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EDITORIAL

Refractory angina: new drugs on the block

Andreas A. Giannopoulos[a], George D. Giannoglou[a] and Yiannis S. Chatzizisis[b]

[a]First Department of Cardiology, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece; [b]Cardiovascular Division, University of Nebraska Medical Center, Omaha, NE, USA

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Refractory angina constitutes an advanced form of stable angina and refers to patients with symptomatic myocardial ischemia refractory to standard medical treatment. Surgical or percutaneous coronary revascularization is not considered a vital option for those patients due to the anatomical complexity of coronary artery disease (CAD) and/or pertinent comorbidities [1]. This subgroup of CAD patients represents a continuously growing population. Recent epidemiological data estimate that approximately up to 15% of the stable CAD population fall into this category [2,3]. Traditional treatment approaches include increasing coronary blood oxygen supply and decreasing oxygen consumption while novel new treatments target myocyte metabolism modulation and coronary flow redistribution. Current multidisciplinary management of refractory angina patients combines intensified traditional and newer medical agents with novel non-pharmacological interventional and non-interventional techniques [4]. These include among others, enhanced external counterpulsation, spinal cord stimulation, reduction of coronary sinus, gene therapy, and embolization/intermittent occlusion of internal thoracic arteries aiming to improve non-coronary collateral myocardial blood flow [4–6].

Pharmacotherapy constitutes the basis of refractory angina management [7]. While standard antianginal therapy, i.e. beta-blockers, calcium channel blockers, and nitrates, fails to provide adequate symptoms relief, a number of newer agents have emerged and are currently in use. Ivabradine, ranolazine, and trimetazidine are the most frequently utilized amongst the 'non-traditional' antianginal regimens. These agents target either well-established mechanisms of ischemia, i.e. the imbalance between myocardial oxygen supply/demand or metabolic routes in the ischemic myocardium promoting more efficient energy utilization. Their safety and efficacy have been evaluated in large clinical studies and some of those drugs have been already implemented in clinical practice guidelines of European and American cardiovascular societies for the treatment of patients with stable CAD [8,9].

1. Ivabradine: lowering heart rate

Elevated heart rate is independently implicated in coronary atherosclerosis and consequently in myocardial ischemia and angina symptomatology. Ivabradine inhibits the I*f* current in the sinoatrial node, thereby reducing the heart rate without affecting blood pressure or myocardial contractility [10]. Several studies and randomized trials have shown the antianginal efficacy of ivabradine. When tested in patients with stable angina, ivabradine was found to be non-inferior to beta blockers, as well as to calcium channel blockers in reducing the number of angina attacks [11–13]. More recently, addition of ivabradine to optimal individualized dose of beta blockers was associated with a decrease in angina episodes and nitroglycerin consumption and improvement of quality of life in patients with stable angina and history of coronary revascularization [14,15]. Despite the antianginal effects of ivabradine, its effect on cardiovascular outcomes remains elusive as large clinical studies were not able to show superiority when tested versus placebo [16]. Similarly, in stable CAD patients without heart failure, addition of ivabradine on standard medical therapy did not improve outcomes [17]. According to current recommendations, ivabradine is indicated for the symptomatic treatment of refractory angina in patients with normal sinus rhythm, who have intolerance to beta-blockers or in combination with beta-blockers in patients with inadequately controlled angina [9].

2. Ranolazine: reduction of calcium overload in the ischemic myocardium

Ranolazine is a selective inhibitor of the late sodium current that prevents pathological increase in sodium in the ischemic myocytes, thereby preventing calcium overload [18]. As a result, left ventricular diastolic function is improved and the equilibrium between myocardial oxygen supply and demand is restored. When evaluated in stable CAD population, ranolazine demonstrated sufficient angina relief in a number of clinical studies either as monotherapy or as an add-on to traditional medical therapy [19–21]. A meta-analysis showed that the addition of ranolazine to either beta blockers or calcium channel blockers results in significant improvement of angina symptoms [22]. However, the recent ranolazine in patients with incomplete revascularization after percutaneous coronary intervention trial failed to show incremental benefit

CONTACT Yiannis S. Chatzizisis ychatzizisis@icloud.com Cardiovascular Division, University of Nebraska Medical Center, 982265 Nebraska Medical Center, Omaha, NE 68198, USA

of ranolazine in reducing angina or improving quality of life in patients with incomplete percutaneous revascularization [23]. In a nonrandomized trial involving purely refractory angina patients, ranolazine was shown to be an effective antianginal regimen; albeit with a number of side effects that resulted in discontinuation of the drug 1 year after the initiation of treatment [24]. Ranolazine has been available for more than 10 years and is indicated as add-on therapy in stable angina patients who are not adequately controlled or are intolerant to first-line antianginal agents [8,9].

3. Trimetazidine: targeting metabolic pathways

Trimetazidine is a metabolic agent that has been used in patients with stable CAD. It reversibly blocks an enzyme based in the mitochondria of the cardiac muscle cells, important for fatty acid β-oxidation. Consequently, the ischemic myocardial cell metabolism is shifted to glucose oxidation which is energetically more efficient and myocardial oxygen demand is reduced [25]. It is also considered to hold a cytoprotective role in reducing myocyte loss during ischemia as shown in experimental models. Trimetazidine has not been studied in refractory angina patients and robust data on its efficiency in symptoms relief remain not clear [26]. Several studies in stable CAD patients comparing trimetazidine to placebo or other antianginal agents demonstrated reduction in weekly angina episodes [27]. Of note, a recent meta-analysis did not prove the superiority of trimetazidine over traditional regimens [28]. Clinical experience shows that trimetazidine may be beneficial for the refractory angina patients; however, further studies are needed to evaluate its efficacy in long-term cardiovascular outcomes.

4. Agents under investigation

Several other agents have also been suggested, aiming at symptoms control and disease modification. These largely include vasodilators such as nicorandil, fasudil, molsidomine, and L-arginine. Metabolic agents (e.g. perhexiline), regimens reducing vascular oxidative stress (e.g. allopurinol), and selective serotonin reuptake inhibitors (e.g. escitalopram) are also under consideration. However, none of these have been evaluated in refractory angina, their mechanism of action in alleviating symptoms is not well established and they are not yet implemented in practice guidelines for stable CAD, least of all refractory angina patients.

5. Conclusion and clinical perspectives

As a concluding remark, the lack of up-to-date refractory angina-dedicated guidelines is becoming apparent. Although considered to be a subgroup of stable CAD, management of refractory angina population is challenging. Our primary focus is to amend quality of life for the 'no-option' patients as long-term prognosis is improving and physicians will continuously face them in routine clinical settings [29]. Larger clinical studies are needed to further elucidate the role of drugs in refractory angina. Combined research and clinical efforts are warranted toward implementation of newer pharmacological agents in clinical practice.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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