Author's response to reviews

**Title:** Intravenous magnesium prevents atrial fibrillation after coronary artery bypass grafting: a meta-analysis of 7 double-blind, placebo-controlled, randomized clinical trials

**Authors:**

Wan-Jie Gu (wanjiegu@yahoo.com.cn)
Zhen-Jie Wu (wuzhenjie523@126.com)
Peng-Fei Wang (uuwpf@163.com)
Lynn Htet Htet Aung (lifeinnivana@gmail.com)
Rui-Xing Yin (yinruixing@yahoo.com.cn)

**Version:** 3  **Date:** 21 February 2012

**Author's response to reviews:** see over
Dear Profs. Doug Altman, Curt Furberg, Jeremy Grimshaw and Peter Rothwell:

Please find attached a revised version of our manuscript “Intravenous magnesium prevents atrial fibrillation after coronary artery bypass grafting: a meta-analysis of 7 double-blind, placebo-controlled, randomized clinical trials (MS: 1597715802611509)”, which we would like to resubmit for publication in Trials.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in Trials.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

Rui-Xing Yin

Feb. 21, 2012
Responses to the comments of Reviewer

Reviewer: jeffrey kluger

Reviewer's report:

Dear Prof. jeffrey kluger:

Thank you for your kind instructive comments and suggestions.

1. Introduction, second paragraph. The authors list a variety of agents previously used to prevent POAF following CABG. They fail; however, to list amiodarone and statins, both which have been extensively studied for this purpose and found to be efficacious. I do not believe that digoxin or CCBs merit mention for prevention in POAF. Finally, the reference provided (#14) for this statement doesn’t seem to match.

Response: In accordance with your insightful suggestion, we have revised this paragraph and changed the reference (#14) into another (14.Ho KM, Lewis JP: Prevention of atrial fibrillation in cardiac surgery: time to consider a multimodality pharmacological approach. Cardiovasc Ther 2010, Spring;28:59-65.).

2. Introduction, paragraph 3. The authors note a previous meta-analysis has been conducted on the topic that included 8 RCTS. Please provide some more detail as to why your meta-analysis is needed, if this one exists? How do your inclusion/exclusion criteria differ? How much overlap in studies exists? You results are nearly identical to those of this 2005 meta-analysis.

Response: We feel really sorry that we do not provide a more complete description of these points in our original manuscript. This 2005 meta-analysis included some clinical studies which had a modest sample size. Moreover, some of these included studies are of low quality. On the base of your deep understanding of meta-analysis, as you know, the quality of a meta-analysis relies upon one of the important factors: the quality of selected studies. Concerning article quality, our meta-analysis is only based on double-blind, placebo-controlled, randomized clinical trials. The Jadad score was ≥ 3 for all the included studies, indicating high quality of the individual studies. We therefore performed this update meta-analysis only based on double-blind, randomized, placebo-controlled clinical trials to re-examine the efficiency of intravenous magnesium in preventing POAF following CABG.
As for the differences of inclusion/exclusion criteria between the two meta-analyses, except for the quality of selected studies, our meta-analysis included was based on placebo-controlled trials enrolling patients undergoing CABG only. We also excluded the studies reporting with pre-existing atrial fibrillation in some patients. Considering your suggestion, we have given a more detailed description of our inclusion/exclusion criteria in the revised manuscript. These two meta-analyses included four same studies (Reference No. 23-26).

3. Introduction, paragraph 3. What is a “registered controlled trial”? Did you mean randomized?

Response: We really appreciate your serious comments. Yes, “registered controlled trial” means “randomized controlled trial”. We have corrected the mistake in the revised manuscript.

4. Introduction, paragraph 3. The authors state “inconsistent and controversial” results have arisen from new studies. Please provide the references here for these studies. Also, reviewing the forest plots from this meta-analysis, I do not see any studies that reported “inconsistent or controversial” results. It appears that all included studies showed a reduction in POAF with IV magnesium (albeit some did not reach statistical significance). This appears to be a gross overstatement of the need for this meta-analysis.

Response: Regarding this point, we have changed the sentence (However, the results of these studies are inconsistent and controversial.) into another (However, the results have contrasted in these randomized controlled trials.) and modified the contents of this part. Not all included studies showed a reduction in POAF with IV magnesium. In these included studies, three of them (Reference No. 23,24,26) reported that intravenous magnesium is effective in reducing the incidence of AF after CABG, but the remaining four (Reference No. 11, 21,22,25) showed the opposite results.

5. Materials and Methods, first paragraph. The authors make no mention of whether valve surgery was allowed in this meta-analysis. Could studies enrolling patients undergoing CABG and valve surgery at the same time be included?
Response: This problem is related to our inclusion/exclusion criteria. It is a mistake that we do not provide a complete description of our inclusion/exclusion criteria in the original manuscript. Considering your suggestion, we have given a more detailed description of our inclusion/exclusion criteria in the revised manuscript. We exclude studies enrolling patients undergoing CABG and valve surgery at the same time.

6. Materials and Methods, first paragraph. Was there an inclusion/exclusion criteria related to follow-up for POAF?

Response: This problem is similar to comment 5, which is related to our inclusion/exclusion criteria. In this meta-analysis, we treat follow-up for POAF as an exclusion criterion. We excluded the studies that the duration of follow-up was not available.

7. Materials and Methods, last paragraph (page 6). The authors say they use the I2 value to assess statistical heterogeneity; however, it appears that throughout the paper a heterogeneity p-value (Cochrane Q?) is reported instead. The I2 is the preferred means of reporting in meta-analyses, and should take the form of a percent value between 0 and 100. Also, what was the threshold value for choosing a random- vs. fixed effect model? Was this value determined a priori?

Response: We feel embarrassed to make these careless, little mistakes in the original manuscript.

Thank you again for your kindly reminders. With respect to your proposal, we have added a reference (No. 19 Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMJ. 2003, 327:557-60. ). As stated in this study, studies with an I^2 statistic of 25 to 50% are considered to have low heterogeneity, those with an I^2 statistic of 50% to 75% are considered to have moderate heterogeneity, and those with an I^2 statistic of > 75% are considered to have a high degree of heterogeneity. There was no heterogeneity between the trials included in our meta-analysis heterogeneity \( P = 0.784; I^2 = 0\% \). We combined the data with a fixed-effects model.

8. Results, page 7. It appears the authors allowed 2 studies that had only one day of follow-up
for AF into the meta-analysis. This seems a questionable decision to me since POAF (as the authors themselves note in the Introduction) most commonly occurs on days 2-3 post-op.

**Response:** It is really true as you said that we allowed 2 studies that had only one day of follow-up for AF into the meta-analysis. We find that the duration of follow-up in the Colquhoun et al. trial is four days instead of one day (sic). We have updated the original manuscript’s incorrect data in tables.

As for the Hamid et al. trial, the follow-up is still postoperative period for 24 hours. Remarkably, the incidences of POAF in magnesium group and placebo group are lower than those of other studies significantly, which can be explained by a short duration of follow-up in this study. In addition, POAF generally occurs between 24 and 96 hours postoperatively, with a peak incidence on the second postoperative day. This may lead to potential underestimation and/or overestimation of the true incidence of POAF and have potential impact on our results. To address this problem, we further conduct a sensitivity analysis excluding this trial to assess the robustness of our results (shown in Table 4).

9. It is very difficult to assess the external validity of these results since the authors do not report any information/data regarding patients risk for POAF (i.e., concomitant valve surgery, co-morbidities such as AF, HF, COPD, etc) or the use of other POAF prevention strategies (beta-blockers (a gold-standard) amiodarone, statins, etc). These need to be added to the tables.

**Response:** It is certainly true as you commented that it is very difficult to assess the external validity of these results since we do not report any information/data regarding patients risk for POAF. These are important factors that may have significant impact on occurrence of postoperative atrial fibrillation. These variables should be assessed and compared in both groups prior to reaching to conclusion. Considering your suggestion, we have added perioperative variables of patients (Table 3) to the section of Results. Analysis of pooled prevalence of preoperative patient group characteristics revealed that no differences were observed for history of coexistence of basic diseases (eg, diabetes mellitus, hypertension), routine prophylactic therapies (eg, β-blocker). Unfortunately, because of sparse or even not reported across trials, we were unable to assess the impact of other variations in the use of routine prophylactic therapies (eg, amiodarone, statins, etc.), coexistence of basic diseases (eg,
heart failure, COPD, etc.), and other confounding factors on our results.

10. The authors use Begg’s test to assess for publication bias. Begg’s will not give a robust result unless a minimum of 15-20 studies are included in a meta-analysis. I suggest removing it from the paper, using Egger’s only.

**Response:** As you say, Begg’s test is fairly powerful for large meta-analyses with 75 component studies, but has only moderate power for meta-analyses with 25 component studies. However, in many of the configurations in which there is low power, there is also relatively little bias in the summary effect size estimate. Nonetheless, the test must be interpreted with caution in small meta-analyses (sic). Considering your suggestion, we have removed it from the revised manuscript, using Egger’s only.

11. Discussion section, first sentence. The author state that theirs is the second meta-analysis evaluating the effect of magnesium on POAF. However, a quick search of MEDLINE shows that at least 4 other meta-analyses (not including the one identified by the authors) have been published. This includes Henyan et al., Ann ThoracSurg 2005;2414-6; Burgess et al., Eur Heart J 2006;27:2846-57; and a Health Technology Assessment by Shepard and colleagues in 2008. Each gives appreciably the same result as this new meta-analysis (~30-40% reduction in POAF).

**Response:** It is still a mistake in our original manuscript and we have corrected it in the revised manuscript.

**Reviewer:** Colin Berry

**Reviewer's report:**

Dear Prof. Colin Berry:

Thank you for your kind instructive comments and suggestions.

**Major comments**

The authors should add more to the discussion about the clinical relevance of their results. Do their results support magnesium for treatment of post-operative AF (yes); how is magnesium given in clinical practice; how will their results help move clinical practice forward (change in clinical guidelines, physician preference to improve, etc)
**Response:** Thank you for your highly insightful comments. For more than a decade, an increasing number of studies on the efficacy of intravenous magnesium on the prevention of POAF have been published. They included clinical trials, reviews, and meta-analyses and most of them reported that intravenous magnesium therapy was associated with a different degree of reduction in the incidence of POAF. In the meantime, there were also a small number of studies showed that magnesium had no effect on the incidence of POAF, even increased the incidence of POAF. Currently, magnesium is a novel preventive measure with limited experience in clinical practice. Our meta-analysis indicates that intravenous magnesium significantly reduces the incidence of POAF after CABG. This finding encourages the use of intravenous magnesium as an alternative to prevent POAF after CABG. In addition, in the Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010, intravenous magnesium was considered as conditional recommendation and moderate-quality evidence for prophylactic therapy to prevent POAF when patients who have a contraindication to blocker therapy and to amiodarone therapy before or after cardiac surgery.

**Minor comments**
Page 4, last line ~ "monitor" should change to "monitoring"

**Response:** We have corrected it in the revised manuscript.

Page 4, What do the authors mean by "under-ten-patient studies" ie sample size with less than 10 patients?

**Response:** Yes, "under-ten-patient studies" means sample size with less than 10 patients. We have corrected it in the revised manuscript.

The abbreviation 'CABGS' should change to 'CABG'

**Response:** We have corrected it in the revised manuscript.

Page 10 - change 'We admitted that' to 'We accept that our meta-analysis included some clinical studies which had a modest sample size
Response: We have corrected it in the revised manuscript.

Associate Editor comments:
"Please report p values to one significant figure e.g. p=0.8 rather than p=0.784"

Response: Yes, We have corrected them in the revised manuscript.

Thank you very much!

Sincerely yours,
Rui-Xing Yin
Intravenous magnesium prevents atrial fibrillation after coronary artery bypass grafting: a meta-analysis of 7 double-blind, placebo-controlled, randomized clinical trials

Wan-Jie Gu¹, Zhen-Jie Wu², Peng-Fei Wang³, Lynn Htet Htet Aung¹, Rui-Xing Yin¹*

¹Department of Cardiology, Institute of Cardiovascular Diseases, the First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, People’s Republic of China.

²Department of Colorectal and Anal Surgery, the First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, People’s Republic of China.

³Department of Orthopaedics, China-Japan Union Hospital, Jilin University, Changchun, Jilin, People’s Republic of China.

Email: WJG - wanjiegu@yahoo.com.cn; ZJW - wuzhenjie523@126.com; PFW - uuwpf@163.com; LHHA - lifeinnivana@gmail.com; RXY - yinruixing@yahoo.com.cn

* Corresponding author

¹ Department of Cardiology, Institute of Cardiovascular Diseases, the First Affiliated Hospital, Guangxi Medical University, 22 Shuangyong Road, Nanning 530021, Guangxi, People’s Republic of China
Abstract

**Background:** Postoperative atrial fibrillation (POAF) is the most common complication after coronary artery bypass grafting (CABG). The preventive effect of magnesium on POAF is not well known. This meta-analysis was undertaken to assess the efficacy of intravenous magnesium on the prevention of POAF after CABG.

**Methods:** Eligible studies were identified from electronic databases (Medline, Embase, and the Cochrane Library). The primary outcome measure was the incidence of POAF. The meta-analysis was performed with the fixed-effect model or random-effect model according to heterogeneity.

**Results:** Seven double-blind, placebo-controlled, randomized clinical trials met the inclusion criteria including 1,028 participants. The pooled results showed that intravenous magnesium reduced the incidence of POAF by 36% [RR 0.64; 95% confidence interval (CI) 0.50-0.83; \( P = 0.001 \); with no heterogeneity between trials (heterogeneity \( P = 0.8, I^2 = 0\% \)).

**Conclusions:** This meta-analysis indicates that intravenous magnesium significantly reduces the incidence of POAF after CABG. This finding encourages the use of intravenous magnesium as an alternative to prevent POAF after CABG. But more high-quality randomized clinical trials are still need to confirm the safety.
Introduction

Postoperative atrial fibrillation (POAF) is the most common complication encountered following coronary artery bypass grafting (CABG). It generally occurs between 24 and 96 hours postoperatively, with a peak incidence on the second postoperative day [1-3]. With continuous electrocardiographic monitoring, the incidence of atrial fibrillation after CABG reported in previous studies varies from 10% to 50% [1,2,4], and this incidence has not decreased despite improvements in anesthetic and surgical techniques [5,6]. Furthermore, atrial fibrillation potentially leads to complications, including stroke [7-9], extended duration of hospitalization [7-10], and increasing costs [1,9,10].

The etiology of atrial fibrillation after CABG is unclear. The cause may be multifactorial, such as advanced age, previous history of atrial fibrillation, and low blood magnesium concentrations [11-13]. There are many pharmacologic agents to prevent POAF, but none of them are effective for all patients and are free of complications [14]. Particularly, magnesium seems to be with great promise to prevent POAF following CABG.

A previous meta-analysis of magnesium for prevention of atrial fibrillation after CABG including 8 randomized controlled trials has been published in 2005 [15]. The analysis showed that intravenous magnesium is associated with a significant reduction in the incidence of atrial fibrillation after CABG, with a relative risk of 0.64 [95% confidence interval (CI) 0.47-0.87]. But this meta-analysis included some clinical studies which had a modest sample size. Moreover, some of these included studies are of low quality. Recently, an increasing number of studies on the efficacy of intravenous magnesium on the prevention of POAF have been published. These studies have contrasted in these randomized controlled trials. Therefore,
we performed an updated meta-analysis only based on double-blind, placebo-controlled, randomized clinical trials to re-examine the effects of intravenous magnesium on the prevention of POAF after CABG.

Materials and Methods

Search strategy and selection criteria

Two investigators (Wan-Jie Gu and Zhen-Jie Wu) independently searched the literatures collected in Medline, Embase, and the Cochrane Library up to August 1, 2011. Search terms included: magnesium, fibrillation. The searches were limited to English publications in humans. We screened the reference lists of included studies and related publications. The results were then hand searched for eligible trials. We did not include abstracts or meeting’s proceedings. This search strategy was performed iteratively until no new potential citations could be found on review of the reference lists of retrieved articles.

We included full-text publications when the following inclusion criteria were met: adult patients undergoing CABG only; randomized allocation to magnesium group or control group (only placebo); double-blind, placebo-controlled, randomized clinical trial; and providing available data on the incidence of POAF. Exclusion criteria included a) the duration of follow-up was not available; b) some patients were reported with pre-existing atrial fibrillation. The trials with small sample size of \( n < 10 \) were also excluded to avoid selection bias.

Data extraction and quality assessment
Two investigators (Wan-Jie Gu and Zhen-Jie Wu) independently extracted the following information from each study: the first author’s name, year of publication, country origin, participants characteristic, study design (randomized), type of controls (placebo), data collection (prospective or not), sampling method (consecutive or not), type of blinding (double blind), duration of follow-up, regimen of magnesium administration, the timing of magnesium infusion was initiated (preoperative, intraoperative or postoperative), number, mean age and percentage male in each trial, total number of individuals and the incidence of POAF in each group. When the same population was reported in several publications, we retained only the most informative article, or completed study to avoid duplication of information. Any disagreements were resolved through discussion and consensus.

The methodological quality of the studies included in the meta-analysis was scored using validated Jadad 5 point scale. The scale consists of three items describing randomization (0–2 points), double-blind (0–2 points), and dropouts and withdrawals (0–1 points) in the report of a randomized-controlled trial. One point was given when one quality criterion was met. The quality scale ranges from 0 to 5 points. Higher scores indicate better reporting. The studies are said to be of low quality if the Jadad score is \( \leq 2 \) and high quality if the score is \( \geq 3 \) [16,17].

**Statistical analysis**

Data were analyzed using Stata version 11 (Stata Corporation, College Station, TX, USA). A statistical test with a \( P \)-value less than 0.05 was considered significant. The incidence of POAF was treated as dichotomous variables and was expressed as risk ratio (RR) with 95% CI for each study. Pooled estimates of efficacy were calculated using the Man-tel-Haenszel
fixed-effects model [18]. But if there was heterogeneity, the following methods were used to deal with it: (a) subgroup analysis; (b) sensitivity analysis performed by excluding the trials which potentially biased the results. If the heterogeneity still potentially existed, the DerSimonian and Lair random-effects model was used. A test for heterogeneity, defined as variation among the results of individual trials for a given treatment beyond that expected from chance, was used to assess whether the magnitude of a given preventive effect varied between the trials. We assessed heterogeneity with $I^2$, which describes the percentage of total variation across studies due to heterogeneity rather than chance. $I^2$ can be calculated as: $I^2 = 100\% \times (Q - df)/Q (Q =$ Cochrane’s heterogeneity statistics, df = degrees of freedom). Negative values of $I^2$ equaled zero, so that $I^2$ ranged between 0% (ie, no observed heterogeneity) and 100%. High values would show increasing heterogeneity. Studies with an $I^2$ statistic of 25% to 50% are considered to have low heterogeneity, those with an $I^2$ statistic of 50% to 75% are considered to have moderate heterogeneity, and those with an $I^2$ statistic of > 75% are considered to have a high degree of heterogeneity [19]. The presence of publication bias was evaluated by using the Egger test [20].

Results

Seven double-blind, placebo-controlled, randomized clinical trials consisting of 1,028 individuals were included in this study. Four of the 8 randomized controlled trials published by Alghamdi et al. [15] were also included and the remaining four trials were excluded because they were non-double-blind. Three eligible studies were published after 2003. The flow of identified studies through the selection process is shown in Figure 1.
Description of eligible trials

The efficacy of intravenous magnesium with placebo on the prevention of POAF was compared in these trials. The baseline characteristics of included studies are shown in Table 1 and the design characteristics are presented in Table 2. Of the seven trials, two were done in the USA, one in UK, one in Turkey, one in Switzerland, one in Iran and one in Pakistan. The number of participants ranged from 50 to 345. All trials included both men and women. The total dosage of intravenous magnesium in the intervention groups ranged from 8 mmol to 100 mmol (one trial [21] is not available). The follow-up time ranged from 1 day to 5 days (one trial [11] is followed up until atrial fibrillation developed and needed therapeutic intervention). All trials reported perioperative prophylactic use of intravenous magnesium: one trial [21] initiated during preoperative period, 2 trials [11,22] during intraoperative period, 4 trials [23-26] during postoperative period.

Quality assessment of the trials

The trials included in this meta-analysis appeared to have been reasonably designed and conducted. All studies had a statement regarding randomization and double-blind. Four trials described the methods of randomization. Four trials reported the withdrawals or dropouts. All trials described the main outcome, and no missing data seemed to influence the results. The quality of the included studies was assessed by the Jadad score. The median Jadad score of the studies included was 4 (range from 3 to 5, Table 2).
The incidence of POAF

Analysis of pooled prevalence of preoperative patient group characteristics revealed that no differences were observed for history of coexistence of basic diseases (eg, diabetes mellitus, hypertension), routine prophylactic therapies (eg, β-blocker; Table 3).

Pooling all seven trials, of 511 patients in the pooled intervention (intravenous magnesium) group, 76 developed POAF, compared to 116 out of 517 patients in the pooled control group. The pooled analysis showed that intravenous magnesium significantly reduced the incidence of POAF by 36% (RR 0.64; 95% CI 0.50-0.83; P = 0.001; Figure 2), with no heterogeneity between trials ((heterogeneity P = 0.8; I^2 = 0%).

Subgroup analyses were done according to data collection, sampling method and the duration of follow-up. Pooled results of five prospective trials [11,21,23,24,26] showed intravenous magnesium significantly reduced the incidence of POAF by 37% (RR 0.63, 95% CI 0.48–0.83; P = 0.001; heterogeneity P = 0.7, I^2 = 0%). Pooled results of four consecutive patients trials [11,23,24,26] showed that intravenous magnesium significantly reduced the incidence of POAF by 44% (RR 0.56, 95% CI 0.37–0.83; P = 0.005; heterogeneity P = 0.7, I^2 = 0%). Exclusion of the Hamid et al. trial [22] in which the duration of follow-up is just one day yielded similar results (RR 0.66, 95% CI 0.51-0.85; P = 0.002; heterogeneity P = 0.8; I^2 = 0%). The summary of subgroup analyses results is shown in Table 4.

Publication bias

Assessment of publication bias using Egger’s test showed that moderate publication bias existed among the included trials (Egger’s test: P = 0.045; Figure 3).
Discussion

This is a further meta-analysis to evaluate the relationship between intravenous magnesium and POAF. All trials included in this analysis are double-blind, placebo-controlled, randomized clinical trials. The data can give greater power to assess the efficacy of intravenous magnesium on the prevention of atrial fibrillation after CABG. We combined the effect sizes of all seven included trials that used intravenous magnesium for preventing POAF through a fixed-effects model and found that intravenous magnesium significantly reduced the incidence of POAF by 36%. A meta-analysis of data collected before December 2003 [15] found a cumulative RR of 0.64 (95% CI: 0.47–0.87) for the randomized controlled trials. Our findings are consistent with this previous meta-analysis.

This meta-analysis shows diversity in the dosing, timing and duration of magnesium administration. The diversity accounts for the inconsistency in the reported outcomes of the included trials as listed in Table 1. In three [23,24,26] of the prospectively controlled clinical trials [11,21,23,24,26], intravenous magnesium significantly reduced the incidence of POAF after CABG. In three trials, magnesium was dosed for at least 2 consecutive days postoperatively. Given that the onset of POAF following CABG generally occurs between 24 and 96 hours postoperatively, with a peak incidence on the second postoperative day and that it is often associated with hypomagnesaemia, intravenous magnesium supplementation during this period may play a key role in the suppression of POAF.

Demographic bias owing to generating the sequence of randomization inadequately may be another reason for the discordance in the reported results of magnesium prophylaxis. The
biased variable, if it happens to be a powerful predictor of POAF, would apparently have a strong influence on the outcome of the study. For example, one trial [22] showed that prophylactic magnesium supplementation does not significantly reduce the incidence of POAF, patients in the magnesium group had a higher ratio of male gender (98% versus 86%, \( P = 0.02 \)). This characteristic, male gender has been consistently a risk factor for the development of POAF.

Up to now, various preventive methods including pharmacologic and nonpharmacologic interventions have been proposed in the preventive strategy of POAF. Current evidences from meta-analyses [27-29] suggest that beta-blockers are effective and safe for most patients and advise that clinicians should not discontinue beta-blockers before cardiac surgery, unless contraindicated. Amiodarone can be safely added in patients at high-risk for atrial fibrillation. In a recent meta-analysis, however, Patel et al. [30] found that amiodarone increases the risk of bradycardia and hypotension, particularly when administered intravenously. Meta-analyses of the clinical trials [8,29,31] investigating the effect of prophylactic pacing have consistently suggested that single- or dual-site atrial pacing significantly reduces the incidence of POAF; however, it is limited in practical use because of its complexity. Furthermore, there are some other pharmaceuticals such as statins [32,33], N-3 polyunsaturated fatty acids [34], and anti-inflammatory agents [35,36] being used to prevent POAF following CABG. However, the number of enrolled patients in these trails was small, and the pharmaceutical doses and administration times varied widely among studies. Thus, further studies are still necessary before confirmed conclusion. In a prospective, randomized, double-blind, placebo-controlled study, Cagli and his partners [37] have concluded that low-dose amiodarone and magnesium
combination is an effective, simple, well-tolerated, and possibly cost-effective regimen to prevent atrial fibrillation after CABG for high-risk patients. Perhaps appropriate combinations of these pharmacologic and nonpharmacologic interventions might be of benefit for further reducing POAF. In this meta-analysis, the patient population enrolled was quite homogeneous in its presentation. The studies included are of high quality, and all of the 7 studies are double-blind, placebo-controlled, randomized trials having a Jadad score of $\geq 3$. We combined all the studies using a fixed-effects mode and tested heterogeneity between trials with $I^2 (0.0\%)$ and with $P$ value (0.8), indicating no heterogeneity.

Several potential limitations of this meta-analysis merit consideration. First, we accept that our meta-analysis included some clinical studies which had a modest sample size. Although we aimed to retrieve additional data from investigators, it was inevitable that some missing and unpublished data may still exist. Second, the exclusion of non-English-language studies and under-ten-patients studies may lead to bias in effect size. In addition, follow-up time varied among included studies, and different total dose of intravenous magnesium was adopted in these studies. The discrepancy may explain clinical heterogeneity among studies, although no statistical heterogeneity is found.

**Conclusion**

This meta-analysis of all seven double-blind, placebo-controlled, randomized clinical trials shows that intravenous magnesium significantly reduced the incidence of POAF after CABG by 36%. Pooled analysis of five prospective trials shows intravenous magnesium significantly reduced the incidence of POAF by 37%, and pooled analysis of four consecutive patients
trials shows that intravenous magnesium significantly reduced the incidence of POAF by 44%. This finding encourages the use of intravenous magnesium as an alternative to prevent POAF after CABG. But more high-quality randomized clinical trials are still need to confirm the safety.

Author details

1Department of Cardiology, Institute of Cardiovascular Diseases, the First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, People’s Republic of China. 2Department of Colorectal and Anal Surgery, the First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, People’s Republic of China. 3Department of Orthopedic Surgery, the First Affiliated Hospital, Xinxiang Medical University, Xinxiang, Henan, People’s Republic of China.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

WJG conceived the study, participated in the design, collected the data, and drafted the manuscript. ZJW collected the data, and performed statistical analyses. PFW and LHHA helped to collect the data. RXY conceived the study, participated in the design, and helped to draft the manuscript. All authors read and approved the final manuscript.
Acknowledgments

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Figure 1 Process of study selection of double-blind, placebo-controlled, randomized trials.

Figure 2 All included studies, RR (fixed effect model).

Figure 3 Tests for publication bias for RR of the incidence of POAF.
<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Regimen of Magnesium Administration*</th>
<th>Control regimen (Route)</th>
<th>Total Dose Mg²⁺ (mmol)</th>
<th>Magnesium Age(years) n (male, %)</th>
<th>Controls Age(years) n (male, %)</th>
<th>POAF Magnesium (%) Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanning et al.[23]</td>
<td>99</td>
<td>168 mEq over the first 4 postoperative days</td>
<td>5% dextrose solution (IV)</td>
<td>84 mmol</td>
<td>59(43-75) 49(71.4) 62(42-79) 50(78)</td>
<td>7/49(14.3) 14/50(28)</td>
<td></td>
</tr>
<tr>
<td>Colquhoun et al.[24]</td>
<td>130</td>
<td>50 mmol during the first 48 h after surgery</td>
<td>5% dextrose solution (IV)</td>
<td>50 mmol</td>
<td>57.1 ± 8.4 66(83.3) 58.7±7.9 64(79.7)</td>
<td>11/66(16.7) 15/64(23.4)</td>
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<tr>
<td>Nurozler et al.[26]</td>
<td>50</td>
<td>100 mEq on the first operative day and 25 mEq per day from second to fifth days</td>
<td>Placebo (IV)</td>
<td>100 mmol</td>
<td>56.3 ± 1.6 25(92) 53.6±2.0 25(92)</td>
<td>1/25(4) 5/25(20)</td>
<td></td>
</tr>
<tr>
<td>Treggiari-Venzi et al.[25]</td>
<td>98</td>
<td>4 g per 24 h continuous infusion for 72 h starting within 1 h of arrival in the ICU</td>
<td>0.9% NaCl solution (IV)</td>
<td>48 mmol</td>
<td>65(46-81) 47(89.4) 65(37-88) 51(84.3)</td>
<td>11/47(23) 14/51(27)</td>
<td></td>
</tr>
<tr>
<td>Hazelrigg et al.[21]</td>
<td>202</td>
<td>80 mg/kg (ideal body weight) before cardiopulmonary bypass (CPB), 8 mg/kg/h (ideal body weight) intravenous (IV) infusion continued for 48 hours</td>
<td>5% dextrose solution (IV)</td>
<td>NA</td>
<td>62.1 ± 9.5 105(74) 63.7±11.1 97(68)</td>
<td>32/105(30.5) 41/97(42.3)</td>
<td></td>
</tr>
<tr>
<td>Najafi et al.[11]</td>
<td>345</td>
<td>2 g after induction of anesthesia until the start of cardio-pulmonary bypass (CPB) and 8 g after CABG until 24 h after surgery</td>
<td>Placebo (IV)</td>
<td>40 mmol</td>
<td>59.1(9.1) 166(75.9) 59.7(9.9) 179(76.5)</td>
<td>12/166(7.2) 22/179(12.3)</td>
<td></td>
</tr>
<tr>
<td>Hamid et al.[22]</td>
<td>104</td>
<td>2 g after intubation</td>
<td>0.9% NaCl solution (IV)</td>
<td>8 mmol</td>
<td>58.3 ± 7.6 53(98) 56.3±8.9 51(86)</td>
<td>2/53(3.77) 5/51(9.8)</td>
<td></td>
</tr>
</tbody>
</table>

*To convert units of g and mEq to mmol, the following conversions were used: 1 g = 4 mmol = 8 mEq for MgSO₄. IV: intravenous; NA: data not available; POAF: postoperative atrial fibrillation; ICU: intensive care unit; CPB: cardiopulmonary bypass; CABG: coronary artery bypass grafting; n: number of participants
### Table 2 Included studies design characteristics

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication year</th>
<th>Country</th>
<th>Study design</th>
<th>Data collection</th>
<th>Sampling method</th>
<th>Blind</th>
<th>Follow-up (Days)</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanning et al.[23]</td>
<td>1991</td>
<td>USA</td>
<td>randomized, placebo-controlled</td>
<td>prospective</td>
<td>consecutive</td>
<td>DB</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Colquhoun et al.[24]</td>
<td>1993</td>
<td>UK</td>
<td>randomized, placebo-controlled</td>
<td>prospective</td>
<td>consecutive</td>
<td>DB</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Nurozler et al.[26]</td>
<td>1996</td>
<td>Turkey</td>
<td>randomized, placebo-controlled</td>
<td>prospective</td>
<td>consecutive</td>
<td>DB</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Treggiari-Venzi et al.[25]</td>
<td>2000</td>
<td>Switzerland</td>
<td>randomized, placebo-controlled</td>
<td>NA</td>
<td>NA</td>
<td>DB</td>
<td>until AF developed and needed therapeutic intervention</td>
<td>5</td>
</tr>
<tr>
<td>Hazellrigg et al.[21]</td>
<td>2004</td>
<td>USA</td>
<td>randomized, placebo-controlled</td>
<td>prospective</td>
<td>NA</td>
<td>DB</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Najafi et al.[11]</td>
<td>2007</td>
<td>Iran</td>
<td>randomized, placebo-controlled</td>
<td>prospective</td>
<td>consecutive</td>
<td>DB</td>
<td>until AF developed and needed therapeutic intervention</td>
<td>4</td>
</tr>
<tr>
<td>Hamid et al.[22]</td>
<td>2008</td>
<td>Pakistan</td>
<td>randomized, placebo-controlled</td>
<td>NA</td>
<td>NA</td>
<td>DB</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

NA: data not available; DB: double-blind; AF: atrial fibrillation
### Table 3 Perioperative variables of the patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Magnesium [% (n)]</th>
<th>Control [% (n)]</th>
<th>$\chi^2$ value</th>
<th>$P$ value</th>
<th>Total prevalence [% (n)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus [11,24-26]</td>
<td>22.4 (68/304)</td>
<td>21.9 (70/319)</td>
<td>0.016</td>
<td>0.9</td>
<td>22.2 (138/623)</td>
</tr>
<tr>
<td>Hypertension [24-26]</td>
<td>31.2 (43/138)</td>
<td>27.1 (38/140)</td>
<td>0.543</td>
<td>0.5</td>
<td>29.1 (81/278)</td>
</tr>
<tr>
<td>$\beta$-blocker [21-25]</td>
<td>45.6 (146/320)</td>
<td>48.6 (152/313)</td>
<td>0.548</td>
<td>0.5</td>
<td>47.1 (298/633)</td>
</tr>
</tbody>
</table>

### Table 4 The summary of subgroup analyses results

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>n of studies</th>
<th>n of participants</th>
<th>RR (95% CI)</th>
<th>$I^2$ (%)</th>
<th>$P$ heterogeneity</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective</td>
<td>5</td>
<td>826</td>
<td>0.63 (0.48-0.83)</td>
<td>0.00</td>
<td>0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Consecutive</td>
<td>4</td>
<td>624</td>
<td>0.56 (0.37-0.83)</td>
<td>0.00</td>
<td>0.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Follow-up</td>
<td>6</td>
<td>924</td>
<td>0.66 (0.51-0.85)</td>
<td>0.00</td>
<td>0.8</td>
<td>0.002</td>
</tr>
</tbody>
</table>

N: number of studies; RR: risk ratio; CI: confidence interval