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Pharmacological approaches of refractory angina

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ABSTRACT

Refractory angina refers to a group of patients with stable coronary atherosclerotic disease and angina symptoms, unresponsive to traditional medical management, while considered to be suboptimal candidates for revascularization procedures. Up to 15% of angina patients are considered to have refractory angina and, taking into account the aging population and the improvements in the treatment of stable coronary artery disease, the incidence of this entity is expected to increase. This review describes traditional and novel pharmacotherapies for symptoms relief and for long-term management of refractory angina. Mechanisms of action and relevant clinical trials are discussed and current recommendations from major European and US cardiovascular societies are reported.

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1. Introduction

A group of coronary artery disease (CAD) patients has persistent, ischemia-related symptoms and remains in part unresponsive to traditional medical management, while considered to be suboptimal candidates for revascularization procedures due to advanced age, significant comorbidities or patient-specific anatomical grounds (i.e. diffuse coronary disease, lack of vascular conduits). These patients are often characterized as "no-option" patients and constitute the constantly increasing CAD subgroup of refractory angina. The current definition of refractory angina according to the European Society of Cardiology (ESC) Joint Study Group on the Treatment of Refractory Angina, as it stands since the most recent treatment guidelines dated back in 2002, refers to the presence of persistent, chronic (at least 3 months) angina due to coronary insufficiency, that cannot be controlled by combination of medical treatment, angioplasty or coronary bypass surgery (Mannheimer et al., 2002).

Angina is the result of myocardial ischemia caused by the imbalance between myocardial blood supply and oxygen demand and is most commonly associated with obstructive coronary atherosclerotic disease. Luminal stenosis can lead to insufficient distribution of oxygen in myocardial cells either at rest or more frequently at stress. Recent data suggest that microvascular coronary artery disease constitutes another

Abbreviations: CAD, coronary artery disease; CCBs, calcium channel blockers; ESC, European Society of Cardiology; AHA, American Heart Association.

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source of refractory angina and is usually attributed to augmented vasoconstriction due to reduced nitric oxide release and subsequently impaired endothelium-dependent vasodilation (Camici & Crea, 2007; Crea et al., 2014).

Traditional antianginal drugs, i.e. beta-blockers, calcium channel blockers (CCB) and nitrates aim either to decrease oxygen consumption or augment oxygen supply by enhancing myocardial blood flow. Although efficient in treating angina symptoms to a certain extent, traditional agents do not produce symptom relief in all patients. Approximately 5%–15% of patients appear to be refractory to "triple therapy", highlighting the need to develop novel pharmacotherapies. During the last decades, a number of novel antianginal drugs have emerged targeting both pathophysiology mechanisms of ischemia, as well as myocardium metabolic pathways and coronary blood flow redistribution. Moreover, an integral part of the management of the refractory angina patient is risk factor modification, achieved by life style changes and statins, renin–angiotensin system inhibitors and antithrombotic agents (Fig. 1).

The purpose of this review is to describe conventional and novel pharmacotherapies for symptoms relief and for long-term management of refractory angina. Mechanisms of action and relevant clinical trials are discussed and current recommendations from major European and US cardiovascular societies are reported. Finally, non-pharmacological approaches are briefly summarized. Of note, refractory angina constitutes an advanced form of chronic ischemic heart disease and pharmacotherapies used for refractory angina overlap to a great extent with those used in chronic stable angina.

2. Epidemiology

Mannheimer et al. reported that approximately 5%–15% of patients suffering from angina meet the criteria of refractory angina. These data, combined with more recent results (Hemingway et al., 2008), provide a rough estimation of 490,000 to 1,470,000 patients in the United States suffering from refractory angina. The annual incidence rate is 25,000–75,000 newly diagnosed cases each year (Soran, 2009). The ESC estimates that 15% of patients who experience angina can be characterized as having refractory angina with an annual incidence of 30,000–50,000. Approximately 67%–77% of the patients with refractory angina are men with an average age of 64–70 years. The majority of these patients have previously sustained a myocardial infarction (64%–71%) and most of them have undergone at least one revascularization procedure (64%–88%) (Andréll et al., 2011).

Although initial data regarding the natural history and the prognosis of refractory angina patients have considered them as a high-risk mortality group, a recent study reported that over 70% of those patients are expected to survive 9 years following diagnosis (Henry et al., 2013). Similarly, refractory angina patients were shown to have intermediate rates of myocardial infarction and/or death, but increased hospitalization rates (Povsic et al., 2015).

3. Current pharmacotherapy

3.1. Traditional antianginal pharmacotherapy

3.1.1. Beta-blockers

Beta-blockade reduces myocardial oxygen demand via reducing myocardial contractility, heart rate and blood pressure. Myocardial beta-adrenergic receptors are transmembrane G-coupled proteins which upon activation via circulating catecholamines stimulate adenyl cyclase to synthesize cyclic adenosine monophosphate, which serves as a second intracellular messenger (Xiang, 2011). Raised intracellular cyclic adenosine monophosphate levels increase sarcoplasmic reticulum calcium release and ultimately the rate and force of sarcomere contraction. Beta-blockers competitively block the effects of catecholamines on myocardial beta-receptors, thereby exerting a negative inotropic, chronotropic and dromotropic effect (Fig. 2). Furthermore, beta-blockers decrease systolic blood pressure possibly through their inhibitory effect in renin release from the juxtaglomerular apparatus (Buhler et al., 1972).

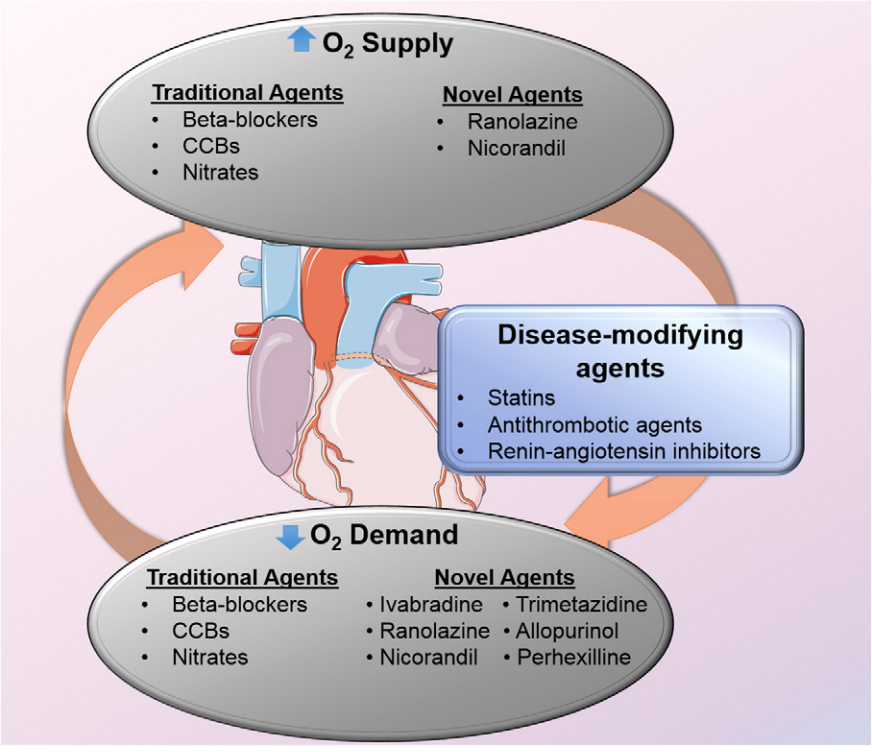

Fig. 1. Pharmacotherapeutic approaches targeting refractory angina. Traditional and novel antianginal agents facilitate symptoms relief either by decreasing oxygen demand or by increasing oxygen supply. Disease-modifying agents hold a key role in halting or reversing the progression of ischemic coronary disease.