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# Ranolazine: Beyond the Treatment of Chronic Stable Angina Pectoris

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## Abstract

The aims in the treatment of angina are relief of pain and prevention of disease progression through risk reduction. A number of patients may have contraindications or remain unrelieved from anginal discomfort with conventional drugs. Among newer alternatives, ranolazine indirectly prevents the intracellular calcium overload involved in cardiac ischemia and it is a considered as a valid addition to traditional treatments. Recent findings showed potential positive side effect of ranolazine in the treatment of arrhythmias. This review gives an overview of the basic principles of ranolazine in the treatment of myocardial ischemia and examines its applications in the new field of anti-arrhythmic effects.

## Keywords

Coronary artery disease, Ischemic heart disease, Myocardial oxygen balance, Refractory angina, Arrhythmias, Anti-arrhytmic drug

## Introduction

Coronary artery disease (CAD) represents one of the leading causes of morbidity and mortality worldwide, with onerous medical, social and financial impact. One of the clinical manifestations of CAD is represented by chronic stable angina pectoris, defined as a clinical syndrome characterized by discomfort in the chest (usually retrosternal) and resulting from an imbalance between myocardial oxygen supply and requirement in the setting of an atherosclerotic coronary plaque. The most important determinant of an augmented myocardial oxygen demand is an increased heart rate (HR) in response to emotion, physical exertion, stress, excessive metabolic requirements caused for example by fever, thyrotoxicosis or hypoglycemia. In the setting of a fixed atherosclerotic plaque, a transient reduction of oxygen supply can be also a cause of angina. The atherosclerotic disease is characterized by an endothelial disfunction that manifests itself in a decreased production of vasodilator substances and iper responsiveness to vasoconstrictor stimuli. These pathogenetic features represent the starting point on which the standard pharmacological and medical treatment of stable angina has been built. Conventional medical therapies, such as beta-blockers or calcium channel blockers, exert their antianginal effect by improving the ischemic imbalance through the reduction of HR, blood pressure, ventricular contractility, thus leading to a reduction of myocardial oxygen demand [1]. Ranolazine is a novel antianginal agent, approved by the Food and Drug Administration in 2006, that, unlike beta-blockers, nitrates, or calcium channel blockers, does not affect either heart rate or blood pressure. Its peculiar mechanisms of action consent to assess several potential applications beyond the control of stable angina symptoms. Aim of this work is to provide a description of the mechanisms of action of ranolazine, focusing on its role as antianginal tool and on its potential future applications [2].

## Chronic Stable Angina: Definition, Pathophysiology and Current Treatment

The first introduction of the term "angina pectoris" has been provided in 1772 by Heberden [3], to describe a clinical condition characterized by a sense of "strangling and anxiety", in the chest. The etiological substrate of this syndrome has been elucidated only some years later. Angina pectoris is now described as a clinical syndrome characterized by discomfort in the chest or in adjacent areas, such as jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin. Its onset can be attributed tomyocardial ischaemia, caused by an imbalance between myocardial oxygen consumption and supply that occurs when muscles perfusion is inadequate to meet an augmented cardiac metabolism, as can be every condition characterized by an increased heart rate (HR) and left ventricular (LV) contractility [1]. The leading cause of myocardial ischemia is represented by atherosclerotic CAD, affecting one or more epicardial coronaries, however other causes of myocardial ischemia, occurring in the absence of atherosclerotic obstructions of the vessels, such as cardiomyopathies or aortic stenosis, need to be mentioned as a cause of anginal pain. More in detail, the anatomo-pathological substrate of stable angina is represented by an atherosclerotic plaque determining a narrowing of the luminal cross-section of the vessel with a consequent reduction of the ability of the coronary vascular bed to reduce its resistance during maximal exercise. Thus, the onset of myocardial ischemic suffering is strongly dependent on the degree of obstruction and on cardiac oxygen demands [4]. Although a proper assessment of the epidemiological impact of stable angina is difficult, due to the clinical diagnosis and to the symptoms variability in the patients, approximately it can be estimated that, in most European countries, 20 000–40 000 individuals of the population permillion suffer from angina, with an annual incidence of 0,5% in western population aged >40 [1].

The treatment of stable anginapectoris aims to improve quality of life by reducing the severity and/or frequency of symptoms and

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to improve the prognosis of the patient, preventing myocardial infarction (MI) and cardiovascular death. Lifestyle changes, drugs, and revascularization play an important role in minimizing or eradicating symptoms of angina. Lifestyle changes mainly rely on cessation of smoking, dietary intervention and physical activity. Concomitant disorders associated with an increased risk of cardiovascular disease, such as hypertension, diabetes mellitus or other features of metabolic syndrome should also be managed appropriately [1]. In recent years, pharmacological therapies has been largely improved and, for some groups of patients, has been clearly demonstrated a superiority of pharmacological treatment in comparison with revascularization; thus, pharmacotherapy can be considered to date a viable alternative to invasive strategies for the treatment of most patients with stable angina pectoris [5-8]. In the MASS (Medicine, Angioplasty or Surgery Study) - II, the pharmacological treatment of stable angina patients has been associated with fewer complications than surgery or percutaneous coronary intervention (PCI) during a 1-year follow-up [9]. An invasive treatment should be preferred for all those patients with poorly controlled symptoms with a pharmacological approach, or for those at high risk of a major cardiovascular event [7]. To date, the cornerstone of chronic stable angina therapy is represented by beta-blockers agents, such as metoprolol, propanolol, atenolol. These compounds have antihypertensive, anti-ischemic and anti-arrhythmic properties, exerting their action by blocking the effects of catecholamines on beta-receptors and reducing in this way HR, ventricular contractility and blood pressure. Calcium channel blockers inhibit calcium ion movements through voltage-dependent calcium channels, exerting in this way several effects, such as a dose-dependent negative inotropic action, a reduction of arterial pressure and systemic vascular resistance with a consequent decrease of myocardial oxygen consumption. Nitrates have vasodilating effects on systemic arteries (including epicardial coronary arteries) and veins, improving in this way myocardial perfusion and reducing oxygen consumption by decreasing preload and arterial pressure [1]. Despite the proved efficacy of these drugs, used both in monotherapy and in combination, there is still the need of new compounds to treat stable angina, especially for those patients in whom the standard therapy is contraindicated or when adverse effects come out or when there is a poor control of symptoms.

## Ranolazine: A Novel Antianginal Compound

Ranolazine ([(+)N-(2,6-dimethylphenyl)-4(2-hydroxy-3-(2-methoxyphenoxy)-propyl)-1-piperazine acetamidedihydrochloride]) (Figure 1) is an active piperazine whose anti ischemic effect was originally attributed to a selective inhibition of fattyacid oxidation, with a consequent shift of metabolism to more energy efficient glucose oxidation [10]. An alternative mechanism of action proposed in the past for ranolazine was the inhibition of β1- andβ2-adrenoceptor [11]. More recent evidences suggest that ranolazine reduces calcium overload in the ischemic myocyte through inhibition of the late sodium current ($I_{Na}$) [2]. Under physiologic conditions, myocytes depolarization results from rapid activation of membrane sodium channels, leading to a temporary intracellular accumulation of sodium. The subsequent release of calcium from the sarcoplasmic reticulum induces myocardial contraction, through the binding with actin and myosin. During depolarization, the intracellular homeostasis is restored by means of sodium/potassium-ATPases (Na+/K+-ATPase) and sodium/calcium ($Na^+/Ca^{2+}$) exchangers. Several pathological states, such as myocardial ischemia, left ventricular hypertrophy, and heart failure can exchange ionic currents, leading to intracellular acidosis, excess of cytosolic $Ca^{2+}$, cellular dysfunction, and, if sustained, cell injury and death. During myocardial ischemia a prolonged late sodium current (late $I_{Na}$) during the plateau of the action potential has been described [12,13]. Under normal conditions, late $I_{Na}$ constitutes only 1% of peak $I_{Na}$. This rise in intracellular sodium results in intracellular $Ca^{2+}$ overload via reverse transport across the $Na^+/Ca^{2+}$ exchanger, leading to sustained myocardial contraction and, later on, persisting the pathological conditions, to myocardial dysfunction, increased diastolic wall tension and electrical instability [14]. An increased diastolic wall tension could represent a cause of increased myocardial oxygen demand, leading to a compression of the vascular beds with a consequent reduction of coronary blood flow. Several studies pointed out that ranolazine exert its antianginal effects by inhibiting the late $I_{Na}$ [15-17] and preventing in this way the intracellular calcium overload and its subsequent deleterious effects. On normal resting myocytes, where the contribution of late $I_{Na}$ is minimal, ranolazine seems to have a weak effect [18]. Thus, ranolazine exerts its antianginal effects by acting on ion currents over expressed during ischemia and, consequently, resulting effective only in pathologic conditions (Table 1).

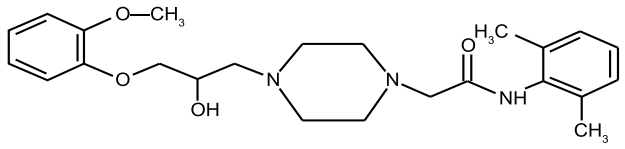


**Figure 1:** Ranolazine

**Table 1:** Ranolazine: pharmacological and clinical features

- Inhibits the late sodium channels, not only lowering total inward sodium flux but also the subsequent intracellular calcium overload.
- Reduces the late inward calcium current, the inward $Na^+/Ca^{2+}$ exchange current, and the outward repolarizing, delayed rectifier potassium current.
- Peak plasma levels occur 4–6 hours after an oral dose, with 50%–55% bioavailability.
- Cleared by the hepatic enzymes CYP3A4 (70%–85%) and CYP2D6 (10%–15%) and is also a substrate of P-glycoprotein, a widely expressed membrane transporter protein.

Clinical drug interactions of importance:

- Ketoconazole significantly raises ranolazine levels up to4.5-fold
- Diltiazem, due to mild CYP3A4 inhibition, may raise ranolazine levels 1.5-fold.
- Paroxetine may raise plasma ranolazine concentrations by a factor of 1.2 because of CYP2D6 inhibition.
- Ranolazine may nearly double levels of simvastatin since it is a mild inhibitor of both CYP3A4 and
- CYP2D6. Simultaneous administration of CYP3A4inhibitors together with some statins remains a clinical concern.
- verapamil may raise ranolazine levels upto 3-fold.
- Digoxin levels may rise 1.4–1.6-fold because ofP- glycoprotein competition by ranolazine.
- Ranolazine may prolong the rate-corrected QT interval, about 6msec at a dose of 2g/d.

## Ranolazine in Chronic Stable Angina

One of the first study compared ranolazine with atenolol and placebo in a double blind randomized crossover design involving 158 patients [19]. In this study, Rousseau and coll. found a significant improvement of time to angina onset, time to ST segment depression and exercise duration related to ranolazine in comparison with placebo, however only the total exercise duration was significantly improved comparing ranolazine with atenolol. In this study has been used the immediate-release formulation of ranolazine, while in all the subsequent trials has been evaluated the effect of the sustained-release ranolazine, that in the oral formulation represents the only available for clinical use. The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial represents a multicenter, double-blind, crossover study, in which 191 patients with angina-limited exercise have been randomized toranolazine 500mg, 1000mg, 1500mg or placebo twice daily for one week [20]. Exclusion criteria were non-diagnostic electrocardiogram, New York Heart Association Class III or IV, congestive heart failure, unstable angina, myocardial infarction, recent coronary revascularization (<two months), corrected QT interval ($QT_c$) >500msec, or medication prolonging the QT interval or affecting metabolism of Cytochrome P450 (CYP)3A4. The enrolled

patients were required to have exercise-limiting angina with ≥ 1mm horizontal or downsloping ST depression on exercise treadmill testing. Exercise testing was performed during both peak (four hours after the intake of the drug) and trough (12 hours after the intake) of plasma ranolazine concentration and at the end of each treatment phase, in order to assess the clinical response and to establish a dose-response relationship. Chaitman et al. pointed out that ranolazine 500mg, 1000mg and 1500mg twice daily significantly (P<0.005) increased exercise duration in comparison with placebo and in an incremental way by 94sec, 103 sec and 116 sec respectively. They further demonstrated dose-related increases in exercise duration at peak, as well as trough and peak times to 1mm ST segment depression and times to angina onset. Adverse events, as well as the higher rate of early withdrawal from the study, were registered particularly with the 1500mg dose. Moreover, differently from other common antianginal drugs, they found that ranolazine did not significantly affect HR or blood pressure both at rest and during exercise. Thus, MARISA represents the first major clinical trial showing that ranolazine improves exercise performance in a dose-dependent manner in patients with chronic stable angina, without clinically relevant hemodynamic alterations and with a good safety profile. In this study, except for sublingual nitroglycerin, all other antianginal treatments were discontinued prior to enrollment. Differently, in the Combination Assessment of Ranolazine in Stable Angina (CARISA) trial, more than 800 patients with chronic angina on concurrent therapy with beta-blockers or calcium channel blockers have been investigated [21]. In this randomized, double-blind, placebo-controlled design, patients were assigned to ranolazine 750mg, 1000mg or placebo. At the time of enrollment, appropriate therapies to be continued throughout the study were as follows: atenolol 50mg, diltiazem 180mg once daily or amlodipine 5mg once a day. Exclusion criteria were almost the same to those described in MARISA trial. Treadmill exercise test was performed at peak and trough drug intervals, after 2, 6 and 12 weeks of treatment. In this study, Chaitman et al. found a significant improvement of exercise duration in both ranolazine groups, compared with the placebo one (115.6 sec in ranolazine groups (pooled) versus 91.7 sec in placebo group; P=0.01). Furthermore, exercise duration resulted increased at both trough and peak of plasma ranolazine concentration, with a higher benefit at peak concentrations. This response was independent of background standard treatments and sustained during the 12 weeks of therapy, with a significant reduction of the number of angina attacks per week (from 3.3 in placebo group to 2.5 and 2.1 in ranolazine 750mg and 1000mg respectively) and with a concomitant reduction of nitroglycerin consumption. No alterations in blood pressure or HR have been detected. These two trials demonstrated the efficacy of ranolazine both as monotherapy (MARISA trial) and as additional therapy in patients who remained symptomatic despite optimal doses of traditional antianginal treatments. The efficacy of Ranolazine in Chronic Angina (ERICA) trial enrolled 565 patients similar to those included in the previous clinical trials [22]. Aim of this randomized, double-blinded, study was to determine if ranolazine provided additional benefit to those obtained with a maximal dosing of a standard antianginal therapy, comparing placebo versus ranolazine 1000mg twice daily in patients with symptomatic (≥3 angina attacks per week) chronic stable angina despite amlodipine 10mg daily. Differently from the antecedent trials, in which exercise duration was assessed performing an exercise test, the primary endpoint was the frequency of anginal attacks per week. Stone et al. found a significant reduction of anginal episodes in ranolazine group compared with placebo (2.88 ± 0.19 versus 3.31 ± 0.22 on placebo; P=0.028), with a greater effect observed for those patient with more than 4.5 angina attacks per week and with a concomitant reduction in nitroglycerin consumption (2.03 ± 0.20 versus 2.68 ± 0.22 on placebo; P=0.014). These clinical trials highlighted that ranolazine is a well tolerated drug, without significant adverse events and without increased mortality in CAD patients, including elderly and patients with diabetes and heart failure. These findings have been well elucidated in The Ranolazine Open Label Experience (ROLE) trial [23], in which Koren et al. enrolled 746 patients who completed either MARISA or CARISA trials with a severe symptomatic angina. The mean follow-up was of 2.82 years and in this period 9.7% of patients discontinued ranolazine due to adverse events, such as dizziness, constipation, asthenia, nausea, syncope, headache and abdominal pain. Of the aforementioned adverse events, dizziness and constipation were the most common (11.8% and 10.9% respectively); $QT_c$ prolongation by 2.4msec was observed, however there were no treatment discontinuations due to $QT_c$ prolongation and no reported cases of torsade de pointes. Five episodes of syncope were reported in the CARISA trial, however all cases involved patients using medications known to affect ranolazine's plasma levels by increasing its concentrations. MARISA trial reported a higher number of adverse effects for those patients taking 1550mg of ranolazine twice daily. Consequently, ranolazine 1000mg twice a day became the maximum recommended dose. Combining data derived from MARISA, CARISA and ROLE trials, the mortality for patients with stable CAD treated with ranolazine was 2.8% in comparison with >5% as predicted by the Duke Treadmill score. The effect of ranolazine have been tested also in patients with acute coronary syndrome (ACS) in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36 trial [24], a placebo-controlled, double-blind randomized study, in which 6560 patients were assigned to placebo or ranolazine treatment within 48 hours of ACS presentation. In this trial, ranolazine has been administered first intravenously and later in oral formulation at 1000mg twice a day. The patients had continuous Holter monitoring for seven days after the event, the median duration of the follow-up was of 348 day and the primary endpoint was a composite of cardiovascular death, myocardial infarction or recurrent ischemia. The analysis of the primary endpoint showed no significant differences between the two groups, however, analyzing the individual elements, Morrow et al. found that, while cardiovascular death rate and myocardial infarction did not differ significantly between ranolazine and placebo groups (showing how, even in ACS patients, with higher-risk of major cardiovascular events, ranolazine does not increase cardiovascular death or total mortality), ranolazine significantly lower the incidence of recurrent ischemia if compared with placebo (13.9% versus 16.1% respectively). The MERLIN trial further demonstrated the effectiveness of ranolazine in controlling angina symptoms, with a favorable safety profile, even in higher risk patients with ACS.

## Ranolazine and Arrhythmias

The basis for the use of ranolazine is likely related to inhibition of late sodium channels with resultant beneficial downstream effects. The mechanisms involved channels currents have a key role in the potential use of ranolazine not only in ischemic heart disease but also in patients with arrhythmias.

## Ranolazine and Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, and is related to substantial morbidity and mortality mostly related to stroke, and other thrombo-embolic events. AF is also associated with left ventricular (LV) dysfunction, heart failure and increased cardiovascular mortality independently of thromboembolic complications. Class IC antiarrhythmics are the most effective drugs to convert AF, although the potential proarrhythmic (ventricular) risk of is a major drawback; for this reason several drugs are currently under investigation, with the aim to discover new compounds which could act specifically on atrial tissue through the blockade of ion currents involved exclusively in the genesis of atrial action potential. At this regard, selective sodium channel blockers have been demonstrate to have a paradoxical atrial selectivity; this feature seems due to differences between atrial and ventricular action potentials occurring at high heart rates; in this setting atrial cells are characterized by a resting membrane potential more depolarized

than ventricular ones, which leads to an increased number of sodium channels in the inactivated state in the atria. Another atrial specific feature of sodium current ($I_{Na}$) blockade is the induction of post-repolarization refractoriness, which consists of a prolongation of effective refractory period without change of the duration of atrial potential duration [25-27]. The first interesting result about a possible use of ranolazine for the conversion of atrial fibrillation was reported by Burashnikov et al. who studied the electrophysiological effects of therapeutic concentration of ranolazine in canine isolated coronary perfused atrial and ventricular preparations, finding that ranolazine was able to suppress AF, through a use-dependent block of sodium channels [28]. Furthermore, Scirica et al. analyzing data from the MERLIN-TIMI 36 trial, showed that patients in the ranolazine arm, although not characterized by a lower mortality when compared with placebo treated ones, showed a reduced incidence of ventricular and supraventricular arrhythmias and a trend toward a lower detection of new-onset AF during the first 7 days of treatment after NSTEMI [29]. Burashnikov et al. carried out another study in order to evaluate the electrophysiological effects of ranolazine, both alone and in combination with dronedarone, in canine isolated coronary-perfused right and left atrial and left ventricular preparations, pointing out how the combination of both drugs was able to cause an atrial-selective depression of sodium channel-dependent parameters, resulting in an effective and significant conversion to sinus rhythm of 90% of "fibrillant" preparations [30]. Furthermore, Sosalla and colleagues, studying the electrical modifications during chronic AF (a condition characterized by an alterated expression of ion channels), highlighted how ranolazine could have an antiarrhythmic effect but also improve diastolic function [31]. Finally, in order to investigate a role for ranolazine using a "pill in the pocket" approach, Murdock et al. treated with 2000mg of the oral drug 18 patients, both with new or paroxysmal AF of recent onset (from 3 to 48 hours), finding a conversion rate to sinus rhythm of 72%, almost comparable to other "pill in the pocket" protocols (e.g. using propafenone or flecainide) [32]. Notably, in none of the aforementioned studies ranolazine was associated with severe adverse events, and no cases of ventricular proarrhythmia have been described; this is an important feature, since all the current drugs for AF, exerting their activity also at ventricular level, could prolong action potential, promoting the development of an electrical substrate for malignant ventricular arrhythmias, such as torsade de pointes. More recently it is investigated whether ranolazine, compared with flecainide and sotalol, can suppress AF in an experimental rabbit whole heart model, in which acute haemodynamic changes trigger AF. Ranolazine suppresses stretch-induced AF by increasing interatrial conduction time and atrial post-repolarization refractoriness (aPRR). These results give us further evidence on the potential role of ranolazine in the prevention of AF, applying it to clinical conditions that are associated with haemodynamic or mechanical disorders, leading to acute dilatation of the atria. Ranolazine is also evaluated for antiarrhythmic therapy of atrial fibrillationin combination with class-III drugs studied in an isolated whole-heart model of stretch-related AF, in the study it is found that ranolazine might have beneficial effect: the increase in interatrial conduction time and marked atrial postrepolarization refractoriness suppressed AF [33]. The antiarrhythmic properties of this novel agent were investigated regarding its ability to conversion of postoperative atrial fibrillation when added to amiodarone after coronary artery bypass graft surgery. After randomization to receive either ranolazine 375mg twice daily orally plus intravenous amiodarone (active group) or intravenous amiodarone alone (control group); it is shown that mean time of conversion was significantly shorter in the active group (19.9 ± 3.2 vs 37.2 ± 3.9 hours, P<.001), suggesting that compared to amiodarone alone, the ranolazine-amiodarone combination had a superior antiarrhythmic effect. The management of AF plays a critical role in the setting of heart failure (HF); in coronary-perfused right atrial preparations isolated from the hearts of HF dogs, clinically relevant concentration of ranolazine (5μmol/L) significantly depressed sodium channel current–dependent parameters causing a reduction of maximum rate of rise of the action potential upstroke, a prolongation of the effective refractory period secondary to the development of post repolarization refractoriness, and an increase in diastolic threshold of excitation and atrial conduction time versus normal dogs[34]. From the laboratory to the clinical setting in the last years some studies have tried to validate the potential positive effective on AF. Recent results of the dose-ranging RAFFAELLO (Ranolazine in Atrial Fibrillation Following An ELectricaLCardiOversion) study, a prospective, multicenter, randomized, double-blind, placebo-control parallel group phase II dose-ranging trial, showed no dose of ranolazine significantly prolonged time to AF recurrence, but at the same time in the patients underwent to 500 and 750mg treatment (group combined) it is found a reduced AF recurrences [35].

## Ranolazine and Ventricular Arrhythmias

In contrast to the observations made in isolated atrial tissue, in large animal models in which therapeutic drug plasma levels have been achieved, consistent with clinical observations, ranolazine confers dual protection against ventricular as well as atrial arrhythmias. The effects of ranolazine in suppressing ventricular arrhythmias have been recently investigated. As mentioned above, in the MERLIN-TIMI 36 trial patients treated with ranolazine experienced less episodes of ventricular tachycardia lasting at least 8 beats [29]. Kaliebe et al. reported a case of suppression of symptomatic non-sustained ventricular tachycardia [36]. Furthermore Dhalla et al. showed the ability of ranolazine in preventing and reducing the duration of ventricular arrhythmias induced by ischemia and ischemia-reperfusion, configuring itself as a new therapeutic strategy for the management of ventricular arrhythmias in the setting of the ischemic heart disease [37]. Later on, ranolazine has been proved to be effective in restoring sinus rhythm in both pacing-induced re-entrant ventricular fibrillation and early after-depolarization -mediated multifocal ventricular fibrillation [38], and in preventing ventricular arrhythmias during severe coronary stenosis [39]. Sosalla et al. in isolated healthy rabbit heart evaluated the effects of ranolazine on Torsades de pointes (TdP), polymorphic ventricular arrhythmias arising from early after depolarizations (EADs) and increased dispersion of repolarization, reproducibly induced with d-sotalol (104mol/L) and low potassium (K) (1.0mmol/L for 5min, pacing at CL 1000ms); The combination of d-sotalol and two concentrations of ranolazine did not increase dispersion of ventricular APD90 as compared to vehicle. Ranolazine at 5lmol/L did not cause additional induction of EADs and/or TdP but also did not significantly suppress arrhythmogenic triggers the higher concentration of ranolazine (10lmol/L) in combination with d-sotalol caused further prolongation ofAPD90, at the same time reduction in APD90 dispersion. In parallel, the incidence of EADs was reduced and an antitorsadogenic effect was seen [40]. This finding—despite additional APD prolongation—supports the safety of a combined use of both drugs and merits clinical investigation. All these evidences need further investigations, with the aim to better define the effective utility of the drug in *in vivo* models.

## Ranolazine and Long QT Syndrome

Long QT syndrome is an inborn heart condition characterized by a delayed repolarization of the heart, identifiable as prolonged QT interval in the ECG, associated with syncope and sudden cardiac death subsequent to ventricular arrhythmias, commonly torsade de pointes [41]. Several mutations of genes encoding cardiac ion channels or membrane proteins have been demonstrated to be responsible of the syndrome. Particularly, long QT syndrome variant 3 (LQT-3) is characterized by mutations in SCN5A, the gene coding for the alpha subunit of the primary heart voltage gated $Na^+$ channel, which result in a defect in channel inactivation and persistent late $Na^+$ current ($I_{NaL}$) during ventricular depolarization, which cause a transient inward current (ITI) after repolarization is completed [42]. ITI could be responsible of malignant arrhythmias in conditions characterized by sarcoplasmic reticulum (SR) calcium $Ca^{2+}$ overload. Ranolazine has been demonstrated to improve diastolic function in LQT-3 patients [43], and more recently, Lindegger et al. found that it inhibits mutation-induced $I_{NaL}$ and ITI, and reduces $Ca^{2+}$ concentrations

myocytes with the most frequent SCN5A mutation. Thus ranolazine could constitute a new tool for the management of LQT-3 and other disorders, such as heart failure, in which enhanced late Na+ channel activity and spontaneous diastolic $Ca^{2+}$ release may occur [44]. The role of ranolazine has also been explored in the setting of LQT-8, also known as Timothy syndrome, a condition characterized by long QT and other developmental defects, such as round face, flat nasal bridge, receding upper jaw, thin upper lip, and syndactyly. The mutation underlying this disorder regards L-type $Ca^{2+}$ channels, which is subsequently activated, bringing to a calcium overload in the cell. Sicouri et al. using coronary-perfused left ventricular wedge preparations treated with BayK8644 (a compound able to prolong action potential duration with subsequent prolongation of the QT interval and to induce an increase in transmural dispersion of repolarization), demonstrated the effectiveness ranolazine in preventing and suppressing torsade de pointes also in this variant of LQT syndrome, hypothesizing a role in ranolazine in all the variant of the syndrome [45]. Moreno et colleagues, based on the rationale that the ranolazine blocks the human ether-a-go-go–related gene–based current IKr at therapeutic concentrations and causes QT interval prolongation, developed a computational model to predict if therapeutic effects of pharmacological targeting of INaL by ranolazine prevailed over the off-target block of IKr in the setting of inherited long-QT syndrome type 3 and heart failure. They then simulated clinically relevant concentrations of ranolazine and predicted the combined effects of $Na^+$ channel and IKr blockade by both the parent compound ranolazine and its active metabolites, which have shown potent blocking effects in the therapeutically relevant range. Their simulations suggest that ranolazine is effective at normalizing arrhythmia triggers in bradycardia-dependent arrhythmias in long-QT syndrome type 3 as well tachyarrhythmogenic triggers arising from heart failure–induced remodeling [46].

## Metabolic, Endothelial and Analgesic effects of Ranolazine

In the CARISA trial, ranolazine reduced glycosylated haemoglobin (HbA1C) concentrations by almost 0.5%, maybe increasing insulin sensitivity [21]. The same effect was also observed in the MERLIN-TIMI 36 trial, in which ranolazine significantly reduced HbA1C at 4 months, and decreased the incidence of impaired fasting glucose levels [24]. The hypothesized mechanisms for such effects could be related to the effects of the drug on pancreatic islet cells ion channels, in which it seems to increase glucose related insulin secretion. Recent evidences suggest that insulin could also improve endothelial function, as demonstrated by Deshmukh et al. who found that ranolazine therapy significantly increase endothelial vasodilation if compared with placebo [47]. Since non-selective sodium channel block constitutes an integral part of the pharmacotherapy for peripheral neuropathic pain, although gravated by a number of adverse effects, ranolazine has also been studied, demonstrating to inhibit the mechanical and cold allodynia associated with spared nerve injury, without producing ataxia or other behavioral side effects; the relative selectivity of sodium channel block operated by ranolazine could justify the absence of side effects associated with this analgesic therapy. Again, new randomized studied are needed in order to assess the role of ranolazine in pain modulation [48].

## Conclusions

Despite the efficacy of conventional pharmacological therapies for chronic stable angina, in several conditions, novel compounds with different targets and properties are required: this can happen for the treatment of those patients with contraindication of beta-blockers, nitrates, or calcium channel blockers, or for the coming up of adverse effect, or also for patients in whom standard treatments in combination do not achieve symptoms relief. Ranolazine is a late $I_{Na}$ inhibitor that exerts its action specifically on ischemic myocardiocytes, or in other pathological settings, without affect normal resting cardiomyocytes. Several clinical trials pointed out the efficacy of ranolazine as antianginal drug in patients with CAD, and alsoin patients at higher risk, such as ACS patients. These studies showed also a favorable safety profile and highlighted that ranolazine controls angina symptoms and improves exercise tolerance without affecting hemodynamic parameters, such as HR or blood pressure, manifesting itself as an ideal antianginal tool where the use of traditional agents is limited by bradycardia or hypotension. Its unique mechanism of action has lead to several other studies, investigating other applications of ranolazine; however these recent findings, although promising, need to be further validated in large clinical trials.

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