JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 2, NO. 1, 2016

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2015.09.016

Colchicine for Prevention of Post-Operative Atrial Fibrillation

A Meta-Analysis

Justin Z. Lee, MD,[a] Nirmal Singh, MD,[a] Carol L. Howe, MD,[b] See-Wei Low, MD,[a] Jennifer J. Huang, DO,[a] Gilbert Ortega, BS,[c] Kwan S. Lee, MD,[d] Anil Pandit, MD[e]

ABSTRACT

OBJECTIVES This study sought to investigate the efficacy and safety of colchicine for prevention of post-operative atrial fibrillation.

BACKGROUND Proinflammatory processes induced during cardiac surgery may contribute toward post-operative atrial fibrillation (AF). Colchicine is a potent anti-inflammatory agent, which may have a role in post-operative AF prevention.

METHODS We searched PubMed, EMBASE, Web of Science, CINAHL, ClinicalTrials.gov, and the Cochrane Library databases for randomized controlled trials (RCT) comparing colchicine versus placebo for prevention of post-operative AF. The main outcome measure of interest was the development of AF within 12 months after cardiac surgery. The overall risk ratio (RR) for the development of post-operative AF was computed using a random-effects model.

RESULTS Data analyzed from 3 randomized studies with a total of 912 patients, where 457 patients received colchicine and 455 patients received placebo, showed that perioperative colchicine therapy was associated with a reduced incidence of post-operative AF (RR: 0.65; 95% confidence interval [CI]: 0.46 to 0.91; $p < 0.01$). Although colchicine therapy was associated with increased incidence of gastrointestinal intolerance (RR: 2.20; 95% CI: 1.31 to 3.70; $p = 0.003$), it was not associated with early treatment discontinuation (RR: 1.37; 95% CI: 0.95 to 1.96; $p = 0.09$).

CONCLUSIONS In conclusion, current evidence suggests that colchicine therapy is efficacious for the prevention of post-operative AF, and may be considered as adjunctive prophylaxis. Further studies may be required to determine the optimal treatment protocol to reduce the incidence of gastrointestinal intolerance. (J Am Coll Cardiol EP 2016;2:78–85)

Atrial fibrillation (AF) is the most common arrhythmia and is a significant source of morbidity and mortality (1). It has a high occurrence rate following cardiac surgery (2). Post-operative AF may lead to longer hospital stays, increased health care costs, poorer neurocognitive outcomes, and increased incidence of stroke (3–6). Given the increased morbidity, prevention of post-operative AF is becoming an important management goal supported by many guidelines (7–9). It has been postulated that increased inflammation may precede AF (10). Inflammatory processes triggered by cardiac surgery have been implicated in the development of post-operative AF (11). Therefore, the use of an agent with anti-inflammatory properties may be effective in the goal of preventing post-operative AF. Corticosteroid therapy has been shown to be successful due to its potent anti-inflammatory effect, but its use remains controversial owing to potential adverse effects, including perioperative hyperglycemia, wound healing impairment, and infection (12). Colchicine, which may be a relatively safer alternative, has been evaluated for the use of prevention of post-operative AF (13–15). There has yet to be a

Listen to this manuscript's audio summary by *JACC: Clinical Electrophysiology* Editor-in-Chief Dr. David J. Wilber.

From the [a]Department of Internal Medicine, University of Arizona, Tucson, Arizona; [b]Arizona Health Sciences Library, University of Arizona, Tucson, Arizona; [c]College of Medicine, University of Arizona, Tucson, Arizona; [d]Department of Cardiovascular Diseases, University of Arizona, Tucson, Arizona; and the [e]DeBakey Heart Institute, Hays, Kansas. Dr. Kwan Lee has received honoraria from St. Jude Medical and Maquet Medical Systems. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 15, 2015; revised manuscript received September 1, 2015, accepted September 4, 2015.

systematic overview that would provide a more precise estimate of the efficacy and safety of the colchicine in post-operative AF. In our study, we aim to summarize the available data on colchicine's efficacy to prevent AF post-operatively, as well as to ascertain the significance of colchicine related adverse events.

SEE PAGE 86

METHODS

SEARCH STRATEGY. A systematic literature review was planned and performed using methods specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic review (16). Both controlled vocabulary terms (e.g., MeSH) and key words were used to search for articles addressing the post-operative use of colchicine in patients undergoing cardiac surgery. The following databases were searched: PubMed/MEDLINE (1946 to 2014), Embase (1947 to 2014), Cochrane Library (1898 to 2014), Web of Science (1898 to 2014), EBSCO/CINAHL (Plus with Full Text) (1981 to 2014), and ClinicalTrials.gov (1997 to 2014). Literature searches were completed on June 18, 2014. The complete PubMed/MEDLINE search strategy, upon which the other database searches were also built, is available in the Online Appendix. Citations to and reference lists within the selected articles were also searched for studies that would meet inclusion criteria. All retrieved references were reviewed to identify prospective randomized trials that compared the clinical outcome of colchicine therapy for prevention of post-operative AF. No language or study type restriction was used for initial extraction of the data. No restrictions on the subheadings were applied. All references of relevant trials were also reviewed. We did not limit the language of the manuscript to be included in our meta-analysis. All non-English manuscripts were translated prior to consideration for inclusion.

STUDY SELECTION. Our pre-specified selection criteria were as follows: 1) randomized controlled trials; 2) head-to-head comparisons of perioperative administration of colchicine versus placebo; and 3) study participants who underwent any cardiac surgery. Exclusion criteria were: 1) studies with inadequate reporting of outcome data to meet our primary endpoint; 2) studies without peer-reviewed publication of the manuscripts; and 3) studies on procedures other than cardiac surgery. Our primary endpoint was the development of post-operative AF. Other outcomes of interest included the incidence of adverse events and early treatment discontinuation.

DATA EXTRACTION. Two independent reviewers performed the study selection (J.Z.L., S.-W.L.). In case of disagreements, a third reviewer (C.L.H.) cast the deciding vote. Titles and abstracts of retrieved references were screened for inclusion and full texts of potential articles were further analyzed to see if they met inclusion criteria (Figure 1). Case reports, letters, editorials, and systematic reviews or meta-analyses were excluded. Both individuals who collected the data used the following study-specific characteristics: study name, sample size of treatment group and control group per intention-to-treat analysis, event number and rate in both the treatment group and control group, statistical effect estimates used in the individual studies, dose and time period of colchicine, specific cardiac surgery performed, inclusion and exclusion criteria of individual studies, AF as specified in individual studies, rate of adverse

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

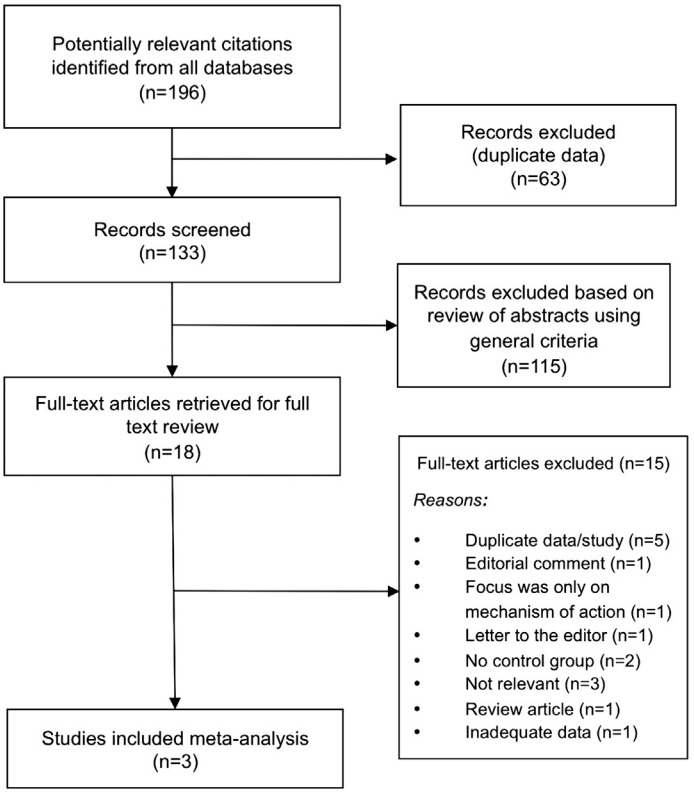
CABG = coronary artery bypass grafting

CI = confidence interval

RCT = randomized controlled trial

RR = risk ratio

FIGURE 1 Study Selection Diagram



Flow diagram of identification of published records retrieved from published data searches and from other sources. Reasons for exclusion of potentially eligible studies are listed.

TABLE 1 Characteristics of Included Studies

First Author, Year (Ref. #)	N	Design	Protocol	Type of Cardiac Surgery	Primary Endpoint	Definition of AF to Meet Endpoint	Follow-Up
Imazio et al., 2011 (13)	336	Prospective, randomized, double blind, placebo controlled	Colchicine/placebo = 1 mg BID for 1 day (started on third day post-op), maintenance dose 0.5 mg BID for 1 month (≥70 kg and half dose if ≤70 kg)	Cardiac surgery (CABG, valvular surgery, aorta surgery, combined surgery, and others)	Rate of postoperative AF on placebo/colchicine treatment*	No consistent P waves before each QRS complex and irregular ventricular rate, lasting more than 5 min.	12 months
Imazio et al., 2014 (15)	360	Prospective, randomized, double blind, placebo controlled	Colchicine/placebo = 0.5 mg BID (or 0.5 mg daily if ≤70 kg) starting between 48 and 72 h before surgery and continued for 1 month	Cardiac surgery (included CABG, valvular disease, aortic disease and combined surgery)	Postpericardiotomy syndrome within 3 months; secondary endpoint was postoperative AF in 3 months after cardiac surgery	AF lasting more than 30 s.	3 months
Sarzaeem et al., 2014 (14)	216	Prospective, randomized, double blind, placebo controlled	Colchicine/placebo = 1 mg night before and on day of surgery, 0.5 mg BID for 5 days post-op	CABG only	Incidence of postoperative AF	AF for at least 10 min	6 months

*Post-operative AF events in day 1 and 2 were excluded from the analysis as therapy was initiated on day 3.
AF = atrial fibrillation; BID = twice daily; CABG = coronary artery bypass grafting.

effects, early treatment discontinuation, and baseline patient characteristics within each study including the presence comorbid conditions such as hepatic or renal impairment along with treatment with antiarrhythmic drugs.

STATISTICAL ANALYSIS. Statistical analysis was performed using Review Manager 5.2.9 software (available from The Cochrane Collaboration) and STATA/IC 13.1 (StataCorp, College Station, Texas). A study or trial level pooled analysis of the included randomized controlled trial (RCT) was performed to evaluate the effect of pre-treatment with colchicine on prevention of AF. The analysis was performed according to the intention-to-treat strategy. Mantel-Haenszel risk ratio (RR) with 95% confidence interval (CI) was calculated. The chi-square statistic was calculated and a formal test of heterogeneity was conducted. The I^2 index was used to summarize the proportion of the total variability in the estimates due to between-study variation. We regarded I^2 of <25%, 25% to 50%, and >50% as low, moderate, and high amounts of heterogeneity, respectively. The random-effects model rather than the fixed-effects model was used to assess the overall estimate because of high degree of clinical and methodological heterogeneity. We assessed for potential publication bias by using the funnel plots of standard error of RR versus RR. Sensitivity analysis was performed by repeating the analysis 5 times and by removing 1 study at a time. The baseline study characteristics were analyzed to assess the difference in proportions using the proportion test calculator. All the tests were 2-tailed and a p value <0.05 was regarded as significant in this meta-analysis.

RESULTS

BASELINE CHARACTERISTICS. We found 196 articles through database searching and zero additional articles through citation analysis of the selected articles. Of the 133 articles, which remained after duplicates were removed, 115 were excluded because of irrelevance to the topic (Figure 1). Strict inclusion and exclusion criteria as outlined above were applied to the full text of 18 articles. We excluded 2 studies

TABLE 2 Overall Baseline Characteristics of Populations of Included Studies

	Colchicine (n = 457)	Placebo (n = 455)	p Value
Age, yrs	63.8 ± 3.9	65 ± 4.1	<0.001
Male	328/457 (71.8)	306/455 (67.3)	0.17
Diabetes mellitus	114/457 (25)	124/455 (27.3)	0.72
Hypertension	292/457 (63.9)	297/455 (65.3)	0.79
Chronic kidney disease	47/457 (10.3)	37/455 (8.1)	0.25
LVEF	51.8 ± 5	52.2 ± 4.4	0.20
Previous history of AF	26/349 (7.4)	26/347 (7.5)	0.96
Current smoker	77/288 (27)	90/288 (31)	0.29
COPD	26/349 (7.4)	30/347 (8.6)	0.56
CABG surgery	154/349 (44)	135/347 (39)	0.18
Valvular surgery	105/349 (30)	118/347 (34)	0.26
Aortic surgery	15/349 (4.3)	18/347 (5.2)	0.58

Values are mean ± SD or n/n (%).
AF = atrial fibrillation; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction.

(17,18) published as abstracts because of insufficient data in the abstract for accurate analysis. Figure 1 shows our search strategy, which yielded 3 RCTs with 912 patients (13–15), with 457 patients randomized to receive colchicine and 455 patients to receive placebo.

PATIENT CHARACTERISTICS AND INTERVENTIONS. Table 1 summarizes the study characteristics of the 3 included RCTs. All 3 RCTs were prospective, randomized, double blinded, placebo controlled trials. Among the RCTs, 2 trials (13,15) had 1-month treatment duration, and 1 trial (14) had only a 5-day treatment duration. Cardiac surgery included patients undergoing coronary artery bypass grafting (CABG), surgery for valvular diseases, and surgery for aortic diseases.

Baseline clinical characteristics of selected studies are reported in Table 2. The mean age was 64-years and on average, males accounted for 70% of subjects. Comparison between colchicine and placebo groups revealed no difference in prevalence of diabetes mellitus (25% vs. 27%; p = 0.72), hypertension (64% vs. 65%; p = 0.79), smoking status (27% vs. 31%; p = 0.29), chronic obstructive pulmonary disease (7.4% vs. 8.6%; p = 0.56), chronic kidney disease (10.3% vs. 8.1%; p = 0.25), CABG surgery (44% vs. 39%; p = 0.18), valvular surgery (30% vs. 34%; p = 0.26), and aortic surgery (4.3% vs. 5.2%; p = 0.58).

Table 3 displays the quality assessment of the included studies. A modified version of quality assessment was done using the format mentioned in the PRISMA guidelines. We used similar baseline characteristics, inclusion/exclusion criteria, allocation concealment, randomization, blinding, follow-up completion, and analysis of study as the main determinants of the quality of a study.

TABLE 3 Quality Assessment of Included Studies

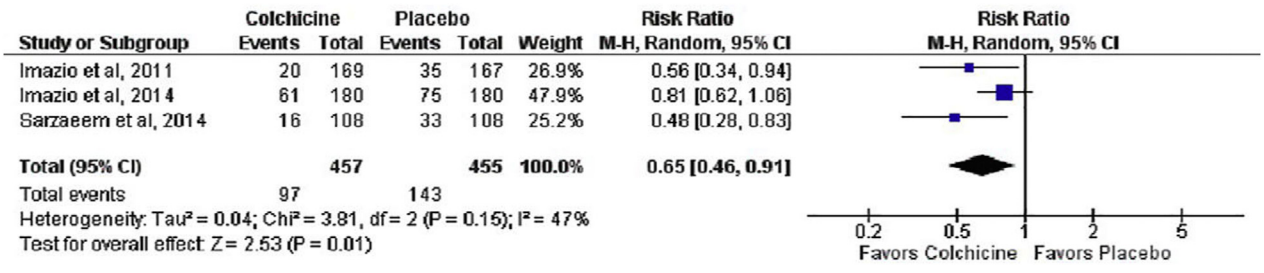
First Author, Year (Ref. #)	AC	Randomization	Blinding	Analysis	Follow-Up Completion	Similar Baseline	I/E Criteria
Imazio et al., 2011 (13)	YES	YES	DB	ITT	YES	YES	YES
Imazio et al., 2014 (15)	YES	YES	DB	ITT	YES	YES	YES
Sarzaeem et al., 2014 (14)	UC	YES	DB	UC	UC	YES	YES

AC = allocation concealment; DB = double blind; I/E criteria = inclusion and exclusion criteria; ITT = intention-to-treat analysis; UC = unclear.

PREVENTION OF POST-OPERATIVE AF. Pooled estimates across the 3 RCTs showed that colchicine use was associated with a reduced risk of post-operative AF when compared to placebo (RR: 0.65; 95% CI: 0.46 to 0.83; p = 0.01) (Figure 2). We drew our conclusions using the random-effects model for this analysis given the clinical and methodological heterogeneity of the RCTs included in the meta-analysis. There was moderate heterogeneity among the studies using the random method (I^2 = 47, chi-square = 3.91, df = 2, p = 0.15). The I^2 measure was used to quantify heterogeneity as it is independent of the number of studies in the meta-analysis and has better power as compared to using the chi-squared method. Publication bias was assessed by Funnel plot (Figure 3) with standard error of log RR against RR. It shows an asymmetrical distribution of the plot around the summary effect size, which could indicate potential publication bias. It should be read in the context of the heterogeneity of the studies included in the analysis.

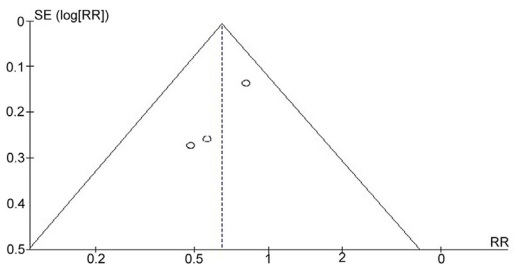
ADVERSE EVENTS AND EARLY TREATMENT DISCONTINUATION. Table 4 displays a detailed list of adverse event occurrences. Pooled analysis revealed that colchicine use was associated with an increased incidence of gastrointestinal adverse

FIGURE 2 Prevention of Post-Operative Atrial Fibrillation With Colchicine



CI = confidence interval; M-H = Mantel-Haenszel.

FIGURE 3 Funnel Plot With 95% Confidence Interval to Evaluate the Evidence of Publication Bias



RR = risk ratio.

effects compared to placebo (RR: 2.20; 95% CI: 1.31 to 3.70; p = 0.003) (Figure 4). The most common gastrointestinal symptom was nausea, followed by vomiting, diarrhea, and abdominal pain. However, the rate of early treatment discontinuation was not significantly different between colchicine group compared to placebo (RR: 1.37; 95% CI: 0.95 to 1.96; p = 0.09) (Figure 5).

DISCUSSION

This meta-analysis based on 3 randomized controlled trials demonstrates that perioperative administration of colchicine results in significantly lower rate of post-operative occurrence of AF.

The development of post-operative AF is multifactorial, including pericardial inflammation, autonomic nervous system imbalance during the postoperative period, and metabolic and electrolyte derangements (2). The brief administration of corticosteroids has been shown to reduce immediate AF recurrences after cardiac surgery (12), supporting the hypothesis that perioperative proinflammatory processes are a major factor contributing to the development of postoperative AF. Colchicine disrupts microtubule assembly of leukocytes by binding β-tubulin with the formation of tubulin-colchicine complexes (19). Microtubules are important in numerous cellular cytoskeletal and intracellular transport activities. This allows colchicine to inhibit various leukocytes functions and exert its anti-inflammatory effect.

Post-operative AF may be transient, but it increases morbidity and is associated with longer hospital stays, increased health care costs, poorer neurocognitive outcomes, and increased an incidence of stroke (3–6). The role of colchicine in the reduction of these end points is unclear, but was partially reflected in the COPPS (COlchicine for the Prevention of the Post-pericardiotomy Syndrome) trial, in which patients who received colchicine had a shorter overall hospital stay and rehabilitation (13).

Our results also highlight the issue of a statistically higher incidence of gastrointestinal intolerance (nausea, vomiting, diarrhea, and abdominal pain) in the colchicine group. This finding is similar to another meta-analysis performed on colchicine for pericarditis prevention (20). However, the rate of early treatment discontinuation was not statistically significant in the colchicine group. Nonetheless, it is still appropriate to consider colchicine in well-selected patients, especially those at higher risk of post-operative AF, such as those with advanced age, chronic obstructive pulmonary disease, obesity, valvular heart disease, atrial enlargement, and perioperative heart failure (8), or those who are more likely to have debilitative consequences from the development of post-operative AF, instead of routine administration to all patients undergoing cardiac surgery.

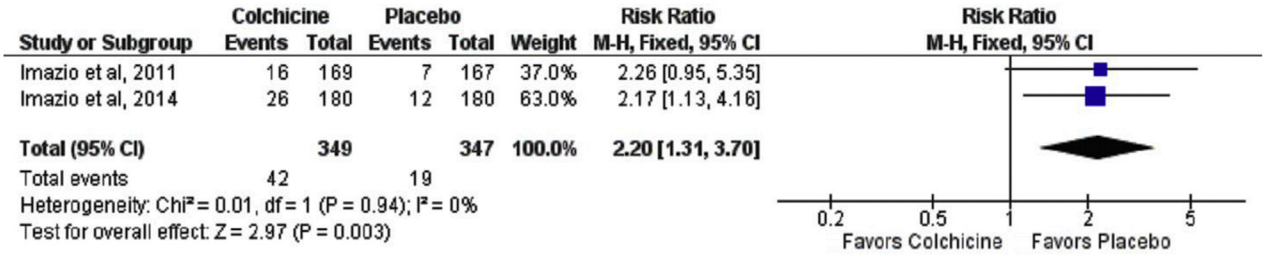
Colchicine is significantly associated with gastrointestinal intolerance, although there was no association with overall early treatment discontinuation. One strategy to reduce in gastrointestinal intolerance may be to optimize timing and dosage of colchicine therapy, and avoid pre-operative colchicine administration. Patients in the COPPS-2 (COlchicine for the Prevention of the Post-pericardiotomy Syndrome and Postoperative Atrial Fibrillation) trial were given

TABLE 4 Occurrence of Adverse Event and Early Treatment Discontinuation in Included Studies

	Hepatotoxicity		Gastrointestinal Intolerance		Myotoxicity		Early Treatment Discontinuation	
First Author, Year (Ref. #)	Colchicine	Placebo	Colchicine	Placebo	Colchicine	Placebo	Colchicine	Placebo
Imazio et al., 2011 (13)	0/169 (0.0)	0/167 (0.0)	16/169 (9.5)	7/167 (4.2)	0/169 (0.0)	1/167 (0.6)*	20/169 (11.8)	11/167 (6.6)
Imazio et al., 2014 (15)	1/180 (0.6)	2/180 (1.1)	26/180 (14.4)	12/180 (6.7)	NA	NA	39/180 (21.7)	32/180 (17.8)
Sarzaeem et al., 2014 (14)	NA	NA	NA	NA	NA	NA	NA	NA

Values are n/N (%). *Myotoxicity in placebo group was related to concomitant use of statin.

FIGURE 4 Overall Risk of Gastrointestinal Intolerance



Abbreviations as in Figure 2.

colchicine therapy 2 to 3 days prior to the planned procedure, and they observed a 2-fold increase in adverse events (15). The Imazio et al. (13) trial administered colchicine 3 days after the procedure, and the Sarzaeem et al. (14) RCT administered colchicine the night before the procedure.

The ideal medication regimen for prevention of post-operative AF remains unclear. It would be interesting to determine if colchicine's post-operative AF prevention efficacy is additive to the efficacy of other medications mentioned in the guidelines for use in patients undergoing cardiac surgery, such as amiodarone (Class IIa) (9,21). Colchicine and sotalol are currently Class IIb recommendations for reduction of post-operative AF. It is possible that patients may benefit from adjunctive prophylaxis with colchicine.

Our overall meta-analysis results are in discordant with those of the COPPS-2 trial, which showed that colchicine failed to prevent postoperative AF based on the intention-to-treat cohort (15). We postulate that this discordance is due to the greater rate of early colchicine treatment discontinuation in the COPSS-2 trial, as suggested by the fact that the per-protocol cohort in that trial displayed evidence of reduction of postoperative AF.

STUDY LIMITATIONS. First, there is significant heterogeneity in the initial cardiac surgery performed among the included trials. In the COPPS and COPPS-2 RCTs, the inclusion criteria was various types of cardiac surgery ranging from CABG to aortic surgery (13,15). In Sarzaeem et al. (14), only patients undergoing CABG were included. Other sources of significant heterogeneity include different follow-up time periods (ranging from 3 months to 12 months), and diverse colchicine administration protocols among the RCTs.

There is also a potential for AF underdetection during the follow-up period after the initial procedure, and each of the RCTs had their own follow-up protocol and means of AF detection. In the COPPS-2 trial (15), continuous electrocardiographic monitoring was performed for at least 5 days post-operatively, with 12-lead electrocardiograms daily and more frequently at the discretion of the treating

FIGURE 5 Overall Risk of Early Treatment Discontinuation

Abbreviations as in Figure 2.

physicians for clinically suspected arrhythmia. Twelve-lead electrocardiograms were also collected at each follow-up visit. However, there should only be a minimal difference in AF detection between the colchicine groups and the placebo groups given the similar follow-up protocol between treatment and placebo groups in each trial. Another potential confounding factor is the use of perioperative antiarrhythmic medications. In the COPPS study, there was no significant difference in the use of perioperative amiodarone in patients with and without post-operative AF (12.7% vs. 14.9%; p = 0.83) (13). In the COPPS-2 trial, the colchicine group had numerically lower use of amiodarone compared to the placebo group (7.2% vs. 10%) (15). The COPPS study had a lower perioperative use of beta-blockers in patients with post-operative AF compared with those without post-operative AF (32.7% vs. 55.5%, p = 0.003) (13), and the COPPS-2 study had almost similar use of perioperative beta-blockers in both colchicine and placebo groups (57.2% vs. 56.1%) (15).

Our meta-analysis is also limited by the small number of studies included, with 2 out of the 3 included studies performed by Imazio et al. (13,15). This highlights the need for more randomized controlled trials on the use of colchicine to prevent post-operative AF.

CONCLUSIONS

The results of this meta-analysis suggest that perioperative initiation of colchicine therapy may reduce the incidence of post-operative AF. Further studies may be required to determine the optimal treatment protocol, including timing of administration as well as dosing, to reduce the incidence of adverse events and early treatment discontinuation.

ACKNOWLEDGEMENT Simin Golestani, BS, medical student from the University of Arizona College of Medicine, assisted with language translation of one of the included manuscripts.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Kwan S. Lee, Department of Cardiovascular Disease, University of Arizona, 3950 S. Country Club Road, Suite 200, Tucson, Arizona 85714. E-mail: klee@shc.arizona.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Perioperative initiation of colchicine, a potent anti-inflammatory agent, either in combination with amiodarone or alone is efficacious for the prevention of AF following cardiac surgery. The regimen is limited by gastrointestinal side effects in approximately 10% of patients leading to early discontinuation.

TRANSLATIONAL OUTLOOK: Further studies on the use of colchicine to prevent post-operative AF will be required to determine the optimal duration and treatment protocol to optimize patient tolerance and prophylactic efficacy.

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Executive summary: heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation 2012;125:188–97.

2. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Annals of internal medicine 2001;135:1061–73.

3. 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.

4. Creswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperative atrial arrhythmias. Ann Thorac Surg 1993;56:539–49.

5. Stanley TO, Mackensen GB, Grocott HP, et al. The impact of postoperative atrial fibrillation on neurocognitive outcome after coronary artery bypass graft surgery. Anesth Analg 2002;94:290–5, table of contents.

6. Gialdini G, Nearing K, Bhave PD, et al. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. JAMA 2014;312:616–22.

7. Mitchell LB. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: prevention and treatment of atrial fibrillation following cardiac surgery. Can J Cardiol 2010;27:91–7.

8. Fuster V, Rydén LE, Cannom DS, et al. 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 Developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol 2011;57:e101–98.

9. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation. Europace 2010;12:1360–420.

10. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001;104:2886–91.

11. Ishii Y, Schuessler RB, Gaynor SL, et al. Inflammation of atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and atrial fibrillation. Circulation 2005;111:2881–8.

12. Ho KM, Tan JA. Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose-response meta-analysis. Circulation 2009;119:1853–66.

13. Imazio M, Brucato A, Ferrazzi P, et al. 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.

14. Sarzaeem M, Shayan N, Bagheri J, Jebelli M, Mandegar M. Low dose Colchicine in prevention of atrial fibrillation after coronary artery bypass graft: a double blind clinical trial. Tehran Univ Med J 2014;72:147–54.

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

16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.

17. Egami Y, Nishino M, Kato T, et al. Impact of short duration colchicine use on reduction of immediate atrial fibrillation after catheter ablation: prospective study. J Am Coll Cardiol 2013;61:E408.

18. Egami Y, Nishino M, Tanouchi J, Yamada Y. Colchicine can reduce early recurrence of atrial fibrillation after pulmonary vein isolation. Circulation 2012;126:A11249.

19. Bhattacharyya B, Panda D, Gupta S, Banerjee M. Anti-mitotic activity of colchicine and the structural basis for its interaction with tubulin. Med Res Rev 2008;28:155–83.

20. Imazio M, Brucato A, Forno D, et al. Efficacy and safety of colchicine for pericarditis prevention. Systematic review and meta-analysis. Heart 2012;98:1078–82.

21. January CT, Wann LS, Alpert JS, et al. 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.

KEY WORDS **atrial fibrillation, colchicine, post-operative atrial fibrillation**

APPENDIX **For an expanded Methods section, please see the online version of this article.**