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Review

The Role of Ranolazine in the Treatment of Ventricular Tachycardia and Atrial Fibrillation: A Narrative Review of the Clinical Evidence

Kyosuke Murai [1], Amir Vasigh [1], Tamás Alexy [2], Kálmán Tóth [1,3] and László Czopf [1,*]

[1] 1st Department of Medicine, Medical School, University of Pécs, Ifjúság útja 13, H-7624 Hungary
[2] Department of Medicine, Division of Cardiology, University of Minnesota, Minneapolis, MN 55127, USA
[3] Szentágothai János Research Centre, Medical School, University of Pécs, Ifjúság útja 20, H-7624 Hungary
* Correspondence: czopf.laszlo@pte.hu

Abstract: Cardiac arrhythmias are among the leading causes of morbidity and mortality worldwide. While antiarrhythmic drugs traditionally represent the first-line management strategy, their use is often limited by profound proarrhythmic effects. Several studies, including randomized control trials (RCTs), have demonstrated the antiarrhythmic efficacy of ranolazine, registered as an antianginal agent while also establishing its safety profile. This review compiles clinical evidence investigating the antiarrhythmic properties of ranolazine, focusing primarily on ventricular tachycardia (VT) and atrial fibrillation (AF), as common rhythm abnormalities with serious complications. Data from RCTs indicate that ranolazine reduces VT incidence, although this effect is not universal. Therefore, we attempt to better describe the patient population that gains the most benefit from ranolazine by VT suppression. Additionally, ranolazine is known to enhance the conversion rate of AF to sinus rhythm when combined with other antiarrhythmic drugs such as amiodarone, highlighting its synergistic effect in the atrium without provoking ventricular dysrhythmias. Despite the heterogeneity in currently available data, ranolazine appears to be an effective and safe option for the management of various arrhythmias.

Keywords: Ranolazine; Ventricular tachycardia; Atrial fibrillation; Antiarrhythmic agents

1. Introduction

Cardiac arrhythmias not only represent a serious challenge for the field of cardiovascular medicine, but also contribute significantly to morbidity and mortality worldwide. Historically, antiarrhythmic drugs represented the therapeutic mainstay to suppress a wide range of arrhythmias. The Cardiac Arrhythmia Suppression Trial (CAST) as well as subsequent studies showed that, while these drugs reduce the incidence of arrhythmias significantly, they may lead to a 3.6-fold increased risk of sudden cardiac death. This perceived pro-arrhythmogenic effect led to an overall decline in their utilization and are now restricted to a limited range of indications (1–3). In contrast, ablation therapy has grown increasingly popular for the management of various arrhythmias, including atrial fibrillation (AF) and ventricular tachycardia (VT). However, ablation may not be universally successful with its use limited to certain scenarios. For instance, it is clearly effective for paroxysmal AF, yet the success rate for the treatment of persistent or permanent AF is lower (4). Additionally, it is an invasive intervention which carries some risks for complications, requires specialized expertise as well as potentially costly equipment to perform.

Amiodarone, a potent antiarrhythmic drug, is commonly used among patients with persistent and symptomatic arrhythmias. One of the major drawbacks to amiodarone use however is its long-term side effect profile. It may adversely affect the structure or function of multiple organ systems, such as the lungs, liver, thyroid, nervous system, and the skin. Delayed onset of action of the oral formulation is another challenge, particularly when an immediate therapeutic effect is desired (5).

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On the other hand, intravenous administration may provoke hypotension and worsening cardiogenic shock in select patient populations.

Owing to these challenges, ranolazine, a piperazine derivative, has been proposed as a potential alternative therapy for arrhythmia management, primarily owing to its excellent safety profile. It was initially approved by the Food and Drug Administration (FDA) in 2006 for the management of chronic stable angina pectoris. Multiple studies have since demonstrated its antiarrhythmic effect, a property that may present a promising future for this drug. The present review analyzes the clinical data available on the use of ranolazine specifically as an antiarrhythmic agent. We aimed to answer the following primary question: Does ranolazine administration reduce the prevalence or severity of cardiac rhythm disorders when compared with placebo or standard of care among patients with a history of arrhythmias or at risk for developing arrhythmia?

2. Methods

Authors performed a literature search on PubMed and Embase databases in October 2023, using the following search terms: "ranolazine AND arrhythmia cardiac," or "ranolazine AND heart arrhythmia." All relevant articles published in English were carefully examined, specifically those focusing on the primary question listed above. The scope of the review included observational studies, clinical trials, and randomized controlled studies. Reviews and summaries of molecular studies that did not include human observations were reviewed yet not included when synthesizing and aggregating the data. Additionally, case reports and articles lacking full-text availability were excluded.

3. Results

Following the inclusion and exclusion criteria, 11 studies were included in the final synthesized review. Basic study information, the performed intervention, and outcomes are summarized in tables 1 and 2.

Table 1. Effect of ranolazine on reducing VT burden or severity.

Authors	Population	Intervention/Comparison	Outcome
Scirica (MERLIN-TIMI 36) (6)	Randomized, double-blind study, 6,351 patients with NSTEMI or unstable angina randomly assigned to ranolazine (63±11 years, 2,093 males) or placebo (63±11 years, 2,031 males)	IV ranolazine with 200 mg bolus then 80 mg/h infusion for 12-96 hours, then PO 1,000 mg ranolazine BID. Continuous ECG monitoring for the first 7 days	The number of VT episodes exceeding 8 beats was significantly reduced in the ranolazine group vs. placebo (166 [5.3%] vs. 265 [8.3%]; p<0,001)
Zareba, Younis (RAID trial) (7,8)	Randomized, double-blind, placebo-controlled, multicenter, intention-to-treat study, 1,012 patients with ICD randomly divided into ranolazine (64.3±10.3 years, 410 males) and placebo (64.2±9.9 years, 416 males) groups	Ranolazine 500 mg BID for 1 week, increased to 1,000 mg BID if dosage tolerated. Follow-up for mean 28.3±15.8 months	Significantly reduced recurrence of VT/VF requiring ATP or ICD shock in the ranolazine group vs. placebo (433 vs. 650, HR=0.70 [0.51-0.96]; p=0.028). The benefit of ranolazine was limited to the following subgroups: 1) ranolazine

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			monotherapy (HR=0.68 [0.55-0.84] vs. HR=1.33 [0.90-1.96], p=0.003); 2) implanted CRT-D (HR=0.64 [0.47-0.86] vs. HR=0.94 [0.74-1.18]; p=0.047); 3) No AF (HR=0.66 [0.54-0.81] vs. HR=1.56 [1.02-2.39], p=0.003)

Abbreviations: **NSTEMI**: Non-ST elevation myocardial infarction; **VT**: ventricular tachycardia; **ICD**: implantable cardioverter defibrillator; **BID**: twice daily; **VF**: ventricular fibrillation; **ATP**: anti-tachycardia pacing; **CRT-D**: cardiac resynchronization therapy-defibrillator; **AF**: atrial fibrillation; **IV**: intravenous; **PO**: per os; **HR**: hazards ratio; **mg**: milligram.

Table 2. Effect of ranolazine on AF prevention and on AF conversion to sinus rhythm.

Authors	Population	Intervention/Comparison	Outcome
Scirica (MERLIN-TIMI 36) (6,9)	Randomized, double-blind study, 6,351 patients with NSTEMI or unstable angina randomly assigned to ranolazine (63±11 years, 2,093 males) or placebo (63±11 years, 2,031 males)	IV ranolazine 200 mg bolus followed by 80 mg/h infusion for 12-96 hours, then 1,000 mg PO BID. Continuous ECG monitoring for the first 7 days, follow-up for 12 months	Trend towards reduced AF occurrence within the first 7 days with ranolazine vs. placebo (55 vs. 75, HR=0.74 [0.52-1.05]; p=0.08). Reduced clinically significant AF* after 12 months in ranolazine group vs. placebo (2.9% vs. 4.1%, HR=0.71 [0.55-0.92]; p=0.01)
Koskinas (10)	Randomized, single-blind study, 121 patients with symptomatic AF (< 48 hours) randomly assigned to amiodarone plus ranolazine (66±11 years, 25 males) or amiodarone-only (64±9 years, 29 males)	Amiodarone: 5 mg/kg IV loading dose in 1 hour then 50 mg/h for 24 hours or until cardioversion	Amiodarone plus ranolazine significantly increased AF conversion rate within 24 hours (53 vs. 42; p=0.024) and reduced mean time for AF

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		Ranolazine: 1,500 mg PO at randomization	conversion (10.2±3.3 vs.13.3±4.1 hours; p=0.001)
Tsanaxidis (11)	Randomized, single-center study, 173 patients with recent onset AF randomly assigned to amiodarone plus ranolazine (92, 70±10 years, 38 males) and amiodarone-only (81, 67±11 years, 41 males)	Amiodarone: 5 mg/kg IV loading dose, 50 mg/h maintenance infusion. After conversion, 200 mg PO BID for a week and then 200 mg PO daily for a week. Ranolazine: 1,000 mg PO then 375 mg BID 6 hours after arrhythmia termination	Amiodarone plus ranolazine significantly increased conversion of AF within 24 hours (90 vs. 47; p<0.001) and reduced mean time to AF termination (8.6±2.8 hours vs. 19.4±4.4 hours; p<0.0001) vs. the amiodarone-only group
Simopoulos (12)	Randomized, single-blind study, 511 patients with post-CABG AF randomly assigned to amiodarone plus ranolazine (65.3±9.5 years) or amiodarone-only (65.5±9.6 years)	Amiodarone: 300 mg IV in 30 minutes, followed by 1,125 mg in 36 hours Ranolazine: 500 mg PO, 375 mg after 6 hours and then 375 mg PO BID	Amiodarone plus ranolazine increased AF conversion to sinus rhythm significantly within 24 hours (235 vs. 37; p<0.0001) and reduced mean time of AF conversion (10.4±4.5 hours vs. 24.3±4.6 hours; p<0.0001) vs. amiodarone alone

Table 2. Continued.

Authors	Population	Intervention/Comparison	Outcome
Reiffel (Harmony trial) (13)	Randomized, double-blind, placebo-controlled, intention-to-treat study. 131 patients with paroxysmal AF randomized to 1) placebo (72±8.4 years, 13 males); 2) ranolazine 750 mg (70±10.8 years, 10 males); 3) dronedarone 225 mg (75±7.8 years, 10 males); 4) dronedarone 150 mg plus ranolazine 750 mg (73±9.4 years, 15 males); 5) dronedarone 225 mg plus ranolazine 750 mg (71±7.1 years, 15 males)	Each given BID for 12 weeks	Significantly reduced AF burden** in group 5 vs. placebo (4.8% vs. 11.1%; p=0.008)

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De Ferrari (Raffaello trial) (14)	Randomized, double-blind, placebo-controlled, multicenter, intention-to-treat study. 238 patients with persistent AF (7 days to 6 months) randomly assigned to: 1) placebo (55, 65.2±9.5 years, 41 males); 2) ranolazine 375 mg (65, 66.9±11.8 years, 46 males); 3) ranolazine 500 mg (60, 65.5±8.5 years, 51 males); 4) ranolazine 750 mg (58, 63.6±11.3 years, 46 males)	Each given BID for 16 weeks after electrical cardioversion	Significantly reduced AF recurrence in group 3 vs. placebo when patients were still in sinus rhythm after 48 hours (HR=0.56, [0.31-1.01]; p=0.0495)

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Miles (15)	Retrospective, single-center cohort study. 393 patients after CABG received either amiodarone (211, 64.9±10.9 years, 162 males) or ranolazine (182, 66.7±9.3, 127 males)	Amiodarone: 400 mg daily preoperatively (7 days prior to elective CABG or immediately before urgent CABG), 200 mg BID postoperatively for 10-14 days Ranolazine: 1,500 mg on the day prior to elective CABG or on the day of urgent CABG. 1,000 mg BID postoperatively for 10-14 days	Ranolazine significantly reduced the incidence of new onset AF compared to amiodarone (17.5% vs. 26.5%; p=0.035)
Hammond (16)	Retrospective, single-center, cohort study. After matched-pair analysis, 114 patients post-CABG or valve surgery received either ranolazine (57, 60.3±11.1 years, 38 males) or placebo (57, 59.6±11.5 years, 38 males)	Preoperative ranolazine 1,000 mg on the morning of surgery, 1,000 mg BID afterwards for 7 days	Ranolazine significantly reduced the incidence of new onset AF vs. placebo (10.5% vs. 45.6%; OR=0.09 [0.021-0.387]; p< 0.0001)

Abbreviation: **NSTEMI**: Non-ST elevation myocardial infarction; **BID**: twice daily; **HR**: hazard ratio; **CABG**: coronary artery bypass graft; **OR**: odds ratio. *Clinically significant AF as the authors used it includes paroxysmal AF (AF burden between 0.01% and 98%) and predominantly chronic AF (AF burden more than 98%). **AF burden was calculated as the proportion of recording time (%) in AF

3.1. Ventricular Tachycardia

The Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) was a randomized, double-blind study in which 6,550 patients with NSTEMI were randomly assigned to take either ranolazine or placebo (17). In a subset analysis Scirica found ranolazine to significantly reduce the number of VT episodes lasting longer than 8 beats during the first 7 days, when compared to placebo (166 vs. 265, p<0.001). Continuous ECG monitoring was employed to detect arrhythmia burden (6).

Ranolazine in High-Risk Patients with Implanted Cardioverter-Defibrillators (RAID Trial) was another randomized, double-blind, placebo-controlled intention-to-treat study that enrolled 1,012 patients with an implantable cardioverter defibrillator (ICD) in situ. Patients were randomly assigned to receive ranolazine or placebo. After a mean of 28.3 months follow-up, ranolazine was found to significantly reduce the incidence of VT or ventricular fibrillation (VF) episodes requiring anti-tachycardia pacing (ATP) or ICD shock to terminate, when compared to placebo (433 vs. 650, HR=0.70 [0.51-0.96]; p=0.028) (7). In a subset of the RAID trial, Younis observed that the benefits of ranolazine were limited to the following subgroups: 1) patients receiving ranolazine monotherapy (without any concomitant antiarrhythmics); 2) those who have cardiac resynchronization therapy-defibrillator (CRT-D) in place; and 3) patients without atrial fibrillation (8).

3.2. Atrial Fibrillation

Scirica demonstrated in a subset of patients from the MERLIN-TIMI 36 trial that, within the first 7 days after NSTEMI, those in the ranolazine group had a trend towards lower incidence of AF compared to placebo (55 vs. 75, HR=0.74 [0.52-1.05]; p=0.08) (6). After one year follow-up, ranolazine

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led to a substantial decrease in clinically significant AF burden in this population (2.9% vs. 4.1%, HR=0.71 [0.55-0.92]; p=0.01). Additionally, it reduced the time spent in AF (calculated as proportion of recording time), when compared to placebo (4.4% vs. 16.1%; p=0.015) (9).

Several studies evaluated the potential synergistic effect of ranolazine when used in combination with another antiarrhythmic drug, particularly amiodarone, for the treatment of AF. Koskinas performed a randomized, single-blind study in which 121 patients with recent-onset symptomatic AF were randomly assigned to a combination of amiodarone plus ranolazine or amiodarone alone. Those in the amiodarone plus ranolazine group not only had a significantly higher conversion rate to sinus rhythm within 24 hours (53 vs. 42; p=0.024), but the mean time to AF termination was also significantly shorter (10.2±3.3 hours vs. 13.3±4.1 hours; p=0.001) (10). Similarly, Tsanaxidis completed a randomized, single-center study enrolling 173 patients with recent-onset AF. Participants were assigned to amiodarone plus ranolazine or amiodarone alone. Amiodarone plus ranolazine increased the conversion rate of AF significantly within 24 hours (90 vs. 47; p<0.001) and reduced the mean time to conversion (8.6±2.8 hours vs. 19.4±4.4 hours; p<0.0001) (11).

Simopoulos performed a randomized, single-blind study including 511 patients who developed AF following coronary artery bypass graft surgery (CABG). Patients were randomized to receive amiodarone plus ranolazine or amiodarone only. The combination of ranolazine and amiodarone significantly increased the conversion rate of AF within 24 hours (235 vs. 37; p<0.0001) and also reduced the mean time needed for AF termination (10.4±4.5 hours vs. 24.3±4.6 hours; p<0.0001) (12). In a retrospective single-center cohort study directly comparing the antiarrhythmic effects of amiodarone and ranolazine in 393 post-CABG patients (within 10-14 days), Miles showed that ranolazine was more effective in reducing the incidence of new-onset AF versus amiodarone (17.5% vs. 26.5%; p=0.035). Importantly, there were significant differences in the baseline group characteristics, particularly in the proportion of patients with New York Heart Association (NYHA) class IV symptoms as well as the ejection fraction (EF). This raises an important and valid concern for potential selection bias (15). Finally, Hammond published a retrospective cohort study with 76 patients who underwent either CABG or valve surgery and received ranolazine or placebo. After matched-pair analysis, ranolazine was found to reduce the incidence of new onset AF after 7 days significantly, when compared to placebo (10.5% vs. 45.6%, OR=0.09 [0.021-0.387]; p<0.0001) (16).

Harmony was a randomized, double-blind, controlled, intention-to-treat study in which 131 patients with paroxysmal AF were randomized into one of 5 groups: 1) placebo; 2) ranolazine 750 mg; 3) dronedarone 225 mg; 4) dronedarone 150 mg plus ranolazine 750 mg; 5) dronedarone 225 mg plus ranolazine 750 mg. Compared to placebo, the study demonstrated a significantly reduced AF burden when using a combination of dronedarone 225 mg plus ranolazine 750 mg (group 5; 4.8% vs. 11.1%; p=0.008) (13).

Ranolazine in Atrial Fibrillation Following an Electrical Cardioversion (RAFFAELLO) study was a randomized, double-blind, placebo-controlled, multicenter, intention-to-treat study. It enrolled 238 patients with persistent AF (7 days to 6 months duration) following electrical cardioversion. Patients were randomly assigned to one of four groups: 1) placebo; 2) ranolazine 375 mg; 3) ranolazine 500 mg; 4) ranolazine 750 mg. The treatment duration was 16 weeks. AF recurrence was 56.4%, 56.9%, 41.7%, and 39.7% in groups 1-4, respectively. None of the ranolazine doses extended the time until the first AF recurrence. However, 500 mg ranolazine significantly reduced the rate of AF recurrence versus placebo when patients were still in sinus rhythm after 48 hours (HR=0.56 [0.31-1.01]; p=0.0495) (14).

4. Discussion

This narrative review is aimed at compiling existing clinical evidence on the benefits of ranolazine in treating cardiac arrhythmias, specifically VT and AF.

4.1. Brief Mechanism of Action

Ranolazine is a medication well-established to act as an inhibitor of various ion channels, including late I_{Na}, peak I_{Na}, the rapid-activating delayed rectifier I_{Kr}, and, to a clinically lesser extent,

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L-type I_{Ca} (18). The mechanisms by which ranolazine acts on the late I_{Na} and peak I_{Na} channels are complex and warrant a limited further discussion, because this will aid in understanding the rationale for the studies reviewed here. In brief, ranolazine is a more effective inhibitor of the late I_{Na} channels in ventricular myocytes, whereas it predominantly inhibits peak I_{Na} channels in atrial myocytes (19). Additionally, I_{Kr} only has a limited role in the atrium. A recent study also demonstrated that ranolazine inhibits TASK-1 potassium channels, which are selectively expressed on the surface of atrial myocytes, although the clinical significance of this inhibition remains limited (20).

4.1.1. Late Sodium Current

Ranolazine functions as an inhibitor of the slowly inactivating domain of the cardiac sodium current, referred to as late I_{Na}. Late I_{Na} is found predominantly on the surface of M cells and in Purkinje fibers (21). Under physiologic conditions, the amplitude of the late I_{Na} represents less than 1% of the peak I_{Na} current. However, under various pathological conditions, such as myocardial ischemia or heart failure, there is a significant increase in the number of late I_{Na} channels on the surface of ventricular myocytes. The consequently intensified late I_{Na} current prompts an enhanced sodium influx into the cytoplasm of these cells raising the intracellular concentration of sodium. In response, reverse-mode sodium-calcium exchange is activated that prompts a rise in the cytosolic calcium concentration. In ventricular myocytes this can impair mechanical relaxation and induce electrical instability by prolonging the cardiac action potential. In addition, it provokes further spontaneous calcium release from the sarcoplasmic reticulum. These events can lead to two different, yet closely related activities in the myocardium: 1) transmural dispersion of repolarization (TDR) as indicated by the time between the peak and the end of T wave, and 2) early afterdepolarization (EAD) or T-wave alternans (22). All of these can potentially induce ventricular arrhythmias, including torsades de pointes (21). Ranolazine selectively inhibits the late I_{Na} current in ventricular myocytes thereby limiting sodium overload and cytosolic calcium accumulation. This leads to a decrease in diastolic wall stress and improved coronary flow, thereby contributing to enhanced cardiac function (23).

4.1.2. Peak Sodium Current

Ranolazine exploits the differences in peak sodium current between the atrial and ventricular cells. Burashnikov and others demonstrated that ranolazine exerts an atrium-selective, use-dependent inhibition of the maximum action potential slope and prolongs the effective refractory period in isolated canine coronary-perfused atria and ventricles. These results indicated that ranolazine has the potential to treat AF without unwanted, proarrhythmic effects at the ventricular level (24,25).

4.2. Clinical Benefits of Ranolazine

4.2.1. Ventricular Tachycardia

Two large randomized controlled trials have demonstrated the efficacy of ranolazine in reducing the number of VT episodes. Given that the majority of patients in both of these studies had underlying myocardial ischemia (51.0% of the ranolazine group in MERLIN-TIMI 36 had NSTEMI while 47.1% had unstable angina, and 58% in the RAID trial had ischemic cardiomyopathy), the anti-ischemic effects of ranolazine may have contributed to the reduction in the observed arrhythmia burden. Contrasting these, Benjamin documented a comparable reduction in the incidence of VT with ranolazine in patients with and without myocardial ischemia in the MERLIN-TIMI 36 trial (6). Similarly, Younis found in RAID that the reduction of VT events did not differ significantly between patients with ischemic and non-ischemic cardiomyopathy (8). These findings indicate that ranolazine has direct antiarrhythmic properties.

Our thorough data review suggests that, when used specifically for the management or prevention of VT, certain populations may experience greater benefit from ranolazine therapy. For example, Younis demonstrated that it was more effective in reducing VT in patients not receiving any other antiarrhythmic agents, individuals without baseline AF, and among those with a CRT-D

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device in situ. These observations are of great importance as, in the RAID trial, 17% of all participants were on an antiarrhythmic agent with 10% taking amiodarone. Several explanations may be plausible for these findings. Ranolazine may elicit an antiarrhythmic effect similar to other agents and its additional benefit may no further be detectable. Another explanation may be related to its largely rate-independent effect on the ventricle. That is, the antiarrhythmic properties of ranolazine are not enhanced by increased ventricular rates. These suggest that a strong synergistic effect is highly unlikely to exist between ranolazine and other antiarrhythmic drugs to reduce the incidence of VT. Interestingly, this is in stark contrast with the results documented in AF where the combined use of ranolazine and amiodarone demonstrated a strong synergistic effect. Another important observation is that ranolazine appears to have a stronger benefit in patients at low to moderate risk of VT, with its efficacy more limited in higher-risk groups (e.g., older individuals, patients with underlying AF, and those already taking antiarrhythmics). Finally, ranolazine was significantly more effective in patients with an implanted CRT-D device compared to those with an ICD. This may be attributed to ranolazine's mechanism of action, which involves the inhibition of late I_{Na} in the ventricle making it especially effective in conditions with greater dispersion in transmyocardial repolarization, such as ischemia and heart failure. Likewise, left bundle branch block (LBBB), a common indication for CRT-D, leads to greater dispersion in repolarization. This indicates a potential synergistic effect when combining ranolazine with CRT-D therapy (8,26). Importantly, based on a limited number of animal experiments, ranolazine does not appear to alter the defibrillation threshold and therefore it does not reduce the safety margin for successful defibrillation (27). As it is a frequently used anti-ischemic agent, and ischemic cardiomyopathy is a common indication for primary or secondary prevention ICD implantation, the clinical relevance of this finding might be highly significant.

4.2.2. Atrial Fibrillation

Despite a positive trend noted in the MERLIN-TIMI 36 and RAFFAELLO trials, prolonged treatment with ranolazine was not effective in reducing the incidence of new onset and recurrent AF (6,14). The limited number of studies in this field and their heterogeneity underscore the need for further research in this area.

Several studies have demonstrated that ranolazine, when combined with amiodarone, promoted a more rapid AF termination and conversion to sinus rhythm. This finding aligns with the experimental data demonstrating a favorable synergistic effect between the two agents that is achieved without any undesirable proarrhythmic effect (23,26). While discussing the clinical significance of the time reduction until AF termination is beyond the scope of this narrative review, such a decrease may potentially lower hospital costs by shortening inpatient stays. This might ultimately benefit the patients, their caregivers as well as the society.

4.3. Safety Profile of Ranolazine

The risk of new-onset or worsening arrhythmias (proarrhythmic effect) and/or toxicity with prolonged exposure limit the use of many antiarrhythmic drugs currently available on the market. However, substantial clinical evidence supports the safety of chronic ranolazine treatment. It does not cause clinically significant bradycardia or hypotension (28,29). The most common adverse effects associated with ranolazine use include nausea, constipation, dizziness, fatigue and, less frequently, syncope (7,12,14,17,28,29). Many clinical trials have established that ranolazine does not provoke torsades de pointes or sudden cardiac death, despite its modest QT prolonging effect (10,30). This is frequently attributed to the fact that ranolazine does not induce EAD or increase TDR.

5. Limitations

This narrative review has certain limitations. First, there is a considerable heterogeneity among studies analyzed. Variations in study design, patient populations, interventions, and outcomes across these may limit the ability to directly compare their results. Second, the small number of studies available on each topic limits our possibility to draw a robust conclusion. Third, this review was

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limited to VT and AF and did not include other arrhythmias, specifically those based on congenital long QT syndrome and supraventricular tachycardias other than AF.

6. Conclusions

Based on available clinical trial data, ranolazine appears to be an effective and safe agent to reduce the incidence of VT. However, information regarding its effects on survival is lacking. It may accelerate the conversion of AF into sinus rhythm when used in combination with amiodarone, thus decreasing the time spent in AF and promoting hemodynamic stabilization especially in cases when left ventricular ejection fraction is severely reduced. The antiarrhythmic properties of ranolazine can provide significant additional clinical benefits to its established antiischemic and antianginal effects.

There is a growing number of studies on the use of ranolazine in cardiovascular diseases beyond angina pectoris, including arrhythmias and heart failure. Its mechanism of action is complex and not yet fully understood. Since ranolazine was introduced to the U.S. market in 2006, its long-term safety and efficacy are not yet well-established, which may hinder its use as a first-line agent. Gathering further clinical evidence, by clinical trials and observational studies, is essential to solidify the information on the beneficial cardiovascular effects of ranolazine.

Although the term 'proarrhythmic' is commonly used in the context of antiarrhythmic therapy, whether the full scale of its impact is understood remains unclear. Further biomolecular studies are essential to understand the underlying mechanisms which may, in turn, assist in choosing the most appropriate antiarrhythmic strategy for individual patients.

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