Chapter 18

Contrast-Induced Nephropathy: Risk Factors, Clinical Implication, Diagnostics Approach, Prevention

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Additional information is available at the end of the chapter

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1. Introduction

Contrast induced nephropathy (CIN) is an important and well-known complication in patients with chronic renal insufficiency undergoing both coronary angiography and coronary interventions. The estimated incidence of CN after coronary angiography was around 15%. In fact, CIN is the third leading cause of acute renal failure in hospitalized patients [1]. CIN is usually transient disorder, but in some cases may result in residual permanent renal damage, prolong hospital stay and increase medical cost [2]. Renal failure increases the risk of developing severe nonrenal complications that can lead to death. The mortality rate in subjects without renal failure was 7%, compared with 34% in patients with renal failure [3]. With the increasing number of patients undergoing percutaneous coronary intervention, it is expected that the burden of such iatrogenic complications will exponentially increase and effective preventive measures are necessary.

2. Definition of CIN

Contrast induced nephropathy is an important cause of nosocomial renal impairment. This deleterious effect of contrast agents on renal function is defined as an impairment of renal function with increase in serum creatinine level by more than 25% or 44umol/l occurring within 3 days after intravascular administration of contrast agents and in the absence of alternative cause [4].

3. Incidence and clinical significance of CIN:

The incidence of CIN in the general population has been estimated to be less than 2% [5]. However in high risk patients the incidence can increase to more than 50%. Pre-existing renal impairment and diabetes mellitus have been identified as the main conditions predisposing to the development of CIN. Other risk factors include decreased effective blood volume, age > 75 years, heart failure, use of non-steroid anti-inflammatory drugs, diuretics, previous parenteral contrast medium administration within 72 hours and large volume of contrast medium [6].

During the last two decades the number of computed tomographies has increased by 800% and between 1979 and 2002 the number of percutaneous cardiac interventions in the USA has risen by 390% [7]. As the number of susceptible patients exposed to parenteral iodinated contrast media expands, contrast-induced nephropathy represents an ever-growing clinical problem. Meanwhile, the main predisposing factors for CIN, namely diabetes mellitus and previous renal impairment are currently augmented. CIN represents the third most frequent cause of hospital acquired acute renal failure.

The first reported case of CIN was an acute renal failure following intravenous pyelography with 20 ml of Diodrast in patient with myelomatosis in 1954 year [8].

Renal failure following exposure to radiocontrast agents is usually nonoliguric. Creatinine rises within 48 hours, peaks 4 to 5 days after exposure and returns to baseline in 7 to 10 days. Complete recovery is expected in more than 75% of patients, who develop this complication, but approximately 10% requires dialysis [9]. Introduction of low- and iso-osmolar contrast media has resulted in decreased frequency of contrast-induced nephropathy [10].

Effect and safety of iodixanol, a new generation iso-osmolar contrast medium, even when administered to high-risk patients was assessed in the Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media (NEPHRIC) study [11]. In this multicenter randomized study were enrolled patients with diabetes mellitus (type 1 or 2) and either a stable serum creatinine concentration (133 to 308 μmol per liter for men and 115 to 308 μmol per liter for women) as measured within three months before enrollment referred for coronary or aortofemoral angiography, had or a calculated creatinine clearance of no more than 60 ml per minute, according to the formula of Cockcroft and Gault. Study was designed to compare the renal effects of a nonionic, iso-osmolar, dimeric contrast medium, iodixanol (320 mg of iodine per milliliter; 290 mOsm per kilogram of water), with nonionic, low-osmolar, monomeric contrast medium iohexol (350 mg of iodine per milliliter; 780 mOsm per kilogram of water). Iodixanol induced a significantly smaller mean increase in the serum creatinine level than did iohexol. The peak increase in the serum creatinine concentration within three days after the administration of contrast medium was 11.2 μmol per liter in the iodixanol group, as compared with 48.2 μmol per liter in the iohexol group (P=0.001). The effect of the base-line serum creatinine concentration was different in the two groups. Among patients who received iohexol, but not among those who received iodixanol, a higher base-line serum creatinine concentration was associated with a higher

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peak increase between day 0 and day 3 (P for interaction <0.001). Peak increase of serum creatinine level was higher in iohexanol group (Figure 1).

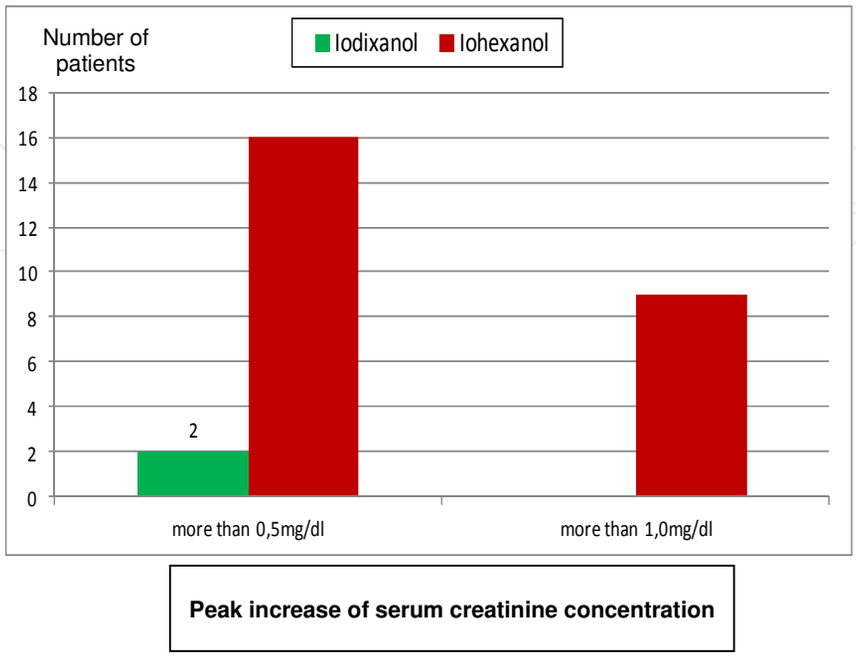

Figure 1. Nephrotoxicity in iodixanol and iohexanol

All seven serious events deemed to be related to contrast medium occurred in the iohexol group; five patients in this group had acute renal failure related to the use of iohexol, and one patient had both acute renal failure and arrhythmia related to the use of iohexol. Three of these six patients recovered, two died, and one had persistent renal failure. [11].

CIN is a significant cause of morbidity and mortality.

Renal failure increases the risk of developing severe nonrenal complications that can lead to death. In analysis of 16 248 patients undergoing radiocontrast procedures, were identified 183 subjects who developed contrast media associated renal failure. These cases were matched for age and baseline serum creatinine level, with 174 paired subjects, who underwent similar contrast procedures but without developing renal failure. The mortality rate in subjects without renal failure was 7%, compared with 34% in patients with renal failure (odds ratio, 6,5; *P*<0,001). After adjusting for differences in co morbidity, renal failure was associated with an odds ratio of dying of 5,5. Subjects who died after developing renal failure had complicated clinical courses characterized by sepsis, bleeding, delirium, and respiratory failure; most of these complications developed after the onset of renal failure [3].

Likelihood of death increases approximately 8.5-13.5 times in patients with CIN and need for hemodialysis comparing with CIN patients but without hemodialysis [12, 13].

Observation made by Gruber and coworkers confirmed that acute renal failure that requires dialysis after percutaneous coronary interventions is associated with very high in-hospital

and 1-year mortality rates and a dramatic increase in hospital resource utilization. They compared clinical course in 51 consecutive patients who were not on dialysis on admission and developed acute renal failure that required in-hospital dialysis after coronary intervention and 7 690 patients who did not require dialysis after PCI. Patients who required dialysis were older, with a higher incidence of hypertension, diabetes, prior bypass surgery, chronic renal failure, and a significantly lower left ventricular ejection fraction. Despite similar angiographic success, these patients had a higher incidence of in-hospital mortality (27.5% vs. 1.0%, $P < 0.0001$), non–Q-wave myocardial infarction (45.7% vs. 14.6%, $P < 0.0001$), vascular and bleeding complications, and longer hospitalization. At 1-year follow-up, mortality (54.5% vs. 6.4%, $P < 0.0001$), myocardial infarction (4.5% vs. 1.6%, $P = 0.006$), and event-free survival (38.6% vs. 72.0%, $P < 0.0001$) were significantly worse in patients who required dialysis compared to patients who did not [12].

Similarly, analysis of 1 826 consecutive patients undergoing coronary intervention from aspect of the incidence, predictors, and mortality related to acute renal failure (ARF) and acute renal failure requiring dialysis (ARFD) after coronary intervention has shown that occurrence of ARFD after coronary intervention is rare (<1%) but is associated with high in-hospital lethality and poor long-term survival. Individual patient risk can be estimated from calculated CrCl, diabetic status, and expected contrast dose prior to a proposed coronary intervention [13]. The incidence of ARF and ARFD was 144,6/1,000 and 7,7/1,000 cases respectively. The cutoff dose of contrast below which there was no ARFD was 100 ml. No patient with a CrCl > 47 ml/min developed ARFD. These thresholds were confirmed in the validation set. Multivariate analysis found CrCl [odds ratio

Variable (%)	CIN (n=254)	**No CIN (n=7332)**	**P-value**
Procedural success	72,8	94,0	< 0,0001
Death	22,0	1,4	< 0,0001
Q-wave myocardial infarction	3,9	0,9	< 0,0001
Creatinine kinase elevation	16,9	6,1	< 0,0001
Shock	13,0	3,1	< 0,0001
Cardiac arrest	11,4	1,5	< 0,0001
Intraaortic balloon pump use	11,4	3,1	< 0,0001
Femoral bleeding	3,1	1,4	0,03
Stroke	1,2	0,03	0,05
Adult respiratory distress syndrome	9,4	0,7	< 0,0001
Gastrointestinal bleeding	4,3	1,2	< 0,0001

CIN = contrast induced nephropathy

Table 1. Procedural complications in patients both with and without CIN after coronary intervention

(OR) = 0.83, 95% confidence interval (CI) 0.77 to 0.89, P <0.00001], diabetes (OR = 5.47, 95% CI 1.40 to 21.32, P = 0.01), and contrast dose (OR = 1.008, 95% CI 1.002 to 1.013, P = 0.01) to be independent predictors of ARFD. The in-hospital mortality for those who developed ARFD was 35,7% and the 2-year survival was 18,8% [13].

Moreover, development of CIN significantly prolongs hospitalization among survive patients and is often associated with increased procedural complications rate (table 1) [2].

4. Contrast agents

All modern contrast agents are based on iodine, because of its high atomic number and chemical versatility has proved to be an excellent agent for intravascular opacification. First reported parenteral application of an iodinated contrast agents was during an intravenous pyelography in 1919. Inorganic sodium iodide cause often toxic reactions. In 1929 was explored an organic iodide preparation with one iodine atom per benzoic acid ring and in 1950s, more substituted tri-iodobenzoic acid derivates were developed (with three iodine atoms per ring). Specific side chains in position 1, 3 and 5 influence both solubility and toxicity.

First generation contrast agents were ionic monomers containing a benzene ring with three iodine atoms, exhibiting high osmolarity in the range of 1500 to 1800 mOsm/kg (high osmolar contrast agents), roughly six times that of blood. This ratio-1,5 ionic compounds are substituted ionic triiodobenzoic acid derivatives that contain three atoms of iodine for every two ions (substituted benzoic acid ring and accompanying cation). To have an iodine concentration of 320 do 370 mg I/ml, as is required for coronary artery angiography, solution of these agents are extremely hypertonic with osmolarity more than 1500 mOsm/kg (Figure 2).

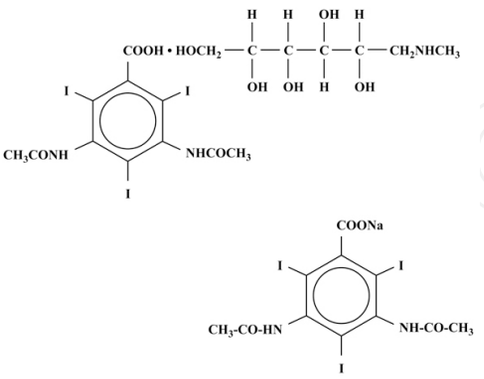

Figure 2. Ionic monomer contrast agent (Diatrizoat)

Ratio-3 lower-osmolarity contrast agents were introduced in 1980s. This contrast ages (ioxaglate) was still ionic with dimeric structure that include six molecules iodine on the dimeric ring (three atoms of iodine per one ion) (Figure 3).

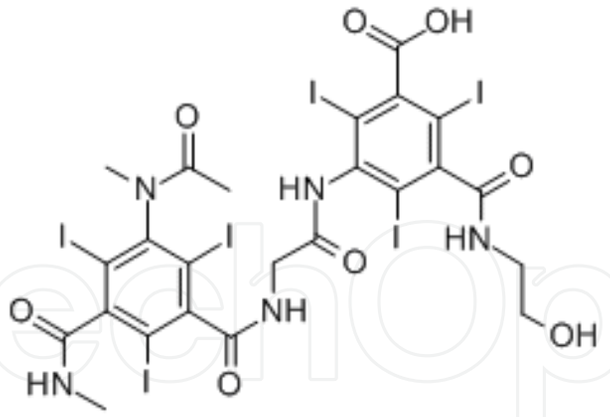

Figure 3. Ionic dimeric contrast agent (Ioxaglate)

The introduction of nonionic ratio-3 contrast agents was very important step in late 1980s. An iodine content of 320 to 370 mg I/ml can be achieved with an osmolarity of 600 to 700 mOsm/kg (between two and three times that of blood) (low osmolar contrast agents). Their viscosity is approximately 6 to 10 times that of water (Figure 4).

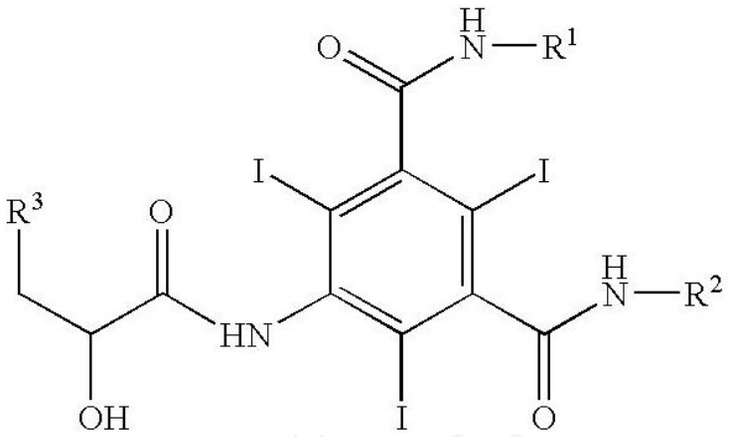

Figure 4. Nonionic monomer contrast agent (iopamidol)

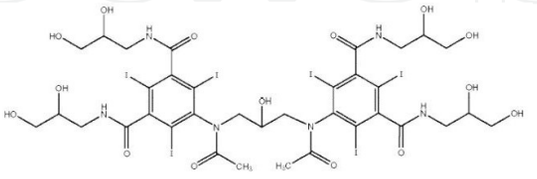

Figure 5. Nonionic dimeric contrast agent (Iodixanol)

Third generation agents are dimmers almost iso-osmolar to plasma (iso-osmolar contrast agents) but with increased viscosity, which results in complicated injection through small vascular catheters. This iso-osmolar contrast agent is a ratio-6 nonionic dimeric compound

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(iodixanol). There are data suggesting a reduction of nephrotoxicity with this agent [11]. Nevertheless even third generation contrast agents have been implicated by some authors for potential nephrotoxicity [14] (Figure 5).

The osmolarity of a solution is proportional to the number of dissolved particles (ions, molecules). Thus, the osmolarity of contrast agent solution can be decreased by increasing the number of iodine atoms per dissolved particle (Table 2).

COMPOUND	Iodine atoms	Particles	Ratio
Ionic monomers	3	2	1,5
Nonionic monomers	3	1	3,0
Ionic dimmers	6	2	3,0
Nonionic dimmers	6	1	6,0

Table 2. Osmolarity in the four categories of contrast media

In table 3 are summarized properties of current available contrast agents.

CLASS	EXAMPLES	IODINE (mg I/ml)	Osmolarity (mOsm/kg)	Viscosity (at 37°C)
High-osmolar ionic Ratio 1,5 (3:2)	Diatrizoate	370	2076	8,4
	iothalmate	325	1797	2,8
Low-osmolar nonionic Ratio 3 (3:1)	Iopamidol	370	796	9,4
	Iohexol	350	844	10,4
	Ioversol	350	792	9,0
	Ioxilan	350	695	8,1
Low-osmolar ionic dimmer Ratio 3 (6:2)	Ioxaglate	320	600	7,5
Iso-osmolar nonionic dimmer Ratio 6 (6:1)	Iodixanol	320	290	11,8

Table 3. Properties of available contrast agents

5. Patothophysiology of CIN:

The exact pathogenesis of CIN is still unclear. Several injury pathways have been proposed. Important possible pathogenetic mechanisms of CIN involve:

a. a medullar hypoxia due to altered hemodynamics, which in the presence of impaired adaptive responses leads to tubular damage and

b. a direct cytotoxic effect of the contrast agents on tubular cells.

Probably, a combination of various pathophysiologic mechanisms is involved. The contrast agent may have direct cytotoxic effects due to relatively high tissue osmolarity. The contrast medium induces renal vasoconstriction, leading to tubular injury or even necrosis.

It has been shown in experimental animal model that after parenteral administration of contrast media they exhibit short-term renal vasodilatation, which is followed by prolonged vasoconstriction, resulting in a decrease in total renal blood flow and a reduction of glomerular filtration rate [15].

Elevated endothelia levels and other vasoconstrictor levels were detected in patients with CIN. Administration of radiocontrast agents in normal rats induces endothelia release [16]. Subsequent reperfusion injury may increase free radical formation and create oxidative stress. The contrast medium may precipitate with Tamm- Horsfall glycoprotein in distal tubule lumen and form casts [17].

Increased adenosine-induced renal vasoconstriction in combination with attenuated renal NO-dependent vasodilatation, may account for the predisposition of diabetic patients to CIN [18].

There is a relationship between osmolarity and viscosity in monomeric contrast media (Figure 6) [19].

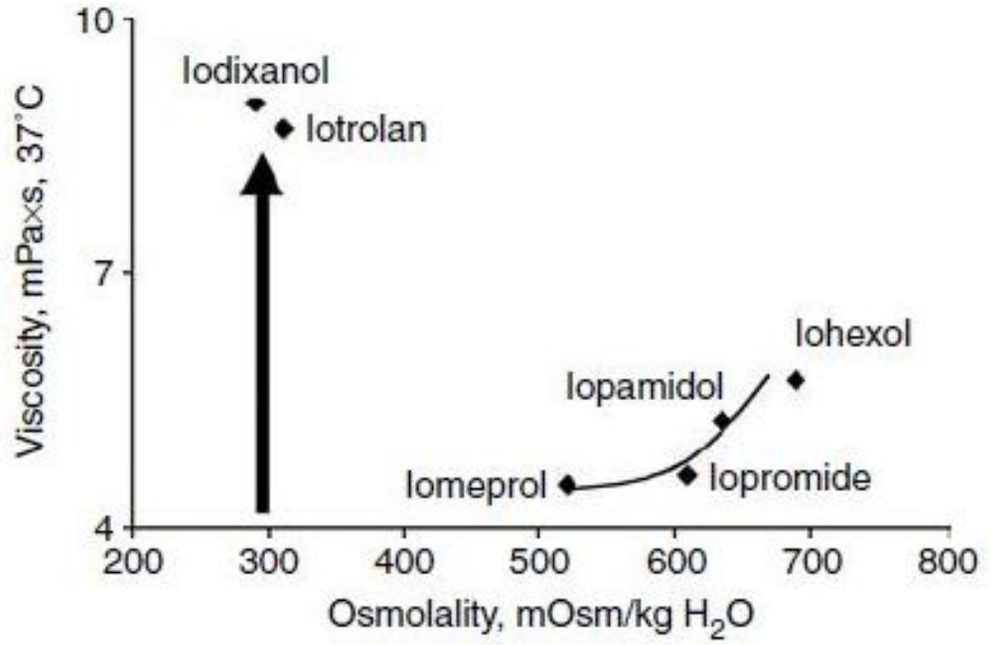

Figure 6. Osmolarity and viscosity for I-concentration of 300 mg/ml

Available izo-osmolar contrast agents exhibit considerably higher viscosity and should impair renal medullar blood flow to a greater extent than low osmolar agents. This situation is indicated by a particularly reduced pO2 levels caused by iso osmolar contrast media in experimental model (Figure 7) [20].

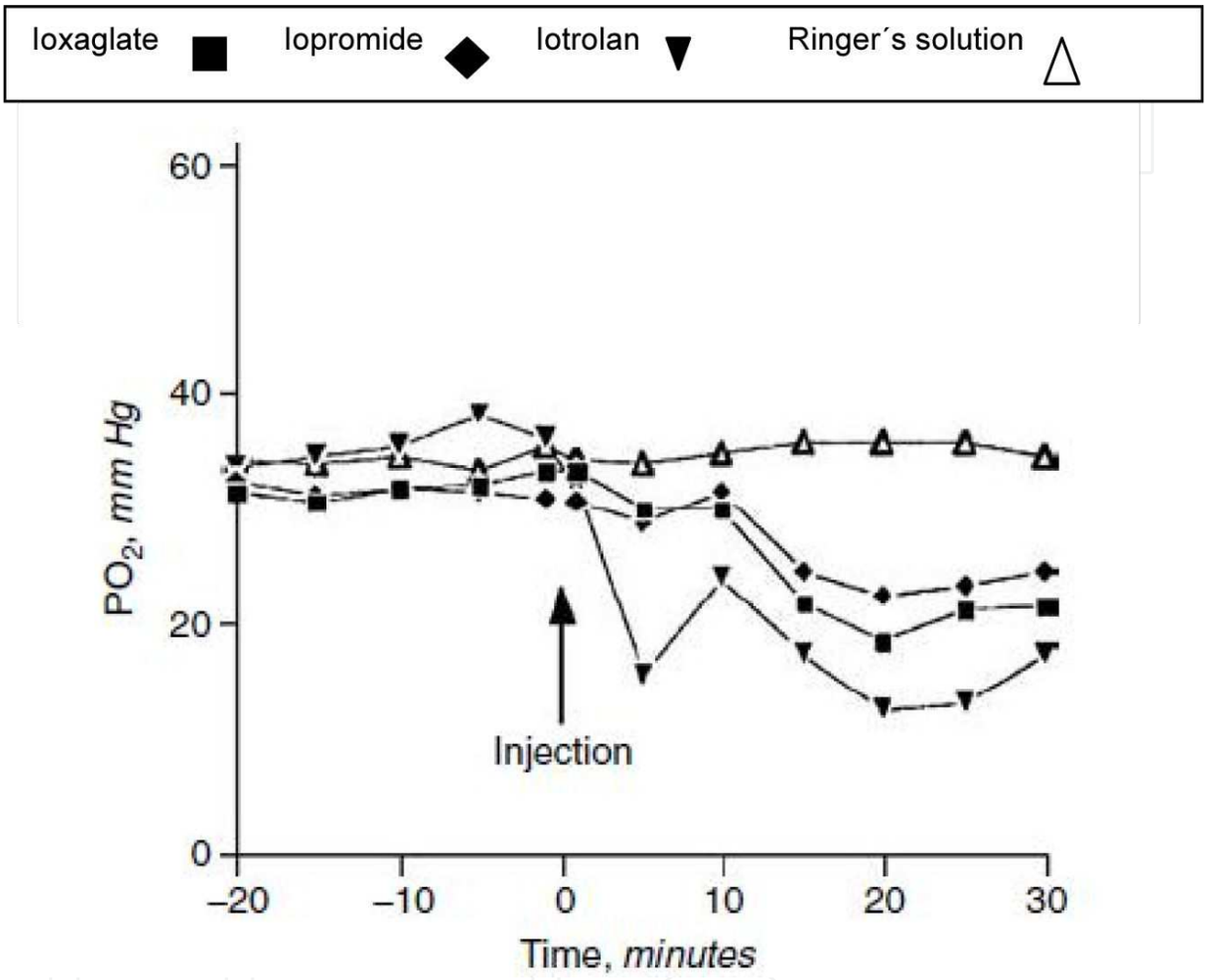

Figure 7. Medullar hypoxia induced by contrast media (ioxaglate, iopromide, and iotrolan in comparison to Ringer's solution).

Reduction of pO2 is greater for iotrolan (iso-osmolar nonionic dimer) followed by ioxaglate (low-osmolar ionic dimer). Iopromide (low-osmolar monomer) had the least effect of the contrast media.

Tubular viscosity will increase markedly toward distal sections of the kidney due to fluid reabsorbtion. When urine becomes very concentrated, tubular fluid viscosity will increase and tubular plugging may occur. Hydration attenuates fluid reabsorbtion in the collecting ducts and is therefore very beneficial [19].

Adverse effects of pronounced increases of viscosity on the kidney are schematically shown in figure 8 [19].

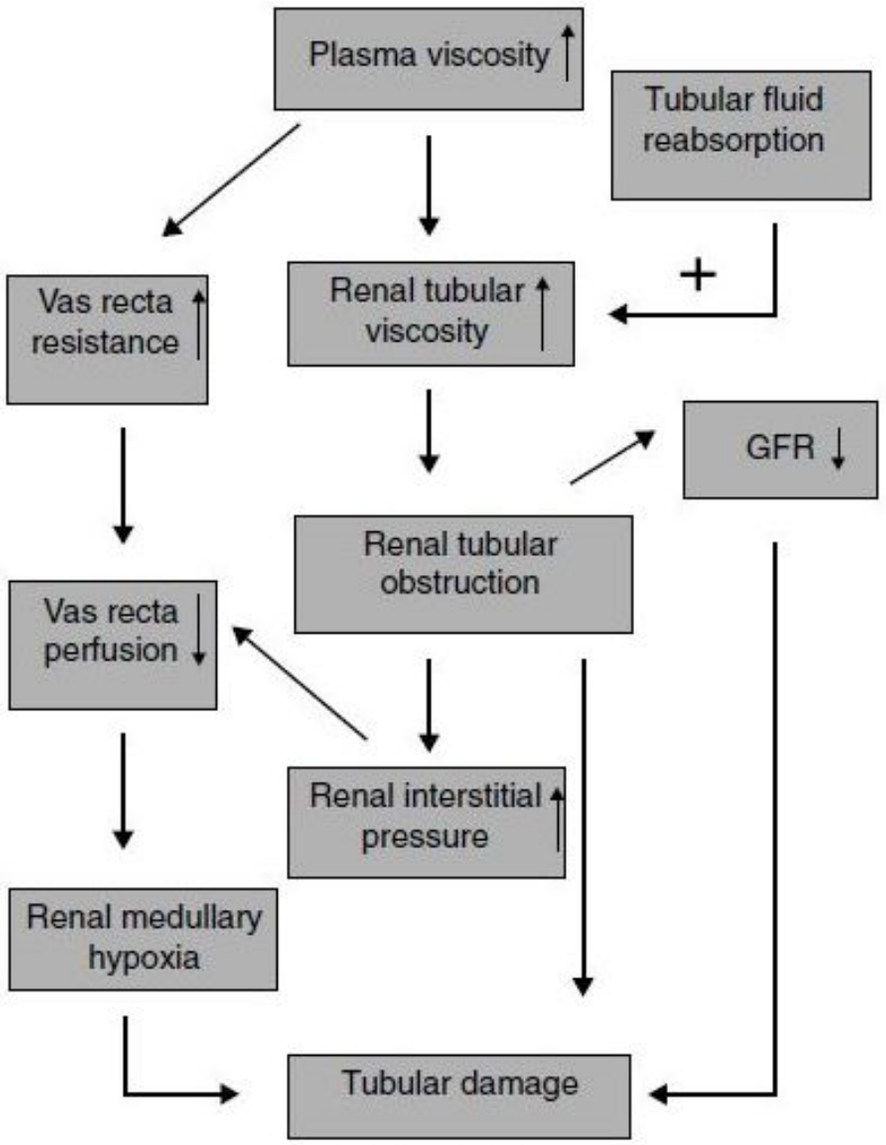

Figure 8. Flow chart of mechanisms linking fluid osmolarity to renal damage, GFR = glomerular filtration rate

As a consequence of contrast media administration, tubular cell damage can occur. Except for vacuolization, there was described pertubation of mitochondrial enzyme activity and mitochondrial membrane potential as a cause of alteration of proximal tubular functions (Figure 9) [21].

Extend of mitochondrial enzyme activity impairment relies primarily on two features of the contrast media: ionicity and the molecular structure. Remarkably, low-osmolar (monomeric) contrast media had the least effect, followed by the iso-osmolar (dimeric, nonionic) agents. Ionic compounds revealed the most profound effects [21].

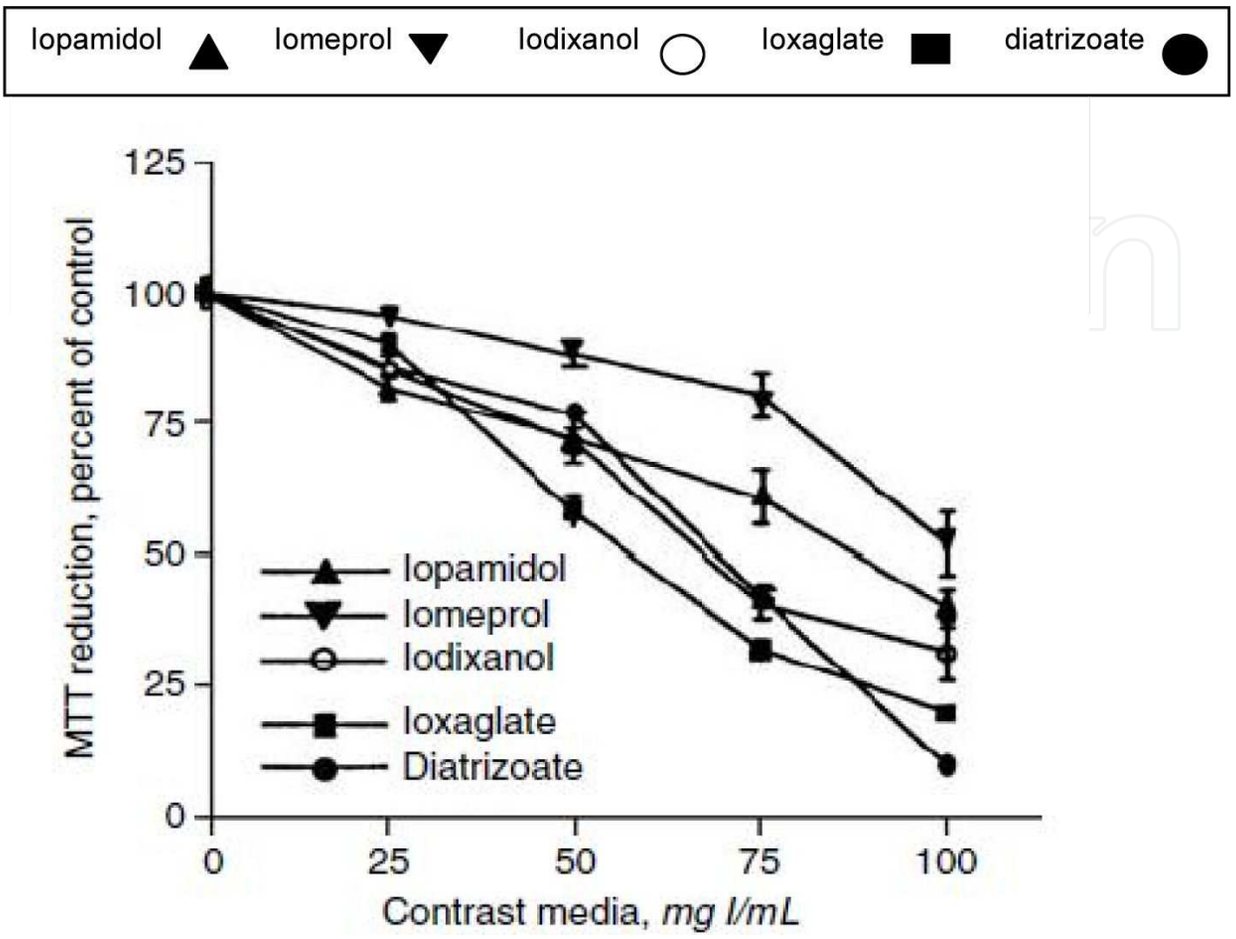

Figure 9. Altered mitochondrial function in a proximal tubular cell line as determined by 3- (4,5-dimethylthiasol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction (24-hour treatment)

The least influence was found by the low-osmolar agents, followed by theiso-osmolar contrast media (Iodixanol). The ionic substances showed the greatest effect.

6. Risks factors

Numerous studies have identified predisposing risk factors such as preexisting chronic kidney disease, particularly diabetic kidney disease, degree of renal dysfunction, volume depletion, co administration of nephrotoxic agents, high doses of radiocontrast, particularly ionic and high osmolar, repeated examinations at short intervals, as well as advanced cardiac failure [22, 23], perhaps also age, smoking, and hypercholesterolemia [23].

Multiple CIN risk factors, including both patient's factors and procedural factors are summarized in table 4 and 5.

Baseline creatinine level or creatinine clearance
Diabetes mellitus
Female gender
Advanced age ("/> 70 year)
Nephrotoxic medication
Anemia
Acute coronary syndrome
Volume depletion, hypotension, hypovolemia
Low cardiac output
Intra aortic balloon pump use
Congestive heart failure
Renal transplantant patient
Hypoalbuminemia
Multiple myeloma

Table 4. Patients factors associated with CIN

Contrast agents amount
Osmolarity of contrast agents
Multiple contras media application within 72 hours

Table 5. Procedural factors associated with CIN

Risk factor	Score
Hypotension (syst. BP < 80mmHg for 1 h requiring inotropic support	5
Intra aortic balloon pump (within 24h periprocedurally)	6
Congestive heart failure. NYHA class III/IV	5
Age "/> 75 years	4
Anemia (hematocrit < 39% for mean and <36% for women)	3
Diabetes mellitus	3
Contrast media volume	1 for each 100 ml
Serum creatinine "/> 1,5 mg/ml	4
Estimated glomerular filtration rate < 60 ml/min/1,73m2	2 for 40-60ml/min/1,73m2 4 for 20-40ml/min/1,73m2 6 for < 20ml/min/1,73m2

Table 6. Risk factor scores for a predictive score for CIN

Most important predictor of CIN is baseline renal function (creatinine clearance < 60 ml/s). Presence of diabetes mellitus and the type and amount of contrast agents are strong risk factors as well ([24, 25].

Using these risk factors, there have been simple and reliable predictive scores for CIN developed (Table 6 and 7) [6, 26].

Risk score	Risk of CIN	Risk of dialysis
≤ 5	7,5%	0,04%
6-10	14,0%	0,12%
11-16	26,1%	1,09%
≥ 16	57,3%	12,6%

Table 7. Risk scores for CIN and outcomes

7. Prevention of CIN

At present there is no specific therapy, which could reduce or reverse development of the CIN, once it is occurs. However, there is possibility of CIN prophylaxis. There are available published data on many different methods of prevention, but many of them failed in efficiency and quality of study design. The most important step in preventing CIN is to determine whether a patient belongs to a risk group. If it is not so, there are not specific measures required. In the case of risk, it should be consider using another method of investigation without need for contrast agent.

7.1. Hydration

Hydration is the most important preventing tool consistently resulting in a decrease of CIN incidence.

In long-term study of 537 consecutive patients undergoing angiography (average dose of contrast agent 2ml/kg) there was not observed either clinical nor biochemical instance of acute renal failure, despite high risk profile of population. Prevalence of underlying clinical abnormalities was: prior stroke or myocardial infarction (58%), diabetes mellitus (33%), hypertension (46%), renal insufficiency (27%), liver disease (14%), proteinuria (14%), elevated uric acid level (13%). In 53% of patients two or more clinical abnormalities was detected. In 24%, there were two or more of the risk factors witch increased likelihood of renal failure. There was not restriction of fluids prior to angiography, infusing about 500 ml/hr during the procedure and encouraging fluids following the examination [27].

An important aspect is to ensure optimal volume repletion prior the procedure. It is recommended to parenterally administer of at least total 1 l of isotonic saline. Infusion usually begins at least 3 hours before and continues 6-8 hours after procedure. Initial infusion rate of

100-150ml/hr are recommended with adjustment post procedure as clinically indicated [28].Caution should be applied in the patient with reduced left ventricular ejection fraction or congestive heart failure.

Prospective, randomized, controlled, open-label study was organized to compare the incidence of CIN with isotonic or half-isotonic hydration [29]. Patient scheduled for elective or emergency coronary angioplasty were randomly assigned to receive isotonic (0,9% saline) or half-isotonic (0,45% sodium chloride plus 5% glucose) hydration beginning the morning of the procedure for elective intervention or immediately before emergency intervention. CIN was defined as increase of serum creatinine at least 44umol/l within 48 hours. There were 15,7% diabetics, 25,6% women and 20,7% patients had chronic renal insufficiency, in this study population (Table 8),

Characteristic	Isotonic (n=685)	Half-isotonic (n=698)	P value
Age, year	64 (63-65)	64 (63-65)	0,71
Female sex	178 (26%)	176 (25%)	0,74
Chronic renal insufficiency	138 (20%)	148 (21%)	0,92
Diabetes mellitus	107 (16%)	110 (16%)	0,94
Arterial hypertension	445 (65%)	425 (61%)	0,12
Previous MI	327 (48%)	353 (51%)	0,29
Acute MI	54 (8%)	60 (9%)	0,63
Single vessel disease	244 (36%)	251 (36%)	0,90
3-vessel disease	252 (37%)	236 (34%)	0,25
LVEF ≥ 60%	287 (42%)	285 (41%)	0,70
LVEF 45-60%	292 (43%)	313 (45%)	0,39
LVEF 30-45%	88 (13%)	82 (12%)	0,54
LVEF < 30%	18 (3%)	17 (2%)	0,82

LVEF= left ventricular ejection fraction, MI=myocardial infarction

Table 8. Baseline clinical characteristics

CIN developed in 5 patients with isotonic infusion vs. 14 patients with half-isotonic infusion. Therefore, incidence of CIN was significantly reduced with isotonic (0,7%, 95% confidence interval, 0,1%-1,4%) vs. half-isotonic (2%, 95% CI, 1,0%-3,1%) hydration (p=0,04) (Figure 10).

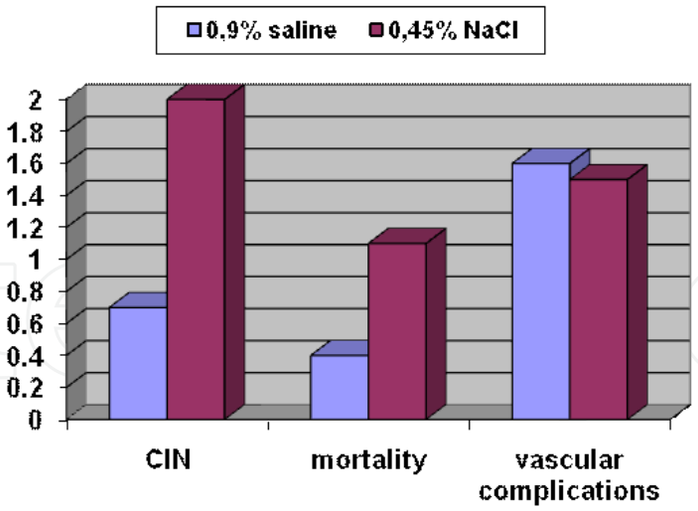

Figure 10. Incidence of CIN, mortality and peripheral vascular complications

Length of hospital stay was significantly increased in patients developing CIN in comparison without nephropathy (8,1 vs. 4,7 days, p<0,001). However, it was similar in both treatment regimens.

In multivariate risk factors analysis, female sex and baseline creatinine level were revealed as independent risk factors for CIN (Table 9).

Risk factor	P value	Odds ratio (95% confident interval)
Female sex	0,005	3,9 (1,5-10,1)
Baseline creatinine	<0,001	6,6 (3,2-13,8) *
Isotonic hydration	0,037	0,3 (0,1-0,9)

* for an increase in baseline creatinine of 88 µmol/l

Table 9. Multivariate risk factor analysis for the development of CIN

7.2. Bicarbonate

In single-center, randomized controlled trial was compared infusion of sodium chloride vs. sodium bicarbonate as the hydration fluid to prevent renal failure in patients with stable renal insufficiency undergoing diagnostic or interventional procedures requiring radiographic contrast [30]. Patients received 154 mEq/L of either sodium chloride or sodium bicarbonate, as a bolus of 3 ml/kg per hour for 1 hour before iopamidol contrast, followed by an infusion of 1 ml/kg per hour for 6 hours after the procedure.

The primary outcome (development of contrast-induced nephropathy, defined by an increase in serum creatinine of 25% or more within 2 days after administration of the radiographic contrast) was observed in 1.7% (1 of 60) patients receiving sodium bicarbonate compared with 13.6% (8 of 59) in patients who received sodium chloride (mean difference, 11.9%; 95% confidence interval [CI], 2.6%-21.2%; *P* = 0,02) Figure 11).

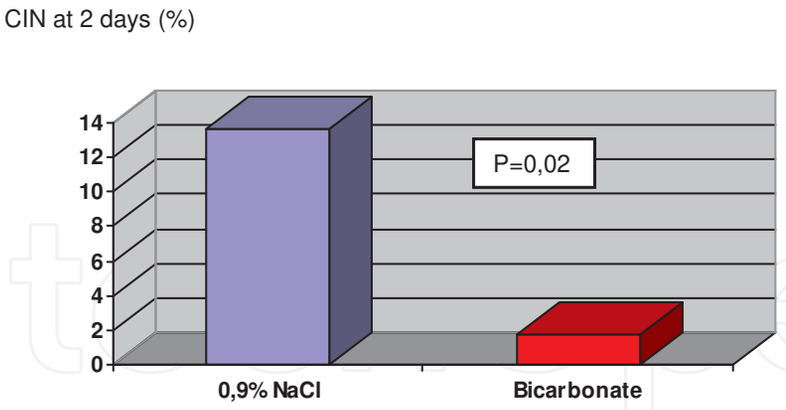

Figure 11. Prevention of CIN by bicarbonate

The absolute risk reduction of CIN, using sodium bicarbonate compared with sodium chloride was 11.9%, resulting in a number needed to treat of 8.4 patients to prevent 1 case of renal failure.

When results were analyzed by another common definition of CIN (at least ≥44.2 μmol/l change in serum creatinine), 7 (11.9%) of 59 patients who were treated with sodium chloride developed contrast nephropathy vs. only 1 (1.7%) of 60 who received sodium bicarbonate (mean difference, 10.2%; 95% CI, 1.3%-19.1%; *P* =0,03).

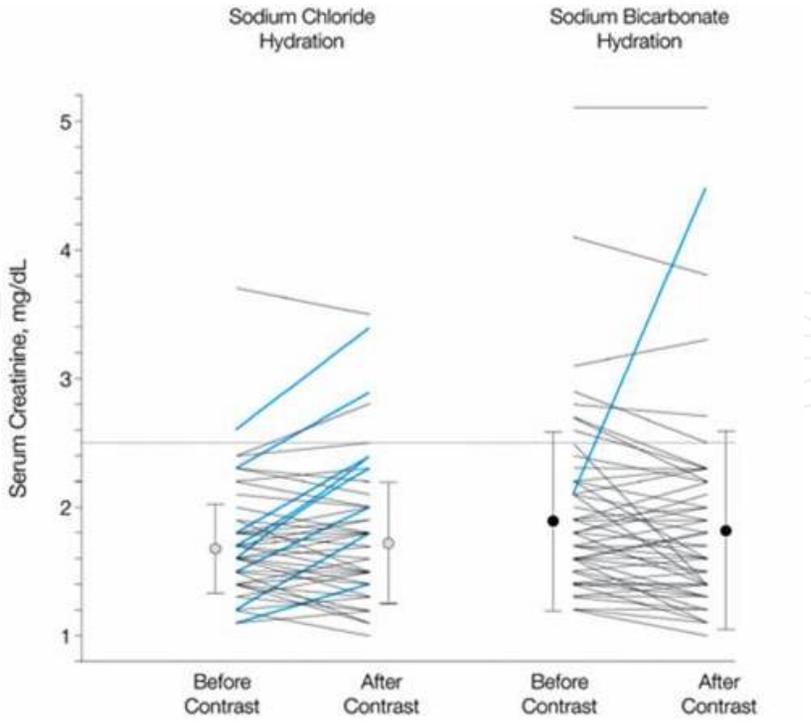

Figure 12. Percentage change in estimated glomerular filtration rate in randomized patients following contrast

Post hoc analysis revealed that the percentage change in glomerular filtration rate after contrast was significantly improved in patients receiving sodium bicarbonate treatment (+8.5%) compared with those receiving sodium chloride (–0.1%) (mean difference, –8.6%; 95% CI, −17.0% to −0.2%; *P* = 0,02) (Figure 12) [30].

Blue heavy lines represent cases of contrast-induced renal failure. Dotted line indicates threshold for severe renal insufficiency (serum creatinine ≥221 μmol/L).

Solomon R et al performed randomized comparison saline hydration and different types of diuretic strategies in patients scheduled for cardiac angiography who had serum creatinine concentrations exceeding 140 μmol/l or creatinine clearance rates below <1.0 ml/s [31].

All the patients received 0.45% saline intravenously at a rate of 1 ml /kg of body weight/1 hour beginning 12 hours before the angiography. This saline infusion was continued during the angiography (saline group) or was supplemented with 25 g of manitol, infused intravenously during the 60 minutes immediately before angiography (manitol group), or with 80 mg of furosemide, infused intravenously during the 30 minutes immediately before angiography (furosemide group). All the patients continued to receive 0.45 % saline intravenously at the same rate for 12 hours after angiography. A CIN was defined as an increase in the base-line serum creatinine concentration of at least ≥ 44 μmol per liter within 48 hours after the injection of radiocontrast medium.

Study confirmed that hydration with 0.45 percent saline for 12 hours before and 12 hours after the administration of radiocontrast agents was the most effective means of preventing acute decreases in renal function in patients with chronic renal insufficiency with or without diabetes mellitus. Neither manitol nor furosemide offered any additional benefit when added to this hydration protocol (Figure 13).

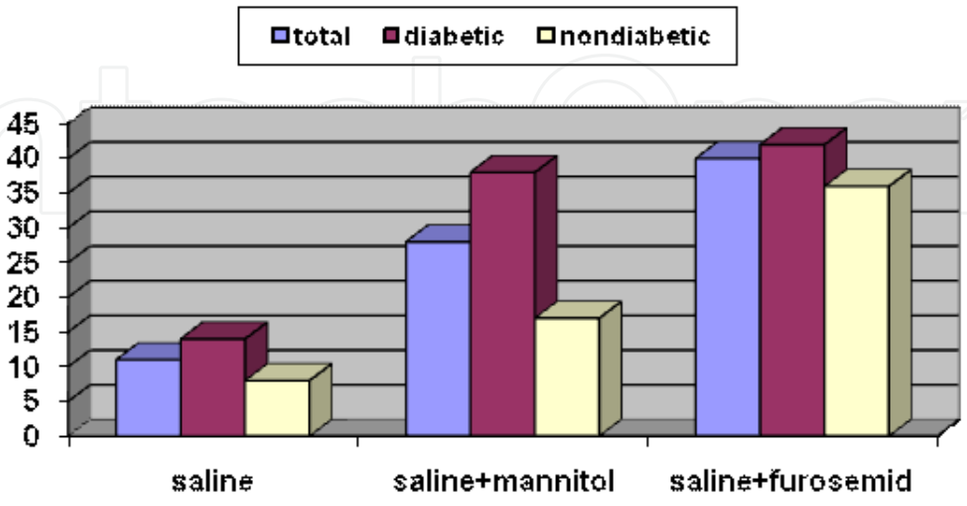

Figure 13. Effect of saline, manitol, and furosemide on the prevention of contrast-induced nephropathy

It is necessary for optimal preprocedural management of patients at risk for CIN, carefully evaluate pharmacotherapy and withdrawn potentially nephrotoxic drugs, as clinically appropriate, (nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, antirejection therapy) [2, 29, 31]. Angiotensin converting enzyme inhibitor therapy should continue without neither initiating nor changing dose until the patient safely past the risk period for CIN development [28]. In patient with diabetes mellitus, metformin should be withheld after procedure until it is clear that renal functions are without deterioration because risk of lactate acidosis [32].

7.3. Dopamine

Dopamine in low doses (0.5 to 2.5 μg/kg/min) stimulates dopaminergic receptors in the renal and mesenteric vasculature, resulting in selective vasodilatation. Low dose of dopamine increases renal plasma flow, glomerular filtration rate, and sodium excretion in subjects with normal renal function and with congestive heart failure [27, 33, 34].

Effect of low-dose dopamine in prevention of CIN was studied in prospective randomized trial in patients with chronic renal failure (CRF) (serum Cr <200 μmol/l) and/or diabetes mellitus who underwent coronary angiography. All patients received intravenous hydration for 8 to 12 h before and 36 to 48 h after angiography with 0.45% saline/5% dextrose. In addition, the patients were randomly assigned to receive either 120 ml/day of 0.9% saline plus dopamine 2 μg/kg/min (Dopamine group), or saline alone (Control group) for 48 h [35].

There were 36 Dopamine-treated (30 diabetics and 6 with CRF) and 33 Control (28 diabetics and 5 with CRF) patients compared. Plasma creatinine (Cr) level increased in the Control group from 100,6 ± 5,2 before to 112,3 ± 8,0 μmol/liter within five days after angiography ($p = 0,003$), and in the Dopamine group from 100,3 ± 5,4 before to 117,5 ± 8,8 μmol/liter after angiography ($p = 0,0001$), respectively. There was no significant difference in the *change* of Cr level (ΔCr) between the two groups (Figure 14).

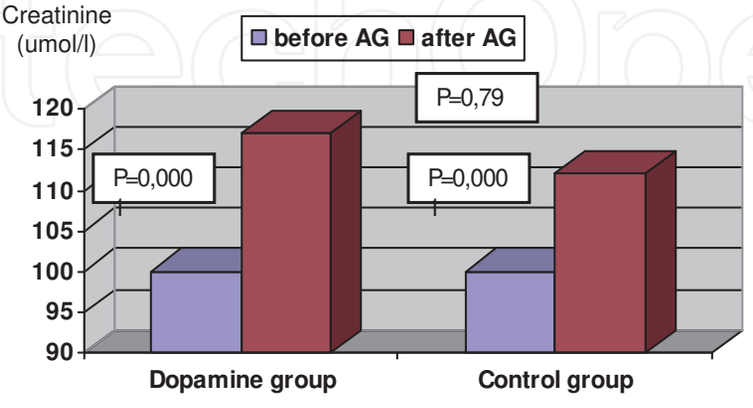

Figure 14. Effect low-dose dopamine on creatinine level in patients after angiography, AG=coronary angiography

However, in a subgroup of patients with peripheral vascular disease (PVD), ΔCr was −2,4 ± 2,3 in the Control group and 30,0 ± 12,0 μmol/l in the Dopamine group (p = 0,01). No significant difference occurred in ΔCr between Control and Dopamine in subgroups of patients with preangiographic CRF or DM.

Administration of contrast agent caused a small but significant increase in Cr blood level in high-risk patients. There is no advantage of dopamine over adequate hydration in patients with mild to moderate renal failure or DM undergoing coronary angiography [35].

7.4. Fenoldopam

Fenoldopam mesylate is a dopamine A1 receptor agonist, augment renal plasma flow and preserves renal blood flow after iodinated contrast administration. It appeared promising in prevention of CIN in a pilot randomized placebo controlled double blind study in 45 patients with chronic renal insufficiency who underwent angiography [36]. Patients were randomized to receive normal saline solution or saline solution with fenoldopan mesylate at 0,1 ug/kg/min at lease 1hr before administration of contrast agent.

Renal plasma flow (primary endpoint) at 1 hour after angiography was 15,8% above baseline in fenoldopan group compared with 33,2% below baseline in the normal saline group (p<0,05). Incidence of CIN at 48 hour (secondary endpoint) was 41,0% in the normal saline group vs. 21% in the fenoldopam group (p=0,148). Renal plasma flow was significantly (p<0,001) reduced in patients with CIN compared with patients without development of CIN [36].

Effect of fenoldopam mesylate was investigated in larger prospective randomized controlled CONTRAST study [37]. There were 315 patients with creatinine clearance less than 1.00 ml/s at 28 centers in the United States randomized to receive fenoldopam mesylate (0.05 μg/kg/min titrated to 0.10 μg/kg/min) (n = 157) or placebo (n = 158), starting 1 hour prior to angiography and continuing for 12 hours. Within 96 hours, the primary end point of contrast-induced nephropathy had been reached in 33.6% of patients in the fenoldopam group vs. 30.1% of patients in the placebo group (relative risk [RR], 1.11; 95% confidence interval [CI], 0.79-1.57; *P* =.61) (Figure 15).

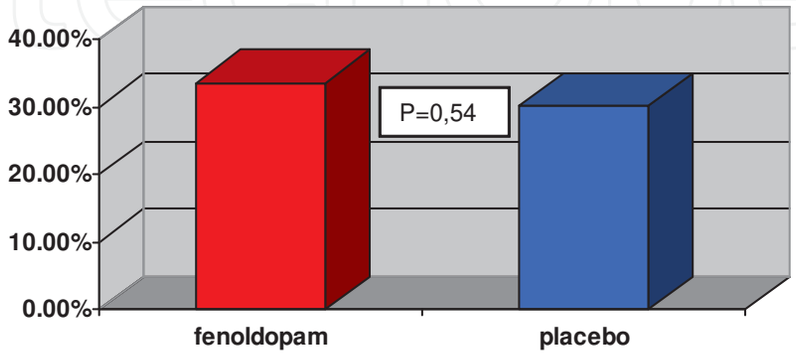

Figure 15. Effect of fenoldopam on CIN prevention

The incidence of contrast-induced nephropathy was also similar in both groups when defined by an absolute increase in serum creatinine level. There were no significant interactions between treatment group and diabetic status, hypertension, baseline renal function, N-acetylcysteine use, or amount of hydration or contrast use.

7.5. Acetylcystein

N-acetylcysteine is a modified form of the amino acid cysteine, which is a nitrogen atom bound via an acetyl group (Figure 16). Molecular weight of N-acetylcysteine is 163,2. The main therapeutic indication is its use as an antidote for paracetamol overdose, as well as a mucolytic therapy.

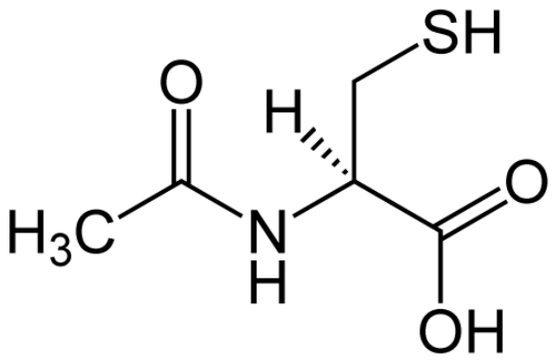

Figure 16. Formula N-acetyl cysteine.

The mechanism by which N-acetylcysteine may reduce the incidence of CIN remains unclear so far. In its most important feature is considered a strong antioxidant effect, which can dispose of a wide range of oxygen radicals. Moreover, N-acetylcysteine is the precursor of the endogenous antioxidant glutathione. Reduce damage from oxygen radicals by N-acetylcysteine have been observed in myocardial infarction [38]. Similarly, N-acetylcysteine can preserve cell death in ischemia-reperfusion renal injury [39]. N-acetylcysteine increases the expression of NO synthase and also enhances the biological effect of nitric oxide itself by creating a compound S-nitrozotiole, which is also a strong and stable vasodilator. In this way, N-acetylcysteine reduces the renal vasoconstriction, and thereby improves blood flow to the kidneys.

N-Acetylcysteine is a free-radical scavenger and has been shown to be renoprotective in some studies [40]. There were performed a lot of randomized trials and meta-analysis with an acetylcysteine in prevention of CIN in high risk patients. Some contradictory results from these studies may be caused by different type or volume of used contrast agents as well as different dosage, timing and route of acetylcystein administration.

Tepel at al. prospectively assessed 83 patients with chronic renal insufficiency (serum creatinine level 216+/-116 μmol/l, mean +/-SD) who were undergoing computed tomography with a nonionic, low-osmolarity contrast agent. Patients were randomly assigned either to receive the

antioxidant acetylcysteine (600 mg orally twice daily) and 0.45 percent saline intravenously, before and after administration of the contrast agent, or to receive placebo and saline [40].

Ten of the 83 patients (12 percent) had an increase of creatinine level at least 44 μmol/l at 48 hours after administration of the contrast agent: 1 of the 41 patients in the acetylcysteine group (2 percent) and 9 of the 42 patients in the control group (21 percent; P=0.01; relative risk, 0.1; 95 percent confidence interval, 0.02 to 0.9) (Figure 17).

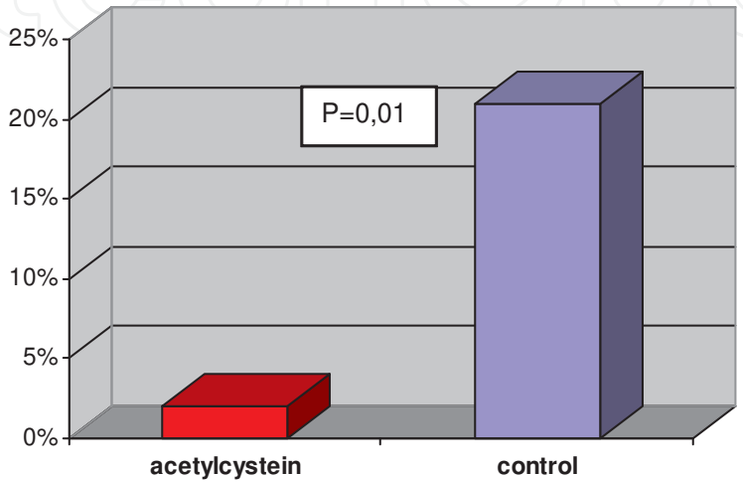

Figure 17. Effect of an acetylcystein on incidence of CIN

In the acetylcysteine group, the mean serum creatinine concentration decreased significantly (P<0.001), from 220+/-118 to 186+/-112 μmol/l at 48 hours after the administration of the contrast medium, whereas in the control group, the mean serum creatinine concentration increased nonsignificantly (P=0.18), from 212+/-114 to 226+/-133 μmol/l (P<0.001 for the comparison between groups).

In prospective randomized RAPPIDE study, 80 patients with stable renal dysfunction undergoing coronary angiography and/or intervention were allocated to an administration of 150mg/kg acetylcystein in 500 ml saline over 30 min immediately before contrast followed by 50mg/kg acetylcystein in 500 ml saline over 4 hours or intravenously hydration (1ml/kg saline for 12hours pre and post-contrast) [41].

Acute CIN occurred in 10 of the 80 patients (12,5%), 2 of the 41 (5%) in acetylcysteine group and in 8 of the 39 fluid-treated patients (21%), p=0,045, relative risk: 0,28; 95% confidence interval: 0,08 to 0,98 (Figure 18).

Prophylactic preventive double dose of N-acetylcystein was investigated in prospective randomized trial in population of 224 patients with chronic renal insufficiency (creatinine level ≥1.5mg/dl or eGFR< 1ml/s) undergoing intravascular administration of non-ionic, low-osmolarity contrast agent [42].

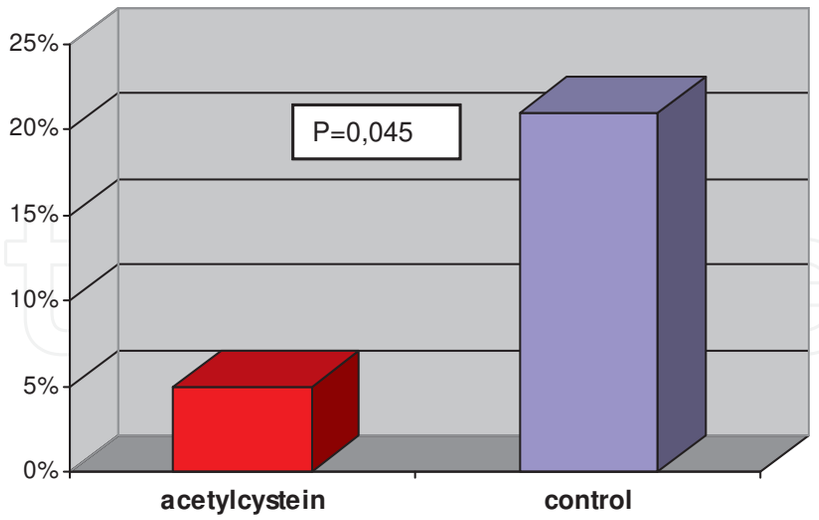

Figure 18. Incidence of CIN, RAPPIDE study results

Patients were randomly assigned to receive 0.45% saline intravenously and acetylcysteine at the standard dose (600mg orally twice daily; *n*=110) or at a double dose (1200mg orally twice daily; *n*=114) before and contrast agent administration.

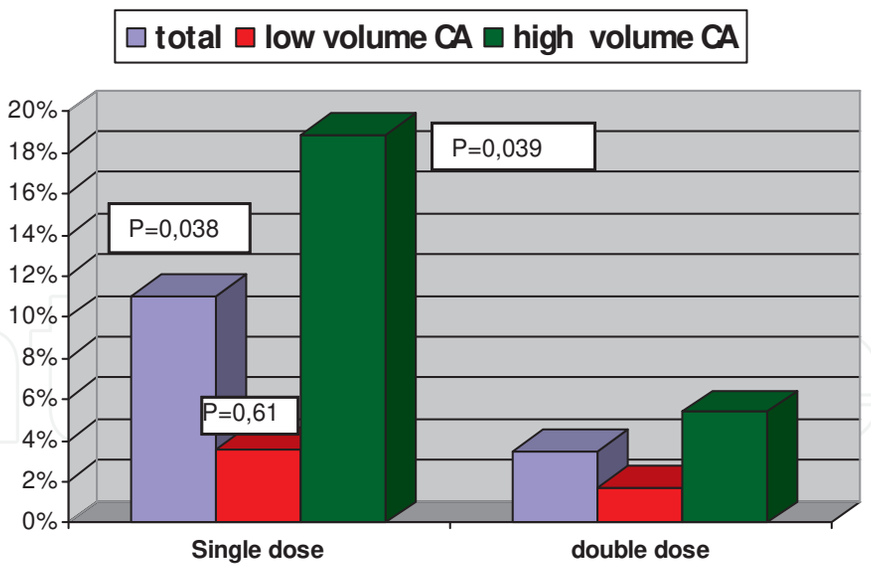

Figure 19. Effect of single and double dose of N-acetylcystein on CIN incidence at 48h, CA=contrast agent

Increase of the creatinine level at least 44umol/l at 48h after the procedure occurred in 12/109 patients (11%) in the standard dose group and 4/114 patients (3.5%) in the double dose group (*P*=0.038; OR=0.29; 95% CI=0.09–0.94). In the subgroup (n=114) with low (<140ml) con-

trast dose (mean value 101±23ml), no significant difference in renal function deterioration occurred between the 2 groups (3,6% in single dose group vs. 1,7% in double dose group, p=0,61). In the subgroup (n=109) with high (≥140ml) contrast dose (mean value 254±102ml), the event was significantly more frequent in the single dose group vs. double dose group (18,9% vs. 5,4%, p=0,039, OR=0,24; CI=0,06-0,94) (Figure 19).

Effect of N-acetylcysteine was studied in several meta-analyses (Table 10) [43-51].

First author	Year of publication	No of trials included in meta analysis	Relative risk (99% CI)
Birck	2003	7	0,435 (0,215-0,879)
Isenbarger	2003	7	0,370 (0,160-0,840)
Alonso	2004	12	0,550 (0,340-0,910)
Bangshaw	2004	14	0,540 (0,320-0,910)
Pannu	2004	15	0,650 (0,430-1,000)
Kshirsagar	2004	16	ND
Nallamothu	2004	20	0,730 (0,520-1,000)
Liu	2005	9	0,430 (0,240-0,750)
Duong	2005	14	0,570 (0,370-0,840)

Table 10. Meta-analyses of randomized prospective trials on effect of acetylcysteine for prevention of CIN

7.6. Hemodialysis

Although hemodialysis is an appropriate method in rapid elimination of the contrast agent, but in clinical trials it did not showed to be effective in the prevention of CIN [52, 53]. The probably reason is, that the potential kidney damage by contrast media occurs rapidly after its application. Although dialysis starts 1 hour before procedure or concurrently with administration of contrast medium, it did not reduce the incidence of CIN.

7.7. Hemofiltration

Hemofiltration has been shown to be effective in reducing CIN in high-risk patients with advanced stage renal failure undergoing coronary intervention and is associated with improved in-hospital and long-term outcomes.

In a prospective study were 114 consecutive patients with serum creatinine level > 176,8umol/l randomly assigned to groups [54]. One group consisted of patients who undergone hemofiltration 4 to 6 hours before and 18 to 24 hours after coronary intervention, in the second patient group was given isotonic saline in the same time frame. A mean [±SD] serum creatinine level was 265,2±88,4 μmol/l in hemofiltration group and 274,0±88,.4 μmol/l in control group (p=0,63).

Incidence of CIN in patients undergoing hemofiltration was much lower than that of only hydrated patients (5% vs. 50%, p<0,001). The rate of in-hospital events was 9 percent in the hemofiltration group and 52 percent in the control group (P<0.001). In-hospital mortality was 2 percent in the hemofiltration group and 14 percent in the control group (P=0.02), and the cumulative one-year mortality was 10 percent and 30 percent, respectively (P=0.01) (Figure 20) [54].

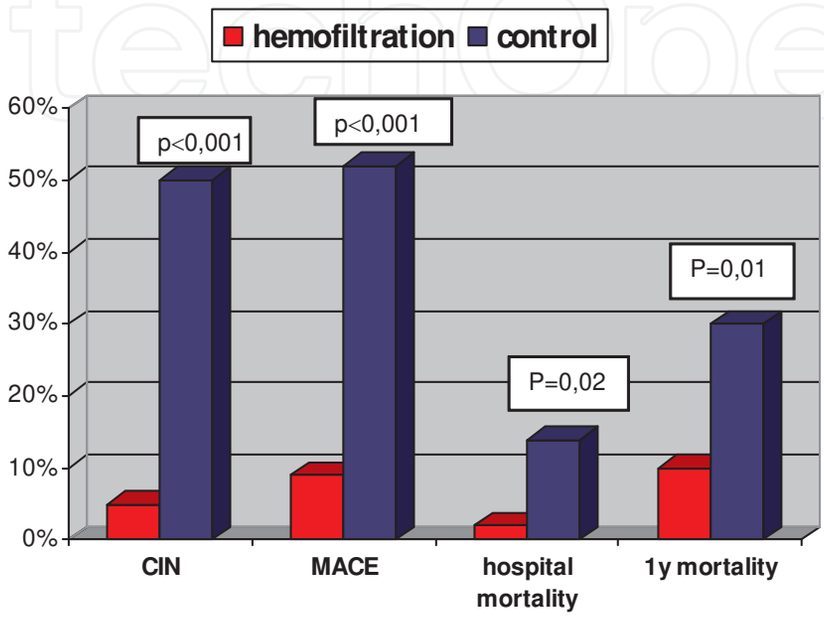

Figure 20. Influence of hemofiltration on incidence of CIN and both hospital and long-term outcome

Important post procedural complications were similar in both groups, except of pulmonary edema, renal replacement therapy (Table 11).

Complication	Hemofiltration group (n=58)	Control group (n=56)	P value
Q MI	0	2(4%)	0,24
nonQ MI	1(2%)	1(2%)	1,00
Emergency CABG	0	0	1,00
Pulmonary edema	0	6(11%)	0,02
Hypotension or shock	1(2%)	3(5%)	0,36
Blood transfusion	1(2%)	3(5%)	0,36
Renal replacement the	2(3%)	14(25%)	<0,001
All clinical events	5(9%)	29(52%)	<0,001

Table 11. Post procedural complications in both hemofiltration and control groups

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Interpretation of the study results has some limitations. CIN was defined as more than 25% increase in serum creatinine, but hemofiltration itself remove creatinine from the blood, thus it is impossible to objectively evaluate true creatinine growth. Since the incidence of CIN in the control group far exceed the percentage incidence observed in other studies, it is likely that patients included in this study represent the specific, high risk group that is way the result cannot be simply applied to a wide population. Furthermore, hemofiltration is also an expensive elimination method, and thus cannot be generally recommended as a standard measure for CIN prevention.

Practical recommendations for prevention of CIN are summarized in Table 12 (Schweiger MJ, 2006)

Identify risk
Low risk – eGFR "/> 60ml/min/1,73m2
Optimize hydration status
High risk – eGFR < 60ml/min/1,73m2
Schedule outpatient for early or delay procedure time to allow time to accomplish the hydration
Consider the following recommendation (No 2-No 5)
Manage medications
Withhold, if clinically appropriate, potentially nephrotoxic drugs including aminoglycoside antibiotics, anti-rejection drugs and nonsteroidal anti-inflammatory drugs
Administer N-acetylcysteine
600mg orally q 12hrs "/> 4 doses beginning prior to contrast
Manage intravascular volume (avoid dehydration)
Administer a total of at least 1 l of isotonic saline beginning at least 3hrs before and continuing at least 6-8hr after procedure
Initiation infusion rate 100-150ml/hr adjusted post procedure as clinically indicated
Sodium bicarbonate
154mEq/l @ 3ml/kg/hr starting 1hr before contrast
154mEq/l @ 1ml/kg/hr for 6hrs following contrast
Radiographic contrast media
Minimize volume
Low- or iso-osmolar contrast agents
Postprocedure: discharge/follow-up
Obtain follow-up S-Cr 48 hrs post procedure
Consider holding appropriate medications until renal function returns to normal, i.e. metformin, nonsteroidal anti-inflammatory drugs

eGFR = estimated glomerular filtration rate, S-Cr = serum creatinine level

Table 12. Recommendation for prevention of CIN

8. Contrast induced nephropathy among patients undergoing coronary angiography or percutaneous coronary intervention. Results from 12-months' consecutive cases analysis from University Hospital Martin, Slovakia

8.1. Objective

The primary objective of this work was to evaluate the incidence of contrast-induced nephropathy in patients undergoing coronary angiography examination (KG) or percutaneous coronary intervention (PCI) and was hospitalized at the coronary care unit, I. Internal clinic, University hospital, Martin, Slovakia.

A secondary objective was to identify and assess the impact of major risk factors for developing CIN. At the same time, we assessed the incidence of CIN according to the recommended definition, significance of serum creatinine at 24 hours, and at third to fifth day after administration of contrast medium and the use of scoring systems to estimate the risk of CIN development.

8.2. Methods

In the period from January 2008 to February 2009, we prospectively followed patients admitted to the coronary care unit and department of invasive and interventional cardiology of I. Internal clinic, who underwent coronary angiography or coronary intervention. We studied basal serum creatinine level (SCr0), creatinine value at 16-24 hours after contrast administration (SCr1) and creatinine value at 3rd-5th day after contrast administration (SCr2), which was mostly obtained after hospitalization discharge during ambulatory collection and sent via mail by patients or their GPs. If there was a significant increase in creatinine level at 24 hours after invasive procedures, we recommend extending hospitalization in patients till normalization of values.

Patients without obtained SCr2 values and patients in chronic hemodialysis were excluded from the analysis.

Major risk factors for developing CIN (age, sex, diabetes mellitus, chronic kidney disease, type and amount of contrast medium administration) were monitored at the same time as well.

The invasive procedures contrast agent iopamidol (SCANLUX 370 ®) was used in all patients. Iopamidol represents a non-ionic low-osmolar contrast agent with osmolarity 796 mOsm / kg. It is therefore hypertonic compared with blood plasma osmolarity which is approximately 300 mOsm / kg. Its half-life after intravascular administration is approximately 2 hours with normal renal function. In patients with renal insufficiency there is prolonged elimination, depending on the degree of renal impairment and may takes several days.

In order to determine the risk of CIN, patients were divided into four groups according to the CIN risk score by Mehran. Patients at low and medium risk for the CIN developing were

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orally hydrated (with the recommendation approximately 2000 ml of fluid on the examination day), High risk patients were hydrated parenteral with saline at a dose of 0,5 to 1 ml / kg body weight per hour.

8.3. Definitions

Contrast-induced nephropathy (CIN) was defined as an increase in baseline creatinine level of ≥ 25% (CIN25) or ≥ 44,2 micromol / l (CIN 0,5) or decrease baseline GFR of ≥ 25% within 24 to 48 hours after administration of contrast medium. Baseline glomerular filtration rate (eGFR) was calculated according to the Cockcroft-Gault formula.

Severe renal dysfunction (SRD) was defined as an acute renal failure requiring dialysis or a rise in baseline creatinine over 50% during 24 hours to 120 hours after the procedure.

Chronic kidney disease was determined according to the history with the presence of kidney disease in nephrologic observation.

8.4. Statistic methods

The incidence of contrast-induced nephropathy was evaluated by Pearson Chi-square test. Quantitative parameters (age, BMI, sex, number of KL, SCr0, GFR0, left ventricular ejection fraction), were evaluated by the Mann-Whitney U - test and qualitative parameters (age over 75 years, DM, chronic renal disease), by the Fisher's exact test.

To assess correlation of the endpoints, we used the Spearmen correlation coefficient. Numerical values are expressed as median and quartile range or as a percentage of the total amount. As statistically significant, we considered the value of $p < 0.05$.

8.5. Results

There were excluded 19,2% patients with incomplete documentation of sampling creatinine values at 24 hours (SCr1) or at third to fifth day after contrast agent administration (SCr2) and patients in the chronic hemodialysis. In the final data analysis was then included 529 patients, whose basic clinical characteristics are listed in Table 13.

Age "/> 75 years	15,1% (80/529)
Diabetes mellitus (DM)	30,3% (160/529)
Preexisting renal disease (CKD)	14,6% (77/529)
DM + CKD	6,6% (35/529)
PCI procedure	62,38% (330/529)

DM = diabetes mellitus, CKD = chronic kidney disease, PCI = percutaneous coronary intervention

Table 13. Clinical characteristics

CIN25 was observed in 3, 97% (21/529) patients and CIN 0,5 in 2,27% (12/529) patients. The decrease of eGFR ≥ 25% occurred in 2, 27% (12/529) patients. SRD occurred in 1, 51% (8/529) patients, dialysis was needed in 0,76% (4/529) patients. Severe hypotension requiring combined inotropic support was observed in 3 patients (0, 57%). There were 4 deaths from529 patients (0, 76%) as a consequence of the contrast induced nephropathy (2 men and 2 women). Mortality rate of patients with CIN was 19% (4/21).Distribution of patients according to Mehranś risk score model is shown in Table 14.

Score	Number of pts	CIN25 incidence
Low risk	77,5% (410/529)	2,44% (10/410)
Medium risk	17,9% (95/529)	4,21% (4/95)
High risk	3,59% (19/529)	21,05% (4/19)
Very high risk	0,95% (5/529)	60% (3/5)

Table 14. Distribution of patients according risk score model (Mehran)

Patients with the development of CIN, compared with patients in whom CIN was not confirmed, differed statistically significantly in age (p = 0.043), left ventricle systolic function (p <0.001), and the amount of administered contrast medium (p = 0.004). On the contrary statistically significant differences were not found in sex, BMI, the initial value of creatinine (SCr0), or the initial value calculated glomerular filtration rate (eGFR0). Both groups of patients also differed significantly in the presence of chronic kidney disease (p <0.001) and in the combined appearance of diabetes and chronic kidney disease (p = 0.001). In contrast, both groups of patients did not differ significantly according of the risk age (over 75 years), or diabetes mellitus (Table 15, Figure 21).

Parameter	with CIN	without CIN	P value
	(n = 508)	(n = 21)	
Age (year)	62	71	0,043
Age > 75y (No of pts)	14,8% (75/508)	23,8% (5)	0,345
Sex (men/women)(No of pts)	63/37%(318/190)	62/38%(13/8)	1,00
BMI (kg/m2)	28,4 (25,8-31,2)	29,8 (27,7-34,0)	0,121
Diabetes mellitus (No of pts)	30% (152/508)	38,1% (8)	0,469
CKD (No of pts)	13,2% (67/508)	47,6% (10)	< 0,001
Both DM and CKD (No of pts)	5,7% (29/508)	28,6% (6)	0,001
LVEF (%)	55 (50-60)	45 (40-50)	< 0,001
Serum creatinine level (μmol/l)	100 (88-112)	105 (91-136)	0,129
eGFR (ml/min)	72,6 (60,6-90,0)	62,4 (45,6-91,2)	0,291

CKD = chronic kidney disease, LVEF = left ventricle ejection fraction, BMI = body mass index, eGFR = estimated glomerular filtration rate, DM = diabetes mellitus

Table 15. Comparison of clinical parameters in patients with and without the occurrence of CIN

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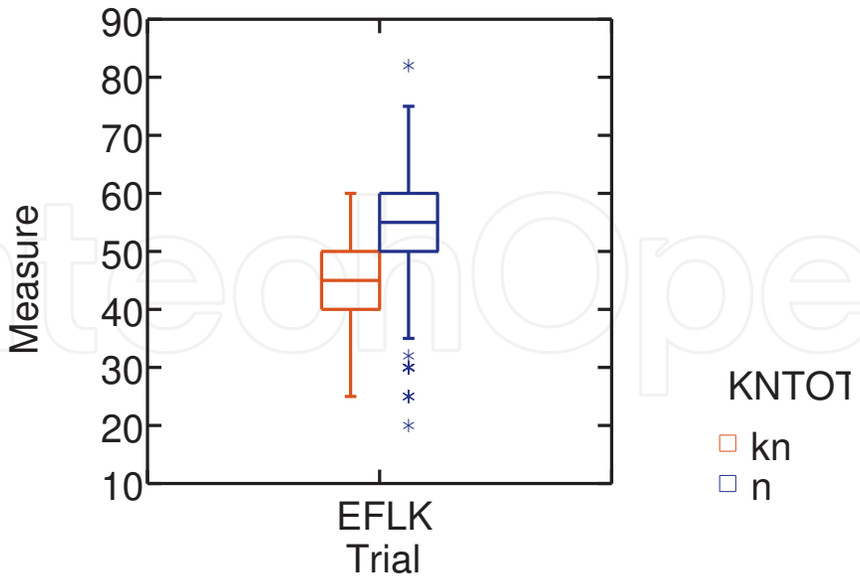

Figure 21. Left ventricle ejection fraction (EFLK) (%) in patients with CIN (kn) and without CIN (n)

There was not observed correlation between the amount administered contrast agent and development of CIN (0.50), although patients with the development of CIN received significantly higher amount of contrast agent (Figure 22).

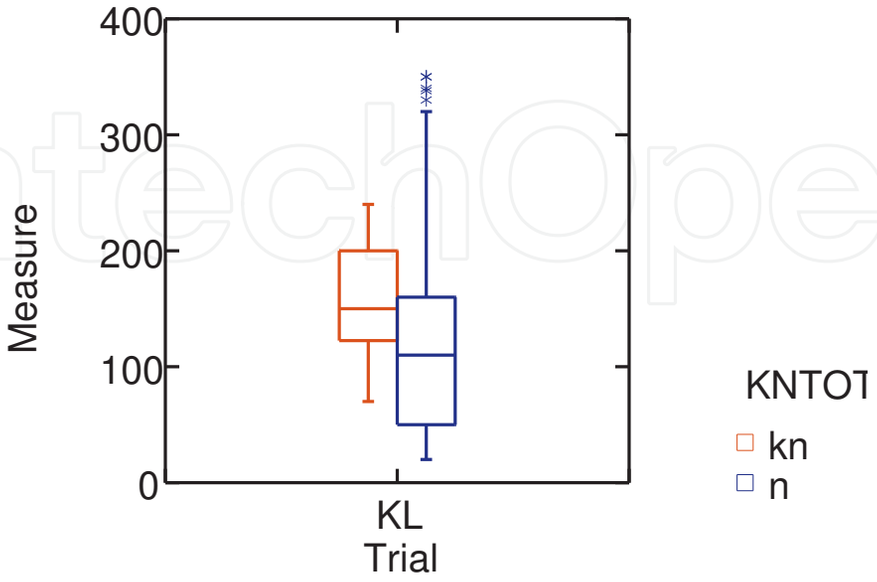

Figure 22. Amount of contrast agent administered in patients with CIN (kn) and without CIN (n)

If the criterion value was chosen CIN25, diagnosis of CIN was determined by the value of delta SCr1 in 1,89% (10/519) and the delta SCr2 in 2,65% (14/515) of cases, together in the 3,97% (21/509) of cases. If the criterion value was determined CIN 0,5, CIN, diagnosis of CIN was established based on the value deltaSCr1 in 0,76% (4/524) and deltaSCr2 in 2,08% (11/517) of cases, together in 2,27% (12/516) of cases.

If the definition of CIN was used decrease in creatinine clearance, than diagnosis of CIN was determined by delta eGFR1 in 0.57% (3/524) of patients and delta eGFR2 in 1, 9% (10/517) of cases, together in 2,28% (12/515) of cases.

In a subset of patients with CIN, according of CIN25 definition, there were based on result of SCr1, diagnosed 47, 62% (10/21) and on SCr2 52,38% (11/21) patients. Using the definition CIN 0,5 there were based on result of SCr1 diagnosed 33,33% (4/12) and on SCr2 66,67% (8/12) patients. According of the reduction in eGFR as a definition of CIN, there were based on result of SCr1 diagnosed 25% (3/12) and on SCr2 75% (9/12) cases.

8.6. Discussion

The incidence of CIN depends on the study population and diagnostic criteria that define it and is reported in the range 4.4% -20%. While in the general population is low and ranges from 0,6 to 2,3% [55], significantly increases in patients with risk factors especially with documented cardiovascular disease and the acute coronary syndromes and may be as high as 57,3% [56]. In 250 patients with creatinine clearance <60 ml/min, the incidence of CIN ranged from 6,0% -21,6%. Similarly, using different definitions of CIN incidence was 4,4% -20% in diabetics and 2,8% -17,3% in 469 patients with elevated cardiac markers before PCI [57]. There are four currently used CIN definitions, but only two (CIN CIN25 and 0,5) allow more consistently predict the clinical course. In comparison to CIN25, the definition of CIN 0,5 provides greater differences between unselected group of patients and patients with high risk of CIN and is a stronger indicator of the unfavorable course.

A large variation in the incidence of CIN emphasizes the need for a uniform definition of CIN, which would allow proper comparison of results from different databases. The CIN25 and CIN 0,5 independently correlated with the clinical course. Patients with a seemingly small increase in creatinine level have adverse cardiovascular variables. The relationship between increases in serum creatinine and glomerular filtration current is nonlinear. A small increase in creatinine level may represent significant deterioration in renal function, particularly at lower values of basal serum creatinine. Moreover, work dealing with a rise in serum creatinine showed that the peak levels are often not achieved until several days after exposure to contrast medium [58-60]. Because most of the patients are discharged after 24-48 hours after PCI, a small increase in creatinine may be a sign of further renal damage in the coming days. Besides of a consistent prognostic value, ideal definition of CIN should distinguish between patients with moderate and high risk. Although the value of CIN25 and CIN 0,5 provide consistent prognostic value, CIN 0,5 clearly distinguishes between a whole population and a subgroup of patients with chronic kidney disease at highest risk. In contrast, CIN25 has only low discriminatory value, but very high in patients with the lowest risk. Combining these two definitions, we can divide the patients into 3 groups: The lowest risk

for adverse events - level 0 (deltaCr <25% <44 μmol / l), the highest (deltaCr> 25%> 44 μmol / l) - level 2 and intermediate (deltaCr> 25% <44 μmol / l) - level 1. Trend toward a worse clinical outcome is observed in patients at higher degrees of nephropathy. Multivariate analysis revealed stage 1 and 2 as an independent and significant indicator of 6-month MACE (major adverse cardiovascular events) compared with the degree 0. This scoring system reflects the fact that those patients who experienced an increase in CIN CIN25 or CIN0,5 are in fact two prognostic categories (nephropathy Level 1 and nephropathy Level 2) [57].

In our study, the overall incidence of CIN varied, according to the chosen definition of the baseline increase in serum creatinine, from 2,27% with the definition of CIN 0.5 to 3,97% using the definition of CIN25. Using the definition of impairment eGFR of ≥ 25% compared to baseline, the overall incidence of CIN was 2,28%. Therefore, as the most-sensitive diagnostic tool for CIN, was the determination of the CIN25 value.

In most of the studies was the incidence of CIN based on an increase in creatinine levels at 24 hours after contrast agent administration. Management of patients with complete follow-up serum creatinine at 48 hours after contrast medium administration evaluated only Huber et al., while many others have failed to adequate monitoring of all patients enrolled, which bring potentially serious problem in interpreting their results. While our results suggest that CIN can be diagnosed according to the definition based on SCr1 value only in 25 - 47,6% cases and in 52,4 -75% of cases based on SCr2 value. Moreover, among patients developing severe renal dysfunction in the future (hemodialysis or death), 60% (3/5) had CIN diagnosed until just based on the SCr2 value. This raises the question of the need for routine clinical assessment of SCr2 (in the third to fifth day after contrast administration) in all patients at risk [61, 62].

The overall low incidence of CIN in our study can be attributed to several factors. There was present very high proportion of patients with low and moderate risk of developing CIN (77,5%, respectively. 17,96%). Moreover, before invasive procedure were patients hydrated both oral and parenteral way with saline. Hydration is widely recognized as the simplest and most effective preventive measure of CIN. In our series we noted paradoxical decrease in serum creatinine level after 16-24 hours following invasive procedure compared to baseline in 35,16% (186/529) patients, despite of administration of contrast agent. This finding demonstrates importance of standard saline hydration for patients prior to invasive procedures, as patients are admitted for coronary angiography or percutaneous coronary intervention often dehydrated. Another factor that can be attributed to a low incidence of CIN is the type and amount of contrast medium. In our study, non-ionic low-osmolar contrast medium iopamidol was used. This contrast agent has safety renal profile that is comparable with the safety profile of iso-osmolar contrast agent iodixanol.

In our study was not confirmed a significant relationship between amount of used contrast agent and the incidence of CIN. However, dose of contrast medium was significantly higher in patients with development of CIN25, in comparison with dose used in patients who did not develop CIN25 (150 ml vs. 110 ml, p = 0,004).

This may explain the low prevalence of patients with age above 75 years (15,12%), diabetes mellitus (30,24%), with chronic kidney disease (14,56%) and also low doses of used contrast medium, the maximum dose was 350 ml.

Generally, a safe dose of intravascular administrated iodinated contrast media is considered below 70 ml. The dose more than 5 ml / kg of patient weight is considered high risk [63, 64]. In patients with chronic kidney disease, dose of contrast medium for coronary angiography should be planned below 30 ml and if procedure will be followed by percutaneous coronary intervention than dose should be below 100 ml [64]. Even in our study, we confirmed that the dose of contrast medium into 70 ml can be considered relatively safe, because in this dose no CIN did occur in our study group.

Results of several studies suggested that the prevalence of CIN is more common in women than men in older age groups, mainly in the context of low eGFR in this group. These findings are supported by other studies that found a higher risk for developing of renal complications after angiography in women than in men. However, previous findings were related to influencing factors such as age, which caused that women seemed to be a higher risk for developing CIN than men. In our group of patients had preexisting renal impairment 12,63% women and 16,61% men, which is one possible explanation for higher incidence of CIN in males.

Anemia seems also to be an independent risk factor for CIN. Several studies have shown that women more incline to anemia before angiography than men and have a trend to higher risk of bleeding during periprocedural period [55]. The decrease in hematocrit of more than 6% doubles the risk of developing CIN, especially in women. Such a reduction in hematocrit can cause renal hypoperfusion, which potentiates renal damage caused by exposure to contrast media.

Patients with chronic kidney disease have a reduced vasodilatory response that is important factor in the development of CIN. At the same time, in these patients due to reduced glomerular filtration extends elimination of contrast agent from circulation, thus potentiating its both cytotoxic and hemodynamic effect. Chronic kidney disease as a highly significant predictor of CIN was also confirmed by our study.

In our study, age was a marginally significant predictor of CIN and age over 75 years has not been demonstrated as important.

Advanced congestive heart failure and reduced left ventricle ejection fraction are characterized by reduced cardiac output, increased neurohumoral vasoconstrictor activity and reduced NO-dependent renal vasodilatation, which can lead to hypoperfusion of renal medulla [64]. Left ventricle systolic dysfunction was in our study recognized as highly significant predictor of CIN.

Diabetes mellitus was not an independent predictor, but in combination with chronic kidney disease has become a significant predictor of CIN development.

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9. Conclusion

Contrast induced nephropathy is common cause of renal functions impairment. Incidence of CIN in unselected patients undergoing angiographic procedures (coronary angiography, percutaneous coronary intervention) varies approximately 2-30%. Once occurs, CIN is associated with a significant increase in potentially serious morbidity and mortality. If possible, in patients at the highest risk for development of CIN, very useful is avoiding of contrast agent administration (or strongly limiting contrast volume of low or iso-osmolar contrast agents). To this high risk group are usually includes patients with diabetes mellitus, preexisting renal insufficiency, hypotension (or incipient shock), congestive heart failure, anemia or at advanced age. This risky patients population requires appropriate both peri and postprocedural management. Most important measure is adequate hydration in order to avoid hypovolemia. Preferred type of solutions is parenteral isotonic saline or an isotonic sodium bicarbonate. Still limited evidence is for pharmacologic intervention (N-acetylcystein) in CIN prevention.

Since most cases of CIN, including patients with an unfavorable course in the future, were diagnosed on the basis of serum creatinine level at third to fifth day after administration of contrast medium, it is recommended for high-risk patients to assess serum creatinine level at day 3 to 5 after invasive procedures.

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