REVIEW

Update on the medical treatment of stable angina

Mise au point sur le traitement médical de l’angor stable

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Summary
Stable angina is a form of coronary artery disease. Its potential to progress requires the most appropriate treatment in order to reduce the incapacitating effect of an acute angina attack and to avoid long-term cardiovascular events. With or without revascularization, pharmacological treatment is an essential component of this treatment strategy, which also involves lifestyle and diet. Statins and aspirin have been shown to be effective in preventing different aspects of coronary artery disease overall. The efficacy of other classes of treatment has been demonstrated in contexts such as stable angina (including postmyocardial infarction) and heart failure (under specific conditions of dosing) for beta-blockers and in contexts such as heart failure, postinfarction and following revascularization for angiotensin-converting enzyme inhibitors. Along with the oldest classes of treatment, such as nitrates (and related derivatives), beta-blockers and calcium channel blockers, new classes of treatments with entirely (trimetazidine, ivabradine) or partly (nicorandil) different mechanisms of action have now been added. The latest antianginal to obtain marketing authorization, ranolazine, is not yet available in France. The different levels of evidence of the efficacy of these pharmaceutical products vary greatly and overall are higher for those developed most recently. None is devoid of side effects, which must be taken into account in these patients, many of whom are elderly and polymedicated.

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Abbreviations: ACE, angiotensin-converting enzyme; BPM, beats per minute; cGMP, cyclic guanosine monophosphate; LDL, low-density lipoprotein.

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Background

Coronary artery disease is the leading cause of death in France, ahead of the different forms of cancer [1]. One of its clinical manifestations is stable angina, which is defined as a clinical syndrome typically characterized by discomfort in the chest elicited by exertion or emotional stress that is relieved by rest or nitroglycerine and can be attributed to myocardial ischaemia [2]. Unlike the different acute coronary syndromes, stable angina is not immediately life-threatening [2]. However, progression to a more severe form of the disease is impossible to exclude. This risk alone merits a robust treatment strategy consistent with current scientific knowledge [2,3]. Two recent French surveys have shown that a significant proportion of coronary artery disease patients deemed to be stable still develop angina attacks [4,5]. The European [2] and American [3] recommendations are relatively old (2006 and 2007, respectively) and do not (or only to a very limited extent) take account of recent strategic and pharmacological developments. This is probably one of the reasons why several reviews on the management of stable angina have recently been published [6–11].

Medical treatment is the cornerstone of stable angina

Beyond the context of refractory symptoms in medically treated patients, the place of revascularization compared with medical treatment has been debated for a long time. In its recommendations on stable angina (2006), the European Society of Cardiology emphasized that the treatment of patients with stable angina has two goals [2]. First, to improve prognosis by preventing myocardial infarction and death. Second, to minimize or abolish symptoms. On the other hand, the most recent European Recommendations on Myocardial Revascularization (2010) stressed that revascularization has a favourable effect on prognosis only in patients with patent myocardial ischaemia, even when they have no symptoms [12]. Regardless, medical treatment remains the basis of management in all situations, including when revascularization has already been performed [13]. This supposes that the likelihood of severe coronary artery disease has been properly assessed, because this assessment influences the choice of the different diagnostic and treatment strategies [6].

Several studies (COURAGE [14], AVERT [15], MASS II [16], BARI 2D [17], etc.) have questioned the respective roles of and indications for revascularization and medical treatment — particularly when medical treatment achieves its objectives in terms of controlling risk factors (COURAGE [14]) — but the door still remains open [7,11,18].

In France, percutaneous revascularization still has a major place, even as a first-line treatment. We do not intend to enter this debate, which is far from being closed. Rather, in this update on the medical treatment of stable angina, we intend to deal with the different medical options, with a special focus on pharmacological agents that either are already commercialized in France or are currently applying for it. We will also emphasize the optimization of medical strategies, including patient-tailored medications. However, setting a global strategy is a difficult task because the different data available are not necessarily comparable for the different options.

Medical treatments for stable angina

Medical treatment forms part of all of the management options, including revascularization strategies. In addition to antianginal medications, it includes essential rules for the medical treatment of stable angina, which is defined as a clinical syndrome typically characterized by discomfort in the chest elicited by exertion or emotional stress that is relieved by rest or nitroglycerine and can be attributed to myocardial ischaemia [2]. Unlike the different acute coronary syndromes, stable angina is not immediately life-threatening [2]. However, progression to a more severe form of the disease is impossible to exclude. This risk alone merits a robust treatment strategy consistent with current scientific knowledge [2,3]. Two recent French surveys have shown that a significant proportion of coronary artery disease patients deemed to be stable still develop angina attacks [4,5]. The European [2] and American [3] recommendations are relatively old (2006 and 2007, respectively) and do not (or only to a very limited extent) take account of recent strategic and pharmacological developments. This is probably one of the reasons why several reviews on the management of stable angina have recently been published [6–11].
Disease-modifying treatments that influence prognosis

In stable angina, the clear context of secondary prevention should lead to the systematic use of drugs proven to be effective in improving the prognosis of patients with coronary artery disease, in terms of morbidity and mortality. Most secondary prevention studies have recruited patients with various forms of established coronary disease, which did not involve stable angina as a single clinical presentation (follow-up of acute coronary syndrome, asymptomatic coronary artery disease, etc.). However, the context is sufficiently similar and occasionally confused (stable angina, proportions unstated) to justify extrapolating the same secondary prevention rules to all coronary artery disease patients. The basis of non-specific treatment still remains the adoption of an appropriate lifestyle (stopping all forms of smoking, physical exercise, balanced diet, influenza vaccination, etc.).
the prevalence and sometimes the increased risk associated with some form of resistance to these agents [21].

**Statin**

The effectiveness of statins in reducing the risk of cardiovascular events in secondary prevention has been well proven, with, in most cases, a low-density lipoprotein (LDL)-cholesterol treatment goal of 1.00 g/L. The current question concerns the effectiveness and tolerability of more intensive treatments aimed at reaching lower goals. A meta-analysis comparing more or less stringent goals shows increased benefit with more intensive treatments, without tolerability problems [22]. However, these studies were generally conducted on patients with more severe forms of coronary artery disease and it is difficult to extrapolate these results to isolated stable angina. The results of the DUAL study, which showed atorvastatin andamlodipine to have similar antianginal effects, should be confirmed and would, were it needed, be an additional reason for the systematic prescription of a statin in patients with stable angina [23].

**Angiotensin-converting enzyme inhibitors**

The findings of the HOPE study support the prescription of an angiotensin-converting enzyme (ACE) inhibitor for prevention of cardiovascular complications in all high-risk patients, which therefore includes those with stable angina [24]. The results of the EUROPA study further support this indication following myocardial revascularization [25]. These situations are, of course, complementary to the classical indications that may also be present in patients with stable angina, notably following myocardial infarction and in left ventricular dysfunction or heart failure.

**Beta-blockers**

Beta-blockers have been proven to provide benefit in reducing long-term morbidity and mortality after myocardial infarction [26]. They are therefore formally indicated in this situation in patients with stable angina. On the other hand, in the absence of a past history of myocardial infarction, their systematic use is not mandatory in isolated stable angina. In addition, they are potent anti-ischaemic agents.

**Antianginal drugs**

For a long time, the evaluation of antianginal drugs was only based on exercise-testing criteria, sometimes associated with an evaluation of the frequency of ambulatory heart attacks, which is slightly more clinically relevant [27]. Specific morbidity-mortality data on antianginal drugs in patients with stable angina are only available for one calcium channel blocker (nifedipine; ACTION trial [28]) and the potassium channel activator, nicorandil (IONA trial [29]).

**Beta-blockers**

Beta-blockers remain the pivotal treatment for angina pectoris. They have long been used to treat stable angina, which usually occurs in the context of increased adrenergic drive associated, for example, with effort or stress. They selectively block the beta-adrenergic receptors and thus prevent binding of the G-protein and activation of adenyl cyclase. They have a dual haemodynamic effect with negative inotropism and prolongation of diastole because of the bradycardia they induce. By decreasing blood pressure, they also reduce wall stress. Altogether, these effects reduce myocardial oxygen requirements and improve coronary artery perfusion.

In patients with coronary artery disease, the doses usually recommended are those that keep the heart rate less or equal to 60 beats per minute (bpm) or even lower in severe angina. The exercise test can be used to adjust the exercise heart rate on treatment below the pain threshold. No study has shown any one beta-blocker to be more effective than another in this indication [8].

Tolerability is a limiting factor in the use of beta-blockers, at least at optimal doses. Severe bradycardia, conduction abnormalities, severe peripheral arterial disease, asthma and severe obstructive bronchopulmonary disease are all contraindications limiting their use. Additional factors limiting their use are the decreased physical, psychological and sexual function that they may cause. Some of these obstacles can be partly avoided by the use of cardioselective beta-blockers. Heart failure has become an indication for the use of some of these drugs, although under specific dosing conditions.

As noted above, beta-blockers have been proven to be of benefit for improvement of the prognosis after myocardial infarction, particularly following early administration, but not in stable angina [30].

**Calcium channel blockers**

Calcium channel blockers reduce calcium influx into the cell, producing dual vasodilating and negative inotropic effects, which respectively vary depending on the different compounds. Dihydropyridines (amlodipine, felodipine, isradipine, nicardipine and nifedipine) mostly have a peripheral vasodilating action and increase heart rate. Their prolonged release pharmaceutical forms cause less tachycardia and could therefore be preferred. They must be associated with a beta-blocker or, failing this, with an alternative cardiac slowing agent (e.g., ivabradine). The non-dihydropyridines (diltiazem and verapamil) both have a peripheral vasodilating action and probrradycardic and myocardial depressant effects. Because of this, they are an alternative to beta-blockers but are contraindicated in left ventricular dysfunction or poorly controlled heart failure. They have been proven to be effective in exercise tests and 24-hour Holter monitoring but they have no influence on prognosis. In the ACTION trial, after a 4.9-year mean follow-up, no effect of nifedipine compared with placebo was demonstrated on a composite endpoint (death, acute myocardial infarction, refractory angina, new onset heart failure, debilitating stroke or peripheral revascularization) or on mortality and acute myocardial infarction, which were secondary endpoints [28].

Calcium channel blockers have not always been objectively shown to improve stress angina when associated with beta-blockers. They remain the reference treatment for spastic angina.
Nitrates

Nitrates are historically the leading therapeutic class used to treat angina pectoris. There have been many studies on their mechanism of action [31]. They are indirect nitric oxide donors, which block calcium entry in smooth muscle cells and promote their relaxation through production of cyclic guanosine monophosphate (cGMP). Their main haemodynamic effect is to reduce preload by venodilatation, although at high doses they have an arterial vasodilating effect, causing dilatation of the epicardial arteries. They promote redistribution of coronary blood flow from healthy to ischaemic areas [32]. Their antiaggrgant effect, which is, however, very limited, is explained by their action on platelet cGMP.

The duration of action of nitrates has been increased through the development of many pharmaceutical forms (sprays, patches, prolonged release tablets containing different metabolites, etc.). However, the risk of tolerance and the possibility of a rebound effect, for which many mechanisms have been suggested [8], prevents the desired effect from being obtained over the whole 24-hour cycle [31,33,34]. Because of this, a therapeutic window must be observed with the different long-acting forms, particularly by removing patches at night. Sublingual tablets remain the reference treatment for acute attacks. Failure to respond to sublingual treatment of an attack is an important indicator of accelerated progression of angina, which every patient must be able to recognize.

Nitrates are usually well tolerated, although they may cause headaches, restricting their use. Because of their vasodilating action, they increase heart rate and it is recommended to combine them with preventative treatments such as beta-blockers or calcium channel blockers, which have a heart rate-lowering effect. Association with treatments for erectile dysfunction is contraindicated as, by inhibiting type 5 phosphodiesterase, these prevent the degradation of cGMP and potentiate the effect of the nitrates [35].

Molsidomine

The mechanism of action of molsidomine is very similar to that of nitrates, to which it is often linked. Because of its biotransformation, molsidomine acts through the release of endothelial nitric oxide. Together with nitrates, it also has a very slight antiaggregant action, although, unlike nitrates, it is not indicated for use in the treatment of acute angina but only as a disease-modifying treatment to prevent attacks. Molsidomine has common adverse effects with the nitrates, particularly headaches, which may be worsened when it is used in association with other vasodilators. In particular, for nitrates, its association with type 5 phosphodiesterase inhibitors is contraindicated because of the risk of severe hypotensive episodes.

Nicorandil

Nicorandil has a dual mechanism of action [36,37]. Part of its chemical structure gives it the same effect as nitrates. The other part of the compound makes it similar to the nicotinamide-group vitamins, with the property of activating adenosine triphosphate-sensitive potassium channels. This causes hyperpolarization, which inhibits calcium influx into muscle cells and promotes relaxation (indirect calcium channel blocking effect). Because of this dual mechanism of action, nicorandil does not suffer the treatment escape phenomenon seen with nitrates alone. Because it activates potassium channels, nicorandil has a beneficial effect on ischaemic preconditioning and has been shown to have a cardioprotective effect in animal studies [37].

The antianginal activity of nicorandil has been demonstrated in many studies [29,37]. Its prognostic benefit was shown against placebo in coronary artery disease patients in the IONA study [29]. In this study, a significant benefit was found for several composite indicators, including the primary endpoint (deaths from coronary artery disease, non-fatal myocardial infarction or unplanned hospitalization for coronary artery disease: hazard ratio 0.83; 95% confidence interval 0.72–0.97; \( P = 0.014 \)). This result was mainly supported by a reduction in acute coronary events. Curiously, in this study, nicorandil had no benefit on symptoms assessed by the Canadian classification.

The main side effect of nicorandil is headache when treatment is started, which may be avoided by increasing doses gradually up to the optimal level. Ulcers were initially described as buccal and rare at the beginning of its clinical development [37]. However, several case reports describing many other locations were subsequently described (anal, colonic, vulvovaginal and penile), which may be severe although always reversible with treatment cessation.

Trimetazidine

Trimetazidine has a complex antianginal mechanism of action [38]. It acts mostly as a metabolic modulator, which optimizes myocardial energy expenditure on effort by promoting myocardial glucose use to the detriment of that of fats (partial inhibition of fatty acid \( \beta \)-oxidation by reducing the mitochondrial activity of an enzyme, 3-ketoacyl coenzyme A thiolase) [38]. It increases coronary reserve, although its antianginal effect is not due to reduced heart rate, myocardial depression or vasodilatation.

A meta-analysis by the Cochrane Collaboration grouped together comparative trials of trimetazidine versus placebo or other antianginal agents in patients with stable angina [39]. The analysis showed that compared with placebo, trimetazidine significantly reduces the number of weekly attacks, nitrate use and the time to onset of significant ST-segment depression. The authors, however, concluded that there was too little information to propose the use of trimetazidine either as monotherapy or in association in angina pectoris, although fewer people seemed to give up treatment because of side effects than with the other antianginals. There are, indeed, only a few such studies, each of which included only a small number of patients. A recent report by the French National Pharmacovigilance Commission (19 May 2009) found that trimetazidine could induce or increase Parkinsonian symptoms and asked for a reassessment of the whole benefit-risk balance of this drug [40]. Further to a procedure of re-evaluation, a decision of suspension (but not withdrawal) of the French Authorization of trimetazidine was pronounced (7 April, 2011) [41].
Ivabradine

Ivabradine acts purely by decreasing heart rate through a blockade of sinoatrial node If entry currents. It was first shown to be effective as an antianginal against placebo (superiority) in coronary artery disease patients with stable angina [42], and then against atenolol (non-inferiority) in the INITIATIVE study [43]. These studies first led to it being proposed as an alternative to beta-blockers when beta-blockers cannot be used, particularly because of contraindications or intolerance. Ivabradine was also shown to be complementary to atenolol in stable coronary artery disease patients, based on ergometric criteria, in the ASSOCIATE study [44].

In the BEAUTIFUL morbidity-mortality study conducted in patients with coronary artery disease and left ventricular dysfunction, ivabradine did not affect the primary composite outcome (cardiovascular death or admission for new-onset or worsening heart failure). However, it was shown to have a positive effect in patients who had a pre-treatment heart rate greater or equal to 70 bpm, but only on two secondary endpoints (fewer hospitalizations for fatal or non-fatal myocardial infarction and fewer revascularizations) [45]. In this trial, 87% of patients had already received a beta-blocker as background therapy. Both ASSOCIATE and BEAUTIFUL results demonstrate that ivabradine should be also indicated when angina is not sufficiently controlled with a heart rate greater or equal to 70 bpm in patients optimally treated with beta-blockers.

The most common adverse effect is the induction of phosphenes, which resolve spontaneously when the treatment is stopped and are responsible for discontinuation in less than 1% of patients [46]. Phosphenes are caused by hyperpolarization-activated cyclic nucleotide-gated receptor inhibition in the retina [47]. Excessive bradycardia has been reported, with an incidence of 2% at the recommended dose of 7.5 mg twice daily [46].

Ranolazine

Ranolazine is a selective inhibitor of late sodium current, which prevents the intracellular calcium overload that has been implicated as a negative factor in myocardial ischaemia [48–50]. Ranolazine reduces myocardial wall rigidity and improves myocardial perfusion without changing either heart rate or blood pressure.

Ranolazine has been shown to have antianginal efficacy in three studies in coronary artery disease patients with stable angina (MARISA, CARISA and ERICA) and is therefore indicated for use in association with conventional antianginal therapy in patients who remain symptomatic [27,51,52]. Compared with placebo, ranolazine reduced worsening of angina pectoris and improved exercise tolerance during stress testing in a large study in patients with a history of angina pectoris after acute coronary syndrome (MERLIN) [53]. It has been used since 2006 in the USA and in most European countries, with a favourable decision by the French Commission of Transparency [54].

The main side effects of ranolazine are dizziness, nausea and constipation [49]. Prolongation of the QT interval may occur, although this has never been deemed to be responsible for torsades de pointes, particularly in patients who experience dizziness [49]. Ranolazine also appears to reduce haemoglobin A1c in diabetic patients but the mechanism and implications of this finding remain to be established. A few precautions for use are required as it is metabolized by cytochrome P450.

Medical treatment strategies in stable angina

The choice of disease-modifying treatments that influence prognosis raises a few problems. The COURAGE study clearly demonstrated that all of these treatments should be used at the maximum tolerated doses, closest to those that have been proven to be effective in improving prognosis [14]. The questions already raised are those of the LDL cholesterol goal and whether or not an ACE inhibitor should be administered routinely.

In the absence of contraindications, beta-blockers remain the reference treatment to prevent angina attacks, particularly after myocardial infarction. The role of other antianginals as an alternative or in addition depends on individual patient features, cardiovascular risk factors and concomitant diseases. Poor lifestyle (including smoking, sedentary or dietary errors), which is common in this situation, also contributes to diseases other than angina and increases the numbers of drugs that are being taken. The recent emergence of new antianginals offers additional options to take these different factors into account.

The maximum tolerated dose of beta-blocker (or a highly selective beta-blocker) should be used in patients with a high heart rate. Whenever this is impossible, adding ivabradine should be considered. Ivabradine has also become the treatment of choice in cases of beta-blocker intolerance (asthma, atrioventricular block, non-cardiovascular side effects). Probradycardic calcium channel blockers can also be used as an alternative.

The most common coexisting cardiovascular risk factor is hypertension and, therefore, dihydropyridines or other calcium channel blockers (diltiazem or verapamil) have a role in combined treatment with or as a substitute for beta-blockers.

Conversely, if achieving optimal doses of these treatments either alone or in association is limited by an excessively low heart rate or blood pressure, ranolazine becomes valuable because of the non-haemodynamic-effect profile.

Nitrates and related compounds such as molsidomine or nicorandil can be used in association with the treatments described above. Apart from their common risks of adverse effects, particularly concomitant use of erectile dysfunction drugs, prescribers must be aware of the specific risk of ulceration with nicorandil.

Nitrates and ivabradine (when heart rate is greater or equal to 70 bpm) have a role in association with beta-blockers in patients with left ventricular dysfunction but non-dihydropyridine calcium channel blockers are not recommended in this context. Patent heart failure has its own management regimens, which may include drugs with proven antianginal effects, such as beta-blockers (under their own conditions of use in this indication), nitrates or...
ivabradine. Calcium channel blockers no longer have a role in this situation.

Better knowledge of the antianginals currently available is needed, as many studies in the past have shown that stable angina is often inadequately treated and that management does not follow current recommendations [55, 56]. More recently, based on European findings, the investigators from the EuroHeart Survey in stable angina demonstrated a direct relationship between inadequate treatment of stable angina (antiaggregants, statins and beta-blockers) and death or myocardial infarction [57]. Finally, despite an indisputable improvement, more than half of patients admitted for angioplasty in a United Kingdom study still had an inadequately controlled heart rate (≥ 60 bpm) or blood pressure over values recommended by the European Society of Cardiology/European Society of Hypertension for at-risk patients (systolic blood pressure ≥ 130 mmHg) [58].

Patients with stable angina are becoming increasingly older and, in parallel, have an increasing number of coexisting diseases [57]. These diseases expose patients to the risks of side effects when combinations of drugs (antianginals or others) are needed. The findings of the EuroHeart Survey showed that 42% and 16% of stable coronary artery patients were taking two and three antianginals, respectively [57]. This is important if we consider that antianginals such as beta-blockers, calcium channel blockers and nitrates are not always devoid of side effects, especially of haemodynamic nature.

The important harmful effect of increased heart rate has been emphasized [59]. However, several clinical practice studies have also shown that a large number of patients treated for stable angina have heart rates or blood pressures that are far too low and are liable to limit the necessary adjustments to treatment. The risk of excessively low blood pressure in hypertensive coronary artery disease patients, particularly the elderly, has recently been reviewed [60, 61] and the availability of new antianginals that do not have potentially harmful haemodynamic effects is therefore useful.

**Conclusion**

The increasing number of antianginal treatments may not have the desired effect if both the older and the new agents are not correctly chosen and administered at the optimal recommended doses. The latest recommendations of the European Society for Cardiology date from 2006 [2] and the American College of Cardiology/American Heart Association recommendations date from 2007 [3]. In France, the French National Health Authority (Haute Autorité de santé) proposed a guide for the management of coronary artery disease in 2007. This relates more to the long-term management strategy and makes limited reference to the pharmacological treatment of stable angina (but more to preventative disease-modifying treatment) [62]. It would therefore be useful to have the recommendations updated, taking account of recent findings about the effectiveness of non-interventional measures on prognosis and new treatments that have emerged in recent years.

**Disclosure of interest**


**References**


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