HHS Public Access

Author manuscript

*Nat Rev Nephrol*. Author manuscript; available in PMC 2015 June 22.

Published in final edited form as:

*Nat Rev Nephrol*. 2010 November ; 6(11): 679–688. doi:10.1038/nrneph.2010.116.

# Contrast-induced acute kidney injury and diabetic nephropathy

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## Abstract

Contrast-induced acute kidney injury (CIAKI) is a leading cause of iatrogenic renal failure. Multiple studies have shown that patients with diabetic nephropathy are at high risk of CIAKI. This Review presents an overview of the pathogenesis of CIAKI in patients with diabetic nephropathy and discusses the currently available and potential future strategies for CIAKI prevention.

## Introduction

In 2008, contrast-induced acute kidney injury (CIAKI) was proposed as the consensus name for what was formerly termed 'contrast-induced nephropathy'.[1] CIAKI is the most common cause of iatrogenic, drug-induced, acute kidney injury (AKI) in hospitals.[2–5] CIAKI primarily presents as a nonoliguric form of AKI with an increase in serum creatinine level within 48–72 h after administration of contrast medium. Serum creatinine levels typically return to baseline after 7–10 days, although some patients develop a chronic reduction in kidney function or a permanent need for renal replacement therapy. CIAKI is associated with a 1-year mortality rate of up to 30%.[5–10] In a study of more than 8,000 patients,[11] diabetes, female sex, and the amount of contrast agent administered were the strongest predictors of CIAKI-associated death. The mortality rate associated with CIAKI might even be >30% in patients with diabetes who receive intravenous contrast media.[12] This Review presents an overview of the pathogenesis of CIAKI in patients with diabetic nephropathy and discusses both currently available therapies and potential future strategies for CIAKI prevention. Given the limited evidence that CIAKI is associated with the use of gadolinium-based contrast agents, this Review will focus on iodinated contrast media.



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**Competing interests**

The authors declare no competing interests.

**Author contributions**

A. D. Calvin and A. Pflueger researched data for the article, made substantial contributions to the discussion of content, wrote the article and reviewed/ edited the manuscript before submission. S. Misra made substantial contribution to the discussion of content and wrote the article.

## Types of contrast media

### Gadolinium

Gadolinium, the contrast medium commonly used in MRI, was once considered to be non-nephrotoxic.[13] However, reports of nephrotoxic and dermatotoxic[14] effects of gadolinium have led to gadolinium being administered predominantly to patients with preserved renal function.[15] Gadolinium-associated CIAKI has been reported in patients with diabetes,[16] but supporting evidence is limited and is not discussed further in this article.

### Iodinated agents

CIAKI can occur after intra-arterial and intravenous administration of iodinated contrast media.[17] The risk of CIAKI in patients with diabetic nephropathy depends on the characteristics of the contrast medium, including its osmolality, viscosity and volume.[3,18]

## The effects of osmolality and viscosity

High-osmolality contrast media (>800 mmol/kg) are associated with a higher incidence of CIAKI than low-osmolality (600–800 mmol/kg) contrast media in patients with diabetic nephropathy.[2,19] Iso-osmolal contrast media (approximately 290 mmol/kg) were originally developed to reduce the risk of CIAKI. However, iso-osmolal contrast media have a higher viscosity than low-osmolal contrast media,[20,21] and increased viscosity has been shown to reduce renal tubular flow and decrease glomerular filtration rate (GFR).[22] The desirability of low-osmolality contrast agents has, therefore, been questioned.[20,21,23,24]

Early studies showed a lower incidence of CIAKI in patients with diabetic nephropathy who had received an iso-osmolar contrast medium than in patients who had received a low-osmolarity contrast medium;[25,26] however, larger studies have not confirmed this finding.[27,28] The results of the double-blind, multi-center CARE study[27] showed no difference in the rate of CIAKI, defined as a >50% increase in serum creatinine level with respect to baseline, between patients with diabetic nephropathy who had received the low-osmolal contrast medium iopamidol and patients who had received the iso-osmolal contrast medium iodixanol. By contrast, in the VALOR trial,[28] researchers studied the incidence of CIAKI in patients with chronic kidney disease (CKD) without diabetes ($n$ = 145) and in patients with both CKD and diabetes ($n$ = 154) receiving either the iso-osmolar contrast medium iodixanol or the low-osmolar contrast medium ioversol. CIAKI was defined as an increase in serum creatinine level from baseline of ≥44 μmol/l. In patients with CKD but without diabetes, no difference was observed in the incidence of CIAKI between the two treatment groups. However, in patients with both CKD and diabetes (most of whom were likely to have diabetic nephropathy[29,30]), the incidence of CIAKI tended to be lower in the iodixanol group than in the ioversol group (21.9% versus 26.4%; $P$ = 0.57). Furthermore, the mean peak percentage increase in serum creatinine levels from baseline after administration of contrast medium was significantly lower in patients with CKD and diabetes who received iodixanol than in those who received ioversol (12.9% versus 22.4%; $P$ = 0.01). The VALOR and CARE trials differ in several important aspects, however, which might account for their disparate findings. Some of these aspects are discussed below. In summary, although strong

evidence is lacking, iso-osmolar contrast media might be safer than low-osmolar and high-osmolar contrast media.

## Renal function assessment

The results of the CARE and VALOR studies also illustrate that the definition of CIAKI can make an important difference to trial outcomes and, therefore, to the reported incidence of CIAKI. Efforts to implement a reasonable classification and definition of CIAKI have, however, been made only in the past couple of years.[6]

All studies published to date have defined the development of CIAKI as an increase in serum creatinine level from baseline either in absolute terms (such as 44–88 μmol/l) or as a percentage increase (25% or 50%).[3,4,31–34] However, serum creatinine level is an insensitive marker of GFR in patients with normal kidney function—these levels can vary by 10–20% in such individuals, depending on hydration status. Hyperfiltration occurs in a small subset of patients with diabetes, dependent on the degree of hyperglycemia.[35] Furthermore, changes in serum creatinine level may take a day or more to become apparent after a substantial decrease in GFR has occurred. Creatinine clearance seems to be a more sensitive marker of GFR than serum creatinine level, but measurement of creatinine clearance requires 24 h urine collection, which is impractical in many settings. Studies of the short-term renal clearance of iothalamate suggest that this marker might be more promising than creatinine clearance as a measure of GFR. Measurement of serum cystatin C concentration might be a more accurate measure of GFR than serum creatinine level, although further studies are needed.[36]

The RIFLE criteria have been developed to standardize and improve care of patients with AKI.[37,38] By using both GFR and urine output criteria, the RIFLE criteria avoid the pitfalls of using serum creatinine levels alone to categorize the severity of renal impairment. Patients are grouped according to the RIFLE acronym: at risk of AKI (R), with renal injury (I), with renal failure (F), with sustained loss of renal function (L), and with end-stage renal disease (E). Several studies have shown that the RIFLE criteria correlate with outcomes in different populations,[39] including hospitalized patients,[40] patients in intensive care units,[41–43] cardiac surgery patients,[44] and patients on continuous venovenous hemodialysis.[45] Whether different etiologies of AKI, including CIAKI, affect the clinical outcome of each degree of renal dysfunction in the RIFLE classification is not yet known.[37] Staging the severity of AKI according to the RIFLE criteria might be reasonable in future studies of CIAKI.

## Pathogenesis of CIAKI

CIAKI is primarily an ischemic form of AKI caused by the vasoconstrictive properties of contrast media (Figures 1 and 2). In addition, contrast media can potentially have direct toxic effects on endothelial cells and renal tubules, reduce erythrocyte flexibility, and activate leukocyte adhesion molecules, which results in leukocytes binding to endothelial cells.[2,3,46]

Animal studies have shown that after injection of contrast media into the renal vasculature, renal blood flow transiently increases followed by a substantial decrease to levels below the original baseline.[47,48] This biphasic response of renal blood flow to contrast-medium injection is also characteristic of the response to adenosine in the renal vasculature,[47–51] so adenosine has been postulated to have an important role in the pathogenesis of CIAKI.[47–51] The overall net effect of infusion of either adenosine or contrast media into the renal artery is a prolonged reduction in renal blood flow.[51–54]

Iodine-based contrast media seem to cause renal vaso-constriction in the afferent arteriole via stimulation of [47,48,55–57] In addition to adenosine receptor $A_1$ (Figure 1). stimulation of adenosine receptor $A_1$, adenosine also causes renal vasodilation via stimulation of the adenosine receptor $A_{2a}$ in the efferent arteriolar and medullary capillaries. Contrast media seem to reduce renal blood flow directly through afferent arteriole vasoconstriction via activation of adenosine receptor $A_1$.[57]

In animal studies, intravenous administration of contrast media increases renal excretion of adenosine[47,48,58] and endothelin.[46,59] Indirectly, contrast media are thought to induce the release of various renal vasoconstrictors within the kidney, including adenosine, endothelin, angiotensin II, and reactive oxygen species (ROS), which collectively cause renal hypoxia and increased adenosine generation through ATP hydrolysis.[2,4,19,46–48] This hypothesis is supported by studies that demonstrate that CIAKI can be prevented by administration of adenosine-receptor antagonists.[55,60–62]

Furthermore, administration of contrast media results in increased renal tubular osmotic load, which can upregulate tubular transport mechanisms and ATP hydrolysis (Figure 1). The effects of contrast media on the renal tubules include diuresis, natriuresis, alterations in regulatory mechanisms, increases in intratubular pressure, tubular obstruction and necrosis.[34] The role of direct toxic tubular effects in CIAKI remains controversial but they are probably a contributory factor.[2,4,62–64]

## Risk factors for CIAKI

Since CIAKI is primarily caused by renal vasoconstriction, an individual with diminished renal vasodilatory capacity, such as a patient with diabetic nephropathy, is at increased risk of developing CIAKI. Numerous factors that increase the risk of CIAKI have been reported, including impaired renal function, diabetes, reduced intravascular volume, cardiovascular disease, use of diuretics, advanced age, female sex, multiple myeloma, hypertension, hyperuricemia and surgical interventions. Among these factors, pre-existing renal impairment seems to have the most prominent effect.[65,66]

CIAKI (when defined as an increase in baseline serum creatinine level of ≥25%) has an incidence <5% among individuals with normal renal function.[3] However, the risk of CIAKI is increased in patients with CKD and in those with diabetic nephropathy.[2,4,52] The Contrast-Induced Nephropathy (CIN) Consensus Working Panel concluded that the risk of CIAKI is significantly higher in patients with an estimated GFR (eGFR) of <60 ml/ min/ 1.73 $m^2$ and is amplified when other risk factors are present.[67]

Diabetic nephropathy is an important risk factor for CIAKI.[3,4,64,68,69] The incidence of CIAKI in patients with diabetic nephropathy is 9–40% in individuals with a serum creatinine level >124 μmol/l[3,52,69] and 50–95% in those with a serum creatinine level >177 μmol/l.[3,31,33,70]

In addition, evidence suggests that even patients in a prediabetic state are at increased risk of CIAKI if they also have CKD. Toprak *et al.*[65] showed that CIAKI occurred in 20% of patients with CKD and diabetes and in 11.4% of patients with CKD and prediabetes (defined as having a fasting glucose level of 5.55–6.94 mmol/l), versus 5.5% of patients with CKD but no evidence of diabetes or prediabetes. This observation suggests that mild glucose intolerance, which does not fulfill the current criteria for diabetes mellitus, increases the risk of CIAKI in the presence of renal impairment.

Whether patients with diabetes and normal renal function have an increased propensity to develop CIAKI remains controversial. The results of some studies suggest that these patients might have an increased risk of CIAKI,[71] whereas other studies have failed to show this association.[72] The heterogeneity of these findings might be due to the existence of different phenotypes of diabetic nephropathy, particularly in early stages of the disease, as is discussed below.

## Pathogenesis of diabetic nephropathy

Patients with diabetes have an up to 40% lifetime risk of developing diabetic nephropathy.[73] In one-third of patients, diabetic nephropathy is a progressive disease characterized by increasing proteinuria (mainly albuminuria) and a subsequent decline in GFR (Table 1). However, results from studies published in the past few years indicate that several phenotypes of diabetic nephropathy exist, and the majority of patients do not develop the classic phenotype of progressive diabetic nephropathy. For example, the renal function of some patients with diabetes is characterized by a decreased GFR and little or no albuminuria.[74,75]

Diabetic nephropathy is characterized by renal vascular dysfunction, which manifests as an increased sensitivity to renal vasoconstrictors and renal ischemia, and a decrease in nitric oxide-dependent vasodilation.[51,76] Ishimura *et al.*[77] demonstrated that patients with stage 1 diabetic nephropathy have increased renal resistive indices in their renal vasculature, which indicate a diminished renal vasodilatory blood flow reserve. Furthermore, Frauchiger *et al.*[78] showed that patients with early diabetic nephropathy have a lower renal blood flow (vasodilatory) response to administration of glyceryl trinitrate than healthy controls. In addition, Epstein *et al.*[79] elegantly demonstrated that renal blood oxygenation (as quantified by MRI techniques that are dependent on blood oxygenation levels) is lower in patients with stage 1 diabetic nephropathy than in healthy controls after a water load. This observation suggests that oxygen delivery is impaired in patients with early stages of diabetic nephropathy. This effect might be at least partly accounted for by vascular and/or endothelial dysfunction. Numerous other factors might also contribute to this impairment in renal blood oxygenation, including defective nitric oxide production, high concentrations of advanced glycosylation end products, increased generation of cytokines, and increased

generation of ROS.[80–82] Several animal studies have demonstrated that nitric-oxide-dependent renal vasodilation is critical in countervailing the vasoconstrictive effects of both adenosine[51,76] and contrast media[49] and that the responsiveness of this vasodilation mechanism is diminished in patients with diabetes (Figure 2).[77,81–83]

CIAKI causes renal ischemia, and repeated ischemic insults to the renal vasculature of patients with diabetes cause progression of diabetic nephropathy and deterioration of renal function.[72] Prevention of CIAKI in patients with diabetes is, therefore, important for the long-term preservation of renal function. In addition, given the evidence from Toprak *et al.*'s study[65] that the incidence of CIAKI is increased in patients in a prediabetic state as well as in those with diabetes, it seems likely that many patients with diabetes would also have renal vascular dysfunction, even in the absence of overt diabetic nephropathy. Such patients are frequently considered to have 'normal renal function' and thus the risk of CIAKI is not fully appreciated in this group. New tests must be devised to detect early renal dysfunction and identify patients at risk of CIAKI. In addition, therapeutic and preventative measures for CIAKI are potentially important for the prevention of diabetic nephropathy in patients with diabetes at risk of CIAKI. Consequently, until appropriate screening tests are available, a prudent approach would be to implement CIAKI prophylaxis in all patients with diabetes.

## CIAKI prevention in diabetic patients

Although CIAKI is the most common form of iatrogenic renal failure, only about 40% of patients with an eGFR <60 ml/min/1.73 $m^2$ receive any sort of CIAKI prophylaxis.[1] Furthermore, even when prevention strategies are implemented, few patients receive a standardized regimen.[17] The renal vasodilatory capacity represents a vital mechanism to counter the vasoconstrictive effects of contrast media. Potential therapeutic agents for the prevention of CIAKI in patients with diabetes are presented in Table 2 and discussed below. Further suggestions for reducing the risk of CIAKI are shown in Box 1.

**Box 1**

**Suggestions for reducing the risk of CIAKI**

- Imaging studies with contrast media should only be performed when the benefits outweigh the risks; alternative protocols that do not require iodinated contrast media should be considered if they can provide the necessary information
- The use of iso-osmolar contrast media might reduce the incidence of CIAKI
- Avoidance of concomitant administration of nephrotoxic agents, such as angiotensin-converting-enzyme inhibitors and NSAIDs, seems prudent, although no conclusive evidence exists to support such clinical decision making
- Intravascular volume expansion should be provided, preferably via intravenous hydration, if this technique is not contraindicated

- Our experience indicates that *N*-acetylcysteine should be administered at a dose of 1,200 mg orally twice daily for 7 days, starting 1 day before contrast-medium administration

Abbreviation: CIAKI, contrast-induced acute kidney injury.

### Hydration

Hydration is the intervention best supported by evidence of a preventive effect on CIAKI and is the foundation of most approaches that prevent CIAKI. However, the mechanism by which hydration prevents CIAKI is unclear,[84] although intravenous hydration seems to be more effective than unrestricted oral hydration.[85] Standardized, prospective studies to determine the optimal hydration strategy and evaluate the cost-effectiveness of oral hydration are needed.[84]

In a randomized trial that included 1,620 patients, 217 of whom had diabetes, Mueller and colleagues[86] showed that intravenously administered 0.9% saline solution was superior to 0.45% saline solution, although this difference was not apparent in the subgroup of patients with serum creatinine level >141 μmol/l regardless of diabetes status. Although data are limited, 0.9% saline solution is claimed to be superior to 0.45% saline solution for CIAKI prevention in general.[84] Furthermore, two small studies suggest that sustained fluid administration within 12 h before and within 12 h after administration of contrast medium is superior to bolus administration at the time of contrast administration.[87,88]

### Mannitol and diuretics

In the general population as well as in patients with diabetes, mannitol and furosemide diuresis have both been shown to increase the risk of CIAKI.[27] Despite the lack of definitive evidence of a pathogenic link between CIAKI and administration of these two diuretics, these agents should be avoided in patients with diabetes.

### Vasodilators

Renal vasodilators, including calcium-channel antagonists, are promising agents in the prevention of CIAKI;[89] so far, however, their administration has failed to show conclusive evidence of a beneficial effect.[90–93] Low-dose dopamine has a dilatory effect on renal vasculature, but confers no advantage over hydration in the prevention of CIAKI, and may be harmful in patients with peripheral vascular disease.[94] These observations are not surprising since the renal vasodilatory response is impaired in patients with diabetes, and thus administration of renal vasodilators is likely to be of little or no benefit in the prevention of CIAKI.

### Sodium bicarbonate

The intravenous administration of sodium bicarbonate solutions for CIAKI prevention was first studied by Merten and colleagues.[94] In this small study, intravenous sodium bicarbonate administration was associated with a decreased incidence of CIAKI. Subsequent studies have failed to show any benefit of the intravenous administration of sodium

bicarbonate over isotonic sodium chloride in CIAKI prevention.[95,96] The rationale for a potential role of sodium bicarbonate in the prevention of CIAKI might involve the ability of bicarbonate to increase tubular fluid pH level and prevent the formation of free radicals, but whether these effects actually decrease risk of CIAKI is unclear and highly controversial. Typically, bicarbonate acts as a pro-oxidant, particularly in the presence of ROS; as the pathogenesis of CIAKI seems to involve both renal ischemia and ROS generation, the administration of a pro-oxidant seems counterintuitive and might be associated with an increased incidence of CIAKI.[17]

Furthermore, contrast-medium-induced apoptosis of renal cells is inhibited by the antioxidants *N*-acetylcysteine and ascorbic acid, but not by sodium bicarbonate.[97] A small trial published in 2010 demonstrated that intravenous administration of sodium bicarbonate and 0.45% saline solution 48 h after elective coronary angiography was not superior to intravenous administration of 0.45% saline solution alone for the prevention of CIAKI; however, only about one-third of the participants had diabetes.[98]

Two meta-analyses have been published on the use of sodium bicarbonate in the prevention of CIAKI, and both reported substantial study heterogeneity and publication bias.[99,100] In most studies, only a minority of patients had diabetes, and until larger controlled trials have been conducted to study the effects of sodium bicarbonate on the risk of CIAKI in patients with diabetes, the usefulness of this compound remains uncertain.

### *N*-acetylcysteine

CIAKI and diabetic nephropathy are both associated with increased generation of ROS and thus some researchers have suggested that antioxidants, such as *N*-acetylcysteine, might potentially prevent or treat CIAKI. The first study of the use of *N*-acetylcysteine for CIAKI prevention was conducted by Tepel and colleagues.[101] In this study, the investigators compared the efficacy of oral administration of 600 mg of *N*-acetylcysteine twice daily on the day before and on the day of contrast-medium administration alongside intravenous hydration with 0.45% saline with the efficacy of intravenous hydration with 0.45% saline alone. 48 h after administration of contrast medium, patients who received saline hydration alone experienced a small, insignificant increase in serum creatinine level from 212 μmol/l to 220 μmol/l ($P = 0.18$), whereas patients in the *N*-acetylcysteine group experienced a significant decrease in serum creatinine level from 221 μmol/l to 186 μmol/l ($P = 0.01$). Several subsequent studies demonstrated ambiguous results on the effectiveness of *N*-acetylcysteine in preventing CIAKI.[102,103]

Several factors might contribute to these disparate results, among them the dose administered and treatment duration. *N*-acetylcysteine is commonly only given for 2 days[101] on the assumption that ROS production occurs for only a short time after being induced by contrast media. However, this concept may need to be revised since the effects of ROS induction may last much longer than previously assumed, particularly in patients with diabetes. El-Osta *et al.*[104] demonstrated that short-term (1 h) exposure to high glucose concentrations induced long-lasting ROS-mediated activation of the transcription factor nuclear factor κB both *in vitro* and *in vivo*, and was associated with increases in the expression of C–C motif chemokine 2 and vascular cell adhesion molecule 1 that persisted

for at least 6 days. Whether ongoing ROS generation that might be a target for antioxidant therapy continues after glucose levels normalize has yet to be proven, but this evidence illustrates that ROS-mediated processes could propagate long after the initial insult. On the other hand, achieving a sufficiently high serum concentration of *N*-acetylcysteine at the time of contrast-medium exposure might be more important than the duration of *N*-acetylcysteine administration. Unfortunately, levels of *N*-acetylcysteine are difficult to measure accurately, as this compound has a very short half-life in plasma owing to extensive first-pass metabolism. This characteristic might explain why this agent seems to have greater efficacy in the prevention of CIAKI when it is administered intravenously rather than orally.[102,103,105–107] Two daily doses of oral *N*-acetylcysteine might, therefore, be insufficient to achieve consistent renoprotective effects.

The doses of *N*-acetylcysteine that have been investigated might also be too low to achieve a meaningful reduction in ROS. *N*-acetylcysteine has been successfully used in the treatment of acetaminophen-induced toxic effects on the liver, which are mediated by ROS. Daily doses of *N*-acetylcysteine for this indication are typically 40-fold higher than those currently recommended for CIAKI prevention (1,200 mg daily or $7 \times 10^{-3}$ mol). Daily physiological production of the superoxide anion is estimated to be 1.75 kg or $5.5 \times 10^{4}$ mol.[108] As ROS production is increased to above this amount in patients with diabetes and CIAKI, the presumption that only $7 \times 10^{-3}$ mol/l of *N*-acetylcysteine would cause a meaningful reduction in a daily ROS generation of $\geq 5.5 \times 10^{4}$ mol/l of super-oxide anion seems to be ill-founded. Marenzi *et al.*[109] demonstrated that 1,200 mg of *N*-acetylcysteine given twice daily is more effective in CIAKI prevention than 600 mg of *N*-acetylcysteine given twice daily.[109] Given also the favorable adverse-effect profile[110] and low cost of *N*-acetylcysteine, higher doses of this antioxidant and longer treatment periods than those currently implemented would, therefore, seem appropriate to improve CIAKI prevention. Current practice in our clinic is to administer 1,200 mg of *N*-acetylcysteine orally twice daily on the day before contrast-medium administration, and on days 1–7 after. This regimen is associated with good tolerability and outcomes (Calvin, A. D. *et al.*, unpublished data).

## Adenosine-receptor antagonists

Since adenosine-induced vasoconstriction seems to be markedly enhanced in patients with diabetes, and as CIAKI is thought to cause renal vasoconstriction by an adenosine-mediated mechanism (see above), adenosine-receptor antagonists have been investigated as a potential option for CIAKI prevention. When given before contrast media, oral or intravenously administered theophylline, a nonselective adenosine-receptor antagonist, reduces the incidence of CIAKI.[55,56,61] The use of theophylline to prevent CIAKI might be limited by inter-individual variability in drug metabolism, drug–drug interactions, and risk of tachyarrhythmias,[111] although adverse cardiac effects associated with theophylline administration seem to be rare at the doses given in these studies (single doses of 5 mg/kg intravenously,[55] 2.88 mg/kg orally,[56] and 165 mg intravenously[61]). The conclusions of a meta-analysis stated that these and other studies provide some evidence of a beneficial effect of theophylline administration in the prevention of CIAKI.[112] However, factors such as differences in theophylline dose, volume and type of contrast medium administered, hydration status, comorbidities such as diabetes, and the lack of a consistent method to

measure plasma levels of theophylline might contribute to the variability of results obtained in different studies.

Selective antagonists of adenosine receptor $A_1$ inhibited adenosine-induced renal vasoconstriction and restored renal blood flow after renal ischemia in non-diabetic and diabetic animals.[51,76] Furthermore, antagonists of adenosine receptor $A_1$ have protective effects on the renal tubular system by increasing sodium excretion in humans with heart failure[113] and in diabetic animal models.[114] Both of these effects could help to prevent CIAKI. The diuretic and natriuretic properties of selective antagonists of adenosine receptor $A_1$ are of particular interest, since natriuresis occurs without increased potassium excretion. By contrast, loop diuretics increase potassium excretion, which could aggravate cardiac arrhythmias. Administration of selective antagonists of adenosine receptor $A_1$ might have additional beneficial properties, such as improving glucose tolerance (as shown in animal models of diabetes)[115] and inhibiting platelet aggregation.[3] Newly developed selective antagonists of adenosine receptor $A_1$ do not seem to be associated with adverse cardiac effects[55,56,61] and cardioprotective effects have even been demonstrated in animal models of ischemia–reperfusion injury.[116–119] Although not yet clinically available, several selective antagonists of adenosine receptor $A_1$ (DPCPX, FK453 and FR113452) have been studied in both animals and in humans.[115–118] The intravenous administration of FK453 increased GFR and fractional excretion of sodium in animals[117] and in humans[120] without disturbing potassium homeostasis. Other selective antagonists of adenosine receptor $A_1$ (BW-1433 and CVT-124) are under investigation.[121–123]

In summary, CIAKI seems to result, at least in part, from renal vasoconstriction mediated by stimulation of adenosine receptor $A_1$. Nonselective adenosine-receptor antagonists, such as theophylline, reduce the risk of CIAKI in patients with diabetes. Administration of novel, investigational, selective antagonists of adenosine receptor $A_1$ might prevent CIAKI in patients with diabetes and could have both higher efficacy in preventing CIAKI and fewer adverse effects than theophylline.

## Statins

Statin administration might reduce the progression of CKD and diabetic nephropathy,[124] perhaps through pleiotropic, antioxidant and anti-inflammatory effects. Statins might also have beneficial effects in the prevention of CIAKI. In an animal model of ischemia–reperfusion injury, administration of pravastatin limited renal damage via inhibition of the mevalonate–isoprenoid pathway, independently of the lipid-lowering action of statins.[125]

In a retrospective study that included more than 29,000 patients who underwent percutaneous coronary angiography, Khanal *et al.*[126] found that patients who were on statin therapy before the procedure had a lower incidence of CIAKI than patients who were not taking a statin at that time. These results are in line with those of a prospective, observational study that included 434 participants, in which patients who were taking statins before undergoing coronary angiography had a lower rate of CIAKI (defined as an increase in serum creatinine level of ≥44 mmol/l or >25% from baseline). This association was also evident among the 161 patients with diabetes included in the study.[127] In the PROMISS study,[128] however, researchers administered simvastatin or placebo to patients before they

underwent coronary angiography and observed no reduction in CIAKI (defined as an increase in serum creatinine of ≥25% or an absolute increase of ≥44 mmol/l within 48 h after contrast-medium administration) in the statin-treated group compared with the placebo-treated group. Only 59 of the 247 participants in the PROMISS study had diabetes, and in this subgroup a trend towards a beneficial effect of simvastatin was observed (the incidence of CIAKI was 6.3% in the treatment group versus 11.1% in the placebo group, $P = 0.65$). However, a 2010 trial of atorvastatin in 304 patients with CKD (estimated creatinine clearance <60 ml/min) failed to demonstrate benefits of treatment with atorvastatin versus placebo. In the subgroup of 64 patients with diabetes, the incidence of CIAKI did not differ between the treatment and placebo groups.[129]

## Hemodialysis and hemofiltration

Hemodialysis is effective in removing contrast media from the circulation[130–133] and some reports indicate that hemodialysis can prevent CIAKI.[134] However, several studies have failed to show that prophylactic hemodialysis soon after contrast-medium exposure is effective in preventing CIAKI in patients who are not already on renal replacement therapy.[135–137] Hemodialysis has failed to prevent CIAKI even when dialysis was performed within 1 h of contrast-medium administration[138] or concurrently with coronary angiography,[139] and results from one study suggested that prophylactic hemodialysis might actually cause harm when performed after administration of contrast medium to patients with renal insufficiency.[140] However, the CIN Consensus Working Panel agreed that in patients with severe renal impairment (eGFR <20 ml/min) who require contrast-medium administration, hemodialysis should be undertaken if CIAKI develops.[67]

The role of hemofiltration in CIAKI prevention has been assessed in a single study.[141] Patients undergoing coronary angiography with a baseline serum creatinine level >177 μmol/l and eGFR <50 ml/min, 30% of whom had diabetes, were randomly assigned to receive usual care (intravenous high-volume hydration with 1 ml $kg^{-1}$/h isotonic saline solution for most patients or 0.5 ml $kg^{-1}$/h isotonic saline solution for patients with a left ventricular ejection fraction <40%), starting 6–8 h before the procedure and for 24 h afterwards, or preemptive venovenous hemofiltration before contrast-medium administration and for 18–24 h afterwards. Patients who received continuous hemofiltration were less likely to experience CIAKI, defined as a rise in serum creatinine level of >25%, than patients receiving standard care. In-hospital and 1-year mortality rates were significantly lower in patients who underwent hemofiltration than in those who received standard care. However, these results have been called into question as hemofiltration is generally ineffective in the removal of contrast media,[130] and CIAKI is thought to occur immediately upon exposure to contrast media,[130] whereas in this study hemofiltration was interrupted during contrast-medium administration. The benefits of hemofiltration observed in this study have been suggested to be due to the concomitant administration of heparin,[142] which has anti-inflammatory effects[143] and might reduce ROS generation.[144] Furthermore, patients randomly assigned to hemofiltration also underwent controlled, high-volume hydration and monitoring in the intensive care unit, both of which could reduce the incidence of CIAKI. The CIN Consensus Working Panel concluded that hemofiltration merits further study.[67]

## Conclusions

CIAKI incidence and CIAKI-associated mortality are high in patients with diabetes and diabetic nephropathy, and good screening tools for early diabetic nephropathy are lacking. We recommend, therefore, that CIAKI prophylaxis should be considered in all patients with diabetes who require either intra-arterial or intravenous administration of contrast media, regardless of renal function. To date, the only intervention clearly proven to prevent CIAKI is hydration. Unfortunately, the optimal hydration strategy has not yet been established, although intravenous hydration seems to be superior to oral hydration. Although additional studies are needed, administration of high-dose *N*-acetylcysteine also seems to be effective in preventing CIAKI. Statins might reduce the risk of CIAKI, and continuing statin treatment in patients who are already taking these agents seems reasonable. Currently, the administration of sodium bicarbonate for CIAKI prevention cannot be recommended in patients with diabetes or other conditions in which there is an increased generation of ROS. Selective antagonists of adenosine receptor $A_1$ have shown promise in preventing CIAKI, but are not yet commercially available.

## Acknowledgments

A. D. Calvin's research is supported by the Mayo Clinic Clinician–Investigator Training Program. The authors gratefully acknowledge D. Mackenburg and E. Pflueger, who contributed to this Review with editorial support, including help with references and figures. Both D. Mackenburg and E. Pflueger are affiliated with the Mayo Clinic College of Medicine, Rochester, MN, USA.

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**Key points**

- Contrast-induced acute kidney injury (CIAKI) is caused by the intra-arterial and intravenous administration of contrast media and is associated with a high risk of mortality
- Diabetes, even in the absence of renal impairment, might increase the risk of CIAKI, and CIAKI might favor progression of diabetic nephropathy
- CIAKI prophylaxis should be considered in all patients with diabetes who require intra-arterial or intravenous administration of contrast medium
- Intravenous hydration is the cornerstone of CIAKI prophylaxis, whereas the administration of sodium bicarbonate is of unclear benefit and might be harmful in patients with diabetes owing to its pro-oxidant properties
- *N*-acetylcysteine administration might have protective effects and has low toxicity and should be considered for CIAKI prevention in patients with diabetes
- Adenosine $A_1$ receptor antagonists seem to be promising agents for CIAKI prophylaxis, but additional studies in humans are needed

### Review criteria

Articles were identified through a search of the PubMed database using the search terms “contrast-induced nephropathy”, “radio-contrast nephropathy”, “contrast nephropathy”, and “contrast medium-induced nephropathy”, using the ‘related articles’ function, and through review of consensus documents and published guidelines. No restrictions were imposed with regard to language or year of publication.

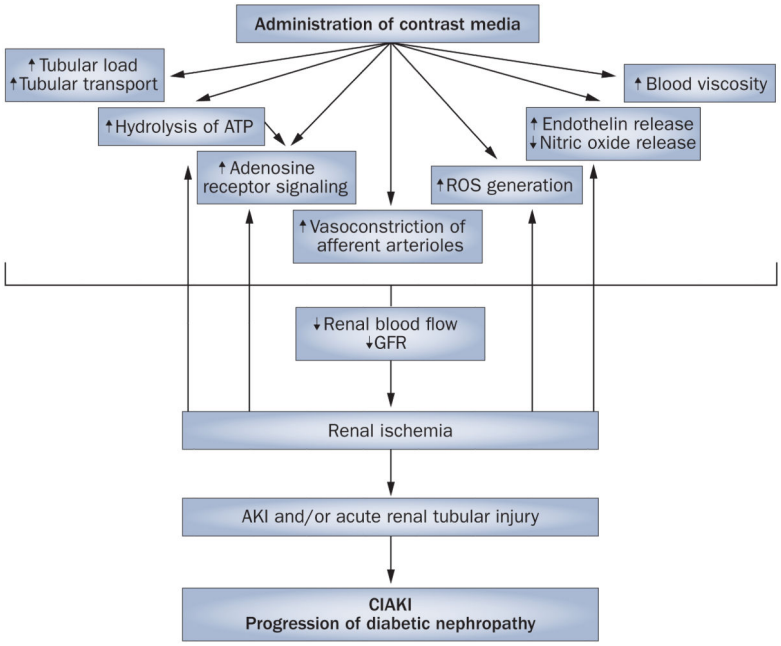


**Figure 1.**

The pathways potentially underlying the pathogenesis of CIAKI in patients with diabetes. Abbreviations: AKI, acute kidney injury; CIAKI, contrast-induced acute kidney injury; GFR, glomerular filtration rate; ROS, reactive oxygen species.

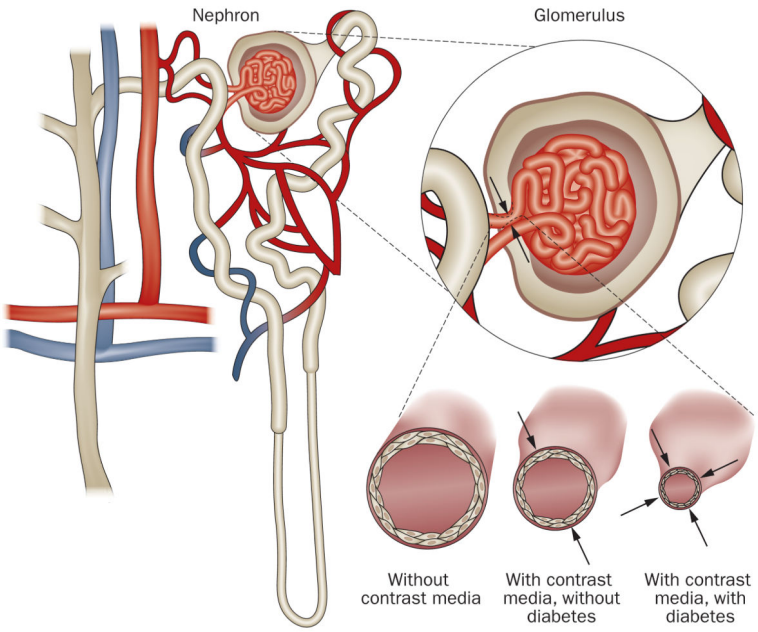


**Figure 2.**

Both contrast media and diabetes affect dilation of the renal vasculature. Permission obtained from International Scientific Literature Inc. © Pflueger, A. *et al. Med. Sci. Monit.* **15**, RA125–RA136 (2009).

**Table 1**

Classification of diabetic nephropathy

| Stage of diabetic nephropathy | gFr (ml/min/1.73 $m^2$) | Albuminuria (mg/g) |
|---|---|---|
| 1 | ≥90 | Absent or <30 |
| 2 | ≥60 | 30–300 |
| 3 | ≥60 | >300 |
| 4 | <60 | >3,000 |
| 5 | <15 | Absent or present |

Abbreviation: GFR, glomerular filtration rate.

## Table 2

Potential therapeutic agents for the prevention of CIAKI in patients with diabetes

| Agent | Administration | putative mechanism of action | evidence |
|---|---|---|---|
| Renal vasodilators (e.g. dopamine) | Oral or intravenous | Increased renal blood flow | Numerous studies failed to show benefit; some suggestions of harm[94] |
| Sodium bicarbonate | Intravenous | Increased pH of tubular urine | Unclear; might cause harm through pro-oxidant properties[96,100] |
| *N*-acetylcysteine | Oral or intravenous (treatment duration is controversial) | Antioxidant effects, reduction of reactive oxygen species | Mixed evidence, but seems to be beneficial[101] |
| Adenosine-receptor antagonists (theophylline and antagonists of adenosine receptor $A_1$) | Oral or intravenous | Antagonism of adenosine-mediated vasoconstriction | Theophylline: some evidence of benefit[112,113] Selective adenosine receptor $A_1$ antagonists: preliminary animal[116] and human[113] data suggest that these agents increase GFR |
| Statins (simvastatin and atorvastatin) | Oral | Pleiotropic, antioxidant, and anti-inflammatory effects | Conflicting results from trials[125,126] |

Abbreviations: CIAKI, contrast-induced acute kidney injury; GFR, glomerular filtration rate.