

## Living friendly summaries of the body of evidence using Epistemonikos (FRISBEE)

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# Should acetylcysteine be used to prevent contrast induced nephropathy?

¿Debe indicarse acetilcisteína para prevenir la nefropatía por contraste?

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## Resumen

La infusión de contrastes para la realización de procedimientos diagnósticos o terapéuticos se asocia a complicaciones como la nefropatía por contraste la cual puede generar morbilidad significativa para los pacientes. La administración de acetilcisteína ha sido propuesta como medida potencialmente efectiva para prevenir esta condición. Utilizando la base de datos Epistemonikos, la cual es mantenida mediante búsquedas en 30 bases de datos, identificamos 20 revisiones sistemáticas que en conjunto incluyen 64 estudios aleatorizados. Realizamos un metanálisis y tablas de resumen de los resultados utilizando el método GRADE. Concluimos que si bien acetilcisteína podría no producir efectos adversos importantes, no disminuye la necesidad de diálisis, mortalidad ni otros desenlaces importantes.

## Abstract

Diagnostic and therapeutic procedures that require the infusion of iodine containing contrast solutions are associated with the risk of contrast-induced nephropathy, a condition that can cause significant morbidity. Acetylcysteine has been proposed as a measure to prevent this condition. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified 20 systematic reviews including 64 randomized trials. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded that even though acetylcysteine might not cause important adverse effects, it does not decrease need for dialysis, mortality or other important outcomes.

### Problem

Diagnostic and therapeutic procedures requiring administration of iodinated contrast are frequently used in contemporary clinical practice. Contrast-induced nephropathy leads to significant morbidity [1],[2] and the risk is higher in procedures requiring more contrast [3],[4],[5]; as well as in patients older than 70 years, chronic renal disease, diabetes, cardiac failure or hypotension [4].

Acetylcysteine could prevent contrast-induced nephropathy and its consequences by modifying renal hemodynamics and reducing direct tissue oxidative injury.

## Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a

summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

### Key messages

- Acetylcysteine does not reduce hemodialysis requirement in patients with low or moderate risk of contrast-induced nephropathy, and probably does not reduce mortality. It probably neither does it in patients with high risk but the certainty of the evidence for this group is moderate.
- Acetylcysteine probably does not lead to clinically significant adverse effects.

## About the body of evidence

What is the evidence. See evidence matrix in Epistemonikos further on	We identified 20 [7-26] systematic reviews including 64 randomized controlled trials [27-90].*
What types of patients were included.	All the studies recruited patients that required diagnostic or therapeutic procedures with iodinated contrast infusion. The contrast-induced nephropathy baseline risk was variable.  Overall, 10 030 patients were included in the identified randomized controlled trials.
What types of interventions were included.	Intravenous or oral acetylcysteine. The dose varied between 2400 mg and 6000 mg.
What types of outcomes were measured.	All-cause mortality; hemodialysis requirement; contrast-induced nephropathy (creatinine increase); length of hospital stay; adverse effects.

\*For reasons of space, these references were not disaggregated. You can access them through the references section.

## Summary of findings

Acetylcysteine effectiveness information is based on 64 randomized controlled trials that included 10030 patients. Twelve studies reported all-cause mortality, 28 reported hemodialysis requirement, sixty-four reported contrast-induced nephropathy, eight reported length of hospital stay and nine reported adverse effects.

- Acetylcysteine does not reduce hemodialysis requirement in patients with low or moderate risk of contrast-induced nephropathy. The certainty of the evidence is high.
- Acetylcysteine probably does not reduce hemodialysis requirement in patients with high risk. The certainty of the evidence for this group is moderate.
- Acetylcysteine probably does not reduce mortality. The certainty of the evidence is moderate.
- Acetylcysteine probably leads to little or no difference in the length of hospital stay. The certainty of the evidence is moderate.
- Acetylcysteine might not be associated to clinically significant adverse effects, but the certainty of the evidence is low.

<b>Acetylcysteine to prevent contrast-induced nephropathy</b>					
<b>Patients</b>	Patients requiring diagnostic or therapeutic procedures with iodinated contrast infusion				
<b>Intervention</b>	Acetylcysteine				
<b>Comparison</b>	Placebo				
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)	
	WITHOUT Acetylcysteine	WITH Acetylcysteine			
	Difference: patients per 1000				
<b>Mortality</b>	24 per 1000	23 per 1000	RR 0.95 (0.6 to 1.5)	⊕⊕⊕○ <sup>1</sup> Moderate	
	Difference: 1 less per 1000 (Margin of error: 10 less to 12 more)				
<b>Hemodialysis requirement</b>	<b>Low baseline risk</b>		RR 0.98 (0.31 to 2.83)	⊕⊕⊕⊕ <sup>2</sup> High	
	1 per 1000	1 per 1000			
	Difference: 1 patient less per 1000 (Margin of error: 0 to 1 more)				
	<b>Moderate baseline risk</b>			RR 0.98 (0.31 to 2.83)	⊕⊕⊕⊕ <sup>2</sup> High
	10 per 1000	9 per 1000			
	Difference: 1 less per 1000 (Margin of error: 7 less to 18 more)				
	<b>High baseline risk</b>				⊕⊕⊕○ <sup>1,2</sup> Moderate
120 per 1000	113 per 1000				
Difference: 7 less per 1000 (Margin of error: 87 less to 220 more)					
<b>Length of hospitalization</b>	3.9 days	3.45 days	DM-0.45 (-0.11 to -0.78)	⊕⊕⊕○ <sup>1</sup> Moderate	
	Difference: 0.45 less (Margin off error: 0.11 to 0.78 days less)				
<b>Adverse effects related to acetylcysteine</b>	55 per 1000	64 per 1000	RR 1.17 (0.89 to 1.55)	⊕⊕○○ <sup>1,3</sup> Low	
	Difference: 0.45 less (Margin of error: 7 less to 30 more)				
<p>RR: risk ratio MD: mean difference Margin of error = 95% confidence interval. GRADE: evidence grades of the GRADE Working Group (see later in this article)</p> <p>* The risk in the group <b>WITHOUT acetylcysteine</b> for death, adverse effects and length of hospitalization is based on the risk in the control group of the trials. The risk <b>WITHOUT acetylcysteine</b> for hemodialysis and contrast-induced nephropathy (not presented in the summary of findings table but discussed in the section "Other considerations in clinical decision making") are based on the results of an observational study (4). The risk <b>WITH acetylcysteine</b> and its margin of error) is calculated from relative effect (and its margin of error).</p> <p>** The relative effects for death, hemodialysis and contrast-induced nephropathy were calculated using the information provided by the low risk of bias subgroup of studies because heterogeneity of the results was observed when all the included studies results were pooled, which resolved when moderate and high risk of bias studies were excluded.</p> <p><sup>1</sup> There is important imprecision. The decision would substantially vary in both extremes of the confidence interval.</p> <p><sup>2</sup> For the group of patients with low or moderate baseline risk the presence of imprecision does not implies a change in the clinical course of action; but it could significantly change the clinical decision in the high-risk group determining a decrease in the level of certainty.</p> <p><sup>3</sup> Selective reporting bias (reported by nine of the 64 included studies)</p>					

### [N-acetylcysteine for prevention of contrast-inducd nephropathy](#)

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## Other considerations for decision-making

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### To whom this evidence does and does not apply

- The evidence applies to patients that require diagnostic or therapeutic procedures with iodinated contrast infusion irrespective of its baseline risk of contrast-induced nephropathy.

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### About the outcomes included in this summary

- Many studies evaluated contrast-induced nephropathy as the only effectiveness outcome which should be considered as a surrogate outcome that may predict hemodialysis requirement or death. Although evidence of this association exists [1],[2], it is difficult to estimate how many patients will obtain significant benefits on the clinically important outcomes (hemodialysis or death).
- Results of the "contrast-induced nephropathy outcome" are difficult to interpret and hence to translate into a clinical decision (low risk group: two less patients will develop contrast-induced nephropathy per 1000 if treated with acetylcysteine (confidence interval: 13 less to 13 more); high risk group: 10 less patients will develop contrast-induced nephropathy per 1000 if treated with acetylcysteine (confidence interval: 85 less to 85 more)).
- The fact that only a small proportion of the studies reported on adverse effects reduces our confidence in these outcome results.

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### Balance between benefits and risks, and certainty of the evidence

- The existing evidence suggests that acetylcysteine is not related to clinically significant benefits. The confidence in this statement is moderate for patients with high iodinated infusion related complication basal risk and high for those with low complication basal risk.
- Acetylcysteine was not related to significant adverse effects although the confidence for this outcome is low.

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### What would patients and their doctors think about this intervention

- Considering the intervention may not be related to significant adverse effects or discomfort related to its administration, we assume that all patients will choose the proposed intervention if it proves to be effective.

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### Resource considerations

- The costs of the intervention would not be relevant if the intervention proves effective.

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### Differences between this summary and other sources

- There is inconsistency between the conclusions of the different systematic reviews included in the present analysis. Our key messages are in line with some of them that concluded that existing evidence suggests that acetylcysteine is not effective in preventing the complications related to iodine contrast infusion while others have reached the opposite conclusion.
- The main clinical practice guidelines are also contradictory; ACCF/AHA/SCAI [91] recommends against acetylcysteine, while KDIGO [92] recommends its use as a prophylactic measure against contrast-induced nephropathy.

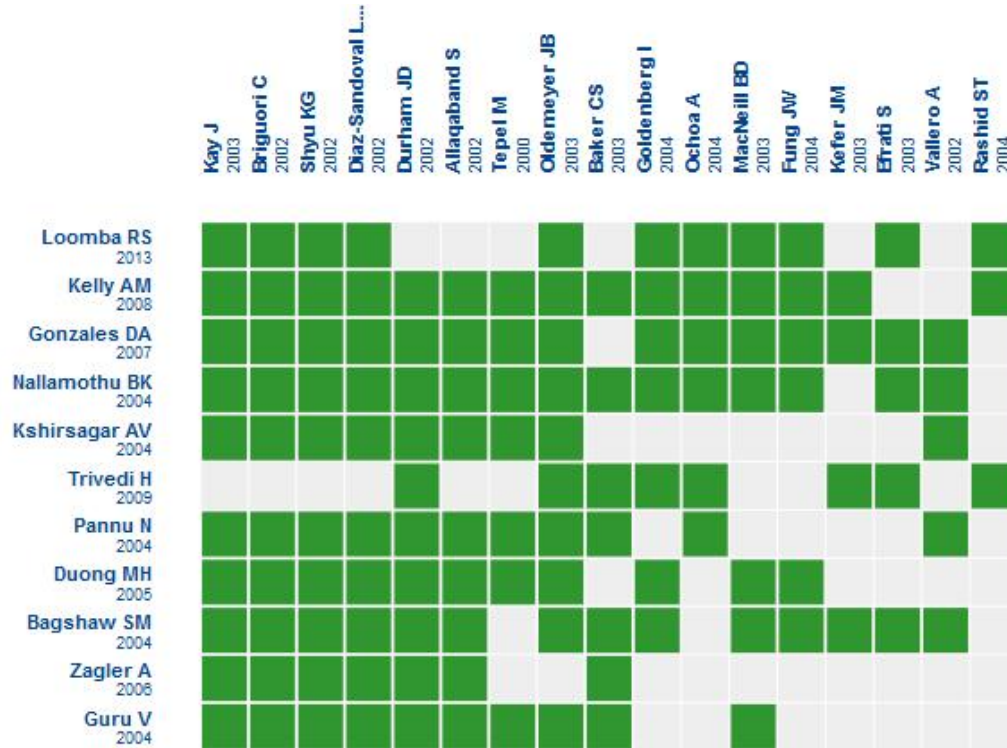
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### Could this evidence change in the future?

- The chance that the conclusions reached in the present analysis could be significantly modified by new evidence is very low.
  - The PRESERVE study [93] which will recruit more than 8500 patients with high risk for iodine contrast infusion complications will probably provide valuable information, specially in relation to the group of high risk patients.
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### How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence. An illustrative part of the matrix is shown.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database (the review from which the matrix is built, appears highlighted). The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question. The rows represent systematic reviews that share at least one primary study, and columns display the studies. The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the interactive version [N-acetylcysteine for prevention of contrast-induced nephropathy](#)

## About the certainty of the evidence (GRADE)\*



**High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.



**Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate



**Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.



**Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

\*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision.

## Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here

<http://dx.doi.org/10.5867/medwave.2014.06.5997>.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database ([www.epistemonikos.org](http://www.epistemonikos.org)).

These summaries follow a rigorous process of internal peer review.

### Conflicts of interest

The authors have completed the ICMJE uniform disclosure form for potential conflicts of interest, (available on request from the corresponding author), and declare not having conflicts of interest with the subject of the article.

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