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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).

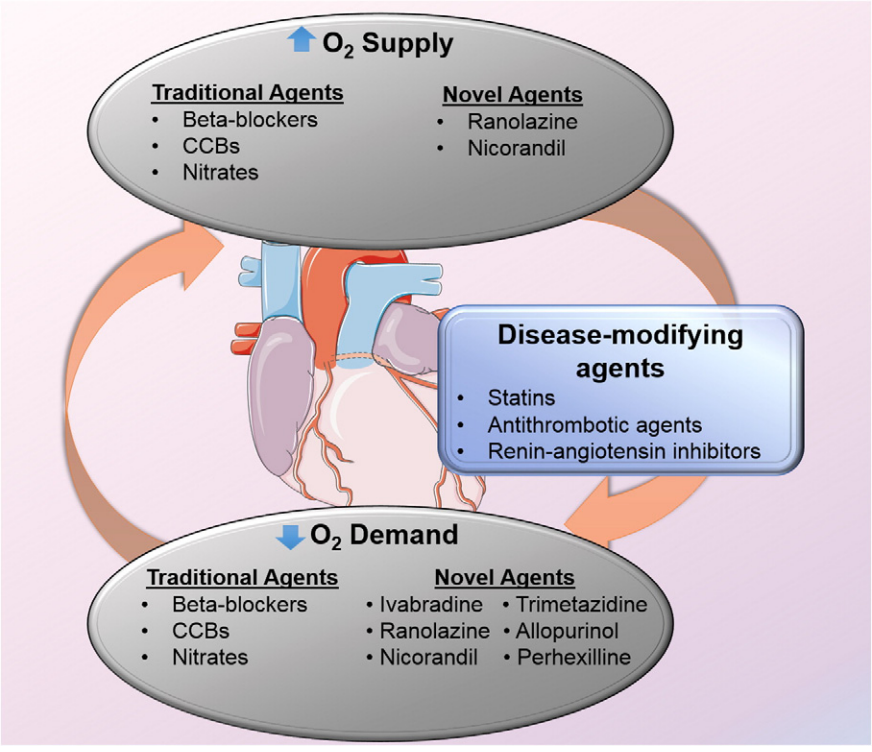

Fig. 1. Pharmacotherapeutic approaches targeting refractory angina. Traditional and novel antianginal agents facilitate symptoms relief either by decreasing oxygen demand or by increasing oxygen supply. Disease-modifying agents hold a key role in halting or reversing the progression of ischemic coronary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

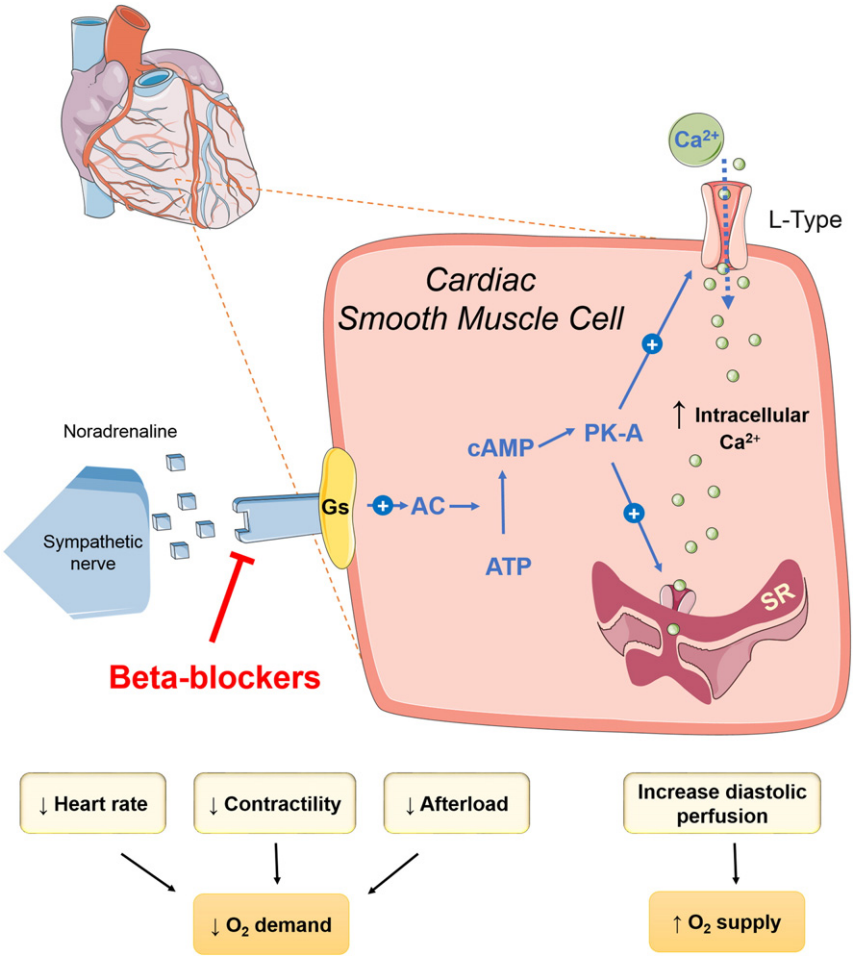

Fig. 2. Mechanism of action of beta-blockers in cardiac smooth muscle cells. Beta-adrenoceptors are coupled to Gs-proteins, which, upon noradrenalin binding, activate adenylyl cyclase (AC) to form cAMP from ATP. Increased cAMP activates a cAMP-dependent protein kinase A (PK-A) that phosphorylates L-type calcium channels, which causes increased calcium entry into the cell. PK-A also phosphorylates sites on the sarcoplasmic reticulum (SR), which lead to enhanced release of calcium intracellularly. Beta-blockers via blocking beta-adrenoreceptors reduce heart rate and contractility, thereby reducing afterload and reducing myocardial oxygen demand. Reduced heart rate prolongs the diastolic phase of the cardiac cycle resulting in increased diastolic coronary perfusion, thereby increased myocardial oxygen supply.

All types of beta-blockers, regardless of their inherent properties appear to be equally effective in managing angina symptoms. Long-acting cardioselective agents, such as atenolol and metoprolol, are preferred for the treatment of stable angina patients. In addition, beta-blockers are the only antianginal drugs proven to prevent reinfarction and to improve survival in patients who sustained a myocardial infarction (Gibbons et al., 2003). Although recent data questioned the benefit of beta-blockers in patients with stable CAD and no prior myocardial infarction (Andersson et al., 2014; Goldberger et al., 2015), beta-blockers still remain the first-line therapy for the treatment of angina (Kones, 2010). However, commonly prescribed doses are usually below the doses used in the trials that showed the efficacy of these agents (Table 1).

3.1.2. CCBs

CCBs are classified into two major categories based on chemical structure and mechanism of action (i.e. dihydropyridines and non-dihydropyridines). CCBs reduce cell transmembrane inward calcium flux via blocking L-type calcium channels and subsequently attenuate vascular smooth muscle cell contraction, thereby reducing myocardial oxygen demands (via lowering peripheral vascular resistance) and to some extent improve coronary blood flow, thereby increasing myocardial oxygen supply (via coronary artery relaxation) (Fig. 3). Moreover, the non-dihydropyridines (i.e. diltiazem and verapamil), demonstrate additional antianginal effects by depressing cardiac pacemaker rate and slowing conduction (Gibbons et al., 2003; Kones, 2010; Henderson & O'Flynn, 2012).

Studies have shown the safety of long-acting agents in this category when used to treat stable angina, while short-acting dihydropyridines appear to have increased risk of cardiovascular events (Alderman et al., 1997; Fihn et al., 2012). CCBs reduce symptoms and increase exercise tolerance, especially when used in combination with other antianginal agents. CCBs can be added to therapeutic schemes or replace beta-blockers in cases of serious adverse effects. Of note, they do not seem to improve mortality and care should be taken when prescribed due to a number of contraindications and side effects (Fihn et al., 2012) (Table 1).

3.1.3. Nitrates

Nitrates act as exogenous nitric oxide donors and a process of biotransformation is required for them to become biologically active. Nitric oxide stimulates soluble guanylate cyclase, which converts guanosine triphosphate into cyclic guanosine monophosphate. Cyclic guanosine monophosphate activates protein kinase G, which in turn exerts a direct lusitropic effect by relaxing both myocardial and vascular smooth muscle cells (Tsai & Kass, 2009). Exogenous nitrates are characterized by a graded dose–response relationship. In low doses, they exert venodilatory properties, whereas in higher doses they promote arterial dilation. By reducing left ventricle preload and afterload, nitrates reduce myocardial oxygen demands. Nitrates induced coronary arteries and

Table 1
Drugs against refractory angina: traditional agents. Mechanisms of action, common adverse effects, contraindications, recommendations from major cardiology societies (*, Recommendations refer to stable angina).

Agents	Mechanism of action	Common adverse effects	Contraindications	Class/level of evidence*	
Traditional agents				ESC	AHA
Beta-blockers	• Chronotrope-negative • Inotrope-negative • Afterload reduction	• Bradycardia • Conduction disturbances • Bronchospasm • Peripheral vasoconstriction • Reduced libido • Hypotension	• Severe bradycardia • Conduction system disease • Asthma • Refractory heart failure • Active peripheral artery disease	I/A	I/B
CCBs	Dihydropyridines • Vasodilation • Afterload reduction	• Hypotension • Headache • Peripheral edema • Reflex tachycardia	• Severe aortic stenosis • Obstructive cardiomyopathy	I/B	I/B
	Non-dihydropyridines • Chronotrope-negative • Inotrope-negative • Vasodilation	• Bradycardia • Conduction impairment • Constipation	• Congestive heart failure • Severe bradycardia • Conduction system disease • Wolff–Parkinson–White syndrome • Concomitant beta-blockage	I/B	I/B
Nitrates	• Coronary vasodilation • Ventricular wall stress reduction	• Hypotension • Headache • Flushing • Reflex tachycardia • Nocturnal or rebound angina	• Hypertrophic obstructive cardiomyopathy • Severe aortic stenosis • Concomitant phosphodiesterase type 5 (PDE5) inhibition	I/B	I/B

collaterals dilation enhance coronary perfusion, thus increasing exercise tolerance and decreasing the frequency of anginal attacks (Fig. 4). In combination with beta-blockers or CCBs, nitrates produce even more potent anti-ischemic effect (Gibbons et al., 2003; Kones, 2010).

Despite the fact that, nitrates are regarded as one of the traditional antianginal drugs they confer no survival benefit. In a meta-analysis comparing the efficacy of beta-blockers, CCBs and nitrates in stable angina patients, beta-blockers were shown to be superior to CCBs in decreasing the frequency of episodes of angina (Heidenreich et al., 1999). The combination of beta-blockers with nitrates is favored as they both lower myocardial oxygen demand and redistribute coronary blood flow into the subendocardial layers. Furthermore, beta-blockers can prevent reflex tachycardia caused by nitrate-induced hypotension, whereas nitrates attenuate any potential rise in left ventricular-end diastolic pressure, due to beta-blockers' negative inotropic effects.

Short-acting nitrates should be prescribed to all refractory angina patients for immediate symptoms control (Table 1). Long-acting agents are recommended for the management of angina when initial therapy with beta blockers or non-dihydropyridine CCBs is contraindicated, is poorly tolerated or is not adequate, as in cases with refractory angina (Fihn et al., 2012). Due to the frequent side effects and tolerance development, nitrate doses should be titrated to control symptoms at the lowest possible dose (Husted & Ohman, 2015) (Table 2).

3.2. Disease-modifying agents

Even though these agents are not used as direct antianginal medications, there is strong evidence supporting their efficacy in halting or even reversing atherosclerotic process, thereby reducing anginal episodes in the long term. These agents are not dedicated to refractory angina therapy, however they constitute the corner stone of stable CAD treatment and therefore incorporation into therapeutic schemes for the no-option patients should be always contemplated (Table 3).

3.2.1. Statins

Milestone studies have shown that reduction of serum low-density lipoproteins with the use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase agents, namely, statins, reduces the risk of major cardiovascular events by 20%–45% (Sacks et al., 1996; Pitt et al., 1999; Cholesterol Treatment Trialists, 2010). Interestingly, more intensive statin therapy results in greater risk reduction compared to less intensive approaches (Homocysteine Collaborative Group, 2010). Cannon et al. recently showed that the addition of ezetimibe (a non-statin lipid-lowering agent) to standard statin therapy with simvastatin resulted in significant lowering of low-density lipoprotein cholesterol levels and improved cardiovascular outcomes (Cannon et al., 2015). Besides reducing low-density lipoprotein cholesterol, statins exert pleiotropic effects (e.g. anti-inflammatory and plaque-stabilizing properties) (Tahara et al., 2006; Puri et al., 2014).

The level of low-density lipoprotein cholesterol reduction optimal for refractory angina is not clearly defined; as with all stable CAD patients, lipid-modification therapy is recommended and maximally tolerated intensity of statins should be considered, adjusted to related co-morbidities (i.e. diabetes) and age (Fihn et al., 2012).

3.2.2. Antithrombotic agents

Patients with established refractory angina should be administered appropriate antithrombotic therapy. Platelets are implicated in thrombus formation following plaque disruption leading to the precipitation of acute coronary syndromes. Aspirin, an irreversible cyclooxygenase inhibitor, blocks synthesis of thromboxane A2, thereby attenuating platelet inhibition. Aspirin decreases the risk of major cardiovascular events (Antithrombotic Trialists' Collaboration, 2002). Inhibition of platelet aggregation is a guidelines' mandate for all patients with refractory angina and is recommended that all patients should be prescribed aspirin indefinitely, unless contraindicated (Mannheimer et al., 2002).

$P2Y_{12}$ receptor inhibitors (i.e. clopidogrel, prasugrel and ticagrelor) also prevent platelet inhibition (through a different mechanism than aspirin and with reduced risk of major bleeding) and constitute an alternative to aspirin for secondary prevention of CAD. Combination with aspirin, dual antiplatelet therapy did not show superiority in reducing major atherothrombotic events in CAD patients vs. monotherapy with aspirin (Bhatt et al., 2006) and is recommended for a limited time period post-stenting (i.e. 12 months in patients after percutaneous coronary intervention with drug eluting stent implantation and 1–6 months with bare metal stent) (Montalescot et al., 2013).

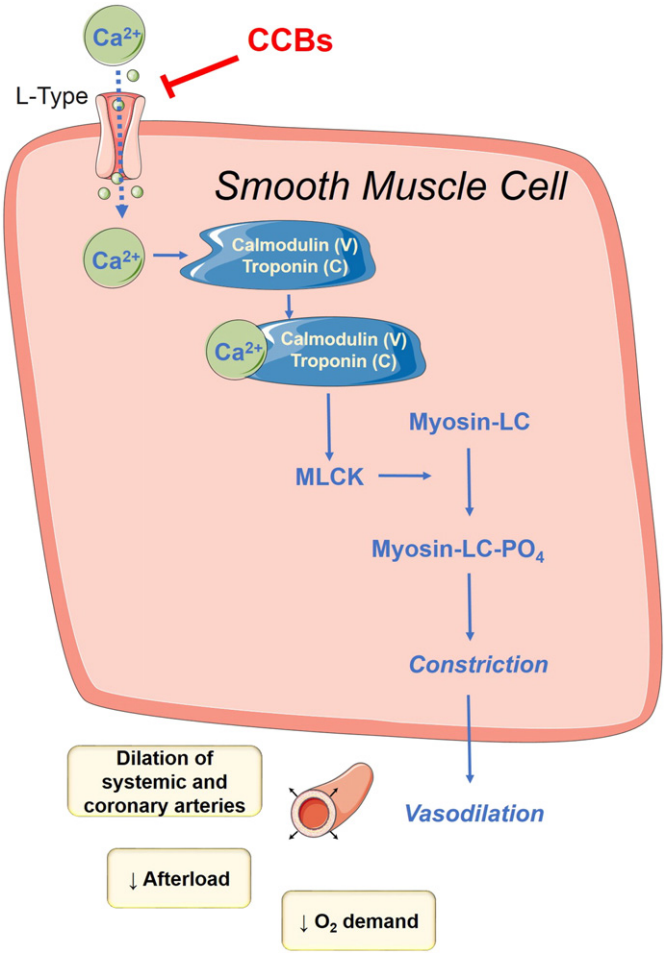

Fig. 3. Mechanism of action of calcium channel blockers in cardiac and vessel smooth muscle cells. Voltage-sensitive Ca^{2+} channels (L-type) open following membrane depolarization and calcium ions enter the cell. The elevation of intracellular calcium results in enhanced binding to calmodulin in vascular (V) smooth muscle cells and to troponin in heart (H) smooth muscle cells. The calcium–calmodulin/troponin complex activates the enzyme myosin light-chain kinase (MLCK), which phosphorylates light-chain myosin (Myosin-LC). Phosphorylated Myosin-LC favors actin and myosin interaction, which results in smooth muscle contraction. Calcium channel blockers via blocking L-type Ca^{2+} channels reduce the sarcomere contraction thereby reducing contractility, increasing vasodilation, reducing afterload and finally reducing myocardial oxygen demand.

3.2.3. Renin–angiotensin system inhibitors

Renin–angiotensin system inhibitors (i.e. angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) have cardioprotective effects and reduce long-term mortality in CAD patients. While multiple large-scale trials (Mitchell et al., 2007) have demonstrated the efficacy of angiotensin-converting enzyme inhibitors in patients with stable coronary atherosclerosis, their effectiveness in reducing angina symptoms remains unclear. The mechanisms of action that could potentially explain the antianginal effect include, amongst others, improvement in myocardial oxygen supply and demand relationship. Data are limited regarding the effect of novel agents in this category (e.g. direct inhibitors of renin and angiotensin receptor neprilysin inhibitors) in patients with stable CAD. Aiming to improve long-term prognosis, hypertensive refractory angina patients with diabetes, left ventricular ejection fraction <40% or chronic renal disease should be administered angiotensin-converting enzyme inhibitors and, in the case of intolerance, angiotensin receptor blockers (Fihn et al., 2012; Montalescot et al., 2013).

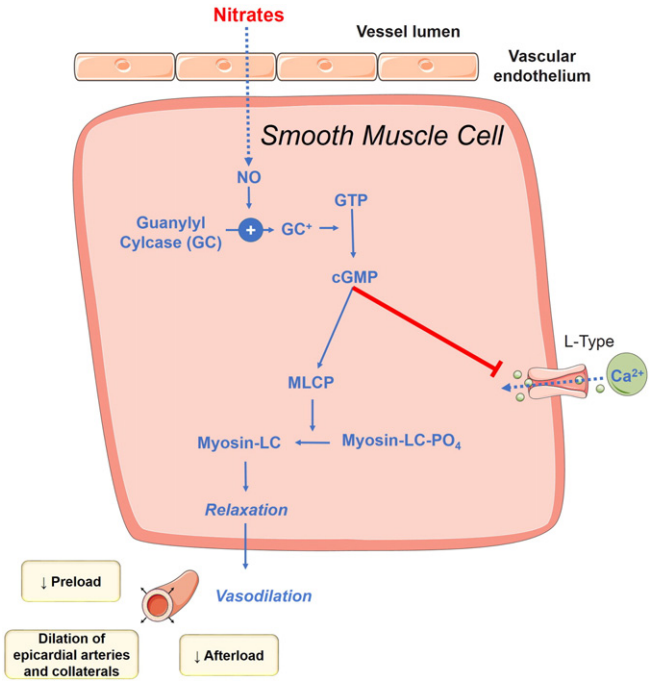

Fig. 4. Mechanism of action of nitrates. Circulating nitrates are converted to nitric oxide (NO) in vascular endothelial cells and enter the smooth muscle cells. NO activates guanyl cyclase (GC) and the activated GC^{+} converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). Increased cGMP decreases intracellular levels of calcium (Ca^{2+}) via inhibition of calcium channels thereby decreasing intracellular calcium concentrations. cGMP also activates the myosin light chain phosphatase (MLCK), which dephosphorylates myosin light chains, resulting in decreased interaction between myosin heads and actin thus leading to smooth muscle cells relaxation and consequently vasodilation. Vasodilation in peripheral vasculature reduces preload and afterload. Dilation of the epicardial coronary arteries and collaterals increases myocardial oxygen supply.

4. Novel pharmacological therapies

Novel pharmacotherapies for refractory angina exert their antianginal effects via restoring balance in the myocardium supply/demand equilibrium either by augmenting the same mechanisms as traditional agents or by targeting other pathways, mainly through modulation of the energy metabolism of the ischemic myocardium (Table 4).

4.1. Ivabradine

Ivabradine is the only agent known with pure heart rate-slowing properties and no clinically meaningful effect on blood pressure, myocardial contractility and atrioventricular node conduction. Ivabradine's

Table 2
Short- and long-acting nitrates. Dosages, onset and duration of action.

Nitrates		Dose	Onset	Duration
		Short-acting		
Nitroglycerin	Spray/tablet sublingual	0.3–0.6 mg every 5 min to max 1.2 mg	1–3 min	30–40 min
	Ointment	7.5–30 mg applied to an area of ~10 cm^2	~30 min	2–12 h
Isosorbide dinitrate	Tablet	5 mg	~5 min	>1 h
		Long-acting		
Isosorbide-5-mononitrate	Tablet	60–240 mg once daily	60–120 min	5–12 h
Isosorbide dinitrate	Tablet	10–45 mg three or four times daily	20–40 min	4–6 h
	Transdermal patches	0.2 to 0.8 mg/h once daily	40–60 min	18–24 h

Table 3
Drugs against refractory angina: disease-modifying agents. Mechanisms of action, common adverse effects, contraindications, recommendations from major cardiology societies (*, Recommendations refer to stable angina).

Agents	Mechanism of action	Common adverse effects	Contraindications	Class/level of evidence*	
Disease modifying agents				ESC	AHA
Statins	• Plaque stabilization • Pleiotropic effects	• Myopathy • Liver function abnormalities	• Hypersensitivity • Active liver disease • Pregnancy • Concomitant CYP3A4 inhibition	I/A	I/A
Antithrombotic agents	• Incremental in thrombosis prevention	• Erosive gastritis • Gastrointestinal bleeding • Salicylism • Hypersensitivity reactions • Thrombotic thrombocytopenic purpura	• Active peptic ulcer • Active bleeding • Hypersensitivity	Aspirin	Aspirin
				I/A	I/A
				$P2Y_{12}$ inhibitors	$P2Y_{12}$ inhibitors
				I/B	I/B
Renin–angiotensin system inhibitors	• Improve long-term prognosis	• Hypotension • Acute renal failure • Hyperkalemia • Cough • Angioedema • Anaphylaxis	• Angioneurotic edema • Pregnancy • Renal artery stenosis • Aortic stenosis • Hypertrophic obstructive cardiomyopathy	I/B	I/B

action is mediated via decreasing the slope of spontaneous diastolic depolarization in sino-atrial pacemaker cells by selectively inhibiting I_f channels; it is therefore only effective when sinus rhythm is present (Vilaine, 2006) (Fig. 5).

Early clinical studies demonstrated ivabradine efficacy in increasing time to limiting angina and to 1-mm ST segment depression during standardized exercise protocols compared to placebo (Borer et al., 2003). Randomized trials established its non-inferiority to beta-blockers (atenolol) (Tardif et al., 2005) and CCBs (amlodipine) (Ruzyllo et al., 2007; Tardif et al., 2009) in decreasing the number of angina attacks as well as its excellent safety profile. Investigators in the BEAUTIFUL study randomly assigned 10,917 patients with stable CAD and left ventricular systolic dysfunction to either ivabradine or placebo (Fox et al., 2008). Although cardiovascular outcomes did not improve, in a subgroup of patients with symptom-limiting angina, ivabradine did reduce the incidence of myocardial infract hospitalizations. In the

Table 4
Drugs against refractory angina: novel agents. Mechanisms of action, common adverse effects, contraindications, recommendations from major cardiology societies (*, Recommendations refer to stable angina).

Agents	Mechanism of action	Common adverse effects	Contraindications	Class/level of evidence*	
Novel agents				ESC	AHA
Ivabradine	• Inhibition of sinus node I*f* pacemaking current • Pure heart rate reduction • Prolongation of diastole	• Luminous phenomena • Bradycardia • Headache	• Severe bradycardia • Sick sinus syndrome • Severe hepatic impairment • Concomitant CYP3A4 inhibition • Agents prolonging QT interval	IIa/B	N/A[¥]
Ranolazine	• Inhibition of late inward Na^+ current • Reduction of Ca^{2+} in ischemic myocytes • Improved left ventricular diastolic function	• Constipation • Nausea • Headache • Vomiting • Prolongation of QT interval	• Concomitant cytochrome P450 inhibition • Advanced hepatic impairment • Agents prolonging QT interval	IIa/B	IIa/B
Nicorandil	• Release nitric oxide free radicals • Vasodilation of arterial and venous system • Activation of adenosine triphosphate sensitive potassium channels	• Hypotension • Flushing • Headache • Constipation • Gastrointestinal ulcerations	• Hypotension • Cardiogenic shock • Concomitant phosphodiesterase type 5 (PDE5) inhibition	IIa/B	N/A
Trimetazidine	• Inhibition of fatty-acid β-oxidation in mitochondria • Improved myocyte tolerance to ischemia	• Parkinsonism • Restless leg syndrome • Nausea • Headache	• Extrapyramidal disorders • Severe renal impairment	IIb/B	N/A
Perhexiline	• Inhibition of carnitine-palmitoyltransferase 1 and 2 • Shifting myocardial metabolism from fatty acids to carbohydrates • Enhancement of energy efficiency in ischemic myocytes	• Nausea • Headache • Hypoglycemia in diabetics • Hepatotoxicity • Peripheral neuropathy	• Hypersensitivity • Severe renal impairment • Severe hepatic impairment • Porphyria	N/A	N/A
Allopurinol	• Inhibition of xanthine oxidase • Reduction of vascular oxidative stress	• Headache • Rash • Gastrointestinal distress	• Hypersensitivity • Severe renal impairment	N/A	N/A
Fasudil	• Inhibition of Rho-kinase • Reducing calcium sensitization of vascular smooth muscle • Maintenance of coronary vasodilation	• Inadequate data available	• Inadequate data available	N/A	N/A

[¥] Ivabradine is approved in the United States for use in stable, symptomatic heart failure with heart rate of >70 bpm and on maximally tolerated doses of beta-blockers.

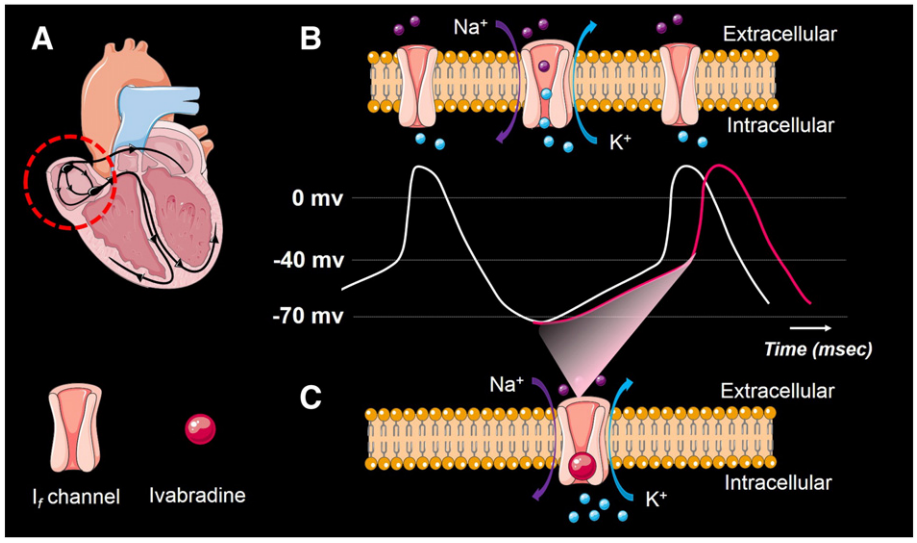

Fig. 5. Mechanism of action of ivabradine. Ivabradine is a selective antagonist of the I*f* current and exhibits its actions mainly in the sinoatrial node (**A**; dashed red circle). (**B**) The I*f* channels determine the slope of the diastolic depolarization, which controls the frequency of action potentials and in this way the heart rate. The I*f* channels open at the end of the action potential, allowing I*f* current to flow, thus driving the membrane voltage towards the threshold of the next action potential. (**C**) By selectively blocking the I*f* channels with ivabradine, diastolic depolarization is delayed, prolonging diastole and slowing the heart rate. This allows increased coronary flow and myocardial perfusion.

SHIFT trial, 6558 patients with symptomatic heart failure and on stable guideline-based background therapy, addition of ivabradine was shown to improve clinical outcomes (Swedberg et al., 2010).

Initial enthusiasm from studies that demonstrated reduction in the rate of adverse cardiac outcomes (Fox et al., 2008; Swedberg et al., 2010) was replaced by skepticism when data from other studies emerged (Fox et al., 2014). In the Study assessInG the morbidity–mortality beNefits of the I*f* inhibitor ivabradine in patients with coronary artery disease (SIGNIFY), the larger study to date, that enrolled 19,102 stable CAD patients without heart failure and left ventricle systolic dysfunction and on standard medical therapy, the addition of ivabradine did not improve prognosis (Fox et al., 2014). It has been proposed that elevated heart rate should be considered a risk factor in CAD patients with heart failure, whereas in those without left ventricular dysfunction, it appears to be rather a risk marker of other processes that influence CAD progression (Ferrari & Fox, 2015). Certainly, further studies are warranted to better understand the potential mechanisms, if any, that ivabradine, via reducing heart rate, can influence adverse clinical outcomes.

Ivabradine is currently approved for use in Europe and is indicated for the symptomatic treatment of refractory angina in patients with normal sinus rhythm, who have a contraindication or are intolerant to beta-blockers (Montalescot et al., 2013). It is also indicated in combination with beta-blockers for patients whose angina symptoms are inadequately controlled and with a resting heart rate of >60 bpm. Recently, the Food and Drug Administration has given approval for its use in stable, symptomatic heart failure, with heart rate of >70 bpm and on maximally tolerated doses of beta-blockers.

4.2. Ranolazine

Ranolazine, a relatively new agent, is an active piperazine derivative that acts as a selective inhibitor of the late sodium current (Belardinelli et al., 2006). In the ischemic myocardium, increased intracellular sodium levels lead to intracellular calcium overload via decreased efflux of calcium ions through the sodium/calcium exchanger (Sossalla & Maier, 2012). Ranolazine inhibits pathological increase in late sodium current leading to reduction of calcium overload in the ischemic myocytes, thereby improving left ventricular diastolic function (Fraser et al., 2006) (Fig. 6). Enhanced myocardial relaxation decreases oxygen demand and increases coronary blood supply. Ranolazine is also, though in supra-therapeutic plasma levels, a partial inhibitor of free-fatty acid oxidation, thereby promoting glucose utilization instead which is far more energy-efficient.

The antianginal role of ranolazine has been demonstrated in several clinical studies (Pepine & Wolff, 1999; Chaitman et al., 2004a, 2004b; Stone et al., 2006; Koren et al., 2007). Amongst them, MERLIN-TIMI 36, which enrolled 6560 CAD patients following non-ST-elevation acute coronary syndrome demonstrated improvement in exercise duration and sufficiently reduced angina (Morrow et al., 2007). This effect was also appreciated in the TERISA study, where the regimen was administered to patients with diabetes and chronic angina despite treatment with up to 2 antianginal agents; aside from leading to an improvement of symptoms, the addition of ranolazine resulted in a reduction of hemoglobin A1c (Kosiborod et al., 2013). Further studies have been designed (Arnold et al., 2015) and others are warranted to investigate the association between ranolazine and glycemic levels.

More recently, and on the contrary to other studies, investigators from the RIVER-PCI trial showed no incremental benefit in reducing angina or improving quality of life in patients with incomplete revascularization after percutaneous coronary intervention, a subgroup that falls into the description of refractory angina patients (Alexander et al., 2015). Furthermore, the investigators reported that there was no improvement in the primary endpoint of ischemia-driven revascularization or hospitalization with no revascularization (Weisz et al., 2015). It has been suggested that ranolazine might not be the ideal first-line treatment for incomplete revascularized patients, and the functional significance of untreated lesions should be estimated, for example, with fractional flow reserve, so as to identify whether medical treatment alone is sufficient for non-stented plaques (Head & Kappetein, 2015).

In general, ranolazine is considered safe and has been in clinical use for several years. It has been approved by the Food and Drug Administration as a first-line angina treatment and is indicated in Europe as add-on therapy for the symptomatic treatment of patients with stable angina who are inadequately controlled or are intolerant to first-line antianginal therapies (Montalescot et al., 2013).

4.3. Nicorandil

Nicorandil is a nicotinamide ester that has both nitrate-like properties as well as cardioprotective effects (Gross et al., 1992; Kukovetz et al., 1992; Treese et al., 1992). It has been shown to induce release of nitric oxide free radicals in the same fashion as nitrates and it also

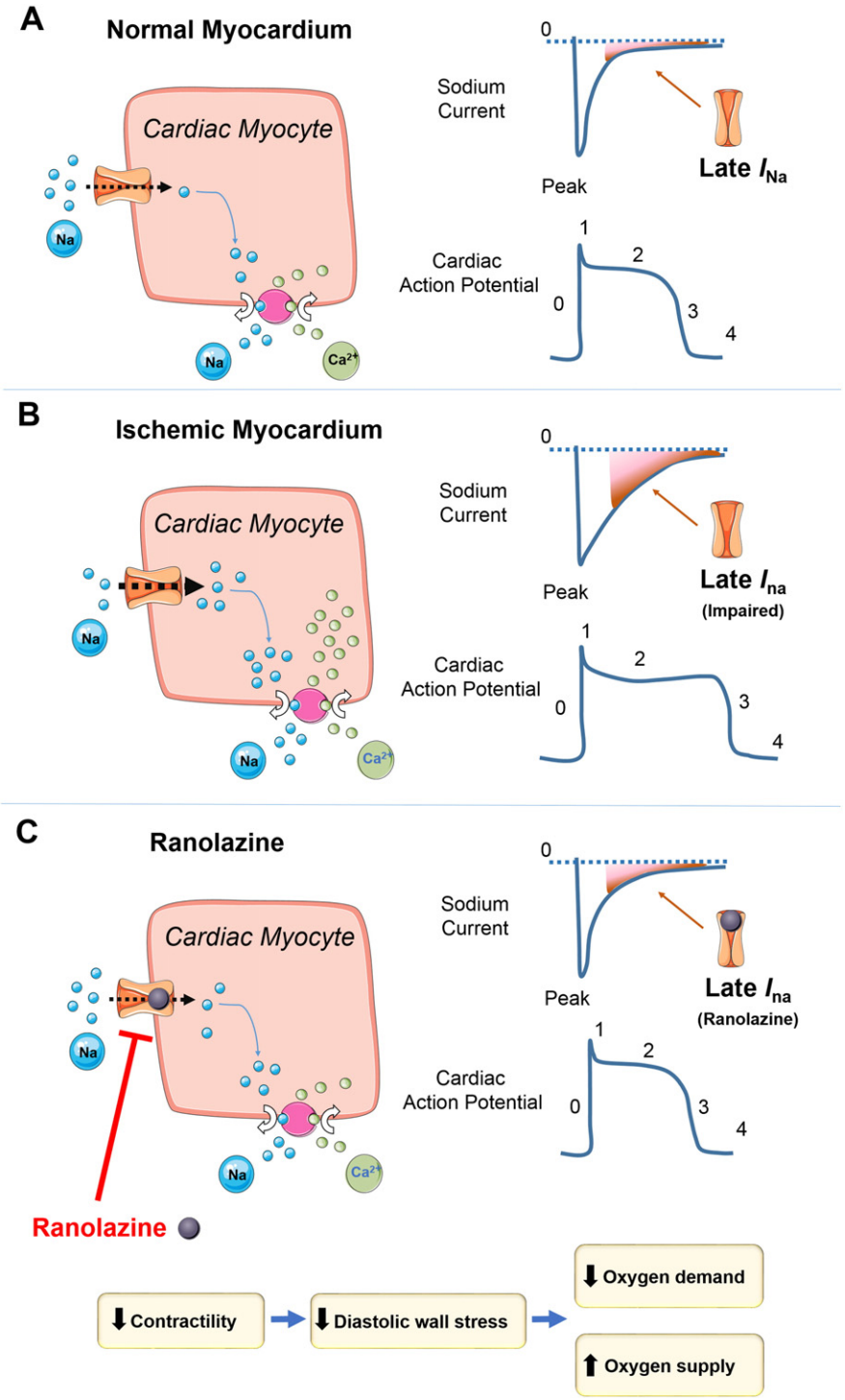

Fig. 6. Mechanism of action of ranolazine. (**A**) Sodium channels allow sodium transport intracellularly. The sodium current peaks at the onset of the action potential (Phase 0) and continues throughout systole, with a so-called late component (late $I_{Na;}$ Phase 2). (**B**) In the ischemic myocardium, late inward I_{Na} currents contribute to an elevation in intracellular sodium, which leads to an increase in intracellular calcium through the sodium-calcium exchanger. Calcium overload in ischemic cells leads to impaired relaxation. (**C**) Ranolazine, selectively inhibits late I_{Na} current. By decreasing the magnitude of the pathologically enhanced late I_{Na}, it prevents or reduces Ca^{2+} overload, thereby decreasing contractility. The reduction in wall tension during diastole reduces consumption of oxygen and ATP and thus oxygen demand. Moreover the reduction of wall stress reduces vascular compression, leading to increased myocardial blood flow and oxygen supply to the myocardium during diastole (Phase 0: rapid depolarization; Phase 1: partial repolarization; Phase 2: plateau; Phase 3: repolarization; Phase 4: pacemaker potential).

exhibits mitochondrial adenosine triphosphate–potassium channel activating properties in vascular smooth muscle cells (Fig. 7). Nicorandil increases coronary blood flow by reducing both preload and afterload via vasodilation of the venous and arterial systems.

Several small randomized trials have shown the antianginal efficacy of nicorandil compared to beta-blockers, nitrates and CCBs (Ulvenstam et al., 1992; Raftery et al., 1993; Somma et al., 1993). Nicorandil has also been shown to improve myocardial perfusion both at rest and during exercise. The possible cardioprotective effects of nicorandil were investigated in the IONA study (Iona Study Group, 2002) as well as by Matsuo et al. (2003), where nicorandil pretreatment induced beneficial myocardial preconditioning, independently of the severity of ischemia. A

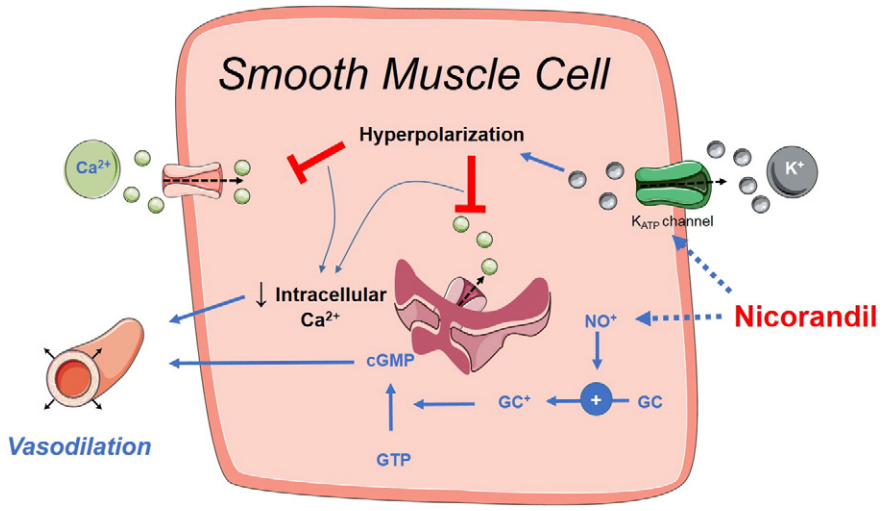

Fig. 7. Mechanism of action of nicorandil. Nicorandil exhibits vasodilation properties via two distinct mechanisms. Similarly to nitrates, nicorandil releases nitric oxid free radicals (NO^+) increasing guanosine monophosphate (cGMP) thus leading to smooth muscle relaxation. Moreover, by selectively opening membranous K_{ATP} channels, which results in hyperpolarization of the cell membrane, nicorandil reduces intracellular Ca^{2+} thus promoting vasodilation.

recent, single-centered, randomized trial of nicorandil in patients with slow coronary blood flow, characterized by frequent angina attacks, resulted in improved symptomatic relief when compared to nitrates (Sani et al., 2015). Of note, a meta-analysis reported that there are no data to support its role as an add-on therapy with respect to the magnitude of clinical efficacy of different antianginal classes (Belsey et al., 2015). Further studies are warranted to establish whether the unique pharmacodynamic characteristics of nicorandil are advantageous for the treatment of refractory angina.

Clinical experience indicates that nicorandil, combining two distinct mechanisms of action, offers an effective alternative to established vasodilator therapy with conventional nitrates and CCBs in the long term treatment of stable angina (Zhu et al., 2007). Nicorandil is available in most European countries approved for long-term management of angina as an add-on regimen to beta-blockers and CCBs (Montalescot et al., 2013). Currently, it is not cleared for clinical use by the Food and Drug Administration.

4.4. Trimetazidine

Trimetazidine, a metabolic modulator used for decades in cardiology, is a partial inhibitor of the terminal enzyme in mitochondrial long-chain 3-ketoacyl CoA thiolase, an enzyme incremental for fatty-acids β-oxidation (Kantor et al., 2000). By inhibiting the last step of free fatty-acids catabolism, trimetazidine promotes a reciprocal activation of carbohydrates oxidation (Fig. 8). Unlike conventional antianginal agents, in which efficacy is mediated through hemodynamic modulation aiming to restore the balance between myocardial oxygen supply and demand, trimetazidine appears to protect myocytes against ischemia by inhibiting fatty acid metabolism and to a smaller extent by stimulating glucose metabolism. In theory, this cytoprotective activity should limit myocyte loss during ischemia in patients with angina and could ultimately lead to improved prognosis. Experimental models of ischemia and reperfusion have shown that trimetazidine limits cell acidosis and calcium overload, preserves intracellular high-energy deposits, modulates the inflammatory response, and reduces free radicals-induced myocardial injury and subsequent infarct size.

Clinical studies have evaluated the effectiveness of trimetazidine in stable angina, as monotherapy in ischemic cardiomyopathy and in acute myocardial infarction (Labrou et al., 2007) or in combination with other antianginal agents in stable angina patients (Szwed et al., 2001; Kolbel & Bada, 2003; Chazov et al., 2005). Although a meta-analysis has not shown superiority against other first-line antianginal agents or reduction in mortality (Ciapponi et al., 2005), addition in the standard antianginal treatment for the refractory angina patient is supported by more recent studies and meta-analysis (Peng et al., 2014; Belsey et al., 2015; Tsioufis et al., 2015; Y. Zhang et al., 2015). Currently, trimetazidine is in use in Europe; however, it has not yet been cleared by the Food and Drug Administration.

4.5. Perhexiline

The antianginal efficacy of perhexiline was demonstrated early, even in patients poorly controlled with other antianginal drugs (Horowitz et al., 1986). Perhexiline, yet another cardiac metabolic agent, inhibits the enzymes carnitine palmitoyltransferase-1 and -2 that regulate mitochondrial uptake of long-chain fatty acids. Like trimetazidine, the main mechanism of action of perhexiline is through shifting myocardial substrate utilization from fatty acids to carbohydrates, which is energetically more efficient for the heart to metabolize (Kennedy et al., 2000). Perhexiline further potentiates platelet responsiveness to nitric oxide both in stable angina and in acute coronary syndrome patients (Willoughby et al., 2002) (Fig. 8).

Initial reports demonstrated its effectiveness, however, its use markedly declined after reports of hepatotoxicity and peripheral neuropathy (Cole et al., 1990). These adverse reactions were later shown to occur in patients who were “slow hydroxylators”, due to a polymorphic variant of the cytochrome P-450 enzyme which metabolizes the drug (Ashrafian et al., 2007). A review of 26 randomized, double-blinded trials where perhexiline was used as monotherapy or added to standard antianginal treatment reported its potency in angina symptoms relief (Killalea & Krum, 2001).

Recently, a United Kingdom multi-centre study reported the efficacy and safety of perhexiline in patients with chronic heart failure and/or refractory angina (Phan et al., 2009), and demonstrated minimal side effects or toxicity, while patients suffering from refractory angina exhibited the greatest improvement of symptoms. In the United Kingdom, perhexiline is available for off-label use, while in Australia, it is widely used in the treatment of refractory angina. It is not approved by the Food and Drug Administration.

4.6. Allopurinol

Allopurinol is a xanthine oxidase inhibitor used in the treatment of gout that inhibits the xanthine oxidase-catalyzed formation of uric acid from hypoxanthine and xanthine (Manchanda et al., 2011).

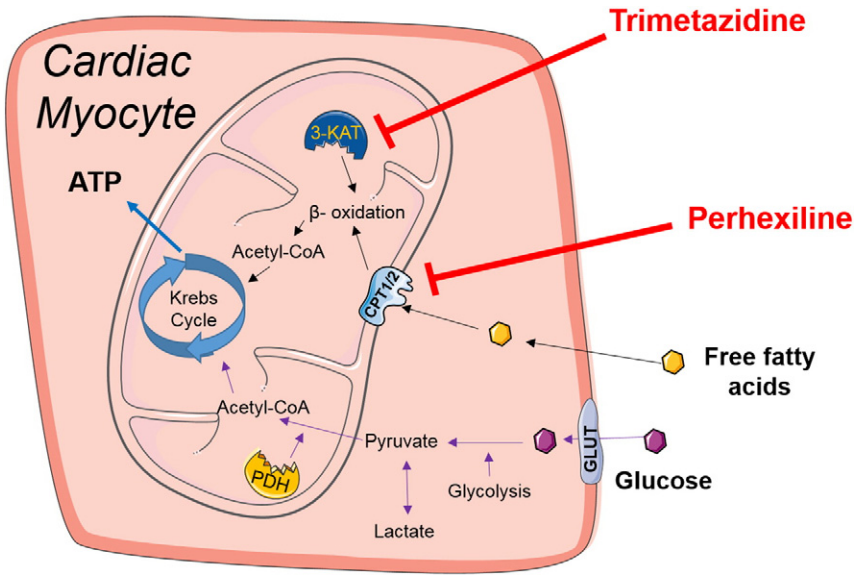

Fig. 8. Mechanism of action of trimetazidine and perhexiline. Metabolic agents such as trimetazidine and perhexiline are considered to increase glucose oxidation in ischemic myocytes thereby enhancing energy efficiency. Trimetazidine blocks mitochondrial 3-ketoacyl-CoA thiolase (3-KAT), an incremental enzyme for β-oxidation of fatty acids. Perhexiline enhances mitochondrial glucose oxidation by inhibiting carnitine *O*-palmitoyltransferase 1 and 2 (CPT1/2), the enzymes which transfer free fatty acids from the cytosol into the mitochondria.

Xanthine oxidase is a potent mediator of oxidative stress. It is considered that xanthine oxidase inhibitors can reduce myocardial oxygen consumption by reducing tissue oxidative stress (Stone, 2011). It is also considered to improve endothelial dysfunction in high doses by reducing vascular oxidative stress (George et al., 2006).

Noman et al. (2010) demonstrated, in a recent randomized placebo-controlled study, the possible role of allopurinol as an effective anti-ischemic medication. Sixty-five patients with CAD under beta-blockage were enrolled and randomly assigned to placebo or allopurinol (600 mg per day) for 6 weeks. High-dose allopurinol significantly prolonged the time to ST depression, total exercise time and time to angina in patients with chronic stable angina, suggesting that endogenous xanthine oxidase activity is involved in exercise-induced myocardial ischemia. Yet another study showed that, at the same doses, allopurinol can lead in reduction of left ventricular hypertrophy in CAD patients and to the improvement of endothelial dysfunction (Rekhraj et al., 2013).

Although allopurinol is low cost and has a long-term (>40 years) safety record (for treatment of gout), no large-scale trials have examined the efficacy, dosages and possible side effects when administered as an antianginal agent in CAD patients, let alone in refractory angina patients (Antony & Dargie, 2010). Allopurinol is not cleared by the Food and Drug Administration and is not in use in Europe for the treatment of angina.

4.7. Rho-kinase inhibitor

Rho-kinase has been identified as one of the effectors of the small guanosine triphosphate-binding protein Rho and is substantially involved in the pathogenesis of a wide spectrum of cardiovascular diseases including angina (Mohri et al., 2003). Fasudil is an inhibitor of Rho kinase implicated in vascular smooth muscle contractile response that has known anti-ischemic effects. It is regarded to exhibit its mechanism by reducing calcium sensitization of vascular smooth muscle in order to maintain coronary vasodilation and prevent vasospasm (Shimokawa et al., 2002). By inhibiting Rho kinase, fasudil may inhibit the effects of vasoconstrictors that are unaffected by current therapies.

Vicary et al. reported that fasudil prolonged time to ST-segment depression on exercise testing, improved exercise duration, and significantly reduced the number of anginal attacks (Vicari et al., 2005). The potential usefulness of Rho kinase inhibitors for the treatment of refractory angina remains to be examined in future studies.

4.8. Other pharmacological approaches

Agents that might also be of benefit for the refractory angina patients include molsidomine, antidepressants (such as escitalopram and imipramine), testosterone, chelation therapy and thrombolytic regimens (such as urokinase). None of these agents have been tested in a placebo-controlled trial and their mechanism of action with respect to alleviation of angina symptoms remains elusive. Finally, commonly used as a last resort for pain control, opioids can be administered under close monitoring and caution due to their frequent side effects.

5. Pharmaceutical management of refractory angina in the setting of coronary microvascular dysfunction

Microvascular angina secondary to microvascular dysfunction, without obstructive epicardial CAD, accounts for a percentage of the refractory angina patients. No refractory angina-dedicated study has been performed to date examining therapeutic options in this group of patients. Symptom management remains challenging and there is little evidence to support any of the current treatment strategies (Marinescu et al., 2015).

Risk factor control and life style modification are considered to be the basis; smoking cessation and weight control are known to improve endothelial dysfunction (Crea et al., 2014). Similarly, disease-modifying agents such as renin angiotensin system inhibitors and statins have been shown to ameliorate endothelial function in the coronary microcirculation and represent first-line treatment options (Chen et al., 2002). With regards to symptoms control, traditional antianginal agents are in use; albeit considered to be less effective compared to obstructive CAD. The efficacy of novel antianginals, such as ranolazine, nicorandil and fasudil has been evaluated in small-scale clinical trials (Jaw-Wen et al., 1997; Mohri et al., 2003) with promising results (Fig. 9).

Other agents that have been evaluated for the management of microvascular angina include nitric oxide modulators (sildenafil), xanthines, estrogens, alpha-antagonists and tricyclic antidepressants (i.e. imipramine) (Loffler & Bourque, 2016). Targeting several pathophysiologic mechanisms, results have been inconsistent in improving

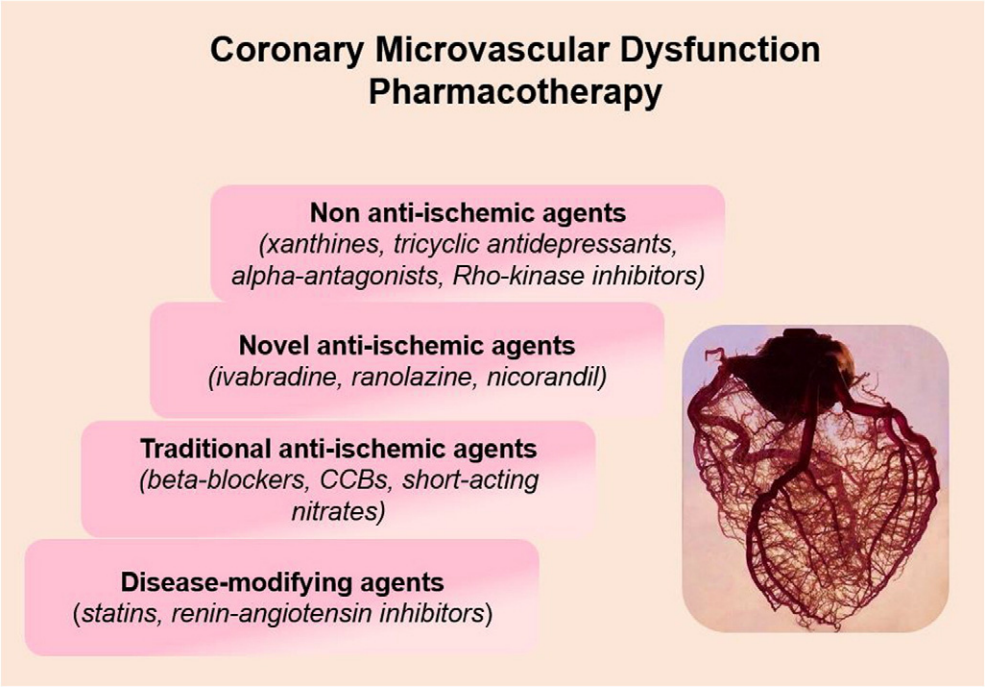

Fig. 9. Pharmacotherapy of refractory angina patients in the setting of coronary microvascular dysfunction disease.

symptoms and in modifying the natural history of endothelial microvascular dysfunction. As current treatment approaches may not be effective in refractory microvascular angina patients, future goals should include larger-scale studies with longer follow-up periods, evaluating both traditional antianginal drugs, as well as regimens targeting the unique pathophysiologic mechanisms of coronary microvascular dysfunction.

6. Non-pharmacological approaches for the management of refractory angina

A detailed description of the non-pharmacological approaches for the management of refractory angina is beyond the scope of this review. Invasive and non-invasive approaches are currently in use and others are under evaluation. Amongst them, enhanced external counterpulsation, spinal cord stimulation, transmyocardial laser revascularization and reduction of coronary sinus have been widely used.

Enhanced external counterpulsation consists of ECG-gated sequential lower limb compressions and has been shown to improve angina symptoms, myocardial perfusion and quality of life in patients with refractory angina (Arora et al., 1999; Loh et al., 2008; C. Zhang et al., 2015). The sequential cuff inflations create a retrograde arterial pressure wave that augments diastolic pressure, therefore increasing coronary perfusion pressure and preload. The beneficial effects of enhanced external counterpulsation in patients with CAD appears to persist after completion of therapy for even up to 3 years. Enhanced external counterpulsation is typically provided on an outpatient basis in 35 one-hour sessions over a seven-week period. The ESC recommends enhanced external counterpulsation for symptoms relief in patients with angina refractory to optimal medical and revascularization strategies (Class IIa, level of evidence B) and similarly the AHA supports its use for angina relief and improvement of quality of life (Class IIb, level of evidence B).

Spinal cord stimulation is performed through minimal invasive implantation of electrodes to the epidural space typically between C7 and T4 inducing bilateral paresthesia across the subjective area affected by angina pectoris. The electrodes are attached to an implanted device, allowing the patient to control the presence, the continuity as well as the intensity of the stimuli. Neuromodulation, mainly spinal cord stimulation, inhibits nociceptive afferent nerve fibers and leads to augmented release of the inhibitory neurotransmitter γ-aminobutyric acid, thus resulting in local analgesia. Moreover, it is considered that it enhances coronary microcirculatory blood flow, thereby improving myocardial ischemia (Latif et al., 2001). Spinal cord stimulation is considered to be a safe, reversible modality, with anti-ischemic effects and has been shown to improve quality of life, without concealing angina during an acute coronary syndrome. Both the ESC and AHA recommend spinal cord stimulation (Class IIb, level of evidence B and C, respectively) for the treatment of refractory angina.

Transmyocardial laser revascularization is performed either epicardially during open heart surgery or endocardially following percutaneous approach. These laser-based modalities, in principle, create transmural microchannels in the ischemic myocardium and are considered to restore myocardial perfusion, most likely via injury-stimulating angiogenesis and denervation (Henry et al., 2014). Although transmyocardial laser revascularization is approved by the Food and Drug Administration and has a class IIb (level of evidence B) recommendation from the AHA (Fihn et al., 2012), no new trials have been published in the last ten years and it is considered very unlikely that new research will be undertaken in this field. A recent review has indicated that risks associated with transmyocardial laser revascularization outweigh the potential clinical benefits and that the procedure may pose unacceptable risks (Briones et al., 2015). Transmyocardial laser revascularization is not recommended by the ESC.

Percutaneous reduction of coronary sinus is an evolving modality for the alleviation of symptoms in refractory angina patients. Controlled narrowing of the coronary sinus creates an upstream pressure gradient that results in the redistribution of blood from the less ischemic epicardium to the ischemic endocardium thus reducing myocardial ischemia (Banai et al., 2007). A recent, double-blinded, sham-controlled trial of a coronary sinus reducing device in patients with refractory angina, showed significant improvements in reducing angina and improving quality of life (Verheye et al., 2015). Coronary sinus reduction is not currently included in European or US cardiovascular societies guidelines.

7. Conclusions and future perspectives

As the population ages and CAD mortality decreases, the number of patients suffering from refractory angina will most likely increase and apparently we should shift our focus on symptoms relief and improvement of quality of life of these patients. Evidently, pharmacological approaches play a key role in the management of refractory angina. The value of intensified medical treatment in newly diagnosed patients has been demonstrated (Dourado et al., 2015) and efforts to achieve well-tolerated, optimal dosages and schemes cannot be overemphasized. Traditional agents, with novel drugs that are joining our armamentarium, and others that are under development and investigation, need to remain in the focus of future studies. Several non-pharmacological approaches are in use or under investigation; however, few have provided sufficient clinical data, potentially explaining the lack of dedicated guidelines for the treatment of refractory angina. First and foremost, along with pharmaceutical regimens and other treatment options, lifestyle modifications should be the basis of the therapeutic plans, as no pill or intervention will completely relieve the patient. Clinicians should treat the refractory angina patient with a formulated plan that includes behavioral strategies to achieve effective disease management supplemented by individualized selection of pharmacologic agents. A patient-centered approach is imperative, built around a multidisciplinary team that will aim to treat the patient as an entity and not merely the heart.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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