Harvard Medical School and Massachusetts General Hospital
Internal Medicine Comprehensive Review and Update
Course: 2022

Update in Management of Chronic Kidney Disease, including ESRD

David Steele MD

Nephrology Division

Massachusetts General Hospital

Boston MA.

Conflicts of Interest

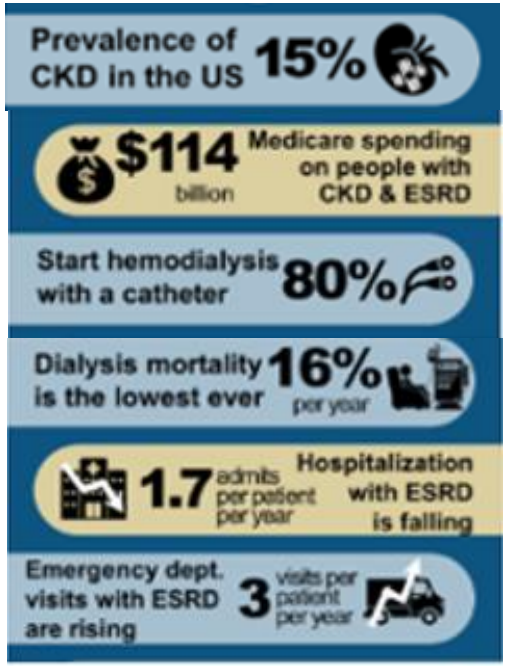
- Fresenius Medical Care – Medical Director

Aims

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

CKD and ESRD
Demographics and Clinical Outcomes

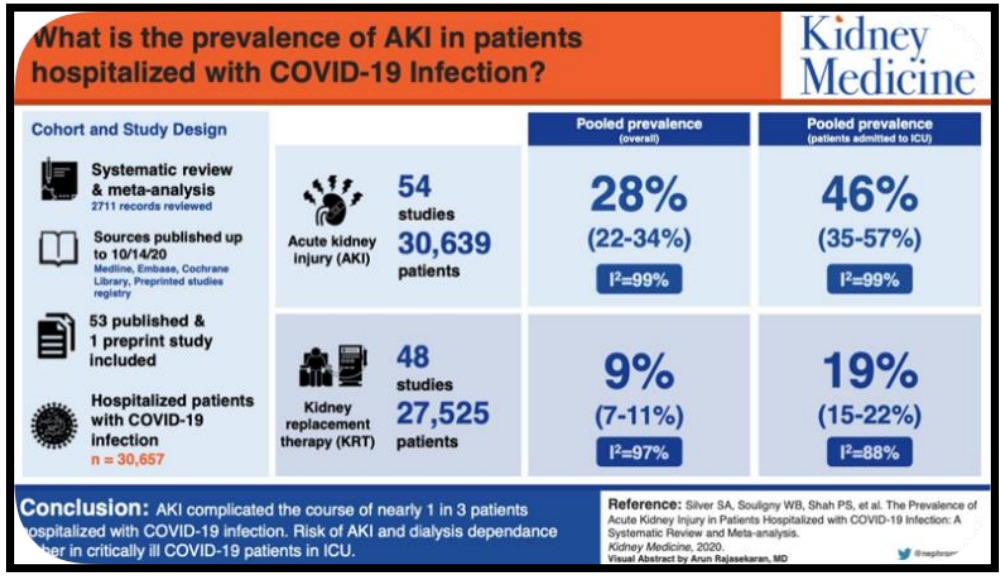
- **US ESRD Demographics:**
  - 554,038 (70.7%) patients undergoing dialysis
  - 229,887 (29.3%) patients with a functioning kidney transplant
  - ESRD Incidence 1-3% pa (2.3% in 2018)
  - 131636 patients initiated HD in 2018
- **Home Dialysis:**
  - There were nearly 69,000 patients performing dialysis in the home, or 12.5% of all patients undergoing dialysis. Nearly 85% of patients on home dialysis performed peritoneal dialysis
- **Racial Disparities:**
  - The adjusted incidence of ESRD among African Americans fell 1.7% between 2017 and 2018. The ratio of adjusted incidence in African Americans versus Whites was 2.7, the lowest value since at least 1980



USRDS ADR 2020

The Prevalence of Acute Kidney Injury in Patients Hospitalized With COVID-19 Infection

- Meta-analysis of 54 studies reporting AKI and 48 studies including renal replacement therapy (RRT) rates among hospitalized patients with COVID-19
- AKI complicated nearly 1 in 3 (28%) patients hospitalized with COVID-19.
- 9% required RRT
- The risk for AKI was higher in critically ill patients, with a substantial number receiving kidney replacement therapy at rates higher than the general intensive care unit population.



- Conclusion: Because COVID-19 will be a public health threat for the foreseeable future, these estimates should help guide kidney replacement therapy resource planning.

Kidney Med Dec 2020

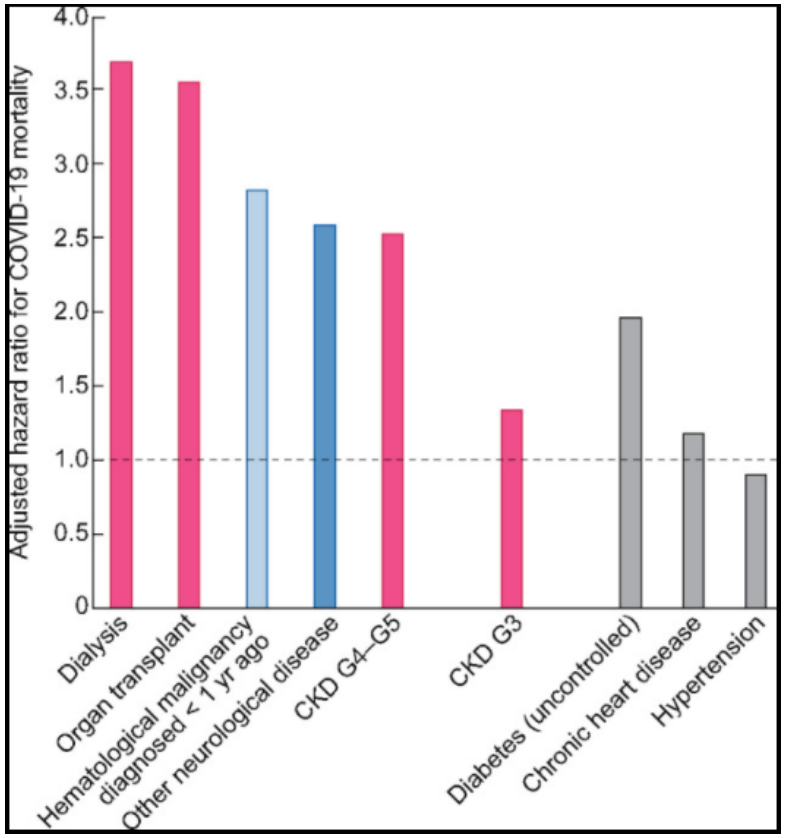
Chronic kidney disease is a key risk factor for severe COVID-19

OpenSAFELY project analysed factors associated with COVID-19 death in 17 million patients.

Risk factors:

- Dialysis (aHR 3.69)
- Organ transplantation (aHR 3.53)
- CKD (aHR 2.52 for patients with eGFR <30 mL/min/1.73 m2)

Three of the five comorbidities associated with the highest mortality risk from COVID-19.



. Nephrol Dial Transplant 2021 Jan 1;36(1):87-94.

Estimating GFR

- Historically, estimating glomerular filtration rate (GFR) has included a racial modified.
- In the context of minimizing racial disparities in medicine the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) has recommended defining GFR without a racial modifier
- The task force also recommended increased use of Cystatin C combined with serum Creatinine as a confirmatory assessment of kidney function.
- CKD eGFR Refit Equation = $142 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female]

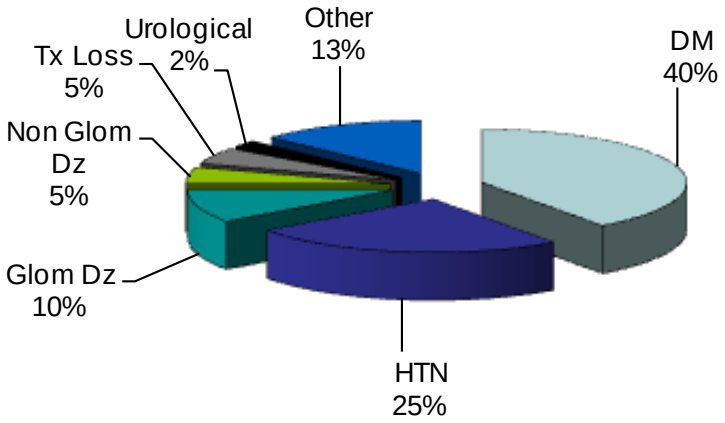
Cystatin C

- Cystatin C is produced by all nucleated cells; it is a lysosomal proteinase inhibitor
- It is a sensitive and accuracy biomarker of kidney function
- CKD EPI Cystatin C eGFR = 133 x min(Scys/0.8, 1)-0.499 x max (Scys/0.8, 1)-1.328 x 0.996Age x 0.932 [if female]

Clinical circumstances where Cystatin C is useful:

1. In patients with muscular atrophy or hypertrophy, or significant chronic illness like heart failure or cirrhosis
2. To confirm or refute an initial diagnosis of chronic kidney disease (eGFR <60 ml/min/1.73 m^2)
3. When making medication dosing changes based on eGFR
4. When patients with progressive CKD require clinical decision making that is contingent on an eGFR threshold. Eg: transplant referral, dialysis modality choice, and dialysis vascular access planning
5. When evaluating a patient as a potential kidney donor

Evaluating CKD



- Kidney damage of > 3 months
- GFR < 60ml/min/1.73m2
- Albuminuria >30mg/g
- CKD results from many pathophysiologically distinct diseases which share a common natural history
- CKD should be staged using eGFR (eg MDRD)

Albuminuria Categories in CKD

Category	ACR (mg/g)	Terms
A1	<30	Normal to mildly increased
A2	30-300	Moderately increased*
A3	>300	Severely increased**

*Relative to young adult level. ACR 30-300 mg/g for >3 months indicates CKD.
**Including nephrotic syndrome (albumin excretion ACR >2220 mg/g).

GFR Categories in CKD

Category	GFR	Terms	Clinical Presentations
G1	≥90	Normal or high	Markers of kidney damage (nephrotic syndrome, nephritic syndrome, tubular syndromes, urinary tract symptoms, asymptomatic urinalysis abnormalities, asymptomatic radiologic abnormalities, hypertension due to kidney disease)
G2	60-89	Mildly decreased*	

G3a	45-59	Mildly to moderately decreased	• Mild to severe complications:
			  ○ Anemia
			  ○ Mineral and bone disorder
			  ▪ Elevated parathyroid hormone
			  ○ Cardiovascular disease
			  ▪ Hypertension
			  ▪ Lipid abnormalities
			  ○ Low serum albumin

G3b	30-44	Moderately to severely decreased	
G4	15-29	Severely decreased	
G5	<15	Kidney failure	• Includes all of the above • Uremia

GFR = mL/min/1.73m²
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.
Refer to a nephrologist and prepare for kidney replacement therapy when GFR <30 mL/min/1.73m².

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

Classification of CKD Based on GFR and Albuminuria Categories: "Heat Map": Nephrology Referral

CKD is classified based on:

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

GFR catagproes (ml/min/1.73 m²) Description and range				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
	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 Suppls.* 2013;3:1-150.

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%

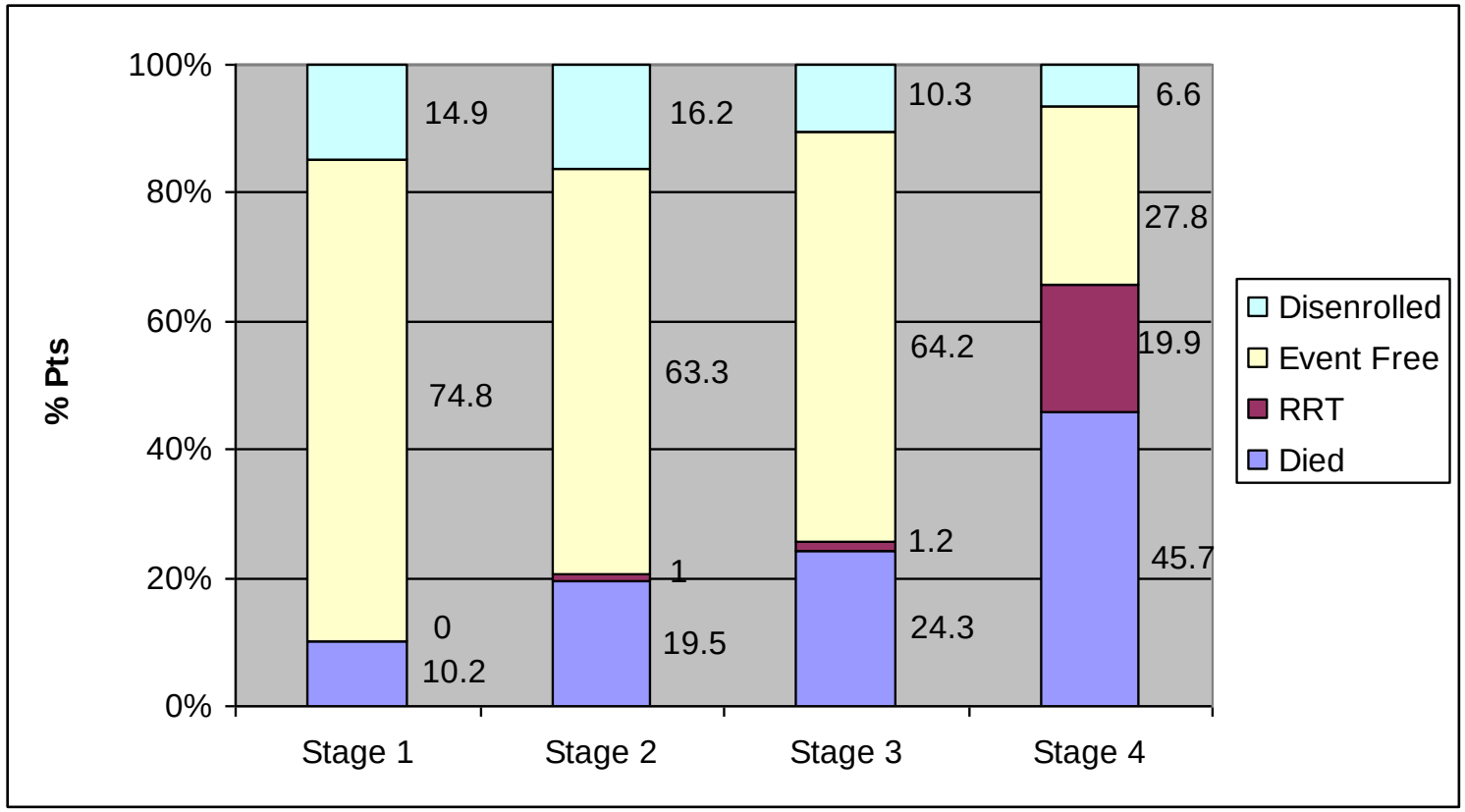
B. 10%

C. 12%

D. 25%

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

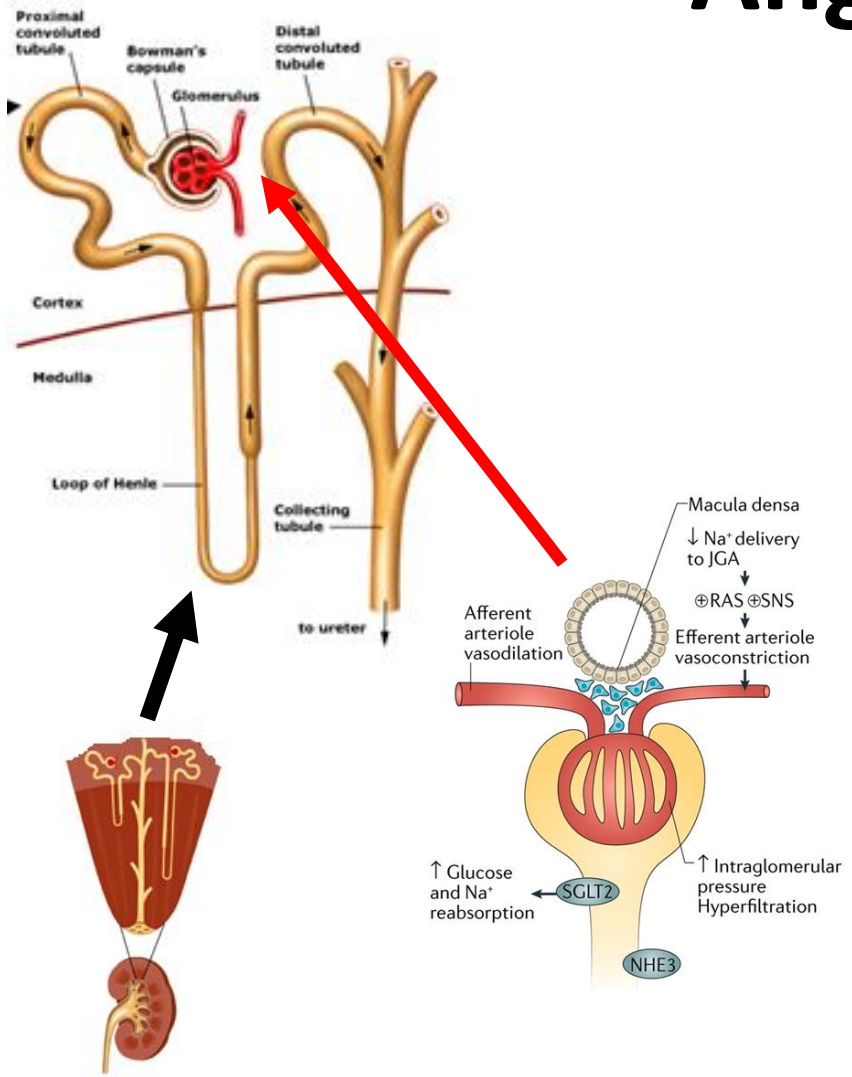


Arch Intern Med. 2004;164:659-663

Strategies for Caring with Patients with CKD 4

- Delay Progression
  - ACE Inhibition
  - SGLT2 inhibitors
  - Minimize AKI risk
  - Review dietary options
- Manage Comorbids
  - Cardiovascular risk
  - Anemia management
  - Metabolic Bone Disease Management
- Prepare for ESRD
  - Isolate high-risk populations
  - Patient education
  - Refer to Nephrology
  - Prepare for angioaccess
  - Review Medical Management options

Progression of CKD
- Angiotensin II effects

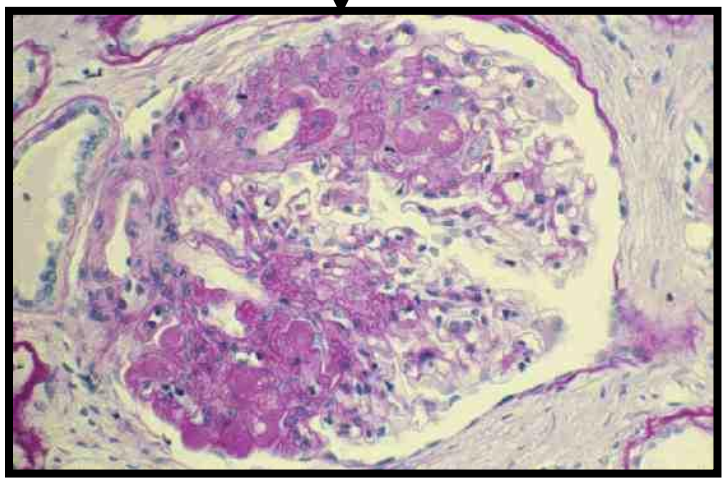


Primary Injury
with loss of Nephron mass

↓

Hyperfiltration of
remaining healthy Nephrons

↓



Secondary Focal
Segmental
Glomerulosclerosis

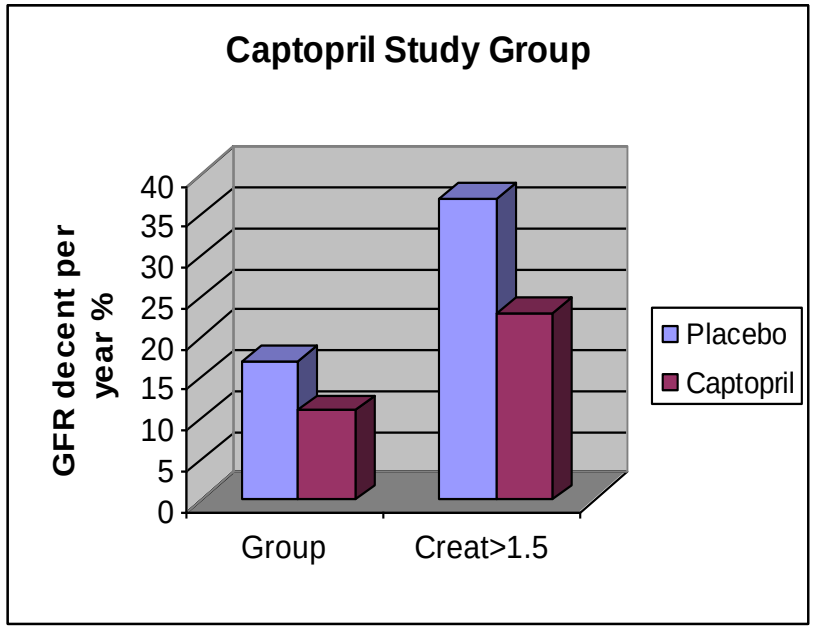
Angiotensin II

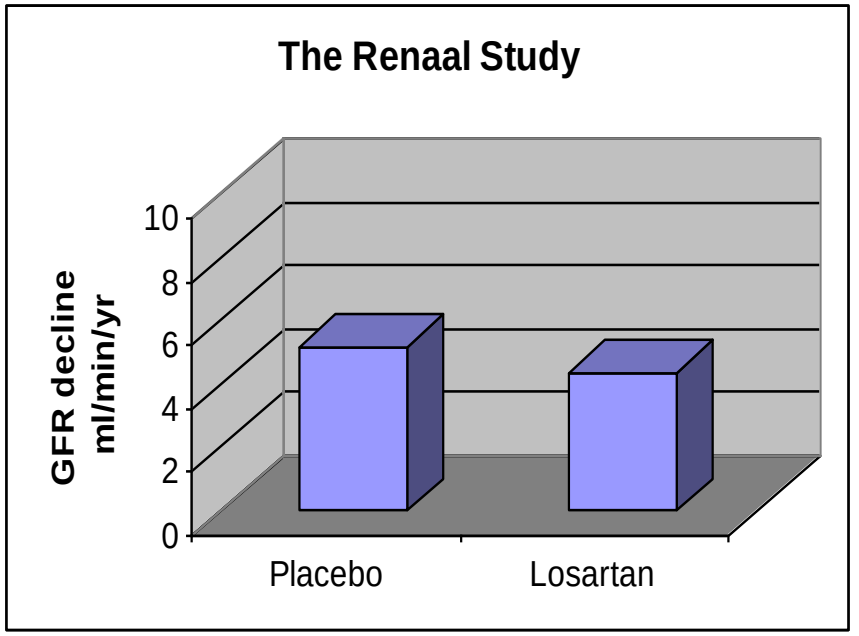
- Hemodynamic effects
  - Single nephron increased GFR
  - Increased intraglomerular pressure

- 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%
- Renaal Study (Brenner) - 25%

Angiotensin-Converting Enzyme Inhibitors and Progression of Nondiabetic Renal Disease

- 11 RCT's comparing the efficacy of anti-HTN regimens including ACEi
- Data on 1860 nondiabetic patients analyzed.
- Data adjusted for:
  - Patient and study characteristics at baseline
  - Changes in systolic BP and urinary protein excretion during follow-up.
- RR for ACE inhibitor group:
  - 0.69 (CI, 0.51 to 0.94) for ESRD
  - 0.70 (CI, 0.55 to 0.88) for the combination of doubling of baseline serum creatinine or ESRD.
- Patients with greater urinary protein excretion at baseline benefited more from ACEi ($P = 0.03$ and $P = 0.001$)
- Data were inconclusive for patients with baseline urinary protein excretion less than 0.5 g/d.

Ann Int Med: Vol 135(2) 2001

ACEI/ARB's in CKD: Summary

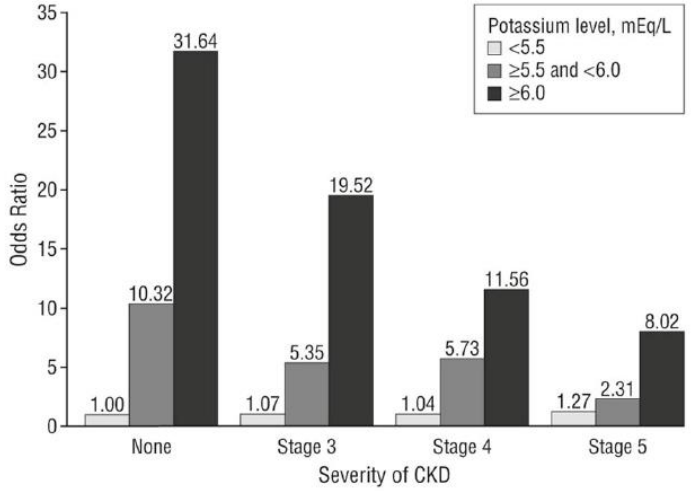
- ACEI or ARB are indicated for diabetic patients with uAlb/Creat ratio>0.03 (microalbuminuria)
- ACEI or ARB are indicated for non diabetic CKD patients with uAlb/Creat ratio>0.5 (overt proteinuria)
- Combination ACEI plus ARB provides no benefit and some harm (OnTarget Study)

1. Maximize dose and target decreased proteinuria
2. Tolerate a small (15-20%) rise in serum creatinine
3. Attempt to manage Hyperkalemia without withdrawal of ACEI/ARB:
   - Dietary K restriction
   - GI Potassium Binders/Exchangers
   - Loop diuretics; Fludrocortisone

The frequency of hyperkalemia and its significance in chronic kidney disease

Lisa M. Einhorn, BS[1], Min Zhan, PhD[2], Van Doren Hsu, PharmD[3], Lori D. Walker, BS[3], Maureen F. Moen, BS[1], Stephen L. Seliger, MD[1,2], Matthew R. Weir, MD[1], and Jeffrey C. Fink, MD[1,2]

- 66,529 hyperkalemic events (3.2% of records)
- 34937 (52.7%) inpatient versus 31322 (47.3%) outpatient
- Adjusted rate of hyperkalemia higher in:
  - CKD vs no CKD
  - Pts on RAAS blocker vs without RAAS blocker



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

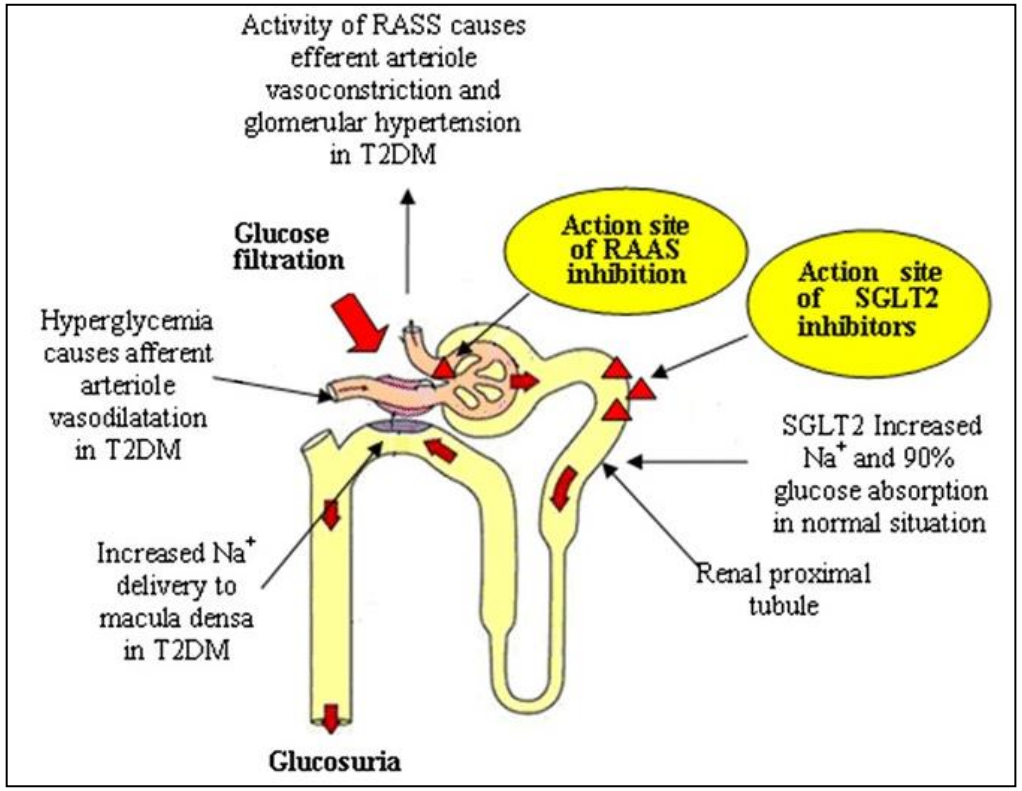
Sodium Zirconium Cyclosilicate ("Lokelma")

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

NEJM Nov 2014

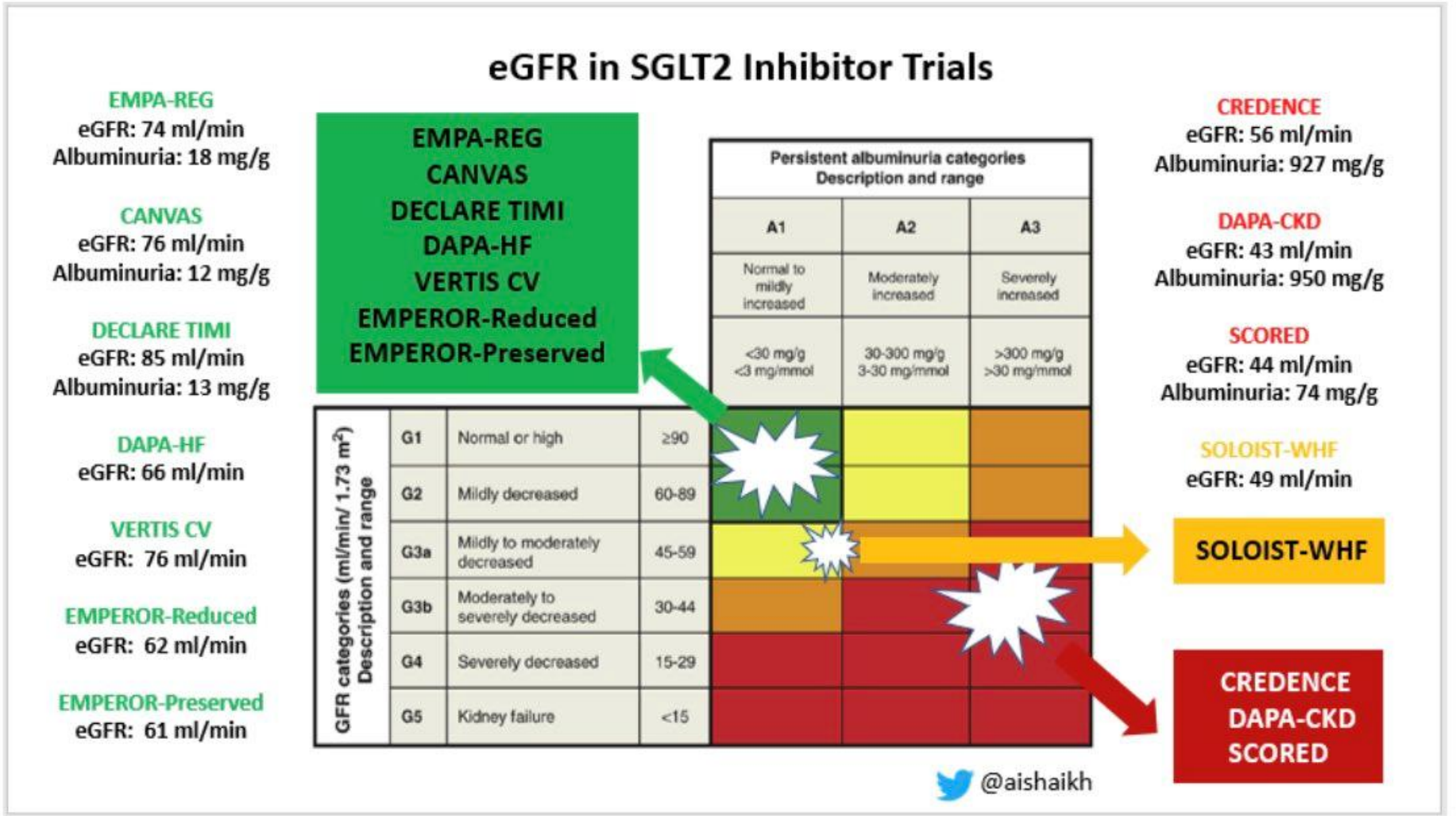
SGLT2 Inhibitors

- **Hyperglycemia** activates **sodium/glucose co-transporter 2 (SGLT2) receptor** leading to enhanced glucose (and Na) reabsorption along the proximal convoluted tubule
- This leads to decreased Na (and Cl) delivery to the macula densa resulting in:
  - **afferent arteriolar dilation**
  - **efferent arteriolar vasoconstriction**
  - **intraglomerular hypertension**.
- Inhibition of SGLT2 co-transporter increases delivery of glucose and Na to the distal convoluted tubule; sensed by the juxtaglomerular apparatus as increased kidney perfusion; resulting in:
  - **increased vasoconstriction of the afferent arteriole**
  - **decreased intra glomerular pressure.**



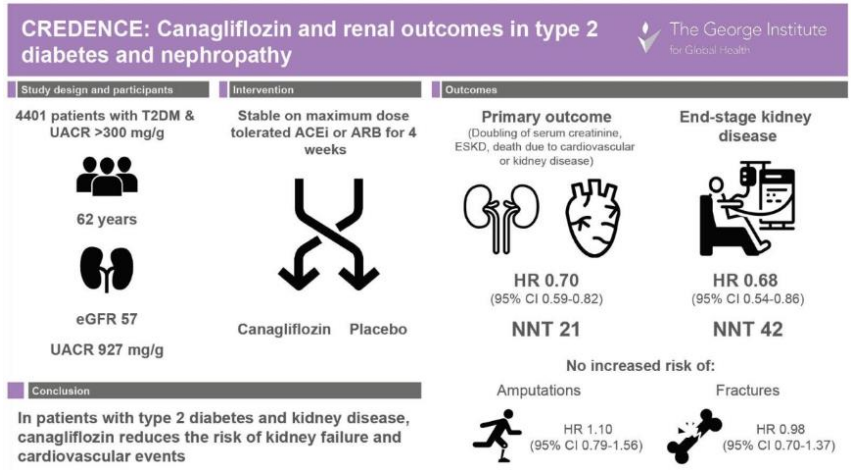
CardioVasc Diabetology 2017

SGLT2 Inhibitor Trials: eGFR and Albuminuria



Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

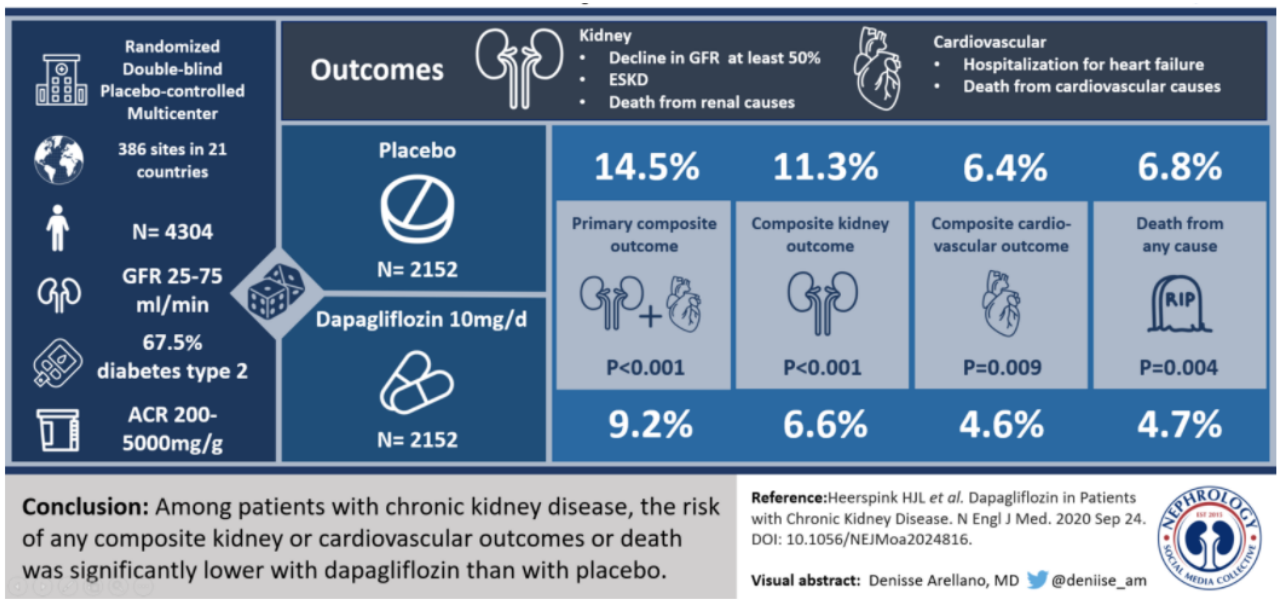
- CKD Patients:
  - 4401 pts with type 2 DM and proteinuria>300mg/g
- End Point:
  - Doubling serum create, ESRD, death due to CVD or CKD/ESRD
- Result:
  - Canagliflozin significantly reduced risk of kidney failure and CVD events



DOI: 10.1056/NEJMoa1811744

DAPA-CKD Trial

- CKD patients:
  - GFR>25ml/min; mean eGFR 44ml/min
  - Mean UACr: 950mg/g
  - DM and Non DM
- EndPoint:
  - Risk of composite of sustained decline in eGFR of at least 50%
  - End-stage kidney disease
  - Death from renal or cardiovascular causes
- Result:
  - End Point significantly lower with dapagliflozin than with placebo.

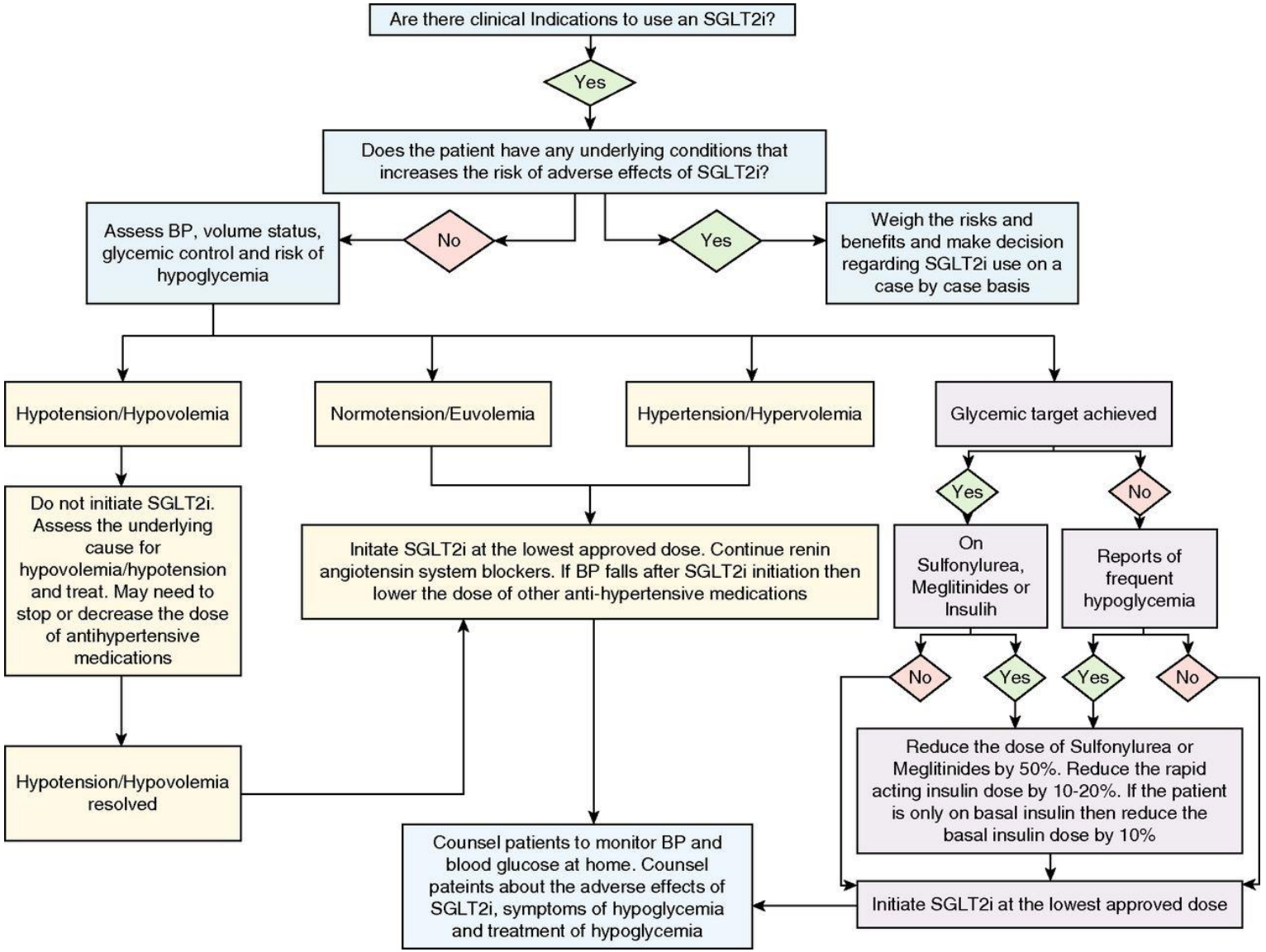


NEJM. Sept 24th, 2020

SGLT2i Complications

@NWiegley	EMPA-REG N= 7020 Cohort: DM2, eGFR 74.1, UACR: ~60% < 30 mg/g Duration: 3.1 years Empaglaflozin vs placebo Event rate %	CANVAS N= 10142 Cohort: DM2, eGFR 76.5, UACR: 70% < 30 mg/g Duration: 2.4 years Canagliflozin vs placebo Event rate per 1000 pt-yr	CREDENCE N= 4401 Cohort: DM2, eGFR 56.2 +/- 18.2 Mean UACR: 927 mg/g Duration: 2.6 years Canagliflozin vs placebo Event rate per 1000 pt-yr	DECLARE-TIMI N= 17160 Cohort: DM2, eGFR 85.4 +/- 16 UACR: NA Duration: 4.2 years Dapagliflozin vs placebo Event rate %	DAPA-HF N= 4744 Cohort: DM2 and non-DM, eGFR 66 +/- 19.6; UACR NA Duration: 18.2 months Dapagliflozin vs placebo Event rate %	DAPA-CKD N= 4304 Cohort: DM2 & non-DM; eGFR 43.1+/-12.4; UACR 949 mg/g Duration: 2.4 years Dapagliflozin vs placebo Event rate %
Hypoglycemia	**No difference** (1.3 vs 1.5)	**No difference**	**No difference**	**No difference**	**No difference** (0.2 vs 0.2)	More in placebo (0.7 vs 1.3)
DKA	Rare **No Difference** (0.1 vs < 0.1)	Rare **higher in CANA** (0.6 vs 0.3)	Rare **higher in CANA** (2.2 vs 0.2)	Rare **higher in DAPA** (0.3 vs. 0.1)	Rare **3 cases in DAPA** (0.1 vs 0)	Rare 0 in DAPA; 2 in placebo
UTI	**No difference** Complicated (1.7 vs 1.8) Uncomplicated (18.1 vs 18)	**No difference** (40 vs 37)	**No difference** (48 vs 45)	**No difference** (1.5 vs 1.6)	**No difference**	**No difference**
Genital mycotic infections	**Higher in EMPA** (6.4 vs 1.8)	**Higher in CANA** (69 vs 18)	**Higher in CANA** Men (8.4 vs 0.9) Women (12.6 vs 6.1)	**Higher in DAPA** Uncomplicated (0.9 vs 0.1) 6 cases- Fournier gangrene (1 in DAPA; 5 in placebo)	**No difference** (0 vs <0.1%) 1 case- Fournier gangrene (0 in DAPA; 1 in placebo)	**No difference** (0 vs <0.1%) 1 case-m Fournier gangrene (0 in DAPA; 1 in placebo)
Bone fracture	**No difference** (3.8 vs 3.9)	**Higher in CANA** (15.4 vs 11.9)	**No difference** (11.8 vs 12.1)	**No difference** (5.3 vs 5.1)	**No difference** (2.1 vs 2.1)	**Higher in DAPA** (4% vs 3.2%)
Limb amputation	**No difference**	higher in CANA (6.3 vs 3.4)	**No difference** (12.3 vs 11.2)	**No difference** (1.4 vs 1.3)	**No difference** (0.5 vs 0.5)	**No difference** (1.6 vs 1.8)

SGLT2i Clinical Application



Kidney360 April 2021, 2 (4) 742-746

SGLT2i Summary

- Outcomes data
  - Reduced 3-point MACE in patients with ASCVD
  - Reduced HF regardless of ASCVD or HF hx, and in CKD w/ eGFR>30
  - Reduced 3-point Major Kidney Events regardless of ASCVD and in CKD w/ eGFR >30 (>25 in DAPA CKD)
- Postulated mechanism of action:
  - Decrease hyperfiltration via JG apparatus action
  - Natriuresis
- Side effects
  - Volume contraction; prerenal Azotemia
  - UTI's (real incidence)
  - Rare: Forniers Gangrene; Amputation risk

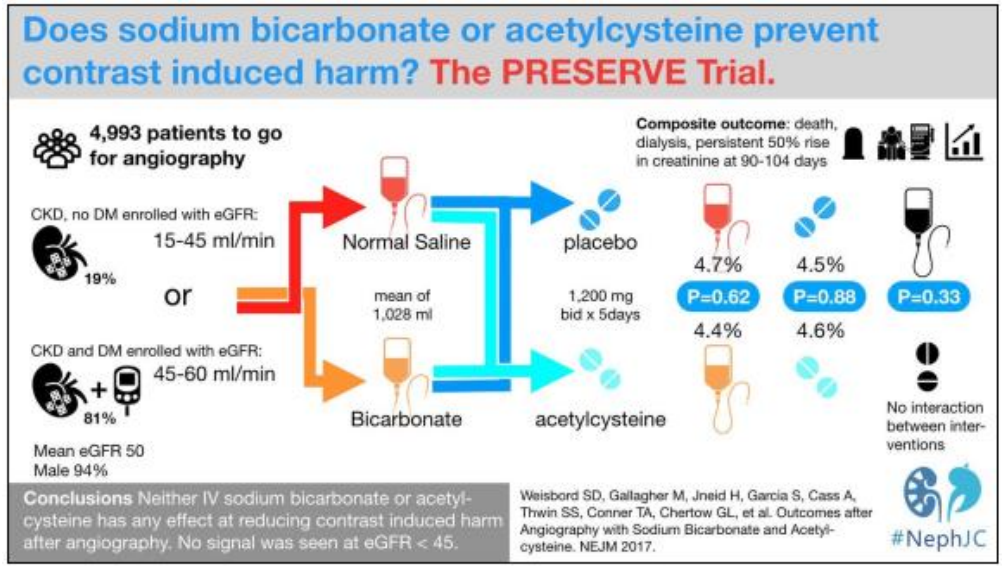
Avoiding Nephrotoxic Injury
RadioContrast Use in CKD: The PRESERVE Trial

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*



- 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
  - 116 of 2482 (4.7%) in the sodium chloride group (odds ratio, 0.93; P = 0.62)
  - 114 of 2495 patients (4.6%) in the acetylcysteine group
  - 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 NaHCO3 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.

N Engl J Med 2018;378:603-14.

Radio Contrast use in CKD

Identify High Risk Populations:

- Proteinuric CKD
- CKD 4 and 5
- Diabetic Nephropathy
- Myeloma associated kidney disease
- AKI
- Recent (within 48 hrs) contrast exposure

Recommendations:

1. Use Low Dose non ionic isotonic contrast
2. Ensure patient well hydrated:
   - NSS: 300ml over one hour pre contrast dose then 1ml/kg/hr for 4-6hrs post contrast for outpatients
   - NSS: 1ml/kg/hr for 6-12hrs pre and post contrast (inpatients)
   - If mild CHF present reduce hydration dose by 50%
   - If unable to tolerate hydration defer study or proceed based on clinical indication emphasizing lowest dose contrast compatible with complete study

Strategies for Caring with Patients with CKD 4

- Delay Progression
  - ACE Inhibition
  - Manage metabolic abnormalities
  - Minimize AKI risk
  - Review dietary options
- Manage Comorbids
  - Cardiovascular risk
  - Anemia management
  - Metabolic Bone Disease Management
- Prepare for ESRD
  - Isolate high-risk populations
  - Patient education
  - Refer to Nephrology
  - Prepare for angioaccess
  - Review Medical Management options

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
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- AASK. JAMA. 2002
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Diabetes
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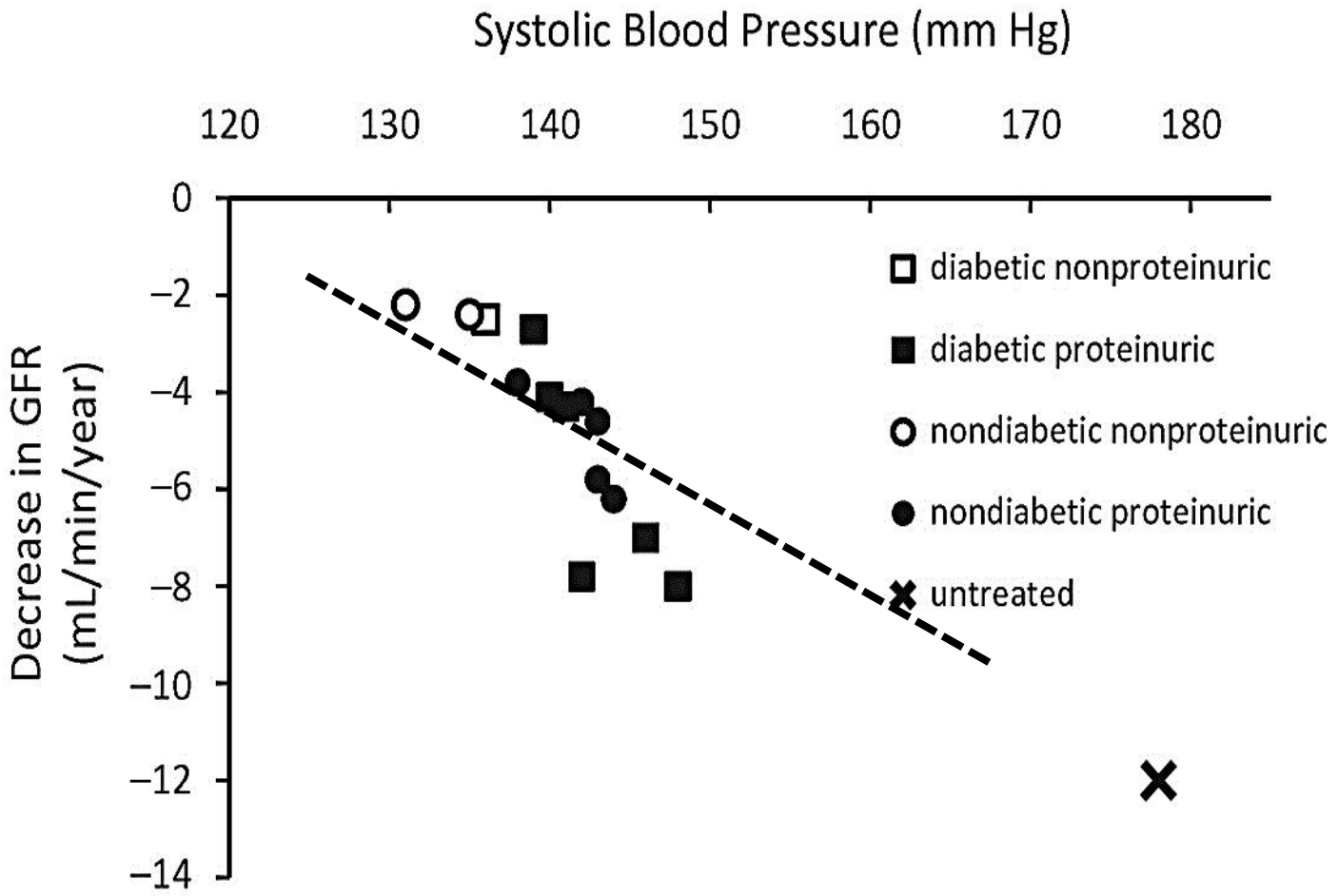
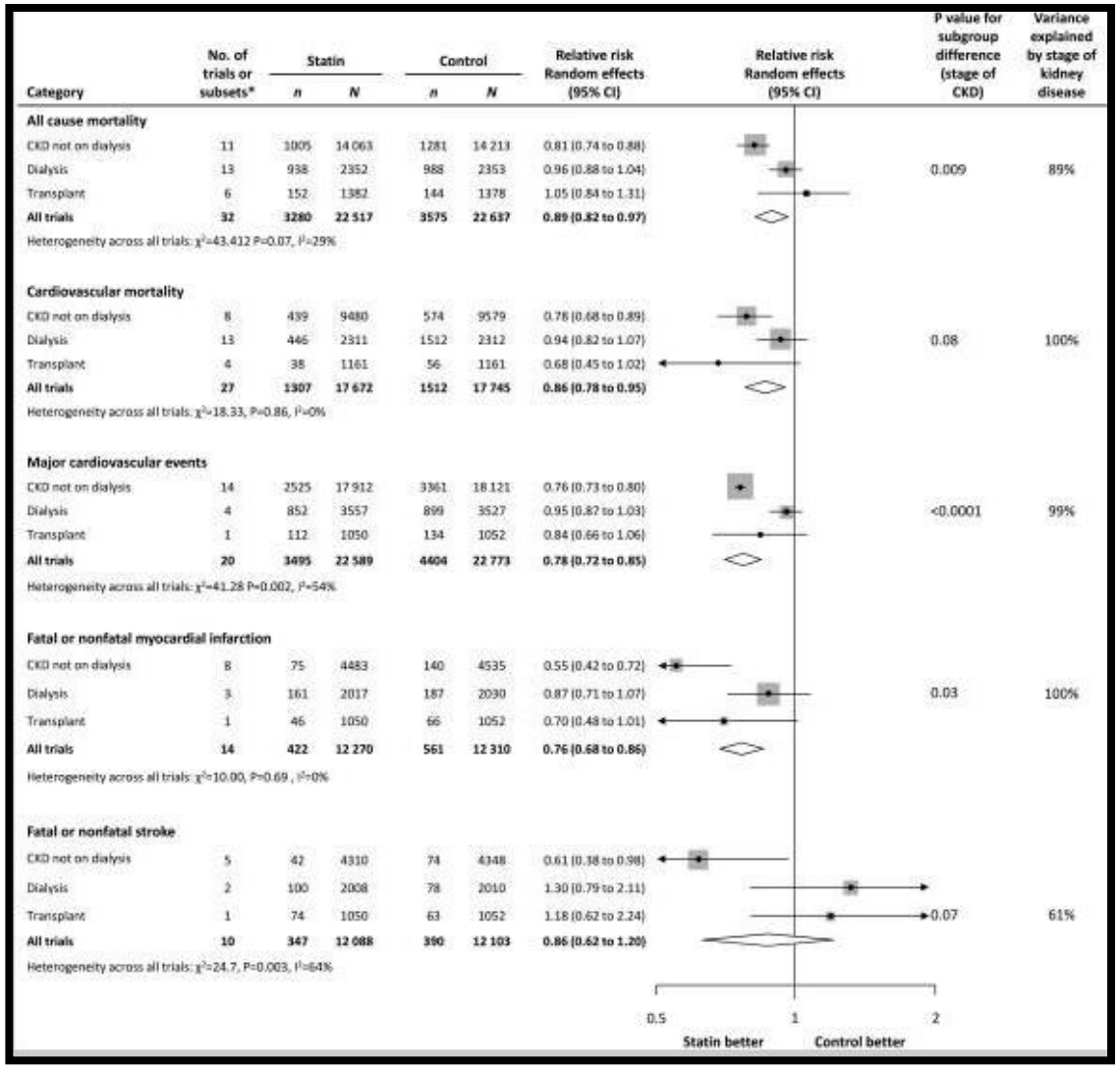
- ABCD. Diabetes Care (Suppl). 2000



Update from Kalaitzidis R and Bakris GL In: Handbook of Chronic Kidney Disease. Daugirdas J (Ed.) 2011.

Lipid Management



Category	No. of trials or subsets*	Statin n	Statin N	Control n	Control N	Relative risk Random effects (95% CI)	P value for subgroup difference (stage of CKD)	Variance explained by stage of kidney disease
All cause mortality								
CKD not on dialysis	11	1005	14 063	1281	14 213	0.81 (0.74 to 0.88)		
Dialysis	13	938	2352	988	2353	0.96 (0.88 to 1.04)	0.009	89%
Transplant	6	152	1382	144	1378	1.05 (0.84 to 1.31)		
All trials	**32**	**3280**	**22 517**	**3575**	**22 637**	**0.89 (0.82 to 0.97)**		
Heterogeneity across all trials: χ^2=43.412 P=0.07, I^2=29%								
Cardiovascular mortality								
CKD not on dialysis	8	439	9480	574	9579	0.78 (0.68 to 0.89)		
Dialysis	13	446	2311	1512	2312	0.94 (0.82 to 1.07)	0.08	100%
Transplant	4	38	1161	56	1161	0.68 (0.45 to 1.02)		
All trials	**27**	**1307**	**17 672**	**1512**	**17 745**	**0.86 (0.78 to 0.95)**		
Heterogeneity across all trials: χ^2=18.33, P=0.86, I^2=0%								
Major cardiovascular events								
CKD not on dialysis	14	2525	17 912	3361	18 121	0.76 (0.73 to 0.80)		
Dialysis	4	852	3557	899	3527	0.95 (0.87 to 1.03)	<0.0001	99%
Transplant	1	112	1050	134	1052	0.84 (0.66 to 1.06)		
All trials	**20**	**3495**	**22 589**	**4404**	**22 773**	**0.78 (0.72 to 0.85)**		
Heterogeneity across all trials: χ^2=41.28 P=0.002, I^2=54%								
Fatal or nonfatal myocardial infarction								
CKD not on dialysis	8	75	4483	140	4535	0.55 (0.42 to 0.72)		
Dialysis	3	161	2017	187	2030	0.87 (0.71 to 1.07)	0.03	100%
Transplant	1	46	1050	66	1052	0.70 (0.48 to 1.01)		
All trials	**14**	**422**	**12 270**	**561**	**12 310**	**0.76 (0.68 to 0.86)**		
Heterogeneity across all trials: χ^2=10.00, P=0.69 , I^2=0%								
Fatal or nonfatal stroke								
CKD not on dialysis	5	42	4310	74	4348	0.61 (0.38 to 0.98)		
Dialysis	2	100	2008	78	2010	1.30 (0.79 to 2.11)		
Transplant	1	74	1050	63	1052	1.18 (0.62 to 2.24)	0.07	61%
All trials	**10**	**347**	**12 088**	**390**	**12 103**	**0.86 (0.62 to 1.20)**		
Heterogeneity across all trials: χ^2=24.7, P=0.003, I^2=64%								

Relative risk Random effects (95% CI)

0.5 1 2

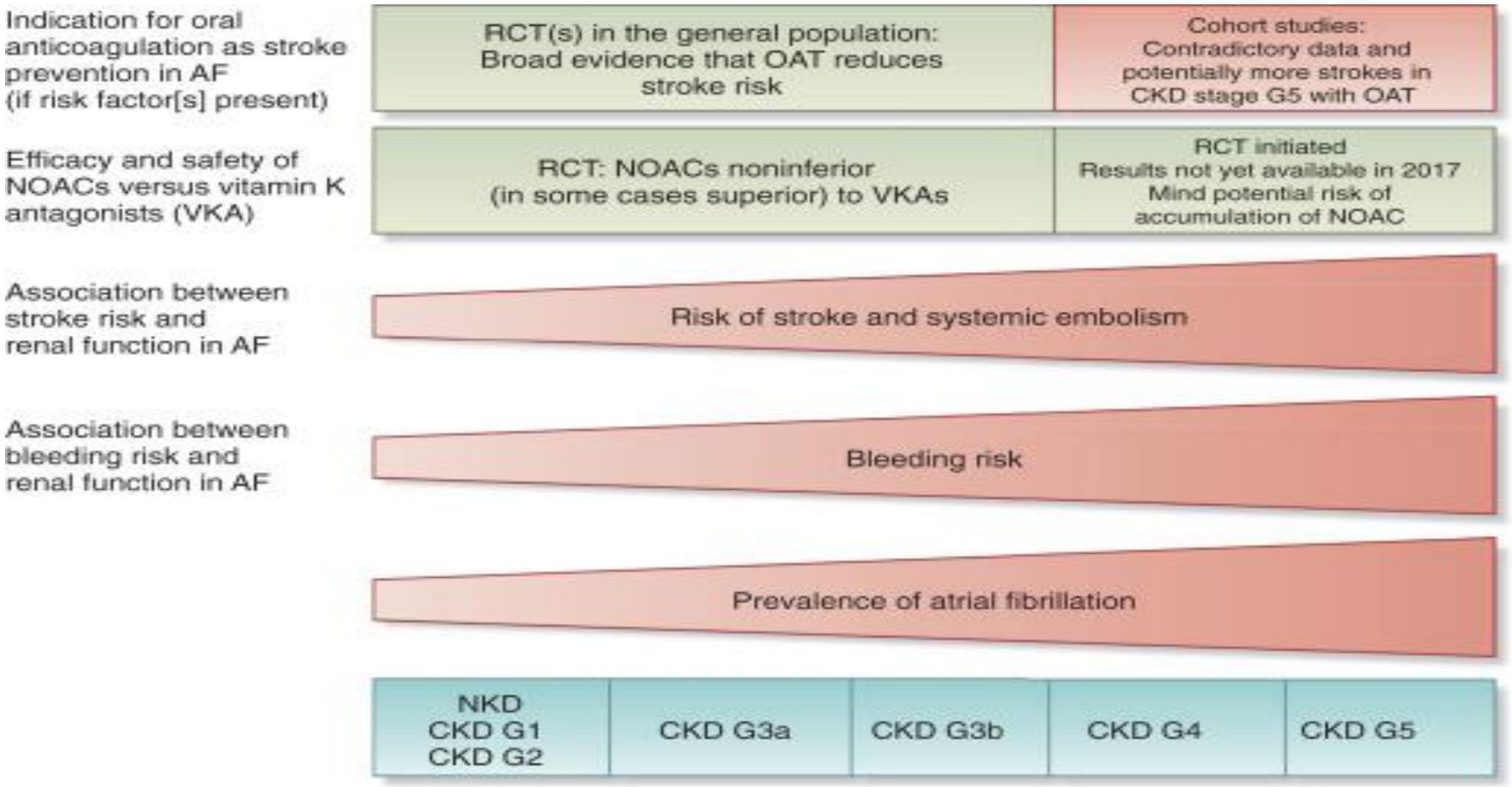
Statin better Control better

Statins:

- Lower mortality and cardiovascular events in persons with early stages of CKD,
- Have little or no effect in persons on dialysis,
- Have uncertain effects in kidney transplant recipients.

Ann Int Med 2012, 157(4): 263-275

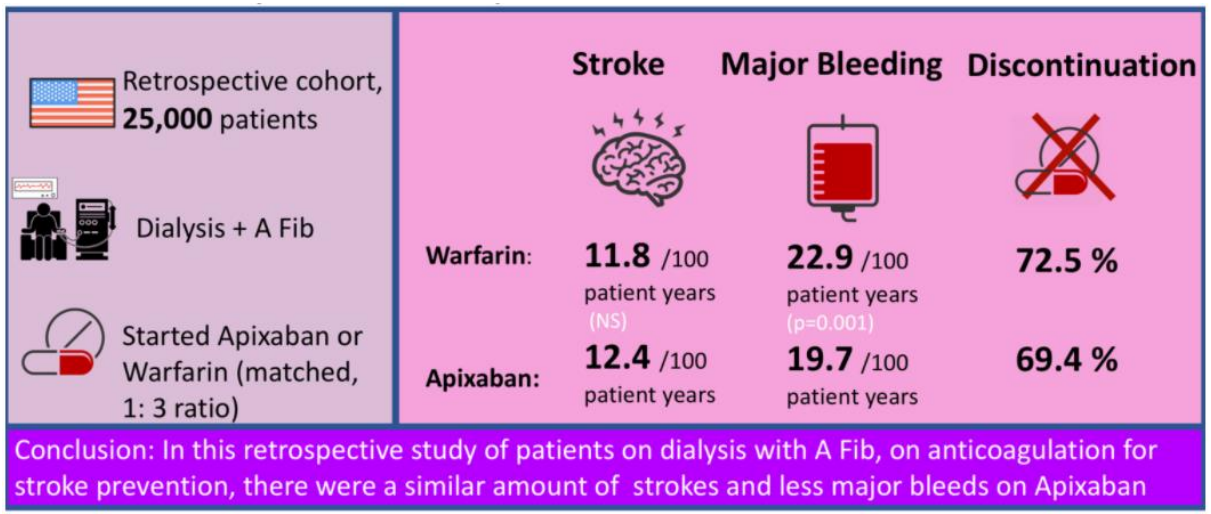
Current evidence on Oral Anticoagulant Therapy for patients with Atrial Fibrillation across the spectrum of CKD



Kidney International 2017

Apixiban use versus Warfarin in Chronic Kidney Disease

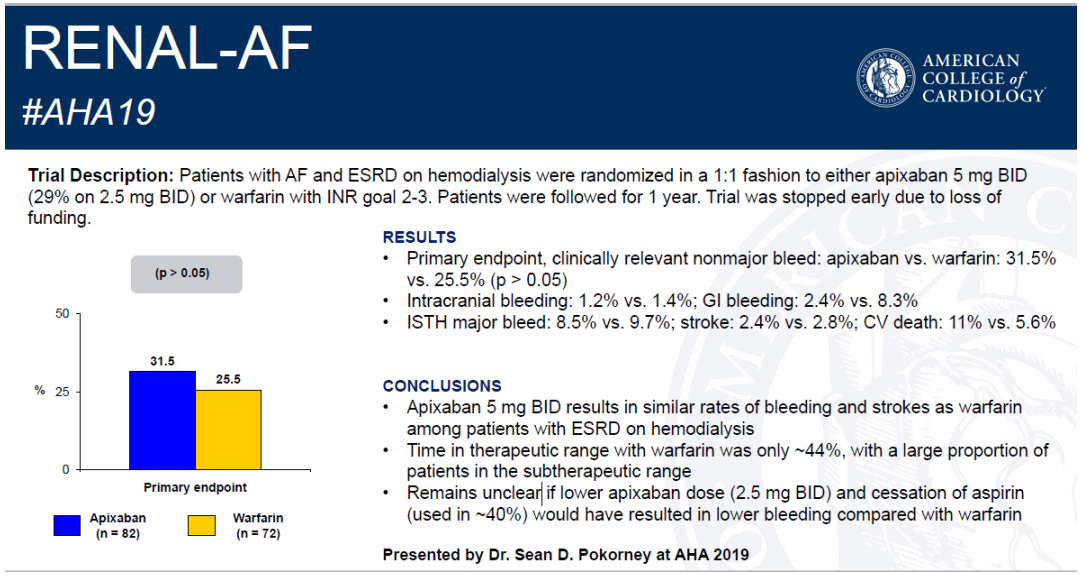
Outcomes Associated with Apixaban Use in End-Stage Kidney Disease Patients with Atrial Fibrillation in the United States.



@Sarah_Gleeson_

RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation - RENAL-AF

Nov 17, 2019



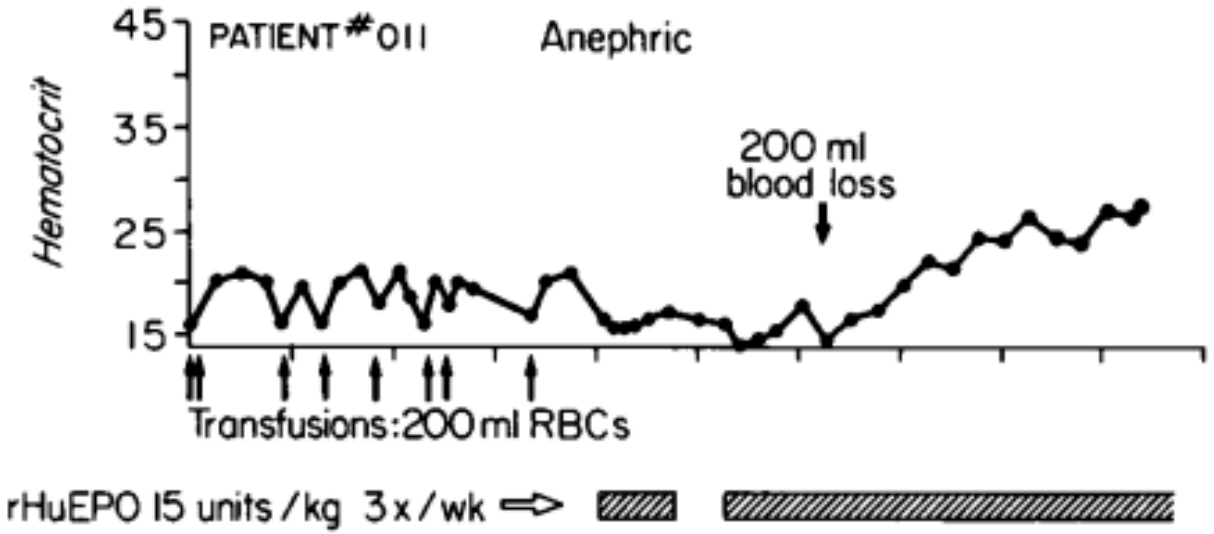
Circulation. 2018 Jun 28

Anemia Management in CKD

CORRECTION OF THE ANEMIA OF END-STAGE RENAL DISEASE WITH RECOMBINANT HUMAN ERYTHROPOIETIN

Results of a Combined Phase I and II Clinical Trial*

JOSEPH W. ESCHBACH, M.D., JOAN C. EGRIE, PH.D., MICHAEL R. DOWNING, PH.D., JEFFREY K. BROWNE, PH.D., AND JOHN W. ADAMSON, M.D.



NEJM 1987, Vol 316 pg. 73-78

Question

The target Hemoglobin level for patients on dialysis receiving Erythropoetin Stimulating Agents (ESA's) should be:

A. 9-10mg/dl
B. 10-11mg/dl
C. 11-12mg/dl
D. >12mg/dl

Studies of Anemia Management and the use of Erythropoetin in CKD

Normal Hct Study Besarab A et al. N Engl J Med 1998;339:584-590	183 deaths and 19 non fatal MI's in nl-Hct group and 150 deaths and 14 non fatal MI's in low-Hct group (RR 1.3; 95% CI, 0.9 to 1.9). Study halted.	Pts in nl-Hct group had a decline in the adequacy of dialysis and received more IV iron dextran.
CHOIR Study Ajay Singh et al. N Engl J Med 2006;355:2085-98.	125 events (Death, MI, CHF, Stroke) in the high-Hb group vs 97 events in the low-Hb group (HR, 1.34; 95% CI, 1.03 to 1.74; P = 0.03).	Improvements in the quality of life were similar in the two groups.
CREATE Study Drueke et al N Engl J Med 2006;355:2071-84	No effect on first cardiovascular event	General health and physical function improved significantly (P = 0.003 and P<0.001) in high Hb group.
TREAT Study Marc Pfeffer et al N Engl J Med 2009;361:2019-32	Death or a cardiovascular event in 632 pts in Rx group vs 602 pts in placebo group (P = 0.41)	Fatal or nonfatal stroke in 101 pts in Rx grp vs 53 in placebo group (P<0.001).

Hypoxia Inducible Factor (HIF): Role in Anemia Management

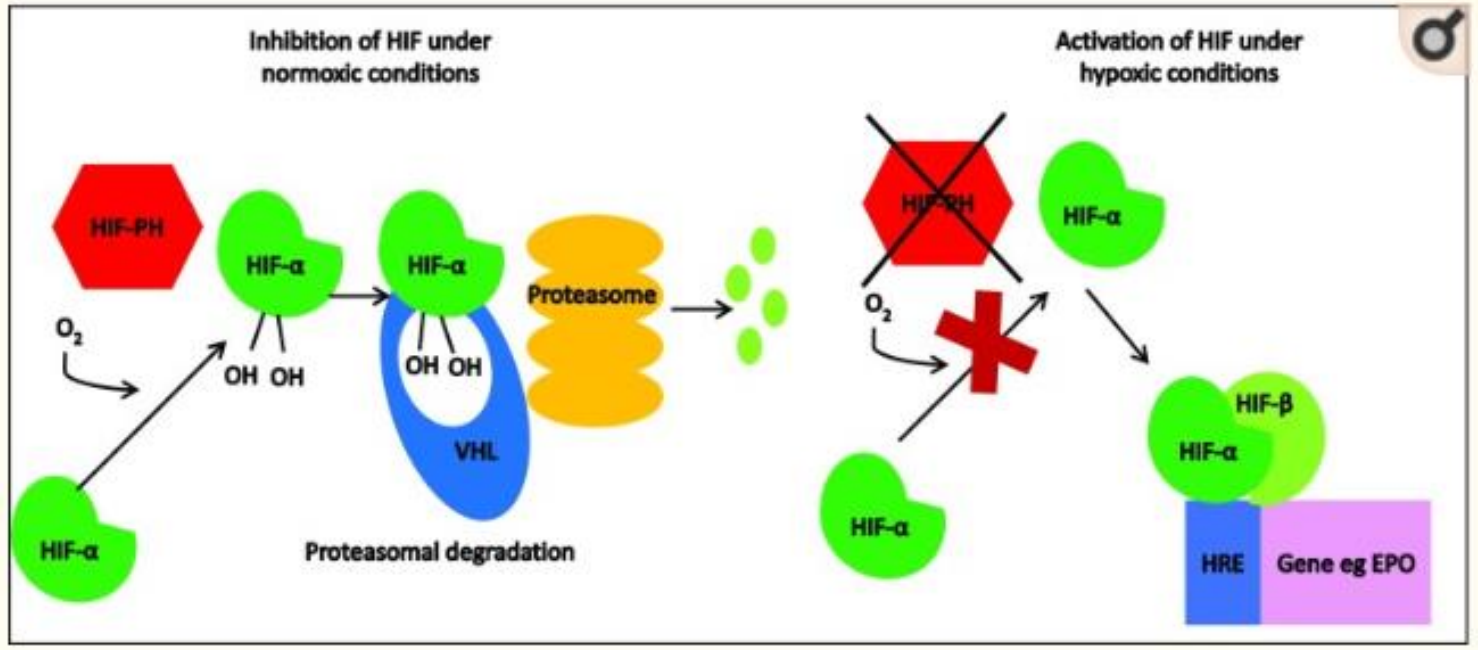


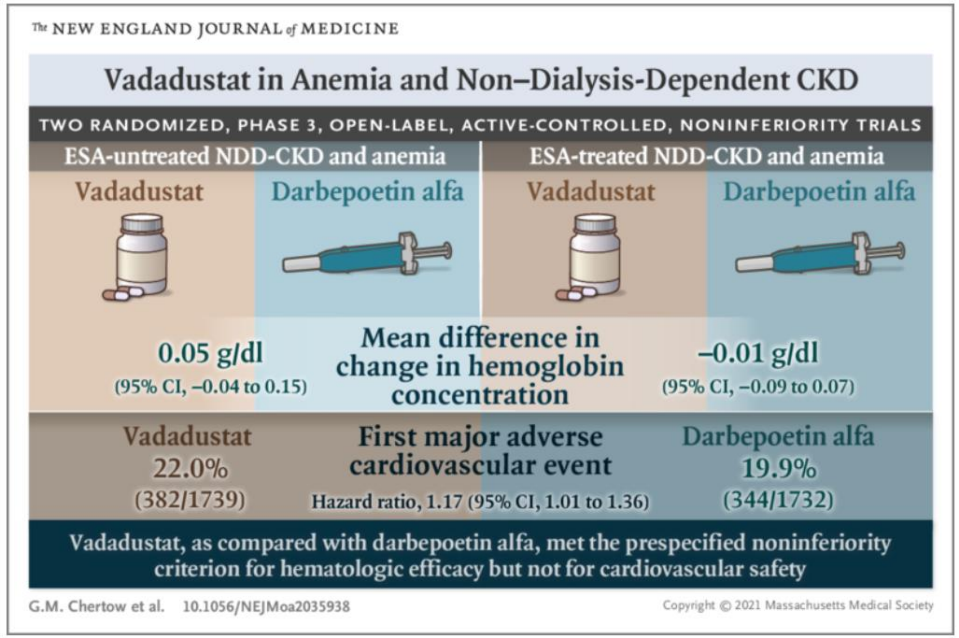
Fig. 1

Regulation of hypoxia inducible factor (HIF) activity. *HIF-PH* hypoxia inducible factor prolyl-hydroxylase, *HIF-α* hypoxia inducible factor alpha, *HIF-β* hypoxia inducible factor beta, *HRE* hypoxia response element, O_2 oxygen, *OH* hydroxyl group, *VHL* von Hippel-Lindau, *EPO* erythropoietin gene

Ped Nephrol: 2019; 34(3): 365–378.

Vadadustat in Patients with Anemia and Non–Dialysis-Dependent CKD

Glenn M. Chertow, M.D., M.P.H., et al.



- Two randomized, phase 3, open-label noninferiority trials
- Compared vadadustat with darbepoetin alfa
- Pt population:
  - non DM CKD.
- Findings:
  - Vadadustat compared with darbepoetin met the prespecified noninferiority criterion for hematologic efficacy
  - Did not meet prespecified noninferiority cardiovascular safety targets.

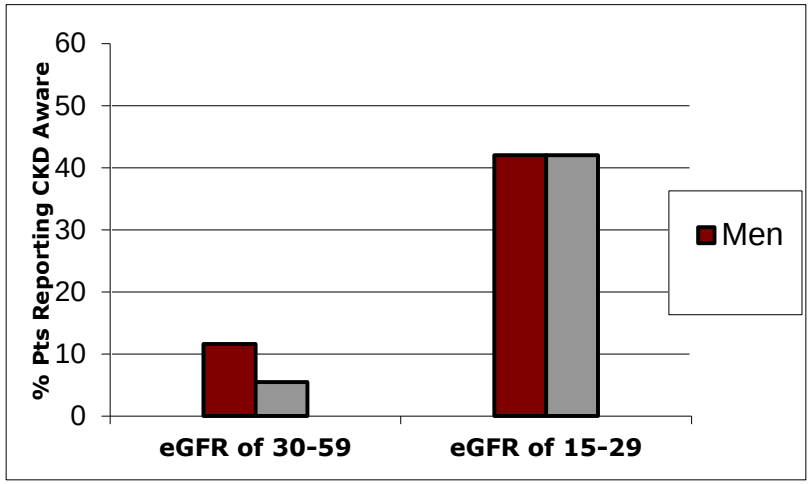
N Engl J Med 2021; 384:1589-1600

Strategies for Caring with Patients with CKD 4

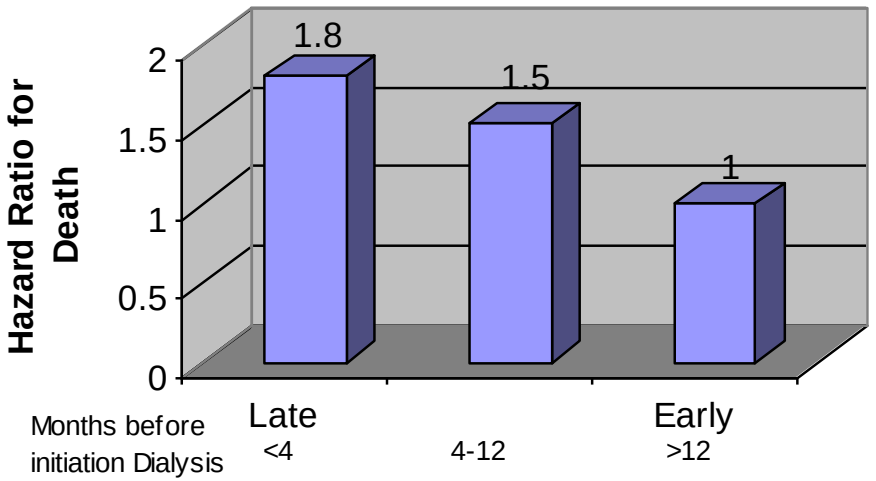
- Delay Progression
  - Control BP
  - ACE Inhibition
  - Manage metabolic abnormalities
  - Minimize Renal injury
- Manage Comorbids
  - Cardiovascular risk
  - Anemia management
  - Metabolic Bone Disease Management
- Prepare for ESRD
  - Isolate high risk populations
  - Patient education
  - Refer to Nephrology
  - Prepare for angioaccess
  - Review Medical Management options

Preparing for ESRD:

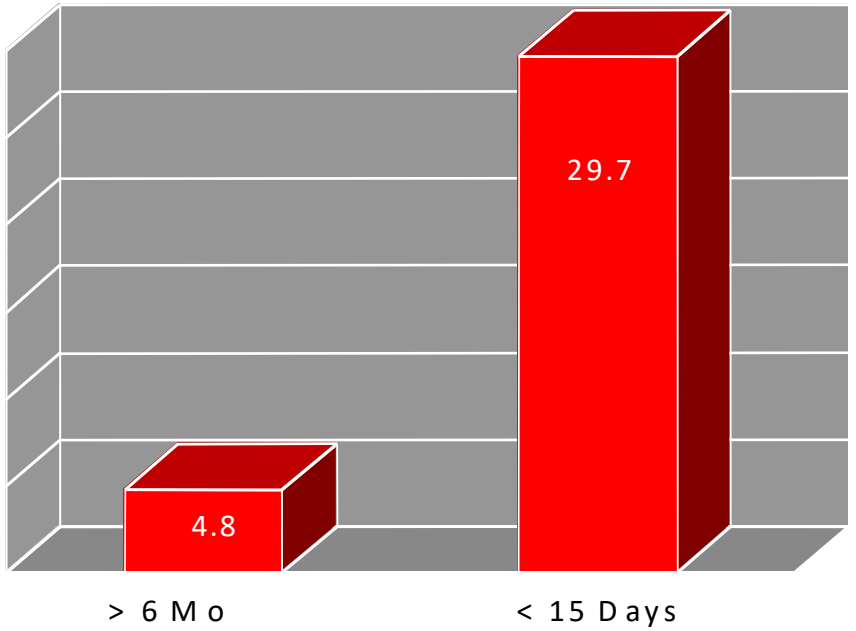
The Timing of Specialist Evaluation in Chronic Kidney Disease; effect on Morbidity and Mortality



Rate of death measured from initiation of dialysis to average of 2.2 years follow up



Effect of timing of referral on length of stay at the initiation of dialysis



Jungers et al, J Am Nephrol 1997; 8:140A

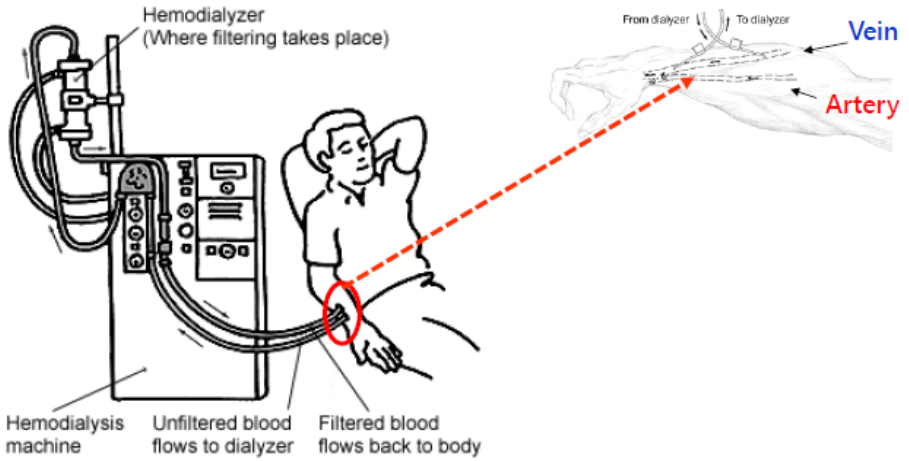
Kinchen et al *Ann Intern Med.* 2002;137:479-486.

Question

The percentage of patients initiating hemodialysis with a dialysis catheter as their primary access (versus a fistula or a graft) is:

A. 10%
B. 30%
C. 60%
D. 80%

Hemodialysis:
Benefits of a native vein AV Fistula

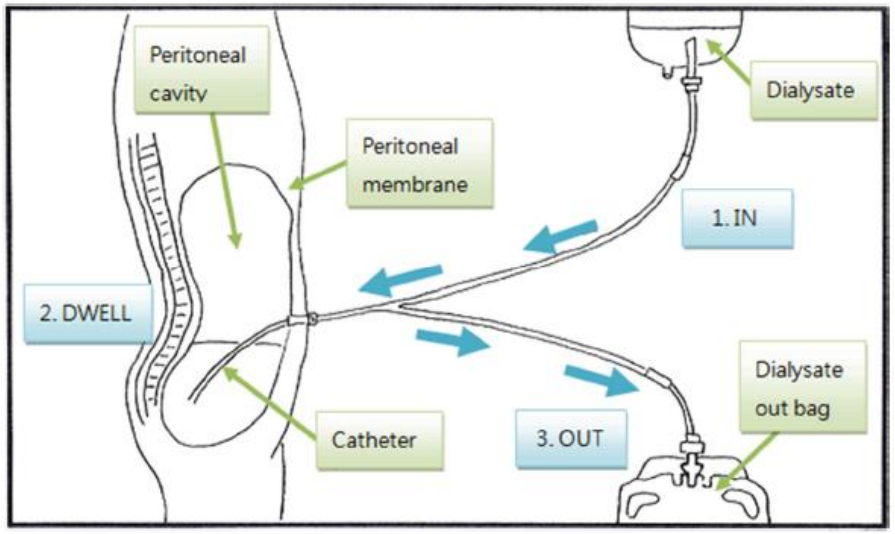


	Relative Risk of death	P value
Diabetics:		
AVF	1.00	
PTFE	1.39	0.0004
Catheter	1.49	0.0004
Non-Diabetics:		
AVF	1.00	
PTFE	1.09	0.26
Catheter	1.72	0.0001

- Preserve non dominant arm veins:
  - Avoid Blood draws
  - Avoid IV access
  - Avoid PICC lines
- Patient education and referral for AVF at CKD 4-5 transition
- Time from fistula creation to useability is variable (3-6 months)

Peritoneal Dialysis

- 8-10% of prevalent ESRD patients in the US are on PD; significantly less than in other developed countries
  - subtle differences in practice patterns
  - unintended financial considerations
- Medical outcome date would seem to favor more utilization of PD
  - Improved mortality
- Most home dialysis units are small
  - some have minimal clinical experience
  - consolidation of PD programs may be needed.



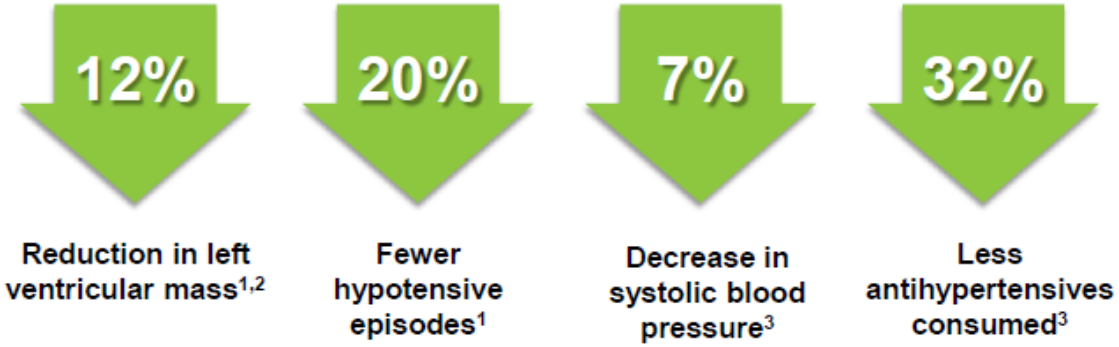
Multidisciplinary pre-dialysis programs increase the proportion of patients initiating dialysis with PD.

Burkhart J, CJASN 2009 Dec;4 Suppl 1:S125-31

Ribitisch et al Peritonal Dial Int 2013 Jul-Aug;33(4):367-71

Home Hemodialysis:
Clinical Benefits of More Frequent Hemodialysis

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



[1]FHN 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. [2]Rocco 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. [3]Kotanko P, et al. Effects of frequent hemodialysis on blood pressure: Results from the randomized frequent hemodialysis network trials. Hemodial Int. 2015 Jul;19(3):386-401. doi: 10.1111/hdi.12255. Epub 2015 Jan 5.

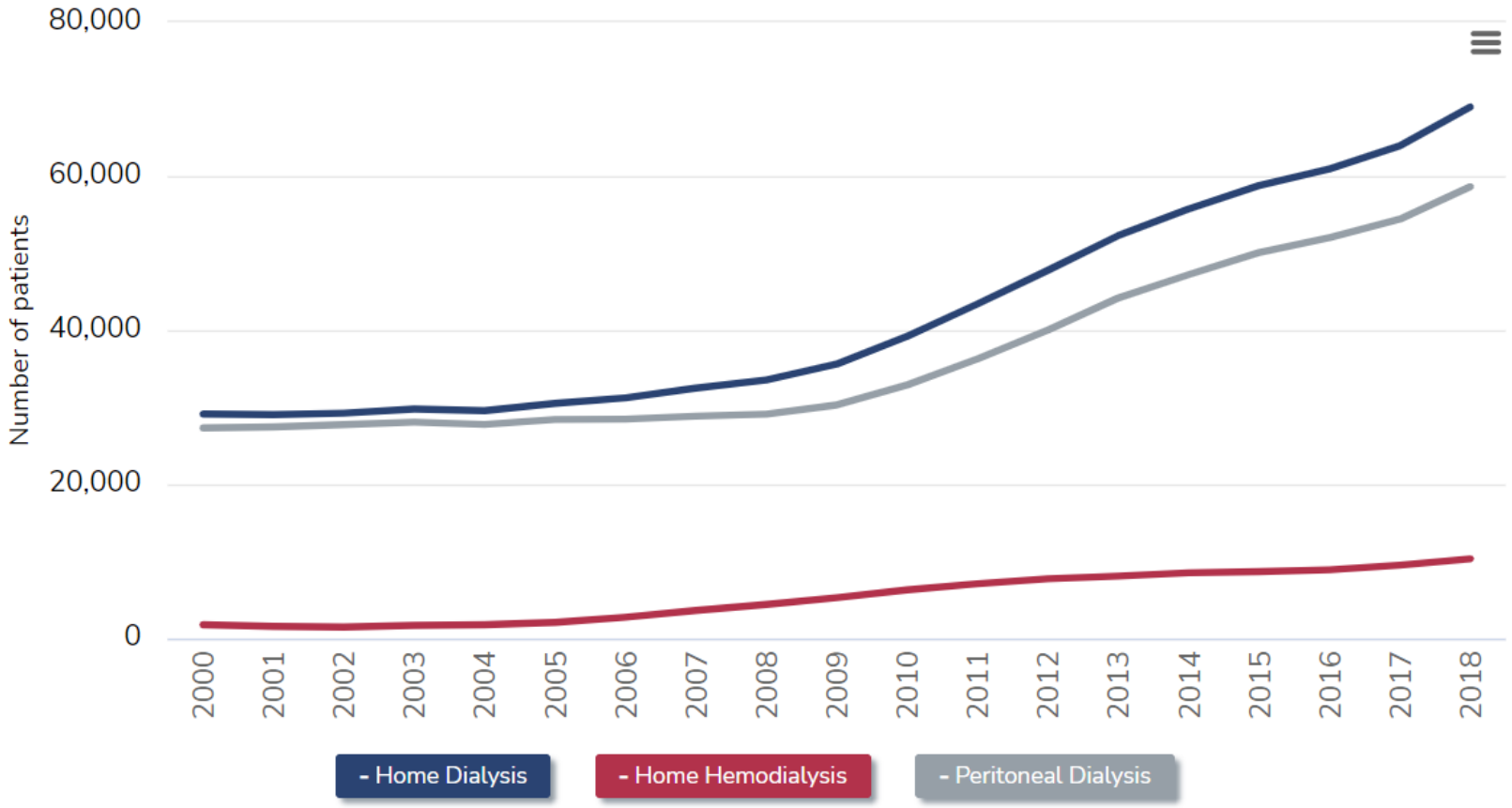
Home HD Equipment

- 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 incenter 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

Wikipedia

Growth in Home Modalities in the US.

Figure 1.13 Number of prevalent ESRD patients performing home dialysis, 2000-2018



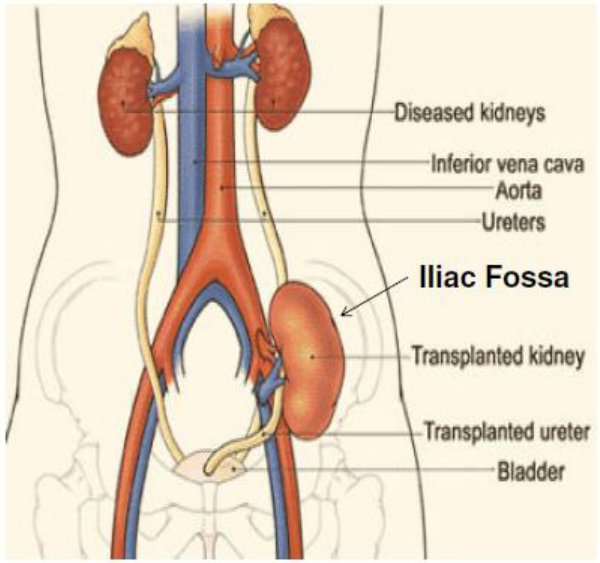
Data source: USRDS ESRD database. ESRD prevalence was identified on December 31 of each year.

Question

The best time to refer a CKD patient for initial transplant assessment based on level of GFR is:

A. GFR <60 ml/min
B. GFR 30-45 ml/min
C. GFR <20ml/min
D. GFR <15ml/min

Kidney Transplantation



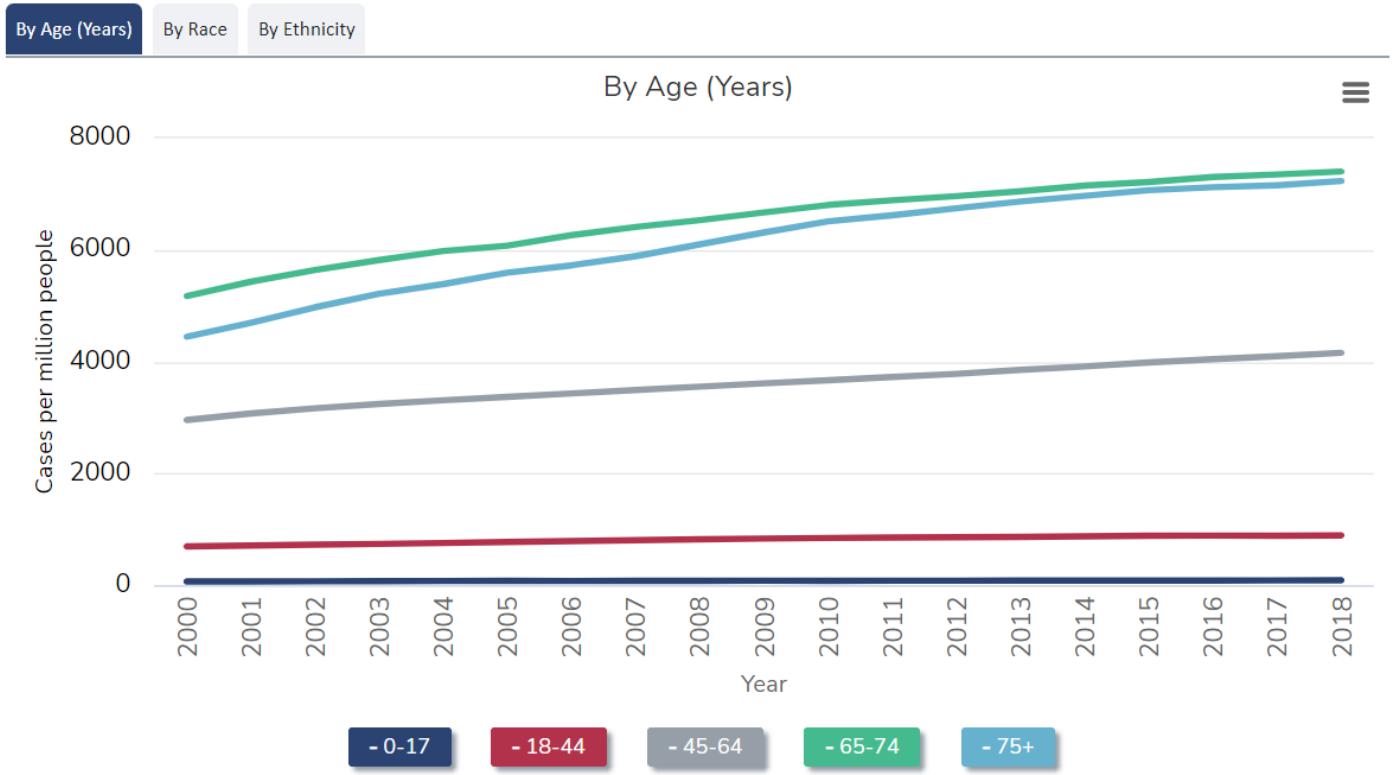
Key Concepts

- **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.**

Palliative Care Nephrology: Incidence of ESRD by Age

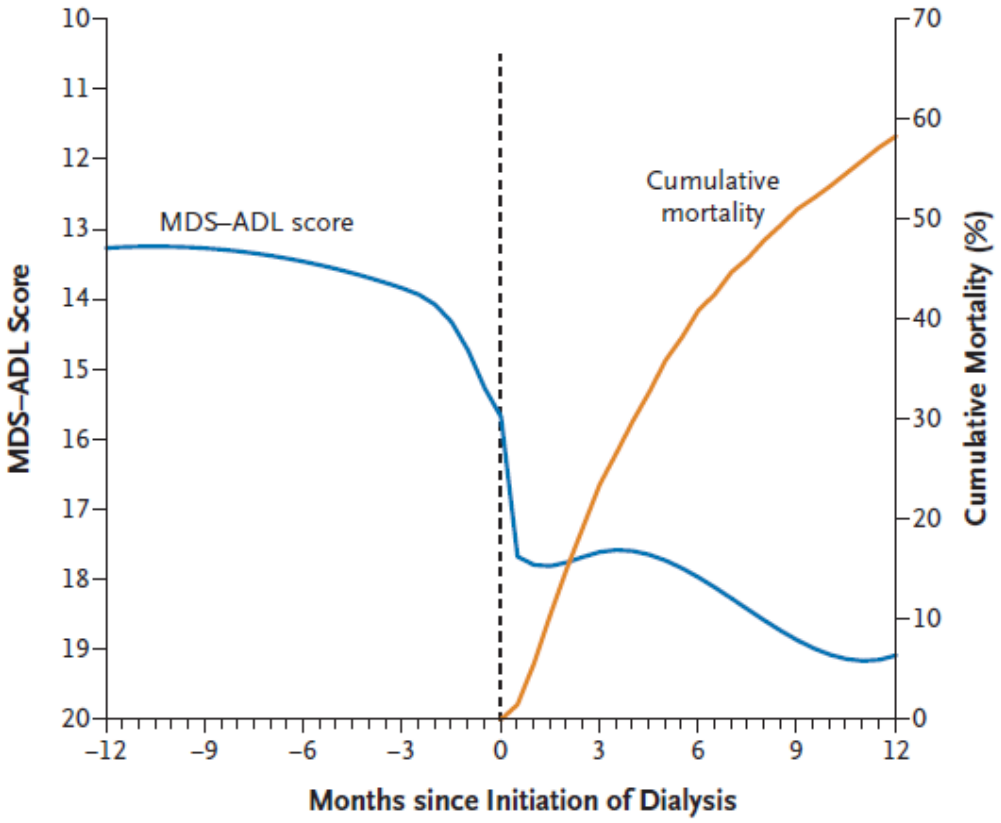
- the ageing of the dialysis population

Figure 1.8 Adjusted ESRD prevalence, by age, race, and ethnicity, 2000-2018



Data source: USRDS ESRD database. ESRD prevalence was identified on December 31 of each year.

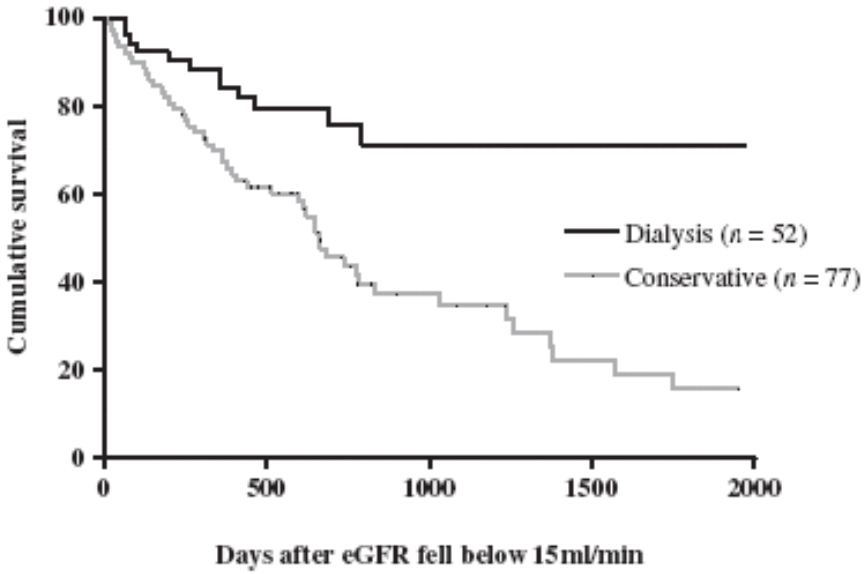
Functional Status of Elderly Adults before and after Initiation of Dialysis



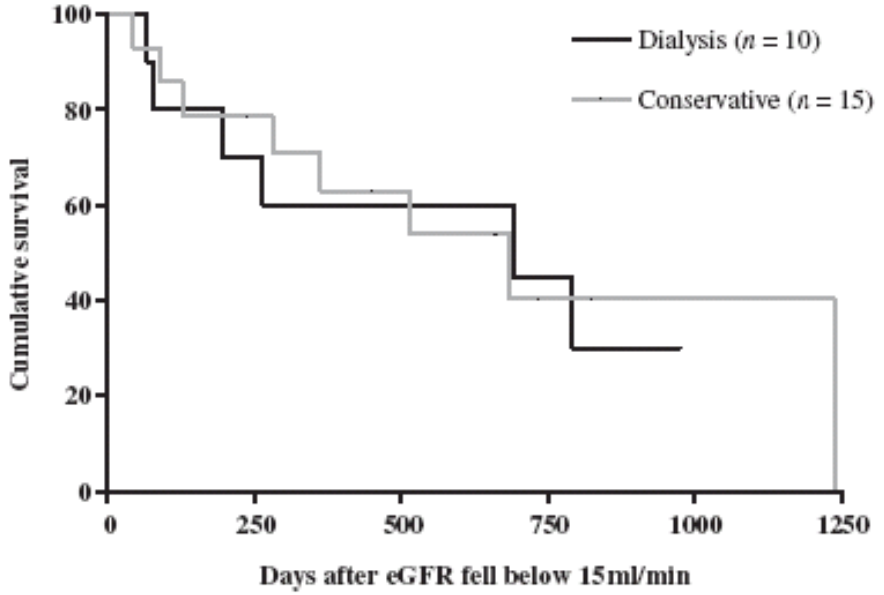
- 3702 nursing home residents in the United States
- Initiated dialysis dialysis between June 1998 and October 2000.
- At least one measurement of functional status was available before dialysis.
- Functional status was measured by assessing the degree of dependence in seven ADL's (on the Minimum Data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

Tamura et al N Engl J Med 2009;361:1539-47.

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

Murtagh et al Nephrol Dial Transplant (2007)

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.

Kidney International Supplements (2013) 3, 5–14

Conclusions

- Kidney Disease is common and management is complicated
- The majority of patients with CKD have non progressive disease
- Cardiovascular disease is a major co-morbidity
- For patients with progressive CKD care strategies should be initiated 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