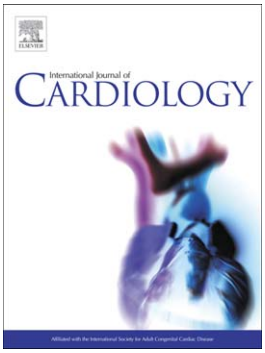

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Colchicine for Primary Prevention of Atrial Fibrillation after Open-Heart Surgery: Systematic Review and Meta-Analysis

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Atrial fibrillation, cardiac surgery, colchicine, meta-analysis, postoperative period, POAF

Abstract

Background: Atrial fibrillation occurs frequently after open-heart surgery. It is associated with increased morbidity and mortality, longer hospital stays, and increased healthcare costs. Prophylactic administration of colchicine may mitigate post-operative atrial fibrillation (POAF).

Methods: We searched PubMed, ClinicalTrials.gov and CENTRAL databases to identify randomized controlled trials (RCTs) that; (1) compared prophylactic use of colchicine to placebo, or usual care, in patients with sinus rhythm who underwent elective open-heart surgery and (2) reported POAF-incidence. We excluded trials focused on incidence of atrial fibrillation after percutaneous interventions or colchicine treatment of diagnosed pericarditis or post-pericardiotomy-syndrome. A random-effects model was used to pool data for POAF-incidence as the primary outcome and for drug-related adverse effects, major adverse events (death and stroke), and hospital length-of-stay as secondary outcomes.

Results: We included five RCTs (1,412 patients). Colchicine treatment reduced POAF-events by 30% versus placebo or usual care (18% vs. 27%, risk ratio (RR) 0.69, 95% confidence interval (CI) 0.57 to 0.84, p=0.0002). Adverse drug-related effects, especially gastrointestinal intolerance, increased with colchicine; (21% vs. 8.2%, RR 2.52, 95% CI 1.62 to 3.93, p<0.0001). However, major adverse events were unchanged (3.2% vs 3.2%, RR 0.96, 95% CI 0.48 to 1.95, p=0.92). Length-of-stay decreased by 1.2 days with colchicine (95% CI -1.89 to -0.44, p=0.002).

Conclusion: Colchicine demonstrated superior efficacy versus usual care for prevention of atrial fibrillation after cardiac surgery. Moreover, colchicine treatment was associated with shorter hospital stays. These benefits outweigh increased risk of adverse drug-related effects; although further work is needed to minimize gastrointestinal effects.

1. Introduction

Post-operative atrial fibrillation (POAF) is a frequent complication of cardiac surgery. POAF occurs in 25-40% of coronary artery bypass graft (CABG) surgeries and 50-60% of valve surgeries.[1-3] POAF differs from non-valvular AF because it is usually transient, often resolves without treatment, is generally limited to the hospital stay, and rarely develops into a chronic condition.[4-5] Nevertheless, POAF is associated with increases in morbidity and mortality, hospital length-of-stay, and healthcare costs.[4,6-8] The annual financial burden of POAF in the United States is estimated to exceed 1 billion dollars. [3,9]

POAF development is multifactorial and probably involves; (1) surgically-created structural substrates for electrical re-entry pathways or ectopic activity, (2) pericardial inflammation, (3) excess catecholamine production, and (4) increased sympathetic tone.[3,10] Consequently, many studies evaluated POAF reduction strategies; including prophylactic administration of antiarrhythmic agents, heart-rate control drugs, and anti-inflammatory agents.[10-12] Of these, beta-blockade is currently indicated and amiodarone is suggested for high-risk patients.[13] Recent American guidelines for managing AF suggest colchicine might also be considered to treat cardiac POAF; but, with only weak recommendation (CLASS IIb, Level of evidence B).[13] Nevertheless, because colchicine possesses both anti-inflammatory properties and sympatholytic activity, it appears a logical candidate for POAF therapy. Although colchicine reduced early AF recurrence after pulmonary vein isolation [14], its narrow therapeutic range and frequent gastrointestinal intolerance are disadvantages.[15]

Recent meta-analyses have drawn opposing conclusions regarding colchicine's efficacy in POAF reduction.[16-19] Discrepancies probably occurred because these analyses used different inclusion criteria, different procedures, and assessed outcomes at different times. Therefore, our systematic review and meta-analysis focussed on a specific outcome with a specific time-frame in response to a specific injury; i.e., AF incidence early

after open-heart surgery in adults. Secondary endpoints were colchicine's effect on hospital length-of-stay (LOS), drug-related adverse effects, and major adverse events.

2. Methods

2.1. Search parameters

The study followed PRISMA-guidelines.[20] We searched PubMed, ClinicalTrials.gov, and CENTRAL databases to July 2016. The search terms for PubMed were; “atrial fibrillation”, or “Afib”, or “AF”, or “atrial”, or “supraventricular tachycardia”, or “arrhythmia” combined with “colchicine” (Appendix Table 1). For the other databases, the only search term was “colchicine”. No restriction regarding language or publication year was applied.

Identified articles were independently screened at the title and abstract level for pertinence by three investigators. Potential studies were retrieved as full-length papers and examined for inclusion based on the following predetermined criteria: only RCTs, comparison of the colchicine’s prophylactic use versus placebo, or usual care, in patients in sinus rhythm who underwent elective open-heart surgery and where the occurrence of POAF was reported. We defined “usual care” to mean continuation of established medication (including beta-blocker, ACE-inhibitors and angiotensin receptor-blockers). Open-heart surgery included CABG, valve surgery, aortic surgery, and any combination. Furthermore, any colchicine dose and treatment regime were accepted. However, we excluded colchicine trials focused on AF prevalence after interventions performed via vascular access (e.g., pulmonary vein isolation and left atrial appendage occlusion) or treatment of pericarditis and post-pericardiotomy-syndrome. Any disagreements that arose during this process were resolved by discussion among co-authors.

2.2. Data extraction

We extracted information on study design, population characteristics, treatment details, and outcomes and results (Appendix Table 2). If available, we also examined the ‘design description papers’ of included trials to obtain additional details.[21,22] Information was extracted using a defined data-extraction form independently by two researchers. The primary outcome was the risk ratio (RR) of the incidence of POAF. Secondary outcomes

were the difference in LOS, drug-related adverse effects, and major adverse events (death and stroke). Drug-related adverse events included; gastrointestinal intolerance (diarrhea, nausea, cramping, abdominal pain or vomiting), alopecia, anorexia, hepatotoxicity, myotoxicity, and bone marrow toxicity. [12,23,24] One study also reported the incidence of post-operative infection; although the exact nature of the infections was unspecified.[25]

2.3. Risk of bias

We assessed risk of bias; i.e., flaws in study design, conduct, analysis, and reporting.[26] Whenever possible, quality assessment included trial registration protocols and study-design publications.[21,22] Information was extracted on; (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel and also outcome assessment, (4) incomplete outcome data - did investigators report completeness of outcome data for POAF; including participant attrition and exclusion of participants from analysis and the use of intention-to-treat analysis, (5) selective reporting, and (6) deviations between study protocols and reported outcomes.[27]

2.4. Statistics

Categorical variables are presented as percentages and continuous variables as mean ± standard deviation (SD). Risk ratios (RR) were used for binary outcomes and mean difference was used for LOS; both with their 95% confidence intervals (CI). The pooled RR was calculated using a random effects model; DerSimonian-Laird method.[28] We also calculated the absolute risk reduction or absolute risk increase and the corresponding number needed to treat (NNT) or number needed to harm (NNH).

To assess heterogeneity, we applied the Cochrane Q-statistic [27] and assessed inconsistency using the I^2-statistic.[29] We also assessed potential publication and reporting bias.

Statistical analysis was performed using ReviewManager software (Version 5.3.0.) and Stata (12.1; StataCorp, College Station, TX).

3. Results

3.1 Search

Results are shown in Appendix Figure 1. Six RCTs were reviewed for eligibility and five included. [12, 23-25,30] One paper written in Farsi (with an English abstract) was translated using online tools and checked by a cardiologist who was a native Farsi-speaker.

3.2. Study characteristics

Table 1 summarizes study and intervention characteristics of the RCTs. In total, 1,412 patients were enrolled; 707 received colchicine around the time of open-heart surgery and 705 received standard treatment (control group). All studies used a colchicine maintenance-dose of 0.5 mg twice daily; however, treatment varied with respect to initiation time, loading-dose, and duration. Colchicine was used for one week in END-AF and in Sarazeem et al. [30] versus one month in both COPPS trials (Table 1). Follow-up ranged from one week to three months. Two RCTs measured POAF only after CABG [25,39], whereas the other three (COPPS, COPPS-2 and END-AF) enrolled patients after valve surgery or combined valve and CABG surgery [12,23,24]. Atrial fibrillation was diagnosed objectively either by continuous ECG monitoring or by 12-lead ECG-recording. Appendix Table 3 provides baseline patient characteristics.

3.3. Risk of within-study bias

The risk-of-bias summary is presented in Appendix Figure 2 (for detailed assessment see Appendix Table 4). All studies used true random processes to generate study groups; but, only two studies provided information on allocation concealment. [23,24] Three studies were double blinded, while two used open-label design.[12,25] No study showed evidence of bias from incomplete data. Three studies specified intention-to-treat analysis.[23,24,30] No study reported >5% randomized patients with missing outcome data; however, in one, the proportion of excluded patients was unclear.[30] Two RCTs (Sarzaeem et al., Zarpelon et al.) were not registered, no study protocol was available, and so deviation between pre-

specified and reported outcomes was not assessed.[25,30] The incidence of POAF was not a pre-specified endpoint of the COPPS trial, thus reporting bias is possible. All other studies specified POAF incidence as a pre-specified primary or secondary endpoint.

3.4. Meta-Analysis

Because the studies differed in colchicine treatment regime, length of follow-up, and type of surgery, different effect sizes might be anticipated. Therefore, we used random effects models to assess all parameters.

3.5. POAF incidence and risk:

In controls, POAF incidence ranged from 13% to 42%. Peri-operative colchicine therapy was associated with a reduction of >30% in POAF risk (RR 0.69, 95% CI 0.57 to 0.84, p=0.0002, I^2=1%; Figure 1); 18% (128/707) who received colchicine experienced POAF versus 27% (189/705) of control patients. The forest plot was arranged in order of increasing proportion of CABG-only cases. CABG-only surgeries accounted for 32% of the COPPS-2 trial, 50% in the COPPS trial, and 69% in END-AF. [12, 23, 24] In contrast, two RCTs included only CABG surgery.[19,30] All studies were relatively comparable in size. Individually, three studies failed to show differences between colchicine treatment and usual care.

3.6. Drug-related adverse effects:

The reported drug-related adverse effects included all forms of gastrointestinal (GI) intolerance and all other reported adverse effects. The pooled data from four studies resulted in a 2.5-fold increased risk for all adverse effects for colchicine-treated patients versus placebo or usual care (RR 2.52, 95% CI 1.62 to 3.93, p<0.0001, I^2=46%). In the colchicine group, 21% (126/599) experienced adverse effects versus 8% (49/597) of controls (Figure 2A).

Colchicine use is often limited because of GI intolerance. In a sub-group analysis, we separated GI distress (Figure 2B) from other drug-induced adverse effects (Figure 2C).

The pooled data revealed colchicine treatment was associated with a 2.8-fold increased risk for gastrointestinal distress versus controls (Figure 2B), whereas there was only weak evidence for a difference in non-GI adverse effects (Figure 2C).

3.7. Major adverse events:

Four trials (COPPS, COPPS-2, END-AF and Zarpelon et al.) reported major adverse events (death and stroke), while one (END-AF) limited this definition to death. The overall incidence of major adverse events was low; 3% in both groups; (19/599) for colchicine and (19/597) for controls (RR 0.96, 95% CI 0.48 to 1.95, p=0.92, I^2=12%). There was no evidence against the null hypothesis of no difference between colchicine and control (Figure 3).

3.8. Hospital length-of-stay:

LOS was reported in three trials.[23,25,30] Colchicine treatment was associated with a one-day reduction in LOS (mean difference -1.2 days, 95% CI -1.9 to -0.4, p=0.002, I^2=43%) (Figure 4).

4. Discussion

Colchicine reduced the incidence of atrial fibrillation early after cardiac surgery by 30% and reduced hospital length-of-stay by approximately one day. Moreover, colchicine therapy was not associated with increased mortality or stroke. However, we found a greater than two-fold increase in side-effects; specifically, gastrointestinal intolerance.

The hypothesis was that by restricting assessment of colchicine's potential benefit to a specific outcome, time-frame, and injury, this would maximize the opportunity to determine colchicine's efficacy against POAF and minimize potential confounding effects of incongruous study combinations. Previous, less focused, evaluation produced equivocal results. For example, a meta-analysis of colchicine for prevention of cardiovascular events examined long-term effects (39 RCTs; 4,992 participants; at least six-month follow-up).[31] Although for many parameters (including all-cause mortality, cardiovascular mortality, heart failure, and stroke; AF was not assessed) risk ratios were less than one (favoring colchicine), the 95% CIs crossed one. Similarly, there was no clear evidence to indicate increased risk of total adverse events with colchicine (the 95% CIs again crossed one). Only myocardial infarction exhibited benefit; RR = 0.28 [95% CI 0.07 to 0.57].

Other colchicine-related meta-analyses combined short-term and long(er)-term studies, combined short-term RCTs likely to produce different degrees of inflammatory response (e.g., surgery and percutaneous intervention), or even combined studies with different outcomes (Appendix Table 5). Such approaches sometimes produced conflicting results and conclusions. For example, Wang et al. concluded colchicine had no effect on POAF.[18] However, they included an RCT designed to examine pericardial effusion that enrolled participants and began colchicine treatment 16 days after surgery with two RCTs that randomized participants either on day-three after surgery or two-to-three days prior to surgery. Because POAF typically occurs in the first week after surgery, we suggest such combination is invalid unless the question is, "*can colchicine prevent AF at any time after surgery*".[32] Similarly, two meta-analyses combined the outcomes of POAF and AF

recurrence after pulmonary vein isolation for treatment of previous symptomatic AF.[17,33] Again, we suggest combination of different disease entities (non-valvular and post-surgery atrial fibrillation) and interventions (minimally invasive transvenous ablation and open-heart surgery) can mislead.

These examples emphasize that the specific question addressed in meta-analysis is a crucial determinant of the result. The eligibility criteria we applied were more discriminating than in the above-mentioned meta-analyses. In particular, outcomes and procedures were specified. Specificity restricts generalizability of results and conclusions; however, it does mean the results and conclusions apply unambiguously to colchicine as an early treatment to prevent AF after cardiac surgery. In addition, since publication of these meta-analyses, two additional RCTs have been published which increased the number of patients by 500.[12,19]

4.1.POAF reduction

The overall incidence of POAF decreased from 27% (189/705) to 18% (128/707) in colchicine-treated patients. This difference yielded a number-needed-to-treat of 11.5. Three of the studies found only weak evidence against the null hypothesis of no benefit of colchicine-associated protection against POAF (Figure 1). Two of these studies [12,25] were underpowered to detect the 30% reduction in POAF indicated by our meta-analysis. Both RCTs performed pre-study power-analysis; however, they assumed the AF incidence reduction would be 52% and 70% respectively. The third study was also underpowered to detect a 30% reduction in AF (70% power). Nonetheless, the pooled effect estimate provided strong statistical evidence of POAF reduction with colchicine treatment.

Numerous approaches to managing cardiac POAF have been used and these come with various classes of recommendation and levels of evidence.[32,33] Of these approaches, β-blockade is considered the foundation. A meta-analysis of 33 studies (4,698 patients) found an odds ratio of 0.33 (95% CI 0.26 to 0.43) for POAF reduction with β-blockers versus control.[34] In the three studies in our meta-analysis that reported β-blocker

use [23,25], more than 50% of patients in both groups received this treatment. Thus, the apparent protection conferred by colchicine seen in the current analysis may be in addition to β-blocker-mediated benefit. Only two studies reported data on amiodarone use and neither indicated any effect.

4.2. Sensitivity Analysis

When we reanalysed the data, removing each study in turn (Appendix Figure 3), the overall risk ratio ranged from 0.59 [95% CI 0.45 to 0.77] (COPPS-2 omitted) to 0.73 [95% CI 0.60 to 0.90] (Sarzaeem et al. omitted). Neither the point estimates nor the 95% CIs changed appreciably and so our interpretations are not dependent upon a single study. This was also true when the COPPS study was excluded.

Use of the DerSimonian-Laird method has been criticized because it can provide falsely precise estimates.[35] Two alternative methods for random effects models, the Knapp-Hornung and profile likelihood approaches have been recommended to reduce the risk of false positive conclusions.[36] When we applied these methods, colchicine still reduced POAF; Knapp-Hornung RR = 0.71 [95% CI 0.44 to 0.98] and profile likelihood RR = 0.71 [95% CI 0.47 to 0.90]. Similarly, when we used a fixed effects model, there was no material change in the results; RR = 0.68 [95% CIs 0.56 to 0.82]).

There are, as far as we are aware, four ongoing RCTs (ISRCTN72835417, ACTRN12613001345774, NCT01985425 and NCT02177266).[17] These will add approximately 1,100 patients. We constructed a model and ran simulated meta-analysis that assumed each of these studies would produce results as unfavourable as the study currently indicating the smallest effect (COPPS-2; RR = 0.81; Figure 1).[37] With the added assumption that the incidence of AF in their control groups would equal the average of the five included studies (25%), the simulated RR was 0.74 (95% CI [0.65 to 0.86]) versus 0.69 (95% CI [0.57 to 0.84] in the original analysis). If we assumed the incidence of AF in control groups increased to that of the maximum of the included studies (42%), the simulated RR

was 0.76 (95% CI [0.68 to 0.85]). Therefore, it appears unlikely additional studies will materially alter the results and, more importantly, the conclusion of our meta-analysis.

In summary, sensitivity analysis indicates the conclusion of colchicine's benefit in POAF reduction is robust.

4.3 Adverse effects of colchicine

Only three RCTs provided data on GI-related problems. The effect was large (RR = 2.87; 95% CI [1.77 to 4.64]; Figure 2B), albeit with wide confidence intervals. This finding is consistent with other studies. In the previously mentioned meta-analysis of colchicine's long-term effects, the risk of gastrointestinal adverse events with colchicine was similarly increased (RR = 1.83; 95% CI 1.03 to 3.26). Increased risk was also reported in an RCT of colchicine's effect on myocardial injury after CABG surgery (RR = 4.83; 60 patients, [38]) and in an RCT to examine the effect of colchicine on recurrent AF after pulmonary vein isolation (RR = 4.49; 206 patients, [36]). This is important because GI-related problems are often the reason for discontinuation of colchicine.

Only one RCT [25] reported infection as an adverse effect; the rate was approximately three times higher with colchicine than controls. There are at least two explanations. First, this finding may be related to colchicine's action on immune response. [39] Second, colchicine's anti-inflammatory properties may impair wound healing.[40] More data on this complication are required.

The lack of any effect on major adverse events, specifically death and stroke, is consistent with previous meta-analysis for several indications.[29,31]

In summary, colchicine therapy for POAF does not appear to result in major adverse events; however, GI problems are often severe and frequent enough to stop treatment.

4.4. Bias

The risk of bias in the studies appears unlikely to have affected our conclusions. Two RCTs used open-label study design and both staff and patients were aware of treatment

allocation. We do not believe this source of bias influenced the primary outcome because AF was measured objectively; documented by holter-monitor or ECG-recording. However, if both open-label studies were excluded, the benefit of colchicine remained; RR = 0.65 [95% CI 0.46 to 0.91; P = 0.01]. In contrast, for adverse events such as gastrointestinal intolerance, subjective judgement may play a role and thereby produce bias.

With only five studies in the POAF analysis, there is insufficient data to yield robust statistical analysis of funnel plot asymmetry to assess publication bias. Nevertheless, current interest in the effect of colchicine on AF means negative studies are unlikely to be subject to publication bias; for example, although the study by Tabbalat et al. failed to show unequivocal benefit, it was published.

4.5. Unanswered questions and future research

We demonstrated ongoing RCTs appear unlikely to alter the conclusion that colchicine reduces POAF (unless their results are considerably different from all previous RCTs). Nonetheless, these studies will be valuable. One potential use of meta-analysis is to identify specific populations that might derive greater benefit from colchicine therapy. When we arranged the studies in the POAF forest plot in order of increasing proportion of CABG-alone surgeries (Figure 1), there was a shift towards greater effect size as the proportion of CABG-alone cases in the trial increased. That is, colchicine was more effective in reducing the incidence of AF in studies with the highest proportion of CABG cases. This is somewhat surprising because the incidence of POAF is typically lowest in CABG-only surgery. The small number of studies included in our meta-analysis precluded meta-regression and so confirmation of this potential relationship awaits the addition of more RCTs. Of the four registered, but unpublished, RCTs one is of CABG alone, two include CABG and aortic valve surgery, and one is for lung tumour resection. This distribution should enable any relationship between outcome effect and type of surgery to be determined.

Future studies may optimize therapy. Evidence indicates considerable variability in response to colchicine and the existence of ‘non-responders’.[39,44] Correlation of plasma

levels to treatment response may therefore provide a method of customized individual therapy. None of the ongoing RCTs indicated an intention to measure plasma levels. Nonetheless, inter-study differences in dose may provide insight. All studies in the meta-analysis used 0.5 mg twice-a-day maintenance dose. In contrast, two of the unpublished trials, conducted in Canada and the United States, indicated they would use 0.6 mg twice-a-day (the formulation currently available in North America). Will a 20% dose increase also increase the proportion of 'responders', thereby increasing efficacy, or will there just be more side-effects? Also, future research could determine whether colchicine dose reduction leads to reduction in gastrointestinal intolerance without diminished efficacy of POAF prevention. Gunda et al. found that "low dose"-colchicine (0.3 mg bid) reduced GI side-effects by 66% (4% vs. 12%) in patients after left atrial appendage ligation, but maintained efficacy, i.e., a lower incidence of severe pericarditis versus "high dose"-colchicine (0.6 mg bid).[45] The optimal outcome would be that lower colchicine doses remained efficacious, while adverse gastrointestinal events decreased.

The ongoing studies could also enable the COPPS trial to be replaced in this meta-analysis. The trial is problematic because colchicine was started three days after surgery; even though POAF incidence peaks on day-two. Given the late treatment start, it is surprising COPPS had a more favourable effect than COPPS II in which therapy began before surgery. However, COPPS II included more valve surgery cases, fewer CABG cases, and 20% of patients discontinued therapy. These factors could explain the increased incidence of POAF in COPPS II.

As far as we are aware, there has been no cost-utility study conducted to assess colchicine and POAF. The estimated one-day reduction in LOS could produce considerable savings because colchicine treatment costs would be small (~2 Euros per day). However, this speculation is tempered because only three RCTs provided LOS data and a causal link with POAF treatment was not established.

5. Conclusion

In conclusion, there is strong statistical evidence to support colchicine therapy to reduce POAF after open-heart surgery. Colchicine may also serve as a complementary strategy to the current recommended postoperative use of beta-blockade. Colchicine treatment for POAF has a current class IIb indication with level of evidence B.[13] The results of our meta-analysis, and specifically its robustness, prompt us to propose the recommendations be reassessed and upgraded to endorse prophylactic use of colchicine. Nevertheless, there remains scope for refinement of therapy through identification of populations and individuals who could derive greatest benefit and by optimizing therapy to minimize adverse gastrointestinal effects.

References

1 Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med. 2001;135:1061-73.

2 Gillinov AM, Bagiella E, Moskowitz AJ et al.; CTSN. Rate Control versus Rhythm Control for Atrial Fibrillation after Cardiac Surgery. N Engl J Med. 2016;374:1911-21

3 Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol. 2008;51:793-801

4 Rostagno C, La Meir M, Gelsomino S et al. Atrial fibrillation after cardiac surgery: incidence, risk factors, and economic burden. J Cardiothorac Vasc Anesth. 2010;24:952-8.

5 Mathew JP, Fontes ML, Tudor IC et al. Investigators of the Ischemia Research and Education Foundation; Multicenter Study of Perioperative Ischemia Research Group. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA. 2004 Apr 14;291(14):1720-9.

6 LaPar DJ, Speir AM, Crosby IK et al. Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs. Ann Thorac Surg. 2014;98:527-33.

7 Almassi GH, Wagner TH, Carr B et al. VA #517 Randomized On/Off Bypass (ROOBY) Study Group. Postoperative atrial fibrillation impacts on costs and one-year clinical outcomes: the Veterans Affairs Randomized On/Off Bypass Trial. Ann Thorac Surg. 2015;99:109-14.

8 Aranki SF, Shaw DP, Adams DH et al. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation. 1996;94:390-7.

9 Patel D, Gillinov MA, Natale A. Atrial fibrillation after cardiac surgery: where are we now? Indian Pacing Electrophysiol J. 2008;8:281-91.

10 Fuster V, Rydén LE, Cannom DS et al. American College of Cardiology Foundation/American Heart Association Task Force. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;15;123:e269-367

11 Bidar E, Bramer S, Maesen B, Maessen J.G., Schotten U; Post-operative atrial fibrillation - Pathophysiology, Treatment and Prevention. JAFIB. 2013;6:136-145.

12 Tabbalat RA, Hamad NM, Alhaddad IA, Hammoudeh AJ, Akasheh BF and Khader YS. Effect of colchiciNe on the inciDence of atrial fibrillation in open heart surgery patients: End-AF trial. Effect of ColchiciNe on the InciDence of Atrial Fibrillation in Open Heart Surgery Patients: END-AF Trial, Am Heart J. 2016;178:102-107

13 January CT, Wann LS, Alpert JS et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64:e1-76

14 Deftereos S, Giannopoulos G, Kossyvakis C et al. Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study. J Am Coll Cardiol. 2012;60:1790-6.

15 Tong DC, Wilson AM, Layland J. Colchicine in cardiovascular disease: an ancient drug with modern tricks. Heart. 2016;102:995-1002

16 Trivedi C, Sadadia M. Colchicine in prevention of atrial fibrillation following cardiac surgery: systematic review and meta-analysis. Indian J Pharmacol. 2014;46:590-5.

17 Verma S, Eikelboom JW, Nidorf SM et al. Colchicine in cardiac disease: a systematic review and meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2015;15:96.

18 Wang MX, Deng XL, Mu BY et al. Effect of colchicine in prevention of pericardial effusion and atrial fibrillation: a meta-analysis. Intern Emerg Med. 2016;11:867-76.

19 Papageorgiou N, Briasoulis A, Lazaros G, Imazio M, Tousoulis D. Colchicine for prevention and treatment of cardiac diseases: a meta-analysis. Cardiovasc Ther. 2017;35:10-18.

20 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.

21 Imazio M, Cecchi E, Demichelis B et al. COPPS Investigators. Rationale and design of the COPPS trial: a randomised, placebo-controlled, multicentre study on the use of colchicine for the primary prevention of postpericardiotomy syndrome. J Cardiovasc Med. 2007;8:1044-8.

22 Imazio M, Belli R, Brucato A et al. Rationale and design of the Colchicine for Prevention of the Post-pericardiotomy Syndrome and Post-operative Atrial Fibrillation (COPPS-2 trial): a randomized, placebo-controlled, multicenter study on the use of colchicine for the primary prevention of the postpericardiotomy syndrome, postoperative effusions, and postoperative atrial fibrillation. Am Heart J. 2013;166:13-9.

23 Imazio M, Brucato A, Ferrazzi P et al. COPPS Investigators. Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) atrial fibrillation substudy. Circulation. 2011;124:2290-5

24 Imazio M, Brucato A, Ferrazzi P, et al. COPPS-2 Investigators. Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial. JAMA. 2014;312:1016-23.

25 Zarpelon CS, Netto MC, Jorge JC et al. Colchicine to Reduce Atrial Fibrillation in the Postoperative Period of Myocardial Revascularization. Arq Bras Cardiol. 2016.pii:S0066-782X2016005015103

26 Higgins JPT, Altman DG, Gøtzsche PC et al. Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.BMJ. 2011;343:d5928.

27 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions Version 5.1.0 Cochrane Collaboration, 2011

28 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986:7;177-188

29 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-1558

30 Sarzaeem M, Shayan N, Bagheri J, Jebelli M and Mandegar M. Low dose Colchicine in prevention of atrial fibrillation after coronary artery bypass graft: A double blind clinical trial. Tehran University Medical Journal, 2014, 72:147.

31 Hemkens LG, Ewald H, Gloy VL et al. Colchicine for prevention of cardiovascular events. Cochrane Database Syst Rev. 2016 Jan 27

32 Bessissow A, Khan J, Devereaux PJ, Alvarez-Garcia J, Alonso-Coello P. Postoperative atrial fibrillation in non-cardiac and cardiac surgery: an overview. J Thromb Haemost. 2015;13 Suppl 1:S304-12.

33 Ha AC, Mazer CD, Verma S, Yanagawa B, Verma A. Management of postoperative atrial fibrillation after cardiac surgery. Curr Opin Cardiol. 2016;31:183-90.

33 Mulrow CD. Rationale for systematic reviews. BMJ. 1994;309:597-9.

34 Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, Whitlock RP.Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database Syst Rev. 2013;

35 Cornell JE, Mulrow CD, Localio R et al. Random-effects meta-analysis of inconsistent effects: a time for change. Ann Intern Med. 2014;160:267-70.

36 IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014;14:25.

37 Sutton AJ, Abrams KR, Jones DR, SheldonTA, Song F, Methods for Meta-Analysis in Medical Research. Wiley 2000; ISBN: 978-0-471-49066-1

38 Giannopoulos G, Angelidis C, Kouritas VK et al. Usefulness of colchicine to reduce perioperative myocardial damage in patients who underwent on-pump coronary artery bypass grafting. Am J Cardiol. 2015;115:1376-81.

39 Stack J, Ryan J, McCarthy G. Colchicine: New Insights to an Old Drug. Am J Ther. 2015;22:151-7.

40 Mathisen B, Loennechen T, Gedde-Dahl T, Winberg JO. Fibroblast heterogeneity in collagenolytic response to colchicine. Biochem Pharmacol. 2006;71:574-83.

41 Pildal J, Hróbjartsson A, Jørgensen KJ et al. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. Int J Epidemiol. 2007;36:847-57

42 Siebert J, Anisimowicz L, Lango R et al. Atrial fibrillation after coronary artery bypass grafting: does the type of procedure influence the early postoperative incidence? Eur J Cardiothorac Surg. 2001;19:455-9

43 Katz EZ, Ehrenfeld M, Levy M, Eliakim M. Plasma colchicine concentration in patients with recurrent polyserositis (familial Mediterranean fever) on long-term prophylaxis. Arthritis Rheum. 1982;25:227-31.

45 Gunda S, Reddy M, Nath J et al. Impact of Periprocedural Colchicine on Postprocedural Management in Patients Undergoing a Left Atrial Appendage Ligation Using LARIAT. Cardiovasc Electrophysiol. 2016;27:60-4.

46 Meurin P, Lelay-Kubas S, Pierre B et al. French Society of Cardiology. Colchicine for postoperative pericardial effusion: a multicentre, double-blind, randomised controlled trial. Heart. 2015;101:1711-6.

47 Deftereos S, Giannopoulos G, Efremidis M et al. Colchicine for prevention of atrial fibrillation recurrence after pulmonary vein isolation: mid-term efficacy and effect on quality of life. Heart Rhythm. 2014;11:620-8.

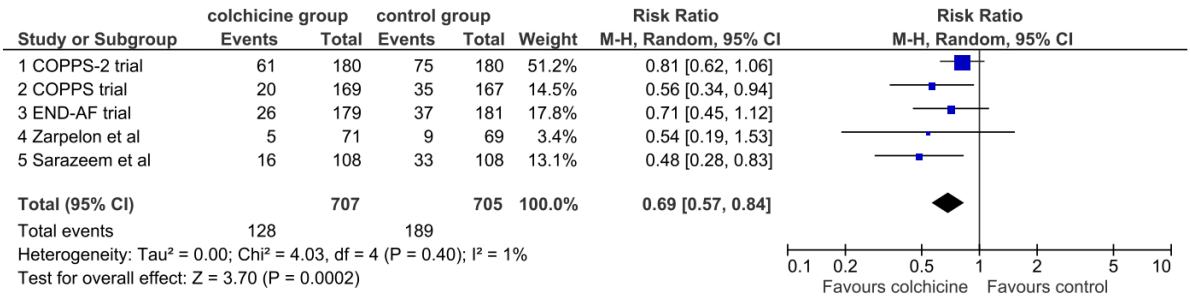
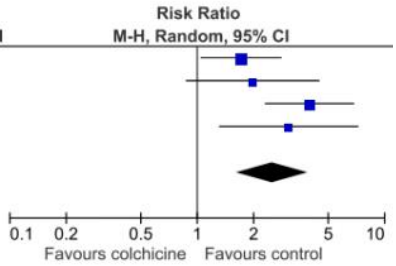


Figure 1: Forest Plot for risk ratio of post-operative atrial fibrillation. Individual and pooled risk ratios with 95% confidence intervals for RCTs enrolling patients undergoing open-heart surgery comparing colchicine therapy versus placebo or usual care.

A

Study or Subgroup	colchicine Events	Total	control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1 COPPS-2 trial	36	180	21	180	32.7%	1.71 [1.04, 2.82]
2 COPPS trial	16	169	8	167	19.1%	1.98 [0.87, 4.49]
3 END-AF trial	55	179	14	181	30.0%	3.97 [2.29, 6.88]
4 Zarpelon et al	19	71	6	69	18.1%	3.08 [1.31, 7.24]
Total (95% CI)		**599**		**597**	**100.0%**	**2.52 [1.62, 3.93]**
Total events	126		49			

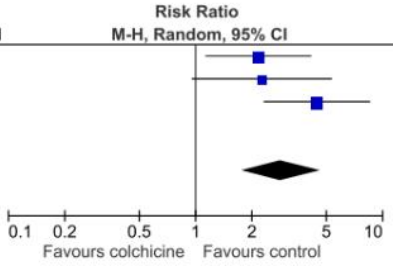
Heterogeneity: Tau² = 0.09; Chi² = 5.53, df = 3 (P = 0.14); I² = 46%
Test for overall effect: Z = 4.08 (P < 0.0001)



B

Study or Subgroup	colchicine Events	Total	control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1 COPPS-2 trial	26	180	12	180	37.7%	2.17 [1.13, 4.16]
2 COPPS trial	16	169	7	167	24.9%	2.26 [0.95, 5.35]
3 END-AF trial	44	179	10	181	37.5%	4.45 [2.31, 8.56]
4 Zarpelon et al	0	0	0	0		Not estimable
Total (95% CI)		**528**		**528**	**100.0%**	**2.87 [1.77, 4.64]**
Total events	86		29			

Heterogeneity: Tau² = 0.05; Chi² = 2.75, df = 2 (P = 0.25); I² = 27%
Test for overall effect: Z = 4.28 (P < 0.0001)



C

Study or Subgroup	colchicine Events	Total	control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1 COPPS-2 trial	10	180	9	180	34.8%	1.11 [0.46, 2.67]
2 COPPS trial	0	169	1	167	4.2%	0.33 [0.01, 8.03]
3 END-AF trial	11	179	4	181	25.1%	2.78 [0.90, 8.57]
4 Zarpelon et al	19	71	6	69	35.8%	3.08 [1.31, 7.24]
Total (95% CI)		**599**		**597**	**100.0%**	**1.92 [0.98, 3.75]**
Total events	40		20			

Heterogeneity: Tau² = 0.14; Chi² = 4.25, df = 3 (P = 0.24); I² = 29%
Test for overall effect: Z = 1.90 (P = 0.06)

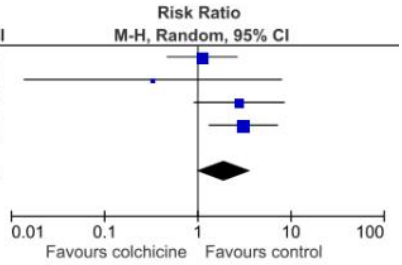


Figure 2: (A) Forest plot for all drug-related adverse effects. Individual and pooled risk ratios with 95% confidence intervals for RCTs enrolling patients undergoing open heart surgery comparing colchicine versus placebo or usual care.

(B) risk ratio for colchicine-induced gastrointestinal adverse effects.

(C) colchicine-associated non-gastrointestinal adverse effects.

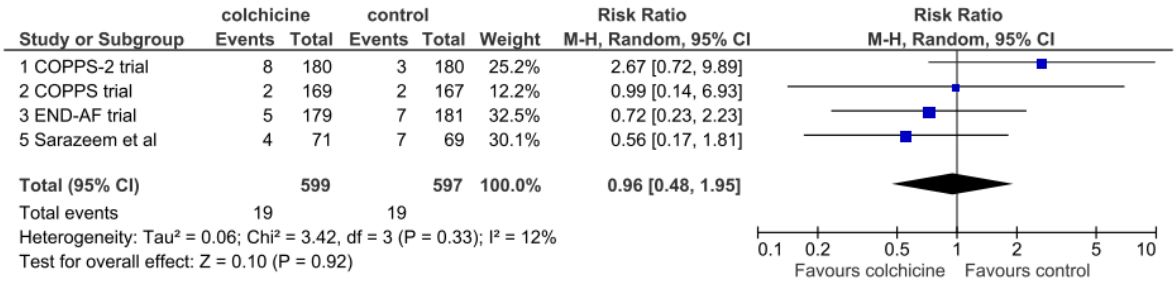


Figure 3: Major adverse events (death and stroke). Individual and pooled risk ratios (RR) with 95% confidence intervals.

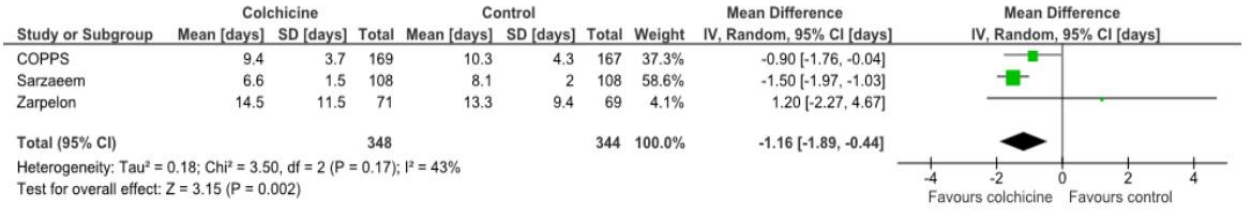
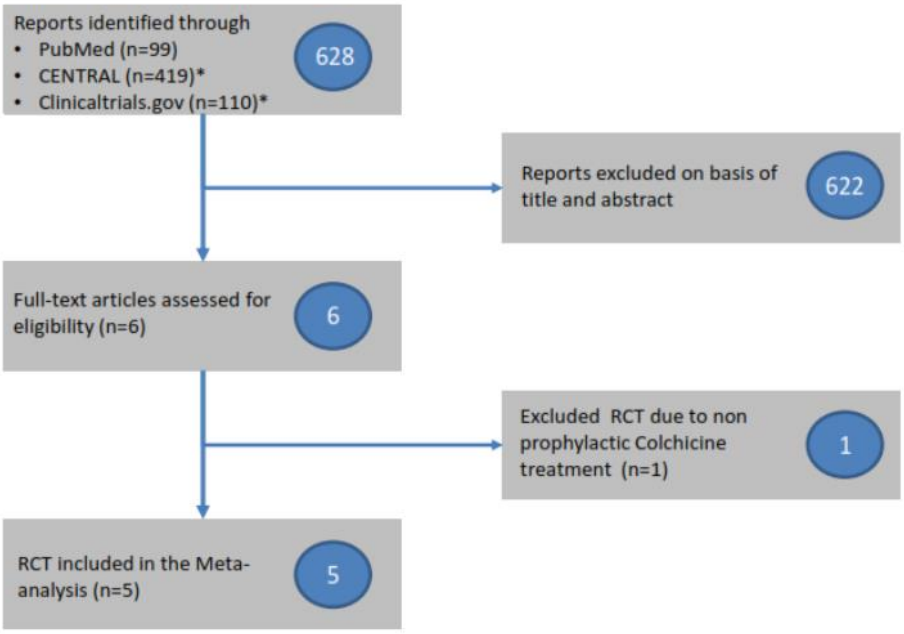


Figure 4: Forest Plot for hospital length-of-stay. Mean difference with 95% confidence intervals

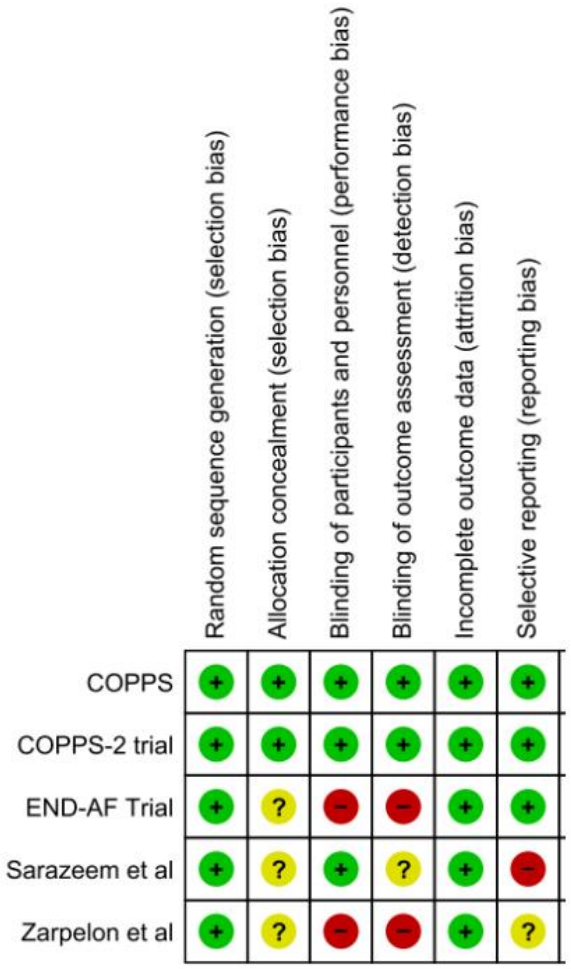
Table 1: Study and intervention characteristics of the included randomized controlled trials

Study Characteristics													Invention Characteristics				
Study	Year	Study design	Study arms	Sample size	# of participants colchicine group	# of participants control group	Date of registration	Enrolment period	Country	# of centres	POAF occurrence	Study design paper	Article language	Colchicine start	Colchicine loading	Colchicine dose	Colchicine treatment duration	Follow up duration
COPPS I Imazio et al. (23)	2011	multicentre, double-blind, placebo controlled, randomized trial	two (colchicine vs placebo)	336	169	167	Nov. 2005	June 2005 - June 2010	Italy	6	substudy of COPPS trials	yes	English	3d post-op	no loading	0.5mg BID (0.5mg qd <70kg)	1 month	1 month
COPPS II Imazio et al. (24)	2014	multicentre, double blind, placebo controlled, randomized trial	two (colchicine vs placebo)	360	180	180	Mar. 2012	Mar. 2012 - Mar. 2014	Italy	11	secondary endpoint	yes	English	2-3d pre-op	no loading	0.5mg BID (0.5mg qd <70kg)	1 month	3 months
END-AF Tabbalat et al. (12)	2016	multicentre, open-label, randomized trial	two (colchicine vs no treatment)	360	179	181	Dec. 2015	Oct. 2012 - Jan. 2015	Jordan	5	primary endpoint	no	English	1d pre-op	2mg 12-24h pre-op 1mg 4h pre- or post-op	0.5mg BID (0.5mg qd <70kg)	until discharge mean 8d	until discharge mean 8,3d
Sarzaeem et al. (30)	2014	singlecentre, double blind, placebo controlled randomized trial	two (colchicine vs. placebo)	216	108	108	n.a.	Jan. 2013 - Jul. 2013	Iran	1	primary endpoint	no	Abstract: English Text: Persian	0.5d pre-op	2mg 24h pre-op	0.5mg BID (0.5mg qd <70kg)	1 week	until discharge mean 7d
Zarpelon et al. (25)	2016	singlecentre, open-label, randomized trial	two (colchicine vs no treatment)	140	71	69	Mar. 2015	May 2012 - Nov. 2013	Brazil	1	primary endpoint	no	English	1d pre-op	2mg 24h or 1mg 12h pre-op	0.5mg BID	until discharge	until discharge



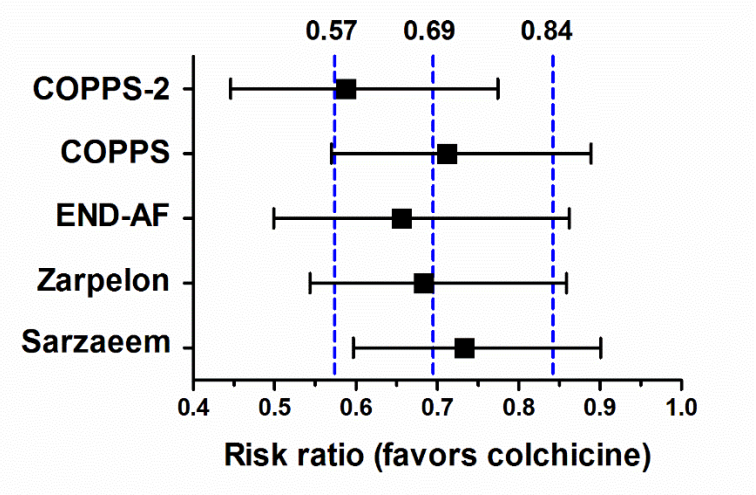
Appendix Figure 1: Flow chart showing the search strategy and number of studies screened, assessed, and included.

* search term limited to “colchicine”



Appendix Figure 2: Risk of bias assessments for included studies:

Plus/green suggests low of risk bias, question mark/yellow shows uncertain risk of bias, minus/red indicates potential high risk of bias



Appendix Figure 3**:** Robustness-analysis (risk ratio and corresponding 95% confidence interval) by removal of each individual study in turn (study named on the left-hand side is omitted)

Appendix Table 1: References identified in “PubMed” applying the described search terms.

History Download history

Search	Add to builder	Query	Items found
#3	Add	Search **(#1 and #2)**	99
#2	Add	Search **(“Atrial Fibrillation” or “Afib” or “AF” or “atrial“ or “supraventricular tachycardia” or “arrhythmia”)**	206679
#1	Add	Search **“Colchicine”**	18493

Appendix Table 2: Extracted parameters
POAF = post-operative atrial fibrillation, BMI = body mass index, AF = atrial fibrillation

Study Characteristics
Study design
Trial name
Reference
Sample size and calculation
Participants in colchicine group
Participants in control group
Registration number
Registration year
Date start enrollement
Date close enrollemnet
Publication year
Country
Number of centres
Predetermined endpoints
Paper language
Inclusion criteria
Exclusion criteria
Design paper
Reference design paper

Patient Population and Setting
Age
Sex
BMI
Coronary risk factors
Risk faktors for AF
Medical and surgical history
Comorbidities
Perioperative medications
Type of cardiac surgery

Study Design Characteristics
Follow up duration
Patients loss to follow up
AF measurement
Randomization mode
Blinding
Allocation concealment
Intention-to-treat analysis vs.
On treatment analysis

Intervention Characteristics
Colchicine regime
Colchicine loading
Colchicine dose
Treatmend duration

Binary Outcomes
Occurance of POAF
Adverse effects
Adverse events
Drug discontinuation rate

Continous Outcomes
Hospital length of stay
AF duration

Appendix Table 3: Baseline patient characteristics of the included randomized controlled trials

Participants baseline characteristics														
Study	Mean age	% male	Selected coronary risk factors				Risk factor for AF	Comorbid Conditions		Type of cardiac surgery during index hospital stay				
			% Diabetes	% Hypertension	% current Smoker	% Dyslipidaemia	Mean EF	Chronic renal failure	Creatinine mg/dL	CABG surgery	Valvular surgery	Aortic surgery	Combined surgery	others
COPPS I Imazio et al. (23)	65.7	68.5%	22.9%	68.8%	n.a.	n.a.	54.0	15.8%	n.a.	50%	27%	3%	18%	2%
COPPS II Imazio et al. (24)	67.5	68.9%	22.2%	67.5%	28.6%	n.a.	55.4	7.2%	n.a.	34%	36%	6%	24%	n.a.
END-AF Tabbalat et al. (12)	60.6	79.0%	49.4%	64.4%	21.7%	69.2%	54.7	n.a.	0.9	69%	14%	1%	13%	3%
Sarzaeem et al. (30)	59.9	78.0%	40.5%	57.5%	32.0%	n.a.	46.7	n.a.	1.1	100%	0%	0%	0%	0%
Zarpelon et al. (25)	60.9	67.9%	51.4%	88.6%	40.7%	62.9%	n.a.	n.a.	n.a.	100%	0%	0%	0%	0%

Appendix Table 4: Quality and risk of bias assessment of included RCTs

Study	Random sequence generation	Concealed allocation	Blinding of participants and personal	Blinding of outcome assessment	Not stopped early for benefit	<%5 randomized patients with missing outcome data	Intention to treat analysis	Report of unfavourable outcome data (adverse events, adverse effects, without significance)	Deviation between study protocol and reported trial outcome
COPPS I Imazio et al. (21) (23)	**Yes** *(Randomization by a central computer based, automated sequence based on permuted blocks with a block size of 4)*	**Yes** (random allocation sequence was implemented by sequentially numbered containers)	**double blinded** *(All participants and trial investigators were blinded to randomized treatment.)*	**yes** (Data were managed by investigators blinded to treatment assignments)	**Yes**	**Yes**	**Yes**	**Yes** *adverse effects adverse events*	**No** *(Rationale and design paper online available, registration prior to enrollement)*
COPPS II Imazio et al. (22) (24)	**Yes** *(central computer-based automated sequence, randomization was based on permuted blocks with a block size of 4)*	**Yes** (random allocation sequence was implemented using sequentially numbered study drug containers. Allocation concealment was achieved by using opaque sealed envelopes, sequentially numbered containers, and central randomization)	**double blinded** *(all participants and trial investigators will be blinded to randomized treatment; a blinded clinical end point committee will adjudicate all events)*	**yes** (a blinded clinical end point committee will adjudicate all events)	**Yes**	**Yes**	**Yes**	**Yes** *adverse effects adverse events primary outcone not significant*	**No** *(Rationale and design paper online available, registration prior to enrollement)*
END-AF Tabbalat et al. (12)	**Yes** *(using an online research randomizer (www.randomizer.com)*	**not reported**	**lack of blinding** *(both patient and investigators are aware of allocation)*	**not blinded**	**Yes**	**Yes**	**Yes**	**Yes** *adverse effects adverse events primary outcone not significant*	**unclear** *(registration after finishing enrollment)*
Sarzaeem et al. (30)	**Yes** *(using a table of random numbers)*	**not reported**	**double blinded** *(patients and clinical staff are not aware of treatment groups assigment)*	**not reported**	**Yes**	**unclear** (excluded patients unable to tolerate enteral medication within 48h post-op)	**not reported**	**No** *adverse data missing*	**not reported**
Zarpelon et al. (25)	**Yes** *(using an online research randomizer (http://stattrek.com/statistics/random-number-generator.aspx))*	**not reported**	**lack of blinding** *(participants and researchers were instructed on the treatment)*	**not blinded**	**Yes**	**Yes**	**not reported**	**Yes** *adverse events primary outcone not significant*	**unclear** *(registration after finishing enrollment)*

Appendix Table 5: Comparison of the present with prior published meta-analysis on Colchicine and the occurrence of atrial fibrillation after cardiac procedure

Meta-Analysis (year)	# of trials included	Total # of pt in Colchicine group	Q-statistics	I^2-statistics	pooled estimate RR or Odds ratio (95% CI)	Trials included (year)	# of pt in Colchicine group	weight	cardiac procedure	Indication for Colchicine
Trivedi et al. (2014)	3	286	0.45	0%	ODDS 0.44 (0.16 ; 0.96)					
						1) Imazio et al. (2011) (COPPS)	169	48,3%	open cardiac surgery	primary prevention of AF
						2) Egami et al. (2013)	36	21,4%	pulmonary vein isolation	secondary prevention AF
						3) Deftereos et al. (2012)	81	30,4%	pulmonary vein isolation	secondary prevention AF
Verma et al. (2015)	4	560	4.35	31%	RR 0.65 (0.51 ; 0.82)					
						1) Imazio et al. (2011) (COPPS)	169	17,0%	open cardiac surgery	primary prevention of AF
						2) Imazio et al. (2014) (COPPS 2)	180	38,9%	open cardiac surgery	primary prevention of AF
						3) Deftereos et al. (2012)	103	28,7%	pulmonary vein isolation	secondary prevention AF
						4) Sarzaeem et al. (2014)	108	15,3%	open cardiac surgery	primary prevention of AF
Wang et al. (2016)	3	458	n.a.	47%	RR 0.77 (0.52 ; 1.13)					
						1) Imazio et al. (2011) (COPPS)	180	31,8%	open cardiac surgery	primary prevention of AF
						2) Imazio et al. (2014) (COPPS 2)	180	47,2%	open cardiac surgery	primary prevention of AF
						3) Meurin et al. (2015) (POPE) [46]	98	20,9%	open cardiac surgery	post-operative pericardial effusion
Papageorgiou (2016)	4	560	n.a.	1%	ODDS 0.54 (0.41 ; 0.70)					
						1) Imazio et al. (2011) (COPPS)	169	22,5%	open cardiac surgery	primary prevention of AF
						2) Deftereos et a. (2014) [47]	103	24,1%	pulmonary vein isolation	secondary prevention AF
						3) Sarzaeem et al. (2014)	108	19,3%	open cardiac surgery	primary prevention of AF
						4) Imazio et al. (2014) (COPPS 2)	180	34,0%	open cardiac surgery	primary prevention of AF
Lennerz et al. (current study)	5	707	4.03	1%	RR 0.69 (0.57 ; 0.84)					
						1) Imazio et al. (2011) (COPPS)	169	14,5%	open cardiac surgery	primary prevention of AF
						2) Imazio et al. (2014) (COPPS 2)	180	51,2%	open cardiac surgery	primary prevention of AF
						3) Sarzaeem et al. (2014)	108	13,1%	open cardiac surgery	primary prevention of AF
						4) Tabbalat et al. (2016) (END-AF)	179	17,8%	open cardiac surgery	primary prevention of AF
						5) Zarpelon et al. (2016)	71	3,4%	open cardiac surgery	primary prevention of AF