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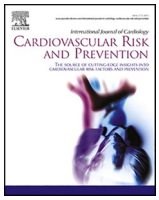

Ranolazine - could an antianginal drug be used in stroke prevention?

1. Atrial fibrillation - epidemiology and clinical significance

Atrial fibrillation (AF) is the most common arrhythmia in the world. The incidence of AF is increasing from year to year. In Europe, in 2010, it occurred in approximately 9 million people aged 55 and over [1]. It is estimated that in 2060 the number of patients with AF in Europe will reach 17.9 million [2].

Prevention of AF is critically important because AF is one of the most powerful causal risk factors for stroke. A recent meta-analysis of 16 clinical trials by Yang et al. including 53,141 subjects showed that patients with AF burden >5 min had an significant increased risk of stroke (RR = 2.49; 95% CI: 1.79–3.47) [3]. Apart from the negative influence on the risk of stroke occurrence, AF ucreases the risk of other conditions (Table 1).

Following the diagnosis of AF, due to its negative impact on human health, appropriate treatment should be implemented.

2. Ranolazine - mechanism of action

Ranolazine is an inhibitor of the fast Na^+ current (I_{NaF} - fast inactivating, Na^+ current) and the late Na^+ current (I_{NaL} - late inactivating, Na^+ current), which is responsible for depolarization of the myocardial cell. The effects of ranolazine are mainly related to the influence on Na^+ - I_{NaL} late current [7].

I_{NaL} current activation is induced by "acquired" pathological conditions such as: ischaemia, myocardial infarction, left ventricular hypertrophy, heart failure with preserved and impaired ejection fraction, as well as atrial fibrillation. It is also activated in genetically determined diseases: LQTS (types 3, 9, 10) and Brugada syndrome [8].

The effect of I_{NaL} activation is the accumulation of Na^+ ions inside the cell, which in turn leads to increased activity of the sodium-calcium exchanger (NCX) and secondary accumulation of Ca^{2+} ions. Intracellular excess of Ca^{2+} contributes to contractile dysfunction of the heart muscle (excessive activation of myofilaments) and its electrical instability (time extension the duration of the action potential with the early ones and late subsequent depolarizations). Ranolazine therefore counteracts this phenomenon increasing the level of inactivated channels I_{NaL}. Reducing the concentration of Na^+ decreases the intracellular concentration Ca^{2+} ion, which improves the intracellular ion balance [9].

It is very important that ranolazine inhibits both sodium currents (I_{NaL} and I_{NaF}), and has an influence on electrophysiological phenomena in the cells of the atria and ventricles. The late current inhibition dominates – ranolazine works stronger (40–60x) on I_{NaL} »> I_{NaF} which at therapeutic doses (2 × 500 mg; 2 × 1000 mg) inhibits I_{NaL} without significant effect on I_{NaF}, which conditions the correct behavior excitability and conduction of myocardial cells. Moreover, braking power I_{NaF} sodium current is much greater in cells of the atria than in the cells of the ventricles [7]. Therefore, the inhibitory effect of ranolazine on the ion channels that determine its electrophysiology in the atria and ventricles can be ranked as follows:

→ atrial myocytes: I_{NaL} »> I_{NaF} »> I_{Kr}
→ ventricular myocytes: I_{NaL} »> I_{Kr} [7]

Ranolazine inhibits cellular (repolarizing) currents - responsible for the transport of K^+ ions It inhibits the potassium channels: I_{Kr} and I_{Ks} – present in both atrial and ventricular cells. The I_{Kr} current can be considered pro-arrhythmic (elongating the duration of the action potential, QT prolongation), hence its inhibition may have clinical significance [7].

The effect of ranolazine on calcium channels is small. Ranolazine weakly inhibits L-type channels calcium (I_{CaL}) in atrial and ventricles cells [7].

In summary, ranolazine through inhibition ion channels, mainly sodium and to a lesser degree potassium, reduces the amount of Na^+ and secondarily intracellular Ca^{2+}, which reduces excitability, the number of follow-up potentials, reduces the reentry phenomenon and positively modifies other electrophysiological parameters - which may be important for the reduction of arrhythmia [7]. The ranolazine mechanism of action is summarized in Fig. 1.

It should also be mentioned that ranolazine, in addition to acting on the heart muscle, affects the vascular system, skeletal muscles, blood sugar control, and cancer [10].

3. Ranolazine as an antiarrhythmic drug – data from clinical studies

Ranolazine was first used as an antianginal drug. Information regarding its antiarrhythmic properties emerged from the MERLIN-TIMI36 study [11]. In a group of 6560 patients with acute coronary syndrome without ST segment elevation in whom ranolazine was started and the ambulatory ECG was monitored to assess ischemic changes, a significant reduction in arrhythmias including AF and ventricular tachycardia was observed. After a year of follow-up in patients treated

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Table 1
Different complications of atrial fibrillation.

Atrial fibrillation	Influence of atrial fibrillation on risk of: **Worse prognosis in COVID-19: ↑ 14%** (OR = 1.14; 95% CI: 1.03–1.26) **All-cause mortality in COVID-19: ↑ 297%** (OR = 3.97; 95% CI: 2.76–5.71) **Peripheral arterial disease: ↑ 31%** (RR = 1.31; 95% CI: 1.19–1.45) **All-cause mortality: ↑ 46%** (RR = 1.46; 95% CI: 1.39–1.53) **Ischaemic heart disease: ↑ 61%** (RR = 1.61; 95% CI: 1.38–1.87) **Chronic kidney disease: ↑ 64%** (RR = 1.64; 95% CI: 1.41–1.91) **Sudden cardiac death: ↑ 88%** (RR = 1.88; 95% CI: 1.36–2.60) **Major cardiovascular events: ↑ 96%** (RR = 1.96; 95% CI: 1.53–2.51) **Cardiovascular mortality: ↑ 103%** (RR = 2.03; 95% CI: 1.79–2.30) **Stroke: ↑ 149%** (RR = 2.49; 95% CI: 1.79–3.47) **Heart failure: ↑ 399%** (RR = 4.99; 95% CI: 3.04–8.22)	Bibliography [4,5] [3,6]

with ranolazine, paroxysmal AF occurred significantly less frequently (4.4% *versus* 16.1%, p = 0.010) [11].

A meta-analysis by Li et al. of five randomized clinical trials assessed the efficacy of ranolazine as monotherapy in the treatment of AF. Ranolazine was shown to significantly reduce the risk of developing AF by 34% (OR = 0.66; 95% CI: 0.50–0.87). Subgroup analysis showed that ranolazine had the greatest reduction in the risk of AF in patients following cardiac surgery (OR = 0.33; 95% CI: 0.13–0.79). The meta-analysis also showed that the antiarrhythmic efficacy of ranolazine was dose-dependent (dose ≤500 mg/day - insignificant antiarrhythmic effect; dose >500 mg/day - significant antiarrhythmic effect) [12]. Another meta-analysis by Gong et al. also assessed the antiarrhythmic efficacy of ranolazine. Eight randomized clinical trials were included in the meta-analysis. Ranolazine was shown to significantly reduce by 33% (RR = 0.67; 95% CI: 0.52–0.87) the risk of AF in patients after cardiac surgery, in acute coronary syndromes, and post-electrical cardioversion of AF. Moreover, ranolazine was shown to increase the antiarrhythmic effect of amiodarone by 23% (RR = 1.23; 95% CI: 1.08–1.40). The conversion time of AF in patients taking ranolazine + amiodarone was 10 hours shorter (WMD = −10.38; 95% CI: 18.18 to −2.57) than in those taking amiodarone alone. This effect was dependent on the dose of ranolazine [13]. A meta-analysis of the results of five clinical trials conducted by Leelapatan et al. summarized the knowledge about the effectiveness of ranolazine in the prevention and treatment of AF in patients with left ventricular systolic dysfunction. It was shown that the addition of ranolazine to amiodarone led to significantly increased restoration of sinus rhythm compared to amiodarone alone (RR = 2.87, 95% CI: 2.48–3.32). The combination of amiodarone and ranolazine also resulted in a 2.46 hour reduction (95% CI: 2.27–2.64) time to sinus rhythm restoration [14].

Moreover, studies showed a benefit of combining ranolazine with dronedarone for anti-arthythmic treatment [15]. The randomized clinical trial HARMONY evaluated the effectiveness of midrange ranolazine (750 mg BID) combined with two low doses of dronedarone (150 mg BID and 225 mg BID; chosen to reduce dronedarone's negative inotropic effect-see text below) over 12 weeks in 134 patients with paroxysmal AF and implanted pacemakers where AF burden (AFB) could be continuously assessed. Ranolazine 750 mg BID + dronedarone 225 mg BID reduced AFB by 59% *versus* placebo (p = 0.008), whereas ranolazine 750 mg BID + dronedarone 150 mg BID reduced AFB by 43% (p = 0.072) [16].

Ranolazine, apart from its high antiarrhythmic effectiveness, is characterized by high safety of use. The safety of ranolazine was assessed in a meta-analysis by Guerra et al. including eight randomized clinical trials and two observational studies. It was shown that ranolazine did not significantly affect the risk of: death (OR = 0.99; 95% CI: 0.78–1.25), QTc prolongation (SMD = 0.11; 95% CI: −0.79 to 1.01) and hypotension (OR = 1.59; 95% CI: 0.86–2.94) [17].

Thus, ranolazine has documented anti-arrhythmic activity and a satisfactory safety profile.

Based on all the data summarized above and on evidence obtained from the HARMONY trial, ranolazine appears to significantly decrease the rate of AF in a variety of clinical settings. Thus, the drug could have potential to prevent strokes, independently from antithrombotic medication use. The new critical question emerges: could this drug be used in stroke prevention not only in angina treatment?

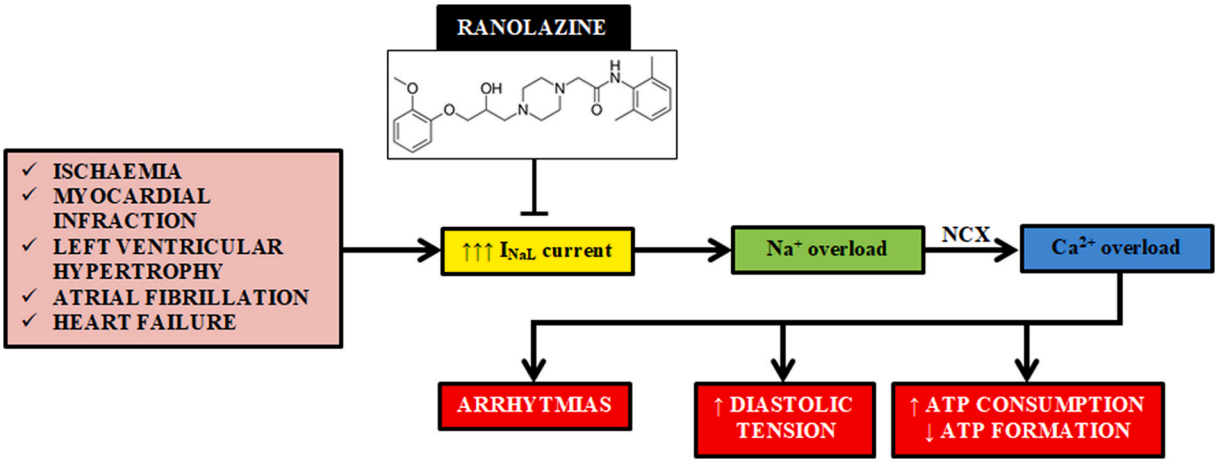

Fig. 1. Ranolazine – mechanism of action. NCX – sodium-calcium exchanger; I_{NaL} - late inactivating, Na^+ current; ATP - adenosine triphosphate.

Declaration of competing interest

None.

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