INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

# RANOLAZINE: A NEW DRUG INDICATED FOR THE TREATMENT OF CHRONIC ANGINA

**Haritha Allu*, Prasad Reddy M, Kupili Sai Kiran, P.S.S. Durga Devi, K. R. Vinay Rajan, Penugonda Vineela.**

*Doctor of Pharmacy, GIET School of Pharmcy, NH-16,Chaitanya Knowledge City, GIET Campus, Rajahmundry, Andhra Pradesh, India.*

**ARTICLE INFO**

**Article history**
Received 21/11/2014
Available online
30/11/2014

**Keywords**
Ranolazine,
Mechanism Of Ranolazine,
Chronic Angina,
Clinical Trials Of Ranolazine.

**ABSTRACT**

Ranolazine is a new drug indicated for the treatment of chronic angina. Ranolazine has a novel mechanism of action of inhibiting the late sodium current during ventricular depolarization. A number of clinical trials have demonstrated the ability of ranolazine to increase exercise tolerance, decrease weekly anginal episodes, and effective in reducing angina symptoms. Ranolazine should be reserved for patients who have not achieved an adequate response with other antianginal drugs as ranolazine is identified to extend the QT interval. The therapeutic dose choice of 500 to 1000 mg twice daily is generally well tolerated, with constipation, nausea, asthenia, and dizziness being the most common adverse events reported. Ranolazine is extensively metabolized predominantly through the CYP3A4 pathway with a small amount excreted in the urine unchanged. Ranolazine is contraindicated in patients with hepatic impairment and have severe renal insufficiency should be more closely monitored for side effects. Ranolazine has been studied in wide range of clinical patient subgroups with chronic angina, is effective, and is usually well tolerated. There are few data in blacks, Hispanics, and Asians. The reduction in HbA1c levels in diabetic subjects that were observed in the CARISA trial requires prospective validation.

***Corresponding author***
**Haritha Allu**
D.No-45-29-16,
Sarada Nagar,
Gorakshanapeta, Thaditota,
Rajahmundry, Andhra Pradesh.
Phone number: +919493493808
harithaajay14@gmail.com

*Please cite this article in press as **Haritha Allu** et al. Ranolazine: A new drug indicated for the treatment of chronic Angina. Indo American Journal of Pharm Research.2014:4(11).*

## INTRODUCTION

Many patients stay symptomatic for angina pectoris caused by difference between myocardial perfusion and oxygen demand. Ranolazine, a selective inhibitor of the late sodium current, has been proven effective in treating chronic angina [1]. Ranolazine was accepted by the U.S. Food and Drug Administration (FDA) in 2006 for the management of stable angina pectoris [2, 3]. Ranolazine, a piperazine derivative, is a new antianginal medication with a novel mechanism of action that is prescribed to recommend freedom from most adverse hemodynamic effects [2, 4]. The anti-anginal effect of ranolazine is independent on changes in heart rate or blood pressure or raise in coronary blood flow. It acts via different pharmacological mechanisms where inhibition of the late inward sodium current (reducing calcium overload and thereby left ventricular diastolic tension) is one probable mechanism of decreased oxygen consumption [5]. Ranolazine is well tolerated; the principal side effects include dizziness, nausea, asthenia, constipation, and headache. Ranolazine is metabolized in the liver and excreted in the urine and is contraindicated with hepatic impairment. Initially it is metabolized by cytochrome (CYP3A), which is potently inhibited by diltiazem and verapamil, neither of which should be used concomitantly. Ranolazine inhibits metabolic pathways for simvastatin and digoxin, and dose tapering of these agents may be necessary [6].The standard terminal elimination half-life is approximately 7 hours after several dosing to steady state, and the peak/trough difference is 1.6-fold with dosing of 500 to 1000 mg twice daily. Steady state is usually attained within 3 days of twice-daily dosing. Ranolazine plasma concentrations 2 to 6 µmol/lit that is clinically useful for chronic angina [3]. The Food and Drug Administration have recommended that the efficacy of ranolazine may be lower in women than men on the basis of the Efficacy of Ranolazine in Chronic Angina and Combination Assessment of Ranolazine in Stable Angina trials. MERLIN-TIMI, recommends that ranolazine is an efficacious antianginal in women with ischemic heart disease [7]. In patients with stable Coronary Artery Disease and persisting angina ranolazine was an effective antianginal agent. The daily dosage should be restricted to 1,000 mg ranolazine twice a day considerably decreases the incidence of angina attacks and precautions are suggested regarding QTc prolongation. The FDA approval is restricted to patients who have not responded to other antianginal drugs, because ranolazine prolongs the QTc, and its use in combination with amlodipine, beta-blockers, or long-acting nitrates is optional [6]. The aim of this present review is to review the efficacy and safety profile of ranolazine and also aim to focus the benefits and risks of ranolazine as an antianginal, and antiarrythmatic.

## MECHANISM OF ACTION FOR RANOLAZINE:

The mechanism of action of ranolazine is yet uncertain [3, 8]. Inhibition of the persistent or late Na current (INa) using ranolazine represents a novel mechanism of action in patients with stable angina pectoris, inhibition of late INa is distinct at therapeutic plasma concentrations in healthy cells, predominantly in M cells and Purkinje fibers, where this current is most outstanding [3]. Ranolazine, a precise inhibitor of late INa, reduces Na influx and hence ameliorates disturbed Na and Ca homeostasis [8]. Ranolazine's preliminary mechanism of action was thought to be the inhibition of cardiac metabolism of fatty acids [2, 3]. At therapeutic doses ranolazine inhibits the cardiac late Na+-current (INa+) thus reducing Ca2+ overload, ameliorating cross-bridge kinetics of the cardiomyocytes, and reducing diastolic myofilament activation which is useful to treat diastolic dysfunction, but its impact as an antianginal mechanism is speculative, even if some believe that net result is reduced oxygen consumption and reduced wall tension thereby improving micro vascular blood flow. Ranolazine also inhibits the IKr-current and this effect explains its electrophysiological effects, but it is does not explain its anti-ischemic and antianginal effect. Ranolazine has the potential to partially disrupt the consequences of cell hypoxia during transient myocardial ischemia by reducing excess late Na+influx; there by reducing calcium overload and ultimately reducing the concomitant increase in left ventricular barrier tension. Decrease in diastolic left ventricular wall tension would decrease myocardial oxygen requirements in marginally ischemic myocytesand has the potential to reduce vascular density, allowing more coronary blood flow to the affected area. Further research is necessary to prove this concluding hypothesis [3, 8].

## PHARMACOKINETICS:

Ranolazine is a new compound under development as an antianginal agent [10]. Ranolazine pharmacokinetics are unaffected by sex, congestive heart failure and diabetes mellitus [5].

## ABSORPTION:

The complete bioavailability ranges from 30% to 55%. Food has no effect on rate or extent of absorption from the Extended Release(ER) formulation [3, 5].

## DISTRIBUTION:

Ranolazine protein binding is about 61–64% over the therapeutic concentration range. Volume of distribution at steady state ranges from 85 to180L. Following management of an oral solution or Immediate Release (IR) capsule, within 1 hour peak plasma concentrations (Cmax) are observed [5].

## METABOLISM:

Ranolazine is widely metabolized by cytochrome P450 (CYP) 3A4 mediated pathway accounts for the majority of ranolazine biotransformation, to a lesser extent, by CYP2D6 (10% to 15%) glucuronidation (<5%) [3, 5].

**EXCRETION:**

After administration of radio-labeled ranolazine, 73% of the dose was excreted in urine, and unchanged ranolazine accounted for <5% of radioactivity in both urine and faeces. Elimination half-life of ranolazine is 1.4–1.9 hours but is actually prolonged, on average, to 7 hours for the Extended Release formulation as a result of unlimited absorption. Elimination appears through parallel linear and saturable elimination pathways, where the saturable pathway is correlated to CYP2D6, which is moderately withdrawn by ranolazine [5].

**SPECIAL POPULATION:**

**HEPATIC FAILURE:**

Over the time interval studied, ranolazine was well tolerated in healthy subjects and hepatically impaired subjects [11]. Clearance of ranolazine is decreased by moderate hepatic impairment. In 8 subjects with mild hepatic impairment (Child-Pugh grade A), ranolazine pharmacokinetics were not much altered. There are no clear gender differences in ranolazine pharmacokinetics, nor are pharmacokinetics significantly changed by diabetes mellitus or heart failure (in the absence of renal insufficiency). Ranolazine clearance decreases moderately with age [3].

**RENAL IMPAIRMENT:**

Clearance of ranolazine is reduced by renal insufficiency [3].

**PREGNENCY:**

Category C. Ranolazine should be used during pregnancy only if the potential benefit to the mother overweighs the potential risk to the foetus, due to lack of human safety information [12].

**EFFICACY AND SAFTY:**

Many patients with chronic angina, experience anginal episodes despite revascularization and antianginal drugs [13]. Efficacy and safety of a new anti-anginal agent, ranolazine, assessed during a randomized, double-blind, placebo-controlled crossover study. In the qualifying phase, at least one antianginal drug withdrew from the drug schedule of 312 patients with chronic stable angina while they took placebo. After exercise time had shortened by ≥1.0 minute, so randomly assigned patients to receive either immediate-release ranolazine in 3 dosing regimens or placebo during each treatment period. After each week of treatment, measured exercise tolerance and ranolazine plasma concentrations at both peak and trough. All exercise parameters considerably ($p \leq 0.02$) better (intention-to-treat analysis) with ranolazine (all regimens combined) at mean peak plasma concentrations varying from 1,576 to 2,492 ng/ml differentiate with placebo without differences in double product. While related trends persisted at mean trough, plasma concentrations (range 275 to 602 ng/ml), only the time to 1.0 mm ST-segment depression remained statistically important. This clinical trail concluded that, immediate-release ranolazine is effective and well tolerated. However, short-acting immediate-release formulation with this dosing regimen is not sufficient for permanent protection. Either better or additional frequent doses or a sustained-release formulation would be needed for clinical use [14].

In advance clinical trials with immediate-release ranolazine led to the existing sustained-release version tested in the Monotherapy Assessment of Ranolazine In Stable Angina (MARISA) (n = 193) was a placebo-controlled, randomized trial that compared ranolazine monotherapy (500 mg, 1000 mg, and 1500 mg, twice daily) to placebo and Combination Assessment of Ranolazine In Stable Angina (CARISA) (n = 823) was a placebo-controlled trial that randomized patients on background 1β-blocker or calcium antagonist therapy to placebo or ranolazine (750 mg or 1000 mg, twice daily) trials of subjects with chronic angina and severe drawback of exercise capability (i.e., < 5 metabolic equivalents). Both studies result a considerable increase in total exercise period, time to angina onset, and time to 1 mm ST segment depression. The normal magnitude of increase in exercise time over placebo was 29 to 56 seconds at peak and 24 to 46 seconds at trough with the 3 doses experienced in MARISA, and 24 to 34 seconds more than placebo with the 2 doses used in CARISA. The useful effect was attained lack of clinically significant changes in rest or exercise heart rate or blood pressure. Weekly angina attack incidence and nitroglycerin usage were much reduced in a dose-dependent approach in the 12-week CARISA trial. Reported adverse effects were related in MARISA and CARISA and consisted of asthenia, nausea, constipation, and dizziness. Syncope, observed in 8 patients at doses of 1000 mg twice daily or more may be related to reduction of α-1 receptor activity. The mean QTc interval improved with dose and was less than 10 msec on ranolazine at 1000 mg twice daily. The fatality rates at 1 and 2 years in MARISA and CARISA open-label run-on studies were 2% and less than 5%, suitable for this high-risk population with inadequate exercise capacity [15].

**ADVERSE EVENETS:**

The majority of frequent dose-related adverse events reported were dizziness, nausea, asthenia, and constipation. At higher plasma concentrations (egg,>8000ng/ml), ranolazine may cause nausea, vomiting, dizziness, vertigo, abnormal vision, confusion, postural hypotension, and syncope. Mild transient eosinophilia has also been reported in a small number of angina patients [2, 3, and 13].

**DOSES:**

A 2000 mg of oral ranolazine, given as a single oral dose for paroxysmal or new onset atrial fibrillation was associated with an alteration rate to sinus rhythm [16]. Monotherapy, twice daily Ranolazine Extended Release(ER) 500–1500mg for 1 week significantly improved exercise duration at trough plasma concentrations. As add-on therapy, ranolazine ER 750 and 1000mg twice

daily for 12 weeks significantly improved exercise duration at trough plasma concentrations in patients on background antianginal therapy with β-adrenoceptor antagonists, calcium channel antagonists and nitrates, and decreased angina occurrence at a dosage of 1000mg twice daily for 6 weeks in patients not controlled effectively with the maximum recommended dosage of amlodipine (10mg once daily) [17]. At an initial dose of 500 mg orally twice daily; increased to the maximum recommended dose of 1000 mg orally twice daily as needed based on clinical symptoms [12].

**INDICATIONS:**

Ranolazine may be well suited for patients with lower blood pressure or heart rate, in whom the institution or upward titration of antianginal drugs with important hemodynamic effects, may not be tolerated [12]. Ranolazine, improve ischemic symptoms by reducing myocardial cellular sodium and calcium overload [18]. Due to its ability to prolong QT interval, ranolazine should be reserved for patients who have not achieved an adequate response with other antianginal therapies [12].

**RANOLAZINE IN CHRONIC ANGINA:**

In chronic angina patients, ranolazine monotherapy was well tolerated and increased exercise performance throughout its dosing interval at all doses studied without clinically meaningful hemodynamic effects [19].

**RANOLAZINE IN HEART FAILURE:**

In a study of 15 patients with prior myocardial infarction (average ejection fraction 35%) who received an intravenous ranolazine infusion (200 or 500 µg/kg), local function was observed in ischemic, infarcted, and normal left ventricular segments. Global left ventricular function was not changed significantly after ranolazine infusion; left ventricular ejection fraction was 37% after dosing (P=NS). However, ranolazine was associated with a significant increase in peak filling rate and regional wall lengthening during the isovolumic relaxation phase in ischemic left ventricular segments, signifying evidence of better local diastolic function [3].

**DRUG INTERACTIONS:**

Due to the dependence of ranolazine on CYP3A metabolic pathways, the co administration of a wide range of drugs can influence its clearance [2]. The ranolazine interact with inhibitors and substrates of the CYP3A isoenzyme. Ranolazine is a weak inhibitor of CYP3A4 and CYP2D6. In exacting, ketoconazole, a potent CYP3A inhibitor, can elevate steady-state concentrations of ranolazine to more than 3 times the estimated value; consequently, ketoconazole is contraindicated in patients who are taking ranolazine, and raised ranolazine plasma concentrations and reduced the CYP3A4-mediated metabolic transformation of ranolazine, confirming that CYP3A4 is the most important metabolic pathway for ranolazine. Diltiazem reduced oral clearance of ranolazine in a dose-dependent manner. Supervision of ranolazine in combination with diltiazem or simvastatin was safe and well tolerated during the interval studied. Simvastatin, a weak inhibitor of CYP3A, does not appear to enhance ranolazine levels [2, 3, 5, and 20]. Drugs such as diltiazem (240 mg daily), a moderateCYP3A inhibitor, increase ranolazine plasma levels, in a dose-dependent manner, <1.5-fold; ranolazine has no significant effect on diltiazem pharmacokinetics. Moderate inhibitors of CYP3A, such as diltiazem and verapamil, should be used with caution. Ranolazine is a substrate and an inhibitor of p-glycoprotein.Verapamil (360 mg daily), a drug that inhibits P-glycoprotein, increases the absorption of ranolazine with a 2.3-fold raise in ranolazine plasma levels. So it should be used with caution by patients who are taking verapamil [2]. Ranolazine increases digoxin concentrations 1.4- to 1.6-fold at trough and <2-fold at peak plasma levels, most probably through antagonism for intestinal and renal P-glycoprotein. Simvastatin Cmax is increased <2-fold after ranolazine; simvastatin has no significant effect on ranolazine pharmacokinetics. In phase II studies of ranolazine with patients on statin drugs, major increases in creatine kinase, clinical myositis, or elevated liver function tests have not been reported. No drug interactions with warfarin have been reported [3]. Ranolazine has been shown to increase serum digoxin levels by 1.5 times, leading to the recommendation that digoxin dosages be altered in patients who are taking both drugs [2].

**CONTRA INDICATIONS:**

The drug brand indicates that ranolazine is contraindicated in patients on potent and moderately potent CYP3A inhibitors such as ketoconazole, diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, and grapefruit juice [2, 3].

**PRECAUTIONS**:

Ranolazine does not cause lethal changes in laboratoryvalues. Less significant rise in Creatinine has been noticed with no decrease in glomerular filtration [12].

**CLINICAL TRIALS:**

The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) and subsequent Combination Assessment of Ranolazine in Stable Angina (CARISA) trials .enrolled patients with chronic effort angina for at least 3 months who had reproducible treadmill-induced, exercise-induced angina and ST-segment depression at low exercise workloads (>5 metabolic equivalents [METs]) with the use of a modified Bruce protocol at baseline. The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial was the first placebo-controlled trial to establish the antianginal and anti-ischemic effects of ranolazine monotherapy, demonstrating increased exercise tolerance and prolonged times to exercise-induced angina and ischemic ST-segment depression with twice-daily ranolazine doses ranging from 500 mg to 1500 mg. The Combination Assessment of Ranolazine in Stable Angina (CARISA) trial assessed the antianginal and anti-ischemic effects of ranolazine in symptomatic chronic angina patients with severe coronary disease, evidenced by exercise-induced myocardial ischemia at low workloads despite treatment with standard doses of atenolol, amlodipine,

or diltiazem. An exercise test was conducted at trough (12 hours after dose) and peak (4 hours after dose) at the end of each treatment week. All 3 doses resulted in significant increase in exercise duration at trough compared with placebo (P≤0.005) in a dose-dependent method. Exercise time better with progressive raise in plasma concentrations, even if the incremental advantage was reduced at dosage >1000 mg twice daily [3, 13]. The CARISA study tested 823 patients with chronic angina on once-daily atenolol (50 mg), once-daily diltiazem (180mg), or once-daily amlodipine (5 mg). Eligible patients were stratified according to their setting therapy. Exercise tests were performed 2, 6, and 12 weeks subsequent to randomization at trough and 2 and 12 weeks at peak. The results showed that, compared with placebo, ranolazine extensively improved symptom-limited exercise time (mean increase 24 to 34 seconds).The improvement was sustained over the 12 weeks of therapy, indicating lack of acceptance over this time period. At enrollment, 43%, 31%, and 26% of the patients were on background atenolol, amlodipine, or diltiazem treatment. The treatment-by-background interaction term indicated no evidence of differential treatment effect according to background therapy expected. However, it should be noted that the number of patients and power to test differences between the 3 background treatment strategies were relatively small and that the absolute increase in exercise time from baseline was slightly greater with background calcium antagonist treatment. No therapeutically significant changes compared with placebo on rest or exercise heart rate or blood pressure was noted, although some small changes achieved statistical importance. At baseline, the standard number of angina attacks for each week was 4.5 in all groups. The represent number of weekly angina attacks and nitroglycerin use over the 12 weeks of treatment with ranolazine was significantly reduced in a dose-dependent fashion for ranolazine 750 and 1000 mg BID, correspondingly). At the conclusion of the 12-week double-blind treatment period, patients entered a 2-day rebound evaluation phase during which half of the patients on active double-blind ranolazine were continued on that therapy for an further 2 days, and the others were switched in a double-blind approach to placebo. All recipients had their ultimate exercise test at trough. Unexpected withdrawal of ranolazine did not effect in a rebound worsening of the patient's underlying angina. The beneficial effect of ranolazine on exercise duration was no longer evident within 2 days after therapy was withdrawn.

The antianginal efficacy of ranolazine was examined in several patient subsets in the MARISA and CARISA trials. Diabetes mellitus did not affect the beneficial effect of ranolazine on improvement of exercise parameters. The probability values for the treatment-by-subgroup interaction for exercise duration were 0.77 in MARISA and 0.89 in CARISA, indicating no statistical evidence of a differential treatment effect by history of diabetes mellitus. The side effect profile and frequency of adverse events was also similar. HbA1c values were obtained from 160 of 189 diabetic patients (85%) at baseline and 140 of 189 diabetic patients (74%) at 12 weeks in the CARISA trial. Ranolazine 750 and1000 mg reduced HbA1c compared with placebo by 0.48±0.18% (P=0.008) and 0.70±0.18% (P=0.002), respectively was shown in the below figure.

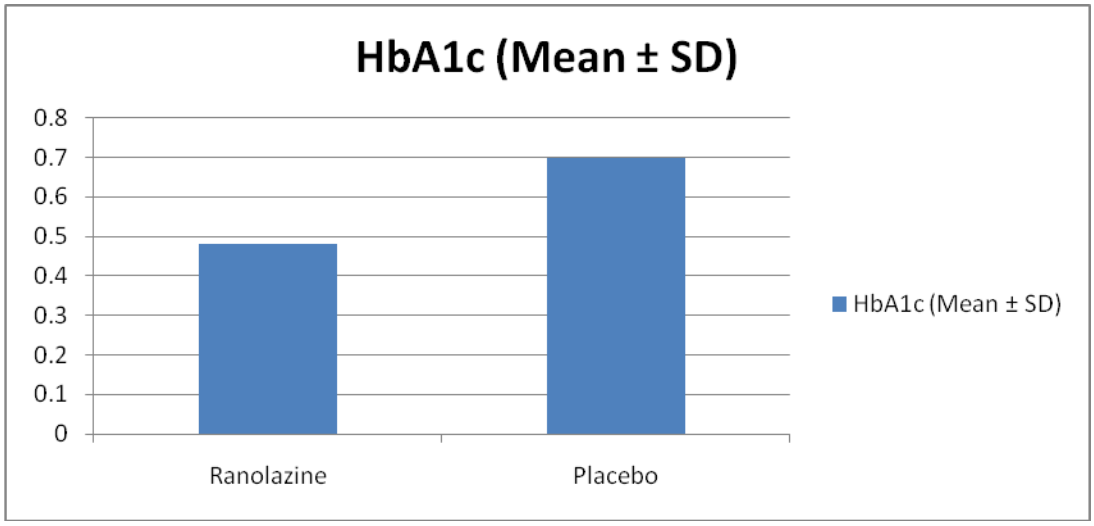


**Figure: Comparison of Ranolazine versus Placebo in terms of HbA1c reduction in Diabetes mellitus patients.**

When the diabetic patients in CARISA were stratified by insulin treatment, the reduction in HbA1c compared with placebo in those receiving insulin was greater. Similar analyses were conducted by prior history of heart failure (NYHA class I and II), gender, and age (≥65 and ≤65 years). Although the relative number of patients is relatively small, there is no data that the treatment effects of ranolazine within any of the separticular subgroups were inconsistent with the results observed in the overall inhabitants, even though the placebo corrected raise in treadmill exercise duration on ranolazine was less in women than in men [3]. Among patients with established coronary artery disease at moderate to high risk for death or recurrent ischemic events in the MERLIN-TIMI trial, ranolazine, appears to have antiarrhythmic effects as assessed by cECG monitoring of patients in the first week after admission. In particular, patients treated with ranolazine had fewer episodes of ventricular tachycardia lasting at least 8 beats, supraventricular tachycardia, and ventricular pauses lasting at least 3 seconds. This is the first clinical report of the effect of ranolazine on the incidence of cardiac arrhythmias, and it supports the experimental data that have identified several potential antiarrhythmic properties of ranolazine. The electrophysiological basis for drug-related suppression or induction of arrhythmias is complex. The potential clinical relevance of these experimental findings is supported by the present results of the MERLIN-TIMI trial, which demonstrate that

ranolazine use was associated with a decrease rather than an increase in the incidence of arrhythmic activity in cECG recordings. The use of most antiarrhythmic agents is limited by the risk of life-threatening arrhythmias or toxicity with prolonged exposure. But several, particularly class Ia and Ic agents such as flecainide and encainide and class III agents such as sotalol, may increase susceptibility to life-threatening arrhythmia or actually increase the risk of death after MI. In the patients in MERLIN-TIMI with cECG recordings, ranolazine reduced nonsustained ventricular arrhythmias. Although this analysis does not exclude the potential for drug-induced arrhythmia, we find no evidence for a significant excess risk of polymorphic ventricular tachycardia with ranolazine during the time of cECG monitoring in these high-risk patients.

Moreover, the numerically, but not statistically, lower incidence of sudden cardiac death in patients treated with ranolazine over the entire study period provides important data supporting the apparent safety of longer-term treatment with ranolazine in high-risk patients with established coronary artery disease. It is possible that the anti-ischemic effect of ranolazine contributed to the observed reduction in arrhythmia, but the similar reduction in the incidence of ventricular tachycardia with ranolazine in patients with and without ischemia as detected on cECG suggests that ranolazine has direct antiarrhythmic properties. Agents such as β-blockers, calcium channel blockers, amiodarone, and lidocaine suppress tachycardia but typically, and in contrast to ranolazine, decrease heart rate and actually increase bradyarrhythmias. We found no imbalance among antianginal agents with negative chronotropic properties to potentially explain this finding. Further research examining the effects of Ranolazine on pacemaker activity and atrioventricular nodal conduction is needed to understand better the observed reduction in bradyarrhythmias by Ranolazine [4]. Ranolazine has not been considered in a combination regimen with a maximum suggested dosage of a conventional antianginal agent. The purpose of the ERICA (Efficacy of Ranolazine in Chronic Angina) trial was to resolve if ranolazine could reduce angina in patients with persisting angina despite treatment with maximum recommended daily dosage of amlodipine (10 mg/day) over a 6-week period. Amlodipine was chosen as the conventional antianginal agent to be deliberate at most suggested dosage (10 mg/day) in a combination schedule, as the maximum suggested dosages of other conventional agents, such as atenolol (200 mg/day), diltiazem (540 mg/day), or verapamil (480 mg/day), were less possible for everyday use [21]. Timothy D. Henry evaluated quality of life (QOL) in 90 repeated patients seen at a committed Ranolazine clinic at the Minneapolis Heart Institute using the SF-36(Medical Outcomes Study 36-Item Short-Form Health Survey) and Seattle Angina Questionnaire (SAQ). Patients were treated with a selection of clinically offered therapies or novel research protocols (cell therapy). More than 1 year, main adverse cardiac events include 3 deaths, revascularization 17 and myocardial infarction 5. For patients who concluded the SF-36 and SAQ at base line and 1 year. SF-36 results showed the quantity of patients who rated their health as good or excellent more than double from base line to 1-year. Similarly, the SAQ QOL score was extensively improved at 1 year compared to base line (p=0.025) as was angina stability (p=0.017) and angina frequency (p=0.010). This study concludes using a variety of treatment options, patients seen in a committed Ranolazine clinic had improvement in QOL at 1 year [22].

## CONCLUSION

After reviewed the so many literatures this review conclude that ranolazine was an effective antianginal agent in patients with stable CAD and persisting angina despite a maximum recommended dosage of 1,000 mg Ranolazine twice a day significantly reduced the frequency of angina episodes and rate of nitroglycerin consumption and had a consistent treatment effect across subgroups including gender, age, and antianginal efficacy was unrelated to changes in blood pressure or heart rate. Ranolazine is a promising anti-ischemic therapy that may be valuable in a wide variety of subsets of patients with CAD who remain symptomatic despite treatment with other anti-ischemic agents, with minimal hemodynamic effects and without evident adverse long-term survival consequences over 1 to 2 years of therapy. It may be particularly useful in patients who cannot tolerate the initiation or upward titration of currently available antianginal drugs because of their depressive effects on blood pressure and heart rate. Amongst patients with T2DM and stable angina, the clinical benefits of Ranolazine were better in those with elevated $HbA_{1c}$ values. As per our review Ranolazine,is one of the drug choice used as an anti-anginal agent with electrophysiological effects, may decrease the incidence of paroxysmal AF in recipients with non-ST elevation ACS with a pattern of lower overall AF burden in this group and Ranolazine decreased the generally 1-year frequency of clinical AF events. These information suggested that Ranolazine is particularly useful in patients with stable angina who have sub optimally controlled T2DM.In case of an atrial-specific anti-arrhythmic properties of ranolazine may be of clinical interest and justify further investigation.

## REFERENCES


1. Simone C, Temistocle T, Roberta C, Salvi N, Maria L, Pasqualina B, Alberto Fo, Aurora ID, Massimo M, Francesco F, complete coronary revascularization in different clinical settings is not enough: role of ranolazine,J Am Coll Cardiol. 2014, 63, (12_S).
2. Bharath MR, Howard SW**,** Arthur ZS, Ranolazine, A New Approach to Treating an Old Problem,Tex Heart Inst J. 2010, 37, 641-647.
3. Bernard R. Chaitman, Ranolazine for the Treatment of Chronic Angina and Potential Use in Other Cardiovascular Conditions, Circulation, 2006, 113, 2462-2472.
4. Benjamin MS, David AM, Hanoch, Sabina AM, Luiz B, Chester MH, Peter M, et. al, Effect of Ranolazine, an Antianginal Agent With Novel Electrophysiological Properties, on the Incidence of Arrhythmias in Patients With Non–ST-Segment–Elevation Acute Coronary Syndrome, Circulation, 2007,116,1647-1652.
5. Jerling M, Clinical pharmacokinetics of ranolazine, Clinical pharmacokinetics, 2006, 45(5), 469-491.
6 Amal K Banerjee, Recent Advances in Management of Chronic Stable Angina: Newer Drugs, Available from: http://www.apiindia.org/pdf/pg_med_2007/Chapter-6.pdf.

7. Jessica LM, Judith SH, Benjamin MS, Sabina AM, Sarah Sloan, Carolyn H, McCabe, Piera Merlini, David AM, Clinical Features and Outcomes of Women With Unstable Ischemic Heart Disease, Circulation, 2010, 121, 1809-1817.
8. Giuseppe C, Management of myocardial ischemia. Is ranolazine needed? For all or some patients with myocardial ischemia?, Expert Opin. Pharmacother 2012, 13, 2429-2432.
9. Maier LS, A Novel Mechanism for the Treatment of Angina, Arrhythmias, and Diastolic Dysfunction: Inhibition of Late INa Using Ranolazine, Journal of Cardiovascular Pharmacology, 2009, 54,279-286.
10. Markus J, Stavgardsgatan B, Effect of renal impairment on multiple-dose Pharmacokinetics of extended-release ranolazine, Clinical Pharmacology & Therapeutics, 2005, 78, 288–297.
11. Abdallah, Hisham, and Markus J, Effect of Hepatic Impairment on the Multiple-Dose Pharmacokinetics of Ranolazine Sustained-Release Tablets, The Journal of Clinical Pharmacology, 2005, 45(7), 802-809.
12. Jose J, Jimmy B, Saravu K., Shastry BA, Ranolazine: A novel therapeutic option in chronic stable angina, Kathmandu university medical journal, 2007, 4,596-599.
13. Bernard RC, Carl JP., John OP, Jaroslav S, Galina C, Jerzy K, Whedy W, Sandra LS, Andrew AW, Effects of Ranolazine with Atenolol, Amlodipine, or Diltiazem on Exercise Tolerance and Angina Frequency in Patients With Severe Chronic Angina JAMA, 2004, 291,309-316.
14. Carl JP, Andrew AW, A controlled trial with a novel anti-ischemic agent, ranolazine, in Chronic stable angina pectoris that is responsive to conventional antianginal agents, American Journal of Cardiology, 1999, 84, 46-50.
15. Bernard RC, Efficacy and safety of a metabolic modulator drug in chronic stable angina: review of evidence from clinical trials, Journal of cardiovascular pharmacology and therapeutics, 2004, 9(1), S47-S64.
16. David KM, Mary K, Jeff K, German L, The Use of Oral Ranolazine To Convert New or Paroxysmal Atrial Fibrillation: A Review of Experience With Implications for Possible "Pill In The Pocket" Approach To Atrial Fibrillation, Indian Pacing and electrophysiology journal, 2009,9,260–267.
17. M. Asif AS, Susan JK., Ranolazine, Drugs, 2006, 66, 693-710.
18. Benjamin MS, Ranolazine in patients with coronary artery disease, Expert opinion in pharmacotherapy 2007, 8, 2149-2157
19. 19. Bernard RC, Sandra LS, John OP, Peter H, Jaroslav M, Jerzy K, Carl JP, Whedy W, Jeanenne J, David Ah., Andrew AW, Anti-ischemic effects and long-term Survival during ranolazine monotherapy in patients with chronic severe angina, J AmColl Cardiol. 2004, 43, 1375-1382.
20. Jerling, Markus, et al. Studies to investigate the pharmacokinetic interactions between ranolazine and ketoconazole, diltiazem, or simvastatin during combined administration in healthy subjects, The Journal of Clinical Pharmacology, 2005, 45,422-433.
21. Peter HS, Nikolay AG, Alexey B, I-Zu H, Lixin M, Antianginal Efficacy of Ranolazine When Added to Treatment with Amlodipine (Efficacy of Ranolazine in Chronic Angina) J Am Coll Cardiol. 2006, 48, 566-575.
22. Henry, Timothy D., et al., A Dedicated Refractory Angina Clinic Improves Quality Of Life, Journal of the American College of Cardiology, 2014, 63, (12_S).


5487847845**1141145**