- **Medical Education**
  UP College of Medicine
- **Residency: Internal Medicine**
  Veterans Memorial Medical Center
- **Clinical Fellowship in Nephrology and Research Fellowship in Hypertension**
  University of Philippines-
  Philippine General Hospital
  Department of Medicine
  Section of Nephrology
- **Research Interests**
  Diabetic Nephropathy
  Renovascular Hypertension

- **Clinical Appointments**
  Active Consultant in various hospitals in Bulacan mainly
  Sacred Heart Hospital, Malolos
- **Patient Advocacy**
  Internal Vice President,
  Philippine Association for Renal Health

Agnes Bridget I. Estrella, M.D.

Keto Amino Acids: New Strategies in Diabetic Renal Disease

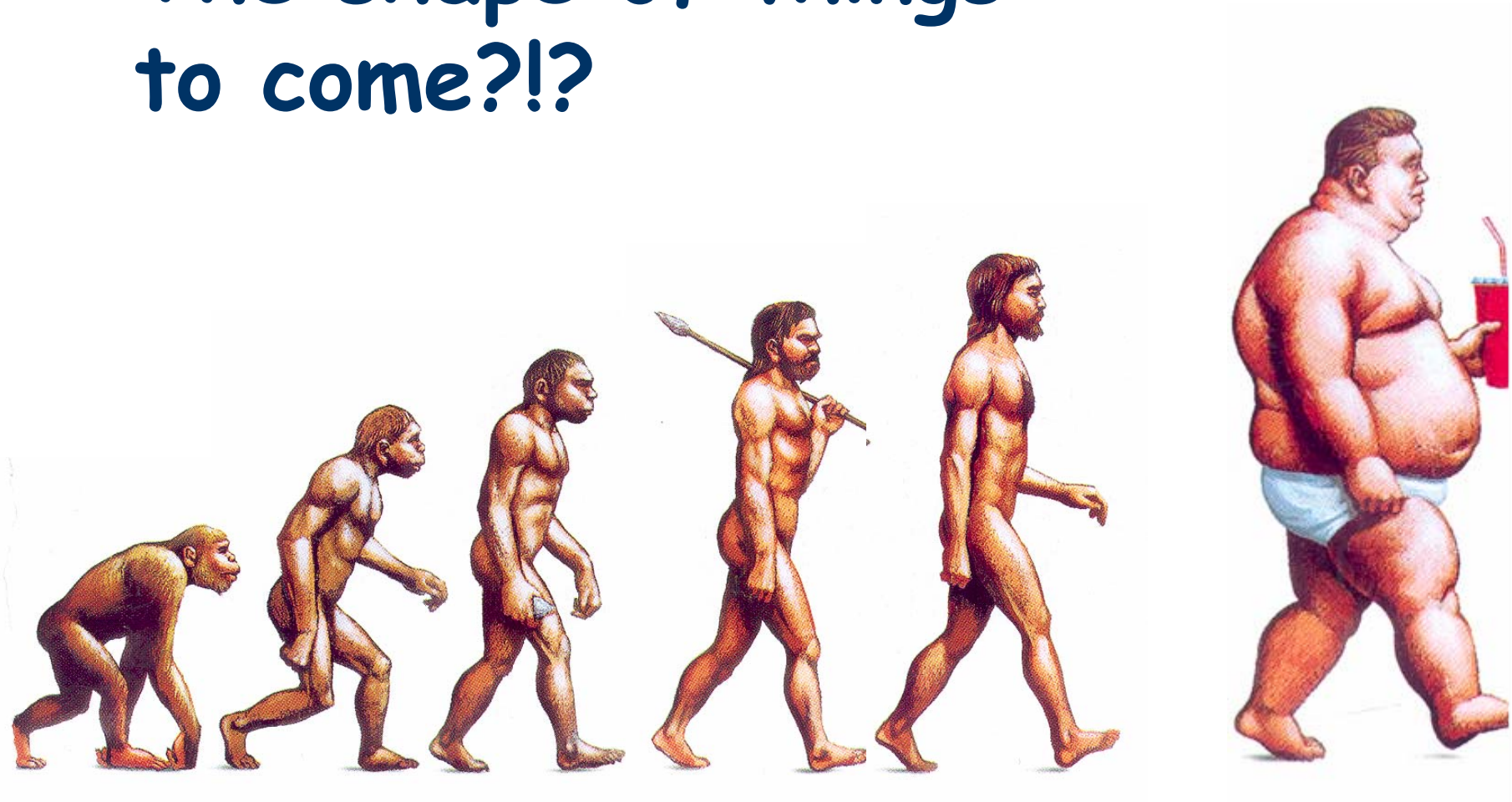
Agnes Bridget I. Estrella, M.D.

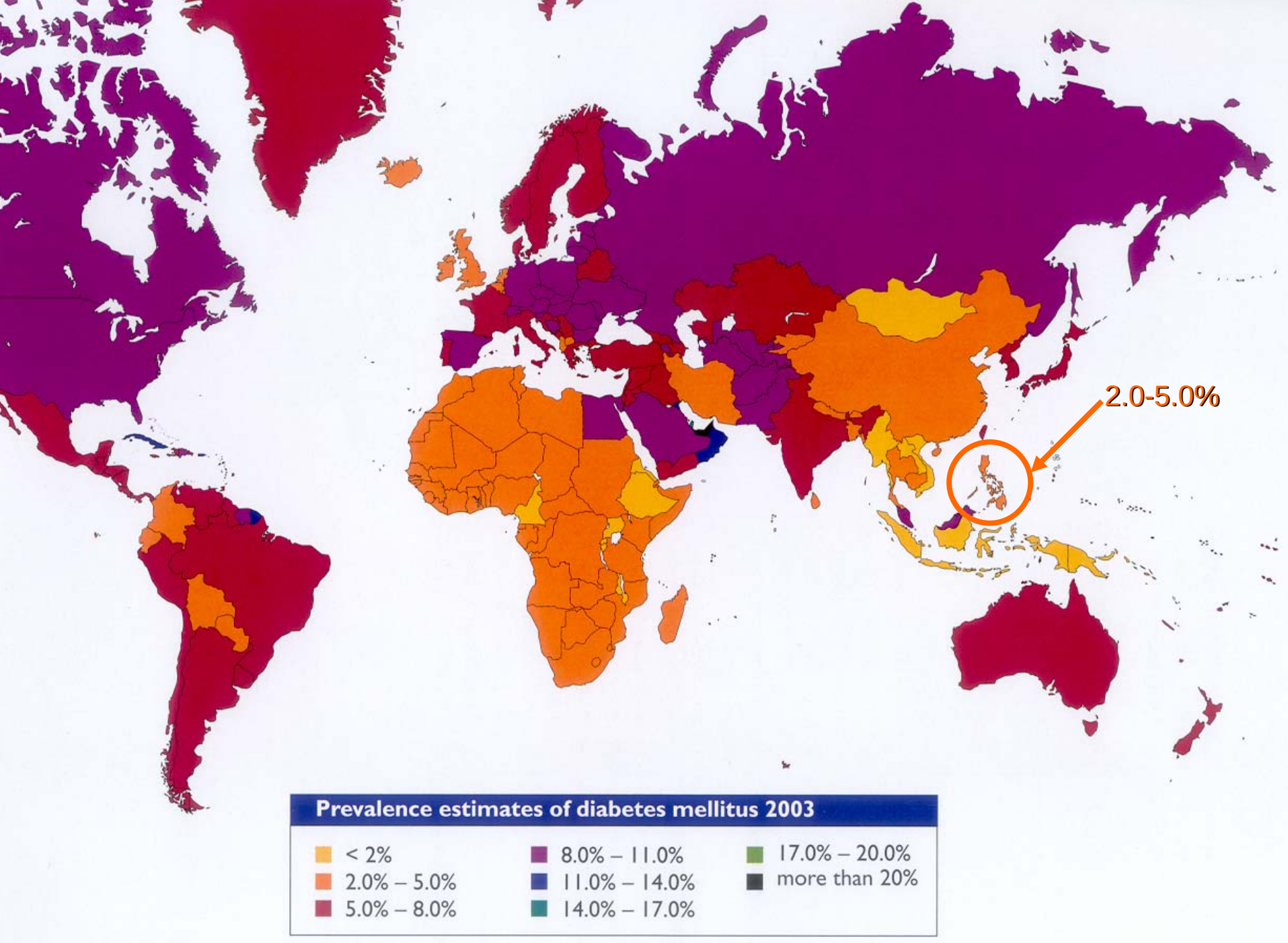
Which is an early sign of kidney disease?

A. Pyuria
B. Hematuria
C. Rise in serum creatinine
D. Proteinuria

In the evolution of MAN

The shape of things to come?!?

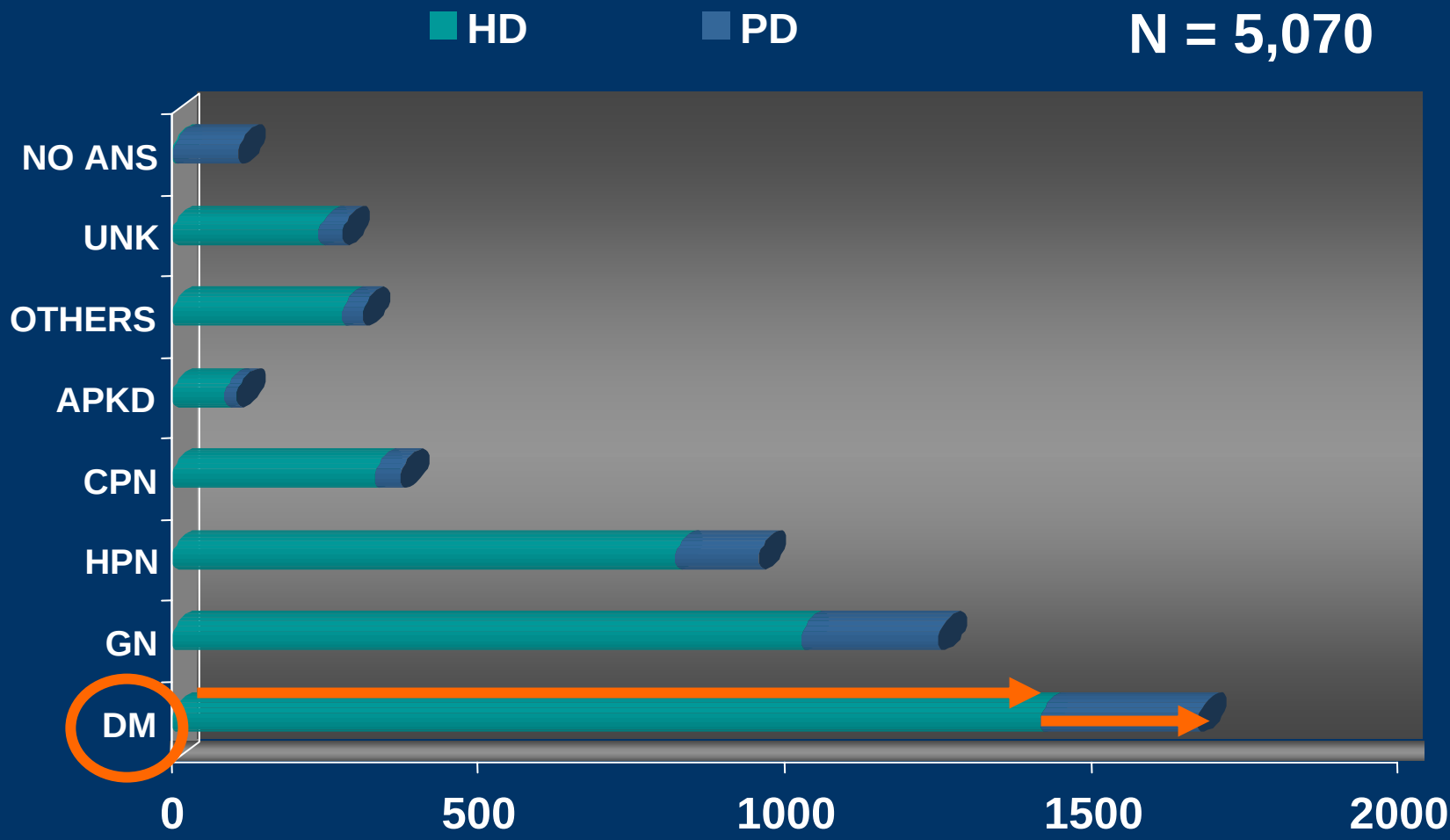




Source: Diabetes Atlas, International Diabetes Federation

PRIMARY RENAL DISEASE OF ALL NEW DIALYSIS PATIENTS

(Philippine Renal Registry, 2003)



PRIMARY RENAL DISEASE OF ALL NEW DIALYSIS PATIENTS

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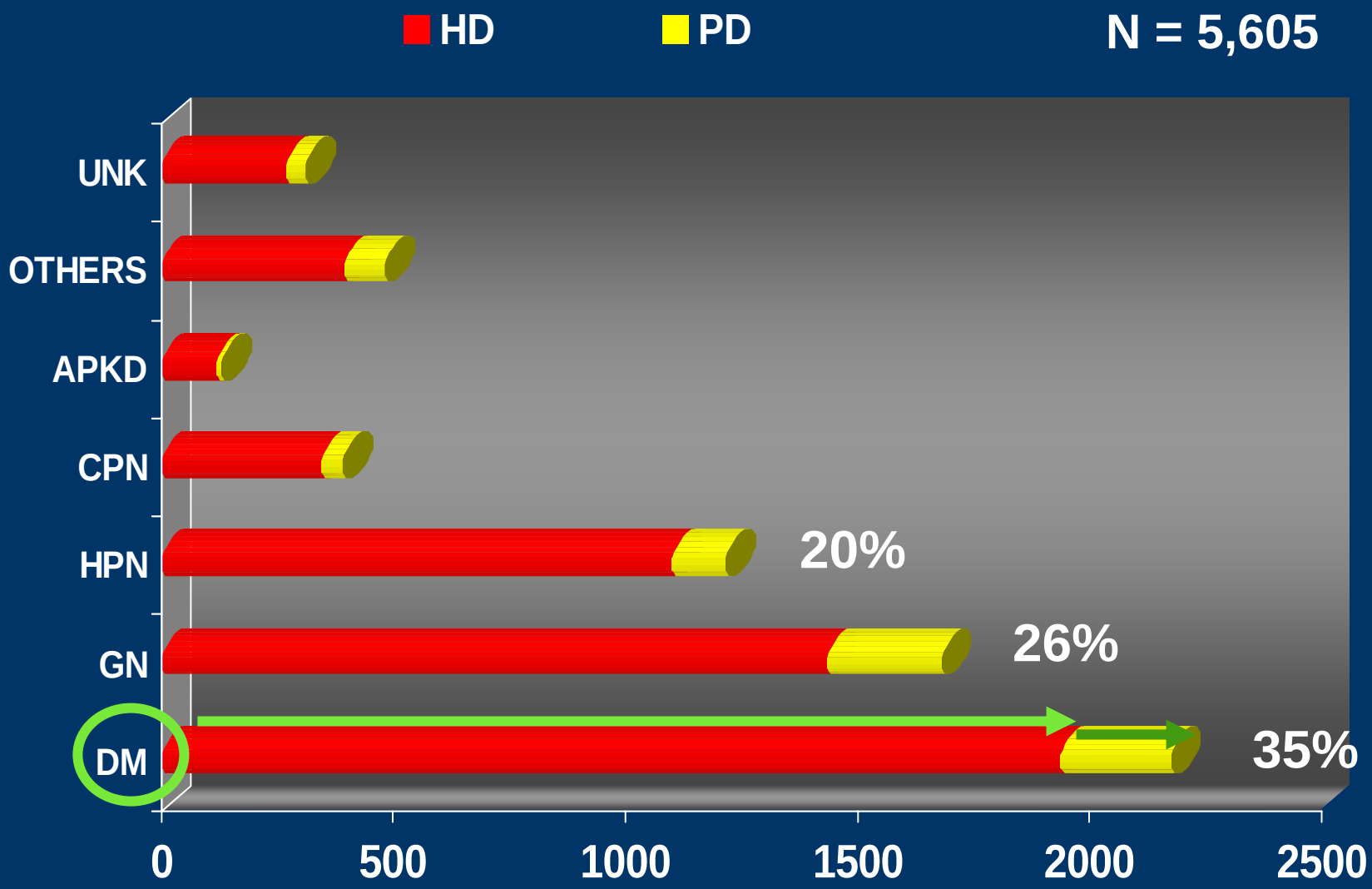
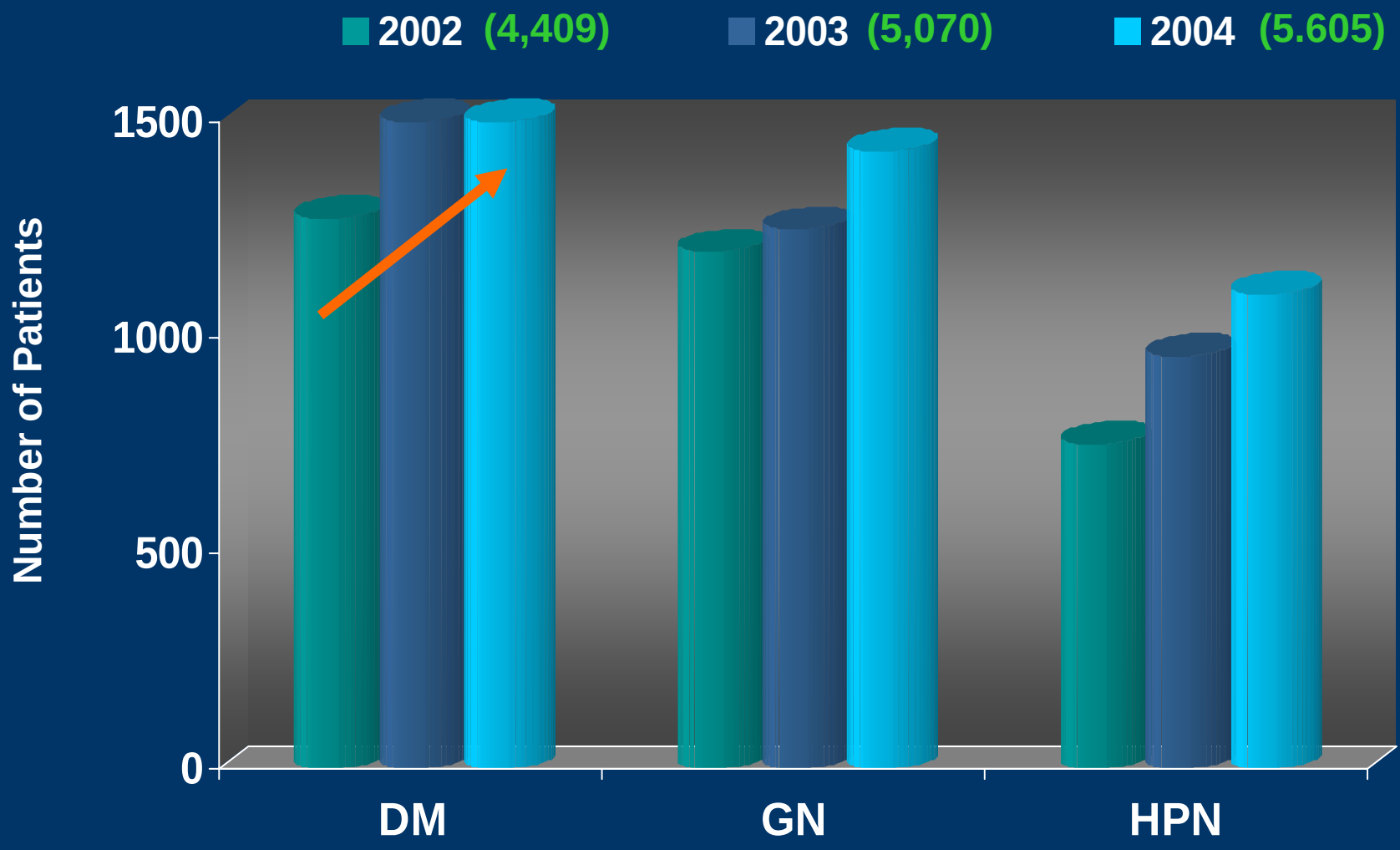
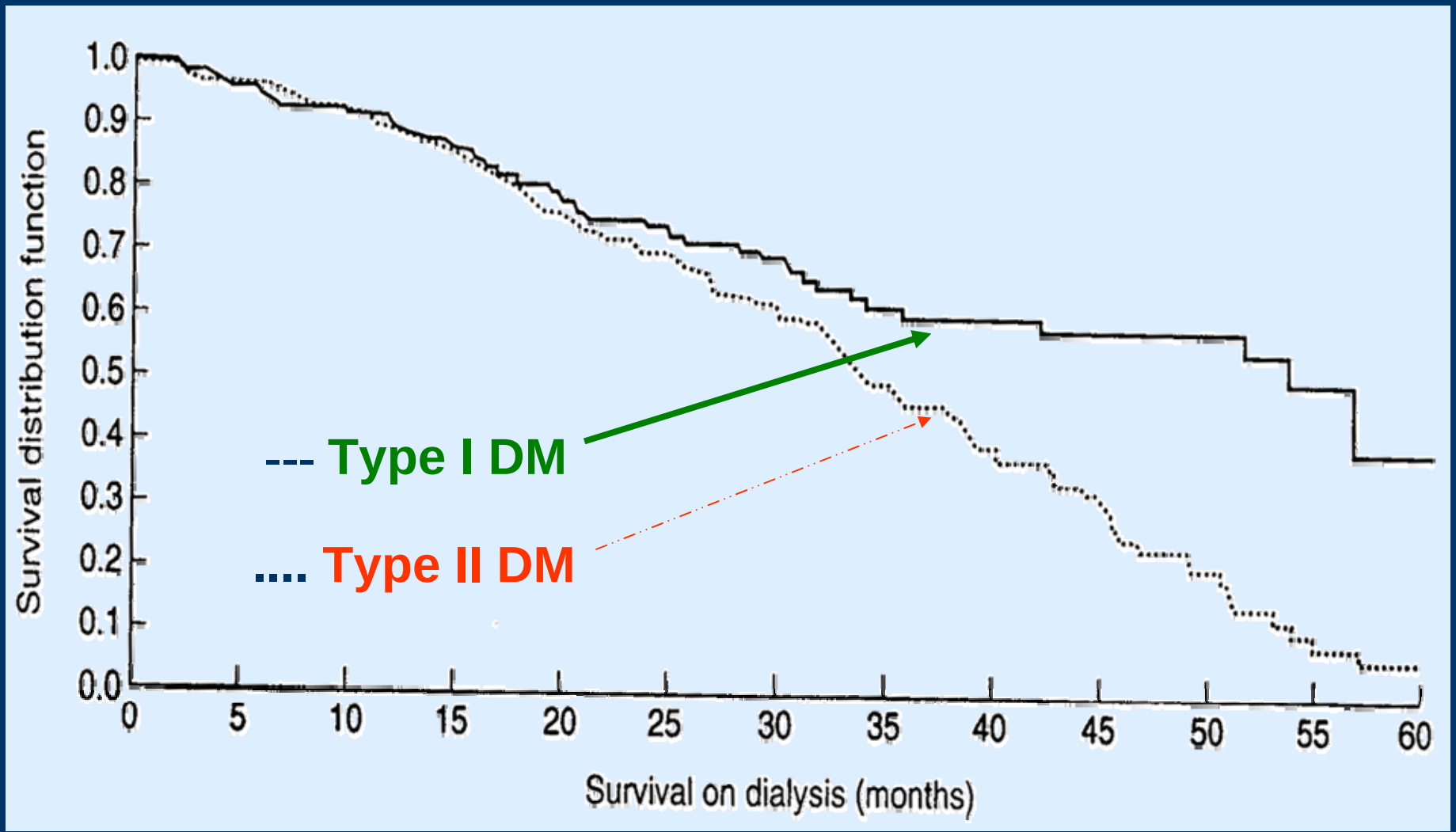


DISTRIBUTION OF TOP 3 CAUSES OF ESRD

Philippine Renal Registry, 2005





Actuarial survival of patients with type 1 (n = 181) and type 2 (n = 231) diabetes on haemodiaysis in a prospective multicentre study in Germany

Koch et. al., NDT, 1997

QUESTIONS

- Do we have other options for diabetic nephropathy apart from or in association with dialysis?
- How can we improve the quality of life of patients on dialysis?

Low Protein Diets and Chronic Kidney Disease Progression

HYPOTHESIS

Animal studies with experimental chronic kidney disease

Small numbers of patients with chronic kidney disease from diabetes or other kidney disease

Adherence to a protein-restricted diet will slow the loss of GFR in patients with chronic kidney disease

Progression of CRF in Diabetic Nephropathy

Clearance (Δ,ml/min/mo)	**Control (31.4 ± 2.5 mo)**	**Low Protein (37.1 ± 3.1)**	p
Creatinine	-0.83 ± 0.18	-0.32 ± 0.12	<0.05
Iothalamate	-1.06 ± 0.32	-0.32 ± 0.09	<0.05

Progression of CRF in Diabetic Nephropathy

Risk Factors	Control	Low-Protein	p
Hba1c (N=5.1%)	8.0 ± 0.4	7.8 ± 0.2	NS
MAP (mm Hg)	105 ± 0.9	102.3 ± 1.2	NS
Examinations (visits/yr)	13.0 ± 1.8	10.6 ± 1.2	NS

Zeller, et al, 1991

MDRD:

Modified Diet in Renal Disease

MDRD STUDY: STRUCTURE

STUDY A

- 585 patients
- GFR = 25-55
- Usual Protein Diet= 1.3 g/KBW/D or
- Low Protein Diet = 0.6 g/KBW/D
- Mean BP 107 or 92

STUDY B

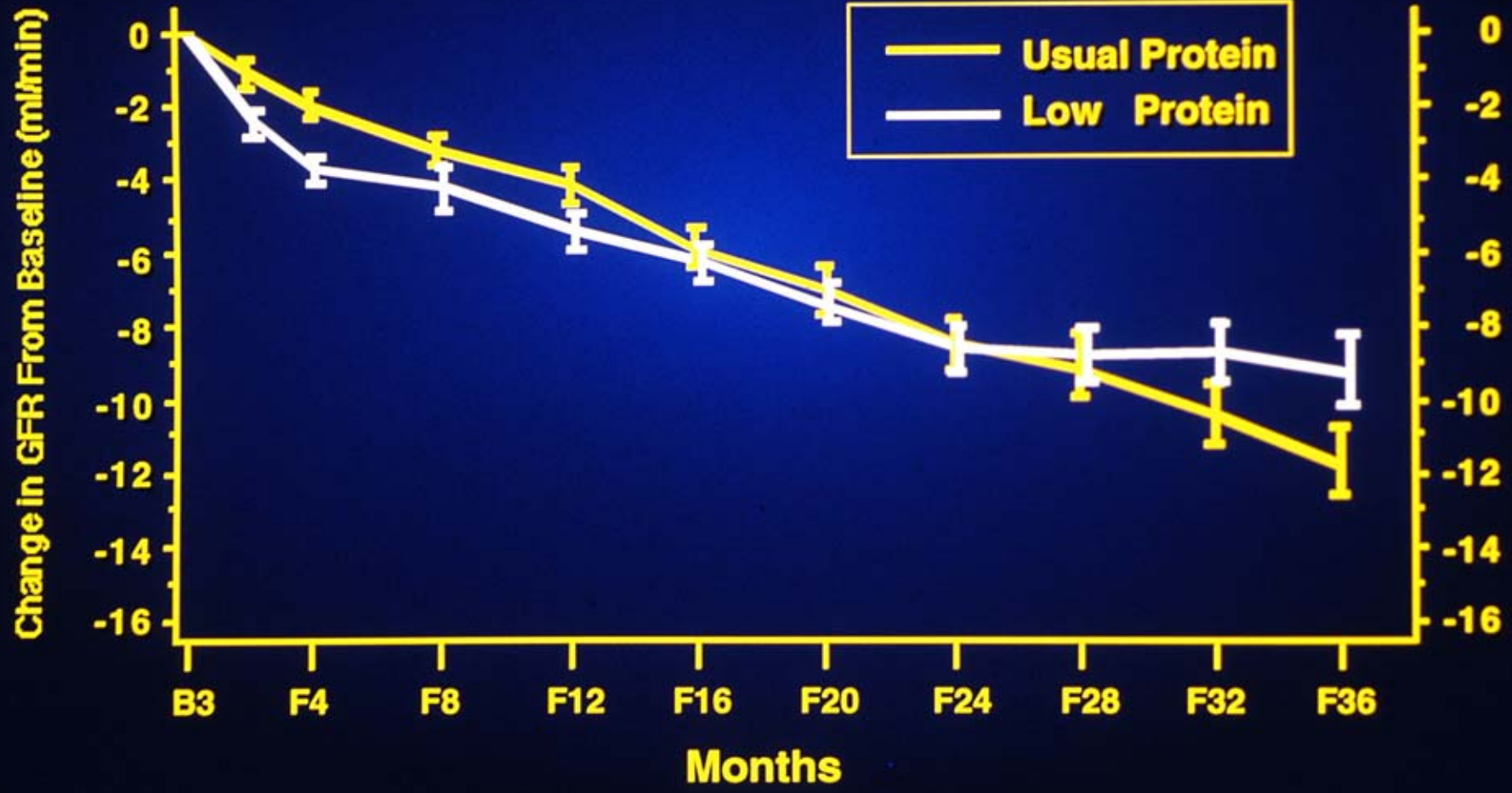
- 255 patients
- GFR = 13-24
- Low Protein Diet = 0.6 g/KBW/D or
- Very Low Protein Diet =0.3 g/KBW/D
- Mean BP 107 or 92

Duration = 2.2 years

MDRD

The Modification of Diet in Renal Disease Study

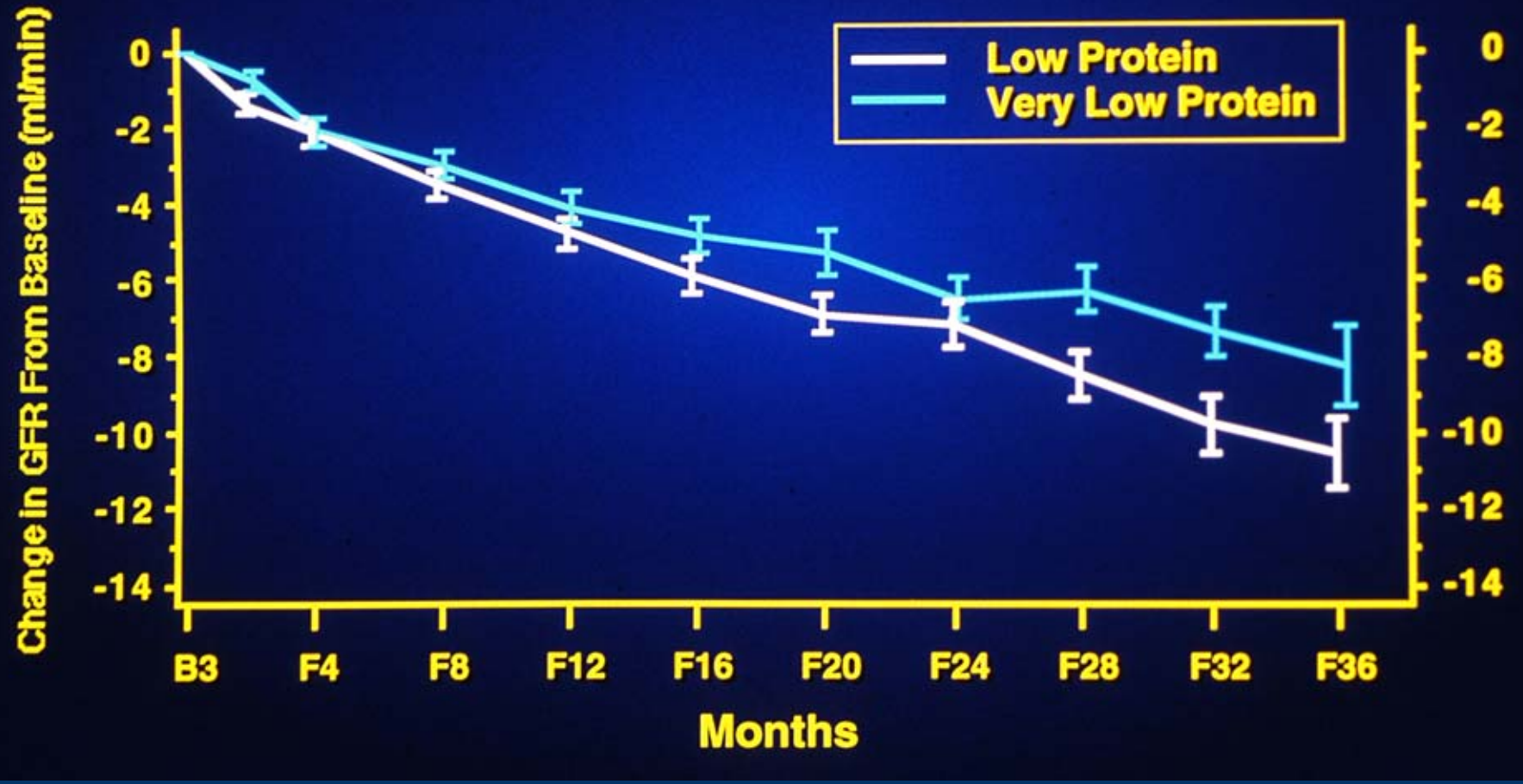
GFR Estimated Mean Changes (± SE) From Baseline in Study A



MDRD

The Modification of Diet in Renal Disease Study

GFR Estimated Mean Changes (± SE) From Baseline in Study B



MDRD RESULTS, NEJM 1994

Did this report prove that dietary protein restriction does not slow CKD progression ?

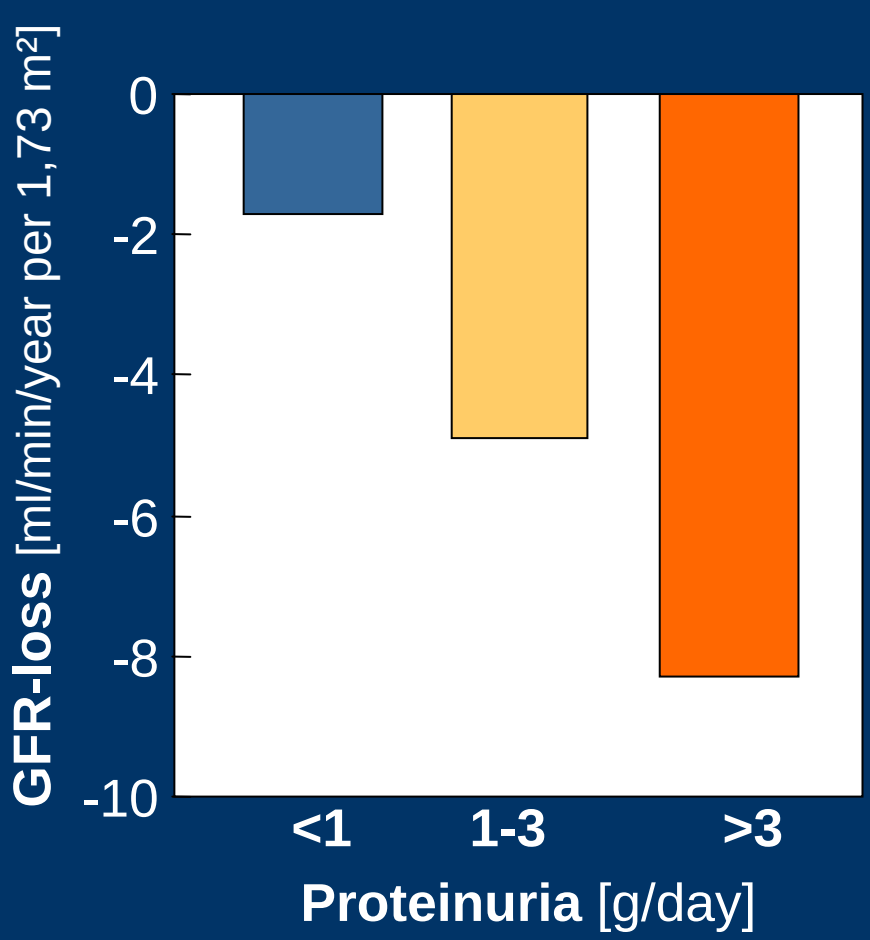
1) Entry criteria: did not include progression
2) GFR loss below predicted rate-followed only 2.2 yrs
3) No control diet for patients with advanced CKD
4) Outcome analysis: Prescribed, not actual intake of dietary protein as monitored during the study and
5) ACEi used randomly in all groups

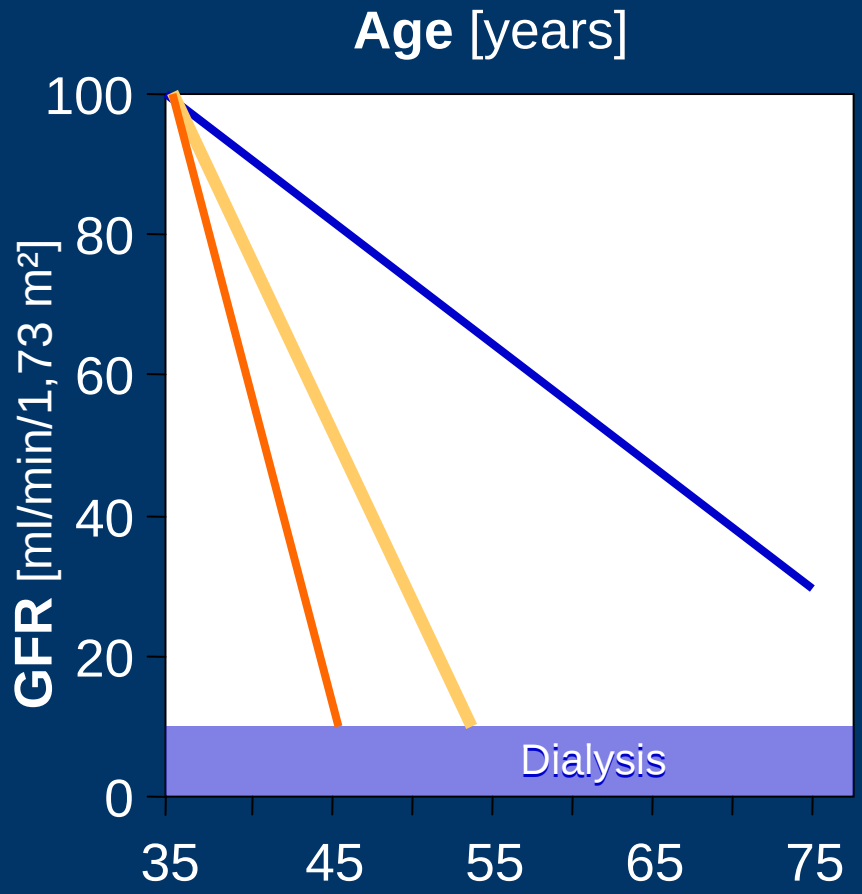
KETOACIDS AND MORTALITY IN THE MDRD STUDY

In MDRD patients who died:

- Interval therapy not identified
- Cause of death not identified
- Compliance with ketoacid regimen not examined
- No comparison with untreated patients or those assigned to 0.6 g protein/KBW/D

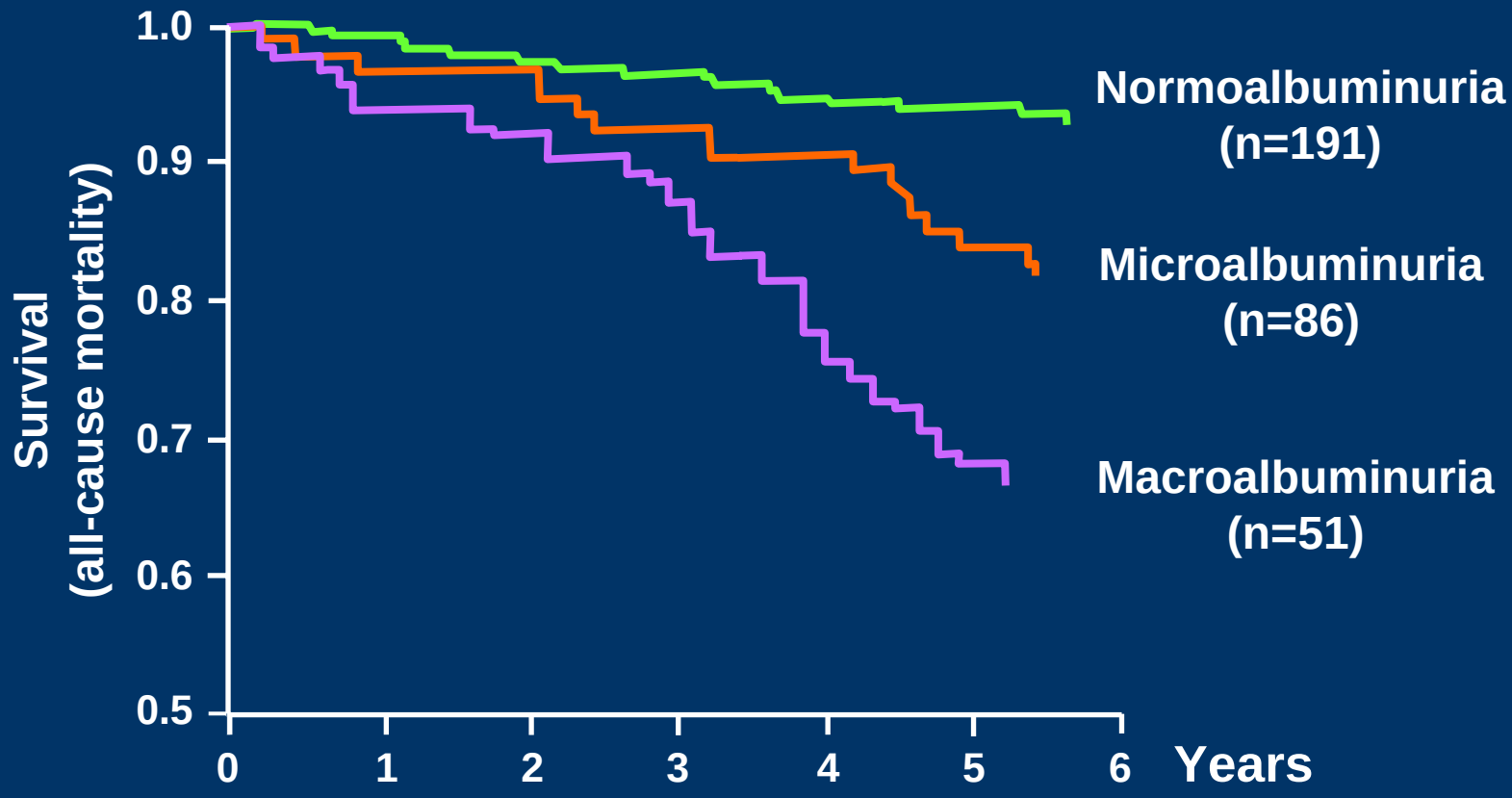
Proteinuria, progression and time of dialysis free survival





Peterson, Ann Intern Med (1995) 123: 754

ALBUMINURIA: RISK FACTOR FOR MORTALITY IN TYPE 2 DIABETES



p<0.01 normo vs micro- or macroalbuminuria
p<0.05 micro vs macroalbuminuria

Gall et al., *Diabetes,* 1995

Treatment Goals

- Lowering of systolic blood pressure
- Reduction of proteinuria < 1g/24h
- Pharmacologic blockade of renin-angiotensin system

Treating Diabetic Nephropathy: Achieving Blood Pressure Control

- **Recommended blood pressure targets**
  - **General population: < 140/90 mmHg**
  - **High risk population:**

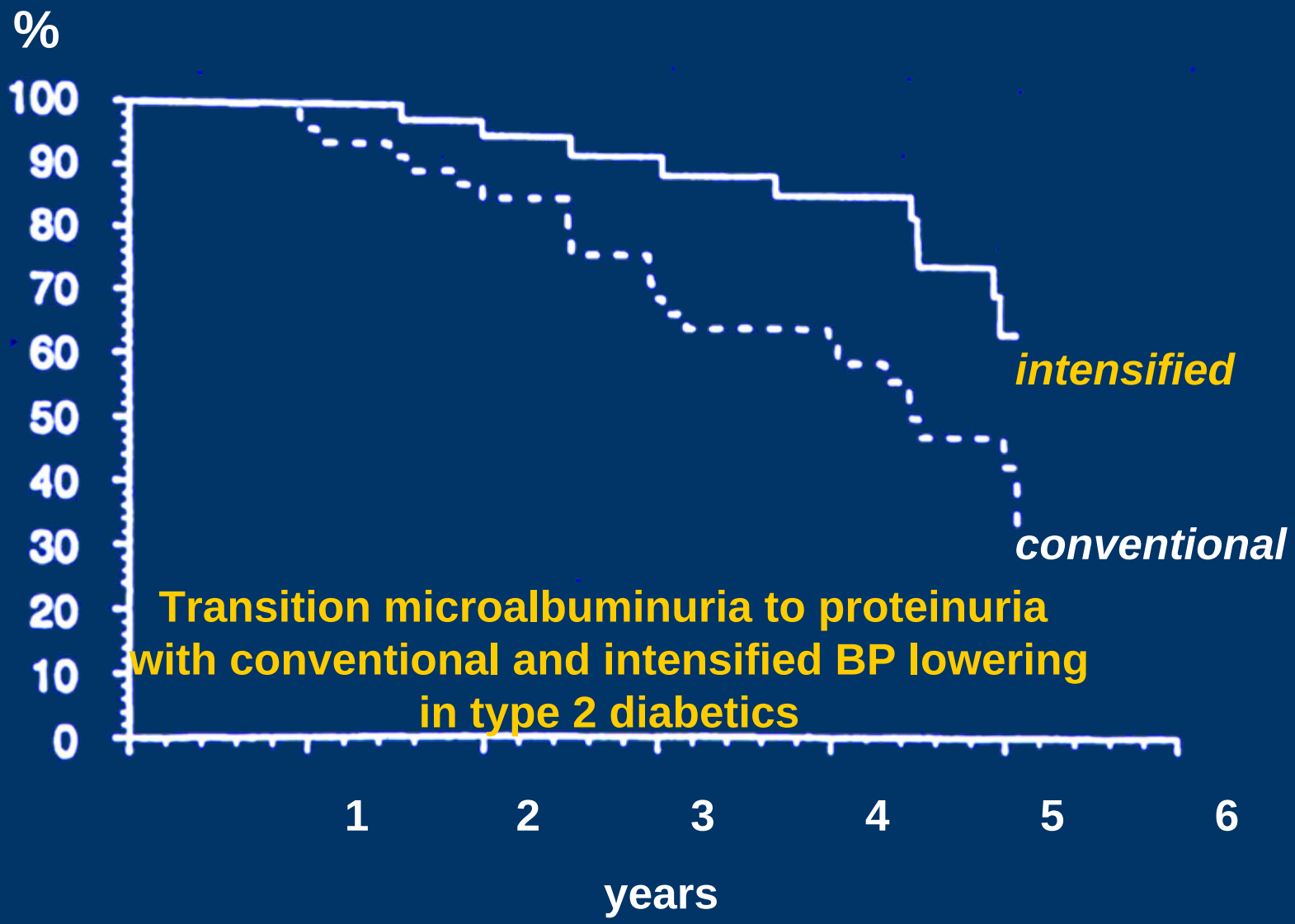
•Diabetes: < 130/85 mmHg

Renal insufficiency and proteinuria ≤ 1 g/day: < 130/85 mmHg

Renal insufficiency and proteinuria > 1 g/day: < 125/75 mmHg

Arch Intern Med (1997) 157, 2413

Treating Diabetic Nephropathy:
Blood Pressure Control & Level of Proteinuria



Schrier, Kidney Intern (2002) 61: 1086

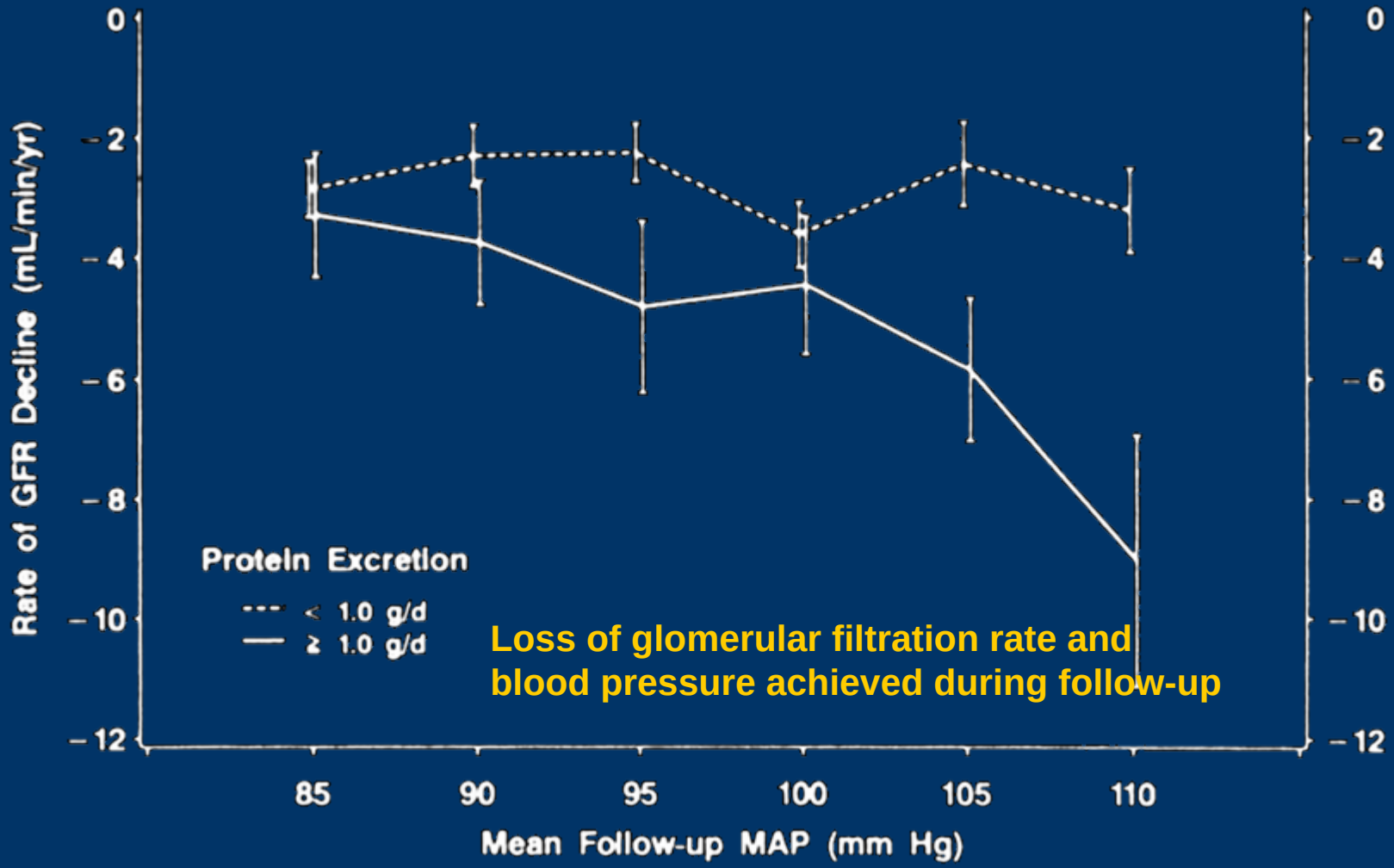
Treating Diabetic Nephropathy: Achieving Blood Pressure Control

Blood Pressure Control in the MDRD

blood pressure control		loss of GFR (ml/min/year)
ordinary	107 mmHg MAP	3.4 (2.6-4.1)
intensified	91 mmHg MAP	1.9 (1.1-2.7)

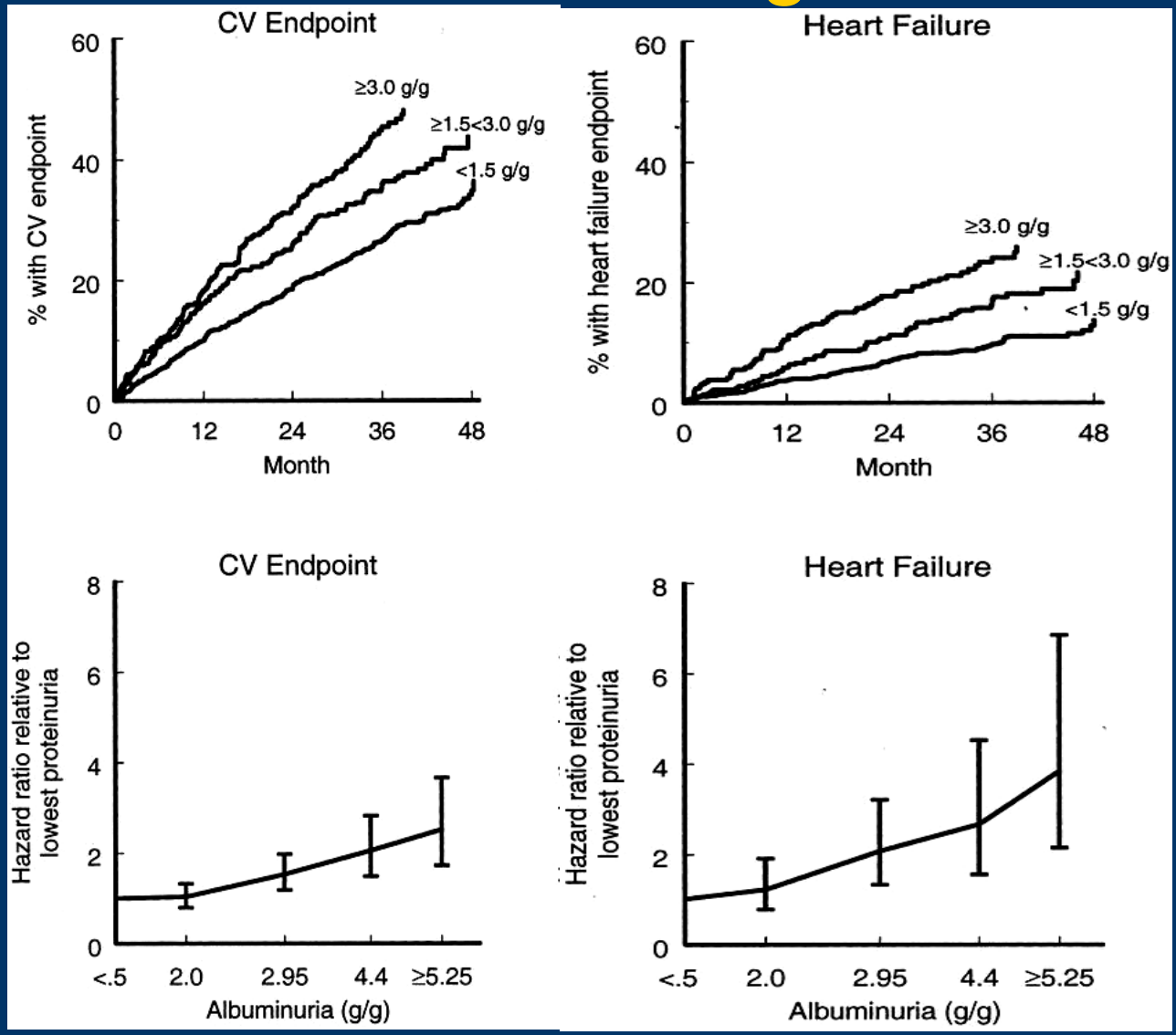
Klahr, NEJM (1994) 350: 877

Treating Diabetic Nephropathy: Achieving Blood Pressure Control



Peterson, Ann Int Med 1995, 123, 745

Treating Diabetic Nephropathy: Decreasing Proteinuria



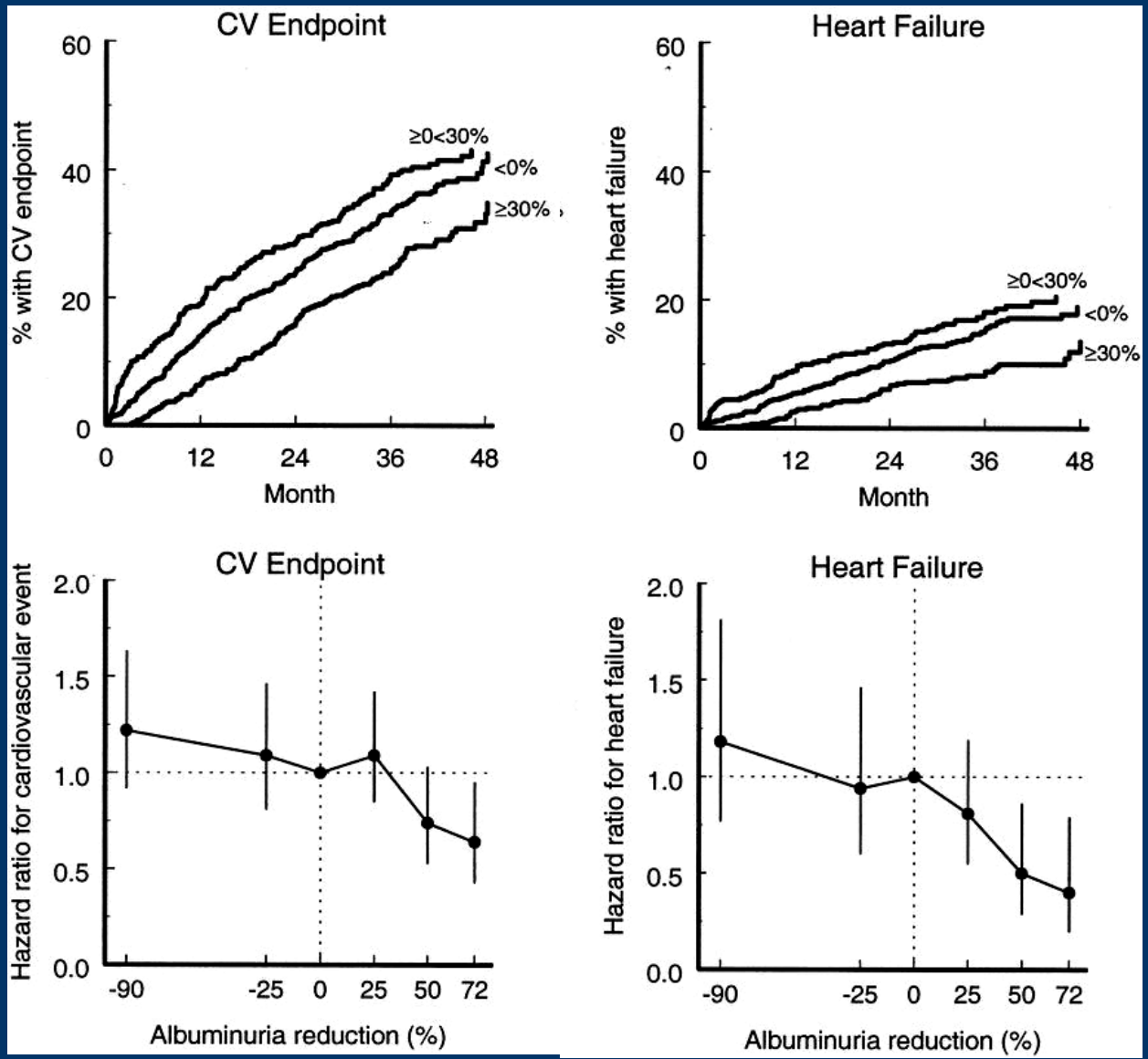
Baseline albuminuria:

predictor

of renal and cardiovascular endpoints

DeZeeuw, Circulation (2004) 110:921

Treating Diabetic Nephropathy: Decreasing Proteinuria



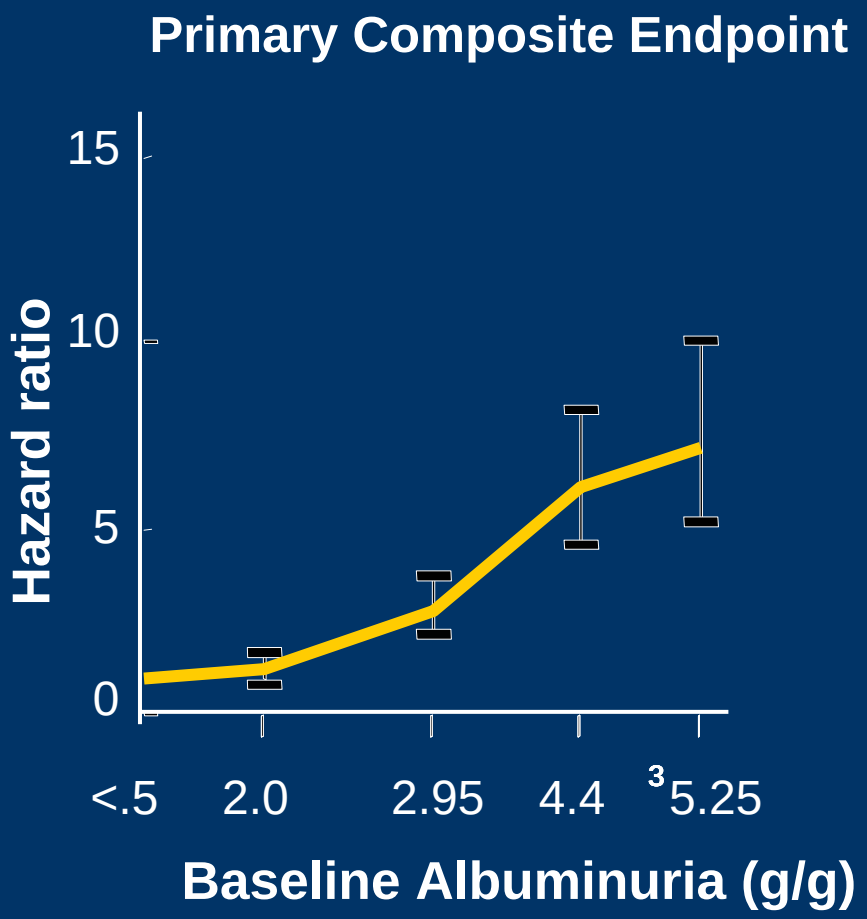
Change of albuminuria during treatment:

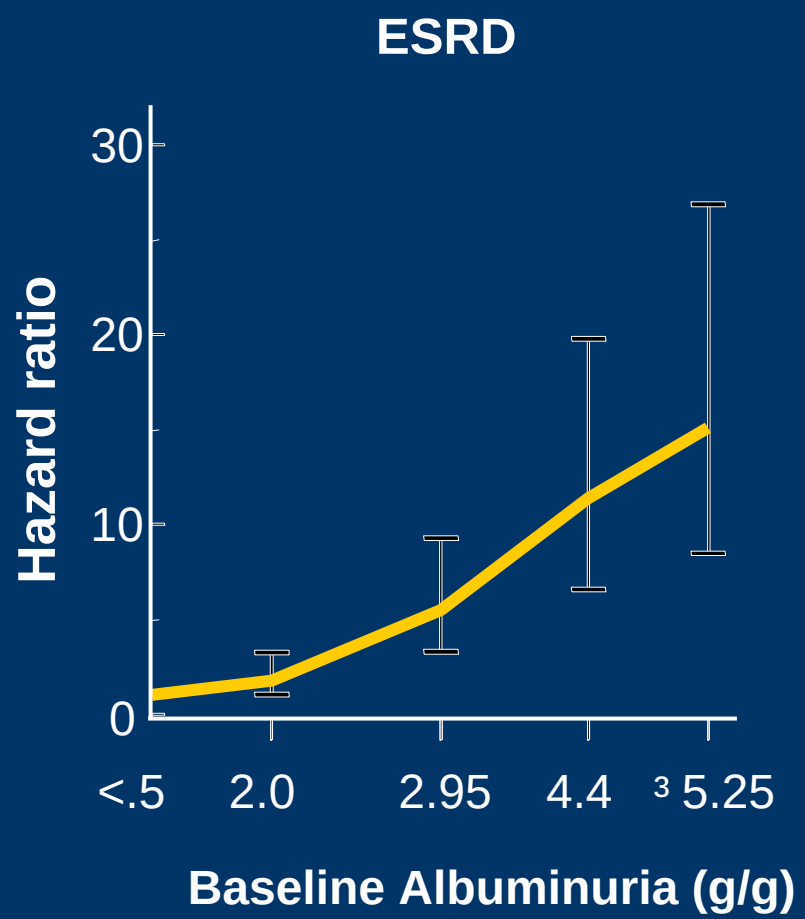
predictor

of renal and cardiovascular endpoints

DeZeeuw, Circulation (2004) 110:921

Baseline Proteinuria Determines Renal Events



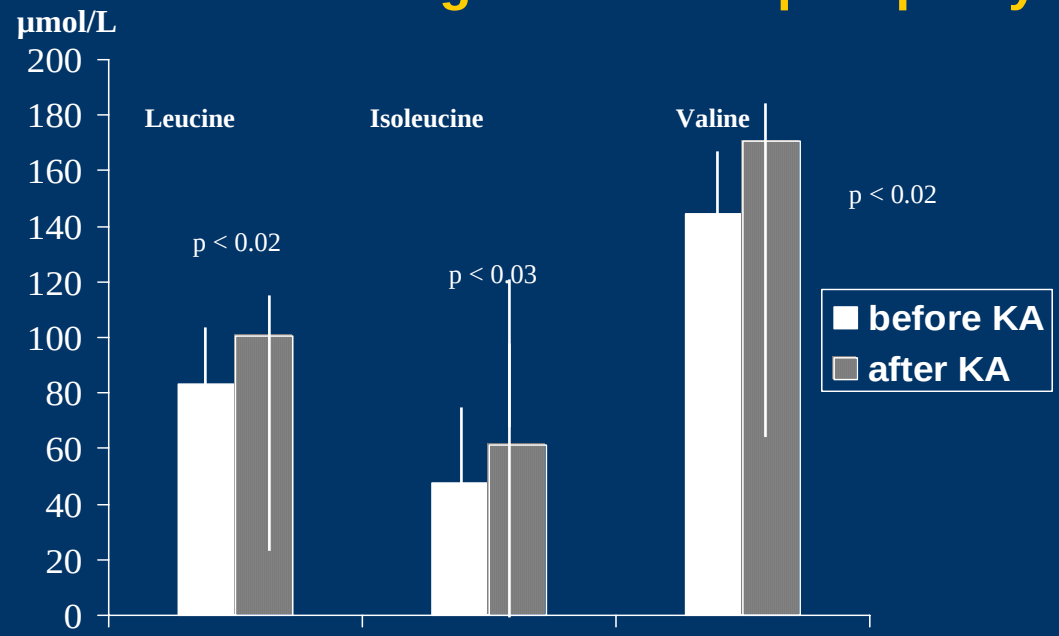


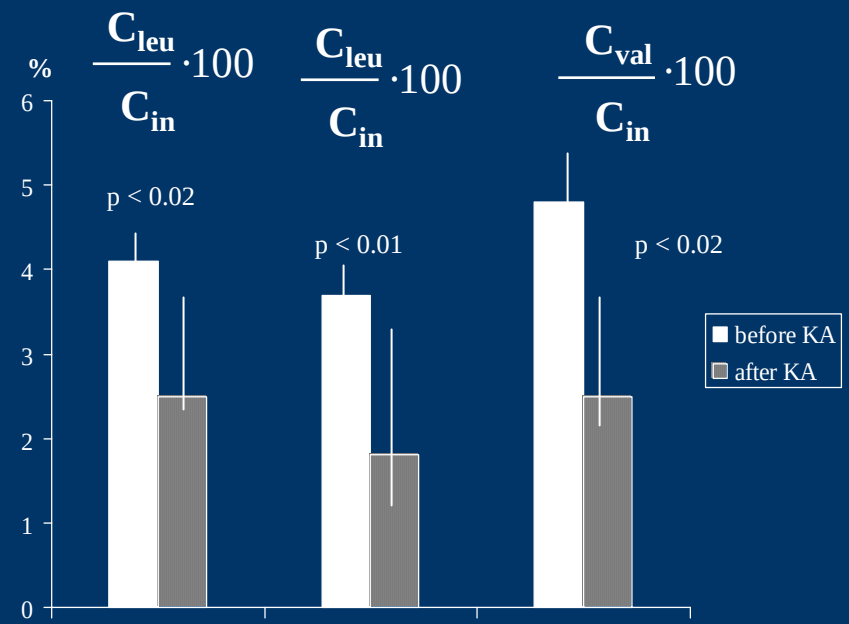
De Zeeuw et al; Kidney Int , 2004

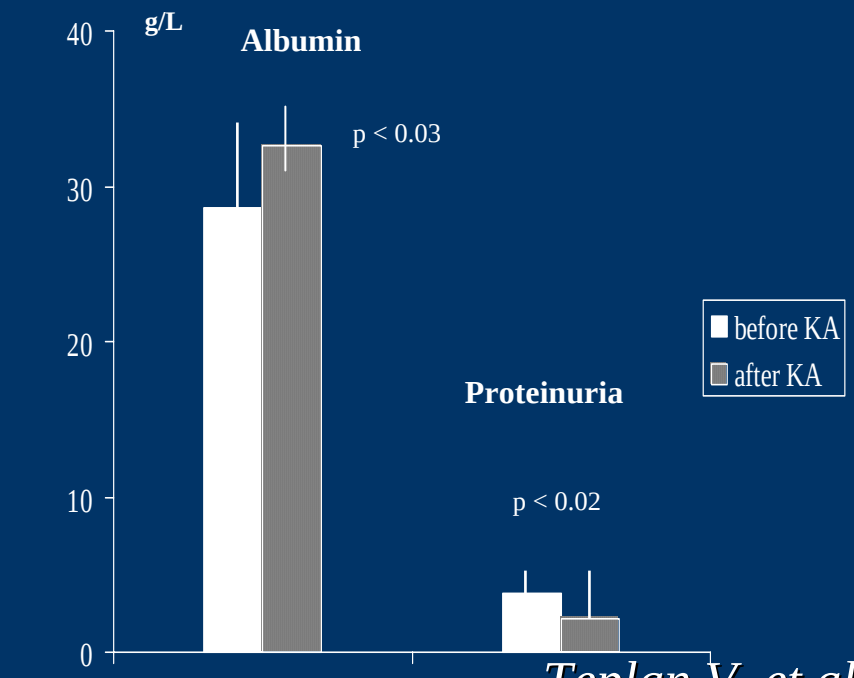
How do we usually decrease proteinuria?

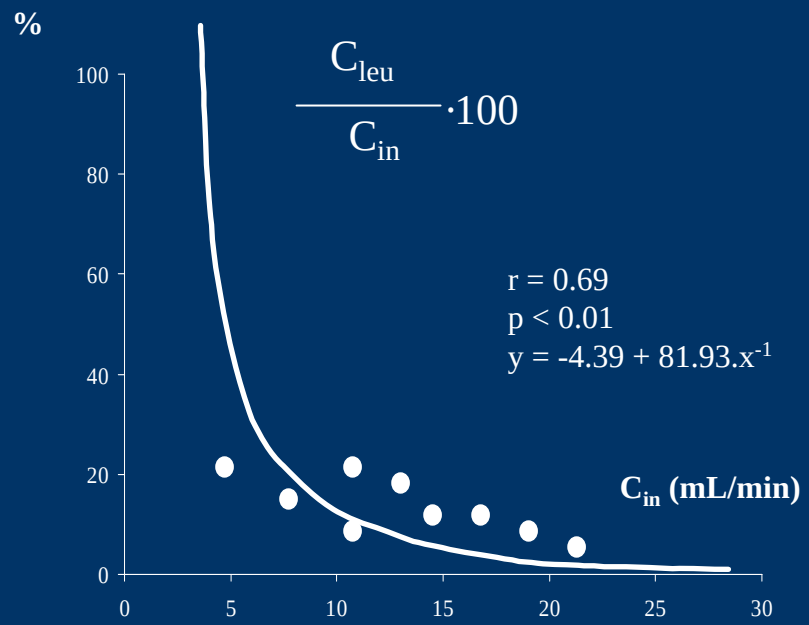
- Blocking the RAAS
- Low Protein Diet
- Ketoanalogues

Treating Diabetic Nephropathy: Decreasing Proteinuria









Teplan,V et al, Wiener Klin.Wschr., 112 (20), 2000, s.876-881.

Treating Diabetic Nephropathy:

Achieving Blood Pressure Control
Decreasing Proteinuria
Pharmacologic blockade of renin-angiotensin system

Antiproteinuric and Metabolic Effect of Long-term Administration of keto amino acids and ACE inhibitors in CRF patients with diabetic nephropathy

V. Teplan, et al

Klin Bioch Met 11, 2003, Diabetik, 5, 2004

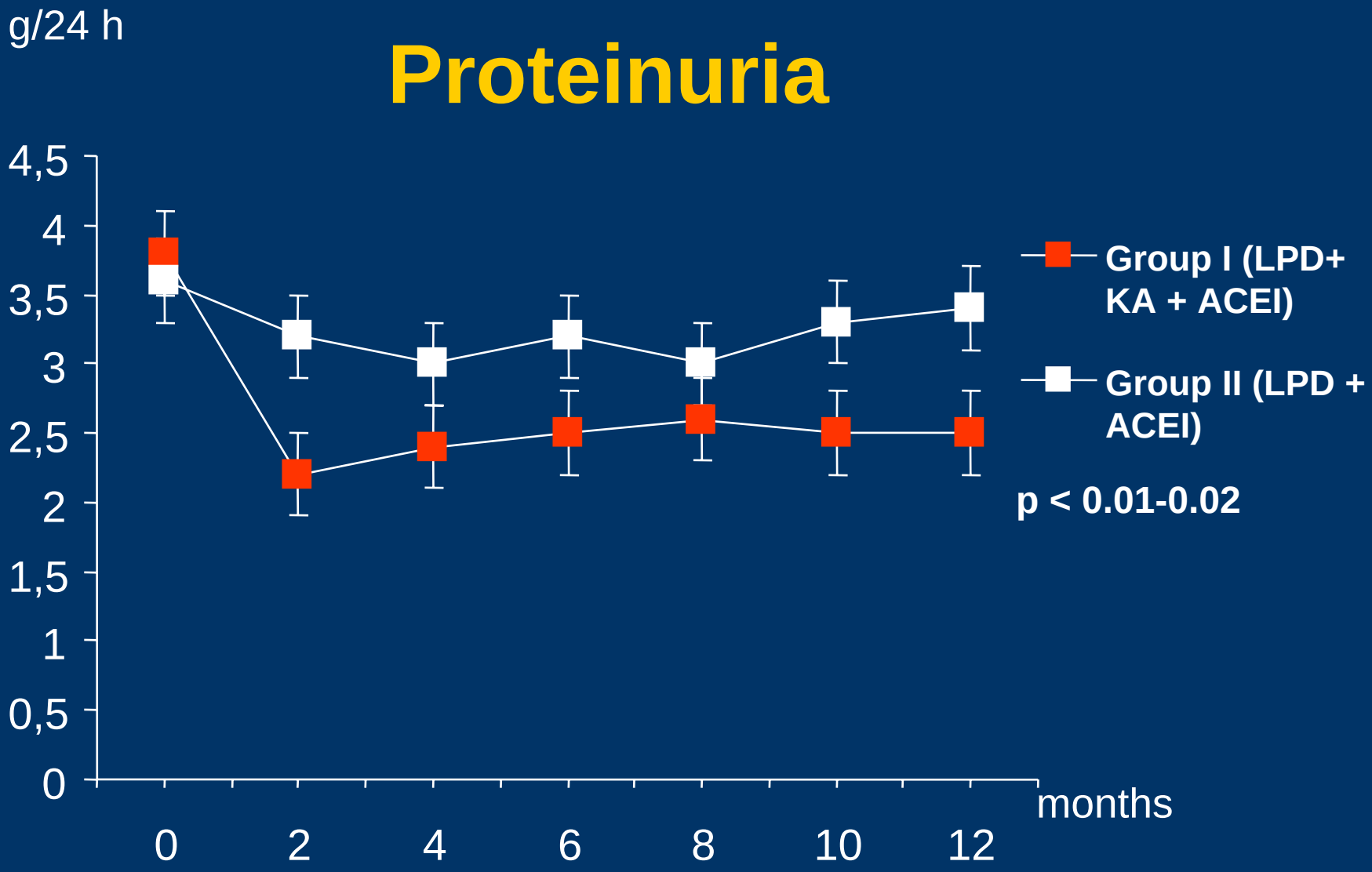
Aim

- Analysis of data in patients in chronic renal insufficiency (CRI) with diabetic nephropathy on low-protein diet (LPD).
  - prospective long-term randomized multicentric study
  - evaluate the effect of concomitant administration of
    - keto amino acids (KA)
    - ACE inhibitors (ACEI)
  - proteinuria and aminoaciduria

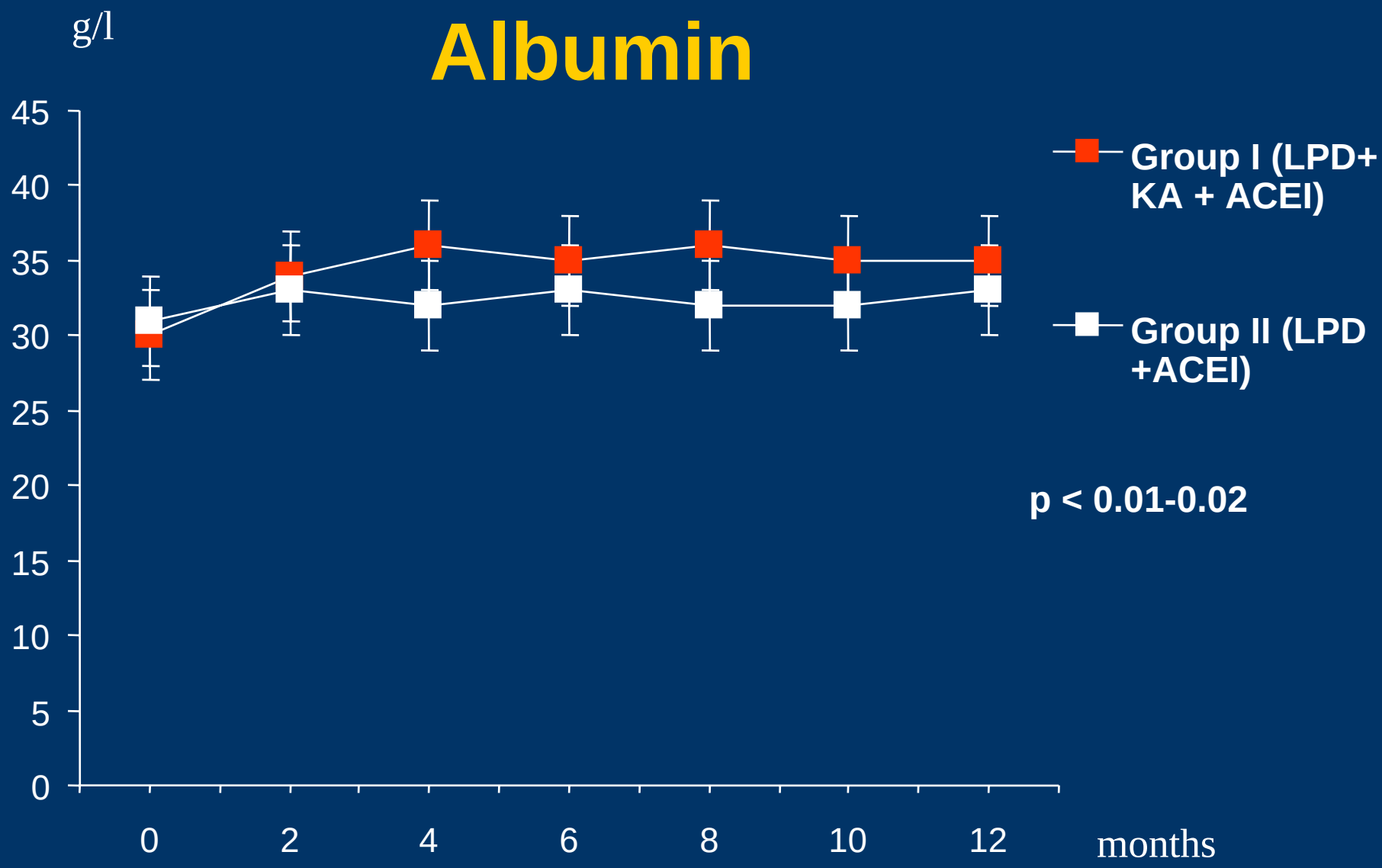
Methods

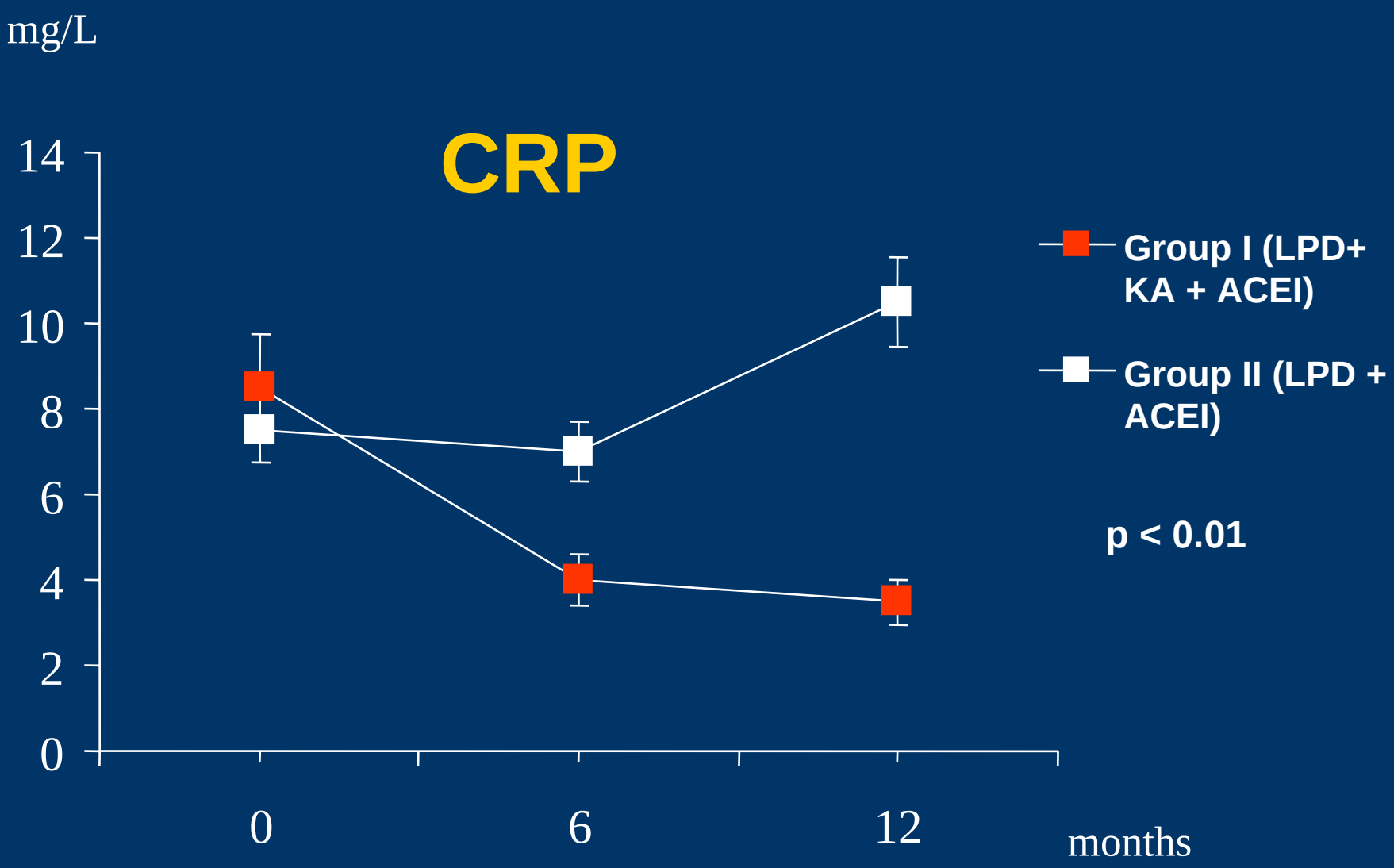
- 12 month period
- 50 patients
- Group I (n=25)
  - LPD (0,6 g protein/kg/day)
  - keto acids (100 mg/kg/day)
  - ACEI (perindopril 4 mg/d)
- Group II (n=25)
  - LPD
  - ACEI in equal doses.

Proteinuria

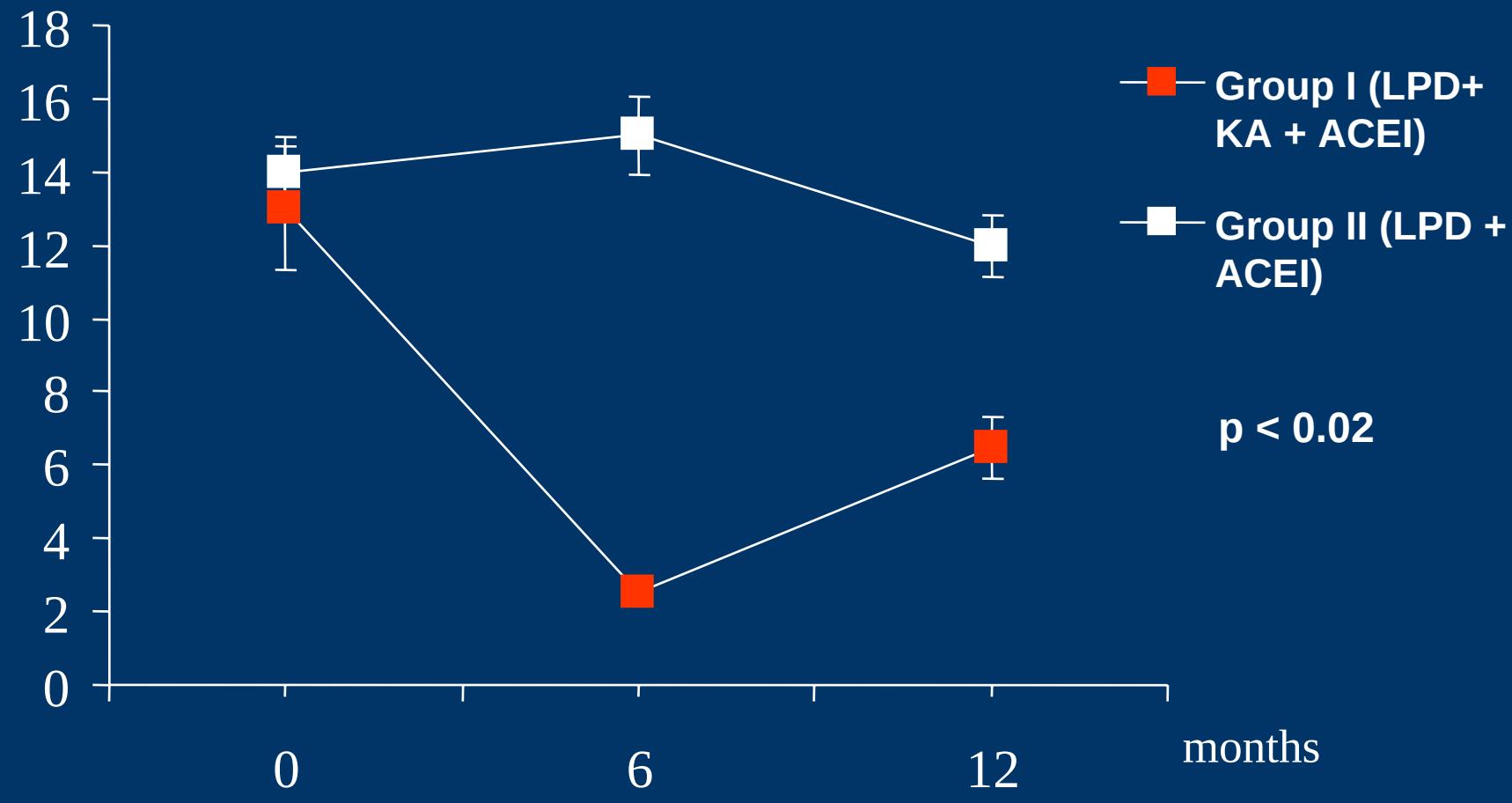


Albumin

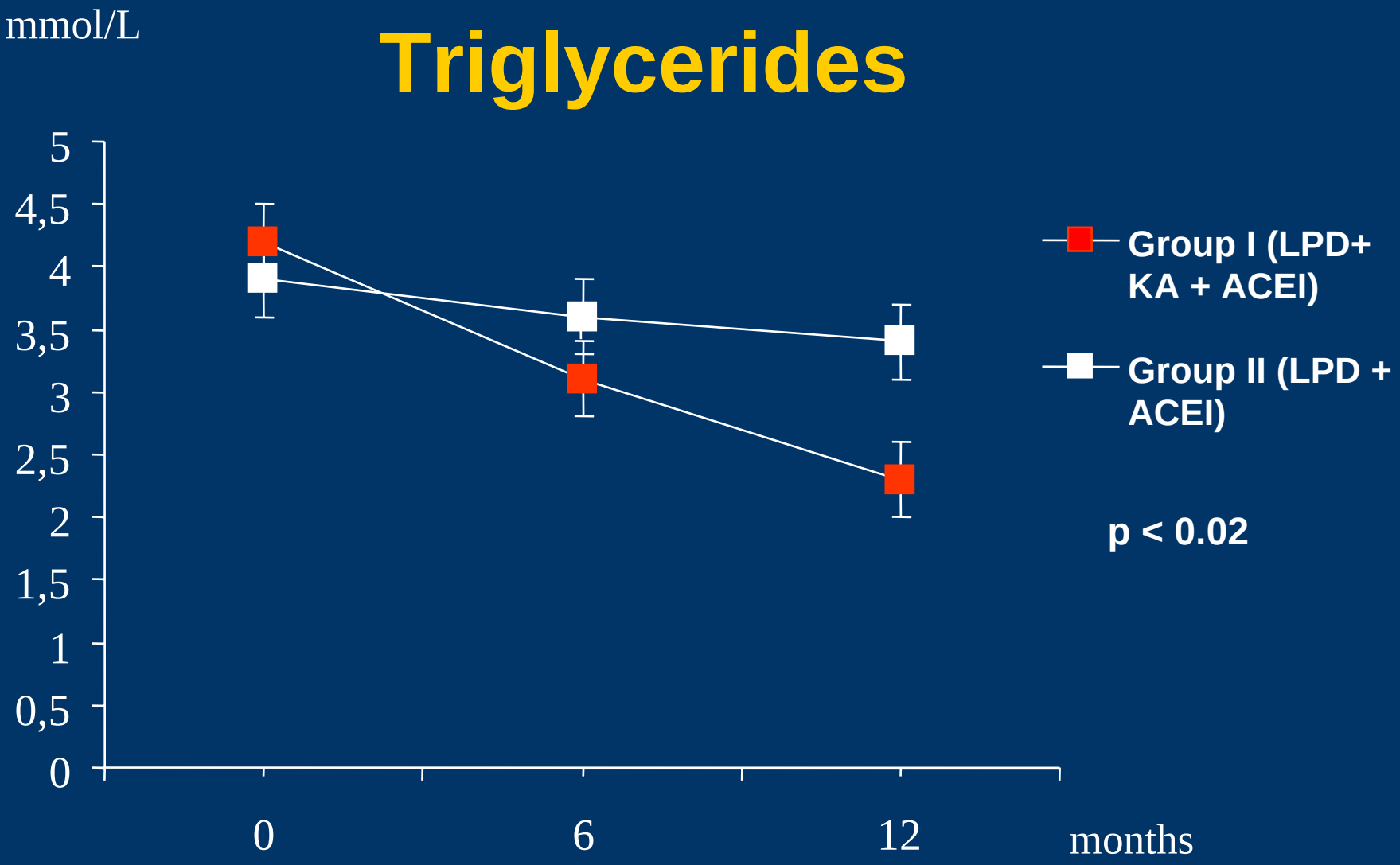

g/l
45
40
35
30
25
20
15
10
5
0
0
2
4
6
8
10
12
months
Group I (LPD+ KA + ACEI)
Group II (LPD +ACEI)
p < 0.01-0.02


mg/L
CRP
14
12
10
8
6
4
2
0
0
6
12
months
Group I (LPD+ KA + ACEI)
Group II (LPD + ACEI)
p < 0.01

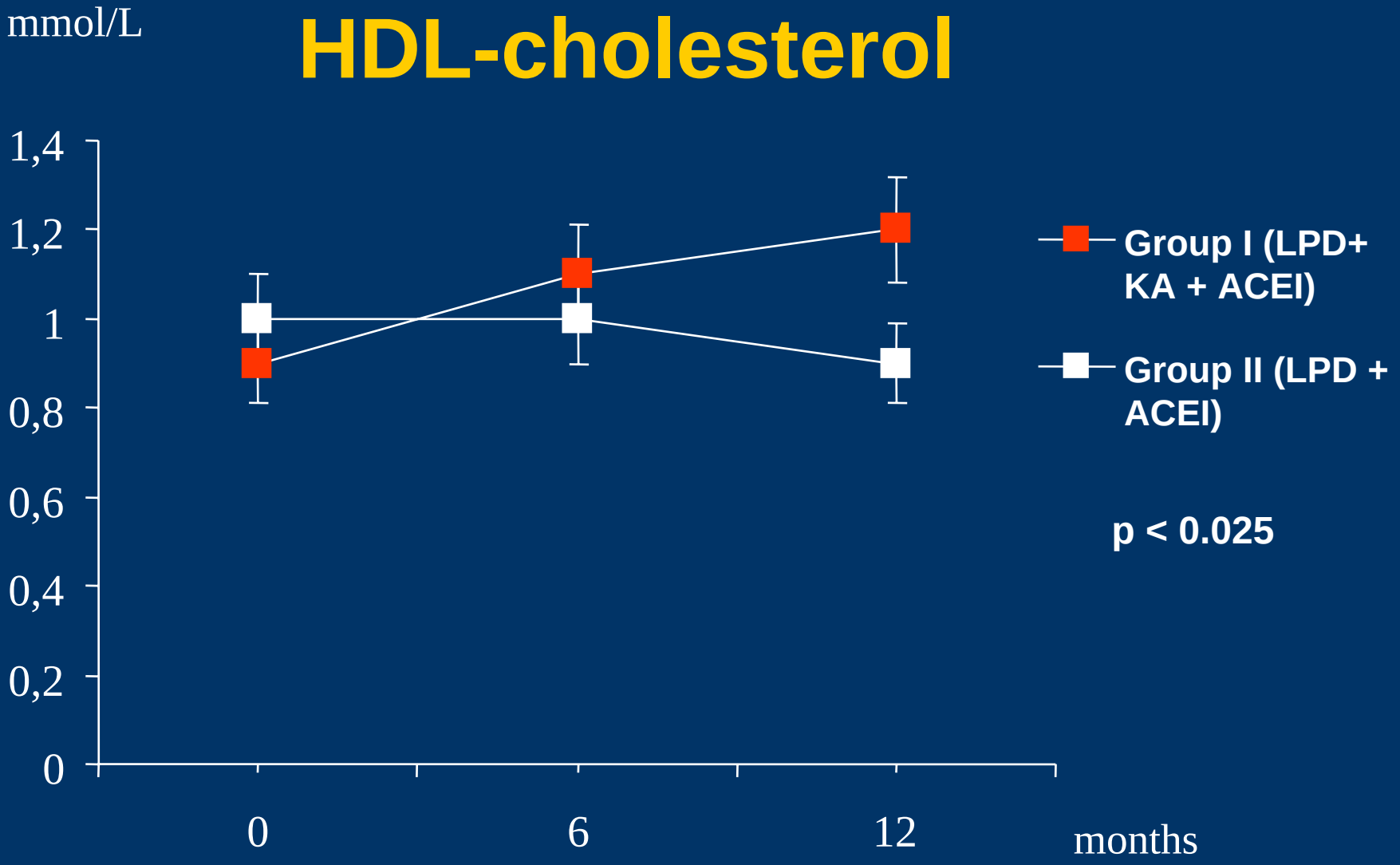
TGF β


pg/mL x 10³
18
16
14
12
10
8
6
4
2
0
0
6
12
months
Group I (LPD+ KA + ACEI)
Group II (LPD + ACEI)
p < 0.02

Triglycerides



HDL-cholesterol



Results and Conclusions

- Decrease in proteinuria ($p<0.01$) predominantly in Group I
  - Associated with improved protein metabolism parameters
  - Slower CRI progression was observed as assessed using inulin clearance ($p<0.01$)
- KA and ACEI co-administration
  - Had a beneficial effect on the examined metabolic parameters
  - Through its glomerulo-tubular action, it also had an effect on the long-term progression of CRI.

CONSENSUS

Keto Acid Therapy in Diabetic Nephropathy

- Due to the exponential growth of diabetic nephropathy (as one major cause of ESRD) alternative conventional strategies – including Keto Acid Therapy – for the treatment of diabetic nephropathy are absolutely indicated
- Keto Acid Therapy as part of a treatment program in diabetic nephropathy patients based on published literature is considered to be entirely safe and efficacious.

Am J Nephrol 2005;25 (suppl 1):1-28

Proper Implementation of Keto Acid Therapy

- Does not induce malnutrition or even improve nutritional status (e.g.albumin, BMI)
- Can improve metabolic abnormalities associated with renal insufficiency (e.g. bicarbonate, phosphorus, calcium)
- Can improve/correct diabetes associated metabolic disturbances in Type II (good glycemic control, improvement of insulin sensitivity, reduction of hyperinsulinemia)
- Enables good glycemic control in Type I DM
- May slow progression of renal insufficiency and will delay the time until dialysis is required to treat uremic symptoms

Am J Nephrol 2005;25 (suppl 1):1-28

Specific International Guidelines and Recommendations for Keto Acid Therapy

- Low protein diet (0.6-0.7 g protein/KBW/D) is indicated at a Cr Cl of 50 ml/min/1.73 sq m, Keto Acid Therapy is indicated at a Cr Cl of 20-25 ml/min/1.73 sq m
- Daily protein intake at a low protein diet supplemented with keto acids should not exceed 0.6 g/KBW/D, optimal protein intake is 0.4-0.6 g/KBW/D
- Recommended dosage of keto acids (Ketosteril®) is 0.1 g/KBW/D
- Daily energy intake of 35 kcal/KBW/D should be recommended
- Protein calories must be replaced by complex carbohydrates – not lipids

Am J Nephrol 2005;25 (suppl 1): 1-28

Crucial Aspects for Efficacy
Keto Acid Therapy in Diabetic Nephropathy

- Patients have to be properly selected to **motivation and ability to follow a protein-restricted diet**
- In order to reap the benefits for diabetic nephropathy patients, it is absolutely necessary that **all disciplines involved in treatment** (nephrologist, physicians/ nutritionists, nurses) **act as a highly motivated team**
- **Support for increasing patients' compliance** is needed: recipes, dietary computer program
- Development of guidelines as well as convincing Diabetes Assn/ Diabetologists about the efficacy and safety of Keto Acid Therapy is regarded as a major issue for **increasing the awareness of Keto Acid Therapy.**

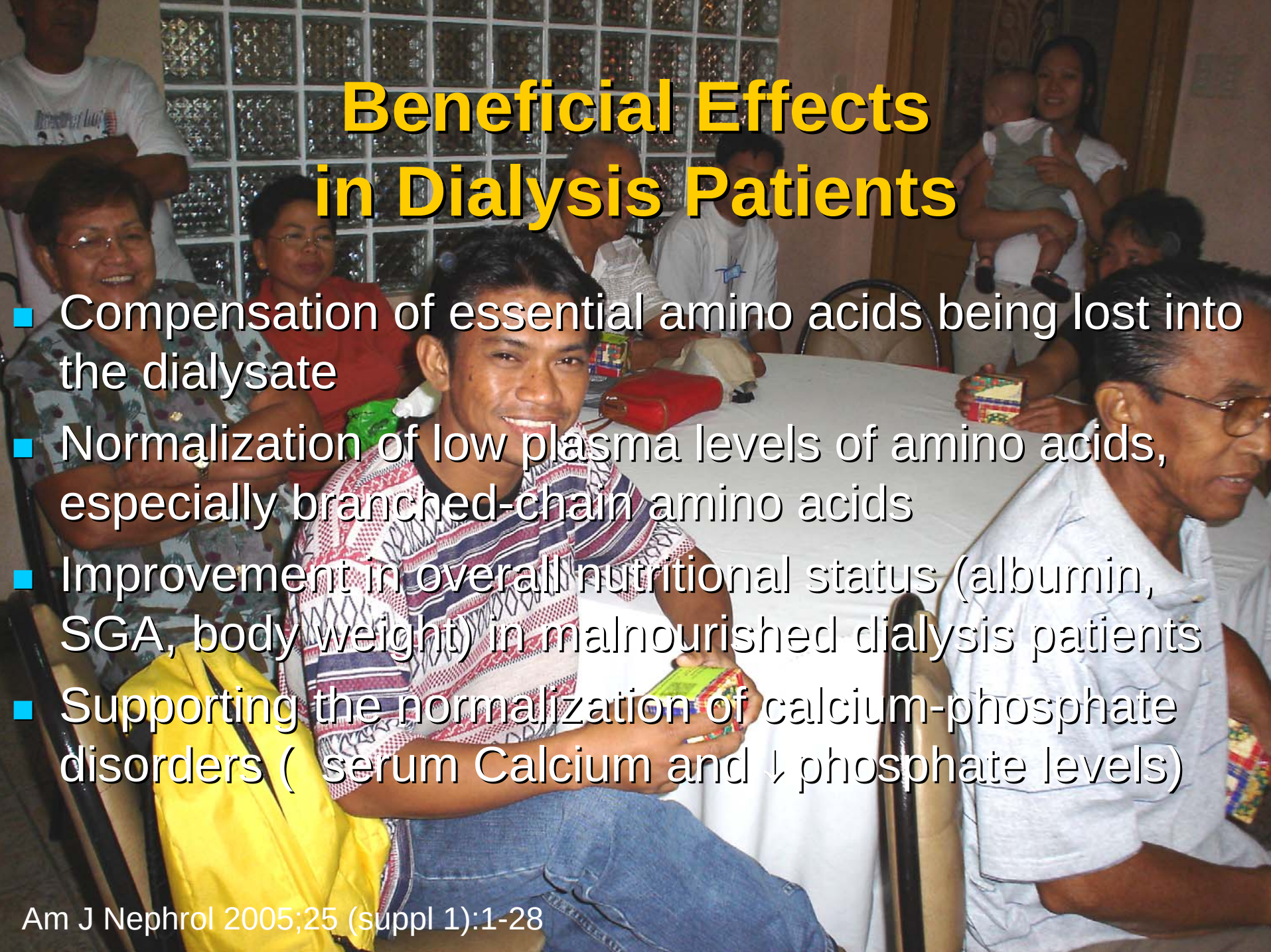
Am J Nephrol 2005;25 (suppl 1):1-28

CONSENSUS

Keto Acid Supplementation in Patients Being Treated by Dialysis

- An estimated 30-50% of dialysis patients suffer from protein-energy malnutrition.
- Uremic malnutrition is strongly associated with an increased risk of death and hospitalization events
- Thus, nutritional status is an important predictor of clinical outcome in chronic hemodialysis patients
- Abnormalities in nutritional markers are common
  - ↓ serum protein/albumin
  - Lower body mass as assessed by anthropometric measurements and subjective global assessment
  - ↓ nutrient intake
- Decreased muscle mass is the most significant predictor of morbidity and mortality in these patients

Am J Nephrol 2005;25 (suppl 1) 1-28



Beneficial Effects in Dialysis Patients

- Compensation of essential amino acids being lost into the dialysate
- Normalization of low plasma levels of amino acids, especially branched-chain amino acids
- Improvement in overall nutritional status (albumin, SGA, body weight) in malnourished dialysis patients
- Supporting the normalization of calcium-phosphate disorders (serum Calcium and ↓ phosphate levels)

Am J Nephrol 2005;25 (suppl 1):1-28

Recommendations

for protein and energy intake and keto/amino acid supplementation in dialysis patients

- Dietary protein intake: 1.2 g/KBW/D
- Dietary energy intake:
  - 35 kcal/KBW/D: $\leq$ 60 years
  - 30-35 kcal/KBW/D: $\geq$ 60 years
  - Recommended dosage of keto acids (Ketosteril®): 1 tablet/5-8 KBW/D

Am J Nephrol 2005;25 (suppl 1):1-28

One Last Question!

A 36 year old diabetic woman weighing 36 kg with a creatinine of 2 mg/dl

A. Does not require Ketosteril
B. Will benefit from Ketosteril, 600 mg, 1 tab 3x/day
C. Will benefit from Ketosteril, 600 mg, 2 tabs 3x/day

How does one estimate severity of CKD:

Cockcroft and Gault Formula:

$$\frac{(140 - \text{age}) \times \text{weight kg}}{72 \times \text{SCr mg/dL}} \times 0.85$$

(for women)

If SCr = 2 mg/dl

36 yr old woman, 36 kg:

$$\frac{(140 - 36) \times 36 \text{ kg}}{72 \times 2 \text{ mg/dL}} \times 0.85 = 22.1 \text{ ml/min}$$

(ABNORMAL)

Ketosteril Requirement

0.1 gm Ketosteril/KBW/day

Daily dose of Ketosteril

=0.1 gm X 36 kg

=3.6 gm or 3600 mg/600 mg per tablet

=6 tabs/day or 2 tabs 3x/day


Life is God's gift…
Let us give LIFE the QUALITY it deserves!