# AST-120: A NOVEL DRUG TO PREVENT PROGRESSION OF CKD?

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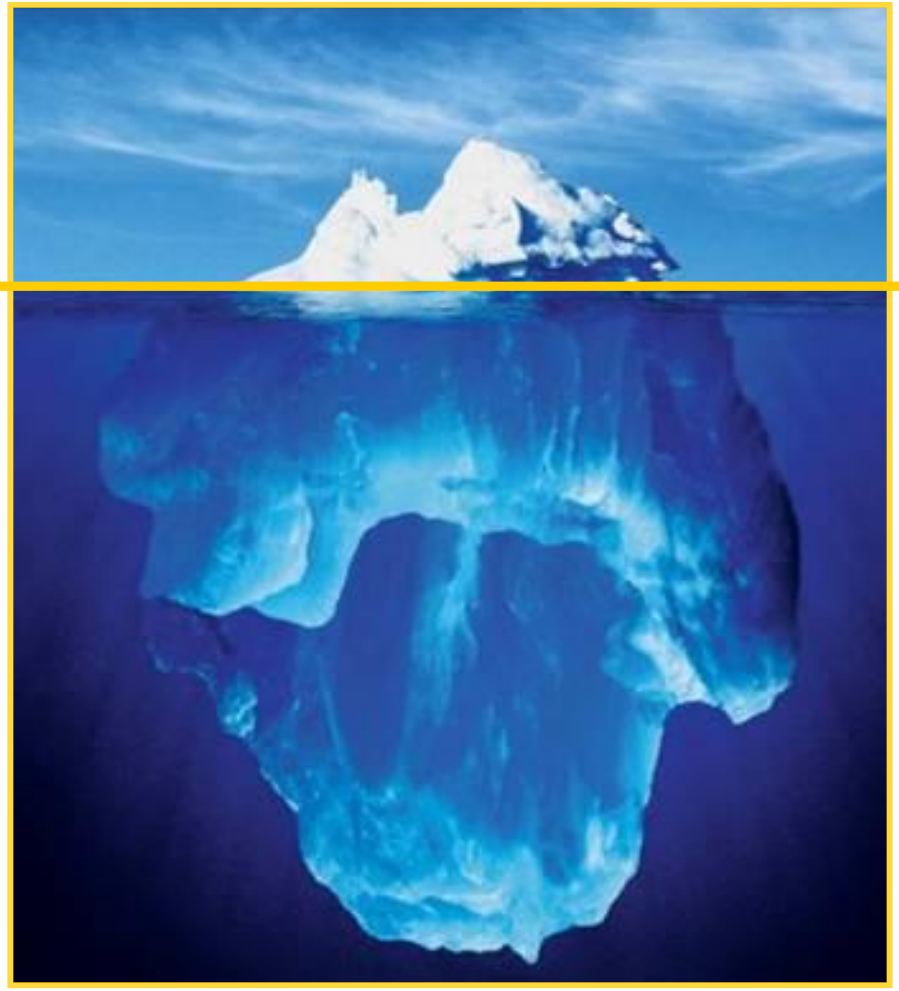
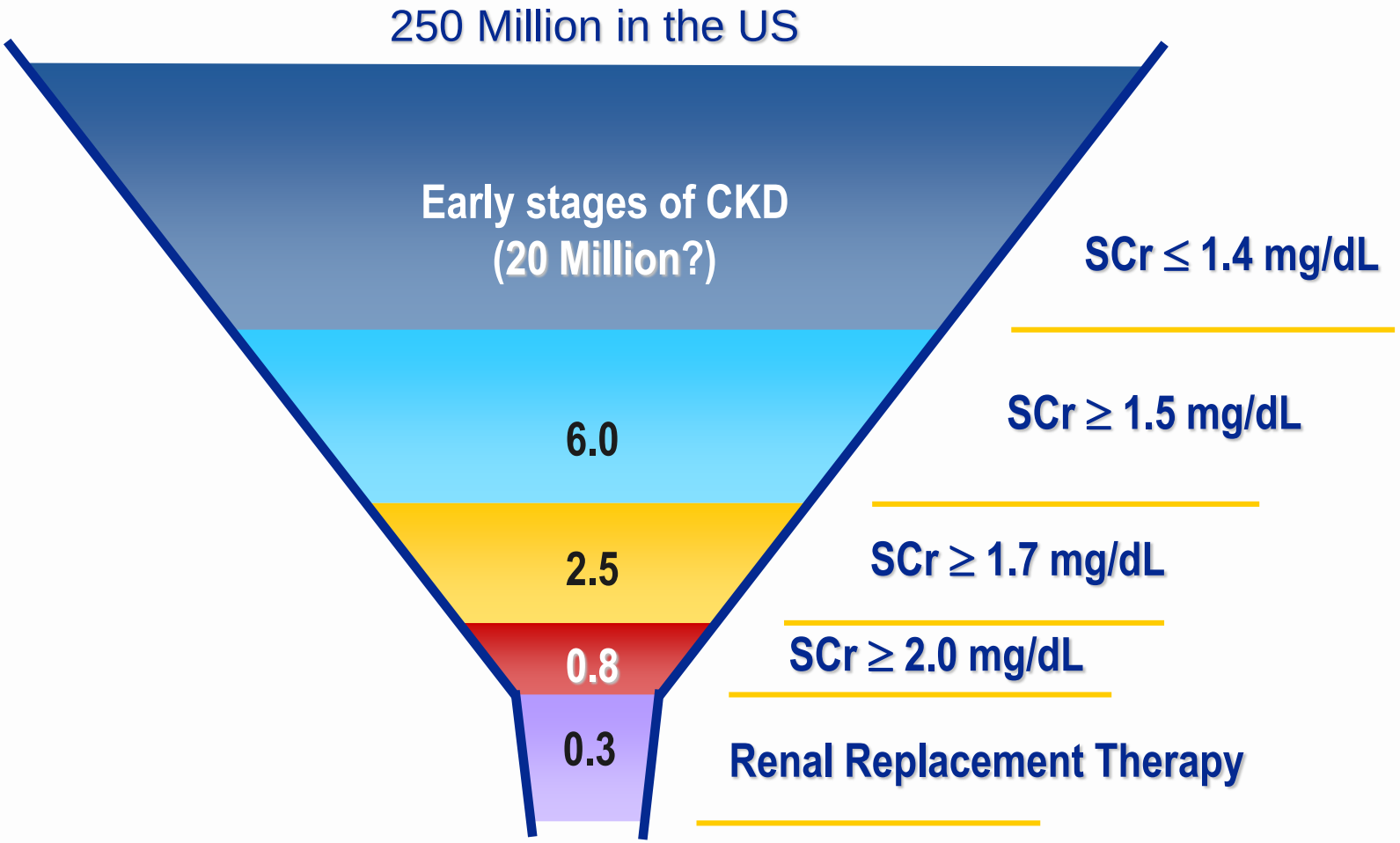
# The Renal Disease Iceberg



DIALYSIS
ESRD

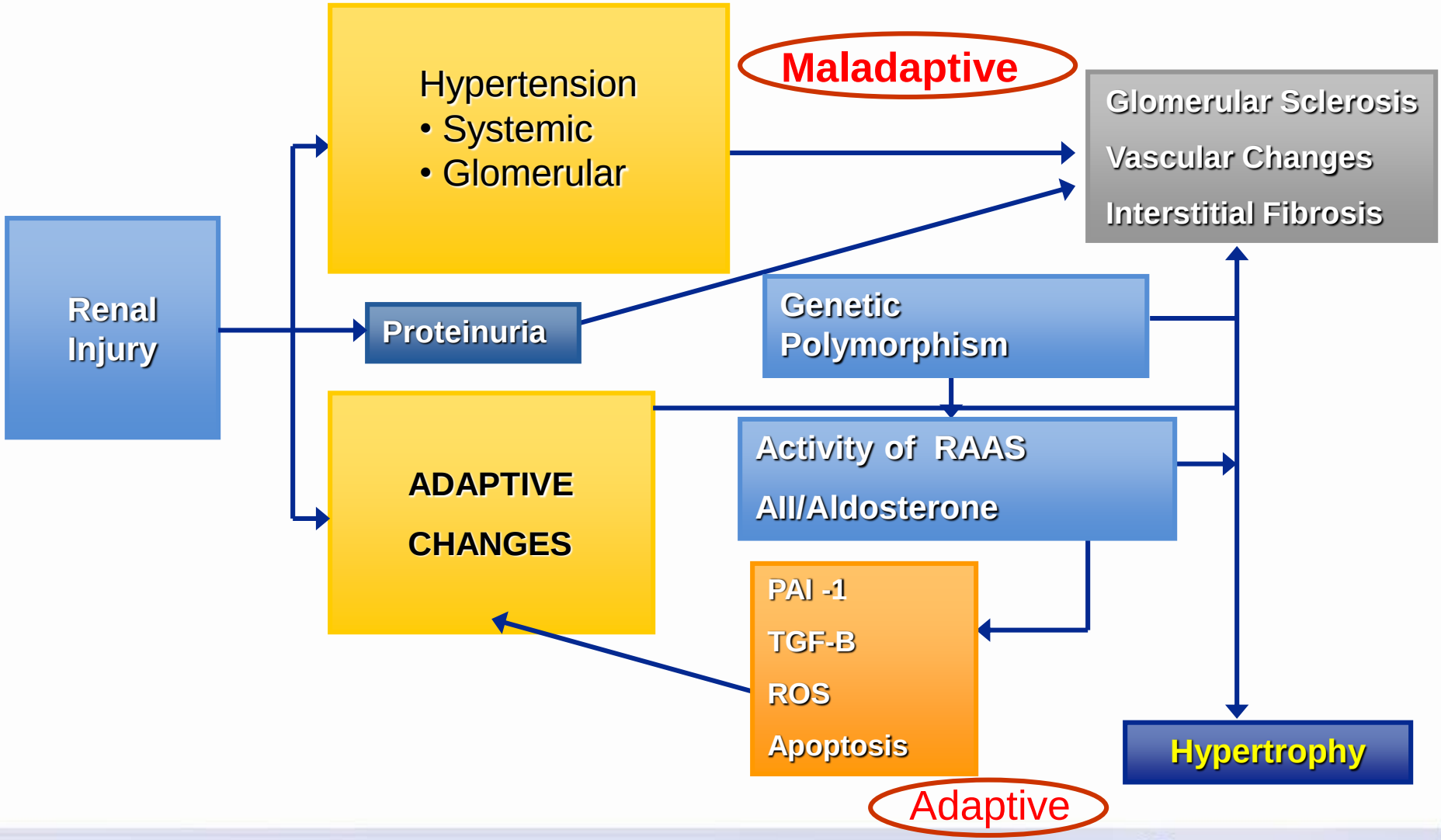
CHRONIC KIDNEY DISEASE

# Estimates of CKD within the USA Based on Creatinine (NHANES III Data)

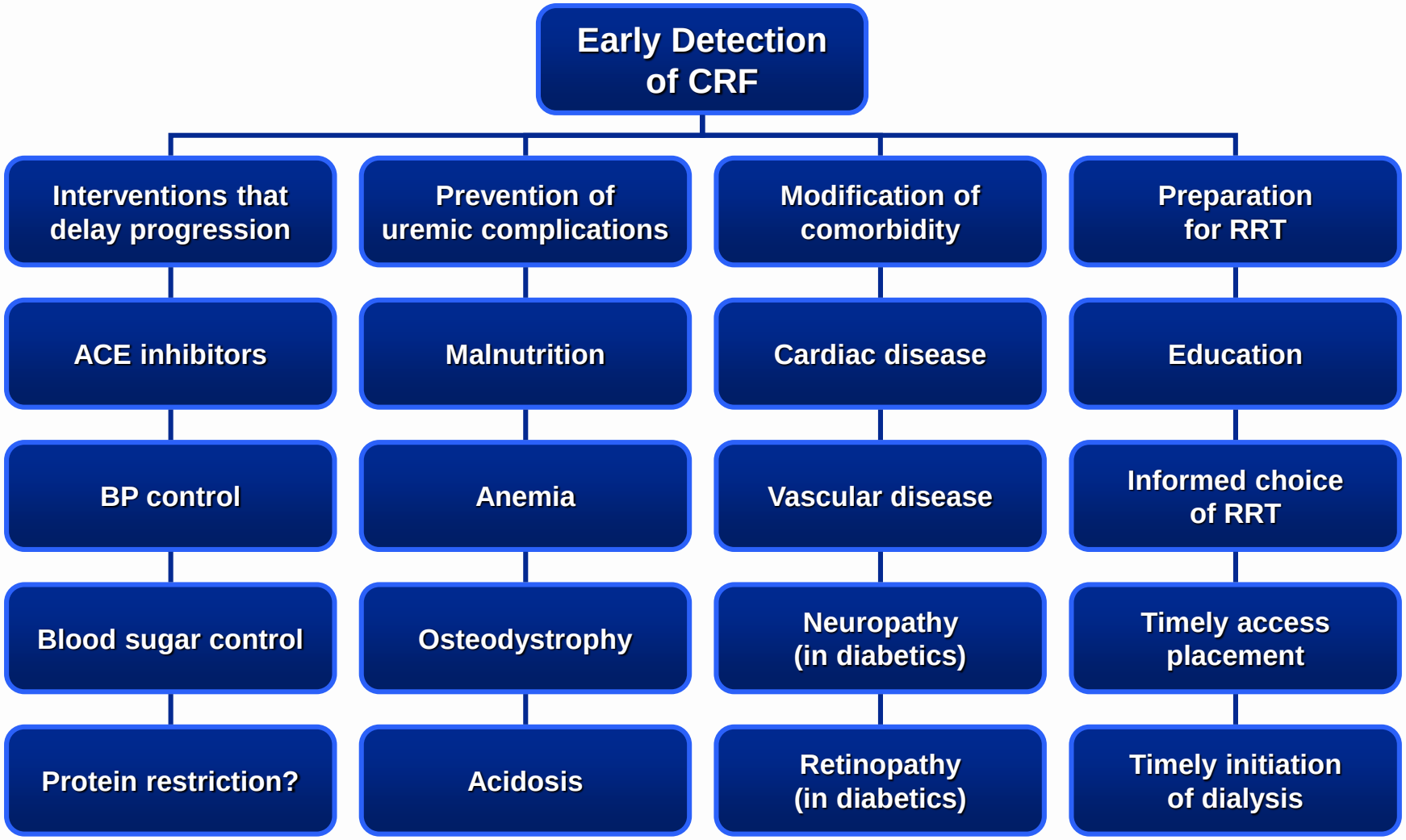



Jones et al. *Am J Kidney Dis*. 1998, US Renal Data System, 2000

# Factors Associated with Progression of CKD



# Optimal Pre-ESRD Care



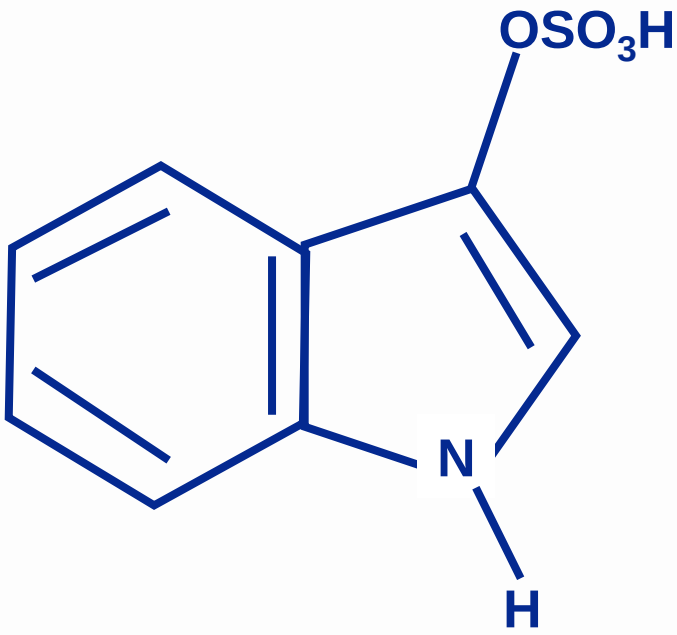
# PROPOSED UREMIC TOXINS

**Table 1.** Main known uremic retention solutes

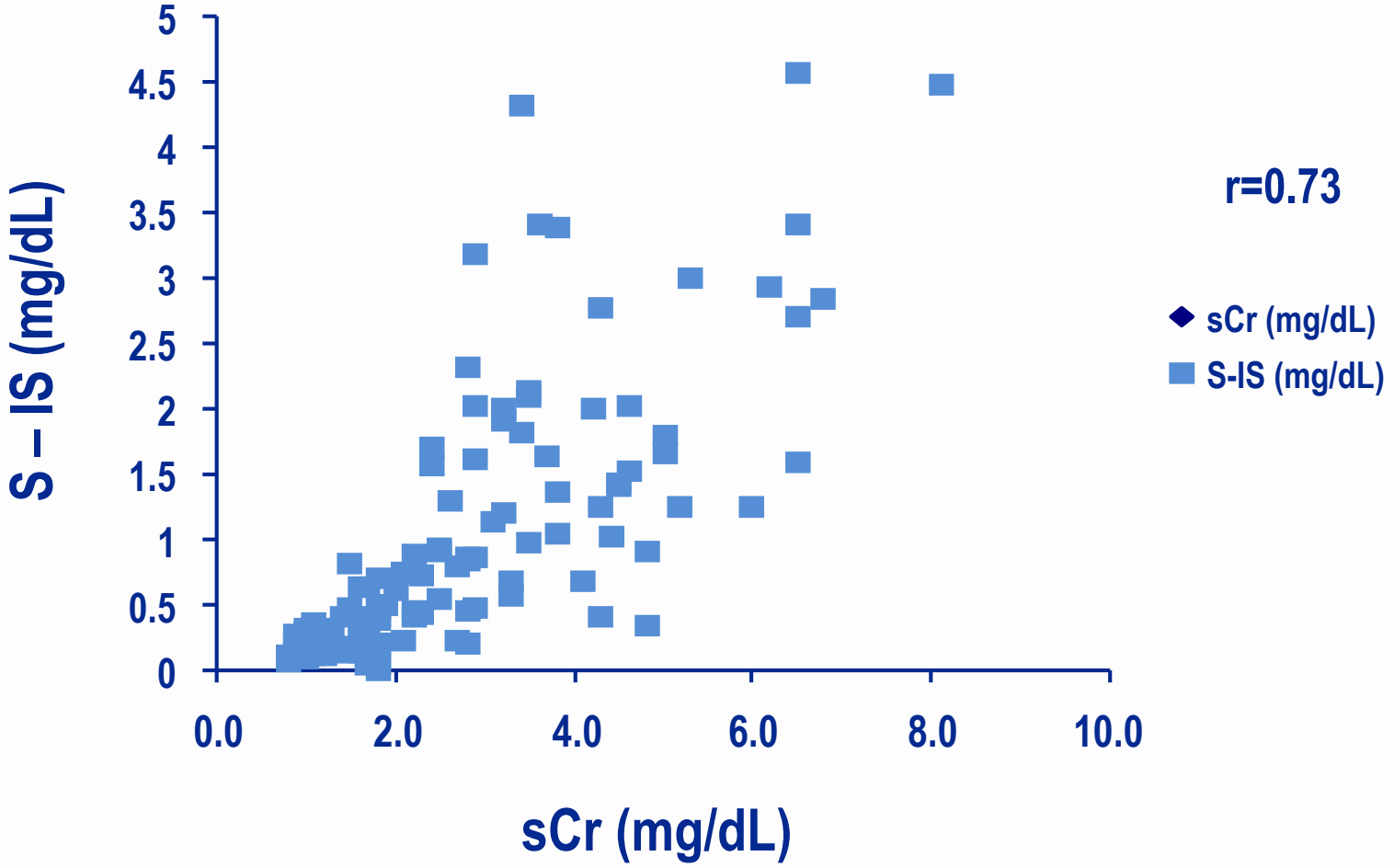
| Small water soluble solutes | Protein-bound solutes | Middle molecules |
|---|---|---|
| Asymmetric dimethylarginine | 3-Deoxyglucosone | Adrenomedullin |
| Benzylalcohol | CMPF | Atrial natriuretic peptide |
| β-Guanidinopropionic acid | Fructoselysine | $\beta_2$-Microglobulin |
| β-Lipotropin | 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.

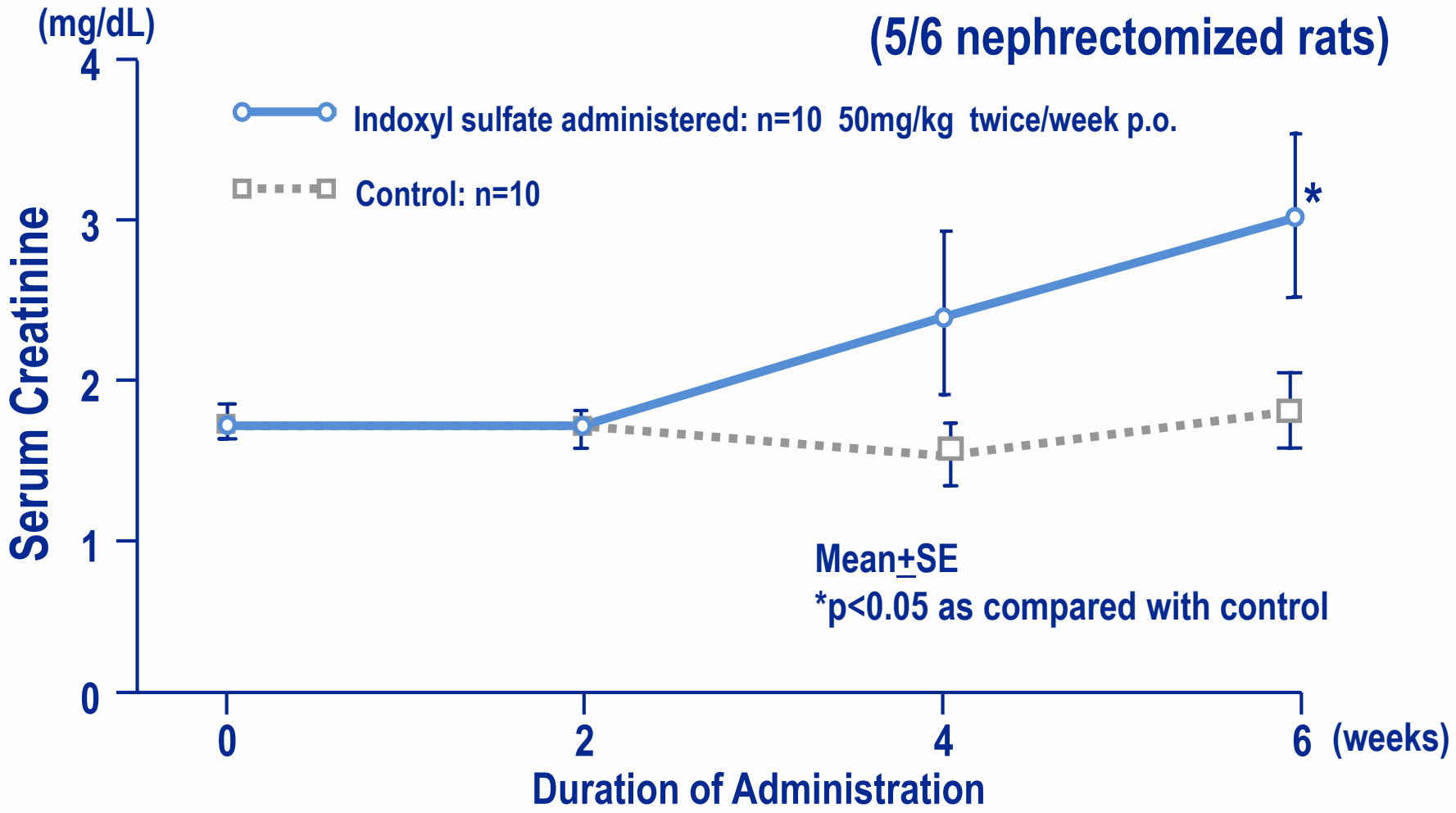
# INDOXYL SULFATE



# Serum Creatinine and Indoxyl Sulfate Levels in Chronic Kidney Disease in the U.S.



# Effect of Indoxyl Sulfate on Serum Creatinine in Uremic Rats

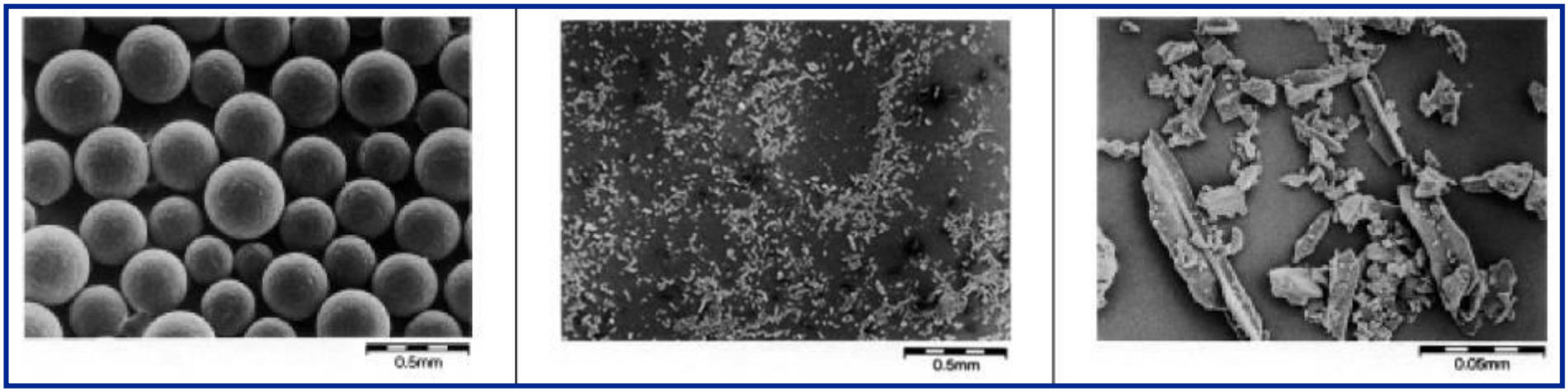



*Niwa, T. et al: J Lab Clin Med, 124(1), p96,1994*

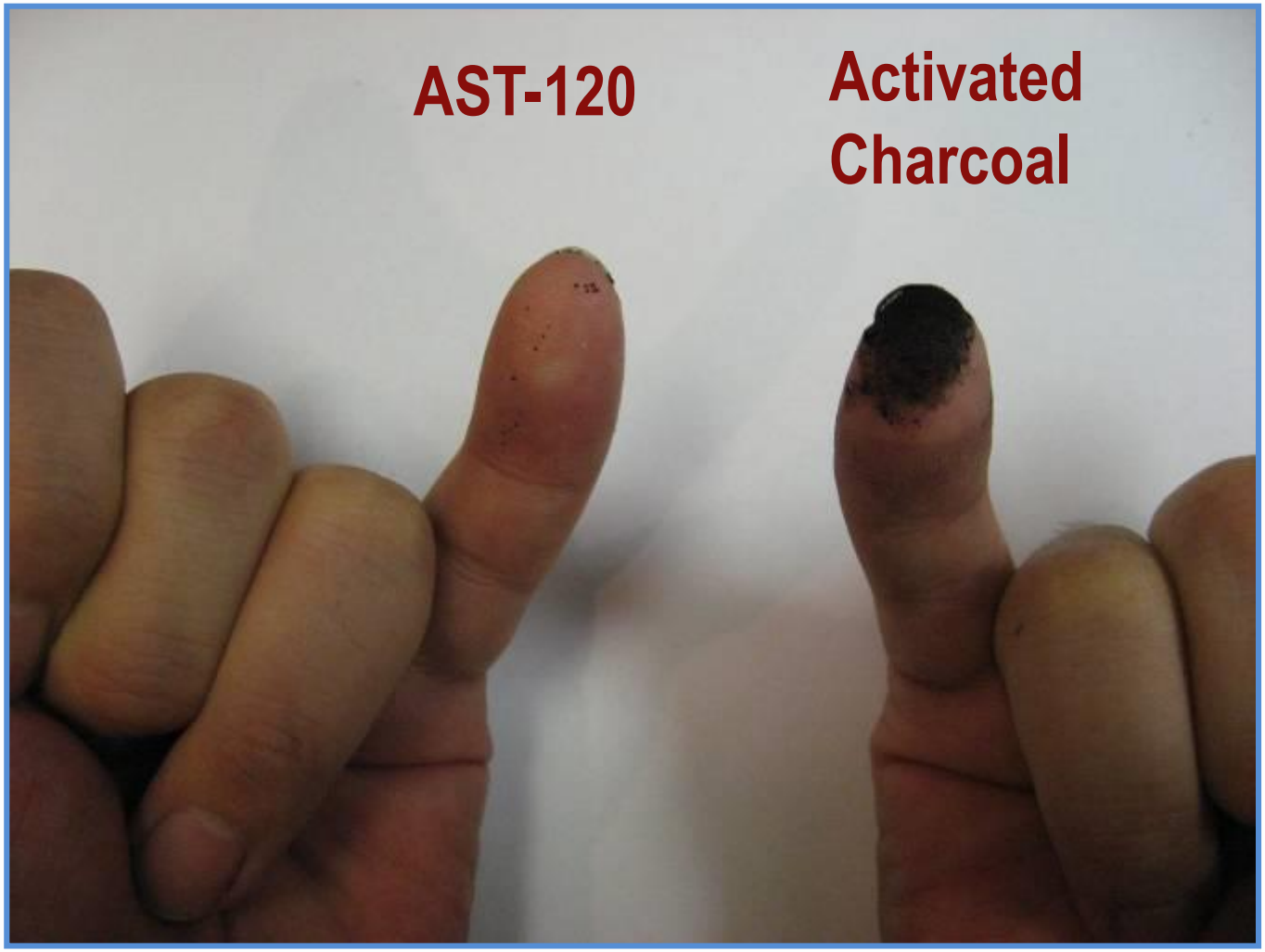
# AST-120

- 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

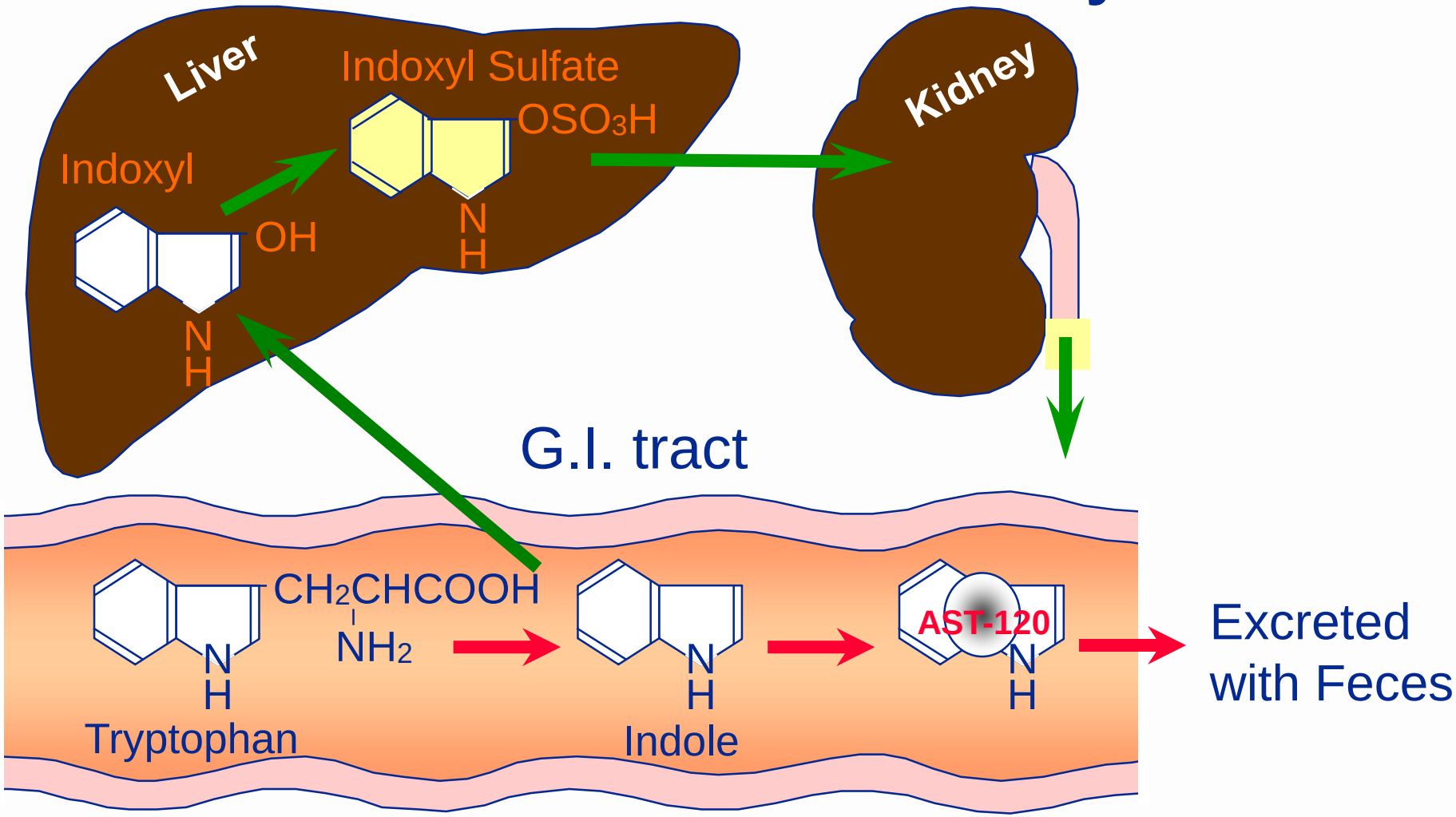
# Difference between AST-120 and Activated Charcoal



# AST-120 vs Activated Charcoal Physical Appearance



# Excretion Process of Indole by AST-120




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

# The Effect of AST-120 on the Glomerulus

Normal Rat

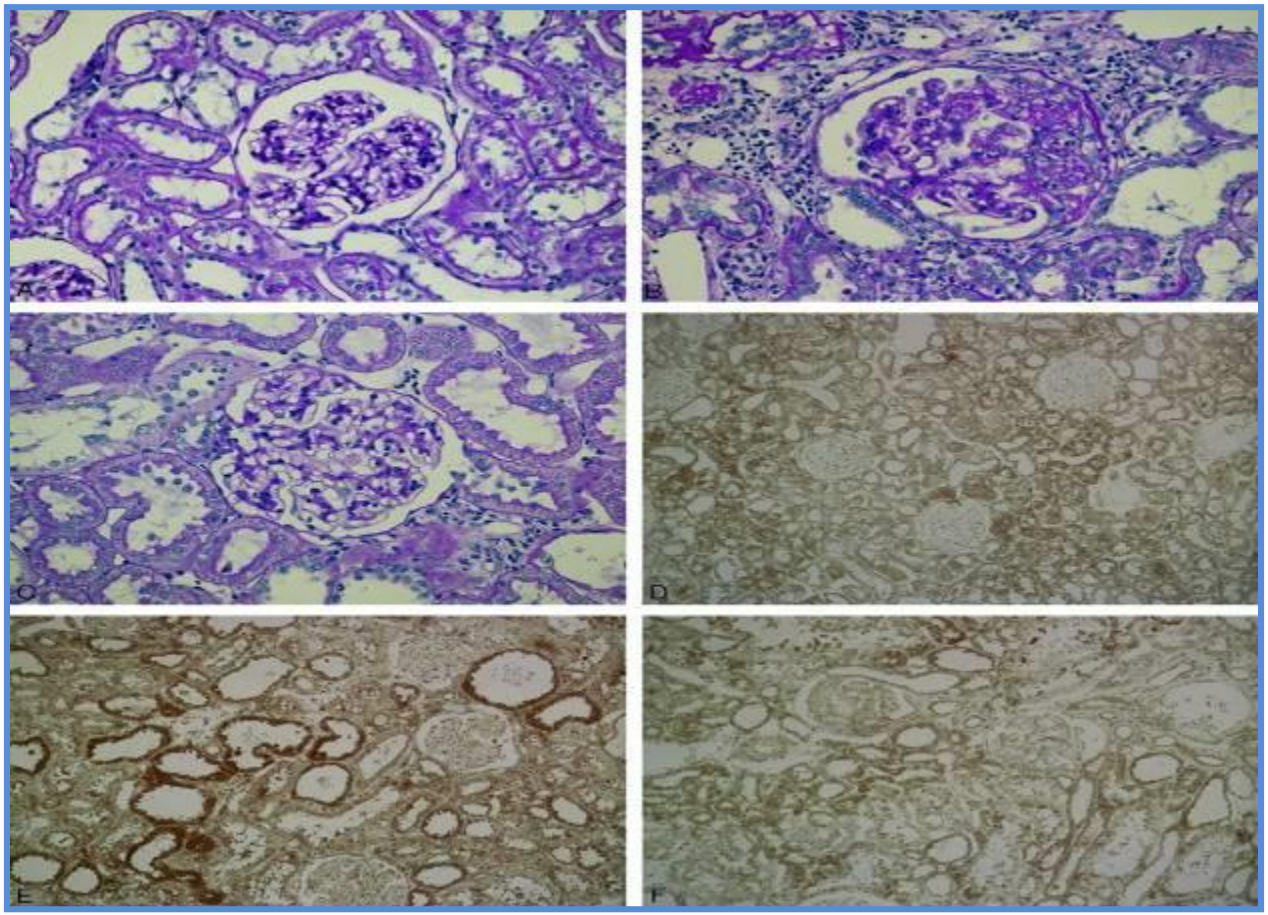
Control Uremic Rat

Uremic Rat with AST-120

Immunostaining of IS in the renal cortices of a normal rat

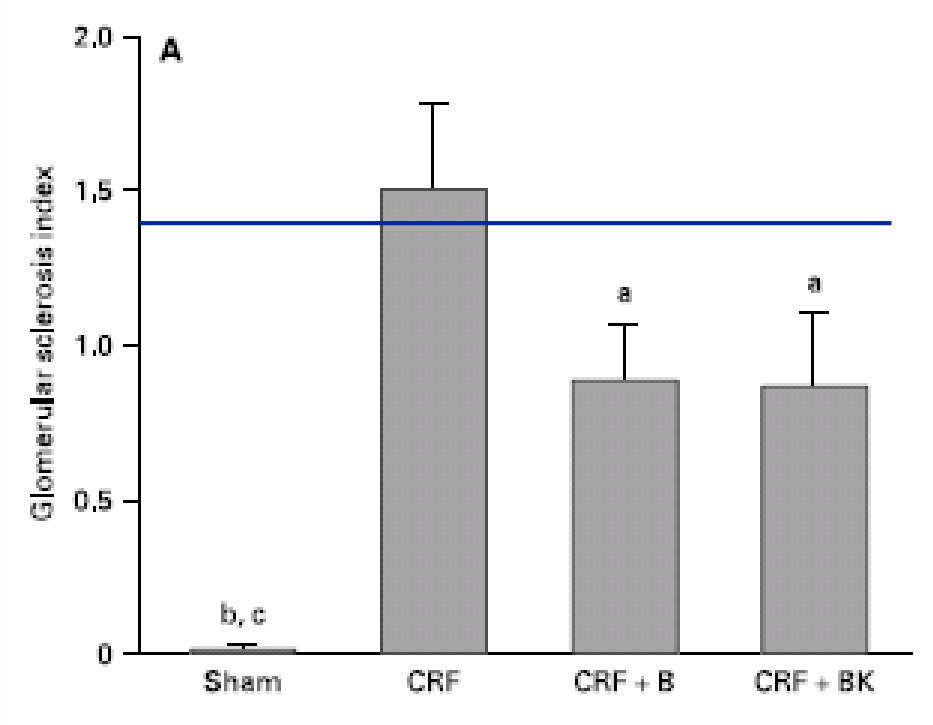
Immunostaining Control Uremic Rat

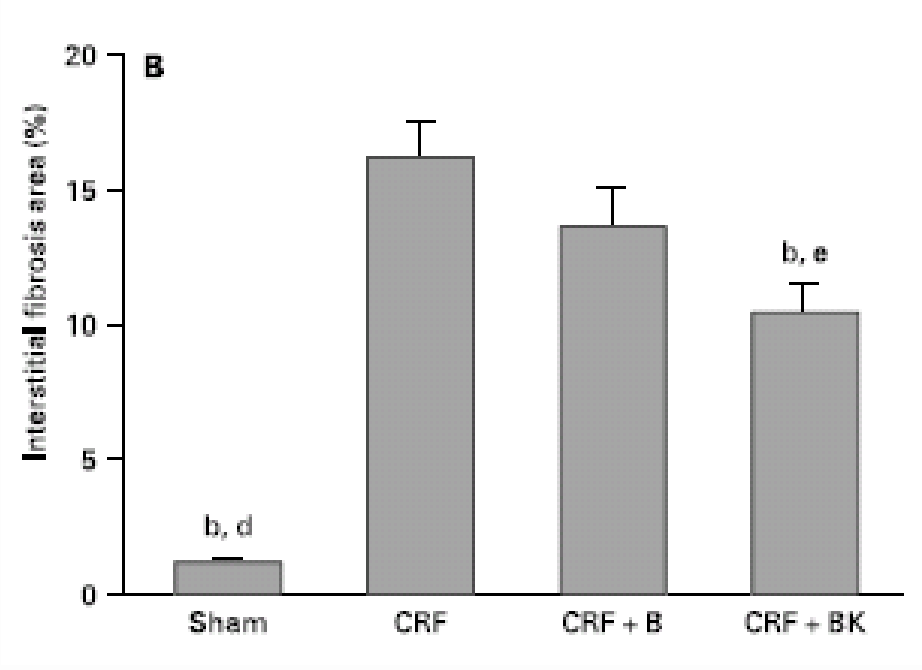
Immunostaining Uremic Rat with AST-120



*Miyazaki, T. et al. Nephrol. Dial. Transplant ,15, 2000*

# IS, AST-120 AND ACE-I



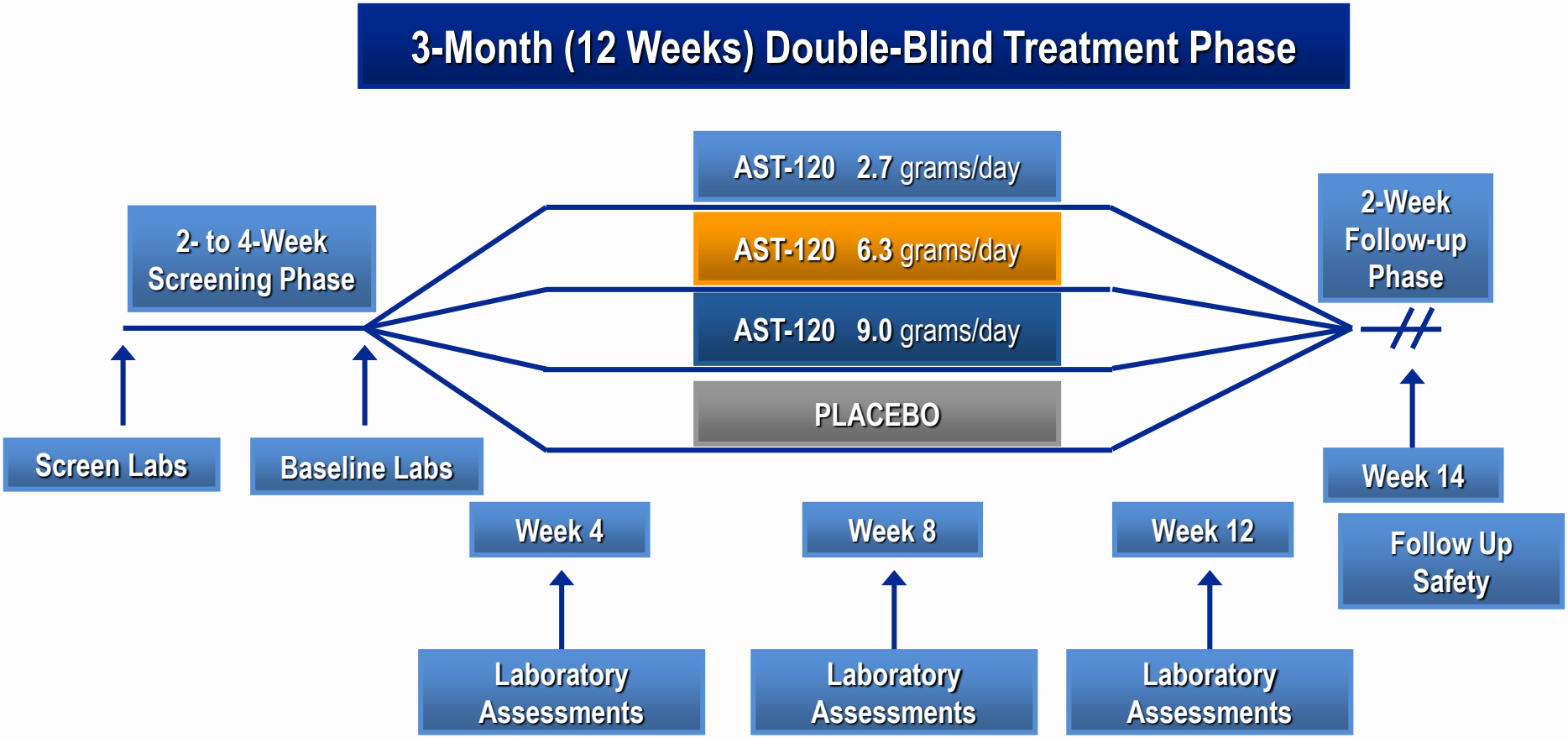




Aoyama I, et al. *Nephron.* 2002;90:297–312

# INDOXYL SULFATE AND CKD

- TGF β-1
- METALLOPROTEINASE
- PAI-1
- ABNORMALITIES IN TRYPTOPHAN METABOLISM
- CARDIOVASCULAR EFFECTS?

# Study Schematic



# Direct Adsorption of Creatinine in the Intestine

- No changes of Cr excretion in urine *)
- Creatinine production is 1-1.5 g/day
- 6 g (daily dose) of Kremezin is deduced to adsorb 60 mg of Cr *) in the intestine

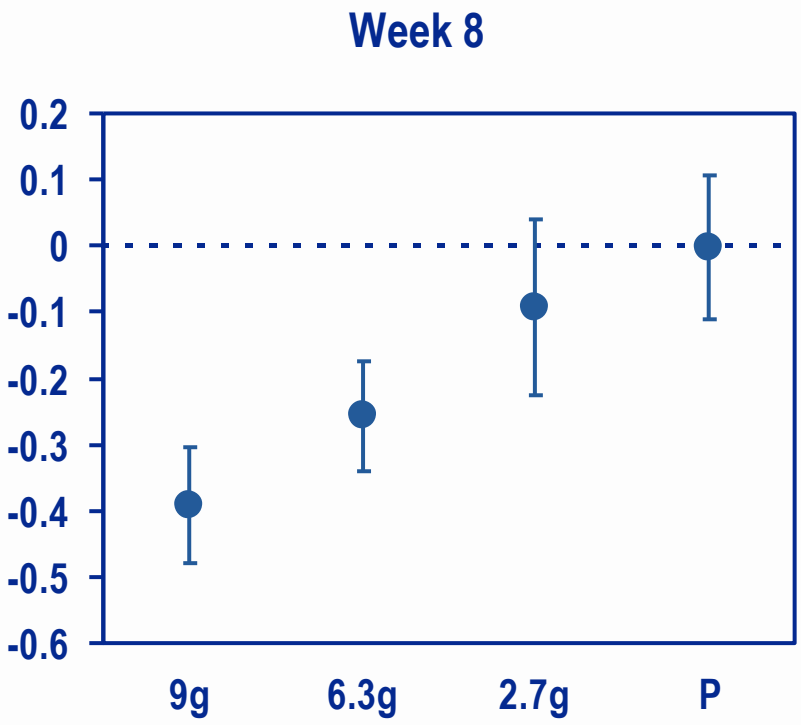
↓

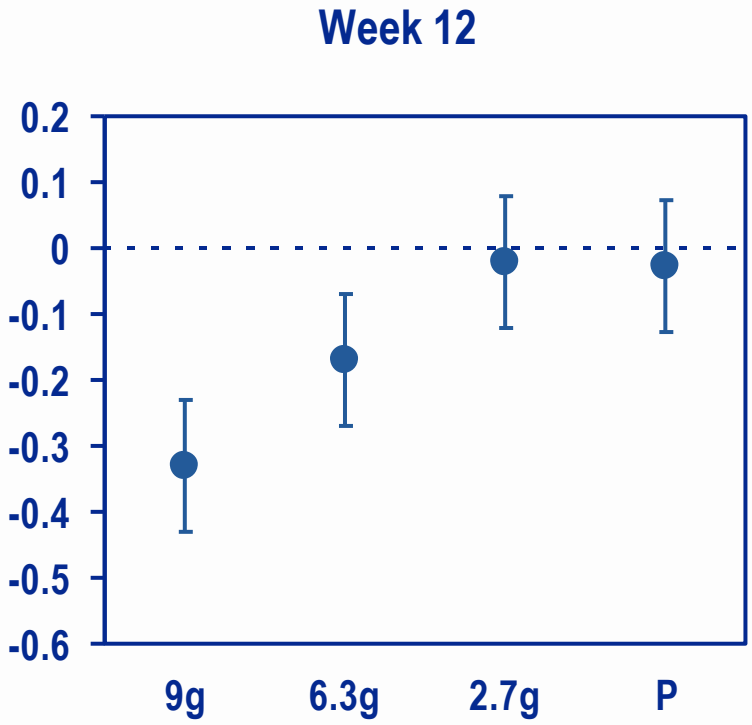
The effect of Cr adsorbed by Kremezin in the intestine is negligible

** Data submitted to MHW for NDA*

# MEAN CHANGE IN SERUM IS FROM BASELINE TO WEEK 8 AND WEEK 12

## (Mean + 95% Confidence Interval)



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

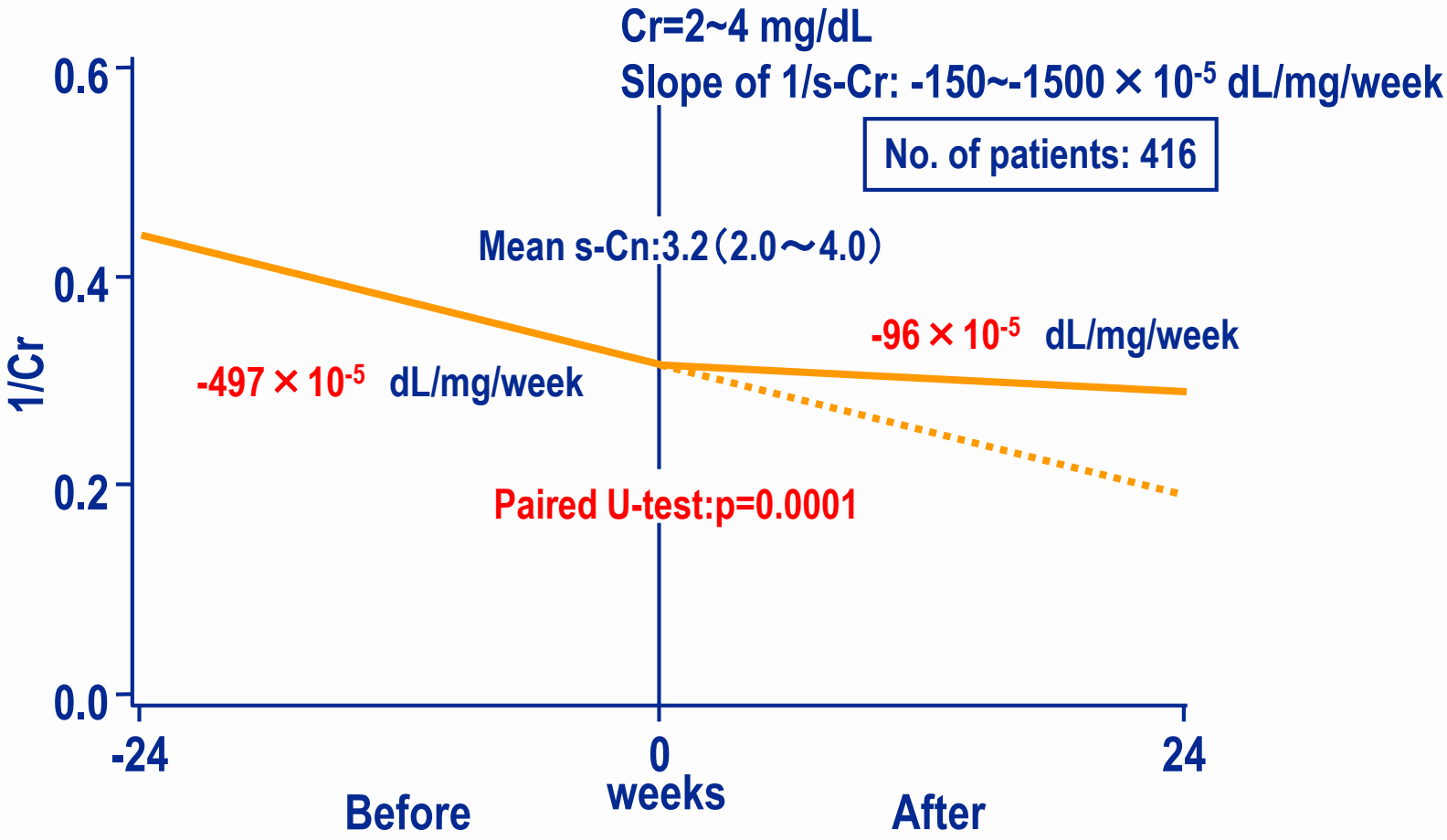
- Randomized, double-blind, cross-over study
  - 2 7-day treatment periods: AST-120 (3 g, 3 x daily) and placebo
  - 20 patients with mild CKD (mean baseline sCr: ~2 mg/dL)
  - In controlled Phase I unit during each treatment period

| | AST-120 9.0 g/day | Placebo | Geometric Mean Ratio (90% CI) |
|---|---|---|---|
| Urinary Creatinine Excretion (mg/dL) | 1264.7 | 1286.1 | 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

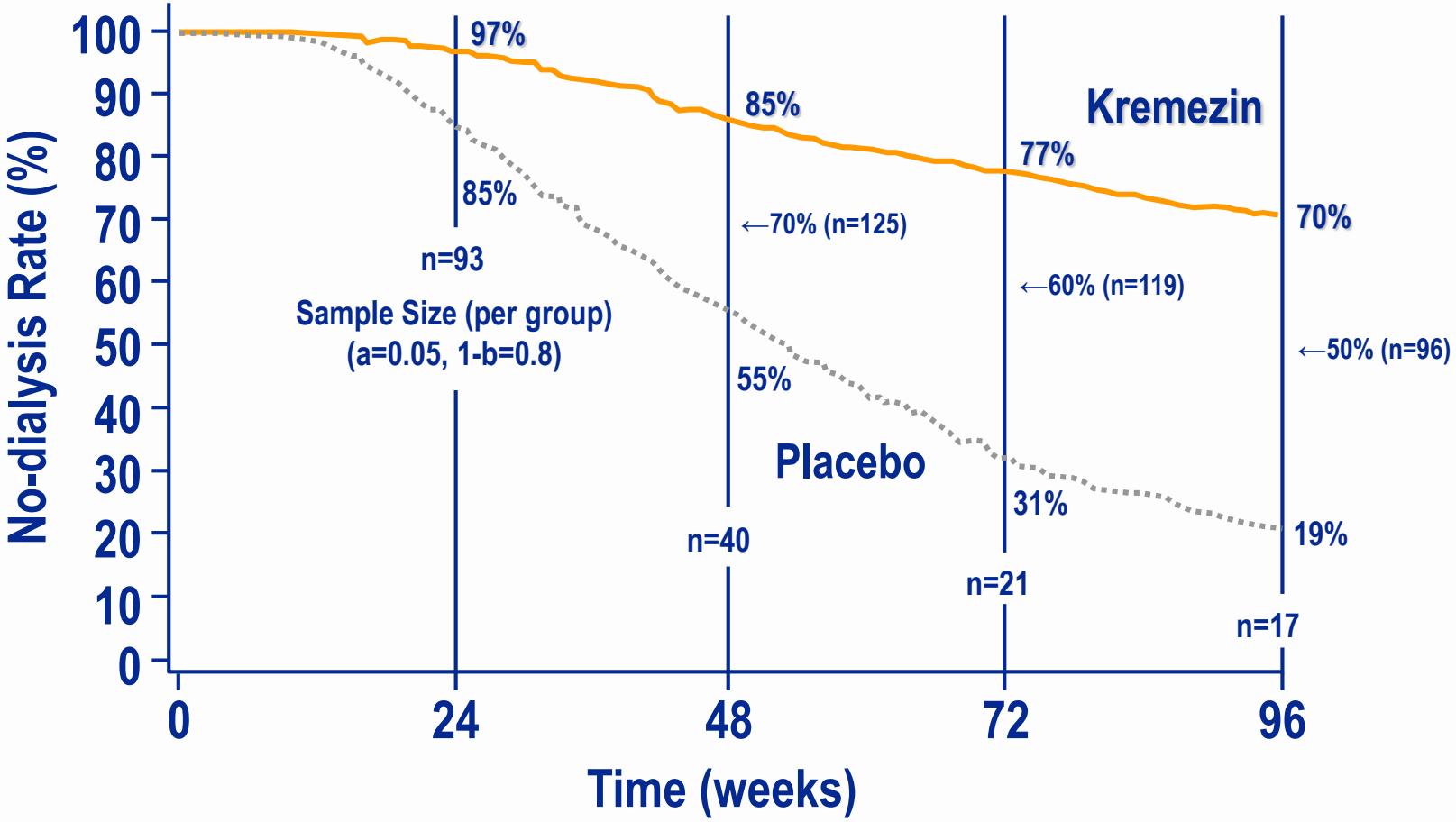
# 1/s-Cr slope Before and After the Initiation of Kremezin Administration

## (from Phase IV data)

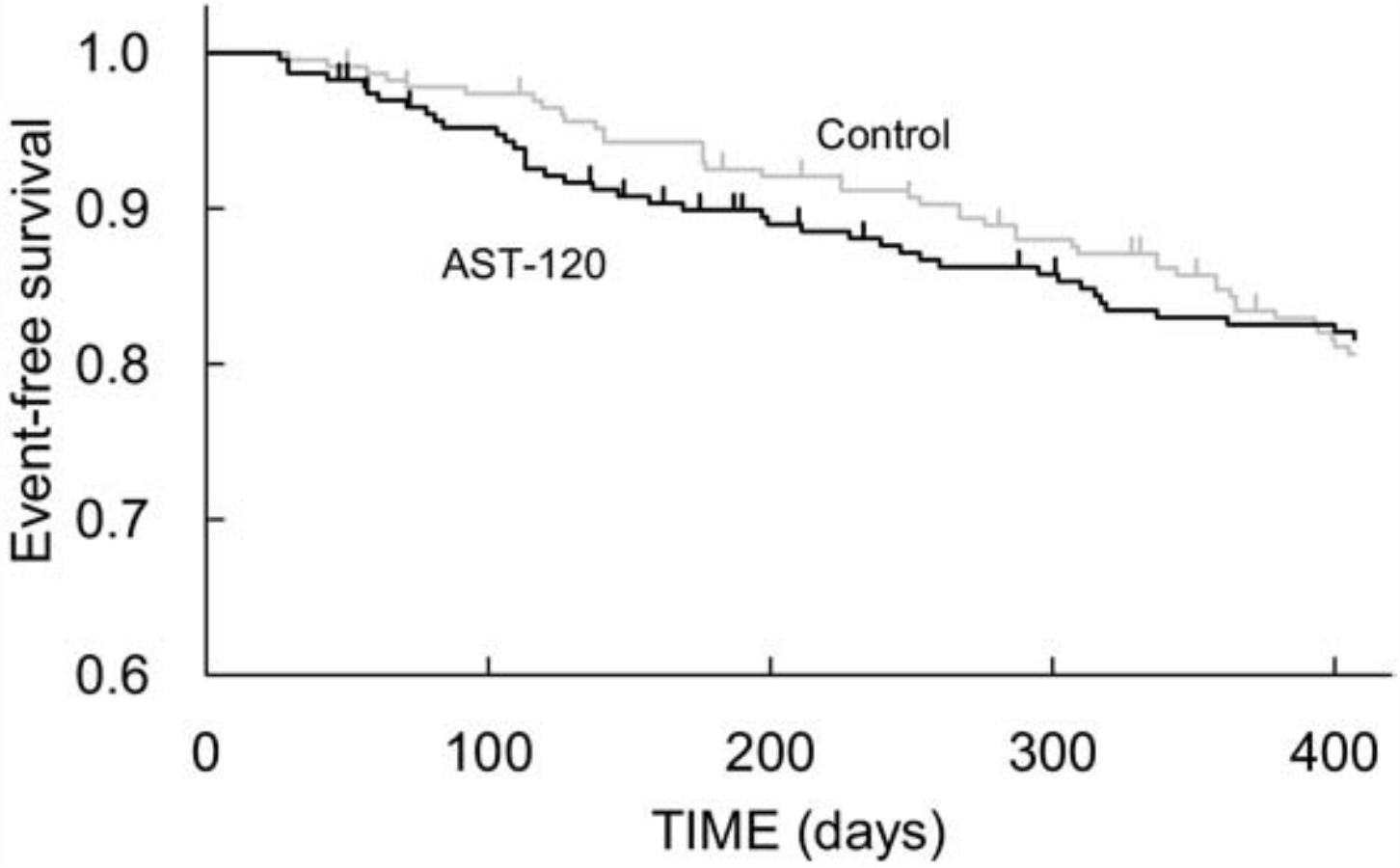


# Estimated No-dialysis Rate & Sample Size

## (from Phase IV data)

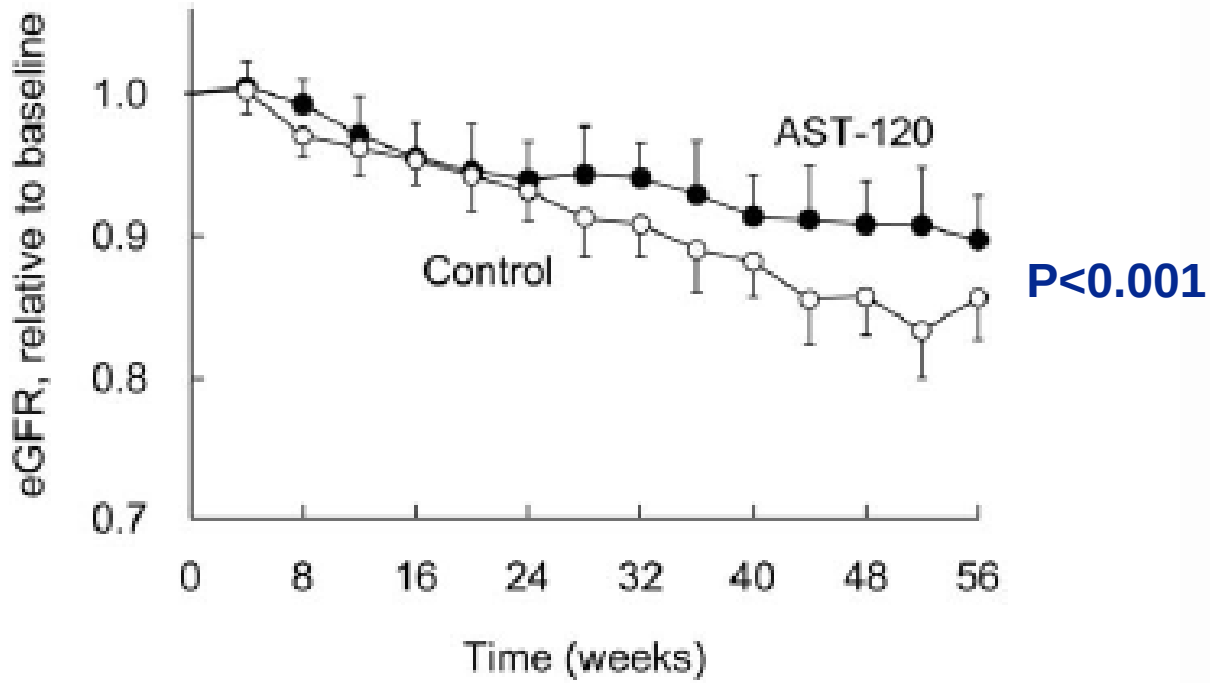


# Primary Endpoint: Doubling Serum Creatinine, Creatinine ≥ 6 mg/dl, Death, Dialysis, Transplant




*Akizawa T et al, AJKD: 54, 2009*

# Effect of AST-120 on estimated Glomerular Filtration Rate Over Time in Japan (6 g/day)

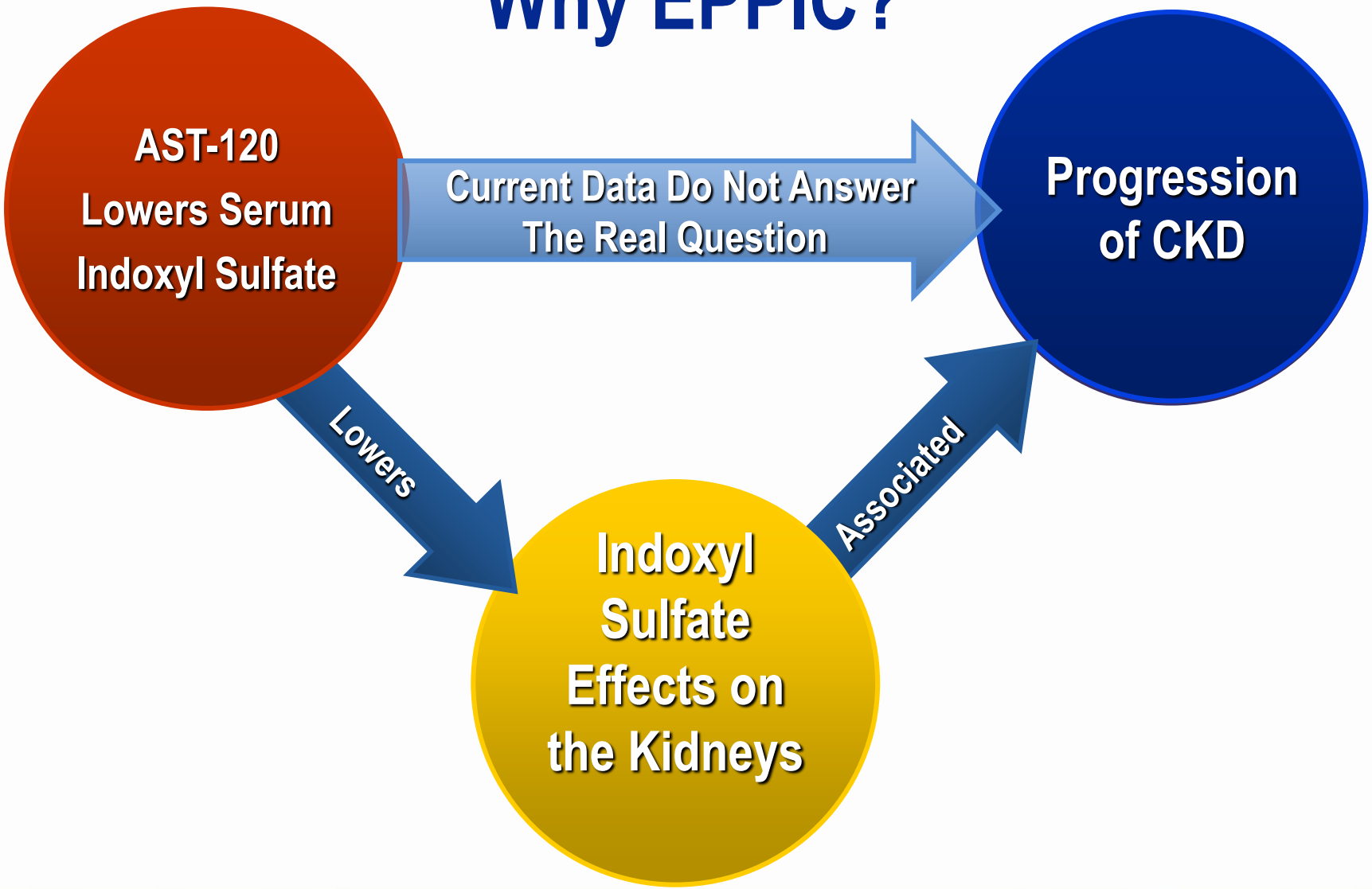



**P<0.001**

**Figure 3.** Estimated glomerular filtration rate (eGFR; estimated as described in Matsuo et al[18]) over time, by treatment group. Vertical lines indicate 95% confidence intervals.

*Akizawa T et al, AJKD: 54, 2009*

# Why EPPIC?


AST-120
Lowers Serum
Indoxyl Sulfate
Current Data Do Not Answer
The Real Question
Progression
of CKD
Lowers
Associated
Indoxyl
Sulfate
Effects on
the Kidneys

# Primary Objectives

- **Demonstrate that AST-120 reduces the risk of developing a component of the triple composite endpoint—"time to"**
  - Doubling of sCr
  - Dialysis
  - Transplantation
- **Assess long-term safety of AST-120 in CKD patients**

# Secondary Objectives

- Quadruple endpoint: Primary + Death*
- Effects of AST-120 on protein and creatinine excretion, $C_{Cr}$, $C_{Urea}$
- Effects on fat soluble vitamins, B-12, folate

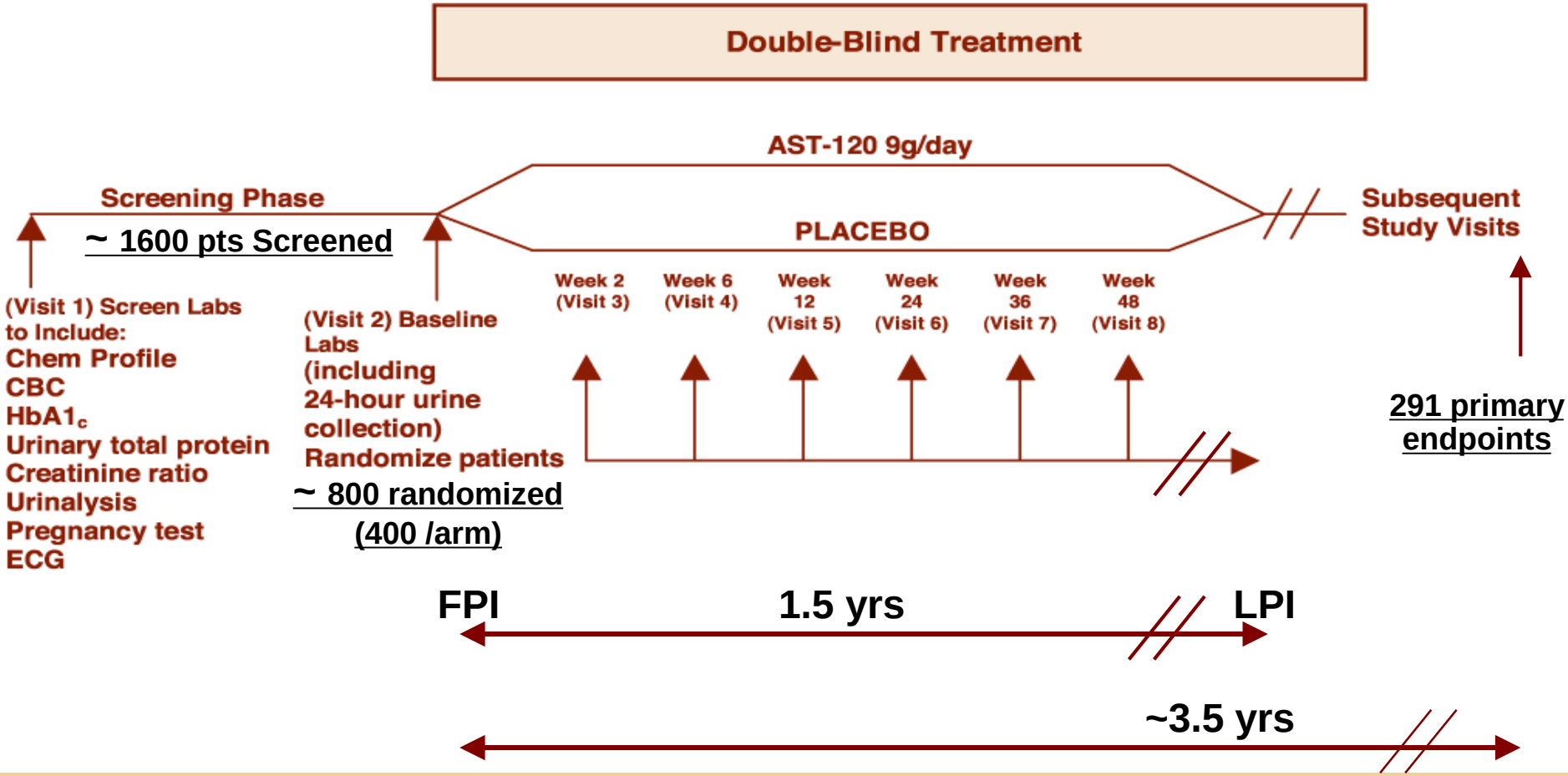
*Death is "all-cause"

*Cause of death = SAE

*Endpoint Adjudication Committee will review and assess causality of deaths

*Statistical Analysis Plan will detail these procedures

# Study Design




**Two clinical trials will be conducted at a total of approximately 240 study centers worldwide**

# Demography - Preliminary data

## All Randomized Patients as of December 1, 2010

EPPIC

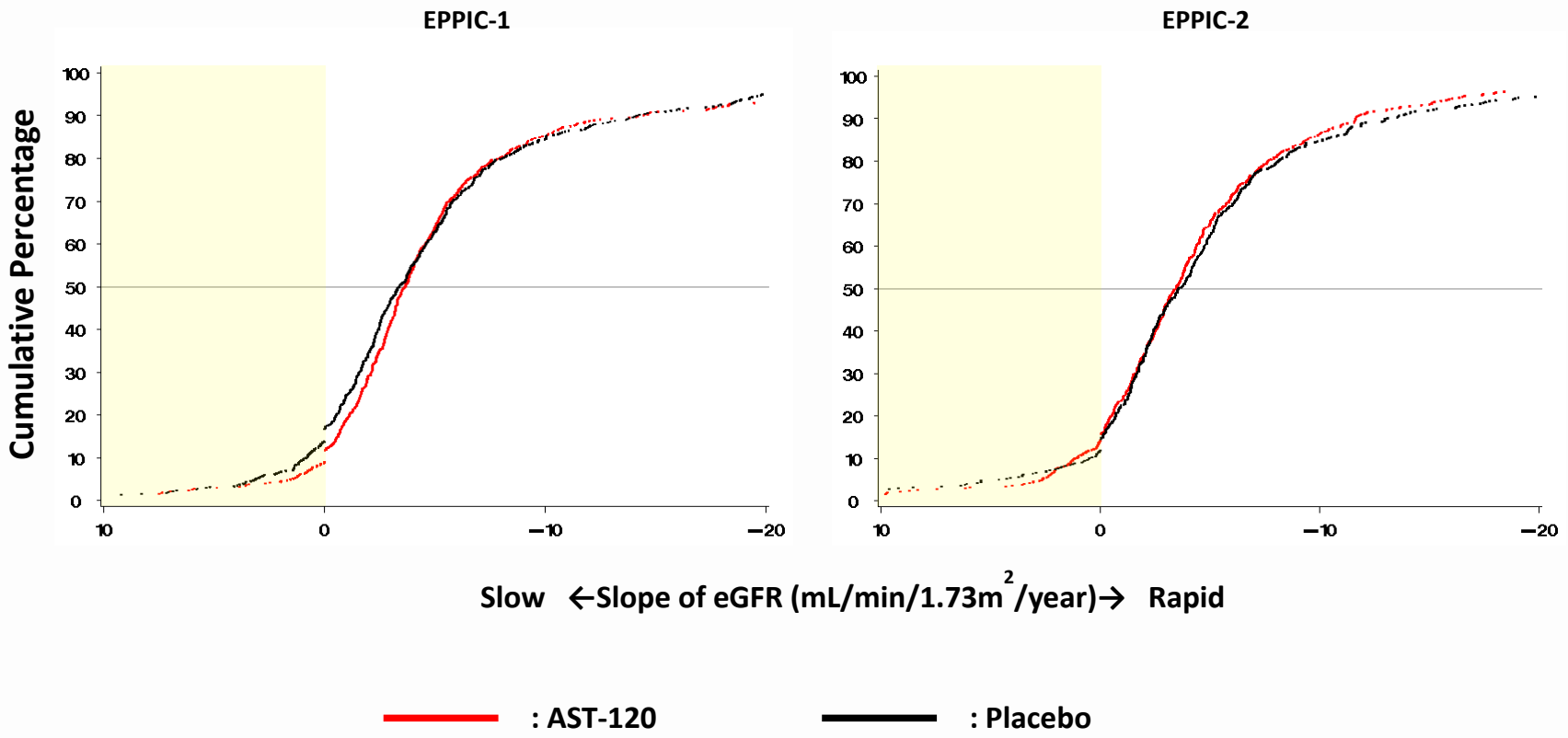
| Protocol | Gender | N | Screening Age (Avg) | DM-Nephropathy ratio (%) | Screening Ur.Prot/Cr (mg/mg Cr) (Avg) | Baseline sCr (mg/dL) (Avg) | Baseline eGFR* (mL/min /1.73m$^2$) (Avg) | CKD ** (N) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Stage 3 | Stage 4 | Stage 5 |
| KRM-306 | male | 646 | 57.9 | 293<br>45.4% | 2.0 | 3.2 | 23.9 | 143<br>22.1% | 435<br>67.3% | 68<br>10.5% |
| | female | 375 | 53.0 | 141<br>37.6% | 2.0 | 3.0 | 20.2 | 35<br>9.3% | 239<br>63.7% | 101<br>26.9% |
| KRM-307 | male | 560 | 55.7 | 221<br>39.5% | 2.1 | 3.2 | 23.6 | 104<br>18.6% | 407<br>72.7% | 49<br>8.8% |
| | female | 455 | 54.3 | 177<br>38.9% | 1.9 | 3.0 | 20.2 | 44<br>9.7% | 278<br>61.1% | 133<br>29.2% |

* The coefficient of African-American is tentatively excluded from eGFR calculation because the race data aren't available at this time.

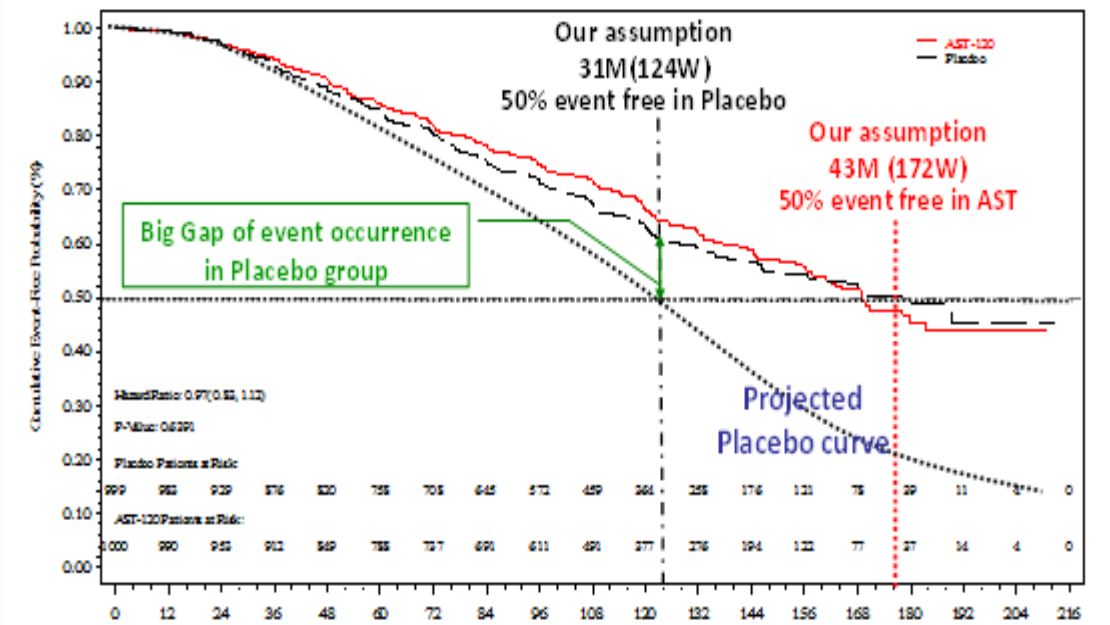
eGFR(mL/min/1.73m²) = 186x(sCr) $^{-1.154}$ x(Age) $^{-0.203}$ x(0.742 if female)x(1.210 if African-American)

** CKD stage is tentatively categorized by eGFR at baseline.

# RESULTS OF THE TWO EPPIC TRIALS



# PRIMARY AND SECONDARY POOLED ITT ENDPOINTS




| | AST-120 | | Placebo | | AST-120 vs P | |
|---|---|---|---|---|---|---|
| | N | n(%) | N | n(%) | HR(95% CI) | P-value |
| Primary Endpoint (triple) * | | | | | | |
| ITT | 1000 | 350(35.0) | 999 | 360(36.0) | 0.97(0.83, 1.12) | 0.6391 |
| Secondary Endpoint (quadruple) ** | | | | | | |
| ITT | 1000 | 417(41.7) | 999 | 418(41.8) | 0.99(0.86, 1.13) | 0.8606 |

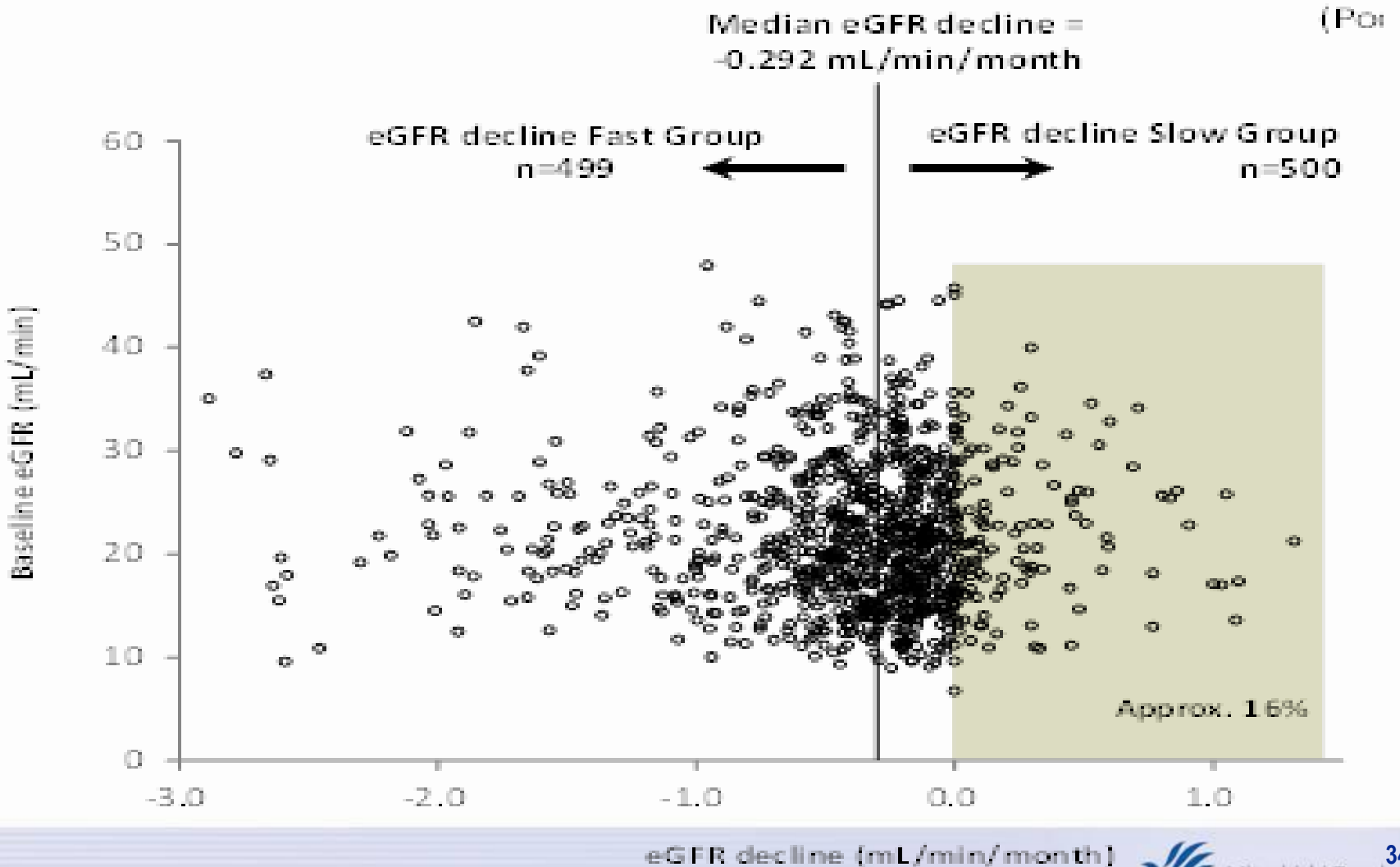
# Summary of Estimated Glomerular Filtration Rate and Serum Creatinine Level at Time of Dialysis Initiation.

| | EPPIC-1 | | | EPPIC-2 | | |
|---|---|---|---|---|---|---|
| | n | eGFR, Mean ± SD | sCr, Mean ± SD | n | eGFR, Mean ± SD | sCr, Mean ± SD |
| **Total** | 302 | 10.90 ± 5.25 | 6.59 ± 3.16 | 289 | 9.95 ± 4.67 | 6.81 ± 3.00 |
| **CKD Etiology** | | | | | | |
| **Diabetic nephropathy** | 147 | 13.02 ± 5.19 | 5.26 ± 2.00 | 124 | 11.32 ± 5.02 | 5.91 ± 2.28 |
| **Nondiabetic nephropathy** | 155 | 8.88 ± 4.47 | 7.84 ± 3.54 | 165 | 8.92 ± 4.10 | 7.48 ± 3.30 |
| **Gender** | | | | | | |
| **Female** | 99 | 8.89 ± 4.49 | 6.81 ± 3.43 | 126 | 8.99 ± 4.22 | 6.61 ± 3.33 |
| **Male** | 203 | 11.88 ± 5.33 | 6.48 ± 3.03 | 163 | 10.70 ± 4.87 | 6.96 ± 2.72 |
| **Region** | | | | | | |
| **Europe (with Russia and the Ukraine)** | 113 | 8.22 ± 3.74 | 8.23 ± 3.78 | 108 | 8.10 ± 4.18 | 8.31 ± 3.50 |
| **Europe (without Russia and the Ukraine)** | 35 | 10.81 ± 3.40 | 5.92 ± 1.55 | 33 | 10.39 ± 3.35 | 6.37 ± 2.75 |
| **Latin America** | 43 | 8.61 ± 3.30 | 7.19 ± 2.50 | 74 | 9.46 ± 4.18 | 6.56 ± 2.50 |
| **North America** | 146 | 13.64 ± 5.34 | 5.13 ± 1.90 | 107 | 12.16 ± 4.57 | 5.47 ± 1.92 |

# COMPLIANCE

| Categorical summary, n (%) | | | | |
|---|---|---|---|---|
| <33% | 4 (0.8) | 4 (0.8) | 4 (0.8) | 5 (1.0) |
| ≥33%-<50% | 9 (1.8) | 14 (2.8) | 12 (2.4) | 10 (2.0) |
| ≥50%-<67% | 20 (4.0) | 29 (5.8) | 24 (4.8) | 22 (4.4) |
| ≥67%-<83% | 41 (8.2) | 40 (8.0) | 49 (9.7) | 59 (11.9) |
| ≥83%-<100% | 356 (70.8) | 349 (69.5) | 366 (72.5) | 329 (66.3) |
| ≥100%-<110% | 71 (14.1) | 65 (12.9) | 47 (9.3) | 69 (13.9) |
| ≥110% | 2 (0.4) | 1 (0.2) | 3 (0.6) | 2 (0.4) |
| Total | 503 | 502 | 505 | 496 |

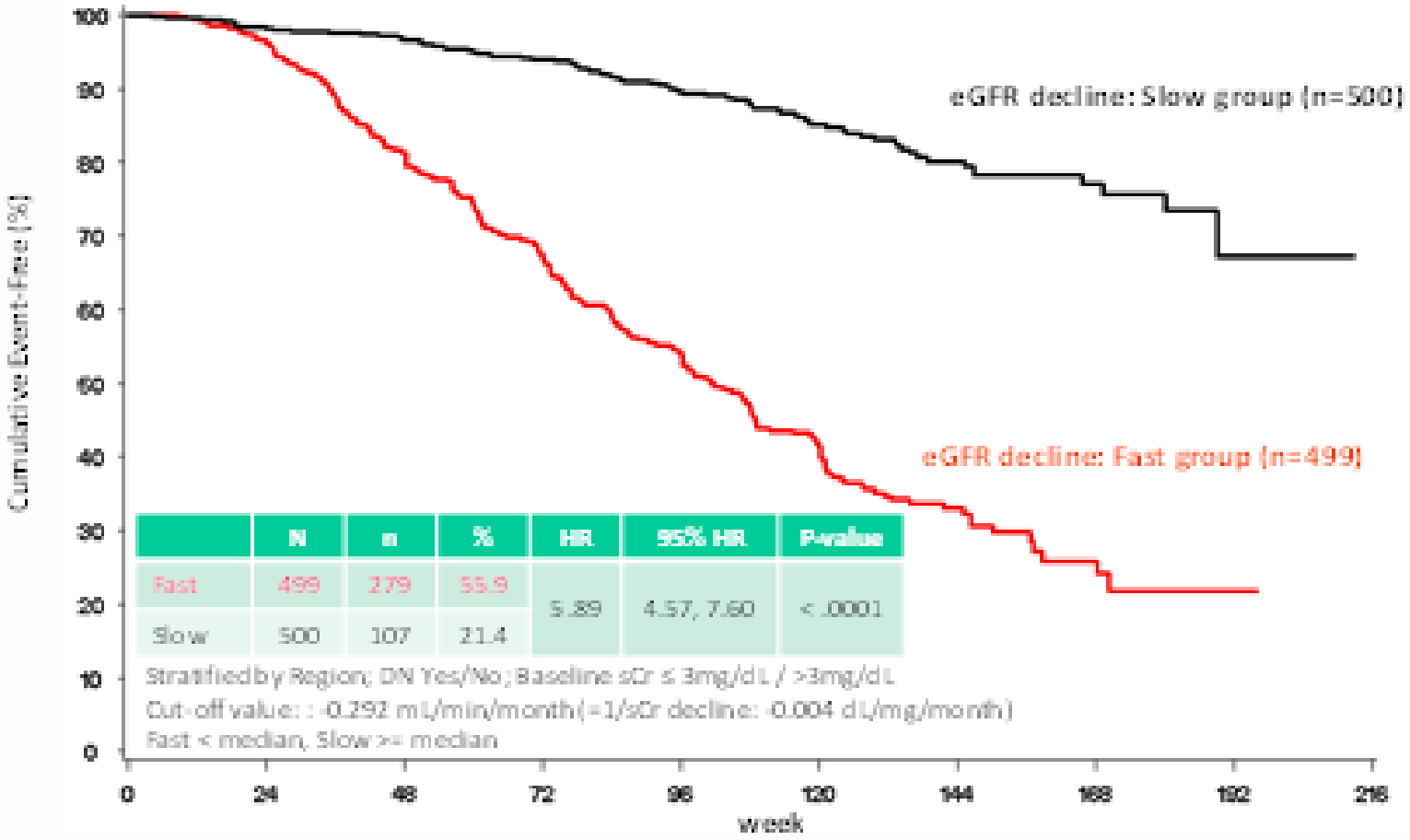
# SLOW vs RAPID PROGRESSORS IN PLACEBO GROUP





Mitsubishi Tanabe Pharma

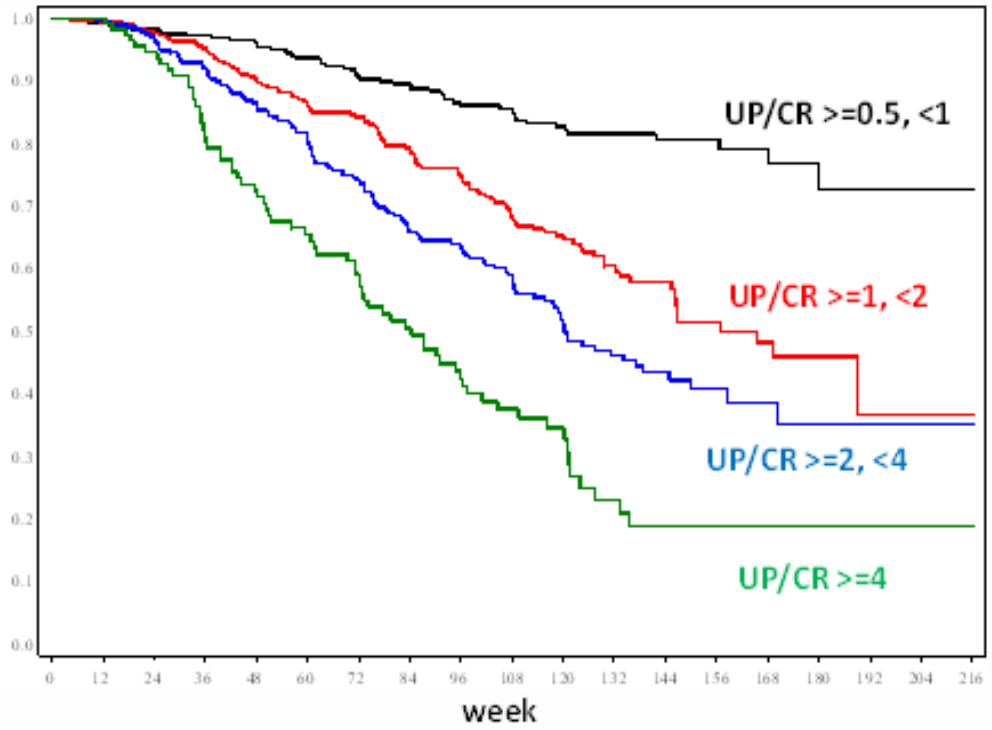
# END POINT ACHIEVEMENT FAST vs SLOW PLACEBO GROUPS (ITT)

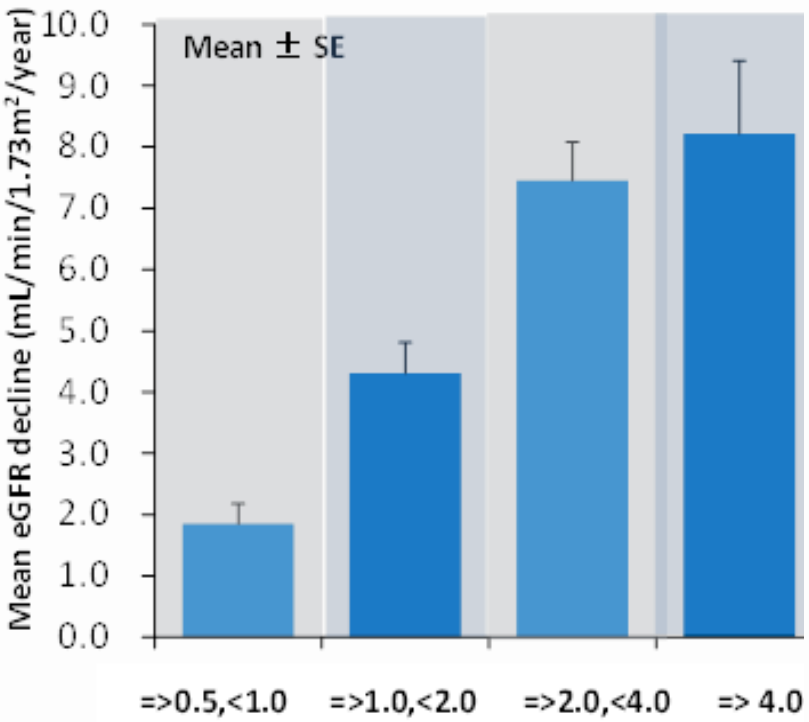



| | N | n | % | HR | 95% HR | P-value |
|---|---|---|---|---|---|---|
| Fast | 499 | 279 | 55.9 | 5.89 | 4.57, 7.60 | < .0001 |
| Slow | 500 | 107 | 21.4 | | | |

Stratified by Region; DN Yes/No ; Baseline sCr ≤ 3mg/dL / >3mg/dL
Cut-off value: : -0.292 mL/min/month (=1/sCr decline: -0.004 dL/mg/month)
Fast < median, Slow >= median

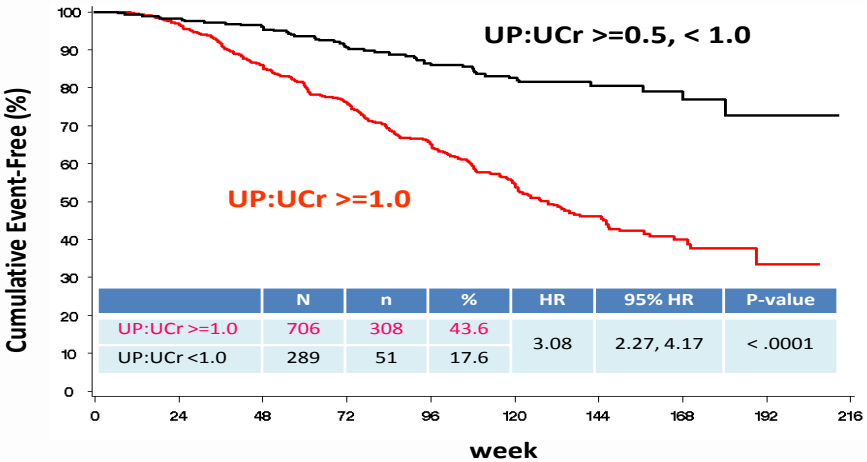
## Chronic kidney disease progression by urinary protein: urinary creatinine ratio level (pooled placebo – intent-to-treat population).



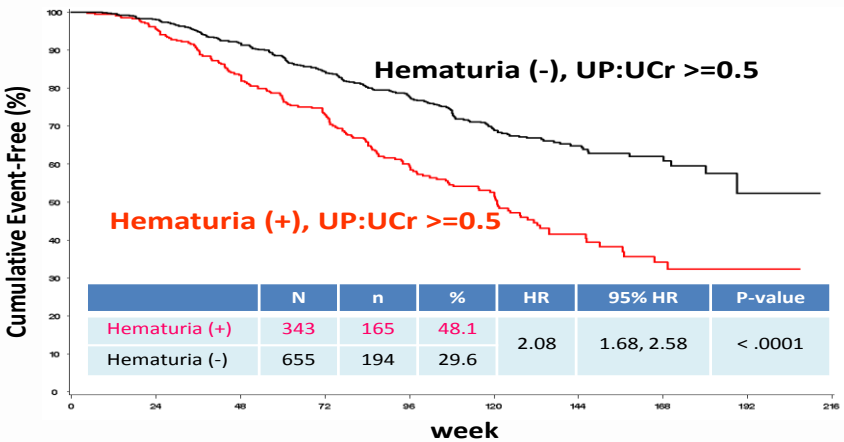




| P/CR | =>0.5,<1.0 | =>1.0,<2.0 | =>2.0,<4.0 | => 4.0 |
|---|---|---|---|---|
| umber of patients | 289 | 306 | 286 | 114 |
| imary endpoint (%) /K-M plot | 27.4 | 63.2 | 64.8 | 81.1 |

# Chronic kidney disease progression by urinary protein: urinary creatinine ratio level and hematuria (pooled placebo – intent-to-treat population).

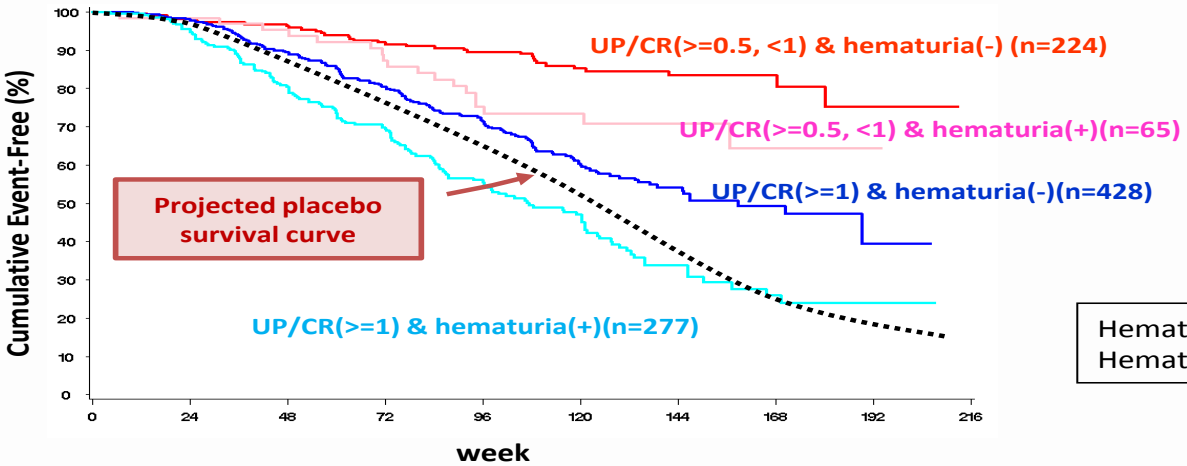



| | N | n | % | HR | 95% HR | P-value |
|---|---|---|---|---|---|---|
| UP:UCr >=1.0 | 706 | 308 | 43.6 | 3.08 | 2.27, 4.17 | < .0001 |
| UP:UCr <1.0 | 289 | 51 | 17.6 | | | |




| | N | n | % | HR | 95% HR | P-value |
|---|---|---|---|---|---|---|
| Hematuria (+) | 343 | 165 | 48.1 | 2.08 | 1.68, 2.58 | < .0001 |
| Hematuria (-) | 655 | 194 | 29.6 | | | |

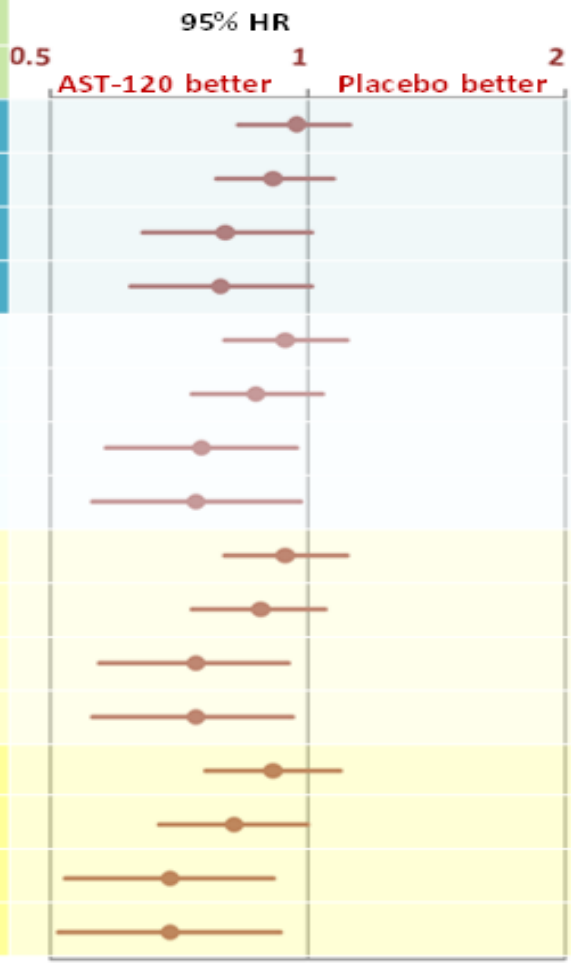
Stratified by Region; DN Yes/No; Baseline sCr ≤ 3mg/dL / >3mg/dL




Hematuria(-) : NEGATIVE
Hematuria(+) : TRACE, 1+, 2+, 3+

## Primary Endpoint in Patients with Factors Associated with Fast Progressing Chronic Kidney Disease, Study Medication Compliance ≥80%, and Baseline ACEI/ARB Use (Pooled Intent-to-Treat Population

| Sub group | | AST-120 | | | Placebo | | | P-value |
|---|---|---|---|---|---|---|---|---|
| | | N | n | % | N | n | % | |
| ITT | ALL (UP:Ucr >=0.5) | 1000 | 350 | 35 | 999 | 360 | 36 | 0.64 |
| | UP:UCr >=1 | 715 | 295 | 41.3 | 706 | 308 | 43.6 | 0.26 |
| | HU (+) (UP:Ucr >=0.5) | 357 | 144 | 40.3 | 343 | 165 | 48.1 | 0.06 |
| | UP/CR >=1 and HU (+) | 279 | 126 | 45.2 | 277 | 147 | 53.1 | 0.06 |
| ITT 80% COMP | ALL (UP:Ucr >=0.5) | 860 | 286 | 33.3 | 838 | 296 | 35.3 | 0.46 |
| | UP/CR>=1 | 603 | 237 | 39.3 | 583 | 251 | 43.1 | 0.13 |
| | HU (+) (UP:Ucr >=0.5) | 312 | 116 | 37.2 | 279 | 132 | 47.3 | 0.03 |
| | UP/CR >=1 and HU(+) | 239 | 101 | 42.3 | 223 | 116 | 52 | 0.04 |
| ACE/ ARB+ | ALL (UP:Ucr >=0.5) | 844 | 285 | 33.8 | 841 | 296 | 35.2 | 0.50 |
| | UP:UCr>=1 | 610 | 244 | 40 | 591 | 255 | 43.1 | 0.14 |
| | HU(+) (UP:Ucr >=0.5) | 303 | 113 | 37.3 | 292 | 139 | 47.6 | 0.02 |
| | UP/CR>=1 and HU(+) | 238 | 103 | 43.3 | 236 | 124 | 52.5 | 0.03 |
| ACE/ ARB + 80% COMP | ALL (UP:Ucr>=0.5) | 729 | 234 | 32.1 | 712 | 245 | 34.4 | 0.30 |
| | UP/CR>=1 | 516 | 196 | 38 | 493 | 210 | 42.6 | 0.05 |
| | HU (+) (UP:Ucr >=0.5) | 270 | 93 | 34.4 | 237 | 110 | 46.4 | 0.01 |
| | UP/CR>=1 and HU(+) | 207 | 83 | 40.1 | 188 | 97 | 51.6 | 0.02 |




ACE/ARB+ : Patients take ACE/ARB at baseline, Hematuria(+) HU(+): Trace, +1, +2, +3 at baseline

# AST-120: Future Investigation

- EFFECT ON RESIDUAL RENAL FUNCTION
  - CCPD, CAPD, PET CLASS, HEMODIALYSIS
- SYNERGY WITH OTHER AGENTS
  - RAAS BLOCKERS, PROBIOTICS, TGF-β ANTAGONISTS
- EFFECTS ON CARDIOVASCULAR EVENTS

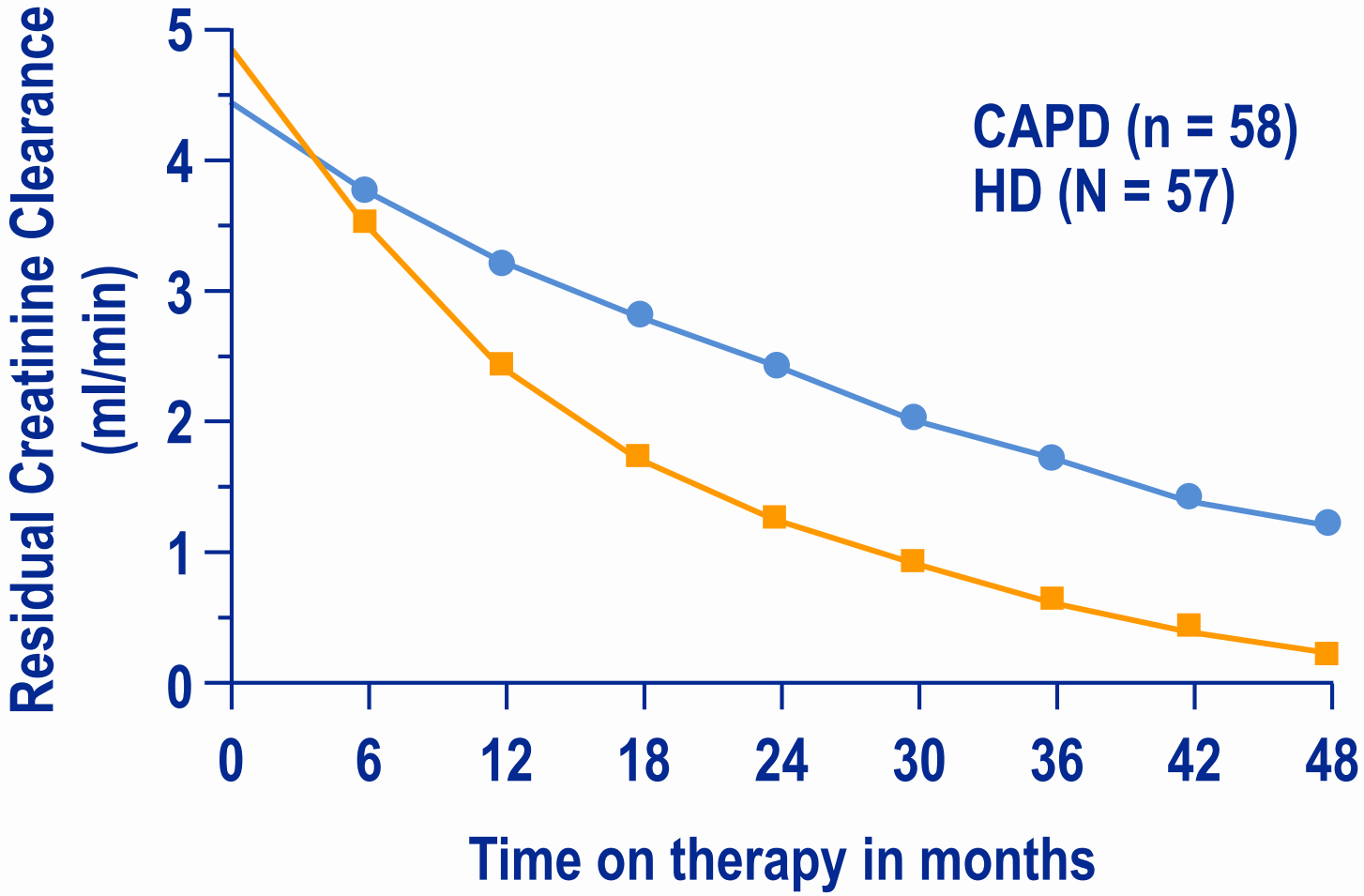
# AST-120 and Changes in Indicators of Arterial Stiffness in Japan (6 g/day)

| | 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, $p < 0.05$.

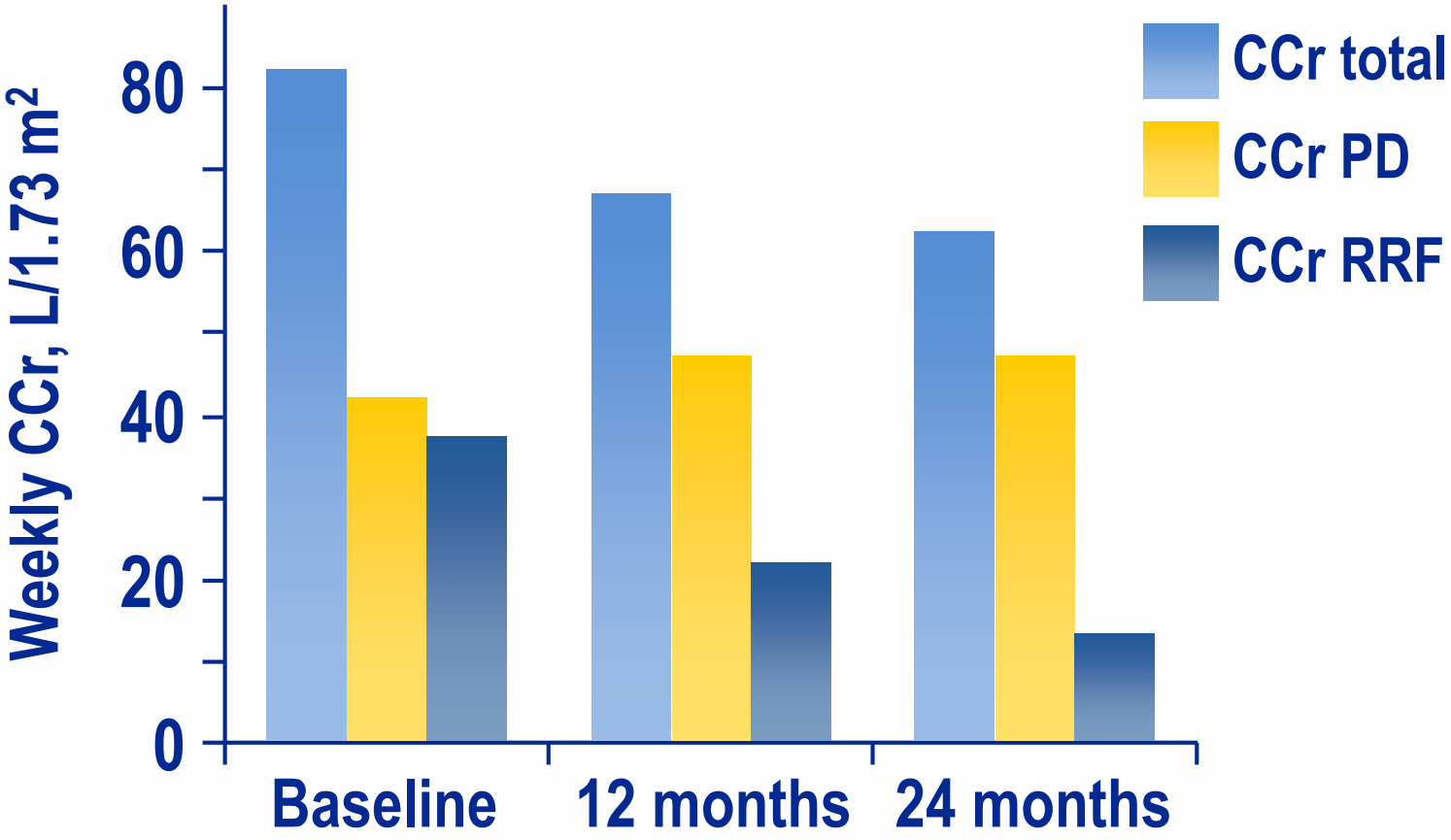
*PWV: Pulse Wave Velocity, IMT: Intima-Media Thickness*
*Nakamura T et al, Kidney Blood Press Res., 2004:27, 2004*

# Issues in Modality Selection: Residual Renal Function




Lysaght et al. ASAIO Trans. 1991;37:598-604.

# Decline in Creatinine Clearance During PD



# WHAT CAN BE DONE NEXT?

- CONSIDER ANOTHER STUDY
  - GREAT EXPENSE
  - ENRICH STUDY POPULATION BY ENSURING THAT PROGRESSORS ONLY ARE ENROLLED
  - LIBERALIZE ENDPOINTS e.g., 50% INCREASE IN CREATININE
  - INCLUDE CARDIAC ENDPOINTS
- LOOK AT AST-120 IN PRESERVING RESIDUAL RENAL FUNCTION IN DIALYSIS PATIENTS
- CONTINUE RESEARCH IN ANTI-FRIBOTIC THERAPIES