Additional and emerging drugs for standard therapy for patients with stable angina

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The prevalence of stable angina increases with age and it can be refractory to standard treatment in up to 10% of cases. Management aims to improve prognosis and reduce symptoms. Besides lifestyle modifications and the control of risk factors, drugs include therapy to prevent myocardial infarction and death. Pharmacological therapy includes anti-anginal drugs in addition to antiplatelet agents, beta-blockers and renin-angiotensin aldosterone blockers. The first-choice anti-ischaemic agents are beta-blockers (or non-dihydropyridine calcium channel blockers) and nitrates. Additional and emerging anti-anginal drugs are nicorandil, ivabradine, ranolazine and trimetazidine. In this review, aspects regarding the pharmacological update of these anti-anginal drugs including their mechanisms of action, indications, contraindications and adverse effects will be addressed.

Topic(s): *Coronary Artery Disease, Acute Coronary Syndromes, Acute Cardiac Care;*

Background

The prevalence of angina pectoris is 3.4% in the population ≥20 years, and the age-adjusted prevalence is higher in women, especially Hispanic women, considering the population between 40 and 75 years. Data from the National Center for Health Statistics and National Heart, Lung, and Blood Institute demonstrate the increase in angina pectoris with age, reaching a frequency of 11.8% and 10.9% for women and men, respectively, who are at least 80 years old [1]. A recent European registry in 10 countries including 2,420 patients with chronic coronary artery disease showed that the age was more advanced and the patients presented more comorbidities when compared to the Euro Heart Survey data, published in 2005, which included 3,779 patients [2]. The

prognosis of angina pectoris depends on the patient's clinical profile and its approach, resulting in an annual mortality of up to more than 3% [3]. When, in spite of optimal medical treatment, angina is persistent, it is defined as refractory angina. This presentation occurs in between 5% and 10% of cases and it is responsible for an annual mortality of between 2% and 4% [4]. In addition to traditional pharmacological treatment, which is the first choice, there are other emerging anti-anginal drugs, whose prescription rate is low, e.g., 1.4% for ranolazine and 4.1% for ivabradine [2].

Pharmacological treatment: recent anti-anginal agents

The 2013 European guidelines on stable coronary artery disease recommend adding ivabradine, nicorandil, ranolazine (class IIa), or trimetazidine (class IIb) for second-line treatment [5]. In the United States of America, the 2014 guidelines recommended ranolazine as class IIa; the other anti-anginal agents were not considered for medical therapy [6].

Nicorandil

The effects of nicorandil on coronary vasodilation have been known since the late 1970s [7]. It is a nicotinamide nitrate derivative with a dual mechanism of action. It increases cyclic guanosine monophosphate and facilitates the opening of mitochondrial potassium adenosine triphosphate channels. This results in venous and arterial vasodilation, and the coronary arteries, and protects ischaemic myocytes by opening the mitochondrial adenosine triphosphate-sensitive potassium channels [8]. Nicorandil is considered as a second-line option to treat patients with stable angina when they do not tolerate or cannot use beta-blockers (or calcium channel antagonists such as verapamil and diltiazem) or when they do not respond enough to first-line medications. The most recently updated European Medicine Agency guidelines did not indicate the use of nicorandil to prevent heart attacks in patients with stable coronary artery disease [9]. However, a recent prospective, randomised and controlled study of 402 patients with stable angina demonstrated a decrease in the number of ischaemic attacks in those using nicorandil for 12 weeks in addition to the standard anti-anginal treatment [10].

Among the adverse effects are gastrointestinal, skin and mucosal ulcerations (especially if there is concomitant use of acetylsalicylic acid or non-steroidal anti-inflammatory drugs). In this case, the drug should be discontinued permanently [9].

Ivabradine

This drug has been approved by the European Medicines Agency since 2005 [9]. Ivabradine selectively inhibits the If current, an important current involved in generating the early phase of spontaneous diastolic depolarisation in sino-atrial cells, reducing the frequency of action potential initiation and lowering heart rate. It decreases the body's demand for myocardial oxygen, without any effect on blood pressure or myocardial contractility or conduction times, and results in a reduction in angina symptoms and sublingual nitrate consumption. Its use is indicated for patients with sinus rhythm with heart rate ≥70 bpm, alone (in patients with contraindications or intolerance to beta-

blockers) or in combination with a beta-blocker, based on the BEAUTIFUL trial [11]. However, the benefit of ivabradine in reducing cardiovascular events was not demonstrated by the SIGNIFY study in patients without clinical heart failure [12]. Among 12,049 patients with angina class ≥II on the Canadian Cardiovascular Society scale, there was an increased absolute risk of cardiovascular death or non-fatal myocardial infarction by 1.1 percentage points. The incidence of adverse events was higher with ivabradine compared to placebo: 18% versus 2.3% for bradycardia and 5.3% versus 3.8% for atrial fibrillation. These outcomes can, in part, be attributed to a dose of 10 mg twice a day, which is higher than the recommended dose [9]. However, further analysis found no impact of bradycardia and atrial fibrillation on cardiovascular outcomes in the whole population or in the angina subgroup [13]. Therefore, physicians should be aware of these adverse effects, preventing the heart rate from falling below 50 bpm, and limiting the use of ivabradine to three months if there is no improvement in angina symptoms or if improvement is limited. In addition, since ivabradine is metabolised by CYP3A4, there is drug interaction with CYP3A4 inhibitors and inducers. Therefore, its concomitant use with verapamil or diltiazem is not recommended [9].

Ranolazine

Ranolazine was approved for clinical use in 2006 in the USA and in July 2008 in Europe for the treatment of chronic angina, based on the results of the MARISA and CARISA studies [14,15]. It selectively inhibits the late sodium influx in the myocardium, reducing calcium overload, attenuating the ischaemic abnormalities of ventricular repolarisation and the resulting reduced contractility. Thus, it improves exercise tolerance while reducing the frequency of angina episodes. Ranolazine can improve myocardial ischaemia without affecting heart rate or blood pressure. Although its exact mechanism has not been clarified, this anti-ischaemic effect seems to be related to the displacement of myocardial adenosine triphosphate production from fatty acid metabolism to an oxygen-efficient carbohydrate oxidation and reduction in oxygen consumption [9,14-16]. In patients with previous chronic angina, there was a decrease in the primary endpoint composed of cardiovascular death and acute myocardial infarction with the use of ranolazine. In addition, the drug has a positive effect on glucose metabolism. There was a decrease in the level of HbA1c in diabetics (of the order of 0.43% in a meta-analysis), especially in those with inadequate glycaemic control, when compared with a placebo group. There is evidence of decreased weekly frequency of episodes of angina and the use of a sublingual nitrate, also in diabetic patients [14,15]. Therefore, the use of ranolazine should be considered in patients with increased levels of HbA1c and in patients with low basal blood pressure and heart rate.

Recently, a secondary analysis of the RIVER-PCI trial demonstrated that anti-ischaemic and glycaemic control actions are observed at six months of treatment with ranolazine. However, these effects were not detected at 12 months of treatment in diabetic patients undergoing percutaneous coronary intervention with incomplete revascularisation [17].

Among its adverse effects, QT prolongation may occur. Despite this, there were no pro-arrhythmic effects, with a low incidence of ventricular tachycardia [14].

Trimetazidine

Although the anti-anginal action of trimetazidine has been known for more than 40 years in Europe, its use has only been approved since 2012 as adjunctive therapy for patients with stable angina as a class IIb recommendation. It inhibits reduction of intracellular adenosine triphosphate levels via conservation of cellular metabolism in ischaemic regions and stimulates myocardial glucose consumption through inhibition of fatty acid metabolism. Trimetazidine is effective in the treatment of stable angina compared with placebo, alone or combined with conventional anti-anginal agents, resulting in a decrease in the number of episodes of angina and nitrate consumption, and improved exercise tolerance [18,19]. It has very limited haemodynamic effects, but can cause symptoms of Parkinsonism. Therefore, among its main contraindications is Parkinson's disease. If Parkinsonian symptoms are caused by trimetazidine and persists for more than four months after its permanent interruption, a consultation with the neurologist should be arranged [9,14,19].

The mechanisms of action, posology, major contraindications and adverse effects of these anti-anginal drugs are shown in Table 1. The pharmacokinetic characteristics of these drugs are shown in Table 2.

Table 1. Mechanism of action, dose, contraindications, adverse effects of the additional anti-anginal agents (5,6,9,14).

Drugs	Ivabradine
Mechanism of action	Reduction of pacemaker activity in sinus node
Dose	Oral dose of 5 to 7.5 mg twice daily; 2.5 mg twice daily (>75 years of age or according to symptoms and heart rate)
Contraindications	Severe liver disease, low heart rate or heart rhythm disorder, allergy
Major adverse effects	Bradyarrhythmia, visual disturbances

Drugs	Nicorandil
Mechanism of action	Opening the mitochondrial adenosine triphosphate-sensitive potassium channels

Dose	10 mg twice daily or 5 mg twice a day (if headache); maximum dose of 20 mg twice daily
Contraindications	Low blood pressure, hypovolaemia, severe heart failure, concomitant use of phosphodiesterase 5 inhibitors and/or soluble guanylate cyclase stimulators
Major adverse effects	Gastrointestinal ulcerations, skin and mucosal ulcerations

Drugs	Ranolazine
Mechanism of action	Inhibition of the late inward sodium channel
Dose	375 mg twice daily to 750 mg twice daily (prolonged-release tablets)
Contraindications	Severe renal insufficiency, moderate or severe hepatic impairment; concomitant administration of potent CYP3A4 inhibitors or class Ia or class III anti-arrhythmic drugs (such as dofetilide, sotalol)
Major adverse effects	Nausea, constipation, dizziness, headache, asthenia, prolongation of the QT interval

Drugs	Trimetazidine
Mechanism of action	Inhibition of the reduction of adenosine triphosphate, stimulation of glucose consumption by the myocardium
Dose	20 mg three times a day or 35 mg twice daily

Contraindications	Parkinson's disease, tremors and movement disorders, severe renal impairment
Major adverse effects	Parkinsonian symptoms, gastric discomfort, headache, movement disorders

Drugs	Mechanism of action	Dose	Contraindications	Major adverse effects
Ivabradine	Reduction of pacemaker activity in sinus node	Oral dose of 5 to 7.5 mg twice daily; 2.5 mg twice daily (>75 years of age or according to symptoms and heart rate)	Severe liver disease, low heart rate or heart rhythm disorder, allergy	Bradyarrhythmia, visual disturbances
Nicorandil	Opening the mitochondrial adenosine triphosphate-sensitive potassium channels	10 mg twice daily or 5 mg twice a day (if headache); maximum dose of 20 mg twice daily	Low blood pressure, hypovolaemia, severe heart failure, concomitant use of phosphodiesterase 5 inhibitors and/or soluble guanylate cyclase stimulators	Gastrointestinal ulcerations, skin and mucosal ulcerations

Drugs	Mechanism of action	Dose	Contraindications	Major adverse effects
Ranolazine	Inhibition of the late inward sodium channel	375 mg twice daily to 750 mg twice daily (prolonged-release tablets)	Severe renal insufficiency, moderate or severe hepatic impairment; concomitant administration of potent CYP3A4 inhibitors or class Ia or class III anti-arrhythmic drugs (such as dofetilide, sotalol)	Nausea, constipation, dizziness, headache, asthenia, prolongation of the QT interval
Trimetazidine	Inhibition of the reduction of adenosine triphosphate, stimulation of glucose consumption by the myocardium	20 mg three times a day or 35 mg twice daily	Parkinson's disease, tremors and movement disorders, severe renal impairment	Parkinsonian symptoms, gastric discomfort, headache, movement disorders

Table 2. Pharmacokinetic characteristics of the additional anti-anginal agents (9,16,19,20).

Drug characteristics	Oral bioavailability, %
Ivabradine	40
Nicorandil	75-80
Ranolazine	35-55

Trimetazidine	-

Drug characteristics	Plasma protein blinding, %
Ivabradine	70
Nicorandil	weakly bound
Ranolazine	62
Trimetazidine	15

Drug characteristics	Time to peak levels
Ivabradine	1 hr
Nicorandil	30-60 min
Ranolazine	2-6 hours
Trimetazidine	1.8 hrs

Drug characteristics	Half-life, hours
Ivabradine	2 (main), 11 (effective)
Nicorandil	1
Ranolazine	About 7
Trimetazidine	6 (12 in the elderly)

Drug characteristics	Steady state, days
Ivabradine	6
Nicorandil	4-5
Ranolazine	3
Trimetazidine	1

Drug characteristics	Excretion
Ivabradine	via faeces and urine to a similar extent
Nicorandil	mainly by the urinary route
Ranolazine	75% renal, 20% faeces
Trimetazidine	79%-84% renal

Drug characteristics	Ivabradine	Nicorandil	Ranolazine	Trimetazidine
Oral bioavailability, %	40	75-80	35-55	-
Plasma protein blinding, %	70	weakly bound	62	15
Time to peak levels	1 hr	30-60 min	2-6 hours	1.8 hrs
Half-life, hours	2 (main), 11 (effective)	1	About 7	6 (12 in the elderly)

Drug characteristics	Ivabradine	Nicorandil	Ranolazine	Trimetazidine
Steady state, days	6	4-5	3	1
Excretion	via faeces and urine to a similar extent	mainly by the urinary route	75% renal, 20% faeces	79%-84% renal

Other anti-anginal medications

There are other anti-anginal drugs that have not been authorised for use [4-6]. Among them, there is allopurinol, a xanthine oxidase inhibitor. Their potential mechanisms include decreased myocardial oxygen demand and improved vascular endothelial function; however, clinical data are limited [14,15]. Another medication is fasudil, a specific RhoA kinase inhibitor, which is a class of calcium antagonists, with vasodilator properties [21]. It has been used for the treatment of cerebral vasospasm. Molsidomine, a direct nitric oxide donor, can improve endothelial function. However, a double-blind, parallel-group, randomised, multicentre and placebo-controlled study in patients with stable angina undergoing percutaneous coronary intervention did not demonstrate significant differences between treatment with molsidomine compared to placebo for 12 months [22].

Conclusions

The emerging class IIa anti-anginal agents are nicorandil (nitrate-like effect, vasodilator), ivabradine (If current inhibitor) and ranolazine (late sodium current inhibitor). Trimetazidine, a partial fatty acid oxidation inhibitor, has a class IIb recommendation. They are effective for the control of episodes of stable angina, as monotherapy or in combination with beta-blockers. Ranolazine is mainly useful in those patients who cannot tolerate upward titration of conventional anti-anginal agents due to the depressive effects on heart rate and blood pressure. A reduction in cardiovascular events and in the level of HbA1c with ranolazine has been shown. The choice of treatment should be personalised, based on the particularities of the patient and taking into account the contraindications and adverse effects of each medication.

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Notes to editor

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The author has no conflicts of interest to declare.