Contrast induced nephropathy in vascular surgery

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Abstract

Contrast induced nephropathy (CIN) is traditionally associated with outpatient imaging studies. More recently, patients afflicted with vascular pathologies are increasingly undergoing endovascular treatments that require the use of iodinated contrast media (CM) agents, thus placing them at risk of developing CIN. As perioperative physicians, anaesthetists should be aware of the risk factors and measures that might minimize acute kidney injury caused by CM. This review evaluates recent data regarding preventive measures against CIN and where possible, places the evidence in the context of the patient receiving endovascular surgical treatment. Measures including the use of peri-procedural hydration, N-acetylcysteine, statins, remote ischaemic preconditioning, renal vasodilators and renal replacement therapy and the use of alternatives to iodinated contrast agents are discussed. It should be noted that most of the available data regarding CIN are from non-surgical patients.

Key words: acute kidney injury; contrast media; endovascular procedures

Editor’s key points

- A systematic review estimated the overall frequency of CIN in vascular surgery patients exposed to angiography to be 9.2%.
- Patients who develop CIN suffer an increased burden of in hospital and longer term morbidity.
- Maintaining adequate hydration remains a cornerstone of preventing CIN but evidence to support a particular hydration strategy is lacking.
- There is no evidence to support the routine use of NAC in prophylactic protocols for surgical patients at risk of CIN.

Despite efforts to prevent it, contrast induced nephropathy (CIN) remains a significant cause of iatrogenic acute kidney injury (AKI). With the increasing use of endovascular procedures requiring iodine containing contrast media (CM) in older patients and those with significant co-morbidities, the prevention of AKI is assuming greater importance. This narrative review will serve as an update to one previously published in this journal¹ and will concentrate on areas where there have been noteworthy changes, with a focus on patients undergoing vascular surgery where such data are available. Readers are referred to the previous review for more in depth discussion on the risk factors (Table 1),²⁻⁴ the pathophysiology of CIN and renal handling of CM, the details of which remain largely unchanged, and will be mentioned only in brief here.

Definitions

The widely accepted definition for contrast induced nephropathy is a deterioration of renal function, indicated by either an increase in serum creatinine concentration of 25% from baseline, or an absolute increase of 26⁻⁴⁴ µmol litre⁻¹ (0.3⁻⁰.⁵ mg dl⁻¹) within 48⁻⁷₂ h of i.v. contrast administration.⁵ In order to standardize the definition of acute kidney injury from different aetiologies, two groups, the Acute Dialysis Quality Initiative (ADQI) and Acute Kidney Injury Network (AKIN) have separately proposed a system of defining and staging AKI, regardless of the likely cause. These include the RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) and the AKIN systems respectively, the latter being a modification of the former, which should theoretically improve sensitivity and specificity.⁶
According to the AKIN criteria, stage 1 AKI may be diagnosed if one of the following occurs within 48 h:

- An absolute serum creatinine increase $>26.4 \mu\text{mol litre}^{-1}$ ($\geq 0.3 \text{ mg dl}^{-1}$).
- An increase in serum creatinine $>50\%$ ($\geq 1.5$-fold) above baseline.
- Urine output reduced to $\leq 0.5 \text{ ml kg}^{-1} \text{ h}^{-1}$ for at least 6 h.

These are not specific to suspected contrast-induced AKI and differ from the previously used definitions of CIN. These criteria may be seen more frequently in future studies of CIN, which will aid the comparison of different studies.

### Incidence of CIN in patients with vascular disease

In the Manual on Contrast Media by the American College of Radiology, the authors made a distinction in terminology between the diagnoses of post-contrast acute kidney injury and contrast induced nephropathy. In the latter CM is considered to be the cause of the renal injury. Be that as it may, very few studies have adequate controls to separate between the two entities and quoted incidences are likely to include a combination of both. Furthermore, the reported incidences of CIN after cardiology and radiology procedures vary widely, owing to variation in the definitions used in earlier studies and the inclusion of patients with different numbers of known risk factors. The aetiology of AKI in patients undergoing endovascular aneurysm repair (EVAR) in the perioperative period is multifactorial, with the kidneys being potentially subjected to a variety of haemodynamic, mechanical and pharmacological insults. Hence it is difficult to attribute AKI after EVAR solely to the adverse effects of CM and data are relatively scarce. An earlier study in patients undergone AAA repairs, 9877 of who had EVAR.11 The investigation divided these patients as having undergone AAA repairs, 9877 of who had EVAR.11 The investigators divided these patients as having moderate baseline renal impairment if their eGFR was between 30–60 ml min$^{-1}$, and severe impairment if their eGFR was $<30$ ml min$^{-1}$. Patients with moderate baseline renal impairment had an AKI rate of 1% and a dialysis rate of 1.1%. This compares with an AKI rate of 4.1 and 6.3% respectively in those with severely impaired baseline renal function. However, the definition of AKI used was a creatinine increase by $>50\%$ based on the AKI criteria. Other studies investigating various preventative measures for AKI have shown incidences of CIN between 3–8% of vulnerable patients undergoing angiography in the vascular surgical setting. In a systematic review by Zaraca and colleagues the overall frequency of CIN from six eligible studies was 9.2% (79 out of 862 patients).

### Clinical consequences of CIN

The sequelae of CIN are variable and difficult to quantify, as there is not a well-demarcated pathophysiological pathway to account for the morbidity and mortality in patients who develop CIN. For the most part, AKI associated with CIN is asymptomatic and transient; like other mild forms of AKI, it requires only observation and supportive management, and rarely requires renal replacement. However, observational studies consistently point to a greater chance of death in those who develop CIN, compared with those who do not, with the odds lasting beyond one yr after detection. Furthermore, data gleaned from randomized trials of therapeutic interventional measures also indicate an added morbidity attributable to the occurrence of CIN. Earlier data indicated an in-hospital mortality rate of up to 30% and a two yr mortality rate of 80%.

In a prospective cohort analysis, the development of CIN after contrast-enhancing CT scan was shown to be associated with a similar risk of death in one yr as coronary artery disease, heart failure or advanced age. In a prospective study of 9877 subjects with a median follow up of 42 months, the rate of CIN was 11% in those with chronic kidney disease (CKD) and 2% in those without CKD, calculated after adjusting for known confounders of death and excluding patients who had died in hospital (24), had surgery (2999), were on dialysis (250) and had incomplete laboratory data (2233). CIN was associated with long-term mortality for the entire cohort (HR=2.26, CI=1.62 to 2.29, P<0.0001). Subgroup analysis showed that patients with CKD also had a higher long-term mortality if they developed CIN (HR 2.62, CI=1.91 to 3.57, P<0.0001) but CIN had no effect on mortality in patients without CKD (HR=1.23, CI 0.47 to 2.62, P=0.8).

### Pharmacology of iodinated contrast media (CM)

Commercially available CM are based on either one (monomers) or two (dimers) tri-iodinated benzene rings. They are further classified according to their ionization and osmolality. CM vary in their chemical and physical properties but the imaging efficacy is solely based on their ability to attenuate x-rays, which is dependent on the number of iodine molecules present. The ionic form affects the electrical potential of the cell membranes, which accounts for an increased toxicity.

The improved safety profiles of the non-ionic low-osmolar or iso-osmolar CM (osmolality equal to that of blood) have resulted in universal uptake in clinical practice. Osmolality was thought to play an important role in the pathogenesis of CIN, but the anticipated benefit of lower incidence of CIN by reducing osmolality has not been borne out in meta-analyses that compared the risks of CIN between high-osmolar and low-osmolar CM; and between low-osmolar and iso-osmolar CM regardless of the routes of administration.

There has been a shift in thinking that suggests viscosity may be a particularly important contributing factor in the development of CIN, especially with low-osmolar CM having up to a 50-fold increase in viscosity.
osmolality and viscosity in the development of CIN, may explain the mixed results with iso-osmolar CM in reducing CIN. All CM are similar, essentially having low lipopolysaccharide, low protein binding and undergoing renal excretion without significant metabolism. CM are distributed from the intravascular compartment to highly perfused organs, such as the liver and kidney with the exception of the brain parenchyma when there is an intact blood-brain barrier. CM elimination half-life is between 90–120 min with normal excretory function, but is delayed in the presence of renal insufficiency. A number of earlier studies pointed to the association of volume of contrast used with the development of CIN such that it has been incorporated as a component of a proposed risk scoring system. It has to be stressed however that there are no randomized trials designed to evaluate this issue specifically, as it may be considered unethical to expose patients to unnecessary amounts of contrast. As the volume of CM used may reflect the complexity of the pathology or required procedure, it may be argued that observational studies could be biased towards selecting out a subset of patients at higher risk of developing CIN. Some are of the opinion that limiting the volume of CM may in fact negatively impact upon the evaluation of patients undergoing diagnostic procedures and have produced retrospective data refuting the association between CM dose and rate of CIN. Yet others are still producing observational evidence, indicating that exceeding the maximal allowable dose still adversely affects patient outcome. On balance, irrespective of the type of contrast used, judiciously limiting the contrast load should still form an essential part of CIN prophylaxis until more convincing data suggest otherwise.

Preventative measures

Hydration

Although there are no direct trials comparing hydration to placebo, hydration remains the foundation of preventative strategies against the development of CIN. Many of the studies evaluating potential benefits of other strategies have incorporated hydration for both the control and intervention groups. Consensus, however, has not yet been achieved with respect to the optimal volume, composition and regime of fluid administration. A meta-analysis suggested that there is minimal difference in efficacy between oral and i.v. hydration. However, it may be difficult to coordinate oral hydration with fasting time in the immediate preoperative period and some will favour i.v. hydration for high risk patients shortly before surgery. Hydration with 0.9% saline may be superior to hypotonic saline, as is the administration of fluids over a longer period compared with a shorter time.

Based on the premise that alkalinization of the urine may decrease the generation of hydroxyl free radicals that can harm the renal tubules, several studies have been performed to evaluate the use of isotonic bicarbonate rather than isotonic 0.9% saline as the hydration agent. Many of these have similar deficiencies in methodology such as small sample sizes and lack of power. Meta-analyses have also found a moderate to high degree of heterogeneity, publication bias and different treatment effect, thus resulting in different overall effects. On the whole, some of the studies suggest bicarbonate is not inferior to 0.9% saline, while others show some benefits. Nevertheless, not many international organizations have recommended choosing bicarbonate over 0.9% saline, but have suggested hydration with either solution over no hydration. However, physicochemical drug compatibilities are a concern and concomitant drug administration through the i.v. line used for isotonic bicarbonate, should be avoided.

There is a body of evidence around forced diuresis with matching fluid replacement. This was studied in the REMEDIAL II and MYTHOS trials. Where forced diuresis was achieved using diuretics or osmotic agents alone and without adequate fluid replacement, the treatment was ineffective or even detrimental. In comparison using an automated fluid delivery system that matches fluid administration to urine output, investigators from both these trials were able to achieve urine output in the range of 300 ml h⁻¹ in some of their patients and were able to reduce the event rate of CIN to roughly half that of their comparator arms respectively. The event rate for pulmonary oedema in the REMEDIAL II trial was 2.1% in the hydration group compared with 0.7% in the control group (P=0.62). This compares with rates of 6 and 12% in the treatment and control groups respectively (P=0.15) in the MYTHOS trial.

In the absence of this fluid delivery device, or a clinical environment where a regimen of high volume forced diuresis can be safely delivered, a practical protocol for elective patients undergoing procedures involving CM, may be the administration of either isotonic 0.9% saline, or sodium bicarbonate, at a rate of 1 ml kg⁻¹ h⁻¹ for 12 h before and 12 h after the anticipated contrast administration, and for more emergent procedures a regime of 3 ml kg⁻¹ h⁻¹ for 1 h before and 1 ml kg⁻¹ h⁻¹ for 6 h after is appropriate. The abbreviated regime may also be indicated for those in whom sustained volume expansion is not feasible.

The Prevention of Serious Adverse Events following Angiography (PRESERVE) trial is in the pipeline (NCT01467466). This study aims to enrol 8680 patients, and to evaluate the effectiveness of isotonic sodium bicarbonate compared with isotonic saline and oral N-acetyl cysteine vs oral placebo.

N-acetylcysteine

As far as pharmacological prophylaxis is concerned, N-acetylcysteine (NAC) is probably the most widely studied pharmacological agent for the prevention of CIN. NAC is inexpensive, easy to administer and has a favourable safety profile (although not totally harmless, as anaphylactoid reactions have been reported when used via the i.v. route in other clinical contexts); it also may have free radical scavenging and organ protective effects. However the results regarding its efficacy are equivocal and to date no firm recommendations can be given for its routine use, especially in light of the ACT trial (see Table 2). This is probably attributable to heterogeneity in the design of the studies, ranging from definition of CIN, types of CM used, co-morbidities of patients, dose of NAC, routes of administration and of the co-interventions used, most notably that of hydration protocols. The disparity in study designs is reflected in differences in rates of baseline events and effect sizes reported. To complicate matters, NAC has been shown to decrease serum creatinine, an effect that is likely to be independent of changes in glomerular filtration rate (GFR). Direct comparison studies suggest that the higher dose oral regimen of 1200 mg twice daily, may be more beneficial than 600 mg twice daily. More relevant to the perioperative setting, Lawlor and colleagues could find no additional benefit of NAC over hydration alone in patients undergoing vascular procedures in a small (n=78), single centre trial. It is of interest that NAC at high doses was not reno-protective in patients undergoing cardiac bypass and abdominal aortic aneurysm repair.

In the largest and most methodologically rigorous trial to date, the Acetylcysteine for Contrast-Induced Nephropathy...
Table 2 Summary of evidence for N-Acetylcysteine from clinical trials comparing NAC with control. This table contains randomized trials involving patients undergoing either coronary or peripheral angiography, with a primary outcome that measures the incidence of CIN as defined as a 25% increase in serum creatinine from baseline or a 0.5 mg dl\(^{-1}\) (44 \(\mu\)mol litre\(^{-1}\)) increase in the absolute value, within 48-72 h of i.v. contrast administration. C, coronary angiography; P, peripheral angiography; PO, per oral; RR, relative risk; CI, 95% confidence interval

<table>
<thead>
<tr>
<th>Study</th>
<th>NAC (N) (dose in mg)</th>
<th>Control (N)</th>
<th>Procedure</th>
<th>PO or i.v.</th>
<th>Incidence NAC vs Control</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigators ACT (2011)(^{14})</td>
<td>1172 (1200)</td>
<td>1136 C</td>
<td>PO</td>
<td>12.7 vs 12.7%</td>
<td>RR=1 (0.81-1.25) P=0.97</td>
<td></td>
</tr>
<tr>
<td>Amini et al. (2009)(^{17})</td>
<td>45 (600)</td>
<td>45 C</td>
<td>PO</td>
<td>11.1 vs 14.3% (P=0.656)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arazmus et al. (2005)(^{18})</td>
<td>196 (600)</td>
<td>201 C</td>
<td>PO</td>
<td>7.1 vs 8.4% (P=0.62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Briguglio et al. (2004)(^{19})</td>
<td>92 (600)</td>
<td>91 P, C</td>
<td>PO</td>
<td>4.1 vs 13.7% (P=0.019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbonell et al. (2007)(^{20})</td>
<td>107 (600)</td>
<td>109 C</td>
<td>i.v.</td>
<td>10.2 vs 10.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbonell et al. (2010)(^{21})</td>
<td>39 (600)</td>
<td>42 C</td>
<td>i.v.</td>
<td>5.1 vs 23.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coyle et al. (2006)(^{22})</td>
<td>68 (600)</td>
<td>69 C</td>
<td>PO</td>
<td>9.2 vs 1.4% (P=0.043)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Díaz-Sandoval et al. (2002)(^{23})</td>
<td>25 (600)</td>
<td>29 C</td>
<td>PO</td>
<td>8 vs 45% (P=0.005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrario et al. (2009)(^{24})</td>
<td>99 (600)</td>
<td>101 C, P</td>
<td>PO</td>
<td>8.1 vs 5.9% (P=0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fung et al. (2004)(^{25})</td>
<td>46 (400)</td>
<td>45 C</td>
<td>PO</td>
<td>17.4 vs 13.3% (P=0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldenberg et al. (2004)(^{26})</td>
<td>41 (600)</td>
<td>39 C</td>
<td>PO</td>
<td>10 vs 8% (P=0.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gomes et al. (2005)(^{27})</td>
<td>77 (600)</td>
<td>79 C</td>
<td>PO</td>
<td>10.4 vs 10.1% (P=1)</td>
<td></td>
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<tr>
<td>Gulel et al. (2005)(^{28})</td>
<td>25 (600)</td>
<td>25 C</td>
<td>PO</td>
<td>12 vs 8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kay et al. (2003)(^{29})</td>
<td>102 (600)</td>
<td>98 C</td>
<td>PO</td>
<td>4 vs 12%</td>
<td></td>
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<tr>
<td>Kim et al. (2010)(^{30})</td>
<td>80 (600)</td>
<td>86 C</td>
<td>PO</td>
<td>5 vs 15.1% (P=0.05)</td>
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<tr>
<td>MacNeill et al. (2003)(^{31})</td>
<td>21 (600)</td>
<td>22 C</td>
<td>PO</td>
<td>5 vs 32% (P=0.046)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miner et al. (2004)(^{32})</td>
<td>95 (2000)</td>
<td>85 C</td>
<td>PO</td>
<td>9.6 vs 22.2% (P=0.04)</td>
<td></td>
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</tr>
<tr>
<td>Ochoa et al. (2004)(^{33})</td>
<td>36 (1000)</td>
<td>44 C</td>
<td>PO</td>
<td>8 vs 25% (P=0.051)</td>
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</tr>
<tr>
<td>Oldemeyer et al. (2003)(^{34})</td>
<td>49 (1500)</td>
<td>47 C</td>
<td>PO</td>
<td>8.2 vs 6.4% (P=0.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rashid et al. (2004)(^{35})</td>
<td>46 (1000)</td>
<td>48 P</td>
<td>i.v.</td>
<td>17.6 vs 14.3% (P=0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sadat et al. (2011)(^{36})</td>
<td>21 (600)</td>
<td>19 P</td>
<td>PO</td>
<td>1/21 vs 3/19 (P=0.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sandhu et al. (2006)(^{37})</td>
<td>53 (600)</td>
<td>53 P</td>
<td>PO</td>
<td>2.8 vs 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seyon et al. (2007)(^{38})</td>
<td>20 (600)</td>
<td>20 C</td>
<td>PO</td>
<td>2.5 vs 7.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shyu et al. (2002)(^{39})</td>
<td>60 (400)</td>
<td>61 C</td>
<td>PO</td>
<td>3.3 vs 24.6% (P&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiele et al. (2010)(^{40})</td>
<td>126 (1200)</td>
<td>125 C</td>
<td>i.v.</td>
<td>14 vs 20% (P=0.28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(ACT) Trial Investigators, have convincingly demonstrated a lack of efficacy for NAC in reducing the incidence of CIN, mortality or need for dialysis at 30 days, a finding that was observed in all subgroups analysed, including those with renal impairment.\(^{41}\) This was a multicentre trial involving 46 different sites and 2308 patients with at least one risk factor for the development of CIN, randomized to receive either 1200 mg of NAC or placebo. The usual definition of CIN (see above) was used as the primary endpoint and an intention to treat analysis was used. The event rate for both groups was 12.7% (RR=1, CI=0.81 to 1.25, P=0.97). There was no difference in the combined end point of 30 day mortality or need for dialysis (2.2% in treatment vs 2.3% in the control group, HR 0.97, CI=0.56 to 1.69, P=0.92). These effects were consistent across all subgroup analyses. Hence there is no evidence of overall benefit to support the routine use of NAC in prophylactic protocols for surgical patients at risk of CIN.

**Statins**

Evidence for possible perioperative benefit from the pleiotropic effects of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), has continued to emerge over the past decade.\(^{75}\) With respect to CIN, initial retrospective analysis pointed to an association with pre-procedural statin use and a reduction in the incidence of CIN.\(^{76}\) In a follow-up study of 434 patients undergoing PCI, statin-treated patients had a lower incidence of CIN (3 vs 27%, P<0.0001) and a superior post-procedural creatinine clearance (80 (20) vs 65 (16) ml min\(^{-1}\), P<0.0001). These benefits were seen across all subgroups except those with a pre-existing creatinine clearance <40 ml min\(^{-1}\).\(^{77}\) Prospective, randomized trials involving large numbers are difficult because of the ubiquitous use of statins in patients with cardiovascular co-morbidities. However, the randomized trials in patients undergoing coronary angiography, using high dose statins seem beneficial.\(^{78-81}\)

In a trial involving 241 statin-naive patients with acute coronary syndrome undergoing PCI, 120 patients were randomized to receive atorvastatin (80 mg+40-mg) before the procedure, compared with 121 placebo controls, with all patients receiving atorvastatin 40 mg daily post-procedure. The treatment group had a significantly lower rate of CIN compared with placebo (5 vs 13.2%, P=0.046) and were independently associated with a decreased risk of CIN (OR=0.34, CI=0.12 to 0.97, P=0.043) and a shorter hospital stay (p<0.007).\(^{79}\) Similar results were reported by the Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induce Acute Kidney Injury and Myocardial Damage in Patients With Acute Coronary Syndrome (PRATO-ACS) Study. In this study, consecutive statin-naive patients with non-ST elevation ACS undergoing early invasive intervention, were randomly assigned to receive rosvastatin (40+20 mg per day; n=252) or no statin treatment control group (n=252). The results showed a beneficial effect of statins on CIN (6.7 vs. 15.1%; adjusted OR=0.38; CI=0.20 to 0.71, P<0.003). There was also a lower 30-day
incident of adverse cardiovascular and persistent damage (3.6 vs. 7.9%, P=0.036).

Conversely, there is contrary evidence in one single-centre prospective study enrolling patients with chronic renal disease, where statins did not confer additional benefits over standard preventative measures. On balance, although the data are promising, it would be premature to recommend high dose statins for the sole purpose of preventing CIN. However, given the favourable side-effect profile, it may be argued that escalation of dose in those already on statins and starting statin-naïve patients on the medication (if it is otherwise indicated) for the perioperative period, is a reasonable approach for reducing CIN. Table 3 summarize the trials involving statins in the prevention of CIN.

Remote ischaemic preconditioning

Remote ischaemic preconditioning (RIPC) involves the application of series of intermittent non-lethal ischaemic stimuli, to a particular region of the body (often a limb), in order to mitigate ischaemic damage to an organ in another region. In practice the preconditioning stimulus may be applied to either an upper or lower limb, using a non-invasive BP cuff. Recent clinical trials have shown a potential beneficial renal effect from this technique when used in cardiac surgery. Several small single-centre prospective trials showed a reduced rate of CIN in patients undergoing coronary angiography or percutaneous interventions, with further research in progress (Table 4). However, patients in the control groups of these studies had unusually high event rates, which raises concerns over the generalizability of the results to other lower risk patient groups. Nevertheless, when the preconditioning stimulus is being applied to an upper or lower limbs using non invasive BP cuffs, the reported complication rates are very low to nil in the vast majority of studies, and the potential protection may spread beyond the kidneys. Thus there appears to be little downside to using RIPC and this technique warrants further study in patients at risk of CIN.

Renal replacement therapy (RRT)

As CM can be effectively removed by haemodialysis (HD) or haemofiltration (HF), these interventions have been developed as a means of preventing CIN. Although earlier trials on high risk patients using HF held promise, there were some methodological weaknesses that may have influenced the results, such as differential medical management in the intervention group. In a meta-analysis that examined the use of HD or HF, RRT vs standard medical therapy was shown not to affect the incidence of CIN. This meta-analysis suffered from significant heterogeneity in terms of patient background, treatment protocols and types of contrast used. Interestingly, in a subgroup analysis that examined only HD (n=6 trials), where the heterogeneity was significantly reduced, the relative risk of developing CIN was actually higher in HD than in the comparator groups. This was similar to the findings of an earlier meta-analysis. A trend towards a reduction in temporary rescue RRT in the HD/HF groups was reported, but again heterogeneity between the included trials was significant. When limited to only the HF studies (n=3 trials), the heterogeneity was substantially reduced and the difference in temporary RRT requirements was significantly less in the treatment groups. Looking at individual trials, it would appear that HD might have more benefit in those with a lower baseline renal function than in those with slightly more reserve. On balance, given the resource implications, risks associated with RRT and the marginal benefits over less invasive measures, the prophylactic use of RRT cannot be recommended.

Agents acting on the renal circulation

Renal vasoconstriction has been implicated in the pathogenesis of CIN although much of the evidence comes from animal studies. As such, agents with renal vasodilating effects have been investigated and, disappointingly, there is no strong evidence for their efficacy in CIN prophylaxis across several classes of agents tested. Trials involving dopamine mostly did not demonstrate any benefit with its use. Similarly patients given fenoldopam also did not experience any benefits in terms of reduction in CIN. Calcium channel antagonists did not fare any better, with only one small trial showing some benefits whilst others showed less favourable results. Owing to both its renal vasodilatory and diuretic effects, the adenosine antagonist theophylline and, to a lesser degree, aminophylline have also been investigated for protective effects. There was also no impact on mortality or need for dialysis. There were also no benefits seen in subgroup analyses of patients with poorer baseline renal function or of trials of higher quality.

A relative newcomer to the family of renal vasodilators to be tested for the prevention of CIN is the prostacyclin analogue iloprost. To date there is a single-centre randomized, double-blind, placebo-controlled study of iloprost involving 208 patients. The drug was well tolerated and resulted in a reduction of CIN from 22% in the control group to 8% in the treatment group, with the latter demonstrating a slight increase in eGFR. Further larger confirmatory trials are required before a recommendation can be given for the use of iloprost.

Peri-procedural management

The cornerstone of successful prevention and management of CIN is vigilance of the clinical team; the first step is to identify patients at risk. These comprise patients who have received CM in the days leading up to surgery and those having known risk factors, which include increased serum creatinine, diabetes mellitus, dehydration, congestive heart failure, age more than 70 yr and concurrent administration of nephrotoxic drugs. The limitations of serum creatinine in reflecting renal function are well known and, therefore, estimation of GFR using one of the established formulas would be preferable in identifying those with reduced renal reserve, and an eGFR of <60 mls min⁻¹ 1.73 m² should raise concern.

As the vast majority of the trials on preventative measures for CIN have been performed during diagnostic or minimally invasive procedures, we have concentrated on a small number of interventions to maintain academic rigour. However, the kidneys of surgical patients may face several concurrent or sequential insults in the perioperative period and minimizing the occurrence of CIN is just one part of management aimed at preventing AKI. Close communication within the operating team is essential and concerns regarding any potential nephrotoxic drugs or interventions (such as manipulations likely to compromise renal blood flow) should be discussed.

Given the recent evidence regarding forced diuresis, it is inappropriate to expose dehydrated patients to contrast in the...
Table 3 Summary of the effect of statins on contrast induced nephropathy. Adj OR, Adjusted odds ratio; CKD, chronic kidney disease; CI, 95% confidence interval; Cr, creatinine; NAC, N acetylcysteine; NS, normal saline; NTSE-ACS, non ST elevation acute coronary syndrome; PRCT, Prospective Randomized Control Trial

<table>
<thead>
<tr>
<th>Author &amp; Yr</th>
<th>Study Type &amp; Number of patients</th>
<th>Procedure</th>
<th>Primary Outcome</th>
<th>Treatment &amp; Incidence</th>
<th>Comparator &amp; Incidence</th>
<th>Statistical Significance</th>
<th>Effect size</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khanal et al. (2005)</td>
<td>Prospective multicentre audit (n=29409)</td>
<td>PCI</td>
<td>Cr ↑ 0.5 mg dl⁻¹</td>
<td>Pre - procedural statins (n=10831); 4.37%</td>
<td>Statin naïve patients (n=18040); 5.93%</td>
<td>P&lt;0.0001 Adj. OR 0.87 (0.77-0.99, P=0.03)</td>
<td>Preprocedural renal failure patients excluded</td>
<td></td>
</tr>
<tr>
<td>Patti et al. (2008)</td>
<td>Prospective cohort study; (n=434)</td>
<td>PCI</td>
<td>Cr ↑ 0.5 mg dl⁻¹ or 25% from baseline</td>
<td>Pre - procedural statins (n=260); 3%</td>
<td>Statin naïve patients (n=174); 27%</td>
<td>P&lt;0.0001 90% risk decrease</td>
<td>4 year follow up</td>
<td></td>
</tr>
<tr>
<td>Xinwei et al. (2009)</td>
<td>RCT (n=228)</td>
<td>ACS patients PCI</td>
<td>Cr ↑ 0.5 mg dl⁻¹ or 25% from baseline</td>
<td>Simvastatin 80 mg (S80) (n=113)</td>
<td>Simvastatin 20 mg (S20) (n=115)</td>
<td>Not given CIN incidence not stated Cr returned to normal in S80 but not S20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toso et al. (2010)</td>
<td>Single centre PRCT (n=304)</td>
<td>Patients with pre-existing CKD for PCI</td>
<td>Cr ↑ 0.5 mg dl⁻¹ within 5 days</td>
<td>Atorvastatin 80 mg day⁻¹ n=151; 10%</td>
<td>Placebo (n=152); 11%</td>
<td>P=0.86 Cotreatment NS hydration plus NAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patti et al. (2011)</td>
<td>Multi-centre PRCT (n=241)</td>
<td>ACS patients PCI</td>
<td>Cr ↑ 0.5 mg dl⁻¹ within 5 days</td>
<td>Atorvastatin 80 mg then 40 mg day⁻¹ (n=120); 5%</td>
<td>Placebo (n=121); 13.2%</td>
<td>P=0.046 OR=0.34 CI=0.12 to 0.97, P=0.043</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Han et al. (2014)</td>
<td>Multi-centre PRCT (n=2998)</td>
<td>DM and CKD patients for PCI, peripheral angiography</td>
<td>Cr ↑ 0.5 mg dl⁻¹ or 25% from baseline at 72h</td>
<td>Rosuvastatin10 mg day⁻¹ for 5 days (n=1,498); 2.3%</td>
<td>Standard care (n=1,500); 3.9%</td>
<td>P=0.01 NS hydration for both groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leoncini et al. (2014)</td>
<td>Single centre PRCT</td>
<td>NSTE-ACS patients</td>
<td>Cr ↑ 0.5 mg dl⁻¹ or 25% from baseline within 72h</td>
<td>Rosuvastatin 40+20 mg day⁻¹ (n=252); 6.7%</td>
<td>Standard care (n=252); 15.1%</td>
<td>Adj OR=0.38 CI=0.2 to 0.71, P=0.003</td>
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</tr>
</tbody>
</table>
Table 4 Summary of evidence for remote ischaemic preconditioning and renal protection. AKI, Acute Kidney Injury; CAGB, Coronary Artery Bypass Graft; CI, 95% confidence interval; KDIGO, Kidney Disease Improving Global Outcome; MCRCT, Multi-Centre Randomized Control Trial; OR, Odds Ratio; PCI, Percutaneous Coronary Intervention; PRCT, Prospective Randomized Control Trial; RCT, Randomized Control Trial; RIPC, Remote ischaemic preconditioning

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Procedure</th>
<th>RIPC (N)</th>
<th>Control (N)</th>
<th>Outcome (RIPC vs CON)</th>
<th>Effect size</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venugopal et al. (2010)\textsuperscript{13}</td>
<td>Secondary analysis</td>
<td>CAGB*</td>
<td>38</td>
<td>40</td>
<td>AKI stages: I: 3 vs 25% II: 0 vs 0% III: 0 vs 0%</td>
<td>P=0.005</td>
<td>data from 2 prospective trials</td>
</tr>
<tr>
<td>Zarbock et al. (2015)\textsuperscript{9}</td>
<td>MCRCT</td>
<td>Cardiac surgery*</td>
<td>120</td>
<td>120</td>
<td>KDIGO AKI 37.5 vs 52.5% 12 vs 40%</td>
<td>ARR, 15%; CI=2.56-27.44%; P=0.02</td>
<td>OR=0.21</td>
</tr>
<tr>
<td>Er et al. (2012)\textsuperscript{12,85}</td>
<td>PRCT</td>
<td>Coronary angiography</td>
<td>50</td>
<td>50</td>
<td>12.4 vs 29.5%</td>
<td>P=0.002; OR=0.34; CI=0.16 to 0.71</td>
<td>P=0.03</td>
</tr>
<tr>
<td>Deftereos et al. (2013)\textsuperscript{96}</td>
<td>PRCT</td>
<td>PCI</td>
<td>113</td>
<td>112</td>
<td>10 vs 36%</td>
<td>P=0.003</td>
<td>OR=0.18 CI 0.05-0.64; P=0.008</td>
</tr>
<tr>
<td>Yamanaka et al. (2014)\textsuperscript{87}</td>
<td>RCT</td>
<td>PCI</td>
<td>63</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

elective setting. At a minimum the patient should receive prehydration either with 0.9% saline or isotonic bicarbonate.

Where patients are admitted on the day of surgery they should be instructed to drink oral fluids liberally the night before. Preoperative anaemia should be sought and treated before. Preoperative anaemia should be sought and treated before. Preoperative anaemia should be sought and treated before. Preoperative anaemia should be sought and treated before. Preoperative anaemia should be sought and treated before. Preoperative anaemia should be sought and treated before.

Apart from incorporating measures that are directed specifically at minimizing CIN, one must not forget other common sense measures to preserve renal function. These include maintenance of renal blood flow and renal perfusion pressure, avoidance of nephrotoxic agents, judicious glycemic control, and the appropriate management of any postoperative complications.\textsuperscript{118} With respect to perioperative management of medications, one must not overlook the potential for a postoperative decrease in renal clearance of drugs such as metformin, with the potential to cause lactic acidosis. Other drugs that undergo renal excretion may also need closer monitoring.

There is a scarcity of robust data regarding the influence of anaesthetic technique on CIN/AKI incidence. Multivariate analyses of patients from the EUROSTAR data in 2007, indicated a lower incidence of systemic complications, including renal outcomes, from the use of loco-regional techniques compared with general anaesthesia in EVAR, especially in the higher risk patients.\textsuperscript{111} However in another single centre retrospective analysis of 302 patients undergoing EVAR, there was no statistically significant difference between the two techniques in terms of all complications and all-cause mortality.\textsuperscript{112}

Alternatives to iodinated contrast media

For those who are allergic or at very high risk of developing CIN, alternatives may be considered. The most practical alternative in endovascular surgery is carbon dioxide (CO\textsubscript{2}) but because of its cumbersome inferior image quality and potential for embolism, it has not gained popularity. Carbon dioxide is a highly soluble gas that briefly displaces the blood, before being rapidly dissolved and excreted through exhalation.\textsuperscript{113} Being non-allergic, non-nephrotoxic and of low viscosity relative to blood, makes CO\textsubscript{2} a safe contrast medium.\textsuperscript{114,115} Even though CO\textsubscript{2} possesses these favourable characteristics, the risk of neurotoxicity, limiting its use to infra-diaphragmatic arteriography has been recommended.\textsuperscript{116,117} Other limitations include being less user-friendly and the complication of vapour lock that may risk impeding blood flow and result in tissue ischaemia.\textsuperscript{118,119} Notwithstanding these limitations, practitioners have successfully used CO\textsubscript{2} digital subtraction angiography (CO\textsubscript{2}-DSA) either to assist or as an alternative to CM for EVAR in high-risk patients, with similar results.\textsuperscript{110,119} It has also been investigated for the detection of endoleaks post graft placement, where it has shown moderate sensitivity and specificity for type I but not type 2 endoleaks and the authors have suggested that it may have a potential for initial evaluation of endoleak in order to minimize CM exposure.\textsuperscript{122} Therefore, this technique is gaining acceptance as a credible alternative to CM in endovascular procedures. Needless to say, its use requires careful planning and good communication between members of the operating team.

Gadolinium

Gadolinium was once thought to be a suitable alternative to CM. This was disproved after the report of its association with nephrogenic systemic sclerosis (NSF).\textsuperscript{123} NSF is a serious fibrosing dermatopathy associated with hardened skin nodules, joint contractures and multi-organ involvement in its severe form, but no effective treatment is currently available.\textsuperscript{124} Furthermore, gadolinium is more nephrotoxic than CM in equivalent doses that produce the same x-ray attenuating function.\textsuperscript{125} Therefore, the European Society of Urogenital Radiology (ESUR) does not recommend its use for angiography and CT.\textsuperscript{26}

Concluding remarks

CIN prevention is continually evolving. The data regarding N-acetyl cysteine, and to lesser extent, bicarbonate, theophylline and renal replacement therapy, is illustrative of the problems that physicians face in their endeavour to minimize patient harm. Multiple small trials with different designs and co-treatments, spanning over a long time have predominated in the literature and limited interpretation of the efficacy of
treatments, even with meta-analysis. Thankfully, some better quality evidence, especially with regards to hydration and NAC, is beginning to emerge attributable, in part, to standardization of definitions and more rigorous study design. Maintaining a high urinary flow rate around the time of contrast exposure is pivotal in minimizing harm from the CM. However, evidence is equivocal at best for the strategy of reducing oxidative damage, by either antioxidants or urinary alkalinization. The renal vasodilator iloprost is promising but further data are awaited. Patients taking statins should be maintained on therapy and there is evidence that initiation of treatment may have other benefits also. Intraoperative remote ischaemic preconditioning is simple and safe but requires further validation before it can be recommended as a prophylaxis.

Authors’ contributions
Writing paper: G.T.C.W., E.Y.P.L.
Revising paper: all authors

Declaration of interest
None declared.

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