義大醫療財團法人
E-DA HEALTHCARE GROUP

After all, you may consider Dispersed Absorptive Elements (DAE) — a special form of activated charcoal

義大醫院 洪士元醫師

2020.1.11

Outline

- CKD and ESRD epidemiology
- Uremic toxins vs. CKD
- The effectiveness of AST-120 (Kremezin®)
- Comparison of uremic toxin adsorbents
  - Traditional activated charcoal
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Definition of CKD

- **Kidney damage for ≥ 3 months** with or without decreased GFR (Glomerular Filtration Rate), as confirmed by kidney biopsy or markers of damage.
  - Markers of damage: proteinuria, abnormalities on the urine dipstick or sediment examination, or abnormalities on imaging studies of the kidneys.
- **GFR < 60 mL/min/1.73 m^2 for ≥ 3 months** with or without kidney damage.
  - GFR can be estimated from prediction equations based on serum creatinine and other variables, including age, sex, race, and body size.

NKF K/DOQI Clinical Practice Guidelines, 2004

CKD staging guideline

Stage	Description	GFR (ml/min/1.73 m²)
1	**Kidney damage** with normal or ↑ GFR	>90
2	**Kidney damage** with mild ↓ in GFR	60-89
3	Moderate ↓ in GFR	30-59
4	Severe ↓ in GFR	15-29
5	Kidney failure	<15 or dialysis

NKF K/DOQI Clinical Practice Guidelines, 2004

Clearance of Creatinine(CCr)

If Cr filtrated = Cr excreted

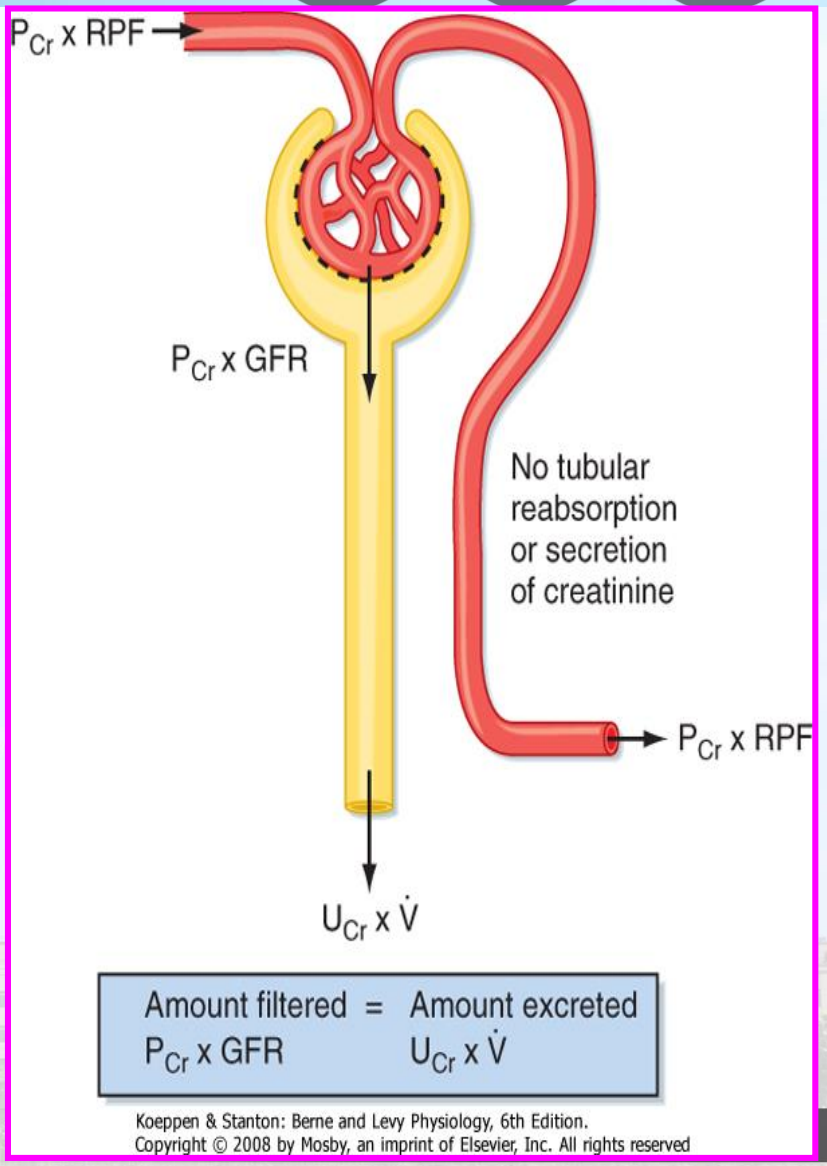
PCr x GFR = UCr x UV

GFR (ml/day) = UCr x UV / PCr

- **GFR (ml/min)**

= UCr x UV / PCr x 1440

- Ex: Cr 1.5 mg/dl, UCr 75 mg/dl, 24 hr urine 2880 ml.
  - CCr = 100 ml/min



Clinical CKD staging

MDRD-Simplified-GFR

$$= 186 \times Cr^{-1.154} \times Age^{-0.203} \times 0.742 \textit{ (if Female)} \times 1.212 \textit{ (if black)}$$

≥ 90 cc/min	89-60 cc/min	59-30 cc/min	29-15 cc/min	< 15 cc/min
Normal function + Proteinuria	Mild **deteriorated + Proteinuria**	**Moderate deterioration**	**Severe deterioration**	**Uremia**
Stage 1	**Stage 2**	**Stage 3**	**Stage 4**	**Stage 5**

By MDRD-Simplified-GFR

Male, Cr:1.8 mg/dl, 55y/o, eGFR = 41.8 cc/min – Stage 3

Female, Cr:1.8 mg/dl, 75y/o, eGFR = 29.2 cc/min – Stage 4

MDRD: Modification of Diet in Renal Disease equation

CKD risk categories

Percentage of NHANES (2013-2016) participant in each category of CKD (KDIGO 2012)

GFR categories (ml/min/1.73 m²)				Albuminuria categories			Total
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g	30-300 mg/g	>300 mg/g	
	G1	Normal to high	≥90	54.9	4.2	0.5	59.6
	G2	Mildly decreased	60-89	30.2	2.9	0.3	33.5
	G3a	Mildly to moderately decreased	45-59	3.6	0.8	0.3	4.7
	G3b	Moderately to severely decreased	30-44	1.0	0.4	0.2	1.7
	G4	Severely decreased	15-29	0.13	0.10	0.15	0.37
	G5	Kidney failure	<15	0.01	0.04	0.09	0.13
Total				89.9	8.5	1.6	100

USRDS 2018 ADR, CKD Chapter 1

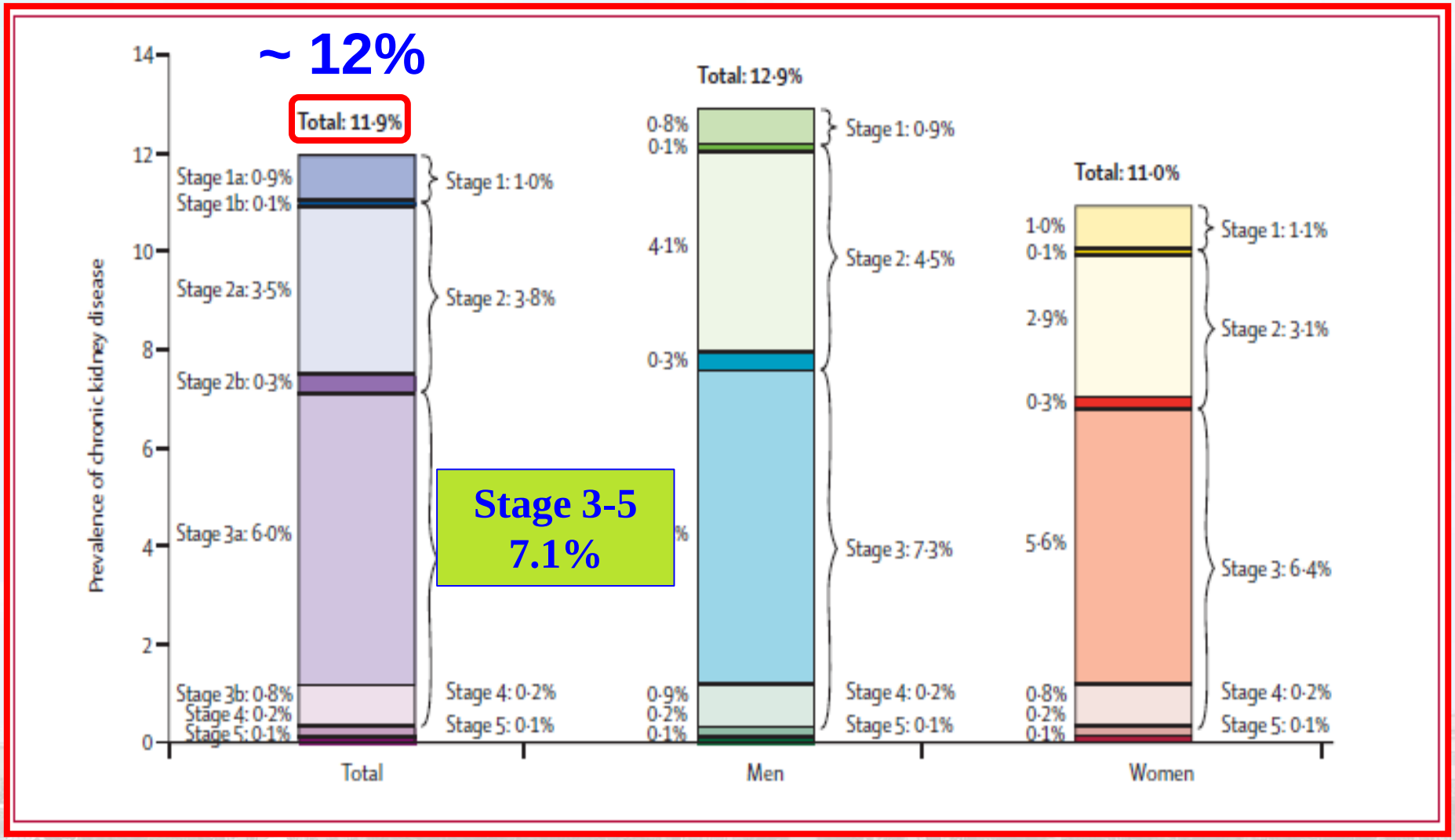
CKD prevalence, USA

Summary of prevalence in each risk category, by cohort of NHANES participants (2001-2016)

	2001-2004	2005-2008	2009-2012	2013-2016
Low risk	85.8	85.6	86.5	85.1
Moderately high risk	10.6	10.3	9.7	10.7
High risk	2.4	2.7	2.4	2.7
Very high risk	1.2	1.4	1.4	1.4
CKD prevalence	14.2	14.4	13.5	**14.8**

USRDS 2018 ADR, CKD Chapter 1

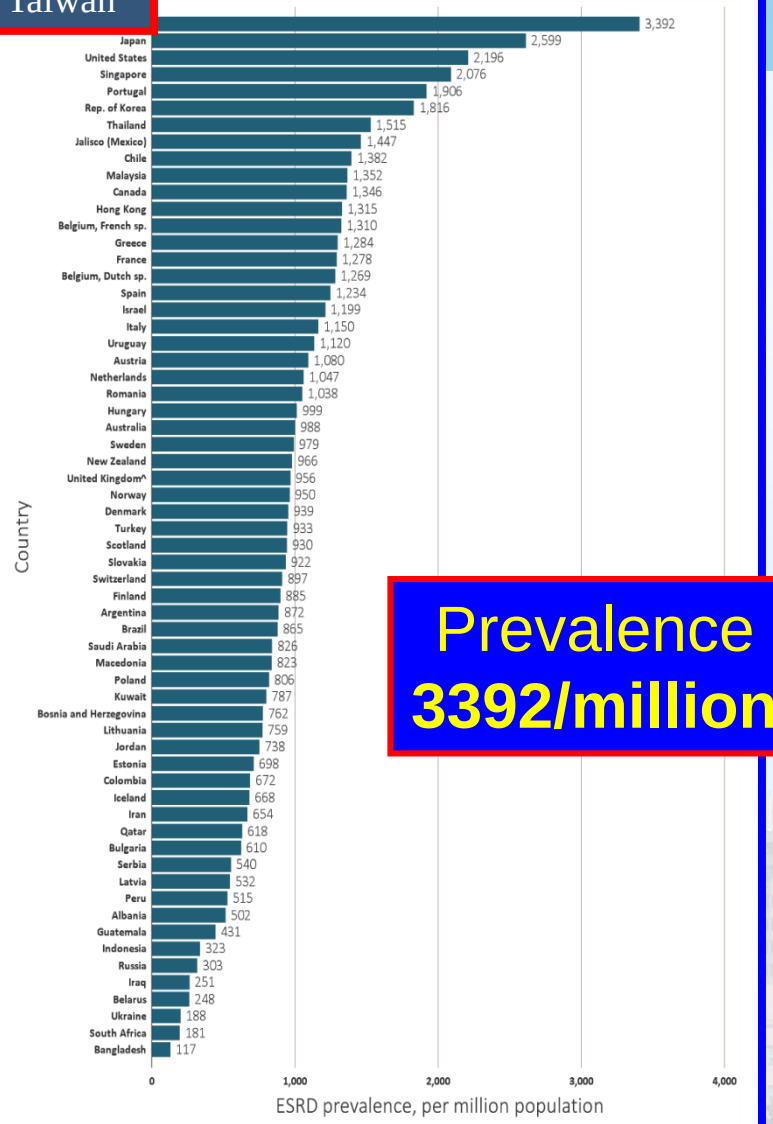
CKD prevalence, Taiwan



Wen CP. Lancet. 2008 Jun 28;371(9631):2173-82

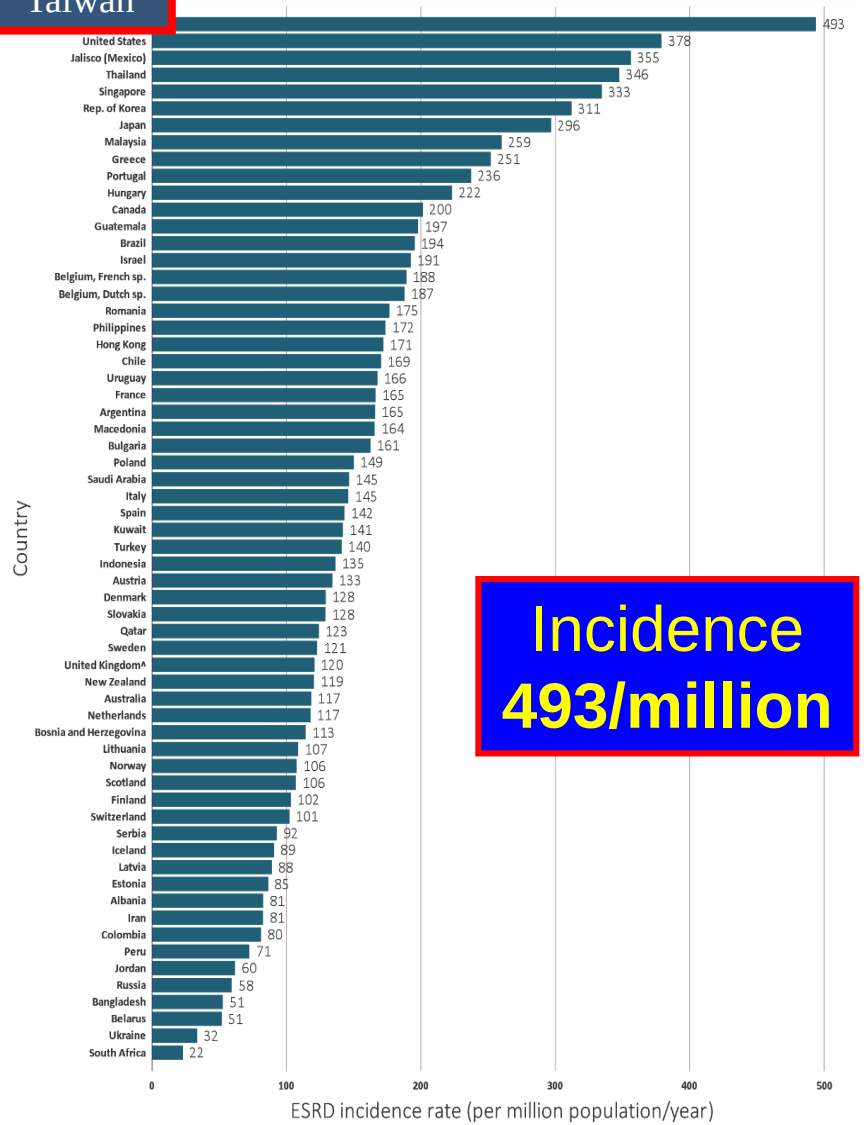
End-Stage Renal Disease (ESRD)

Taiwan



Prevalence
3392/million

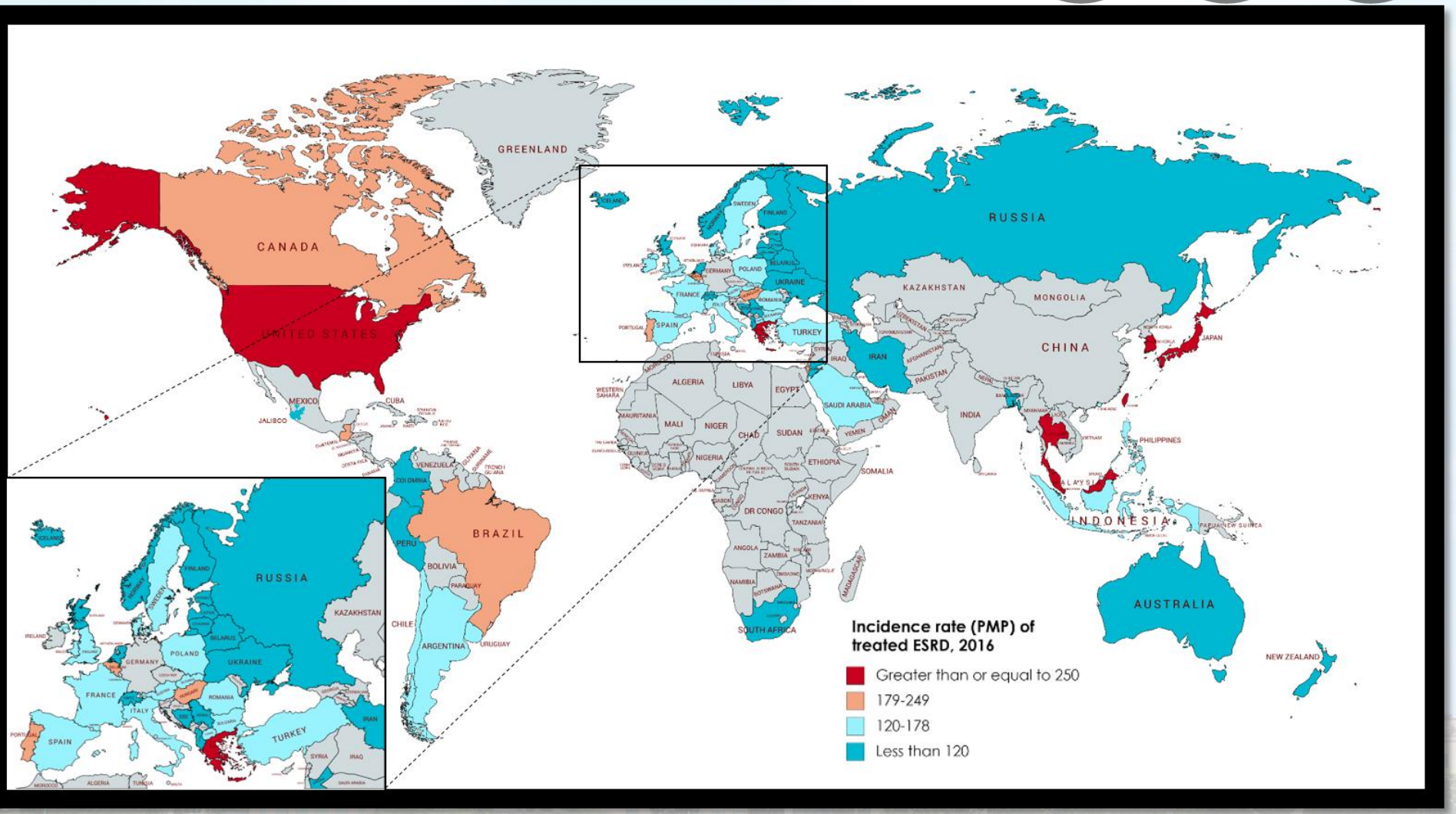
Taiwan



Incidence
493/million

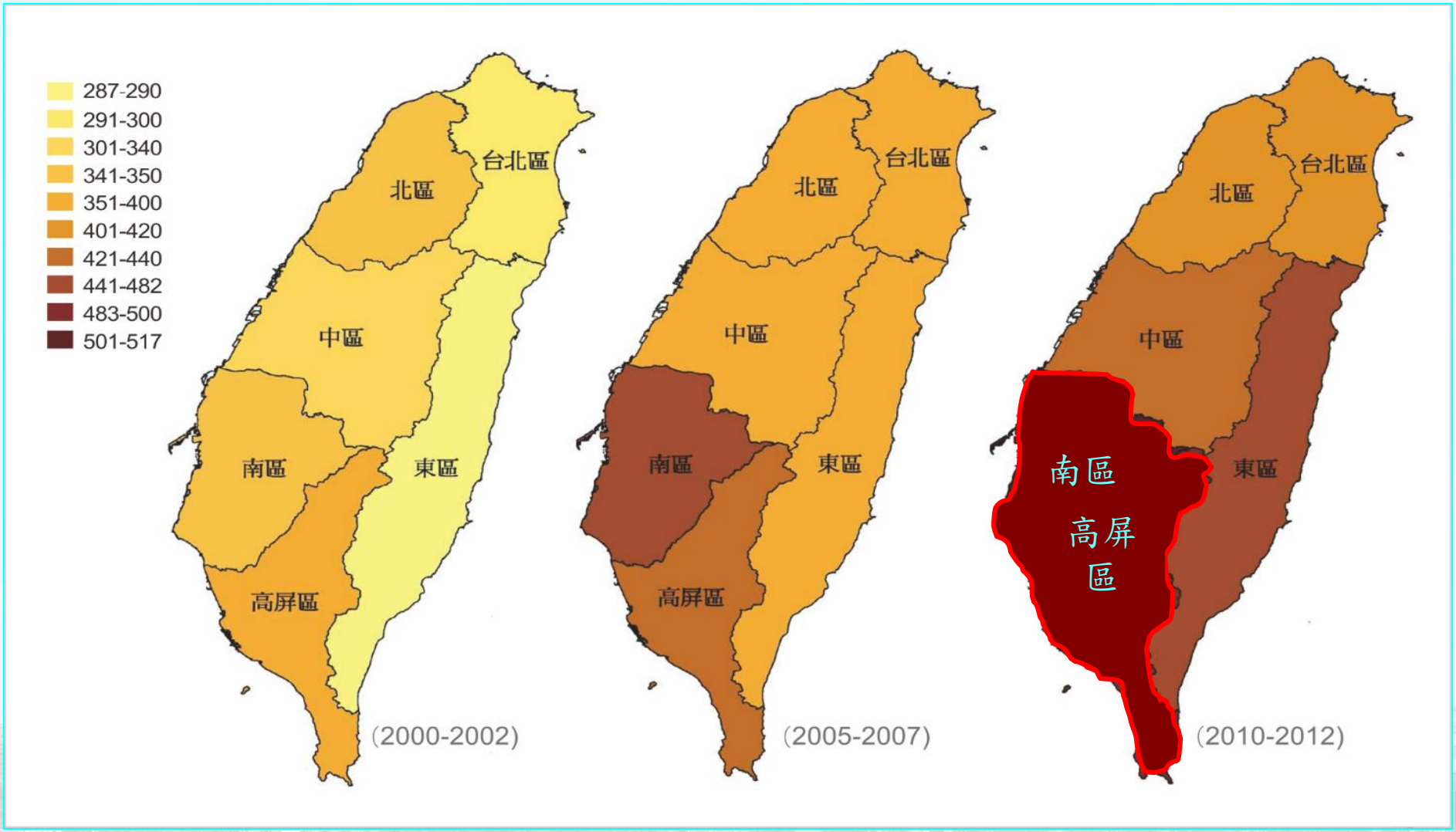
USRDS 2018 ADR

ESRD incidence



USRDS 2018 ADR

ESRD incidence, Taiwan



2014 Annual Report on Kidney Disease in Taiwan, per million

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Possible risk factors

- **Diabetes Mellitus**
- **Hypertension**
- Family history of CKD
- Hyperlipidemia
- Long-term NSAID use
- Herbs abuser (Aristolochic acid)
- Acute kidney injury
- Old age (> 65 y/o)
- Obesity; Metabolic syndrome
- Smoking
- Lifestyle factors
- Hyperuricemia or Gout
- Heavy metal
  - Lead
  - Cadmium
- Vitamin D deficiency

Taiwan chronic kidney disease clinical guideline, 2015

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- **Uremic toxins ??**

Taiwan chronic kidney disease clinical guideline, 2015

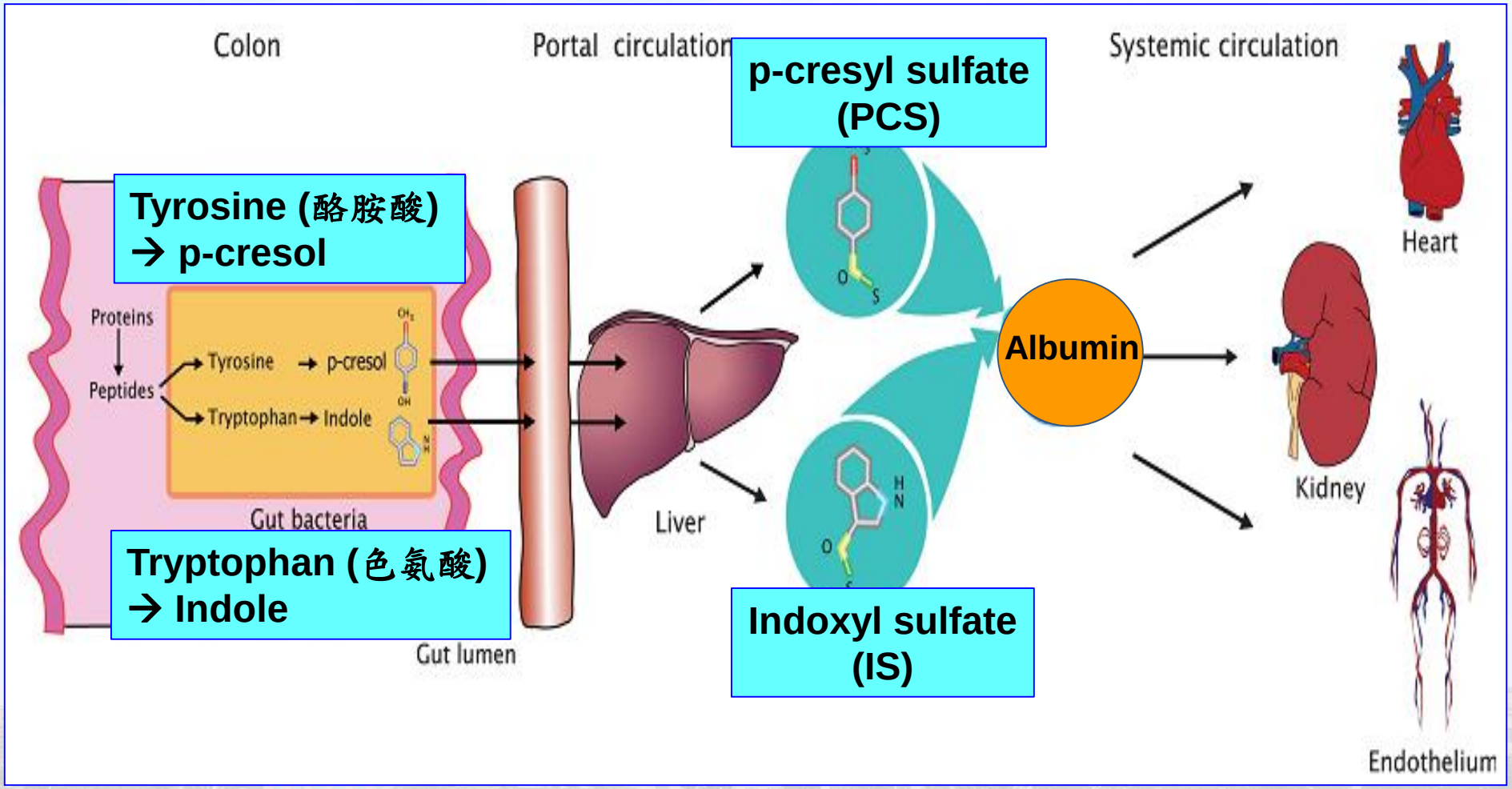
Uremic toxins

The European Toxin work group (EUTox) classification

- Small, water-soluble, non-protein bound: creatinine, urea
- Middle molecules: β2-microglobulin, peptides/proteins
- Small, protein-bound compounds: Indoxyl sulfate (IS), *p*-cresyl sulfate (PCS)
  - fermentation of tyrosine and tryptophan by intestinal microbiota generates p-cresol and indole, respectively. Both are further metabolized to p-cresyl sulfate (PCS) and Indoxyl sulfate (IS)
  - circulate in equilibrium between free solute versus bound to carrier proteins
  - tight protein binding severely limit clearances even by dialysis

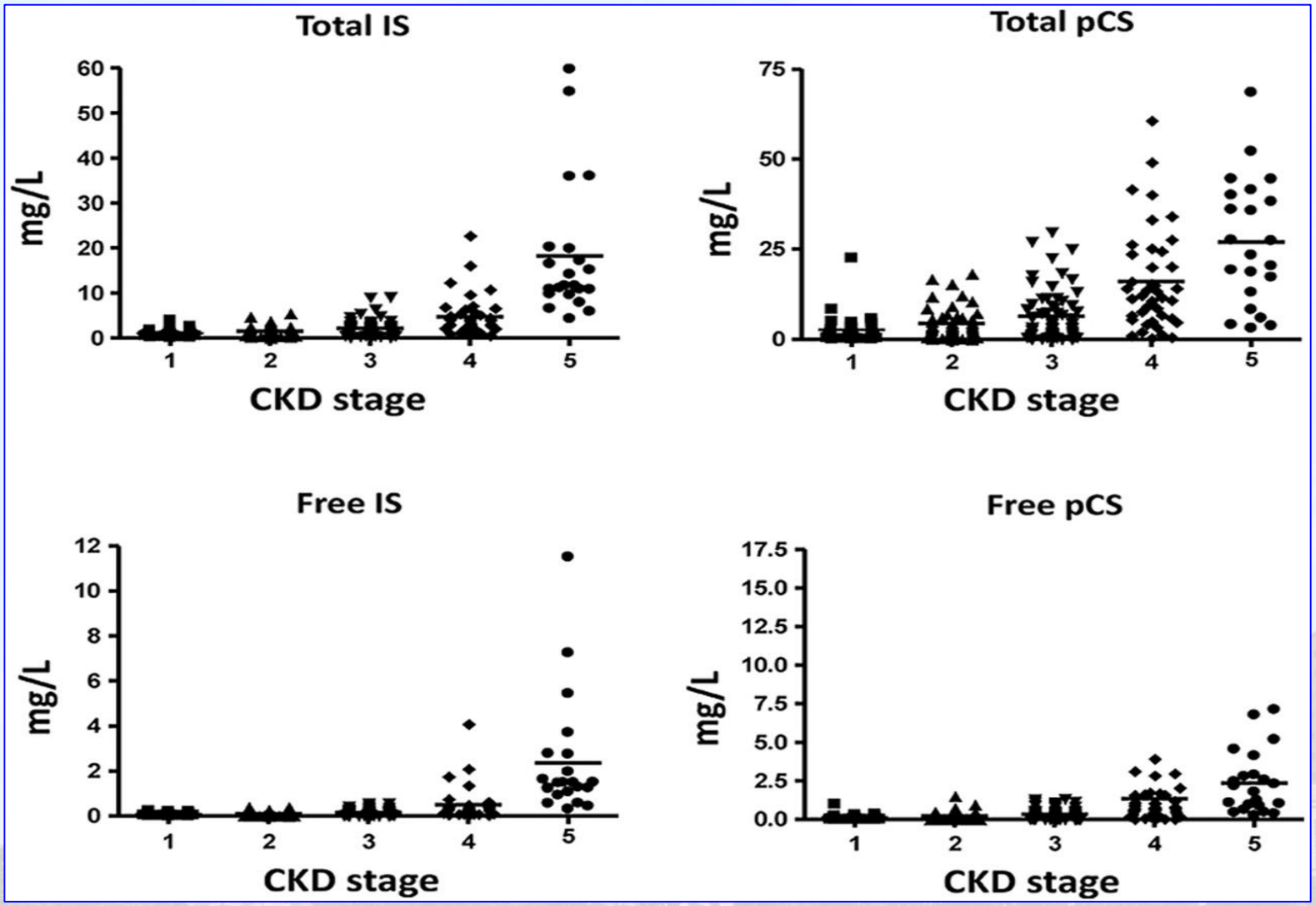
Vanholder R. Kidney Int. 2003; 63: 1934–1943
Björn K.I. Nephrol Dial Transplant. 2011: 26: 759-761

Uremic toxins



Björn K.I. Nephrol Dial Transplant. 2011: 26: 759-761

PCS and IS vs. CKD stage



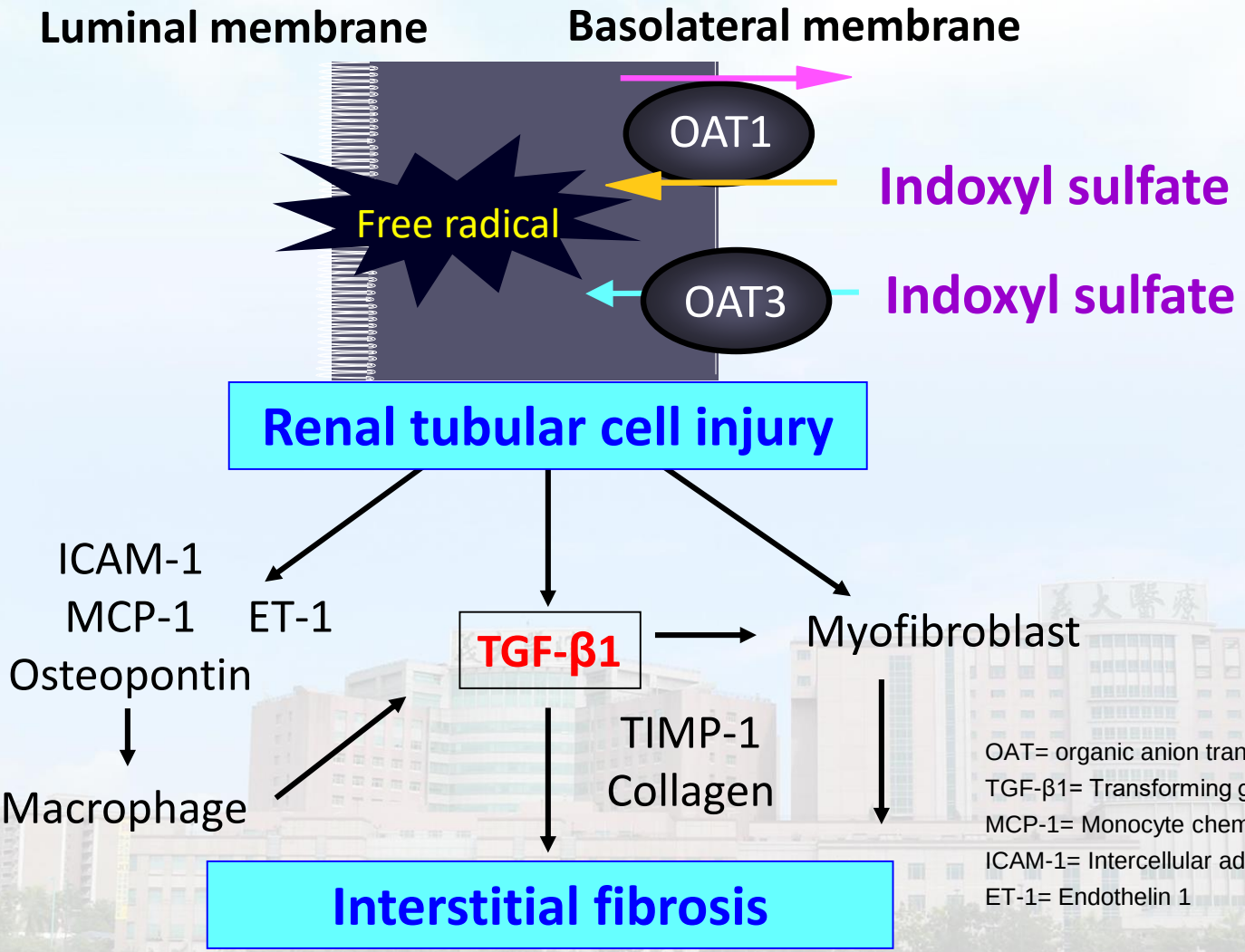
Lin CN. Journal of Food and Drug Analysis. Available online 4 December 2018

PCS and IS

- Closely correlated to
  - Renal tubular injury, interstitial fibrosis, and renal survival.
  - Endothelial cell dysfunction
  - Atherosclerosis
  - Vascular calcifications
  - T-cell mediated inflammation
  - Increase oxidative stress
  - Activate catabolism of vitamin D
  - Activate RAAS
- p-cresol (mainly reflecting PCS) correlated to overall mortality and cardiovascular disease in ESRD and CKD patients
- IS correlated to overall mortality and cardiovascular disease

Björn K.I. Nephrol Dial Transplant. 2011: 26: 759-761

IS induce Tubular Injury & Interstitial Fibrosis



OAT= organic anion transporter
TGF-β1= Transforming growth factor beta 1
MCP-1= Monocyte chemoattractant protein 1
ICAM-1= Intercellular adhesion molecule 1
ET-1= Endothelin 1

JASN 13:1711-1720, 2002; J Lab Clin Med 124:96-104, 1994

Predict CKD progression

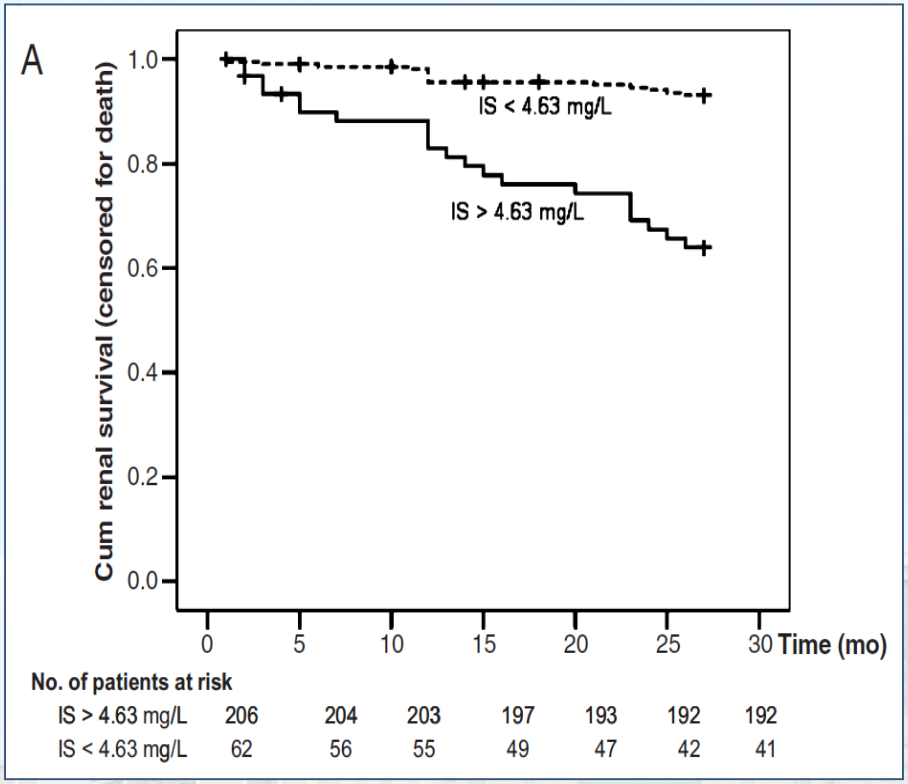
- Human study by Wu IW et al. in 2011
- 268 CKD patients, mean F/U of 21 ± 3 months
  - 35 (13.1%) had renal progression
  - 14 (5.2%) died
- High-serum PCS associated with renal progression and all-cause mortality
  - independent of **creatinine**, age, gender, diabetes, albumin, IS, Ca×P product, i-PTH, Hgb and hs-CRP
- High-serum IS associated with renal progression
  - however, the predictive power of IS was weakened when serum PCS was also present in the analytical model.

Wu IW. Nephrol Dial Transplant . 2011: 26: 938–947

Indoxyl sulfate (IS)

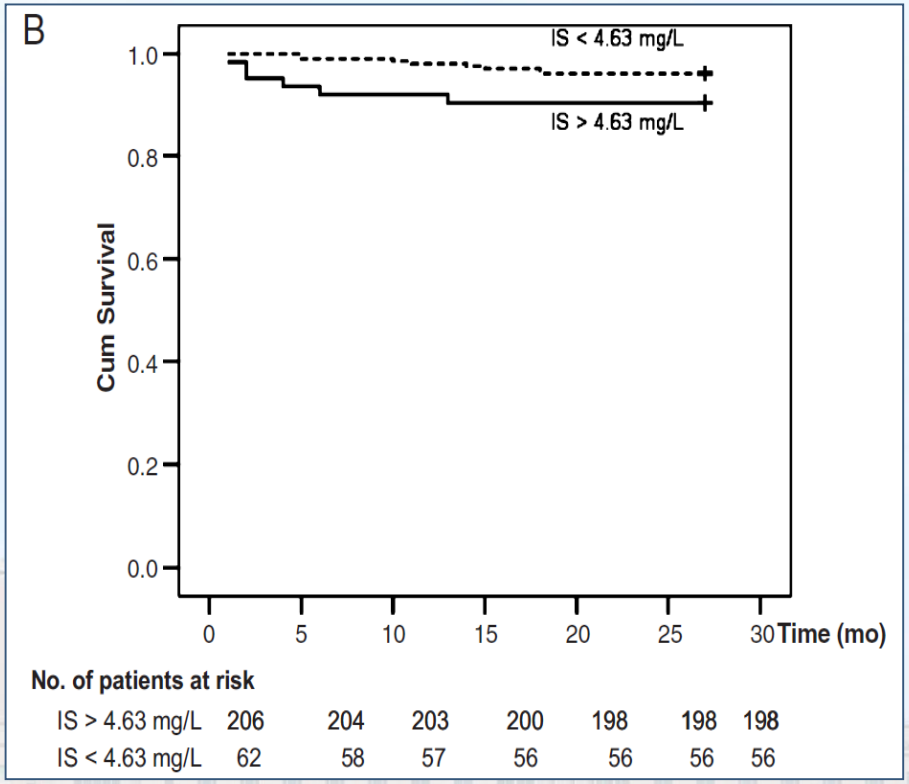
Cumulative renal survival

log-rank, P < 0.001



Cumulative survival

log-rank, P = 0.062

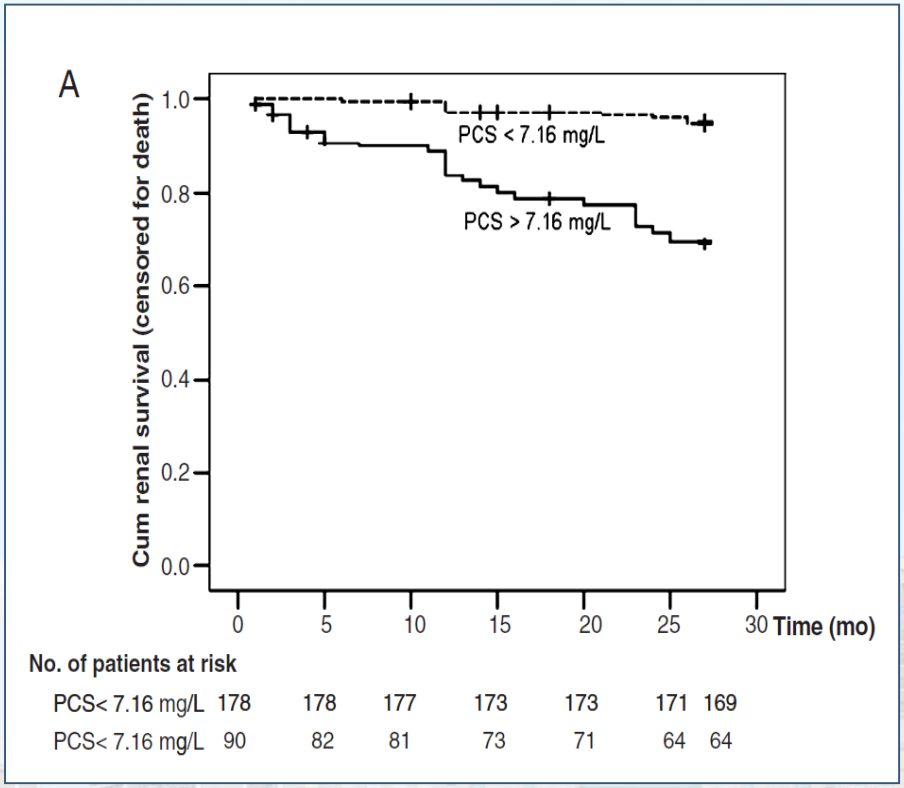


Wu IW. Nephrol Dial Transplant . 2011: 26: 938–947

p-cresyl sulfate (PCS)

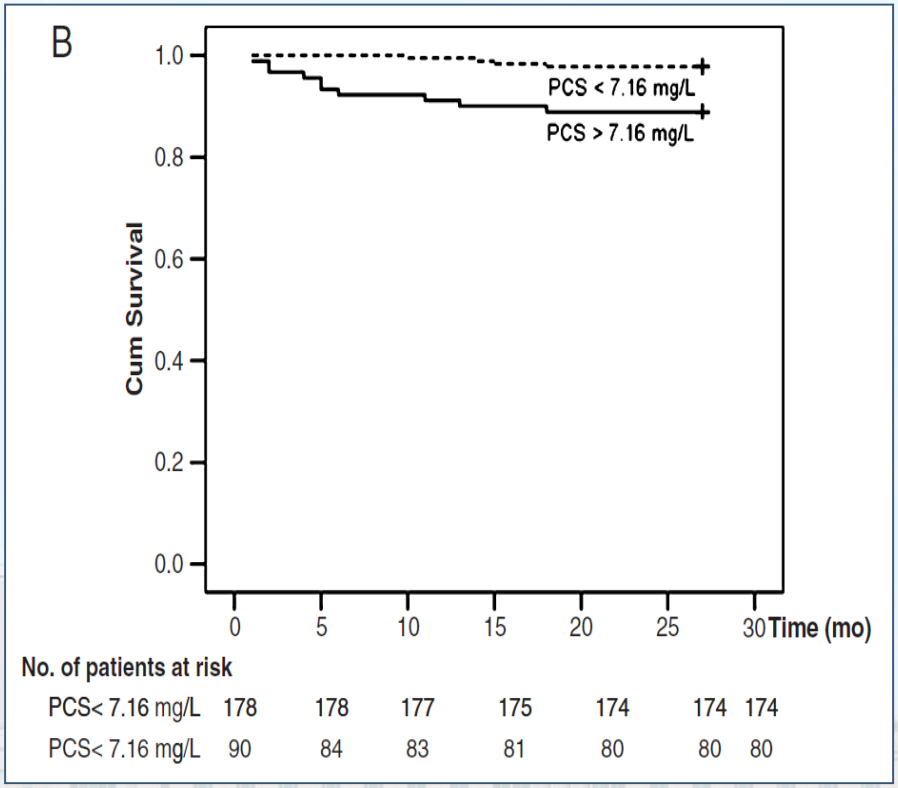
Cumulative renal survival

log-rank, P < 0.001



Cumulative survival

log-rank, P = 0.002



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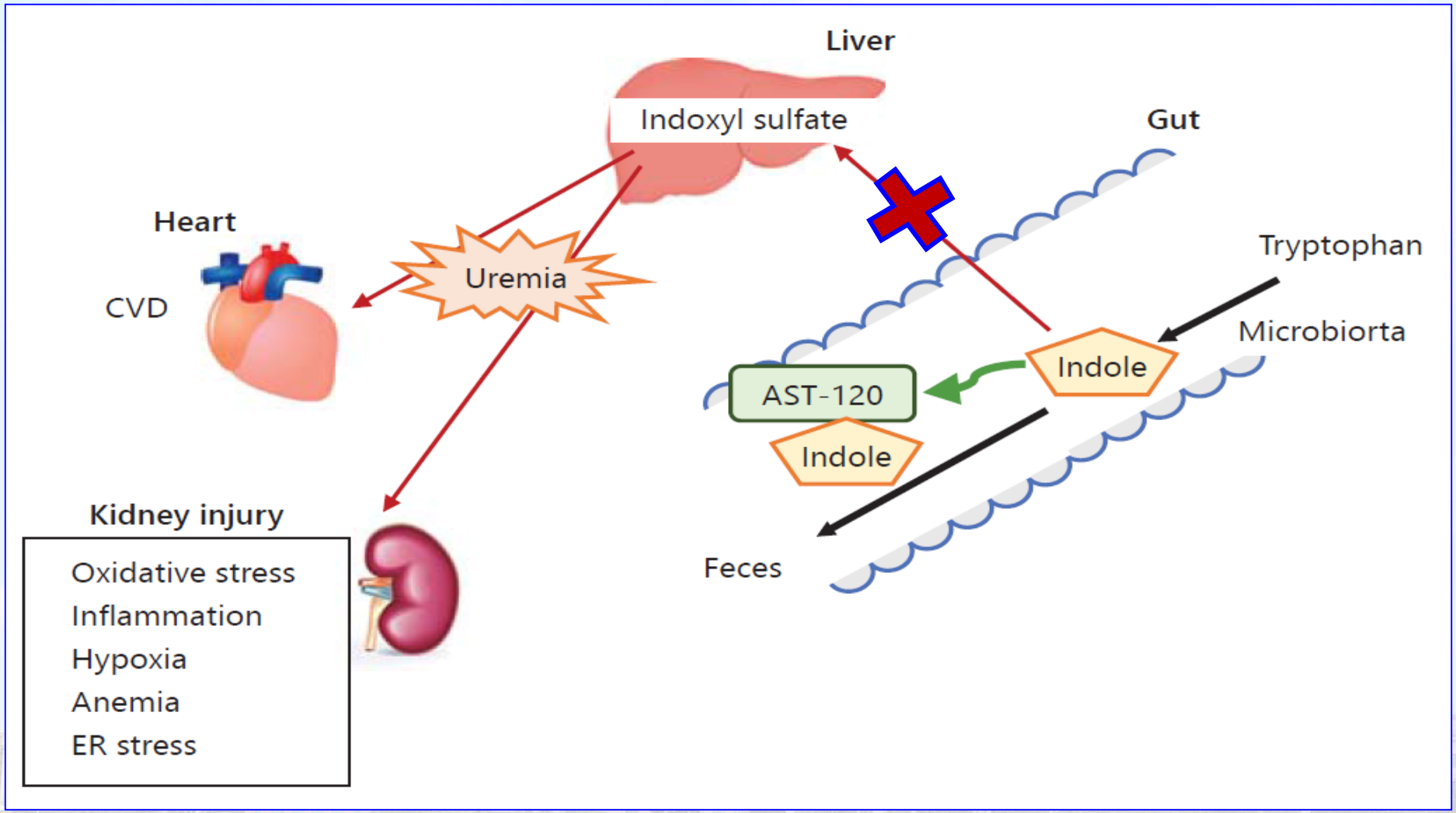
AST-120 (Kremezin®)

- Oral spherical carbon adsorbent, black, odorless, water insoluble, spherical particles, 0.2 - 0.4 mm in diameter, extensive surface area (1600 m^2/g)
- Composed mainly of carbon (approximately 96%)
- Compared to activated charcoal
  - similar or superior adsorption ability for certain acidic and basic organic compounds accumulated in renal failure
  - lower adsorption ability for digestive enzymes
  - superior adsorption ability for the precursors of IS/PCS, thus reduce IS/PCS accumulated in serum

Schulman G. J Am Soc Nephrol. 2015;26:1732–1746

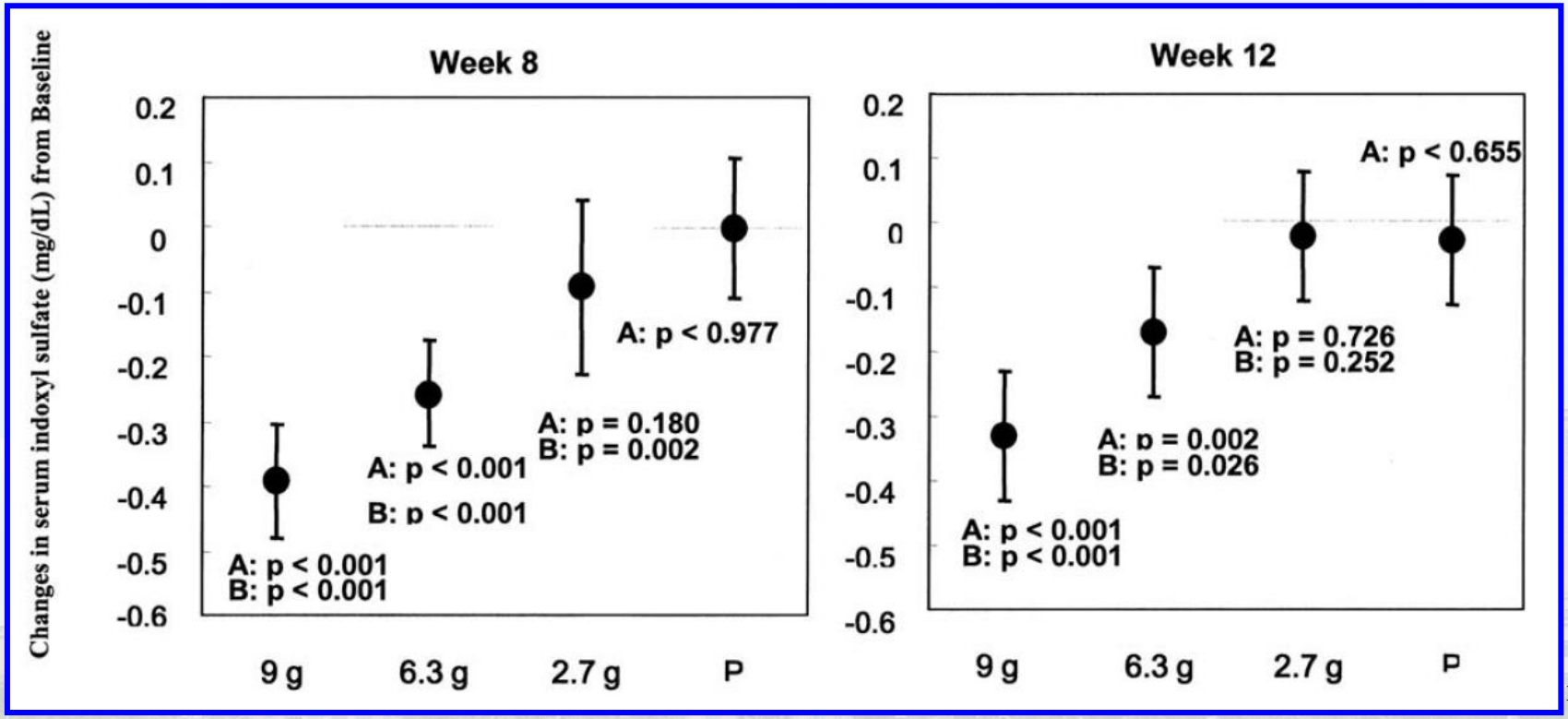
Expected action (AST-120)



Yamaguchi J. Nephron. 2017;135(3):201-06.

Dose-dependent IS reduction

- A multicenter, randomized, double-blind,placebo-controlled study in USA, 2003-4
- 164 patients taking AST-120, sCr: 3.0-6.0 mg/dl.



Schulman G. Am J Kidney Dis. 2006;47:565–577.

AST-120 Phase III trial -1

- The first phase III trial, 1982-3, Japan
- 156 patients with CKD at 25 hospitals, sCr 5-8mg/dL.
- AST-120 or a placebo for 24weeks, in addition to conventional Tx
- 3.6 g/day for the first 4weeks, and then 5.4 g/day for 4 weeks, and then up to 7.2 g/day at the investigator's discretion.
- After 24weeks, there were no differences with regard to
  - hemodialysis score, final sCr improvement and final Hct improvement.
- Post-hoc analysis, focused on the patients with fast progression
  - 25 in the AST-120 group and 28 in the placebo group
  - a significant attenuation in the 1/Cr slope over the course in the AST-120 group
  - suggest assess the efficacy of AST-120 in patients with fast-progressing CKD

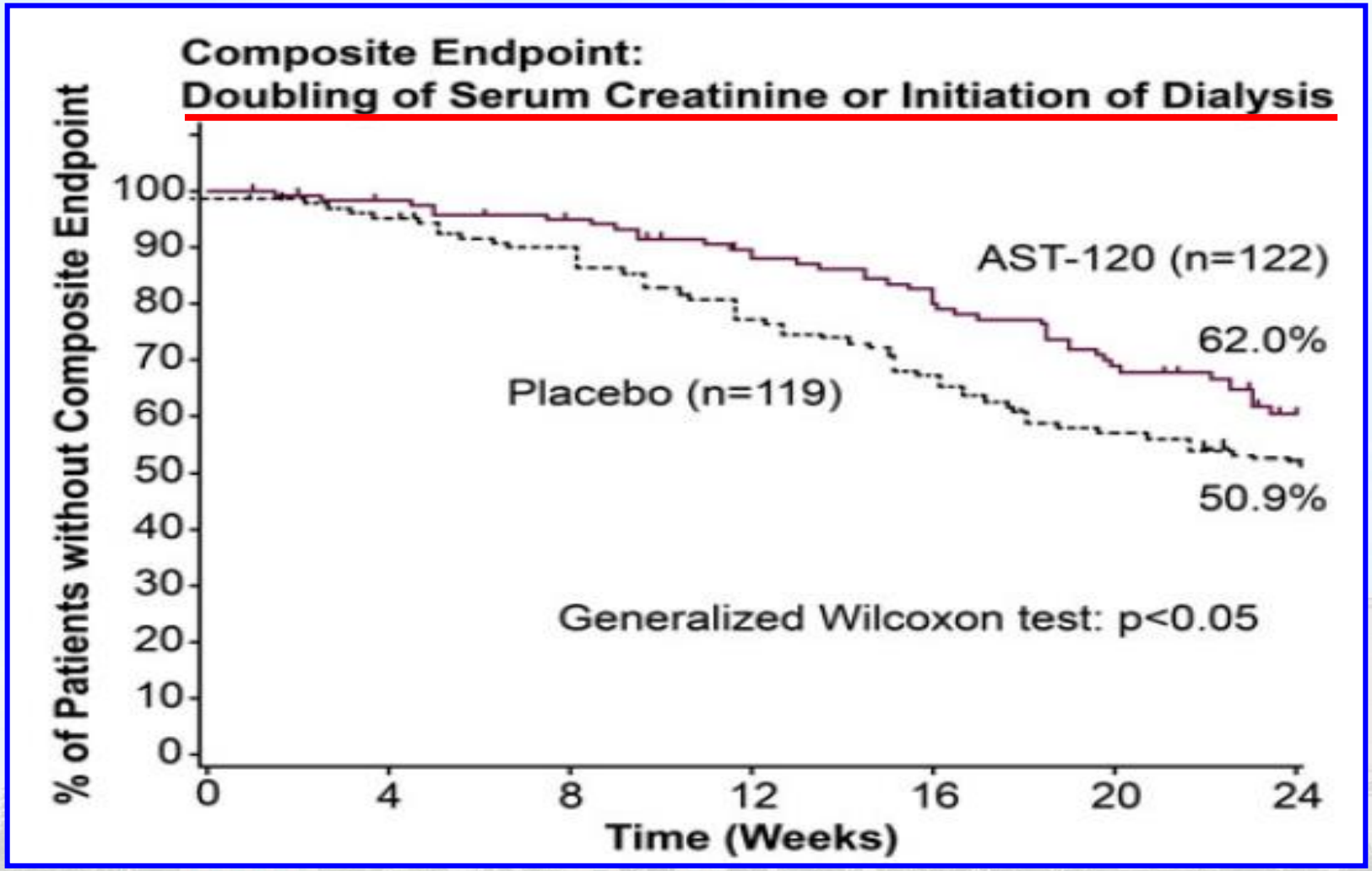
Koide K. Clin Eval. 1987;15:487–525.

AST-120 Phase III trial -2

- The second phase III trial, 1984-6, Japan
- Add a 24week observation period prior to the 24week double-blind treatment phase
- Enrollment : sCr 5-8mg/dL, as well as an increase in sCr of 1.2 mg/dL during the 24week observation period
- 244 patients with CKD from 41 hospitals
- Receive AST-120 or a placebo in addition to conventional Tx.
- AST 4.2 g/day for the first 2weeks, then increased to 6.0 g/day.
- Results showed that AST-120 group
  - improve in the change of 1/Cr (43% vs. 24%, p<0.01)
  - improve in uremic symptoms (22% vs. 8%, p<0.01)
  - No significant difference in overall safety rating and adverse events

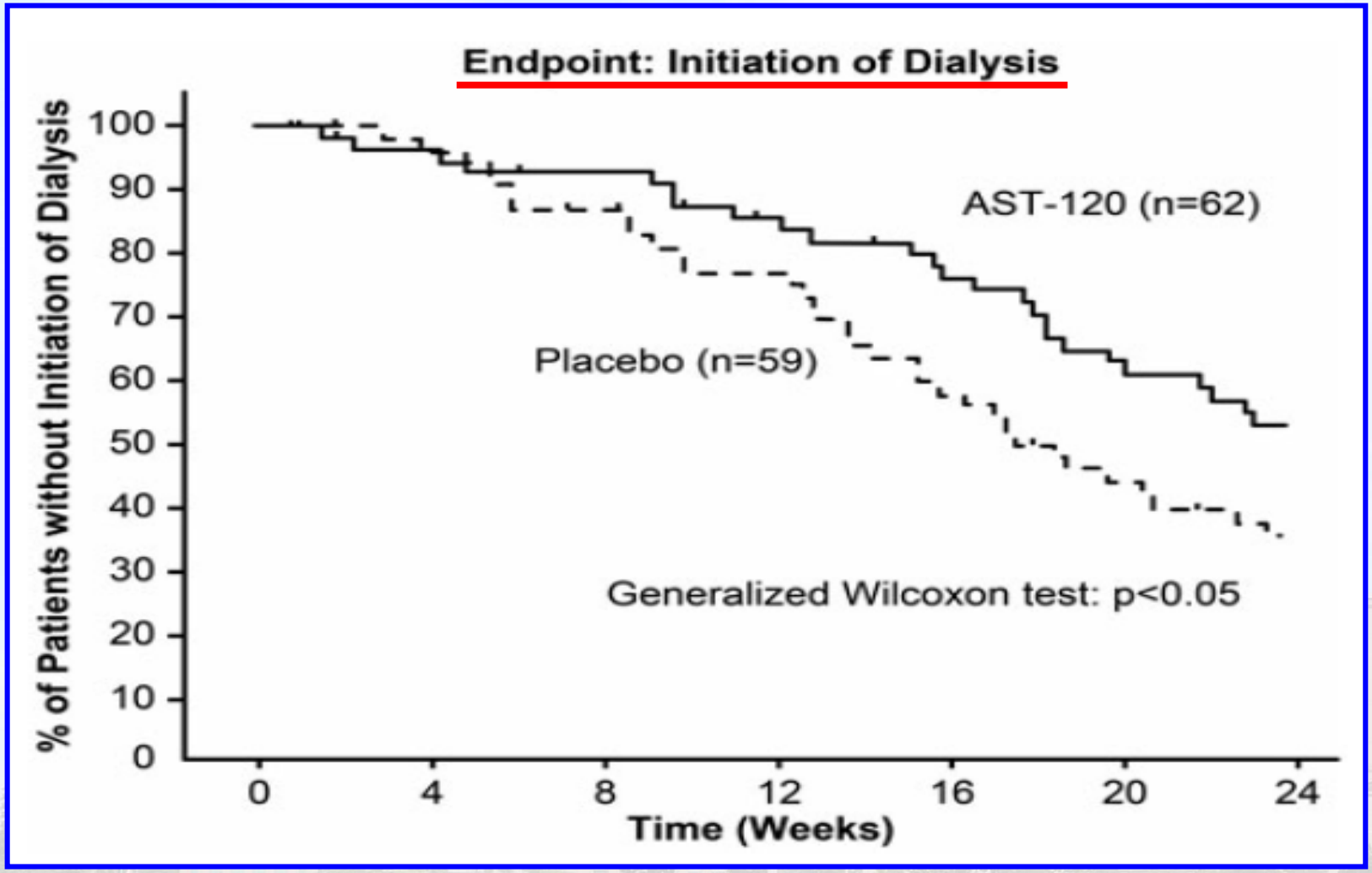
Koide K, Clin Eval. 1987;15: 527–564

AST-120 Phase III trial -2



Koide K, Clin Eval. 1987;15: 527–564

AST-120 Phase III trial -2



Koide K, Clin Eval. 1987;15: 527–564

AST-120（Kremezin®）

- Based on phase III trial, AST-120 was approved in **Japan** in **1991**
  - **For treating uremic symptoms**
  - **Prolonging the time to the initiation of dialysis** in CKD patients
- AST-120 was approved upon post-marketing reexamination in Japan in **1998**
- Approved subsequently
  - Korea, 2005
  - **Taiwan, 2007**
    - 緊急治療藥物或化學品中毒之病人
    - 吸附干擾胃腸道的細菌性毒素、消化性毒素及其他有機性廢物、解除腸內滯留氣體及有關症狀
  - Philippines, 2010

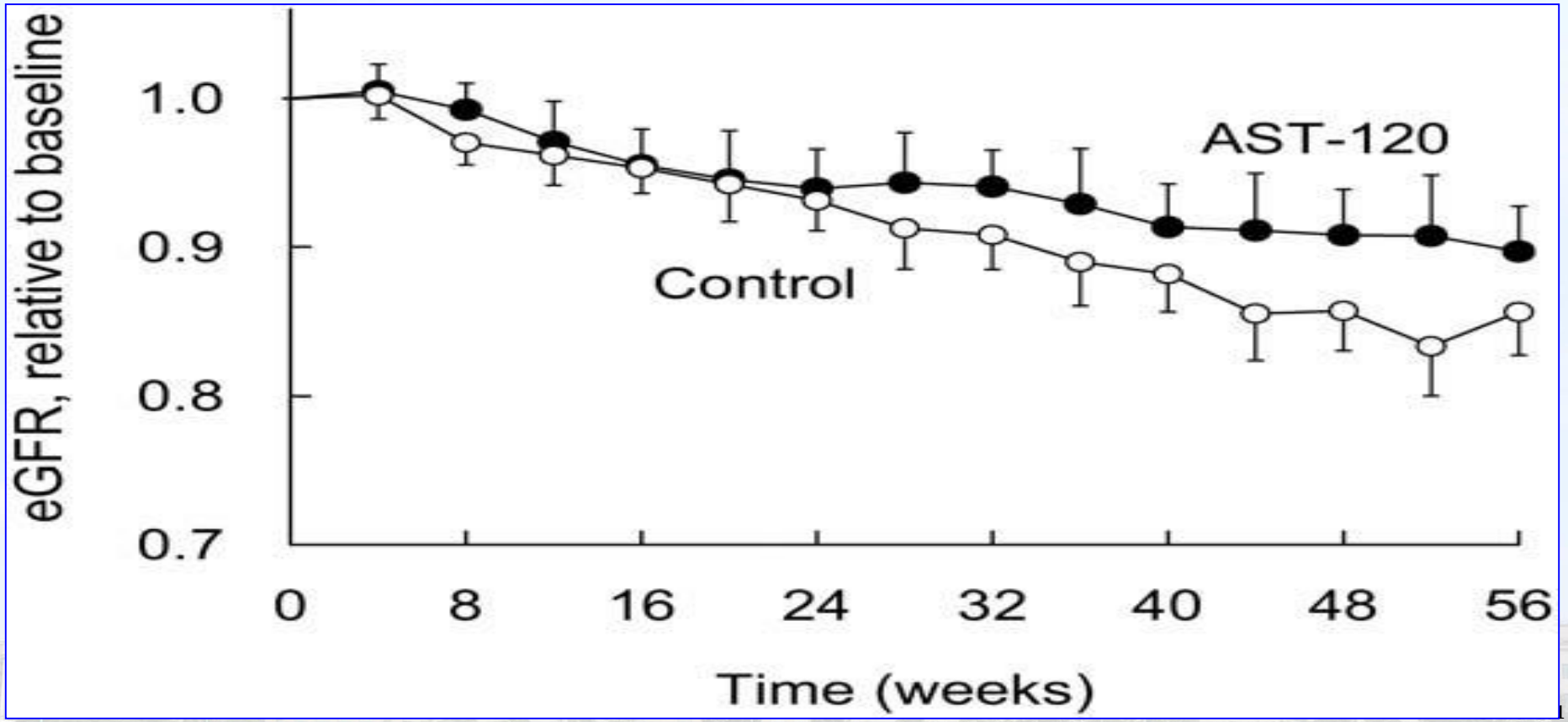
CAP-KD study

- Carbonaceous oral Adsorbent's effects on Progression of CKD (CAP-KD)
- 75 medical facilities in Japan, **2004-7**
- 460 patients with CKD (**Cr< 5.0mg/dL**, not undergoing dialysis).
- **2 groups**
  - Intervention: low-protein diet, anti-HT, and AST-120 (6 g/d)
  - Control: low-protein diet and anti-HT
- **Results:**
  - 1 year primary end-point events and event-free survival: no difference
  - eGFR decreased more in the control group than in the AST-120 group (0.15 versus 0.12 mL/min/y; *P* = 0.001).
- **Conclusion:**
  - AST-120 **did not** slow the progression of kidney disease in patients with moderate to severe CKD during 1 year

Akizawa t. Am J Kidney Dis 2009: 54:459-467.

CAP-KD study

- Estimated GFR decreased more in the control group than in the AST-120 group (0.15 versus 0.12 mL/min/y; *P* = 0.001).



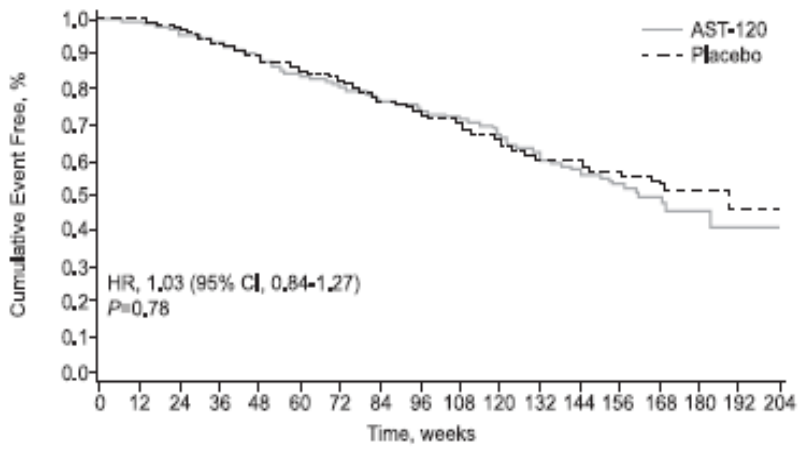
Akizawa t. Am J Kidney Dis 2009: 54:459-467.

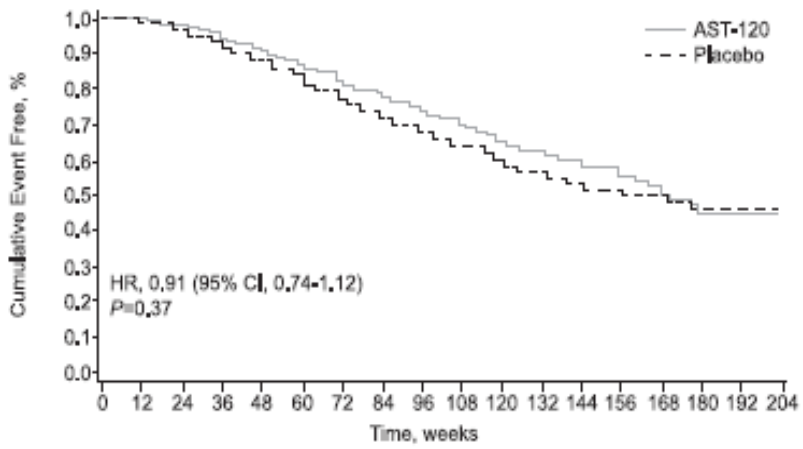
EPPIC-1 & 2 study

- Evaluating Prevention of Progression In CKD (EPPIC) trial
- Multinational, randomized, double-blind, placebo-controlled EPPIC-1 and EPPIC-2 trials in North America, Latin America and Europe, 2007-12
- 2035 CKD patients, sCr at screening, 1.5-5.0 mg/dL
- HT patients should take ACEi/ARB unless contraindicated
- AST-120 (9 g/day) vs. placebo, in 96 weeks
  - No difference in primary endpoint: a composite of dialysis initiation, kidney transplantation and sCr doubling (in each trial or pooled analysis)
  - A significant difference in the change of eGFR from baseline, p=0.04

Schulman G. J Am Soc Nephrol. 2015;26:1732–1746

Cumulative event-free





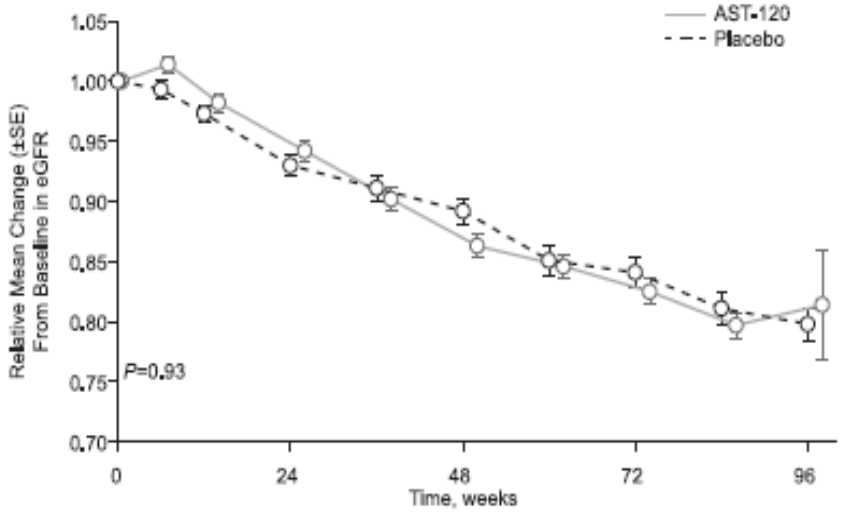
Patients at risk, n

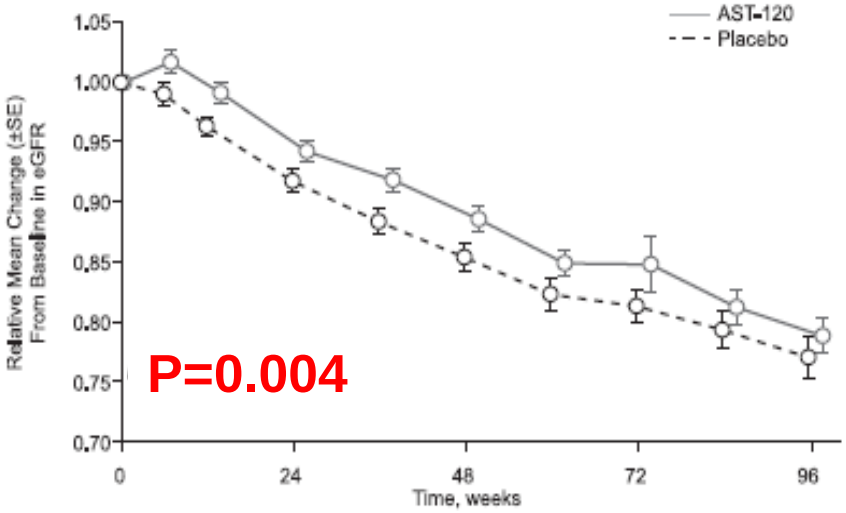
AST-120	500	494	470	451	416	386	365	343	326	269	191	135	91	49	29	14	6	1
Placebo	502	500	472	441	416	392	373	342	318	263	205	142	93	63	38	19	8	3

Patients at risk, n

AST-120	500	496	483	461	433	402	372	348	285	222	186	141	103	73	48	23	8	3
Placebo	497	483	457	435	404	366	335	303	254	196	159	116	83	58	40	20	3	1

Change of eGFR from baseline





Patients with eGFR data, n

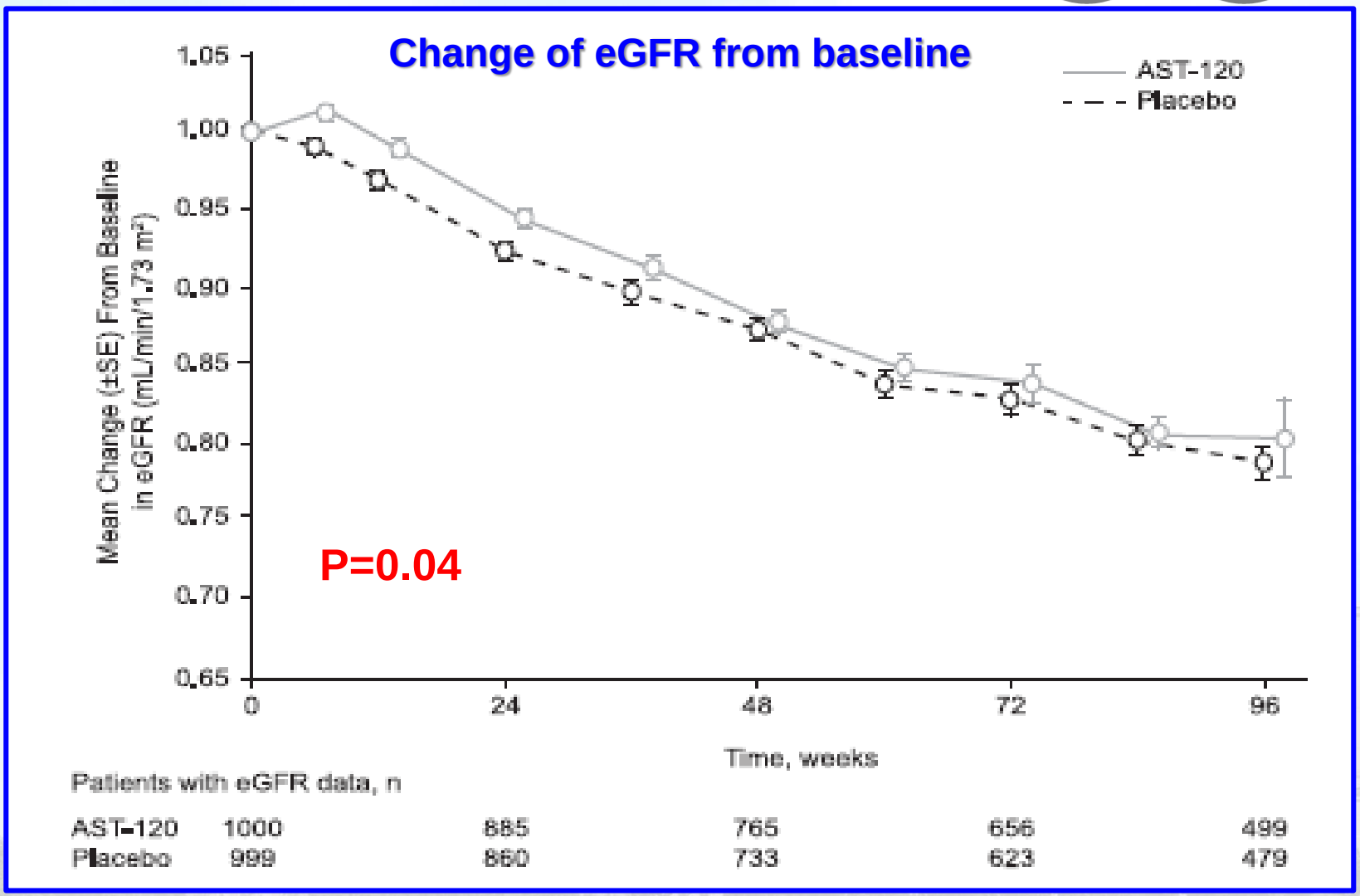
AST-120	500	436	374	317	263
Placebo	502	429	362	317	268

Patients with eGFR data, n

AST-120	500	449	391	339	236
Placebo	497	431	371	306	211

Schulman G. J Am Soc Nephrol. 2015;26:1732–1746

Pooled EPPIC-1 & 2



Schulman G. J Am Soc Nephrol. 2015;26:1732–1746

Post hoc analysis

- Focus on CKD progression and to determine the risk factors for the primary endpoint in the EPPIC I & II trial
- Placebo population analysis
  - baseline UPCR >= 1.0 and hematuria were independent risk factors for event occurrence and eGFR lowering
- High risk patients analysis (UPCR >= 1.0 and hematuria)
  - Reduced primary endpoint in AST-120 group, if ACEi /ARB were administered (HR:0.74, p=0.026)
  - Smaller GFR changes from baseline in AST-120 group (P = 0.035).

Schulman G. Clin Exp Nephrol, 2018;22:299–308.

Post hoc analysis

ACEI/ARB	Hematuria	UP/UCr	AST-120			Placebo			HR (95% CI) log scale	HR (95%CI)	P-value
			N	n	%	N	n	%	0.2 1 5		
ITT (censored at last contact)			1000	350	35.0	999	360	36.0	Favors AST-120 / Favors Placebo	0.97 (0.83,1.12)	0.64
Yes	Positive	All	303	113	37.3	291	139	47.8		0.74 (0.57,0.95)	0.02
		≥1.0	238	103	43.3	236	124	52.5		0.74 (0.56,0.96)	0.03
		<1.0	65	10	15.4	55	15	27.3		0.58 (0.25,1.36)	0.21
	Negative	All	541	172	31.8	546	156	28.6		1.11 (0.89,1.38)	0.36
		≥1.0	372	141	37.9	354	130	36.7		1.01 (0.79,1.29)	0.94
		<1.0	169	31	18.3	192	26	13.5		1.36 (0.78,2.37)	0.27
No	Positive	All	53	31	58.5	51	26	51.0		1.57 (0.85,2.90)	0.15
		≥1.0	41	23	56.1	41	23	56.1		1.95 (0.94,4.05)	0.07
		<1.0	12	8	66.7	10	3	30.0		0.80 (0.16,4.08)	0.79
	Negative	All	101	34	33.7	106	37	34.9		0.96 (0.59,1.56)	0.87
		≥1.0	64	28	43.8	74	30	40.5		1.33 (0.76,2.34)	0.32
		<1.0	37	6	16.2	32	7	21.9		0.33 (0.08,1.47)	0.15

Schulman G. Clin Exp Nephrol, 2018;22:299–308.

Outline

- CKD and ESRD epidemiology
- Uremic toxins vs. CKD
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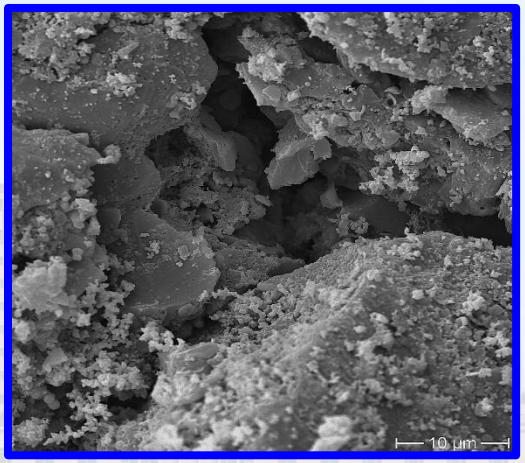
Charcoal, activated or not

- **Charcoal**
  - a lightweight porous black carbon residue produced by removing water and volatile constituents from animal and plant materials
  - produced by slow pyrolysis (熱解), heating in the absence of oxygen
- **Activated Charcoal**
  - created when ordinary charcoal is heated to a very high temperature
  - the elements and compounds bound with the carbon atoms are removed, and all the binding sites for carbon are “free”
  - a lot of activated carbon surface carbonyl groups (C=O), carboxyl groups (COOH), phenolic hydroxyl groups and lactone groups (C-O-C), so it can adsorb organic matters
  - much more porous and absorptive than ordinary charcoal, has a number of medicinal and industrial uses

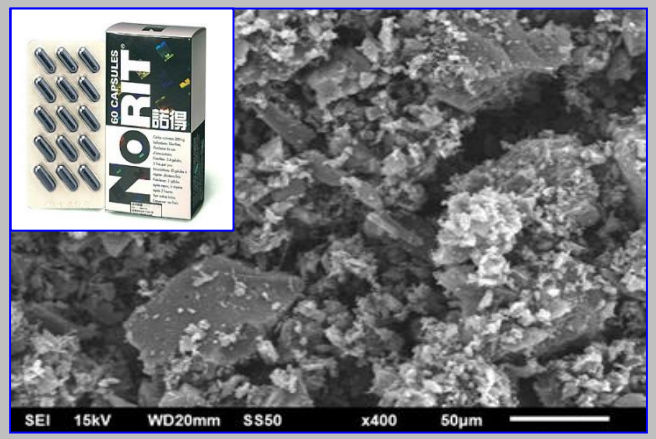
Characteristic	Charcoal	Activated charcoal
Nature	Carbon residue of dehydrated, burned organic material	Carbon residue of dehydrated, burned organic material that has been heated to a very high temperature
Porosity	More porous than most other forms of carbon	Even more porous than charcoal
Temperature	Always involves high temperatures	Involves even higher temperatures than charcoal
Uses	Metallurgy, cooking, and filtering	Medicine and removal of toxins

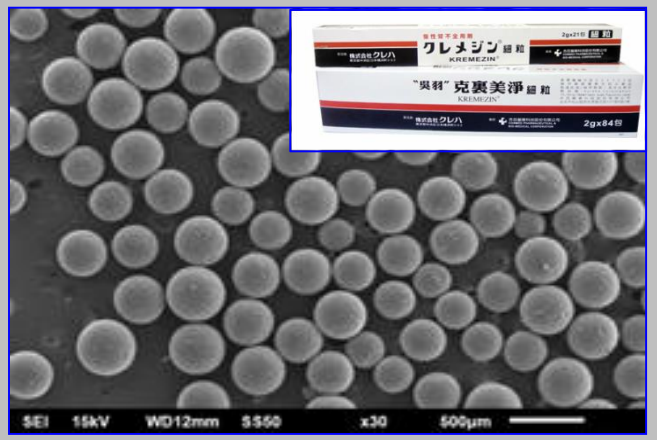
DB Difference Between.net



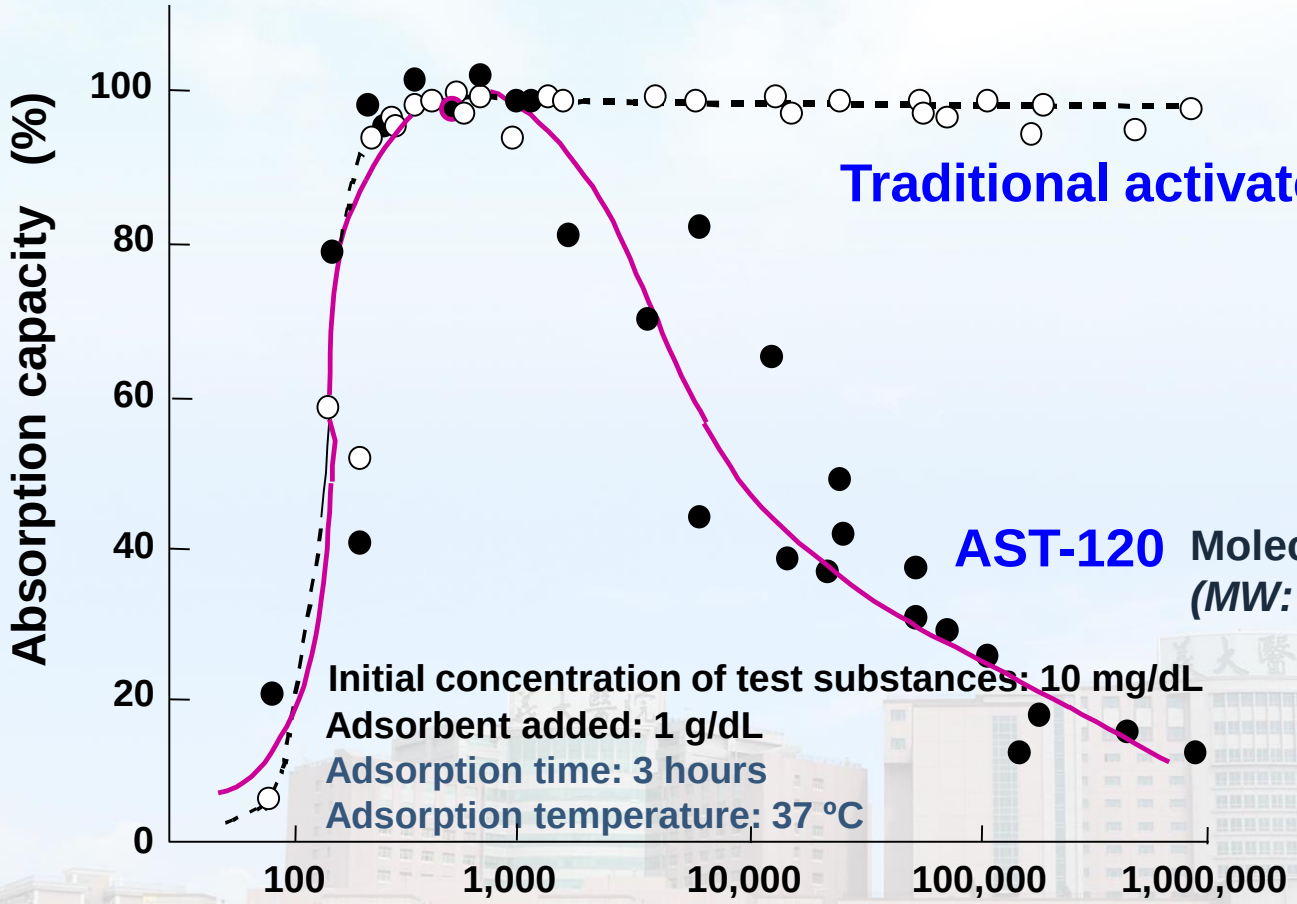
Activated charcoal

Product	Norit (諾得膠囊)	Kremezin (AST-120)
Shape	Irregular particles	Spherical
Adsorption	Non-selective	Selective
Material	Peat, Wood, Lignite, Coal, Coconut shells, Olive pits	Asphalt (瀝青)



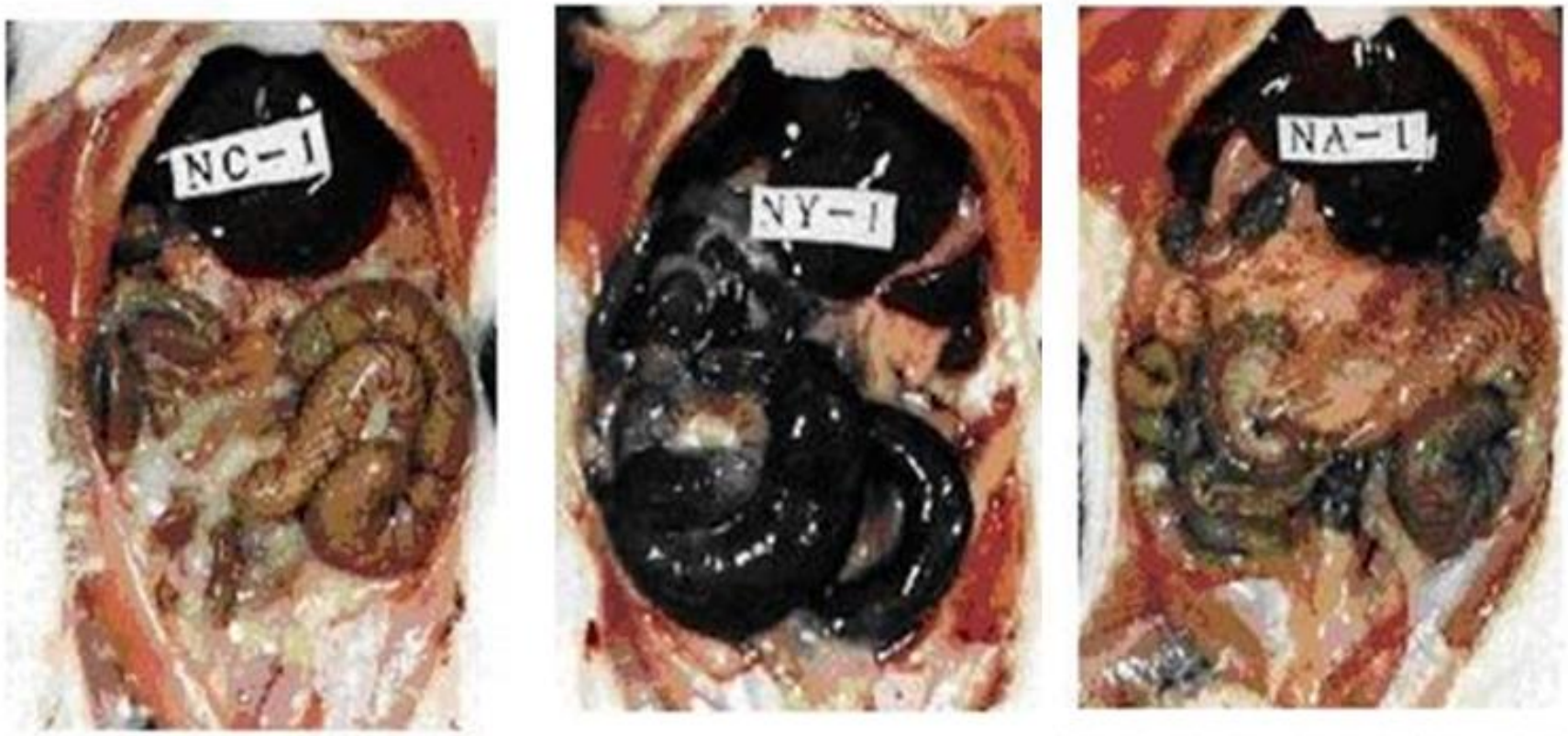


Selectivity of AST-120



Honda Y, et al., Clinical Report. 28(10): 2873-2811, 1994

AST-120 reduce adhesion



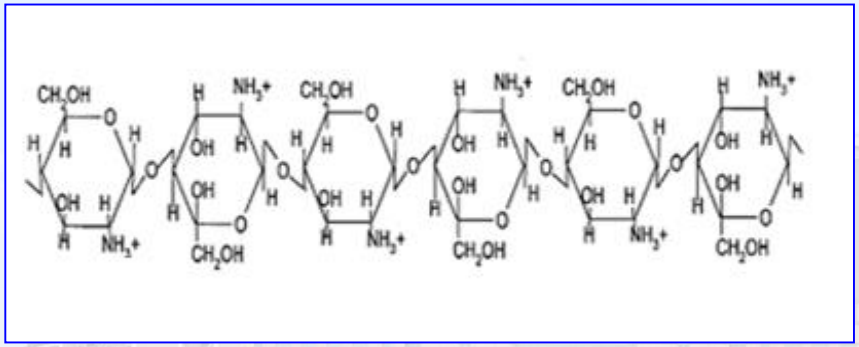
Conventional diet
（普通食物）

Medicinal charcoal
5 % diet

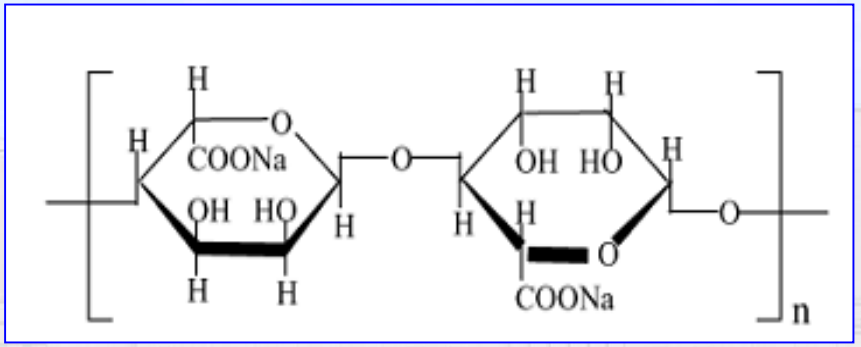
Kremezin® 5 % diet
AST-120

Activated bamboo charcoal

- Activated bamboo charcoal (ABC) by 900℃ (900-ABC)
- Dispersed Absorptive Elements (DAE) technology
  - cladding the ABC to be microsphere with Chitosan (幾丁聚醣) or Alginate (海藻酸鈉)
  - both have good biocompatibility, and easy to form spherical particles
  - make the ABC not adhere to the gastrointestinal tract



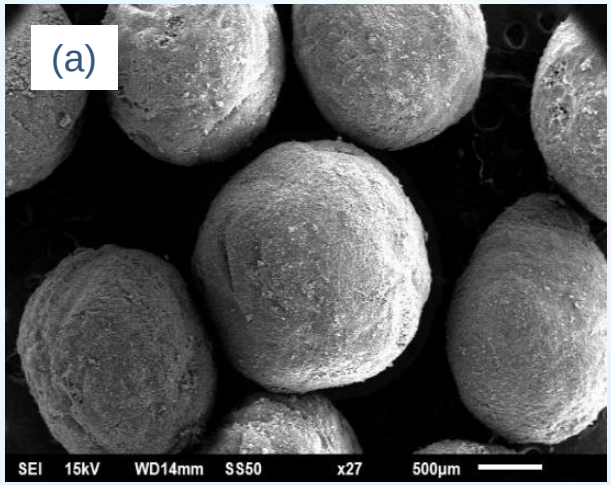
Structure of Chitosan

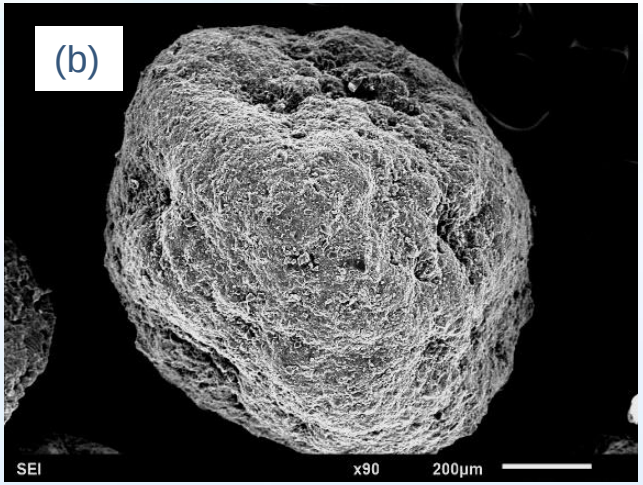


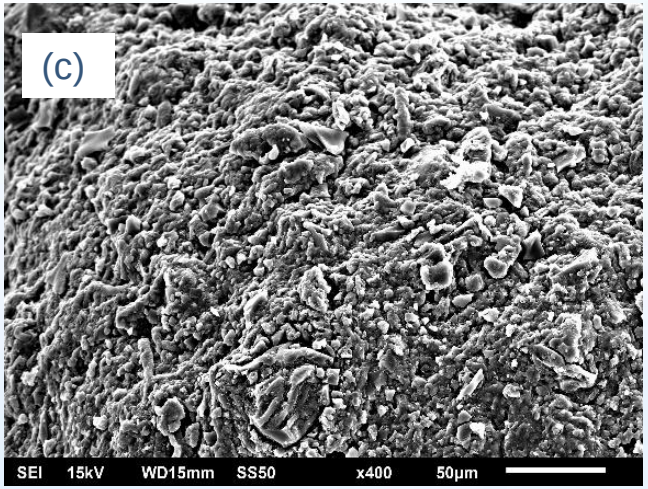
Structure of Alginate

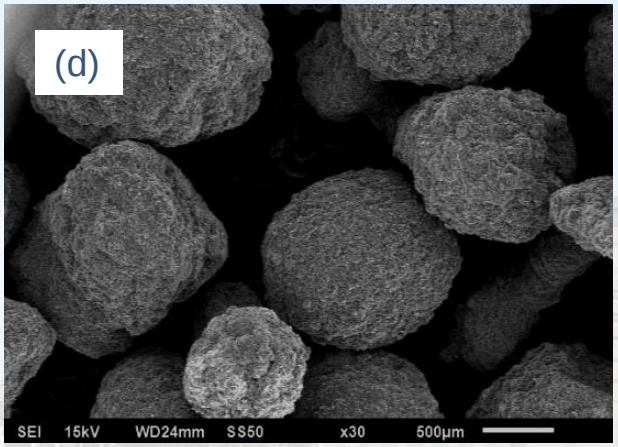
Chitosan- and Alginate-900-ABC

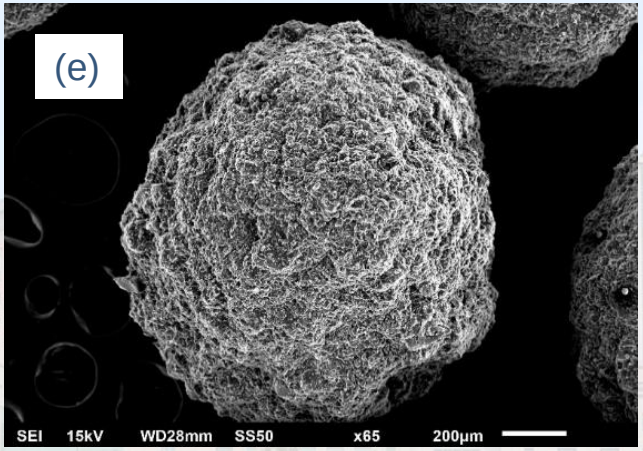
Scanning Electron Microscope

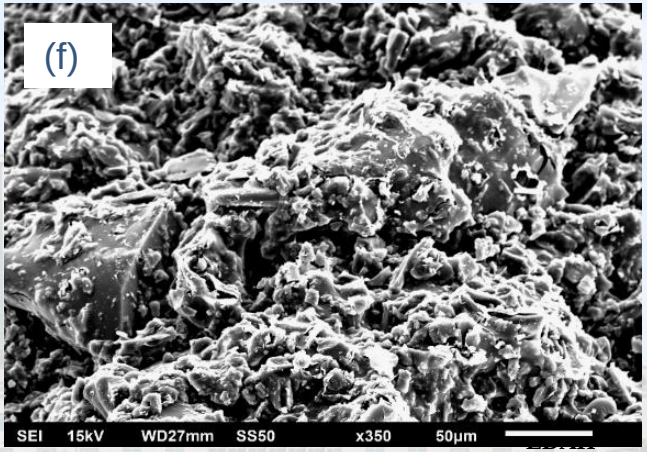








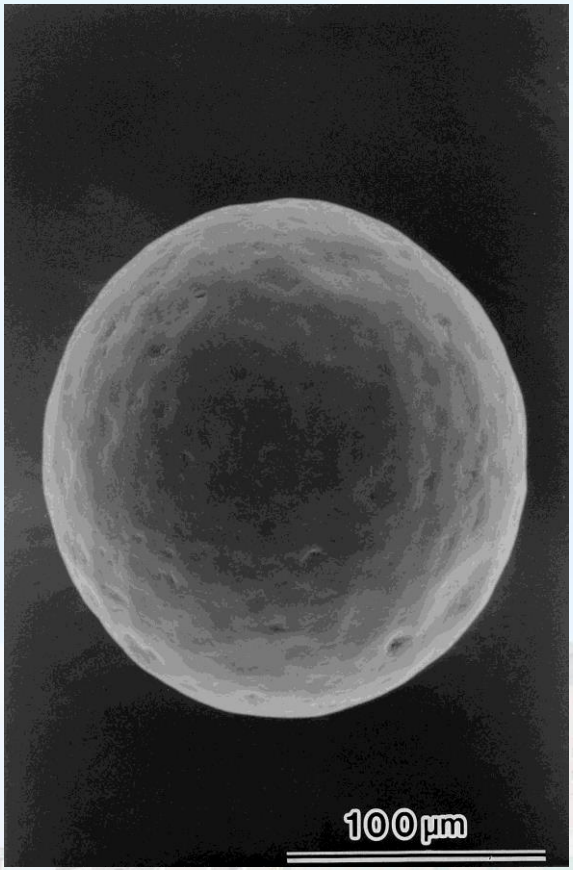


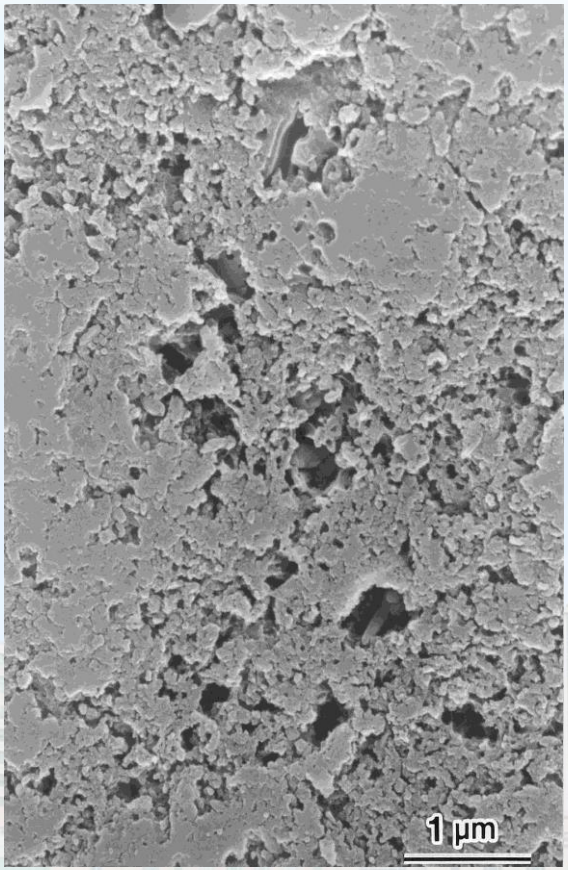


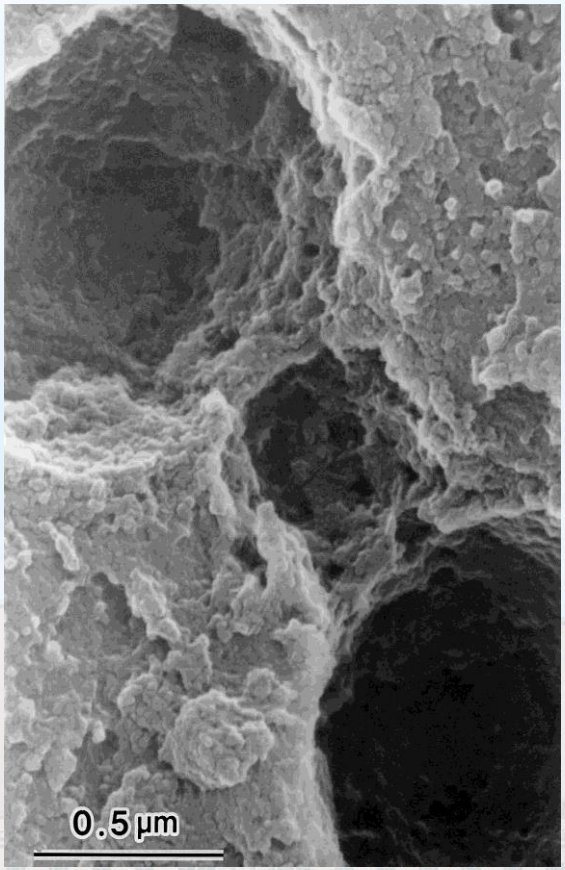
(a) (b) (c) Chitosan- 900-ABC microsphere; (d) (e) (f) Alginate-900-ABC microsphere

AST-120 microsphere

Scanning Electron Microscope







Magnification ×400 ×20,000 ×60,000

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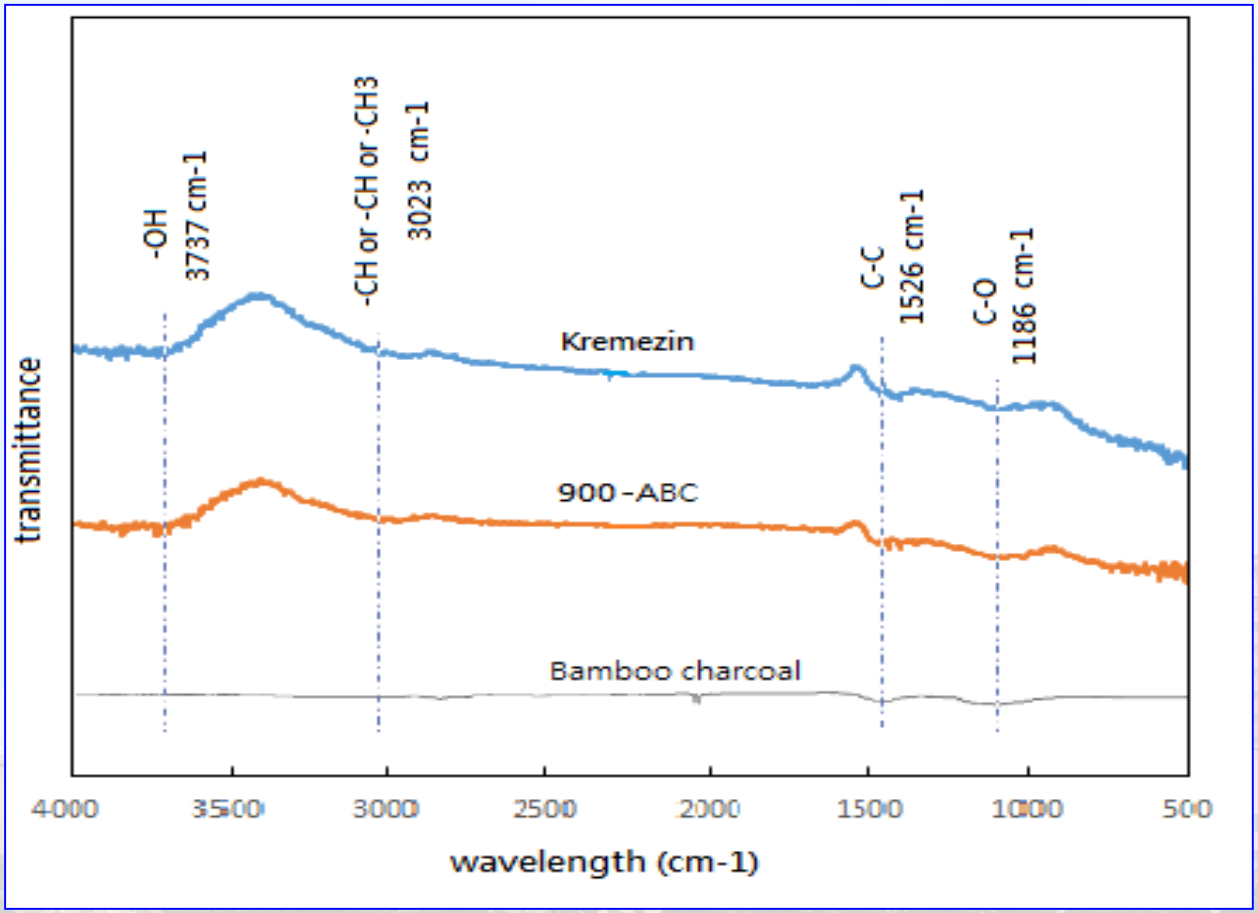
Fourier-transform infrared spectroscopy (FTIR)

FTIR spectra of
Bamboo charcoal, 900 ℃ Activated bamboo charcoal, and Kremezin



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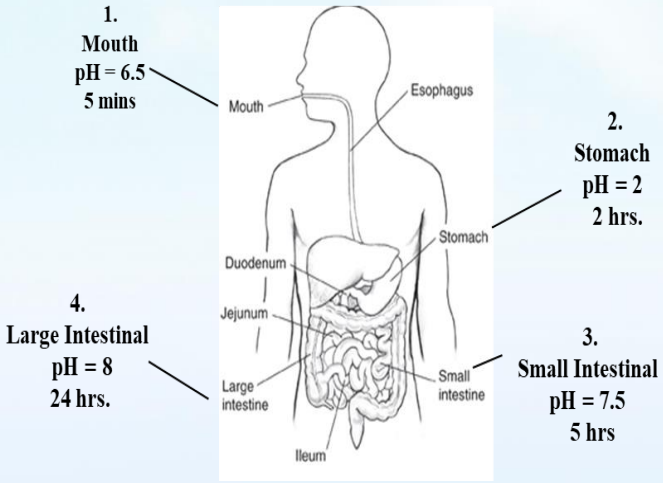
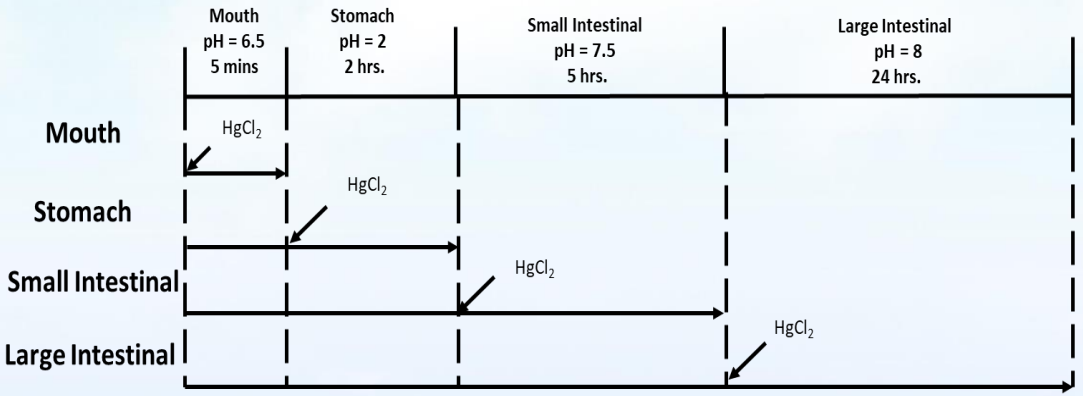
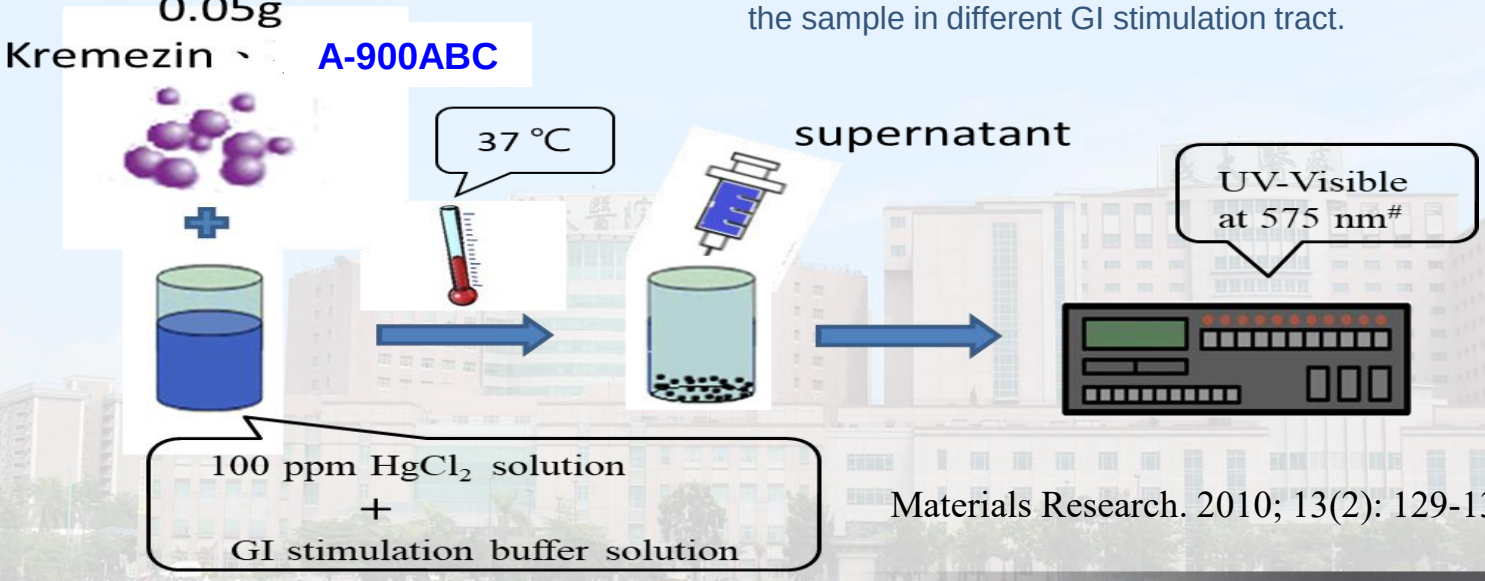
GI simulation study





- To detect the maximum absorption heavy metal value of the sample in different GI stimulation tract.



Materials Research. 2010; 13(2): 129-134

EDAH
HSY202001

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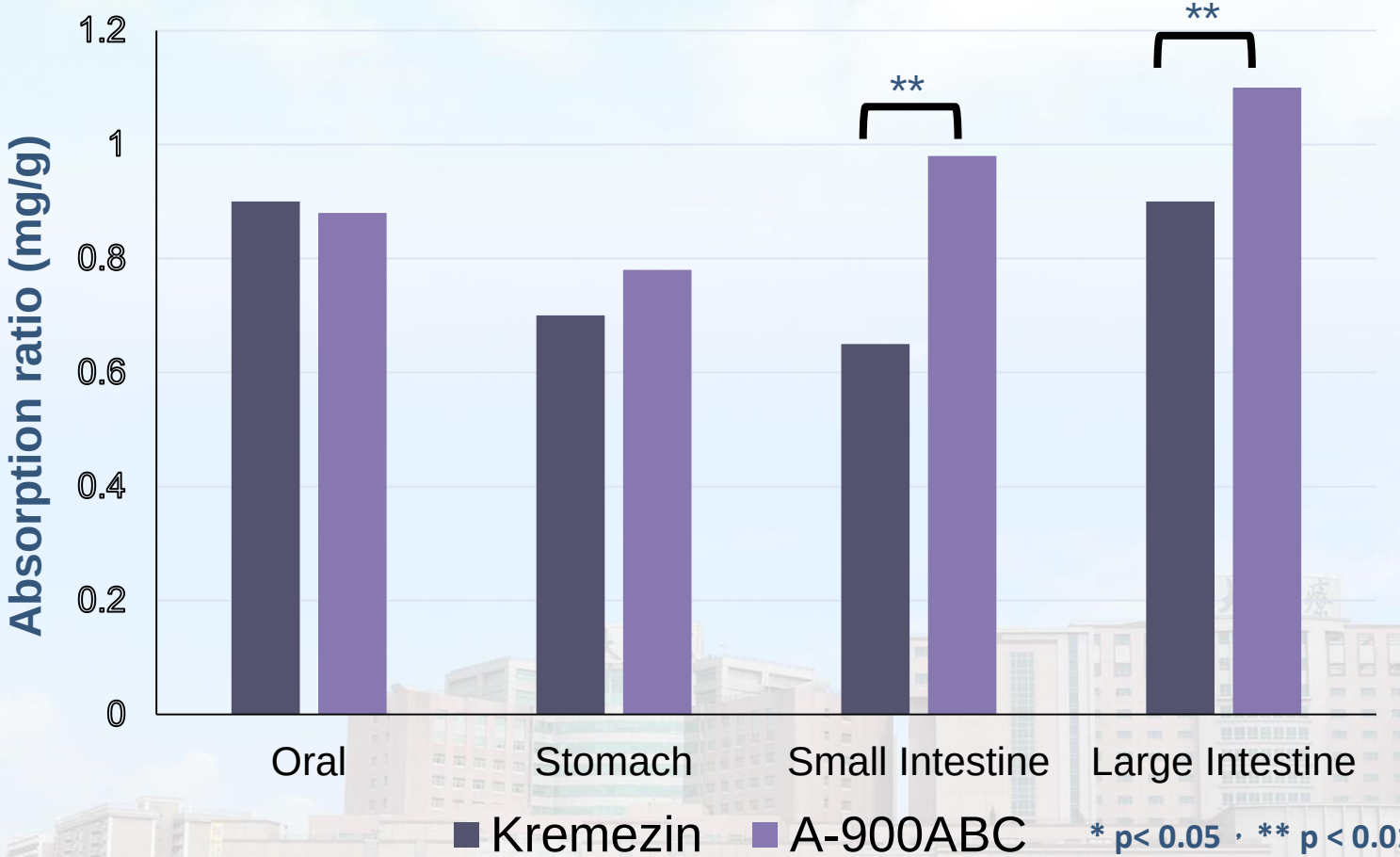
Heavy Metal (Pb^{2+})



By GI tract simulation test

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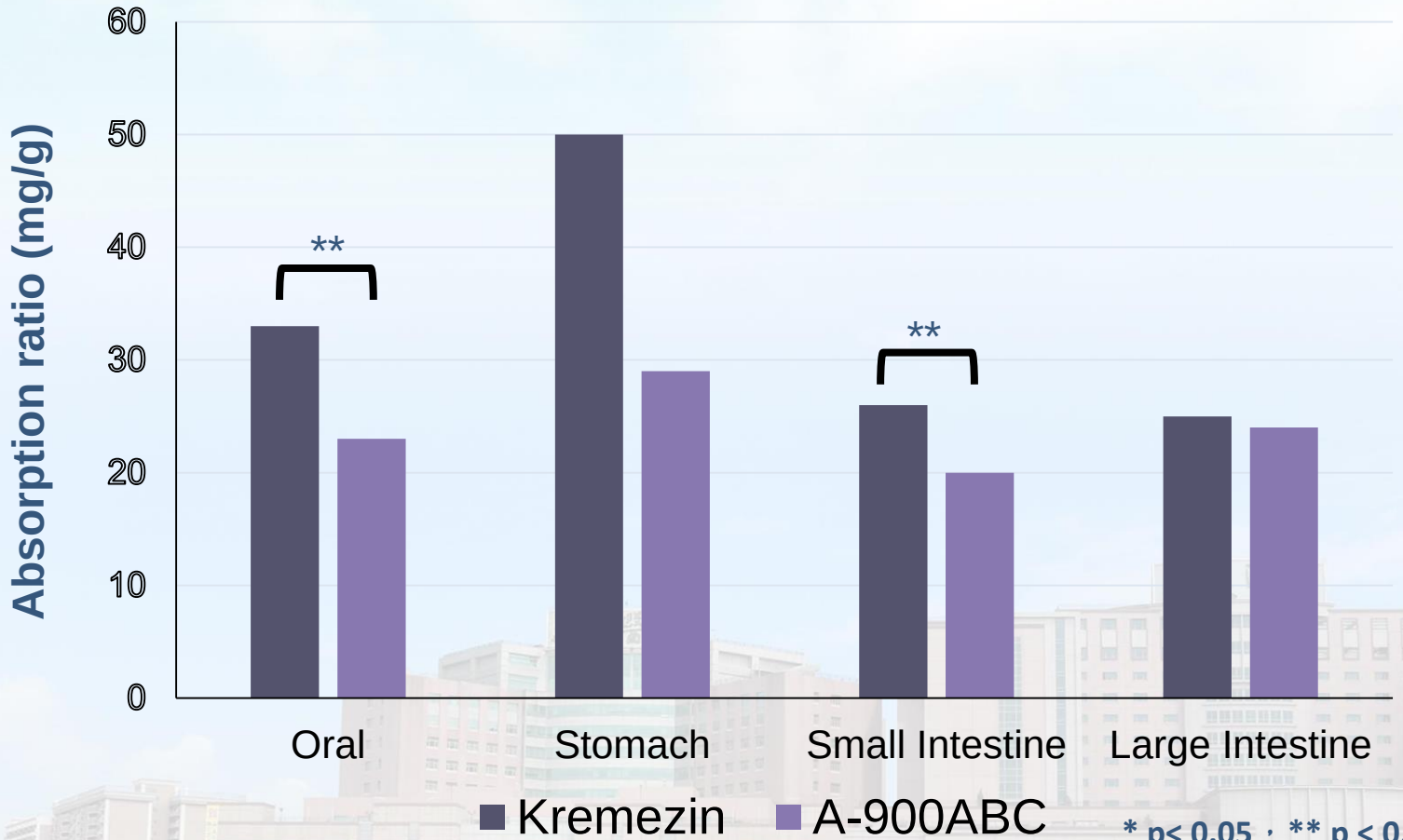
Heavy Metal (Al^{3+})



* p< 0.05 , ** p < 0.01 , n = 3

By GI tract simulation test

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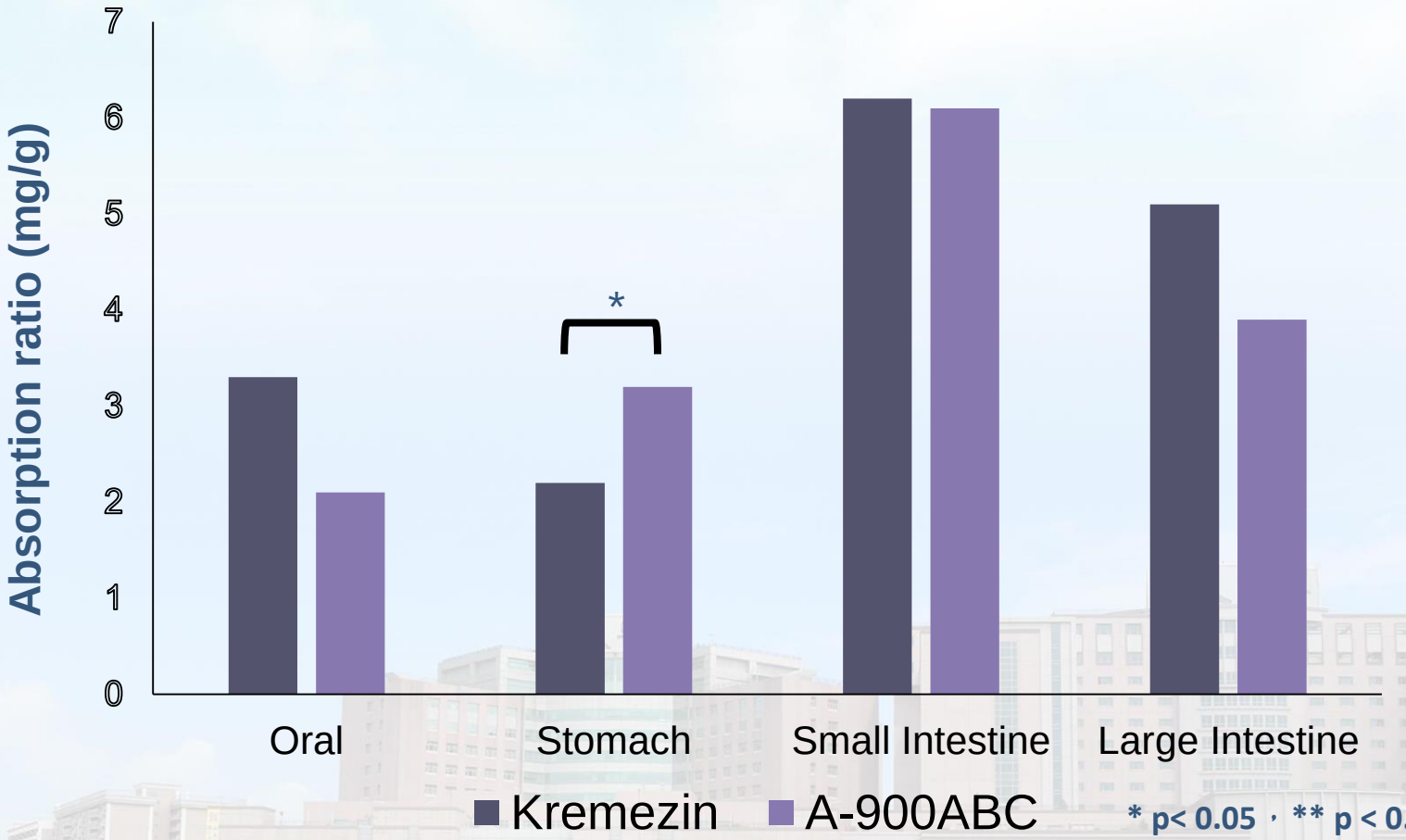
Heavy Metal (Hg^{2+})



* p< 0.05，** p < 0.01， n = 3

By GI tract simulation test

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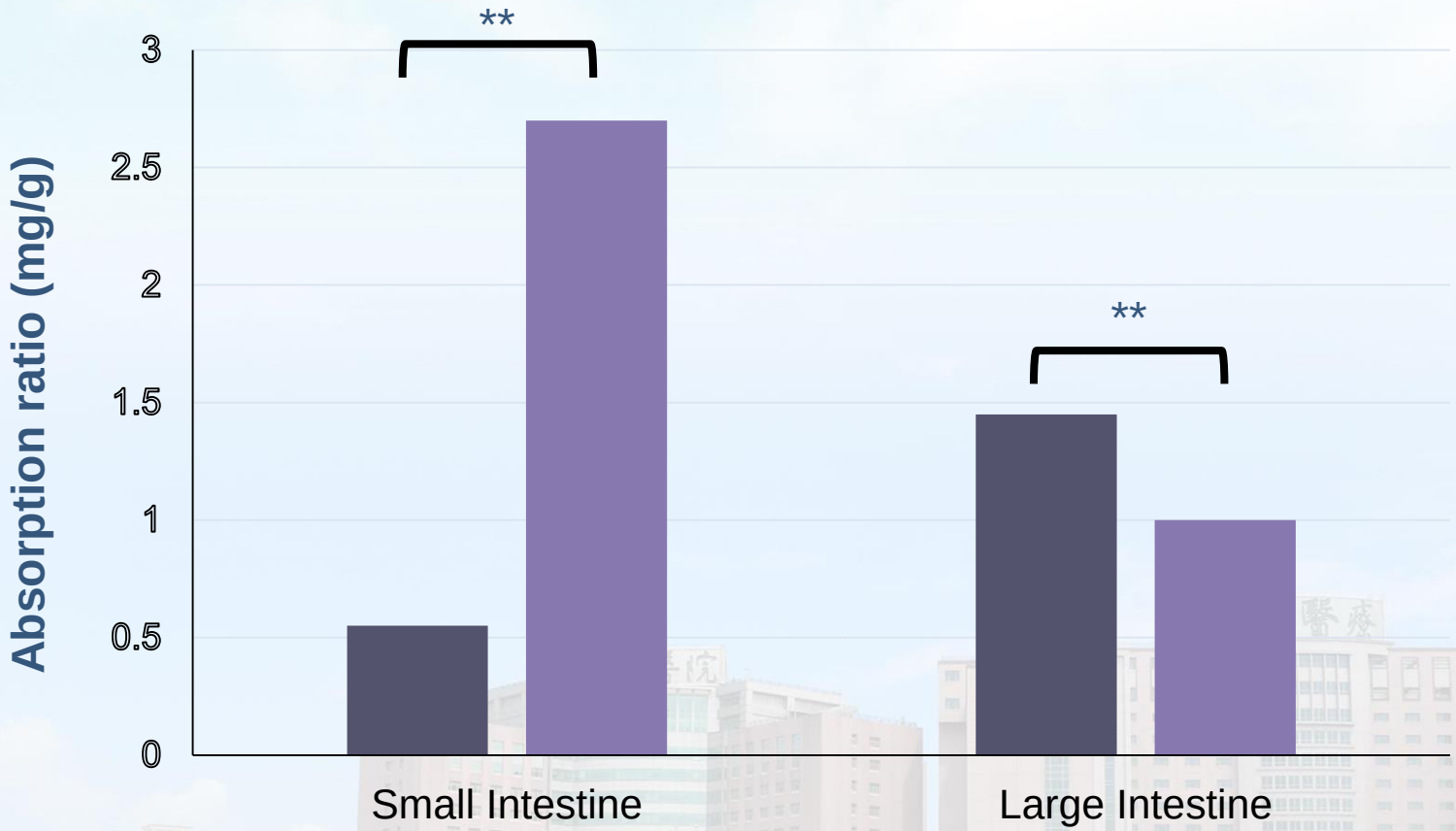
Indole



* p< 0.05，** p < 0.01， n = 3

By GI tract simulation test

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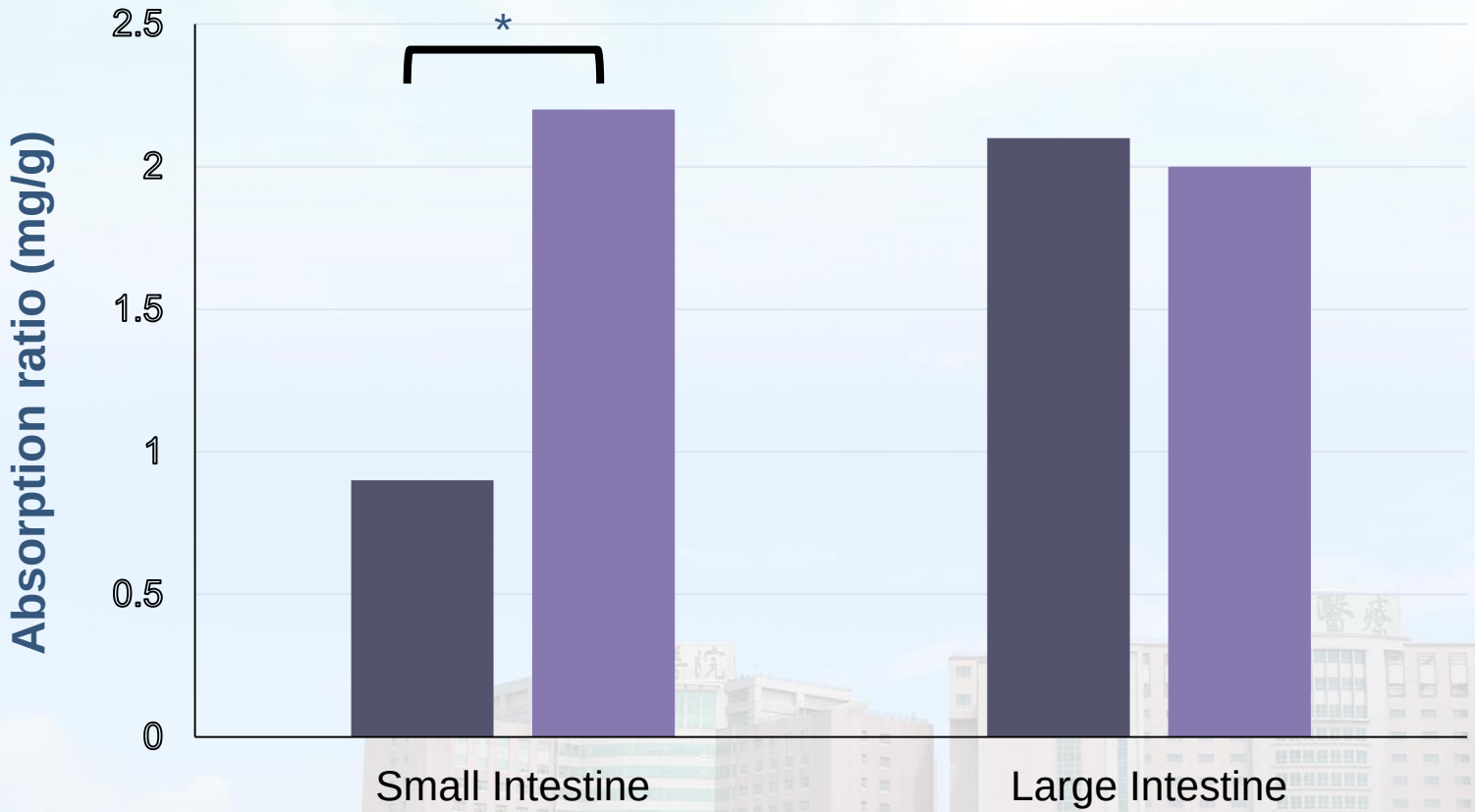
p-Cresol



* p< 0.05 · ** p < 0.01 · n = 3

By GI tract simulation test

Absorption of enzymes

- lower adsorption ability for digestive enzymes

Test Enzyme	Absorption (%)		
	Kremezin (n=4)	A-900ABC(DAE) (n=4)	藥用活性炭（日本藥典）
α-Amylase	16.7±9.8	18.2±3.2	>99
Pepsin	21±7.5	7.7±6.7	>99
Lipase	40.8±2.6	37.2±0.8	>99
Trypsin	33±6.4	36.2±9.3	>99

Animal study

- 5/6 subtotal nephrectomy rat CKD model

AST-120 (Kremezin®)

A-900ABC(DAE) (CharXen®)

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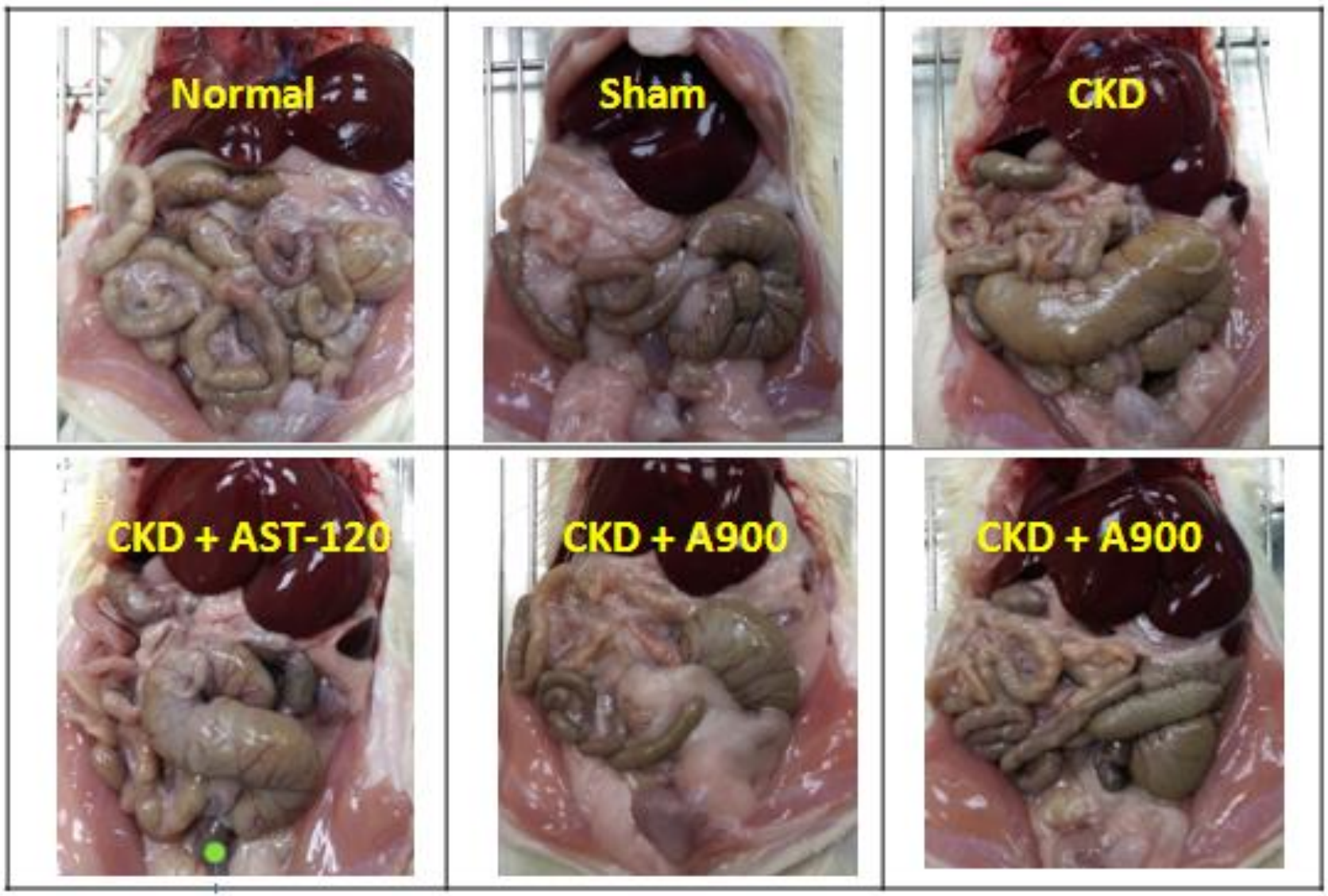
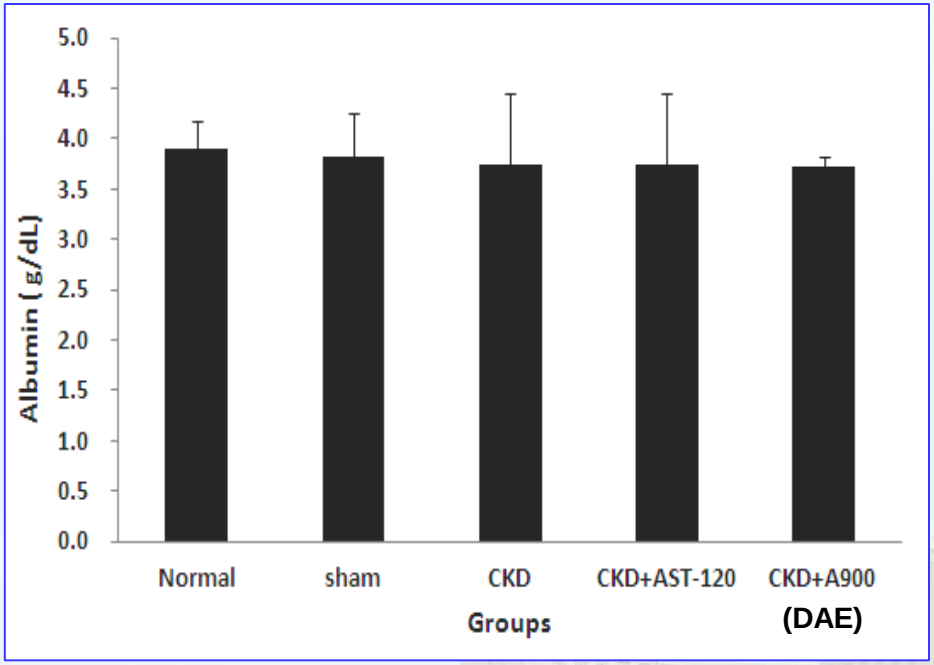
GI tract adhesion, 24 hrs

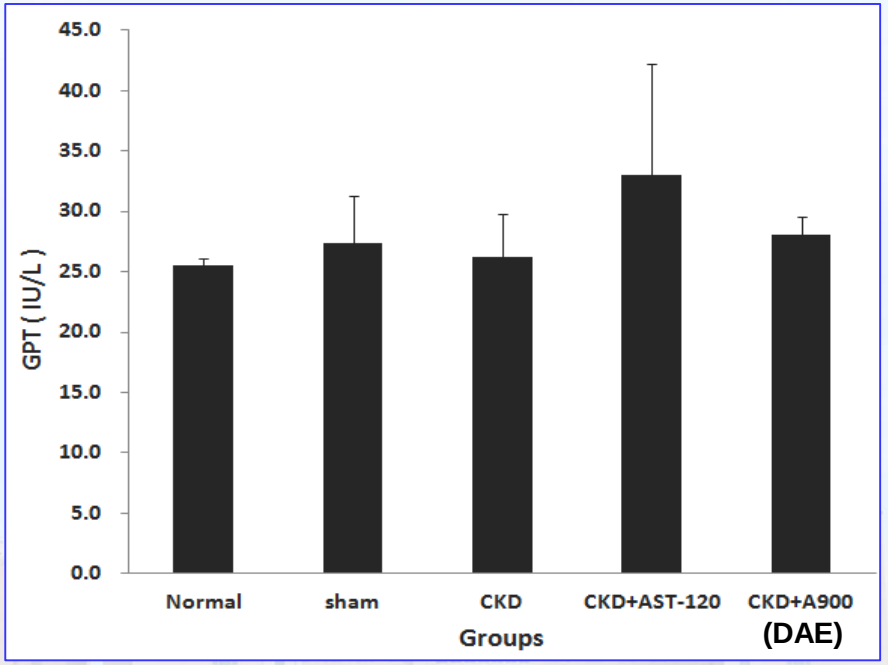


Albumin and GPT

Albumin



GPT



N = 5

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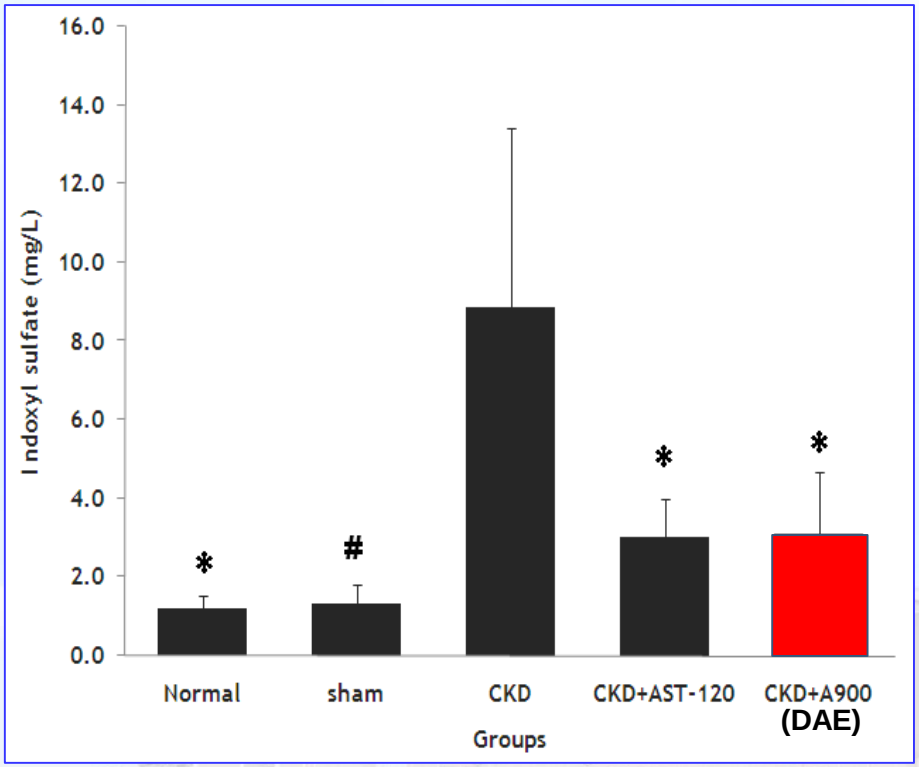
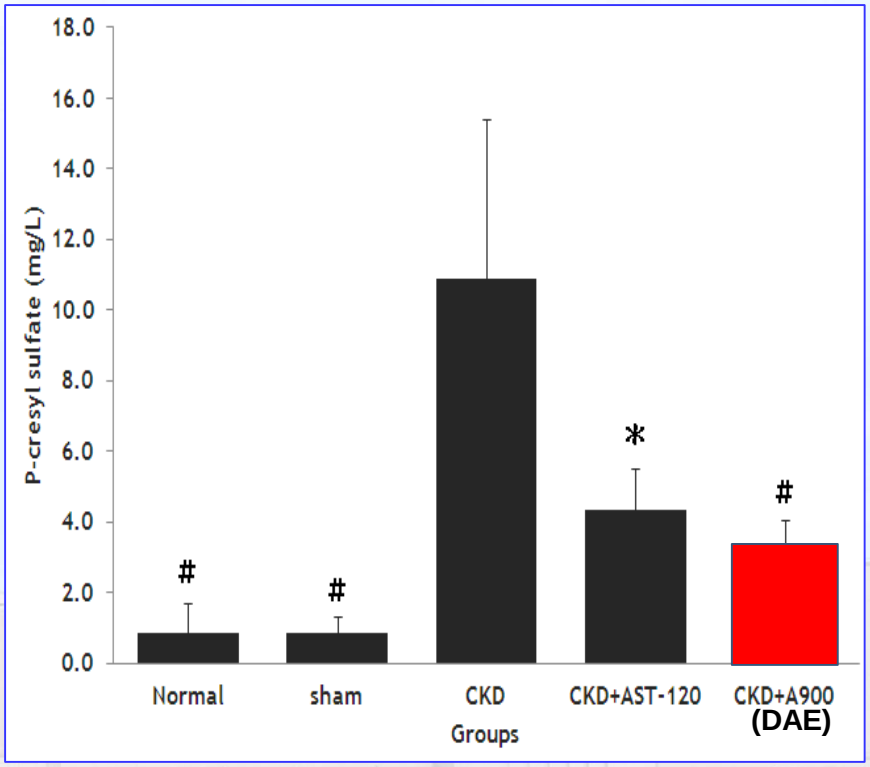
IS and PCS

IS



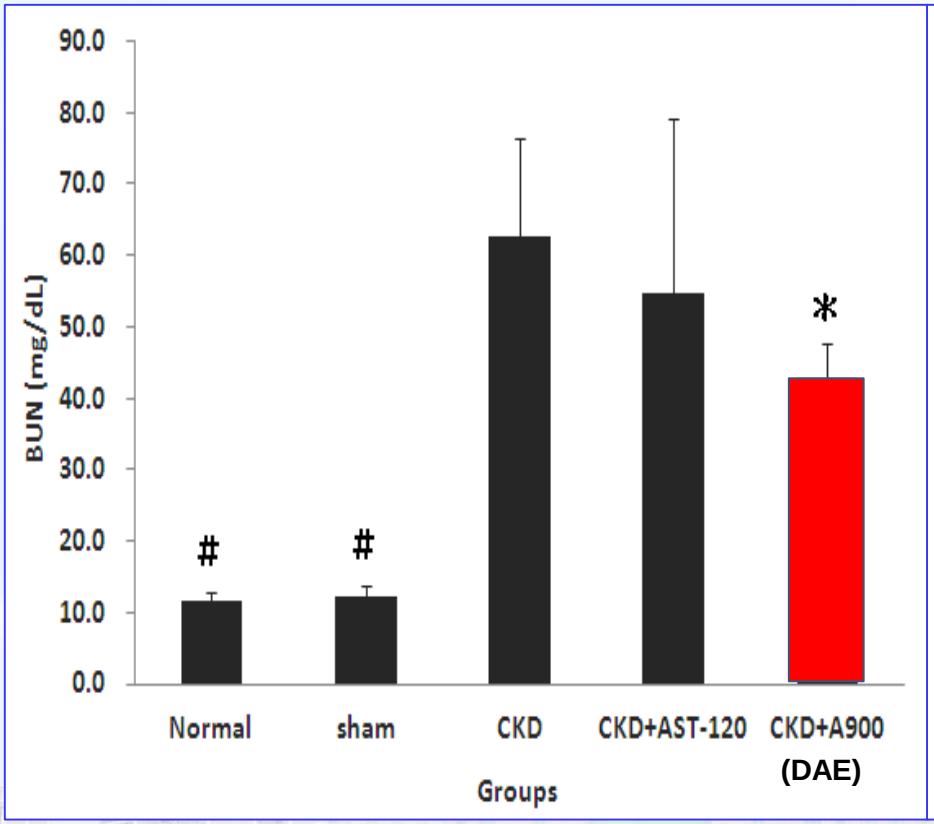
PCS



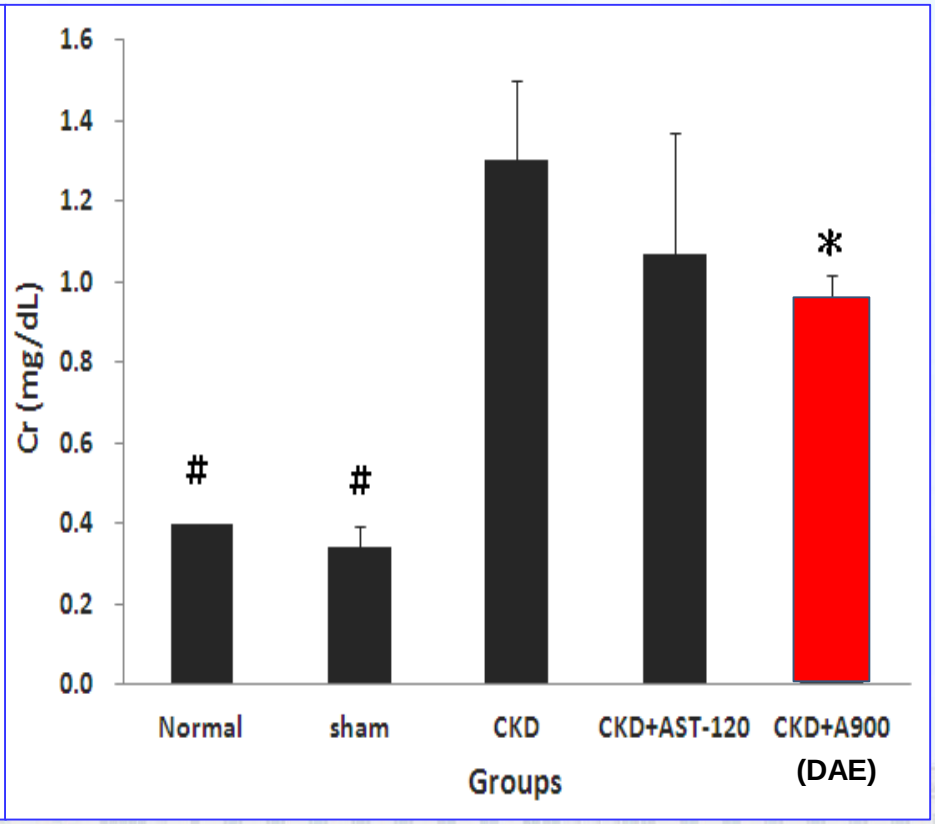
N = 5, #P<0.01; *P<0.05, compared with CKD group

BUN and Creatinine

BUN



Cr



N = 5, #P<0.01; *P<0.05, compared with CKD group

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- Take home message

Take home message

- Extremely high CKD and ESRD prevalence in Taiwan
- Uremic toxins contribute to CKD progression
- Oral absorbents indeed reduce uremic toxins
- AST-120 (Kremezin)
  - Postpone the initiation of dialysis and reduce uremic symptoms
  - slow GFR declining, statistically or clinically significant ?
    in selective patient group or selective situation ?
- A-900ABC (DAE), promising results in animal studies,
  but lack large-scale human study
- Multifactorial risk factors and etiologies for CKD
- Consider add-on treatment with uremic toxin absorbents

Thanks for Your Attention !