CHRONIC KIDNEY DISEASE: A MAJOR SOCIO-ECONOMIC, MEDICAL AND SCIENTIFIC CHALLENGE

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MECHANISMS KIDNEY FAILURE

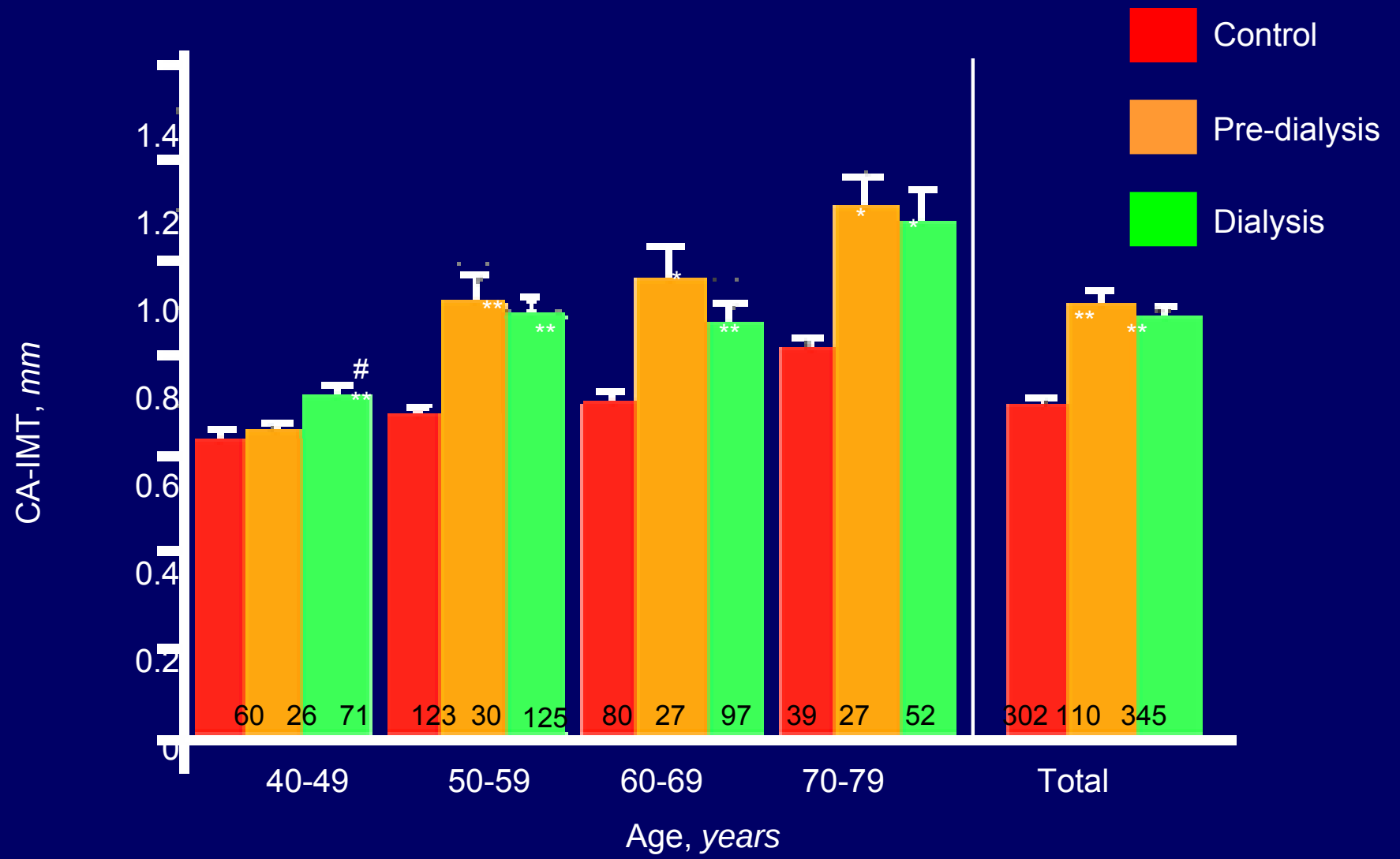
- Healthy kidneys purify the blood from waste products by excreting them in the urine
- Normally, 120 mL of blood are purified per minute (GFR)
- In kidney failure this blood purifying process is blunted: waste products are accumulated in the body
- This induces a progressive process of intoxication, which affects all organ systems, leading to an accelerated death, even if dialysis is performed (worse than cancer)

K/DOQI stages of renal failure (1)

Stage	*Characteristics*	*Creatinine Clearance (~GFR, ml/min/1,73m²)*	*Metabolic consequences*
1	Normal or increased GFR	> 90	
2	Early renal failure	60 – 89*	Concentration PTH increased
3	Moderate renal failure	30 – 59	Decrease Ca absorption Lipoprotein activity decreased Malnutrition Left ventricular hypertrophy Anemia
4	Pronounced renal failure (pre-end stage renal failure)	15 – 29	TG concentration increases Hyperphosphatemia Metabolic acidosis Trend towards hyperkalemia
5	Terminal renal failure (ESRD)	< 15 and/or RRT	Azotemia

1: Parmar, BMJ, 2002, 325: 85-90

PRE-DIALYSE VS DIALYSE VERDIKKING CAROTIDEN

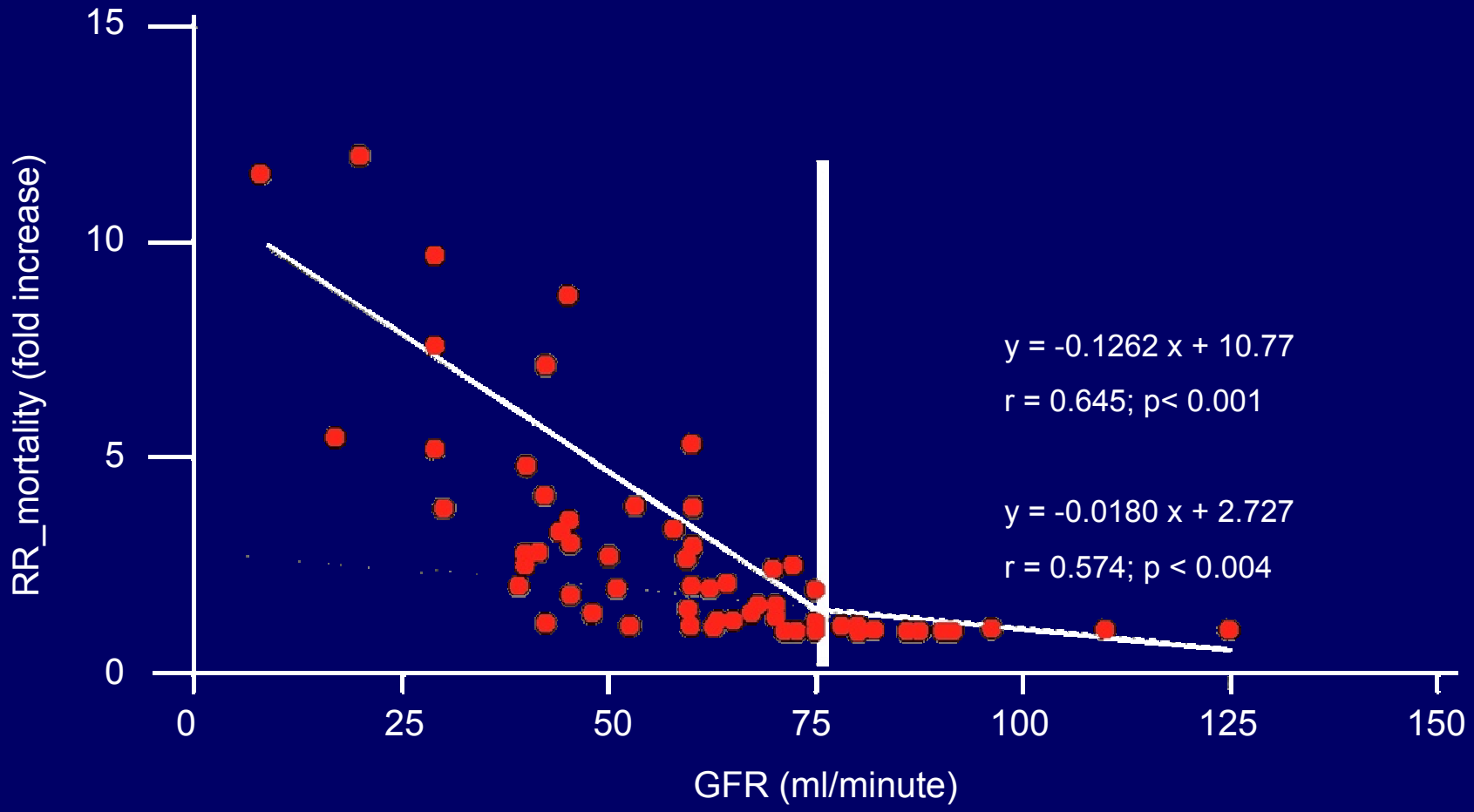


Shoji et al, KI, 61, 2187-2192, 2002

CLINICAL EVIDENCE OF AN ASSOCIATION BETWEEN RENAL FAILURE AND VASCULAR DISEASE PRE-DIALYSIS

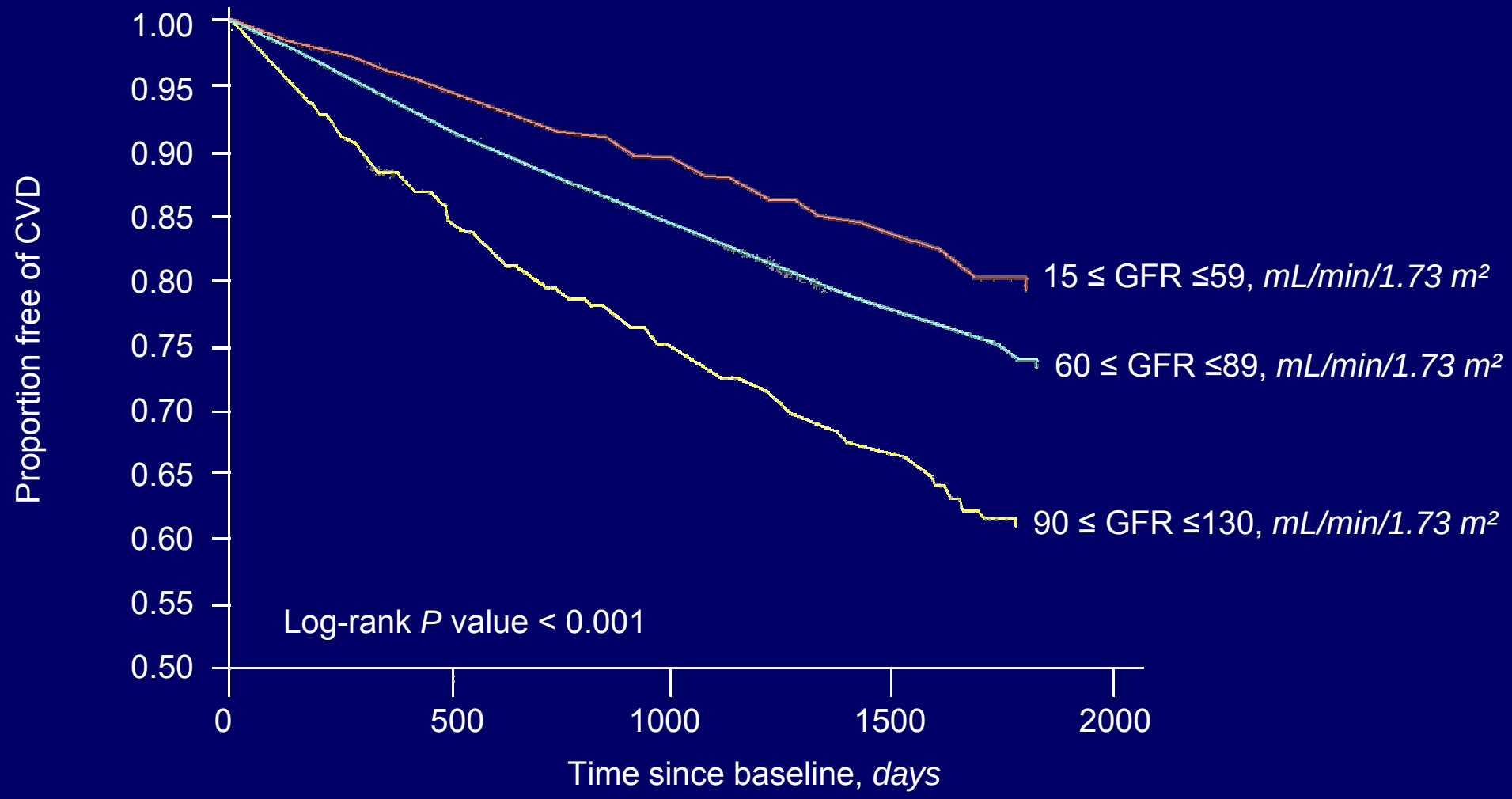
- 85 studies (1986-2003)
  - 552,258 patients
  - 71 with correction for “traditional” risk factors
- Sharpest threshold
    - Screa: 0,90 mg/dL
    - GFR: 90 mL/min

RELATIEF RISICO



Vanholder et al, NDT, 20, 1048-1056, 2005

GFR & CVD (> 65 y)



Manjunath et al, KI, 63, 1121-1129, 2003

AHA Scientific Statement

Kidney Disease as a Risk Factor for Development of Cardiovascular Disease

A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention

Mark J. Sarnak, MD, Cochair; Andrew S. Levey, MD, Cochair;
Anton C. Schoolwerth, MD, Cochair; Josef Coresh, MD, PhD; Bruce Culleton, MD;
L. Lee Hamm, MD; Peter A. McCullough, MD, MPH; Bertram L. Kasiske, MD; Ellie Kelepouris, MD; Michael J. Klag, MD, MPH; Patrick Parfrey, MD;
Marc Pfeffer, MD, PhD; Leopoldo Raij, MD;
David J. Spinosa, MD; Peter W. Wilson, MD

Sarnak et al, Circulation, 108, 2154-2169, 2003;
Hypertension, 42, 1050-1065, 2003

•NHANES III / AUSDIAB

- Prevalence renal failure
  - Third National Health and Nutrition Examination Survey > 15,000 subjects (USA)
    - GFR < 60 mL/min (↓ 50%): 4.7%
    - GFR < 90 mL/min (↓ 25%): 35.9%
  - AusDiab → 11,247 subjects (Australia)
    - GFR < 60 mL/min (↓ 50%): 10.9%
      - 45-64 j old: 2.5%
      - ≥ 65 j old: 53.1%

•Coresh et al, AJKD, 41, 1-12, 2003; Chadban et al,JASN, 14, S131-S138, 2003

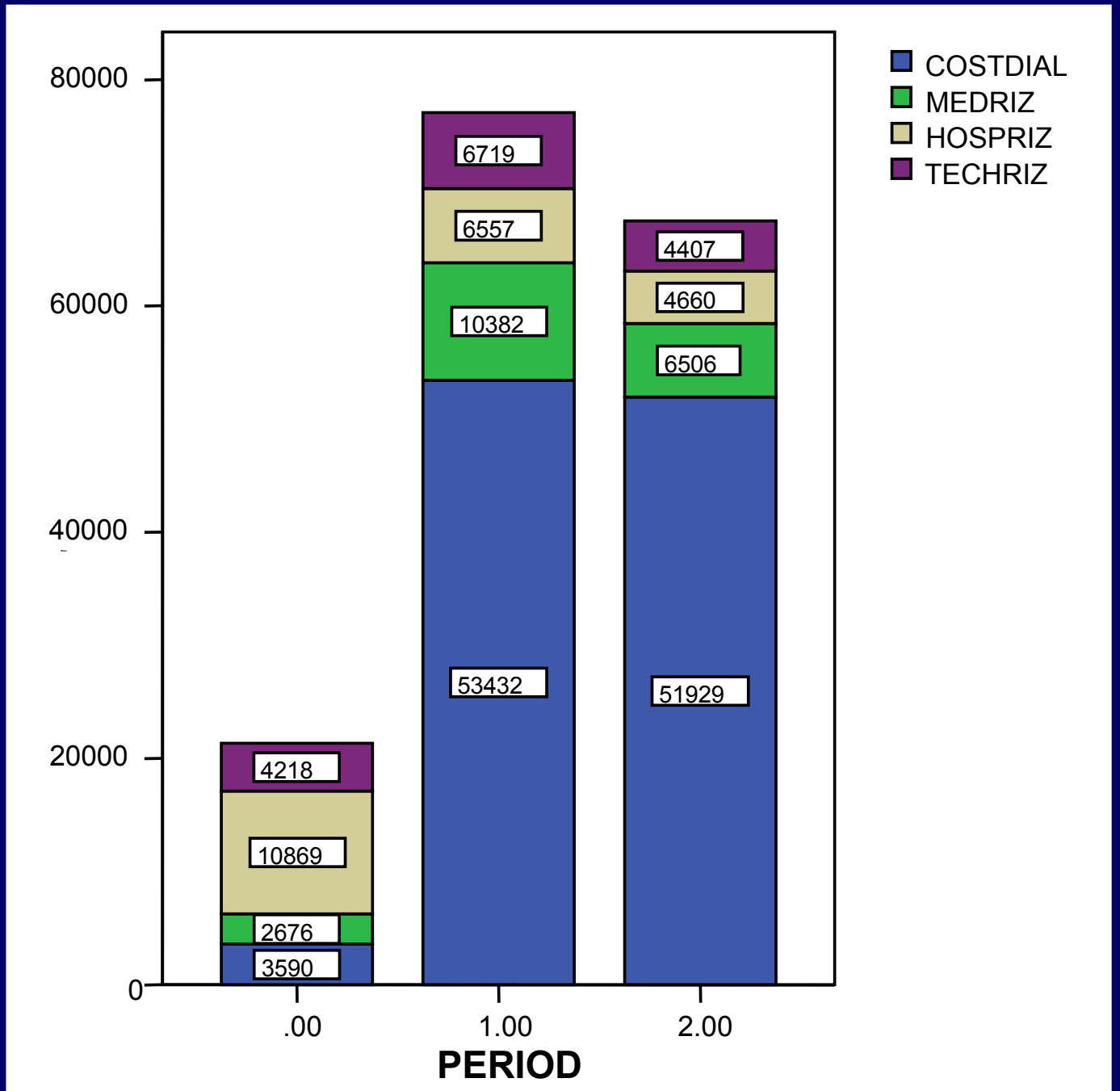
POPULATIONS AT RISK

- Worldwide in dialysis or transplanted: ± 2,000,000 persons
- Worldwide with GFR < 60 mL/min:
  - 6,000,000,000 x 0.05 = 300,000,000
- This problem has similar epidemic proportions as diabetes mellitus, but is unfortunately strongly underestimated

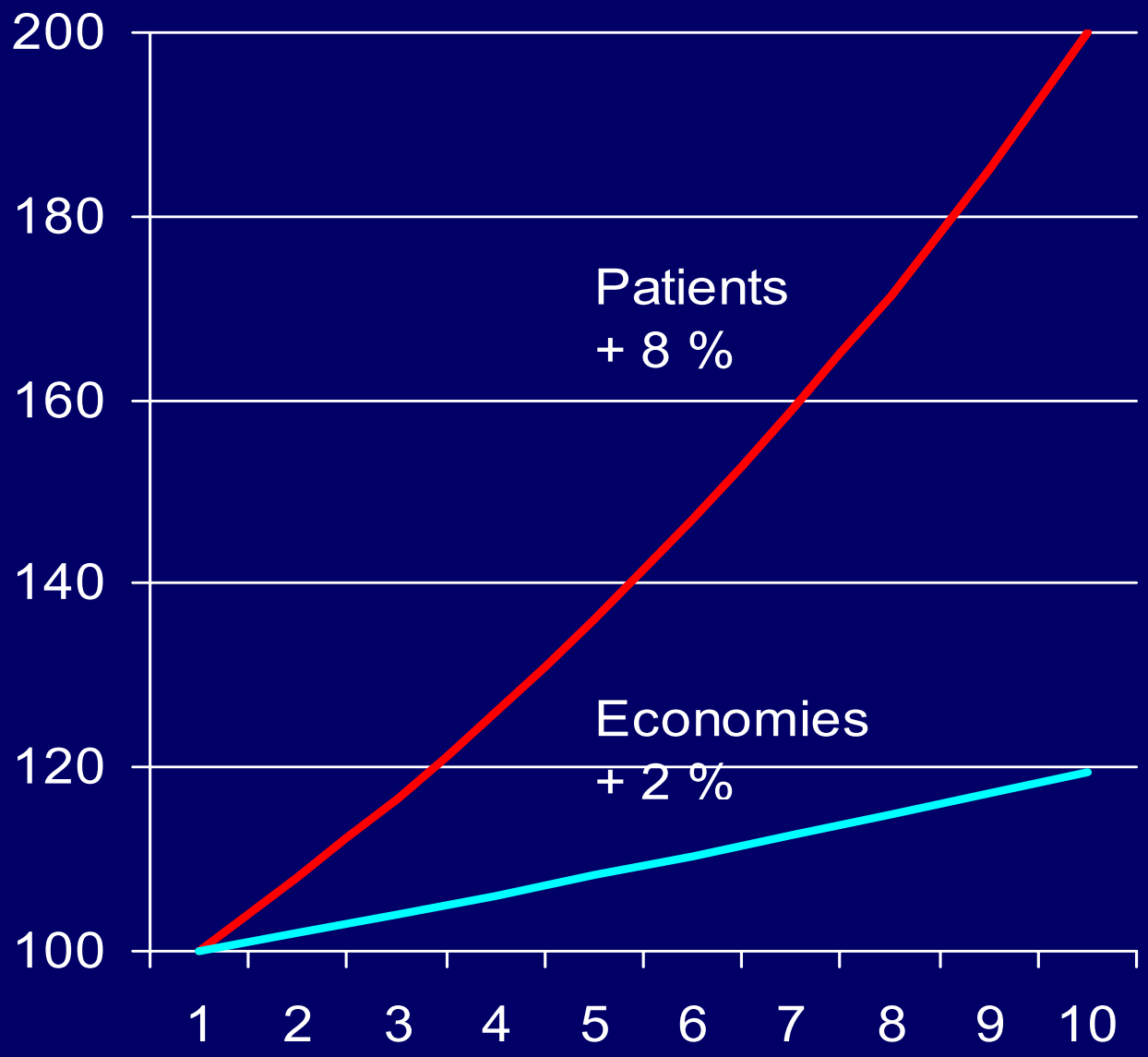
Cost of HD

Type:
0 = PD
1 = HD
2 = TX

Period:
0 = 1th hospital
1 = Year 1
2 = Year X



Rise of cost



FUTURE AIMS

- Correct and timely estimation kidney function, especially in risk groups: diabetes, hypertension, familial renal failure, > 60j, nephrotoxic medication, proteinuria
- If GFR < 60 mL/min → secundary prevention: life style, smoking stop, correction tension, treatment diabetes, angiotensin blockers, correction lipid disturbances, hypercoagulability blood, inflammation
- Prevention of both the early complications and the progression towards dialysis

MORTALITY

Age	CO	HD	HD/CO
25-34	0.008	3	375.0
35-44	0.03	4.5	150.0
45-54	0.1	6	60.0
55-64	0.3	8	26.7
65-74	0.9	10	11.1
75-84	3	15	5.0

Foley et al, AJKD, S3, S112-S119, 1998

COX-PROPORTIONAL ANALYSIS*

	Coeff	P-value
LDL-cholesterol	-0.002	NS
Triglycerides	-0.003	NS
Predialysis MAP	-0.110	NS
BMI	-0.066	NS
Hypertension	-0.57	NS
Smoking	0.04	NS

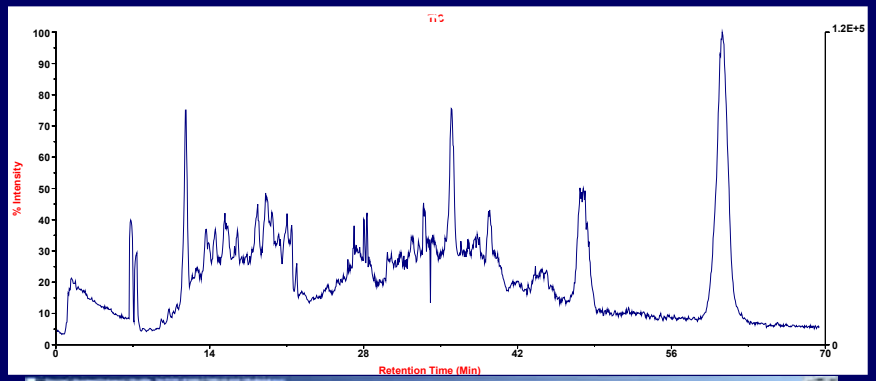
*: adjusted for age, gender and race (n=453);
Fleischmann et al, Clin Nephrol, 56, 221-230, 2001

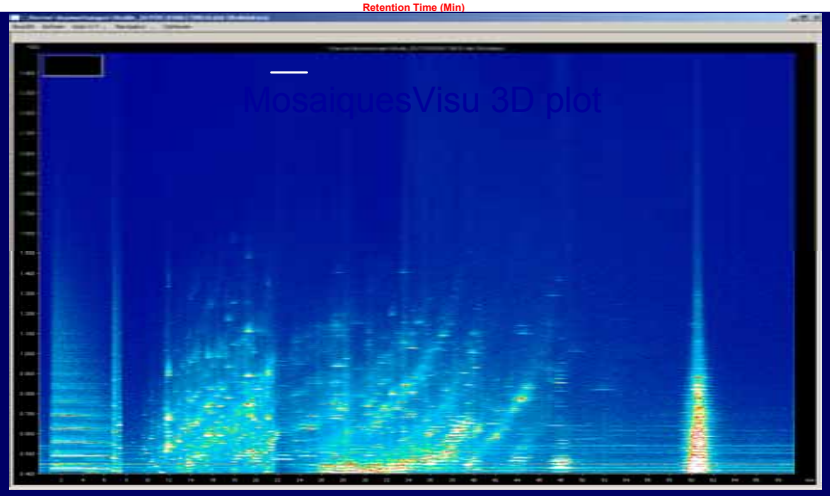
ATHEROSCLEROTIC CARDIOVASCULARE RISK IN CHRONIC HEMODIALYSIS PATIENTS

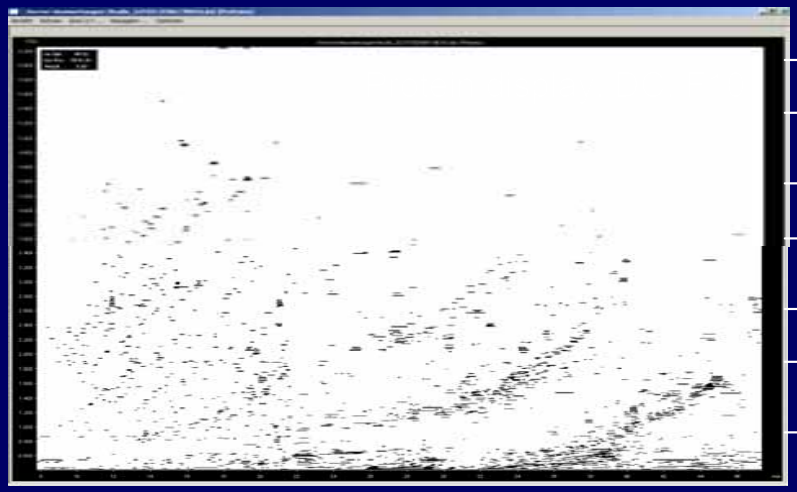
Some of the traditional coronary factors in the general population appear to be also applicable to the hemodialysis population, while other factors did not correlate with atherosclerotic cardiovascular disease in this cross-sectional study. Nontraditional risk factors, including the uremic milieu and perhaps the hemodialysis procedure itself, are likely to be contributory. Further studies are necessary to define the cardiovascular risk factors in order to devise preventive and interventional strategies for the chronic hemodialysis population.

Alfred K. Cheung et al, Kidney International, 58: 353-5362; 2000

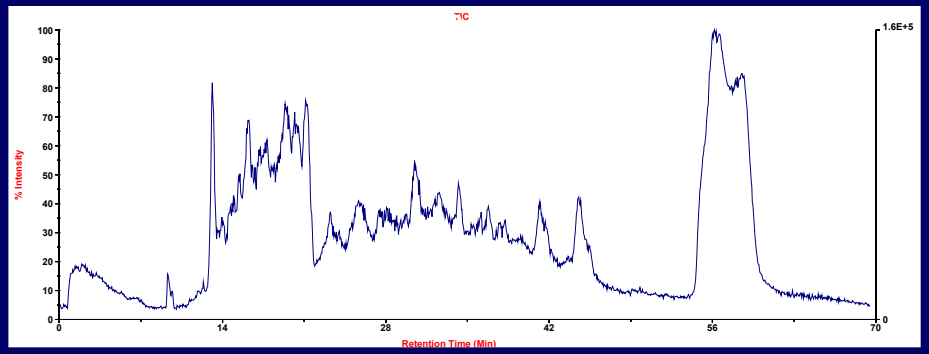
Sample 1: DC dialysate with F10 membrane

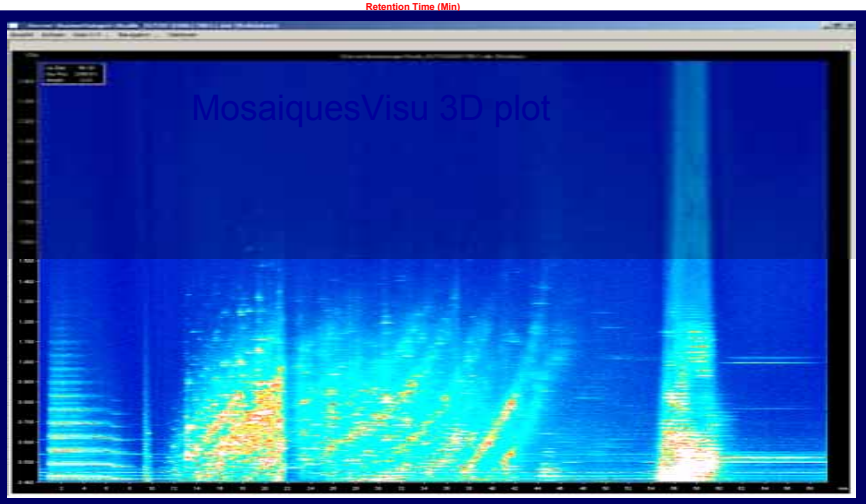


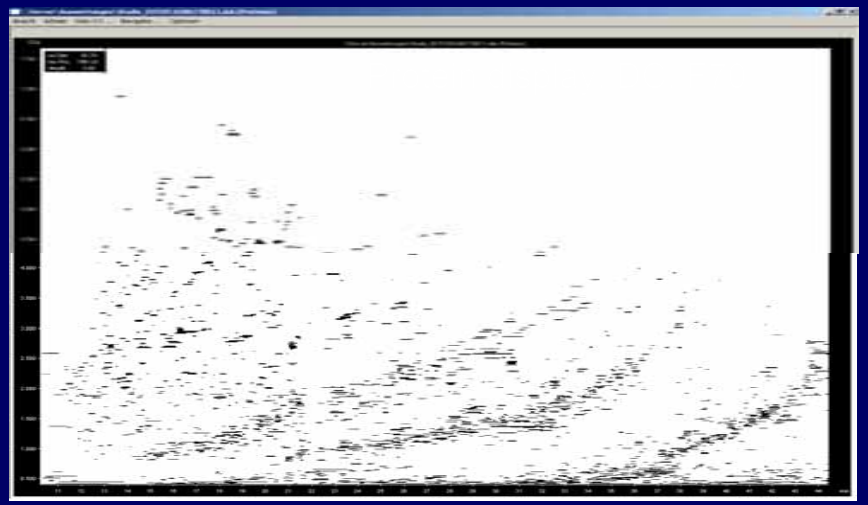




Sample 2: DC dialysate with F70 membrane







mass/charge(KD/z

7 kD
6 kD
5 kD
4 kD
3 kD
2 kD
1 kD

CE-retention time (min)

CE-retention time (min)

ADDITIVE RISK FOR HYPERTENSION, DIABETES AND RENAL FAILURE

Table 2 Stratification of risk to quantify prognosis

Other risk factors and disease history	Blood pressure (mmHg)				
	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 SBP 140–159 or DBP 90–99	Grade 2 SBP 160–179 or DBP 100–109	Grade 3 SBP ⩾ 180 or DBP ⩾ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors or TOD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
ACC	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

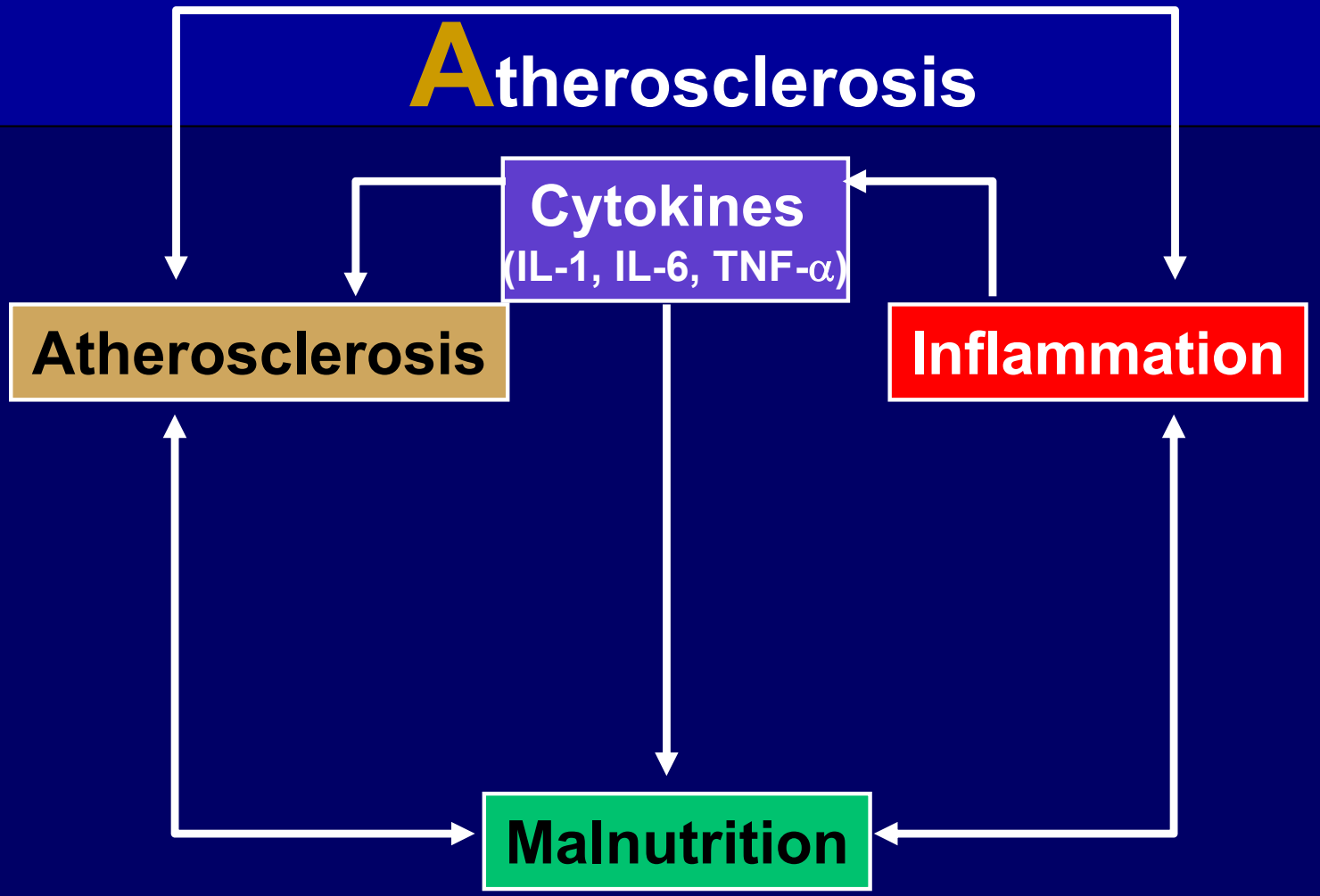
ACC, associated clinical conditions; TOD, target organ damage; SBP, systolic blood pressure; DBP, diastolic blood pressure.

TOD: GFR 90-60 mL/min; ACC: GFR < 60 mL/min

MIA hypothesis

Pro-inflammatory cytokines are the common link between

Malnutrition, Inflammation and Atherosclerosis



Stenvinkel et al. *Nephrol Dial Transplant* 2000; 15: 953–60

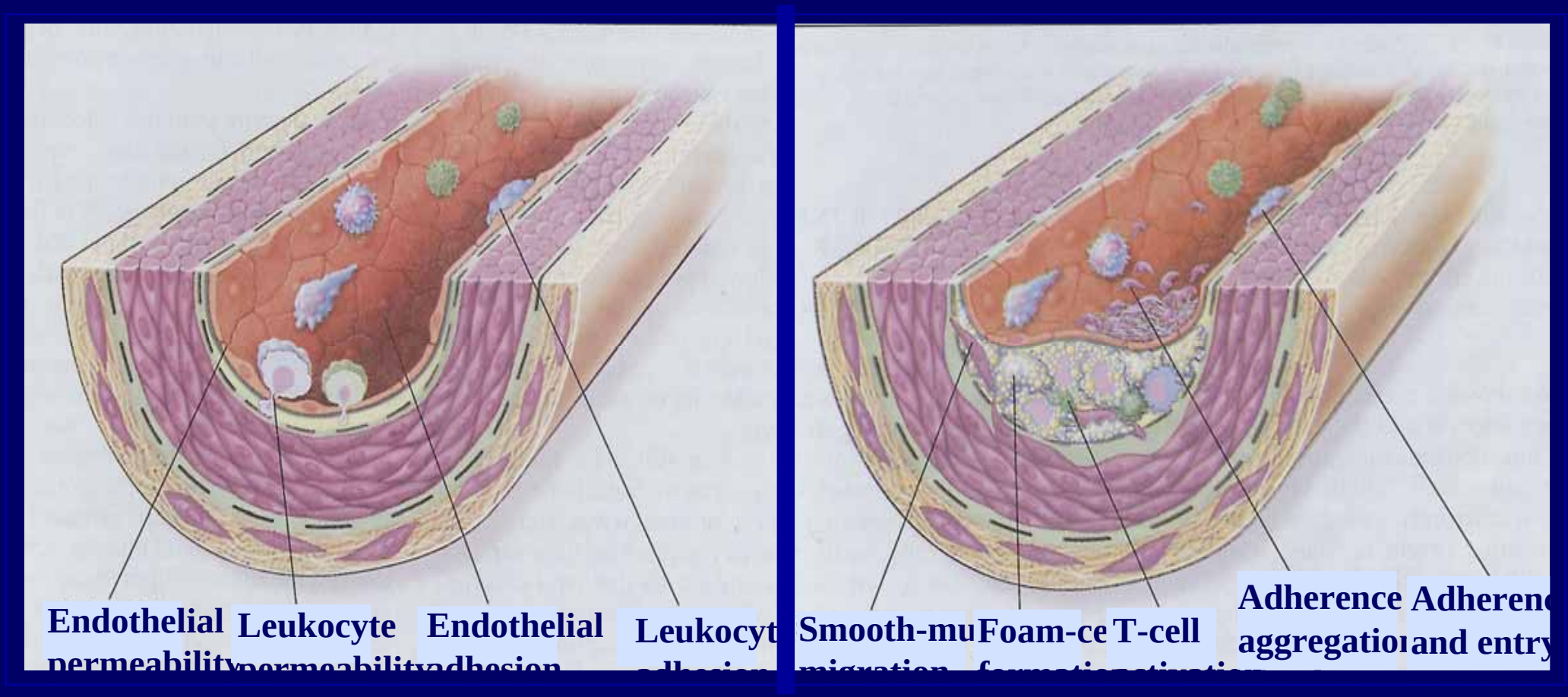
DEAD VS ALIVE AT 34 MTHS

	DEAD (41)	ALIVE (50)
CRP (μg/mL)	10.1	3.4**
Alb (g/dL)	3.7	3.8*
BUN (mg/dL)	53±15	64±18*
Crea (mg/dL)	9.0±3.0	11.1±3.2*
PCRn (g/kg.d)	0.93±0.19	1.06±.21*

*: p<0.01, **: p<0.001

Yeun et al, AJKD, 35, 469-476, 2000

ATHEROMATOSIS



Ross New Engl J Med 340 (2) : 115, 1999

UREMIC TOXINS WITH VASCULAR IMPACT

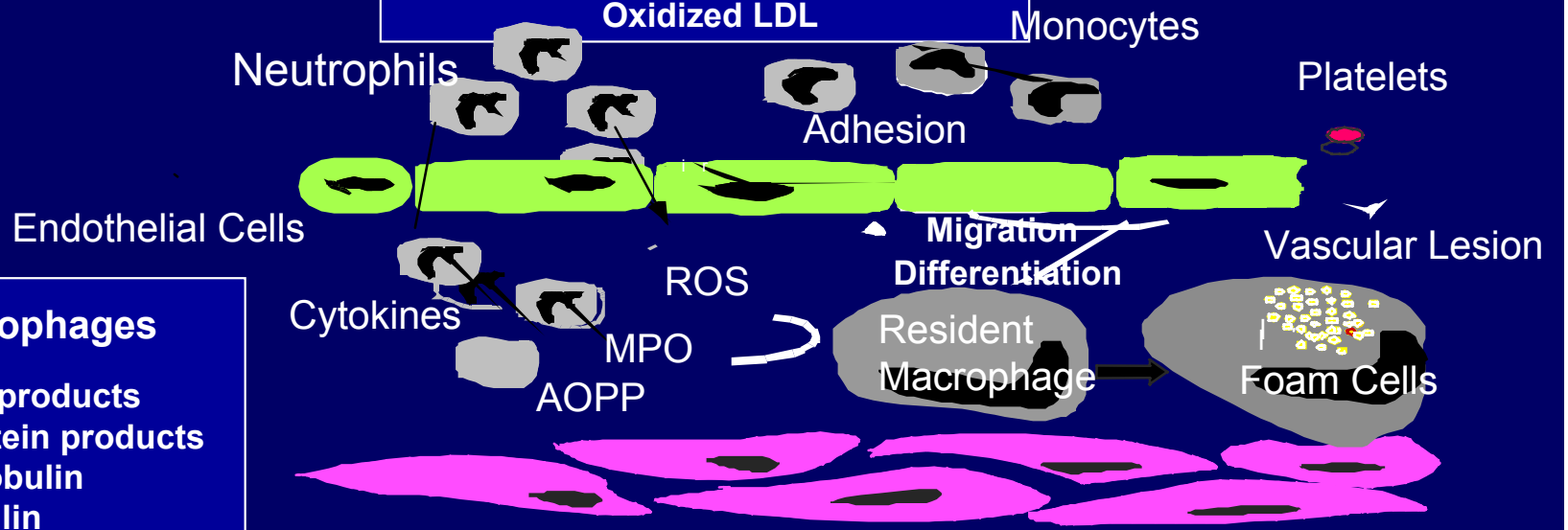
Polymorphnuclear Neutrophils

Advanced glycation products
Advanced oxidation protein products
Angiogenin (DIP I)
Complement factor D (DIP II)
Cytokines
Ig Light chains
Leptin

Endothelial Cells

Advanced glycation products
Advanced oxidation protein products
ß2-microglobulin
Cytokines
Homocysteine
Leptin
Oxalic Acid
Oxidized LDL

Platelets
Cytokines
Leptin



Monophages/Macrophages

Advanced glycation products
Advanced oxidation protein products
AGE-ß2-microglobulin
ß2-microglobulin
Cytokines
Homocysteine
Leptin

Smooth muscle cells
ß2-microglobulin
Homocysteine

Vanholder et al, IJAO, 24, 695-725, 2001

FUTURE AIMS

- Detection of the factors which are specific for renal failure to cause vascular damage (genome, proteome, secretome)
- Since renal failure is an accelerated model of atheromatosis, these factors should then also be checked in the non-renal failure population, where they may as yet have remained unrecognized

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- Amgen
- Baxter Healthcare
- Fresenius Medical Care
- Gambro
- Genzyme
- Membrana
- Roche