

UpDates in Renal Medicine

Update in General Internal Medicine for
Specialists CME Course - 2020

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Boston MA

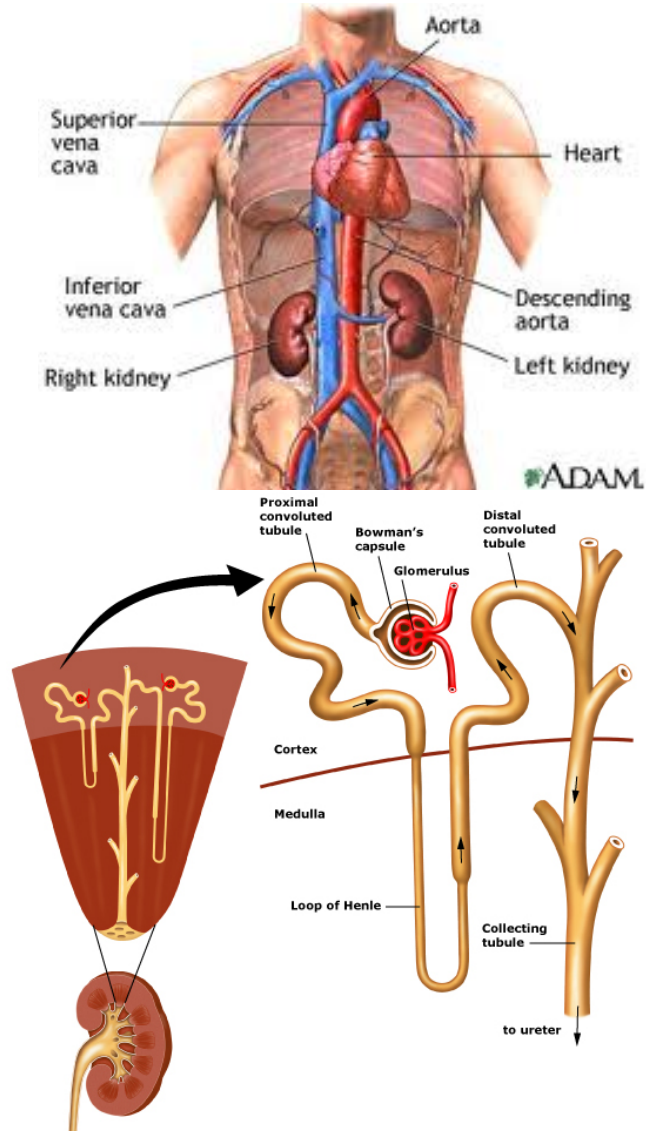
Conflict of Interests Statement

- Medical Director Fresenius Kidney Care Dialysis Facility
- Consultant to HealthReveal

Aims

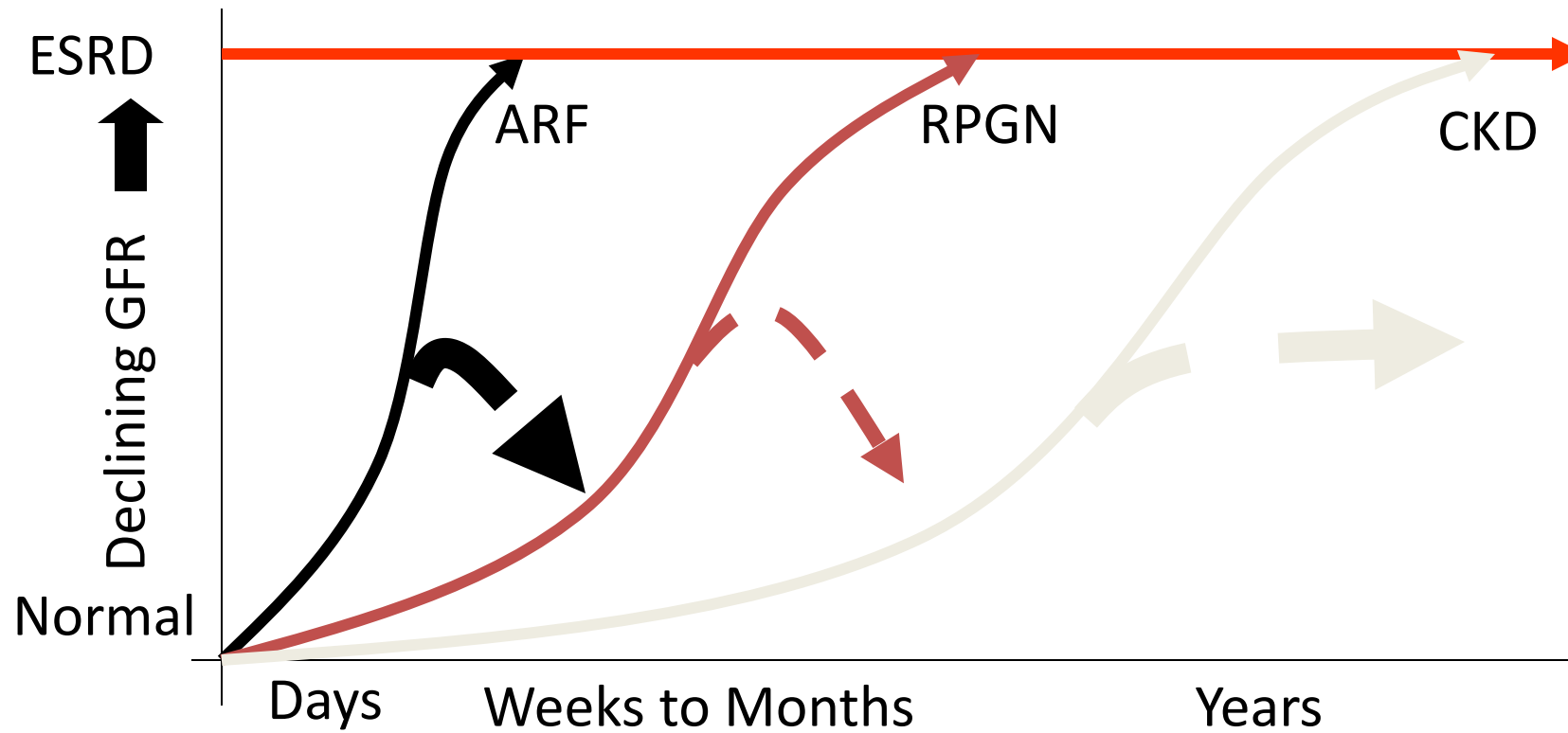
- Gather a sense of the demographics and natural history of Chronic Kidney Disease (CKD)
- Understand the impact of CKD and its associated co-morbidities on the patient's clinical care
- Review ESRD management options including medical management

Nephrology Factoids

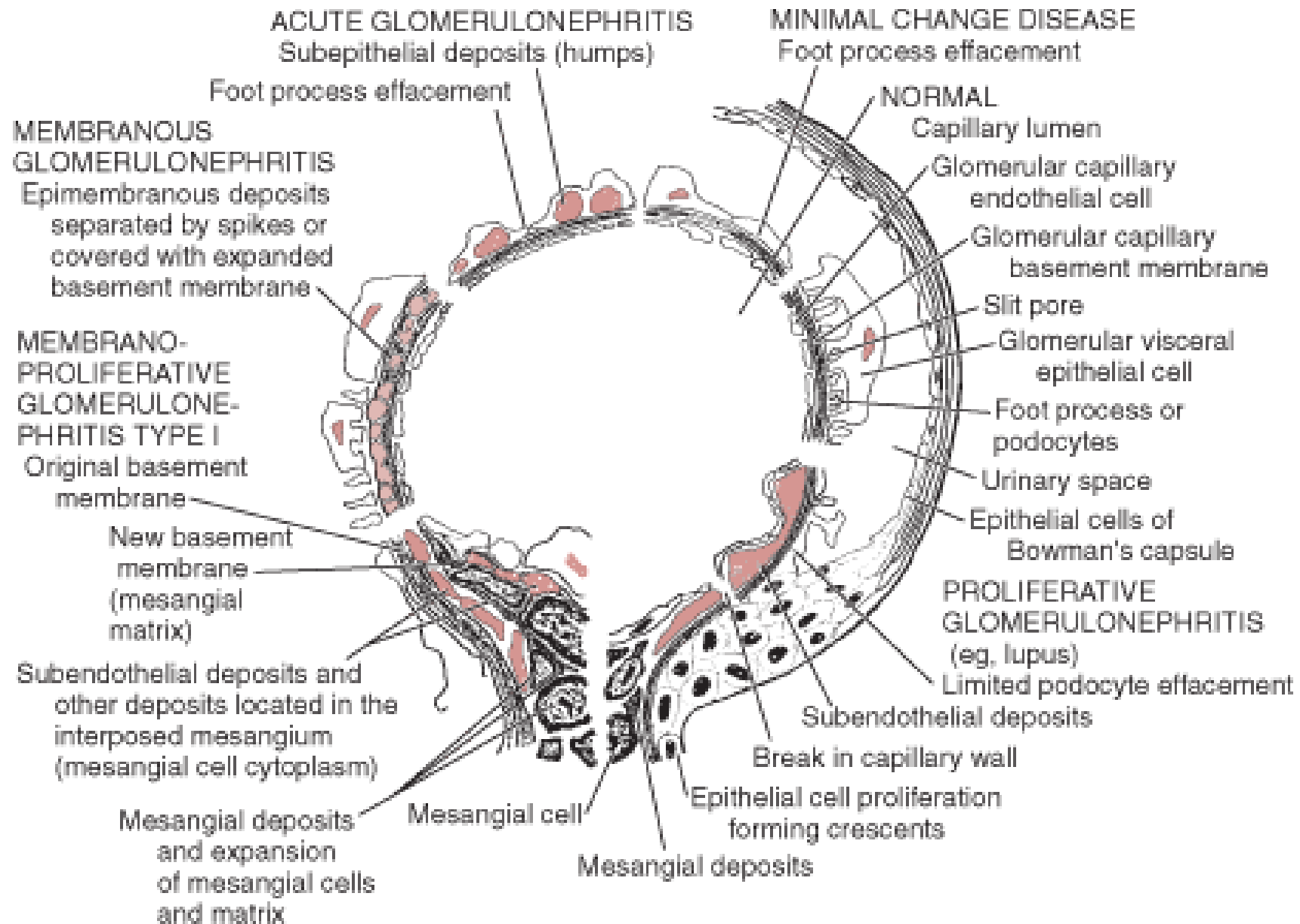


- Kidneys get ~ 20% of cardiac output
- Generate ultrafiltrate of 180L a day
- Produce 1-1.5L urine output
- Excrete ~ 600-800 mosm
- Regulates
 - Volume (Na Metabolism)
 - Tonicity (Water Metabolism)
 - Potassium metabolism
 - Acid/Base balance
 - Excretion of Nitrogenous wastes
 - Anemia (Erythropoetin)
 - Bone metabolism (1 alpha Hydroxylase)
 - Blood pressure (Renin)

Natural History of Renal Failure



Glomerular Injury



GLOMERULAR DISEASES

- Nephrotic Syndrome

Clinical: >3.5g Proteinuria; Hypoalbuminemia; Hyperlipidemia; Edema;
“Bland” urine sediment

Primary Glomerulopathies

1. Minimal Change Disease
2. Membranous GN
 - PLAR2 associated
 - Immune Mediated (Hep B)
 - Cancer associated
3. FSGS
 - Primary:
 - Cellular, Tip Lesion Variant; NOS; Collapsing
 - Secondary:
 1. HTN; APOL1
4. MPGN

Secondary (Systemic) Diseases

1. Systemic illnesses
 - Amyloidosis; Diabetes; HTN
2. Infectious Disease
 - HIV
3. Drug associated
 - NSAIDs; Gold
4. Oncological
 - Myeloma; Hodgkins, Lymphoma, Solid tumors

GLOMERULAR DISEASES

- Nephritic Syndromes; RPGN

Clinical: Hypertension; Elevated Creatinine; Hematuria; Proteinuria; “Active”
Urine Sediment

Hypocomplementemic GN

- Complement titers are low
- Circulating immune complexes present with immune complex deposition seen in renal biopsy
- Differential Diagnosis:
 1. SLE
 2. Endocarditis
 3. Hep C; Cryoglobulemia
 4. MPGN
 - Inflam Disease Assoc;
 - MGUS assoc;
 - C3 Nephritic factor assoc

Pauci immune GN

- Complement titers are normal
- Circulating immune complexes absent and no immune complex deposition in renal biopsy specimen
- Differential diagnosis:
 1. Anti-glomerular basement membrane (anti-GBM) disease; Goodpasture's syndrome.
 2. ANCA Associated Vasculitis
 3. IgA Associated Glomerulonephritis
 - Henoch Schonlein Purpura;
 - Acute IgA Nephropathy

Treatment Options

Nephritic Syndromes

- Steroids alone usually not enough
- Immune suppressants
 - Cyclophosphamide
 - Mycophenolate
- B cell Depleting Therapy
 - Rituximab
 - Anti CD 20
 - Chimeric monoclonal antibody with proven benefit in ANCA Associated Vasculitis

Nephrotic Syndrome

- Many patients are Steroid responsive
 - Some require a second agent (steroid resistant Minimal Change Disease; Primary FSGS)
- PLA2R positive Membranous Nephropathy responds to Rituximab
- Phase 2 trial for APOL1 gene polymorphism associated FSGS

Thrombotic Microangiopathies

Clinical: AKI; Hypertension; Bland Sediment or tubular injury

- **TTP**

- Presentation:
 - Fever; MAHA; AKI; Hypertension; Encephalopathy
- Etiology:
 - Reduced activity of the von Willebrand factor-cleaving protease ADAMTS13

- **HUS**

- Presentation:
 - MAHA; AKI; Hypertension
- Etiology:
 - Shiga toxin producing E. coli

- **aHUS**

- Presentation:
 - MAHA; AKI; Hypertension
- Etiology:
 - Complement dysregulation
 - Gene mutations
 - Antibodies to complement factor H
 - Infection associated
 - Streptococcus pneumoniae
 - HIV
 - Drug toxicity
 - Cancer Chemotherapy
 - Solid organ transplant
 - Rare associations with autoimmune diseases e.g. SLE
 - Rare inborn errors of cobalamin C metabolism

Treatment options for TMA's

Thrombotic Thrombocytopenic Purpura (TTP)

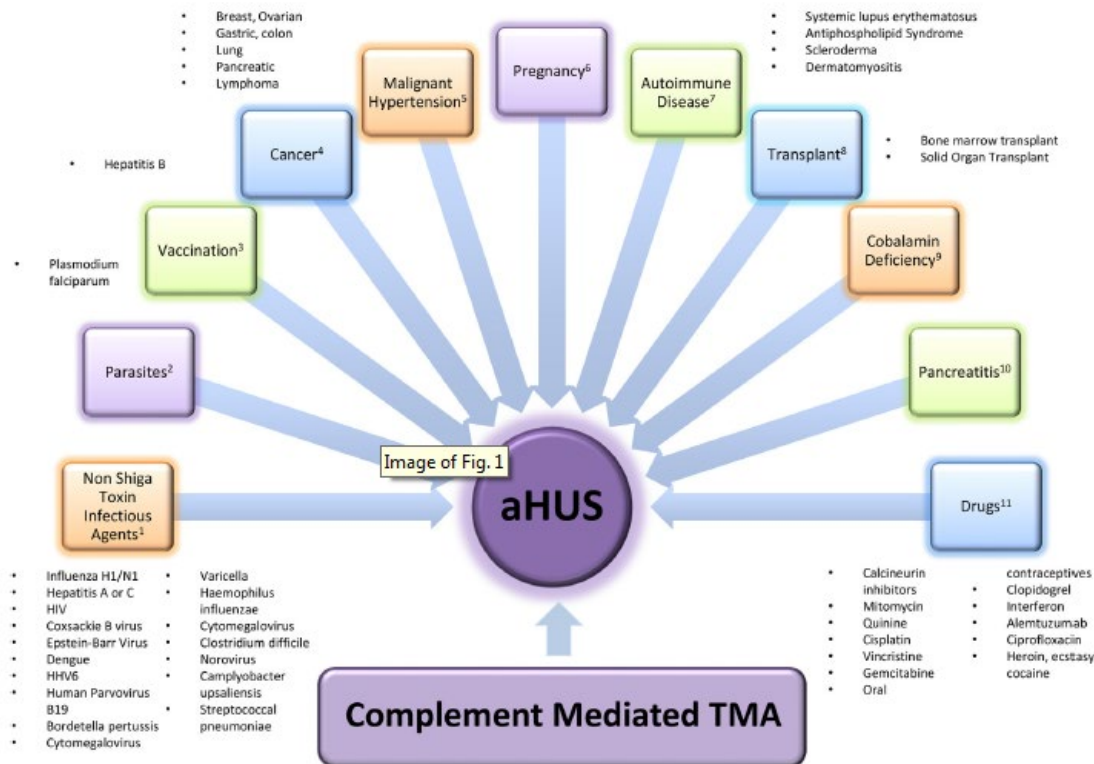
- Role of ADAMTS 13 deficiency
 - Hereditary
 - Acquired (autoantibody)
- Plasmapheresis with Fresh Frozen Plasma repletion is cornerstone of care

Hemolytic Uremic Syndrome (HUS)

- Shiga Toxin Mediated TMA
- Enteric infection with a Shiga toxin–secreting strain of *Escherichia coli* or *Shigella Dysenteriae*
- Initial presentation is more common in young children, typically with acute kidney injury; most cases are sporadic; large outbreaks also occur.
- Supportive care

Role of Complement in atypical HUS

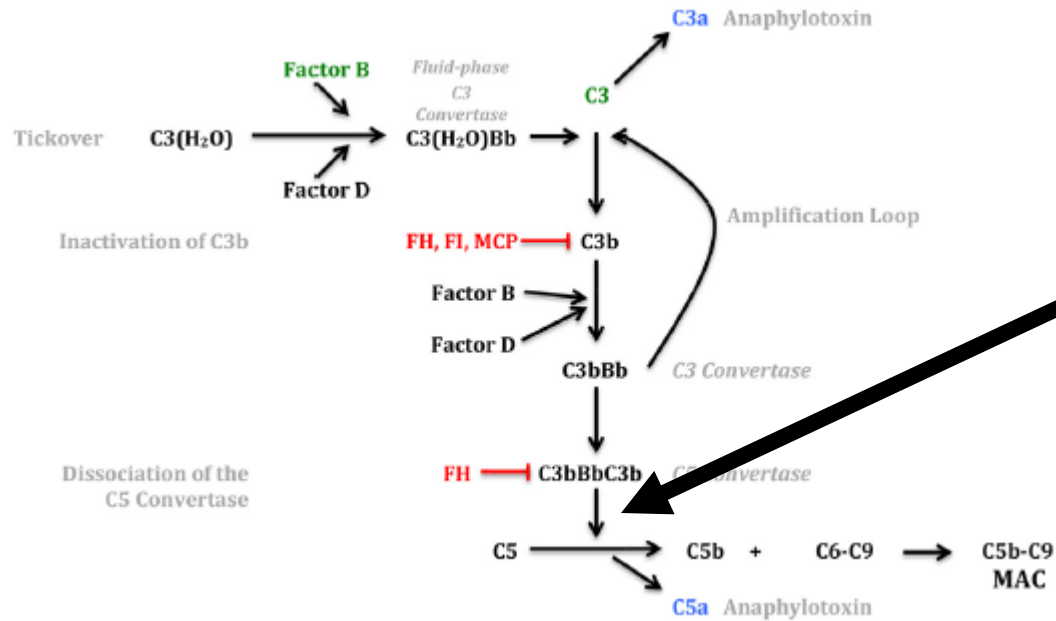
- Many cases of aHUS are now felt to be mediated via abnormalities of Complement Regulation:
 - Hereditary disorders of Complement Regulators
 - Acquired (inhibitors of Complement regulators)
 - Other causes



Complement Inhibitors

Eculizumab

- Humanized monoclonal antibody directed at terminal component of complement cascade C5
- Meningococcal vaccine mandatory
- Very expensive



Question

- 69 y.o. male with CAD (four prior MIs), Heart Failure with Reduced Ejection Fraction (HFrEF) (EF=24%), severe Mitral Regurgitation, Paroxysmal Atrial Fib, Ventricular Tachycardia s/p ICD, Hypertension, Hyperlipidemia, CKD (baseline Cr 1.4), metastatic prostate cancer (on leuprolide), admitted for HFrEF exacerbation with course complicated by oliguric renal failure and concern for worsening cardiogenic shock, transferred to CCU for tailored therapy. Urine sediment was bland (no ATN casts no RBC casts) Renal function remains impaired despite optimizing CHF regimen. Work up of AKI should include:
 - A. Renal Ultrasound
 - B. Renal Biopsy
 - C. Renal Nuclear Medicine Scan
 - D. Upper extremity venous mapping for AV Fistula
 - E. No additional work up needed

Answer

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OncoNephrology

Table 1. Common clinical issues related to nephrological management in patients with cancer

Volume depletion
Acute kidney injury (AKI)
Sepsis and septic shock
Severe fluid and electrolytes derangements
Severe acid–base disorders
Hyponatraemia
Hypokalaemia
Hyperkalaemia
Hypercalcaemia
Renal toxicity of chemotherapeutic agents
Renal toxicity of non-chemotherapeutic drug treatments
Tumour lysis syndrome
Myeloma-related kidney injury
Tumour- or tumour treatment-related microangiopathies and glomerular diseases
Tumour- or tumour treatment-related nephritic syndrome
Stem-cell transplant-associated acute and chronic kidney injuries
Cancer-associated obstructive uropathies
Modifications of dosing of chemotherapy in patients with CKD and ESRD who have cancer
Management of nutrition and dialysis in patients with ESRD-receiving cancer therapy

- Renal Toxicity of Oncological agents
- Nephrotoxic/Tubulotoxic
 - Cisplatin; Etoposide; Methotrexate
- TMA picture
 - VEGF Inhibitors (Bevacizumab)
- Allergic Interstitial Nephritis
 - PD1 ligand inhibitors/Immunotherapy (Pembrolizumab)

Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors

- CPI-induced AKI is a new entity that presents with clinical and histologic features similar to other causes of drug-induced acute tubulointerstitial nephritis, though with a longer latency period.
- Glucocorticoids appear to be a potentially effective treatment strategy.
- AKI due to CPIs may be caused by a unique mechanism of action linked to reprogramming of the immune system, leading to loss of tolerance.
- AKI is common in patients receiving checkpoint inhibitor therapy.
 - 8% overall
 - ~3% AIN
- The causes of sustained AKI in this population are heterogenous and merit thorough evaluation.
- The role of PPI and other nephritis-inducing drugs in the development of sustained AKI needs to be better defined.

Acute Renal Failure

Causes and Classification of Acute Renal Failure in Hospitalized Patients

Acute Renal Failure

Complicates 5-7% of hospitalizations

1. Pre Renal Causes: 35-40%

2. Intrinsic Renal Causes: 55-60%

Acute Glomerulonephritis: 5% Acute
Tubular Necrosis:

Ischemic: 50%

Toxic: 35%

Interstitial Nephritis: 10%

3. Post Renal Causes: 2-5%

KDIGO Classification of AKI:

Stage 1 – Increase in serum creatinine 1.5 to 1.9 times baseline, or creatinine increase ≥ 0.3 mg/dL or reduction in urine output to <0.5 mL/kg/hour for 6 to 12 hrs.

Stage 2 – Increase in creatinine to 2.0 to 2.9 times baseline, or reduction in urine output to <0.5 mL/kg/hour for ≥ 12 hours.

Stage 3 – Increase in creatinine to 3.0 times baseline, or increase in creatinine to ≥ 4.0 mg/dL or reduction in urine output to <0.3 mL/kg/hour for ≥ 24 hours, or anuria for ≥ 12 hours

ARF Management - General Principles cont

Medical Management

- Identify cause and preempt and prevent further injury
 - Renal Ischemia
 - Nephrotoxin exposure
- Optimize hemodynamics
 - Renal perfusion requires MAP > 65mmHg
- Metabolic Control
 - Manage Hyperkalemia medically where possible
 - Treat Acidosis although remember the use of IV Bicarbonate is controversial
- Involve Nephrologist early
 - ICU mortality rate has been shown to be increased when renal consultation was delayed for more than 48 hours

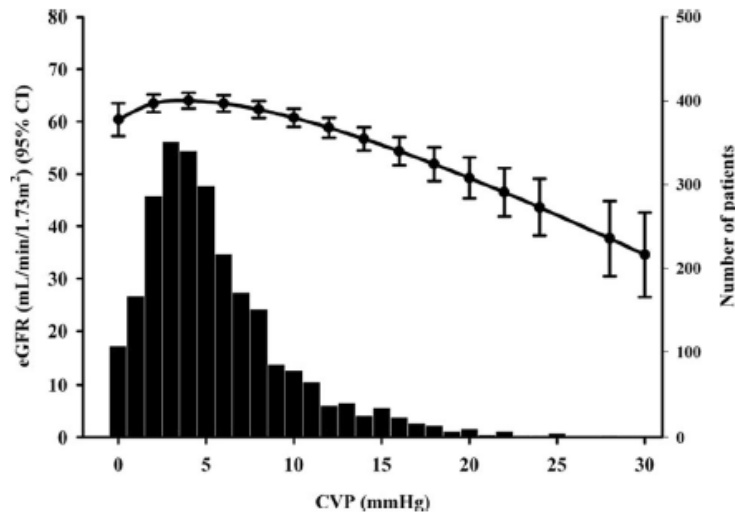
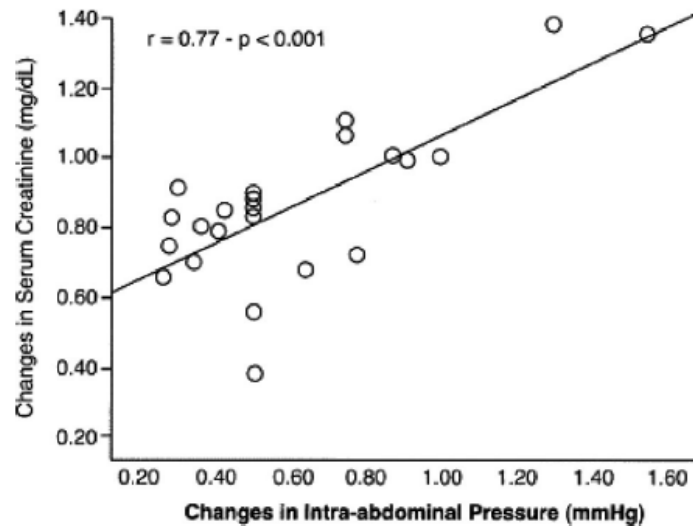
Indications for Dialysis

- Volume Control
- Hyperkalemia
- Acidosis
- Uremia
- Toxin Ingestion

CardioRenal Syndromes: Classification

Syndromes	Definition	Example
Acute cardiorenal (type 1)	Acute worsening of heart function (AHF-ACS) leading to kidney injury and/or dysfunction	Acute decompensated heart failure, acute coronary syndrome
Chronic cardiorenal (type 2)	Chronic abnormalities in heart function (CHF-CHD) leading to kidney injury or dysfunction	Chronic heart failure (Diastolic or Systolic)
Acute renocardiac (type 3)	Acute worsening of kidney function leading to heart injury and/or dysfunction	Acute kidney injury
Chronic renocardiac (type 4)	Chronic kidney disease leading to heart injury, disease and/or dysfunction	Chronic Kidney Disease (Diabetic Kidney Disease; Hypertensive Kidney Disease)
Secondary CRS (type 5)	Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney	Sepsis, noncardiogenic shock

AKI: Cardiorenal Syndrome



Reduced Cardiac Output

- In many patients a clinically significant reduction in CO is rare even after effective diuresis.
- Prerenal hypoperfusion secondary to reduced CO or intravascular volume depletion alone, cannot explain many cases of CRS.

Venous Congestion

- Multiple studies have demonstrated a link between elevated venous pressure and decreasing renal function
- As an encapsulated organ the kidney is functionally susceptible to increased venous pressures:
 - net pressure gradient across the glomerulus and decreased GFR
 - increased intrarenal interstitial pressure complicating tubular functional processes

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

- 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40%. PARADIGM Heart Failure Clinical Trial
- Sacubitril/Valsartan vs Enalapril

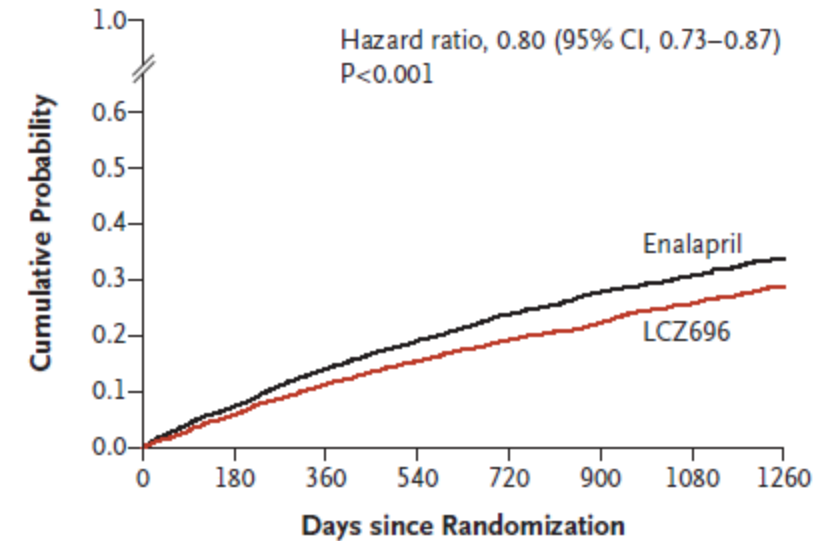
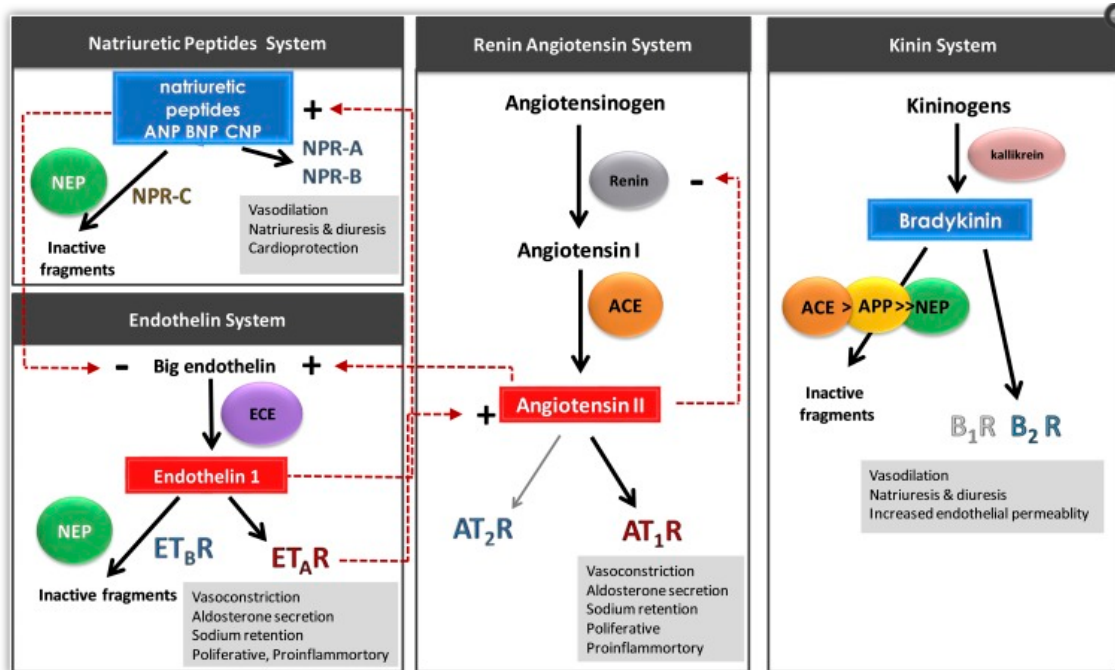
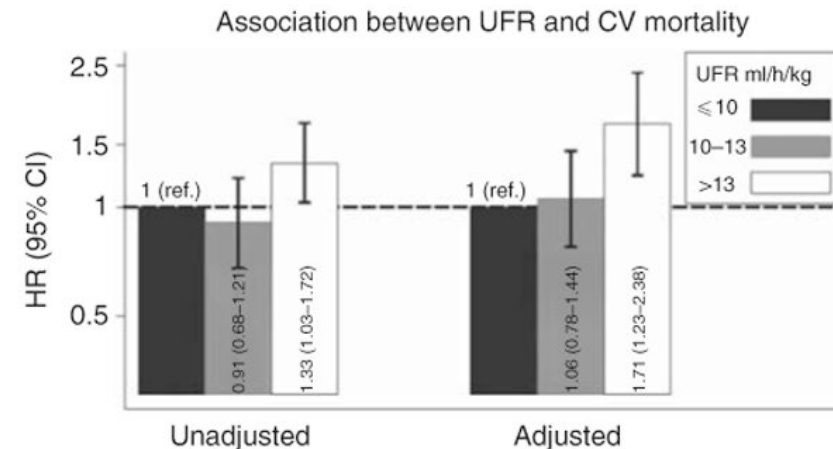
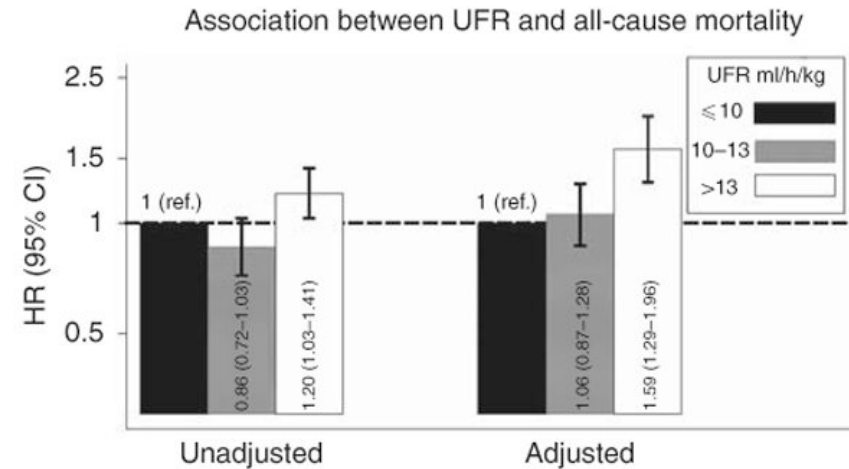


Table 2. Primary and Secondary Outcomes.*

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

Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality (“CardioRenal Type 4”)

- Review of Hemodialysis Study data
- 1846 patients receiving 3 times a week chronic HD.
- Ultrafiltration rates divided into three categories:
 - 10 ml/h/kg,
 - 10–13 ml/h/kg,
 - over 13 ml/h/kg.
- Compared to UF rates in the lowest group, rates in the highest group were significantly associated with increased all-cause and cardiovascular-related mortality with adjusted hazard ratios of 1.59 and 1.71, respectively.



AKI: Hepatorenal Syndrome (HRS)

- Diagnosis of Cirrhosis and Ascites
- Diagnosis of AKI (Stage I, II, III)
- No response after 2 days to:
 - Diuretic withdrawal
 - Plasma Volume Expansion with IV Albumin 1mg/Kg/day
- Absence of shock
- No current NSAIDs, aminoglycosides or recent IV contrast
- No structural signs of kidney injury
 - Urine protein < 500mg a day
 - Urine RBC < 50 per HPF
 - Normal renal ultrasound

HRS: Comprehensive Treatment

- **Supportive care; treat underlying liver insult**
 - Sobriety
 - Address bleeding
 - Antibiotics for SBP or systemic infection
 - New antivirals for HCV and for HBV
- **Volume expansion (IV albumin, hold diuretics)**
 - Helps remove prerenal AKI from DDx, addresses low effective circulating volume; part of diagnostic criteria
 - Albumin Dose 1g/Kg/day max dose 100 g (day 1), 50 g/day (days 2 and subsequently)
- **Hemodynamic support**
 - Midodrine, Octreotide, Terlipressin, Norepinephrine, Vasopression
- **Liver transplant**
 - Short/long term outcomes better with normal renal function after liver transplant
 - Balance risks to patient with needs of population
- **Combined Liver Kidney Transplant**
 - How long on dialysis before dual liver-kidney?
 - ~4-12 weeks if pure HRS (without other CKD/AKI)

Prognosis of Patients with Cirrhosis and AKI Who Initiate RRT

Prognosis of Patients with Cirrhosis and AKI Who Initiate RRT

Andrew S. Allegretti,¹ Xavier Vela Parada,¹ Nwamaka D. Eneanya,¹ Hannah Gilligan,¹ Dihua Xu,¹ Sophia Zhao,¹ Jules L. Dienstag,² Raymond T. Chung,² and Ravi I. Thadhani¹

Abstract

Background and objectives Literature on the prognosis of patients with cirrhosis who require RRT for AKI is sparse and is confounded by liver transplant eligibility. An update on outcomes in the nonlisted subgroup is needed. Our objective was to compare outcomes in this group between those diagnosed with hepatorenal syndrome and acute tubular necrosis, stratifying by liver transplant listing status.

Design, setting, participants, & measurements Retrospective cohort study of patients with cirrhosis acutely initiated on hemodialysis or continuous RRT at five hospitals, including one liver transplant center. Multivariable regression and survival analysis were performed.

Results Four hundred seventy-two subjects were analyzed (341 not listed and 131 listed for liver transplant). Among nonlisted subjects, 15% (51 of 341) were alive at 6 months after initiating RRT. Median survival was 21 (interquartile range [IQR], 8, 70) days for those diagnosed with hepatorenal syndrome and 12 (IQR, 3, 43) days for those diagnosed with acute tubular necrosis ($P=0.25$). Among listed subjects, 48% (63 of 131) received a liver transplant. Median transplant-free survival was 15 (IQR, 5, 37) days for those diagnosed with hepatorenal syndrome and 14 (IQR, 4, 31) days for those diagnosed with acute tubular necrosis ($P=0.60$). When stratified by transplant listing, with adjusted Cox models we did not detect a difference in the risk of death between hepatorenal syndrome and acute tubular necrosis (hazard ratio [HR], 0.81; 95% confidence interval [95% CI], 0.59 to 1.11, among those not listed; HR, 0.73; 95% CI, 0.44 to 1.19, among those listed).

Conclusions Cause of AKI was not significantly associated with mortality in patients with cirrhosis who required RRT. Among those not listed for liver transplant, mortality rates were extremely high in patients both with hepatorenal syndrome and acute tubular necrosis.

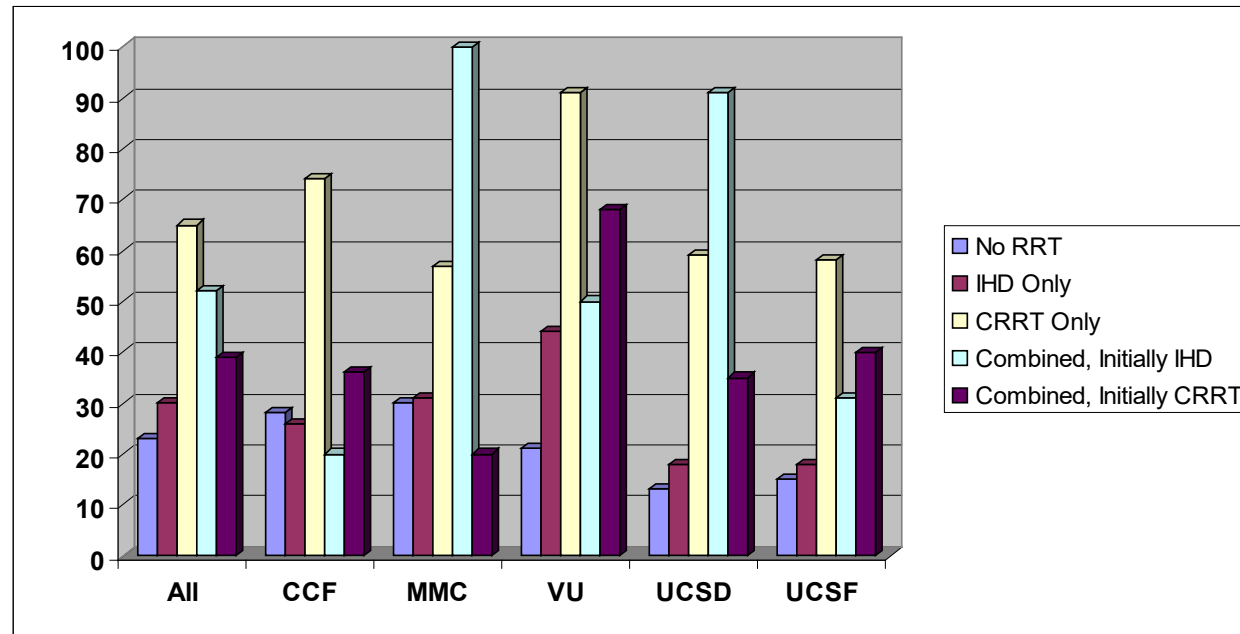
Clin J Am Soc Nephrol 13: 16–25, 2018. doi: <https://doi.org/10.2215/CJN.03610417>

- Patients with hepatorenal syndrome who progress to renal failure are sometimes treated with dialysis.
- Mortality 84%(median survival, 21 days) among patients not listed for transplant who developed hepatorenal syndrome and initiated dialysis in this retrospective study
- Recovery of kidney function sufficient to stop dialysis 4% in this study
- In patients with cirrhosis and hepatorenal syndrome, the most appropriate use of dialysis is as a bridge to liver transplantation

Mortality in ARF and by Dialysis Method

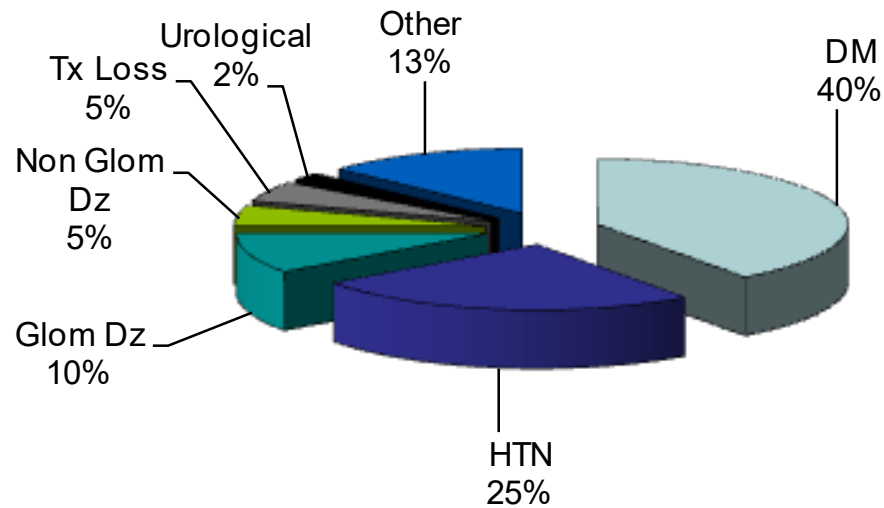
- The PICARD Experience

- Overall mortality rate = 34%
- Mortality for patients receiving intermittent HD mortality = 30%
- Mortality for patients receiving Continuous Renal Replacement Therapies = 67%



In patients who survive majority do not remain dialysis dependent

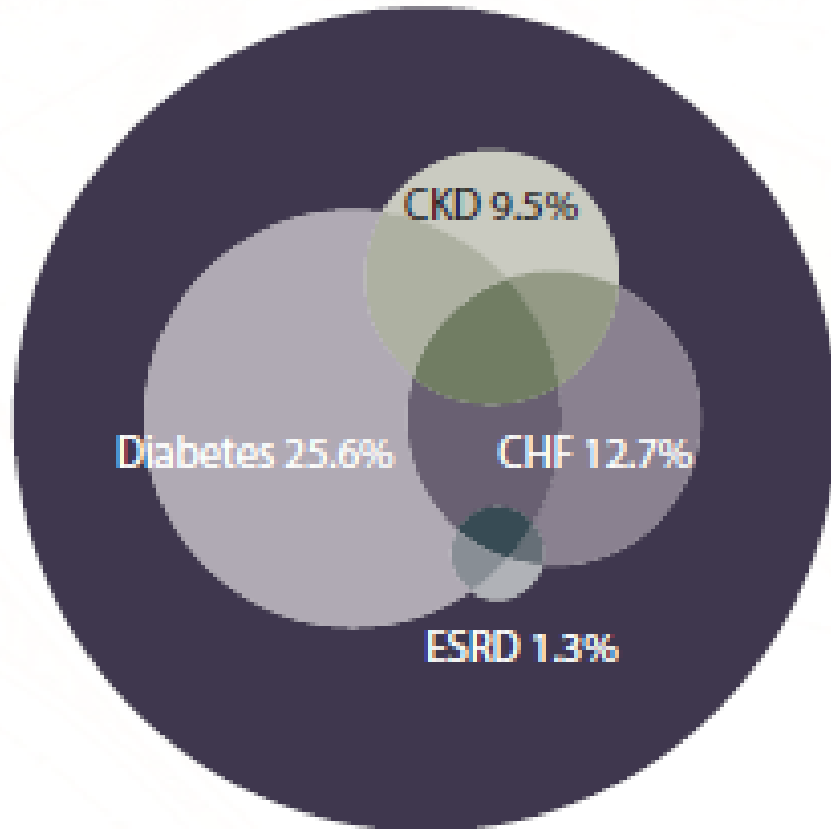
Chronic Kidney Disease: Defining (CKD)



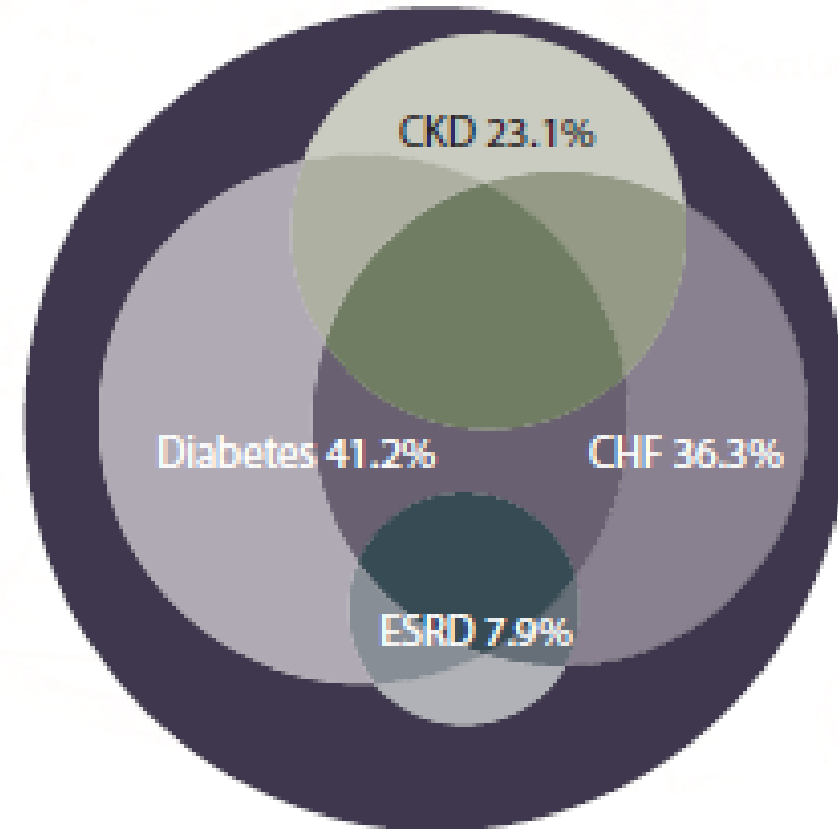
- Kidney damage of > 3 months
- $GFR < 60 \text{ ml/min/1.73m}^2$
- CKD results from many pathophysiologically distinct diseases which share a common natural history
- CKD should be staged using eGFR (eg MDRD)

Distribution of Costs General Medicare Population CKD and ESRD

General Medicare: population, 2008
(n = 31,387,561; mean age 68.3)



General Medicare: costs, 2008
(\$273.8 billion)

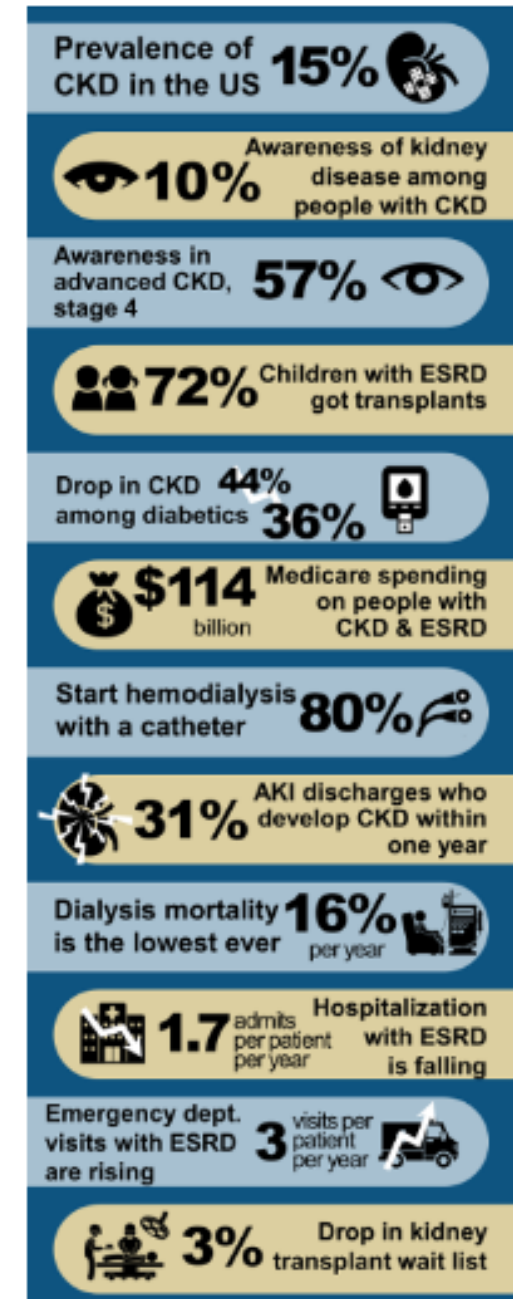


- ESRD Program costs \$32 Billion a year
- \$85000 pa to keep a patient on dialysis in New England

CKD and ESRD

Demographics and Clinical Outcomes

- As of Dec 31, 2016, there were 726,331 prevalent cases of ESRD in the United States:
 - This represents an increase of 3.0% since 2015, and of 86.0% since 2000
 - 63.1% receiving hemodialysis,
 - 6.9% peritoneal dialysis
 - 29.6% kidney transplant
- ESRD incidence rate increasing 1-3% pa
 - 124670 patients initiated HD in 2016



Question

All of the following adult patients should be referred for nephrology consultation, EXCEPT?

- A. Initial visit: eGFR 26 & 3 months later: eGFR 28 (mL/min/1.73m²)
- B. Initial visit: eGFR 55, & 3 months later: eGFR 43 confirmed with repeat eGFR 45 (mL/min/1.73m²)
- C. Initial visit: ACR 450 & 3 months later: ACR 355 (mg/g) on both dates the eGFR >60 mL/min/1.73m²
- D. Initial visit: eGFR >60 & 3 months later: eGFR >60 (mL/min/1.73m²) with personal history of Autosomal Dominant Polycystic Kidney Disease
- E. Initial visit: eGFR 42 & 3 months later: eGFR 44 (mL/min/1.73m²) on both dates the ACR <30 mg/g

Answer

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Predicting CKD Progression

KIDNEY FAILURE
RISK CALCULATION

If you don't have the information required below talk to your doctor.

Age (Yrs)

Sex
Select ▾

Region
Select ▾

GFR (mL/Min/1.73M2)

Urine Albumin: Creatinine Ratio

Units
Select ▾

CALCULATE

Progression: Albuminuria as a Risk Factor

YOUR RESULTS

 **400**
URINE ALBUMIN-CREATININE
RATIO

M
SEX

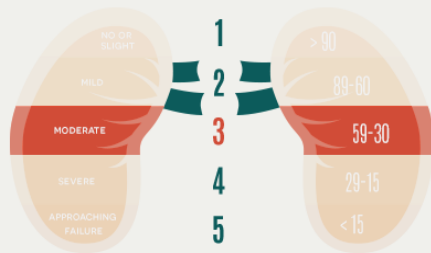
 **60**
AGE

30
GFR

ASSESSMENT

STAGE 3

MODERATE DECREASE IN FUNCTION



Patient risk of progression to kidney failure requiring dialysis or transplant:

AT 2 YEARS

9.76 %

AT 5 YEARS

27.45

%

YOUR RESULTS

 **0**
URINE ALBUMIN-CREATININE
RATIO

M
SEX

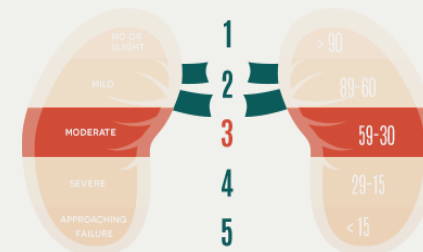
 **60**
AGE

30
GFR

ASSESSMENT

STAGE 3

MODERATE DECREASE IN FUNCTION



Patient risk of progression to kidney failure requiring dialysis or transplant:

AT 2 YEARS

0 %

AT 5 YEARS

0 %

0-5 % IS LOW RISK 5-15 % IS INTERMEDIATE RISK 15 % IS HIGH RISK

Classification of CKD Based on GFR and Albuminuria

Categories: “Heat Map”

CKD is classified based on:

- Cause (C)
- GFR (G)
- Albuminuria (A)

				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73 m ²) Description and range	G1	Normal or high	≥90	1 if CKD	Monitor 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Monitor 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Monitor 1	Monitor 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Monitor 2	Monitor 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Colors: Represents the risk for progression, morbidity and mortality by color from best to worst. Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

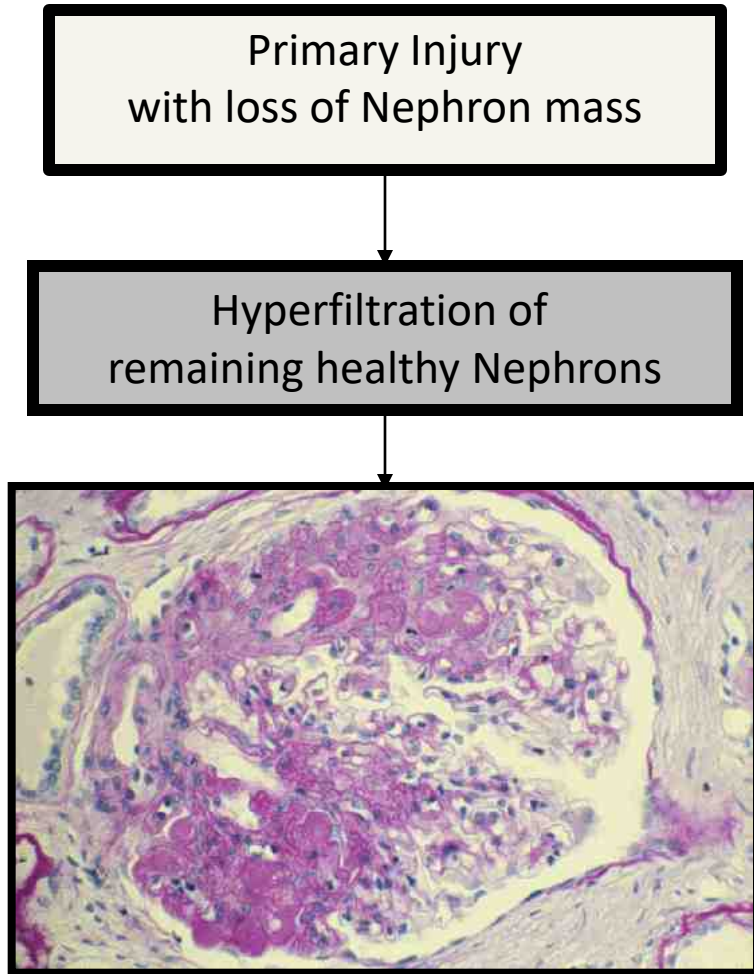
Numbers: Represent a recommendation for the number of times per year the patient should be monitored.

Refer: Indicates that nephrology referral and services are recommended.

*Referring clinicians may wish to discuss with their nephrology service depending on local arrangements regarding monitoring or referral.

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppl.* 2013;3:1-150.

Angiotensin II effects in CKD



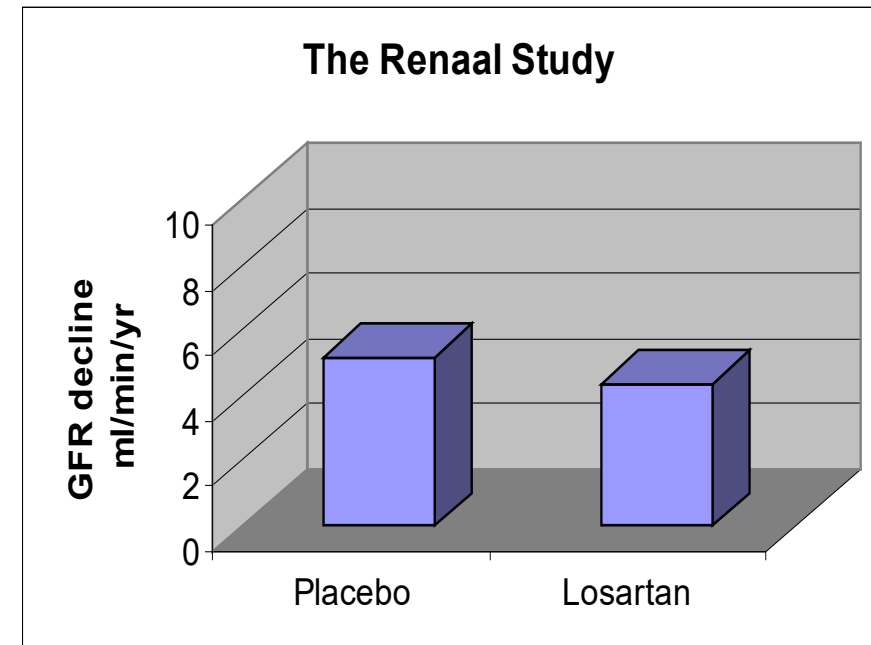
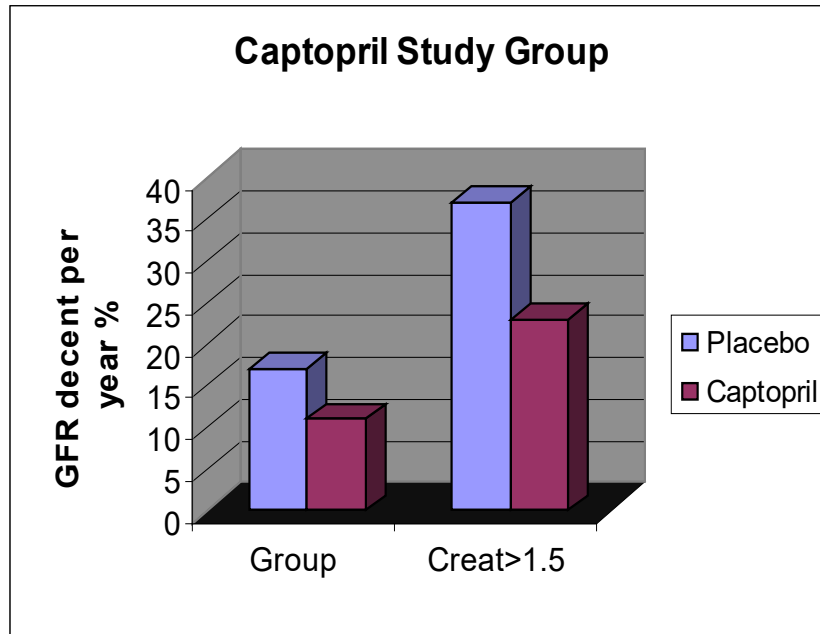
Secondary Focal Segmental
Glomerulosclerosis

- Angiotensin II
 - Hemodynamic effects
 - Single nephron increased GFR
 - Increased intraglomerular pressure
 - Non Hemodynamic effects
 - Inflammation and oxidative stress
 - Cellular hypertrophy and proliferation

Decline in GFR: ACEI and ARB use in Type 1 and Type 2 Diabetics

Lewis et al NEJM 329(20), 1993

Brenner et al NEJM 345(12), 2001



Reduction in risk of doubling serum creatinine

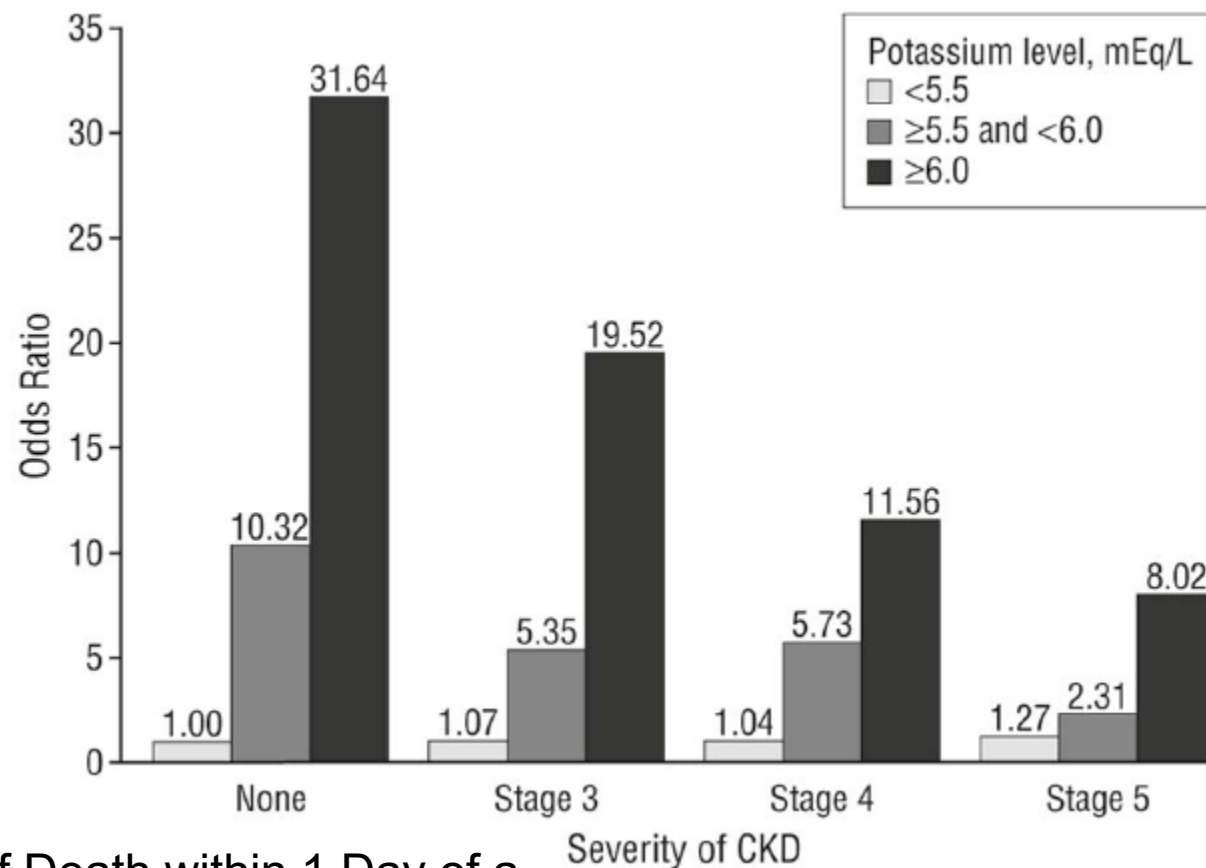
- Captopril Study (Lewis) - 48%
- Renal Study (Brenner) - 25%

ACEI/ARB's in CKD

- ACEI or ARB are indicated for diabetic patients with uAlb/Creat ratio > 0.03 (microalbuminuria)
 - ACEI or ARB are indicated for CKD patients with uAlb/Creat ratio > 0.5 (overt proteinuria)
1. Tolerate a small (+/- 25%) rise in serum creatinine
 2. Attempt to manage Hyperkalemia without withdrawal of ACEI/ARB:
 - Dietary K restriction
 - Potassium Binding Medications
 - Sodium Polystyrene Sulfonate
 - Patiromer
 - Loop diuretics; Fludrocortisone
 3. Use ARB in patients intolerant to ACEI (cough)

The frequency of hyperkalemia and its significance in chronic kidney disease

Lisa M. Einhorn, BS¹, Min Zhan, PhD², Van Doren Hsu, PharmD³, Lori D. Walker, BS³, Maureen F. Moen, BS¹, Stephen L. Seliger, MD^{1,2}, Matthew R. Weir, MD¹, and Jeffrey C. Fink, MD^{1,2}



Odds of Death within 1 Day of a Hyperkalemic Event, by Potassium Category and CKD

HyperKalemia Treatment

Sodium Polystyrene Sulfonate (“Kayexalate”)

- Approved in 1958, before requirements to prove the effectiveness and safety
- Associated with rare complication of intestinal necrosis
- Acts in GI tract to bind and exchange Na for K
 - GI cramping and diarrhea
 - Na retention

Patiromer (“Valtessa”)

- Nonabsorbed polymer that binds potassium in exchange for calcium
- OPAL-HK trial studied mild (mean K 5.3) and moderate-to-severe (mean K 5.7) hyperKalemia
- Study showed efficacy in both groups

Sodium Zirconium Cyclosilicate (“Lokelma”)

- selective cation exchanger
- Patients with hyperkalemia (mean K 5.3) who received ZS-9, as compared with those who received placebo had a significant reduction in potassium levels at 48 hours, with normokalemia maintained during 12 days of maintenance therapy

Question

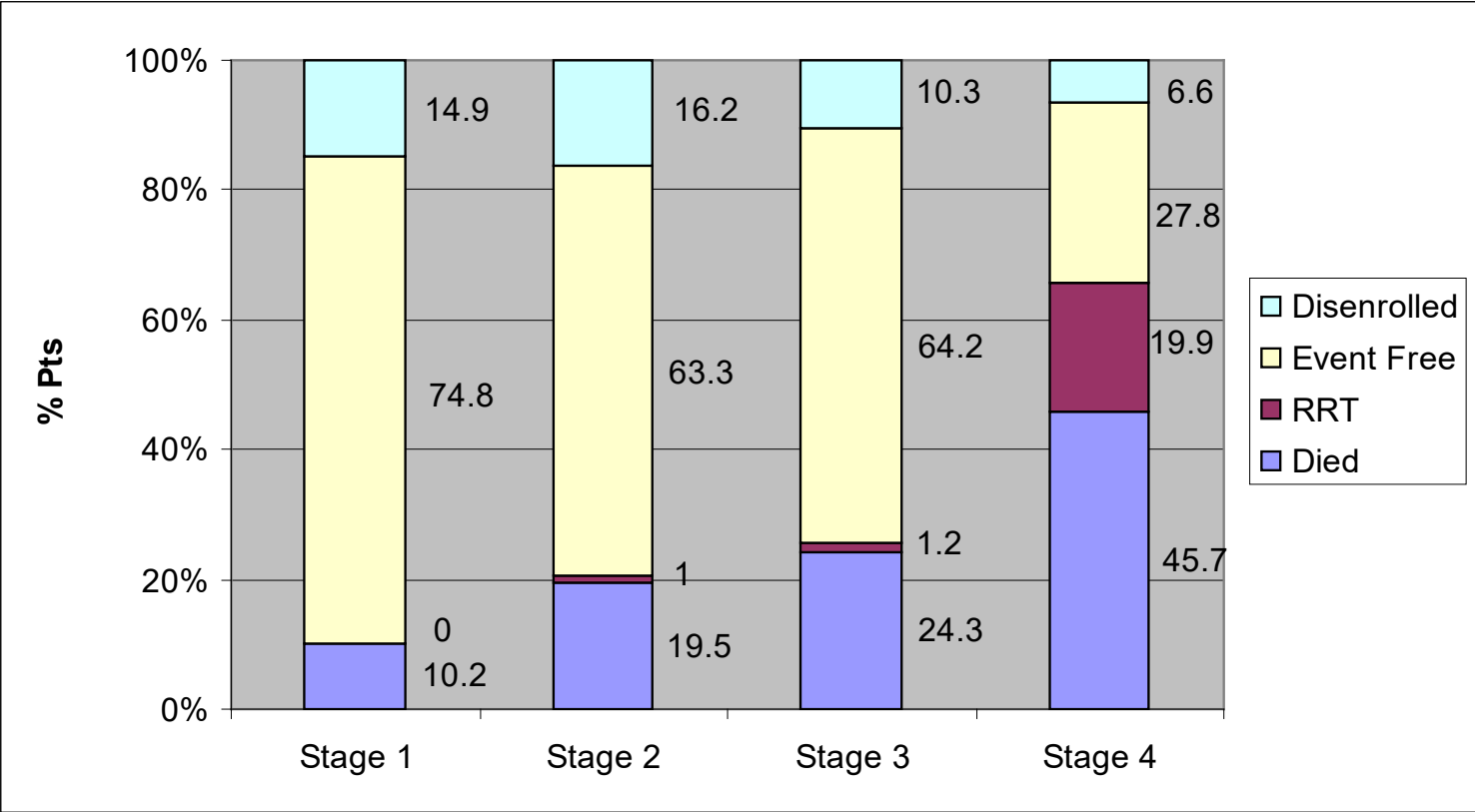
- The Tromsø study looked at the natural history of CKD in a population of 58000 patients in Scandinavia. 3047 patients were found to have a GFR between 30 and 60 ml/min. Patients were followed for 10 years and the rate of progression to ESRD was:
 - A. 4%
 - B. 10%
 - C. 12%
 - D. 25%

Answer

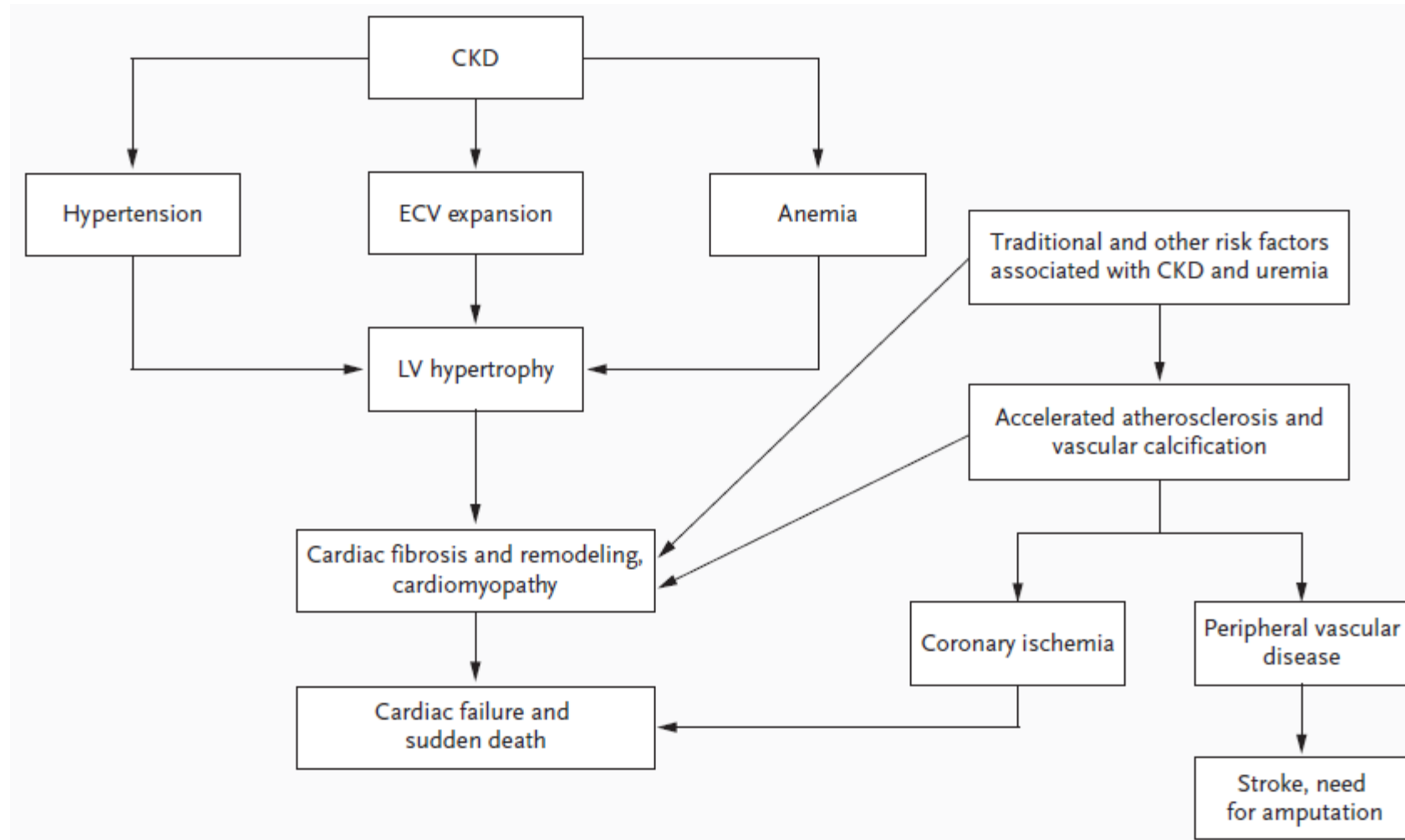
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 - A. 4%
 - B. 10%
 - C. 12%
 - D. 25%

Longitudinal Follow-up and Outcomes Among a Population With Chronic Kidney Disease in a Large Managed Care Organization

27998 patients identified with GFR < 90ml/min and
followed for 5 years



Cardiovascular Disease in Patients with CKD: CardioRenal Syndrome Type 4



Lipid Management

- Statins decrease risk for CVD events and death by 20% in pts not on dialysis.
- Pts with traditional CV risks (diabetes, coronary disease, prior stroke, or increased 10-year risk) should receive statin therapy according to current guidelines
- In the absence of traditional risk factors, strongly consider statin therapy if:
 - Age ≥ 50 years
 - History of transplantation (cyclosporine increases serum levels of some statins)

Statin	eGFR G1-G2	eGFR G3-G5 (including transplant recipients and patients on dialysis)
Atorvastatin	Any dose approved for general population	20 mg
Fluvastatin		80 mg
Lovastatin		No trial data
Pravastatin		40 mg
Rosuvastatin		10 mg
Simvastatin		40 mg
Simvastatin/ezetimibe		20 mg/10 mg

Adapted from Tonelli, et al *Ann Int Med.* 2014; 160:184

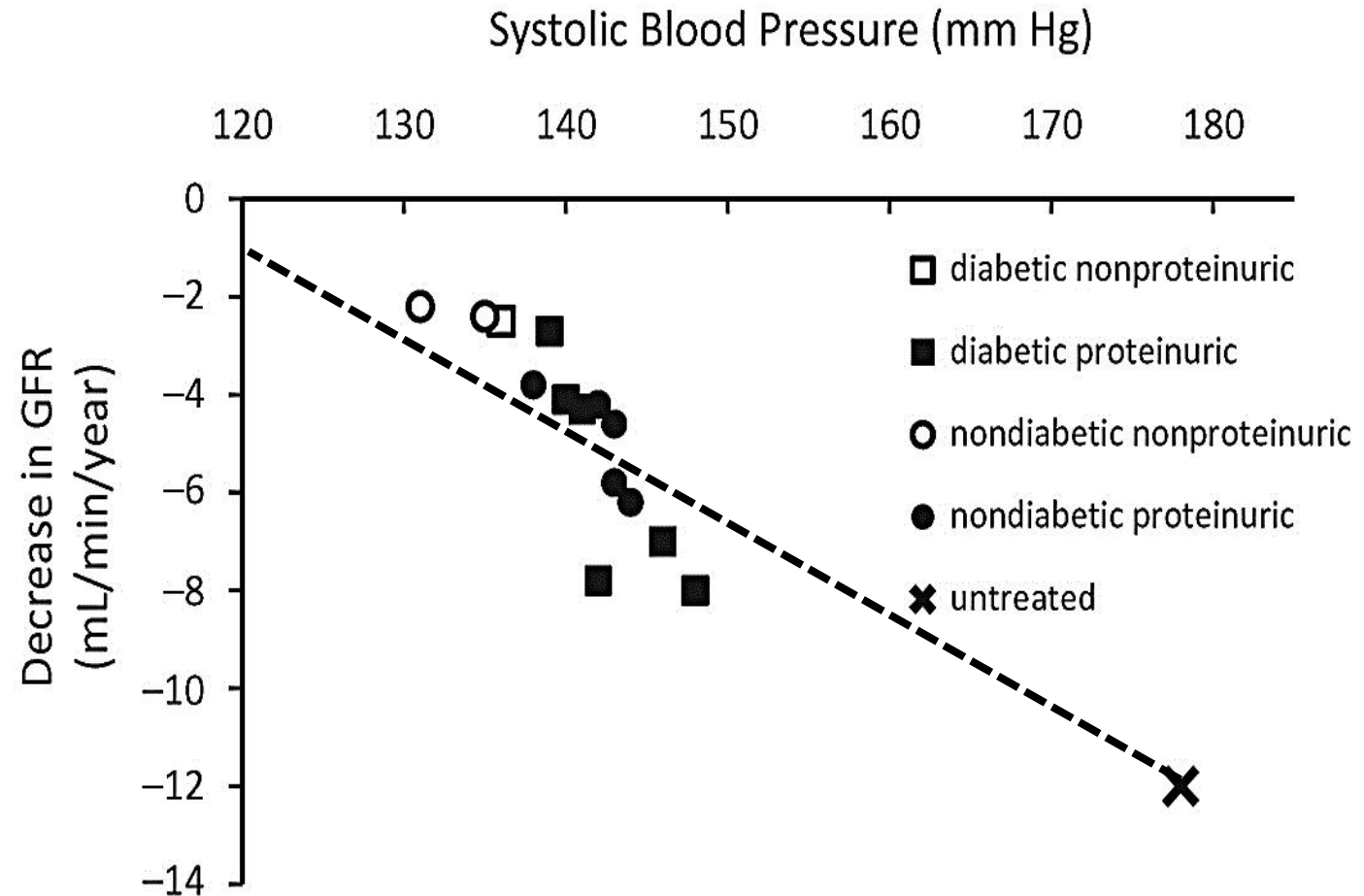
Relationship Between Achieved BP and Decline in Kidney Function from Primary Renal Endpoint Trials

Nondiabetes

- MDRD. N Engl J Med. 1993
- AIPRI. N Engl J Med. 1996
- REIN. Lancet. 1997
- AASK. JAMA. 2002
- Hou FF, et al. N Engl J Med. 2006
- Parsa A et.al. NEJM 2013

Diabetes

- Captopril Trial. N Engl J Med. 1993
- Hannadouche T, et al. BMJ. 1994
- Bakris G, et al. Kidney Int. 1996
- Bakris G, et al. Hypertension. 1997
- IDNT. NEJM. 2001
- RENAAL. NEJM. 2001
- ABCD. Diabetes Care (Suppl). 2000



Management of HTN

JNC 8:

- In the general population aged ≥ 60 years
 - Treat BP $> 150/90$
- In the general population < 60 years
 - Treat BP $> 140/90$
- In patients with established atherosclerotic disease consider a lower target
- In the population aged ≥ 18 years with CKD
 - Treat BP $> 140/90$ and use ACEI or ARB

KDIGO Guidelines:

- In diabetic and non-diabetic adults with CKD and with urine albumin excretion of > 30 mg/24 hours
 - Treat BP $> 130/80$ and use ACEI/ARB(2D level of evidence)

Avoiding Nephrotoxin Injury: Contrast and Phosphate Nephropathy

<u>Iodinated Contrast Studies</u>	<u>Gadolinium-based contrast studies</u>	<u>Bowel preparation</u>
▪ Avoid high osmolar agents ▪ Use lowest possible contrast dose compatible with complete study ▪ Withdraw potentially nephrotoxic agents before and after the procedure ▪ Give adequate hydration with saline before, during, and after the procedure ▪ Measure GFR 48–96 hours after the procedure	• Do not use gadolinium in Pts with GFR <15 ml/min/1.73 m² (unless there is no alternative appropriate test) • For pts with a GFR <30 ml/min use a macrocyclic chelate preparation • Newer agents have to date not been associated with Nephrogenic Systemic Sclerosis	Avoid oral phosphate-containing bowel preparations in pts with GFR <60 ml/min due to risk of phosphate nephropathy

PRESERVE Trial

- Multi-center 2-by-2 factorial design

- 4993 patients at high risk for renal complications
- IV 1.26% sodium bicarbonate or IV 0.9% sodium chloride and 5 days of oral acetylcysteine or oral placebo
- Primary end point occurred in 110 of 2511 patients (4.4%) in the sodium bicarbonate group as compared with 116 of 2482 (4.7%) in the sodium chloride group (odds ratio, 0.93; $P = 0.62$) and in 114 of 2495 patients (4.6%) in the acetylcysteine group as compared with 112 of 2498 (4.5%) in the placebo group (odds ratio, 1.02; $P = 0.88$).
- Among patients at high risk for renal complications undergoing angiography, there was no benefit of IV NaHCO_3 over IV NSS 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.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

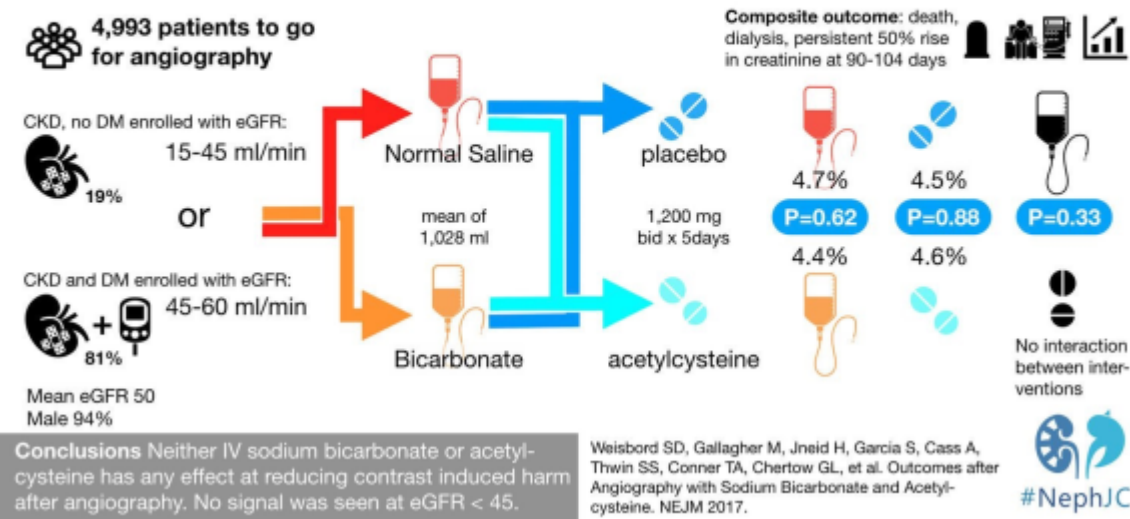
FEBRUARY 15, 2018

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*

Does sodium bicarbonate or acetylcysteine prevent contrast induced harm? The PRESERVE Trial.



Avoiding Nephrotoxin Injury:

Lithium Nephropathy

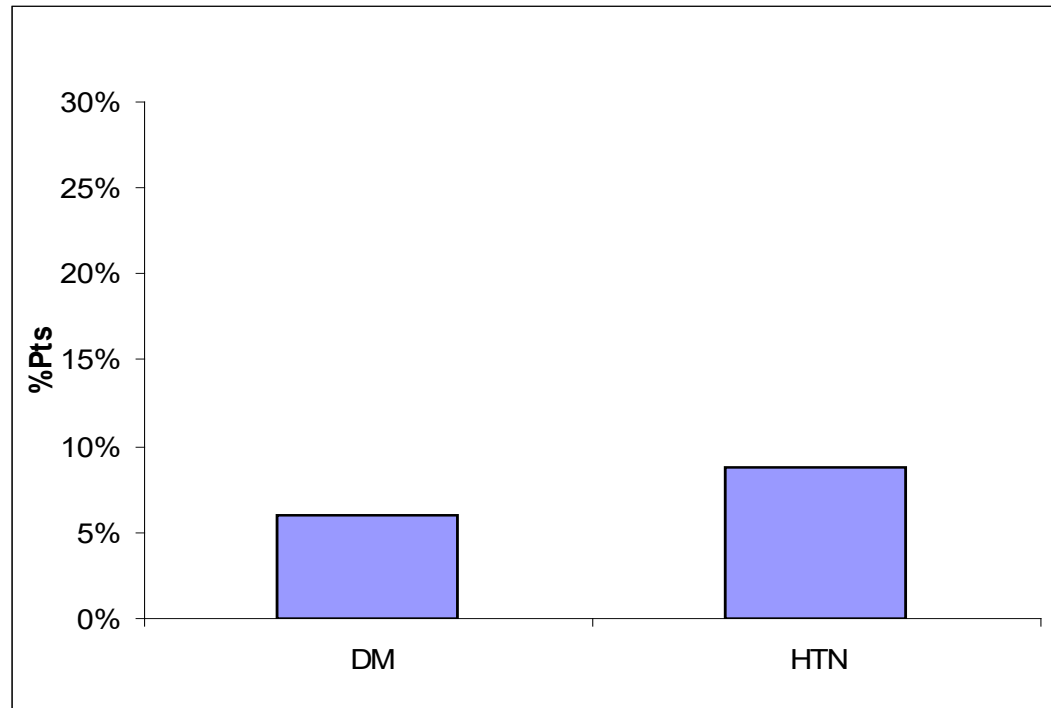
- Lithium salts produce a natriuresis associated with impairment of Na channels in the cortical collecting tubule.
- The most common complication of chronic lithium therapy is nephrogenic diabetes insipidus.
- ~30% of patients have at least one episode of acute lithium toxicity
- Continued debate regarding true incidence of chronic lithium nephropathy.
 - 15% have GFRs of more than 2 standard deviations below the age-corrected normal values

Lithium Cont

- Nephrogenic DI
 - Obligate UO in range of 2-4L a day
 - Predisposes to dehydration in acute care setting;
 - dehydration predisposes to acute Lithium toxicity
- Associated with renal microcysts on imaging studies
- Lithium associated CKD
 - Tends to occur after many years of exposure (often decades) and progresses slowly
 - Woman more susceptible
 - Associated with thyroid and parathyroid abnormalities; hypercalcemia common
- Strategies for alternative therapies should be discussed with treating Psychiatrist if CKD occurs

Avoiding Nephrotoxin Injury : NSAID Associated Renal Injury

587 Medicare pts <75 years with documented renal disease



Adverse Renal Effects of NSAIDs

- Reduced GFR/pre renal Azotemia often in concert with ACEI/ARB and dehydration
- Hypertension
- Volume retention
- Electrolyte disturbances
- Allergic Nephritis
- Proteinuria and Nephrotic Synd.

Executive Order on Advancing American Kidney Health



- Prevent kidney failure whenever possible through better diagnosis, treatment, and incentives for preventive care;
- Increase patient choice through affordable alternative treatments for ESRD by encouraging higher value care, educating patients on treatment alternatives, and encouraging the development of artificial kidneys
- Increase access to kidney transplants by modernizing the organ recovery and transplantation systems and updating outmoded and counterproductive regulations
- Develop a payment model to evaluate the effects of creating payment incentives for greater use of home dialysis and kidney transplants for Medicare beneficiaries on dialysis.

THE WHITE
HOUSE,
July 10, 2019

Home HD Equipment

- Multiple options for home hemodialysis:
 - Fresenius Baby K, NxStage, B. Braun Melsungen, Tablo
- The systems have some differences:
 - **B Braun** is a standard hemodialysis machine; used in center and at home.
 - **Fresenius "Baby K"** home machine is close to a standard hemodialysis machines, but somewhat more user friendly and smaller.
 - B Braun and the Fresenius Baby K require a separate reverse osmosis water treatment system; Dialysate flow rates 300 to 800 ml/minute.
 - **NxStage** System uses either pre prepared dialysate or on demand
 - DFR 200 ml/minute but generally runs at rates less than 150 ml/minute.
 - Ultrapure system: bags of ultrapure dialysate; uses 15 to 60 liters per treatment
 - Pureflow system: on demand dialysate production; uses a deionization process to create a 60, 50 or 40 liter batch of dialysate depending on the SAK (bag of dialysate concentrate) specified by the MD.
 - **Tablo**: In center self care
 - Creates dialysate on demand
 - Portable built in RO: 150-300ml/min DFR

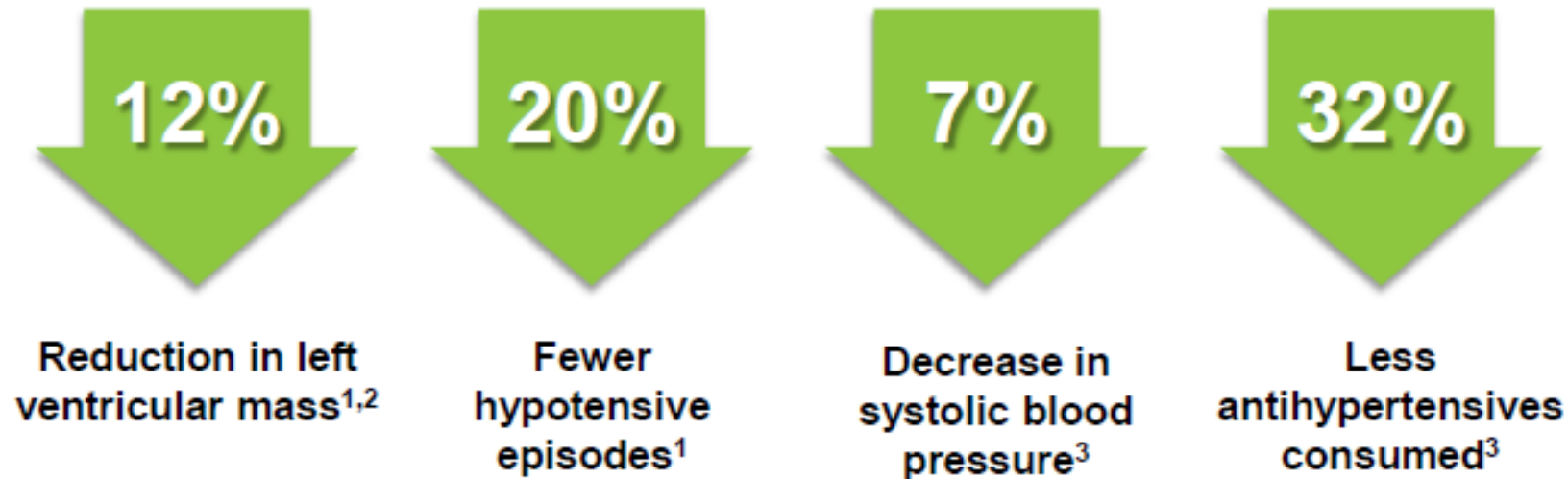


Home Hemodialysis:

Clinical Benefits of More Frequent Hemodialysis

- Improved Fluid Management
- Mitigation of the Two-Day “Killer Gap”
- Less Cardiovascular Injury
- Reduced Cardiovascular-related Hospitalizations and Overall Mortality
- Improved Health-Related Quality of Life

Frequent Hemodialysis Associated with 12-month Improvements



¹FHN Trial Group, Chertow GM, Levin NW, et al. In-center hemodialysis six times per week versus three times per week. *N Engl J Med.* 2010;363(24):2287-2300. doi:10.1056/NEJMoa1001593. ²Rocco MV, Lockridge RS, Beck GJ, et al. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. *Kidney Int.* 2011;80(10):1080-1091. doi:10.1038/ki.2011.213. ³Kotanko P, et al. Effects of frequent hemodialysis on blood pressure: Results from the randomized frequent hemodialysis network trials. *Hemodial Int.* 2015 Jul;19(3):388-401. doi: 10.1111/hdi.12255. Epub 2015 Jan 5.

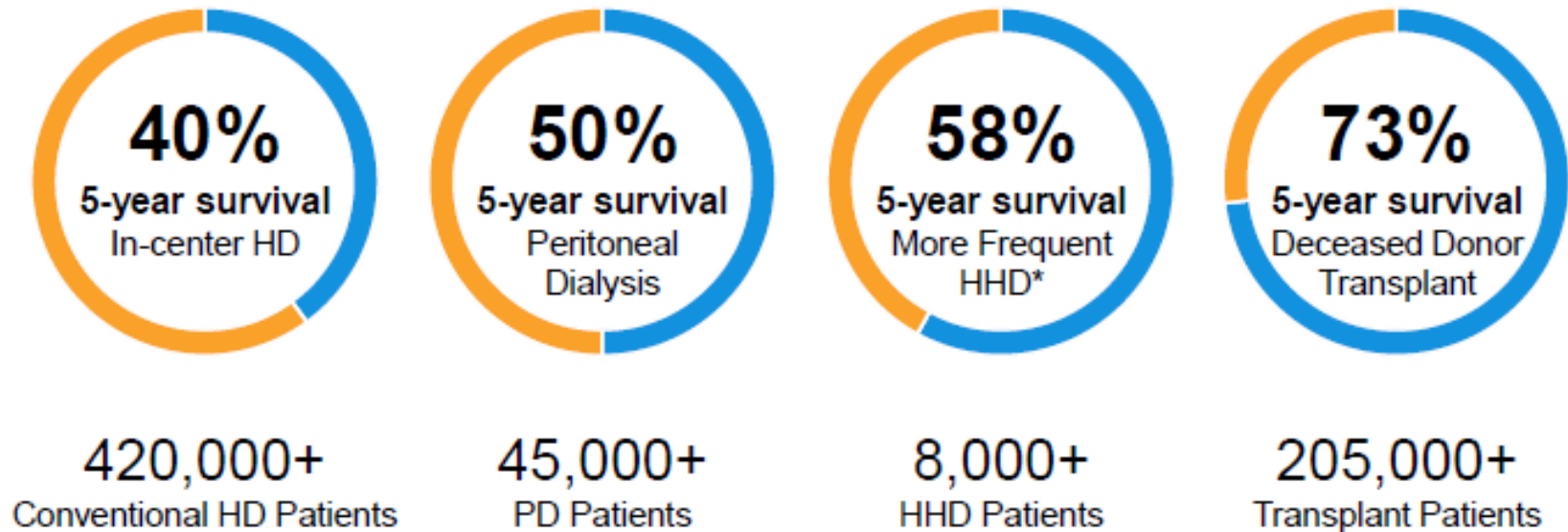
Cardiovascular-related Hospitalizations

More frequent home hemodialysis as compared to conventional, thrice-weekly hemodialysis



E.Weinhandl, K.Nieman, D.Gilbertson, A.Collins. American Journal of Kidney Disease; Hospitalization in Daily Home Hemodialysis and Matched Thrice- Weekly In-Center Hemodialysis Patient. 2014.

5-year Patient Survival After Initiating Treatment

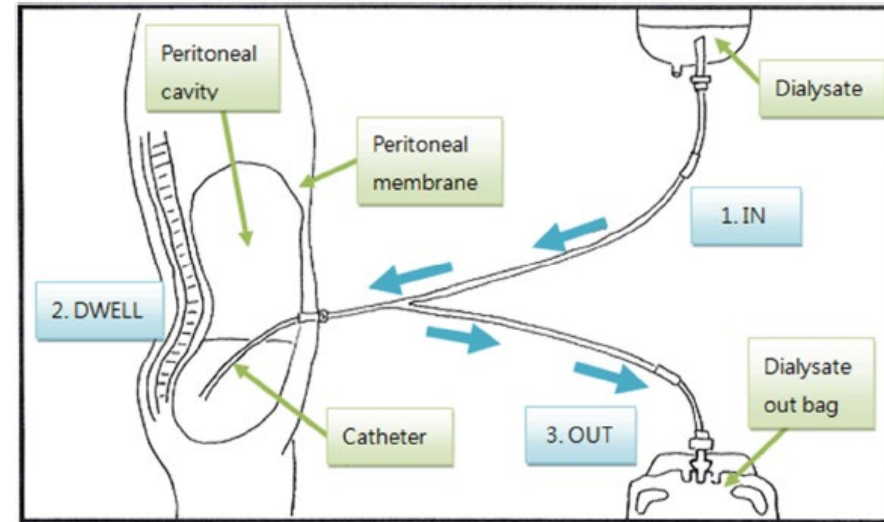


*Data source: NxStage patient data on file.

U.S. Renal Data System, USRDS 2015 Annual Data Report: Table 6.3. Adjusted survival (%) by (a) treatment modality and incident cohort year (year of ESRD onset), and (b) age, sex, race, and primary cause of ESRD, for ESRD patients in the 2008 incident cohort (initiating ESRD treatment in 2008) Abbreviation: ESRD, end-stage renal disease.

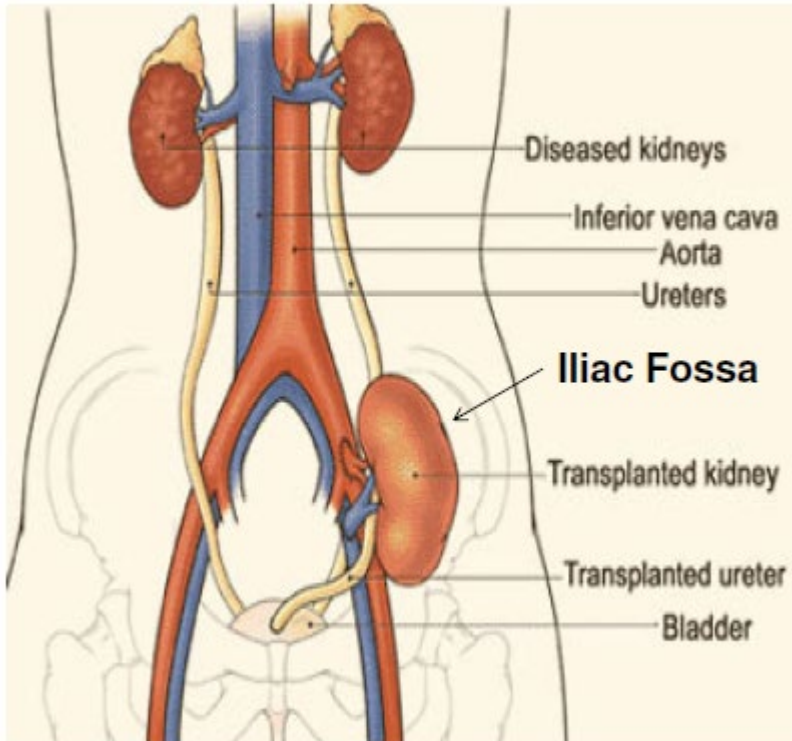
Peritoneal Dialysis

- Peritoneal dialysis (PD) has been in use since 1976
- **<8% of prevalent ESRD patients in the United States are treated with PD significantly less than in other developed countries**
- Reasons maybe related to subtle differences in practice patterns and unintended financial considerations
- **Medical outcome data would seem to favor more utilization of PD.**
- Currently most home dialysis units are small, and some have minimal clinical experience; consolidation of PD programs may needed.



Multidisciplinary pre-dialysis programs increase the proportion of patients initiating dialysis with PD.

Kidney Transplantation

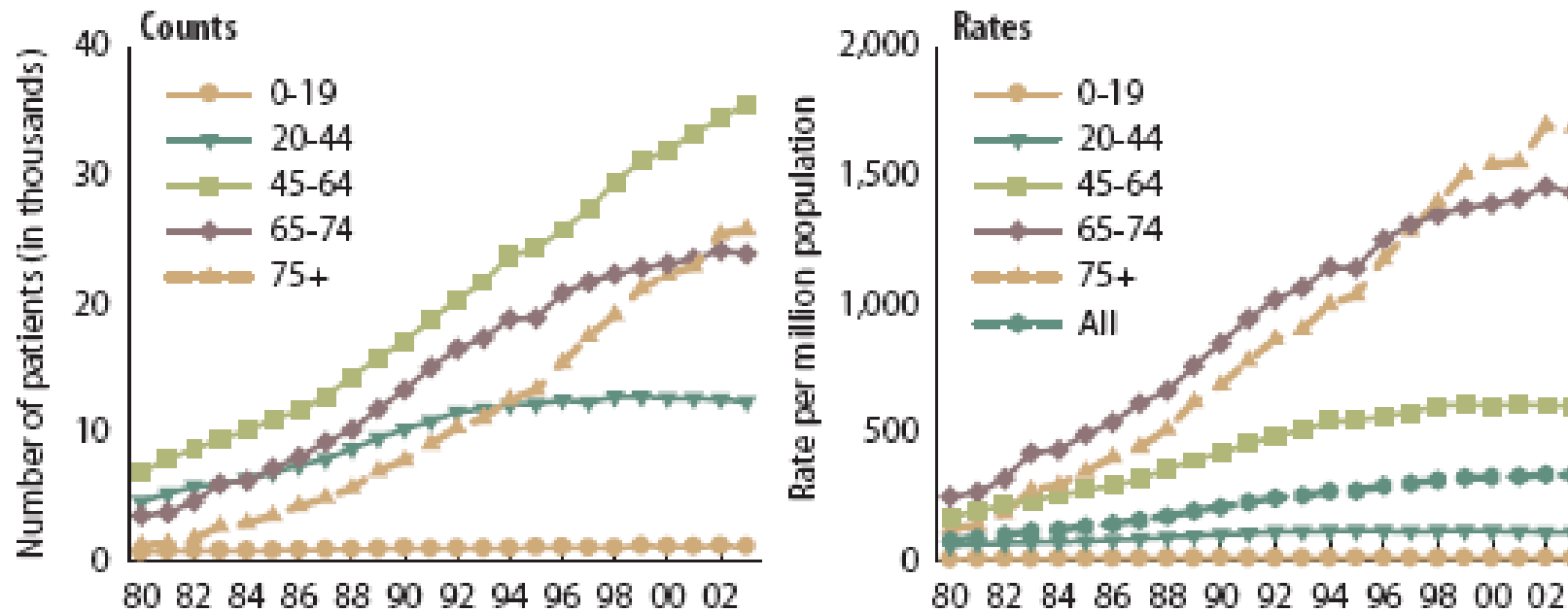


Key Concepts

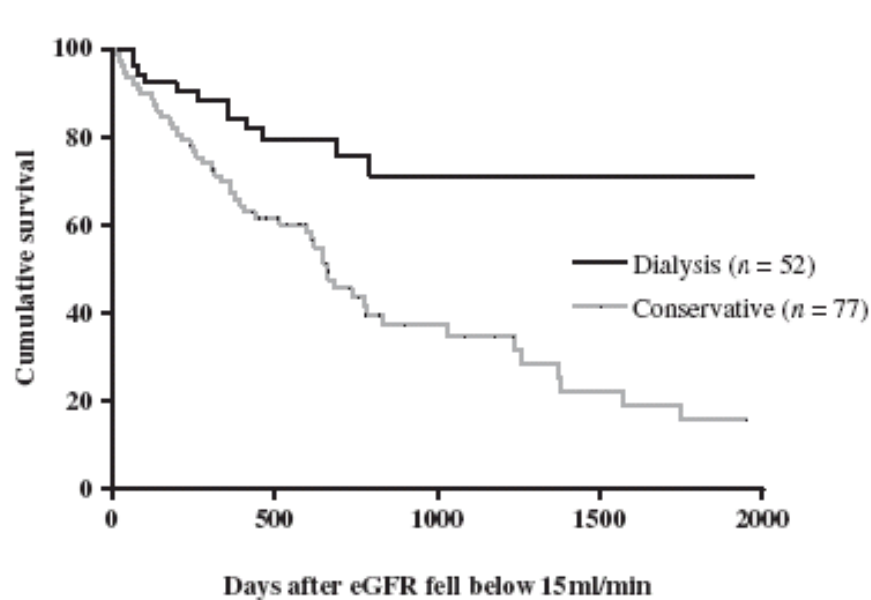
- **Kidney transplantation is the most cost-effective modality of renal replacement.**
- **Transplanted patients have a longer life and better quality of life.**
- Early transplantation (before [pre-emptive] or within 1 year of dialysis initiation) yields the best results.
- Living donor kidney outcomes are superior to deceased donor kidney outcomes.
- Early transplantation is more likely to occur in patients that are referred early to nephrologists.
- **Refer for transplant evaluation when eGFR <20 mL/min/1.73m².**

ESRD incident counts and adjusted rates by age.

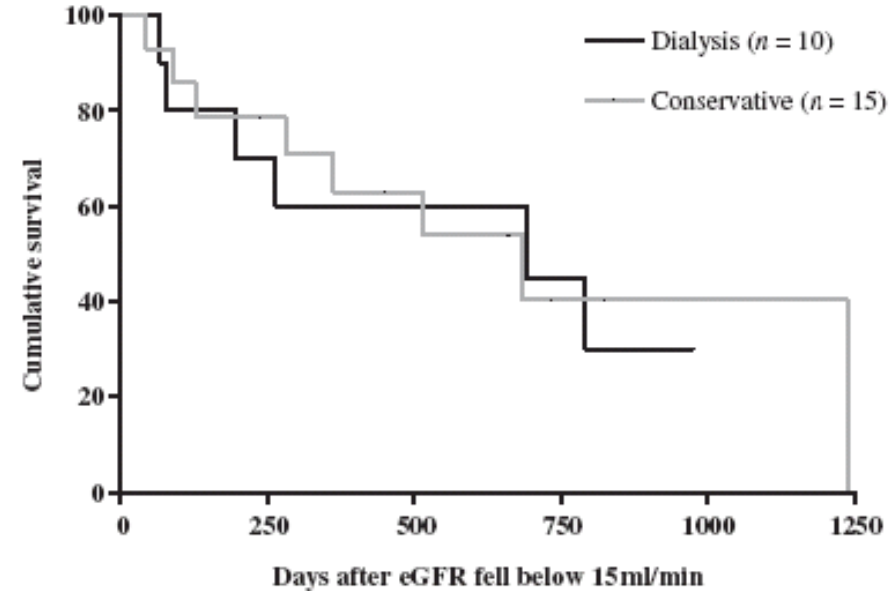
- the ageing of the dialysis population



A comparative survival study of patients over 75 years with chronic kidney disease stage 5

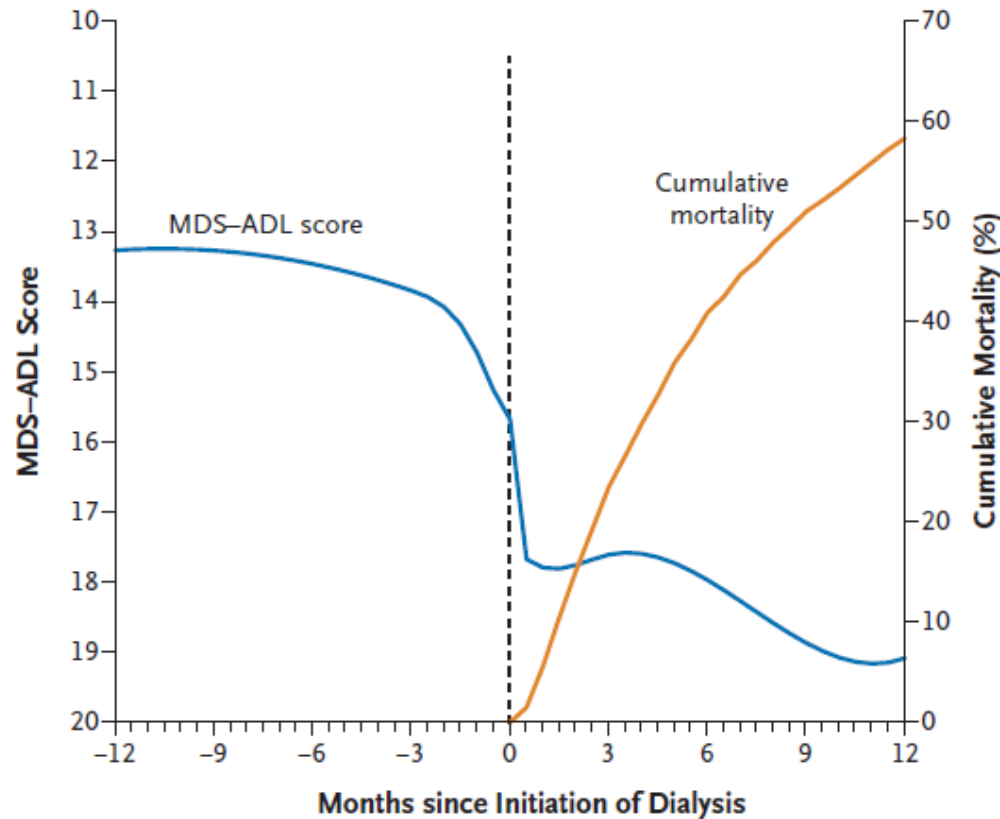


Kaplan–Meier survival curves comparing the dialysis and conservative groups ($P < 0.001$).



Kaplan–Meier survival curves for those with high comorbidity (score > 2), comparing dialysis and conservative groups

Functional Status of Elderly Adults before and after Initiation of Dialysis



- 3702 nursing home residents in the United States
- Initiated dialysis between June 1998 and October 2000.
- At least one measurement of functional status was available before dialysis.
- Functional status was measured by assessing the degree of dependence in seven ADL's (on the Minimum Data Set–Activities of Daily Living [MDS–ADL] scale of 0 to 28 points, with higher scores indicating greater functional difficulty).

Conservative Management of Stage V CKD

- Conservative management should be an option
- It should be supported by a comprehensive management program.
- It should be available to people and families through either primary care or specialist care as local circumstances dictate.
- The comprehensive conservative management program should include:
 - protocols for symptom and pain management,
 - psychological care, spiritual care
 - culturally sensitive care for the dying patient and their family (whether at home, in a hospice or a hospital setting)
 - provision of culturally appropriate bereavement support.

Conclusions

Key Points

- Kidney Disease is common in both the inpatient and outpatient settings
- Acute Renal Failure in hospitalized patients is associated with high mortality rates in those requiring replacement therapy
- The majority of patients with CKD have non progressive disease
- Cardiovascular disease is a major co-morbidity

Next Best Steps

- For patients with progressive CKD care strategies should be evaluated early to improve long term morbidity and mortality
- A team approach is required
- Pre-planning for renal replacement therapies is necessary in those with progressive disease