Received: 26 September 2017 | Accepted: 29 November 2017

DOI: 10.1002/joa3.12031

REVIEW ARTICLE

WILEY Journal of Arrhythmia Open Access

Impact of ranolazine on ventricular arrhythmias – A systematic review

George Bazoukis MD, MSc[1] | Gary Tse MD, PhD[2,3] | Konstantinos P. Letsas MD, PhD[1] | Costas Thomopoulos MD, PhD[4] | Katerina K. Naka MD, PhD[5] | Panagiotis Korantzopoulos MD, PhD[6] | Xenophon Bazoukis MD, MSc[7] | Paschalia Michelongona MD[1] | Stamatis S. Papadatos MD[8] | Konstantinos Vlachos MD[1] | Tong Liu MD, PhD[9] | Michael Efremidis MD[1] | Adrian Baranchuk MD, PhD[10] | Stavros Stavrakis MD, PhD[11] | Costas Tsioufis MD, PhD[12]

[1]Department of Cardiology, Catheterization Laboratory, Evangelismos General Hospital of Athens, Athens, Greece

[2]Department of Medicine and Therapeutics, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, China

[3]Li Ka Shing Institute of Health Sciences, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, China

[4]Department of Cardiology, Helena Venizelou Hospital, Athens, Greece

[5]Second Department of Cardiology, School of Medicine, University of Ioannina, Ioannina, Greece

[6]First Department of Cardiology, School of Medicine, University of Ioannina, Ioannina, Greece

[7]Department of Cardiology, General Hospital of Ioannina, "G Hatzikosta", Ioannina, Greece

[8]Faculty, Department of Internal Medicine, Athens School of Medicine, Sotiria General Hospital, National and Kapodistrian University of Athens, Athens, Greece

[9]Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, China

[10]Division of Cardiology, Electrophysiology and Pacing, Kingston General Hospital, Queen's University, Kingston, ON, Canada

[11]University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

[12]First Cardiology Clinic, Hippokration Hospital, University of Athens, Athens, Greece

Correspondence
George Bazoukis, Department of Cardiology, General Hospital of Athens "Evangelismos", Athens, Greece.
Email: gbazoykis@med.uoa.gr

Abstract

Ranolazine is a new medication for the treatment of refractory angina. However, except its anti-anginal properties, it has been found to act as an anti-arrhythmic. The aim of our systematic review is to present the existing data about the impact of ranolazine in ventricular arrhythmias. We searched MEDLINE and Cochrane databases as well clinicaltrials.gov until September 1, 2017 to find all studies (clinical trials, observational studies, case reports/series) reported data about the impact of ranolazine in ventricular arrhythmias. Our search revealed 14 studies (3 clinical trials, 2 observational studies, 8 case reports, 1 case series). These data reported a beneficial impact of ranolazine in ventricular tachycardia/fibrillation, premature ventricular beats, and ICD interventions in different clinical settings. The existing data highlight the anti-arrhythmic properties of ranolazine in ventricular arrhythmias.

KEYWORDS
anti-arrhythmic drugs, ranolazine, ventricular arrhythmias, ventricular fibrillation, ventricular tachycardia

1 | INTRODUCTION

Ranolazine is a new medication indicated for the cases of refractory angina despite conventional anti-ischemic regimens.[1,2] Its anti-ischemic effects have been demonstrated by several clinical trials.[3-6] Additionally, it exerts modulatory effects on ion channels that have been similarly observed after chronic amiodarone use, such as reductions in I_{Kr}, I_{Ks}, late I_{Na}, and I_{Ca}.[7] Consequently, ranolazine appears to have beneficial roles in both atrial and ventricular arrhythmias. The aim of our systematic review is to present the existing data about the impact of ranolazine in ventricular arrhythmias.

2 | METHODS

2.1 | Search strategy

Two independent investigators (G.B. & G.T.) searched MEDLINE and Cochrane databases as well clinicaltrials.gov, without year or language restriction or any other limitations, until September 1, 2017. The following algorithm was used: "ranolazine AND arrhythmias." Furthermore, the reference list of all included studies, as well as relevant review articles, was also manually searched.

2.2 | Study selection

2.2.1 | Inclusion/exclusion criteria

The inclusion criteria were clinical trials, observational studies, case series, or case reports that reported data about the impact of ranolazine on ventricular arrhythmias. The exclusion criteria were studies that included only data on atrial arrhythmias, reported data about the impact of ranolazine in electrophysiologic properties only, or that involved experiments in animal models.

2.3 | Data extraction

The following information was extracted for each study: (i) publication details (first author's last name, journal, year of publication), (ii) general characteristics of the study (country of origin, follow-up duration, number of patients included), (iii) characteristics of the study population [age, gender, type of cardiomyopathy, left ventricular ejection fraction (LVEF), ranolazine dosage, concomitant use of other anti-arrhythmic medications], and (iv) the reported outcome about the impact of ranolazine in ventricular arrhythmias.

3 | RESULTS

A total of 14 studies,[8-21] which reported data about the impact of ranolazine in ventricular arrhythmias, included in our systematic review (Figure 1). Of these, 2 were randomized controlled trials (MERLIN-TIMI 36 and RAID), 1 was a randomized crossover trial (RYPPLE), 2 were observational studies, 1 was a case series, and 8 were case reports (Table 1).

The included observational studies and case reports/series showed that ranolazine may have a beneficial role in reducing premature ventricular complexes (PVCs), ventricular tachycardia (VT), and ventricular fibrillation (VF) episodes as well appropriate implantable cardioverter-defibrillator therapies. According to MERLIN-TIMI 36 trial,[10] ranolazine suppresses ventricular arrhythmias during the first week after admission for non-ST elevation acute coronary syndrome, which can decrease the incidence of sudden cardiac death.[22] Additionally, the RAID trial showed that ranolazine can significantly decrease VT episodes requiring antitachycardia pacing (ATP) compared to placebo patients while did not show a significant difference in the combined endpoint VT/VF or death. In regard to recurrent events, ranolazine showed a significant decrease in recurrent ventricular arrhythmias requiring ICD therapy. Finally, the RYPPLE trial showed that ranolazine can reduce complex ventricular arrhythmias compared to placebo.

The baseline characteristics and the main outcomes of the included studies are summarized in Table 1.

4 | DISCUSSION

Our systematic review showed that ranolazine appears to have a beneficial effect in reducing the incidence of ventricular arrhythmias. This is consistent with its ventricular effects through inhibition of the late inward sodium current I_{Na} while possessing greater potency in modulating peak I_{Na} in atrial cardiomyocytes.[23] Increased late I_{Na} leads to Ca^{2+} overload through Na/Ca exchange in the reverse mode, leading with that way in electrophysiologic instability with action potential duration prolongation, early afterdepolarizations, and delayed afterdepolarizations.[24,25] Additionally, ranolazine leads to a reduction in the transmural dispersion of repolarization response to agents and pathophysiological conditions that reduce the repolarization reserve with a preferential abbreviation of midmyocardial cell action potential duration (where late I_{Na} is most prominent).[7] Furthermore, ranolazine inhibits the I_{Kr}, which leads to action potential prolongation in the ventricles. Thus, the net effect of ranolazine is determined by the relative magnitude of late I_{Na} (inward) and I_{Kr} (outward) currents during the repolarization period.[24] Furthermore, I_{kr} inhibition is the reason of the QT interval prolongation caused by ranolazine.[4,26] Another possible mechanism for its beneficial role in arrhythmias is the anti-ischemic properties. Moreover, ranolazine is a weak inhibitor of L type calcium channel current (I_{Ca}, L),[27] and for that reason, it does not affect significantly the myocardial contractility and heart rate at therapeutic doses.

The beneficial effect of ranolazine in ventricular arrhythmias has been demonstrated in several animal studies. Specifically, ranolazine showed to reduce the dofetilide- or clofilium-induced *torsades de pointes* episodes in experimental models.[28,29] Additionally, ranolazine can reduce the *torsades de pointes* liability of agents that prolong the QT interval.[30] In long QT-2 syndrome, ranolazine was shown to prevent Ca^{2+} overload by stabilizing and desensitizing the ryanodine receptors, resulting in the suppression of early afterdepolarizations and *torsades de pointes*.[31] Moreover, ranolazine exerted a concentration-dependent block of I_{NaL} in experimental models of LQT3 harboring the D1790G mutation in *SCN5A* without reducing peak I_{Na} significantly.[32] As a result, ranolazine can be safely used in LQT3 patients who are at risk for developing Brugada syndrome during sodium channel blocker therapy. In a small registry of 8 patients with LQT3, the QT-shortening effect of ranolazine persisted during the entire follow-up period of 22 months and remained during nocturnal bradycardia.[32] The clinical significance of this finding is highlighted by the fact that cardiac arrest events in LQT3 tend to occur at night.[32] Ranolazine has been shown to have a comparable effect with mexiletine in action potential duration shortening in LQT3 mutant cells with lower occurrence of paradoxical action potential duration prolongation.[33] Furthermore, its beneficial role in ventricular arrhythmias has been depicted in an experimental model of Timothy syndrome (long QT-8).[34] By contrast, in a short QT syndrome model, ranolazine reversed the induction of VF caused by pinacidil, an effect that was attributed to an increase in the effective refractory period (ERP). This would in turn increase the excitation wavelength given by the product of the ERP and conduction velocity (CV), thereby decreasing the likelihood of developing reentry.[35] An interesting finding was the beneficial impact of ranolazine in post-VF animal models.[36] Particularly, ranolazine showed to reduce the susceptibility to subsequent refibrillation, but further testing in cardiac arrest models is needed.[37] An interesting finding is that ranolazine has a potent suppressant effect on both reentrant and multifocal VF at concentrations considered therapeutic in humans.[38]

In ischemia and ischemia-reperfusion models, ranolazine showed to reduce the incidence, frequency, and duration of VT during reperfusion subsequent to 5 min of ischemia, while it reduced the incidence and duration of VT and VF during 20 minutes of ischemia.[39] Additionally, in another model, during 5 minutes of reperfusion, ranolazine showed to reduce except the incidence and duration of VT, the number of ventricular premature beats.[40] Furthermore, ranolazine showed to be as effective as other anti-arrhythmic drugs (sotalol, lidocaine) to reduce reperfusion-induced ventricular arrhythmias.[41] An interesting finding is that concurrent administration of ranolazine and dronedarone had a beneficial role in the protection against ischemia-induced vulnerability to AF and ventricular arrhythmias.[42] The antifibrillatory effects of ranolazine in cases of severe acute coronary stenosis do not seem to be mediated by inhibition of I_{Kr} but is instead attributable to inhibition of late I_{Na}.[43]

Ranolazine was found to maintain the anti-arrhythmic properties in heart failure. Specifically, it produced postrepolarization refractoriness and prevented the induction of VF episodes in a heart failure model.[44] Mechanical stretch is an arrhythmogenic mechanism in cases of cardiac overload or dyssynchronous contraction. In an experimental study, ranolazine showed to attenuate the acceleration and the complexity of VF produced by myocardial stretch.[45] In another experimental model of pulmonary arterial hypertension, the administration of ranolazine prevented the isoproterenol-induced VT/VF,[46] while it has been found that play a beneficial role in the right ventricular dysfunction.[47] Additionally, ranolazine can be used on top of class III drugs as it has been shown that it does not cause pro-arrhythmia despite a marked effect on ventricular repolarization.[48-50] The beneficial role of ranolazine has also been demonstrated by experimental and human studies in atrial arrhythmias.[10,44,51-61]

5 | CONCLUSIONS

Ranolazine seems to have a beneficial role in ventricular arrhythmias in different clinical settings.

CONFLICT OF INTERESTS

The authors declare no conflict of interests regarding the systematic review, but C.Th. declares consultancy fees from Astra Zeneca, and lecture honoraria from Sanofi, MSD, and Servier.

ORCID

George Bazoukis http://orcid.org/0000-0003-1009-9772
Gary Tse http://orcid.org/0000-0001-5510-1253
Panagiotis Korantzopoulos http://orcid.org/0000-0002-4228-3593
Adrian Baranchuk http://orcid.org/0000-0002-3042-6569

REFERENCES

1. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012;60:e44–164.
2. Rayner-Hartley E, Sedlak T. Ranolazine: a contemporary review. J Am Heart Assoc. 2016;5:e003196.
3. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol. 2004;43:1375–82.
4. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA. 2004;291:309–16.
5. Stone PH, Gratsiansky NA, Blokhin A, et al. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA

(Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol. 2006;48:566–75.
6. Melloni C, Newby LK. Metabolic efficiency with ranolazine for less ischemia in non-ST elevation acute coronary syndromes (MERLIN TIMI-36) study. Expert Rev Cardiovasc Ther. 2008;6:9–16.
7. Antzelevitch C, Belardinelli L, Zygmunt AC, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. Circulation. 2004;110:904–10.
8. Bunch TJ, Mahapatra S, Murdock D, et al. Ranolazine reduces ventricular tachycardia burden and ICD shocks in patients with drug-refractory ICD shocks. Pacing Clin Electrophysiol. 2011;34:1600–6.
9. Curnis A, Salghetti F, Cerini M, et al. Ranolazine therapy in drug-refractory ventricular arrhythmias. J Cardiovasc Med (Hagerstown). 2017;18:534–8.
10. Scirica BM, Morrow DA, Hod H, et al. 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;116:1647–52.
11. Yeung E, Krantz MJ, Schuller JL, et al. Ranolazine for the suppression of ventricular arrhythmia: a case series. Ann Noninvasive Electrocardiol. 2014;19:345–50.
12. Kaliebe JW, Murdock DK. Suppression of non-sustained ventricular tachycardia with ranolazine: a case report. WMJ. 2009;108:373–5.
13. Margos P, Margos N, Mokadem N, et al. Ranolazine: safe and effective in a patient with hypertensive cardiomyopathy and multiple episodes of electrical storm. Clin Case Rep. 2017;5:1170–5.
14. Murdock DK, Kaliebe J, Overton N. Ranolozine-induced suppression of ventricular tachycardia in a patient with nonischemic cardiomyopathy: a case report. Pacing Clin Electrophysiol. 2008;31:765–8.
15. Murdock DK, Kaliebe JW. Suppression of frequent ventricular ectopy in a patient with hypertrophic heart disease with ranolazine: a case report. Indian Pacing Electrophysiol J. 2011;11:84–8.
16. Nanda S, Levin V, Martinez MW, et al. Ranolazine–treatment of ventricular tachycardia and symptomatic ventricular premature beats in ischemic cardiomyopathy. Pacing Clin Electrophysiol. 2010;33:e119–20.
17. van den Berg MP, van den Heuvel F, van Tintelen JP, et al. Successful treatment of a patient with symptomatic long QT syndrome type 3 using ranolazine combined with a beta-blocker. Int J Cardiol. 2014;171:90–2.
18. Vizzardi E, D'Aloia A, Salghetti F, et al. Efficacy of ranolazine in a patient with idiopathic dilated cardiomyopathy and electrical storm. Drug Discov Ther. 2013;7:43–5.
19. Zareba W, Daubert JP, Beck CA, et al. Ranolazine in high-risk ICD patients (RAID) trial. Heart Rhythm. 2017;14:944–7.
20. Pelliccia F, Campolongo G, Massaro R, et al. Ranolazine reduces symptoms of palpitations and documented arrhythmias in patients with ischemic heart disease — The RYPPLE randomized cross-over trial. IJC Metabolic & Endocrine. 2015;7:8.
21. Shah DP, Baez-Escudero JL, Weisberg IL, et al. Ranolazine safely decreases ventricular and atrial fibrillation in Timothy syndrome (LQT8). Pacing Clin Electrophysiol. 2012;35:e62–4.
22. Scirica BM, Braunwald E, Belardinelli L, et al. Relationship between nonsustained ventricular tachycardia after non-ST-elevation acute coronary syndrome and sudden cardiac death: observations 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. 2010;122:455–62.
23. Burashnikov A, Di Diego JM, Zygmunt AC, et al. Atrium-selective sodium channel block as a strategy for suppression of atrial fibrillation: differences in sodium channel inactivation between atria and ventricles and the role of ranolazine. Circulation. 2007;116:1449–57.
24. Sossalla S, Maier LS. Role of ranolazine in angina, heart failure, arrhythmias, and diabetes. Pharmacol Ther. 2012;133:311–23.
25. Tse G. Mechanisms of cardiac arrhythmias. J Arrhythm. 2016;32:75–81.
26. Wilson SR, Scirica BM, Braunwald E, et al. Efficacy of ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 Trial. J Am Coll Cardiol. 2009;53:1510–6.
27. Allen TJ, Chapman RA. Effects of ranolazine on L-type calcium channel currents in guinea-pig single ventricular myocytes. Br J Pharmacol. 1996;118:249–54.
28. Antoons G, Oros A, Beekman JD, et al. Late na(+) current inhibition by ranolazine reduces torsades de pointes in the chronic atrioventricular block dog model. J Am Coll Cardiol. 2010;55:801–9.
29. Wang WQ, Robertson C, Dhalla AK, et al. Antitorsadogenic effects of ({+/-})-N-(2,6-dimethyl-phenyl)-(4[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazine (ranolazine) in anesthetized rabbits. J Pharmacol Exp Ther. 2008;325:875–81.
30. Jia S, Lian J, Guo D, et al. Modulation of the late sodium current by ATX-II and ranolazine affects the reverse use-dependence and proarrhythmic liability of IKr blockade. Br J Pharmacol. 2011;164:308–16.
31. Parikh A, Mantravadi R, Kozhevnikov D, et al. Ranolazine stabilizes cardiac ryanodine receptors: a novel mechanism for the suppression of early afterdepolarization and torsades de pointes in long QT type 2. Heart Rhythm. 2012;9:953–60.
32. Chorin E, Hu D, Antzelevitch C, et al. Ranolazine for congenital long-QT syndrome type III: experimental and long-term clinical data. Circ Arrhythm Electrophysiol. 2016;9:e004370.
33. Paci M, Passini E, Severi S, et al. Phenotypic variability in LQT3 human induced pluripotent stem cell-derived cardiomyocytes and their response to antiarrhythmic pharmacologic therapy: an in silico approach. Heart Rhythm. 2017;14:1704–12.
34. Sicouri S, Timothy KW, Zygmunt AC, et al. Cellular basis for the electrocardiographic and arrhythmic manifestations of Timothy syndrome: effects of ranolazine. Heart Rhythm. 2007;4:638–47.
35. Tse G, Lai ET, Lee AP, et al. Electrophysiological Mechanisms of Gastrointestinal Arrhythmogenesis: lessons from the Heart. Front Physiol. 2016;7:230.
36. Frommeyer G, Ellermann C, Dechering DG, et al. Ranolazine and vernakalant prevent ventricular arrhythmias in an experimental whole-heart model of short QT syndrome. J Cardiovasc Electrophysiol. 2016;27:1214–9.
37. Azam MA, Zamiri N, Masse S, et al. Effects of late sodium current blockade on ventricular refibrillation in a rabbit model. Circ Arrhythm Electrophysiol. 2017;10:e004331.
38. Morita N, Lee JH, Xie Y, et al. Suppression of re-entrant and multifocal ventricular fibrillation by the late sodium current blocker ranolazine. J Am Coll Cardiol. 2011;57:366–75.
39. Dhalla AK, Wang WQ, Dow J, et al. Ranolazine, an antianginal agent, markedly reduces ventricular arrhythmias induced by ischemia and ischemia-reperfusion. Am J Physiol Heart Circ Physiol. 2009;297:H1923–9.
40. Kloner RA, Dow JS, Bhandari A. The antianginal agent ranolazine is a potent antiarrhythmic agent that reduces ventricular arrhythmias: through a mechanism favoring inhibition of late sodium channel. Cardiovasc Ther. 2011;29:e36–41.
41. Kloner RA, Dow JS, Bhandari A. First direct comparison of the late sodium current blocker ranolazine to established antiarrhythmic agents in an ischemia/reperfusion model. J Cardiovasc Pharmacol Ther. 2011;16:192–6.
42. Verrier RL, Pagotto VP, Kanas AF, et al. Low doses of ranolazine and dronedarone in combination exert potent protection against

atrial fibrillation and vulnerability to ventricular arrhythmias during acute myocardial ischemia. Heart Rhythm. 2013;10:121–7.
43. Nieminen T, Nanbu DY, Datti IP, et al. Antifibrillatory effect of ranolazine during severe coronary stenosis in the intact porcine model. Heart Rhythm. 2011;8:608–14.
44. Frommeyer G, Schmidt M, Clauss C, et al. Further insights into the underlying electrophysiological mechanisms for reduction of atrial fibrillation by ranolazine in an experimental model of chronic heart failure. Eur J Heart Fail. 2012;14:1322–31.
45. Chorro FJ, del Canto I, Brines L, et al. Ranolazine attenuates the electrophysiological effects of myocardial stretch in langendorff-perfused rabbit hearts. Cardiovasc Drugs Ther. 2015;29:231–41.
46. Liles JT, Hoyer K, Oliver J, et al. Ranolazine reduces remodeling of the right ventricle and provoked arrhythmias in rats with pulmonary hypertension. J Pharmacol Exp Ther. 2015;353:480–9.
47. Gong M, Fragakis N, Zhang C, et al. Ranolazine as a novel therapy for pulmonary arterial hypertension. Int J Cardiol. 2016;223:860–2.
48. Frommeyer G, Kaiser D, Uphaus T, et al. Effect of ranolazine on ventricular repolarization in class III antiarrhythmic drug-treated rabbits. Heart Rhythm. 2012;9:2051–8.
49. Frommeyer G, Milberg P, Uphaus T, et al. Antiarrhythmic effect of ranolazine in combination with class III drugs in an experimental whole-heart model of atrial fibrillation. Cardiovasc Ther. 2013;31:e63–71.
50. Sossalla S, Wallisch N, Toischer K, et al. Effects of ranolazine on torsades de pointes tachycardias in a healthy isolated rabbit heart model. Cardiovasc Ther. 2014;32:170–7.
51. Burashnikov A, Antzelevitch C. Atrial-selective sodium channel blockers: do they exist? J Cardiovasc Pharmacol. 2008;52:121–8.
52. Bhimani AA, Yasuda T, Sadrpour SA, et al. Ranolazine terminates atrial flutter and fibrillation in a canine model. Heart Rhythm. 2014;11:1592–9.
53. Burashnikov A, Sicouri S, Di Diego JM, et al. Synergistic effect of the combination of ranolazine and dronedarone to suppress atrial fibrillation. J Am Coll Cardiol. 2010;56:1216–24.
54. Kumar K, Nearing BD, Carvas M, et al. Ranolazine exerts potent effects on atrial electrical properties and abbreviates atrial fibrillation duration in the intact porcine heart. J Cardiovasc Electrophysiol. 2009;20:796–802.
55. Burashnikov A, Di Diego JM, Barajas-Martinez H, et al. Ranolazine effectively suppresses atrial fibrillation in the setting of heart failure. Circ Heart Fail. 2014;7:627–33.
56. De Ferrari GM, Maier LS, Mont L, et al. 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;12:872–8.
57. Fragakis N, Koskinas KC, Katritsis DG, et al. Comparison of effectiveness of ranolazine plus amiodarone versus amiodarone alone for conversion of recent-onset atrial fibrillation. Am J Cardiol. 2012;110:673–7.
58. Hammond DA, Smotherman C, Jankowski CA, et al. Short-course of ranolazine prevents postoperative atrial fibrillation following coronary artery bypass grafting and valve surgeries. Clin Res Cardiol. 2015;104:410–7.
59. Koskinas KC, Fragakis N, Katritsis D, et al. Ranolazine enhances the efficacy of amiodarone for conversion of recent-onset atrial fibrillation. Europace. 2014;16:973–9.
60. 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;108:673–6.
61. Gong M, Zhang Z, Fragakis N, et al. Role of ranolazine in the prevention and treatment of atrial fibrillation: a meta-analysis of randomized clinical trials. Heart Rhythm. 2017;14:3–11.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Bazoukis G, Tse G, Letsas KP, et al. Impact of ranolazine on ventricular arrhythmias – A systematic review. *J Arrhythmia*. 2018;34:124–128. https://doi.org/10.1002/joa3.12031