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REVIEW

# Mechanisms of ranolazine's dual protection against atrial and ventricular fibrillation

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Coronary artery disease and heart failure carry concurrent risk for atrial fibrillation and life-threatening ventricular arrhythmias. We review evidence indicating that at therapeutic concentrations, ranolazine has potential for dual suppression of these arrhythmias. Mechanisms and clinical implications are discussed.

**Keywords** Ranolazine • T-wave alternans • Ventricular fibrillation • Atrial fibrillation • Sodium current

## Introduction

Coronary artery disease and heart failure carry a dual risk for atrial fibrillation (AF) and life-threatening ventricular arrhythmias.[1–4] Medical management of these conditions is challenging because of the complex and differing factors underlying arrhythmogenesis in the atria and ventricles. The difficulty of the problem is underscored by the fact that the main contemporary agents used for rhythm control in AF can result in ventricular proarrhythmia including torsade de pointes.[5] Drugs with Class IC effects of blocking peak $I_{Na}$ can cause myocardial depression, promote reentrant ventricular tachycardia, and increase mortality in patients with coronary disease. Anti-AF agents with the Class III action of blocking $I_{Kr}$, such as dofetilide and sotalol, can precipitate torsade de pointes. The multichannel blocking agent amiodarone is currently widely employed, although its use can be problematic due to the potential for significant extra-cardiac toxicity, particularly in lung and thyroid tissue.[6] Dronedarone, a non-iodinated benzofuran derivative of amiodarone that exhibits all four classes of antiarrhythmic action, was developed to achieve a better safety profile by eliminating the iodine moiety and substituting a methanesulfanyl group.[7,8] Whereas most studies have shown that dronedarone reduces mortality and morbidity in patients with paroxysmal AF,[7] it increased rates of heart failure, stroke, and death from cardiovascular causes in patients with permanent AF or moderate to severe heart failure.[9] Although the exact basis for the increased risk in these patients is unclear, the potential for negative inotropy related to L-type calcium channel blockade at the currently recommended dosage has been suggested.

Ranolazine was developed as an antianginal agent and was initially thought to confer its therapeutic effects primarily through partial inhibition of fatty acid oxidation.[10] These drug actions were generally observed at concentrations exceeding the plasma levels found in clinical trials (>10 μM).[11] More recent evidence indicates that the anti-ischaemic effects of ranolazine relate to its inhibition of late $I_{Na}$, which, through an effect on reverse sodium–calcium exchange, improves diastolic compliance, thereby increasing coronary artery blood flow.[12] Subsequent experimental studies have revealed a potent antiarrhythmic effect of ranolazine against both atrial and ventricular arrhythmias.[12–15]

Clinical evidence of ranolazine's antiarrhythmic efficacy has emerged from the MERLIN-TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 36) trial, which enrolled 6560 patients and was directed to the treatment of myocardial ischaemia in patients with non-ST elevation acute coronary syndrome.[16] Ranolazine reduced the incidence of supraventricular arrhythmias with a trend towards lowering the incidence of new-onset AF across 6 days of continuous electrocardiographic recordings.[17] A subsequent analysis indicated that among patients with paroxysmal AF, the overall burden tended to be lower with ranolazine than with placebo, with fewer AF-related adverse events.[18] Ranolazine has also been demonstrated to be superior to amiodarone in reducing the incidence of AF following coronary artery bypass graph surgery[19] and in combination therapy to improve conversion from recent onset AF over amiodarone alone.[20] Murdock *et al.*[21] recently reported in a case series that ranolazine

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can facilitate electrical cardioversion of AF in patients with cardioversion-resistant AF. Further analysis of the ambulatory electrocardiogram recordings from MERLIN TIMI-36 revealed that ranolazine can suppress not only supraventricular arrhythmias but also episodes of non-sustained ventricular tachycardia.[22]

The main goals of the present review are to summarize knowledge and discuss mechanisms of ranolazine's effects on both atrial and ventricular arrhythmogenesis.

# Influence of ranolazine on atrial and ventricular electrical properties in the normal, intact heart

Programmed electrical stimulation was employed in anaesthetized canine and porcine models to evaluate the effects of intravenous ranolazine on excitability, refractoriness, dromotropy, and vulnerability to AF and ventricular fibrillation (VF).[23–27]

## Atrial electrical properties

Experiments in large animals demonstrated ranolazine's potent atrial effects,[24] consistent with findings in isolated tissue studies by Antzelevitch and colleagues.[14,28,29] Specifically, significant effects on atrial refractoriness were found in each atrial site tested, namely high right atrium, right atrial appendage, and posterolateral left atrium (*Table 1*). These changes occurred in a non-frequency-dependent manner, in contrast to reports of $I_{Kr}$ blockade by agents such as dofetilide and d-sotalol and to results expected with peak $I_{Na}$ blockade and post-repolarization refractoriness. The phenomenon of non-frequency dependence may result from reverse frequency-dependent $I_{Kr}$ inhibition coupled with frequency-dependent peak $I_{Na}$ inhibition. The magnitude of the increase in atrial effective refractory period in atrial sites (>20% increase from baseline) was greater than the effect on the right ventricular endocardium (<10% increase from baseline). No significant changes were observed in atrial or ventricular diastolic thresholds. Ranolazine increased median atrial conduction time, a surrogate marker for conduction velocity, from high right atrium to posterolateral left atrium in a frequency-dependent manner in agreement with prior studies and consistent with inhibition of peak $I_{Na}$ in atrial tissue.

**Table 1 Ranolazine's effects on atrial and ventricular effective refractory periods**

| Site | Median effective refractory period (milliseconds) | Interquartile range (milliseconds) | *P* value |
|---|---|---|---|
| High right atrium | | | |
| Control | 167 | 159–179 | 0.006 |
| Ranolazine | 202 | 183–231 | |
| Right atrial appendage | | | |
| Control | 158 | 136–164 | 0.002 |
| Ranolazine | 202 | 187–211 | |
| Posterolateral left atrium | | | |
| Control | 140 | 117–150 | 0.014 |
| Ranolazine | 163 | 143–193 | |
| Right ventricle | | | |
| Control | 253 | 243–260 | 0.006 |
| Ranolazine | 275 | 271–281 | |

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## Atrial fibrillation suppression

To test whether ranolazine alters susceptibility to AF, the muscarinic transmitter acetylcholine (ACh) was administered into the pericardial space by percutaneous transatrial access.[24] This approach incorporates multiple sites of action including atrial tissue, ganglionic plexi, and pulmonary veins, all of which have been implicated clinically in atrial arrhythmogenesis. A significant reduction in AF duration (*Figure 1*) and tendency to suppress AF re-initiation were observed following ranolazine administration. Despite the QT prolongation associated with AF-cardioversion, torsade de pointes was not observed. These results are likely indicative of the effect of ranolazine on atrial conduction velocity due to peak $I_{Na}$ inhibition and are similar to the actions of other potent sodium channel blockers, including flecainide and propafenone, and suggest that ranolazine affects factors that are important not only in maintaining AF but also possibly in initiating AF.

Ranolazine reduced the dominant frequency of AF,[24] an index of organization of AF and the propensity for successful defibrillation,[30] in both the left and right atria. Consistent with previous reports of AF in humans and in other animal models,[31] the dominant frequency of AF in the left atrium was always greater than that in the right atrial appendage, indicating that the drivers for AF in

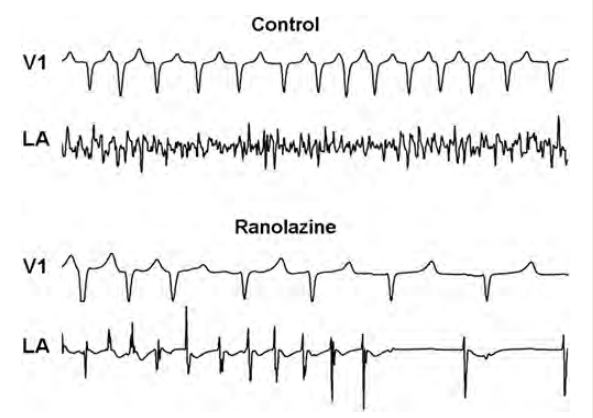


**Figure 1** Representative example of surface (lead $V_1$) and intracardiac electrograms (posterolateral left atrium, LA) at 12 min after atrial fibrillation (AF) initiation demonstrating early termination of AF by ranolazine. Note in the upper tracing (control) that AF is characterized by low voltage and high frequency. At the same time period, with ranolazine treatment, the arrhythmia became more organized, followed by conversion to sinus rhythm. (Reprinted from ref.[24] with permission from John Wiley & Sons.).

this model reside in the left atrium, where susceptibility to ACh-induced changes in rotor dynamics is enhanced.[32] Ranolazine did not change this relationship, despite decreasing dominant frequency of AF in both atria.

The cellular and ionic mechanisms by which ranolazine reduces ACh-mediated AF are likely multifold: (i) depression of $I_{Na}$-dependent parameters, which reduces action potential upstroke, and increases in diastolic threshold of excitation and post-repolarization refractoriness; (ii) $I_{Kr}$ inhibition, which counteracts ACh-induced shortening of action potential duration; (iii) late $I_{Na}$ inhibition, which suppresses late phase 3 early after-depolarizations and reduces $I_{Ti}$, thereby suppressing delayed after-depolarizations and triggered activity.[14,33] Ranolazine at the concentrations tested has minimum effect on $I_{Ca}$. The anti-AF capacity of ranolazine has also been shown by Lemoine *et al.*[34] in terms of suppression of occurrence of early after-depolarizations and triggered activity in an animal model of LQT3 (SCN5A inactivation-impairing mutation).

## Ventricular effects

### Surface electrocardiogram analysis

Ranolazine moderately prolonged the QTc interval in the intact porcine model,[23] consistent with previous reports in dogs[35] but to a larger extent than is observed in humans.[10,36] The drug did not alter $T_{peak}$–$T_{end}$ interval, an index of transmural dispersion of repolarization, a parameter identified in a canine wedge preparation to be attributable to differential effects on epicardial vs. M cells.[14] These effects were at variance from d-sotalol, a selective $I_{Kr}$ blocker, despite prolongation of action potential duration and the QT interval of the *in-vitro*-modelled electrocardiogram by both drugs.[14]

### Electrophysiological testing

Ranolazine prolonged ventricular effective refractory period in the porcine model by a mean of 40 ms over a large range of stimulation strengths.[23] Schram *et al.*[35] had previously observed a mild but non-significant increase in effective refractory period in canines at both low and high doses of ranolazine. The significant changes in effective refractory period detected by Kumar *et al.*[23] may be attributable to the larger sample size.

Ranolazine caused substantial increases in the magnitude of the depolarization threshold current needed to induce the repetitive extrasystoles (RE) and VF (*Figure 2*).[23] Because the intensity of the stimulus required to provoke either RE or VF is inversely proportional to the intrinsic level of cardiac electrical heterogeneity, these measures yield an index of dispersion of refractoriness.[37] The ventricular vulnerable period width has been shown to correlate with dispersion of repolarization,[38] lending further support to these observations and to interpretation of the electrophysiological effects of ranolazine described. Accordingly, ranolazine's increase in the RE and VF thresholds and reduction in vulnerable period width may indicate its potential antiarrhythmic mechanism, namely, reduction in the dispersion of repolarization and refractoriness. These changes to the underlying myocardial substrate may be complementary to ranolazine's suppression of triggered activity due to early after-depolarizations.[39] These findings are further supported by the report that in remodelled canine hearts

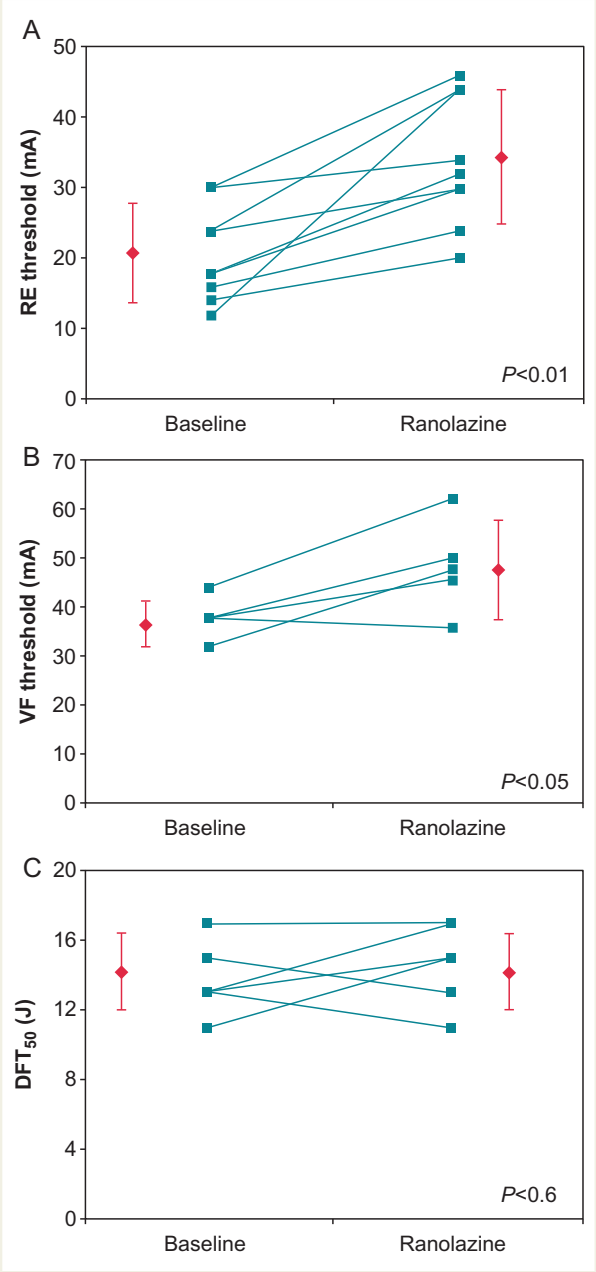


**Figure 2** Connected dot plots of the (*A*) repetitive extrasystole (RE) ($N = 9$), (*B*) ventricular fibrillation (VF) ($N = 5$), and (*C*) 50% probability of defibrillation ($DFT_{50}$) ($N = 6$) thresholds. Each line represents an individual experiment, while the diamonds represent the means ± SD. (Reprinted from ref.[23] with permission from John Wiley & Sons.)

with complete heart block, ranolazine suppressed drug-induced torsade de pointes, with concomitant changes in beat-to-beat variability of repolarization.[40]

### Defibrillation threshold testing

Ranolazine did not alter the 50% probability of successful ventricular defibrillation ($DFT_{50}$), likely as a consequence of the countervailing influences of $I_{Kr}$ and $I_{Na}$ inhibition (*Figure 2*).[23] Notably, $I_{Kr}$

inhibition would be expected to lower $DFT_{50}$, whereas $I_{Na}$ inhibition would increase it. Ranolazine exerts minor influences on peak $I_{Na}$ at slow to moderate heart rates, but at short cycle lengths in depolarized cells, as during VF, the drug may inhibit peak $I_{Na}$ more effectively. Use dependence and increased binding at less negative, that is, at more depolarized, membrane potentials is a typical characteristic of sodium channel blockers and should also apply to ranolazine.[41] Enhanced peak $I_{Na}$ inhibition during VF is consistent with the finding that ranolazine reduces the dominant frequency of VF, indicative of active tissue binding during VF notwithstanding the absence of an influence on $DFT_{50}$. The observation that ranolazine's antifibrillatory effect is not associated with a significant increase in ventricular defibrillation threshold indicates that the drug appears unlikely to affect the margin of safety for defibrillation. In light of the importance of this issue, further experimentation is warranted including testing defibrillation threshold during acute myocardial ischaemia.

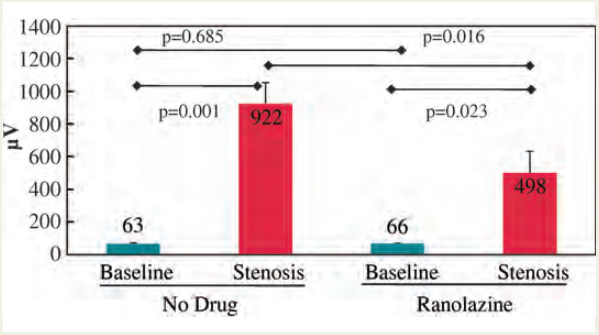


**Figure 3** Coronary stenosis resulted in a significant increase in T-wave alternans (TWA) level, which was significantly reduced by ranolazine ($N = 12$). Numbers in the columns refer to the mean levels of T-wave alternans (TWA) in microvolts. (Reprinted from ref.[25] with permission from Heart Rhythm Society.)

# Antifibrillatory effects of ranolazine in the ischaemic heart

## Ventricular effects during severe coronary artery stenosis

Because ischaemic heart disease is associated with increased risk for ventricular arrhythmias, the effects of ranolazine during severe left anterior descending coronary artery (LAD) stenosis were assessed in the intact porcine model.[25] Electrode catheters allowed assessment of the effects of severe LAD stenosis on the levels of VF threshold and T-wave alternans (TWA), a beat-to-beat fluctuation in the ST-segment and T-wave, which has been shown to reflect susceptibility to malignant ventricular arrhythmias.[42]

Ranolazine significantly increased VF threshold not only in the normal heart but more importantly during myocardial ischaemia, when the effects occurred independently of changes in LAD coronary blood flow, which was controlled with a hydraulic occluder. During normal coronary artery flow, blockade of $I_{Kr}$ and consequent prolongation of action potential duration contributed to increases in VF threshold induced by both ranolazine and the $I_{Kr}$ blocker E-4031. However, during severe myocardial ischaemia, E-4031 was profibrillatory, as it decreased VF threshold from control stenosis, whereas ranolazine increased it. Importantly, TWA tracked the ranolazine- and E-4031-induced changes in VF threshold during myocardial ischaemia, that is, ranolazine decreased but E-4031 did not alter TWA levels from the control stenosis (*Figures 3* and *4*).[25] Studies involving assessment of lactate production by sampling coronary venous effluent or other methods involving wall motion abnormalities and measurement of regional myocardial blood flow with microspheres are required to establish an effect of ranolazine on metabolism during myocardial ischaemia.

Ranolazine's effects on VF threshold and TWA levels indicate significant blunting of ischaemia-induced dispersion of repolarization and refractoriness.[25] TWA reflects spatiotemporal heterogeneity of repolarization between neighbouring myocardial regions, as has been shown in investigations in intact large animals.[43,44] and in patients with cardiomyopathy.[45] The effects of ranolazine and

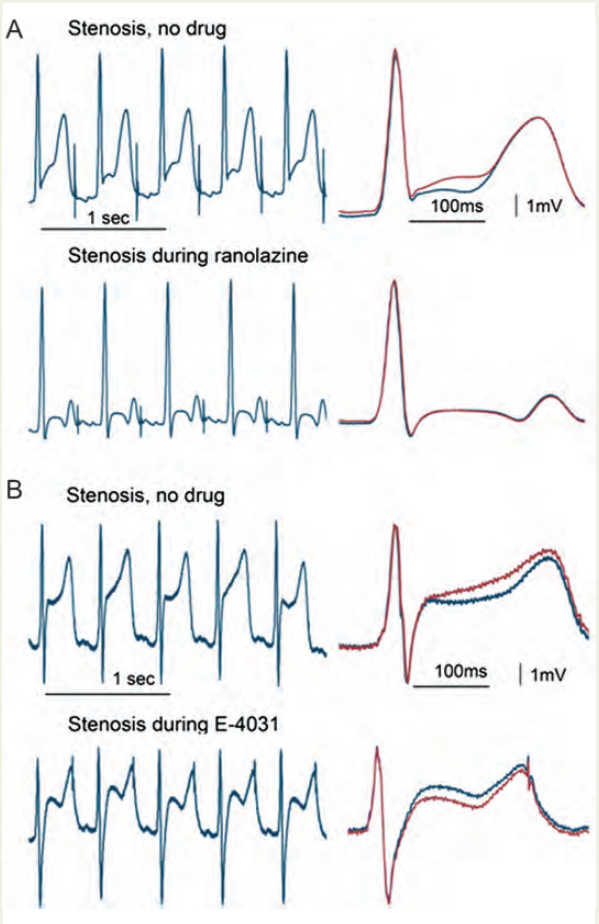


**Figure 4** T-wave alternans (TWA) during left anterior descending coronary artery stenosis. The tracings with and without ranolazine (*A*) or E-4031 (*B*) are continuous (left panels) and with QRS-aligned superimposition (right panels). The stenosis-induced TWA was suppressed by ranolazine but not by E-4031. (Reprinted from ref.[25] with permission from Heart Rhythm Society.)

E-4031 on VF threshold and TWA reflect their direct influences on the electrophysiological properties of the ventricular myocardium and are not attributable to changes in coronary artery blood flow as stenoses were maintained at the same level before and after drug administration. These results are consistent with findings reported by Kloner *et al.*,[46] who showed in rats subjected to proximal left coronary artery occlusion followed by reperfusion that ranolazine at a dose consistent with inhibition of late $I_{Na}$ exerts a potent antiarrhythmic effect and is superior to sotalol or lidocaine.

## Ischaemia-induced atrial fibrillation

Ischaemic heart disease is associated not only with increased risk for malignant ventricular arrhythmias[2] but also for AF.[1,4] In patients with acute coronary syndromes, the incidence of AF has been reported to be 6–22% and is associated with increased short- and long-term morbidity and mortality. Nattel and coworkers[27] provided experimental evidence indicating that atrial ischaemia can create a substrate for maintenance of AF by increasing local conduction slowing, leading to unidirectional block and reentry. They found that the L-type calcium channel blocker diltiazem and the beta-adrenergic receptor blocker nadolol were protective but that peak $I_{Na}$ and $I_{Kr}$ inhibition with flecainide and dofetilide, respectively, were not effective.[26]

Recently, we induced concurrent atrial and ventricular ischaemia to evaluate simultaneously the effects of antiarrhythmic agents on vulnerability to AF and ventricular tachyarrhythmias.[47,48] Stenosis at the origin of the left circumflex coronary artery, which supplies all three major branches to the left atrium, namely, the proximal, intermediate, and distal arteries,[49] induces significant left atrial ischaemia (*Figure 5*). In a preliminary report,[48] we found that ranolazine at a plasma concentration in the clinical dose range completely suppressed the ischaemia-induced reduction in AF threshold. This protective effect against ischaemia-induced AF appears to be due to direct effects on atrial electrical properties independent of coronary flow, as this variable was controlled.

We also demonstrated that ranolazine and dronedarone at low dosages exhibit a synergistic, antiarrhythmic effect on vulnerability to AF and ventricular tachyarrhythmias during concurrent atrial and ventricular ischaemia.[47] Specifically, when low doses of either agent were given alone, there was no protective effect, but the drug combination prevented the ischaemia-induced fall in AF threshold, reduced AF inducibility, and shortened AF duration while decreasing T-wave heterogeneity, a clinically relevant measure of susceptibility to life-threatening ventricular arrhythmias. Overall, these findings are consistent with the discovery by Burashnikov *et al.*[50] that ranolazine and dronedarone afford synergistic antiarrhythmic actions with respect to AF susceptibility. The clinical relevance of synergistic antiarrhythmic protection by the combination of low doses of ranolazine and dronedarone is under investigation in 'A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients with Paroxysmal AF' (HARMONY) trial (NCT 01522651). The effect of the drugs on AF burden will be studied

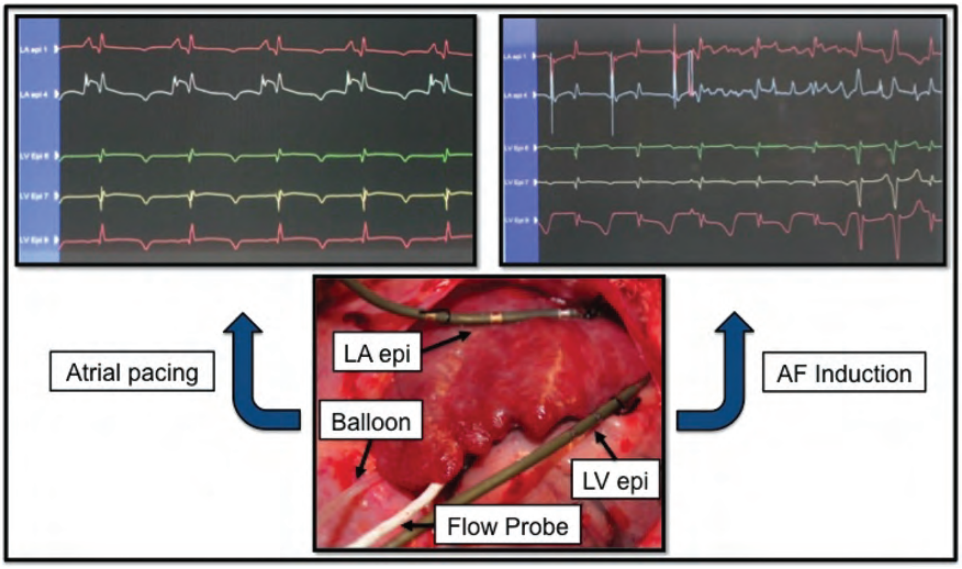


**Figure 5** Experimental setup. Upper left panel: left atrial (LA) and left ventricular (LV) epicardial electrocardiograms obtained prior to balloon occlusion of the left circumflex (LCx) coronary artery to reduce flow by 75% during atrial pacing at 150 beats/min. Upper right panel: Induction of atrial fibrillation (AF) by a 6-mA S2 test stimulus following the last S1 pacing stimulus. Note visible T-wave heterogeneity compared to the uniform pattern observed in the upper left panel. Lower panel: Hydraulic balloon occluder positioned around the proximal LCx coronary artery upstream of the Doppler flow probe. Electrode catheters are affixed to the left atrial appendage and left ventricular epicardium within the atrial and ventricular regions supplied by the LCx. (Reprinted from ref. [47] with permission from Heart Rhythm Society.)

in patients with implanted dual chamber programmable pacemakers with AF detection capabilities.

## Ionic basis for ranolazine's antiarrhythmic effects

The three most likely ion channel currents responsible for the electrophysiological effects of ranolazine in the normal or ischaemic atrial and ventricular myocardium are late $I_{Na}$, peak $I_{Na}$, and $I_{Kr}$[12] (Tables 2, 3). Analysis of excised atrial appendages from patients with AF have implicated late $I_{Na}$ inhibition,[51] while experimental studies in canine isolated perfused atrial tissue have provided evidence that ranolazine's antifibrillatory effect in the atria is attributable primarily to inhibition of peak $I_{Na}$.[14] At therapeutic concentrations, ranolazine also inhibits the delayed rectifier potassium current ($I_{Kr}$),[12,14] which has been extensively investigated as a target to suppress AF.[52] In isolated tissue studies, evidence suggests that ranolazine's combined action on peak $I_{Na}$ and $I_{Kr}$ currents may enhance its efficacy in reducing susceptibility to AF, as this combination of ion channel effects contributes to atrial-selective reduction in AF vulnerability.[53]

On a cellular level, it is likely, based on results of studies in isolated single and multicellular preparations that ranolazine suppresses non-sustained ventricular tachycardia by inhibition of late $I_{Na}$, which results in increase in repolarization reserve and suppression of triggered activity caused by early and/or delayed afterdepolarizations.[14] Inhibition of late $I_{Na}$ may also be implicated in ranolazine's capacity to reduce or abolish TWA, which results from mishandling of Ca2+ transients in the sarcoplasmic reticulum.[42] Investigations in a canine heart failure model demonstrated that ranolazine reversibly blocked diastolic intracellular Ca2+ accumulation and spontaneous Ca2+ release by late $I_{Na}$ inhibition.[54] In terms of improvement in myocardial mechanical function, Lovelock *et al.*[55] demonstrated in a murine model that diastolic dysfunction can be reversed by ranolazine, most likely resulting from a direct influence on myofilaments.

It is unlikely that ranolazine's antifibrillatory effects in both atrial and ventricular tissue during myocardial ischaemia without overt proarrhythmia are solely due to inhibition of peak $I_{Na}$ and $I_{Kr}$ as flecainide and E-4031, potent inhibitors of peak $I_{Na}$ and $I_{Kr}$, respectively, were not protective during ischaemia, while ranolazine was antifibrillatory.[25,47] Inhibition of late $I_{Na}$, with consequent reductions in the arrhythmogenic effects of intracellular calcium overload and

**Table 2 Effects of ranolazine on various ion channel currents**

| Ion channel current | Preparation | Potency ($IC_{50}$, μM) | Comments | References |
|---|---|---|---|---|
| Peak $I_{Na}$ | Canine ventricular myocytes | 294 | Tonic block | Undrovinas *et al.*[56] |
| | KPQ murine cardiomyocytes | 135 | | Fredj *et al.*[57] |
| | HEK293 cells | 428 | | Rajamani *et al.*[41] |
| | HEK293 cells | 285 | | Zygmunt *et al.*[58] |
| Late $I_{Na}$ | Canine ventricular myocytes | 5.9 | Tonic block | Antzelevitch *et al.*[53] |
| | Canine ventricular myocytes KPQ | 6.5 | | Undrovinas *et al.*[56] |
| | Murine cardiomyocytes | 15 | | Fredj *et al.*[57] |
| | HEK293 cells | 6.9 | | Wu *et al.*[59] |
| | Rabbit ventricular myocytes | 16.5 | | Jia *et al.*[60] |
| $I_{Kr}$ | Canine ventricular myocytes | 11.5 | | Antzelevitch *et al.*[53] |
| | HEK293 cells | 14.4 | | Wu *et al.*[59] |
| $I_{NCX}$ | Canine ventricular myocytes | 91 | | Antzelevitch *et al.*[53] |
| | tsA201 cells | 1.7 | | Soliman *et al.*[61] |
| | Rabbit ventricular myocytes | >100 | | Gilead, unpublished data |
| $I_{Ca,L}$ | Canine ventricular myocytes | 296 | | Antzelevitch *et al.*[53] |

**Table 3 Effects of ranolazine on G protein-coupled receptors (GPCR)**

| GPCR | Preparation | Potency ($K_i$, μM) | Comments | References |
|---|---|---|---|---|
| $\alpha_1$ | Rat salivary gland | 8.2 | Radioligand binding | Zhao *et al.*[62] |
| | Rat liver | 19.5 | | |
| | Rat ventricle | 10.5 | | |
| $\beta_1$ | Rat ventricle | 8.6 | Binding | Zhao *et al.*[62] |
| | Rat heart | 1.4 | | Letienne *et al.*[63] |
| $\beta_2$ | Guinea pig lung | 14.8 | Binding | Zhao *et al.*[62] |
| | Guinea pig lung | 0.5 | Binding | Letienne *et al.*[63] |
| | $DDT_1MF$-2 cells | 9.0 | Binding | Gilead, unpublished data |

improvement in repolarization reserve, is a plausible mechanism of the antifibrillatory effects of ranolazine and freedom from proarrhythmia.

## Conclusions and future directions

Collectively, these experimental studies in intact large animal models indicate that at therapeutic concentrations, ranolazine exerts significant beneficial effects on electrophysiological properties of both the atria and ventricles, with greater effects on the former structure. Ranolazine's potent cardioprotective effects offer distinct advantages over other contemporary agents, as proarrhythmia was found not to be a factor in the MERLIN TIMI-36 clinical trial[16,17,22] and in these large, intact animal models. Rather, the agent provides safe, dual protection against ischaemia-induced atrial and ventricular arrhythmias.[25,47] Ranolazine also reduces ischaemia-induced TWA[25] and T-wave heterogeneity,[47] electrocardiographic phenomena indicating risk for ventricular arrhythmogenesis. As TWA can be assessed during routine exercise testing or ambulatory electrocardiogram monitoring,[42] it can be employed to gauge clinical relevance of the experimental findings.

Notwithstanding this progress, there remains a need to explore further the underlying mechanisms responsible for ranolazine's antiarrhythmic action, in particular, to understand better the potential involvement of metabolic and antiischaemic influences in ranolazine's action. Also, it is important to study the effects of the agents in models in which chronic disease is simulated by infarction and electrical and structural remodelling.

Several clinical trials are underway that address these issues in populations with diverse indications, as referenced at www.clinicaltrials.gov. Collectively, the information reviewed and heightened interest in this compound with its unique mode of action are likely to contribute to important inroads in the management of supraventricular and ventricular arrhythmias.

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## References


1. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP *et al.* Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997;**96**:2455–61.
2. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001;**345**:1473–82.
3. Deedwania PC, Lardizabal JA. Atrial fibrillation in heart failure: A comprehensive review. *Am J Med* 2010;**123**:198–204.
4. Alasady M, Abhayaratna WP, Leong DP, Lim HS, Abed HS, Brooks AG *et al.* Coronary artery disease affecting the atrial branches is an independent determinant of atrial fibrillation after myocardial infarction. *Heart Rhythm* 2011;**8**:955–60.
5. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ *et al.* HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society Task Force on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2007;**4**:816–61.
6. Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. *JAMA* 2007;**298**:1312–22.
7. Patel C, Yan G-X, Kowey PR. Dronedarone. *Circulation* 2009;**120**:636–644.
8. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A *et al.* Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;**357**:987–999.
9. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J *et al.*; for the PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;**365**:2268–76.
10. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. *Circulation* 2006;**113**:2462–72.
11. MacInnes A, Fairman DA, Binding P, Rhodes JA, Wyatt MJ, Phelan A *et al.* The antianginal agent trimetazidine does not exert its functional benefit via inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res* 2003;**93**:e26–e32.
12. Belardinelli L, Shryock JC, Fraser H. Inhibition of the late sodium current as a potential cardioprotective principle: Effects of the late sodium current inhibitor ranolazine. *Heart* 2006;**92**(Suppl 4):iv6–iv14.
13. Reffelmann T, Kloner RA. Ranolazine: An anti-anginal drug with further therapeutic potential. *Expert Rev Cardiovasc Ther* 2010;**8**:319–29.
14. Antzelevitch C, Burashnikov A, Sicouri S, Belardinelli L. Electrophysiologic basis for the antiarrhythmic actions of ranolazine. *Heart Rhythm* 2011;**8**:1281–90.
15. Tamargo J, Caballero R, Delpón E. Ranolazine: an antianginal drug with antiarrhythmic properties. *Expert Rev Cardiovasc Ther* 2011;**9**:815–27.
16. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, Murphy SA, Budaj A, Varshavsky S *et al.* Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. *JAMA* 2007;**297**:1775–83.
17. Scirica BM, Morrow DA, Hod H, Murphy SA, Belardinelli L, Hedgepeth CM *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.
18. Scirica BM, Belardinelli L, Chaitman BR, Waks JW, Volo SC, Karwatowska-Prokopczuk E *et al.* Effect of ranolazine on atrial fibrillation among patients with Non-ST elevation acute coronary syndromes (NSTEACS): Observations from the MERLIN-TIMI 36 Trial [abstract]. *Circulation* 2011;**124**:A13789.
19. 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.
20. Fragakis N, Koskinas KC, Katritsis DG, Pagourelias 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;**110**:673–7.
21. Murdock DK, Kaliebe J, Larrain G. The use of ranolazine to facilitate electrical cardioversion in cardioversion-resistant patients: a case series. *Pacing Clin Electrophysiol* 2012;**35**:302–7.
22. Scirica BM, Braunwald E, Belardinelli L, Hedgepethi CM, Spinar J, Wang W *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. Kumar K, Nearing BD, Bartoli CR, Kwaku KF, Belardinelli L, Verrier RL. Effect of ranolazine on ventricular vulnerability and defibrillation threshold in the intact porcine heart. *J Cardiovasc Electrophysiol* 2008;**19**:1073–9.
24. Kumar K, Nearing BD, Carvas M, Nascimento BCG, Belardinelli L, Verrier RL. 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.
25. Nieminen T, Nanbu DY, Datti IP, Vaz GR, Tavares CAM, Pegler JRM *et al.* Antifibrillatory effect of ranolazine during severe coronary stenosis in the intact porcine model. *Heart Rhythm* 2011;**8**:608–14.
26. Rivard L, Sinno H, Shiroshita-Takeshita A, Schram G, Leung TK, Nattel S. The pharmacological response of ischemia-related atrial fibrillation in dogs: evidence for substrate-specific efficacy. *Cardiovasc Res* 2007;**74**:104–13.
27. Sinno H, Derakhchan K, Libersan D, Merhi Y, Leung TK, Nattel S. Atrial ischemia promotes atrial fibrillation in dogs. *Circulation* 2003;**107**:1930–6.
28. Sicouri S, Glass A, Belardinelli L, Antzelevitch C. Antiarrhythmic effects of ranolazine in canine pulmonary vein sleeve preparations. *Heart Rhythm* 2008;**5**:1019–26.
29. Burashnikov A, Di Diego JM, Zygmunt AC, Belardinelli L, Antzelevitch C. 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**:1449–1457.
30. Everett TH, Kok LC, Vaughn RH, Moorman JR, Haines DE. Frequency domain algorithm for quantifying atrial fibrillation organization to increase defibrillation efficacy. *IEEE Trans Biomed Eng* 2001;**48**:969–78.
31. Berenfeld O. Quantifying activation frequency in atrial fibrillation to establish underlying mechanisms and ablation guidance. *Heart Rhythm* 2007;**4**:1225–34.
32. Sarmast F, Kolli A, Zaitsev A, Parisian K, Dhamoon AS, Guha PK *et al.* Cholinergic atrial fibrillation: I(K,ACh) gradients determine unequal left/right atrial frequencies and rotor dynamics. *Cardiovasc Res* 2003;**59**:863–73.

33. Chou CC, Nguyen BL, Tan AY, Chang PC, Lee HL, Lin FC *et al.* Intracellular calcium dynamics and acetylcholine-induced triggered activity in the pulmonary veins of dogs with pacing-induced heart failure. *Heart Rhythm* 2008;**5**:1170–7.
34. Lemoine MD, Duverger JE, Naud P, Chartier D, Qi XY, Comtois P *et al.* Arrhythmogenic left atrial cellular electrophysiology in a murine genetic long QT syndrome model. *Cardiovasc Res* 2011;**92**:67–74.
35. Schram G, Zhang L, Derakhchan K, Ehrlich JR, Belardinelli L, Nattel S. Ranolazine: Ion-channel-blocking actions and in vivo electrophysiological effects. *Br J Pharmacol* 2004;**142**:1300–8.
36. Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, Kuch J *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.
37. Moore EN, Spear JF. Ventricular fibrillation threshold: Its physiological and pharmacological importance. *Arch Intern Med* 1975;**135**:446–53.
38. Kirchhof PF, Fabritz CL, Zabel M, Franz MR. The vulnerable period for low and high energy T-wave shocks: Role of dispersion of repolarization and effect of d-sotalol. *Cardiovasc Res* 1996;**31**:953–62.
39. Morita N, Lee JH, Xie Y, Sovari A, Qu Z, Weiss JN *et al.* Suppression of reentrant and multifocal ventricular fibrillation by the late Na current blocker ranolazine. *J Am Coll Cardiol* 2011;**57**:366–75.
40. Antoons G, Oros A, Beekman JD, Engelen MA, Houtman MJ, Belardinelli L *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.
41. Rajamani S, El-Bizri N, Shryock JC, Makielski JC, Belardinelli L. Use dependent block of cardiac late Na(+) current by ranolazine. *Heart Rhythm* 2009;**6**:1625–31.
42. Verrier RL, Klingenheben T, Malik M, El-Sherif N, Exner D, Hohnloser S *et al.* Microvolt T-wave alternans: Physiologic basis, methods of measurement, and clinical utility. Consensus guideline by the International Society for Holter and Noninvasive Electrocardiology. *J Am Coll Cardiol* 2011;**44**:1309–24.
43. Konta T, Ikeda K, Yamaki M, Nakamura K, Honma K, Kubota I *et al.* Significance of discordant ST alternans in ventricular fibrillation. *Circulation* 1990;**82**:2185–9.
44. Nearing BD, Verrier RL. Tracking cardiac electrical instability by computing interlead heterogeneity of T-wave morphology. *J Appl Physiol* 2003;**95**:2265–72.
45. Selvaraj RJ, Picton P, Nanthakumar K, Mak S, Chauhan VS. Endocardial and epicardial repolarization alternans in human cardiomyopathy: evidence for spatiotemporal heterogeneity and correlation with body surface T-wave alternans. *J Am Coll Cardiol* 2007;**49**:338–46.
46. 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.
47. Verrier RL, Pagotto VPF, Kanas AF, Sobrado MF, Nearing BD, Zeng D *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* (in press) http://dx.doi.org/10.1016/j.hrthm.2012.09.015.
48. Verrier RL, Kanas AF, Pagotto VPF, Sobrado MF, Nearing BD, Zeng D *et al.* Ranolazine protects against ischemia-induced atrial fibrillation in an intact porcine model [abstract]. *Heart Rhythm* 2012;**9**:S186–7.
49. Rodrigues M, Silva AC, Aguas AP, Grande NR. The coronary circulation of the pig heart: comparison with the human heart. *Eur J Anat* 2005;**9**:67–87.
50. Burashnikov A, Sicouri S, Di Diego JM, Belardinelli L, Antzelevitch C. Synergistic effect of the combination of dronedarone and ranolazine to suppress atrial fibrillation. *J Am Coll Cardiol* 2010;**56**:1216–24.
51. Sossalla S, Kallmeyer B, Wagner S, Mazur M, Maurer U, Toischer K *et al.* Altered Na(+) currents in atrial fibrillation: effects of ranolazine on arrhythmias and contractility in human atrial myocardium. *J Am Coll Cardiol* 2010;**55**:2330–42.
52. Ehrlich JR, Nattel S. Novel approaches for pharmacological management of atrial fibrillation. *Drugs* 2009;**69**:757–74.
53. Antzelevitch C, Belardinelli L, Zygmunt AC, Burashnikov A, Di Diego JM, Fish JM *et al.* Electrophysiologic effects of ranolazine: a novel anti-anginal agent with antiarrhythmic properties. *Circulation* 2004;**110**:904–10.
54. Undrovinas NA, Maltsev VA, Belardinelli L, Sabbah HN, Undrovinas A. Late sodium current contributes to diastolic cell Ca2+ accumulation in chronic heart failure. *J Physiol Sci* 2010;**60**:245–57.
55. Lovelock JD, Monasky MM, Jeong EM, Lardin HA, Liu H, Patel BG *et al.* Ranolazine improves cardiac diastolic dysfunction through modulation of myofilament calcium sensitivity. *Circ Res* 2012;**110**:841–50.
56. Undrovinas AI, Belardinelli L, Undrovinas NA, Sabbah HN. Ranolazine improves abnormal repolarization and contraction in left ventricular myocytes of dogs with heart failure by inhibiting late sodium current. *J Cardiovasc Electrophysiol* 2006;**17**(Suppl 1):S169–77.
57. Fredj S, Sampson KJ, Liu H, Kass RS. Molecular basis of ranolazine block of LQT-3 mutant sodium channels: evidence for site of action. *Br J Pharmacol* 2006;**148**:16–24.
58. Zygmunt AC, Nesterenko VV, Rajamani S, Hu D, Barajas-Martinez H, Belardinelli L *et al.* Mechanisms of atrial-selective block of Na+ channels by ranolazine: I. Experimental analysis of the use-dependent block. *Am J Physiol Heart Circ Physiol* 2011;**301**:H1606–14.
59. Wu L, Rajamani S, Li H, January CT, Shryock JC, Belardinelli L. Reduction of repolarization reserve unmasks the proarrhythmic role of endogenous late Na(+) current in the heart. *Am J Physiol Heart Circ Physiol* 2009;**297**:H1048–57.
60. Jia S, Lian J, Guo D, Xue X, Patel C, Yang L *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.
61. Soliman D, Wang L, Hamming KS, Yang W, Fatehi M, Carter CC *et al.* Late sodium current inhibition alone with ranolazine is sufficient to reduce ischemia- and cardiac glycoside-induced calcium overload and contractile dysfunction mediated by reverse-mode sodium/calcium exchange. *J Pharmacol Exp Ther* 2012;**343**:325–32.
62. Zhao Z, Fefelova N, Shanmugam M, Bishara P, Babu GJ, Xie LH. Angiotensin II induces afterdepolarizations via reactive oxygen species and calmodulin kinase II signaling. *J Mol Cell Cardiol* 2011;**50**:128–36.
63. Letienne R, Vie B, Puech A, Vieu S, Le Grand B, John GW Evidence that ranolazine behaves as a weak beta1- and beta2-adrenoceptor antagonist in the cat cardiovascular system. *Naunyn Schmiedebergs Arch Pharmacol* 2001;**363**:464–71.
64. Galimberti ES, Knollmann BC. Efficacy and potency of class I antiarrhythmic drugs for suppression of Ca2+ waves in permeabilized myocytes lacking calsequestrin. *J Mol Cell Cardiol* 2011;**51**:760–8.