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Review Article

Elucidation and Possible Mechanism of Action of Cardio Protective Drugs viz. Ranolazine, Ivabradine, Cilostazol and Inamrinone in Ischemic Reperfusion Induced Cardiac Injury

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Abstract

Ranolazine is an anti-ischemic that inhibit late sodium channel(INal), reduces calcium excess, lowers diastolic tension and improves cardiac relaxation. Ivabradine inhibits the open state of the intracellular portion of the hyperpolarization-activated cyclic nucleotide-gated(HCN) channel in sinoatrial-node, transporting sodium(Na+) and potassium(K+) ions. Inward funny current (If), hyperpolarized, is inhibited. If lengthen diastole, decrease slope of the pacemaker action potential's diastolic depolarization without changing the action potential's. Phosphodiesterase-III(PDE3)-inhibitor, clostazol and inamrinone, break down cGMP and core cAMP. In review on elucidation and possible mechanism of action of cardioprotective drugs viz. Ranolazine, Ivabradine, Cilostazol and Inamrinone found beneficial in Ischemic Reperfusion induced cardiac injury. But secondary biological mediators like nitric-oxide, bradykinin, K+ATPase channels, serotoninergic pathway, adenosine involvement have not been elucidated yet. These secondary mechanisms are of prime importance because ischemic pre-conditioning involves cardioprotection by above biological mediators. Full mechanisms of action of above four drugs are essential in cardioprotection in ischemia reperfusion injury model.

Keywords: Coronary artery disease; Myocardial infraction; Angina pectoris; Cardioprotective Drugs mechanism of action; Ischemia reperfusion injury

Introduction

Cardio protection refers to all techniques and methods that lessen or even stop myocardial damage in order to preserve the heart. [1] Cardio protection includes a number of protocols that have demonstrated to maintain the survival and function of cardiac muscle cell tissue in the face of ischemia insult or re oxygenation. Precondition ing (PC), per conditioning (Per C), pre-ischemic event management (PEDM), post-ischemic event management (PEDM), and reperfusion are all examples of cardio protection techniques (post conditioning, Post C). [2] These tactics can be further subdivided into classes of conditioning known as remote ischemic PC (RIPC), remote ischemic Post C, and remote most ischemic Per C depending on whether the inter-

vention is carried out locally or remotely. [2,3] Myocardial infarction is prevented by the early phase of classical (local) preconditioning, which has an immediate onset and lasts for two to three hours. [3]

The activation of G protein-coupled receptors, as well as downstream MAPKs and PI3/Akt, results in the early phase's post-translational modification of already-existing proteins. As a result of these signalling events, the MTP (mitochondrial permeability transition pore) is not allowed to open by activating PKC and the RISK pathway, which operate on the ROS-producing mitochondria. [4] The late phase, which starts between 12 and 24 hours after an ischemia event and lasts for three to four days, prevents both myocardial stunning and reversible post ischemic contractile dysfunction [5-7]. As a result of the actions of kinases like PKC and Src, which in turn increase gene transcription and upregulate late PC molecular players, this phase involves the creation of novel cardio protective proteins (e.g., antioxidant enzymes, iNOS). [8] There has been evidence or speculation that PKC plays a role in more modern cardio protection techniques including RIPC, local Post C, and remote Post C. It has been demonstrated that with RIPC activation, PKC moves from the cytosol to the particulate fraction, and that the PKC inhibitor chelerythrine can reduce the protection provided by RIPC [12,13]. Similar to local Post C models, it has been demonstrated that PKC activation and phosphorylation are enhanced, and PKC inhibition reduces the therapeutic benefits of these regimens [14,15]. Inhibiting Hsp90 activity with geldanamycin prevents Post C protection and PKC translocation, according to a recent study. [16] It has not been convincingly shown that PKC has a function in remote Post C and Per C, hence more research is needed to explore this.

Ranolazine

Ranolazine is currently approved as a second-line treatment in Europe and the United States agent for the treatment of chronic stable angina pectoris (CSAP) [17]. Both in experimental animal and in people with coronary artery disease, this medication's anti-ischemic and anti-anginal properties have been well examined. Ranolazine is clinically efficacious at plasma concentrations of 2–6μm, which do not significantly alter the rate–pressure product, unlike other anti–anginal medications. Other factors that affect myocardial oxygen consumption, such as cardiac contractility and preload, were not assessed in these clinical studies. Ranolazine is believed to have an anti-ischemic effect by inhibiting the late sodium channel (inal), which reduces the NaI-dependent cellular calcium excess and, as a result, lowers diastolic tension and improves cardiac relaxation [18]. The first antianginal medication that can prevent ischemia consequences without affecting blood pressure or heart rate is Ranolazine [19]. Although the exact way ranolazine shields the myocardium is unknown, it has been suggested that it modifies myocardial metabolism, lessening the severity of acidosis and lactate build up brought on by anaerobic metabolism. Others have hypothesised that this substance might boost oxygen uptake by switching the substrate used from fatty acids to carbohydrates. The finding that ranolazine increases the amount of active pyruvate dehydrogenase in isolated hearts during low flow ischaemia is consistent with the latter mechanism with respect to its anti-ischaemic and cardio protective properties [20].

Ivabradine

Ivabradine reduces heart rate by specifically inhibiting the sinoatrial node's pacemaker activity. Few researches have after a re-perfused myocardial infarction, the effects of ivabradine on the mechanical characteristics of the heart were studied. [21] Advances using ultrasound speckle-tracking, strain assessments in small-animal models can be carried out, allowing the evaluation of regional strain a mechanical process. The recently approved US Food and Drug Administration Ivabradine, a medicine for the heart, specifically blocks the cyclic nucleotide-gated hyperpolarization-activated (HCN) the sinoatrial node's channels [22]. This obstruction causes a decreased cardiac pacemaker, or humorous, current (If),lowering the sluggish diastolic depolarization phase's slope of the sinoatrial node action potential, resulting in heart rate slowdown usage ivabradine's effect on the HCN channel is rate making the medication more effective in people with dependent an increased heart rate [23]. Two significant multicenter investigations have shown the advantages of ivabradine as a supplement to recommended therapeutic options such b-blockers and angiotensin-enzyme inhibitors in people with left ventricular dysfunction (LV) having heart rates over 70 bpm and malfunction [24].

Cilostozol

Cilostazol is an antiplatelet agent that blocks phosphodiesterase-III, raises cellular levels of cyclic adenosine monophosphate (AMP), and activates protein kinase A [25]. The prevention of platelet aggregation and cilostazol-induced vessel dilatation are attributed to the enhanced amounts of cyclic AMP in platelets and vascular smooth muscle cells [26]. Currently, clostazol is therapeutically used to treat peripheral vascular disease, arterial disease [27,28] and ischemic stroke [29,30]. However, because peripheral arterial disease is frequently linked to coronary artery disease, [31,32] it is crucial to investigate if cilostazol is also a cardio protective. Ischaemic preconditioning is an innate cardio protective process, and its mechanism involves adenosine, [33] nitric oxide, and oxide (NO)[34] and the opening of mitochondrial KATP channels. It has been suggested that superoxide has a role in the heart's ischaemia-reperfusion injury [35].

Inamrinone

Inamrinone has a significant influence on the creation of novel cardiotonic agents and served as a major precursor to non-catechol and non-glycoside medicines. Inamirone's unexpected failure to help the chronic heart failure patients led to a significant paradigm change from inotropic to cardioprotective therapy and advancements in the field of pharmacotherapy for chronic heart failure [36].

Mechanism of Action of Ranolozine

Myocardial ischemia is characterised by decreased ATP fluxes and energy supplies, which affect the intracellular ion balance of cardiac myocytes. Increased persistent (late) sodium current has been theorised to contribute to disrupted ion homeostasis by increasing intracellular sodium concentration, which in turn causes intracellular cal-

cium to increase. Ranolazine, a brand-new anti-ischemia medication, works by inhibiting late sodium current specifically, which lessens salt excess and improves disrupted ion homeostasis. This is linked to a reduction in angina symptoms in individuals. Ranolazine was also found to have anti-arrhythmic properties. The importance of late sodium inhibition is reviewed in this article, and we also provide an overview of the most current findings from both basic and clinical research [37].

Current therapeutic strategies

The therapeutic goals of medical treatment for coronary heart disease can be divided into three categories [38-54], according to the 2006 European Society of Cardiology guidelines [54]:

a. Immediate short-term relief,

b. Treatment targeted at symptom relief, and

c. Treatment aims at improving prognosis.

With the exception of -blockers after myocardial infarction, it's interesting to note that there is no overlap between medications that enhance prognosis and those that reduce symptoms. This implies that mechanisms influencing thrombocyte function and anti-inflammatory or cytokine-neurohumoral effects may be advantageous for survival, whereas ischemia, which causes symptoms, may not be a primary mechanism relevant to prognosis. In order to address the imbalance between the heart's oxygen supply and demand, which is relevant to myocardial ischemia and angina pectoris, current drug-induced symptom relief treatments try to reduce symptoms [54]. The oxygen demand of the myocardium is decreased by all of the substances in this category: -blockers, calcium channel antagonists, nitrates, K-channel openers, and sinus node inhibitors. This can happen directly by affecting the myocardium or indirectly by having complex impacts on factors that determine hemodynamics [51]. Nitrates, K-channel openers, and calcium channel antagonists can all help the heart's blood flow and oxygen delivery. Ranolazine (Figure 1), a piperazine derivative, is a new anti-ischemic drug for the treatment of angina, whose mode of action is different from the pharmacological principals mentioned above [40].

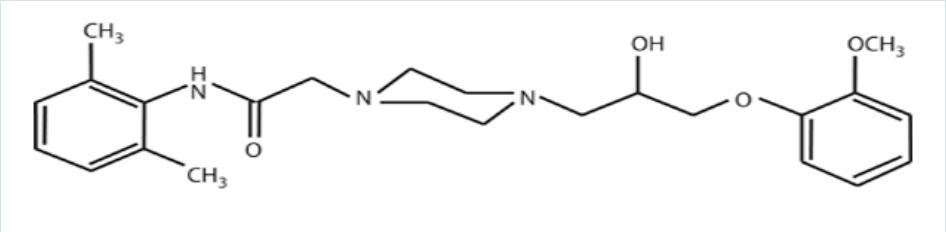

Figure 1: Structure of Ranolazine.

Pathophysiology of myocardial ischemia relevant to action of ranolazine

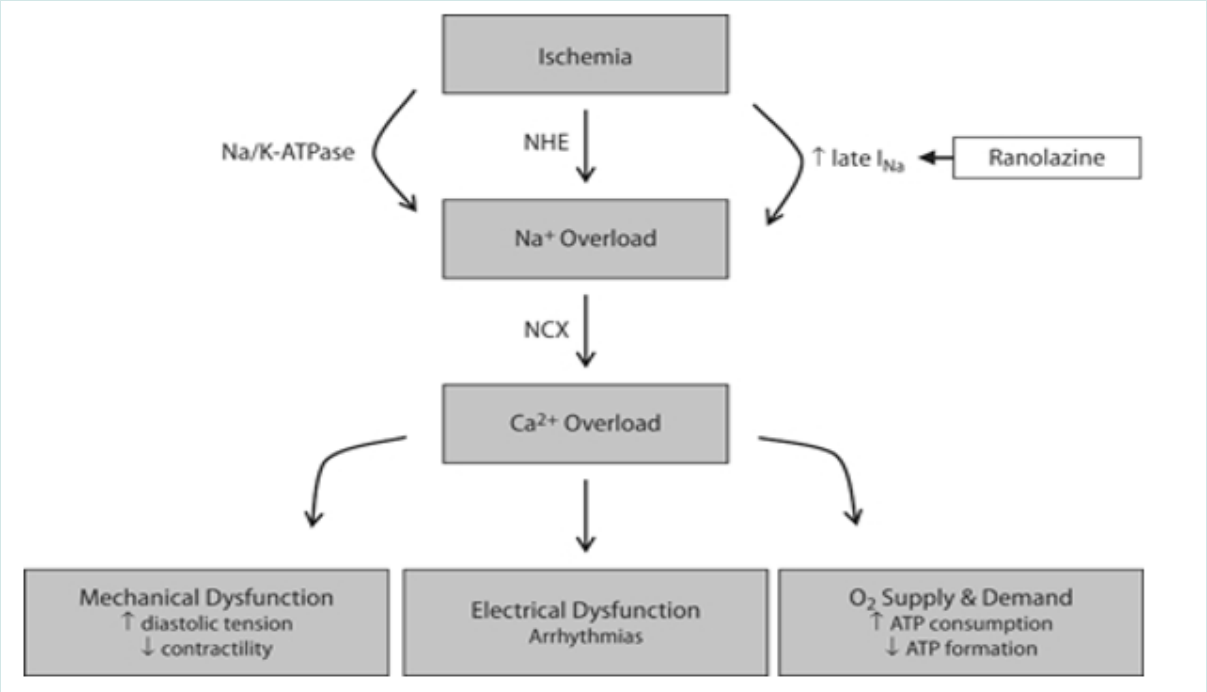

Figure 2: Scheme for the pathophysiology of myocardial ischemia and the role of late INa inhibition with Ranolazine.

Reduced ATP fluxes and decreased energy supply to several essential proteins for the contraction-relaxation cycle of the individual cardiac myocyte are the immediate effects of myocardial ischemia. These include the proteins that manage the homeostasis of myocyte ions. As a result, the concentrations of intracellular sodium and calcium are disrupted, which is important for the myocardial injury that results from ischemia. Energy deficiency raises intracellular sodium through a number of methods (Figure 2). Sodium enters the cell primarily through the cardiac sodium channel after depolarization during the action potential's fast upstroke phase. This additional fast depolarization brought on by the sodium influx results in the activation of voltage-gated L-type calcium channels, which then results in the influx of calcium. Within one to three milliseconds, sodium channels spontaneously deactivate. The following membrane depolarization has the potential to activate channels that recycle [45]. This usual rapid sodium current has been found to be susceptible to changes under pathological circumstances such hypoxia, exposure to ischemia metabolites, and reactive oxygen species [46-69]. When this occurs, the sodium channel opens distinctly up to a few hundred milliseconds after depolarization, and this phenomenon is known as late (or persistent) sodium current (late INa, Figure 3) [52,66-69]. During ischemia, a significant portion of the increased intracellular sodium may come from late INa. Sodium inflow via the sodium-proton pump [44] or a lack of sodium removal via the sodium potassium ATPase are two other mechanisms causing an abnormal sodium balance.

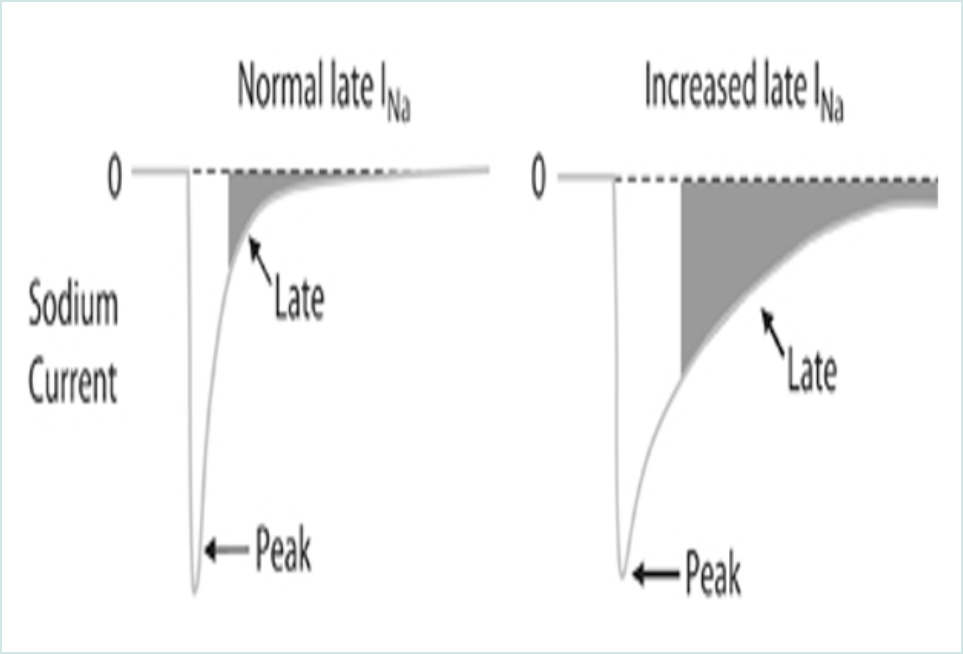

Figure 3: Late INa under normal and increased late INa under pathophysiological conditions.

Lack of energy causes the phosphorylation potential to drop, which reduces the free energy available for calcium transport into the sarcoplasmic reticulum. As a result, intracellular calcium builds up in the cytosol. Due to the activation of contractile proteins even during diastole caused by high diastolic calcium levels, diastolic dysfunction results. Elevated intracellular sodium significantly worsens disturbed sarcoplasmic reticulum calcium buildup. One calcium ion is exchanged for three sodium ions during each cycle of the sarcolemmal sodium-calcium exchanger. There are two ways the sodium-calcium exchanger might function. To achieve diastolic relaxation, it removes calcium from the cell when in the forward mode (in addition to calcium reuptake into the sarcoplasmic reticulum). In its reverse mode, it delivers calcium into the cell in return for transsarcolemmal sodium removal (often during the action potential). The protein concentration, membrane potential, intracellular sodium, and intracellular calcium concentrations all affect the activity and direction of transport. Following cardiac hypoxia, sodium buildup (via late INa) encourages reverse mode sodium-calcium exchange, which lowers the capacity of the cell as a whole to remove calcium from the extracellular space. This worsens diastolic dysfunction brought on by contractile protein activation and increases the increased diastolic calcium caused by decreased sarcoplasmic reticulum calcium pump functioning. Energy expenditure increases when contractile proteins are activated during diastole [55]. Additionally, increasing diastolic tone worsens the ischemic myocardium's energy balance by raising microcirculatory resistance. As a result, diastolic dysfunction after myocardial ischemia leads to an increase in energy consumption and an aggravation of the disrupted energy balance. Ranolazine has been shown to be a potent inhibitor of late INa and therefore interrupts a major step in the pathophysiology of myocardial ischemia [48].

Ranolazine has been demonstrated to suppress late INa in myocytes from the hearts of dogs and guinea pigs in a concentration, voltage, and frequency-dependent manner [48]. Ranolazine has also been demonstrated to stop H2O2 from increasing late INa [63]. In particu-

lar, ranolazine has been demonstrated to reverse the steady increase in diastolic and systolic calcium brought on by the sea anemone toxin ATX-II, a well-known activator of late INa [47 64]. Ranolazine's primary method of action is to inhibit late INa, preventing sodium overload of the cell as a result. As a result, ranolazine blocks reverse mode sodium-calcium exchange and subsequently diastolic calcium buildup, which may enhance diastolic tone [50,65] and coronary blood flow [47]. Ranolazine has therefore been demonstrated to lessen post-ischemic contracture inn rabbit isolated perfused hearts subjected to ischemia and reperfusion [48]. As a late INa inhibitor, ranolazine was also shown to increase action potential duration and thus modestly QT interval by 2–5 ms [42,43]. This effect, however, is not heart rate-dependent and cannot be exaggerated during bradycardia [39,57-70]. Furthermore, ranolazine does not induce early after depolarisations and does not increase dispersion of repolarisation across the left ventricular wall [71-82]. According to this profile ranolazine does not increase the risk of Torsade de pointes tachycardia as it is observed with many other QT interval prolonging agents.

Clinical effects of Ranolazine

Several clinical trials have been conducted so far to study ranolazine. The effectiveness of quick release ranolazine has been studied in three preliminary trials [46,58,61]. Sustained release ranolazine's effectiveness in treating patients with chronic stable angina has been investigated in two bigger phase 3 studies. In MARISA (Monotherapy Assessment of Ranolazine In Stable Angina), 191 patients were randomly assigned to receive ranolazine or a placebo in a cross-over design for a one-week treatment period [43]. Patients were assigned at random in the CARISA (Combination Assessment of Ranolazine in Stable Angina) study to receive placebo or ranolazine in addition to prior anti-anginal medication. For 12 weeks, the treatment was continued [42]. In individuals with stable angina, ranolazine monotherapy dramatically enhanced exercise performance, according to MARISA. This held true for the length of the workout, the elapsed time before angina, and the interval between each event. More particular, only 52% of patients in the ranolazine group discontinued their activity test because to angina, compared to 70% of patients in the placebo group who did so (1.5 g bidaily). Time to angina, peak and trough exercise duration, and time to 1 mm ST depression all improved with CARISA. A 12-week treatment period resulted in these effects remaining. Additionally, ranolazine (1 g bidaily) decreased the frequency of angina events from a baseline of 4.5 per week to 2.1 per week compared to 3.3 per week for placebo. Most notably, there were no clinically significant changes in blood pressure or heart rate as a result of ranolazine's anti-anginal effects in MARISA and CARISA. The impact of ranolazine medication on patients with acute coronary syndromes was investigated in the MERLIN (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST elevation Acute Coronary Syndrome) TIMI-36 trial [18]. A total of 6560 patients with non-ST elevation ACS who were receiving standard therapy participated in the multi-national, double-blind, randomised, placebo-controlled, parallel-group clinical trial known as MERLIN to assess the effectiveness and safety of ranolazine during acute and long-term treatment.

Eligible hospitalised patients were entered in the study within 48 hours of the onset of angina caused by ACS and randomly assigned to receive intravenous ranolazine or a placebo, followed by long-term treatment with ranolazine tablets or a placebo. Despite the fact that ranolazine had no discernible effect on the primary composite endpoint of cardiovascular death, myocardial infarction, or recurrent ischemia, subsequent studies have shown 13% relative reduction in the risk of recurrent ischemia. Ranolazine also had positive safety endpoint results. Ranolazine may have possible antiarrhythmic properties, in particular [62]. The results of the trial support this [41]. Ranolazine is hence safe for use in inhibiting late INa, especially in terms of electrophysiological characteristics. The findings of MERLIN support prior findings regarding the safety and benefit of ranolazine as an antianginal therapy and suggest a benefit of ranolazine as an antianginal therapy in a large population of patients with established ischemic heart disease, despite the fact that the results do not support its use for the acute management of ACS.

Future aspects for clinical application of Ranolazine

Ranolazine's ability to inhibit elevated late INa may offer a fresh approach to treating cardiac conditions characterised by altered myocardial ion homeostasis. Elevated intracellular sodium has been seen in various animal failure models as well as in human heart failure [53, 59]. Recent research has demonstrated that higher intracellular sodium levels in heart failure may, in part, be caused by CaMKII-dependent phosphorylation of sodium channels, which leads to an increase in late INa [67]. Therefore, by restoring disrupted sodium homeostasis, ranolazine may be a promising treatment for systolic heart failure. A significant pathophysiological component in diastolic heart failure may potentially be calcium excess following disrupted sodium homeostasis [68]. Therefore, we hypothesise that ranolazine may be a novel, alluring therapy option in diastolic heart failure caused by disrupted sodium/calcium homeostasis. To investigate the potential therapeutic efficacy of ranolazine, investigations in heart failure with systolic and diastolic dysfunction are therefore necessary [69].

Mechanism of Action of Ivabradine

Ivabradine's therapeutic application has developed and is still developing along lines based on its mode of action. It works differently from other negative chronotropic drugs in that it specifically suppresses the funny current (If) in sinoatrial nodal tissue, which lowers the rate of diastolic depolarization and, as a result, the heart rate. As a result, it has been examined and is used in a small number of patients with chronic stable angina and systolic heart failure without causing clinically significant side effects. Even though it hasn't been approved for other uses, ivabradine has showed potential in the treatment of unneeded sinus tachycardia. In this article, the writers discuss the ivabradine mechanism of action and significant studies that helped to determine its current therapeutic applications. Based on regional regulatory approval, the indications for the use of ivabradine have changed over time in different ways (Figure 1).

Expectations for its potential influence in cardiovascular medicine were high because it is a rare pharmacological agent that may

precisely lower heart rate without causing the adverse effects associated with other similar drugs. This medication has been investigated as a treatment agent for problems in all 3 major fields of cardiology in numerous small and big trials (i.e., coronary artery disease, heart failure [HF], and electrophysiology). We intend to present a succinct and concentrated assessment of the pharmacological features of ivabradine in this review, followed by a review of much significant research that have contributed to its current clinical use. Ivabradine's indications for use have changed throughout time and depend on the region (Figure 4). The results of several randomised controlled trials since it was first approved by the European Medicines Agency (EMA) for use in angina in 2005 have led to expanded indications to include specific heart failure patients and only recent approval by the U.S. Food and Drug Administration (FDA) for this indication. BEAUTIFUL = Morbidity-Mortality Assessment of Ivabradine, an If Inhibitor, in Patients With Coronary Disease and Left Ventricular Dysfunction; Heart failure with reduced ejection fraction (HFrEF), left ventricular ejection fraction (LVEF), myocardial infarction (MI), coronary artery disease (CAD), normal sinus rhythm (NSR), and cardiovascular disease (CV) are all abbreviations for the same condition. Systolic Heart Failure Treatment with the Ivabradine Trial (SHIFT); SIGNIFY = Study Assessing the Morbidity-Mortality Benefits of the If Inhibitor Ivabradine in Patients With Coronary Artery Disease [70].

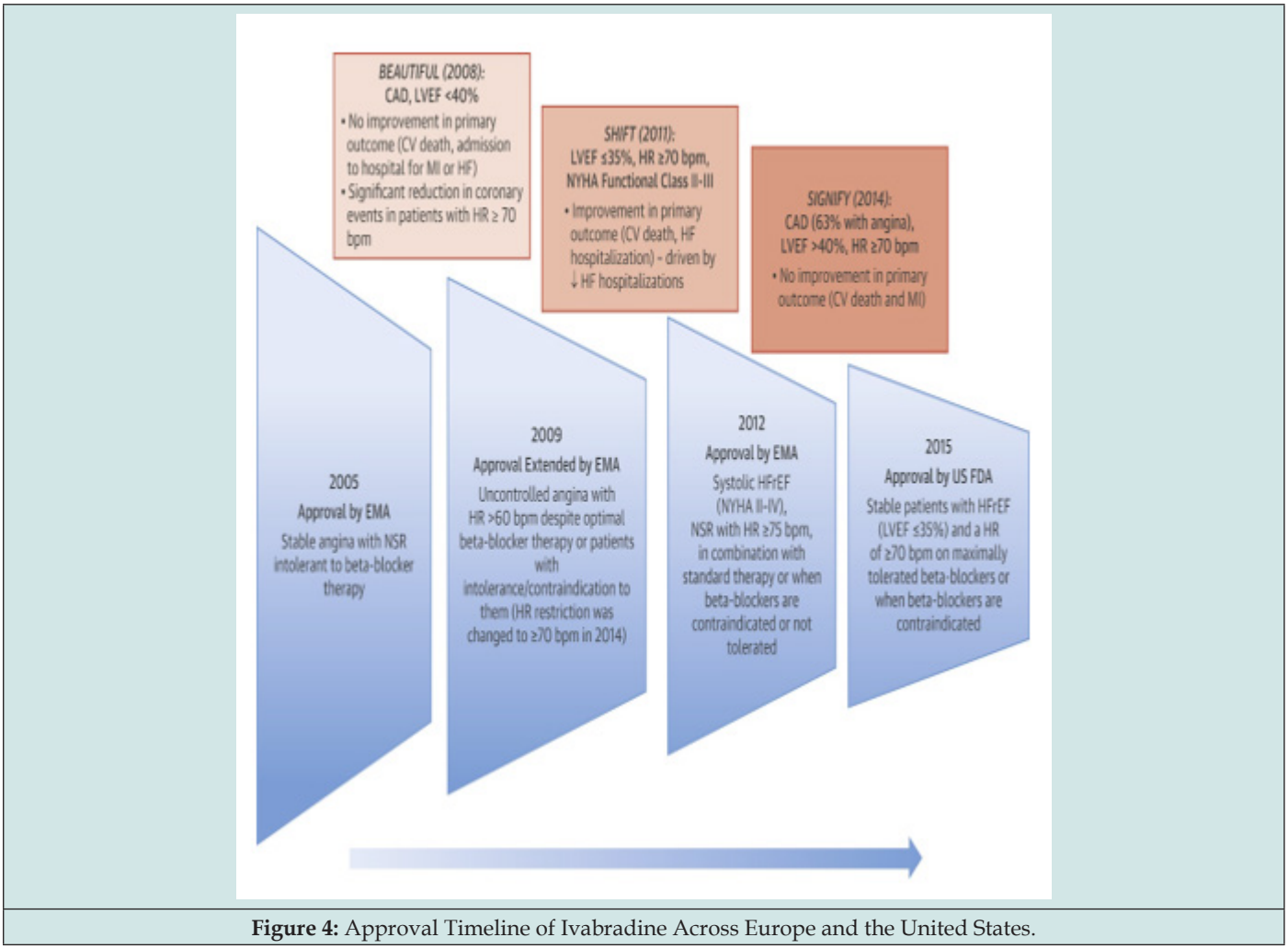

Figure 4: Approval Timeline of Ivabradine Across Europe and the United States.

The sinoatrial node is distinct in that it is driven toward the threshold required for spontaneous depolarization by the natural ability of its cells to produce a cyclical shift in their resting membrane potential. Its automaticity is explained by the recurrent, spontaneous action potentials that are produced as a result of this depolarization. This depolarization is brought on by the activation of certain ion channels that carry the pacemaker or "funny" current, a slow, inward-depolarizing mixed sodium-potassium current (If).[71] is produced via a nonselective, hyperpolarization-activated cyclic nucleotide-gated transmembrane channel (Central Illustration). Ivabradine inhibits cation flow with a high degree of selectivity, blocking the intracellular portion of this transmembrane channel. This slows the heart rhythm by lowering the slope of the diastolic depolarization of the pacemaker action potential. Ivabradine blocks the channel in its open state, resulting in the use dependence—a very positive quality (i.e., it becomes more potent at faster heart rates). Ivabradine lowers heart rate in a

dose-dependent manner without influencing cardiac inotropy or systemic vascular resistance as a result of its unique mechanism of action [72,73].

a) The sinoatrial (SA) node, located at the intersection of the right atrium and superior vena cava (SVC), is the site of ivabradine's main mode of action on cardiac tissue (RA).

b) Ivabradine inhibits the open state of the intracellular portion of the hyperpolarization-activated cyclic nucleotide-gated (HCN) transmembrane channel in the sinoatrial node, which is in charge of transporting sodium (Na+) and potassium (K+) ions across the cell membrane.

c) As a result, the inward funny current (If), which is only triggered at membrane potentials that are too hyperpolarized, is inhibited.

d) By specifically inhibiting If, it is possible to lengthen diastole and decrease the slope of the pacemaker action potential's diastolic depolarization (shaded region) without changing the action potential's other phases. Reduced heart rate is the outcome of this. IVC is for inferior vena cava, PA stands for pulmonary artery, and RV stands for right ventricle.

Clinical use in Electrophysiological Disorders (Inappropriate Sinus Tachycardia)

The most common use of ivabradine in electrophysiology is to treat improper sinus tachycardia (IST) [74]. It is commonly acknowledged that this illness is a challenging condition to adequately treat. Beta-blockers and non-dihydropyridine calcium-channel antagonists commonly cause negative effects and only seldom relieve symptoms. Ivabradine may be useful in IST, according to various case reports and short nonrandomized studies [75,76]. There is just one tiny randomised, double-blind, placebo-controlled, crossover experiment [77]. Ivabradine was connected to significant decreases in heart rate at rest (12 beats/min), after standing (16 beats/min), over the 24-hour period (11 beats/min), and during exercise (18 beats/min) in 21 patients. In comparison to placebo, ivabradine generally reduced symptoms by more than 70%. There were several noteworthy findings, including the following:

a. Subjects with completely resolved symptoms did not show a greater reduction in heart rate compared to those with partially resolved symptoms; [78]

b. Symptoms were not always resolved despite similar reductions in heart rate; and

c. Side effects were less frequently reported when compared to other trials.

Further randomised investigations are necessary despite the fact that this study showed short-term efficacy in IST. Ivabradine was given a Class IIa recommendation for the treatment of symptoms in the 2015 Heart Rhythm Society expert consensus statement due to the limited quantity and high quality of the data supporting it for IST . It should be emphasised that the use of ivabradine for IST is not an EMA/FDA-approved indication [79]. The potential effectiveness of ivabradine in treating postural orthostatic tachycardia syndrome, sinus tachycardia observed after ablation of atrioventricular nodal re-entrant tachycardia, and refractory junction ectopic tachycardia is only partially supported by the available data, [80-83].

Mechanism of Action of Cilostozol

A phosphodiesterase III (PDE3) inhibitor is clostazol. PDE3s are enzymes that break down cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate using a catalytic core (cAMP). [84] In order to control the contractility of arteries and veins' smooth muscle and the cardiac sarcoplasmic reticulum, respectively, phosphodiesterase III enzymes are largely found in these tissues. Cilostazol works by preventing phosphodiesterase activity and preventing the breakdown of cAMP. A increase in cAMP in platelets and blood arteries is made possible by the inhibition of PDE3. Protein kinase A (PKA) in its active state is directly linked to the suppression of platelet aggregation, and increased PKA is a direct result of higher cAMP concentrations [85]. By inhibiting contraction by inactivating myosin light-chain kinase, increased intracellular PKA concentrations also have a vasodilatory impact on smooth muscle cells [86]. In the presence of calcium and calmodulin, myosin light-chain kinase usually phosphorylates the myosin light chain, activating myosin to bind with actin. Myosin-actin contact is prevented by PKA's inactivation of myosin light-chain kinase, which prevents the production of a smooth muscle contraction [87]. Cilostazol has also recently been shown to raise HDL cholesterol levels and lower plasma triglyceride levels [88]. Although the precise processes of how cilostazol lowers plasma triglycerides and raises HDL levels are currently unknown, its effects on lipoproteins are probably due to its suppression of cyclic nucleotide phosphodiesterase and precipitous increase in intracellular cAMP. There are currently a number of hypothesised ways by which elevated cAMP could lead to decreased plasma triglycerides. One explanation is that the improved ability of glucagon to decrease VLDL secretion has the potential to reduce hepatic triglyceride output (directly or indirectly) [89]. As an alternative, elevated cAMP intracellular concentrations are shown to encourage the release of lipoprotein lipase from rat adipocytes, which may similarly result in decreased plasma triglycerides [90].

Mechanism of Action of Inamrinone

A phosphodiesterase-III (PD3) inhibitor is inamrinone. Cyclic adenosine monophosphate (cAMP) hydrolysis is reduced when normal phosphodiesterase-III activity is inhibited, which raises the intracellular quantities of cAMP [91,92]. It is still unclear exactly how this increased bioavailability of cyclic adenosine monophosphate raises cardiac output. In cardiac myocytes, an increase in cyclic adenosine monophosphate concentration may lead to an upregulation of the calcium/cyclic adenosine monophosphate/protein kinase A pathway [93]. Increased calcium cycling is caused by this pathway's elevated activity acting on particular cellular channels. It increases the action potential of the heart muscle and causes an influx of calcium into the cardiac myocyte [94,95]. In the end, this makes the heart more capable of contracting. The increased bioavailability of cyclic adenosine monophosphate caused by inamrinone across the vascular network

has the opposite effect on the mechanisms of action in the myocardium (Figure 5). In fact, a decrease in the intracellular calcium concentration results from an increase in cyclic adenosine phosphate within the vascular smooth muscle, which relaxes the smooth muscle [96]. Preload and afterload are decreased as a result of this systemic vasodilation, which also lowers total peripheral and pulmonary vascular resistance [97]. Increased pulse and stroke volume are the results of the subsequent relative ease of blood flow across the vascular network. These vasodilatory and beneficial inotropic effects are crucial for treating the potentially fatal heart failure symptoms.

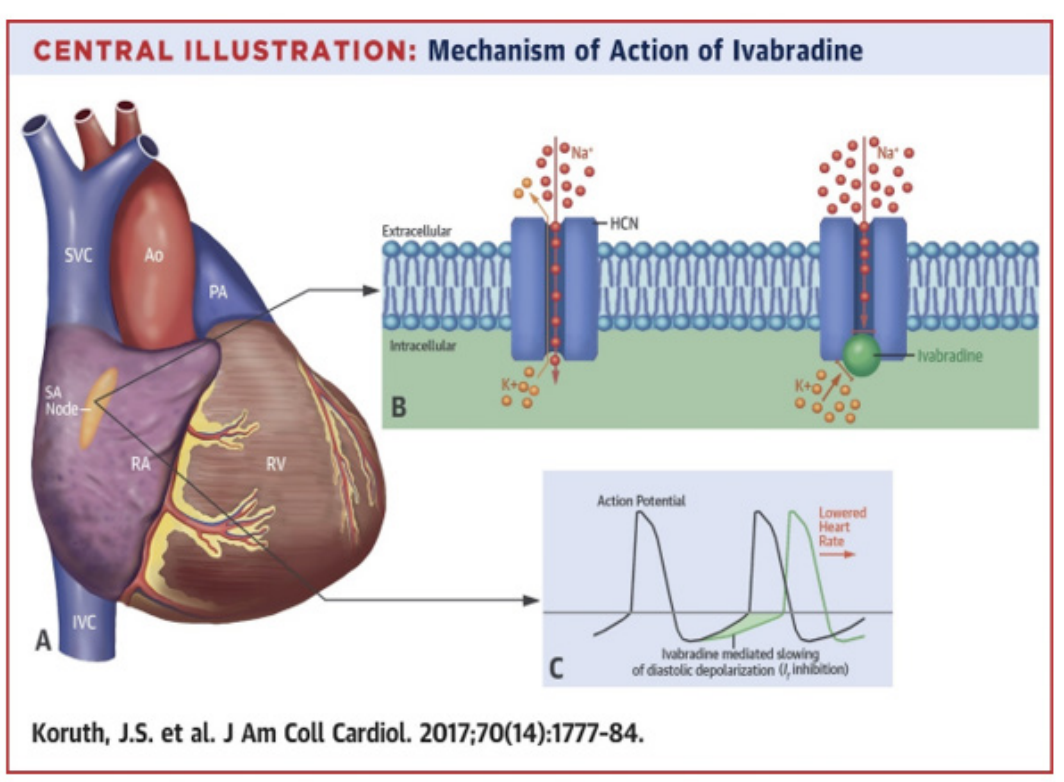

Figure 5: Central illustration of Ivabradine.

Contraindications

a) Patients who are known to be hypersensitive to inamrinone should not take the medication, according to the FDA.

b) The FDA lists providing inamrinone as a contraindication if the patient has a known hypersensitivity to bisulfites because the medication contains sodium metabisulfite.

c) In addition, doctors shouldn't administer inamrinone to anyone who have aortic or pulmonary valvular disease.

d) If the patient is taking disopyramide, it should be given with caution because the two medications have the potential to cause severe hypotension [98].

Enhancing Health Care Team Outcomes

Significant side effects are linked to using inamrinone. However, when digoxin, diuretics, and/or vasodilators are unable to increase cardiac output, inamrinone is an effective short-term therapy option. It is crucial that the medical team keep an eye out for any side effects of inamrinone and report any abnormalities in electrolytes, renal function, hepatic function, blood pressure, heart rate, or ECG. If the platelet count falls to less than 150,000 cells/mm3, doctors must use even greater caution. To enhance patient outcomes, nursing personnel should make sure that inamrinone is only used temporarily while closely monitoring any negative effects. Reconciliation of prescriptions should be done by pharmacists, who should also alert the prescriber if there are any possible drug interactions (Figure 6). An interprofessional team approach is necessary for inamrinone therapy, which includes cardiologists, doctors, nurses with specialised training, physician assistants, and pharmacists all collaborating across disciplines to achieve optimal patient outcomes [98].

Discussion

Only when used during ischemia does ranolazine demonstrate positive benefits in cardiomyocytes subjected to ischemia/reperfusion. Its enhancement of calcium management during ischemia helps provide this effect. Myocardium is adversely affected by increased HR. Although beta-blockers are useful for lowering HR, many patients also benefit from other treatments that can lower HR. Additionally, some patients may not be able to use beta-blockers because of a contraindication or intolerance. Beta-blockers have the potential to lower hospital stays and significantly enhance quality of life in HF patients. According to several studies, ivabradine is a desirable, efficient, and

secure option for HF patients. Ivabradine reduces HR in a manner akin to that of beta-blockers. When combined with other antianginal medications like beta-blockers, ivabradine has added advantages (except diltiazem and verapamil). Ivabradine is significantly beneficial when added to beta-blocker therapy in symptomatic patients. The only medication that has so far been shown to consistently treat IC patients in clinical studies is cilostazol. Cilostazol has also been demonstrated to have pleotropic effects in addition to limb-specific outcomes; however, clinical trials are required to confirm these effects. The effects of cilostazol and inamrinone supervised exercise training in individuals with IC to either therapy alone need to be studied as well.

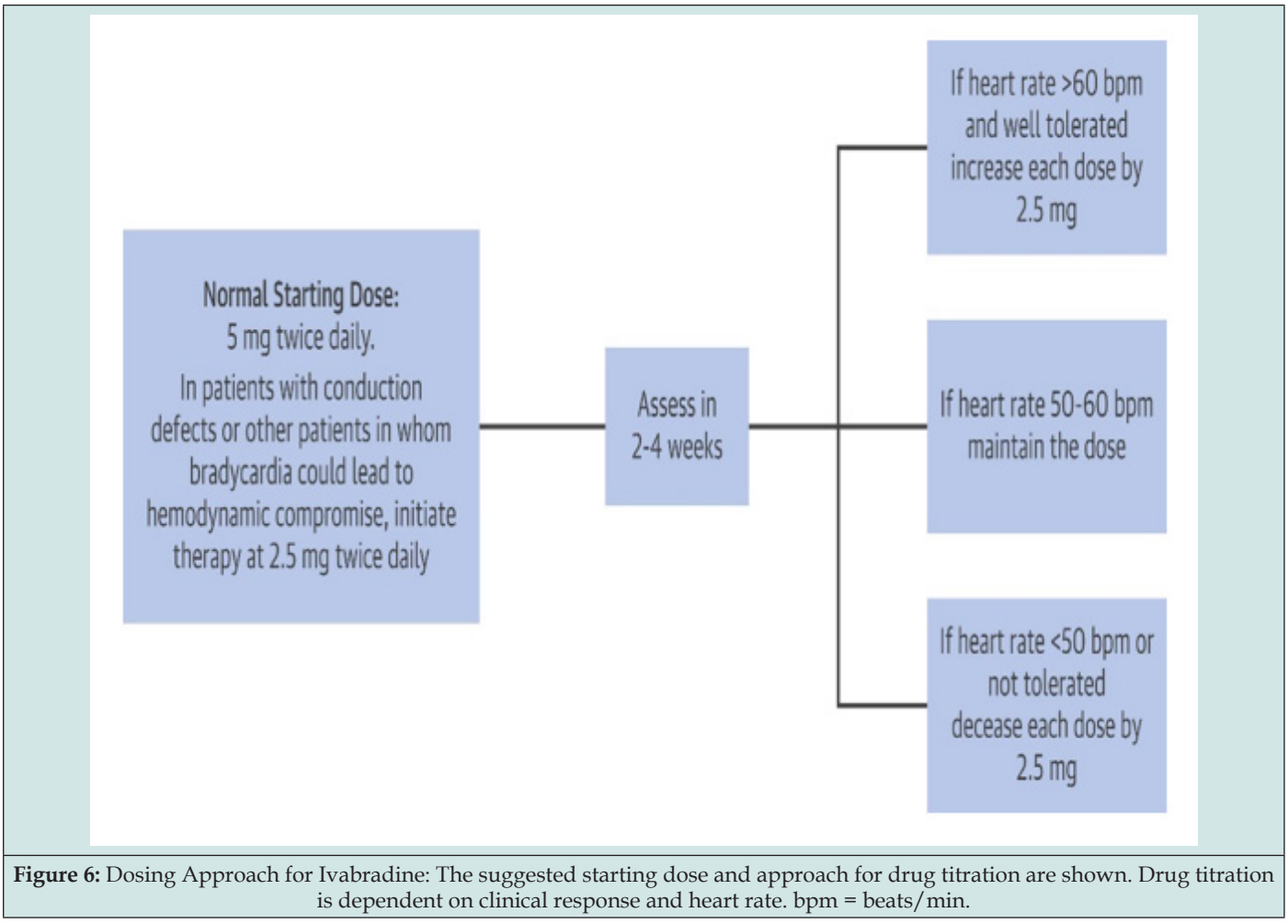

Figure 6: Dosing Approach for Ivabradine: The suggested starting dose and approach for drug titration are shown. Drug titration is dependent on clinical response and heart rate. bpm = beats/min.

Conclusion

As per above review on elucidation and possible mechanism of action of cardio protective drugs viz. Ranolazine, Ivabradine, Cilostazol and Inamrinone in Ischemic Reperfusion induced cardiac injury has been demonastrated but mechanism of action already established are not sufficient to which biological mediators like nitric oxide, bradykinin, K+ATPase channels, serotoninergic pathway, adenosine may be involved in mechanism of action of above said drugs in detail has not been elucidated yet. These mechanisms are of prime importance because ischemic preconditioning involves cardio protection by above said biological mediators. Full mechanism of action of above four drugs are essential in cardioprotective effect in ischemia reperfusion injury model. These mediators are essential to elucidate cardio protection of above said drugs which leads to new drug discovery of cardioprotective drugs.

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