Review

Medical treatment of stable angina: A tailored therapeutic approach

Athanassios J. Manolis a,⁎, Leonidas E. Poulimenos a, Giuseppe Ambrosio b, Manolis S. Kallistratos a, Jose Lopez-Sendon c, Ralf Dechend d, Giuseppe Mancia e, A. John Camm f

a Asklepeion General Hospital, Cardiology Department, Greece
b University of Perugia School of Medicine, Division of Cardiology, Italy
c Hospital Universitario La Paz, La Paz Research Institute (IddPaz), Cardiology Department, Spain
d Charite-Campus Buch, Experimental and Clinical Research Center, Helios-Klinikum Berlin, Department of Cardiology and Nephrology, Germany
e University of Milano-Bicocca and IRCCS Istituto Auxologico Italiano, Italy
f St George’s University of London, Cardiovascular & Cell Sciences Research Institute and Imperial College London, United Kingdom

A R T I C L E   I N F O

Article history:
Received 6 April 2016
Received in revised form 18 May 2016
Accepted 24 June 2016
Available online 25 June 2016

Keywords:
Stable angina
Prognosis
Symptom relief
Angina drugs

A B S T R A C T

Treatment of stable angina is often challenging. In spite of several therapeutic approaches, many of these patients still have symptoms, which inevitably affect their daily activity and quality of life. Current ESC guidelines suggest an algorithm for the medical treatment of stable angina categorizing antianginal drugs as first- or second-line therapy, and then providing little suggestions to guide choice within each step. However, several questions emerge: Is there evidence for such an approach? Is there a true difference between first and second-line drugs in terms of prognosis and symptom relief? Is it possible to individualize patients and tailor treatment according to their comorbidities or risk factors?
The purpose of this review is to summarize the evidence behind stable angina treatment recommendations, and to suggest a systematic therapeutic approach tailored to patients’ cardiovascular profile, risk factors, and comorbidities.

© 2016 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Coronary artery disease is one of the leading causes of cardiovascular morbidity and mortality worldwide while angina represents its most common symptom. It is estimated that approximately 9 million patients in the USA suffer from angina [1], and for half of them angina represents the initial manifestation of ischemic heart disease [1,2]. The debate between medical therapy and revascularization is mostly based on evidence gathered using and methods of revascularization which are no longer state-of-the-art, or on assumptions largely derived by generalizing results of limited inclusion criteria trials to the broad and diverse stable coronary artery disease (SCAD) patient population.

We should be aware, in light of current results of clinical trials and modern PCI or CABG approaches, that properly selected patients, namely those with more severe symptoms, with extensive CAD (especially those with previous myocardial infarction, left ventricular dysfunction, multivessel or otherwise extensive disease and left main disease), and documented moderate-to-severe ischaemia, when offered a PCI or CABG-based approach, may have significant gains in terms of symptom relief, quality of life, exercise capacity and survival [3]. Evidence based event prevention drug regimens are also mandatory for these patients, as indicated by guidelines. For a sizable proportion of patients, antianginal drugs are still needed, even after an attempt to provide “complete” revascularization. Collectively, randomized clinical trials [4–7], registry data [8], and meta-analysis [9], have all consistently shown that around 30% of patients revascularized for stable CAD continue to experience angina symptoms. Importantly, this seems to occur independently of choice of procedure (PCI vs CABG) and of use of drug-eluting stents. Thus, even for patients in whom revascularization is to be undertaken, antianginal drugs should be considered as complementary, rather than competitive approach [10].

Current ESC guidelines for the management of stable angina suggest the use of first and second line drug classes for the management of stable angina [11]. However, several questions emerge: Is there a difference between first and second line of treatment in terms of prognosis and symptom relief? If not, is it better to individualize patient treatment according to their characteristics and comorbidities?

The purpose of this review is to summarize the evidence behind stable angina treatment recommendations and to suggest a systemic
therapeutic approach tailored on patients' cardiovascular profile, risk factors and comorbidities.

2. Stable angina treatments and prognosis

2.1. 1st class antianginal drugs

2.1.1. Short acting nitrates

Short-acting nitrates are a “first-line” approach according to current ESC guidelines, for immediate symptom relief, but not as chronic medication [11]. The use of short acting nitrates, although useful to improve symptoms, does not seem to affect survival in SCAD patients [11]. We lack studies assessing the effect of nitrates on survival in patients with stable angina, and indeed nitrates are usually considered purely for symptom-relief.

2.1.2. Calcium channel blockers

Calcium channel blockers (CCBs) are not a homogeneous group, and can be classified chemically into dihydropyridines (DHPs) and non-DHP CCBs. All classes of CCBs are effective in reducing angina episodes, they increase exercise duration, and reduce the use of sublingual nitroglycerin in patients with CHD and angina, but because of their differential effects on heart rate, AV conduction, and contractility, the choice of a specific drug should be individualized according to their contraindications, side effects and patient characteristics [12-14].

In terms of survival, except from the ACTION study [15], the majority of the data were derived from post-hoc analyses of other studies (assessing the use of these drugs in the secondary prevention in patients with CAD). Short-acting DHPs seem to be deleterious in terms of survival when used for secondary prevention in these patients, since they increased the risk of myocardial infarction while, at higher doses, they increased mortality rates [16,17]. Although long-acting DHPs do not alter survival, they are safe to administer and decrease the number of angina attacks. The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) [18], a randomized double-blind study, assessed the effect of amlodipine on death from any cause and hospitalizations for major cardiovascular events in patients with severe chronic heart failure. Amlodipine did not improve mortality in the subgroup with angina. Moreover, in the A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system (ACTION) study (randomized double-blind study that enrolled 7665 patients with angina), the addition of nifedipine (slow release) to standard treatment decreased the need for coronary interventions and angiography but didn't affect survival [15]. There are insufficient data concerning the non-DHPs. A meta-analysis of 100 randomized controlled trials evaluating 47,694 patients with CAD showed that CCBs were not associated with an increased risk of all-cause mortality, cardiovascular mortality, nonfatal myocardial infarction, or heart failure. In this meta-analysis, the addition of CCBs was associated with a 21% reduction in the risk of stroke, 18% reduction in the risk of angina pectoris and when compared with placebo with a 28% reduction in the risk of heart failure [19]. The results were similar for both dihydropyridines and nondihydropyridine CCBs. The non-DHP verapamil has comparable antianginal effect to metoprolol [20], with an increased risk of heart block, bradycardia and heart failure, while diltiazem has a similar therapeutic effect with fewer side effects.

2.1.3. Beta blockers

Beta-blockers are effective in controlling exercise-induced angina, improving functional capacity, and limiting symptomatic and asymptomatic ischemic episodes. There are differences among beta-blockers concerning their cardioselectivity, intrinsic sympathomimetic activity or vasodilator properties; however, it seems that all of them are equally effective concerning symptom relief in SCAD [11,21]. The most prescribed beta-blockers in Europe overall are: atenolol, bisoprolol, carvedilol, metoprolol, and nebivolol (alphabetical order).

Despite the proven lifesaving qualities of beta-blockers in post-infarct patients, long term administration of this drug class does not seem to affect survival or coronary event rates in patients with SCHD [11,21]. In the REACH registry (Reduction of Atherothrombosis for Continued Health), a longitudinal, observational study that included 21,860 patients with stable CAD, the use of beta-blockers in patients with either risk factors only, known prior MI, or known coronary artery disease without MI, was not associated with any improvement in survival [22].

In a meta-analysis of seven observational studies, oral beta-blocker therapy was associated with decreased all-cause mortality in patients with STEMI who were treated with primary PCI and had a preserved ejection fraction [23]. In a post-hoc analysis of the CHARISMA trial, the use of beta-blockers in patients with prior MI but no heart failure was associated with a lower composite cardiovascular outcome driven by lower risk of recurrent MI with no difference in mortality [24]. In a meta-analysis of sixty trials with 102,000 patients the use of beta-blockers post-MI showed no mortality benefit, but it reduced recurrent myocardial infarction and angina (in the short term) with later increased rates of heart failure, cardiogenic shock, and drug discontinuation [25].

There were some studies showing benefit in post-MI patients due to reductions of CV death and MI, but all of them were performed about 30 years ago, before the implementation of other secondary prevention therapies, such as statins and ACEIs, and the mean follow-up was 1.4 years, leaving some uncertainty regarding their efficacy especially in the long term, when added to modern therapeutic strategies.

Combination of first line drugs in the treatment of stable angina is more effective than monotherapy in controlling symptoms [26], however depending on baseline systolic blood pressure, and it is important to avoid the combination of beta-blockers with diltiazem or verapamil because of the risk of bradycardia or atioventricular block [26,27].

2.2. 2nd class antianginal drugs

ESC guidelines indicate long-acting nitrates, ivabradine, ranolazine, nicorandil, and trimetazidine, as second-class agents. Although divided by the guidelines as first and second line treatments, it seems that all of these drugs are similarly effective regarding symptom relief.

Ivabradine, Nicorandil and Ranolazine, have been introduced much more recently (compared to the first-line drugs and to long-acting nitrates), and as such they have been tested in clinical trials according to much more stringent protocols. In particular, for these agents we have data on much larger sample sizes, with much longer duration of follow up, and data on safety are also available [28]. The use of second line treatment does not seem to improve survival in SCAD patients.

2.2.1. Long-acting nitrates

Long-acting nitrates can be used as a second-line approach when initial therapy with beta-blockers or CCBs is contraindicated or in case additional therapy is needed. Nitrates improved exercise tolerance, time to ST-segment depression, and time to angina onset, but all were observed in small studies with short duration [29,30]. However, when nitrates are continuously applied, their vasodilatory activity decreases within 17–24 h and this can cause reduction in exercise capacity and increased angina attacks [31]. An older meta-analysis of 90 randomized or crossover studies that compared antianginal drugs from different classes (long-acting nitrates, calcium antagonists and beta-blockers) showed equivalent effectiveness of all three classes in the treatment of stable angina [32].

Long-acting nitrates have been in use for the management of stable angina since many years; however, their long-term effects on outcome have never been thoroughly investigated.

Besides the issue of possible development of tolerance, long-term therapy with nitrates may have mixed results in terms of outcome. Specifically, it has been associated with development of endothelial dysfunction, with accumulation of oxygen free radicals which increase
arterial sensitivity to angiotensin II and can counteract the concomitant actions of ACE inhibitors in patients with SCAD [33,34]; on the other hand, it is possible that background nitrate use may instead “precondition” the heart toward future acute ischemic episodes, thus reducing myocardial injury. Analysis of the large Global Registry of Acute Coronary Events (GRACE) registry of over 50,000 acute coronary syndromes revealed that patients on chronic nitrate therapy prior to an index event had significantly lower release of cardiac biomarkers of necrosis, suggesting smaller extent of myocardial injury [35].

2.2.2. I v abradine

When compared to placebo [36], or on top of conventional therapy [37,38] it showed favorable results in terms of anginal symptoms relief. Adding ivabradine to the treatment plan improves treadmill exercise tolerance test criteria such as total exercise duration, timing to limiting angina, time to angina onset and time to 1 mm ST segment depression [38]. In other studies, ivabradine was as effective as atenolol or amlodipine in patients with SCHD [37,39]. In the Study Assessing the Morbidity–Mortality Benefits of the II Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY) study, a randomized, double-blind, placebo-controlled trial that enrolled 19,102 patients with stable CAD, ivabradine did not improve the primary end point (a composite of death from cardiovascular causes or nonfatal myocardial infarction), while in the subgroup analysis on patients who had class II angina according to the Canadian Cardiology Society (CCS) scale or higher, the incidence of the primary end point was increased [40].

2.2.3. Ranolazine

Compared to placebo, or as additional therapy to atenolol, amlodipine, and nitrates, ranolazine improved angina symptoms, exercise tolerance, and decreased angina attacks and nitroglycerin consumption in several medium-sized trials of patients with stable angina [41–44]. Ranolazine also seems to exert a beneficial effect on glycemic control with significant reduction of HbA1C in patients with and without diabetes [45,46]. In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST elevation acute coronary syndromes (MERLIN-TIMI) trial, a randomized, double-blind, placebo-controlled study, the addition of ranolazine didn’t improve the incidence of cardiovascular death or myocardial infarction with respect of symptoms after enrollment [41], while in the subgroup with prior angina the primary end-point (CV death, MI or recurrent ischemia was significant lower (p<0.017). However, in the recent published Ranolazine for Incomplete Vessel Revascularization Post-Percutaneous Coronary Intervention (RIVER-PCI) trial, ranolazine in patients with incomplete revascularization after PCI did not reduce the composite rate of ischemia-driven revascularization or hospitalizations [47].

2.2.4. Nicorandil

The antianginal efficacy of nicorandil is similar to beta-blockers, CCBs and nitrates [48–50], and can be added to beta-blockers and CCBs, although tolerance can be developed with long-term use [51]. In the IONA trial (Impact Of Nicorandil in Angina), the addition of nicorandil to standard treatment decreased the incidence of major cardiovascular events, but this result was mainly driven by the effect of nicorandil in reducing the incidence of hospital admission for cardiac chest pain, while the risk reduction due to cardiac deaths or non-fatal MIs during treatment was non-significant [52]. However in a recent letter from the Medicines and Healthcare products Regulatory Agency (MHRA) there is a warning for the use of Nicorandil due to risk of serious skin, mucosal, and eye ulceration, which persists unless treatment is discontinued. Also the use of nicorandil with aspirin increased the risk of gastrointestinal ulcers, perforations, and hemorrhages [53]. Finally, it should be pointed out that nicorandil is not available in many European countries.

2.2.5. Trimetazidine

Trimetazidine exerts its antianginal efficacy in chronic angina patients through a mechanism which is not well defined, but its impact on prognosis has not been established. The medication has similar antianginal effects to propranolol [54], while when added to atenolol, it further improved effort-induced myocardial ischemia [55–57].

Until recently, trimetazidine-containing medicinal products were approved in the European Union for the treatment of SCAD, and also for the symptomatic treatment of vertigo and tinnitus, and vascular-related visual acuity loss and visual field disturbances. However, because of concerns over the effectiveness of trimetazidine in those latter conditions and reports of movement disorders (including parkinsonism, ‘restless leg’ syndrome, tremors and gait instability), the European Medicines Agency (EMA) recently reviewed the safety and effectiveness of this drug and concluded that its use should be restricted solely to the therapeutic indication of stable angina pectoris [58]. The EMA also recommended caution when prescribing trimetazidine to patients with moderate renal impairment or elderly patients and to consider dose reduction in these subjects. This can be a limitation for use of the drug in patients with angina and diabetic nephropathy. So far, its effect on survival was only been explored in patients with acute myocardial infarction; the EMIP–FR (European Myocardial Infarction Project–Free Radicals) trial which included over 19,000 patients and showed no benefit. There is an ongoing trial for secondary prevention in ischemic heart disease patients [59].

In Table 1 there is a summary for the evidence from ESC and ACC/AHA guidelines for the treatment of SCHD.

Based on all the above it seems that no first- or second-line antianginal drug improves survival of patients SCHD. Although many doctors continue to believe that traditional old drugs are such as beta-blockers do reduce mortality, future guidelines must reconsider the strength of recommendations for beta-blockers in SCAD.

2.3. Other antianginal drugs

Current ESC guidelines mentioned also the use of allopurinol or molsidomine administration in patients with stable angina and CAD [11]. Allopurinol seems to increase the time of ST segment elevation as well as time to angina onset. Molsidomine is a direct NO donor and seems to have similar antiischemic effects with isosorbide dinitrate. However, the evidence for the use of those two drugs is limited and thus, is not suggested in current ESC guidelines as 1st or 2nd antianginal drugs [11].

3. Selection of the anti-ischemic agent

Based on all the above data, it is clear that no study shows significant reduction in cardiovascular mortality with either first or second line medical treatment of SCHD. Also, there are no head-to-head comparisons between first and second line treatment that demonstrate a superiority of one vs. the other in terms of antianginal efficacy. So, how
should clinicians make the best selection of medications for their patients with angina?

According to the ESC guidelines, in addition their recommendation for beta-blockers and CCBs as class I/level of evidence (LOA) A (for the reduction of symptomatic angina), it is also stated that beta-blockers may be cardioprotective in patients with SCHD, but without any supportive evidence from placebo-controlled clinical trials, which weakens the strength for the class IA recommendation. Additionally, trials with beta-blockers post-MI were performed before the widespread implementation of revascularization and other secondary preventive measures, such as treatment with statins and ACE-Is and antiplatelet agents, which leaves uncertainty regarding their efficacy within to modern treatment strategies.

The ACC/AHA guidelines [21] note that ranolazine has shown in clinical trials comparable results to other agents in alleviating angina, but has been approved by the USA/FDA for first line use, they recommend it only where beta-blockers, CCBs and nitrates are not tolerated or effective.

The authors of the current ESC guidelines concede that they recommend older drugs as first line treatment because they are cheap, effective, and available everywhere. Regarding the novel antianginal drugs, they state that there is roughly the same level of evidence as with the 1st line drugs [60]. Hence, the question emerges that: if there is no difference between the first and second line of treatment in terms of prognosis and symptom relief, could it be better to individualize patient treatment according to their characteristics, comorbidities, and contraindications?

3.1. Stable angina and specific conditions

The majority of patients with CHD, have diverse co-morbidities, such as hypertension, dyslipidemia, diabetes mellitus, heart failure with reduced or preserved ejection fraction, hypotension, chronic obstructive pulmonary disease, peripheral arterial disease, etc. In the prospective observational Longitudinal Registry of patients with stable coronary artery disease (CLARIFY) [61,62], hypertension was present in up to 70%, dyslipidemia in up to 75%, and diabetes mellitus up to 30% in patients with angina.

Thus, better treatment may be achieved by individualizing therapy by taking into account concurrent drug indications or contraindications, due, for example to the presence of co-morbidities [62].

3.1.1. Diabetes mellitus

Cardiovascular atherosclerosis is often accelerated in diabetic patients. Patients with diabetes mellitus have more extensive vascular disease and have a more severe ischemic burden both anginal and silent. Treatment of stable angina in these patients must include drugs that have a positive or at least a neutral metabolic profile [63].

Ranolazine is an agent with not only antianginal actions, but also with favorable effects in HbA1c levels in patients with type 2 diabetes [64]. In a double-blind, placebo-controlled trial, type 2 diabetic patients were randomized to receive ranolazine or placebo. The study prospectively assessed the safety and efficacy of ranolazine in subjects presenting inadequate glycemic control managed by lifestyle alone. A greater decline from baseline HbA1c levels was noted after 24 weeks in patients taking ranolazine compared to placebo, while the proportion of subjects achieving an HbA1c <7.0% was greater with ranolazine (25.6% vs. 41.2%; P = 0.0004). Moreover, ranolazine was associated with significant reductions in fasting and 2-h postprandial glucose. Similar results were obtained in other studies involving ranolazine [46,65], while a subgroup analysis of the Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) trial [66] showed a greater efficacy of ranolazine (in terms of the average number of angina episodes per week) versus placebo among patients with stable angina and higher HbA1c levels.

Although beta-blockers possibly facilitate or accelerate new onset diabetes in predisposed patients or aggravate the glycemic profile in diabetics [67], these observations are valid for “older” beta-blockers such as atenolol. Vasodilating beta-blockers seem to overcome these metabolic limitations without worsening glucose tolerance, since they cause less insulin resistance [68]. Nebivolol a beta, selective blocker with a favorable metabolic profile, improves insulin sensitivity and does not cause deleterious effects on lipid profile [69,70]. Likewise, carvedilol, a non-selective beta- and a, blocker, maintains glycemic control, while improving insulin sensitivity [71].

There are some data supporting the use of trimetazidine in patients with diabetes [57,63]. Most evidence comes from TRIMetazidine in POLand–1 (TRIMPOL-1) trial, an open-label, single-arm, multicenter trial of 700 patients with stable angina, documented CAD or previous MI and a positive exercise test, treated with one anti-anginal agent (long-acting nitrate, beta-blocker or CCB) as background therapy. Patients received trimetazidine 20 mg t.i.d. in addition to background treatment for 4 weeks. Analysis of the subgroup of patients with DM (n = 50) showed that trimetazidine induced significant improvements in all exercise parameters evaluated [72]. Severeity of anginal pain and intensity of anginal pain during exercise were also significantly decreased. Trimetazidine also significantly reduced the mean number of weekly anginal attacks and nitrate consumption, and it was well tolerated in this population. However, this trial has a number of limitations, most notably the small number of patients with DM, the open-label design, and the retrospective analysis.

As already pointed out, it is important to avoid the use of trimetazidine in patients with diabetic nephropathy, or neurological symptoms.

Thus, ranolazine and vasodilating beta-blockers exert a favorable effect in terms of metabolic profile and should be preferred to other antianginal agents with a neutral metabolic profile such as ivabradine, nicorandil, CCBs and probably trimetazidine.

3.1.2. Stable angina and atrial fibrillation

Atrial fibrillation (AF), among other consequences can aggravate anginal symptoms due to increased heart rate. Thus, agents that offer efficient rate control as non-DHP CCBs and beta-blockers have to be preferred. Beta-blockers represent a safe choice in the treatment of stable angina in patients with a history of AF and are recommended in the current ESC guidelines not only for acute rate control of AF but also for long term rate control, along with non-DHP CCBs [73,74].

Among available drugs, Ivabradine is ineffective in patients with AF (because of its mechanism of action). Furthermore, it seems to increase the incidence of AF in patients with stable angina. In the SIGNIFY study, ivabradine increased the incidence of AF compared to placebo (5.3% vs. 3.8%, p < 0.001) [40] while a metanalysis that assessed AF data from 11 studies with ivabradine showed that treatment with this agent was associated with a relative risk of AF of 1.15 (95% CI 1.07 to 1.24, p = 0.0027) among 21,571 patients [75]. Thus, Ivabradine is indicated only in sinus rhythm and is contraindicated in patients with AF.

Ranolazine on the other hand, acting as an antiarrhythmic agent, seems to suppress supraventricular arrhythmias as well as atrial fibrillation [76], decreasing the incidence of this arrhythmia. A retrospective study that enrolled 393 consecutive patients undergoing CABG, compared amiodarone versus ranolazine for the prevention of AF after CABG [77] AF occurred in 26.5% of the amiodarone-treated patients compared to 17.5% of the ranolazine-treated patients (p = 0.035). In a post-hoc analysis of the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation acute coronary syndromes (MERLIN) trial using continuous ECG during the first 7 days after randomization patients assigned to ranolazine tended to have fewer episodes of AF (75% vs. 55% [1.7%] patients, P = 0.08). In the recently published (Phase 2, proof of concept, randomized, placebo-controlled, parallel study to evaluate the effect of Ranolazine and dronedarone when given alone and in coMbinaton On atrial fibrillation burden in subjects with paroxYsmal atrial fibrillation study (HARMONY) trial [78] the
combination of ranolazine (750 mg b.i.d.) and low doses of dronedarone (225 mg b.i.d.) caused a significant reduction in AF burden compared to placebo over 12 weeks in 134 subjects with paroxysmal AF.

3.1.3. Left ventricular systolic dysfunction

A significant percentage of patients with left ventricular systolic dysfunction (LVSD) suffer from coronary artery disease with anginal symptoms. In the morBidity-mortality Evaluation of the IF Inhibitor ivabradine in patients with coronary artery disease and left ventricular dysfunction (BEAUTIFUL) trial, ivabradine, reduced the composite of fatal and nonfatal myocardial infarction by 36% (p = 0.001) and the need for revascularization by 30% (p = 0.016) in patients with heart rate ≥ 70 bpm and LVEF <40%. In the subgroup of patients with angina symptoms, ivabradine showed a trend in reducing the primary end point of cardiovascular death, hospitalization for heart failure, or for myocardial infarction by 31% (p = 0.06) [79].

Current ESC guidelines for the management of heart failure with reduced LVEF suggest the use of beta-blockers and ivabradine [80]. These two agents with antiangiial effects reduce effectively cardiovascular morbidity and mortality, and thus should be preferred in patients with LVSD and stable angina. The recommendation for the use of hydralazine/isosorbide dinitrate as an alternative or additional therapy to renin angiotensin aldosterone system inhibition in patients with heart failure (HF) may be tricky in patients with angina, as hydralazine has the potential to elicit angina attacks. Nevertheless, nitrates may have a role in patients with heart failure along with RAAS inhibitors which may confer nitrate tolerance benefits, combining vasodilating and antiangiial effects [10].

CCBs on the other hand (with the possible exception of amlodipine and felodipine) should not be used in patients with HF and reduced ejection fraction as they have a negative inotropic effect and can worsen HF [80]. Finally, the safety of nicorandil and ranolazine in patients with HF and reduced ejection fraction is uncertain, and thus these agents should be avoided [80].

3.1.4. Increased heart rate

Heart rate increases myocardial oxygen consumption aggravating angina. Heart rate lowering agents such as beta-blockers, ivabradine and non-DHP CCBs can effectively decrease heart rate, decreasing angina symptoms [11]. However, after the results of SIGNIFY [40] there is a question on the optimal nature of the heart rate target. Current ACC guidelines suggest a decrease of the HR down to 55–60 bpm [21]. However there is a possibility of a J curve in HR. The EMA recommends that this agent should be administered when HR is above 70 bpm and the dose must be decreased or discontinued if HR remains below 50 bpm [81].

3.1.5. Blood pressure

Patients with SCHD and high blood pressure (BP) levels should be receiving RAS blockers as they may favorably alter prognosis, and according to the first line treatment of the ESC SCAD guidelines, beta-blockers [82] and/or CCBs.

However, in the presence of angina and low BP the combination of beta-blockers with CCBs or nitrates may not be ideal, since they significantly decrease BP levels potentially impairing coronary perfusion. Although there is not a validated threshold dividing SCHD patients into a high and low BP levels, a threshold of 120 mm Hg in systolic blood pressure can be used as a reference [83,84]. Some have recently advocated a threshold of 100 mm Hg of systolic blood pressure, below which not to further push treatment with antiangiial drugs that have vasodilating properties [85]. However, in our opinion, an antiangiial treatment algorithm based on a higher cut-off value (systolic BP: 120 mm Hg) is justified for two reasons. First, the possibility of a J-curve phenomenon, i.e. an increased incidence of outcomes when the BP is markedly reduced cannot be excluded, particularly in patients with high cardiovascular risk in whom organ damage may impair the ability of autoregulation to preserve vital organ perfusion as BP falls [86]. Indeed, an increased incidence of myocardial infarction for systolic BP reductions to less than 120–130 mm Hg has been repeatedly reported in patients with a history of cardiac disease [87–90]. In a recent metaanalysis enrolled 73.738 diabetic participants, in patients with baseline systolic BP levels less than 140 mm Hg, further BP lowering treatment was associated with an increased risk of cardiovascular mortality [91].

Secondly, there is no question that pursuing an aggressive BP reduction is accompanied by a major increase of serious side effects. In the diabetic patients of the Action to Control Cardiovascular Risk in Diabetes ACCORD trial, for example, the group of patients in which systolic BP was reduced to less than 120 mm Hg exhibited three times as many serious side effects as the group remaining at an on-treatment systolic BP more than 130 mm Hg [92]. Recently this has also been found in the high cardiovascular risk patients of the Systolic Blood Pressure Intervention Trial (SPRINT) [93] in whom reducing systolic BP to about 120 mm Hg was associated with an increase of multiple side effects, including a 66% greater incidence of acute renal injury [94]. In clinical practice side effects are the most important case of discontinuation of or low adherence to treatment, which notoriously leads to a disappearance or an attenuation of the treatment-induced benefits [95,96]. It thus makes sense to avoid a further BP reduction in patients with angina and a low BP by using antiangiial drugs with little or no BP lowering effect, reserving antiangiial medications known to reduce systemic BP to those with a higher BP. Thus, inpatients with low BP levels, the use of ranolazine, ivabradine or trimetazidine is preferable since those drugs, do not affect BP levels.

3.1.6. Women and microvascular angina

A particular challenge can be posed by patients in whom ischemic symptoms are not clearly (or solely) attributable to epicardial coronary artery stenoses [55]. Impaired vasodilation at the level of distal coronary microcirculation has been invoked to explain persistent angina episodes in patients who have been successfully revascularized, or in the absence of flow-limiting stenosis of epicardial coronary arteries. This latter condition seems to be more frequent in women [97].

With respect to “classical” antiangiial drugs, firm evidence for treatment of these conditions is limited, or is lacking, mostly due to insufficient number of women recruited in earlier trials. More recently, however, data have accumulated favoring ranolazine therapy in women. Data from 1737 patients with stable angina pectoris in four international trials (Monotherapy Assessment of Ranolazine In Stable Angina [MARISA] [44], Combination Assessment of Ranolazine In Stable Angina [CARISA] [98], Ranolazine Versus Atenolol Comparison in Chronic Angina [RAN080] [99], and Efficacy of Ranolazine in Chronic Angina [ERICA] [42]) were pooled to compare efficacy and safety of ranolazine therapy for angina in women and men. In subgroup analyses, women showed less improvement than men in exercise testing. However, similar improvements for women and men were noted in angina frequency and nitroglycerin consumption, and (in ERICA) in the angina frequency dimension of the Seattle Angina Questionnaire [99]. While it is entirely possible that other drugs may have comparable, gender-neutral effects, only ranolazine has been tested in a sufficient number of women with angina.

With specific reference to the issue of women and microcirculatory dysfunction, a small-scale trial did suggest improvement of anginal symptoms in women with evidence of myocardial ischemia but no obstructive coronary artery disease treated with ranolazine [100]. Subsequently, 142 women with effort angina and no obstructive coronary artery disease were randomized in a double-blind, placebo-controlled, crossover, trial of short-term oral ranolazine 500–1000 mg twice daily for 2 weeks (vs. placebo) [101].

Trial results were overall non-significant, although benefits were observed in the subgroup of women with impaired coronary flow reserve at baseline. Thus, it might be that ranolazine requires a certain degree of
flow impairment/ischemia to manifest its benefits. The very short duration of therapy may also have contributed.

4. Operative suggestions for a pragmatic approach

It is clear from the literature that some antianginal agents when compared to others possess auxiliary properties not only limited to the relief of anginal symptoms. Improving glucose profile in patients with DM and angina, achieving rate control or decreasing the incidence of AF in such patients, improving prognosis in patients with HF, decreasing HR in patients with stable angina, or avoiding high or low arterial blood pressure must also be objectives when considering a particular therapeutic approach. Treatment has to be individualized taking into account comorbidities and risk factors (Fig. 1) (Tables 2, 3).

Patients could be divided according their BP levels and HR. In patients with systolic BP levels less than 120 mm Hg, drugs with no- or limited impact on BP should be preferred (always taking into account comorbidities since auxiliary properties exerted by those drugs may be of value). Likewise, in patients with a HR < 60 bpm, drugs with no- or limited impact on HR are preferable. In patients with a systolic BP 120 mm Hg or more or a HR of 60 bpm or greater, all antianginal drugs can be used taking into consideration diverse comorbidities.

5. Conclusions

Patients with stable coronary artery disease and angina have several comorbidities and risk factors. Since all antianginal drugs have roughly the same level of evidence and no measurable survival benefit for this particular indication, agents with actions most suited to hemodynamic status and associated comorbidities should be preferred.

### Table 2

<table>
<thead>
<tr>
<th>Intolerance</th>
<th>Preferred Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st step Intolerance</td>
<td>Ivabradine, LA nitrates, nicorandil, ranolazine, trimetazidine</td>
</tr>
<tr>
<td>Significant AV conduction abnormalities</td>
<td>DHPs, ivabradine, nitrates, nicorandil, ranolazine, trimetazidine</td>
</tr>
<tr>
<td>Low HR</td>
<td>DHP, nitrates, nicorandil, ranolazine, trimetazidine</td>
</tr>
<tr>
<td>Low BP</td>
<td>Ivabradine, ranolazine, trimetazidine</td>
</tr>
<tr>
<td>AF</td>
<td>Beta-blockers (rate control), non DHP CCBs (rate control), la nitrates, possibly rhythm control</td>
</tr>
<tr>
<td>CHF</td>
<td>Beta-blockers, ivabradine, possibly nitrates</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Vasodilating beta-blockers, CCBs, ivabradine, ranolazine</td>
</tr>
</tbody>
</table>

Drugs are listed in alphabetical order.

HR: Heart rate, BP: blood pressure, AF: atrial fibrillation, CHF: chronic heart failure, AV: atrioventricular, DHPs: Dihydropyridines, CCBs: calcium channel blockers,
Conflict of interest

J Camm has received clinical trial funding from Gilead and has served as an advisor to Gilead and Menarini. Dechend R received honorarium from Novartis, Berlin Chemie/Menarini, MSD, Novartis, Alynam, Servier, Boehringer Ingelheim, received grant in aid from Novartis, Boehringer Ingelheim, Ambrosio G received honoraria for consultancies from Angelini, Behring, Menarini, Merck, and as a speaker bureaus from Menarini, Merck and Novartis. Aj Manolis has received honoraria for lecturing for Servier, Menarini, Pfizer and Bayer. MS Kalistos has received honoraria for consultancies from Servier Hellas. Dechend R received honorarium from Recordati, Sano, Boehringer Ingelheim, Alnylam. Giuseppe Mancia has received speaker’s or consulting fees from: Actavis, Bayer, Boehringer Ingelheim, Ferrer, Lilly, Medtronic Vascular Inc., Menarini Int, Merck Serono, MSD, Novartis, Recordati, Sanofi, Servier, Takeda. LE Poulomenos has no conflict of interest.

References


Trimetazidine. Questions and answers on the review of medicines containing trimetazidine (20 mg tablets, 35 mg modified release tablet and 20 mg/ml oral solution) nd.


