Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Review article | Published 19 June 2012, doi:10.4414/smw.2012.13608
Cite this as: Swiss Med Wkly. 2012;142:w13608

Contrast-induced nephropathy in invasive cardiology

Incidence, pathophysiology, diagnosis, prevention and prognosis

Tilman Perrin, Eric Descombes, Stéphane Cook

Department of Cardiology and Nephrology, University and Hospital Fribourg, Switzerland

Summary

Contrast-induced nephropathy (CIN) is an acute renal injury due to the renal toxicity of iodinated contrast media. It is classically defined as a relative (≥25%) or absolute (≥0.5 mg/dl; 44 µmol/l) increase in serum creatinine from baseline value. CIN accounts for 10 to 15% of hospital-acquired acute renal failure and may rarely lead to irreversible renal function loss. Following percutaneous coronary intervention, reported incidence of CIN varies between 0 to 24%, depending on the prevalence of risk factors and used definition. Nowadays, the diagnosis of CIN relays on serum creatinine monitoring, although, it is a late marker of acute kidney injury. Given the expanding number of percutaneous coronary interventions made in outpatient settings and the morbidity and mortality associated with CIN, early detection of CIN is *of utmost* clinical relevance. Several plasmatic and urinary biomarkers have been studied in that view, with plasmatic cystatine-C and urinary NGAL being the most promising. As no treatment specifically targets CIN once it develops, the main goal for clinicians remains prevention, with hydration status optimisation being the only proven strategy to date.
Here, we will review the recent evidence concerning CIN incidence, proposed early diagnostic biomarkers, as well as its treatment and prognostic implication.

Key words: *contrast-induced nephropathy (CIN); percutaneous coronary interventions (PCI); review;biomarkers*

Introduction

Contrast-induced nephropathy (CIN) is a decrease in glomerular filtration rate (GFR) following the injection of iodinated contrast media (CM). It is the third most common cause of in-hospital acute renal failure (12%) after decreased renal perfusion (42%) and post-operative acute renal failure (18%) [1]. Several routine diagnostic examinations are CM-based and may therefore be complicated by CIN. Reported incidence of CIN is 11% following out-patient computed tomography [2], 9% after peripheral angiography [3], and 4% after intravenous pyelography [4]. When the vast majority of CIN cases still develop after standard radiologic examinations, this complication may also be increasingly encountered after percutaneous coronary interventions (PCI) due to growing numbers of procedures, multiple comorbidities in patients undergoing PCI and larger amounts of CM used for complex coronary lesions.
Functionally, CIN is considered an intrinsic acute kidney injury (AKI), usually with conserved diuresis, but in severe cases acute tubular necrosis and even end-stage renal disease may develop. As acute renal failure is associated with disabling morbidity and mortality [5], prevention and early detection of CIN are of utmost clinical relevance [6, 7].

Definition

After intravascular CM injection, immediate renal toxicity may occur, and in most cases it remains fortunately free of significant clinical consequences. However, renal function can diminish and serum creatinine (SCr) may increase in the following days. In absence of an universally accepted definition [8], most authors define CIN as a relative (≥25%) or an absolute (≥0.5 mg/dl = 44 µmol/l) increase in SCr from baseline. In case of contrast-induced toxicity SCr typically rises within the first 24–48 hours after exposition, peaks at 3–5 days and returns near to baseline within 1–3 weeks [9]. How-ever, irreversible renal function losses occur in rare cases. Obviously, in addition to CM exposure, the diagnosis of CIN requires (1.) a temporal relationship between CM exposure and SCr elevation, and (2.) the exclusion of an alternative cause to the acute renal failure.

Epidemiology and prognosis

When considering the largest randomised controlled trials (n ≥250) addressing CIN following PCI during last 5 years, protocol-defined CIN incidence ranges between <1% to >20%, with an increased incidence after emergency PCI [10–29].

An increase in SCr post-PCI is associated with poorer outcome regardless of initial renal function. In *all-comers patients*, even a mild increase in SCr (10–24% or 25–35 µmol/l) is linked to increased 30-day mortality (RR of 1.8 [CI 1.3–2.5]) [30] and, if patients suffering from acute myocardial infarction are excluded, a post-PCI SCr elevation is even associated with a higher 1-year mortality than periprocedural myonecrosis [31]. In a retrospective study of 5967 all-comer patients with *normal renal function* undergoing PCI, Lindsay and colleagues reported that both the 1-year myocardial infarction rate (24.0% vs 11.6%, p <0.005) and the 1-year mortality rate (9.5% vs 2.7%, p <0.005) were significantly higher in those 208 patients (3.5%) developing significant CIN. This trend was even stronger in patients needing temporary dialysis (1.5% of CIN patients) and remained significant after adjustment for potentially confounding factors (age, diabetes, prior myocardial infarction).[32] Similarly, in 439 patients with *chronic renal failure* undergoing PCI, Gruberg and colleagues showed that 7% required transitory haemodialysis and 0.9% were discharged on chronic dialysis. Among the 161 (37%) patients developing CIN, there was a 2 to 3-fold increase in in-hospital (15% vs 5%, p = 0.001) and 1-year mortality (35–45% vs 19%, p = 0.001) in comparison to patients without CIN [33].

Finally, in an attempt to stratify the prognosis of patients who already developed CIN after PCI, Harjai and colleagues proposed a 3-level scoring system (grade 0 [SCr <25% and <44 µmol/l], grade 1 [SCr ≥25% and <44 µmol/l] and grade 2 [SCr ≥44 µmol/l]), and suggest that an increasing grade is correlated with a worse long-term outcome after PCI (6-month MACEs [12.4 vs 19.4 vs 28.6%, p = 0.003]; 6-month all-cause mortality [10.2 vs 10.4 vs 40.9%, p <0.0001]; n = 985) [34].

Physiopathology of renal iodine toxicity

CIN is a reduction in renal function consequent to the renal toxicity of intravascular iodine contrast. The physiopathology of CIN is multifactorial and is still incompletely understood. As shown in figure 1, at least five mechanisms could contribute to its pathogenesis:

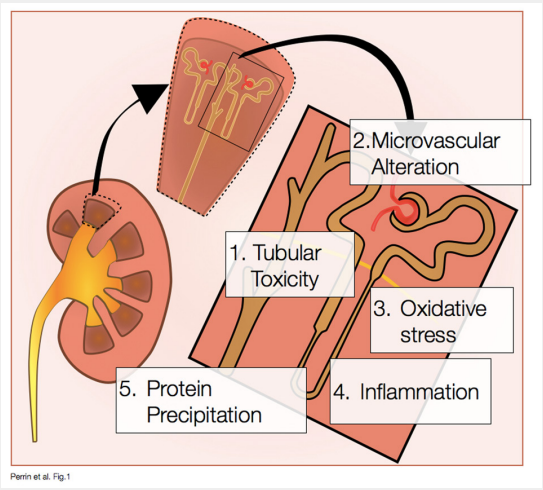

Figure 1

Scheme of hypothesised pathways contributing to CIN pathogenesis.

1. *Direct toxicity of CM to tubular epithelial cells*: CM increase tubular osmolarity, as they are freely filtered and not resorbed. Tubular cells exposed to high osmotic load have been showed to suffer from impairment in intracellular transport and energy metabolism. They develop cytopathological changes called “osmotic nephrosis”, ranging from tubular cell vacuolisation to necrosis [35].
2. *CM-induced alteration in renal microvascular haemodynamics*: Trials investigating modifications of blood flow in renal arteries exposed to CM have shown an initial increase in blood flow followed by a sustained reduction.[36] This might be the result of (a) a CM-induced increase in intratubular pressure leading to a decrease in renal blood flow, (b) a direct vasoconstrictor effect of CM on smooth muscle cells, (c) an increased tubuloglomerular feedback due to increased tubular osmolarity, and (d) CM-induced release of several endogenous vasoconstrictors such as adenosine and endothelin.[35] Blood flow reduction unfortunately affects particularly the outer medulla, which is particularly susceptible to ischaemia due to its high metabolic activity [36]. Ischaemia is obviously worsened by the impaired microvascular self-regulation found in diabetic and hypertensive patients.
3. *Reperfusion and reactive oxygen species toxicity*: Reactive oxygen species released by the subsequent reperfusion also contribute to renal damages. As the antioxidant reserve is decreased in elderly and the baseline oxidative stress is increased with CKD or diabetes, theses patients are especially vulnerable [36].
4. *Toxicity due to inflammation*: Similarly to other tissues, renal parenchymal damages may be worsened by CM-mediated complement cascade activation and inflammatory cytokine release [36].
5. *Toxicity due to tubular obstruction*: Precipitation of intratubular proteins induces by CM has been proposed to contribute to CIN. However, CM failed to precipitate Tamm-Horsfall protein *in vitro* and no evidence support this theory in clinical trials [35, 36]. Similarly, although some trials report massive precipitation of Bence-Jones protein in myeloma patients, the risk is decreased with new generation CM and hydration [35, 37, 38].

Therefore, the osmolarity as well as the viscosity and ionic properties of CM are involved in nephrotoxicity. It should finally be stressed that CIN remains an exclusion diagnosis with only spare histopathological findings. Therefore, a nontrivial proportion of “CIN”-labelled AKI might be of different aetiology, such as due to cholesterol or thromboembolic emboli, peri-interventional- hypotension, or interstitial nephritis due to different mechanisms.

Risk factors and risk assessment

Risk factors for CIN can be divided into *patient-related* or *intrinsic* risk factors, and *procedure-related* or *extrinsic* risk factors. Most prevalent *intrinsic* risk factors are pre-ex-

istence of renal failure, concomitant hypotension, presence of congestive heart failure, older age, anaemia, diabetes mellitus, and concomitant use of nephrotoxic drugs [6, 39, 40]. On the other hand, *extrinsic* risk factors comprise the total amount and type of CM used, its route of administration (arterial versus venous) and the time period between two (or iterative) CM expositions [41, 42].

To help clinicians to minimise or stratify the risk of CIN, several score have been proposed. Mehran et al. compiled a "simple risk score" illustrated in table 1 to predict CIN occurrence after PCI, with weighted coefficients for independent predictors of CIN. Risk 1 category (≤5 points) is associated with a 7.5% risk of CIN and 0.04% risk of dialysis; risk 2 category (6 to 10 points) with risks of 14% and 0.12%; risk 3 category (11 to 16 points) with risks of 26.1% and 1.09%; and risk 4 category (≥16 points) with risks 57.3% and 12.6% respectively [40]. As it is known that CM volume is an important factor for renal toxicity, other authors tried to determine a volume to risk correlation, particularly in high-risk patients. In patients with CKD, Brown and colleagues proposed the calculation of a "maximal allowable contrast dose" (MACD; contrast volume limit [ml = 5 × body weight {kg}]/[88.4 × SCr {µmol/l}]). Their results showed that patients receiving contrast volumes exceeding the MACD were more likely to develop CIN or to need dialysis (propensity-matched OR if exceeding the MACD 1.75 [95%CI 1.49–2.07, p <0.001] and 3.13 [1.73–5.65, p <0.001] respectively) [43]. In patients with ST-elevation myocardial infarction, Nymann et al. proved that an adjustment of contrast amount to the eGFR allows a reduction of the incidence of CIN [44].

Early diagnosis

CIN induces the same clinical and laboratory abnormalities than other causes of acute renal failure. Most patients developing CIN are asymptomatic, but in severe cases they become oliguric or anuric. Metabolic acidosis and hyperkalaemia are the most frequent laboratory findings, with potential fatal consequences. Microscopic urine examination may show renal tubular cell casts and/or debrits as well as urate and/or oxalate crystals. However, these findings are not specific for CIN [45]. A persistent nephrogram on radiograph or CT-scan has been studied for detection of CIN [46], but its clinical relevance has not been validated. Therefore, the diagnosis of acute kidney injury (AKI) relies on the monitoring of functional markers and/or biomarkers in serum and urine. To improve patient management, an ideal marker should be accurate and proportional to renal injury, and have an early kinetic after renal damage. Moreover it should help to differentiate acute structural damage (AKI) from functional impairment (prerenal azotaemia) or chronic kidney disease (CKD). This is even more important as intrinsic acute renal failure is grieved with an increased risk of in-hospital mortality and/or need for dialysis [47].

In daily practice, changes in *SCr* are used to estimate acute modifications in renal function and SCr monitoring remains the cornerstone for diagnosis of CIN. Unfortunately creatinine is a late and insensitive indicator of acute changes in renal function as there is a 24–48 hours delay between renal insult and SCr changes [48].

Because of this pitfall and since an early diagnosis may decrease morbidity and improve patient survival [49], accurate biomarkers are eagerly awaited for the early detection of tubular dysfunction/lesion. In invasive cardiology, early detection of CIN could allow a pre-discharge selection of outpatients needing hospitalisation for closer renal, metabolic and volaemic control. Recently, several promising biomarkers of tubular insult have been under investigation and the following plasmatic or urinary ones are of special interest. Table 2 summarises some of their characteristics relevant for the diagnosis of CIN.

Potential plasmatic biomarkers

Plasma Neutrophil Gelatinase-Associated Lipocalin (NGAL or Lipocalin-2 [LCN2]).

NGAL is of particular interest in this setting and has been considered as the "renal troponin" [50]. NGAL is a small protein of the lipocalin superfamily that was first isolated in 1993 from the supernatant of activated human neutrophils [7, 51]. It is also expressed and secreted by immune cells, hepatocytes and renal tubular cells in various pathologic states. Beside its bacteriostatic effects by transmembranous iron shuttling, NGAL acts as a growth and differentiation factor in multiple cell types, including renal epithelia, where it limits apoptosis and contributes to maintain the tubular structure [52]. NGAL is massively and rapidly upregulated in kidneys following an ischemic or nephrotoxic injury, and is thought to participate in limiting parenchymal damage [52, 53]. It is primarily synthesised in the ascend-

Table 1: Independent risk factors for Contrast-Induced Nephropathy (CIN) and calculation of Mehran simple risk-score.

CIN risk factors	Mehran simple risk-score definition [40]	Integer score
Decreased renal perfusion	Systolic blood pressure <80 mm Hg for at least 1 h requiring inotropic support with medications or intra-aortic balloon pump within 24 h of the procedure	5
	Intra-aortic balloon pump within 24 h of the procedure	5
	Congestive heart failure class III or IV by New York Heart association classification and/or pulmonary oedema	5
Older age	Age >75 years	4
Anaemia	Baseline haematocrit value <39% for men and <36% for women	3
Diabetes	Present or not	3
Contrast media volume	Absolute amount	1 for each 100 ml
Impaired baseline renal function	Baseline serum creatinine >1.5 mg/dl or Baseline eGFR <60 ml/min	4 2 for 40–60 4 for 20–40 6 for <20

ing loop of Henle and in collecting ducts but has also nephroprotective effects in the proximal tubule [52]. NGAL – as marker of AKI – is increasingly studied since its serum and urinary levels increase well before the increase of SCr [54] and have a better sensitivity than SCr alone for acute kidney injury detection [48]. More specifically, plasma and urine NGAL levels are also known to be powerful independent predictors of CIN, in-hospital outcomes, and risk for dialysis or death [7, 48, 55]. However, despite being considered as a promising biomarker for early diagnosis of acute tubular necrosis by several authors [56], plasma NGAL (pNGAL) is less specific than its urinary counterpart. In fact, pNGAL is already increased in patients with CKD [53] or systemic illnesses [52], and increases 6-times less than urinary NGAL in case of renal injury [52].

Plasma cystatine C (CysC)

CysC is produced at a constant rate by all nucleated cells. Under normal circumstances, it is freely filtered by the glomeruli and totally reabsorbed in the proximal tubule. In the absence of tubular dysfunction, its serum level reflects glomerular filtration and can be used as a functional marker for acute and chronic changes in GFR [57]. In intensive care settings, plasma cystatine C (pCysC) was able to detect AKI earlier and was more sensitive than SCr in detecting minor glomerular filtration rate reductions [58, 59]. This early increase of pCysC following a renal insult is also reported in trials addressing renal CM toxicity [60, 61]. In CKD patients, a >10% increase in pCysC 24 hours after PCI predicts CIN (as defined by a >0.3 mg/dL increase in SCr) with a sensitivity of 100% and a specificity of 86% (n = 410) [62]. Unfortunately, pCysC levels may also be influenced by several non-renal factors including corticosteroids administration, thyroid dysfunction, systemic inflammation, neoplasia, age and eventually muscular mass [57].

Potential urinary biomarkers

Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL or Lipocalin-2 [LCN2])

Urinary NGAL (uNGAL) is increased in case of AKI and remains low in patients with prerenal azotaemia or normal renal function [49, 63]. To note, less than 0.2% of tagged NGAL injected in the circulation appears in urine during the first hour [64]. uNGAL is of interest for the early diagnosis of CIN, as it increases already 2 hours after tubular injury [54]. Haase M. et al. analysed data from 191 patients in 3 studies and found that when uNGAL is measured within 6 hours after CM exposition, the sensitivity is 0.78, the specificity is 0.96, and the area under the receiver operating characteristic (ROC) curve is 0.89 for the diagnosis of CIN (cut-off for uNGAL: 100 ng/ml) [56].

Urinary interleukin-18 (IL-18, interferon-gamma-inducing factor)

In 2004, Parikh and colleagues demonstrated that patients with acute tubular necrosis had significantly greater median urinary IL-18 (uIL-18) concentrations than those with other renal conditions (normal renal function, pre-renal azotaemia, urinary tract infection, and chronic renal insufficiency). Therefore, they proposed it as a specific biomarker of proximal acute tubular necrosis [65]. More recently, the same group showed in patients undergoing cardiac surgery that increased uIL-18 levels were associated with AKI, longer hospital stay and higher risk for dialysis or death (cut-off: 60 pg/ml) [55]. On the other hand, 24 hours after PCI uIL-18 levels are significantly increased in patients developing CIN compared to controls, reducing the diagnostic delay by 24 hours [66].

Urinary liver-type fatty acid-binding protein (L-FABP)

L-FABP is a cytoplasmic protein that facilitates the long-chain fatty acid transport from the plasma membrane to beta-oxidation sites and reduces the oxidative stress by binding of fatty acid oxidation products [67]. Its urinary levels are significantly elevated in patients with AKI [67, 68]. This biomarker is of particular interest as a sensitive and predictive early biomarker of AKI, but it might have a low specificity due to interferences with different systemic processes regularly found in critically-ill patients [67]. Interestingly, according to the study by Nakamura and colleagues (n = 66), even *pre*-PCI urinary L-FABP levels predict CIN [69].

Urinary kidney injury molecule-1 (KIM-1)

KIM-1 is a transmembranous protein normally not detectable in urine, but expressed at very high levels in proximal tubular epithelial cells soon after an ischemic or toxic injury [70]. Han and colleagues report that urinary KIM-1 is able to rapidly detect AKI [70], with higher levels for "pure" ischaemic insult than for other types of acute renal failure [71]. Since the pathogenesis of CIN is multifactorial, the use of this biomarker seems limited in this particular context [71, 72].

Urinary N-Acetyl-β-glucosaminidase (β-NAG)

β-NAG is a lysosomal enzyme found mainly in proximal tubular cells that is a sensitive marker of proximal tubular injury from various aetiologies [70]. Compared with SCr, urinary β-NAG peaks earlier [73]. However, its discrimat-

Table 2: Relevant characteristics of biomarkers for the diagnosis of CIN after PCI.

Biomarker■*	Molecular weight (kDa)	Site of lesion	Significant increase in CIN-patients	AUC for CIN-prediction (cut-off)
pNGAL	25	Distal and collector tubules	2 hours [111]	0.92 (≥100 ng/ml at 2 hours) [112]
pCysC	13	Glomeruli and proximal tubule	8 hours [111]	0.92 (≥10% increase at 24 hours) [62]
uNGAL	25	Distal and collector tubule	2 hours [111]	0.92 (≥100 ng/ml at 2 hours) [112]
uIL-18	18	Distal tubule	8 hours [111]	0.75 (≥25% increase at 24 hours) [66]
uL-FABP	14	Proximal tubule	24 hours [111]	NA
uβNAG	130	Proximal tubule	24 hours [73]	NA

* ■; βNAG = n-acetyl-β-glucosaminidase; CysC = cystatin C; IL-18 = interleukin 18; L-FABP = liver fatty acid-binding protein; NGAL = neutrophil gelatinase-associated lipocalin; p = plasma; u = urinary.

ive power seems insufficient to allow clinical use for AKI diagnosis [63].

Prevention and therapy of CIN

Patients developing CIN should receive similar supportive care as every patient with acute renal failure: monitoring and correction of serum electrolytes abnormalities and metabolic acidosis, and tight control of fluid balance. Therefore, as no treatment specifically targets CIN, the main goal for clinicians remains prevention and support. Table 3 summarises the main preventive guidelines. First of all, some *general considerations* should be kept in mind: the *indication* for contrast-based procedures should always be pondered carefully and outweighed against the potential risk of CIN. Then, whenever possible, concomitant *nephrotoxic drugs* such as non-steroidal anti-inflammatory drug, nephrotoxic antibiotics or chemotherapeutic agents and/or *iterative exposition* to CM should be avoided.

Contrast media (CM)

The type and amount of contrast medium impact on the risk of CIN. Briefly, all iodine CM consist in ≥1 benzene ring linked to three iodine atoms. Three generations have been described according to the osmolality. The *first-generation* contrast agents (*iothalamate, diatrizoate, metrizoate*) are composed of iodinated ionic monomers and are considered "ionic high osmolar" (about 2000 mOsm/l), as an ionizing carboxyl group dissociates in solution. The *second-generation* contrast agents (*iohexol, ioversol, iopromide, iomeprol, iopamidol*), called "low-osmolar", are nonionic monomers with intermediate osmolality. Finally, the *last generation* of contrast agents (*iodixanol*) are dimers of two benzene rings and are virtually "iso-osmolar" in comparison to plasma (290 mOsm/l) [8, 74]. It is considered that osmolality *per se* contributes to the reported difference in CIN incidence, with lessened osmotic load and tubular work for last-generation CM [75, 76]. In a meta-analysis Barrett et al. concluded that the incidence of CIN is significantly reduced by use of "low-osmolar" compared to "ionic high-osmolar" CM only among patients with pre-existing CKD [77]. In addition, From et al. report that "iso-osmolar" agents shows a significant benefit when compared to iohexol but not in comparison to other "low-osmolar" CM [78]. However, "high-osmolar ionic" CM have progressively been replaced by "low or iso-osmolar" agents in current routine practice.

As discussed previously, the volume of the CM used also contributes to the risk of renal toxicity. Therefore, in high-risk patients and even more in patients with pre-existing renal failure or diabetes, the CM volume should be limited as much as possible and, in example, levography done only if echocardiographic measurement is not possible.

Hydration

Hydration is the best-proven way to prevent CIN [13, 79]. Isotonic normal saline (NaCl 0.9%) is routinely used. The use of sodium bicarbonate (NaBic 1.4% or NaHCO3 154 to 166 mEq/l) is also of interest since it reduces the production of free radicals by decreasing tubular acidity and scavenges the oxidant pernitrite [80]. Individual results from trials comparing normal saline (NaCl 0.9%) to sodium bicarbonate (154 mEq/l in dextrose 5%) gave contradictory results [12, 13, 17, 19, 21, 22], but a recent meta-analysis by Kunadian et al. favours the use of sodium bicarbonate [80].

Hydration is usually performed using a peripheral line, with a classical infusion rate of 1 ml/kg/h during 12 hours before and after PCI. To note, the pre-PCI hydration can be replaced by a rapid one-hour perfusion (3 ml/kg) in emergency situations. Using a combination of oral volume supplementation and intravenous isotonic or half-isotonic infusion at a rate of 1 ml/kg/h between 8 a.m. the day of procedure and 8 a.m. the following morning, Mueller and colleagues reported a CIN-incidence (≥0.5 mg/dl increase in SCr within 48 hours of procedure) as low as 1.4% after PCI in a Swiss cohort of 425 consecutive patients (mean baseline eGFR: 89 ml/min). Even in the subgroup of patients with eGFR ≤60 ml/min (n = 43), the incidence of CIN remained low (4.7%), with no patient requiring dialysis [81].

To maintain an optimal hydration status and a high urinary output (≥300 ml/h), while minimising the risk of pulmonary edema, Briguori et al. proposed the use of the RenalGuard System, which matches urinary output with intravenous hydration and furosemide administration. The nephro-protective effect of this system may be due to an increased urine output diluting the tubular CM, and to the blockade of the Na-K-2Cl co-transporter, decreasing the oxygen consumption of tubular cells. Briguori et al. showed that the use of the RenalGuard System with normal saline hydration in high-risk patients (eGFR ≤30 ml/min and/or Mehran risk score ≥11 points) significantly decreases the incidence of CIN (2.7%), when compared to usual hydration with sodium bicarbonate (13%; p = 0.001) [82]. Although the hydration solution was different in both groups, the nephron-protective effect of the RenalGuard system was already shown with use of normal saline in both control and RenalGuard groups by Bartorelli et al. [83]. Finally it is worth noting that patients treated with

Table 3: Prevention of CIN (based on references [39, 113, 114]).

Clinicians should:
1. Be aware that CIN is a potentially serious complication.
2. Ponder the risk and benefit of any CM-based exam.
3. Optimise hydration status with oral and intravenous fluids.
4. Stop concomitant nephrotoxic medications (diuretics, NSAIDs, chemotherapy).
5. Use only new generation CM.
6. Use the lowest amount of CM.
7. Monitor SCr at 24–72 hours after CM-exposition, at least in high-risk patients.
8. Try keeping 1 week interval between 2 CM-based exams.

the RenalGuard System had no increased risk of periprocedural pulmonary edema or electrolyte imbalance [82]. However, , even if RenalGard gated hydration seems to be a promising tool for prevention of CIN, one should not forget the difficulty of its use in emergency settings and the risk of urinary tract infection brought by ureteral catheterisation.

Nephroprotective drugs

N-acetylcysteine (NAC)

The prophylactic use of NAC is under debate. Being a precursor for glutathione synthesis, NAC has the potential to diminish oxidative stress by directly scavenging superoxide radicals and increasing intracellular glutathione. In addition, NAC improves renal haemodynamics by combining and stabilising bioavailable nitric oxide [10, 84, 85]. However, since the first positive study addressing NAC for the prophylaxis of CIN in 2000 [86], several trials have given discordant results [10, 27, 87, 88]. The recently published Randomised Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT) addressing 2308 patients with at least 1 risk factor for CIN undergoing coronary or peripheral angiography fails to show a beneficial effect of high-dose NAC on CIN-incidence (12.7%) or other composite outcomes. Even subgroups analysis, for example in patients with pre-existing kidney disease or diabetes, does not show a significant benefit of NAC [10].

Statins

Beside their hypolipaemic role, statins improve endothelial function and decrease oxidative stress and inflammation [89]. In a review by Zhang and colleagues, chronic statin treatment (≥1 week) reduces the risk of CIN ($p < 0.05$), whereas a short-term high-dose therapy does not [89]. These results have to be interpreted cautiously due to heterogeneity in statin regimens (drug used, doses and duration of therapy) and in procedural characteristics [90–92].

Vasoactive drugs

As contrast administration elicits an afferent arteriolar vasoconstriction that decreases renal blood flow and glomerular filtration rate, several vasoactive treatments have been studied in small collectives with some encouraging results.

Prostaglandin E_1

Prostaglandin E_1 (PGE_1) is a well-known vasodilator that improves renal blood flow. A 20 ng/kg/min PGE_1 infusion has a significant protective effect on post-PCI SCr elevation [93, 94], but higher infusion rates are not associated with increased benefits, probably due to the associated decrease in systemic blood pressure [93].

Dopamine

"Low-dose" or "renal-dose" dopamine (0.5–2.5 µg/kg/min) has also been proposed for CIN prevention as it (1.) increases renal plasma flow and glomerular filtration rate via a dilatory effect on renal vasculature, (2.) improves tubular function and (3.) increases cardiac output [95]. However, neither Gare et al. nor Abizaid et al. show any significant beneficial effect of dopamine for CIN-incidence reduction in CKD patients [95, 96].

Fenoldopam mesylate

Fenoldopam mesylate is a specific dopamine-1 receptor agonist that selectively increases both the renal cortical and outer medullary blood flow while decreasing systemic vascular resistance. Unfortunately it also fails to reduce CIN-incidence in CKD patients [97, 98]. To note, some dedicated catheters, such as the *Benephit system*, have been designed in order to deliver per-procedural protective treatments directly into the kidney arteries. In a retrospective serie of 285 patients, Weisz et al. reported a 71% decreased in CIN incidence with local fenoldopam therapy (0.05–0.8 µg/kg/min) [99].

Theophylline

Adenosine is a vasoactive mediator which levels increase secondary to oxygen consumption or decreased intracellular ATP and contributes to afferent arteriolar vasoconstriction in kidneys following CM-exposure. The clinical benefit of the competitive adenosine antagonist theophylline is debated. Erley and colleagues reported that theophylline administration prevents a post-PCI fall in GFR measured by inuline clearance during the 4 post-procedural hours [100]. However other groups found no significant protective effect of theophylline on renal function [88, 96, 100, 101].

Calcium channel inhibitors

It has been shown that calcium channel inhibitors antagonise pre-glomerular vasoconstriction in dogs [102] and prevent increases in intracellular calcium concentrations in anoxic animal cell culture [103]. However, their short-term use for CIN prevention yielded various results: only one trial showed benefit of initiating a calcium inhibitor treatment shortly before PCI [104], while the others did not [105, 106].

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors (ACEIs) play an important role in treating heart disease and some of its risk factors. Angiotensine-II acts on renal micovascular haemodynamic homeostasis by inducing efferent arteriolar vasoconstriction. As ACEI are known for decreasing GFR, several groups have addressed their role in CIN. In a recent review, Patel and colleagues found conflicting results of the short- and long-term ACEI use on CIN-incidence, even in high-risk patients [107]. On the other hand, pre-procedural withholding of long-term (≥1 month) ACEI or ARB therapy in patients with stage III-IV CKD undergoing elective PCA has shown no beneficial effect on SCr levels measured one day after contrast medium exposure [24].

Conclusions

In view of these elements, several unresolved questions remain concerning the management of CIN. First of all, CIN is usually an asymptomatic complication, which diagnosis relies on SCr increase following CM exposition, but without clear-cut diagnostic criteria. Second, the physiopathology of CIN is multifactorial and still incom-

pletely understood, making it hard to improve diagnostic and therapeutic tools. Third, the comparison of CIN-incidence between trials is matter of caution, as CIN definitions and prevalence of risk factors are often quite different among the studies. However, once the contributing variables are taken into account, it appears that in the era of modern contrast media, CIN remains, fortunately, reversible in most cases. Even in patients with risk factors such as CKD or diabetes, the risk of dialysis-dependent end-stage renal disease due to CIN remains low (<1%). It is important to note that although gadolinium has been proposed as CM for angiography in high-risk patients for CIN, its use is grieved with the risk of development of nephrogenic systemic fibrosis (NSF) in CKD patients, especially those with eGFR ≤30 ml/min or dialysis-dependent [108]. In CKD patients, the incidence of NSF could even exceed the risk of CIN, as some series show the incidence to be as high as 5% [109, 110]. As there is no available treatment to stop the chronic progressive course of the disease resulting in variable organ damage (skin, joints, lungs, kidneys…) and leading to death, the European Society of Urogenital Radiology does not recommend the use of gadolinium to avoid the nephrotoxicity associated with iodinated CM [108].

As no treatment specifically targets CIN once it develops, the main goal for clinicians remains prevention. They can use several scores to carefully estimate the risk of CIN before referring a patient for elective PCI, particularly for high-risk patients and/or procedures. Once decision for CM-injection is made, clinicians have only 2 proven ways to reduce the incidence of CIN: (1.) optimal hydration – with some data favouring the use of sodium bicarbonate over normal saline – and (2.) the use of lowest amount of CM. To date, N-acetylcysteine, as well as all other drugs, failed to confirm any beneficial preventive effect in large-scale randomised studies.

In current practice, the standard method for renal function monitoring remains SCr, although it is late and insensitive. As the number of PCI made on outpatient basis grows, there is an urgent need for tools allowing an early and accurate detection of CIN. In this regard urinary NGAL and plasma cystatin C seem to be the most promising. Permitting closer renal function monitoring after CM exposure, these early biomarkers will also help developing new preventive and/or therapeutic methods for the management of CIN. However, in view of the very rare long-term consequences of CIN after PCI, and as long as no specific treatment targets CIN, we recommend the use of theses costly biomarkers only for selected patients.

Funding / potential competing interests: This work was funded by the “Schweizerische Herzstiftung” (Bern, Switzerland) and the “Fondation Lausannoise pour la Recherche en Hypertension” (Lausanne, Switzerland).

Correspondence: *Professor Stéphane Cook, MD, Department of Cardiology, University & Hospital Fribourg, CH-1708 Fribourg, Switzerland, stephane.cook[at]unifr.ch*

References

1 Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. Am J Med. 1983;74(2):243–8.

2 Mitchell AM, Jones AE, Tumlin JA, Kline JA. Incidence of contrast-induced nephropathy after contrast-enhanced computed tomography in the outpatient setting. Clin J Am Soc Nephrol. 2010;5(1):4–9.

3 Karlsberg RP, Dohad SY, Sheng R. Contrast-induced acute kidney injury (CI-AKI) following intra-arterial administration of iodinated contrast media. J Nephrol. 2010;23(6):658–66.

4 Chuang FR, Chen TC, Wang IK, Chuang CH, Chang HW, Ting-Yu Chiou T, et al. Comparison of iodixanol and iohexol in patients undergoing intravenous pyelography: a prospective controlled study. Ren Fail. 2009;31(3):181–8.

5 Radovanovic D, Urban P, Simon R, Schmidli M, Maggiorini M, Rickli H, et al. Outcome of patients with acute coronary syndrome in hospitals of different sizes. A report from the AMIS Plus Registry. Swiss Med Wkly. 2010;140(21–22):314–22.

6 Dangas G, Iakovou I, Nikolsky E, Aymong ED, Mintz GS, Kipshidze NN, et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. Am J Cardiol. 2005;95(1):13–9.

7 Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL): a new marker of kidney disease. Scand J Clin Lab Invest Suppl. 2008;241:89–94.

8 Sandler CM. Contrast-agent-induced acute renal dysfunction – is iodixanol the answer? N Engl J Med. 2003;348(6):551–3.

9 Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. Kidney Int Suppl. 2006(100):S11–5.

10 Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-induced nephropathy Trial (ACT). Circulation. 2011;124(11):1250–9.

11 Bolognese L, Falsini G, Schwenke C, Grotti S, Limbruno U, Liistro F, et al. Impact of iso-osmolar versus low-osmolar contrast agents on contrast-induced nephropathy and tissue reperfusion in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the Contrast Media and Nephrotoxicity Following Primary Angioplasty for Acute Myocardial Infarction [CONTRAST-AMI] Trial). Am J Cardiol. 2012;109(1):67–74.

12 Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, et al. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. JAMA. 2008;300(9):1038–46.

13 Briguori C, Airoldi F, D’Andrea D, Bonizzoni E, Morici N, Focaccio A, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. Circulation. 2007;115(10):1211–7.

14 Chen SL, Zhang J, Yei F, Zhu Z, Liu Z, Lin S, et al. Clinical outcomes of contrast-induced nephropathy in patients undergoing percutaneous coronary intervention: a prospective, multicenter, randomized study to analyze the effect of hydration and acetylcysteine. Int J Cardiol. 2008;126(3):407–13.

15 Holscher B, Heitmeyer C, Fobker M, Breithardt G, Schaefer RM, Reinecke H. Predictors for contrast media-induced nephropathy and long-term survival: prospectively assessed data from the randomized controlled Dialysis-Versus-Diuresis (DVD) trial. Can J Cardiol. 2008;24(11):845–50.

16 Laskey W, Aspelin P, Davidson C, Rudnick M, Aubry P, Kumar S, et al. Nephrotoxicity of iodixanol versus iopamidol in patients with chronic kidney disease and diabetes mellitus undergoing coronary angiographic procedures. Am Heart J. 2009;158(5):822-8 e3.

17 Lee SW, Kim WJ, Kim YH, Park SW, Park DW, Yun SC, et al. Preventive strategies of renal insufficiency in patients with diabetes undergoing intervention or arteriography (the PREVENT Trial). Am J Cardiol. 2011;107(10):1447–52.

18 Maioli M, Toso A, Leoncini M, Gallopin M, Tedeschi D, Micheletti C, et al. Sodium bicarbonate versus saline for the prevention of contrast-

induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. J Am Coll Cardiol. 2008;52(8):599–604.

19 Maioli M, Toso A, Leoncini M, Micheletti C, Bellandi F. Effects of hydration in contrast-induced acute kidney injury after primary angioplasty: a randomized, controlled trial. Circ Cardiovasc Interv. 2011;4(5):456–62.

20 Morikawa S, Sone T, Tsuboi H, Mukawa H, Morishima I, Uesugi M, et al. Renal protective effects and the prevention of contrast-induced nephropathy by atrial natriuretic peptide. J Am Coll Cardiol. 2009;53(12):1040–6.

21 Ozcan EE, Guneri S, Akdeniz B, Akyildiz IZ, Senaslan O, Baris N, et al. Sodium bicarbonate, N-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy. A comparison of 3 regimens for protecting contrast-induced nephropathy in patients undergoing coronary procedures. A single-center prospective controlled trial. Am Heart J. 2007;154(3):539–44.

22 Pakfetrat M, Nikoo MH, Malekmakan L, Tabandeh M, Roozbeh J, Nasab MH, et al. A comparison of sodium bicarbonate infusion versus normal saline infusion and its combination with oral acetazolamide for prevention of contrast-induced nephropathy: a randomized, double-blind trial. Int Urol Nephrol. 2009;41(3):629–34.

23 Reinecke H, Fobker M, Wellmann J, Becke B, Fleiter J, Heitmeyer C, et al. A randomized controlled trial comparing hydration therapy to additional hemodialysis or N-acetylcysteine for the prevention of contrast medium-induced nephropathy: the Dialysis-versus-Diuresis (DVD) Trial. Clin Res Cardiol. 2007;96(3):130–9.

24 Rosenstock JL, Bruno R, Kim JK, Lubarsky L, Schaller R, Panagopoulos G, et al. The effect of withdrawal of ACE inhibitors or angiotensin receptor blockers prior to coronary angiography on the incidence of contrast-induced nephropathy. Int Urol Nephrol. 2008;40(3):749–55.

25 Shin DH, Choi DJ, Youn TJ, Yoon CH, Suh JW, Kim KI, et al. Comparison of contrast-induced nephrotoxicity of iodixanol and iopromide in patients with renal insufficiency undergoing coronary angiography. Am J Cardiol. 2011;108(2):189–94.

26 Solomon RJ, Natarajan MK, Doucet S, Sharma SK, Staniloae CS, Katholi RE, et al. Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. Circulation. 2007;115(25):3189–96.

27 Thiele H, Hildebrand L, Schirdewahn C, Eitel I, Adams V, Fuernau G, et al. Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) Trial. J Am Coll Cardiol. 2010;55(20):2201–9.

28 Toso A, Maioli M, Leoncini M, Gallopin M, Tedeschi D, Micheletti C, et al. Usefulness of atorvastatin (80 mg) in prevention of contrast-induced nephropathy in patients with chronic renal disease. Am J Cardiol. 2010;105(3):288–92.

29 Wessely R, Koppara T, Bradaric C, Vorpahl M, Braun S, Schulz S, et al. Choice of contrast medium in patients with impaired renal function undergoing percutaneous coronary intervention. Circ Cardiovasc Interv. 2009;2(5):430–7.

30 Coca SG, Peixoto AJ, Garg AX, Krumholz HM, Parikh CR. The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. Am J Kidney Dis. 2007;50(5):712–20.

31 Lindsay J, Canos DA, Apple S, Pinnow E, Aggrey GK, Pichard AD. Causes of acute renal dysfunction after percutaneous coronary intervention and comparison of late mortality rates with postprocedure rise of creatine kinase-MB versus rise of serum creatinine. Am J Cardiol. 2004;94(6):786–9.

32 Lindsay J, Apple S, Pinnow EE, Gevorkian N, Gruberg L, Satler LF, et al. Percutaneous coronary intervention-associated nephropathy foreshadows increased risk of late adverse events in patients with normal baseline serum creatinine. Catheter Cardiovasc Interv. 2003;59(3):338–43.

33 Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol. 2000;36(5):1542–8.

34 Harjai KJ, Raizada A, Shenoy C, Sattur S, Orshaw P, Yaeger K, et al. A comparison of contemporary definitions of contrast nephropathy in patients undergoing percutaneous coronary intervention and a proposal for a novel nephropathy grading system. Am J Cardiol. 2008;101(6):812–9.

35 Katzberg RW. Urography into the 21st century: new contrast media, renal handling, imaging characteristics, and nephrotoxicity. Radiology. 1997;204(2):297–312.

36 Tumlin J, Stacul F, Adam A, Becker CR, Davidson C, Lameire N, et al. Pathophysiology of contrast-induced nephropathy. Am J Cardiol. 2006;98(6A):14K–20K.

37 Cwynarski MT, Saxton HM. Urography in myelomatosis. Br Med J. 1969;1(5642):486.

38 McCarthy CS, Becker JA. Multiple myeloma and contrast media. Radiology. 1992;183(2):519–21.

39 Arkouche W, Brillet G, Cao-Huu T, Issad B, Siohan P, Souid M, et al. Recommendations for prevention of contrast-media induced nepropathy. Nephrologie. 2004;25(4):149–50.

40 Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol. 2004;44(7):1393–9.

41 Cigarroa RG, Lange RA, Williams RH, Hillis LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am J Med. 1989;86(6 Pt 1):649–52.

42 Stacul F, van der Molen AJ, Reimer P, Webb JA, Thomsen HS, Morcos SK, et al. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol. 2011;21(12):2527–41.

43 Brown JR, Robb JF, Block CA, Schoolwerth AC, Kaplan AV, O'Connor GT, et al. Does safe dosing of iodinated contrast prevent contrast-induced acute kidney injury? Circ Cardiovasc Interv. 2010;3(4):346–50.

44 Nyman U, Bjork J, Aspelin P, Marenzi G. Contrast medium dose-to-GFR ratio: a measure of systemic exposure to predict contrast-induced nephropathy after percutaneous coronary intervention. Acta radiologica. 2008;49(6):658–67.

45 Tublin ME, Murphy ME, Tessler FN. Current concepts in contrast media-induced nephropathy. Am J Roentgenol. 1998;171(4):933–9.

46 Love L, Johnson MS, Bresler ME, Nelson JE, Olson MC, Flisak ME. The persistent computed tomography nephrogram: its significance in the diagnosis of contrast-associated nephrotoxicity. Br J Radiol. 1994;67(802):951–7.

47 Nickolas TL, Schmidt-Ott KM, Canetta P, Forster C, Singer E, Sise M, et al. Diagnostic and prognostic stratification in the emergency department using urinary biomarkers of nephron damage: a multicenter prospective cohort study. J Am Coll Cardiol. 2012;59(3):246–55.

48 Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, et al. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol. 2011;57(17):1752–61.

49 Singer E, Elger A, Elitok S, Kettritz R, Nickolas TL, Barasch J, et al. Urinary neutrophil gelatinase-associated lipocalin distinguishes prerenal from intrinsic renal failure and predicts outcomes. Kidney Int. 2011;80(4):405–14.

50 Devarajan P. Review: neutrophil gelatinase-associated lipocalin: a troponin-like biomarker for human acute kidney injury. Nephrology. 2010;15(4):419–28.

51 Bachorzewska-Gajewska H, Poniatowski B, Dobrzycki S. NGAL (neutrophil gelatinase-associated lipocalin) and L-FABP after percutaneous coronary interventions due to unstable angina in patients with normal serum creatinine. Adv Med Sci. 2009;54(2):221–4.

52 Schmidt-Ott KM, Mori K, Li JY, Kalandadze A, Cohen DJ, Devarajan P, et al. Dual action of neutrophil gelatinase-associated lipocalin. JASN. 2007;18(2):407–13.

53 Mitsnefes MM, Kathman TS, Mishra J, Kartal J, Khoury PR, Nickolas TL, et al. Serum neutrophil gelatinase-associated lipocalin as a marker of renal function in children with chronic kidney disease. Pediatr Nephrol. 2007;22(1):101–8.

54 Bennett M, Dent CL, Ma Q, Dastrala S, Grenier F, Workman R, et al. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. Clin J Am Soc Nephrol. 2008;3(3):665–73.

55 Parikh CR, Devarajan P, Zappitelli M, Sint K, Thiessen-Philbrook H, Li S, et al. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. JASN. 2011;22(9):1748–57.

56 Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009;54(6):1012–24.

57 Soto K, Coelho S, Rodrigues B, Martins H, Frade F, Lopes S, et al. Cystatin C as a marker of acute kidney injury in the emergency department. Clin J Am Soc Nephrol. 2010;5(10):1745–54.

58 Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis. 2002;40(2):221–6.

59 Herget-Rosenthal S, Marggraf G, Husing J, Goring F, Pietruck F, Janssen O, et al. Early detection of acute renal failure by serum cystatin C. Kidney Int. 2004;66(3):1115–22.

60 Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, Malyszko JS, Poniatowski B, Pawlak K, et al. NGAL (neutrophil gelatinase-associated lipocalin) and cystatin C: are they good predictors of contrast nephropathy after percutaneous coronary interventions in patients with stable angina and normal serum creatinine? Int J Cardiol. 2008;127(2):290–1.

61 Rickli H, Benou K, Ammann P, Fehr T, Brunner-La Rocca HP, Petridis H, et al. Time course of serial cystatin C levels in comparison with serum creatinine after application of radiocontrast media. Clin Nephrol. 2004;61(2):98–102.

62 Briguori C, Visconti G, Rivera NV, Focaccio A, Golia B, Giannone R, et al. Cystatin C and contrast-induced acute kidney injury. Circulation. 2010;121(19):2117–22.

63 Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med. 2008;148(11):810–9.

64 Mori K, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J, et al. Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. J Clin Invest. 2005;115(3):610–21.

65 Parikh CR, Jani A, Melnikov VY, Faubel S, Edelstein CL. Urinary interleukin-18 is a marker of human acute tubular necrosis. Am J Kidney Dis. 2004;43(3):405–14.

66 Ling W, Zhaohui N, Ben H, Leyi G, Jianping L, Huili D, et al. Urinary IL-18 and NGAL as early predictive biomarkers in contrast-induced nephropathy after coronary angiography. Nephr Cli Prac 2008;108(3):c176–81.

67 Ferguson MA, Vaidya VS, Waikar SS, Collings FB, Sunderland KE, Gioules CJ, et al. Urinary liver-type fatty acid-binding protein predicts adverse outcomes in acute kidney injury. Kidney Int. 2010;77(8):708–14.

68 Portilla D, Dent C, Sugaya T, Nagothu KK, Kundi I, Moore P, et al. Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery. Kidney Int. 2008;73(4):465–72.

69 Nakamura T, Sugaya T, Node K, Ueda Y, Koide H. Urinary excretion of liver-type fatty acid-binding protein in contrast medium-induced nephropathy. Am J Kidney Dis. 2006;47(3):439–44.

70 Han WK, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, et al. Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int. 2008;73(7):863–9.

71 Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int. 2002;62(1):237–44.

72 Rosen S, Heyman S. Concerns about KIM-1 as a urinary biomarker for acute tubular necrosis (ATN). Kidney Int. 2003;63(5):1955.

73 Ren L, Ji J, Fang Y, Jiang SH, Lin YM, Bo J, et al. Assessment of urinary a-acetyl-β-glucosaminidase as an early marker of contrast-induced nephropathy. J Int Res. 2011;39:647–53.

74 Rudnick MR, Kesselheim A, Goldfarb S. Contrast-induced nephropathy: how it develops, how to prevent it. Cleve Clin J Med. 2006;73(1):75–80, 3–7.

75 Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med. 2003;348(6):491–9.

76 Solomon R, Dumouchel W. Contrast media and nephropathy: findings from systematic analysis and Food and Drug Administration reports of adverse effects. Investigative radiology. 2006;41(8):651–60.

77 Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology. 1993;188(1):171–8.

78 From AM, Al Badarin FJ, McDonald FS, Bartholmai BJ, Cha SS, Rihal CS. Iodixanol versus low-osmolar contrast media for prevention of contrast induced nephropathy: meta-analysis of randomized, controlled trials. Circ Cardiovasc Interv. 2010;3(4):351–8.

79 Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med. 1994;331(21):1416–20.

80 Kunadian V, Zaman A, Spyridopoulos I, Qiu W. Sodium bicarbonate for the prevention of contrast induced nephropathy: a meta-analysis of published clinical trials. Eur J Radiol. 2011;79(1):48–55.

81 Mueller C, Seidensticker P, Buettner HJ, Perruchoud AP, Staub D, Christ A, et al. Incidence of contrast nephropathy in patients receiving comprehensive intravenous and oral hydration. Swiss Med Wkly. 2005;135(19-20):286–90.

82 Briguori C, Visconti G, Focaccio A, Airoldi F, Valgimigli M, Sangiorgi GM, et al. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury. Circulation. 2011;124(11):1260–9.

83 Bartorelli C, Ferrari C, Trabattoni D, Teruzzi G, Marana I, Assanelli E, et al. Furosemide-induced diuresis with matched hydration compared to standard hydration for contrast-induced nephropathy prevention. The MYTHOS Trial. J Am Coll Cardiol. 2010;56:B77.

84 Drager LF, Andrade L, Barros de Toledo JF, Laurindo FR, Machado Cesar LA, Seguro AC. Renal effects of N-acetylcysteine in patients at risk for contrast nephropathy: decrease in oxidant stress-mediated renal tubular injury. Nephrol Dial Transplant. 2004;19(7):1803–7.

85 Lopez BL, Snyder JW, Birenbaum DS, Ma XI. N-acetylcysteine enhances endothelium-dependent vasorelaxation in the isolated rat mesenteric artery. Ann Emerg Med. 1998;32(4):405–10.

86 Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med. 2000;343(3):180–4.

87 Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. Ann Intern Med. 2008;148(4):284–94.

88 Kinbara T, Hayano T, Ohtani N, Furutani Y, Moritani K, Matsuzaki M. Efficacy of N-acetylcysteine and aminophylline in preventing contrast-induced nephropathy. J Cardiol. 2010;55(2):174–9.

89 Zhang T, Shen LH, Hu LH, He B. Statins for the prevention of contrast-induced nephropathy: a systematic review and meta-analysis. Am J Nephrol. 2011;33(4):344–51.

90 Ozhan H, Erden I, Ordu S, Aydin M, Caglar O, Basar C, et al. Efficacy of short-term high-dose atorvastatin for prevention of contrast-induced nephropathy in patients undergoing coronary angiography. Angiology. 2010;61(7):711–4.

91 Patti G, Ricottini E, Nusca A, Colonna G, Pasceri V, D'Ambrosio A, et al. Short-term, high-dose Atorvastatin pretreatment to prevent contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention (from the ARMYDA-CIN [atorvastatin for reduction of myocardial damage during angioplasty--contrast-induced nephropathy] trial. Am J Cardiol. 2011;108(1):1–7.

92 Xinwei J, Xianghua F, Jing Z, Xinshun G, Ling X, Weize F, et al. Comparison of usefulness of simvastatin 20 mg versus 80 mg in prevent-

ing contrast-induced nephropathy in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Am J Cardiol. 2009;104(4):519–24.

93 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? PGE1 Study Group. Nephrol Dial Transplant. 2000;15(1):43–9.

94 Sketch MH, Jr., Whelton A, Schollmayer E, Koch JA, Bernink PJ, Woltering F, et al. Prevention of contrast media-induced renal dysfunction with prostaglandin E1: a randomized, double-blind, placebo-controlled study. Am J Ther. 2001;8(3):155–62.

95 Gare M, Haviv YS, Ben-Yehuda A, Rubinger D, Bdolah-Abram T, Fuchs S, et al. The renal effect of low-dose dopamine in high-risk patients undergoing coronary angiography. J Am Coll Cardiol. 1999;34(6):1682–8.

96 Abizaid AS, Clark CE, Mintz GS, Dosa S, Popma JJ, Pichard AD, 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(2):260–3, A5.

97 Stone GW, McCullough PA, Tumlin JA, Lepor NE, Madyoon H, Murray P, et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. JAMA. 2003;290(17):2284–91.

98 Tumlin JA, Wang A, Murray PT, Mathur VS. Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. Am Heart J. 2002;143(5):894–903.

99 Weisz G, Filby SJ, Cohen MG, Allie DE, Weinstock BS, Kyriazis D, et al. Safety and performance of targeted renal therapy: the Be-RITe! Registry. J Endovasc Ther. 2009;16(1):1–12.

100 Erley CM, Duda SH, Schlepckow S, Koehler J, Huppert PE, Strohmaier WL, et al. Adenosine antagonist theophylline prevents the reduction of glomerular filtration rate after contrast media application. Kidney Int. 1994;45(5):1425–31.

101 Matejka J, Varvarovsky I, Vojtisek P, Herman A, Rozsival V, Borkova V, et al. Prevention of contrast-induced acute kidney injury by theophylline in elderly patients with chronic kidney disease. Heart Vessels. 2010;25(6):536–42.

102 Deray G, Martinez F, Cacoub P, Baumelou B, Baumelou A, Jacobs C. A role for adenosine calcium and ischemia in radiocontrast-induced intrarenal vasoconstriction. Am J Nephrol. 1990;10(4):316–22.

103 Esnault VL. Radiocontrast media-induced nephrotoxicity in patients with renal failure: rationale for a new double-blind, prospective, randomized trial testing calcium channel antagonists. Nephrol Dial Transplant. 2002;17(8):1362–4.

104 Neumayer HH, Junge W, Kufner A, Wenning A. Prevention of radiocontrast-media-induced nephrotoxicity by the calcium channel blocker nitrendipine: a prospective randomised clinical trial. Nephrol Dial Transplant. 1989;4(12):1030–6.

105 Carraro M, Mancini W, Artero M, Stacul F, Grotto M, Cova M, et al. Dose effect of nitrendipine on urinary enzymes and microproteins following non-ionic radiocontrast administration. Nephrol Dial Transplant. 1996;11(3):444–8.

106 Khoury Z, Schlicht JR, Como J, Karschner JK, Shapiro AP, Mook WJ, et al. The effect of prophylactic nifedipine on renal function in patients administered contrast media. Pharmacotherapy. 1995;15(1):59–65.

107 Patel K, King CA, Jovin IS. Angiotensin-converting enzyme inhibitors and their effects on contrast-induced nephropathy after cardiac catheterization or percutaneous coronary intervention. Cardiovasc Revasc Med. 2011;12(2):90–3.

108 Thomsen HS. ESUR guideline: gadolinium-based contrast media and nephrogenic systemic fibrosis. Eur Radiol. 2007;17(10):2692–6.

109 Kuo PH, Kanal E, Abu-Alfa AK, Cowper SE. Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. Radiology. 2007;242(3):647–9.

110 Perazella MA. Current status of gadolinium toxicity in patients with kidney disease. Clin J Am Soc Nephrol. 2009;4(2):461–9.

111 Malyszko J, Bachorzewska-Gajewska H, Poniatowski B, Malyszko JS, Dobrzycki S. Urinary and serum biomarkers after cardiac catheterization in diabetic patients with stable angina and without severe chronic kidney disease. Ren Fail. 2009;31(10):910–9.

112 Hirsch R, Dent C, Pfriem H, Allen J, Beekman RH, 3rd, Ma Q, et al. NGAL is an early predictive biomarker of contrast-induced nephropathy in children. Pediatr Nephrol. 2007;22(12):2089–95.

113 Solomon R, Deray G. How to prevent contrast-induced nephropathy and manage risk patients: practical recommendations. Kidney Int Suppl. 2006(100):S51–3.

114 McCullough PA. Multimodality prevention of contrast-induced acute kidney injury. Am J Kidney Dis. 2008;51(2):169–72.

Figures (large format)

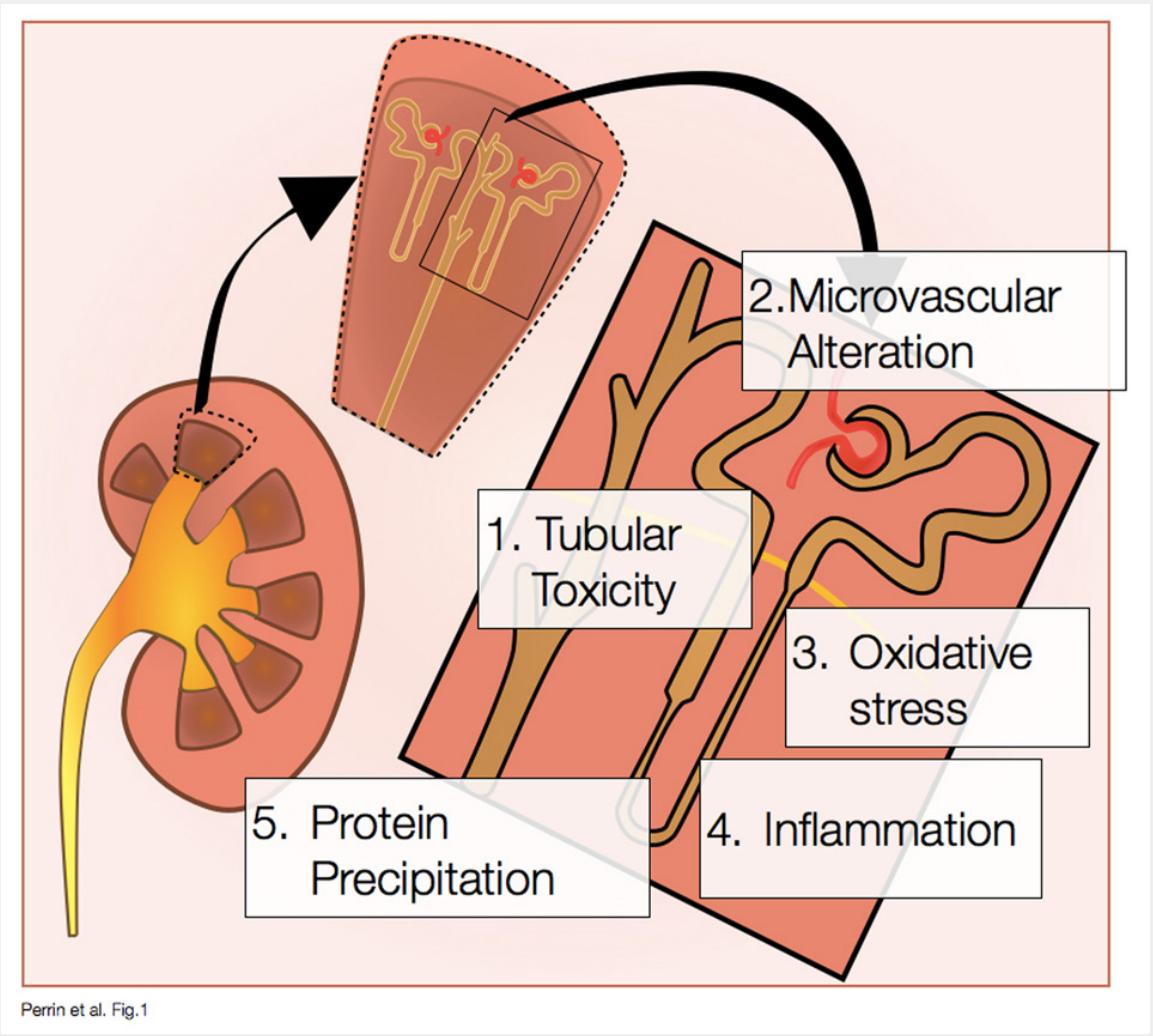

Figure 1

Scheme of hypothesised pathways contributing to CIN pathogenesis.