การวินิจฉัยภาวะไตวายเฉียบพลันโดยการตรวจปัสสาวะหาค่า cystatin C ต่อ creatinine ในผู้ป่วยที่ได้รับการตรวจหลอดเลือดหัวใจด้วยสารรังสีทึบแสง

พันโท อำนาจ ชัยประเสริฐ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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ปีการศึกษา 2549

DIAGNOSIS OF ACUTE RENAL FAILURE BY URINARY CYSTATIN C TO CREATININE RATIO IN PATIENTS UNDERGOING CORONARY ANGIOGRAPHY

Lt. Col. Amnart Chaiprasert

A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science Program in Health Development

Faculty of Medicine

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Thesis Title	DIAGNOSIS OF ACUTE RENAL FAILURE BY URINARY CYSTATIN C TO CREATININE RATIO IN PATIENTS UNDERGOING CORONARY ANGIOGRAPHY
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Field of Study	Health Development
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อำนาจ ชัยประเสริฐ: การวินิจฉัยภาวะไตวายเฉียบพลันโดยการตรวจปัสสาวะหาค่า cystatin C ต่อ creatinine ในผู้ป่วยที่ได้รับการตรวจหลอดเลือดหัวใจด้วยสารรังสีทึบแสง (DIAGNOSIS OF ACUTE RENAL FAILURE BY URINARY CYSTATIN C TO CREATININE RATIO IN PATIENTS UNDERGOING CORONARY ANGIOGRAPHY) อ.ที่ปรึกษา: ศ.นพ.ธานินทร์ อินทรกำธรชัย, อ.ที่ปรึกษาร่วม: พันเอก สามารถ นิธินันทน์, 50 หน้า.

วัตถุประสงค์: ภาวะไตวายเฉียบพลันในผู้ป่วยที่ได้รับการตรวจหลอดเลือดหัวใจด้วยสารรังสีทึบแสงวินิจฉัยได้โดยการเจาะเลือดวัดระดับครีอะตินีนในเลือดทุกวัน ซึ่งไม่สะดวกทำให้ทำการสืบค้นน้อยกว่าที่ควรจะเป็น น่าสนใจว่าภาวะนี้สามารถวินิจฉัยได้ง่ายโดยการตรวจ cystatin C ต่อ creatinine ในปัสสาวะ (UCCR) หรือไม่

รูปแบบการวิจัย: เปรียบเทียบความถูกต้องของการทดสอบกับวิธีมาตรฐาน

สถานที่ทำการวิจัย: กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า กรุงเทพฯ

วิธีการศึกษา: ทำการศึกษาในผู้ป่วยที่มีการทำหน้าที่ของไต GFR 15-59 ml/min/1.73m^2 ที่นัดมาสวนหลอดเลือดหัวใจ ผู้ป่วยที่เข้าร่วมการศึกษาจะได้รับการตรวจ serum creatinine, serum cystatin C, urine creatinine และ urine cystatin C ก่อนที่จะทำหัตถการ ที่ 24 และ 48 ชั่วโมงหลังทำหัตถการ ผู้ป่วยที่มีการเพิ่มขึ้นของค่า serum creatinine $\geq$ 0.5 mg/dl หรือ $\geq$ 25 % จากค่าเดิมถือว่ามีภาวะไตวายเฉียบพลัน

ผลการศึกษา: ผู้ป่วยที่เข้าร่วมการศึกษา 122 ราย แต่มีข้อมูลครบถ้วนสำหรับการวิเคราะห์ทั้งสิ้น 115 ราย ผู้ป่วยเกิดภาวะไตวายเฉียบพลัน 12 ราย (10.4%) จากกราฟ ROC ตัวแทนที่ดีที่สุดของ UCCR สำหรับการวินิจฉัยภาวะไตวายเฉียบพลันคือ ค่าที่สูงที่สุดของ UCCR ภายใน 48 ชั่วโมงหลังทำหัตถการ (AUC=0.63; 95%CI 0.46-0.80) โดยมีความไว 92% และความจำเพาะ 28% ถ้าตัดค่าที่ $\geq 0.07*10^{-3}$ ส่วนค่า Likelihood ratio ของ UCCR ที่ระดับ 0-0.3, 0.31-0.5, > 0.5 ($*10^{-3}$) เท่ากับ 0.73, 1.34, 1.98 ตามลำดับ ถ้าใช้ค่า urine cystatin C เพียงอย่างเดียวในการวินิจฉัย ตัวแทนที่ดีที่สุดของ urine cystatin c คือค่าร้อยละการเปลี่ยนแปลงของ urine cystatin C ที่ 24 ชั่วโมงหลังทำหัตถการเทียบกับก่อนทำ (AUC=0.81; 95%CI 0.67-0.95) โดยมีความไว 70% และความจำเพาะ 67% ถ้าตัดค่าที่การเปลี่ยนแปลง $\geq$ 3% ส่วนค่า Likelihood ratio ที่การเปลี่ยนแปลง $\leq$ 0, 0.1-100, 101-200, > 200 % เท่ากับ 0.45, 0.82, 3.64, 9.10 ตามลำดับ

สรุป: การตรวจปัสสาวะหาค่า cystatin C หรือ cystatin C ต่อ creatinine มีประโยชน์จำกัดในการวินิจฉัยภาวะไตวายเฉียบพลันในผู้ป่วยที่ได้การตรวจหลอดเลือดหัวใจด้วยสารรังสีทึบแสง

สาขาวิชา การพัฒนาสุขภาพ.....ลายมือชื่อนิสิต.....

ปีการศึกษา 2549.....ลายมือชื่อ อาจารย์ที่ปรึกษา.....

ลายมือชื่อ อาจารย์ที่ปรึกษาร่วม.....

477 50104 30: MAJOR HEALTH DEVELOPMENT
KEY WORD: SENSITIVITY/ URINARY CYSTATIN C/ ACUTE RENAL FAILURE/ CONTRAST NEPHROPTHATY

AMNART CHAIPRASERT: DIAGNOSIS OF ACUTE RENAL FAILURE BY URINARY CYSTATIN C TO CREATININE RATIO IN PATIENTS UNDERGOING CORONARY ANGIOGRAPHY. THESIS ADVISOR: PROF. THANIN INTRAGUMTORNCHAI, THESIS CO-ADVISOR: COL. SAMART NIDHINANDANA. 50 PP.

Objective: Acute renal failure (ARF) in patients undergoing coronary angiography diagnosed by daily serum creatinine monitoring is inconvenient and under-investigated. It is interesting whether ARF can be easily diagnosed by urinary cystatin C to creatinine ratio; UCCR.

Design: Prospective cross-sectional study (Diagnostic test)

Setting: Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand

Method: Patients with GFR 15-59 ml/min/1.73m^2 scheduled for coronary angiography were enrolled. All eligible patients were studied for baseline characteristics, serum creatinine, serum cystatin C, urine creatinine and urine cystatin C at baseline, 24 and 48 hours after procedure. ARF was defined as serum creatinine rising $\geq$ 0.5 mg/dl or $\geq$ 25 % from baseline.

Results: One hundred and twenty two patients were enrolled, 115 patients completed data for analysis. ARF developed in 12 patients (10.4%). From ROC, the best diagnostic test was the maximum value of UCCR within 48 hours post procedure (AUC=0.63; 95%CI 0.46-0.80) with sensitivity of 92% and specificity of 28% at cut-off value $\geq 0.07*10^{-3}$. Likelihood ratio of UCCR at level of 0-0.3, 0.31-0.5, > 0.5 ($*10^{-3}$) were 0.73, 1.34, 1.98 respectively. If urine cystatin C alone was evaluated as a diagnostic tool, the best diagnostic test was the percent change of urine cystatin C at 24 hours post procedure from baseline (AUC=0.81; 95%CI 0.67-0.95) with sensitivity of 70% and specificity of 67% at cut-off value $\geq$ 3%. Likelihood ratio of this test at level of $\leq$ 0, 0.1-100, 101-200, > 200 % were 0.45, 0.82, 3.64, 9.10 respectively.

Conclusion: Urine cystatin C and urinary cystatin C to creatinine ratio have only fair usefulness for diagnosis of acute renal failure in patients undergoing coronary angiography.

Field of study Health Development.....Student's signature.....

Academic year 2006.....Advisor's signature.....

Co-advisor's signature.....

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CHAPTER I

RATIONALE AND BACKGROUND

Acute renal failure (ARF), a syndrome characterized by a rapid decline in glomerular filtration rate (GFR), is a common complication in hospitalized patients and is associated with high mortality especially in patients who require renal replacement therapy.[1,2]

One of the leading causes of ARF is contrast nephropathy. Despite advances in supportive therapy, the incidence of contrast nephropathy may continue to increase significantly with the broader utilization of radio-contrast media for diagnostic and intervention procedures. Furthermore, contrast nephropathy is associated with a greater risk of in-hospital and long-term morbidity and mortality, prolonged hospitalization, increased heath care costs and potentially irreversible reduction in kidney function. [2-4]

Although presently no specific therapy for ARF exists, diagnosis of ARF is critical to prevent its complication. ARF is usually asymptomatic in the early phase and is diagnosed when routine biochemical screening of hospitalized patient reveals a recent increase in the concentrations of blood urea nitrogen (BUN) and serum creatinine (Screatinine).

Contrast nephropathy usually manifests as an acute non-oliguric decline in GFR within 24 to 48 hours after administration. Contrast nephropathy is usually diagnosed by the rising of Screatinine, the standard clinical marker of ARF. There was a study showing that serum cystatin C (Scystatin-C), the promising marker to estimate GFR as well as Screatinine, increased earlier after radio-contrast application compared with Screatinine.[5]

In general practice, diagnosis of ARF from radio-contrast nephrotoxicity is less attended and may be overlooked if blood sample is not obtained daily for Screatinine after radio-contrast study. So, if ARF can be easily detected by using spot urine sample analysis, it will be very useful and very convenient.

Under normal condition cystatin C does not enter the final excreted urine to any significant degree, unlike urine creatinine (Ucreatinine). However there was a study in urine cystatin C (Ucystatin-C) excretion showing that Ucystatin-C to Ucreatinine ratio (UCCR) was a reliable screening tool for detecting decreased GFR that did not require a serum sample. [6] Also, Uchita K found that UCCR can be a marker of renal tubular dysfunction, [7] corresponding to the mechanisms of contrast-induced renal injury which favor a combination of medullary ischemia and direct contrast-mediated tubule toxicity. In ARF, acute tubular necrosis, there was a study by Herget-Rosenthal S in 2004 showing that UCCR was a marker of renal disorders and a good predictor of the severity of the disease. [8]

Interestingly, from the incoming data, whether ARF can be easily diagnosed by UCCR or not in patients undergoing coronary angiography.

CHAPTER II

REVIEW OF LITERATURES

ARF is a syndrome characterized by a rapid (hours to weeks) decline in GFR and retention of nitrogen waste products such as BUN and Screatinine. [1] ARF is associated with a significant morbidity and mortality.

Contrast nephropathy

Contrast nephropathy, one of the leading causes of ARF, typically manifests as an acute decline in GFR within 24 to 48 hours after administration. Screatinine, a standard clinical marker, will rise and return to the normal range within 1 week. Although most patients recover renal function and the need for dialysis is unusual, contrast nephropathy is associated with a significant prolongation of hospital stay and an increase in patient mortality. [2-4]

Several risk factors for contrast nephropathy have been identified. Chronic kidney disease is considered one of the most important predisposing factors. Gruberg L et al studied 439 consecutive patients who had a baseline Screatinine > 1.8 mg/dl who underwent percutaneous coronary intervention in a tertiary referral center. All patients were hydrated before the procedure, and almost all received ioxaglate meglumine; 161 (37%) patients had an increase in Screatinine > 25% within 48 hours or required dialysis. [3]

A retrospective analysis of the Mayo Clinic PCI registry of 7,586 patients undergoing percutaneous coronary intervention, the incidence of ARF (defined as an increase in Screatinine > 0.5 mg/dl from baseline) after procedure was high as 30.6% in patients with a Screatinine $\geq$ 3.0 mg/dl. [4]

Roxana Mehran et al, studied a simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention in 8,357 patients, found that the overall occurrence of contrast nephropathy was 13.1% (range 7.5% to 57.3%). The incidence of contrast nephropathy was 30% in patients with baseline Screatinine of > 1.5 mg/dl or an estimated GFR of < 60 ml/min/1.73m^2. [9]

Serum cystatin C

Human cystatin C is a low molecular weight protein of 13,359 Dalton. Scystatin-C is a promising endogenous marker to estimate GFR. There were a lot of studies showing that Scystatin-C concentration correlates negatively with GFR as well as Screatinine. [10]

Galteau MM found that the reference values were 0.74 ± 0.100 mg/l for males and 0.65 ± 0.085 mg/l for female (aged 20-59 years) and 0.83 ± 0.103 mg/l for older individuals (≥ 60 years), and no effect of hormonal status in women (puberty, menopause, oral contraceptives or hormonal replacement therapy) or alcohol intake on Scystatin-C. [11]

Erlandsen EJ studied cystain C, using DAKO Cystatin C PET Kit, found that no gender-related difference, [12] a common reference interval in women and men were 0.54–1.21 mg/l (median 0.85 mg/l, range 0.42-1.39 mg/l).

There was a study showing that Scystatin-C increased earlier after radio-contrast application compared with Screatinine. At 5 hours after angiography, there was no significant change compared to baseline in neither Screatinine nor Scystatin-C. In comparison with the value immediately before coronary angiography, the increase of Scystatin-C achieved a maximum at 24 hours after the application of the contrast agent. Within 48 hours, Scystatin-C decreased to the level before angiography. Screatinine increased at 24 hours and continued to increase at 48 hours. [5]

Measurement of serum cystatin C

Finney H et al studied an automated and rapid particle-enhanced nephelometric immunoassay (PENIA) for measuring Scystatin-C on the Behring nephelometer systems (BNA, BN II) found that the assay covered the range 0.23-7.25 mg/l, up to seven times the upper limit of normal. The intra- and inter-assay imprecision were < 3.3% and 4.5% respectively. Hemoglobin ≤ 8.0 g/l, bilirubin ≤ 488 micromol/l, triglycerides ≤ 23 mmol/l, rheumatoic factor ≤ 2000 kIU/l and myeloma paraprotein ≤ 41 g/l did not interfere with the assay. [13] The study of Mussap M et al provided the similar results. [14]

Erlandsen EJ et al evaluated the Dade Behring N Latex Cystatin C assay, imprecision studies revealed within-run CVs < 1.8% and between-run CVs < 1.8% in the concentration range 0.87-4.63 mg/l. Recovery was 92.4-101.3%. No interference were detected from hemoglobin < 1.0 mmol/l, bilirubin < 512 micromol/l, intralipid < 20 g/l. Stability of cystatin C in serum was 7 days at temperatures at 20 degrees C and 6 months at -80 degrees C. Measurements of cystatin C in heparin-plasma and EDTA-plasma did not differ significantly from cystatin C measured in serum. [15]

Same as Dharnidharka VR study, immunonephelometric methods of cystatin C assay was of greater value than other assay methods. [10]

Urine cystatin C

Under normal condition, cystatin C does not enter the final excreted urine to any significant degree. Uchita K and Gotoh A investigated the kinetics of Ucystatin-C excretion and found that UCCR was a good index of the state of cystatin C reabsorption in the proximal tubule, so UCCR can be a marker of renal tubular dysfunction. They also found that Ucystatin-C concentration was not affected by muscle mass and remained constant for all ages. [7]

Measurement of urine cystatin C

Herget-Rosenthal S et al measured Ucystatin-C by particle-enhanced nephelometric immunoassay found that the upper reference value for Ucystatin-C was 0.28 mg/l independent of age and gender. Accuracy and linearity (r^2 = 0.996) were excellent. Intra- and inter-assay precision were $\leq$ 4.8% and $\leq$ 5.2% respectively. Albumin $\leq$ 160 g/l, bilirubin $\leq$ 500 micromol/l and hemoglobin $\leq$ 210 micromol/l did not show interferences. Ucystatin-C was stable, at urine pH $\geq$ 5, at -20 degrees C and 4 degrees C for 7 days, and at 20 degrees C for 48 hours. Freezing and thawing did not influence Ucystatin-C concentration. There was no adsorption of cystatin C to plastic. So, Ucystatin-C measurement by PENIA is precise, high stability and no interference. [16]

In non-oliguric acute tubular necrosis, increased urinary excretion of cystatin C may predict an unfavorable outcome, as reflected by the requirement of renal replacement therapy (RRT). Patients who required RRT had higher Ucystatin-C (median (interquartile range); 1.7 (1.2-4.1) g/mol of creatinine) than patients who did not require RRT (0.1(0.02-0.5) g/mol of creatinine). Sensitivity and specificity were 92% and 83% respectively for Ucystatin-C > 1 g/mol of creatinine. [8]

CHAPTER III

RESEARCH DESIGN

3.1 Research question

What is the diagnostic accuracy of urinary cystatin C to creatinine ratio comparing with serum creatinine for diagnosis of acute renal failure within 48 hours in patients undergoing coronary angiography?

3.2 Objectives

Primary objective:

- To estimate diagnostic accuracy of UCCR comparing with Screatinine for diagnosis of ARF in patients undergoing coronary angiography

Secondary objectives:

- To estimate diagnostic accuracy of Ucystatin-C, Scystatin-C comparing with Screatinine for diagnosis of ARF patients undergoing coronary angiography
- To assess whether UCCR, Ucystatin-C, Scystatin-C can diagnose ARF earlier than Screatinine or not in patients undergoing coronary angiography

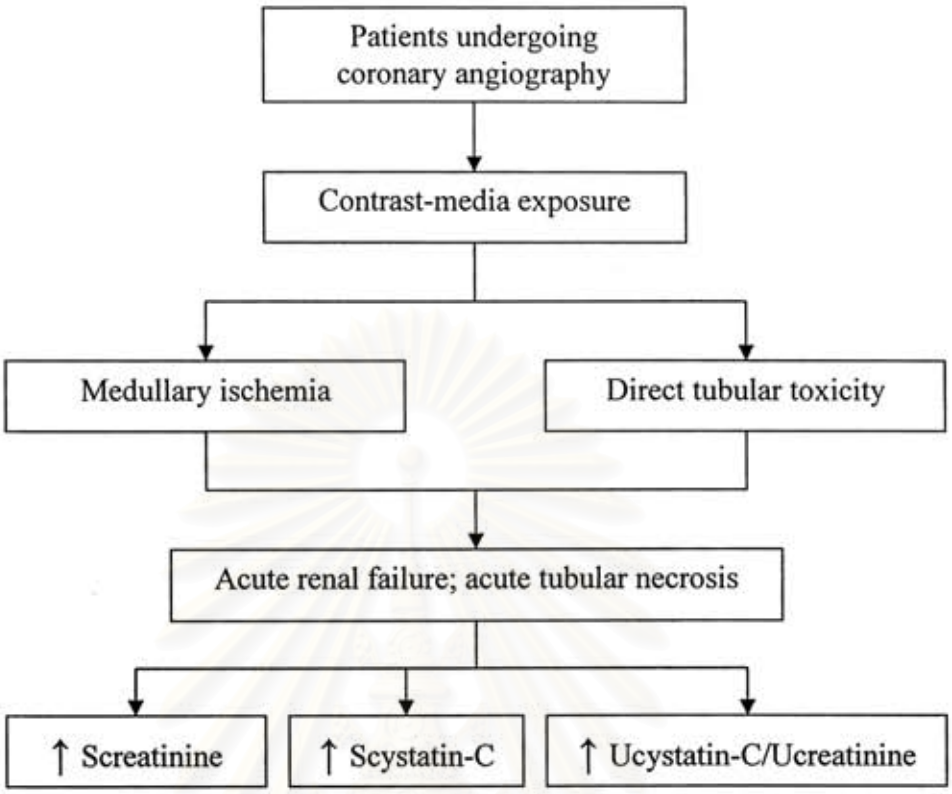
3.3 Hypothesis

This study is about parameter estimation, so there is no statistical hypothesis to be tested. True sensitivity was estimated and reported with 95% confidence interval (CI).

Parameter estimation: 95% CI of true sensitivity = $p \pm 1.96\ SE(p)$

when p = estimated sensitivity (from sample)

3.4 Conceptual framework



3.5 Definitions

Acute renal failure (ARF): ARF is defined according to the decline in kidney function within 48 hours post coronary angiography when Screatinine increases by $\geq$ 0.5 mg/dl or $\geq$ 25% from baseline. [3, 4, 9] In analogy, ARF will be diagnosed when UCCR increases.

Glomerular filtration rate (GFR): Estimates of GFR, the best overall indices of the level of kidney function, is calculated using simplified Modification of Diet in Renal Disease (sMDRD) equation. [17, 18]

GFR, in ml/min/1.73m^2 = 186.3 x (Screatinine exp[-1.154]) x (Age exp[-0.203]) x (0.742 if female); where exp is the exponential.

3.6 Research design

Prospective cross-sectional study (Diagnostic test)

CHAPTER IV

RESEARCH METHODOLOGY

4.1 Population and sample

Target population : patients scheduled for coronary angiography

Study population : patients scheduled for coronary angiography during April 2005 to December 2006 at Phramongkutklao Hospital, Bangkok, Thailand

4.2 Inclusion and exclusion criteria

Inclusion criteria

1. age $\geq$ 18 years
2. chronic kidney disease stage 3 – 4 (GFR of 15 – 59 ml/min/1.73m^2) [17]
3. patients scheduled for coronary angiography and/or coronary intervention
4. patients agree to participate in the study with informed consent

Exclusion criteria

1. patients with organ transplantation
2. patients on the following medications: methylprednisolone, cyclosporin A, cimetidine or trimethoprim
3. patients with prior radio-contrast study within 1 week

4.3 Sample size calculation

Sample size was calculated separately for sensitivity and specificity based on 95% CI as the following formula

$$n = \frac{Z^2_{\alpha/2}PQ}{d^2}$$

where α = probability of type I error = 0.05 (2-sided)

n_1 = number of patients with ARF

P = sensitivity of the test = 0.9

Q = 1 – P = 0.1

d = allowable error = 0.1

$$n_1 = \frac{(1.96)^2 (0.9*0.1)}{(0.1)^2} = 34.57$$

Incidence of ARF in patients undergoing coronary angiography is 30%. [3, 4, 9]

n = number of patients undergoing coronary angiography

n = n_1/incidence of ARF

= 34.57/0.3 = 115.25

= 120

n_2 = number of patients with no ARF

P = specificity of the test = 0.8

Q = 1 – P = 0.2

d = allowable error = 0.1

$$n_2 = \frac{(1.96)^2 (0.8*0.2)}{(0.1)^2} = 61.47$$

Incidence of no ARF in patients undergoing coronary angiography is 70%.

n = number of patients undergoing coronary angiography

n = n_2/incidence of no ARF

= 61.47/0.7 = 87.8

= 90

The sample size for this study was then 120 patients due to higher calculated number of patients and the aim of this diagnostic test as a screening test.

4.4 Method

1. Consecutive series of patients defined by selection criteria were studied for baseline characteristics and routine laboratory tests during admission. Simplified MDRD equation was used to predict GFR in adults based on Screatinine.

2. Random blood (10 ml.) and urine samples were obtained for Screatinine, Scystatin-C, Ucreatinine and Ucystatin-C as baseline laboratory tests during admission.

3. Serum was sent to the Laboratory center immediately or was stored in temperatures of 20 degrees C for 7 days and upto 6 months at -80 degrees C. Automated and rapid particle-enhanced nephelometric immunoassay (PENIA) for measuring Scystatin-C on the Behring nephelometer systems (BNA, BN II) was used.

4. Spot urine sample was collected in a plastic bottle and sent to the Laboratory center immediately or was stored in temperature of 20 degrees C for 48 hr up to 7 days at 4 degrees C. Automated and rapid particle-enhanced nephelometric immunoassay (PENIA) for measuring Ucystatin-C on the Behring nephelometer systems (BNA, BN II) was used.

5. Serum and urine creatinine concentrations were measured by a modified Jaffe method and an alkaline picrate reaction. [17]

6. All of the tests were analyzed by the trained technicians in Laboratory center without any patients' clinical information.

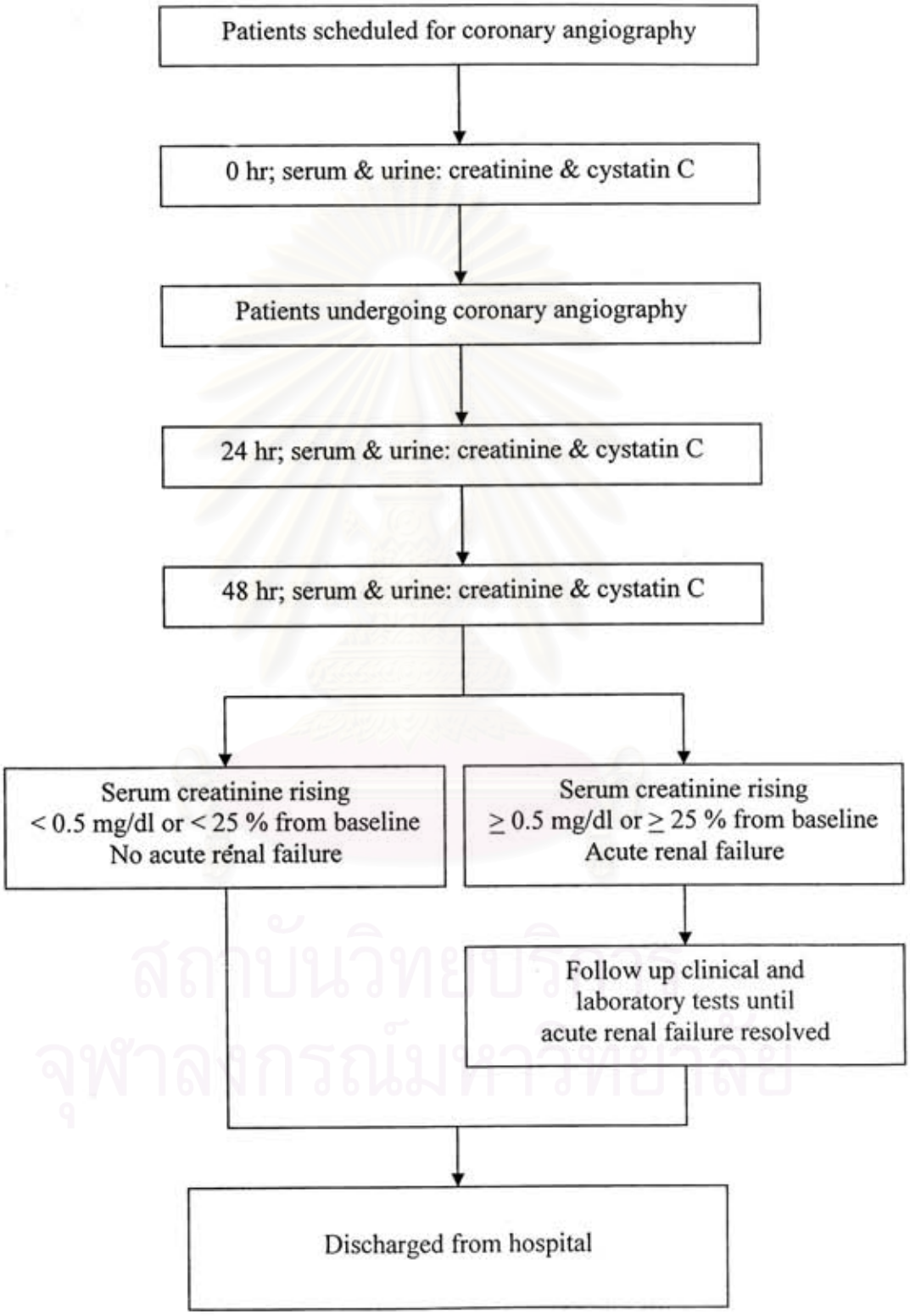
7. Patients underwent coronary angiography and/or coronary intervention as indicated. The preventive measures of contrast nephropathy including the administration of intravenous hydration, antioxidant acetylcysteine and the use of low or iso-osmolar nonionic contrast agents were used according to the risks and clinical of the patients. [19]

8. Random blood (10 ml.) and urine samples were obtained again for Screatinine, Scystatin-C, Ucreatinine and Ucystatin-C at 24 and 48 hours after the procedure; urine volume per day was also recorded.

9. If Screatinine rising < 0.5 mg/dl or $< 25\%$ from baseline, the patient was diagnosed as having no ARF and was discharged from the hospital.

10. If Screatinine rising ≥ 0.5 mg/dl or $\geq 25\%$ from baseline, the patient was diagnosed as having ARF. Patient with ARF was cared with standard treatment until ARF resolved before discharging from the hospital.

Operational flow chart



4.5 Outcome measurement

Primary outcomes

Level of UCCR at 24 and 48 hours post coronary angiography

Number of patients having ARF if the cut-off point to diagnose ARF is the rising of UCCR $\geq$ 25% or $\geq$ 50% from baseline within 48 hours post coronary angiography

Secondary outcomes

Level of Ucystatin-C, Scystatin-C at 24 and 48 hours post coronary angiography

Proportion of patients having ARF at 24 and 48 hours post coronary angiography between diagnosed by UCCR, Ucystatin-C, Scystatin-C and Screatinine

4.6 Data collection

Case record form was generated for each individual patient. Data were collected as continuous variables (age, body mass index, Screatinine, Scystatin-C, Ucreatinine, Ucystatin-C and urine output per day) or categorical variables (gender, underlying diseases).

4.7 Data analysis

Patients' baseline characteristics were presented using descriptive statistics.

Continuous data were presented as mean and standard deviation, whereas categorical data as number and percentages.

Patients with incomplete 48 hours data collection of the tests were not analyzed.

Data analysis for primary objective

To determine diagnostic values of UCCR at 24 hours, 48 hours and maximum value within 48 hours post coronary angiography comparing with Screatinine (gold standard)

- Receiver operating characteristics (ROC) curves were first created
- Area under the curve (AUC) of the ROC curves were analyzed

- At each cut point, sensitivity and specificity were calculated to determine the best cut point
- Likelihood ratio (LR) of UCCR was analyzed

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and LR were calculated if cut-off point to diagnose ARF was the rising of UCCR $\geq$ 25% or $\geq$ 50% from baseline within 48 hours post coronary angiography.

Data analysis for secondary objectives

To determine diagnostic values of Ucystatin-C and Scystatin-C, these two tests were analyzed the same as UCCR in primary objective data analysis.

Difference in proportion of patients having ARF at 24 and 48 hours post coronary angiography between diagnosed by UCCR, Ucystatin-C, Scystatin-C and Screatinine were analyzed.

4.8 Ethical consideration

The protocol was approved by the ethics committee of Chulalongkorn university and Royal Thai Army Medical Department. This diagnostic study had only minimal risk to patients; however informed consents were obtained in all eligible patients. The identification of the patients was kept confidential. The patients' withdrawal from the study did not interfere with routine care or benefit.

CHAPTER V

RESULTS

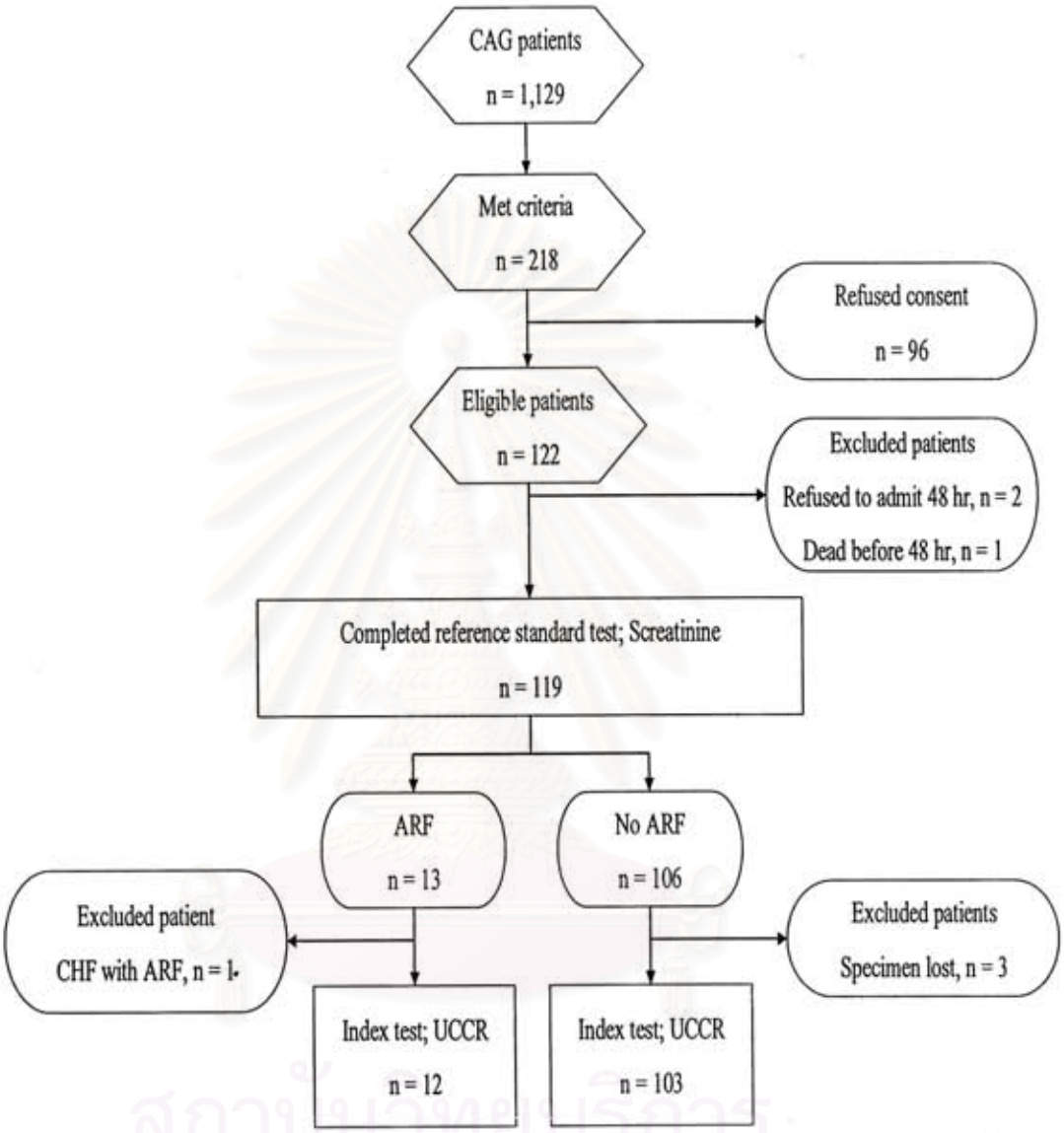
One thousand one hundred and twenty nine patients were scheduled for coronary angiography (CAG) during study period. Two hundred and eighteen patients met study criteria but 96 patients refused consent to enter the study.

One hundred and twenty two patients were enrolled; 119 patients completed standard tests (Screatinine). Two patients refused to admit for 48 hours and 1 patient was dead because of acute myocardial infarction within the first day after CAG. Screatinine of these three excluded patients were not rising to meet the criteria of ARF.

One hundred and fifteen of 119 patients completed the index tests (UCCR) and completed data for analysis. Three patients in non ARF group (by Screatinine criteria) were excluded because of specimen lost. One patient in ARF group experienced congestive heart failure and was excluded from the analysis because the rising of Screatinine may be not from contrast nephropathy alone.

Finally, 115 patients completed data for analysis with 12 patients in ARF group and 103 patients in non ARF group. (Figure 1)

Figure 1 A flow diagram about the method of recruitment of patients and the number of patients undergoing the tests



One hundred and fifteen patients completed data for analysis; 78 (68%) patients were male. Mean age was 68.7 ± 9.9 years and mean GFR was 47.8 ± 11.1 ml/min/1.73m^2. Baseline mean Screatinine, Ucystatin-C and UCCR were 1.51 ± 0.40 mg/dl, 0.120 ± 0.206 mg/l and 0.205 ± 0.336 (*10^{-3}) respectively. (Table 1)

Table 1 Baseline characteristics and laboratory tests before coronary angiography

Baseline variables	Number (%) or Mean ± SD
N (patients)	115
Male	78 (68%)
Age (years)	68.7 ± 9.9
GFR (ml/min/1.73m^2)	47.8 ± 11.1
BMI (kg/m^2)	23.6 ± 3.4
Underlying diseases: Diabetes Hypertension	 87 (76%) 113 (98%)
Screatinine (mg/dl)	1.51 ± 0.40
Scystatin-C (mg/l)	1.69 ± 0.91
Ucreatinine (mg/dl)	77.2 ± 59.9
Ucystatin-C (mg/l)	0.120 ± 0.206
UCCR	0.205 ± 0.336 (*10^{-3})

BMI is body mass index. GFR is glomerular filtration rate, calculated using simplified MDRD equation.

Intravenous hydration and N-acetylcysteine were used for prophylaxis of contrast nephropathy in 114 (99%) and 61 (53%) patients respectively. CAG studies were done using iopromide (a nonionic, low-osmolar contrast media) in all patients with the mean duration of 27.6 ± 19.3 min and dosage of 76.9 ± 55.2 ml. Thirty nine percent of CAG was done with coronary intervention (balloon angioplasty and/or vascular stenting). (Table 2)

Table 2 Coronary angiography procedure

Coronary angiography	Number (%) or Mean ± SD
Intravenous hydration before CAG	114 (99%)
N-acetylcysteine before CAG	61 (53%)
Low-osmolar contrast usage	115 (100%)
Duration of CAG (min)	27.6 ± 19.3
Dose of contrast media (ml)	76.9 ± 55.2

One hundred of 115 patients were free from any complications after CAG. ARF occurred in 12 (10.4%) patients. Two (1.7%) patients experienced congestive heart failure and 1 (0.9%) patient had gross hematuria after the procedures. (Table 3)

Table 3 Complications after coronary angiography

Complications	N (percent)
Acute renal failure	12 (10.4)
Congestive heart failure	2 (1.7)
Gross hematuria	1 (0.9)
No complication	100 (87)

* Seven excluded patients from analysis: one patient was dead because of acute myocardial infarction within the first day after CAG, one patient experienced CHF with ARF and five patients were without any complications

GFR in ARF group, 44.6 ± 13.0 ml/min/1.73m^2, was slightly lower than in non ARF group, 48.2 ± 10.9 ml/min/1.73m^2. Other baseline characteristic and laboratory tests in patients with and without ARF were similar except Ucreatinine in non ARF group, 79.8 ± 60.8 mg/dl, was significantly higher than in ARF group, 55.3 ± 33.3 mg/dl. (Table 4)

Table 4 Baseline characteristics and laboratory tests in patients with and without ARF after CAG

Baseline variables	ARF group; Number (%) or Mean ± SD	Non ARF group; Number (%) or Mean ± SD
N (patients)	12	103
Male	8 (67%)	70 (68%)
Age (years)	66.4 ± 10.6	68.9 ± 9.8
GFR (ml/min/1.73m^2)	44.6 ± 13.0	48.2 ± 10.9
BMI (kg/m^2)	25.0 ± 3.8	23.4 ± 3.3
Underlying diseases:		
Diabetes	9 (75%)	78 (76%)
Hypertension	10 (83%)	103 (100%)
Screatinine (mg/dl)	1.63 ± 0.46	1.50 ± 0.40
Scystatin-C (mg/l)	1.98 ± 1.31	1.66 ± 0.86
Ucreatinine (mg/dl)	55.3 ± 33.3	79.8 ± 60.8
Ucystatin-C (mg/l)	0.127 ± 0.219	0.120 ± 0.205
UCCR	0.254 ± 0.305 (*10^{-3})	0.199 ± 0.341 (*10^{-3})

Primary objective: Diagnostic values of UCCR

Diagnostic values of UCCR were analyzed using ROC curves. Level of UCCR, change of UCCR from baseline and percent change of UCCR from baseline at 24 hours, 48 hours and maximum value within 48 hours post CAG were analyzed comparing with Screatinine.

The best diagnostic value was obtained from the maximum value of UCCR within 48 hours post CAG; AUC 0.630, SE0.087, 95%CI 0.458-0.801. (Figure 2.1-2.3 and Table 5)

The best sensitivity 92% was obtained if cut-off value of the maximum value of UCCR within 48 hours post CAG $\geq 0.07*10^{-3}$ but the specificity will be only 28%. Likelihood ratio of this test at level of 0-0.3, 0.31-0.5, > 0.5 (*10^{-3}) were 0.73, 1.34, 1.98 respectively. (Table 6 and Table 7)

If cut-off point to diagnose ARF was the rising of UCCR by ≥ 25% or ≥ 50% from baseline within 48 hours post CAG; sensitivity, specificity, PPV, NPV, accuracy and likelihood ratio will be 50%, 57%, 11%, 91%, 56%, 1.17 and 50%, 65%, 14%, 92% 63%, 1.42 respectively.

Figure 2.1 ROC curves of UCCR: Level of UCCR at 24 hours, 48 hours and maximum value within 48 hours

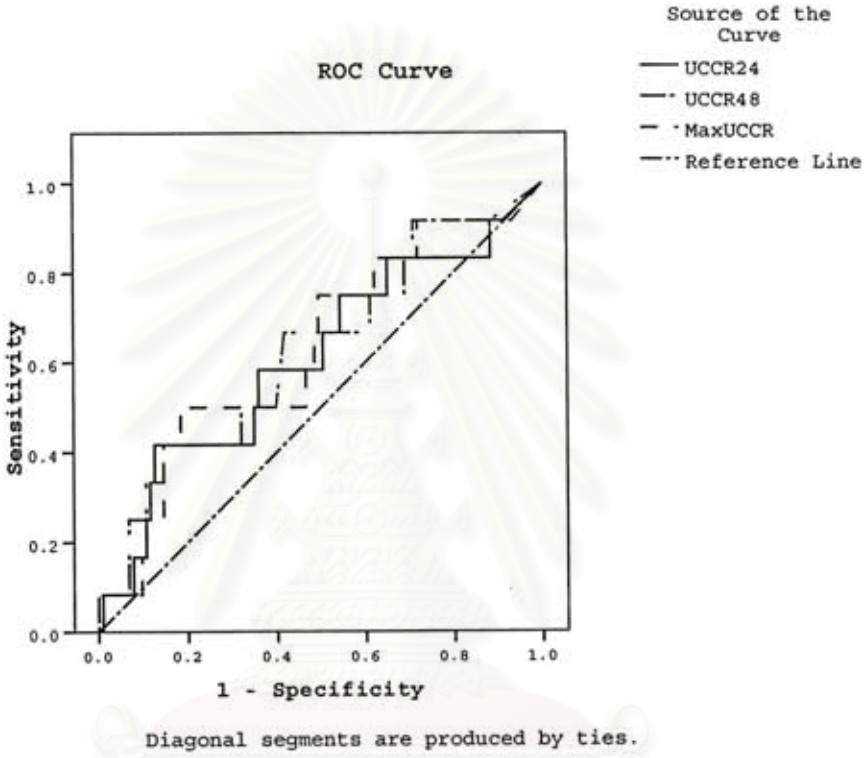


Figure 2.2 ROC curves of UCCR: Change of UCCR from baseline at 24 hours, 48 hours and maximum value within 48 hours

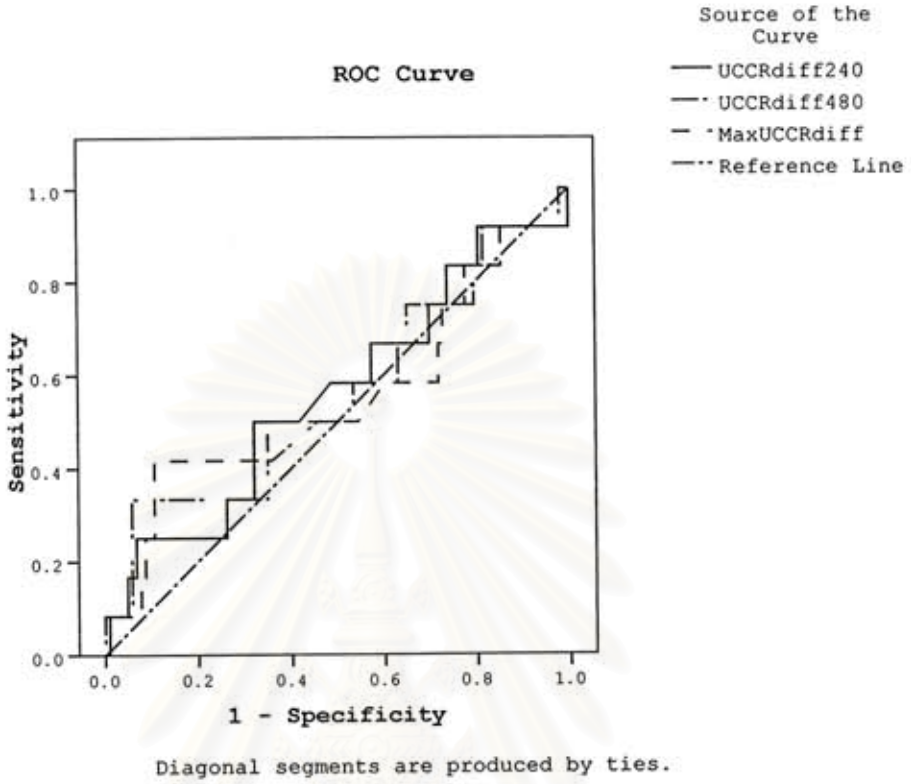


Figure 2.3 ROC curves of UCCR: Percent change of UCCR from baseline at 24 hours, 48 hours and maximum value within 48 hours

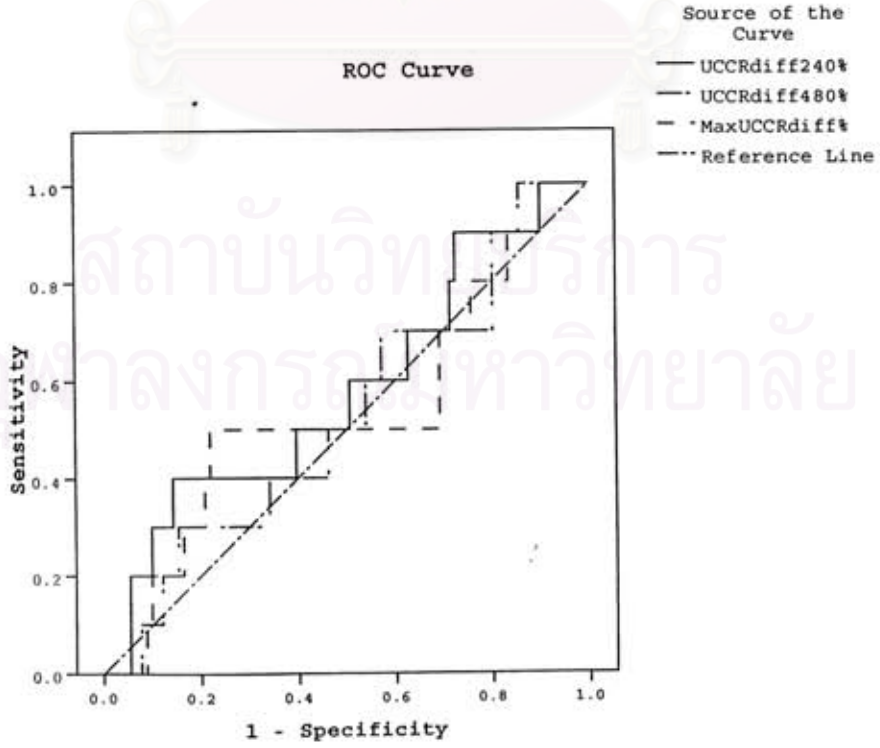


Table 5 AUC of ROC curves of UCCR

Test variables: UCCR	n	AUC	SE	95% CI
Hr24	115	.610	.093	.428-.792
Hr48	115	.627	.089	.452-.802
Maximum value of Hr24 or Hr48	115	.630	.087	.458-.801
Hr24-Hr0	115	.559	.094	.375-.742
Hr48-Hr0	115	.555	.098	.363-.747
Maximum value of Hr24-Hr0 or Hr48-Hr0	115	.551	.103	.349-.753
Hr24-Hr0 (%)	101	.578	.100	.382-.774
Hr48-Hr0 (%)	101	.527	.094	.343-.712
Maximum value of Hr24-Hr0 (%) or Hr48-Hr0 (%)	101	.534	.105	.329-.740

* Percent change of UCCR from baseline can be calculated in only 101 cases because some denominator data were equal to zero.

Table 6 Sensitivity and specificity of maximum value of UCCR within 48 hours post CAG

Mamimum value of UCCR within 48 hours	% Sensitivity	% Specificity
$\geq 0.74 * 10^{-3}$	17	90
$\geq 0.61 * 10^{-3}$	25	89
$\geq 0.32 * 10^{-3}$	50	82
$\geq 0.12 * 10^{-3}$	75	50
$\geq 0.09 * 10^{-3}$	83	38
$\geq 0.07 * 10^{-3}$	92	28

Table 7 Likelihood ratio of maximum value of UCCR within 48 hours post CAG

Maximum value of UCCR within 48 hours	ARF (n = 12)	No ARF (n = 103)	LR
> 0.5 $(*10^{-3})$	3	13	1.98
$0.31 - 0.5$ $(*10^{-3})$	3	19	1.34
$0 - 0.3$ $(*10^{-3})$	6	71	0.73

ARF is acute renal failure, defined as Screatinine rising $\geq$ 0.5 mg/dl or > 25% from baseline.

Secondary objectives: Diagnostic value of Ucystatin-C

Diagnostic values of Ucystatin-C were analyzed using ROC curves. Level of Ucystatin-C, change of Ucystatin-C from baseline and percent change of Ucystain-C from baseline at 24 hours, 48 hours and maximum value within 48 hours post CAG were analyzed comparing with Screatinine.

The best diagnostic value was obtained from the percent change of Ucystatin-C at 24 hours post CAG from baseline; AUC 0.809, SE0.074, 95%CI 0.665-0.954. (Figure 3.1-3.3 and Table 8)

The best sensitivity 70% was obtained if cut-off value of the percent change of Ucystatin-C at 24 hours post CAG from baseline $\geq$ 3% with the specificity of 67%. Likelihood ratio of this test at level of $\leq$ 0, 0.1-100, 101-200, > 200 % were 0.45, 0.82, 3.64, 9.10 respectively. (Table 9 and Table 10)

If cut-off point to diagnose ARF was the rising of Ucystatin-C at 24 hours post CAG from baseline $\geq$ 50%; sensitivity, specificity, PPV, NPV, accuracy and likelihood ratio will be 70%, 82%, 30%, 96%, 81% and 3.98 respectively.

Figure 3.1 ROC curves of Ucystatin-C: Level of Ucystatin-C at 24 hours, 48 hours and maximum value within 48 hours

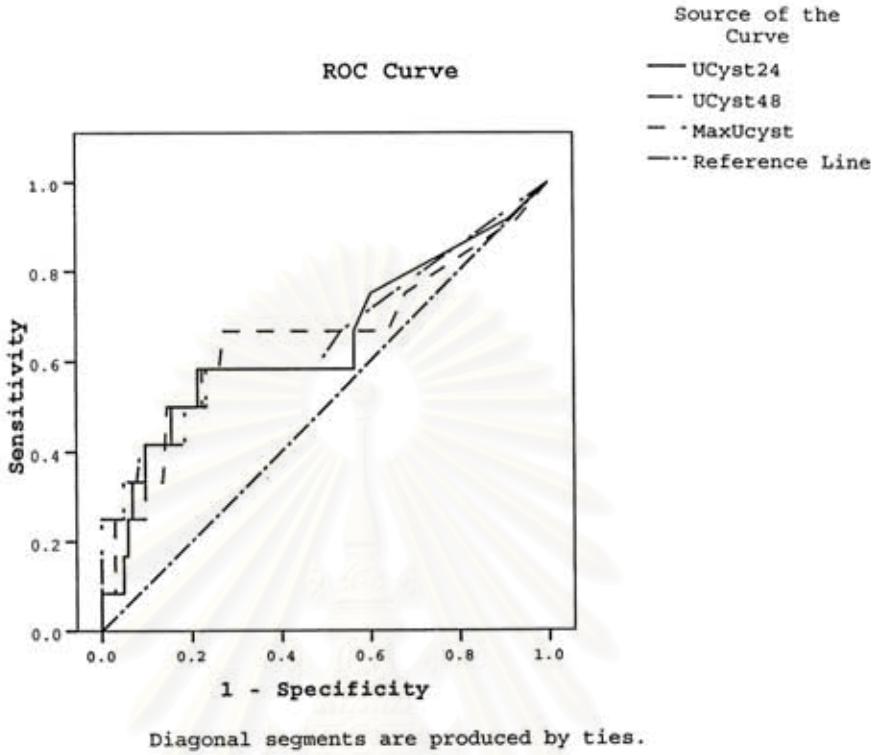


Figure 3.2 ROC curves of Ucystatin-C: Change of Ucystatin-C from baseline at 24 hours, 48 hours and maximum value within 48 hours

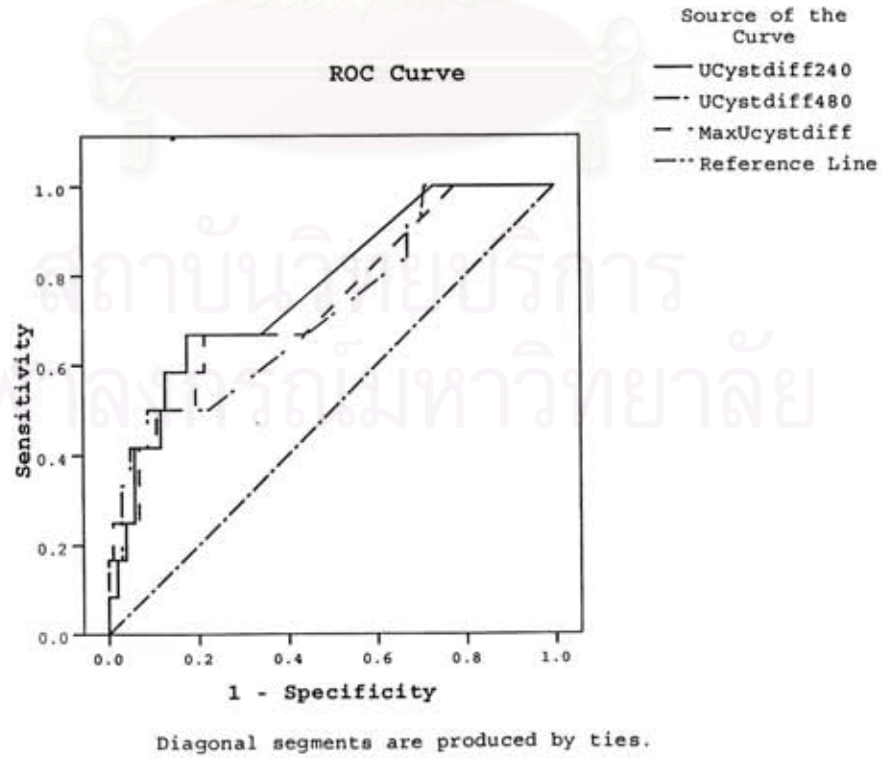


Figure 3.3 ROC curves of Ucystatin-C: Percent change of Ucystatin-C from baseline at 24 hours, 48 hours and maximum value within 48 hours

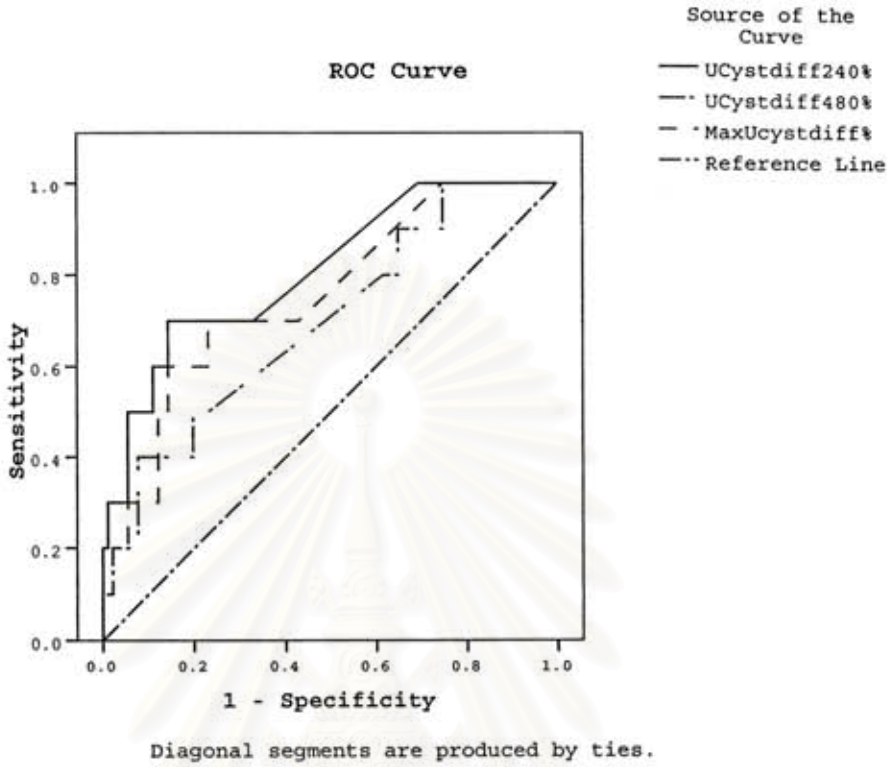


Table 8 AUC of ROC curves of Ucystatin-C

Test variables: Ucystatin-C	Cases	AUC	SE	95% CI
Hr24	115	.645	.098	.453-.838
* Hr48	115	.657	.099	.462-.852
Maximum value of Hr24 or Hr48	115	.653	.101	.455-.851
Hr24-Hr0	115	.773	.071	.634-.911
Hr48-Hr0	115	.722	.081	.562-.882
Maximum value of Hr24-Hr0 or Hr48-Hr0	115	.743	.079	.588-.898
Hr24-Hr0 (%)	101	.809	.074	.665-.954
Hr48-Hr0 (%)	101	.696	.087	.525-.867
Maximum value of Hr24-Hr0 (%) or Hr48-Hr0 (%)	101	.754	.080	.598-.911

* Percent change of Ucystatin-C from baseline can be calculated in only 101 cases because some denominator data were equal to zero.

Table 9 Sensitivity and specificity of the percent change of Ucystatin-C at 24 hours post CAG from baseline

Percent change of Ucystatin-C at 24 hours from baseline (%)	% Sensitivity	% Specificity
≥ 200	20	99
≥ 140	30	94
≥ 80	50	89
≥ 64	60	86
≥ 50	70	82
≥ 3	70	67

Table 10 Likelihood ratio of the percent change of Ucystatin-C at 24 hours post CAG from baseline

Percent change of Ucystatin-C at 24 hours from baseline (%)	ARF (n = 10)	No ARF (n = 91)	LR
> 200	3	3	9.10
101 – 200	2	5	3.64
0.1 – 100	2	22	0.82
≤ 0	3	61	0.45

Secondary objectives: Diagnostic value of Scystatin-C

Another secondary objective; diagnostic values of Scystatin-c were analyzed using ROC curves. Level of Scystatin-C, change of Scystatin-C from baseline and percent change of Scystain-C from baseline at 24 hours, 48 hours and maximum value within 48 hours post CAG were analyzed comparing with Screatinine.

Diagnostic values of Scystatin-C were much better than UCCR and Ucystatin-C because many studies showed that Scystatin-C was a promising marker for GFR estimation same as Screatinine (gold standard test). (Figure 4.1-4.3 and Table 11) However the diagnostic usefulness of Scystatin-C was not much interested in this study because Scystatin-C must be obtained from venopuncture same as Screatinine.

Figure 4.1 ROC curves of Scystatin-C: Level of Scystatin-C at 24 hours, 48 hours and maximum value within 48 hours

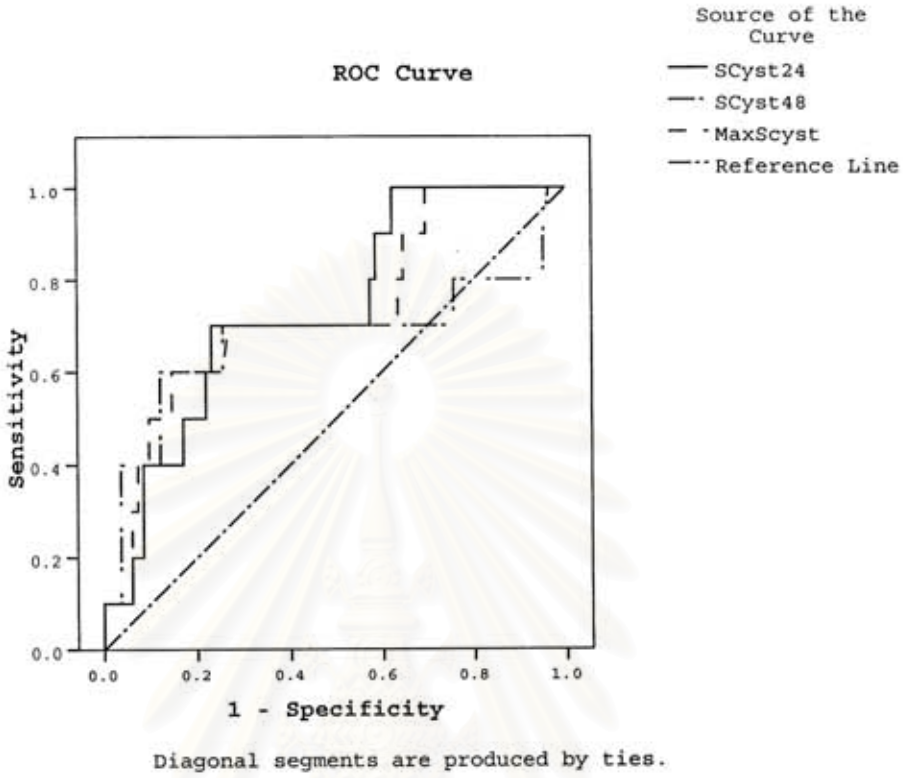


Figure 4.2 ROC curves of Scystatin-C: Change of Scystatin-C from baseline at 24 hours, 48 hours and maximum value within 48 hours

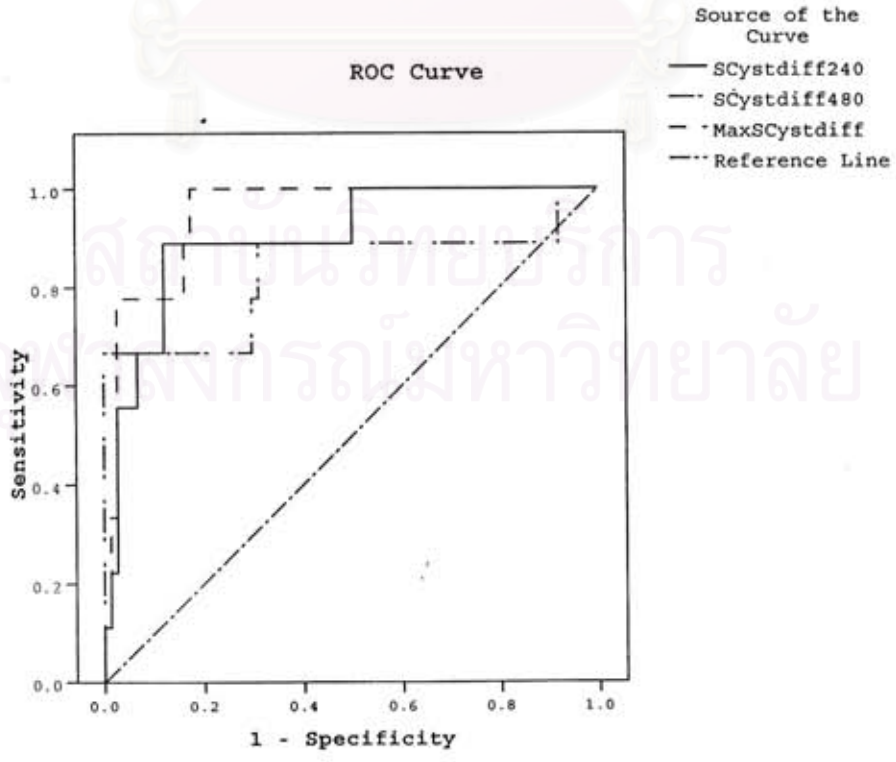


Figure 4.3 ROC curves of Scystatin-C: Percent change of Scystatin-C from baseline at 24 hours, 48 hours and maximum value within 48 hours

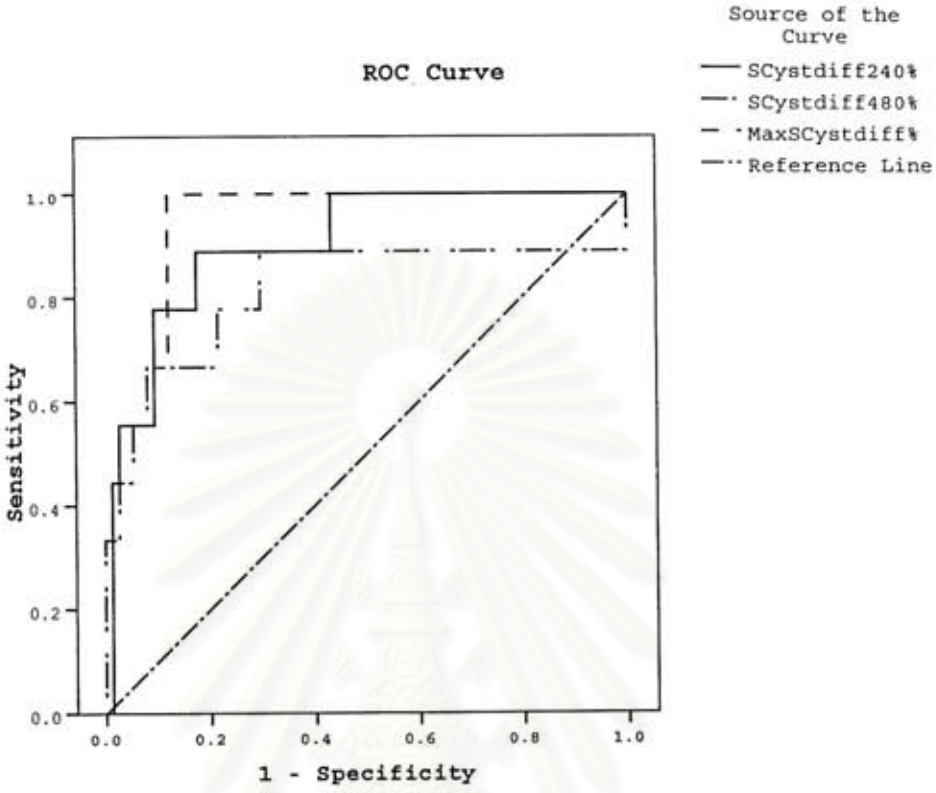


Table 11 AUC of ROC curves of Scystatin-C

Test variables: Scystatin-C	Cases	AUC	SE	95% CI
Hr24	104	.737	.074	.592-.882
Hr48	99	.681	.111	.463-.899
Maximum value of Hr24 or Hr48	92	.732	.088	.559-.905
Hr24-Hr0	92	.902	.052	.800-1.00
Hr48-Hr0	89	.781	.100	.585-.977
Maximum value of Hr24-Hr0 or Hr48-Hr0	83	.947	.028	.894-1.00
Hr24-Hr0 (%)	92	.906	.048	.813-.999
Hr48-Hr0 (%)	89	.775	.101	.577-.973
Maximum value of Hr24-Hr0 (%) or Hr48-Hr0 (%)	83	.940	.027	.887-.993

Secondary objectives: whether Ucystatin-C can diagnose AFR earlier than Screatinine

The last secondary objective; from the above results whether Ucystatin-C can diagnose ARF earlier than Screatinine or not in patients undergoing CAG.

The difference in proportion of patients having ARF at 24 hours and 48 hours post CAG between diagnosed by Ucystatin-C and Screatinine was analyzed. (Table 12)

Table 12 Proportion of patients having ARF at 24 hours and 48 hours post CAG comparing between diagnosis by Ucystatin-C and Screatinine

		Diagnosis by Screatinine (gold standard)					
		At 24 hr		At 48 hr		Within 48 hr	
		ARF (n = 4)	No ARF (n = 97)	ARF (n = 9)	No ARF (n = 92)	ARF (n = 10)	No ARF (n = 91)
% change Ucystatin-C at 24 hr	≥ 50% ARF	3 Sn = 75%	20	6 Sn = 67%	17	7 Sn = 70%	16
	< 50% No ARF	1	77 Sp = 79%	3	75 Sp = 82%	3	75 Sp = 82%
% change Ucystatin-C within 48 hr	≥ 50% ARF	3	29	6	26	7	25
	< 50% No ARF	1	68	3	66	3	66

ARF is acute renal failure, defined as Screatinine rising ≥ 0.5 mg/dl or > 25% from baseline.

True ARF can be diagnosed at 24 hours post CAG by percent change of Ucystatin-C ≥ 50% from baseline criteria in 7/10 cases and by Screatinine (gold standard) criteria in 4/10.

True ARF can be diagnosed at 48 hours post CAG by percent change of Ucystatin-C ≥ 50% from baseline criteria in 7/10 cases and by Screatinine (gold standard) criteria in 10/10.

CHAPTER VI

DISCUSSION

Recruitment of patients and baseline characteristics

Two hundred and eighteen from 1,129 patients scheduled for coronary angiography (CAG) met study criteria but 96 patients refused consent to enter the study. The main obstacles were the limited available bed for 48 hours admission in elective CAG and the preference to early discharge the patient within 24 hours if no immediate cardiac complication after CAG was detected.

Patients with no ARF at 24 hours post CAG by Screatinine criteria and cannot completed 48 hours data collection were excluded from the analysis because they cannot be defined as ARF or not. And also, patients with specimens lost were excluded from the analysis from the same reason. One patient in ARF group experienced congestive heart failure was excluded from the analysis because the rising of Screatinine may be from congestive heart failure not from contrast nephropathy alone and the value of Ucystatin-C was error, extremely abnormal high even more than Scystatin-C.

Underlying renal insufficiency is a major risk factor for development of contrast-induced ARF. Patients enrolled in this study also had other risk factors which included advanced age (68.7$\pm$9.9 years), male gender (68%), diabetes mellitus (76%) and hypertension (98%). These factors may be covariate rather than independent variables. This probably accounts for reports that fail to confirm many of these as risk factors. [20]

Prevention of contrast-induced nephropathy

Effective prevention of contrast-induced nephropathy includes hydration prior to the procedure and the use of the lowest possible dose of contrast media. Intravenous hydration was used for prophylaxis of contrast nephropathy in almost all patients, 114 (99%) cases, unless it was contra-indicated.

Administration of N-acetylcysteine in addition to intravenous saline hydration may have a beneficial effect in the prevention of contrast-induced nephropathy after cardiovascular procedures in patients with impaired renal function. Many randomized controlled trials and at least 11 systematic reviews studied N-acetylcysteine for prevention of contrast-induced nephropathy. These studies yield inconsistent results to warrant a conclusion on efficacy or a recommendation for its routine use. [21-31] However many cardiologists used N-acetylcysteine to reduce contrast-induced nephropathy before CAG because this agent is nontoxic and inexpensive. In this study, oral N-acetylcysteine was added to conventional intravenous hydration in 63 (53%) cases.

Coronary angiography procedure: type of contrast media

Decrease GFR is a major risk factor for contrast-induced nephropathy, however type and dosage of contrast media are also important.

Low-osmolar contrast media is clearly preferred in high risk patients (e.g., renal insufficiency, history of allergies). In the Iohexol Cooperative Study; patients with renal insufficiency alone or combined with diabetes who received diatrizoate (an ionic, monomeric, high-osmolar contrast media) were more likely to develop renal injury than those receiving iohexol (a nonionic, low-osmolar contrast media). [32] A meta-analysis of 45 comparative studies showing that low-osmolar contrast media is associated with reduced nephrotoxicity compared with high-osmolar contrast media especially in patients with preexisting renal failure. [33] In this study, iopromide (a nonionic, low-osmolar contrast media) was used in all patients.

Recent study of a new iso-osmolar contrast media, iodixanol (a nonionic, dimeric, iso-osmolar contrast media) was significantly less nephrotoxic than ioxaglate (an ionic, dimeric, low-osmolar contrast media) in patients with renal impairment undergoing coronary angiography. [34] However, no patient in this study received iso-osmolar contrast media during CAG. The role of osmolality may have been over-interpreted. A number of characteristics of contrast media have been suggested as possible causes of nephrotoxicity e.g. osmolality, direct tubular toxicity and more recently viscosity. While pathophysiology of contrast-induced nephropathy is not yet completely understood, it most certainly involves the interplay of multiple factors leading to

hypoxia of the outer medulla. [35] The results of the Swedish registry study which included data on over 57,000 patients, strongly indicated that the contrast media iodixanol, iso-osmolar contrast media but has a high viscosity, is not better tolerated by the kidneys than contrast agents with low osmolality and low viscosity. [36] The study results suggest the hypothesis that higher viscosity of contrast media is associated with inferior renal tolerance.

Coronary angiography procedure: dosage of contrast media

ARF is more likely to occur if high dose contrast media is used (> 200 ml) during CAG. [37] Limitation of the volume of contrast media used during CAG could reduce the incidence of nephropathy. Cigarroa RG et al showing that dosage of contrast media could be given without impairing renal function by using this formula; 5 ml of contrast per kg of body weight (maximum 300 ml) / Screatinine (mg/dl). [38] Dose of contrast media usage is associated with duration of procedure and coronary intervention during CAG. In this study, mean duration of CAG and dosage of contrast media used were 27.6 $\pm$ 19.3 min and 76.9 $\pm$ 55.2 ml respectively. Thirty nine percent of CAG was done with coronary intervention.

Coronary angiography procedure: complications

One hundred of 115 patients were free from any complications after CAG. ARF occurred in 12 (10.4%) patients. In Gruberg L et al study, patients who had a baseline Screatinine > 1.8 mg/dl, underwent percutaneous coronary intervention with ioxaglate meglumine contrast-media, 37 % had an increase in Sceatinine > 25% within 48 hours or required dialysis. [3] Incidence of ARF from contrast nephropathy in this study was lower than expected in this high risk group of patients may be due to, firstly the use of iopromide (a nonionic, low-osmolar contrast media) as a media study in all patients, secondly the more awareness of the cardiologist to prevent contrast nephropathy by addition oral N-acetylcysteine to conventional intravenous hydration and finally the minimal dosage of contrast was used with limited therapeutic intervention during CAG as possible.

ARF from contrast media is typically reversible with non-oliguric being more common than oliguric renal failure. Renal replacement therapy is rarely needed and usually only in patient

whose baseline GFR is very low. In this study, mean urine volume per day in ARF group (808 ± 200 ml) was significantly lower than in non ARF group (1,098 ± 258 ml). Only one patient in ARF group had decreased urine volume to oliguric range and no patient in ARF group needed dialysis.

Characteristics and laboratory tests in patients with and without ARF after CAG

Decrease GFR is a major risk factor for contrast-induced nephropathy. Baseline GFR in ARF group (44.6± 13.0 ml/min/1.73m^2) was slightly lower than in non ARF group (48.2 ± 10.9 ml/min/1.73m^2) corresponding with the higher level of Screatinine and Scystatin-C in ARF group than in non ARF group.

Baseline Ucreatinine in non ARF group was significantly higher than in ARF group. Creatinine in urine comes from glomerular filtration and tubular secretion. Spot Ucreatinine measurement can not be a marker of GFR estimation and the level was influenced by the concentration or flow of the urine. Baseline Ucystatin-C and UCCR which adjusted Ucsytatin-C with Ucreatinine were not significantly different between ARF group and non ARF group; 0.127 ± 0.219 VS 0.120 ± 0.205 mg/l and 0.254 ± 0.305 (*10^{-3}) VS 0.199 ± 0.341 (*10^{-3}) respectively.

Unit of Ucystatin-C and Ucreatinine were expressed in mg/l and mg/dl respectively. UCCR, a ratio of Ucystatin-C to Ucreatinine, was very low because the correction of the two markers to the same unit and the higher value of the numerator and the lower value of the denominator.

Primary objective: Diagnostic values of UCCR

The best diagnostic test of UCCR to diagnose ARF was the maximum value of UCCR within 48 hours post CAG. However the usefulness of this test was limited because the value of AUC from ROC curve was only 0.630. The best sensitivity 92% was obtained if cut-off value of the maximum value of UCCR within 48 hours post CAG $\geq 0.07*10^{-3}$ but the specificity will be only 28%. Likelihood ratio table of this test at various levels was not good enough for clinical

decision. If cut-off point to diagnose ARF was the rising of UCCR by ≥ 25% or ≥ 50% from baseline within 48 hours post CAG; sensitivity, PPV and likelihood ratio were also very low.

In this study, UCCR was investigated as the primary diagnostic test because there were more previous studies of UCCR than Ucystatin-C. However all previous data of UCCR in patients with decreased kidney function were descriptive. This is the first diagnostic study of UCCR although the results showed that UCCR had limited diagnostic usefulness in ARF from contrast media.

Secondary objectives: Diagnostic value of Ucystatin-C

Ucystatin-C not adjusted with Ucreatinine gave a better result than UCCR for diagnosis of ARF from contrast nephropathy. The percent change of Ucystatin-C at 24 hours post CAG from baseline represented the best diagnostic test of Ucystatin-C (AUC 0.809). An example; if the percent change was ≥ 50%, this test will have a sensitivity 70%, specificity of 82% and likelihood ratio of 3.98 to diagnose ARF. There was a problem when trying to obtain a good likelihood ratio table of this test because the incidence of ARF in this study was lower than expected, so the numbers of ARF patients to fill at each level were limited. Likelihood ratio of this test that had positive diagnostic impact was the percent change of greater than 100% from baseline.

Diagnostic values of Ucystatin-C seem to be better than UCCR. This finding has an advantage to use in clinical practice because the easier measurement and less cost of Ucystatin-C than UCCR.

Secondary objectives: Diagnostic value of Scystatin-C

The diagnostic value of Scystain-C was much better than UCCR and Ucystatin-C because Scystatin-C was considered as one of the serum markers for GFR estimation same as Screatinine. However diagnostic usefulness of Scystatin-C was not much interested in this study because Scystatin-C must be obtained from venopuncture and further analysis found that it can not diagnosed ARF earlier than standard Screatinine.

Secondary objectives: whether Ucystatin-C can diagnose AFR earlier than Screatinine

From the above diagnostic results; diagnostic values of Ucystatin-C seem to be better and more clinical usefulness than UCCR and Scystatin-C. Ucystatin-C was then investigated, whether it can diagnose ARF earlier than Screatinine or not. ARF diagnosed by change of Ucystatin-C $\geq$ 50% from baseline criteria was maximum at 24 hours post CAG (sensitivity of 75%) and was not increased at 48 hours post CAG (sensitivity of 70%) but specificity was slightly increased. Contrary to Ucystatin-C, all true ARF diagnosed within 48 hours post CAG had been diagnosed at 24 hours post CAG by Screatinine criteria (gold standard test) in only 40% of cases.

Diagnostic value of urine cystatin C

There are many previous studies show that various renal tubular enzyme markers increased after tubular damage. Most of these studies are descriptive and no diagnostic study has ever done especially for urine cystatin C which under normal condition does not enter the final excreted urine to any significant degree.

This is the first study evaluated diagnostic value of urine cystatin C in contrast nephropathy. The aim of this diagnostic study is to find a good screening test for diagnosis of ARF using urine cystatin C, however sensitivity of UCCR or Ucystatin-C at the acceptable high value had a low likelihood ratio. In conclusion, this study showed that although urine cystatin C increased early within 24 hours after CAG but the diagnostic impact for ARF was limited.

This diagnostic study was done in ARF from contrast nephropathy in high risk adult patients undergoing coronary angiography. UCCR and Ucystatin-C showed a limited usefulness for diagnosis of ARF. The diagnostic impact of these markers for other types of renal injury such as prolonged aminoglycoside usage in normal GFR patients is not known and may be further studied.

CHAPTER VII

CONCLUSION AND IMPLICATION

Conclusion: Urine cystatin C increases early after radio-contrast media exposure however urine cystatin C and urinary cystatin C to creatinine ratio (UCCR) have only fair usefulness for diagnosis of acute renal failure in patients undergoing coronary angiography.

Implication: Many elective CAG patients without immediate cardiologic complication will be early discharged within 24 hours after procedures. They may develop ARF unnoticed and its complication will increase both short and long-term morbidity and mortality. This study showed that urine cystatin C increased early after radio-contrast exposure. For clinical application; if no or only modest rising of urine cystatin C at 24 hour post CAG from baseline, likelihood to have ARF from contrast nephropathy will be low and patient may be early discharged as appropriated. However if the rising of urine cystatin C at 24 hour post CAG from baseline is very high, the likelihood ratio and specificity of this test will also be very high. The patient should be further admitted to repeat serum creatinine from the blood test at 48 hours post CAG to see whether ARF occur or not. Although this test had limited diagnostic usefulness, it may be more useful in easily bruised or obese patients which daily repetitive venopunctures for serum creatinine are difficult, painful and inconvenient.

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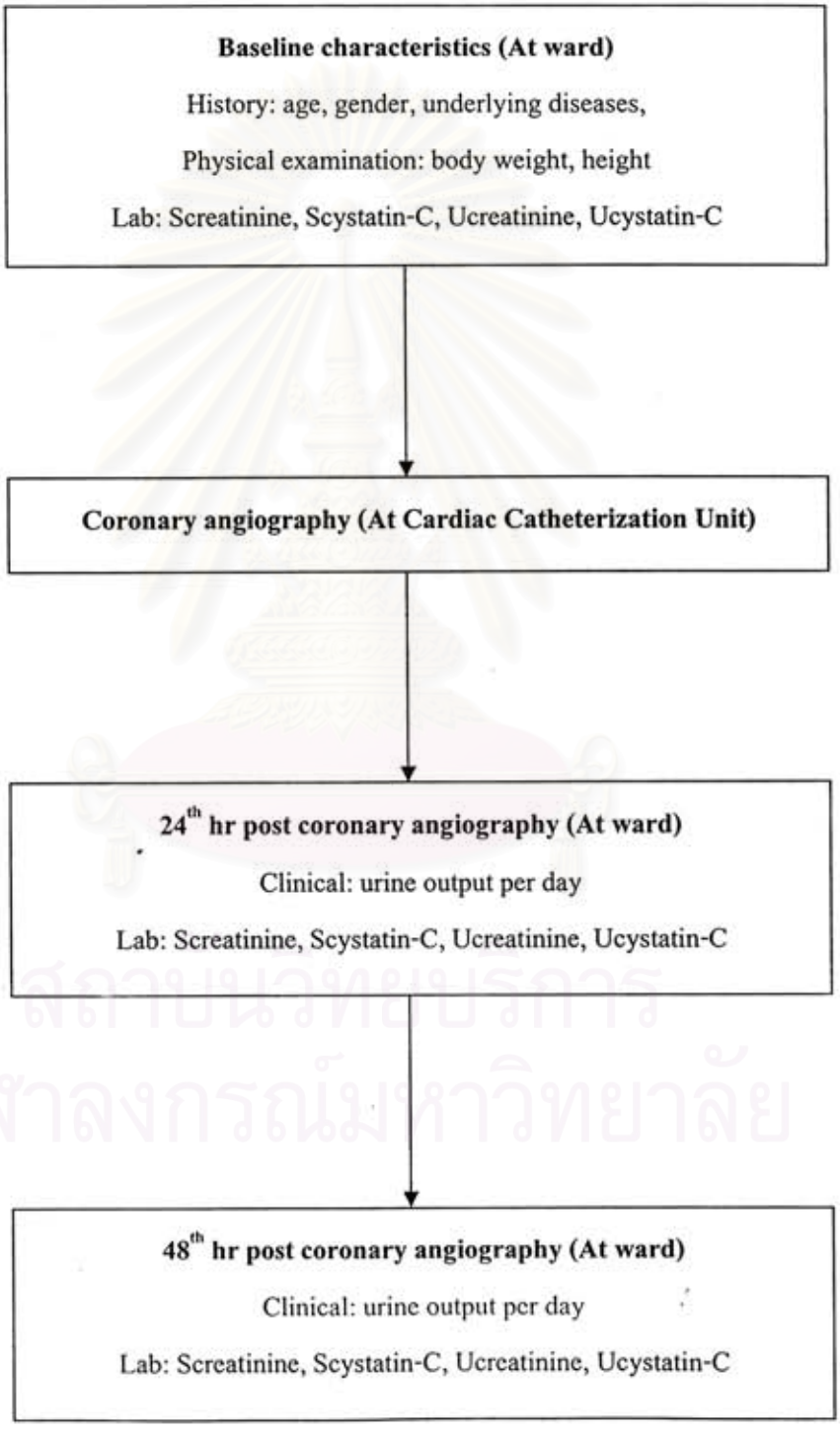
APPENDICES

APPENDIX A

Study protocol



APPENDIX B

Patient Information Sheets

เอกสารชี้แจงโครงการวิจัยทางการแพทย์

โครงการวิจัย "การวินิจฉัยภาวะไตวายเฉียบพลันโดยการตรวจปัสสาวะหาค่า cystatin C ต่อ creatinine ในผู้ป่วยที่ได้รับการตรวจหลอดเลือดหัวใจด้วยสารรังสีทึบแสง"

ขอเรียนชี้แจงเหตุผลและรายละเอียดในโครงการวิจัยทางการแพทย์นี้ ก่อนที่ท่านจะตกลงเข้าร่วมโครงการวิจัย ดังนี้ เมื่อท่านจำเป็นต้องได้รับการตรวจหลอดเลือดหัวใจด้วยสารรังสีทึบแสง ท่านจะได้รับการฉีดสารรังสีทึบแสงเข้าไปในหลอดเลือดดำ ซึ่งการกระทำดังกล่าวก็เพื่อประโยชน์ในการวินิจฉัย โรคหรือเพื่อการรักษาโรคที่ท่านเป็นอยู่ อย่างไรก็ตามหัตถการทางการแพทย์ทุกอย่างย่อมมีความเสี่ยงไม่มากก็น้อย การฉีดสารรังสีทึบแสงเข้าไปในร่างกายนั้นอาจทำให้เกิดภาวะไตวายเฉียบพลันเกิดขึ้นได้ ความเสี่ยงนี้ขึ้นกับหลายปัจจัย เช่นผู้ป่วยที่เป็นเบาหวาน หรือผู้ป่วยที่มีภาวะไตเสื่อมอยู่เดิมย่อมมีความเสี่ยงมากกว่าบุคคลทั่วไป

ภาวะไตวายเฉียบพลันที่เกิดจากสารรังสีทึบแสง มักจะเกิดขึ้นเร็วภายใน 24 – 48 ชั่วโมงหลังการทำหัตถการ ผู้ป่วยที่เกิดภาวะไตวายเฉียบพลันนี้ ส่วนมากมักไม่มีอาการแสดงให้เห็นชัดเจน ผู้ป่วยส่วนมากยังคงมีปริมาณปัสสาวะปกติ แต่การตรวจเลือดจะพบว่าค่าของเสียครีอะตินีน (creatinine) ในร่างกายสูงขึ้น ทั้งนี้เนื่องจากไตผู้ป่วยไม่สามารถทำงานขับของเสียได้ตามปกติ ภาวะไตวายเฉียบพลันที่เกิดจากสารรังสีทึบแสงนี้มักจะดีขึ้นได้เองภายในเวลาประมาณหนึ่งสัปดาห์

แม้ว่าผู้ป่วยส่วนมากที่เกิดภาวะไตวายเฉียบพลันนี้จะอาการไม่รุนแรง แต่ในผู้ป่วยบางรายอาจมีอาการรุนแรงได้ เกิดความผิดปกติของดุลน้ำและเกลือแร่ของร่างกาย และพบของเสียคั่งในร่างกายอย่างมาก ผู้ป่วยบางรายอาจต้องได้รับการรักษาด้วยการล้างไตชั่วคราวจนกว่าไตจะฟื้นกลับมาทำหน้าที่ได้ปกติตามเดิมหรือใกล้เคียงเดิม

การป้องกันภาวะไตวายเฉียบพลันที่เกิดจากสารรังสีทึบแสง สามารถทำได้โดยการใช้สารรังสีทึบแสงปริมาณน้อยที่สุดเท่าที่จำเป็น ใช้สารรังสีทึบแสงชนิดน้ำหนักมวลต่ำ การให้สารน้ำทางหลอดเลือดดำก่อนและหลังทำหัตถการ รวมทั้งการพิจารณาให้ยาบางชนิดที่อาจป้องกันภาวะนี้ได้ ทั้งนี้ขึ้นกับการพิจารณาของแพทย์ผู้ทำการรักษาและความเสี่ยงของผู้ป่วยที่จะเกิดภาวะนี้

อย่างไรก็ตามแม้จะทำการป้องกัน และระมัดระวังอย่างดีแล้ว ผู้ป่วยยังมีโอกาสที่จะเกิดภาวะไตวายเฉียบพลันที่เกิดจากสารรังสีทึบแสงนี้ได้ การวินิจฉัยภาวะนี้ผู้ป่วยจำเป็นจะต้องได้รับการเจาะเลือดเพื่อตรวจหาค่าครีอะตินีนว่าสูงขึ้นกว่าก่อนฉีดสารรังสีทึบแสงหรือไม่ เพื่อที่จะได้ให้การรักษาที่รวดเร็วและเหมาะสมต่อไป ดังนั้นผู้ป่วยจะได้รับการเจาะเลือดครั้งละ 10 มิลลิลิตร รวม

3 ครั้งคือ ก่อนฉีดสารรังสีทึบแสง และที่เวลา 24 และ 48 ชั่วโมงหลังฉีดสารรังสีทึบแสง ซึ่งในการโครงการวิจัยนี้จะขอเก็บปัสสาวะผู้ป่วยร่วมด้วย เพื่อตรวจดูสาร ซีสเตตินซี (cystatin C) และครีอะตินีน (creatinine) ในปัสสาวะ ว่าสามารถให้การวินิจฉัยภาวะไตวายเฉียบพลันที่เกิดจากสารรังสีทึบแสงได้ดีเช่นเดียวกับการตรวจหาครีอะตินีนในเลือด และรวดเร็วกว่าหรือไม่

ผู้เข้าร่วมโครงการวิจัยนี้ไม่ต้องเสียค่าใช้จ่ายเพิ่มเติมใด ๆ นอกเหนือจากค่าใช้จ่ายในการตรวจหลอดเลือดหัวใจด้วยสารรังสีทึบแสงและการดูแลที่ท่านจำเป็นต้องได้รับหรือต้องรับผิดชอบอยู่แล้ว ประโยชน์ที่คาดว่าจะได้รับจากโครงการวิจัยต่อผู้เข้าร่วมวิจัยโดยตรงคือท่านจะได้รับการตรวจและติดตามว่าเกิดภาวะไตวายเฉียบพลันหรือไม่ เพื่อการรักษาที่รวดเร็วและเหมาะสมต่อไป นอกจากนี้ความรู้ที่ได้รับจากโครงการวิจัยนี้จะเป็นประโยชน์ต่อความก้าวหน้าทางการแพทย์ในการดูแลผู้ป่วยเช่นเดียวกับท่านต่อไปในอนาคตด้วย

APPENDIX C

Consent Form

หนังสือยินยอมเข้าร่วมโครงการวิจัยทางการแพทย์

วันที่.....เดือน.....พ.ศ.....

ข้าพเจ้า.....ได้รับทราบเกี่ยวกับโครงการวิจัยเรื่อง " การวินิจฉัยภาวะไตวายเฉียบพลันโดยการตรวจปัสสาวะหาค่า cystatin C ต่อ creatinine ในผู้ป่วยที่ได้รับการตรวจหลอดเลือดหัวใจด้วยสารรังสีทึบแสง " โดยข้าพเจ้าจะได้รับการซักประวัติ ตรวจร่างกาย ตรวจเลือด และตรวจปัสสาวะ ก่อนการตรวจหลอดเลือดหัวใจด้วยสารรังสีทึบแสง และหลังการตรวจเป็นเวลา 48 ชั่วโมง

ข้าพเจ้าได้รับการชี้แจงวัตถุประสงค์ของโครงการวิจัย วิธีการศึกษา ประโยชน์ที่จะได้รับและผลข้างเคียงที่อาจเกิดขึ้น พร้อมทั้งซักถามถึงสิ่งที่สงสัย ซึ่งในกรณีที่มีผลแทรกซ้อนเกิดขึ้นข้าพเจ้าจะได้รับการดูแลอย่างเหมาะสมโดยแพทย์ผู้ทำการวิจัย และข้าพเจ้าได้รับทราบว่าข้อมูลส่วนตัวของข้าพเจ้าจะได้รับการปกปิดไว้เป็นความลับ

ข้าพเจ้าได้พิจารณาแล้วว่า การศึกษาวิจัยนี้จะเป็นประโยชน์ต่อตนเอง สังคม และการสาธารณสุข ข้าพเจ้าจึงมีความยินดีและเต็มใจที่จะเข้าร่วมการศึกษาวิจัยนี้ ในระหว่างการศึกษานี้ข้าพเจ้ามีสิทธิ์ที่จะถอนตัวจากการเข้าร่วมศึกษาเวลาใดก็ได้ และการถอนตัวนี้จะไม่มีผลกระทบต่อการให้การรักษาของแพทย์ผู้ทำการวิจัยต่อข้าพเจ้าแต่อย่างใด

หากข้าพเจ้ามีปัญหา ข้อสงสัยใด ๆ ข้าพเจ้าสามารถติดต่อผู้ดำเนินโครงการวิจัยได้ทางโทรศัพท์ โดยติดต่อ นพ.อำนาจ ชัยประเสริฐ แผนกโรคไต กองอายุรกรรม รพ.พระมงกุฎเกล้า หมายเลขโทรศัพท์ 01-4479984 ตลอด 24 ชั่วโมง

ข้าพเจ้าได้อ่าน และทำความเข้าใจในหนังสือยินยอมเข้าร่วมโครงการวิจัยนี้โดยตลอดแล้วจึงลงลายมือชื่อไว้เป็นหลักฐานต่อหน้าพยาน

ลงชื่อ.....ผู้เข้าร่วมโครงการวิจัย

(.....)

ลงชื่อ.....ผู้ดำเนินโครงการวิจัย

(นพ. อำนาจ ชัยประเสริฐ)

ลงชื่อ.....พยาน

(.....)

ลงชื่อ.....พยาน

(.....)

APPENDIX D

CRF-1-

Patient number | | | |

Diagnosis of acute renal failure by urinary cystatin C to creatinine ratio in patients undergoing coronary angiography

CASE RECORD FORM

Principle investigator

Name Dr.Amnart Chaiprasert

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Department of Internal Medicine
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CRF-2-

Patient number [ ][ ][ ]

Assessment date [ ][ ][ ][ ][ ][ ]

d d m m y y

Eligible criteria

Inclusion criteria	No	Yes
- age ≥ 18 years	[ ]	[ ]
- chonic kidney disease stage 3 – 4 (GFR of 15 – 59 ml/min/1.73m^2)*	[ ]	[ ]
- scheduled for coronary angiography and/or angioplasty	[ ]	[ ]
- agree to participate in the study with informed consent	[ ]	[ ]
Exclusion criteria	**No**	**Yes**
- with organ transplantation	[ ]	[ ]
- methylprednisolone, cyclosporin A, cimetidine or trimethoprim usage	[ ]	[ ]
- prior radiocontrast study within 1 week	[ ]	[ ]
Conclusion	**No**	**Yes**
- patient fulfills all inclusion criteria and none of exclusion criteria	[ ]	[ ]

*Simplified MDRD equation : GFR, in ml/min/1.73m^2 = 186.3 x ((Screatinine) exp[-1.154]) x (Age exp[-0.203]) x (0.742 if female); where exp is the exponential.

CRF-3-

Patient number | | | |

Assessment date | | | | | | | |

d d m m y y

Patient description

Age [__ __] years [__ __] months

Gender [ ] male [ ] female

Body weight [__ __ __] kg

Height [__ __ __] cm

Underlying diabetes [ ] No [ ] Yes

Underlying hypertension [ ] No [ ] Yes

Screatinine [__ __ __ __] mg/dl

Scystatin-C [__ __ __ __] mg/l

Ucreatinine [__ __ __ __] mg/dl

Ucystatin-C [__ __ __ __] mg/l

CRF-4-

Patient number | | | |

Coronary angiography [__ __ / __ __ / __ __]

d d m m y y

24th hr post coronary angiography

urine output per day [__ __ __ __] ml

Screatinine [__ __ __ __] mg/dl

Scystatin-C [__ __ __ __] mg/l

Ucreatinine [__ __ __ __] mg/dl

Ucystatin-C [__ __ __ __] mg/l

48th hr post coronary angiography

urine output per day [__ __ __ __] ml

Screatinine [__ __ __ __] mg/dl

Scystatin-C [__ __ __ __] mg/l

Ucreatinine [__ __ __ __] mg/dl

Ucystatin-C [__ __ __ __] mg/l

VITAE

Name	Lt.Col. Amnart Chaiprasert
Address	639 Sivalee2 Rangsit-Nakhonnayok52 Thanyaburi Pathumthani 12130 Thailand
Date of Birth	19th May 1968
Sex	Male
Nationality	Thai
Marital Status	Married
Education	
1985–1991	Doctor of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok Thailand
1994–1997	Diplomate Thai Board of Internal Medicine, Phramongkutklao Hospital, Bangkok Thailand
1998–2000	Diplomate of Nephrology, Phramongkutklao Hospital, Bangkok Thailand
2003	Diplomate Thai Board of Family Medicine
Work	
1991–1994	Promyothee Fort, Prachinburi Thailand
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2000–2001	Suranaree Fort Hospital, Nakhonrachasema Thailand
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