Journal of Arrhythmia ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Review

Efficacy of ranolazine in preventing atrial fibrillation following cardiac surgery: Results from a meta-analysis

Chintan Trivedi, MD, MPH[a,*], Ankit Upadhyay, MD[b], Kinjal Solanki, MD[b]

[a] St David's Healthcare, 1015 East 32nd Street, Austin, TX 78705, USA
[b] Department of Internal Medicine, Jamaica Hospital Medical Center, Jamaica, NY, USA

ARTICLE INFO

Article history:
Received 12 September 2016
Received in revised form
8 October 2016
Accepted 4 November 2016

Keywords:
Atrial fibrillation
Cardiac surgery
Metaanalysis
Ranolazine
Post-operative atrial fibrillation

ABSTRACT

Background: Atrial fibrillation (AF) is a common complication after cardiac surgery. Ranolazine is a Food and Drug Administration approved anti-ischemic drug, which also has anti-arrhythmic properties. Recent studies have demonstrated the benefit of ranolazine in preventing post-operative AF (POAF) in patients undergoing cardiac surgery. Hence, we performed a meta-analysis of published studies comparing ranolazine plus standard therapy versus standard therapy for POAF prevention in patients undergoing cardiac surgery.

Methods: We performed a comprehensive search of Medline, Google Scholar, PubMed, abstracts from annual scientific sessions, and Cochrane library database for studies that assessed the effectiveness of ranolazine plus standard therapy by comparing it with standard therapy alone in preventing POAF in patients undergoing cardiac surgery. From all the studies, data on POAF events among groups were collected, and the random-effects (DerSimonian and Laird) method was used for meta-analysis.

Results: Four studies with 663 patients were included in the final analysis, with 300 and 363 patients in the ranolazine plus standard therapy and standard therapy groups, respectively. The types of cardiac surgeries were coronary artery bypass grafting (CABG), valve surgery or combination of CABG, and valve surgeries. After pooled analysis, ranolazine plus standard therapy was associated with a significant reduction in POAF events compared to standard therapy alone (risk ratio=0.44 [0.25, 0.78], p-value=0.005). There was no difference in adverse events between the two therapies. However, in one study, more patients in the ranolazine group had transient symptomatic hypotension after the surgery.

Conclusions: Ranolazine may prove beneficial in POAF prevention following cardiac surgeries. Although the pooled treatment effect is quite impressive with a reduction of more than 50% of risk of developing POAF, small number of studies and variation in ranolazine dose regimen in each study make our results inconclusive, but worthy of further investigation. That is why this result has to be interpreted as only hypothesis generating, rather than conclusion drawing.

Contents

* Corresponding author.
E-mail address: drchintantrivedi@yahoo.com (C. Trivedi).

http://dx.doi.org/10.1016/j.joa.2016.10.563
1880-4276/

Please cite this article as: Trivedi C, et al. Efficacy of ranolazine in preventing atrial fibrillation following cardiac surgery: Results from a meta-analysis. J Arrhythmia (2016), http://dx.doi.org/10.1016/j.joa.2016.10.563

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and it commonly occurs after cardiac surgery. AF is often associated with stroke, congestive heart failure, and myocardial infarction, all of which contribute to the increase in the length of hospital stay, higher medical costs, and increase in morbidity and mortality [1–6]. Approximately 20%–50% of patients experience post-operative atrial fibrillation (POAF) after cardiac surgery [1,6]. Based on the American and European task forces, AF prevention is one of the essential goals after any cardiac procedure [4,7,8]. POAF prevention has been a therapeutic challenge so far, and a number of medications have been studied, such as beta-blockers, amiodarone, colchicine, and calcium channel blockers [4,5,9,10]. Recent meta-analysis showed that beta-blockers reduces POAF incidence rate from 31% to 16.3% compared with controls, whereas amiodarone decreased the incidence of POAF to 19.4% compared with a 33.3% incidence rate in the control group [5,6]. Ranolazine is a Food and Drug Administration-approved anti-anginal drug (AAD), which also blocks abnormal late sodium channels and rapidly activates delayed rectifier potassium channels, which leads to attenuation of sodium–calcium currents and excessive electrical activity in atrial tissue. Thus, reduced after depolarization reserve suppresses AF [6,11,12]. Moreover, the mechanism of ranolazine to increase the refractory period after repolarization [5,13] could decrease AF after cardiac surgery. Ranolazine has been studied to prevent POAF; however, ranolazine is not required to prevent POAF, based on formal guidelines. Recent studies demonstrated promising results of ranolazine plus standard therapy compared to standard therapy in preventing POAF in patients undergoing cardiac surgery. Effectiveness of ranolazine in preventing POAF has been studied in a few randomized control trials, and the data suggests that ranolazine may have a role in preventing POAF without causing a significant increase in postoperative complications or mortality.

2. Materials and methods

2.1. Search strategy and study selection

We evaluated all the relevant studies published before December 2015. We included all the studies where ranolazine plus standard therapy was used and compared with the standard therapy for prevention of AF following cardiac surgeries. The studies were searched from Medline, Google Scholar, PubMed, Cochrane library database, annual scientific sessions of American Heart Association, American College of Cardiology, Heart Rhythm Society, and European Society of Cardiology. Two independent reviewers performed the search electronically or manually. Disagreements were resolved through discussion to reach final decisions. All the animal, editorial, and review studies were excluded. Data on the type of cardiac surgery, ranolazine dosage, duration of therapy, type of comparison group, type of cardiac surgery, and AF incidence rate following cardiac surgery were collected.

2.2. Selected published clinical studies

We reviewed 116 manuscript publications and 44 conference abstracts (Fig. 1). Out of those, 19 studies assessed the effect of ranolazine on AF after cardiac surgery. We excluded 12 studies because they were review articles, and 1 article was excluded because ranolazine was used in combination with amiodarone in the study group instead of ranolazine alone. Two studies were excluded because they were abstract presentations at conferences for the same study, which was included in our final analysis. Finally, four studies (three manuscript publications and one abstract publication from the American Heart Association's Scientific Session) [14–17] were included in the final analysis.

2.3. Statistical analysis

We performed a meta-analysis by including four clinical studies to provide an overall estimate of the effect of ranolazine therapy in preventing post-operative AF in patients undergoing cardiac surgery. The presence of heterogeneity among these studies was evaluated with Cochrane Q $\chi 2$ test, and inconsistency was assessed with I^2 test that describes the percentage of the variability in effect estimates that is due to heterogeneity. Publication bias was assessed and displayed as a funnel plot of precision. Furthermore, we performed Egger's test and Begg and Mazumdar's rank correlation test to assess publication bias. Statistical level of significance for the summary treatment effect estimate was analyzed by random effect method [18]. Overall p-value of less than 0.05 was considered as statistically significant except for heterogeneity and publication bias testing where a two-tailed p-value of less than 0.1 considered as statistically significant. The meta-analysis was

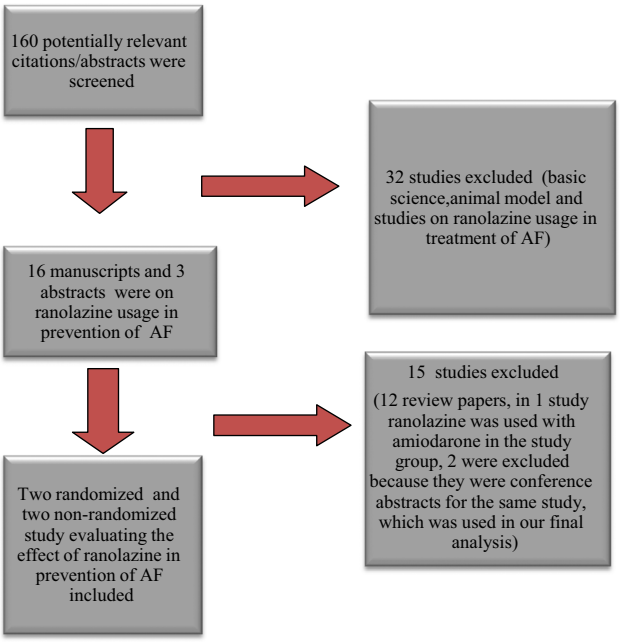

Fig. 1. Selection process of studies included in the systematic review. (AF=atrial fibrillation) Search criteria: ("ranolazine"[MeSH Terms] OR "ranolazine"[All Fields]) AND ("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields]).

Please cite this article as: Trivedi C, et al. Efficacy of ranolazine in preventing atrial fibrillation following cardiac surgery: Results from a meta-analysis. J Arrhythmia (2016), http://dx.doi.org/10.1016/j.joa.2016.10.563