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# Ranolazine New Potential Therapeutic Aspects

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**Abstract**

Since Ranolazine approval as an antianginal medication by the US Food and Drug Administration in 2006, it has been administered to specific patient populations with stable angina. Originally, it was thought that ranolazine's therapeutic actions were due to its inhibition of the metabolism of fatty acids. However, as research progressed, it became clear that ranolazine's primary advantageous benefits come from its influence on the heart's late sodium current. Numerous experimental and clinical studies have tested ranolazine either directly or indirectly on heart failure since late-sodium currents have been found to be involved in various heart pathologies such as ischemia, arrhythmias, systolic and diastolic dysfunctions, and all these conditions are associated with heart failure. The inhibition of the underlying mechanisms of cardiac remodeling, such as ion disruptions, oxidative stress, inflammation, apoptosis, fibrosis, metabolic dysregulation, and neurohormonal dysfunction, by ranolazine is reviewed after any kind of severe injury, along with open questions. Ranolazine additional metabolic properties contribute to its efficacy in treating conditions other than coronary artery disease. Our publication will focus on potential therapeutic applications of ranolazine, extending beyond cardiology.

**Keywords:** Ranolazine, Coronary artery diseases, Angina, Diabetes, Co-morbidities of diabetes.

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## 1. Introduction

Ranolazine is a first-in-class antianginal drug with cardio protective properties that does not affect heart rate or blood pressure the proposed mechanism of its anti-ischemic effects is inhibition of late sodium current due to blockade of the cardiac isoform of the sodium channel, Nav1.5 [1]. Additionally, ranolazine has beneficial metabolic properties. North American and European guidelines for the treatment of chronic stable angina now include ranolazine as a second-line antianginal based on available data. North American and European guidelines for the treatment of chronic stable angina now include ranolazine as a second-line antianginal based on available data [2]. Beyond relieving angina, ranolazine has demonstrated advantages since it was approved. In addition to diastolic dysfunction, pulmonary hypertension (PH), extended advantages have been noted in the management of arrhythmias, particularly atrial fibrillation (AF). Ranolazine has also shown promise in the management of diabetes mellitus [2].

## 2. Objectives

The objectives of this review were to study the mechanism of action of ranolazine, ranolazine role in treatment of heart diseases and effect of ranolazine on diabetes and associated co-morbidities.

## 3. Pharmacology

### *3.1. Absorption and dosage forms*

Ranolazine is an acetanilide and piperazine derivative with a molecular weight of 427.545 g/mol. 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 [3]. The time to reach peak serum concentration is quite variable but has been observed to be in the range of 2-6 hours, with steady state within 3 days [4]. Dosage Forms of ranolazine is: extended-release tablet and extended-release granules. The FDA indicates a Tmax of 3-5 hours. The average steady state Cmax is about 2600 ng/mL. Absorption of ranolazine is not significantly affected by food consumption. The bioavailability of ranolazine taken in the tablet form compared to that from a solution of ranolazine is about 76% [4].

### *3.2. Protein binding*

Approximately 62% of the administered dose of ranolazine is bound to plasma proteins. Ranolazine appears to have a higher binding affinity for alpha-1 acid glycoprotein [4].

### *3.3. Volume of distribution*

The mean apparent volume of distribution of ranolazine is reported to be 53.2 L and the average steady-state volume of distribution is estimated to range from 85 to 180 L. Since ranolazine is about 62% bound to plasma proteins, hemodialysis is unlikely to be effective in clearing ranolazine [4].

### *3.4. Metabolism*

Ranolazine is rapidly heavily metabolized in the liver a gastrointestinal tract through the activity of the CYP3A4 enzyme with minor contributions from CYP2D6 [4]. More than 40 ranolazine metabolites have been found in plasma and more than 100 metabolites have been identified in the urine. Ranolazine and some of its metabolites are known to weakly inhibit CYP3A4. However, the activity of the metabolites of ranolazine has not been fully [5].

### *3.5. Route of elimination*

From the administered dose, about 3/4 of the dose is excreted renally, while 1/4 of the dose is excreted in the feces. An estimated 5% of an ingested dose is excreted as unchanged drug [5].

### *3.6. Interactions/Precautions*

Hepatic metabolism of ranolazine is mediated through CYP3A4 and, to a lesser degree, CYP2D6. There have been several reported interactions between herbal items and pharmaceuticals. Strong CYP3A4 pathway inhibitors, such as some antifungals (ketoconazole and other azole class), antibiotics (macrolides, clarithromycin), HIV protease inhibitors, diltiazem, and grapefruit products, should not be taken with ranolazine. With the exception of tricyclic antidepressants and some antipsychotics, co-administration of ranolazine with medications that inhibit CYP2D6 frequently does not require dose modification [6].

### *3.7. 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]. 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 ($I_{Na}$). (Figure 1) In the presence of ischemia, 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 [7]. 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 ischemia and creating a dangerous feedback loop. Ranolazine selectively inhibits the late $I_{Na}$, reducing $Na^+$ overload and the subsequent intra-cytosolic $Ca^{2+}$ accumulation and leading to a reduction in diastolic wall stress and improved coronary blood flow as figure (1) [1]. In animal studies, ranolazine also exhibited weak β1 and β2 and Ca channel antagonist activity. However, in clinical trials, ranolazine doses had no clinically significant effect on resting heart rate or arterial blood pressure [1].

### *3.8. Side Effects*

Ranolazine is contraindicated in patients with severe renal impairment (creatinine clearance of <30 mL/minute). Given the three-fold increased risk of QT prolongation, ranolazine is also contraindicated in patients with hepatic impairment**.** Nausea, Constipation, Headache, Fast, pounding, or irregular heartbeat, Difficulty breathing and Fainting is common side effects of ranolazine [9].

### *3.9. Toxicity*

High oral doses of ranolazine have led to dizziness, nausea, and vomiting. These effects have been shown to be dose related. High intravenous doses can cause diplopia, confusion, paresthesia, in addition to syncope. In the case of an overdose, provide supportive therapy accompanied by continuous ECG monitoring for QT interval prolongation [1].

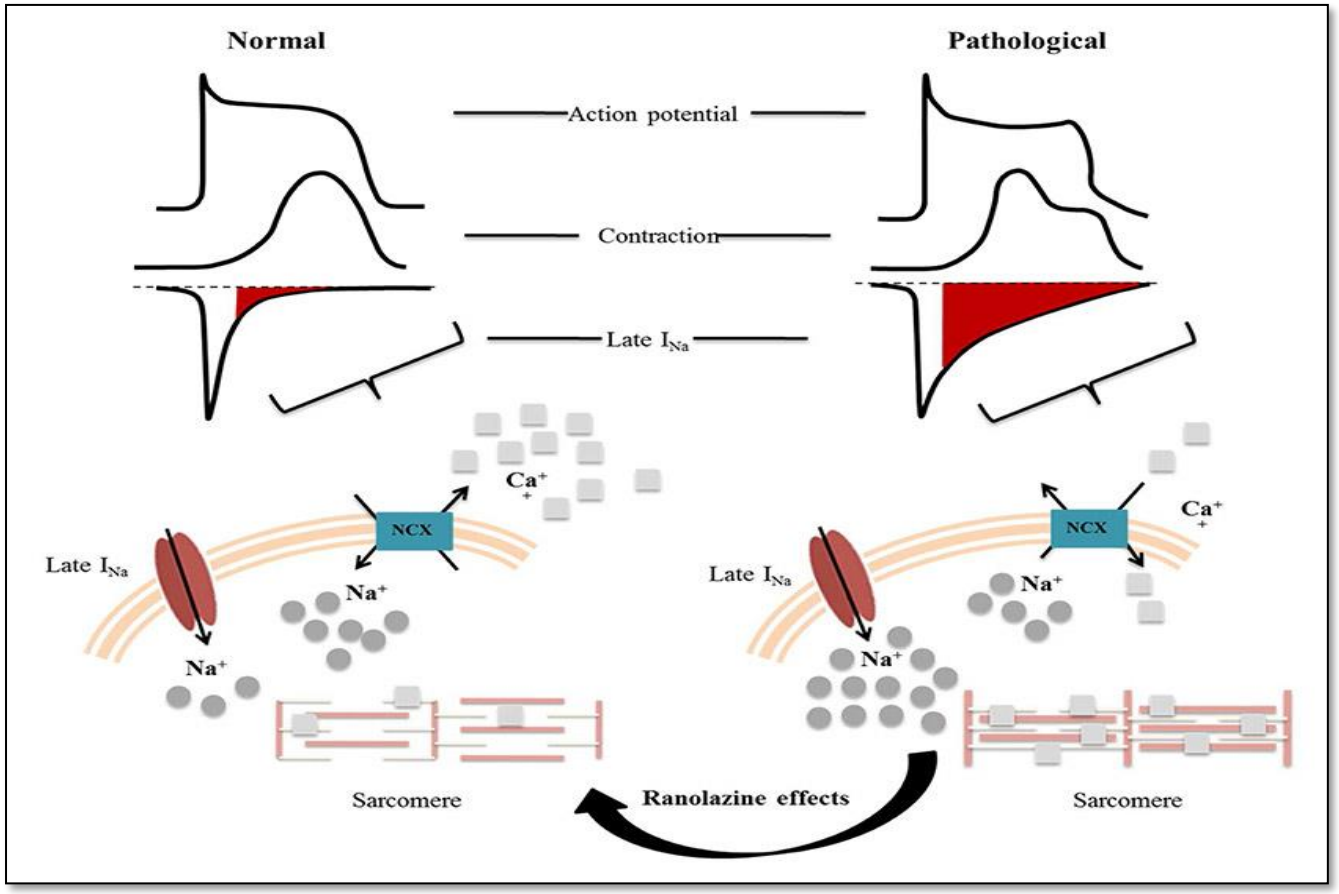
### *3.10. Ranolazine therapeutic uses*

#### *3.10.1. Heart Failure*

Ranolazine may have good effects on patients who have heart failure with preserved ejection fraction with a higher left ventricular end-diastolic volume value and reduced early diastolic mitral annular tissue velocity (E/e′) as a marker of diastolic function compared to the standard treatment alone. It is particularly safe, as ranolazine does not affect blood pressure, heart rate and rate of ventricular repolarization (shortening of the QT interval) [10]. Ranolazine displays beneficial effects in cardiomyocytes because of inhibition of late sodium current apart from its antianginal properties for patients with chronic coronary syndromes. Ranolazine is advantageous regarding cellular metabolism and energy substrate utilization in the failing heart and could improve myocardial diastolic function [11].

#### *3.10.2. Atrial Arrhythmias*

Although ranolazine is considered an anti-angina drug, it may also be, according to the available data, used in patients with AF.




$I_{Na}$ = late Na current; NCX= Na-Ca exchange

**Figure 1.** Ranolazine mechanism of action [8]

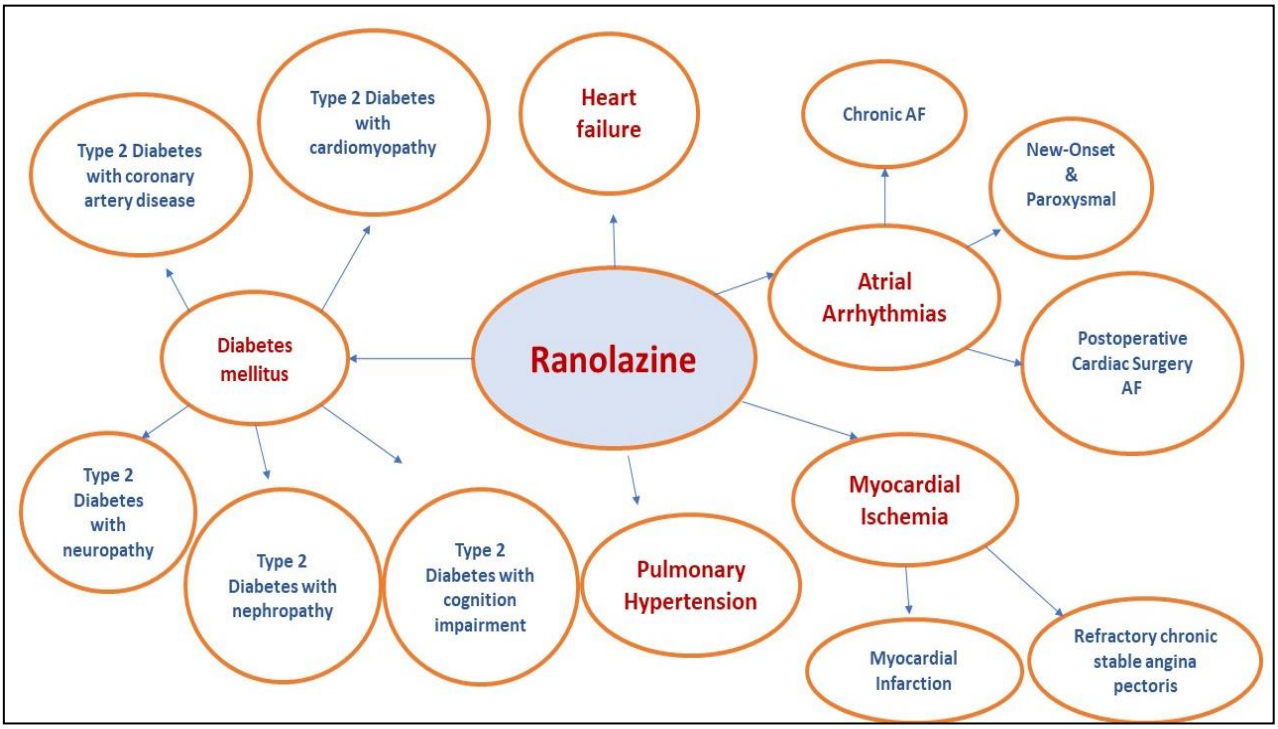



**Figure 2.** Ranolazine Theraputic uses

**Table 1**: Demonstrates uses of ranolazine and its references.

| Disease State | Studies support benefit (references) | Conclusion |
|---|---|---|
| **Heart failure** | [10], [11]. | Ranolazine may have good effects on patients who have heart failure with preserved ejection fraction with a higher left ventricular end-diastolic volume value and reduced early diastolic mitral annular tissue velocity as a marker of diastolic function compared to the standard treatment alone. It is particularly safe, as ranolazine does not affect blood pressure, heart rate and rate of ventricular repolarization (shortening of the QT interval). |
| **New-Onset and Paroxysmal Atrial Fibrillation.** | [13], [14]. | Ranolazine efficacy in atrial fibrillation due to its reduction of peak $I_{Na}$ and especially its atrial-selective inhibition of the rapid delayed rectifier K+ current (IKr) carried by Kv11.1, the cardiac human. Ether-a-go-go-related gene (hERG) K+ channel. Together, these three mechanisms allow ranolazine to increase atrial. Post repolarization refractoriness and slow interatrial conduction without affecting atrial action potential duration. |
| **Chronic AF** | [15]. | Ranolazine is safe and well tolerated in patients with persistent AF. |
| **Postoperative cardiac surgery AF** | [16]. | Ranolazine help in reduction in the incidence of Postoperative Cardiac Surgery AF by 38% |
| **Refractory chronic stable angina pectoris** | [17], [18], [19]. | Ranolazine reduced angina and sublingual nitroglycerin use and was well tolerated [TERISA]. |
| **Myocardial Infarction** | [16]. | Ranolazine has cardioprotective effects, including antiarrhythmic and anti-ischemic effects. ranolazine improves recovery of function after myocardial infarction, with a greater effect in postinfarcted diabetic myocardial |
| **Pulmonary Hypertension** | [19], [20]. | Ranolazine alters metabolism in patients with precapillary pulmonary hypertension by Decreasing glucose uptake in the right ventrical, Regulating redox homeostasis towards more robust defense mechanism against oxidative stress, Favorable effect on the pulmonary blood flow associated with key changes in bile acid and aromatic amino acid metabolism. |
| **Diabetes mellitus** | [21], [22], [23], [24]. | Ranolazine may be enhancing insulin sensitivity also ranolazine improves HbA1c. |
| **Type 2 Diabetes with coronary artery disease** | [25], [19]. | Ranolazine is a very promising therapeutic option in the management of diabetes in patients with coronary artery disease. |
| **Type 2 Diabetes with cardiomyopathy** | [16] | Ranolazine have a preventive effect on diabetic cardiomyopathy. |
| **Type 2 Diabetes with neuropathy** | [26], [27] | Ranolazine reduce neuronal excitability in neuropathic pain, which is mediated by Nav 1.7 and 1.8 channels. |
| **Type 2 Diabetes with nephropathy** | [28] | Ranolazine was successful in preventing the changes in diabetic nephropathy such as basement membrane thickening, mesangial matrix expansion, interstitial nephritis, and focal tubular necrosis as compared to the diabetic control rats. |
| **Type 2 Diabetes with cognation impairment** | [29] | Ranolazine may exert beneficial actions against cognitive decline and depression. |

**Abbreviations. AF:** Atrial fibrillation, **TERISA:** Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina.**, $I_{Na}$:** late Na current **Nav:** voltage-gated sodium channel**, HbA1c**: glycated hemoglobin, **IKr:** Rapid delayed rectifier K+ current, **hERG:** human ether-a-go-go related gene

Ranolazine has anti-AF efficacy, both alone or in combination with other drugs such as amiodarone and dronedarone. Indeed, its efficacy has been demonstrated in various settings such as the termination of paroxysmal AF, the facilitation of AF electrical cardioversion, and postoperative AF prevention [12].

#### *3.10.2.1. New-Onset and Paroxysmal Atrial Fibrillation*

Ranolazine has been shown to work by lowering atrial excitability and extending the atrial refractory period [13]. Numerous trials have assessed ranolazine's potential as an additional anti-arrhythmic medication for atrial fibrillation (AF). The impact of amiodarone infusion plus ranolazine against amiodarone infusion alone for conversion to sinus rhythm was assessed in 121 patients with recent onset AF in a randomized study. The ranolazine with amiodarone infusion group showed a significantly greater effect [13]. In addition, it was hypothesized that the combination of this ranolazine and dronedarone would have complimentary electrophysiological properties, perhaps leading to an improved safety and tolerability profile [14].

#### *3.10.2.2. Chronic atrial fibrillation*

Most recently, the Ranolazine in Atrial Fibrillation Following an Electrical Cardioversion (RAFFAELLO) study evaluated 241 patients with persistent AF after successful electrical cardioversion. Patients were treated with dose-ranging ranolazine (375, 500, or 750 mg BID) or placebo 2 hours after cardioversion and followed by Trans telephonic electrocardiographic monitoring during a 4-month follow-up period. According to the current dose-finding trial, patients with chronic AF can safely and well tolerate ranolazine. While the two higher dosages of 500 mg and 750 mg were linked to a comparable 35% reduction in the incidence of AF, the 375 mg daily dose shown no antiarrhythmic benefits [15].

#### *3.10.2.3. Postoperative Cardiac Surgery AF*

Time to sinus rhythm conversion was compared between amiodarone alone and treatment with ranolazine with IV amiodarone, PO amiodarone, and so on. When compared to amiodarone alone, the group that received amiodarone plus ranolazine saw a notably faster time to sinus rhythm conversion. In conclusion, this study showed a reduction in the incidence of AF by 38% [16].

### *3.10.3. Myocardial Ischemia*

#### *3.10.3.1. Refractory chronic stable angina pectoris*

Ranolazine affords additional anti-anginal and anti-ischemic efficacy in patients with severe chronic angina who remain symptomatic while taking standard doses of atenolol, amlodipine, or diltiazem, 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 [17]. Among patients with diabetes and chronic angina despite treatment with up to 2 agents, ranolazine reduced angina and sublingual nitroglycerin use and was well tolerated. (Type 2 Diabetes). Evaluation of Ranolazine in Subjects with Chronic Stable Angina [TERISA] [18]. Ranolazine has been shown to improve diastolic function in patients with coronary artery disease by increasing the regional peak filling rates and regional wall lengthening during isovolumic relaxation period [19].

#### *3.10.3.2. Myocardial Infarction*

Ranolazine has cardioprotective effects, including antiarrhythmic and anti-ischemic effects. ranolazine improves recovery of function after myocardial infarction, with a greater effect in postinfarcted diabetic myocardial [16].

### *3.10.4. Pulmonary Hypertension*

Ranolazine may improve RV function in patients with precapillary PH. Future larger studies and mechanistic studies are needed to confirm the benefit of ranolazine in patients with PH [19]. QJ Han study suggests that the beneficial effects of ranolazine: 1. Decreasing glucose uptake in the RV; 2. Regulating redox homeostasis towards more robust defense mechanism against oxidative stress; 3. Favorable effect on the pulmonary blood flow associated with key changes in bile acid and aromatic amino acid metabolism [19]. It has also been shown to decrease pulmonary capillary wedge pressure and left ventricular end diastolic pressure in patients with heart failure with preserved ejection fraction [20].

### *3.10.5. Effect on Type 2 Diabetes mellitus and its complications*

#### *3.10.5.1 Type 2 Diabetes mellitus*

The burden of cardiovascular disease among patients with diabetes is extensive. On the one hand, diabetes is a common comorbidity in angina patients. On the other hand, patients with diabetes have a two- to four-fold increased risk of cardiovascular events. In diabetic patients over the age of 65 years, 68% of deaths are due to coronary artery disease. The high mortality and risk for cardiovascular events have led to considerable interest in identifying new therapeutic approaches to improve glycemic control in patients with coronary artery disease [21]. CARISA was the first trial to show improved glycemic control in ranolazine-treated patients since the duration of the double-blind treatment was long enough for HbA1c to reach a new equilibrium. Treatment with ranolazine produced similar improvements in exercise parameters, nitroglycerin use, and angina frequency in diabetic as compared to non-diabetic patients [21]. Patients with diabetes and a HbA1c of 8–10% at randomization had an absolute HbA1c reduction in the ranolazine group of 1.2% and the placebo adjusted decrease in HbA1c by ranolazine was 0.6%. In patients with fasting plasma glucose of 150–400 mg/dl at randomization, ranolazine-treated patients compared to placebo had significantly reduced fasting plasma glucose by 25.7 mg/dl without effects in individuals with normal fasting plasma

glucose. Furthermore, when changes in either HbA1c or fasting plasma glucose were correlated to HbA1c or fasting plasma glucose at randomization, the slopes were significantly steeper for ranolazine than placebo. This might demonstrate that lowering of HbA1c and fasting plasma glucose by ranolazine is related to hyperglycemia at randomization [22]. A recent study using isolated rats and human pancreatic islets suggests that ranolazine may promote glucose-stimulated insulin secretion. In addition, mice treated with ranolazine had healthier islet morphology and significantly higher ß-cell mass as well as a reduction of apoptotic cells in the pancreas as compared to the vehicle group. Nevertheless, the mechanism by which ranolazine improves HbA1c is still under debate and remains a speculative issue and must be elucidated in the future. Experimental studies Timmis and coworkers speculated that the underlying mechanism might be that in exogenous insulin users, ranolazine may be enhancing insulin sensitivity [23]. The two trials CARISA and MERLIN-TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes- Thrombolysis in Myocardial Infarction demonstrated 1.2% absolute decrease in HbA1C in diabetic arm compared to placebo with an oral dose of 1000mg twice daily. Another trial on glycemic effects of ranolazine monotherapy in diabetics showed that there was a decline in HbA1C levels by 0.56% at 24 weeks of therapy and more patients achieved goal A1C compared to placebo [24].

#### *3.10.5.2. Effect on Type 2 Diabetes with coronary artery disease*

The TERISA (Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina) evaluated the efficacy of ranolazine in chronic angina. This trial found that diabetics on ranolazine had decreased use of sublingual nitroglycerin and reduced anginal episodes compared to placebo [25]. A These results make ranolazine seem like a very promising therapeutic option in the management of diabetes in patients with coronary artery disease (CAD). The fact that diabetes contributes to risk factors for adverse outcomes in CAD adds more weight to this point [19]. Ranolazine is a very promising therapeutic option in the management of diabetes in patients with coronary artery disease (CAD). The fact that diabetes contributes to risk factors for adverse outcomes in CAD adds more weight to this point [19].

#### *3.10.5.3. Effect on Type 2 Diabetes with cardiomyopathy*

The beneficial effect of ranolazine on cardiac electrophysiological changes should have a preventive effect on diabetic cardiomyopathy [16].

#### *3.10.5.4. Effect on Type 2 Diabetes with neuropathy*

Ranolazine exhibited neuroprotective properties in neuron and glia cells. It reduced the expression of interleukin (IL)-1β and tumor necrosis factor-alpha (TNF-α) and raised the expression of the PPAR-γ protein in those cells. Neuronal excitability in neuropathic pain, which is mediated by Nav 1.7 and 1.8 channels, was reduced by ranolazine [26]. HJ Gould III et al reported that ranolazine reduces nerve injury-induced mechanical allodynia and cold hypersensitivity [27].

#### *3.10.5.5. Effect on Type 2 Diabetes with nephropathy*

Ma, C et al 2021 showed through in vivo and in vitro studies that ranolazine ameliorates renal injury in CA-AKI by modulation of intracellular calcium homeostasis, and suppression of oxidative stress and apoptosis Also Ranolazine monotherapy significantly reduced random blood glucose ($p<0.0001$), HbA1c%, urine albumin, serum creatinine and inflammatory markers like CRP, IL-6, and TNF-α ($p\leq0.001$) as compared to the diabetic control group. Histopathological examination of the rat kidneys showed ranolazine was successful in preventing the changes in diabetic nephropathy such as basement membrane thickening, mesangial matrix expansion, interstitial nephritis, and focal tubular necrosis as compared to the diabetic control rats [28].

#### *3.10.5.6. Effect on Type 2 Diabetes with cognation impairment*

Velia Cassano et al results confirmed the hypoglycemic effect of ranolazine and showed that this drug may exert beneficial actions against cognitive decline and depression. ranolazine considered as the drug of choice in individuals with T2DM with increased risk of cognitive decline [29].

## 4. Conclusion

Ranolazine, an antianginal medicine licensed for the treatment of people with stable coronary artery disease, works by specifically blocking the late sodium inward current (late INa). It lessens the harmful effects of excess intracellular calcium and salt, which can both accompany and contribute to myocardial ischemia. Because of this mode of action, ranolazine is beneficial not only for stable coronary artery disease but also for heart failure and glucose regulation in diabetes. Owing to its flexibility, ranolazine may have therapeutic uses that are now understudied.

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