A TRAIL OF TRIALS IN CHRONIC KIDNEY DISEASE

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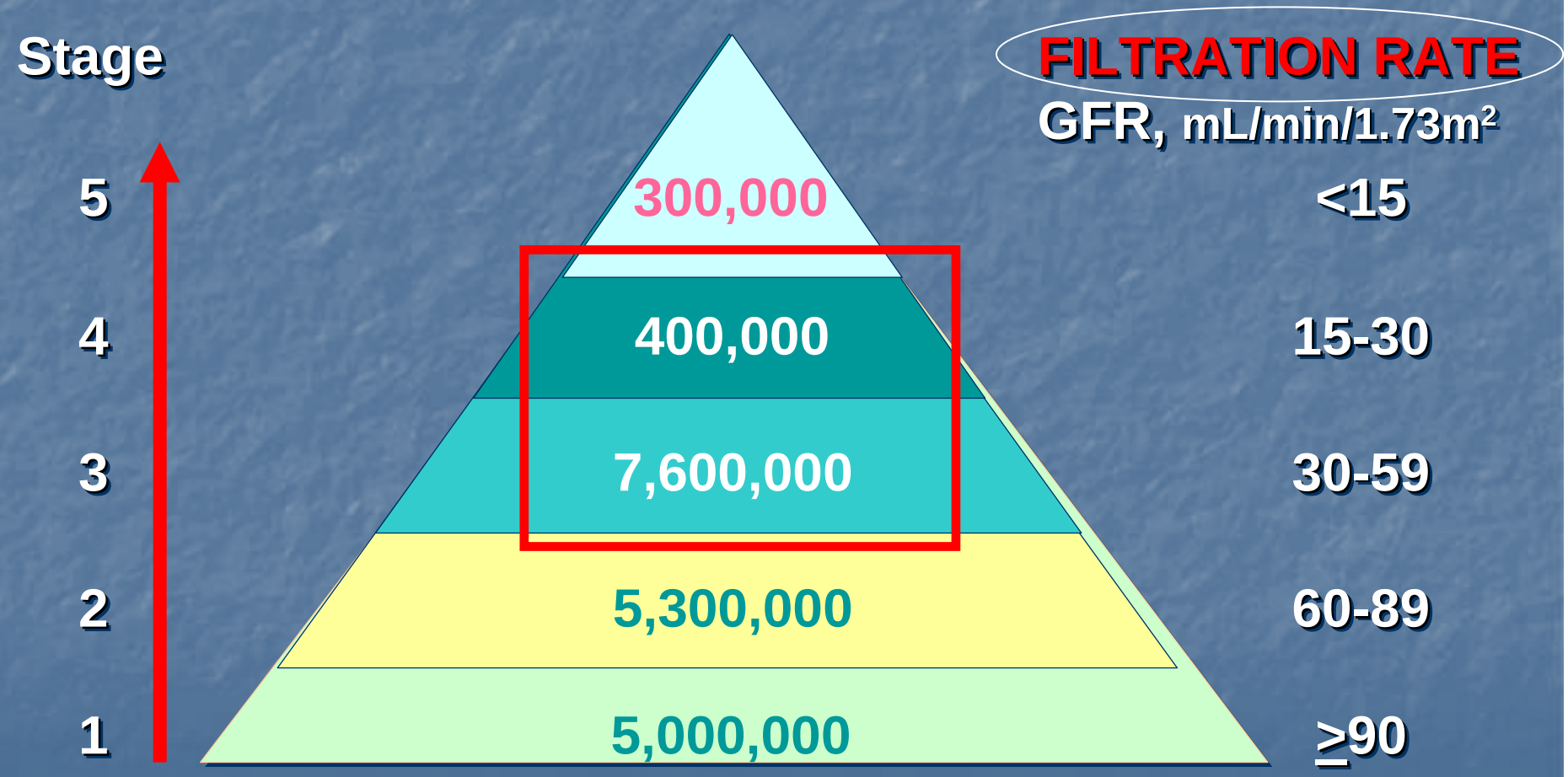
THE RENAL DISEASE ICEBERG

DIALYSIS
ESRD

CHRONIC KIDNEY DISEASE

PREVALENCE OF CHRONIC KIDNEY DISEASE NHANES III (1988-1994)

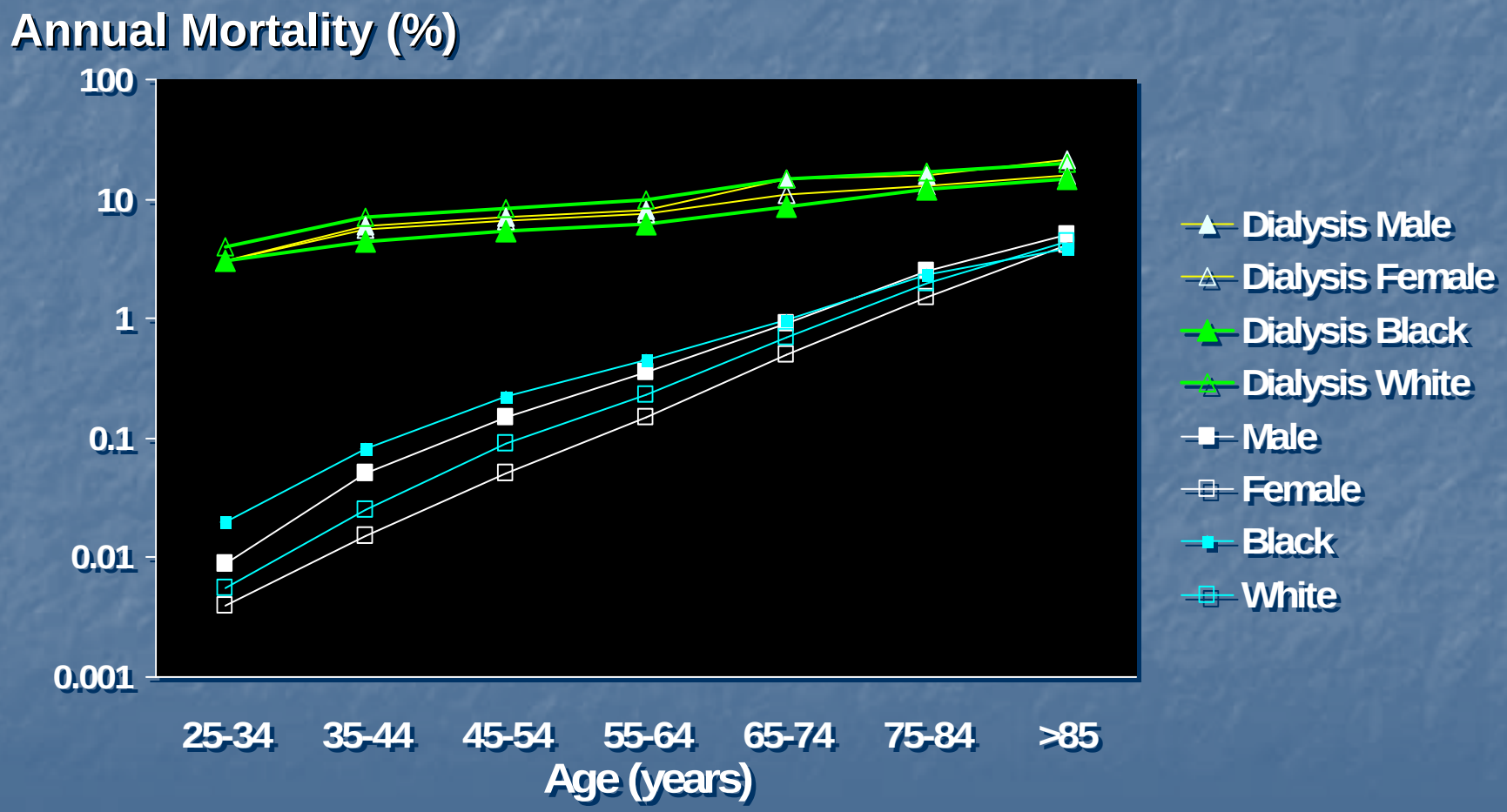


Jones et al, AJKD 32: 992-999, 1998

WHY ATTEMPT INTERVENTION IN CKD AND ESRD?

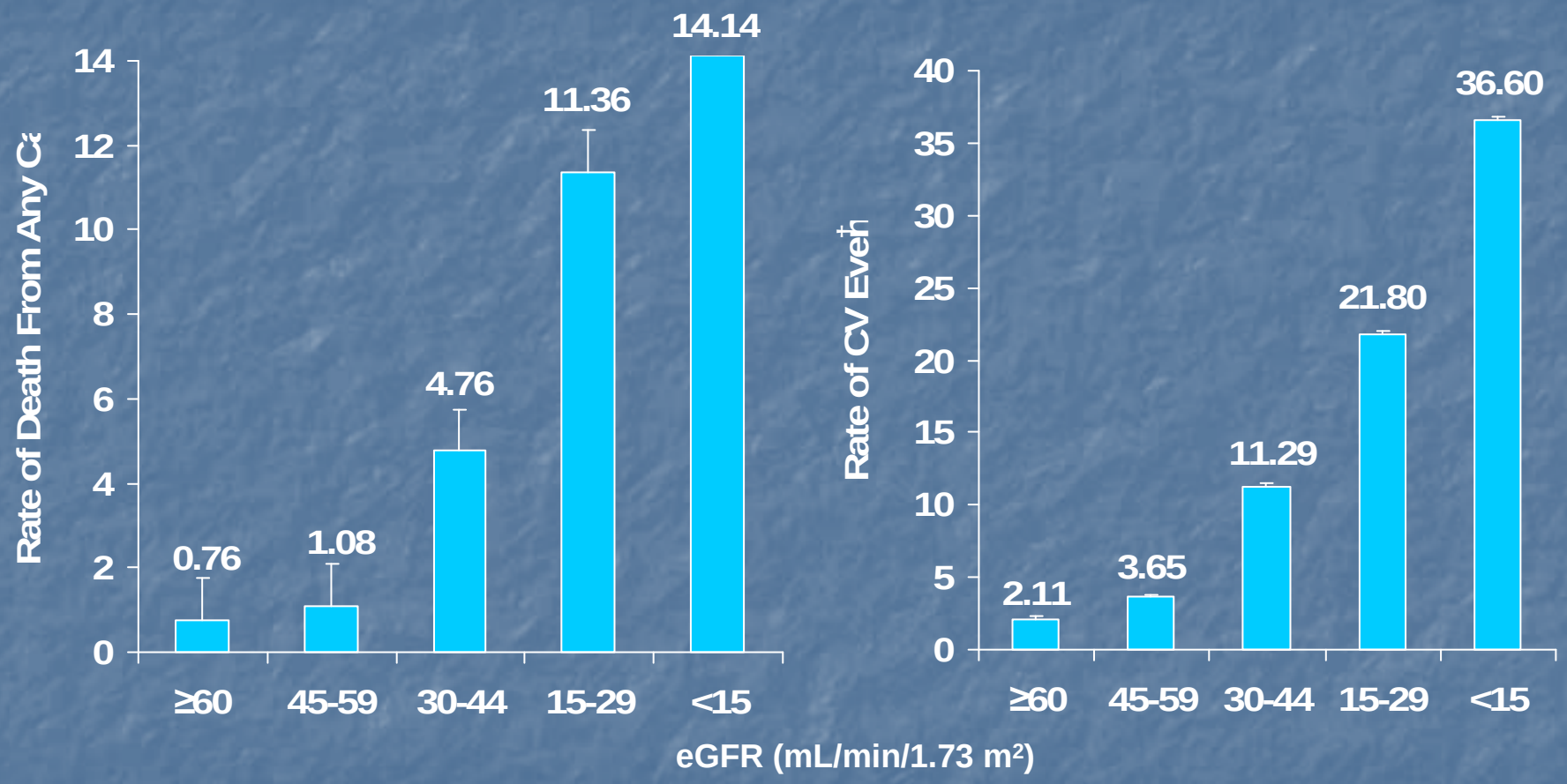
- CARDIOVASCULAR MORTALITY IS EPIDEMIC IN PATIENTS WITH CKD AND ESRD
- CKD IS PROGRESSIVE AND LEADS TO DIALYSIS DEPENDENCE
- THE ANNUAL UNADJUSTED MORTALITY IN DIALYSIS PATIENTS IS ~20%

Cardiovascular Mortality in ESRD



Parfrey, Sarnak and Levey, from USRDS and NCHS, AJKD 1998

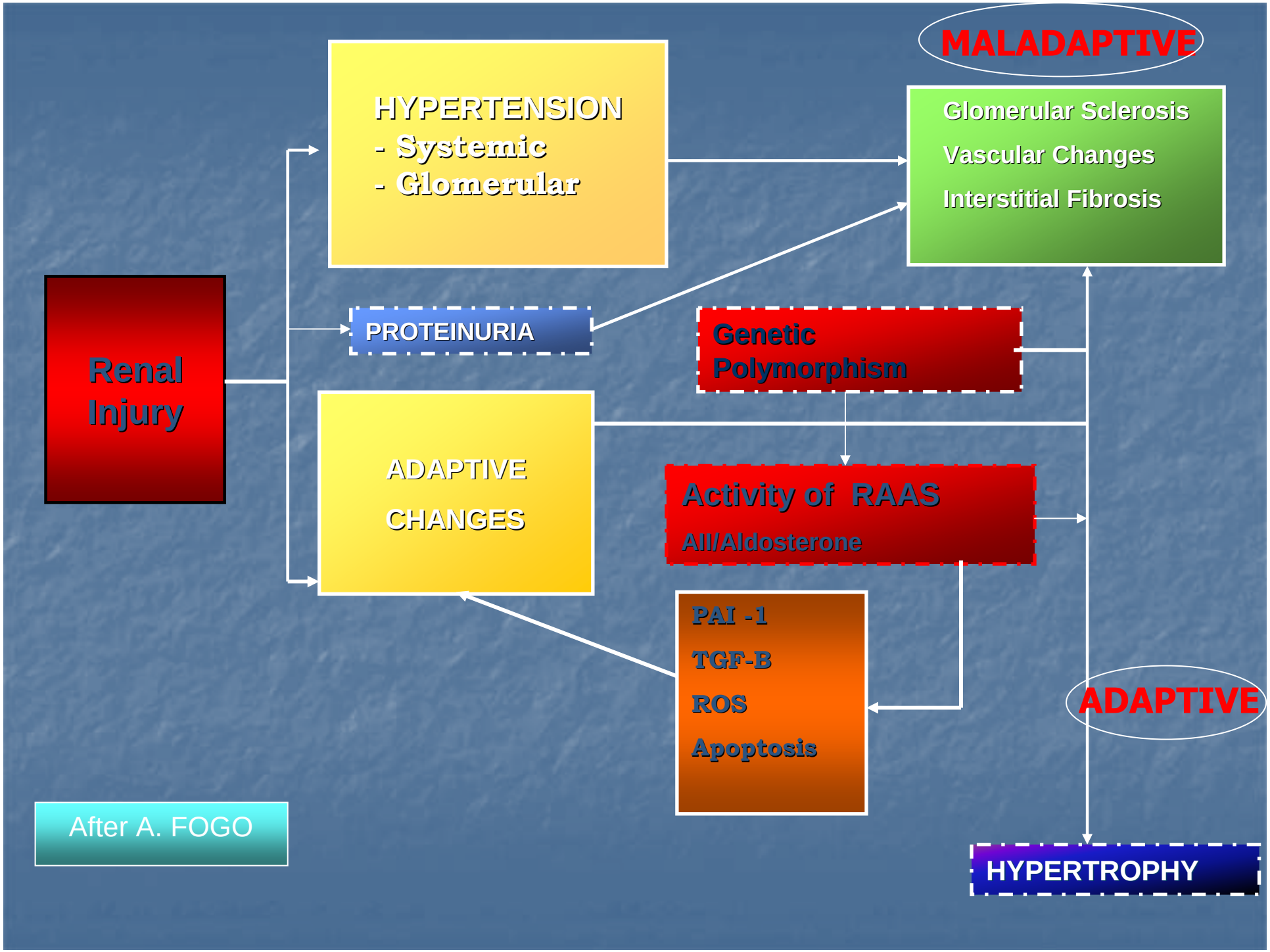
Rates of Death and Cardiovascular Events in Patients According to GFR



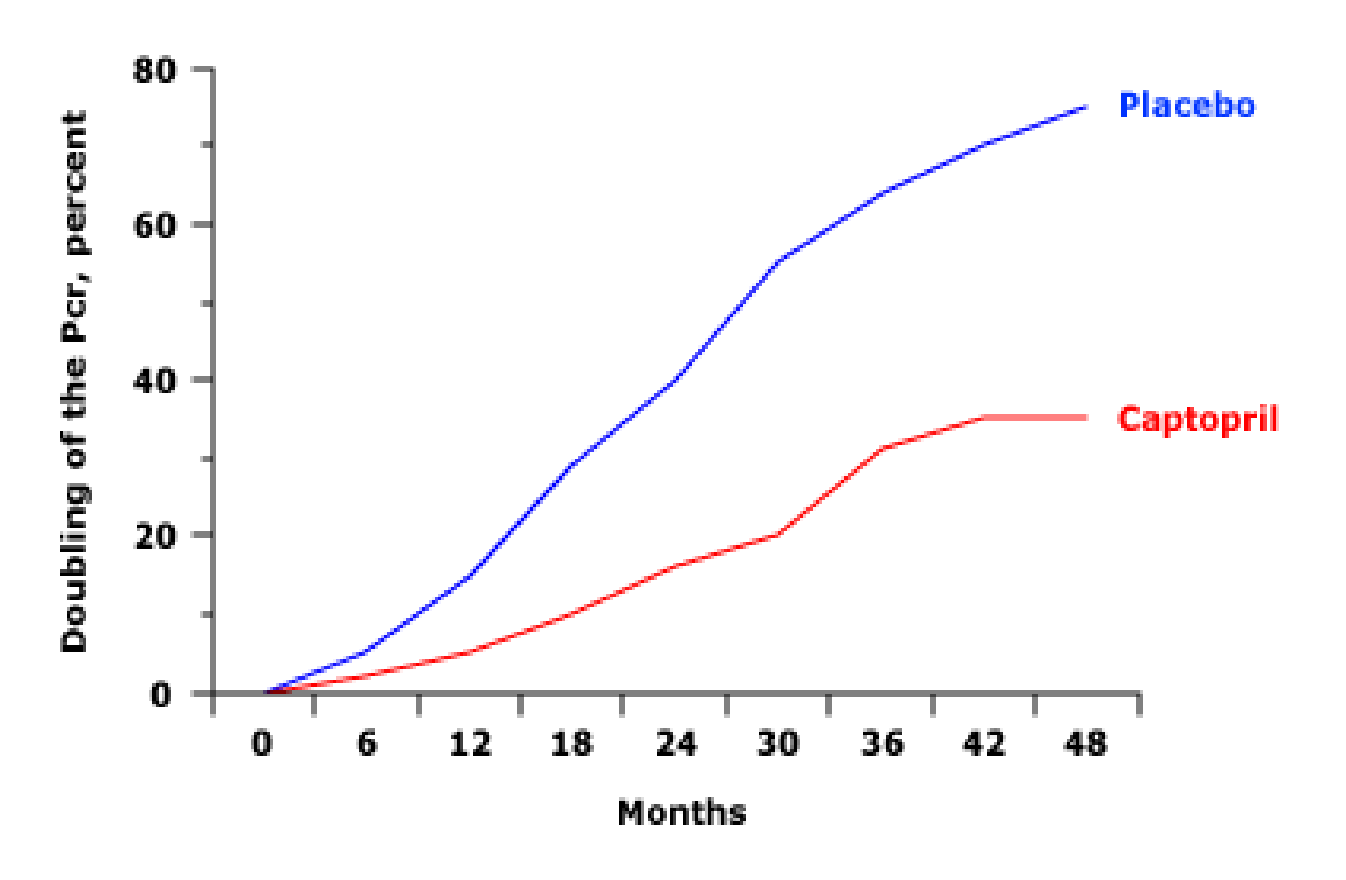
N = 1,120,295 adults.
CV = cardiovascular.
*Age-standardized rates per 100 person-years; †CV event defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease per 100 person-years.
Go et al. *N Engl J Med.* 2004;351:1296-1305.

FACTORS ASSOCIATED WITH PROGRESSION

- SYSTEMIC BLOOD PRESSURE
- INTRAGLOMERULAR PRESSURE
- PROTEINURIA
- CYTOKINES
- REACTIVE OXYGEN SPECIES

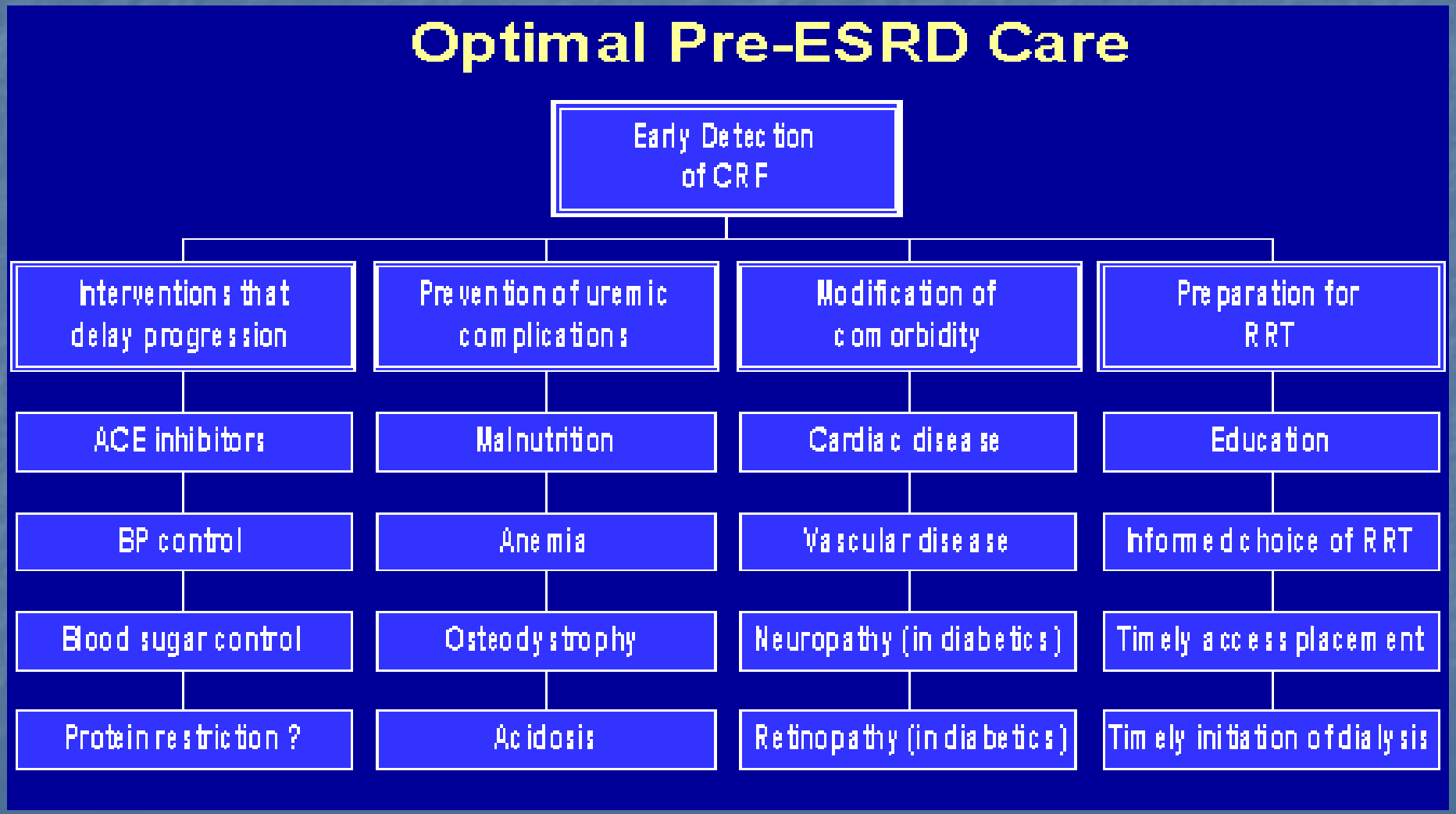

MALADAPTIVE
HYPERTENSION
- Systemic
- Glomerular
Glomerular Sclerosis
Vascular Changes
Interstitial Fibrosis
Renal Injury
PROTEINURIA
Genetic Polymorphism
ADAPTIVE CHANGES
Activity of RAAS
AII/Aldosterone
PAI -1
TGF-B
ROS
Apoptosis
ADAPTIVE
HYPERTROPHY
After A. FOGO

ACE-I IN TYPE 1 DM



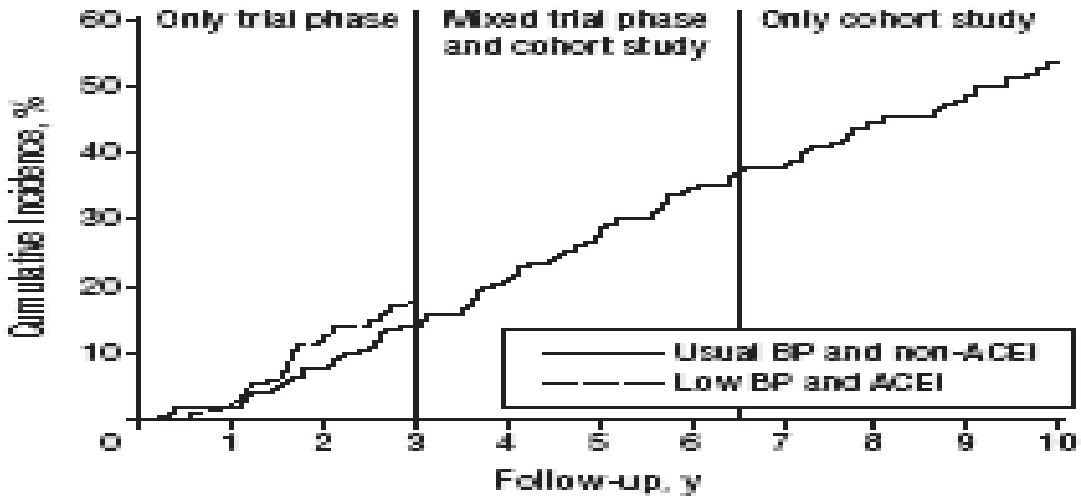
THE OTHER LEWIS ET AL, 1993

MANAGEMENTOF CKD



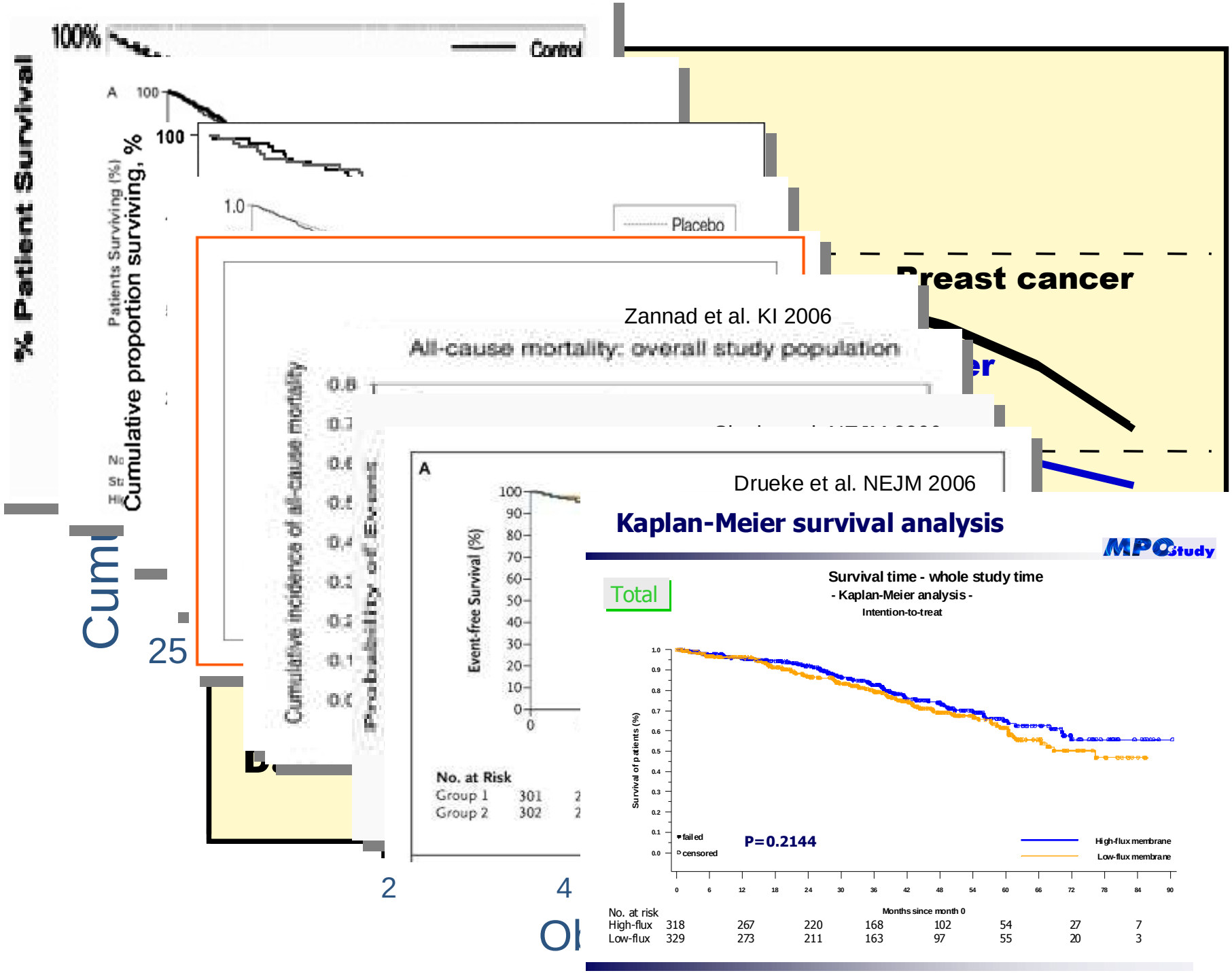
By Brian Pereira

AASK COHORT STUDY

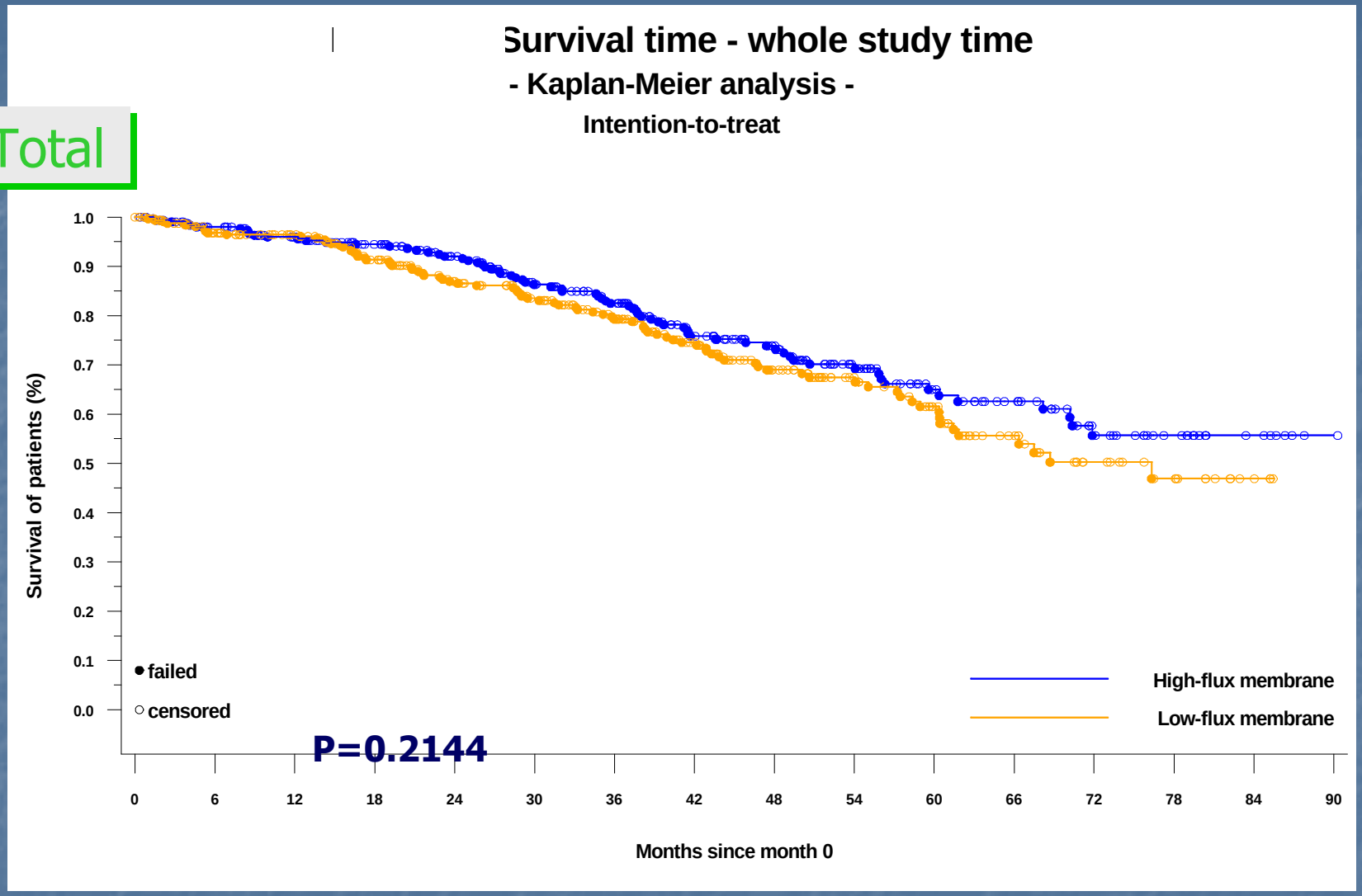


No. at risk:											
Usual BP and non-ACEI therapy:	333	324	293	273							
Low BP and ACEI therapy:	215	210	196	183	168	151	130	120	106	93	55

Figure 3. Cumulative incidence of composite outcome (doubling of the serum creatinine level from trial baseline, end-stage renal disease, or death) separately for those assigned to a low blood pressure (BP) goal and angiotensin-converting enzyme inhibitor (ACEI) therapy during the trial phase and the cohort study and for those assigned to the usual BP goal and non-ACEI therapies (β-blockers or calcium channel blockers) during the trial phase. All participants had at least 3 years of follow-up in the trial phase. The period between 3 and 6.5 years is a mixed period and corresponds to the trial phase for early enrollees and to the cohort study for late enrollees. The last 3.5 years (6.5-10 years) include cohort data only.


% Patient Survival
100%
Control
Patients Surviving (%)
Cumulative proportion surviving, %
Placebo
Breast cancer
Zannad et al. KI 2006
All-cause mortality: overall study population
Cumulative incidence of all-cause mortality
Probability of Events
Drueke et al. NEJM 2006
Event-free Survival (%)
No. at Risk
Group 1 301
Group 2 302
Kaplan-Meier survival analysis
MPO Study
Total
Survival time - whole study time
- Kaplan-Meier analysis -
Intention-to-treat
Survival of patients (%)
failed
censored
P=0.2144
High-flux membrane
Low-flux membrane
Months since month 0
No. at risk
High-flux 318 267 220 168 102 54 27 7
Low-flux 329 273 211 163 97 55 20 3

Total



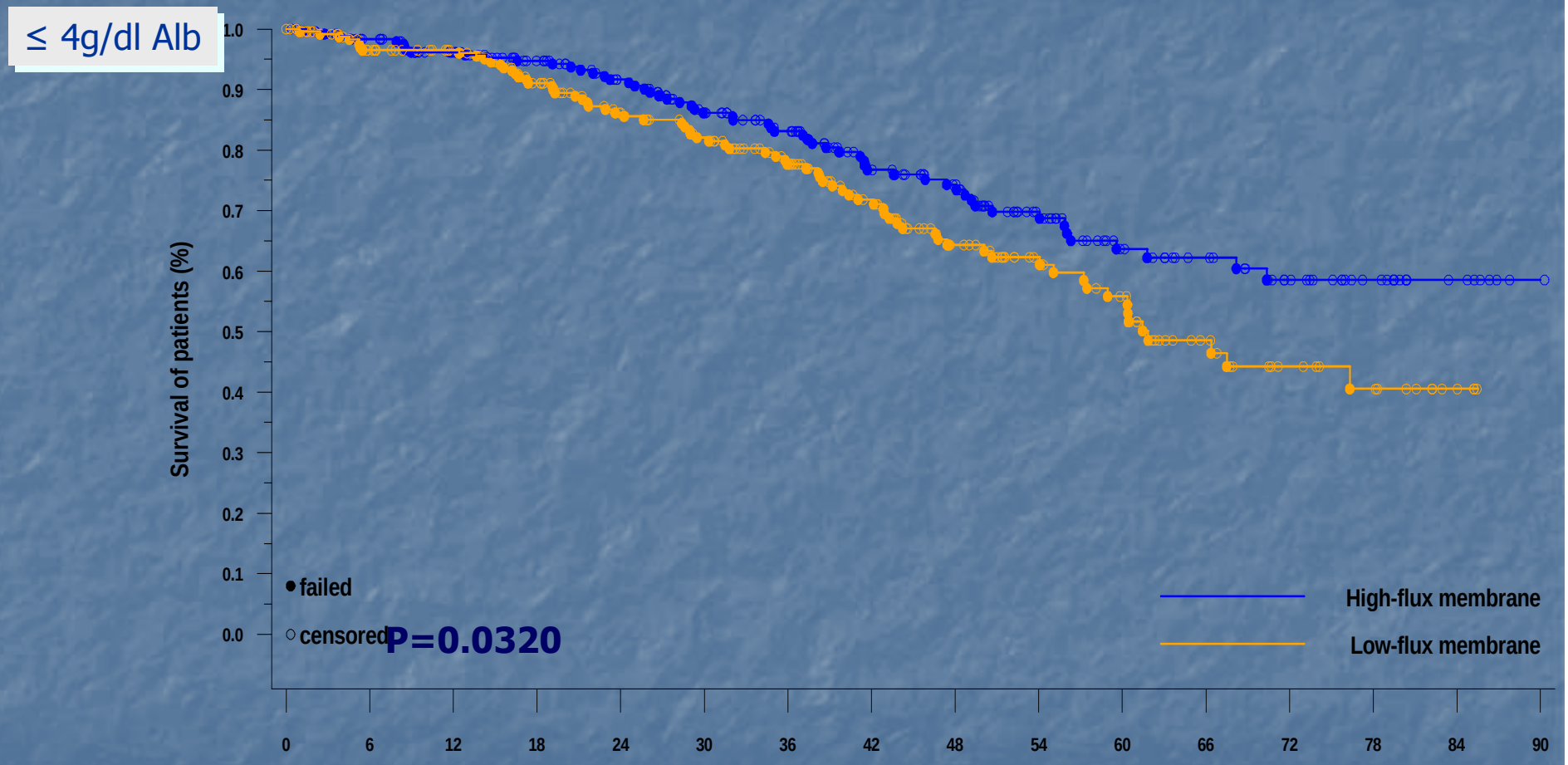
No. at risk

High-flux	318	267	220	168	102	54	27	7
Low-flux	329	273	211	163	97	55	20	3

Figure 7 : Survival time - whole study time - Albumin <= 4

- Kaplan-Meier analysis -

Intention-to-treat, n=492



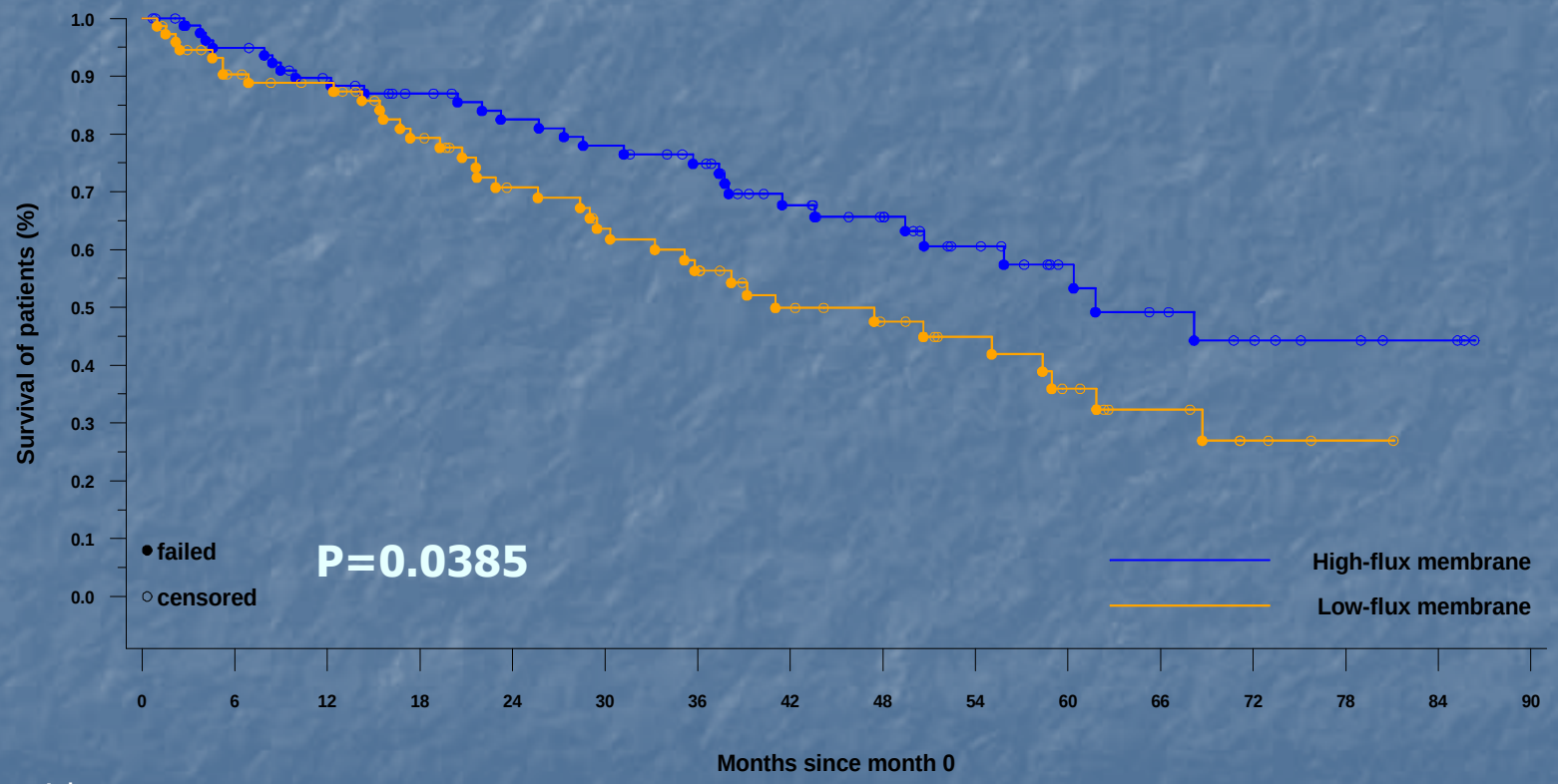
No. at risk								
High-flux	250	212	173	134	85	44	26	7
Low-flux	243	202	152	117	67	41	15	3

Total

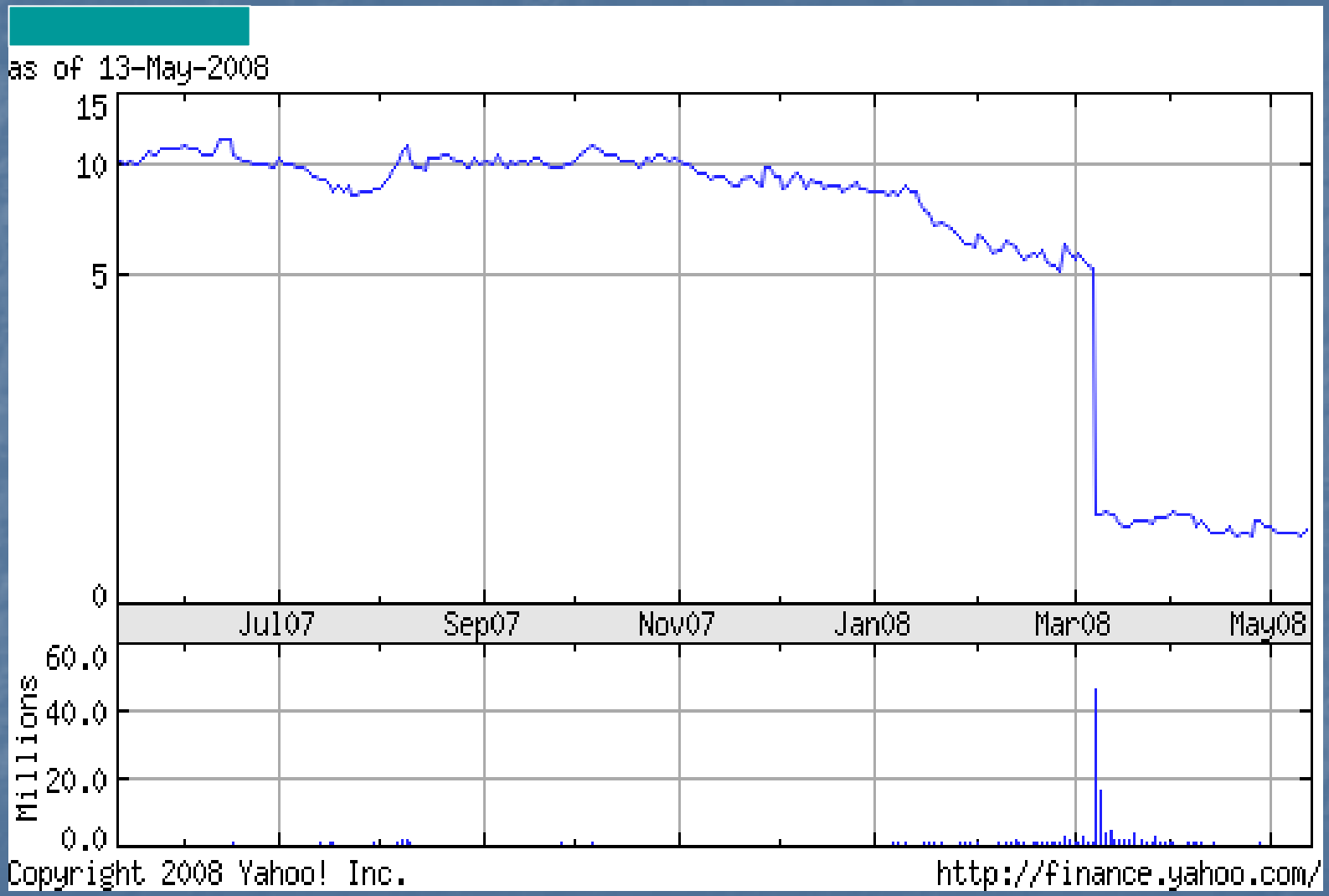
Figure 9 : Survival time - whole study time - patients with diabetes

- Kaplan-Meier analysis -

Intention-to-treat, n=157



No. at risk								
High-flux	83	67	55	46	27	14	7	3
Low-flux	74	59	40	29	19	11	3	0


as of 13-May-2008
15
10
5
0
Jul07
Sep07
Nov07
Jan08
Mar08
May08
60.0
40.0
20.0
0.0
Millions
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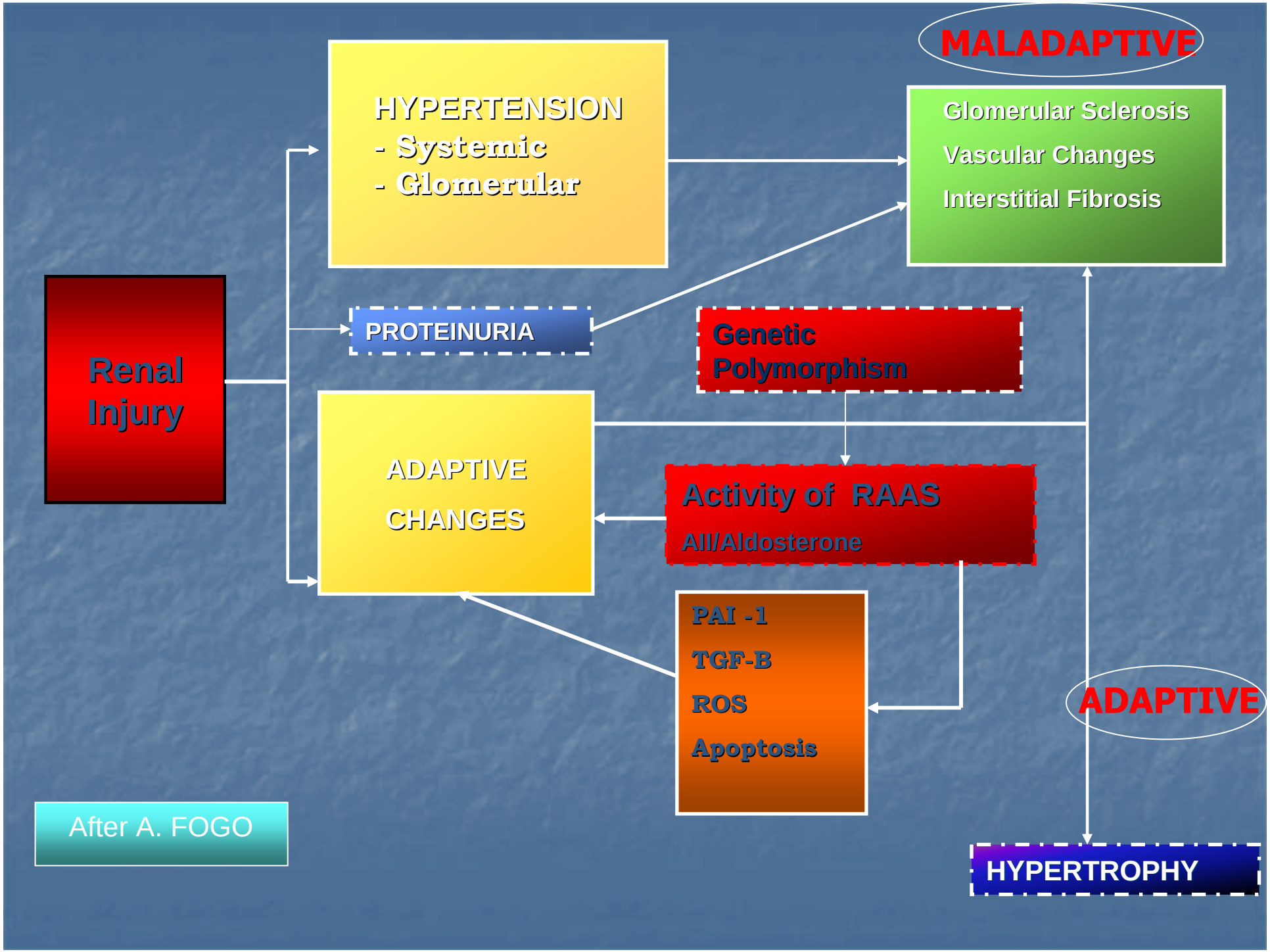
50 cents

REASONS FOR LACK OF SUCCESSFUL CLINICAL TRIALS IN CKD

- INCLUSION OF PATIENTS WITH ONLY EARLY CKD (GFR>50 mL/min)
- STUDY COMBINES PREDIALYSIS AND DIALYSIS PATIENTS
  - INSUFFICIENT PATIENTS IN SUBGROUPS
- STUDY INCLUDES ONLY DIALYSIS PATIENTS
  - DIALYSIS PATIENTS WITH ELEVATED BMI HAVE BETTER SURVIVAL
  - J-CURVE FOR BLOOD PRESSURE
  - LOW CHOLESTEROL ASSOCIATED WITH HIGHER MORTALITY
- WIDESPREAD INHIBITION OF RAAS IN CKD


MALADAPTIVE
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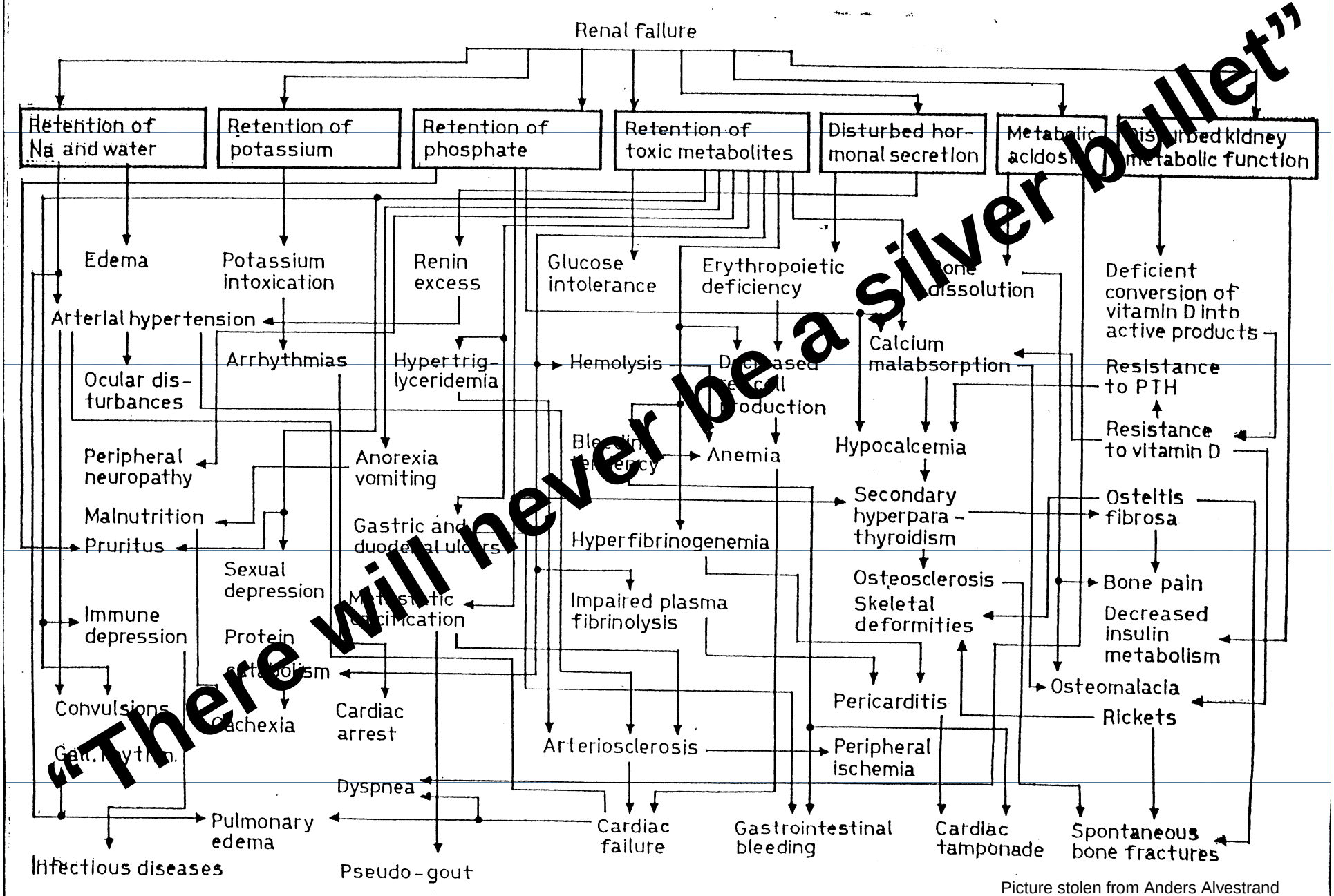
Genetic Polymorphism
ADAPTIVE CHANGES
Activity of RAAS
AII/Aldosterone
PAI -1
TGF-B
ROS
Apoptosis
ADAPTIVE
HYPERTROPHY
After A. FOGO

Simplified flow schedule of uremia and its complications



"There will never be a silver bullet"

Picture stolen from Anders Alvestrand

THE NEXUS OF TRYPTOPHAN, PROFIBROTIC CYTOKINES AND CHARCOAL ON THE PROGRESSION OF CHRONIC KIDNEY DISEASE

PROPOSED UREMIC TOXINS

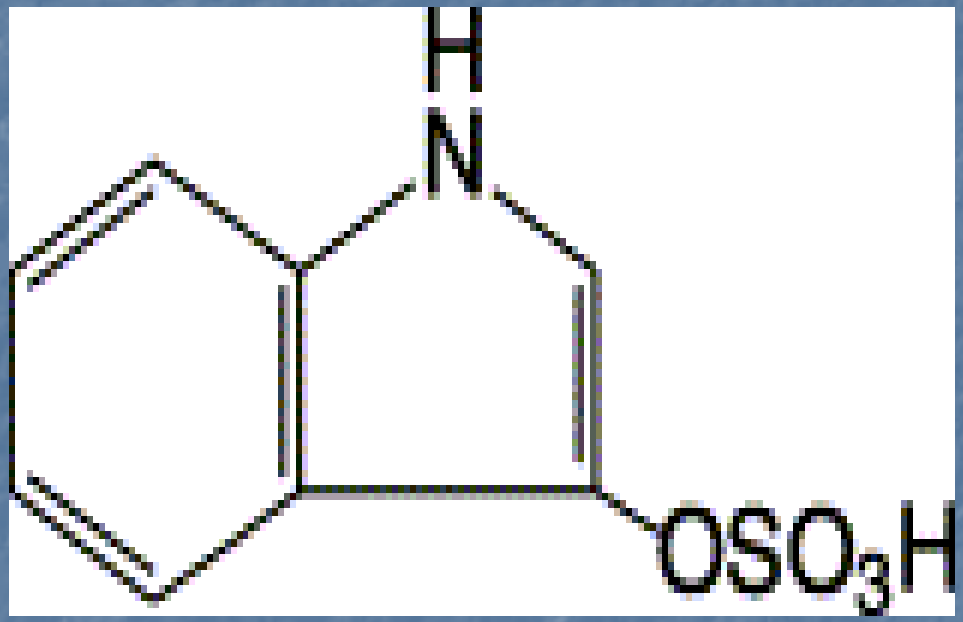
Table 1. Main known uremic retention solutes

Small water soluble solutes	Protein-bound solutes	Middle molecules
Asymmetric dimethylarginine	3-Deoxyglucosone	Adrenomedullin
Benzylalcohol	CMPF	Atrial natriuretic peptide
β-Guanidinopropionic acid	Fructoselysine	β_2-Microglobulin
β-Lipotropin	Glyoxal	β-Endorphin
Creatinine	Hippuric acid	Cholecystokinin
Cytidine	Homocysteine	Clara cell protein
Guanidine	Hydroquinone	Complement factor D
Guanidinoacetic acid	Indole-3-acetic acid	Cystatin C
Guanidinosuccinic acid	Indoxyl sulfate	Degranulation inhibiting protein I
Hypoxanthine	Kinurenine	Delta-sleep-inducing peptide
Malondialdehyde	Kynurenic acid	Endothelin
Methylguanidine	Methylglyoxal	Hyaluronic acid
Myoinositol	N-carboxymethyllysine	Interleukin 1β
Orotic acid	P-cresol	Interleukin 6
Orotidine	Pentosidine	Kappa-Ig light chain
Oxalate	Phenol	Lambda-Ig light chain
Pseudouridine	P-OHhippuric acid	Leptin
Symmetric dimethylarginine	Quinolinic acid	Methionine-enkepahlin
Urea	Spermidine	Neuropeptide Y
Uric acid	Spermine	Parathyroid hormone
Xanthine		Retinol binding protein
		Tumor necrosis factor alpha

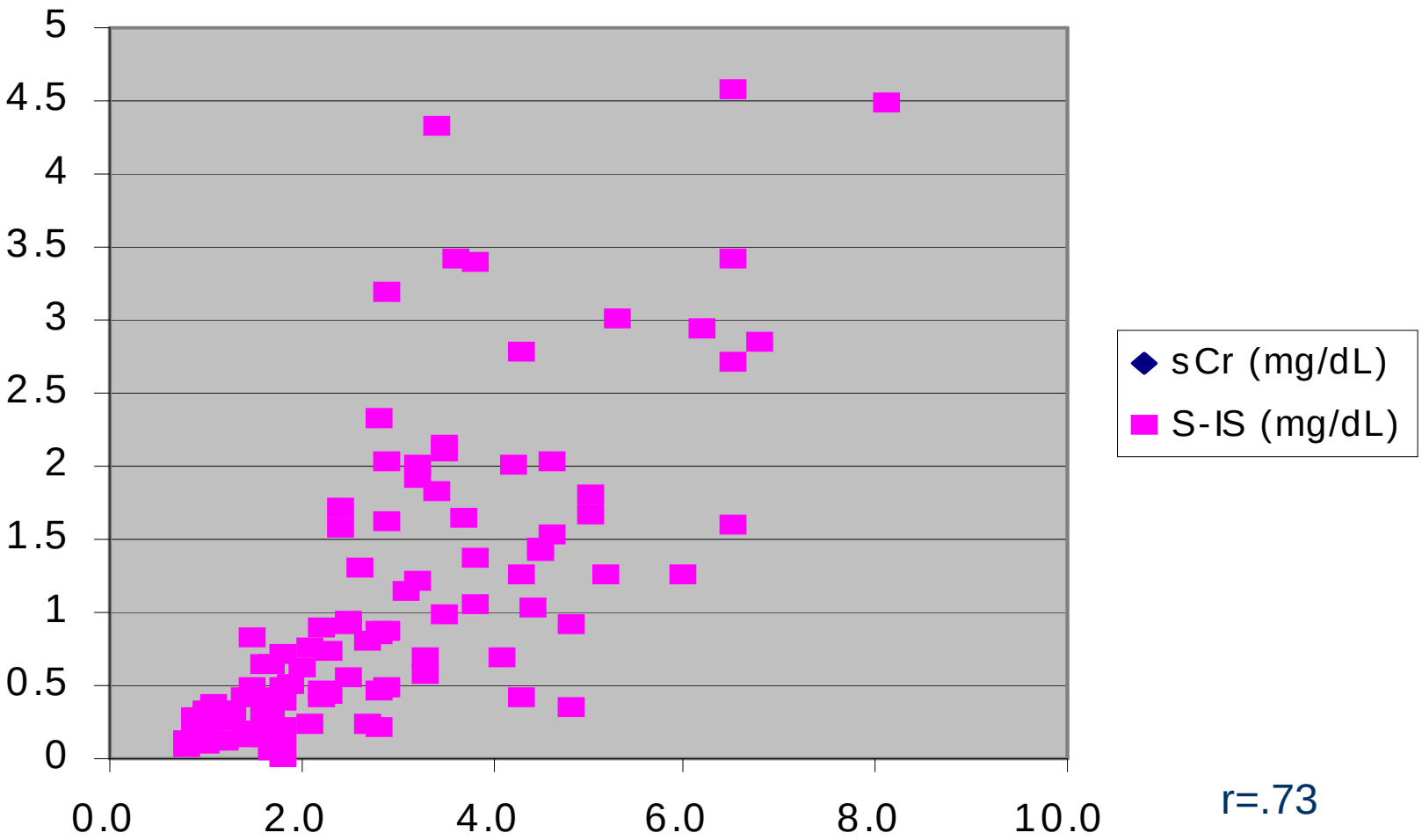
CMPF is carboxy-methyl-propyl-furanpropionic acid.

INDOXYL SULFATE

INDOXYL SULFATE

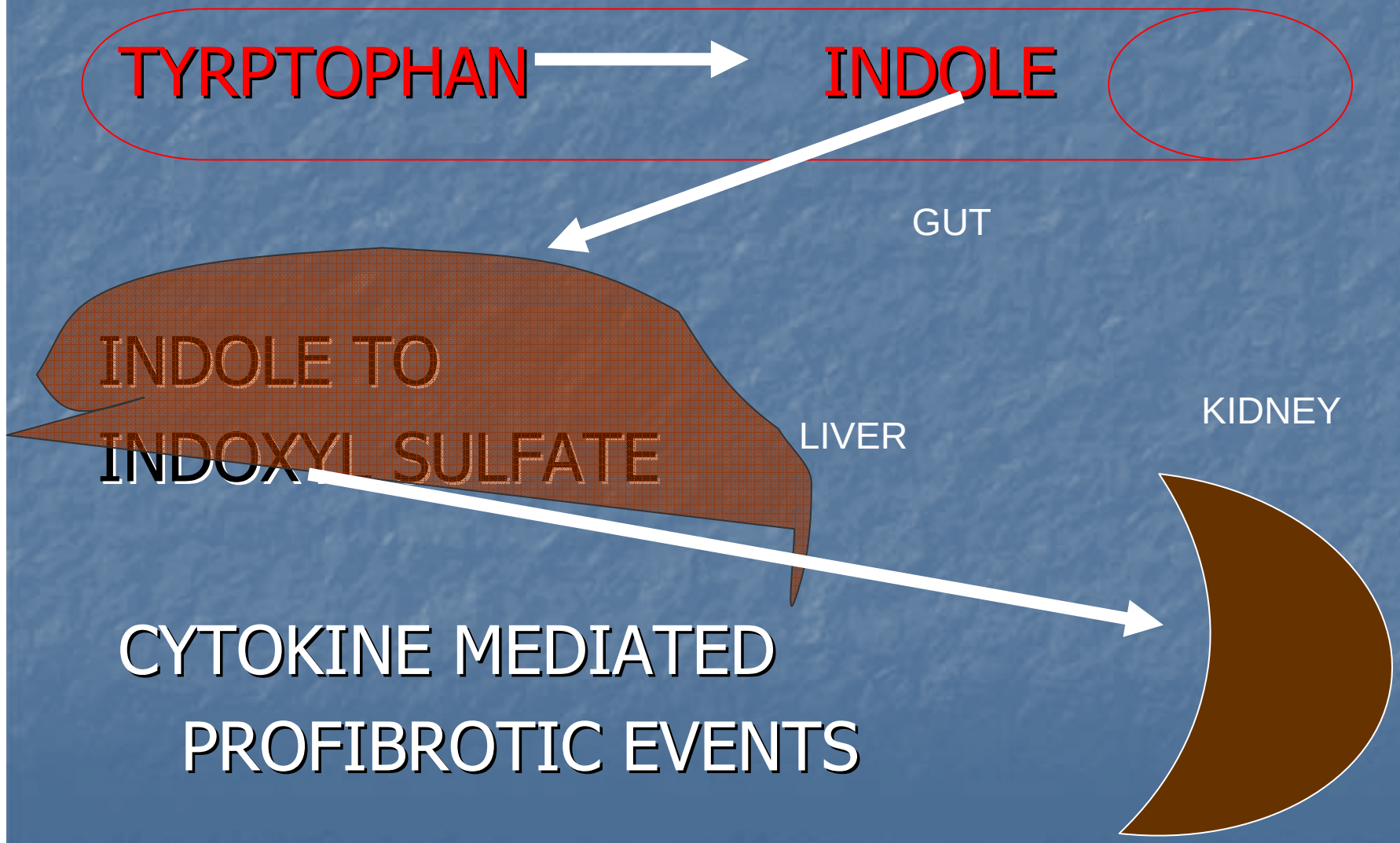


SERUM CREATININE AND INDOXYL SULFATE LEVELS CHRONIC RENAL FAILURE IN THE US

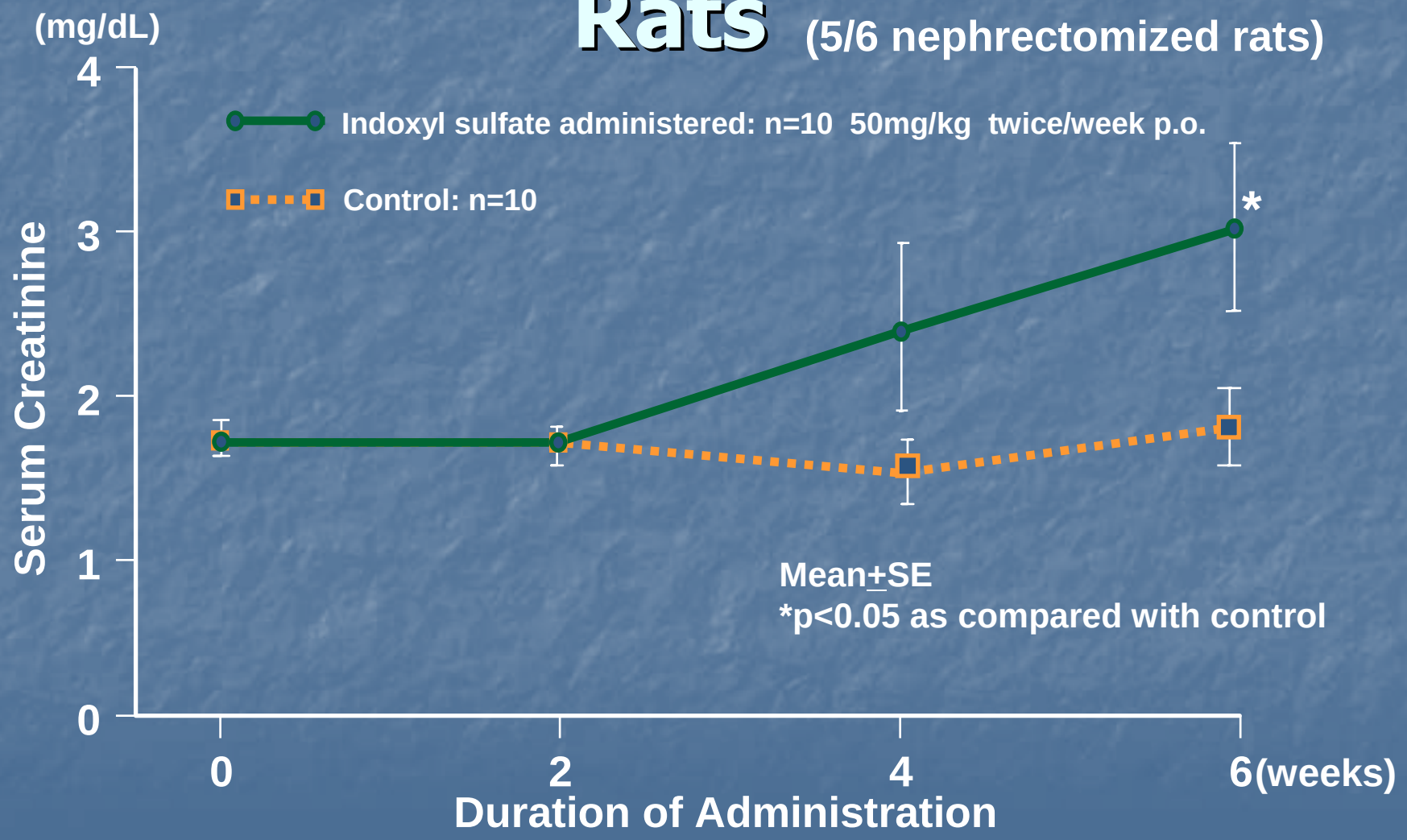


r=.73

Indoxyl Sulfate and Progression



Effect of Indoxyl Sulfate on Serum Creatinine in Uremic Rats (5/6 nephrectomized rats)



Niwa, T. et al: J Lab Clin Med, 124(1), p96,1994

INDOXYL SULFATE AND CKD

- TGF Beta-1
- TISSUE INHIBITOR OF METALLOPROTEINASE (TIMP-1)
- PAI-1
- ABNORMALITIES IN TRYPTOPHAN METABOLISM
- CARDIOVASCULAR EFFECTS?

AST-120

- AST-120 is an orally administered adsorbent that was approved in Japan in 1991 for prolonging the time to initiation of hemodialysis and improving uremic symptoms in patients with chronic kidney disease (CKD).

AST-120

- AST-120 consists of black spherical particles ca. 0.2 to 0.4 mm in diameter. Composed mainly of carbon (approximately 96%), AST-120 exhibits similar or superior adsorption-ability to activated charcoal for certain acidic and basic organic compounds that are known to be increased in renal failure patients. The clinical utility of AST-120, therefore, is believed to reside in its ability to adsorb uremic toxins in the gastrointestinal (GI) tract, thereby reducing systemic absorption of uremic toxins and related contributions to the CKD disease process

Manufacturing Process of Spherical Activated Carbon & AST-120

Petroleum Hydrocarbon

↓

Molecular Modification

↓

Spherical Shape Formation

↓

Infusibilization

↓

Carbonization & Activation

Spherical Activated Carbon

F-AST (Starting Material)

↓

Oxidation

↓

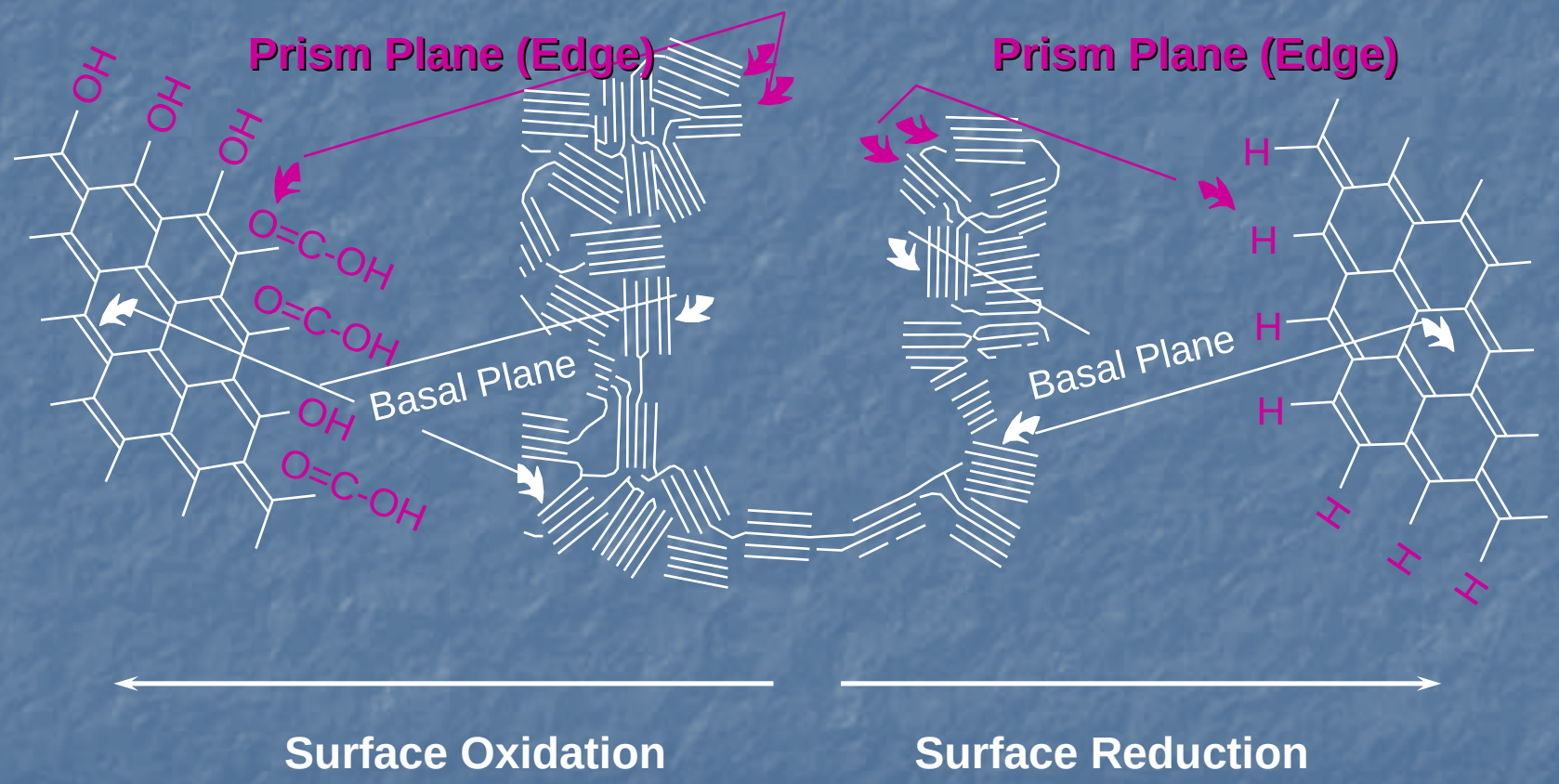
Reduction

Surface Treatment

↓

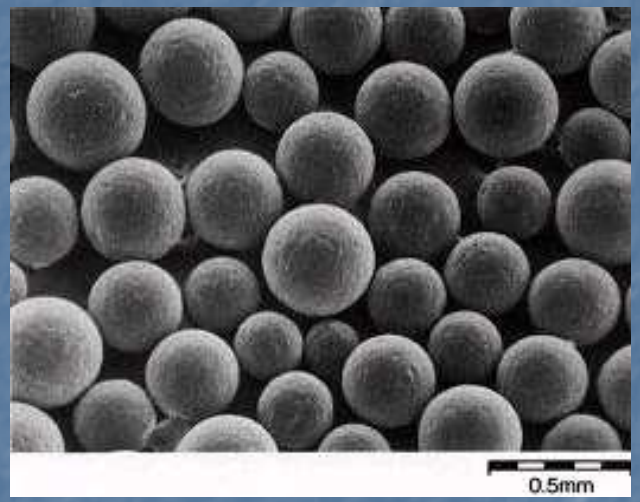
AST-120

Model of Functional Groups on the Adsorption Surface

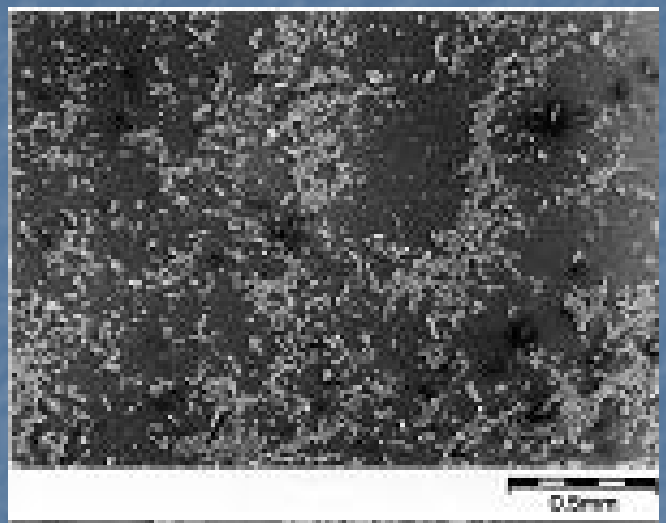


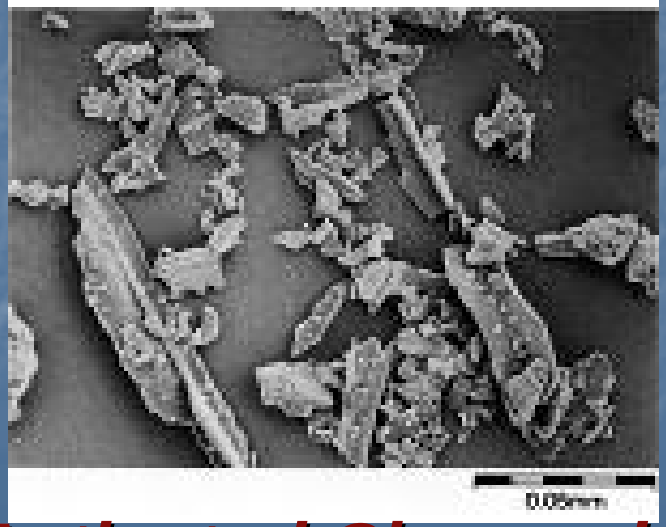
** Hagiwara S, Poisoning Res. 2: 11-18, 1989*

Difference between AST-120 and Activated Charcoal



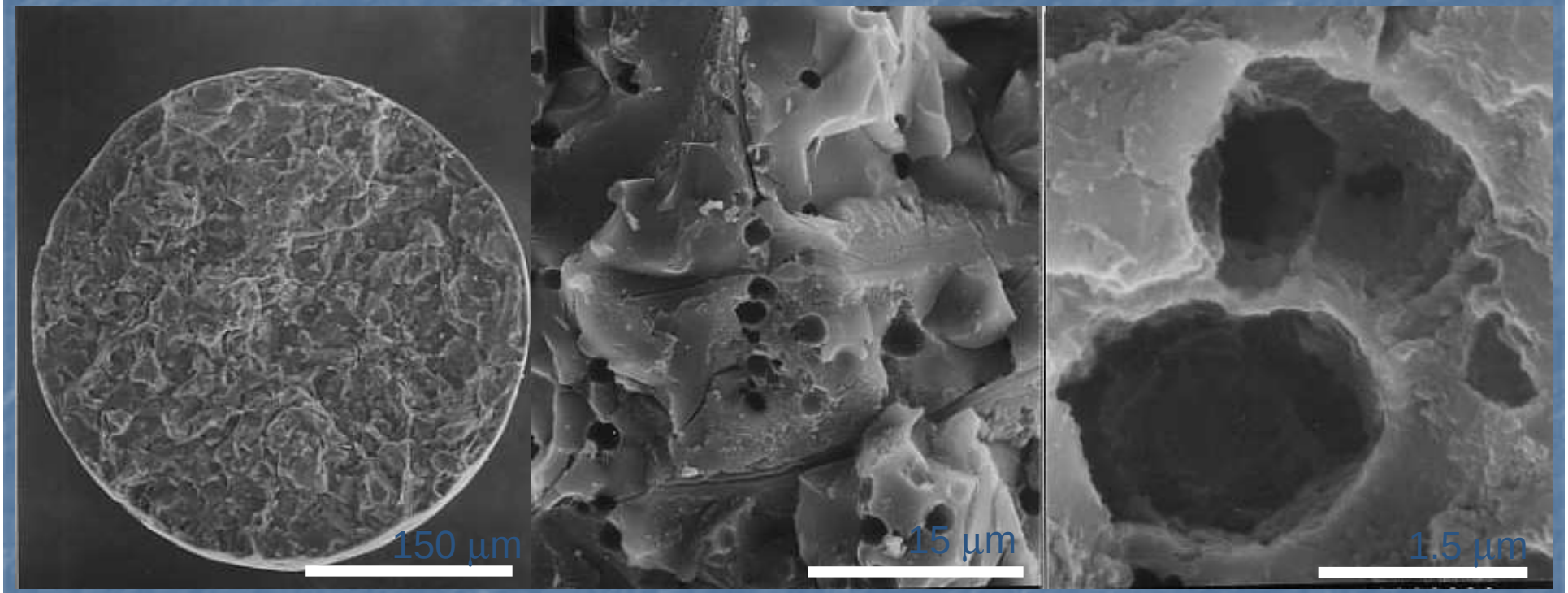
AST-120





Activated Charcoal

Cross Section of AST-120



X 180 ***X 1,800*** ***X 18,000***

Difference between AST-120 and Activated Charcoal

	AST-120	Activated Charcoal
Shape & Size	Spherical, 200-400 μm	Irregular, 10-100 μm
Fluidity	High	Low
Molec. Wt. Selectivity	Yes	No
Animal with CKD	Effective	Not effective
Long Term Administration	Possible	Difficult *,**,***)

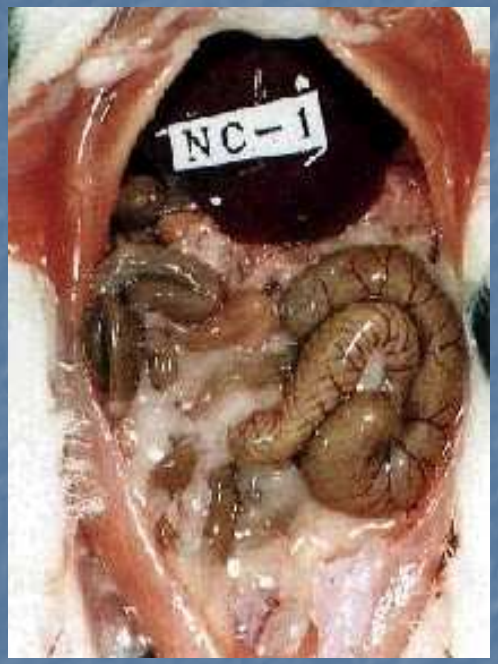
* Giordano C, et al., Sorbents and Their Clinical Application, Academic Press NY, 1980
** Gardner DL, et al., Trans. Amer. Soc. Artif. Int. Org.,17: 239-245, 1971
*** Yatzidis H, et al., Kidney Int. 10: S215-S217, 1976

AST-120 vs Activated Charcoal
- Physical Appearance

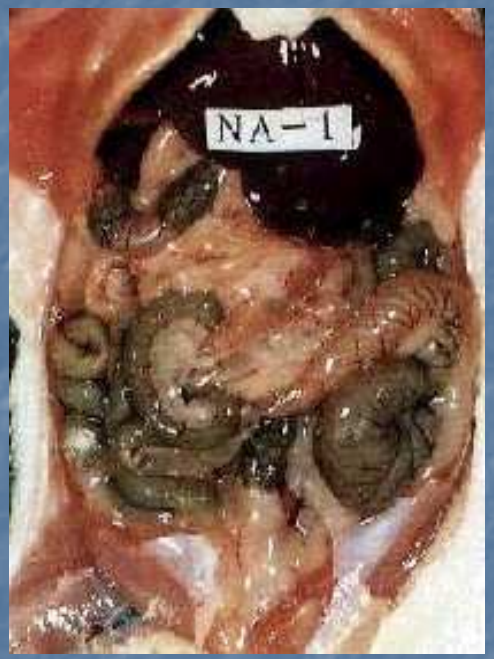
AST-120 vs Activated Charcoal – Bulk Density

AST-120 (6 g) *Activated Charcoal (6 g)*

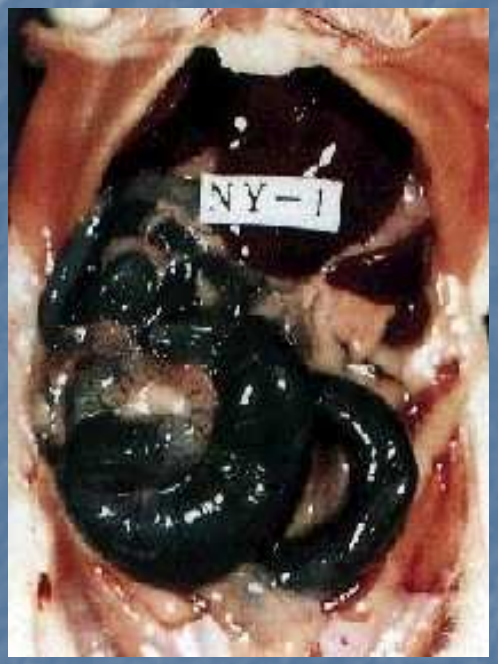
External Observation of GI-tract



Conventional diet

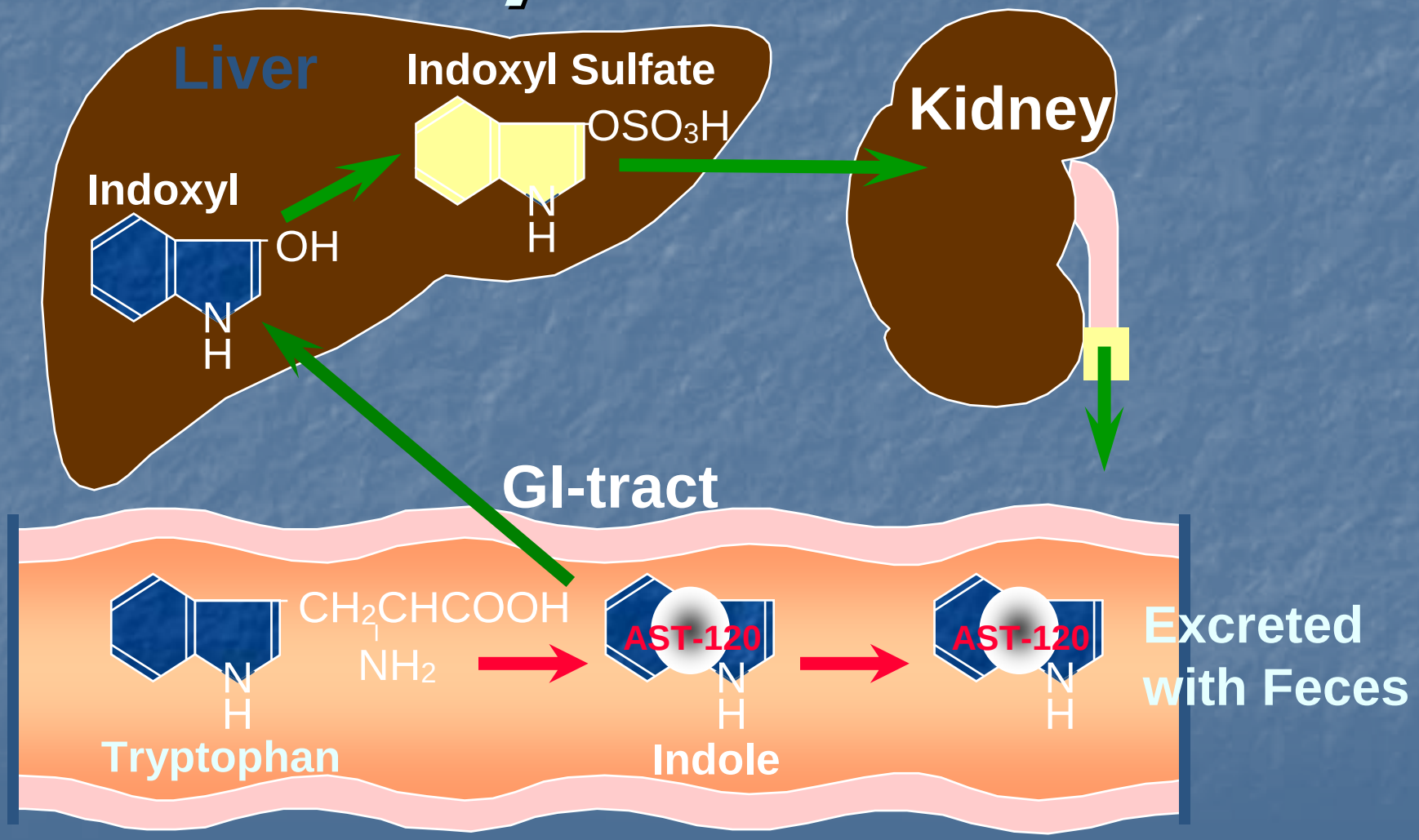


AST-120 5 % diet



Medicinal charcoal 5 % diet

Excretion Process of Indole by AST-120



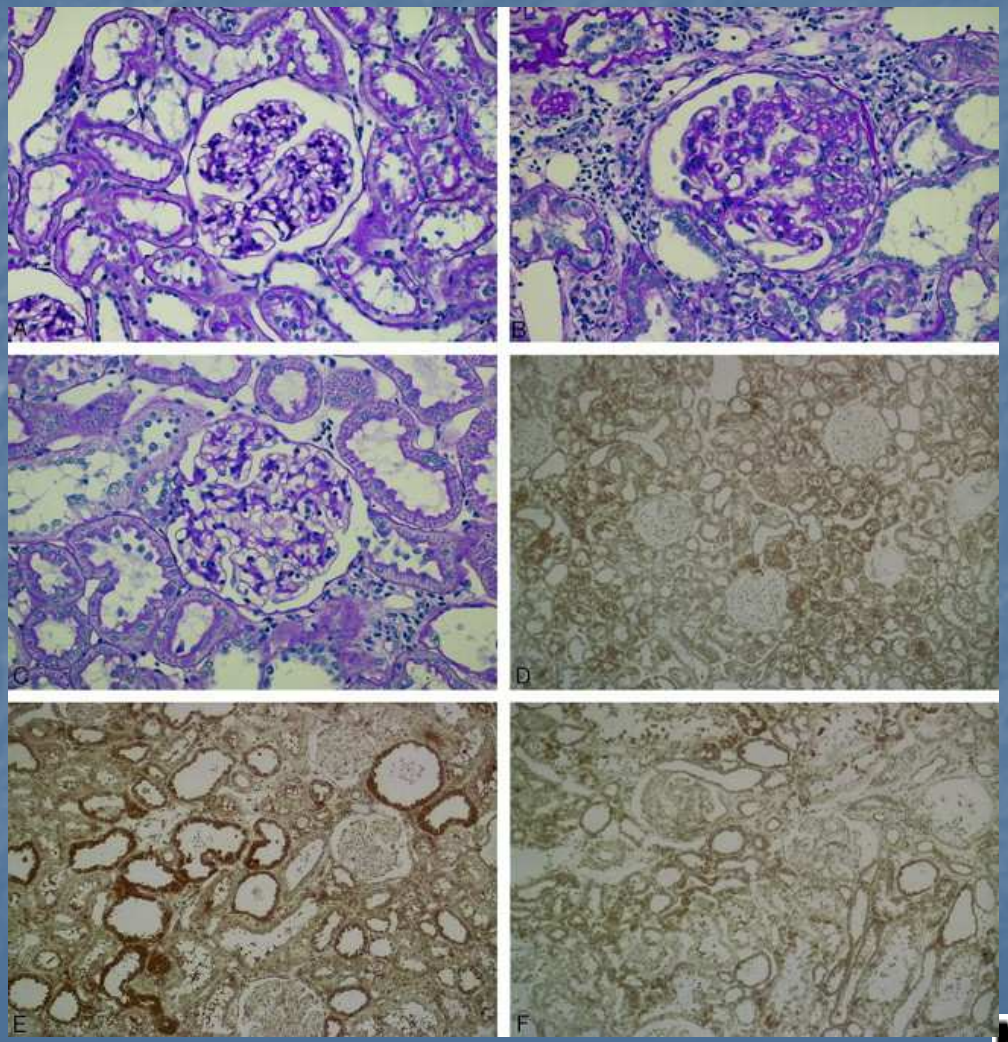
Niwa,T.et al Kidney Int 52 Suppl.62 :S23, 1997

AST-120 Mechanisms of Action in Slowing Progression of CKD

Proposed Action Mechanism of AST-120

Adsorption of Uremic Toxins in the GI-tract

THE EFFECT OF AST-120 ON GLOMERULOSCLEROSIS AND INDOXYL SULFATE IMMUNOSTAINING IN 5/6 NEPHRECTOMY CKD MODEL

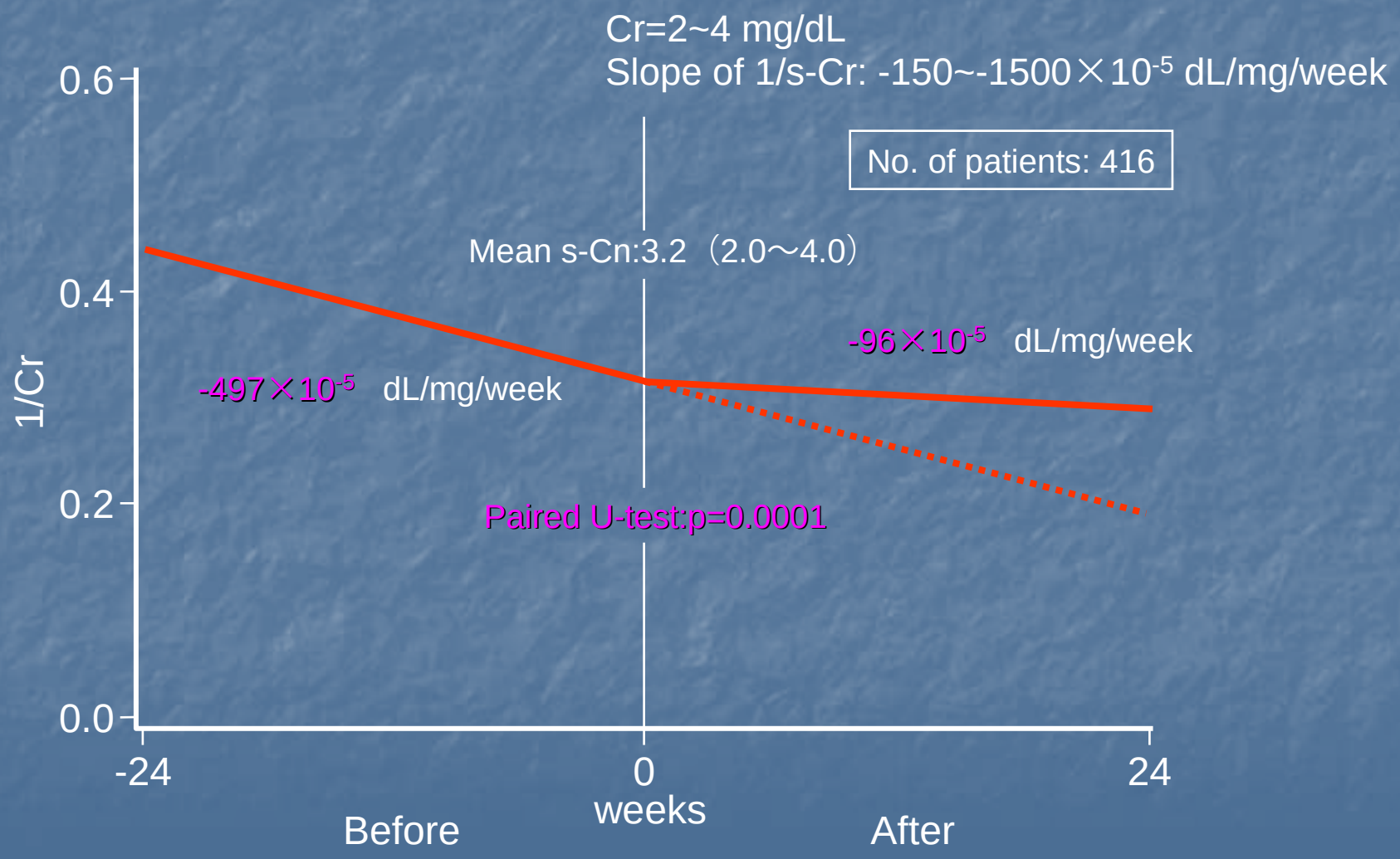


Miyazaki, T. et al. Nephrol. Dial. Transplant. 2000 15:1773-1781; doi:10.1093/ndt/15.11.1773

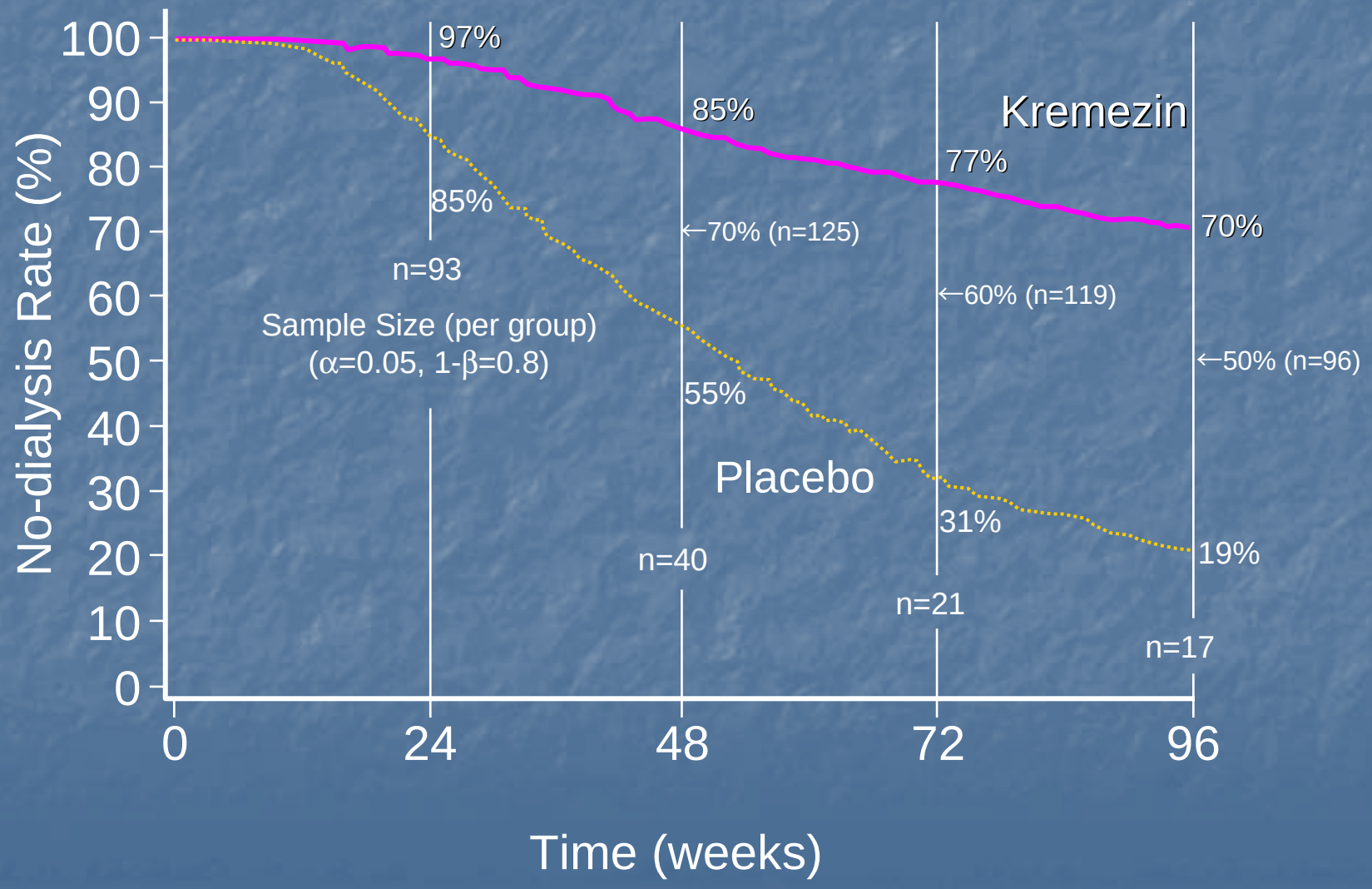
Nephrology Dialysis Transplantation

1/s-Cr slope Before and After the Initiation of AST-120 Administration

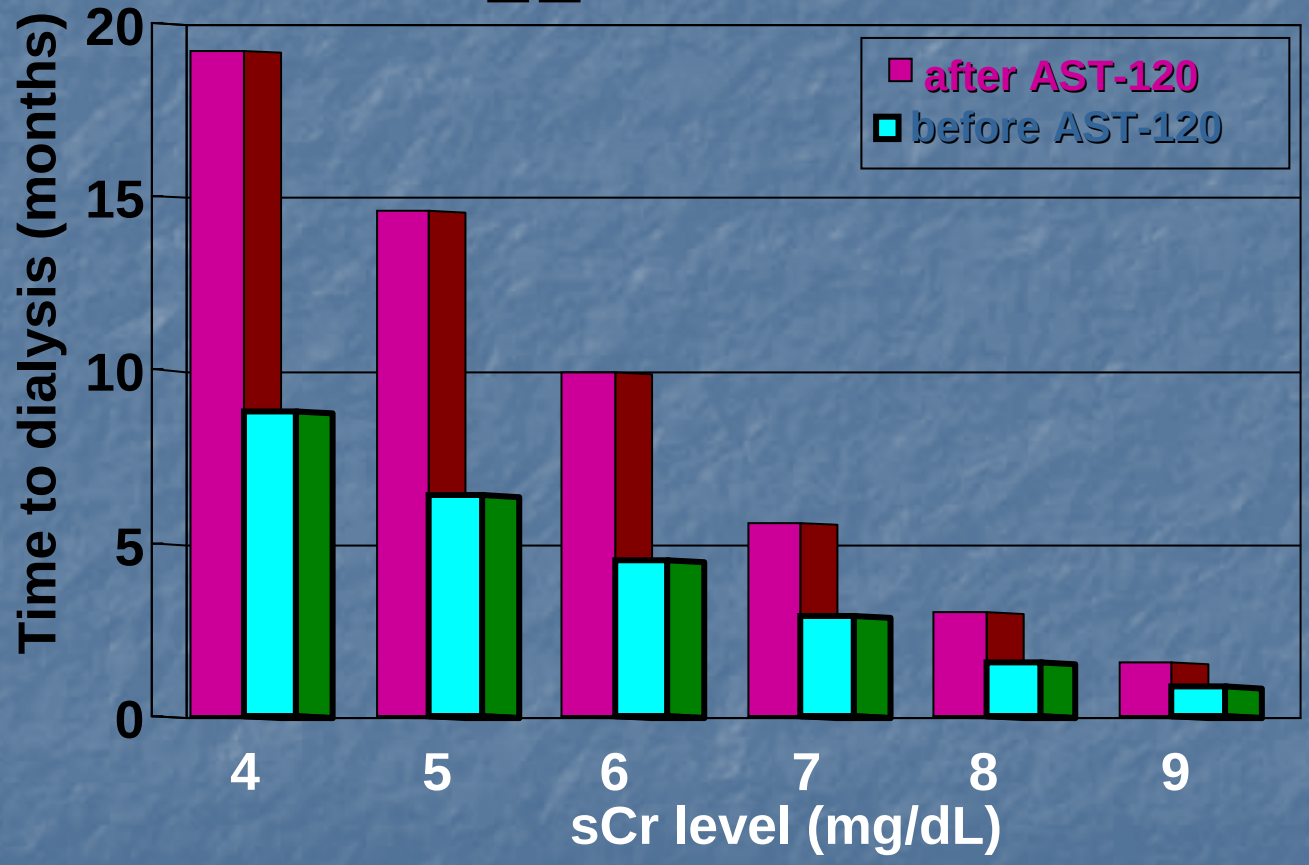
(from Phase Ⅳ data)



Estimated No-dialysis Rate & Sample Size
(from Phase Ⅳ data)



Estimated Time to Dialysis Classified by sCr Level - Phase II -



Assumption: sCr level to initiate the dialysis 10 mg/dL

Koshikawa S. at.el. Kidney and Dialysis 23 :373-381, 1987

AST-120 AND CHANGES IN ARTERIAL PULSE WAVE VELOCITY AND CAROTID ARTERY INTIMA-MEDIA THICKNESS

	AST-120	No AST-120	Healthy controls
PWV, cm/s			
Before	1,980 ± 330*	1,940 ± 360*	1,280 ± 240
12 months	1,840 ± 280**	2,020 ± 380	
24 months	1,780 ± 260**	2,140 ± 410**	
IMT, mm			
Before	0.90 ± 0.22*	0.88 ± 0.20*	0.64 ± 0.14
12 months	0.84 ± 0.20	0.90 ± 0.24	
24 months	0.78 ± 0.18**	0.93 ± 0.26	

* Versus healthy controls, $p < 0.01$. ** Versus before, $p < 0.05$.

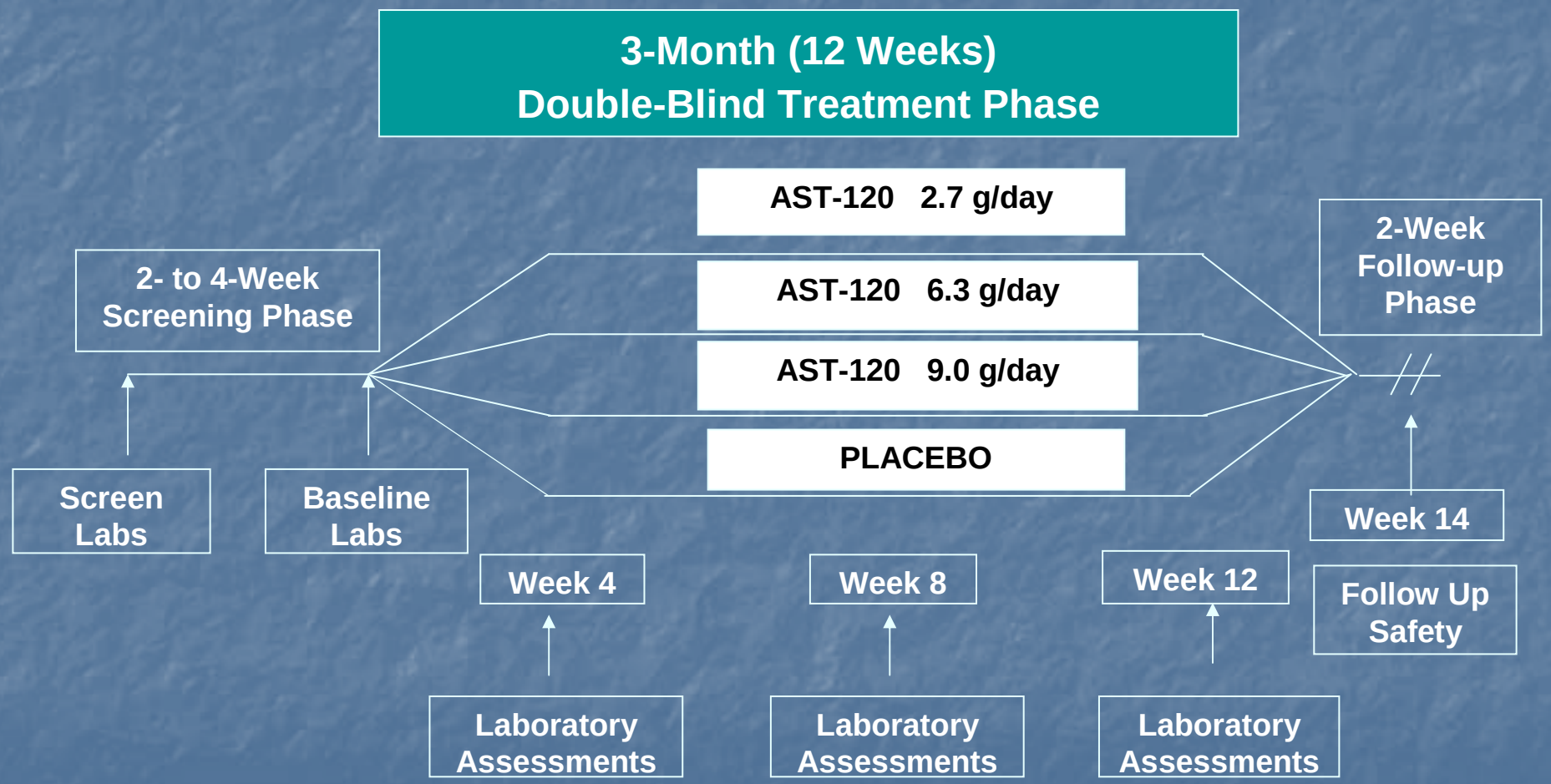
FDA REQUIREMENTS

- INDOXYL SULFATE LEVELS ARE ELEVATED IN THE US POPULATION WITH CHRONIC KIDNEY DISEASE

- AST-120 LOWERS INDOXYL SULFATE

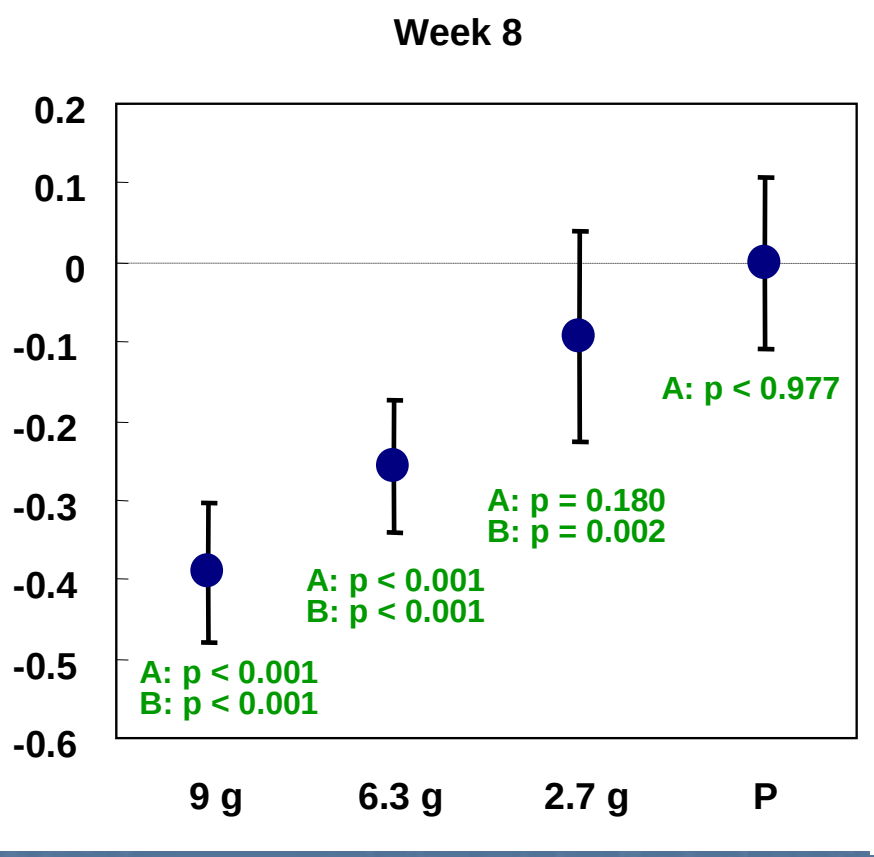
- THE URINARY APPEARANCE OF CREATININE (U X V) IS NOT CHANGED BY BINDING OF CREATININE BY AST-120 IN THE GUT

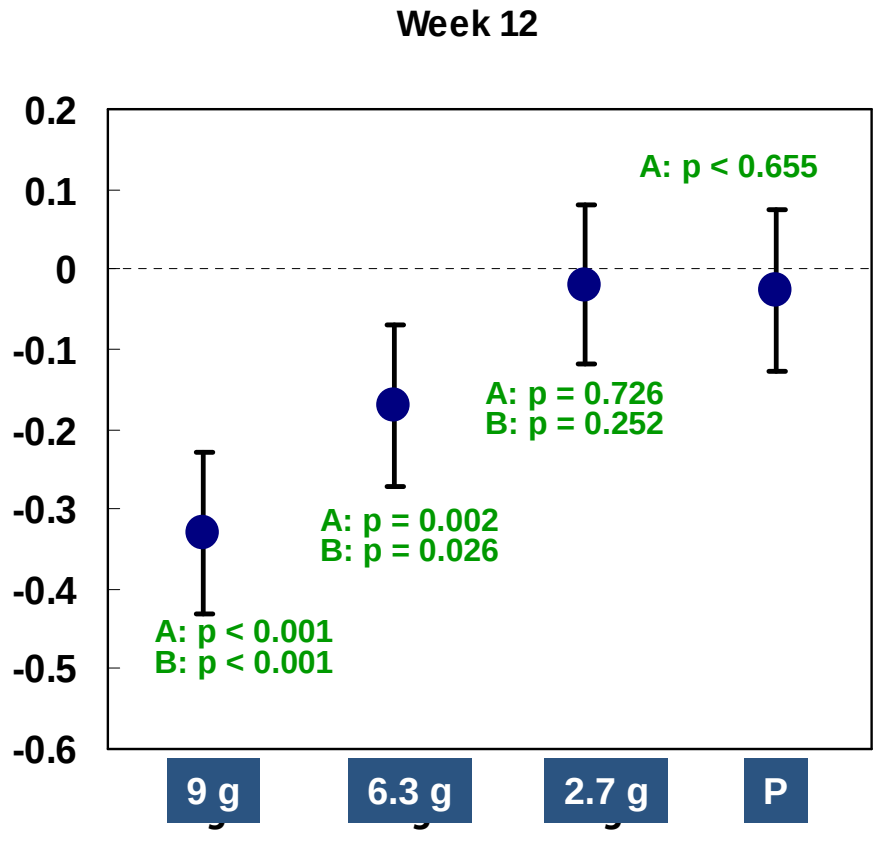
Study Schematic



MEAN CHANGE IN S-IS FROM BASELINE TO WEEK 8 AND WEEK 12

(Mean ± 95% Confidence Interval)





A: Paired t-Test within Treatment Group
B: ANCOVA Model (AST-120 vs Placebo)

URINARY CREATININE EXCRETION STUDY (KRM-102) -RESULTS-

	AST-120 9.0 g/day	Placebo	Geometric Mean Ratio (90% CI)
Urinary Creatinine Excretion (mg/day)	1,264.7	1,286.1	0.98 (0.91 – 1.07)
Creatinine Clearance (mL/min)	46.1	45.4	1.02 (0.92 – 1.12)
Serum Creatinine (mg/dL)	1.73	1.79	0.97 (0.91 – 1.02)

Geometric mean values at end of each 7-day treatment period

CHANGE IN MALAISE FROM BASELINE TO WEEK 12

Change	AST-120			Placebo
	9.0 g	6.3 g	2.7 g	
Improved	16(42%)	11(28%)	11(28%)	3(8%)
Unchanged	17(45%)	24(62%)	21(54%)	25(66%)
Aggravated	5(13%)	4(10%)	7(18%)	10(26%)
χ^2-test (vs Placebo)	p=0.002	p=0.028	p=0.066	--

THE EPPIC STUDY: Evaluating Prevention of Progression In CKD

ENROLLMENT GOAL IN TWO STUDIES	1600
SCREENED	572
RANDOMIZED	232 (40.5%)

- PRIMARY ENDPOINT: DOUBLING OF CREATININE+DIALYSIS+TRANSPLANT
- 80% POWER TO DETECT ~30% REDUCTION IN RISK: 291 TOTAL EVENTS REQUIRED
- 18 MONTH ENROLLMENT AND 24 MONTH MINIMAL TREATMENT TIME

PREBIOTIC AND PROBIOTIC AGENTS IN CKD

- PREBIOTIC AGENTS: NONDIGESTIBLE FOOD INGREDIENTS THAT STIMULATE COLONIC BACTERIAL GROWTH OR ACTIVITY

- PROBIOTIC AGENTS: VIABLE ORGANISMS WHICH COLONIZE THE GASTROINTESTINAL TRACT OR PROVIDE ENZYMES WHICH PRODUCE BENEFICIAL EFFECTS (e.g., Bifidobacterium longum)

PROBIOTIC AGENTS IN CKD

- B. longum: 27 CKD Patients for 6 Months
  - CKD IV (> 4 mg/dl)/P_i > 4 mg/dl
  - DELAYED PROGRESSION
    - Nippon Jinzo Gakkai Shi, 2003; 45:759-764
- B. pasteurii: 5/6 Nephrectomized Rats
  - DELAYED PROGRESSION/INCREASED SURVIVAL
    - Scientific World Journal, 2005; 5:652-660

PROBIOTICS

- ENTERIC INTRODUCTION BACTERIA OR BACTERIAL PRODUCTSPRODUCTS
- BIFIDOBACTERIUM longum prevents progression after 5/6 nephrectomy
- Inhibition of pro-inflammatory cytokines

THANKS FOR YOUR ATTENTION!!

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