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Treatment of stable ischaemic heart disease: the old and the new

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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. Furthermore, recent evidences supported the use of low doses direct anticoagulant, or a second antiplatelet agent in patients with previous MI. Similarly, a very low LDL cholesterol level, such as obtained with PCKS9 inhibitors, seems very beneficial in these patients. It is possible that in the near future a specific role for neo-angiogenesis factors and cellular therapies, could be proven, albeit, presently these treatments are not supported by solid evidences.

Introduction

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.

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.[2]

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. In this work,

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we will analyse the state of the art in the pharmacological treatment of stable CAD.

The old

Beta-blockers

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.[3] The above mechanisms improve the balance between oxygen supply and demand and increase the threshold of appearance of angina (*Figure 1*). Beta-blockers improve prognosis, in addition to anti-angina symptoms, in patients with a history of MI or left ventricular dysfunction.[5,6]

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.[7,8] 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.*[12] 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.[13] In contrast, BB therapy was associated with adverse effects and a non-significant increase in hospitalization rates.

Again in contrast to previously reported historical data, analyses performed by Bangalore *et al.*[14] using data from the REACH register and CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance) showed no difference in mortality with BB therapy in patients with previous history of MI. This temporal discrepancy in results with an apparent lack of benefit in more recent studies could be explained by the overall improvements in the treatment of ACS, with aggressive reperfusion, secondary prevention (concomitant use of drugs such as aspirin, enzyme inhibitors of angiotensin conversion and statins), and lifestyle interventions. This accounts for the position of the 2013 European Society of Cardiology (ESC) guidelines that exclude BBs from treatments that improve prognosis in SIHD patients.

Nitrates

Organic nitrates are among the oldest drugs used in the treatment of angina. Nitrates increase the distribution of

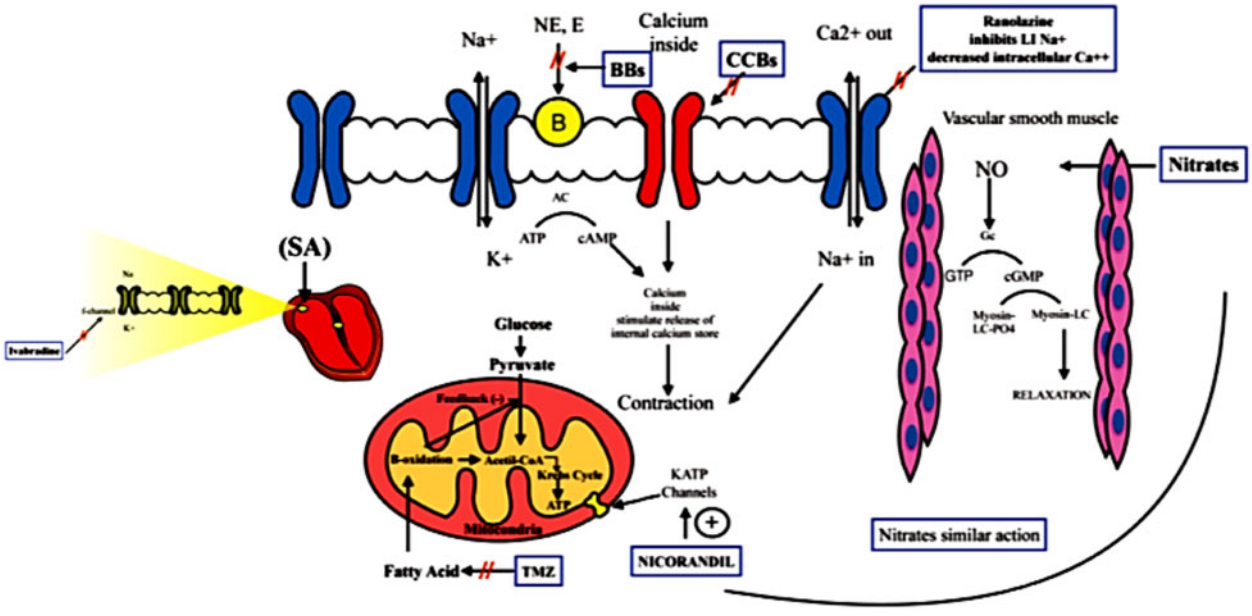

Figure 1 Therapeutic targets of anti-angina therapies (modified by Padala *et al.*[4]).

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.[15]

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.[7,8]

Although previous studies have clearly shown the role of nitrates in improving exercise capacity and reducing angina episodes, high-quality studies that examine the impact of nitroglycerine on 'hard' clinical endpoints are lacking. In fact, nitrates are thought to have a minimal impact on long-term prognosis, based on the GISSI-3 and ISIS-4 trials conducted in patients with MI.[16,17] These studies did not show a mortality benefit from chronic nitrate administration. Currently, nitrates are therefore recommended for the management of the angina crisis and to reduce the frequency of episodes, by virtue of a low cost and the absence of serious side effects. The most frequent adverse reaction is indeed the headache.[18]

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.[19] Calcium channel blockers are currently recommended in angina as second-line therapy after BBs, along with nitrates.[7,8] 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.[20] 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.*[21] 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 23 studies showed that trimetazidine is effective in reducing the occurrence of stress-induced ischaemia at electrocardiogram.[22] 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.

The new

Ranolazine

Ranolazine is a new anti-angina agent belonging to the class of metabolic modulators. The mechanism of action with which it acts in angina is not entirely clear: the hypothesis foresees that ranolazine blocks the delayed sodium current in the ischaemic myocardium, leading to the decrease of intracellular calcium and, finally, to the reduction of oxygen demand. This drug does not affect heart rate or blood pressure.[23]

The efficacy of ranolazine as anti-angina has been evaluated in multiple randomized clinical trials as monotherapy and in combination with other drugs. The guidelines suggest it if the symptoms are not well-controlled with BB, calcium channel blockers, or nitrates or if hypotension and bradycardia limit the use of these drugs (Class IIa indication of European and American guidelines).[7,8] The relatively high cost and the absence of generic formulations have so far limited its adoption in a widespread manner in clinical practice. The propensity of ranolazine to prolong QTc, although without an increase in malignant arrhythmias or arrhythmic deaths, combined with pharmacological interactions contributed to limiting its adoption.

Several studies have confirmed the effectiveness of ranolazine in reducing angina symptoms and angina-free

exercise time. The MARISA trial (Monotherapy Assessment of Ranolazine in Stable Angina) evaluated the efficacy of ranolazine in patients with stress angina treated with nitrates, calcium antagonists, and BBs.[24] In patients treated, during stress test, there was a significant increase in the duration of the effort and an increase in the time to onset of angina and of the ST-segment subsidence. The CARISA trial (Combination Assessment of Ranolazine in Stable Angina) evaluated whether ranolazine was able to improve the total exercise time of patients with symptoms of chronic angina, and manifestation of angina and ischaemia after reduced workloads, despite the assumption of standard dosages of atenolol (50 mg), amlodipine (5 mg), or diltiazem (180 mg). The study, carried out with 12-week follow-up, involved 823 adults with chronic symptomatic angina, who were randomized to receive placebo or two different dosages of ranolazine (750 mg or 1000 mg × 2/day). In patients treated with the two dosages of ranolazine, the duration of exercise increased by 115.6 s from baseline to 91.7 s in patients in the placebo group ($P = 0.01$). Ranolazine also reduced angina episodes and the use of nitroglycerine.[25] In a *post hoc* analysis, the group treated with ranolazine 750 and 1000 mg showed a reduction in glycosylated haemoglobin of 0.48% ($P = 0.008$) and of 0.70% ($P = 0.0002$), respectively, over placebo.[26] Finally, in the ERICA trial (Efficacy of Ranolazine in Chronic Angina), the efficacy of ranolazine in the chronic treatment of patients with SIHD and at least three angina attacks/week was evaluated.[27] In the treated group a reduction in the frequency of angina attacks and a reduction in the use of sublingual nitrates was highlighted.

However, data on the reduction of mortality with ranolazine have not yet emerged. The MERLIN-TIMI 36 study examined the role of ranolazine in ACS patients. No improvement in the composite endpoint of cardiovascular death, non-fatal MI, or recurrent ischaemia was demonstrated.[28] Wilson *et al.*[29] performed a subgroup analysis in patients with a history of SIHD and demonstrated a reduction in the primary endpoint (mainly driven by lower recurrent ischaemia) but no change in mortality or MI.

In the recent multicentre randomized trial, the RIVER-PCI, conducted in patients treated by percutaneous coronary intervention (PCI) but incomplete revascularization, ranolazine did not benefit in reducing the risk of the combined endpoint of revascularization for ischaemia or admission for angina.[30]

Ivabradine

Ivabradine is the only drug belonging to the class of sinus node inhibitors that has been approved for clinical use. It acts through the inhibition of the late Na current (also known as If), which controls the spontaneous diastolic depolarization of the sinus node cells. The BEAUTIFUL trial evaluated the efficacy of ivabradine in reducing cardiovascular mortality and morbidity in patients with CAD and left ventricular systolic dysfunction. Between 2004 and 2006, 10 917 patients with CAD and left ventricular ejection fraction <40% were enrolled. Ivabradine had no effect on the primary composite endpoint [hazard ratio (HR) 1.0; $P = 0.94$].[31] However, in the subgroup of patients with resting heart rate >70 b.p.m., ivabradine significantly reduced the incidence of secondary endpoints of admission for fatal and non-fatal AMI [HR 0.64; 95% confidence interval (CI) 0.49–0.84; $P = 0.001$] and coronary revascularization (HR 0.7; 95% CI 0.52–0.93; $P = 0.016$). The most important results were obtained in the subgroup of patients presenting with limiting stress angina (13.8% of patients enrolled in the study). In this group, ivabradine significantly reduced (−24%) the primary endpoint of cardiovascular death, hospitalizations for fatal and non-fatal MI or heart failure (HR 0.76; 95% CI 0.58–1.00; $P = 0.05$) and 42% hospitalizations for AMI (HR 0.58; 95% CI 0.37–0.92; $P = 0.05$).[31]

These positive data have not been confirmed by the recent randomized SIGNIFY study (Study Assessing the Morbidity-Mortality Benefits of the If Inhibitor in Patients with Coronary Artery Disease), conducted in patients with stable CAD and resting HR >70 b.p.m. in the absence of left ventricular dysfunction (FE > 40%). This trial enrolled 19 102 patients and the primary endpoint was a composite of death from cardiovascular causes and MI. Ivabradine did not reduce the primary endpoint during a median follow-up of 27.8 months. The drug led to a significant improvement in angina in CCS > II patients, at the price of an increased incidence of the primary endpoint in this subgroup.[32] Ivabradine is not approved in the USA for angina treatment.

Non-anti-angina drugs

In addition to symptom control therapies, prognosis-improving drugs such as antithrombotics and statins play a central role in SIHD. Indeed, the SIHD population presents a high risk of cardiovascular events, particularly if a previous MI or a revascularization for ACS is present in the history.[33]

Antiplatelet therapy is a cornerstone in patients with CAD and is historically represented by aspirin.[34] Recently, the opportunity of a dual antiplatelet therapy in patients with post-infarct SIHD was evaluated in the PEGASUS trial: in selected (low haemorrhagic risk) patients the addition of ticagrelor 60 mg b.i.d. at 1–3 years after the acute event, it has allowed to save in 10 000 patients 42 cardiovascular events/year at the price of 31 TIMI major haemorrhages/year.[35]

In the COMPASS study, three antithrombotic regimens were compared in coronary heart disease patients (previous MI, angina, previous percutaneous, or surgical coronary revascularization): rivaroxaban 2.5 mg b.i.d. plus ASA, rivaroxoban 5 mg bid, ASA alone: a significant reduction in the combined primary endpoint (cardiovascular death, MI, and stroke) was observed in the ASA + rivaroxaban group: 347 (4%) out of 8313 vs. 460 (6%) out 8261 (HR 0.74, 95% CI 0.65–0.86, $P < 0.0001$)[36]; at the same time, an increase in bleeding was observed with this latter treatment compared to ASA alone, however with a clear clinical benefit in favour of dual therapy and a reduction in mortality.

The reduction of systemic inflammation using an anti-interleukin 1β monoclonal antibody has been shown to significantly reduce events; canakinumab was tested vs. placebo in the CANTOS trial in post-MI patients and with

C-reactive protein >2 mg/dL and led to a reduction in MACE: HR 0.85 (0.76–0.96) in a 5-year follow-up.[37]

Among the other pharmacological and non-pharmacological interventions capable of modifying the prognosis, the inhibitors of the renin–angiotensin system, the control of diabetes, the cessation of smoking, the control of weight, and the reduction of cholesterol by statins are to be mentioned. With regard to the latter aspect, the recent Fourier study showed an important reduction in cardiovascular events in patients with a history of previous MI, previous stroke, or peripheral arterial disease using Evolocumab, a PCSK9 inhibitor; the drug was compared with placebo in patients already on high-dose statin treatment, thus demonstrating the benefit of achieving particularly low LDL cholesterol.[38]

Hyper-uricaemia has been associated with a worse prognosis in patients with heart failure; some evidence seems to suggest a negative impact also in ischaemic heart disease, through a mechanism of increased oxidative stress and consequent endothelial dysfunction; to support this, some studies have shown that allopurinol can reduce angina symptoms and increase exercise capacity.[39]

The future

Therapeutic angiogenesis using vascular endothelial growth factors, although promising, is still premature for a clinical setting.[40] Important studies on the use of stem cells are underway, however, it is not yet clear which cells are most suitable for the treatment of patients with angina, as well as the best method of administration. Attention is currently focusing on autologous CD34 + cells, which appear to be quite promising.[41]

Conclusions

The medical treatment of chronic ischaemic heart disease is often underutilized, despite the good efficacy, and solid scientific proof, in reducing symptoms. However, the lack of clarity of the guidelines, combined with the difficulty in managing association therapies, still lead a large part of patients with SHID to undergo PCI before having optimized anti-angina therapy. The most recently introduced drugs, ranolazine and ivabradine, have not been shown to modify the patients' prognosis and their adoption in clinical practice has been anything but disruptive, however, they are an important resource in hypotensive and bradycardic patients.

Future scenarios will probably see the arrival of cellular therapies and the use of angiogenic factors that will change the scenario in patients suffering from refractory angina and not candidate for revascularization. However, the road to their concrete adoption is still very long.

Undoubtedly, a central role in the prognosis of patients with SIHD can be played by measures that slow the progression of atherosclerotic disease and reduce the risk of acute ischaemic events.

Conflict of interest: none declared.

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