แบบจำลองคะแนนความเสี่ยงเพื่อทำนายการเกิดภาวะไตทำงานบกพร่องจากสารทึบรังสีในผู้ป่วยที่ได้รับหัตถการรักษาหลอดเลือดโคโรนารีผ่านสายสวน

นางสาวธศิกานต์ แซ่มซ้อย

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
สาขาวิชาเภสัชกรรมคลินิก ภาควิชาเภสัชกรรมปฏิบัติ
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2553

RISK SCORE MODEL FOR PREDICTION OF CONTRAST-INDUCED NEPHROPATHY AFTER PERCUTANEOUS CORONARY INTERVENTION

Miss Tasigan Chaemchoi

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Pharmacy Program in Clinical Pharmacy

Department of Pharmacy Practice
Faculty of Pharmaceutical Sciences
Chulalongkorn University

Academic Year 2010

Thesis Title	RISK SCORE MODEL FOR PREDICTION OF CONTRAST-INDUCED NEPHROPATHY AFTER PERCUTANEOUS CORONARY INTERVENTION
By	Miss Tasigan Chaemchoi
Field of Study	Clinical Pharmacy
Thesis Advisor	Baralee Punyawudho, Ph.D.
Thesis Co-Advisor	Associate Professor Suphot Srimahachota, M.D.

Accepted by the Faculty of Pharmaceutical Sciences, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

..... Dean of the Faculty of
(Associate Professor Pintip Pongpech, Ph.D.) Pharmaceutical Sciences

THESIS COMMITTEE

..... Chairman
(Associate Professor Duangchit Panomvana Na Ayudhya, Ph.D.)

..... Thesis Advisor
(Baralee Punyawudho, Ph.D.)

..... Thesis Co-Advisor
(Associate Professor Suphot Srimahachota, M.D.)

..... Examiner
(Associate Professor Titinun Auamnoy, Ph.D.)

..... External Examiner
(Boonthum Jirajan, M.D.)

ธศิกานต์ แซ่มซ้อย : แบบจำลองคะแนนความเสี่ยงเพื่อทำนายการเกิดภาวะไตทำงานบกพร่องจากสารทึบรังสีในผู้ป่วยที่ได้รับหัตถการรักษาหลอดเลือดโคโรนารีผ่านสายสวน. (RISK SCORE MODEL FOR PREDICTION OF CONTRAST-INDUCED NEPHROPATHY AFTER PERCUTANEOUS CORONARY INTERVENTION)
อ. ที่ปรึกษาวิทยานิพนธ์หลัก : อ. ดร.บราลี ปัญญาวุธโธ,
อ. ที่ปรึกษาวิทยานิพนธ์ร่วม : รศ. นพ.สุพจน์ ศรีมหาโชตะ, 91 หน้า.

ภูมิหลัง การได้รับสารทึบรังสีมีความสัมพันธ์กับการเกิดภาวะไตทำงานบกพร่องจากสารทึบรังสี (CIN) ปริมาณสารทึบรังสีที่ใช้ สภาวะและคุณลักษณะของผู้ป่วยอาจเป็นปัจจัยเสี่ยงต่อการเกิด CIN การหาปริมาณสารทึบรังสีและปัจจัยที่มีความสัมพันธ์กับการเกิด CIN อาจช่วยลดความเสี่ยงต่อการเกิด CIN

วัตถุประสงค์ เพื่อ (1) วิเคราะห์หาปัจจัยที่มีความสัมพันธ์กับการเกิด CIN ในผู้ป่วยที่ทำหัตถการรักษาหลอดเลือดโคโรนารีผ่านสายสวน (PCI) และ (2) สร้างแบบจำลองคะแนนความเสี่ยงเพื่อทำนายการเกิด CIN ภายหลังการทำ PCI

วิธีทำการศึกษา ผู้ป่วยที่ทำ PCI จำนวน 181 รายถูกคัดเลือกเข้าการศึกษา ข้อมูลเกี่ยวกับคุณลักษณะของผู้ป่วยและรายละเอียดกระบวนการทำหัตถการจะถูกบันทึก กำหนดให้ CIN หมายถึง การตรวจพบการเพิ่มขึ้นของค่าครีแอทินินในซีรัมมากกว่าร้อยละ 25 หรือ 0.5 มิลลิกรัม/เดซิลิตรจากค่าเดิมของผู้ป่วย ภายในระยะเวลา 72 ชั่วโมงภายหลังการทำ PCI หรือได้รับการวินิจฉัยว่าเกิด CIN ใช้ Receiver-operator characteristics (ROC) methods เพื่อวิเคราะห์หาจุดตัดของ ปริมาณสารทึบรังสี (V) และ อัตราส่วนระหว่างปริมาณสารทึบรังสีต่อน้ำหนักตัว (V/BW) ที่เป็นปัจจัยเสี่ยงต่อการเกิด CIN ตรวจสอบจุดตัดที่ได้จากการวิเคราะห์ ROC methods และปัจจัยเสี่ยงอื่นๆ ต่อความสัมพันธ์กับการเกิด CIN โดยใช้ multivariate logistic regression analysis สร้างแบบจำลองคะแนนความเสี่ยงทำนายการเกิด CIN ภายหลังการทำ PCI โดยแปลงค่า odds ratio ของแต่ละปัจจัยเสี่ยงเป็นคะแนนความเสี่ยง ศึกษาความสัมพันธ์ระหว่างคะแนนความเสี่ยงกับอัตราการเกิด CIN

ผลการศึกษา พบอุบัติการณ์การเกิด CIN ในผู้ป่วยที่ทำ PCI 6.1% จากการวิเคราะห์ ROC methods พบว่าที่ V/BW เท่ากับ 2.6 มิลลิลิตร/กิโลกรัม เป็นจุดตัดที่สามารถทำนายแยกระหว่างกลุ่มผู้ป่วยที่เกิดและไม่เกิด CIN ได้ดี โดยมีค่า concordance statistic (C-statistic) = 0.73 จากการวิเคราะห์ multivariate logistic regression พบว่า V/BW มากกว่าหรือเท่ากับ 2.6 มิลลิลิตร/กิโลกรัม (OR 8.184; p=0.003), ภาวะหัวใจล้มเหลว (OR 6.465; p=0.010), และอัตราการกรองของไตน้อยกว่า 30 มิลลิลิตร/นาที (OR 6.141; p=0.019) เป็นปัจจัยที่มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติต่อการเกิด CIN แบบจำลองคะแนนความเสี่ยงที่สร้างขึ้นสามารถจำแนกกลุ่มผู้ป่วยที่เกิดและไม่เกิด CIN ได้ดี (C-statistic = 0.849) อุบัติการณ์การเกิด CIN แปรผันตามคะแนนความเสี่ยง

สรุป แบบจำลองคะแนนความเสี่ยงที่สร้างขึ้นซึ่งประกอบด้วย 3 ปัจจัยทำนายคือ V/BW มากกว่าหรือเท่ากับ 2.6 มิลลิลิตร/กิโลกรัม, ภาวะหัวใจล้มเหลว, และอัตราการกรองของไตน้อยกว่า 30 มิลลิลิตร/นาที สามารถนำไปประยุกต์ใช้เป็นเครื่องมือในการประเมินความเสี่ยงของผู้ป่วยแต่ละรายต่อการเกิด CIN ภายหลังการทำ PCI

ภาควิชา.....เภสัชกรรมปฏิบัติ.....ลายมือชื่อนิสิต.....ธศิกานต์ แซ่มซ้อย.....
สาขาวิชา.....เภสัชกรรมคลินิก.....ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก.....บราลี ปัญญาวุธโธ
ปีการศึกษา.....2553.....ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์ร่วม.....

5176567633 : MAJOR CLINICAL PHARMACY

KEYWORDS : CONTRAST-INDUCED NEPHROPATHY / CIN / ACUTE KIDNEY INJURY / PERCUTANEOUS CORONARY INTERVENTION / PCI

TASIGAN CHAEMCHOI : RISK SCORE MODEL FOR PREDICTION OF CONTRAST-INDUCED NEPHROPATHY AFTER PERCUTANEOUS CORONARY INTERVENTION. THESIS ADVISOR : BARALEE PUNYAWUDHO, Ph.D., THESIS CO-ADVISOR : ASSOC. PROF. SUPHOT SRIMAHACHOTA, M.D., 91 pp.

Background The use of contrast media has been closely related to contrast-induced nephropathy (CIN) in several studies. The volume of contrast media and patient characteristics may be important risk factors for CIN. Identifying and quantifying these risk factors may be useful in predicting risk of CIN.

Objectives To (1) identify important risk factors associated with CIN, and (2) develop a risk score model for prediction of CIN after percutaneous coronary intervention (PCI).

Methods A total of 181 patients underwent PCI were enrolled. Patient- and procedure-related factors were prospectively collected. CIN was defined as an increase in serum creatinine > 25% or > 0.5 mg/dl from pre-PCI value within 72 hours after PCI or diagnosed with CIN. Receiver-operator characteristics (ROC) methods were used to determine the optimal cutoff point of contrast media volume (V) and volume/body weight (V/BW) ratio. All risk factors including the cutoff point values obtained from ROC curve analysis were tested for an association with CIN by multivariate logistic regression analysis. A CIN risk score model was developed by using odds ratio from multivariate analysis as risk score values for each of risk factor. The relationship between risk score and occurrence of CIN after PCI was evaluated.

Results The incidence of CIN after PCI was 6.1%. The ROC curve analysis indicated that V/BW ratio of 2.6 ml/kg was a good discriminator for CIN with concordance statistic (C-statistic) of 0.73. Multivariate logistic regression analysis showed that V/BW ratio $\geq$ 2.6 ml/kg (OR 8.184; p=0.003), congestive heart failure (CHF) (OR 6.465; p=0.010), and creatinine clearance (CrCl) < 30 ml/min (OR 6.141; p=0.019) were associated with CIN after PCI. The CIN risk score model demonstrated good discriminative ability with C-statistic of 0.849. The incidence of CIN increases with risk score.

Conclusion The CIN risk score model, incorporating 3 risk predictors including V/BW ratio ≥ 2.6 ml/kg, CrCl < 30 ml/min, and CHF, can be used as a tool to assess individual patient risk of developing CIN after PCI.

Department : Pharmacy Practice Student's Signature Tasigan Chaemchoi

Field of Study : Clinical Pharmacy Advisor's Signature Baralee Punyawudho

Academic Year : 2010 Co-Advisor's Signature Suphot Srimahachota

ACKNOWLEDGEMENTS

My thesis would have not been completed without support and encouragement from many people. First of all, I would like to express my sincere gratitude to my thesis advisor, Mrs. Baralee Punyawudho, Ph.D. from Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, for her valuable advice, continual guidance, suggestions, keen interest and encouragement throughout the course of the study.

To Associate Professor Suphot Srimahachota from Cardiac center and Division of Cardiovascular Diseases, Department of Medicine, King Chulalongkorn Memorial Hospital, my thesis co-advisor, he devoted helpful discussion and suggestion for this study. My appreciation is also extended to the thesis committee; Associate Professor Duangchit Panomvana Na Ayudhya, Associate Professor Titinun Auamnoy and Mr. Boonthum Jirajan, M.D., for their critical evaluation and helpful suggestions for this research, and providing information for improvement until success.

I am grateful to thank the Cardiac Center and all staffs at Catheterization Laboratory, Coronary Care Unit (CCU), Intermediate Coronary Care Unit (ICCU) and Cardiac Intervention Care Unit (CICU), King Chulalongkorn Memorial Hospital for the contribution and collaboration.

Thanks are also due to Graduate School, Chulalongkorn University for granting financial support to fulfill this study. Not lastly, I wish to thank King Chulalongkorn Memorial Hospital which gave me the best chance for continuing education. I hold in the highest regard, thank you.

I eventually wish to express my deeply grateful to my family for their understanding and support from beginning to end of my graduate study. My acknowledgement would not be completed without expressing regards and gratitude to all patients involved in this study, without them this study would have not been possible.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CT	=	computer tomography
MRI	=	magnetic resonance imaging
CIN	=	contrast-induced nephropathy
PCI	=	percutaneous coronary intervention
NAC	=	N-acetylcysteine
CrCl	=	creatinine clearance
PRBC	=	packed red blood cell
DM	=	diabetes mellitus
CHF	=	congestive heart failure
CKD	=	chronic kidney disease
MI	=	myocardial infarction
mOsm/kg	=	milliosmoles/kilogram
HOCM	=	high-osmolar contrast media
LOCM	=	low-osmolar contrast media
IOCM	=	iso-osmolar contrast media
ACEI	=	angiotensin-converting enzyme inhibitors
ARB	=	angiotensin II receptor blockers
GFR	=	glomerular filtration rate
OR	=	odds ratio
MCD	=	maximum contrast dose
IABP use	=	intraaortic balloon pump use
C-statistic	=	concordance statistics
NRD	=	nephropathy requiring dialysis
ROC curve analysis	=	receiver-operator characteristics curve analysis
V/BW ratio	=	volume/body weight ratio
AUC	=	area under the ROC curve
BMI	=	body mass index
q 12 hours	=	every 12 hours

CHAPTER I
INTRODUCTION

Background and Rationale

Contrast media are being widely used for both diagnostic and therapeutic purposes *(1, 2)*. In 2003, over 80 million doses of intravascular contrast media, corresponding to approximately 8 million liters, were administered worldwide, making it one of the most commonly prescribed medications in the history of modern medicine *(3)*. The general indication for the use of contrast media is to create an X-ray attenuation differential in tissues in order to increase the visualization of disease processes *(3)*. Radiological procedures utilizing intravascular contrast media include computer tomography (CT), intravenous pyelography, angiography/venography and magnetic resonance imaging (MRI) *(3)*.

All imaging modalities using contrast media have rapidly raised, especially CT scanning which has increased by 800% in the last two decades and cardiac catheterization which increased by 390% from 1979 to 2002 in the USA and by 112% from 1992 to 1999 in Europe *(3)*. An increasing number of radiological procedures utilizing contrast media have led to a rise in the incidence of acute kidney injury caused by an exposure to contrast media, known as contrast-induced nephropathy (CIN) *(1-3)*. The exact mechanism of CIN is unclear; however, an evidence suggests that a combination of direct toxic effects on tubular epithelial cells and renal ischemia may play a pathogenic role *(4)*. CIN is traditionally defined as an increase in serum creatinine of either 0.5 mg/dl or 25% from baseline within 72 hours of exposure *(1, 5, 6)*. Although, the incidence of CIN is low (0.6-2.3%) in general population, it is significantly higher in some groups of patients, especially in patients with cardiovascular pathology undergoing coronary angiography and percutaneous coronary intervention (PCI) *(2)*. The reported incidence of CIN after PCI was 3.3-20% *(2, 7, 8)*.

Even though, serum creatinine usually increases to a peak level 3-5 days after receiving contrast media and returns to the baseline level within 1-3 weeks, 0.3-0.7% of the patients progress to acute renal failure (ARF) requiring dialysis *(2)*. Moreover, patients who developed CIN after receiving contrast media have higher complication rates, longer hospital stay, and higher mortality rate compared with patients who did not develop CIN *(6, 9-12)*. A possible reason for this association is that CIN initiates or aggravates pathologies *(13)*. Once CIN is established, only supportive care is currently provided until renal function resolves, infrequently, hemodialysis may be required, either transiently or even permanently *(14)*. Therefore, at present, the main method to reduce this complication is its prevention *(15)*. Several interventions have shown to be effective in reducing risk of CIN development such as administration of preprocedural and postprocedural intravenous isotonic fluid, minimizing the dose of contrast media, using low- or iso-osmolar contrast media, and avoiding short interval between procedures requiring contrast media *(15-17)*. Although the benefit of N-acetylcysteine (NAC) is controversial, findings from some trials suggest that this agent decreases the incidence of CIN, and the use of NAC has become common at many institutions *(18)*.

As the majority of patients undergoing cardiac procedures are likely to be discharged within 24 hours after the procedure *(19)*, an assessment of CIN development beyond 24 hours is limited. Therefore, an ability to predict CIN after the procedure would be of clinical benefit. Several risk factors associated with CIN after PCI have been identified; however, in daily practice, the combination of two or more risk factors is rather common *(14)*. The effect of risk factor is additive and the likelihood of CIN rises sharply as the number of risk factors increases *(20)*. This additive nature of risk factors has allowed the development of prognostic scores to predict the probability of CIN in order to support decision about patient management and preventive measure *(20)*. However, none of the published risk model has been prospectively validated in different populations *(20)*. In addition, the differences in patient characteristics, type and volume of contrast media administered in the procedures may affect the sensitivity of patient's renal function to contrast media. The purpose of this study was therefore to identify risk

factors associated with CIN after PCI and develop a risk score model for prediction of CIN after PCI in Thai patients.

Objectives

(1) To determine the incidence of CIN after PCI.

(2) To identify risk factors associated with CIN after PCI.

(3) To develop a risk score model for prediction of CIN after PCI.

Operation Definitions

(1) **Contrast media** was defined as iodinated intravascular contrast media.

(2) **CIN** was defined as an increase in serum creatinine > 25% or > 0.5 mg/dl from pre-PCI value within 72 hours after PCI or diagnosed with CIN.

(3) **The creatinine clearance (CrCl)** was estimated using the Cockcroft-Gault method as presented in equation 1.

CrCl (ml/min) = [(140-age) x weight (kg)]/72 x serum creatinine (mg/dl) {x 0.85 for female subjects} ---------- **(equation 1)**

(4) **Anemia** was defined as baseline hematocrit value < 39% for men and < 36% for women based on World Health Organization criteria.

(5) **Transfusion of packed red blood cell (PRBC)** was defined as hematocrit dropped and need for transfusion of PRBC before PCI.

(6) **Diabetes mellitus (DM)** was defined as hyperglycemia requiring insulin and/or oral hypoglycemic drug treatment or diagnosed with DM.

(7) **Hypertension** was defined as the mean of two or more properly measured of systolic blood pressure (SBP) more than 140 mmHg or diastolic blood pressure (DBP) more than 90 mmHg or diagnosed with hypertension.

(8) **Emergency PCI** was defined as PCI that was performed immediately to open an occluded coronary artery.

(9) **Elective PCI** was defined as a planned PCI.

(10) **Congestive heart failure (CHF)** was defined as left ventricular ejection fraction below 40% or diagnosed with CHF.

Scope of the Study

This study was a prospective analytical study. Patients underwent elective or emergency PCI at King Chulalongkorn Memorial Hospital between 10 November 2009 and 31 March 2010 were enrolled in the study.

Expected Benefit and Application

(1) By using this CIN risk score model, patients can be effectively assessed for the risk of developing CIN before contrast media exposure. Therefore, patients who are at risk of developing CIN can be identified and prophylactic measures can be provided in advance.

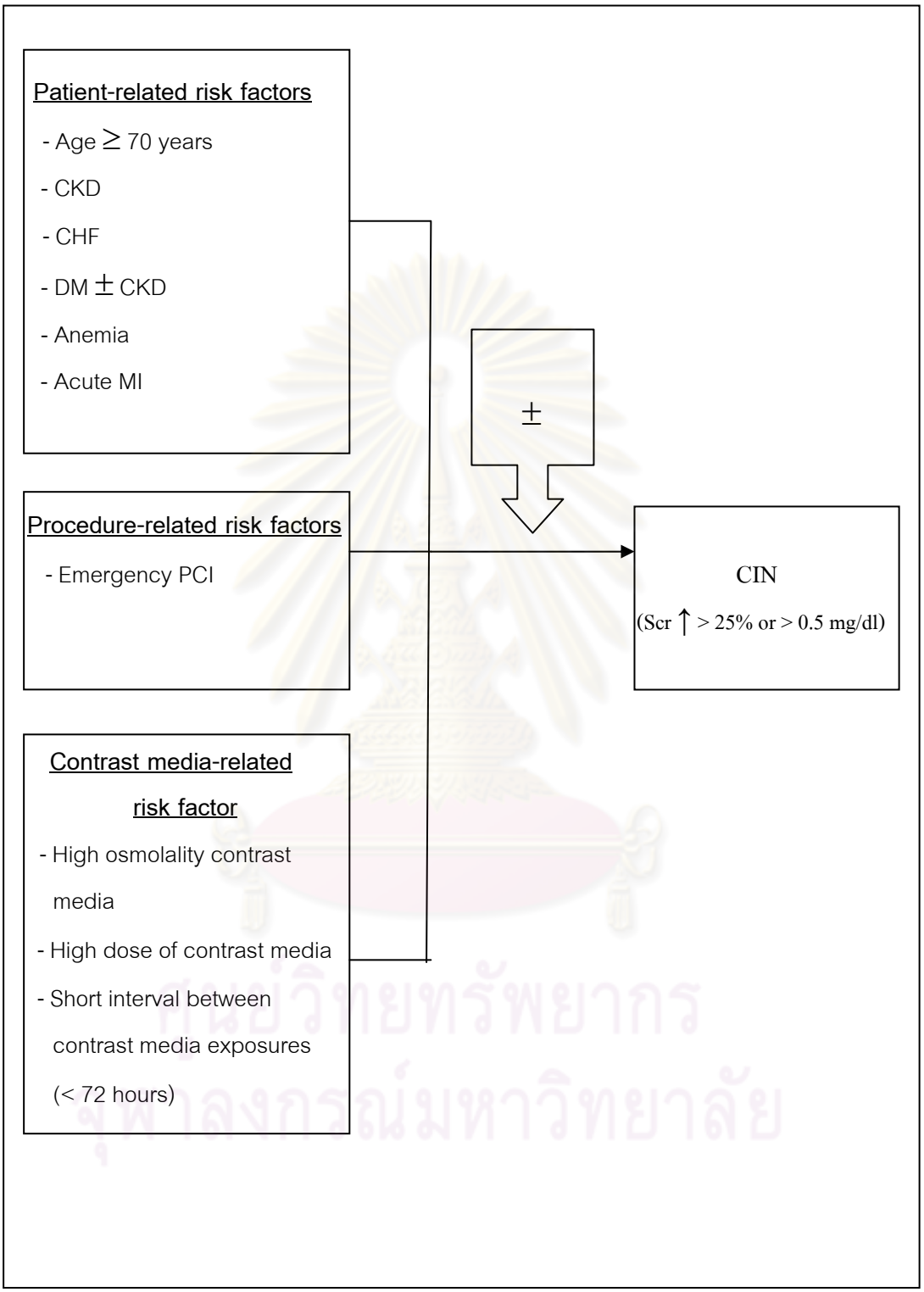
(2) Obtain information on the incidence of CIN after PCI.

(3) Obtain information on the risk factors associated with CIN after PCI in Thai patients.

Conceptual Framework

According to the guidelines for CIN and review of related articles, specific factors that increase risk of CIN development were categorized as risk factors that related to the patient, contrast media and a procedure. The most common patient-related risk factors include age ≥ 70 years, chronic kidney disease (CKD), DM with or without CKD, CHF and reduced left ventricular ejection fraction, anemia, and acute myocardial infarction (MI). Moreover, a high dose of contrast media, short interval (< 72 hours) between contrast media exposures, a high osmolality of contrast media and emergency procedure have been reported to increase risk of developing CIN. As the role of NAC for prevention of CIN remains controversial; therefore, the preventive effect of NAC was also evaluated in this study (Figure 1).

Figure 1. Conceptual framework



CHAPTER II
REVIEW OF LITERATURE

1. Contrast Media

1.1 Chemistry and pharmacology *(3, 21, 22)*

Iodinated contrast media are generally used for creating an X-ray attenuation differential in tissues in order to increase the visualization of disease processes. All currently used contrast media are based on chemical alteration of the 2, 4, 6 tri-iodinated benzene ring (Figure 2). The iodine provides the radio-opacity, whereas the other elements of the contrast media molecule provide no radio-opacity but act as carriers of the iodine. The contrast media are hydrophilic and demonstrate low protein binding. Following intravascular injection, peak concentrations only last for a few seconds and 70% of the injected dose diffuses from plasma to the extracellular space within 2 - 5 minutes. In highly perfused tissues such as the liver, heart, lungs and brain, a fall in plasma concentration is rapid; whereas, diffusion into the extracellular space is slower in skin, fat and skeletal muscle. An equilibrium diffusion between plasma and the interstitial space occurs about 2 hours after injection. The contrast media are rapidly excreted, with over 90% being eliminated by glomerular filtration within 12 hours in patients with normal renal function. In patients with renal impairment, the excretion by the kidneys can last for several weeks.

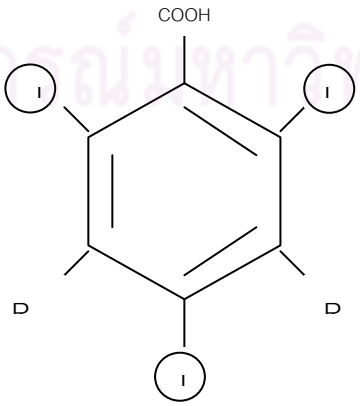


Figure 2. Chemical structure of triiodobenzoic acid

1.2 Contrast media classification *(3, 21-23)*

Contrast media are classified as ionic or non-ionic and as monomers or dimers. In clinical practice, contrast media are generally classified by osmolality, which is defined by the number of osmoles of solute per kilogram of solvent (Osm/kg). On a basis of osmolality, contrast media are divided into three categories as following, (A comparison of commonly used contrast media is presented in Table 1)

1.2.1 High-osmolar contrast media (HOCM) – The osmolality ranges from 1500 - 1800 milliosmoles/kilogram (mOsm/kg), whereas the osmolality of human plasma is 290 mOsm/kg. It is widely acknowledged that the osmolality of HOCM is a major contribution to their adverse effects and that a reduction in osmolality is desirable. The HOCM include diatrizoate, iothalamate and loxithalamate.

1.2.2 Low-osmolar contrast media (LOCM) - The osmolality ranges from 600 – 700 mOsm/kg, more than twice that of blood. The two types of LOCM include non-ionic monomers and ionic dimers. The non-ionic monomers LOCM are the contrast media of choice because they are potentially less toxic. The common non-ionic monomers include iohexol, iopromide, iopamidol and ioversol.

1.2.3 Iso-osmolar contrast media (IOCM) – The IOCM is iso-osmolar to blood. Iodixanol is the only agent in this class available for intravascular use.

2. Contrast-Induced Nephropathy

2.1 Definition and incidence

The most common definition of CIN in clinical trials is an increase of 25% or more, or an absolute increase of 0.5 mg/dl or more in serum creatinine from baseline value, at 48-72 hours following the exposure to contrast media *(1, 2)*. The European Society of Urogenital Radiology (ESUR) defines CIN as an impairment in renal function

(an increase in serum creatinine by > 0.5 mg/dl or > 25%) within 3 days after intravascular administration of contrast media, without an alternative etiology *(5)*. The first 24 hours post-exposure appear to be crucial in the development of CIN *(2, 24)*. A study of the trajectory of serum creatinine elevation indicated that in 80% of CIN cases serum creatinine started to rise within the first 24 hours post contrast media exposure, and nearly all patients who progressed to serious renal failure (requiring either nephrology consultation or dialysis) had a rise in serum creatinine within this time frame *(2, 24)*.

An overall incidence of CIN in a general population is 0.6-2.3% *(2)*. However, in some populations, the incidence of CIN is significantly higher especially in patients with cardiovascular pathology undergoing coronary angiography and percutaneous coronary intervention (PCI) *(2)*. In an unselected group of 1,826 patients treated with PCI, the incidence of CIN was 14.5% *(9)*. A larger study among 8,357 patients undergoing elective PCI, CIN occurred in 13 % of the cases *(14)*. The risk of CIN is especially high (19-20%) in patients underwent emergency PCI for acute myocardial infarction *(7, 8)*. Moreover, the incidence of CIN can rise to 50% or more in patients with multiple risk factors *(20)*.

Table 1. Properties of commonly used contrast media *(25)*

Generic Name	Trade Name(s)	Manufacturer*	Type, Ionicity	Iodine Content (mg/mL)	Osmolality (mOsm/kg H_2O)†,‡	Viscosity at 20 °C (mPa.s)§	Viscosity at 37 °C (mPa.s)‖
Diatrizoate, amidotrizoate			HOCM Ionic (monomer)	140–146	550–700	—	1.4–1.9
				282	1,400–1,500	—	4.1
				292	1,420–1,539	—	4.0–8.5
				300	1,270–1,550	—	2.4
				306	—	9.2–9.5	4.9–5.0
				370	1,940–2,140	—	8.3–9.1
				462	2,938	—	19.5
Iothalamate			HOCM Ionic (monomer)	141	600	—	1.5
				282	1,400	—	4.3
				325	1,700	—	3
				400	2,150–2,300	—	4.5
				480	2,400	—	9.0
Ioxithalamate			HOCM Ionic (monomer)	120	610	—	1.1
				300	1,500–1,890	—	5.2
				320	—	—	3.8
				350	2,160	—	7.5
				380	1,970	—	8.5
Ioxaglate	Hexabrix	Guerbet (licensed to Tyco Healthcare/ Mallinckrodt)	LOCM Ionic (dimer)	160	295	—	1.7
				200	370	—	2.2
				320	600	15.7	7.5
				350	680	—	10.5
Iohexol	Omnipaque	GE Healthcare Bio-sciences/Amersham Health	LOCM Nonionic (monomer)	180	—	3.3	2.2
				200	410	3.8	2.4
				240	—	5.6	3.3
	Omnitrast	Schering		250	520	6.3	3.6
	Omnigraf	Juste		300	640	11.6	6.1
				350	780	23.3	10.6
Iopamidol	Isovue	Bracco Diagnostics Inc.	LOCM Nonionic (monomer)	150	300–340	—	1.5
				200	412–438	3.3	2.0–2.2
	Iopamiro(n)	Bracco (Intl)		240	480	—	3.0
	Jopamiro(n)	Bracco (Intl)		300	616–680	8.8	4.5–4.7
	Niopam	Bracco (UK)		350	730	—	7.0
	Solutrast	Bracco–Altana Pharma		370	796–832	20.9	9.4–9.5
Ioversol	Optiray	Tyco Healthcare/ Mallinckrodt	LOCM Nonionic (monomer)	160	355–380	—	1.6–1.9
				240	502–550	5.2	2.6–3.0
				300	630	10.0	5.0
				320	695–720	—	5.8–6.1
				350	790	18	8.0–9.0
Iopromide	Ultravist	Schering Berlex	LOCM Nonionic (monomer)	150	340	2.3	1.2–1.5
				180	390	—	1.5
				200	420	—	1.9
				240	480–500	4.8	2.8
				300	610–620	8.7	4.6
				350	730	—	7.7
				370	774–780	20.1	9.5
				400	880	—	12.3
Iobitridol¶	Xenetix	Guerbet	LOCM Nonionic (monomer)	250	585	6	4.0
				300	695	11	6.0
				350	915	21	10.0
Iomeprol¶	Iomeron	Bracco (Intl)	LOCM Nonionic (monomer)	150	301	2.1	1.4
				200	362	3.1	2.0
				250	440	4.9	2.9
				300	521–609	8.1–8.7	4.5
				350	620	14.5	7.5
				400	730	27.5	12.6
Iodixanol	Visipaque	GE Healthcare Bio-sciences/Amersham Health	IOCM Nonionic (dimer)	150	(109),‖ 290	2.7	1.7
				270	(209),‖ 290	11.1	5.7
				320	(240),‖ 290	24.4	11.1

HOCM = high-osmolar contrast media; IOCM = isosmolar contrast media; LOCM = low-osmolar contrast media.

* Berlex, Montville, NJ; GE Healthcare Biosciences/Amersham Health, Piscataway, NJ; Bracco–Altana Pharma, Constance, Germany; Bracco Diagnostics Inc., Princeton, NJ; Bracco House, Bucks, United Kingdom; Bracco International BV, Amsterdam, Netherlands; Guerbet LLC, Bloomington, IN; Juste, Madrid, Spain; Schering, Madrid, Spain; Tyco Healthcare/Mallinckrodt, St. Louis, MO.

† Osmolality values differ with measuring technique.

‡ Values can be measured in a pure solution of the active substance in water, or in the commercial product.

§ For ionic HOCM, viscosity values depend on type of salt.

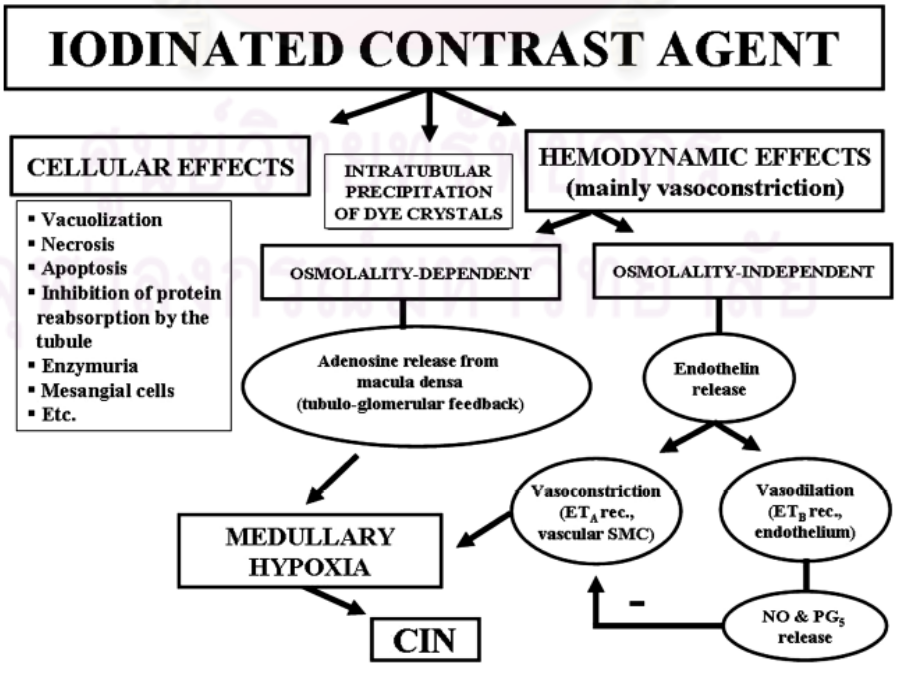
‖ Pure solution in water, before adjusted to isotonicity with NaCl and $CaCl_2$.

¶ Not available in the United States.

2.2 Pathophysiology of contrast-induced nephropathy *(4, 20)*

Although the exact mechanism of CIN has not been completely elucidated, there is increased evidence that a combination of direct toxic effects on tubular epithelial cells and renal ischemia may play a pathogenic role (Figure 3). First, direct toxic effects in the proximal convoluted tubular cells and in the inner cortex of the kidneys have been demonstrated following exposure to contrast media. Injury due to enhanced production of oxygen-free radicals and lipid peroxidation of biological membranes may also be implicated. Second, an immediate vasoconstriction and reduction in renal blood flow to outer medulla after contrast media exposure lead to medullary hypoxia, ischemic injury and death of renal tubular cells. Two possible mechanisms by which medullary hypoxia and ischemia may occur in response to contrast media exposure have been proposed; (1) contrast media may cause renal vasoconstriction by both increasing activity of several intrarenal mediators (adenosine, vasopressin, angiotensin II, dopamine-1 and endothelin) and decreasing activity of renal vasodilators (nitric oxide and prostaglandins), (2) contrast media may decrease renal blood flow indirectly by causing erythrocyte aggregation.

Figure 3. The postulated mechanisms in the pathophysiology of CIN *(4)*.



ET_A = endothelin A; ET_B = endothelin B; SMC = smooth muscle cells; NO = nitric oxide; and PG_5 = Prostaglandin 5.

2.3 Impact of contrast-induced nephropathy

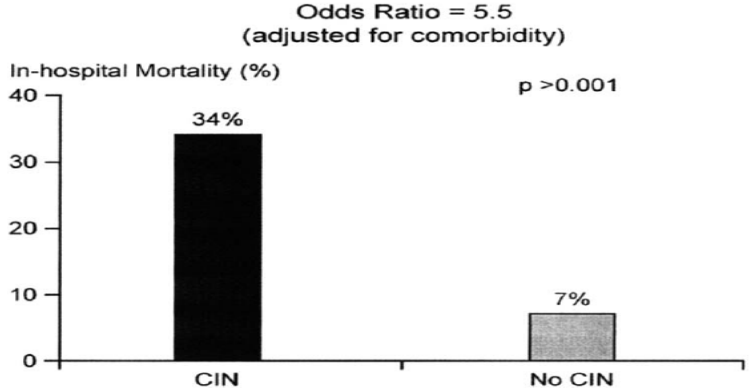
2.3.1 Contrast-induced nephropathy requiring dialysis

Although most cases of CIN reflect mild transient impairment of renal function, a small proportion of patients require dialysis. The need for dialysis after CIN varies according to patients' underlying risks at the time of contrast administration, but generally it is less than 1% *(9, 26)*. Although CIN requiring dialysis is relatively rare, the impact on patient prognosis is considerable *(6)*. The in-hospital mortality rate for patients who developed CIN requiring dialysis after coronary intervention was 35.7% with the 2-year survival rate of 18.8% compared with the in-hospital mortality rate of 7.1% in a group of patients who developed CIN but not requiring dialysis *(9)*.

2.3.2 Increased mortality risk

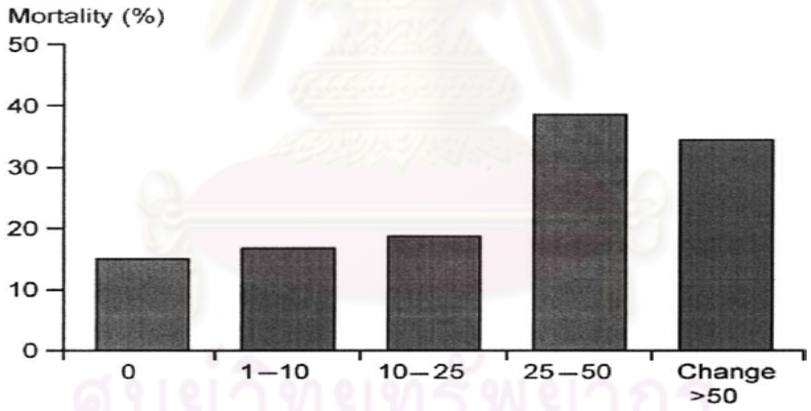
It has been recognized that the risk of death increased in patients developing CIN. Among approximately 16,000 patients undergoing procedures requiring contrast media in a large retrospective study, a total of 183 subjects developed CIN. Although the incidence of CIN in this study was less than 2%, the risk of death during hospitalization in subjects developing CIN was 34%, compared with 7% in matched controls who had received contrast media but did not develop CIN. Even after adjusting for comorbid disease, patients with CIN had a 5.5-fold increased risk of death and a complicated clinical course (Figure 4) *(27)*.

Figure 4. In-hospital mortality is higher in patients with CIN *(6, 27)*



The high risk of in-hospital death associated with CIN has also been noted in a retrospective analysis of 7,586 patients, 3.3% of cases developed CIN after exposure to contrast media. The hospital mortality rate was 22% in the patients who developed CIN, compared with only 1.4% in patients who did not develop CIN *(10)*. The increased risk of death was found to be persisted long term. The mortality rates at 1 year and 5 years after CIN development (12.1% and 44.6%) were significantly higher than the mortality rates in patients who did not develop CIN (3.7% and 14.5%) ($p < 0.0001$) *(10)*. In an analysis of the relation between postprocedure increase in serum creatinine and mortality, a significant increase in 1-year mortality was observed when an increase in serum creatinine was higher than 25% ($p < 0.0001$), supporting the use of this cut-off value as a predictor of worse outcomes (Figure 5) *(28)*.

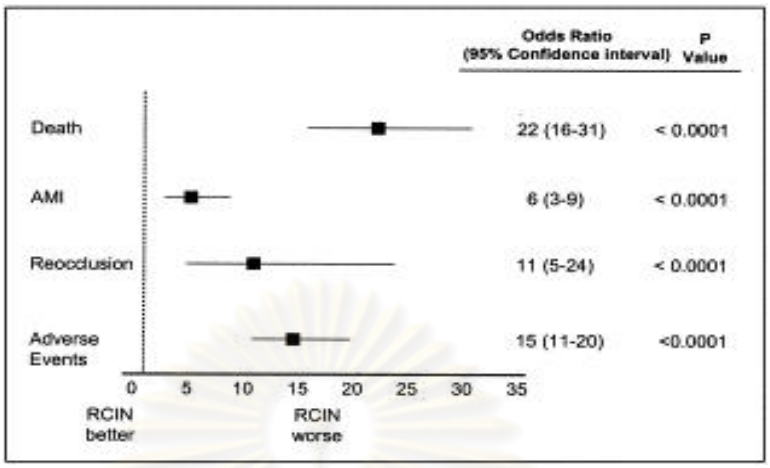
Figure 5. Depiction of 1-year mortality rate according to post-PCI increase in serum creatinine *(28)*



2.3.3 Increased adverse clinical outcome

CIN is associated with other adverse outcomes, including cardiovascular events. In a large registry of 20,479 patients undergoing PCI, CIN occurred in 2% of patients and was associated with a 15-fold increase in major adverse cardiac events, regardless of the need for hemodialysis. Among the patients who developed CIN, there was a 5.5-fold increase in myocardial infarction (MI), an 11-fold increase in target vessel reocclusion, and a 22-fold increase in the mortality rate (Figure 6) *(29)*.

Figure 6. Odds ratio of major adverse events after CIN development *(29)*



Another study also found a relationship between CIN after PCI and late cardiovascular events. The development of CIN was associated with an increased incidence of MI (24% in patients with CIN versus 11.6% in patients without CIN; $p < 0.001$) and target vessel revascularization at 1 year (28.8% in patients with CIN versus 20.3% in patients without CIN; $p = 0.008$) *(30)*.

2.3.4 Longer hospital stay

Several reports document the association between the development of CIN and a longer hospital stay. The postprocedure hospital stay was longer in patients who developed CIN, regardless of baseline renal function (6.8 ± 7.1 days versus 2.3 ± 2.5 days in patients with prior CKD and 3.6 ± 5.1 days versus 1.8 ± 2.4 days in patients without CKD) *(31)*. In another study, patients developing CIN were 15 times more likely to have an extended hospitalization (> 4 days) (90% versus 20%, $p < 0.0001$) *(29)*.

2.3.5 Economic impact

A recent economic analysis of the direct costs associated with CIN showed that the average additional cost was $ 10,345 for the hospital stay. The major reason of the increased costs associated with CIN was the cost of the longer initial hospital stay *(32)*.

3. Risk Markers for Contrast-Induced Nephropathy

Identifying high-risk patients is the first step to minimize the overall risk of CIN. Specific factors that increase risk of developing CIN are related to patient characteristics, contrast media and procedure. The strongly associated risk markers for CIN are preexisting renal disease, DM, age greater than 70 years, concurrent use of nephrotoxic drugs, hypovolemia, use of a large amount of contrast media or an ionic high-osmolar contrast media (HOCM) and CHF *(33, 34)*. The use of the term "*risk marker"* is typically preferred than "*risk factor"* in the literature because many of these factors are nonmodifiable patient characteristics that are not necessarily directly causative *(20, 33)*. According to the guidelines for CIN and the review of related articles, risk markers for CIN were categorized as classic risk markers (Table 2), risk markers with limited data (possible risk markers) (Table 3), and new and conflicting risk markers (Table 4).

Table 2. Classic risk markers for the development of CIN *(33)*

Modifiable Risk Markers	Nonmodifiable Risk Markers
Low effective circulatory volume	CKD
Use of nephrotoxic drugs	DM with CKD
Increased dose of contrast media	Older age
Short duration of two contrast media administrations	Class III-IV CHF and reduced left ventricular ejection fraction
High-osmolar and ionic contrast media	

Table 3. Possible risk markers for the development of CIN *(33)*

Modifiable Possible Risk Markers	Nonmodifiable Possible Risk Markers
Hypertension	Prior kidney surgery
Hypoalbuminemia	Acquired immunodeficiency syndrome
Hypercholesterolemia	Polyarteritis nodosa
Periprocedural hypotension	Multi-vessel coronary involvement
Trauma	Peripheral vascular disease

Table 3. Possible risk markers for the development of CIN *(33)* (continue)

Modifiable Possible Risk Markers	Nonmodifiable Possible Risk Markers
Urgent/Emergency procedure	Renal artery stenosis
Anemia	Acute myocardial infarction
Sepsis	
Rhabdomyolysis	
Low serum sodium level	
Pulmonary edema	
Urine albumin-creatinine ratio > 3056	
Bypass graft intervention	
Use of intra-aortic balloon pump	
Delayed coronary reperfusion	
Intra-arterial contrast administration	

Table 4. New and conflicting risk markers for the development of CIN *(33)*

New Risk Markers	Conflicting Risk Markers
Metabolic syndrome	ACEI and ARB*
Impaired fasting glucose	DM with normal renal function
Hypertriglyceridemia	Multiple myeloma
Pre-diabetes	Female gender
Hyperuricemia	Cirrhosis
	Renal transplantation

ACEI and ARB* = Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers

Risk Markers for Contrast-Induced Nephropathy

1. Chronic kidney disease

A patient with normal renal function rarely has CIN, but the incidence progresses with the decreasing of glomerular filtration rate (GFR). The contrast media are excreted mainly by glomerular filtration. The half-life for contrast media in patients with normal GFR is between 40 and 120 minutes, but it is between 16 and 84 hours in patients with severe renal impairment *(33)*. McCullough et al noted that with an estimated GFR (eGFR) of greater than 60 ml/min, the chance of CIN was less than 5% *(9)*. Several studies agreed that an eGFR of 60 ml/min is a reliable cutoff point for identifying patients at high risk for the development of CIN *(2)*. The CIN Consensus Working Panel reported that the risk of CIN is elevated and become clinically important when baseline serum creatinine level is ≥ 1.3 mg/dl in men and ≥ 1.0 mg/dl in women *(35)*. The higher the baseline creatinine value, the greater is the risk of CIN, as shown in Table 5. However, baseline creatinine is not reliable enough for identification of patients at risk for CIN. This is because serum creatinine value varies with age, muscle mass, and gender. Therefore, it is recommended to calculate eGFR before an exposure to contrast media *(2)*. Moreover, preexisting renal disease with an elevated level of serum creatinine is considered as another crucial risk marker of CIN development *(2)*. The risk of CIN is especially higher if the underlying renal disease is diabetes *(33)*.

Table 5. Relationship between baseline serum creatinine and CIN development

Study	Procedure	Number of patients	CIN Definition	Baseline SCr* (mg/dl)	% CIN development
Rihal et al. 2002 *(10)*	PCI	7,586	SCr* ↑ ≥ 0.5 mg/dl	< 1.1	2.4
				2.0 – 2.9	22.4
				≥ 3	30.6
Hall KA et al. 1992 *(36)* (abstract)	Angiographic procedure	222	N/A	≤ 1.2	2
				1.4 – 1.9	10.4
				≥ 2.0	62

SCr* = serum creatinine

2. Diabetes mellitus with chronic kidney disease

Among all predisposing factors for CIN, diabetic patients with CKD constitue the group at highest risk for CIN *(2, 20, 33, 34)*. However, it is not clear whether the risk of CIN is significantly increased in patients with DM and normal renal function *(2, 20)*. Some studies showed that diabetic patients with preserved renal function and absence of other risk factors, the rates of CIN are usually comparable to those of a non-diabetic population *(37)*, while clinically important CIN usually occurs in a subset of diabetic patients with underlying renal insufficiency *(2, 38)*. Patients with DM and CKD have a greater risk of CIN, oliguria, and need dialysis than nondiabetic patients with similar levels of CKD *(39)*. In a recent study, a total of 421 patients with creatinine clearance between 15 and 60 ml/min undergoing coronary angiography, it was found that CIN occurred in 20% of diabetic and 5.5% of nondiabetic patients. Hemodialysis was required in 3.6% of diabetic patients, and none of the patients with normal fasting glucose required hemodialysis ($p = 0.036$) (Table 6) *(40)*. In another registry of 1,575 diabetic patients undergoing PCI, CIN was observed in 15% of diabetes patients with preserved renal function (serum creatinine < 1.5 mg/dl or eGFR > 60 ml/min) compared with 27% of diabetes patients with CKD ($p < 0.0001$), and dialysis was instituted in 0.1 and 3.1%, respectively ($p < 0.0001$) *(38)*. The most appropriate role of diabetes with respect to CIN is that it acts as a risk amplifier in the presence of CKD *(20)*.

Table 6. Relationship between diabetes mellitus with chronic kidney disease and CIN development

Study	Number of patient	Procedure	Patient characteristics	% CIN development	%Hemodialysis requirment
Toprak et al 2007 *(40)*	421	CAG	CKD with DM	20	3.6
			CKD with non-DM	5.5	0
				($p = 0.001$)	($p = 0.036$)
Nikolsky et al 2004 *(38)*	1,575	PCI	DM with CKD	27.4	3.1
			DM with non-CKD	15.1	0.1
				($p < 0.0001$)	($p < 0.0001$)

CAG = coronary angiography

3. Older age

Several studies provided evidence that older age is a risk predictor of CIN. Mehran et al reported that age > 75 years was a significant predictor of CIN after elective PCI (OR = 2.195; 95% CI = 1.780-2.706) *(14)*. Marenzi et al also found that age > 75 years was significantly associated with the risk of CIN development in acute MI patients undergoing emergency PCI (OR = 5.28; 95% CI = 1.98-14.05) *(8)*. A study in 219 nondiabetic patients with reduced kidney function, age ≥ 70 years was an independent predictor of CIN (OR = 6.78; 95% CI = 2.1-21.28) *(41)*. The reasons for higher risk to develop CIN in elderly were not studied specifically and probably are multifactorial, including age-related changes in renal function (diminished GFR, tubular secretion and concentrating ability), and the presence of multivessel coronary artery disease, necessitating complex PCI, coupled with more difficult vascular access resulting in greater amount of contrast media needed *(2)*.

4. Type of contrast media

A meta-analysis of 25 studies indicated a significant reduction in risk of CIN with LOCM compared with HOCM (OR = 0.61, 95% CI = 0.48 - 0.77) *(42)*. Studies published since this meta-analysis generally support these findings *(43)*. Most studies comparing different LOCM agents have been small trials that have not shown clinically relevant variation within this class *(25)*. Iodixanol, an iso-osmolar contrast media (IOCM), has been shown to have the lowest risk for CIN in patients with CKD and DM *(1, 44)*. The CIN Consensus Working Panel supports the view that iodixanol is the least nephrotoxic agent available for intravascular use *(1)*. The American College of Cardiology/ American Heart Association guidelines for the management of acute coronary syndromes patients with CKD listed the use of IOCM as a class I, Level of Evidence: A recommendation *(45)*. The National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines have also recommended the use of IOCM in renal dialysis patients to minimize the chances of volume overload and complications before the next dialysis session *(25)*.

5. Volume of contrast media

The evidence suggests that the risk of CIN is dose dependent *(25)*. Several studies have shown that the volume of contrast media is a significant predictor of CIN after PCI and the mean of contrast volume is higher in patients with CIN *(1, 9, 25, 39)*. According to difference sources, the relatively safe cut point of contrast volume varies from 70 ml to 220 ml *(33)*. However, dose as low as 20 ml to 30 ml are capable of inducing CIN in very high risk patients *(33)*. Although, a significant correlation between CIN incidence and volume of contrast media has been observed, the data are not completely consistent. Other studies have suggested that there is no association between contrast media volume and a decline in renal function *(23, 25)*. Some investigators have analyzed the incidence of CIN in relation to volume of contrast media adjusted to patient characteristics. Cigarroa and colleagues were the first to propose a formula to calculate a safe weight- and creatinine- adjusted maximum contrast dose (MCD) (equation 2) *(46)*. Two studies confirmed that the exceeding use of MCD was associated with a higher risk of CIN after PCI *(7, 26)*.

$$MCD = \frac{5 \times \text{body weight (kg)}}{\text{Serum creatinine (mg/dl)}} \quad \textbf{(equation 2)}$$

The CIN Consensus Working Panel concluded that, in patients at risk, receiving contrast media greater than 100 ml is associated with a higher rate of CIN. Therefore, in patients with an eGFR < 60 ml/min, a contrast volume < 100 ml is preferable. The panel also concluded that there may not be a threshold volume below which CIN does not occur, because even small (~30ml) volumes of contrast media can cause CIN in very high risk patients *(25)*.

6. Class III-IV Congestive Heart Failure

Studies have shown that advanced congestive heart failure (CHF) and reduced left ventricular ejection fraction (LVEF) are significant risk predictors of CIN. Rihal et al *(10)* and Bartholomew et al *(29)* found that CHF is a significant predictor of CIN in

patients underwent PCI (OR = 1.53, p = 0.007 and OR = 2.2, p < 0.0001, respectively). Consistent with the above studies, Dangas et al showed that LVEF below 40% is a predictor of CIN after PCI *(31)*.

7. Use of nephrotoxic drugs

There is an expectation that the addition of further renal insults, such as the use of nephrotoxic drugs (e.g., high-dose loop diuretics, NSAIDs, coxibs, aminoglycosides, amphotericin B, cisplatin and cyclosporine A), would increase the risk of CIN. The use of diuretics has been reported to be associated with an increased risk of CIN, but this may indicate the presence of CHF *(20)*. Although, the supporting evidence is relatively limited, it is reasonable to hold these nephrotoxic drugs if possible for several days before contrast media exposure *(1)*. There is controversy over whether drugs that block the rennin angiotensin system should be held or continued for contrast procedures. Given the overall long-term beneficial effects of ACEI and ARB, many believe these drugs should remain a base of treatment for CKD and DM, irrespective of contrast administration *(20)*. In general, these drugs account for a 10%-25% increase in baseline serum creatinine, and this should be concerned when evaluating a patient before and after contrast exposure *(20)*. It is a routine practice to hold metformin before all contrast procedures to avoid the development of lactic acidosis which could lead to systemic complications and death. Therefore, metformin is generally withheld 48 hours before exposure to contrast media *(1)*.

8. Anemia

Recently, it has been shown that a low baseline hematocrit is a predictor of CIN in patients undergoing PCI. The partial oxygen pressure of the outer medulla in the kidney is very low during normal function, and hence the combination of contrast-induced vasoconstriction and anemia may decrease oxygen delivery sufficiently to cause renal medullary hypoxia *(20)*. Thus, it is intuitive that anemia may play a role in CIN risk *(20)*. In a registry of 8,357 patients undergoing elective PCI, the results showed

that a baseline hematocrit value of less than 39% for men and less than 36% for women is a risk for CIN (OR = 1.827; 95% CI = 1.518 - 2.199) *(14)*. Another registry of 570 diabetes patients undergoing elective PCI, it was found that patients who developed CIN had significantly lower baseline hematocrit compared with those who did not develop CIN (36.5 ± 5.7% and 38.9 ± 4.3%, respectively; p = 0.001), and the need for blood transfusion was reported to be a significant predictor of CIN after PCI (OR = 14.2, 95% CI = 3.0 – 66.9) *(12)*. One study showed that patients with the lowest eGFR and hematocrit had the highest rates of CIN *(47)*. The threshold hematocrit at which the risk of CIN increased was < 41.2% in men and < 34.4% in women *(47)*.

9. Short duration of two contrast media administrations

Patients with no risk markers of CIN, angiography should be delayed more than 48 hours after a previous exposure to intravascular contrast media *(33)*. Spacing out contrast exposures is meant to eliminate the possibility of giving contrast media to a patient who is in the early phases of CIN, which may not yet be recognized by the rise in serum creatinine. In patients with diabetes or preexisting renal disease, this time interval should be increased to more than 72 hours *(33)*. The CIN Consensus Working Panel recommended that when possible, 2 weeks should be allowed between the procedures requiring contrast media *(25)*.

10. Other risk factors

Dehydration, periprocedural hypotension, the use of intraaortic balloon pump (IABP) and acute MI patients undergoing emergency PCI also have been reported to be risk markers for CIN ***(2, 20, 33)***.

In conclusion, CIN most commonly occurs in patients with chronic kidney disease, diabetes mellitus, hypovolemia, advanced age, nephrotoxic agent administration, the use of a large amount and ionic high osmolar contrast media, and congestive heart failure. Most of the classic and possible risk markers for CIN are

modifiable. Therefore, identifying high risk patients and providing prophylactic measures before contrast media using procedures may decrease risk of CIN development.

4. Strategies for Reducing Risk of CIN Development

1. Volume expansion

Volume expansion has a well-established role in CIN prevention, although, there are limited data on the most appropriate choice of intravenous fluid. The evidence indicates that isotonic crystalloid (saline or bicarbonate solution) is probably more effective than half-normal saline *(48)*. Additional confirmatory trials with sodium bicarbonate *(49)* are needed because the largest trial to date shows no benefit of sodium bicarbonate over normal saline *(50)*. There is also no clear evidence to guide the choice of the optimal rate and duration of infusion. However, good urine output (> 150 ml/hour) within 6 hours after the procedure has been associated with reduced rates of CIN in one study *(51)*. In order to achieve a urine flow rate of at least 150 ml/hour, ≥ 1.0 to 1.5 ml/kg/min of intravenous fluid has to be administered for 3 to 12 hours before and 6 to 12 hours after contrast exposure *(1)*. Oral volume expansion may have some benefit, but there is not enough evidence to show that it is as effective as intravenous volume expansion *(52)*.

2. Dialysis and hemofiltration

Contrast media is removed by dialysis, but there is no clinical evidence that prophylactic dialysis can reduce the risk of CIN, even when carried out within 1 hour or simultaneously with contrast administration *(1)*. Hemofiltration, performed 6 hours before and 12 to 18 hours after contrast media exposure, deserves consideration because of a reduced mortality and a need for hemodialysis in the postprocedure period in very high risk patients (serum creatinine 3.0 to 4.0 mg/dl, eGFR 15 to 20 ml/min) *(53, 54)*.

Nevertheless, this approach should be considered only in the very highest-risk patient in conjunction with nephrology consultation and dialysis planning *(1)*.

3. Pharmacologic strategies

There are currently no approved pharmacologic agents for the prevention of CIN. The pharmacologic agents tested in small trials that deserve further evaluation include the antioxidants, ascorbic acid and NAC; statins; aminophylline/theophylline; and prostaglandin E_1 *(1)*. Of these agents, only ascorbic acid has been tested in a multicenter, blinded, placebo-controlled trial (n = 231) and has been shown to reduce rates of CIN. The dose of ascorbic acid used in this trial was 3 grams orally the night before and 2 gram orally twice a day after the procedure *(55)*.

Although widely used, NAC has not been consistently shown to be effective. The recently published REMEDIAL (Renal Insufficiency Following Contrast Media Administration) trial suggested that the use of volume supplementation with sodium bicarbonate together with NAC was more effective than NAC alone in reducing the risk of CIN *(56)*. Dosing of NAC has varied in the trials; however, the most successful approach has been with 1,200 mg orally twice a day on the day before and after the procedure *(1)*. An algorithm for the management of CIN is presented in Figure 7.

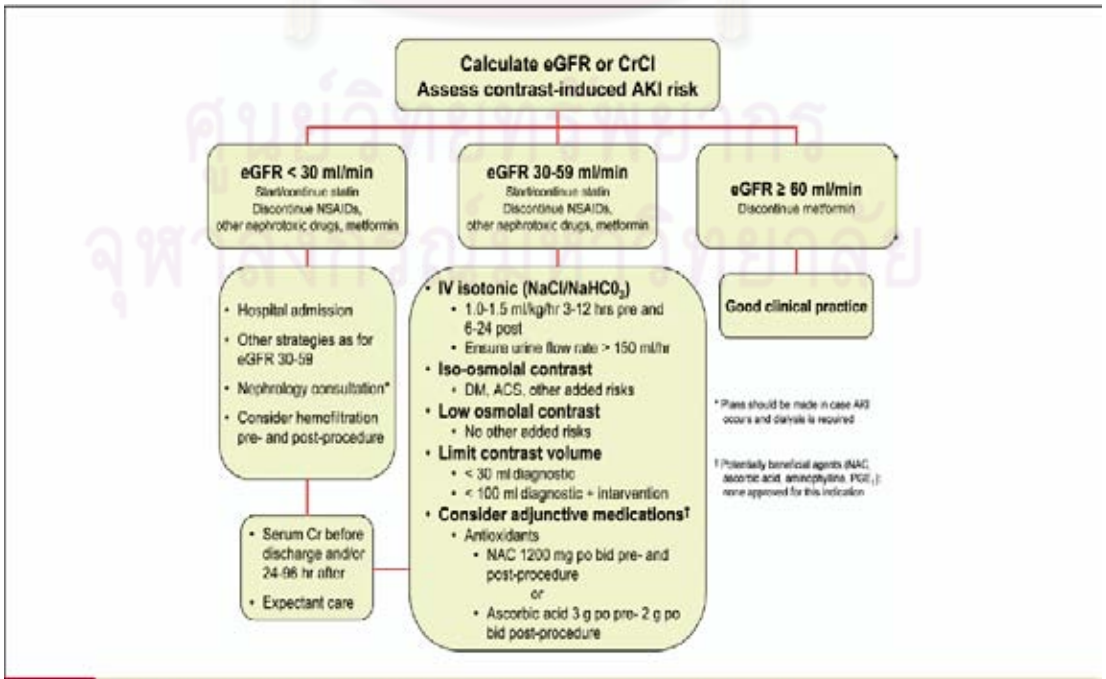


Figure 7. Algorithm for management of patients receiving contrast media *(1)*

ACS = acute coronary syndromes; bid = twice daily; Cr = creatinine; DM = diabetes mellitus; IV = intravenous; NAC = N-acetylcysteine; NSAIDs = nonsteroidal anti-inflammatory drugs; PGE_1 = prostaglandin E_1; po = by mouth; other abbreviations as in Figure 2.

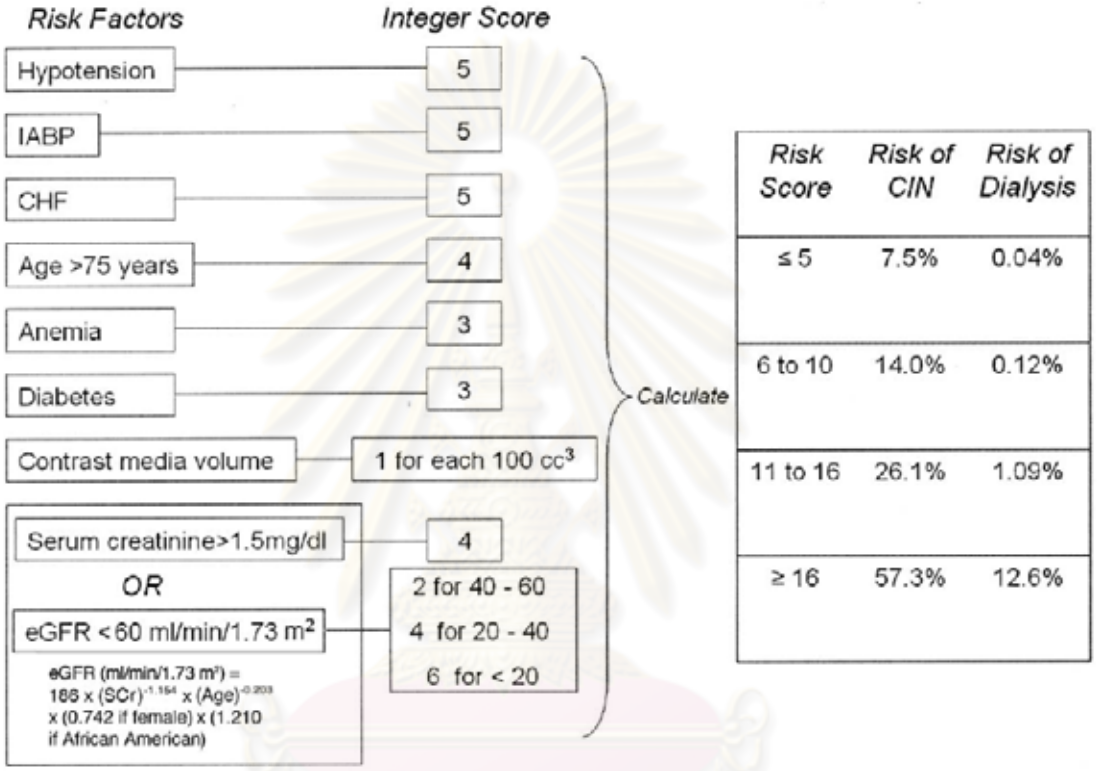
Several risk markers for the development of CIN have been reported. However, the combination of two or more risk markers is rather common in daily practice *(20)*. The effect of risk markers is additive, and the likelihood of CIN rises sharply as number of risk markers increases *(20)*. A study by Cochran and colleagues in renal angiography showed that the risk of CIN was 50% in patients with 5 risk factors including age > 55 years, proteinuria, abnormal baseline serum creatinine, the use of high osmolar contrast media and preexisting renal disease *(57)*. The additive nature of risk has allowed the development of risk score model to facilitate risk prediction of CIN in clinical practice. All of the recently published models have been developed from database of patients undergoing PCI.

Mehran et al *(14)* developed a simple CIN risk score that integrated eight clinical variables to assess the risk of CIN after PCI. These variables included hypotension, IABP use, CHF, CKD, DM, age > 75 years, anemia and volume of contrast. Based on the odds ratio (OR) derived from multivariate logistic regression model, these variables were assigned a weighted integer; the sum of the integers was a total risk score for each patient (Figure 8). The occurrence of CIN was found to be 7.5-57.3% for patients with low ($\leq$ 5) and high ($\geq$ 16) risk score, respectively. The model demonstrated good discriminative ability to distinguish high-risk patients from low-risk patients with concordance statistics (C-statistic) of 0.67. The risk predictors used in other published risk models are summarized in Table 7.

Freeman et al *(26)*, however, developed a risk scoring system for prediction of a more severe nephropathy, nephropathy requiring dialysis (NRD), after PCI. Six predictors of NRD after PCI were identified including renal insufficiency (defined as a presence of preprocedural serum creatinine > 2 mg/dl), diabetes mellitus, congestive heart failure, peripheral vascular disease, cardiogenic shock and receiving contrast media higher than weight- and creatinine- adjusted maximum contrast dose (MCD) [MCD = 5 x body weight/serum creatinine (mg/dl)]. There was a direct relation between the number of risk factors and incidence of NRD. A progressive increase in incidence

was found with an increasing number of risk factors. The model performed good discriminative ability with C-statistic of 0.89.

Figure 8. An example of a CIN risk score model and its application in predicting the risk of CIN and CIN requiring dialysis *(14)*.



CHF = congestive heart failure, eGFR = estimated glomerular filtration rate, IABP = intra-aortic balloon pump, SCr = serum creatinine

Table 7. Risk predictors of CIN from published CIN risk score model

Study	Procedure	N	% CIN development	Risk Predictors	Odds ratio	95% CI	Discriminative ability
Mehran et al *(14)* (2004)	Elective PCI	8,357	13.1*	1. Hypotension	2.676	2.1-3.4	C-statistic = 0.67
				2. IABP[a]	2.547	1.8-3.7	
				3. Congestive heart failure	2.698	2.0-3.6	
				4. Age > 75 years	2.195	1.8-2.7	
				5. Anemia	1.827	1.5-2.2	
				6. Diabetes mellitus	1.597	1.3-1.9	
				7. Contrast volume	1.276	1.2-1.4	
				8. SCr[b] > 1.5 mg/dl or GFR < 60 ml/min	1.194	1.1-1.3	
Marenzi et al *(8)* (2004)	Emergency PCI	208	19**	1. Age ≥ 75 years	5.28	2.0-14.1	N/A[c]
				2. Anterior AMI	2.17	0.9-5.3	
				3. time-to-reperfusion ≥ 6 hrs	2.51	1.0-6.2	
				4. contrast volume ≥ 300 ml	2.80	1.2-6.7	
				5. IABP[a]	15.51	4.7-51.6	

* CIN was defined as an increase ≥ 25% and/or ≥ 0.5 mg/dl in serum creatinine at 48 hours after PCI versus baseline

** CIN was defined as a rise in serum creatinine > 0.5 mg/dl during hospital admission after PCI versus baseline

IABP[a] = Intra-aortic balloon pump use, SCr[b] = serum creatinine, N/A[c] = not available information

Study	Procedure	N	% CIN development	Risk Predictors	Odds ratio	95% CI	Discriminative ability
Bartholomew et al *(29)* (2004)	PCI	20,479	2[#]	1. eGFR < 60 ml/min	5.0	3.6-6.9	C-statistic = 0.89
				2. Urgent/Emergency PCI	4.4	2.9-6.5	
				3. IABP[e]	5.1	3.6-7.2	
				4. Diabetes mellitus	3.1	2.3-4.2	
				5. Congestive heart failure	2.2	1.6-2.9	
				6. Hypertension	2.0	1.4-2.8	
				7. PVD[f]	1.9	1.4-2.7	
				8. Contrast volume > 260 ml	1.8	1.4-2.4	
Freeman et al *(26)* (2002)	PCI	16,592	NRD[d] = 0.44%	1. Renal insufficiency[g]	5.0	2.4-10.4	C-statistic = 0.89
				2. Diabetes mellitus	2.3	1.2-4.5	
				3. Congestive heart failure	4.5	2.2-9.2	
				4. PVD[f]	3.6	1.8-7.1	
				5. Cardiogenic shock	3.7	1.5-9.3	
				6. Exceeding MCD[h]	6.2	3.3-12.8	

[#] CIN was defined as a $\geq$ 1.0 mg/dl increase in serum creatinine during hospital admission after PCI versus baseline, NRD[d] = Nephropathy requiring dialysis, IABP[e] = Intra-aortic balloon pump use, PVD[f] = Peripheral vascular disease, Renal insufficiency[g] = Presence of preprocedural serum creatinine > 2 mg/dl, Exceeding MCD[h] = Receiving contrast media higher than weight- and creatinine- adjusted maximum contrast dose (MCD).

CHAPTER III
PATIENTS AND METHODS

1. Patient Population

This study was a prospective analytical study. Patients underwent elective or emergency PCI at King Chulalongkorn Memorial Hospital between 10 November 2009 and 31 March 2010 were enrolled in the study. The study was approved by The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, and informed consent was obtained from all patients.

An estimation of sample size is calculated from this formula

$n \geq 15p$ *(58)*

p refers to the number of tested variables

In this study, tested variables were categorized as patient- , contrast media- and procedure-related factors as following,

Patient-related factors consisted of age, gender, weight, CrCl < 60 ml/min, CHF, DM and transfusion of PRBC.

Contrast media-related factors consisted of type and volume of contrast media, and short interval (<72 hours) between contrast media exposures.

Procedure-related factors were emergency PCI and receiving NAC pre and/or post procedure for prevention of CIN

Therefore; p = 12, $n \geq 15 \times 12$

$n \geq 180$

Estimated sample size = 180 patients

Inclusion criteria

(1) Patients undergoing elective or emergency PCI

(2) Patients aged older than 18 years

Exclusion criteria

(1) Patients with no record of serum creatinine before and/or within 72 hours after the procedure

(2) Patients with pre-existing end-stage renal disease requiring dialysis

(3) Patients who were using other nephrotoxic drugs, i.e., cisplatin, aminoglycosides, amphotericin B and cyclosporine A

2. Research Protocol (Figure 9)

(1) Recruiting the eligible patients

(2) Patient demographics and procedural characteristics of all patients were recorded in the patient data collection form (appendix A) which consists of 3 following parts,

Part I Patient demographics such as gender, age, weight, comorbidity and medication history

Part II Procedural characteristics such as type and volume of contrast media administered, date and time of procedure, number of vessels attempted and NAC administration pre and/or post procedure for prevention of CIN

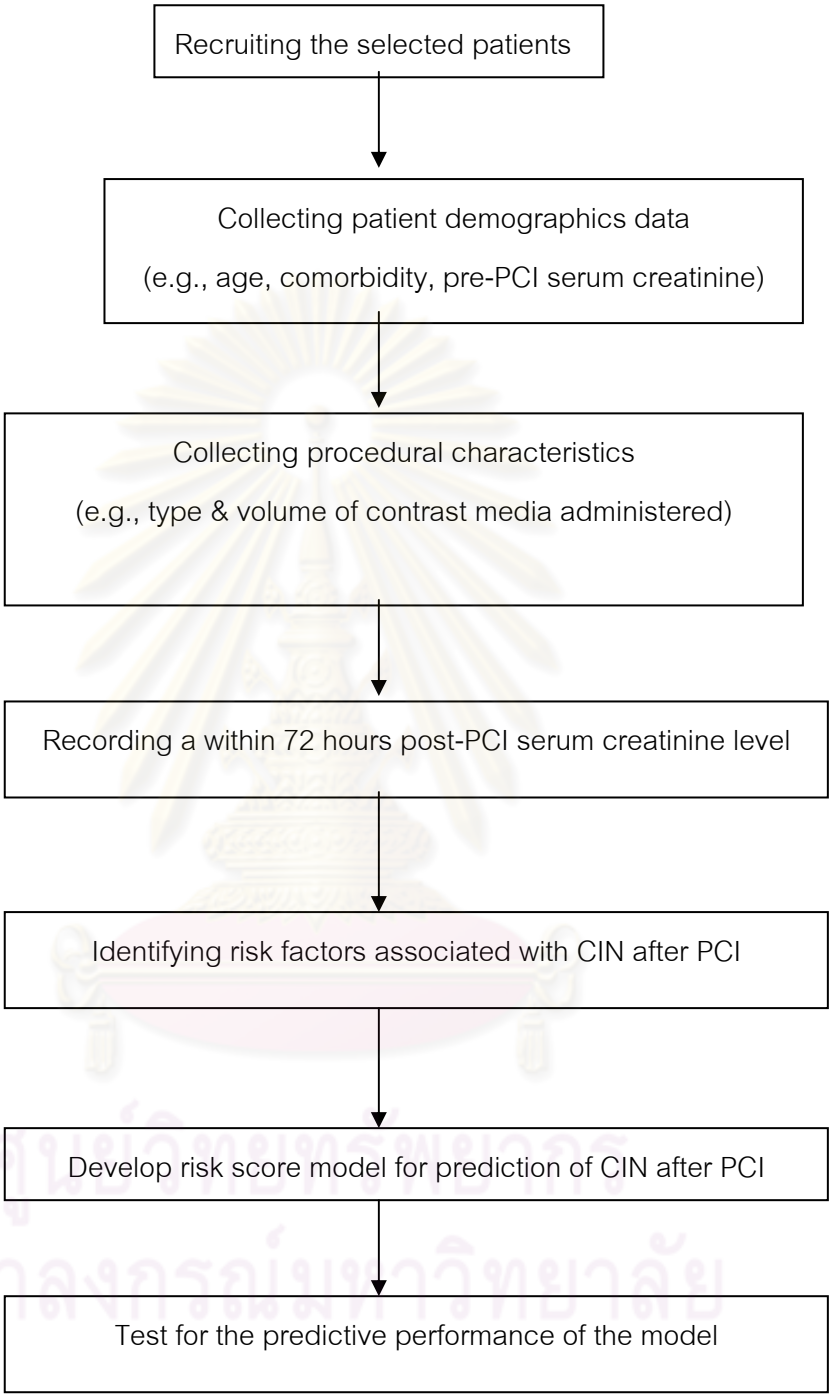
Part III Related laboratory results such as serum creatinine before and within 72 hours after PCI, blood urea nitrogen (BUN) and hematocrit.

(3) Investigating the incidence and risk factors associated with CIN after PCI

(4) Develop a risk score model for prediction of CIN after PCI

(5) Test for the predictive performance of the model

Figure 9. Research protocol



3. Statistical Analysis

(1) Continuous data were summarized as the mean value ± standard deviation (SD). Categorical data were presented as absolute values and percentages.

(2) Comparison of continuous variables was performed by Student *t* test and Wilcoxon rank sum test. Chi-square or Fisher exact tests was used for a comparison of categorical variables as appropriate. Statistical significance for all comparisons was defined when p-value < 0.05.

(3) Receiver operating characteristics (ROC) analysis, a graphical technique for assessing the ability of a diagnostic test to distinguish high-risk subjects from low-risk subjects (discriminative ability), was used to determine the optimal cutoff point of total volume of contrast media (V) and volume/body weight (V/BW) ratio in this population using SPSS (version 17.0, SPSS Inc., Chicago, Illinois). The ROC curve is obtained by plotting the sensitivity of a test on the *y* axis, from 0 to 1 (0-100%) against 1-specificity (false positive) on the *x* axis, from 0 to 1 (0-100%). The area under the ROC curve (AUC) is a reflection of how good the test is at distinguishing between patients with disease and those without disease. The AUC values range from 0 to 1; however, the sensible models have AUC between 0.5 and 1.0 (the higher the better). Furthermore, the ROC curve is also used for selecting an optimal cutoff point, which optimal sensitivity and specificity are achieved, for differentiating between people with disease and those without disease. The results which are above this cutoff point are considered abnormal while results which are below the cutoff point are regarded as normal *(59-61)*.

(4) All risk factors including the cutoff point values obtained from ROC curve analysis of V and V/BW ratio were initially screened for an association with CIN by a univariate logistic regression analysis at p-value < 0.20. (Figure 10).

(5) The selected variables from univariate analysis were then tested by multivariate logistic regression in a forward stepwise manner using p-value < 0.05 as a cutoff criteria.

(6) The goodness of fit of the multivariate logistic regression model was assessed by the Hosmer-Lemeshow method and satisfied when p-value > 0.05.

(7) The discriminative ability of the multivariate logistic regression model was evaluated by using concordance statistic (C-statistic), which is identical to area under the ROC curve, and satisfied when C-statistic > 0.5. *(59)*.

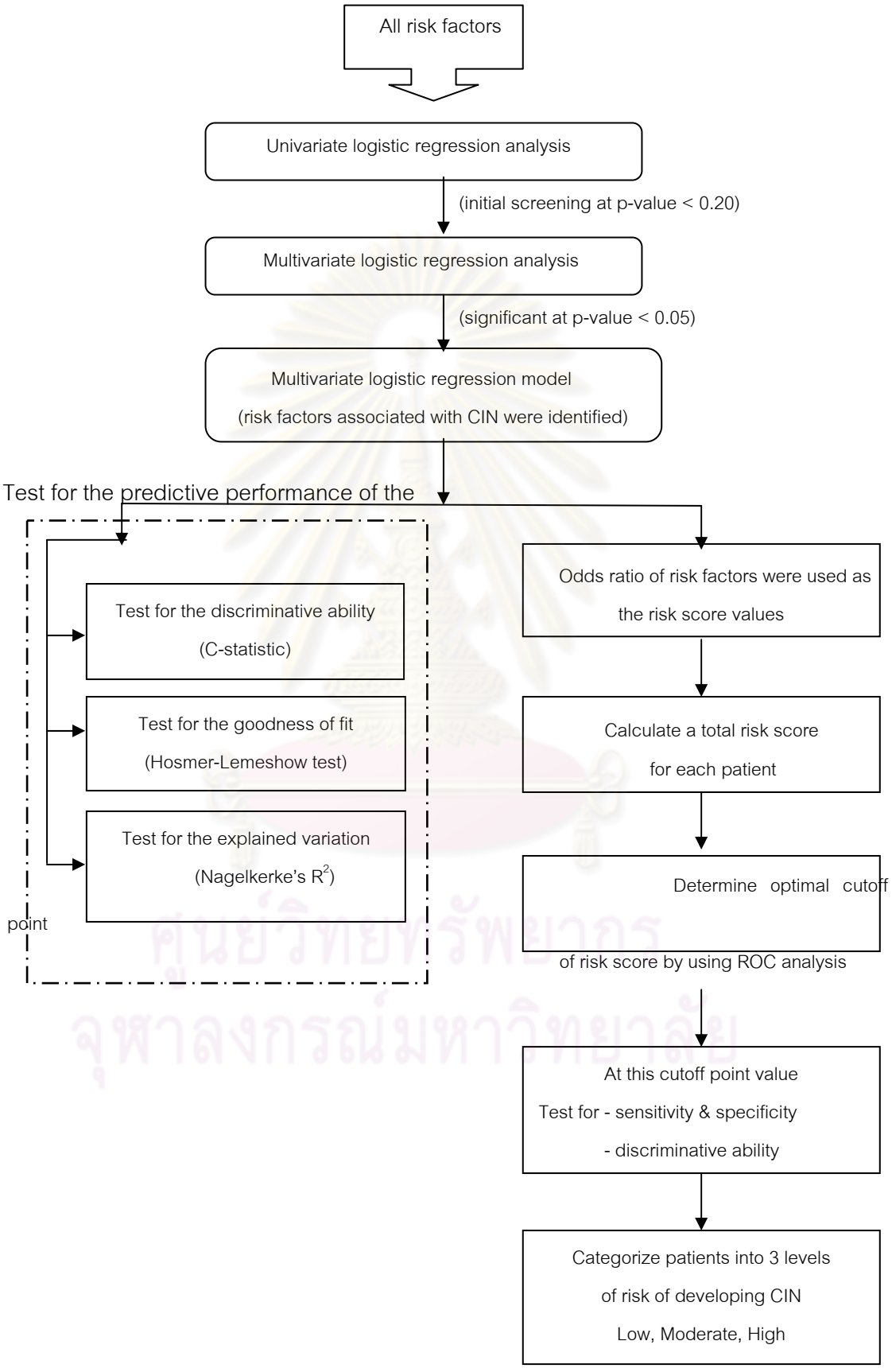
(8) Develop a risk score model by using odds ratio from multivariate analysis as the risk score values for each of risk predictors.

(9) Calculate a total risk score for each patient.

(10) ROC analysis was used to determine the optimal cutoff point of risk score value for identifying the patients who are at risk of developing CIN.

(11) Based on the occurrence of CIN associated with different risk score and the cutoff point of risk score identified by ROC analysis, patients were further categorized into three groups; low risk, moderate risk and high risk of CIN development after PCI.

Figure 10. Development of risk score model for prediction of CIN after PCI



CHAPTER IV
RESULTS AND DISCUSSION

One hundred and eighty one eligible patients underwent either elective or emergency PCI at King Chulalongkorn Memorial Hospital between 10 November 2009 and 31 March 2010 were enrolled in this study. The results of the present study will be discussed in details as following topics;

(1) Patient demographics

(2) Procedural characteristics

(3) Incidence of contrast-induced nephropathy after percutaneous coronary intervention

(4) Risk factors associated with contrast-induced nephropathy after percutaneous coronary intervention

(5) Risk score model for prediction of contrast-induced nephropathy after percutaneous coronary intervention

1. Patient Demographics

From all 181 patients enrolled in the study, there were 132 male patients (72.9%) and 49 female patients (27.1%). The patient demographics are presented in Table 8. The mean age was 64.7 ± 11.6 years. Female patients were older than male patients (69.1 ± 11.2 years versus 63.1 ± 11.4 years, p = 0.002). The mean body weight (BW) and body mass index (BMI) were 65.1 ± 12.1 kilograms (kg) and 24.8 ± 3.9 kg/m^2, respectively. According to the classification of weight using BMI in adult Asians *(62)*, 121 patients (66.8%) were classified as overweight (BMI ≥ 23 kg/m^2), and 86 patients (47.5%) were classified as obese (BMI ≥ 25 kg/m^2). The mean and median pre-PCI serum creatinine were 1.1 ± 0.4 mg/dl and 1.0 mg/dl (interquartile range 0.8 to 1.2 mg/dl). When CrCl was estimated, the mean CrCl was 61.9 ± 22.3 ml/min, and 75 patients (41.4%) had CrCl lower than 60 ml/min.

Table 8. Patient demographics

Variable	Patients (n=181)
Age (years)	64.7 ± 11.6
Age ≥ 70 years	66 (36.5%)
Female	49 (27.1%)
Body weight (kg)	65.1 ± 12.1
Body mass index (kg/m^2)	24.8 ± 3.9
underweight (< 18.5 kg/m^2)	10 (5.5%)
normal range (18.5 – 22.9 kg/m^2)	41 (22.7%)
at risk (23-24.9 kg/m^2)	35 (19.3%)
obese I (25-29.9 kg/m^2)	68 (37.6%)
obese II (≥ 30 kg/m^2)	18 (9.9%)
unknown[a]	9 (5%)
Diabetes mellitus (DM)	71 (39.2%)
DM with CrCl < 60 ml/min	35 (19.3%)
Hypertension	123 (68%)
Congestive heart failure	23 (12.7%)
Dyslipidemia	104 (57.5%)

Table 8. Patient demographics (continued)

Variable	Patients (n=181)
Sepsis	2 (1.1%)
Transfusion of packed red blood cell (PRBC)[b]	14 (7.7%)
ACEI/ARB[c]	94 (52.5%)
pre-PCI blood urea nitrogen (mg/dl)	17.56 ± 10.07
pre-PCI serum creatinine (mg/dl)	1.1 ± 0.4
pre-PCI serum creatinine ≥ 1.5 mg/dl	19 (10.5%)
CrCl (ml/min)	61.9 ± 22.3
CrCl ≥ 60	106 (58.6%)
30-59	56 (30.9%)
15-29	16 (8.8%)
< 15	3 (1.7%)
CrCl < 60 ml/min without DM	40 (22.1%)
Baseline hematocrit (%)	39.4 ± 5.2
baseline hematocrit of male patients (%)	40.6 ± 5.2
baseline hematocrit of female patients (%)	36.5 ± 4.1

[a]unknown = BMI can not be estimated due to missing value of patient body weight and height in 2 patients, and missing data of patient height in 7 patients.

[b]Transfusion of packed red blood cell (PRBC) = Patients who had hematocrit drop and need transfusion of PRBC before PCI

[c]ACEI/ARB = Patients receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

2. Procedural Characteristics

Procedural characteristics are demonstrated in Table 9. The contrast media used were Iopromide (Ultravist-370®), Iopamidol (Iopamiro®) and Iodixanol (Visipaque®). The volume of contrast media administered ranges from 30 to 430 ml, with a mean and median of 128.2 ± 62.1 ml and 110 ml (interquartile range 85 to 155 ml), respectively. Patients receiving Iodixanol had lower baseline CrCl compared with those who received Iopromide (36.44 ± 18.42 ml/min and 64.87 ± 20.91 ml/min, respectively ($p < 0.001$)).

Table 9. Procedural characteristics

Variable	Patients (n=181)
Emergency PCI	26 (14.4%)
Time of procedure (min)	72.9 ± 40.0
Volume of contrast media administered (ml)	128.2 ± 62.1
< 100 ml	66 (36.5%)
100-199 ml	93 (51.4%)
200-299 ml	17 (9.4%)
> 300 ml	5 (2.8%)
Type of contrast media	
Iopromide	161 (89%)
Iodixanol	18 (9.9%)
Iopromide + Iodixanol	1 (0.55%)
Iopamidol	1 (0.55%)
N-Acetylcysteine (NAC)*	41 (22.7%)
Single vessel PCI	120 (66.3%)
Multivessel PCI	61 (33.7%)

*N-Acetylcysteine (NAC) = Patients receiving NAC pre and/or post PCI for prevention of CIN

Forty one patients (22.7%) received N-Acetylcysteine (NAC) before and/or after PCI for prevention of CIN. Of them, 32 patients (78.0%) had CrCl lower than 60 ml/min. The number of patients received NAC stratified by level of renal function is shown in Table 10. Among 41 patients receiving NAC, 25 patients (61%) received NAC both pre- and post- PCI, and 16 patients (39%) received NAC only pre- or post- PCI. NAC doses administered are presented in Table 11.

Table 10. Number of patients receiving NAC stratified by level of renal function

Creatinine clearance (ml/min)	No NAC (n)	NAC pre- or post-PCI (n)	NAC pre- and post-PCI (n)
≥ 60	97	3	6
30-59	39	8	9
15-29	4	4	8
< 15	0	1	2
Total	140	16	25

Table 11. Doses of NAC administered

Receiving NAC only pre- or post- PCI					Number of patients
NAC 1200 mg		X 1 dose	pre-PCI		1
NAC 1200 mg	q 12 hours*	X 2 doses	pre-PCI		1
NAC 600 mg	q 12 hours*	X 2 doses	pre-PCI		1
NAC 1200 mg + NSS 100 cc IV drip[a]			pre-PCI		1
NAC 1200 mg	q 12 hours*	X 2 doses		post-PCI	9
NAC 1200 mg	q 12 hours*	X 4 doses		post-PCI	1
NAC 1200 mg	q 12 hours*	X 5 days		post-PCI	1
NAC 600 mg	q 12 hours*	X 2 doses		post-PCI	1
				Total	16

Receiving NAC both pre- and post- PCI			pre-PCI	post-PCI	Number of patients
NAC 600 mg	q 12 hours*	X 4 doses	2 doses	2 doses	2
NAC 1200 mg	q 12 hours*	X 4 doses	2 doses	2 doses	14
NAC 1200 mg	q 12 hours*	X 4 doses	1 dose	3 dose	2
NAC 1200 mg	q 12 hours*	X 4 doses	3 dose	1 dose	1
NAC 600 mg pre-PCI and NAC 1200 mg q 12 hours* x 2 doses post-PCI					1

Table 11. Doses of NAC administered (continued)

Receiving NAC both pre- and post- PCI	Number of patients
NAC 600 mg q 12 hours* x 2 doses pre PCI & NAC 1200 mg q 12 hours* x 2 doses post-PCI	1
NAC 1200 mg q 12 hours* x 2 doses pre PCI & NAC 600 mg q 12 hours* x 2 days post-PCI	1
NAC 1200 mg pre-PCI & NAC 1200 mg q 12 hours* x 2 doses post-PCI	1
NAC 1200 mg pre- and post-PCI (total = 2 doses)	1
Unknown NAC dose	1
Total	**25**

*q 12 hours = every 12 hours

[a]NSS 100 cc IV drip = 0.9% Sodium chloride 100 cc intravenous drip

3. Incidence of Contrast-Induced Nephropathy after Percutaneous Coronary Intervention

From 181 patients included in this study, 11 patients (6.1%) developed CIN (one of them required a continuous veno-venous hemofiltration (CVVH)). The mean absolute difference of serum creatinine between post- and pre-PCI in patients with and without CIN were 0.677 $\pm$ 0.85 mg/dl and -0.098 $\pm$ 0.15 mg/dl ($p = 0.013$). The mean percent relative difference of post- and pre-PCI serum creatinine in patients with and without CIN were 42.5 $\pm$ 30% and -9.4 $\pm$ 13.6% ($p < 0.001$), respectively. CIN was observed in 2.8% of patients with CrCl $\geq$ 60 ml/min, which is consistent with a previous study stating that the chance of CIN was less than 5% in patients with CrCl greater than 60 ml/min *(33)*. The incidence of CIN raised to 10.7% in patients with CrCl < 60 ml/min ($p = 0.042$). The occurrence of CIN in relation to level of baseline renal function is illustrated in Table 12.

Table 12. The occurrence of CIN in relation to level of baseline renal function

Creatinine clearance (ml/min)	% Observed CIN
≥ 60	2.8%
30-59	7.1%
15-29	12.5%
< 15	66.7%

4. Risk Factors Associated with Contrast-Induced Nephropathy after Percutaneous Coronary Intervention

Factors found to be associated with CIN from the univariate analysis are presented in Table 13. Patients developing CIN were older, had lower body weight, higher pre-PCI serum creatinine, lower CrCl, and more likely to receive higher volume of contrast media compared with patients who did not develop this complication. The mean volume/body weight (V/BW) ratio was 3.2 ± 2.0 ml/kg in patients with CIN and 2.0 ± 1.0 ml/kg in patients without CIN; whereas, the median V/BW ratio for those with and without CIN were 2.92 ml/kg (interquartile range 1.78 to 4.29 ml/kg) and 1.75 ml/kg (interquartile range 1.27 to 2.32 ml/kg), respectively. The relationship between V/BW ratio and CIN development after PCI is shown is Figure 11.

Table 13. Univariate association of patient demographics and procedural characteristics with CIN after PCI

Variable	CIN (n = 11)	No CIN (n = 170)	p-value
Age (years)	74.9 ± 12.1	64.1 ± 11.3	0.004*
Age ≥ 70 years	8 (72.7%)	58 (34.1%)	0.019*
Female	6 (54.5%)	43 (25.3%)	0.045*
Body weight (kg)	54.8 ± 14.9	65.8 ± 11.7	0.005*
Diabetes mellitus	3 (27.3%)	68 (40%)	0.408
Diabetes with CrCl < 60 ml/min	2 (18.2%)	33 (19.4%)	0.920

Table 13. Univariate association of patient demographics and procedural characteristics with CIN after PCI (continued)

Variable	CIN (n = 11)	No CIN (n = 170)	p-value
Hypertension	8 (72.7%)	115 (67.6%)	0.727
Congestive heart failure	5 (45.5%)	18 (10.6%)	0.003*
Sepsis	2 (18.2%)	0	0.999
Transfusion of PRBC[a]	3 (27.3%)	11 (6.5%)	0.023*
ACEI/ARB[b]	5 (45.5%)	89 (53%)	0.629
pre-PCI SCr[c] (mg/dl)	1.45 ± 0.8	1.04 ± 0.4	0.004*
pre-PCI SCr[c] ≥ 1.5 mg/dl	4 (36.4%)	15 (8.8%)	0.009*
CrCl (ml/min)	40.7 ± 24.5	63.3 ± 21.5	0.002*
CrCl < 60 ml/min	8 (72.7%)	67 (39.4%)	0.042*
CrCl < 60 ml/min without DM	6 (54.5%)	34 (20%)	0.014*
CrCl < 30 ml/min	4 (36.4%)	15 (8.8%)	0.009*
Emergency PCI	3 (27.3%)	23 (13.5%)	0.220
Multivessel PCI	2 (18.2%)	59 (34.7%)	0.275
< 72 hours between contrast media exposures	0	2 (1.2%)	0.999
Iopromide	10 (90.9%)	151 (88.8%)	1.000
Volume of contrast media (ml)	160.9 ± 79.3	126.1 ± 60.6	0.081
Volume of contrast ≥ 240 ml	3 (27.3%)	9 (5.3%)	0.017*
V/BW ratio (ml/kg)	3.2 ± 2.0	2.0 ± 1.0	0.001*
NAC[d]	5 (45.5%)	36 (21.2%)	0.074

*significance at p-value < 0.05

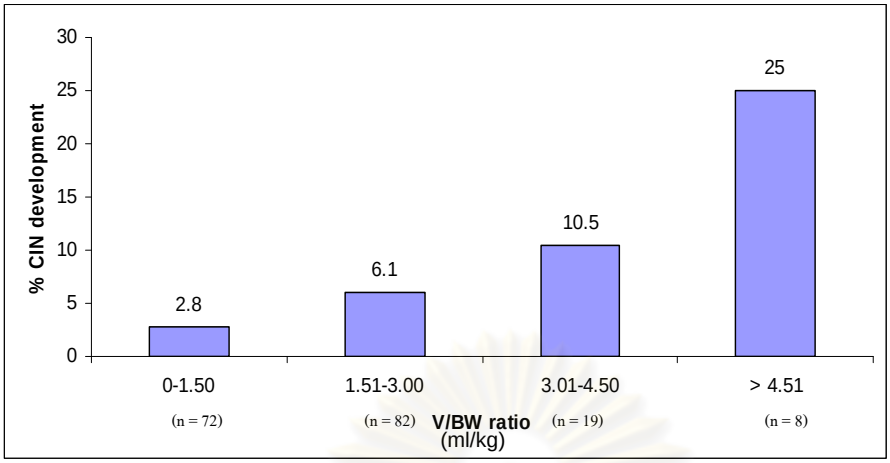
[a]Transfusion of PRBC = Patients who had hematocrit drop and need transfusion of PRBC before PCI

[b]ACEI/ARB = Patients receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

[c]SCr= serum creatinine

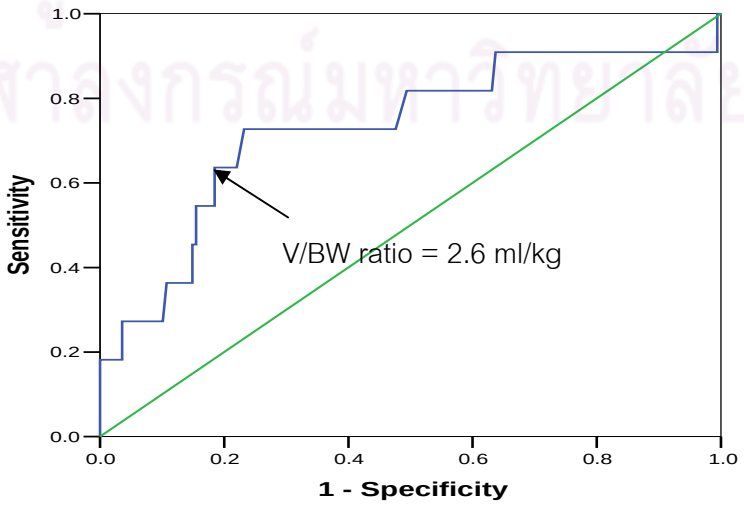
[d]NAC = Patients receiving NAC pre and/or post PCI for prevention of CIN

Figure 11. Relationship between V/BW ratio and CIN development after PCI



The ROC curve analysis was performed to test whether the V/BW ratio was a discriminator for CIN (Figure 12). The C-statistic of 0.73 (p = 0.011), indicating that this index was a significant discriminator for CIN. It also showed that the optimal cutoff value for V/BW ratio was 2.6 ml/kg. At this value, the sensitivity and specificity for detection of CIN were 64% and 82%, respectively. On the other hand, ROC curve analysis showed that the total volume of contrast media was not a significant discriminator for CIN with p-value of 0.104 (C-statistic = 0.647) as presented in Figure 13. Moreover, the univariate analysis indicated that the volume of contrast media as a continuous variable was not significantly associated with CIN after PCI.

Figure 12. ROC curve analysis indicated an optimum cutoff value for V/BW ratio is 2.6 ml/kg

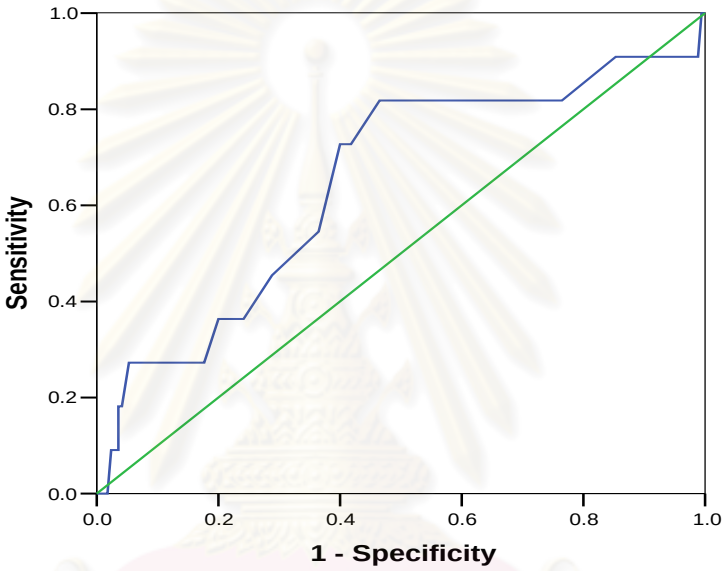


Area Under the ROC Curve (AUC) (a)	Std. Error	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.730	.091	.011	.552	.909

(a) Under the nonparametric assumption. Of note, AUC is identical to C-statistic.

(b) Null hypothesis: AUC = 0.5

Figure 13. ROC curve analysis of total volume of contrast media for prediction of CIN



Area Under the ROC Curve (AUC) (a)	Std. Error	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.647	.092	.104	.467	.827

(a) Under the nonparametric assumption. Of note, AUC is identical to C-statistic.

(b) Null hypothesis: AUC = 0.5

Using p-value < 0.2, sixteen variables were selected from the univariate analysis including age, age ≥ 70 years, female gender, weight, congestive heart failure (CHF), transfusion of PRBC, pre-PCI serum creatinine, pre-PCI serum creatinine ≥ 1.5 mg/dl, CrCl, CrCl < 60 ml/min, CrCl < 60 ml/min without DM, CrCl < 30 ml/min, volume of contrast media, volume of contrast media ≥ 240 ml, V/BW ratio ≥ 2.6 ml/kg, and NAC.

All the selected variables were then tested by a multivariate logistic regression analysis. The multivariate analysis showed that CHF, CrCl < 30 ml/min and V/BW ratio ≥ 2.6 ml/kg were significant predictors of CIN after PCI (Table 14). The correlation between any two predictors in the model was examined. No correlation coefficient value of higher than 0.7 was found, suggesting that there was no multicollinearity (Table 15). The multivariate logistic regression model demonstrated good discriminative ability with C-statistic of 0.849 (Figure 14). The p-value of the Hosmer-Lemeshow statistics was 0.807 (chi-square = 0.43) indicating that the model was appropriate. The Nagelkerke R^2 was 0.308, indicating that approximately 31% of the variation in CIN development after PCI could be explained by this multivariate logistic regression model.

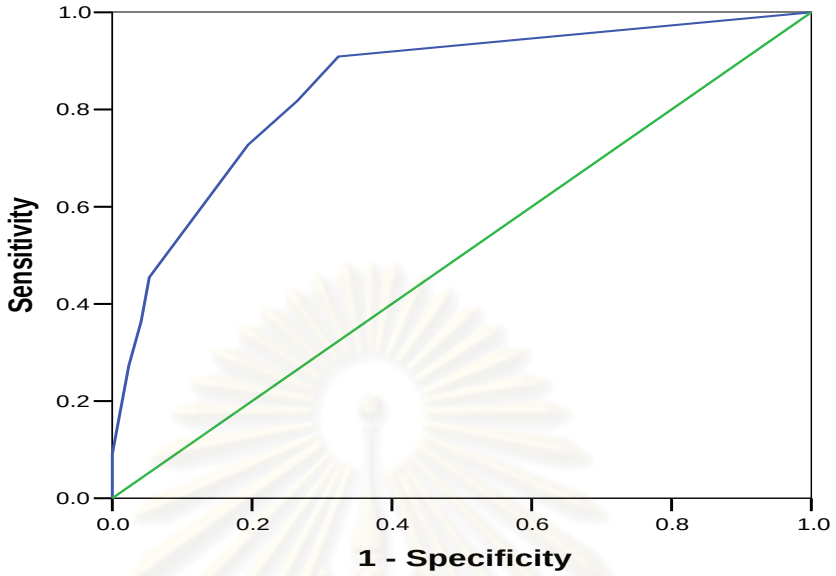
Table 14. Multivariate predictors of CIN after PCI

Variable	Regression Coefficient (β)	OR	95% CI	p-value
CHF	1.866	6.465	1.566 - 26.686	0.010
CrCl < 30 ml/min	1.815	6.141	1.349 - 27.957	0.019
V/BW ratio ≥ 2.6 ml/kg	2.102	8.184	2.015 – 33.245	0.003
Constant	-4.432	0.012		0.000

Table 15. Correlation coefficient matrix between variables in the multivariate logistic regression model

Variable	Constant	V/BW ≥ 2.6 ml/kg	CHF	CrCl < 30 ml/min
Constant	1.000	-0.685	-0.477	-0.458
V/BW ≥ 2.6 ml/kg	-0.685	1.000	0.101	0.164
CHF	-0.477	0.101	1.000	0.072
CrCl < 30 ml/min	-0.458	0.164	0.072	1.000

Figure 14. The ROC curve analysis showed that the multivariate logistic regression model demonstrated good discriminative ability with C-statistic of 0.849



Area Under the ROC Curve (AUC) (a)	Std. Error	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.849	.061	.000	.730	.969

(a) Under the nonparametric assumption. Of note, AUC is identical to C-statistic.

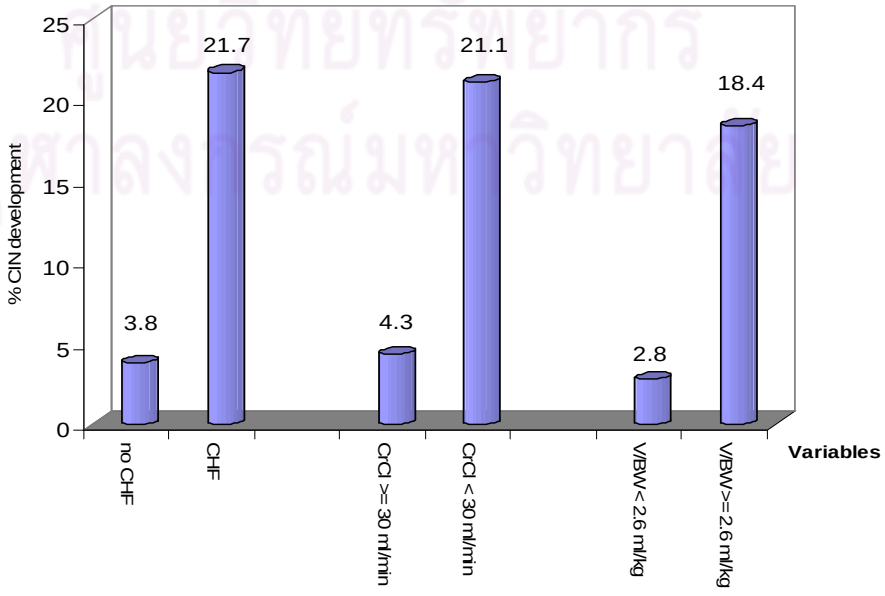
(b) Null hypothesis: AUC = 0.5

The nephrotoxicity effect of contrast media is dose dependent *(25)*. Several studies have shown that the total volume of contrast media is an independent predictor of CIN *(8, 10, 14, 29, 38)*. However, the data are not completely consistent *(25, 33)*. The different characteristics of the patients in each study may play a role in the difference of the consequences. This study is consistent with previous studies *(7, 26, 46, 63, 64)* in that a corrected contrast media dose according to patient characteristics would predict the risk of CIN development better than consideration of volume of contrast media alone. An association between contrast volume/body surface area (V/BSA) and the risk of CIN has been reported, suggesting an adjustment of contrast media volume to patient size, regardless of a presence or absence of CKD *(31)*. In this study the authors used a more practical index, V/BW ratio for predicting risk of CIN. The results of the present study

showed that the V/BW ratio ≥ 2.6 ml/kg was the strongest predictor of CIN after PCI. Patients who received contrast volume higher than this cutoff value were 8 times more likely to develop this complication. Therefore, the cutoff value of 2.6 may be used in clinical practice as a cutoff criteria for estimating an optimal volume of contrast media for individual patient to prevent the risk of CIN. In contrast, the total volume of contrast media as a continuous variable was not significantly associated with CIN in the univariate analysis. Although, a high volume of contrast media (≥ 240 ml) was associated with CIN in the univariate analysis, this index was not retained in the final model in the multivariate analysis.

Additionally, this study found that CrCl < 30 ml/min was a significant predictor of CIN after PCI which consistent with previous studies showing that chronic kidney disease is a major risk factor of CIN *(20, 33, 35)*. Patients with CrCl < 30 ml/min were 6 times more likely to develop this complication. Furthermore, the results also showed that there was an association between CHF and CIN after PCI (OR = 6.465, 95% CI = 1.566 – 26.686, p-value = 0.010) which is consistent with previous studies *(20, 31, 33, 65)*. The occurrence of CIN in relation to the presence and absence of CHF, CrCl < 30 ml/min and V/BW ratio ≥ 2.6 ml/kg is presented in Figure 15.

Figure 15. The occurrence of CIN in relation to the presence and absence of CHF, CrCl < 30 ml/min and V/BW ratio ≥ 2.6 ml/kg



This study did not find the association between type of contrast media and the risk of CIN (p = 1.00). Although, iso-osmolar iodixanol was recommended in CKD patients *(1, 25, 45)*, subgroup analysis in patients with CrCl < 60 ml/min did not find the the impact of contrast media type on the risk of CIN (p = 0.767). The role of DM as a risk factor of CIN remains conflicting *(20, 33)*. Despite, DM with CKD was reported to be the strongest risk factor of CIN after PCI *(20, 33)*, this study did not find this relationship. Moreover, the CIN rate and patient characteristics in this study are comparable to a study of CIN in diabetic patients undergoing elective PCI at Siriraj Hospital (Table 16) *(66)*. This may suggests that DM is not a significant risk factor of CIN.

Table 16. A comparison of CIN rate between diabetic and unselected patients undergoing PCI

	Worasuwannarak S. and Pornratanarangsi S. *(66)*	**Chaemchoi T.***
Setting	Siriraj Hospital	King Chulalongkorn Memorial Hospital
Total patients (n)	248	181
Procedure	Elective PCI	Elective & Emergency PCI
Age (year)	65 ± 9	64.7 ± 11.6
Male (%)	50.8	72.9
Body mass index (kg/m^2)	25.6 ± 4	24.8 ± 3.9
CrCl (ml/min)	60.6 ± 27.4	61.9 ± 22.3
CIN development (%)	5.2	6.1

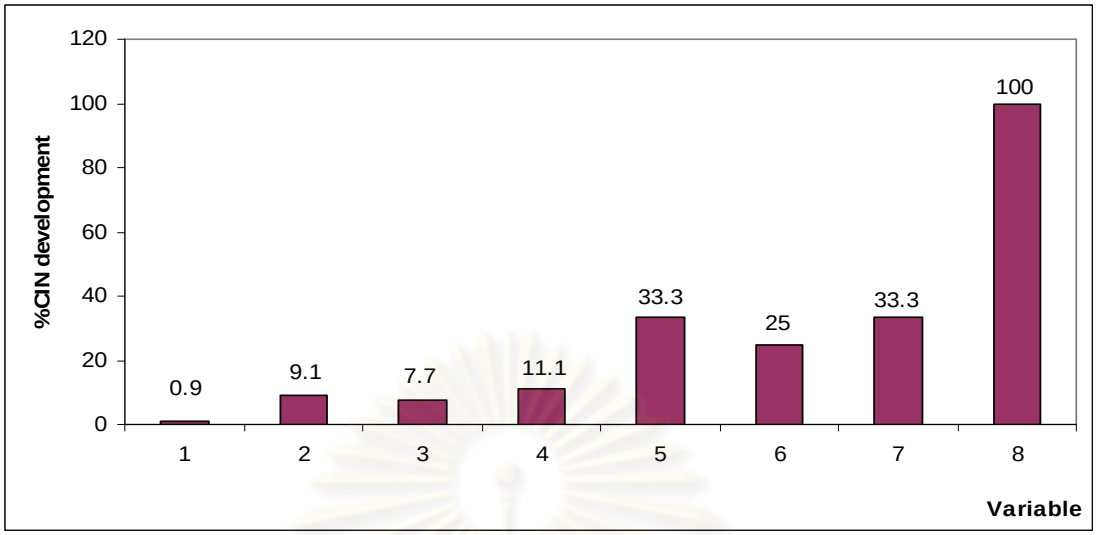
* The study comprised 39.2% diabetic patients

The literature on the effectiveness of NAC, a potent antioxidant, for preventing CIN remains controversial, especially in high risk patients *(1, 15)*. In the present study, NAC administration was added into the univariate model as a binary variable and was not found to be a significant variable (p = 0.074). From 41 patients receiving NAC, 5 patients (12.2%) developed CIN. All of them had baseline CrCl lower than 60 ml/min. Subgroup analysis in patients with CrCl < 60 ml/min was performed; however, we did

not find preventive effect of NAC (OR = 2.469, 95% CI = 0.544 – 11.203). The mean baseline CrCl of patients received NAC and developed CIN was 23.58 ml/min, compared with 45.54 ml/min in patients receiving NAC but did not develop this complication (p = 0.043). The NAC doses administered in CIN group were 1200 mg every 12 hours pre- and post-PCI (total = 4 doses) in 2 patients, 1200 mg every 12 hours x 2 doses post-PCI in 1 patient, 1200 mg every 12 hours x 5 days post-PCI in 1 patient and 1200 mg 12 hours pre- and post-PCI in 1 patient.

The results of the present study support that the chance of developing CIN is very low in patients with no risk; however, it increases as the number of risk factors increase *(2, 14)*. In this study, less than 1% of patients with no risk factor developed CIN. However, the CIN rate raised to 7-11% in patients with one risk factor, and it is incredibly higher in patients with multiple risk factors (Figure 16). Patients with 2 risk factors have approximately 3-fold higher incidence rate of CIN (33.3% vs 11.1%) compared with those with only one risk factor. Unsurprisingly, one patient having all these 3 risk factors developed this complication. Therefore, a special attention on patients with at least 2 risk factors is recommended.

Figure 16. The occurrence of CIN by number of risk factor



Variable	1	2	3	4	5	6	7	8
Risk factor	none[a]	CrCl<30[b]	CHF	V/BW≥2.6[c]	CHF & CrCl<30[b]	V/BW≥2.6[c] & CrCl<30[b]	CHF & V/BW≥2.6[c]	CHF & CrCl<30[b] & V/BW≥2.6[c]
CIN (n)* (%)	1 (0.9)	1 (9.1)	1 (7.7)	3 (11.1)	1 (33.3)	1 (25.0)	2 (33.3)	1 (100)
Total (N)**	116	11	13	27	3	4	6	1

[a]none = patients with no risk factor, [b]CrCl<30 = CrCl < 30 ml/min, [c]V/BW≥2.6 = V/BW ratio ≥ 2.6 ml/kg

*CIN (n) = Number of patients developing CIN

**Total (N) = Total number of patients within each risk factor group

The multivariate logistic regression model can be used to calculate the predicted probability of CIN for individual patient as following;

$$P(CIN) = \frac{e^{\beta_0+\beta_{1X1}+\beta_{2X2}+.....+\beta_{nXn}}}{1+ e^{\beta_0+\beta_{1X1}+\beta_{2X2}+.....+\beta_{nXn}}}$$

which P(CIN) refers to the probability of CIN development

β_0 refers to the regression constant

β_n refers to the regression coefficient of the variable n

From the results of multivariate analysis (Table 14), the developed model was;

$$P(CIN) = \frac{e^{-4.432 + 1.866(\text{if patient having CHF}) + 1.815(\text{if CrCl} < 30\ \text{ml/min}) + 2.102(\text{if V/BW ratio} \geq 2.6\ \text{ml/kg})}}{1 + e^{-4.432 + 1.866(\text{if patient having CHF}) + 1.815(\text{if CrCl} < 30\ \text{ml/min}) + 2.102(\text{if V/BW ratio} \geq 2.6\ \text{ml/kg})}} \quad \textbf{(Equation 3)}$$

For example, patient with CrCl < 30 ml/min, absence of CHF and received contrast media volume ≥ 2.6 ml/kg, the probability of developing CIN in this patient would be

$$P(CIN) = \frac{e^{-4.432 + 1.866(0) + 1.815(1) + 2.102(1)}}{1 + e^{-4.432 + 1.866(0) + 1.815(1) + 2.102(1)}}$$

$$P(CIN) = 0.3795$$

Therefore, this patient had a probability of developing CIN after PCI of 0.3795 or approximately 38%.

This equation may be useful for predicting a probability of CIN after PCI; however, the nature of the exponential function makes it difficult to calculate in daily practice. Therefore, the authors sought to develop a risk score model that could easily be used by clinicians to evaluate individual patient risk in developing CIN. In that case, patients who are at risk of developing CIN can be identified and prophylactic measures can be provided in advance.

5. Risk Score Model for Prediction of Contrast-Induced Nephropathy after Percutaneous Coronary Intervention

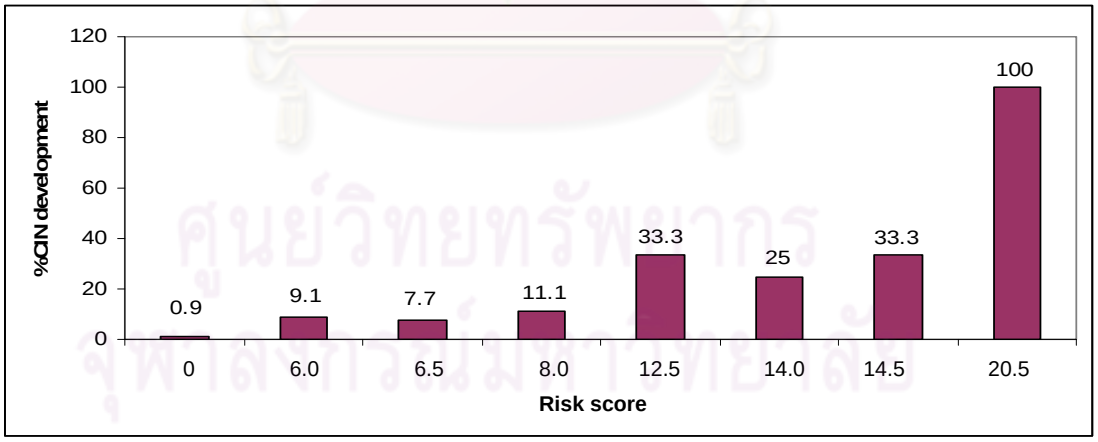
A risk score model for prediction of CIN after PCI was developed by using odds ratio of risk predictors of CIN from multivariate analysis. Therefore, the risk score values of 6.5, 6.0 and 8.0 for CHF, CrCl < 30 ml/min and V/BW ratio ≥ 2.6 ml/kg were obtained as presented in Table 17. A total risk score was then calculated for each patient. The total risk score for individual patient ranges from 0 to 20.5. The occurrence of CIN by risk score value is depicted in Figure 17.

Table 17. Risk score assignment for each risk predictor

Variable	β^*	OR	Risk Score
CHF	1.866	6.465	***6.5***
CrCl < 30 ml/min	1.815	6.141	***6.0***
V/BW ratio ≥ 2.6 ml/kg	2.102	8.184	***8.0***
Constant	-4.432	0.012	

β^* = Regression coefficient

Figure 17. The occurrence of CIN by risk score value



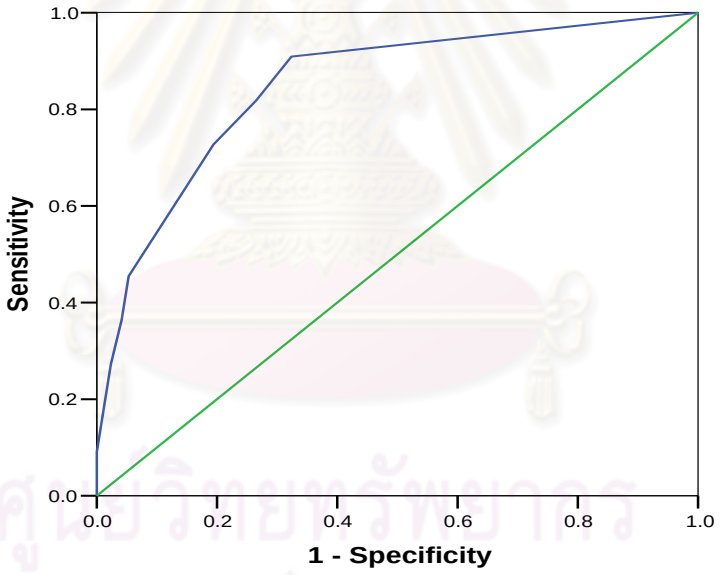
Risk score	0	6.0	6.5	8.0	12.5	14.0	14.5	20.5
CIN (n)* (%)	1 (0.9)	1 (9.1)	1 (7.7)	3 (11.1)	1 (33.3)	1 (25.0)	2 (33.3)	1 (100)
Total (N)**	116	11	13	27	3	4	6	1

*CIN (n) = Number of patients developing CIN

**Total (N) = Total number of patients within each risk score group

ROC curve analysis showed that the risk score model was also a good discriminator for CIN with identical discriminative ability to multivariate logistic regression model (C-statistic = 0.849) (Figure 18). Furthermore, it showed that an optimal risk score for detection of CIN was 7.25 (Table 18). At this cutoff value, the sensitivity and specificity for detection of CIN were 72.7% and 80.6%, respectively. The overall accuracy, positive predictive value (PPV) and negative predictive value (NPV) of this cutoff point were 80.11%, 19.5% and 97.85%, respectively. By using risk score value of 7.25 as a cutoff point for detection of CIN, the relationship between predicted and observed CIN is presented in Table 19. For more practical use, patients were further categorized into three groups based on the occurrence of CIN associated with different risk score as shown in Figure 19.

Figure 18. ROC curve analysis of risk score model



Area Under the ROC Curve (AUC) (a)	Std. Error	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.849	.061	.000	.730	.969

(a) Under the nonparametric assumption. Of note, AUC is identical to C-statistic.

(b) Null hypothesis: AUC = 0.5

Table 18. The relationship between risk score and sensitivity and specificity for detection of CIN after PCI

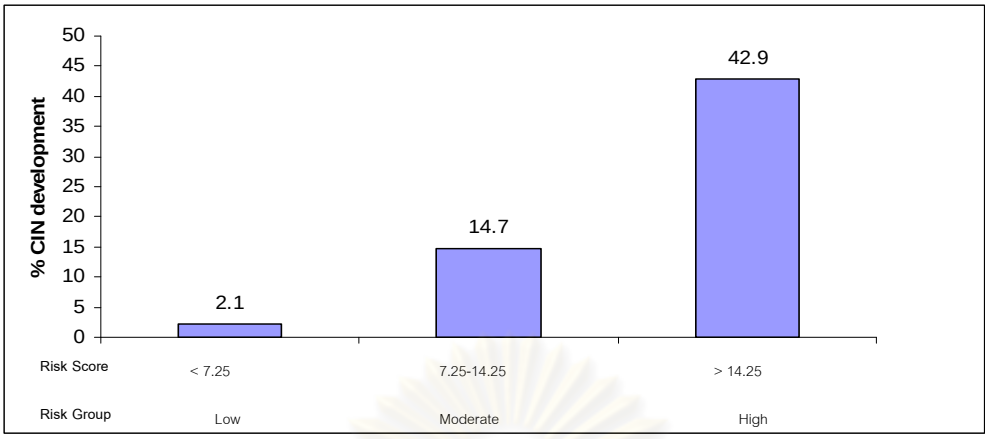
Positive if greater than or equal to	Sensitivity (%)	Specificity (%)
3.00	90.9	67.6
6.25	81.8	73.5
7.25	***72.7***	***80.6***
10.25	45.5	94.7
13.25	36.4	95.9
14.25	27.3	97.6
17.5	9.1	100
21.5	0	100

Table 19. The relationship between predicted and observed CIN

	Observed		
Predicted	CIN	No CIN	Total
CIN	8	33	41
No CIN	3	137	140
Total	11	170	181

sensitivity = 72.7%, specificity = 80.6%, accuracy = 80.11%, positive predictive value = 19.5%, negative predictive value = 97.85%

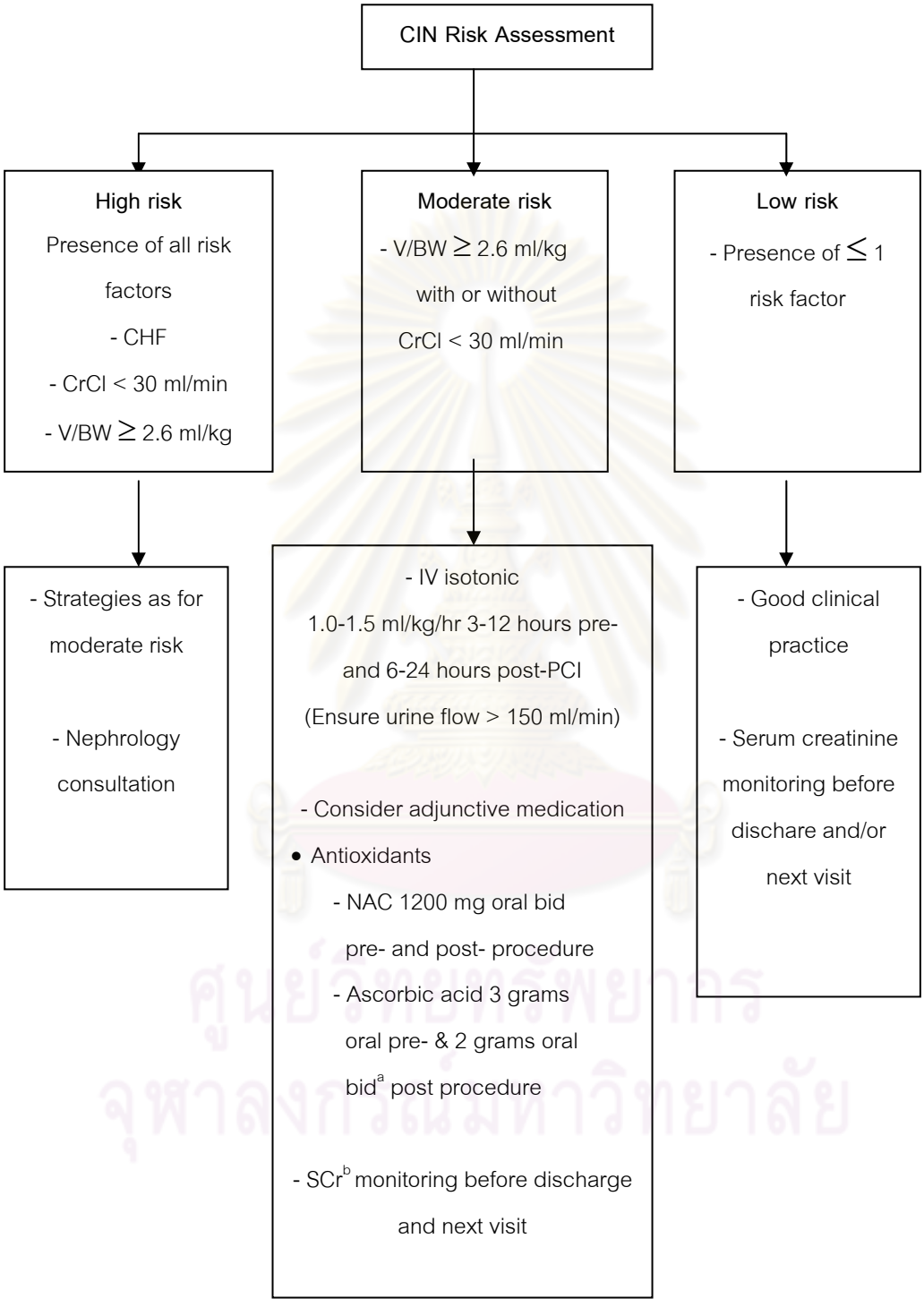
Figure 19. Risk score model for prediction of CIN after PCI



Predictor	Risk score
CHF	6.5
CrCl < 30 ml/min	6.0
V/BW ratio ≥ 2.6 ml/kg	8.0

This proposed CIN risk score model may be used as a tool for assessing individual patient risk for developing CIN after PCI, and it may be helpful for planning patient management according to each individual risk. Therefore, properly preventive measures can be provided in advance. For example, by adapting algorithm for management of patients receiving contrast media proposed by McCullough *(1)*, the patient management according to patient's risk is presented in Figure 20.

Figure 20. Algorithm for patient management according to patient's risk of developing CIN (Adapted from J Am Coll Cardiol *(1)*).



[a]bid = twice daily

[b]SCr = serum creatinine

Among published risk score models for prediction of CIN irrespective of hemodialysis after PCI, only those proposed by Mehran et al and Bartholomew et al reported discriminative ability of the model. The discriminative ability of our CIN risk score model is comparable to that of Bartholomew study, suggesting that this proposed model still performed a good discriminative performance. In comparison with the two published CIN risk score models (Table 20), this study found that CHF and severe CKD were significant predictors of CIN. However, the authors did not find the relationship between DM, hypertension, emergency PCI, advanced age, anemia and the risk of CIN. In contrast to two previous studies, total volume of contrast media was not associated with CIN. However, an adjusted volume of contrast media to patient body weight was found to be the strongest predictor of CIN in our study. The authors believed that using V/BW as a predictor of CIN should be more precisely predict safety profile of contrast media than the use of volume of contrast media. Moreover, in this study, some predictors were not tested for the relationship with CIN such as an intra-aortic balloon pump (IABP) use, hypotension and peripheral vascular disease.

Table 20. Comparison of CIN risk score model

Study	Mehran et al	Bartholomew et al	Tasigan
Procedure	Elective PCI	Elective & Emergency PCI	Elective & Emergency PCI
Total number of patients (N)	8,357	20,479	181
% CIN development	13.1*	2**	6.1
Risk Predictors	1. Hypotension 2. IABP[a] 3. CHF 4. Age > 75 years 5. Anemia 6. Diabetes mellitus 7. Contrast volume 8. SCr[b] > 1.5 mg/dl or CrCl < 60 ml/min	1. Urgent/Emergency PCI 2. IABP[a] 3. CHF 4. Hypertension 5. PVD[c] 6. Diabetes mellitus 7. Contrast volume > 260 ml 8. CrCl < 60 ml/min	1. V/BW ratio $\geq$ 2.6 ml/kg 2. CrCl < 30 ml/min 3. CHF

Table 20. Comparison of CIN risk score model (continued)

Study	Mehran et al	Bartholomew et al	Tasigan
Discriminative ability	C-statistic = 0.67	C-statistic = 0.89	C-statistic = 0.85

*CIN was defined as an increase ≥ 25% and/or ≥ 0.5 mg/dl in serum creatinine at 48 hours after PCI versus baseline

**CIN was defined as a ≥ 1.0 mg/dl increase in serum creatinine after PCI during hospital admission

IABP[a] = intra-aortic balloon pump use, SCr[b] = serum creatinine, PVD[c] = peripheral vascular disease

CHAPTER V
CONCLUSION

The present study was a prospective analytical study. The purpose of this study were to identify risk factors associated with CIN after PCI and develop a risk score model for prediction of CIN after PCI in Thai patients.

A total of 181 patients underwent PCI at King Chulalongkorn Memorial Hospital between 10 November 2009 and 31 March 2010 were enrolled in the study. CIN was observed in 11 patients (6.1%). One of them required a continuous veno-venous hemofiltration (CVVH). The mean absolute difference of serum creatinine between post- and pre-PCI in patients with and without CIN were 0.677 $\pm$ 0.85 mg/dl and -0.098 $\pm$ 0.15 mg/dl ($p = 0.013$). The mean relative difference of post- and pre-PCI serum creatinine in patients with and without CIN were 42.5 $\pm$ 30% and -9.44 $\pm$ 13.6% ($p < 0.001$), respectively.

Multivariate logistic regression analysis showed that V/BW $\geq$ 2.6 ml/kg (OR = 8.184, 95% CI = 2.015 - 33.245, $p = 0.003$), CHF (OR = 6.465, 95% CI = 1.566 - 26.686, $p = 0.010$), and CrCl < 30 ml/min (OR = 6.141, 95% CI = 1.349 - 27.957, $p = 0.019$) were associated with CIN after PCI. The V/BW $\geq$ 2.6 ml/kg was found to be the strongest predictor of CIN. The multivariate logistic regression model demonstrated good discriminative ability with C-statistic of 0.849.

The CIN risk score model was developed to assess the cumulative risk of these risk factors. By using odds ratio from multivariate logistic regression model, the risk score value of 8, 6.5 and 6 were assigned to V/BW $\geq$ 2.6 ml/kg, CHF, and CrCl < 30 ml/min, respectively. A total risk score was calculated for each patient by equation 4

Total risk score = 8(V/BW $\geq$ 2.6 ml/kg) + 6.5(CHF) + 6(CrCl < 30) **(Equation 4)**

The ROC curve analysis demonstrated good discriminative ability (C-statistic = 0.849) at risk score of 7.25. At this cutoff value, the sensitivity and specificity for the detection of CIN were 72.7% and 80.6%, respectively. The occurrence of CIN was found to be 2.1 and 42.9% for a low (< 7.25) and high (> 14.25) risk score.

Study Limitations

This study has some limitations,

1. This study included a small population, admitted to a single center. The findings from our study should be confirmed, and the validation of the proposed CIN risk score model is warranted in other large data bases.

2. The definition of CIN used in this study is based on the absolute or relative increase in serum creatinine concentration from a baseline value. Serum creatinine concentration at hospital admission; however, may not be considered a true baseline value because dehydration or acute hemodynamic impairment may have already increased it. For this reason, the authors could have underestimated both the incidence and the severity of CIN and overestimated the percentage of patients with renal insufficiency.

3. This study did not use baseline CrCl value based on 24-hours urine collection, but using the calculated CrCl. Therefore, the calculated CrCl may not represent the true baseline renal function. However, an assessment the risk of CIN based on calculated CrCl has been widely used and more practical than the measurement of CrCl based on 24-hours urine collection.

4. Although, 80% of the patients have the rise in serum creatinine within the first 24 hours after exposure to contrast media *(24)*, the limited data on serum creatinine beyond 24 hours after PCI in this study might resulted in a slight underestimation of CIN. However, it is doubtful that a delayed creatinine elevation beyond 24 hours after PCI may be at all clinically significant *(14)*.

5. Several factors such as dehydration, hemodynamic, and rheologic disturbances during PCI were not taken into account. Therefore, the authors cannot exclude the

possibility that other factors, apart from variables identified in this study may also contribute to the risk of renal impairment.

Future studies

1. A prospective validation of this proposed CIN risk score model in other data bases or a large multicenter trial is required before clinical practice application.

2. Additional studies for evaluating the use of the V/BW ratio ≥ 2.6 ml/kg as a cutoff criteria in other contrast media utilizing procedures such as CT scanning or MRI would be clinically informative.

3. Further studies should be performed to determine the proper patient management according to the level of CIN risk, which is stratified by CIN risk score model.

REFERENCES

(1) McCullough, P. A. Contrast-induced acute kidney injury. J Am Coll Cardiol 51 (2008): 1419-1428.

(2) Mehran, R. and Nikolsky, E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. Kidney Int Suppl (2006): S11-15.

(3) Katzberg, R. W. and Haller, C. Contrast-induced nephrotoxicity: clinical landscape. Kidney Int Suppl (2006): S3-7.

(4) Bartorelli, A. L. and Marenzi, G. Contrast-induced nephropathy. J Interv Cardiol 21 (2008): 74-85.

(5) Thomsen, H. S. Guidelines for contrast media from the European Society of Urogenital Radiology. AJR Am J Roentgenol 181 (2003): 1463-1471.

(6) McCullough, P. A., Adam, A., Becker, C. R., Davidson, C., Lameire, N., Stacul, F., et al. Epidemiology and prognostic implications of contrast-induced nephropathy. Am J Cardiol 98 (2006): 5K-13K.

(7) Marenzi, G., Assanelli, E., Campodonico, J., Lauri, G., Marana, I., De Metrio, M., et al. Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. Ann Intern Med 150 (2009): 170-177.

(8) Marenzi, G., Lauri, G., Assanelli, E., Campodonico, J., De Metrio, M., Marana, I., et al. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 44 (2004): 1780-1785.

(9) McCullough, P. A., Wolyn, R., Rocher, L. L., Levin, R. N. and O'Neill, W. W. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 103 (1997): 368-375.

(10) Rihal, C. S., Textor, S. C., Grill, D. E., Berger, P. B., Ting, H. H., Best, P. J., et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 105 (2002): 2259-2264.

(11) From, A. M., Bartholmai, B. J., Williams, A. W., Cha, S. S. and McDonald, F. S. Mortality associated with nephropathy after radiographic contrast exposure. Mayo Clin Proc 83 (2008): 1095-1100.

(12) Roy, P., Raya, V., Okabe, T., Pinto Slottow, T. L., Steinberg, D. H., Smith, K., et al. Incidence, predictors, and outcomes of post-percutaneous coronary intervention nephropathy in patients with diabetes mellitus and normal baseline serum creatinine levels. Am J Cardiol 101 (2008): 1544-1549.

(13) Solomon, R. and Barrett, B. Follow-up of patients with contrast-induced nephropathy. Kidney Int Suppl (2006): S46-50.

(14) Mehran, R., Aymong, E. D., Nikolsky, E., Lasic, Z., Iakovou, I., Fahy, M., et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 44 (2004): 1393-1399.

(15) Pannu, N., Wiebe, N. and Tonelli, M. Prophylaxis strategies for contrast-induced nephropathy. JAMA 295 (2006): 2765-2779.

(16) Kelly, A. M., Dwamena, B., Cronin, P., Bernstein, S. J. and Carlos, R. C. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. Ann Intern Med 148 (2008): 284-294.

(17) Barrett, B. J. and Parfrey, P. S. Clinical practice. Preventing nephropathy induced by contrast medium. N Engl J Med 354 (2006): 379-386.

(18) Weisbord, S. D., Mor, M. K., Resnick, A. L., Hartwig, K. C., Sonel, A. F., Fine, M. J., et al. Prevention, incidence, and outcomes of contrast-induced acute kidney injury. Arch Intern Med 168 (2008): 1325-1332.

(19) American College of Cardiology National Cardiovascular Data Registry Catheter PCI Registry. Institutional Outcomes Report 2005 Y4. American College of Cardiology Foundation, 2006.

(20) McCullough, P. A., Adam, A., Becker, C. R., Davidson, C., Lameire, N., Stacul, F., et al. Risk prediction of contrast-induced nephropathy. Am J Cardiol 98 (2006): 27K-36K.

(21) Adam, A., Dixon, A. K., Grainger, R. G. and Allison, D. J. Grainger & Allison's Diagnostic Radiology: a textbookof medical imaging. vol.1. 5 th ed. Philadelphia: Elsevier, 2008.

(22) Dickinson, M. C. and Kam, P. C. Intravascular iodinated contrast media and the anaesthetist. Anaesthesia 63 (2008): 626-634.

(23) Solomon, R., Briguori, C. and Bettmann, M. Selection of contrast media. Kidney Int Suppl (2006): S39-45.

(24) Guitterez, N. V., Diaz, A., Timmis, G. C., O'Neill, W. W., Stevens, M. A., Sandberg, K. R., et al. Determinants of serum creatinine trajectory in acute contrast nephropathy. J Interv Cardiol 15 (2002): 349-354.

(25) Davidson, C., Stacul, F., McCullough, P. A., Tumlin, J., Adam, A., Lameire, N., et al. Contrast medium use. Am J Cardiol 98 (2006): 42K-58K.

(26) Freeman, R. V., O'Donnell, M., Share, D., Meengs, W. L., Kline-Rogers, E., Clark, V. L., et al. Nephropathy requiring dialysis after percutaneous coronary intervention and the critical role of an adjusted contrast dose. Am J Cardiol 90 (2002): 1068-1073.

(27) Levy, E. M., Viscoli, C. M. and Horwitz, R. I. The effect of acute renal failure on mortality. A cohort analysis. JAMA 275 (1996): 1489-1494.

(28) Gruberg, L., Mintz, G. S., Mehran, R., Gangas, G., Lansky, A. J., Kent, K. M., et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 36 (2000): 1542-1548.

(29) Bartholomew, B. A., Harjai, K. J., Dukkipati, S., Boura, J. A., Yerkey, M. W., Glazier, S., et al. Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. Am J Cardiol 93 (2004): 1515-1519.

(30) Lindsay, J., Apple, S., Pinnow, E. E., Gevorkian, N., Gruberg, L., Satler, L. F., et al. Percutaneous coronary intervention-associated nephropathy foreshadows increased risk of late adverse events in patients with normal baseline serum creatinine. Catheter Cardiovasc Interv 59 (2003): 338-343.

(31) Dangas, G., Iakovou, I., Nikolsky, E., Aymong, E. D., Mintz, G. S., Kipshidze, N. N., et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. Am J Cardiol 95 (2005): 13-19.

(32) Subramanian, S., Tumlin, J., Bapat, B. and Zyczynski, T. Economic burden of contrast-induced nephropathy: implications for prevention strategies. J Med Econ 10 (2007): 119-134.

(33) Toprak, O. Risk markers for contrast-induced nephropathy. Am J Med Sci 334 (2007): 283-290.

(34) Toprak, O. and Cirit, M. Risk factors for contrast-induced nephropathy. Kidney Blood Press Res 29 (2006): 84-93.

(35) Lameire, N., Adam, A., Becker, C. R., Davidson, C., McCullough, P. A., Stacul, F., et al. Baseline renal function screening. Am J Cardiol 98 (2006): 21K-26K.

(36) Hall, K. A., Wong, R. W., Hunter, G. C., Camazine, B. M., Rappaport, W. A., Smyth, S. H., et al. Contrast-induced nephrotoxicity: the effects of vasodilator therapy. J Surg Res 53 (1992): 317-320(abstract).

(37) Lasser, E. C., Lyon, S. G. and Berry, C. C. Reports on contrast media reactions: analysis of data from reports to the U.S. Food and Drug Administration. Radiology 203 (1997): 605-610.

(38) Nikolsky, E., Mehran, R., Turcot, D., Aymong, E. D., Mintz, G. S., Lasic, Z., et al. Impact of chronic kidney disease on prognosis of patients with diabetes mellitus treated with percutaneous coronary intervention. Am J Cardiol 94 (2004): 300-305.

(39) Manske, C. L., Sprafka, J. M., Strony, J. T. and Wang, Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am J Med 89 (1990): 615-620.

(40) Toprak, O., Cirit, M., Yesil, M., Bayata, S., Tanrisev, M., Varol, U., et al. Impact of diabetic and pre-diabetic state on development of contrast-induced nephropathy in patients with chronic kidney disease. Nephrol Dial Transplant 22 (2007): 819-826.

(41) Toprak, O., Cirit, M., Yesil, M., Byrne, D. W., Postaci, N., Bayata, S., et al. Metabolic syndrome as a risk factor for contrast-induced nephropathy in non-diabetic elderly patients with renal impairment. Kidney Blood Press Res 29 (2006): 2-9.

(42) Barrett, B. J. and Carlisle, E. J. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology 188 (1993): 171-178.

(43) Rudnick, M. R., Goldfarb, S., Wexler, L., Ludbrook, P. A., Murphy, M. J., Halpern, E. F., et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. Kidney Int 47 (1995): 254-261.

(44) Aspelin, P., Aubry, P., Fransson, S. G., Strasser, R., Willenbrock, R. and Berg, K. J. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 348 (2003): 491-499.

(45) Anderson, J. L. ACC/AHA 2007 guide lines for the management of patients with unstable Angina/Non-ST-Elevation myocardial infraction - Executive summary. Journal of the American College of Cardiology 50 (2007): 652-726.

(46) Cigarroa, R. G., Lange, R. A., Williams, R. H. and Hillis, L. D. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am J Med 86 (1989): 649-652.

(47) Nikolsky, E., Mehran, R., Lasic, Z., Mintz, G. S., Lansky, A. J., Na, Y., et al. Low hematocrit predicts contrast-induced nephropathy after percutaneous coronary interventions. Kidney Int 67 (2005): 706-713.

(48) Mueller, C., Buerkle, G., Buettner, H. J., Petersen, J., Perruchoud, A. P., Eriksson, U., et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 162 (2002): 329-336.

(49) Merten, G. J., Burgess, W. P., Gray, L. V., Holleman, J. H., Roush, T. S., Kowalchuk, G. J., et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA 291 (2004): 2328-2334.

(50) Brar, S. S., Shen, A. Y., Jorgensen, M. B., Kotlewski, A., Aharonian, V. J., Desai, N., et al. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. JAMA 300 (2008): 1038-1046.

(51) Stevens, M. A., McCullough, P. A., Tobin, K. J., Speck, J. P., Westveer, D. C., Guido-Allen, D. A., et al. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C.E. Study. Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. J Am Coll Cardiol 33 (1999): 403-411.

(52) Taylor, A. J., Hotchkiss, D., Morse, R. W. and McCabe, J. PREPARED: Preparation for Angiography in Renal Dysfunction: a randomized trial of inpatient vs outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. Chest 114 (1998): 1570-1574.

(53) Marenzi, G., Marana, I., Lauri, G., Assanelli, E., Grazi, M., Campodonico, J., et al. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. N Engl J Med 349 (2003): 1333-1340.

(54) Marenzi, G., Lauri, G., Campodonico, J., Marana, I., Assanelli, E., De Metrio, M., et al. Comparison of two hemofiltration protocols for prevention of contrast-induced nephropathy in high-risk patients. Am J Med 119 (2006): 155-162.

(55) Spargias, K., Alexopoulos, E., Kyrzopoulos, S., Iokovis, P., Greenwood, D. C., Manginas, A., et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. Circulation 110 (2004): 2837-2842.

(56) Briguori, C., Airoldi, F., D'Andrea, D., Bonizzoni, E., Morici, N., Focaccio, A., et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. Circulation 115 (2007): 1211-1217.

(57) Cochran, S. T., Wong, W. S. and Roe, D. J. Predicting angiography-induced acute renal function impairment: clinical risk model. AJR Am J Roentgenol 141 (1983): 1027-1033.

(58) Hair, J., Tatham, R., Anderson, R. and Black, W. Multivariate Data Analysis. 5 th ed. New Jersy: Prentice Hall, 1998.

(59) Steyerberg, E. W., Harrell, F. E., Jr., Borsboom, G. J., Eijkemans, M. J., Vergouwe, Y. and Habbema, J. D. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 54 (2001): 774-781.

(60) Akobeng, A. K. Understanding diagnostic tests 3: Receiver operating characteristic curves. Acta Paediatr 96 (2007): 644-647.

(61) Park, S. H., Goo, J. M. and Jo, C. H. Receiver operating characteristic (ROC) curve: practical review for radiologists. Korean J Radiol 5 (2004): 11-18.

(62) Kantachuvessiri, A. Obesity in Thailand. J Med Assoc Thai 88 (2005): 554-562.

(63) Laskey, W. K., Jenkins, C., Selzer, F., Marroquin, O. C., Wilensky, R. L., Glaser, R., et al. Volume-to-creatinine clearance ratio: a pharmacokinetically based risk factor for prediction of early creatinine increase after percutaneous coronary intervention. J Am Coll Cardiol 50 (2007): 584-590.

(64) Nyman, U., Almen, T., Aspelin, P., Hellstrom, M., Kristiansson, M. and Sterner, G. Contrast-medium-Induced nephropathy correlated to the ratio between dose in gram iodine and estimated GFR in ml/min. Acta Radiol 46 (2005): 830-842.

(65) Brown, J. R., DeVries, J. T., Piper, W. D., Robb, J. F., Hearne, M. J., Ver Lee, P. M., et al. Serious renal dysfunction after percutaneous coronary interventions can be predicted. Am Heart J 155 (2008): 260-266.

(66) Worasuwannarak, S. and Pornratanarangsi, S. Prediction of contrast-induced nephropathy in diabetic patients undergoing elective cardiac catheterization or PCI: role of volume-to-creatinine clearance ratio and iodine dose-to-creatinine clearance ratio. J Med Assoc Thai 93 Suppl 1 S29-34.

APPENDICES

APPENDIX A

Patient data collection form

แบบบันทึกผู้ป่วยโรคหัวใจที่ทำหัตถการรักษาหลอดเลือดโคโรนารีย์ผ่านสายสวน
โรงพยาบาลจุฬาลงกรณ์

เลขที่บันทึก_____

ส่วนที่ 1 ข้อมูลผู้ป่วยและภาวะของโรค

1. เพศ_____อายุ_____ปี

2. น้ำหนัก_____กิโลกรัม ส่วนสูง_____เซนติเมตร BMI_____kg/m^2

3. vital sign : BP_____mmHg Heart rate_____beat/min BT_____C RR_____/min

4. ระยะเวลาที่รักษาตัวในโรงพยาบาล_____วัน (date of admission_____;Discharge_____)

5. โรคประจำตัว รวมจำนวน_____โรค

_____

_____

_____

_____

_____

6. ประวัติการใช้ยา

_____

_____

_____

_____

7. Active Problem list

_____

_____

_____

8. ประวัติการใช้ยาที่เป็นพิษต่อไต ☐ ไม่มี ☐ มี คือ_____

☐ Sulfonamide ☐ Aminoglycoside ☐ Diuretics (_____)

☐ CSA ☐ Cisplatin ☐ NSAIDS (_____)

☐ Amphotericin B ☐ Tacrolimus ☐ Intravenous immunoglobulin

☐ Metformin ; หยุดยาก่อนให้สารทึบรังสี O ใช่ O ไม่ใช่

อื่นๆ_____

_____

ส่วนที่ 2 ยาที่ผู้ป่วยได้รับระหว่างรักษาตัวในโรงพยาบาล (หอผู้ป่วย_____)

Date	MEDICATION ORDER FOR ONE DAY	Date	MEDICATION ORDER FOR CONTINUATION

ส่วนที่ 3 สารทึบรังสีที่ผู้ป่วยได้รับและกระบวนการทำหัตถการหลอดเลือดโคโรนารีย์ผ่านสายสวน

1. สารทึบรังสีที่ใช้_____วิถีการให้ยา_____ปริมาณที่ใช้_____มิลลิลิตร

2. การให้ pre-medication ☐ ไม่มี ☐ มี ด้วย

O Hydration ด้วย_____

O NAC _____

อื่นๆ_____

3. การให้ post-medication ☐ ไม่มี ☐ มี ด้วย

O Hydration ด้วย_____

O NAC _____

อื่นๆ_____

4. การทำหัตถการหลอดเลือดหัวใจผ่านสายสวนชนิด ☐ Elective ☐ Emergency

5. ข้อบ่งชี้สำหรับการทำหัตถการหลอดเลือดหัวใจผ่านสายสวน_____

6. วันที่ทำหัตถการหลอดเลือดหัวใจ_____เวลา_____ถึง_____ใช้เวลา_____นาที

7. ทำหัตถการหลอดเลือดหัวใจผ่านสายสวนครั้งที่_____ ห่างจากรอบที่แล้ว_____วัน

8. Angiographic diagnosis_____

9. vital sign ก่อนทำ PCI: BP_____mmHg Heart rate____beat/min BT_____C RR_____/min

10. จำนวนหลอดเลือดหัวใจที่ทำหัตถการผ่านสายสวน_____เส้น

11. ภาวะแทรกซ้อนระหว่างการทำหัตถการหลอดเลือดหัวใจผ่านสายสวน

☐ Hypotension ☐ Cardiogenic shock ☐ Sepsis

☐ มีการใส่ Intraaortic balloon pump ☐ ต้องการ Blood transfusion

อื่นๆ_____

12. ภาวะแทรกซ้อนหลังทำหัตถการหลอดเลือดหัวใจผ่านสายสวน

_____**ส่วนที่ 4** ผลการตรวจทางห้องปฏิบัติการที่เกี่ยวข้อง

วันที่ตรวจ	เวลา	S_{cr} (mg/dL)	BUN (mg/dL)	Hgb (gm/dL)	Hct (mg%)	AST (units/L)	ALT (units/L)	ALB (g/dL)

Baseline CrCl =_____ml/min

APPENDIX B

Certificate of Approval from The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University

COA No. 898/2009
IRB No. 357/52

INSTITUTIONAL REVIEW BOARD
Faculty of Medicine, Chulalongkorn University
1873 Rama 4 Road, Patumwan, Bangkok 10330, Thailand, Tel 662-256-4455 ext 14, 15

Certificate of Approval

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, has approved the following study which is to be carried out in compliance with the International guidelines for human research protection as Declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

Study Title : RISK SCORE MODEL FOR PREDICTION OF CONTRAST-INDUCED NEPHROPATHY AFTER PERCUTANEOUS CORONARY INTERVENTION

Study Code : -

Study Center : Chulalongkorn University

Principal Investigator : Miss Tasigan Chaemchoi

Document Reviewed :

1. Protocol Version 2.0 Dated 1 September 2009
2. Information sheet for research participant Version 3.0 Dated 15 October 2009
3. Consent Form Version 2.0 Dated 1 September 2009
4. Case Record Form Version 3.0 Dated 1 October 2009

Signature:.....
(Professor Tada Sueblinvong MD)
Chairman of
The Institutional Review Board

Signature:.....
(Associate Professor Sopit Thamaree)
Committee and Secretary of
The Institutional Review Board

Date of Approval : October 29, 2009

Approval Expire Date : October 29, 2010

Approval is granted subject to the following conditions: (see back of this Certificate)

COA No. 898/2009
IRB No. 357/52

คณะกรรมการจริยธรรมการวิจัยในคน
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
1873 ถ.พระราม 4 เขตปทุมวัน กรุงเทพฯ 10330 โทร. 0-2256-4455 ต่อ 14, 15

เอกสารรับรองโครงการวิจัย

คณะกรรมการจริยธรรมการวิจัยในคน คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ดำเนินการให้การรับรองโครงการวิจัยตามแนวทางหลักจริยธรรมการวิจัยในคนที่เป็นมาตรฐานสากลได้แก่ Declaration of Helsinki, The Belmont Report, CIOMS Guideline และ International Conference on Harmonization in Good Clinical Practice หรือ ICH-GCP

ชื่อโครงการ : แบบจำลองคะแนนความเสี่ยงเพื่อทำนายการเกิดภาวะไตทำงานบกพร่องจากสารทึบรังสีในผู้ป่วยทำหัตถการรักษาหลอดเลือดโคโรนารีย์ผ่านสายสวน

เลขที่โครงการวิจัย : -

ผู้วิจัยหลัก : นางสาวรศิกานต์ แซ่มซ้อย

สังกัดหน่วยงาน : คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

รายงานความก้าวหน้า : ส่งรายงานความก้าวหน้าอย่างน้อยทุก 6 เดือน

เอกสารรับรอง :

1. โครงการวิจัย Version 2.0 Dated 1 September 2009
2. เอกสารข้อมูลคำอธิบายสำหรับผู้เข้าร่วมในโครงการวิจัย Version 3.0 Dated 15 October 2009
3. เอกสารแสดงความยินยอมเข้าร่วมในโครงการวิจัย Version 2.0 Dated 1 September 2009
5. แบบบันทึกข้อมูลผู้ป่วย Version 3.0 Dated 1 October 2009

ลงนาม ..... ลงนาม .....

(ศาสตราจารย์แพทย์หญิงธาดา สืบหลินวงศ์)
ประธาน
คณะกรรมการจริยธรรมการวิจัยในคน

(รองศาสตราจารย์โสภิต ธรรมอารี)
กรรมการและเลขานุการ
คณะกรรมการจริยธรรมการวิจัยในคน

วันที่รับรอง : 29 ตุลาคม 2552
วันหมดอายุ : 29 ตุลาคม 2553

ทั้งนี้ การรับรองนี้มีเงื่อนไขดังที่ระบุไว้ด้านหลังทุกข้อ (ดูด้านหลังของเอกสารรับรองโครงการวิจัย)

APPENDIX C

Information sheet for research participant

เอกสารข้อมูลคำอธิบายสำหรับผู้เข้าร่วมในโครงการวิจัย

ชื่อโครงการวิจัย **แบบจำลองคะแนนความเสี่ยงเพื่อทำนายการเกิดภาวะไตทำงานบกพร่องจากสารทึบรังสีในผู้ป่วยทำหัตถการรักษาหลอดเลือดโคโรนารีย์ผ่านสายสวน**

ผู้วิจัย

ชื่อ นางสาวธศิกานต์ แช่มช้อย

สถานที่ติดต่อ ฝ่ายเภสัชกรรม โรงพยาบาลจุฬาลงกรณ์

เบอร์โทรศัพท์ 0-2256-4587, 08-9896-3201

(ที่ทำงานและมือถือ)

เรียน ผู้เข้าร่วมโครงการวิจัยทุกท่าน

ท่านได้รับเชิญให้เข้าร่วมในโครงการวิจัยนี้เนื่องจากท่านเป็นผู้ที่มีคุณสมบัติครบตามเกณฑ์การคัดเลือกตามที่กำหนด ก่อนที่ท่านจะตัดสินใจเข้าร่วมในการศึกษาวิจัยดังกล่าว ขอให้ท่านอ่านเอกสารฉบับนี้อย่างถี่ถ้วน เพื่อให้ท่านได้ทราบถึงเหตุผลและรายละเอียดของการศึกษาวิจัยในครั้งนี้ หากท่านมีข้อสงสัยใดๆ เพิ่มเติม กรุณาซักถามผู้วิจัยซึ่งจะเป็นผู้สามารถตอบคำถามและให้ความกระจ่างแก่ท่านได้

ท่านสามารถขอคำแนะนำในการเข้าร่วมโครงการวิจัยนี้จากครอบครัว เพื่อน หรือแพทย์ประจำตัวของท่านได้ ท่านมีเวลาอย่างเพียงพอในการตัดสินใจโดยอิสระ ถ้าท่านตัดสินใจแล้วว่าจะเข้าร่วมในโครงการวิจัยนี้ ขอให้ท่านลงนามในเอกสารแสดงความยินยอมของโครงการวิจัยนี้

เหตุผลความเป็นมา

ภาวะไตทำงานบกพร่องจากสารทึบรังสีเป็นภาวะแทรกซ้อนที่สำคัญอย่างหนึ่งของการใช้สารทึบรังสีชนิดฉีดเข้าหลอดเลือด การทำงานของไตที่ลดลงนี้ถึงแม้ว่าส่วนใหญ่จะเกิดขึ้นชั่วคราวแต่มีความสัมพันธ์กับการพยากรณ์โรคและผลลัพธ์ทางคลินิกที่แย่ลง ทำให้ระยะเวลาที่ผู้ป่วยพักรักษาตัวในโรงพยาบาลนานขึ้น ส่งผลให้ค่าใช้จ่ายในการรักษาพยาบาลสูงขึ้นตาม ซึ่งจากการศึกษาที่ผ่านมาพบว่าการให้การป้องกันที่เหมาะสมในผู้ป่วยที่มีปัจจัยเสี่ยงสามารถลดอัตราการเกิดพิษต่อไตจากสารทึบรังสีได้ ในการที่จะให้การป้องกันกับผู้ป่วยได้อย่างมีประสิทธิภาพและทันท่วงที อันดับแรกต้องอาศัยวิธีการหรือเครื่องมือในการประเมินความเสี่ยงของผู้ป่วยต่อการเกิดภาวะดังกล่าวที่ถูกต้อง แม่นยำและรวดเร็ว ผู้วิจัยจึงทำการศึกษานี้ขึ้นโดยมีวัตถุประสงค์เพื่อศึกษาปัจจัยเสี่ยงที่มีความสัมพันธ์ต่อการเกิดภาวะไตทำงานบกพร่องจากสารทึบรังสี และสร้างแบบจำลองคะแนนความเสี่ยงที่สามารถประเมินโอกาสเกิดภาวะดังกล่าวได้อย่างถูกต้อง แม่นยำและสะดวกต่อการนำไปใช้ในทางคลินิก

วัตถุประสงค์ของการศึกษา

วัตถุประสงค์หลักจากการศึกษาในครั้งนี้คือเพื่อสร้างแบบจำลองคะแนนความเสี่ยงเพื่อทำนายการเกิดภาวะไตทำงานบกพร่องจากสารทึบรังสีในผู้ป่วยทำหัตถการรักษาหลอดเลือดหัวใจ รวมทั้งปัจจัยที่มีความสัมพันธ์ต่อการเกิดภาวะดังกล่าว

จำนวนผู้เข้าร่วมในโครงการวิจัย คือ 200 คน

วิธีการที่เกี่ยวข้องกับการวิจัย

หลังจากท่านให้ความยินยอมที่จะเข้าร่วมในโครงการวิจัยนี้ ท่านจะได้รับการเจาะเลือดเพื่อเก็บส่งตรวจทางห้องปฏิบัติการ จำนวน 5 ซีซี ทั้งก่อนและหลังการทำหัตถการหลอดเลือดหัวใจ เพื่อประเมินการเปลี่ยนแปลงการทำงานของไตภายหลังได้รับสารทึบรังสีในช่วงการทำหัตถการหลอดเลือดหัวใจ โดยท่านจะอยู่ในโครงการวิจัยเป็นเวลา 1-3 วันขึ้นกับระยะเวลาที่ท่านพักรักษาตัวในโรงพยาบาลภายหลังการทำหัตถการหลอดเลือดหัวใจ สำหรับตัวอย่างเลือดที่เหลือจากการวิเคราะห์จะถูกกำจัดทิ้งทันที

ความเสี่ยงที่อาจได้รับจากการเจาะเลือด

ท่านมีโอกาสที่จะเกิดอาการเจ็บ เลือดออก ช้ำจากการเจาะเลือด อาการบวมบริเวณที่เจาะเลือดหรือหน้ามืด และโอกาสที่จะเกิดการติดเชื้อบริเวณที่เจาะเลือดพบได้น้อยมาก

ประโยชน์ที่อาจได้รับ

ท่านจะได้รับการประเมินการเกิดภาวะแทรกซ้อนต่อไตจากสารทึบรังสีภายหลังการทำหัตถการหลอดเลือดหัวใจ ซึ่งหากเกิดภาวะดังกล่าวผู้วิจัยจะประสานงานกับแพทย์เจ้าของไข้เพื่อให้การรักษาที่เหมาะสมต่อไป

อันตรายที่อาจเกิดขึ้นจากการเข้าร่วมในโครงการวิจัยและความรับผิดชอบของผู้ทำวิจัย

หากพบอันตรายที่เกิดขึ้นจากการวิจัย ท่านจะได้รับการรักษาอย่างเหมาะสมทันที ผู้ทำวิจัยยินดีจะรับผิดชอบค่าใช้จ่ายในการรักษาพยาบาลของท่าน และการลงนามในเอกสารให้ความยินยอม ไม่ได้หมายความว่าท่านได้สละสิทธิ์ทางกฎหมายตามปกติที่ท่านพึงมี

ค่าตอบแทนสำหรับผู้เข้าร่วมวิจัย

ท่านจะไม่ได้รับเงินค่าตอบแทนจากการเข้าร่วมในการวิจัย แต่ท่านจะได้รับเงินชดเชยจากความไม่สะดวกไม่สบายที่ถูกเจาะเลือดเป็นจำนวนเงินทั้งสิ้น 150 บาท

ในกรณีที่ท่านได้รับอันตรายใด ๆ หรือต้องการข้อมูลเพิ่มเติมที่เกี่ยวข้องกับโครงการวิจัย ท่านสามารถติดต่อกับผู้ทำวิจัยคือ นางสาวธศิกานต์ แช่มช้อย ได้ตลอด 24 ชั่วโมง

หากท่านไม่ได้รับการชดเชยอันควรต่อการบาดเจ็บหรือเจ็บป่วยที่เกิดขึ้นโดยตรงจากการวิจัย หรือท่านไม่ได้รับการปฏิบัติตามที่ปรากฏในเอกสารข้อมูลคำอธิบายสำหรับผู้เข้าร่วมในการวิจัย ท่านสามารถร้องเรียนได้ที่ คณะกรรมการจริยธรรมการวิจัย คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ตึกอานันทมหิดลชั้น 3 โรงพยาบาลจุฬาลงกรณ์ ถนนพระราม 4 ปทุมวัน กรุงเทพฯ 10330 โทร 0-2256-4455 ต่อ 14, 15 ในเวลาราชการ

ขอขอบคุณในการร่วมมือของท่านมา ณ ที่นี้

APPENDIX D

Consent Form

เอกสารแสดงความยินยอมเข้าร่วมในโครงการวิจัย

การวิจัยเรื่อง แบบจำลองคะแนนความเสี่ยงเพื่อทำนายการเกิดภาวะไตทำงานบกพร่องจากสารทึบรังสีในผู้ป่วยทำหัตถการรักษาหลอดเลือดโคโรนารีย์ผ่านสายสวน

วันให้คำยินยอม วันที่.....เดือน.....พ.ศ.....

ข้าพเจ้า นาย/นาง/นางสาว.....ได้อ่านรายละเอียดจากเอกสารข้อมูลสำหรับผู้เข้าร่วมโครงการวิจัยวิจัยที่แนบมาฉบับวันที่ ..... และข้าพเจ้ายินยอมเข้าร่วมโครงการวิจัยโดยสมัครใจ

ข้าพเจ้าได้รับสำเนาเอกสารแสดงความยินยอมเข้าร่วมในโครงการวิจัยที่ข้าพเจ้าได้ลงนามและ วันที่ พร้อมด้วยเอกสารข้อมูลสำหรับผู้เข้าร่วมโครงการวิจัย ทั้งนี้ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย ระยะเวลาของการทำวิจัย วิธีการวิจัย อันตราย หรืออาการที่อาจเกิดขึ้นจากการวิจัย รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัย ข้าพเจ้ามีเวลาและโอกาสเพียงพอในการซักถามข้อสงสัยจนมีความเข้าใจอย่างดีแล้ว โดยผู้วิจัยได้ตอบคำถามต่าง ๆ ด้วยความเต็มใจไม่ปิดบังซ่อนเร้นจนข้าพเจ้าพอใจ

ข้าพเจ้ารับทราบจากผู้วิจัยว่าหากเกิดอันตรายใด ๆ จากการวิจัยดังกล่าว ผู้เข้าร่วมวิจัยจะได้รับการรักษาพยาบาลโดยไม่เสียค่าใช้จ่าย โดยผู้วิจัยจะเป็นผู้ให้ความช่วยเหลือในการติดต่อประสานงานเพื่อให้ผู้เข้าร่วมการวิจัยได้เข้ารับการตรวจรักษาจากแพทย์เจ้าของไข้ สำหรับค่าใช้จ่ายในการดูแลรักษาอาการผิดปกติที่เกิดขึ้นจากการวิจัย ผู้วิจัยจะเป็นผู้รับผิดชอบค่าใช้จ่ายที่เกิดขึ้นเองทั้งหมด

ข้าพเจ้ามีสิทธิที่จะบอกเลิกเข้าร่วมในโครงการวิจัยเมื่อใดก็ได้ โดยไม่จำเป็นต้องแจ้งเหตุผล และการบอกเลิกการเข้าร่วมการวิจัยนี้ จะไม่มีผลต่อการรักษาโรคหรือสิทธิอื่น ๆ ที่ข้าพเจ้าจะพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลส่วนตัวของข้าพเจ้าเป็นความลับ และจะเปิดเผยได้เฉพาะเมื่อได้รับการยินยอมจากข้าพเจ้าเท่านั้น บุคคลอื่นในนามของคณะกรรมการพิจารณาจริยธรรมการวิจัยในคน สำนักงานคณะกรรมการอาหารและยาอาจได้รับอนุญาตให้เข้ามาตรวจและประมวลข้อมูลของผู้เข้าร่วมวิจัย ทั้งนี้จะต้องกระทำไปเพื่อวัตถุประสงค์เพื่อตรวจสอบความถูกต้องของข้อมูลเท่านั้น โดยการตกลงที่จะเข้าร่วมการศึกษานี้ข้าพเจ้าได้ให้คำยินยอมที่จะให้มีการตรวจสอบข้อมูลประวัติทางการแพทย์ของผู้เข้าร่วมวิจัยได้

ผู้วิจัยรับรองว่าจะไม่มีการเก็บข้อมูลใด ๆ ของผู้เข้าร่วมวิจัย เพิ่มเติม หลังจากที่ข้าพเจ้าขอยกเลิกการเข้าร่วมโครงการวิจัยและต้องการให้ทำลายเอกสารและ/หรือ ตัวอย่างที่ใช้ตรวจสอบทั้งหมดที่สามารถสืบค้นถึงตัวข้าพเจ้าได้

ข้าพเจ้าเข้าใจว่า ข้าพเจ้ามีสิทธิ์ที่จะตรวจสอบหรือแก้ไขข้อมูลส่วนตัวของข้าพเจ้าและสามารถยกเลิกการให้สิทธิในการใช้ข้อมูลส่วนตัวของข้าพเจ้าได้ โดยต้องแจ้งให้ผู้วิจัยรับทราบ

ข้าพเจ้าได้ตระหนักว่าข้อมูลในการวิจัยรวมถึงข้อมูลทางการแพทย์ของข้าพเจ้าที่ไม่มีการเปิดเผยชื่อ จะผ่านกระบวนการต่าง ๆ เช่น การเก็บข้อมูล การบันทึกข้อมูลในแบบบันทึกและในคอมพิวเตอร์ การตรวจสอบ การวิเคราะห์ และการรายงานข้อมูลเพื่อวัตถุประสงค์ทางวิชาการ รวมทั้งการใช้ข้อมูลทางการแพทย์ในอนาคตหรือการวิจัยทางด้านเภสัชภัณฑ์ เท่านั้น

ข้าพเจ้าได้อ่านข้อความข้างต้นและมีความเข้าใจดีทุกประการแล้ว ยินดีเข้าร่วมในการวิจัยด้วยความเต็มใจ จึงได้ลงนามในเอกสารแสดงความยินยอมนี้

ลงชื่อ.....ผู้เข้าร่วมโครงการวิจัย/
ผู้แทนโดยชอบธรรม
(..... ชื่อ-นามสกุล ตัวบรรจง)

ในกรณีที่ผู้เข้าร่วมโครงการวิจัยไม่สามารถลงลายมือชื่อด้วยตนเองได้ ให้ผู้แทนโดยชอบตามกฎหมายซึ่งมีส่วนเกี่ยวข้องเป็น.....ของผู้เข้าร่วมโครงการวิจัยเป็นผู้ลงนามแทน

วันที่ .....เดือน.....พ.ศ.....

ข้าพเจ้าได้อธิบายถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย อันตราย หรืออาการไม่พึงประสงค์หรือความเสี่ยงที่อาจเกิดขึ้นจากการวิจัย หรือจากยาที่ใช้ รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด ให้ผู้เข้าร่วมในโครงการวิจัยตามนามข้างต้นได้ทราบและมีความเข้าใจดีแล้ว พร้อมลงนามลงในเอกสารแสดงความยินยอมด้วยความเต็มใจ

.....ลงนามผู้ทำวิจัย
(.....) ชื่อผู้ทำวิจัย ตัวบรรจง
วันที่ .....เดือน.....พ.ศ.....

.....ลงนามพยาน
(.....) ชื่อพยาน ตัวบรรจง
วันที่ .....เดือน.....พ.ศ.....

APPENDIX E

Patients' data

ID	CrCl (ml/min)	CHF	Volume of contrast (ml)	V/BW ratio	Risk score	CIN development
1	83.10	0	85	1.02	0	0
2	75.00	1	230	3.29	14.5	0
3	25.80	0	70	1.17	6.0	0
4	78.10	0	100	1.28	0	0
5	62.90	0	340	5.23	8.0	0
6	64.20	0	70	0.92	0	0
7	71.10	0	170	3.24	8.0	0
8	81.70	0	90	1.27	0	0
9	32.60	1	150	2.14	6.5	0
10	54.40	0	140	1.79	0	0
11	60.30	0	110	2.06	0	0
12	93.60	0	125	1.62	0	0
13	60.70	0	240	3.24	8.0	1
14	71.40	0	110	1.96	0	0
15	76.30	1	180	2.08	6.5	0
16	91.60	0	130	1.75	0	0
17	94.50	0	110	1.38	0	0
18	25.30	0	110	2.10	6.0	0
19	43.60	0	60	1.20	0	0
20	73.00	0	280	3.78	8.0	0
21	35.20	0	150	2.59	0	0
22	42.40	0	150	2.93	8.0	0
23	48.50	0	85	1.31	0	0
24	78.50	0	115	1.38	0	0
25	70.90	0	130	2.36	0	0
26	85.50	0	100	1.25	0	0
27	102.40	0	30	0.45	0	0
28	90.00	0	140	N/A	0	0
29	62.70	0	100	1.50	0	0
30	88.20	0	120	1.48	0	1
31	72.70	0	90	1.11	0	0
32	55.90	0	165	2.16	0	0

ID	CrCl (ml/min)	CHF	Volume of contrast (ml)	V/BW ratio	Risk score	CIN development
33	55.20	0	90	1.50	0	0
34	61.10	0	100	1.42	0	0
35	54.30	0	100	1.51	0	0
36	52.50	0	40	0.73	0	0
37	55.50	0	125	1.85	0	0
38	77.00	0	160	1.89	0	0
39	68.40	0	165	2.08	0	0
40	71.10	0	150	2.32	0	0
41	75.40	0	175	3.19	8.0	0
42	47.50	0	190	3.20	8.0	0
43	67.40	0	260	3.13	8.0	0
44	68.80	0	85	1.30	0	0
45	51.90	0	220	5.12	8.0	0
46	72.30	0	70	1.06	0	0
47	92.10	0	70	1.08	0	0
48	16.90	0	45	0.77	6.0	0
49	67.50	1	110	1.47	6.5	0
50	31.70	0	180	3.27	8.0	0
51	26.80	0	60	1.50	6.0	0
52	63.40	0	100	1.61	0	0
53	48.70	0	130	2.33	0	0
54	60.20	0	90	1.14	0	0
55	52.10	0	140	2.06	0	0
56	52.80	0	85	1.70	0	0
57	59.60	0	80	1.31	0	0
58	52.20	0	110	1.99	0	0
59	48.00	0	210	2.74	8.0	0
60	76.70	1	220	3.38	14.5	0
61	81.80	0	110	1.71	0	0
62	91.50	1	120	1.71	6.5	0
63	68.60	1	100	1.96	6.5	0
64	54.10	0	80	1.33	0	0

ID	CrCl (ml/min)	CHF	Volume of contrast (ml)	V/BW ratio	Risk score	CIN development
65	33.50	1	150	2.42	6.5	0
66	60.40	0	90	1.41	0	0
67	57.40	0	210	4.06	8.0	0
68	47.20	0	110	1.36	0	0
69	79.70	0	130	2.17	0	0
70	47.70	1	130	2.36	6.5	1
71	52.30	0	90	1.44	0	0
72	52.70	1	140	1.75	6.5	0
73	68.60	1	130	2.60	14.5	1
74	63.10	0	70	1.05	0	0
75	63.20	0	160	2.76	8.0	0
76	97.00	0	240	3.00	8.0	0
77	53.60	0	130	1.85	0	0
78	83.20	0	100	1.85	0	0
79	120.60	0	80	1.14	0	0
80	63.80	0	50	0.67	0	0
81	60.90	0	240	3.37	8.0	0
82	61.30	0	110	1.57	0	0
83	64.60	0	90	1.50	0	0
84	81.90	0	280	3.73	8.0	0
85	44.50	0	110	2.75	8.0	0
86	62.80	0	60	0.75	0	0
87	80.60	0	90	1.13	0	0
88	103.00	0	140	2.11	0	0
89	75.20	0	100	1.51	0	0
90	96.80	0	80	1.29	0	0
91	33.00	0	270	6.75	8.0	1
92	34.00	0	140	1.48	0	0
93	36.30	1	140	2.92	14.5	1
94	88.70	0	180	3.16	8.0	0
95	50.90	1	210	2.84	14.5	0
96	22.00	0	95	2.35	6.0	0

ID	CrCl (ml/min)	CHF	Volume of contrast (ml)	V/BW ratio	Risk score	CIN development
97	57.20	0	90	1.74	0	0
98	43.00	0	80	1.17	0	0
99	20.60	1	40	0.56	12.5	1
100	53.50	1	120	1.56	6.5	0
101	84.10	0	150	1.85	0	0
102	45.10	0	50	1.03	0	0
103	77.50	0	70	1.13	0	0
104	40.90	0	180	2.38	0	0
105	35.80	0	50	1.00	0	0
106	84.20	0	80	1.33	0	0
107	79.80	0	60	0.86	0	0
108	26.70	0	90	1.90	6.0	0
109	101.80	0	90	1.12	0	0
110	69.10	0	180	2.56	0	0
111	95.10	0	85	0.95	0	0
112	56.10	0	100	1.49	0	0
113	41.50	0	80	1.21	0	0
114	50.60	0	150	2.22	0	0
115	72.40	0	70	0.86	0	0
116	74.40	0	150	1.78	0	0
117	71.80	0	80	1.00	0	0
118	44.70	0	130	2.16	0	0
119	80.00	0	165	2.12	0	0
120	75.20	0	70	1.08	0	0
121	23.20	0	220	4.78	14.0	0
122	67.40	0	80	1.36	0	0
123	51.00	0	80	1.10	0	0
124	57.00	0	120	2.36	0	0
125	67.80	0	200	3.38	8.0	0
126	67.80	1	125	2.08	6.5	0
127	39.10	0	110	1.57	0	0
128	76.90	0	140	1.78	0	0

ID	CrCl (ml/min)	CHF	Volume of contrast (ml)	V/BW ratio	Risk score	CIN development
129	68.60	0	100	1.14	0	0
130	78.60	0	70	0.94	0	0
131	47.00	0	140	1.65	0	0
132	13.70	0	80	1.78	6.0	1
133	72.00	0	90	1.29	0	0
134	26.90	0	180	4.07	14.0	0
135	43.10	0	170	2.97	8.0	1
136	61.10	0	80	1.45	0	0
137	40.20	0	140	2.25	0	0
138	106.80	0	80	1.27	0	0
139	46.80	1	60	.92	6.5	0
140	29.80	0	300	6.67	14.0	1
141	82.10	0	60	1.12	0	0
142	65.00	0	85	1.43	0	0
143	76.60	0	90	1.20	0	0
144	39.00	1	160	4.00	14.5	0
145	106.80	0	80	1.27	0	0
146	70.30	0	170	2.31	0	0
147	79.40	0	300	5.00	8.0	0
148	68.80	0	70	1.17	0	0
149	71.30	0	90	1.23	0	0
150	81.70	0	430	5.91	8.0	0
151	48.60	0	50	0.77	0	0
152	86.30	0	175	3.13	8.0	0
153	71.90	0	120	1.92	0	0
154	62.40	0	170	2.05	0	0
155	31.20	0	140	2.26	0	0
156	98.00	0	170	1.86	0	0
157	112.00	0	80	N/A	0	0
158	6.10	1	150	4.29	20.5	1
159	95.30	0	120	1.72	0	0
160	27.10	0	110	1.94	6.0	0

ID	CrCl (ml/min)	CHF	Volume of contrast (ml)	V/BW ratio	Risk score	CIN development
161	95.90	0	120	1.85	0	0
162	91.60	0	180	2.28	0	0
163	17.90	0	50	0.93	6.0	0
164	75.30	0	85	1.21	0	0
165	60.90	0	140	2.55	0	0
166	61.80	0	100	1.89	0	0
167	48.90	0	190	3.66	8.0	0
168	64.90	0	110	1.49	0	0
169	46.40	0	110	1.55	0	0
170	26.80	0	70	1.56	6.0	0
171	22.00	0	140	2.17	6.0	0
172	20.60	1	120	2.00	12.5	0
173	60.30	0	80	1.78	0	0
174	86.00	1	160	2.29	6.5	0
175	66.10	0	120	2.11	0	0
176	64.90	0	200	3.00	8.0	0
177	29.40	0	200	2.84	14.0	0
178	82.20	0	320	4.92	8.0	0
179	63.40	0	140	1.86	0	0
180	12.60	1	95	2.57	12.5	0
181	44.90	1	90	1.31	6.5	0

VITAE

Miss Tasigan Chaemchoi was born on the 4th of July in 1980 at Udonthani. She graduated from The Faculty of Pharmaceutical Sciences, Chulalongkorn University in 2002. She has been working as hospital pharmacist at King Chulalongkorn Memorial Hospital since 2002 until present. She had joined in a study program for the Degree of Master of Science in Pharmacy Program in Clinical Pharmacy, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University since 2008.