Author’s response to reviews

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Efficacy of N-acetylcysteine in preventing atrial fibrillation after cardiac surgery: a meta-analysis of published randomized controlled trials

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Keywords: N-acetylcysteine; postoperative atrial fibrillation; cardiac surgery; meta-analysis

Abstract
BACKGROUND: Atrial fibrillation is the most common complication after cardiac surgery. The aim of this study is to evaluate the effect of N-acetylcysteine on the prevention of postoperative atrial fibrillation (POAF).
METHODS: PubMed, Embase and Cochrane Center Register of Controlled Trials were searched from the date of their inception to 1 July 2013 for relevant studies. Eligible studies were of randomized controlled trials, reporting use of N-acetylcysteine in the prevention of POAF.
RESULTS: Ten randomized controlled trials were included in the present meta-analysis. Prophylactic N-acetylcysteine effectively reduced the incidence of POAF (OR 0.56; 95% CI 0.40 to 0.77; P=0.0005) and all-cause mortality (OR 0.40; 95% CI 0.17 to 0.93; P=0.03), while it failed to show significant beneficial effects on intensive care unit and hospital length of stay and cerebrovascular accident.
CONCLUSIONS: This meta-analysis supports the prophylactic use of N-acetylcysteine to reduce the incidence of POAF and all-cause mortality. However, adequately powered randomized controlled trials evaluating these and other postoperative complications with or without routine prophylaxis are needed.
Background
Atrial fibrillation (AF) is the most common complication that occurs after cardiac surgery. The incidence of postoperative atrial fibrillation (POAF) ranges from 10% to 65% depending on the type of surgery, perioperative characteristics, methods of monitoring and the definition of AF [1,2]. Previous studies [2-7] indicated that this complication was associated with prolonged length of hospital stay, risk of stroke, mortality and increased hospital costs, thus extensive research has been conducted to explore the mechanism of POAF and identify the effective method for preventing POAF. Of the many prophylactic agents, beta-blockers and amiodarone are used widely and recommended by current guidelines [8]. However, their use requires caution because of potential drug-related side effects. At present, clinical trials suggest that oxidative stress and inflammatory reaction may play a major role in the pathophysiology of POAF because of high inflammatory cytokines level and oxidative damage are significant in patients developing POAF when compared with patients who do not [9-11].

N-acetylcysteine (NAC) is well known as a novel antioxidant and anti-inflammatory agent, which can reduce cellular oxidative damage and systematic inflammation during cardiac surgery [12,13]. Previous meta-analyses showed that the NAC supplementation effectively reduced the incidence of POAF [14,15]. However, half of these trials with a small sample size (n<60), and only one study showed a positive result [12] and considered POAF as a primary endpoint [12], respectively. Recently, a published trial, the largest sample size of this kind, demonstrated that there was no statistical difference when compared with control group [16]. Thus, we conducted an updated meta-analysis including these trials to further elevate the efficacy of NAC on the prevention of POAF for adult patients undergoing cardiac surgery. Besides, the effects of NAC on hospital and intensive care unit (ICU) stay, all-cause mortality, and cerebrovascular event were also assessed in the present meta-analysis.

Methods
Literature search
Using the PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) database, a comprehensive literature search was performed to identify all published randomized controlled trials (RCTs) of NAC versus controls during heart surgery. Searched terms including N-acetylcysteine, acetylcysteine, acetadote, mucomyst and heart surgery, cardiac surgery, cardiothoracic surgery, cardiopulmonary bypass, CPB, coronary artery bypass graft, CABG, valve surgery, valvular surgery and atrial fibrillation. To maximize the sensitivity, no year and language limitation were imposed. The last time for this search was 1 July 2013.

Inclusion and exclusion criteria
Only RCTs reporting the use of NAC in the prevention of POAF were included in the meta-analysis (including those reporting the concomitant use of other anti-arrhythmic agents). Studies were excluded from this review if: (1) duplicated data; (2) laboratory study; (3) abstract, review or letter to editor; and (4) patient age less than 18. Based on these criteria, two investigators (Liu and Xu) independently selected studies for further screening by reading title and/or abstract of all identified literatures. All potential eligible studies were retrieved in full for further assessment.

Data extraction
Two investigators (Liu and Xu) independently extracted all data with a standardized data-abstraction tool. Disagreements were resolved through discussion and consensus. The following information was sought from each article: first author’s name, year of publication, country of origin, surgery type, perioperative characteristics, NAC protocol, incidence of POAF, length of ICU and hospital stay, all-cause mortality and cerebrovascular accident in each trial. The primary outcome was the incidence of POAF. The length of hospital and ICU stay, mortality and incidence of cerebrovascular accident were considered as the secondary outcomes.

Quality assessment
The methodological quality of the studies included in the meta-analysis was assessed using validated Jadad 5 point scale [17]. This evaluation system places emphasis on the following three main parts when defining the quality of a RCT: (1) randomization; (2) blinding; and (3) description of withdrawals and dropouts. A score of one is given for each of the points described. A further point is obtained where the method of randomization and/or blinding is given and is appropriate; where it is inappropriate, a point is deducted. The studies are considered to be of low quality if the Jadad score is 2 or less and of high quality if the score is 3 or more.

Statistical analysis
The incidences of POAF, all-cause mortality and cerebrovascular accident were treated as dichotomous variables and expressed as odds ratios (ORs) with 95% confidence intervals (CIs) for each trial. ICU and hospital length of stay were treated as continuous variables. For comparing the treatment effect of ICU and hospital length of stay, the weighted mean difference (WMD) with 95% CI was calculated. Inter-study heterogeneity was explored using $I^2$, which describes the percentage of total variation across trials due to heterogeneity rather than chance alone. When $I^2$ was exceeding 50%, the heterogeneity of studies was considered to be present [18]. If the heterogeneity of included studies was significant, a pooled effect was calculated with a random-effects model. Otherwise, a Mantel-Haenszel fixed-effects model was used to derive the pooled effects. Sensitivity analyses were conducted to test the robustness
of pooled effect of included studies. The presence of publication bias was evaluated by using funnel plot. A two-tailed P-value < 0.05 was considered as significant difference. All statistical analyses were performed using Review Manager version 5.2.

Results
Identification of eligible studies
One hundred and fifteen records were identified by the initial literature search. However, after screening the title and/or abstract, ninety reports were excluded because they were either laboratory study, review, letter, duplication data, or irrelevant to the meta-analysis. Therefore, 25 potentially relevant studies were retrieved for further review by reading full texts. Fifteen studies were further excluded because they did not evaluate POAF as an outcome. Consequently, the remaining 10 trials were included for the present meta-analysis (Figure 1).

Characteristics of eligible studies
Patient characteristics of included studies are shown in Table 1. The sample size of studies range from 20 [19,20] to 240 [16] patients, for a total of 1 026 included patients. Of the 10 included RCTs, half of the trials were conducted in Turkey [12,19-22], two in Canada [23,24], and the rest of them in Iran [16], Germany [25] and Korea [26], respectively. With the use of Jadad 5 point score, all of the studies were classified as high quality. Patients in Male and female were included in all trials. All studies except one [25] included patients with a prior history of AF. Diabetic mellitus, hypertension, chronic heart failure, myocardial infraction and angina pectoris were the major concomitant diseases in patients. Half of included trials [19,20,22,24,26] including a total of 228 patients undergoing CABG alone, while the patients in the rest of studies [12,16,21,23,25] undergoing valve surgery or combination valve surgery and CABG. NAC was administered by intravenous and/or oral with different regimens, and the specific NAC regimens of trials are showed in Table 1. Of these studies, oral-NAC was used in two trials[16,24], one used throughout the entire duration of NAC supplementation, the other used only before surgery. The duration of NAC administration after CPB varied from 4 hours [23] to 72 hours [16]. Only one study [21] investigated the efficacy of NAC on the prevention of POAF on the basis of beta-blocker (carvedilol).

Primary analyses
Incidence of POAF
The data of outcomes of included studies are showed in Table 2, and the method of monitoring and definition of POAF are presented in Tabled 3. Of these trials, only 3 studies considered POAF as their primary endpoint. Pooling all included trials, 20.5% (105 of 513) given NAC and 28.8% (148/513) of controls developed POAF. The pooled effect of ten trials was
conducted using a fixed-effects model, no heterogeneity of inter-study was observed ($I^2=15\%$, $P=0.31$). The overall effect estimate was an OR of 0.56 (95% CI 0.40 to 0.77; $P=0.0005$), showing that NAC significantly reduced the incidence of POAF compared with control groups (Figure 2).

Sensitivity analyses were conducted to test the robustness of the pooled effect. Given the sample size of four studies less than 60, a pooled effect was assessed excluding these small size trials. The pooled result was still in favor of prophylactic NAC with an OR of 0.57 (95% CI 0.40 to 0.80; $P=0.001$), and no significant heterogeneity was showed ($I^2=42\%$, $P=0.12$). Despite a trial [25] enrolled several patients with a prior AF, the pooled outcome did not change obviously without the trial (OR 0.50; 95% CI 0.35 to 0.71; $P<0.0001$; $I^2=0\%$, $P_{\text{heterogeneity}}=0.56$), too. In addition, we tested whether different duration of NAC supplementation after CPB would alter the direction of the overall result. Using the fixed-effects model, the meta-analysis outcome (OR 0.64; 95% CI 0.39 to 1.06; $P=0.09$) of trials [19,23,24,26] with a short-term (within 24h after surgery) NAC supplementation contradicted in the overall effect, with no statistical heterogeneity between the trials ($I^2=0\%$; $P=0.7$). However, the meta-analysis of studies [12,16,21,22,25] with a long-term (lasting for 48h-72h after operation) presented an encouraging results (OR 0.40; 95% CI 0.25 to 0.65; $P=0.0003$; $I^2=22\%$, $P_{\text{heterogeneity}}=0.28$).

**Length of ICU stay**

A total of 5 studies [16,20,23,25,26] reported the data of ICU length of stay, while only three [16,20,26] studies reported the values as mean ± standard deviation. All the data were converted from days into hours for analysis. Prophylactic NAC was not associated with a significant reduction in ICU length of stay (WMD 0.60; 95% CI -0.97 to 2.16; $P=0.45$). No heterogeneity of included studies was noted ($I^2=0\%$; $P=0.64$).

**Hospital length of stay**

Half [12,16,20,24,26] of the included studies reported values as mean ± standard deviation, two [23,25] expressed data as median and interquartile range, one [21] showed values by bar graph, and the data of rest of trials were not available. The pooled effect analysis using a fixed-effects model presented that NAC treatment did not significantly reduce mean length of hospital stay (WMD 0.09; 95% CI -0.13 to 0.31; $P=0.40$; Figure 3). Additionally, no statistical heterogeneity was observed across pooled studies ($I^2=0\%$; $P=0.76$).

**All-cause mortality**

Death occurred in 5 of 513 patients (0.9%) treated with NAC and in 16 of 513 patients (3.1%) in the control groups. Use of NAC was associated with a significant reduction in all-cause death (OR 0.40; 95% CI 0.17 to 0.93; $P=0.03$; $I^2=0\%$; $P_{\text{heterogeneity}}=0.44$; Figure 4).
Incidence of cerebrovascular accidents
Seven [12,16,19,21-23,26] of the 10 included studies reported the incidence of cerebrovascular accidents after operation. Cerebrovascular accidents occurred in 8 of 423 patients (1.9%) treated with NAC and in 5 of 424 patients (1.2%) treated with placebos. Use of NAC failed to present a significant reduction in cerebrovascular accidents (OR 1.68 95% CI 0.60 to 4.69; \(P=0.32; I^2=0\%; P_{\text{heterogeneity}}=0.64\)).

Publication bias
The funnel plot for the incidence of POAF was showed in Figure 5. The funnel plot appeared symmetrical, suggesting there was no potential publication bias among the included trials.

Discussion
This meta-analysis showed that prophylactic NAC effectively reduced the incidence of POAF, a conclusion that was similar to the previous meta-analyses [14,15]. However, the pooled effect analysis of trials (OR 0.64; 95% CI 0.39 to 1.06) with a short-term NAC administration, differing from the pooled effect of studies with a long-term (OR 0.51; 95% CI 0.33 to 0.79) and the overall effect of 10 studies (OR 0.56; 95% CI 0.40 to 0.77), demonstrated that there was no significant difference between the two groups. These findings suggested that antioxidant NAC may be a novel and encouraging agents for patients undergoing cardiac surgery to prevent AF. Furthermore, prolonging the duration of NAC administration up to postoperative day 2-3, the patient may receive more beneficial effects. Previous studies presented that on postoperative day 2-3, corresponding to the day of the highest incidence of POAF, the inflammatory cytokines levels were the highest [7,27]. To some extent, the different results between short-term and long-term NAC administration may be associated with the anti-inflammatory property of NAC. Additionally, NAC is a relatively safe drug with the potential for widespread use [16,21,23]. Despite one [23] of included studies reported evident side effects among patients, while there was no statistical difference when compared with control groups.

There is increasing evidence showing the influence of oxidant injury and inflammatory reaction in the pathogenesis of POAF [7,9,28]. Antioxidants, including NCA, have proved to decrease serum levels of molecules markers of cellular oxidative stress in patients undergoing heart surgery [9-11,16,28,29]. NAC is a thiol and mucolytic agent, a precursor of glutathione and stimulates glutathione synthesis by entering cells and being hydrolyzed to cysteine[12,16]. In this way, it increases the level of intracellular reduced glutathione, which is often reduced as a response of increased status of oxidative stress and inflammation reaction [16,30]. Moreover, it may also scavenge several reactive oxygen species including hydroxyl radical and block renin-angiotensin system.
and/or atrial remodeling through its property of antioxidant or anti-inflammation [12,20,31]. These properties make NAC a potentially useful prophylaxis for reducing the incidence of POAF.

Although POAF is often considered both transient and self-limiting [7,15], it can result in increased the length of ICU and hospital stay, cerebrovascular accident, and mortality [3-7]. With regard to ICU and hospital stay, the pooled effects were similar to the existing meta-analyses [13-15], failing to show any beneficial effects of NAC. There was also no significant reduction in the risk of cerebrovascular accidents (OR 1.68 95% CI 0.60 to 4.69) between two groups. The present meta-analysis, however, demonstrated that prophylactic NAC reduced the occurrence of all-cause mortality (OR 0.40; 95% CI 0.17 to 0.93), which contradicts the result concluded by Wang et al. (OR 0.81; 95% CI 0.52-2.11) [13].

There are several limitations to the present meta-analysis that should be taken into account. First, there was significant heterogeneity in both the methods of monitoring and the definition of POAF between studies. AF after cardiac surgery was only considered as a clinical outcome in majority of the included studies [19,20,22-26], and one study [23] used any new AF as its endpoint. All these would affect the numbers of patients developing POAF. Second, as we know, beta-blockers and amiodarone are considered as classical agents for preventing POAF and recommended by current guidelines [8,32]. However, these agents were withdrew after cardiac surgery in several studies [12,23,24,26], thus it was hard to assess the adjunctive efficacy of NAC in addition to these standard agents. Only Ozaydin et al. demonstrated that carvedilol plus NAC significantly reduced the incidence of POAF compared with carvedilol plus placebo group [21]. Next, due to different NAC protocol used in these trials, we are unable to evaluate this heterogeneity on clinical outcomes and identify an optimal NAC dose from this meta-analysis. Finally, approximately half the subjects of this meta-analysis come from just two trials [16, 21], and the positive effect seen is based almost entirely on two trials from the same group [12, 21], the results of which have not been re-produced in the majority of the other trials.

In the future, novel research should focus on an adequately powered multicenter double-blinding placebo-controlled randomized trial. Furthermore, future studies should compare various doses of NAC, including varying lengths of therapy, to explore the exact dose of NAC and the optimal length of therapy. In addition, these studies should also assess the effect of adding NAC on top of routine prophylactic agents on the prevention postoperative complications, including beta-blockers, amiodarone and any other potentially prophylaxis.

Conclusions
This meta-analysis shows that prophylactic NAC reduces the incidences of POAF and all-cause mortality for patients undergoing cardiac surgery.
However, adequately powered RCTs evaluating the effects of NAC on these and other postoperative complications with or without routine prophylaxis are needed.

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**Authors’ contributions** LXH conceived the study, participated in the design, collected the data, performed statistical analyses and drafted the manuscript. XCY helped to collect data. FGH conceived the study, participated the design. All authors read and approved the final manuscript.

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3. Hubei University of Chinese Medicine, Wuhan, 430061, Hubei Province, China.

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**Competing interests** None

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6. Kim MH, Deeb GM, Morady F, Bruckman D, Hallock LR, Smith KA,


29. Liu T, Li G, Korantzopoulos P, Goudevenos JA: Statins and prevention of


<table>
<thead>
<tr>
<th>Study reference</th>
<th>Jaded score</th>
<th>Surgery type</th>
<th>NAC/Control</th>
<th>NAC protocol</th>
<th>Medical history</th>
<th>Previous medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozaydin 2008[12]</td>
<td>4</td>
<td>CABG ± valve</td>
<td>58 /57</td>
<td>50mg/kg for 1h before surgery, then 50mg/kg/day 48h after operation</td>
<td>DM, Hypertension Stable angina, Unstable angina/MI</td>
<td>BRB, Acetylsalicylic acid</td>
</tr>
<tr>
<td>Kazemi 2013[16]</td>
<td>5</td>
<td>CABG ± valve</td>
<td>120 /120</td>
<td>1200mg orally 2 times per day from 48h before and up to 72h after heart surgery</td>
<td>DM, CRF, ACS, CAD, CHF, CLD, MI, Hypertension, High cholesterol</td>
<td>BRB, Stains, ACEI/ARB, Diuretic</td>
</tr>
<tr>
<td>Eren 2003[19]</td>
<td>3</td>
<td>CABG</td>
<td>10 /10</td>
<td>100mg/kg iv for 1h before and 40mg/kg/day at 24h after CPB</td>
<td>COPD</td>
<td>Not reported</td>
</tr>
<tr>
<td>Orhan 2006[20]</td>
<td>3</td>
<td>CABG</td>
<td>10 /10</td>
<td>50mg/kg iv at the start of induction of anesthesia</td>
<td>DM, MI Hypertension Hyperlipidemia</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ozaydin 2013[21]</td>
<td>5</td>
<td>CABG ± valve</td>
<td>104 /104</td>
<td>50mg/kg iv 1h before and at the same doses for 48h after surgery</td>
<td>CHF, COPD, DM, Hypertension, Stable angina, Unstable angina</td>
<td>BRB, ACEI/ARB, Stains</td>
</tr>
<tr>
<td>Peker 2008[22]</td>
<td>4</td>
<td>CABG</td>
<td>19 /21</td>
<td>50mg/kg iv 1h before surgery and 50mg/kg/day 48h after the operation</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wijeysundera 2007[23]</td>
<td>5</td>
<td>CABG ± valve</td>
<td>88 /87</td>
<td>100mg/kg iv over 30 min after induction of anesthesia, then 20mg/kg/h for 4h after CPB</td>
<td>CHF, COPD, DM, CVD, PVD Hypertension</td>
<td>BRB, CCB, ACEI/ARB NSAIDs</td>
</tr>
<tr>
<td>El-Hamamsy 2007[24]</td>
<td>3</td>
<td>CABG</td>
<td>50 /50</td>
<td>600mg orally the day before and the morning of the operation, 150mg/kg iv before skin incision, followed by 12.5mg/kg/h over 24h</td>
<td>CHF, MI Unstable angina</td>
<td>BRB, CCB, ACEI</td>
</tr>
<tr>
<td>Haase 2007[25]</td>
<td>5</td>
<td>CABG ± valve</td>
<td>30 /30</td>
<td>150mg/kg iv after anesthesia induction, followed 50mg/kg iv over 4h, then 100mg/kg iv over 20h</td>
<td>DM, COPD, MI PVD, Stroke Hypertension High cholesterol Carotid disease.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kim 2011[26]</td>
<td>4</td>
<td>CABG</td>
<td>24 /24</td>
<td>100mg/kg iv after anesthetic induction, then 40mg/kg/day iv for 24h</td>
<td>DM, Hypertension</td>
<td>BRB, CCB RAI, Diuretics</td>
</tr>
</tbody>
</table>

**Table 1** Characteristics of the included studies
ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ACS, acute coronary syndrome; BRB, beta-blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, chronic heart failure; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; SD, standard deviation; DM, diabetes mellitus; CVD, cerebrovascular disease; MI, myocardial infarction; NSAIDs, non-steroid anti-inflammatory drugs; PVD, peripheral vascular disease; RAI, renin-angiotensin inhibitor.

Table 2 Outcomes of included studies in the meta-analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>POAF</th>
<th>Duration of ICU (h)</th>
<th>Hospitalization (days)</th>
<th>Mortality</th>
<th>Nonfatal CVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NAC</td>
<td>Control</td>
<td>NA</td>
<td>NA</td>
<td>7.7±3</td>
</tr>
<tr>
<td>Ozaydin 2008[12]</td>
<td>3/58</td>
<td>12/57</td>
<td>120±45.6</td>
<td>115.2±79.2</td>
<td>7.4±1.3</td>
</tr>
<tr>
<td>Kazemi 2013[16]</td>
<td>14/120</td>
<td>19/120</td>
<td>23.2±1.75</td>
<td>22.6±1.84</td>
<td>7.2±0.42</td>
</tr>
<tr>
<td>Eren 2003[19]</td>
<td>2/10</td>
<td>1/10</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Orhan 2006[20]</td>
<td>0/10</td>
<td>1/10</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ozaydin 2013[21]</td>
<td>9/104</td>
<td>25/104</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Peker 2008[22]</td>
<td>0/19</td>
<td>2/21</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Wijeysundera 2007[23]</td>
<td>50/88</td>
<td>58/87</td>
<td>45.6</td>
<td>40.8*</td>
<td>8 (6-12)</td>
</tr>
<tr>
<td>El-Hamamsy 2007[24]</td>
<td>4/50</td>
<td>6/50</td>
<td>NA</td>
<td>NA</td>
<td>5.4±2.3</td>
</tr>
<tr>
<td>Haase 2007[25]</td>
<td>19/30</td>
<td>16/30</td>
<td>44</td>
<td>45*</td>
<td>8(7-11)</td>
</tr>
<tr>
<td>Kim 2011[26]</td>
<td>4/24</td>
<td>8/24</td>
<td>72±36</td>
<td>81.6±50.4</td>
<td>11.3±6.3</td>
</tr>
</tbody>
</table>

Data are number or mean ± deviation; CVA, cerebrovascular accident; NA, data not available; *, values expressed as median; †, data expressed as median (interquartile range).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Method of atrial fibrillation assessment</th>
<th>Definition of atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozaydin 2008[12]</td>
<td>ECGs performed continuously at the first 2 postoperative days in the ICU, and 2 times a day routinely when new symptom developed or observed in the wards.</td>
<td>An irregular narrow complex rhythm with absence of discrete p-waves lasting longer than 5 minutes.</td>
</tr>
<tr>
<td>Kazemi 2013[16]</td>
<td>Holter performed continuously for 72h after surgery</td>
<td>More than 5 minutes of AF or associated with hemodynamic compromise requiring therapy immediately.</td>
</tr>
<tr>
<td>Eren 2003[19]</td>
<td>ECGs were recorded on the first postoperative day</td>
<td>Not reported</td>
</tr>
<tr>
<td>Orhan 2006[20]</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ozaydin 2013[21]</td>
<td>ECGs performed continuously during ICU stay and all-day Holter was used during the rest of hospitalization.</td>
<td>The incidence of AF lasting longer than 5 minutes during hospitalization.</td>
</tr>
<tr>
<td>Peker 2008[22]</td>
<td>ECGs conducted continuously during the first 2 postoperative days in the ICU, and 2 times per day routinely when new symptom developed or noted</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wijeysundera 2007[23]</td>
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<td>El-Hamamsy 2007[24]</td>
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<td>Haase 2007[25]</td>
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<tr>
<td>Kim 2011[26]</td>
<td>Not reported</td>
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</tr>
</tbody>
</table>

**Table 3** POAF outcome definition and assessment

ECG, electrocardiogram.
Figure 1 Flow diagram of trials included in the meta-analysis

Figure 2 Effects of N-acetylcysteine on the prevention of postoperative atrial fibrillation.
**Figure 3** Effects of N-acetylcysteine on the length of hospital stay.

**Figure 4** Effects of N-acetylcysteine on the all-cause mortality.

**Figure 5** Funnel plot of N-acetylcysteine on the prevention of atrial fibrillation after cardiac surgery.