Integrating CKD into Primary Care:
Bridging the Knowledge and Implementation Gaps

Matthew R. Weir, MD
Professor and Director
Division of Nephrology
University of Maryland School of Medicine
Baltimore, MD

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Disclosure

Consultant: AstraZeneca; Bayer; Boehringer Ingelheim; Corcept; CSL Vifor; Mineralys; Novo Nordisk; Vera

Salary Support: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

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Overview

- Primary care education and implementation gaps in CKD from the perspectives of testing, detection of disease, and education
- Interventions for management, interdisciplinary care
- Patient safety considerations
- Quality improvement

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Prevention Requires Timely Evaluation and Education of Those at Risk for Kidney and Heart Disease:

- Hypertension
- Diabetes
- African heritage
- Obesity

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Perspective

- CKD affects 10-15% of adults who experience high rates of cardiovascular events and are at risk of kidney failure.
- Mortality is under-recognized as a competing event versus end-stage kidney disease (ESKD).

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All of the Following Are True About US Population Level Care for People with GFR Below 60 ml/min Except:

A. Approximately 40% receive UACR testing
B. Only 12-20% have a CKD diagnosis
C. Less than 50% have controlled hypertension
D. 40% have controlled diabetes
E. Most patients are on ACEi or ARB

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- Recent evaluation of US population-level care for individuals with eGFR below 60 ml/min per 1.73 m2 reveals that
- Approximately 40% receive UACR testing
- Only 12% to 20% have evidence of a CKD diagnosis
- Less than 50% have controlled hypertension
- 40% have controlled diabetes
- 29% to 31% use statins to reduce cardiovascular events,6 less than 50% are treated with angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) drugs,6 and nephrology services are delivered to only approximately 50% of patients with CKD G4 and G5

USRDS 2021
CJASN 2019; 14: 1142
PLOS One 2014; 9:e110535

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Kidney Health Inequities by Black Race and Ethnicity

- Twice the prevalence of hypertension that causes or contributes to CKD
- Approximately 3 times the prevalence of ESKD
- Less use of patient-centric kidney replacement therapies, home dialysis, and kidney transplantation.

AJKD 2021;78:103-115
USRDS 2021

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Primary Care Implementation of CKD Testing

- Routine primary care case finding for CKD with eGFR and UACR should focus on risk conditions:
  - Diabetes
  - Hypertension
  - Cardiovascular disease
  - Family history of kidney disease

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Perspective

- Annual UACR testing is approximately 40% for diabetes and less than 10% for hypertension in national data sets from Medicare, commercial insurance, health systems, and clinical laboratories, supporting the need for interventions to improve targeted albuminuria testing
- There are some challenges for clinicians to order UACR
- Laboratories do not universally offer the test
- Reporting formats vary, introducing inconsistencies and complexity in the interpretation of the results.

Diabetes Care 2021;44:2000-2009
Diabetes Care 2021;44:2025-2032

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- Clinicians are unlikely to order tests that they are not sure how to interpret, suggesting low rates of albuminuria testing may simply reflect an underappreciation in the utility of the results or challenges in the interpretation.

Kidney Int Reports 2020;5:392-395

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True or False

Primary Care CKD Detection Rate in Patients with T2DM Was Only 12% in the ADD-CKD Study of More Than 9000 Patients

A. True
B. False

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Primary Care CKD Detection

- Detection of CKD using CKD diagnosis codes remains low in primary care practice, although chart review or natural language processing analysis more accurately reflects clinician diagnosis.
- The ADD-CKD study of more than 9 thousand US patients with type 2 diabetes managed by 466 primary care clinicians revealed a CKD detection in only 12% of the population with laboratory evidence for the condition.
- Importantly, awareness or patient self-reported CKD was 81.1% with practitioner detection versus 2.6% in the absence of diagnosis.

Plos One 2014;26e110535

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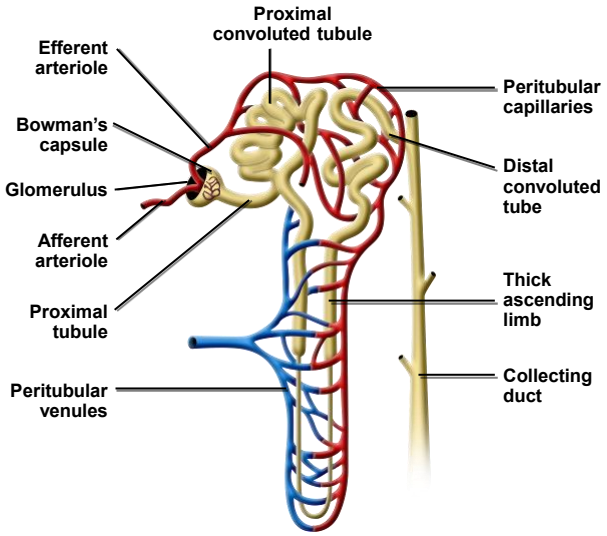
The Nephron Is the Functional Unit of the Kidney – Loss of Nephrons Translates to Loss of Function



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Clinical Evaluation of Patients at Increased Risk of CKD

- All patients
  - Blood pressure
  - Serum creatinine
  - RBC or WBC in urine samples
  - Protein in urine
  - Serum glucose and lipids
  - Serum electrolytes

- Selected patients, depending on risk factors
  - Ultrasound imaging (polycystic kidney, infection, obstruction of stones)
  - Urine Protein: Creatinine or albumin: creatinine ratio
  - Urinary microalbumin
  - Urinary concentration or dilution
  - Urinary acidification

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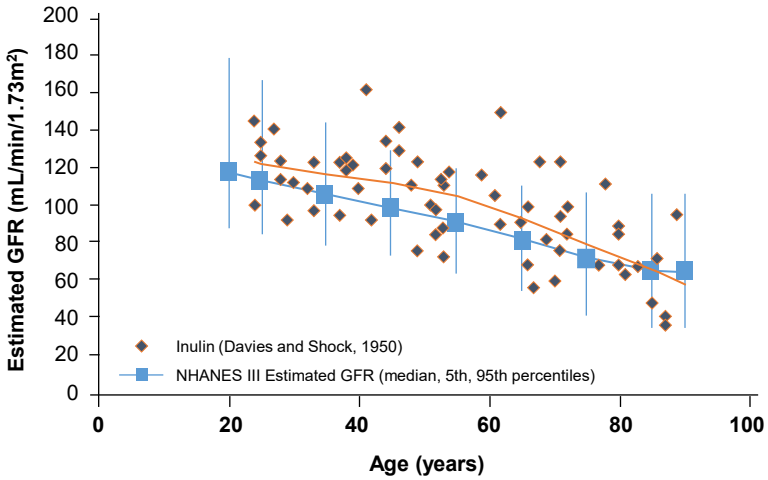
Estimated Glomerular Filtration and Normal Aging



Uremia, Ca-PO_4 imbalance, volume overload, oxidative stress, inflammation, anemia → incident CVD, CVD death

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Definitions of Proteinuria

Urine Collection Method	Normal	Microalbuminuria	Albuminuria or Clinical Proteinuria
Total protein			
24-Hour excretion (varies with method)	< 300 mg/d	NA	≥ 300 mg/d
Spot urine dipstick	< 30 mg/dL	NA	≥ 30 mg/dL
Spot urine protein-to-creatinine (varies with method)	< 200 mg/g	NA	≥ 200 mg/g
Albumin			
24-Hour excretion	< 30 mg/d	30–300 mg/d	> 300 mg/d
Spot urine albumin-specific dipstick	< 3 mg/dL	> 3 mg/dL	NA
Spot urine albumin-to-creatinine ratio (varies by sex)	< 17 mg/g (men) < 25 mg/g (women)	17–250 mg/g (men) 25–355 mg/g (women)	> 250 mg/g (men) > 355 mg/g (women)

NA indicates not applicable.

* Sex-specific cutoff values are from a single study. Use of the same cutoff value for men and women leads to higher values of prevalence for women than men. Current recommendations from the American Diabetes Association define cutoff values for spot urine albumin-to-creatinine ratio for microalbuminuria and albuminuria as 30 and 300 mg/g, respectively, without regard to sex.

Reproduced and modified with permission from the National Kidney Foundation.

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True or False

eGFR Below 30 ml/min Is Associated 22-37-fold Increase in CV Events and 11-14-fold Increased Risk of Death

A. True
B. False

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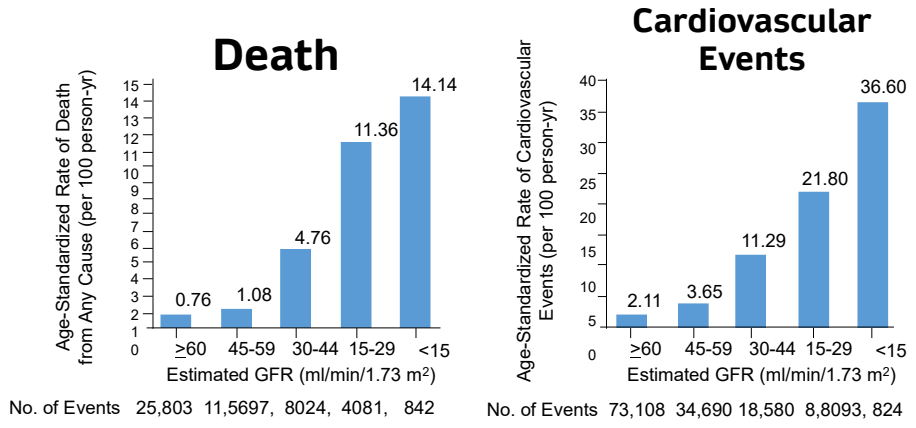
Lower eGFR Is Associated with Cardiovascular Events and Death



A large integrated health system including 1,120,295 patients with serum creatinine measured between 1996-2000 and median follow-up of 2.84 years.
Go AS, et al. *N Engl J Med*. 2004;351:1296-1305.

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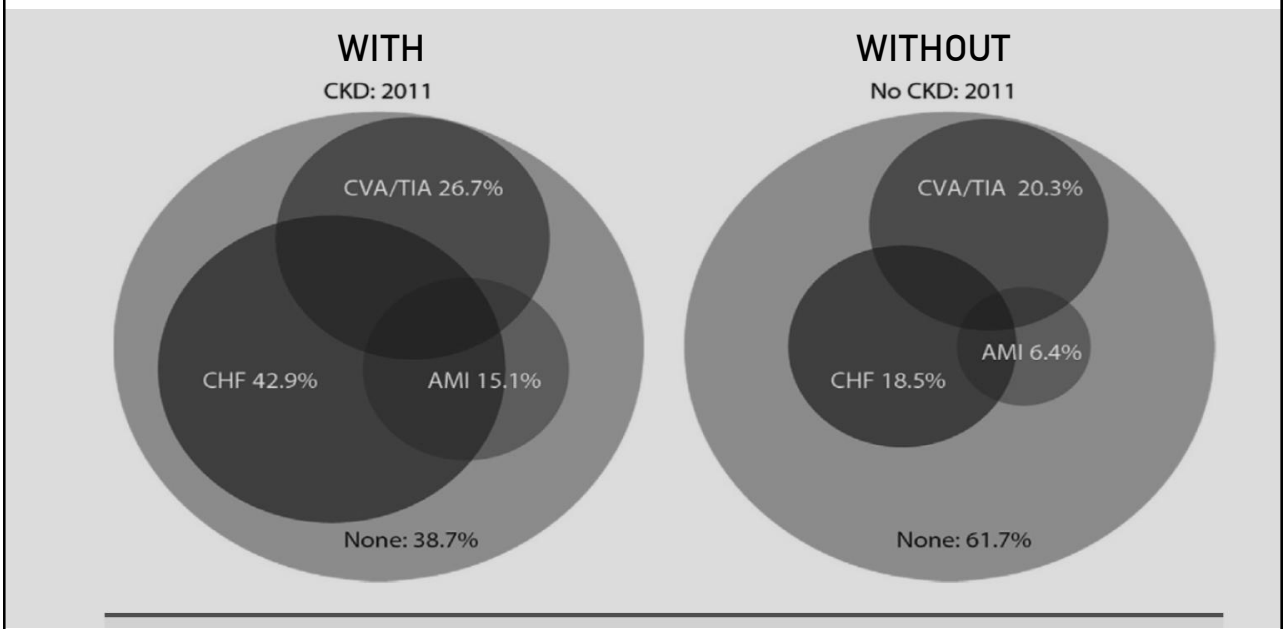
Cardiovascular Disease in Patients With or Without Chronic Kidney Disease



House AA Am J Kidney Dis 2018;72:284

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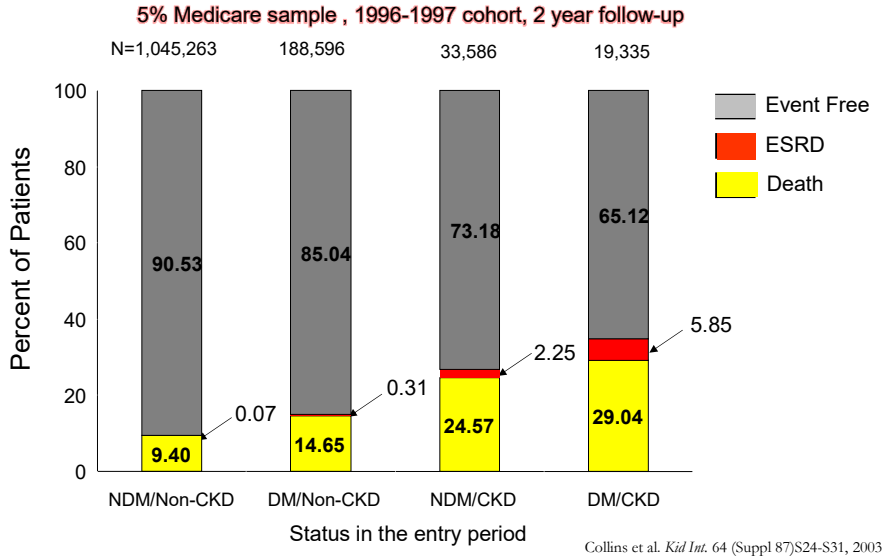
Patients Diagnosed with CKD Have a Greater Likelihood of Death Than ESRD



Collins et al. *Kid Int.* 64 (Suppl 87)S24-S31, 2003

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Percentage of individuals in the various CKD (eGFR and albuminuria) risk categories (KDIGO 2012)

GFR categories (ml/min/1.73 m²)				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal to high	≥ 90	54.7	4.3	0.4
	G2	Mildly decreased	60-89	30.4	2.6	0.3
	G3a	Mildly to moderately decreased	45-59	3.9	0.9	0.2
	G3b	Moderately to severely decreased	30-44	1.0	0.5	0.2
	G4	Severely decreased	15-29	0.1	0.1	0.2
	G5	Kidney failure	< 15	<0.001	0.001	0.01

2016 Annual Data Report, Vol 1, CKD, Ch 1

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Outcomes Associated with CKD

All-cause mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	1.1	1.5	2.2	5.0
eGFR 90–105	Ref	1.4	1.5	3.1
eGFR 75–90	1.0	1.3	1.7	2.3
eGFR 60–75	1.0	1.4	1.8	2.7
eGFR 45–60	1.3	1.7	2.2	3.6
eGFR 30–45	1.9	2.3	3.3	4.9
eGFR 15–30	5.3	3.6	4.7	6.6

Kidney failure (ESRD)

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	Ref	Ref	7.8	18
eGFR 90–105	Ref	Ref	11	20
eGFR 75–90	Ref	Ref	3.8	48
eGFR 60–75	Ref	Ref	7.4	67
eGFR 45–60	5.2	22	40	147
eGFR 30–45	56	74	294	763
eGFR 15–30	433	1044	1056	2286

Acute kidney injury (AKI)

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	Ref	Ref	2.7	8.4
eGFR 90–105	Ref	Ref	2.4	5.8
eGFR 75–90	Ref	Ref	2.5	4.1
eGFR 60–75	Ref	Ref	3.3	6.4
eGFR 45–60	2.2	4.9	6.4	5.9
eGFR 30–45	7.3	10	12	20
eGFR 15–30	17	17	21	29

Levey et al., Kidney Int 2011; 80: 17-28

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KDIGO “Heat Map”: Risk of CKD Progression and CVD Events and Monitoring

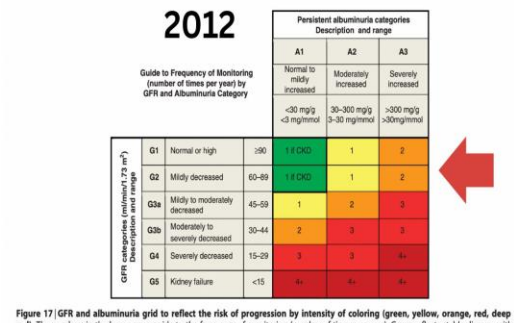

Figure 17 | GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). Green reflects stable disease, with follow-up measurements annually if CKD is present; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements at 3 times per year while deep red may require closest monitoring approximately 4 times or more per year (at least every 1–3 months). These are general parameters only based on expert opinion and must take into account underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient. CKD, chronic kidney disease; GFR, glomerular filtration rate. Modified with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al.[19] The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17–28; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

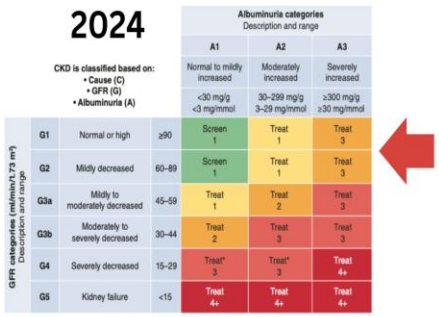

Figure 13 | Frequency of monitoring glomerular filtration rate (GFR) and albuminuria in people with chronic kidney disease (CKD). Albuminuria and GFR grid reflects the risk of progression by intensity of coloring (green, yellow, orange, red, and deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). Reproduced from de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2022;102:974–989.[20] Copyright © 2022, International Society of Nephrology, American Diabetes Association, and KDIGO. Published by Elsevier Inc. and American Diabetes Association. All rights reserved.

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SCREENING

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Recommend Screening Techniques for CKD Include All of the Following Except:

A. Serum creatinine to estimate GFR
B. 24-hour urine collection for protein
C. Spot urine albumin: creatinine ratio
D. Spot urine: protein creatinine ratio

*Estimate GFR
*Quantitate albuminuria/proteinuria
*Measure longitudinal changes over time

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Decreased GFR Has Consistently Been Found to Be an Independent Risk Factor for CVD Outcomes and All Cause Mortality!

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The Key Understanding Is That Patients with CKD Benefit as Much as Non-CKD Patients with Appropriate Medications and Therapies, If Not More, Because of Their Increased Risk!

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Treatment

- Evidence-based approaches to slow chronic kidney disease
  - Blood Pressure
  - RAAS blockade
  - Glucose control
- Correction of acidosis
- Albuminuria Suppression
- Pathophysiology of kidney disease progression
  - Glomerular capillary hypertension
  - Inflammation
- Newer opportunities

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Blood Pressure Goals

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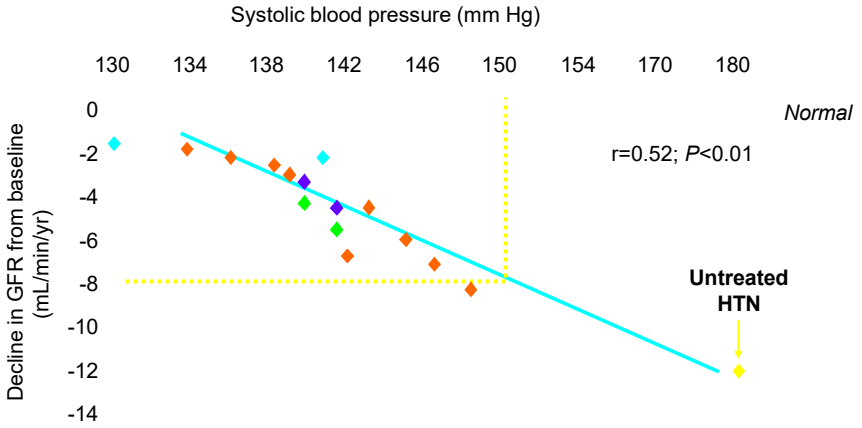
Lowering Blood Pressure Slows Progression of Chronic Kidney Diseases



Trials included: MDRD, RENAAL, IDNT,AIPRI, Captopril Trail, REIN, AASK.
Modified from Bakris GL et al. Am *J Kidney Dis.* Sept. 2000.

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RAAS Blockade:

Provides on Average a 20% Relative Risk Reduction!

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Try Not To Stop ACEi or ARB: Hyperkalemia

- Dietary potassium counseling
  - Review dietary habits (high potassium foods)
  - Make sure patient not on salt substitute
  - Make sure patient not taking herbals or NSAIDS
- Diuretic dose adjustment
  - Increase dose if
    - BP not low
    - Creatinine not increasing

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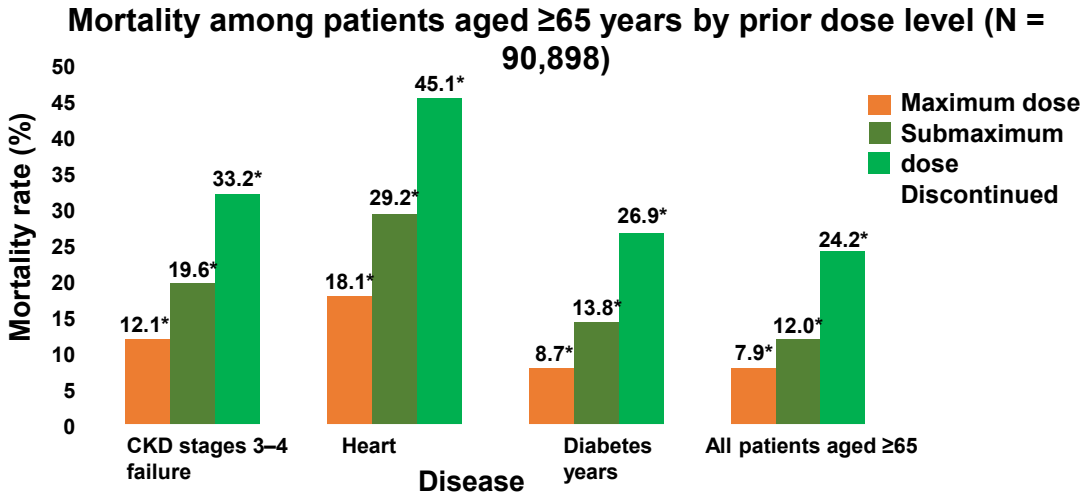
Higher Mortality Among Patients Discontinued or Lower-Dose RAASi Compared with Patients Prescribed RAASi At Maximum Dose



*All comparisons differed significantly ($P<.0001$)
RAAS = renin-angiotensin-aldosterone system; RAASi = RAAS inhibitor.

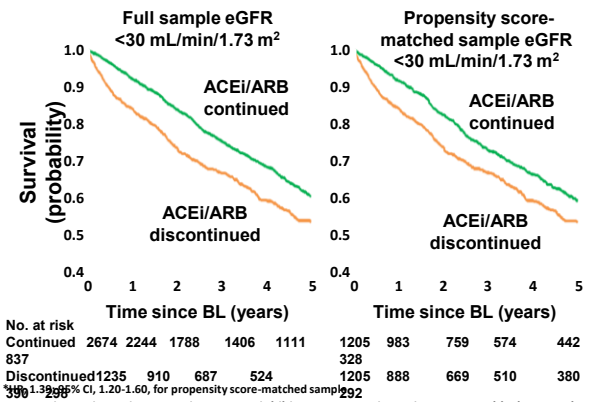
Epstein M, et al. *Am J Manag Care*. 2016;22(11 suppl):S311-S324 and supplement.

35

Cumulative Incidence of All-Cause Mortality and ESKD Accounting for Competing Risk of Death by ACEi and ARB Discontinuation Status

Retrospective, propensity-matched study
3909 patients from Geisinger healthcare system

All-cause mortality



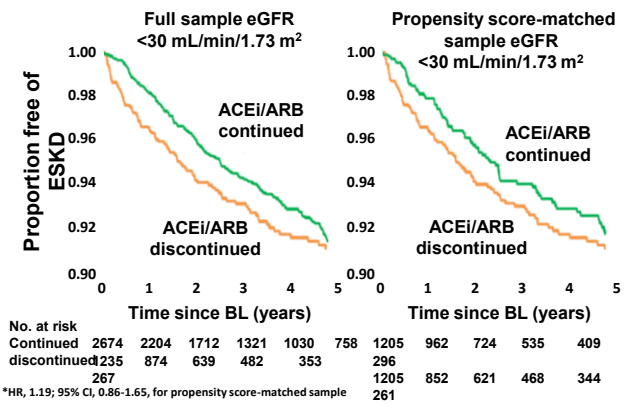
No. at risk										
Continued	2674	2244	1788	1406	1111	1205	983	759	574	442
Discontinued	1235	910	687	524	388	1205	888	669	510	380

*HR, 1.39; 95% CI, 1.20-1.60, for propensity score-matched sample

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BL = baseline.

Qiao Y, et al. *JAMA Intern Med*. 2020;180:718-726.

ESKD accounting for competing risk of death



No. at risk										
Continued	2674	2204	1712	1321	1030	758	1205	962	724	535	409
discontinued	1235	874	639	482	353	267	1205	852	621	468	344

*HR, 1.19; 95% CI, 0.86-1.65, for propensity score-matched sample

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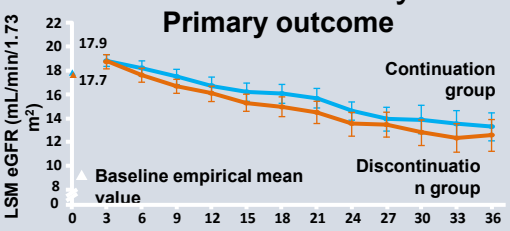
Primary Outcome of STOP ACEi Study



Difference, -0.7; 95% CI, -2.5 to 1.0, P=0.42, with negative value favoring outcome in continuation group

Subgroup analysis of primary outcome at year 3

Subgroup	Discontinuation (no. of patients)		Continuation (no. of patients)		Mean difference in eGFR at 3 years (95% CI)
Diabetes					
Type 1	9		11		2.89 (−1.22 to 6.99)
Type 2	66		67		−0.24 (−3.33 to 2.84)
None	131		127		−1.36 (−3.57 to 0.84)
Mean arterial pressure					
<100 mmHg	132		129		−0.61 (−2.65 to 1.43)
≥100 mmHg	74	76			−0.82 (−4.30 to 2.65)
Age					
<65 years	116		110		−0.32 (−2.92 to 2.28)
≥65 years	90		95		−0.32 (−2.72 to 2.09)
Protein : creatinine ratio					
<885	97		98		−1.12 (−3.41 to 1.16)
≥885	109		107		0.14 (−2.37 to 2.65)
Estimated GFR					
<15 mL/min/1.73 m²	58	60			−0.51 (−3.92 to 2.91)
≥15 mL/min/1.73 m²	148	145			−0.62 (−2.52 to 1.27)

0.0

Continuation better — Discontinuation better

CI = confidence interval; LSM = least squares mean.

Bhandari S, et al. *N Engl J Med.* 2022;387:2021-2032.

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RAS Inhibitors: Safety and Tolerability

- ARB and ACEi agents are well-tolerated, conferring multiple benefits
  - Lower BP and prevent target-organ damage
  - Reduce mortality in HF
  - Lower proteinuria
  - Slow progressive loss of kidney function
- ACEi can cause cough
- Expect a 10–30% reduction in eGFR
  - Acute and reversible
- Expect an approximate 0.4–0.5 mEq/L increase in K^+

HF = heart failure; K^+ = potassium.

Burnier M. *Kidney Med.* 2020;2:231=234. de Boer IH, et al. *Diabetes Care.* 2022;45:3075-3090. KDIGO CKD Work Group. *Kidney Int.* 2024;105(4 suppl):S117-S314. Shubrook JH, et al. *Postgrad Med.* 2022;134:376-387.

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RAASIs ARE RECOMMENDED BY MULTIPLE ORGANIZATIONS FOR THE PREVENTION OF HEART FAILURE AND KIDNEY FUNCTION DECLINE

Class IA recommendation

- ACEi is recommended, in addition to a BB, for symptomatic patients with HF[1–3]*
- ACEi/ARB is recommended for treatment of hypertension[4,5]† and ACEi/MRA for HF in patients with DM[4]
- ARB is recommended when ACEi is not tolerated[1,2]
- MRA is recommended for patients with HF*, who remain symptomatic despite treatment with an ACEi, and a BB[2]

Highest tolerated targeted doses recommended[1,2]

Slow the progression of kidney disease[4]

- Reduce proteinuria[6,7]
- Valuable in CKD and indicated in proteinuria[6–8]
- More effective at reducing kidney function decline than other BP-lowering drugs[6]

* With reduced ejection fraction; † Class A level of evidence.

1. Yancy CW *et al. Circulation* 2017;136:e137–61; 2. Ponikowski P *et al. Eur J Heart Fail* 2016;18:891–975; 3. Lindenfeld J *et al. J Card Fail* 2010;16:475–539; 4. Cosentino F, *et al. Eur Heart J* 2020;41:255–323; 5. American Diabetes Association. *Diabetes Care* 2020;43:S111–34; 6. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013;3:1–150; 7. National Kidney Foundation. K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. 2004. Available at: kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_bp/index.htm (accessed July 2020); 8. National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management. 2014 (updated 2015). Available at: nice.org.uk/CG182 (accessed July 2020).

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GLYCEMIC GOALS

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Implications of ACCORD, ADVANCE, and VADT for Microvascular Risk

Microvascular disease:

- Lowering A1C to ≤7.0% reduces microvascular and neuropathic complications in type 2 diabetes
- If achievable without causing significant hypoglycemia or other adverse events, even lower A1C goals may be suggested for selected individuals having:
  - Short duration of diabetes
  - Long life expectancy
  - No significant CVD

Skyler JS, et al. *Diabetes Care.* 2009;32:187-192.

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Implications of ACCORD, ADVANCE, and VADT for Macrovascular Risk

Macrovascular disease:

- Intensive glycemic control that exceeds an A1C goal of <7.0% yields no significant reduction in CVD outcomes compared to standard glycemic control
- Lowering A1C to a goal of **≤7.0%** is a reasonable glycemic goal until more evidence becomes available
- Long-term follow-up of the DCCT and UKPDS cohorts suggests that treating to an A1C goal below or near 7.0% yields long-term reductions in the risk of macrovascular disease if it is instituted in the years soon after diagnosis of diabetes

Skyler JS, et al. *Diabetes Care.* 2009;32:187-192.

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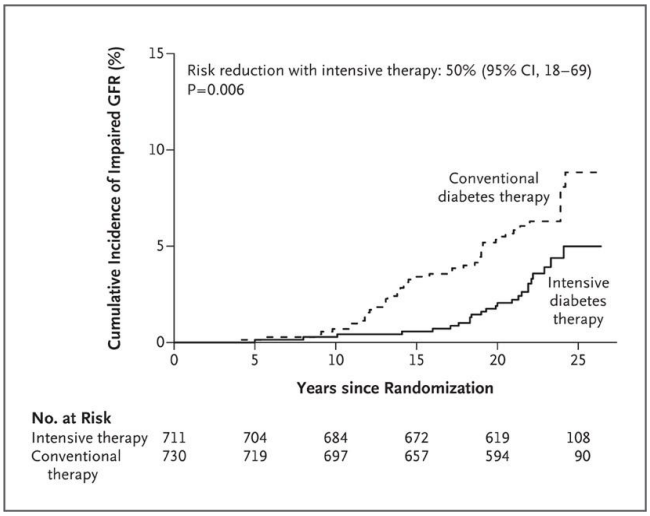
Cumulative Incidence of an Impaired Glomerular Filtration Rate, According to Treatment Group



The DCCT/EDIC Research Group. N Engl J Med 2011;365:2366-2376.

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Rationale for Lipid Lowering Clinical Trials in the CKD Population

- CKD and ESRD patients are at increased risk of cardiovascular complications
- CKD and ESRD patients have abnormal lipid profiles
- Secondary analyses of lipid lowering studies indicated statin treatment improved CV outcomes in CKD patients
- Secondary analyses of these studies also demonstrated slowing of CKD progression
- Need for randomized placebo-controlled statin trials in CKD and ESRD patients

1. Scandinavian Simvastatin Survival Study (4S). *Lancet*.1994;344(8934):1383–1389.
2. Shepherd J et al. *N Engl J Med*. 1995;333(20):1301–1307.
3. Heart Protection Study Collaborative Group. *Lancet*. 2002;360(9326):7–22.
4. Seliger SL et al. *Kidney Int*. 2002;61(1):297–304.
5. Liao JK. *Am J Cardiol*. 2005;96(5A):24F–33F.
6. Fellström BC et al. *Kidney Int*. 2003;63(Suppl 84):S204–S206.

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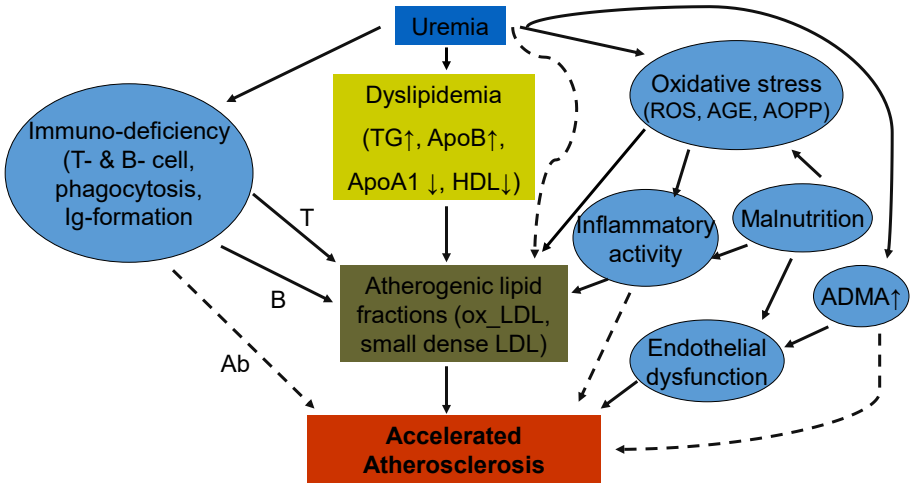
All of the Following Statements Are True Except:

A. Patients with T2DM should receive lipid lowering therapy
B. Patients CKD should receive lipid-lowering therapy
C. A 40% reduction of LDL from baseline with lipid lowering therapy recommended for higher risk of CVD patients

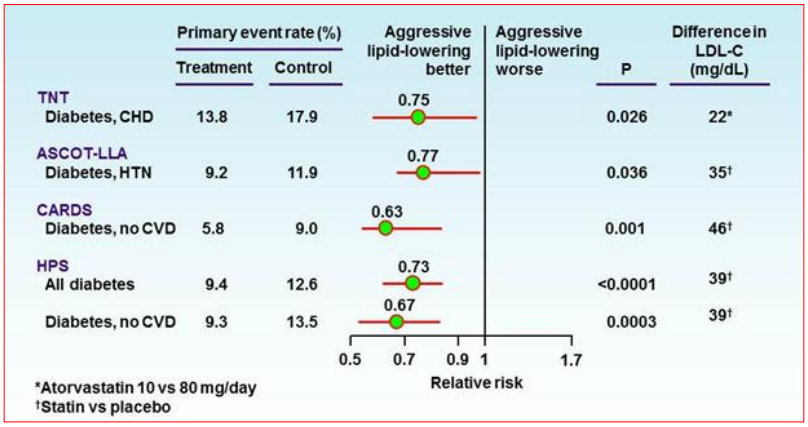
Mechanism of CVD Development in Patients with Uremia



TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein; ROS, reactive oxygen species; AGEs, advanced glycation end products; AOPP, advanced oxidation of plasma proteins; ADMA, asymmetric dimethylarginine

Fellström BC et al. *Kidney Int*. 2003;63(Suppl 84):S204–S206.

Benefits of Aggressive LDL-C Lowering in T2DM



Shepherd J, et al. *Diabetes Care* .2006.
Sever PS, et al. *Diabetes Care.* 2005.
HPS Collaborative Group. *Lancet.* 2003.
Colhoun HM, et al. *Lancet.* 2004.

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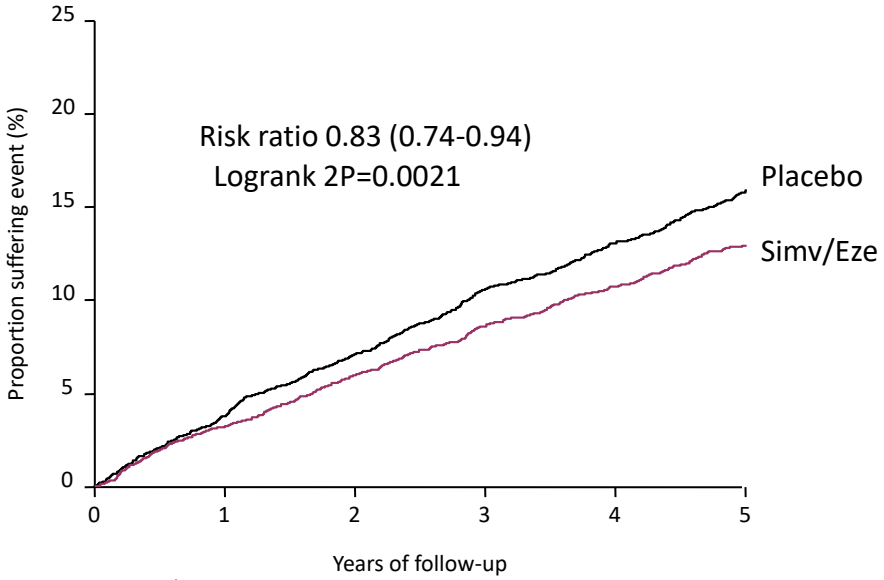
SHARP: Major Atherosclerotic Events



Baigent C et al. Lancet 2011; 377:2181-2192

Baigent C et al.
Lancet 2011;
377:2181-2192.

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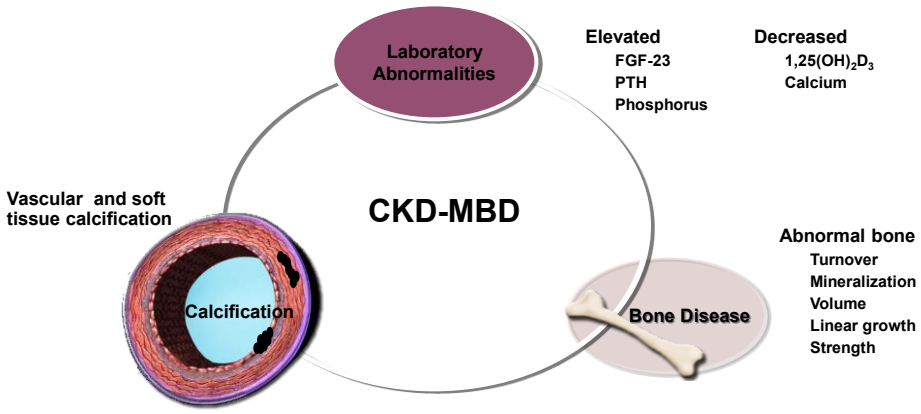
CKD-MBD: A Complex Multisystem Disorder



CKD-MBD = chronic kidney disease-mineral bone disorder; PTH = parathyroid hormone.

Kidney Int. 2009;76(suppl 113).

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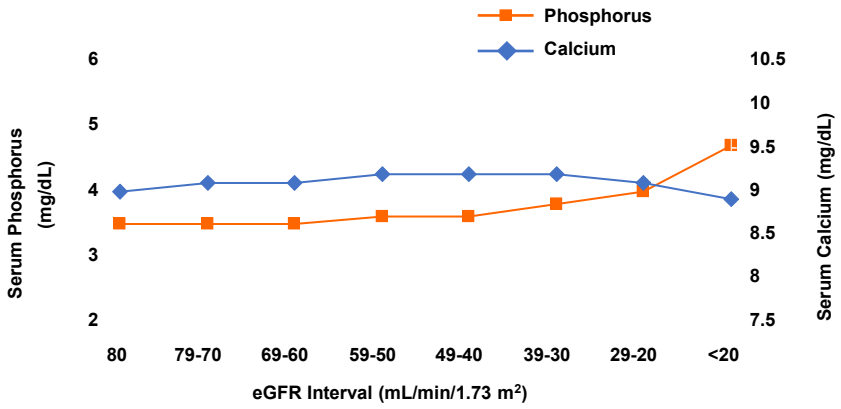
Phosphorus and Calcium Concentrations Remain in the Normal Range Until Late in CKD



Data presented are median values.

SEEK Study; N = 1814.

eGFR = estimated glomerular filtration rate.

Adapted from Levin A et al. *Kidney Int*. 2007;71:31-38.

50

Summary

- Disordered mineral and bone disease occurs very early in CKD
  - The earliest changes may be unrelated to mineral disorder
  - These early hormonal abnormalities set into play a complex disruption of the normal mineral regulatory system
  - Disruptions in phosphorus and calcium balance appear as CKD progresses and further disrupts the normal physiology of vascular and bone health
  - As these disturbances progress, serum levels of phosphorus and calcium may become evident and further worsen cardiovascular and bone disease
- The disordered phosphorus, calcium, and iPTH seen in most ESRD patients are the result of this progressive disease process

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Treatment

- In CKD predialysis: observational studies suggest that:
  - Phosphate binders may be beneficial
  - Vitamin D replacement may be beneficial
  - Active vitamin D analogues may be beneficial
- None of these therapies have been adequately tested

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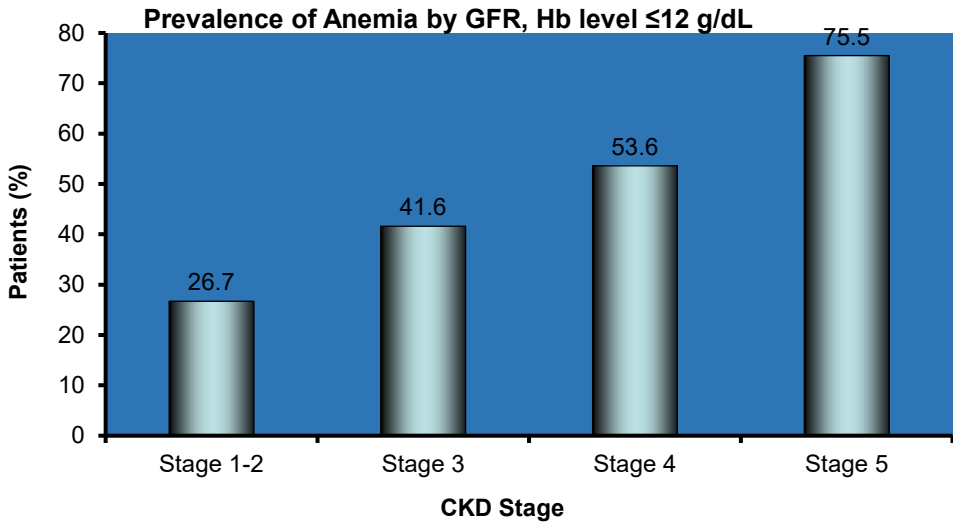
The Prevalence of Anemia in CKD Is High



Hb=hemoglobin.
McClellan et al. *Curr Med Res Opin.* 2004;20(9):1501-1510.

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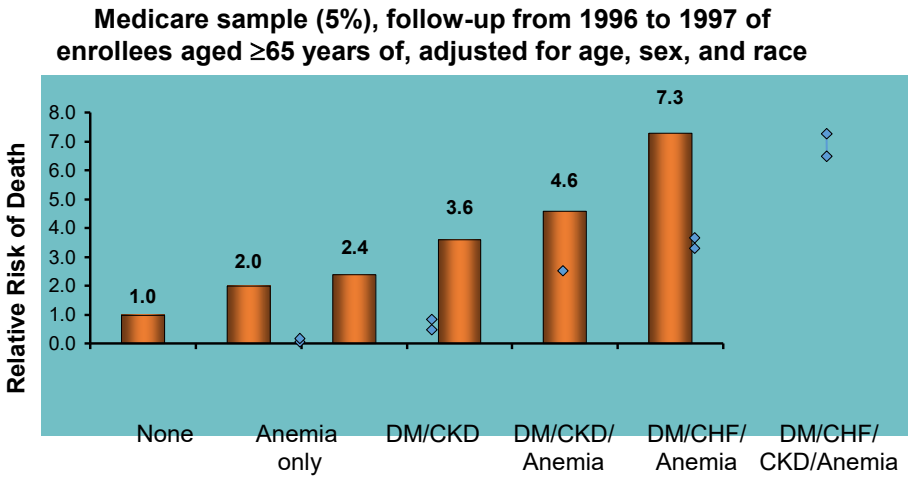
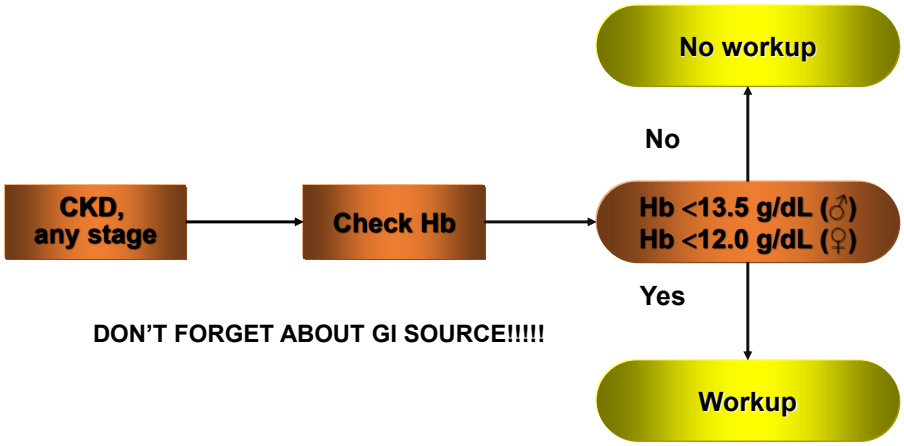
Anemia Significantly Impacts Mortality in CKD Patients



DM=diabetes mellitus; CHF=congestive heart failure.
Collins et al. *Adv Stud Med.* 2003;3(3C):S14-S17.

54

Hb Levels Should Be Evaluated in ALL CKD Patients, Regardless of Stage[a]



[a]Note that these are screening recommendations, not treatment recommendations.
Modified from National Kidney Foundation. *Am J Kidney Dis*. 2006;47(suppl 3):S1-S146 (A).

55

Published Randomized Controlled Trials in CKD: The Bottom Line

Study	N	Study Population	Hb (g/dL) or Hct(%) Target	CV Outcome	Quality of Life
Besarab. *N Engl J Med*. 1998	1233	HD + CHF/CAD	30 42	No benefit	Improved?
Foley. *Kidney Int*. 2000	146	HD - CHF/CAD	9.5-10.5 13-14	No benefit	Improved
Roger. *J Am Soc Nephrol*. 2004	155	Stage 3-4	9-10 12-13	No benefit	No difference
Parfrey. *J Am Soc Nephrol*. 2005	596	HD - CHF/CAD	9.5-11.5 13.5 -14.5	No benefit	Improved
Levin. *Am J Kidney Dis*. 2005	172	Stage 2-5	9-10.5 12-14	No benefit	Improved
Singh. *N Engl J Med*. 2006	1432	Stage 3-4	10.5-11 13-13.5	No benefit	No difference
Drüeke. *N Engl J Med*. 2006	603	Stage 3-4	10.5-11.5 13-15	No benefit	Improved

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Overall Goal:

Keep Hgb in the 10-11 Range!

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Slowing of CKD Progression by Correction of Acidosis

These results were confirmed by a larger open-label trial of 740 patients with stage 3, 4, or 5 CKD (mean creatinine clearance of 30 mL/min) and a mean baseline serum bicarbonate of 21.5 mmol/L. Patients were assigned to oral sodium bicarbonate or no treatment. At three years, the following significant benefits of bicarbonate therapy were observed:

- A lower all-cause mortality (3.1 versus 6.8 percent)
- A lower risk of requiring renal replacement therapy (6.9 versus 12.3 percent)
- A lower risk of a doubling of serum creatinine (6.6 versus 17 percent)

Di Iorio BR. J Nephrol 2019:32:989.

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Primary Care Interventions Proportional to the CKD Risk

- CKD is a heterogeneous state
- The controversy regarding the distinction between loss of eGFR with normal aging and CKD among seniors with eGFR 45 to 60 ml/min per 1.73 m2 in the absence of albuminuria (CKD G3aA1).
- Seniors include patient medication safety factors, cardiovascular risk, cognitive impairment risks, and risks of major surgery perioperative acute kidney injury

Kidney Int 2020; 97:37-40.

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Drug Safety in Chronic Kidney Disease

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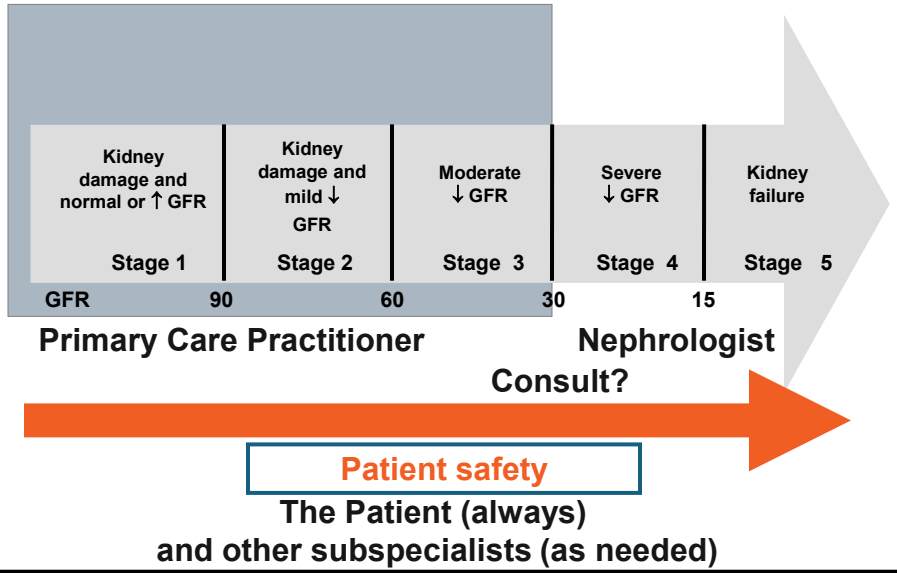
Who Should be Involved in the Patient Safety Approach to CKD?



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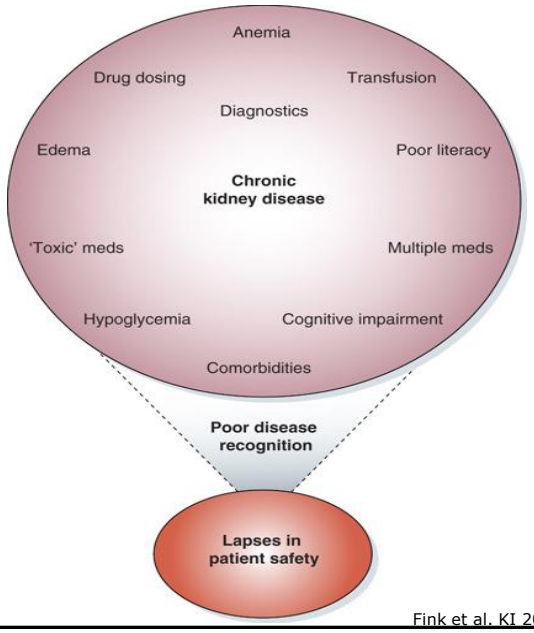
How Often? And Who's At Risk?

- Occurs in ~50% of patients with estimated GFR (eGFR) <60 ml/min
- Risk factors
  - Non-white
  - Older age
  - ACEi/ ARB use
  - Diabetes
  - More advanced CKD

Ginsberg JS, et al. *J Am Soc Nephrol* 2014.

62

CKD and Medication Safety



Fink et al. KI 2009;76:1123–1125

63

Rate of Adverse Drug Events in Ambulatory Patients with CKD

N=267	Rate (per 100 patients)*
PATIENT REPORTED	
Hypoglycemia	57.6
Falling/ severe dizziness	23.1
Nausea, vomiting ± diarrhea	21.1
Hyperkalemia	18.1
Confusion	16.9
DETECTED AT STUDY VISIT	
Hypoglycemia	8.3
Hyperkalemia	8.3
Bradycardia	6.4
*Adjusted for sociodemographics, comorbid conditions, GFR, and number of medications	

Adapted from Ginsberg JS, et al. *J Am Soc Nephrol* 2014.

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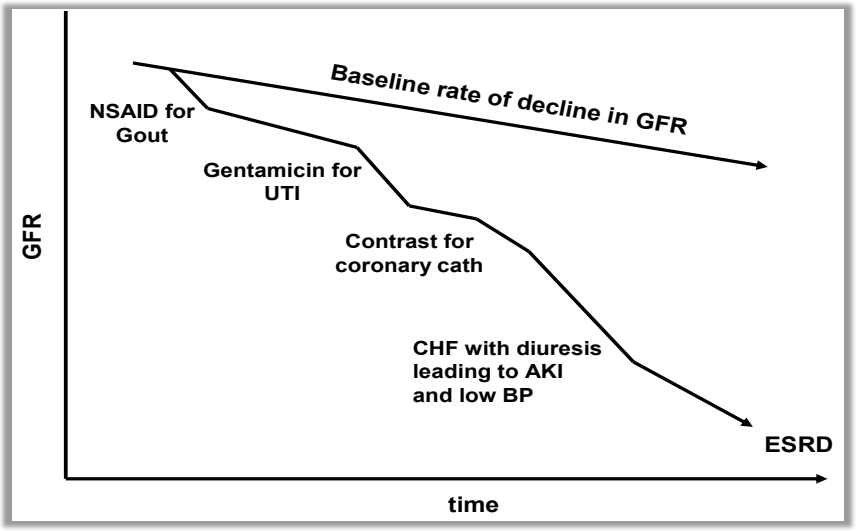
CKD Progression: Biology versus "Iatrogenesis"?



Fink, et al, AJKD, 2009

65

Modes of Drug-Related Adverse Events in CKD

- Direct kidney injury
- Dosing error
- Drug-drug interaction

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Drug Elimination in CKD

- Adjustments usually needed when >25-30% of active drug/metabolite eliminated renally:
  - Azithromycin 5-12%
  - Moxifloxacin 15-21%
  - Pioglitazone (Actos) 15-30%
  - Ciprofloxacin 30-57%
  - Amoxicillin 50-70%
  - Digoxin 57-80%

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Drugs to Avoid in CKD Patients

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NSAIDs

- Injure kidneys directly
  - Induce acute kidney injury (AKI) from “pre-renal” or ATN
  - Interstitial nephritis
  - Nephrotic syndrome
- Decrease kidney potassium excretion → hyperkalemia
- Decrease sodium excretion → HTN, edema

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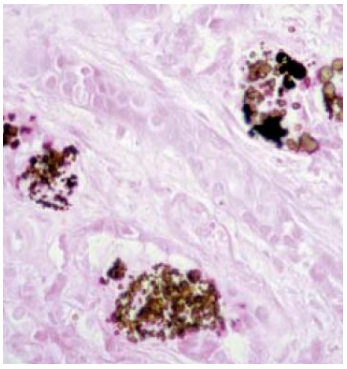
Oral Sodium Phosphate Preparations

- Hyperphosphatemia + volume depletion
- Acute Phosphate Nephropathy
  - Ca-phosphate deposits in tubules & interstitium
  - Leads to AKI/ CKD within days to months



Desmeules S, et al. *N Engl J Med.* 2003

70

Iodinated Contrast

- Leads to AKI
- Risk factors
  - CKD (esp. eGFR <30 ml/min/1.73m^2)
  - Diabetes, CHF, gout
  - Dehydration
  - Concurrent use of NSAIDs or RAAS-antagonists
  - High osmolality agents, large or repeated doses
  - Intra-arterial injection

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Minimizing Risk of Adverse Drug Events

- Minimize pill burden as possible
  - 10 – 12 MEDICATIONS PER CKD PATIENT; 17 FOR TRANSPLANTED INDIVIDUALS
- Review medications carefully for
  - Dosing
  - Potential interactions
- Educate patient on:
  - OTC meds to avoid (mainly NSAIDs)
  - Signs/symptoms of potential drug adverse effects

St. Peter WL, Adv Chronic Kidney Dis. 2010;17:413-9
Yee J. Adv Chronic Kidney Dis. 2010;17:379-380

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Dosing Adjustments

- Don't rely on SCr alone – calculate eGFR or Cr clearance
  - SCr misleading in: extremes of body weight, poor nutrition
- Cannot rely on eGFR in AKI
  - If SCr rapidly rising, assume eGFR <10 ml/min
- When in doubt, look up dosing adjustment/ potential interactions or call pharmacy

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Quality Improvement

- An integrated health system albuminuria CKD testing quality initiative study resulted in a 56.1% increase capture of urine albumin in year one and 50.1% increase in 2 years; however, there was no correlated statistical improvement in use of ACEi or ARB in these patients, possibly indicating an opportunity for evaluation of the patient cycle and enhancements in education and operational flow.

Per MJ 2020;25:1.

74

Quality Improvement

- A quality improvement project implementing primary care population health for diabetes and hypertension with interventions based on the eGFR and UACR risk stratification revealed reduced hospitalization, decreased 30-day readmissions, and selected medical per patient per month cost-containment in a commercial health insurance plan's patient-centered medical home model.

Am J Managed Care 2019;25:e326-e353

75

Quality Improvement

- An impressive longer-term quality improvement initiative in the Indian Health Service resulted in dramatic 54% reduction of incident ESKD for the type 2 diabetes population.

Am J Kid Dis 2018; 407-411

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Indications for Referral to Specialist Kidney Care Services for People with CKD

Acute kidney injury or abrupt sustained fall in GFR
GFR <30 ml/min/1.73 m2 (GFR categories G4-G5)
Persistent albuminuria (ACR > 300 mg/g)*
Progression of CKD**
Urinary red cell casts, RBC more than 20 per HPF sustained and not readily explained
CKD and hypertension refractory to treatment with 4 or more antihypertensive agents
Persistent abnormalities of serum potassium
Recurrent or extensive nephrolithiasis
Hereditary kidney disease

*Significant albuminuria is defined as ACR ≥300 mg/g (≥30 mg/mmol) or AER ≥300 mg/24 hours, approximately equivalent to PCR ≥500 mg/g (≥50 mg/mmol) or PER ≥500 mg/24 hours
**Progression of CKD is defined as one or more of the following: 1) A decline in GFR category accompanied by a 25% or greater drop in eGFR from baseline; and/or 2) rapid progression of CKD defined as a sustained decline in eGFR of more than 5ml/min/1.73m^2/year. KDOQI US Commentary on the 2012 KDIGO Evaluation and Management of CKD.

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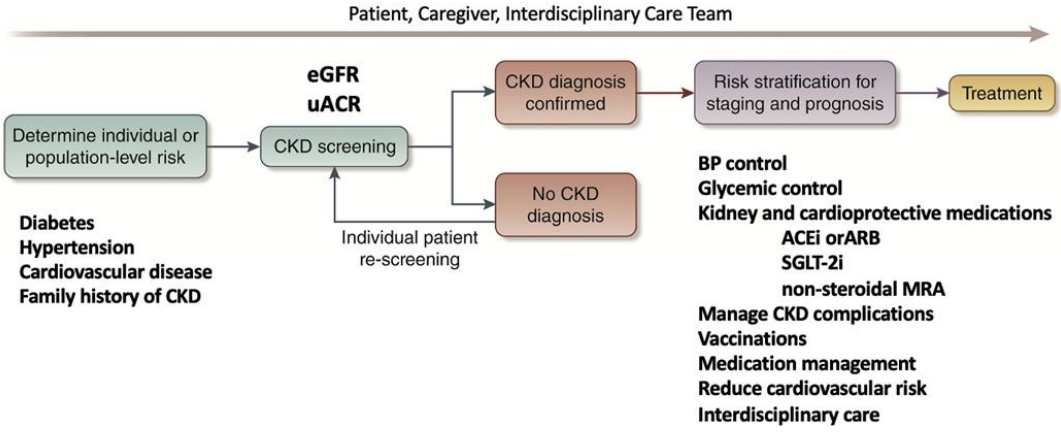
Patient, Caregiver, Interdisciplinary Care Team



Kidney International Reports 2022 7389-396DOI: (10.1016/j.ekir.2022.01.1066)

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