# Ranolazine: Electrophysiologic Effect, Efficacy, and Safety in Patients with Cardiac Arrhythmias

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**KEYWORDS**

• Antiarrhythmic drug therapy • Atrial fibrillation • Late sodium current channel blocker • Ranolazine • Ventricular arrhythmias

**KEY POINTS**

- Ranolazine is currently approved as an antianginal agent in patients with chronic angina (class IIA).
- Ranolazine exhibits antiarrhythmic effects that are related to its multichannel blocking effect, predominantly inhibition of late sodium (late $I_{Na}$) current and the rapid potassium rectifier current ($I_{Kr}$), as well as $I_{Ca}$, late $I_{Ca}$, and $I_{Na\text{-}Ca}$. It also suppresses the early and delayed afterdepolarizations.
- Ranolazine is effective in the suppression of atrial and ventricular arrhythmias (off-label use) without significant proarrhythmic effect.
- Currently, ongoing trials are evaluating the efficacy and safety of ranolazine in patients with cardiac arrhythmias; preliminary results suggest that ranolazine, when used alone or in combination with dronedarone, is safe and effective in reducing atrial fibrillation.
- Ranolazine is not currently approved by the US Food and Drug Administration as an antiarrhythmic agent.

## INTRODUCTION

Ranolazine, a piperazine derivative, was initially introduced as an antianginal/anti-ischemic agent.[1–8] The mechanism(s) of anti-ischemic effects assumed to be related to the shifting of the myocardial adenosine triphosphate (ATP) production from the fatty acid metabolism to an oxygen-efficient carbohydrate oxidation and reduction in oxygen consumption.[1] In general, myocardial ischemia disrupts the oxygen supply and demand process. As a result, ischemia produces intercellular $Na^+$ and $Ca^{2+}$ overload. In this process, most of the $Na^+$ influx due to the ischemia enters the cells via the cardiac $Na^+$ channels. This increase in intracellular $Na^+$ causes activation of voltage-gated L-type $Ca^{2+}$ influx. Furthermore, as a result of ischemia, late opening of $I_{Na}$ (sodium current) occurs in early phase of repolarization.[9] Ranolazine was later found to have a cardiac multichannel blocking property, specifically a blockade of the late sodium current (late $I_{Na}$) and of the rapid delayed-rectifier potassium current ($I_{Kr}$). It also exhibits minor effects on other cardiac channels, such as $I_{Ca}$ (calcium current), late $I_{Ca}$, and $I_{Na\text{-}Ca}$ (sodium-calcium current).[7,8,10–19] More recently, ranolazine was found to exhibit the mechanosensitive property of $I_{Na}$ current. Unlike potassium-activated stress channels, this effect is less explored

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on $Na^+$ currents.[20–22] Studies on the isolated ischemic myocytes suggest that ranolazine reduces $Ca^{2+}$ overload through inhibition of the late $I_{Na}$.[1] For full detail on the mechanism of anti-ischemic effect of ranolazine, see Ref.[1]

In a large randomized trial, the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation acute coronary syndrome (MERLIN)-Thrombolysis In Myocardial Infarction (TIMI) 36 (MERLIN-TIMI 36), effect of ranolazine was evaluated in patients with non-ST-segment elevation acute coronary syndrome and found that ranolazine prescribed in the first week after admission for acute coronary syndrome was also effective in reducing atrial and ventricular arrhythmias.[7,8,11]

Several recent reports evaluated the electrophysiologic effects, safety, and efficacy of ranolazine in patients with cardiac arrhythmias. In this review, we discuss the electrophysiologic effects and safety profile of ranolazine based on the current data from the available trials.

## ELECTROPHYSIOLOGIC EFFECTS OF THE LATE SODIUM CURRENT

The sodium current has 2 components[8,10,12–15,17,23–26]:

1. Peak $I_{Na}$ occurs at phase zero of action potential (AP) and has a rapid inward current in approximately 1 to 2 ms.
2. The late $I_{Na}$ takes place in phase 2 and early phase 3 of AP and lasts approximately 100 to 300 ms. Increase in late $I_{Na}$ prolongs action potential duration (APD) and blockade of it shortens APD. Most sodium channel blockers exhibit both early and late $I_{Na}$ block effect; however, at different magnitudes. Ranolazine, for example, exerts 9 to 5 times higher late than early $Na^+$ blocking effect.[12]

Although $I_{Na}$ occurs during phase zero (upstroke) of AP, late $I_{Na}$ operates during phase 2 and early phase 3 of AP. Thus, any enhancement of late $I_{Na}$ prolongs APD. On the other hand, agents that block the late $I_{Na}$ current shorten the APD.[12]

In general, atrial AP is shorter in the atrium than the ventricle and becomes significantly shorter in remodeled atria, such as atrial fibrillation (AF). It has been shown that late $I_{Na}$ and its blocking agent, such as ranolazine, respond in a concentration, voltage, and rate-dependent (use-dependent) fashion.[8,12,23,27] Interestingly, the effect of shortening the APD in late $I_{Na}$ blockades is more prominent in healthy than remodeled atrial cells.[12] The role of late $I_{Na}$ in the genesis of arrhythmias is well described in a review by Shryock and colleagues.[28] Augmentation of late $I_{Na}$ has an arrhythmogenic effect that induces a variety of arrhythmias, summarized in **Fig. 1**.

Compared with early $I_{Na}$, late $I_{Na}$ dissociates faster from $Na^+$ channels. This effect has important electrophysiological significance, in which the latter has less proarrhythmic effect. In clinical scenario, the early $Na^+$ channel blockers had a significant proarrhythmic effect that is less commonly used.[8]

Augmentation of the late $I_{Na}$ induces early (EAD) and delayed afterdepolarization (DAD). They play as a trigger for induction of sustained arrhythmias.[8,29] It is therefore conceivable that blockade of the late $I_{Na}$ would eliminate both EAD and DAD.

Interestingly, the 2 major $I_{Na}$ and $I_{Kr}$ blocking properties have a contrasting effect; that is, late $I_{Na}$ causes prolongation of APD, whereas $I_{Kr}$ shortens APD. Furthermore, ranolazine has a diverse and differential effect of different areas of the myocardium; that is, atrial, myocardial, and Purkinje fibers. Ranolazine also exhibits different magnitude of effect on the epicardium and endocardium.[8,23]

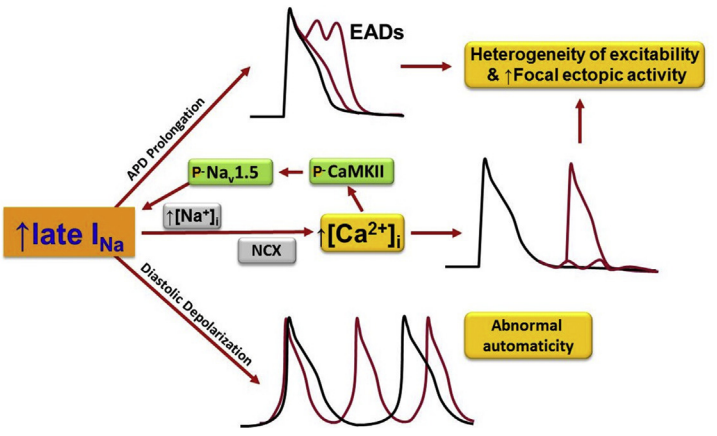


**Fig. 1.** Mechanisms of late $I_{Na}$-induced arrhythmia. ↑, increase. (*From* Shryock JC, Song Y, Rajamani S, et al. The arrhythmogenic consequences of increasing late INa in the cardiomyocyte. Cardiovasc Res 2013;99(4):603; with permission.)