Potential Application of Late Sodium Current Blockade in the Treatment of Heart Failure and Atrial Fibrillation

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The cardiac action potential consists of the sequential activation of various ion channels in a precisely orchestrated manner. Pathologic alterations of ion channel currents disrupt this coordinated behavior and have been linked to arrhythmias, such as atrial fibrillation, as well as to heart failure. The late sodium current is increased in the ventricular myocytes in patients with heart failure and can result in contractile dysfunction. The most likely mechanism whereby elevated intracellular Na^+ levels may lead to heart failure is through calcium overload. Sodium channel blockade is a proven strategy in the treatment of atrial fibrillation. Although all class I anti-arrhythmic drugs inhibit the sodium current, ranolazine has been shown to be a more specific and potent blocker of the late sodium current. In clinical trials, ranolazine has significantly decreased episodes of nonsustained ventricular tachycardia and supraventricular tachycardia as compared with placebo.
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Key words: Heart failure • Atrial fibrillation • Late sodium current • Sodium channel blockade • Tachycardia • Ranolazine

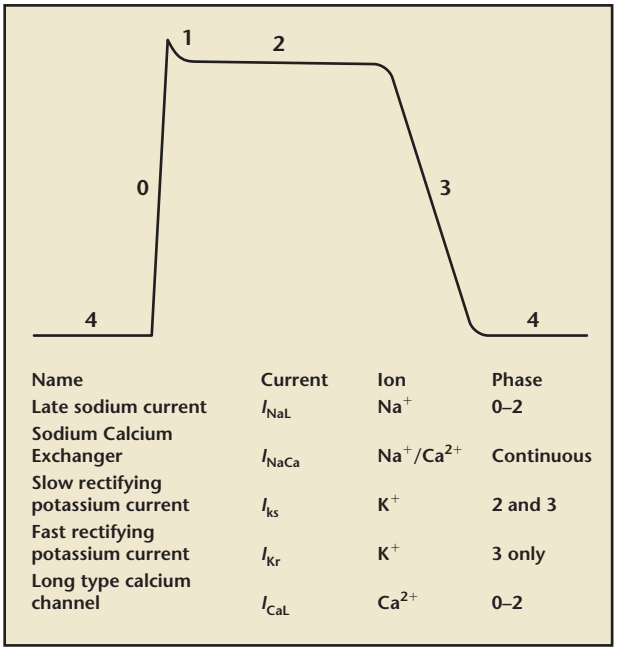
Ion channels play an integral role in the membrane excitability and contractility of cardiac myocytes. The flow of ions across the cellular membrane, performed in a precisely orchestrated fashion by these proteins, creates the cardiac action potential (AP). The AP in turn is responsible for the propagation of the excitatory impulse from myocyte to myocyte, allowing the heart to beat as an electrical and mechanical syncytium. Pathologic alterations of ion channels can disrupt this coordinated behavior and have been linked to heart failure (HF) and atrial fibrillation (AF).

HF is a clinical syndrome characterized by cardiac injury and volume overload. HF affects more than 5 million people in the United States alone, and more than 15 million people in Europe.[1,2] Approximately 50% of deaths from HF are sudden and unexpected, presumably due to the occurrence of a lethal arrhythmia.[3] The pathophysiology involves complex interactions among genetic, inflammatory, and neurohormonal factors. Despite significant scientific progress, the pathophysiology of HF has not been fully elucidated. One phenomenon that has been relatively well characterized in HF is the electrical remodeling that occurs at the molecular, cellular, and histologic levels, which predisposes patients with HF to arrhythmias. One of the more common arrhythmias found in HF is AF, and HF in and of itself is a powerful risk factor for the development of AF.[4]

With or without HF, AF is the most frequently encountered clinical arrhythmia, with an estimated prevalence of 0.4% to 1% in the general population.[5] Disruption of normal electrical activity, from alterations in the expression and/or function in atrial ion channels, is believed to be a precondition for AF. The 2 strategies that have been implemented to manage AF are rate control and rhythm control. Unfortunately, most attempts at suppressing the arrhythmia itself have been ineffective, in part because the underlying pathophysiology is not well understood. Because AF, as well as HF, is linked to ion channel dysfunction, it is imperative to find ion channel targets for more effective pharmacotherapy.

The human cardiac AP predominantly represents the sequential activation and inactivation of ion channels that conduct depolarizing, inward (Na^+ and Ca^{2+}) and repolarizing, outward (K^+) currents. The influx of sodium ions results in the fast sodium current, which is represented by the initial upstroke or phase 0 of the AP (Figure 1). There is a sustained component of this sodium influx that persists into the plateau phase or phase 2, known as the late sodium current (I_{NaL}). It has recently been appreciated that abnormal I_{NaL} enhancement can contribute to both electrical and contractile dysfunction, contributing to AF and HF. The aim of this article is to delve into the late sodium current and explore how its blockade may be effective for the treatment of both HF and AF.

Figure 1. *Cardiac myocyte action potential.*



Overview of I_{NaL}, $Na_v1.5$, and SCN5A

The ion channel believed to be responsible for both the regular sodium current and the late sodium current (I_{Na} and I_{NaL}) is $Na_v1.5$, which is encoded by the SCN5A gene located on the short arm of chromosome 3 at position 21. $Na_v1.5$ is a glycosylated membrane protein that is approximately 220 kDa in size. It is made up of 4 homologous domains, each of which has 6 transmembrane segments (Figure 2). Both the *N*- and C-terminus are cytoplasmic, along with 3 intracellular linkers that connect the 4 domains. The protein associates with ankyrin proteins, calveolin-3, and 4 different β-subunits (β1-β4). The exact location of the channel within the cardiac myocytes is still under investigation and somewhat controversial. Currently, it is believed to be found in intercalated discs and, possibly, in lateral membranes and *t*-tubules as well.

Studies of Na_v 1.5 knock-out and over-expression mice have helped elucidate the role of this channel in the heart. Homozygous knock-out mice of $Na_v1.5$ exhibit embryonic lethality during midgestation due to several defects in ventricular morphogenesis.[6] Heterozygote knock-out mice, on the other hand, survive but exhibit impaired intra-atrial, atrioventricular, and intraventricular conduction, as well as increased ventricular refractoriness and ventricular tachycardia with characteristics

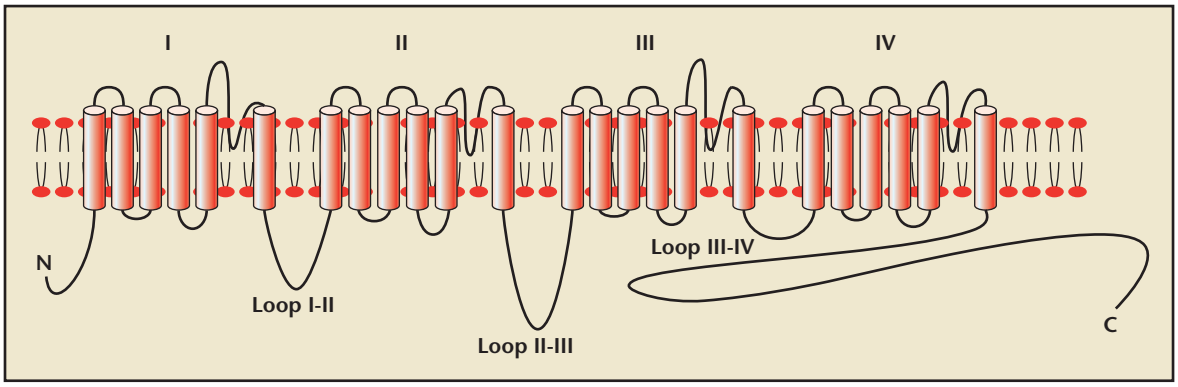


Figure 2. *The structure of the sodium channel.*

of reentrant excitation. $Na_v1.5$-overexpressing mice exhibit a mild shortening of the P-wave and the PR interval, but no change in the total inward sodium current or AP duration.[7]

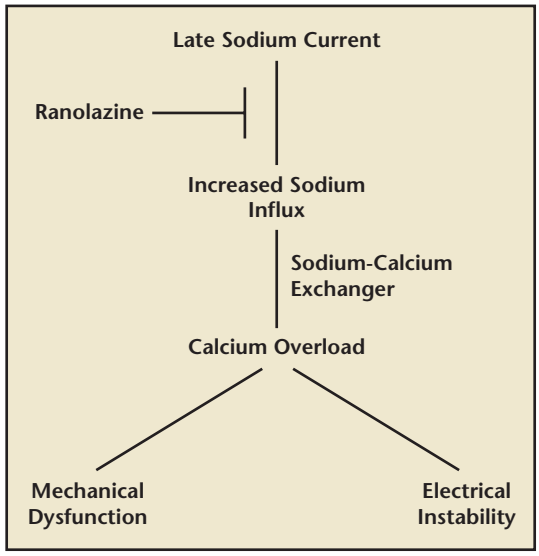
In humans, deletions or mutations of the SCN5A gene have been associated with a broad array of cardiac diseases, including the long QT syndrome type 3 (LQT3), Brugada syndrome, and progressive cardiac conduction disease. In LQT3, most of the 84 known SCN5A mutations result in a "gain-of-function" effect, usually leading to persistent late sodium current causing AP prolongation. In contrast, Brugada syndrome and conduction system disease are generally characterized by a "loss-of-function" in sodium current through various mechanisms, such as decreased protein trafficking, more rapid inactivation kinetics, or altered voltage-dependence of activation.

Recently, genetic analyses of patients with lone AF have revealed mutations in the SCN5A gene as well.[8] Biophysical studies performed on some of these mutations reveal a gain-of-function that favors atrial hyperexcitability.[9] Moreover, it has been shown that AF can occur in combination with several of the previously mentioned genetic syndromes.[10] Additionally, there are heritable SCN5A defects that are associated with susceptibility to early onset dilated cardiomyopathy and AF.[11] The clinical phenotypes, as well as the animal phenotypes, convincingly stress the importance of Na_v 1.5 in normal cardiac function, and its importance in pathologic conditions such as AF and HF.

I_{NaL} and Pathogenesis in Heart Failure and Atrial Fibrillation

The late sodium current is increased in the ventricular myocytes in both animal models of HF and in patients with HF.[12] Abnormal regulation of I_{NaL} has been linked to the pathogenesis of both HF and AF (Figure 3). In brief, increased I_{NaL} can result in contractile dysfunction and HF. The most likely mechanism whereby elevated Na^+ levels may lead to HF is through calcium overload. Sodium in cardiac myocytes is not only regulated through SCN5A, but also through the Na-Ca exchanger (NCX). The enhanced activity of I_{NaL} results in a pathologic state because there is an increase in the intracellular concentration of Na^+, resulting in Na^+–Ca^{2+} exchange through NCX, and increased Ca^{2+} entry into myocytes. In other words, the additional Na^+ acts as a substrate for

Figure 3. *The pathogenesis of heart failure and atrial fibrillation.*



increasing intracellular Ca^{2+} by the NCX. The consequence is calcium overload and, thus, abnormal excitation-coupling and contractile dysfunction. Therefore, by decreasing Na^+ entry into cardiac myocytes through late sodium channel blockade, it may be possible to decrease intracellular Ca^{2+} and improve cardiac function.

Prolonged late sodium current may also contribute to arrhythmias. There are 2 possible mechanisms: first, by preventing timely repolarization and causing early afterdepolarizations (EAD) and second, by triggering delayed afterdepolarizations (DAD) attributable to calcium oscillations in sodium-calcium overload conditions such as previously described. Therefore, decreasing the late sodium current could be useful in treating arrhythmias such as AF in patients with HF.

Although all class I antiarrhythmic drugs inhibit the sodium current, ranolazine has been shown to be a more specific and potent blocker of the late sodium current.[13] As a result, this review focuses predominantly on ranolazine and contains brief discussions of other sodium channel blockers.

Overview of Ranolazine

Ranolazine is a piperazine derivative with a chemical structure resembling lidocaine, which is a Vaughan-Williams class IB antiarrhythmic drug. Ranolazine is a blocker of late sodium current, but it has also been shown to be a weak inhibitor of other ion currents as well. The repolarizing currents of the rapidly activating delayed-rectifier K^+ (I_{Kr}) and slowly activating delayed-rectifier K^+ (I_{Ks}), as well as Ca^{2+} (I_{Ca}) currents, can be blocked by ranolazine ($I_{Kr} > I_{Ca} > I_{Ks}$).[14] Moreover, there is a relative specificity of ranolazine for atrial myocytes rather than for ventricular myocytes, which may decrease the risk of ventricular proarrhythmia.[15]

Ranolazine is also known to have anti-ischemic properties without affecting hemodynamic parameters, such as heart rate and blood pressure. It has been consistently shown in clinical trials to significantly prolong exercise duration and time to angina, as monotherapy or when administered with conventional antianginal therapy. In January 2006, the Food and Drug Administration approved its use for the treatment of chronic angina pectoris based on its efficacy and favorable side-effect profile. The mechanism of action of its antianginal effects has not yet been determined. In addition to being an inhibitor of the late sodium current, ranolazine has been recognized as a partial fatty oxidation (pFOX) inhibitor as well as an inhibitor of the late sodium current.[16] It is postulated that its antianginal abilities stem from this inhibition of pFOX, which causes a shift in ATP production away from fatty acid oxidation toward carbohydrate oxidation. Myocardial oxygen demand is then reduced without any substantial decrease in cardiac work, thus alleviating angina symptoms.

Ranolazine is metabolized predominantly by the liver, mainly by CYP3A4. Although it is not metabolized by CYP2D6, it does inhibit this enzyme. As a result, the dosage of several cardiac drugs metabolized by CYP2D6 may need to be reduced when given in conjunction with ranolazine. At doses less than 1000 mg bid, the use of immediate and sustained-release formulations resulted in some minor side effects, such as constipation, nausea, dizziness, headache, asthenia, and dyspepsia. A minor prolongation of the QTc has also been demonstrated in some trials with sustained-release ranolazine, but there have been no documented cases of torsades de pointes. It is postulated that ranolazine's ability to block I_{Kr} is responsible for this phenomenon. Additionally, it has been shown that the drug can decrease hemoglobin A_{1c} levels in diabetic patients in a dose-related fashion. The mechanism of this action has yet to be elucidated, but it may also be related to the inhibition of fatty acid oxidation. Recent preclinical and clinical trials have also demonstrated ranolazine's efficacy in the treatment of HF and arrhythmias.

Preclinical Studies of Ranolazine and Heart Failure

In the setting of HF, several animal models have shown ranolazine to be beneficial in improving left ventricular function. In a study by Sabbah and colleagues[17] that used a canine model of HF induced by multiple intracoronary microembolizations, a single loading dose of ranolazine followed by an infusion for 40 minutes decreased left ventricular diastolic pressure and increased left ventricular stroke volume and ejection fraction (EF).[17] Moreover, these improvements in systolic function occurred without a concomitant increase in heart rate, blood pressure, or oxygen consumption.[18] Additionally, in a follow-up study of this canine model of HF, ranolazine caused isolated ventricular cardiac myocytes to have a shortened AP duration, markedly fewer EADs, and improved contraction.[19]

In contrast to these findings, a study by Aaker and colleagues[20] seemed to indicate that the exercise endurance capacities of rats with a surgically induced myocardial infarction decreased compared with those of sham controls after 2 to 4 weeks of chronic ranolazine administration. The authors of this study contend that they may have used too high a dose of the drug.

Clinical Studies of Ranolazine and Heart Failure

There is some evidence that ranolazine may improve diastolic function in patients with HF. In one study, patients with ischemic cardiomyopathy (with average EF of 35%) were given intravenous ranolazine infusions and then underwent echocardiographic assessment of ischemic, infarcted, and normal left ventricular segments function. Left ventricular EF was not changed significantly after ranolazine infusion (average EF was 37% after the drug). Ranolazine was associated with a significant increase in peak filling rate and regional wall lengthening during the isovolumic relaxation phase in ischemic segments, likely indicating improved diastolic function.[21]

Preclinical Studies of Ranolazine and Atrial Fibrillation

Recent animal studies have implicated the late sodium channel in proarrhythmic atrial activity. A study by Song and colleagues[22] revealed that an increase of I_{NaL} is a mechanism for the initiation of atrial arrhythmic activity, and that I_{NaL} blockade by ranolazine was able to inhibit some of this adverse atrial activity. Guinea pig atrial myocytes were first given anemone toxin II (ATX-II), which is known to enhance the late sodium channel and cause EADs, DADs, and triggered activity. Subsequently, the administration of ranolazine to block ATX-II–induced late I_{NaL} completely abolished triggered activity, and DADs were reduced upon application of ranolazine. The findings of this study were corroborated by another study in which ranolazine was able to decrease EAD- and DAD-mediated triggered activity in canine pulmonary vein sleeve preparations.[23]

In a study of isolated canine atrial myocytes, ranolazine was able to prevent the initiation of acetylcholine-mediated AF, terminating persistent AF and preventing its reinduction.[15] These findings were demonstrated in vivo in a study by Kumar and colleagues,[24] in which episodes of AF induced by intrapericardial acetylcholine injections in pigs could be decreased in both duration and dominant frequency with the administration of ranolazine. The reinitiation of AF was shown to be decreased as well, although the difference did not reach statistical significance.

Clinical Studies of Ranolazine and AF

The largest clinical trial with ranolazine to date is the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36 (MERLIN-TIMI 36) study, in which 6560 patients hospitalized with a non–ST-elevation acute coronary syndrome were randomized to ranolazine or placebo.[25] Patients had continuous electrocardiogram (ECG) monitoring for 7 days after enrollment. The trial was designed to test if ranolazine would reduce ischemia, but the ECG monitoring allowed for an analysis of the antiarrhythmic properties of the drug in this specific patient population. Fewer patients in the ranolazine group had episodes of nonsustained ventricular tachycardia, using a cut-off of either 3 beats or 8 beats (52.1% vs 60.6% for 3 beats, and 5.3% vs 8.3% for 8 beats; both $P < .001$).[26] The rate of polymorphic ventricular tachycardia was low in both groups, though slightly lower in the ranolazine group than in the placebo group (1.2% vs 1.4%; not statistically significant), indicating that the QT effect of ranolazine is probably not clinically significant (Table 1). Also, there was no significant difference in sudden cardiac death between treatment groups, with 56 (1.7%) in the ranolazine group versus 65 (1.8%) in the placebo group ($P = .40$).

Ranolazine also had a beneficial effect on supraventricular tachycardias in MERLIN-TIMI 36. Using a cut-off of 4 beats or more, supraventricular tachycardia was significantly less common in the group treated with ranolazine (1413 [44.7%] vs 1752 [55.0%]; $P < .001$). New-onset AF was infrequent in this trial but was also reduced with ranolazine (55 [1.7%] vs 75 [2.4%]; $P = .08$) (Table 1). Reassuringly, this finding does not appear to be due to a negative chronotropic effect or by a block of the atrioventricular node, because pauses of 3 seconds or more were less frequent with ranolazine (97 [3.1%] vs 136 [4.3%]; $P = .01$). Clinical trials of ranolazine in patients with AF are warranted to assess its effectiveness in this patient population.

Other Sodium Channel Blockers and Future Therapeutics

Sodium channel blockade is a proven strategy in the treatment of AF. For instance, the Vaughan-Williams class IA and IC antiarrhythmics are routinely used to manage AF. IA agents block the fast sodium current, which depresses the phase 0 depolarization, prolongs AP duration, slows conduction, and increases refractoriness. They can be used to convert AF back into normal sinus rhythm. However, the agents in this class have considerable drawbacks. Their use is limited by adverse reactions, such as the lupus-like syndrome caused by procainamide and cinchonism and torsades de pointes that can occur with quinidine.

Table 1
Rate of Tachyarrhythmias Detected on cECG Monitoring After Non–ST-Segment Elevation MI in MERLIN-TIMI 36

	Ranolazine, n (%)	Placebo, n (%)	RR (95% CI)	*P* Value
Ventricular arrhythmias				
VT 3 beats 100 bpm	1646 (52.1)	1933 (60.6)	0.86 (0.82-0.90)	< .001
VT 4 beats 100 bpm	662 (20.9)	941 (29.5)	0.71 (0.6-0.78)	< .001
VT 8 beats (lasting < 30 s)	166 (5.3)	265 (8.3)	0.63 (0.52-0.76)	< .001
Polymorphic VT 8 beats	38 (1.2)	46 (1.4)	0.83 (0.54-1.28)	.40
Sustained VT (30 s)	14 (0.44)	14 (0.44)	1.01 (0.48-2.13)	.98
Monomorphic	4 (0.13)	7 (0.22)	0.59 (0.17-2.06)	.37
Polymorphic	10 (0.32)	7 (0.22)	1.41 (0.52-3.78)	.46
Supraventricular arrhythmias				
New-onset atrial fibrillation	55 (1.7)	75 (2.4)	0.74 (0.52-1.05)	.08
Other SVT 120 bpm lasting at least 4 beats	1413 (44.7)	1752 (55.0)	0.81 (0.77-0.85)	< .001

cECG, continuous electrocardiographic; CI, confidence interval; MERLIN-TIMI 36, Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36; MI, myocardial infarction; RR, relative risk; SVT, supraventricular tachycardia; VT, ventricular tachycardia. Reprinted with permission from Scirica BM et al.[26]

Class IC agents, such as flecainide and propafenone, have a more potent sodium channel blocking effect. These agents markedly depress the phase 0 depolarization and decrease conduction without affecting AP duration. The main disadvantage of these agents is that they are proarrhythmic, especially in patients with HF due to structural heart disease and coronary artery disease, and they are contraindicated in these settings.

Given the lack of atrial specificity and the potential for proarrhythmic activity, particularly in the setting of HF, these agents appear to be inferior to selective late sodium channel blockers, such as ranolazine. Other agents that block the late sodium channel are also on the horizon. Le Grand and colleagues[27] report on the development of a compound (3,4-dihydro-*N*-[(2S)-3-[(2-hydroxy-3-methylphenyl)thio]-2-methylpropyl]-2H-(3R)-1,5-benzoxathiepin-3-amine) that, like ranolazine, was able to block the late sodium channel blocker without affecting hemodynamic properties. Although the antiarrhythmic properties have not been studied, the compound was able to reduce infarct size in a porcine model of ischemia with reperfusion injury. The compound is clearly in its early experimental stages, but it supports the idea that late sodium channel blockers have a potentially profound role in alleviating cardiovascular injury. Further studies are in the works for this and other such novel compounds.

Conclusion

HF is a leading cause of morbidity and mortality, and its incidence continues to rise annually. AF is the most commonly encountered clinical arrhythmia. Thus, it is fair to say that the effective and safe pharmacological treatment of both AF and HF are 2 of the greatest medical needs in our society today. There is a growing body of evidence that the selective blockade of the late sodium current may have therapeutic benefits in both disease entities. Of all the late sodium current blockers, ranolazine is the best studied agent, with a wide array of benefits and very few drawbacks.

The advantages of ranolazine are numerous. For instance, in the treatment of AF, ranolazine has been shown to be relatively atrial selective, unlike the other class I antiarrhythmics. It has also been demonstrated to increase systolic function in HF without increasing heart rate or blood pressure. Furthermore, its benefits extend outside the realms of AF and HF. As previously mentioned, ranolazine has antianginal properties, as well as possible antidiabetic properties, as evident by its ability to decrease glycosylated hemoglobin A_{1c} levels. Nevertheless, ranolazine may block other ion channels at higher doses, and it can prolong the QT interval with a theoretical risk of torsades de pointes.

With our continually improving understanding of myocardial biology, new therapies for AF and HF are

emerging. Late sodium channel blockade is already one such promising treatment modality that clearly warrants further research. ■

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Main Points

- Abnormal regulation of the late sodium current has been linked to the pathogenesis of both heart failure (HF) and atrial fibrillation (AF).
- Disruption of normal electrical activity, from alterations in the expression and/or function in atrial ion channels, is believed to be a precondition for AF.
- Sodium channel blockade is a proven strategy in the treatment of AF.
- Although all class I antiarrhythmic drugs inhibit the sodium current, ranolazine has been shown to be a more specific and potent blocker of the late sodium current.
- In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36 (MERLIN-TIMI 36) study, ranolazine significantly decreased episodes of nonsustained ventricular tachycardia and supraventricular tachycardia as compared with placebo.