

How to Treat Patients with Hypertension and Chronic Kidney Disease

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2012 Hypertension Symposium
SCPMG



U.S. Department of Health
and Human Services
National Institute of Health



Objectives

- Describe the burden of kidney disease in US
- Utilize lab tests for identifying and monitoring CKD and assessing risk for progression
- Attain goal blood pressures in patients with chronic kidney disease.
- Optimize use of diuretics and ACEi/ARB in patients with chronic kidney disease.



CKD is reduced kidney function and/or kidney damage

- Chronic Kidney Disease
 - **Kidney function**
 - Glomerular filtration rate (GFR) $< 60 \text{ mL/min/1.73 m}^2$ for ≥ 3 months with or without kidney damage
 - AND/OR
 - **Kidney damage**
 - ≥ 3 months, with or without decreased GFR, manifested by either
 - Pathological abnormalities
 - Markers of kidney damage, i.e., proteinuria (albuminuria)
 - » Urine albumin-to-creatinine ratio (UACR) $> 30 \text{ mg/g}$



Reference: National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. American Journal of Kidney Diseases. 2002; 39: (Suppl 1) S18.

Slide 1

PA1 Says "Module 1" and has picture of woman
Presentation Account, 11/2/2011

PA2 Chronic Kidney Disease Basics:
Presentation Account, 11/2/2011

More than 10% of U.S. adults *may* have CKD

- More than 20 million, aged 20 years or older

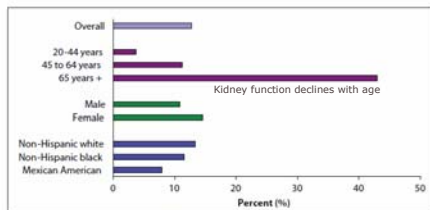
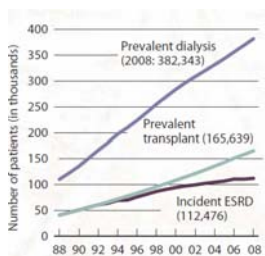


Figure legend: Percent with CKD among adult U.S. population by age, sex, and race/ethnicity.



Reference: <http://www.cdc.gov/diabetes/pubs/factsheets/kidney.htm> (CDC, 2010)

ESRD Patient Counts, by Modality 2008



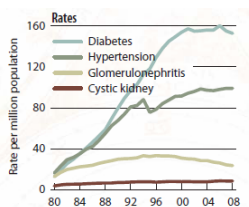
- Prevalent dialysis population
 - Increased 3.6% in 2008
 - Up 34.7% since 2000
- Transplant population
 - Increased 4.4% in 2008
- Incident population
 - Increased 1.4% in 2008



Reference: USRDS Annual Data Report (NIDDK, 2010)

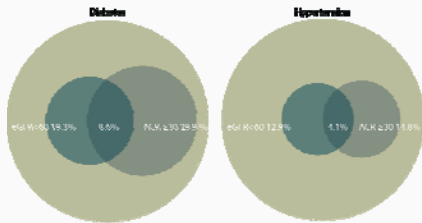
Diabetes is the leading cause of ESRD, followed by hypertension

Incidence



Reference: USRDS Annual Data Report (NIDDK, 2010)

Distribution of markers of CKD in NHANES participants with diabetes & hypertension, 2005–2010
Figure 1.11 (volume 1)



NHANES III (1988–1994) & 2005–2010 participants age 20 & older; eGFR calculated using CKD-EPI equation; urine albumin creatinine ratio (ACR).

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Identify and Monitor CKD.

FUNCTIONAL ASSESSMENT



PA3

CKD usually means fewer functioning nephrons.



Slide 9

PA3 This is aligned left in ADA's
Presentation Account, 11/2/2011

What is the glomerular filtration rate (GFR)?

- GFR is equal to the sum of the filtration rates in all of the *functioning* nephrons.
- GFR is not routinely measured in clinical settings.
- Estimation of the GFR (eGFR) gives a rough measure of the number of functioning nephrons.



What is the GFR?

- Cardiac output (CO) = 6 L/min
- x 20% of CO goes to kidneys = 1.2 L/min
- x Plasma is 50% blood volume = 600 mL/min
- x Filtration Fraction of 20% = 120 mL/min



“Normal” serum creatinine may not be normal

- Serum creatinine levels reflect muscle mass, age, gender, race
- A typical “normal” reference range of 0.6–1.2 mg/dL listed on many lab reports does not account for muscle mass, age, gender, and race.
- A 28-year-old African American man with serum creatinine of 1.2 has an *eGFR* > 60.
- A 78-year-old white woman with serum creatinine of 1.2 has an *eGFR* of 43.



Use an estimating equation for eGFR

- The Modification of Diet in Renal Disease (MDRD) study equation is widely used for estimating GFR.
- The variables are serum creatinine, age, race, and gender.
- The estimate is normalized to body surface area.

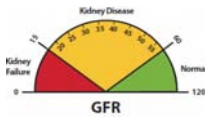
$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{S}_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$



Reference:
Stevens et al. *J Am Soc Nephrol* 2007; 18:2749-2757; Poggio et al. *Am J Kid Dis* 2005; 46:242-252; Verhave et al. *Am J Kid Dis* 2005; 46:233-241

How to explain eGFR results to patients

- Normal: ≥ 60 mL/min/1.73 m²
- Kidney disease: 15–59 mL/min/1.73 m²
- Kidney failure: < 15 mL/min/m²



Annals of Internal Medicine

Established in 1953 by the American College of Physicians

From: A New Equation to Estimate Glomerular Filtration Rate

Ann Intern Med. 2009;150(9):604-612. doi:10.1093/ajcp/150-9-200905050-00008

Table 3. Comparison of the CKD-EPI and MDRD Study Equations in Estimating Measured GFR in the Validation Data Set*

Variable and Equation	All Patients	Patients With Estimated GFR < 60 mL/min per 1.73 m ²	Patients With Estimated GFR ≥ 60 mL/min per 1.73 m ²
Median difference (95% CI), mL/min per 1.73 m ²			
CKD-EPI	2.8 (2.1-3.6)	2.1 (1.7-2.4)	5.5 (2.8-8.5)
MDRD Study	5.5 (5.0-5.9)	3.4 (2.8-4.0)	10.6 (9.8-11.3)
Interquartile range for differences (95% CI), mL/min per 1.73 m ²			
CKD-EPI	16.6 (15.9-17.3)	11.3 (10.7-12.0)	24.2 (22.8-25.3)
MDRD Study	18.1 (17.4-18.9)	13.9 (13.2-14.6)	25.7 (24.4-27.1)
P _{ave} (95% CI), % [†]			
CKD-EPI	84.1 (83.0-85.3)	79.9 (78.5-81.7)	88.3 (86.9-89.7)
MDRD Study	80.6 (79.5-81.7)	77.2 (75.9-78.5)	84.7 (83.0-86.3)
Mean mean square error (95% CI)			
CKD-EPI	0.260 (0.241-0.278)	0.288 (0.276-0.298)	0.219 (0.208-0.230)
MDRD Study	0.274 (0.263-0.285)	0.294 (0.280-0.308)	0.238 (0.238-0.238)

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

* 15 patients (9.3%) had a measured GFR that was < 15 mL/min per 1.73 m², and 15 (9.3%) had a measured GFR that was ≥ 120 mL/min per 1.73 m².

† Values are percentages of measured GFR.

‡ Interquartile range refers to the 25–75th percentiles.

§ P_{ave} refers to percentage of GFR patients that are within 30% of measured GFR.

Figure Legend:

Comparison of the CKD-EPI and MDRD Study Equations in Estimating Measured GFR in the Validation Data Set

eGFR

- P30 refers to the percent of GFR estimates that are within 30% of mGFR



Atlas of CKD & ESRD (USRDS, 2010) www.usrds.org/atlas.htm

What does this mean?

MDRD: There is an **77.2%** chance that the estimated GFR (for patients with eGFR <60) is +/- 30% of the measured GFR

▪e.g a patient with an eGFR of 59 has an **77.2%** chance of having a measured GFR **between 42 and 78**

vs

CKD-Epi: There is an **79.9%** chance that the estimated GFR (for patients with eGFR <60) is +/- 30% of the measured GFR

▪e.g a patient with an eGFR of 59 has an **79.9%** chance of having a measured GFR **between 42 and 78**



Kidney function and eGFR decline with age

Reference Table for Population Mean eGFR from NHANES III

Age (years)	Mean eGFR (mL/min/1.73 m ²)
20-29	116
30-39	107
40-49	99
50-59	93
60-69	85
70+	75



Reference: http://nkddep.nih.gov/professionals/gfr_calculators/gfr_fac.htm

eGFR estimates the measured GFR

- eGFR is **not** the measured GFR.
- The formula to estimate GFR was derived from a population-based study.
- The eGFR is a good estimate of the risk of having decreased kidney function
- Like other risk predictors, when it is the solitary indicator it should be used cautiously, especially when diagnosing "disease"



Use urine albumin-to-creatinine ratio (UACR) to assess and monitor.

KIDNEY DAMAGE

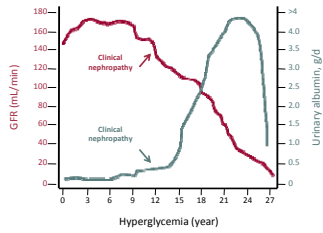


Urine albumin results are used for screening, diagnosing, and treating CKD

- Diagnosis
 - Forty percent of people are identified with CKD on the basis of urine albumin alone.
- Prognosis
 - Important prognostic marker, especially in diabetes mellitus (DM)
 - Used to monitor and guide therapy
- Tool for patient education and self-management (such as A1C or eGFR)
- Urine albumin is a marker for cardiovascular disease and is a hypothesized marker of generalized endothelial dysfunction.
- Standard of diabetes care (annual screen)

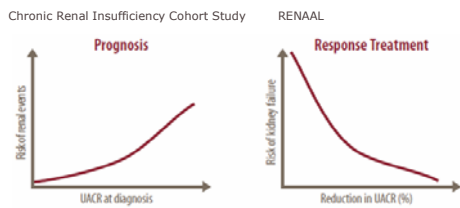


Natural history of diabetic nephropathy: hyperglycemia causes hyperfiltration, may be followed by albuminuria



Reference: Adapted from Friedman, 1999

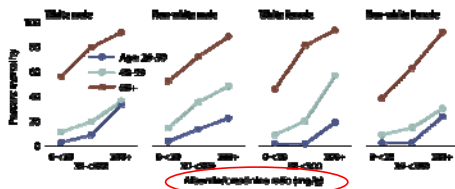
Elevated UACR is associated with risk of renal events; lowering UACR may lower risk of progression



Renal events = loss of half of eGFR, dialysis, or death

Albuminuria is associated with mortality

NHANES 1988-1994 participants



Reference: USRDS Annual Data Report (NIDDK, 2010)

Use urine albumin-to-creatinine ratio (UACR) for urine albumin assessment

- UACR uses a spot urine sample.
- In adults, ratio of urine albumin to creatinine correlates closely to total albumin excretion.
- Ratio is between two measured substances (not dipstick).

$$\frac{\text{Urine albumin (mg/dL)}}{\text{Urine creatinine (g/dL)}} = \text{UACR (mg/g)} \approx \text{Albumin excretion in mg/day}$$

- UACR of 30 mg/g is generally the most widely used cutoff for "normal."



Reference: http://nkddep.nih.gov/resources/uacr_qfr_quickreference.htm

UACR quantifies all levels of urine albumin

- UACR is a continuous variable.
- The term albuminuria describes all levels of urine albumin.
- The term microalbuminuria describes abnormal urine albumin levels *not* detected by dipstick test.
 - 30 mg/g – 300 mg/g
- The term macroalbuminuria describes urine albumin > 300 mg/g.



Staging: Population vs Individual

- Estimating equations are developed from data from groups of patients and may be best for describing risk for populations
- "It is counterintuitive that more patients are classified as having stage 3 of a chronic disease than earlier stages, ie, stage 1 and 2 combined, in sharp contradistinction to other chronic disease states such as heart failure. The result has been that the nephrology community appears to have undermined its own important work in public health by overdiagnosing a nonexistent disease in millions of elderly persons as well as in women ...or in adults with larger muscle mass or other nutritional states associated with higher serum creatinine independent of kidney function. **Use of the epidemiological classification of such an imperfect surrogate as estimated GFR does not square with the clinical reality of patient diagnosis and treatment.**"



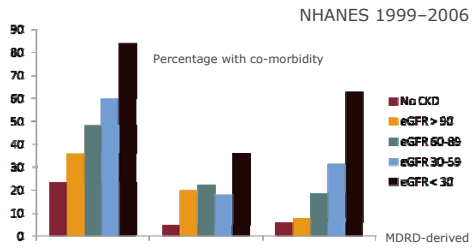
Kalantar-Zadeh, JAMA vol 307, 2012

KPSC Modification of Stage 3

- Modified staging by splitting stage 3 into:
 - High risk: proteinuria, DM, eGFR + 1/2 age <85
 - Low risk: chronic stage 3
 - Not DM
 - UACR < 300mg/g
 - eGFR + age/2 > 85
- 48,734 members Chronic Stage 3 vs. 55,485 Stage 3 modified
- 71% > 70 years
- Not targeted for population management

Rutkowski et al. AJKD. 2009

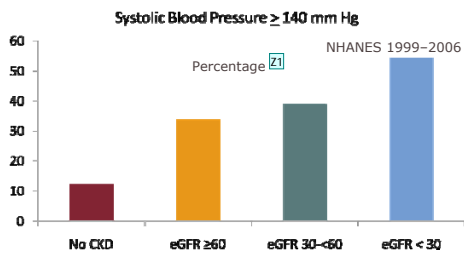
Prevalence of co-morbidities by eGFR



NHANES = National Health and Nutrition Examination Survey; eGFR = estimated GFR; HTN = hypertension; DM = diabetes mellitus; CVD = cardiovascular disease
Reference: Adapted from USRDS 2010 Annual Data Report



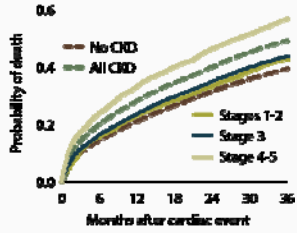
Blood pressure is poorly controlled in people with CKD



Slide 30

Z1 this is in the wrong place. Needs to be the left of the y axis, ideally facing up. See original.
ZawislanskiA, 11/15/2011

Probability of death following a diagnosis of CHF, by CKD status, 2010
 Figure 4.6 (volume 1)



Jan. 1 pt. prev. Medicare pts. age 66 & older; first CVD diag. in 2007-2008.

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Adjusted mortality rates (per 1,000 patient years at risk) in Medicare patients, by CKD diagnosis code, 2010
 Table 3.c (volume 1)

	No CKD	All CKD	s8s.1-2	s8s.3	s8s.4-5	Unk/unspec
All	53.7	77.0	59.7	69.5	114.7	79.3
Age: 66-69	23.3	37.2	20.7	41.4	44.2	37.1
70-74	27.5	42.4	26.7	35.6	79.2	42.1
75-84	48.3	72.7	48.4	64.6	137.5	72.4
85+	127.5	166.7	152.1	143.5	198.8	183.1
Male	58.0	81.4	67.1	77.2	122.1	80.5
Female	49.2	75.0	50.6	63.2	112.7	81.2
White	53.0	77.6	55.1	69.5	120.5	80.7
Black/Af Am	53.8	71.4	79.9	67.1	90.7	70.2
Other	44.9	70.1	46.9	61.8	95.6	71.3

January 1, 2010 point prevalent patients age 66 & older. Adj: age/gender/race/prior hospitalization/comorbidities. Ref: 2010 all patients.

USRDS 2012 ADR



Goals of Antihypertensive Rx in CKD

- Lower blood pressure
 - Most (60-100%) of patients with CKD have HTN
- Reduce the risk of CVD
 - LVH is common in CKD, almost universal in ESRD
- Slow progression of kidney disease

Higher levels of proteinuria are associated with more rapid progression of CKD and CVD in CKD.

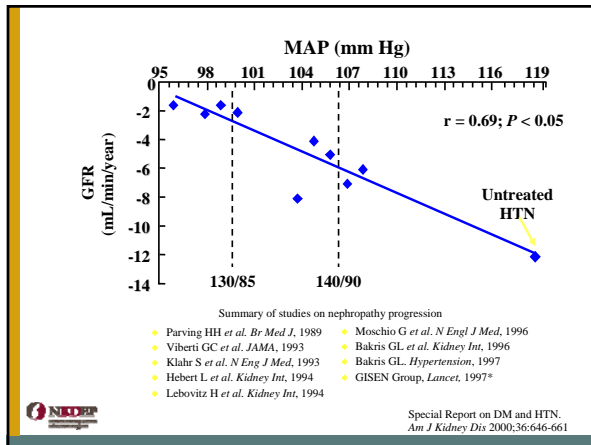


Treatment: blood pressure goals in CKD

- Target of < 130/80 mmHg is often recommended but without strong evidence.
- Uncontrolled hypertension (systolic blood pressure ≥ 160) is a major challenge.



Reference: Chobanian et al., 2003; Jafar et al., 2003



Management of Chronic Kidney Disease Stages 1–3: Evidence Report

Center for Outcomes and Evidence
Agency for Healthcare Research and Quality (AHRQ)



Treatment: ACEI or ARB, Outcome: ESRD

- ACEI vs. placebo (overt proteinuria, DM, HTN)
 - Decreased the risk of ESRD by 40 percent
 - ARR = 8.7%; 12% vs. 20.7%; RR = 0.60, 95% CI 0.43–0.83; 3 trials
 - Strength of Evidence = Moderate
- ACEI vs. placebo (microalbuminuria or impaired eGFR)
 - No reduced risk for ESRD
 - ARR=0.8 versus 0.9 %; RR 0.88, 95% CI, 0.27 to 2.88; 2 trials
- ARB vs. placebo (overt proteinuria, most w/DM & HTN)
 - Reduced the relative risk of ESRD by 22 percent
 - ARR = 2.9%; 10% vs. 12.9%; RR = 0.78, 95% CI 0.67–0.90;
 - Strength of Evidence: High

Treatment: other, Outcome: ESRD



- Conclusion: no significant difference, SOE= Low
 - Beta-blocker versus placebo
 - Calcium channel blocker versus placebo
 - Calcium channel blocker versus beta-blocker
 - Statin versus a control
 - Strict versus standard blood pressure control
 - Low-protein diet versus usual diet
 - Carbohydrate-restricted, low-iron-available, polyphenol-enriched diet versus low-protein diet

Treatment: ACEI or ARBs, Outcome: Mortality (1)

- The risk for mortality was not significantly different for these comparisons:
 - ACEI versus placebo (SOE = Moderate)
 - ARB versus placebo (SOE = High)
 - ACEI versus ARB, CCB, or beta-blocker (SOE = Low)
 - ARB versus CCB (SOE = Low)
 - ACEI plus ARB versus ACEI (SOE = Moderate)
 - ACEI plus ARB versus ACEI or ARB (SOE = Moderate)
 - ACEI plus diuretic versus placebo (SOE = Low)



Treatment: ACEI or ARBs, Outcome: Mortality (2)

- Subgroup Analysis
 - ACEI vs. placebo (microalbuminuria+CV, DM+other CV risk factors)
 - Reduced mortality risk by 21 percent (ARR = 2.8%; 9.3% vs. 12.1%; RR = 0.79, 95% CI 0.66–0.96; 8 trials)
 - Strength of Evidence: Moderate





Treatment: B-blocker, Outcome: Mortality

- B-blocker versus placebo (congestive heart failure and impaired eGFR)
 - Reduced the mortality risk by 31 percent (ARR = 5.7%; 12.4% vs. 18.1%; RR = 0.69, 95% CI 0.53-0.91; 2 trials)
 - Strength of Evidence: Low



Treatment: Other, Outcome: Mortality

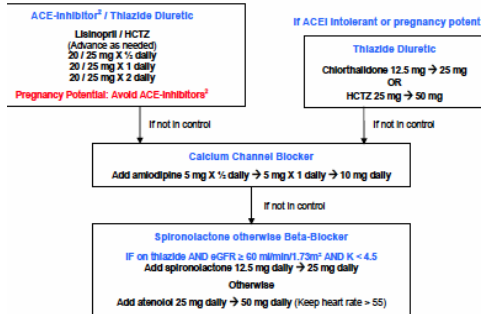
- The risk for mortality was not significantly different for these comparisons (Strength of Evidence = Low):
 - Calcium channel blocker versus placebo
 - Strict versus standard blood pressure-target treatment
 - Gemfibrozil versus placebo
 - Dietary interventions



Conclusions: Treatment

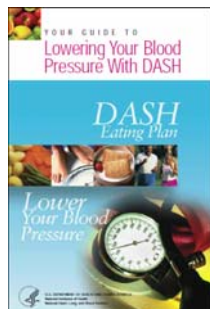
- In patients with CKD stages 1–3 who have overt proteinuria (macroalbuminuria) with concomitant diabetes and hypertension, an ACEI or an ARB will reduce the risk of ESRD.
- In patients with CKD stages 1–3 with only microalbuminuria or impaired eGFR, ACEIs did not reduce the risk for ESRD when compared with a placebo, but these trials were not powered to detect a difference.
- There was no increased benefit for reducing the risk of ESRD if an ACEI and an ARB were taken as combination therapy when compared with taking either an ACEI or an ARB alone.
- Taking an ACEI or an ARB did not reduce the risk of mortality, except when an ACEI was used for patients with microalbuminuria and cardiovascular disease or diabetes and other cardiovascular risk factors.

KP Management of Hypertension



22

The DASH diet lowers blood pressure in the general population



Slide 48

Z2

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ZawislanskiA, 11/22/2011

The DASH diet may help prevent CKD, but it is not generally used with CKD

- DASH and DASH-Sodium patterns lower blood pressure.
- The lowest sodium level is the most effective, even with the usual (control) diet.
- The DASH pattern *may* be too high in protein, potassium, and phosphorus for CKD.



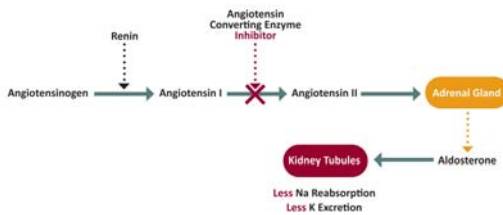
Reducing sodium intake may reduce urine albumin levels

- In the Netherlands, higher sodium intake was associated with increased urine albumin excretion.
- In a 2006 literature review, increasing salt consumption was associated with worsening urine albumin.

Reference: Verhave et al., 2004; Jones-Jones-Burton et al., 2006



ACEi medications block the RAAS and increase the risk for hyperkalemia



Use of Angiotension II Blockers: ACE-i and ARBs

- GFR decline over four months is <30% from baseline value
- Serum potassium is <5.5 mEq/L



Potassium restriction is not indicated in the absence of hyperkalemia

- Specific level of eGFR does not determine need for dietary potassium restriction.
- Restriction is to help achieve and maintain a safe serum potassium level (≤ 5 mEq/L).
- The level of potassium restriction should be individualized.



Use of Diuretics in CKD

- Thiazide diuretics given once daily in patients with GFR ≥ 30 mL/min/1.73 m² (CKD Stages 1-3)
- Loop diuretics given once or twice daily in patients with GFR <30 mL/min/1.73 m² (CKD Stages 4-5)



K-Sparing Diuretics: Use with Caution in CKD

- In patients with GFR <30 mL/min/1.73 m² (CKD Stages 4-5)
- In patients receiving concomitant therapy with ACE inhibitors or ARBs
- In patients with additional risk factors for hyperkalemia (DM)



Common Reasons for Poor HTN Control in CKD Patients

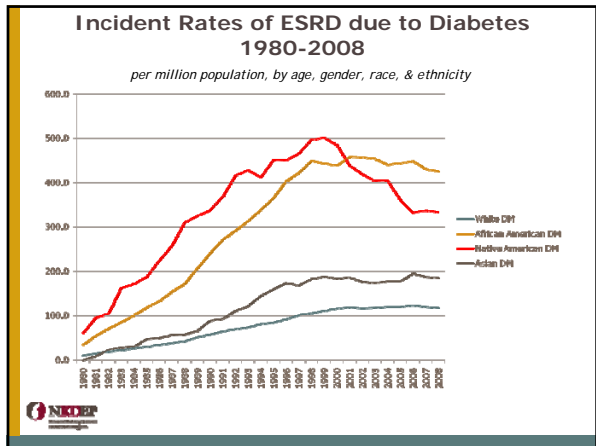
- Failure to restrict dietary salt
- Insufficient anti-hypertensive medication
- Inadequate doses of diuretics
- Fear of side effects: patient and provider
- Inappropriate withdrawal of AT II blockers: rise in Cr and K




HTN and CKD

- Most patient with CKD have HTN
- Lowering BP (<140/80) reduces CV and renal risk
- ACE/ARBs are first line therapy
- Diuretic/Na restriction are necessary
- >2 drugs usually needed
- Monitor BP and proteinuria





QUESTIONS & COMMENTS



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<http://nkdep.nih.gov/>

NIDDK
