

# **Kidney Disease**

## **-Presentation to Primary Care Internal Medicine 2015**

David Steele MD

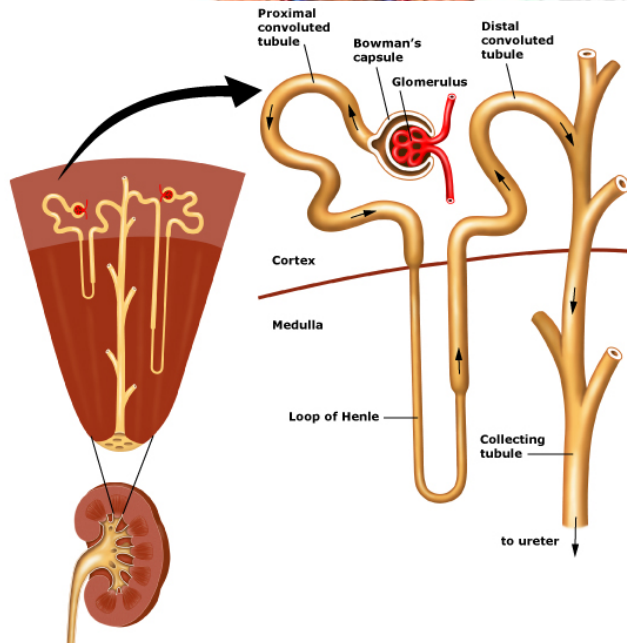
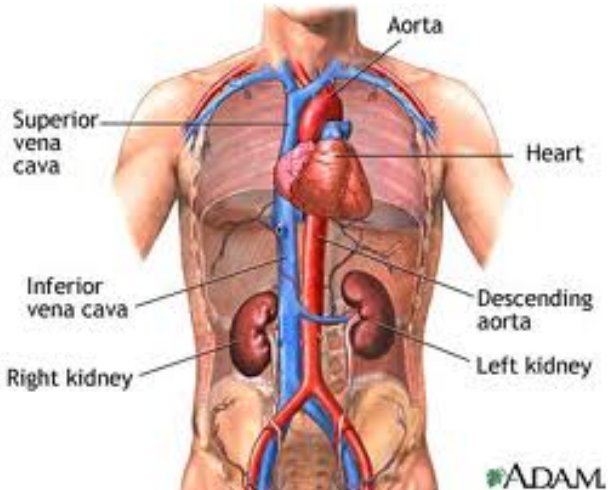
Renal Unit

Massachusetts General Hospital

Boston MA

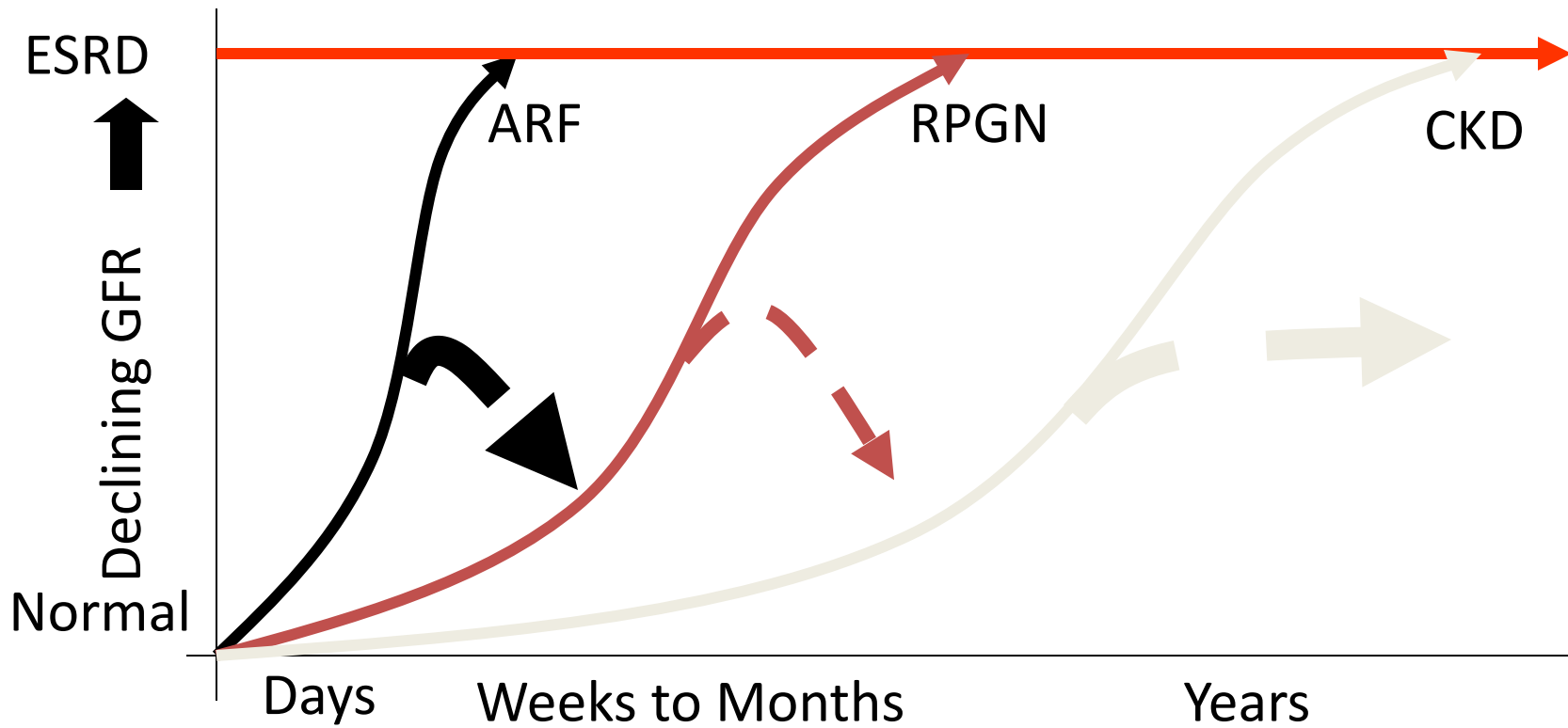
I have no conflicts of interest to declare

# Nephrology Factoids

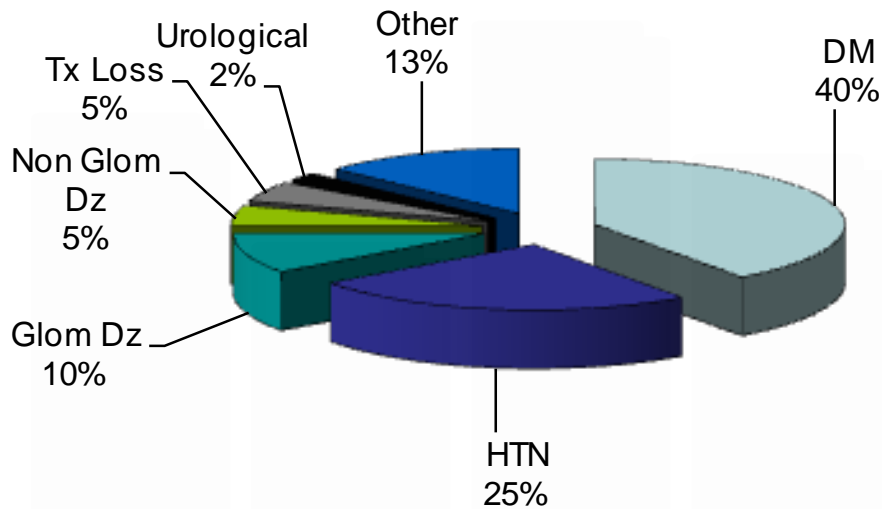


- Kidneys get ~ 20% of cardiac output
- Generate ultrafiltrate of 180L a day
- Produce 1-1.5L urine output
- Excrete ~ 600-800 mosm
- Regulates
  - Volume (Na Metabolism)
  - Tonicity (Water Metabolism)
  - Potassium metabolism
  - Acid/Base balance
  - Excretion of Nitrogenous wastes
  - Anemia (Erythropoetin)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

# Natural History of Renal Failure



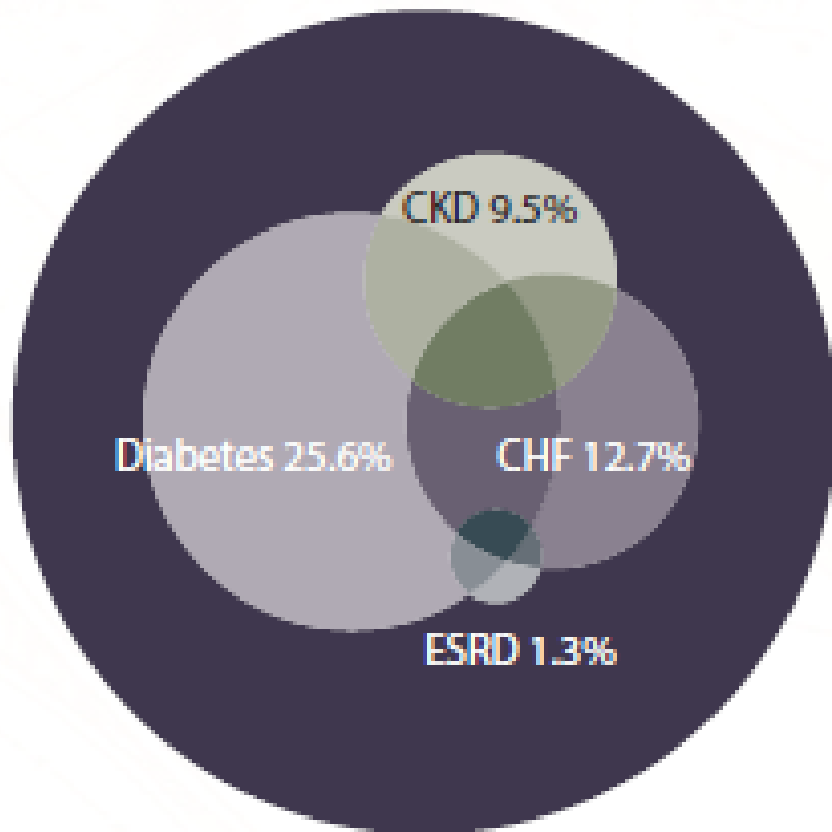
# Chronic Kidney Disease: Defining (CKD)



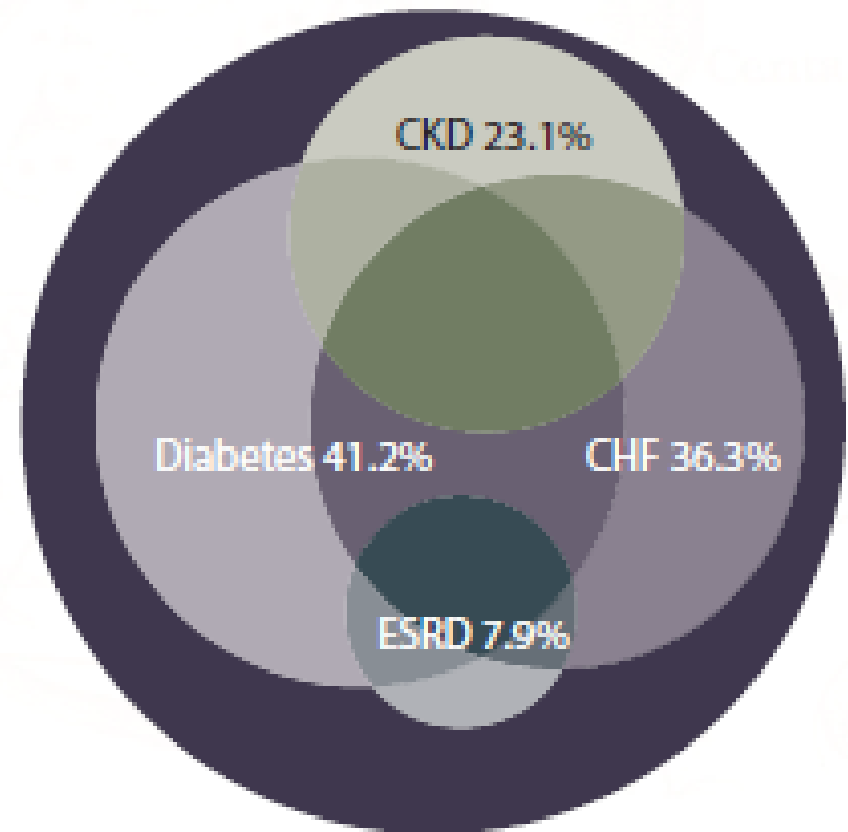
- Kidney damage of > 3 months
- $GFR < 60 \text{ml/min/1.73m}^2$
- CKD results from many pathophysiologically distinct diseases which share a common natural history
- CKD should be staged using eGFR (eg MDRD)

# Distribution of Costs General Medicare Population CKD and ESRD

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



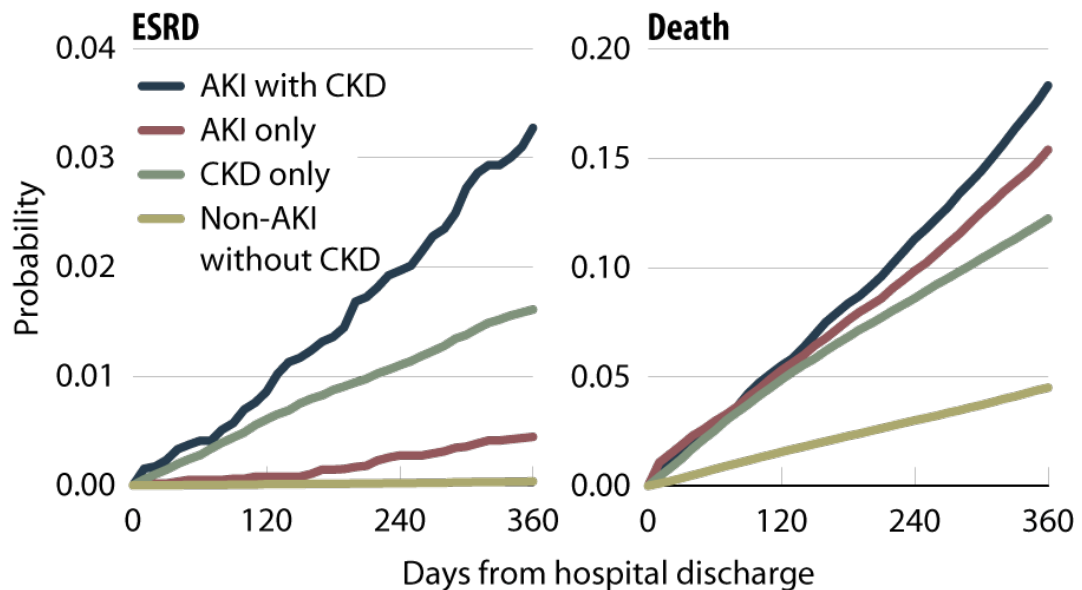
General Medicare: costs, 2008  
(\$273.8 billion)



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

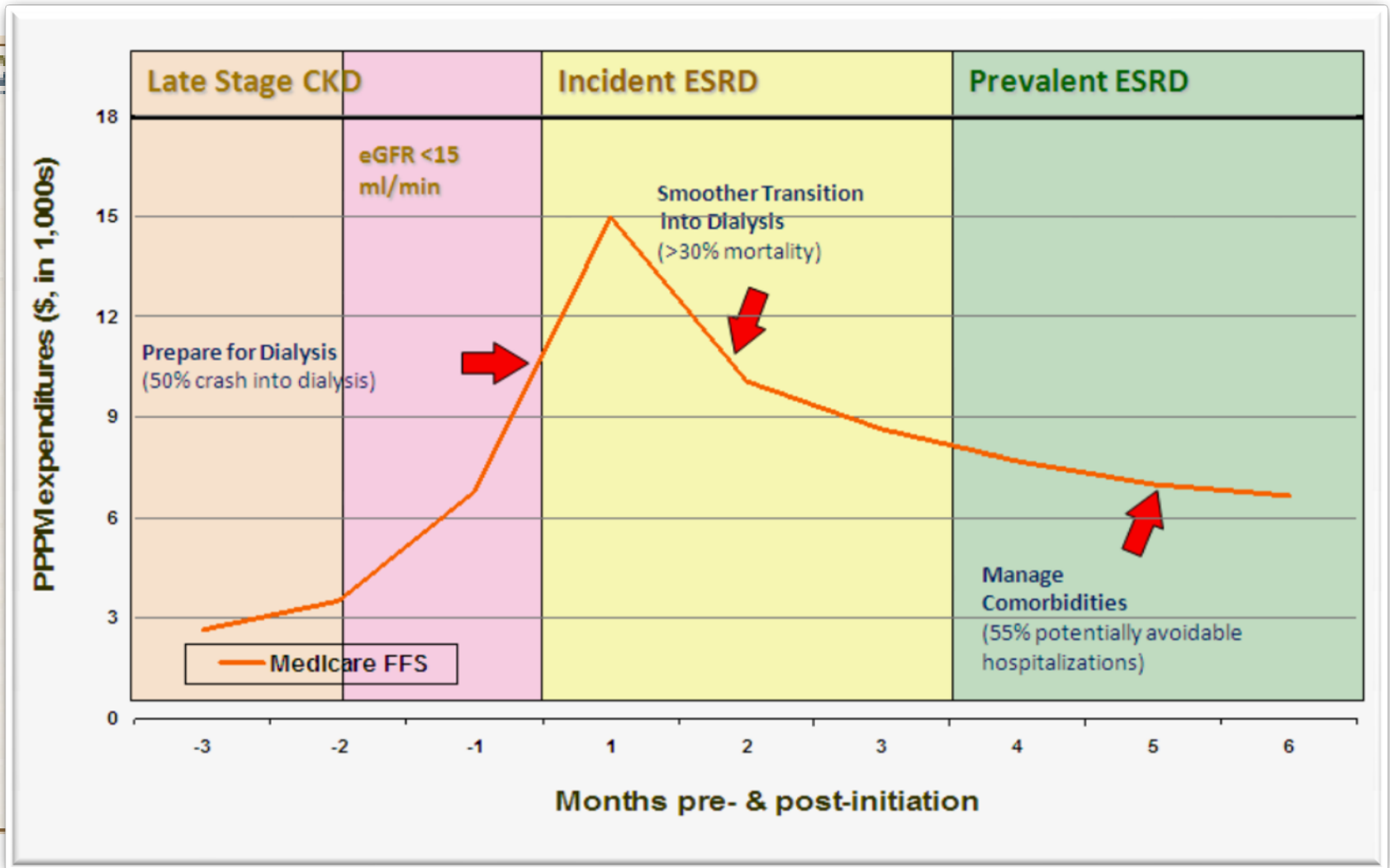
# CKD predisposes hospitalized patients to Acute Renal Failure

- CKD increases the risk of AKI seven fold in hospitalized patients.
- In AKI patients with CKD, the hazards for:
  - ESRD 85.0
  - Death 3.1(in AKI patients with no CKD, hazards are 11.7 and 2.5, respectively)



**These are the patients who “crash” onto dialysis**

# Costs Associated with Transition to Dialysis



# Markers of Renal Disease

## eGFR

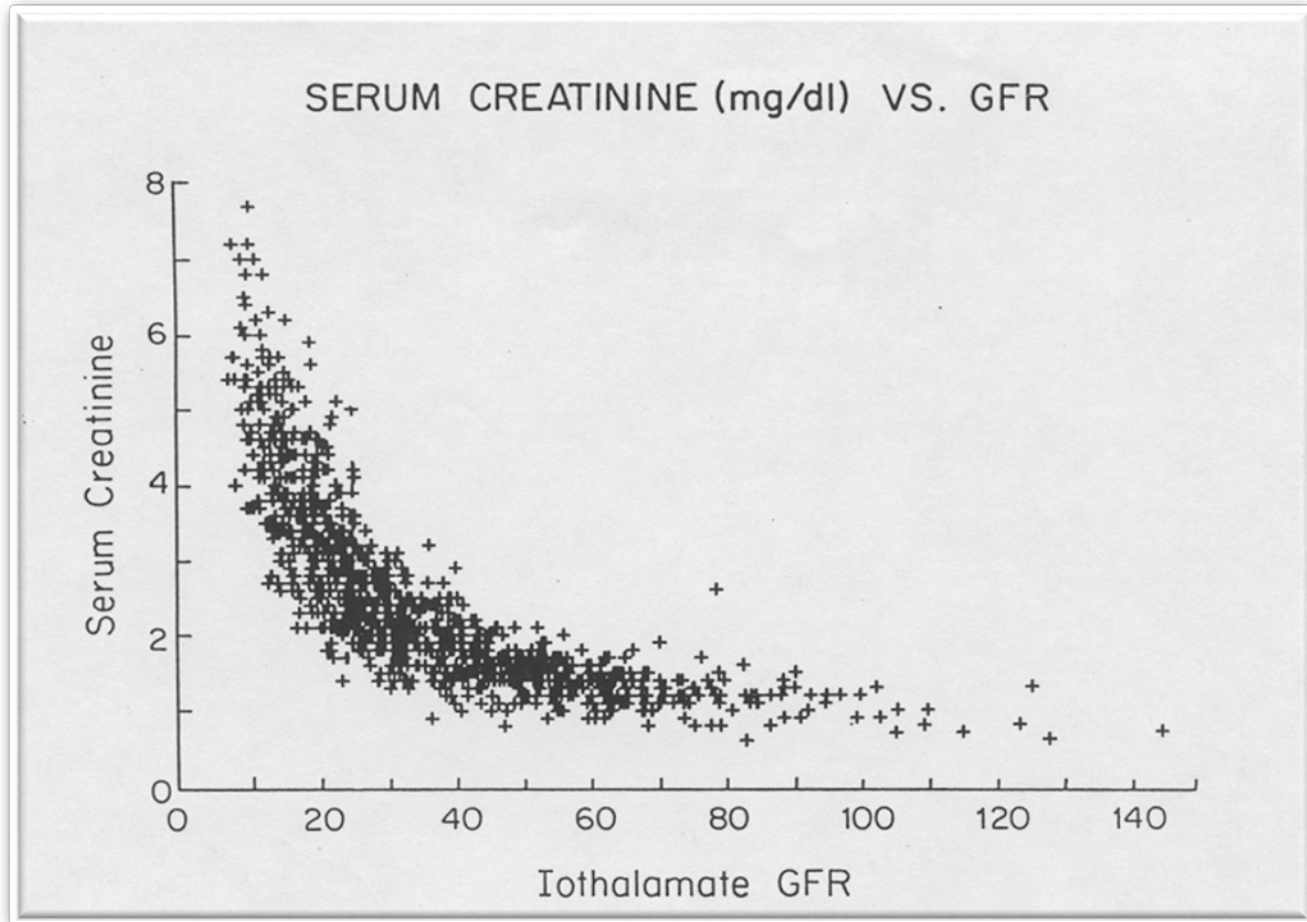
- MDRD Equation
- CKD Epi Equation
- If eGFR <60ml/min repeat within 14 days
- Review creatinine trend and repeat eGFRs over time to evaluate progression
- Automated reporting has lead to increased referrals to Nephrology

## Proteinuria

- 24-hour urine not necessary
- “Spot” urine Protein (or Albumin) to Creatinine ratio recommended
- Microalbuminuria
  - 30-300mg per 24 hrs
  - Not detectable by dipstix
  - Marker of incipient renal disease
- Proteinuria
  - 300mg to 3.5grams per 24 hrs
  - Marker of overt renal disease



# Markers of Renal Disease



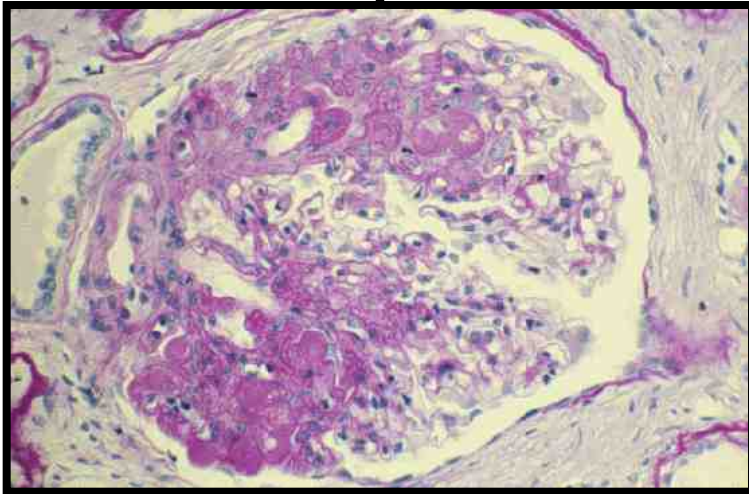
# Strategies for Caring with Patients with CKD 4

- 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

# Angiotensin II effects in CKD

Primary Injury  
with loss of Nephron mass

Hyperfiltration of  
remaining healthy Nephrons

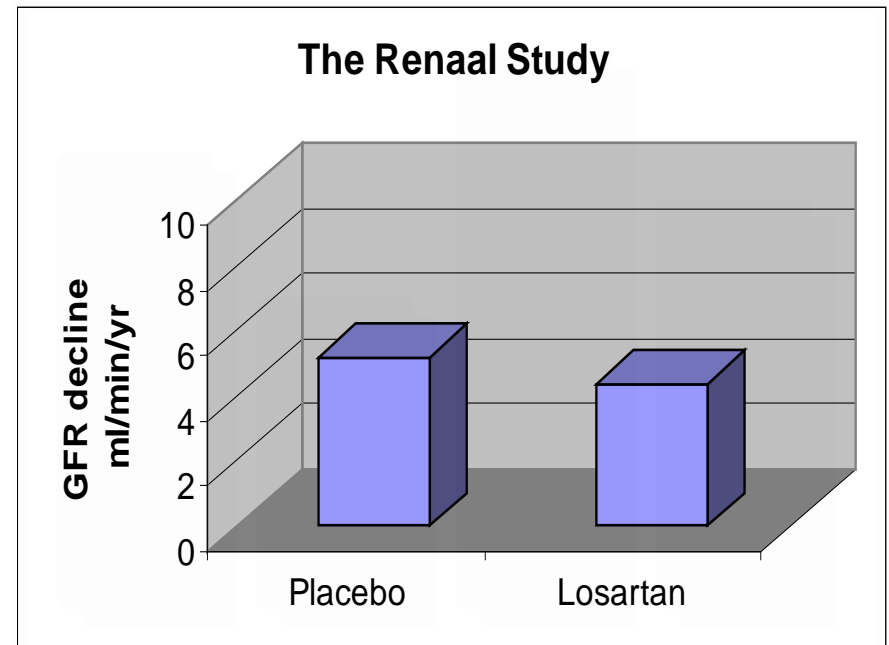
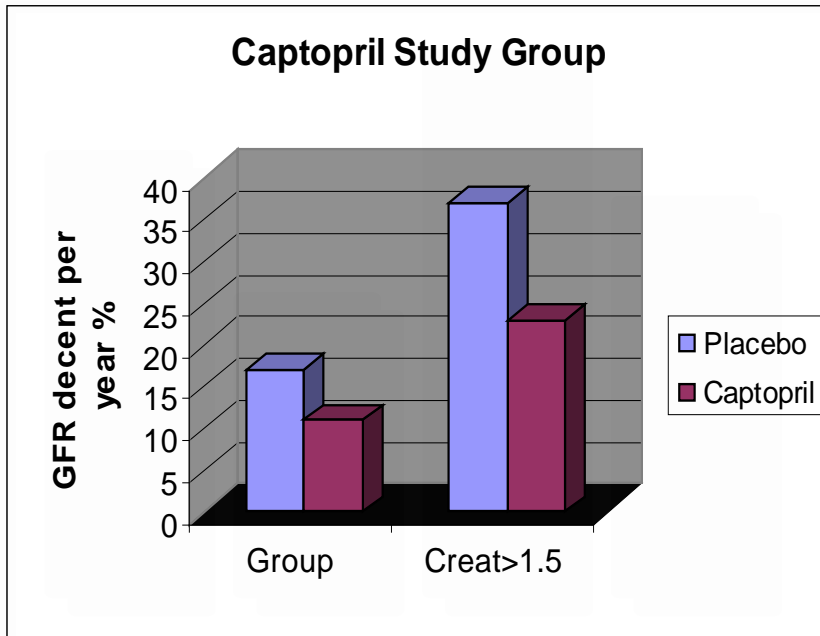


Secondary Focal Segmental  
Glomerulosclerosis

- 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

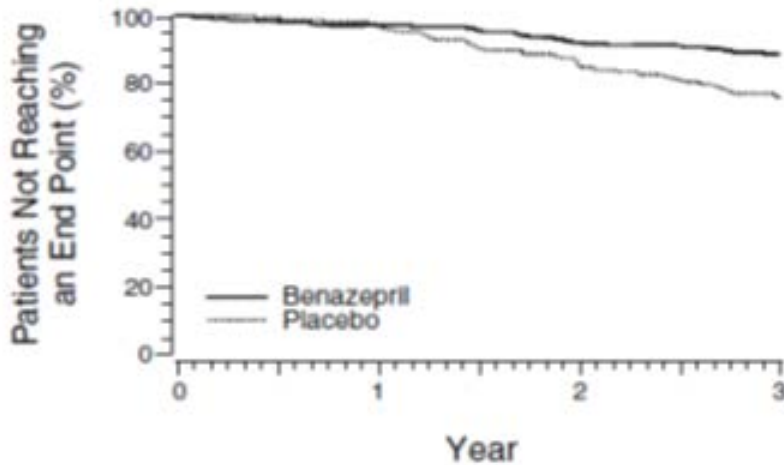
- Captopril Study (Lewis) - 48%
- Renaal Study (Brenner) - 25%

# ACEI and ARB Use in CKD

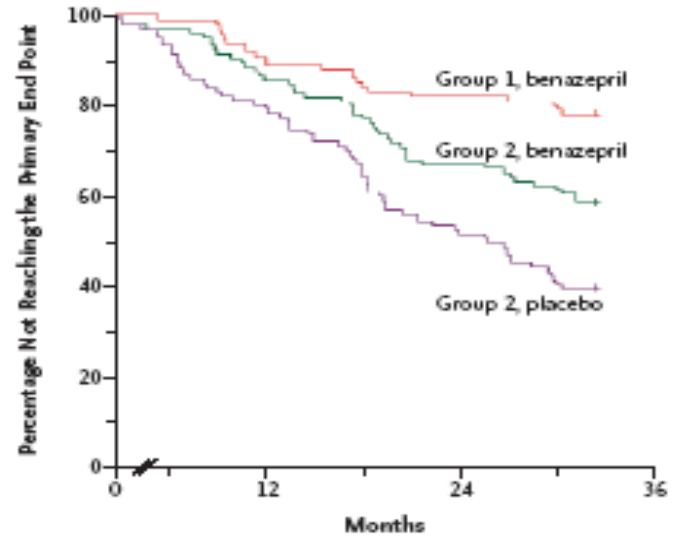
N Engl J Med 2014;371:2267-76. N Engl J Med 1996;334:939-45.

Hou et al N Engl J Med 2006;354:131-40. JFE Mann et al. Lancet 2008; 372: 547-53

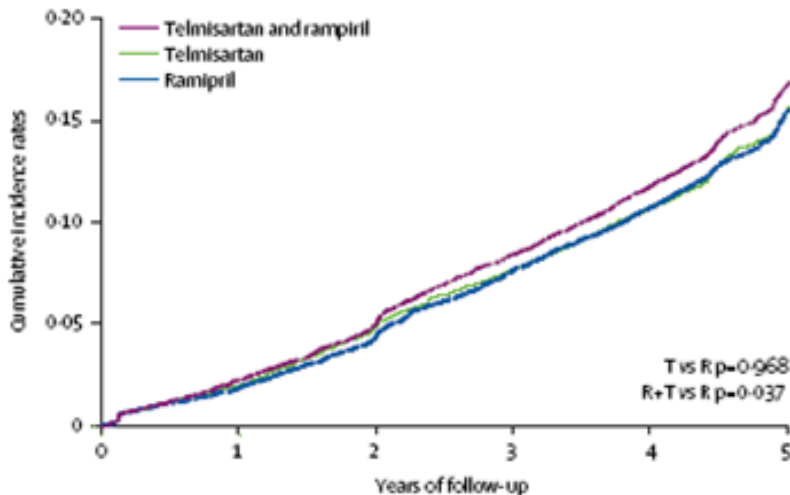
## ACEI/ARB in Non Diabetic CKD (>500mg Proteinuria)



## ACEI/ARB in advanced CKD

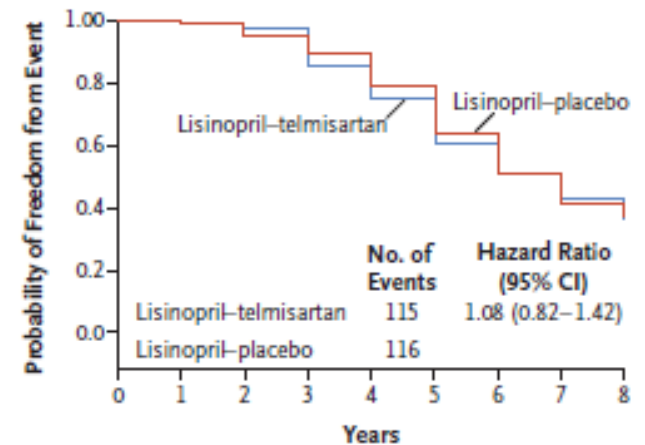


## ACEI/ARB Combination in CKD



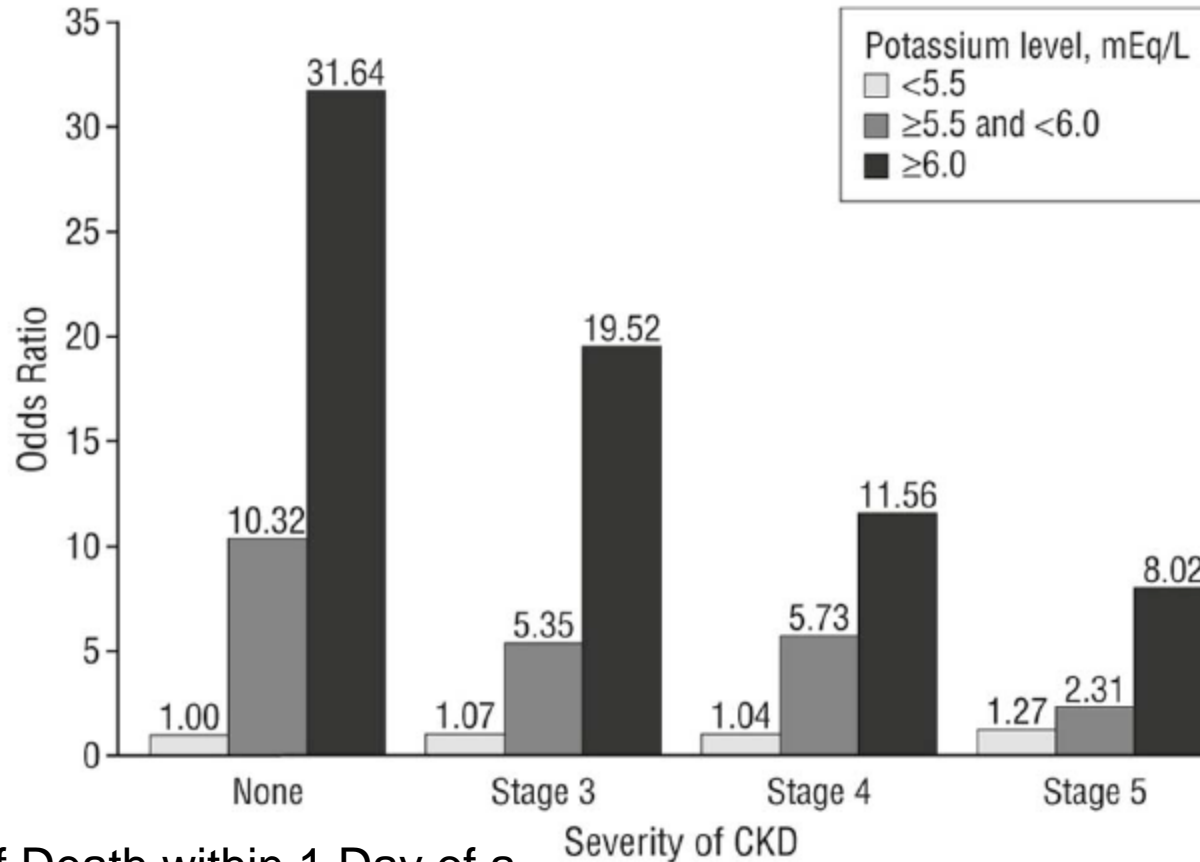
## ACEI/ARB HALT PKD

Composite Outcome



# The frequency of hyperkalemia and its significance in chronic kidney disease

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



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

# HyperKalemia Treatment

## **ZS-9 sodium zirconium cyclosilicate**

- Exchanges Na for K
- HARMONIZE Trial and Phase 3 study report efficacy vs Placebo
- Increased edema
- Long term and efficacy vs Kayexalate may need to be studied

## **Patiromer**

- 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) hyperK
- Study showed efficacy in both groups

# Stages of Chronic Kidney Disease and levels in the US population based on third NHANES Study

Stage	GFR (ml/min/1.73m <sup>2</sup> )	% of Population	No. of Pts
1	>90	1.0-2.0	3.0 – 3.9m
2	60–89	2.0-3.5	6.0-7.0m
3a	45-59	5.0-6.0	15.5m
3b	30-44		(3a-12.4m; 3b-3.1m)
4	15-29	0.2-0.3	0.7m
5	<15 or dialysis	0.2-0.3	0.6m

~ 17(+/- 1)m people with GFR less than 60ml/min



# Kidney Disease Improving Global Outcomes (KDIGO): Current CKD Nomenclature

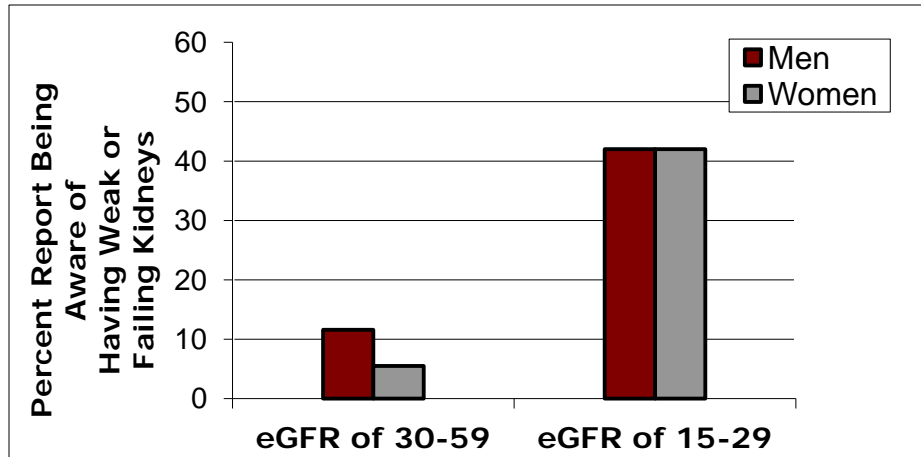
**Albuminuria defines additional risk over and above eGFR reduction in CKD**

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased  <30 mg/g <3 mg/mmol	Moderately increased  30-300 mg/g 3-30 mg/mmol	Severely increased  >300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

# Patient and Physician Awareness of CKD

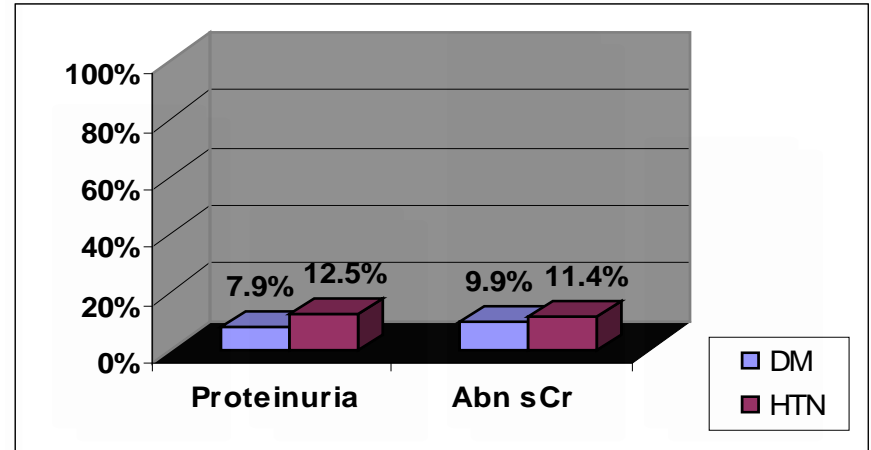
**Patients are frequently unaware of impairments in Kidney function**



Coresh, et al., 2007

**Renal disease is infrequently documented even among high risk groups**

Screening of 587 Medicare hospitalized patients <75yrs without h/o renal disease



McClellan, AJKD 1997, 29:368-75

# Diet and Lifestyle

## Diet

- CKD patients should receive expert dietary advice if available
- Lower protein intake to 0.8 g/kg/day in patients with GFR <30 ml/min
- Avoid high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression.
- Target HbA1c of <7.0% (extended above 7.0% in individuals with comorbidities or limited life expectancy and risk of hypoglycemia)
- Lower salt intake to <2 g per day of sodium

## Lifestyle

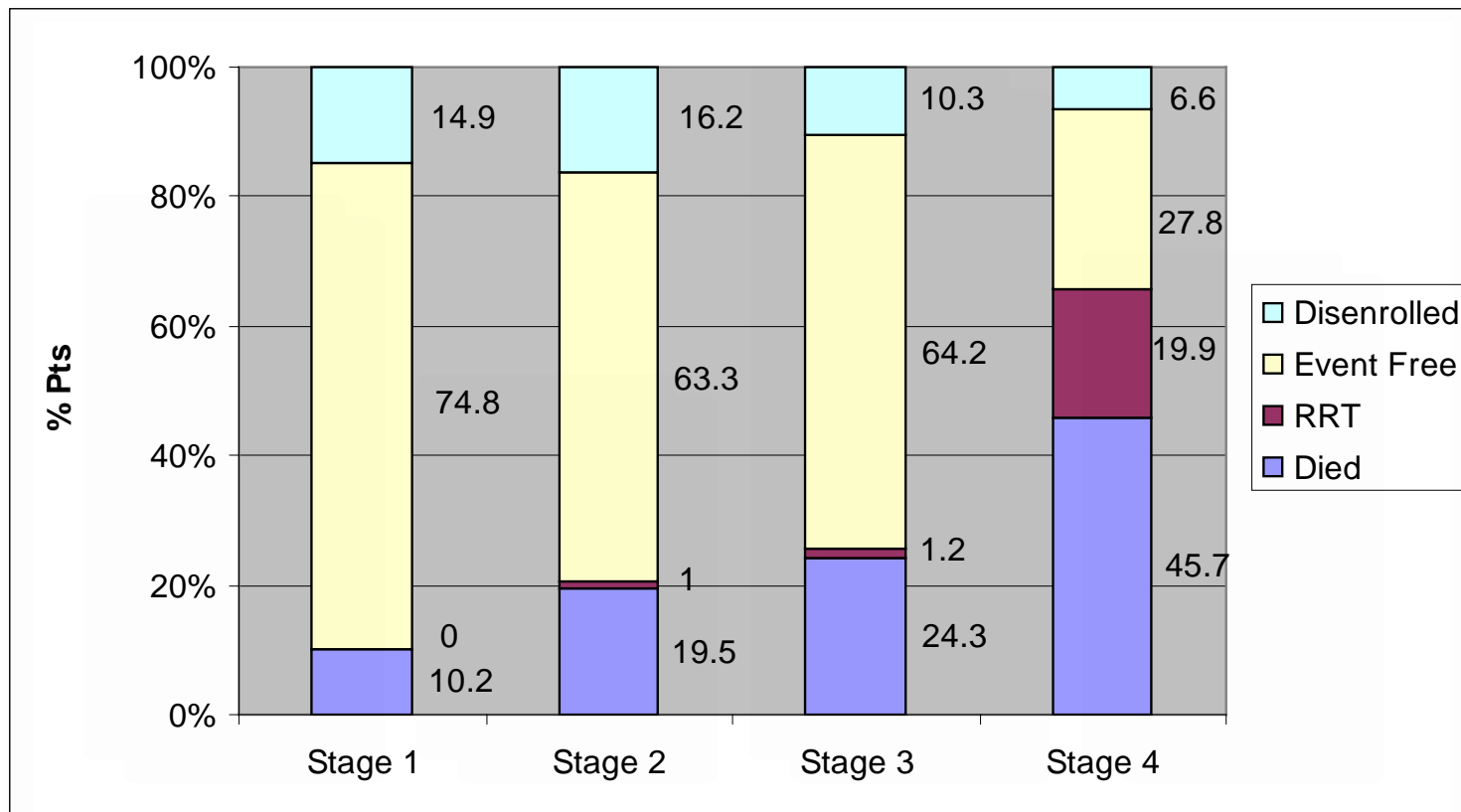
- Undertake physical activity
  - 30 minutes 5 times per week
- Achieve a healthy weight
  - BMI 20 to 25
- Stop smoking
- Avoid NSAID's

# Indications for referral to a Nephrologist for patients with CKD

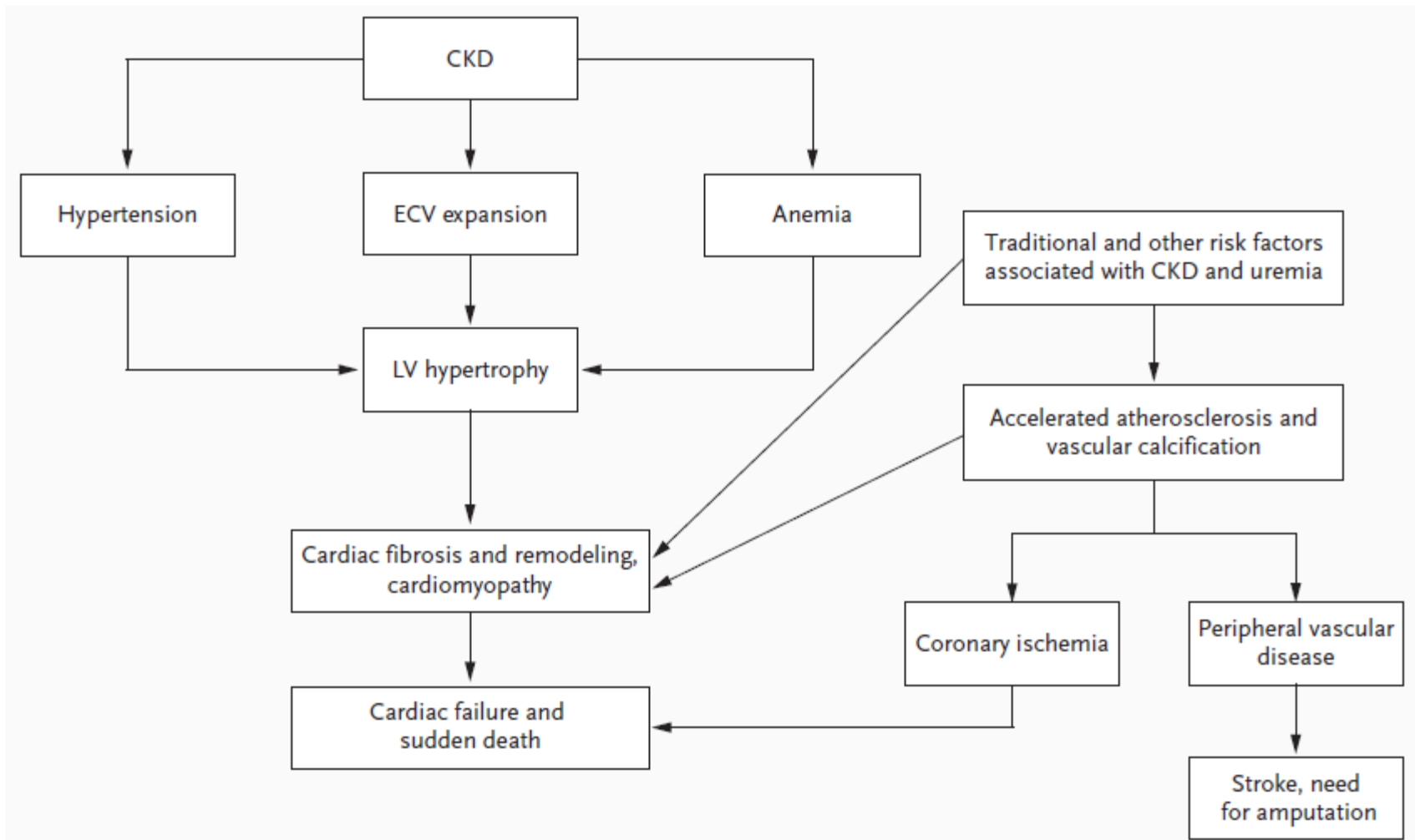
- Stage 4 and 5 (with or without diabetes); eGFR < 30ml/min
- Higher levels of proteinuria: urinary protein excretion  $\geq 1$  g/24 h); Proteinuria together with hematuria
- A rapidly declining estimated glomerular filtration rate ( $>5$  ml/min/1.73 m<sup>2</sup> in one year or  $>10$  ml/min/1.73 m<sup>2</sup> within five years)
- GFR $<60$ ml/min and difficult to control hypertension
- Suspected or rare or genetic causes of chronic kidney disease (eg: Polycystic disease)

# 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



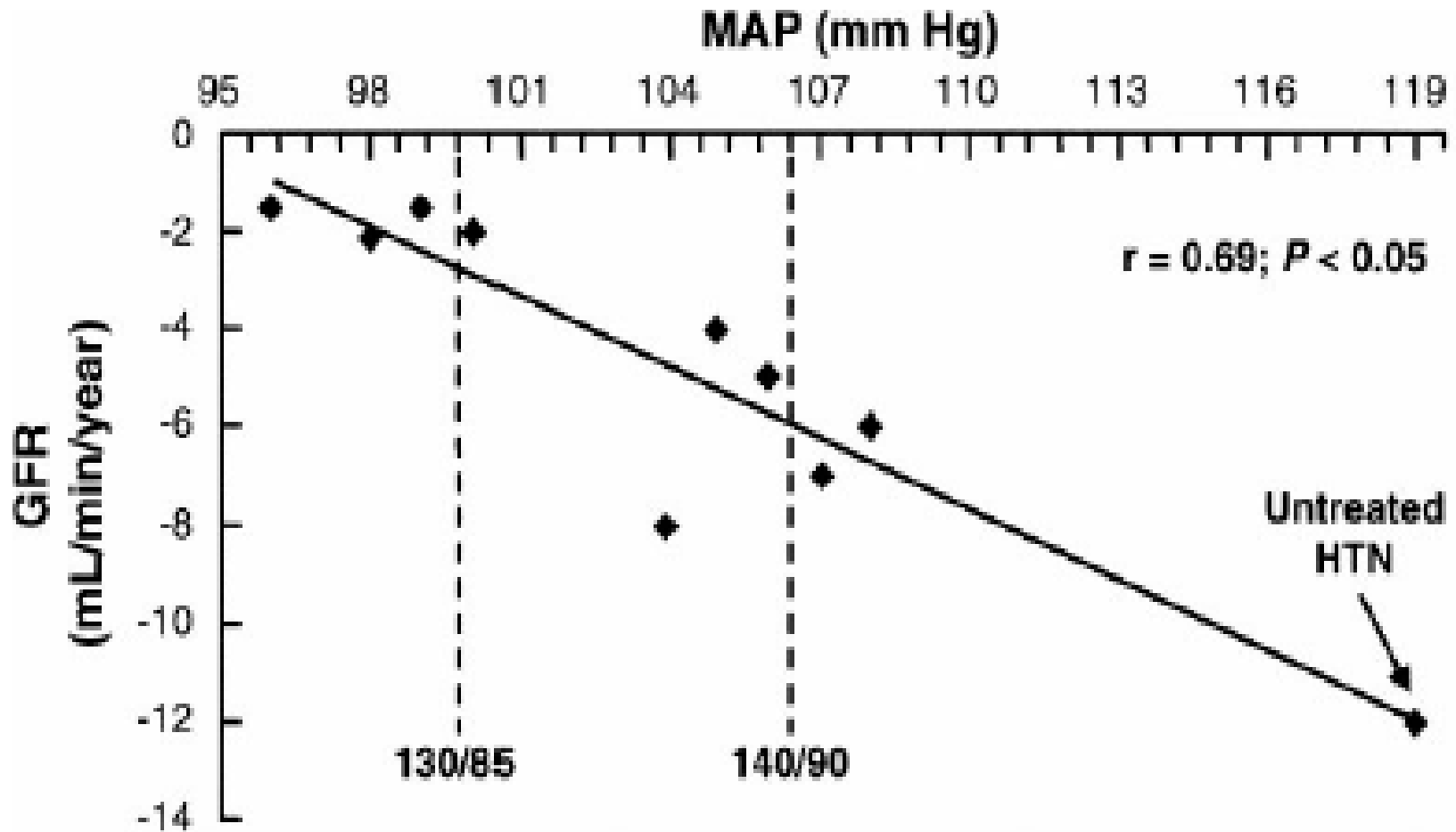
# Cardiovascular Disease in Patients with Chronic Kidney Disease



# Statins and Chronic Kidney Disease

<u>Study</u>	<u>Description</u>	<u>Results</u>
<b>4D:</b> NEJM, 2006	1255 subjects with type 2 Diabetes on hemodialysis randomly assigned to atorvastatin 20 mg qd or placebo.	<b>LDL reduced by 42%; no statistically significant effect on cardiovascular death, nonfatal myocardial infarction, and stroke</b>
<b>AURORA</b> NEJM, 2008	2776 patients at high cardiovascular risk, 50 to 80 years of age, on hemodialysis randomly to rosuvastatin, 10 mg daily, or placebo	<b>43% reduction in LDL; no statistically significant effect on cardiovascular death, nonfatal myocardial infarction, and stroke</b>
<b>Meta-analysis</b> BMJ. 2008 Mar 22;336(7645):645-51	53 studies: randomised and quasi randomised controlled trials of statins compared to placebo or with other statins in CKD	<b>Statins significantly reduced Total Cholesterol and LDL and proteinuria; reduced non fatal and fatal CV events; no impact on all cause mortality; no impact on GFR</b>
<b>Sharp Study</b> Lancet. 2011 Jun25;377(9784):2181-92	RCT: 9270 patients with CKD (3023 on dialysis and 6247 not) with no known history of myocardial infarction or coronary revascularisation; compared simvastatin plus ezetimibe to placebo	<b>Non-significantly fewer patients allocated to simvastatin plus ezetimibe had a non-fatal myocardial infarction or died from coronary heart disease</b>

# Benefits of Treating Hypertension and CKD





# Management of HTN

## JNC 8:

- In the general population aged  $\geq 60$  years
  - Treat BP  $> 150/90$
- In the general population  $< 60$  years
  - Treat BP  $> 140/90$
- In the population aged  $\geq 18$  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>
<ul style="list-style-type: none"><li>▪ Avoid high osmolar agents</li><li>▪ Use lowest possible contrast dose compatible with complete study</li><li>▪ Withdraw potentially nephrotoxic agents before and after the procedure</li><li>▪ Give adequate hydration with saline before, during, and after the procedure</li><li>▪ Measure GFR 48–96 hours after the procedure</li></ul>	<ul style="list-style-type: none"><li>• Do not use gadolinium in Pts with GFR &lt;15 ml/min/1.73 m<sup>2</sup> (unless there is no alternative appropriate test)</li><li>• For pts with a GFR &lt;30 ml/min use a macrocyclic chelate preparation</li></ul>	<p>Avoid oral phosphate-containing bowel preparations in pts with GFR &lt;60 ml/min due to risk of phosphate nephropathy</p>

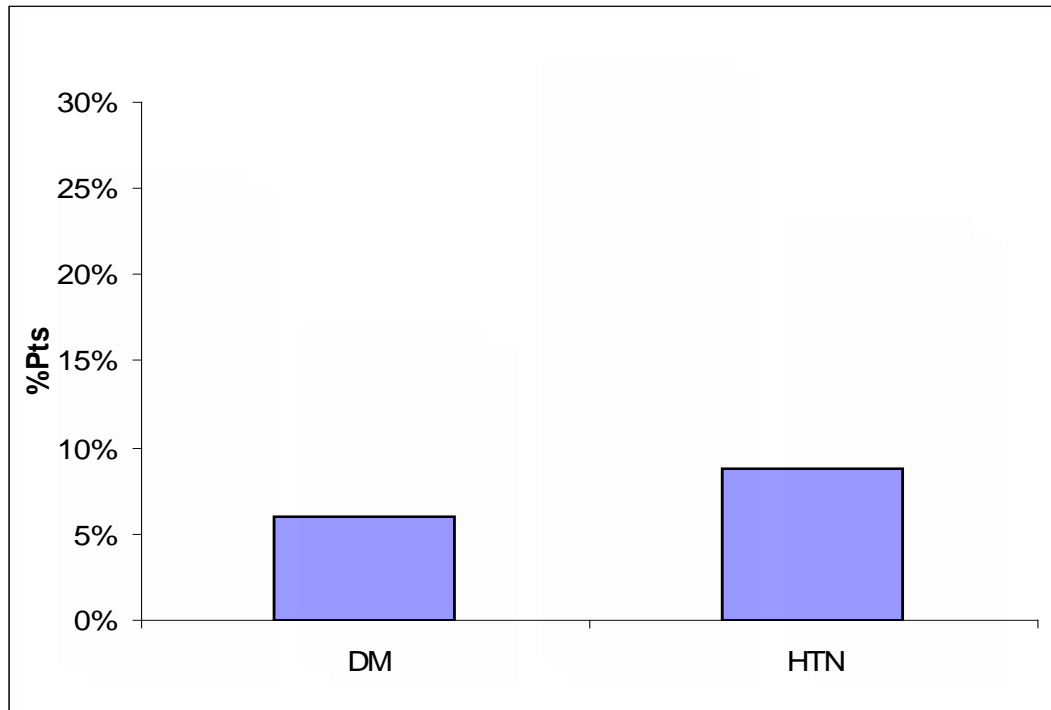
# Avoiding Nephrotoxin Injury :

## 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 re incidence and of chronic lithium nephropathy.
  - 15% have GFRs of more than 2 standard deviations below the age-corrected normal values

# Avoiding Nephrotoxin Injury : NSAID Associated Renal Injury

587 Medicare pts <75 years with documented renal disease



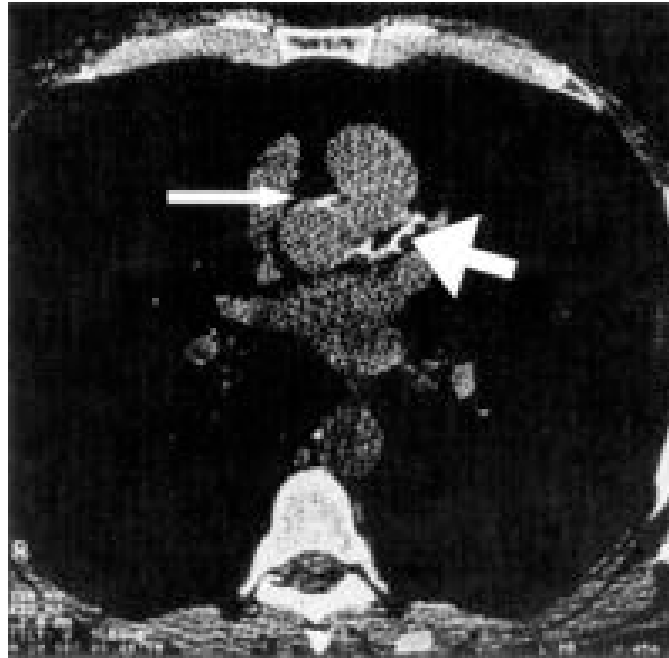
## Adverse Renal Effects of NSAIDs

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

# Vascular Biology is abnormal in CKD.

## Coronary-Artery Calcification in Young Adults with End-Stage Renal Disease Undergoing Dialysis

(N Engl J Med 2000;342:1478-83. AIN May 1998 Vol 128:10; 839-847)



Sample electron-beam computed tomographic scan showing calcification of the left anterior descending coronary artery (thick arrow) and the aortic root (thin arrow).

1. Coronary-artery calcification is common and progressive in young adults with end-stage renal disease who are undergoing dialysis.
2. The mean serum phosphorus, the mean calcium-phosphorus ion product, and the daily intake of calcium were higher among the patients with coronary-artery calcification

# Mineral Metabolism in CKD

- Measure serum calcium and phosphate if eGFR < 45ml/min
- Maintain phosphate in normal range
  - Restrict dietary phosphate intake
  - Use phosphate binders when indicated
- When vitamin D supplementation is indicated offer:
  - 25 OH Vit D to people with eGFR > 30 ml/min
- Use calcitriol (1,25 Vit D analogue) in patients with GFR < 30 ml/min and
  - PTH > 70ng/L in CKD 3
  - PTH > 120ng/L in CKD 4
- Offer bisphosphonates for the prevention and treatment of osteoporosis in
  - people with eGFR > 30 ml/min on the same indications as for all other patients

# Studies of Anemia Management and the use of Erythropoetin in CKD

<p><b>Normal Hct Study</b>          Besarab A et al. N Engl J Med 1998;339:584-590</p>	<p>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.</p>	<p>Pts in nl-Hct group had a decline in the adequacy of dialysis and received more IV iron dextran.</p>
<p><b>CHOIR Study</b>          Ajay Singh et al. N Engl J Med 2006;355:2085-98.</p>	<p>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).</p>	<p>Improvements in the quality of life were similar in the two groups.</p>
<p><b>CREATE Study</b>          Drueke et al N Engl J Med 2006;355:2071-84</p>	<p>No effect on first cardiovascular event</p>	<p>General health and physical function improved significantly (P = 0.003 and P&lt;0.001) in high Hb group.</p>
<p><b>TREAT Study</b>          Marc Pfeffer et al N Engl J Med 2009;361:2019-32</p>	<p>Death or a cardiovascular event in 632 pts in Rx group vs 602 pts in placebo group (P = 0.41)</p>	<p>Fatal or nonfatal stroke in 101 pts in Rx grp vs 53 in placebo group (P&lt;0.001).</p>

# Anemia Management

- Check hemoglobin in people with eGFR < 45 ml/min
- Exclude other causes of anemia before attributing to CKD
- If the patient is likely to benefit in terms of quality of life, consider referral for ESA candidacy if Hb < 9g/dl



# Preparation for ESRD

## Vascular Access Placement:

### Fistula First Program

#### Mortality Risk by Type of Vascular Access

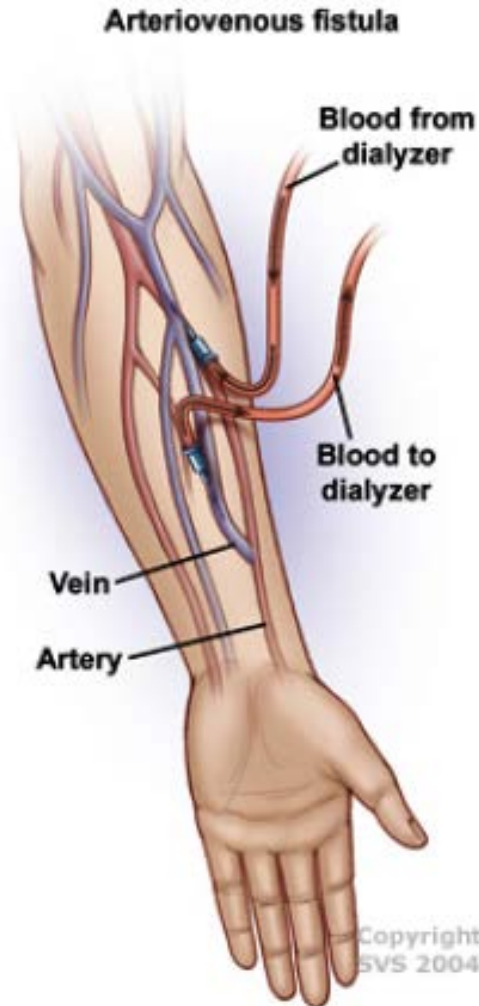
	<u>Relative Risk</u> <u>of death</u>	<u>P value</u>
<u>Diabetics:</u>		
AVF	1.00	
PTFE	1.39	0.0004
Catheter	1.49	0.0004
<u>Non-Diabetics:</u>		
AVF	1.00	
PTFE	1.09	0.26
Catheter	1.72	0.0001

1. 80% of patients initiating dialysis do so via catheter
2. CMS FistulaFirst program targets 66% fistula rate for patients > 90 days on dialysis
3. Current Rate is 54.7%
4. Best practices encouraged
  - I. Patient education
  - II. Vein preservation

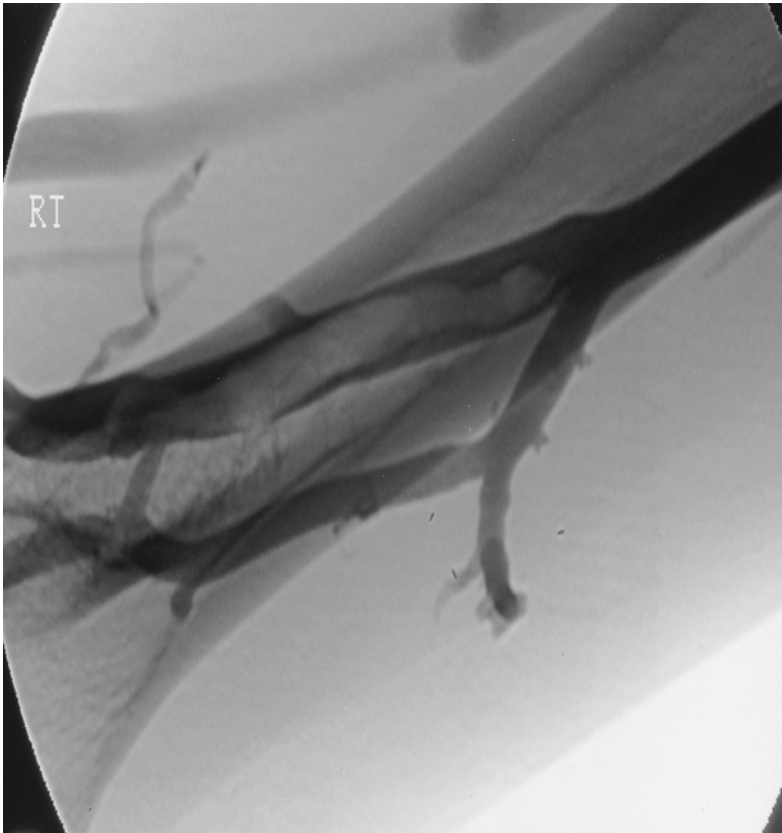
Dhingra et al; KI 2000

# Preparation for ESRD

## Vascular Access Placement: Fistula First Program



# Thrombosis following PICC placement

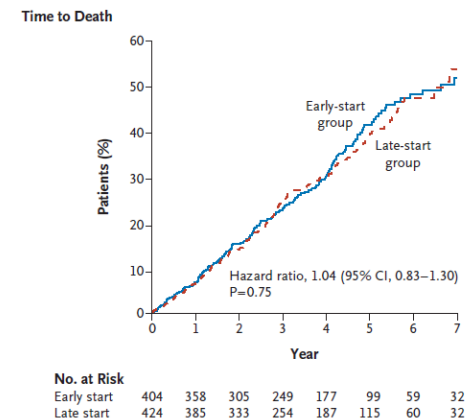


**Figure 1.** A 38-year-old asymptomatic woman 1 day after PICC placement with inadvertent removal. Venography demonstrates non-occlusive thrombus in a brachial vein

- Identify CKD stages 3,4 or 5, including current hemodialysis, peritoneal dialysis or transplant patients as a special population when planning central venous access
- Plan appropriate venous access in these cases
  - dorsal hand veins for phlebotomy
  - internal jugular veins are preferred for central venous access
  - external jugular veins are acceptable alternative
  - Avoid any catheters in subclavian veins

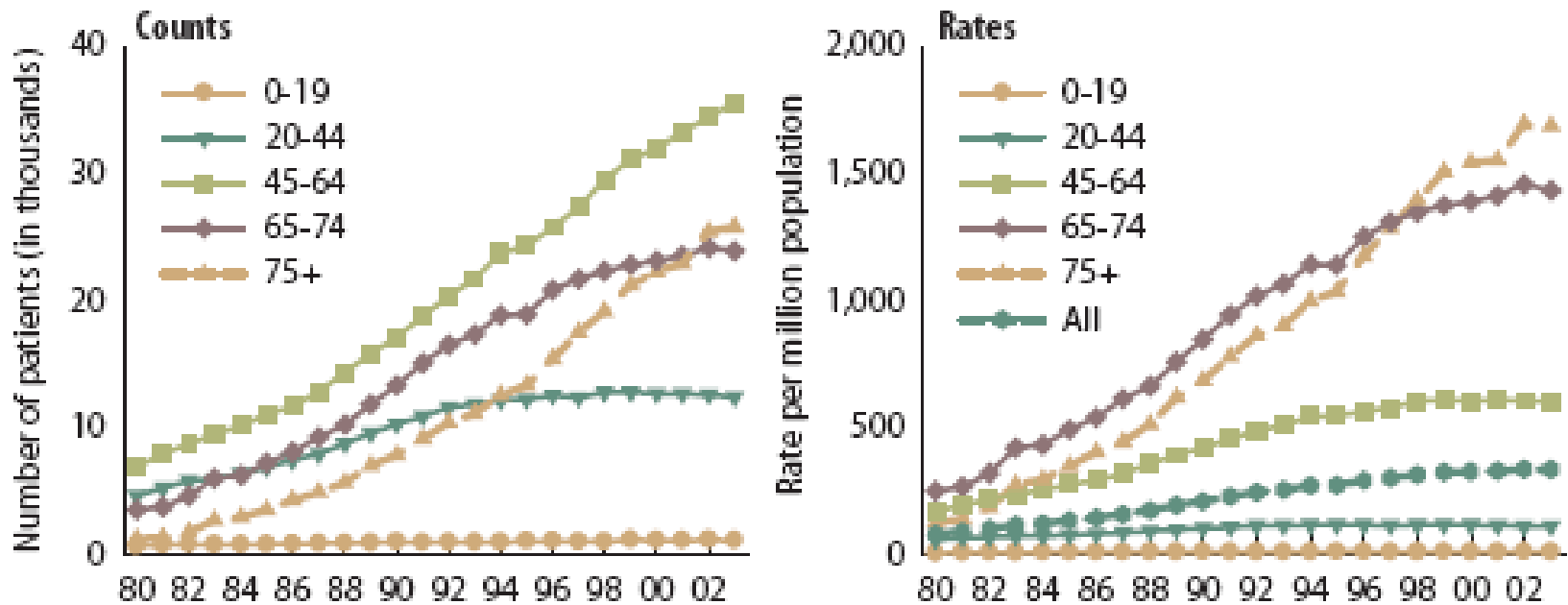
# Initiation of ESRD Care

- Consider dialysis initiation when one or more of following is present
  - symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus);
  - inability to control volume status or blood pressure;
  - progressive deterioration in nutritional status refractory to dietary intervention;
  - cognitive impairment.
- Often occurs in the GFR range between 5 and 10 ml/min
- Consider Living donor preemptive renal transplantation when GFR is <20 ml/min and
  - evidence of progressive
  - and irreversible CKD over the preceding 6–12 months.

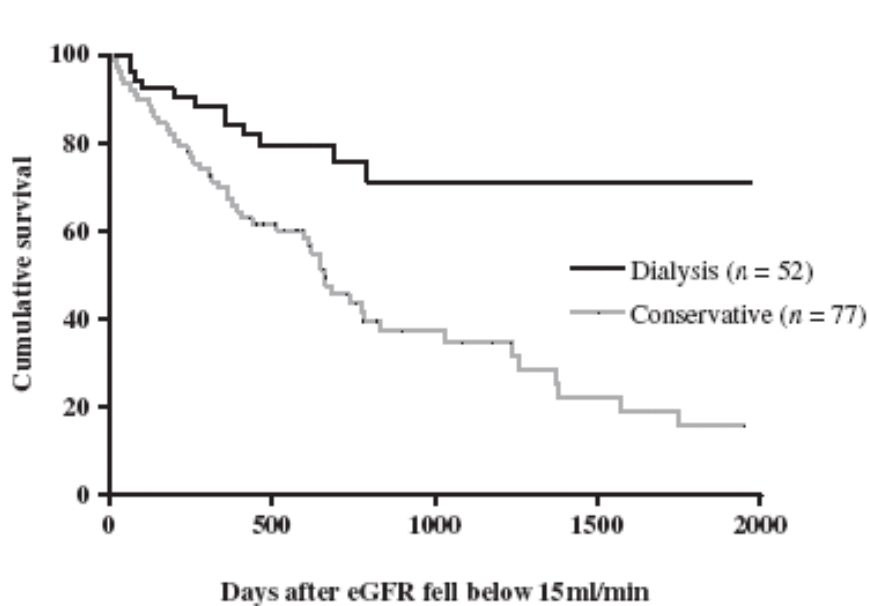


# ESRD incident counts and adjusted rates by age.

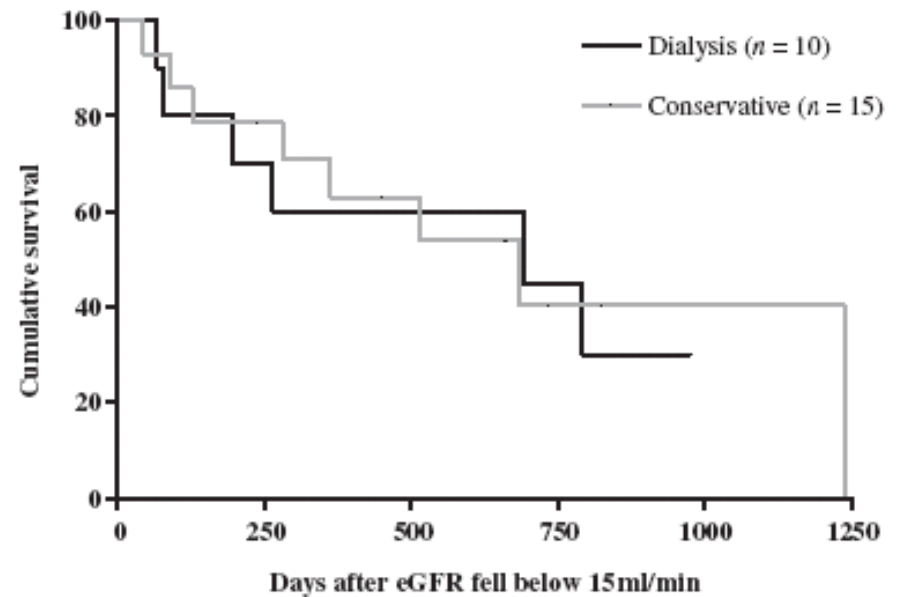
- the ageing of the dialysis population



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

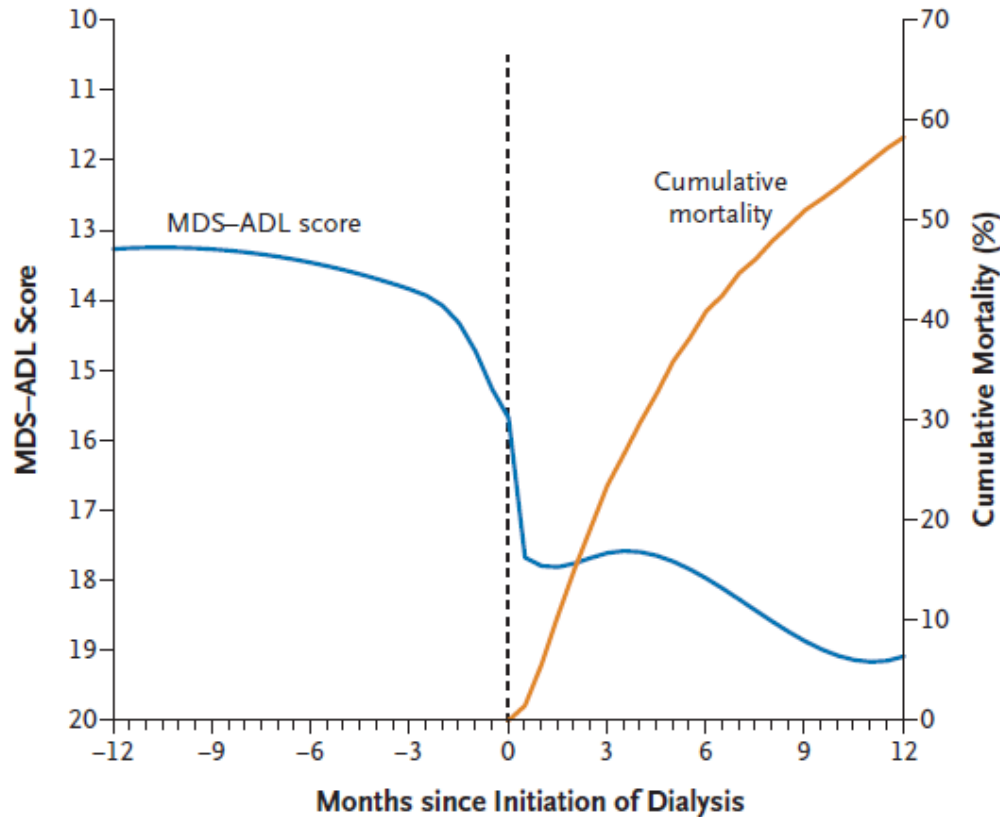


Kaplan–Meier survival curves comparing the dialysis and conservative groups ( $P < 0.001$ ).



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

- 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
- 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