Aus der Medizinischen Klinik mit Schwerpunkt Kardiologie,
Campus Virchow-Klinikum der Medizinischen Fakultät der Charité -
Universitätsmedizin Berlin

DISSERTATION

Risk of Contrast-Induced Nephropathy (CIN) after Diagnostic Cardiac Catheterization and Percutaneous Coronary Intervention Using Iopromide

Zur Erlangung des akademischen Grades
Doctor medicinae (Dr.med.)

vorgelegt der Medizinischen Fakultät der Charité -
Universitätsmedizin Berlin

von
Wenhua Li
aus Jiangsu, V.R. China

Gutachter: 1 Priv.-Doz. Dr. med. W. Bocksch

2 Prof. Dr. med. H. Hampl

3 Prof. Dr. med. F. X. Kleber

Datum der Promotion: 21. 06. 2007

Contents

Abbreviations and Acronyms

ACEI	angiotensin-converting enzyme inhibitor
AMI	acute myocardial infarction
ANP	atrial natriuretic peptide
A_2	adenosine-2 receptor
BMI	body mass index
CABG	coronary artery bypass graft
CIN	contrast-induced nephropathy
CK-MB	creatine kinase muscle-brain
CrCl	creatinine clearance
DM	diabetes mellitus
ET	endothelin
eGFR	estimated glomerular filtration rate
HOCM	high osmolality contrast media
IOCM	iso osmolality contrast media
LOCM	low osmolality contrast media
LVEF	left ventricular ejection fraction
NAC	N-acetyl-cysteine
NO	nitric oxide
NSAID	non-steroidal anti-inflammatory drug
PCI	percutaneous coronary intervention
PGE_1	prostaglandin E_1
RBF	renal blood flow
ROS	reactive oxygen species
UAP	unstable angina pectoris

1. Introduction

1.1 Definition of Contrast-Induced Nephropathy

Contrast-Induced Nephropathy (CIN) is defined as a sudden decline in renal function occurring after exposure to intravenous radiographic contrast agents that is not attributable to other causes. Typically, the serum creatinine level begins to increase 24-72 hours after administration of contrast medium, peaks at 3-5 days and requires further 3-5 days to return to baseline. In most studies, the acute radiocontrast-agent-induced reduction in the renal function was defined as an absolute (≥ 0.5 mg/dl) or relative (> 25%) increase in serum creatinine concentration within 48 h after the administration of contrast agents (1-3).

The contrast agent can lead to a reversible form of acute renal failure that begins soon after administration of the contrast dye and generally is benign. It accounts for 10% of all cause of hospital-acquired acute renal failure and represents the third leading cause of in-hospital renal dysfunction. The administration of radiographic contrast agents remains an important cause of hospital-acquired acute renal failure, which contributes to morbidity and mortality during hospitalization, prolongs the hospital stay, and increases the incidence of chronic end-stage renal disease and the cost of health care (4-7).

1.2 Epidemiology of CIN

The rate of incidence of CIN as a complication of radiographic diagnostic and interventional studies varies markedly depending on the definition used or on other variables such as the type of radiologic procedure performed, the dose and the type of contrast agent administered, the different patients population in regard to number and type of risk factors, and the length of patient follow-up. The incidence of CIN in patients with normal renal function before injection of contrast medium is low (< 10%) (5,8-10). However, it is important to recognize that the incidence of CIN in selected subjects is much higher, i.e., 9-40% among diabetic patients with mild-to-moderate chronic renal insufficiency and 50-90% with severe chronic renal insufficiency has been reported (11,12).

1.3 Pathophysiology of CIN

The mechanism of CIN is complex and not fully understood. The most important pathophysiologic links for CIN identified so far include direct tubular toxicity and disturbances of the renal hemodynamics with altered glomerular function and renal medullary ischemia.

Cytotoxicity

Contrast media have a direct cytotoxic effect on renal structures, including reduction of transepithelial resistance, insult permeability, polarized cellular enzyme release and other parameters of renal tubular cell viability (13-15). In vitro studies of proximal tubular cells incubated with contrast media demonstrated altered cellular metabolism pathologic changes consistent with toxicity and intracellular enzyme release (16). Patients who have received radiocontrast material have been noted to have an increased urinary excretion of lysosomal enzymes and small molecular weight proteins, which are nonspecific indicators of tubular toxicity (17). The direct renal tubular cytotoxicity is suggested by histologic changes such as cell injury and the presence of enzymuria following contrast administration (18). Andersen et al. (19) reported an in vitro model of proximal and distal tubule monolayer cell cultures which demonstrated an increase in cellular mortality with high osmolar contrast media (HOCM) compared with low osmolar contrast media (LOCM). An increased production of oxygen free radicals was documented in an experimental model of CIN (20). According to this finding, oxidant-mediated injury has been suggested as a mechanism of cytotoxic effect in the pathogenesis of CIN. Yoshioka et al. (21) found that contrast agents can reduce the activity of antioxidant enzyme catalase and superoxide dismutase in the renal cortex of volume depleted rats.

Renal Hemodynamics

In addition to these direct tubular effects, radiocontrast agent may induce a biphasic hemodynamic response, with an initial brief period of vasodilation, followed by a variable period of renal vasoconstriction (22). Most of the animal studies (23-26) documented decreases in renal blood flow (RBF) and glomerular filtration rate (GFR) after exposure to contrast media, compared to baseline. Perhaps more important than the effect on global RBF is the contrast-induced shunting of RBF from the relatively hypoxic medullary regions to the renal cortex (27).

Weiberg et al. (28) demonstrated that all patients have an early initial increase in renal blood flow after radiocontrast administration. Surprisingly, in contrast to non-diabetic patients, diabetic patients with a lower baseline renal blood flow manifest an earlier, more sustained and more pronounced increase in renal blood flow after contrast injection (28). The mechanism by which contrast medium causes subsequent vasoconstriction is still not fully understood. Alteration in the metabolism of prostaglandin, nitric oxide, endothelin, or adenosine possibly plays a role (29). Contrast media also cause an osmotic diuresis, which further aggravates renal ischemia (13,30). Barkris et al. (31) found a reduced GFR after the administration of a dopamine-1 receptor antagonist and an improvement by using the selective dopamine-1 receptor agonist fenoldopam. Interestingly, the use of vasodilators such as dopamine and atrial natricuretic peptide (ANP) may actually exacerbate medullary ischemia by causing redistribution of blood flow from the medulla to the cortex. A study by Tumlin and colleagues confirmed the ability of fenoldopam to prevent contrast-induced reduction in RBF in patients with higher risk of developing CIN (32).

Vasoactive Substances in the Pathogenesis of CIN

The release of endothelin and vasopressin, along with a reduction in prostacyclin synthesis and release, reduces blood flow to anoxic medulla (13). Endothelin, a strong endogenous vasoconstrictor, may contribute to the pathogenesis of CIN. After exposure to contrast material, the level of serum endothelin in animal models and in humans increases and is especially higher in patients with diabetes mellitus or impaired renal function (33-35).

There is some evidence of a protective role of prostaglandins and nitric oxide (NO) in the genesis of CIN. Hatcheson et al. (36) demonstrated an inhibition of NO production resulting from the direct effect of nonionic contrast media on the endothelium in the isolated arterial preparation in animals. A decreased level of medullary oxygenation in rats as a result of inhibition of prostaglandins and NO, as well as after intravenous administration of contrast media has been reported (37,38).

Experimental studies showed increased adenosine induced vasoconstriction in the kidney of diabetic animals (39). The decrease in RBF and GFR following contrast administration is prevented by an adenosine A1 receptor antagonist (24,40). Increased release of renal adenosine and stimulation of renal adenosine receptors have been proposed to be important mechanisms in

the development of CIN (39,41). Potential additional participants are serotonin, bradykinin, leukotrienes, histamine, catecholamines and the sympathetic nervous system.

Katzberg (42) summarized three major pathways proposed for the pathophysiology in CIN (Figure 1-1).

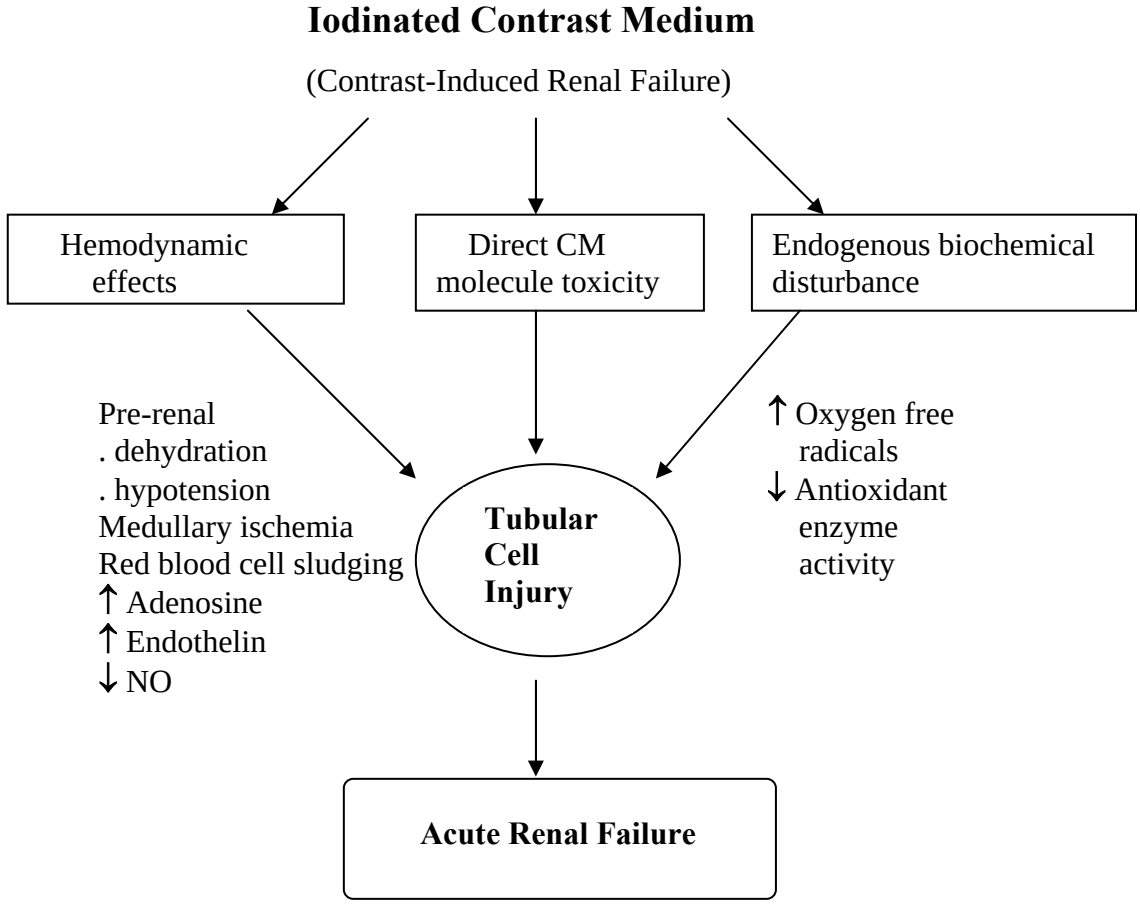


Figure 1-1 Proposed pathways that lead to contrast-induced nephropathy (42). These pathways include hemodynamic effects (direct and indirect), direct contrast medium (CM) molecule toxicity, and endogenous biochemical disturbance. Interrelationships and/or combinations of these effects are also possible. (*NO* = nitric oxide)

1.4 Prognosis of CIN

The recovery from CIN is very likely and dialysis is infrequently required (43). Some degree of residual renal impairment has been reported in as many as 30% of those affected by CIN (44). The acute renal failure seen in CIN is generally nonoliguric and reversible. In high-risk patients, oliguria may develop within 24 hours of contrast medium administration. Currently, CIN is one of the most common causes of acute renal failure among hospitalized patients. The occurrence of acute renal failure prolongs the hospital stay. Several studies demonstrated the close relationship between CIN and prognosis after PCI (6,45). The development of CIN has been associated with an increase in morbidity and both in-hospital and long-term mortality. In a retrospective study, Levy et al. (7) concluded that patients who developed CIN had higher mortality (34%) compared with patients (7%) who did not develop CIN after contrast administration ($p < 0.001$, odds ratio 5.5). In another study, Guberg et al. (6) studied the effects of contrast administration on morbidity and mortality in 439 patients with a baseline creatinine > 1.8 mg/dl. The in-hospital mortality rate was 22.6% for those requiring hemodialysis as a result of contrast administration. The cumulative 1-year mortality rate was 45.2% for those who required dialysis. Iakovou et al. (46) reported that patients with CIN versus those without CIN had significantly elevated rates of hospitalization (4.7% vs. 0.9%, respectively) and 1-year mortality (32.3% vs. 13.9%). In a study of McCullough et al. (5), acute renal failure requiring dialysis after coronary angioplasty was 1%, and creatinine clearance, diabetes and contrast dose were shown to be independent predictors of acute renal failure requiring dialysis. The in-hospital mortality for those developed acute renal failure was 35.7% and the 2-year survival was 18.8%. According to the result of Rihal and coworkers (47) in-hospital mortality in patients undergoing PCI and developing CIN was 22% versus only 1.4% in patients without CIN. Furthermore, among hospital survivors with acute renal failure, 1- and 5-year estimated mortality rate was 12.1% and 44.6%, respectively. These rates were much higher than the 3.7% and 14.5% mortality rates in patients without acute renal failure.

1.5 Prevention of CIN

Several studies have been performed to prevent CIN. These include hydration, N-acetylcysteine (NAC), dopamine and fenoldopam, theophylline, diuretics, atrial natriuretic peptide (ANP), calcium channel blockers, endothelin antagonist, infusion of sodium bicarbonate and prophylactic hemodialysis. Some of the most important strategies studied are discussed below.

Hydration

Adequate hydration is the simplest and most effective way of protecting renal function. Currently hydration is the only universally accepted method to prevent CIN (29,48,49). Intravenous hydration seems better than oral hydration. When the patient is well hydrated, it appears more likely that renal medullary perfusion is increased due to the inhibition of vasopressin and the reduction of fluid viscosity of contrast media in the distal portion of tubular system (50). Many studies have demonstrated the benefits of hydration in preventing CIN. Solomon et al. (48) randomized 78 patients who underwent cardiac angiography to 0.45% saline only (1 ml/kg body weight/h), mannitol with saline, or furosemide with saline. Among the patients, 11% in the saline-only group, 28% in the mannitol with saline group, and 40% in the furosemide with saline group developed CIN. The authors suggested that saline was beneficial in preventing CIN. In most studies, a uniform protocol with half-isotonic (0.45%) saline at a rate of 1 ml/kg/h before and after contrast exposure was employed (51-54). Mueller et al. (55) performed a randomized comparison of 2 hydration regimens (isotonic versus half-isotonic) in 1620 patients undergoing coronary angiography. CIN occurred in 0.7% of the patients with 0.9% saline versus 2.0% of those with half-isotonic saline ($p = 0.04$). The predefined subgroups benefited in particular from isotonic hydration: women, patients with diabetes and those receiving prevention of CIN. In another study, Taylor et al. (56) tested the efficacy of outpatient oral precatheteriziation hydration (oral hydration with 1000 ml clear liquid over 10 h) followed by 6 h of intravenous hydration (0.45% saline solution at 300 ml/h) beginning just before contrast material exposure and compared this protocol with overnight intravenous hydration (0.45% normal saline solution at 75 ml/h for 12 h before and after catheterization). The authors concluded that a hydration strategy compatible with outpatient cardiac catheterization was as effective as the traditional pre and post catheterization intravenous hydration protocol but was associated with a decrease in length of stay in hospital. Brown et al. (56) also found the benefits of hydration in preventing CIN in patients with serum creatinine concentration ≥ 2.0 mg/dl. The disadvantages of hydration include its unsuitability for patients with cardiac failure and its limited use in emergency situation resulting from its requirement of fluid administration for several hours before contrast medium exposure (58). Based on the above evidence, all patients undergoing contrast-related procedure should receive adequate hydration. The most widely accepted protocol is administering 0.45% saline at 1 to 1.5 ml/kg/h beginning 6 - 12 h prior to the procedure and continuing for up to 12 h following contrast administration (29,48,51,59).

N-Acetylcysteine (NAC)

NAC is an antioxidant and scavenger of oxygen free radical. It also increases the biogenic effect of nitric oxide (NO) by combining with NO to form S-nitrosothiol, which is a more stable and potent vasodilator than NO. It also increases the expression of NO synthase and may thus also improve blood flow (60). Based on the theory that CIN is caused primarily by reactive oxygen species, Tepel et al. (61) compared the oral administration of the antioxidant NAC (600 mg twice a day on the day before and the day of examination) plus standard hydration to hydration alone in 83 patients undergoing computer tomography with intravenous administration of 75 ml of nonionic, low-osmolality contrast agent. A significantly lower-incidence of CIN in the NAC group (2%) was observed compared to the placebo group (21%, $p = 0.01$). Some studies also revealed similar protective effects of NAC (62,63). Baker et al. (62) randomized 80 patients with stable renal dysfunction undergoing cardiac catheterization and intervention to a rapid protocol of intravenous NAC. CIN occurred in 5% in the NAC group and in 21% in the hydration group ($p = 0.045$). The study concluded that the administration of infusion NAC should be considered in all patients to preclude adequate oral prophylaxis, provided the patient is able to tolerate this degree of volume loading (62). More recently, a protective effect of high dose (1200 mg twice daily) versus a standard dose (600 mg twice daily) along with saline hydration was reported (63). In a cohort of 224 patients with chronic renal insufficiency (creatinine > 1.5 mg/dl or creatinine clearance < 60 ml/min), CIN occurred in 11% of patients in the standard dose group and in 3.5% in the high dose group ($p = 0.04$). In the subgroup with the contrast dose ≥ 140 ml, CIN was more frequent in the standard group (18.9%) than in the high dose group (5.4%, $p = 0.04$), whereas no difference was found in the low-dose (< 140 ml) subgroup.

Although several studies showed a protective effect, others demonstrated that oral administration of NAC does not protect renal function; particularly when moderate to high dose of contrast medium are used (64-66). Allaqqband et al. (64) randomized 123 patients to either saline alone or saline plus NAC at a dose of 600 mg orally on the day before and after the day of procedure: no significant difference in CIN was observed between the NAC and the saline-only group. In a trial by Boccaluandro et al. (66), the incidence of CIN in patients with chronic renal insufficiency (creatinine clearance < 50 ml/min) undergoing cardiac catheterization was 13% in the NAC group (600 mg twice daily for 48 h starting the day before the procedure) and 12% in the control group ($p = 0.84$). Both groups received intravenous hydration (75 ml/h of 0.45% saline solution for 24 h starting 12 h before the procedure). The study concluded that NAC with

intravenous fluid is as effective as fluid alone in the prevention of CIN when moderate to high doses of contrast media are used in patients with chronic renal insufficiency. A large meta analysis to access the efficacy of NAC in preventing CIN was performed by Pannu et al. (67), who reviewed 15 studies in NAC effect. The analysis indicates a significant heterogeneity in NAC effect among studies. NAC may reduce the incidence of CIN, but this finding is of borderline statistical significance, and there is significant heterogeneity among trials.

In conclusion, NAC may be recommended for patients receiving lower doses of contrast, but its role in higher-risk population needs to be further investigated. If NAC is to be used as a preventive measure, it should be given at a dose of 600 mg oral bid (1200 mg bid if creatinine > 2.5 mg/dl) on the day before and day of the procedure. In addition, adequate hydration should be given at a rate of 1 ml/kg/h for 6 to 12 h prior to contrast and up to 12 h following contrast administration.

Dopamine and Fenoldopam

Dopamine (DA), a non-selective dopaminergic agent, activates two types of DA receptors(DA-1 and DA-2). At high doses, it also stimulates alpha and beta-adrenergic receptors, functioning as a vasopressor and inotrope. Whereas activation of DA-1 receptor is associated with increased renal blood flow and natriuresis, stimulation of DA-2 and adrenergic receptor is associated with vasoconstriction. A low dose of dopamine (< 5 ug/kg/h) stimulates dopamine and possibly beta-receptors by increasing renal blood flow and glomerular filtration (68). This property has made it very attractive as a potential means for preventing CIN, but clinical studies have shown contradictory results. Hall et al. (69) reported that dopamine reduced the risk of CIN in patients with preexisting renal insufficiency but there were few diabetic patients in this study. Some studies (28,70,71) have shown no benefit of dopamine in preventing CIN. Therefore, dopamine is not recommended as an agent to prevent CIN.

Fenoldopam, a selective dopamine-1 receptor agonist, has the advantage over dopamine by increasing cortical and medullary renal blood flow without stimulating the alpha and beta adrenergic receptor or DA-2 receptors, even at high doses (72). Fenoldopam has shown to prevent the diatrizoate-induced reduction in the glomerular filtration rate in anesthetized volume-depleted dogs (73). Early retrospective studies of fenoldopam reveal a benefit in reducing CIN (74,75). More recently, prospective, randomized studies fail to show the benefit of fenoldpam.

Allaqaband et al. (64) performed a prospective, randomized study evaluating the use of fenoldopam for the prevention of CIN. Patients were randomized to three different groups: 0.45% saline only, saline plus fenoldopam at 0.1 ug/kg/min starting 4 h prior to the procedure and continual for 4 h after, or saline plus NAC 600 mg twice daily on the day before and the day of procedure. There was no statistical difference in the incidence of CIN, 15.3% in the saline only group, 15.7% in the fenoldopam group and in 17.7% in the NAC group. In a multicenter prospective randomized study (76), 315 patients with creatinine clearance below 60 ml/min who were undergoing invasive cardiac procedures in 28 different centers were randomized to receive a regimen of fenoldopam and IV hydration or IV fluids alone. CIN occurred in 33.6% of the fenoldopam group versus 30.1% in the placebo group (p = NS). Therefore, there is conflicting evidence regarding the effectiveness of fenoldopam in preventing nephropathy, it should not be routinely recommended.

Theophylline

Adenosine is a potential mediator in contrast induced renal medullary ischemia. Theophylline, an adenosine antagonist, has been investigated as a means to reduce the risk of this complication. Several studies (77,78) showed it might have a potential effect in preventing CIN. In a prospective randomized study, Kapoor and colleagues (79) evaluated 70 patients with diabetes mellitus undergoing coronary angiography, who received theophylline orally 200 mg twice daily at 24 h prior to contrast administration and 48 h following the angiography or no theophylline. CIN developed in 31% of the control group but only one patient in the theophylline group. The study of Shammes et al. (80) and Erley et al. (81) showed no benefit by using theophylline. In conclusion, the administration of theophylline does not provide any additional benefit beyond hydration alone for the prevention of CIN. Therefore, theophylline should not be routinely used in patients as a preventative.

Diuretics

It has been hypothesized that loop diuretics might decrease medullary oxygen consumption through their inhibition of sodium absorbtion, and therefore decrease medullary ischemia (82). The data with regards to diuretics with either furosemide or mannitol in the prevention of CIN is controversial. A beneficial effect of furosemide has not been demonstrated in humans. In a large study, Solomen et al. (48) evaluated 78 patients with chronic renal insufficiency (creatinine level

> 1.6 mg/dl) who were undergoing cardiac angiographies. Patients were randomized to receive one of the three treatments, saline plus mannitol, saline plus furosemide or saline alone. All patients received 0.45% saline at a continuous rate of 1 ml/kg/h beginning 12 h before angiography and for the following 12 h. Of patients who received saline alone, only 11% demonstrated significant increase in creatinine, compared to 28% of patients with saline and mannitol and 40% with saline and furosemide. Only the furosemide group showed a significant difference to the saline group ($p = 0.02$). In the PRINCE study (83), furosemide was part of the regimen in the treatment group, but the incidence of CIN was similar in control and treatment groups. Weisberg et al. (28) also demonstrated increased nephrotoxicity among diabetic patients with moderate renal dysfunction who received hydration plus furosemide compared to those with hydration alone.

Mannitol, an osmotic diuretic, similar to furosemide, showed disappointing results in those patients. Weisberg et al. (28) studied 50 patients comparing fluid therapy against fluid therapy plus either dopamine, mannitol or ANP, and observed no protective effect by the addition of any of the previous mentioned agents. Solomon et al. (48) also found a trend toward a deleterious effect from mannitol compared with saline alone. Some uncontrolled clinical evidence indicates that temporary discontinuation of diuretics before contrast administration may be beneficial (84). In summary, neither diuretics nor mannitol have been shown to prevent CIN definitely.

Sodium Bicarbonate

Experimental studies have demonstrated that pretreatment with sodium bicarbonate is more protective than sodium chloride in animal models of acute ischemic renal failure (85). Formation of free radical is promoted by an acid environment but inhibited by increasing PH of normal extracellular fluid, with the use of bicarbonate (86). The protective effect results from antioxidant effects and scavenging reactive free radical but not from better volume expansion in comparison with saline solution infusion (86). A prospective single-center randomized study of 119 patients by Mertern et al. (86) has suggested that the use of sodium bicarbonate hydration is superior to sodium chloride hydration. Patients were randomly received a 154 mEq/L infusion of sodium chloride or sodium bicarbonate. The fluids were given as a bolus of 3 ml/kg per hour for 1 h before contrast media administration followed by an infusion of 1 ml/kg/h for 6 h after the procedure. The group receiving sodium bicarbonate treatment had a 1.7% incidence in CIN compared to 13.6% with sodium chloride. Although confirmation in a larger multicenter study is

necessary, infusion of sodium bicarbonate may provide a simple, safe and effective method for the prevention of CIN.

Hemodialysis and Hemofiltration

In order to valuate the effect of hemodialysis on preventing CIN, Vogt et al. (87) studied 113 patients with advanced renal insufficiency (creatinine 3.5 ± 1.2 mg/dl) undergoing different procedures with administration of LOCM. Patients were given either periprocedural hydration or preprocedural hydration followed by a 3 h hemodialysis. There was no difference in incidence of CIN and no benefit of hemodialysis in the subgroup receiving > 150 ml of contrast agents. Therefore, prophylactic hemodialysis in patients with renal insufficiency who received radiocontrast is not recommended.

Hemofiltration has been used to decrease the incidence of CIN. It refers to the use of hydrostatic pressure gradient to induce the filtration of plasma water across the membrane of the hemofilter. More recently, 114 patients (88) with renal insufficiency were scheduled to undergo elective PCI to treatment with renal hemofiltration or saline hydration for the prevention of CIN. Hemofiltration and saline hydration were initiated 4 to 8 h before the coronary intervention and continued for 18 to 24 h after the completion of the procedure. LOCM was used in all patients. The results showed a reduction of the incidence of CIN from 50% in the control group to 5% in the treated group. In-hospital mortality was 2% in the treatment group and 14 % in the control group, and the cumulative 1-year mortality was 10% and 30%, respectively. All of these differences reached statistical significance. Although the patients had advanced renal disease (mean baseline creatinine level 3 mg/dl) and received a large volume of contrast medium (mean 247 ml), the hemofiltration offered impressive protection against CIN.

Other Medication

Endothelin is a potent endogenous vasoconstrictor that has been implicated in the pathogenesis of CIN. There are 2 receptors for endothelin, endothelin-A and endothelin-B. Endothelin-A mediates vasoconstriction and is found in smooth muscle, while endothelin-B mediates vasodilation through the release of NO and prostacyclin and is found in endothelial cells (89). In animal studies, endothelin-A antagonists reduced CIN (90). In a clinical study, Wang et al. (91) randomized 158 patients to SB290670 (a mixed endothelin-A and B antagonist) or a placebo. All

patients received intravenous hydration with 0.45% saline before and after radiocontrast administration. The incidence of nephropathy was significantly higher in treatment group (56% vs. 29%, P = 0.002), which suffered from more adverse effects such as hypotension. It is possible that a selective endothelin-A antagonist would have better results.

Atrial Natriuretic Peptide (ANP) is a potent vasodilator and may prevent CIN by increasing renal blood flow in animals (92). Clinical studies to date have failed to establish a role for this agent in the prevention of CIN. In a large, multicenter, prospective, double-blind, randomized, placebo-controlled trial performed by Kurnik and coworker (93), 247 patients (50% with diabetes mellitus) with stable chronic renal insufficiency were randomized to placebo or 1 of 3 dose of intravenous ANP (0.01, 0.05, or 0.1 ug/kg/min for 30 min before and continuing for 30 min after contrast media administration). The results showed the frequency of CIN to be higher in ANP group (23 - 25%) than in placebo group (19%). Subgroup analysis showed no treatment benefit in patients with diabetes. Weisberg et al. (28) also found no additional benefit from treatment with ANP when compared to fluid hydration alone. Based on this evidence ANP should not be recommended for prophylaxis of CIN.

Prostaglandin E1 has vasodilatory effects that may be beneficial in preventing CIN (94). More recently, the effect and compatibility of prostagland E1 in preventing CIN at three different doses was assessed in 130 patients with renal insufficiency (94). All patients received 2 L of fluid before and after the contrast procedure. In all three of prostagland E1 group, the mean rise in serum creatinine levels in the placebo group was significantly higher than that in prostaglandin E1 group. Therefore, prostaglandin E1 may be a promising prophylactic agent against CIN. Further studies are needed to confirm the effectiveness of this agent.

Calcium ions are another potential mediator in contrast induced renal medullary ischemia. Khoury et al. (95) performed a prospective randomized clinical trial of nifedipine but found that a 10 mg dose administered 1 h before imaging made no statistically significant difference in renal function between the 42 treated patients and the 43 controls. The authors concluded that prophylactic nifedipine was not clinically beneficial and should not be routinely administered for prophylaxis of CIN. Another study (96) with felodipine did not confirm the prevention effects of calcium channel blockers on CIN.

Management of CIN and Therapeutic Recommendation

CIN is an iatrogenic disorder and the major cause of in-hospital renal failure and contributes to overall morbidity and mortality. In most cases, the functional impairment is reversed within 1 or 2 weeks and the need for dialysis is rare. There is no specific therapy for the treatment of CIN. Prevention of CIN relies on careful procedure selection and patient assessment. Patients with underlying renal insufficiency and a history of diabetes represent the highest risk population. Potential nephrotoxic agents should be withdrawn at least 24 h before contrast exposure, LOCM or IOCM should be used when possible, the total dose of contrast media should be minimized and repeated contrast administration within a short period of time should be avoided. Patients should have their renal function checked by serum creatinine before and at 48 to 72 h after contrast administration. All patients undergoing angiography should receive adequate hydration. Guidelines (97) recommended at least 100 ml oral intake or intravenous administration per hour starting 4 h before to 24 h after contrast exposure.

It is suggested to use an intravenous hydration regime (saline 0.9%, at least 1 ml/kg/h 12 h before and after contrast exposure) for all patients with impaired renal function. Although there are many new promising modalities in the prevention of CIN, such as $NaHCO_3$ and hemofiltration, hydration remains the most effective methods of prevention. Patients with chronic renal insufficiency receiving large contrast dose (> 140 ml) should receive high-dose NAC (2 × 1200 mg) (98). Figure 1-2 provided a possible algorithm to choose the optimal prophylactic strategy in high-risk patients scheduled to undergo a contrast-requiring angiographic procedure.

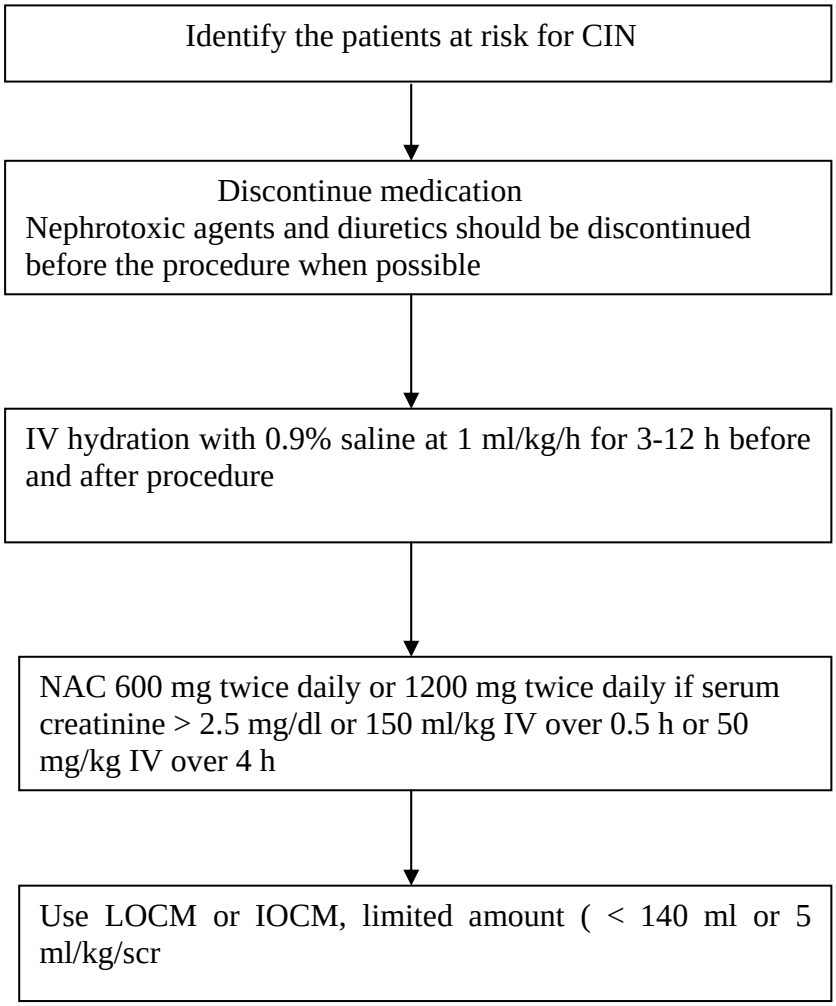


Figure 1-2 Algorithm for the management of the high-risk patients to prevent CIN (63,97).

1.6 Aim of the Study

The purposes of this study were:

(1) To assess the incidence of CIN in different groups undergoing routine and emergency cardiac catheterization and percutaneous coronary intervention (PCI) using optimal, guideline based prophylactic treatment of CIN.
(2) To define patient groups who are at high risk for CIN after cardiac catheterization and PCI.
(3) To find the correlation between the amount of contrast agent administered and the change of serum creatinine concentration.
(4) To reveal the clinical predictors of CIN in an unselected population of consecutive patients undergoing coronary angiography or PCI.

2. Patients and Methods

2.1 Study Population and Prophylaxis of CIN

All enrolled patients had elective coronary angiography, coronary interventional procedure and emergency coronary interventional procedure between April 1, 2001 and June 30, 2003. Patients with reduced renal function were hydrated with 0.9% saline at 1 ml/kg/h for 12 h before and after catheterization. For emergency coronary interventional procedures, physiologic (0.9%) saline was given intravenously at a rate of 1 ml/kg/h for 12 h after contrast exposure. In patients with LVEF < 40% or overt heart failure, the hydration rate was reduced to 0.5 ml/kg/h. Acetylcysteine was given orally at dose of 300 mg twice daily, on the day before and the day of administration of the contrast agent, for a total of two days. All elective patients and nearly all emergency patients except those who were unable to understand and sign provided written informed consent for cardiac catheterisation and PCI.

2.2 Study Protocol

PHILIPS Integris® biplane equipment was used in our catheterization laboratory. All patients underwent cardiac catheterization and intervention by standard techniques. Percutaneous femoral arterial catheterization was the most widely used vascular access technique, transradial and transbrachial approach was restricted to patients with severe peripheral vascular disease. After arterial access is obtained, a sheath was inserted into the femoral artery. Patients received a bolus of 70 IU per kg body weight heparin before the diagnostic procedure and 100 IU per kg body weight before the intervention. The Judkins technique was used in left heart catheterization and coronary angiography in most cases. The 5F diagnostic catheters and 6F or 7F guiding catheters were used for cardiac diagnostic and interventional procedures. During coronary angiography, standardized projection acquisition was made for most patients, although tailored views may be needed to accommodate variations in patient's anatomy. Each coronary artery was visualized in multiple projections (frame rate of 12.5/sec.), 6 projections were made for left coronary artery and 4 projections for right coronary artery. Motorized power injection of 40 ml of contrast medium (10 ml/s) into the left ventricle (25 frames/sec) was used to assess left ventricular function. In the process of coronary angiography, injection of 6 to 8 ml contrast medium by hand is given 2 to 3 seconds into coronary arteries. For acute coronary syndrome (ACS) patients, especially in non-ST-elevation myocardial infarction, a platelet glycoprotein IIb/IIIa receptor inhibitor (Tirofiban) was given before interventional procedure. The diagnostic procedure only

included left ventriculography and coronary angiography. The diagnostic and interventional procedure included left ventriculography, coronary angiography and coronary intervention. The emergency diagnostic/interventional procedure included left ventriculography, coronary angiography and, if necessary, coronary intervention. Percutaneous coronary intervention (PCI) included percutaneous transluminal coronary balloon angioplasty (PTCA), stent implantation, and plaqueablative techniques like high frequency rotational atherectomy, directional coronary atherectomy and laser angioplasty. The exact procedures performed and the amount of contrast medium administered depended on the clinical status of the patient and at the discretion of responsible angiographer. Emergency PCI was defined as immediate coronary angiography for ongoing ischemia or myocardial infarction. During the interventional procedure heparin was administered to achieve an activated clotting time > 225 sec. The absolute amount of contrast media, the procedural hemodynamics, the estimate of calculated ejection fraction derived from left ventriculography, the duration of examination and the radiation time were obtained from the catheterization laboratory database. Laboratory data including pre- and postprocedure serum creatinine, glucose, serum sodium, serum potassium, and baseline hemoglobin were collected using a hospital laboratory database system (MedVision). Serum creatinine values were measured before and within 48 h of administration of contrast agents in every patient, further measurement were performed in all patients developing CIN. Data were entered in a database that contained demographic, clinical and angiograhic data.

2.3 Clinical Definitions

2.3.1 Definitions of Clinical Variables

Arterial hypertension was defined as a blood pressure ≥ 140/90 mmHg or normal blood pressure under effective antihypertensive medication (99).

Diabetes mellitus was diagnosed by WHO criteria (100) when hyperglycemia meeting the criteria for diabetic type (fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl), 2 h plasma glucose ≥ 11.1 mmol/l (200 mg/dl), and/or casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl) is recognized on two or more occasions examined on separate days.

Hypercholesterolemia was defined as TC level ≥ 240 mg/dl, high LDL-C as LDL-C ≥ 160 mg/dl (101) or normal values under effective lipid lowering therapy.

Anemia was defined as hemoglobin (Hgb) < 12 g/dl in women and <13 g/dl in men, according to the World Healthy Organization criteria (102).

Renal function was assessed by the estimated creatinine clearance (CrCl) using the Cockcroft-Gault (103) formula: CrCl= {(140 - age) × weight (kg) } / {serum creatinine (mg/dl)× 72}, with female gender adjustment : $CrCl_{female} = CrCl \times 0.85$. This equation has a close correlation with measured creatinine clearance and gives a more accurate assessment of renal function than serum creatinine alone. Renal function was categorized according to the stages set by the National Kidney Foundation (104), with ≥ 90 ml/min normal, 60 to 89 ml/min mildly impaired, 30 to 59 ml/min moderately impaired and < 30 ml/min severely impaired renal function.

2.3.2 Definitions of Clinical Events

Contrast-Induced Nephropathy

Contrast-induced nephropathy was defined as an increase in serum creatinine concentration of ≥ 0.5 mg/dl from preprocedure values within the hospital stay.

Myocardial Infarction

Myocardial infarction (MI) was defined by the presence of two of three criteria: chest pain, electrocardiographic changes and raised CK-MB levels at least twice the upper limit of the normal range. The frequency of MI included all patients with ST-elevation and Non-ST-elevation myocardial infarction.

Unstable Angina

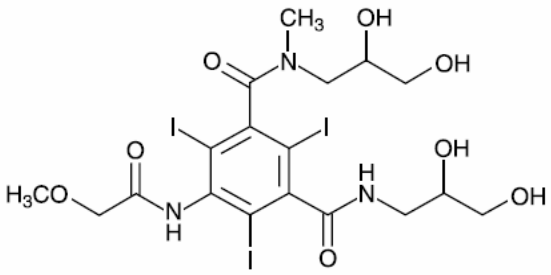
Unstable angina was defined as angina pectoris (or equivalent type of ischemic discomfort) with at least one of three features: (1) occurring at rest (or with minimal exertion) and usually lasting more than 20 min (if not interrupted by nitroglycerin), (2) being severe and described as frank pain and of new onset (i.e., within 1 month), and (3) occurring with a crescendo pattern (i.e., more severe, prolonged, or frequent than previously (105). Classification of unstable angina is listed in Table 2-1 (106).

Table 2-1 Braunwald clinical classification of unstable angina (106)

Class	Definition
Severity	
Class I	New onset of sever angina or accelerated angina; not pain at rest
Class II	Angina at rest wiyhin past month but not within preceding 48 hr (angina at rest, subacute)
Class III	Angina at rest within 48 hr (angina at rest, subacute)
Clinical circumstance	Develops in the presence of extracardiac condition that intensifies
A (secondary angina)	myocardial ischemia
B (primary angina)	Develops in the absence of extracardiac condition
C (postinfarction angina)	Develops within 2 wks after acute myocardiac infarction
Intensity of treatment	Patients with unstable angina may also be divided into three groups Depending on whether unstable angina occurs (1) in the absence of treatment for chronic stable angina, (2) during treatment for chronic stable angina, or (3) despite maximal antiischemic drug therapy. The three groups may be designated by subscripts 1, 2 and 3, respectively.

2.4 Type of Contrast Medium

Iopromide (Ultravist-370, 0.769 mg/ml, 370 mg iodine/ml; Schering AG, Berlin, Germany), a nonionic, low-osmolality (774 mOsm/kg H_2O) contrast agent, was used almost exclusively in our laboratory. Iopromide injection is a nonionic, water-soluble x-ray contrast agent for intravascular administration. The chemical name for iopromide is 1,3-benzenedicarboxamide, N, N'-bis (2,3-dihydroxypropyl)-2,4,6-triiodo-5-[(methoxyacetyl)amino]-N-methyl-. Iopromide has a molecular weight of 791.12 (iodine content 48.12%). Iopromide has the following structural formula:



2.5 Analysis of Left Ventricular and Coronary Angiography

Left Ventricular Ejection Fraction

Left ventricular ejection fraction was obtained from left ventriculography by angiographer using computer assist system (Philips Inturis® Suite) or visual assessment.

Quantification of Coronary Stenosis

The degree of coronary stenosis was usually a visual estimation of the percentage of diameter narrowing using the proximal assumed normal arterial segment as a reference (with increase 25%, 50%, 75%, 90%, 99% and 100%). The number of diseased coronary arteries was defined by the number of major coronary arteries with luminal diameter stenosis ≥ 50%. Patients with stenosis ≥ 50% in the left main coronary artery were considered to have two vessel diseases if there was right dominance and three-vessel disease if there was left dominance.

Angiographic success of PCI was defined as with ≥ 20% improvement in luminal diameter stenosis of at least one treatment site with residual stenosis < 50%. Procedural success was defined as angiography success without death, Q-wave MI or coronary artery by-pass graft surgery (CABG) during the initial hospitalization.

2.6 Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD), and categorical data were presented as absolute values and percentages. T-test and ANOVA with post sheffe test were used for parametric comparison. Mann-Whitney U and Kruskal-Walli test were used for nonparametric comparison. Chi-square or the Fisher exact tests were used for comparison of categorical variables as required. Correlations between the amount of contrast agent administered and the change of serum creatinine concentration were evaluated with Pearsson's correlation coefficient. Multivariate predictors of CIN were identified by logistic regression using stepwise selection with entry and exit criteria of $p < 0.1$. A two-sided 95% confidence interval (CI) was constructed around the point estimate of the odds ratio (OR). The variables chosen by the model included all the potential confounding variables. All hypothesis testing was two tailed. A p value < 0.05 was considered as statistically significant. Analyse was performed by using SPSS 10.0 statistical software.

3. Results

3.1 Incidence of CIN after Diagnostic Coronary Angiography and Percutaneous Coronary Intervention (PCI)

3878 patients underwent coronary angiography and/or percutaneous coronary intervention between April 1, 2001 and June 30, 2003. 967 (24.9%) of these patients had pre-existing chronic renal failure. 887 (22.9%) of these patients had diagnostic coronary angiography and PCI within one setting. Emergency cardiac catheterization was done in 803 (20.7%) of patients. 110 out of the entire study population of 3878 patients suffered CIN after cardiac catheterization (2.8%). The mean amount of contrast medium administered was 190 ± 90 ml. In these patients, the mean serum-creatinine level increased from 2.61 ± 2.5 mg /dl to 3.78 ± 3.1 mg/dl. The mean difference in serum creatinine was 1.17 mg/dl. The distribution of clinical, laboratory, angiographic and procedural basline data will be shown in detail.

3.1.1 Clinical Characteristic

The baseline clinical characteristics of patients with CIN and non-CIN are summarized in Table 3-1. Of the 3878 patients in this study, diabetes mellitus was present in 946 (24.4%) and anemia in 964 (24.9%) of patients at baseline. 110 (2.8%) experienced CIN after the procedure. These patients were significant older, had a lower diastolic blood pressure and a higher incidence of anemia.

Table 3-1 Baseline clinical data in patients with and without CIN

Characteristic	CIN (n = 110)		Non-CIN (n = 3768)		p Value
	n	%	n	%	
Age (yrs)	66.0 ± 12.0		63.4 ± 11.7		0.02
Male gender	75	68.2	2625	69.7	0.74
Body mass index (kg/m^2)	27 ± 4		27 ± 4		0.83
Systolic blood pressure (mmHg)	137 ± 35		141 ± 29		0.11
Diastolic blood pressure (mmHg)	69 ± 12		72 ± 11		0.01
Arterial hypertension	63	57.3	2262	60.0	0.56
Hypercholesterolemia	29	26.4	1292	34.3	0.08
CAD	79	71.8	2923	77.6	0.16
Diabetes mellitus	30	27.3	916	24.3	0.48
Anemia	53	48.2	911	24.2	< 0.001
AMI	13	11.8	510	13.5	0.60
UAP	8	7.3	272	7.2	0.98
PCI	52	47.3	1899	50.4	0.52
Prior CABG	21	19.1	497	13.2	0.07
Prior PCI	22	20.0	632	16.8	0.30
Prior myocardial infarct	17	15.5	720	19.1	0.34

Data are presented as the mean value ± SD or number (%) of patients

AMI = acute myocardial infarction UAP = unstable angina pectoris CABG = coronary artery bypass graft PCI = percutaneous coronary intervention

3.1.2 Baseline Medication

The concomitant medication administered with CIN is shown in Table 3-2. Patients who developed CIN were less likely to be treated with a beta-receptor blocker or a statin, although they were more likely to receive diuretics.

Table 3-2 Concomitant medications in patients with and without CIN

Medication	CIN (n = 110)		Non-CIN (n = 3768)		p Value
	n	%	n	%	
Aspirin	68	61.8	2497	66.3	0.33
Beta-receptor blocker	62	56.4	2486	66.0	0.04
ACE inhibitors	53	48.2	2101	55.8	0.12
Clopidogrel	39	35.5	1623	43.1	0.11
Statin	44	40.4	2126	56.4	0.001
Diuretics	33	30.3	759	20.1	0.01
AT-2 antagonists	4	3.6	119	3.2	0.78
Calcium antagonists	12	10.9	250	6.6	0.08

Data are presented as the number (%) of patient

3.1.3 Laboratory Data

Patients who developed CIN had a higher baseline serum creatinine and a lower creatinine clearance (Table 3-3). In comparison to patients without CIN, patients with CIN also had higher blood glucose levels, higher serum potassium levels, and more often presented with lower hemoglobin values.

Table 3-3 Laboratory data in patients with and without CIN

Characteristic	CIN (n = 110)	Non-CIN (n = 3768)	p Value
Serum certinine (mg/dl)			
≥ 1.5	58 (52.7%)	355 (9.4%)	<0.001
Baseline	2.61 ± 2.5	1.14 ± 2.25	<0.001
After catheterization	3.78 ± 3.1	1.08 ± 0.78	<0.001
Creatinine Clearance (ml/min)			
< 60	74 (67.3%)	893 (23.7%)	<0.001
Baseline	66 ± 97	86 ± 37	<0.001
After catheterization	32 ± 23	87 ± 37	<0.001
Serum sodium (mmol/l)	138 ± 3.6	138 ± 3.4	0.14
Serum potassium (mmol/l)	4.3 ± 0.7	4.1 ± 0.5	<0.001
Glucose (mg/dl)	151 ± 85	134 ± 62	0.04
Hemoglobin (g/dl)	12.6 ± 2.0	13.6 ± 1.7	<0.001

Data are presented as the mean value ± SD or number (%) of patient

3.1.4 Angiographic Data

The angiographic baseline data of patients with and without CIN listed in Table 3-4. There were no significant differences between CIN patients and non-CIN patients regarding the incidence (71.8% vs. 77.6%; p = 0.16) and extent of coronary artery disease and mean left ventricular ejection fraction (p = 0.19).

Table 3-4 Angiographic data in patients with and without CIN

Characteristic	CIN (n = 110)		Non-CIN (n = 3768)		p Value
	n	%	n	%	
Coronary artery disease	79	71.8	2923	77.6	0.16
Single-vessel	15	19.0	689	23.6	0.34
Double-vessel	21	26.6	861	29.5	0.58
Triple-vessel	43	54.4	1373	46.9	0.19
LVEF (%)	55 ± 15		57 ± 16		0.19

Data are presented as the mean value ± SD or number (%) of patients.
LVEF = left ventricular ejection fraction

3.1.5 Procedural Data

As shown in Table 3-5, the amount of contrast agent administered for the CIN group and the non-CIN group was similar (190 ± 90 ml vs. 187 ± 83 ml; p = 0.78). In addition, the duration of examination (64 ± 32 min vs. 60 ± 33 min) and radiation time (13 ± 11 min vs. 12 ± 12 min) showed no significant difference between the two groups (p > 0.05). There was also no significant difference of proportion in diagnostic procedure, PCI and emergency cases for the CIN group and the non-CIN group.

Table 3-5 Procedural characteristics in patients with CIN

Characteristics	CIN (n = 110)		Non-CIN (n = 3768)		p Value
	n	%	n	%	
Amount of contrast agent (ml)	190 ± 90		187 ± 83		0.78
Duration of examination (min)	64 ± 32		60 ± 33		0.29
Radiation time (min)	13 ± 11		12 ± 12		0.38
Diagnostic catheterization	57	51.8	1870	49.6	0.65
PCI	52	47.3	1899	50.4	0.52
Emergency cases	21	19.1	782	20.8	0.67

Data are presented as the mean value ± SD or number (%) of patients.

PCI = percutaneous coronary intervention

3.2 Subgroup Analysis

3.2.1 Elderly Patients (≥ 70 years)

Incidence of CIN in elderly subgroup

As seen in Figure 3-1, although age differed between the CIN group and the non-CIN group, the incidence of CIN in patients older than 70 years was higher than in younger patients, but the difference was not statistically significant (3.6% vs. 2.5%; p = 0.057).

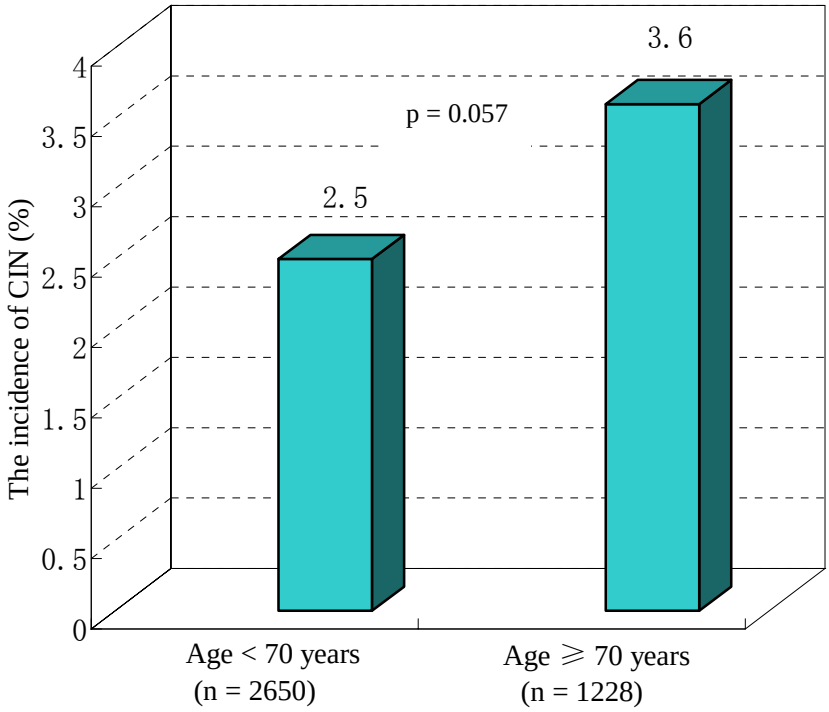


Figure 3-1 The incidence of CIN in elderly patients

Amount of contrast agent administered in elderly patients

The amount of contrast agent administered was similar for patients above and under 70 years (189 ± 83 ml vs. 187 ± 84 ml; p = 0.47). There were no significant difference regarding the amount of contrast agent administered between the CIN group and the non-CIN group with different baseline creatinine clearance levels (Table 3-6).

Table 3-6 Amount of contrast agent administered in elderly patients stratified by CIN and baseline creatinine clearance

Baseline Creatinine Clearance (ml/min)	CIN	Non-CIN	p Value
< 30	183 ± 52 (n = 9)	173 ± 70 (n = 75)	0.37
30-59	180 ± 96 (n = 23)	189 ± 81 (n = 543)	0.35
60-89	221 ± 134 (n = 9)	189 ± 85 (n = 463)	0.73
≥ 90	257 ± 31 (n = 3)	197 ± 85 (n = 103)	0.12

Data are presented as the mean vaule ± SD

Correlation between the amount of contrast agent administered and the change of serum creatinine in elderly patients

No direct correlation between the amount of contrast agent administered and the change of serum creatinine was observed in elderly patients (Figure 3-2).

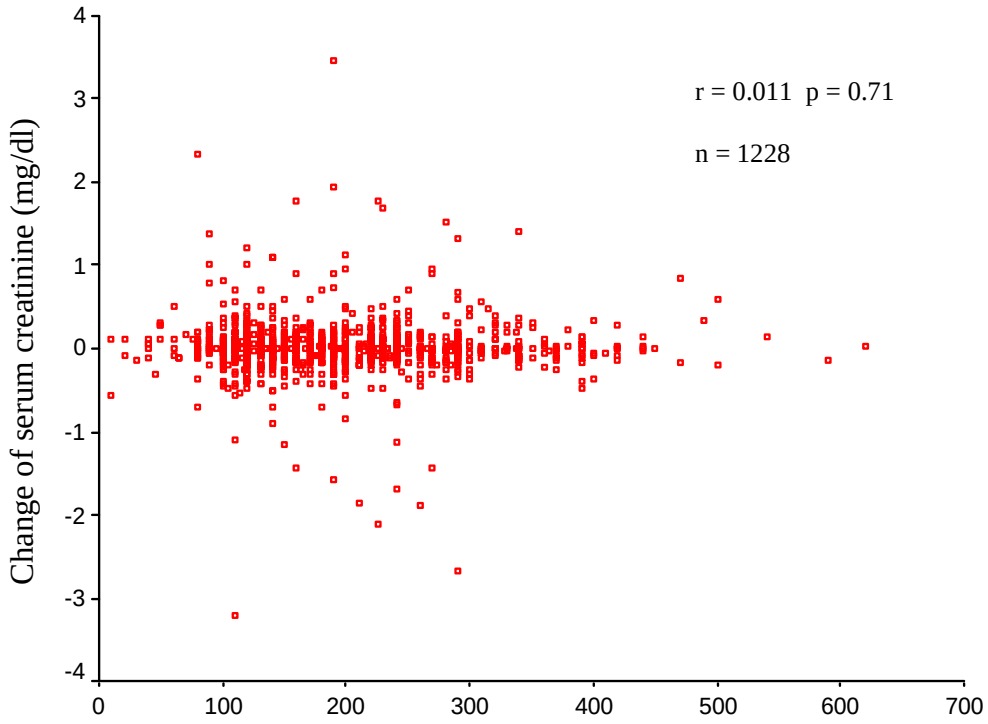


Figure 3-2 Correlation between the amount of contrast agent administered and the change of serum creatinine concentration in elderly patients.

3.2.2 Diabetes Mellitus

Incidence of CIN in diabetes mellitus

The comparison of incidence of CIN between diabetic and non-diabetic patients is seen in Figure 3-3, the incidence of CIN in diabetic patents did not show siginificant difference when compared with non-diabetic patients (3.2% vs. 2.7 %, p = 0.48).

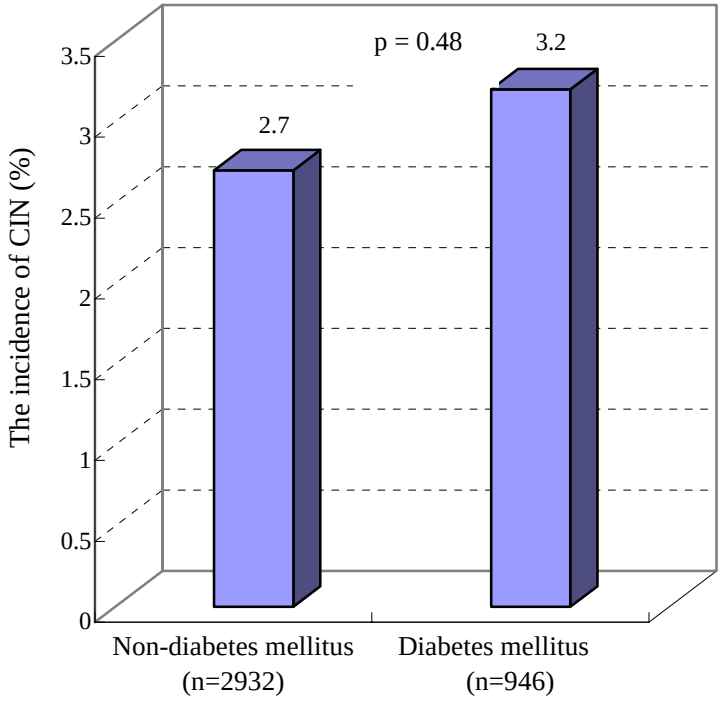


Figure 3-3 Incidence of CIN in diabetic and non-diabetic patients.

The incidence of CIN in patients with preexisting renal dysfunction was 8.0% in diabetics and 7.2% in non-diabetics (p = 0.66). The incidence of CIN stratified by diabetes mellitus and baseline creatinine clearance is shown in Figure 3-4. Among patients with baseline creatinine clearance 60 - 89 ml/min and ≥ 90 ml /min, there was no significant difference in the incidence of CIN between diabetic and non-diabetic patients (1.7% vs. 1.6%, p = 0.93; 0.8% vs. 1.1%, p = 0.78, respectively). In patients with baseline creatinine clearance 30 - 59 ml/min, a slightly higher incidence of CIN in diabetic patients than in non-diabetic patients was observed (6.0% vs. 4.7 %; p = 0.45). However, a high proportion of both diabetic and non-diabetic patients experienced CIN (19.5% vs. 19.0%; p = 0.94) when baseline creatinine clearance was < 30 ml/min.

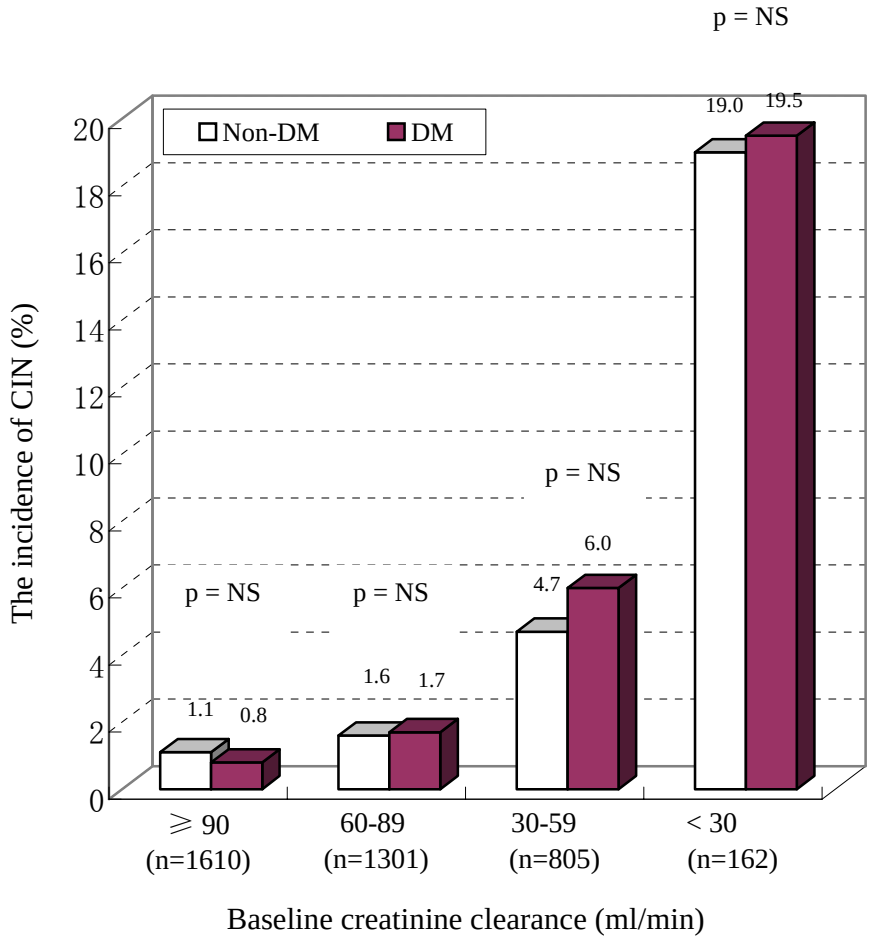


Figure 3-4 Incidence of CIN stratified by diabetes mellitus and baseline creatinine clearance.

DM = diabetes mellitus

Amount of contrast agent administered in diabetes mellitus

The comparison of amount of contrast agent administered between diabetic and non-diabetic patients is seen in Figure 3-5. The amount of contrast agents administered in diabetic patients was slightly higher than in non-diabetic patients (193 ± 82 ml vs. 185 ± 84 ml, p = 0.001).

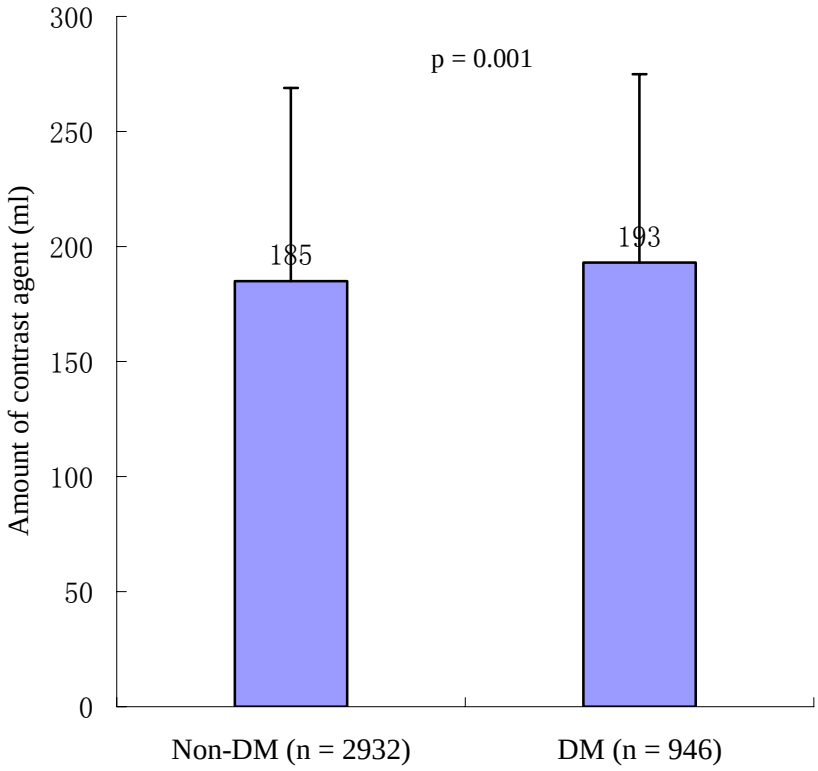


Figure 3-5 Comparison of amount of contrast agent administered between diabetic and non-diabetic patients.
DM = diabetes mellitus

Correlation between the amount of contrast agent administered and the change of serum creatinine in diabetes mellitus

As seen in Figure 3-6, there was no correlation between the amount of contrast agent administered and the change of serum creatinine concentration in diabetic patients.

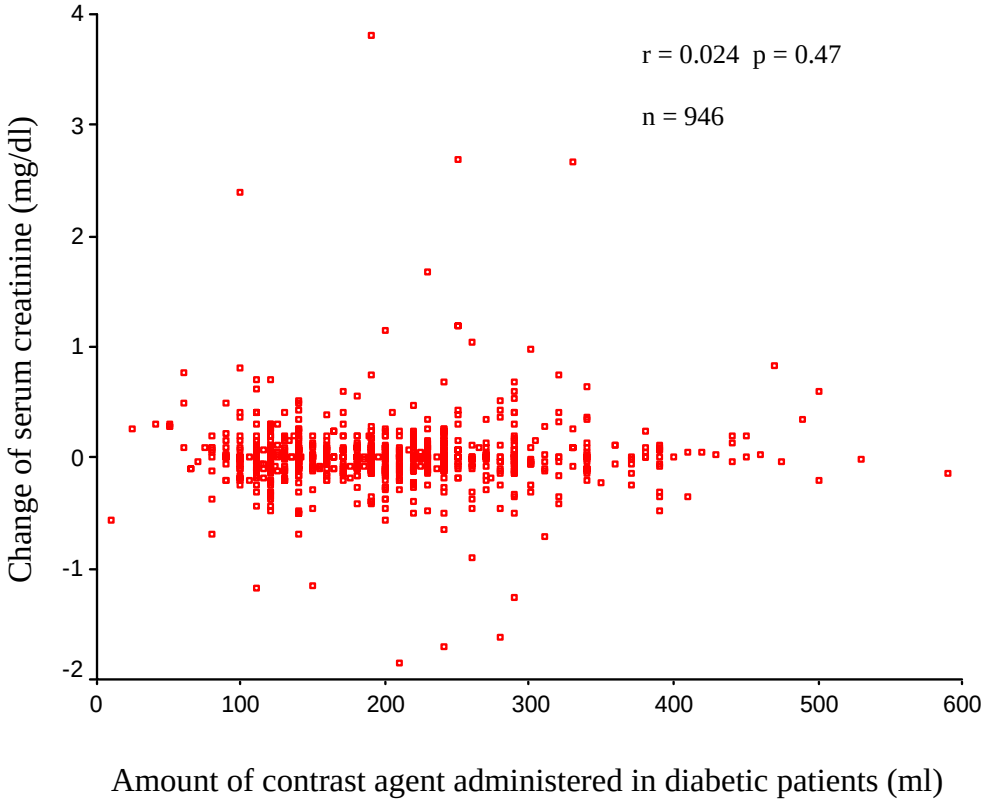


Figure 3-6 Correlation between the amount of contrast agent administered and the change of serum creatinine concentration in diabetic patients.

3.2.3 Preexisting Impairment of Renal Function

The incidence of CIN in patients with preexisting impairment of renal function

The incidence of CIN in patients with preexisting impairment of renal function (baseline creatinine clearance < 60 ml/min) was 7.4% vs. 1.3% in patients with baseline creatinine clearance ≥ 60 ml/min ($p < 0.001$). The incidence of CIN increased with the decrease of baseline creatinine clearance (Figure 3-7). The incidence of CIN in patients with baseline creatinine clearance < 30 ml/min was significantly higher than in those with baseline creatinine clearance 30 - 59 ml/min (19.1% vs. 5.1%; $p < 0.001$). The incidence of CIN in patients with baseline creatinine clearance ≥ 60 ml/min was much lower.

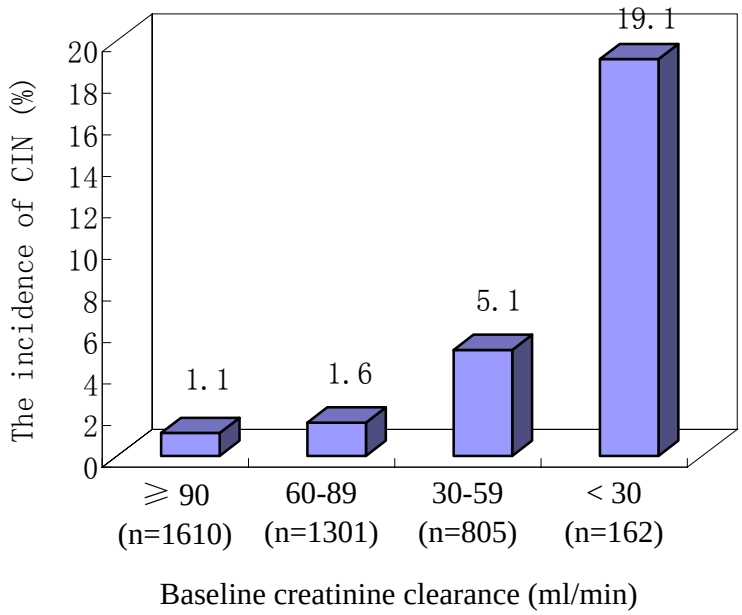


Figure 3-7 Incidence of CIN stratified by baseline creatinine clearance.

Amount of contrast agent administered in preexisting impairment of renal function

There was no difference regarding the amount of contrast agent administered between patients with different baseline creatinine clearance (Figure 3-8).

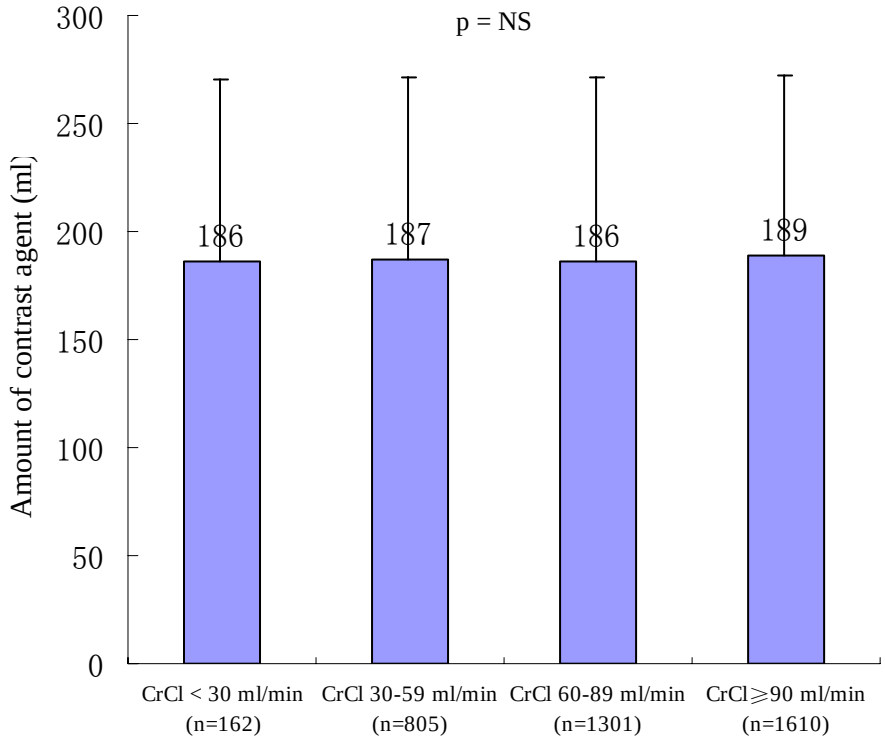


Figure 3-8 Amount of contrast agent stratified by baseline creatinine clearance.

Furthermore, in each group, the amount of contrast agent administered in CIN patients did not show differences compared to non-CIN patients (Table 3-7).

Table 3-7 Amount of contrast agent stratified by CIN and baseline creatinine clearance

Baseline Creatinine Clearance (ml/min)	CIN	Non-CIN	p Value
< 30	180 ± 69 (n = 33)	188 ± 87 (n = 129)	0.99
30-59	191 ± 99 (n = 41)	187 ± 82 (n = 764)	0.89
60-89	210 ± 116 (n = 21)	185 ± 84 (n = 1280)	0.56
≥ 90	176 ± 62 (n = 15)	189 ± 93 (n = 1595)	0.69

Data are presented as the mean vaule±SD

The amount of contrast agent administered in patients with both preexisting impairment of renal function and diabetes mellitus

All patients were divided into four groups: baseline CrCl < 60 ml/min with and without diabetes mellitus, baseline CrCl ≥ 60 ml/min with and without diabetes mellitus. In each group, the amount of contrast agent administered in CIN patients did not significantly differ from non-CIN patients (Figure 3-9).

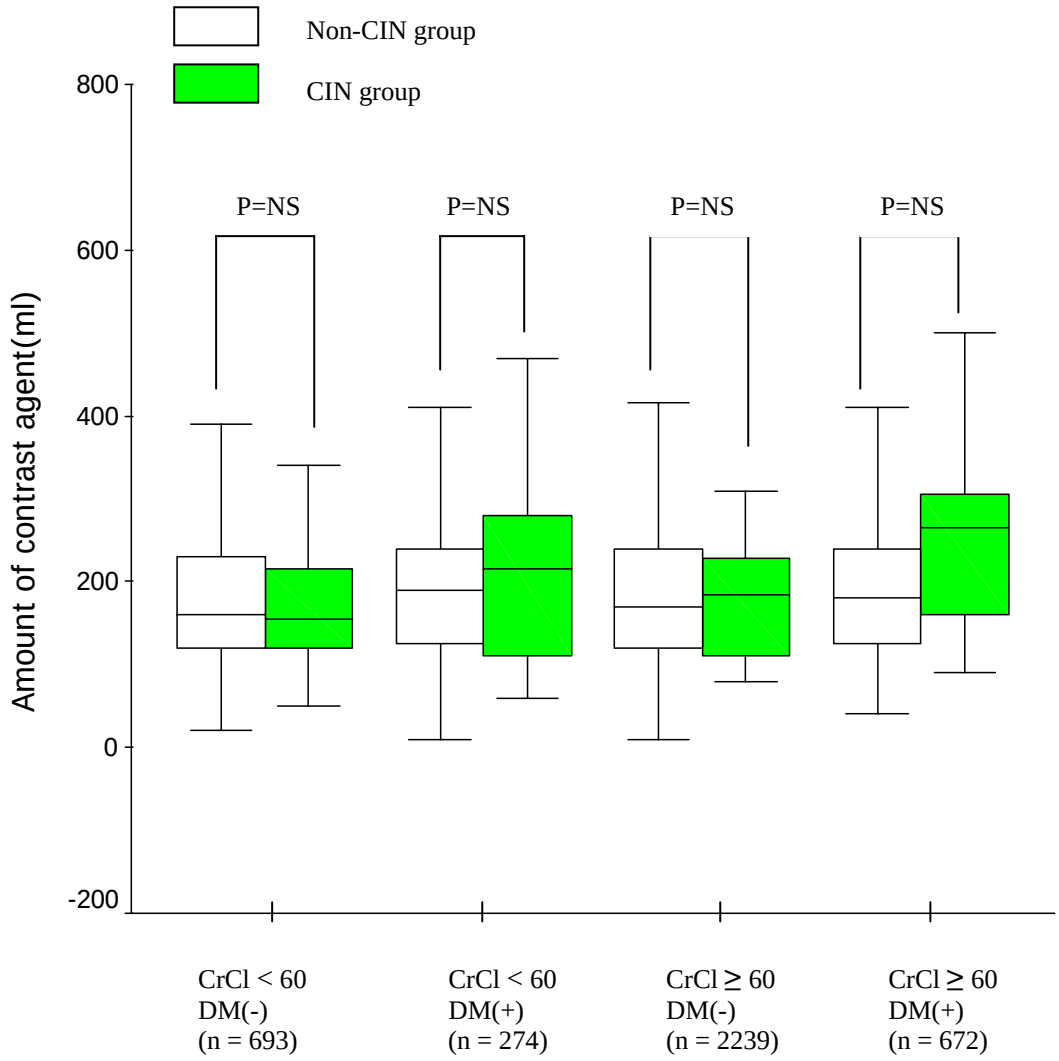


Figure 3-9 The comparison of amount of contrast agent administered in CIN group and non-CIN group stratified by DM and baseline creatinine clearance. Box plots display medians, 25th and 75th centiles (boxes), and 10th and 90th centiles (whiskers).
CrCl = creatinine clearance DM = diabetes mellitus

Among diabetic patients with baseline creatinine clearance of 60 - 89 ml/min, patients who had developed CIN were administered a higher dose of contrast agent than in non-CIN patients (298 ± 132 ml vs 187 ± 78 ml, p = 0.02, Table 3-8). There was no significant difference regarding the amount of contrast agents administered in other baseline creatinine clearance subgroups between the CIN group and non-CIN group (p > 0.05).

Table 3-8 Amount of contrast agent administered in diabetes mellitus stratified by CIN and baseline creatinine clearance

Baseline Creatinine Clearance (ml/min)	CIN	Non-CIN	p Value
< 30	181 ± 88 (n = 8)	171 ± 64 (n = 33)	0.89
30-59	229 ± 111 (n = 14)	200 ± 85 (n = 219)	0.29
60-89	298 ± 132 (n = 5)	187 ± 78 (n = 295)	0.02
≥ 90	187 ± 100 (n = 3)	194 ± 82 (n = 369)	0.80

Data are presented as the mean vaule ± SD

Correlation between the amount of contrast agent administered and the change of serum creatinine in patients with preexisting impairment of renal function

As seen in Figure 3-10, there was no direct correlation between the amount of contrast agent administered and the change of serum creatinine in patients with preexisting impairment of renal function.

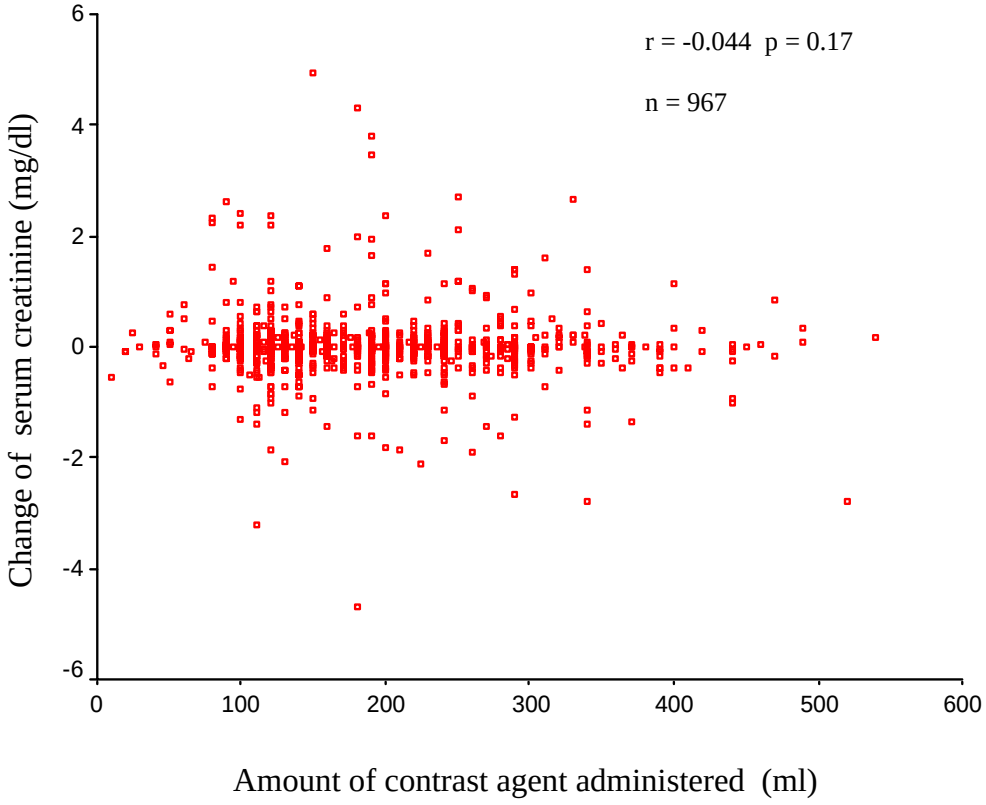


Figure 3-10 Correlation between the amount of contrast agent administered and the change of serum creatinine concentration in patients with preexisting impairment of renal function.

3.2.4 PCI Subgroup

Incidence of CIN in PCI subgroup

As seen in Figure 3-11, the incidence of CIN was similar for the PCI and non-PCI subgroup (2.7% vs. 3.0%; p = 0.65). In addition, the incidence of CIN in elective cases and in emergency cases also showed no significant difference (2.9 % vs. 2.6 %; p = 0.69).

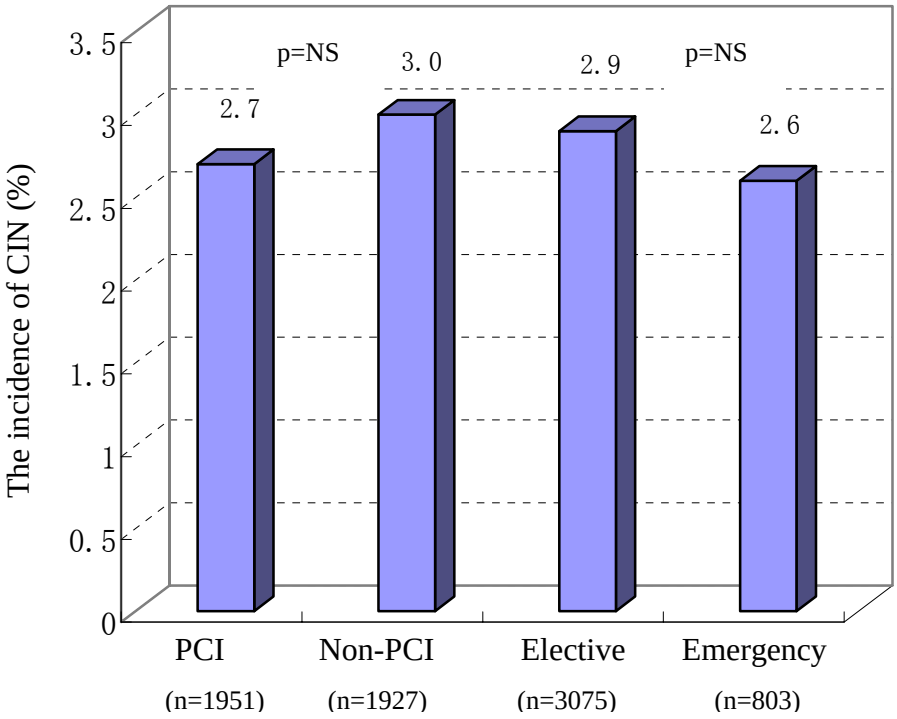


Figure 3-11 Incidence of CIN in PCI, non-PCI, elective cases and emergency cases.

PCI = percutaneous coronary intervention

Amount of contrast agent administered in PCI subgroup

As shown in Table 3-9, there was no significant difference regarding the amount of contrast agent in PCI subgroups with different baseline creatinine clearance between CIN and Non-CIN patients ($p > 0.05$).

Table 3-9 Amount of contrast agent administered in PCI subgroup stratified by CIN and baseline creatinine clearance

Baseline Creatinine Clearance (ml/min)	CIN	Non-CIN	p Value
< 30	216 ± 60 (n = 17)	272 ± 85 (n = 73)	0.69
30-59	261 ± 83 (n = 18)	239 ± 75 (n = 370)	0.16
60-89	280 ± 114 (n = 11)	234 ± 85 (n = 622)	0.12
≥ 90	217 ± 100 (n = 6)	238 ± 78 (n = 834)	0.49

Data are presented as the mean vaule±SD
PCI = percutaneous coronary intervention

Correlation between the amount of contrast agent administered and the change of serum creatinine in PCI subgroup

As seen in Figure 3-12, there was no correlation between the amount of contrast agent administered and the change of serum creatinine in PCI subgroup.

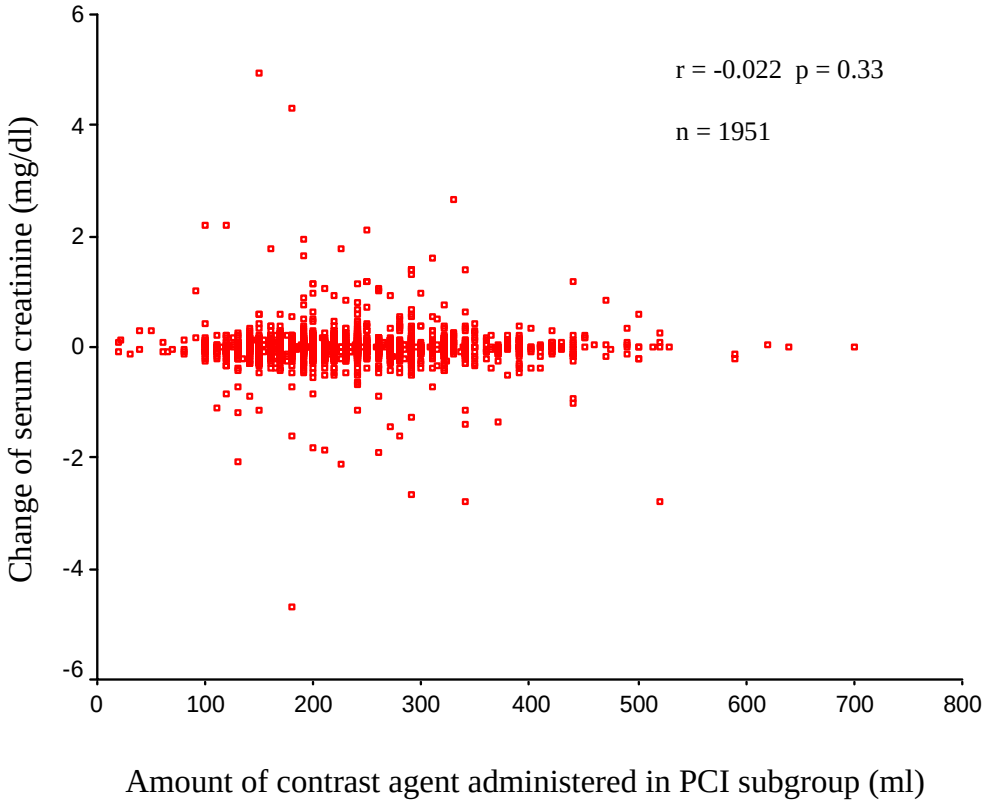


Figure 3-12 Correlation between the amount of contrast agent administered and the change of serum creatinine concentration in PCI subgroup.

3.2.5 Anemia

Incidence of CIN in patients with anemia

As shown in Figure 3-13, the incidence of CIN in anemic patients (hemoglobin < 12 g/dl in women and < 13 g/dl in men) was significantly higher than in non-anemic patients (5.5% vs. 2.0%; $p < 0.001$)

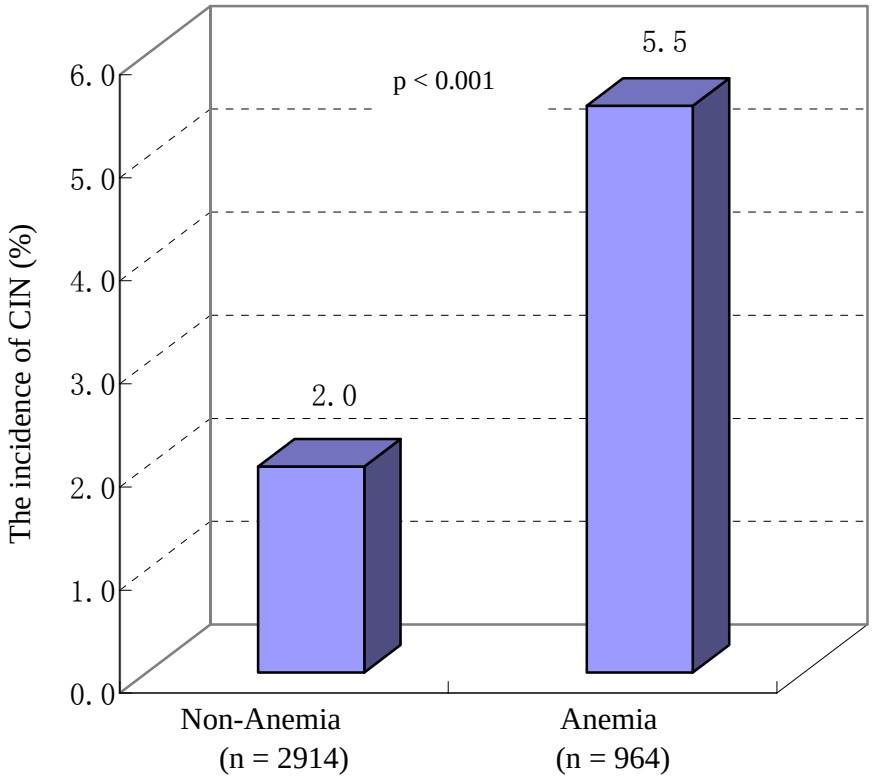


Figure 13 Incidence of CIN in anemic and non-anemic patients.

The incidence of CIN increased with decreasing of baseline creatinine clearance in both the anemia and non-anemia groups. In patients with baseline creatinine clearance < 30 ml/min, a high proportion of both anemic and non-anemic patients experienced CIN (22.9% vs. 15.8%; p = 0.29, Figure 3-14). When baseline creatinine clearance was 30 - 59 ml/min, the incidence of CIN in anemic patients was 2-fold higher than in non-anemic patients (7.9% vs. 3.7%; p = 0.01). Among patients with baseline creatinine clearance 60 - 89 ml/min and ≥ 90 ml/min, there was no significant difference in the incidence of CIN between anemic and non-anemic patients (1.3% vs. 1.7%, p = 0.62; 1.4 % vs. 0.8 %; p = 0.37).

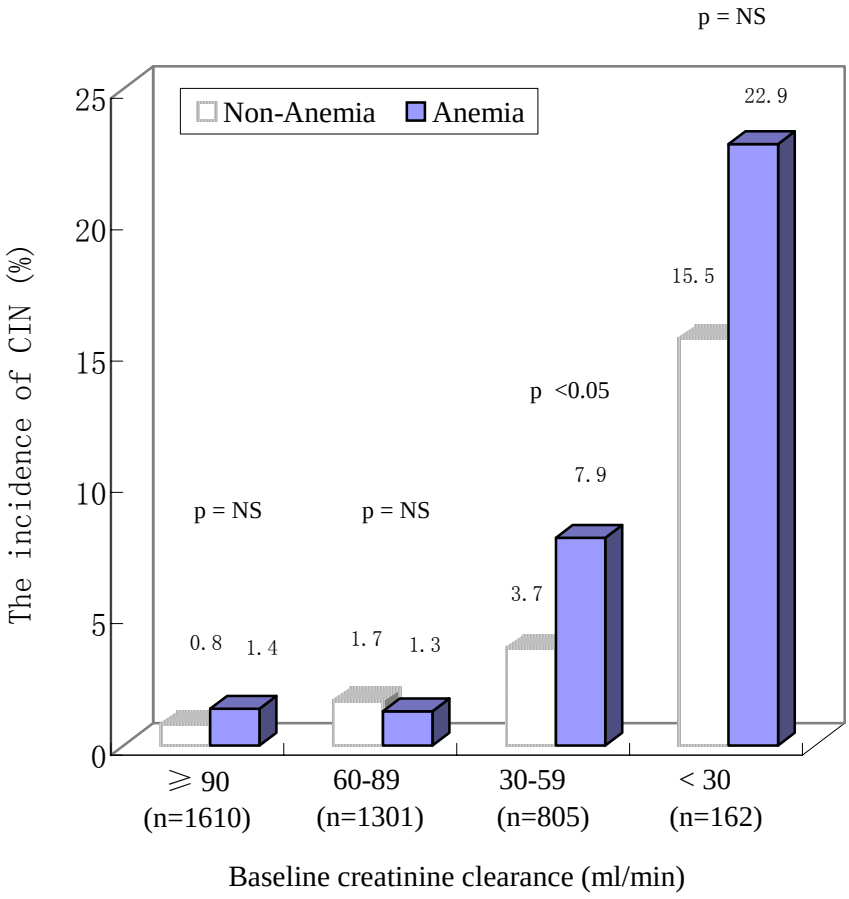


Figure 3-14 Incidence of CIN in patients with anemia and reduced baseline creatinine clearance.

The amount of contrast agent administered in anemia subgroup

The amount of contrast agent administered was similar for anemic and non-anemic patients (191 ± 89 ml vs. 186 ± 82 ml; p = 0.32). The amount of contrast agent administered to anemic patients stratified by CIN and baseline creatinine clearance is listed in Table 3-10. There was no significant difference regarding the amount of contrast agent in anemic patients with different baseline creatinine clearance between CIN and non-CIN patients (p > 0.05).

Table 3-10 Amount of contrast agent administered in anemic patients stratified by CIN and baseline creatinine clearance

Baseline Creatinine Clearance (ml/min)	CIN	Non-CIN	p Value
< 30	186 ± 75 (n = 24)	188 ± 91 (n = 81)	0.75
30-59	230 ± 109 (n = 21)	195 ± 90 (n = 245)	0.13
60-89	223 ± 101 (n = 4)	183 ± 90 (n = 303)	0.40
≥ 90	200 ± 83 (n = 4)	193 ± 83 (n = 282)	0.67

Data are presented as the mean vaule ± SD

Correlation between the amount of contrast agent administered and the change of serum creatinine in anemia

As seen in Figure 3-15, there was no direct correlation between the amount of contrast agent administered and the change of serum creatinine in anemic patients.

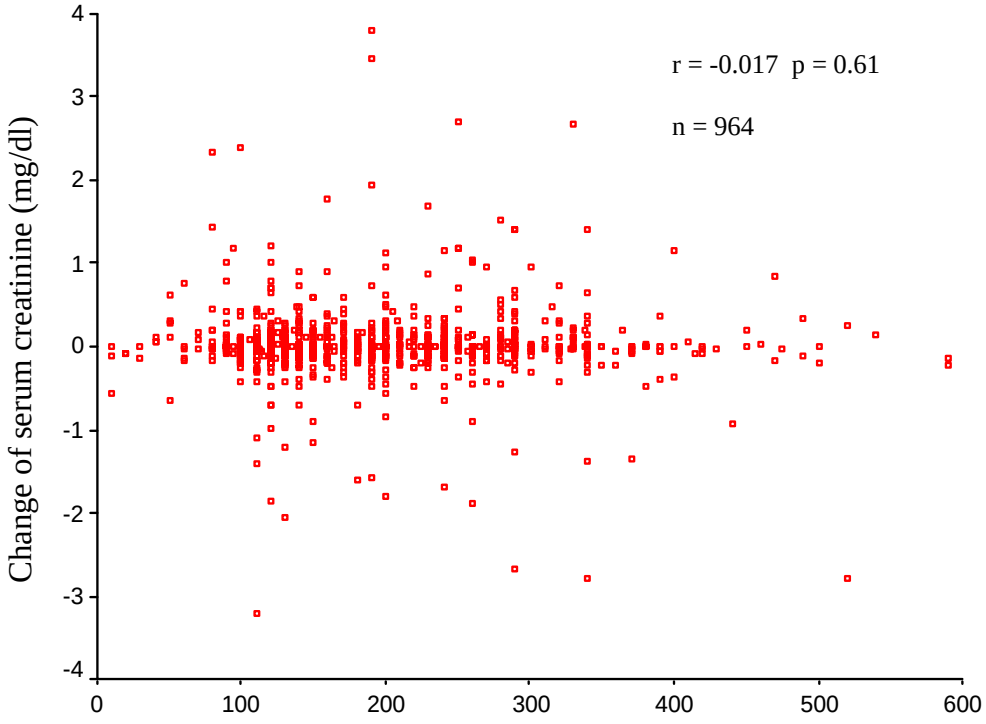


Figure 3-15 Correlation between the amount of contrast agent administered and the change of serum creatinine concentration in anemic patients.

3.3 Multivariate Logistic Regression Analysis

Multivariate logistic regression analysis revealed baseline creatinine clearance, hemoglobin, diuretics medication and baseline serum potassium as independent predictors (Table 3-11) for CIN after cardiac catheterization. The variables included in the first step of these multivariate analysis were age, sex, BMI, systolic blood pressure, diastolic blood pressure, arterial hypertension, hypercholesterolemia, LVEF, presence of coronary artery disease, presence of diabetes mellitus, AMI, UAP, PCI, prior CABG, prior PCI, prior MI, baseline creatinine clearance, amount of contrast agent administered, serum sodium, serum potassium, glucose level, hemoglobin level, aspirin medication, beta-blocker medication, ACE inhibitor medication, Clopidogrel medication, statin medication, diuretic medication, AT-2 antagonist medication and calcium channel blocker medication.

Anemia was also an independent predictor of CIN (OR 2.123, 95%CI 1.405 to 3.206, $p < 0.001$) when it was introduced into the multivariates model instead of baseline hemoglobin.

The relative risk (RR) for the CIN after exposure of contrast agent was significant for the following categorical variables: baseline creatinine clearance < 60 ml/min (RR 5.704, 95% CI 3.876 to 8.392, $p < 0.001$), anemia (RR 2.811, 95% CI 1.948 to 4.056, $p < 0.001$) and diuretic medication (RR 1.670, 95% CI 1.119 to 2.492, $p = 0.04$).

Table 3-11 Multivariate logistic regression analysis of risk factors for CIN in patients

	OR	95% CI	p Value
Baseline Creatinine Clearance	0.987	0.978- 0.995	0.001
Hemoglobin	0.813	0.727- 0.904	< 0.0001
Diuretic	1.631	1.024- 2.599	0.039
Serum potassium	1.664	1.145- 2.361	0.007
Age	0.995	0.975- 1.015	0.608
Male gender	0.774	0.496- 1.207	0.259
BMI	1.030	0.981- 1.082	0.230
Systolic blood pressure	0.999	0.991- 1.007	0.775
Diastolic blood pressure	0.987	0.965- 1.008	0.228
Arterial hypertension	1.114	0.689- 1.802	0.659
Hypercholesterolemia	1.103	0.624- 1.674	0.458
Diabetes mellitus	1.763	0.610- 1.611	0.972
Coronary artery disease	0.935	0.770- 1.136	0.498
LVEF	0.999	0.987- 0.996	0.912
AMI	0.941	0.657- 1.974	0.713
UAP	0.845	0.392- 1.822	0.668
PCI	1.013	0.721- 1.873	0.782
Prior CABG	1.553	0.956- 2.522	0.070
Prior PCI	1.241	0.771- 1.995	0.370
Prior MI	0.774	0.459- 1.306	0.340
Amount of contrast agent	1.001	0.999- 1.004	0.346
Serum sodium	1.017	0.965- 1.073	0.527
Glucose	1.002	0.999- 1.004	0.164
Aspirin	1.103	0.678- 1.832	0.657
Beta-receptor blocker	0.848	0.520- 1.383	0.509
ACE inhibitors	0.922	0.581- 1.463	0.729
Clopidogrel	0.906	0.529- 1.552	0.720
Statins	0.734	0.447- 1.223	0.251
AT-2 antagonists	1.025	0.307- 3.419	0.968
Calcium channel blocker	1.580	0.841- 3.065	0.793

OR = Odds Ratio

4. Discussion

Contrast-induced nephropathy represents the third cause of in-hospital renal function deterioration after decreased renal perfusion and postoperative renal insufficiency (4). Therefore, CIN is also a possible complication after coronary diagnostic and interventional procedures. With increasing number of diagnostic and therapeutic catheterizations each year, particularly among patients who may have serious conditions predisposing to CIN, the incidence of CIN will continuously increase. The ability of effective prevention of CIN in high-risk patients will provide significant public health benefits as we potentially reduce the in-hospital mortality rate, the length of hospital stay and the subsequent use of chronic hemodialysis.

The major results of the present study are: (1) Using guideline-based prophylactic therapy, the overall incidence of CIN after exposure to contrast medium during cardiac catheterisation and PCI is low (2.8%) in the entire study population. (2) Patients with both preexisting renal insufficiency and anemia are at high risk for CIN. Anemia especially increases the incidence of CIN in patients with moderate renal dysfunction. (3) Baseline creatinine clearance, baseline hemoglobin, baseline serum potassium and diuretics medication are independent predictors of CIN after cardiac catheterization and PCI.

4.1 The Incidence and Prognosis of CIN

In the present study, the incidence of CIN was 2.8% in the unselected population of consecutive patients undergoing cardiac catheterization. Contrast-induced nephropathy was defined as an increase in serum creatinine concentration of ≥ 0.5 mg/dl from preprocedure values within the hospital stay as accepted in the literature. Postprocedure creatinine value were measured within 48 hours or before discharge. We may have missed a later increase in serum creatinine in some patients who did not have renal function deterioration within 48h of their procedure. The comparison of incidence of CIN after angiography with other large studies is given in Table 4-1. The incidence of CIN in patients undergoing PCI in our study was 2.7%, which is slightly lower than the results of Rihal et al. (47). In emergency procedures of this study, the incidence of CIN was 2.6%. The incidence of CIN in patients with impaired renal function was higher than those with preserved renal function (7.4 % vs. 1.3%). In patients with severe renal insufficiency (baseline creatinine clearance < 30 ml/min), the incidence of CIN was 19.1 %. This was consistent with previous studies, which suggested a higher incidence of CIN in patients with

greater reduction in renal function (47, 109-111). In a series of 7,586 patients undergoing cardiac catheterization, Rihal et al. (47) found a low risk (2.4 %) of CIN (defined as an increase in serum creatinine levels ≥ 0.5 mg/dl) in patients with normal renal function, but a high risk (30.6%) in those with serum creatinine levels ≥ 3.0 mg/dl. In patients with underlying renal disorder, CIN rates were extremely high, from 14.8% to 55% (5,47). Moore et al. (109) demonstrated a high, significant relationship between an increasing baseline level of serum creatinine and the frequence of nephrotoxicity (varying from 2% in those with baseline creatinine of < 1.5 mg/dl to 20% in those with levels of > 2.5 mg/dl). CIN is associated with increased morbidity and mortality, particularly in high-risk patients who underwent percutaneous coronary interventions (5,6,47). The in-hospital mortality rate in patients developing renal insufficiency is directly related to the magnitude of the increase in the serum creatinine concentration (5,112). Even small increments in serum creatinine can translate into significant increase in morbidity and mortality (6,113). Renal failure after contrast administration requiring in-hospital dialysis is associated with poor outcome including 36 % in-hospital mortality and 19% two-year survival (5,112). The mortality rates vary from 3.8% with an increase in serum creatinine of 0.5 to 0.9 mg/dl to 64% with an increase of > 3.0% mg/dl (114). A recent study demonstrates that CIN is a frequent complication after PCI in AMI even in patients with normal baseline renal function, and is associated with increased in-hospital morbidity, mortality and prolonged hospitalization (111). These data suggest that the development of CIN is highly correlated with death during the index hospitalization as well as during long-term follow-up.

Table 4-1 Comparison of incidence of CIN after coronary angiography/PCI

	Our study	Rihal et al.. (47)	Dangas et al.. (107)	Nikolsky et al.. (108)
Number of patients	3878	7586	7230	6773
Type of procedure	Both diagnosis and intervention	coronary intervention	coronary intervention	coronary intervention
Contrast Osmolality	low (iopromide)	low (iopamidol)	low (ioxaglate)	low
Contrast amount in Intervention in CIN(ml)	245±82	292±139	285±154	273±123
Definition of CIN	Increase in creatinine of 0.5 mg/dl	Increase in creatinine of 0.5 mg/dl	Increase in creatinine of o.5mg/dl or 25%	Increase in creatinine of 0.5 mg/dl or 25%
Incidence of CIN	2.8%	3.3%	14.8%	13.9%
Independent predictors of CIN	baseline CrCl hemoglobin baseline serum potassium diuretics medication	baseline serum Cr AMI shock Volume of contrast agent administered	decreased eGFR periprocedural hypotension higher contrast agent volumes lower baseline hemotocrit diabetes pulmonary edema at presentation intra-aortic balloon pump use LVEF<40 %	estimated glomerular filtration rate (10 ml/min/1.73 m^2 decrease) baseline hematocrit volume of contrast media (increase by 100 ml) hypotension diabetes mellitus hypertension LVEF <40%

4.2 CIN in Elderly Patients

In this study, the incidence of CIN in patients ≥ 70 years was 3.6%. Patients in the CIN group were older than those in the non-CIN group (66.0 ± 12.0 vs. 63.4 ± 11.7, p = 0.02). Multivariate analysis found that age was not an independent predictor of CIN. The result was consistent with the finding of McCullough et al. (5). Some studies (111,115) reported ≥ 70 years appeared to be an independent predictor of CIN. Advanced age is reported to predispose patients to renal sodium and water wasting due to reduction in renal mass, function and perfusion (116). Rich and Crecelius (113) reported an incidence of CIN in patients of the same age group of 11%. The reasons for this higher risk have not been studied but are probably multifactorial, including age-related changes in renal function, the presence of multivessel disease, and more difficult vascular access due to tortuosity and calcification of the vessels requiring relatively large amounts of contrast.

4.3 CIN in Diabetes Mellitus

Besides preexisting impairment of renal function, diabetes mellitus is another well-recognized risk factor for CIN. Diabetes mellitus with associated renal insufficiency has been identified as an independent risk factor for contrast nephropathy. Clinically important CIN usually occurs in subset of diabetics who have underlying renal insufficiency (10,47). In the present study, the diabetes alone was not an independent risk factor for the development of CIN. There was no significant difference in the incidence of CIN between diabetic and nondiabetic patients (3.2% and 2.7%, respectively). The incidence of CIN in patients with preexisting renal dysfunction was 8.1% in diabetics and 7.5% in nondiabetics. However, the incidence of CIN in patients with diabetes mellitus but preserved renal function was rather low. This finding was consistent with Parfery et al. (10), who showed that in diabetics with preserved renal function and absence of other risk factors, the rate of CIN was comparable to that in a healthy population. Lautin et al. (117) reported that the incidence of CIN was rather low (2%) in patients with neither diabetes nor azotemia, but significantly higher (16%) in individual patients with diabetes but preserved renal function, and much higher (38%) in patients who had both diabetes and azotemia. In a large study of 1,196 patients (118), the incidence of CIN associated with the administration of low-osmolar contrast medium in patients with normal renal function was 7.2% in diabetic patients and 8.5% in nondiabetics. In a study by Berns (112), CIN occurred in 27% of diabetics with a baseline serum creatinine from 2.0 to 4.0 mg/dl and 81% of those with a serum creatinine > 4.0

mg/dl. In a study of 1,826 consecutive patients undergoing coronary intervention, McCullough et al. (5) concluded that diabetes mellitus is one of the strongest predictors of acute renal failure after coronary intervention. Some literatures (6,46) have been inconsistent with respect to diabetes as strong risk factors for CIN after PCI. Parfrey et al. (10) showed that none of 85 patients with diabetes and normal function developed clinically significant renal impairment (defined as an increase of > 50% in serum creatinine levels). However, those with diabetes alone were found to be at slightly higher risk of renal failure than the general population. More recently, Rihal et al. (47) have shown in a large scale study of 7,586 patients who underwent percutaneous transluminal coronary interventions at the Mayo clinic that diabetes increases the risk of CIN in patients with baseline serum creatinine (SCr) < 2.0 mg/dl (3.7% vs. 2.0 % from 0 to 1.1 mg/dl SCr, $p = 0.005$; 4.5% vs. 1.9% from 1.2 to 1.9 mg/dl SCr, $p < 0.001$), but not in patients with SCr > 2.0 mg/dl before the procedure.

4.4 CIN in Preexisting Impairment of Renal Function

Often in cardiovascular literature, a serum creatinine level < 1.5 mg/dl has been used to identify "normal renal function". GFR < 60 ml/min per 1.73 m^2 is selected as the cutoff value for definition of chronic kidney disease because it represents a reduction by more than half of normal value of $\approx$ 125 ml/min per 1.73 m^2 in healthy subjects. Estimation of GFR from serum creatinine and prediction equations including age, sex, race and body size is recommended to avoid the misclassification of individuals on the basis of serum creatinine alone (99,119). Using creatinine clearance calculation estimated with the Cockroft-Gault formula more accurately defines renal function. Using serum creatinine level as an indicator of renal function grossly underestimates the prevalence of renal insufficiency. In the study of left ventricular dysfunction (SOLVD), which excluded patients with a serum creatinine level > 2.0 mg/dl, 35.5% of patients had an estimated creatinine clearance < 60 ml/min with the Cockroft-Gault formula (120). Thus, the prevalence of chronic kidney disease is severely underestimated when it is defined on the basis of serum creatinine level instead of creatinine clearance.

In this study, we used creatinine clearance rather than serum creatinine to assess the level of renal function. When creatinine clearance was calculated in our population, a greater number of patients (24.9%) showed reduced baseline renal function (creatinine clearance < 60 ml/min). Multivariate logistic regression analysis confirmed that baseline creatinine clearance was an independent risk factor for CIN in the entire study population. This result was consistent with

other studies (5,20,107). Rihal et al. (47) used multivariate analysis, baseline serum creatinine was identified as an independent predictor of CIN. In multivariate analysis by McCullough et al. (5), creatinine clearance is an independent predictor of CIN requiring dialysis after coronary intervention. Renal function deterioration after exposure to contrast medium is common in patients with impaired renal function (113). McCullough et al. (5) found that creatinine clearance of 30ml/min or less markedly increased the incidence and severity of CIN. In addition, no patient with a creatinine clearance ≥ 47 ml/min developed CIN requiring dialysis. The renal function deterioration is an important predictor of in-hospital mortality. Dangas et al. (107) found CIN was one of the most powerful predictors of 1-year mortality in patients with preexisting chronic kidney disease or preserved eGFR.

4.5 CIN in Patients with Anemia

It is well known that patients with a GFR < 60 ml/min per 1.73 m^2 are more likely to have anemia and that prevalence and severity of anemia increase with declining renal function (121). In this study, 38.3% of patients with chronic kidney disease (baseline creatinine clearance < 60 ml/min) had anemia. Our study demonstrated that baseline hemoglobin was an independent risk factor for contrast-induced nephropathy in all patients. When anemia was introduced into the multivariate model instead of baseline hemoglobin, it was also an independent predictor of CIN. This is the first study indicating an independent association between baseline hemoglobin and CIN after injection of contrast agent for cardiac catheterization. This finding paralleled the recent clinical trial finding of Nikolsky et al. (108), who found that lower baseline hematocrit was an independent predictor of contrast-induced nephropathy, each 3% decrease in baseline hematocrit resulted in significant increase in the odds of contrast-induced nephropathy in patients with and without chronic kidney disease. Among 7,230 consecutive patients after percutaneous coronary interventions, Dangas and colleagues (107) showed that decreased eGFRs and lower baseline hematocrit were most significant independent predictors of CIN in patients with chronic kidney disease.

In the present study, the incidence of CIN in patients with severe renal impairment (baseline creatinine clearance < 30 ml/min) was 22.9% in anemic patients and 15.8% in non-anemic patients ($p = 0.29$). The incidence of CIN in anemic patients with normal renal function was low. Anemia increased the risk of CIN in patients with baseline creatinine clearance 30 - 59 ml/min (7.9% vs. 3.7 %; $p = 0.01$). A possible interpretation of the result was that higher hemoglobin

might attenuate the risk of contrast-induced nephropathy in patients with moderate renal impairment. Our study showed that patients with anemia were older and had lower LVEF and lower creatinine clearance. This was possibly the mechanism to explain an association between anemia and higher incidence of CIN. What is the possible mechanism to explain that baseline hemoglobin is an independent predictor for CIN? In the pathophysiology of CIN, one main factor is a reduction in renal perfusion caused by a direct effect of contrast media on the kidney. The outer medullary region is particularly susceptible to ischemic injury because of its high metabolic activity and low prevailing oxygen tension (50). The partial oxygen pressure of the outer medulla in the kidney is very low during normal function. Contrast media aggravates hypoxic injury to this region by increasing renal vascular resistance. Kim et al. (122) reported that contrast media could increase oxygen affinity of hemoglobin, so oxygen delivery to the peripheral tissues might be impaired. Local renal hypoxia can be more aggravated in patients with low hemoglobin after exposure to contrast media, hence the combination of contrast-induced vasoconstriction and anemia may decrease oxygen delivery sufficiently to cause renal medullary hypoxia. Thus, it is intuitive that anemia may play a role in CIN risk. Nikolsky and colleagues (108) demonstrated that patients with the lowest eGFR and hematocrit had the highest rates of CIN. The threshold hematocrit at which the risk of CIN increased was < 41.2% in men and < 34.4% in women. Anemia-induced deterioration of renal ischemia and hypoxia may be one reason for the higher incidence of CIN in anemic patients.

In addition, it has been suggested that reactive oxygen species (ROS) are important in the renal damage caused by contrast agent (20,21). ROS may play a role in the effects of various vasoconstrictors that have been considered important for the development of CIN. Since ROS are extracellular signalling molecules, they may be significant in mediating the actions of vasoconstrictions, such as angiotensin II, thromboxane $A_{2,}$ endothelin-1, adenosine, and norepinephrine. Moreover, various models of renal inflammation and ischemia have shown a role of ROS in glomerular injury (123). In a study of oxidant injury following contrast injection, Sandua and associates (124) measured the increase in urinary malondialdehyde-to-creatinine ratio as a marker of oxidative stress. The malondialdehyde-to-creatinine ratio increased following contrast infusion, suggesting a link between contrast infusion and free radical generation. More recently, ROS have been proposed to play several roles in the pathogenesis of chronic-degenerative conditions, such as some forms of anemia (125). Chronic renal failure is connected with oxidative stress which correlates with the degree of renal anemia. The lower the hemoglobin, i.e. the stronger the degree of renal anemia, the higher the serum concentration of

hyodroxynonenal and malondialdehyde. The serum level of hyodroxynonenal and malondialdehyde could be reduced during correction of renal anemia by epoetin (126). In general, the erythrocytes are in the whole blood one of the major components of the antioxidative capacity. The circulating erythrocytes can be called as mobile free radical scavengers which are able to protect other tissues and organs. The renal anemia contributed to the increase of the oxidative stress in chronic renal failure. In relation to free radical metabolism, the best way was a complete correction of renal anemia (127). Grune et al. (128) found it was possible that some of complications of uremia were at least partially due to the action of ROS. Erythropoietin therapy directed towards the normalization of the blood erythrocyte content was a step to the improvement of the oxidative stress in uremic patients. Strategies to strengthen the complex endogenous free radical defence could thus be predicted to show long-term benefit. Siems and coworkers (129) concluded that optimized correction of renal anemia might result in a significant reduction of oxidative stress and therefore in the reduction of organ tissue damage. In anemic patients, increase of ROS resulting in renal injury may be another reason for the higher incidence of CIN.

In the present study, anemia is an independent risk factor for contrast-induced nephropathy in all patients. Anemia significantly increases the incidence of CIN in patients with moderate renal dysfunction. Patients with both preexisting renal insufficiency and anemia are at the highest risk to develop CIN. Before cardiac catheterization, correction of anemia especially in patients with preexisting renal failure might be a modifiable risk factor for CIN, even though this has to be proven by prospective randomized trials.

4.6 CIN in Patients on Diuretic Therapy

The use of diuretics had been considered effective for prevention of CIN, since loop diuretics attenuate the decrease in PaO_2 in the outer medulla of the kidney by inhibiting the electrolyte transporters. However, in the clinical trial, diuretic compounds such as furosemide and mannitol may deteriorate the renal dysfunction after injection of contrast medium. In this study, 30% of the patients in CIN group vs. 20.1% in non-CIN group were administrated diuretics, the use of loop diuretics before procedure appeared to aggravate renal dysfunction. Administration of diuretics is an independent predictor for CIN. This finding paralleled the clinical trial finding of Solomon et al. (48), who found that furosemide given immediately before the procedure led to more acute decrease in renal function. The mechanism of this adverse effect is unclear. Weisberg

et al. (28) also demonstrated increased nephrotoxicity among patients with diabetes with moderate renal dysfunction who received hydration plus furosemide compared to those who received hydration alone. These trials conclude that furosemide offers no additional benefit in preventing CIN and may be even detrimental when given in addition to saline hydration. Although the precise reason for the deteriorative effect of furosemide on renal dysfunction is unclear, it may be associated with the vasoconstriction and decrease in renal blood flow, which is mediated by the enhanced renin release/angiotensin synthesis in response to the action on the macula densa (130). It is beneficial to discontinue diuretics administration temporarily before and after exposure to contrast medium, unless it is clinically indicated.

4.7 Role of Contrast Media

There is a debate whether the quantity of contrast agent predicts the degree of renal dysfunction. Some studies reported no relationship between the amount of contrast material and the occurrence of renal function deterioration, whereas others suggested a direct correlation (5, 47). Neither in the whole study population nor in any subgroup was the amount of contrast agent administered an independent predictor of CIN in the present study. The amount of the contrast agent was similar for CIN and non-CIN patients (190 ± 90 ml vs. 187 ± 83 ml; $p = 0.78$). No correlation was observed between the amount of contrast agent administered and the change of serum creatinine concentration. In patients with different baseline creatinine clearance, the amount of contrast agent administered in CIN patients did not show any difference when compared to non-CIN patients (Table 7). There is a general consensus on the use of small dose of contrast agent, and that the avoidance of repetitive, closely spaced studies represents one of the most import recommendations to prevent CIN (131). McCullough et al. (5) found that 100 ml contrast medium was the cutoff dose below which there was no CIN requiring dialysis undergoing coronary angiography. Briguroci et al. (65) identified a volume of 140 ml as the best cutoff value for predicting the occurrence of CIN. These data emphasize the necessity for limiting the amount of contrast dye administered when dealing with patients with impaired renal function.

Currently, four main types of contrast media are used in routine practice: nonionic low-osmolar, ionic low-osmolar, nonionic iso-osmolar, and ionic high-osmolar contrast media (132). Ionic contrast agents produce more side effects than nonionic contrast media and therefore are no longer widely used in the catheterization laboratories. The most commonly used agents are

nonionic agents, which do not dissociate into positively and negatively changed ions in solution. Nonionic agents can be formulated at lower osmolalities than most ionic agents and reduce the incidence of cardiac effects and minor side effects. The difference in type of contrast media might influence the obtained results. In this study, Iopromide, a nonionic, low-osmolality contrast agent, was used almost exclusively in our laboratory. It is well–recognized that the LOCM are less nephrotoxic than HOCM in patients with preexisting renal impairment (8,109,118,134). Rudnick et al. (118) found in diabetic patients with underlying chronic renal insufficiency, the incidence of CIN was 27% in patients received HOCM vs. 12.2% in patients received LOCM. Another group studied 101 patients with serum creatinine levels 1.4-2.4 mg/dl undergoing cardiac catheterization and found a statistically significant incidence of CIN in patients randomized to receive HOCM (14%) versus those who received LOCM (3%) with the highest incidence of nephropathy occurring in the diabetic group (134). This finding was supported by a meta-analysis of 25 trials, which demonstrated that the risk of CIN was 40% lower with LOCM than with HOCM (131).

It has also been suggested that the IOCM is less nephrotoxic than LOCM. In the NEPHRIC study (135), Aspelin et al. reported that iohexol, one of the most widely nonionic contrast media, was significantly more nephrotoxic than the nonionic dimer iodixanol in patients with preexisting chronic renal insufficiency undergoing coronary angiography. The incidence of CIN was 3% versus 26% in the iodixanol and iohexol groups, respectively. The authors clearly documented that IOCM offer protection against CIN that is above and beyond the prophylaxis offered by LOCM in the high-risk group. While another study (136) showed a high incidence (21%) of CIN with iodixanol. Sharma et al. (137) reported that the pooled incidence of CIN was higher after iohexol (25.0%) than after iopamidol (13.5%) and iodixanol (11.0%). A significant difference in the occurrence of CIN was observed between iohexol and iodixanol ($p = 0.001$) and between iohexol and iopamidol ($p = 0.024$), while the difference between iopamidol and iodixanol was not statistically significant ($p = 0.277$). Very recently, Aspelin et al. (138) analyzed 125 patients and demonstrated that the isosmolar contrast medium iodixanol appears to be cost-effective compared to a low-osmolar contrast medium iohexol in diabetic patients with renal impairment undergoing angiography. Current evidence suggests that non-ionic isosmolar contrast presents the lowest risk for CIN in patients with chronic kidney disease, particularly in those patients with diabetes mellitus (139). Further studies are required to elucidate whether the isomolar dimer has less associated nephrotoxicity in comparison with other types of contrast media in patients with renal impairment.

4.8 Potential Mechanism of CIN

The exact mechanism of contrast-induced nephropathy remains poorly understood. Contrast medium has been shown to have various deleterious effects on the kidney. A reduction in renal perfusion caused by a direct effect of contrast media on the kidney and toxic effects on the tubular cells are generally accepted as the main factors in the pathophysiology (50). Other factors included apoptosis (138), vasoactive substances, complement activation (139) and effect of osmolality. It has been suggested that the development of CIN is affected by changes in renal hemodynamics because of the effects of the contrast dye on the action of many substance, including increased activity of renal vasoconstrictor and decreased activity of renal vasodilators (31,37). In addition, reactive oxygen species are important in the renal damage caused by contrast agents (21,140). Contrast media have been found to reduce antioxidant enzyme activity in rat kidney, and direct cytotoxic effects mediated by oxygen free radicals have been found in rat models of CIN (20).

4.9 Prevention of CIN

The prevention of CIN begins with the identification of risk factors and the attempt to control or modify them prior to the administration of contrast media. Prevention of CIN relies on careful procedure selection and patient assessment. All of the risk factors can be identified from a routine medical history and baseline blood tests. Any risk factors for CIN should be corrected before contrast administration. When contrast administration is deemed appropriate, the lowest possible dose of contrast agent should be used. If contrast must be administered in the presences of an uncorrected risk factor, it is advisable to monitor renal function by serum creatinine before and at 48 h to 72 h after the procedure. After the high-risk patient population has been identified and risk factors addressed, the next step in preventing CIN is the use of different prophylactic therapies. An intravenous hydration regime (saline 0.45%, at least 1 ml/kg/h 12 h before and after contrast exposure) is suggested for all patients with impaired renal function. In addition, the use of low or iso-osmolar agents and acetylcysteine are also beneficial in selected higher-risk patients.

4.10 Study Limitations

Although data were collected prospectively by independent monitors and entered into a dedicated database, this analysis was retrospective. Because the follow-up assessment of renal function in our study was 1-2 days after catheterization, therefore, we might have missed a later increase in serum creatinine in some patients who did not have renal function deterioration within 48 h of their procedure. This might result in a slight underestimation of CIN. We did not have the etiology of anemia of the vast majority of the anemic patient. In addition, we did not have data on erythropoietin levels and plasma volume information that might have provided better understanding of the role of low baseline hemoglobin in the development of CIN.

5. Conclusions

(1) The overall incidence of CIN after cardiac catheterization/PCI exposure in entire populations is low (2.8%) using guideline-based recommendations for prophylaxis of CIN. (2) Patients with both preexisting renal insufficiency and anemia are at high risk of CIN. Anemia significantly increases the incidence of CIN in patients with moderate renal dysfunction. (3) Baseline creatinine clearance, baseline hemoglobin (or anemia), baseline serum potassium and concomitant diuretics medication are independent predictors of CIN.

6. Summary

Background: Contrast-induced nephropathy (CIN) is an iatrogenic disorder resulting from exposure to contrast media. With the number of diagnostic and therapeutic procedures increasing each year, the clinical significance of CIN will be increasing as well. CIN is associated with increased morbidity and mortality, particularly in high-risk patients who have undergone coronary angiography and/or percutaneous coronary interventions. Although many studies demonstrate that preexisting renal dysfunction, diabetes mellitus, older age and reduced left ventricular systolic function are the most important risk factors for CIN, the association between baseline hemoglobin and CIN after injection of contrast agents has not been completely clarified. In order to assess the incidence and clinical predictors of CIN in unselected populations, consecutive patients undergoing coronary angiography or percutaneous coronary intervention were studied in the era of guideline-based prophylactic measures to prevent CIN.

Methods: The subject group consisted of 3878 patients who had undergone coronary angiography and coronary intervention procedure between April 1, 2001 and June 30, 2003. All patients underwent guideline-based prophylactic measures to prevent CIN. Among them 2700 were men and 1178 women; median age was 64 years (23-102 years). A coronary interventional procedure was performed in 1951 patients. A nonionic, low osmolality contrast agent (Iopromide) was used almost exclusively in our laboratory at this time. Serum creatinine values were measured before and within 48 h of administration of contrast agents, further measurement were performed in all CIN patients. Contrast-induced nephropathy was defined as an increase in serum creatinine concentration of ≥ 0.5 mg/dl from preprocedure values. Creatinine clearance (CrCl) was calculated by applying the Cockcroft-Gault formula to the baseline serum creatinine level. Patients were divided into four categories of renal function by their baseline creatinine clearance: ≥ 90 ml/min, 60 to 89 ml/min, 30 to 59 ml/min, and < 30 ml/min. Anemia was defined as baseline hemoglobin (Hgb) < 12 g/dl in women and < 13 g/dl in men.

Results: Among the 3878 patients studied, diabetes mellitus was present in 946 (24.4%) and anemia in 964 (24.9%) patients at baseline, 110 (2.8%) experienced CIN after procedure. 38.3% of patients with baseline creatinine clearance < 60 ml/min had anemia. The incidence of CIN in patients with baseline creatinine clearance < 30 ml/min was 22.9% in anemic patients and 15.8% in non-anemic patients. Anemia increased the risk of CIN in patients with baseline creatinine clearance 30-59 ml/min (7.9% vs. 3.7%; p = 0.01). There was no significant difference in the

incidence of CIN between patients with and without diabetes mellitus. The amount of the contrast agent administered was similar for CIN and non-CIN patients (190 ± 90 ml vs. 187 ± 83 ml; $p = 0.78$). No correlation was found between the amount of contrast agent administered and the change of serum creatinine concentration. Multivariate logistic regression analysis found that baseline creatinine clearance, baseline hemoglobin, diuretics medication and baseline serum potassium were independent predictors for CIN in the entire population. When presence of anemia was introduced into the multivariate model instead of baseline hemoglobin, it was also an independent predictor of CIN (OR 2.123, 95% CI 1.405 to 3.206, $p < 0.0001$).

Conclusions: (1) The overall incidence of CIN after exposure to contrast medium in the entire population is low (2.8%). (2) Patients with both preexisting renal insufficiency and anemia are at high risk of CIN. Anemia increases the incidence of CIN in patients with moderate renal dysfunction. (3) Baseline creatinine clearance, baseline hemoglobin (or anemia), baseline serum potassium and diuretics medication are independent predictors of CIN.

Zusammenfassung

Hintergrund:

Die durch Kontrastmittel induzierte Nephropathie (Contrast-induced nephropathy, CIN) ist eine iatrogene Funktionsstörung nach Kontrastmittelexposition. Mit der jährlich zunehmenden Zahl diagnostischer und therapeutischer Eingriffe wächst auch der klinische Stellenwert der CIN, welche mit einer erhöhten Morbidität und Mortalität assoziiert ist, insbesondere bei Hoch-Risiko-Patienten nach Koronarangiographie bzw. perkutanen Koronarinterventionen. Obwohl in vielen Studien präexistierende Nierenfunktionsstörungen, Diabetes mellitus, höheres Lebensalter und eingeschränkte systolische linksventrikuläre Funktion als wichtigste Risikofaktoren für die Entstehung einer CIN herausgearbeitet wurden, wurde der Zusammenhang zwischen dem Ausgangs-Hämoglobinwert und der Entwicklung einer CIN nach Kontrastmittelapplikation noch nicht untersucht. Zur Ermittlung von Inzidenz und klinischen Prädiktoren der CIN in einer unselektierten Population wurden konsekutive Patienten untersucht, welche sich einer Koronarangiographie oder Koronarintervention unterzogen.

Methoden:

Die Studiengruppe bestand aus 3878 Patienten, welche sich zwischen dem 1. April 2001 und dem 30. Juni 2003 einer Koronarangiographie und Koronarintervention unterzogen. Alle Patienten wurden leitliniengerecht prophylaktisch behandelt. Untersucht wurden 2700 Männer und 1178 Frauen im mittleren Alter von 64 Jahren (Range 23 bis 102 Jahre). 1951 Patienten erhielten eine Koronarintervention. In unserem Labor wurde fast ausschließlich ein nicht-ionisches, iodhaltiges, niederosmolares Kontrastmittel (Iopromide) benutzt. Das Serumkreatinin wurde vor und 48 Stunden nach Kontrastmittelapplikation bestimmt, im Falle einer CIN erfolgten weitere Messungen. CIN wurde definiert als eine Zunahme des Serumkreatinins ≥ 0,5 mg/dl gegenüber dem präprozeduralen Wert. Die Kreatinin-Clearance wurde mit der Cockroft-Gault-Formel ermittelt. Gemäß ihrer basalen Kreatinin-Clearance wurde alle Patienten in 4 Gruppen eingeteilt: ≥ 90 ml/min, 60-89 ml/min, 30-59 ml/min und < 30 ml/min. Eine Anämie lag definitionsgemäß bei einem Ausgangs-Hämoglobin (Hb) < 13 g/dl (Männer) bzw. < 12 g/dl (Frauen) vor.

Ergebnisse:

946 (24,4%) der 3878 Studienpatienten hatten einen Diabetes mellitus, 964 (24,9%) waren bereits initial anämisch, 110 (2,8%) Patienten entwickelten postprozedural eine CIN. 38,3% der Patienten mit einer initialen Kreatinin-Clearance < 60 ml/min hatten eine Anämie. Die CIN-Inzidenz bei Patienten mt einer Kreatinin-Clearance < 30 ml/min betrug 22,9% bei anämischen und 15,8% bei nicht anämischen Patienten. Eine Anämie erhöhte das Risiko einer CIN bei Patienten mit einer Kreatinin-Clearance von 30 bis 59 ml/min (7,9% vs. 3,7%; p = 0,01). Die CIN-Inzidenz unterschied sich nicht signifikant zwischen Patienten mit und ohne Diabetes mellitus. Die mittlere Kontrastmittelmenge unterschied sich nicht signifikant bei Patienten mit und ohne CIN (190 ± 90 ml vs. 187 ± 83 ml; p = 0,78). Es konnte kein Zusammenhang zwischen der verabreichten Kontrastmittelmenge und der Veränderung des Serumkreatinins aufgezeigt werden. Mittels multivariater logistischer Regressionsanalyse konnte gezeigt werden, dass die präprozeduralen Werte von Kreatininclearance, Serum-Hämoglobin und -kalium neben einer vorbestehenden Diuretikatherapie unabhängige Prädiktoren für eine CIN in der gesamten Studienpopulation waren. Floss das Vorhandensein einer Anämie an Stelle der absoluten Hämoglobinkonzentration in das statistische Modell ein, so war diese auch ein unabhängiger Prädiktor der CIN (OR 2.123, 95% CI 1.405 - 3.206, p < 0,0001).

Schlussfolgerungen:

(1) Die Gesamtinzidenz der CIN ist mit 2,8% niedrig. (2) Patienten mit vorbestehender Niereninsuffizienz und Anämie haben ein hohes CIN-Risiko. Eine Anämie erhöht das CIN-Risiko bei Patienten mit mäßig eingeschränkter Nierenfunktion. (3) Ausgangs-Kreatinin-Clearance, -serumhämoglobin (oder eine Anämie), -serumkalium und Diuretikatherapie sind die wichtigsten unabhängigen Prädiktoren eines CIN.

7. Reference

1. Barrett BJ, Parfrey PS. Prevention of nephrotoxicity induced by radiocontrast agents. N Engl J Med 1994; 331:1449-1450
2. Idee JM, Beaufiles H, Bonnemain B. Iodinated contrast media-induced nephropathy: pathophysiology, clinical aspects and prevention. Fundam Clin Pharmacol 1994; 8:193-206
3. Porter GA. Radiocontrast-induced nephropathy. Nephrol Dial Transpl. 1994; 9:146-156
4. Hou SH, Buschinsky DA, Wish JB, et al. Hospital-accquired renal insufficiency: a prospective study. Am J Med 1983; 742:43-248
5. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors and relationship to mortality. Am J Med 1997; 103:368-375
6. Gruberg L, Mintz GS, Mehran R, et al. The prognostic implications of further renal function deterioration with 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 2000; 36: 1542-1548
7. Levy EM, Visoli CM, Horwitz RL. The effect of acute renal failure on mortality. a cohort analysis. J A M A 1996; 275: 1489-1494
8. Morcos SK, Thomsen HS, Webb JA, et al. Contrast-media-induced nephrotoxicity, a consensus report. Eur Radiol 1999; 9:1602-1613
9. Solomon R. Contrast medium-induced acute renal failure. Kidney Int 1998;53:230-242
10. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both prospective controlled studies. N Engl J Med 1989; 320:143-149
11. Harkonen S, Kjellstrand CM. Exacerbation of diabetic renal failure following intravenous pyelography. Am J Med 1977; 63:939-946
12. Manske CL, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am J Med 1990; 89: 615-620
13. Rudnick MR. Contrast-induced nephropathy. Pathophysiology and strategies for prevention. J Invasive Cardiol 2004; 16(suppl: 7s-11s)
14. Veda N, Shah SV. Tubular cell damage in acute renal failure-apoptosis, necrosis, or both. Nephrol Dial Transplant 2000; 15:318-23
15. Tervahartiala P, Kivisari L, Kivisarri R, et al. Structural changes in the renal proximal tubular cells induced by iodinated contrast media. Nephron 1997; 76:96-102

16. Humes HD, Hunt DA, White MD. Direct toxic effect of the radiocontrast agent diatrizoate on renal proximal tubule cells. Am J Physiol 1987; 252: F246-F255
17. Waybill MM, Waybill PN. Contrast media-induced nephrotoxocity: identification of patients at risk and algonithms for prevention. J Vasc interv Radiol 2001;12:3-9
18. Rudnick MR, Berns JS, Cohen RM, et al. Contrast media-associated nephrotoxocity. Semin Nephrol 1997; 17:15-26
19. Andersen K-J, Christensen EI, Vik H. Effect of iodinated x-ray contrast media on renal epithelial cells in culture. Invest Radiol 1994; 29:855-962
20. Bakris GL, Lass N, Gabber AO, et al. Radiocontrast medium-induced declines in renal function: a role for oxygen free radicals. Am J Physiol 1990; 258(1 pt 2):F115-F120
21. Yoshioka T, Fogo A, Beckman JK. Reduced activity of antioxidant enzymes underlies contrast media-induced renal injury in volume depletion. Kidney Int 1992; 41:1008-1015
22. Barrett BJ. Contrast nephrotoxicity. J Am Soc Nephrol 1994; 5:125-137
23. Duarte CG, Zhang J, Ellis S. The SHR as a small animal model for radiocontrast renal failure relation of nephrotoxocity to animal's age, gender, strain, and dose of radiocontrast. Ren Fail 1997; 19:723-743
24. Erley CM, Heyne N, Rossmeier S, et al. Adenosine and extracellular volume in radiocontrast media-induced nephropathy. Kidney Int 1998; 67:s192-s194
25. Deray G, Baumelou B, Martinez F, et al. Renal vasoconstriction after low and high osmolar contrast agents in ischemic and non-ishemic canine kidney. Clin Nephrol 1991; 36:93-96
26. Liss P, Nygren A, Olsson U, et al. Effects of contrast media and mannitol on renal medullary blood flow and red cell aggregation in rat kidney. Kidney Int 1996; 49:1268-1275
27. Liss P, Nygren A, Erikson U, et al. Injection of low and iso-osmolar contrast medium decreases oxygen tension in the renal medulla. Kidney Int 1998;53:698-702
28. Weisberg LS, Kurnik PB, Kurnik BRC. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. Kidney Int 1994; 45:259-265
29. Murphy SW, Barrett BJ, Parfrey PS. Contrast nephropathy.
J Am Soc Nephrol 2000; 11:177-182
30. Berg KL. Nephrotoxicity related to contrast media. Scand J Urol Nephrol 2000; 34: 317-22
31. Bakris GL, Lass NA, Glock D. Renal hemodynamic in radiocontrast medium induced renal dysfunction: a role for dopamine-1 receptors. Kidney Int 1999; 56:206-210
32. Tumlin JA, Werg A, Murray PT, Mathur VS. Fenoldopam mesylate blocks reduction in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. Am Heart J 2002 143:894-903

33. Duarte CG, Zhang J, Ellis S. Effects of radiocontrast and endothelin administration on systolic blood pressure and renal damage in male spontaneously hypertensive and wistar Kyoto rats with phentolamine-induced adrenergic blockade.
Invest Radiol 1998; 33:104-112
34. Clark BA, Ducksoo K, Epstein FH. Endothelin and atrial natriuretic peptide levels following radiocontrast exposure in humans. Am J Kidney Dis 1997; 30:82-86
35. Heyman CN, Clark BA, Kaiser N, et al. Radiocontrast agents induced endothelin release in vivo and vitro. J Am Soc Nephrol 1992; 3:58-65
36. Hutcheson LR, Griffith TM, Pitman MR, et al. Iodinated radiographic contrast media inhibit shear stress and agonist evoked release of NO by the endothelium.
Br J Pharmacol 1999; 128 :451-457
37. Parsad PV, Priatna A, Spokes E, Epstein FH. Changes in intrarenal oxygenation as evaluated by BOLD MRI in rat kidney model for radiocontrast nephropathy. J Magn Reson Imaging 2001;13:744-747
38. Heyman SN, Brezis M, Epstein FH, et al. Early renal medullary hypoxic injury from rediocontrast and indomethascin. Kidney Int 1991; 40: 632-642
39. Pfluger A, Lonson TS, Nath KA, et al. Role of adenosine in contrast media-induced acute renal failure in diabetes mellitus. Mayo Clin Prco 2000;75:1275-1283
40. Kapoor A, Kumar S, Gulati S, et al. The role of theophylline in contrast-induced nephropathy, a case-control study. Nephrol Dial Transplant 2002; 17: 1936-1947
41. Oldtoyd SD, Fang L, Haylor JL, et al. Effective of adenosine receptor antagonists on the responses to contrast media in the isolated rat kidney. Clin Sci (Lond) 2000: 303-313
42. Katzberg RW. Contrast medium-induced nephrotoxicity: which pathway?
Radiology 2005, 235:752-755
43. Barett BJ, Rarey PS, Vavaour H, et al. Contrast nephropathy in patients with impaired renal function: High versus low osmolar media. Kidney Int 1992; 41:1274-1279
44. Proter GA: Contrast-associated nwphropathy. Am J Cardiol 1989; 64:22E-26E
45. Best PJ, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcome in patients undergoing percutaneous coronary interventions.
J Am Coll.Cardiol 2002; 39: 1113-1119
46. Iakovou I, Dangas G, Lansky AJ, et al. Incidence, predictors and economic impact on contrast induced nephropathy: result in 8628 patients treated with percutaneous coronary interventions (abstract). J Am Coll Cardiol 2002; 39:2A

47. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002; 105: 2259-2264
48. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol and furosemide to prevent acute decrease in renal function induced by radiocontrast agents. N Engl J Med 1994; 331:1416-1420
49. Trivedi HS, Moore H, Nasr S et al. Arandomized prospective trial to access the role of saline hydration on the development of contrast nephrotoxicity.
Nephron Clin Pract 2003; 93:C29-C34
50. Persson PB, Patzak A. Renal haemodynamic alternation in contrast medium nephropathy and the benefit of hydration. Nephrol Dial Transplant 2005;20 (suppl):i2-i5
51. Goldnberg I, Shechter M, Matetzky S, et al. Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography. Eur Heart J 2004; 25:211-8
52. Shyu KJ, Cheng JJ, Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoning a coronary procedure.
J Am Coll Cardiol 2002 ;40 :1383-8
53. Briguori C, Colombo A, Violante A, et al. Standard vs double dose of n-acetylsysteine to prevent contrast agent associated nephrotoxicity. Eur Heart J 2004;25:206-11
54. Oldenmeyer JB, Biddle WP, Wurdermann RL, et al. Acetylcysteine in the prevention of contrast-induced nephropathy after coronary angiography. Am Heart J 2003;146 :e23
55. Mueller C, Buerkle G, Buettner HJ. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hyfration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 2002; 162:329-336
56. Taylor AJ, Jotchkiss D, Morse RW, McCabe J. PREPARED Preparation for Angiography in Renal Dysfunction: a randomized trial of inpatients vs outpatients hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. Chest 1998; 114: 1570-1574
57. Brown RS, Ransil B, Clark BA. Prehydration protects against contrast nephyrpathy in high risk patients undergoing cardiac catheterization (abstract). J Am Soc Nephrol 1990;1: 330
58. Erley CM. Does hydration prevention radiocontrast-induced acute renal failure?
Nephrol Dial Transplant 1999; 14: 1064-1066
59. Agrawal M, Stouffer GA. Contrast induced nephropathy after angiography. Am Med Sci 2002; 323 (5): 252-258
60. Safirstein R, Andrade L, Vierira JM. Acetylcysteine and nephrotoxic effects of radiographic contrast agent: a new use for and old drug (editorial). N Engl J Med 2000; 343:210-212

61. Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic contrast-agent induced reduction in renal function by acetylcysteine. N Engl J Med 2000;343:180-184
62. Baker CS, Wragg A, Kumer S et al. A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. J Am Coll Cardiol 2003; 41:2114-2118
63. Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled. J A M A 2003, 289: 553-558
64. Allaqaband S, Tumuluri R, Melik AM, et al. Prospective randomized study of N-acetylcysteine, fenoldopam and saline for prevention of radiocontrast-induced nephropathy. Cathet Cardiovasc Intervent 2002; 57:279-283
65. Briguori C, Manganelli F, Scarpato P, et al. Acetylcysteine and contrast agent associated nephrotoxicity. J Am Coll Cardiol 2002; 40:298-303
66. Boccalandro F, Amhad M, Smalling RW, et al. Oral acetylcysteine does not protect renal function from moderate to high doses of intravenous radiographic contrast. Cathet Cardiovasc Intervent 2003; 58:336-341
67. Pannu N, Manns B, Lee H, Tonelli M. Systematic review of the impact of N-acetylcysteine on contrast nephropathy. Kidney Int 2004; 65:1366-1374
68. Care M, Haviv YS, Ben-Yehuda A, et al. The renal effect of low-dose dopamine in high-risk patients undergoing coronary angiography. J Am Coll Cardiol 1998; 34:1682-8
69. Hall KA, Wong RW, Hunter GC, et al. Contrast-induced nephrotoxicity, the effects of vasodilator therapy. J Surg Res 1992; 53:317-320
70. Abizaid AS, Clark CE, Mintz GS, et al. Effects of dopamine and aminophylline on contrast induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. Am J Cardiol 1999;83:260-263
71. Gare M, Haviv YS, Ben-Yehuda A, et al. The renal effect of low-dose dopamine in high-risk patients undergoing coronary angiography. J Am Coll Cardiol 1993; 34:1682-1688
72. Mathur VS, Ellis D, Fellmann J, Luther RR. Therapeutics for hypertensive urgencies and emergencies-fenoldopam: a novel systemic and renal vasodilator. Cardiovasc Interven Tadiol 1998; 1:43-53
73. Bakris GL, Lass NA, Glock D.Renal hemodynamics in radiocontrast medium-induced renal dysfunction: a role for dopamine-1 receptors. Kidney Int 1999; 56: 206-210
74. Madyoon H, Croushore L, Weaver D, Mathur V. Use of fenoldopam to prevent radiocontrast nephropathy in high-risk patients. Cathet Cardiovasc Intervent 2001; 53:341-345

75. Chamsuddin AA, Kowalik KJ, Bjarnason H, et al. Using a dopamine type 1 a receptor angonist in high-risk patients to ameliorate contrast-associated nephropathy.
A J R 2002; 179:591-596
76. Stone G, McCullough P, Tumlin J, et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy, a randomized controlled trial. J A M A. 2003,290:2284-91
77. Erley CM, Duda SH, Schlepakow S, et al. Aderosine antagonist theophylline prevents reduction of the glomerular filtration rate after contrast media application.
Kidney Int 1994,45:1425-1431
78. Katholi RE, Taylor GJ, McCann WP, et al. Nephrotoxicity from contrast media, attenuation with theophylline. Radiology 1995; 195:17-22
79. Kapoor A, Kumar S, Gulati S, et al. The role of theophylline in contrast-induced nephropathy, a case-control study. Nephrol Dial Transplant 2002; 17:1936-1941
80. Shammes NW, Kapalis MJ, Harris M, et al. Aminophylline does not protect against radiocontrast nephropathy in patients undergoing percutaneous angiographic procedure.
J Invasive Cardiol 2001; 13: 738-740
81. Erley CM, Duda SH, Rehfuss D, et al. Prevention of radio contrast-media-induced nephropathy in patients with pre-existing renal insufficiency by hydration in combination with the adenosine antagonist theophylline. Nephrol Dial Transplant 1999; 14:1146-1149
82. Heyman SN, Brezis M, Epstein FH et al. Earily renal medually hypoxic injury from radiocontrast and indomethacin. Kidney Int 1991; 40:632-642
83. Stevens MA, McCullough PA, Tobin KJ, et al. A prospective randomized trial of prevention measure in patients at high risk for contrast nephropathy.
J Am Coll Cardiol 1999; 33:403-411
84. Kramer BK, Kammerl M, Schweda F, et al. A primer in radiocontrast induced nephropathy. Nephrol Dial Transplant 1999; 14: 2830-2834
85. Atkins JL. Effect of sodium bicarbonate preloading on ischemic renal failure. Nephron 1986; 44:70-74
86. Mertern GJ, Burgess WP, Gray LN, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. J A M A 2004; 291:2328-2334
87. Vogt B, Ferraip, Schoenholzer C, et al. Prophylatic hemodialysis after radiocontrast media in patients with renal insufficiency is potientially harmful. Am J Med. 2001;111: 692-698
88. Marenzi G, Marnna I, Laurig G, et al. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. N Engl J Med 2003; 349:1333-1340

89. Pollck DM, Polakonski JS, Wegner CD, et al. Beneficial effect of ETA receptor blockade in rat made of radiocontrast-induced nephropathy.
Ren Fail 1997; 19:753-761
90. Gross P, Bussemaker E. Endothelin: What role in acute contrast nephropathy? Nephro Dial Transplant 1996; 11:1716-1718
91. Wang A, Holcslew T, Beshore TM, et al. Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. Kidney Int 2000; 57:1675-80
92. Marygulies KB, Mckinley LJ, Allgren RL, et al. Intraarterial atrial natriuretic factor (ANF) attenuates radiontrast induced nephropathy in human (abstract).
J Am Soc Nephrol 1991; 2: 666A
93. Kurnik BR, Allgren RL, Genter FC, et al. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. Am J Kidney Dis 1998; 31:674-80
94. Koch JA, Plum J, Grabensee B, Modder U: Prostaglandin E1: a new agent for the prevention of renal dysfunction in high-risk patients caused by radiocontrast media? Nephrol Dial Transplant 2000; 15: 43-49
95. Khoury Z, Schlich JE, Como J, et al. The effect of prophylactic nifedipine on renal function in patients administered contrast media. Pharmacotherophy 1995; 15:59-65
96. Spangberg-Viklund B, Berglind J, Nikonoff T et al. Does prophylactic treatment with felodipine, a calcium antagonist, prevent low-osmolar contrast-induced renal dysfunction in hydrated diabetic and nondiabetic patients with normal and moderately reduced renal function? Scand J Urol Nephrol 1996; 30: 63-68
97. Thomsen HS. Guideline for contrast media from the European Society of Urogenital Radiology. Am J Roentgenol 2003; 181:1463-1471
98. Billinger M, Hessom, Meier B. Prevention of contrast-induced renal dysfunction by N-acecysteine: truth or myth? Eur heart J 2004; 25:188-9
99. 2003 European Society of Hypertension-European Society of Cardiology guideline for the management of arterial hypertension. Journal of Hypertension 2003; 21:1011-1053
100. Report of WHO Consulation, Definition, diagnosis and classification of diabetes mellitus and its complication. Part 1 Diagnosis and classification of diabetes mellitus. World Health Organization, Department of Noncommunicable Disease Surveillance, Geneva, 1999.
101. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NECP) expert panel on education, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel Ⅲ). JAMA 2001; 285:2486-2497

102. World Health Organization: Iron Deficiency Anemia: Assessment, Prevention and Control. A Guide for Program Managers. Geneva. WHO, 2001, 33-45
103. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41
104. National Kidney Foundation kidney Disease Outcome Quality Initiative Advistory Board. Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guideline for chronic kidney disease: evaluation, classification and stratification.
Am J Kidney Dis 2002; 39 Suppl: S1-246
105. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the anagement of patients with unstable angina and non-ST-segment elevation myocardial Summary article: A report of the American Colllege of infarction-2002: Cardiology/ American Heart Association Task Force on practice Guidelines (Commitee on the Management of Patients With Unstable Angina). Circulation 2002; 106:1893
106. Braunwald E: Unstable angina: A classification. Circulation 1989, 80: 410
107. Dangas G, Lakovou I, Nikolsky E, et al. Contrast induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. Am J Cardiol 2005; 95:13-19
108. Nikolsky E, Mehran R, Lasic Z, et al. Low hemotorit predicts contrast-indeced nephropathy after percutaneous coronary interventions. Kidney International 2005; 67: 706-713
109. Moore RD, Steinberg EP, Power NR, et al. Nephrotoxicity of high osmolality versus low-osmolity contrast media, randomized clinical trial. Radiology 1992; 182: 649-655
110. Vlietstra RE, Nunn CM, Narvarte J, et al. Contrast nephropathy after coronary angiography in chronic renal insufficiency. Am Heart J 1996 ;132:1049-1050
111. Marenzi G, Lauri G, Assanelli E, et al. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 2004; 44:1780-5
112. Gruberg L, Mehran R, Dangas G, et al. Acute renal failure requiring dialysis after percutaneous coronary intervention. Cathet Cardiovase Interven 2001; 52:409-416
113. Rich MW, Crecelius CA. Incidence, risk factor and clinical course of acute renal insufficiency after cardiac catheterization in patients 70 years of age or older, prospective study. Arch intern Med 1990; 150:1237-1242
114. Berns AS. Nephrotoxicity of contrast media. Kidney Int. 1989; 36:730-740
115. Cigarroa RG, lange RA, Willians RH, Hillis LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am J Med 1989; 86:649-652

116. Byrd L, Sherman RL. Radiocontrast-induced acute renal failure: a clinical and pathophysiologic review. Medicine 1979;58:270-279
117. Lautin EM, Freeman NJ, Choenfeld AH, et al. Radiocontrast-associated renal dysfunction: incidence and risk factors. AJR Am J Roentgend 1991; 157:49-58
118. Rudnick MR, Goldberg S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized teial. Kidney Int 1995; 47: 254-261
119. Levey AS, Greene T, Kusek JW, et al. A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol. 2000; 11: 155A
120. Dries Dl, Exner DV, Domanski MJ, et al. The prognostic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000; 35:681-689
121. Astor BC, Munter P, Levin A, et al. Association of kidney function with anemia. Arch Intern Med 2002 ;162:1401-1408
122. Kim SJ, Salem MR, Joseph NJ, et al. Contrast media adversely affect oxyhemoglobin dissociation. Anesth Analg 1990;71:73-76
123. Persson PB, Hansell P, Liss P. Pathophysiology of contrast medium-induced nephropathy. Kidney International 2005;68:14-22
124. Sandhu C, Newman DJ, Morgan R, et al. The role of oxygen free radical in contrast induced Nephrotoxicity. Acad Radiol 2002;9:S436-S437
125.Galli F, Piroddi M, Annetti, et al. Oxidative stress and reactive oxygen species. Contrib Nephrol 2005;149:240-260
126. Siems W, Carluccio F, Radenkovic S, et al. Oxidative stress in renal anemia of hemodialysis patients is mitigated by epoetin treatment. Kidney Blood Res 2005, 28,295-301
127. Siems W, Sommerburg O, Grune T. Energie-und Radikalstoffwechsel der Erythrozyten. Nieren-und Hochdruckkrankheiten 1999,suppl: S14-S23
128. Grune T, Sommerburg O, Siems. Oxidatever stress bei anämie.
Nieren-und Hochdruckkrankheiten 1999,suppl: S24-S29
129. Siems W, Carluccio F, Jakstadt M, et al. Erhöhte Serumkonzentrationen kardiotoxischer Lipideroxidationsproduckte bei chronischer Niereninsuffizien in Abhängigkeit vom Grad der renalen Anämie. Nieren-und Hochdruckkrankheiten 2002, suppl: S22-S27
130. Briggs JP, Schnermann J. Macula densa control of rennin secretion and glomerular vascular tone: evidence for common cellular mechanism. Ren Physiol. 1986; 9:193-203
131. Barret BJ, Carlisle EJ: Meta-analysis of the relative nephrotoxicity of high and low-osmolity iodinated contrast media. Radiology 1993; 188:171-178

132. Schwab SJ, Hlathy MA, Pieper KS, et al. Contrast nephrotoxicity, A randomized controlled trial of nonionic and an ionic radiographic contrast agent. N Engl J Med 1989; 320:149-153
133. Chalmer N, Jackson RW: Comparison of iodixanol and iohexol in renal impairment. Br J Radiol 1999; 72:701-703
134. Harris KG, Smith TP, Cragg AH, Lemke JH. Nephrotoxicity from contrast material in renal insufficiency: ionic versus nonionic agents. Radiology 1991;179: 849-52
135. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 2003; 348(6):491-499
136. Stone GW, McCullough PA, Tumlin JA, et al. CONTRAST investigators Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. J A M A 2003; 290:2284-2291
137. Sharma S, Kini A. Effect of nonionic radiocontrast agents on the occurance of contrast-induced nephropathy in patients with mild-moderate chronic renal insufficiency: pooled analysis of the randomized trials. Cathet Cardiovase Interven 2005; 65: 386-393
138. Aspelin P, Aubry P, Fransson SG, et al. Cost- effectiveness of iodixnol in patients at high risk of contrast-induced nephropathy. Am Heart J 2005; 149: 298-303
139. Mccullough PA, Bertrand ME, Brinker JA, et al. A meta-analysis of the renal safety of isomolar iodixamol compared with low-osmolar contrast media. J Am Coll Cardiol 2006;48:692-699
140. Hizoh I, Haller C. Radiocontrast-induced renal tubular cell aptosis: hypertonic versus oxidative stress. Invest Radiol 2002;37:428-434
141. Gross P, Bussemaker E. Endothelin: what role in acute contrast nephropathy? Nephrol Dial Transplant 1996; 11:1176-1178
142. Baliga R, Ueda N, Walker PD, et al. Oxidant mechanism in toxic acute renal failure. Am J Kidney Dis 1997; 29:465-477

8. Acknowledgements

I am deeply thankful to my supervisor, Priv-Doz. Dr. Wolfgang Bocksch for offering me the opportunity to undertake my doctoral project in the catheterization laboratory. Many thanks to his advice, guidance and encouragement in my research work through this study. Also his critical reading of this manuscript and insight comments are highly appreciated. The way he shows me is invaluable for my future work and life.

I also extend my sincere thanks to Dr. Juergen Waigand, Dr. Martin Steeg and Dr. Sonja Huehus for their kind help in accomplishing my research.

I wish to express my thanks to Prof. Dr. Yu-Guo Weng. I will never forget his kind help and care in my work and life.

In addition, I am grateful to all members of the catheter laboratory for their help.

Thanks also to Dr.Wenyu Dong, Dr. Shizheng Mao, Dr. Jianpei Li and Dr. Feiqiong Huang for their valuable suggestions in my thesis.

Furthermore, I would like to show my thanks to my old friend Martin Dinziol, Iganaz and his wife Henny, Peter and his wife Stephanie. I appreciate and cherish their warm friendship and help.

Special and warmest thanks to Kathy Whitt, Yunying Wu, Tianyu Chen, Xiaoning Miao, Xinan Guo, Xiuxia Tang, Huaiyu Mu, Chunyan Lei, Xiaobei Tang and all the other Chinese friends for their warm friendship, encouragement and help.

Finally, I devote this thesis to my wife Qiuning Yang and my daughter Chunyang Li for their understanding and support. Special appreciation to my parents in law for their taking care of my daughter all throughout my study in Berlin.

9. Curriculum Vitae

Due to protection of data privacy the Curriculim Vitae is not published online

10. Erklärung

„Ich, Wenhua Li, erkläre, dass ich die vorgelegte Dissertationschrift mit dem Thema:
´ Risk of Contrast-Induced Nephropathy (CIN) after Diagnostic Cardiac Catheterization and Percutaneous Coronary Intervention Using Iopromide ´
selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.“

Berlin, im November 2006 Wenhua Li