




[Update in Nephrology]

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[Case Presentation]

- 68 y.o. WM with HTN, Chronic Stable Angina and Hyperlipidemia
 - Meds: Procardia, Atenolol, Zocor, Aspirin
 - Very active, walks several miles/day
 - Blood pressure 132/74
 - Serum Creatinine 1.6
- What management is recommended with regard to his kidneys?



[Clinical Questions]

- What is the best way to assess the this patient's kidney disease?
 - Current status and Prognosis
 - Degree of renal impairment
- What treatment is indicated to delay progression of his kidney disease?




[Current state of knowledge about Chronic Kidney Disease]

- Worldwide health problem
- Incidence and prevalence have doubled in the US in the last 10 years
- Outcomes remain poor
- Estimates suggest nearly 20 million Americans have some degree of CKD
- The major outcomes are progression to ESRD, complications related to CKD and Cardiovascular disease
 - Most persons with mild to moderate reductions in GFR die from CVD before they develop ESRD



[Road Map]

- Review recent guideline on approach to chronic kidney disease
 - Categorization of disease
 - Estimation of GFR
 - Assessment of Proteinuria
- Review the role of blockade of Angiotensin II in non diabetic nephropathy
- Review the interplay of proteinuria and BP control on renal outcomes



[National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification]

Levey AS et al. *Ann Intern Med.* July 15, 2003;139:137-147.

Guideline	Description	Recommendation	Rating
1	Definition and Stages of CKD	Define CKD	A
		Classification of Stages	A
2	Evaluation and Treatment	Clinical Action Plan	B
		Refer CKD pts. to nephrologists	B
3	Persons at increased risk for CKD	Assess risk for CKD	C
		Test persons at risk	C
4	Estimation of GFR	Estimate GFR from prediction equations	A
		Not using 24 hour CrCl measurements to estimate GFR	A
5	Assessment of Proteinuria	Quantify using untimed urine prot-creatinine ratio	A
		Not using 24 hr. urine collections to quantify proteinuria	A

Adapted from Levey AS et al. *Ann Intern Med.* 2003;139:137-147.

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Definition of CKD

- Kidney damage or decreased kidney function for at least 3 months
 - Persistent proteinuria is the principal marker of kidney damage
 - Best measure of kidney function is GFR
 - GFR of 60 ml/min represents half or less of normal function in adults
 - Below this level, the prevalence of CKD complications increases

Levey AS et al. *Ann Intern Med.* 2003;139:137-147

Stages of Chronic Kidney Disease: A clinical action plan

Stage	Description	GFR (mL/min/1.73m)	Action*
1	At increased risk	≥90 (with CKD RF's)	Screening, CKD risk reduction
	Kidney damage with normal or increased GFR	≥90	Dx and Rx of comorbid dz, Slowing progression, CVD risk reduction
2	Kidney damage with mildly decreased GFR	60–89	Estimating progression
3	Moderately decreased GFR	30–59	Evaluating and treating complications
4	Severely decreased GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

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A more accurate method to estimate GFR from serum creatinine: A new prediction equation

- MDRD study: multicenter controlled trial to evaluate efficacy of dietary protein restriction and strict BP control on progressions of CKD
- Several variables measured at baseline
- An equation was developed from this data to improve prediction of GFR from serum Creatinine

Levey AS et al. *Ann Intern Med.* 1999;130:461-470

A more accurate method to estimate GFR from serum creatinine: A new prediction equation

- 1628 patients included
- GFR measured as renal clearance of ¹²⁵I-iothalamate
- Sample of 1070 patients and their data used to create prediction equations
- These equations were then validated on the remaining patients' data
- Key factors affecting prediction included: race (B>W), age, sex (M>F), and protein intake

Levey AS et al. *Ann Intern Med.* 1999;130:461-470

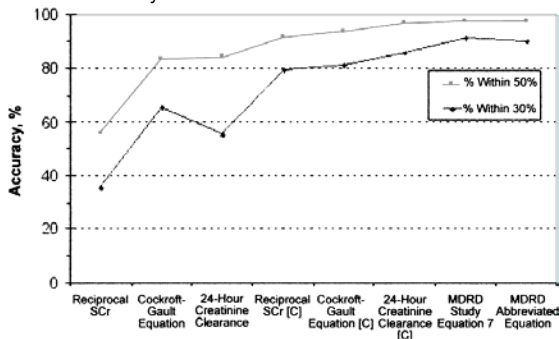


Table 3. Comparison of Equations To Predict Glomerular Filtration Rate (mL/min per 1.73 m²) from Serum Creatinine Concentration*

- Equation 1: Serum creatinine
GFR = 0.69 × [100/P_{Cr}]
- Equation 2: Cockcroft–Gault formula
GFR = 0.84 × [Cockcroft–Gault formula]
- Equation 3: Creatinine clearance
GFR = 0.81 × [C_{Cr}]
- Equation 4: Average of creatinine and urea clearance
GFR = 1.11 × [(C_{Cr} + C_{urea})/2]
- Equation 5: Creatinine clearance, urea clearance, and demographic variables
GFR = 1.04 × [C_{Cr}]^{+0.751} × [C_{urea}]^{+0.226} × [1.109 if patient is black]
- Equation 6: Demographic, serum, and urine variables
GFR = 198 × [P_{Cr}]^{-0.858} × [Age]^{-0.167} × [0.822 if patient is female] × [1.178 if patient is black] × [SUN]^{-0.293} × [UUN]^{+0.249}
- Equation 7: Demographic and serum variables only
GFR = 170 × [P_{Cr}]^{-0.999} × [Age]^{-0.176} × [0.762 if patient is female] × [1.180 if patient is black] × [SUN]^{-0.170} × [Alb]^{+0.318}

Levey AS et al. *Ann Intern Med.* 1999;130:461-470.

Accuracy of different estimates of GFR in adults



MDRD Study validation sample (n = 558). Estimates denoted with [C] include a calibration correction to show performance after bias is eliminated using a multiplicative correction factor.

Levey AS et al. *Ann Intern Med.* 1999;130:461-470.

Table 48. Abbreviated MDRD Study Equation

$$\begin{aligned} \text{Estimated GFR (mL/min/1.73m}^2\text{)} \\ &= 186 \times (S_{Cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American}) \\ &= \exp(5.228 - 1.154 \times \ln(S_{Cr}) - 0.203 \times \ln(\text{Age}) - (0.299 \text{ if female}) + (0.192 \text{ if African-American})) \end{aligned}$$

For explanation, see text and references 17,18.

K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification
PART 5. EVALUATION OF LABORATORY MEASUREMENTS FOR CLINICAL ASSESSMENT OF KIDNEY DISEASE
http://www.kidney.org/professionals/doqi/kdoqi/p5_lab_g4.htm

A more accurate method to estimate GFR from serum creatinine: A new prediction equation

- Conclusions:
 - Serum Creatinine alone is inadequate to estimate renal function
 - 24 hour collections for CrCl are cumbersome and fraught with error
 - The MDRD equation was more accurate than any others in this study (including Cockcroft-Gault)

Levey AS et al. *Ann Intern Med.* 1999;130:461-470



Table 52. Clinical Situations in Which Clearance Measures May be Necessary to Estimate GFR

- Extremes of age and body size
- Severe malnutrition or obesity
- Disease of skeletal muscle
- Paraplegia or quadriplegia
- Vegetarian diet
- Rapidly changing kidney function
- Prior to dosing drugs with significant toxicity that are excreted by the kidneys

http://www.kidney.org/professionals/doqi/kdoqi/p5_lab_g4.htm



Testing for Proteinuria

- “For the quantification of proteinuria, there is now convincing evidence that the urine protein to creatinine or albumin to creatinine ratio in a spot urine sample accurately predicts the level of protein excretion”
- Testing should be repeated for confirmation

Eknoyan G. Testing for Proteinuria: Time for a Change. CKD Update. Feb 5, 2003.
<http://www.imakenews.com/ckdupdate/e/article000125540.cfm>

Clinical Questions

- What is the best way to assess the this patient’s kidney disease?
 - Current status/Prognosis
 - Degree of renal impairment
- What treatment is indicated to delay progression of his kidney disease?

Current state of knowledge about Chronic Kidney Disease

- Blockade of the renin-angiotensin axis is effective in preventing progression
 - ACEI’s efficacy over other anti-hypertensives well established
 - Benefit appears largely unrelated to the BP lowering effects
- Tight BP control is effective in preventing progression (JNC VII suggests a goal of <130/80)
- Dietary protein restriction still controversial
- Treating anemia and lipids are important

Combination therapy with ACEI and ARB: COOPERATE

- The benefit of ACEI’s is well established, yet many patients still have progression to ESRD
- Double blind RCT at one center in Japan
- Patients referred by PCP’s for management of renal disease
- Inclusion criteria: ages 18-70 with chronic nephropathy (GFR 20-70), non diabetic renal disease, persistent proteinuria >300mg/24hr
- Single blind run in period
 - Determine response to trandolapril after stopping all antihypertensives for 3 weeks
 - Monitoring of Adherence and Safety

Nakao N. et al. *Lancet* 2003; 361: 117–24.

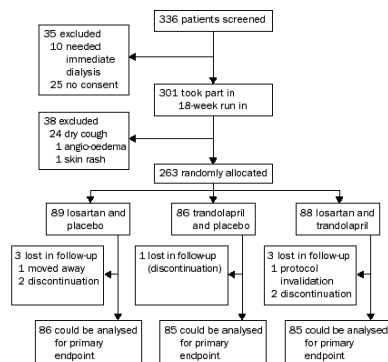


Figure 1: Trial profile

Nakao N. et al. *Lancet* 2003; 361: 117–24.

Outcomes

- Primary endpoint: Time to doubling of serum creatinine or ESRD
- Secondary endpoint: effect of treatment on three parameters
 - Blood pressure
 - Urinary protein excretion
 - Adverse effects

Table 1: COOPERATE

	Losartan (n=89)	Trandolapril (n=86)	Combination (n=88)
Age	44.8	45.9	45.2
Sex (%M)	54%	53%	53%
Calc GFR	38.4	37.9	37.5
Proteinuria (gm/d)	2.4	2.5	2.5
BP	130/74	130/76	130/75
Glomerular disease	65%	65%	65%
Nephrosclerosis	17%	19%	17%

Nakao N. et al. *Lancet* 2003; 361: 117-24.

Combination therapy with ACEI and ARB: COOPERATE

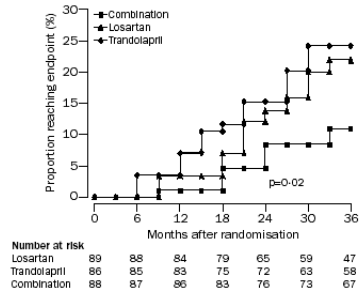


Figure 2: Proportion of patients reaching endpoint

Nakao N. et al. *Lancet* 2003; 361: 117-24.

COOPERATE: results

- Trial stopped at year 3 due to survival benefit in combination group
- No difference between groups in risk factors or BP reductions
- Protein excretion reduction was highest in the combination group, and the effect was seen across all levels of baseline renal function and protein excretion

Combination therapy with ACEI and ARB: COOPERATE

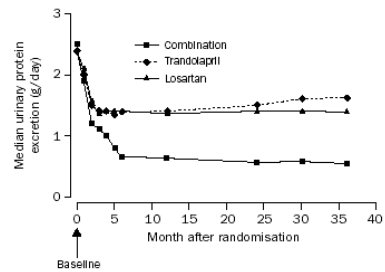


Figure 4: Median urinary protein excretion by treatment group

Nakao N. et al. *Lancet* 2003; 361: 117-24.

COOPERATE: Adverse effects

- No severe adverse events reported
- The frequency of non-fatal adverse events was similar across all treatment groups
 - Hyperkalemia slightly higher, usually treatable
 - No instances of ARF

Combination therapy vs losartan alone or trandolapril alone for nondiabetic renal disease at 3 yrs.

Outcome	Comparisons	Event rates	RRR (95% CI)	NNT (CI)
Combined Endpoint*	Comb. therapy vs. losartan	11% vs 23%	49% (0.5-75)	9 (5-1722)
	Comb. therapy vs. trandolapril	11% vs 23%	50% (1.7- 75)	9 (5-359)

*Combined endpoint = time to doubling of serum Cr or ESRD

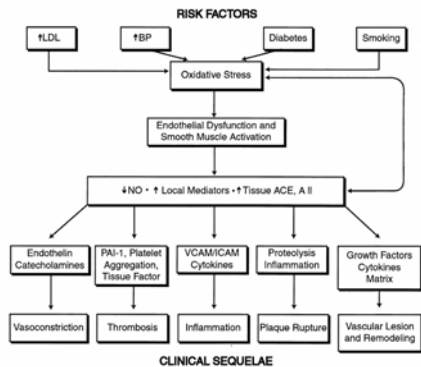
Weise W. *ACP Journal Club* Sept/Oct 2003;139(2).

COOPERATE: in context

- COOPERATE suggests that patients with nondiabetic renal disease benefit from combination rx (ACEI + ARB)
- Since many patients with CKD die from Cardiovascular disease, we must consider the effects of combination therapy on that as well...

COOPERATE: in context

- Background facts:
 - Angiotensin II appears to be directly involved in atherothrombosis
 - Blockade of Ang II is beneficial in patients at risk for vascular disease (HOPE)
 - Ang II levels remain elevated in some patients on chronic ACEI therapy



Yusuf S. From the HOPE to the ONTARGET and the TRANSCEND Studies: Challenges in Improving Prognosis. *Am J Cardiol* 2002;89(suppl):18A-26A

CHARM

- Candesartan vs. placebo in patients with CHF already taking ACEI's
- RCT of ~2500 pts. with median f/u of 41 months
- Demonstrated significant reduction in:
 - Overall mortality and Cardiovascular mortality
 - Hospitalization for CHF
- NNT of 23 to prevent one CV death or CHF admission
- No difference in patients on β blockers (refuting the findings of the Val-HeFT trial)

McMurray JJ et al. *Lancet*. Sept 6, 2003;362:767-71.

ONTARGET

- Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
- Large RCT involving 23,400 patients with similar characteristics as those in the HOPE trial
- Completion expected in 2007

Unger T. *Am J Cardiol* 2003;91(suppl): 28G-34G.
Yusuf S. *Am J Cardiol* 2002;89(suppl): 18A-26A.

Combination therapy summary

- The combination of ACEI and ARB appears to be an effective therapy both for CHF and CKD
- Angiotensin II appears to play an important role in atherosclerotic dz
- Given the risk of CVD in patients with CKD, combination therapy should be considered
- Combination therapy appears to be well tolerated

- What is the appropriate target level for Blood Pressure in CKD?
 - JNC 7 suggests 130/80 for all with CKD
- Are there factors that modify this target? (degree of impairment, protein excretion etc.)

Progression of CKD: The role of BP control, Proteinuria and ACE inhibition

- Patient level meta-analysis from AIPRD study group database
 - 1860 nondiabetic patients enrolled in 11 RCT's evaluating ACEI's in kidney disease
 - Included only studies that compared the effect of regimens with ACEI's vs. those without
 - All included studies used other meds to achieve target BP<140/90
 - Included patients had HTN, CKD or both and were followed for 2-3 years

Jafar, T et al. *Ann Intern Med.* 2003;139:244-252.

Progression of CKD: The role of BP control, Proteinuria and ACE inhibition

- Outcome: doubling of serum Cr or ESRD
- Patients were evaluated regularly for BP, proteinuria and worsening kidney disease
- Multivariable analysis was performed to assess the association of SBP, DBP, and urine protein excretion on progression of CKD at 22, 610 patient visits

Jafar, T et al. *Ann Intern Med.* 2003;139:244-252.

Table 2. Adjusted Relative Risk for Kidney Disease Progression by Systolic Blood Pressure during Follow-up*

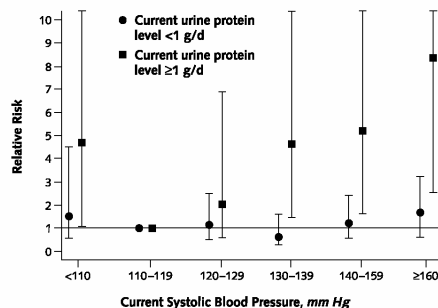
Systolic Blood Pressure† mm Hg	Patients‡	Visits§	Events	Adjusted Relative Risk (95% CI)
<110	253	947	10	2.48 (1.07-5.77)
110-119	546	1976	12	1.00
120-129 (JNC normal)	959	3746	32	1.23 (0.83-2.40)
130-139 (JNC high-normal)	1220	4506	59	1.81 (0.97-3.44)
140-159 (JNC stage 1 hypertension)	1501	7359	113	2.08 (1.13-3.80)
≥160 (JNC stage 2 and 3 hypertension)	1068	4066	85	3.14 (1.64-5.99)
Total	5569	22 610	311	

Table 3. Adjusted Relative Risk for Kidney Disease Progression by Urine Protein Excretion during Follow-up*

Urine Protein Excretion† g/d	Patients‡	Visits§	Events	Adjusted Relative Risk (95% CI)
<0.50	1022	9708	52	1.00
0.5-0.9	699	3340	35	0.96 (0.62-1.49)
1.0-1.4	616	2249	23	0.89 (0.54-1.47)
1.5-1.9	648	3752	26	1.21 (0.74-1.96)
2.0-2.9	629	2316	48	1.67 (1.09-2.54)
3.0-3.9	423	1280	38	2.28 (1.43-3.53)
4.0-4.9	320	737	29	3.43 (2.09-5.64)
5.0-5.9	194	476	20	3.41 (1.91-6.06)
≥6.0	234	792	40	4.77 (2.92-7.81)
Total	4685	22 610	311	

Jafar, T et al. *Ann Intern Med.* 2003;139:244-252.

Relative risk for CKD progression based on current level of SBP and current urine protein excretion




Jafar, T et al. *Ann Intern Med.* 2003;139:244-252.

Progression of CKD: The role of BP control, Proteinuria and ACE inhibition

- Conclusions of the study:
 - SBP predicts CKD progression better than DBP
 - Proteinuria is a strong predictor of progression
 - The risk of CKD progression depends on both:
 - Level of current SBP and
 - Level of current protein excretion
 - In patients with <1gm/d of proteinuria, the goal BP of <130/80 appears appropriate
 - In patients with >1gm/d of proteinuria, SBP levels between 110-129 may be more appropriate


Jafar, T et al. *Ann Intern Med.* 2003;139:244-252.

[Back to our patient...]



- Degree of proteinuria should be assessed using a spot urine protein to creatinine ratio
- GFR should be estimated using the MDRD equation
- ACE inhibitor therapy should be initiated barring contraindications
- If proteinuria is $>1\text{gm/d}$, the goal SBP for this patient should be reduced to 110-129.

[Back to our patient...]



- Combination therapy (ARB + ACEI) should be considered, particularly if proteinuria or BP do not respond adequately
- Risk factor modification and treatment of Cardiovascular disease are essential

[Selected References]



- Jafar, T et al. Progression of Chronic Kidney Disease: The role of Blood Pressure Control, Proteinuria and Angiotensin-Converting Enzyme Inhibition. *Ann Intern Med.* 2003;139:244-252.
- Levey AS et al. A More Accurate Method to Estimate GFR from Serum Creatinine: A New Prediction Equation. *Ann Intern Med.* 1999;130:461-470
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- Nakao N. et al. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet* 2003; 361: 117-24.
- National Kidney Foundation K/DOQI Clinical Practice Guidelines for CKD: <http://www.kidney.org/professionals/doqi/kdoqi/toc.htm>
- Remuzzi G. et al. Chronic Renal Diseases: Renoprotective Benefits of Renin-Angiotensin System Inhibition. *Ann Intern Med.* 2002;136:604-615.