

Ranolazine alone or as a complement to the amiodarone for both prevention and cardioversion of atrial fibrillation: A meta-analysis of the literature

Renato De Vecchis *, Carmelina Ariano

Cardiology Unit, Presidio Sanitario Intermedio "Elena d'Aosta", ASL Napoli 1 Centro, via Cagnazzi 29, 80137 Napoli, Italy

Corresponding author: Renato De Vecchis, Via P.Gaurico 21, 80125 Napoli, Italy; e-mail address: devecchis.erre@virgilio.it; phone: +393483313530

Abstract:

Introduction Recent evidence from relatively small randomized controlled trials would seem to support a useful role of ranolazine for the prevention and treatment of atrial fibrillation (AF). The present study is aimed at providing information about the possible beneficial anti-arrhythmic properties of ranolazine. In particular, the meta-analysis carried out in this study focuses on the application of ranolazine to prophylaxis and treatment of atrial fibrillation.

Methods Both randomized controlled trials (RCTs) and non randomized observational studies concerning the effects of ranolazine on AF were included in the meta-analysis. In each of the considered studies, a comparison was made between a group of patients taking ranolazine and a second group treated instead with another antiarrhythmic therapy, or assigned to placebo. Efficacy outcomes were the risk of new-onset AF, the probability of conversion to sinus rhythm of patients with recent occurrence (≤ 48 h) of AF and the time to conversion to sinus rhythm. Safety endpoints were death, adverse events, QTc prolongation and hypotension.

Results Ten studies (8 RCTs and 2 nonrandomized observational studies) were gathered on the whole. Ranolazine was effective in preventing the occurrence of AF when compared to controls (RR= 0.60; 95% CI: 0.43–0.83; $p = 0.002$). Subgroup analysis showed a more pronounced preventive effect of ranolazine against AF in the postoperative setting of coronary artery bypass grafting (CABG) surgery (RR= 0.39; 95% CI: 0.18–0.83; $p=0.02$) when compared to non- postoperative AF (RR= 0.76; 95% CI: 0.63–0.92; $p=0.04$). Ranolazine enhanced the chances of successful cardioversion when added to intravenous amiodarone compared to amiodarone alone (RR 1.18; 95% CI: 1.05–1.33; $p = 0.004$) and significantly decreased the time to cardioversion (SMD= -10.35 h; 95% CI: -18.13 hours to -2.57 hours; $p < 0.001$). Overall risks of death, adverse events, and QTc prolongation were shown to be similar in the comparison between patients treated with ranolazine and controls.

Conclusions Ranolazine given orally at appropriate doses showed the property to significantly quicken the conversion of AF to sinus rhythm when combined with the iv amiodarone, compared to iv amiodarone alone. Furthermore, in patients in sinus rhythm, ranolazine proved to reduce the frequency of new onset AF as well as of its recurrences, especially in patients undergone CABG surgery, known to be at high risk of developing postoperative AF. In addition, ranolazine use seems to be safe and associated with relatively few adverse events.

Key words: ranolazine; atrial fibrillation; prevention; pharmacological cardioversion; meta-analysis

Background

Ranolazine is a drug successfully used for the prevention and treatment of myocardial ischemia, in refractory angina pectoris, in combination with beta-blockers and / or as a substitute or an adjunct for oral nitrates(1-3). Moreover, recent evidence from relatively small randomized controlled trials would seem to

support a useful role of ranolazine for the prevention and treatment of atrial fibrillation(4). The present study is aimed at providing information only about the possible beneficial anti-arrhythmic properties of ranolazine, and therefore does not include any reference to the previous studies concerning the anti-ischemic effects of the drug. In particular, the meta-analysis performed in this study focuses on the application of ranolazine to prophylaxis and treatment of atrial fibrillation.

Methods

A metaanalysis was conducted on the databases Pubmed, SCOPUS and EMBASE using the key words "ranolazine" and "atrial fibrillation", by recruiting both non randomized observational studies or randomized controlled trials (RCTs) provided that they were centered around the effects of ranolazine on atrial fibrillation. The present meta-analysis was projected and accomplished according to current MOOSE recommendations on observational studies[5] and PRISMA recommendations on randomized clinical trials[6].

Study selection

Studies had to be prospective randomized controlled studies(RCTs)or not randomized observational studies . In each of the studies admitted to meta-analysis, a comparison had to be made between a group of patients taking ranolazine and a second group treated instead with another antiarrhythmic therapy (e.g., amiodarone alone), or assigned to placebo. Studies were incorporated in the metaanalysis provided that they brought sufficient information about the efficacy and safety of ranolazine when used as a preventive or therapeutic tool against atrial fibrillation.

Outcomes of interest

In our metaanalysis, the strength of the association of the ranolazine use with some efficacy and safety outcomes was evaluated. In particular, the efficacy outcomes were i) the risk of new-onset atrial fibrillation, ii) the probability of conversion to sinus rhythm of patients with recent occurrence(≤ 48 h)of atrial fibrillation, iii) the time to conversion to sinus rhythm.

With regard to the association with the risk of developing atrial fibrillation, differentiated calculations were provided to assess the prophylactic effect of ranolazine on the risk of new-onset atrial fibrillation occurring after coronary artery bypass graft (CABG) surgery (postoperative atrial fibrillation, POAF) and on the risk of recurrence of atrial fibrillation in patients previously converted to sinus rhythm (secondary prevention of atrial fibrillation).

As regards the effect on the probability of achieving the pharmacological cardioversion of atrial fibrillation, it was allowed to incorporate in the meta-analysis even the data relating to the use of ranolazine in combination with other anti-arrhythmic drugs .

In our meta-analysis, there has been also the quantitation of effects exerted by ranolazine on several safety endpoints; in particular, the association of ranolazine use with all-cause mortality as well as its association with adverse events, QTc prolongation and symptomatic hypotension were calculated.

Data extraction

The search procedure was carried out independently by two Reviewers (R.D.V. and C.A.) . In the event of a possible disagreement during data extraction, any conflicting interpretation was solved by discussion. Notably, it was stated that the studies selected for the meta-analysis should have included patients aged over 18 years. In addition, animal experimental studies as well as case reports of ranolazine administration without a control group should have been eliminated from the meta-analysis. Similarly, all studies not written in English, duplicated studies, review articles, editorials, and expert opinions should have been excluded.

Quality assessment

The authors (R.D.V. and C.A.) assessed the risk of bias for both a) non randomized observational studies and b) RCTs. The Newcastle-Ottawa quality assessment scale was used for quality evaluation of the nonrandomized observational studies incorporated in the meta-analysis, whereas the risk of bias for RCTs was evaluated using the Cochrane Collaboration Risk of Bias Tool.

In the case of nonrandomized observational studies, according to the Newcastle-Ottawa quality assessment scale eligibility was ascertained based on the following criteria: the selection of the study groups (0–4 points), the comparability of the groups (0–2 points), and the ascertainment of either the exposure or outcome of interest (0–3 points), with a total score of 9. A score ≥ 5 was deemed suitable for inclusion in the meta-analysis.

In the case of RCTs, the following risks of bias were evaluated: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; and (6) other bias

Statistical analysis

In case of dichotomous variables (for example, new episodes of atrial fibrillation in the course of ranolazine prophylaxis, or conversion to sinus rhythm during therapy with ranolazine, the effect size was expressed as relative risk with 95% confidence interval, using inverse variance as the weighting method. Instead, when the endpoint was a continuous variable, such as "time to conversion to sinus rhythm" or "change in duration of QTc interval", the effect size was expressed as a difference in means (MD) with 95% confidence interval, using inverse variance once again as the weighting method. Due to large variety of patients, the relative risk was calculated using a random effects model, even in case no heterogeneity was found. Statistical heterogeneity across studies was tested using the Cochran's Q test and I^2 statistic (coefficient of variability due to inter-study variability). Statistical analyses were performed using Review Manager 5.0.4 software (available from the Cochrane Collaboration; <http://www.cochrane.org>) and Stata version 10 (Stata Corp LP, College Station, TX, USA).

Results

Fig.1 illustrates the flow diagram for meta-analysis we used. A total of 237 articles were initially detected. Among them, 218 were excluded because of the ascertained inconsistency with our inclusion criteria, as inferred on the basis of the abstracts (185 articles because they referred to anti-ischemic properties of ranolazine without addressing its use in the atrial fibrillation, 33 articles as being review articles [no.27] or letters to editors [no.6]). Among the remaining 19 full-text articles assessed for eligibility, further 9 articles were excluded, because they brought inconsistent or contradictory data (no.2) or due to missing or incomplete data (no.7). Consequently 10 studies were included in the meta-analysis (2 nonrandomized observational studies and 8 randomized clinical trials), including 6745 patients on the whole. The characteristics of the studies incorporated in the meta-analysis are summarized in Table 1. Of the 10 included studies, 9 were published as full manuscripts (7-15) and one as an abstract (16).

Ranolazine for primary or secondary prevention of atrial fibrillation

5 studies (7,9,12-14) were aimed to evaluate the efficacy and safety of ranolazine as a prophylactic agent for the prevention of new-onset AF (4 studies) or of recurrences of AF (one study) within different clinical settings.

In particular, the study of Miles et al. (7) and the one of Tagarakis et al. (9), both RCTs, as well as that of Hammond et al. (14), a retrospective cohort study, focused on the prophylaxis of the postoperative AF in patients in sinus rhythm who underwent coronary artery bypass graft surgery. Instead, the study by Scirica et al. (12) was conceived to explore the effect of ranolazine on the overall AF burden in acute coronary syndromes (ACS) and ascertain whether ranolazine reduces the incidence of clinical AF after an ACS over

a one year follow-up. Finally, the RAFFAELLO multicenter study by De Ferrari et al. (13) was aimed to evaluate the risk of AF recurrence over a follow-up of 16 weeks in patients previously affected by paroxysmal or persistent AF whose sinus rhythm had been retrieved by means of electrical cardioversion. In these studies, ranolazine was effective in reducing episodes of AF when compared to controls (RR=0.60; 95% CI:0.43 to 0.83; figure 2, bottom panel). In particular, based on subgroup analyses, a larger effect size was detected for the prevention of post-operative AF (RR=0.39; 95% CI:0.18-0.83 Figure 2, top panel) when compared to the prevention of non-postoperative AF (RR=0.76; 95% CI: 0.63-0.92, figure 2, intermediate panel).

Ranolazine for conversion of AF to sinus rhythm

Four studies(8,10-11,16) explored the effects of ranolazine on conversion to sinus rhythm of recent-onset AF. Ranolazine improved the probability of successful pharmacological cardioversion when added to intravenous (iv) amiodarone compared to iv amiodarone alone (RR= 1.18; 95% CI: 1.05 – 1.33; p = 0.04; Fig. 3).

As regards the time to cardioversion, the combination of oral ranolazine with iv amiodarone significantly shortened the time from drug administration to retrieval of sinus rhythm when compared to iv amiodarone alone (weighted mean difference= – 10.35 hours; 95% CI: -18.13, -2.57 hours; Fig. 4).

Ranolazine for decreasing AF burden

One study, namely the Harmony trial by Reiffel et al. (15), reported on the effect of ranolazine on AF burden in patients with paroxysmal AF and implanted pacemakers, where AF burden could be continuously assessed. Patients were randomized double-blind to placebo, ranolazine alone (750 mg bid), dronedarone alone (225 mg bid), or one of the combinations. Both drugs when assumed alone were unable to reduce AF burden with respect to placebo. Conversely, ranolazine 750 mg twice daily/dronedarone 225 mg twice daily reduced AF burden by 59% versus placebo ($p=0.008$), whereas ranolazine 750 mg twice daily /dronedarone 150 mg twice daily reduced AF burden by 43% ($p=0.072$).

Because of its particular design, the study was not used as a source of data for estimates of the efficacy endpoints but exclusively for the estimates of safety endpoints.

Safety endpoints

Overall, lack of significant differences was noticeable when comparing ranolazine and control group as regards the risk of death, with three out of five studies reporting mortality rates showing no events at all (RR= 0.99; 95% CI: 0.79–1.24; Fig. 5).

Moreover, no difference was noticeable in the comparison between patients taking ranolazine and control group with regard to the risk of serious adverse events as well as the extent of QTc prolongation(figures 6 and 7). Conversely, a significantly increased risk of symptomatic hypotension was noted in patients treated with ranolazine (RR=1.37; 95% CI:1.1-1.7;Fig. 8). This unfavorable feature was guided by the retrospective cohort study of Hammond et al(14), in which a greater use of hemodynamically active medications may have increased the incidence of symptomatic hypotension in the ranolazine group, according to the interpretation provided by these authors(see Discussion).

Discussion

Overall, our meta-analysis points out that ranolazine significantly reduces the episodes of new-onset AF (7,9,14) as well as the AF recurrences after cardioversion(12)(fig 2). Furthermore, ranolazine, when orally co-administered with iv amiodarone, achieves the conversion of AF to sinus rhythm more frequently than iv amiodarone alone (8,10,16) and causes a significant reduction in the time required for pharmacological cardioversion(8,10-11,16; fig 4). In particular, on the basis of four studies (8,10 – 11,16) including a total of 278 patients (Figure 4) the time to achieve pharmacological cardioversion was reduced by an average of 10.3

hours compared with the iv amiodarone alone. These results pave the way for possible major advances in the AF prevention and treatment.

Indeed, the demonstrated synergism between amiodarone and ranolazine would entail an increased probability of successful therapeutic intervention for paroxysmal AF as well as a greater speed in the achievement of pharmacological cardioversion, using such a combination therapy. In this regard, the documented synergistic electrophysiologic effect of the two drugs may ensue from different modalities of interaction with myocardial sodium channels. Indeed, differently from amiodarone, which is as an inactivated-state blocker of sodium channels

(17-18), ranolazine acts as an activated-state blocker(19). More in detail, the simultaneous usage of oral ranolazine at proper doses with iv amiodarone induces an atrial selective use-dependent lowering of maximum conduction velocity and excitability, while at the same time both drugs enhance the post-repolarization refractoriness. Notably, addition of ranolazine to amiodarone does not generate proarrhythmia. As regards the safety evidenced for such an association, several favorable features of ranolazine have been proposed as key-factors: in particular, the suppression of early afterdepolarizations and the lack of increase in dispersion of repolarization acknowledged to ranolazine(19) seem to play a paramount role in preventing any proarrhythmic effect to the amiodarone-ranolazine combination regimen for paroxysmal AF.

Conversely, as regards the favorable preventive effect of ranolazine against new-onset AF in patients in sinus rhythm, as found in our meta-analysis, one can express some doubts because in several studies (7,9,13-14) the follow-up was relatively short.

In addition, in the considered studies, either those aimed at preventing AF occurrence or those aimed at achieving AF pharmacological cardioversion, in which the parameters of left ventricular (LV)systolic function were systematically reported (7-11,13,15-16), all patients had LV ejection fraction preserved (> 50%). The lack of cases with reduced LV ejection fraction among the enrolled patients belonging to the studies incorporated in the metaanalysis might represent a limit for efficacy and safety evaluations. However ranolazine has already proven to exert its AF-suppressing effect even in patients with cardiac structural abnormalities, without additional pro-arrhythmic or extra-cardiac side-effects (20).

Based on our metaanalysis, among the explored safety endpoint, symptomatic hypotension was significantly increased with the use of ranolazine. This unexpected result of our safety metaanalysis was guided by the study by Hammond et al.(see figure 8).

In effect, in this abovementioned retrospective cohort study, that included patients undergone cardiac valve replacement and/ or CABG surgery, symptomatic hypotension in the first 72 h occurred more frequently in the ranolazine group. Due to the production of oxygen-free radicals and intracellular calcium overload during coronary artery reperfusion, the myocardium may be stunned and recovering following cardiac surgery [21]. However, ranolazine's mechanisms of action do not suggest it should greatly aggravate these effects [22]. Indeed, when used as an anti-anginal drug, ranolazine has minimal effects on blood pressure and heart rate, with incidence being $\leq 4\%$ in patients [10]. Moreover, due to nonrandomized design of this study, a significantly greater amount of hemodynamically active medications(namely, beta-blockers and ACE-inhibitors) was used in the ranolazine group and this may have increased the incidence of hypotension in this subset(14). However, there was no difference in late hypotension (72 h after surgery) between the two groups. In any case, according to Hammond et al.(14), further studies assessing the incidence of early, symptomatic hypotension should be conducted in patients undergone ranolazine alone or coupled to beta-blockers or amiodarone for prevention of postoperative AF in the setting of cardiac valve and/or CABG surgery, because an appreciable rate of symptomatic hypotension had never been reported in this patient population previously.

Conclusions

Ranolazine has proven to be a useful complement of iv amiodarone for achieving the pharmacological cardioversion of recent-onset AF. Moreover, ranolazine given orally at proper doses has displayed the property to significantly quicken the conversion to sinus rhythm when combined with the iv amiodarone, compared to iv amiodarone alone. Furthermore, in patients in sinus rhythm, ranolazine has been shown to

reduce the frequency of new onset AF as well as of its recurrences. The prophylactic efficacy of ranolazine against the occurrence of AF has been greater in patients undergone CABG surgery, known to be at high risk of developing postoperative AF.

References

- 1) Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. *Circulation*. 2006 May 23;113(20):2462-72.
- 2) Siddiqui MA, Keam SJ. Spotlight on ranolazine in chronic stable angina pectoris. *Am J Cardiovasc Drugs*. 2006;6(5):357-9.
- 3) Rosano GM, Vitale C, Volterrani M. Pharmacological Management of Chronic Stable Angina: Focus on Ranolazine. *Cardiovasc Drugs Ther*. 2016 Aug;30(4):393-8.
- 4) Banerjee K, Ghosh RK, Kamatam S, Banerjee A, Gupta A. Role of Ranolazine in cardiovascular disease and diabetes: Exploring beyond angina. *Int J Cardiol*. 2017 Jan 15;227:556-564.
- 5) Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000 Apr 19;283(15):2008-12.
- 6) Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009 Aug 18;151(4):264-9.
- 7) Miles RH, Passman R, Murdock DK. Comparison of effectiveness and safety of ranolazine versus amiodarone for preventing atrial fibrillation after coronary artery bypass grafting. *Am J Cardiol*. 2011 Sep 1;108(5):673-6.
- 8) Fragakis N, Koskinas KC, Katritsis DG, Pagourelis ED, Zografos T, Geleris P. Comparison of effectiveness of ranolazine plus amiodarone versus amiodarone alone for conversion of recent-onset atrial fibrillation. *Am J Cardiol*. 2012 Sep 1;110(5):673-7.
- 9) Tagarakis GI, Aidonidis I, Daskalopoulou SS, Simopoulos V, Liouras V, Daskalopoulos ME, Parisis C, Papageorgiou K, Skouleringis I, Triposkiadis F, Molyvdas PA, Tsilimingas NB. Effect of ranolazine in preventing postoperative atrial fibrillation in patients undergoing coronary revascularization surgery. *Curr Vasc Pharmacol*. 2013 Nov;11(6):988-91.
- 10) Koskinas KC, Fragakis N, Katritsis D, Skeberis V, Vassilikos V. Ranolazine enhances the efficacy of amiodarone for conversion of recent-onset atrial fibrillation. *Europace*. 2014 Jul;16(7):973-9.
- 11) Simopoulos V, Tagarakis GI, Daskalopoulou SS, Daskalopoulos ME, Lenos A, Chryssagis K, Skouleringis I, Molyvdas PA, Tsilimingas NB, Aidonidis I. Ranolazine enhances the antiarrhythmic activity of amiodarone by accelerating conversion of new-onset atrial fibrillation after cardiac surgery. *Angiology*. 2014 Apr;65(4):294-7.
- 12) Scirica BM, Belardinelli L, Chaitman BR, Waks JW, Volo S, Karwatowska-Prokopczuk E, Murphy SA, Cheng ML, Braunwald E, Morrow DA. Effect of ranolazine on atrial fibrillation in patients with non-ST elevation acute coronary syndromes: observations from the MERLIN-TIMI 36 trial. *Europace*. 2015 Jan;17(1):32-7.
- 13) De Ferrari GM, Maier LS, Mont L, Schwartz PJ, Simonis G, Leschke M, Gronda E, Boriani G, Darius H, Guillaumón Torán L, Savelieva I, Dusi V, Marchionni N, Quintana Rendón M, Schumacher K, Tonini G, Melani L, Giannelli S, Alberto Maggi C, Camm AJ; RAFFAELLO Investigators (see Online Supplementary Appendix for List of Participating Centers and Investigators). Ranolazine in the treatment of atrial fibrillation: Results of the dose-ranging RAFFAELLO (Ranolazine in Atrial Fibrillation Following An Electrical Cardioversion) study. *Heart Rhythm*. 2015 May;12(5):872-8.

- 14) Hammond DA, Smotherman C, Jankowski CA, Tan S, Osian O, Kraemer D, DeLosSantos M. Short-course of ranolazine prevents postoperative atrial fibrillation following coronary artery bypass grafting and valve surgeries. *Clin Res Cardiol*. 2015 May;104(5):410-7
- 15)Reiffel JA, Camm AJ, Belardinelli L, Zeng D, Karwatowska-Prokopczuk E, Olmsted A, Zareba W, Rosero S, Kowey P; HARMONY Investigators. The HARMONY Trial: Combined Ranolazine and Dronedronone in the Management of Paroxysmal Atrial Fibrillation: Mechanistic and Therapeutic Synergism. *Circ Arrhythm Electrophysiol*. 2015 Oct;8(5):1048-56.
- 16)Tsanaxidis N, Aidonidis I, Hatziefthimiou A, Triposkiadis F, Skoularigis I. Acute ranolazine plus amiodarone vs amiodarone alone for conversion of recent onset atrial fibrillation: a prospective clinical study, *Eur Heart J. Suppl*. 2015 36: 910–911.
- 17)KhanI A,Mehta NJ,Gowda RM.Amiodarone for pharmacological cardioversion of recent-onset atrial fibrillation.*Int J Cardiol* 2003;89:239–248.
- 18)ChevalierP,Durand-Dubief A, Burri H, Cucherat M,KirkorianG,Touboul P. Amiodarone versus placebo and classic drugs for cardioversion of recent-onset atrial fibrillation: ametaanalysis. *J Am Coll Cardiol* 2003;41:255–262.
- 19)Frommeyer G, Milberg P, Uphaus T, Kaiser D, Kaese S, Breithardt G, Eckardt L. Antiarrhythmic effect of ranolazine in combination with class III drugs in an experimental whole-heart model of atrial fibrillation. *Cardiovasc Ther* 2013;31: 63–71.
- 20)Scirica BM, Morrow DA, Hod H, Murphy SA, Belardinelli L, Hedgepeth CM, Molhoek P, Verheugt FW, Gersh BJ, McCabe CH, Braunwald E. Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome: results from the Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial. *Circulation*. 2007 Oct 9;116(15):1647-52.
- 21)Kim SJ, Depre C, Vatner SF Novel mechanisms mediating stunned myocardium. *Heart Fail Rev* 2003 8:143–153
- 22)Vizzardi E, D'Aloia A, Quinzani F, Bonadei I, Rovetta R, Bontempi L, Curnis A, Dei Cas L A focus on antiarrhythmic properties of ranolazine. *J Cardiovasc Pharmacol Ther* 2012 17:353–356

First author	Miles	Fragakis	Tagarakis	Koskinas	Simopoulos	Scirica (MERLIN)	De Ferrari (RAFFAELLO)	Hammond	Reiffel (HARMONY)	Tsanaxidis
Year	2011	2012	2013	2014	2014	2015	2015	2015	2015	2015
Design	NROS	RCT, SB	RCT,SB,PC	RCT,SB	RCT,SB	RCT,DB,PC	RCT,DB,PC	NROS	RCT,DB	RCT,SB
Intervention group	Oral ranolazine 1500 mg before surgery+ 1000mg bid after surgery	Oral ranolazine 1500 mg once plus IV amiodarone	Oral ranolazine 375 mg twice daily for 3 days prior to surgery and until discharge	Oral ranolazine 1500 mg once plus IV amiodarone	Oral ranolazine 500 mg loading dose followed by 375 mg 6 hours later and 375 mg bid plus IV amiodarone	Intravenous ranolazine with a 200 mg bolus, followed by 80 mg /h infusion for 12-96 h; subsequently 1000 mg of oral ranolazine bid	Oral ranolazine 375 mg bid for 16 weeks or 500 mg bid for 16 weeks or 750 mg bid for 16 weeks	Oral ranolazine 1000 mg bid starting on surgery day	Oral ranolazine 750 mg bid	Oral ranolazine 1000 mg once daily
Control group	Amiodarone	IV amiodarone loading dose 5 mg /kg in 1 hour , then 50 mg /h for 24 hours	Placebo	IV amiodarone loading dose 5 mg /kg in 1 hour , then 50 mg /h for 24 hours	IV amiodarone 300 mg in 30 min, then 750 mg in 24 hours	Placebo	Placebo	Placebo	Placebo or dronedarone	IV amiodarone loading dose of 5 mg /kg in 1 hour , then 50 mg /h for 24 hours
Main endpoint	Occurrence of post-operative AF	Conversion of AF to SR within 24 hours	Occurrence of post-operative AF	Conversion of AF to SR within 24 hours	Conversion of AF to SR	Overall 1-year incidence of clinical AF events; overall AF burden.	AF recurrence	Occurrence of post-operative AF	Overall AF burden.	Conversion of AF to SR
Method of AF detection	c-ECG monitoring throughout the hospital stay	c-ECG monitoring for 24 hours	Holter monitoring for the first 24 hours and ECG monitoring every 4 hours until discharge	c-ECG monitoring	Holter monitoring for the first 24 hours and ECG monitoring every 4 hours until discharge	c-ECG monitoring for the first 7 days	TT-ECG monitoring for 16 weeks	c-ECG monitoring throughout the hospital stay	c-ECG monitoring in patients with implanted devices	Not reported

Follow-up period	Until discharge	24 hours	Until discharge	24 hours	Until discharge	12 months	16 weeks	7 days/until discharge	12 weeks	48 hours
Study population	Post – CABG,SR	Recent-onset AF(<48- hour duration)	Post –CABG,SR	Recent-onset AF(<48- hour duration)	Post –CABG,SR	Non -ST elevation ACS, SR	Post-electrical cardioversion, SR	Post –CABG and/or valve surgery,SR	Paroxysmal AF in patients with recent dual chamber pacemaker implant	Recent-onset AF(<48- hour duration)
No. of patients	182(R) 211(C)	25(R) 26(C)	34(R) 68(C)	61(R) 60(C)	20(R) 21(C)	3162(R) 3189(C)	65(R 375) 60(R500) 58(R750) 55(C)	69(R) 136(C)	26 (R) 52 (C)	36(R) 29 (C)
Mean age (years)	66.7±9. (R) 65± 10.9(C)	62±8(R) 64±7(C)	69±7(R) 67±8 (C)	66±11(R) 64±9 (C)	69±7(R) 67±9 (C)	63±10(R) 63±11(C)	67±11.8(R 375) 65± 8.5(R500) 63±11.3(R 750) 65.2±9.5 (C)	59.5±10.8 (R)) 62.2± 11.8(C)	70±10.8(R) 73.5±11.5 (C)	67± 10(R) 62± 11 (C)
LVEF(%)	57.7± 9.8(R) 54.7± 12.7(C)	55± 9 (R) 58± 7 (C)	52.5± 8.5 (R) 53.9±9(C)	54.5± 10(R) 58.2± 7(C)	52.6±8.5(R) 53.8±9.6 (C)	Not reported	57±11 (R 375) 56± 10(R500) 55±11 (R 750) 57±9 (C)	Not reported	57±10 (R) 57± 7(C)	54.3±5.9(R) 54.5± 3.8(C)

Table 1 Legend: NROS, non-randomized observational study; RCT, randomized controlled trial; SB, single-blind; PC, placebo-controlled; DB, double-blind; bid, twice a day; IV, intravenous; AF, atrial fibrillation; SR, sinus rhythm; c-ECG, continuous ECG; TT-ECG, transtelephonic ECG; CABG, coronary artery bypass graft; ACS, acute coronary syndrome; R, ranolazine; C, control; LVEF, left ventricular ejection fraction