# VALIDATION OF THE MEHRAN RISK SCORING TOOL TO PREDICT RISK FOR CONTRAST INDUCED NEPHROPATHY IN THAI PATIENTS UNDERGOING CARDIAC CATHETERIZATION OR PERCUTANEOUS CORONARY INTERVENTION

**CAPT. PARICHART JAIMOON**

**A THESIS SUBMITTED IN PARTIAL FULFILLMENT**
**OF THE REQUIREMENTS FOR**
**THE DEGREE OF MASTER OF SCIENCE**
**(EPIDEMIOLOGY)**
**FACULTY OF GRADUATE STUDIES**
**MAHIDOL UNIVERSITY**
**2013**

Thesis
entitled

# VALIDATION OF THE MEHRAN RISK SCORING TOOL TO PREDICT RISK FOR CONTRAST INDUCED NEPHROPATHY IN THAI PATIENTS UNDERGOING CARDIAC CATHETERIZATION OR PERCUTANEOUS CORONARY INTERVENTION

.....Parichart.....Jaimoon...
Capt. Parichart Jaimoon
Candidate

.....
Asst. Prof. Kamol Udol,
M.D., M.Sc.(Clinical Epidemiology)
Major advisor

.....
Assoc. Prof. Chumpol Piamsomboon,
M.D., Interventional Cardiology
Co-advisor

.....
Lect. Sukhontha Siri, Ph.D.
(Tropical Medicine)
Co-advisor

.....
Prof. Banchong Mahaisavariya
M.D., Dip Thai Board of Orthopedics
Dean
Faculty of Graduate Studies
Mahidol University

.....
Prof. Prasert Assantachai,
M.D., F.R.C.P. (London)
Program Director
Doctor of Science Program in
Epidemiology
Faculty of Medicine, Siriraj Hospital
Mahidol University

Thesis
entitled

# VALIDATION OF THE MEHRAN RISK SCORING TOOL TO PREDICT RISK FOR CONTRAST INDUCED NEPHROPATHY IN THAI PATIENTS UNDERGOING CARDIAC CATHETERIZATION OR PERCUTANEOUS CORONARY INTERVENTION

was submitted to the Faculty of Graduate Studies, Mahidol University
for the degree of Master of Science (Epidemiology)
on
April 1, 2013

.....Parichart...Jaimoon.....
Capt. Parichart Jaimoon
Candidate

.....
Assoc. Prof. Dilok Piyayotai, Ph.D.
M.D., Thai Board of International Medicine
Chair

.....
Asst. Prof. Kamol Udol,
M.D., M.Sc. (Clinical Epidemiology)
Member

.....
Lect. Sukhontha Siri, Ph.D.
(Tropical Medicine)
Member

.....
Assoc. Prof. Chumpol Piamsomboon,
M.D., Interventional Cardiology
Member

.....
Prof. Banchong Mahaisavariya,
M.D., Dip Thai Board of Orthopedics
Dean
Faculty of Graduate Studies
Mahidol University

.....
Clinical Prof. Udom Kachintorn,
Dean
Faculty of Medicine, Siriraj Hospital
Mahidol University

# ACKNOWLEDGEMENTS

My thesis had been accomplished by collaboration of many distinguished persons. First, I would like to express my sincere gratitude to my major adviser, Assist. Prof. Kamol Udol, M.D. from Department of Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, for his valuable advice, continual guidance, constructive criticism and encouragement throughout this course of the study until this thesis is completed.

To Assoc. Prof. Chumpol Piamsomboon, M.D. from Division of Cardiology, Phramongkutklao Hospital and Dr. Sukhontha Siri, Lect. from Department of Epidemiology, Faculty of Public Health, Mahidol University, my co-advisors, they devoted helpful suggestions for this thesis until success.

I am also grateful to all staffs at Catheterization Laboratory, Coronary Care Unit (CCU), wards of Somdejya 90 Building and Chalermprakeat 80 years Building, Phramongkutklao Hospital for their help and cooperation to data collection and the Sirindhron Cardiac center which gave me the best chance for continuing education and granting financial support to fulfill this study. I hold in the highest regard, thank you.

I wish to thank all study patients for their cooperation in collecting data.

Finally, I would like to express my deeply grateful to my family for their understanding, support and encouragement, this is my inspiration to the graduate study.

Capt. Parichart Jaimoon

VALIDATION OF THE MEHRAN RISK SCORING TOOL TO PREDICT RISK FOR CONTRAST INDUCED NEPHROPATHY IN THAI PATIENTS UNDERGOING CARDIAC CATHETERIZATION OR PERCUTANEOUS CORONARY INTERVENTION

CAPT. PARICHART JAIMOON 5336600 SIEP/M

M.Sc. (EPIDEMIOLOGY)

THESIS ADVISORY COMMITTEE : KAMOL UDOL, M.D., M.Sc. (CLINICAL EPIDEMIOLOGY), CHUMPOL PIAMSOMBOON, M.D., INTERVENTIONAL CARDIOLOGY, SUKHONTHA SIRI, Ph.D. (TROPICAL MEDICINE)

ABSTRACT

This hospital based prospective cohort study was performed to evaluate the Mehran risk scoring tool for prediction of contrast induced nephropathy (CIN) in Thai patients undergoing cardiac catheterization with or without percutaneous coronary intervention (PCI). Two hundred patients scheduled for cardiac catheterization / PCI at Phramongkutklao Hospital were enrolled. For each patient, the Mehran risk score was calculated and the presence of CIN was confirmed with serum creatinine determined 48 – 72 hours after the procedure. Discriminatory power of the Mehran risk score was evaluated using receiver-operating characteristic (ROC) curve and *c*-statistics.

The overall incidence of CIN was 6.5%. There was a positive correlation between the incidence of CIN and the Mehran risk score. ROC curve analysis demonstrated that the C-statistic of the Mehran risk score was 0.86 (95% CI 0.78 to 0.94) for prediction of CIN.

In conclusion, the Mehran risk score has a good discriminatory power to predict CIN in Thai patients undergoing cardiac catheterization with or without PCI.

KEY WORDS: MEHRAN RISK SCORING TOOL / CONTRAST INDUCED NEPHROPATHY / CARDIAC CATHETERIZATION OR PERCUTANEOUS CORONARY INTERVENTION

79 pages

การศึกษาแบบประเมินคะแนนความเสี่ยงของ Mehran ต่อการเกิดภาวะไตทำงานบกพร่องเนื่องจากสารทึบรังสีในผู้ป่วยคนไทยที่เข้ารับการตรวจรักษาหลอดเลือดหัวใจผ่านสายสวน

VALIDATION OF THE MEHRAN RISK SCORING TOOL TO PREDICT RISK FOR CONTRAST INDUCED NEPHROPATHY IN THAI PATIENTS UNDERGOING CARDIAC CATHETERIZATION OR PERCUTANEOUS CORONARY INTERVENTION

ร้อยเอกหญิง ปาริชาติ ใจมูล 5336600 SIEP/M

วท.ม. (วิทยาการระบาด)

คณะกรรมการที่ปรึกษาวิทยานิพนธ์: กมล อุดล, พ.บ., M.Sc. (CLINICAL EPIDEMIOLOGY), ชุมพล เปี่ยมสมบูรณ์, พ.บ., Interventional Cardiology, สุคนธา ศิริ, Ph.D. (TROPICAL MEDICINE)

บทคัดย่อ

การศึกษานี้เป็นแบบ hospital-based prospective cohort study มีวัตถุประสงค์หลักเพื่อศึกษาความสามารถในการทำนายการเกิดภาวะไตทำงานบกพร่องเนื่องจากสารทึบรังสีโดยใช้แบบประเมินคะแนนความเสี่ยงของ Mehran ในผู้ป่วยที่เข้ารับการตรวจรักษาหลอดเลือดหัวใจผ่านสายสวนจำนวน 200 รายในโรงพยาบาลพระมงกุฎเกล้า ผู้ป่วยได้รับการประเมินความเสี่ยงต่อการเกิดภาวะไตทำงานบกพร่องเนื่องจากสารทึบรังสีโดยแบบประเมินความเสี่ยงของ Mehran และได้รับการตรวจ serum creatinine ภายใน 48 – 72 ชั่วโมงหลังการทำหัตถการ วิเคราะห์ความสามารถของแบบประเมินความเสี่ยงของ Mehran ในการทำนายการเกิดภาวะไตทำงานบกพร่องเนื่องจากสารทึบรังสีโดยการวิเคราะห์ ROC curve และ *c*-statistics

ผลการศึกษาพบอุบัติการณ์ของภาวะไตทำงานบกพร่องเนื่องจากสารทึบรังสีเท่ากับ 6.5% อุบัติการณ์เพิ่มขึ้นตามคะแนนความเสี่ยงของ Mehran ที่เพิ่มขึ้น ค่า *c*-statistics ของแบบประเมินความเสี่ยงของ Mehran ในการทำนายการเกิดภาวะไตทำงานบกพร่องเนื่องจากสารทึบรังสีเท่ากับ 0.86 (95% CI 0.78 to 0.94)

จากผลการศึกษาสรุปได้ว่าแบบประเมินความเสี่ยงของ Mehran สามารถใช้ทำนายการเกิดภาวะไตทำงานบกพร่องเนื่องจากสารทึบรังสีในผู้ป่วยที่ได้รับการตรวจรักษาหลอดเลือดหัวใจผ่านสายสวนได้ดี

79 หน้า

# CONTENTS

# CONTENTS (cont.)

# LIST OF TABLES

# LIST OF TABLES (cont.)

# LIST OF FIGURES

# LIST OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| CIN | contrast induced nephropathy |
| PCI | percutaneous coronary intervention |
| CrCl | creatinine clearance |
| CHF | congestive heart failure |
| CKD | chronic kidney disease |
| DM | diabetes mellitus |
| MI | myocardial infarction |
| HOCM | high-osmolar contrast media |
| LOCM | low-osmolar contrast media |
| IOCM | iso-osmolar contrast media |
| mOsm/kg | milliosmoles/kilogram |
| IABP | intra-aortic ballon pump |
| C-statistic | concordance statistics |
| ROC analysis | receiver operating characteristics analysis |
| BMI | body mass index |
| mg/dl | milligrams/deciliter |
| μmol/L | micromoles/liter |
| CT | computer tomography |
| MRI | magnetic resonance imaging |
| NAC | N-Acetylcysteine |

# CHAPTER I
# INTRODUCTION

## 1.1 Rationale and Background

Cardiovascular disease (CVD) remains an important cause of death in Thailand and in other countries around the world. During the last decade, CVD has been one of the three most common causes of death in Thailand as reported during the period of 2002-2009 by the National Statistical Office (1).

In addition, CVD is also well known as the leading cause of morbidity which affects the individual's ability to work, increases burden of medical expenses and eventually impacts on economy of the country (2).

Important forms of cardiovascular disease include coronary heart disease, cerebrovascular disease or stroke and peripheral vascular disease (3). They are among the common causes of hospital admission worldwide.

A variety of risk factors for coronary heart disease have been studied .The most recognized causes are age, hypertension, hyper cholesterolemia, diabetes mellitus, smoking, obesity, lack of exercise, history of CVD in close relatives, and nephropathy or albuminuria. One or more of these risk factors are present in at least two-thirds of CAD patients (4).

There is a relationship between CVD and chronic kidney disease (CKD). Some studies showed that, the prevalences of CKD in patients with coronary artery (CAD) were approximately 23% - 46%. In addition, cardiovascular disease accounts for more than half of end–stage renal disease (ESRD) deaths. Patients with CKD have a higher risk of cardiovascular events than do the general population (5-8).

Intravascular contrast media is administered worldwide, making it one of the most commonly prescribed medications in the history of modern medicine (9). Radiologic procedures utilizing intravascular contrast media include computer tomography (CT), intravenous pyelography and angiography/venography (9), the

latter being widely applied for both diagnostic and therapeutic purposes (10). The objective of using contrast media is to create an x–ray attenuation differential in tissues in order to increase the visualization of disease processes (9).

The procedure utilizing contrast media that is commonly performed in CVD patients is cardiac catheterization. During the procedure, a catheter is inserted into the femoral or radial artery and is advanced into the selected coronary arteries or cardiac chamber. Radiocontrast media is injected to visualize the luminal anatomy of the coronary arteries or the cardiac chamber. If there is atherosclerotic plaque causing significant stenosis of the coronary arteries and the lesion are suitable, angioplasty and stenting can be performed during the same procedure (11, 12).

A significant increase in the 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, also known as contrast–induced nephropathy (CIN) (9, 10, 13). CIN is defined as an increase of $\geq$ 0.5 mg/dL or $\geq$ 25% from baseline serum creatinine within 48 hours of contrast media exposure (10, 14, 15). A rising serum creatinine level begins within 24 hours after receiving contrast media, usually peaks within 3-5 days and returns to baseline level within 10–14 days(15). The exact mechanisms of CIN have yet to be clarified, however, the suggestion of evidence that a combination of renal ischemia and direct toxic effects on tubular epithelial cells are likely to play a pathogenic role (16).

CIN is associated with increased risk of mortality. The mortality rates after development of CIN were 12.1% at 1 year and 44.6% at 5 years, which were higher compared to the rates of 3.7% and 14.5%, respectively, in the patients who did not develop CIN ($p < 0.001$) (14, 17).

The majority of patients undergoing cardiac catheterization or percutaneous coronary intervention can be discharged within 24 hours after the procedure (18). However, patients who develop CIN usually require longer stay in the hospital. Patients who developed CIN after exposure to contrast media not only have higher complication rates which could result in longer hospital stay, but also have higher mortality rate when compared with patients who did not developed CIN (14, 19-22). Moreover,0.3% – 0.7% of patients who progressed to acute renal failure (ARF) required dialysis(13).

The development of CIN could affect the length of hospital stay. In patients without previous chronic kidney disease (CKD), the length of hospital stay of those who developed CIN was 3.6±5.1 days, which was longer than that of patients who did not develop CIN (1.8±2.4 day) (23). Furthermore, CIN could affect mental health of the patients and their family (24).

Even though, the incidence of CIN is low (0.6% – 2.3%) in general population, it is significantly higher in selected patient subsets (up to 20% or more) especially in patients with cardiovascular pathology undergoing coronary angiography and percutaneous coronary intervention (PCI) (13, 18). Once CIN is established, only supportive care is currently provided until renal function resolves, infrequently, hemodialysis may be required, either transiently or even permanently(10). Thus, the prevention is presently the main method to reduce the effect of this complication (10).

At present, only administration of intravenous isotonic fluid and avoidance of nephrotoxic drugs are widely used to decrease the incidence of CIN (15). However, some studies have shown that additional interventions may be effective to reduce the risk of CIN, such as minimizing the dose of contrast media, using low–osmolar or iso–osmolar contrast media and avoiding short interval between procedures requiring contrast media (25-27). The benefit of N–acetylcysteine (NAC) in reducing the risk of CIN is still controversial. However, findings of several trials suggest that this agent could decrease the incidence of CIN and the use of NAC has become common at many institutions (28).

Several assessment models have been developed to predict the risk of CIN after the procedures that utilize radiocontrast media. The general reason for using these assessment models of CIN development is to allow radiologists and clinicians alike to increase awareness and identification of CIN (15) and to provide appropriate interventions to prevent its development.

The Mehran risk scoring tool is one of these assessment models (10). It was developed by Roxana Mehran et al in 2004. This tool is interesting not only because it is available in graphic form, making the tool easy for clinicians to use, but also because it is the most comprehensive tool that has been well-tested (29). However, 2 previous studies validating the Mehran risk scoring tool presented different results. In 2010, Aguiar-Souto et al reported that the Mehran risk scoring

tool could not predict the development of CIN after percutaneous coronary interventionin 227 patients (30). In contrast, Raingruber B et al reported in 2011 that serum creatinine levels after PCI were correlated with Mehran risk scores (29). There has never been any study using the Mehran risk scoring tool in Thai patients before. This study aims to determine the validity of the Mehran risk scoring tool for prediction of CIN in Thai patients undergoing cardiac catheterization or percutaneous coronary intervention.

## 1.2 Objectives

**General objective**

To determine the validity of the Mehran risk scoring tool for prediction of contrast induced nephropathy in Thai patients undergoing cardiac catheterization or percutaneous coronary intervention.

**Specific objective**

To determine the incidence of contrast induced nephropathy in Thai patients undergoing cardiac catheterization or percutaneous coronary intervention according to different levels of Mehran risk scores.

## 1.3 Scope of research

This study was a prospective cohort study of Thai patients undergoing either elective percutaneous coronary intervention or, elective cardiac catheterization at Phramongkutklao Hospital.

## 1.4 Operational definitions

1. Contrast media was defined as intravascular iodinated contrast media.

2. Cardiac catheterization was defined as a diagnostic procedure in which a catheter is inserted through a peripheral blood vessel (femoral or radial artery) and advanced to the heart with x-ray guidance. Contrast media is injected to visualize the luminal anatomy of major coronary arteries and their branches (12).

Percutaneous coronary intervention was defined as the management of coronary artery stenosis or occlusion by any of various catheter-based techniques, such as percutaneous transluminal coronary angioplasty, atherectomy, angioplasty using the excimer laser, and implantation of coronary stents and related devices (12).

2.1) Elective cardiac catheterization or PCI was defined as a planned cardiac catheterization or PCI.

2.2) Urgent cardiac catheterization or PCI was defined as cardiac catheterization or PCI that had to be performed shortly after the presentation of patients.

2.3) Emergency cardiac catheterization or PCI was defined as cardiac catheterization or PCI that had to immediately performed in the emergency circumstance, usually with the aim to open an occluded coronary artery.

3. CIN was defined as an increase of $\geq$ 25% or $\geq$ 0.5mg/dL in pre-procedural serum level of creatinine within 48 hours after the procedure (10).

4. The Mehran risk scoring tool was defined as a predictive risk score for the development of CIN, as developed by Mehran et al (10).

5. Hypotension was defined as blood pressure < 90/50 mmHg and requiring inotropic drug for hemodynamic support (31).

6. Congestive heart failure (CHF) was defined as physician diagnosed CHF. The severity of CHF is classified by New York Heart Association Classification (32, 33) (Table 1.1).

**Table 1.1** The classification of Congestive heart failure (CHF) by New York Heart Association Classification (32, 33).

| Class | Patient Symptoms |
|---|---|
| Class I (Mild) | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath). |
| Class II (Mild) | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea. |
| Class III (Moderate) | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. |
| Class IV (Severe) | Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased. |

7. Pulmonary edema was defined as physician diagnosed pulmonary edema.

8. Anemia was defined, based on the World Health Organization criteria, as a hematocrit value < 39% for men and < 36% for women (10).

9. Diabetes mellitus (DM) was defined as hyperglycemia (fasting plasma glucose > 126 mg/dL), usually requiring treatment by insulin and/or oral hypoglycemic drugs (34).

10. Chronic kidney disease (CKD) was defined as glomerular filtration rate or GFR < 60 mL/min/1.73m$^2$, which persisted more than 3 months (35).

11. Serum creatinine was defined as laboratory value measuring the impairment of renal function before the procedure and within 48 hours after the procedure. The normal serum creatinine value is 0.6-1.2mg/dL for men and 0.5-1.1 mg/dL for women (36).

# CHAPTER II
# LITERATURE REVIEW

This study aims to determine the validity of the Mehran risk scoring tool in predicting the development of CIN. The following topics related to the study are reviewed in this chapter.

## 2.1 Contrast media

The agent which increases the radio-opacity of the interested area, thereby making it more contrast with the surrounding tissues, is called contrast media. Iodinated contrast media has been commonly used in various diagnostic and therapeutic procedures in medicine. Percutaneous diagnostic and therapeutic cardiovascular procedures such as cardiac catheterization and PCI depend enormously on using intravascular iodinated contrast agents to increase visualization of coronary and cardiac anatomy in the cardiac catheterization laboratory (37).

### 2.1.1 Pharmacology

Iodinated contrast media consists of iodine atoms, which are radiopaque, attached to carbon based molecules, which are water soluble (17). The plasma concentration of iodinated contrast media peaks in a few seconds after injection, and 70% of the injected dose diffuses from plasma into extracellular space within 2-5 minutes. However, diffusion into highly perfused organs such as the brain, heart, lungs and liver may be faster whereas diffusion into the extracellular space is slower in skin, fat and skeletal muscle. For patients with normal renal function, the contrast media is rapidly eliminated by glomerular fitration over 90% within 12 hours. Nevertheless, the excretion by kidneys of patients with renal impairment can last for several weeks (9, 38, 39).

2.1.1.1 Classification

Various characteristics can be used to classify contrast media into categories. An important characteristics classifies contrast media into ionic and non-ionic contrast media. The difference between the two are demonstrated in Table 2.1

**Table 2.1** The difference between ionic and non-ionic contrast media (11)

| **Contrast media** | |
|---|---|
| **Ionic contrast media** | **Non-ionic contrast media** |
| 1. Molecules are disintegrated into ions in the body | 1. Molecules are intact in the body |
| 2. High viscosity | 2. Low viscosity |
| 3. Increase osmolarity | 3. Low effect on osmolarity |
| 4. High risk of side effects, some may be serious | 4. Low risk of side effects |
| 5. Cannot be used in persons allergic to seafood | 5. Can be used in persons allergic to seafood |
| 6. Less expensive | 6. More expensive |

Although non-ionic contrast media has low or even no side effects compared to ionic contrast media, it is more expensive. However, both are comparable in terms of cost-effectiveness when the disadvantages of ionic contrast media, such as risk of CIN or other complications, prolonged hospitalization, and increased treatment costs, are taken into consideration. Therefore, the choice of one agent over the other usually depends on individual's preference and economic status (11).

Another system of contrast media categorization classifies contrast media according to its osmolality, which reflects the number of molecules dissolved in a specific amount of fluid. This system of classification is commonly used in clinical practice. Contrast media is classified into 3 categories (9, 17, 38-40). (Table 2.2.)

2.1.1.2 High–osmolar contrast media (HOCM)

This group of contrast media has a range of osmolality between 1500 and 1800 milliosmoles/kilogram (mOsm/kg), whereas the osmolality of human plasma is 290 mOsm/kg. It is generally acknowledged that the osmolality of HOCM is a major contributor to their adverse effects and reducing in osmolality is desirable. The HOCM include diatrizoate, iothalamate and loxithalamate.

2.1.1.3 Low–osmolar contrast media (LOCM)

The range of osmolality in this group is 600-700 mOsm/kg, which is still more than twice that of plasma. The two types of LOCM include non-ionic monomers and ionic dimers. The non-ionic monomers LOCM are the contrast media of choice in most situations because by they are potentially less toxic. The common non-ionic monomers include iohexol, iopromide, iopamidol and ioversol.

2.1.1.4 Iso–osmolar contrast media (IOCM)

The osmolality of IOCM is equal to that of plasma. Iodixanol is the only agent in this class available for intravascular use.

**Table 2.2** Classification of contrast media in clinical practice (41)

| Type | Generic Name | Osmolality (mOsm/kg) |
|---|---|---|
| First-generation: HOCM[a] ionic monomers | Sodium iothalamate Meglumine diatrizoate | ~1,500-1,800 |
| Second-generation: LOCM[b] ionic dimer | Sodium ioxaglate Meglumine ioxaglate | ~600-900 |
| Non-ionic monomer | Iopamidol, iohexol, ioversol, iopromide | |
| Newer agents: IOCM[c] Non-ionic dimer | Iotrolan, iodixanol | ~290 |

*a = high-osmolar contrast media; b = low-osmolar contrast media; c = iso-osmolar contrast media*

## 2.2 Cardiac Catheterization or Percutaneous Coronary Intervention

2.2.1 Definition

Cardiac catheterization is defined as a diagnostic procedure in which a comprehensive examination of the heart and coronary arteries is performed. One or more catheters are inserted through femoral or radial artery and advanced to the heart under x-ray guidance. Anatomy of cardiac chambers and coronary arteries is delineated using contrast media injection. Hemodynamic information and collection of blood sample can also be obtained if required (12).

Percutaneous coronary intervention was defined as the management of coronary artery stenosis or occlusion by any of various catheter-based techniques, such as percutaneous transluminal coronary angioplasty, atherectomy, angioplasty using the excimer laser, and implantation of coronary stents and related devices (12).

2.2.2 Timing of cardiac catheterization or percutaneous coronary intervention

The procedures can be classified according to the elapsed time allowed to perform the procedure after the decision is made.

2.2.2.1 Elective procedure: The procedure can be delayed, usually for more than 24 hours, until a prespecified date and time. Patients are usually in a stable condition, without immediate risk of life-threatening events.

2.2.2.2 Urgent procedure: The procedure has to be performed within 24 hours of presentation, or immediately during the observation period if the patients develop worsening clinical situations such as

a) sudden chest pain
b) chest pain at rest
c) congestive heart failure
d) acute myocardial infarction (MI) failed with thrombolytic therapy
e) unstable angina not responding to medical treatment

2.2.2.3 Emergent procedure: The procedure has to be performed immediately at the presentation, usually in order to open the occluded coronary artery in ST elevation myocardial infarction or in cardiogenic shock.

## 2.3 Contrast-Induced Nephropathy

### 2.3.1 Definition

The most general definition of contrast-induced nephropathy (CIN) is acute renal failure occurring within 48 hours of exposure to intravascular idionated contrast media that is not attributable to other causes. Ideally, the impairment of renal function should be measured by serial creatinine clearance. However, as this measurement is neither practical nor cost-effective in clinical practice, most literature describes the use of serum creatinine levels to define CIN. This parameter may be less sensitive at reflecting subtle early changes in renal function and may be slower to reach maximal sensitivity than creatinine clearance. However, serum creatinine levels may prove to be more sensitive in patients with preexisting renal impairment. Practically, contrast–induced nephropathy has been generally defined as a 25% increase in serum creatinine concentration from the baseline value, or an absolute increase of at least 0.5 mg/dL (44.2 μmole/L), which appears within 48 hours after the administration of intravascular idionated contrast media, and is usually maintained for 2-5 days (15).

### 2.3.2 Incidence of contrast-induced nephropathy

The overall incidence of CIN in the general population varies within the range of 0.6-2.3% (13). However, in specific groups of patients, the incidence can be significantly higher (13). It can increase to 20% or more in patients with cardiovascular disease undergoing cardiac catheterization and percutaneous coronary intervention (13).

### 2.3.3 Pathophysiology of contrast-induced nephropathy (15, 16, 20)

The exact mechanisms of contrast-induced nephropathy have not been fully elucidated. Existing evidence suggests the combination of increased vasoconstrictive forces and decreased local prostaglandin and nitric oxide (NO) mediated vasodilatation as the potential mechanisms. First, a direct toxic effect on proximal renal tubular cells in the renal cortex have been demonstrated. Following exposure to contrast media, there is enhanced production of oxygen free radicals and lipid peroxidation of biological membranes, resulting in increased oxygen consumption, increased intratubular pressure secondary to contrast-induced diuresis, increased urinary viscosity and tubular obstruction and destruction. Second, an immediate vasoconstriction results from alterations of various intrarenal mediators, e.g. increasing activities of vasoconstrictors such as adenosine, vasopressin, angiotension II, dopamine-1, and endothelin, and decreasing activities of vasodilators such as nitric oxide and prostaglandins. These changes cause reduction in renal blood flow to outer medulla after contrast media exposure, which consequently leads to medullary hypoxia, ischemic injury and death of renal tubular cells. In addtition, contrast media may cause some degree of hemolysis, which indirectly further reduces renal blood flow.

The pathophysiologic mechanisms of CIN are demonstrated in Figure 2.1.

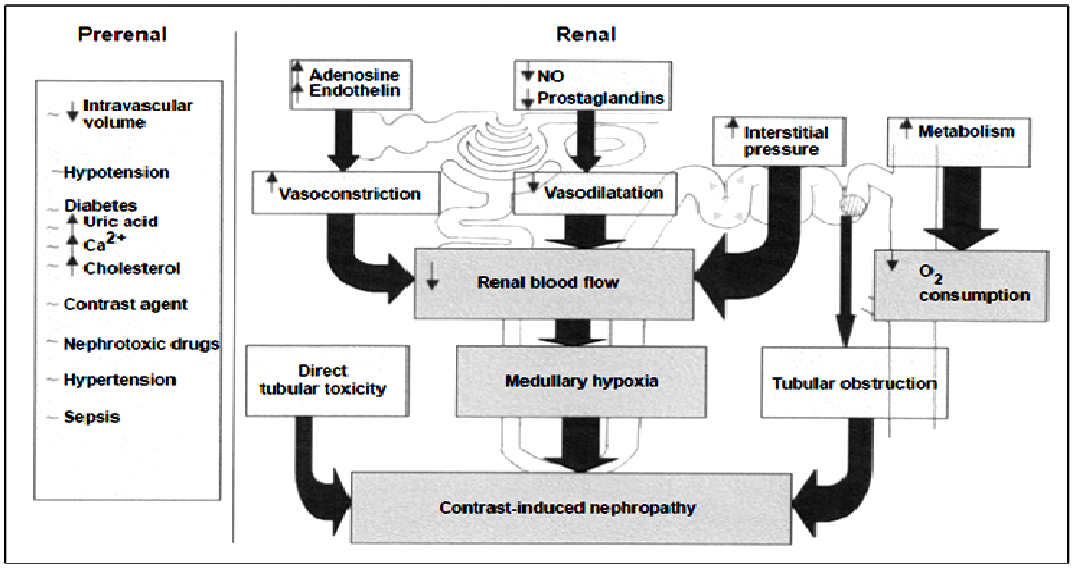


**Figure 2.1** Diagram showing proposed pathophysiologic mechanisms of CIN (15)

### 2.3.4 Burden of contrast-induced nephropathy

#### 2.3.4.1 Requirement for dialysis

Most cases of CIN experience only mild transient impairment of renal function. Only a small proportion of patients require dialysis for CIN. The dialysis rates after CIN varies according to patients' underlying risks at the time of contrast agent administration, but it is less than 1% in general population (17, 19, 42). Although contrast-induced nephropathy requiring dialysis is relatively rare, the impact on patient prognosis is considerable (17). The in-hospital mortality rate of patients undergoing coronary intervention who developed CIN requiring dialysis was 35.7%, which was higher than the 7.1% rate of patients who developed CIN but not requiring dialysis (19). By 2 years, the mortality rate in patients who required dialysis was 81.2% (19).

#### 2.3.4.2 Increased risk of death

The risk of death is increased in patients who develop CIN. In a large retrospective study of approximately 16,000 hospitalized patients undergoing procedures requiring contrast media, the risk of death during hospitalization was 34% in patients who developed CIN compared with 7% in patients who had received

contrast media but did not develop CIN. Even after adjusting for comorbid diseases, patients with CIN had a 5.5 fold increased risk of death (43). In the interventional cardiology registry from Mayo Clinic including 7,586 patients, 3.3% of patients developed CIN after exposure to contrast media. The in-hospital mortality rate was 22% in patients developing CIN compared with only 1.4% in patients who did not develop CIN (14). The mortality rates at 1 and 5 years after the development of CIN was 12.1% and 44.6% respectively, which were higher compared to the rates of 3.7% and 14.5%, respectively, in patients who did not develop CIN ($p < 0.001$), indicating that the increased risk of death persisted in the long term (14, 17).

2.3.4.3 Increased adverse outcomes

Contrast-induced nephropathy is associated with other adverse outcomes, including late cardiovascular events after cardiac catheterization. Although CIN occurred in only 2% in a large registry of 20,479 patients undergoing PCI, CIN was associated with a 15-fold increase in major adverse cardiac events, regardless of the need for hemodialysis. The development of CIN was also associated with a 5.5-fold increase in myocardial infarction (MI), an 11-fold increase in target vessel revascularization, and a 22-fold increase in mortality rate (44)

2.3.4.4 Increased hospital stay

Many studies have documented the association between the development of CIN and increased hospital stay. The post-procedure hospital stay was longer in patients who developed CIN, regardless of baseline renal function (6.8±7.1 days vs. 2.3±2.5 days in patients with prior CKD and 3.6±5.1days vs. 1.8±2.4 days in patients without prior CKD) (23).

2.3.4.5 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 driver of the increased costs associated with CIN was the cost of the longer initial hospital stay (45).

## 2.4 Risk factors

Identification of patients at high risk for the development of CIN is of major importance (13). Although, several factors have been reported to be associated with contrast-induced nephropathy, few have been proven to be independent risk factors (46). The specific factors which increase the risk of developing CIN are related to patient characteristics, contrast media and the procedure (47, 48).

### 2.4.1 Pre-existing impairment of renal function

Contrast media are excreted mainly by glomerular fitration. The half-life of 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 (47). Pre-existing impairment of renal function appears to be the most important risk factor for CIN (49). The incidence of CIN in patients with underlying chronic kidney disease is extremely high, ranging from 14.8% to 55% (13, 14, 19). In one study, a half of patients with a creatinine level of 176 μmol/L (2 mg/dL) or higher had a deterioration in renal function (50). Similarly, in two other studies of a population with a baseline serum creatinine concentration averaging 2.5 mg/dL (221 μmol/L), contrast-induced nephropathy occurred in 30%-50% of patients (15, 51, 52). The higher the baseline creatinine value, the greater the risk of CIN (13). However, baseline creatinine is not reliable enough for identification of patients at risk for CIN, as it can vary with age, muscle mass and gender. To reliably evaluate renal function, the creatinine clearance assessment should be performed before an exposure to contrast media. However, it is not practical to measure creatinine clearance directly. It is recommended to use an estimated GFR (eGFR) of 60 mL/min as a reliable cutoff point for identifying patients at high risk for the development of CIN (13). Mehran et al reported the assessment of CIN risk based on the utilization of either serum creatinine or eGFR was fairly accurate for clinical purpose and was certainly more practical and more readily available than direct measurement of creatinine clearance (10). The relationship between baseline serum creatinine and CIN development are shown in Table 2.3.

**Table 2.3** Relationship between baseline serum creatinine and CIN development (18)

| Study | Procedure | Number of patients | CIN Definition | Baseline SCr*(mg/dL) | % CIN development |
|---|---|---|---|---|---|
| Rihal et al. 2002 (14) | PCI | 7,586 | SCr*↑ ≥ 0.5 mg/dL | < 1.1<br>2.0-2.9<br>≥ 3 | 2.4<br>22.4<br>30.6 |
| Hall KA et al. 1992 (53) | Angiographic procedure | 222 | N/A | ≤ 1.2<br>1.4-1.9<br>≥ 2.0 | 2<br>10.4<br>62 |

SCr* = serum creatinine

### 2.4.2 Diabetes mellitus

Diabetic patients represent a significant group of those undergoing contrast exposure due to high prevalence of diabetes in general population and the ability of the disease to cause a broad spectrum of cardiovascular conditions that require radiological procedures using contrast media (13). The incidence of CIN in diabetic patients varies from 5.7% to 29.4% (54, 55). Particularly, diabetic patients with CKD constitute the group at highest risk of developing CIN (13, 20, 47). It is not yet clear whether the risk of CIN is increased or not in patients with diabetes mellitus and normal renal function (13, 20). In diabetic patients with preserved renal function and the absence of other risk factors, the rates of CIN are usually comparable to those of a non-diabetic population (54), while clinically important CIN usually occurs in a subset of diabetics with underlying renal insufficiency (55, 56). In one study, it was found that CIN occurred in 27% of diabetic patients with baseline serum creatinine 2.0-4.0 mg/dl and in 81% of those with serum creatinine > 4.0 mg/dL (57). In another study, CIN occurred in 15.1% of diabetic patients with preserved renal function (serum creatinine < 1.5 mg/dl or eGFR > 60 mL/min) compared with 27.4% in those with

chronic kidney disease ($p < 0.0001$) and dialysis was instituted in 0.1% and 3.1%, respectively ($p < 0.0001$) (55).

### 2.4.3 Age

The evidence that older age is one of the risk predictors of CIN was provided from many studies. Marenzi et al reported that age > 75 years was significantly associated with the risk of development of CIN in patients with acute myocardial infarction undergoing emergency PCI (OR 5.28, 95% CI 1.98 to 14.05) (10).

However, the specific study explaining the reason of higher risk to develop CIN in the elderly was not available. The mechanisms may be multifactorial, including age-related changes in renal function, presence of multivessel coronary artery diseases, requirement for complex PCI, and more difficult vascular access resulting in greater amount of contrast media used (13, 18).

### 2.4.4 Type and volume of contrast media

Iso-osmolar contrast media is usually recommended as several studies have provided evidence that it was least associated with side effect, especially in patients with chronic kidney disease and diabetes mellitus (17). In addition, the evidence that volume of contrast media is a risk factor for CIN was provided in numerous studies.

However, even small volume of contrast media (~30 mL) can have adverse effects on renal function in patients at particularly high risk. As a common rule, the volume of contrast media received should not exceed twice the baseline level of eGFR in mL/min. It is also advised that in a diagnostic catheterization, the volume of contrast media should not exceed 30 mL, and if followed by PCI it should be kept below 100 mL (17).

### 2.4.5 Use of nephrotoxic drugs

Although the association between nephrotoxic drugs and the development of CIN is not clearly evident, it is common practice to withhold, if possible, potentially nephrotoxic drugs such as amphotericin B, NSAIDs, high-dose loop diuretics and other nephrotoxic agents for several days before contrast media exposure (20).

In general, these drugs can result in a 10%-25% increment of serum creatinine level from baseline. Therefore, patients taking these drugs should be closely monitored both before and after contrast media exposure (20).

It is a routine practice to withhold metformin before contrast media exposure. Although metformin is not a nephrotoxic drug, it could lead to systemic complication and death due to the development of lactic acidosis. Metformin is generally resumed when the clinician is confident that the patient has not encountered CIN (17).

### 2.4.6 Anemia

Recently, anemia or low hematocrit has been shown to be a risk factor for CIN in patients undergoing PCI. In normal physiology, the partial pressure of oxygen is very low in the outer medulla of the kidney. The combination of contrast-induced vasoconstriction and anemia might disturb the sufficient delivery of oxygen to renal medulla, resulting in medullary hypoxia (18).

In a study of 8,357 patients undergoing elective PCI, anemia, defined according to WHO criteria as hematocrit value lower than 39% for men and 36% for women, was significantly associated with the development of CIN (OR 1.83, 95% CI 1.52 to 2.20) (10, 22).

### 2.4.7 Interval between two contrast media administrations

Even in patients who have no risk factor for CIN, the interval between 2 consecutive exposures to contrast media should be at least 48 hours, to allow for elimination of contrast media by the kidney before exposure to the next dose. In patient with diabetes or preexisting renal disease the interval should be extended to at least 72 hours (47). Too short interval between 2 consecutive exposures to contrast media may cause a rise in serum creatinine and the development of CIN.

### 2.4.8 Other risk factors

Some studies have reported other risk factors for CIN, e.g. dehydration, periprocedural hypotention, and utilization of intra-aortic balloon pump (IABP) (13, 47).

In summary, CIN usually occurs in patients with underlying chronic kidney disease or preexisting renal impairment, diabetes mellitus, anemia, old age, congestive heart failure, exposure to nephrotoxic drugs, and administration of high concentration and a large amount of contrast media. These risk factors are able to predispose to the development of CIN. Not only a careful consideration of risk–benefit balance of contrast media administration is required, but also an effective screening and close monitoring is necessary, especially in patient with high risk markers (13).

## 2.5 Strategies for reducing the risk of contrast-induced nephropathy

### 2.5.1 Hydration

Volume expansion and adequate hydration is a well–established intervention to prevent CIN. Although there are limited data supporting the most appropriate intravenous fluid but in high–risk patients it is usually recommended to administer 0.9% saline solution by intravenous (IV) infusion at a rate of approximately 1 mL/kg/hour. The infusion rate could be adjusted appropriately according to the cardiovascular condition and the current fluid status of the patients (15).

This intervention should begin 6–12 hours before contrast exposure and should be continued for up to 12–24 hours after the procedure, if diuresis is appropriate. However, studies have not shown uniformly that dehydration is a definite risk factor for CIN. Iodinated contrast media increases urine volume and osmolar clearance, and its effect on the kidney is prolonged by the decrease in both renal blood flow and GFR seen in dehydration states (58).

### 2.5.2 Preventive hemodialysis or hemofiltration

Contrast media could be removed by hemodialysis after the procedure in patients with preexisting renal failure. However, there is no clinical evidence of reducing the risk of CIN and the procedure is not justified as a routine practice (15, 17).

Hemofiltration performed 6 hours before and 12–18 hours after contrast media exposure deserves consideration because of associated reduced mortality and need for hemodialysis in postprocedural period in very high risk patients (serum creatinine 3.0 to 4.0 mg/dL, eGFR 15 to 20 mL/min/1.73$m^2$ ) (59, 60).

However, this approach should be considered only in the very highest risk patients in conjunction with nephrology consultation and dialysis planning (17).

### 2.5.3 Pharmacologic strategies

There are currently no approved pharmacologic agents for the prevention of CIN. There are many agents tested in small trials which deserve further evaluation, including the antioxidants ascorbic acid and N–acetylcysteine (NAC), statins, aminophylline/theophylline and prostaglandin $E_1$ (17). Of these agents, only ascorbic acid has been tested in a multicenter, randomized, double-blind, placebo–controlled trial of 231subjects with serum creatinine ≥ 1.2 mg/dL and has been shown to reduce rates of CIN significantly. The dose of ascorbic acid (vitamin C over the counter) used in this trial was 3 g orally at least 2 hours before the procedure and 2 g in the night and the morning after the procedure (61).

Although NAC is widely used for CIN prevention, it has not been consistently shown to be effective. A meta–analysis reported that NAC reduced serum creatinine (SCr) below baseline values because of decreased skeletal muscle production rather than the reduction of rates of renal injury. Thus, NAC appears to falsely lower creatinine and does not fundamentally protect against CIN (62). 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 (63). Dosing of NAC has varied in the trials; however, the most successful approach has been with1,200 mg orally twice a day on the day before and after the procedure (17).

## 2.6 CIN risk score model

Several risk factors for the development of CIN have been reported. The combination of two or more of these risk factors is rather common in daily practice (20). A study in patients undergoing renal angiography by Cochran et al 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 osmolarity contrast media and preexisting renal disease (64).

At present, many risk score models have been developed to simplify risk prediction of CIN. All of the published models have been based on the database of cardiovascular disease patient undergoing PCI.

In 2004, Mehran et al (10) developed a simple risk score , based on 8 clinical variables, to evaluate individual patient's risk of developing CIN after PCI. These variables included:

1) Patient–related characteristics (i.e., age > 75 years, diabetes mellitus, chronic congestive heart failure or admission with acute pulmonary edema, hypotension, anemia and chronic kidney disease)

2) Procedure–related characteristics (i.e., the use of IABP, volume of contrast media)

First, a total of 8,357 patients were randomly divided into the development dataset and validation dataset in a 2:1 manner.

1) Development dataset

After the univariate analysis of association between baseline clinical and key procedural characteristics and CIN, there were 16 variables that were significantly associated with the development of CIN. (Table 2.4)

**Table 2.4** Association between baseline clinical, angiographic, and procedural characteristics and CIN after PCI (Development dataset, Univariate analysis) (10)

| Variable | Patients (%) | Incidence of CIN (%) | OR | 95% CI | P Value |
|---|---|---|---|---|---|
| Chronic kidney disease | 8.1 | 30.0 | 2.89 | 2.32-3.59 | <0.0001 |
| Congestive heart failure* | 6.0 | 38.5 | 2.68 | 2.09-3.44 | <0.0001 |
| Hypotension | 8.3 | 26.4 | 2.36 | 1.89-2.95 | <0.0001 |
| Intra-aortic balloon pump use | 3.5 | 24.9 | 2.05 | 1.47-2.87 | <0.0001 |
| Anemia | 25.8 | 21.4 | 2.02 | 1.72-2.36 | <0.0001 |
| Age > 75 yrs | 17.1 | 21.8 | 1.90 | 1.59-2.27 | <0.0001 |
| Diabetes mellitus | 30.7 | 19.2 | 1.73 | 1.48-2.02 | <0.0001 |
| Peripheral vascular disease | 18.0 | 19.6 | 1.61 | 1.35-1.93 | <0.0001 |
| Female gender | 28.8 | 18.3 | 1.54 | 1.31-1.80 | <0.0001 |
| Hypertension | 62.1 | 15.9 | 1.45 | 1.24-1.71 | <0.0001 |
| Prior stroke | 11.0 | 18.0 | 1.37 | 1.10-1.71 | 0.0007 |
| Contrast type (Ioxaglate) | 49.9 | 15.9 | 1.29 | 1.09-1.52 | 0.0006 |
| Multivessels disease | 26.5 | 16.7 | 1.20 | 1.03-1.40 | 0.003 |
| Acute coronary syndrome | 35.7 | 15.8 | 1.20 | 1.03-1.40 | 0.02 |
| Hypercholesterolemia | 69.8 | 13.2 | 0.75 | 0.64-0.88 | 0.0004 |
| Contrast amount | 80.4 | 14.6 | 1.24 | 1.01-1.54 | 0.45 |

**New York Heart Association functional classification III/IV and/or history of pulmonary edema.*

*CI = confidence interval; CIN = contrast-induced nephropathy; OR = odds ratio.*

A total of 16 variables were available by a bootstrap method for selection in the final multivariate model which was developed into two separate regression models: the first accounted for baseline serum creatinine value (model A) and the second accounted for eGFR (model B). (Table 2.5)

**Table 2.5** Multivariate predictors of CIN after PCI (Development dataset) (10)

| Variable | Integer Score | Model Coefficient | OR | 95% CI | P Value |
|---|---|---|---|---|---|
| **Model A*** | | | | | |
| Hypotension | 5 | 0.9310 | 2.537 | 1.973-3.262 | <0.0001 |
| Intra-aortic balloon pump use | 5 | 0.8910 | 2.438 | 1.677-3.544 | <0.0001 |
| Congestive heart failure[#] | 5 | 0.8111 | 2.250 | 1.682-3.011 | <0.0001 |
| Serum creatinine >1.5 mg/dL | 4 | 0.7194 | 2.053 | 1.586-2.658 | <0.0001 |
| Age > 75 yrs | 4 | 0.6133 | 1.847 | 1.509-2.260 | <0.0001 |
| Anemia | 3 | 0.4705 | 1.601 | 1.328-1.930 | <0.0001 |
| Diabetes mellitus | 3 | 0.4109 | 1.508 | 1.260-1.806 | <0.0001 |
| Contrast volume | 1 for 100 ml | 0.2549 | 1.290 | 1.210-1.375 | <0.0001 |
| **Model B†** | | | | | |
| Congestive heart failure[#] | 5 | 0.9923 | 2.698 | 2.019-3.603 | <0.0001 |
| Hypotension | 5 | 0.9845 | 2.676 | 2.082-3.441 | <0.0001 |
| Intra-aortic balloon pump use | 5 | 0.9350 | 2.547 | 1.751-3.706 | <0.0001 |
| Age > 75 yrs | 4 | 0.7861 | 2.195 | 1.780-2.706 | <0.0001 |
| Anemia | 3 | 0.6028 | 1.827 | 1.518-2.199 | <0.0001 |
| Diabetes mellitus | 3 | 0.4681 | 1.597 | 1.335-1.910 | <0.0001 |
| Contrast volume | 1 for 100 ml | 0.2434 | 1.276 | 1.197-1.360 | <0.0001 |
| Estimated glomerular filtration rate(mL/min/1.73m$^2$) | 2 for 40-60, 4 for 20-40, 6 for<20 | 0.1772 | 1.194 | 1.099-1.297 | <0.0001 |

*Using serum creatinine as a criterion for renal function. † Using estimated glomerular fitration rate as a criterion for renal function. [#]New York Heart Association functional classification III/IV and/or history of pulmonary edema.

There are 8 variables with p<0.001 remaining for each of the final models, shown below and presented in Figure 2.2.

- Hypotension
- The use of intra–aortic balloon pump (IABP)
- Congestive heart failure
- Diabetes mellitus
- Age > 75 years

- Anemia
- Contrast volume
- Chronic kidney disease (serum creatinine level >1.5 mg/ dL for model A and eGFR < 60 mL/min/1.73m$^2$ for model B)

Based on the odds ratio (OR) derived from multivariate logistic regression analysis, the eight variables were assigned a weighted integer coefficient value. The sum of integers was a total risk score for each patient.

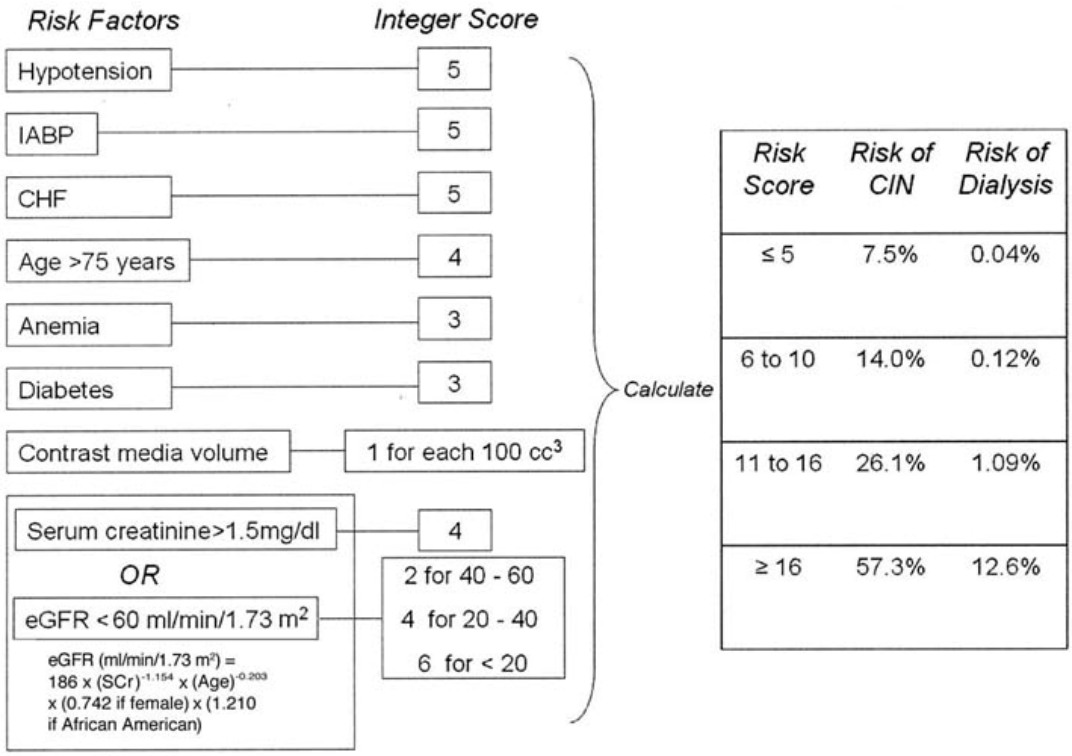


**Figure 2.2** The CIN risk score model of Mehran et al and its application in predicting the risk of CIN and CIN requiring dialysis (10).

2) Validation dataset

The risk score derived from the development dataset was tested in the validation dataset and showed that whether the model used serum creatinine or eGFR to define risk attributed to chronic kidney disease, the actual rates of CIN in the validation set were close to those predicted from the model in each of the four risk groups.

The comparison of the development of CIN between the development dataset and the validation dataset are presented in Figure 2.3.

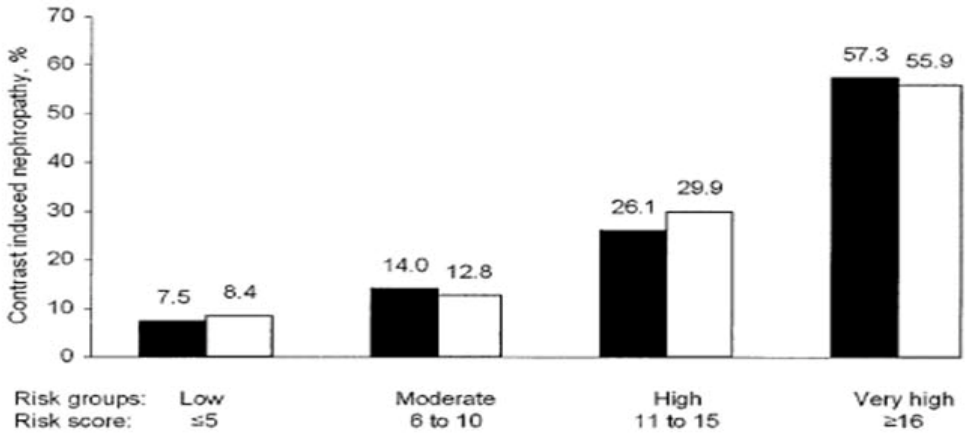


**Figure 2.3** The rates of CIN in the development (solid bar) and validation (open bar) dataset according to the risk score derived from the development dataset (10)

The risk score were categorized into four groups as demonstrated in Table 2.6.

**Table 2.6** The four categories of the Mehran risk score (10)

| Risk groups | Risk score |
|---|---|
| Low | ≤ 5 |
| Moderate | 6 – 10 |
| High | 11 – 15 |
| Very high | ≥ 16 |

Bartholomew et al (44) used a cohort study of 20,479 patients who underwent PCI to derive the William Beaumont Hospital (WBH) CIN risk score. The weighted score variables of the Bartholomew risk score are shown in Table 2.7.

**Table 2.7** The weighted score variables of the Bartholomew risk score (44)

| Risk factors | Risk score |
|---|---|
| • A creatinine clearance of 60 mL/min or less | 2 |
| • Urgent PCI | 2 |
| • IABP use | 2 |
| • Diabetes mellitus | 1 |
| • Congestive heart failure | 1 |
| • Volume of contrast media greater than 260 mL | 1 |

In 2007, Skelding et al (37) validated the WBH risk score by examining data on 4,814 patients who had PCI procedures at the Mayo Clinic. The result indicated that the WBH risk score could be utilized to detect patients with high and low risk for the development of CIN and to guide the use of preventive measures that may improve patients' prognosis.

In 2008, Nyman et al (65) studied the use of contrast medium dose-to-GFR ratio to predict the risk of CIN in 391 Swedish patients who underwent primary PCI for ST-elevation acute myocardial infarction. The independent predictors of CIN were dose of contrast media, eGFR, left ventricular ejection fraction and cardiogenic shock. The investigators concluded that relating the dose of contrast media to eGFR is a good way to assess CIN.

Ghani and Tohamy (66) studied in 347 Kuwait patients who underwent PCI. Patients were assigned to the development dataset (247 patients) and the validation dataset (100 patients). There were 5 variables shown to predict the risk of CIN. (Table 2.8)

**Table 2.8** The variable of the Ghani and Tohamy risk score (66)

| Risk factor | Risk score |
|---|---|
| • Renal impairment before PCI (baseline serum creatinine greater than 115 μmol/L (1.3 mg/dL)) | 7 |
| • Diabetes mellitus | 2 |
| • Presence of shock | 3 |
| • Female sex | 2 |
| • Multivessel PCI | 2 |

Ghani and Tohamy acknowledged the need for additional validation in larger, multicenter cohort of patients and greater participation of women before their risk scoring tool is ready for clinical use

In 2010, Aguiar–Souto et al (30) did a retrospective analysis in 227 patients undergoing PCI by using the Mehran's tool. The results showed that the majority of patients were at low risk for CIN and indicated that volume of contrast media, Mehran risk score and eGFR calculated using either the MDRD or Cockcroft equations were not predictive of CIN after PCI.

Recently, in 2011, Bonnie Raingruber et al (29) analyzed data on 196 patients admitted for cardiac angiography. By using Mehran's risk scoring tool, the patients who had Mehran risk scores higher than 6 were analyzed retrospectively and were evaluated at day 2, day 3 and day 4 through day 7. The result showed that serum creatinine levels were significantly higher in patients with a Mehran risk score of ≥ 11 when compared with those of patients with risk scores of 6 to 10, indicating that the Mehran's tool provided reliable risk assessment before patients underwent percutaneous angiography.

# CHAPTER III
# MATERIALS AND METHODS

## 3.1 Study design

This study is a hospital–based prospective cohort study.

## 3.2 Target population

The target population of this study are patients who undergo cardiac catheterization or PCI for the diagnosis and/or treatment of coronary artery disease

## 3.3 Study sample

The study sample was a group of patients who underwent cardiac catheterization or PCI at Somdejya 90 Building and Chalermprakiat 80 years Building, Phramongkutklao Hospital.

## 3.4 Inclusion criteria

1. Thai patients, at least 18 years of age, who were scheduled to undergo elective cardiac catheterization or PCI, or patients diagnosed with “acute myocardial infraction (MI)”, who required cardiac catheterization or PCI but the procedure could be delayed for at least 24 hours after the diagnosis.
2. Patients agreed to participate and signed the consent form.

## 3.5 Exclusion criteria

1. Patients who required urgent or emergent cardiac catheterization or PCI for acute myocardial infarction.
2. Patients in shock.
3. Patients with pre–existing end–stage renal disease requiring dialysis
4. Patients who were exposed to contrast media within one week prior to the index procedure
5. Patients with no record of serum creatinine in 48-72 hours after the procedure.

## 3.6 Study instruments

This study used the questionnaire and the Mehran risk scoring tool as data collection form for individual patient.

1. Data were collected using questionnaire which consisted of 3 parts.

| | |
|---|---|
| Part I | Demographic data such as age, gender, body mass index(BMI), comorbidity and medication history. |
| Part II | Procedural characteristic data such as volume of contrast media administered, number of vessels attempted and pre- and/or post-procedural medication administered for prevention of CIN. |
| Part III | Laboratory data such as serum creatinine before and at 48-72 hours after cardiac catheterization or PCI and hematocrit. |

2. Data were collected using the Mehran risk scoring tool which recorded the following 8 variables.

2.1) Patient–related characteristics:

- Age>75 years (score = 4)
- Diabetes mellitus (score = 3)
- Congestive heart failure (CHF) or admission with acute pulmonary edema (score = 5)
- Hypotension (score = 5)
- Anemia (score = 3)
- Chronic kidney disease
    a) serum creatinine > 1.5 mg/dL (score = 4)
    b) eGFR < 60/mL/min/ 1.73 $m^2$
    (score = 2 for 40-60
    score = 4 for 20-40
    score = 6 for < 20)

[eGFR (mL/min/1.73 $m^2$) = $186 \times Scr^{-1.154} \times Age^{-0.203} \times 0.742$ (if female)$\times 1.21$ (if African American)]

2.2) Procedure–related characteristics:

- The use of intra–aortic balloon pump (IABP)
  (score = 5)
- Volumes of contrast media
  (score = 1for each 100 mL)

The Mehran risk score was classified into 4 categories as shown in table 2.4.

## 3.7 Data collection

The method of data collection consists of 3 steps:

1) Direct interview for some personal data of the patients.
2) Data collection from medical records of the patients.

3) Using the Mehran risk scoring tool for evaluate individual the CIN risk score of the patients before the procedure.

## 3.8 Sample size

Sample size is estimated by the following formula (67):

1) $\hat{V}(\hat{A}) = (0.0099 \times e^{-a^2/2}) \times[(5a^2 + 8) + (a^2 + 8)/k]$

A = the conjectured area under the ROC curve
(A refer to *c* statistic, which is 0.67 according to the original Mehran risk scoring tool data)

$\hat{V}(\hat{A})$ = variance of area under the ROC curve

$a = \Phi^{-1}(A) \times 1.414$ ($\Phi^{-1}$ = the inverse of the cumulative normal distribution function; $\Phi^{-1}(0.67) = 0.439$, **thus a** = 0.439 × 1.414 = **0.622**)

k = the ratio of the number of patients without the condition to patients with the condition (the incidence of CIN = 20% so; **k** is 0.8/0.2 = **4**)

1) $\hat{V}(\hat{A}) = (0.0099 \times e^{-a^2/2}) \times [(5a^2 + 8)+(a^2 + 8)/k]$

$= (0.0099 \times e^{-((0.622)^2/2)}) \times [(5(0.622)^2 + 8) + ((0.622)^2 + 8)/ 4]$

$= (0.008158764) \times [9.93442+2.096721]$

$= (0.008158764) \times (12.031141)$

$= 0.\ 09815924$

Where $V(\hat{A}) \approx \hat{v}(\hat{\vartheta})$

Total sample size = m(1+k)

$$2) \quad m = \frac{z^2_{1-\alpha/2}\, v(\hat{\vartheta})}{L^2}$$

m = number of patients with the condition (CIN)

$Z_{1-\alpha/2}$ = 1-$\alpha$/2 percentile of the standard normal distribution (= 1.96, when $\alpha$ = 0.05)

$\vartheta$ = true accuracy of a test. In this study, the area under the ROC curve is used to represent the accuracy of the Mehran risk scoring tool.

$v(\hat{\vartheta})$ = variance function of $\vartheta$

$L$ = limit of uncertainty of area under the ROC curve (set within ±0.10)

Therefore

$$2) \quad m = \frac{z^2_{1-\alpha/2}\, \hat{v}(\vartheta)}{L^2}$$

$$= \frac{1.96^2(0.09815924)}{0.01}$$

$$= 37.70885364$$

$$\approx 38$$

Where; total sample size = m(1+k)

Therefore; total sample size = 38(1+4)

**= 190 patients**

## 3.9 Research protocol

1. Extracting the eligible patients by using purposive sampling technique.
2. Explaining the objective, goal, benefit/risk and protocol of this study to patients and relatives. Patients agreeing to participate were required to sign informed consent form.
3. Patients' blood (~ 5mL) were drawn before the procedure and sent to a laboratory for the analysis of serum creatinine and hematocrit.
4. Evaluating the CIN risk score before cardiac catheterization or PCI by using the Mehran risk scoring tool as shown previously.
5. Patients' blood (~5 mL) after cardiac catheterization or PCI were drawn and sent to a laboratory for analysis of serum creatinine.
6. Comparing serum creatinine levels before the procedure and at 48–72 hours after the procedure to determine the development of CIN after cardiac catheterization or PCI. CIN was developed if there was a 25% increase in serum creatinine concentration at 48-72 hours after the procedure, or an absolute increase of at least 0.5 mg/dL, compared to the baseline value before the procedure.
7. Demographic data, procedural characteristic data and laboratory data of all patients were recorded in the data collection form.
8. All data were entered into a database program for analysis.

## 3.10 Data analysis

### 3.10.1 Descriptive statistics

3.10.1.1 Categorical data were presented as frequency and percentages.

3.10.1.2 Continuous data were summarized as mean ± standard deviation, median, maximum and minimum.

### 3.10.2 Analytic statistics

Statistical tests were used for comparison between groups according to the type of variables being compared. Specifically, categorical variables were compared using chi-square or Fisher's exact tests, Continuous variables were compared using independent t-test.

Receiver operating characteristics (ROC) curve was constructed based on Mehran risk scores and the occurrence of CIN. The area under the ROC curve, which corresponds to the *c* statistics and its 95% confidence interval (CI) were calculated to represent the discriminatory power of the Mehran risk scoring tool in prediction of CIN in this study population. Calibration of the Mehran risk scoring tool in study population was evaluated by categorizing subjects into 4 groups as originally proposed in Mehran's study. The actual rates of CIN in each group were then compared with those reported in original Mehran's study without using any statistical test. Subjects were then divided into quartiles and the rate of CIN in each quartile was presented.

# CHAPTER IV
# RESULTS

This prospective cohort study aimed to evaluate the Mehran risk scoring tool for prediction of CIN in Thai cardiac patients who underwent elective cardiac catheterization (CAG) or percutaneous coronary intervention (PCI). A number of variables were analyzed as follows:

Demographic factors:

- Gender
- Age
- Body weight and Body mass index (BMI)
- Diabetes mellitus
- Anemia
- Use of nephrotoxic drugs

Procedural and clinical factors:

- Duration of the procedure (minutes)
- Contrast media amount (mL)
- Hydration
- Use of N-Acetycysteine (NAC)
- IABP use
- Hypotension

Laboratory factors:

- Baseline serum creatinine level and eGFR
- Post-CAG or PCI serum creatinine level and eGFR
- Hematocrit

The study results were presented as follows:

## 4.1 The general characteristics of cardiovascular disease patients

The subjects of this study were Thai patients with cardiovascular disease who underwent cardiac catheterization or PCI at Somdejya 90 Building and Chalermprakiat 80 years Building, Phramongkutklao Hospital, between August 8 and September 30, 2012. Two hundred and six patients were initially enrolled, but serum creatinine level and eGFR after the procedure were missing in 6 patients and had to be excluded. A total of 200 patients were finally analyzed in this study. Baseline characteristics of the patients are presented in Table 4.1.

- Gender

Most of the patients were male (133 patients, 66.5%) and 67 were female (33.5%).

- Age

The average age was 67.0±13.8 years. Male patients were younger than female (64.4±13.0 vs. 72.2±14.0 years). The maximum age was 95 years and the minimum age was 21 years. About two-thirds of the subjects aged more than 75 years.

- Body weight and Body mass index (BMI)

The average body weight and body mass index (BMI) were 63.5±11.5 kilograms and 24.0±3.8 $kg/m^2$, respectively. According to Asian criteria (68), 9 patients (4.5%) were classified as underweight (BMI < 18.5 $kg/m^2$) and 71 patients (35.5%) were classified to be obese (BMI ≥ 25 $kg/m^2$).

- Diabetes mellitus

There were 82 patients (41.0%) with diabetes mellitus. The prevalence in male was 35.3% (47 patients) and it was 52.2% (35 patients) in female.

- Anemia

More than half of the subjects had anemia (114 patients, 57.0%). The prevalence was higher in female (48 patients, 71.6%) than in male (66 patients, 49.6%).

- Use of nephrotoxic drugs

Fifty patients (25 %) had a history of exposure to nephrotoxic drugs. The figure in male patients was 22.6% (30 patients) and in female patients, it was 29.9% (20 patients).

- Baseline serum creatinine level and eGFR

The average serum creatinine level and eGFR were 1.38±0.79 mg/dL and 64.20±28.97 mL/min/1.73 $m^2$, respectively.

**Table 4.1** Baseline characteristics of study patients

| Variable | Patients (n=200) |
|---|---|
| Male sex, n (%) | 133 (66.5) |
| Age (years), mean ± SD | 67.0 ± 13.8 |
| Age > 75 years, n (%) | 63 (31.5) |
| Body weight (kg), mean ± SD | 63.5 ± 11.5 |
| Body mass index($kg/m^2$), mean ± SD | 24.0 ± 3.8 |
| Underweight (< 18.5 $kg/m^2$), n (%) | 9 (4.5) |
| Normal (18.5-22.9 $kg/m^2$), n (%) | 72 (36.0) |
| Overweight (23-24.9 $kg/m^2$), n (%) | 48 (24.0) |
| Obese I (25-29.9 $kg/m^2$), n (%) | 61 (30.5) |
| Obese II (≥30 $kg/m^2$), n (%) | 10 (5.0) |
| Diabetes mellitus (DM), n (%) | 82 (41.0) |
| Anemia, n (%) | 114 (57.0) |
| Congestive heart failure, n (%) | 50 (25.0) |

**Table 4.1** Baseline characteristics of study patients (cont.)

| Variable | Patients (n=200) |
|---|---|
| Baseline hematocrit (%), mean ± SD | 36.6 ± 5.8 |
| Male, mean ± SD | 38.2 ± 5.6 |
| Female, mean ± SD | 33.3 ± 4 .8 |
| Use of nephrotoxic drugs, n (%) | 50 (25.0) |
| Baseline serum creatinine (mg/dL), mean ± SD | 1.4 ± 0.8 |
| < 1.5 mg/dL, n (%) | 143 (71.5) |
| 1.5-2.0 mg/dL, n (%) | 33 (16.5) |
| > 2.0 mg/dL, n (%) | 24 (12.0) |
| Baseline eGFR (mL/min/1.73 $m^2$), mean ± SD | 64.2 ± 29.0 |
| > 60 mL/min/1.73 $m^2$, n (%) | 110 (55.0) |
| 40-60 mL/min/1.73 $m^2$, n (%) | 47 (23.5) |
| 20-40 mL/min/1.73 $m^2$, n (%) | 31 (15.5) |
| < 20 mL/min/1.73 $m^2$, n (%) | 12 (6.0) |

## 4.2 The procedural and clinical characteristics

The procedural and clinical characteristics of study patients are demonstrated in Table 4.2

- Duration of the procedure (minutes)

The average duration of the procedure was 52.0±38.1 minutes. The longest duration was 270 minutes and the shortest duration was 5 minutes.

- Contrast media amount (mL)

The contrast media used were LOCM, such as Iopromide (Ultravist-370®), and IOCM, such as Iodixanol (Visipaque®) in patient with history of allergic reaction to contrast media. The average amount of contrast media was 93.7±63.9 mL. The greatest amount was 312 mL and the smallest amount was 5 mL.

- Hydration

There were many types of intravenous fluid used for hydration in this study, e.g. NSS (68.5%), 5% DNSS (1.5%), 5% DN/2 (13.5%), 10% DNSS (0.5%), 10% DN/2 (0.5%) and others (15.5%).

- Use of N-Acetylcysteine (NAC)

N-Acetylcysteine (NAC) was given pre and/or post CAG or PCI for prevention of CIN in 29 patients (14.5%).

- IABP use

There were 10 patients (5.0 %) who required hemodynamic support with intra-aortic balloon pump.

- Post-CAG or PCI serum creatinine level and eGFR

The average post-CAG or PCI serum creatinine level and eGFR were 1.40±1.0 mg/dL and 66.8±29.8 mL/min/1.73 $m^2$, respectively.

**Table 4.2** Procedural and clinical characteristics of study patients

| Variable | Patients (n=200) |
|---|---|
| Duration of the procedure (minutes), mean ± SD | 52.0 ± 38.1 |
| Hypotension, n (%) | 25 (12.5) |
| Contrast media amount (mL), mean ± SD | 93.7 ± 63.9 |
| < 100 mL, n (%) | 112 (56.0) |
| 100 – 199 mL, n (%) | 74 (37.0) |
| 200 – 299 mL, n (%) | 13 (6.5) |
| > 300 mL, n (%) | 1 (0.5) |

**Table 4.2** Procedural and clinical characteristics of study patients (cont.)

| Variable | Patients (n=200) |
|---|---|
| Hydration | |
| NSS, n (%) | 137 (68.5) |
| 5% DNSS, n (%) | 3 (1.5) |
| 5% DN/2, n (%) | 27 (13.5) |
| 10% DNSS, n (%) | 1 (0.5) |
| 10% DN/2, n (%) | 1 (0.5) |
| Others, n (%) | 31 (15.5) |
| Number of vessels attempted | |
| Single vessel PCI or stent, n (%) | 87 (43.5) |
| Double vessel PCI or stent, n (%) | 8 (4.0) |
| Triple vessel PCI or stent, n (%) | 2 (1.0) |
| None of vessel attempted, n (%) | 41 (20.5) |
| None of vessel attempted and plan for CABG, n (%) | 56 (28.0) |
| Failed PCI or stent, n (%) | 6 (3.0) |
| Use of N-Acetylcysteine (NAC), n (%) | 29 (14.5) |
| IABP use, n (%) | 10 (5.0) |
| Post-CAG or PCI serum creatinine (mg/dL), mean ± SD | 1.4 ± 1.0 |
| <1.5 mg/dL, n (%) | 146 (73.0) |
| 1.5 – 2.0 mg/dL, n (%) | 26 (13.0) |
| > 2.0 mg/dL, n (%) | 28 (14.0) |
| Post-CAG or PCI eGFR (mL/min/1.73m$^2$), mean ± SD | 66.8 ± 29.8 |
| > 60 mL/min/1.73 m$^2$, n (%) | 117 (58.5) |
| 40 – 60 mL/min/1.73 m$^2$, n (%) | 41 (20.5) |
| 20 – 40 mL/min/1.73 m$^2$, n (%) | 28 (14.0) |
| < 20 mL/min/1.73 m$^2$, n (%) | 14 (7.0) |

## 4.3 Incidence of CIN after cardiac catheterization or percutaneous coronary intervention

CIN after cardiac catheterization (CAG) or percutaneous coronary intervention (PCI) occurred in 13 patients (6.5%) in this study. Their characteristics are presented in table 4.3. The number of male and female patients were similar. The average age was 75.5±8.0 years. There were 7 patients (53.8%) who were older than 75 years. There were 9 patients (69.2%) who had a history of diabetes mellitus and all 13 patients had anemia. Three patients (23.1%) developed hypotension and one of them required IABP. Four patients (30.8%) required hemodialysis.

**Table 4.3** Characteristics of patients who developed CIN

| Variable | Patients (n=13) |
|---|---|
| Gender | |
| Male, n (%) | 6 (46.2) |
| Female, n (%) | 7 (53.8) |
| Age (years), mean ± SD | 75.5 ± 8.0 |
| Age > 75 years, n (%) | 7 (53.8) |
| Body weight (kg), mean ± SD | 60.8 ± 10.8 |
| Body mass index ($kg/m^2$), mean ± SD | 25.0 ± 4.4 |
| Diabetes mellitus (DM), n (%) | 9 (69.2) |
| Anemia, n (%) | 13 (100.0) |
| Congestive heart failure, n (%) | 9 (69.2) |
| Baseline hematocrit (%), mean ± SD | 32.2 ± 3.8 |
| Baseline serum creatinine (mg/dL), mean ± SD | 2.5 ± 1.3 |
| Baseline eGFR (mL/min/1.73 $m^2$), mean ± SD | 33.5 ± 25.1 |
| Use of nephrotoxic drugs, n (%) | 3 (23.1) |
| Duration of the procedure (minutes), mean ± SD | 51.5 ± 41.9 |

**Table 4.3** Characteristics of patients who developed CIN (cont.)

| Variable | Patients (n=13) |
|---|---|
| Contrast media amount (mL), mean ± SD | 65.2 ± 45.2 |
| History of CAG or PCI, n (%) | 7 (53.8) |
| Angiographic diagnosis | |
| Single vessel disease, n (%) | 1 (7.7) |
| Double vessel disease, n (%) | 4 (30.8) |
| Triple vessel disease, n (%) | 6 (46.2) |
| Multivessel disease, n (%) | 2 (15.4) |
| Number of vessels attempted | |
| Single vessel PCI or stent, n (%) | 5 (38.5) |
| None of vessel attempted, n (%) | 3 (23.1) |
| None of vessel attempted and plan for CABG, n (%) | 5 (38.5) |
| Use of N-Acetylcysteine (NAC), n (%) | 2 (15.4) |
| Hydration | |
| NSS, n (%) | 8 (61.5) |
| Others, n (%) | 5 (38.5) |
| IABP use, n (%) | 1 (7.7) |
| Post-CAG or PCI serum creatinine (mg/dL), mean ± SD | 3.8 ± 1.7 |
| Post-CAG or PCI eGFR (mL/min/1.73 $m^2$), mean ± SD | 18.7 ± 11.1 |

## 4.4 Risk factors, risk score and occurrence of CIN after cardiac catheterization or percutaneous coronary intervention

The risk factors that are associated with CIN by the univariate analysis are presented in Table 4.4. Patients who developed CIN were older, had higher rate of DM, CHF, anemia, hemodialysis and had longer hospital stay compared with patients who did not develop CIN. The average baseline serum creatinine and eGFR were 2.5±1.3 mg/dL and 33.5±25.1 mL/min/1.73 $m^2$ in the patients with CIN. The corresponding figures in patients without CIN were 1.30±0.68 mg/dL and 66.3±28.1 mL/min/1.73 $m^2$, respectively.

**Table 4.4** Univariate association between procedural / clinical characteristics and CIN after CAG or PCI

| Variable | CIN (n=13) | No CIN (n=187) | p-value |
|---|---|---|---|
| Age (years), mean ± SD | 75.5 ± 8.0 | 66.4 ± 13.9 | 0.002 |
| Hypotension, n (%) | 3 (23.1) | 22 (11.8) | 0.211 |
| Body weight (kg), mean ± SD | 60.8 ± 10.8 | 63.7 ± 11.8 | 0.383 |
| Body mass index (kg/$m^2$), mean ± SD | 25.0 ± 4.4 | 24.0 ± 3.8 | 0.372 |
| Diabetes mellitus, n (%) | 9 (69.2) | 73 (39.0) | 0.042 |
| Anemia, n (%) | 13 (100.0%) | 101 (54.0) | 0.001 |
| Congestive heart failure, n (%) | 9 (69.2) | 41 (21.9) | 0.001 |
| Baseline hematocrit (%), mean ± SD | 32.2 ± 3.8 | 36.9 ± 5.8 | 0.004 |
| Baseline serum creatinine (mg/dL), mean ± SD | 2.5 ± 1.3 | 1.3 ± 0.7 | 0.000 |
| Baseline eGFR (mL/min/1.73 $m^2$), mean ± SD | 33.5 ± 25.1 | 66.3 ± 28.1 | 0.000 |
| Use of nephrotoxic drugs, n (%) | 3 (23.1) | 47 (25.1) | 1.000 |
| Duration of the procedure (minutes), mean ± SD | 51.5 ± 41.9 | 52 ± 37.9 | 0.961 |
| Contrast media amount (mL), mean ± SD | 65.2 ± 45.2 | 95.7 ± 64.6 | 0.097 |

**Table 4.4** Univariate association between procedural/clinical characteristics and CIN after CAG or PCI (cont.)

| Variable | CIN (n=13) | No CIN (n=187) | p-value |
|---|---|---|---|
| History of CAG or PCI, n (%) | 7 (53.8 | 76 (40.6) | 0.392 |
| Use of N-Acetylcysteine, n (%) | 2(15.4) | 27 (14.4) | 1.000 |
| IABP use, n (%) | 1(7.7) | 9 (4.8) | 0.498 |
| Hospital stay (day), mean ± SD | 22.54 ± 17 .92 | 10.82 ± 11.32 | 0.037 |
| Hemodialysis, n (%) | 4 (30.8) | 9 (4.8) | 0.006 |

The risk score in this study were calculated from both the model using serum creatinine level and the model using eGFR.

Risk scores calculated from the model using serum creatinine level ranged between 7 and 20, and those calculated from the model using eGFR ranged between 7 and 26.

**Table 4.5** The occurrence of CIN related to the risk scores calculated from the model using serum creatinine level

| Risk score | Observed CIN (%) |
|---|---|
| 7 | 1 (7.7) |
| 8 | 1 (7.7) |
| 10 | 2 (15.4) |
| 15 | 3 (23.1) |
| 16 | 1 (7.7) |
| 17 | 1 (7.7) |
| 19 | 3 (23.1) |
| 20 | 1 (7.7) |
| Total | 13 (100) |

**Table 4.6** The occurrence of CIN related to the risk scores calculated from the model using eGFR

| Risk score | Observed CIN (%) |
|---|---|
| 7 | 1 (7.7) |
| 10 | 2 (15.4) |
| 14 | 1 (7.7) |
| 15 | 1 (7.7) |
| 17 | 2 (15.4) |
| 19 | 2 (15.4) |
| 20 | 1 (7.7) |
| 21 | 1 (7.7) |
| 25 | 1 (7.7) |
| 26 | 1 (7.7) |
| Total | 13 (100) |

## 4.5 Mehran risk scoring tool for prediction of CIN in Thai patients after cardiac catheterization or percutaneous coronary intervention

Data on Mehran risk score and the occurrence of CIN in each patients were used to construct the ROC curve. For risk scores calculated from the model using serum creatinine level, the area under the ROC curve, which is identical to *c*-statistic, was 0.856 (95% CI 0.781 to 0.930, $p < 0.001$) for the determination of CIN (figure 4.1 and table 4.7). For risk scores calculated from the model using eGFR, the *c*-statistic was 0.885 (95% CI 0.819 to 0.950, $p < 0.001$) (figure 4.2 and table 4.8).

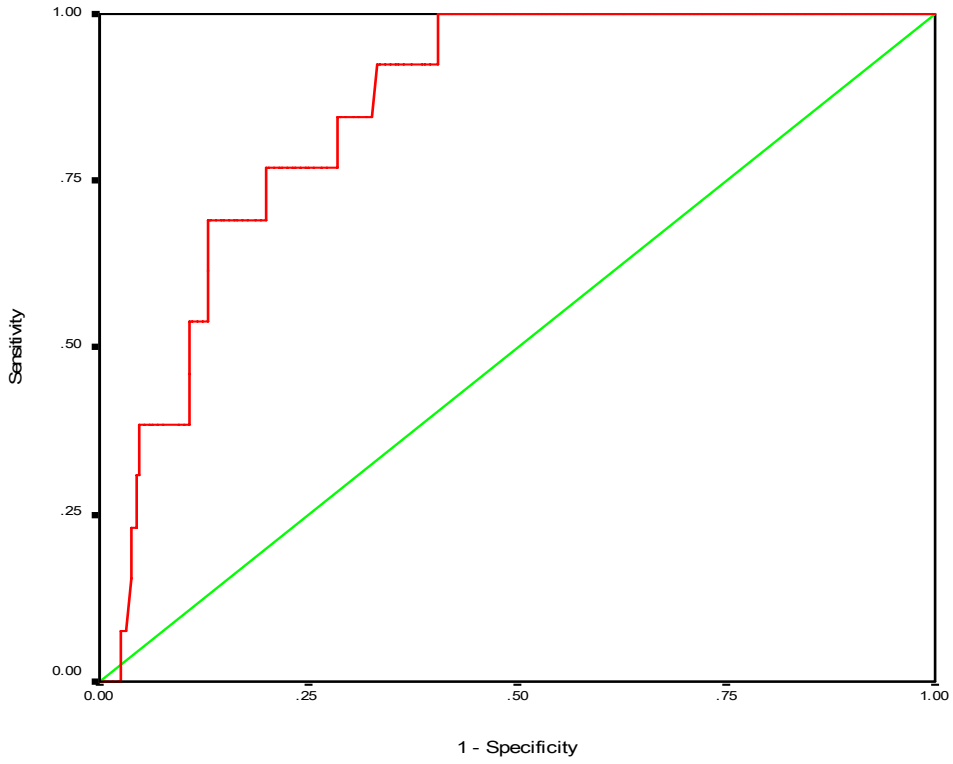


**Figure 4.1** ROC curve of Mehran risk score (model using serum creatinine) for prediction of CIN

**Table 4.7** Analysis of ROC curve of Mehran risk score (model using serum creatinine) for prediction of CIN

| Area under the ROC curve (AUC)[a] | Std.Error | Asymptotic Sig.[b] | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 0.856 | 0.038 | 0.000 | 0.781 | 0.930 |

a Under the nonparametric assumption. Of note, AUC is identical to *c*-statistic.

b Null hypothesis: AUC = 0.5

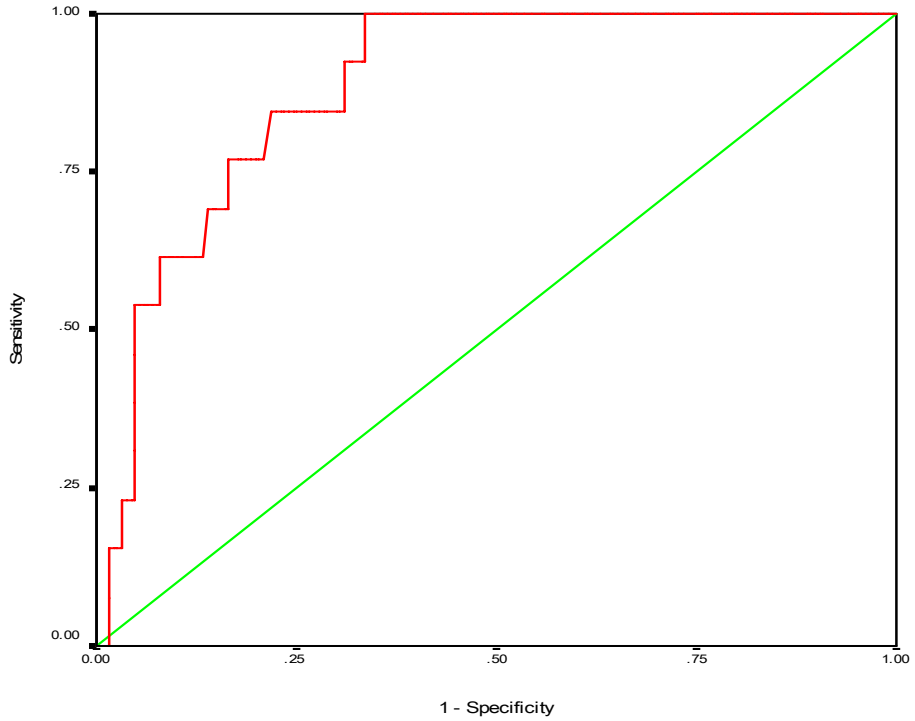


**Figure 4.2** ROC curve of Mehran risk score (model using eGFR) for prediction of CIN

**Table 4.8** Analysis of ROC curve of Mehran risk score (model using eGFR) for prediction of CIN

| Area under the ROC curve (AUC)[a] | Std.Error | Asymptotic Sig.[b] | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 0.885 | 0.034 | 0.000 | 0.819 | 0.950 |

a Under the nonparametric assumption. Of note, AUC is identical to *c*-statistic.

b Null hypothesis: AUC = 0.5

In the Mehran risk scoring tool (10), 2 out of the 8 variables used for calculation of risk score can be obtained only after the completion of the procedure (IABP use and the amount of contrast media administered). In clinical practice, however, it is more interesting to predict the risk of CIN in a particular patient before

the procedure. A modification of the Mehran risk scoring tool by omitting these 2 variables was therefore evaluated in this study to determine its predictive ability for CIN in Thai patients before CAG or PCI.

The ROC curve of the modified Mehran risk score for prediction of CIN, based on 6 variables that can be obtained before the procedure and using serum creatinine level, are shown in figure 4.3. The *c*-statistic was 0.861 (95% CI 0.779 to 0.943, $p < 0.001$), for prediction of CIN (table 4.9)

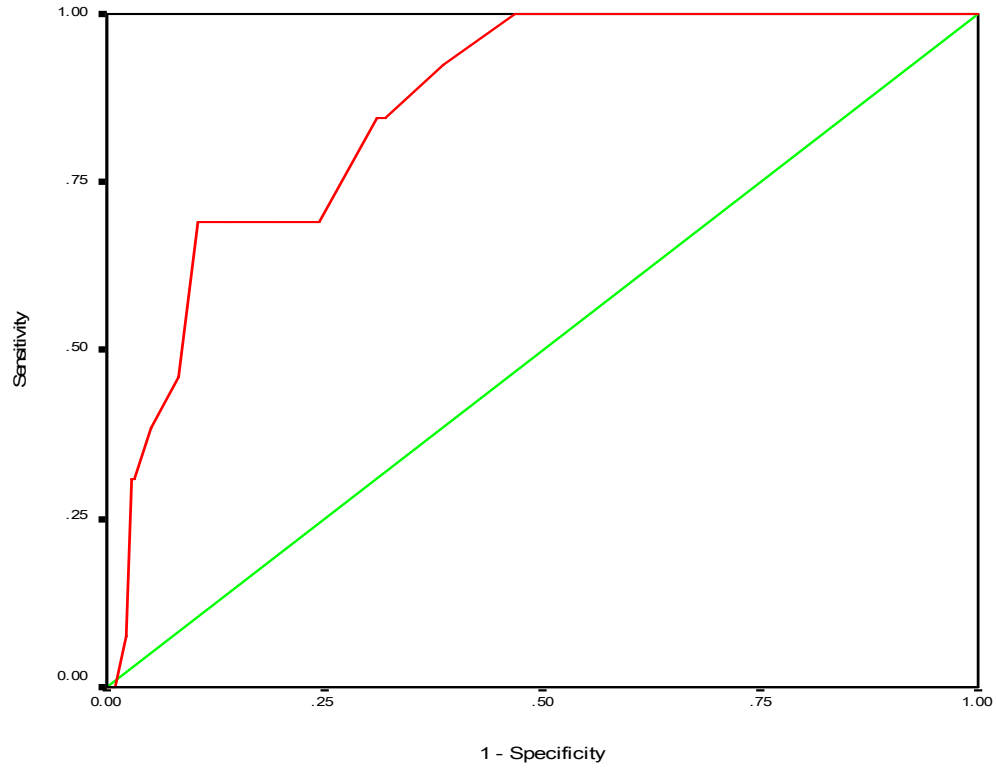


**Figure 4.3** ROC curve of modified Mehran risk scoring tool, based on 6 variables that can be obtained before the procedure, and using serum creatinine level, for prediction of CIN

**Table 4.9** Analysis of ROC curve of modified Mehran risk score based on 6 variables and using serum creatinine

| Area Under the ROC curve (AUC)[a] | Std. Error | Asymptotic Sig.[b] | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 0.861 | 0.042 | 0.000 | 0.779 | 0.943 |

a Under the nonparametric assumption. Of note, AUC is identical to *c*-statistic.

b Null hypothesis: AUC = 0.5

The discriminatory power of the original Mehran risk score (based on 8 variables) and the modified Mehran risk score (based on 6 variables) are comparable (figure 4.4 and table 4.10).

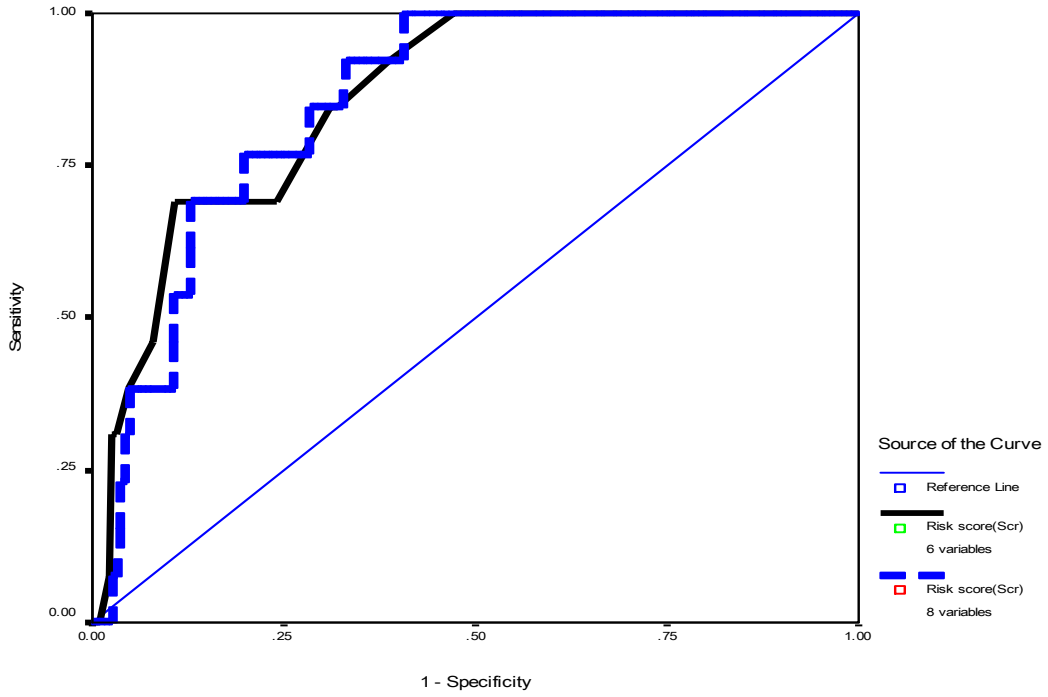


**Figure 4.4** The comparison between ROC curve derived from the original Mehran risk score (using 8 variables, dotted line) and that derived from the modified Mehran risk score (using 6 variables, solid line), both using serum creatinine level

**Table 4.10** Analysis of ROC curve derived from the original Mehran risk score (using 8 variables) and the modified Mehran risk score (using 6 variables), both using serum creatinine level

| Model | Area Under the ROC curve (AUC)[a] | Std. Error | Asymptotic Sig.[b] | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| Original (8variables) | 0.856 | 0.038 | 0.000 | 0.781 | 0.930 |
| Modified (6variables) | 0.861 | 0.042 | 0.000 | 0.779 | 0.943 |

a Under the nonparametric assumption. Of note, AUC is identical to *c*-statistic.

b Null hypothesis: AUC = 0.5

Similar analysis of the modified Mehran risk scoring tool, using eGFR, is shown in figure 4.5 and table 4.11. The *c*-statistic was 0.878 (95% CI 0.798 to 0.958, $p < 0.001$) for prediction of CIN, which was comparable to that analyzed from the original model shown in table 4.8.

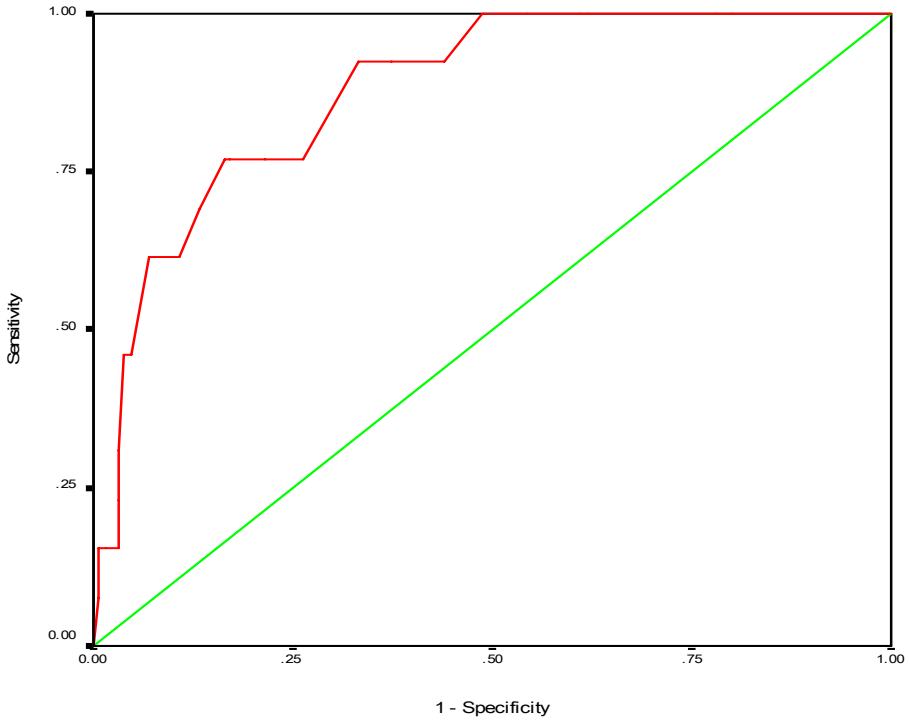


**Figure 4.5** ROC curve of modified Mehran risk scoring tool, based on 6 variables, and using eGFR for prediction of CIN

**Table 4.11** Analysis of ROC curve of modified Mehran risk score based on 6 variables and using eGFR

| Area under the ROC curve (AUC)[a] | Std.Error | Asymptotic Sig.[b] | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 0.878 | 0.041 | 0.000 | 0.798 | 0.958 |

a Under the nonparametric assumption. Of note, AUC is identical to *c*-statistic.

b Null hypothesis: AUC = 0.5

To calculate sensitivity and specificity of the modified Mehran risk score using serum creatinine level, a cutoff score has to be set. According to the ROC curve shown in figure 4.3, the score of 7 seems to be appropriate. At this cutoff score, the sensitivity was 92.3% (95% CI 66.7% to 98.6%) and the specificity was 61.3% (95% CI 53.8% to 67.7%). (Table 4.12)

**Table 4.12** Sensitivity and specificity at each cutoff score of modified Mehran risk score based on 6 variables and using serum creatinine level

| Positive if Greater Than | Sensitivity | 1 - Specificity | Specificity |
|---|---|---|---|
| 3.0 | 1.000 | 0.586 | 0.414 |
| 4.0 | 1.000 | 0.564 | 0.436 |
| 5.0 | 1.000 | 0.530 | 0.470 |
| 6.0 | 1.000 | 0.470 | 0.530 |
| 7.0 | 0.923 | 0.387 | 0.613 |
| 8.0 | 0.846 | 0.320 | 0.680 |
| 9.0 | 0.846 | 0.309 | 0.691 |
| 10.0 | 0.692 | 0.243 | 0.757 |
| 11.0 | 0.692 | 0.193 | 0.807 |

There were 85 patients (42.5%) with modified Mehran risk score > 7, and 115 patients (57.5%) with score ≤ 7 (table 4.13). The positive predictive value (PPV) for the development of CIN was 14.1% (95% CI 8.3% to 23.1%), and the negative predictive value (NPV) was 99.1 % (95% CI 95.2% to 99.8%).

Similar analyses were carried out for modified Mehran risk score using eGFR. At the similar cutoff score of 7, the sensitivity was 92.3% (95% CI 66.7% to 98.6%) and the specificity was 56.1% (95% CI 49.0% to 63.1%). The PPV was 12.8% (95% CI 7.5% to 21.0%) and the NPV was 99.1 % (95% CI 94.8% to 99.8%).

**Table 4.13** The categorization of patients according to the modified Mehran risk score using the cutoff score of 7

| Status | Number of patients (n) | Percent (%) |
|---|---|---|
| Risk score > 7 | 85 | 42.5 |
| Risk score ≤ 7 | 115 | 57.5 |
| Total | 200 | 100 |

In terms of calibration of the modified Mehran risk score using serum creatinine, patients were categorized into 4 groups according to the original Mehran risk scoring system (10). The actual rates of CIN in each group were presented in table 4.14 and figure 4.6. The predicted risk of CIN in each group as demonstrated in original Mehran's study was also presented in table 4.14 for comparison.

**Table 4.14** Actual rate of CIN compared to predicted risk of CIN based on original Mehran's study

| Risk score | n in each group | n (%) of CIN | Predicted risk of CIN according to original Mehran's study (10) |
|---|---|---|---|
| ≤ 5 | 88 | 0 (0%) | 7.5% |
| 6 to 10 | 58 | 4 (6.9%) | 14.0% |
| 11 to 15 | 33 | 3 (9.1%) | 26.1% |
| ≥ 16 | 21 | 6 (28.6%) | 57.3% |

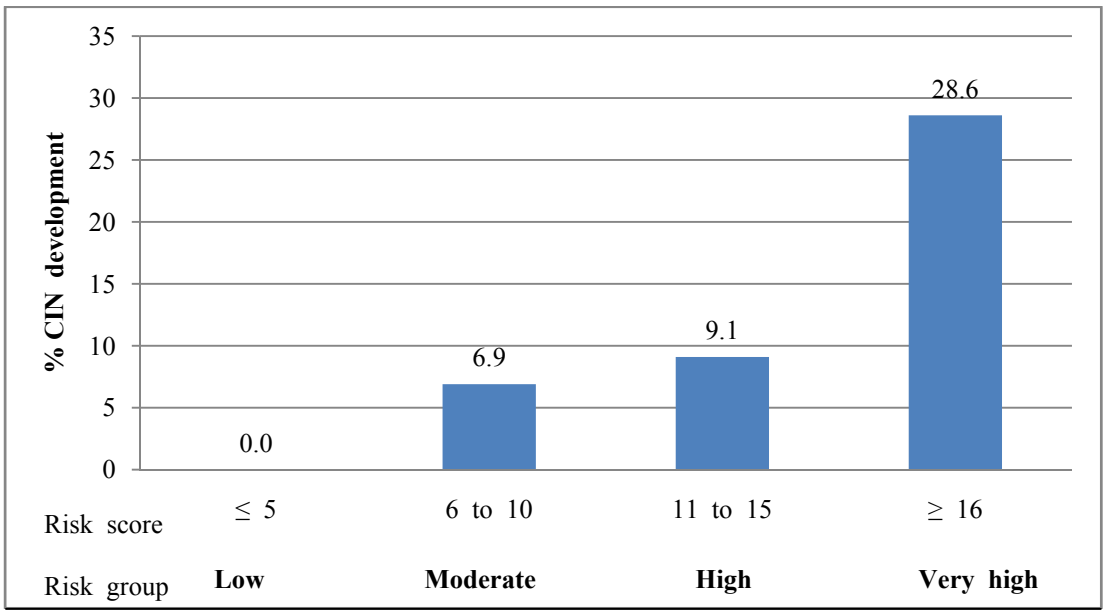


**Figure 4.6** Actual rate of CIN in each risk group

As the categorization based on original Mehran's study results in over-estimation of risk of CIN in subjects in this study, a new categorization method is proposed. To maximize the power of analysis, patients were categorized into quartiles using the cutoff at 25$^{th}$, 50$^{th}$, and 75$^{th}$ percentile. The results are shown in table 4.15 and figure 4.7.

**Table 4.15** Risk of CIN in each quartile of risk score

| Risk score | n in each group | n developed CIN | Risk of CIN |
|---|---|---|---|
| ≤ 3 | 78 | 0 | 0.0% |
| 4 to 7 | 37 | 1 | 2.7% |
| 8 to 11 | 40 | 3 | 7.5% |
| ≥ 12 | 45 | 9 | 20.0% |

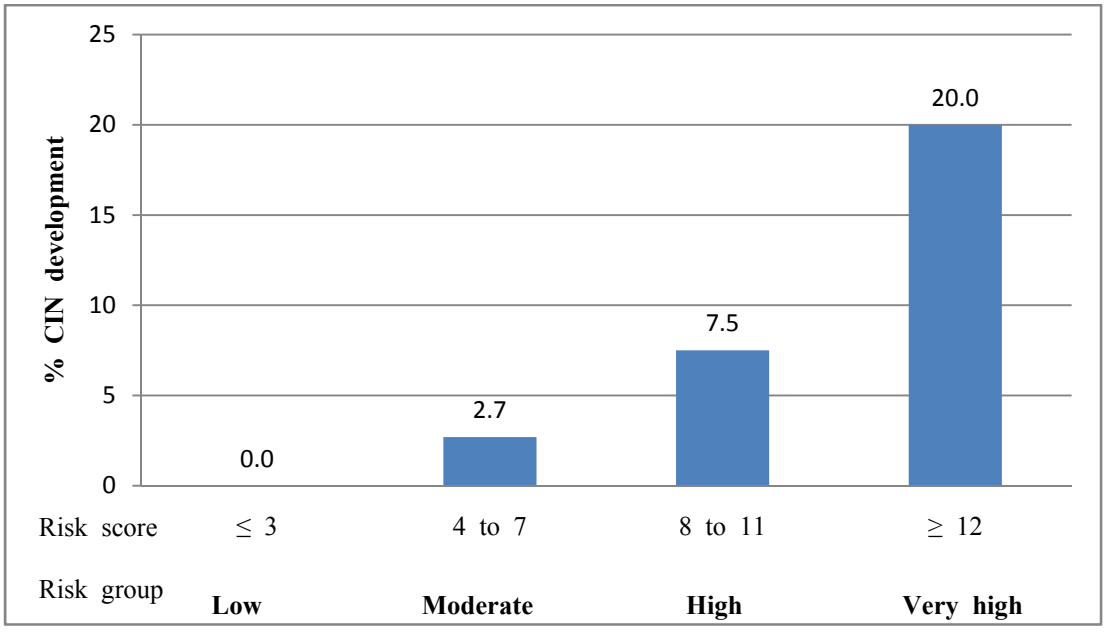


**Figure 4.7** Risk of CIN according to quartile of risk score

# CHAPTER V
# DISCUSSION

Many variables were analyzed in this prospective cohort study as shown below.

1) Demographic variables
   - Gender
   - Age
   - Body weight and Body mass index (BMI)
   - Diabetes mellitus
   - Anemia
   - Use of nephrotoxic drugs

2) Clinical and procedural variables
   - Duration of the procedure (minutes)
   - Contrast media amount (mL)
   - Hydration
   - Use of N-Acetycysteine (NAC)
   - IABP use
   - Hypotension

3) Laboratory variables
   - Baseline serum creatinine level and eGFR
   - Post-CAG or PCI serum creatinine level and eGFR
   - Hematocrit

Although there were more male (66.5%) than female (33.5%) in this study, the proportion of female patients in this study is higher than that in previous studies. In the study by the Nyman et al (65), women comprised only 20% of study participants and this was a limitation in their study. In the study by Mehran et al (10), 28.8% of the subjects were females. Ghani and Tohamy (66) found that female sex was one of the 5 variables which were identified as risk factors for CIN.

In univariate analysis, it was found that age, diabetes mellitus, anemia, congestive heart failure, baseline hematocrit, baseline serum creatinine, baseline eGFR, length of hospital stay and hemodialysis had association with the occurrence of CIN. However, age > 75 years, body weight, body mass index, use of nephrotoxic drugs, duration of the procedure, hypotension, contrast media amount, history of CAG or PCI, use of NAC and IABP had no significant association with CIN.

Many significant variables found in this study to be associated with CIN such as age, diabetes mellitus, anemia, congestive heart failure, baseline hematocrit, baseline serum creatinine, baseline eGFR and hospital stay, were similar to the results of several studies (44, 66, 69). For example, the results of the study by Mehran et al (10) found that diabetes mellitus, anemia, congestive heart failure, baseline serum creatinine and baseline eGFR were significantly associated with CIN.

Although age was a significant variable but age > 75 years was not. This finding was different from that observed in the study by Mehran et al (10), which reported that age > 75 years was strongly associated with CIN development (OR 1.90, 95% CI 1.59 to 2.27, $p < 0.0001$) and was included in the CIN risk score. Another study by Maioli et al (69) also showed that age at least 73 years was significantly associated with CIN.

The association between CIN development and diabetes mellitus was significant in the results of Mehran et al' s study (10) (OR 1.73, 95% CI 1.48 to 2.02, $p < 0.0001$). Bartholomew et al (44) reported that diabetes mellitus was associated with CIN, which was similar to the results of the study by Ghani and Tohamy (66) showing that diabetes mellitus was one of the significant variables used to assigned the risk score.

The correlation between CIN development and congestive heart failure was significant in the study's result of Mehran et al (10) (OR 2.68, 95% CI 2.09 to 3.44, p-value < 0.0001). Bartholomew et al (44) also reported that congestive heart failure was associated with CIN development. In addition, Mehran et al (10) reported that anemia had positive association with CIN development (OR 2.02, 95% CI 1.72 to 2.36, p-value < 0.0001).

Mehran demonstrated the correlation between CIN and baseline serum creatinine (OR 2.053, 95% CI 1.586 to 2.658, p-value < 0.0001) or baseline eGFR (OR 2.053, 95% CI 1.586 to 2.658, p-value < 0.0001) (10). Maioli et al (69) also showed a positive association between CIN and baseline serum creatinine.

In the present study, volume of contrast media was not associated with the development of CIN. This result was different from that reported by Mehran et al (10), who reported that contrast media amount was a risk factor for CIN.

In this study, the use of IABP had no significant association with CIN development. This result was different from the study by Mehran et al (10), who reported that there was a positive correlation between the use of IABP and CIN development. The insertion of elective IABP may be related to CIN due to various reasons (10).

1) The use of IABP may be a marker of hemodynamic disturbance during CAG or PCI.

2) It may be a marker of severe atherosclerotic disease, which may also involve renal artery.

3) It may result in atheroemboli throwing to the renal circulation during insertion, pulsation, or removal.

4) It may cause partial occlusion of the renal blood flow if the position of the IABP is inappropriate (i.e., in the abdominal instead of the descending thoracic aorta).

5) It may be a marker of increased vascular complications and post CAG or PCI hypotension.

This study found that the original Mehran risk scoring tool either using serum creatinine or eGFR to represent pre-existing renal impairment has sufficient discriminatory power to predict risk of CIN in Thai patients. The *c* statistic derived from the ROC curve is high, and actually it is even higher than that originally reported by Mehran (10).

This study proposed a modification of Mehran risk score to suit clinical practice. Clinicians would like to predict the risk of CIN at the time the decision to perform CAG or PCI is made. Patients also would like to know their risks in order to make informed decision whether to take the procedure or not. Among the 8 variables used to calculate Mehran risk score, 6 can be obtained prior to the procedure and can be useful to predict risk at the decision point. The other 2 variables, IABP use and the volume of contrast media administered, are available only at the completion of the procedure; they are not useful in prediction of risk when the decision is to be made. These 2 variables are left out in the modified Mehran risk score. The modified Mehran risk score can still be calculated using either serum creatinine or eGFR. The ROC analysis showed that, despite 6 variables, the modified model still expresses good discriminatory power, with the *c* statistic being comparable to that of original model. This result certainly has clinical implication. It suggests that the risk of CIN can be reliably predicted prior to cardiac catheterization or PCI, based on readily available variables. However, this finding should be confirmed in other studies before it can be generally applied in clinical practice.

If a simplistic classification is preferred, a cutoff score of 7 can be used to dichotomized the risk groups. This cutoff resulted in high sensitivity, low specificity, high NPV and low PPV. The dichotomized score will be clinically useful in patients with low score, as the NPV is high and the risk of CIN can be reasonably acceptable.

In terms of calibration, the ability of a model to correctly predict a particular outcome, this study showed that the Mehran risk score overestimates the risk of CIN in Thai patients. However, there is a clear trend of increased risk with higher score, suggesting that the score can still be useful in risk prediction if appropriate calibration is applied. This study then proposed another cutoff values to classify patients into various risk group, using the $25^{th}$, $50^{th}$, and $75^{th}$ percentile as cutoff scores. The result demonstrated even clearer trend of increased risk according

to higher scores. Nonetheless, this findings requires further validation in larger, or multicenter studies.

The adequate risk score model for assessing the development of CIN in Thai patients before CAG or PCI is believed to increase the opportunity to screen and to provide appropriate preventive measures and supportive care to patients at risk of developing CIN. Given the widespread of procedures utilizing contrast media, such the score can have significant economic impact on health care cost.

This study, although well planned and designed, has some limitations. Only 13 patients (6.5%) developed CIN. The small number of outcome events cannot reduce the level of uncertainty as much as required. The sample size may be considered small as the actual rate of CIN (6.5%) was much less than the estimate of 20% used in sample size calculation. In addition, this study was carried out in a single center. The result may not be fully applicable in other settings.

# CHAPTER VI
# CONCLUSION AND RECOMMENDATION

## 6.1 Conclusion

The present study was a hospital-based prospective cohort study which aim to evaluate the Mehran risk scoring tool for prediction of risk of contrast induced nephropathy in Thai patients undergoing cardiac catheterization or percutaneous coronary intervention.

A total of 200 Thai patients who underwent cardiac catheterization or PCI at Somdejya 90 Building and Chalermprakiat 80 years Building, Phramongkutklao Hospital between August 8 and September 30, 2012 were enrolled into this study. The development of CIN, defined as a 25% increase in serum creatinine concentration at 48-72 hours after the procedure, or an absolute increase of at least 0.5 mg/dL, compared to the baseline value before the procedure, occurred in 13 patients (6.5%). About half of patients who developed CIN were male. One of these 13 patients required IABP, and 4 patients (30.8%) required hemodialysis.

The univariate analysis showed the following factors to be associated with the occurrence of CIN:

1) Age
2) Diabetes mellitus
3) Anemia
4) Congestive heart failure
5) Baseline hematocrit
6) Baseline serum creatinine
7) Baseline eGFR
8) Length of hospital stay
9) Hemodialysis

There were four risk variables that had significant association with the occurrence of CIN in this study but they were different from the results of the study by Mehran et al (10) such as age, baseline hematocrit, hospital stay and hemodialysis. However, they should be analyzed based on data of Thai patients for evaluation of CIN risk score in the future.

The ROC curve analysis showed that the optimum cutoff point for risk score was 7, which gave the sensitivity of 92.3% (95% CI 66.7% to 98.6%) and the specificity of 61.3% (95% CI 53.8% to 67.7%). The Mehran risk score has good discriminative ability with *c*-statistic of 0.861 (95% CI 0.779 to 0.943, $p < 0.001$). The PPV was low but the NPV was high.

The Mehran risk scoring tool was effective for prediction of the risk of CIN in Thai patients undergoing cardiac catheterization or percutaneous coronary intervention. The scoring system is simple and can be easily used in clinical practice.

However, The important issues of this study can be concluded as follow:

1) The *c*-statistic in this study was 0.861 (95% CI 0.779 to 0.943, $p < 0.001$) which indicated that the Mehran risk scoring tool had a good discriminatory power for prediction of CIN in Thai patients. The *c*-statistic obtained in this study was actually higher than the value of 0.67, which was reported in the original study by Mehran

2) Although the direction of association between Mehran risk score and the level of risk of CIN was in the right direction in this study (the higher the score, the higher the risk), the Mehran risk score overestimated absolute risk level in Thai patients. A research to develop a system of calibration is required.

## 6.2 Limitation of this study

1. The sample size was small resulting from the lower-than-expected rate of CIN. The study was conducted in a single center, which may not represent Thai patients undergoing CAG or PCI in general. The finding should be confirmed in a larger and possibly multicenter study.

2. Women were not well represented in this study, as they comprise only one-third of study subjects.

3. Times of blood collection to determine the development of CIN were not well standardized, as most patients could be discharged within 24 hours of the procedure. It was difficult for some patients to come back at 48-72 hours to have blood sample drawn.

## 6.3 Recommendation on the implementation of this study

1. The number of sample size should be increased to have enough number of events to estimate the CIN risk with certainty.

2. The four risk variables, namely age, baseline hematocrit, hospital stay and hemodialysis, which had significant association with the CIN in this study, should be combined with other risk score to form suitable CIN risk score based on Thai database.

## 6.4 Recommendation for the future research

1. The future research to validate the Mehran risk scoring tool should be larger or be a multicenter trial.

2. The future studies should be performed to evaluate this CIN risk score model in other procedures utilizing intravascular contrast media such as CT scanning.

3. A prospective cohort study for developing a CIN risk score based on data of Thai patients would be specifically informative.

# REFERENCES


1. สำนักงานสถิติแห่งชาติ. จำนวนการตายจำแนกตามสาเหตุการตาย และเพศทั่วราชอาณาจักร พ.ศ. 2545-2552. [ออนไลน์]. เข้าถึงได้จาก :http //www.nso.go.th. (วันที่ค้นข้อมูล : 19 มีนาคม 2554).
2. สุกิจ แย้มวงษ์. โครงการการพัฒนาแบบประเมินความเสี่ยงต่อโรคหัวใจและหลอดเลือด. รายงานวิจัยฉบับสมบูรณ์. สำนักงานกองทุนสนับสนุนการวิจัย, 2548.
3. วิชัย เอกพลากร. "บทที่ 1 สถานการณ์ปัญหา" ใน สถานการณ์โรคระบบหัวใจและหลอดเลือดและทิศทางการวิจัยในประเทศไทย (Situation of Cardiovascular disease and Research direction in Thailand). หน้า7. เครือข่ายวิจัยสุขภาพ, 2554.
4. ดิลก ภิยโยทัย. "บทสรุปสำหรับผู้บริหาร" ใน โครงการการทบทวนองค์ความรู้เกี่ยวกับ Psychosocial factors กับโรคหัวใจและหลอดเลือด. มูลนิธิสาธารณสุขแห่งชาติ, 2547.
5. Wright J, Hutchison A. Cardiovascular disease in patients with chronic kidney disease. Vasc Health Risk Manag 2009;5:713–22.
6. Ohtake T, Kobayashi S, Moriya H, Negishi K, Okamoto K, Maesato K, et al. High prevalence of occult coronary artery stenosis in patients with chronic kidney disease at the initiation of renal replacement therapy: an angiographic examination. J Am Soc Nephrol 2005;16:1141-8.
7. Levin A. Clinical epidemiology of cardiovascular disease in chronic kidney disease prior to dialysis. Semin Dial 2003;16(2):101–5.
8. Collins AJ, Li S, Ma. JZ, Herzog C. Cardiovascular disease in end-stage renal disease patients. Am J Kidney Dis 2001;38(4):S26-9.
9. Katzberg RW, Haller C. Contrast-induced nephrotoxicity: clinical landscape. Kidney Int Suppl 2006;100:S3–7.
10. Mehran R, Aymong ED, 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 2004;44:1393-9.

11. สง่า นิลวรางกูร. สารทึบรังสีคืออะไร. [ออนไลน์]. เข้าถึงได้จาก :http: //www. angelfire.com/ ok/xrayweb/contrast.html (วันที่ค้นข้อมูล : 2 มิถุนายน 2554).
12. Cardiac catheterization, percutaneous coronary intervention. Available from: http://medical-dictionary.thefreedictionary.com/percutaneous+coronary+ intervention, assessed March 8,2013.
13. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. Kidney Int suppl 2006;100:S11–5.
14. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002;105:2259-64.
15. Gleeson TG, Bulugahapitiya S. Contrast-induced nephropathy. Am J Roentgenol 2004;183:1673-89.
16. Bartorelli AL, Marenzi G. Contrast-induced nephropathy. J Interv Cardiol 2008;21:74-85.
17. McCullough PA. Contrast-induced acute kidney injury. J Am Coll Cardiol 2008;51:1420-31.
18. Chaemchoi T. Risk score model for prediction of contrast-induced nephropathy after percutaneous coronary intervention. Bangkok, Chulalongkorn University; 2010, 91p.
19. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997;103:368–75.
20. McCullough PA, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, et al. Epidemiology and prognostic implications of contrast-induced nephropathy. Am J Cardiol 2006;98:5K–13K.
21. From AM, Bartholmai BJ, Williams AW, Cha SS, Mcdonald FS. Mortality associated with nephropathy after radiographic contrast exposure. Mayo Clin Proc 2008;83(10):1095-100.
22. Roy P, Raya V, Okabe T, Slottow TLP, Steinberg DH, 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 2008;101(11):1544-9.

23. Dangas G, lakovou I, Nikolsky E, Aymong ED, Mintz GS, Kipshidze NN. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. Am J Cardiol 2005;95:13-9.
24. Shoukat S, Gowani SA, Jafferani A, Dhakam SH. Contrast-induced nephropathy in patients undergoing percutaneous coronary intervention. Cardiol Res Pract 2010;2010:649164.
25. Pannu N, Wiebe N, Tonelli M. Prophylaxis Strategies for contrast-induced Nephropathy. Am J Med 2006;295:2765-79.
26. Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. Ann Intern Med 2008;148:284-94.
27. Barrett BJ, Parfrey PS. Preventing nephropathy induced by contrast medium. N Engl J Med 2006;354:379-86.
28. Weisbord SD, Mor MK, Resnick AL, Hartwig KC, Sonel AF, Fine MJ, et al. Prevention, incidence, and outcomes of contrast-induced acute kidney injury. Arch Intern Med 2008;168:1325-32.
29. Raingruber B, Kirkland-Walsh H, Chahon N, Kellermann M. Using the Mehran risk scoring tool to predict risk for contrast medium–induced nephropathy in patients undergoing percutaneous angiography. Crit Care Nurse 2011;31:e17-22.
30. Aguiar-Souto P, Ferrante G, Furia FD, Barlis P, Khurana R, Mario CD. Frequency and predictors of contrast-induced nephropathy after angioplasty for chronic total occlusions. J Interv Cardiol 2008;139:68–74.
31. ความดันโลหิต Blood pressure. [ออนไลน์]. เข้าถึงได้จาก : http: //www. med.cmu.ac.th. (วันที่ค้นข้อมูล : 10 กันยายน 2554).
32. ศุภนิมิต ทีฆชุณหเถียร. "Congestive heart failure" ใน Drugs therapy of congestive heart failure บท ที่ 6. หน้า 69, 2554.

33. โรคหัวใจวาย Heart failure. [ออนไลน์]. เข้าถึงได้จาก : http: //health.phahol.go.th/index.php?option=com_content&view=article&id=122&Itemid=149. (วันที่ค้นข้อมูล : 13 ตุลาคม 2554).
34. ความรู้ทั่วไปเรื่องเบาหวาน. [ออนไลน์]. เข้าถึงได้จาก : http://www.student.chula.ac.th/~50370442/diabetes2.htm. (วันที่ค้นข้อมูล : 6 กันยายน 2554).
35. อนุตตร จิตตินันทน์. "แนวทางเวชปฏิบัติที่ 2 การคัดกรองโรคไตเรื้อรัง" ใน แนวทางเวชปฏิบัติสำหรับโรคไตเรื้อรังก่อนการบำบัดทดแทนไต พ.ศ. 2552. หน้า 17. สมาคมโรคไตแห่งประเทศไทย, 2552.
36. Creatinine blood test. Available from: http://www.medicinenet.com/ creatinine_ blood_test/article.htm. assessed September 6,2011.
37. Skelding KA, Best PJM, Bartholomew BA, Lennon RJ, O'Neill WW, Rihal CS. Validation of a predictive risk score for radiocontrast-induced nephropathy following percutaneous coronary intervention. J Invasive Cardiol 2007;19(5):229-33.
38. Adam. A, Dixon AK, Grainger RG, Allison DJ,editors. Grainger & Allison's Diagnostic radiology[Internet]. London: Churchill Livingstone; 2008 [cited 2011 Sep 6]. Avialable from: http://www.us.elsevierhealth.com/Medicine/Radiology/book/9780443101632/Grainger-and-Allisons-Diagnostic-Radiology/
39. Dickinson MC, .Kam PC. Intravascular iodinated contrast media and the anaesthetist. Anaesthesia 2008;63:626-34.
40. Solomon R, Briguori C, Bettmann M. Selection of contrast media. Kidney Int 2006:s39-45.
41. Kapitsinou PP, Rudnick MR. Contrast-induced nephropathy - Pathogenesis and prevention [Internet]. Touch Briefings; 2007 [cited 2011 Oct 12]. Avialable from: http://www.touchbriefings.com/pdf/2968/rudnick.pdf
42. Freeman RV, O'Donnell M, share D, Meengs WL, Kline-Rogers E, clark VL. Nephropathy requiring dialysis after percutaneous coronary intervention and the critical role of an adjusted contrast dose. Am J Cardiol 2002;90:1068-73.
43. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. JAMA 1996;275:1489-94.

44. Bartholomew BA, Harjai KJ, Dukkipati S, Boura JA, Yerkey MW, Glazier S. Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. Am J Cardiol 2004;93:1515-9.
45. Subramanian S, Tumlin J, Bapat B, Zyczynski T. Economic burden of contrast-induced nephropathy: implications for prevention strategies. J Med Econ 2007;10:119-34.
46. Solomon R. Contrast medium induced acute renal failure. Kidney Int 1998; 53:230-42.
47. Toprak O. Risk markers for contrast-induced nephropathy. Am J Med Sci 2007;334:283-90.
48. Toprak O, Cirit M. Risk factors for contrast-induced nephropathy. Kidney Blood Press Res 2006;29:84-93.
49. Parfrey PS, Griffiths SM, Barrett BJ. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. N Engl J Med 1989;320:143-53.
50. Thompson JR, Henrich WL. Nephrotoxic agents and their effects. The principles and practice of nephrology 1995:788-96.
51. Stevens MA, McCullough PA, Tobin KJ. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the PRINCE study - Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. J Am Coll Cardiol 1999;33:403-11.
52. Weisberg LS, Kurnik PB, Kurnik BR. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. Kidney Int 1994;45:259-65.
53. Hall KA, Wong RW, Hunter GC, Camazine BM, Rappaport WA, Smyth SH. Contrast-induced nephrotoxicity: the effects of vasodilator therapy. J Surg Res 1992;53:317-20
54. Lasser EC, Lyon SG, Berry CC. Reports on contrast media reactions: analysis of data from reports to the US Food and Drug Administration. Radiology 1997;203:605-10.
55. Nikolsky E, Mehran R, Turcot D. Impact of chronic kidney disease on prognosis of patients with diabetes mellitus treated with percutaneous coronary intervention. Am J Cardiol 2004;94:300-5.

56. Lautin EM, Freeman NJ, Schoenfeld AH. Radiocontrast-associated renal dysfunction: incidence and risk factors. Am J Roentgenol 1991;157:49-58.
57. Berns AS. Nephrotoxicity of contrast media. Kidney Int 1989;36:730-40.
58. Katzberg RW. Urography into the 21st century: new contrast media, renal handling, imaging characteristics, and nephrotoxicity. Radiology 1997; 204:297-312.
59. 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 2003;349:1333-40.
60. Marenzi G, Lauri G, Campodonico J, Marana I, Assanelli E, De Metriio M, et al. Comparison of two hemofiltration protocols for prevention of contrast-induced nephropathy in high-risk patients. Am J Med 2006;119:155-62.
61. Spargias K, Alexopoulos E, Kyrzopoulos S, Iokovis P, Greenwood DC, Manginas A, et al. Ascorbic acid prevents contrast - mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. Circulation 2004;110:2837-42.
62. Stacul F, Adam A, Becker CR, Davidson C, Lameire N, McCullough PA, et al. Strategies to reduce the risk of contrast-induced nephropathy. Am J Cardiol 2006;98:59K-77K.
63. 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 2007;115:1211-7.
64. Cochran ST, Wong WS, Roe DJ. Predicting angiography-induced acute renal function impairment: clinical risk model. Am J Roentgenol 1983; 141:1027-33.
65. Nyman U, Björk J, Aspelin P, Marenzi G. Contrast medium dose-to-GFR ratio: a measure of systemic exposure to predict contrast-induced nephropathy after percutaneous coronary intervention. Acta Radiol 2008;49:658-67.
66. Ghani AA, Tohamy KY. Risk score for contrast-induced nephropathy following percutaneous coronary intervention. Saudi J Kidney Dis Transpl 2009; 20(2):240-5.

67. Zhou X-H, Obuchowski NA, McCLISH DK. Statistical methods in diagnostic medicine. 2nd ed. New Jersey: John Wiley & Sons, Inc.; 2011.
68. Kantachuvessiri A. Obesity in Thailand. J Med Assoc Thai 2005;88:554-62.
69. Maioli M, Toso A, Gallopin M, Leoncini M, Tedeschi D, Micheletti C, et al. Preprocedural score for risk of contrast-induced nephropathy in elective coronary angiography and intervention. J Cardiovasc Med (Hagerstown) 2010;11(6):444-9.

# APPENDICES

# APPENDIX A
# PATIENT DATA COLLECTION FORM

**แบบบันทึกข้อมูลสำหรับผู้ป่วยที่เข้ารับการตรวจรักษาหลอดเลือดหัวใจผ่านสายสวน**

**เลขที่บันทึก □□□**

**ส่วนที่ 1** ข้อมูลผู้ป่วยและภาวะของโรค

1. เพศ [ ] ชาย [ ] หญิง
2. อายุ _____ปี
3. น้ำหนัก_____กิโลกรัม ส่วนสูง_____เซนติเมตร BMI_____$kg/m^2$
4. Vital sign แรกรับ: BT____°C RR____/ min HR___ bpm BP_____/_____ mmHg
5. วันที่เข้ารับการรักษา_____วันที่กลับบ้าน_____
   ระยะเวลาที่รักษาตัวในโรงพยาบาลรวม _____วัน
6. Diagnosis_____
7. โรคประจำตัว
   - ☐ ไม่มีโรคประจำตัว
   - ☐ ไม่ทราบ
   - ☐ มีโรคประจำตัว คือ 1) _____ 4) _____
     2) _____ 5) _____
     3) _____ 6) _____
8. ประวัติการได้รับยาที่เป็นพิษต่อไต
   - ☐ ไม่มี
   - ☐ มี คือ [ ] Sulfonamide
     [ ] Amphotericin B

[ ] Aminoglycoside

[ ] Diuretics (_____)

[ ] NSAIDS (_____)

[ ] Metformin ; หยุดยาก่อนได้รับสารทึบรังสี ○ ใช่ ○ ไม่ใช่

[ ] อื่นๆ ได้แก่ _____

**ส่วนที่ 2** ข้อมูลลักษณะหัตถการ (Procedural characteristic data)

1. วันที่ทำหัตถการหลอดเลือดหัวใจ_____เวลา_____
   ใช้เวลารวม_____นาที (เริ่ม_____ ถึง_____)
2. Vital sign ☐ Peripheral [ ] manual [ ] monitor
   ☐ Arterial line
   2.1) ที่ห้องสวนหัวใจก่อนเริ่มทำหัตถการ
   BT_____°C RR_____/min HR_____ bpm BP_____/_____ mmHg
   2.2) แรกรับ(At ward) เมื่อกลับจากห้องสวนหัวใจ
   BT_____°C RR_____/min HR_____ bpm BP_____/_____ mmHg
3. ปริมาณสารทึบรังสี (Contrast media) ที่ใช้_____ml
4. Angiographic diagnosis _____
5. จำนวนหลอดเลือดที่ทำหัตถการผ่านสายสวน_____ เส้น
6. ภาวะแทรกซ้อน
   ☐ ไม่มี
   ☐ มี คือ [ ] Hypotension
   [ ] Hematoma
   [ ] Arrhythmia
   [ ] Sepsis
   [ ] ต้องการ Blood transfusion
   [ ] อื่นๆ _____
7. ใช้เครื่อง intra-aortic balloon pump (IABP) ☐ ใช้ ☐ ไม่ใช้

8. การให้ pre-medication

☐ ไม่มี

☐ มี คือ ○ Hydration ได้แก่ _____

○ N-acetylcysteine

9. การให้ post-medication

☐ ไม่มี

☐ มี คือ ○ Hydration ได้แก่ _____

○ N-acetylcysteine

10. การตรวจรักษาหลอดเลือดหัวใจผ่านสายสวนครั้งก่อนหน้า

☐ ไม่มี

☐ มี เมื่อ_____

**ส่วนที่ 3** ข้อมูลผลการตรวจทางห้องปฏิบัติการ (Laboratory data)

| วันที่ | เวลา | ผลการตรวจทางห้องปฏิบัติการ | | |
|---|---|---|---|---|
| | | Serum creatinine (mg/dl) | eGFR(ml/min/1.73m$^2$) | Hematocrit (%) |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

**เลขที่บันทึก □□□**

**แบบประเมินคะแนนความเสี่ยงของ Mehran**

| Risk factor | Mehran risk score | Assessment | | Risk score | Note |
|---|---|---|---|---|---|
| | | Yes | No | | |
| 1) Hypotension : BP ≤ 90 /50 mmHg requiring inotropic support with medications | 5 | | | | |
| 2) CHF rated class III/IV on the NYHA classification* or admission with acute pulmonary edema | 5 | | | | |
| 3) Patient's age >75 years | 4 | | | | |
| 4) Anemia (hematocrit <39% for men and <36% for women) | 3 | | | | |
| 5) Documented history of Diabetes mellitus | 3 | | | | |
| 6) Preprocedural serum level of creatinine >1.5 mg/dl<br><br>**or** An estimated glomerular filtration rate <60 ml/min per 1.73 $m^2$ | 4<br><br>2 for 40– 60<br>4 for 20– 40<br>6 for < 20 | | | | |
| Total risk score | | | | | |

*The Stages of CHF according to the New York Heart Association functional classification system (NYHA Classification)

| Class | Patient Symptoms |
|---|---|
| Class I (Mild) | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath). |
| Class II (Mild) | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea. |
| Class III (Moderate) | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. |
| Class IV (Severe) | Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased. |

# APPENDIX B
# HUMAN SUBJECTS APPROVAL DOCUMENTS

2 PRANNOK Rd. BANGKOKNOI
BANGKOK 10700

Tel. (662) 4196405-6
FAX (662) 4196405

MAHIDOL UNIVERSITY
Since 1888
**Siriraj Institutional Review Board**
**Certificate of Approval**

**COA no. Si 312/2012**

**Protocol Title** : Validation of the Mehran risk scoring tool to predict risk for contrast induced nephropathy in Thai patients undergoing cardiac catheterization or percutaneous coronary intervention

**Protocol number** : 226/2555(EC1)

**Principal Investigator/Affiliation** : Lieutenant Parichart Jaimoon / Department of Preventive and Social Medicine
Faculty of Medicine Siriraj Hospital, Mahidol University

**Research site** : Faculty of Medicine Siriraj Hospital

**Approval includes :**

1. SIRB Submission Form
2. Proposal
3. Informed Consent Form
4. Case Record Form
5. Mehran Assessment Form
6. Principle Investigator's curriculum vitae

**Approval date** : June 12, 2012

**Expired date** : June 11, 2013

This is to certify that Siriraj Institutional Review Board is in full Compliance with international guidelines for human research protection such as the Declaration of Helsinki, the Belmont Report, CIOMS Guidelines and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP).

(Prof. Jarupim Soongswang, M.D.) June 12, 2012
Chairperson date

(Clin. Prof. Udom Kachintorn, M.D.) 15 JUN 2012
Dean of Faculty of Medicine Siriraj Hospital date

Page 1 of 2

หน่วยพิมพ์โรงพยาบาลศิริราช 2341 / 3,000 แผ่น / ก.ย 51 / Mat. 10023252

RL 01_2555

ที่ IRB/RTA ..1033../2555

**คณะอนุกรรมการพิจารณาโครงการวิจัย กรมแพทย์ทหารบก**

317 ถนนราชวิถี เขต ราชเทวี กรุงเทพฯ 10400

รหัสโครงการ: N006h/55

ชื่อโครงการวิจัย : การศึกษาแบบประเมินคะแนนความเสี่ยงของ Mehran ต่อการเกิดภาวะไตทำงานบกพร่องเนื่องจากสารทึบรังสีในผู้ป่วยคนไทยที่เข้ารับการตรวจรักษาหลอดเลือดหัวใจผ่านสายสวน [Validation of the Mehran risk scoring tool to predict risk for contrast induced nephropathy in Thai patients undergoing cardiac catheterization or percutaneous coronary intervention.]

เลขที่โครงการวิจัย : -

ชื่อผู้วิจัยหลัก: ร.ท.หญิงปาริชาติ ใจมูล

สังกัดหน่วยงาน : กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า

สถานที่ทำการวิจัย: โรงพยาบาลพระมงกุฎเกล้า

เอกสารรับรอง :

(1) แบบรายงานการส่งโครงร่างการวิจัยครั้งแรก Version 1 วันที่ 10 พ.ค. 2555
(2) โครงร่างการวิจัยฉบับภาษาไทย Version 2 วันที่ 9 ก.ค. 2555
(3) แบบบันทึกข้อมูล Version 1 วันที่ 10 พ.ค. 2555
(4) ประวัติผู้วิจัย Version 1 วันที่ 10 พ.ค. 2555
(5) เอกสารชี้แจงข้อมูล Version 2 วันที่ 9 ก.ค. 2555
(6) หนังสือแสดงความยินยอม Version 2 วันที่ 9 ก.ค. 2555

ขอรับรองว่าโครงการดังกล่าวข้างต้นได้ผ่านการพิจารณารับรองจากคณะอนุกรรมการพิจารณาโครงการวิจัย กรมแพทย์ทหารบก ว่าสอดคล้องกับปฏิญญาเฮลซิงกิ และแนวปฏิบัติ ICH GCP

วันที่รับรองด้านจริยธรรมของโครงร่างการวิจัย: 8 สิงหาคม 2555
วันสิ้นสุดการรับรอง: 7 สิงหาคม 2556
ความถี่ของการส่งรายงานความก้าวหน้าของการวิจัย: รายงานความก้าวหน้าทุก 1 ปี

.....
พันเอกหญิง เยาวนา ธนะพัฒน์
ประธานคณะอนุกรรมการพิจารณาโครงการวิจัย พบ.

.....
พันเอกสหพล อนันต์นำเจริญ
เลขานุการและอนุกรรมการพิจารณาโครงการวิจัย พบ.

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

ขอมอบประกาศนียบัตรนี้ เพื่อแสดงว่า

ร้อยโทหญิงปาริชาติ ใจมูล

ได้เข้าอบรมเรื่อง จริยธรรมการวิจัยในคนสำหรับนักศึกษาบัณฑิตศึกษา

วันศุกร์ที่ ๔ ตุลาคม ๒๕๕๓

ณ ห้องประชุม หม่อมหลวงบัว กิติยากร อาคารศูนย์โรคหัวใจสมเด็จพระบรมราชินีนาถ

ขอให้นำความรู้และประสบการณ์ที่ได้รับไปใช้เป็นหลักในการปฏิบัติเพื่อเกิดประโยชน์สูงสุด

ให้ไว้ ณ วันที่ ๔ เดือน ตุลาคม พุทธศักราช ๒๕๕๓

ศ.คลินิก นพ.อิรวัฒน์ กุลทนันทน์
คณบดีคณะแพทยศาสตร์ศิริราชพยาบาล

ศ.พญ.จารุพิมพ์ สุขสว่าง
ประธานคณะกรรมการจริยธรรมการวิจัยในคน

ศ.น.พ.ชัยรัตน์ ฉายากุล
รองคณบดีฝ่ายการศึกษาหลังปริญญา

# BIOGRAPHY


| | |
|---|---|
| **NAME** | Capt. Parichart Jaimoon |
| **DATE OF BIRTH** | July 27, 1984 |
| **PLACE OF BIRTH** | Chiang Mai, Thailand |
| **INSTITUTIONS ATTENDED** | The Royal Thai Army Nursing college, 2007<br>Bachelor of Nursing<br>Mahidol University, 2013<br>Master of Science (Epidemiology) |
| **PRESENT POSITION** | Phramongkutklao Hospital<br>315 Rajvithee Road, Ratchathewi, Bangkok,<br>Thailand 10400<br>Tel. 0-2354-7638 |