Medical Management of Chronic Kidney Disease

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Chronic Kidney Disease (CKD)
Definition

Evidence of structural or functional kidney abnormality (urinalysis, imaging study or histology) that persists for 3 months with or without decreased GFR

Or

Decreased GFR with or without structural damage to the kidney

CKD Disease Classification

Stages & Prevalence of CKD

Stage	Description	GFR mL/min/1.73 m²)	Prevalence* 2004	Prevalence* 2010
1	Kidney damage with normal or ↑ GFR	≥90	6,490	10,137
2	Mild ↓ GFR	60 - 89	5,830	9,067
3	Moderate ↓ GFR	30 - 59	8,100	13,058
4	Severe ↓ GFR	15 - 29	428	687
5	Kidney failure	<15 or dialysis	330	616

*n(1000s), numbers obtained from NKF 2003, Stage 3 & 4 growth rate is 7%, Stage 4 growth rate is 10% obtained from NKF 2003

- NKF projects ESRD patient numbers will double by 2010
- NKF estimates 20 million people in the US are at risk for developing CKD
- Medicare spends nearly $18 billion on Stage 5 per year
- The U.S. has one of the highest dialysis mortality rates of ~25%

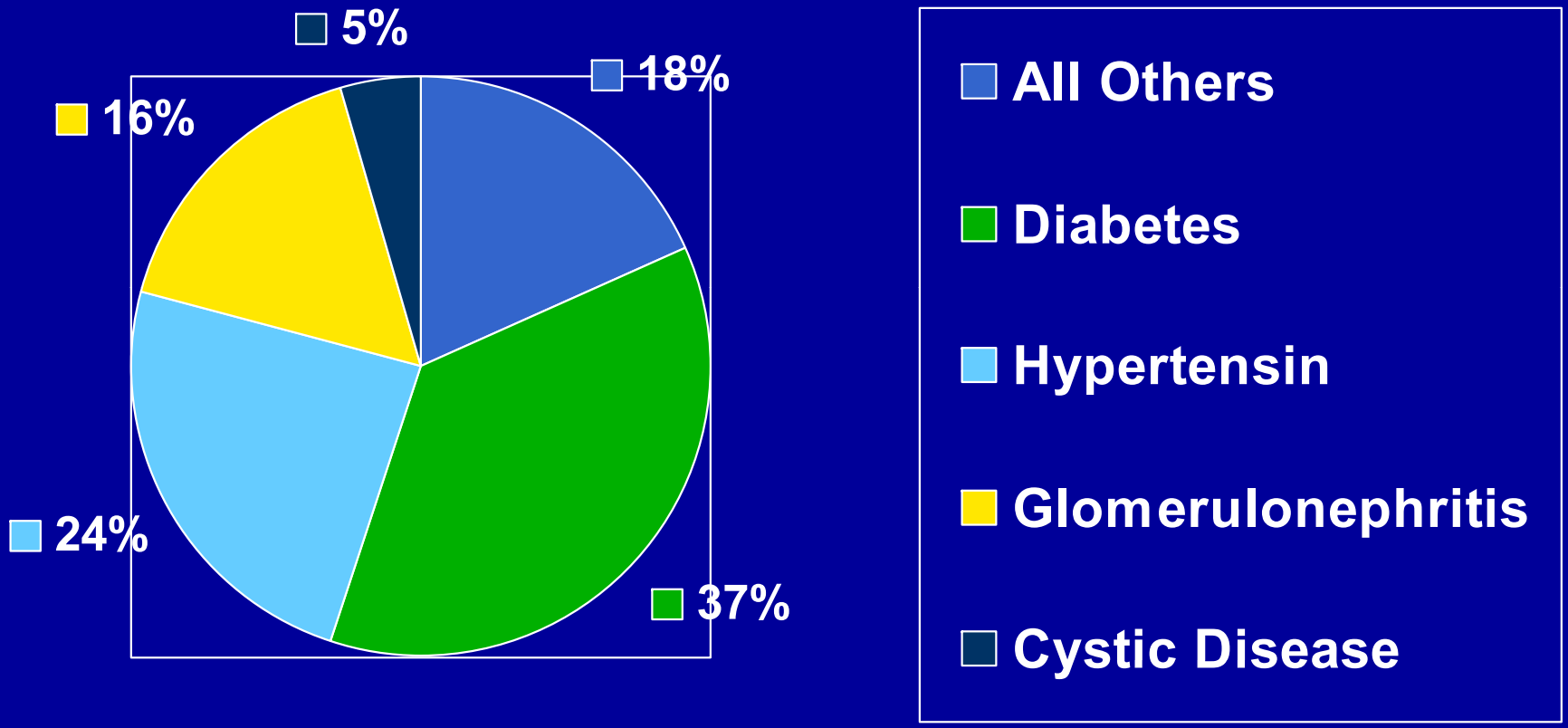
Progression of Kidney Disease

Initial injury to the kidney:

Diabetes Mellitus	Cystic Disease
Hypertension	Glomerulonephritis
Nephrolithiasis	Obstructive uropathy

- Progression in CKD is largely due to secondary factors sometimes unrelated to activity of disease.
- Variable progression to ESRD.

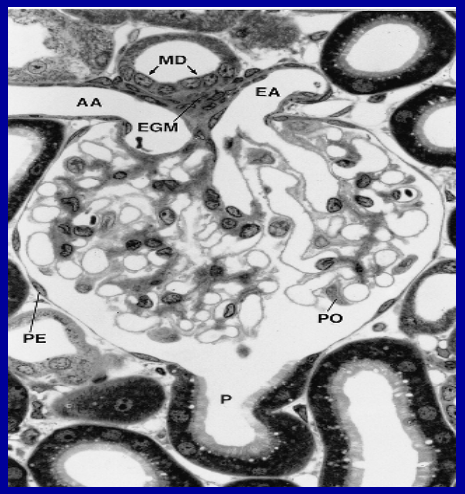
Diseases leading to ESRD



US 2004: 472,099 patients were receiving treatment for ESRD according to the US Renal Data System.

USRDS 2006 Annual Report

Factors Contributing to Progression of CKD



Intraglomerular hypertension

Glomerular hypertrophy

Stage 1

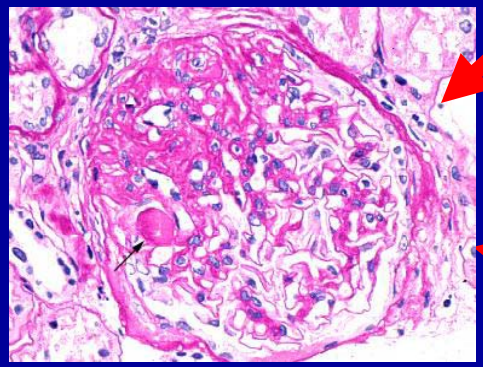
Adaptive Hyperfiltration

Tubulointerstitial Disease

Metabolic Acidosis

Hyperlipidemia

Stage 2

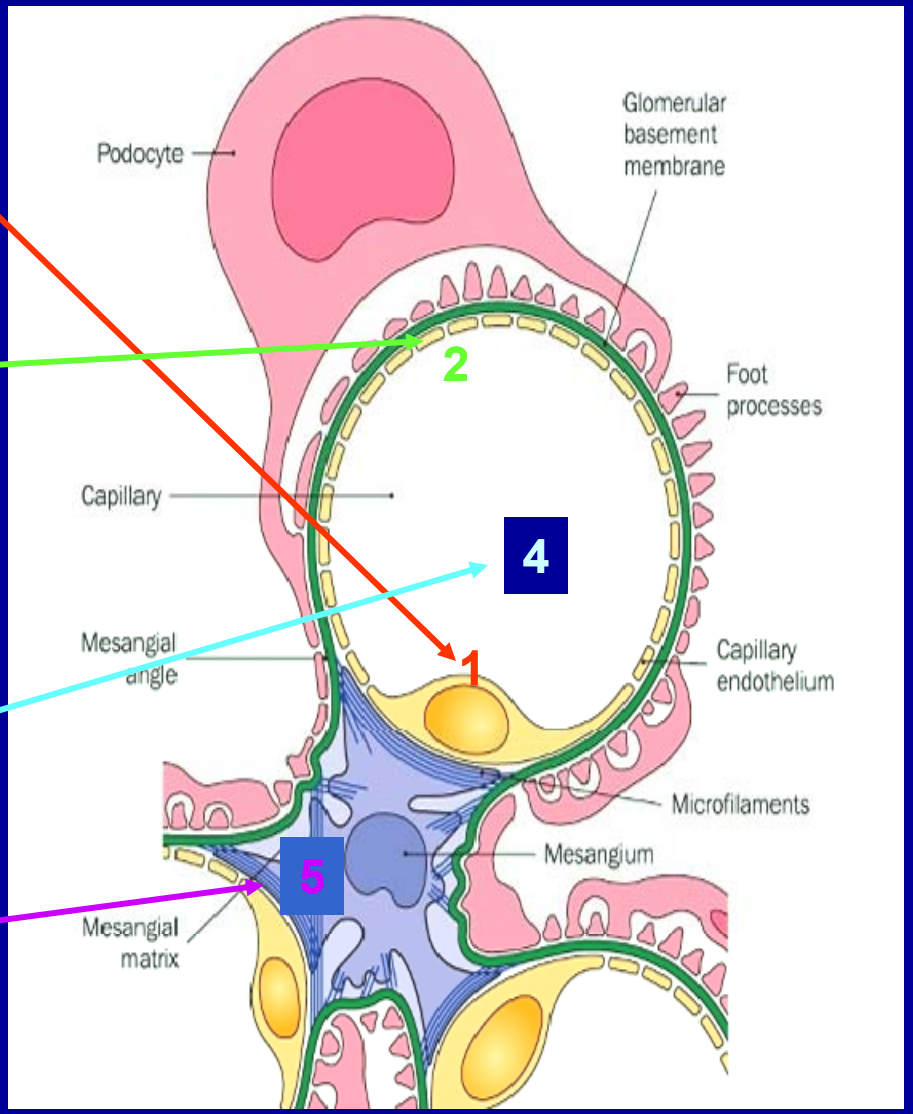


Glomerulosclerosis

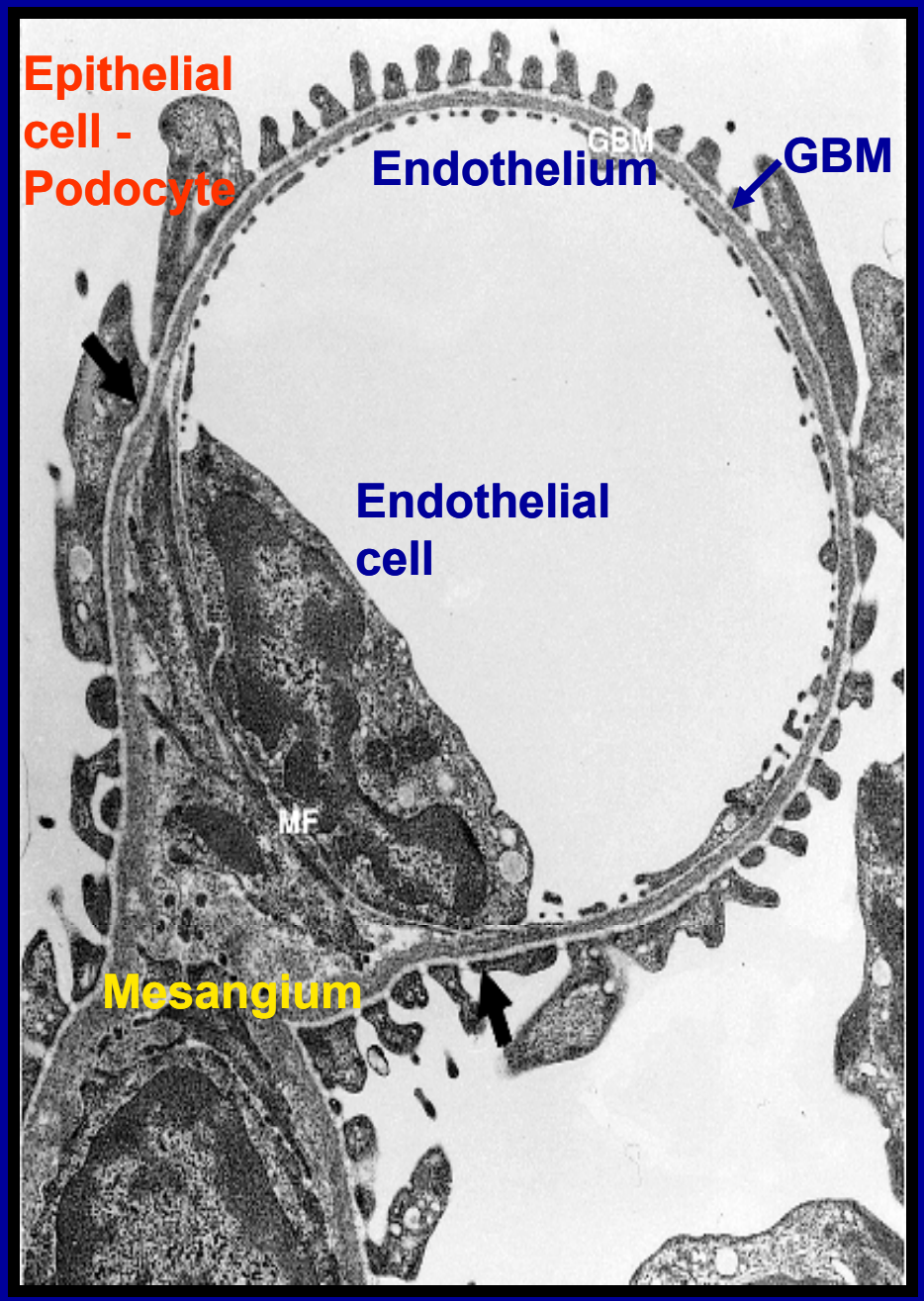
Secondary Focal Segmental Glomerulosclerosis: histologic manifestation of hemodinamically mediated renal injury

Glomerular hypertension and hypertrophy induce glomerular injury

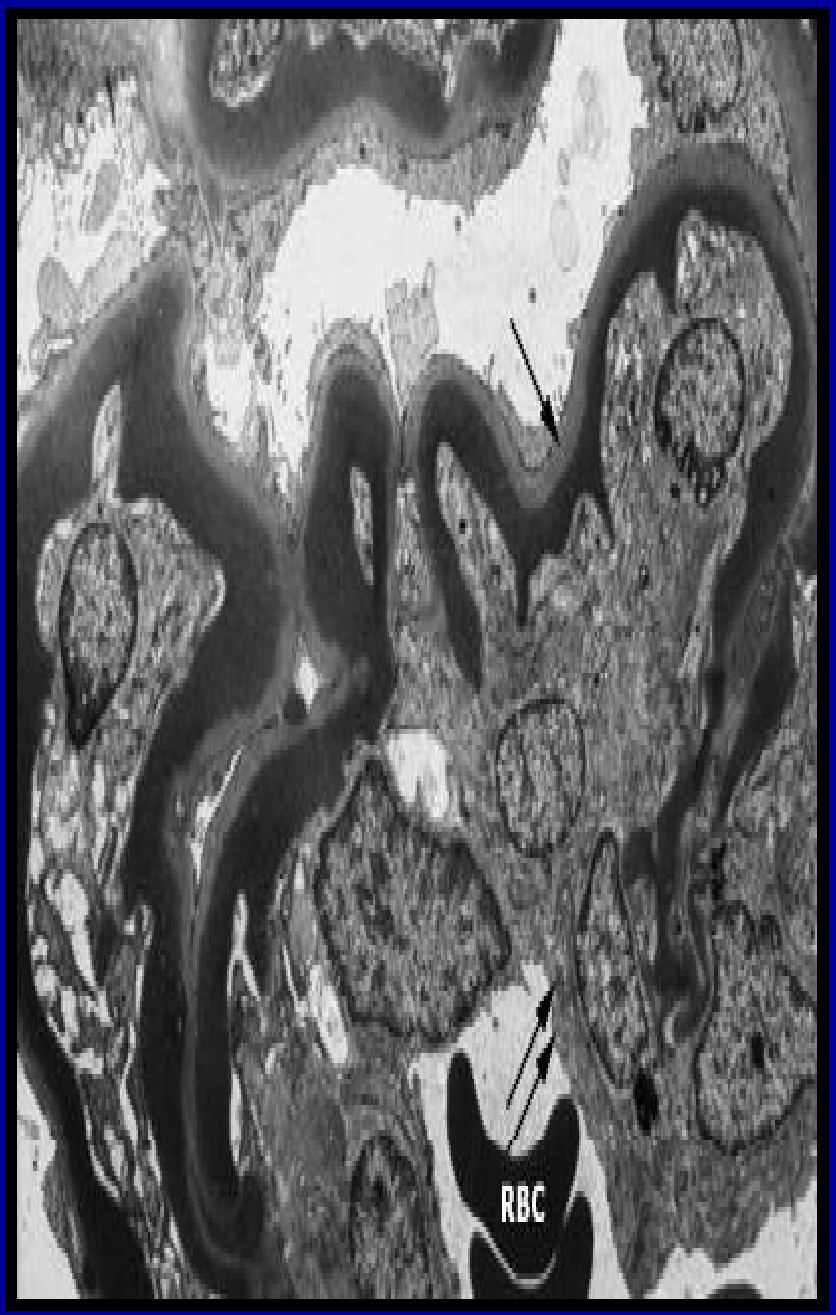
1. Direct endothelial cell damage
2. Detachment of glomerular epithelial cells from glomerular capillary wall.
3. Deposit of large molecules Ig or complements in denuded areas
4. Narrowing of capillary lumen
5. Mesangial cells increase cytokine production



NORMAL



INJURY



Factors Contributing to Progression of CKD

Lesson learned from MDRD:

Glomerular hypertension
Greater Proteinuria
Higher Blood Pressure
Black Race
Lower serum HDL
Lower levels of serum transferrin

Proteinuria and CKD Progression

- Mesangial toxicity
- Tubular Overload and hyperplasia
- Toxicity from filters compounds
- Induction of pro inflammatory cytokines
- Podocyte apoptosis may worsen proteinuria.

Progression of renal disease increases with increasing urine protein excretion

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

Urine Protein Excretion†	Patients‡	Visits§	Events	Adjusted Relative Risk (95% CI)‖
g/d	←	n	→	
<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	548	1712	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	2.25 (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	

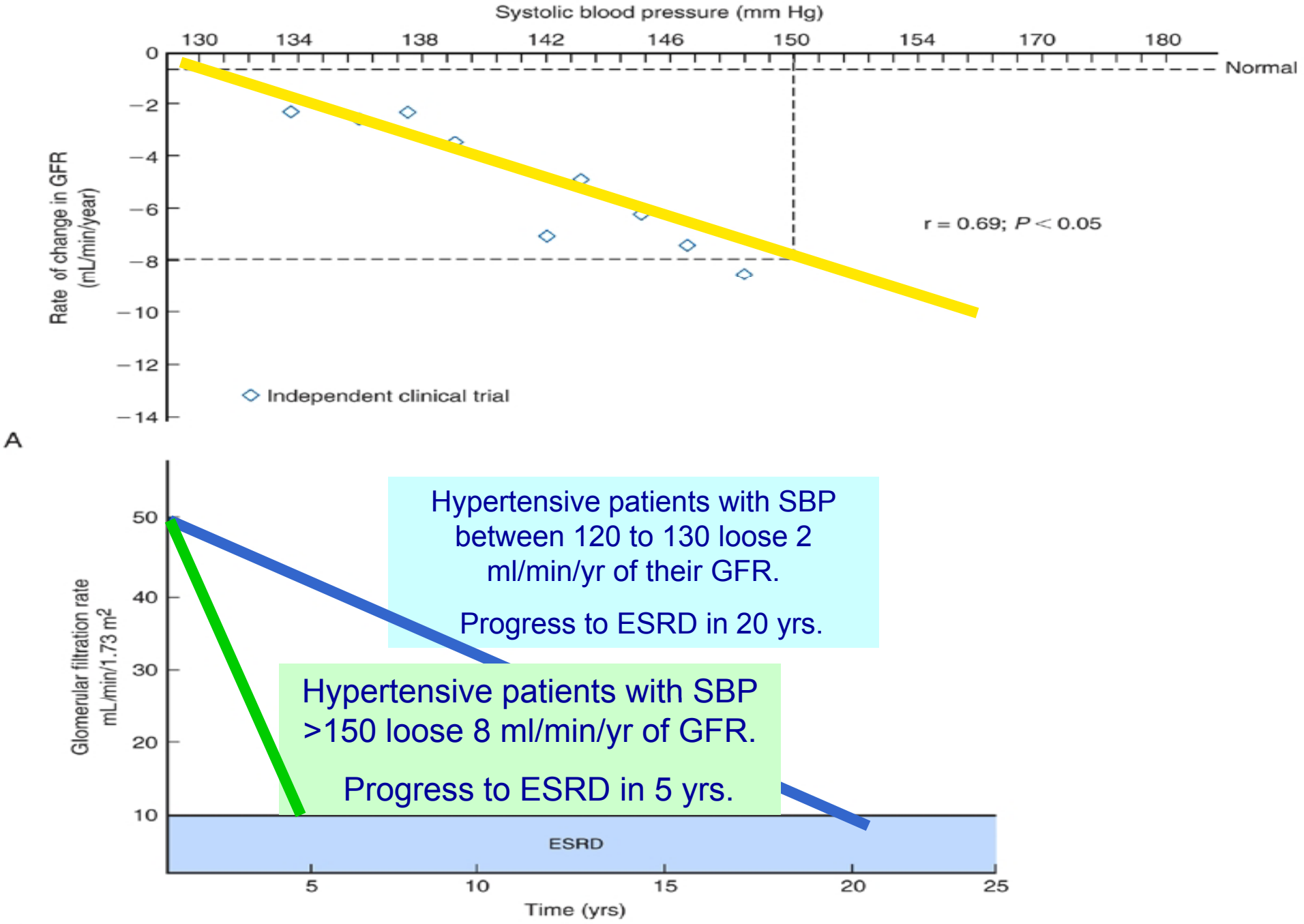
AIPRD Study Group Annals of Internal Medicine 2003; 139: 244-252

Risk for progression of kidney disease increases with increasing systolic BP

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

Systolic Blood Pressure†	Patients‡	Visits§	Events	Adjusted Relative Risk (95% CI)‖
mm Hg	←	*n*	→	
<110	253	947	10	2.48 (1.07–5.77)
110–119	548	1976	12	1.00
120–129 (JNC normal)	959	3746	32	1.23 (0.63–2.40)
130–139 (JNC high-normal)	1220	4506	59	1.83 (0.97–3.44)
140–159 (JNC stage 1 hypertension)	1501	7369	113	2.08 (1.13–3.86)
≥160 (JNC stage 2 and 3 hypertension)	1088	4066	85	3.14 (1.64–5.99)
Total	5569	22 610	311	

AIPRD Study Group Annals of Internal Medicine 2003; 139: 244-252



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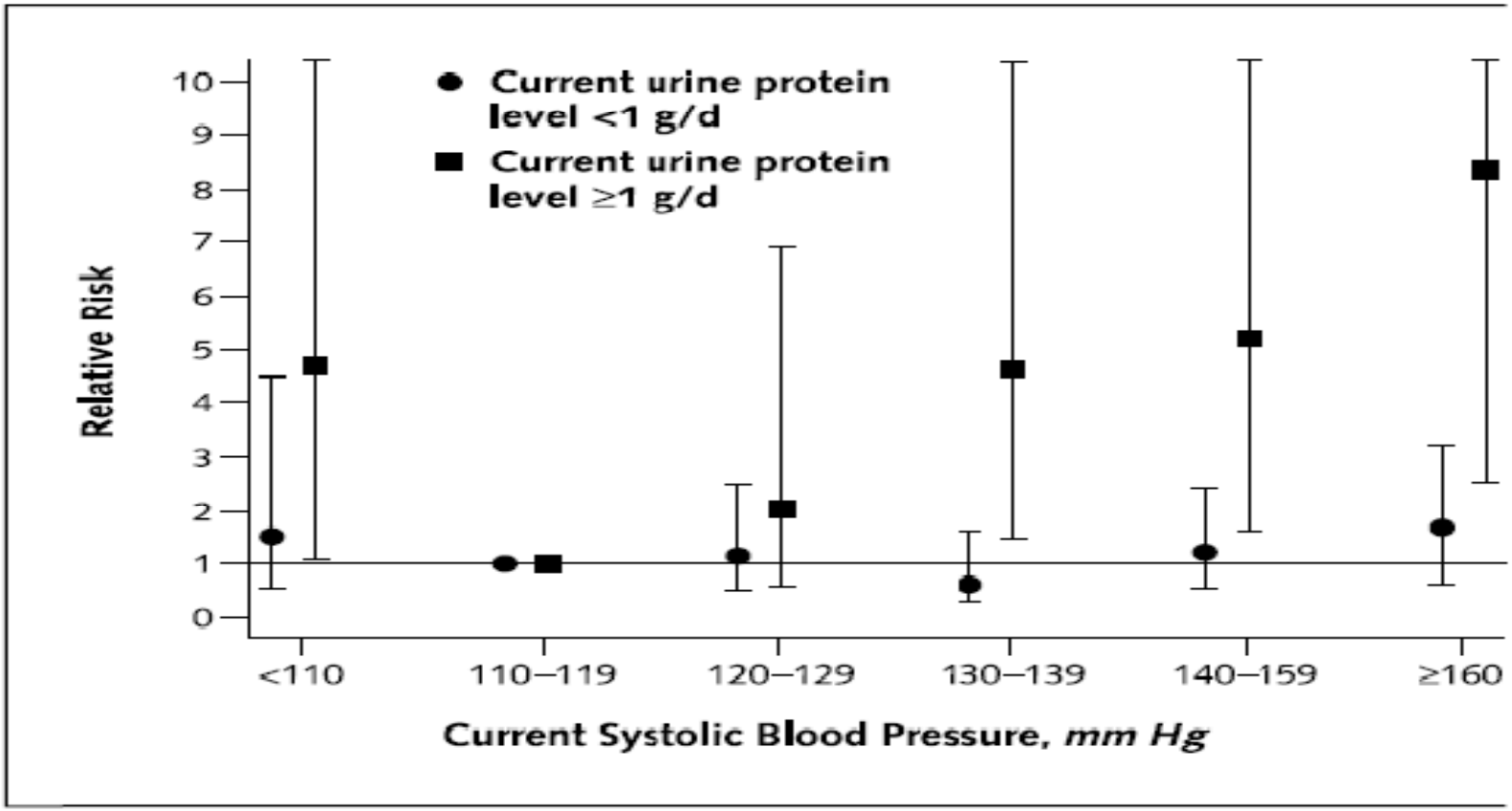
Patients with HBP and proteinuria have higher risk of renal disease progression

Figure. **Relative risk for kidney disease progression based on current level of systolic blood pressure and current urine protein excretion.**



AIPRD Study Group Annals of Internal Medicine 2003; 139: 244-252

Other factors contributing to progression of CKD

Angiotensin II:	Generate fibrosis through stimulus of TGFβ and epidermal growth factor.
Phosphate retention:	Mesangial cell proliferation after LDL receptors in mesangial cells activated. Increases Macrophage chemo-attractant factors, ROS.
Aldosterone:	Mineralocorticoid stimulus leads to vascular remodeling and renal fibrosis.
Metabolic Acidosis:	Remaining nephrons excrete more acid. Increased ammonia generation activates complements leading to tubulointerstitial damage.

Management of Chronic Kidney Disease

I. Treatment of reversible causes of renal dysfunction

II. Preventing or slowing progression of disease

III. Treatment of complications of renal dysfunction

IV. Identification and adequate preparation of the patient in whom renal replacement therapy (RRT) will be required

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Reversible causes of renal dysfunction

- **Renal hypoperfusion**
  - Hypovolemia
  - Hypotension
  - Drugs lowering GFR
    - NSAID's
    - ACE

- **Nephrotoxic drugs**
  - Aminoglycosides
  - NSAID's
  - Contrast material

- **Urinary Tract obstruction**

- Cimetidine, and trimethoprim interfere with creatinine secretion.
- Cefoxitin and flucytosine interfere with assay used to measure serum creatinine.

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Slowing the rate of progression

- Blood Pressure control slows progression of kidney disease particularly in patients with significant proteinuria.
- Evidence in diabetic nephropathy and non-diabetic nephropathy that administration of ACE-I or ARB slows the progression of CKD with the greatest benefit in patients with higher degrees of proteinuria
- The benefit is to be greatest if begun before a great deal of scarring has begun.
- Combination therapy with an ACE-I and ARB gives additive antiproteinuric effect.

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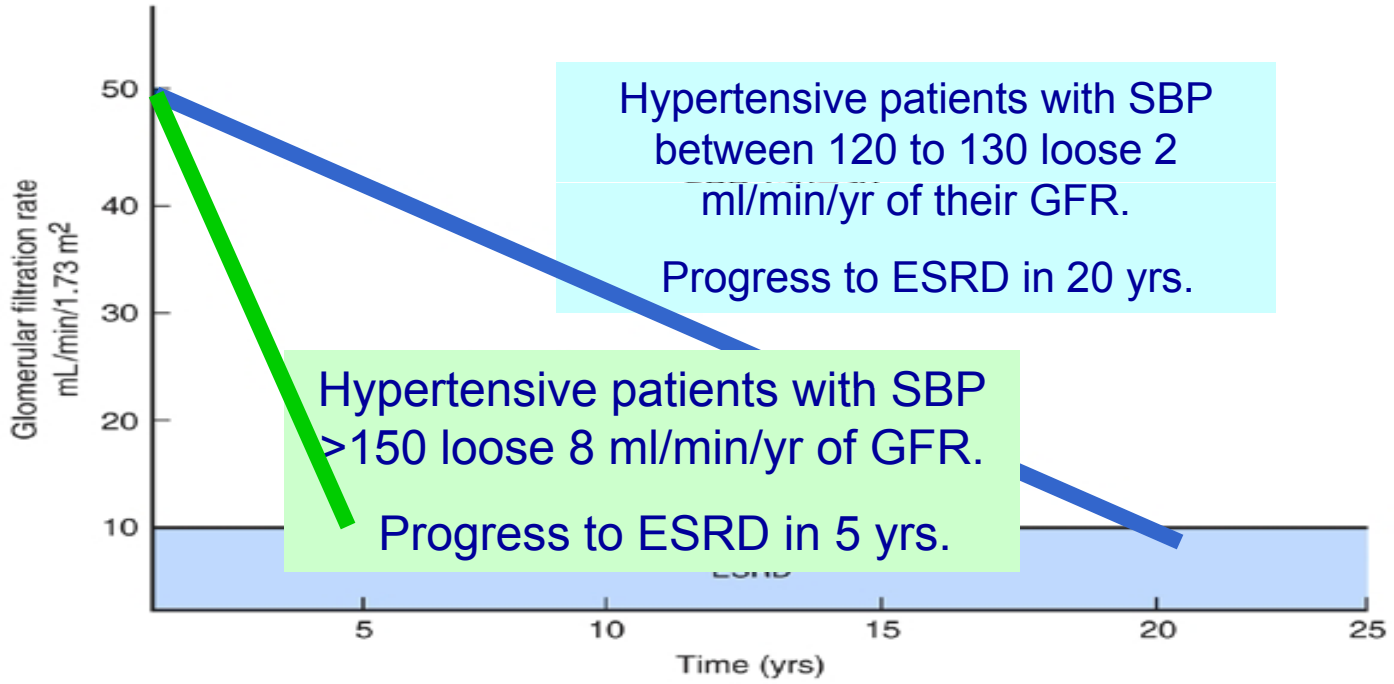
Blood Pressure control slows progression of kidney disease



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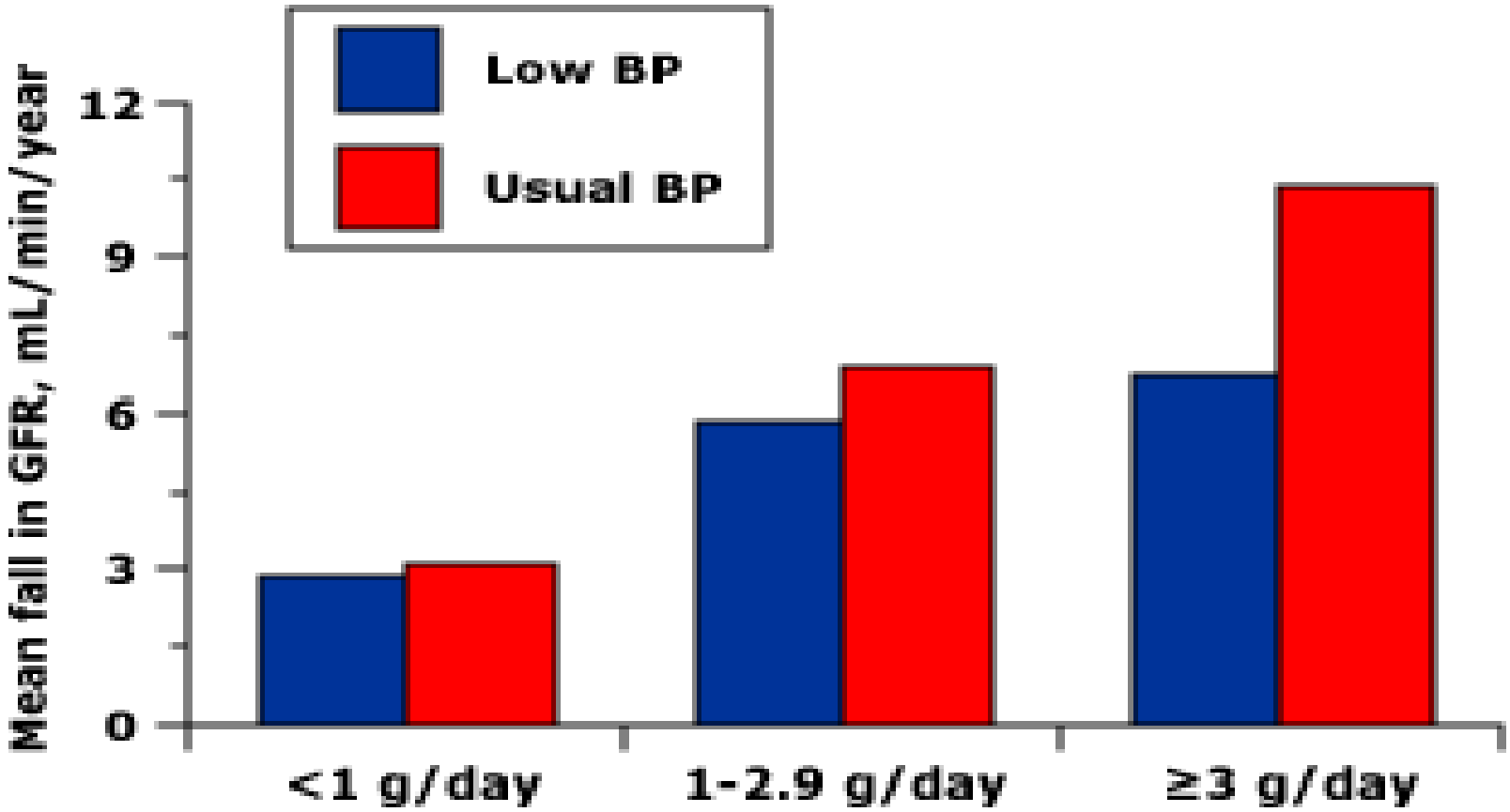
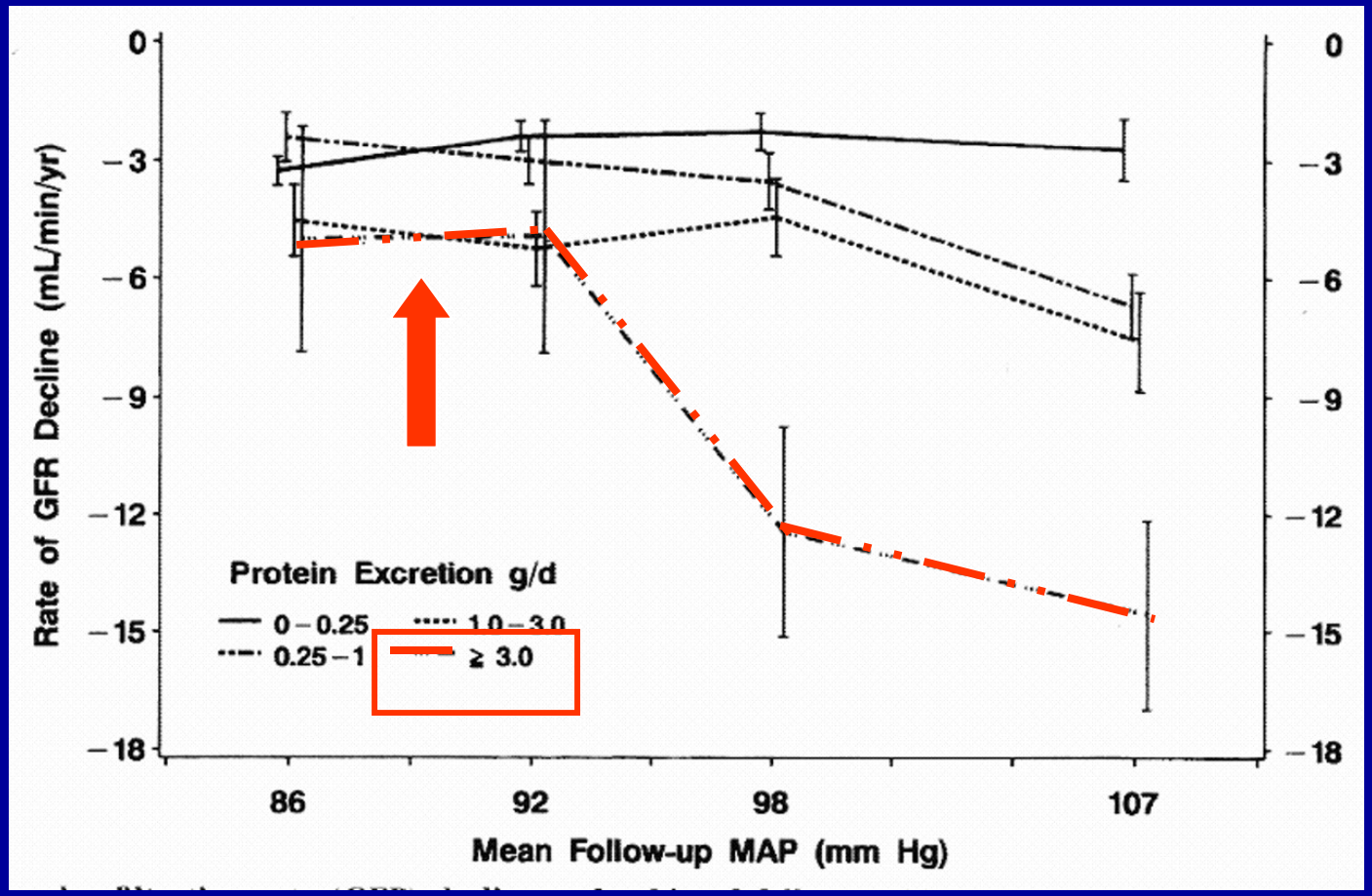
MDRD: Aggressive BP control preserves renal function in proteinuric patients



MDRD: Klahr, S, Levey, AS, Beck, GJ, et al, N Engl J Med 1994; 330:877

MDRD: Tight BP control in patients with GFR 25-55 ml/min and non diabetic proteinuria (> 3g) led to decrease in GFR decline

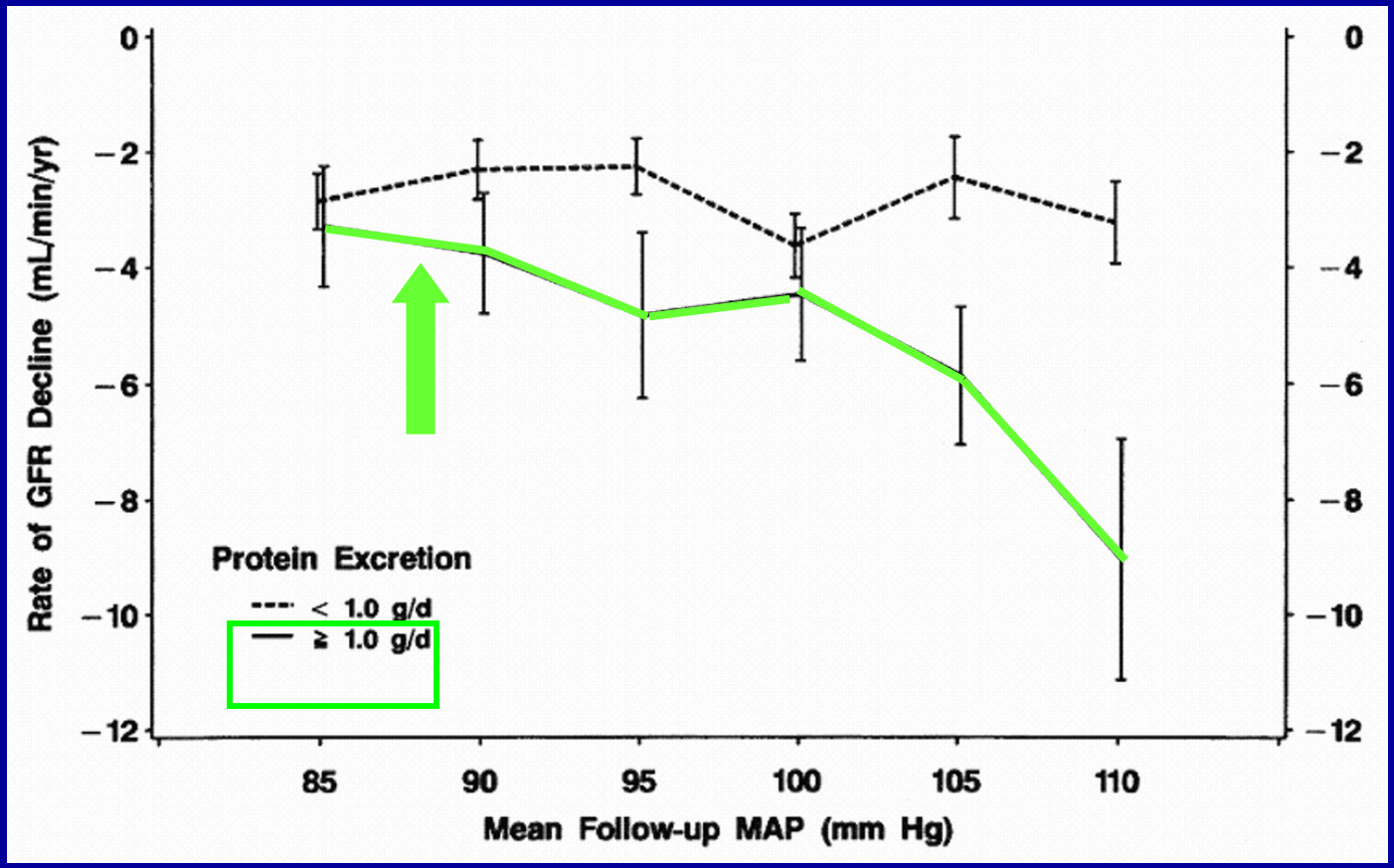


MDRD: Peterson, J. C. et. al. Ann Intern Med 1995;123:754-762

Group A: Patients with GFR 25-55 ml/min

Annals of Internal Medicine

MDRD: Tight BP control in patients with GFR 13-24 ml/min and non diabetic proteinuria (> 1g) led to less decline in GFR



Peterson, J. C. et. al. Ann Intern Med 1995;123:754-762

Annals of Internal Medicine

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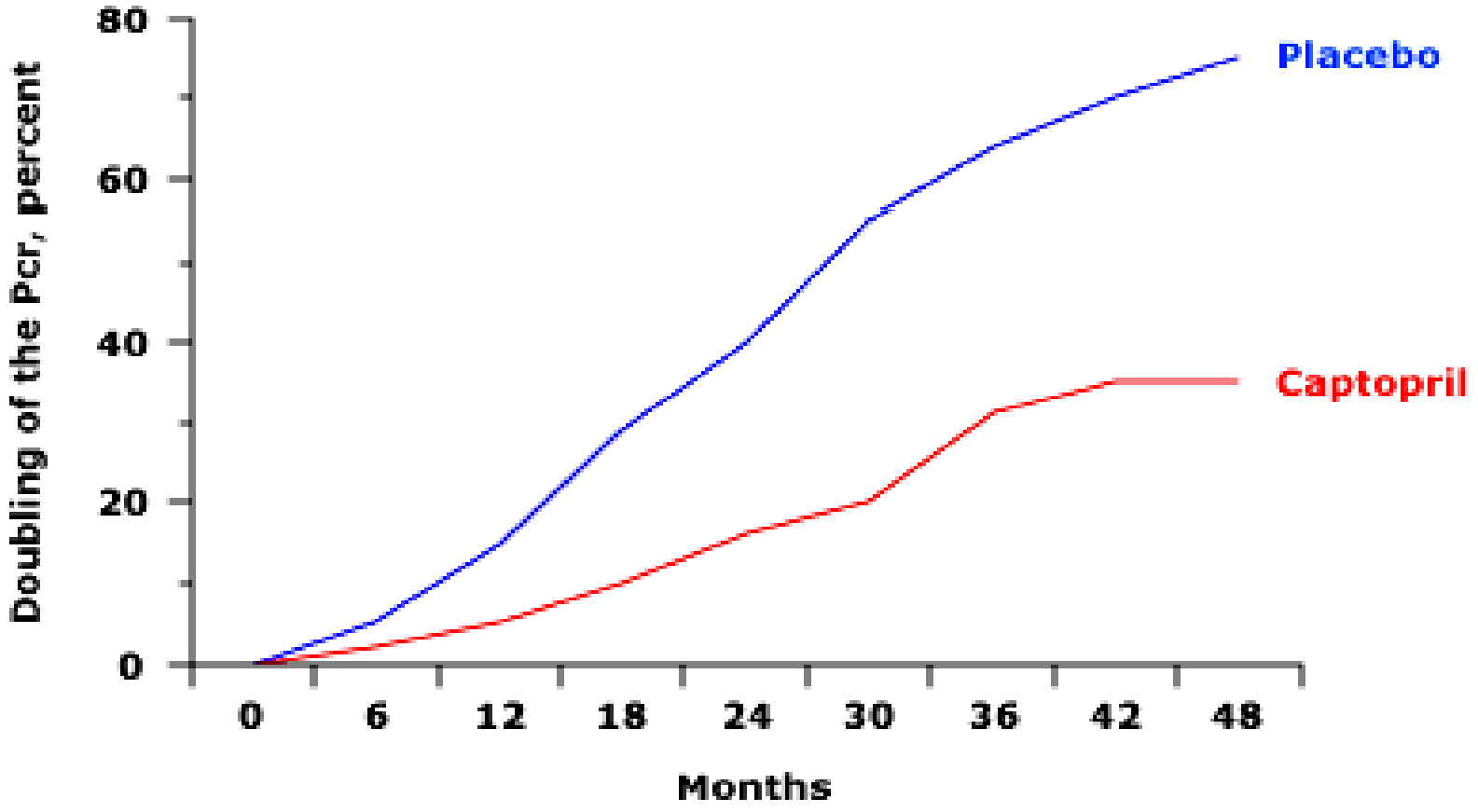
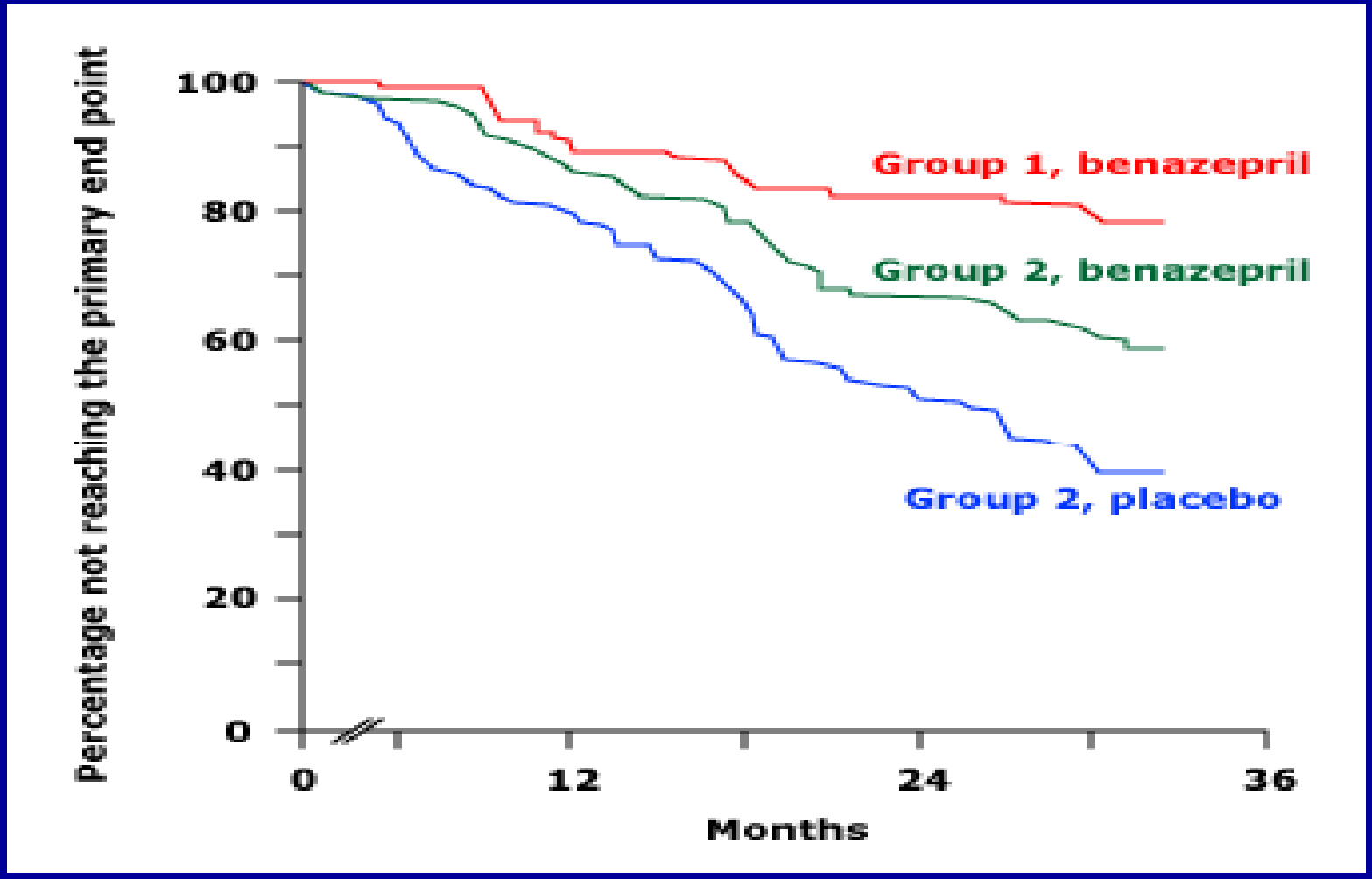
- Combination therapy with an ACE-I and ARB gives additive antiproteinuric effect.

ACE-I reduces likelihood of doubling PCreat by 50% in proteinuric DM-I patients



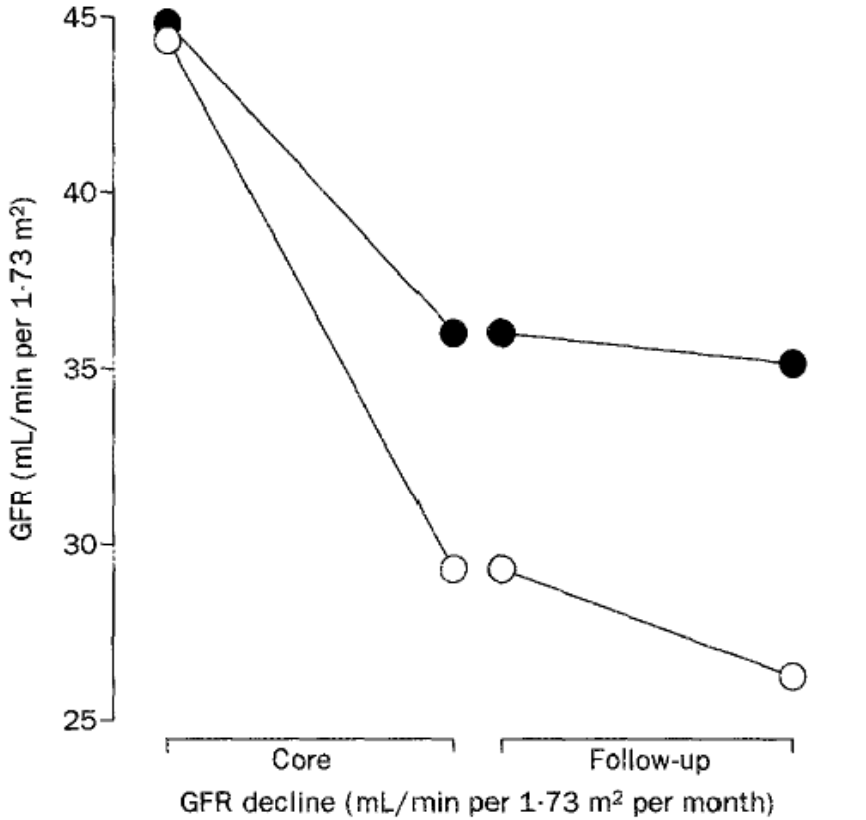
Lewis, EJ, Hunsicker, LG, Bain, RP, Rohde, RD, N Engl J Med 1993; 329:1456

Benazepril trial: ACE-I reduce risk for disease progression by 53%



Hou, FF, Xhang, Xun, Zhang, GG, et al. Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency. N Engl J Med 2006; 354:131

REIN: GFR stabilized in continued ramipril use
REIN: Greater kidney survival in long term ACE use



Group			p
● Continued ramipril	−0·44 (0·54)	−0·10 (0·50)	0·017
○ Switched to ramipril	−0·81 (1·12)	−0·14 (0·87)	0·017

Figure 2: **Mean GFR decline during the REIN core and follow-up study in patients continued on or switched to ramipril**

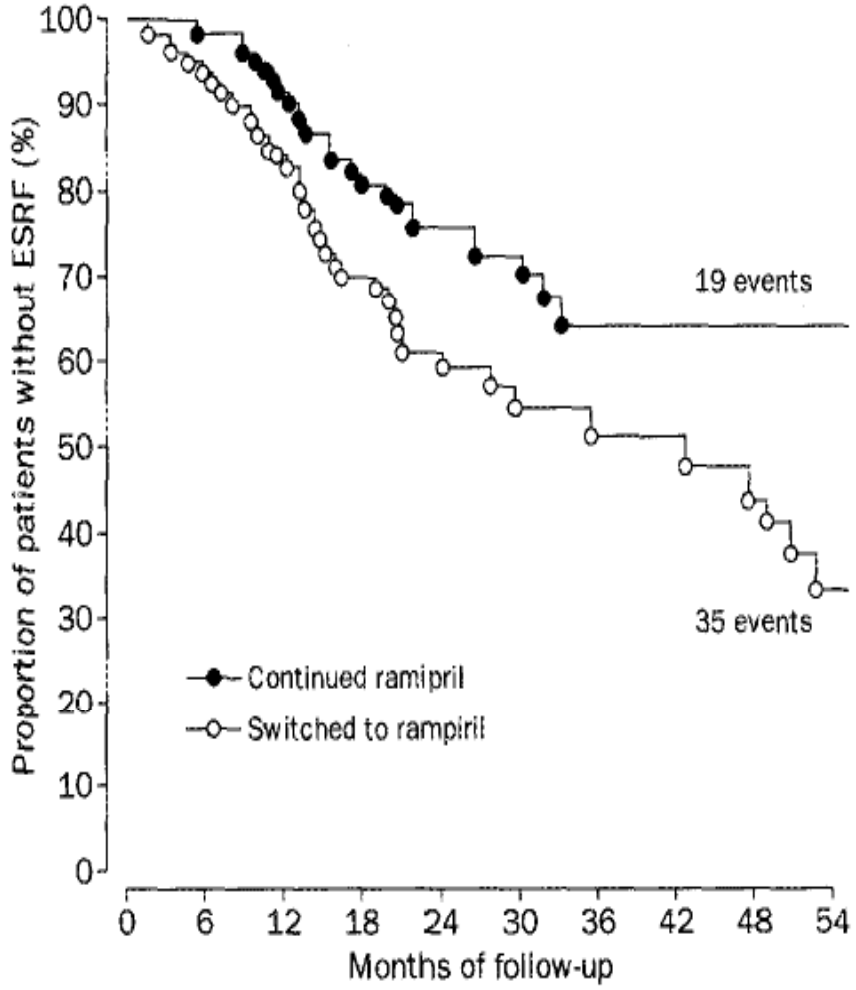


Figure 3: **Kidney survival in patients continued on or switched to ramipril during the whole (core and follow-up) study period**

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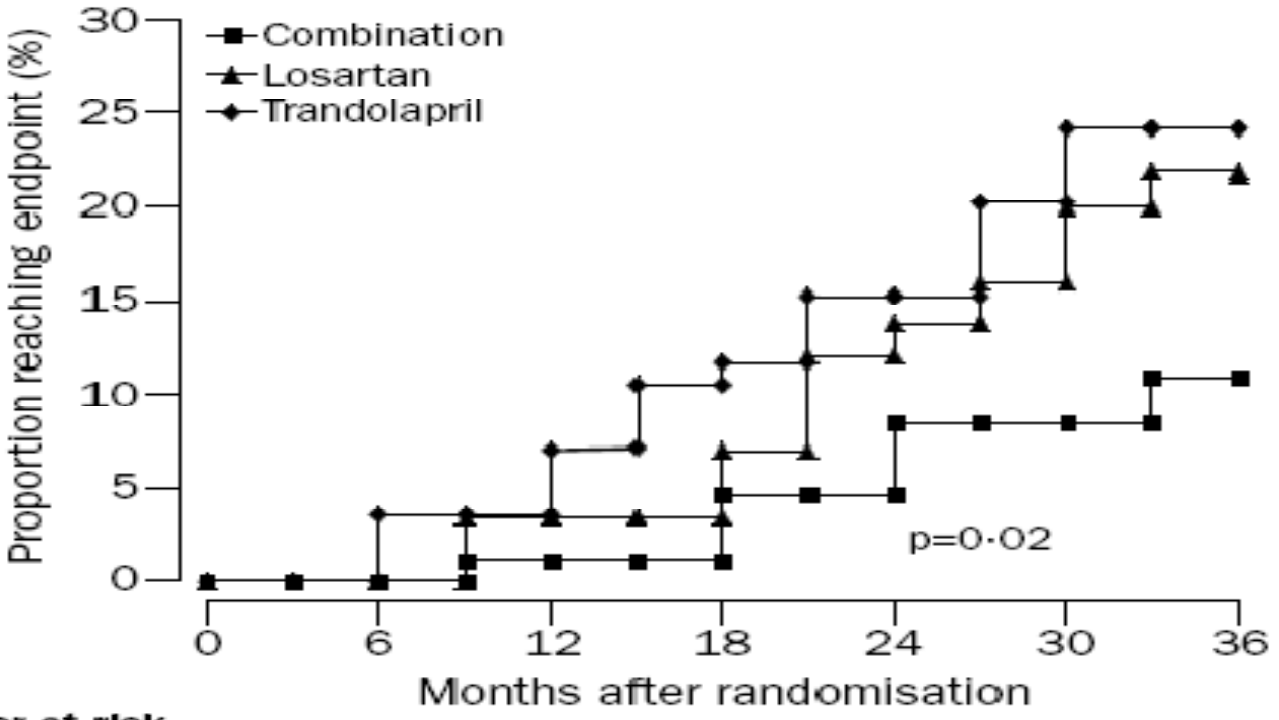
- Evidence in diabetic nephropathy and non-diabetic nephropathy that administration of ACE-I or ARB slows the progression of CKD with the greatest benefit in patients with higher degrees of proteinuria
- The benefit is to be greatest if begun before a great deal of scarring has begun.
- Combination therapy with an ACE-I and ARB gives additive antiproteinuric effect.

COOPERATE: Combined ACE and ARB decreases risk of kidney disease progression



Number at risk

Losartan	89	88	84	79	65	59	47
Trandolapril	86	85	83	75	72	63	58
Combination	88	87	86	83	76	73	67

Figure 2: **Proportion of patients reaching endpoint**

COOPERATE Lancet 2003; 361: 117-124

COOPERATE: There is an added benefit to dual blockade in decreasing proteinuria

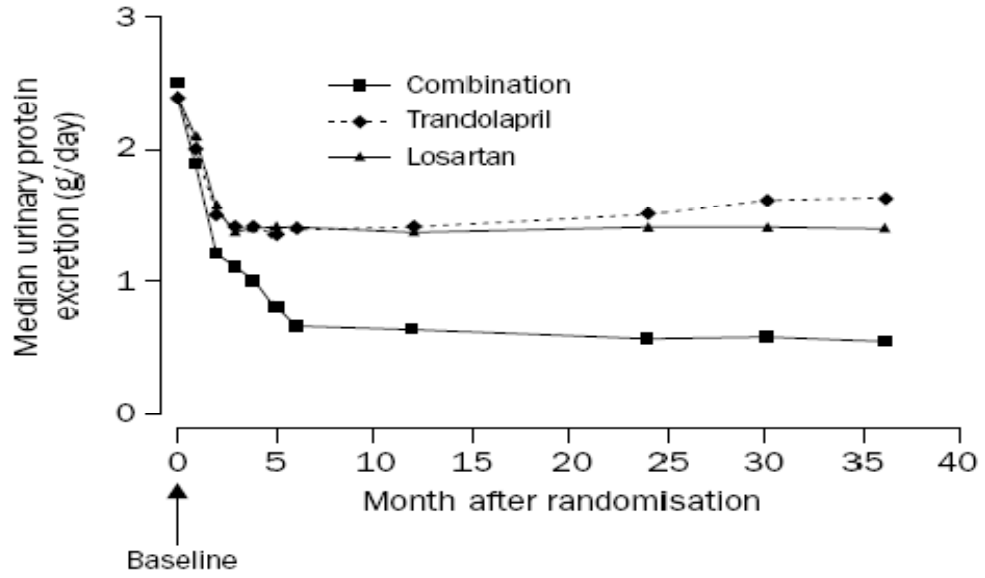


Figure 4: **Median urinary protein excretion by treatment group**

	Hazard ratio (95% CI)	p
Overall	0·34 (0·19–2·68)	0·031
Baseline daily urinary protein excretion rate (g/day)		
<1	0·69 (0·22–2·28)	0·049
1 to >3	0·33 (0·19–0·74)	0·029
⩾3	0·40 (0·21–0·84)	0·033

Table 3: **Effect of baseline daily urinary protein excretion rate on efficacy of combination treatment on combined primary endpoint**

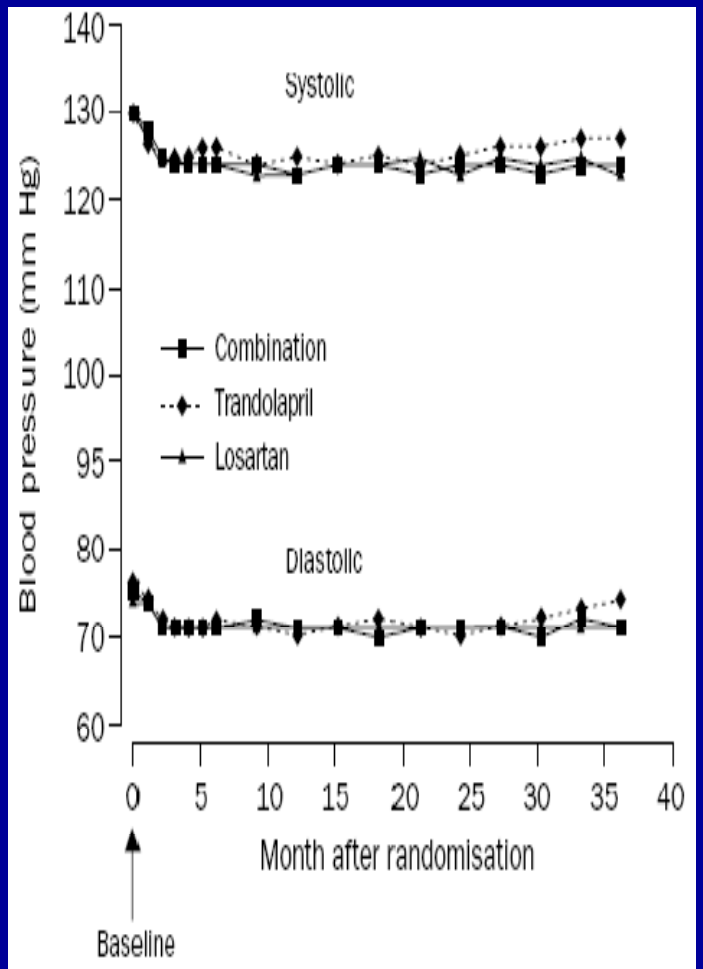
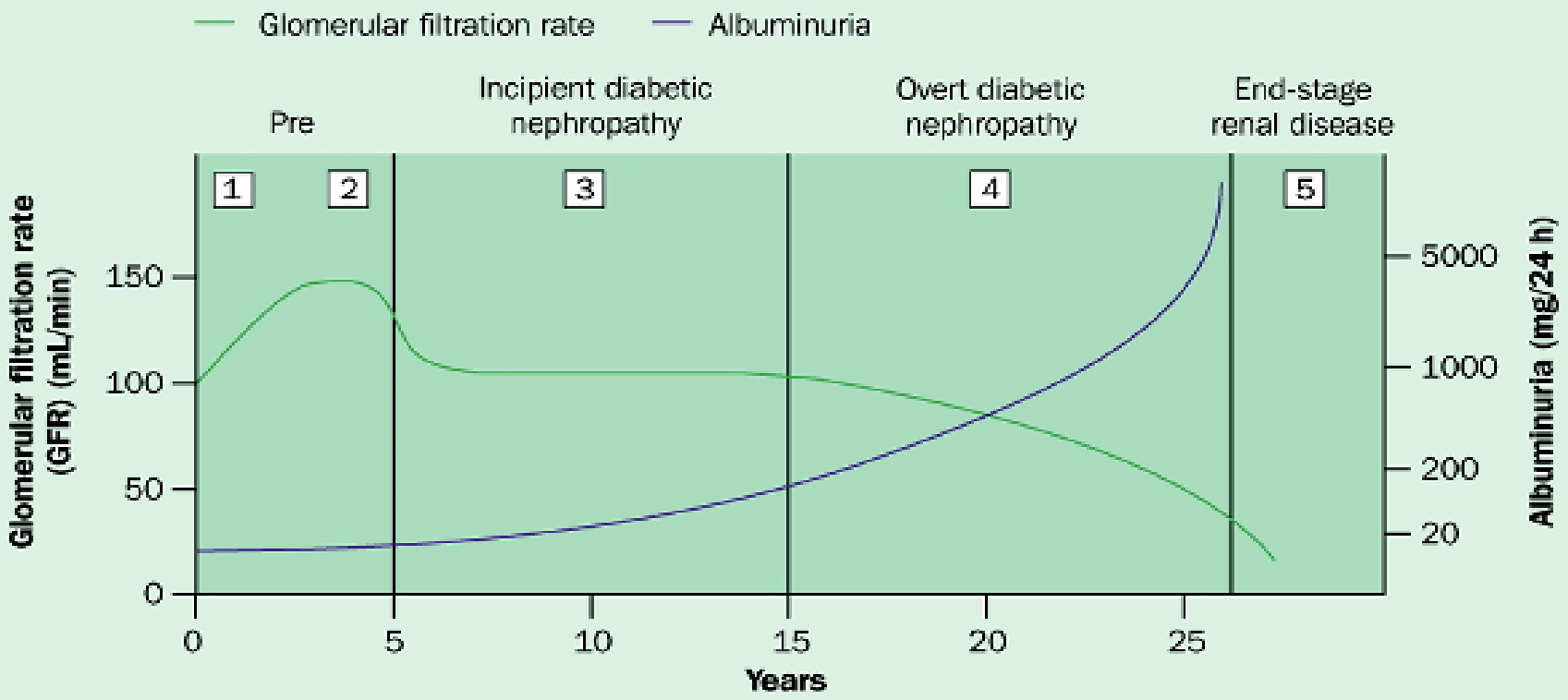


Figure 3: **Blood pressure by treatment group**

COOPERATE Lancet 2003; 361: 117-124

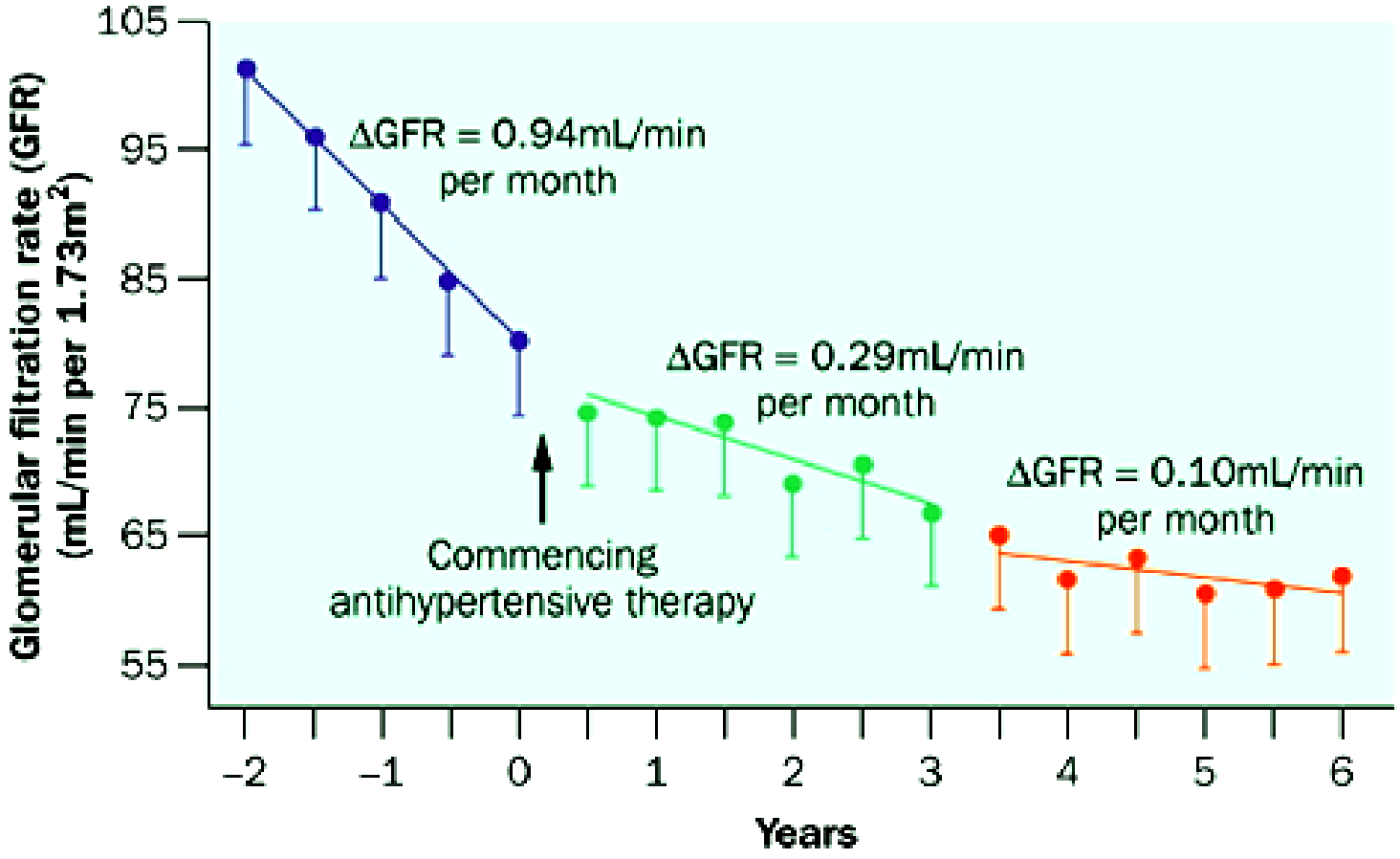
Slowing Progression in Diabetic Nephropathy

Natural history of type 1 diabetic nephropathy

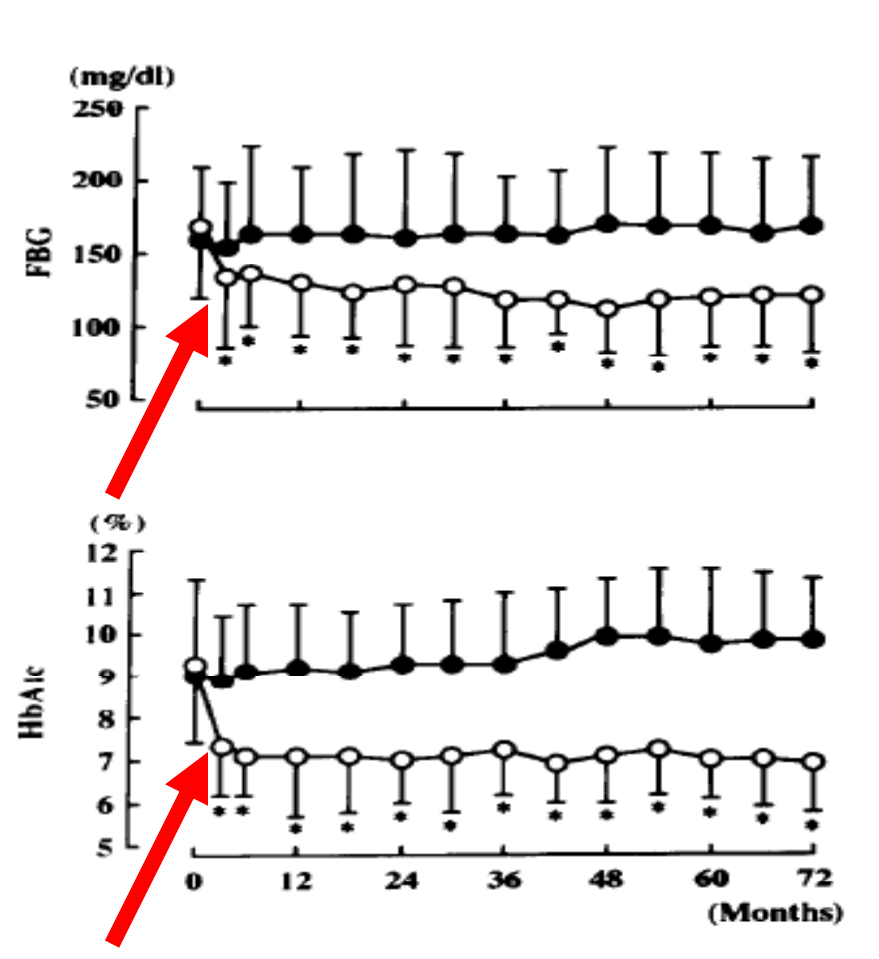


Stage	Pre	Incipient	Overt
Functional	GFR ↑ (25–50%)	Microalbuminuria, hypertension	Proteinuria, nephrotic syndrome, GFR ↓
Structural	Renal hypertrophy	Mesangial expansion, glomerular basement membrane thickening, arteriolar hyalinosis	Mesangial nodules (Kimmelstiel–Wilson lesions) Tubulointerstitial fibrosis

Control of blood pressure retards progression of type 1 diabetic nephropathy



Tight glycemic control with aggressive insulin therapy and effect on Diabetic Nephropathy: Kumamoto Study



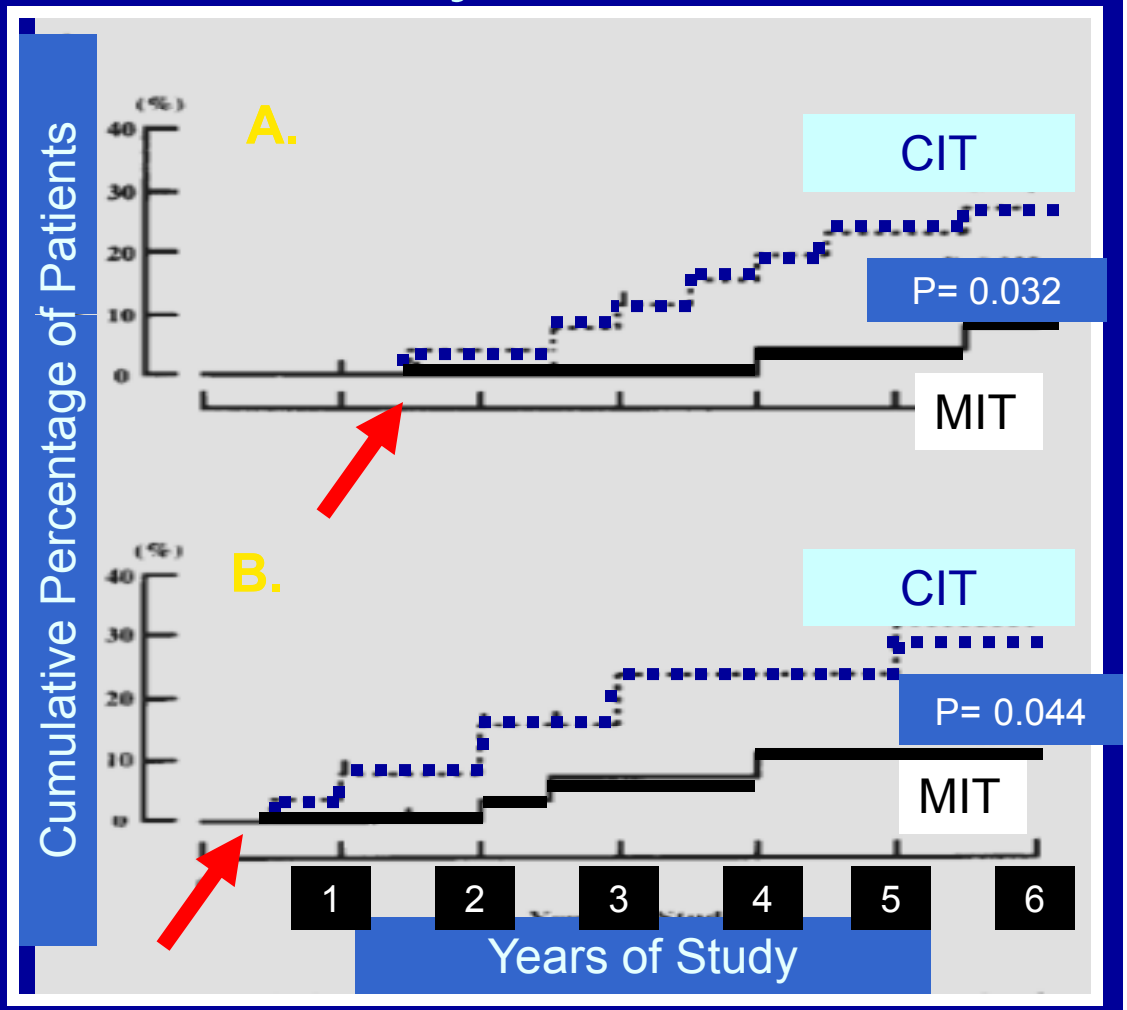
- Normoglycemia was obtained in the patients receiving intensive insulin therapy by the third month.
- This tight control was sustained throughout the remainder of the study period.

Y. Ohkubo et al. /Diabetes Research and Clinical Practice 28 (1995) 103-117

Tight glycemic control with aggressive insulin therapy and prevention of nephropathy: Kumamoto Study

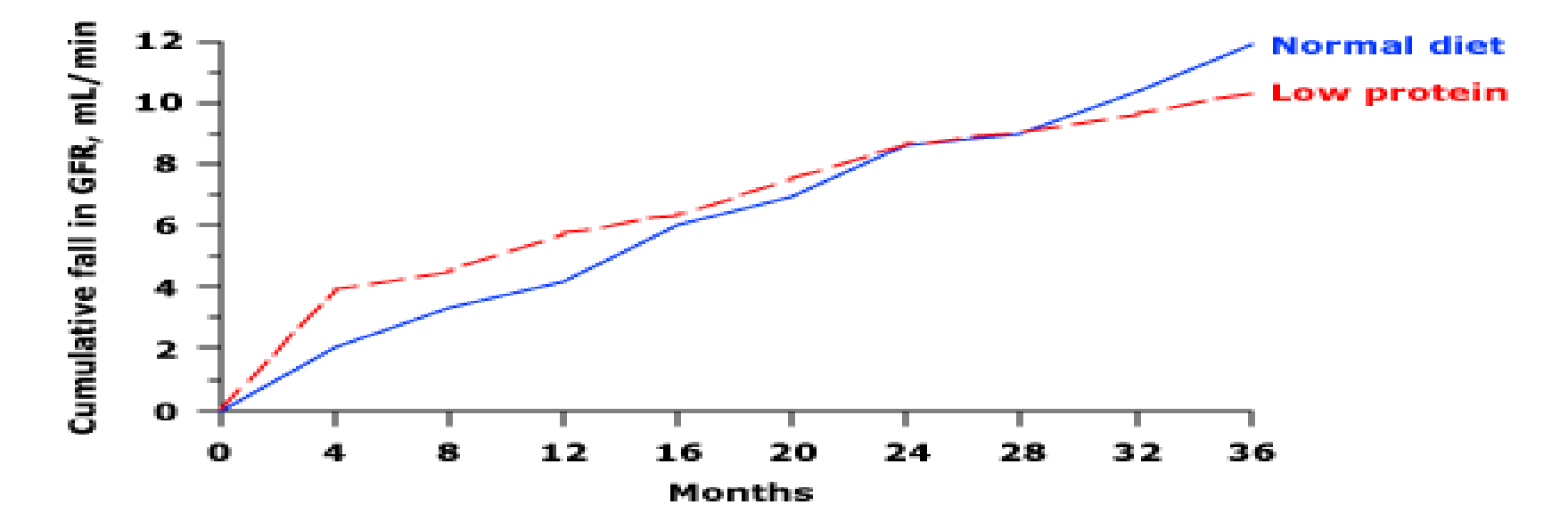
A. In patients without retinopathy and / or UAE <30 mg/24hrs the percentage of patients who developed nephropathy after 6 years was lower in the multiple insulin injection group.

B. In patients with simple retinopathy and / or microalbuminuria < 300 mg/24h the percentage of patients who developed nephropathy after 6 years was lower in the multiple insulin injection group.



Intensive glycemic control by multiple insulin injections reduced the average risk of worsening nephropathy by 70% during the entire study period

Other strategies to slow progression: Protein Restriction



- MDRD largest trial to evaluate protein restriction effect on disease progression.
- Randomized to 1.1 g/kg or 0.7 g/kg of protein per day.
- Little overall benefit with low protein diet.
  - Low protein: greater fall in GFR in first 4 mo, then slower progression

Recommendation: A reasonable regimen consists of rigorous blood pressure control and the intake of 0.8 to 1.0 g/kg of high biologic value protein per day.

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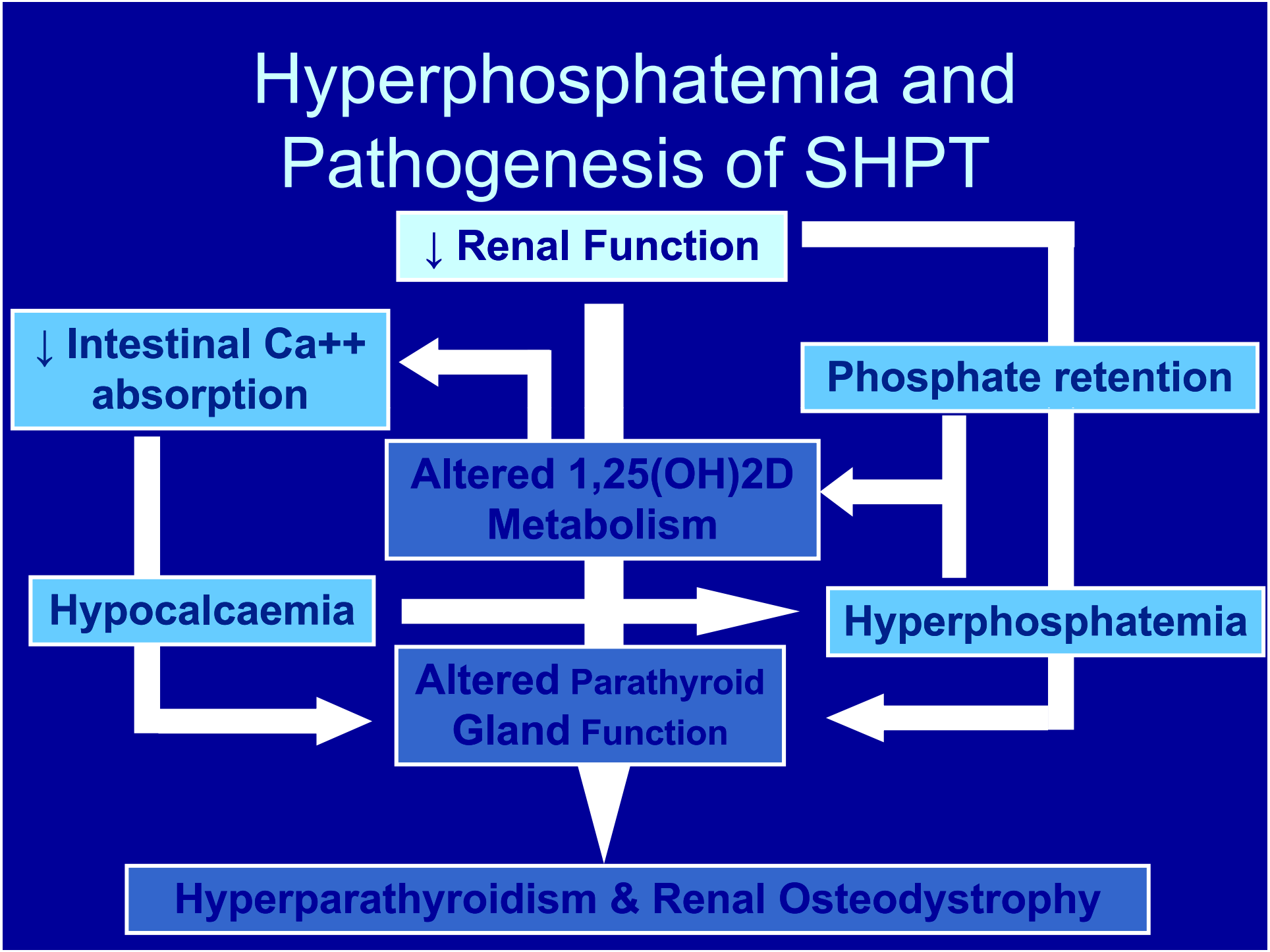
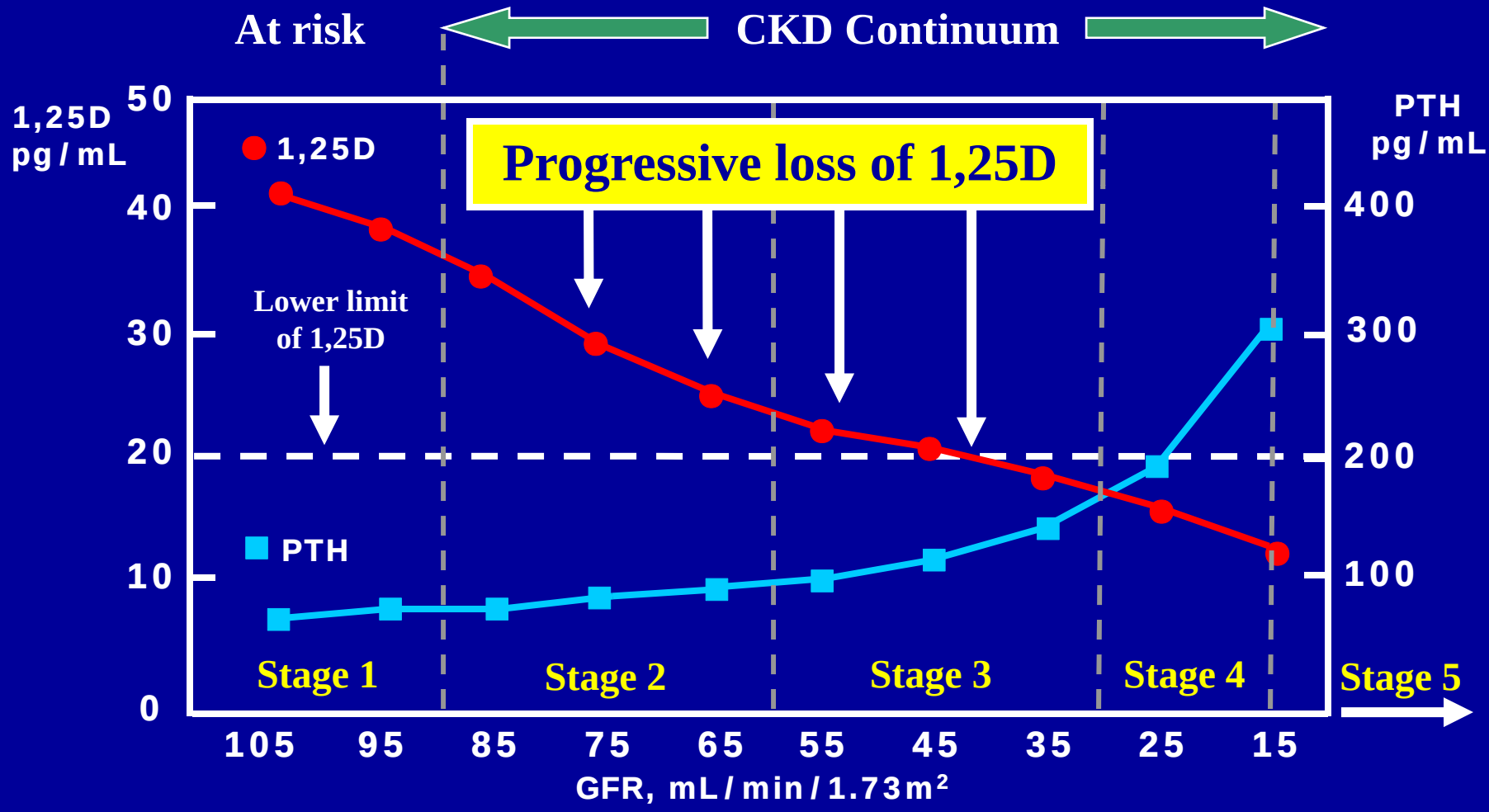
Volume Overload	Decreased ability to respond to rapid infusion of Na+ → overload. **Tx.** Na+ restriction and diuretic therapy
Hyperkalemia	Develops in oliguric patients, high K+ diet, increased tissue breakdown or hypoaldo. Could be due to ACE-I or ARB. **Tx.** low K+ diet and loop diuretic. Consider low dose Kayexalate if persists.
Metabolic Acidosis	Bone buffering of H+ can release Ca++ and PO4= from bone - worsens bone disease. Uremic acidosis can increase skeletal muscle breakdown and diminish albumin synthesis → lean body mass loss. **Tx.** Alkali therapy sodium bicarbonate 0.5-1meq/kg/d. Avoid sodium citrate

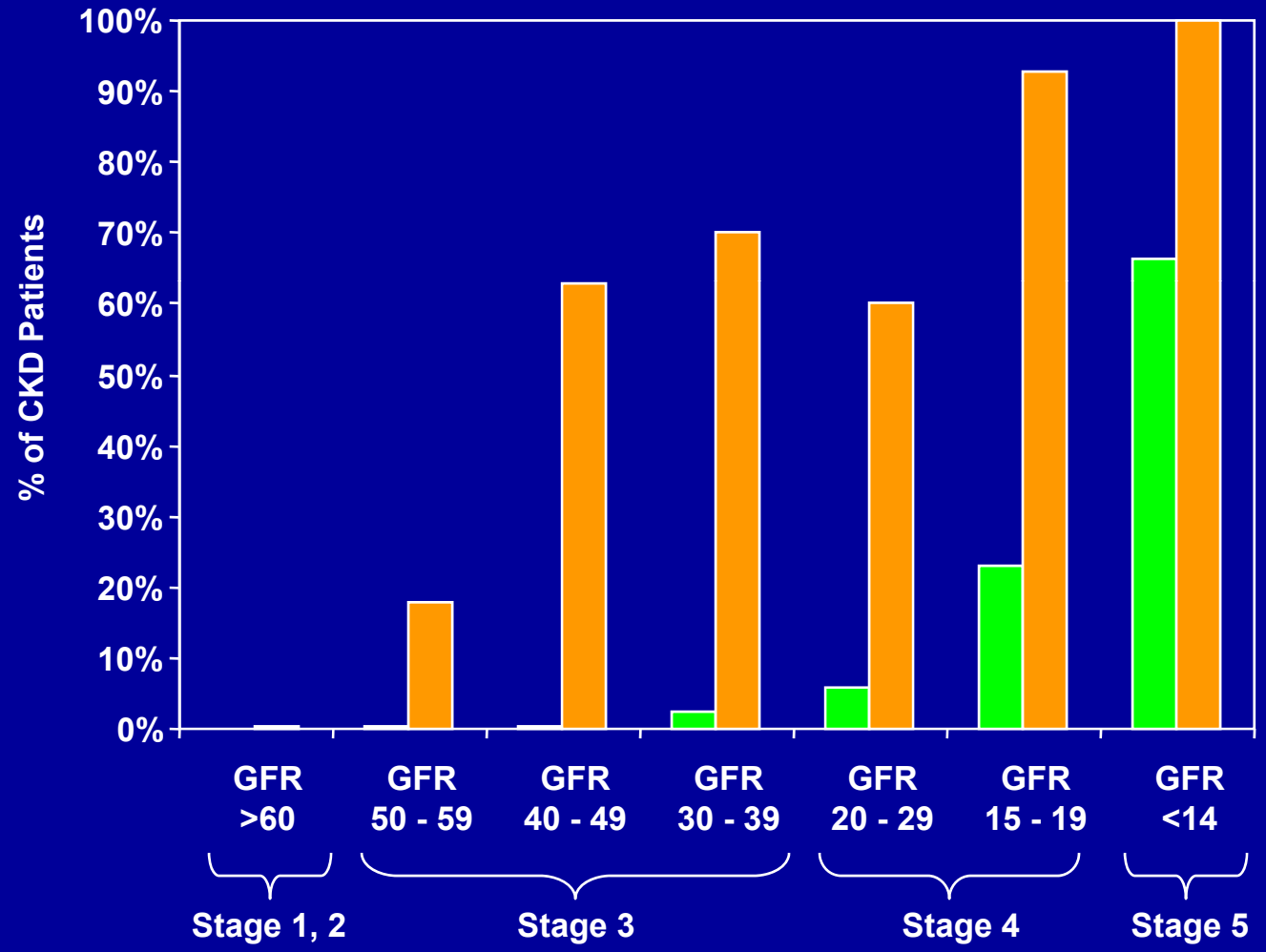
Hyperphosphatemia and Pathogenesis of SHPT



CKD Progression



Bone and mineral issues are prevalent in CKD



High Phosphorus

Abnormal PTH

High Phosphorus

Stages 3 and 4, >4.6 mg/dL

Stage 5 >5.5 mg/dL

Abnormal PTH

Stage 3, >70 pg/mL

Stage 4, >110 pg/mL

Stage 5 >300

Meta-analysis of published data: St. John, Nephron 1992; Fajtova, CTI 1995; Kates AJKD 1997; Marinez AJKD 1997; Smith ASN Abstract 2002; Winkelmayer KI 2003

K/DOQI Guidelines on Bone and Mineral Metabolism

	CKD Stage 3	CKD Stage 4	CKD Stage 5
Phosphorus (mg/dL)	2.7-4.6	2.7-4.6	3.5-5.5
Calcium (mg/dL)	"Normal"	"Normal"	8.4-9.5; Hypercalcemia >10.2
Intact PTH (pg/mL)	35-70	70-110	150-300*

*Evidence

K/DOQI Guidelines on Anemia Management

Parameter	**Recommendation**
Diagnosis of Anemia	Hb <13.5 in males Hb< 12 in females
Target Hb	≥ 11 g/dL Caution with Hb > 13 g/dL
Target TSAT and ferritin	TSAT > 20% Ferritin > 200 in HDD-CKD Ferritin > 100 in non HDD-CKD Ferritin > 500 not recommended

CREATE

- CKD not on dialysis
- Epoetin beta
- Hgb 10.5-11.5 vs 13-15
- Increased rate of progression of CKD
- No significant difference in CV outcomes

Drueke TB et al. ***N Engl J Med. 2006 Nov 16;355(20):2071-84.*** **CREATE study**

CHOIR

- Hgb 11.3 g/dL vs 13.5 g/dL
- CKD not on dialysis
- Stopped early because of excess CV adverse outcomes in higher Hb group
- No QOL benefit in higher Hb group

Singh AK et al. ***N Engl J Med. 2006 Nov 16;355(20):2085-98.*** **CHOIR study**

CHOIR and CREATE Impartial Conclusions

" Taken together, these two studies suggest caution in the full correction of anemia in patients with chronic kidney disease … Although we need more information about the ideal target level and should consider the present guidelines incomplete, it seems wisest to refrain from ***COMPLETE*** correction of anemia in patients with chronic kidney disease."

Remuzzi G et al. ***N Engl J Med. 2006 Nov 16;355(20):2144-6.***

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III. Treatment of complications of renal dysfunction

IV. Identification and adequate preparation of the patient in whom renal replacement therapy (RRT) will be required

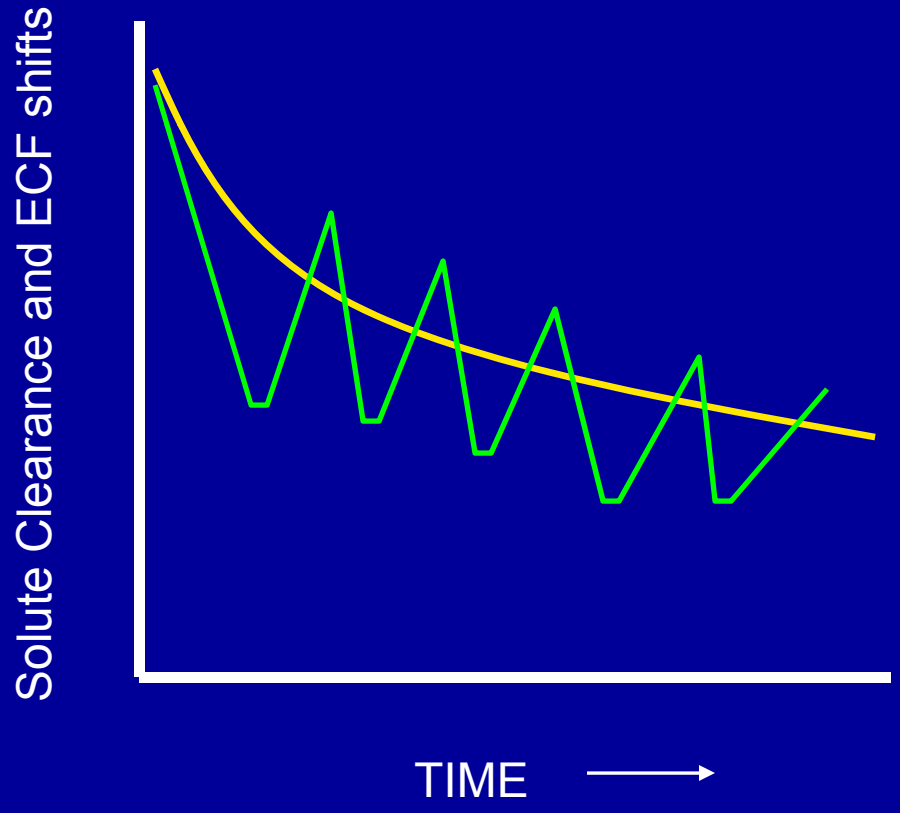
Preparation for and Initiation of Renal Replacement Therapy

- Early referral of patients with CKD to nephrologist.
  - GFR < 60 ml/min
  - Male S Cr > 1.5 mg/dl
  - Female S Cr > 1.2 mg/dl
- Apply strategies to slow progression of disease.
- Once GFR drops < 30 ml/min educate patient with regards to RRT
- Offer counseling with multi-disciplinary team
  - Dietitian
  - Nurses
  - Social Worker

Absolute clinical indications to initiate RRT

- Pericarditis
- Fluid overload or pulmonary edema refractory to diuretics
- Accelerated Hypertension
- Progressive uremic encephalopathy or neuropathy
- Bleeding diathesis
- Persistent nausea and vomiting
- Plasma Creat > 12 mg/dl or BUN > 100 mg/dl
- 2006 K/DOQI GFR < 15 mL/min/1.73m2 or higher GFR but patient with declining health due to loss of kidney function.

Intermittent vs. Continuous



Advantages of Continuous Tx:

1. Less ECF shift
2. Less Hypotension
3. Less treatment-associated renal injury
4. Adequate removal of toxins

Renal Replacement Therapy (RRT)

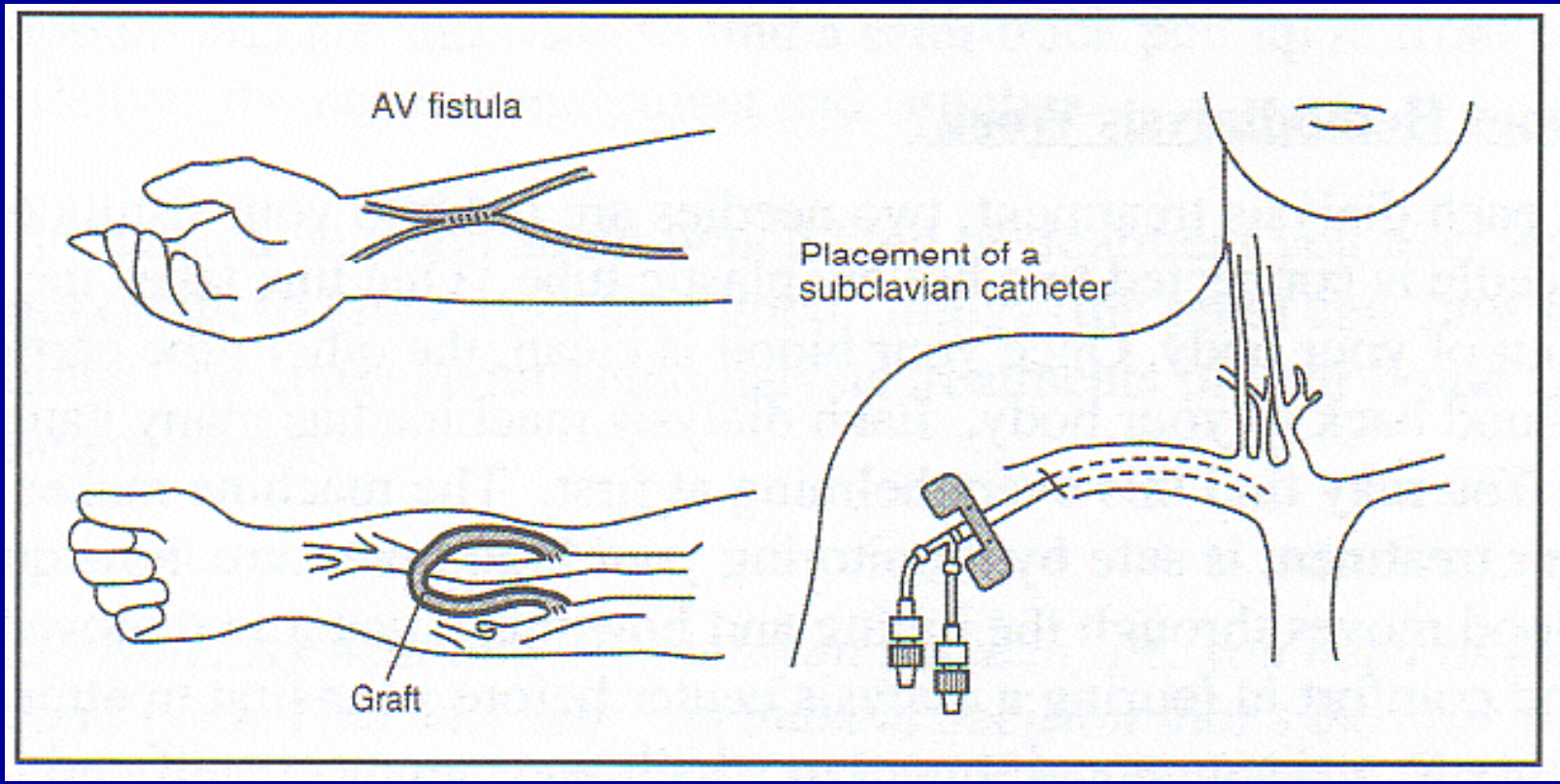
CKD Stage V: ESRD

1. Hemodialysis
2. Peritoneal Dialysis
3. Kidney transplant

Hemodialysis

- Intermittent treatment offered 4 hours three times a week.
- In center therapy
- Requirements
  - Arterio-venous access
  - Filter
  - Nurses

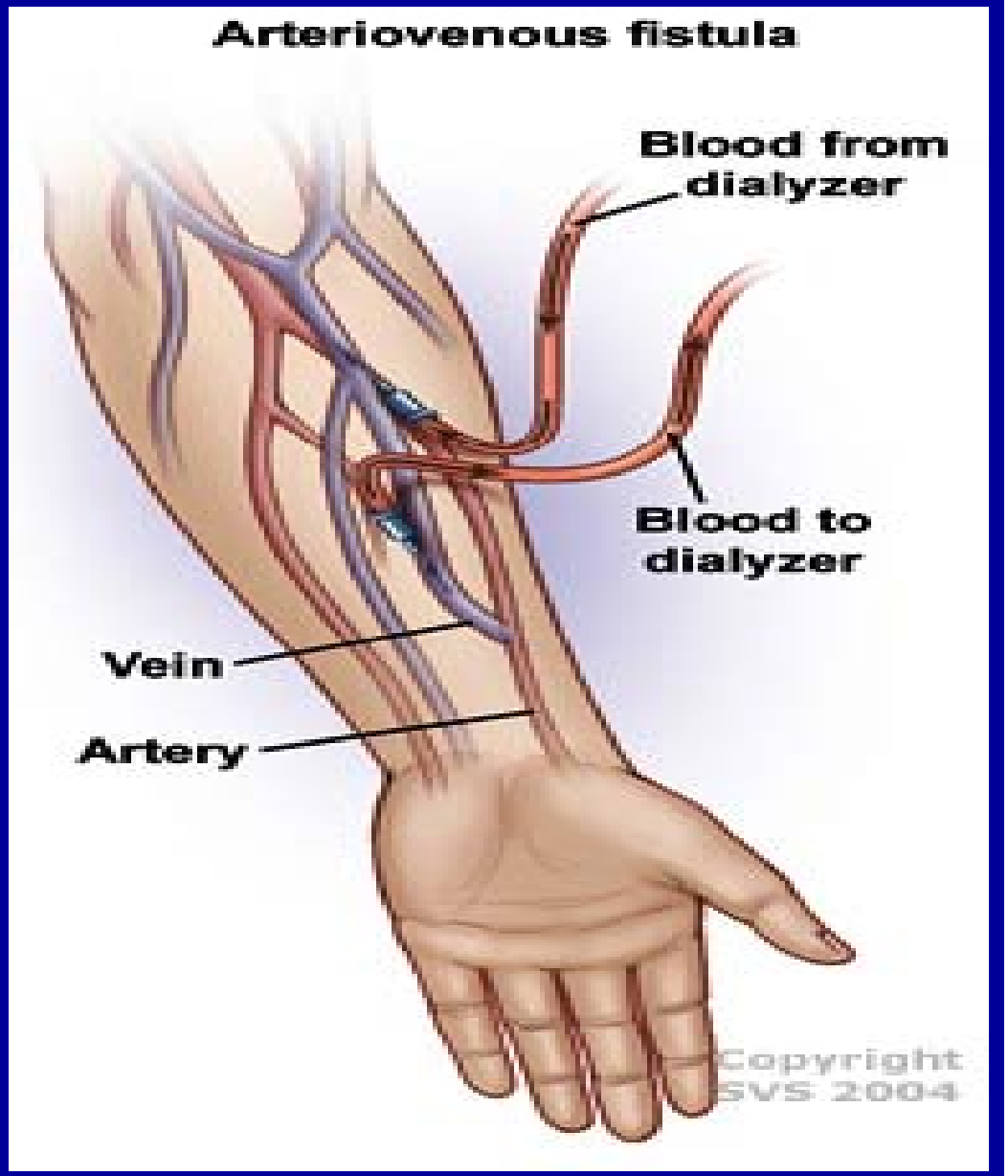
Access



Always Avoid Subclavian Catheters: Have 40 % Superior Vena Cava Stenosis after first implanted

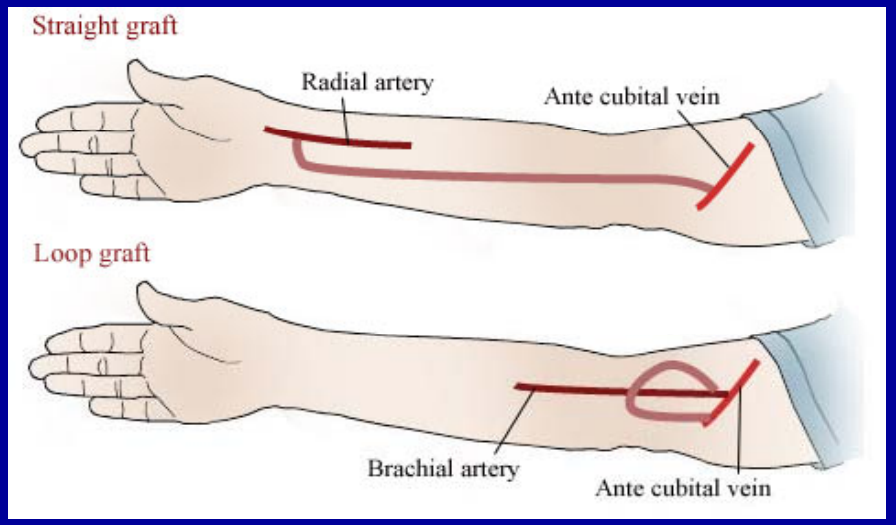
Fistula First: Good Practice

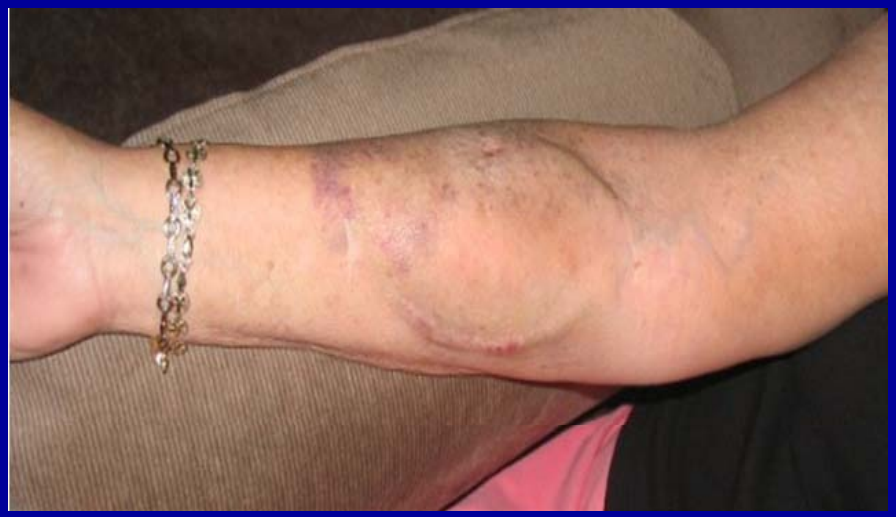
- 2006 K/DOQI guidelines recommend that a fistula be placed at least 6 months prior to the anticipated start of hemodialysis.
- End to side vein to artery anastomosis of cephalic vein and radial artery. (20 yr life)
- Evaluate non maturing AVF



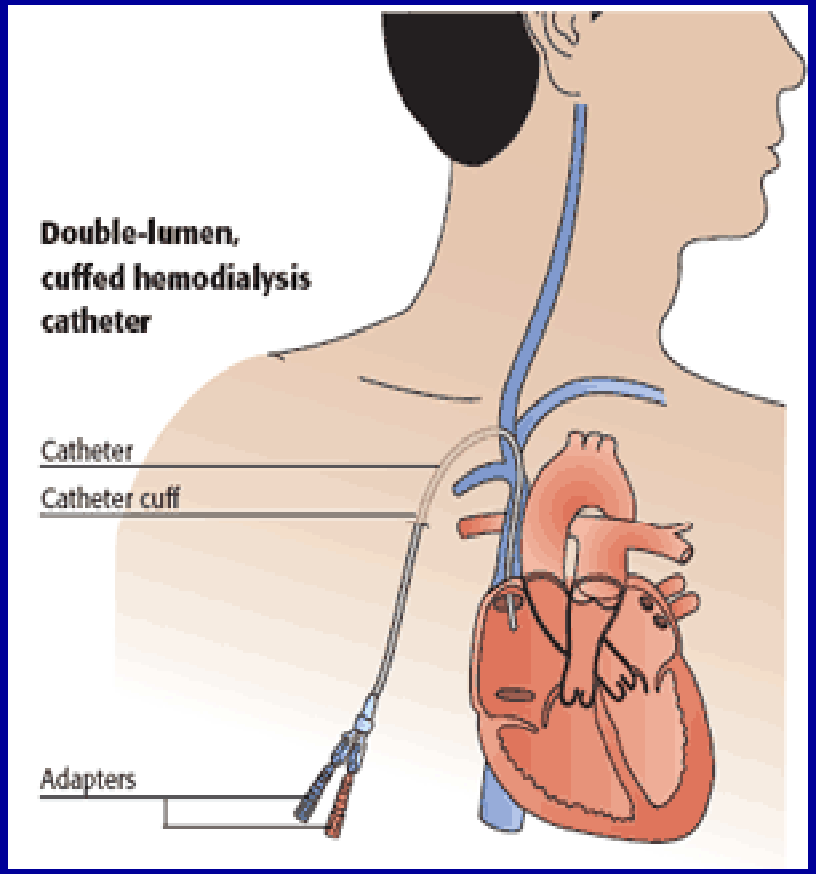
AV Graft: polytetrafluoroehylrnr (PTFE)

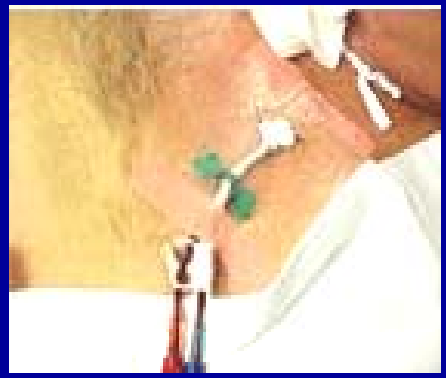
- Usually mature in 2 weeks.
- 2006 K/DOQI guidelines recommend that a synthetic graft be placed at least 3-6 weeks prior to anticipated start of dialysis.





Tunneled catheter: should be short duration until permanent access achieved





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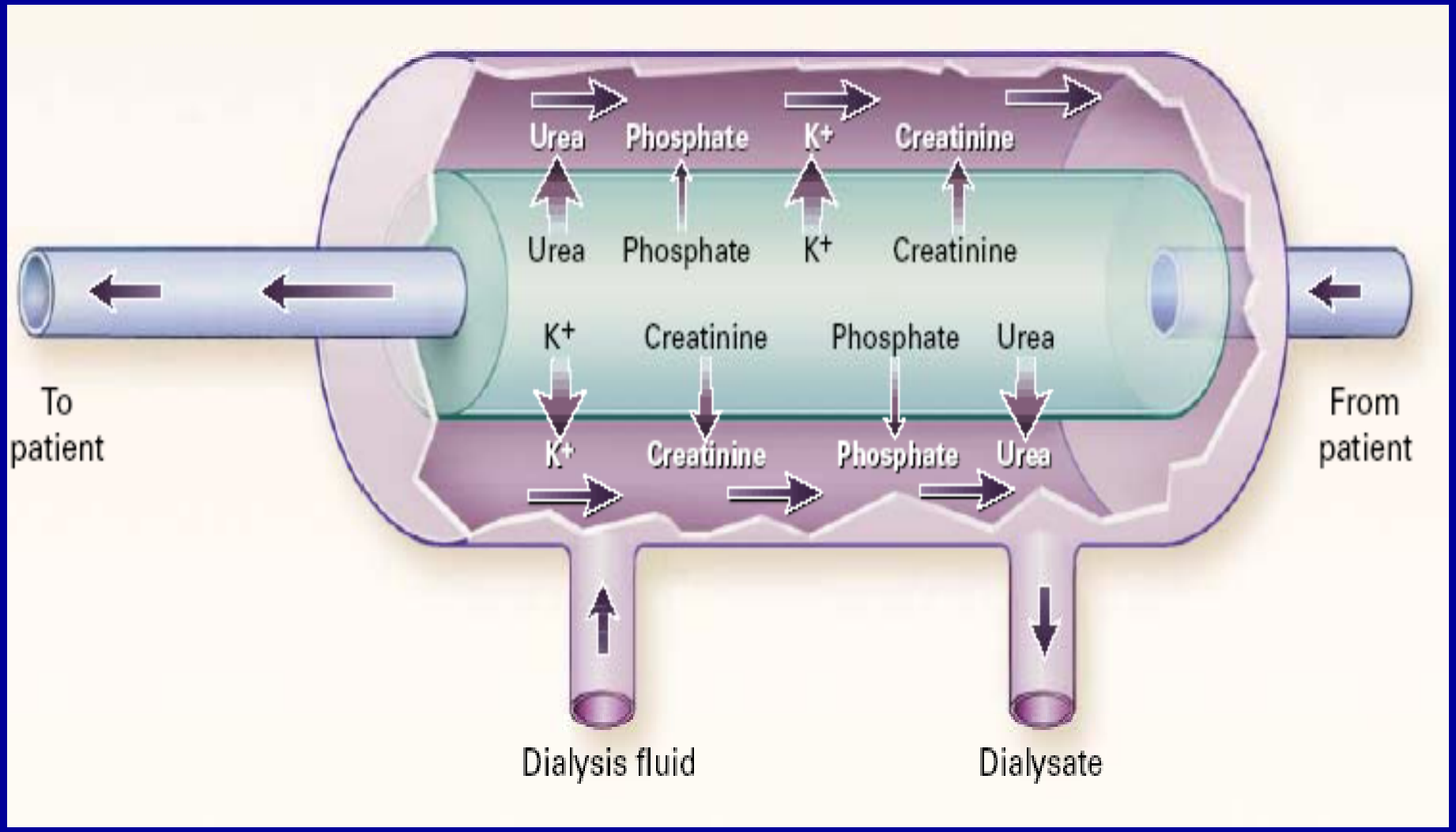
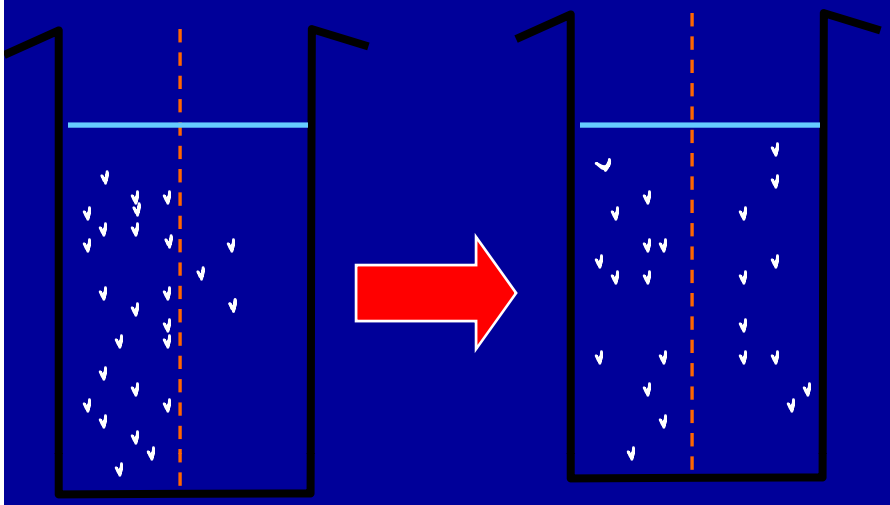


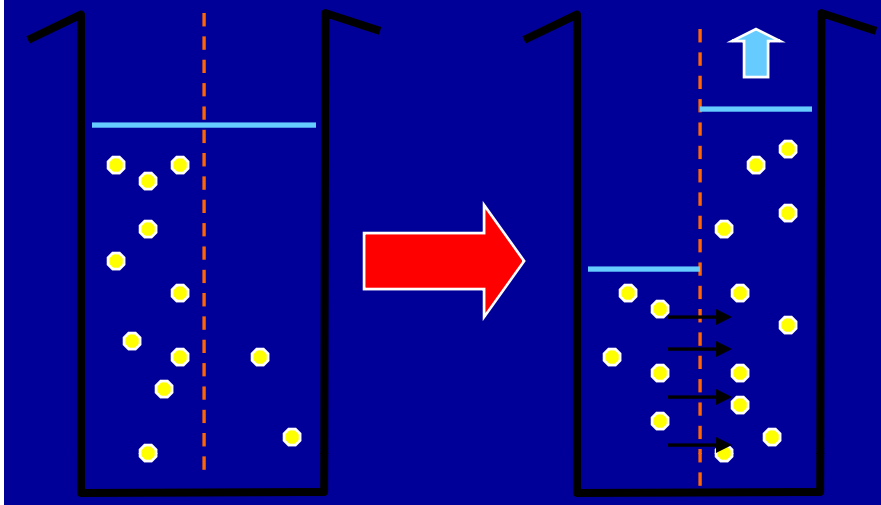
Diffusion



Diffusion: HD

1. Movement of solutes from area of higher concentration to area of lower concentration
2. Dialysate used to create concentration gradient across a semi-permeable membrane
3. Dialysis uses a semi-permeable membrane for selected diffusion

Convection



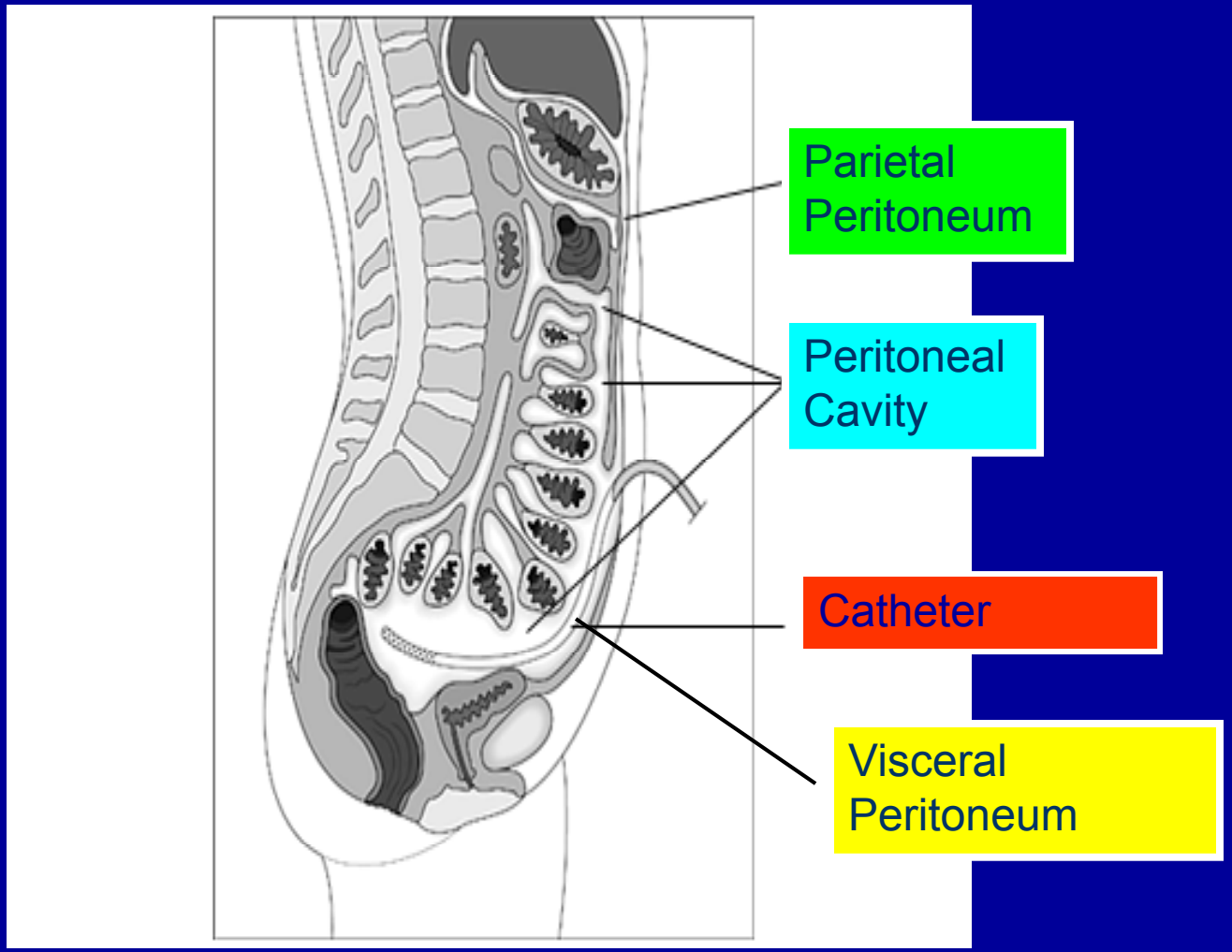
Convection: HF

1. Movement of solutes with water flow, SOLVENT DRAG.
2. Certain membrane materials display adsorptive characteristics

   - Surface adsorption to the membrane

   - Bulk adsorption within the membrane when molecules can permeate it

Peritoneal Dialysis



Advantages of Peritoneal Dialysis

- Independent lifestyle: work and travel
  - More flexible holidays and travel
  - Higher employment rates
- Different diet: less K restriction, less protein restriction, less volume restriction
- Treatment of choice for infants and young children

Advantages of Peritoneal Dialysis

- Similar survival to HD, with superior survival in the first 2-3 years
- Considerable reductions in peritonitis and catheter related infections
- Adequate solute clearance
- Better tolerated hemodinamically, ideal for patients with heart disease

Advantages of Peritoneal Dialysis

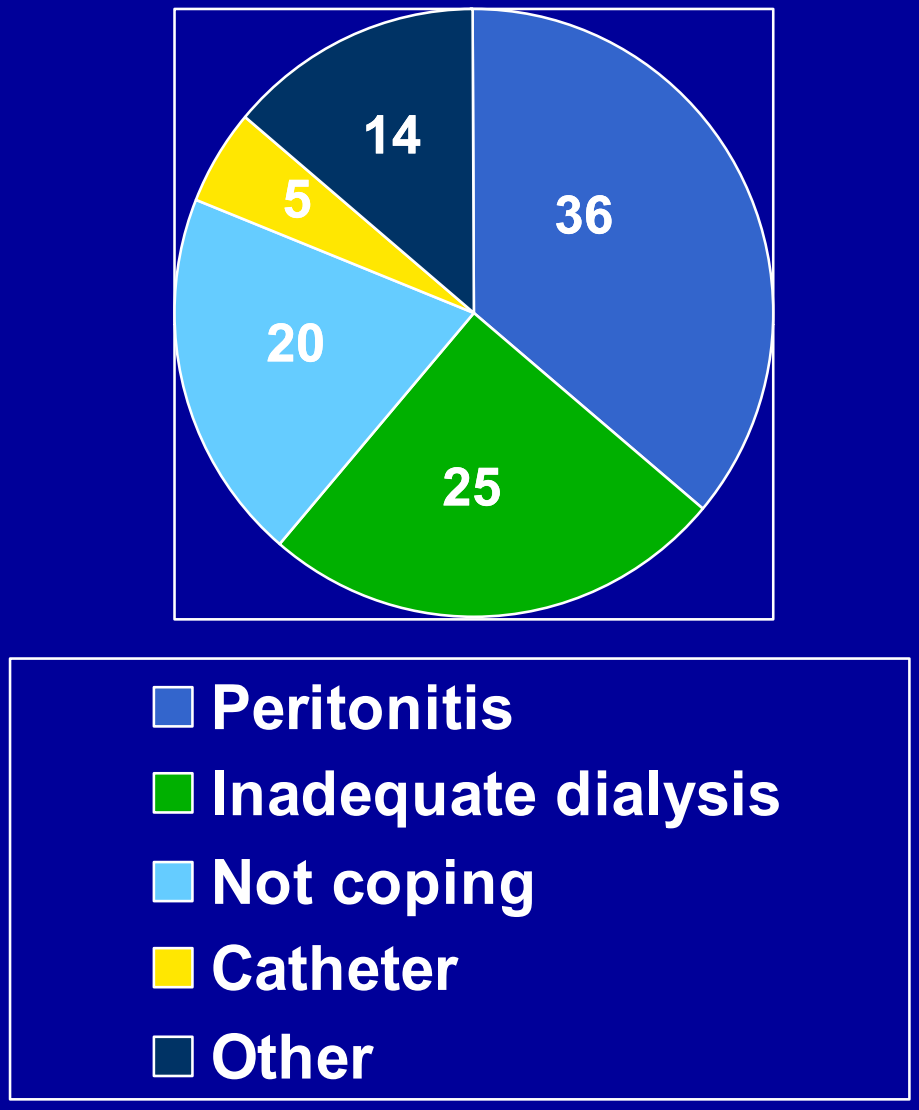
- Better BP and fluid control in the first few years of dialysis
- Better preservation of residual renal function versus HD
- Higher hemoglobin levels, less rhUePO
- Better outcomes after transplant

Advantages of Peritoneal Dialysis

- Ability to expand patient numbers in a dialysis center with limited need for resources and major capital investments.
- Lower staff to patient ratio than center HD
- Less costly than center HD

Disadvantages

- Higher technique failure in PD compared to HD.
- Low rate of achieving long term PD due to changing membrane
- Survival rate at 10 years after initiating PD is 20%
- Reasons for therapy change to HD (see pie graph)



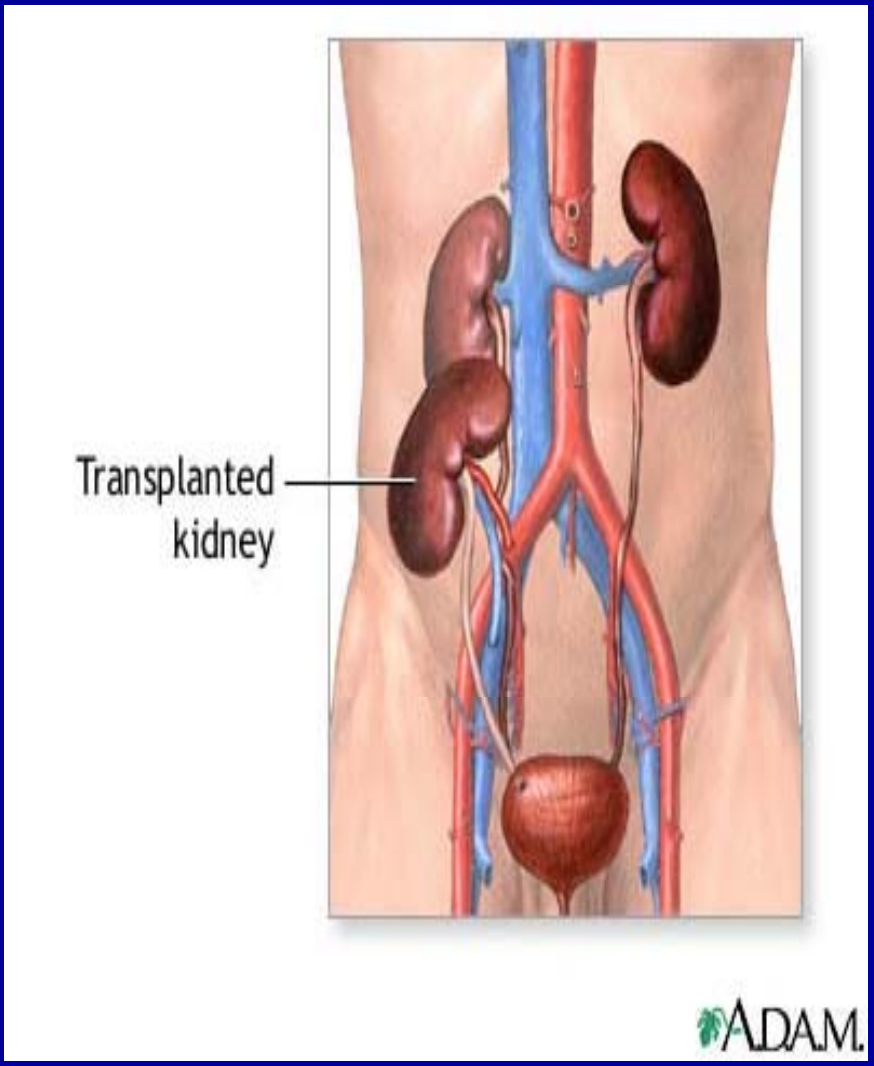
JASN 13: S104-116, 2002.

Disadvantages

- Hands on, individual therapy
- Protein loss make it a poor choice for malnourished patients

Transplant

- Evaluation of potential recipient and living donor if available.
- Timely referral



Conclusion Slow Progression of Disease

- Aggressive BP and proteinuria control
- Protein excretion 500-1000 mg
- BP reduction 130/80 mmHg
- Lower BP in patients with >1g proteinuria
- Add ARB to patient on ACE
- Add Ace to pt on ARB
- Protein intake 0.8-1.0 g/kg/d ???
- Treat complication of CKD

Conclusion

I. Treatment of reversible causes of renal dysfunction

II. Preventing or slowing progression of disease

III. Treatment of complications of renal dysfunction

IV. Identification and adequate preparation of the patient in whom renal replacement therapy (RRT) will be required

Questions?