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Treating angina

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Coronary artery disease remains the leading cause of mortality in industrialized countries and, recently, has played an important role in the developing ones as well. This is true despite the 12.8% age-adjusted death rate for ischaemic heart disease between 2005 and 2015.[1] Half of this decline is due to prevention programmes and containment of risk factors by effective drugs, such as aspirin, lipid-lowering agents, and angiotensin-converting enzyme (ACE) inhibitors, whereas the other half has been attributed to revascularization with either thrombolysis and/or primary angioplasty. In general, coronary artery disease is the result of atherosclerosis, a progressive disorder of the coronary arteries with formation of plaque through the conduct system. Inflammation of the vascular wall may lead to disruption of the endothelium overlapping a plaque and cause subsequent thrombosis.[2] Both lipid-lowering substances (statins and ACE inhibitors), besides reducing cholesterol levels and blood pressure, which are the main risk factors for coronary artery disease, maintain endothelial continuity by reducing its apoptosis and improving its regeneration. In so doing, these drugs delay the progression of coronary atherosclerosis and prevent plaque disruption. This pharmacological effect is often referred to as a 'pleiotropic' action.[3,4]

The same success in preventing and treating the acute phase of coronary artery disease is not shared for the treatment of the symptomatic manifestations of stable coronary artery disease, namely angina pectoris. However, strategies to improve the management of chronic stable angina remain a priority, bearing in mind that chronic angina is one of the most important causes of morbidity worldwide, has a negative impact on functional capacities and quality of life, and drugs for the treatment of angina are among the most prescribed of any treatment today.[5]

Current clinical guidelines recommend antianginal therapy to control symptoms before considering coronary artery revascularization. This is for a series of reasons. Randomized trials have shown that an invasive strategy of coronary revascularization after excluding patients who had significant coronary artery disease (>50% left main narrowing or proximal 3-vessel disease) is not superior to medical therapy.[6] The routine implementation of fractional flow reserve determination before considering an angioplasty has significantly reduced the indication for elective revascularization. Finally, several studies have shown that the recurrence of angina after an angioplasty is not uncommon, occurring up to 20–30% of patients in the first year after the intervention and almost half of the patients 5 years after the angioplasty suffer from recurrent angina.[6] This explains why it is common practice to maintain symptomatic pharmacological therapy after the procedure, despite demonstration of successful reperfusion.

The pharmacological therapy of angina has two main goals: first, to alleviate chest pain and improve quality of life and, second, to prevent cardiovascular events that are not reduced by reperfusion. Unfortunately, these two goals cannot be achieved with the same class of drugs, as pharmacological therapy to prevent cardiovascular events does not alleviate symptoms and, similarly, symptomatic therapy does not improve prognosis.[7] At present, pharmacological therapy of angina is recommended with drugs classified as being first line (beta-blockers, calcium channel blockers, and short-acting nitrates) or second line (long-acting nitrates, ivabradine, nicorandil, ranolazine, and trimetazidine). The first-line drugs were identified almost 50 years ago, as the first effective treatment of angina with amyl-nitrate was described in 1867 and the first available beta-blocker was introduced into clinical practice in 1964, whereas the first calcium antagonist was available in 1975.[7] It follows that these drugs have been recommended and used (not only for angina) for quite a long time and have generated a firm belief of their efficacy in the medical community. At the same time, it is also fair to say that they were approved several years ago with criteria that nowadays would be insufficient and that the (few) randomized studies to assess the success of antianginal therapy used rather immature technologies (nitroglycerine consumption or exercise duration), to say the best.

The second-line drugs were developed later and include modulators of myocardial metabolism (trimetazidine),

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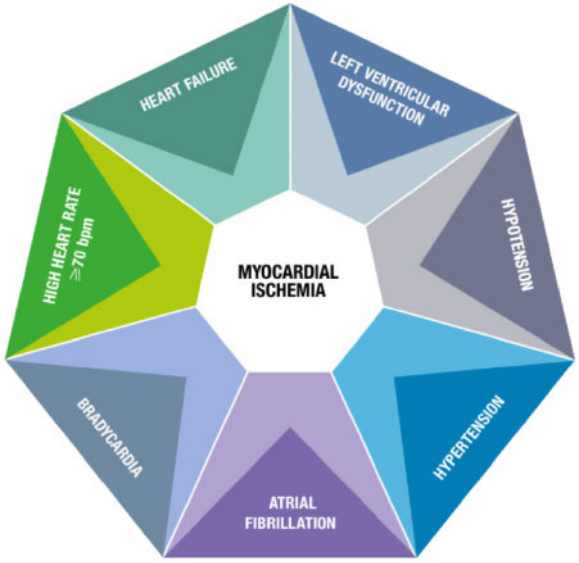

Figure 1. Flexibility of the 'diamond approach' according to the pathophysiology of angina.

Figure 2. Flexibility of the 'diamond approach' according to the patient's comorbidities.

adenosine triphosphate-dependent potassium channel openers (nicorandil), I_f channel inhibitors (ivabradine), and late inward sodium channel inhibitors (ranolazine). Their development was a consequence of a better understanding of the pathophysiology of angina. The fact that all of these drugs have been proven to ameliorate angina and all parameters of an exercise test, as suggested by the European and American Agencies, acting on different mechanisms, suggests that the understanding of the pathophysiology of angina might differ from patient to patient.

Various physiological abnormalities can precipitate myocardial ischaemia and, therefore, its symptom—chronic angina. Ischaemia, in turn, occurs when the myocytes do not have enough oxygen for mitochondrial oxidation because of an imbalance between myocardial oxygen demand and delivery.[8] Several factors contribute to an increase in myocardial oxygen demand, with the most important ones being heart rate, blood pressure or afterload, myocardial wall tension, hypertrophy, and contractility.[9] The major determinants of oxygen delivery include coronary blood flow, which, in turn, depends on the pressure gradient across the coronary circuit and the integrity of the coronary arteries, as well as on the oxygen-carrying capacities of the blood and the haemoglobin level. Under normal conditions, an increase in oxygen demand is met by an increase in coronary blood flow because of dilatation of the coronary arteries, which does not occur in patients with an atherosclerotic lesion of the epicardial coronary arteries.

The concept that chronic stable angina is caused by epicardial stenosis has been accepted for many years and has provided a rationale for considering, at least, mechanical reperfusion. Recently, however, this concept has been challenged and it seems that myocardial ischaemia and angina might occur in the absence of obstructive epicardial lesions. In the majority of these cases, angina is due to coronary microvascular dysfunction, a condition also known as cardiac syndrome X. Another circumstance in which the coronary arteries may appear normal under coronary angiography is with the so-called vasospastic angina. It follows that symptomatic therapy of angina should be tailored to the underlying cause of the symptom. The various classes of drugs available work in different ways. As an example, beta-blockers effectively reduce heart rate and blood pressure and, therefore, myocardial oxygen demand, but, at the same time, they might increase coronary vascular resistance as a result of an increase in α-receptor stimulation, thus provoking epicardial coronary artery spasm and further dysfunction of the microcirculation. In addition, the preferred choice of antianginal drugs should also take into consideration common comorbidities of angina patients, such as hypertension, diabetes, atrial fibrillation, heart failure, autonomic dysfunction, and so on. Accordingly, the newer antianginal drugs that are classified as second choice have a range of different mechanisms of action that could be particularly useful considering the pathophysiology and comorbidities of the patient and have more evidence-based clinical data performed with contemporary and appropriate technologies to support their use than what is available for the traditional first-line drugs.

As a result, the idea and suggestion that a few classes of first-line drugs is good for all patients and is superior to another has been recently questioned.[7–10] To this end, a systematic review covering 50 years of medical treatment of angina was performed. It demonstrated a somewhat worrying paucity of data that no antianginal drug is superior to another one and equivalence is available for the use of beta-blockers (atenolol), calcium antagonists (amlodipine, nifedipine), and I_f channel inhibitors (ivabradine).[11] Thus, the guidelines draw conclusions not from what little data there are available, but from tradition and clinical beliefs.[12]

A few years ago, together with several colleagues with experience and interest in chronic angina, we reached a consensus and proposed a more individualized approach to patients, one that considered their comorbidities and

underlying mechanisms of angina. We called it the 'diamond approach.'[10] We believe that this approach will help clinicians make the best possible therapeutic choice independently from whether the drugs are first or second line. To this end, we are here proposing several simple and representative clinical cases of daily life, each one referring to a particular pathophysiological condition or comorbidity considered in the 'diamond approach.' These cases are examples of a decision-making process, based, before all, on the aetiology (leading cause) of ischaemia and angina, taking into consideration the comorbidities, and the treatment regarding possible drug interactions and side effects. We genuinely believe this should be in the core of the so-called patient-centred or 'diamond approach' (*Figures 1 and 2*).

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