Reviewer's report

Title: N-acetylcysteine does not prevent contrast-induced nephropathy after cardiac catheterization in patients with diabetes mellitus and chronic kidney disease: A randomized clinical trial

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Reviewer: Alvaro Alonso

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Comments on:
N-acetylcysteine does not prevent contrast-induced nephropathy after cardiac catheterization in patients with diabetes mellitus and chronic kidney disease: A randomized clinical trial

Submitted to Trials Journal

General remarks
The authors present us with an interesting article on a very controversial topic. Contrast induced nephropathy and ways to prevent it have been the purpose of dozens of articles and meta-analyses. The authors focus primarily in the patient population that has been shown to be at the greatest risk: diabetics with chronic kidney disease.

The methods are well described, from the calculations of sample size to the calculation of oral fluid intake by counting the number of glasses, trying to limit subjectivity.

The study was apparently well blinded. There were no significant baseline differences between the groups, except for gender and statin use. Their results are well presented and they acknowledge their limitations, particularly that of multiplicity of types of contrast media used.

The authors found no significant difference in the incidence of CIN between the NAC or placebo groups, with one more case of CIN in the NAC group. The incidence of CIN was 14% and 11%, respectively.

I am curious about why it took three years to write the manuscript. It is possible this manuscript was rejected in the past, due to style or because it was considered irrelevant. I do not think this study is irrelevant. Furthermore, it is well known that negative studies are less likely to appear published, because they either are not submitted or because they are not accepted for publication. This is also known as publication bias.

This article adds to the medical literature. To my knowledge, it is the only study about contrast nephropathy in the Middle Eastern population, which I consider
particularly relevant.

I have certain comments, that I hope the authors and the editors find useful. These are described below.

Thank you for including me as a reviewer and allowing me to share my points of view.

Alvaro Alonso, MD

Major revisions

1. Throughout the manuscript, English grammar and overall wording could be markedly improved. I mention some of these problems under minor revisions, but the most of the introduction and the discussion could be improved.

2. Page 3, lines 21 and 22 and first line of page 7. I do not necessarily agree with the statement that acetylcysteine is harmful in diabetic patients. There was indeed a higher incidence of CIN in diabetics who received NAC in the study by Coyle (Am Heart J 2006;151:1032.e921032.e12), but these were only 5 more cases. Furthermore, these patients had near-normal GFR. I agree with the authors in bringing this issue up, however. Durham et al. found a 51% relative increased rate of CIN in NAC-treated diabetics than in non-diabetics, a trend that was not statistically significant. (Kidney Int 2002;62:2202–2207). These findings toward potential harm of NAC in patients with diabetes mellitus may be consistent with earlier findings by Weisberg et al., who found that other vasodilator drugs increased the risk of CIN in diabetic patients (Kidney Int 1994;45:259–265). Indeed, NAC appears to have vasodilatory effects as part of its mechanism of action (in addition to being a free-radical scavenger), thereby preventing the prolonged renal vasoconstrictor phase that follows contrast media administration. Diabetics are known to have abnormal endothelial function and may behave differently. On the other hand, however, Kay et al. found a greater protective benefit of NAC in diabetics (JAMA 2003;289:553–558). Similarly, Briguori et al. found that a strategy of volume supplementation by sodium bicarbonate plus NAC appeared to be superior to the combination of normal saline with NAC alone or with ascorbic acid in preventing CIN in patients at medium to high risk. This study included patients with diabetes, and predefined subgroup analyses showed a consistent protective effect of NAC plus bicarbonate in diabetic or high risk patients (Circulation 2007;115:1211-1217). In the present study, the incidence of CIN was similar between the groups. The authors may choose to elaborate further into this rather than stating that NAC is dangerous in diabetics.

3. Bottom of page 4, methods. The Cockroft-Gault formula is used to estimate the creatinine clearance (CrCl), not the glomerular filtration rate (even though it is an indirect calculation of GFR). This is a common conceptual problem in the literature. Alternatively, the authors could use the MDRD formula to calculate the eGFR, which is more accurate than the Cockroft-Gault formula or the 24-hour

4. Top of page 5, end-points. Neither the Cockcroft-Gault formula nor the MDRD formulas are accurate in cases of acute kidney injury (acute renal failure). Therefore, there is no role for calculating the change in GFR or CrCl 48 hours after angiography. I acknowledge that has been looked at as an endpoint in other trials, again, probably due to a misconception. Therefore, this would be an irrelevant secondary end-point.

5. Page 6, primary end-point. (The incidence of ) “CIN which (was) defined as an increased in serum creatinine concentration of #0.5 mg/dL or #25% above baseline was not significantly different between NAC and placebo groups (5.45 [11.1%] vs. 6.42 [14.3%], respectively; relative risk: 0.78 [95% CI: 0.26-2.36]; P=0.656)” It is not clear where the decimal points I underlined come from. It is a dichotomous variable. Either a patient developed CIN or not. How did 5.45 or 6.42 patients develop CIN? The abstract mentions 5 out of 45 patients and 6 out of 42.


Minor revisions

1. References throughout the text are reported inconsistently, some in [brackets] and some in (parenthesis).

2. Throughout the manuscript, when they refer to meta-analysis in plural. It should say meta-analyses.

3. Page 2, abstract, results. It is not clear in baseline characteristics what percentages correspond to which group.

4. Page 3, background, line 14 “they showed a reduction in the increase”. Authors could rephrase this, e.g., a reduction in the incidence of CIN.

5. Page 3, background, line 18, “with regard to its low cost”, could probably say “because of its low cost”.

6. Page 3, background, line 21, “there are evidences” should read “there is evidence” (noun). The same for the rest of the manuscript where the word “evidences”.

7. Page 7, lines 20 and 21. Reference 26 does NOT state that a hydration protocol of less than 1500cc is insufficient for maximal protection from contrast nephropathy.

9. Page 8, limitations. The effect of a renoprotective strategy is probably irrelevant in patients on chronic renal replacement therapy, either peritoneal dialysis or hemodialysis.

Discretionary revisions

1. Page 2, abstract, methods and page 4, study protocol. The term “triple blind” is controversial. Alternatively, the authors could use “double blind”

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.