Author's response to reviews

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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Author's response to reviews: see over
Dear Editor,

Appreciating your kind attention about our article entitled "N-Acetylcysteine does not prevent contrast-induced nephropathy after cardiac catheterization in patients with diabetes mellitus and chronic kidney disease: A randomized clinical trial" (Registration number: NCT00808795), we considered both honorable reviewers' comments. Will you please pay kindly attention to our reply and revisions according to the respectable reviewers' opinions as following:

A) Dr. Alvaro Alonso's recommendations:

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.

Reply: The whole article revised and edited regarding English grammar and wording.

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, Brigugori 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.

Reply: Authors agree with the respectable reviewer concerning the indefinite consensus on the impact of NAC on diabetic patients. Since there are ambivalent surveys regarding this issue, either supportive or denying the benefit of NAC administration in diabetic patients, we would rather declare the probable adverse effect of NAC on diabetic patients. Besides, the authors declared the controversy about the efficacy of NAC in different populations (including diabetic patients) and heterogeneity of the available data in page 3, lines 16 to 18. Hence, we deleted the statement "In addition, there is evidence that this intervention can even be harmful in patients with diabetes mellitus" (page3, lines 21&22). According to
the mentioned statements, we deleted "also suggested that this intervention could even be harmful." (page 7, line 1) too.

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 urine creatinine clearance. Ann Intern Med 1999;130:461-70.

Reply: We accept that Cockroft-Gault formula is used to estimate the creatinine clearance (CrCl), not the glomerular filtration rate (GFR). So, we will change "glomerular filtration rate (GFR)" to "creatinine clearance (CrCl)" in the whole article. Nonetheless, it seems that the MDRD is a more accurate method for estimating CrCl, but we did not apply this method because the difference between those two methods is insignificantly minor when we estimate the change of CrCl during 48 hours as the end-point.

4) Top of page 5, end-points. Neither the Cockroft-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.

Reply: We are in agreement with respectful reviewer and emphasize that Cockroft-Gault and MDRD formulas should be used in steady-state phase, but it's true for serum creatinine as well. On the other hand, there is no definite definition
of contrast-induced nephropathy. Meanwhile, when there is no better available measurement for estimating renal function in acute kidney injury, the majority of other trials use the Cockroft-Gault or MDRD formulas. It has another benefit: it makes the results comparable. Therefore, we prefer to preserve the creatinine clearance 48h after angiography as a 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.

Reply: It is just a typing mistake! Decimals (".") in "5.45" and "6.42" should be replaced with slash ("/"") characters, and it means "5 of 45" and "6 of 42", respectively. The authors corrected the mistake.


Reply: We accept that it's better to use more evident statistics. So, we will replace the "as high as 50%" with "as high as 40-50%" and also we will delete "and even
could reach 80%”. And also, we will replace reference no 40 with reference no 6 (J Am Coll Cardiol 2000; 36: 1542-1548).

7) References throughout the text are reported inconsistently, some in [brackets] and some in (parenthesis).
Reply: All references reported within brackets.

8) Throughout the manuscript, when they refer to meta-analysis in plural. It should say meta-analyses.
Reply: Meta-analysis changed to meta-analyses.

9) Page 2, abstract, results. It is not clear in baseline characteristics what percentages correspond to which group.
Reply: "the two groups" replaced with "NAC and placebo groups".

10) 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.
Reply: The statement "They showed a reduction in the increase in serum creatinine" changed to "They showed a reduction in the incidence of CIN with".

11) Page 3, background, line 18, “with regard to its low cost”, could probably say “because of its low cost”.
Reply: The statement "with regard to its low cost" changed to "because of its low cost".

12) 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”.
Reply: The sentence "there are evidences" (Page 3, lines 21 and 22) is deleted. The word "evidences" changed to "evidence" (page 3, line 23).
13) 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.

Reply: We deleted the "As previously shown by Taylor et al that outpatient oral pre-catheterization hydration strategy (1L clear liquid over 10h) followed by 6 h of IV hydration (0.45 normal saline solution at 300 mL/h) beginning just before contrast exposure is as effective as overnight IV hydration (0.45 normal saline solution at 75 mL/h for both 12 h pre-catheterization and post-catheterization)" because it was irrelevant. We also changed the "In comparison, prior studies of NAC have typically used standard hydration of 1mL/kg per hour, which is usually lower than 1500mL, an amount that may be insufficient for maximal protection from contrast nephrotoxicity [26]" to "In comparison, other studies which reported higher incidence of CIN, have typically used lower amount of hydration [9, 40, 41], which may be insufficient for maximal protection from contrast nephrotoxicity" (Page 7, lines 16 to 22).

14) Page 7, line 25. “Asplin” should read “Aspelin”.

Reply: Sentence is deleted.

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

Reply: We are completely in agreement with respectful reviewer about irrelevancy of evaluation of efficacy of a renoprotective strategy in patients on chronic renal replacement therapy. So, we will correct the sentence by deleting "or current peritoneal or hemodialysis".
16) Page 2, abstract, methods and page 4, study protocol. The term “triple blind” is controversial. Alternatively, the authors could use “double blind”.

Reply: The term "triple blind" changed to "double-blind".

B) Dr. Brahmajee Nallamothu’s recommendations:

1) The authors should replace the use of trade names like Omnipaque and Visipaque with generic names throughout the manuscript. This is especially true in the Discussion where there appears to be confusion. The authors mistakenly refer to the iso-osmolar agent iodixanol as Omnipaque and the low-osmolar agent iohexol as Visipaque (Page 7 of the pdf). This also seems to be an error in the next sentence that extends to the following page and where the authors comment on the high use of Omnipaque as a reason for their low incidence of CIN. So is it Omnipaque or is it iodixanol that was used in most cases? Also, it is worthwhile noting that the use of iso-osmolar agents to prevent CIN is almost as controversial as NAC (see Heinrich MC et al. Radiology 2009).

Reply: We replaced the trade names like Omnipaque and Visipaque with their generic names in the whole article. Page 7, line 25. We accept that the use of iso-osmolar agents to prevent CIN is controversial. So, we decided to delete the reason no 3 (line 25 of page 7 to line 3 of page 8).

2) I disagree that the study was not under-powered to detect a clinically significant beneficial effect. The authors state that the study was powered based on the Tepel et al. findings, but this is not reassuring to me. Tepel et al. reported findings favoring NAC that were more extreme than others have shown. Just because the NAC may not reduce the incidence of CIN by an
absolute rate of 19% (ie, from 21% to 2%), does not mean it would not have some potential clinical value if the reduction in CIN was more modest. My advice is to tone down that portion of the Limitations section (Page 8 of the pdf) by removing the sentence: “Therefore, the absence of any trend toward benefit…”.

Reply: We are in agreement with dear reviewer that the study sample size is small and there may be a type II error. So, we will change this part of our limitations to "The relatively small sample size of this study calls for caution interpreting the results. Because, this sample size was predetermined from a power calculation based on the findings of Tepel et al [11], which resulted in an expected 9% overall event rate and were more extreme than what others have shown in favoring NAC."

3) I am not sure that NAC necessitates earlier and longer admission of patients (Page 3 of the pdf), since most often it is used orally and can be started as an outpatient. I would consider re-wording this sentence.

Reply: We accept that the sentence" Since administration of NAC necessitates earlier and longer admission of patients, particularly in intravenous use, it can increase the health care costs." May just be true in intravenous use and we can not extend it to oral use, so we will delete the sentence.

4) Did baseline creatinine levels have to be stable? That is, were any requirements made to ensure that patients were not having acute renal insufficiency by comparing levels at the time of catheterization to prior levels available in the medical record? The authors may want to clarify this in the paper.
**Reply:** We understand this logical question well. We declare that we measured serum creatinine concentration just before angiography and 48h after it, Because:

- Past medical records of patients were not available.
- Development of acute renal failure needs some etiologic factors (including pre-renal, renal and post-renal factors) such as heart failure and etc. But, in a randomized trial, we methodologically insert all known and unknown factors to the study. The presence of the known and unknown factors affects similarly the two groups. So, if we consider presence of cases with acute renal failure before angiography probable, it would be almost similar between the two groups and results in a non-differential bias.