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1.3 Current view on cardiocytoprotection - ranolazine, changes in classification and precision approach to prescribing

A precision approach in cardiology, in line with modern management and therapeutic perspectives, should be examined using the example of ranolazine, a drug belonging to the group of late sodium current inhibitors. It has been included in the updated classification of antiarrhythmic drugs [38] for the creation of the novel Class Id [39]. The earlier approach considered ranolazine a piperazine derivative with a molecular structure similar to lidocaine—thus classified as a Class IB antiarrhythmic agent according to E. Vaughan Williams' classification.

Although the drug does not belong to classical pFOX (partial fatty acid oxidation) inhibitors, which aim to reduce fatty acid oxidation in the myocardium to increase glucose utilization efficiency for energy production—thereby reducing oxygen consumption by the heart and improving its function under ischemic conditions—ranolazine instead enhances the metabolic efficiency of the myocardium through a different mechanism. It inhibits the late sodium current, reducing intracellular calcium accumulation and positively affecting the heart’s energy balance.

Representatives of pFOX inhibitors include: Trimetazidine (used for treating angina, it improves myocardial energy balance by reducing ischemic stress), Perhexiline (used for treating angina and heart failure but may have side effects, limiting its application), Etomoxir (a carnitine palmitoyltransferase I (CPT-I) inhibitor that also affects fatty acid oxidation, mainly used in experimental studies), Mildronate/Meldonium (though not a classical pFOX inhibitor, its action is also directed at modifying myocardial metabolism, particularly by reducing fatty acid utilization).

The issue of cardioprotection—measures that prevent or mitigate heart damage regardless of the injurious stimulus—more specifically involves reducing the size of myocardial infarction (MI) and coronary microvascular obstruction by decreasing oxygen demand during heart contraction through hemodynamic manipulation (which

might be unsuccessful, as ischemic myocardium does not contract anyway). This includes the phenomenon of ischemic conditioning (activating self-defense mechanisms through short-term coronary occlusion and reperfusion, which themselves do not cause MI but protect against sustained myocardial ischemia with reperfusion, which leads to MI). Thus, cardioprotection achieved through ischemic conditioning includes: (1) activation of sarcolemmal receptors by neurohormones, autacoids, cytokines, and growth factors; (2) activation of intracellular enzymes (kinases) through the stimulation of these sarcolemmal receptors, as well as small molecules (calcium, nitric oxide, and hydrogen sulfide); (3) Effects of these pathways on mitochondria, where respiration is preserved, ROS (reactive oxygen species) production and mitochondrial permeability transition pore opening are reduced, thereby suppressing cell death activation. Ischemic conditioning can be activated before sustained ischemia (preconditioning), during early reperfusion (postconditioning), or through remote conditioning (ischemia/reperfusion in tissues distant from the heart) [40].

In this process, the main types of programmed cell death are involved [40]:

- type I cell death or apoptosis: Cytoplasmic shrinkage, chromatin condensation, nuclear fragmentation, and cell membrane “blebbing” (vesicle budding from the membrane)—the entire cell content disintegrates into vesicles (apoptotic bodies), which are phagocytosed by neighboring cells and broken down in their lysosomes;
- type II cell death or autophagy: In the cytoplasm of the dying cell, numerous vacuoles are formed, which are subsequently phagocytosed and destroyed by neighboring cells;
- type III cell death or necrosis: Characterized by a complete absence of features typical of apoptosis and autophagy. Residual material from the destroyed cell triggers inflammation.

Additionally, processes such as:

- necroptosis: Formation of intracellular complexes called “necrosomes,” triggered by death receptors (tumor necrosis factor receptor 1);

- pyroptosis: Release of cell contents outward, dependent on caspase-1, with interleukin IL-1β and IL-18 secretion leading to inflammation;
- ferroptosis: Iron-dependent lipid peroxidation

Is it time to recommend cardiovascular system protection for everyone? The known effects of basic medications require supplementation with cardiocytoprotection. Beyond the proven endothelial protective function and blood pressure (BP) reduction of β-blockers (nebivolol) through inhibition of NADPH oxidase activity, prevention of eNOS uncoupling, and promotion of eNOS activity to increase nitric oxide (NO) production (with impacts on antioxidant properties and improved endothelium-dependent vasodilation), calcium channel blockers (CCBs), particularly dihydropyridines, reduce ROS production to protect the endothelium. These help prevent LDL oxidation, increase antioxidants, and reduce oxidative damage during endothelial dysfunction. Furthermore, groups of medications like ACE inhibitors, ARBs, CCBs, and vitamin C are potential therapeutic strategies for oxidative stress processes, while statins exhibit a mild antihypertensive effect through vascular endothelium by inhibiting ROS production, reducing circulating pro-inflammatory cytokines, and suppressing the expression of adhesion molecules in vascular endothelial and smooth muscle cells [41].

The concept of cellular health under ischemic conditions, within the framework of cardiocytoprotection and endothelial dysfunction, determines the potential to influence the likelihood of atherosclerotic damage. It encompasses effects on obesity, hypertension, dyslipidemia, hyperglycemia, platelet hyperactivity, and endothelial dysfunction, which are mediated through the imbalance of nitric oxide (NO), prostacyclin (PGI2), and the loss of regulation of endothelium-dependent hyperpolarization (EDH). This includes the influence of thromboxane A2 (TxA2) and the upregulation of endothelin-1 (ET-1), subsequently affecting pro-inflammatory and oxidative stress through the formation of reactive oxygen species (ROS) in endothelial mitochondria, vascular growth and remodeling stimulation, platelet activation, NO depletion, increased ROS production, and impacts on vasoconstriction mediators [42].

Ranolazine, an inhibitor of late inward sodium current, enhances myocyte relaxation and ventricular compliance by reducing intracellular calcium. It improves angina symptoms and myocardial perfusion reserve in myocardial viability assessment (MVA) and significantly reduced coronary flow reserve (CFR) due to impaired vasodilation [43].

In the CorMicA randomized controlled trial (Coronary Microvascular Angina), under the baseline therapy of aspirin, statin, and ACE inhibitors for all, another important area of ranolazine use has been identified in stratified medical therapy. This involves invasive coronary function testing, evidence-based treatment, and prognosis of INOCA (Ischemia with Non-Obstructive Coronary Arteries).

Thus, for confirmed microvascular angina via invasive testing:

- first-line treatment: β-blockers;
- second-line treatment: Replacement with non-dihydropyridine calcium channel blockers (CCBs);
- third-line treatment: Addition of amlodipine (if on β-blockers), nicorandil, or ranolazine.

For confirmed vasospastic angina:

- first-line treatment: Dihydropyridine CCBs;
- second-line treatment: Addition of isosorbide dinitrate;
- third-line treatment: Replacement of nitrates with nicorandil.

For a combination of microvascular angina and vasospastic angina:

- first-line treatment: Dihydropyridine CCBs;
- second-line treatment: Nicorandil нікорандил [44].

Thus, for patients with the vasomotor endotype of INOCA (epicardial or microvascular spasm), the recommended treatments are calcium channel blockers (CCBs), nitrates, nicorandil, or their combination. Meanwhile, for patients with the structural endotype of INOCA (microvascular dysfunction), it is recommended to use drugs that reduce myocardial oxygen consumption (β-blockers or CCBs, with

ivabradine also being a potential option) along with other agents (ranolazine, trimetazidine, and nicorandil) [45].

From the perspective of evidence-based medicine, ranolazine has a high level of evidence in the latest recommendations for chronic coronary syndrome (CCS). It is stated that the use of long-acting nitrates or ranolazine should be considered as additional therapy for patients with inadequate symptom control during treatment with β-blockers and/or calcium channel blockers (CCBs), or as part of initial treatment for appropriately selected patients [IIa B], particularly emphasizing its role in the treatment of obstructive coronary artery disease and microvascular dysfunction [46].

In the recommendations for the treatment of heart failure with reduced ejection fraction (HFrEF) in the context of chronic coronary syndrome (CCS), it is established that β-blockers are the cornerstone therapy for HFrEF and ischemic heart disease (IHD) due to their prognostic benefits. Ivabradine should be considered as an alternative to β-blockers (in cases of contraindications) or as additional antianginal therapy for a heart rate ≥70 bpm. Other antianginal agents (amlodipine, felodipine, nicorandil, ranolazine, and oral or transdermal nitrates) are effective for symptom relief, although evidence of their impact on outcomes is neutral or lacking. Trimetazidine appears to have additive effects, such as improving left ventricular function and exercise capacity in patients with HFrEF and CCS who are already on β-blockers [47].

In the context of heart failure with preserved ejection fraction (HFpEF) and ischemic heart disease (IHD), nitrates are used (although routine use of nitrates for the treatment of HFpEF is not recommended based on the results of the NEAT-HFpEF randomized controlled trial regarding activity/tolerance). Dihydropyridine calcium channel blockers (CCBs) may be beneficial if there is a concurrent need to manage hypertension, and ranolazine can be used when limited by heart rate (HR) and blood pressure (BP) [48].

In the ESC guidelines for managing patients with ventricular arrhythmias in the prevention of sudden cardiac death, the antiarrhythmic role of ranolazine is considered through its ECG effects, including a reduction in sinoatrial node rate and QT interval prolongation. It is indicated for the treatment of ventricular rhythm disorders, such as

ventricular tachycardia (LQTS3), at doses ranging from 750 to 2000 mg, with an evaluation of potential adverse effects, both cardiac (sinus bradycardia, hypotension) and extracardiac (dizziness, nausea, constipation, gastrointestinal disturbances, headache, rash). Contraindications include severe dysfunction of the sinoatrial node, significant heart failure, and LQTS except for LQTS3. Precautions must also be considered, such as concomitant treatments associated with QT interval prolongation [49].

Regarding atrial fibrillation (AF), a meta-analysis of 8 randomized controlled trials (RCTs) indicated that ranolazine significantly reduced the incidence of AF compared to the control group in various clinical scenarios (after cardiac surgery, in acute coronary syndrome (ACS), and following electrical cardioversion of AF). The relative risk (RR) was 0.67 ($p = 0.002$). Moreover, a higher conversion rate of AF was demonstrated with the combined use of ranolazine and amiodarone compared to amiodarone monotherapy (RR = 1.23; $p = 0.002$), with the conversion time being significantly shorter in the ranolazine and amiodarone group compared to the amiodarone group (weighted mean difference [WMD] = –10.38 hours; $p = 0.009$) [50]. At the meeting of the Expert Council of the Association of Arrhythmologists of Ukraine on October 5-6, 2022, it was established that long-term use of ranolazine for angina reduces the risk of atrial fibrillation (AF). However, the combination of ranolazine with other Class IA and III antiarrhythmic agents (except amiodarone) is prohibited.

Regarding acute coronary syndrome (ACS), the RIMINI randomized controlled trial (Effect of Ranolazine on Ischemic Myocardium IN Patients With Acute Cardiac Ischemia) should be mentioned. In this study, ranolazine reduced the risk of recurrent ischemia and worsening angina in ACS (non-STEMI) patients, possibly by improving myocardial perfusion, reducing the area of ischemic myocardium in ACS patients, and optimizing contractility as assessed by speckle-tracking echocardiography [51].

In the MERLIN-TIMI 36 randomized controlled trial (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes), ranolazine impacted the primary endpoint [a combination of cardiovascular death,

myocardial infarction (MI), or recurrent ischemia] with a hazard ratio (HR) of 0.92 (p = 0.11) and the secondary endpoint with an HR of 0.96 (p = 0.50). In the context of diabetes mellitus (DM), the results were positively influenced by ranolazine, with a reduction in recurrent ischemia (hazard ratio [HR], 0.87; p = 0.03). In the context of ischemia, the results of the RAND-CFR randomized controlled trial should be mentioned. Ranolazine reduced T-wave heterogeneity (TWH), a marker of arrhythmogenic repolarization abnormalities predictive of sudden cardiac death (SCD), at rest compared to placebo. Ranolazine lowered arrhythmogenesis in ischemia independently of coronary artery blood flow [52].

In the context of STEMI, ranolazine has optimized markers of myocardial electrical instability and ischemia according to its own studies. The EQ-VAS analog scale indicates a positive effect of ranolazine on the quality of life of patients with STEMI, with reductions in heart rate (HR), QT interval dispersion, and an increase in the peak velocity ratio (PVR) based on differentiated ECG. It also lowered the probability of recording reduced heart rate variability (HRV) as measured by SDNN (Standard Deviation of NN intervals), which reflects good autonomic nervous system function and high HRV—an indicator of good physical condition and the body's ability to adapt to stress [53].

As a result of the analysis of ranolazine use according to a study conducted by the Department of Internal Medicine, Physical Rehabilitation, and Sports Medicine of Bukovinian State Medical University [54, c. 18], in patients with chronic coronary syndrome (CCS, angina) comparing three groups—baseline medical therapy (BMT: antiplatelets, β-blockers, nitrates, statins) with the addition of lercanidipine and enalapril in the composition of the "polypill" drug vs. BMT plus lercanidipine and enalapril in the "polypill" drug and ranolazine vs. BMT plus ramipril and ranolazine—and in acute coronary syndrome (STEMI) comparing two groups (BMT vs. BMT and ranolazine), optimization of clinical and diagnostic indicators for both angina and STEMI was observed in the groups with the addition of ranolazine.

In all groups for chronic coronary syndrome (CCS), an improvement in quality of life was observed according to the EQ-VAS scale, along with a reduction in the peak

velocity ratio (PVR) in differentiated ECG lead V2. This marker is used to assess hypertrophic changes in the left ventricle (LV) as determined by the differentiation of digitized ECG data. A decrease in this parameter indicates a reduction in hypertrophic modifications of the LV (in both cases, $p<0.05$), as illustrated in Figure 1.

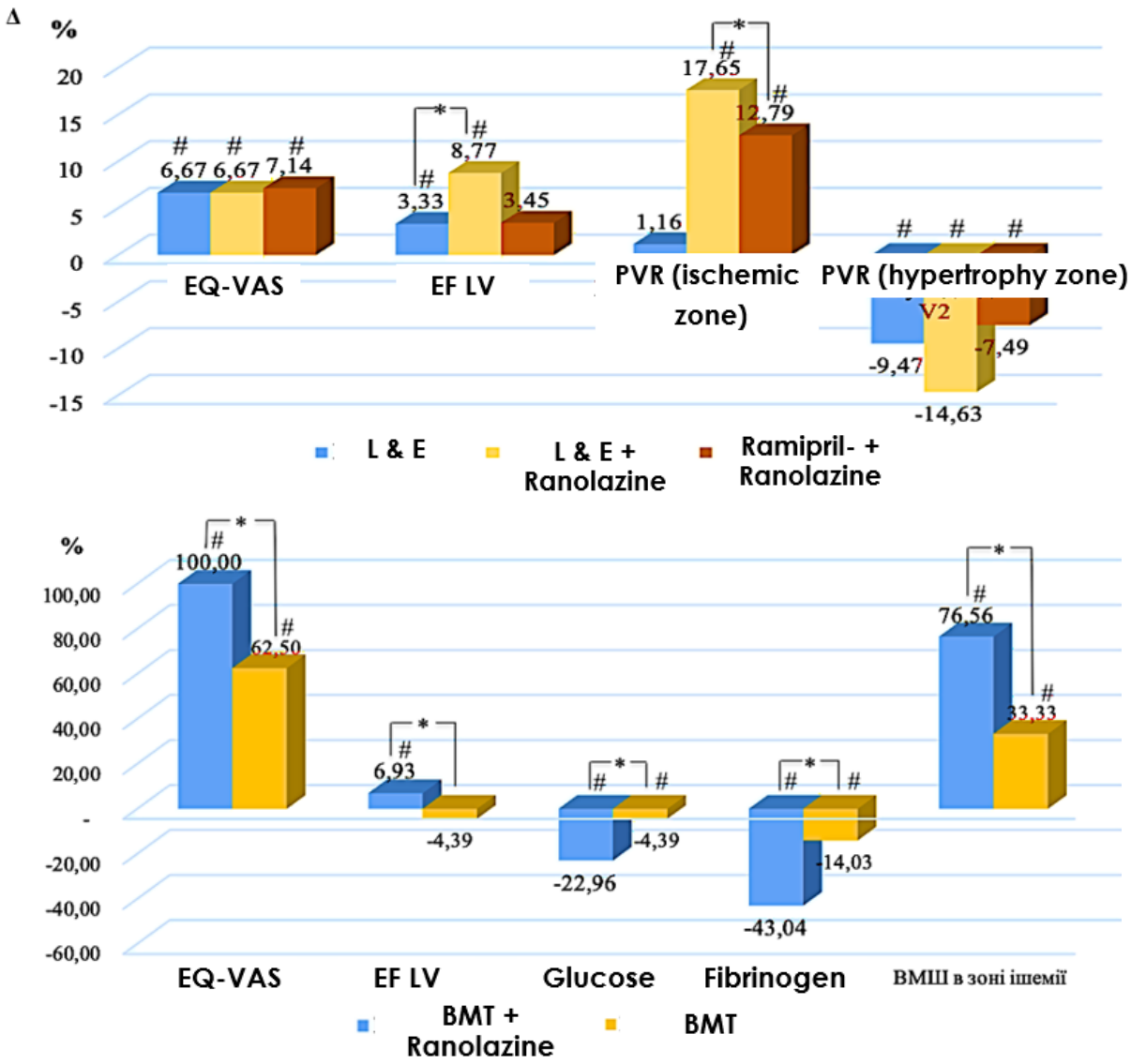

Figure 1. Dynamics of clinical and diagnostic indicators for stable angina and STEMI in groups with the addition of ranolazine compared to baseline medical therapy (BMT), including the analysis of ramipril, lercanidipine, and enalapril as part of the "polypill" drug. The focus is on improvements in quality of life (EQ-VAS), contractility (LVEF), the peak velocity ratio (PVR) in differentiated ECG in the ischemic zone and lead V2, and an analysis of LV hypertrophy based on the treatment received.

The most optimal therapy for chronic coronary syndrome (CCS) was identified as the inclusion of lercanidipine and enalapril in the composition of the "polypill" drug, alongside ranolazine in baseline medical therapy (BMT). This was evidenced by an increase in left ventricular ejection fraction (LVEF) (Δ +8.77%, $p<0.001$) and the most effective rise in peak velocity ratio (PVR) in the ischemic zone (Δ +17.65%, $p<0.001$), corresponding to a reduction in electrical instability of the ischemic myocardium.

The addition of ranolazine to baseline medical therapy (BMT) in patients with STEMI improved quality of life according to the EQ-VAS scale ($p<0.001$), reduced fibrinogen levels ($p<0.05$), optimized glucometabolic homeostasis through a decrease in glucose levels ($p<0.05$), enhanced myocardial contractility with an increase in LVEF (Δ +6.93%; $p<0.001$), and significantly raised the peak velocity ratio (PVR) in the ischemic zone (Δ +75.56%; $p<0.001$). These outcomes describe the positive impact on stabilizing electrogenesis during primary changes in the repolarization phase (illustrated in Figure 1).

According to recommendations for the comprehensive management of patients with diabetes mellitus and ischemic heart disease (IHD), optimization of myocardial oxygen supply can be achieved through long-acting nitrates or calcium channel blockers (CCBs) or by reducing oxygen demand using β-blockers, non-dihydropyridine CCBs, ranolazine, or ivabradine. Thus, ranolazine, which reduces myocardial ischemia at the cellular level, also has a unique effect of normalizing glycated hemoglobin, particularly in patients with poor metabolic control [56].

In the guidelines for cardiomyopathies, it is noted that for chest pain during exertion in patients without obstruction of the left ventricular (LV) outflow tract, ranolazine may be considered to improve symptoms in patients with angina-like chest pain, even in the absence of cardiovascular insufficiency or obstructive ischemic heart disease (IHD) [IIb C]. Regarding antiarrhythmic therapy for patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), there is strong evidence for the use of β-blockers [I C], amiodarone [IIa C], flecainide after β-blockers [IIa C], and catheter ablation [IIa C]. The experience with other antiarrhythmic agents (dofetilide,

ranolazine) is mentioned, although it is limited due to the small number of randomized controlled trials (RCTs) [57].

In conclusion, it should be noted that the key messages and critical approach of the ESC 2024 recommendations on chronic coronary syndrome (CCS), compared to previous guidelines, emphasize a shift. Previously, nicorandil, ranolazine, ivabradine, and trimetazidine were considered second-line agents, recommended only after β-blockers, calcium channel blockers (CCBs), and long-acting nitrates had been tried or excluded due to intolerance or contraindications. In contrast, the new guidelines highlight the lack of studies confirming the superiority of any one antianginal drug over others. They propose considering long-acting nitrates and ranolazine as additional therapy for patients with inadequate symptom control on β-blockers and/or CCBs, or even as part of the initial treatment in selected patients [58].

Ranolazine (500 mg twice daily) or placebo, in combination with optimal medical therapy, reduces the phenomenon of slow coronary blood flow after two months. This is accompanied by improvements in quality of life according to the EuroQol-VAS questionnaire ($p = .013$), reduction in physical limitations ($p = .041$), improvements in stable angina ($p = .016$) and its frequency of occurrence ($p = .042$), as well as increased satisfaction with treatment ($p = .037$) in the ranolazine group [59].

Patients with coronary microvascular dysfunction have an increased risk of developing heart failure with preserved ejection fraction (HFpEF). Ranolazine treatment improves the myocardial perfusion reserve index (ΔMPRI, $r = 0.26$, $p = 0.04$) but does not affect the Seattle Angina Questionnaire (ΔSAQ, $r = 0.03$, $p = 0.80$) or NT-proBNP levels [60]. Evidence supports the beneficial effects of renin-angiotensin-aldosterone system blockers, ranolazine, and sodium-glucose cotransporter-2 inhibitors (and potentially anti-inflammatory agents in the future) for coronary microvascular dysfunction [61].