

Conclusion: In patients hospitalized for a MI, **survivors of AKI were less likely** than propensity-score matched patients without AKI **to receive prescriptions for ACEi/ARB, statins, or ß-blockers** within 1 year of hospital discharge.....especially if they had stages 2 or 3 AKI.

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My Conclusions on Death by Renalism

- **Renalism is still alive and well to this day**
  - Clinicians are still underutilizing cardiorenal-protective interventions in patients with both chronic and acute kidney disease
- **Renalism is misguided**
  - It harms KD patients who are at highest risk and would benefit the most from appropriate management
- **Renalism must die before your patients do!**

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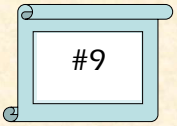

Inadequate pharmacologic management of HFrEF:
diuretics, RAAS blockers, MRAs, and SGLT2 inhibitors

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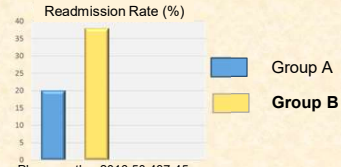
Discharge Diuretic Dose and 30-day Readmission Rate in ADHF

- 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

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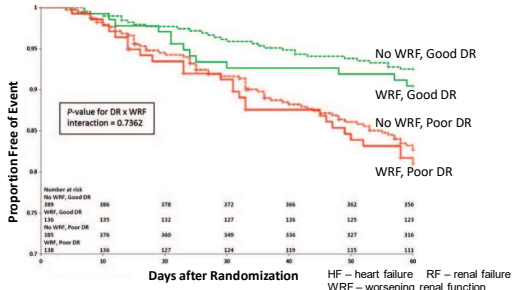
RELAX-AHF Trial

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

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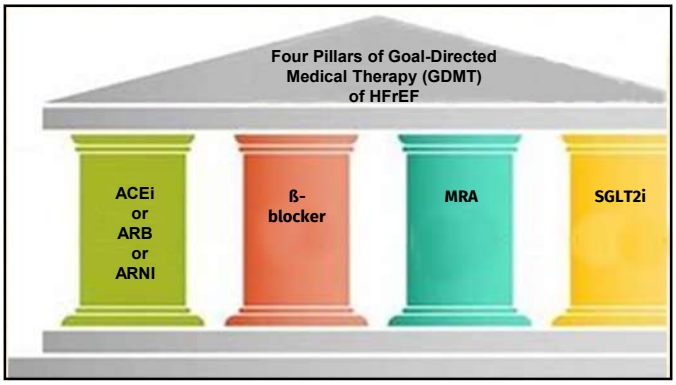

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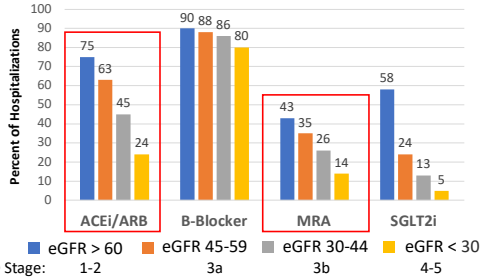
Low Rates of GDMT for HFrEF at Discharge by eGFR



J Am Coll Cardiol 2021;78:330-43; Am J Health-Syst Pharm 2023; doi.org/10.1093/ajhp/zxad177

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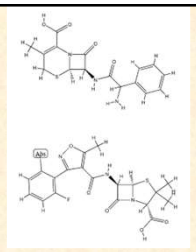
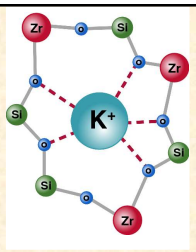


Patiromer

Potassium Binders



Sodium zirconium cyclosilicate

Diuretic dose escalation and/or an SGLT2 inhibitor can help prevent hyperkalemia
Low K^+ diet – poor correlation between dietary K^+ and serum K^+ in CKD

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My conclusions on our management of heart failure…..

- Diuretics are underdosed in treating ADHF for fear of worsening renal function.
  - Result: ↑re-hospitalization for HF and mortality
- GDMT is underused in patients with CKD
  - Fear of hyperkalemia contributes to this
  - Result: ↑morbidity and mortality

Renalism still exists in HF management just as it does in ACS management

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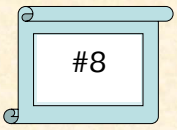

Failure to recognize CKD and thus incorrectly prescribe medications for CKD patients

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CKD is often not recognized

- 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 also not diagnosing chronic kidney disease!

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Two simple tests to screen for kidney disease

- **Estimated glomerular filtration rate (eGFR)**
- **Urine albumin:creatinine ratio (UACR)**

eGFR - kidney function
UACR – kidney and systemic inflammation

Recommended for patients **with diabetes** by:
American Diabetes Association
American College of Cardiology
KDIGO (Kidney Disease Improving Global Outcomes)

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Consider UACR Testing and eGFR determination in these at-risk populations:

- Diabetes (currently recommended in guidelines)
- 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

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What are the consequences of missing early CKD?

- **Failing to initiate renoprotective medications** when they can be of most benefit
- **Inappropriate use of medications** cleared by the kidney
  - Overdosing or prescribing contraindicated dugs
- Patients with CKD most likely to receive inappropriate medications:
  - Older age
  - Lower eGFR (esp. <30 ml/min)
  - Polypharmacy
  - Co-morbidities (DM, HTN, CVD)
  - Living in an aged care facility

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My conclusions on diagnosing and treating CKD…….

- **If you don't think of kidney disease…..you will never diagnose it!!**
- **If you don't diagnose kidney disease…..you will never treat it appropriately** and you will harm or kill your patients and their kidneys (i.e., **you will commit nephrocide and homicide!!**)

Always, Always order a UACR and eGFR in patients at risk of kidney disease……
which, in my opinion, is nearly everybody!

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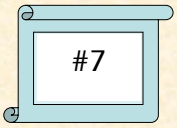

Insufficient understanding of contrast nephropathy:
Does it exist, who is at risk and how to prevent it?

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Does contrast-induced nephrotoxicity exist?

BUT…..In humans: NO RCTs

Observational studies with propensity-score matching yield mixed results:

- CT scans
  - With normal or mildly reduced renal function:
    No difference in AKI with contrast CT vs. non-contrast CT
  - With worse baseline eGFR:
    Conflicting data on rates of AKI with vs. without contrast
- Cardiac catheterization with PCI more commonly is associated with AKI
- The **causal** role of contrast is **uncertain** due to confounders and selection bias

Davenport MS. Radiology 2013;268(3):719 McDonald JS. Radiology 2014;271(1):65

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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)

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

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

- **Moderate to severe kidney disease, esp. with proteinuria**
- Diabetes
- Hypertension
- Heart failure
- Hypovolemia
- Anemia
- Advanced age
- Intra-arterial contrast administration

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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
Mehdi A et al. Cleve Clin J Med 2020;87:683-694

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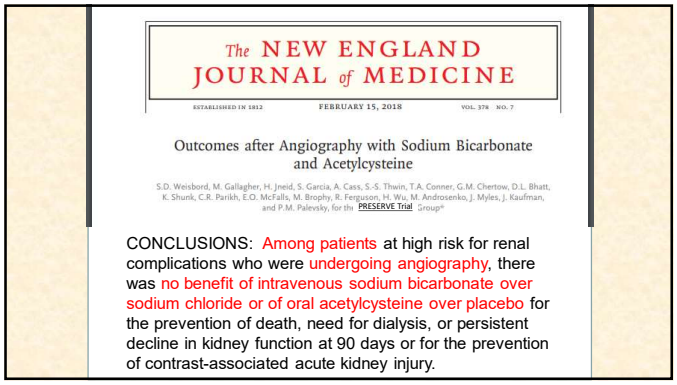

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My conclusions on contrast-associated acute kidney injury

- Prophylaxis is not indicated with stable eGFR ≥45 ml/min
- The risk of AKI is highest with eGFR <30 ml/min, especially if other risk factors co-exist

However….

- Kidney disease should not prompt aversion to contrast studies deemed necessary.
  DO NOT commit renalism and iatrogenic homicide
- Rather, promptly eliminate modifiable risk factors for AKI and assess the risk-benefit balance for using contrast

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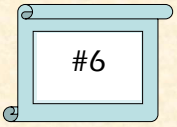

Stopping ACEIs or ARBs prematurely in advanced CKD

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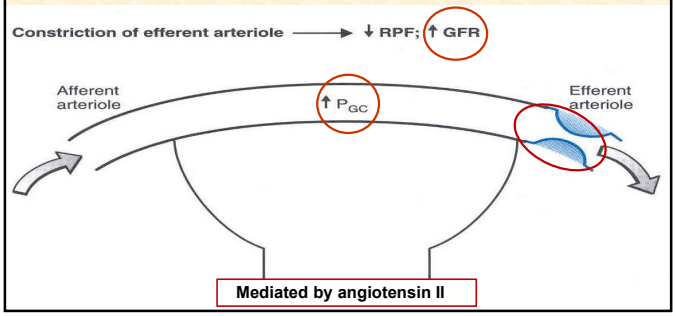
Effect of angiotensin II on glomerular hemodynamics



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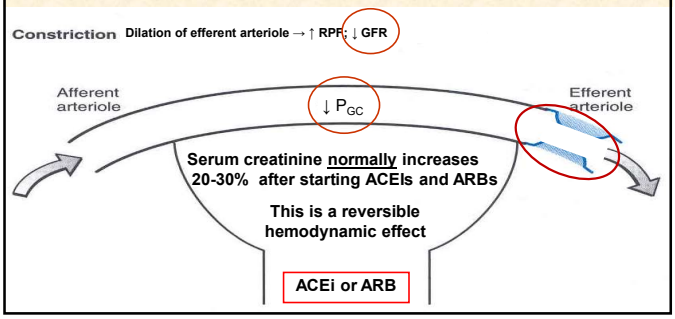
Effect of ACEIs and ARBs on glomerular hemodynamics



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What happens in late-stage CKD (eGFR <30 ml/min)? Can you delay dialysis by stopping RAAS blockers and reversing this hemodynamic effect?

- **YES ….. early observational studies**
  - Goncalves AR et al. Nephron Clin Pract 2011;119:c348–c354
  - Ahmed AK et al. Nephrol Dial Transpl 2010;25:3977-82
  - Onuigbo MA. Int J Clin Pract 2017;71:e12916
- **YES ….. but MACE and mortality increase**
  - Fu EL et al. JASN 2021;32:424-35 (5-year observational study)
- **We need an RCT**
  - STOP-ACEi Trial (3-year trial)

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The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 1, 2022 VOL. 387 NO. 22

Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease

CONCLUSIONS:

- At 3 years, there was **NO difference** in the rate of decline in eGFR or ESKD requiring renal replacement therapy.
- There was **NO difference** in adverse cardiovascular events or death, but the trial was not powered to investigate these outcomes (411 patients)

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My conclusions on RAAS blockers in CKD

- **Do not fear** an initial increase in serum creatinine of less than 30% when starting a RAAS blocker
  - Continue treatment for the cardiorenal benefit of these drugs
- **Continue** RAAS blockers in late-stage CKD
  - No acceleration to renal replacement therapy at least for 3 years
  - Possible cardiovascular and mortality benefit

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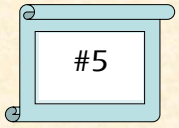

Failure to advise patients about nephrotoxic herbal products and supplements

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

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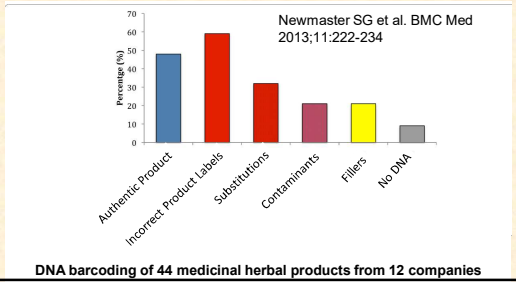
Herbal Remedies

- Used by over one-third of surveyed adults in the United States
- **Government testing and regulation are lacking in U.S.**



DNA barcoding of 44 medicinal herbal products from 12 companies

34

Nephrotoxicity of Alternative Medicine Products

- Grubbs V et al. Am J Kidney Dis 2013;61:739-74
  - NKF: 37 herbs that are nephrotoxic or can harm CKD patients
- Luyckx VA. Adv Chronic Kidney Dis 2012;19(3):129-141
  - 51 alternative medicines associated with acute kidney injury
  - 9 alternative medicines associated with chronic kidney disease
- Coms CM. Ann Clin Biochem 2003;40:489-507
  - 37 drugs found in "herbal" remedies

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BODYBUILDING WITH STEROIDS DAMAGES KIDNEYS

Bulking up with Steroids Harms Kidneys More than Obesity

ASN KIDNEY NEPHROLOGY

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)
Increased 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

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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.

Readily available at convenience stores, smoke shops, and over the internet.

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

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My Conclusions

- Always ask your patients about medicinal products that you did NOT prescribe.
- Always advise your patients about the potential harmful effects of these products.

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#4

Failure to recognize the multiple nephrocidal effects of obesity

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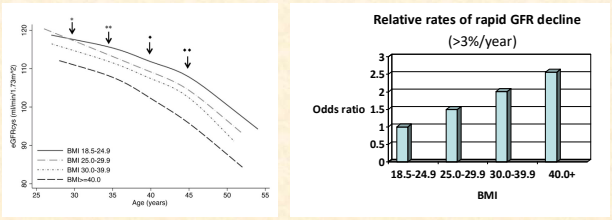
Higher BMI associates with greater decline in kidney function



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

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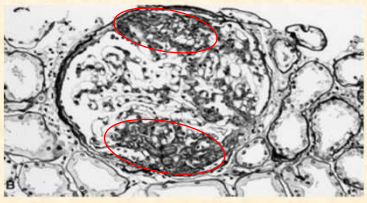
Obesity-related glomerulopathy: An emerging epidemic

- 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

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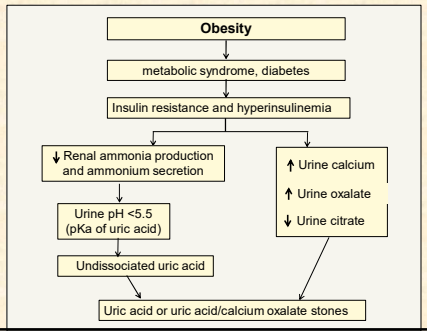
Obesity and Nephrolithiasis: Pathogenetic Path



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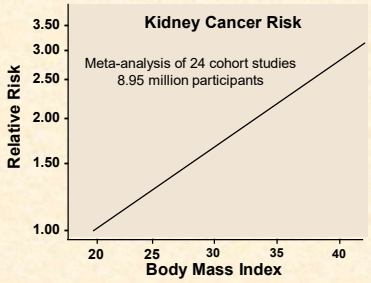
Obesity-Related Cancers

Non-renal cancers
Colorectal
Esophageal
Gastric
Liver
Pancreatic
Gallbladder
Endometrial
Breast
Thyroid

Nature Rev:Cancer 2004;4:579-91



Medicine 2018;97:44

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My conclusion on Obesity and Nephrocide

- Be aware of obesity as a contributor to:
  - Chronic kidney disease
  - Nephrolithiasis
  - Renal cell cancer

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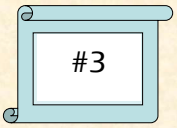

Therapeutic inertia in treating hypertension, thereby increasing CKD risk

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What is Therapeutic Inertia?

- The failure of healthcare providers to initiate or intensify therapy when goal BP is not reached.

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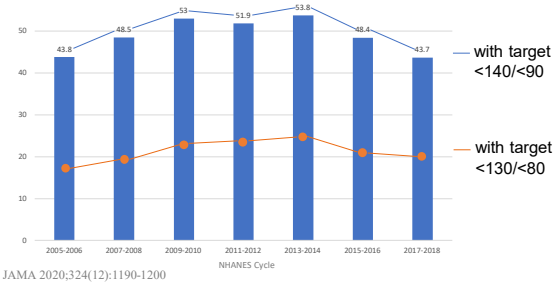
We're doing a poor job at controlling hypertension

Age-Adjusted Estimated Proportion of Adults with Controlled Hypertension



Muntner P et al. JAMA 2020;324(12):1190-1200

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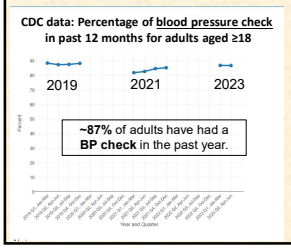
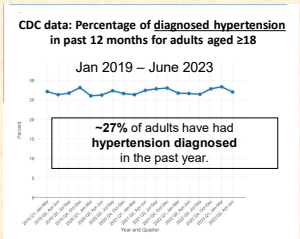
What is the extent of therapeutic inertia in the U.S.?

- Many are unaware of having hypertension
- **Despite having documented high BP, hypertension is neither diagnosed nor treated**





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Utilization Patterns of Antihypertensive Drugs Among the Chronic Kidney Disease Population in the United States: A Cross-sectional Analysis of the National Health and Nutrition Examination Survey

Kalyani B. Sonawane, BS; Jingjing Qian, PhD; and Richard A. Hansen, PhD
Harrison School of Pharmacy, Health Outcomes Research and Policy, Auburn, Alabama

Findings: Among the surveyed U.S. CKD population, less than half were taking antihypertensive drugs.
ß-blockers were the most commonly used and ARBs were the least used.

Conclusion: Antihypertensive drugs are underused in CKD patients and the use of preferred agents is low.

Clin Ther 2015;37:188-196

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Reasons for therapeutic inertia

- **Not due to clinician ignorance of BP treatment goals**
  - Most 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"

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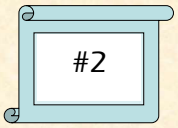

Overtreatment of asymptomatic elevated blood pressure in stable hospitalized patients

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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. BMJ Open Access 2018;362;k3503
  - Anderson TS et al. JAMA Intern Med 2019;179:1528-1536

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JAMA Internal Medicine | Original Investigation | LESS IS MORE

Clinical Outcomes of Intensive Inpatient Blood Pressure Management in Hospitalized Older Adults

Timothy S. Anderson, MD, MAS; Shoshana J. Herzig, MD, MPH; Bocheng Jing, MS; W. John Boscardin, PhD; Kathy Fung, MS; Edward R. Marcantonio, MD, SM; Michael A. Steinman, MD
JAMA Intern Med 2023;183(7):715-723

66,140 veterans hospitalized for noncardiac diagnoses, mean age 74 yrs.
Retrospective cohort study with propensity score matching
Comparison: Treatment vs. no treatment in first 48 hours of hospitalization
Composite outcome: acute kidney injury, mortality, ICU transfer, stroke, ↑BNP, ↑troponin
- Treated vs. untreated OR 1.28
- IV treatment: Composite OR 1.90; mortality OR 1.79

Conclusion: Intensive inpatient antihypertensive treatment, especially with IV drugs, is harmful in older adults without evidence of end organ damage.

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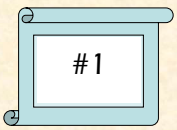

Prescribing NSAIDs and Cox-2 inhibitors without knowing their many nephrotoxic effects

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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 and hence aldosterone secretion	**Hyperkalemia**, esp. in CKD patients (hyporeninemic hypoaldosteronism)
Oppose action of ADH	**Hyponatremia (SIAD)**
Increase sodium excretion	**Sodium retention** → edema, impaired response to diuretics, CHF

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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

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NSAID-related Glomerulopathies

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

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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

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My conclusions: 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.

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Take Home Points

Follow this list of **DO NOTS**:

- Reflexively avoid interventional strategies in kidney disease patients with acute coronary syndromes
- Underutilize diuretics in acute decompensated heart failure because of a rise in creatinine or avoid GDMT because of hyperkalemia
- Discontinue RAAS blockers due to an initial 20-30% rise in creatinine or in advanced chronic kidney disease
- 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, anabolic steroids, or cannabinoids

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