A krónikus veseelégtelenség kezelési lehetőségei: a transzplantált betegek gyógyszeres kezelése

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2014

Definition of Chronic Kidney Disease

Definition of:

Chronic Kidney Disease =**GFR<60 ml/min/1.73 m^2 or persistent albuminuria***

*American Journal of Kidney Diseases Vol 41, No 1, 2003: pp1-12

Chronic Kidney Disease: Another Epidemic

Third National Health and Nutrition Examination Survey:

-19.2 million have Chronic Kidney Disease (11%)
-7.6 million have Stage III Chronic Kidney Disease (4.3%)
-0.7 million have Stage IV and End Stage Renal Disease (0.4%)

Definition of:

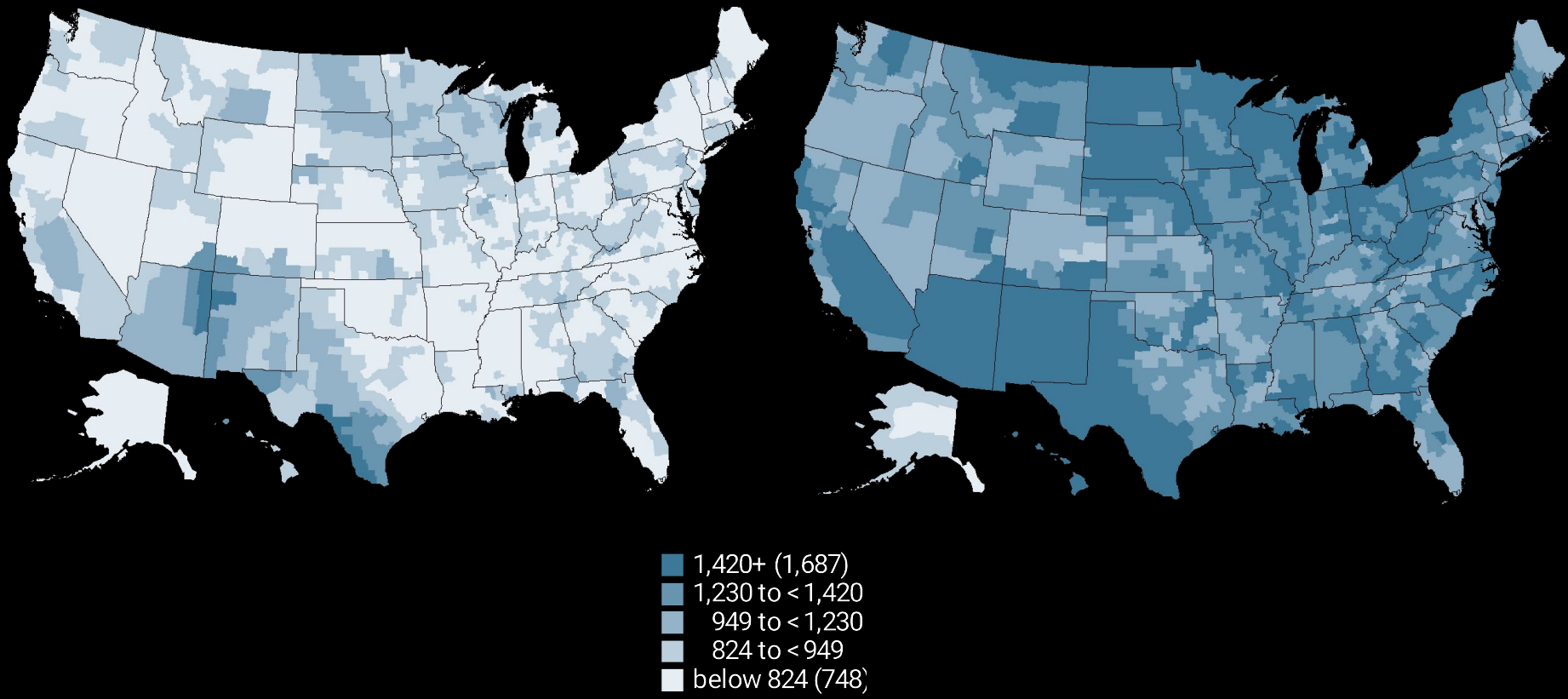
-Chronic Kidney Disease =**GFR<60 ml/min/1.73 m^2 or persistent albuminuria**

-Stage III Chronic Kidney Disease=GFR 20-39 ml/min/1.73 m^2

American Journal of Kidney Diseases Vol 41, No 1, 2003: pp1-12

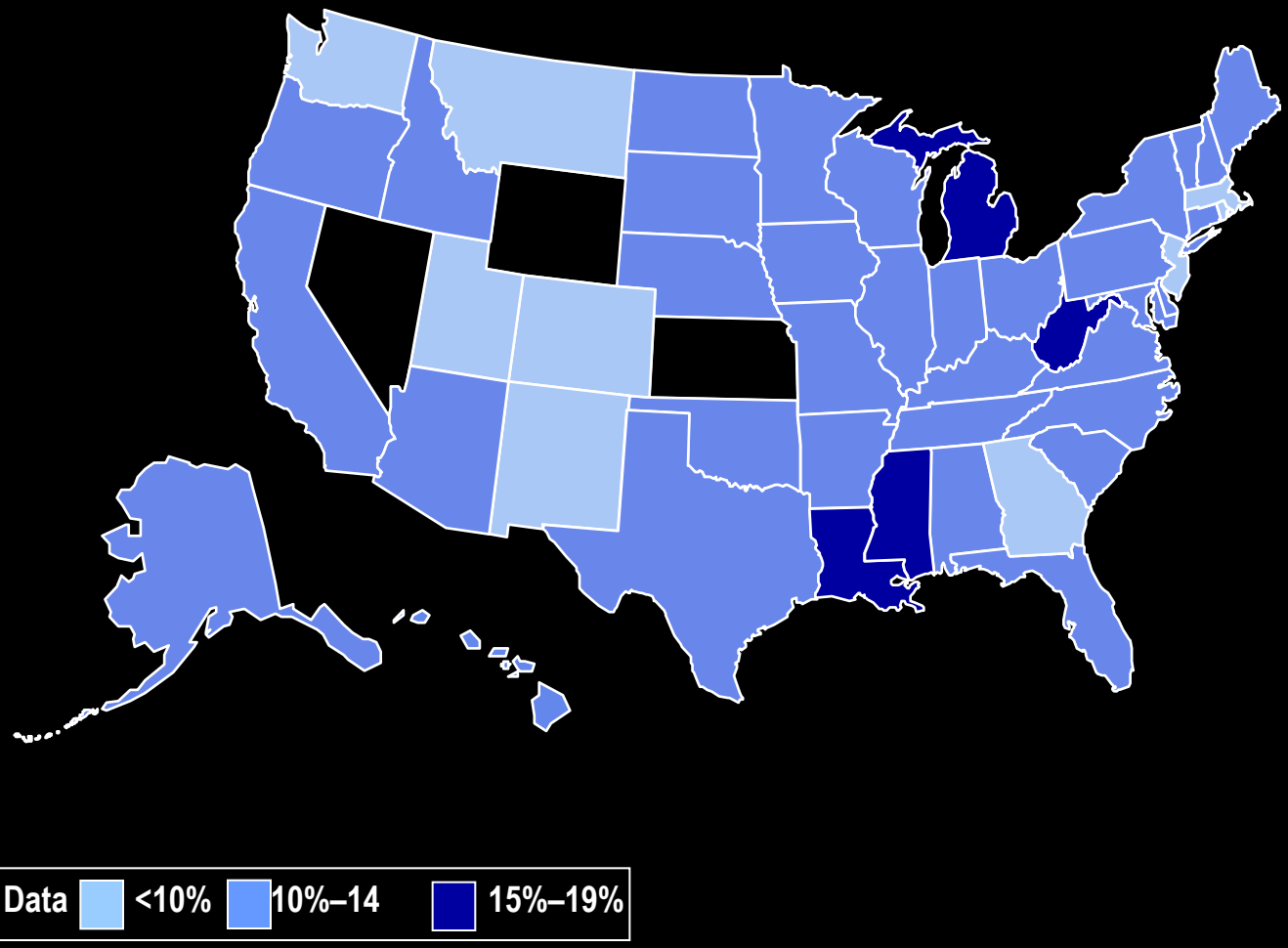
Scope of the problem: CKD is growing

Prevalence of ESRD: 1991 versus 2001 (per million population)



Obesity Trends Among U.S. Adults 1991

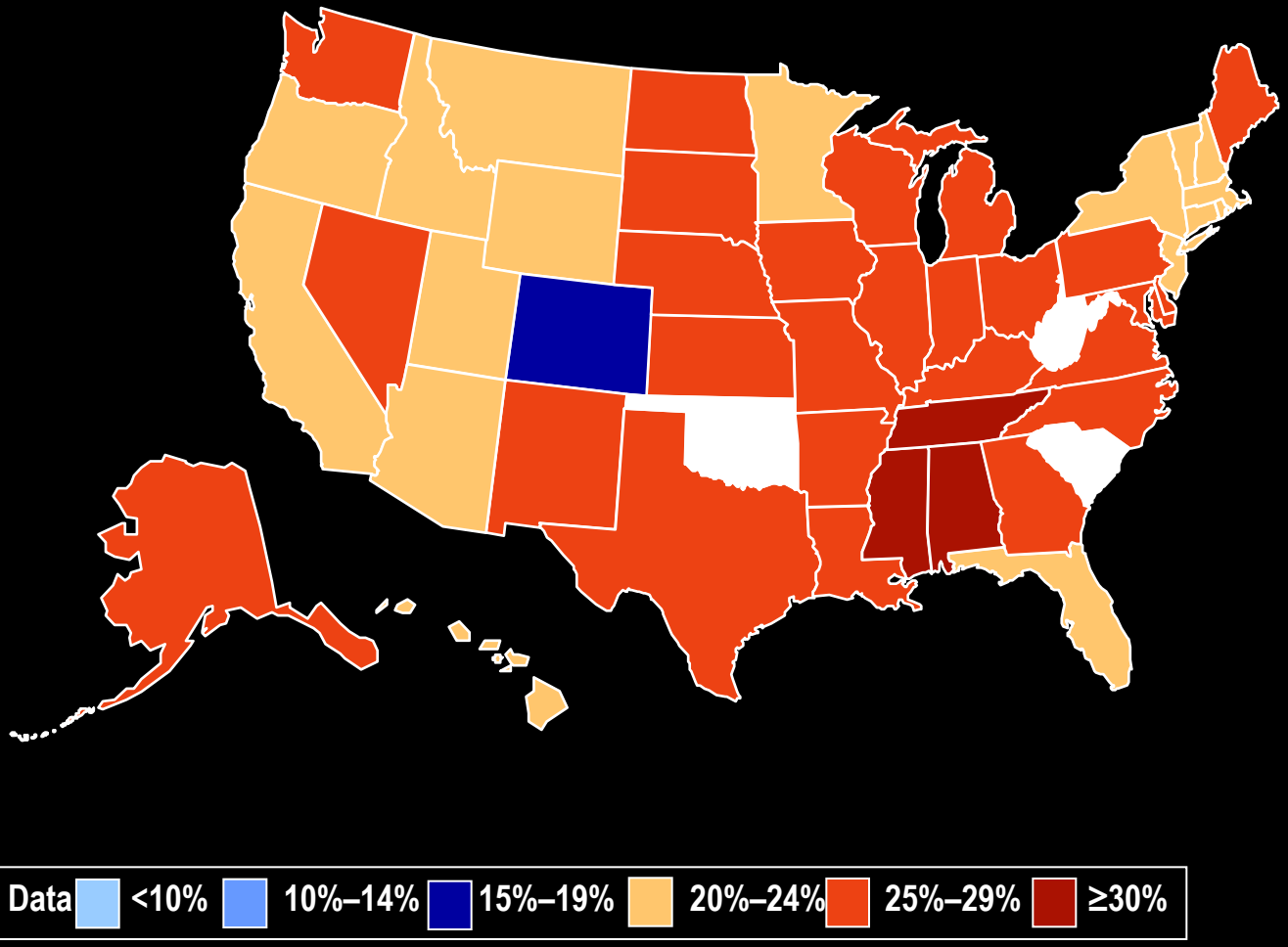
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



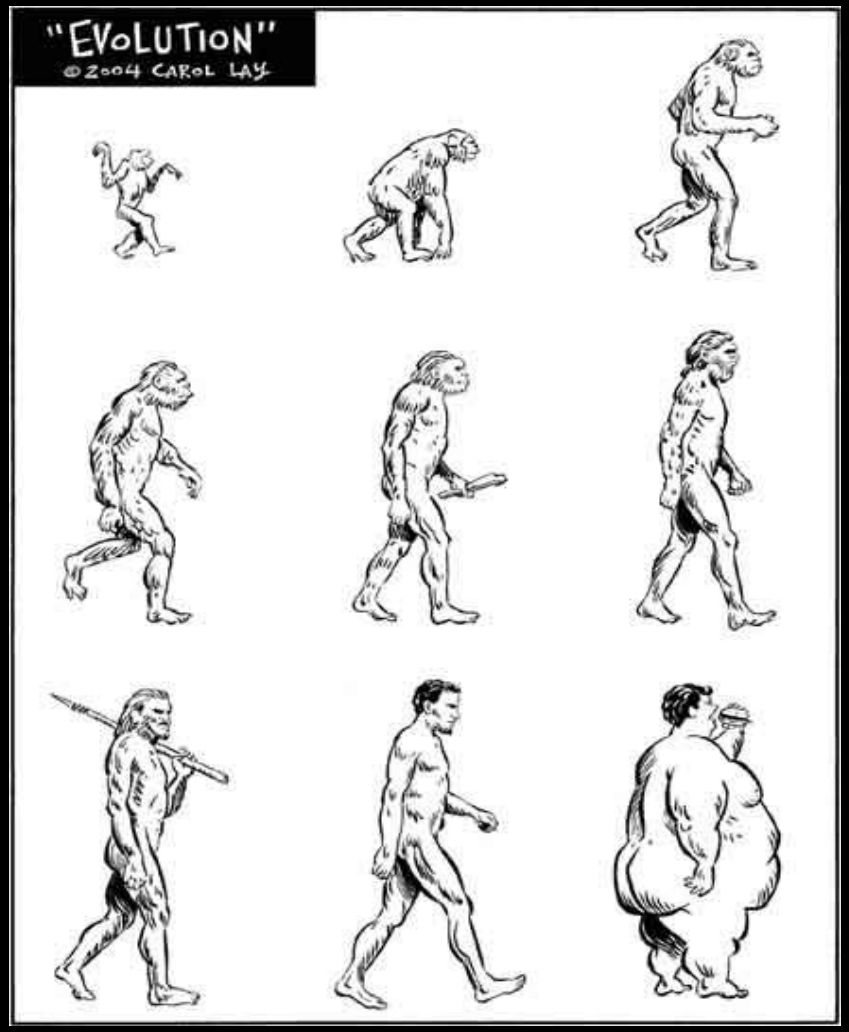
Obesity Trends Among U.S. Adults

2008

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Evolution of *Homo Sapiens* toward *Homo Consumans*



- Hunter-gatherers (tens of thousands of years): more potassium, less salt, less animal and heavy-grain protein (acid), less fat, more exercise, less caloric intake, fiber, fresh food
  =very low blood pressure, very low cholesterol and no proteinuria
- Modern man (neolithicum, agriculture, a few millennia): diet loaded with animal-, wheat-, rice-derived protein (acid); salt, excessive calories, mass-produced sugar and industrial chemicals, congested in small urban areas
  =“normal” or high blood pressure, “normal” or high cholesterol and some proteinuria

Metabolic Syndrome and Renal Progression

Table 1. *Fructose feeding results in development of traits of the metabolic syndrome*

Diet	TG, mg/dl	Cholesterol, mg/dl	Uric Acid, mg/dl	Insulin, pM
Normal	161±12.5	76±3.2	1.6±0.10	3.0±0.3
Dextrose	107±8.9*	64±2.4*†	1.7±0.09	3.2±0.3
Fructose	373±38.7*	90±4.3*	1.5±0.12	4.8±0.5*

Diet	Proteinuria, mg/dl	$C_{creatinine}$, ml/min
Normal	33±5.7	1.23±0.04
Dextrose	35±7.5	1.16±0.08
Fructose	73±15.4*	0.96±0.08*

Gersch Am J Physiol Renal Physiol 293: F1256–F126

Chronic Kidney Disease: The Extreme Of Metabolic Syndrome?

- Ludovicus Giomus (**IInd Century** Roman physician of Greek origin):

"The prospect for chronic renal malady is rendered optimal by the combination of habitual excess of culinary pleasures and physical inactivity."

(N.B. Historical Note:

The physician after this statement was hunted down by the angry Roman populace and forced to withdraw his remark.)

Benefits of Cibus Rapidus!

- Salt: hypertension
- Protein: glomerular hypertension
- Sugars: diabetes melitus (55%)
- Lipid: dyslipidemia

You only need to add smoking. (The Romans did not have that yet...)

Metabolic Syndrome and Renal Progression

Abnormal **diet and anti-rejection drugs**
(high fructose as an example)

-high salt (hypertension, cyclosporin,inflammation, mortality)

-carbohydrates (diabetes mellitus, steroids, tacrolimus, mTor, obesity, salt retention)

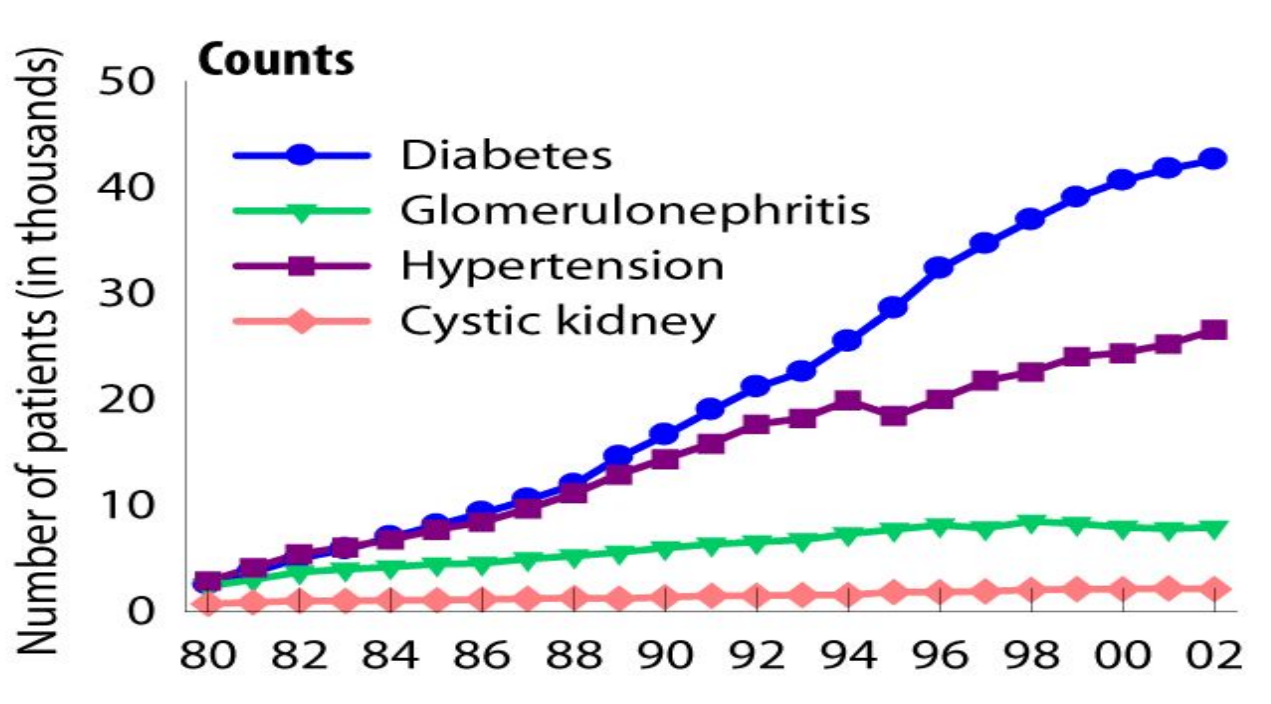
-high protein (glomerular hypertension, CNI protective)

-saturated fatty acid, cholesterol (mTor, cyclosporin, cardiovascular events)

→metabolic syndrome including salt retention (chronic volume overload) →endothelial damage →inflammation →difficult to control hypertension (diabetes, OSA) →proteinuria →renal progression and cardiovascular disease→hypoalbuminemia/mortality

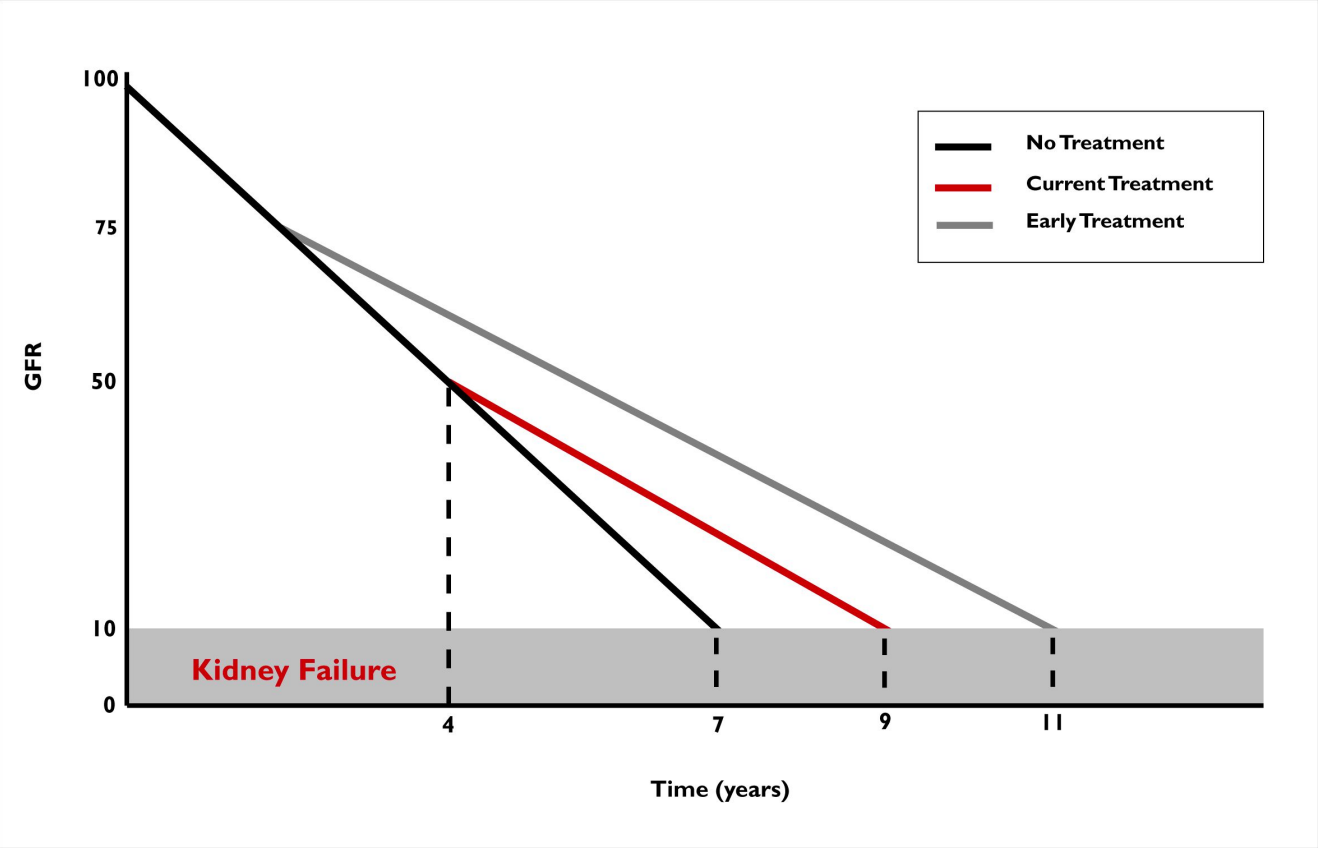
Incident Counts & Adjusted Rates, By Primary Diagnosis

CKD as the extreme of the Metabolic Syndrome



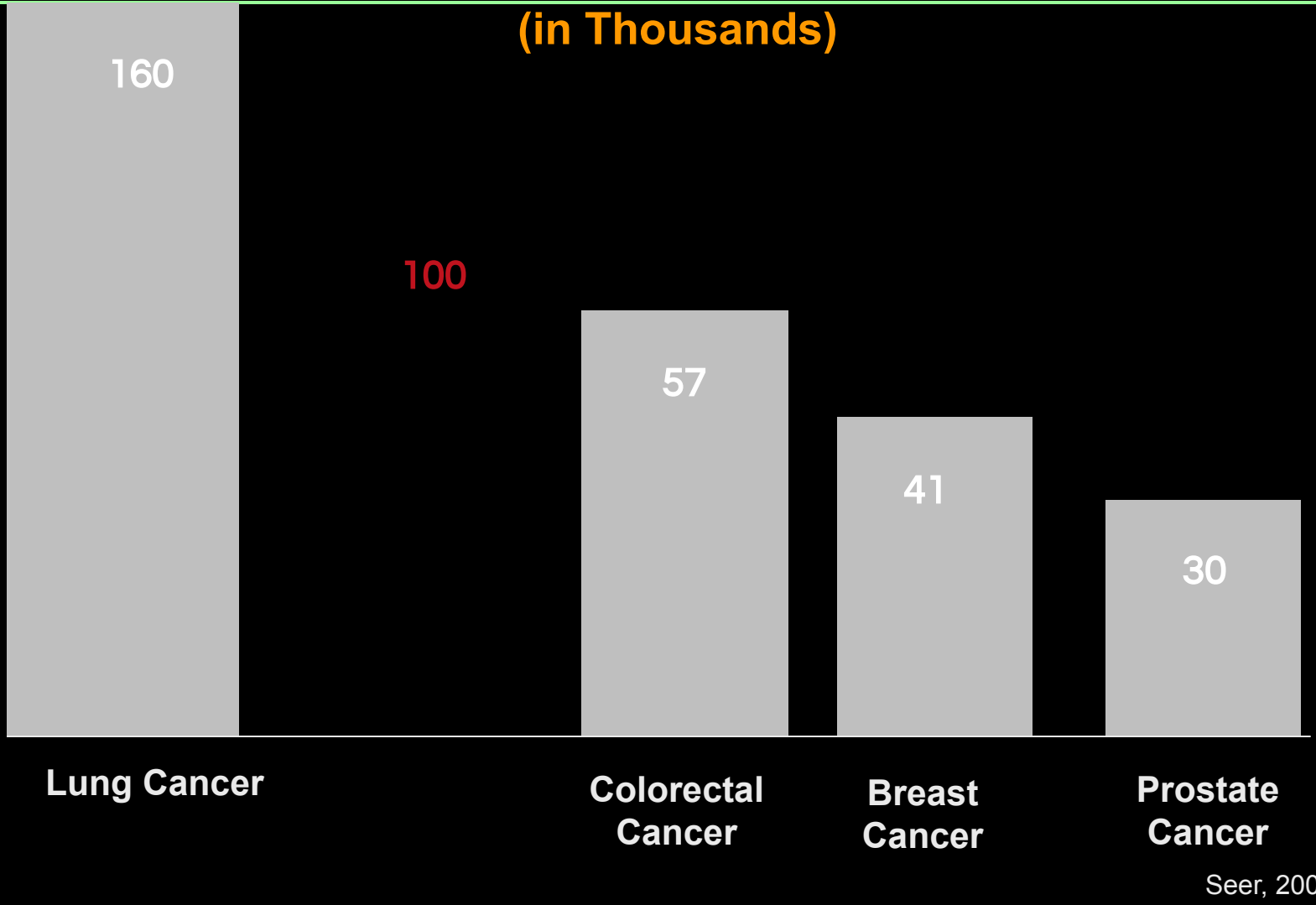
USRDS, 2004

Early Treatment May Make a Difference



Brenner, et al., 2001

Mortality in Kidney Failure versus Cancer Deaths in 2000



Seer, 2004

Expected Survival Times General Population versus Dialysis

	All races			White			Black		
	All	M	F	All	M	F	All	M	F
0	76.7	73.9	79.4	77.3	74.6	79.9	71.4	67.8	74.7
1	76.3	73.5	78.9	76.8	74.1	79.3	71.5	67.9	74.7
5	72.4	69.6	75	72.9	70.2	75.4	67.6	64.1	70.9
10	67.4	64.7	70.1	67.9	65.3	70.5	62.7	59.2	66
15	62.5	59.8	65.1	63	60.3	65.5	57.8	54.3	61
20	57.7	55	60.2	58.2	55.6	60.7	53.1	49.6	56.2
25	53	50.4	55.4	53.4	50.9	55.8	48.5	45.2	51.4
30	48.2	45.7	50.5	48.6	46.2	50.9	43.9	40.7	46.6
35	43.5	41.1	45.7	43.9	41.5	46.1	39.3	36.3	41.9
40	38.8	36.5	41	39.2	36.9	41.3	34.8	31.9	37.4
45	34.3	32	36.3	34.6	32.4	36.6	30.6	27.8	33
50	29.8	27.7	31.7	30.1	28	32	26.6	24	28.7
55	25.5	23.5	27.3	25.7	23.8	27.5	22.8	20.4	24.7
60	21.5	19.6	23.1	21.6	19.8	23.2	19.3	17.2	20.9
65	17.7	16.1	19.1	17.8	16.1	19.2	16	14.3	17.3
70	14.3	12.8	15.4	14.4	12.9	15.5	13	11.6	14
75	11.2	10	12.1	11.2	10	12.1	10.4	9.2	11.1
80	8.5	7.5	9.1	8.5	7.5	9.1	8.2	7.3	8.6
85	6.3	5.5	6.6	6.2	5.5	6.6	6.2	5.6	6.5
90	4.6	4.1	4.8	4.5	4	4.7	4.8	4.4	4.8
95	3.4	3	3.5	3.2	2.9	3.3	3.6	3.5	3.6
100	2.6	2.4	2.7	2.3	2.2	2.4	2.8	2.8	2.7

Dialysis	White		Black		N Am		Asian	
	Male	Female	Male	Female	Male	Female	Male	Female
0-14	19.8	18.5	20.1	18.1	22.5	23.0	30.6	29.5
15-19	17.0	15.8	18.4	16.5	18.9	18.7	24.5	24.0
20-24	14.5	13.5	16.2	14.3	15.9	16.0	21.5	21.1
25-29	12.3	11.3	14.2	12.6	13.7	13.6	18.6	18.5
30-34	10.1	9.6	12.3	11.0	11.7	11.7	15.7	15.9
35-39	8.6	8.2	10.7	9.7	9.8	10.0	13.1	13.5
40-44	7.4	7.2	9.3	8.4	8.3	8.6	11.0	11.5
45-49	6.3	6.0	7.7	7.3	7.0	7.3	9.0	9.5
50-54	5.3	5.1	6.7	6.3	6.0	6.5	7.6	8.0
55-59	4.6	4.5	5.6	5.5	5.3	5.4	6.4	6.7
60-64	3.9	3.8	4.7	4.8	4.4	4.7	5.3	5.7
65-69	3.2	3.2	4.0	4.0	3.7	4.0	4.5	4.9
70-74	2.8	2.8	3.4	3.3	3.2	3.4	3.7	4.1
75-79	2.4	2.4	2.8	2.8	2.5	2.8	3.1	3.3
80-84	2.0	2.0	2.3	2.3	2.1	2.3	2.6	2.8
85+	1.7	1.7	1.9	1.9	1.7	1.8	2.0	2.2

Expected Survival Times: Dialysis versus Transplantation

Dialysis

	White		Black		N Am		Asian	
	Male	Female	Male	Female	Male	Female	Male	Female
0-14	19.8	18.5	20.1	18.1	22.5	23.0	30.6	29.5
15-19	17.0	15.8	18.4	16.5	18.9	18.7	24.5	24.0
20-24	14.5	13.5	16.2	14.3	15.9	16.0	21.5	21.1
25-29	12.3	11.3	14.2	12.6	13.7	13.6	18.6	18.5
30-34	10.1	9.6	12.3	11.0	11.7	11.7	15.7	15.9
35-39	8.6	8.2	10.7	9.7	9.8	10.0	13.1	13.5
40-44	7.4	7.2	9.3	8.4	8.3	8.6	11.0	11.5
45-49	6.3	6.0	7.7	7.3	7.0	7.3	9.0	9.5
50-54	5.3	5.1	6.7	6.3	6.0	6.5	7.6	8.0
55-59	4.6	4.5	5.6	5.5	5.3	5.4	6.4	6.7
60-64	3.9	3.8	4.7	4.8	4.4	4.7	5.3	5.7
65-69	3.2	3.2	4.0	4.0	3.7	4.0	4.5	4.9
70-74	2.8	2.8	3.4	3.3	3.2	3.4	3.7	4.1
75-79	2.4	2.4	2.8	2.8	2.5	2.8	3.1	3.3
80-84	2.0	2.0	2.3	2.3	2.1	2.3	2.6	2.8
85+	1.7	1.7	1.9	1.9	1.7	1.8	2.0	2.2

Transplant

	White		Black		N Am		Asian	
	Male	Female	Male	Female	Male	Female	Male	Female
0-14	50.4	51.3	45.9	45.4	49.4	46.1	56.6	57.0
15-19	39.2	40.3	36.6	36.4	39.2	36.7	45.4	46.3
20-24	35.3	36.5	33.1	33.1	35.4	33.2	41.4	42.5
25-29	31.5	32.9	29.7	29.9	31.9	30.0	37.6	38.8
30-34	27.5	29.0	26.0	26.5	28.0	26.3	33.5	34.8
35-39	24.1	25.7	22.7	23.4	24.5	23.1	29.7	31.3
40-44	20.9	22.8	19.7	20.6	21.4	20.3	26.0	27.8
45-49	17.9	19.9	16.8	17.8	18.4	17.5	22.6	24.4
50-54	15.3	17.4	14.1	15.1	15.7	14.7	19.3	21.1
55-59	12.8	15.0	11.7	12.9	13.5	12.8	16.4	18.3
60-64	10.6	12.8	9.7	11.1	11.5	10.9	13.9	15.7
65-69	8.8	10.9	8.1	9.6	9.9	9.8	11.8	13.7
70-74	7.1	9.1	6.6	8.1	8.2	8.4	10.0	12.0
75-79	6.1	7.7	5.6	7.3	7.1	8.5	8.9	10.5

CKD: Problem for the Internist

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII)

Major Cardiovascular Risk Factors:

- -Hypertension
- -Cigarette Smoking
- -Obesity (BMI>30)
- -Physical Inactivity
- -Dyslipidemia
- -Diabetes Mellitus
- -**Microalbuminemia or Estimated GFR<60**
- -Age (>55 for men, >65 for women)
- -Family history of premature coronary artery disease (men<55, women<65)

More Than Catches the Eye….

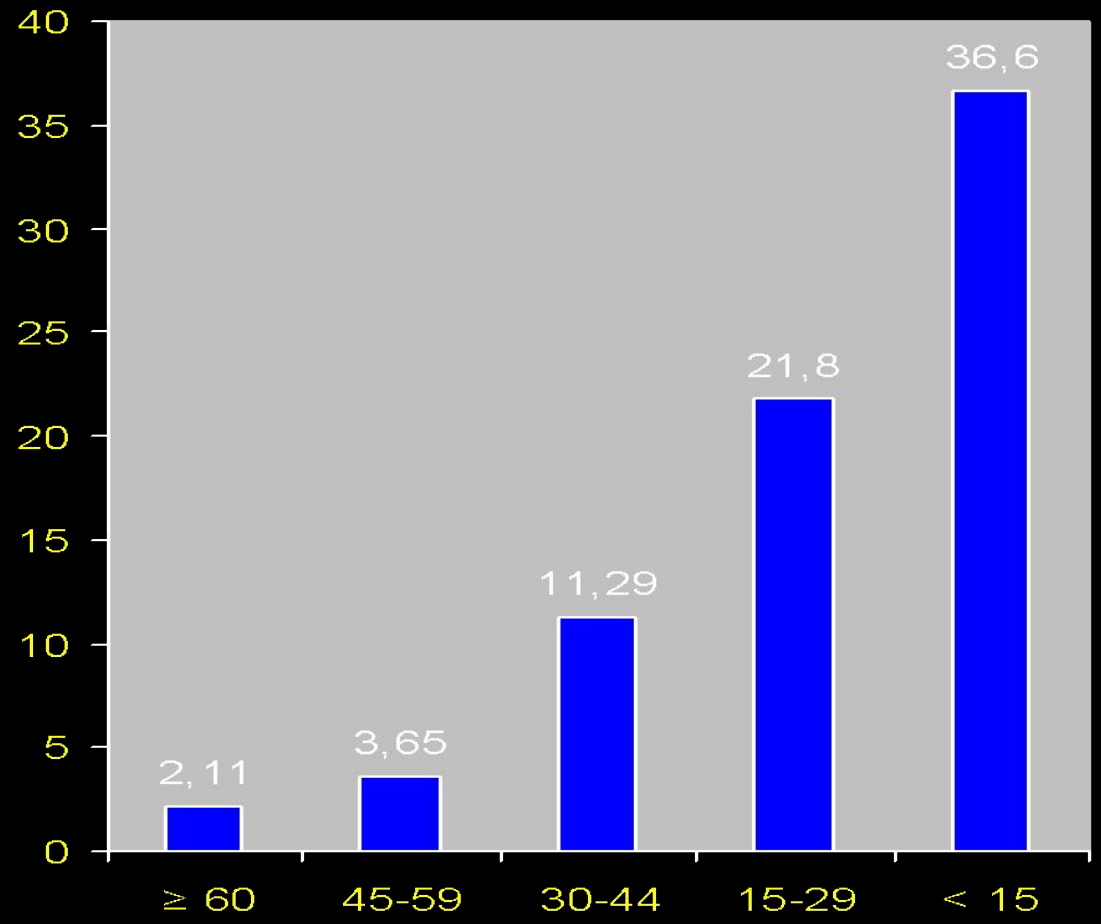
- **CKD is associated with**:

-Hypertension
-Cigarette Smoking
-Obesity (BMI>30)
-Physical Inactivity
-Dyslipidemia
-Diabetes Mellitus
--Age (>55 for men, >65 for women)
-Family history of premature coronary artery disease (men<55, women<65)

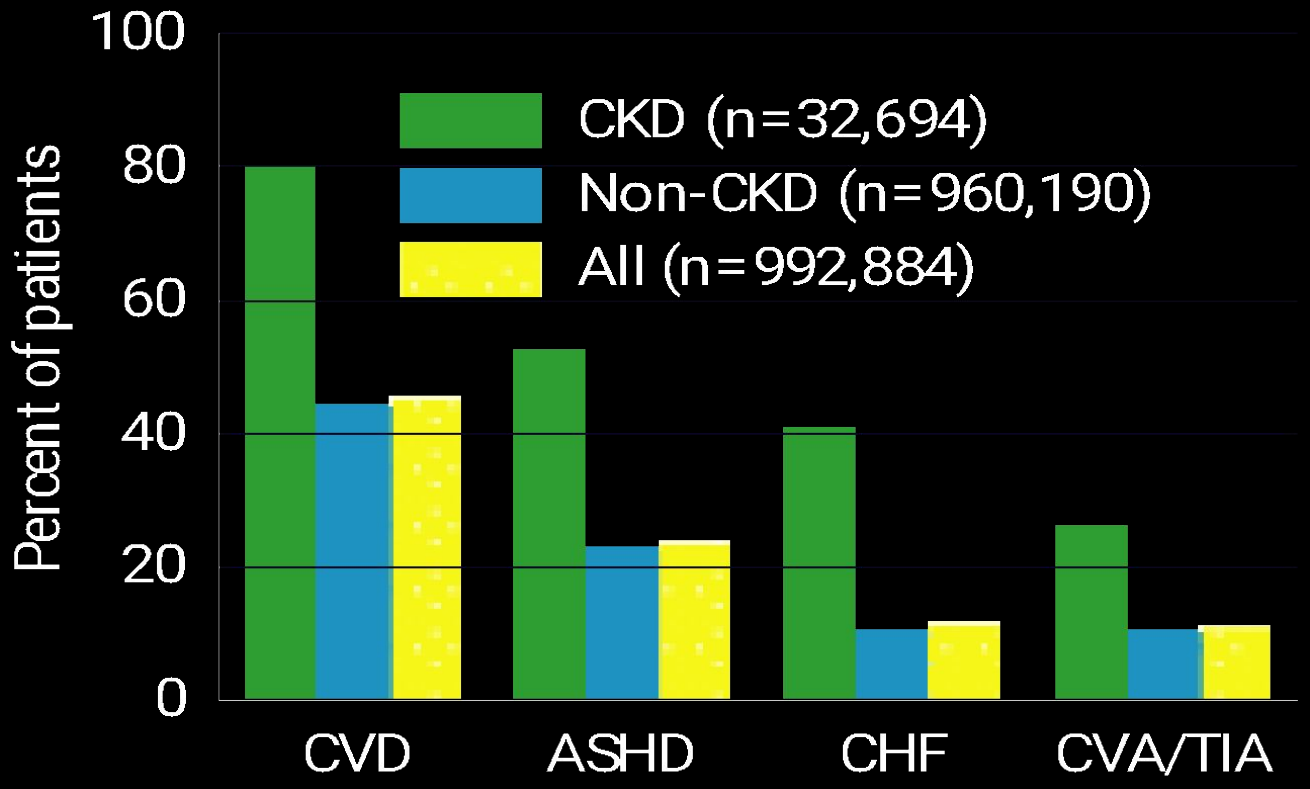
As well as:

-Anemia
-Left Ventricular Hypertrophy
-Inflammation
-Atherosclerosis
-Resistant hypertension/hypervolemia

CKD Predicts CVD



Heart Disease is Highly Prevalent in the CKD Population

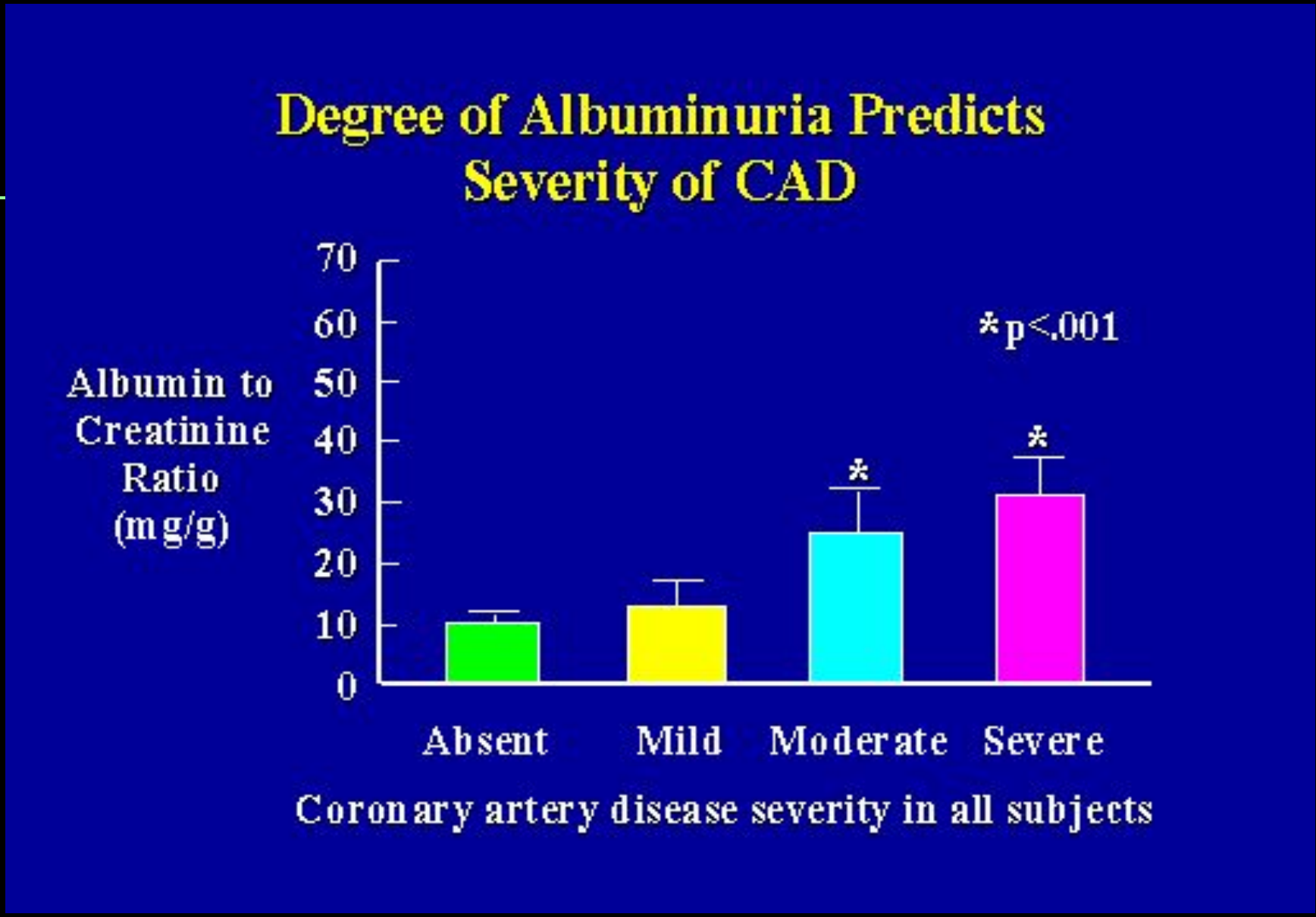


Predictors for Cardiovascular Mortality Specific to or More Common with CKD

- **Volume:** difficult to assess, may contribute to inflammation, major contributor to difficult to control hypertension, LVH may regress when better controlled
- **LVH, diastolic dysfunction, cardiac fibrosis:** more common than ischemic disease, may result in fatal arrhythmia
- **High pulse pressure:** correlates with accelerated atherosclerosis (due to uremia and chronic inflammation) and/or volume
- **Inflammation/malnutrition:** may respond to earlier initiation of renal replacement therapy and volume control

Predictors for Cardiovascular Mortality Specific to or More Common with CKD 2.

- Phosphorus control: effect on cardiovascular mortality and vascular calcification
- 25 OH vitamin D deficiency: correlates with inflammation and cardiovascular mortality
- Sepsis: increases cardiovascular events, often associated with access
- Access: catheters associated with inflammation; 80% in incident ESRD; high risk for sepsis
- Severe anemia (Hgb<10): contributes to hospitalizations and LVH, decreases quality of life and may require specialized treatment with IV (not PO) iron and erythropoetin



Chronic Kidney Disease =**GFR<60 ml/min/1.73 m2** **or persistent albuminuria**

NHANES III on Prevalence of Albuminuria

- 8.3 percent of 14,622 adults had microalbuminuria
- 1 percent had macroalbuminuria (>300 mg/24h)
- Albuminuria 1:3 in Diabetes Mellitus
- Albuminuria 1:7 in Hypertension but no Diabetes
- Albuminuria 1:6 >60 years
- In transplant: not assessed!

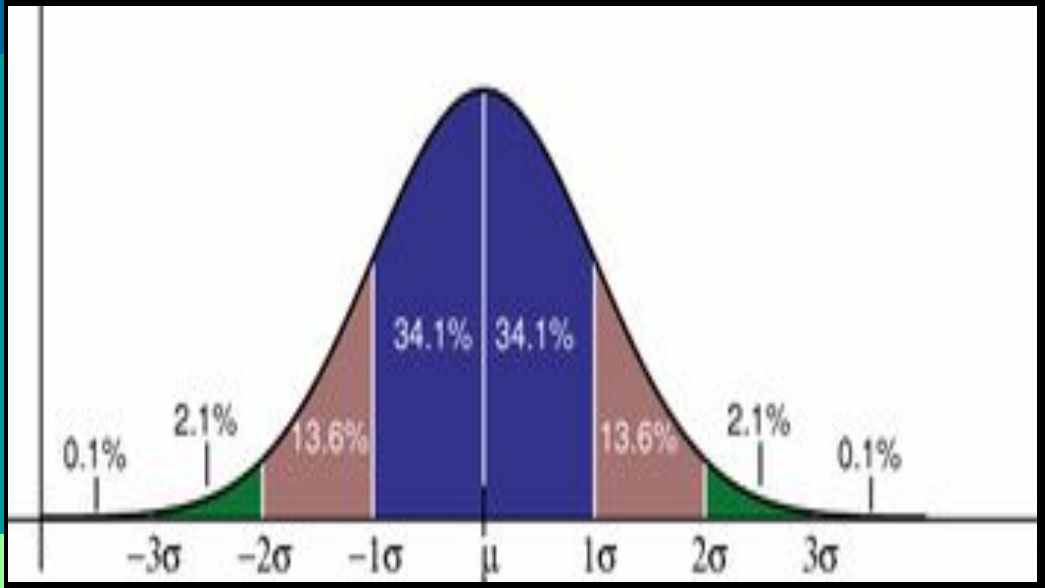
Treatment of proteinuria: blood pressure

- Blood pressure reduction improves proteinuria: target **<125/75 as tolerated**
- Blood pressure reduction decreases cardiovascular risk even in the normotensive range
- Blood pressure reduction by RAS blockade has specific advantages by directly targeting glomerular pressure
- Combination treatment (with CCB or BB or clonidine) often necessary because hypertension is typically difficult to control
- Some CCB have been shown to increase proteinuria by decreasing afferent arteriolar tone (hence autoregulation) but: often necessary as they are potent blood pressure medicines (joke: AASKD study….)
- Transplantation: prevention of chronic rejection and treatment of recurrent disease

CHRONIC RENAL INSUFFICIENCY: GFR TIMELINE

NKF Stage	DESCRIPTION	GFR ml/min/ 1.73 m^2	COMPLICATION	PREVALENCE (adults> 20yrs)
↑ risk	At risk: DM, HTN AfrAm; Native Am	**≥ 90**	Microproteinuria; HTN; hyperfiltration, high BS	>20 million (> 12%)
1	Early renal damage	≥ 90	proteinuria, hematuria HTN; progression	>5.9 million (3.3%)
2	Mild renal insufficiency	60-89	Proteinuria/hematuria; HTN; progression	>5.3 million (3%)
3	Moderate renal insufficiency	30-59	Metabolic acidosis; anemia; hyperparathyroidism	>7.7 million (4.3%)
4	Severe renal insufficiency	15-29	Metabolic acidosis; anemia; hyperparathyroidism; fluid balance; potassium	0.4 million (0.2%)
5	ESRD	< 15	Metabolic acidosis; anemia; hyperparathyroidism; fluid balance; potassium	0.4 million (0.1%)

Laboratory Tests versus Subjective Measures



- Laboratory medicine: population average ±2SD=normal
- Lab tests: easier to use, more convenient
- Take less time to assess
- Easier to document
- More readily standardized (for reporting to supervising agencies)

Proteinuria versus eGFR: CAVEATS!

- Proteinuria may be false positive in the presence of urinary tract infection, hematuria (Foley specimen) or after exercise.
- eGFR equation is based on study with a study population of moderate CKD; it may be low in healthy patients without CKD or falsely high in patients with advanced renal disease (bilateral nephrectomy with eGFR of 20)
- eGFR usually studied in a cross-sectional manner: it may not correlate with disease progression in an individual patient- many patients with low GFR are stable for years so far as blood pressure, proteinuria, volume and underlying disease (diabetes, hypertension, lupus etc) are under control
- eGFR does not necessarily correlate with other manifestation of renal disease in an individual patient: importance of comorbidity (CHF and salt retention, ADPKD and anemia) and control of underlying disease
- Main pitfalls of CKD: labels healthy patients with disease; ignores underlying disease process; selects out disease measures that may not correlate with global disease burden

Hypertension: does it need specialized treatment?

- CKD may exacerbate hypertension by multiple pathways[1-3]
  - ~~Volume overload~~
  - **Renin-angiotensin-aldosterone system stimulation**
  - **Increased sympathetic activity**
  - **Vascular calcification/accelerated atherosclerosis= high pulse pressure**
  - **Close association with OSA in the Mississippi population**
- Hypertension increases the risks of cardiac disease[4] and further decreases renal function, particularly in diabetic patients [5]
- ACE inhibitors and ARBs can slow deterioration of renal function in diabetic and non-diabetic patients [6-8] but risky in ischemic nephropathy (OSA, severe atherosclerosis); related hyperkalemia often responds to diuretics
- Combination treatment often including a diuretic is usually necessary

1. Anderson S et al. In: *Brenner & Rector's The Kidney*, 2000; 2. Laragh JH et al. In: *Brenner & Rector's The Kidney*, 2000; 3. Mailloux LU et al. *Am J Kidney Dis*. 1998;32(suppl 3):S120-S141; 4. Parfrey PS et al. *J Am Soc Nephrol*. 1999;10:1606-1615; 5. ADA. *Diabetes Care*. 2001;24(suppl 1):S69-72; 6. Lewis EJ et al. *N Engl J Med*. 1993;329:1456-1462; 7. Jafar TH et al. *Ann Intern Med*. 2001;135:73-87; 8. Brenner BM et al. *N Engl J Med*. 2001;345:861-869.

Care of patients with GFR > 90

- Renal ultrasound: size, shape, echogenicity; r/o hydronephrosis
- Metabolic screens: HbA1C, fasting lipids, protein quantitation serum electrolytes
- Stop NSAIDS
- **Refer to nephrologist for evaluation**

Interventions for At-Risk Patients

- Control BP: ACEI, ARB, β- and Ca Channel Blockers, etc
- Control Na intake
- Control BGs: DCCT KI 1995; 47:1703.
- Control Lipids: Statins (may decrease chronic inflammation)!
- Nutrition: lower protein intake: MDRD NEJM 1994; 330:877.
- Avoid toxic drugs: NSAIDS (includes Cox-2 I)
- Stop smoking
- Weight reduction, exercise!
- Check for proteinuria rise in serum creatinine
- For diabetic patients: follow the urine albumin to creatinine ratio (initial screening) or protein/creatinine if proteinuria already present (>200 mg/day)

Metabolic Syndrome and Renal Progression-2

Some of the benefits of exercise in CKD:

- Better blood pressure control even in ESRD patients
- Better volume control (sweating)
- Less chronic inflammation
- Improved insulin sensitivity
- Less depression=better compliance
- Weight loss=better OSA control

Moderate CKD

- Anemia: variable production of erythropoietin; iron deficiency almost universal; anemia is often associated with nephrotic syndrome, slow GI bleed
- Metabolic acidosis: as the kidney fails to recover sufficient HCO_3^-, bone is used as a buffer -diet, diuretics
- Hyperphosphatemia: develops as phosphate cannot be sufficiently cleared. Hypocalcemia follows due to lack of 1-25 OH-Vitamin D_3 production by kidney and to "salting out". Secondary hyperparathyroidism is one of the complications from this process.
- Incipient nutritional deficiencies develop with the protein malnutrition/chronic inflammation syndrome
- Variations in drug metabolism and excretion (insulin, antibiotics).

Monitoring CKD and Related Complications: Laboratory and Clinical Checklist

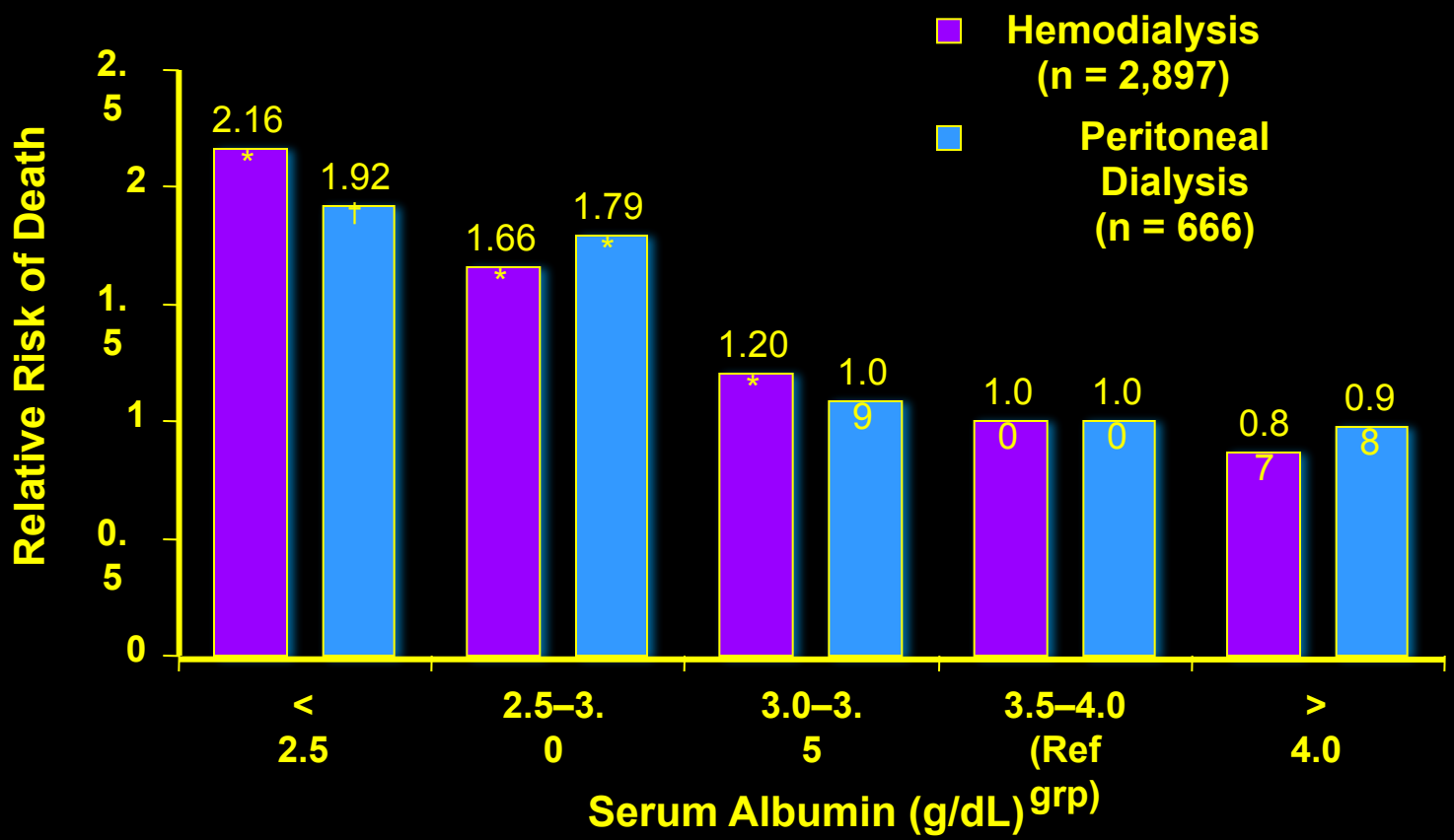
Laboratory Test	Normal Values	Recommended Targets
BP (mm Hg)	< 120/80	< 130/80
Hb (g/dL)	13.5 – 17.5	10 to 11,5
TSAT	20 – 50%	> 20%
HbA_{1c} (%)	4.55 – 5.55	< 7
Phosphorus	<4	< 5.5

Levey AS et al. *Am J Kidney Dis.*1998;32:853-906; NKF-K/DOQI. *Am J Kidney Dis*. 2001;37:S182-S238; Burtis CA et al. *Tietz Textbook of Clinical Chemistry*, 1998. ADA, 2001 (modified).

Nutritional Challenges in CKD

- As the kidney fails, protein intake should be maintained at 1 g/kg/day (early on this is a reduction later on it may be an increase) and caloric intake at 25-35 kcal/kg/day. These goals, if not approached carefully with a disciplined diet, often result in:
  - hyperphosphatemia
  - hyperkalemia
  - uremia
  - hypoalbuminemia ± elevated CRP
  - metabolic acidosis
  - iron deficiency

Hypoalbuminemia at Dialysis Initiation: Mortality Association



*P<0.01 compared to ref group

†P=0.02 compared to ref group

Port FK. *Kidney Int.* 1994;46:1728-1737.

If referred at this stage…..

- Hypervolemia, CHF, uncontrolled BP
- Malnutrition, chronic inflammation: increased cardiac and infectious morbidity
- Untreated anemia, renal bone disease
- Delays in modality teaching and transplant workup and referral (pre-emptive transplant….)
- Access problems (temporary access: increased mortality)
- Etiology for enormous incident mortality (first year) on hemodialysis

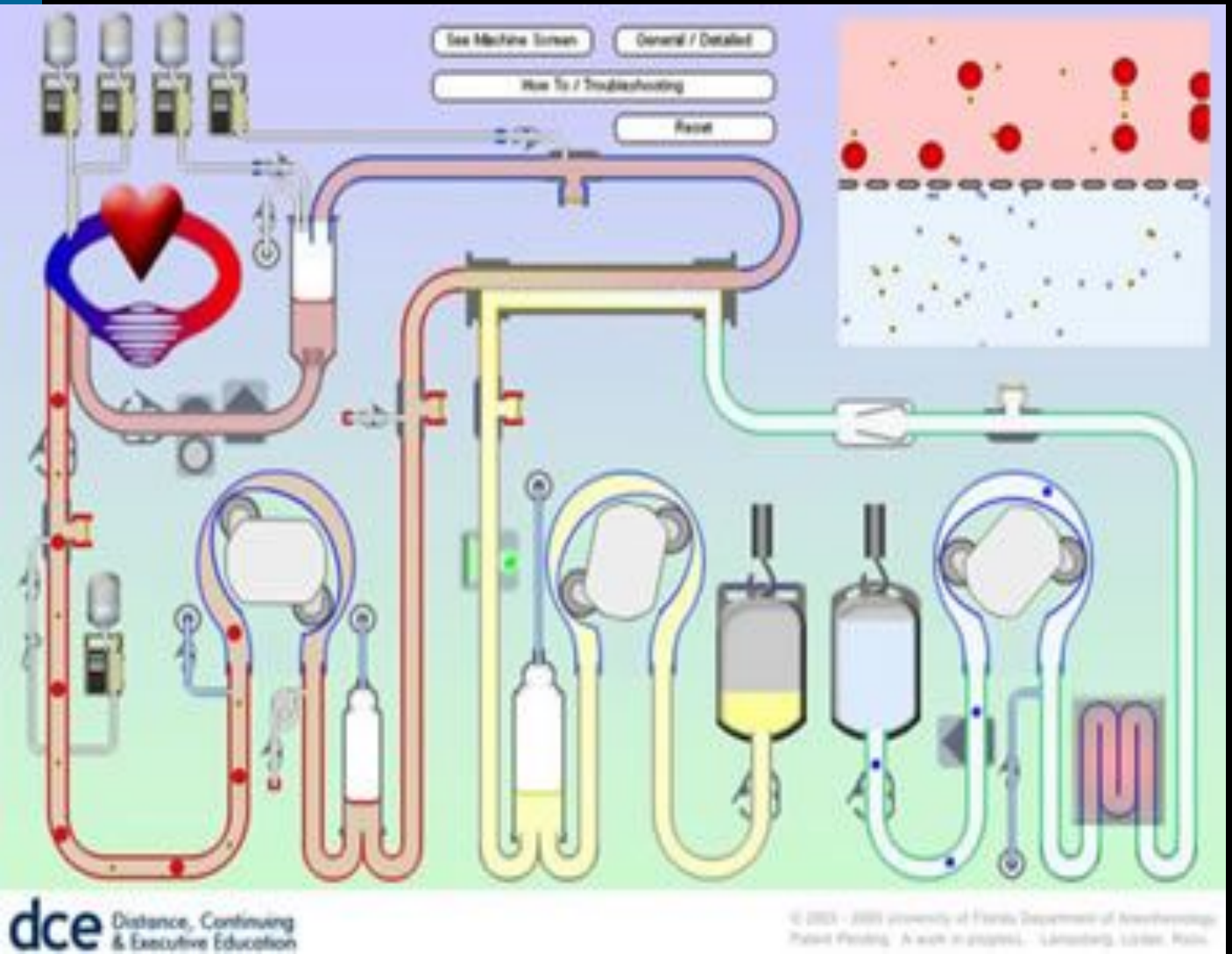
CKD Patients are different

- Different set of mortality predictors
- Different medication pharmacokinetics and adverse effects: sulfonylureas, insulin, methformin, antibiotic dosing, seizure medication dosing, different reaction to antihypertensive medications
- Different and additional problems: bleeding tendency (warfarin and atrial fibrillation), immunocompromized state, volume overload due to diastolic dysfunction……
- Special psychological issues: denial, depression, non-adherence, polypharmacy, decreased quality of life

Common Medications Need-Renal Adjustment!

- Many CKD patients are diabetics- less insulin is needed. Certain medications cannot be used (methformin may cause severe lactic acidosis) certain other medications (sulfonylureas) must be used with caution.
- Higher diuretic dosages are commonly needed
- Many antibiotics need reduction in dosages
- Many common analgesics (non-steroidals) are contraindicated
- Many other medicines need dose adjustmens!
- Consult PDR, pharmacist or a nephrologist

Hemodialysis: the arrangement and weak points



- Hemodialysis is dependent on hemodynamic stability as well as regional blood flow
- Efficiency is strongly dependent on mixing between tissues
- Uremic toxins are largely unidentified but so far as we know display variability in diffusion and distribution
- Viscosity,clotting are important modifiers
- Varying resistances on basis of needle/access characteristics

Once upon a time....

Since:

low flux, low efficiency dialysis improve

1. Hyperkalemia
2. Volume overload
3. Acidosis
4. Encephalopathy
5. Pericarditis
6. Bleeding Diathesis
7. Severe nausea

Therefore:

low flux, low efficiency dialysis must remove

1. Potassium
2. Salt, water
3. Acid
4. Other low molecular, free solutes such as urea that we can name “uremic toxins”

What does dialysis do?

- Dialysis removes things
- When it removes salt and water, we call that ultrafiltration
- When it removes mysterious uremic toxins, we call that clearance
- Why are salt, water, phosphorus, simple acids, potassium not included in the category of uremic toxins? Unlike urea they are actually toxic!!!!

What is hemodialysis?

- Hemodialysis is a complex therapeutic intervention associated with multiple effects and side effects
- Hemodialysis should be renal replacement therapy aiming to replace *most functions of the failing kidney* and to improve quality of life
- Hemodialysis should bridge the time until a transplant kidney becomes available; it also should preserve residual function as long as possible

Egy kis élettan (vissza az egyetemre!)

1. Toxikus anyagok eltávolítása *kis és közepes molekulasúlyú, fehérjekötött vagy sem, extra- vagy intracellularis, példa: p cresol,* foszfor, nátrium
2. Só és vízháztartás szabályozása *vérnyomás, euvolémia, folyadékeltávolitás sebessége-* hemodynamikus stabilitás
3. A sympathikus idegrendszer aktivitása vérnyomás, *cardiac output*
4. Elektrolytszintek homeosztázisa *K, Mg, P, Ca….stb*
5. Pufferek homeosztázisa a csontpuffer aktivitásának minimalizálása
6. Hormonelválasztás *erythropoietin, renin, D vitamin*
7. Gyógyszerek metabolizmusa, eltávolítása *insulin, antibiotics….etc*
8. Megfelelő tápláltság, az immunrendszer optimális készenléte alultápláltság, krónikus gyulladás, fertőzések

Optimális művesekezelés: vese **valamennyi** funkciójának az **elérhető maximális mértékű** pótlása

The Fateful Assumption

alias

"Let us start the battle and then we shall see!"

(Napoléon)

- **Change in urea concentration during dialysis can approximate "dialysis dose"**
- Sargent & Gotch 1975: concentration change during dialysis equals generation during dialysis minus removal during dialysis
- As concentration of urea changes from C_0 to C_t during dialysis from time t_0 to t_d then:

$$\int_{Co}^{Ct} VdC/ [G - (K_d+K_r)C] = \int_{to}^{td} dt$$

where V = distribution volume of urea

Co= pre BUN

Ct = post BUN

G = urea generation during dialysis

Kd= dialyzer clearance

Kr= residual renal function during dialysis

t = time from beginning to end of dialysis

Dialysis Clearance: Definition

- Measure of urea removal ($K_{urea}t$) by a *single dialysis* session irrespective of

-dialysis membrane quality

-speed of dialysis

-modality of dialysis (peritoneal, home, platforms)

-composition of the dialyzate

Normalized by a hypothetical urea distribution volume (V) extrapolated to represent 12-13 dialysis sessions per month irrespective of hemodynamic or other toleration of sessions.

- Gotch 1984: it does not seem to matter *how* urea is removed *so far as we achieve a* $K_{urea}t/V$ *of 0.8*, dialysis can be considered as adequate

CKD Patient Care: *Additional* Suggestions for Advanced Disease

Nephrologist and team to address:

1. Inflammation/malnutrition- timely initiation of renal replacement therapy based on subjective global assessment of nutritional status to avoid catabolism/volume overload/infectious complications ("avoid low albumin")
2. Timely transplant referral when appropriate
3. Access referral based on 1. and 2.-do not use CKD stages alone as it may be misleading (stable vs. progressive disease) and base this also on 4. ("avoid catheters")
4. Dialysis modality and general dialysis education-enhance awareness, lifestyle options, medical factors such as cardiovascular status, metabolic status, volume status; address polypharmacy by modality selection ("quality of life")
5. Address denial, depression, non-adherence ("dispel fear and legends about ESRD")

The Fateful Inference: Renal Clearance to Dialysis Clearance

- CP=UV

where

-P is the plasma concentration of an ideal filtration marker

-U is the urinary concentration of an ideal filtration marker

-V is *urinary flow rate* (or urine volume for 24 h clearance)

- UV: urinary removal of a substance over time
- C: P-independent virtual term representing virtual volume cleared (assumption: even distribution of ideal marker in total body water and instant refill to plasma from extra-vascular space, an assumption

Inference: Renal Clearance to Dialysis Clearance 2.

- Renal clearance as defined for quantification of renal excretory function (continuous filtration by natural membrane plus multiple level of regulation by both filtration and tubular secretion/reabsorption

can be applied (by analogy) to

- Dialysis, a discontinuous filtration by an artificial membrane with different filtration characteristics not supported by multiple level of regulation and subject to characteristics of regional blood flow patterns

  that has hemodynamic (and other) side effects hindering equilibration of marker from tissues to plasma and from plasma to the dialyzate

Dialysis clearance- Why is it misleading?

- The concept of stdKt/V critically omits the dependence of dialysis quality and dialysis tolerance on time exposure (the choice of urea as a marker merely exacerbates this problem) and the qualitative difference between residual renal clearance and dialysis clearance

$$K\uparrow t\downarrow = K\downarrow t\uparrow$$

And

$$Kd = Kr$$

Dialysis modality and general dialysis Education

1. Lifestyle options- dialysis and work, dialysis and travel, dialysis and exercise etc.
2. Medical factors-cardiovascular disease, volume, phosphorus control
3. Polypharmacy- many of the medications can be discontinued or modified

Proper modality selection may improve quality of life, enhance social functioning, dispel fear, improve depression and related non-adherence, perhaps sometimes obviate the need for antidepressives.

Sudden Cardiac Death and the Weekend

Characteristics of sudden death in hemodialysis patients

AJ Bleyer[1], J Hartman[1], PC Brannon[2], A Reeves-Daniel[1], SG Satko[1] and G Russell[2]

[1]Section on Nephrology, Department of Internal Medicine, Wake Forest University School of Medicine, Winston Salem, North Carolina, USA and [2]Section on Biostatistics, Department of Public Health Sciences, Wake Forest University School of Medicine, Winston Salem, North Carolina, USA

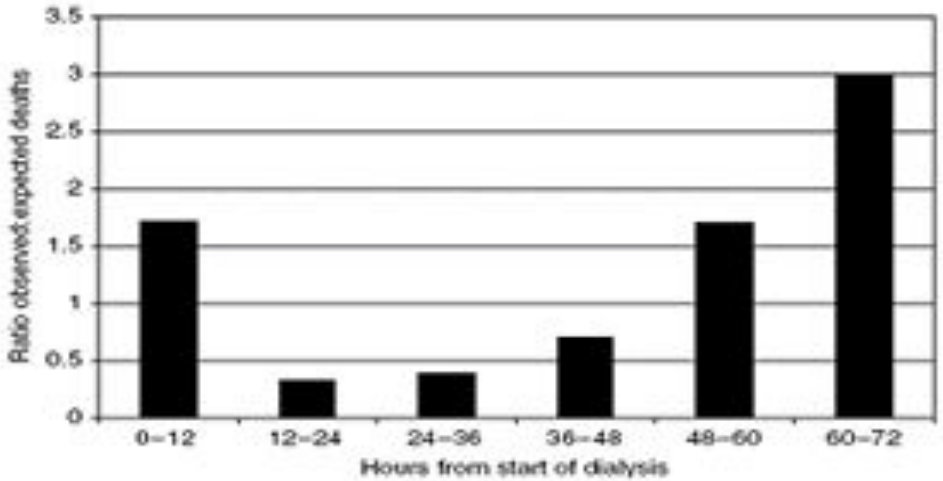


Figure 2 | Ratio of actual to expected number of occurrences of sudden death for each 12 h interval beginning with the start of HD.

Bleyer et al KI 2006

Sudden Cardiac Death and SGA

- Most dialysis patients have cardiac fibrosis predisposing them for arrhythmia
- Most dialysis patient deaths are due to sudden cardiac death
- They tend to occur either immediately after dialysis (rapid electrolyte shifts, acute phase reaction) or after weekends (hypervolemia, hyperkalemia etc)
- So: short of increasing dialysis time and frequency dietary restrictions of Na, K, acid may help
- Ideal dialysis: small differences in electrolyte concentrations due to slow and continuous removal

Fluctuations…..and SGA

- Italian patient with a strong preference for tomato dialyzed MWF: K levels before and after dialysis: Monday 6.5→3.4, Wednesday 5.6→3.2, Friday 5.4 →3.1 dialyzed for 3.5h on a 1 K bath
- Non-Italian patient with no preference for tomato dialyzed MWF: K levels before and after dialysis: Monday 5.5→3.8, Wednesday 5.6→3.9, Friday 5.4 →3.7 dialyzed for 4h on a 3 K bath
- Who is likely to survive longer **with the same pre K level on Wednesday**? How would you modify dialysis in the Italian patient based on subjective assessment of dietary intake/preferences?

Subjective Global Assessment: a Different kind of Inference

- If Subjective Global Assessment of *nutritional status*

  assessed *by a dietician* works
- Then by analogy perhaps Subjective Global Assessment of

  clinical status

  assessed *by a doctor* may also work

Plasma Refill Rates

- Plasma refill rates in stable patients:

-Nephrotic syndrome 19.9 ml/min

-CKD 16.5 ml/min

-CHF 12.7 ml/min

- In acute decompensation may be much lower

Sudden Cardiac Death and CKD

Unlike in the non-CKD population sudden cardiac death in CKD is often:

- not due to coronary artery disease
- risk of coronary events are higher after a major infection (at least in ESRD)
- Is due to cardiac fibrosis-related arrhythmias associated with

-chronic volume overload

-left ventricular hypertrophy (often with diastolic dysfunction)

-hyperkalemia

-sympathetic nervous system activation

-RAS activation

Intermittent versus Continuous Clearance
alias Kd vs. Kr

- Residual Renal Function:

-is continuous therefore does not share rapid loss of efficiency of intermittent techniques

-no compartment effects

-removes middle, large and protein-bound molecules

-does not decrease blood pressure

-perfectly biocompatible

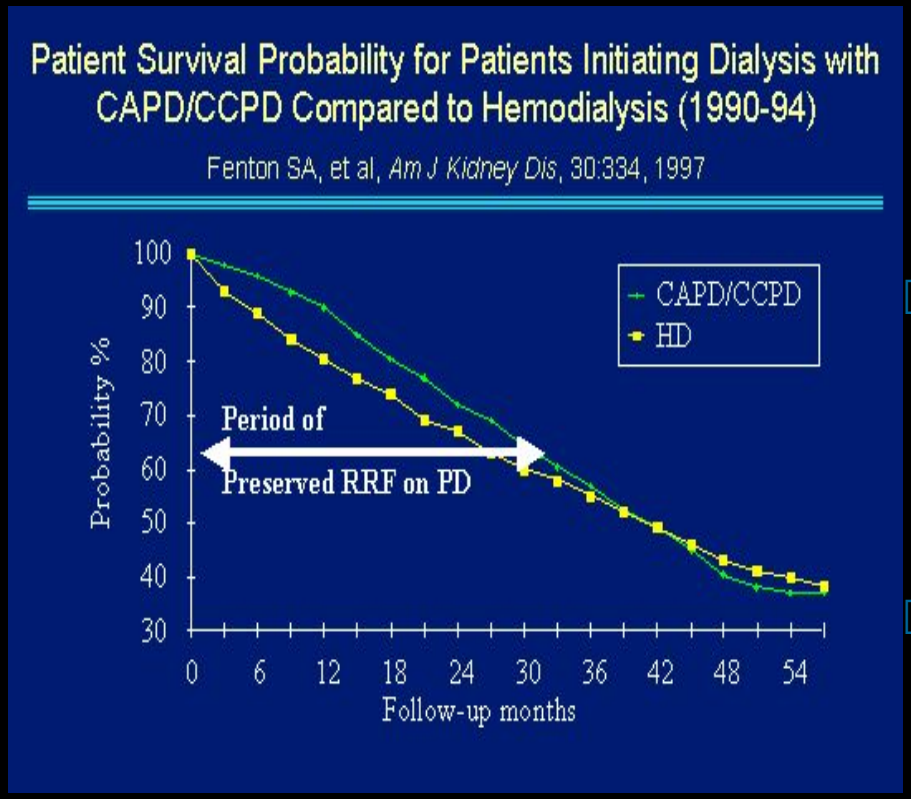
-does not require access and anticoagulation

so……

Long term problems associated with Hemodialysis

1. Rapid loss of residual function
2. Poor efficiency in removing non-urea like uremic toxins *(β2M, P-cresol etc)*
3. Difficulty achieving euvolemia
4. Additional hemodynamic stress due to rapid removal of volume and osmoles
5. Several additional medications needed to control blood pressure and phosphorus
6. Does not replace renal hormones
7. High catabolism, chronic inflammation, immunocompromized state

Importance of Difference in RRF Decline between Modalities



- RRF is relatively preserved in the first 2-4 years after initiating PD
- Survival tends to be better in the first few years on PD then is identical with HD
- Part of this (other possible factors: weight gain, accumulating AGEs, membrane damage etc) may be because of RRF

RRF Decline and Modality

- PD better: less hemodynamic effects than HD
- PD better: no bio-incompatible membranes
- PD better: better BP control
- PD worse: peritonitis?, dialysate volume?
- In PD additional associated factors:

-diabetes

-male sex?

-impaired LV function

-proteinuria

-BP meds, aminoglycosides,

- NSAIDS statistically not a factor (probably does depend on dose)

Életminőség a hemodialízisben-gyakori tünetek

- Kognitív zavarok, szorongás, depresszió
- Étvágytalanság, diétás megszorítások
- Emésztési zavarok, emésztőrendszeri vérzések, székletürítési zavarok
- Fáradtságérzés, heti háromszori szívterhelés (intradialitikus hypotenzió: USA-ban a leggyakoribb tünetek egyike), rossz funkcionális állapot
- Hospitalizáció: kanülfertőzések, szívelégtelenség (folyadékelvonás elégtelensége)
- Izom-, ízületi- és csontpanaszok (foszforeltávolítás elégtelensége)
- Nemi funkció zavarai, meddőség
- Számos kiegészítő gyógyszer: erythropoetin analóg, vitamin D, foszforkötők, vérnyomáscsökkentők stb.

A dialízis és transzplantáció: amerikai eredmények

- A halálozás magasabb a várólistán, mint a transzplantáció után, különösen cukorbetegek esetében (Ojo et al JASN 2001)
- A transzplantációs halálozás és a transzplantált vese túlélésének egyik rizikófaktora a dialízis előzetes tartama (Meier-Kriesche et al Am J Transplant 2001)
- A beteg életminősége gyakran sokkal rosszabb a művesén (mindennapi tapasztalat)

Életminőség és túlélés a hemodialízisben: van közös nevező?

Halálozási tényező	Hozzákapcsolódó tünet
folyadékeltávolítás sebessége	vérnyomásesés
krónikus gyulladás	levertség, fáradtságérzés
foszforeltávolítás elégtelensége	fájdalom, viszketés
érbemeneti fertőzések (kanül)	kardiális morbiditás

- **Mi befolyásolja leginkább e tényezőket a hemodialízisben- s ez a valami talán meghatározza mind az életminőséget, mind a halálozást?**

A halálozást bizonyítottan meghatározó tényezők

1. Gyulladásos és metabolikus változók: Se albumin, CRP, IL-6, BMI, koleszterin, kreatinin, szubjektív táplálkozási felmérés
2. Hemodynamikai változók: 24 h vérnyomás, intradialitikus hypotenzió, pulzusnyomás, UFR, diuretikus hatás, BNP, Troponin T
3. Szérum elektrolytok: Se kálium, Se foszfor, Se kálcium
4. Uremiás anyagok: p-cresol, urea vérszint , urea clearance?, B2 microglobulin?
5. Gyógyszerek: carvedilol, sevelamer?, D vitamin?

   nem: aszpirin, ACEI, atorvastatin, erythropoetin, vérnyomáscsökkentők
6. Egyéb: maradék vesefunkció,

   érbemenet: kanül

   nem: Qb, Qd, high-flux?

Egy változó kimaradt a felsorolásból.....

Jellemezhetjük-e egyetlen változóval (clearance) a vese/művese *valamennyi* funkcióját?

- Művesekezelés elkezdése előtt: **talán (GFR)**

  clearance, vagy eGFR (MDRD)-
  populációs szinten, az egyes betegekben a funkcionális eltérések jelentősek lehetnek

- Művesekezelés alatt: **biztosan nem** (Kt/V_{urea})

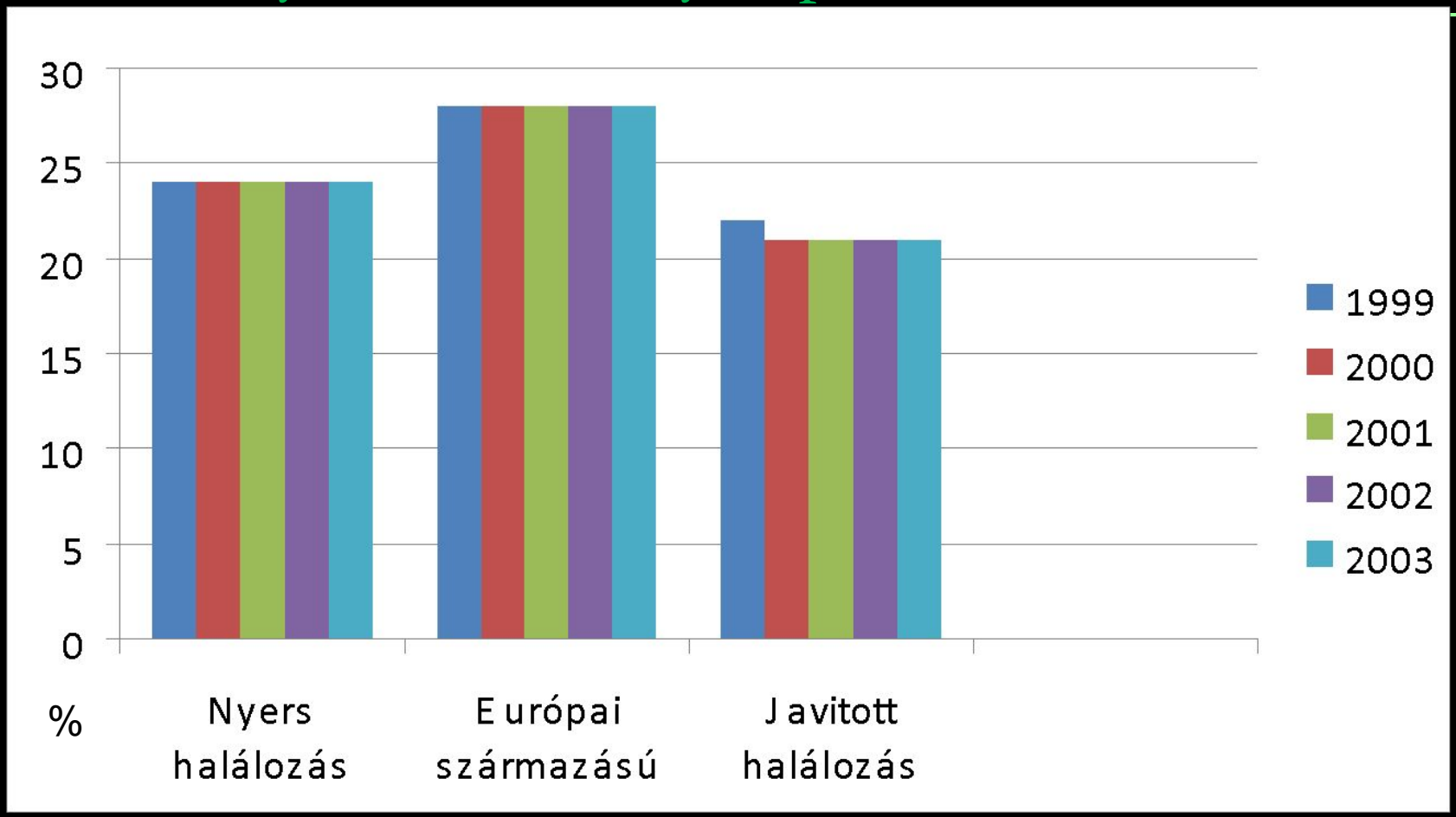
  -nem korrelál más funkciókkal (albuminszint, krónikus gyulladás mértéke, foszforeltávolitás, folyadékeltávolítás, p-cresol, B2 microglobulin
  -a maradék vesefunkció tovább befolyásolja a túlélést, a folyadékháztartás egyensúlyát, számos uraemiás toxin eltávolítását és a krónikus gyulladás mértékét optimális Kt/V_{urea} mellett is

Optimális terápiás megoldások: a közös nevező a kezelés *tartama*

- Transzplantáció: folyamatos vesefunkció
- Peritoneális dialízis*: folyamatos vesefunkció
- Hordozható művese: folyamatos művesefunkció
- Otthoni dialízis-kezelés: folyamatost jobban megközelítő művesefunkció
- Hosszabb hemodialízis: folyamatost jobban megközelítő művesefunkció

*Első 1-2 év, amikor a maradék vesefunkció még számottevő

Mortality of hemodialysis patients 1999-2003



* USRDS 2005 Data Report

Prevalent patients(≥90 days) –corrected mortality by age, sex, race, primary diagnosis, vintage.

Mortality and graft loss is influenced by prior dialysis vintage

Relative risk of mortality by prior dialysis vintage (in years)

- Pre-emptiv (0)

0.75 (0.70-0.81) <.0001 Graft Survival
0.78 (0.72-0.85) <.0001 Death Censored
0.68 (0.61-0.76) <.0001 Death

- 1-<2

1.09 (1.04-1.14) 0.0002 Graft Survival
1.01 (0.96-1.07) Death Censored
1.22 (1.14-1.30) <.0001 Death

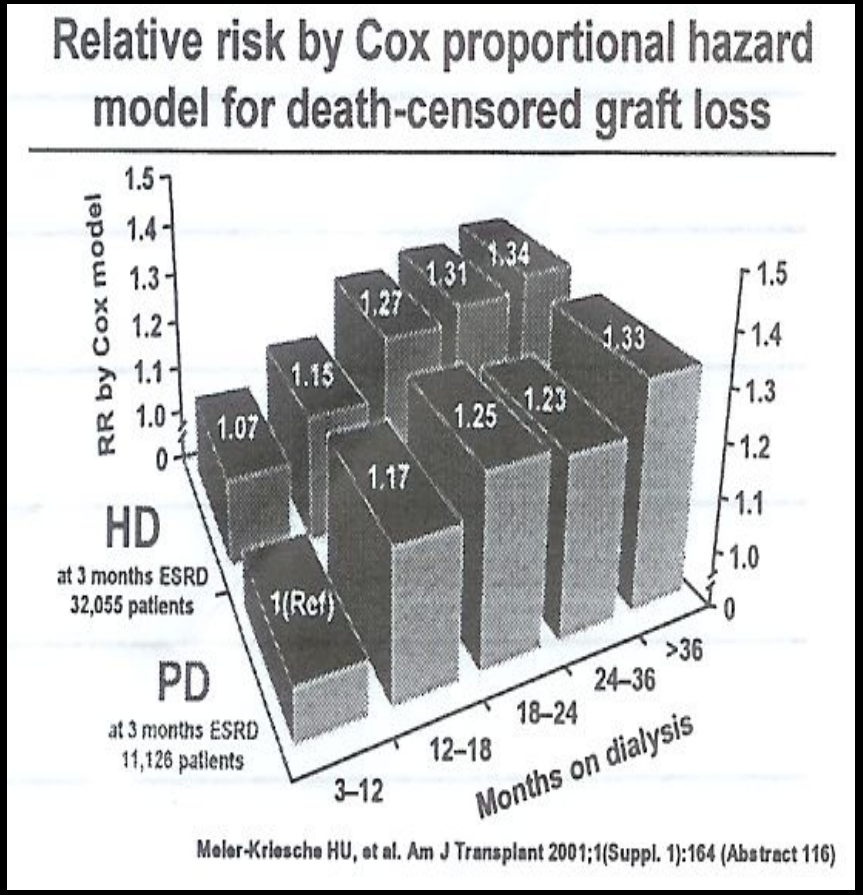
- 2-<3

1.11 (1.06-1.17) <.0001 Graft Survival
0.99 (0.93-1.06) Death Censored
1.32 (1.23-1.42) <.0001 Death

- 3+

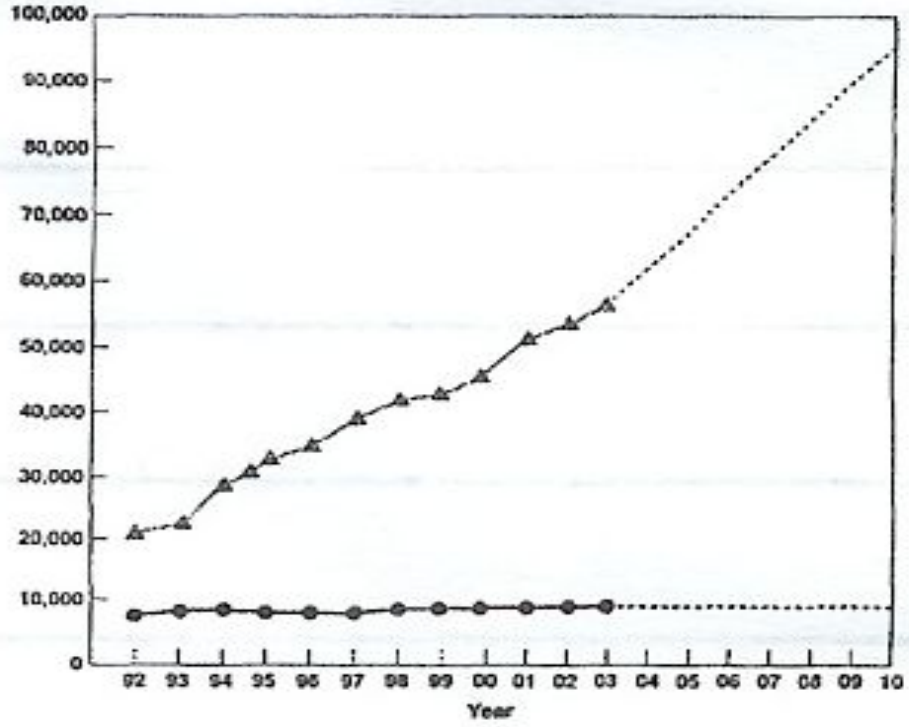
1.16 (1.10-1.22) <.0001 Graft Survival
0.97 (0.92-1.04) 0.42 Death Censored
1.49 (1.39-1.59) <.0001 Death

USRDS Annual Report 2002



Welcome to the Waiting List!

Current and projected waitlist for deceased donor kidneys



As of May 2003
54,000 awaiting CRT

Projected waitlist
95,550 in 2010 (Xue et al. JASN12:2753,2001)

Approx 9,000 CRTs per annum

Who benefits most?

Patient Group	Annual Death Rate Among WLD (%)	Days to Equal Risk	Days to Equal Survival	RR[a] (*P* Value)	Projected Extra Lifetime (yr)
All	6.3	185	531	0.75	5.1
Age (yr)					
18–29	2.2	163	547	0.85	6.4
30–44	5.4	134	309	0.78	4.9
44–54	6.5	196	521	0.70	6.3
55–64	6.5	193	580	0.66	7.3
≥65	10.0	171	475	0.71	3.8
Race					
white	7.5	184	481	0.68	5.9
black	4.8	172	691	0.86	3.1
other	6.3	211	513	0.59	9.9
Gender					
male	6.3	185	526	0.74	5.1
female	6.3	184	528	0.73	5.4
Cause of ESRD					
glomerulonephritis	4.3	192	501	0.82	4.6
hypertension	4.3	169	>700	0.71	8.5
diabetes mellitus	10.8	164	352	0.62	5.6
other diagnoses	4.3	194	663	0.75	6.7

Hemodialysis patients-life quality

- Cognitive impairment
- Anxiety
- Depression of chronic disease
- Loss of appetite, substantial dietary restrictions
- Fatigue -multiple etiology, major hemodynamic stress 3x per week w/wo intradialytic hypotension, uncontrolled hypervolemia, anemia
- Variable functional status (cardiac problems, frequent infections)
- Several chronic associated conditions-chronic bone/joint/muscle pain, neuropathy, dyspepsia, PUD, diverticulosis, GI bleed, constipation, accelerated atherosclerosis, chronic inflammation, recurrent infections etc
- Comorbid conditions (often of metabolic origin: diabetes, hyperlipidemia)

How many medications do you take a day?

- Blood pressure medications ≈5 tablets a day
- Phosphate binders ≈6 tablets a day
- Vitamins, bicarbonate, pain meds, aspirin, diabetic meds, appetite stimulants, antibiotics, calcimimetics, muscle relaxants, sleeping pills, anxiolytics many tablets a day
- Intravenous EPO, vitamin D, iron, heparin

  ? side effects: resistant hypertension,clotting, hypercalcemia, worsening infections, iron overload, free radicals, HIT, bleeding….

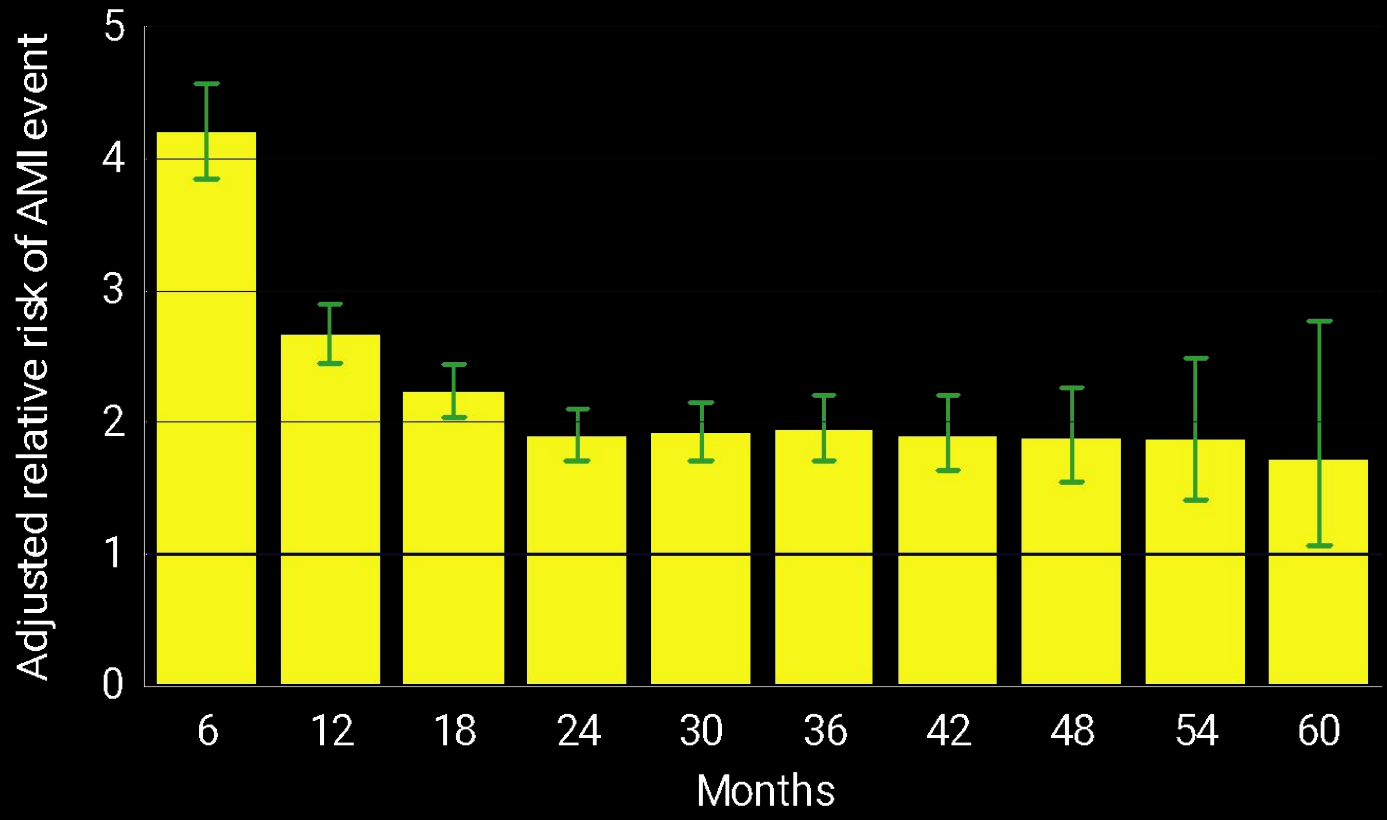
Hemodialysis: most of the outcomes are time dependent

- Dialysis frequency: usually 3x/week except when residual function is still relatively preserved (then it may be rarely 2x/week) or uremic pericarditis, severe uremic symptoms or pregnancy mandate more frequent treatments- but emerging data on superiority of daily hemodialysis
- Dialysis time: traditionally prescribed to achieve a Kt/V_{urea} product of 1.3 or greater; a minimum of 3 hours recommended unless residual function is still present; however, longer times are usually better tolerated and improve fluid status, blood pressure control, nutritional status, phosphorus control, cardiac function, anemia, life quality and survival (possibly also: less inflammation)

Hemodialysis prescription- Residual versus hemodialysis clearance

1. Residual renal function: superior to dialysis clearance; preserve by maintaining euvolemia, controlling high BP, giving ACE inhibitors, avoiding nephrotoxic materials, controlling comorbidities (e.g. diabetes)
2. Dialysis clearance: inferior to renal clearance; modify by dialysis time, maintaining good access, high flux dialyzers, high blood flow rate, high dialysis flow rate, larger needles, appropriate needle direction, hemodynamic stability- usually normalized by “urea distribution volume”

Acute myocardial infarctions after first sepsis event: adjusted relative risk of AMI event



Incident dialysis patients (90-day rule), 1996–1999 combined; adjusted for modality, age, gender, race, & primary diagnosis. Patients with Medicare as a secondary payor or enrolled in an HMO on day 90, & those with AMI claims overlapping the start date of the followup period, are excluded. Reference group: patients without sepsis.

NECOSAD : Relative Risk of Mortality

- Large multi-center prospective observational study in incident HD patients who survived the first 3 months (n=740)
- Follow-up to 36 months, Cox proportional-hazard model used for patient survival
- SGA is again a *strong independent predictor of mortality* (RR=0.89)
- RRF good predictor, dKt/V only a predictor in anuric patients

Nutrition/inflammation-being consistent

- Nutritional status should be closely followed in hemodialysis patients
- Malnutrition is more dangerous than obesity
- Anemia, infections (catheter biofilm, leg ulcers,periodontitis) and poor dialysis are potential risk factors (but the latter can cause both former)
- Constipation (BP meds) needs to be treated
- Exercise/rehab may be important- early mobilization in hospital
- Minimize hemodynamic stress on dialysis (UFR)
- Consider increasing treatment time irrespective of urea-based clearance especially in smaller patients

Summary-main parameters at the dialysis chair: “clearance”

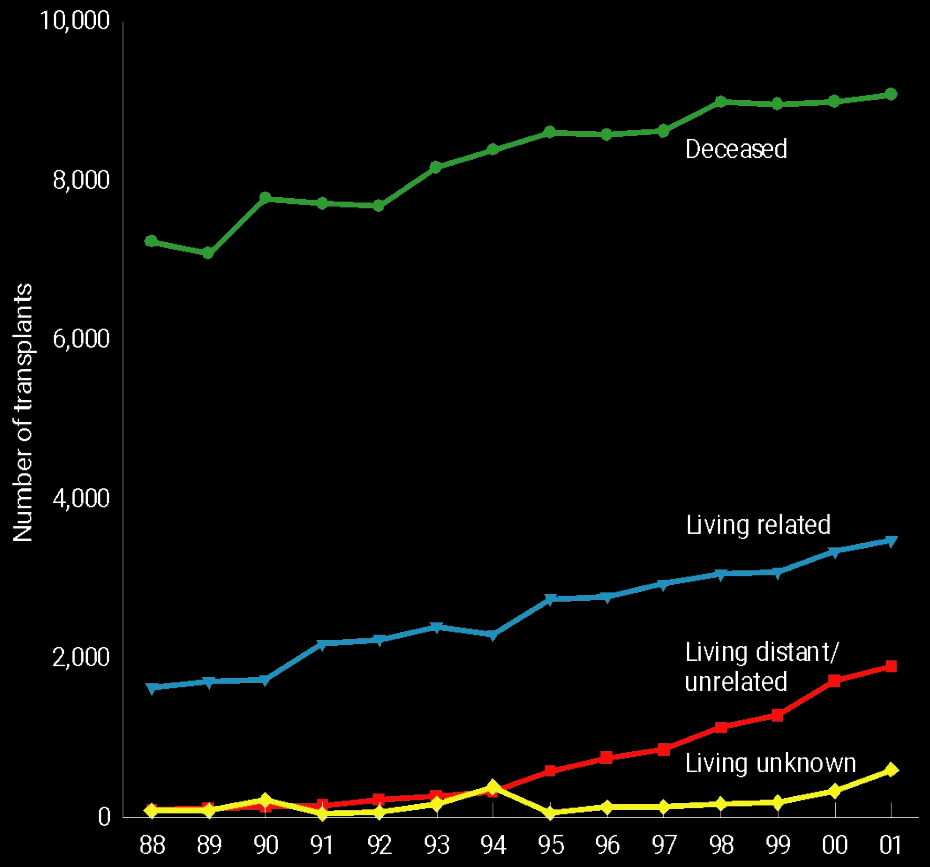
Dialysis dose/adequacy: subjective assessment with special attention to

1. loss of appetite
2. not feeling well
3. fatigue
4. consistent weight loss
5. low albumin
6. epo resistance
7. high inflammatory markers
8. access dysfunction
9. urea-based parameters -special attention to small or anuric patients and short treatment times

Conclusions

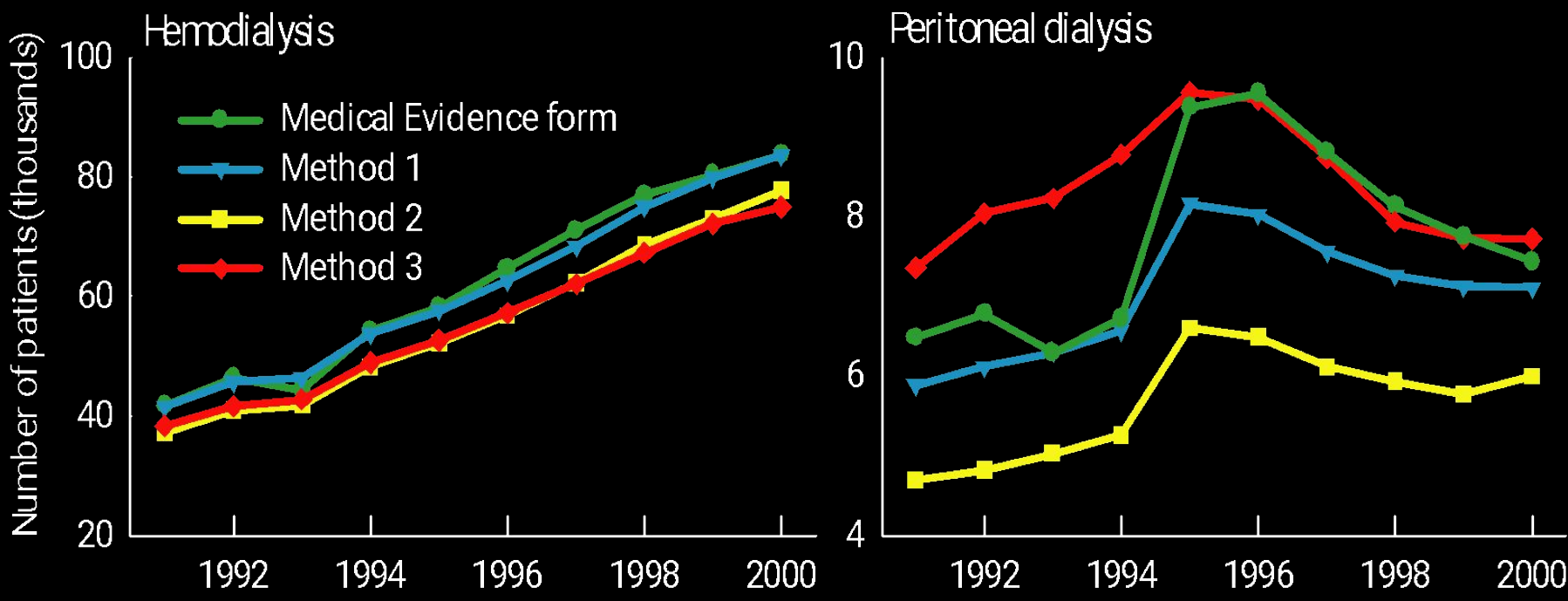
- Hemodialysis patients have numerous comorbidities and are prone to have cardiovascular, GI and infectious problems
- Hemodialysis can be done well: maximize treatment time, slow ultrafiltration and get as close to euvolemia as possible
- Special attention to nutrition then mobilize and discharge
- Rehabilitation, exercise, functional capacity are key on long term

Donor Type

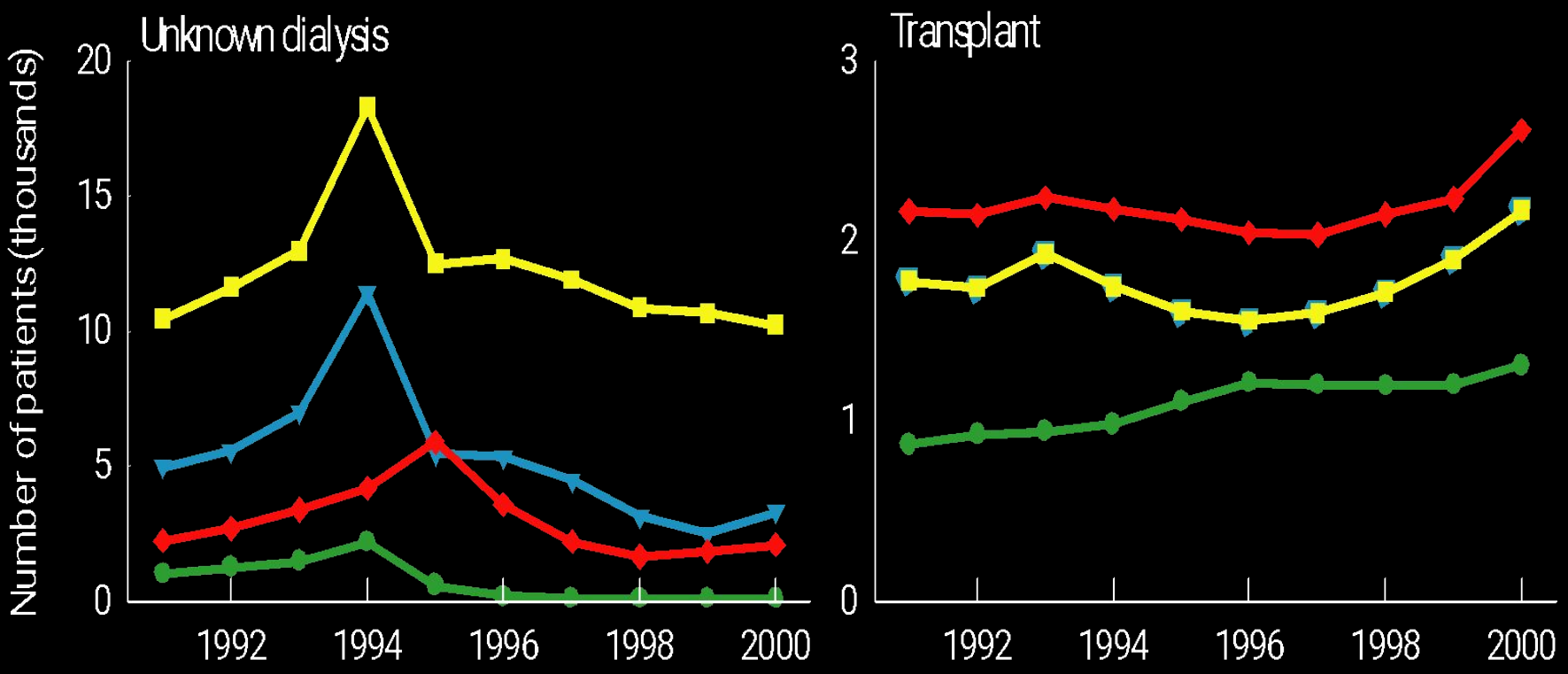


Transplant counts as known to the USRDS (reconciled from various sources).

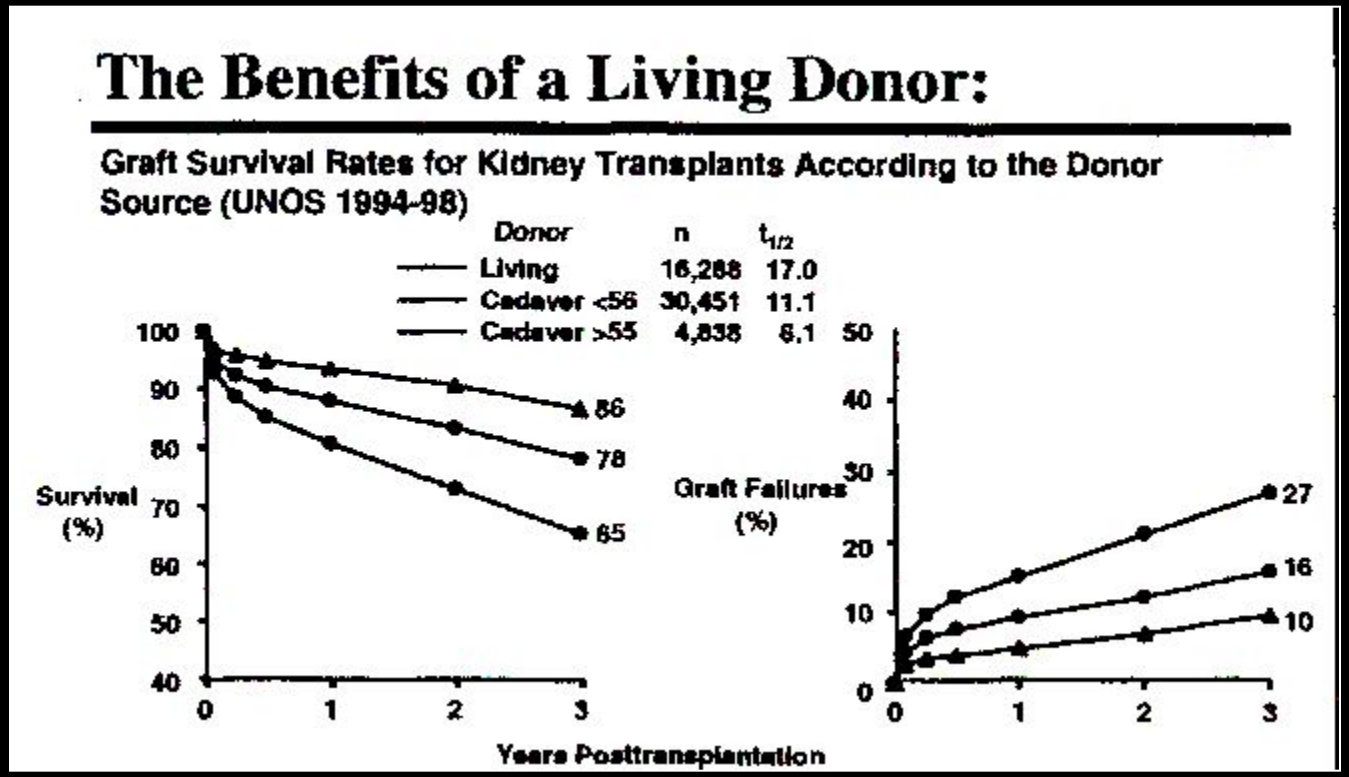
Organ Shortage



Organ Shortage II.



Expanding the Donor Pool: Optimal Solution



Organ Shortage: Why Bother?

- **Hemodialysis**:

-less clearance

-oscillating levels of toxins, potassium, water, osmoles

-frequent hemodynamic compromise-hypervolemia and delayed vascular refill

- **Transplantation:**

-clearances up to 60 ml/min

-continuous clearance

-frequent hypertension but less hemodynamic compromise

-lower cardiovascular risk even despite drug effects

We Pride Ourselves on Service!

- Hemodialysis:

"It is so good patients limp away from it"
(Lu-ya Zhong, **Tang Dynasty** Chinese Scholar)

<u>Expected remaining lifetimes in a 60-64 year old man in years:</u>

Dialysis 3.8
Transplant 10.5
General population 21.6

USRDS 2002 Annual Report

Conclusion from the Introductory Slides

- Get people out of dialysis as soon as possible
- Transplant may not be ideal solution but it is way better than dialysis as it is currently done
- Expand the donor pool by any means that are safe and ethical
- If living donors are not available try to expand the cadaveric donor pool

Death Rates

- WLD: 6.3% annual death rate (selected population!)
- MDK: 4.7% annual death rate ($p<0.001$)
- IDK 3.3% annual death rate ($p<0.001$)
- 5 year survival MDK versus IDK: 77% ;85%
- Survival advantage of IDK maintained at any time after transplantation

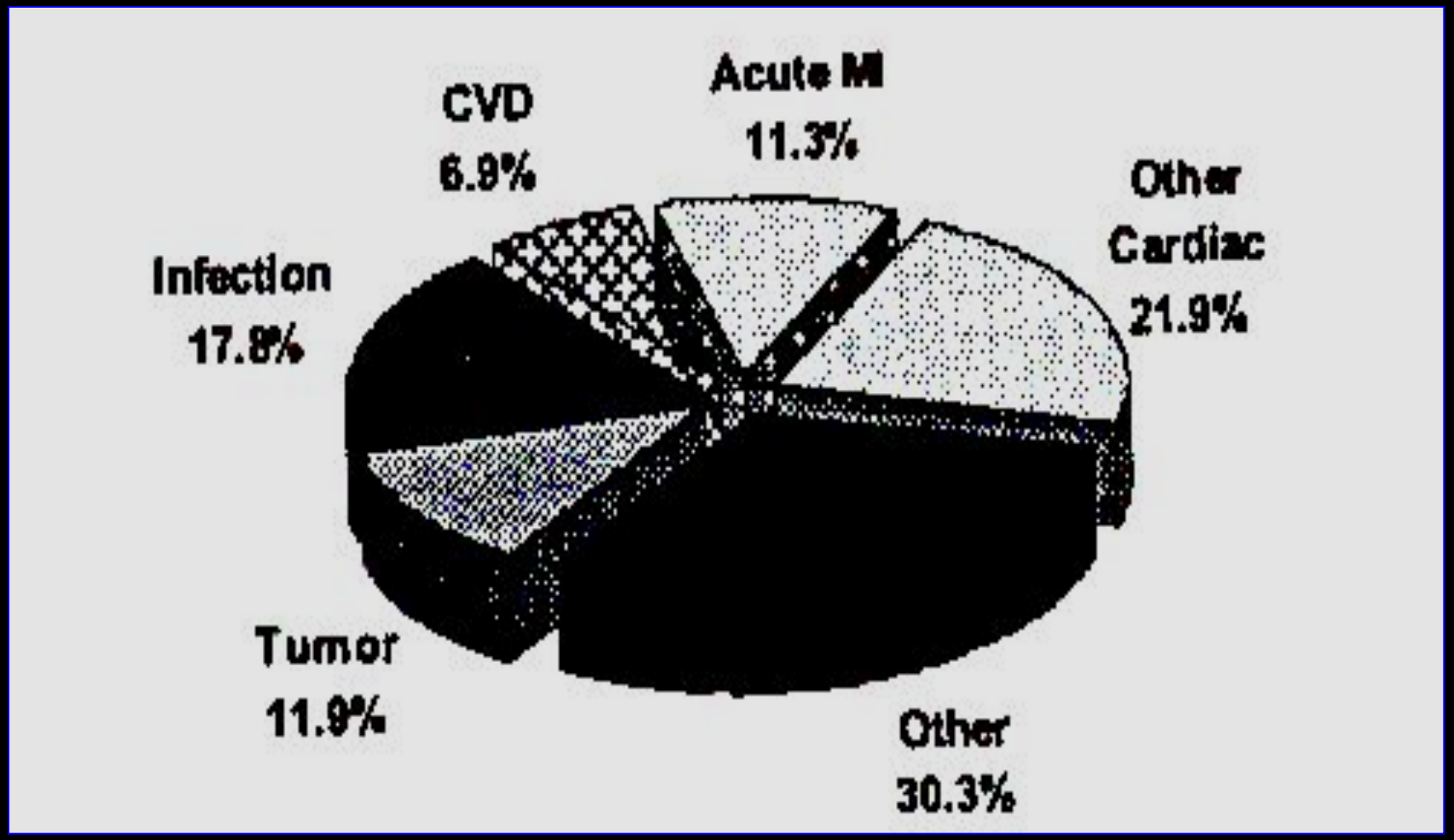
Life Expectancy

- WLD:MDK:IDK- 15.3: 20.4: 28.7 in years
- Young patients had longer survival benefits in years but equal proportional risk benefit
- Subgroup differences: diabetics and Europeans higher risk of death on dialysis
- Patients with lower mortality risk on dialysis benefited less from MKD

What does all of this have to do with Transplantation?

- Progressive Chronic Kidney Disease -termed Chronic Allograft Nephropathy (CAN)- is a major problem in transplantation.
- Renal Transplantation is actually a state of chronic renal disease since all grafts have a GFR of 60 ml/min or less
- Most patients arrive at their first transplant evaluation with already major cardiovascular risk factors
- Many anti-rejection medicines add new risk factors or worsen pre-existing ones
- Many transplant patients die of cardiovascular disease

Causes of Death in the Transplant Population



Organ Shortage III. Why Bother?

- **Hemodialysis**:

-less clearance

-oscillating levels of toxins, potassium, water, osmoles

-frequent hemodynamic compromise-hypervolemia and delayed vascular refill

- **Transplantation:**

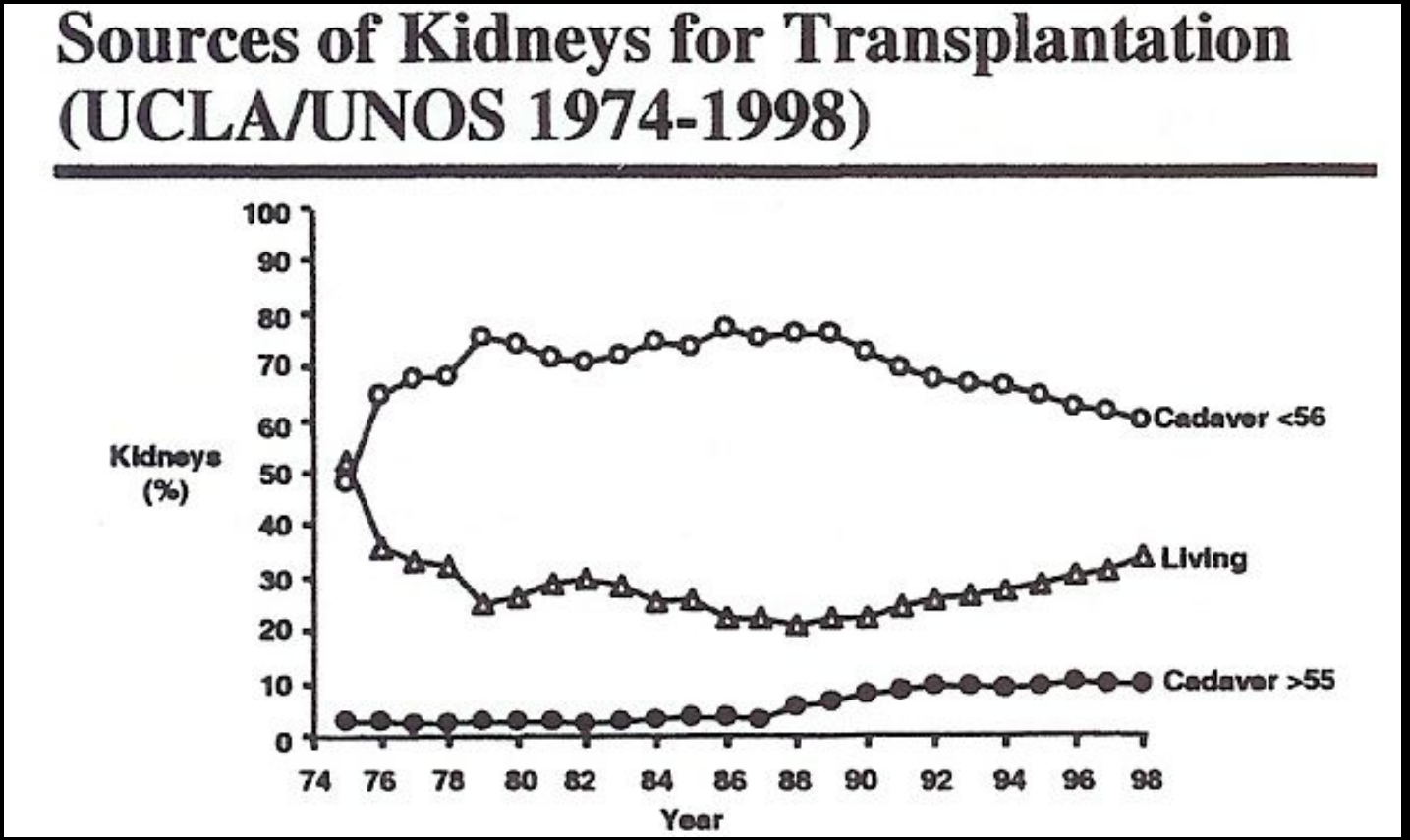
-clearances up to 60 ml/min

-continuous clearance

-frequent hypertension but less hemodynamic compromise

-lower cardiovascular risk even despite drug effects

Organ Shortage: Optimal Solution



Expanding the Living Donor Pool

- Pre-treatment to decrease cross-reactivity
- Transplant across blood type
- Increased public awareness
- Recognition of benefits of living-unrelated donation (cold ischemia time, waiting time decrease, less rejection with better immunosuppressive agents)

Who not to Transplant?

- Who benefit less?

-uncontrolled malignancy

-active systemic infections (HIV, TB…)

-cardiovascular and other organ failure

-high risk of peri-operative mortality

Transplant Menu-High BMI Specials

- Inducing weight gain-steroids
- Inducing hyperlipidemia-steroids, cyclosporine, mTor inhibitors
- Inducing resistant hypertension-steroids, cyclosporine, tacrolimus
- Inducing or worsening impaired glucose tolerance/insulin resistance/post-transplant diabetes mellitus-tacrolimus, steroids, cyclosporine, mTor inhibitors

Got a Transplant? Now Keep It!

- Alias: Immunosuppression in all its Possible Permutations

In the beginning…..we had steroids and azathioprine (an anti-metabolite).

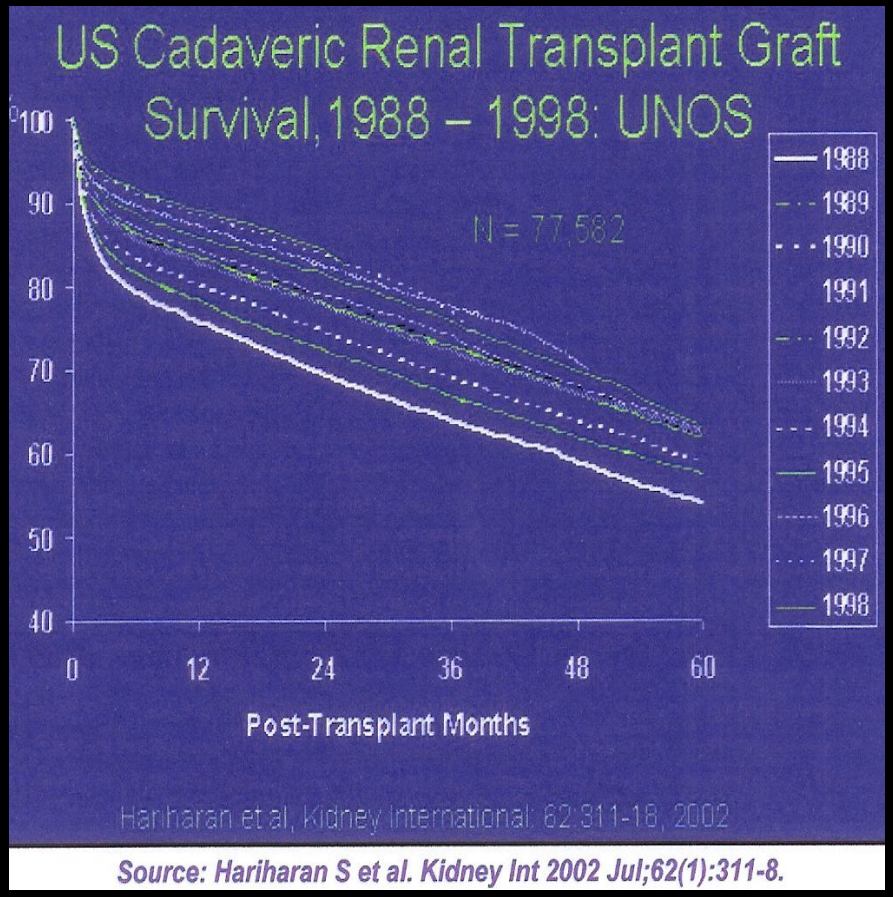
-high rejection rates

-long-term survival driven by acute rejections

-major effect of HLA matching

-UNOS developed-HLA matching optimized at the expense of increased cold ischemia times (time of transplant kidney on cold storage while traveling)

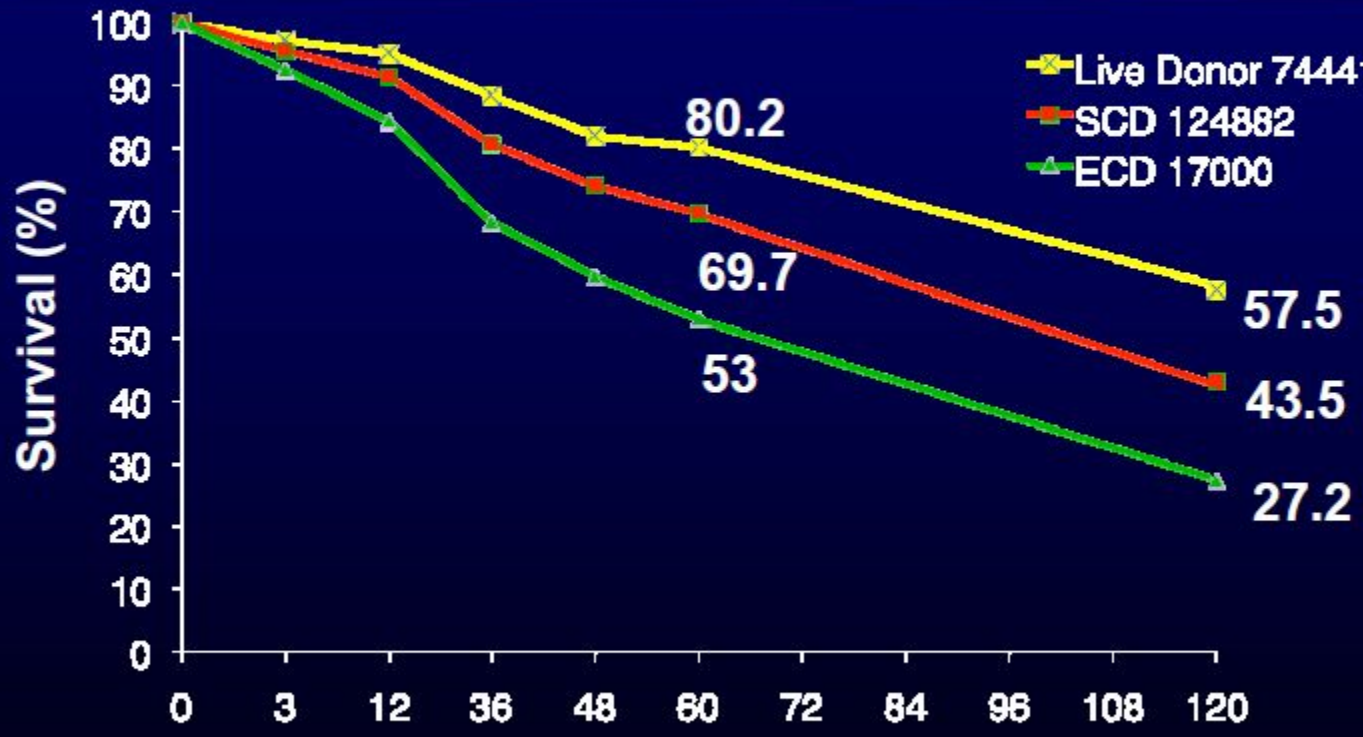
Good Old Days Not so Good….



Source: Hariharan S et al. Kidney Int 2002 Jul;62(1):311-8.

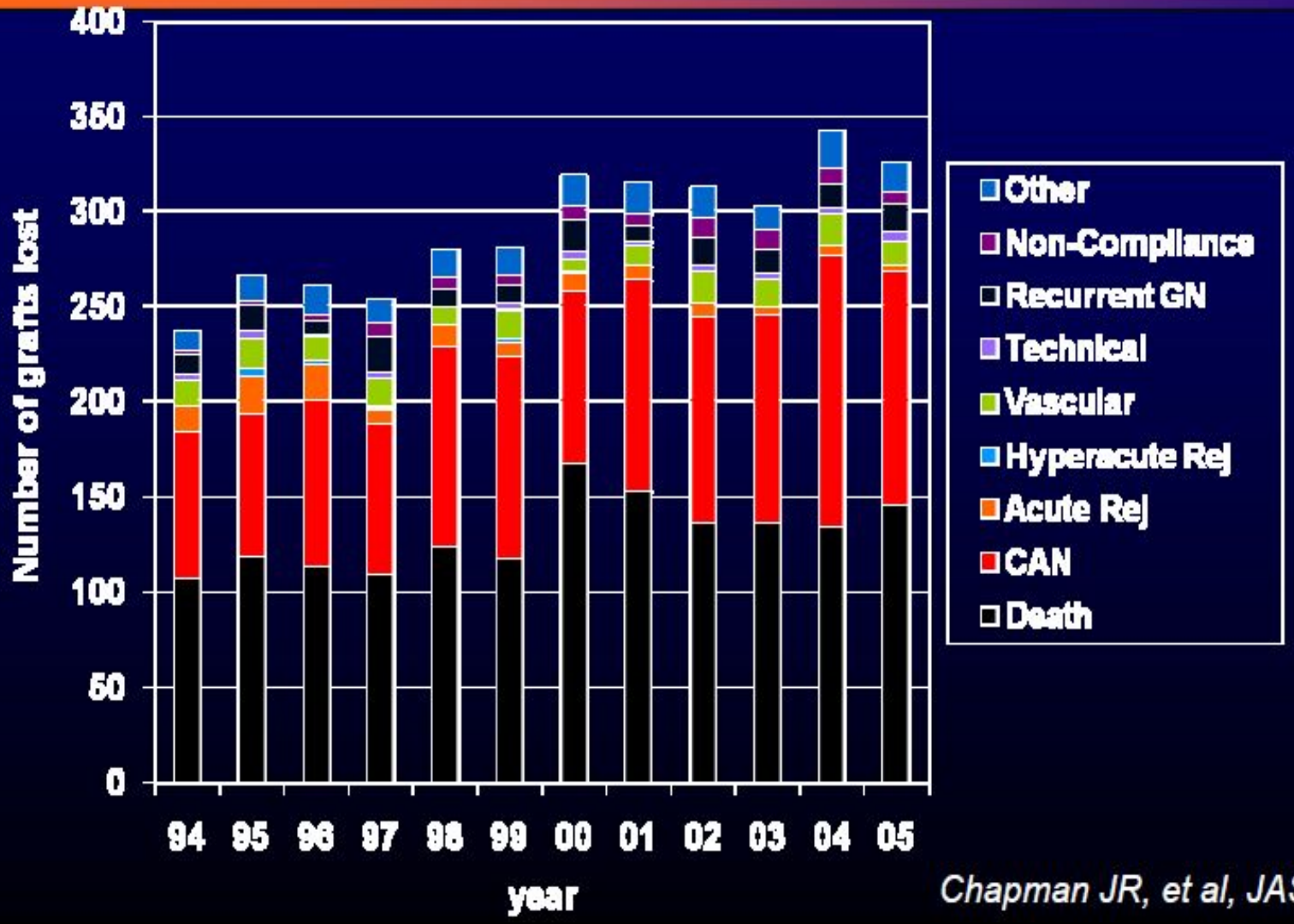
- Major improvement of early acute rejection rates (from close to 50% to close to 10%) made a great benefit in graft survival
- Major steroid adverse effects induced search for alternative

Kidney-Only Graft Survival



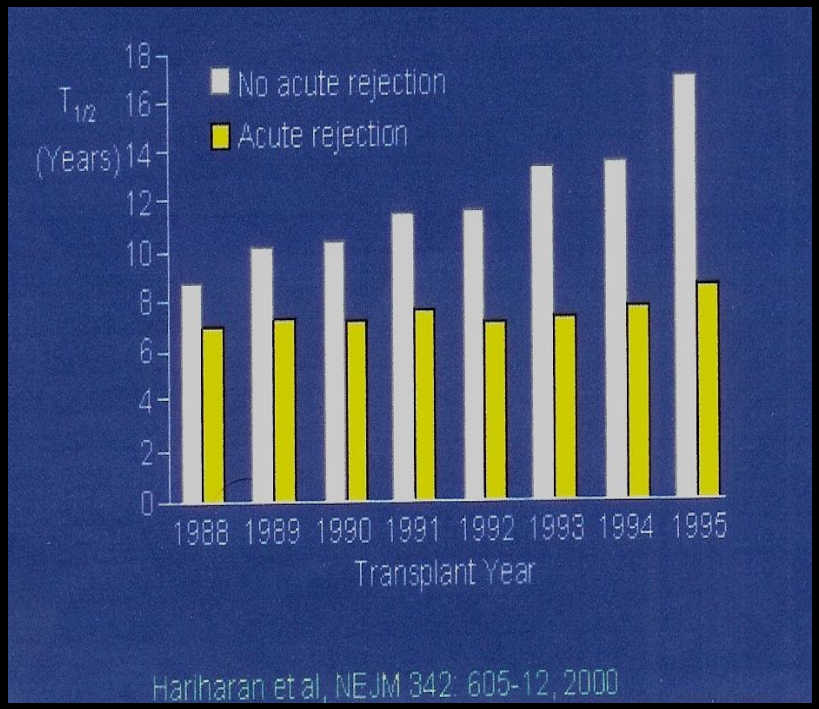
OPTN/SRTR Annual Report 2007

Causes of kidney graft loss in Australia 1994 – 2006



Chapman JR, et al, JASN'07

The Importance of Avoiding Acute Rejections



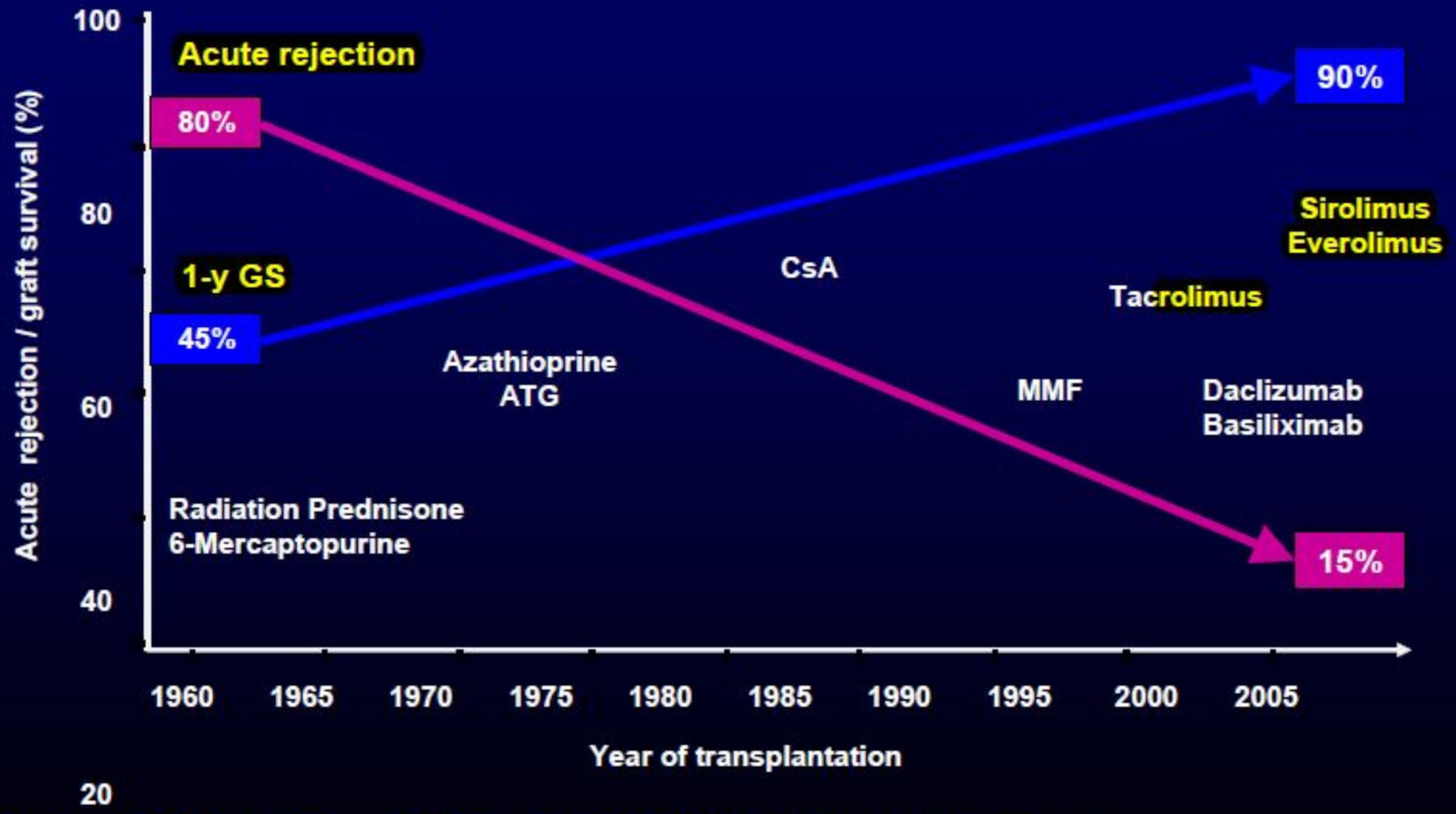
- Most benefit occurred in patients who had no acute rejections
- Steady improvement observed in cadaveric graft survival during the nineties

"The Pathophysiology of Drug Action"

- By Ludwig von Schaum **XIX. Century** German pathologist:

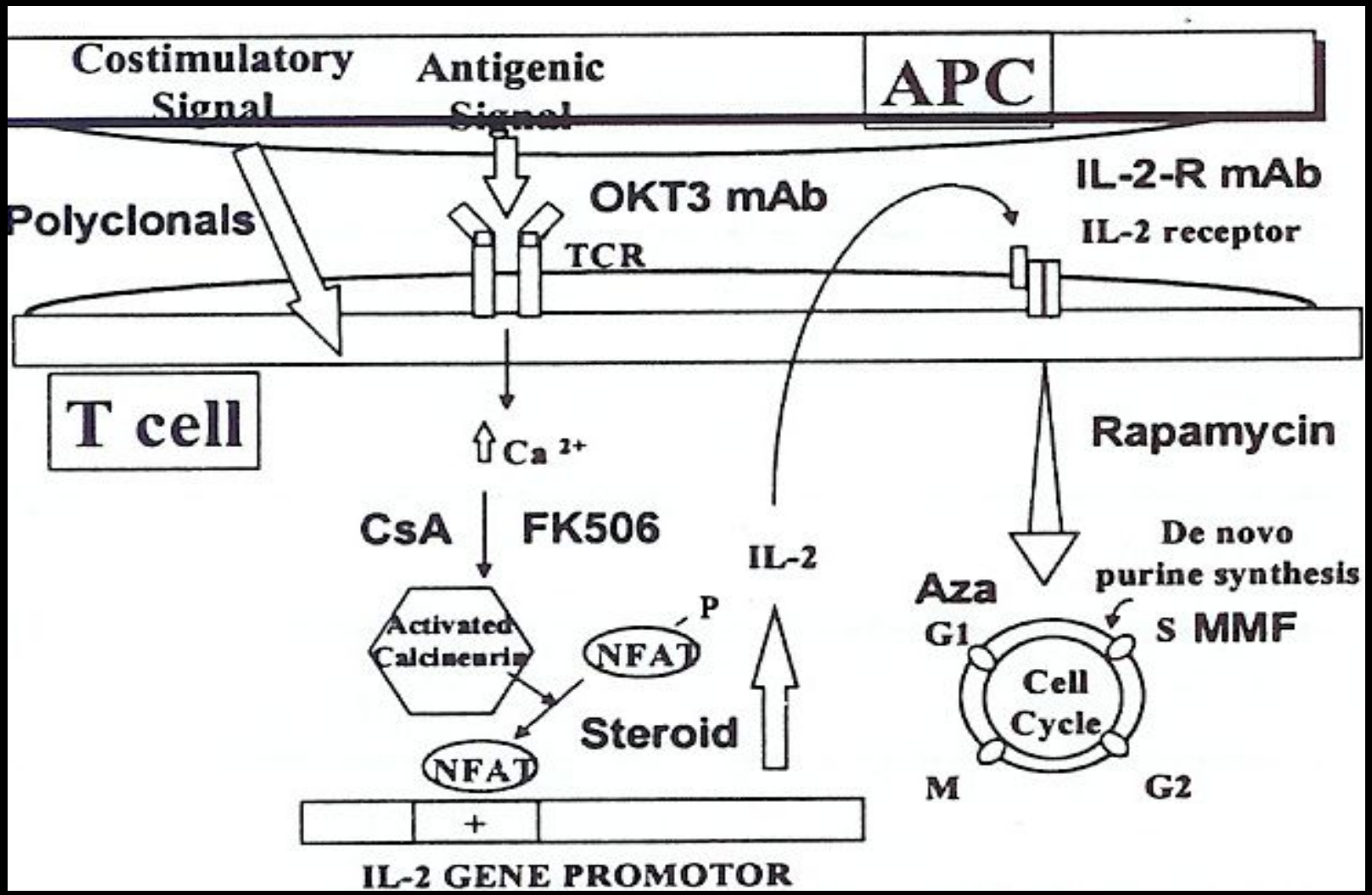
"Short-term benefit of a drug is of value only if such clearly translates into long-term benefit. The long-term benefit must be precisely demonstrated by rigorous examination of evidence."

Improvement in acute rejection and short-term graft survival



GS, graft survival; CsA, cyclosporin A; ATG, antithymocyte globulin; MMF, mycophenolate mofetil

Immunosuppressive Agents: Mode of Action



Our Fungal Friends Again Come to Rescue!

- Calcineurin inhibitors: Cyclosporine and Tacrolimus

- Historically, cyclosporine (CSA) introduced in the 80s and decreased early acute rejections
- Allowed some low risk patients to withdraw steroids
- Cyclosporine toxicity soon recognized to cause chronic allograft nephropathy
- Tacrolimus introduced in the 90s: more potent than CSA
- Tacrolimus often used if cyclosporine fails
- Both CSA and tacrolimus are typically used in conjunction with lower dose steroids and azathioprine

“On the Philosophy of New Drugs”

- By Al-Layash ibn Jumil **XI. Century** Persian physician-poet-philosopher-traveler-scientist-mathematician:

“Short-term benefits of a new medicine are always more immediately obvious than long-term adverse effects. Beware of those who offer you new miracle drugs! If you introduce new medications do so in small dosages in combination with older, well tested ones.”

Calcineurin Inhibitors: a Price to Pay

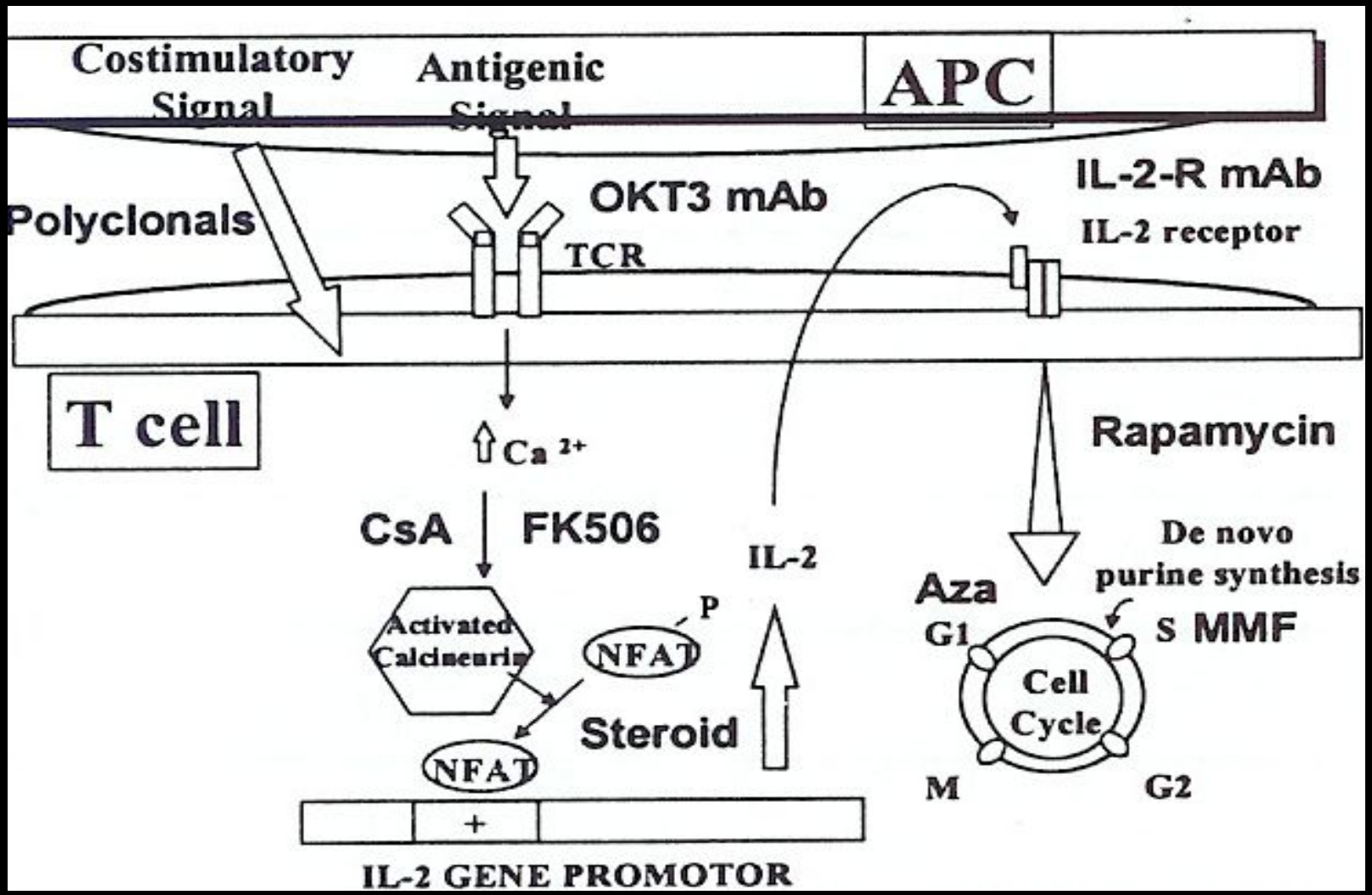
- Cyclosporine

- vascular toxicity
- resistant hypertension
- hyperlipidemia
- diabetes mellitus
- chronic allograft nephropathy/nephrotoxicity
- hirsutism
- gingival hyperplasia

- Tacrolimus

-diabetes mellitus
-hypomagnesemia
-tremors/neuropathy
-resistant hypertension
-chronic allograft nephropathy-possibly less nephrotoxicity in therapeutic dosages

Immunosuppressive Agents: Mode of Action



Mycophenolate Mofetil (MMF): an Upgrade to Azathioprine

- Originally thought to be more specific to T cells-well not quite
- More potent than azathioprine
- No metabolic side effects: main problems with leucopenia, thrombocytopenia, gastrointestinal irritation
- Convincing early long-term benefits
- May be beneficial in Chronic Allograft Nephropathy

Newer Agents without Long-term Follow-up

- Sirolimus or everolimus: recently introduced
- Potential for replacing or decreasing the dose of calcineurin inhibitors
- Especially useful along with MMF to maintain GFR: no vascular- or /nephrotoxicity and potent immunosuppression
- Major potential side effects: hyperlipidemia and thrombocytopenia, may also prolong ATN recovery

Induction Therapy and Drug Withdrawal

- "Clinical strategies in Medicine" by Lewis Schomstein, M.D., **XXth century** American transplantation specialist, induction therapy sub-specialist

"In immunosuppression as in cancer: hit early and hard. You can think about withdrawal later."

Induction Therapy

- Rationale: to prevent acute rejection immediately after transplant when rejection risk is highest
- Allows calcineurin drug-free and potent immunosuppression immediately after surgery when the kidney is most sensitive to their nephrotoxic effects
- Consists of giving anti-T cell antibodies for the first few days after surgery that deplete T cells causing profound temporary immunosuppression
- Short-term decrease in acute rejections but potential of side effects with more viral and other infections, especially with cytomegalovirus
- Newer more potent agents: will they increase long-term cancer risk?

Over-immunosuppression: a New Era in Transplantation?

- Abundance of extremely potent new drugs: lower rejection rate but emergence of viral infections, especially CMV and polyoma BK virus
- Potential for long-term side effects such as malignancy, especially virus-induced
- Necessity to use prophylactic antibiotics, antifungal and antiviral agents
- Gancyclovir-resistant CMV-potential effect of widespread prophylactic gancyclovir use

From "Treatise on Karma and Dharma in Medicine"

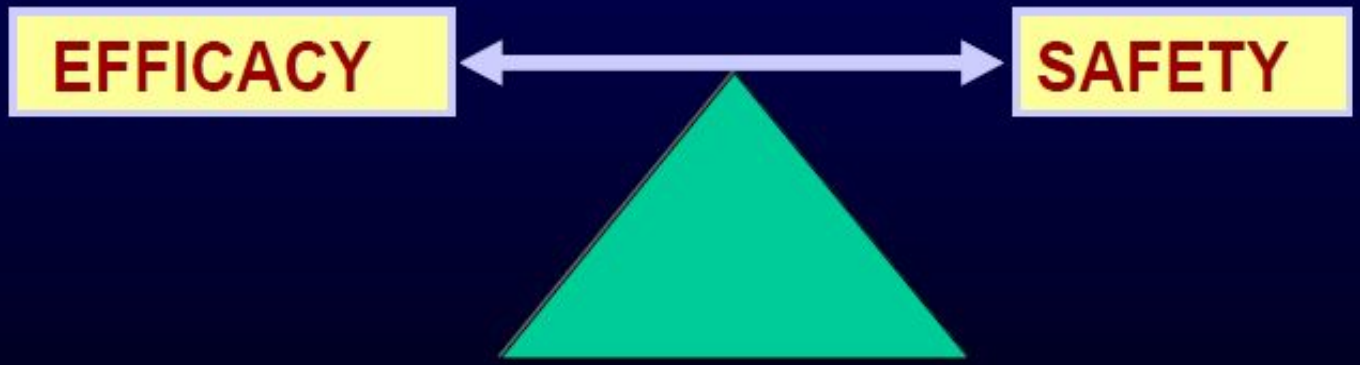
- By Laja Jomakrishna, **XXIst Century** Hindu physician-philosopher:

"In transplantation as in LIFE you must maintain the inner harmony of things. Avoid excess suppression of natural immunity. Be tireless in finding alternative ways."

Immunosuppressive Therapy

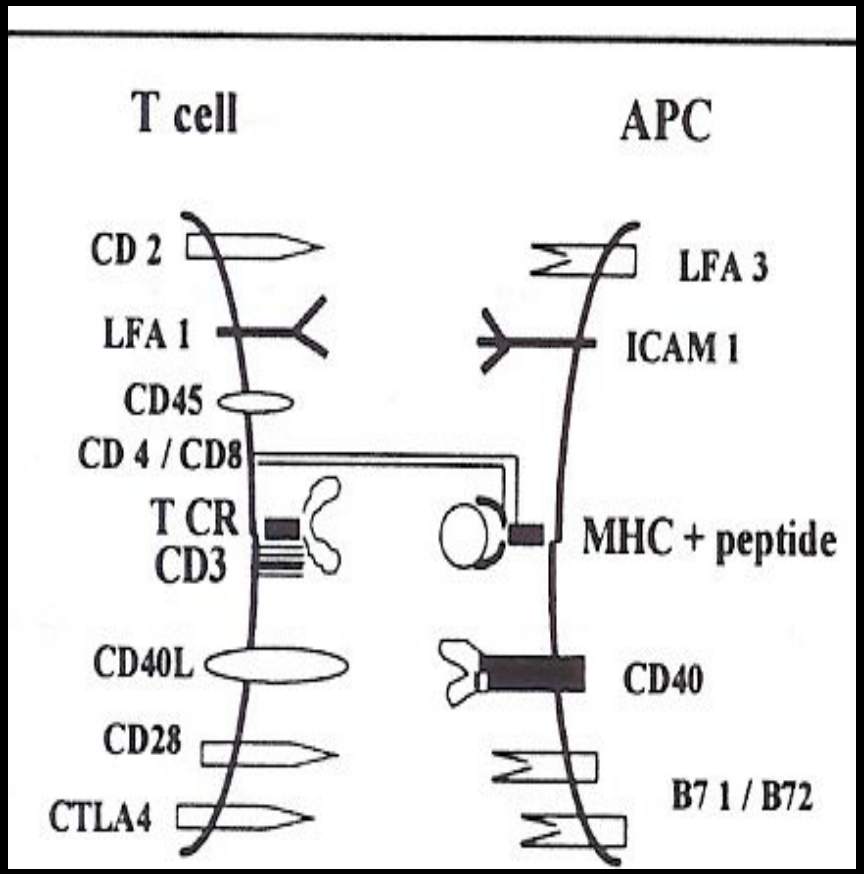
- Cellular response
- Humoral response

- Nephrotoxicity
- Cardiovascular RF
- Cancer
- Opportunistic Infections



LONG-TERM RESULTS ON RENAL TRANSPLANTATION

Blocking Costimulation: a New Hope alias Belatacept



- Hope to induce antigen specific immune tolerance: antigen recognition with no immune response
- Immune tolerance may be persistent
- Problem: multiple pathways need to be blocked
- Early promising results but new pathways are discovered almost every month

Transplantation: the Future

- Individualize drug combinations by assessing individual risk profile for that patient
- Withdraw or minimize immunosuppressive drugs as risk of rejection does decrease in time
- Once a major side effect develops switch to alternative agent
- Newer immunosuppressive agents with less toxicity
- Induce donor-specific immune tolerance