DOCTOR OF PHILOSOPHY

Contrast Induced-Acute Kidney Injury

New Insights into Risk Prediction of Contrast Induced-Acute Kidney Injury and Peri-Procedural Nephroprotective Therapies

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Contrast Induced-Acute Kidney Injury: New Insights into Risk Prediction of Contrast Induced-Acute Kidney Injury and Peri-Procedural Nephroprotective Therapies

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Abbreviations

ACE	angiotensin converting enzyme
ACS	acute coronary syndrome
AKI	acute kidney injury
AMI	acute myocardial infarction
ARF	acute renal failure
CAD	coronary artery disease
CAG	coronary angiography
CCC	calculated creatinine clearance
CHF	congestive heart failure
CI-AKI	contrast induced acute kidney injury
CIN	contrast induced nephropathy
CKD	chronic kidney disease
CKI	chronic kidney injury
CM	contrast media
CMSC	contrast media safety committee
CTO-PCI	chronic total occlusion percutaneous coronary intervention
DBP	diastolic blood pressure
DM	diabetes mellitus
EF	ejection fraction
e GFR	estimated glomerular filtration rate
GFR	glomerular filtration rate
HB	hemoglobin
HTN	hypertension
ICM	Iodinated contrast media
INR	international normalized ratio
IOCM	iso-osmolar contrast media
IV LOCM	intravenous low osmolar contrast media
LAD	left anterior descending
LCX	left circumflex
LOCM	low-osmolar contrast media
LV	left ventricle
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MHFD	matched hydration and forced diuresis
MRS	Mehran Risk Score
NSTEMI	non-ST elevation MI
PAD	peripheral arterial disease

PCI	percutaneous coronary intervention
RCA	right coronary artery
RCTs	randomized clinical trials
RRT	renal replacement therapy
SBP	systolic blood pressure
SCH	Slemani Cardiac Hospital
SCr	serum creatinine
SD	standard deviation
SPSS	Statistical Package for the Social Sciences
TG	triglycerides
TIMI	Thrombolysis In Myocardial Infarction
WBC	white blood cells.

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Author's Declaration

I confirm that I am the author of the work named in this document and that this is the final corrected version of my thesis to be submitted for archiving. I have read and understood the information provided and described at: http://www.dundee.ac.uk/library/research/theses/howtodeposityourthesis/ and hereby grant permission to the Library and Learning Centre administrators to make the work available as described. I have exercised reasonable care to ensure that the work is original and to the best of my knowledge does not break any UK law or infringe any third party's copyright or other Intellectual Property Right.

Aram Jamal Mirza Saeed Date: 5/7/2022

Thesis Summary

As an interventional cardiologist, my PhD research was motivated by the clinical problem of contrast-induced acute kidney injury (CI-AKI) that is a potential complication arising from the numerous coronary angiography and percutaneous coronary interventions that I do. Although most contrast media are considered safe, at-risk individuals can develop CI-AKI. CI-AKI is not an uncommon complication after coronary angiographic procedures with a reported incidence of 1-2% in the general population and could be as high as 50% in high-risk patient subgroups. My PhD, which is divided into 2 parts, is to provide new insights into risk prediction of CI-AKI and peri-procedural nephroprotective therapies. Specifically, my PhD addressed research questions related to firstly, the risk prediction of CI-AKI in patients undergoing percutaneous intervention and examine if patients could be identified for periprocedural intervention and secondly to test the potential benefits of a peri-procedural therapeutic intervention to prevent CI-AKI in patients undergoing percutaneous interventions.

CI-AKI risk prediction scores have been developed but these often involved the use of contrast volume in score calculations that limits their application in identifying patients who might benefit from peri-procedural strategies that protect the kidney. In the **first part** of my PhD thesis, I evaluated 2 recently proposed pre-procedural risk scores that do not include procedural variables including the contrast volume: Modified Mehran Score and the score developed by Liu and colleagues (Liu Prediction Score) to determine their ability to identify at risk patients undergoing chronic total occlusion percutaneous intervention (CTO PCI). I prospectively enrolled 329 consecutive and eligible patients (mean age 60.9±8.6 years, 64.1% Males; baseline eGFR 76.1±22.5 ml/min, serum creatinine 1.0±0.2 mg/dL) undergoing CTO PCI at our institution from December 1st 2017 to October 28 2020. All patients provided written informed consent to participate in this clinical study. The Modified Pre-procedural Mehran Score utilized the variables in Mehran score except the contrast volume. The Liu Prediction Score utilized four key risk factors (age ≥75 years, LVEF < 40%, serum albumin< 30 g/L and Serum Creatinine (SCr) >1.5 mg/dL) for predicting CI-AKI. The performance of the Modified Mehran Score and Liu Prediction

Score were compared with the performance of the original Mehran score using area under the receiver operator characteristic curve (AUROC). Sensitivity and specificity were also compared for different cut-off values. 29 (8.8%) cases developed CI-AKI, defined as a 25% increase or an absolute increase in SCr ≥0.5 mg/dL over baseline within 48–72 h after contrast medium exposure. The removal of contrast volume from Mehran score resulted in no loss of discrimination (AUROC 0.9591 vs 0.9514 for the original Mehran and the modified Mehran respectively, P=NS). Full Mehran score had an optimal cut-point of 11 that resulted in a 0.90 accuracy of predicting CI-AKI with a sensitivity of 93.1% and a specificity of 90.0%. Modified Mehran score had an optimal cut-point of 7 that resulted in a 0.85 accuracy of predicting CI-AKI with a sensitivity of 96.6% and a specificity of 83.3%. With an optimal cut point of 5.5, the Liu score that was determined in 208 patients that had available serum albumin resulted in a 0.90 accuracy of predicting CI-AKI with a sensitivity of 100.0% and a specificity of 89.3%.

A recent meta-analysis of high-volume forced diuresis with matched hydration using the RenalGuard medical device system revealed a significant reduction in the risk of CI-AKI, major adverse cardiac event rate, and the need for renal replacement therapy. However, the RenalGuard device is not widely available and affordable especially in low-middle income countries such as Kurdistan. In the **second part** of my PhD thesis, I designed and conducted the CINEMA trial (ISRCTN Registry Number: 72194653) to evaluate the potential benefits of a non-automated matched hydration and forced diuresis (MHFD) protocol compared to current hydration protocol in the prevention of contrast induced AKI. A total of 1,205 consecutive patients with chronic kidney disease (CKD) undergoing coronary procedures were randomized to either non-automated MHFD (MHFD group, n = 799) or standard intravenous isotonic saline hydration (control group; n= 406). The MHFD group received 250 ml normal saline (NS) bolus over 30 minutes before the coronary procedure followed by an intravenous bolus (0.5 mg/kg) of furosemide. Hydration infusion rate was manually adjusted to replace the patient's urine output. When urine output rate reached >300 ml/h, patients underwent coronary procedure. Matched fluid replacement was maintained during the procedure and for 4 h post-treatment. CI-AKI was defined

conventionally as ≥25% or ≥0.5 mg/dl rise in serum creatinine over baseline. In the MHFD group, less patients developed CI-AKI (MHFD vs control: CI-AKI, 64 (8.01%) patients vs 57 (14.04%), p <0.001). Incidence of cumulative in-hospital clinical complications was similar in both MHFD-treated patients and controls.

In conclusion, in the CINEMA trial, I have shown that a non- automated MHFD protocol is effective and safe method for the prevention of CI-AKI in patients with CKD. I have also shown that both a modified pre-procedural Mehran score as well as the Liu Risk Score have potential use to identify patients undergoing CTO PCI for peri-procedural nephroprotective therapies such as with the matched hydration protocol as in the CINEMA trial. Taken together, my research findings have shown the utility of pre-procedural risk prediction scores to identify at risk individuals who could be targeted for a non-automated MHFD to prevent CI-AKI.

Chapter 1 Introduction

1.1 History of Coronary Angiography and Percutaneous Coronary Intervention

Worldwide, coronary artery disease (CAD) is the leading cause of morbidity and mortality and imposes a major health and economic burden on the majority of developed nations. In the United States alone it is estimated to cause 790,000 heart attacks each year with an estimated cost of $89 billion as of 2016 that is expected to increase to $215 billion by 2035 (1).

In the past decade, improved therapies have decreased the mortality accompanying CAD while increasing survival following a myocardial infarction. Despite this decrease in mortality, the prevalence of CAD is expected to continue to increase due to the increase in the aging population (1).

The treatment of CAD has been transformed by the introduction of percutaneous coronary intervention (PCI), which remains the focus of intensive research and development (1). The field of interventional cardiology has evolved significantly since the development of a procedure that allowed cardiac catheterization.

In 1929, in a small hospital in Eberswalde/ Germany, Werner Forssmann, a young surgical resident, anesthetized his own elbow, inserted a catheter in his antecubital vein and, with the catheter dangling from his arm, he proceeded to a basement x-ray room where he documented the catheter's position in his right atrium—proving that a catheter could be inserted safely into a human heart. His biographic sketch adds "Forssmann's goal was to find a safe way to inject drugs for cardiac resuscitation. He was determined that catheterization was the key, but it was believed at the time that any entry into the heart would be fatal. Forssmann was immediately dismissed from his post for his self-experimentation, despite the significance of his discovery. The popular press acclaimed his work, but the medical establishment branded him as crazy, scorning him and ignoring his work for over a decade. He continued to experiment with catheterization in dogs and it is alleged he stopped self-experimentation only when he had used all of his veins with 17 cut downs. Discouraged by his lack of acceptance in cardiology he switched to urology and

eventually became a country doctor. He never returned to cardiology research but was awarded a Nobel Prize in 1956 (along with cardiology innovators Cournand and Richards) for his pioneering efforts" (2).

The development of cardiac catheterization led to coronary angiography [CAG] that is the gold standard test for detection of atherosclerotic coronary artery disease. Like any invasive procedure, there are minor and major life-threatening complications. Fortunately, such complications have decreased significantly since the beginning of CAG due to advanced equipment design, improved peri-procedural patient care and increased experience of diagnostic centers and operators (3).

The treatment of CAD has been transformed by the introduction of percutaneous coronary intervention (PCI), which remains the focus of intensive research and development (1,4–6).

The field of interventional cardiology has evolved significantly with the following key technological milestones (**Table 1.1**)

1. The first percutaneous transluminal coronary angioplasty (PTCA) was performed by Andreas Grüntzig in 1977 using a balloon catheter mounted on a fixed wire. This was the first milestone in treating CAD (4).

2. The introduction of Bare-metal stents (BMS) that is a mesh like tube of this wire that serves to prevent restenosis (5).

3. First-generation drug-eluting stents (DES) that were developed to reduce the risk of in-stent restenosis through a slowly released drug that blocks cell proliferation that can cause in-stent restenosis (6).

4. Subsequent development of second- and third-generation biodegradable polymer-based DES (5).

5. Bioabsorbable stents are currently under development (4).

Table 1-1. Key Technological Milestones of Percutaneous Coronary Intervention (1)

Table 1-1: Key Technological Milestones of Percutaneous Coronary Intervention (PCI)		
Year	Therapy	Complications
1977	First balloon angioplasty by Andreas Grüntzig	1. Acute occlusion caused by vascular elastic recoil and thrombosis. 2. Very high occurrence of restenosis rates
1987	First generation of BMS	1. Increased risk of stent thrombosis. 2. Frequent restenosis due to neointimal proliferation.
2002/03	First generation DES	1. Impaired reendothelialization due to non-selective drug administration. 2. Elevated risk of late and very late stent thrombosis.
2008	Second generation DES	1. Hypersensitivity to the durable polymer. 2. Diminished late vessel healing and recovery of function.
2011	Third generation DES	
Next generations	1. Bioresobable DES 2. Cell selective DES 3. Personalized therapy	
BMS: Bare metal stent, DES: Drug eluting stent.		

1.1.1 Percutaneous Coronary Angioplasty (PTCA)

The history of coronary angioplasty began with the ground-breaking work of Andreas Grüntzig in 1977, who was the first to use balloon-expandable catheters for the treatment of flow-limiting atherosclerotic coronary artery lesions. Thereafter, early investigators tested self-expanding springs as a solution to abrupt closure and restenosis seen with balloon angioplasty but these devices suffered from difficult delivery and a

high complication rate. Julio Palmaz and Richard Schatz introduced the first balloon-expandable stent as a mechanical support to improve vessel patency. Their pioneering work launched a new era in the treatment of coronary artery disease.

Over the last three and half decades, there has been striking growth in the technology and applicability of percutaneous techniques to treat obstructive coronary artery disease (CAD). Percutaneous coronary interventions (PCI) has a significant evidence base and it is definitely recognized as the most common method used in the invasive therapy of patients with CAD worldwide. Although PCI could be considered as a routine procedure, it requires an experienced multidisciplinary team that can offer high quality care throughout the hospital stay (7). Percutaneous coronary intervention use has increased by more than 60% during a 15-year period [1997-2012]. In the United States alone, an estimated 600,000 PCIs are performed annually with similar trends in Europe and Canada (8).

1.1.2 Bare Metal Stents (BMS)

To combat the shortcomings of elastic recoil, pioneering work performed by Sigwart et al. developed and implanted the first self-expanding bare-metal stent (BMS) following balloon angioplasty, and in 1987 the BMS was the first food and drug administration (FDA)-approved stent in the USA. Although this new technology reduced early elastic recoil, it was accompanied by two major problems: stent thrombosis and in-stent restenosis (ISR). Despite the potentially serious complications associated with the procedure, BMS implantation became the standard of care following the publication of the results from two landmark trials in 1993, the STRESS and the BENESTENT, which indicated that BMS implantations were superior to balloon angioplasty alone. However, follow-up studies found that in-stent restenosis due to neointimal proliferation was still persistent at the rate of 20–30%. (1,9).

1.1.3 What happens after stent implantation in the coronary arteries?

The actual use of balloon angioplasty together with stent deployment disrupts the endothelial cell (EC) layer and initiates a cascade of molecular events that contribute to thrombosis and restenosis. This inevitable EC injury induces platelet activation and aggregation followed by infiltration of leukocytes and monocytes into the lesion site. The resulting inflammatory response plays a critical role in the initiation and progression of neointimal formation. Platelet and inflammatory cells secrete growth factors, chemokines and cytokines, and induce macrophage phagocytosis that clears cell debris and induces proliferation and migration of quiescent vascular smooth muscle cells (VSMCs) and ECs to heal the lesion. The shift in VSMC phenotype from quiescent contractile to synthetic, and subsequent entry into the cell cycle followed by migration into the intima and deposition of the extracellular matrix is the hallmark of intimal hyperplasia (1).

1.1.4 The evolution of the first-generation of drug-eluting stent

In 1999, Edwardo Sousa implanted the first sirolimus-eluting stent (SES). Several randomized controlled trials that followed revealed that SES was superior to BMS in reducing ISR and target lesion revascularizations. In 2003, the FDA approved the SES, CYPHER, and shortly after the paclitaxel-eluting stent (PES), TAXUS. However, follow-up studies showed that patients receiving drug-eluting stent (DES) were at higher risk of developing late clinical events such as myocardial infarction and death owing to late stent thrombosis (ST), when compared to BMS. This devastating complication imposed the use of prolonged regimens of dual anti- platelet therapy (1,10).

1.1.5 Vascular response to Drug-Eluting Stents

A competent endothelium (both in integrity and function) is critical in order to provide an efficient semipermeable barrier capable of regulating vascular tone, lipid, and tissue-fluid homeostasis, as well as suppressing intimal hyperplasia, inflammation, and thrombus

formation. inflammation. DES deployment inevitably disturbs the normal competent endothelium structure. Elution of non-selective cytostatic or cytotoxic drugs drastically reduces the quality of vessel healing and the regenerating endothelium. The exposure of the metal struts of the stents to the circulation results in hypersensitivity reactions, platelet adhesion, and chronic inflammation. Moreover, accelerated neoatherosclerosis in the stented segment, caused by the poorly formed endothelial cell junctions and impaired barrier function that allows lipoproteins to enter the sub-endothelial space, were found to occur more frequently and at an earlier time point in DES when compared with BMS (1,11).

1.1.6 New Generations of Drug-Eluting Stent

In the second-generation DES, improved platforms, made of cobalt–chromium (CoCr) or platinum–chromium (PtCr), reduced thickness and were used to improve radial strength and visibility, while newer derivatives of sirolimus, such as everolimus and zotarolimus, were used to improve lipophilicity and enhance cellular uptake. Second-generation DES showed superiority to first-generation DES, not only with lower target lesion revascularization rates, but also lower rates of stent thrombosis according to large randomized controlled trails enrolling thousands of patients (1,12).

1.1.7 Third generation DES

To overcome the hypersensitivity reaction to the durable polymer, non-polymeric third-generation DES with biodegradable polymers and a semisynthetic analogue of sirolimus, biolimus A-9, with 10 times higher hydrophilicity were also developed. These biodegradable polymer-based DES showed similar safety and efficacy outcomes to the second-generation DES and received FDA approval in 2015 (1,13).

1.1.8 Fourth generation DES

At the same time, fourth-generation DES constructed with fully bioresorbable scaffolds (BRS), designed to provide vessel support and deliver the anti-proliferative drug to prevent neointimal proliferation for a defined period after PCI, followed by gradual resorption leaving behind no permanent foreign material. The most studied bioresorbable Vascular Scaffold system was the Absorb GT1, made of fully biodegradable poly-L-lactic acid that controls the release of everolimus. Although, the FDA approved Absorb GT1 for use in the United States in 2016, a warning was released from the FDA one year later in 2017, related to the increased incidence of device thrombosis and it was subsequently removed from the global market (1,14).

1.1.9 Future Directions for Percutaneous Coronary Intervention

1.1.9.1 Selective anti-restenotic and pro-healing drug

Despite an impressive list of promising technological advances in the field of stent therapy over the past two decades, restenosis and stent thrombosis (primarily late and very late) remain the principal factors contributing to stent-associated morbidity and mortality rates. Current therapies remain incapable of providing a comprehensive treatment that can prevent restenosis and inflammation while concurrently preserving the endothelial layer, which is vital for both vascular healing and preventing thrombosis and neo-atherosclerosis (1,15).

Due to the non-selective mechanism of action of the drugs eluted from the DES, ST will remain a persistent risk, and measures must be implemented to minimize this risk. For example, ensuring that patients are both able and likely to comply with at least 12 months of dual anti-platelet therapy before DES implantation together with ensuring optimal stent deployment during PCI are two effective ways of reducing this incessant risk of ST (1,16).

To date, cell-selective drugs that can discriminate between proliferating VSMCs, inflammatory cells and ECs are not available. Considering that vascular ECs provide crucial protection against thrombosis, lipid uptake, and inflammation, it is of paramount importance to develop a cell-selective therapy that can inhibit VSMC proliferation and inhibit inflammatory cell infiltration, yet spare ECs to carry on their vital functions. In response to this challenge, we have developed an innovative "microRNA (miRNA)-based cell-selective therapy" to selectively target VSMC and inflammatory cells while protecting ECs, thereby enabling them to reendothelialize vessel walls and maintain their crucial function (1,17).

In summary, the treatment of obstructive CAD using minimally invasive PCI has evolved dramatically in the last 30 years. However, the enthusiasm for each advance has been fraught with unforeseen complications. Drug-eluting stents mitigate the risk of stent restenosis and thus represent an important advance in the percutaneous treatment of CAD. New generation DES with thin struts releasing limus-family analogues from durable polymers have further improved clinical outcomes and patient safety. The next major advance in the evolving field of PCI may be the incorporation of biodegradable polymer stents and fully bioresorbable vascular scaffolds into routine clinical practice, although their efficacy, safety and ultimately their place in therapy remain to be determined (18).

1.2. Chronic Total Occlusion-PCI

Advancing stent technology has enabled interventional cardiologists to perform PCI to open chronic total occlusions (CTOs). Because PCI for CTOs improve patient anginal symptoms and quality of life, these procedures have been increasing over the past decade. A CTO is defined as a completely occluded coronary artery without any anterograde blood flow (thrombolysis in myocardial infarction score of 0) for more than 3 months (19).

CTOs are highly prevalent among patients undergoing diagnostic coronary angiography, where they are found in roughly one-quarter to one-third of patients, though the prevalence is related to the group studied (20–24). The reported prevalence of CTO varies in different populations and a Multicenter Canadian registry of CTOs reported CTO rates of 54 and 18% in patients with and without prior coronary artery bypass surgery (CABG), respectively (22). Another contemporary study reported that approximately 25% of the patients with obstructive coronary artery disease (CAD) on coronary angiography had CTOs (24).

All patients with CTO should receive optimal guideline-directed medical therapy and revascularization should be considered only in those with debilitating angina despite medical therapy and in whom benefits exceed potential risk of procedure. In recent years with advances in interventional technology, there has been considerable interest in PCI of CTO lesions. Retrograde techniques have been extensively studied in comparison to antegrade techniques. Retrograde techniques have contributed to increases in CTO PCI success rates and are generally used in higher complexity lesions. Observational data suggest increased short-term complications in procedures requiring the use of retrograde techniques; however, long-term CTO PCI durability and patient outcomes have been shown to be similar among procedures using antegrade only versus retrograde techniques. Because PCI for CTOs improve patient anginal symptoms and quality of life, these procedures have been increasing over the past decade (25).

1.3. Complications of Coronary angiography and angioplasty

Coronary angiography [CAG] and PCI are now standard diagnostic and therapeutic procedures across the world. Like any invasive procedure, there are minor and major life-threatening complications **(Table 1-2).** Although complications have decreased significantly due to advanced equipment design, improved peri-procedural patient care and increased experience of diagnostic centers and operators, complications do occur (3). With the advance of coronary PCI technology, some procedures such as CTO-PCI typically

require longer procedure times, with increased iodinated contrast administration and are associated with higher complication rates compared with non- CTO PCIs (26). The increased use of iodinated contrast carries a substantial risk of contrast- induced AKI which is the focus of my PhD dissertation.

Table 1-2. Complications of Coronary Angiography and Intervention (27)	
Access complications	Bleeding
	Hematoma
	Arterial damage or occlusion
	Distal limb ischemia
	Embolization
Cardiac complications	Myocardial ischemia
	Myocardial infarction
	coronary artery dissection
	Arrhythmia
	Aortic rupture and dissection
Systemic Complications	Contrast induced acute kidney injury
	Allergic response to radiocontrast
	Stroke
	Radiation exposure

Due to evolution of drug-eluting stent and superior pharmacotherapy, contemporary percutaneous coronary intervention is associated with increased patency and relatively low risk of complications. While less frequent than in the past, major complications such as death (0.7%) and myocardial infarction (2%) still occur in these procedures (27). The significant complications of PCI (abrupt closure, coronary dissection and coronary perforation) are described in the following sections.

1.3.1. Abrupt Closure

The incidence of abrupt closure during PCI has decreased from 3% in the balloon angioplasty era to 0.3% in the current era. This decreasing incidence corresponds to the increased use of stents and effective anti-thrombotics (27). The cardiac complications are displayed in **Tables 1-3 to Table 1-9.**

Table 1-3: Causes and treatment of abrupt closure (27)	
Cause	Treatment
Dissection	1. Stent if vessel is 2 mm or more 2. IVUS to confirm presence and extent of dissection 3. Consider GP IIb/IIIa inhibitor
No-reflow	1. Confirm effective anticoagulation 2. Distal delivery of vasodilators 3. Consider GP IIb/IIIa inhibitor
Thrombus	1. Thrombectomy 2. Stenting 3. GP IIb/IIIa inhibitor
Acute stent thrombosis	1. Thrombosuction 2. IVUS 3. Redilatation if under expanded 4. Confirm effective anticoagulation 5. Optimize antiplatelet therapy—consider GPIIb/III a inhibitor
IVUS, intravascular ultrasound; GP, glycoprotein.	

1.3.2. Coronary Perforation

Table 1-4 Classification of coronary dissection. (27)	
Type	Definition
Type A	Minor radiolucency within the coronary lumen without dye persistence
Type B	Parallel tracks or double lumen separated by a radiolucent area during angiography without dye persistence
Type C	Extraluminal cap with dye persistence
Type D	Spiral luminal filling defects
Type E	New persistent filling defects
Type F	Dissection leading to total occlusion

Coronary artery perforation (CAP) is defined as an anatomical breach in the wall of a coronary vessel due to penetration of the 3 layers of the vessel wall, resulting in extravasation of blood or dye into the pericardium, myocardium, or adjacent cardiac chamber or vein (27,28). Coronary perforation is a serious complication with an incidence of less than 1.0%. It is responsible for 20% of cases referred for emergency CABG. Lesions associated with perforation are more complex in nature like American College of Cardiology type B or C, calcified lesions or chronic total occlusion (CTO). Women and elderly are more likely to sustain perforation (27).

Risk factors for coronary perforations are 1. Oversizing balloon (balloon to artery ratio >1.2) 2. High-pressure balloon inflation 3. Stenting of tapering vessel 4. Stenting of lesions recrossed after dissection and 5. Stenting of total occlusion with subintimal navigation of the wire (27).

There are 3 classes of CAP as shown in the following table:

Table 1-5: Classification of Coronary Perforation (27)

Class	Definition	Risk of tamponade (%)
I	Focal extraluminal crater without extravasation	8
II	Pericardial or myocardial 'blush' without contrast agent	13
III	Contrast agent 'jetting' through a frank (>1 mm) perforation	53

1.3.3. Prevention of coronary perforation is shown in the table below:

Table 1-6: : Prevention of Coronary Perforation (27)	
Device	Methods to avoid perforation
Angioplasty balloon	Low balloon: artery ratio, avoid high-pressure pre-dilatation
Stent	Avoid high-pressure initial inflation and oversizing in heavy calcification Post-dilate the stent
Stiff wires	Careful distal navigation to avoid side branch Maintain tip mobility to avoid subintimal space
Rotational atherectomy	Artery ratio (<0.8) Avoid angulated segments

Contemporary PCI is associated with a relatively low risk of dissection, abrupt closure and perforation. Randomized trials have not provided good evidence for blanket recommendations, and avoidance of these feared complications of PCI is best accomplished by operator experience and preventive approaches. Prevention is always the first priority because it is better to stay out of trouble rather than to get out of it. Continued education in the evolving field of PCI will allow further improvement in patient outcomes (27).

Complications of Percutaneous intervention, PPCI, revascularization of ACS are shown in **Table 1-7** (29)**.**

Table 1-7: Complications of Percutaneous intervention, PPCI, revascularization of ACS (29)
Perforations
Hemodynamic collapse
No-reflow
Dissection
Entrapped equipment
Contrast induced acute kidney injury
Radiation risks
Infections: local, systemic
Myocardial infarction: due to thrombus formation
Bleeding: external (site of intervention), internal

The complications of PCI in CTO are shown in **Table 1-8** (30)**.**

Table 1-8: Complications of percutaneous coronary intervention in CTO (30)
Impairment of collateral flow: spasm, distal embolization, dissection of side-branches
Dissection with branch occlusion and perforation: side branch dilation, damage of nanochannels connecting vasa vasorum, intra-wall balloon expansion
Guidewire entrapment
Subacute vessel re-occlusion
Contrast induced acute kidney injury
Arrhythmia requiring treatment
Periprocedural Myocardial infarction
Radiation risks, infections, bleeding

The complications of Percutaneous intervention for LMS are shown in **Table 1-9.**

Table 1-9: Complications of Percutaneous intervention for LMS (31)
Dissection of side-branches
Perforation
Thrombosis
Guidewire entrapment
Late vessel re-occlusion
Contrast induced acute kidney injury
Myocardial infarction
Arrhythmia requiring treatment
Radiation risks, infections, bleeding

1.4. Contrast Induced Acute Kidney Injury CI-AKI: A Potential Complication of Coronary Angiography and Percutaneous Coronary Intervention

Contrast induced acute kidney injury (CI-AKI) is defined as a rise in serum creatinine of ≥0.5 mg/dL (>44 umol/L) or a 25% increase from baseline value, assessed 48-72 hours after the procedure (32,33). CI-AKI is the 3rd leading cause of acute renal failure (ARF) in hospital settings. This is partly due to steadily increasing number of diagnostic and therapeutic angiographic studies including PCI. Most cases of CI-AKI are reversible. Nevertheless, CI-AKI is associated with an increased morbidity and one-year mortality.

Moreover, the hospital stay is lengthened and hence, the cost is increased even if dialysis is not required (32). Chronic total occlusion PCI (CTO–PCI) carries a considerable risk of CI-AKI as it is a long procedure requiring large contrast volume, and often a second or third attempt is required for successful result (34).

1.5. Risk Factors for CI-AKI

In a study from India, Kumar et al observed self-limited CI-AKI in 2.4% of patients who underwent CAG. In their study, the only recognized risk factor was hypertension. Patients with known chronic kidney disease, baseline creatinine more than 0.5 mg/dL, significant hypotension, anemia and an emergency PCI for acute myocardial infarction (AMI) were excluded (35). The role of hypertension in predisposing to CI-AKI can be attributed to atherosclerosis of the aorta and possible atheroembolic phenomenon beside an endothelial injury provoked by hypertension (35).

Parfrey et al showed that diabetic patients with preserved renal function had a comparable rate of CI-AKI to that of a healthy individual (35,36). In one PCI series of 1,575 consecutive patients with diabetes mellitus (DM), CI-AKI was observed in 15.1% of patients with preserved renal function and in 27.4% of patients with pre- existing renal insufficiency (36).

It was found that the higher the baseline serum creatinine value, the greater the risk of CI-AKI. In one study, post-angiographic CI-AKI occurred in 2%, 10.4%, and 62% of patients with baseline serum creatinine levels of less than or equal to 1.2 mg/dL, 1.3 mg/dL to 1.9 mg/dL, and greater than or equal to 2.0 mg/dL, respectively (36). Moreover, advanced age has been demonstrated to be a risk factor for the occurrence of CI-AKI (35).

The physicochemical properties of different radio contrast media are shown in **Table 1-10** (37)**.**

Table 1-10 : Physicochemical properties of different radio contrast media					
Contrast Medium	Type	Structure	Iodine content (mg/ml)	Osmolality (mosmol/kg)	Viscosity 37 °C (mPaxs)
Ioxaglate	Ionic	Dimer	320	600	7.5
Iopamidol	Non-ionic	Monomer	370	796	9.4
Iohexol	Non-ionic	Monomer	350	820	10.5
Iomeron	Non-ionic	Monomer	350	610	7.5
Iodixano	Non-ionic	Dimer	320	319	11.4

1.6. Mechanism of CI-AKI

The high rate of CI-AKI in post-PCI patients could be related either to the patient (advanced age, previous chronic kidney disease [CKD], diabetes, dehydration, and concomitant use of other nephrotoxic drugs) or procedure related (intra-arterial route of administration, use of high osmolar contrast media (CM), repeated exposure to contrast within 48 hours, volume of contrast used, etc.) (35,38). The pathogenesis of CI-AKI is complex and not completely understood but thought to be multifactorial (32). Two frequently proposed mechanisms are renal vasoconstriction resulting in medullary ischemia and free radical injury. Iodinated contrast is known to provoke acute vasoconstriction due to release of adenosine, endothelin, and other renal vasoconstrictor agents (36). The severe vasoconstrictive effect results in loss of autoregulatory function and contributes to renal injury through the release of reactive oxygen species (e.g., superoxide). The kidney's ability to tolerate oxidant injury decreases with age and is believed to be responsible for an increased vulnerability in older adults to developing CI-AKI. Furthermore, increased oxidative stress is present in chronic renal failure and in patients with diabetes (36). The direct and indirect nephrotoxic effects of intravascular administration of contrast media is shown in **Figure 1-1.**

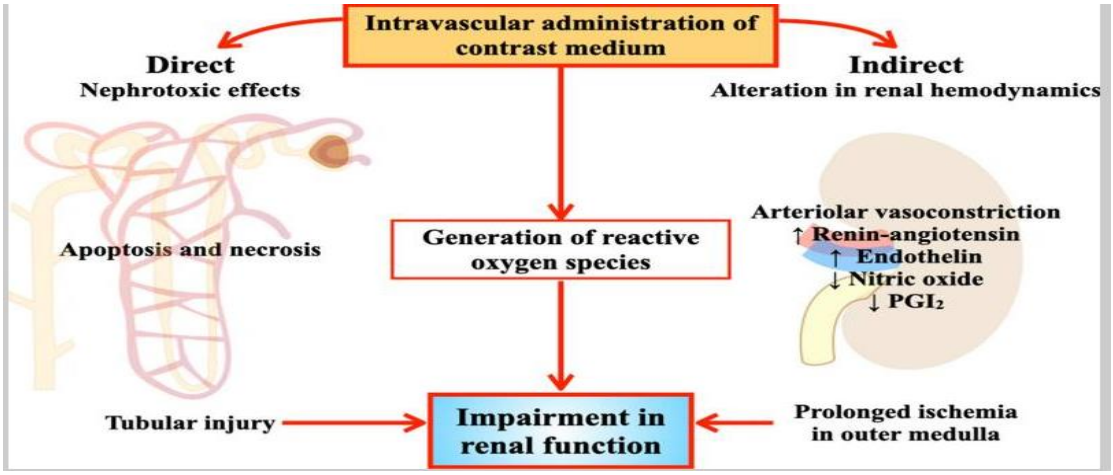

Figure 1-1: The nephrotoxic effects of intravascular contrast media (39).

The evidence that iodinated contrast is nephrotoxic is shown in **Figure 1-2** below:

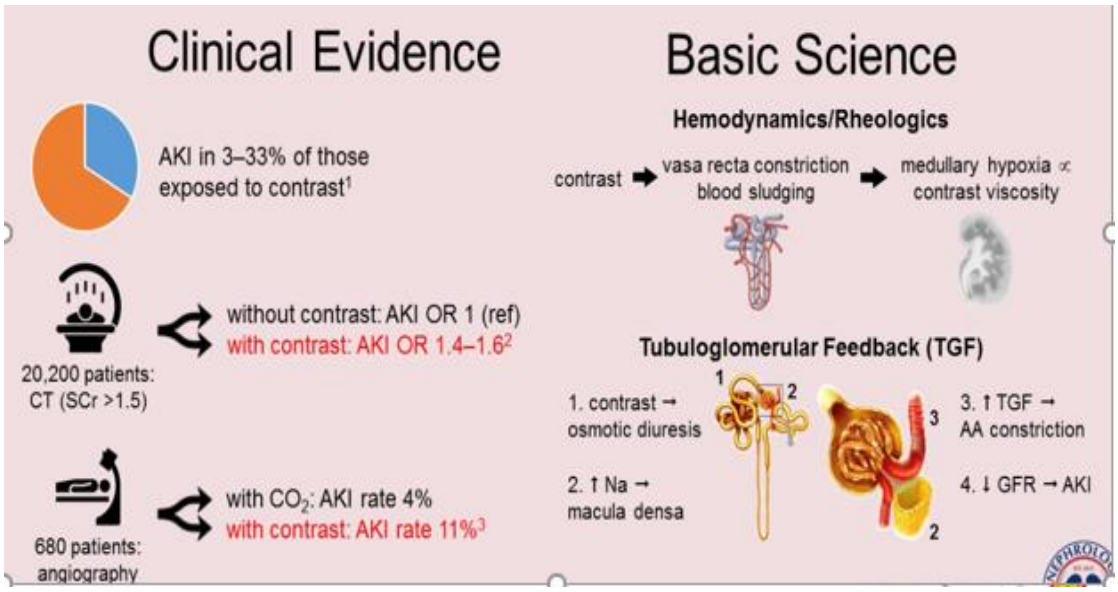

Figure 1-2: Evidence of nephrotoxic effects of iodinated contrast media.

1.7. Contrast Media

In healthy subjects, iodinated contrast has an average half-life of 2 hours and is almost completely eliminated by the kidneys in 24 hours. Initially it was thought that gadolinium-

based contrast media are safer than the iodinated agents. However, subsequent studies showed that both types of contrast media have significant nephrotoxicity (32).

The use of iodinated contrast media (ICM) improves the visualization of blood vessels during image-guided procedures (40). An average contrast-enhanced CT uses ~40 grams of iodine chemically bound to an organic molecule that is injected directly into the vascular system. This is a very large dose of foreign material and reflects the overall safety of these agents (41).

The use of ICM to delineate normal structures for diagnostic or therapeutic purposes represents a major advancement in the field of medical imaging (35). Radiographic contrast agents have been in use for over 60 years. Based upon current data, 2.0 million cardiac catheterizations are performed annually in the USA (32) and nearly 30 million contrast-enhanced CT scans, in addition to the use of contrast for peripheral angiography (41).

Iodinated contrast agents are usually classified based upon their osmolality-high, low, and isosmolar. ICM are also nephrotoxic in some but not all patients resulting in loss of glomerular filtration rate (GFR). Over the past 30 years, nephrotoxicity has been linked to osmolality although the precise mechanism underlying such a link has been vague. Improvements in our understanding of the pathogenesis of nephrotoxicity and prospective randomized clinical trials (RCTs) have attempted to further explore the relationship between osmolality and nephrotoxicity. Despite causing acute kidney injury (AKI) in a small number of high-risk patients, still contrast media are considered extremely safe (41,42).

Despite the remaining uncertainty regarding the degree of nephrotoxicity produced by various contrast agents, nonionic low-osmolar contrast media (LOCM) may be preferred in patients at high risk for CI-AKI (36).

1.8. Intra-arterial vs. Intravenous Contrast Media

Intra-arterial administration compared to intravenous use has been believed to have higher incidence of CI-AKI, particularly when used above the level of renal arteries due to more contrast load reaching the kidneys. The CM Safety Committee [CMSC] consensus is that the danger of CI-AKI is significantly lesser after intravenous CM injection compared to intra-arterial (42,43).

1.9. Risk Prediction Scores

1.9.1. Mehran CI-AKI Risk Score (MRS)

Several risk factors for CI-AKI have been identified and the cumulative risk rendered by their combination was assessed by Mehran et al in 2004. Eight variables were identified [hypotension, intra-aortic balloon pump, congestive heart failure (CHF), chronic kidney disease, DM, age > 75 years, anemia and volume of contrast]. This risk score can be used for both clinical and investigational purposes (44). Beside its usefulness in prediction of CI-AKI after non-urgent PCI, MRS was also shown to be "clinically useful in primary angioplasty setting population and to stratify patients for poor clinical outcomes both in the short- and long-term follow up" (45). R.A. Abella´s-Sequeiros et al validated the Mehran score in a cohort of Spanish patients with acute coronary syndrome [ACS] and concluded that this score was also good for predicting CI-AKI in such patients who underwent CAG (46,47).

1.9.2. Other Scoring Systems

Other models of risk prediction have been developed with many important predisposing factors. However, these models have exclusively focused on patients given intra-arterial CM for coronary angiographic procedures. Yin et al have "successfully established a risk prediction model with excellent predictive ability for CI-AKI in Chinese patients. This

model can be applied to patients administered CM for coronary procedures and other contrast procedures such as intravenous contrast- enhanced CT, CT angiography, and non-coronary angiography. Three new factors were included in the model: the decreased sodium concentration, the International Normalized Ratio [INR] value, and the pre-procedural glucose level" (48). The INR is derived from prothrombin time (PT) which is calculated as a ratio of the patient's PT to a control PT standardized for the potency of the thromboplastin reagent developed by the World Health Organization (WHO) using the following formula: INR = Patient PT ÷ Control PT (49).

Liu et al published a paper in 2015 in which they introduced a new simple risk score for patients with CTO undergoing PCI. This preprocedural risk score showed excellent predictive ability for identifying patients at high risk of CI-AKI and poor long term outcome, thus, allowing the interventional team to make adequate adjustments to the procedures. The new risk score included four peri-procedural variables (age ≥75 years, left ventricular ejection fraction <40%, serum albumin, and SCr >1.5 mg/dL) **(Figure 1-3)** (50)

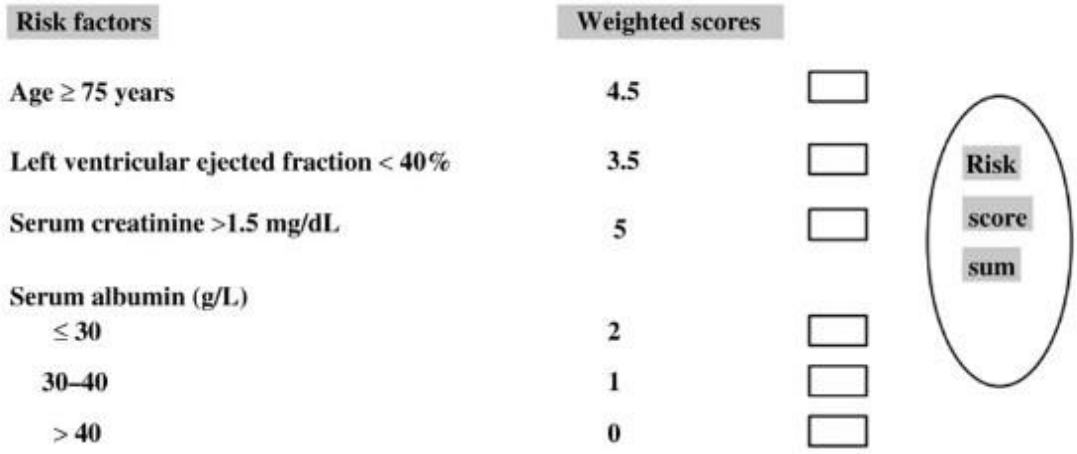

Figure 1-3: Schematic representation of the new risk score for CI-AKI (50).

Silver et al performed a search of Medline, Embase, and CINAHL databases from inception to 2015. Eligible studies evaluated characteristics of predictive models that identified patients at risk of contrast induced AKI among adults undergoing a diagnostic or

interventional procedure using conventional radiocontrast media. 16 studies were identified, describing 12 prediction models. The majority of higher performing models included measures of pre-existing chronic kidney disease, age, diabetes, heart failure or impaired ejection fraction, and hypotension or shock. No prediction model evaluated its effect on clinical decision making or patient outcomes. Most predictive models for contrast induced AKI in clinical use have modest ability, and are only relevant to patients receiving contrast for coronary angiography. Further research is needed to develop models that can better inform patient centered decision making, as well as improve the use of prevention strategies for contrast induced AKI (51).

The use of prediction models for contrast induced AKI could have several benefits. Firstly, they may help identify patients at high risk for the disorder, who might benefit from peri-procedural strategies that protect the kidney. Secondly, patients identified as high risk would also be an ideal population to study novel therapies for the prevention and treatment of the disorder. Finally, prediction models for contrast induced AKI could improve preintervention counselling to facilitate informed patient centered decision making (51).

It is likely that other factors that were not included in the risk models also contribute to the risk of contrast induced AKI. For example, drug treatments such as inhibitors of the renin-angiotensin aldosterone system and diuretic agents could increase susceptibility to contrast induced AKI through alterations in kidney haemodynamics. The contribution of these risk factors could be especially important in emergency settings when these treatments are not discontinued before administration of contrast. In addition, the use of prophylactic drugs and intravenous fluid was not included in the risk scores, despite being administered to patients in 10 of 12 studies. This may have led to differences in the rate of contrast induced AKI among the studies, and contributed to inter-study heterogeneity (51,52).

Predictive models for contrast induced AKI have been available for clinical use for almost 10 years. However, uptake by cardiologists and radiologists has been low, judging by their omission from recent clinical practice guidelines and survey studies (51).

One reason for the low clinical uptake of predictive models for contrast induced AKI is that they have focused exclusively on populations receiving intra - arterial contrast for coronary angiographic procedures. These procedures represent a small proportion of all contrast procedures, with contrast enhanced computer tomography (CT) scans being much more common. Indeed, the risk of contrast induced AKI associated with intravenous, contrast enhanced CT procedures is not rare, occurring in 11% of a low risk population (51).

In addition, the pathophysiological mechanism of contrast induced AKI related to contrast enhanced CT procedures could differ from that associated with coronary angiography procedures. For example, in intravenous procedures involving contrast enhanced CT, a large volume of intravenous contrast is often injected within 10 to 20 seconds compared with small intra-arterial injections of contrast occurring over minutes in coronary procedures. As such, predictive models for contrast induced AKI derived from patients undergoing coronary angiography might not be generalizable to individuals undergoing intravenous contrast enhanced CT procedures or CT angiography (51).

1.10. Peri-procedural treatment strategies to prevent CI-AKI in PCI including the RenalGuard

Although no known pharmaceutical treatment can effectively prevent or treat CI-AKI, various preventative strategies including risk assessment before contrast media exposure, the withdrawal of the nephrotoxic drugs, volume expansion with sodium chloride or sodium bicarbonate, hemofiltration or hemodialysis, and the optimal contrast media policy have been developed to CI-AKI prevention.

1.10.1. Peri-procedural hydration

Peri-procedural intravascular hydration is the single most important measure comprehensively proven to prevent the occurrence of CI-AKI, recommended by guidelines (32,34,35,53).

There are several specific hydration strategies, but an optimal strategy has not been established yet (36,38,40).

1.10.2. Furosemide-induced forced diuresis and Matched hydration

Several small randomized clinical trials have recently shown that in patients with CKD (54), furosemide-induced forced diuresis with matched hydration using the RenalGaurd system can prevent the occurrence of CI-AKI. Scientific databases and websites were searched for relevant RCTs. Data from 3 trials including 586 patients were analyzed. High-volume forced diuresis with matched hydration using the RenalGaurd system decreased risk of CI-AKI by 60% compared with the standard of care (55).

The RenalGuard system (PLC Medical Systems, Milford, Massachusetts, USA) **(Figure 1-4)** is a CE approved system which is being used worldwide and is approved for coronary angiography. A computer system weighs the urine of the patient, calculates the urine rate (ml/min) and delivers matched IV normal saline into the patient, keeping the fluid balance as initially programmed. Hence, it is an automated matched hydration system. A standard 18-22-gauge cannula is inserted into an arm peripheral vein and a standard catheter is placed in the urinary bladder for urine collection. The intravenous line and the urinary catheter are connected to the RenalGuard System. The RenalGuard System is set to 100% match so that the system infuses a volume of IV normal saline matching the volume of urine produced by the patient. The RenalGuard system combines hydration with furosemide forced diuresis, while preventing dehydration or over hydration (56).

Two recent randomized controlled trials have shown that furosemide-induced diuresis with matched isotonic intravenous hydration using the RenalGuard (57,58) decreases AKI

in high-risk subjects undergoing coronary intervention by up to 71%. The patients received an initial 250-ml intravenous bolus of normal saline over 30 min followed by an intravenous bolus (0.5 mg/kg) of furosemide. Hydration infusion rate was automatically adjusted to precisely replace the patient's urine output. When a urine output rate >300 ml/h was obtained, patients underwent the coronary procedure. Matched fluid replacement was maintained during the procedure and for 4 h post-treatment (58). Putzu et al performed a meta-analysis including 4 randomized controlled trials enrolling 698 patients who underwent PCI or trans-catheter aortic valve replacement. The meta-analysis showed a significantly lower incidence of CI-AKI (7.76% vs. 21.43%) and a lower need for renal replacement therapy (0.58% vs. 3.45%) in patients treated with RenalGaurd therapy compared with control treatment (59).

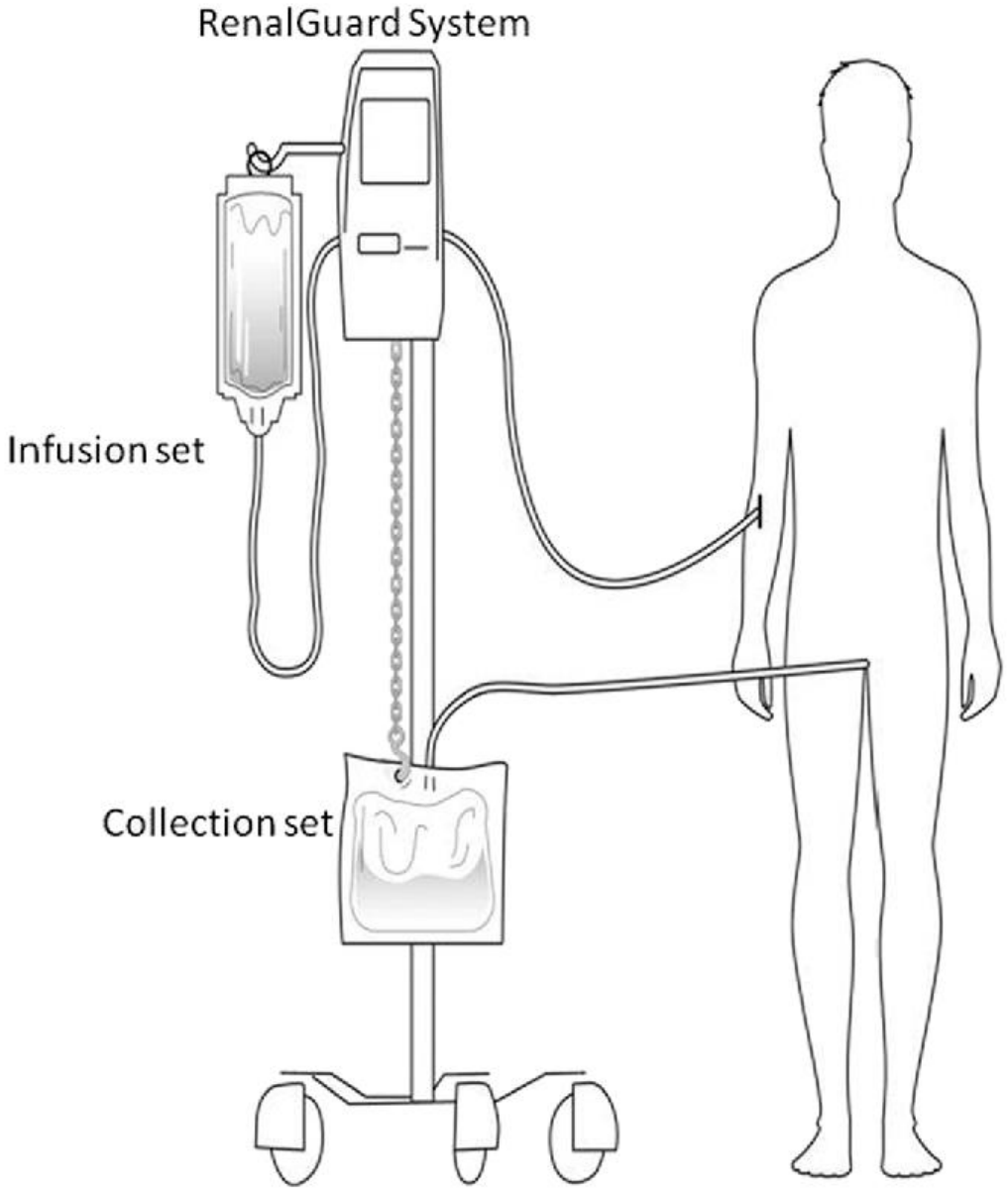

Figure 1-4: The "RenalGaurd" System.

AKI developing after contrast material administration is reversible in most cases, but its development may be associated with adverse outcomes (60) as shown in **Figure 1-5** below:

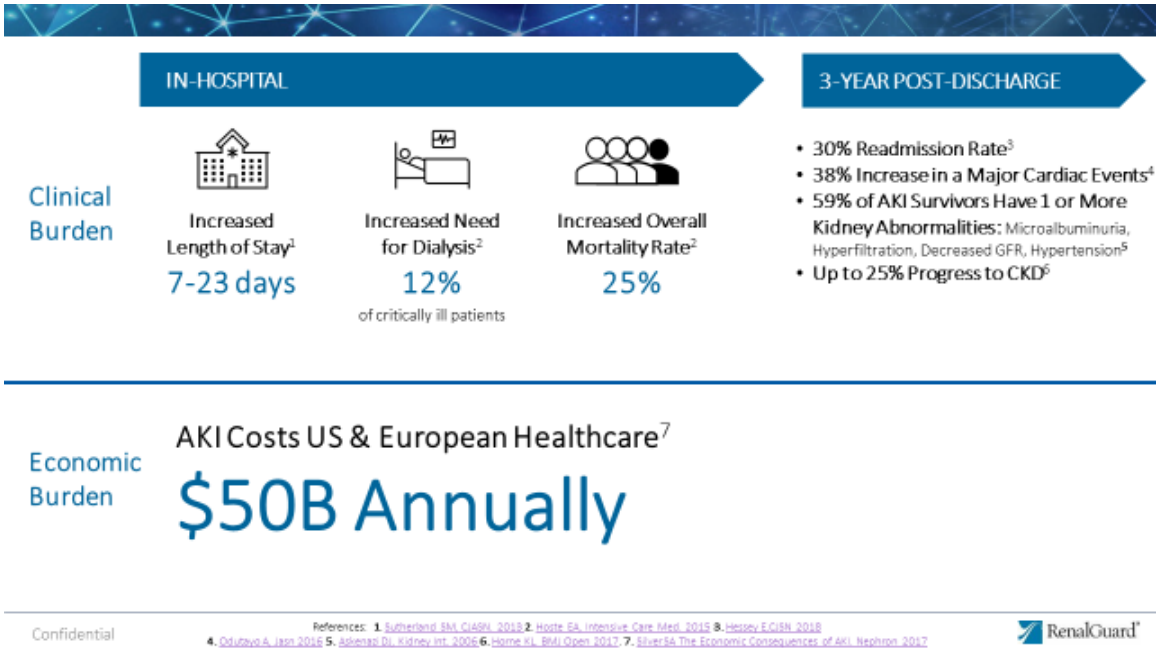

Figure 1-5: The Clinical and Economic Burdens of AKI.

There is no definite treatment of CI-AAKI once it is established. However, there are many preventive strategies (61). The prevention of CI-AKI is of paramount importance, with an ever increasing number of CAGs and PCIs being done on an outpatient basis. The goal of the clinician is to prevent CI-AKI justifying the old saying of "prevention is better than cure." (35). According to the current guidelines, the following strategies for prevention of CI-AKI are recommended: adequate hydration, decreasing contrast amount and using iso-osmolar or some low-osmolar contrast agents. Another practical prophylactic strategy has been suggested in which the total contrast volume is restricted to less than triple the calculated creatinine clearance (CCC) (38,62). The role of various drugs in preventing CI-AKI is still controversial and warrants future studies (62).

1.10.3. Minimizing the volume of CM

Of the modifiable variables, minimizing the volume of contrast medium administered is a primary defense against CI-AKI (3,38,63) Radio-contrast dose is the most powerful independent predictor of nephropathy requiring dialysis. The overall volume appears to be more relevant in patients with baseline CKD, who have a 5-10-fold increase in CI-AKI when >125-140 ml of contrast is administered, irrespective of other preventive measures. Therefore, most experts recommend limitation of contrast volume to 3 ml/kg (3). There are many angiographic and technical tips that can be utilized to reduce the amount of CM needed for CTO-PCI for example, staging the procedure (63). Most studies recommend reducing contrast volume to less than thrice a patient's calculated creatinine clearance [CCC] for all patients undergoing PCI (38). The first step in CI-AKI prevention during CTO-PCI is the recognition of high-risk patients, through evaluation of risk factors (especially such as preexisting renal disease and DM) and calculation of a risk score, such as the Mehran score (63).

1.10.4. Volume Expansion

Among the prophylactic strategies against CI-AKI, volume expansion using oral hydration and/or intravenous normal saline hydration ±sodium bicarbonate supplementation remains the gold standard (43). There is incomplete evidence supporting the use of hydration as a prophylaxis measure for CI-AKI. It is unknown whether all patients get an equal advantage from this treatment. Moreover, the optimal type, route, volume, and timing of hydration administration are not settled yet. Although hydration is a generally benign therapy, it is logistically difficult to employ, as most angiographic procedures are performed on outpatients (in whom 6 to 12 hours of pre-procedural hydration may not be possible). These issues deserve more study (62).

Early studies on dogs confirmed a decline in renal perfusion lasting up to 20 hours after radio-contrast administration. While no randomized clinical trials [RCT] have studied the

benefits of hydration alone, it seems reasonable that sufficient hydration may offset some of the presumed hemodynamic effects that may lead to CI-AKI (62,63) Pannu et al searched the relevant English medical literature between 1966 and 2006 and could identify 10 studies that evaluated the effects of various hydration protocols and diuretics in the incidence of CI-AKI. Four studies compared forced diuresis (furosemide and/or mannitol) with hydration, of which 3 showed a significant increase in the rate of CI-AKI in patients on diuretics (62). Solomon et al concluded that in patients with chronic renal insufficiency who underwent cardiac angiography, hydration with 0.45 percent saline provided better protection against acute decreases in renal function induced by radiocontrast agents than did hydration with 0.45 percent saline plus mannitol or furosemide (64). On the other hand, Stevens et al found that forced diuresis with intravenous crystalloid, furosemide, and mannitol provided a modest benefit against contrast-induced nephropathy (65). In the table below, there is a summary of 9 RCTs investigating hydration and diuretics as prophylactic strategies for CI-AKI (62).

Table1-11 Study Demographics and Clinical Characteristics: Hydration and Diuretics

Source	Osmolality/ Route of Contrast	Intervention Prophylaxis and Regimen	Control Prophylaxis and Regimen	Cointervention and Regimen	No. of Participants	Mean Age, y/ Female, %	Female, %	Diabetic, %	Mean Baseline SCr, mg/dL	Definition of Contrast-Induced Nephropathy
Hydration and Diuretics										
Bader et al,[46] 2004	Low/both IA and IV	Bolus 300 mL during procedure	2000 mL 0.9% saline in total (over 12 h pre/12 h post)	1500-2000 mL po H_20 (12 h pre)	39	65/18	18	26	0.9	>50% decrease in GFR at 48 h
Krasuski et al,[47] 2003	Multiple/IA	Bolus 250 mL saline x 20 min	1 mL/kg/h 0.45% saline (12 h pre)	1 mL/kg/h 0.45% saline (12 h post)	70	68/17	17	54	NR	>0.5 mg/dL in SCr at 48 h
Merten et al,[48] 2004	Low/both IA and IV	3 mL/kg/h IV saline (1 h pre) 1 mL/kg/h IV bolus (6 h post)	3 mL/kg/h IV saline (1 h pre); 1 mL/kg/h IV bolus (6 h post)	None	137	68/25	25	48	1.8	≥25% increase in SCr at 48 h
Mueller et al,[37] 2002	Low/IA	1 mL/kg/h 0.45% saline (same day)	1 mL/kg/h 0.9% saline (same day)	None	1620	64/26	26	16	0.9	≥0.5 mg/dL in SCr at 24 h or 48 h
Solomon et al,[38] 1994	Multiple/IA	Mannitol 25 g (60 min pre); furosemide 80 mg (30 min pre)	Placebo	1 mL/kg/h 0.45% saline (12 h pre/ 12 h post)	78	63/31	31	53	2.1	≥0.5 mg/dL increase in SCr at 48 h
Stevens et al,[49] 1999	Multiple/IA	Furosemide 1 mg/kg (max 100 mg) and mannitol 12.5 g in 250 mL D5W infused x 2 h	Placebo	150 mL/h 0.45% saline (start in laboratory/ 6 h post)	100	70/33	33	53	2.5	Multiple definitions
Taylor et al,[50] 1998	Multiple/IA	1000 mL po H_20 (10 h pre); 0.45% IV saline 300 mL/h (30-60 min pre/ 6 h post)	75 mL/h 0.45% IV saline (12 h pre/ 12 h post)	None	36	70/7	7	14	1.8	≥0.3 mg/dL increase in SCr within 24-48 h
Trivedi et al,[36] 2003	Low/IA	1 mL/kg/h 0.9% saline (12 h pre/ 12 h post)	Unrestricted fluids po	None	53	68/2	2	19	1.2	≥0.5 mg/dL increase in SCr at 48 h
Weinstein et al,[51] 1992	Multiple/IA	Furosemide 1.5 mg/kg (30 min pre)	None	6 mL/kg Hartman's solution x 1 h then 6 mL/kg/h D5W in 0.18% saline (1 h pre/ 2 h post)	18	69/0		25	1.6	None

1.10.5. Intra-venous Hydration

Adequate hydration of patients undergoing CM-enhanced imaging studies was suggested approximately 40 years ago. This was due to observation that dehydration would exacerbate renal insufficiency in a patient exposed to CM. CM safety committee recommends an intravenous regime of 1.0-1.5 mL/kg/hr for at least 6 hr before and after CM administration (43).

1.10.6. Oral Hydration

In an effort to overcome the limitations of outpatient intravenous hydration, investigators have assessed the use of pre-procedure oral hydration followed by post- procedure intravenous hydration in patients admitted for catheterization studies on the day of procedure. Taylor et al. reported an effective protocol comprising of pre-angiography oral hydration (1,000 mL clear fluids over 10 hr) followed by 6 hr of intravenous hydration (0.45% normal saline solution at 300 mL/hr) beginning just before CM exposure. The results were as good as with overnight intravenous hydration (43).

1.10.7. Sodium Bicarbonate-Based Hydration

Acidic environment which is typical of tubular urine promotes free radical production while high pH of normal extracellular fluid inhibits it. Since CM administration increases the oxidative stress and increases generation of free radicals and reactive oxygen species, alkalinizing renal tubular fluid with bicarbonate seems a logical strategy to reduce renal injury. Merten et al reported first study on the use of sodium bicarbonate in humans as a nephro-protective agent. In 2009, Tamura et al. reported that a single-bolus intravenous administration of sodium bicarbonate (20 mEq) 5 minutes before CM exposure along with standard hydration with NaCl (for 12 hr before procedure to 12 hr after procedure) is more effective against CI-AKI than standard hydration alone in patients with mild renal insufficiency. CM safety committee warrants more studies to be undertaken to assess the effectiveness of single bolus of sodium bicarbonate just before CM administration. If validated, this protocol would be extremely useful in daily clinical practice (43,66).

1.10.8. Pharmacological Protection

1.10.8.1. N-Acetylcysteine

The evidence for use of pharmacological agents against CI-AKI such as N-Acetylcysteine [NAC], ascorbic acid, theophylline/aminophylline, statins, targeted renal therapy [TRT], and ischemic preconditioning remains insufficient; hence no recommendations exist for their routine clinical use. However, the CMSC does recommend strict avoidance of nephrotoxic drugs such as NSAIDs before CM administration (43,63).

1.10.8.2. Ascorbic acid

Ascorbic acid acts as an antioxidant. It has also been reported to cause vasodilatation in coronary and brachial arteries. Moreover, in most studies, the vasodilatation effects induced by vitamin C occurred after intra-arterial administration (67). Through which pathway Vitamin C may provide nephroprotection against CI-AKI remains unsolved. Compared to a placebo, the incidence of CI-AKI was 9% in ascorbic acid group vs. 20% in control group in one study. Pooled analysis of many trials suggested that patients receiving ascorbic acid have 33% less risk of CI-AKI compared to patients receiving placebo or alternate pharmacological treatment. Despite the aforementioned evidence, ascorbic acid use has not been recommended yet by the CMSC (43).

1.10.8.3. Statins

Beside their cholesterol lowering capacity, statins seem to have other effects. They enhance NO production from endothelial cells and possess anti-inflammatory and oxidative actions (68). Statins may also modulate renal hypoperfusion occurring after CM administration by down regulating angiotensin receptors and decreasing the synthesis of endothelin. Due to these properties statins have the potential to be used as nephroprotective agents against CI-AKI. Pooled analysis of many trials suggests that use of short-term high-dose statin

treatment is associated with a significant reduction in risk of CI-AKI (RR=0.51, 95% CI 0.34-0.76, p=0.001) (43). However, a large multicenter trial is necessary before its routine use as nephroprotective agent can be recommended (43).

1.10.8.4. Theophylline

Adenosine has been implicated to be responsible for mediating CM-induced renal vasoconstriction; hence use of adenosine antagonists is logical. A meta-analysis of many trials suggests that theophylline significantly decreases the risk of CI-AKI (RR:0.48;95% CI:0.26-0.89; P=0.02) (43). Multicenter RCTs with large sample size evaluating clinically relevant clinical outcomes are required (43).

The table below summarizes RCTs investigating theophylline/aminophylline as preventive measures of CI-AKI (62).

Table 1-12: A Summary of RCTs of Theophylline/Aminophylline as Preventive Measures of CI-AKI

Source	Osmolality/ Route of Contrast	Intervention Prophylaxis and Regimen	Control Prophylaxis and Regimen	Cointervention and Regimen	No. of Participants	Mean Age, y/ Female, %	Female, %	Diabetic, %	Mean Baseline SCr, mg/dL	Definition of Contrast-Induced Nephropathy
Theophylline/Aminophylline										
Abizaid et al,[60] 1999	Low/IA	Aminophylline 4 mg/kg followed by 0.4 mg/kg/h (2 h pre); dopamine 2.5 ug/kg/min (2 h pre)	1 mL/kg/h 0.45% saline (2 h pre)	1 mL/kg/h 0.45% saline (12 h pre/ 12 h post)	60	75/33	33	57	2.0	≥25% increase in SCr at 48 h
Erley et al,[61] 1994	Low/both IA and IV	Theophylline 5 mg/kg IV in saline (45 min pre)	Placebo	None	39	55/28	28	18	1.2	None
Erley et al,[62] 1999	Low/both IA and IV	Theophylline 10 mg/d po (2 d pre/3 d post)	Placebo	0.45% saline, IV or po (24 h pre/ 24 h post); 2000-2500 mL total	80	64/22	22	30	1.8	≥0.5 mg/dL increase in SCr
Gandhi et al,[63] 1992	Low/IA	Theophylline 125 mg tid (1 d pre/2 d post)	Placebo	None	21	54/33	33	NR	NR	None
Huber et al,[64] 2002	Low/both IA and IV	Theophylline 200 mg (30 min pre)	Placebo	None	100	68/82	82	34	2.0	≥0.5 mg/dL increase in SCr at 48 h
Huber et al,[65] 2003	Low/IA	Theophylline 200 mg (30 min pre)	Placebo	None	100	68/17	17	31	1.7	≥0.5 mg/dL increase in SCr at 48 h
Kapoor et al,[66] 2002	High/IA	Theophylline 200 mg po bid (24 h pre/ 48 h post)	None	1 mL/kg/h 0.9% saline (12 h pre/ 12 h post)	70	53/9	9	100	1.2	≥25% increase in SCr or ≥25% decrease in GFR at 48 h
Katholi et al,[67] 1995	Multiple/IA	Theophylline 2.88 mg/kg po bid (1 h pre x 48 h)	Placebo	1.43 mL/kg/h po H_2O or IV D5W x 72 h	93	61/0		18	1.3	None
Kolonko et al,[68] 1998	High/NR	Theophylline 165 mg (30 min pre)	Placebo	None	58	41/21	21	0	1.0	None

Abbreviations: ANP, atrial natriuretic peptide; bid, twice daily; D5W, 5% dextrose; GFR, measured glomerular filtration rate; IA, intra-arterial; IV, intravenous; NAC, *N*-acetylcysteine; NR, not reported; po, by mouth; SCr, serum creatinine; tid, 3 times per day.
SI conversion: To convert SCr to µmol/L, multiply by 88.4.

1.10.9. Targeted Renal Therapy

One proposed hypothesis for failure of different nephro-protective drugs is that systemic administration of such drugs may not achieve adequate drug level in the renal vasculature to be effective against CI-AKI. This has led to the ingenious technique of targeted renal therapy [TRT] in which a drug is selectively infused into the kidneys via the renal arteries instead of systemic administration. Fenoldopam, being a dopamine receptor D 1 agonist, acts as a vasodilator and hence a potential to attenuate CM-induced cortical and medullary vasoconstriction. The safety and performance of TRT were assessed by retrospective analysis of 285 patients receiving fenoldopam via TRT. The incidence of CI-AKI was 71% lower than predicted. However, TRT delivery system and fenoldopam cost~$ 1,200.00.

Hence, strong evidence would be required before it can be considered for use in clinical practice (43).

1.10.10. Ischemic Preconditioning

Ischemic preconditioning involves exposure to short episodes of ischemia reperfusion to prepare a target organ against the main ischemic insult. If the site of generation of these short episodes of ischemic reperfusion is remote from the site of target organ, it is called remote ischemic preconditioning. This method has achieved only a variable success in providing renal protection by minimizing the CM-induced ischemia reperfusion injury (43).

1.10.11. Extracorporeal Removal of Contrast

Hemodialysis efficiently removes radiocontrast and has been proposed as a prophylaxis treatment for CI-AKI. Four small randomized trials have considered this question in patients with impaired renal function. Two found no benefit and the largest (n=113) suggested that hemodialysis was harmful, since more patients in the treatment group required ongoing dialytic support (62). The table below summarizes the different methods used in the prevention of CI-AKI.

Table 1-13: Methods of Prevention of CI-AKI		
Number	Method	Supporting Publications
1	Minimizing the volume of CM to less than thrice a patient's calculated creatinine clearance [CCC] for all patients undergoing PCI	Tavakol, Ashraf and Brener, 2012; Kooiman et al., 2014; Christakopoulos, 2016
2	Recognition of high-risk patients	Christakopoulos, 2016
3	Volume expansion	Sadat, 2013
4	Intravenous hydration	Sadat, 2013
5	pre-procedure oral hydration followed by post-procedure intravenous hydration	Sadat, 2013
6	Sodium Bicarbonate-Based Hydration	Sadat, 2013
7	strict avoidance of nephrotoxic drugs such as NSAIDs before CM administration	Sadat, 2013; Christakopoulos, 2016
8	N-Acetylcysteine	Sadat, 2013
9	Ascorbic acid	Sadat, 2013
10	short-term high-dose statin treatment	Sadat, 2013
11	Theophylline	Sadat, 2013
12	Targeted Renal Therapy (a drug [Fenoldopam] is selectively infused into the kidneys via the renal arteries instead of systemic administration).	Sadat, 2013
13	Ischemic Preconditioning	Sadat, 2013
14	Extracorporeal Removal of Contrast	Pannu, Wiebe and Tonelli, 2006
15	MHFD using the RenalGaurd System.	Briguori et al, 2011; Marenzi et al, 2015

Chapter 2

Following my literature review, as a high volume interventional cardiologist involved in complex interventions, I became interested in CI-AKI and came up with a number of research questions which are listed below:

2.1 The Research Questions

1. Much of the data related to CI-AKI have come from Western populations. What are the factors associated with CI-AKI in patients in Kurdistan? In particular, I was interested in CI-AKI risk prediction scores. I noted that many of these CI-AKI risk prediction scores often involved peri-procedural variables especially the use of contrast volume in score calculations that limits their application in identifying patients who might benefit from peri-procedural strategies that protect the kidney. How useful are pre-procedural risk scores like the Modified Mehran Score and the score developed by Liu and colleagues (Liu Prediction Score) in identifying at risk patients undergoing CTO PCI in Kurdistan?

2. Following my literature review, I then began to consider the potential peri-procedural therapeutic intervention to prevent CI-AKI. I noted in particular the recent meta-analysis of high-volume forced diuresis with matched hydration using the RenalGuard medical device system revealed a significant reduction in the risk of CI-AKI, major adverse cardiac event rate, and the need for renal replacement therapy (69). However, the RenalGuard device is not widely available and affordable especially in low-middle income countries such as Kurdistan. My research question was whether a non-automated matched hydration with forced diuresis protocol would also have beneficial effects in preventing CI-AKI in patients identified to have CKD?

2.2 My Aims and Objectives

1. To explore the factors associated with the development of CI-AKI in patients undergoing percutaneous coronary intervention for chronic coronary total occlusion in Sulaymaniyah, Kurdistan, Iraq. In the process, I evaluated 2 recently proposed pre-procedural risk scores: Modified Mehran Score and the score developed by Liu and colleagues (Liu Prediction Score) to determine their ability to identify at risk patients undergoing CTO PCI.

2. I have designed a randomized controlled trial called the CINEMA study that aims to evaluate the efficacy of matched hydration and forced diuresis in prevention of contrast-induced acute kidney injury in patients with impaired renal function undergoing percutaneous coronary intervention in Sulaymaniyah, Kurdistan, Iraq.

My thesis is driven by the clinical problem of contrast-induced AKI and my research relates to the identification of risks related to CI-AKI and peri-procedural treatment to prevent CI-AKI. My thesis is divided essentially into 2 parts. In the first part of my thesis, I have explored the prevalence in Kurdistan and evaluated 2 recently proposed pre-procedural risk scores: Modified Mehran Score and the score developed by Liu and colleagues (Liu Prediction Score) to determine their ability to identify at risk patients undergoing CTO PCI. In the second part of my thesis, I have designed a randomized controlled trial called the CINEMA study that aimed to evaluate the efficacy of matched hydration and forced diuresis in prevention of contrast-induced acute kidney injury in patients with impaired renal function undergoing percutaneous coronary intervention in Sulaymaniyah, Kurdistan, Iraq.

Chapter 3 Methods: Assessment of CI-AKI Risk and CI-AKI Risk Prediction

3.1 Type of Study

A prospective observational study.

3.2 Setting of the Study

The study was carried out in the Department of Cardiology/Slemani Cardiac Hospital (SCH)/Sulaymaniyah/Region of Kurdistan/Iraq in four different Cath labs.

3.3 Period of the Study

The study lasted 2 years and 11 months starting in December 1, 2017, and ending in October 28, 2020.

3.4 Ethics Approval and Consent to Participate

The study protocol was approved for its ethical consideration by the Ethical Committee of the College of Medicine/University of Sulaimani in a meeting numbered 58 held at November 27, 2017 (**11. Appendix**). Informed consents were obtained from all participants in the study.

3.5 Purpose of Study

1. To identify the prevalence and risk factors of contrast-induced acute kidney injury in patients undergoing percutaneous coronary intervention for chronic total occlusion in Sulaymaniyah, Kurdistan, Iraq

2. To evaluate 2 recently proposed pre-procedural risk scores: Modified Mehran Score and the score developed by Liu and colleagues (Liu Prediction Score) to determine their ability to identify at risk patients undergoing CTO PCI. (208)

3.6 Number of Enrolled Patients

We prospectively enrolled patients undergoing CTO PCI at our institution from December 1st 2017 until October 28 2020. Patients on long term hemodialysis were excluded.

3.7 Inclusion Criteria

(1) Age: Patients whose age ranged between 18 years and 85 years were included. (2) Planned procedures: CTO-PCI.

3.8 Exclusion Criteria

(1) End-stage renal disease. (2) Recent myocardial infarction. (3) Ejection fraction (EF) < 35%. (4) Blood loss and hypotension. (5) Use of left ventricular (LV) assist device or intra-aortic balloon pump. (6) Age >85 years. (7) GFR <60 ml/min/1.73 m^2

3.9 Definitions

● In this study, CTO was defined as Thrombolysis In Myocardial Infarction (TIMI) grade 0 for more than three months, in the presence of typical angina or reversible myocardial ischemia on thallium stress study.

N.B., A thallium stress test is a nuclear imaging test that shows how well blood flows into the heart during exercise and rest. Thrombolysis In Myocardial Infarction (TIMI) Grade Flow is a scoring system from 0-3 referring to levels of coronary blood flow assessed during percutaneous coronary angioplasty. TIMI 3 is normal flow which fills the distal

coronary bed completely. TIMI 2 flow (partial reperfusion) is delayed or sluggish antegrade flow with complete filling of the distal territory. TIMI 1 flow (penetration without perfusion) is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed. TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion.

● Chronic kidney injury (CKI) was defined as an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 based on the recommendations of the National Kidney Foundation.

● According to Cockcroft–Gault formula, the eGFR is calculated based on age, weight, serum creatinine, and gender of the patient. For men the formula is (140 -age) (weight in kg)/ 72 × SCr while for women, this result is multiplied by the factor 0.85.

● CI-AKI was defined as an increase in serum creatinine concentration by 25% or 0.5 mg/dL from the baseline 48-72 hours after contrast media exposure.

● Significant left ventricular systolic dysfunction is defined as an LVEF less than 40%.

3.10 Study Protocol

1. The age, coronary risk factors, previous PCI, and prior PCI attempt for the same CTO lesion were noted.

2. Blood specimens were obtained from all patients before the procedure for biochemical testing (Renal function, HbAIc, serum albumin, lipid profile & complete blood count).

3. Left ventricular (LV) function was assessed by echocardiography.

4. The estimated GFR was determined and serum creatinine (S. Cr) measurement was done 24 hours before the procedure.

5. All patients were on maintenance dose of Aspirin seven days prior to the procedure. All patients received 300 mg Clopedogril a day before the procedure if they were not already on it. Moreover, 5,000 IU unfractionated heparin (UFH) were given at the start of the procedure and extra doses were given according to the ACT level to prevent instent thrombosis.

Prior to percutaneous coronary intervention (PCI), we reviewed the indication for revascularization and the choice between PCI or coronary artery bypass graft surgery (CABG), and have a full discussion with the patient of the benefits and risks. Stable angina or anginal equivalent (such dyspnea on exertion) refractory to optimal medical therapy, as well as the presence of a large ischemic area, were the most common indications for consideration of revascularization for CTO (70,71).

3.11 Informed Consent

We had an extensive discussion about risks and benefits of CTO PCI with the patient. In patients with a history of MI with low left ventricular ejection fraction (LVEF), we considered viability study before CTO PCI. Ischemic mitral regurgitation was another indication that we sometimes considered (usually circumflex artery). We carefully reviewed the films, and based on risk scores and our center's experience, we incorporated the likelihood of technical success and risk of complications in our discussions with the patient. We were careful that the patient was aware of the absence of demonstrated benefit of CTO PCI to improve mortality or MI rates, as many patients were motivated by a belief that an open vessel would lead to improved longevity. Based on our discussion, many patients opt to continue medical l therapy alone, while others, typically the most symptomatic, opt to pursue CTO PCI.

3.12 The Procedure for CTO PCI

In all patients, the indications for CTO recanalization as well as the risk-benefit ratio were discussed with the patients and their families. CTO PCI differ from routine PCIs in several aspects.

First, we evaluated the diagnostic coronary angiogram extensively in order to understand the characteristics of the proximal cap of the occlusion, the true occlusion length, the distal vessel quality and the presence of important side branches as well as the adequacy and course of collaterals in order to decide how the procedure would begin.

Second, two arterial accesses were obtained either through two femoral arteries (mostly in case of retrograde procedures) or one femoral and one radial artery (mainly in cases of antegrade approach when dual injections were necessary).

Almost always, and whenever possible, we have started with antegrade approach, given the higher likelihood of complications with retrograde procedures. Thus, we routinely started in most cases with antegrade wire escalation (It consists of advancing wires with different degrees of stiffness, coating, and maneuverability through the true lumen of the vessel) and if the subintimal space was entered (dissection), we moved to antegrade dissection re-entry (ADR) which includes several techniques in which wires travel through the vessel wall (subintimal space) instead of the lumen and then re-access the true lumen past the occlusion with either specialized wiring technique (limited antegrade subintimal tracking) or specialized devices that enable true luminal reentry. In patients who had good retrograde collaterals, we considered retrograde procedure when ADR failed.

In those patients with a bifurcational lesion i.e in the presence of a branch very close to the distal cap and who had sizable retrograde collaterals, we would start the case with antegrade wire escalation and switch soon to retrograde approach if our antegrade wire went into the subintimal space given that propagation of dissection past the distal cap would jeopardize flow to that particular branch at the bifurcation.

In retrograde approach, approaching the CTO from the distal end of the occlusion via collaterals we did wiring through the retrograde collaterals, commonly through the septal perforators but also through epicardial collaterals, when we delivered a soft wire through a collateral vessel to the target vessel distal to the total occlusion supported by a maneuverable microcatheter.

In some patients with very complex lesions when retrograde wires were not able to be advanced across the occlusion in the true luminal space, we used a technique of controlled antegrade and retrograde tracking" (CART) and in two patients we obliged to use Reverse CART technique.

In all patients, the CTO lesion length was measured following bilateral simultaneous coronary injections in cases with collaterals that would fill the distal occluded artery or by antegrade coronary injection and visualizing filling both the proximal and distal occluded artery. The success of angioplasty was determined by visual appearance of TIMI Grade 3 flow with less than 30% residual stenosis. The volume of contrast (either iohexol or iodixanol contrast agents) was calculated for every patient. The patients with deteriorated left ventricular ejection fraction (LVEF) were closely followed up. JCTO score was calculated for every patient.

JCTO score is a score where one point is given for each of blunt entry stump, calcification, bend > 45 degrees, occlusion length > 20 mm, and a previous failed attempt (72,73).

In all patients, 5000 IU unfractionated heparin were given at the beginning of the procedure and extra doses were given according to the activated clotting time with a cutoff of 300 seconds.

After crossing the true lumen, predilatation was done starting with the smallest available balloon size to bigger one till the vessel was fully dilated followed by drug eluting stent implantation then post dilatation done with non-compliant balloon.

At the end of the procedure, radial sheath (if any) was removed in the cathlab and a radial band was applied and loosened over the next 30 minutes in the ward. The femoral sheath

was removed few hours later when ACT declined to less than 250sec. Some patients were discharged home the same day while others were discharged the next morning. The exact duration of patients, stay in the hospital after the procedure was not recorded.

The following figures demonstrate our procedure.

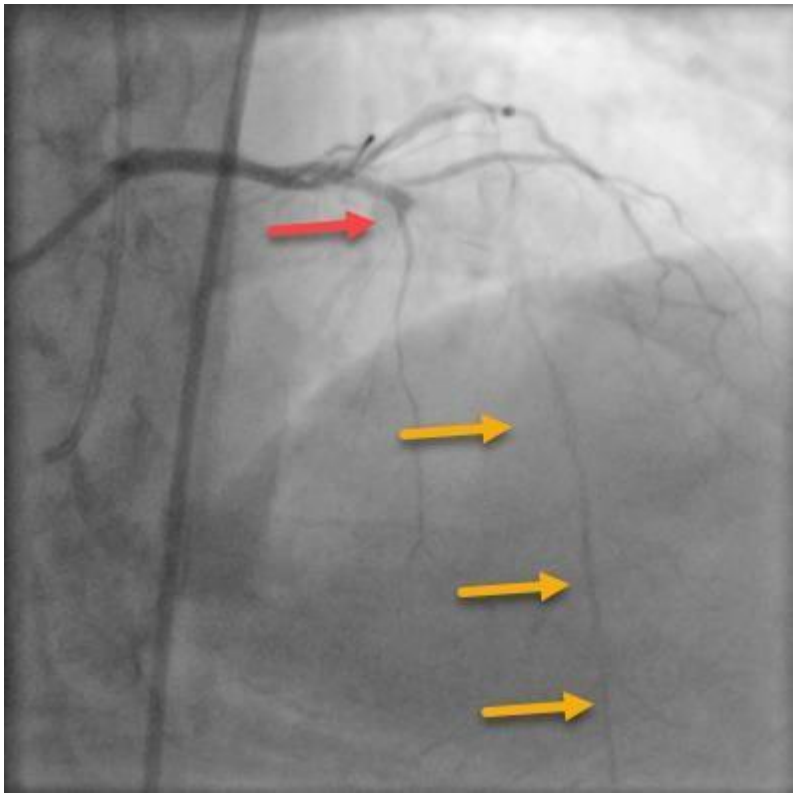

Figure 3-1: Shows total occlusion of the left anterior descending artery (LAD) (red arrow denotes the side of total occlusion while yellow arrow shows retrograde filing of the LAD from the right coronary system.

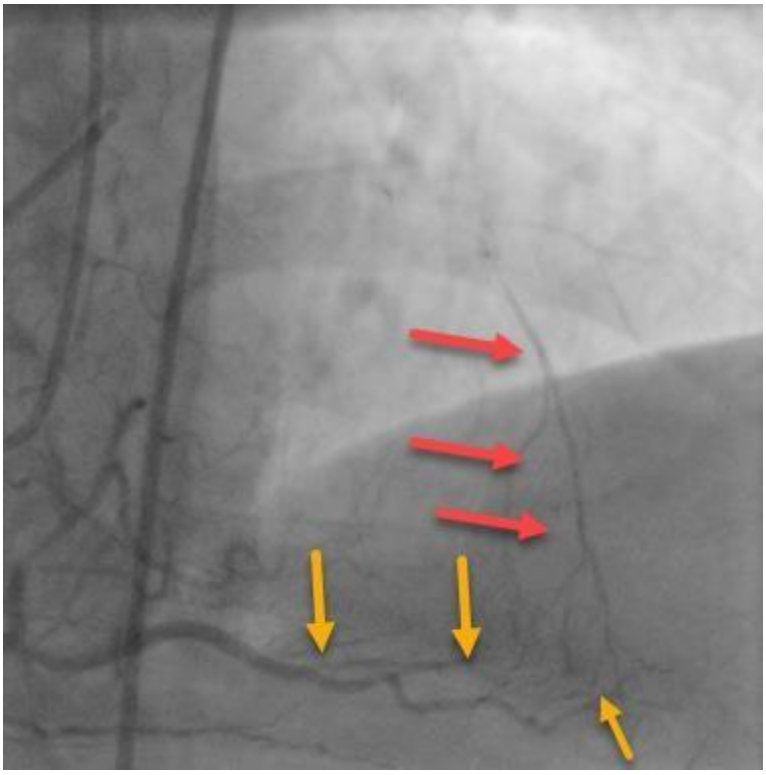

Fig.3-2: Shows the epicardial and septal collaterals (yellow arrows) from the right coronary artery (RCA) supplying the distal and mid part of the LAD) (red arrows).

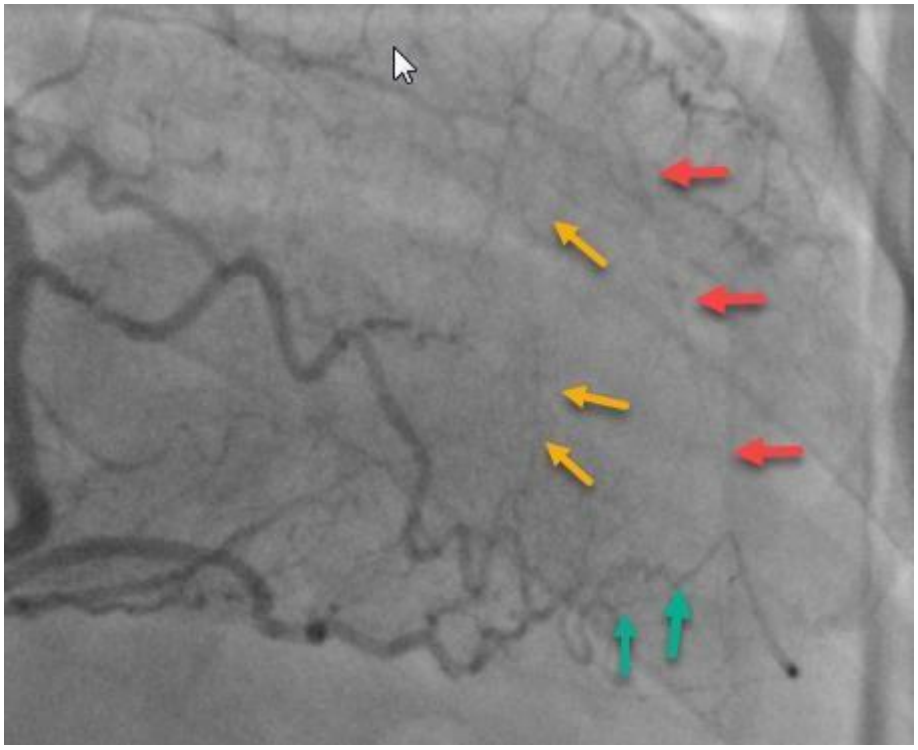

Fig.3-3: Shows the epicardial and septal collaterals (yellow arrows) and epicardial collaterals (green arrows) in magnified view from the RCA supplying the distal and mid part of the LAD (red arrows).

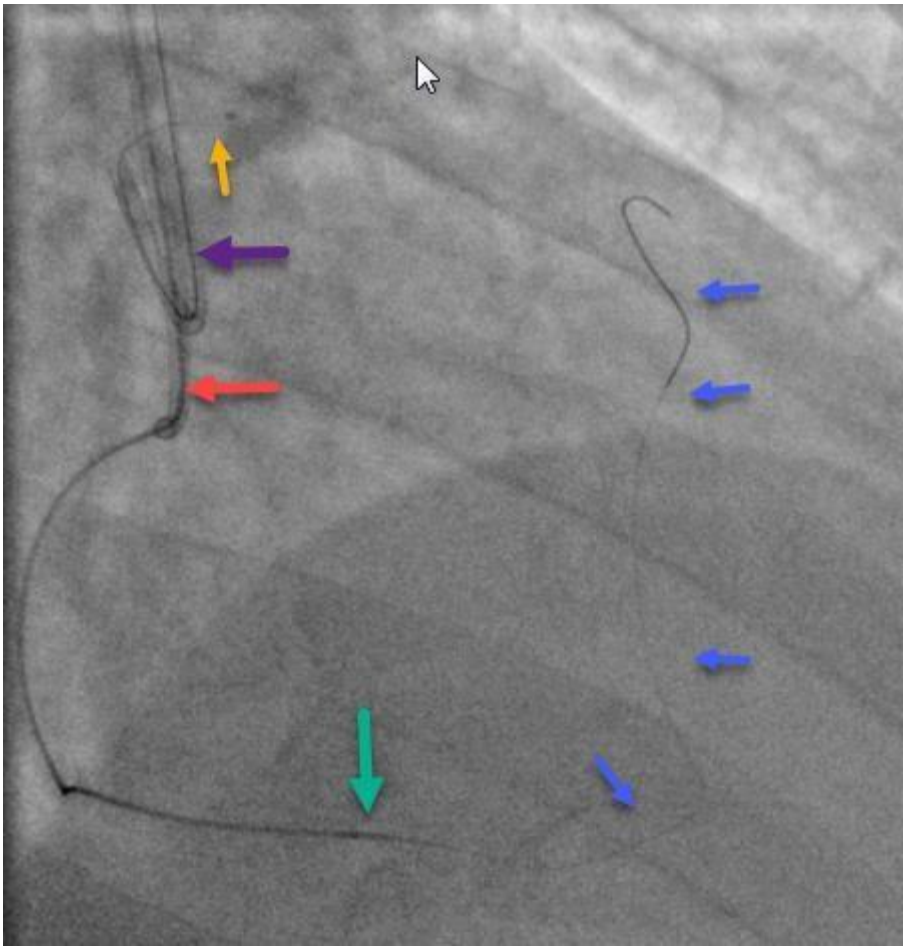

Fig.3-4: Sows Judkin's right (red arrow) guide catheter engaging the RCA, while extra back up (Purple arrow) engaging he left system, the dedicated 0.14mm PCI wire (blue arrows) is crossing to the LAD from the septal collaterals arising from the RCA, coronary microcatheter (green arrow) have inserted to the distal RCA trying to push it upward through the septal collaterals to the LAD.

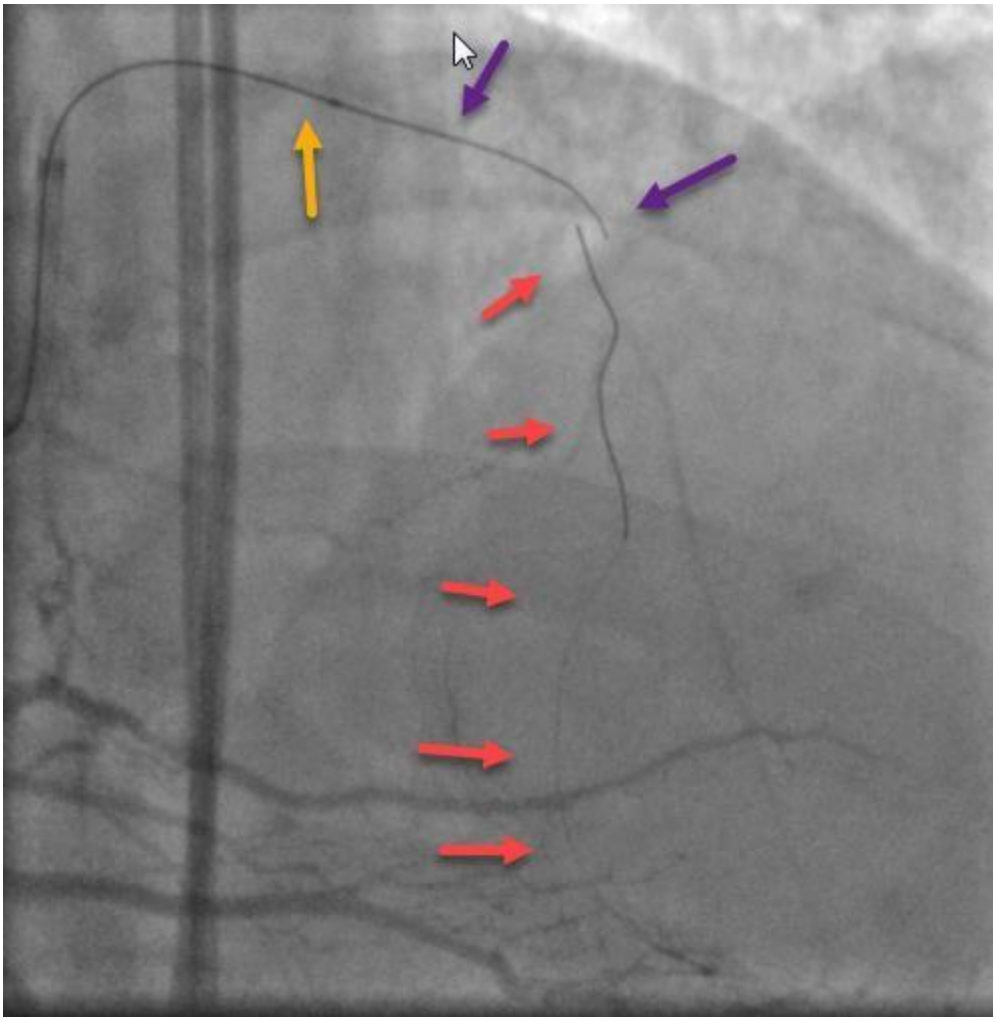

Fig.3-5: Shows a retrograde PCI wire (red arrows) has passed through the septal RCA collaterals toward to distal cup of the mid LAD CTO, while antegrade wire (purple arrows) passing sub-intimaly in the LAD through a coronary microcatheter (yellow arrow) in hope to meet the retrograde wire in the LAD true lumen.

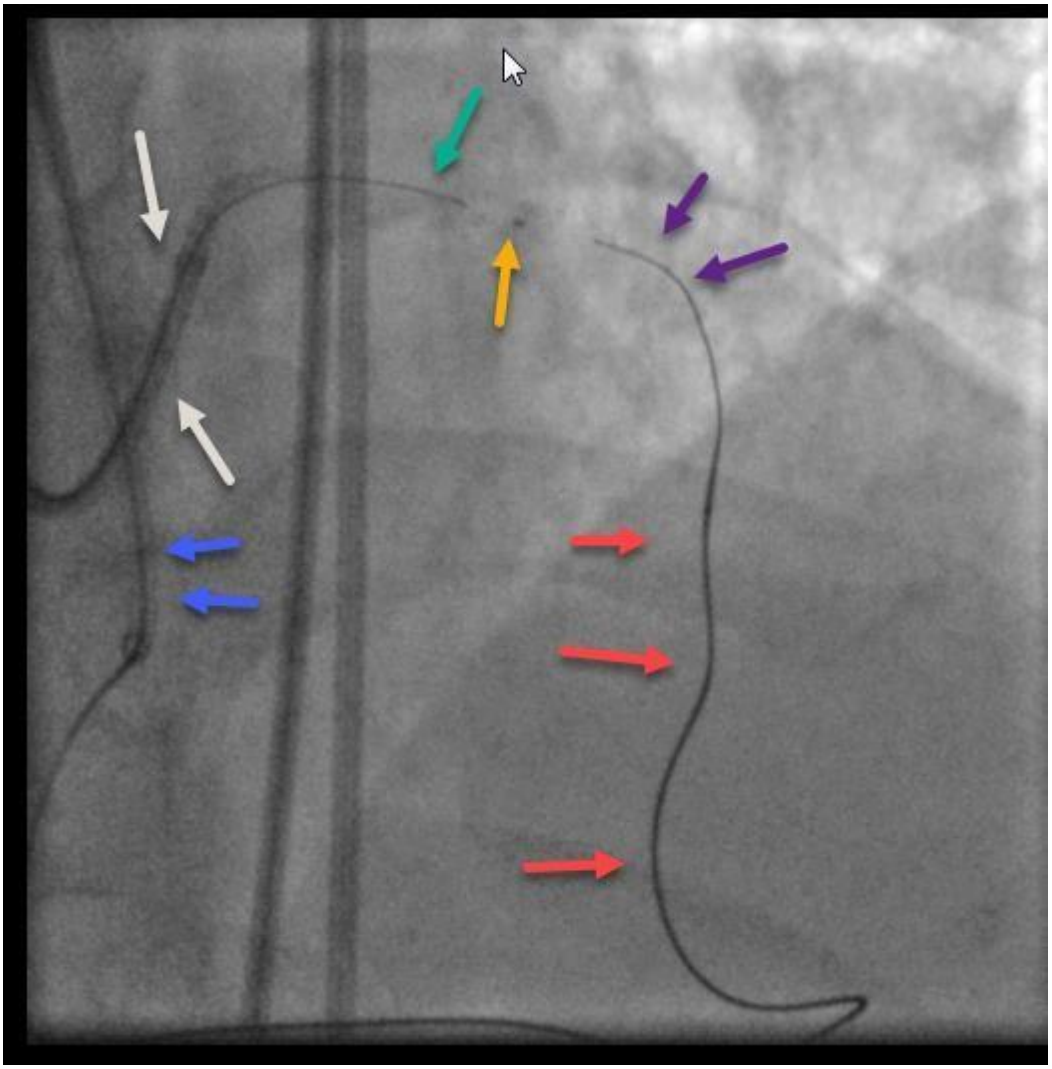

Fig.3-6: Shows a coronary microcatheter (red arrows) have advanced more close to the LAD CTO distal cup when a more sophisticated coronary PCI harder wire passed through to pierce the CTO distal cup, another coronary microcatheter (yellow arrow) have advanced antegrade from the LAD when a softer dedicated coronary PCI wire trying to find out the LAD true lumen, white arrow (extra back up guide catheter engaging the left system), blue arrows Judkin's right guide catheter engaging the RCA.

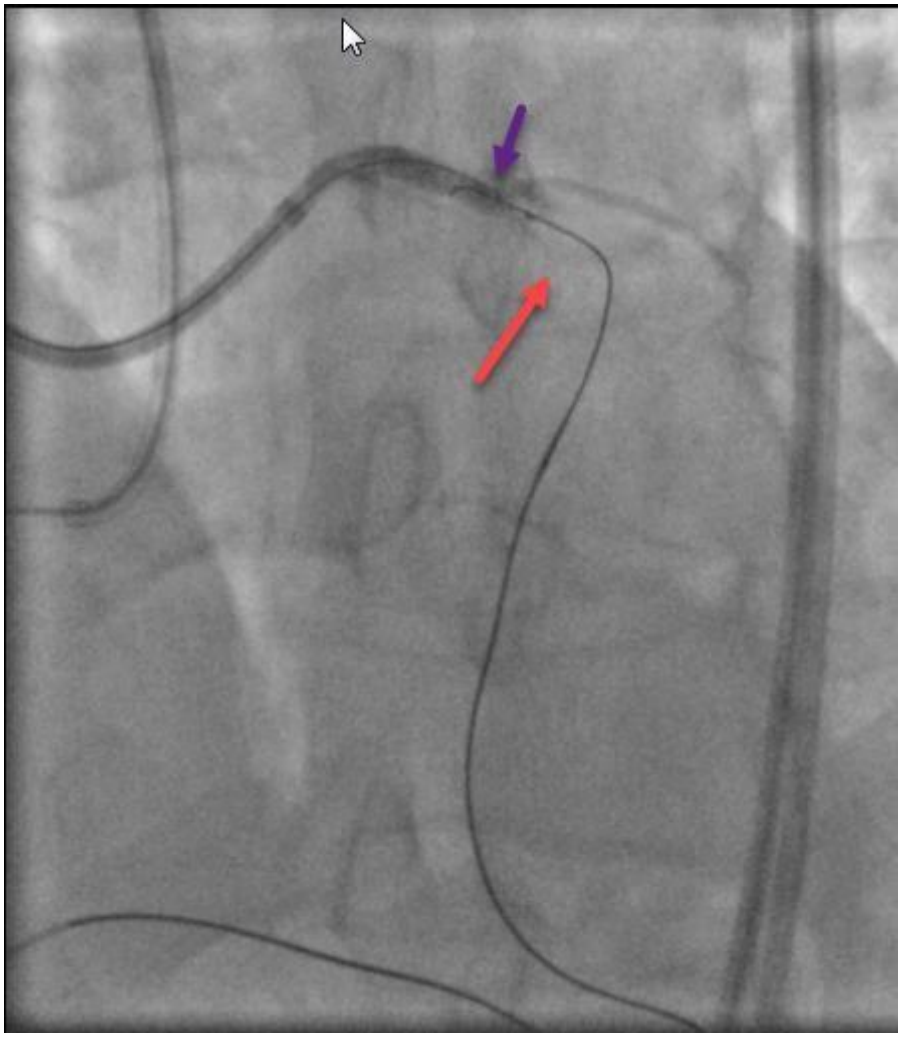

Fig.3-7: Shows the coronary microcatheter and the PCI wire (red arrows) successfully finds their way to the true LAD lumen.

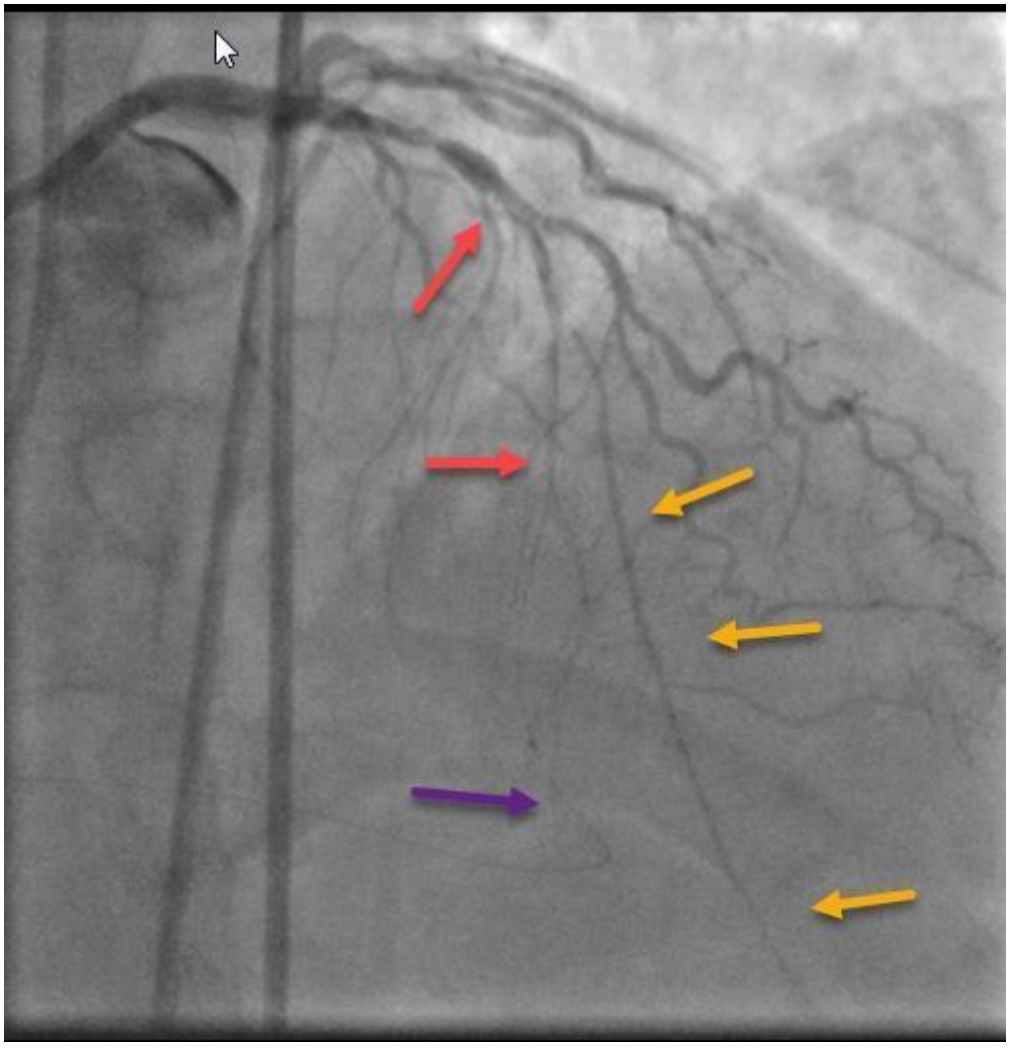

Fig.3-8: Shows the appearance of antegrade flow (yellow arrows) in the LAD after crossing the PCI wire and the microcatheter (red arrows) retrogradely (purple arrow) from the septal branch the mid LAD and balloon dilatation.

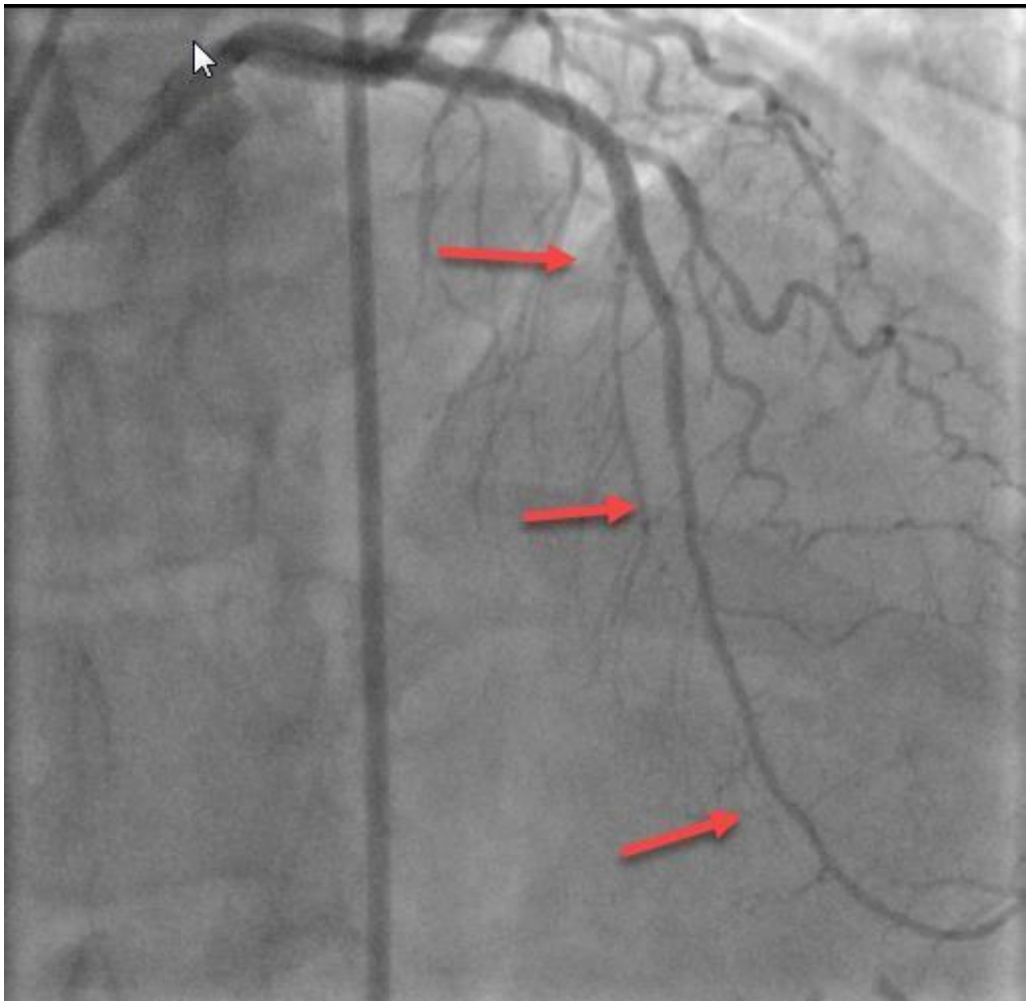

Fig.3-9: Shows finial results with TIMI III flow in the LAD.

3.13 Post PCI

Serum Creatinine and eGFR were measured 72 hours after the procedure. More S. Cr calculations were performed in patients with an early S. Cr elevation or in patients with prolonged hospitalization for other reasons.

3.14 Study Endpoints

The primary endpoint was the development of CI-AKI as defined earlier while the secondary endpoints were: CI-AKI requiring dialysis, significant arrhythmias, cardiogenic shock, pulmonary edema and death.

3.15 Performance of a Pre-Procedural Risk Scores to Predict Contrast Induced Acute Kidney Injury After Chronic Total Occlusion Percutaneous Coronary Intervention

The following criteria were assessed: Age > 70 years, serum albumin, baseline serum creatinine, ejection fraction, hypotension, use of intra-aortic balloon pump (IABP), serum hemoglobin, CTO C JTO Score, Mehran Score, Modified Mehran Score, Liu Score, drugs such as statins, ACE inhibitors and diuretics, contrast volume, study end points including CI-AKI requiring renal replacement therapy (RRT), significant arrhythmias, cardiogenic shock, pulmonary edema and death.

3.16 Statistical Analysis

After data collection, questions of study were coded. Data entry was performed via excel spreadsheet. Statistical analysis was performed by SPSS program, version 21 (IBM SPSS Statistical Package for the Social Sciences). In this study, normality was checked using both Kolmogorov-Smirnov and Shapiro-Wilk tests. The statistical significance of difference in mean between the two groups was assessed using independent sample t-test. The difference in the median and mean ranks between the 2 groups was assessed by non-

parametric test (Mann- Whitney). P values of 0.05 were used as a cut off point for significance of statistical tests.

Analyses of the Modified Pre-procedural Mehran Score utilized the variables in Mehran score except the contrast volume. The Liu Prediction Score utilized four key risk factors (age ≥75 years, LVEF < 40%, serum albumin< 30 g/L and Serum Creatinine (SCr) >1.5 mg/dL) for predicting CIN. The performance of the Modified Mehran Score and Liu Prediction Score were compared with the performance of the original Mehran score using AUROC. Sensitivity and specificity were also compared for different cut-off values.

Chapter 4 Methods (CINEMA Trial)

4.1 Study Design

This was a prospective open-label randomized controlled trial (ISRCTN Registry Number 72194653) conducted in a pragmatic manner in our hospital over 28 months commencing in November 1, 2017. All patients provided written informed consent for participation in this trial that was approved by the Ethical Committee of our Medical College and conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice (**Appendix**).

4.2 Study Population

We enrolled 1,205 consecutive patients with CKD scheduled for coronary angiography at our hospital in four different Cath labs. Inclusion criteria were age of 18-85 years, estimated glomerular filtration rate (e-GFR) of < 60mL/min/1.73 m^2 and elective or urgent coronary angiography and, when indicated, percutaneous coronary intervention. Exclusion criteria were known allergy to furosemide, severe left ventricular dysfunction, primary or rescue PCI, cardiogenic shock, acute respiratory insufficiency, recent acute kidney injury, administration of intravenous contrast media within the 10 days prior to the procedure, planned contrast-enhanced procedure within the 3 days after the procedure, difficult placement of Foley catheter, use of reno-protective drugs or dialysis therapy.

In our study, CKD was defined as an e-GFR of <60 ml/min/1.73 m^2 based on the recommendations of the National Kidney Foundation (71). Patients were admitted to the hospital one day before the procedure for assessment of e-GFR using the Modification of Diet in Renal Disease (MDRD) formula (74,75) Significant left ventricular systolic dysfunction was defined as prior echocardiogram derived Left Ventricular Ejection Fraction <35 %.

4.3 Study Protocol

4.3.1 Randomization

I am aware of the importance of randomization that is the process of assigning clinical trial participants to treatment groups such that each participation has an equal chance of being assigned to any of the groups. Randomization helps minimizes selection bias and avoid imbalances in factors that can influence the outcome. Trials that lack randomization can introduce bias.

There are 4 main types of randomization,

1. Simple Randomisation

2. Block Randomisation

3. Stratified Randomisation stratification

4. Minimisation

Simple randomisation

- commonest method
- each patient has an equal chance of being allocated to each group
- random numbers or computer-generated list
- may result in unequal numbers allocated to each group or unequal distribution of potential confounding factors
-

Block randomization

- aims to keep numbers of patient in each group approximately the same
- e.g. for every block of 8 subjects, 4 must be allocated to each treatment group
- blocks can vary in size

Stratified Randomization

- pre-identified confounding factors act as criteria for separate randomization schedules, ensuring they are equalized between the groups

- aims to minimize confounding and achieve baseline balance between study groups
- useful for small studies to ensure different strata are represented in the study sample

Minimization

- Minimization is used as a tool to balance out the prognostic factors in a clinical trial. The first participant is allocated to a treatment group using simple randomization and the rest of the participants are then assigned to balance out the prognostic factors, based on previous participants and their placement in the clinical trial. Designed to overcome the challenges of stratified randomization

Randomization in CINEMA

The CINEMA study was a pragmatic randomized, controlled, open labelled study. After successful recruitment into the trial, patients were randomized to either MHFD or standard of care in a 2: 1 manner. Randomization was carried out by the research team using simple randomization as described by Altman and Bland (76) (Altman DG, Bland JM. How to randomize. BMJ 1999; 319: 703). Simple randomization was chosen for pragmatic reason for use in my project. To do this, I arranged my treatments in a single column in a systematic order (T1, T2, T3; MHFD, Control, MHFD). I then created a second column of random numbers and then I sorted the treatment using these random numbers.

Patients were randomized into 2 groups in a 2:1 ratio to the study group (matched hydration and forced diuresis; MHFD) and the control group (intravenous hydration) respectively.

In the MHFD group, a peripheral intravenous cannula (18-gauge) was inserted into a peripheral vein of the arm. A Foley catheter was also positioned in the urinary bladder for urine collection. The cannula was connected with a bag of normal saline for fluid infusion.

To avoid fluid over-load and hypovolemia, the amount of normal saline delivered to the patient was matched with the volume of urine produced by the patient.

Before the coronary procedure, MHFD treatment was commenced with an initial intravenous bolus (250 ml) of normal saline solution over 30 min followed by a bolus dose of furosemide (0.5 mg/kg). Injection of contrast media was deferred until urine flow rate exceeded 300 ml/hour. Matched Hydration was continued throughout the cardiac catheterization procedure and up to 4 hours after the procedure. Matched Hydration was achieved by initially giving normal saline intravenously at a rate of 200 ml/h, followed by adjustment in the infusion rate to match the urine output after every 5 minutes. The latter was recorded by nursing staff on the bedside flow sheet. Urine flow rate was maintained at >300 ml/hour with additional doses of furosemide if necessary.

In the control group, patients received a continuous intravenous infusion of isotonic saline at a rate of 1-1.5 ml/kg for at least 12 h before and 12 h after the procedure.

The Foley catheter was removed 12 hours after the procedure. Peri-procedural medical therapy, PCI technique, and contrast dose were left to the preference of the interventional cardiologist in charge of the patient. Serum creatinine was evaluated at baseline, the day of coronary angiography, 72 hours after the procedure, and at hospital discharge.

4.4 Study Endpoints

The primary endpoint was the development of CI-AKI, defined as a ≥25% or ≥0.5 mg/dl rise in serum creatinine over baseline at 48-72 h post-procedure. Secondary endpoints were CI-AKI requiring renal replacement therapy, significant arrhythmias, cardiogenic shock, pulmonary oedema and death.

4.5 Statistical Analysis

Power calculations was based on the MYTHOS Trial that reported the development of CI-AKI in 4.6% of the study group and 18% in the control group (58). Statistical analysis was performed with SPSS, version 21. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) if they followed a normal or non-normal

distribution, respectively. Categorical variables were reported as number and percentages in brackets. The distribution of continuous variables was assessed using Kolmogorov-Smirnov test. Chi-square tests were used to compare the categorical data between the two groups while continuous variables among the two groups of the study were compared with independent sample t-test. As some of the data were not normally distributed, the mean rank was useful for comparing the central tendency (group center) of compared groups. The difference in the mean rank between the 2 groups was assessed by non-parametric test (Mann- Whitney). A p value of 0.05 was required for statistical significance. In this study, normality was checked using both Kolmogorov-Smirnov and Shapiro-Wilk tests which showed that some variables did not follow normal distribution and subsequently non-parametric (Mann-Whitney) test was used for these variables to compare the differences between the groups (**Table 4.1**)

Table 4.1: Tests of Normality

	Kolmogorov-Smirnov[a] Test			Shapiro-Wilk Test		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.089	329	.000	.972	329	.000
e-GFR	.144	329	.000	.920	329	.000
EF%	.277	329	.000	.882	329	.000
Baseline creatinine mg/dl	.125	329	.000	.968	329	.000
Creatinine after 48hrs	.234	329	.000	.727	329	.000
CONTRAST ML	.094	329	.000	.980	329	.000
HbA1c	.180	329	.000	.871	329	.000
S.CHOLESTROL	.095	329	.000	.922	329	.000
S.LDL	.096	329	.000	.906	329	.000
S.HDL	.134	329	.000	.952	329	.000
TG	.211	329	.000	.839	329	.000
HB	.102	329	.000	.968	329	.000
WBC	.160	329	.000	.923	329	.000
LYMPHO	.120	329	.000	.968	329	.000
NEUTROPH	.071	329	.000	.976	329	.000
PLT	.079	329	.000	.967	329	.000
SBP	.126	329	.000	.966	329	.000
DBP	.113	329	.000	.970	329	.000
Lymphocyte/ Neutrophil ratio	.080	329	.000	.947	329	.000

a. Lilliefors Significance Correction

Chapter 5

5.1 Results: Assessment of CI-AKI Risk

The number of patients enrolled in this study was 329. CI-AKI developed in 29 patients (8.81%). There were 211 (64.1%) males and 118 (35.9%) females with a male to female ratio of 1.79 to 1. The median (IQR) age was 60.94 ± 8.59 year. The basic characteristics of the patients are shown in **Table 5-1.**

Table 5-1: The basic characteristics of the patients (n=329)

Variable	**ALL (329)**	**With CI-AKI (29)**	**Without CI-AKI (300)**	**p-value**
Age {Median (IQR)}	60.0 (9)	68 (16)	60 (9)	<0.001 **
Age ≥75 (%)	23 (7)	7 (24.1)	16 (5.3)	0.002
Males (%)	211(64.1)	20 (69)	191 (63.7)	0.57
Smokers	83 (25.2)	5 (17.2)	78 (26)	0.38
Hypertension	201 (61.5)	18 (62.1)	183 (61.4)	0.56
Diabetes	202 (62)	20 (71.4)	298 (61.1)	0.28
Hx of CHF	31 (9.4)	10 (34.5)	21 (7)	<0.001
Baseline SCr (mg/dl) {Median (IQR)}	1.1 (0.3)	1.2 0.6	1.0 (0.3)	0.002 **
SCr>1.5, n(%)	5 (1.5)	5 (17.2)	0	-
Baseline eGFR {Median (IQR)}	70 (29)	62.0 (20.0)	71.0 (28)	< 0.001 **
Baseline eGFR<60, *n* (%)	66 (20.1)	12 41.4	54 18	0.006
LVEF% {Median (IQR)}	56 (11)	43 (6)	56 (5)	< 0.001 **
LVEF<40%, n(%)	23 (7)	7 (24.1)	16 (5.3)	0.002
Cholesterol (mg/dl) {Median (IQR)}	140 (4)	135 (34)	140 (4)	0.30 **
LDL (mg/dl) {Median (IQR)}	90 (40)	90 (22)	89 (40)	0.13 **
Hemoglobin {Median (IQR)}	13 (1.9)	9.9 (2.2)	13.5 (1.5)	< 0.001 **
WBC {Median (IQR)}	8.9 (1.5)	8.9 (1.3)	8.9 (1.5)	0.74 **
Platelet count {Median (IQR)}	327 (175)	296 (220)	334 (170)	0.47 **
HbA1c {Median (IQR)}	6.5 (2.0)	9.8 (5.3)	6.0 (2.0)	< 0.001 **
Serum albumin* {Median (IQR)}	4.4(0.85)	3.25 (0.63)	4.4 (0.83)	< 0.001 **
Statin	325 (98.8)	28 (96.6)	297 (99)	0.25
ACEI/ARB	207 (62.9)	21 (72.4)	186 (62)	0.27
Metformin	129 (39.2)	20 (69)	109 (36.3)	0.001
Diuretics	70 (21.3)	18 (62.1)	52 (17.3)	<0.001
Insulin	75 (22.8)	0 (0)	75 (25)	-
Location of CTO				<0.001

CTO LAD	92 (28)	11 (37.9)	81 (27)	-
CTO LCx	53 (16.1)	1 (3.4)	52 (17.3)	-
CTO RCA	179 (54.4)	14 (48.3)	165 (55)	-
CTO RCA+LCx	5 (1.5)	3 (10.3)	2 (0.7)	-
Contrast volume (mL) {Median (IQR)}	280 (130)	375 (80)	280 (110)	< 0.001 **
J-CTO score {Median (IQR)}	1.0 (2.0)	3.0 (1.0)	1.0 (2.0)	< 0.001 **
Mehran risk score {Median (IQR)}	6.0 (3.0)	16 (4.0)	5.0 (3.0)	<0.001**
Weight	64.9±8.4	64.8±8.4	64.7±8.6	0.46
BMI {Median (IQR)}	26.9 (7.4)	31.45 (6.7)	26.7 (7.2)	0.02 **
Systolic BP {Median (IQR)}	125 (15)	100 (20)	125 (10)	< 0.001 **
Diastolic BP {Median (IQR)}	80 (20)	60 (23)	80 (15)	< 0.001 **
*albumin was measured in 208 patients only.				

** Performed by Non parametric test (Mann – Whitney) test

Old people (≥56 years) comprised the majority (n=263, 80%) of the patients in this study while the relatively young population (≤55 years) formed the minority (n=66, 20%). Almost one quarter of the patients (n=83, 25.2%) were smokers. Hypertension and DM were the top co-morbidities in the study; each was observed in (n=202, 61.4%) of the patients followed by PAD (n=70, 21.3%). See **Figure 5-1**

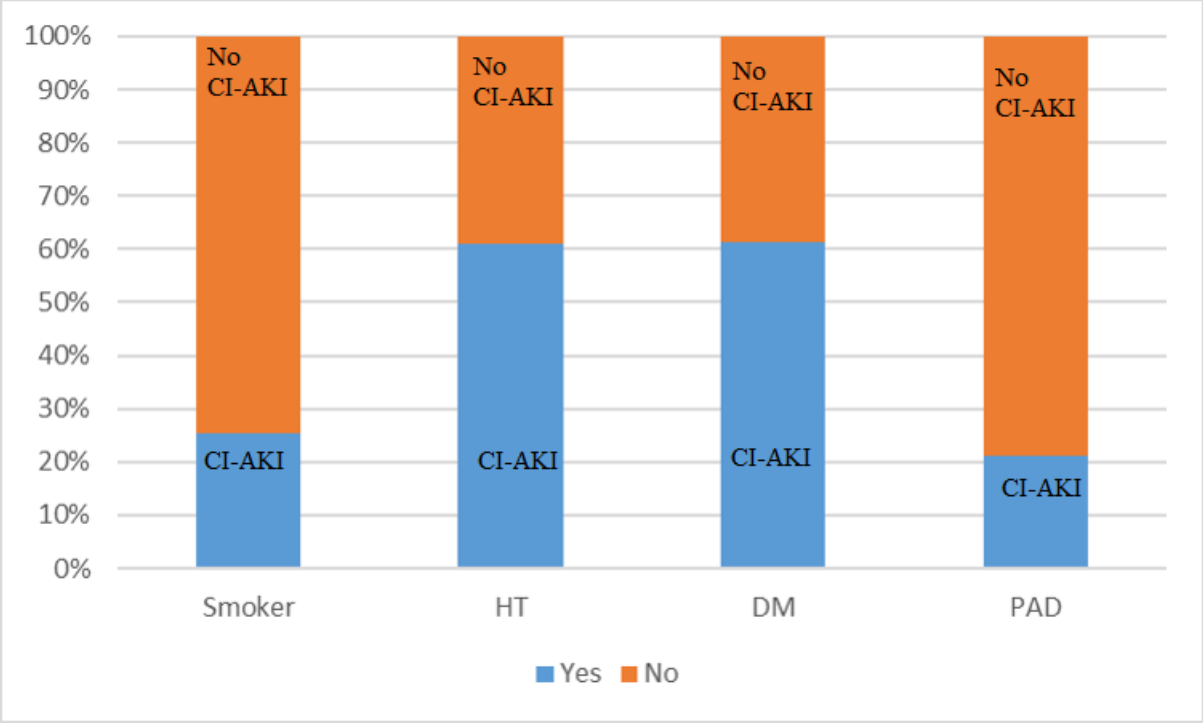

Figure 5-1: Histogram showing the co-morbidities in this study.

Chronic coronary total occlusion (CTO) lesions were located in RCA (n=179, 54.4%), LAD (n=92, 28.0%), LCX (n=53, 16.1%), and in both RCA and LCX (n=5, 1.5%). See **Figure 5-2**

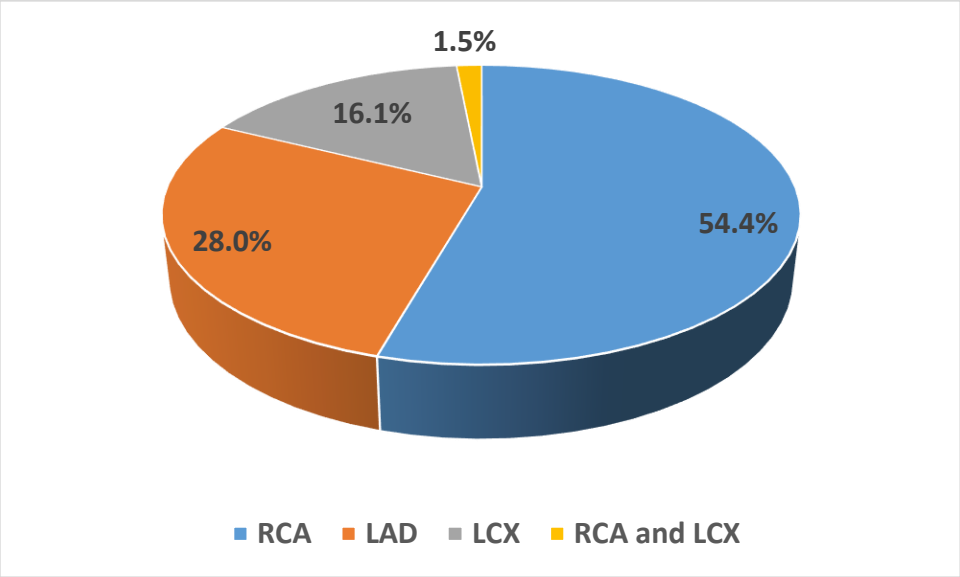

Figure 5-2: Distribution of CTO lesions in the studied patients.

Table 5-2 displays a comparison between the CI-AKI (n=29) and the non-CI-AKI (n=300) groups regarding different variables expressed as mean ± SD using the Independent t –test.

Table 5-2: Comparison between Nephropathy (n=29) and the Non-nephropathy (n=300) groups.

Parameter	CI-AKI (n= 29)		No CI-AKI (n = 300)		p-value **
	Median	IQR*	Median	IQR	
e-GFR	62	20	71	28	< 0.001
EF%	43	6	56	5	< 0.001
S. Creatinine mg/dl	1.2	0.6	1	0.3	0.002
S. Creatinine (48hrs)	2.3	0.78	1.2	0.3	< 0.001
Contrasts (ml)	375	80	280	110	< 0.001
HbA1c	9.8	5.3	6	2	< 0.001
S. Cholesterol	135	34	140	40	0.30
S.LDL	90	22	89	40	0.13
S.HDL	42	7	40.5	8	0.20
TG	132	108	134	155	0.76
HB	9.9	2.2	13.5	1.5	< 0.001
WBC	8.9	1.3	8.9	1.5	0.74
Lymphocyte	3.2	0.5	3.2	0.9	0.83
Neutrophil	5	1.5	5.15	1.3	0.60
Platelets	296	220	334	170	0.47
Systolic blood pressure	100	20	125	10	< 0.001
Diastolic blood pressure	60	23	80	15	< 0.001
Neutrophil / Lymphocyte ratio	1.56	0.59	1.56	0.61	0.99

- * IQR (interquartile range)
- ** performed by the Mann - Whitney test

Both mean systolic and diastolic BP were significantly lower in the CI-AKI group compared to the non-CI-AKI group (105.17 mmHg vs. 125.72 mmHg and 66.90 mmHg vs. 82.05 mmHg respectively). Likewise, the mean HB level was significantly lower in the CI-AKI group (10.46 g/Dl vs. 13.19 g/dl). In contrast, mean HbA1c was significantly higher in the CI-AKI group (9.06% vs. 6.51%). Renal function tests were more impaired

in the CI-AKI group. Mean serum creatinine was significantly higher in CI-AKI group both before and after the PCI (1.21 mg/dl vs. 1.02 mg/dl and 2.27 mg/dl vs. 1.15 mg/dl respectively). The mean e-GFR was significantly lower in the CI-AKI group (64.10 ml/min/1.73 m^2 vs. 77.21 ml/min/1.73 m^2). Moreover, the mean EF% was significantly lower in the CI-AKI group (44.55% vs. 55.00%). The mean contrast volume was significantly higher in the CI-AKI group compared to the non-CI-AKI group (360.86 ml vs. 274.25 ml). On the other hand, the lipid profile, total and differential WBC and platelet counts, and the neutrophil/lymphocyte ratio were not significantly different between the 2 groups of patients.

Table 5-3 shows some drugs whose use proved to have a significant effect on the occurrence of CI-AKI such as Digoxin, diuretics, anti-diabetics and some anti-hypertensive drugs.

Table 5-3: Drugs with significant effect on occurrence of CI-AKI.

Drug	CI-AKI (n=29)	Non-CI-AKI (n=300)	p-value
ACE inhibitors	16	71	< 0.001
ARBs#	5	115	0.024
Metformin	20	109	< 0.001
Sulphonylureas	12	61	0.01
Insulin (intermediate)	0	48	0.02
Furosemide	5	13	0.004
Hydrochlorothiazide	9	37	0.01
Potassium sparing diuretics	15	8	< 0.001
Digoxin	6	8	< 0.001

ARBs: Angiotensin II Receptors Blockers for Hypertension.

Table 5-4 reveals the influence of JCTO score on the occurrence of CI-AKI.

Table 5-4: Impact of JCTO on occurrence of CI-AKI.			
JCTO Score	CI-AKI (n = 29)	Non-CI-AKI (n= 300)	P-value
Zero	0	83	< 0.001
One	0	124	
Two	6	75	
Three	12	16	
Four	9	2	
Five	2	0	
JCTO Score	CI-AKI (n = 29)	Non-CI-AKI (n= 300)	P-value
Zero – One	0	207	< 0.001
Two - Five	29	93	
JCTO Score	CI-AKI (n = 29)	Non-CI-AKI (n= 300)	P-value
Zero - Two	6	282	< 0.001
Three - Five	23	18	

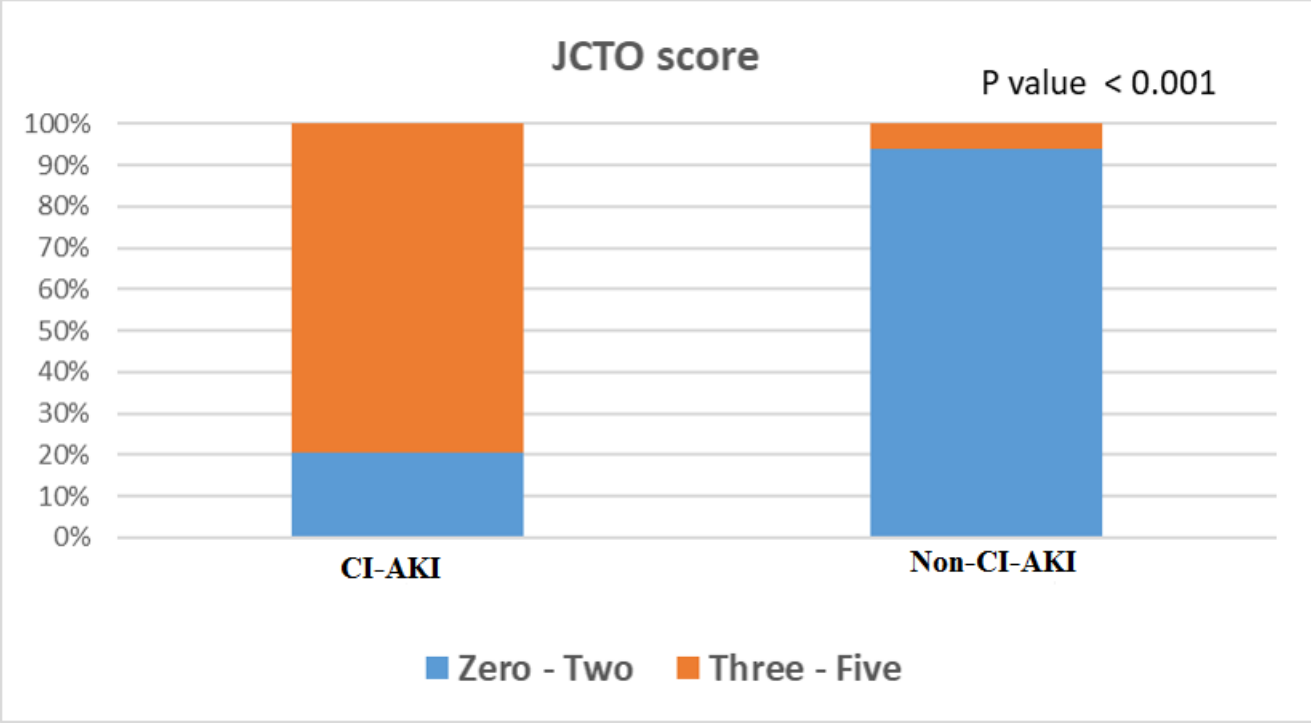

Figure 5-3: Impact of JCTO on CI-AKI rate.

All patients who developed CI-AKI (n=29) had JCTO score of 2-5 and most patients who hadn't CI-AKI (n=207, 69%) had JCTO score of 0-1. Therefore, JCTO score had a significant impact on the occurrence of CI-AKI ($p< 0.001$). Likewise, 23 (79.3%) of patients who developed CI-AKI had a JCTO score of 3-5 whereas 282 (94%) of patients who hadn't CI-AKI had a JCTO score of 0-2 ($p< 0.001$). **Table 5-5** shows the impact of some co-morbid conditions on the occurrence of CI-AKI.

Table 5-5: Impact of co-morbidities on occurrence of CI-AKI.			
Co-morbidity	CI-AKI (n = 29)	Non-CI-AKI (n= 300)	p-value
HT	20	182	0.38
DM	18	183	0.91
Smoking	5	78	0.30

Hypertension, DM and smoking were found to have non-significant influence on the occurrence of CI-AKI ($p>0.05$).

Logistic regression analysis with CI-AKI as the dependent variable was also performed. All variables with P values less than 0.15 in the univariate analysis were entered into a multivariate logistic regression model. Multivariate analysis showed that age [odds ratio (OR), 1.16; 95% CI, 1.06–1.28; P = 0.002] and contrast volume (OR, 1.02; 95% CI, 1.01–1.04; P<0.001), lower baseline eGFR (OR, 0.97; 95% CI, 0.94–1.00; P = 0.049), lower LVEF (OR, 0.84, 95% CI, 0.76–0.92; P < 0.001) and lower Hb (OR, 0.25, 95% CI, 0.13–0.42; P < 0.001) were independent predictors of CI-AKI in CTO patients **(Table 5-6).**

Table 5-6. Independent Predictors of CI-AKI							
Characteristic	**Univariate**				**Multivariable**		
	N	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	329	1.1	1.05, 1.16	<0.001	1.16	1.06, 1.28	0.002
eGFR	329	0.96	0.94, 0.99	0.003	0.97	0.94, 1.00	0.049
EF percent	329	0.86	0.81, 0.90	<0.001	0.84	0.76, 0.92	<0.001
Contrast volume (ml)	329	1.02	1.01, 1.03	<0.001	1.02	1.01, 1.04	<0.001
Hb	329	0.31	0.21, 0.42	<0.001	0.25	0.13, 0.42	<0.001
OR = Odds Ratio, CI = Confidence Interval							

5.2 Results of Pre-Procedural Risk Scores Study

Of the 329 patients studied above, 208 patients had available serum albumin measurements, necessary for calculation of the Liu score, analyzed herein. CI-AKI developed in 12 patients (5.8%). There were 131 (63%) males and 77 (37%) females with a male to female ratio of 1.7 to 1. The mean age was 61.16 ± 9.05 year.

The basic characteristics of the studied patients (n=208) are shown in **Table 5-7.**

Table 5-7: **The basic characteristics of the patients (n=208)**

The Variable	CI-AKI (n= 12)		No CI-AKI (n = 196)		P value**
	Mean	Standard Deviation	Mean	Standard Deviation	
e-GFR	39.92	18.03	77.27	23.73	< 0.001*
EF%	39.25	6.05	55.24	7.42	< 0.001*
Creatinine mg/dl	1.62	0.35	1.03	0.20	< 0.001*
Creatinine 48hrs	2.39	0.59	1.15	0.21	< 0.001*
Serum albumin	3.21	0.50	4.45	0.50	< 0.001*
Contrast (ml)	310.97	68.64	274.46	71.01	< 0.001*
HbA1c	7.88	2.52	6.52	1.07	< 0.001*
S. Cholesterol	145.75	29.54	143.07	143.07	0.76
S.LDL	100.08	37.09	90.52	24.99	0.21
S.HDL	40.08	7.69	40.53	6.18	0.86
TG	131.00	49.63	180.86	98.97	0.18
HB	10.27	1.95	13.19	1.33	< 0.001*
WBC	8.32	1.01	8.75	1.77	0.44
Lymphocyte	3.09	0.79	3.27	0.80	0.45
Neutrophil	5.21	0.73	5.07	1.10	0.66

Platelets	288.17	113.94	330.31	114.81	0.22
Systolic BP	102.67	26.63	129.98	83.12	0.23
Diastolic BP	64.17	21.09	81.05	12.17	< 0.001*
Neutrophil / Lymphocyte ratio	1.80	0.55	1.64	0.56	0.35
* Statistically significant ** Performed by the independent t-test.					

Old people (≥56 years) comprised the majority (n=164, 78.8%) of the patients in this study while the relatively young population (≤55 years) formed the minority (n=44, 21.2%). (This age limit is close to the United Nations definition, who defined a person above the age of 60 as an old person).

The top co-morbidities were DM (n=127, 61%) and hypertension (n=121, 58.2%) followed by PAD (n=41, 19.7%) and CHF (n=22, 10.6%). Almost one quarter of the patients (n=50, 24%) were smokers. Hypertension, DM and smoking were found to have non-significant influence on the occurrence of CI-AKI while advanced age (>70 years) had a significant impact on this issue (p< 0.001). This is shown in **Figure 5-4**.

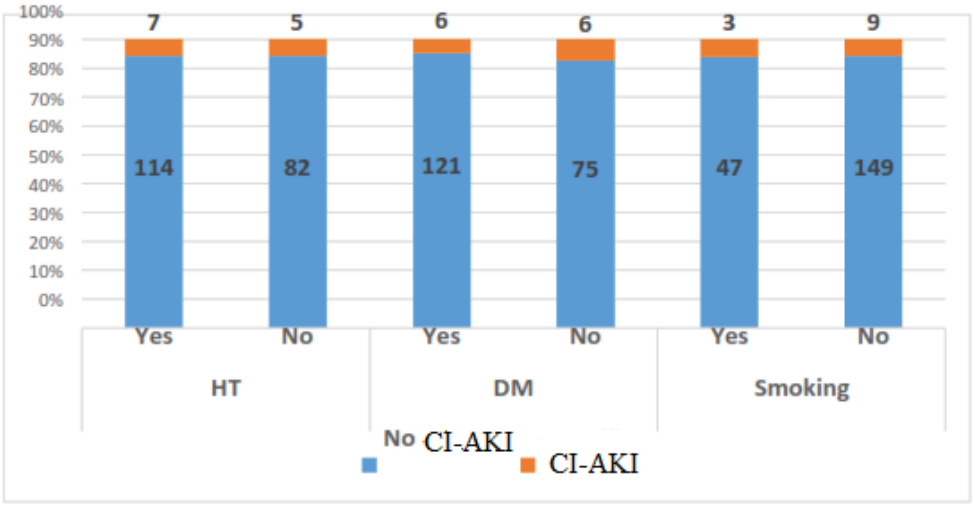

Figure 5-4: Correlation of Some Co-morbidities with CI-AKI.

Chronic coronary total occlusion lesions were located in right coronary artery (RCA) (n=110, 52.9%), left anterior descending artery (LAD) (n=58, 27.9%), left circumflex artery (LCX) (n=37, 17.8%), and in both RCA and LCX (n=3, 1.4%). Overall, the right coronary arterial bed was slightly more frequently involved than the left coronary arterial territory.

All patients who developed CI-AKI (n=12) had JCTO score of 3-5 and most patients who hadn't CI-AKI (n=183, 93.4%) had JCTO score of 0-2. Therefore, JCTO score had a significant impact on the occurrence of CI-AKI ($p < 0.001$). This is also shown in **Figure 5-5**.

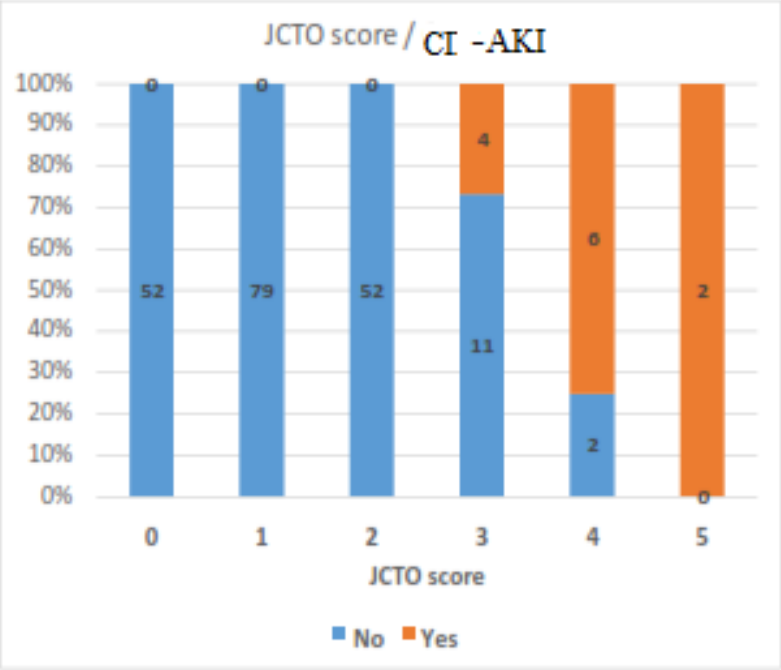

Figure 5-5: Relation of CI-AKI with JCTO Score.

Renal function tests were more impaired in the CI-AKI group. Mean serum creatinine was significantly higher in CI-AKI group both before and after the PCI (1.62 mg/dl vs. 1.03 mg/dl and 2.39 mg/dl vs. 1.15 mg/dl respectively) (see **Figure 5-6**). The mean e-GFR was

significantly lower in the CI-AKI group (39.92 ml/min/1.73 m^2 vs. 77.27 ml/min/1.73 m^2). The mean contrast volume was significantly higher in the CI-AKI group compared to the non-CI-AKI group (310.97 ml vs. 274.46 ml). Mean serum albumin was significantly lower in the CI-AKI group compared to the non-CI-AKI group (3.21 mg /dl vs. 4.45 mg /dl; p< 0.001).

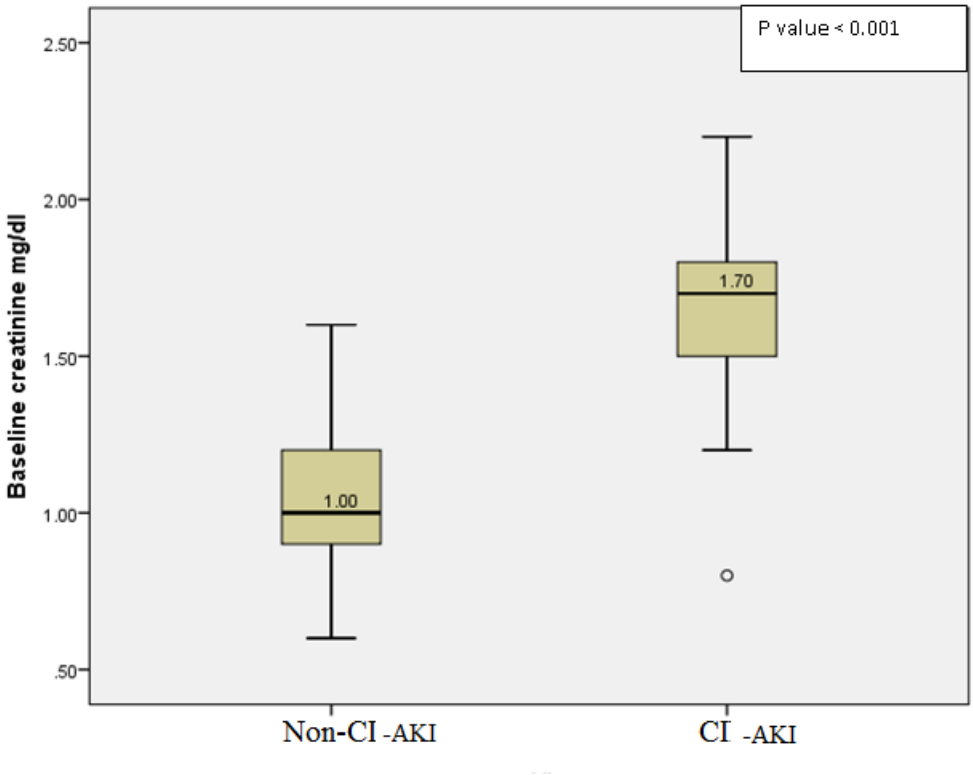

Figure 5-6: Correlation of Baseline Serum Creatinine with CI-AKI.

The systolic BP was not statistically different between the 2 groups. However, the diastolic BP was significantly lower in the CI-AKI group compared to the non-CI-AKI group (64.17 mmHg vs. 81.05 mmHg; p< 0.001). Likewise, the mean HB level was significantly lower in the CI-AKI group (10.27 g/dl vs. 13.19 g/dl; p< 0.001). In contrast, mean HbA1c was significantly higher in the CI-AKI group (7.88% vs. 6.52%; p< 0.001). Moreover, the mean EF% was significantly lower in the CI-AKI group (39.25% vs. 55.24%; p< 0.001) (see

Figure 5-7). On the other hand, the lipid profile, total and differential WBC and platelet counts, and the neutrophil/lymphocyte ratio were not significantly different between the 2 groups of patients.

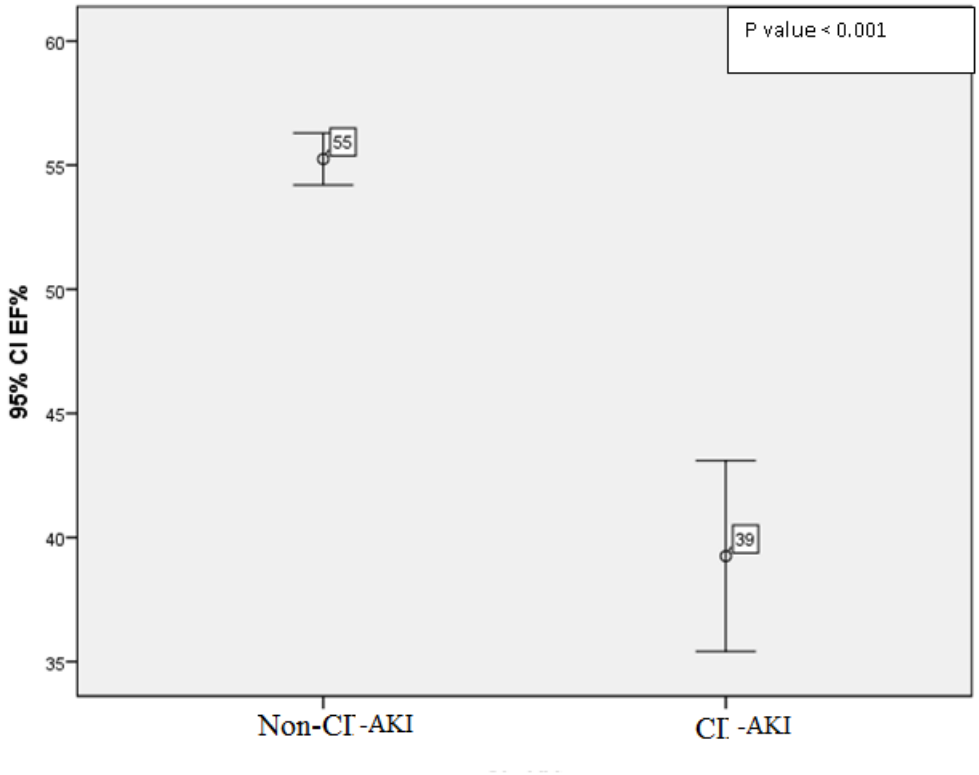

Figure 5-7: Correlation of EF with CI-AKI.

Statins, ACE inhibitors and diuretics were involved in the occurrence of CI-AKI.

Table 5-8 shows some technical aspects and angiographic findings in the studied patients.

Table 5-8: Some technical aspects and angiographic findings in the studied patients.				
The Variable	CI-AKI		Total	P value
	Yes (n = 12)	No (n= 196)		
Bifemoral access	5	143	148	0.020*
Femoral and radial access	7	56	63	0.03*
Blunt proximal cup	7	52	59	0.02*
Severe calcification	10	25	35	< 0.001*
Bended segments within occlusion	8	32	40	< 0.001 *

Bifemoral access, femoral and radial access, blunt proximal cup, severe calcification and bended segments within the occlusion were significantly associated with occurrence of CI-AKI.

Table 5-9 shows the study endpoints.

Table 5-9: The Occurrence of Study Endpoints in CTO-PCI Study.				
Study Endpoint	CI-AKI		Total	P value
	Yes (n = 12)	No (n= 196)		
CI-AKI requiring RRT	5	1	6	< 0.001
Significant arrhythmias	1	0	1	< 0.001
Cardiogenic shock	6	1	7	< 0.001
Pulmonary Oedema	3	2	5	< 0.001
Death	1	2	3	0.04

All study endpoints (CI-AKI requiring RRT, significant arrhythmias, cardiogenic shock, pulmonary oedema and death) were significantly associated with the occurrence of CI-AKI.

The relative risks (RR) of development of CI-AKI in relation to different variables are shown in **Table 5-10**.

Table 5-10: Relative Risk (RR)		
Variable	RR (95% CI)	P value
Age (≥ 75 years)	15.73 (5.59 - 44.28)	< 0.001
HT	1.01 (0.33 - 3.07)	0.99
DM	0.64 (0.21 - 1.91)	0.42
RCA Location	0.64 (0.21 - 1.94)	0.42
JCTO Score 4-5	39.6 (14.3 - 109.6)	< 0.001
Hypotension SBP< 80mm/Hg within 24 hrs	10.73 (3.70 - 31.16)	< 0.001
Serum albumin ≤ 3.775 g/L	0.03 (0.01 - 0.12)	< 0.001
Hb level. ≤ 12.2 mg/dl	15.39 (3.49 – 67.95)	< 0.001
HbA1C level. > 6.25 mg/dl	1.93 (0.60 – 6.20)	0.26
Serum creatinine. > 1.075 mg /dl	10.38 (1.37 - 78.98)	0.004
S. Creatinine 48 hours after the procedure < 1.35 mg / dl	0.73 (0.62 – 0.88)	< 0.001
e-GFR. ≤ 65.5	19.11 (2.52 - 145.12)	< 0.001
EF. ≤ 49.5%	33.86 (4.48 - 255.93)	< 0.001
Use of intra-aortic balloon pump IABP	28.7 (12.35 - 66.8)	< 0.001
Mehran Score > 9	49.0 (15.22 - 157.79)	< 0.001
Mehran Score > 8	123.6 (17.0 - 900)	< 0.001
CHA2VASC score 2 – 3	5.0 (1.54 - 16.27)	0.01

For patients aged ≥ 75 years, the RR was 15 .73 indicating that they were 15 times more prone to develop CI-AKI when compared to patients aged <75 years (P value is < 0.001) and the real risk ranged from 5.59 to 44.28. Patients with a Mehran score > 9, they were 49 times more prone to get CI-AKI than those with a Mehran score <9 (P value is < 0.001). HT, DM and RCA location had small and statistically non- significant RR (P value > 0.05). In regard to serum creatinine, a value > 1.075 mg/dl would increase the risk of CI-AKI by

more than 10 times compared with patients whose serum creatinine was less than this value. In contrast, patients with a serum creatinine 48 hours after procedure < 1.35 mg / dl had 27% reduced risk of developing CI-AKI (P value is < 0.001). HBA1c level of > 6.25 had no statistically increased risk of CI-AKI (p=0.26). Most other variables such as JCTO Score 4-5, SBP< 80mm/Hg within 24 hours, Hb ≤ 12.2 mg/dl, serum albumin ≤ 3.775 g/L, e-GFR ≤ 65.5, EF≤ 49.5%, use of IABP, Mehran score >8 and CHA2VASC score 2 –3 had a statistically significant increase in the RR of CI-AKI (p< 0.001).

Risk prediction of CI-AKI: Comparison of Mehran, Modified Mehran and Liu Scores

The removal of contrast volume from Mehran score resulted in no loss of discrimination (AUROC 0.9591 vs 0.9514 for the original Mehran and the modified Mehran respectively, P=NS). Full Mehran score had an optimal cut point of 11 that resulted in a 0.90 accuracy of predicting CI-AKI with a sensitivity of 93.1% and a specificity of 90.0%. Modified Mehran score had an optimal cut point of 7 that resulted in a 0.85 accuracy of predicting CI-AKI with a sensitivity of 96.6% and a specificity of 83.3%. With an optimal cut point of 5.5, the Liu score that was determined in 208 patients that had available serum albumin resulted in a 0.90 accuracy of predicting CI-AKI with a sensitivity of 100.0% and a specificity of 89.3%.

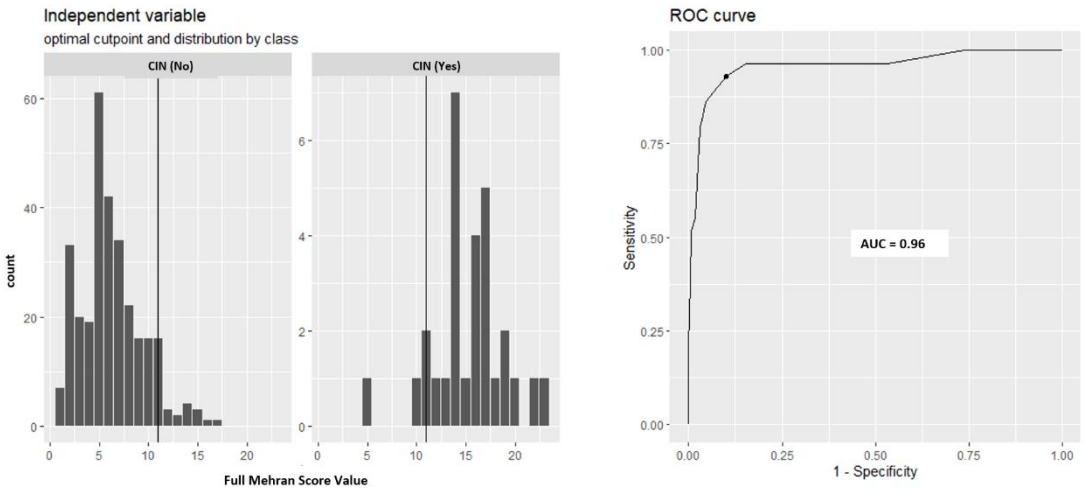

Figure 5-8 A and B: Full Mehran Score performance. The right is ROC with AUC. The optimal cut point is marked as a black dot. The left is the histogram of the score on two subgroups: patients with and without CI-AKI. The optimal cut point is marked as a vertical black line.

Modified Mehran score had an optimal cut point of 7 with 0.84 accuracy of predicting CI-AKI and sensitivity of 96.6% and specificity of 83.3%.

Figure 5-9 A

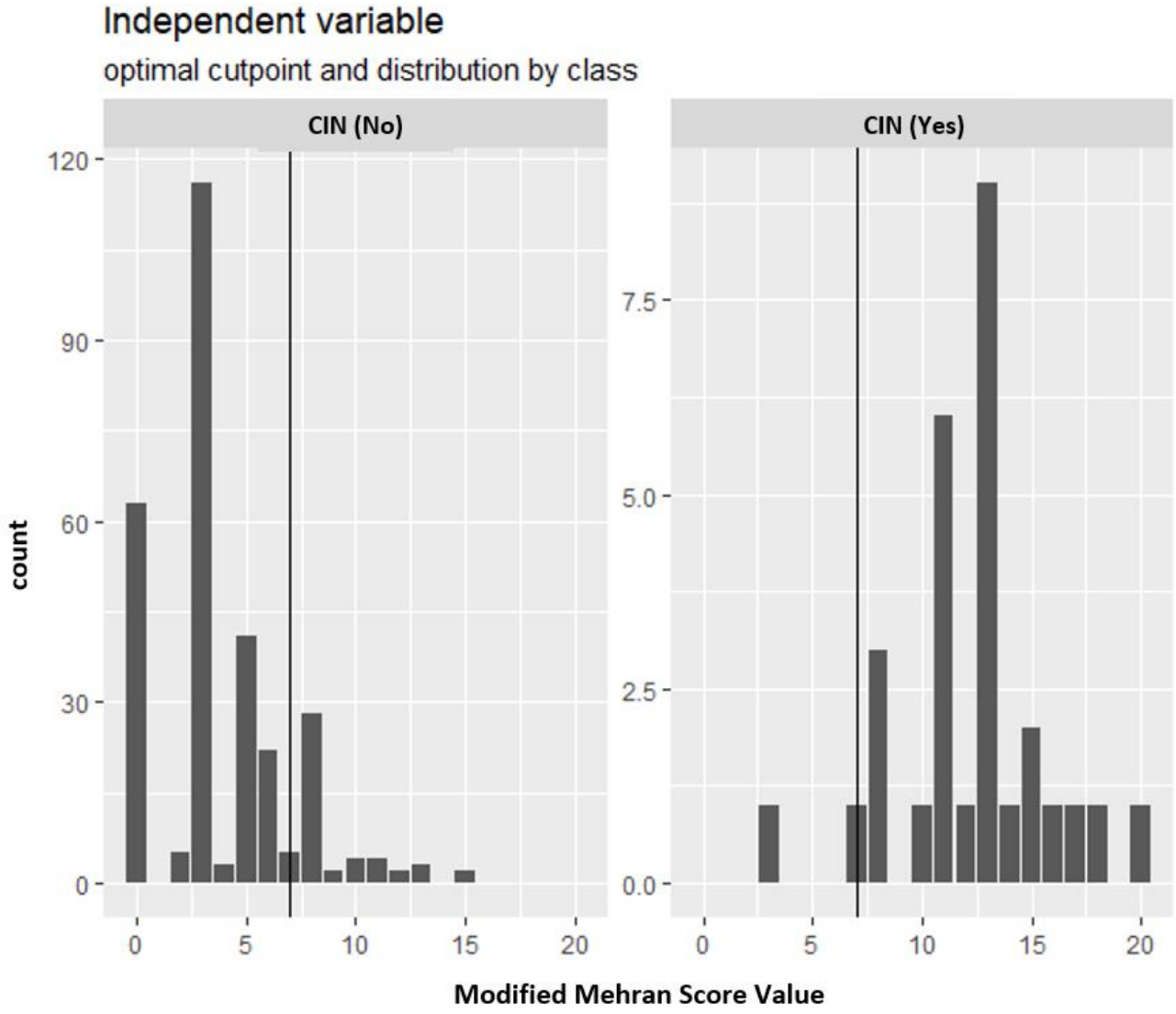
Independent variable
optimal cutpoint and distribution by class
CIN (No)
CIN (Yes)
count
120
90
60
30
0
7.5
5.0
2.5
0.0
0
5
10
15
20
Modified Mehran Score Value

Figure 5-9 B

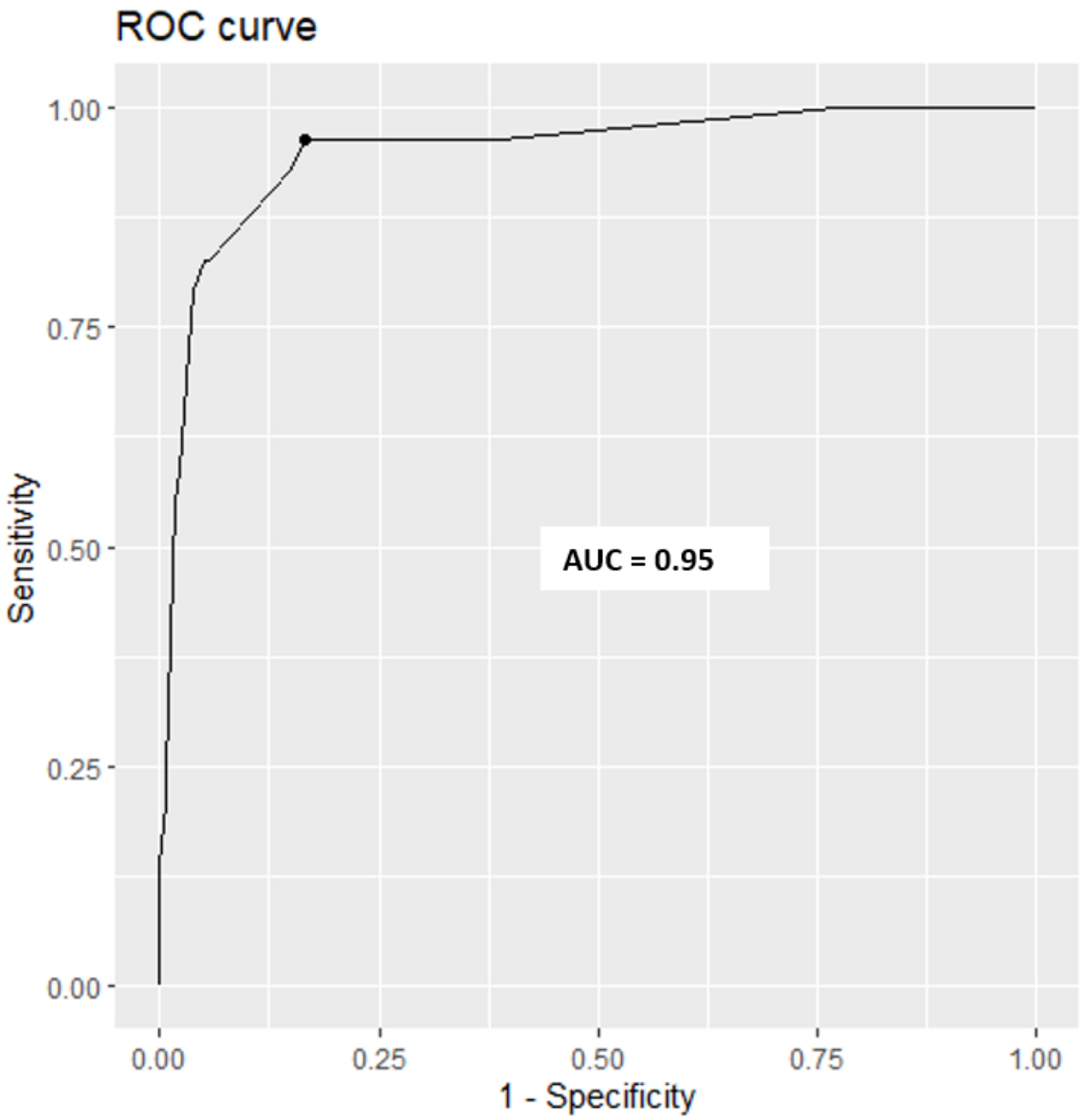

Figure 5-9 A and B: Modified Mehran Score performance. The right is ROC with AUC. The optimal cut point is marked as a black dot. The left is the histogram of the score on two subgroups: patients with and without CI-AKI. The optimal cut point is marked as a vertical black line.

With an optimal cut point of 5, the Liu score that was determined in 208 patients had a 0.90 accuracy of predicting CI-AKI with sensitivity of 100.0% and specificity of 89.3%.

Fig 5-10 A

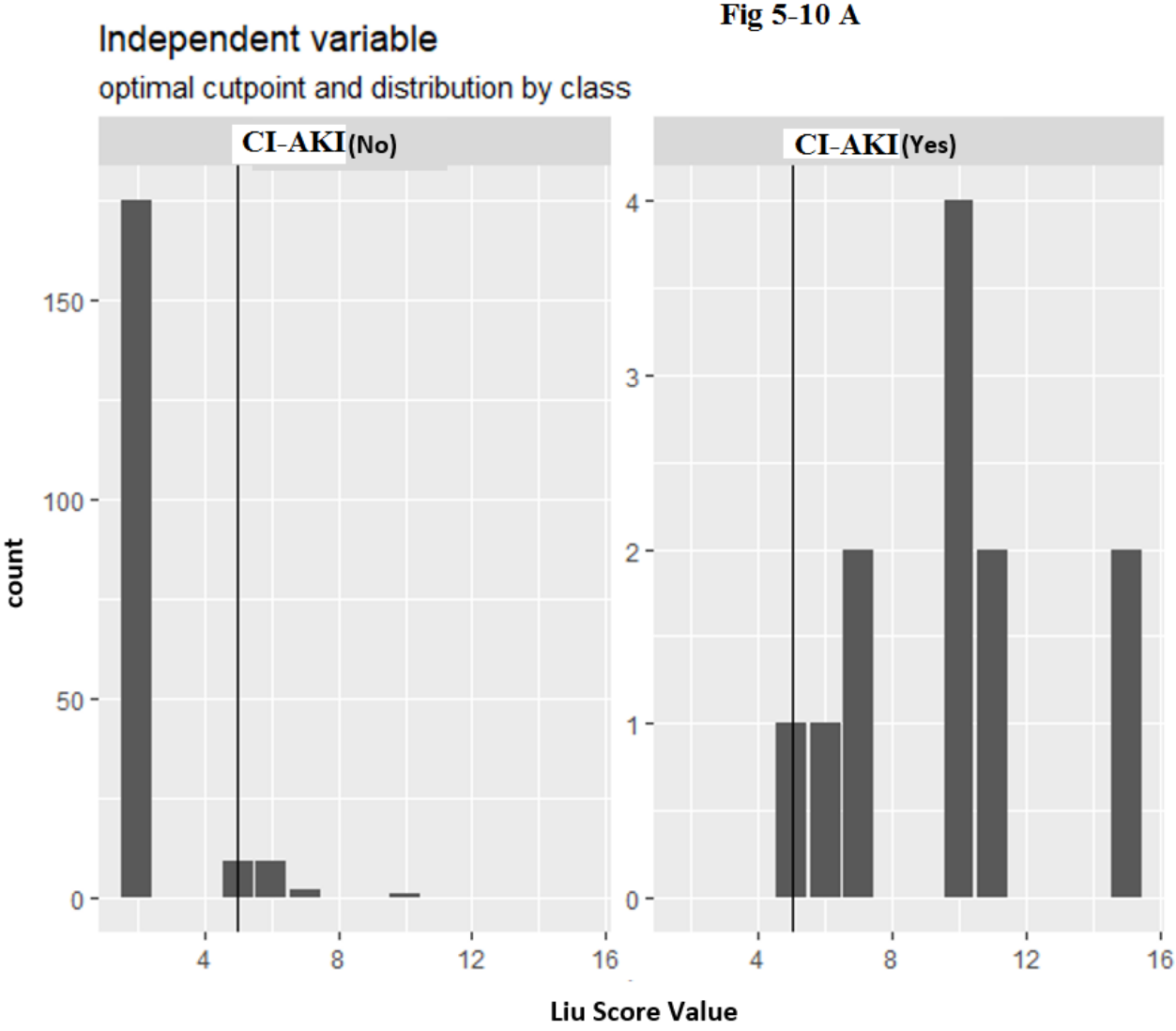

Fig 5-10 B

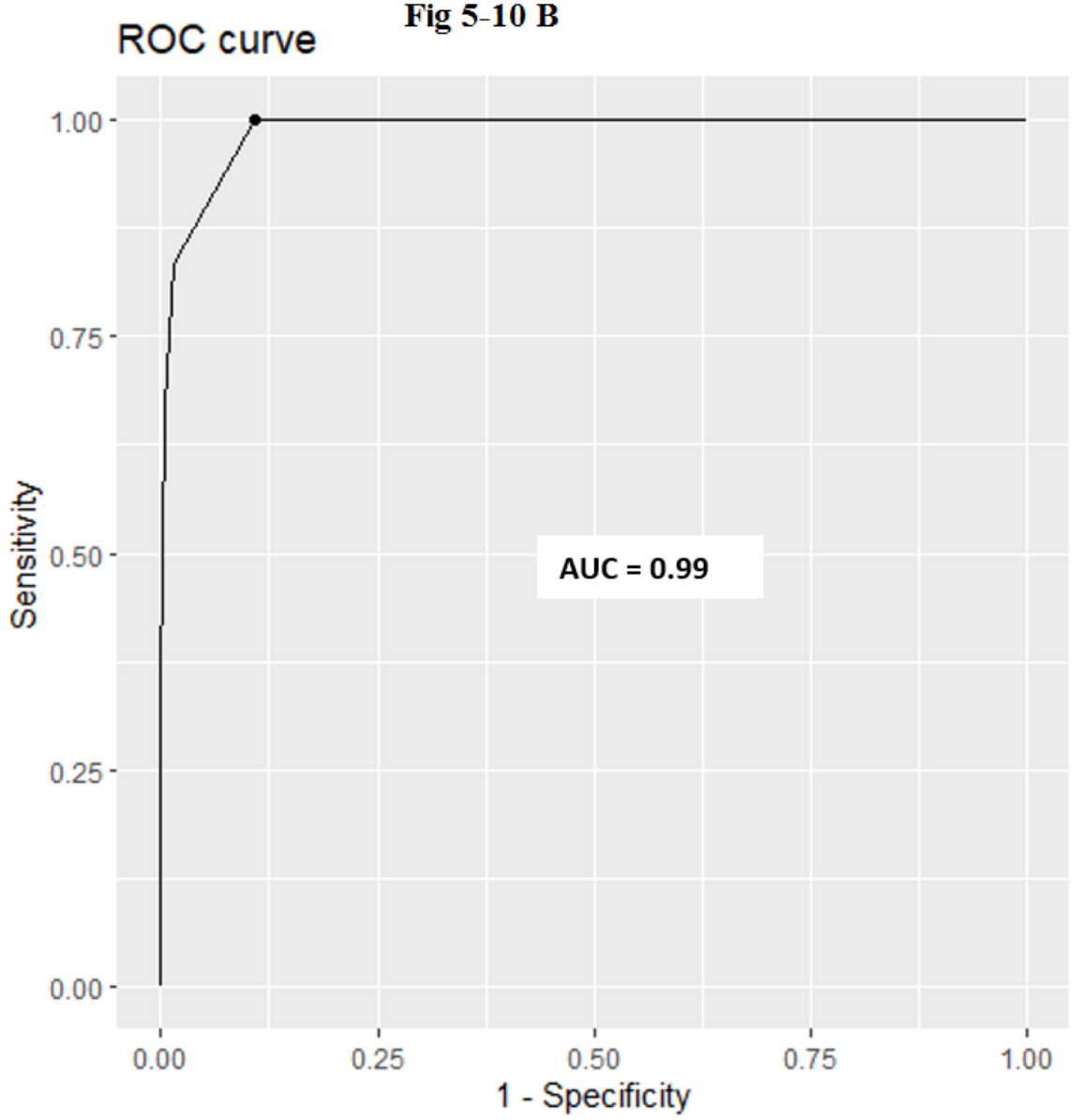

Figure 5-10 A and B: Liu Score performance. The right is ROC with AUC. The optimal cut point is marked as a black dot. The left is the histogram of the score on two subgroups: patients with and without CI-AKI. The optimal cut point is marked as a vertical black line.

Chapter 6 Results (CINEMA Trial)

A total of 1,205 consecutive patients (mean age: 62.3 ±7.5 years, 698 men) with CKD (mean e-GFR: 46.37 ± 10.25 ml/min/1.73 m^2) were included in the study. Of them, 1,086 underwent elective procedures and 119 underwent urgent angiography because of a non-ST elevation myocardial infarction (NSTEMI). The treatment assignment between the 2 groups was determined by randomization in a 2:1 ratio with 799 patients randomized to the MHFD group and 406 to the control group. No patients were lost to follow-up and all eligible patients were analyzed.

Baseline characteristics of the 2 groups are given in **Table 6-1.** The MHFD group patients were younger compared to the control group (Age 62.3 ±7.5 vs. 65.5 ±8.2 years, p<0.001). Diabetes (DM), hypertension (HTN), smoking and peripheral arterial disease were more prevalent in the study group than the control group. There were more patients requiring insulin in the MHFD group (p<0.0001).

Both groups were comparable in regard to the rate of elective and urgent procedures: 717 (89.7%) vs. 369 (90.9%) and 82 (10.3%) vs. 37 (9.1%) respectively. PCI were more frequently performed in the MHFD group compared to the control group: 694 (86.9%) vs. 327 (80.5%) (p=0.004).

The frequency of additional CI-AKI risk factors including baseline eGFR and contrast volume and use of nephrotoxic drugs were similar between the two groups. The target urine flow (>300 ml/hour) was reached in all patients in the MHFD group.

Overall CI-AKI occurred in 121 of 1,205 (10.0%) patients in our study. CI-AKI was significantly higher among patients who underwent elective procedures (n=109, 9.0%) than those who underwent urgent procedures (n=12, 1.0%) (p<0.05). With respect to the primary outcome, 64 (8.01%) of the MHFD patients developed CI-AKI compared with 57 (14.04%) of the control group (p <0.001). When we compared the development of CI-AKI in elective procedures compared to emergency procedures, the MHFD treatment was particularly effective in patients undergoing elective procedures as compared to emergency

procedures. **(Figure 6-1).** Details of medications used by the patients are shown in **Table 6-2.**

No significant MHFD-associated complications were observed as shown in **Table 6-3.** In-hospital renal failure requiring dialysis occurred in 4 patients in the control group (1.0%) compared with 9 patients (1.1%) in the MHFD group (p=NS).

Table 6-1. Baseline Characteristics of the Study Patients

	Study group (MHFD) n = 799	Control group (IVH) n = 406	P value
Baseline clinical characteristics			
Age	62.3 ±7.5	65.5 ±8.2	< 0.001
Men	457 (57.2%)	241 (59.4%)	0.47
Diabetes Mellitus	451 (56.4%)	192 (47.3%)	0.003
Hypertension	587 (73.5%)	234 (57.6%)	< 0.001
Smokers	320 (40.1%)	114 (28.1%)	< 0.001
PAD	353 (44.2%)	103 (25.4%)	< 0.001
EF%	51.17 ± 9.53	52.02 ± 9.94	0.15
No. of procedures performed			
Elective procedures	717 (89.7%)	369 (90.9%)	0.53
Urgent procedures	82 (10.3%)	37 (9.1%)	
Procedure			
Coronary angiography	102 (12.8%)	70 (17.2%)	0.04
PCI	694 (86.9%)	327 (80.5%)	0.004
PCI- CTO	3 (0.4%)	9 (2.2%)	0.002
Contrast volume (ml)	152.82 ± 66.16	146.19 ± 67.99	0.10
Lab measures			
e - GFR	46.37 ± 10.25	46.29 ± 9.6	0.90
Creatinine (mg / dl)	1.52 ± 0.25	1.51 ± 0.20	0.51
Creatinine 48 hours after the procedure (mg / dl)	1.75 ± 0.33	1.69 ± 0.32	0.004
HbA1c	6.85 ± 1.27	6.99 ± 2.93	0.23
S Cholesterol (mg/dl)	152.69 ± 53.79	163.08 ± 33.71	< 0.001
S LDL (mg/dl)	94.12 ± 36.11	107.67 ± 49.18	< 0.001
S HDL (mg/dl)	40.26 ± 6.35	40.18 ± 5.23	0.84
TG (mg/dl)	176.42 ± 92.17	205.41 ± 80.74	< 0.001
Hb%	13.19 ± 1.30	13.49 ± 1.28	< 0.001
WBC	9.12 ± 2.06	9.17 ± 1.98	0.68
Lymphocyte	3.53 ± 0.85	3.48 ± 0.88	0.32
Neutrophil	5.35 ± 1.07	5.30 ± 0.98	0.44
Platelets	354.58 ± 127.47	349.43 ± 128.72	0.51

Table 6-2: Medications				
Drug	Study Group	Control Group	Total	P value
Beta blockers	399 (49.9%)	183 (45.1%)	582 (48.3%)	0.11
ACEI	269 (33.7%)	124 (30.5%)	393 (32.6%)	0.27
ARBS	350 (43.8%)	122 (30.0%)	472 (39.2%)	< 0.001
Calcium channel blockers	182 (22.8%)	96 (23.6%)	278 (23.1%)	0.36
Alfa and Beta blockers	17 (1.1%)	4 (1.0%)	21 (1.7%)	0.16
Nitrates	209 (26.2%)	97 (23.9%)	306 (25.4%)	0.39
Ranolazine	84 (10.5%)	62 (15.3%)	146 (12.1%)	0.02
Trimetazidine	132 (16.5%)	55 (13.5%)	187 (15.5%)	0.18
Statins	639 (80.0%)	342 (84.2%)	981 (81.4%)	0.07
Anti-platelets	794 (99.4%)	404 (99.5%)	1198 (99.4%)	0.77
Procoralon	136 (17.0%)	31 (7.6%)	167 (13.9%)	< 0.001
Metformin	44 (5.5%)	50 (12.3%)	94 (7.8%)	< 0.001
Sofonylur	150 (18.8%)	64 (15.8%)	214 (17.8%)	0.20
Repaglinide	40 (5.0%)	19 (4.7%)	59 (4.9%)	0.80
Pioglitazone	26 (3.3%)	13 (3.2%)	39 (3.2%)	0.96
DPP4I	224 (28.0%)	99 (24.4%)	323 (26.8%)	0.17
SGL2I	149 (18.6%)	87 (21.4%)	236 (19.6%)	0.25
Insulin (short)	67 (8.4%)	29 (7.1%)	96 (8.0%)	0.45
Insulin (intermediate)	143 (17.9%)	53 (13.1%)	196 (16.3%)	0.03
Insulin (long)	106 (13.3%)	33 (8.1%)	139 (11.5%)	0.01
Loop diuretics	99 (12.4%)	53 (13.1%)	152 (12.6%)	0.75
Thiazide	176 (22.0%)	62 (15.3%)	238 (19.8%)	0.01
Acetazolamide	16 (2.0%)	5 (1.2%)	21 (1.7%)	0.33
K sparing	70 (8.8%)	35 (8.6%)	105 (8.7%)	0.94
Digoxin	51 (6.4%)	25 (6.2%)	76 (6.3%)	0.89
Amiodarone	49 (6.1%)	18 (4.4%)	67 (5.6%)	0.22
Flecanide	2 (0.3%)	1 (0.2%)	3 (0.2%)	0.90
Ibutalide	2 (0.3%)	0 (0.0%)	2 (0.2%)	0.31
Lidocaine	2 (0.3%)	0 (0.0%)	2 (0.3%)	0.31
Procainamide	2 (0.3%)	0 (0.0%)	2 (0.3%)	0.31
Quinidine	2 (0.3%)	0 (0.0%)	2 (0.3%)	0.31
NSAIDs	6 (0.8%)	0 (0.0%)	6 (0.8%)	0.80
Antibiotics	3 (0.4%)	0 (0.0%)	3 (0.2%)	0.22
Gentamycin	4 (0.5%)	1 (0.2%)	5 (0.4%)	0.52
Pentoxiphylin	86 (10.8%)	15 (3.7%)	101 (8.4%)	< 0.001

In this study, a large number of drugs were used by the study participants both the study group (MHFD, n=799) and the control (IVH) group (n=406). For convenience, we classified the drugs into a number of classes according to their clinical uses.

a. Drugs for hypertension such as Beta blockers, ACEI (angiotensin-converting enzymes inhibitors), ARBS (angiotensin II receptor blockers), Calcium channel blockers, Alfa and beta blockers, and Repaglinide.

b. Anti-anginal drugs such as nitrates, ranolazine, trimetazidine, and procoralon.

c. Drugs for heart failure such as thiazide diuretics, loop diuretics, K sparing diuretics, and digoxin.

d. Anti-arrhythmic drugs such as amiodarone, flecanide, Ibutalide, lidocaine, procainamide, and quinidine.

e. Anti-diabetic drugs such as metformin, sufonylur, pioglitazone, DPP4I, SGL2I, Insulin (short, long and intermediate).

f. Other cardiovascular drugs such as statins, anti-platelets and pentoxiphylin. g. Miscellaneous drugs: Antibiotics such as gentamycin.

The most frequently used drugs were anti-platelets (n=1198, 99.4%) and statins (n=981, 81.4%), though there was no statistically significant difference between the study and control groups. On the other hand, some drugs were used very occasionally such as antibiotics (n=3, 0.2%), quinidine (n=2, 0.2%), procainamide (n=2, 0.2%), lidocaine (n=2, 0.2%) and Ibutalide (n=2, 0.2%).

It is of interest to note that only several drugs had a statistically significant difference between the study and control groups such as calcium channel blockers ($p<0.001$), ranolazine ($p=0.02$), Procoralon ($p<0.001$), metformin ($p<0.001$), intermediate insulin ($p=0.03$), long insulin ($p=0.01$), and pentoxiphylin ($p<0.001$).

Table 6-3. Post-Procedural Complications			
	Study Group	**Control**	**p**
CI-AKI requiring renal replacement therapy (RRT)	9 (1.1%)	4 (1.0%)	p=NS
Significant arrhythmia	1 (0.1%)	0 (0%)	p=NS
Cardiogenic shock	0 (0%)	0 (0%)	p=NS
Pulmonary edema	3 (0.4%)	3 (0.7%)	p=NS
Death	0 (0%)	0 (0%)	p=NS
All clinical events	13 (1.6%)	7 (1.7%)	p=NS

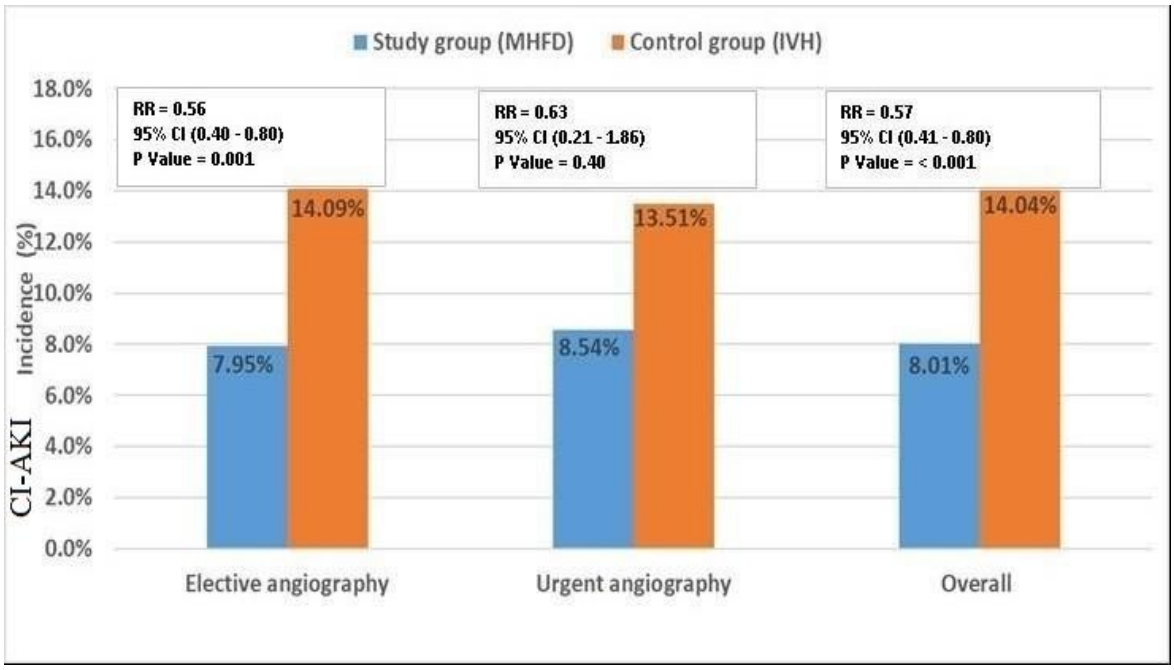

Figure 6-1: Incidence of CI-AKI in All Study Patients and in Those Undergoing Elective or Urgent Coronary Angiography.

Chapter 7

7.1.1 Discussion of Assessment of CI-AKI Risk and CI-AKI Risk Prediction

CI-AKI is a known and important complication of PCI. Because of improvements in PCI techniques, the technical success rate of PCI for coronary chronic total occlusion lesions has steadily increased over the past 15 years, with high recanalization rates, and there is observational evidence that successful CTO-PCI is associated with improvements in angina, left ventricular function, and survival. Complex CTO lesions adversely affect the initial success rates by requiring prolonged X-ray exposure and the use of large contrast medium volumes. Additionally, patients with CTO-PCI are generally older and more likely to have diabetes, and worse renal function than patients without CTO. These factors render patients undergoing CTO-PCI more prone to developing CI-AKI in some cases (77,78).

CI-AKI is not an uncommon complication after diagnostic and therapeutic cardiovascular procedures that is associated with significant mortality and morbidity (36,79). In my study, 29 (8.8%) cases developed CI-AKI, defined as a 25% increase or an absolute increase in SCr ≥0.5 mg/dL over baseline within 48–72 h after contrast medium exposure. According to the study of Zhang MM et al, the hospitalization days and expense of CI-AKI group were significantly longer and higher than the group without CI-AKI (80). The study by Wang et al reported a 16.3% incidence of CI-AKI in patients with CTO who underwent PCI (81). In this study, CI-AKI developed in 29 out of 329 patients subjected to CTO PCI procedure constituting a rate of 8.81%. Liu Y-H et al prospectively observed 85 patients with chronic kidney disease who underwent attempted PCI for CTO and found CI-AKI incidence of 9.4% which is higher than our figure (78). Similarly, Zhang MM et al conducted an important study on diabetic patients who underwent PCI CTO in their institution and found CI-AKI incidence of 9.33% (80). On the other hand, Lin Y-S from Taiwan reported a lower incidence (5.4%) of CI-AKI among patients referred to PCI CTO (79).

Azzalini et al from Italy conducted a study to evaluate the association between complex PCI and CI-AKI. They believe that complex PCI is associated with increased procedural challenges and high contrast load. Complex PCI was defined as a procedure with ≥1 of the following characteristics: 3 vessel treated, ≥3 stents implanted, two-stent bifurcation intervention, total stent length >60 mm, PCI on a chronic total occlusion, saphenous vein graft, or left main, protected PCI, use of rotational /laser atherectomy. The study involved 1,128 complex PCI and 1,532 non- complex PCI. Complex PCI patients tended to be older, and had higher cardiovascular morbidity and Mehran risk score and received higher mean contrast volume. CI-AKI incidence was similar in complex vs. non-complex PCI patients as was the need for in-hospital dialysis. Upon multivariable adjustment, age, female sex, diabetes, ejection fraction, periprocedural hypotension, presentation with acute coronary syndrome, and contrast volume were independently associated with CI-AKI, while complex PCI was not. They concluded that complex PCI was not associated with an increased risk of CI-AKI in all-comers (82).

Another research group from Italy headed by Demir OM, conducted a study to evaluate the incidence of CI-AKI in patients who underwent CTO (n=309) vs. non- CTO PCI (n=2,271). On multivariate analysis, hypotension during/before PCI, acute coronary syndrome, age, female sex, left ventricular ejection fraction, diabetes mellitus, and contrast volume were independent predictors of CI-AKI, while CTO PCI was not. The study, thus concluded that CTO PCI was associated with similar rates of CI-AKI, compared with non-CTO PCI (75).

Zhang MM et al conducted an important study on diabetic patients who underwent PCI CTO in their institution and found that patients with CI-AKI tended to be lighter in body weight and were more often female, and also had a higher prevalence with acute coronary syndrome. As for the preprocedural drugs, statins seemed to decrease the incidence of CI-AKI, and the use of diuretics might increase the occurrence of CI-AKI (80). In a study by Wang et al, a multivariate analysis showed that higher pulse pressure and contrast volume and lower baseline GFR were independent predictors of CI-AKI (81).

In my study, patients who developed CI-AKI were more likely to be older and had a past history of CHF. LVEF was lower in the CI-AKI group. Baseline renal function was lower in the CI-AKI group with higher serum Creatinine and lower eGFR. Serum albumin was lower in the CI-AKI group. During the procedure, patients in the CI-AKI group received a larger volume of contrast and had a higher J-CTO score. Our findings are not unexpected. CI-AKI is more prevalent in patients with well-known risk factors, including older age and those renal insufficiency and congestive heart failure. In my study, the CI-AKI group had more clinical endpoints that included CI-AKI requiring RRT, significant arrhythmias, cardiogenic shock, pulmonary oedema and death. These findings are in keeping with the evidence that CI-AKI has significant clinical consequences.

In the present study, the mean age was 61.16 ± 9.05 years. Older people (≥56 years) comprised the majority (n=164, 78.8%) of the patients. This finding is consistent with all studies which identified old age as a risk factor for CI-AKI. Patients who developed CI-AKI were more likely to have a past history of CHF. LVEF was lower in the CI-AKI group (39.25% vs. 55.24%; p< 0.001).

Diabetes is known to be a risk factor although in our study, the prevalence of diabetes was not higher in the CI-AKI group although the HbA1c level was higher that might suggest worse glycaemic control (HbA1c. 7.88% vs. 6.52%; p< 0.001). This is in contrast to the published studies, all of which consider DM an important risk factor for CI-AKI. In my study, systolic BP was not statistically different between the 2 groups. However, the diastolic BP was significantly lower in the CI-AKI group compared to the non-CI-AKI group (64.17 mmHg vs. 81.05 mmHg; p<0.001).

The mean HB level was significantly lower in the CI-AKI group (10.27 g/Dl vs. 13.19 g/dl; p< 0.001).

Renal function tests were more impaired in the CI-AKI group. Mean serum creatinine was significantly higher in CI-AKI group both before and after the PCI (1.62 mg/dl vs. 1.03 mg/dl and 2.39 mg/dl vs. 1.15 mg/dl respectively). The mean e-GFR was significantly lower in the CI-AKI group (39.92 ml/min/1.73 m^2 vs. 77.27 ml/min/1.73 m^2).

The mean contrast volume was significantly higher in the CI-AKI group compared to the non-CI-AKI group (310.97 ml vs. 274.46 ml). Mean serum albumin was significantly lower in the CI-AKI group compared to the non-CI-AKI group (3.21 mg /dl vs. 4.45 mg /dl; $p< 0.001$).

In the current series, all patients who developed CI-AKI (n=12) had JCTO score of 3-5 and most patients who did not develop CI-AKI (n=183, 93.4%) had JCTO score of 0-2. Therefore, JCTO score had a significant impact on the occurrence of CI-AKI ($p< 0.001$).

In our study, we found that lower serum albumin was associated with CI-AKI. However, meta-analysis published in 2010 provided evidence that low levels of serum albumin (hypoalbuminemia) are a significant independent predictor of acute kidney injury (AKI) and death following AKI (83). In the current study, the mean serum albumin was significantly lower in the CI-AKI group compared to the non-CI-AKI group (3.21 mg /dl vs. 4.45 mg /dl; $p< 0.001$).

CI-AKI Risk Prediction Scores

Mehran et al identified several risk factors for CI-AKI and extracted the cumulative risk by combination of these risk factors. Eight variables were identified [hypotension, intra-aortic balloon pump, congestive heart failure, chronic kidney disease, DM, age > 75 years, anemia and volume of contrast]. Mehran risk score can be used for both clinical and investigational purposes (44). Beside its usefulness in prediction of CI-AKI after non-urgent PCI, Mehran risk score was also shown to be "clinically useful in primary angioplasty setting population and to stratify patients for poor clinical outcomes both in the short- and long-term follow up" (45). Abella´s- Sequeiros et al validated the Mehran score in a cohort of Spanish patients with acute coronary syndrome and concluded that this score was also good for predicting CI- AKI in such patients who underwent coronary angiography (46).

Lin Y-S from Taiwan retrospectively analyzed 516 patients referred for CTO PCI. Analysis of risk using Mehran scoring found that the incidence of CI-AKI was 0.5% (1/207) among low-risk patients, 3.4% (7/205) among moderate-risk patients, 15.9% (14/88) among high-risk patients and 37.5% (6/16) among very high-risk patients. The Mehran score high-risk group (11-15) and the very high-risk group (≥16) were definitely predictors of CI-AKI after CTO PCI (79).

Yin et al have "successfully established a risk prediction model with excellent predictive ability for CI-AKI in Chinese patients. This model can be applied to patients administered contrast media for coronary procedures and other contrast procedures such as intravenous contrast-enhanced CT, CT angiography, and non- coronary angiography. For the first time, three new factors were included in the model: the decreased sodium concentration, the International Normalized Ratio value, and the pre-procedural glucose level" (48)

Using four variables (age ≥ 75 years, LVEF<40%, ALB, and SCr >1.5 mg/dL) as risk indicators for CI-AKI, Liu et al developed a new risk scoring system in which age ≥ 75 years scored 4.5 points, ALB ≤ 30 g/L scored 2 points, ALB 30-40 g/L scored 1 point, ALB>40 g/L scored 0; LVEF<40% scored 3.5 points, and SCr>1.5 mg/dL scored 5 points. For each patient, the score was calculated as the sum of the weighted integer coefficients (range 0–15) (50,77).

CI-AKI risk prediction scores often involved the use of contrast volume in score calculations that limits their application in identifying patients who might benefit from peri-procedural nephroprotective strategies. In this study, we have evaluated 2 proposed pre-procedural risk scores: Modified Mehran Score and the Liu Prediction Score to determine their ability to identify at risk patients undergoing CTO PCI (84).

Several risk score systems have been established to predict the risk of CI-AKI. The Mehran risk score, the most widely used and classic model for CI-AKI, has eight clinical and procedural factors, including age >75 years, CM volume, and the presence of heart failure, hypotension, anemia, diabetes mellitus, and chronic kidney disease. However, this risk score was established for complete risk assessment only after CM administration, that does

not lend itself for prophylactic in clinical practice. A fully pre-procedural risk prediction model would be more useful so that precautionary measures could be adopted and more individually tailored procedures used in those patients who are more prone to developing CI-AKI (84).

Especially for patients with CTO undergoing PCI, a large CM dose, which is considered as the most potent risk factor for CI-AKI, needs to be given in order to complete the procedure. A recent meta-analysis reported that the volume of CM can reach up to 350.3 ± 71.3 mL in these patients. Therefore, it is important to develop a pre-angiographic risk prediction to identify high-risk patients, so that their CM dose can be minimized and prevention measures can be given (84,85).

Recently, pre-proceduarl risk scores have been proposed that had been reported to be predictive of CI-AKI (50,86,87). These pre-procedural risk scores have not been validated in clinical practice. In this study, we have shown that both the Modified Mehran (87) as well as the Liu score (77) were highly predictive of CI-AKI. Importantly, both scores are characterized not only by their high predictive value but also by their simplicity with only a handful of pre-angiographic variables (84).

In my analysis of patients undergoing CTO-PCI, I found that Modified Mehran score had an optimal cut-point of 7 that resulted in a 0.85 accuracy of predicting CI-AKI with a sensitivity of 96.6% and a specificity of 83.3%. As requested, I have compared the cut-offs of the use of Modified pre-procedural Mehran Score in other populations. In a recent report by Rahim and colleagues (88) they reported that the use pre-procedural Mehran score in patients undergoing PCI and not just limited to CTO-PCI. They did not explore optimal cut off like me. Rather they categorized the Modified pre-procedural risk scores according to AKI risk as low (≤2), moderate (3-8), high [8-12], and very high (≥13). The pre-procedural Mehran score resulted in a sensitivity of 95% for the low risk group (score ≤ 2) and a specificity of 96 % for the high-risk group (score ≥ 13). Our findings are supportive of this.

With respect to the Liu Score, in our study the optimal cut-point of 5.5 resulted in a 0.90 accuracy of predicting CI-AKI with a sensitivity of 100.0% and a specificity of 89.3%. I am not able to identify the use of the Liu score except in the original report by Liu and colleagues (50) (Liu Y, Liu YH, Tan N, Chen JY, Zhou YL, Duan CY, Li HL, Chen PY. Novel risk scoring for pre-procedural prediction of contrast-induced nephropathy and poor long-term outcomes among patients with chronic total occlusion undergoing percutaneous coronary intervention *European Heart Journal Supplements*, Volume 17, Issue suppl_C, July 2015, Pages C34–C41). In that study, the Liu score had good discriminating power (C-statistic = 0.876). They did not report an optimal cut-off. Rather, they divided the risk score model into the following three groups: low risk (score <4, CIN incidence 0.75%), moderate risk (score = 4–7, CIN incidence 5.26%), and high risk (score ≥7, CIN incidence 30.77%). Based on this classification, the incidence of CIN in the validation group was 0% in patients with a low-risk score, 8.20% in patients with a moderate-risk score, and 13.33% in those with high-risk scores. The addition of Hb did not improve further the predictive value. It should be emphasized that my study was not powered to develop a new CI-AKI risk score as I did not have a validation cohort.

7.1.2 Conclusion

We have shown that risk factors for CI-AKI in Kurdistan were almost similar to other parts of the world. Moreover, we have found that both a modified preprocedural Mehran score as well as the Liu Risk Score have potential use to identify patients undergoing CTO PCI for peri-procedural nephroprotective therapies such as with matched hydration that can delivered both manually (89) or using the Renalguard system (90).

7.2 Discussion of CINEMA Trial

Prevention of CI-AKI is of paramount importance, with an ever-increasing number of coronary angiographies and interventions being done. Current clinical practice guidelines recommended adequate hydration, minimizing volume of contrast media and using iso-osmolar or low-osmolar contrast agents (91–95). The role of nephroprotective drugs in preventing CI-AKI is not recommended.

Adequate hydration remains the mainstay of CI-AKI prevention since early 1970s (96). This was due to observation that dehydration would exacerbate renal insufficiency in a patient exposed to contrast media. Hydration increases the intravascular blood volume, suppresses the renin-angiotensin-aldosterone system, and promotes dilution and rapid evacuation of contrast media. Contrast Media Safety Committee recommends an intravenous regime of 1.0-1.5 mL/kg/hour for at least 6 hours before and after contrast media administration (93), though concerns regarding volume overload for patients undergoing cardiac catheterization procedures often lead to insufficient pre-hydration. Furosemide may decrease the nephrotoxic effect of contrast agents, first by increasing the urine flow and hence diluting the contrast media, and second by blocking tubular sodium reabsorption in the loop of Henle, thus decreasing tubular workload and associated oxygen requirement. However, the use of furosemide alone is controversial since it decreases the effective circulating volume and prostaglandin mediated vasodilation with the potential dehydration. This concern has prompted the exploration of the use of diuretics together with hydration.

Several studies have evaluated hydration and diuresis with mixed results (97,98). However, in these older studies there was a lack of adequate matching between hydration and urine flow. The PRINCE trial reported a reduction in CI-AKI with forced diuresis resulting in a mean urine flow rate of above 150 ml/min (65). However, in this trial, less than 30% of the enrolled patients reached that urine flow target, even when a forced diuresis approach was used (furosemide plus dopamine plus mannitol administration). Also, fluid administration matched to urine output was commenced after starting the cardiac

catheterization procedure. This contrasts with our study that required matched hydration to be continued throughout the catheterization procedure and up to 4 hours after the procedure, and nearly all patients reached the urine flow target of >300ml/hour. On the other hand, Majumdar et al (99) reported a higher (50%) CI-AKI rate in forced diuresis patients than in those who received saline infusion only. However, there are several differences between the study by Majmudar et al and our study. Unlike our study, the study by Majmudar et al was a small study which used a different treatment protocol including hypotonic saline solution and continuous infusion of furosemide. Also, they had included a greater proportion of patients with more severe CKD (average eGFR: 27 ml/min/1.73 m^2).

The RenalGuard™ System (PLC Medical Systems, Inc. Franklin, MA, USA) is a device that can guide the physician in achieving high urine output with a low furosemide dose while simultaneously balancing urine output and venous fluid infusion to minimize the risk of overhydration or underhydration. Several studies have demonstrated that the approach of controlled, forced diuresis using the RenalGuard therapy is more effective than the conventional therapy in preventing CI-AKI in high-risk patients (57,58). However, the automated RenalGuard system is not widely available especially in many low- and middle-income countries. In our study, we have shown in randomized controlled trial the value of a non-automated matched hydration and forced diuresis in the prevention of CI-AKI in patients with CKD who had undergone coronary procedures. The main finding of this study is the statistically significant lower rate of CI-AKI among patients who received non-automated matched hydration and forced diuresis compared to the control group (8.01% vs. 14.04%, $p<0.001$). In subgroups analysis, the incidence of CI-AKI was not statistically different in patients undergoing urgent coronary procedures. This is likely due to the small sample size of patients who underwent urgent procedures in our study sample.

It is also noteworthy that although mean serum creatinine was similar in both MHFD and control groups, the MHFD group had higher rates of atherosclerosis-related risk factors such as DM, HTN, smoking and PAD, suggesting a higher risk of CI-AKI in this group.

This imbalance in baseline risk is likely to be due to my use of the Simple Randomization method. On reflection, I should have considered the Stratified Randomization Method. Separating participants into groups depending on different factor risk factors. This form of randomization could have reduced the imbalances in characteristics found in treatment groups. This method makes it easier to generate block randomization lists for different atherosclerosis-related risk factors. This is an important learning point from my PhD.

However, it is worth noting that despite this increased risk profile, the rate of CI-AKI was lower in the MHFD group.

The magnitude of benefit seen in our study is similar to that achieved by MYTHOS trial that examined the benefits of furosemide-induced high-volume diuresis and maintenance of intravascular volume through automatic RenalGuard matched hydration system for the prevention of CI-AKI in high-risk patients undergoing coronary procedures (58). Our study suggests that a non-automated MHFD method can be used as an effective alternative to the RenalGuard system.

Chapter 8 Future Directions

Based on my own findings around risk prediction that could be used to identify patients for nephroprotective therapies, I believe an obvious future direction would be a prospective randomized controlled trial utilizing either the Modified Mehran or Liu risk score to identify high CI-AKI risk patients for MHFD as per my CINEMA protocol. This is needed to provide evidence to help change clinical practice guidelines that could impact on patient care.

Another direction for the future research is the needed for a reliable biomarker of acute kidney injury. CI-AKI studies usually rely on serum creatinine as a biomarker of renal injury to indicate that CI-AKI has occurred, but serum creatinine is a poor, indirect, nonspecific, lagging reflection of renal function that relies on the serum accumulation of creatinine after a nephrotoxic event. Serum creatinine values are modified by diet and muscle mass and exhibit daily physiologic variations. In general, serum creatinine level is not well suited for assessing acute nephrotoxic exposures with a small effect size (100). There is much interest in emerging biomarkers of acute kidney injury such as neutrophil gelatinase–associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), cystatin C, IL-18, and liver-type fatty acid–binding protein (L-FABP). An improved biomarker for CI-AKI—one that is sensitive yet specific, detectable within minutes or hours of contrast material exposure, and predictive of long-term adverse events—is desperately needed. If an innovative biomarker can be identified with improved test characteristics for CI-AKI that reduces the demand on patient recruitment, many other avenues will become available for study.

It would be interesting to resolve the dispute regarding the nephrotoxic potential of intra-arterial versus IV administration of low-osmolar contrast medium (LOCM) and iso-osmolar contrast medium (IOCM) (100). Although it is our belief that IV LOCM and IOCM are no different than any other weak nephrotoxin and that acute kidney injury resulting from LOCM and IOCM (and not a concurrent illness or physiologic variation) probably portends increased morbidity and mortality, direct proof of this association is

lacking. Of course, many other accepted nephrotoxins lack this proof: Studies on morbidity and mortality from acute kidney injury often lump all causes of acute kidney injury (as defined by a given level of serum creatinine increase) into one cohort for assessment and do not attempt to discover if the acute kidney injury caused by some nephrotoxins is clinically different from the acute kidney injury caused by other nephrotoxins (100).

CI-AKI needs to be redefined using markers of kidney injury that are sensitive, specific, and predictive of adverse outcomes. This will enable researchers to better address the question of how to prevent and/or treat this condition in the future. The most important question to be answered is whether prevention of kidney injury results in a change in short- and long-term adverse outcomes. Some prevention strategies have been associated with a reduction in long-term adverse events, while others have not (101).

In conclusion, clearly more studies are needed to better understand the pathophysiology of CI-AKI and the utility of biomarkers of acute kidney injury as a tool to assess the development of CI-AKI. Based on the findings of my PhD, I believe there is an urgent need to conduct a prospective randomized controlled trial utilizing either the Modified Mehran or Liu risk score to identify high CI-AKI risk patients for MHFD as per my CINEMA protocol. This is needed to provide evidence to help change clinical practice guidelines that could impact on our patient care.

Chapter 9 Publications and Poster Presentations

9.1 Publications

9.1.1 Mirza AJ, Lang CC, Taha AY, Ahmed FJ, Ezzaddin SA, Abdulrahman ZI. Matched Hydration and Forced Diuresis for Prevention of Contrast-Induced Nephropathy in Patients with Impaired Renal Function Undergoing Coronary Procedures. Journal of the American College of Cardiology. 2021 May 11;77(18_Supplement_1):1578.

9.1.2 Aram J. Mirza, Kashan Ali, Farhad Huwez, Abdulsalam Y. Taha, Farman J. Ahmed, Shahow A. Ezzaddin, Zana I. Abdulrahman, Chim C. Lang. Contrast Induced Nephropathy: Efficacy of matched hydration and forced diuresis for prevention in patients with impaired renal function undergoing coronary procedures–CINEMA trial. IJC Heart & Vasculature April 2022; 39:100959. https://doi.org/10.1016/j.ijcha.2022.100959

1.9.3 Aram Jamal Mirza, Chuang Gao, Kashan Ali, Samira Bell, Emilie Lambourg, Ify Mordi, Abdulsalam Y. Taha, Shahow A. Ezzaddin, Farhad Huwez, Emily Jefferson, Chim C. Lang. Pre-Procedural Risk Scores to Help Identify Patients at Risk of Contrast Induced Nephropathy after Chronic Total Occlusion Percutaneous Coronary Intervention for Peri-Procedural Nephroprotective Therapies. Journal of the American College of Cardiology 2022;79(9) Supplement: 842. https://doi.org/10.1016/S0735-1097(22)01833-2

9.2 Poster Presentations

9.2.1 Mirza A, Ali K, Huwez F, Taha A, Ahmed F, Ezzaddin S, Abdulrahman Z, Lang C. Efficacy of matched hydration and forced diuresis for prevention of contrast induced nephropathy in patients with impaired renal function undergoing coronary procedures (Poster Euro21A-POS128). Available from https://eposter.europa-organisation.com/2021/europcr/index/slide/abstract/154

9.2.2 Aram Mirza, Chuang Gao, Kashan Ali, Samira Bell, Emilie Lambourg, Ify R Mordi, Abdulsalam Y. Taha, Shahow A. Ezzaddin, Farhad U. Huwez, Emily Jefferson, Chim C Lang. Pre-Procedural Risk Scores to Help Identify Patients at Risk of Contrast Induced Nephropathy After Chronic Total Occlusion Percutaneous Coronary Intervention for Peri-Procedural Nephroprotective Therapies. (Poster contribution). Available from https://www.jacc.org/doi/epdf/10.1016/S0735-1097%2822%2901833-2

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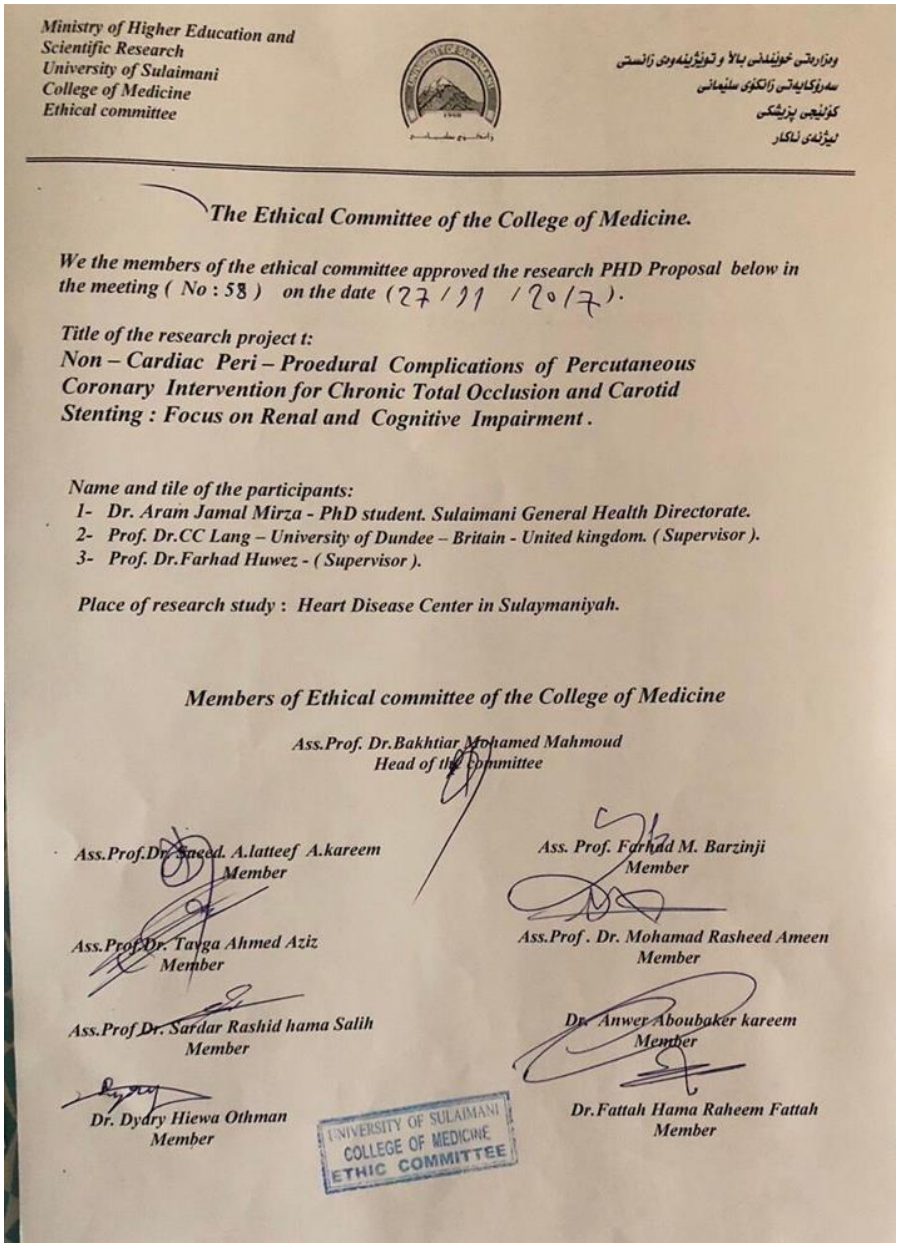
11. Appendices



Ministry of Higher Education and Scientific Research
University of Sulaimani
College of Medicine
Ethical committee

وەزارەتی خوێندنی باڵا و توێژینەوەی زانستی
سەرۆکایەتی زانکۆی سلێمانی
کۆلێجی پزیشکی
لیژنەی ئاکار

The Ethical Committee of the College of Medicine.

We the members of the ethical committee approved the research PHD Proposal below in the meeting (No : 58) on the date (27 / 11 / 2017).

Title of the research project t:
Non – Cardiac Peri – Proedural Complications of Percutaneous Coronary Intervention for Chronic Total Occlusion and Carotid Stenting : Focus on Renal and Cognitive Impairment .

Name and tile of the participants:
1- Dr. Aram Jamal Mirza - PhD student. Sulaimani General Health Directorate.
2- Prof. Dr.CC Lang – University of Dundee – Britain - United kingdom. (Supervisor).
3- Prof. Dr.Farhad Huwez - (Supervisor).

Place of research study : Heart Disease Center in Sulaymaniyah.

Members of Ethical committee of the College of Medicine

Ass.Prof. Dr.Bakhtiar Mohamed Mahmoud
Head of the Committee

Ass.Prof.Dr. Saeed. A.latteef A.kareem
Member

Ass. Prof. Farhad M. Barzinji
Member

Ass.Prof.Dr. Tayga Ahmed Aziz
Member

Ass.Prof . Dr. Mohamad Rasheed Ameen
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Ass.Prof.Dr. Sardar Rashid hama Salih
Member

Dr. Anwer Aboubaker kareem
Member

Dr. Dydry Hiewa Othman
Member

UNIVERSITY OF SULAIMANI
COLLEGE OF MEDICINE
ETHIC COMMITTEE

Dr.Fattah Hama Raheem Fattah
Member

11.1 Approval Letter of the Ethical Committee of the College of Medicine/University of Sulaimani.

11.2 ISRCTN Registry of the Study [(ISRCTN Registry Number: 72194653)]