Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 23, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.07.065

Does Ascorbic Acid Protect Against Contrast-Induced Acute Kidney Injury in Patients Undergoing Coronary Angiography

A Systematic Review With Meta-Analysis of Randomized, Controlled Trials

Umar Sadat, MD, PhD,* Ammara Usman, MB BS, MBA,† Jonathan H. Gillard, MD,‡ Jonathan R. Boyle, MD*

Cambridge, United Kingdom; and Lahore, Pakistan

Objectives This study sought to perform a systematic review with meta-analysis of randomized controlled trials comparing the use of ascorbic acid with placebo or other treatment options for the treatment of contrast induced-acute kidney injury (CI-AKI) in patients undergoing coronary angiography.

Background CI-AKI remains the most widely discussed and debated topic in cardiovascular medicine, with its incidence increasing due to an increasing number of contrast media-enhanced radiological procedures being performed.

Methods MEDLINE, Embase, and Cochrane central databases were searched from inception to May 2013, without language restrictions. For a study to be selected, it had to report the incidence of CI-AKI as an outcome measure. Studies were excluded if at least 1 study arm did not have ascorbic acid administered alone or with saline solution hydration. Data were extracted by 1 author, and random checks were made by another author.

Results Nine randomized, controlled trials reported data on the incidence of CI-AKI in 1,536 patients who had completed the trial and were included in the final analysis. Patients receiving ascorbic acid had 33% less risk of CI-AKI compared with patients receiving placebo or an alternate pharmacological treatment (risk ratio by random-effects model: 0.672; 95% confidence interval, 0.466 to 0.969; $p = 0.034$).

Conclusions Ascorbic acid provides effective nephroprotection against CI-AKI and may form a part of effective prophylactic pharmacological regimens. (J Am Coll Cardiol 2013;62:2167–75) © 2013 by the American College of Cardiology Foundation

Contrast induced-acute kidney injury (CI-AKI) is one of the most widely discussed and debated topics in cardiovascular medicine. The incidence of CI-AKI is increasing. This is due to an increasing number of contrast media–enhanced radiological procedures being performed and an increase in the octogenarian population with comorbidities such as hypertension, diabetes mellitus, and renovascular disease, all of which predispose to renal impairment. It is therefore imperative that more attention be given to develop a better understanding of the etiology of CI-AKI, to devise novel methods of its diagnosis at an earlier stage before renal failure has occurred, and to formulate effective prophylactic and therapeutic regimens to reduce its incidence.

Traditionally, ascorbic acid has been used as a dietary supplement. Today there is strong evidence that it acts as a potent antioxidant by scavenging physiologically relevant reactive oxygen species (ROS) (1,2). As oxidative stress has been implicated as a contributing factor in the etiology of CI-AKI (3), use of ascorbic acid as a nephroprotective agent is therefore logical.

See page 2176

Our objective was to assess whether ascorbic acid reduces the incidence of CI-AKI. We reviewed randomized, controlled trials (RCTs) that assessed its nephroprotective role in reducing CI-AKI compared with placebo or other pharmacological agents in patients undergoing coronary angiography.

From the *Department of Surgery, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; †Department of Internal Medicine, Cardiovascular Medicine Division, Cavalry Hospital, Lahore, Pakistan; and the ‡University Department of Radiology, University of Cambridge, Cambridge, United Kingdom. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 21, 2013; revised manuscript received July 16, 2013, accepted July 31, 2013.

Abbreviations and Acronyms

CI = confidence interval
CI-AKI = contrast-induced acute kidney injury
RCT = randomized, controlled trial
ROS = reactive oxygen species
RR = risk ratio

Methods

Protocol. The research question, search strategy, inclusion criteria, and statistical analyses were pre-specified.

Eligibility criteria. TYPES OF STUDIES. RCTs assessing the use of ascorbic acid in reducing CI-AKI compared with placebo or other pharmacological treatments, in patients undergoing coronary angiography were reviewed. No language, publication date, or publication status restrictions were imposed.

TYPES OF PARTICIPANTS. Participants of any age with or without documented pre-existing renal impairment undergoing coronary angiography were considered.

TYPES OF INTERVENTION. Ascorbic acid alone (or with saline solution hydration) was used in 1 treatment arm. The route of administration of ascorbic acid could be oral and/or intravenous. Patients in the comparison group could either receive saline solution hydration and/or placebo/other nephroprotective agent.

TYPES OF OUTCOME MEASURES. For a RCT to be included, it had to report incidence of CI-AKI as an outcome measure. CI-AKI was defined as an absolute increase in serum creatinine of $\geq$0.5 mg/dl (44 μmol/l) or a relative increase of $\geq$25% from the baseline value after administration of contrast media during angiography.

Information sources. Electronic databases used were MEDLINE, Embase, and Cochrane Central databases from the date of inception until May 15, 2013, were systematically searched. No limits were used for an electronic literature search. Tangential electronic exploration of related articles (i.e., using links to related references to search for additional articles) was also performed. The last search was run on May 20, 2013. Extensive hand searches of bibliographies of relevant reviews and related journals were also done.

Search. Search terms included variants of vitamin C, ascorbic acid, nephropathy, contrast nephropathy, contrast-induced nephropathy, contrast media, contrast agent, kidney, renal, angiography, and arteriography using text words and MeSH terms. Search strategy using the MEDLINE database was as follows.

SEARCH HISTORY.

1. MEDLINE; "vitamin C".ti,ab; 14,581 results
2. MEDLINE; "ascorbic acid".ti,ab; 22,487 results
3. MEDLINE; exp ASCORBIC ACID/; 34,524 results
4. MEDLINE; 1 OR 2 OR 3; 48,039 results
5. MEDLINE; kidney*.ti,ab; 311,331 results
6. MEDLINE; renal.ti,ab; 427,591 results
7. MEDLINE; exp KIDNEY/; 289,995 results
8. MEDLINE; "contrast induced nephropath*".ti,ab; 868 results
9. MEDLINE; "contrast nephropath*".ti,ab; 239 results
10. MEDLINE; nephropathy.ti,ab; 36,572 results
11. MEDLINE; "contrast media".ti,ab; 9,299 results
12. MEDLINE; "contrast agent*".ti,ab; 17,645 results
13. MEDLINE; exp CONTRAST MEDIA/; 88,039 results
14. MEDLINE; 11 OR 12 OR 13; 95,541 results
15. MEDLINE; 5 OR 6 OR 7 OR 10; 722,617 results
16. MEDLINE; 8 OR 9; 1,064 results
17. MEDLINE; 14 AND 15; 10,603 results
18. MEDLINE; 16 OR 17; 10,786 results
19. MEDLINE; "angiograph*".ti,ab; 130,279 results
20. MEDLINE; exp ANGIOGRAPHY/; 189,985 results
21. MEDLINE; "arteriograph*".ti,ab; 17,695 results
22. MEDLINE; 19 OR 20 OR 21; 253,190 results
23. MEDLINE; 4 AND 18 AND 22; 10 results

Study selection. Eligibility assessment was performed by 1 author (U.S.) in an unblinded standardized manner using a study eligibility form based on the Cochrane consumers and communication review group's data extraction template. Random checks were made by another author (A.U.). The title and abstract of the retrieved records were screened. Conference abstracts and letters retrieved from electronic databases were also included in screening process.

Data collection process. Data extraction was performed using Cochrane consumers and communication review group's data extraction template. One author (U.S.) extracted the relevant data from included studies, which was checked by a second author (A.U.). There were no disagreements between the 2 authors. The corresponding author of 1 study included for final analysis was contacted via e-mail for clarification of information, but there was no response (4).

Data items. Information was extracted from each included trial on the variables mentioned in the data eligibility section.

Study quality and risk of bias in individual studies. To assess the quality of the study, guidelines in Cochrane Handbook for Systematic Reviews of Interventions were followed (5). A scoring system to grade the study quality was not used, as strongly discouraged by the Cochrane Collaboration (5). To explore variability in study results (heterogeneity), we specified the following hypothesis before conducting the analysis. We hypothesized that effect size may differ according to the methodological quality of the studies; hence, a random-effects model was to be primarily used.

Statistical analysis. Statistical analysis was performed by 1 author (U.S.) using Comprehensive Meta-analysis statistical software (version 2.2.064) (Biostat Inc., Englewood, New Jersey).

SUMMARY MEASURES. The primary outcome measure was a reduction in risk of CI-AKI with ascorbic acid quantified by computing the pooled risk ratio (RR) with 95% confidence interval (CI) using a random-effects model.

PLANNED METHOD OF ANALYSIS. In addition, influence of using a fixed-effects model on RR was also assessed. The effect

of removal of 1 study each time on RR was also assessed to identify the impact of individual studies on pooled effect size. Cumulative analysis was performed by organizing the studies in chronological order to observe the trend in pooled RR over time. Heterogeneity was quantified using I^2 statistic (with 95% CI), which represents the percentage of the total variation in estimated effects across studies that is due to heterogeneity rather than to chance. Heterogeneity was graded after Higgins et al. (6): I^2 values on the order of 25%, 50%, and 75% may be considered as low, moderate, and high heterogeneity, respectively.

RISK OF BIAS. The possibility of publication bias was assessed by subjectively evaluating a funnel plot of the standard error of a logarithm of RR for asymmetry. Because graphic representation is subjective, we also conducted Egger's regression asymmetry test as formal statistical test for publication bias (7). To assess whether the entire effect was an artifact of bias, Orwin's fail-safe N formula was used (7). To assess how much of an impact bias might have on effect size (RR), the Duval and Tweedie trim and fill method was used. We acknowledge that other factors such a differences in trial quality or true study heterogeneity could produce asymmetry in funnel plots.

Results

Study selection. The search of MEDLINE, Embase, and Cochrane central database provided a total of 63 citations. After adjusting for duplicates, 56 remained. Of these, 47 were discarded because, after reviewing the abstracts, it appeared that these papers clearly did not meet the eligibility criteria. One of these 47 articles was an RCT reported as a conference abstract that, although ascorbic acid was used in 1 treatment arm, but it did not report the incidence of CI-AKI (percentage or number of cases) (8). The authors were not able to be contacted; hence, the study was excluded.

Nine RCTs were identified for inclusion in the review and meta-analysis (4,9–16). Seven of these had full text that was examined in more detail. Two were conference abstracts that met the eligibility criteria and hence were included in the analysis (13,16). No relevant RCTs were identified from the hand search of relevant articles that could be included. Similarly, no unpublished studies were identified. There was no disagreement among the authors regarding study selection. A flow diagram of study selection is presented in Figure 1.

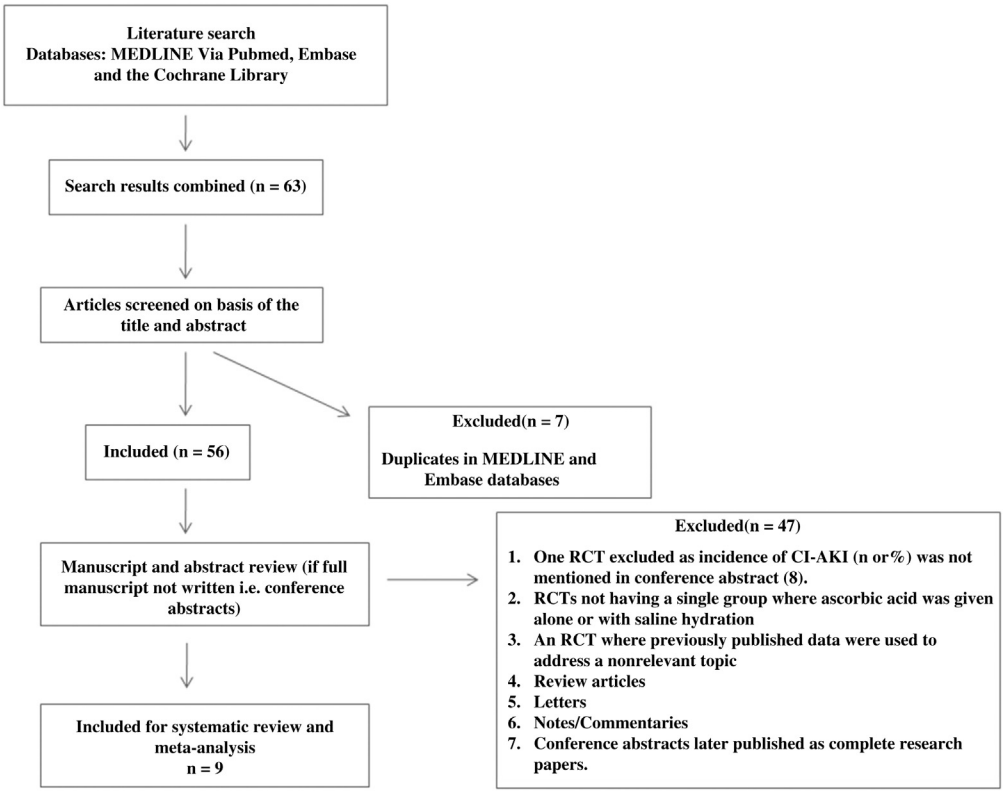

Figure 1 Flow Diagram of Study Selection

Flow of information through the different phases of systematic review from literature search to final analysis. CI-AKI = contrast-induced acute kidney injury; RCT = randomized, controlled trial.

Table 1 Baseline Study Characteristics

First Author (Ref. #)	No. of Patients Recruited	Baseline Renal Function	Definition of CI-AKI	Dose of Ascorbic Acid	Route of Ascorbic Acid Administration	Control Arm
Spargias et al. (9)	238	SCr ≥1.2 mg/dl	≥0.5 mg/dl absolute or 25% relative SCr increase 2–5 days after procedure	3 g at least 2 h before procedure, 2 g night before and morning after procedure. Hydration with NS 50–125 ml/h IV from time of randomization to at least 6 h after procedure	Oral	Placebo with IV hydration as in ascorbic acid arm
Boscheri et al. (10)	143	SCr >120 μmol/l (1.4 mg/dl)	25% increase in SCr from baseline at 48 h	1 g ascorbic acid 20 min before exposure to CM; 500 ml NS 2 h before and 500 ml during angiography and subsequent 6 h	Oral	Placebo with IV hydration as in ascorbic acid arm
Jo et al. (11)	212	SCr ≥1.1 mg/dl and/or CrCl clearance ≤60 ml/min	≥0.5 mg/dl absolute or 25% relative SCr increase within 48 h of CM exposure	3 g (night before) and 2 g morning of procedure; 2 g night before and morning after procedure (all doses 12 h apart)	Oral	1,200 mg *N*-acetylcysteine orally bid day before and on day of procedure
Zhou and Chen (12)	174	SCr ≥1.1 mg/dl and/or eGFR <60 ml/min/1.73 m^2	≥0.5 mg/dl absolute or ≥25% relative SCr increase within 48 h of CM exposure	IV 3 g morning of procedure, oral 0.5 g on the night of procedure and next morning (all doses 12 h apart). IV NS hydration 1 mg/kg/h for 4 h before and at least 12 h after angiography	IV and oral	IV NS hydration 1 mg/kg/h for 4 h before and at least 12 h after angiography
Komiyama et al. (13)	70	Baseline renal insufficiency (threshold not mentioned)	≥0.5 mg/dl absolute or ≥25% relative SCr	3 g before procedure, 2 g night and morning after procedure (12 h apart). NS hydration 1.5–2.5 l	IV	IV NS hydration 1.5–2.5 l
Brueck et al. (14)	520	CrCl ≤60 ml/min	SCr >0.5 mg/dl (44 μmol/l) within 72 h of CM exposure	500 mg in 250 ml NS infusion (over 30 min) at 24 h and 1 h before exposure to CM. NS (1 mg/kg/h) for 12 h before to 12 h after CM exposure	IV	Placebo (per ascorbic acid dose) and IV NS (1 mg/kg/h) for 12 h before to 12 h after CM exposure
Li and Chen (15)	149	Baseline renal insufficiency (threshold not mentioned)	≥0.5 mg/dl absolute or ≥25% relative SCr	IV 3 g 2–4 h before procedure and oral 1.0 g on days 1 and 2 after procedure. IV NS hydration	IV and oral	IV NS hydration
Albabtain et al. (4)	243	SCr ≥1.3 mg/dl	0.5 mg/dl absolute increase in SCr and/or 25% relative decrease of CrCl, 4–5 days after procedure	3 g 2 h before procedure, 2 g after angiogram and 2 g 24 h after angiogram. IV NS 50–125 ml/h from randomization until at least 6 h after procedure	Oral	IV NS hydration
Hamdi et al. (16)	202	Not declared, baseline SCr: 98.6 ± 29 μmol/l	25% increase in SCr 48–72 h after angiogram	3 g 2 h before procedure, 2 g day after and next day	Not reported	IV NS hydration

Shown are the total number of recruited patients in each trial, definition of CI-AKI as used by included trial, dose of ascorbic acid used, and the treatment given to patients in control arm.

CI-AKI = contrast-induced acute kidney injury; CM = contrast media; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; IV = intravenous; NS = normal saline solution; SCr = serum creatinine.

Table 2 Study Characteristics to Assess the Risk of Bias Within Studies

First Author (Ref. #)	Power Calculation	RCT Stopped Early	Randomization	Concealment of Randomization	Blinding	Investigator Blinded	Patients Blinded	Data Assessment Blinded	Patients Lost to Follow-Up, n (%)
Spargias et al. (9)	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7 (2.94)
Boscheri et al. (10)	Not mentioned	No	Yes	Yes	Yes	Yes	Yes	No	0
Jo et al. (11)	Yes	No	Yes	Yes	Yes	Yes	Yes	No	38 (17.92)
Zhou and Chen (12)	Not mentioned	No	Yes	Not declared	No	NA	NA	NA	18 (10.34)
Komiyama et al. (13)	Not mentioned	No	Yes	Not declared	No	NA	NA	NA	0
Brueck et al. (14)	Yes	No	Yes	Not declared	Yes	Yes	Yes	Not declared	37 (7.11)
Li and Chen (15)	Not mentioned	No	Yes	Not declared	No	NA	NA	NA	0
Albabtain et al. (4)	Yes	No	Yes	Yes	No	NA	NA	NA	0
Hamdi et al. (16)	Not mentioned	No	Yes	Not declared	Yes	Not declared	Not declared	Not declared	0

Shown are the relevant study characteristics according to the Cochrane Handbook for Systematic Reviews of Interventions for assessing risk of bias within included trials.
NA = not applicable; RCT = randomized, controlled trial.

Study characteristics. These are presented in Table 1.

METHODS. All 9 studies finally selected for the review and meta-analysis were RCTs and all published in the English language. All included studies had reported the incidence of CI-AKI and had serum creatinine levels checked between 24 h to 5 days.

PARTICIPANTS. All studies reported an adult population undergoing coronary angiography. All studies had patients with baseline renal impairment.

INTERVENTION AND OUTCOMES. The interventions and outcomes are presented in Table 1.

Risks of bias within studies. All included trials were randomized, thus minimizing the chance of bias within studies compared with observational studies. The quality of studies may be assessed from Table 2, which presents the relevant study characteristics according to Cochrane Handbook for Systematic Reviews of Interventions.

Results of individual studies. All studies reported the incidence of CI-AKI as the number of cases, except 1 study by Hamdi et al. (16), for which event rate was imputed. The event rate of the included studies is presented in Figure 2.

Synthesis of results. Nine RCTs reported data on the incidence of CI-AKI in 1,536 patients who had completed the trial and were included in the final analysis. Ascorbic acid was given to 740 patients, whereas 796 patients were in control group and received alternate treatment. The overall incidence of CI-AKI in patients receiving ascorbic acid was 9.59% compared with 16.83% in the control arm. In the pooled analysis using a random-effects model, patients receiving ascorbic acid had 33% less risk of CI-AKI compared with the control group (RR: 0.672 [95% CI: 0.466 to 0.969], $p = 0.034$) (Fig. 2). Evaluation of the 95% CI shows that the range of risk lowering varied from 54% to 4% with ascorbic acid. A low degree of nonsignificant heterogeneity was present ($I^2 = 27.49\%$, chi-square = 11.03, df = 8, $p = 0.200$).

Risk of bias across studies. Due to evidence of low heterogeneity, a funnel plot was created to explore it and assess any bias (Fig. 3). The funnel plot showed evidence of minimal asymmetry that was quantified to be statistically nonsignificant by Egger's regression intercept (intercept = 0.552 [95% CI: −1.428 to 2.533], df = 7, $p = 0.530$). Orwin's fail-safe N is 170, suggesting that there would need to be >150 studies with a mean RR of 1.0 added to the analysis before the cumulative effect would become trivial (defined as an RR of 0.98). Given that we were able to identify only 9 studies for the final analysis, it is quite unlikely that >150 studies were missed. Although there is a possibility that a reduction in the risk of CI-AKI with ascorbic acid is overstated, it is unlikely that the actual risk is zero. Using a random-effects model, trim and fill method suggested no asymmetry on the right of the mean and 1 study on the left of the mean, which if trimmed, the

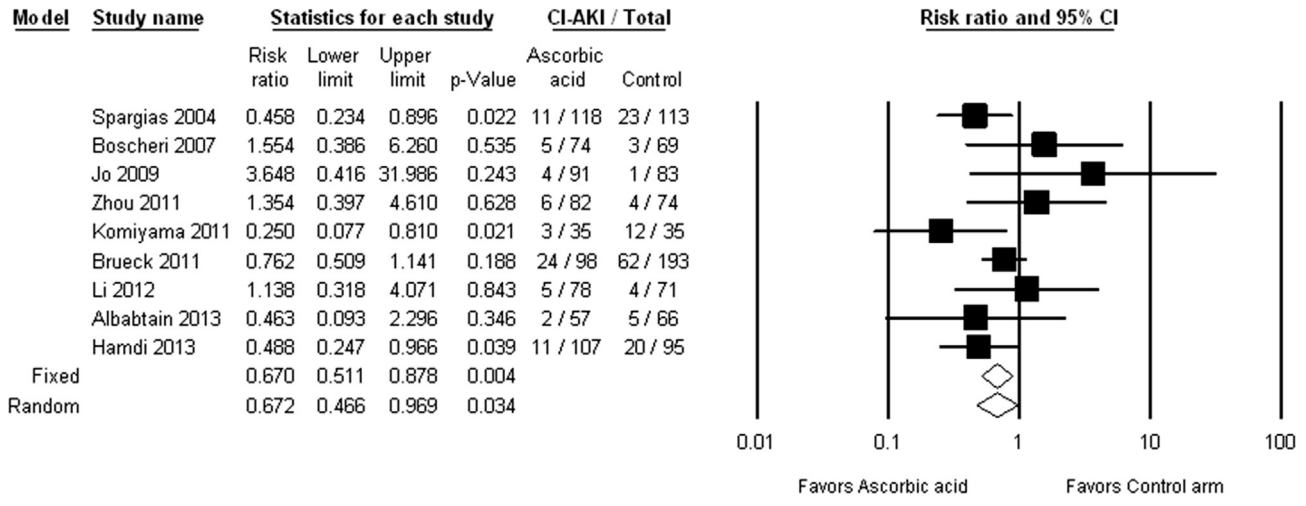

Figure 2 Forest Plot of Included Studies

The event rate in different study arms is presented alongside the computed risk ratio (95% confidence interval [CI] (lower and upper limit) with p value. Forest plot shows effect size **(solid squares)** with 95% CI **(black line through the solid squares)**, in terms of risk ratio for individual studies and pooled risk ratio **(open diamonds)** for fixed- and random-effects model at the **bottom**. Studies favoring reduction of risk with ascorbic acid are on the **left of the center line**, and studies favoring other treatment options are on **right of the center line**. CI-AKI = contrast-induced acute kidney injury.

imputed RR would be 35% (instead of 33%). These analyses reveal that the impact of bias was most likely trivial.

Additional analyses. Use of a fixed-effects model showed a 33% (95% CI: 13% to 49%) lower risk with ascorbic acid (RR: 0.670 [95% CI: 0.511 to 0.878], p = 0.004) (Fig. 2). Although the degree of significance was higher compared with a random-effects model, the pooled effect size was similar, with minor variation in the 95% CI.

The effect of removal of individual studies on the pooled RR using a random-effects model was assessed using a forest plot, showing that it favored ascorbic acid use to protect against CI-AKI at each step (Fig. 4).

Figure 3 Funnel Plot for Subjective Assessment of Bias Among the Included Studies

Studies with larger sample size tend to accumulate at the **top of the funnel and close to the center line**, with small studies toward the base. Funnel plot appears to have minimal asymmetry.

To assess how the trend in RR had changed from the earliest to latest studies, a cumulative analysis was performed with studies arranged in chronological order (Fig. 5). The second row in Figure 5 represents a summary analysis comprising the first 2 studies, the third row represents a summary analysis comprising the first 3 studies, and so on. There was a small but consistent cumulative trend toward a benefit with ascorbic acid. As none of the studies had excessively large sample size, we did not perform a cumulative analysis to try to assess its impact on effect size.

Three studies had a sizable proportion of patients lost to follow up after randomization (12,14,17). After excluding these 3 studies from the analysis, it was observed that the benefit of ascorbic acid for nephroprotection increases, with a further reduction in nonsignificant minimal heterogeneity and no evidence of publication bias (RR: 0.530 [95% CI: 0.349 to 0.860], p = 0.003; I^2 = 9.120, chi-square = 5.502, df = 5, p = 0.358; Egger's regression intercept = 1.086 [95% CI: −2.570 to 4.743], df = 4, p = 0.455).

Discussion

This pooled statistical analysis of systematically selected RCTs provides robust evidence that ascorbic acid reduces the risk of CI-AKI, albeit by somewhat small magnitude, in patients undergoing coronary angiography compared with alternate treatment strategies. Because participants of these studies had documented pre-existing renal

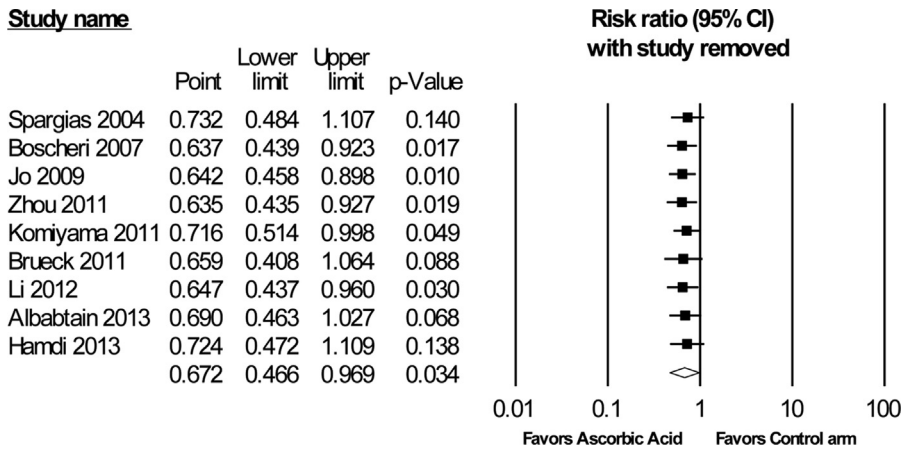

Figure 4 Forest Plot Using a Random-Effects Model Demonstrating the Effect of Removal of Individual Studies on Pooled Effect Size

A consistent trend in favor of ascorbic acid as a nephroprotective agent was observed at each step. **Small solid squares** indicate effect sizes following removal of individual studies. **Open diamonds** indicates pooled effect size. CI = confidence interval.

insufficiency, this indicates that ascorbic acid is effective in offering nephroprotection in this patient group. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system for grading evidence can be used to assess various factors that may decrease the quality of this evidence (18).

Study limitations. The trials included for meta-analysis did not consistently report optimal randomization concealment (Table 2) and had a variable lack of blinding and the outcome measures were not subjective; hence, these may not be considered serious limitations. None of the trials was terminated prematurely, and there was no evidence of selective reporting.

INCONSISTENT RESULTS. Heterogeneity among the trials was minimal. This may be due to true heterogeneity of the study populations. Also important to note is that there was variability among studies about the route in which ascorbic acid was administered. The bioavailability of oral and intravenous administration of ascorbic acid differ (19), and this can affect the drug efficacy and hence variation of effect sizes between studies.

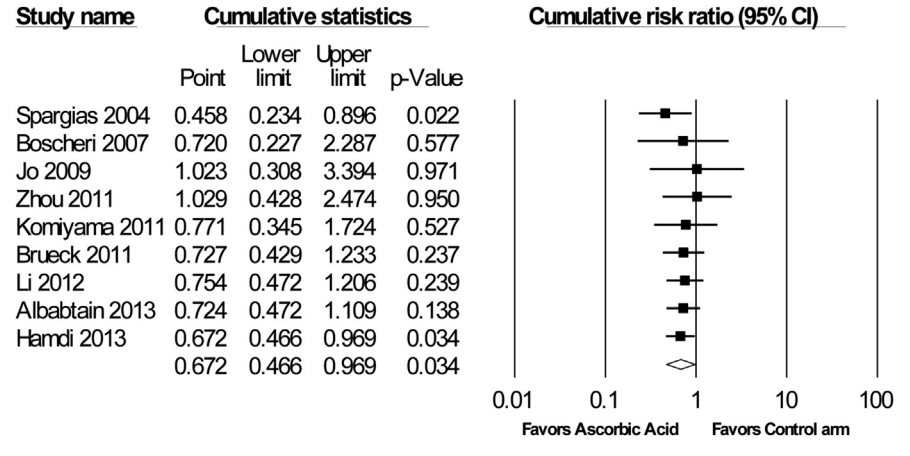

Figure 5 Cumulative Analysis of Included Studies in Chronological Order

The **second bar with a black-filled box** in the cumulative risk ratio forest plot indicates cumulative analysis of the first 2 studies. The **third bar with a black-filled box** in the forest plot indicates the cumulative analysis of first 3 studies and so on. A somewhat consistent trend toward benefit with ascorbic acid is evident. CI = confidence interval.

INDIRECTNESS OF EVIDENCE. All included trials reported head-to-head comparison of ascorbic acid and alternate treatment; hence, there was no evidence of indirectness.

IMPRECISION. None of the trials had very small sample size compared with others, and event rate was not negligible in studies.

PUBLICATION BIAS. Publication bias was nonsignificant and was found not to affect the pooled effect size of our meta-analysis.

Thus, it can be cautiously said that results of this systematic review with meta-analysis are reliable. Would it be possible to overturn the results of this meta-analysis by conducting another clinical trial? It is difficult to answer the question of what would the sample size be for the future trial because there are so many unknowns (e.g., sample size, effect size, risk in each group). But assuming that the true effect size (odds ratio) in the population is 1, indicating no difference between groups, and assuming a risk of 15% in each group (based on the available study data), then a total sample size of 250 (125 patients in each group) will change the conclusions of the meta-analysis provided that the observed effect size is at least as large as the true effect size of 1.

It is to be noted that no trial can be conducted that is guaranteed to change the conclusions of the meta-analysis. Also, it is easier to conclude a significant difference rather than a nonsignificant difference. If the meta-analysis result is changed to nonsignificant, then the best that we can say is that there is insufficient evidence of a beneficial effect of ascorbic acid. The additional analyses performed in this meta-analysis, such as the effect of removal of 1 study at a time (Fig. 4) and cumulative analysis (Fig. 5), also show a persistent benefit of ascorbic acid against CI-AKI. Because of these reasons, it would therefore not be advisable to conduct such a trial.

How ascorbic acid may offer nephroprotection. The exact mechanism by ascorbic acid may offer nephroprotection is unclear, but it has been widely used due to its antioxidant property. ROS-induced oxidative stress and renal vasoconstriction have been implicated in the etiology of CI-AKI. Hydroxyl radical ($OH\cdot$) is one of many free radicals that can cause oxidative stress. The Haber Weiss/Fenton reaction cycle governs the generation of $OH\cdot$ from hydrogen peroxide (H_2O_2) and superoxide radical ($O_2\cdot^-$), with reduction of ferric to ferrous by $O_2\cdot^-$, ferrous acting as a catalyst for this cycle. Ascorbate is an efficient scavenger of ROS such as $O_2\cdot^-$, H_2O_2, and $OH\cdot$ can therefore reduce the oxidative stress (1). Being a reducing agent, ascorbic acid has the ability to reduce ferric to ferrous, thus potentially promoting the generation of ROS and acting as a pro-oxidant. However, this pro-oxidant effect has been demonstrated mainly in vitro; corresponding in vivo data has been inconsistent (2,20,21). Radox-active free iron is required for the Haber Weiss/Fenton reaction, but physiologically this labile iron pool is kept at the lowest sufficient level by keeping iron in bound form, the exception being patients with iron overload conditions such as hemochromatosis (22). Under physiological conditions in vivo, ascorbate seems to predominantly maintain its antioxidant effect (2,20,21,23). Ascorbic acid acts as an antioxidant by donating an electron to potentially damaging oxidizing radicals; this 1-electron oxidation of AH^- (reduced circulating form of ascorbic acid) results in the production of the ascorbyl radical ($A\cdot^-$), also called semidehydroascorbic acid. As a result, the reactive free radical is reduced (24). Further donation of an electron (double oxidation) results in generation of stable dehydroascorbic acid. Among the trials included in this systematic review, the antioxidant effect of ascorbic acid was demonstrated by Spargias et al. (9). Ascorbic acid has also been reported to cause vasodilation (25,26). This effect may be independent of its effect to ameliorate ROS-induced endothelial dysfunction (27). These findings are, however not consistent (28).

In contrast to one's expectation that ascorbic acid can cause acidification of urine, there is consistent evidence that ascorbic acid in a daily dose range of 2 to 6 g/day in divided doses (29–31) (which is equivalent to the maximum daily dose used in the RCTs included in the meta-analysis) does not acidify the urine. Surprisingly, it can increase the urine pH (30). Because an acidic environment, which is typical of tubular urine, promotes free-radical production (32) and high pH of normal extracellular fluid inhibits it (33,34), alkalinizing renal tubular fluid with pharmacological agents is a logical strategy to reduce renal injury.

Effect of route of administration on the efficacy of ascorbic acid. After oral intake, ascorbic acid is absorbed by active transport in the intestine (35). Most of it (80% to 90%) is absorbed when the intake is up to 100 mg/day. With an increase in ascorbic acid intake, the corresponding plasma concentration increases, reaching a plateau at a dose of 90 to 150 mg/day (36). It is freely transported into cells, including leukocytes and red blood cells, becoming saturated with ascorbic acid at doses between 100 and 200 mg/day (19). In contrast to this, intravenous route tends to achieve higher peak plasma concentration (e.g., 3 g of intravenous ascorbic acid produces a peak plasma concentration of 1,760 μmol/l vs. 206 μmol/l for oral route at same dose) (19). After intravenous administration, predicted peak urine concentrations of ascorbic acid can be as much as 140-fold higher compared with oral administration (19). Similar to the high requirement of ascorbic acid in individuals with higher oxidative stress such as in smokers (37), it is possible that a higher plasma concentration of ascorbic acid, which is achievable with higher intravenous doses, may be more beneficial in individuals with pre-existing renal insufficiency. This meta-analysis did not compare the pooled treatment effect of RCTs using exclusive peroral and intravenous ascorbic acid administration because only 2 RCTs used the intravenous route exclusively, and their pooled analysis would not have been meaningful.

Conclusions

Ascorbic acid has the potential to protect against CI-AKI in patients with pre-existing renal impairment and can form part of effective prophylactic pharmacological regimens. The precise mechanism by which it may do so is as unclear, as is the etiology of CI-AKI. To assess its full potential as a nephroprotective agent, further investigation is warranted regarding its optimal dose and route of administration, which affect its bioavailability.

Reprint requests and correspondence: Dr. Umar Sadat, Box 201, Department of Surgery, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, United Kingdom. E-mail: sadat.umar@gmail.com.

REFERENCES

1. Frei B, England L, Ames BN. Ascorbate is an outstanding antioxidant in human blood plasma. Proc Natl Acad Sci U S A 1989;86:6377–81.
2. Carr A, Frei B. Does vitamin C act as a pro-oxidant under physiological conditions? FASEB J 1999;13:1007–24.
3. Heyman SN, Rosen S, Khamaisi M, Idee JM, Rosenberger C. Reactive oxygen species and the pathogenesis of radiocontrast-induced nephropathy. Invest Radiol 2010;45:188–95.
4. Albabtain MA, Almasood A, Alshurafah H, Alamri H, Tamim H. Efficacy of ascorbic acid, N-acetylcysteine, or combination of both on top of saline hydration versus saline hydration alone on prevention of contrast-induced nephropathy: a prospective randomized study. J Interv Cardiol 2013;26:90–6.
5. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Available at: http://handbook.cochrane.org/. Accessed September 16, 2013.
6. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
7. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Publication bias. Introduction to meta-analysis. West Sussex, United Kingdom: John Wiley & Sons, Ltd., 2009;277–92.
8. Momeni A, Ebrahimi A, Khaledi A. Comparison of three methods of contrast nephropathy prophylaxis in azotemic patients. Iranian J Kidney Dis 2011:5–10.
9. Spargias K, Alexopoulos E, Kyrzopoulos S, et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. Circulation 2004;110:2837–42.
10. Boscheri A, Weinbrenner C, Botzek B, Reynen K, Kuhlisch E, Strasser RH. Failure of ascorbic acid to prevent contrast-media induced nephropathy in patients with renal dysfunction. Clin Nephrol 2007;68:279–86.
11. Jo SH, Koo BK, Park JS, et al. N-acetylcysteine versus AScorbic acid for Preventing contrast-Induced nephropathy in patients with renal insufficiency undergoing coronary angiography NASPI study-a prospective randomized controlled trial. Am Heart J 2009;157:576–83.
12. Zhou L, Chen H. Prevention of contrast-induced nephropathy with ascorbic acid. Intern Med 2011;51:531–5.
13. Komiyama K, Tejima T, Tanab Y, Sakurada H. Is ascorbic acid effective in preventing contrast-induced acute kidney injury? Am J Cardiol 2011;105:29A.
14. Brueck M, Cengiz H, Hoeltgen R, et al. Usefulness of N-acetylcysteine or ascorbic acid versus placebo to prevent contrast-induced acute kidney injury in patients undergoing elective cardiac catheterization: a single center, prospective, double-blind, placebo-controlled trial. J Invasive Cardiol 2013;25:276–83.
15. Li R, Chen H. Prevention of contrast-induced nephropathy with ascorbic acid. Heart 2012;98 Suppl 2:E211.
16. Hamdi S, Selmi W, Hraiech A, Jomaa W, Hamda KB, Maatouk F. Prevention of contrast induced nephropathy in patients undergoing coronarography with ascorbic acid. J Am Coll Cardiol Intv 2013;6 Suppl S:S22.
17. Jo SH, Koo BK, Park JS, et al. N-acetylcysteine versus ascorbic acid for preventing contrast-Induced nephropathy in patients with renal insufficiency undergoing coronary angiography NASPI study-a prospective randomized controlled trial. Am Heart J 2009;157:576–83.
18. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336:995–8.
19. Padayatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med 2004;140:533–7.
20. Barja G. Ascorbic acid and aging. In: Robin HJ, editor. Ascorbic Acid: Biochemistry and Biomedical Cell Biology. New York, NY: Plenum; 1996:157–88.
21. Valko M, Morris H, Cronin MT. Metals, toxicity and oxidative stress. Curr Med Chem 2005;12:1161–208.
22. Kruszewski M. Labile iron pool: the main determinant of cellular response to oxidative stress. Mutat Res 2003;531:81–92.
23. Suh J, Zhu BZ, Frei B. Ascorbate does not act as a pro-oxidant towards lipids and proteins in human plasma exposed to redox-active transition metal ions and hydrogen peroxide. Free Radic Biol Med 2003;34:1306–14.
24. Bielski BH, Richter HW, Chan PC. Some properties of the ascorbate free radical. Ann N Y Acad Sci 1975;258:231–7.
25. Gokce N, Keaney JF Jr., Frei B, et al. Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease. Circulation 1999;99:3234–40.
26. Motoyama T, Kawano H, Kugiyama K, et al. Endothelium-dependent vasodilation in the brachial artery is impaired in smokers: effect of vitamin C. Am J Physiol 1997;273:H1644–50.
27. Sridulyakul P, Wongeak-In N, Patumraj S. Correlations between endothelial functions and ROS detection in diabetic microvascular wall: early and late ascorbic acid supplementation. Int J Vasc Med 2012;2012:709695.
28. Duffy SJ, Gokce N, Holbrook M, et al. Effect of ascorbic acid treatment on conduit vessel endothelial dysfunction in patients with hypertension. Am J Physiol Heart Circ Physiol 2001;280:H528–34.
29. Hetey SK, Kleinberg ML, Parker WD, Johnson EW. Effect of ascorbic acid on urine pH in patients with injured spinal cords. Am J Hosp Pharm 1980;37:235–7.
30. Barton CH, Sterling ML, Thomas R, Vaziri ND, Byrne C, Ryan G. Ineffectiveness of intravenous ascorbic acid as an acidifying agent in man. Arch Intern Med 1981;141:211–2.
31. Bannwart C, Hagmaier V, Straumann E, Hofer H, Vuillemier JP, Rutishauser G. [Modification of urinary pH through ascorbic acid]. Helv Chir Acta 1981;48:425–8.
32. Alpern RJ. Renal Acidification Mechanisms. 6th edition. Philadelphia, PA: WB Saunders, 2000.
33. Halliwell B, Gutteridge JM. Role of free radicals and catalytic metal ions in human disease: an overview. Methods Enzymol 1990;186:1–85.
34. Cohen G. The Fenton reaction. Boca Raton, FL: CRC Press; 1985.
35. Sauberlich HE. Bioavailability of vitamins. Prog Food Nutr Sci 1985;9:1–33.
36. Blanchard J, Tozer TN, Rowland M. Pharmacokinetic perspectives on megadoses of ascorbic acid. Am J Clin Nutr 1997;66:1165–71.
37. Lykkesfeldt J, Christen S, Wallock LM, Chang HH, Jacob RA, Ames BN. Ascorbate is depleted by smoking and repleted by moderate supplementation: a study in male smokers and nonsmokers with matched dietary antioxidant intakes. Am J Clin Nutr 2000;71:530–6.

Keywords: acute kidney injury ■ angiography ■ ascorbic acid ■ contrast-induced nephropathy.