Comments and Responses

Is There Enough Evidence to Support Use of N-Acetylcysteine in Contrast-Induced Nephropathy?

To the Editor: I would like to applaud Kelly and colleagues for their exhaustive meta-analysis (1), and I have some comments about their analysis.

First, exactly how many studies involving N-acetylcysteine were included in the meta-analysis? The number of N-acetylcysteine studies in Figure 1 differs from the numbers listed in the Table and Figure 2. Why were 4 studies excluded after they were deemed to have satisfied inclusion criteria? Second, the paper cited as a study involving furosemide and mannitol (Table) is a review relating to clinical outcomes, such as death, on which data are lacking.

Second, the statistically significant heterogeneity with respect to N-acetylcysteine effect merits comment. Some statistical authorities suggest that if there is substantial heterogeneity, then a summary effect should not be derived (4). This is a point that warrants discussion. The random-effects model does not necessarily eliminate the problem of heterogeneity (5). Particularly, if a substantial number of studies differ in treatment effect and direction (Figure 2), then com-

Furthermore, I want to draw attention to the Editors’ Notes. The paper presents no evidence of the benefit of theophylline. The analysis itself, which includes 1 aminophylline trial (6), did not reach statistical significance. On closer examination, 2 included studies were published from the same institute and had similar methods (7, 8). There are differences: For example, the first study was not restricted to individuals undergoing coronary angiography but had 54 such participants. The second study included only participants undergoing coronary angiography. It is possible that the second study included the same 54 coronary angiography patients from the first study. If so, because both studies were positive, this could bias results in favor of theophylline.

Finally, the editors’ comment regarding the benefit of mannitol merits correction. The authors presented only 1 mannitol study, which had shown that mannitol was harmful compared with one half the normal dose of saline (3).

I applaud the authors and the editors for making the point that change in creatinine level has not been confirmed by using simultaneous measurements of cystatin C (4); therefore, effects of N-acetylcysteine on creatinine level may not reflect true benefit with regard to the glomerular filtration rate. Examining a more clinically relevant outcome across 22 trials (2), we found that only 13 patients received dialysis; 5 control participants and 8 N-acetylcysteine–treated individuals (P = 0.42). This result does not suggest a meaningful therapeutic effect.

In addition to the doubtful claim of N-acetylcysteine efficacy, unrefereced statements of proven safety also warrant comment. Clinical trials for the prevention of contrast-induced nephropathy have largely used small, oral doses of N-acetylcysteine in stable outpatient populations. However, critically ill patients with shock and the acute respiratory distress syndrome are also at high risk for con-

References
Larger circles represent larger studies with less variability. The 4 open circles represent a separate cluster of studies that were generally published earlier, were of smaller size, and had lower methodological quality. To convert values to $\mu$mol/L, multiply by 88.402.

trast-induced nephrotoxicity, and some physicians advocate the use of intravenous doses of N-acetylcysteine in these settings. When prospectively studied in acetaminophen poisoning, intravenous N-acetylcysteine produced anaphylactoid reactions in up to 48% of participants (5). Although most of these reactions were mild, at least 1 death has been reported in a patient with asthma (6). Other investigators have reported potentially harmful effects of N-acetylcysteine in septic shock (7, 8), and a trial of oxothiazolidine-4-carboxylic acid (a cysteine prodrug) in the acute respiratory distress syndrome (9) was stopped early because of excess mortality in the treatment group (29.7% vs. 15.8%; $P = 0.014$).

We conclude that the efficacy of N-acetylcysteine for preventing contrast-induced nephrotoxicity remains unknown. Future studies should not use change in serum creatinine level as the primary endpoint. In critically ill patients at risk for contrast-induced nephrotoxicity, the efficacy and safety of N-acetylcysteine have not been established.

Denise A. Gonzales, MD
Presbyterian Hospital
Albuquerque, NM 87110

Robert A. Star, MD
Steven J. Kern, BS
Charles Natanson, MD
Robert L. Danner, MD
National Institutes of Health
Bethesda, MD 20892

Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: We read with interest the meta-analysis by Kelly and colleagues (1), in which the authors assessed the effectiveness of several drugs, including N-acetylcysteine and theophylline, in preventing contrast-induced nephropathy. They assessed a total of 41 studies and concluded that N-acetylcysteine is the most effective agent for preventing contrast-induced nephropathy (1). The authors should be commended in undertaking such a comprehensive review of the literature. However, several issues, particularly with the methods adopted in the meta-analysis, need to be considered before the results are accepted as truly representative of “real-world” practice.

The treatment effect estimates from the selected 41 articles were not combined into a single summary pooled estimate; therefore, it is not known what effect the use of a renoprotective agent has on the occurrence of contrast-induced nephropathy. Moreover, the overall heterogeneity has not been reported. Instead, only subgroup summary estimates are presented as risk ratios, with subgroups according to the specific renoprotective agent and no comparison of the estimates of treatment effect between subgroups as recommended (2). If the aim was to compare different agents, the lack of head-to-head, direct comparisons should then have prompted “an indirect comparison meta-analysis” with a common comparator (3, 4). In the simplest case of an indirect comparison between 2 treatments, each directly compared with placebo (common comparator), the use of an appropriate test on interaction is mandatory (2) to provide the statistical evidence of a qualitative or quantitative interaction between subgroups. Thus, Kelly and colleagues’ meta-analysis cannot conclude whether N-acetylcysteine has a different effect than theophylline. Another factor that may have provided even greater insight is the evaluation of the possible sources of heterogeneity in the sub-

Figure. Clusters of studies on changes in creatinine level.
group of patients taking N-acetylcysteine, including dosage, timing, and duration of administration. This may have been performed through meta-regression analysis. Finally, the authors did not state in the Methods section the level of statistical significance or which test of heterogeneity they used to derive the P value reported in Figure 2. The finding of a P value of 0.14 in the theophylline subgroup cannot rule out the presence of clinical heterogeneity, because the standard Cochran Q test has a poor power (5) and I² of 39.7% is not negligible.

Giuseppe Ferrante, MD
Catholic University of the Sacred Heart
Rome 00168, Italy

Didier Loca, MD
Royal Brompton Hospital
London SW3 6NP, United Kingdom

Peter Barlis, MD
Northern Hospital
Epping, Victoria 3076, Australia

Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: I would like to congratulate Kelly and colleagues (1) on a well-conducted systematic review and comprehensive search strategy, critical appraisal of included studies, duplicate data extraction and adequate meta-analysis model). On the other hand, I disagree with the authors’ conclusion that “the use of . . . N-acetylcysteine is reasonable in high-risk patients who are to receive large or repeated volumes of contrast agents.” Although N-acetylcysteine represents an inexpensive, potentially safe, and widely available intervention, the evidence that it reduces contrast-induced nephropathy (a surrogate outcome) comes from trials with heterogeneous results, most which are of low methodological quality according to the authors’ critical appraisal. Moreover, the impact of N-acetylcysteine on important patient outcomes, such as all-cause mortality, doubling of serum creatinine level, and need for dialysis treatment, is uncertain. The currently available evidence on N-acetylcysteine is encouraging but is too unreliable to allow definitive conclusions. Thus, a well-designed, large-scale, placebo-controlled, randomized trial evaluating clinical outcomes is urgently needed before implementing this intervention in clinical practice.

Otavio Berwanger, MD, PhD
Research Institute Cardiac Hospital
São Paulo S-04005, Brazil

Potential Financial Conflicts of Interest: None disclosed.

Reference

IN RESPONSE: We thank Dr. Trivedi for detecting 2 errors in our article. First, we included 26 studies of N-acetylcysteine, not 30 as indicated in Figure 1. Second, we erroneously cited a review related to the selection of contrast media (1)—we intended to cite a 1994 study by Solomon and colleagues (2). In addition, we agree with Dr. Trivedi that substantial heterogeneity of studies evaluating N-acetylcysteine makes the conclusions of our analysis far from definitive. As stated in our article, head-to-head trials of available agents are needed to define the most effective and safe strategy of preventing contrast-induced nephropathy. Finally, the editors have published a correction about the Editors’ Notes accompanying our article (3).

Dr. Gonzalez and colleagues note that previous meta-analyses have examined the efficacy of N-acetylcysteine in preventing contrast-induced nephropathy and that some of these, including their own in 2007 (4), have reached different conclusions than ours. Their 2007 analysis included 22 trials and suggested that most of the apparent benefit of N-acetylcysteine was attributable to 4 small, relatively early trials (5–8). Our meta-analysis was larger, including 26 studies, and was less prone to the influence of these 4 trials. We acknowledge that creatinine level is an imperfect surrogate outcome measure for nephropathy, that protection against nephropathy based on change in creatinine level has not been confirmed by using other measures, and that the mechanism by which N-acetylcysteine might prevent contrast-induced nephropathy remains uncertain. Although Dr. Gonzalez and colleagues are correct in noting that anaphylactoid reactions occurred in studies of intravenous N-acetylcysteine treatment of acetaminophen poisoning, the doses of N-acetylcysteine used for acetaminophen overdose are larger and the duration of therapy is longer (150 mg/kg of body weight initial bolus dose and 50 mg/kg over 4 hours, and 100 mg/kg for 16 hours). At the N-acetylcysteine doses and durations used in the trials we cited, no major adverse effects were reported. However, it is wise to advise caution in the use of N-acetylcysteine in hospitalized patients. As noted in the discussion of our results, we agree that the efficacy of N-acetylcysteine for preventing contrast-induced nephropathy remains unproven and that creatinine measurement is a surrogate value.

Dr. Ferrante and colleagues raise several issues about our methods. Although we explored the pooling of treatment effects from the 41 included trials to derive a single summary estimate for the effectiveness of the use of a renoprotective agent in reducing contrast-induced nephropathy, we refrained from reporting these analyses after reviewers noted substantial problems with the pooling of these very heterogeneous studies and the uncertain interpretation of the summary estimate in clinical terms. These exploratory analyses suggested that patient age and baseline creatinine level influenced the effects of renoprotective agents on contrast-induced nephropathy and that diabetes mellitus, patient sex, and hypertension did not. However, use of summary measures, such as average age or propor-
tion of female study participants, as independent variables in meta-regression models is subject to potential ecological biases. Pooled analyses using individual patient data and additional high-quality trials are needed to reliably explore these sources of heterogeneity. We did not look into whether the dose, timing, and duration of N-acetylcysteine contributed to heterogeneity, and we agree that this would be interesting to pursue in future analyses. We used the method of DerSimonian and Laird to assess overall and subgroup summary risk ratios and I² to assess overall and subgroup summary risk ratios and to derive the P value reported in Figure 2 of our article.

Dr. Berwanger disagrees with our conclusion that "the use of . . . N-acetylcysteine is reasonable in high-risk patients who are to receive large or repeated volumes of contrast agents." As noted in our article, we agree that clinicians need to understand that evidence supporting N-acetylcysteine’s effectiveness comes from studies that have measured surrogate end points, have been of generally poor quality, and have found heterogeneous results. Yet, clinicians must make decisions with the evidence presently on hand. Although far from definitive, this evidence is more encouraging for the effectiveness of N-acetylcysteine than that for other agents used to prevent contrast-induced nephropathy. High-quality randomized, controlled trials evaluating clinical outcomes may alter our current conclusions about the effectiveness of N-acetylcysteine when they become available.

Aine M. Kelly, MD, MS
Ben Dwamena, MD
Ruth C. Carlos, MD, MS
University of Michigan
Ann Arbor, MI 48109

Potential Financial Conflicts of Interest: None disclosed.

References

CLINICAL OBSERVATIONS

Fever Increases the Risk for Cardiac Arrest in the Brugada Syndrome

Background: The Brugada syndrome is a familial arrhythmia that manifests as ventricular tachycardia or ventricular fibrillation. It leads to syncpe or sudden death in young adults with structurally normal hearts. Episodes are preceded by ST-segment elevation in precordial leads V₁ and V₂. An estimated 18% to 30% of patients carry loss-of-function mutations in SCN5A, the gene that encodes the cardiac sodium channel (1). Anecdotes suggest that fever may be associated with cardiac arrest and preceding electrocardiographic (ECG) changes (Figure 2, 3).

Objective: To assess the association between fever and cardiac arrest or ECG changes in patients with the Brugada syndrome.

Methods: We retrospectively assessed the prevalence of fever-triggered ventricular tachycardia, ventricular fibrillation, or sudden death in 111 consecutive index patients with the Brugada syndrome at our institution (age, 48 years [SD, 15]; male–female ratio, 83:28; 33 with and 68 without SCN5A mutation [10 unknown]). Data were compared with 41 consecutive control participants (age, 62 years [SD, 15]; male–female ratio, 33:8) who were admitted after out-of-hospital cardiac arrest with documented ventricular tachycardia or ventricular fibrillation.

We analyzed fever-induced ECG changes in 24 patients with the Brugada syndrome for whom 12-lead ECGs during both fever and normothermia were available (mean age, 43 years [SD, 21]; male–female ratio, 17:7; mean febrile temperature, 39.1° C [SD, 0.9]); this group included 3 of the 4 patients with fever-triggered cardiac arrest. We performed statistical analysis of ECG changes by using the Wilcoxon matched-pair test. We also compared the ECG changes with those from 10 control participants admitted for non-cardiac reasons (mean age, 49 years [SD, 20]; male–female ratio, 8:2; mean febrile temperature, 39.3° C [SD, 0.8]).

Finally, in the same 24 patients, we studied whether the prevalence of cardiac arrest during fever was modified by acetaminophen use before admission. The study was approved by the institutional ethics committee and participants provided informed consent.

Results: Twenty-two of 111 patients with the Brugada syndrome had cardiac arrest, and 4 had preceding fever (18% [95% CI, 5% to 40%]), compared with no fever in any control participant with out-of-hospital cardiac arrest (0% [CI, 0% to 9%]). Three of the 4 patients had an SCN5A mutation. Nineteen of the other 89 patients with the Brugada syndrome but without an index cardiac arrest had a febrile episode without arrest during follow-up (38 months [SD, 25]).

Among the 24 patients with ECG performed during and after fever, fever source varied (unknown [n = 8], pneumonia [n = 5], upper respiratory tract infection [n = 3], tonsillitis [n = 2], phlebitis [n = 2], cholangitis [n = 1], gastroenteritis [n = 1], urinary tract infection [n = 1], and infected finger ulcer [n = 1]). Thirteen of the 24 required admission during their febrile episode, including 6 for unexplained syncpe and 1 for unexplained chest pain. The remaining 11 were advised to present for ECG because of temperature greater than 38.0° C. Mean PR/QRS intervals and ST-segment amplitude in V₁ and V₂ were markedly increased in these patients (Table). In 10 of the patients (42% [CI, 22% to 63%]), fever-induced ECG changes were associated with chest pain (n = 5), diz-
ziness (n = 4), and palpitations (n = 1). In the 10 control participants who were admitted for noncardiac reasons, mean PR interval decreased and mean QRS interval and ST-segment amplitude remained unchanged.

Among the 24 patients with ECGs performed during and after fever, 11 had used acetaminophen before admission, and none had cardiac arrest (0% [CI, 0% to 28%]). Of 10 patients who had not used acetaminophen, 3 had cardiac arrest during fever (30% [CI, 7% to 65%]). Acetaminophen use was unknown in 3 patients.

Discussion: In this single-center, retrospective case series of patients with the Brugada syndrome, fever seemed to cause Brugada syndrome–type ECG changes and was present in 18% of cases of fever.

Table. ECG Variables during Normothermia and Fever for Patients with the Brugada Syndrome and Control Participants*

<table>
<thead>
<tr>
<th>ECG Variable</th>
<th>Patients with the Brugada Syndrome (n = 24)</th>
<th>P Value for Normothermia vs. Fever</th>
<th>Control Participants (n = 10)</th>
<th>P Value for Normothermia vs. Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No fever</td>
<td>74 (61–84)</td>
<td>&lt;0.001</td>
<td>82 (73–93)</td>
<td>0.005</td>
</tr>
<tr>
<td>Fever</td>
<td>95 (82–108)</td>
<td></td>
<td>98 (88–116)</td>
<td></td>
</tr>
<tr>
<td>PR interval, ms</td>
<td></td>
<td>0.012</td>
<td>143 (131–164)</td>
<td>0.043</td>
</tr>
<tr>
<td>No fever</td>
<td>171 (149–187)</td>
<td></td>
<td>135 (125–165)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>182 (164–199)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS interval, ms</td>
<td></td>
<td>0.001</td>
<td>86 (73–98)</td>
<td>0.23</td>
</tr>
<tr>
<td>No fever</td>
<td>100 (88–106)</td>
<td></td>
<td>81 (71–100)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>110 (95–127)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc duration, ms</td>
<td></td>
<td>0.011</td>
<td>445 (419–452)</td>
<td>0.008</td>
</tr>
<tr>
<td>No fever</td>
<td>407 (386–424)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>425 (393–457)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment amplitude in V1/V2, mV</td>
<td></td>
<td>&lt;0.001</td>
<td>0.7 (0.4–0.7)</td>
<td>0.50</td>
</tr>
<tr>
<td>No fever</td>
<td>1.3 (0.9–2.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>3.6 (2.2–5.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ECG = electrocardiography; QTc = heart rate–corrected QT interval.
* All data are expressed as median (interquartile range).
cardiac arrest. Three patients with fever-triggered cardiac arrest had an SCN5A mutation, which is reported to impair cardiac sodium channel function at higher temperatures (3). Of interest, mutations in genes encoding neuronal sodium channels have been linked to familial diseases with temperature-dependent symptoms, such as generalized epilepsy with febrile seizures (SCN1A mutations) (4) and inherited erythromelalgia with heat-triggered burning pain and skin redness (SCN9A mutations) (5). Acetaminophen use before admission seemed to reduce the risk for fever-triggered cardiac arrest. We therefore recommend timely use of antipyretics in patients with typical Brugada syndrome ECG changes during fever.

Ahmad S. Amin, MD
Paola G. Meregalli, MD
Abdennaser Bardai, MD
Arthur A.M. Wilde, MD, PhD
Hanno L. Tan, MD, PhD
University of Amsterdam
Amsterdam 1105 AZ, the Netherlands

Acknowledgment: The authors thank Jan M. Ruijter, PhD (Heart Failure Research Center, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands) for providing statistical advice.

Grant Support: Dr. Tan was supported by the Royal Netherlands Academy of Arts and Sciences and the Netherlands Organisation for Scientific Research (NWO, ZonMW-VICI 918.86.616). Dr. Wilde was supported by the Netherlands Heart Foundation (NHS 2003T302). The funding sources had no role in the study.

Potential Financial Conflicts of Interest: None disclosed.

References

A Case of Apical Ballooning Cardiomyopathy Associated with Duloxetine

Background: Catecholamine level surges may be associated with myocardial dysfunction, as observed in cases of septic shock, subarachnoid hemorrhage, respiratory failure, and pheochromocytoma (1, 2). Selective serotonin reuptake inhibitors have catecholaminergic activity but generally little cardiovascular toxicity. Duloxetine, a combined norepinephrine and selective serotonin reuptake inhibitor, has not been reported to have any major cardiovascular toxicity.

Objective: To report a case of transient apical ballooning cardiomyopathy associated with duloxetine use.

Case Report: A 60-year-old Hispanic woman presented with 5 days of dizzy spells and 1 day of chest discomfort. Electrocardiography showed ST-segment elevations and T-wave inversions, and serum troponin I level was 3.0 µg/L (upper limit of normal, 0.059 µg/L). She had seen her physician 10 days earlier for dysuria and was given oral ciprofloxacin for a urinary tract infection. Treatment with duloxetine, 60 mg/d, was initiated by a different physician later that week for diabetic neuropathy. One day after starting duloxetine, she began experiencing dyspnea and lightheadedness and fell down at home several times. She noted left-sided chest discomfort and dia phoresis on her way to the hospital for evaluation after the last fall. She reported no emotional stressors. Urgent coronary angiography revealed normal epicardial coronary arteries. The left ventriculogram (Figure) demonstrated apical ballooning with basal hyperkinesis. Serum catecholamine levels were norepinephrine, 20.64 nmol/L (normal range, 0.41 to 4.43 nmol/L); dopamine, 1358.67 pmol/L (normal range, 0 to 195.84 pmol/L); and epinephrine, 829.77 pmol/L (normal range, 0 to 600.49 pmol/L). Repeated transthoracic echocardiography several weeks later showed normalization of left ventricular function. The patient was given a diagnosis of duloxetine-induced transient apical ballooning cardiomyopathy.

Discussion: Apical ballooning cardiomyopathy, also known as takotsubo cardiomyopathy or stress cardiomyopathy, is a disorder simulating acute myocardial infarction. It most commonly affects women age 60 to 69 years. The disorder often occurs in association with severe emotional or respiratory distress (3). The diagnosis is made by history, electrocardiography, and left ventricular imaging showing apical ballooning (that is, akinesis or dyskinesis with preservation of contractility at the base) when there is no obstructive coronary artery disease on angiography.

Figure. Left ventriculogram showing apical ballooning with basal hyperkinesis.
Postmarketing surveillance studies of duloxetine report no adverse cardiovascular side effects at doses up to 120 mg/d (4). Adverse reactions have been reported when duloxetine is used in combination with other medications metabolized through the cytochrome P450 system (2D6 and 1A2), including elevation in the international normalized ratio with warfarin (5); orthostatic hypotension with ciprofloxacin; and the serotonin syndrome with 5-hydroxytryptamine receptor agonists, such as sumatriptan (6). In this case, the timing, physiology, and improvement after withdrawal of treatment indicate a serious adverse effect related to duloxetine.

We report this case to alert clinicians to the possibility of medication-associated surges in catecholamine levels, leading to transient left ventricular dysfunction.

Conclusion: Duloxetine was a possible cause of transient left ventricular dysfunction in this patient. Drug toxicity should be considered in patients with transient apical ballooning cardiomyopathy, particularly those in which no antecedent physical or emotional stress occurred.

Benjamin R. Bergman, MD
Harmony R. Reynolds, MD
Adam H. Skolnick, MD
Demetrio Castillo, MD
New York University School of Medicine
New York, NY 10016

Potential Financial Conflicts of Interest: None disclosed.

References

**Corrections**

**Correction: Effectiveness of Drugs for Preventing Contrast-Induced Nephropathy**

The recent meta-analysis by Kelly and colleagues (1) contained 3 errors. First, the authors included 26 studies of N-acetylcysteine, not 30 as indicated in the bottom box of Figure 1. Second, reference 9 is incorrect. The correct citation for reference 9 is Solomon R, Werner C, Mann D, D’Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med. 1994;331:1416-20. [PMID: 7969280]. Third, in the Editors’ Notes, the Contribution section should say that the meta-analysis found the strongest evidence for the effectiveness of N-acetylcysteine, and the Implication section should say: “The evidence reviewed is weak, but supports the use of N-acetylcysteine to prevent against contrast-associated nephropathy.”

Reference

**Correction: Reported Methodologic Quality and Discrepancies between Large and Small Randomized Trials in Meta-Analyses**

In 2001, we published a study on methodological quality and estimates of intervention effects (1). The results suggested that those estimates were exaggerated in small trials with inadequate allocation sequence (ratio of odds ratios for large vs. small trials, 0.49 [95% CI, 0.30 to 0.81]), allocation concealment (0.60 [CI, 0.31 to 1.15]), and double blinding (0.56 [CI, 0.33 to 0.98]).

We identified problems with that analysis and reanalyzed the data by using improved logistic regression models that allow for separate control group risks in each trial and separate treatment effects in each meta-analysis (2). Our revised analyses found little evidence of association between treatment effects and inadequate allocation sequence (0.95 [CI, 0.86 to 1.04]) or lack of double-blinding (1.02 [CI, 0.94 to 1.11]). The revised analysis still showed that intervention effect estimates suggested greater benefit in trials that did not have adequate allocation concealment than in those that did (0.90 [CI, 0.82 to 0.99]).

We still believe that the overall conclusions of our previous paper are correct for reasons we detail elsewhere (2). However, we wish to correct the scientific record regarding the preceding results in our original analysis.

Lise L. Kjaergard, MD
John Villumsen, MSc
Christian Gluud, MD, DrMSc
Copenhagen University Hospital, H:S Rigshospitalet
DK-2100 Copenhagen, Denmark

References