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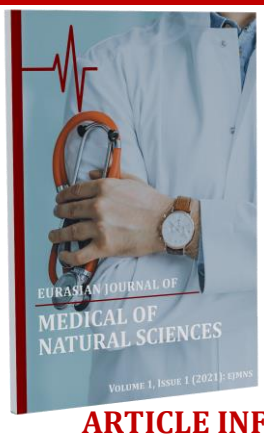

MODERN DRUGS AFFECTING LIPID METABOLISM IN ISCHEMIC HEART DISEASE

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ABSTRACT

Stable ischaemic heart disease is a frequent and very heterogeneous condition. Drug therapy is important, in these patients, for improving their prognosis and controlling their symptoms. The typical clinical manifestation of obstructive coronary disease is angina pectoris. This symptom can be improved by various classes of compounds, namely beta-blockers (BBs), calcium antagonist, and nitrates. More recently, ranolazine and ivabradine have been introduced. All these drugs have been proven to reduce significantly angina. On the other hand, there are no evidences supporting improvement in prognosis, besides for the use of BBs, in patients with previous myocardial infarction (MI) or systolic dysfunction. Besides drugs for symptoms control, these patients also receive antiplatelet drugs, specifically aspirin, and lipid lowering compounds such as statins.

Coronary artery disease (CAD) is one of the main causes of morbidity and mortality in the world.1 Coronary artery disease is a condition characterized by a clinical continuum consisting of stable ischaemic heart disease (SIHD) ranging from asymptomatic patients with subclinical or non-obstructive CAD to those who have obstructive CAD without obvious angina (often referred to as 'silent myocardial ischaemia') with or without previous myocardial infarction (MI), passing through the classical group suffering from chronic stable angina and finally to patients with rapid deterioration or progressive angina that culminate in acute coronary syndrome (ACS). In a nutshell, SIHD can be defined as documentation of ischaemic heart disease in the absence of recent acute events; typically the interval of time free from acute events is considered to be 12 months.[1] The pathophysiology of cardiac ischaemia involves the presence of fibrotic and often calcific atherosclerosis (with a low tendency to rupture) which limits blood flow within a coronary artery causing a discrepancy between the demand and supply of oxygen to the myocardium. This occurs in particular at the increase in heart rate and wall stress of the left ventricle; less frequent alternative mechanisms of

ischaemia are plaque spasm and microvascular dysfunction.

Chronic angina therapy includes drugs that slow the progression of the disease and reduce cardiovascular events (ASA, statins) and drugs that improve symptoms and therefore the quality of life. With regard to the latter, there is clear scientific evidence of the effectiveness in reducing angina, while the data related to the reduction of 'hard' clinical endpoints (mortality, need for revascularization interventions, and MI) are much less solid. For this reason, the definition of optimal medical therapy in SIHD is not of univocal interpretation and presents substantial differences even among the clinical researches that have studied this pathology.[2] In this work, we will analyse the state of the art in the pharmacological treatment of stable CAD.

Beta-adrenergic antagonists, or beta-blockers (BBs), are the most commonly used drugs for the treatment of angina. The BBs exert their anti-angina action by blocking the β1 adrenergic receptor and thereby reducing heart rate, myocardial contractility, left ventricular wall tension, and blood pressure. By reducing the heart rate, the duration of diastole increases, thus improving coronary perfusion. The above mechanisms improve the balance between oxygen supply and demand and increase the threshold of appearance of angina. Beta-blockers improve prognosis, in addition to anti-angina symptoms, in patients with a history of MI or left ventricular dysfunction. The American and European guidelines for the management of SIHD, published respectively in 2012 and 2013, recognize the importance of this class of drugs and recommend their use on the front line for the treatment of angina, even in patients without history of MI or left ventricular dysfunction. However, in this latter population, there is no clear evidence of a prognostic benefit.

Historical randomized studies on BB in stable angina showed no improvement in survival: Pepine et al.9 analysed the issue in the ASIST study, a multicentre, randomized placebo-controlled trial involving patients with asymptomatic or minimally symptomatic ischaemia. Atenolol significantly reduced the primary composite endpoint (death, tachycardia/ventricular fibrillation resuscitation, hospitalization for unstable angina, non-fatal MI, and angina worsening). It should be noted that this result was mainly driven by the reduction in angina frequency, with no difference in mortality. In the TIBET trial, conducted by Dargie et al.,10 subjects with SIHD were randomized to atenolol, nifedipine or a combination of the two drugs. There were no significant differences in mortality or other endpoints (non-fatal MI, need for surgical revascularization, or coronary angioplasty) among the three treatment regimens. Rehnqvist et al.11 conducted the APSIS study in which, in patients with SIHD, the effects of metoprolol vs. verapamil were compared regarding mortality: no differences were found in cardiovascular mortality and for all causes.

A meta-analysis performed by Shu et al. on BB in patients with SIHD found no mortality benefit in patients with or without previous MI. Furthermore, an observational analysis from the REACH registry did not document a survival benefit of BB in patients with SIHD and without previous MI. In contrast, BB therapy was associated with adverse effects and a non-significant increase in hospitalization rates.

Nitrates. Organic nitrates are among the oldest drugs used in the treatment of angina. Nitrates increase the distribution of nitric oxide to vascular smooth muscle, resulting in decreased calcium entry into cells and increased levels of cyclic guanosine monophosphate, thus causing vasodilation. Nitrates mainly cause veno-dilatation, leading to a decrease in preload and a decrease in systolic and diastolic pressure of the left ventricle, thus reducing the stress of the left ventricular wall and myocardial oxygen consumption. Furthermore, nitrates cause coronary vasodilation, leading to redistribution of blood flow to the ischaemic myocardium.

Like calcium channel blockers (CAs) and BBs, nitrates are quite effective in improving angina symptoms. However, their most noteworthy limitation with frequent use is the development of tachyphylaxis. This limitation has been addressed with the development of pharmaceutical preparations and dosage regimens that allow nitrate-free intervals of 8–10 h every day. There are several nitrate preparations for the treatment of angina. Quick-acting preparations such as sublingual nitrates or sprays are used for immediate relief from angina symptoms. Instead, long-term preparations such as isosorbide mononitrate or isosorbide dinitrate are frequently used for angina prophylaxis. Guidelines recommend the use of long-acting nitrates as second-line agents after BBs or when BBs are contraindicated.

Calcium channel blockers. Calcium channel blockers (CAs) work by blocking the L-type calcium receptor which leads to decreased calcium influx into the cell. The dihydopyridine CAs, traditionally represented by nifedipine, act mainly on the systemic and coronary vascularization to produce vasodilation with a consequent decrease in afterload. The peripheral effects (vasodilation) of the dihydropyridine group are more evident than the cardiac effects (negative chronotrope and negative dromotrope). In contrast, drugs of the non-dihydropyridine group, which includes diltiazem and verapamil, produce a more pronounced negative inotropic and negative chronotropic effect and less intense systemic vasodilation.

In terms of anti-angina efficacy, numerous studies over the last few decades have clearly identified calcium channel blockers (dihydropyridines and others) as an effective therapy for reducing angina symptoms. Calcium channel blockers are currently recommended in angina as second-line therapy after BBs, along with nitrates. In particular, CAs remain the therapy of choice for patients with coronary vasospasm or Prinzmetal angina. In the age of statins, the number of high-quality studies examining the role of CA on long-term prognosis is very low.

The randomized ACTION study examined the use of long-acting nifedipine in patients with known CAD by comparing it with placebo. The study dispelled concerns about the increased mortality from reflex tachycardia associated with long-term use of dihydropyridine agents. No reduction in mortality with the use of nifedipine was also observed. Importantly, 80% of patients in both arms of the study took BBs and 50% nitrates, which could explain the lack of benefit with nifedipine.

Subsequently, a meta-analysis from Bangalore et al. examining 15 trials (including the ACTION) compared dihydropyridine agents and non-dihydropyridine agents. This meta-analysis also did not show a mortality benefit with

chronic CA, while documenting a good safety of this class of drugs.

Other drugs. Trimetazidine increases cellular tolerance to ischaemia by inhibiting the metabolism of fatty acids and secondly, by stimulating glucose metabolism. A meta-analysis of studies showed that trimetazidine is effective in reducing the occurrence of stress-induced ischaemia at electrocardiogram. Trimetazidine is recommended as a second-line agent by European guidelines, while it is not recommended in the USA.

Nicorandil exerts its anti-angina effect by vasodilation: the drug stimulates the potassium channels. This drug, like trimetazidine, is recognized by European guidelines.

Medicines used during the acute phase are: Acetylsalicylic acid (aspirin): stops the platelets from aggregating and sticking together inside the artery and therefore reduces the chance of thrombus formation (stationary blood clots). It is the first drug that should be administered at the very onset of chest pain, even while at home.[3]

Other platelet aggregation inhibitors: these reinforce the action of acetylsalicylic acid as they also prevent platelet aggregation. The most common one is clopidogrel, but prasugrel and ticagrelor are also used in particularly severe cases.

Anticoagulants: by means of a different mechanism, these also aim to dissolve any thrombi (clots) inside the artery. Different types of heparin are used and may be administered by either intravenous or subcutaneous injections.

Beta-blockers: they work by slowing down the patient's heart rate so it is in a more restful state and demands less oxygen. They also reduce the risk of arrhythmias. Pain relieving medicines: in several cases patients may require morphine if the pain is very intense.

Nitroglycerine: can be administered as a tablet, sprayed underneath the tongue or by intravenous injections. It is used to dilate the heart's arteries allowing more blood to flow through them.

Thrombolytic or fibrinolytic agents. In cases where a thrombus is completely blocking an artery, these drugs can be administered in order to break the clot down and thin the blood. They are very powerful and only indicated in very specific cases; they are not administered very often, unlike other medicines used for ischaemic cardiomyopathy.[4]

Drug Therapy. Patients with Ischaemic Heart Disease must take a combination of drugs to reduce the heart's oxygen consumption, dilate the coronary arteries and prevent the formation of a new blockage.

Nitroglycerine and its derivatives (nitrates, either as tablets or transdermal patches): these drugs are known as vasodilators. They relax the arteries and veins, including the coronary vessels, thereby increasing blood flow in the affected area and eliminating chest pain from angina. They are also available as 'quick relief' tablets; patients with Ischaemic Heart Disease should carry 1 or 2 tablets in their pocket. Whenever the chest pain appears you should stop any physical activities, sit down and place a tablet under your tongue.[5] If the pain subsides in 10 minutes you can restart the activity, but remember to tell your doctor about the episode at your next appointment. By contrast, if the pain does not disappear you should take a second tablet. And if after this

the pain persists, then you must call the emergency medical services.

Beta-blockers (bisoprolol, carvedilol, nebivolol, metoprolol, atenolol, etc.): decrease blood pressure and heart rate, hence the heart requires less oxygen to function correctly. They can also reduce the risk of arrhythmias. Studies have shown that beta-blockers can increase the life expectancy of patients who have had an infarction.

Platelet aggregation inhibitors. Patients who have suffered any event brought on by atherosclerosis must take platelet aggregation inhibitors permanently, unless they are contraindicated. These drugs stop platelets from clumping together which has the effect of thinning the blood and reduces the risk of thrombus formation inside a coronary artery. Acetylsalicylic acid (aspirin) is the most common platelet inhibitor.

Statins. These drugs reduce blood cholesterol levels. They also help stabilise and prevent the rupture of atheromatous plaques, reduce blood vessel inflammation and decrease the likelihood of an infarction. Statins are therefore indicated in all patients with ischaemic cardiomyopathy, even if they have acceptable cholesterol levels.

Other anti-anginal agents are calcium channel blockers, relax the muscles of the coronary arteries and mitigate the effects of obstructions and spasms; ivabradine reduces heart rate and so the heart requires less oxygen and ranolazine acts on the primary and secondary blood vessels and decreases the risk of angina. This latter it is particularly effective in diabetic patients.[6]

Treatment is tailored to each patient; the drugs and doses may vary greatly from one person to the next. It is important that you know what treatment you are prescribed so you can inform the doctor if you are treated for Ischaemic Heart Disease.

Danqi Pill (DQP), which contains Chinese herbs Salvia miltiorrhiza Bunge and Panax notoginseng, is widely used in the treatment of myocardial ischemia (MI) in China. Its regulatory effects on MI-associated lipid metabolism disorders haven't been comprehensively studied so far. We aimed to systematically investigate the regulatory mechanism of DQP on myocardial ischemia-induced lipid metabolism disorders.

Coronary heart disease (CHD) is one of the major causes of death worldwide . CHD is the progress of the coronary arteries stenosis, usually caused by atherosclerosis, which is the buildup of cholesterol and fatty deposits on the inner walls of the arteries. The plaque formed in the artery could restrict blood flow to the heart muscles and cause myocardial ischemia. Lipid peroxidation induced by lipid infiltration is considered to be the main pathological mechanism of myocardial ischemia [4]. Some novel drugs targeting lipid metabolism have been developed to treat or reduce the risk of myocardial ischemia caused by CHD . Statins, which are HMG-CoA reductase inhibitors, are widely used for their cholesterol-lowering properties and have been proven to be able to reduce cardiovascular disease risk . Statins mainly reduce plasma levels of LDL, while having little effect on TG . Since 1970s, a number of herbal compounds have been developed to treat MI. Among them, Danshen and Sanqi

are the most frequently prescribed . [7]Because they have definitive curative effect and conform to pharmacopoeia standard of quality control (Ministry of Health of the People's Republic of China), Danqi Pill (DQP), which is composed of DanShen and Sanqi, was listed in Chinese Pharmacopoeia 2010 as routine drug in the clinical treatment of myocardial ischemia and impaired cardiac function. Danqi could also improve microcirculation by exerting anti-platelet aggregation effect . However, the effect of DQP on lipid metabolism signaling pathway hasn't been studied comprehensively so far. Our previous study demonstrated that DQP could improve heart function, partly via its regulation of ox-LDL and arachidonic acid metabolism .[8] In this study, we aim to investigate if DQP could regulate lipid metabolism and prevent fat deposition in artery, thus intervening the clinical course of MI in CHD.

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