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Review Article

Contrast Induced Nephropathy in Cardiology, Prevention and Treatment: A Systematic Review

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Abstract

Contrast induced Nephropathy (CIN) is a serious complication of all angiographic procedures, caused by the use of an iodinated contrast media (CM). CM is a substance able to induce a transient and self-limited acute kidney injury (AKI). CIN is the third common cause of AKI and represent the 12% of AKI developed in hospital. Nowadays there is not a treatment for CIN, the only therapeutic strategy is prevention.

Keywords: *Contrast Induced; Nephropathy*

Introduction

Coronary angiography is developed worldwide for the diagnosis and treatment of ischemic cardiopathies. This procedure is based on the use of an iodinated contrast media, which can be dangerous for kidney function. Contrast induced nephropathy is a serious complication in the cardiology unit, which increases morbidity and mortality rates and the time of hospitalization.

The aim of this article is to review the recent evidence concerning CIN incidence, diagnosis, and prevention strategies to reduce the incidence of this complication and to improve the clinical outcomes.

Definition

Contrast induced Nephropathy (CIN) is a serious complication of all angiographic procedures, caused by the use of an iodinated contrast media (CM). CM is a substance able to induce a transient and self-limited acute kidney injury (AKI). The renal damage showed up in 3 - 5 days after the procedure and normalized in 7 - 10 days. CIN is defined as an elevation of serum creatinine (Scr) of more than 25% or ≥ 0.5 mg/dl (44 μmol/l) from baseline within 48h after excluding other factors, such as nephrotoxins, hypotension, urinary obstruction, or atheromatous emboli.

Prevalence incidence

CIN is the third common cause of AKI and represent the 12% of AKI developed in hospital. The incidence of CIN after percutaneous coronary angiography is among 0 and 24%, depending from the presence of risk factors. For a variety of reasons, the incidence of AKI is substantially higher following coronary angiographic procedures than following contrast-enhanced CT [2]. The patient population undergoing coronary procedures typically has more advanced vascular disease and a higher rate of hemodynamic compromise and is

thus more predisposed for AKI than the average population undergoing contrast-enhanced CT [3]. A decreased baseline renal function has consistently been found to be a strong predictor of postcontrast AKI risk. The risk of post-PCI AKI has been shown to be significantly higher with high-osmolar CM, comorbidities (diabetes, proteinuria, hypertension, and dehydration) and nephrotoxic comedications [4]. The presence of CIN rises morbidity and mortality rates and is related with a prolonged hospitalization [1].

Pathophisiology

The mechanism of CIN is not well understood. Today there are some possible theory:

- Renal medullary Hipoxia: Probably CM caused a direct damage or an indirect damage, by the release of the vasoconstrictor factors and a reduction of the vasodilator ones;
- Direct toxicity: CM is a toxic substance, able to increase free radicals, causing oxidative stress and, consequently, cellular and molecular damages [5];
- Apoptosis: CM and increases the caspases 3 and 9 and fragmentation of the poly ADP-ribose and activates the intrinsic apoptosis pathway. CM increases the cellular expression of Bcls pro-apoptosis proteins [6].

Risk factors

The risk of a CIN depends by the presence of procedure related or patient related factors [1].

Patients related factors:

- Preexisting renal insufficiency (estimated glomerular filtration rate (eGFR) < 60 ml/min)
- Diabetes mellitus
- Age >75 years
- Uncontrolled hypertension
- Hypotension requiring inotropes
- Congestive heart failure (CHF)
- Use of intra-aortic balloon pump (IABP)
- Anemia
- Hypoalbuminemia
- Liver cirrhosis
- Concomitant use of diuretics or nephrotoxic drugs.

Procedure related factors:

- High contrast volume
- High osmolality or viscosity CM
- Repeated exposures to CM within 72h.

Contrast media

CM is defined as a water soluble substance, chemically represented by a tri-iodinated benzene ring (1 in the monomeric form, 2 in the dimeric form).

CM can be classified in:

- Ionic and non ionic CM (the first are more water soluble);
- High, low or iso-osmolarity CM (the non ionic dimeric CM are iso-osmolar, the ionic dimeric CM are low-osmolar);
- Different viscosity (dimeric CM are more viscous than monomeric forms) dimer are sono più viscosi dei monomerici).

CM half-life is about 2 hours (the 75% is eliminated within 4 hours, the 98% within 24 hours) and the 99% is eliminated from the kidney. In the renal tubule the CM increases the excretion of water and sodium. This osmotic force increases the intratubular pressure, leading to a reduction of the glomerular filtrate and, consequently, to the development of the AKI. The size of the injury is related to the chemical and physical characteristics of the CM (volume, osmolarity and viscosity).

Which CM?

The 2018 ESC guidelines on myocardial revascularization recommends the use a low or iso-osmolar CM (level IA) [7]. Modern CM are low lipophilic substances with high viscosity. The most used low osmolar CM is Iomeprol (Iomeron) and for the isosmolar one is Iodixanol (Visipaque). A study published in 2010 compared the indigente of CIN in patients treated with lowosmolar CM compared to those were treated with isoosmolar CM. The incidente of CIN was similar in the two groups and there are no reccomandation for the use of one type of CM instead of another one [5].

Optimal CM dosage

The developmente of CIN depends on the volume of CM used during the procedure. To identify a cutoff for a safety volume of CM, numerous parameters were developed. In 1989, Cigarroa., *et al.* described how adherence to a formula for a contrast material limit could be used to significantly reduce the rates of CI-AKI. The Maximal Allowable Contrast Dose (MACD) was defined by the following empiric formula: MACD = 5 mL x body weight (in kg)/serum creatinine (in mg/dL), with a maximum dose of 300 mL [8]. The incidence of CI-AKI among patients receiving contrast media in volumes exceeding the MACD is consistently higher compared to those who do not exceed the MACD (an average of 24% vs. 6%). Furthermore, the MACD is independent predictor of CI-AKI and other adverse events [9]. A study by Laskey., *et al.* involving 3179 all-comers for PCI advocated the use of a volume of contrast to creatinine clearance (V/CrCl) ratio. The cut-off point for the ratio of V/ CrCl was calculated at 3.7. The sensitivity and specificity of this ratio for predicting CI-AKI were 65 and 75%, respectively [10]. In additional studies, in 871 consecutive STEMI patients, the contrast medium volume to GFR ratio of 3.7 has been shown to be independently associated with a 3-fold in- crease in 1-month mortality [11]. The 2018 ESC guidelines on myocardial revascularization recommended the use of this parameter(level IB) [7]. A two-step algorithm incorporating the determination of the MACD and the contrast volume to eGFR ratio prior to a planned cardiovascular procedure is a sound approach to minimize contrast volume and prevent CI-AKI.

Mehran risk score

Mahran., *et al.* developed a simple risk model risk score of contrast induced nephropathy (CIN) after percutaneous coronary intervention. The Mehran CIN risk stratification score based on 8 readily available variables: 1) patient-related characteristics (i.e. age 75 years, diabetes mellitus, chronic congestive heart failure, or admission with acute pulmonary edema, hypotension, anemia, and chronic kidney disease); and 2) procedure-related characteristics (i.e. the use of elective IABP or increasing volumes of contrast media).

Each variable is associated with a score and the summe of the points defines the risk class. There are four classes of risk:

- Low ≤ 5 (risk of CIN 7,5%);
- Moderate 6-10 (risk of CIN 14%);
- High 11-16 (risk of CIN 26,1%);
- Very high ≥16 (risk of CIN 57,3%) [13].

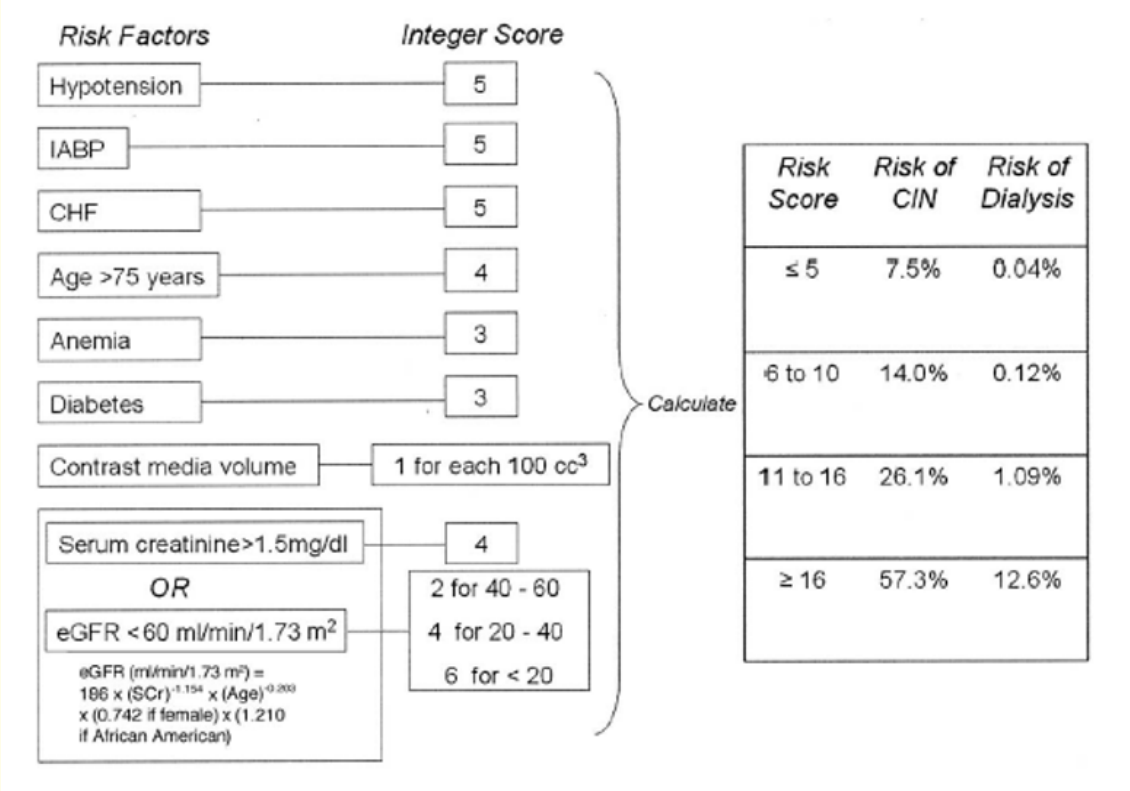

Figure 1: *Scheme to define contrast-induced nephropathy (CIN) risk score. Anemia baseline hematocrit value 39% for men and 36% for women; CHF congestive heart failure class III/IV by new york heart association classification and/or history of pulmonary Edema; Egfr Estimated glomerular filtration rate; Hypotension systolic blood pressure 80 Mm Hg for at least 1H requiring inotropic support with medications or intra-aortic balloon pump (IABP) within 24h periprocedurally [13].*

Diagnosis

The diagnosis of CIN is formuled on the observation of an increase of 25% or 0.5 mg/dl in pre-PCI serum creatinine at 48 h after PCI, after the esclusione of other causes of AKI [1]. Patient may be oliguric, anuric or with a normal urinary output. Additional laboratory findings such as acidosis and/or hyperkalemia may be present. Findings on urine examination are usually nonspecific. The most used markers of renal function is creatinine, but his elevation after AKI rises among 14 - 48 hours (late indicator of AKI). Creatinine values are also important, because are related with the increase of short term mortality. An elevation of serum creatinine around 10 - 24% increases the risk of 1 month death of 1.8 times, elevation around 25 - 49% increases the risk of death of 3 times and an elevation > 50% increases the risk of 6,9 times [12].

Therefore more sensitive and early markers of renal injury are individuated:

- Plasma neutrophil gelatinase-associated lipocalin (NGAL), also known as human neutrophil lipocalin, is an early predictive biomarker of AKI. It is a small protein of the lipocalin superfamily. More studies have identified tubularly secreted NGAL as specific biomarker for the early detection of AKI after contrast agent administration. NGAL increases in serum and urine levels after 2 hours and have a better sensitivity than Scr alone for AKI detection.

- Plasma cystatin-C (CysC) is a low molecular weight protein produced at a constant rate by all nucleated cells, is almost completely catabolized in the proximal tubule, its renal clearance cannot be measured, but its concentration in serum or plasma reflects the GFR. It is significantly increase in patients with CIN after 8 h. Nevertheless, the increment has also been noted in other conditions including corticosteroids administration, thyroid dysfunction, systemic inflammation, neoplasia, age, and an increase in the muscular mass [1].

Treatment

Nowadays there is not a treatment for CIN, the only therapeutic strategy is prevention.

We have to:

- Minimize contrast media volume used;
- Prevent blood volume depletion;
- Avoid nephrotoxic drugs [1].

Nephrotoxic drugs

The following drugs should be avoided: ACEIs, angiotensin receptor antagonists, aminoglycosides, amphotericin B, diuretics, NSAISs/ COX-2 inhibitors and antiviral drugs.

Pay attention on the use of metformin. It is eliminated from the kidney by 90%; AKI development allows metformin accumulati on which couldin creasetheri skofl acticacidosis.

For this reason it is recommended to suspend metformin 14 - 48 hours before exposure to the contrast media [1].

Oxidative stress prevention and idratation

As mentioned above, among the possible responsible mechanisms of CIN we have ROS developement, role of the physician must be the reduction of ROS developement.

Sodium bicarbonate

Sodium bicarbonate (9 ml/Kg iv) is a drug able to reduce CIN developement risk, through pH raising, prevent ROS developement with a net decrease of CIN, compared to the use of hypotonic saline solution alone [22] o with N-acetylcysteine iv [16]. Unfortunately there is not evidence of reduction of rates of: heart failure, in-hospital mortality and dialysis needing [15]. In contrast to previously exposed data, there are other clinical evidences that put in doubt the superiority [17] or show a worsening of clinical picture [18] following sodium bicarbonate infusion.

In conclusion, sodium bicarbonate's role in CIN prevention has to be clarified and needs further study.

N-acetylcysteine

Among antioxidant and vasoactive substances we have N-Acetylcysteine which is able to have a scavenger role on ROS and it is also able to promote dependent endothelial vasodilation [20]. The dose used in CIN prophylaxis is 1,200 mg, two doses before and two doses after the procedure. Despite its proven detoxifying value, as shown in acetaminophen poisoning, its therapeutic value in CIN prevention, in high-risk patients, has recently been revised.

The ACT trial compared CIN incidence in patients treated with NAC compared to a group treated with placebo, complication rate in the two groups is comparable. This show that N-Acetylcysteine alone has no nephroprotective action [21].

Statins

HMG-CoA reductase inhibitors in addition to lipid-lowering role have also an anti-inflammatory and detoxifying role that could be exploited in CIN prevention. Periprocedural statins use show a positive effect on nephroprotection [22,23] and their antioxidant and anti-inflammatory effect is able to reduce the CIN rate by 58% [24] Despite other studies [25] put in doubth the real benefit on nephroprotection, 2018 ESC guidelines on myocardial revascularization recommend the administration of high doses of statins (rosuvastatin 40/20 mg or atorvastatin 80 mg) before the procedure (level IIa) [7].

Saline solution

All the substances cited above are able to reduce CIN risk but the results are not yet consistent, in particular [26] taking into consideration only patients with pre-existing IRC the benefits decreased markedly. So, considering the costs and non-homogeneous results of the treatments analyzed, today the most effective strategy is hydration with saline solution. The mechanism through which hydration with saline solution prevents CIN development is non yet known, but it is hypothesized that it is linked to the dilution of the contrast media and to renal vasodilation obtained by RAAS (renin-angyotensin-aldosterone system) inhibiting [20,21].

Hydration

How many liquids to infuse?

2018 ESC guidelines on myocardial revascularization recommend hydration with isotonic saline before and after exposure to CM, if infused volume is greater than 100 mL (level IIa). Isotonic saline solution infusion must be 1.0 - 1.5 ml/Kg/h in the 3 - 12 hours before the procedure and must be continued for the next 6 - 24 hours maintaining a urinary flow rate greater than 150 mL/h. Also in patients with a previous CRF and left ventricular dysfunction (FE < 35%), after clinical control and hydration status, infusion of saline solution should be considered at rate of 0.5 mL/kg/h [7,28].

A standardized hydration protocol has been proposed in the POSEIDON study [29] and is based on the LVEDP measurement:

- 5 ml/kg/h if LVEDP < 13 mmHg;
- 3 ml/kg/h if LVEDP 13 - 18 mmHg;
- 1.5 ml/kg/h if LVEDP > 18 mmHg.

This algorithm has reduced the rate of complication development by 59% compared to standard protocol [29].

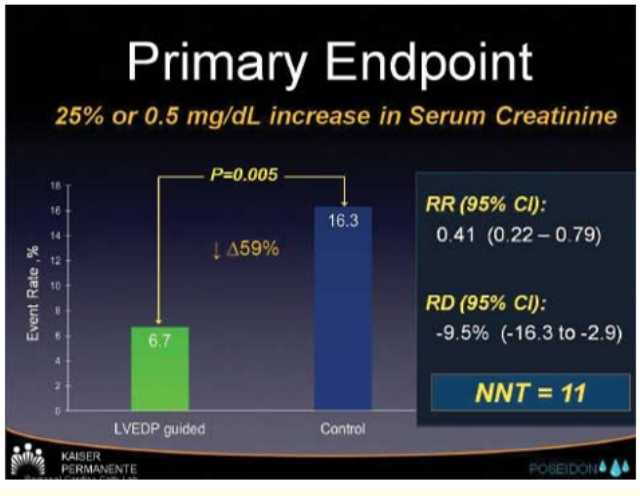

Figure 2: *Primary efficacy endpoint in LVED guided hydration group versus standard hydration protocol.*

Prevention in emergency setting

Even if it is recommended to start hydration several hours before procedure, in emergency situations we must perform PCI immediately and then hydration must take place in the peri and post procedural phase. A randomized trial of Maioli e., *et al.* [30] compared 3 different hydration strategies in STEMI patients to show the beneficial effect of an early hydration even in the acute setting:

- Group 1: Early, pre and post-PCI, hydration with NaCl 154 meq/L in isotonic saline solution (bolus 3 mL/kg and infusion of 1 mL/Kg/h for 12 hours);
- Group 2: Hydration after PCI with isotonic saline solution (1 mL/kg/h infusion for 12 hours);
- Control group: No hydration.

The rate of CIN development was respectively in the 3 groups of 12%, 22.7% and 27.3%. So even in the STEMI patients is recommended to start the hydratation earlier.

Patient with CRF

Particular case is the patient with chronic renal failure (CRF) in which we cannot force hydration. For a long time haemofiltration, after exposure to contrast media, was considered a cornerstone of preventive strategy for CIN in the CRF patient, to reduce in-hospital mortality and improve long-term prognosis.However, this technique is burdened by the needing to hospitalize the patient in ICU and its benefits are not supported by sufficient clinical evidence [1]. 2018 ESC guidelines on myocardial revascularization do not recommend hemodialysis as preventive measure in the CRF patient (IIIB) and advise considering it as a prophylactic treatment 6 hours before a complex PCI (IIbB) [7].

Water balance

Forced diuresis

There are many evidences in favor of hydration but water balance concept must be central. We must also analyze liquid losses and therefore diuresis, that will have to be forced for two reasons: it allows to facilitate contrast media clearance and it allows us to avoid the overload liquids induced by hydration. The theory of forced diuresis, to contrast the risk of AKI, is been proved in the P.R.I.N.C.E. study in which a regime of forced diuresis with intravenous administration of crystalloids, furosemide (if pulmonary capillary filling pressure < 20 mm Hg) and low dopamine doses was compared to standard hydration protocol. Target urine flow rate of greater than 150 ml/h in the first 24 h after the contrast exposure was related to a 52.9% reduction in renal failure [31].

Renal guard system

RenalGuard System (PLC Medical Systes, Inc.) is a device able to calculate fluids to be infused in real time. This system is able to create and maintain an high urinary volume output, allowing a urinary flow > 150 mL/h (ideally > 300 mL/h).

The RenalGuard working independently is able to produce the following effects:

- Reduction of constast media concentration that reaches kidneys;
- Speed up the passage of the CM through kidneys;
- Reduction in exposure to toxicity contrast media induced;
- Reduction of oxygen consumption in the renal medulla.

The fluid control system must be connected to the patient before, during and after the procedure, in particular: The system must be connected 30 minutes before the coronary angiography study, in this first phase a bolus of 250 ml of saline solution will be administered (150 ml if LVEF < 30%). The second step will have administration of diuretic: furosemide (0.5 - 0.25 mg/kg) to increase diuresis that will

reach the optimal target > 300 mL/h. Obviously drugs doses can be modified from patient to patient to reach urinary flow target. RenalGuard will monitor fluid losses to replace them by infusion, it is advisable to continue monitoring up to 4 hours after the last dose of CM [33].

Renal guard system or hydration?

The Remedial II study was a randomized trial, which compared the development of renal damage with RenalGuard System compared to control group (infusion of sodium bicarbonate and N-acetylcysteine), in patients with elevated risk of contrast media nephropathy (score > 11 and GFR < 30 ml/min/1.73 m^2). CIN was found in 11% of patients treated with RenalGuard, in the control group the rate of nephropathy was 20.5%. Serum Cystitin C level in patients of the Renal Guard group were stable despite the control and the urine flow were optimal and returned to normal rate after the RG therapy [33].

These results once again clarify the superiority of the automatic infusion system and establish that its use is beneficial to the patient at high risk, halving nephropathy incidence. It is proven that RenalGuard is able to decrease mortality, dialysis needing, stroke onset and post PCI coronary syndromes. RenalGuard is able to reduce the rate of development of contrast nephropathy by 3 times [32].

A recent meta-analysis [32] collected 4 RCT that compared the use of RenalGuard System to the traditional infusion strategy in patients subjected to PCI angiography or TAVR. The rate of development of nephropathy was 7.7% in the first group, while 23.6% in the control group ($p < 0.01$).

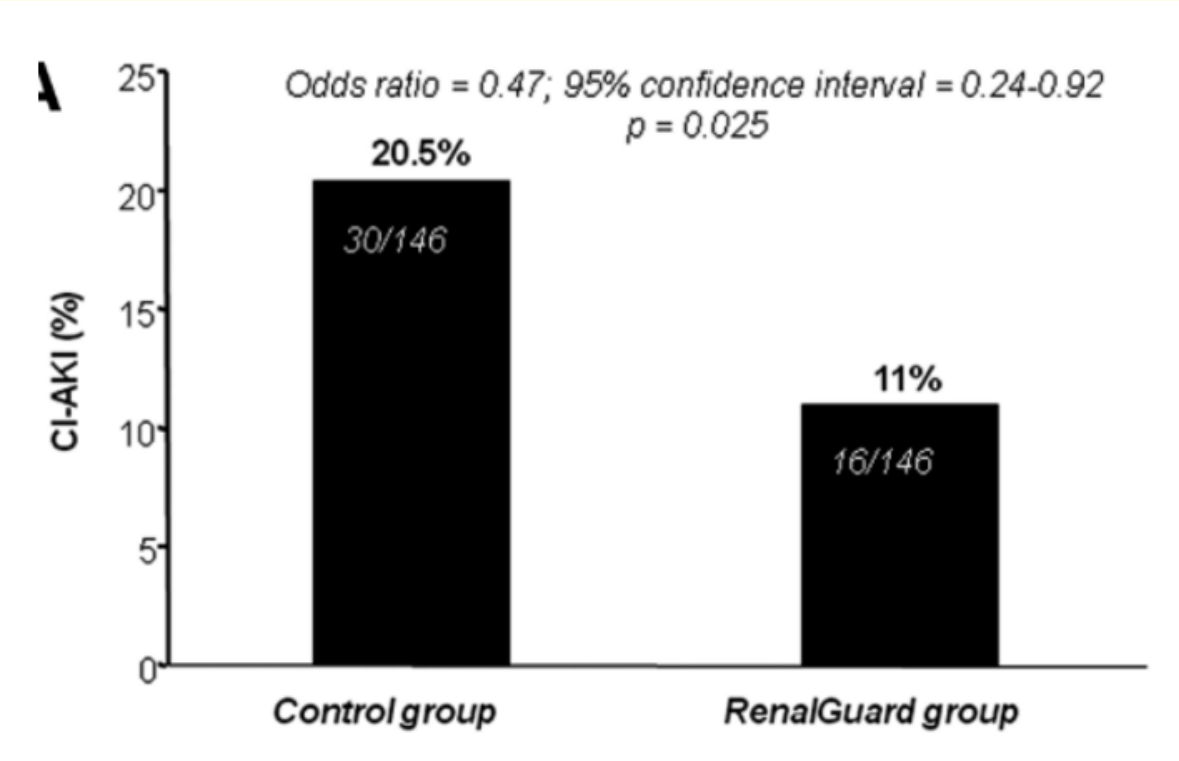

Figure 3: *Incidence of contrast-induced acute kidney injury (CI-AKI) in the control and RenalGuard groups [33].*

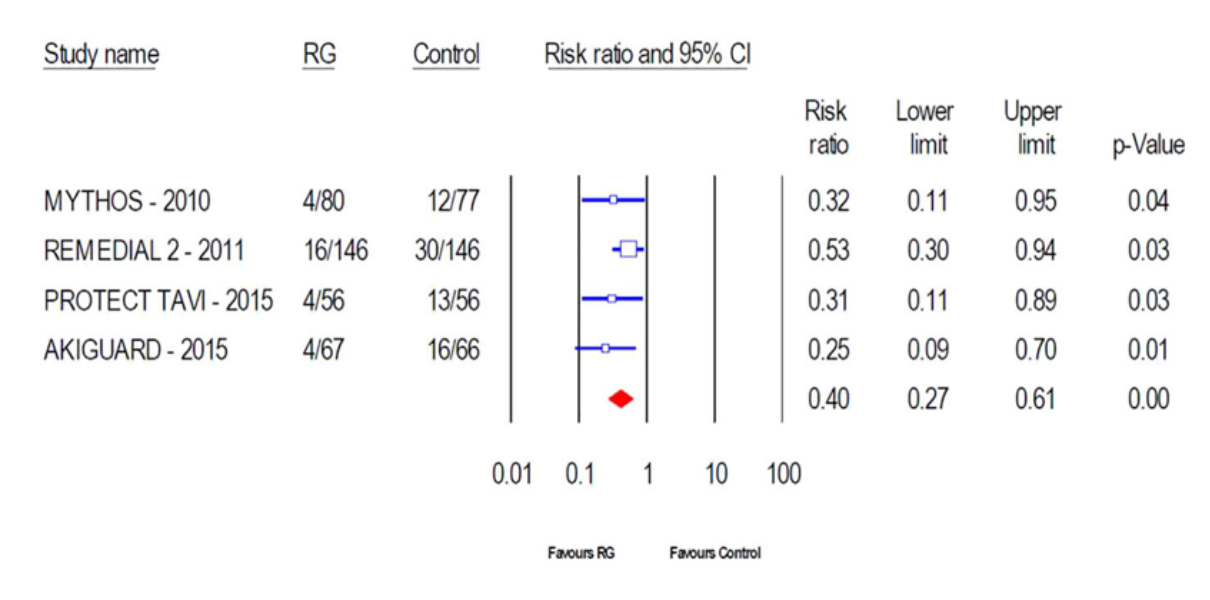

Figure 4: *Relative risk of CI-AKI in RG versus control in coronary angiography/PCI+TAVR.*

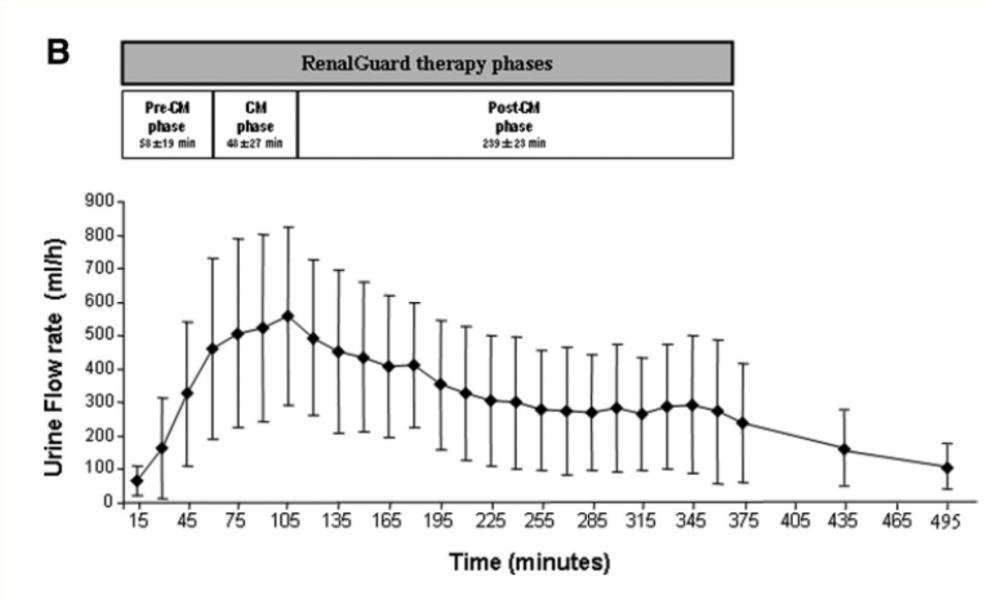

Figure 5: *Mean urine flow in the RenalGuard group. Urine output (mL/h) was recorded every 15 minutes during RenalGuard therapy and every hour after RenalGuard interruption. Pre-CM phase indicates precontrast media exposure or preprocedural time; CM phase, contrast media exposure or intraprocedural time; and post-CM phase, postcontrast media or postprocedural time [33].*

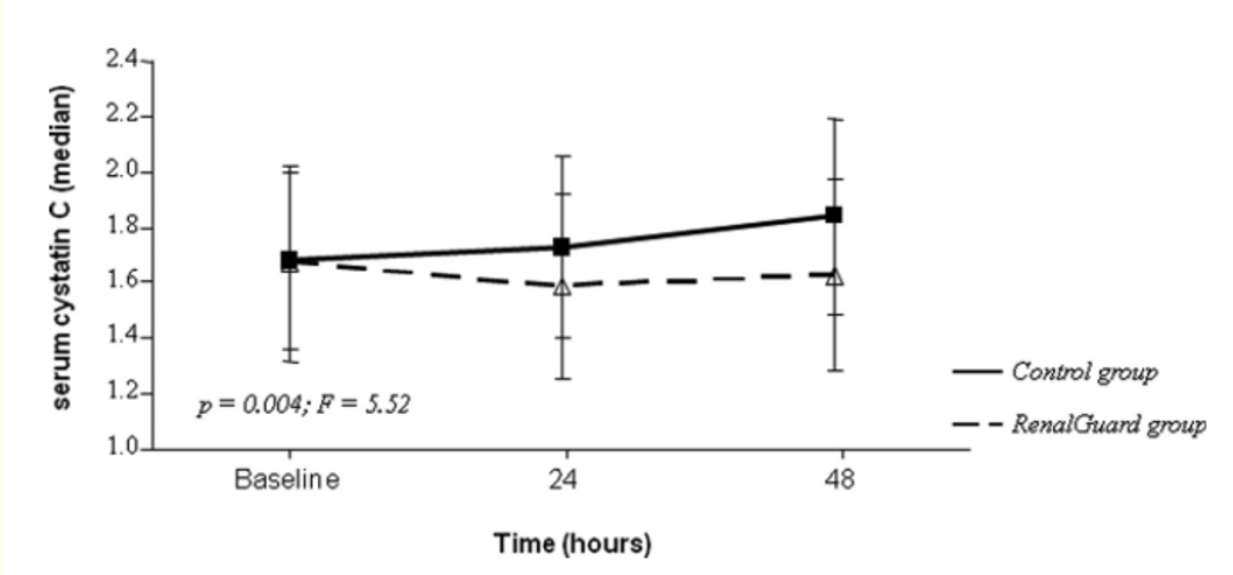

Figure 6: *Serum cystatin C concentration at baseline and 24 and 48 hours after contrast media administration in the control (continuous line) and RenalGuard (dashed line) groups [33].*

Despite these results the system also shows limitations:

- RG cannot be used in patients in whom a bladder catheter cannot be placed;
- Ideal doses of diuretic to maintain a high urinary flow need other studies;
- The POSEIDON study showed that hydration, based on the patient's hemodynamic framework, is more effective and safer [29].
- The clinical benefit obtained in cases in which the study is carried out urgently remains to be clarified.

Conclusion

All patients should be stratified for contrast-induced nephropathy risk with the Mehran score. The best clinical choice is prevention and is carried out by reducing the volume of CM (total contrast volume/GFR < 3.7) and avoiding nephrotoxic substances including diuretics. The best therapeutic and prevention strategy is hydration with saline solution 1 mL/Kg/h 12 hours before the procedure and continued for the next 24 hours (0.5 mL/Kg/h if LVEF < 35% or NYHA > 2). The use of the RenalGuard System is to be considered when EGFR < 30 mL/min/1.73m^2 and the Mehran Risk Score ≥ 11 (high risk).

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