Contrast-Induced Nephropathy (CIN): Current State of the Evidence on Contrast Media and Prevention of CIN

Focus of This Summary

This is a summary of two systematic reviews. One review evaluated the evidence regarding the comparative effects of different contrast media in patients requiring diagnostic imaging studies or image-guided procedures. The other review assessed the evidence regarding the comparative efficacy of measures to prevent CIN. The former systematic review included 29 randomized controlled trials (RCTs) and 10 observational studies published from 1988 through 2015. The latter systematic review included 163 RCTs and 23 observational studies published from 1998 through 2015. The full reports, listing all studies, are available at *www.effectivehealthcare.ahrq.gov/contrast-induced-nephropathy.* This summary is provided to assist in informed clinical decisionmaking. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

CIN is a possible complication of iodinated contrast media used for radiologic imaging. It has been traditionally defined, in the absence of an alternative etiology, as an increase in serum creatinine of more than 25 percent or 0.5 mg/dL within 2 to 3 days after a contrast medium is administered. In 2013, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative recommended the use of these criteria for all types of acute kidney injury, including CIN: an increase in serum creatinine of at least 0.3 mg/dL over a 48-hour period or to at least 1.5 times baseline.

The precise mechanism of CIN is not entirely understood. Leading theories state that CIN results from hypoxic injury of the renal tubules induced by renal vasoconstriction or from the direct cytotoxic effects of contrast media. Oxidative stress, leading to an excess of oxygen free radicals over antioxidants, has been implicated in playing an important role in mediating the cytotoxic effects.

The osmolality of a contrast medium is a key factor in determining its nephrotoxicity. Over a decade ago, low-osmolar contrast media (LOCM) replaced high-osmolar media as the standard of care for intravenous (IV) or intra-arterial (IA) injection. The osmolality of LOCM is generally about two to three times plasma osmolality, although it varies from 322 to 915 mOsm/kg, depending on the concentration of the commercially available solution. Iso-osmolar contrast medium (IOCM) is the newest class of iodinated contrast agents; the only IOCM currently available is iodixanol. The osmolality of the IOCM is the same as plasma osmolality: 290 mOsmol/kg. Characteristics of the IOCM and individual LOCM are shown in Appendix Table A.

Numerous strategies have been used to try to prevent CIN, including oral hydration; intravascular volume expansion with sodium chloride or bicarbonate; administration of N-acetylcysteine (NAC) or statins; withdrawal of nonsteroidal anti-inflammatory drugs; withdrawal of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers; hemofiltration or hemodialysis; and avoiding repeat contrast administration within a short period of time.

Conclusions

The reviewed studies provided the following evidence:

- The risk of CIN does not differ between the various types of LOCM (low strength of evidence [SOE]).
- The IOCM has a slightly lower risk of CIN than an LOCM (moderate SOE). The lower risk was statistically significant but unlikely to be clinically important.
- The risk of CIN was similar for both an LOCM and the IOCM when studies involving IV (low SOE) or IA (moderate SOE) administration were considered separately.

In preventing CIN, evidence to support a statistically significant and potentially clinically important benefit is available for only three interventions, and that evidence is limited to these specific contexts:

- NAC plus IV saline is superior to IV saline (alone or with placebo) when an LOCM is used (moderate SOE).
- Low-dose NAC plus IV saline is superior to IV saline (alone or with placebo) (low SOE). Low-dose NAC was defined as 1200 mg/day or less.
- Statins plus NAC plus IV saline (or bicarbonate) is superior to NAC plus IV saline (or bicarbonate) in patients receiving IA-administered contrast media (low SOE).

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Conclusions (*Continued*)

The evidence is insufficient to determine if outcomes other than CIN differ between LOCM; whether differences in CIN risk are modified by various patient factors (e.g., comorbidities, baseline kidney function) or contrast dose; and how the efficacy of preventive strategies varies according to patient characteristics. For preventive strategies with sufficient evidence to determine whether they prevent CIN, the SOE is often insufficient for other outcomes (e.g., cardiovascular events, mortality).

Overview of Clinical Research Evidence

Table 1: Comparative Effects of Low-Osmolar and Iso-Osmolar Contrast Media

Note: Outcomes with insufficient SOE are not included in this table.

Contrast Media Comparison	Outcome	No. of RCTs	No. of Subjects	Effect on Outcome[a]	Clinically Important Effect[b]	Risk Ratio (95% CI)	SOE
LOCM vs. another LOCM	Development of CIN	5	429	↔	–	NR	●○○
IOCM vs. LOCM	Development of CIN	25[c]	5097	↓	–	0.80 (0.65 to 0.99)	●●○
	Development of CIN (with IV administration)	6	790	↔	–	0.84 (0.42 to 1.71)	●○○
	Development of CIN (with IA administration)	18[d]	4194	↔	–	0.80 (0.64 to 1.01)	●●○
	Need for renal replacement therapy[e]	5	1740	↔	–	NR	●○○
	Cardiovascular outcomes	7	2258	↔	–	NR	●○○
	Mortality	8	2028	↔	–	NR	●○○
	Adverse events[f]	12	3363	↔	–	NR	●○○

CI = confidence interval; CIN = contrast-induced nephropathy; IA = intra-arterial; IOCM = iso-osmolar contrast medium; IV = intravenous; LOCM = low-osmolar contrast medium; NR = not reported; No. = number; RCT = randomized controlled trial; SOE = strength of evidence

[a] Based on statistical significance for meta-analysis or qualitative synthesis of studies when meta-analysis was not performed: ↓ = decreased; ↔ = no difference.

[b] Clinically important effect was defined by a risk ratio less than 0.75 or greater than 1.25.

[c] Twenty-three studies were included in the meta-analysis.

[d] Seventeen studies were included in the meta-analysis.

[e] Renal replacement therapy consisted of hemodialysis or hemofiltration.

[f] All adverse events are included except CIN (e.g., hypersensitivity reactions, need for renal replacement therapy, cardiovascular events, death).

Strength of Evidence Scale*

High: ●●● High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.

Moderate: ●●○ Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low: ●○○ Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

Insufficient: ○○○ Evidence either is unavailable or does not permit a conclusion.

* The overall evidence grade was assessed based on the ratings for the following domains: study limitations, directness, consistency, precision, and reporting bias. Other domains that were considered, as appropriate, included dose-response association, plausible confounding, and strength of association (i.e., magnitude of effect). For additional details on the methodology used to assess strength of evidence, please refer to: Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.

Overview of Clinical Research Evidence *(Continued)*

Table 2: Strategies To Prevent Contrast-Induced Nephropathy

Note: Outcomes and interventions with insufficient SOE are not included in this table.

Preventive Strategy Comparison	Outcome	No. of RCTs	No. of Subjects	Effect on Outcome[a]	Clinically Important Effect[b]	Risk Ratio (95% CI)	SOE
NAC[c] plus IV saline vs. IV saline (alone or with placebo)	Development of CIN (with high-dose NAC[d])	18	4336	⬌	–	0.78 (0.59 to 1.03)	●○○
	Development of CIN (with low-dose NAC[d])	36	5217	⬇	⬇ (borderline)	0.75 (0.63 to 0.89)	●○○
	Development of CIN (in patients receiving an LOCM)	40	6665	⬇	⬇	0.69 (0.58 to 0.84)	●●○
	Development of CIN (in patients receiving the IOCM)	7	1339	⬌	–	1.12 (0.74 to 1.69)	●○○
	Need for renal replacement therapy	20	4881	⬌	–	NR	●○○
	Cardiac events	7	1207	⬌	–	NR	●○○
	Hospitalization, length of stay	9	1461	⬌	–	NR	●○○
IV sodium bicarbonate vs. IV saline	Development of CIN	19	3303	⬌	–	0.93 (0.68 to 1.27)	●○○
	Development of CIN (in studies using an LOCM)	11	1555	⬌	⬇	0.65 (0.33 to 1.25)	●○○
	Development of CIN (in studies using the IOCM)	7	1748	⬌	–	1.02 (0.70 to 1.48)	●○○
	Need for renal replacement therapy	11	1558	⬌	–	NR	●○○
	Mortality	6	1237	⬌	–	NR	●○○
Statins plus IV saline vs. IV saline (alone or with placebo)	Development of CIN (with IA administration)	8	5024	⬌	⬇	0.68 (0.39 to 1.20)	●○○
Statins plus NAC plus IV saline (or bicarbonate) vs. NAC plus IV saline (or bicarbonate)	Development of CIN (with IA administration)	5[e]	1477	⬇	⬇	0.52 (0.29 to 0.93)	●○○
Hemodialysis vs. IV saline	Development of CIN	4[f]	584	⬌ or possibly ⬆	⬆	1.50 (0.56 to 4.04)	●○○
Ascorbic acid plus IV saline vs. IV saline (alone or with placebo)	Development of CIN	6	1387	⬌	⬇	0.72 (0.48 to 1.01)	●○○
	Need for renal replacement therapy[g]	2	397	⬌	–	NR	●○○
	Cardiac events	2	237	⬌	–	NR	●○○
Ascorbic acid plus IV saline vs. NAC plus IV saline	Development of CIN	3	583	⬌	–	0.89 (0.34 to 2.30)	●○○

CI = confidence interval; CIN = contrast-induced nephropathy; IA = intra-arterial; IOCM = iso-osmolar contrast medium; IV = intravenous; LOCM = low-osmolar contrast medium; NR = not reported; NAC = N-acetylcysteine; No. = number; RCT = randomized controlled trial; SOE = strength of evidence

[a] Based on statistical significance for meta-analysis or qualitative synthesis of studies when meta-analysis was not performed: ⬇ = decreased; ⬆ = increased; ⬌ = no difference.

[b] Clinically important effect was defined by a risk ratio less than 0.75 or greater than 1.25. ⬇ = clinically important decrease; ⬆ = clinically important increase.

[c] In the analyzed studies, NAC was usually administered orally.

[d] High-dose = more than 1200 mg/day; low-dose = 1200 mg/day or less.

[e] One study included in this meta-analysis compared a statin + sodium bicarbonate + IV saline versus NAC + sodium bicarbonate + IV saline.

[f] Three studies were included in the meta-analysis.

[g] Renal replacement therapy consisted of hemodialysis or hemofiltration.

Other Findings of the Reviews

- Evidence is too limited to determine how the dose of the different contrast media, patient demographics, comorbid conditions, or baseline renal function modifies CIN risk.
- Although the small beneficial effect of NAC did not appear to differ between IA and IV routes, the SOE was insufficient to rule out a possible difference in benefit.
- The SOE was insufficient to determine the effect of other interventions on the risk of CIN, including adenosine antagonists, diuretics, vasoactive agents, various fluid regimes, probucol, and pentoxifylline. Limited evidence suggests that fenoldopam and dopamine may increase CIN risk.
- Because of methodological heterogeneity between studies, the SOE was insufficient to assess how the effectiveness of strategies to prevent CIN varies according to baseline kidney function and other patient characteristics.

Limitations of the Evidence Base

- Variable definitions of CIN have been used in studies regarding the effects of different contrast media and strategies to prevent CIN. The majority used the traditional definition; few used recent guideline definitions.
- Most studies examining preventive strategies focused on patients receiving IA contrast media. The applicability of those studies to modern-day protocols of LOCM and the IOCM administered via the IV route is uncertain.

Ordering Information

- For electronic copies of this clinician research summary and the full systematic reviews, visit *www.effectivehealthcare.ahrq.gov/contrast-induced-nephropathy.*

Source

The information in this summary is based on two reviews prepared by the Johns Hopkins University Evidence-based Practice Center under Contract 290-2012-00007-I for the Agency for Healthcare Research and Quality. The reviews are *Contrast-Induced Nephropathy: Comparative Effects of Different Contrast Media* (Comparative Effectiveness Review No. 155; published in December 2015) and *Contrast-Induced Nephropathy: Comparative Effectiveness of Preventive Measures* (Comparative Effectiveness Review No. 156; published in January 2016). These reviews are available directly at *www.effectivehealthcare.ahrq.gov/contrast-induced-nephropathy.* This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.

Additional Resources for Clinicians

1. Eng J, Wilson RF, Subramaniam RM, et al. Comparative effect of contrast media type on the incidence of contrast-induced nephropathy: a systematic review and meta-analysis. Ann Intern Med. 2016 Mar;164(6):417-24. PMID: 26830055.
2. Subramaniam RM, Suarez-Cuervo C, Wilson RF, et al. Effectiveness of prevention strategies for contrast-induced nephropathy: a systematic review and meta-analysis. Ann Intern Med. 2016 Mar;164(6):406-16. PMID: 26830221.

Appendix

Table A: Low-Osmolar and Iso-Osmolar Contrast Media

Name	Trade Name	Classification	Osmolality[a] (mOsm/kg)
Iodixanol	Visipaque®	IOCM	290
Iohexol	Omnipaque®	LOCM	322–844
Iopromide	Ultravist®	LOCM	328–774
Ioversol	Optiray®	LOCM	355–792
Iopamidol	Isovue®	LOCM	413–796
Ioxaglate	Hexabrix®	LOCM	580
Ioxilan	Oxilan®	LOCM	585–695
Iobitridol	Xenetix®	LOCM	585–915

IOCM = iso-osmolar contrast medium;
LOCM = low-osmolar contrast medium

[a] Ranges represent the lowest and highest values for the range of commercially available concentrations.

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