The 4th Asian Forum of the CKD Initiatives

June 4, 2010 in Seoul , Korea

An approach for Asian common estimated glomerular filtration rate (eGFR) equation

Yoshinari Yasuda, Li Zuo and Masaru Horio

Asian Forum of CKD Initiative (AFCKDI)

WG1. GFR equation and Cr standardization

➢Reliable eGFR equations should be the fundamental scheme in CKD initiatives, such as epidemiological CKD survey, clinical guideline for CKD and international collaborative study.

➢Asian Forum CKD Initiatives (AFCKDI) constituted a GFR working group (WG), where sCr standardization and an international collaborative study for creating Asian common GFR equation are now in progress.

Masaru Horio	Japan	Co-chair
Li Zuo	China	Co-chair
Hung-Chun Chen	Taiwan	
Ho Yung Lee	Korea	
Yon Su Kim	Korea	
Kearkiat Praditpornsilpa	Thailand	
Kevan Polkinghorne	Australia	
Elizabeth Sebastian	Philippine	
Yoshinari Yasuda	Japan	Secretary

Topics

1) Standardization of the creatinine

2) Controversy for eGFR in Asians: Comparative analyses of different GFR measurement methods

3) Asian Collaborative Study for Creation of GFR Estimation Equation (ACOS-CG-FREE)

CKD definition

(a) Obvious kidney damage shown by urinalysis, blood chemistry, images, or pathology of the kidney; in particular, the presence of proteinuria is important

(b) GFR < 60 mL/min/1.73 m^2

Persistent evidence of (a) and/or (b) for 3 months or longer

Instances of kidney damage

- Urinary abnormalities, such as proteinuria including microalbuminuria
- Abnormalities of imaging testing, such as single kidney or polycystic kidney
- Abnormalities of blood biochemistry, such as those indicating kidney dysfunction
- Abnormal histological findings

CKD stage	Severity	Level of GFR mL/min/1.73 m^2
–	High risk	≥90
1	Kidney damage and normal or increased GFR	≥90
2	Kidney damage and decreased GFR, mild	60–89
3	Decreased GFR, moderate	30–59
4	Decreased GFR, severe	15–29
5	Kidney failure	<15

GFR is essential for CKD diagnosis and staging.

Gold standard for GFR is inulin clearance.

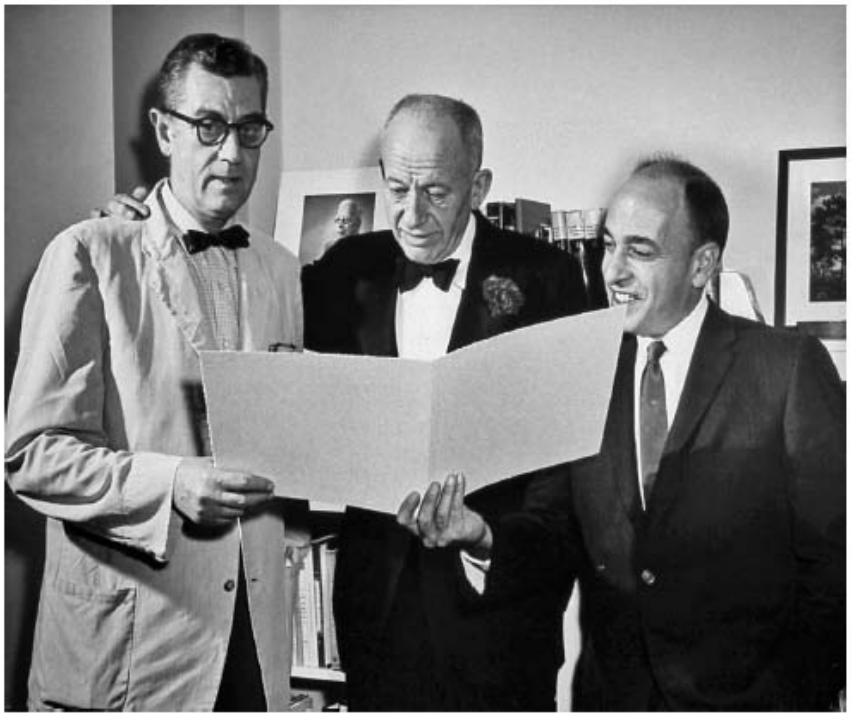


Figure 1
James A. Shannon, Robert Berliner, and Homer W. Smith (center) prior to Smith's lecture on April 26, 1960 (NIH, Bethesda, Maryland, USA). Image courtesy of the National Library of Medicine.

TABLE I

Summary of observations on normal men

Subject	Surface area	Number of observation periods	Average inulin clearance	Average $\frac{\text{urea}}{\text{inulin}}$	Average $\frac{\text{xylose}}{\text{inulin}}$	Inulin given	Inulin excreted in 24 hours
	square meters					*grams*	*per cent*
J. A. S...	2.10	2	142	0.65	0.80	160	92
M. C....	2.08	4	129	0.59	0.82		
R. S....	1.75	6	141		0.71		
B. R....	1.67	4	93		0.81		
		3	84	0.67	0.81	100	95
W. F....	1.69	6	82		0.78	100	97
		9	72		0.79	100	98
		3	76	0.65	0.80	100	103
J. C....	1.63	9	110		0.76		
S. C....	1.79	3	123	0.62	0.73		
		3	128		0.79		
Average .				0.635	0.78		97

(Shannnon JA, Smith HW: J Clin Invest 14: 393-401, 1935)

In clinical setting, kidney function is evaluated by estimated GFR (eGFR).

< Original MDRD >

$$= 186 \times S.Cr^{-1.154} \times Age^{-0.203}$$

x 0.742 (if female)

x 1.210 (if African-American)

JASN 2000; 11 828A

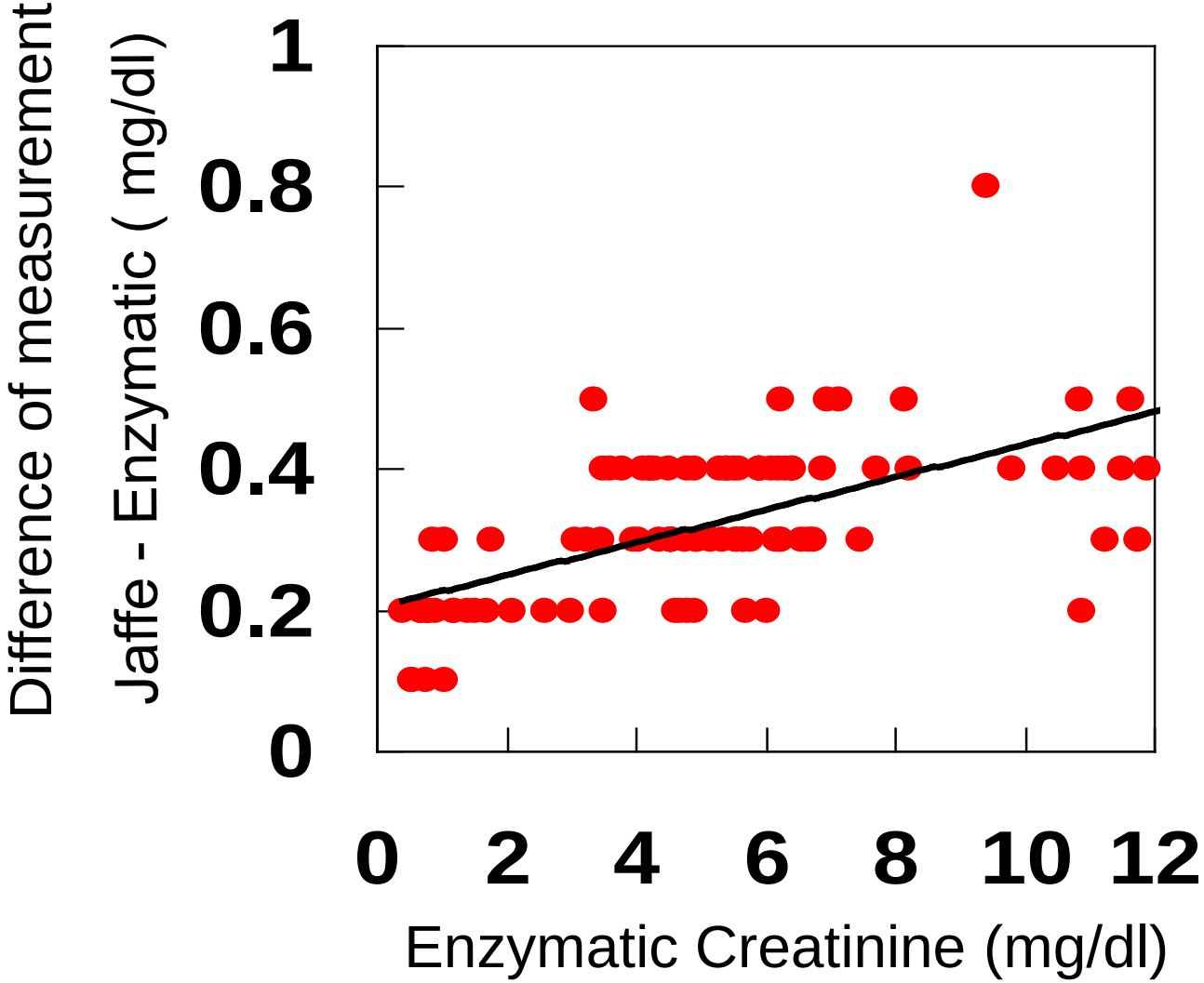
Accuracy of eGFR depends on the accuracy of creatinine measurement.

Methods of creatinine measurement

1) **Jaffe method**
   1. **Jaffe method without offset** (Conventional)
      The results are higher than target values due to non-creatinine chromogens.
   2. **Jaffe method with offset** (Compensated)
      The systemic bias due to non-creatinine chromogens is corrected.
2) **Enzymatic method**
   More accurate than Jaffe method.
3) **IDMS** (Isotope dilution mass spectrometry)
   Reference method of creatinine measurement.
   Target value of standard reference material (SRM) is assigned by this method.

Jaffe method without offset

0.2 - 0.4mg/dl higher than enzymatic method.



Jaffe method with offset

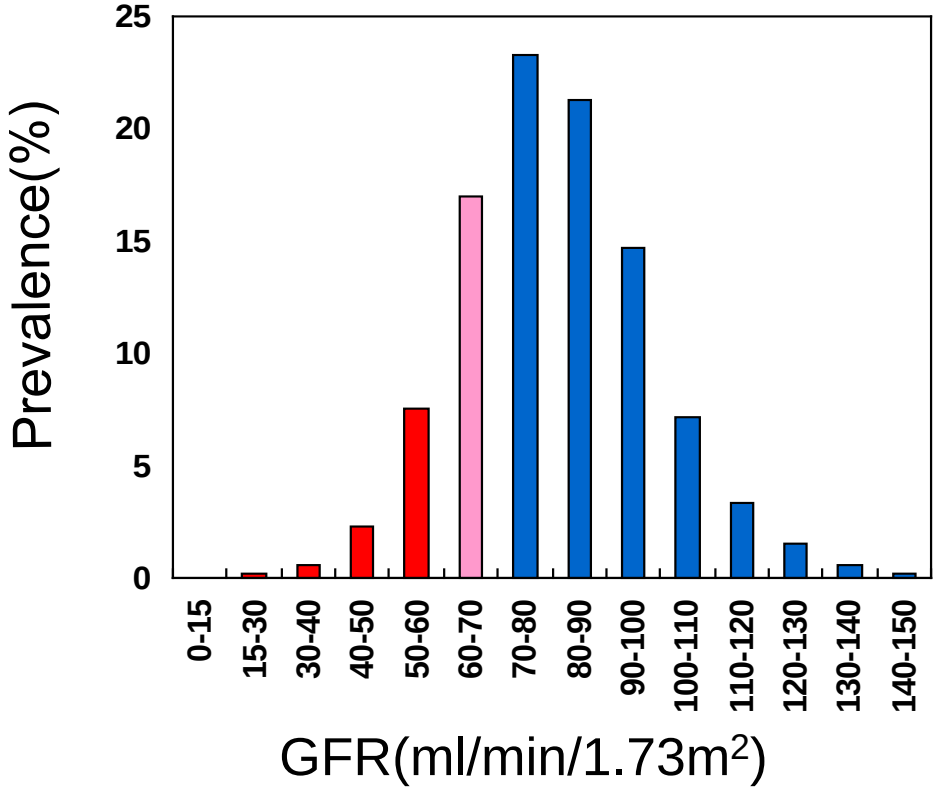
Results are corrected with an “average” (ex, 0.3mg/dl) offset for non-creatinine chromogens.

Sample	**Target mg/dl (µM)**	Roche H917 **Enzymatic**	Roche H917 **Jaffe**	Advia 2400 **Jaffe**
Saline Blank	**0 (0)**	0 (0)	-0.29 (-26)	-0.42 (-33)
SRM967 Lo	**0.75 (66.5)**	0.76 (67)	0.77 (68)	0.68 (60)
SRM967 Hi	**3.91 (346.2)**	3.91 (346)	3.90 (345)	3.73 (330)

(Peake M, Clin Biochem Rex 27:173, 2006)

Effect of positive bias of creatinine measurement on eGFR and prevalence of CKD

50 years Male
Serum Cr: 1.1mg/dl eGFR = 71ml/min/1.73m^2
Serum Cr: 1.3mg/dl eGFR = 58ml/min/1.73m^2
Positive bias (0.2mg/dl) of creatinine value leads to underestimation of eGFR by over 10ml/min/1.73m^2 .



Prevalence of CKD =10.6%. (GFR<60ml/min/1.73m^2)

IF subjects with GFR <70 are included, prevalence of CKD increases to 27.6%.

Evaluation of systemic bias of the MDRD-creatinine

MDRD study equation

Original (Jaffe method)

$GFR = 186 \times Cr^{-1.154} \times Age^{-0.203}$

IDMS-traceable (Enzymatic method)

$GFR = 175 \times Cr^{-1.154} \times Age^{-0.203}$

1) Standard reference materials were measured.
   IDMS = 1.00 x Enzyme
2) Inter-methods bias was evaluated.
   Enzyme = 0.906 x Jaffe(2005)
3) Drift with time in Jaffe method was evaluated.
   Jaffe(2005) = 1.046 x Jaffe(MDRD)
4) Systemic bias was calculated as 5%.
   IDMS = 0.95 x Jaffe(MDRD)

(Levey AS, Clin Chem. 53:766-772, 2007)

eGFR equations should be carefully selected for the adequate Cr measurement.

Jaffe Cr calibrated to the Cleveland Clinic
→ Original MDRD

$$= 186 \times S.Cr^{-1.154} \times Age^{-0.203}$$
$$\times 0.742 \text{ (if female)}$$
$$\times 1.210 \text{ (if African-American)}$$

JASN 2000; 11 828A

IDMS-traceable Cr → Re-expressed MDRD

$$= 175 \times S.Cr^{-1.154} \times Age^{-0.203}$$
$$\times 0.742 \text{ (if female)}$$
$$\times 1.210 \text{ (if African-American)}$$

Ann Intern Med 2006; 145: 247-254

CAP (The College of American Pathologists) Survey

2007

Method/Instrument	No. LABS	CHM-11 Mean	CHM-11 SD
All Method Principles All instruments	5382	0.697	0.073
Traditional calibration			
All Method Principles All instruments	3462	0.715	0.067
Enzymatic	692	0.757	0.054
Kinetic AlK Picrate	2499	0.705	0.065
Rate-BLK-Kinetic AlK Picrate	87	0.662	0.074
IDMS-traceable calibration			
All Method Principles All instruments	1208	0.642	0.059
Enzymatic	368	0.675	0.046
Kinetic AlK Picrate	522	0.637	0.056
Rate-BLK-Kinetic AlK Picrate	283	0.609	0.051

Cr Standardization Project in Asia

JCCRM 521: Standard material by Japanese Committee of Clinical Laboratory Standard, which is certificated by International Federation of Clinical Chemistry.

Protocol

- Two sets of standard materials (normal, high and very high Cr values) will be provided to each collaborating center in Asia (Australia, China, Korea, India, Indonesia, Malaysia, Philippine, Japan, Taiwan, Thai, Vietnam)
- The standard material will be measured 3 to 4 times for 2 days in a week.
- Additional sera prepared by Japanese Association of Medical Technologists will be also provided.
- This study is supported by Japanese research grant for Prof. Seiichi Matsuo.

Summary-1

1. GFR is essential for CKD diagnosis and staging.

2. Cr values is critical in Cr based eGFR equation.

3. IDMS-MDRD equation and IDMS-tracable Cr should be used for eGFR.

4. Cr standardization project is scheduled by AFCKDI.

Controversy in racial coefficient for Asians.

Jaffe Cr calibrated to the Cleveland Clinic
→ Original MDRD

$$= 186 \times S.Cr^{-1.154} \times Age^{-0.203}$$
$$\times 0.742 \text{ (if female)}$$
$$\times 1.210 \text{ (if African-American)}$$

JASN 2000; 11 828A

IDMS-traceable Cr → Re-expressed MDRD

$$= 175 \times S.Cr^{-1.154} \times Age^{-0.203}$$
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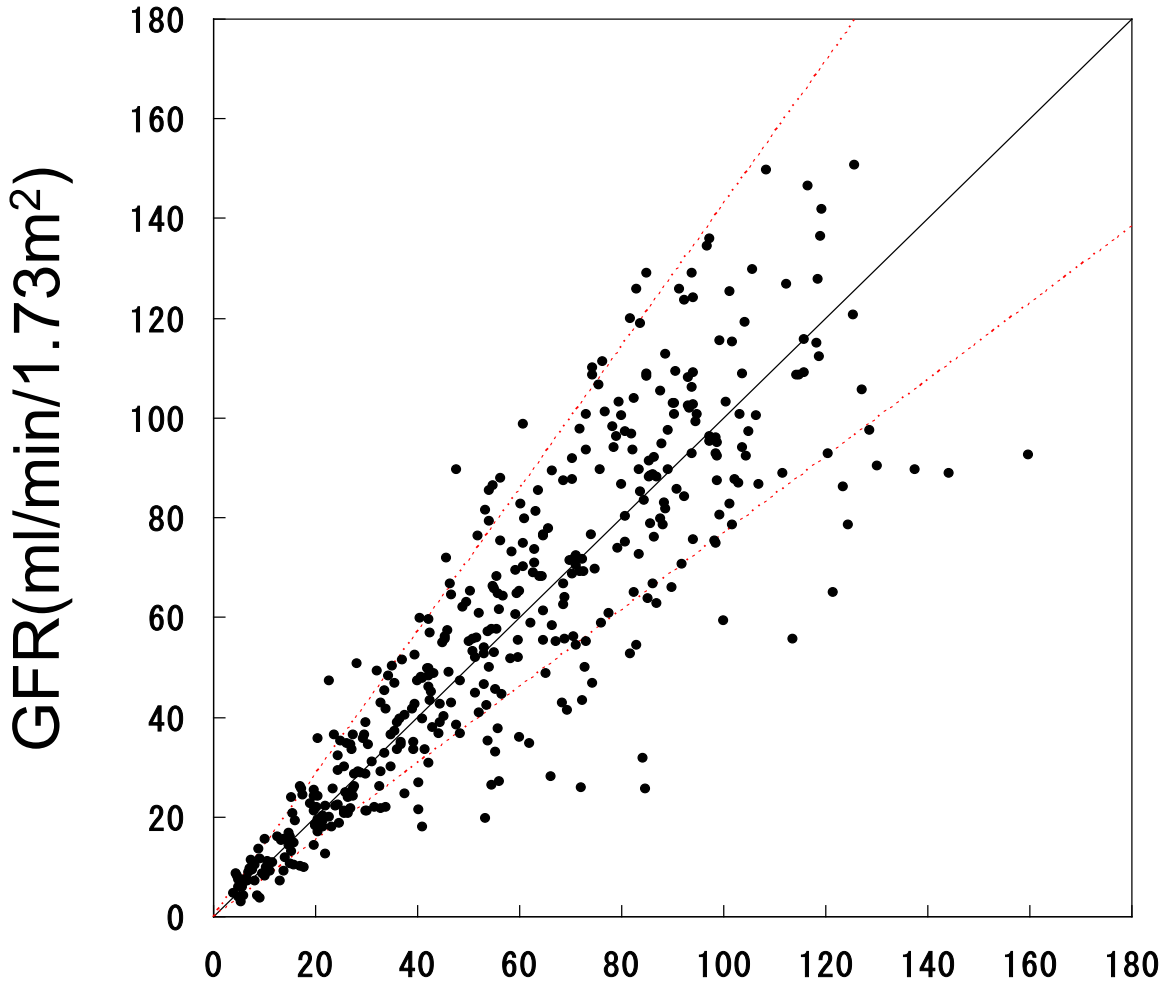
Ann Intern Med 2006; 145: 247-254

Modification of the IDMS-MDRD equation by x0.808 among Japanese.



30% accuracy
=77%

eGFR Equations for Japanese

Three-variable equation

GFR(ml/min/1.73m^2)

$= 194 Cr^{-1.094} Age^{-0.287}$

x0.739 (if female)

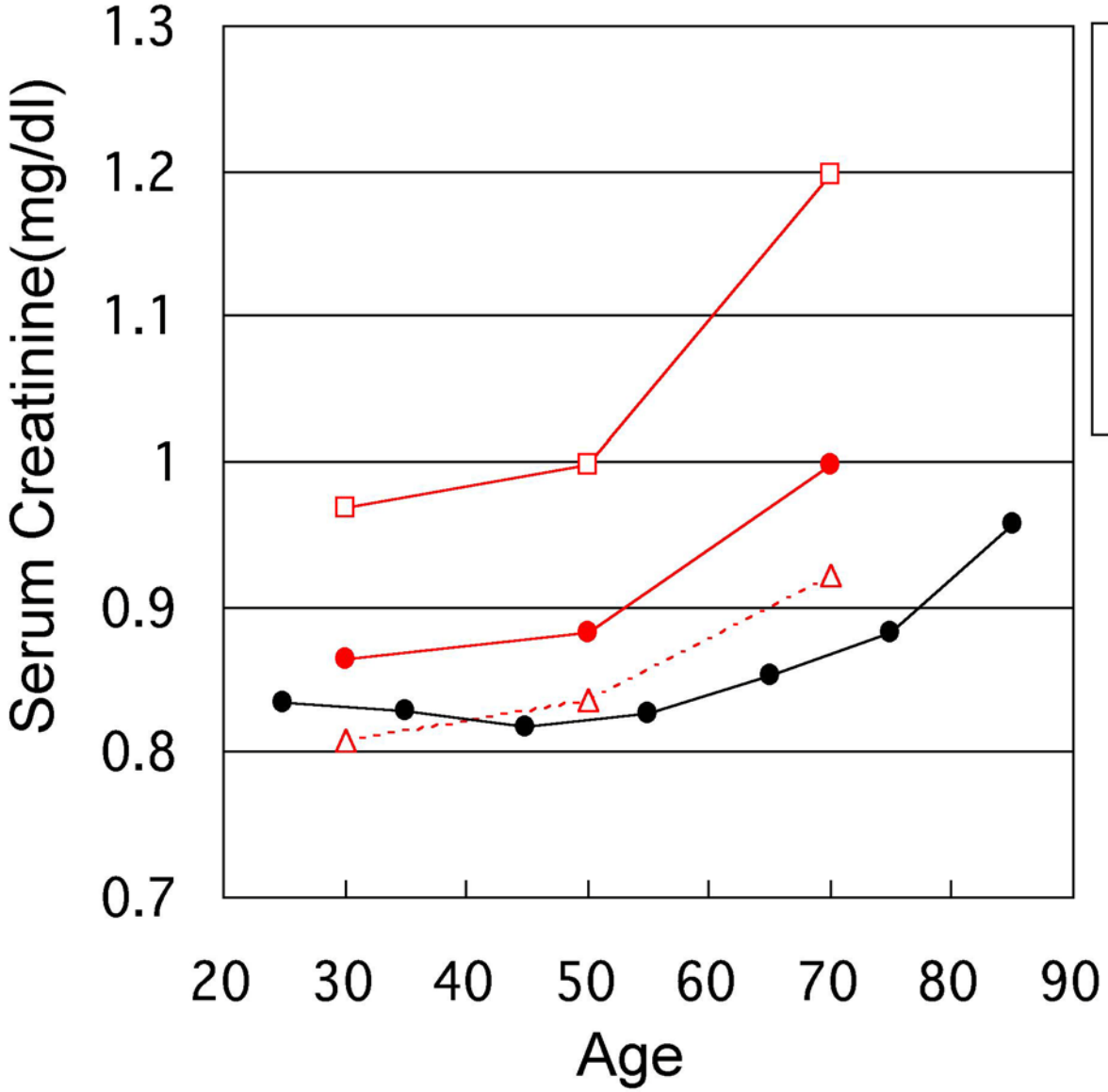
Five-variable equation

GFR(ml/min/1.73m^2)

$= 142 Cr^{-0.923} Age^{-0.185} Alb^{0.414} BUN^{-0.233}$

x0.772 (if female)

Increase in Serum Creatinine with Age in General Population



NHANE III
Creatinine was measured by kinetic Jaffe method.
Standardized Cr
=0.95 x (measure Cr - 0.23)

Japanese
Annual Health Check program
Creatinine was measured by Enzymatic method.

GFR equation for Chinese CKD patients.

- If Pcr is calibrated to Cleveland Clinical Laboratory

(The value should be 5% higher than IDMS-traceable Cr)

$$\text{c-aGFR}_1\ (\text{ml/min per}1.73\ \text{m}^2) = 186 \times \text{Pcr}^{-1.154} \times \text{age}^{-0.203} \times 0.742\ (\text{if female}) \times 1.227\ (\text{if Chinese})$$

- If original Pcr measured in our laboratory is used

$$\text{c-aGFR}_4\ (\text{ml/min per } 1.73\ \text{m}^2) = 175 \times \text{Pcr}^{-1.234} \times \text{age}^{-0.179} \times 0.79\ (\text{if female})$$

JASN 2006; 17 2937-2944

Ethnic coefficient for Chinese is markedly different.

GFR equation for Korean and Thai.

- Tentative modification for Korean

$$= 175 \times S.Cr^{-1.154} \times Age^{-0.203} \times 0.742 \text{ (if female)} \times 0.99096 \text{ (if Korean)}$$

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- Tentative modification for Thai

$$= 175 \times S.Cr^{-1.154} \times Age^{-0.203} \times 0.742 \text{ (if female)} \times 1.18 \text{ (if Thai)}$$

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Possible Reasons for different coefficient

1. Cr measurement methods (Jaffe vs Enzymatic, and its application)
2. Reference GFR method (urinary clearance vs plasma clearance)
3. Patients' characteristics (CKD patients, healthy subject)
4. Body muscle mass

Different method for reference GFR measurement

1) Original MDRD equation: Iothalamate renal clearance

2) Japanese coefficient: Inulin renal clearance

3) Chinese coefficient:
   ^{99m}Tc-DTPA plasma clearance with 2 samples

4) Korean coefficient:
   Inutest plasma clearance with 8 samples
   at blank, 1, 5, 10, 15, 30, 75 and 150 min

5) Thai coefficient:
   ^{99m}Tc-DTPA plasma clearance with 8 samples
   at 5, 10, 20, 30, 60, 90, 120 and 180 min

GFR measurement (Conventional method)

$$GFR = \frac{U \times V}{P}$$

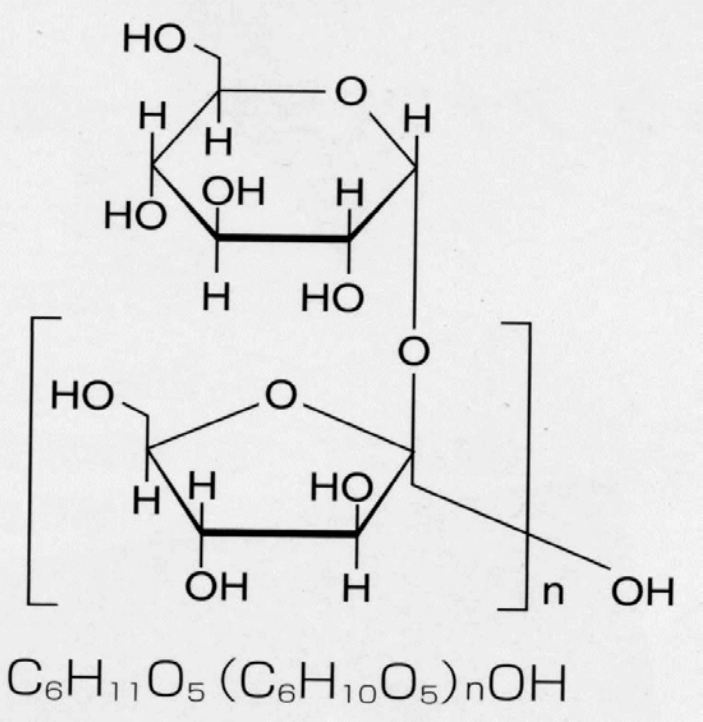
U: urine concentration
V: urine flow (ml/min)
P: plasma concentration

Filtration markers
Inulin, ^{125}I-Iothalamate, ^{51}Cr-EDTA, ^{99m}Tc-DTPA

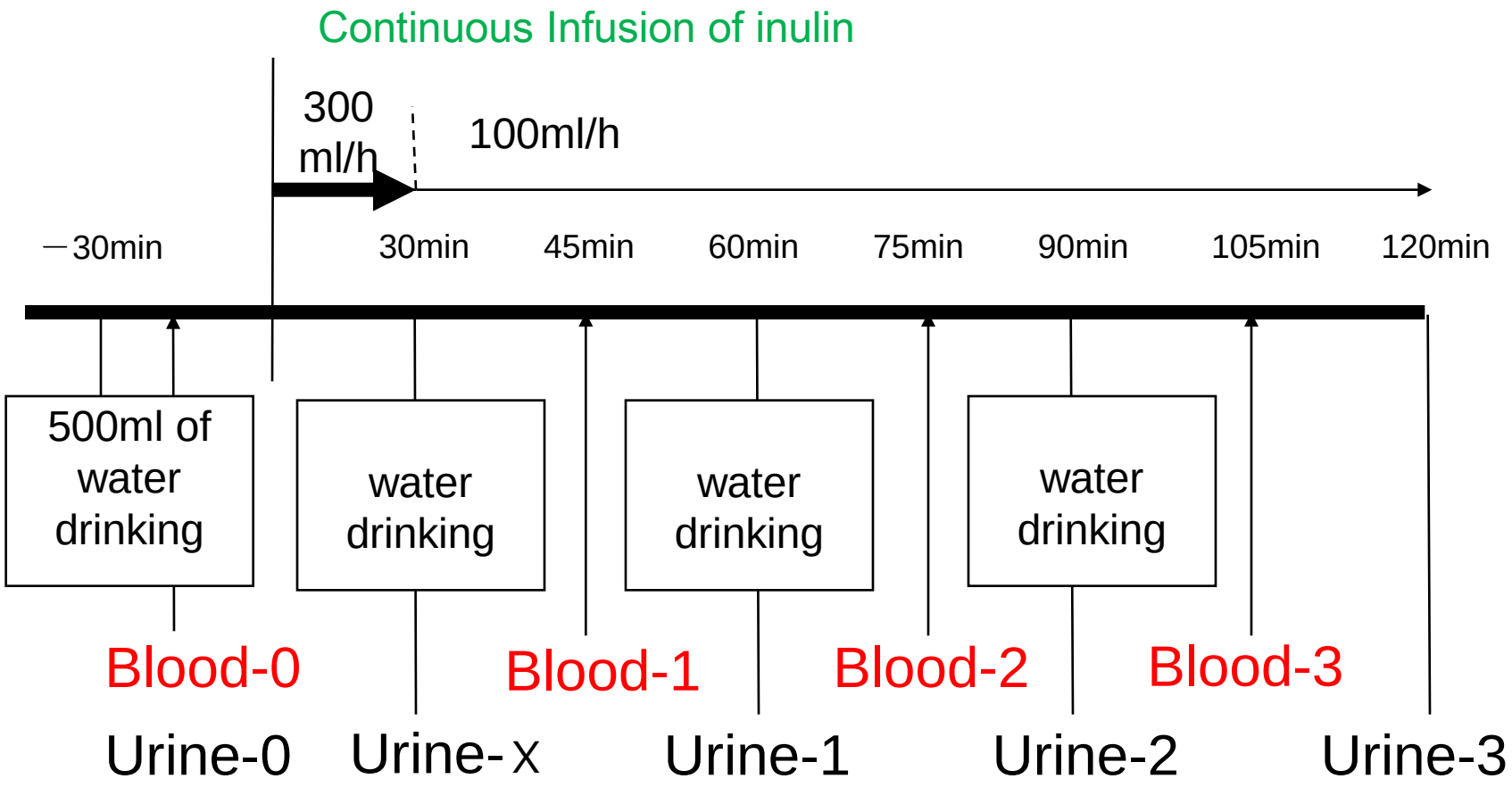
Renal clearances of these markers are almost same.

Inulin

1) Gold standard for GFR measurement.
2) Inulin concentration can be measured by enzymatic method using autoanalyzer.



GFR measurement by Inulin clearance



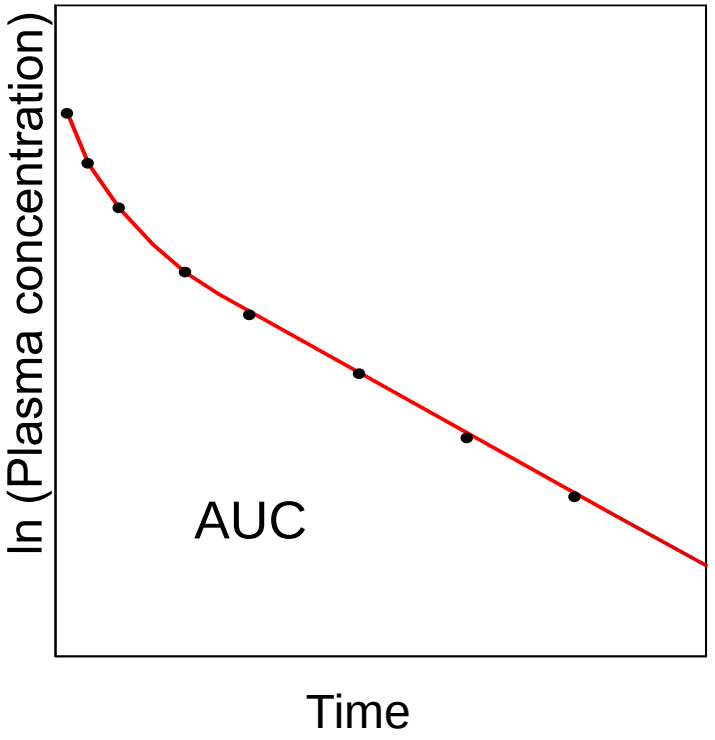
Blood 0, Urine-0: blank for inulin measurement
Blood 1-3: inulin concentration
Urine 1-3: inulin concentration, urine volume
Urine-x: discard

GFR measurement (Plasma clearance)

$$GFR = \frac{\text{Injected dose}}{AUC}$$

AUC is calculated by bi-exponential fitting method.

Many blood samples (5, 10, 15, 30, 45, 60, 90, 120,180,240min after injection) are needed.



Filtration markers
^{51}Cr-EDTA, ^{99m}Tc-DTPA

Total plasma clearance and renal clearance are almost same. Difference is below 5%.

Slope–intercept method

The falling slope is obtained using two～four plasma samples. The first of these samples is taken at 2h after injection.There is missing AUC due to the fast exponential. Therefore, Slope-intercept GFR always overestimates the true value of GFR. Correction methods should be applied.

Correction methods

Chantler C

(Clin Sci 37:169, 1969, Arch Dis Child 47:613, 1972)

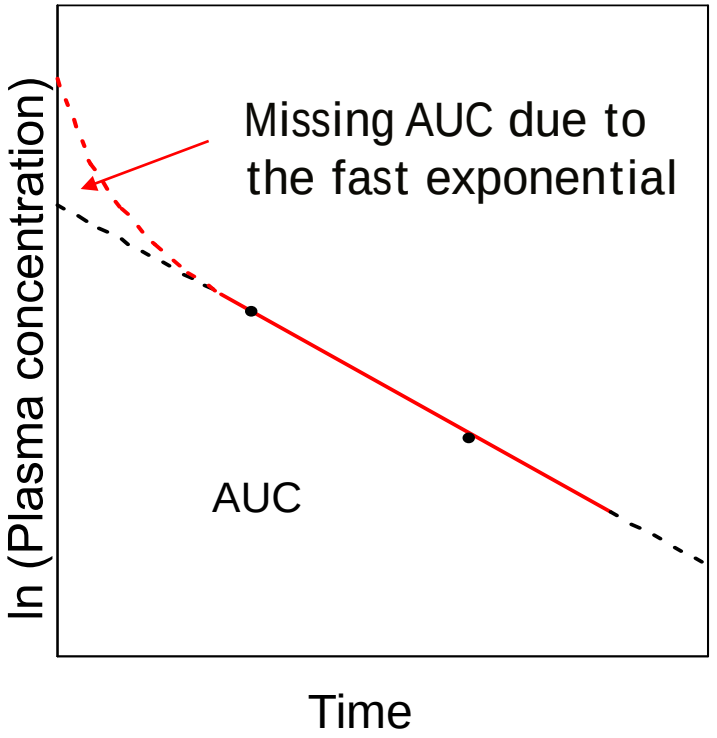
$Y = 0.93\ X$ (adults)

$Y = 0.87\ X$ (adults and children)

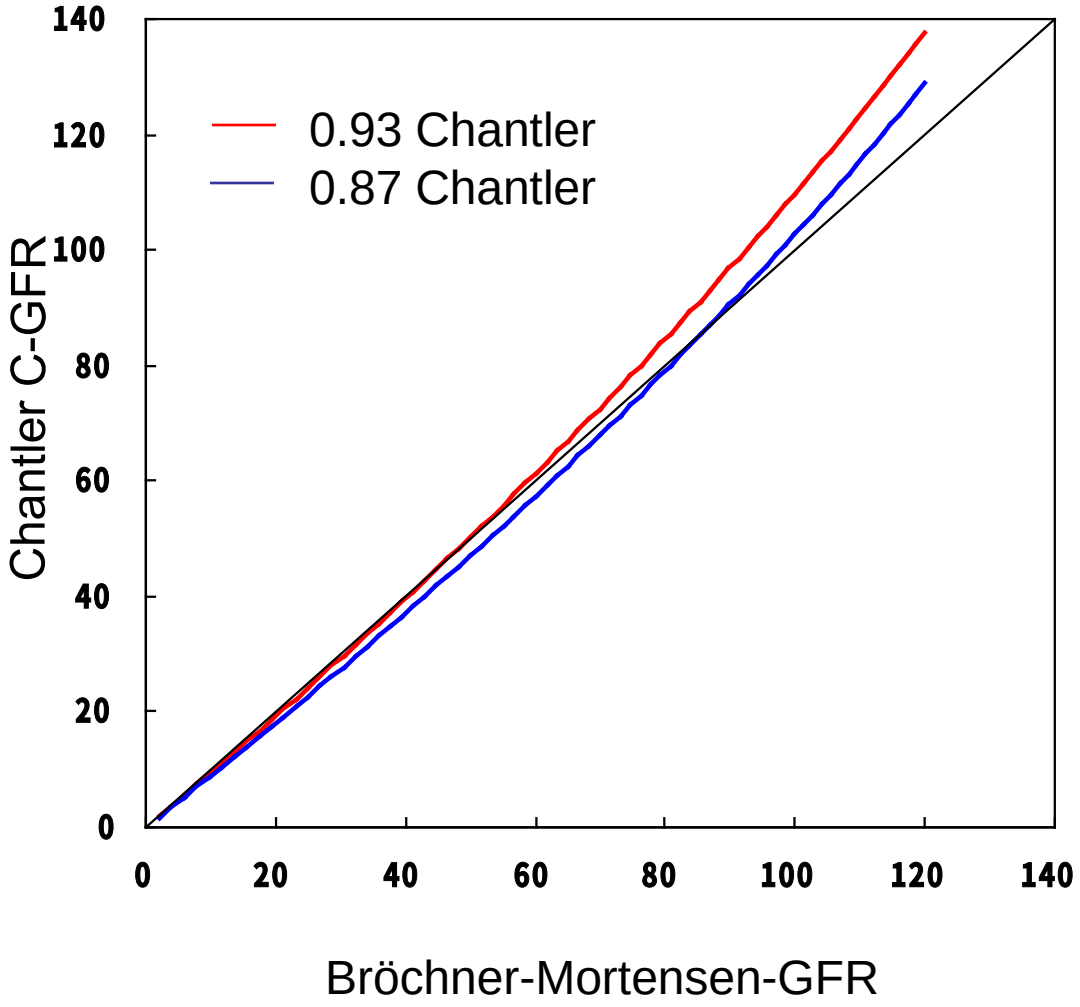
Bröchner-Mortensen (adults)

(J Clin Lab Invest 30: 271, 1972)

$Y=0.990778\ X - 0.001218\ X^2$



Differences of three correction methods



Method	GFR(ml/min)	
B-M	60	
Chantler 0.93	61	+2%
Chantler 0.87	57	- 4%
B-M	100	
Chantler 0.93	110	+10%
Chantler 0.87	103	+3%

Comparative analysis of ref. GFR methods

Urinary inulin clearance vs plasma DTPA clearance

- Prof. Hung-Chun Chen's group evaluates GFR by urinary inulin clearance and then plasma DTPA clearance.

Simultaneous comparative analysis

- Prof Li Zuo's group simultaneously evaluates GFR by urinary inulin clearance and then plasma DTPA clearance.

Summary-2

1. In MDRD Study equation, ethnic coefficient is not available among non-white, non-African American ethnic group, namely Asians.
2. Regardless of similar genetic factors, food culture, life-style, and body muscle mass among Asians compared to Caucasian or African-American, ethnic coefficient for Asians is still a question in controversy.
3. Different reference GFR methods may affect, but it is reported that difference between total plasma clearance and renal clearance is below 5%.
4. Comparative analyses of reference GFR is on going.

Asian Collaborative Study for Creation of GFR Estimation Equation (ACOS-CG-FREE)

(Research Grant from MEXT, Ministry of Education, Cultute, Science and Sports)

To create a simple equation to estimate GFR fit for Asian people by using inulin clearance (Cin) as a gold standard.

Study Group

- **Prof. Ho Yung Lee, Dr. Beom Seok Kim, Dr. Hoon Young Choi** :
  Division of Nephrology, Department of Internal Medicine, Yonsei Unversity Medical College, Korea

- **Prof. Hung-Chun Chen**:
  Division of Nephrology, Kaohsiung Medical University, Taiwan

- **Prof. Kriang Tungsanga**
  Division of Nephrology, Department of Medicine, King Chulalongkorn Memorial Hospital, Thailand

- **Prof. Seiichi Matsuo, Prof. Enyu Imai, Prof. Masaru Horio, Prof. Yasuhiko Tomino, Dr. Yoshinari Yasuda**
  Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Department of Nephrology and Geriatrics, Osaka University Graduate School of Medicine, Department of Nephrology, Juntendo University School of Medicine

ACOS-CG-FREE collaborators in Korea

Yonsei Unversity Medical College:
Prof. Ho Yung Lee, Dr. Beom Seok Kim, Dr. Hoon Young Choi :

Yonsei University Young-dong Severance Hospital : Prof. Sung-kyu Ha

National Health Insurance Corporation Ilsan Hospital :
Prof. Sug Kyun Shin

Hanyang University Kuri hospital : Prof. Ho Joong Kim

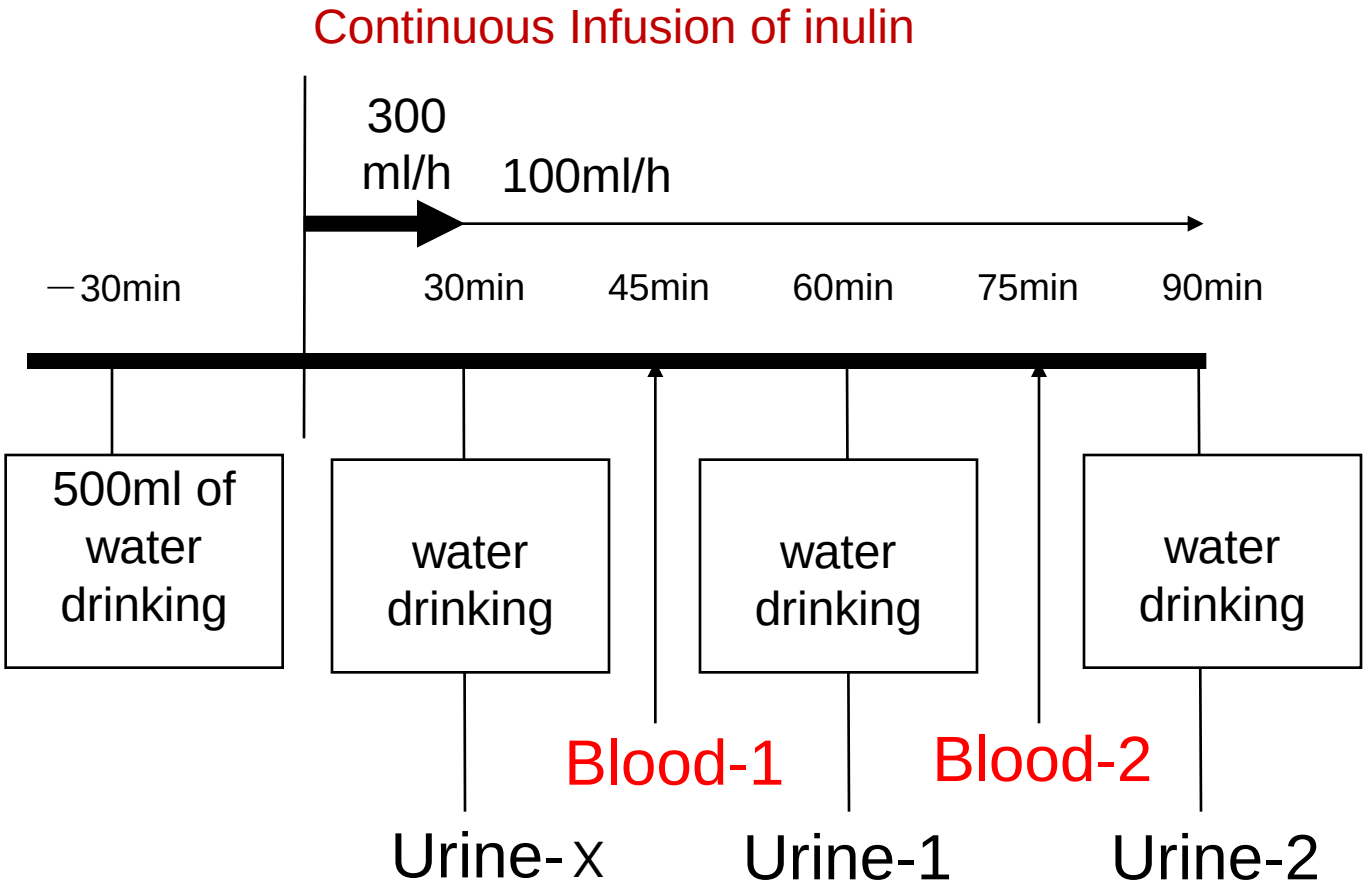
Yonsei University Wonju Christian Hospital :Prof. Seung Ok Choi

Kyungpook National University Hospital : Prof. Yong Lim Kim

Inje University Busan Hospital : Prof. Yang Wook Kim

Chungnam National University Hospital : Prof. Kang wook Lee

Inulin clearance in ACOS-CG-FREE



Blood 1-2: inulin concentration
Urine 1-2: inulin concentration, urine volume
Urine-x: discard

Summary-3

1. Asian Collaborative Study for Creation of GFR Estimation Equation (ACOS-CG-FREE) is on going.
   a. GFR is measured by the same inulin renal clearance protocol.
   b. Cr is measured in a certificated central lab.

2. Midterm results in Taiwanese and Korean are shown.
   a. Better accuracy in IDMS-MDRD equation for Taiwanese
   b. Better accuracy in Japanese GFR equation for Korean
   c. Body muscle mass may affects, but further analysis is necessary.

In conclusion

- Reliable eGFR equations should be the fundamental scheme in CKD initiatives, such as epidemiological CKD survey, clinical guideline for CKD and international collaborative study.

- The fundamentals for eGFR evaluation in Asia are desired to be fixed, soon