How to Reverse Vascular Damage in CKD?

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2011.4.16, Bexco, 부산

신장내과 최대 이슈

만성신장질환:

Chronic Kidney Disease (CKD)

세계 콩팥의 날™

세계 콩팥의 날
3월 8일

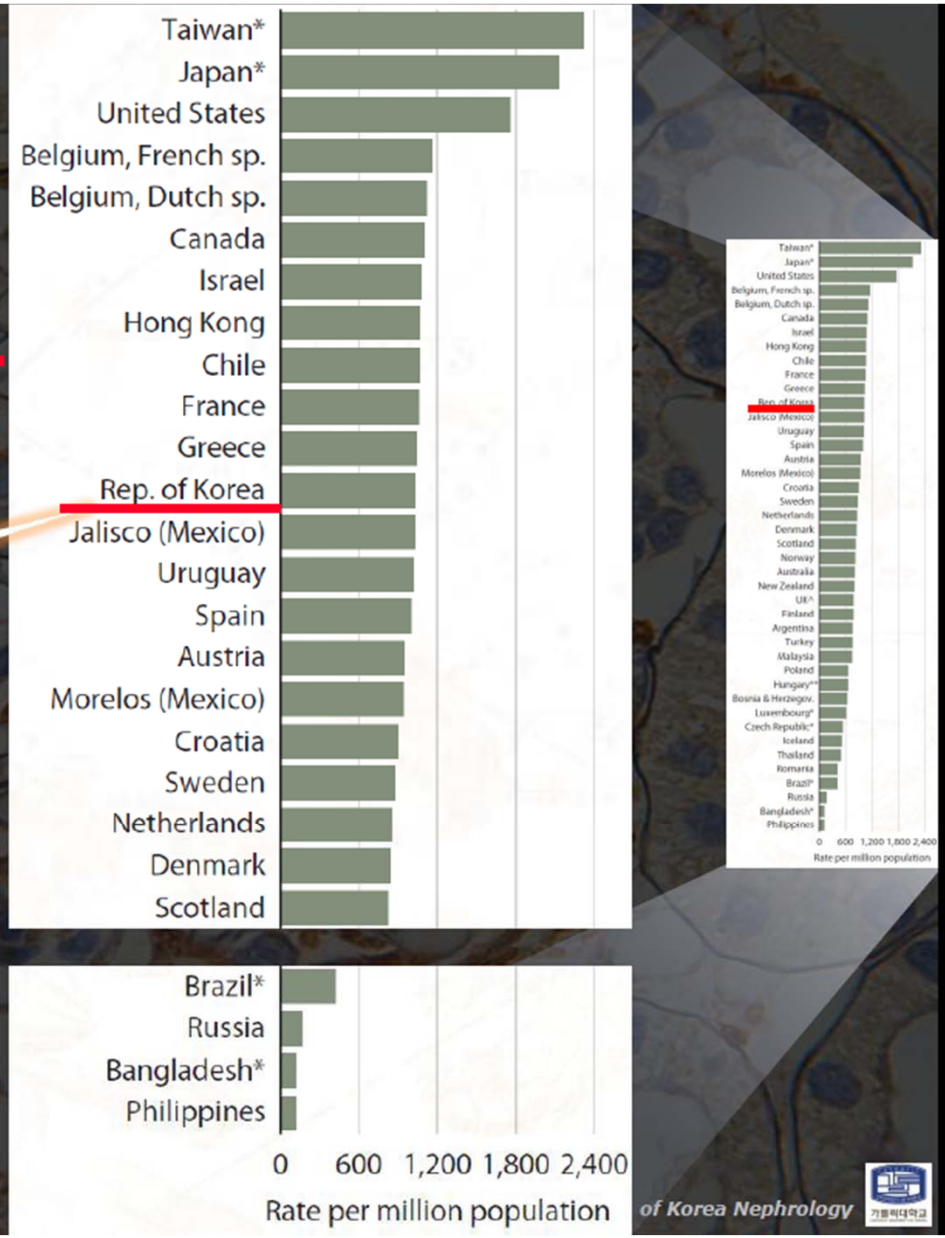
당신의 콩팥은 안녕하십니까?

고혈압 당뇨는
만성콩팥병의 주요 원인입니다

KOREAN ESRD REGISTRY

Prevalence of ESRD

1031.6 PMP
End of 2008



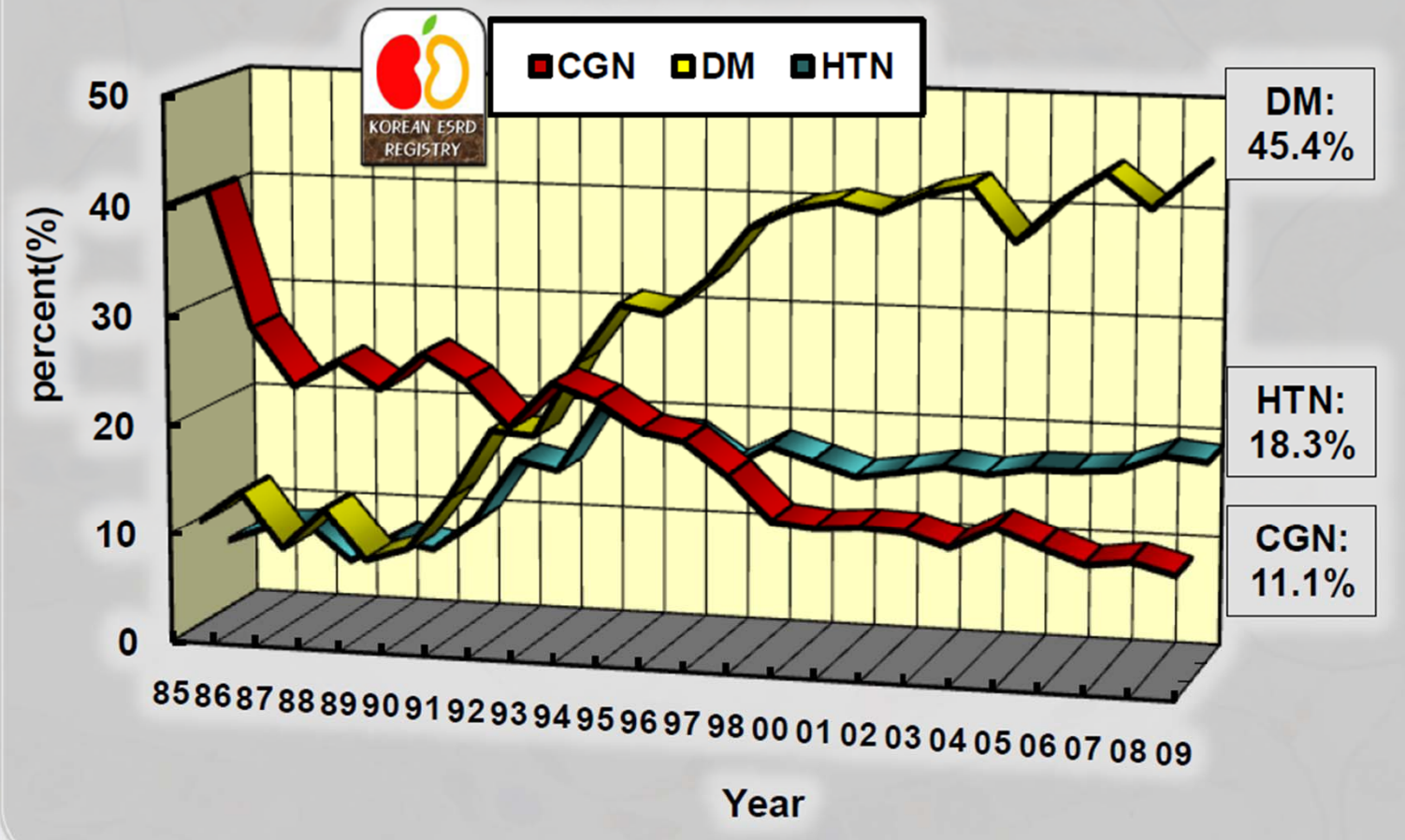
United States Renal Data System
2010 Annual Data Report

U.S. Renal Data System, USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010.

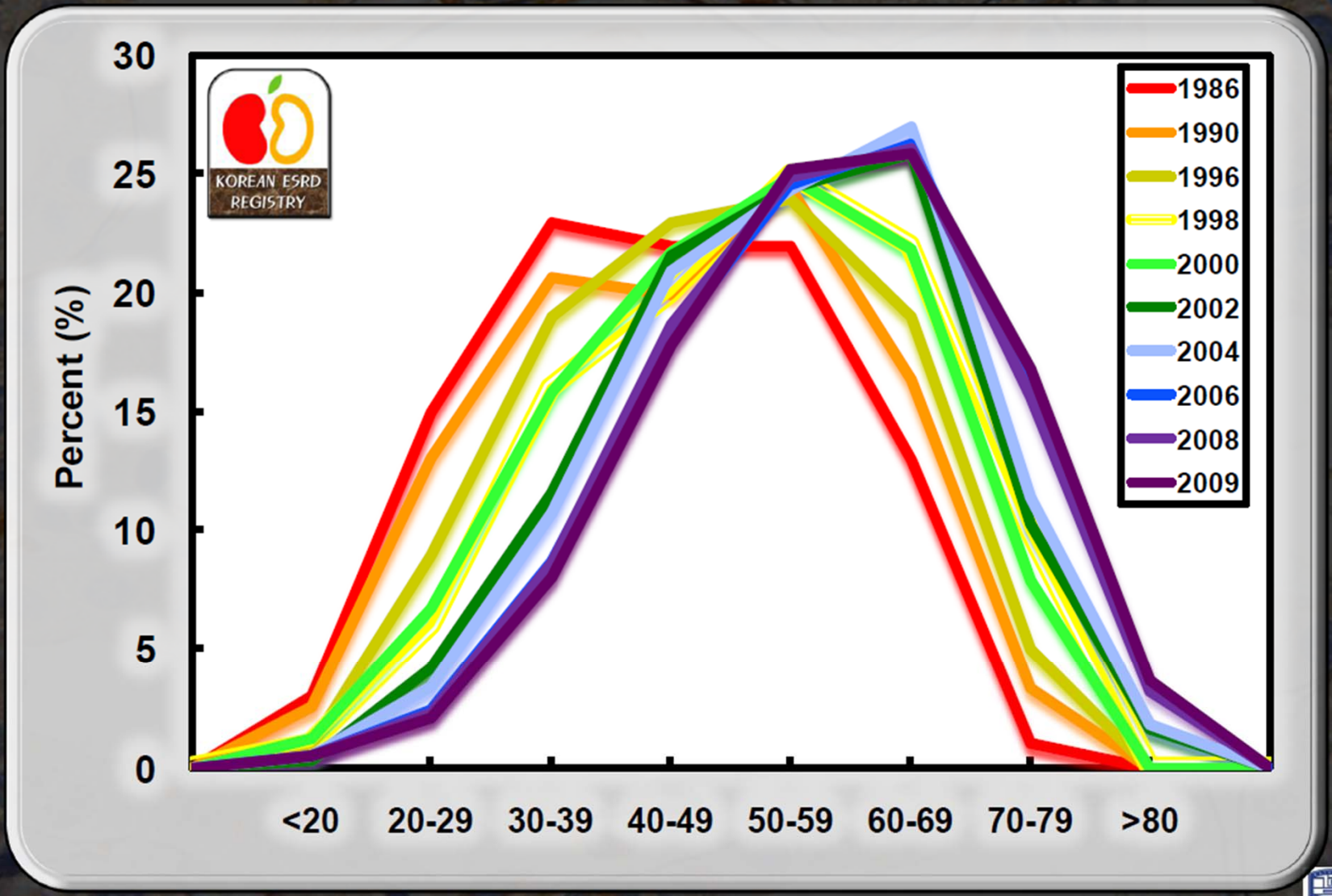
Oct. 2010

of Korea Nephrology

Three Major Causes of ESRD



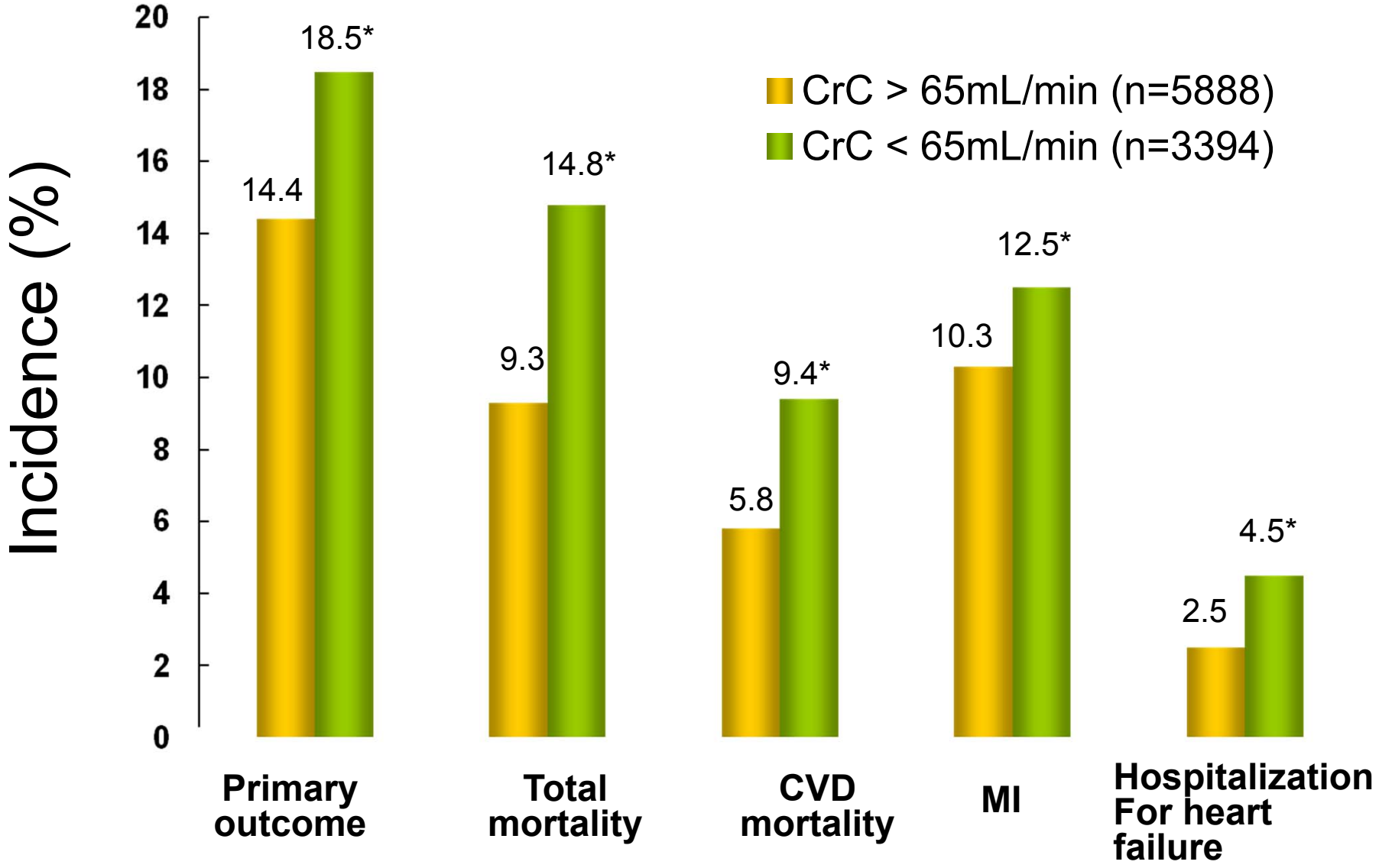
Age Distribution of HD Pts according to Year



Contributing factors to CKD?

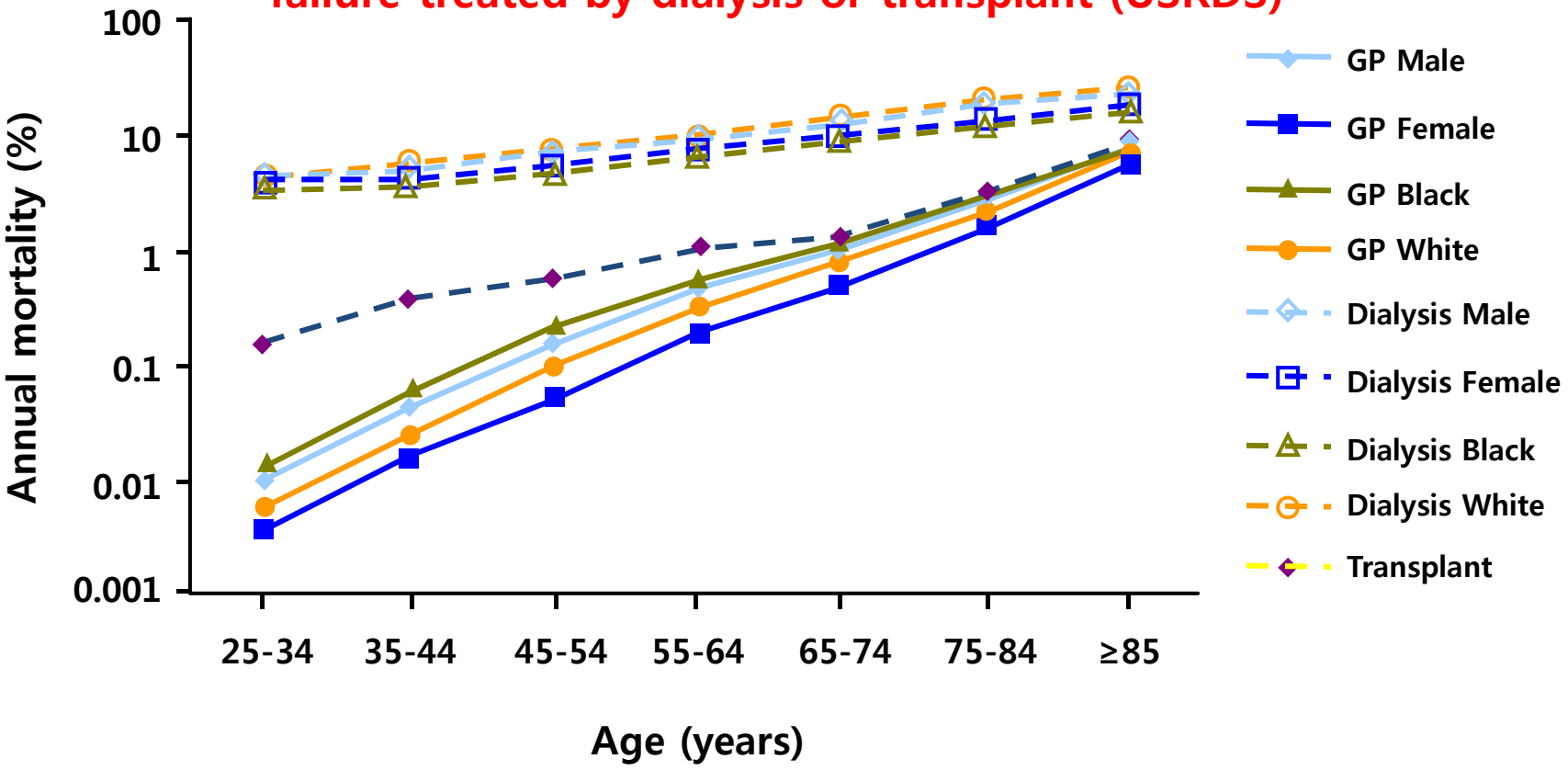
- ↑Economic status
- ↑ Old-aged patients
- ↑ Diabetes

만성콩팥질환과 심혈관계 합병증



Cardiovascular Mortality Is Higher in Patients With ESRD

Cardiovascular mortality in the general population (NCHS) and in kidney failure treated by dialysis or transplant (USRDS)



Adapted from Foley RN et al. *Am J Kidney Dis*. 1998;32(5 Suppl 3):S112–S119.

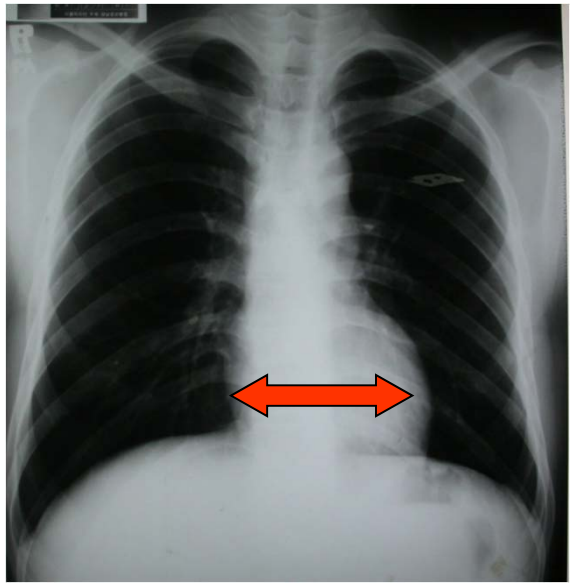
Causes of Death (%), 1994-2009

	1994-96	1998	2001	2002	2003	2004	2005	2006	2007	2008	2009
Cardiac	27.4	27.4	26.9	27.9	31.7	35.5	30.7	33.7	31.7	35.1	29.5
Myocardial infarction	6.4	6.4	7.7	5.5	7.4	8.3	8	9.1	7.5	9.7	8.0
Cardiac arrest, uremia associated	13.7	13.7	11.2	10.6	11.7	13.6	10.4	11.1	10.8	11	8.5
Cardiac arrest, other cause	7.2	7.2	8.1	11.8	12.5	13.6	12.4	13.5	13.3	14.4	13
Vascular	17.2	17.2	22.7	15.7	19.5	17.5	17	16.5	17.8	16	15.9
Cerebrovascular accident	14.3	14.3	15.1	11.6	14.5	12.8	12.3	11.5	13	12.2	11
Pulmonary embolus	0.2	0.2	0.5	0.4	0.1	0.2	0.6	0.7	0.5	0.1	0.2
Gastrointestinal hemorrhage	1.7	1.7	2.7	1.9	2.3	2	1.7	1.9	2.7	1.9	2.3
G											
C											
Infe											
P											
S											
T											
P											
O											
Liv											
L											
L											
So											
F											
S											
T											
Miscellaneous	32	32	23.7	27.4	21.3	21	24	24.2	24.8	24.3	27.1
Cachexia	2.9	2.9	8.1	6.8	6.6	6.1	4	3.9	4.4	3.8	3.3
Malignant disease	2.1	2.1	4.4	4.8	3.5	3.6	6.4	5.4	5.7	4.6	5.7
Accident	1.2	1.2	0.9	0.5	1.1	0.9	1.4	1.6	1.2	1	1.3
Uncertain	25.8	25.8	10.3	15.3	10.1	10.3	12.3	13.2	13.4	14.9	16.8

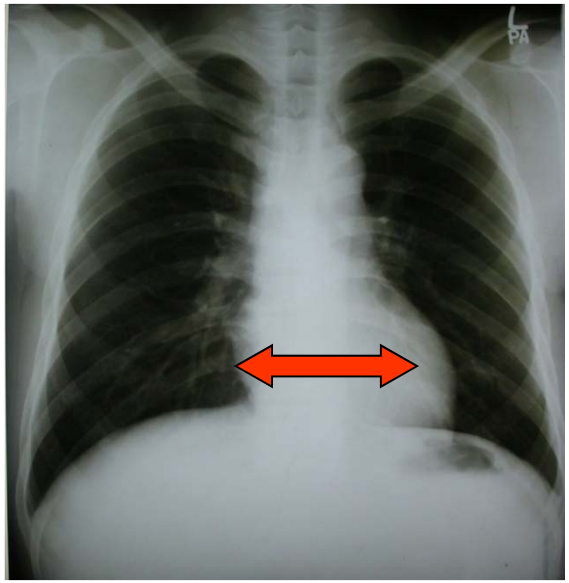
*Number of patients :1994-1996=981, 1998=911, 2001=761, 2002=1,256, 2003=894, 2004=1,162, 2005=1,256, 2006=1,248, 2007=1,531, 2008=1,563, 2009=1,727

심혈관계 합병증으로 사망하는 환자: 45.4%

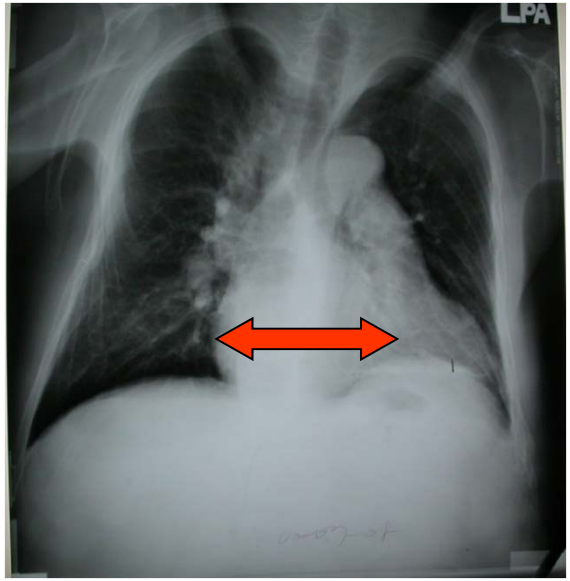
혈액투석시작



7년후



14년후



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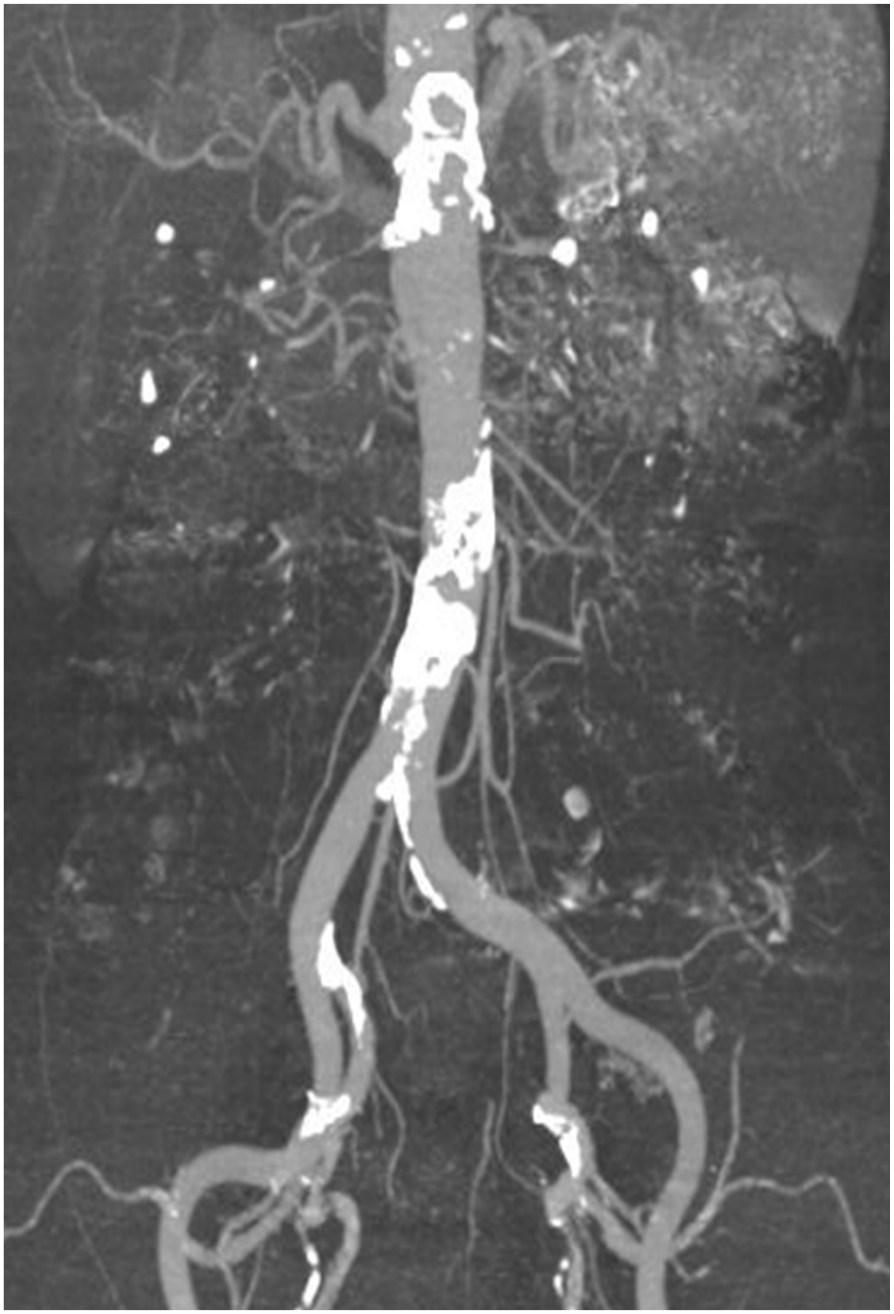
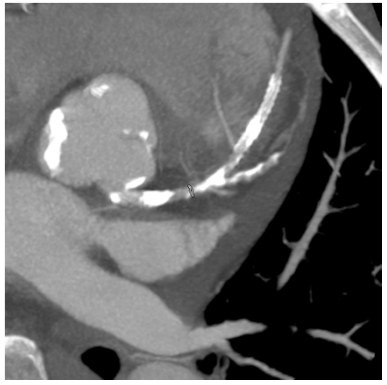
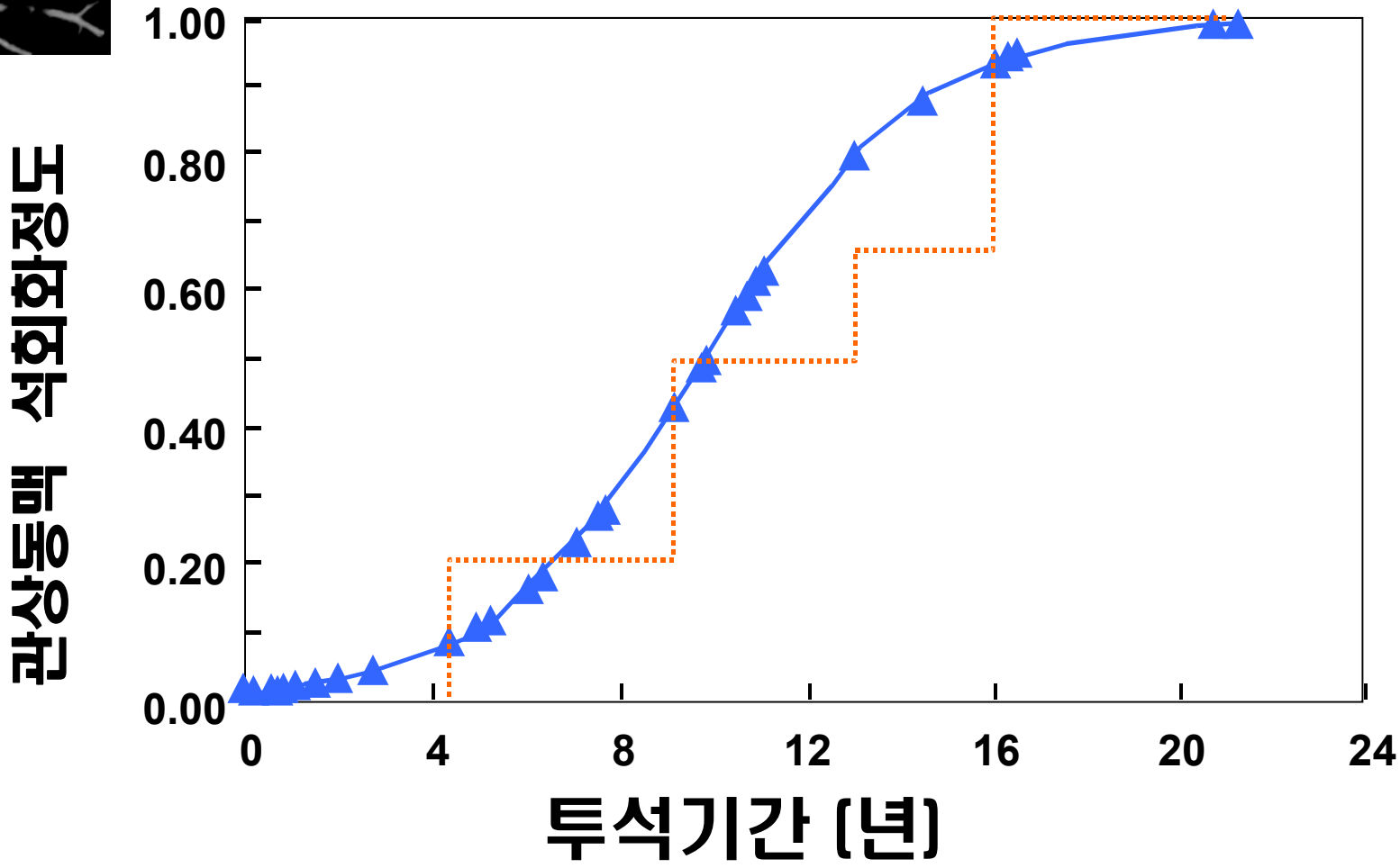
CATHOLIC UNIVERSITY OF KOREA




H
SHADE/SURF
LAO/RAO 15
CRAN/CAUD 0
R
L
F
B 100 W 416
O 100 C 266



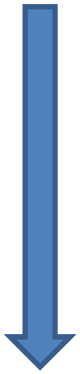
투석기간과 관상동맥 석회화정도



Cardiovascular disease in CKD

The most common cause of death

CKD



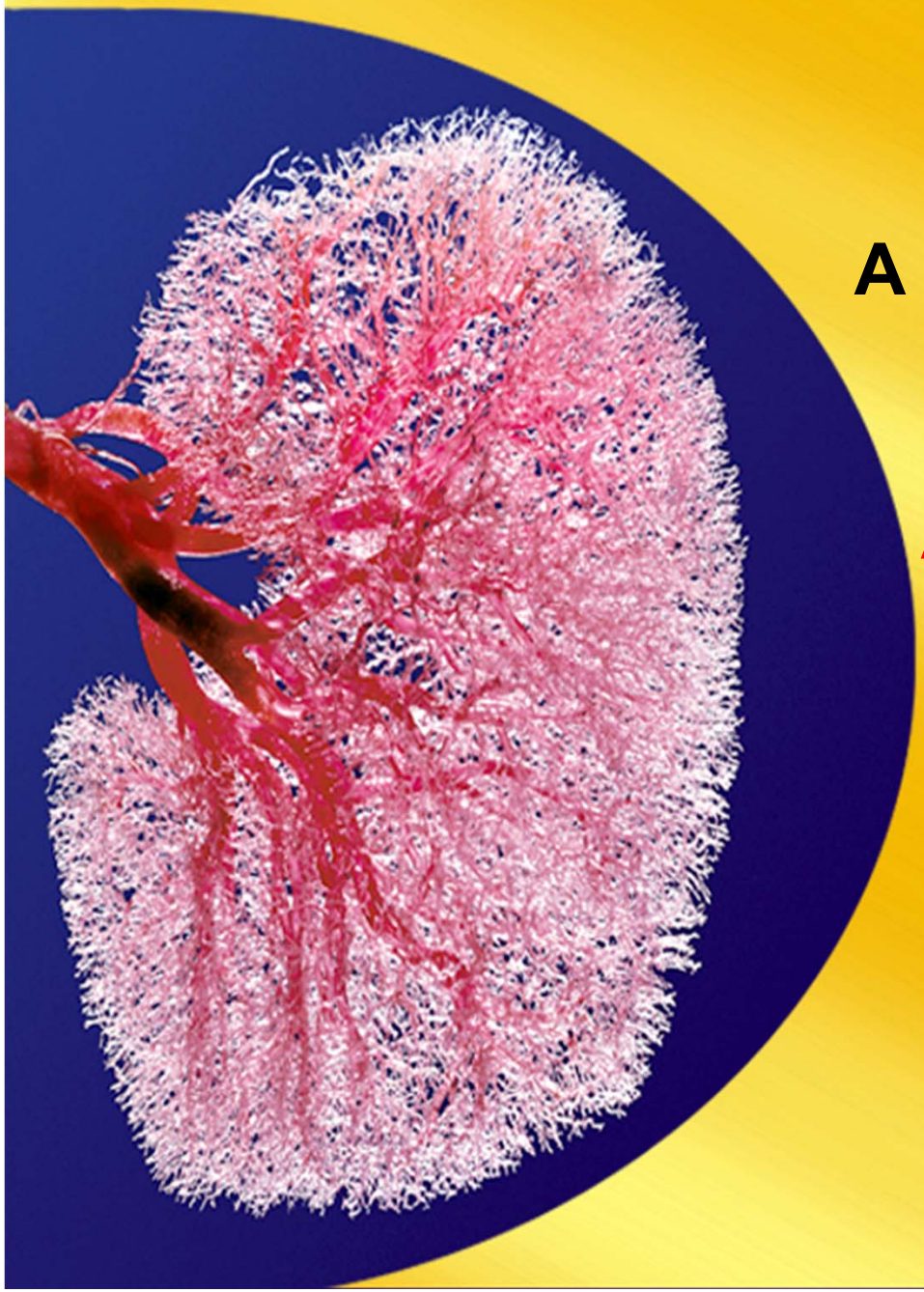
- Hypertension
- Hyperlipidemia
- Diabetes

Accelerated atherogenesis

腎臓 → 心臓


World Kidney Day
10 March 2011
Protect your kidneys, Save your heart


Protect your kidneys, Save your heart.
World Kidney Day
10 March 2011



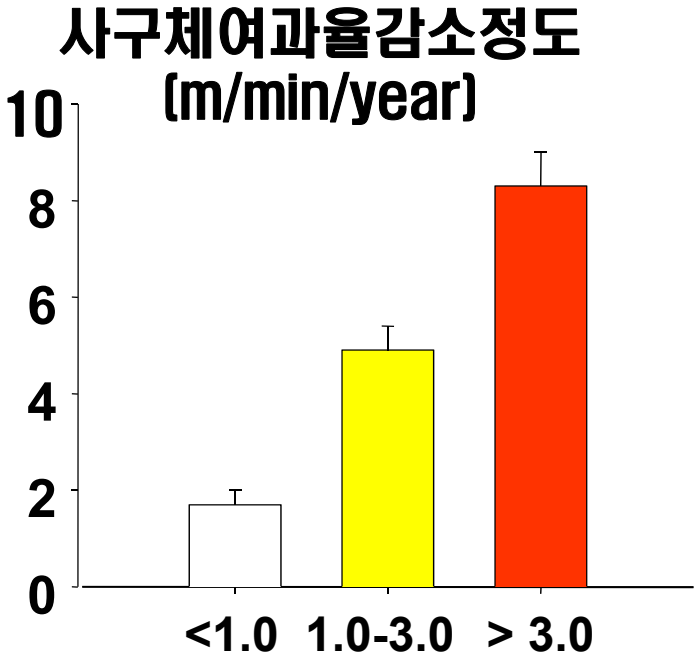
Proteinuria

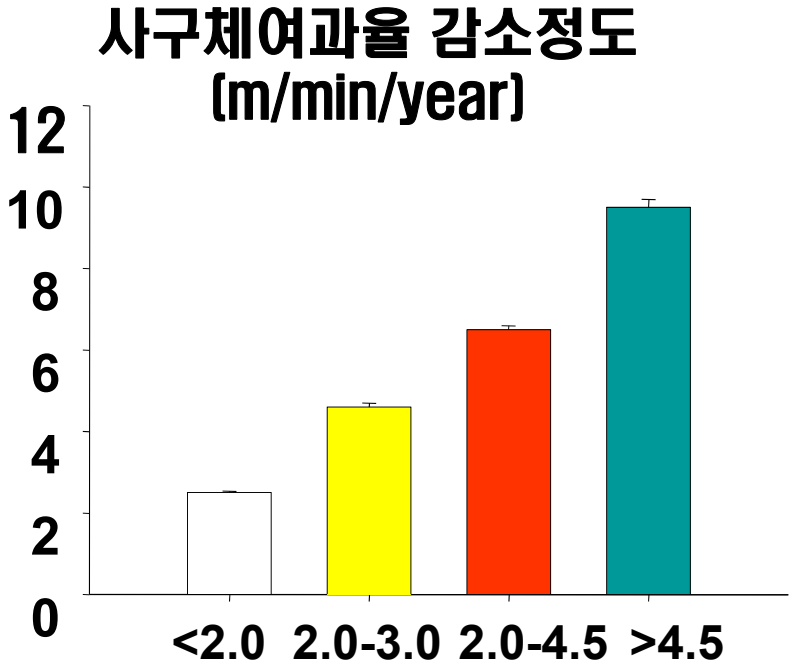
A marker of kidney damage

A marker of vascular damage

CATHOLIC UNIVERSITY OF KOREA

요단백량에 따른 신장기능의 저하정도





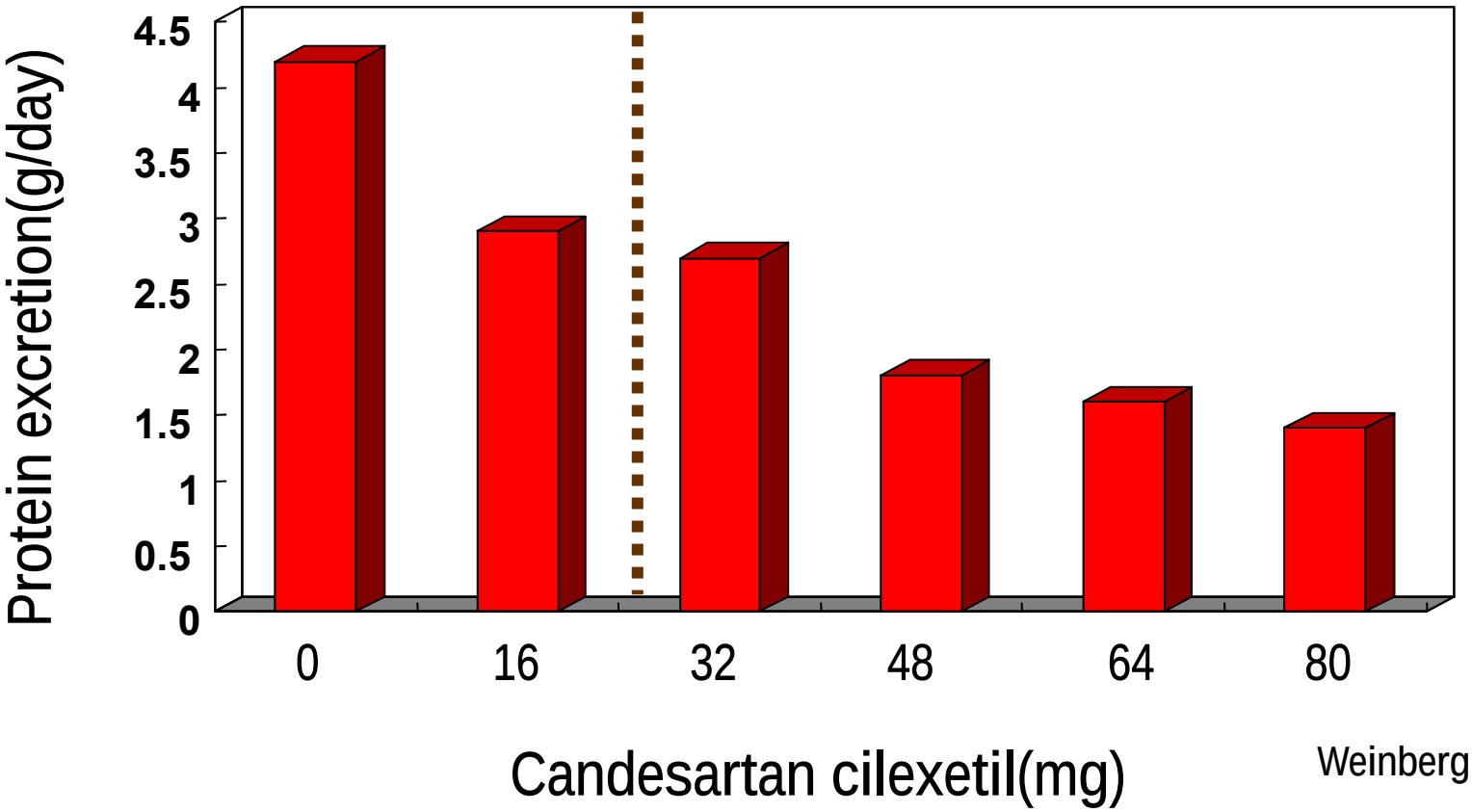
요단백(g/day)

MDRD study (n=585)

REIN study (n=585)

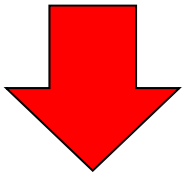
Effect of ARB on proteinuria

ARB 용량에 따른 요단백의 감소정도



Weinberg M, KI, 2000

Optimal RAS inhibition?

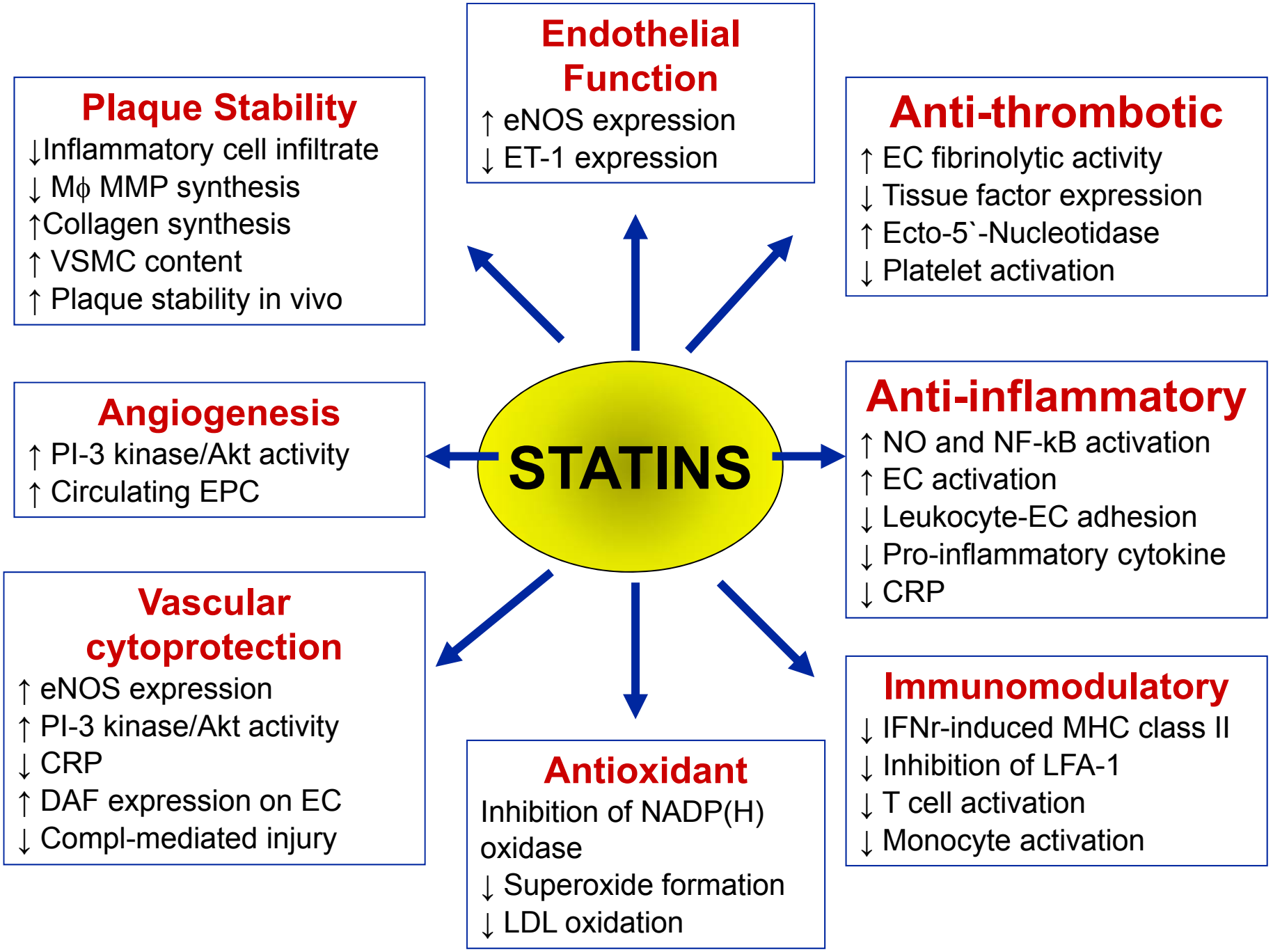


- Effective BP control
- Target organ damage*

*** Reducing proteinuria and optimal nephroprotection (retardation of the loss of glomerular filtration)**

Maximize RAS inhibition to decrease proteinuria less than 1.0 g/day

- Low dose ARB + diuretics
- High dose ARB
- ARB+ACEI
- ARB with T-type CCB


Endothelial Function
↑ eNOS expression
↓ ET-1 expression
Plaque Stability
↓Inflammatory cell infiltrate
↓ Mϕ MMP synthesis
↑Collagen synthesis
↑ VSMC content
↑ Plaque stability in vivo
Anti-thrombotic
↑ EC fibrinolytic activity
↓ Tissue factor expression
↑ Ecto-5`-Nucleotidase
↓ Platelet activation
STATINS
Angiogenesis
↑ PI-3 kinase/Akt activity
↑ Circulating EPC
Anti-inflammatory
↑ NO and NF-kB activation
↑ EC activation
↓ Leukocyte-EC adhesion
↓ Pro-inflammatory cytokine
↓ CRP
Vascular cytoprotection
↑ eNOS expression
↑ PI-3 kinase/Akt activity
↓ CRP
↑ DAF expression on EC
↓ Compl-mediated injury
Antioxidant
Inhibition of NADP(H) oxidase
↓ Superoxide formation
↓ LDL oxidation
Immunomodulatory
↓ IFNr-induced MHC class II
↓ Inhibition of LFA-1
↓ T cell activation
↓ Monocyte activation

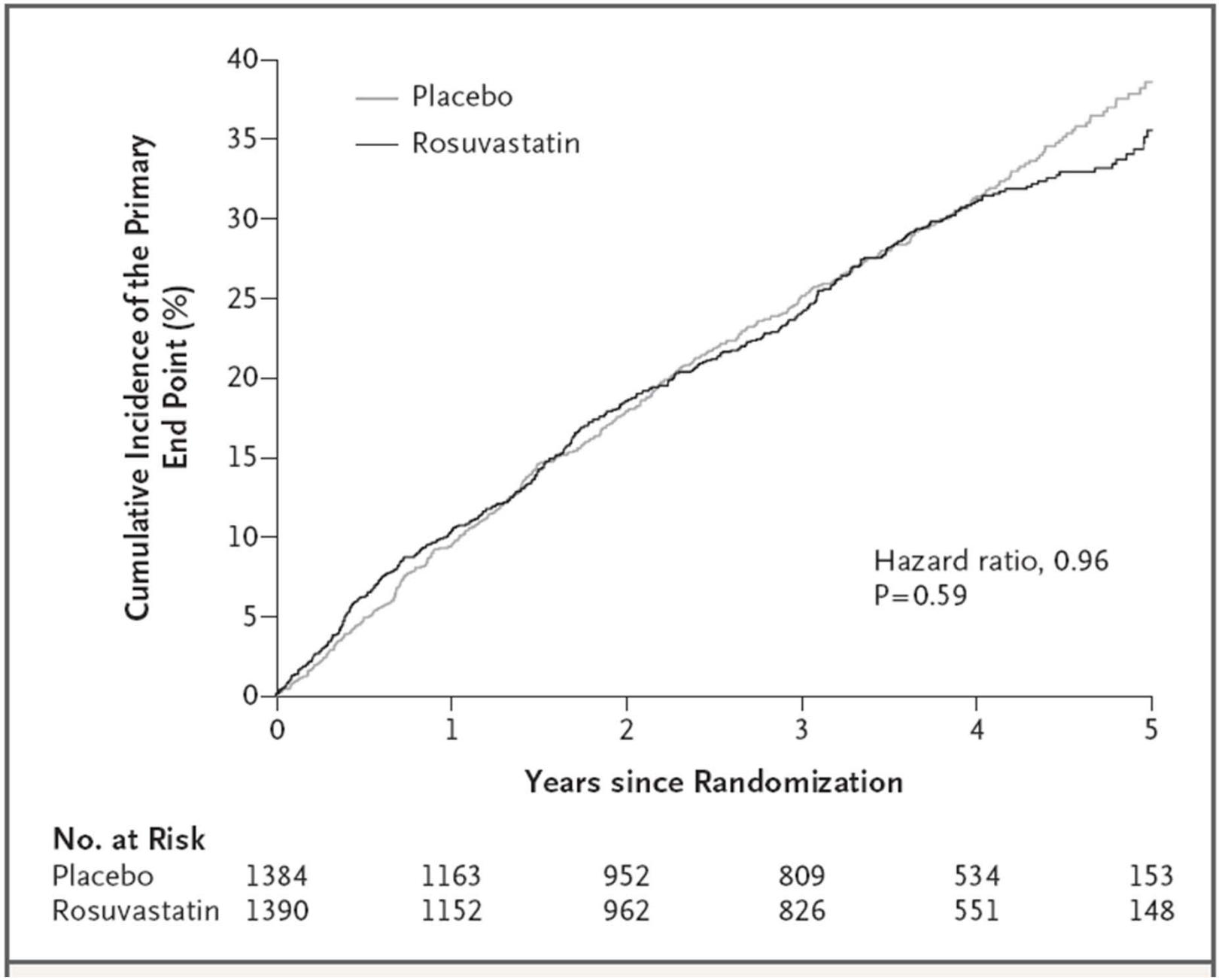
Effect of Statin on CVA in CKD patients.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis

Bengt C. Fellström, M.D., Ph.D., Alan G. Jardine, M.D., Roland E. Schmieder, M.D., Hallvard Holdaas, M.D., Ph.D., Kym Bannister, M.D., Jaap Beutler, M.D., Ph.D., Dong-Wan Chae, M.D., Ph.D., Alejandro Chevaile, M.D., Stuart M. Cobbe, M.D., Carola Grönhagen-Riska, M.D., Ph.D., José J. De Lima, M.D., Ph.D., Robert Lins, M.D., Ph.D., Gert Mayer, M.D., Alan W. McMahon, M.D., Hans-Henrik Parving, M.D., D.M.Sc., Giuseppe Remuzzi, M.D., Ola Samuelsson, M.D., Ph.D., Sandor Sonkodi, M.D., Ph.D., D. Sci., Gultekin Süleymanlar, M.D., Dimitrios Tsakiris, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Vasil Todorov, M.D., Ph.D., Andrzej Wiecek, M.D., Ph.D., Rudolf P. Wüthrich, M.D., Mattis Gottlow, M.Sc., Eva Johnsson, M.D., Ph.D., and Faiez Zannad, M.D., Ph.D., for the AURORA Study Group*



No. at Risk

Placebo	1384	1163	952	809	534	153
Rosuvastatin	1390	1152	962	826	551	148

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis

Christoph Wanner, M.D., Vera Krane, M.D., Winfried März, M.D., Manfred Olschewski, M.Sc., Johannes F.E. Mann, M.D., Günther Ruf, M.D., and Eberhard Ritz, M.D., for the German Diabetes and Dialysis Study Investigators*

Statin for CV events

Effective

?

type 2 DM Without dialysis

type 2 DM Receiving hemodialysis

4D study

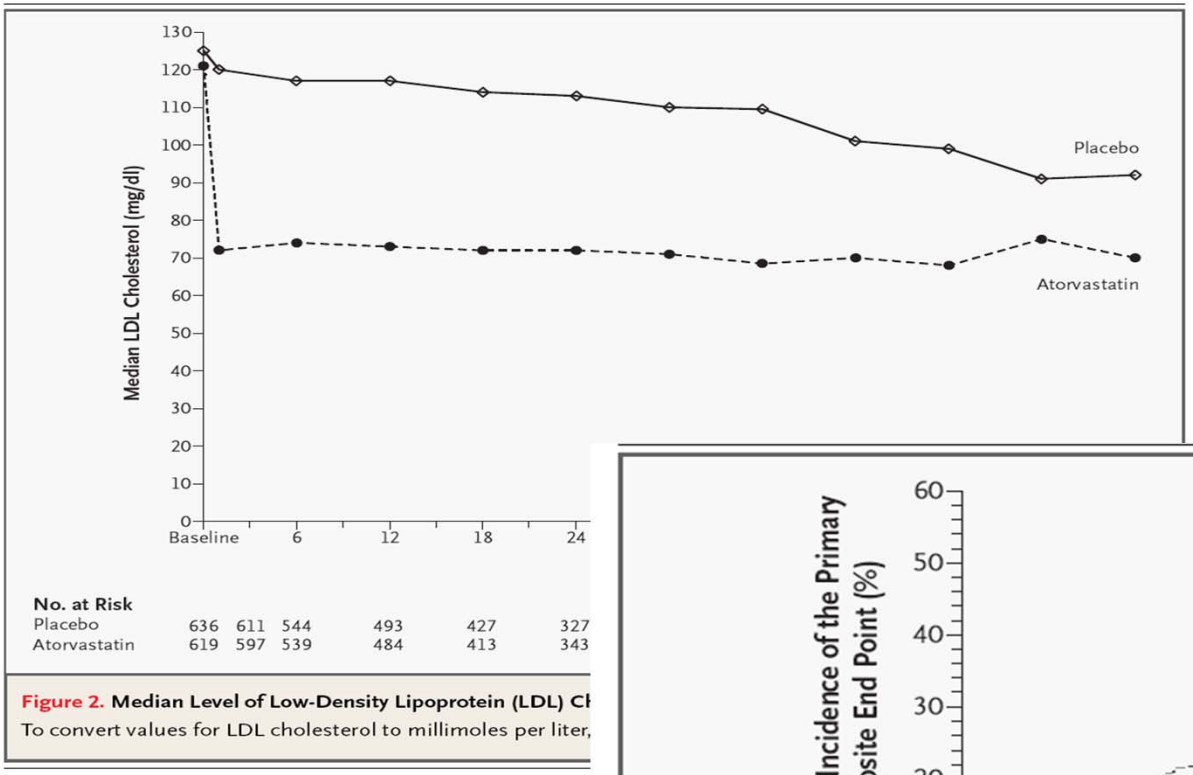


Figure 2. **Median Level of Low-Density Lipoprotein (LDL) Ch**
To convert values for LDL cholesterol to millimoles per liter,

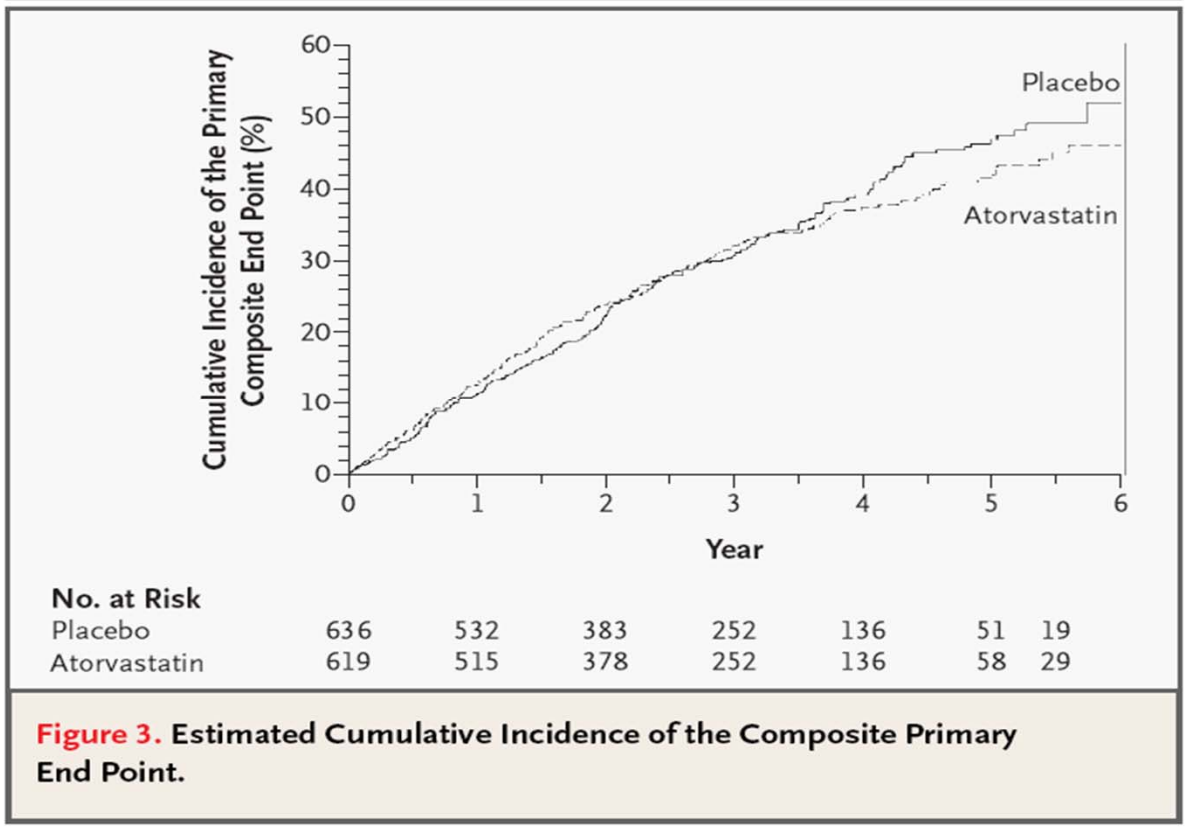
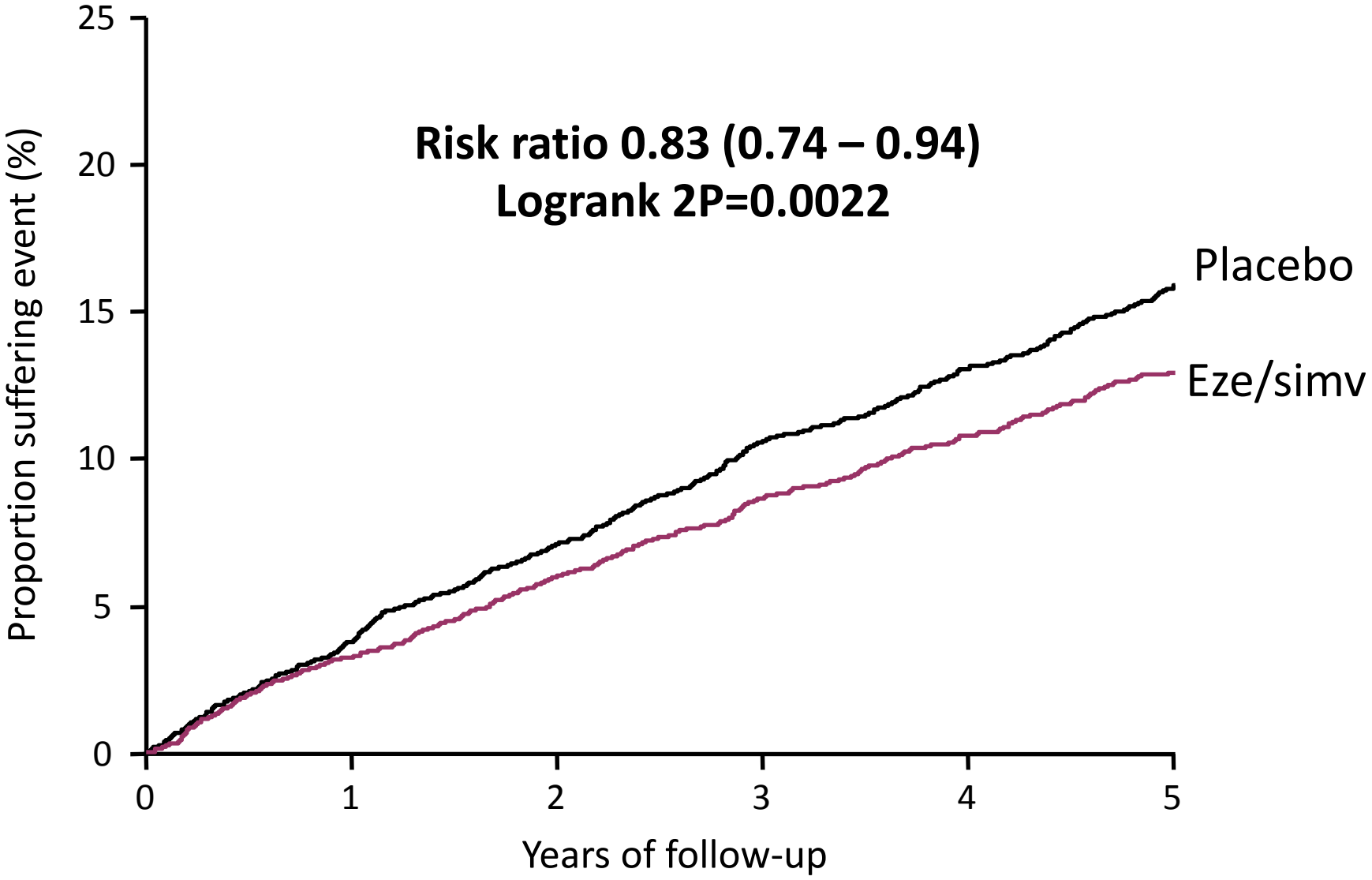


Figure 3. **Estimated Cumulative Incidence of the Composite Primary End Point.**

Heart and Renal Protection Study(SHARP)

- Included patients: History of CKD
  - not on dialysis: elevated Cr on 2 occasions
    - Men: ≥1.7 mg/dL (150 μmol/L)
    - Women: ≥1.5 mg/dL (130 μmol/L)
  - on dialysis: HD or PD
- Age ≥40 years
- No history of MI or coronary revascularization

SHARP: Major Atherosclerotic Events

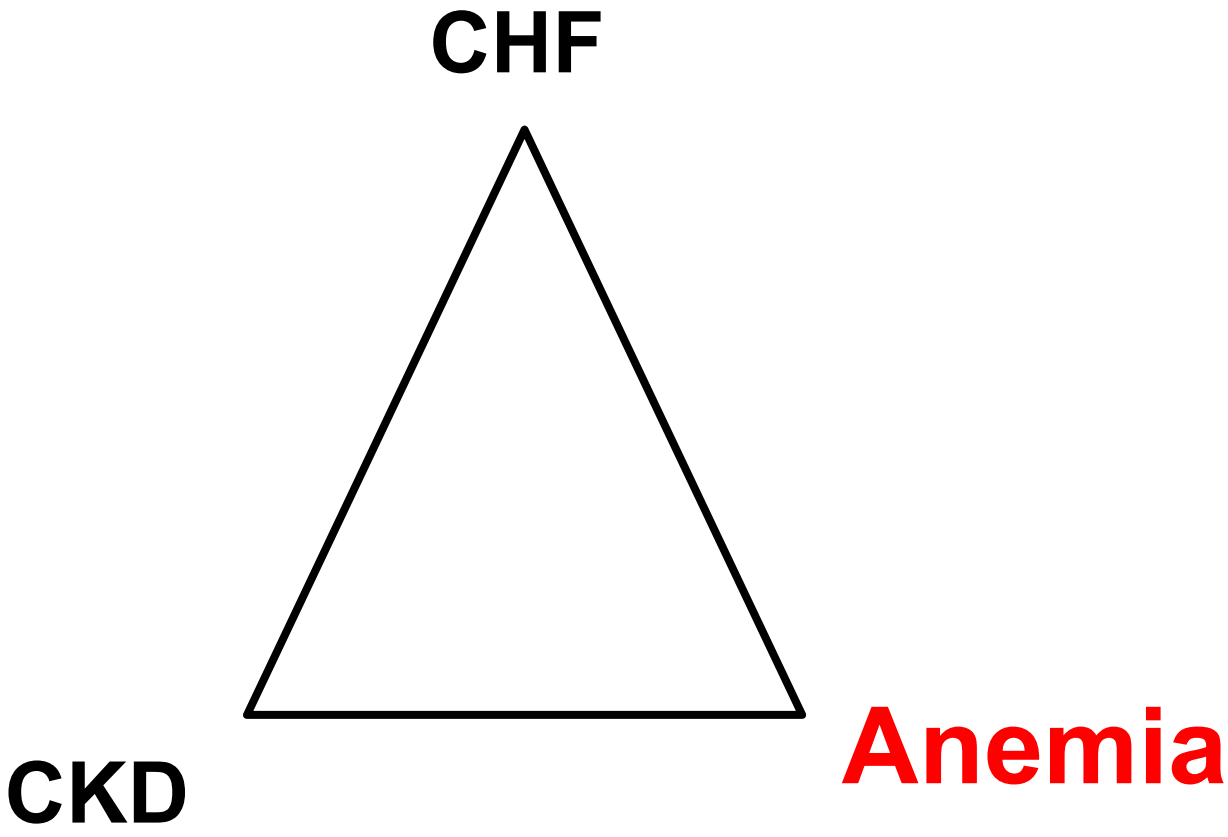


Results of statin trial in CKD patients

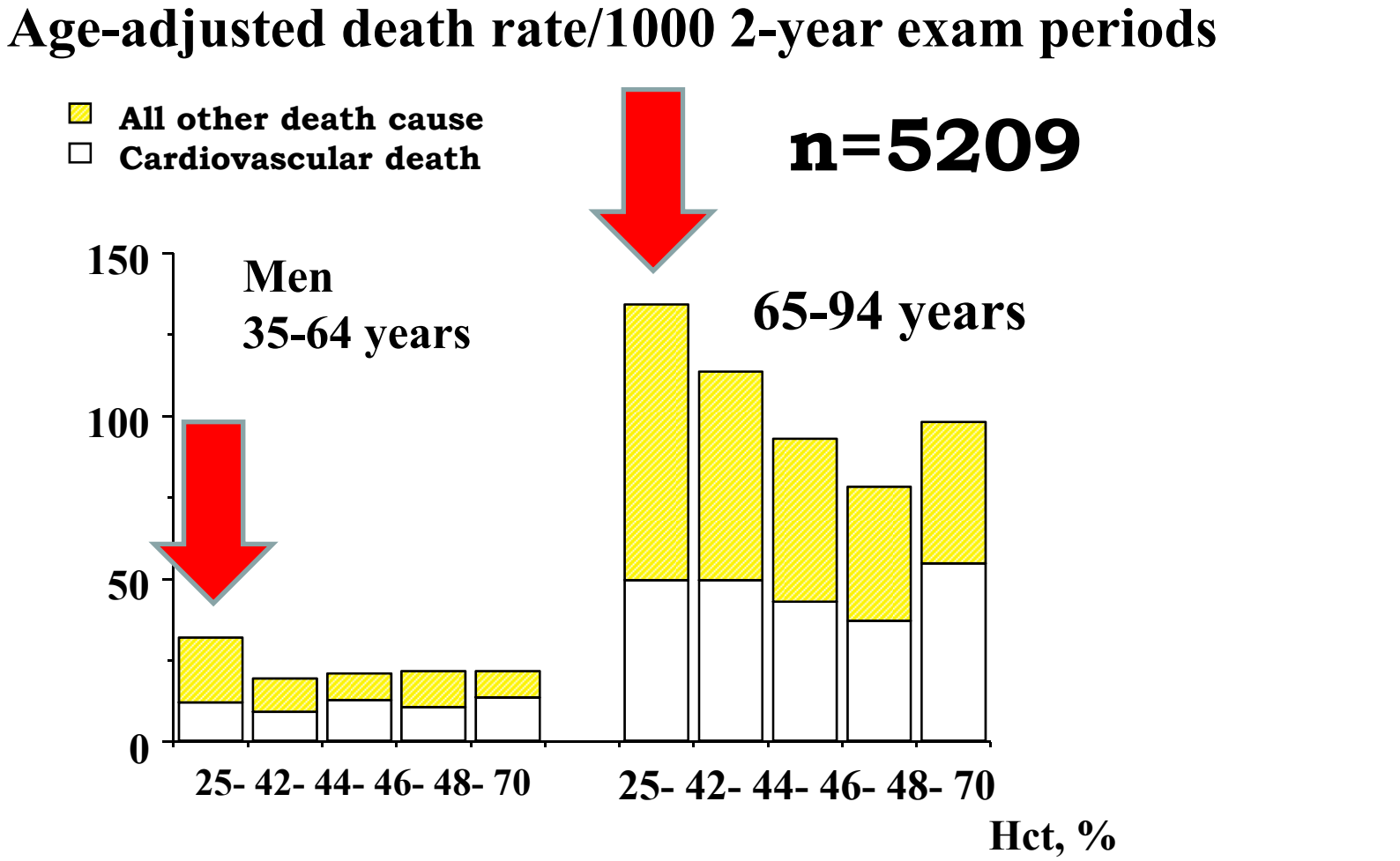
- Use of statin in patients with dialysis is not effective to prevent CVA.

- Early control of dyslipidemia is essential to prevent cardiac damage in CKD patients

Cardio Renal Anemia Syndrome



Hematocrit and the risk of cardiovascular disease--the Framingham study: a 34-year follow



Gagnon et al. Am Heart J 1994:127:674

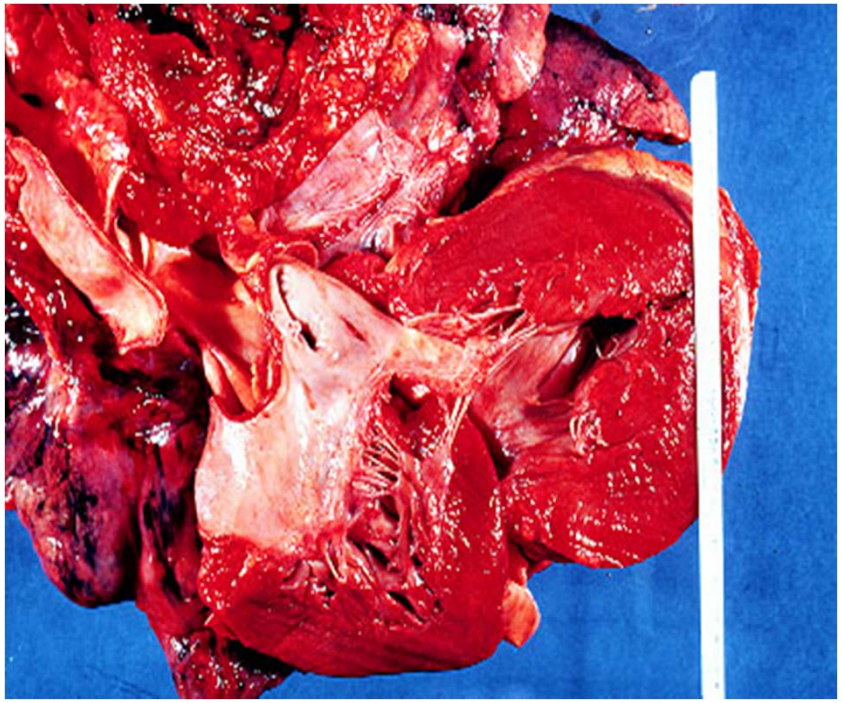
As the CHF worsens, the mean Hb conc. decreases because…

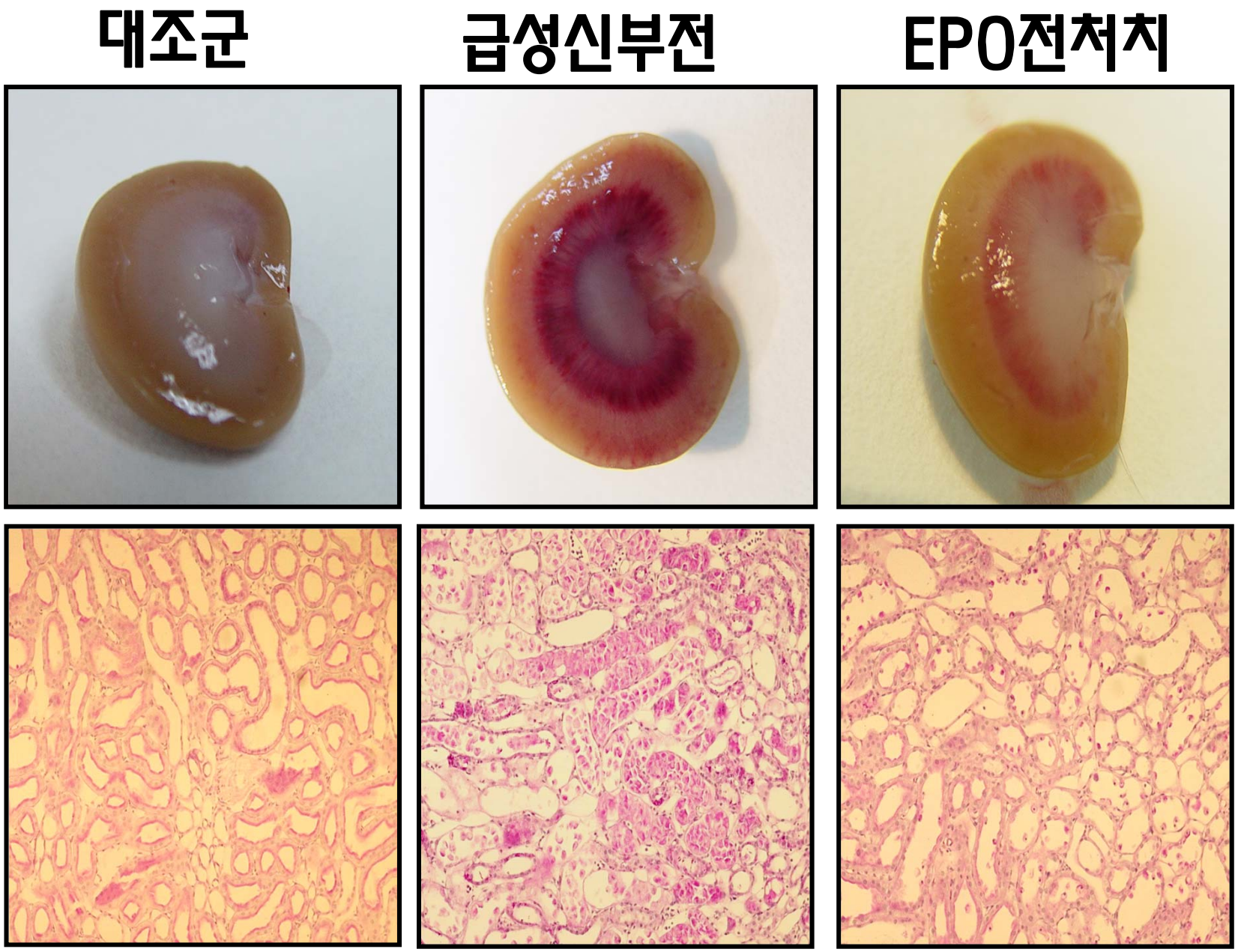
- Combined CKD-↓EPO level
- Plasma cytokine:↑ TNF alpha & IL-6
- Malabsorption
- ACEI or ARB
- hyperglycemia-↓EPO-producing cells
- Antiplatelet drugs

Khan NA, et al. Kidney function and mortality among patients with left ventricular systolic dysfunction. *J Am Soc Nephrol 2006;17:244 –253.*

좌심실비대 억제 약물

- ACE inhibitor
- ARB
- Beta-blocker
- Spirolactone
- rHuEPO





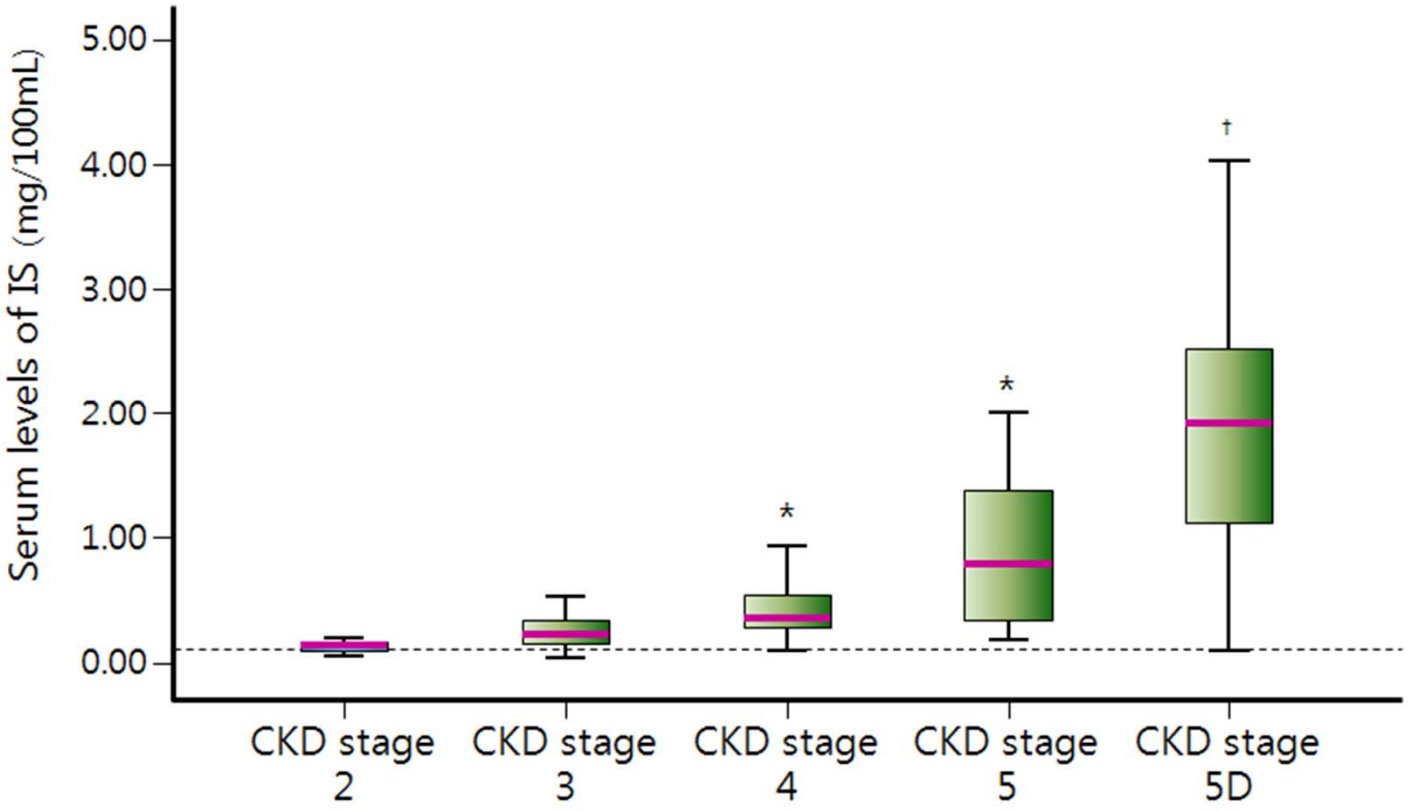
허혈성 손상 24시간후

Yang cw. FASEB J

EPO has renal and cardiac protective effect

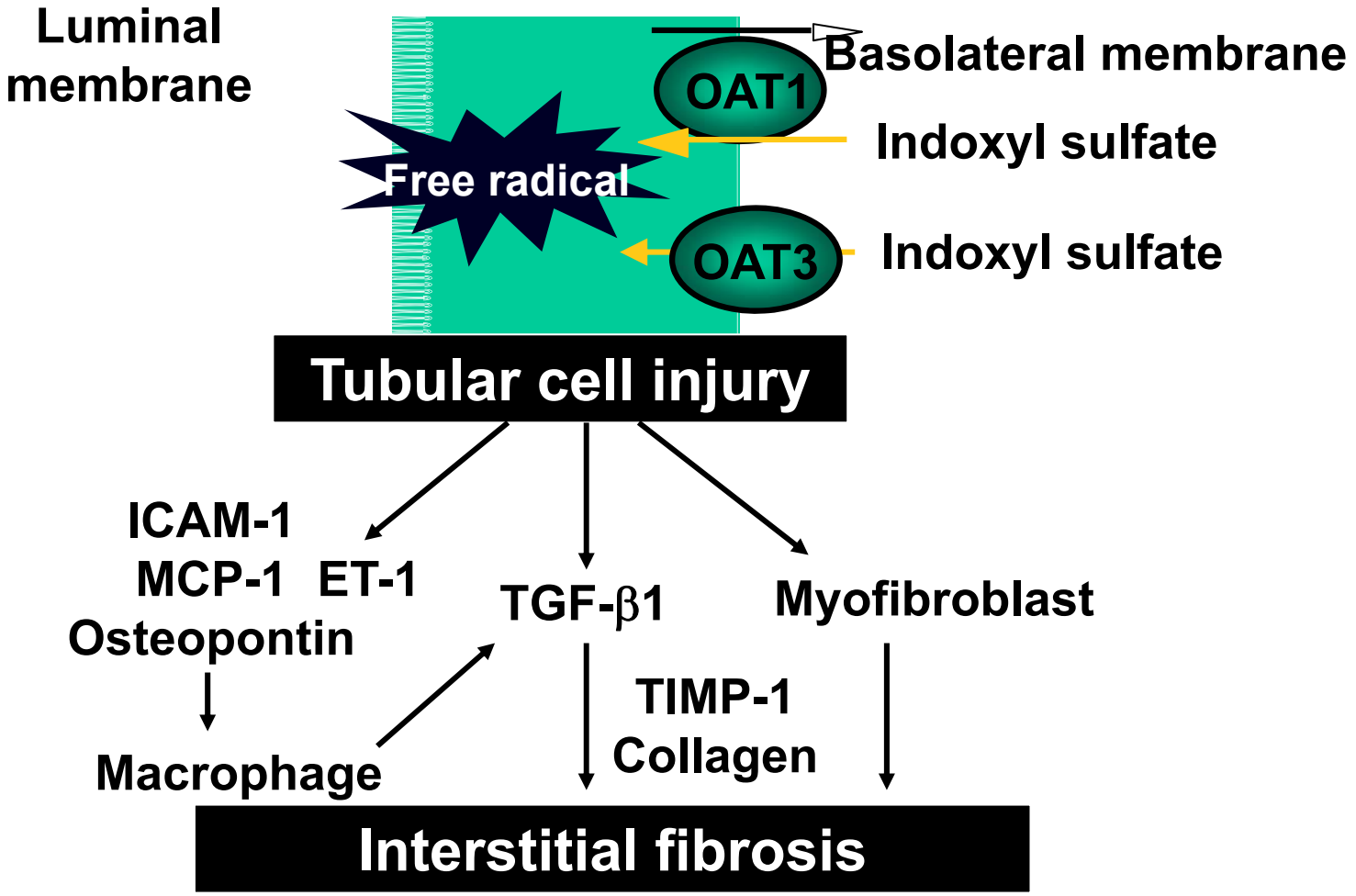
UREMIC TOXIN

Uremic toxin according to CKD stage



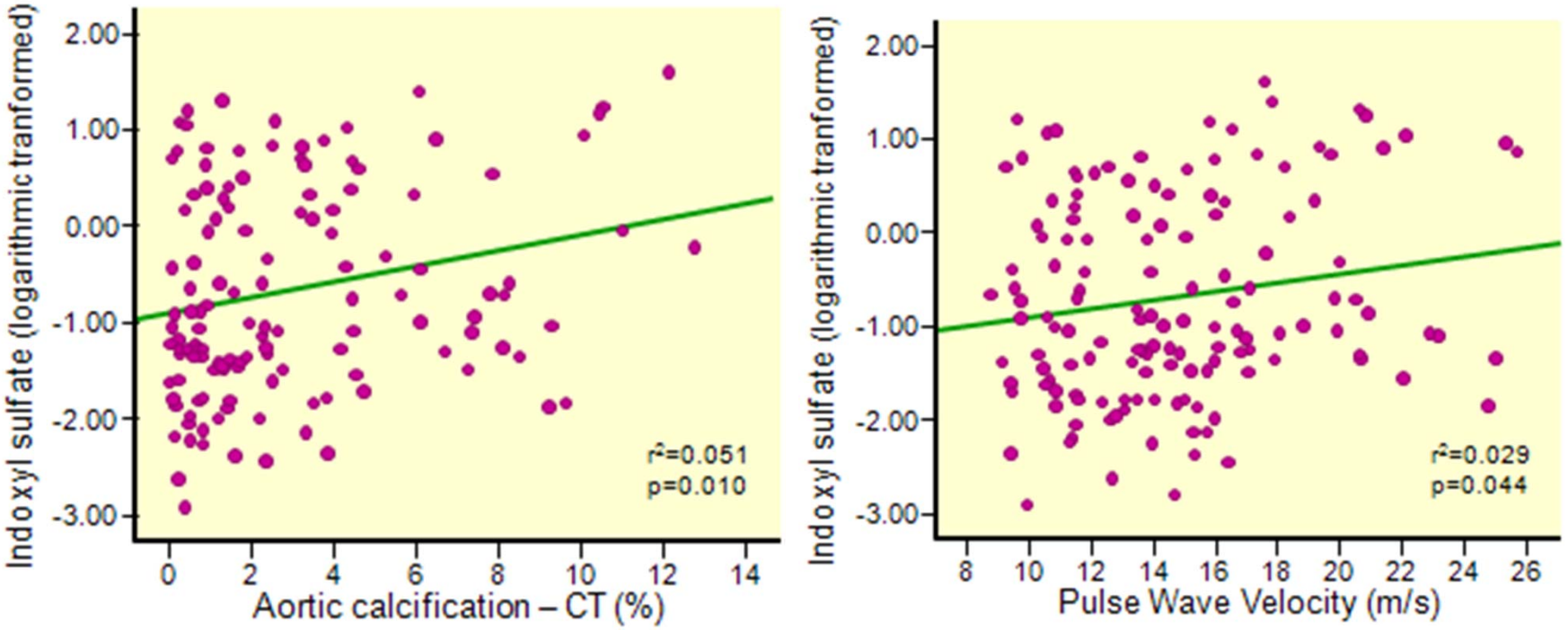
Clin J Am Soc Nephrol 4: 1551–1558, 2009

Uremic toxin and kidney injury



Role of Indoxyl Sulfate and OAT in Renal Tubular Cell Injury

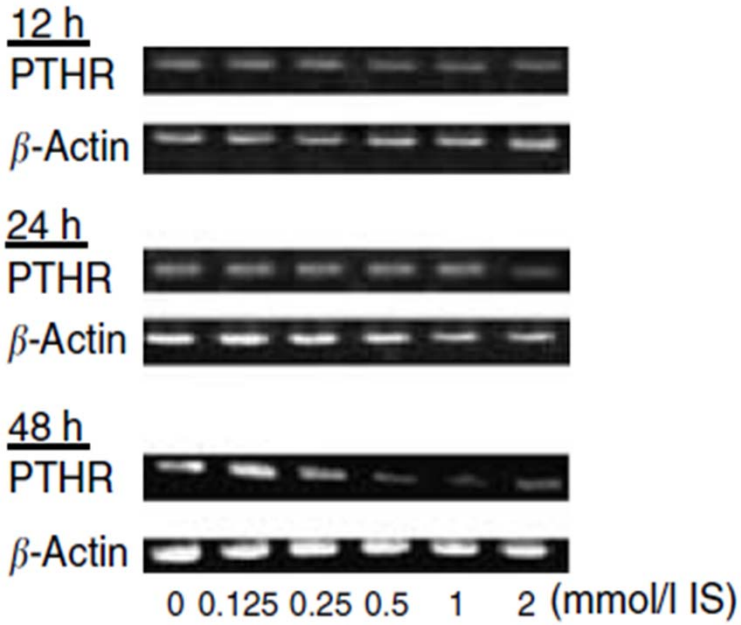
uremic toxins and vascular stiffness

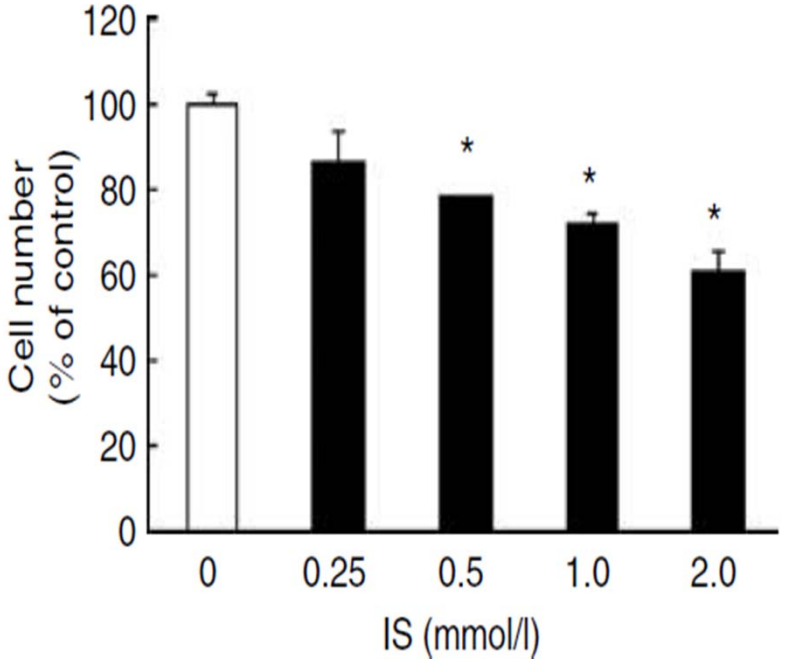


Clin J Am Soc Nephrol 4: 1551–1558, 2009

Uremic toxin and bone disease

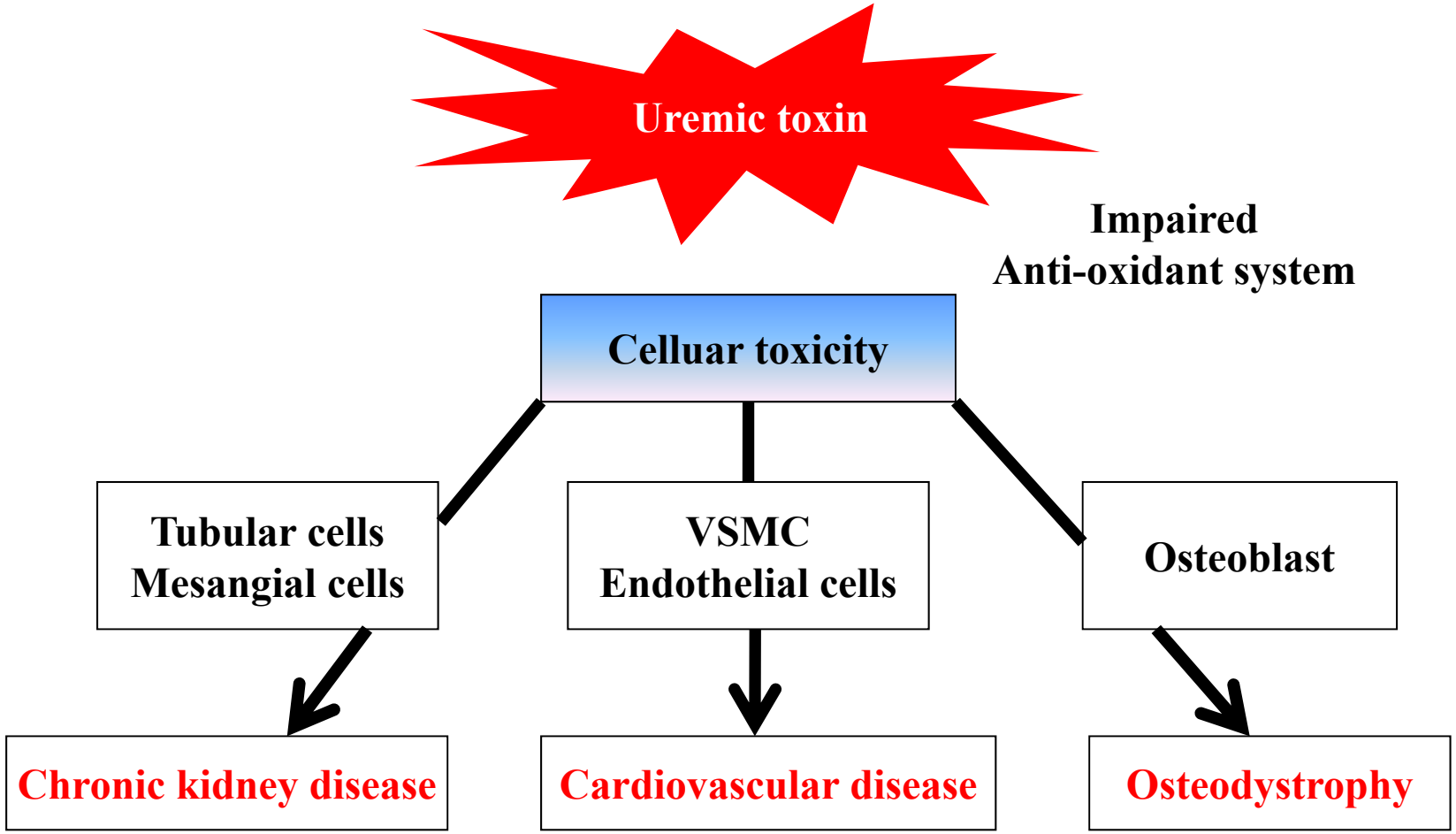
- **Indoxyl sulfate → PTH receptor ↓→ Impair osteoblastic function**





T Nii Kono et al, Kidney int 2007; 71:738-743

Spectrum of Uremic toxicity

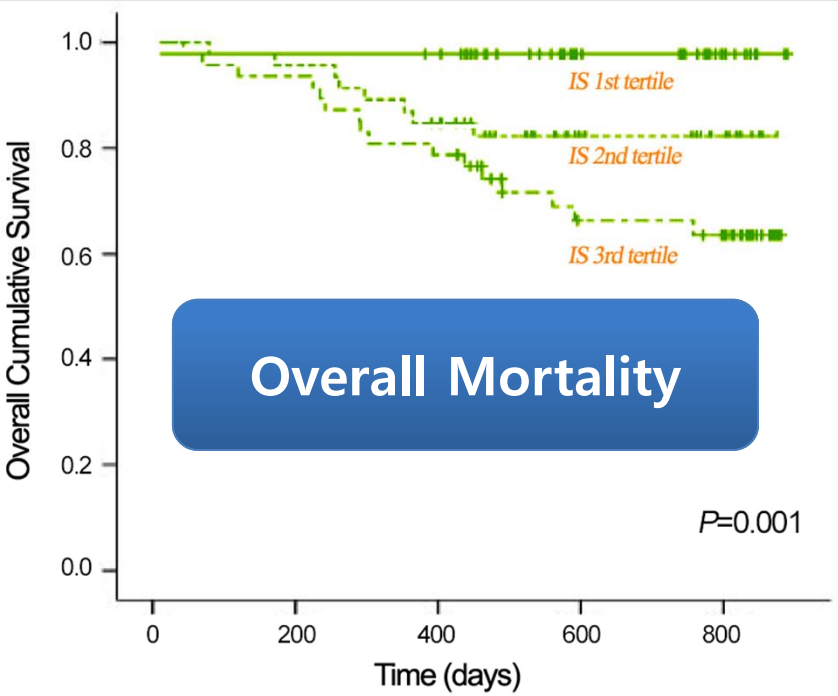


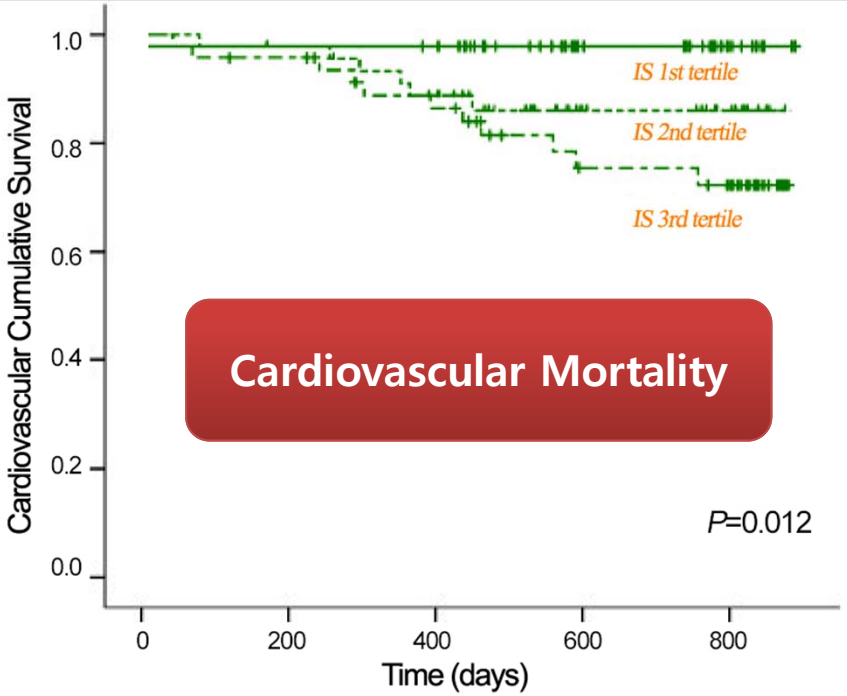
Nagoya J Med Sci 72:1-11, 2010

Serum Indoxyl Sulfate Is Associated with Vascular Disease and Mortality in Chronic Kidney Disease Patients

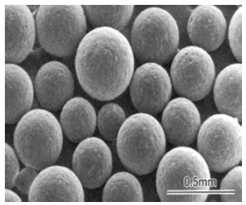
Fellype C. Barreto,*† Daniela V. Barreto,*† Sophie Liabeuf,*† Natalie Meert,‡ Griet Glorieux,‡ Mohammed Temmar,† Gabriel Choukroun,*§ Raymond Vanholder,‡ and Ziad A. Massy*†§ on behalf of the European Uremic Toxin Work Group (EUTox)

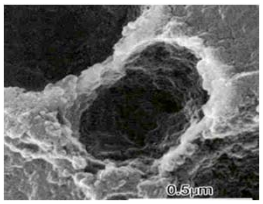
**INSERM ERI-12 (EA 4292), Amiens, France; †Clinical Research Centre, Division of Clinical Pharmacology, Amiens University Hospital, and the Jules Verne University of Picardy, Amiens, France; ‡Nephrology Section, Department of Internal Medicine, University Hospital, Gent, Belgium; and §Division of Nephrology, Amiens University Hospital, Amiens, France*





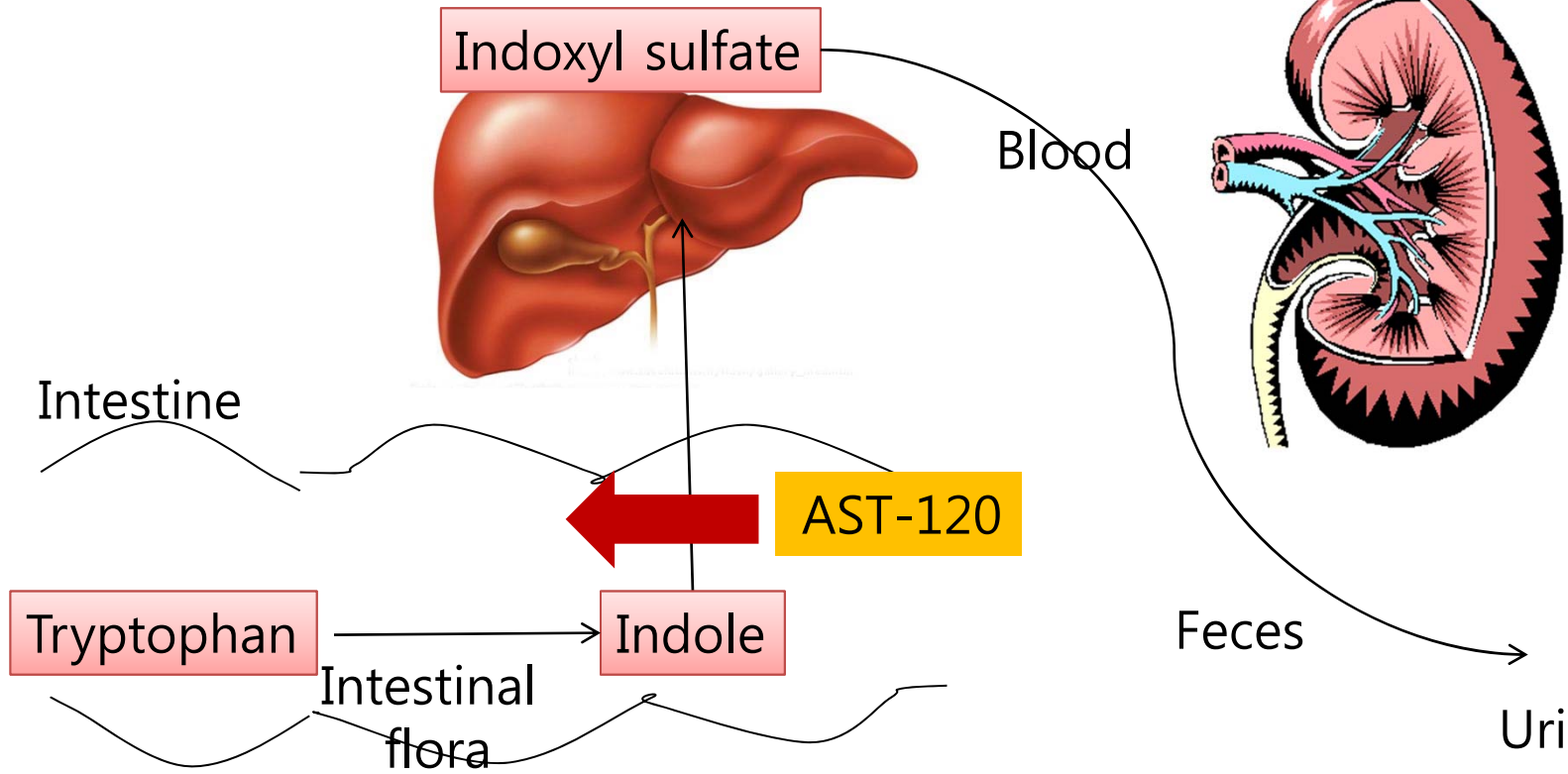
Clin J Am Soc Nephrol 4: 1551–1558, 2009





Uremic toxin absorber: AST-120 (Kremezin®)

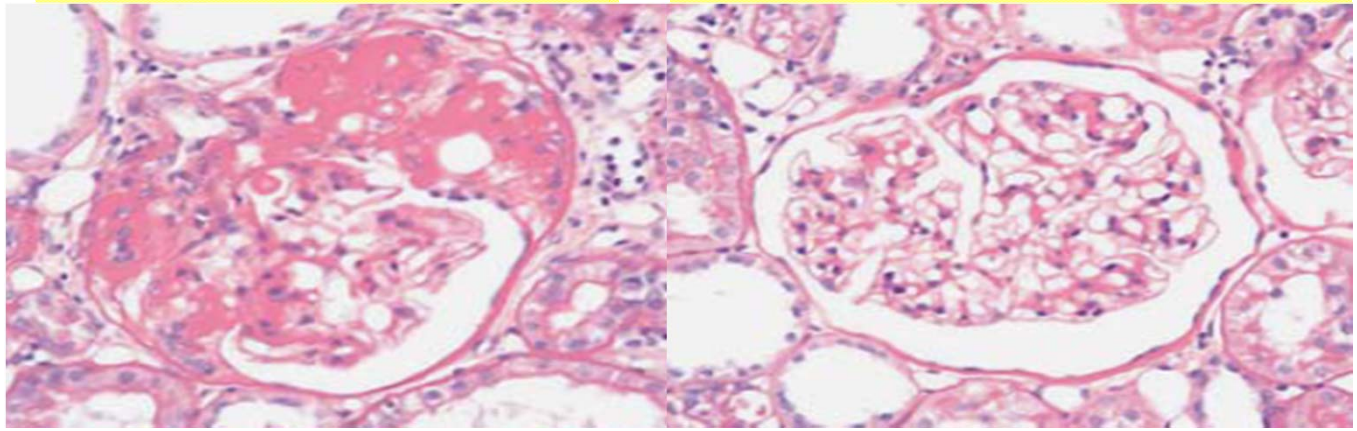
- Indoxyl sulfate is considered to be key target uremic toxin for AST-120

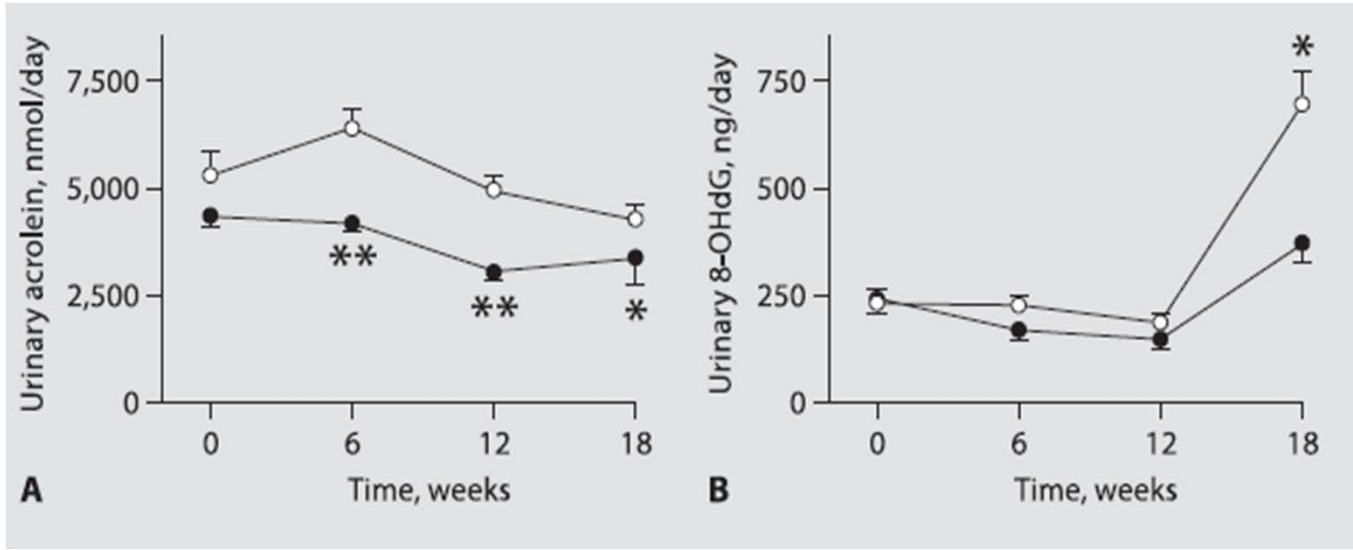


(Yamagishi, Nakamura et al. 2007 Journal/Med Hypotheses)

5/6 Nephretomized Uremic Mode

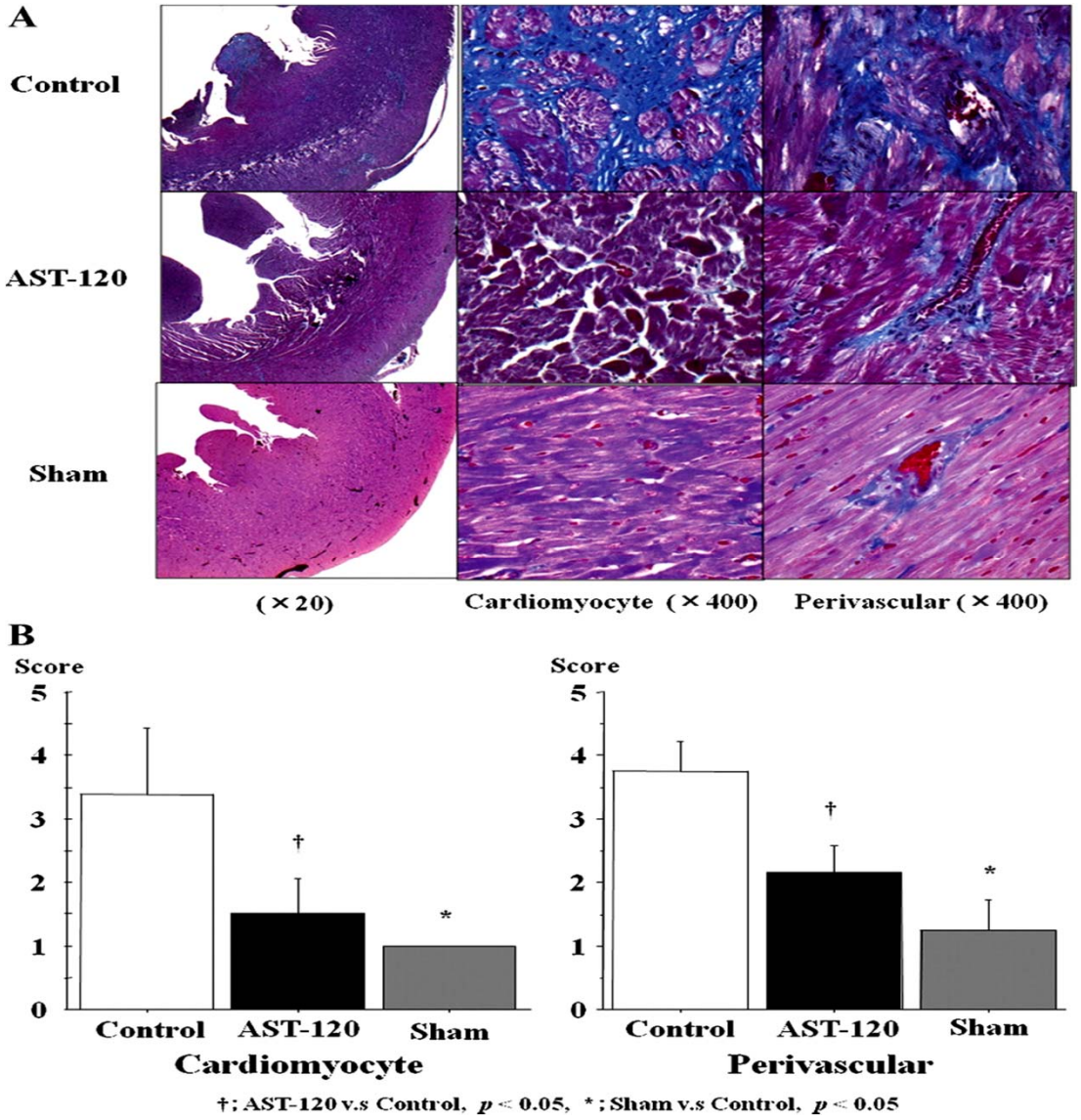
Control uremic group | **AST 120 gruop**





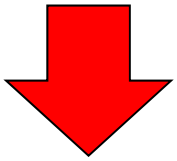
Am J Nephrol 2006; 26: 455-461

Cardiac fibrosis in the control and AST-120-treated CKD, and sham-operated rats

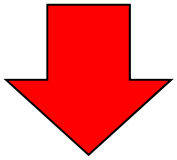


Fujii H, et al., Nephrol Dial Transplant 24:2089-2095, 2009

Removal of uremic toxin



↓ Oxidative stress

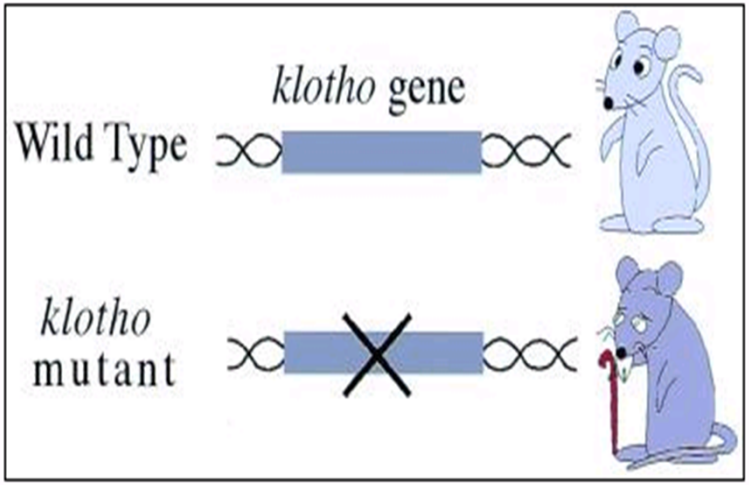


↓Progression of CKD and CHF

KLOTHO, anti-aging gene

Suppressor of multiple aging phenotypes

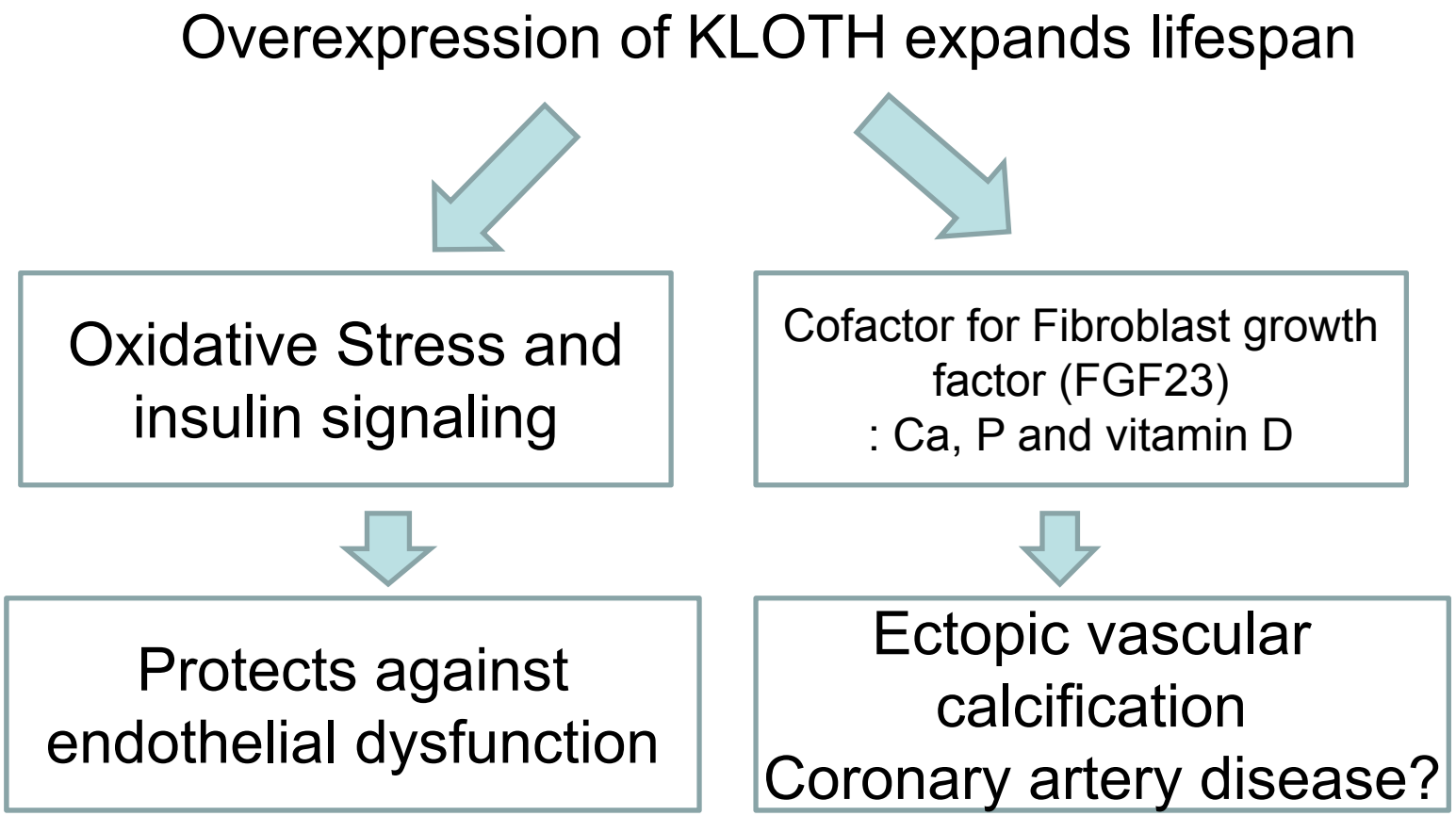
Mutation of the mouse Klotho gene leads to a syndrome resembling aging.



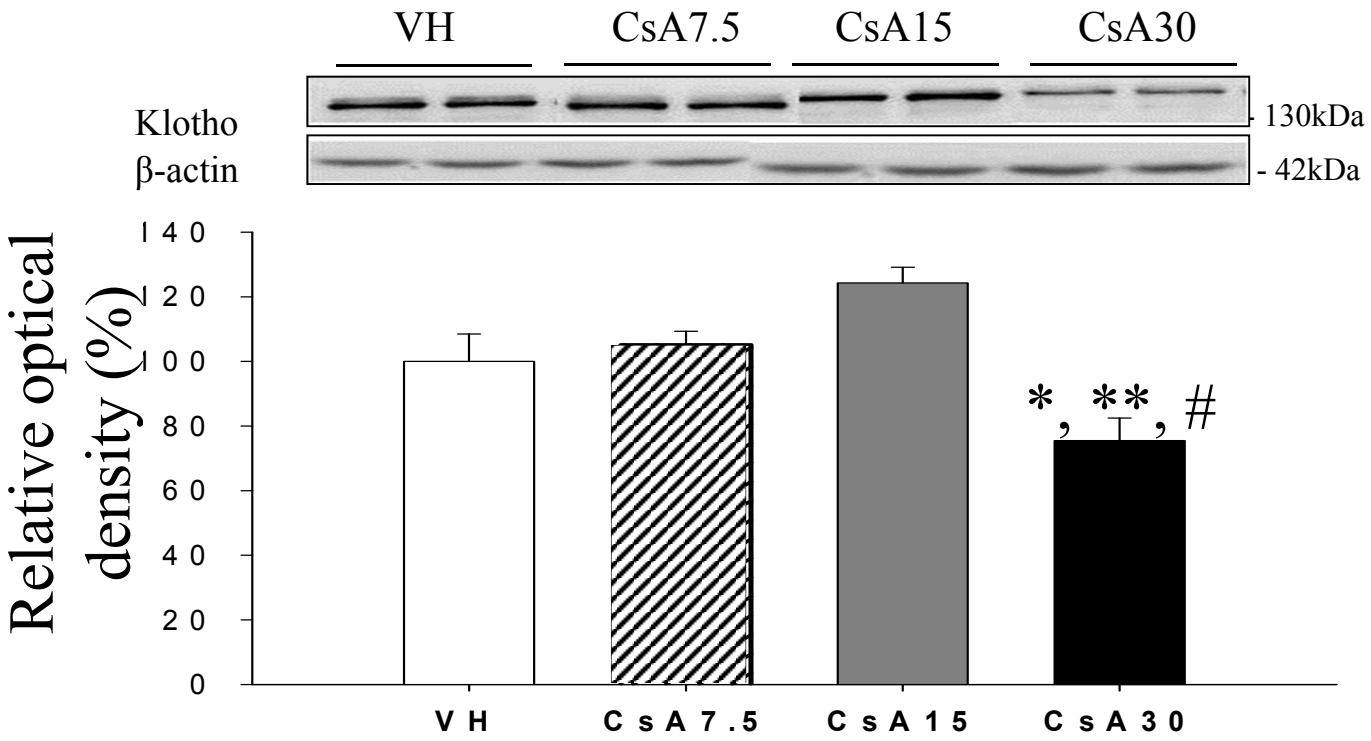
- Shortened lifespan
- Infertility
- Arteiosclerosis
- Mitral annular calcification
- Skin atrophy
- Osteoporosis emphysema

(Makoto Kuro-o et al., *nature* 390: 45-51, 1997)

Current understanding of KLOTHO



Response of KLOTHO against cyclosporine-induced oxidative stress



Nephrol Dial Transplant (2010) 1 of 14
doi: 10.1093/ndt/gfq537

Original Article

NDT
Nephrology Dialysis Transplantation

Angiotensin II blockade upregulates the expression of Klotho the anti-ageing gene, in an experimental model of chronic cyclosporine nephropathy

Hye Eun Yoon[1], Jung Yeon Ghee[2], ShangGuo Piao[2], Ji-Hyun Song[2], Dong He Han[2], Sol Kim[3], Naro Ohashi[4], Hiroyuki Kobori[4], Makoto Kuro-o[5] and Chul Woo Yang[2]

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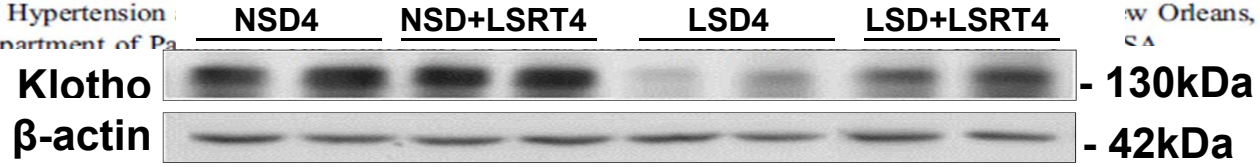
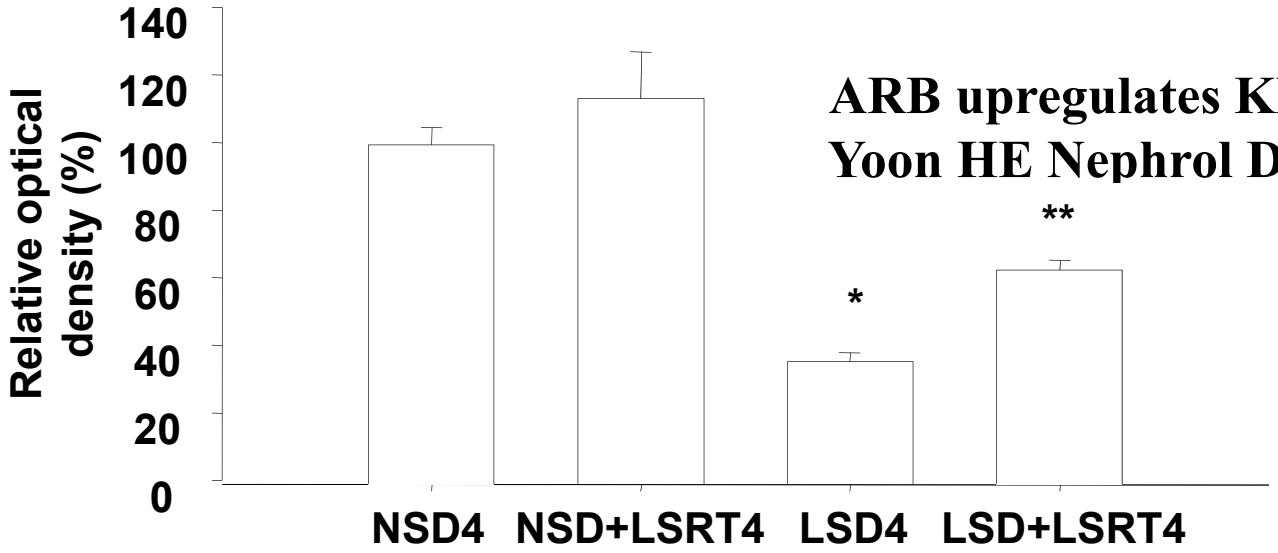
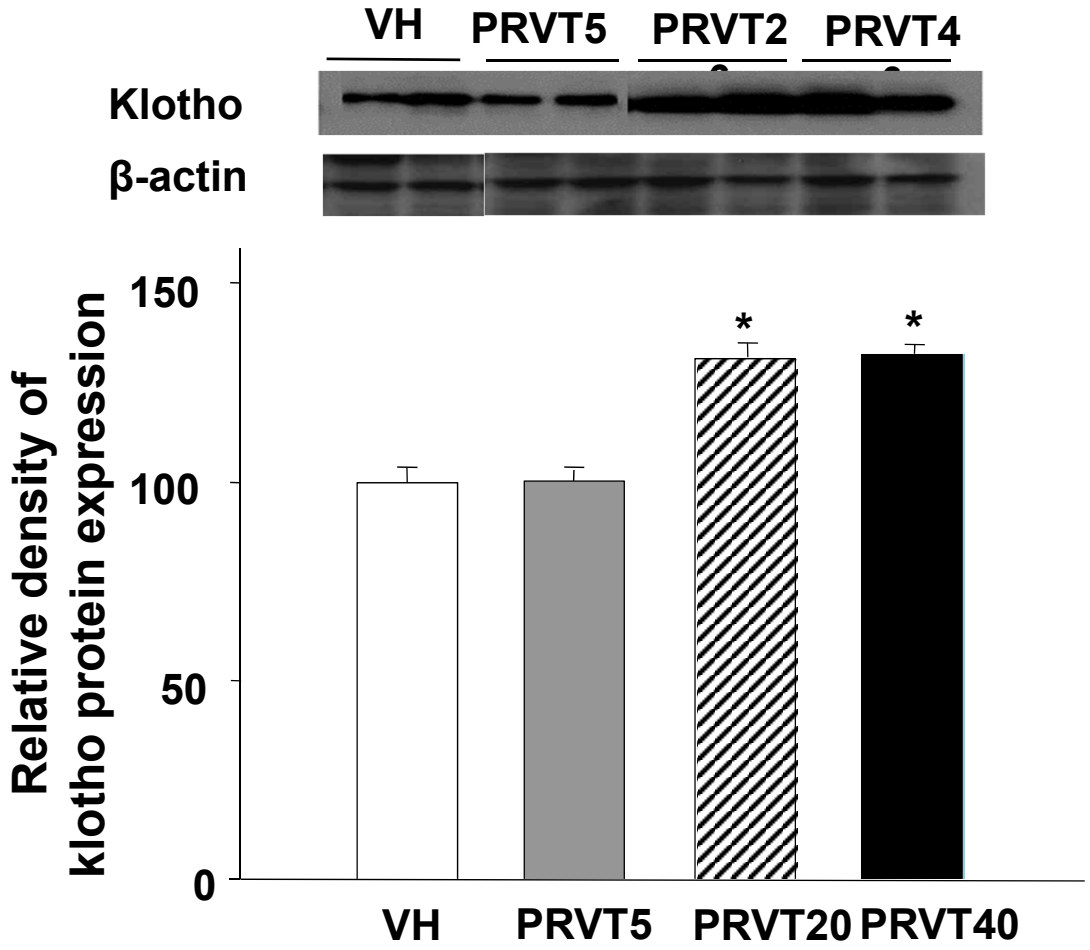
[5]Department of Pa... SA





ARB upregulates KLOTHO expression.
Yoon HE Nephrol Dial Transplant, 2010

Effect of Statin on KLOTHO expression in normal mice kidney



Circulation
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Angiogenesis and Vasculogenesis Are Impaired in the Precocious-Aging klotho Mouse

Toshifumi Shimada, Yoshiaki Takeshita, Toyoaki Murohara, Ken-ichiro Sasaki, Kimiyasu Egami, Satoshi Shintani, Yosuke Katsuda, Hisao Ikeda, Yo-ichi Nabeshima and Tsutomu Imaizumi

Circulation 2004;110;1148-1155; originally published online Aug 9, 2004;
DOI: 10.1161/01.CIR.0000139854.74847.99

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Regulation of Oxidative Stress by the Anti-aging Hormone Klotho*◆

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Masaya Yamamoto, Jeremy D. Clark, Johanne V. Pastor, Prem Gurnani, Animesh Nandi, Hiroshi Kurosu, Masayoshi Miyoshi, Yasushi Ogawa, Diego H. Castrillon, Kevin P. Rosenblatt, and Makoto Kuro-o[1]

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Summary

- Maximal RAS inhibition is needed to reduce target organ injury.
- Statin is effective in early CKD patients with hyperlipidemia.
- rHEPO is recommended in anemic patients with CHF
- Uremic toxin itself is responsible for vascular damage.
- KLOTHO is the promising gene for protecting vascular injury

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