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REVIEW

Ranolazine

A true pluripotent cardiovascular drug or jack of all trades, master of none?

Alice Mezincescu,[1] V. J. Karthikeyan,[2] *Sunil K. Nadar[3]

رنولازين

هل هو دواء حقيقي محفز القلب والأوعية الدموية أو جاك له جميع الصفات، ولكنه سيد لا شيء؟

أليس ميزينسكو، كارتيكيان، سونيل نادر

ABSTRACT: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide. Although the majority of patients with CVD are treated with interventional procedures, a substantial number require medical therapy in terms of both prognosis and symptomatic relief. However, commonly used agents such as β-blockers and calcium channel blockers reduce blood pressure in patients whose resting pressures are often already low. Ranolazine is a promising agent that does not have significant effects on blood pressure or heart rate. Use of this drug has been documented in various cardiovascular conditions, including ischaemic heart disease, heart failure and arrhythmias. This review article aimed to examine current evidence on the use of ranolazine in various cardiovascular conditions in order to determine whether it is a true pluripotent cardiovascular agent or, on the other hand, a "jack of all trades, master of none."

Keywords: Drug Therapy; Cardiovascular Agents; Ranolazine; Cardiovascular Diseases; Ischemic Heart Disease.

الملخص: تعتبر أمراض القلب والأوعية الدموية السبب الرئيسي للمراضه والوفيات في جميع أنحاء العالم. وعلى الرغم من أن غالبية المرضى الذين يعانون من الأمراض القلبية الوعائية يتم التعامل معهم بإجراءات تدخلية، إلا أن عددًا كبيرًا منهم يحتاجون إلى علاج طبي للأعراض وأيضا للتنبؤ بمسار المرض. ومع ذلك، فإن العوامل المستخدمة بشكل شائع مثل حاصرات مستقبلات بيتا وحاصرات قنوات الكالسيوم تقلل من ضغط الدم لدى المرضى الذين تكون عندهم ضغوط الراحة منخفضة بالفعل. رانولازين هو دواء جديد واعد و ليس له أثار كبيرة على ضغط الدم أو معدل ضربات القلب. وقد تم توثيق استخدام هذا الدواء في مختلف الحالات القلبية الوعائية، بما في ذلك مرض نقص تروية القلب، وفشل القلب وعدم انتظام ضربات القلب. هدفت هذه المقالة المرجعية إلى فحص الأدلة الحالية على استخدام دواء الرانولازين في مختلف الحالات القلبية الوعائية من أجل تحديد ما إذا كان هذا الدواء متعدد القدرات فعلا أم، من ناحية أخرى، انه "جاك له جميع الصفات، ولكنه سيد لا شيء."

الكلمات المفتاحية: العلاج بالعقاقير؛ رانولازين؛ عقاقير القلب والأوعية الدموية؛ أمراض القلب والأوعية الدموية؛ مرض القلب الإقفاري.

Cardiovascular disease (CVD) is a leading cause of mortality worldwide; moreover, according to the British Heart Foundation, CVD-related morbidity continues to represent a main cause of hospital admission.[1] Chest pain and stable *angina* are common manifestations of ischaemic heart disease (IHD), while breathlessness is the main presentation of heart failure.[2] Other cardiovascular conditions that result in hospital admission and outpatient visits include arrhythmias, such as atrial fibrillation (AF) or supraventricular tachycardia. Certain cardiovascular agents—such as β-blockers, calcium (Ca) channel blockers and angiotensin-converting enzyme inhibitors—can be used for both patients with IHD and those with heart failure; however, most of these agents lower blood pressure and heart rate among patients who often have low blood pressure to begin with, thus limiting their use.[2] Recently, ranolazine has been increasingly prescribed in IHD cases, in part due to the fact that it does not affect blood pressure. Mihos *et al.* recently summarised ongoing clinical trials of ranolazine for various indications worldwide.[3] This review article aimed to examine the current role of ranolazine in IHD cases and its potential role in other cardiovascular conditions such as heart failure and AF.

Administration and Pharmacokinetics

The chemical name of ranolazine is N-(2,6-dimethylphenyl)-2-(4-(2-hydroxy-3-(2-methoxyphenoxy) propyl)piperazin-1-yl) acetamide.[4] Its molecular formula is $C_{24}H_{33}N_3O_4$. Ranolazine was initially approved by the USA Food and Drug Administration in 2006 and by the European Medicine Agency in 2008; it is currently available in the form of oral prolonged-release tablets at doses of 375, 500 and 750 mg, with twice daily administration recommended.[3] Ranolazine is an

[1]*Cardiovascular & Diabetes Research Unit, University of Aberdeen, Aberdeen, UK;* [2]*Royal Albert Edward Infirmary, Wrightington Wigan & Leigh NHS Foundation Trust, Wigan, UK;* [3]*Department of Medicine, Sultan Qaboos University Hospital, Muscat, Oman*
**Corresponding Author's e-mail: sunilnadar@gmail.com*

acetanilide and piperazine derivative with a molecular weight of 427.545 g/mol.[3] The drug has poor water solubility; after the oral administration of prolonged-release tablets, peak plasma concentration occurs within 2–6 hours but it can take up to three days to reach a steady state.[5]

In the human body, approximately 62% of ranolazine is bound to plasma proteins; as such, haemodialysis is not effective in clearing the drug in cases of an overdose.[4] Ranolazine is eliminated primarily by the metabolism, with less than 5% of the dose excreted unchanged in the urine and faeces. More than 40 and 100 metabolites have been identified in the plasma and urine, respectively, following administration.[3] Ranolazine is metabolised in the hepatocytes and the intestinal tract, primarily via cytochrome P450 3A (CYP3A) but also by CYP2D6.[6] Clearance is dose-dependent, decreasing with an increase in dose. The half-life of slow-release preparations is 7–9 hours and excretion is 75% renal and 25% intestinal.[6] When prescribing ranolazine to patients with mild-to-moderate renal impairment, it is important to remember that the peak serum concentration is increased by 40–50%; therefore, the dose should be adjusted accordingly.[5,6]

Mechanism of Action

It was initially thought that ranolazine exhibits its anti-anginal effects by selectively inhibiting fatty acid oxidation and improving the efficiency of glucose oxidation.[7,8] However, more recent data have invalidated these theories and demonstrated that the anti-anginal effect is mainly due to inhibition of the late inward sodium (Na) ion current (I_{Na}).[9,10] In the presence of *ischaemia*, a decrease in mitochondrial adenosine triphosphate production in the myocyte leads to reduced excitation-contraction coupling and impaired ion homeostasis. As a result, there is increased accumulation of intracellular Na^+ due to disruption in the opening of the I_{Na} channel, Na^+ influx through the Na/hydrogen pump and the lack of Na^+ elimination through the Na/potassium pump.[9,10] The increase in intracellular Na^+ disrupts the Na-Ca exchanger, leading to an intracellular Ca^{2+} overload causing impaired relaxation of the myocytes, diastolic dysfunction and impaired coronary blood flow in the *diastole*, thereby worsening the *ischaemia* and creating a dangerous feedback loop. Ranolazine selectively inhibits the late I_{Na}, reducing Na^+ overload and the subsequent intracytosolic Ca^{2+} accumulation and leading to a reduction in diastolic wall stress and improved coronary blood flow.[11,12] In animal studies, ranolazine also exhibited weak β1 and β2 and Ca channel antagonist activity.[13,14] However, in clinical trials, ranolazine doses had no clinically significant effect on resting heart rate or arterial blood pressure.[15]

Recommendations and Guidelines

In the European Society of Cardiology (ESC) guidelines on the management of stable *angina*, ranolazine is given a class IIa (level of evidence B) recommendation as a second-line agent for the relief of *angina* and *ischaemia*.[2] Its use is also suggested for patients with low blood pressure and those with microvascular *angina*. The National Institute for Health and Care Excellence guidelines from the UK also recommend the use of ranolazine either as monotherapy or in combination with other agents in stable *angina* cases where β-blockers and Ca channel blockers are either contraindicated or cannot be tolerated.[16] The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of stable *angina* give ranolazine a class IIa recommendation either as a substitute for β-blockers when β-blockers are either not tolerated or contraindicated (level of evidence B), or in combination with β-blockers where the initial use of β-blockers alone has not proven effective (level of evidence A).[17]

Ranolazine is not included in the ESC or ACC/AHA guidelines for the management of non-ST-segment elevation myocardial infarctions (NSTEMIs).[18,19] However, the ACC/AHA guidelines for the management of NSTEMIs mention that ranolazine is indicated in chronic stable *angina* (CSA) and that it can be used to control *ischaemia* and symptoms in the post-acute phase. Neither the ACC/AHA nor the ESC mention ranolazine in their guidelines for the management of heart failure.[20–22]

Although they provide a summary of the existing clinical data regarding ranolazine, the ESC guidelines for AF management state that there is currently insufficient evidence to recommend the drug either on its own or in combination with an anti-arrhythmic agent.[23] Similarly, while the ESC guidelines for managing ventricular arrhythmias do mention that ranolazine has been used in combination with other anti-arrhythmic agents to suppress drug-resistant ventricular arrhythmias, they also note that it is currently not approved for this indication.[24] The ACC/AHA guidelines on AF and supraventricular tachycardias do not mention ranolazine at all.[25,26]

Treatment Efficacy

ISCHAEMIC HEART DISEASE

While IHD is often treated with interventional techniques such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), such interventions are unsuitable for patients with certain types of coronary anatomy or those who remain symptomatic due to microvascular disease despite adequate revascularisation.[2] Drugs such as nitrates, β-blockers and Ca channel blockers are the mainstay of medical therapy in these patients. However, an important and unfortunate side-effect of most of these agents is hypotension, often leading to the discontinuation of treatment.[2] Therefore, an anti-anginal agent is needed that is effective, well-tolerated and does not affect blood pressure.

Multiple randomised placebo-controlled trials have shown that ranolazine is a cost-effective treatment for patients with CSA.[27] It decreases the frequency of the *angina* episodes and improves functional capacity whilst having no clinically significant effects on resting heart rate or arterial blood pressure. In the Combination Assessment of Ranolazine in Stable Angina (CARISA) study, a randomised three-group parallel double-blind placebo-controlled trial was performed in which 823 patients with symptomatic chronic *angina* received either 750 or 1,000 mg of slow-release ranolazine twice daily or a placebo in addition to standard anti-anginal therapy (atenolol, amlodipine and diltiazem) for a period of three months.[28] The effects of the therapy were assessed by treadmill testing at two and six weeks at trough levels and two and 12 weeks at peak levels. The study demonstrated that ranolazine significantly increased the patient's exercise capacity (mean treadmill time increase: 24–34 seconds; P <0.05) and reduced *angina* attacks and nitroglycerin use by approximately one per week (P <0.02) in comparison to a placebo.[28] In the CARISA trial and its associated long-term open-label study, the survival rate of patients taking ranolazine was 98.4% at one year and 95.9% at two years.[28,29]

Using a randomised double-blind four-period crossover study design, the Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) study assessed the relationship between ranolazine dose and anti-anginal effects among patients with stable *angina*.[30] After discontinuing their usual *angina* medications, 191 patients with treadmill-inducible stable *angina* of more than three months' duration received either 500, 1,000 or 1,500 mg sustained-release doses of ranolazine or placebo monotherapy twice daily for one week. Exercise testing according to a modified Bruce protocol was performed at baseline, at the end of each period, at trough levels (12 hours post-dose) and at peak levels (four hours post-dose).[30] Plasma levels of ranolazine were assessed to determine the dose-response relationship. The study demonstrated a significant increase in exercise duration in a dose-dependent fashion among patients treated with ranolazine versus those receiving a placebo (P <0.005).[30] Both the MARISA trial and its open-label follow-up study showed a survival rate of 96.3 ± 1.7% at one year.[30,31] Within the cohort, 24% were diabetic; an analysis of the efficacy of ranolazine therapy between diabetic and non-diabetic patients showed that a history of diabetes did not have a statistically relevant impact on the anti-anginal effect of ranolazine (P = 0.77).[30] Moreover, the frequency of adverse reactions and side-effects was comparable in both subgroups. *Asthaenia*, constipation, dizziness and nausea were the most common side-effects reported in both subgroups.[30]

The Efficacy of Ranolazine in Chronic Angina (ERICA) study was a multinational double-blind randomised trial comparing the effects of ranolazine to a placebo among 565 patients with CSA who had more than three *angina* attacks per week despite receiving a maximal dose of amlodipine (10 mg/day).[32] A total of 281 patients were randomly assigned to the ranolazine group, while the remaining 284 subjects formed the placebo group. The patients received either 1,000 mg of ranolazine twice per day or a placebo for a period of six weeks.[32] The primary endpoint was the weekly frequency of *angina* attacks, with responses to the Seattle Angina Questionnaire (SAQ) and nitroglycerin consumption levels also used to assess the efficiency of the treatment.[33] The ERICA trial demonstrated that ranolazine was well-tolerated and significantly reduced the frequency of *angina* attacks compared to a placebo (mean: 2.88 ± 0.19 attacks versus 3.31 ± 0.22 attacks; P = 0.028).[32] Patients who had more frequent weekly *angina* attacks at baseline seemed to benefit from more pronounced treatment effects. Nitroglycerin use was also reduced in the ranolazine group versus the placebo group (mean: 2.03 ± 0.20 doses versus 2.68 ± 0.22 doses; P = 0.014).[24] However, it is worth noting that patients with a corrected QT interval of >500 ms at baseline and those with class III or IV heart failure, recent unstable *angina*, acute coronary syndrome (ACS) or revascularisation within two months of the study period were excluded from both the ERICA and MARISA trials.[30,32]

Known as the Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina (TERISA) study, an international double-blind randomised trial was conducted to evaluate the efficacy of ranolazine versus a placebo among 949 patients with

Table 1: Clinical trials investigating the anti-anginal and anti-ischaemic effects of ranolazine[28,30,32,34,35,37–39]

Clinical trial	N	Study design and type	Ranolazine dosage	Endpoints	Conclusions
CARISA[28]	823 patients with chronic *angina*	Randomised, DB, PC trial	Either 750 or 1,000 mg BID	• Exercise duration according to an ETT • Time before *angina* symptoms • Time to ECG changes (ST-segment depression of 1 mm)	• Increased exercise duration and time before *angina* symptoms • Reduction in *angina* frequency and NTG use per week • No difference in mortality
MARISA[30]	191 patients with stable *angina*	DB, PC crossover study	Either 500, 1,000 or 1,500 mg BID	• Exercise duration according to ETT • Time before *angina* symptoms • Time to ECG changes (ST-segment depression of 1 mm)	• Increased exercise duration and time before *angina* symptoms • Reduction in *angina* frequency
ERICA[32]	565 patients with coronary disease	Randomised, DB, PC, multinational trial	1,000 mg as well as 10 mg of amlodipine BID	• *Angina* frequency per week • QOL	• Reduction in *angina* frequency and NTG use per week • Improved QOL
TERISA[34]	949 type 2 diabetics with coronary artery disease and stable *angina*	Randomised, DB, PC, international trial	1,000 mg BID	• Average number of *angina* episodes per week • Average NTG use per week • Number of *angina* episode-free days (i.e. ≥50% reduction in *angina* frequency) • QOL	• Reduction in *angina* frequency and NTG use per week • More patients achieved a ≥50% reduction in weekly *angina* frequency • No change in QOL
MERLIN-TIMI 36[35,37,38]	6,560 patients with NSTEMIs	Randomised, DB, PC, multinational trial	200 mg IV infusion over one hour, followed by 80 mg IV infusion over 12–96 hours and 1,000 mg extended-release oral tablets BID*	• Composite of CV death, MI or recurrent *ischaemia* • Recurrent *ischaemia* • Documented symptomatic arrhythmia • All-cause mortality	• No change in composite CV death, MI or recurrent *ischaemia* • Reduction in recurrent *ischaemia* and symptomatic documented arrhythmias • No change in all-cause mortality
RIVER-PCI[39]	2,651 patients with incomplete revascularisation after PCI	Randomised, DB, PC, international trial	1,000 mg BID	• Time to first occurrence of *ischaemia*-driven revascularisation or *ischaemia*-driven hospitalisation without revascularisation	• No difference in primary endpoint

CARISA = Combination Assessment of Ranolazine in Stable Angina; DB = double-blind; PC = placebo-controlled; BID = twice daily; ETT = exercise tolerance test; ECG = electrocardiography; NTG = nitroglycerin; MARISA = Monotherapy Assessment of Ranolazine in Stable Angina; ERICA = Efficacy of Ranolazine in Chronic Angina; QOL = quality of life; TERISA = Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina; MERLIN-TIMI 36 = Metabolic Efficiency with Ranolazine for Less Ischaemia in Non-ST Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36; NSTEMI = non-ST-segment elevation myocardial infarction; IV = intravenous; CV = cardiovascular; MI = myocardial infarction; RIVER-PCI = Ranolazine in Patients with Incomplete Revascularisation after PCI; PCI = percutaneous coronary intervention.

**Plus standard non-ST-elevation acute coronary syndrome therapy.*

type 2 diabetes, coronary artery disease and stable *angina* already receiving one or two other anti-anginal agents.[34] Initially, all patients were single-blinded and received a placebo during a four-week period. Subsequently, the cohort was randomised and received either ranolazine (1,000 mg twice daily) or a placebo in a double-blind fashion for eight weeks.[34] The primary outcome of the study was the average number of *angina* attacks per week during the final six weeks of the study period, with the frequency of *angina* attacks and the use of nitroglycerin documented daily. The study demonstrated that ranolazine significantly reduced the frequency of *angina* attacks versus a placebo (3.8 versus 4.3 attacks/week; $P = 0.008$) and also reduced nitroglycerin use (1.7 versus 2.1 doses/week; $P = 0.003$).[34] The incidence of serious adverse events was similar in both groups. In the TERISA trial, the benefits of ranolazine appeared more prominent in patients with high glycated haemoglobin levels.[34]

The Metabolic Efficiency with Ranolazine for Less Ischaemia in Non-ST Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial was a multinational randomised double-blind placebo-controlled parallel group study

Table 2: *In vitro* and *in vivo* studies investigating the effects of ranolazine on atrial arrhythmia models[51–54]

Author and year of study	Study type	Study objective	Conclusions
Kumar *et al.*[51] (2008)	Porcine *in vivo* model	Investigation of surface ECG and electrophysiological parameters in normal closed-chest anaesthetised pigs following ranolazine administration	• Ranolazine produced a mild increase in QT intervals and a marked increase in VF thresholds • Ranolazine does not augment and may improve ventricular repolarisation dispersion • Ranolazine potentially triggers an anti-arrhythmic action
Burashnikov *et al.*[52] (2010)	Canine *in vitro* model	Investigation of the electrophysiological effects of ranolazine and dronedarone in canine-isolated coronary-perfused atrial and ventricular preparations and pulmonary vein preparations	• Low concentrations of ranolazine or dronedarone alone resulted in weak AF suppression • Combined ranolazine and dronedarone resulted in a potent synergistic effect causing atrial-selective depression of I_{Na}-dependent parameters and effective suppression of AF
Burashnikov *et al.*[53] (2007)	Canine *in vitro* model	Investigation of the electrophysiological effects of ranolazine in canine-isolated coronary-perfused atrial and ventricular preparations	• Ranolazine blocked I_{Na}-dependent parameters in the atrial, but not the ventricular preparations, suppressing and preventing the induction of AF
Sossalla *et al.*[54] (2010)	Human *in vitro* model	Investigation of the electrophysiological effects of ranolazine on isolated human right atrial appendages from patients with either AF or normal sinus rhythm	• The inhibition of I_{Na} with ranolazine had anti-arrhythmic effects and resulted in improved diastolic function

ECG = electrocardiography; VF = ventricular fibrillation; AF = atrial fibrillation; I_{Na} = sodium ion current.

analysing the efficacy of ranolazine in the treatment of high-risk ACS.[35] In total, 6,560 patients with NSTEMIs received either ranolazine (initially intravenous and then an oral preparation) or a placebo; the baseline characteristics of the two groups were well-matched. The study had a primary composite endpoint of cardiovascular death, myocardial infarction (MI) or recurrent *ischaemia* at 30 days.[35] The secondary endpoint was the first occurrence of a major cardiovascular event, in which the MI had to be distinct from the index event. In addition, the patient's quality of life was assessed four months after treatment using the SAQ.[33,36] Patients were followed up at four and eight months and *ischaemia* was assessed via an exercise tolerance test.[35] In the ranolazine group, 21.8% and 23.5% of the ranolazine and placebo groups, respectively, experienced cardiovascular death, MI or recurrent *ischaemia* (P = 0.11). The secondary endpoint occurred in 18.7% of the ranolazine group versus 19.2% of the placebo group (P = 0.5).[35]

Accordingly, the MERLIN-TIMI 36 study demonstrated that ranolazine was not an effective add-on therapy for patients presenting with ACS. However, approximately one half of the MERLIN-TIMI 36 cohort had *angina*; a subgroup analysis demonstrated that patients treated with ranolazine could exercise for 32 seconds longer than the placebo group (P = 0.002).[37] The SAQ responses demonstrated a significant decrease in the frequency of *angina* attacks in the ranolazine group versus the placebo group (P <0.001).[33,36] Overall, ranolazine had a favourable safety profile.[35–38]

Recently, the Ranolazine in Patients with Incomplete Revascularisation after Percutaneous Coronary Intervention (RIVER-PCI) study evaluated the use of ranolazine in 2,651 patients with incomplete revascularisation following a PCI procedure.[39] The RIVER-PCI study had a composite endpoint of *ischaemia*-driven revascularisation or hospitalisation without revascularisation. In comparison to a placebo, ranolazine showed no benefit.[39] Table 1 provides details of the clinical trials investigating the anti-anginal and anti-ischaemic effects of ranolazine.[28,30,32,34,35,37–39]

HEART FAILURE

In experimental models of heart failure, ranolazine significantly improved left ventricular (LV) performance by the late inhibition of the I_{Na}.[40,41] Ranolazine has also been shown to significantly reduce LV end diastolic pressure and increase LV ejection fraction in dogs in the absence of any haemodynamic effects.[42] In a normal dog model, there was no effect on LV function.[43] In human subjects with decreased LV function, infusions of ranolazine did not improve LV function but appeared to improve regional diastolic function.[44] In an open-label trial during which ranolazine was given to patients with either diastolic or systolic heart failure on top of guideline-driven therapy, there appeared to be an improvement in LV systolic function and autonomic measures; however, clinical parameters were not investigated.[45]

A prospective single-centre randomised double-blind placebo-controlled proof-of-concept study termed the Ranolazine for the Treatment of Diastolic Heart Failure (RALI-DHF) study was conducted to determine if ranolazine would be more effective in improving diastolic function among patients with heart failure

Table 3: Clinical trials, studies and case series investigating the efficacy of ranolazine in atrial fibrillation[35,37,38,55–63]

Clinical trial/ author and year of study	N	Study design and type	Ranolazine dosage	Findings	Conclusions
MERLIN-TIMI 36[35,37,38,55]	6,560 patients with NSTEMIs	Randomised, DB, PC, multinational trial	200 mg IV infusion over one hour, followed by 80 mg IV infusion over 12–96 hours and 1,000 mg extended-release oral tablets BID*	• Decreased new-onset AF (1.7% versus 2.4%; *P* = 0.08) • Lower AF burden in patients with paroxysmal AF (4.4% versus 16.1%; *P* = 0.015)	• Ranolazine resulted in a trend in decreased new-onset AF, although the study focused on NSTEMI *ischaemia*
HARMONY[56]	134 patients with paroxysmal AF and permanent pacemakers	Randomised, PC, DB, parallel trial	750 mg in combination with either 150 or 225 mg of dronedarone BID	• Reduced AF burden in combination with 225 mg of dronedarone compared to patients receiving a placebo (*P* = 0.008) • However, AF burden was not reduced in combination with 250 mg of dronedarone compared to patients receiving a placebo (*P* = 0.072)	• Ranolazine has a synergistic effect with dronedarone and this combination can be used to reduce the AF burden in patients with paroxysmal AF
Koskinas *et al.*[57] (2014)	121 patients with recent-onset AF undergoing EC	Prospective, SB, randomised study	1,500 mg in combination with IV amiodarone or IV amiodarone alone prior to EC	• Conversion within 24 hours (87% versus 70%; *P* = 0.024) and 12 hours (52% versus 32%; *P* = 0.021) was achieved more frequently compared to patients receiving amiodarone alone • Time to conversion was significantly shorter (10.2 ± 3.3 hours versus 13.3 ± 4.1 hours; *P* = 0.001)	• The addition of ranolazine to amiodarone significantly improved the success rate of EC
Miles *et al.*[58] (2011)	393 CABG patients	Retrospective cohort study	1.5 g preoperatively and then 1 g BID for 10–14 days	• Decreased AF occurrence compared to patients receiving amiodarone (17.5% versus 26.5%; *P* = 0.035)	• Ranolazine was more useful than amiodarone in preventing postoperative AF in patients undergoing CABG
RAFFAELLO[59]	241 patients with persistent AF	Prospective, multicentre, randomised, DB, PC parallel trial	375, 500 or 750 mg	• AF recurrence occurred in 56.9% of patients taking 375 mg, 41.7% of patients taking 500 mg and 39.7% taking 750 mg of ranolazine compared to 56.4% of patients receiving a placebo	• No specific dose of ranolazine significantly reduced the time to AF recurrence • However, higher doses of ranolazine reduced AF recurrence
Murdock *et al.*[60] (2009)	18 patients with paroxysmal AF	Off-label UC study	Single 2,000 mg dose using a 'pill in the pocket' approach	• Following treatment at the time of AF onset, 72% of patients reverted to normal sinus rhythm	• Ranolazine can be useful in converting paroxysmal AF to normal sinus rhythm
Murdock *et al.*[61] (2012)	25 EC-resistant patients	UC case series	2,000 mg prior to cardioversion	• Normal sinus rhythm was successfully maintained in 76% of patients	• Ranolazine can be useful in the pretreatment of patients undergoing EC
Fragakis *et al.*[62] (2012)	51 patients with AF undergoing EC	Prospective randomised pilot study	1,500 mg in combination with IV amiodarone or IV amiodarone alone prior to EC	• Conversion was achieved more frequently compared to patients receiving amiodarone alone (88% versus 65%; *P* = 0.056)	• The combination of ranolazine and amiodarone can improve the rate of cardioversion
Tagarakis *et al.*[63] (2013)	102 patients scheduled for CABG	Prospective, randomised, SB, single-centre trial	375 mg BID for three days prior to CABG until discharge	• Reduced postoperative AF incidence compared to patients receiving a placebo (8.8% versus 30.8%; *P* <0.001)	• Ranolazine is useful in preventing postoperative AF in patients undergoing CABG

MERLIN-TIMI 36 = Metabolic Efficiency with Ranolazine for Less Ischaemia in Non-ST Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36; NSTEMI = non-ST-segment elevation myocardial infarction; DB = double-blind; PC = placebo-controlled; IV = intravenous; BID = twice daily; AF = atrial fibrillation; HARMONY = Study to Evaluate the Effect of Ranolazine and Dronedarone when Given Alone and in Combination in Patients with Paroxysmal Atrial Fibrillation; EC = electrical cardioversion; SB = single-blind; CABG = coronary artery bypass grafting; RAFFAELLO = Ranolazine in Atrial Fibrillation Following an Electrical Cardioversion; UC = uncontrolled.

**Plus standard non-ST-elevation acute coronary syndrome therapy.*

with preserved ejection fraction compared to a placebo.[46] However, despite improving haemodynamic parameters, the RALI-DHF study found no improvement in relaxation parameters according to echocardiography findings.[46] Larger studies with long-term follow-up are required to see whether ranolazine results in clinical benefits for patients with diastolic heart failure.

ARRHYTHMIAS

Atrial Arrhythmias

The anti-atrial arrhythmic properties of ranolazine have been demonstrated in both animal and human experiments.[9,10] The threshold for potential atrial firing is lowered by enhanced I_{Na} in atrial myocytes, leading to increased excitability and atrial arrhythmias. Ranolazine inhibits various Ca^{2+} channels that block both peak and late I_{Na}, thereby affecting the automaticity and excitability of the myocardium.[47,48] It is beyond the scope of this review article to go into the details of the possible mechanism of action of ranolazine in arrhythmias; however, several excellent reviews on this topic are available in the literature.[49,50] Table 2 summarises several experimental studies investigating the effects of ranolazine on myocardial electrophysiology.[51–54]

Clinically, the results of ranolazine among patients with AF are limited. A subgroup analysis of the MERLIN-TIMI 36 study found that patients treated with ranolazine had fewer episodes of new-onset AF versus patients in the placebo group; however, these findings were not significant (1.7% versus 2.4%; $P = 0.08$).[38] Further analysis of the data showed that, among patients with paroxysmal AF, the overall burden was significantly lower with ranolazine than with a placebo (4.4% versus 16.1%; $P = 0.015$).[55] Similarly, over a one-year period, patients treated with ranolazine had fewer AF events compared to those receiving a placebo (2.9 versus 4.1 events; $P = 0.01$). However, this trial was designed to focus on clinical endpoints in NSTEMI management rather than AF; therefore, definitive conclusions on this topic cannot be drawn.[55] It could be that the lower rate of ischaemic events resulted in the lower AF burden.

The Study to Evaluate the Effect of Ranolazine and Dronedarone when Given Alone and in Combination in Patients with Paroxysmal Atrial Fibrillation (HARMONY) trial compared the efficacy of either ranolazine or dronedarone alone or combined in reducing the AF burden among 134 patients with paroxysmal AF and permanent pacemakers.[56] The HARMONY trial found that a combination of both drugs significantly reduced the AF burden as compared to a placebo ($P = 0.008$), whilst either agent on its own was unsuccessful ($P \geq 0.49$). Ranolazine has also been shown to result in a higher conversion rate of AF to normal sinus rhythm when used in combination with amiodarone in comparison to amiodarone alone.[57]

Ranolazine has also been shown to reduce the incidence of postoperative AF in patients undergoing CABG as compared to those receiving a placebo or amiodarone.[58] The Ranolazine in Atrial Fibrillation Following an Electrical Cardioversion (RAFFAELLO) trial demonstrated a decreased recurrence rate in 241 successfully cardioverted patients with persistent AF at high doses of ranolazine.[59] However, there was no significant reduction in the time to recurrence in the RAFFAELLO trial. The 'pill in the pocket' approach—involving the administration of a single dose of oral ranolazine at the time of onset of the AF—has been attempted in a small number of patients, with a success rate of approximately 72%.[60] Various clinical trials, studies and case series involving ranolazine as a treatment for AF are detailed in Table 3.[35,37,38,55–63]

Ventricular Arrhythmias

Some experimental evidence exists to suggest the benefit of ranolazine in treating ventricular arrhythmias.[47,51,64] However, in the clinical setting, data are limited. In patients with ventricular arrhythmias, ranolazine has been shown to significantly shorten QTc intervals and reduce the burden of ventricular tachycardia (VT) and the number of shocks required for patients with implantable cardioverter defibrillators.[65,66] It has also been shown to reduce the QTc in patients with congenital long-QT syndrome.[67] In the MERLIN-TIMI 36 trial, intravenous ranolazine also significantly reduced the frequency of VT lasting eight or more beats over a 24-hour period as compared to a placebo.[38]

In the Ranolazine Implantable Cardioverter-Defibrillator (RAID) trial, 1,012 patients with an implantable cardioverter defibrillator were randomised to receive either ranolazine or a placebo.[68] Although there was no difference in terms of the frequency of the composite endpoint of VT, ventricular fibrillation or death, patients receiving ranolazine experienced a significant reduction in VT events requiring anti-tachycardia pacing.[68] The various clinical trials and studies investigating the use of ranolazine in ventricular arrhythmias are summarised in Table 4.[38,65,66,68]

Side-Effects and Tolerability

Ranolazine is contraindicated in patients with severe renal impairment (creatinine clearance of <30 mL/minute).[4,5] Given the three-fold increased risk of QT prolongation, ranolazine is also contraindicated in patients with hepatic impairment.[4] Furthermore, patients taking strong CYP3A inhibitors (i.e. clarithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors, telithromycin or nefazodone) or CYP3A4 inducers (i.e. rifampicin, phenytoin, phenobarbital, carbamazepine or St. John's wort) should not be prescribed ranolazine.[69] If rano-

Table 4: Clinical trials and studies investigating the efficacy of ranolazine in ventricular arrhythmias[38,65,66,68]

Clinical trial/author and year of study	N	Study design and type	Ranolazine dosage	Findings	Conclusions
MERLIN-TIMI 36[38]	6,560 patients with NSTEMIs	Randomised, DB, PC, multinational trial	200 mg IV infusion over one hour, followed by 80 mg IV infusion over 12–96 hours and 1,000 mg extended-release oral tablets BID*	• Reduced incidence of VT lasting ≥8 beats compared to patients receiving a placebo (5.3% versus 8.3%; *P* <0.001)	• Ranolazine can reduce ventricular arrhythmias in the setting of NSTEMI
Moss *et al.*[65] (2008)	5 patients with congenital LQTS	Cohort study	45 mg/hour IV infusion for three hours followed by 90 mg/hour for five hours	• Digital 24-hour Holter recordings indicated that QTc was shortened in comparison to baseline parameters by 26 ± 3 minutes (*P* <0.0001)	• Ranolazine can shorten QTc duration in patients with congenital LQTS
Bunch *et al.*[66] (2011)	12 patients with drug-resistant VT and recurrent ICD shocks	Prospective cohort study	1,000 mg BID in combination with other anti-arrhythmic agents	• There was a reduction in ICD shocks and VT burden in comparison to baseline data in 92% of patients	• Ranolazine can reduce the VT burden in patients with drug-resistant VT
RAID[68]	1,012 patients with ICDs	Randomised, DB, PC trial	1,000 mg BID	• There was no difference in the combined frequency of VT, VF or death • However, there was a reduction in VT events requiring antitachycardia pacing	• Ranolazine can reduce VT events in patients with an ICD

MERLIN-TIMI 36 = Metabolic Efficiency with Ranolazine for Less Ischaemia in Non-ST Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36; NSTEMI = non-ST-segment elevation myocardial infarction; DB = double-blind; PC = placebo-controlled; IV = intravenous; BID = twice daily; VT = ventricular tachycardia; LQTS = long-QT syndrome; ICD = implantable cardioverter defibrillator; RAID = Ranolazine Implantable Cardioverter-Defibrillator; VF = ventricular fibrillation.

**Plus standard non-ST-elevation acute coronary syndrome therapy.*

lazine is concomitantly administrated with moderate CYP3A inhibitors (e.g. diltiazem, macrolide antibiotics or fluconazole) or P-glycoprotein inhibitors (e.g. verapamil or cyclosporin), the dose should be carefully titrated up to a maximum of 500 mg twice daily.[4] Grapefruit products also have a moderate CYP3A-inhibiting effect and should therefore be avoided.[4]

Data derived from a phase III clinical trial and the MARISA, ERICA and TERISA studies suggest that patients over 75 years old seem to have a higher incidence of ranolazine-related adverse events.[29,30,32,34] These trials also indicate that ranolazine-associated side-effects are more frequent at higher dosages. The main treatment-related adverse events observed were dizziness, headaches, nausea, vomiting, blurred vision, visual disturbance, diplopia, hypotension, fatigue, peripheral oedema and acute renal failure; however, such side-effects were rare.[29,30,32,34]

Cost-Effectiveness

Several studies have analysed the cost-effectiveness of ranolazine.[70–72] In a systematic review of the existing evidence, Vellopoulou *et al.* found that ranolazine, when added to a standard of care, appeared to be cost-effective primarily due to its ability to decrease *angina*-related hospitalisation and marginally improve quality of life.[73]

Conclusion

Ranolazine appears to be a fairly versatile cardiovascular agent with other potential indications beyond that of *angina* control, which was its original purpose. It is a well-tolerated drug and can be used in patients with low blood pressure for whom β-blockers and Ca channel blockers are not advised. Due to its mechanism of action, ranolazine may also have a promising role in the management of heart failure and arrhythmias, particularly AF. Its role in ventricular arrhythmias is also very promising, although the drug is not yet included in the international management guidelines for this condition.

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