International Journal of Cardiology 283 (2019) 55–63

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Anti-anginal drugs: Systematic review and clinical implications

Rita Pavasini [a,*], Paolo G. Camici [b], Filippo Crea [c], Nicolas Danchin [d], Kim Fox [e], Athanasios J. Manolis [f], Mario Marzilli [g,h], Giuseppe M.C. Rosano [i,j], José L. Lopez-Sendon [k], Fausto Pinto [l], Cristina Balla [a], Roberto Ferrari [a,m]

[a] Centro Cardiologico Universitario, University Hospital of Ferrara, Via Aldo Moro 8, 44124 Cona, Ferrara, Italy
[b] Vita Salute University and San Raffaele Hospital, Via Olgettina Milano, 58–60, 20132 Milan, Italy
[c] Department of Cardiovascular and Thoracic Sciences, Catholic University, Largo Francesco Vito, 1, 00168 Rome, Italy
[d] Cardiology, European Hospital Georges-Pompidiou, 20 Rue Leblanc, 75015 Paris, France
[e] National Heart and Lung Institute, Imperial College and Institute of Cardiovascular Medicine and Science, Royal Brompton Hospital, Sydney Street, London SW36NP, UK
[f] Department of Cardiology, Asklepeion General Hospital, 1, Vas. Pavlou Street, 16673 Voula, Athens, Greece
[g] Cardiothoracic Department, Lungarno Antonio Pacinotti, 43, 56126 Pisa, Italy
[h] Nottola Cardiology Division, Località Nottola, 53045, Ospedali Riuniti Valdichiana Sudest, Siena, Italy
[i] Clinical Academic Group, St George's Hospitals NHS Trust, Blackshaw Road, London SW17 0QT, UK
[j] Department of Medical Sciences, IRCCS San Raffaele, Via della Pisana, 235, 00163 Rome, Italy
[k] Cardiology Department, Hospital Universitario La Paz, IdiPaz, Paseo de la Castellana 261, Madrid 28036, Spain
[l] Hospital Universitário de Santa Maria/Centro Hospitalar Lisboa Norte, Centro Académico de Medicina de Lisboa, Centro Cardiovascular da Universidade de Lisboa, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal
[m] Maria Cecilia Hospital, GVM Care & Research, Via Corriera 1, Cotignola, RA, Italy

ARTICLE INFO

Article history:
Received 18 October 2018
Received in revised form 17 November 2018
Accepted 3 December 2018
Available online 4 December 2018

Keywords:
Beta-blockers
Ivabradine
Stable angina
Calcium channel blockers
Ranolazine
Trimetazidine

ABSTRACT

Background: The cornerstone of the treatment of patients affected by stable angina is based on drugs administration classified as first (beta-blockers, calcium channel blockers, short acting nitrates) or second line treatment (long-acting nitrates, ivabradine, nicorandil, ranolazine and trimetazidine). However, few data on comparison between different classes of drugs justify that one class of drugs is superior to another.
Methods: We performed a systematic review of the literature following PRISMA guidelines. Inclusion criteria: i) paper published in English; ii) diagnosis of stable coronary disease; iii) randomized clinical trial; iv) comparison of two anti-angina drugs; v) a sample size >100 patients; vi) a follow-up lasting at least 2 weeks; vii) paper published after 1999, when a meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina of Heidenreich et al. was published. Outcome: to establish whether the categorization in first and second line antianginal treatment is scientifically supported.
Results: Eleven trials fulfilled inclusion criteria. The results show that there is a paucity of data comparing the efficacy of antianginal agents. The little data available show that there are not compounds superior to others in terms of improvement in exercise test duration, frequency of anginal attacks, need for sub-lingual nitroglycerin.
Conclusion: The categorization of antianginal drug in first and second line is not confirmed.

1. Introduction

According to the ESC guidelines [1], drugs for symptomatic relief of angina are classified as being first line (beta blockers, calcium channel blockers, short-acting nitrates) or second line (ivabradine, nicorandil, ranolazine, long-acting nitrates, trimetazidine), with the recommendation to reserve second-line medications for patients who have contraindications to first choice agents, do not tolerate them, or remain symptomatic [1–3].

However, such categorical approach has been recently questioned [4–9]. The reasons for this criticism are multiple:

1) Second line drugs have been introduced more recently and they have been approved according to more stringent protocols, with larger sample size, longer follow-up, and safety data, compared to first line drugs which were studied in the early days with less precise description of methods, smaller sample size and shorter follow-ups [4,9];
2) The suggested and often-used combination of two or even three agents seems to be based on expert opinion rather than on scientific evidence [5–10];

* Corresponding author.
E-mail address: pvsrti@unife.it (R. Pavasini).

https://doi.org/10.1016/j.ijcard.2018.12.008
0167-5273/

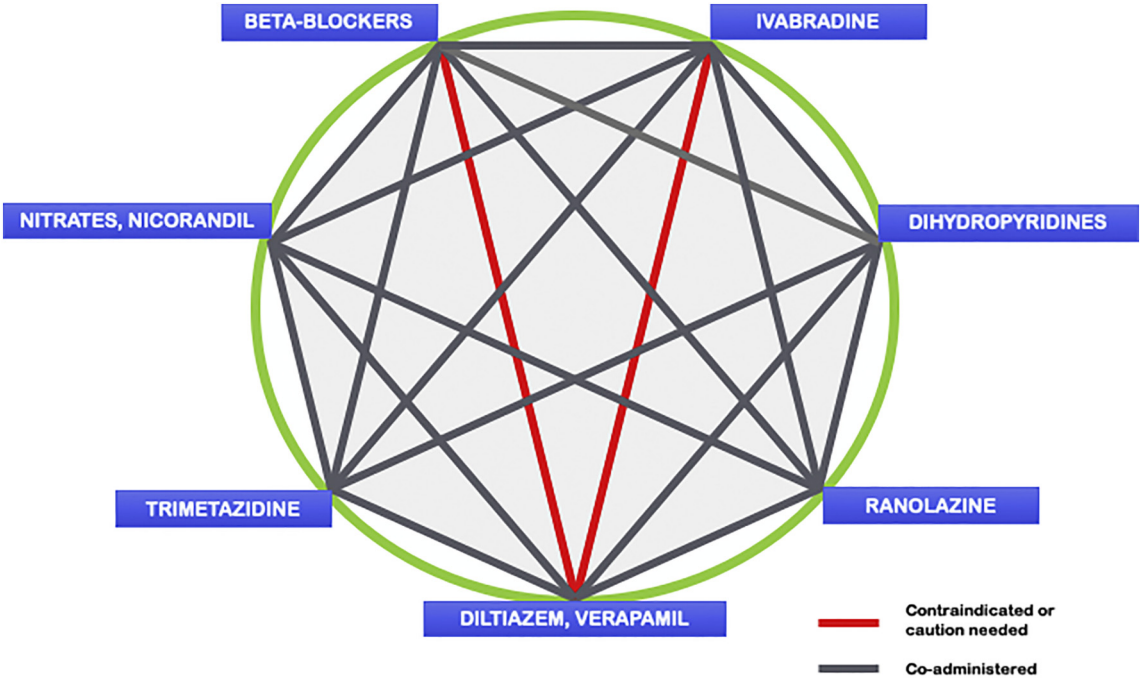

Fig. 1. The diamond approach: possible combination of classes of antianginal drugs. Adapted from Ferrari et al. [4]. In the heptagon, all the vertices represents one of the available categories of antianginal drugs. Red lines represent the contraindicated associations, while the grey lines represent the possible and useful associations. A detailed description of the choice of a class of drug over another depending on patient's characteristics and comorbidities is described elsewhere [4].

3) The categorical guideline recommendations do not take into account the different pathophysiological mechanisms underlying ischemia and angina (*stable atherosclerotic plaque, vasospasm on the epicardial arteries, and coronary microvascular dysfunction*) [4,6];
4) Patients with angina can have several co-morbidities requiring drugs with the appropriate auxiliary properties which are not considered in the guidelines [4,8–10].

Recently, an expert consensus proposed a new algorithm for a more personalized medical treatment of symptomatic angina, a so-called "*Diamond approach*" [4, Fig. 1]. The authors assumed that there was no direct comparison between first-line and second-line treatments to support the superiority of one group of drugs over the other. They referred to an old meta-analysis based only on the three antianginal drugs considered first line published by Heidenreich et al. in 1999 [4,11]. The purpose of the current systematic review is to analyze data about the more recently approved compounds which are classified as second line choice.

2. Methods

We performed a systematic review of the literature following Preferred Reporting Items for systematic Reviews and Meta-analysis (PRISMA) [12,13]. Appropriate articles were searched in MEDLINE and in EMBASE. "Mesh" strategy was used. The terms searched were ((((“Angina, Stable” OR “Coronary Artery Disease”) **AND** (“Diltiazem” OR “Verapamil” OR “Nifedipine” OR “Amlodipine” OR “Felodipine” OR “Nicardipine” OR “Nimodipine” OR “Isosorbide Dinitrate” OR “Nicorandil” OR “Ranolazine” OR “Trimetazidine” OR “Acebutolol” OR “Atenolol” OR “Bisoprolol” OR “Celiprolol” OR “Metoprolol” OR “Nadolol” OR “Propranolol” OR “carvedilol” OR “Penbutolol” OR “Nebivolol” OR “Labetalol” OR “Sotalol” OR “ivabradine”) **AND** (“Randomized Clinical Trial”). The search was carried out between October and November 2017. The inclusion criteria were: i) paper published in English; ii) studies on patients with a diagnosis of stable coronary disease; iii) randomized clinical trial; iv) comparison of two anti-angina drugs; v) a sample size of at least 100 patients; vi) a follow-up lasting at least 2 weeks; vii) paper published after 1999 only if regarding beta-blockers, calcium antagonists and long acting nitrates (a meta-analysis of Heidenreich et al. was published in 1999 regarding trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina [11]) (Fig. 2). Studies with the following characteristics were excluded: i) observational; ii) comparing an anti-anginal drug versus placebo; iii) comparing an anti-anginal drug versus two drug combinations; iv) comparing an anti-anginal drug versus another drug within the same class. The inclusion of the papers in the systematic review was decided after analysis of the full-text of papers selected. Divergences were solved by consensus.

The outcome of interest was related to the effect of the drugs on: i) the frequency of anginal attacks; ii) the need for sub-lingual nitroglycerin; iii) results of exercise testing.

The quality of the studies included was evaluated with the Cochrane Collaboration approach. In particular, the risk of analytical, selection, adjudication, and attrition bias (expressed as low, moderate, or high risk of bias, as well as incomplete reporting leading to inability to ascertain the underlying risk of bias) was assessed.

3. Results

A first screening of the literature retrieved a total of 92 papers. After re-evaluation of the title and abstract, 18 studies were considered for the full-text analysis. Following the scrutiny of inclusion and exclusion criteria, 7 papers were excluded: one because it focused on hypertensive patients; one was a network meta-analysis; one a duplicate of a sample population of another study; in another one the comparator was placebo

Fig. 2. Randomized trial comparing antianginal drugs in patients with stable angina since 1969. Horizontal axis: number of patients enrolled; Vertical axis: year of publication of the study. The dotted line underlines paper published after 1999. The studies selected are randomized studies comparing directly antianginal drugs from 2 or 3 different classes in patients with stable angina, with duration at least 1 week and reporting at least 1 of the following outcomes: angina frequency, exercise test parameters.

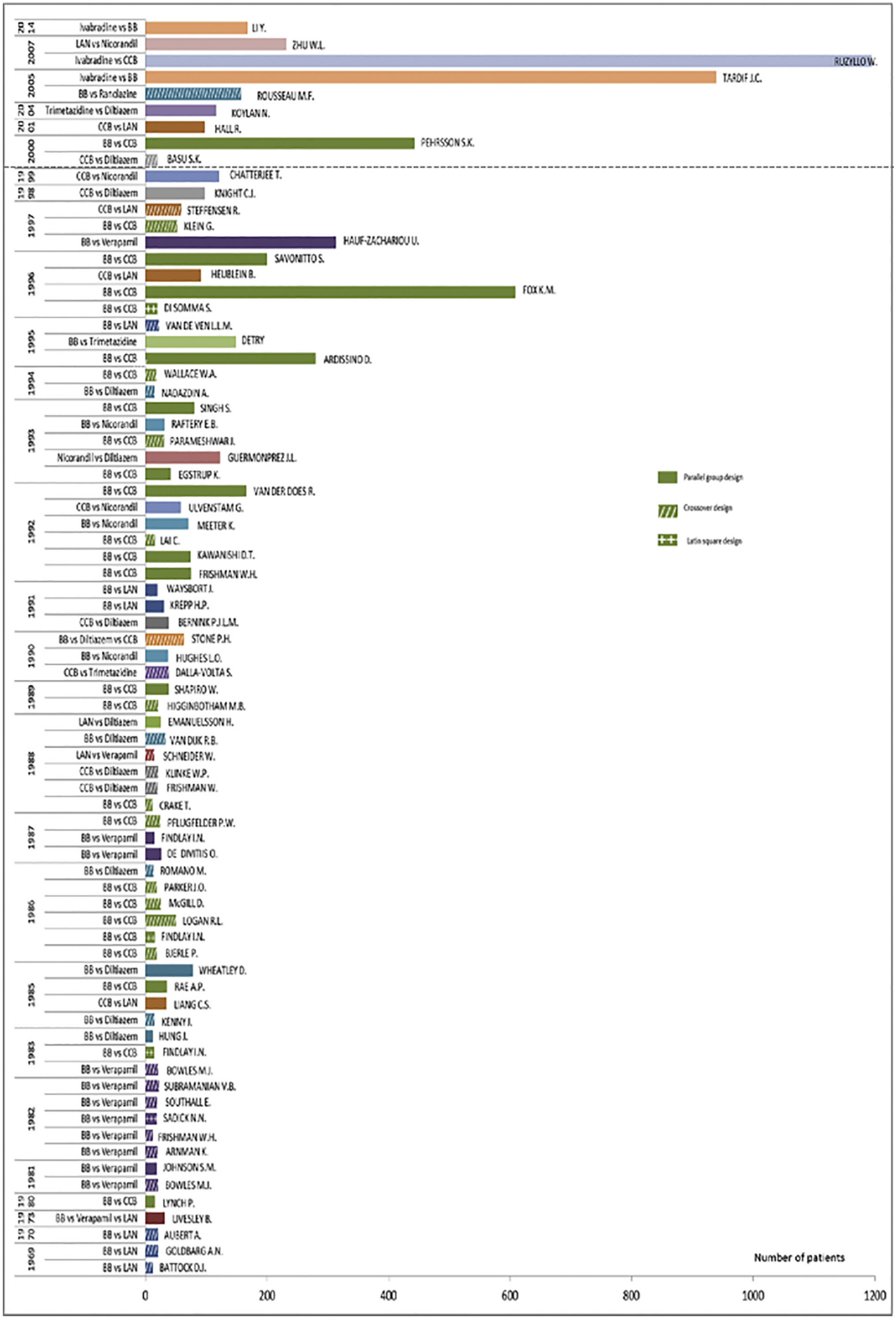
2014 Ivabradine vs BB LI Y.
2007 LAN vs Nicorandil ZHU W.L.
Ivabradine vs CCB RUZYLLO W.
2005 Ivabradine vs BB TARDIF J.C.
BB vs Pardaxine ROUSSEAU M.F.
2004 Trimetazidine vs Diltiazem KOYLAN N.
2001 CCB vs LAN HALL R.
2000 BB vs CCB PEHRSSON S.K.
CCB vs Diltiazem BASU S.K.
1999 CCB vs Nicorandil CHATTERJEE T.
1998 CCB vs Diltiazem KNIGHT C.J.
1997 CCB vs LAN STEFFENSEN R.
BB vs CCB KLEIN G.
BB vs Verapamil HAUF-ZACHARIOU U.
1996 BB vs CCB SAVONITTO S.
CCB vs LAN HEUBLEIN B.
BB vs CCB FOX K.M.
BB vs CCB DI SOMMA S.
1995 BB vs LAN VAN DE VEN L.L.M.
BB vs Trimetazidine DETRY
BB vs CCB ARDISSINO D.
1994 BB vs CCB WALLACE W.A.
BB vs Diltiazem NADAZDIN A.
1993 BB vs CCB SINGH S.
BB vs Nicorandil RAFTERY E.B.
BB vs CCB PARAMESHWAR J.
Nicorandil vs Diltiazem GUERMONPREZ J.L.
BB vs CCB EGSTRUP K.
1992 BB vs CCB VAN DER DOES R.
CCB vs Nicorandil ULVENSTAM G.
BB vs Nicorandil MEETER K.
BB vs CCB LAI C.
BB vs CCB KAWANISHI D.T.
BB vs CCB FRISHMAN W.H.
1991 BB vs LAN WAYSBORT J.
BB vs LAN KREPP H.P.
CCB vs Diltiazem BERNINK P.J.L.M.
1990 BB vs Diltiazem vs CCB STONE P.H.
BB vs Nicorandil HUGHES L.O.
CCB vs Trimetazidine DALLA-VOLTA S.
1989 BB vs CCB SHAPIRO W.
BB vs CCB HIGGINBOTHAM M.B.
1988 LAN vs Diltiazem EMANUELSSON H.
BB vs Diltiazem VAN DUK R.B.
LAN vs Verapamil SCHNEIDER W.
CCB vs Diltiazem KLINKE W.P.
CCB vs Diltiazem FRISHMAN W.
BB vs CCB CRAKE T.
1987 BB vs CCB PFLUGFELDER P.W.
BB vs Verapamil FINDLAY I.N.
BB vs Verapamil DE DIMITIS O.
1986 BB vs Diltiazem ROMANO M.
BB vs CCB PARKER J.O.
BB vs CCB McGILL D.
BB vs CCB LOGAN R.L.
BB vs CCB FINDLAY I.N.
BB vs CCB BJERLE P.
1985 BB vs Diltiazem WHEATLEY D.
BB vs CCB RAE A.P.
CCB vs LAN LIANG C.S.
BB vs Diltiazem KENNY J.
1983 BB vs Diltiazem HUNG J.
BB vs CCB FINDLAY I.N.
BB vs Verapamil BOWLES M.J.
1982 BB vs Verapamil SUBRAMANIAN V.B.
BB vs Verapamil SOUTHALL E.
BB vs Verapamil SADICK N.N.
BB vs Verapamil FRISHMAN W.H.
BB vs Verapamil ARNMAN K.
1981 BB vs Verapamil JOHNSON S.M.
BB vs Verapamil BOWLES M.J.
1980 BB vs CCB LYNCH P.
1973 BB vs Verapamil vs LAN UVESLEY B.
1970 BB vs LAN AUBERT A.
1969 BB vs LAN GOLDBARG A.N.
BB vs LAN BATTOCK D.J.
Parallel group design
Crossover design
Latin square design
Number of patients
0
200
400
600
800
1000
1200

Table 1
Characteristics of the studies included in the systematic review.

Trial	Design	N of pts	Study drugs (with doses)	FU	Primary endpoint	ETT protocol	Results: number of angina attacks and use of short-acting nitrates	Results: ETT parameters
Betablockers								
Pehrsson et al. 2000	Double blind, randomized triple arm parallel group study	351	–Amlodipine 5 to 10 mg –Atenolol 50 to 100 mg –Their combination	10 weeks	Time to onset ST depression>1 mm, time to onset angina, total exercise time, maximum achieved workload, peak intensity angina, total number of ST segment depression, time of ST segment depression.	Bicycle ergometer with a starting work load of 20 W increased by 10 W every min.	NA	Atenolol and amlodipine alone as effective as in combination in term of time to onset of ST depression>1 mm, time to onset of angina, total exercise time, maximum achieved workload and peak intensity of angina. Atenolol alone or in combination was more effective than amlodipine in terms of total time and number of ST depression episodes.
Long acting nitrates								
Hall et al. 2001	Double blind, randomized parallel group study	196	–Amlodipine 5 to 10 mg –Isosorbide mononitrate 25–50 mg	28 weeks	Total exercise time, median incidence of angina attack and short acting nitrates per week	Bruce protocol with the addendum of a 3 min rest at the 0.5 stage inclination before progressing to the routine stage I–IV	Median number of angina attacks in both groups was 0.	Total exercise time was significantly better with amlodipine.
Diltiazem/verapamil								
None								
Nicorandil								
Zhu et al. 2007	Randomized double dummy trial	249	–Nicorandil 5 mg bid –Isosorbide mononitrate 20 mg bid	4 weeks	Exercise time to develop 1 mm ST depression	Bruce protocol for a submaximal treadmill	The consumption of short acting nitrates was significantly reduced only with nicorandil, which showed also to be more effective in the reduction of angina attack	No differences in total exercise time and time to onset of chest pain.
Chatterjee et al. 1999	Randomized double-blind parallel group trial comparing Nicorandil 10 mg bid versus Amlodipine 5 mg od	121	–Nicorandil 10 mg bid –Amlodipine 5 mg od	8 weeks	Time to onset of ST segment depression, time to angina, total exercise duration, quality of life, double product.	Upright bicycle with an initial workload of 50 W, increasing by 25 W every 2 min.	Both drugs reduced the number of angina attack and of short acting nitrates used.	Time to onset of ST-segment depression increased only in the amlodipine-group. Time to angina and total exercise duration increased in both treatment groups, as well as both drugs reduced ST-segment depression at maximal identical workload, weekly anginal attacks and the number of short acting nitrates. HR remained unchanged in both groups. Resting BP decreased only in the amlodipine group. Quality of life

								variables improved over the course of the study.
Guermonprez et al. 1993	Double blind randomized parallel group study	123	–Nicorandil 20 bid –Diltiazem 60 mg tid	3 months	Maximum exercise capacity, angina onset, double product, total exercise duration, time to ST segment depression, time to angina.	Bicycle ergometer, initial workload 30 W then increased every 3 min	Reduction of angina attacks and in consumption of short acting nitrates in both groups without significant differences.	Both drugs increased the maximum exercise capacity, the amount of work performed before ischemic threshold, and the amount of work performed before angina. Neither double products was different after treatment.
Ranolazine								
Rousseau et al. 2005	Randomized 3-period crossover, double blind, double dummy study	154	–Ranolazine 400 mg tid –Atenolol 100 mg	3 weeks	Time to onset angina	Modified Bruce protocol, or upright bicycle exercise test with a 20 W starting load and a 20 W increments per minute	Ranolazine and atenolol had similar effect in the reduction of angina attack and in nitroglycerin use	Ranolazine resulted in longer total exercise duration. Similar time to onset of angina and ST segment depression.
Trimetazidine								
Detry et al. 1994	Randomized, double blind	149	–Trimetazidine 20 mg tid –Propranolol 40 mg tid	3 months	Angina attack per week, exercise duration, time to 1 mm ST depression, double product	Symptom limited maximal text on bicycle ergometer. Initial workload 30 W, increased of 30 W every 3 min.	No differences in the angina attack per week.	No differences in exercise duration, time to 1 mm ST depression. Double product did not change in patients treated with trimetazidine, and it was reduced in patients treated with propranolol.
Koylan et al. 2004	Multicenter double blind comparative trial	116	–Trimetazidine 20 mg tid –Diltiazem 60 mg tid	4 weeks	Exercise performance	Bruce protocol.	Both treatments decreased angina attack and short acting nitrates consumption.	Both treatments reduced maximal ST-segment depression, but none changed time to ST segment depression and ST recovery on exercise test
Ivabradine								
Tardif et al. 2005	Double blind parallel group	939	–Ivabradine 5 mg bid to ivabradine 7.5 –Ivabradine 5 mg bid or ivabradine 10 mg bid –Atenolol 50 mg to 100 mg	12 weeks	Change in total exercise duration	Modified Bruce protocol	Number of angina attack per week and consumption of short acting nitrates reduced in all treatment groups.	Ivabradine was as effective as atenolol.
Ruzyllo et al. 2007	Randomized, double blind, three arm parallel group	1195	–Ivabradine 7.5 mg –Ivabradine 10 mg -Amlodipine 10 mg	3 months	Change in total exercise duration	Ergometric bicycle with initial work load of 50 W increased of 10 W every min	Number of angina attack and short acting nitrates use was reduced in all treatments group without significant differences	Ivabradine has comparable efficacy to amlodipine in improving exercise tolerance.
Li et al. 2014	Randomized, double blind, double dummy study	332	–Ivabradine 5 mg bid –Ivabradine 7.5 mg bid –Atenolol 12.5 bid –Atenolol 25 mg bid	12 weeks	Change in total exercise duration	Bruce protocol	Reduction of angina attack and short acting nitrates use was reduced by both treatments	Ivabradine was as effective as Atenolol in improving exercise tolerance and in reducing heart rate

N: number; FU: follow-up; ETT: exercise test tolerance; SAN: short acting nitrates.

and in three studies the sample size was <100 patients. For all these reasons, 11 studies were included in the final analysis (Fig. 1s, supplemental online material). All 11 studies were randomized trials. Fig. 2s (supplemental online material) summarizes the risk of bias of studies included by Cochrane methods.

3.1. Beta-blockers versus calcium channel blockers

Only one trial fulfilled inclusion and exclusion criteria (Table 1). Pehrsson et al. [14] performed a randomized double-blind, triple arm parallel group study comparing monotherapy with amlodipine or atenolol versus their combination. The analysis involved 351 patients. Short and long acting nitrates were allowed as other anti-angina therapy during the 10 weeks of the study. In terms of time to onset of >1 mm ST depression, time to onset of angina, total exercise time, maximum achieved workload, and peak intensity of angina, amlodipine and atenolol alone were as effective as their combination. During ambulatory monitoring, atenolol was more effective than amlodipine regarding total time and number of ST-depression episodes, and as effective as the combined drugs.

There were no significant differences in terms of adverse effects among the three groups. The study was well planned, and diagnosis of stable angina was based on symptoms and positive exercise test. The presence of obstructive coronary artery disease was not verified by coronary angiography nor was an inclusion criterion (Table 2). Another limitation is that patients received concomitant therapy with long acting nitrates (Table 1). In addition, it is not clear how the sample size was calculated (Table 2).

3.2. Long-acting nitrates versus calcium channel blockers

The report of Hall et al. [15] fulfilled our criteria (Table 1). A total of 196 patients were included in this 28 weeks randomized, double-blind parallel group study comparing amlodipine versus long acting nitrates (Table 2). The efficacy analyses were based on total exercise time, number of anginal attacks per week or the need of short acting nitrates. There was no statistically difference in terms of median number of angina attacks (*surprisingly none in both groups*) and in number of short acting nitrates taken. Amlodipine resulted better than long acting nitrates in terms of total exercise time achieved. No differences were found in relation to adverse events or quality of life tested with the SF36 Questionnaire. The study reported a formal a priori calculation of the sample size. One of the limitations, however, is related to the definition of stable angina. Criteria for this diagnosis were not specified and the presence of coronary artery disease was not proven by coronary angiography. It is not clear how the number of anginal attacks per week and consumption of short acting nitrates were recorded. This information is relevant to understand the reported absence of angina attacks.

3.3. Nicorandil

In 2007 Zhu et al. conducted a randomized double-dummy trial, comparing the effect of nicorandil versus isosorbide mononitrate in 249 patients for 4 weeks [16] (Table 2). Other anti-anginal drugs such as short acting nitrates and beta-blockers were allowed during the study period. However, the difference in the number of patients treated with these drugs at baseline was not statistically significant among study groups. The primary endpoint was exercise time to 1 mm ST segment depression whilst other exercise test parameters and number of anginal attacks were considered secondary endpoints. Sample size was calculated a priori. There were no differences in the primary endpoint between the drugs. Consumption of short acting nitrates and occurrence of angina was significantly reduced only by Nicorandil. However, the analysis on this endpoint was performed on only 41 patients receiving Nicorandil and 40 treated with isosorbide mononitrate, as the vast majority of patients did not need nitro-glycerine. Adverse events were similar between two groups, headache being the most common (Table 1). Again, in this study the presence of obstructive coronary artery disease was not assessed (Table 2).

The SWAN study, published in 1999 and not included in the meta-analysis of Heidenreich et al. [11], is a randomized double-blind parallel group trial comparing Nicorandil 10 mg bid versus Amlodipine 5 mg od in 121 patients for 8 weeks (Table 2) [17]. The presence of coronary artery disease with >50% stenosis in one of the coronary arteries was one of the inclusion criteria (Table 2). The study showed that although time to onset of ST-segment depression improved only with amlodipine, time to angina attack, total exercise duration, reduction in weekly angina episodes, number of short acting nitrates used and quality of life were not different [17]. The analysis was on an intention to treat basis and the calculation of a sample size was reported (Table 2). Nicorandil seemed to be better tolerated than Amlodipine in terms of occurrence of adverse events [17].

Finally, Guermonprez et al. performed a 3 months, double-blind randomized parallel group study, in 123 patients comparing Nicorandil 20 bid versus Diltiazem 60 tid [18]. This study was published in 1993 but was not considered in the meta-analysis of Heidenreich et al. [11]. There were no statistically significant differences between groups in any of the endpoints considered. The double product at peak exercise between groups was similar. (Table 1).

3.4. Ranolazine

Rousseau et al. compared the effect of Ranolazine versus Atenolol in 152 patients in a 3 weeks, randomized 3-period crossover, double-blind, double-dummy study [19] (Tables 1–2). Even in this case, concomitant medications with short acting nitrates and calcium channel blockers were allowed. As result, 54% of the overall population was treated with calcium channel blockers at baseline, and, unfortunately, the difference between groups regarding this co-administration is not described. There was no statistically significant difference in time to angina onset or in time to onset of segment ST depression between ranolazine and atenolol. Total exercise duration was longer with ranolazine compared to atenolol 100 mg (mean difference 21.1 s, 95% CI 6.2–36, $p = 0.006$) though atenolol reduced more than ranolazine the cardiac workload and rate pressure product [19]. Both treatments had similar effect in the reduction of anginal attacks and in nitroglycerin use (Table 1).

3.5. Trimetazidine

We found two studies fulfilling our inclusion and exclusion criteria, both published before 1999 and not considered in the meta-analysis by Heidenreich et al. In the first study, Detry et al. performed a randomized double-blind trial in 149 male patients with stable angina comparing propranolol (40 mg tid) and trimetazidine (20 g tid) for 3 months [20] (Table 2). The results show a similar efficacy profile in terms of angina attacks per week, exercise duration, time to 1 mm segment depression. The double product remained unchanged for patients treated with trimetazidine, but significantly decreased with propranolol, confirming that trimetazidine has anti-ischemic effect not related to the reduction in myocardial oxygen demand [20]. Koylan et al. performed a 4 weeks, multicenter randomized double-blind trial, comparing trimetazidine (20 mg tid) and diltiazem (60 mg tid) in 116 male patients. Both treatments reduced the number of anginal attacks and maximal ST-segment depression, but none changed time to ST segment depression and ST recovery on exercise test. Finally, Diltiazem prolonged PR and QRS duration [21].

Table 2
Inclusion and exclusion criteria in trials selected.

Trial	Sample size calculation	Inclusion criteria	Exclusion criteria
Betablockers			
Pehrsson et al. 2000	N	–Clinically stable angina –Positive exercise test	MI, CABG, PCI in the preceding 3 months, UA, HF, arrhythmias, II or III degree AV block, diastolic blood pressure > 115 mm Hg or systolic blood pressure > 250 mm Hg, and medication influencing ECG. BB or CCB that could not be safely withdrawn. Need of revascularization.
Long acting nitrates			
Hall et al. 2001	Y	–Stable angina –Positive exercise test	AF, HF, MI or CVA in the last 3 months, VHA, CHD, Arrhythmias, LBBB, uncontrolled hypertension
Diltiazem/verapamil			
None			
Nicorandil			
Zhu et al. 2007	Y	Typical stable angina for at least 1 month, achieved relief from anginal attacks with short-acting nitro-glycerine, positive result for an exercise tolerance test at the end of the washout period	MI, UA, PCI or CABG in the last 6 months, HF, PAD limiting ETT, arrhythmias, use of concomitant anti-angina drugs, DM with fasting glucose level > 160 mg/dL
Chatterjee et al. 1999	Y	–Stable angina for 3 months –Coronary disease confirmed by a history of myocardial infarction or a positive angiogram (>50% stenosis of a main coronary artery)	MI, PCI, UA, angina at rest or vasospastic angina within the last 3 months. Hypertension (DBP > 105 mm Hg), ECG recording unfavourable, HF, PAD limiting ETT, VHD, SBP <100 mm Hg, postural hypotension, severe concomitant disease.
Guermonprez et al. 1993	N	–Positive exercise test, previous MI, coronary artery disease detected by CA	NA
Ranolazine			
Rousseau et al. 2005	N	–Evidence of CAD documented by previous MI or with CA (presence of 50% diameter stenosis accompanied by ischemic electrocardiographic signs and angina during exercise); –Chronic angina –Positive exercise test –Improvement of symptoms after antianginal drugs	Arrhythmias, PM, pre-existent ST segment depression, LBBB, digoxin, HF or UA or MI within a month, clinically significant comorbidity, verapamil therapy, inability to discontinue BB.
Trimetazidine			
Detry et al. 1994	N	–Stable exertional angina, –Positive exercise test –Evidence of CAD documented by previous MI or with CA	MI within the last 3 months, HF, UA, arrhythmias, uncontrolled hypertension, II and III degree AV block, WPW, asthma, PAD, DMID, digoxin anti-arrhythmic drugs, use of other anti-anginal medication.
Koylan et al. 2004	Y	–Positive exercise test –Evidence of CAD documented by previous MI or with CA, or with a perfusion scan	Female, MI within the last 6 months, HF, UA, VHD, uncontrolled hypertension, AF, PM, ECG recording unfavourable, renal or hepatic disease, other drugs interfering with the exercise test.
Ivabradine			
Tardif et al. 2005	Y	–Stable effort angina for 3 months –Evidence of CAD manifested by 1 of five criteria (myocardial infarction 3 months before study entry, coronary angioplasty 6 months or bypass surgery 3 months before entry, coronary angiogram showing 1 diameter stenosis 50%, or scintigraphic/echocardiographic evidence of exercise-induced reversible myocardial ischaemia –Two positive exercise test –Time to 1 mm ST-segment depression of the two ETTs within +20% or + 1 min of each other	Heart disease other than CAD; known high-grade left main CAD; HF; symptomatic hypotension or uncontrolled hypertension AF, PM, ICD, II or III degree AV block, resting HR < 50 bpm or sick sinus syndrome; any condition that interferes with ability to perform or interpret exercise tests (e.g. WPW, LBBB, LV hypertrophy); contraindications to atenolol; recent treatment with amiodarone (<3 months) or bepridil (<7 days); ALT >3 times normal value; serum creatinine >180 mmol/L; electrolyte disorders; thyroid disorders unless controlled by thyroxine for 3 months; haemoglobin <100 g/L; or history of severe psychiatric disorders
Ruzyllo et al. 2007	Y	–Stable effort angina for 3 months –Evidence of CAD documented by MI or CABG >3 months previously, or PCI > 6 months previously, or by CA, echo-stress or scintigraphy –Positive exercise test	Inability to perform ETT, ECG not interpretable, UA, Prinzmetal angina, HF, heart disease other than CAD, AF, PM, hypotension, uncontrolled hypertension, resting HR < 50 bpm, recent treatment with amiodarone (<3 months) or bepridil (<7 days), any drug interfering with ivabradine, contraindications to amlodipine.
Li et al. 2014	Y	–Patients symptomatic for angina pectoris with 1 of the following: –Manifested CAD –CAD documented by CA –Effort-induced reversible myocardial ischemia showed by nuclide or echocardiography, ischemic electrocardiogram (ECG) changes	VHD, CHD; PH, COPD, stroke, dissecting aneurism, hypertrophic cardiomyopathy, MI within the last 3 months, PCI or CABG within the last 6 months, known high-grade left main CAD; HF; symptomatic hypotension or uncontrolled hypertension AF, PM, ICD, II or III degree AV block, resting HR < 60 bpm; DM not controlled, anaemia, alcohol abuse, any condition that interferes with ability to perform or interpret exercise tests (e.g. WPW, LBBB, LV hypertrophy); recent treatment with amiodarone (<3 months) or bepridil (<7 days); allergic disorders, BB.

Y: yes; N: no; MI: myocardial infarction; ETT: exercise tolerance test; VHD: valvular heart disease; CHD: congenital heart disease; CAD: coronary artery disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; ICD: implantable cardioverter defibrillator; HR: heart rate; PM: pacemaker; DM: diabetes mellitus; DMID: diabetes mellitus insulin dependent; AF: atrial fibrillation; LBBB: left bundle branch block; AV: atrio-ventricular; WPW: Wolf-Parkinson-White; LV: left ventricle; CA: coronary angiography; HF: heart failure; PH: pulmonary hypertension; COPD: chronic obstructive pulmonary disease; UA: unstable angina; SBP: systolic blood pressure; DBP: diastolic blood pressure; PAD: peripheral artery disease; CVA: cerebrovascular accident.

3.6. Ivabradine

Three studies were selected for Ivabradine, all of them with a follow-up of 3 months (Table 2). Two compared ivabradine and atenolol [22,23] and the other compared ivabradine and amlodipine [24]. Tardif et al. [22], performed a double-blind parallel group trial involving 939 patients. Participants were randomized to receive ivabradine 5 mg bid, up titrated to 7.5 mg or to 10 mg bid for 12 weeks, or atenolol 50 mg od for 4 weeks increased to 100 mg for 12 weeks. Ivabradine was not inferior to atenolol in the primary outcome which was increase in total exercise duration for both the tested doses. At the peak of the activity, non-inferiority of ivabradine 5 mg compared to atenolol 50 mg was demonstrated for all exercise test criteria (time to limiting angina, time to onset angina, time to ST segment depression). Ivabradine, as well as atenolol, reduced the number of angina attack by two thirds. An a priori sample size calculation was reported (Table 2) and evidence of CAD was documented by, at least, one of the following criteria: myocardial infarction ≥3 months before study entry, coronary angioplasty ≥6 months or bypass surgery ≥3 months before entry, coronary angiogram showing ≥1 diameter stenosis ≥50%, or scintigraphic/echocardiographic evidence of exercise-induced reversible myocardial ischemia.

The only missing analysis is the comparison in the safety outcome, partly related to the selection process of the patients (which excluded patients with known beta-blockers intolerance excluded from the trial) [22]. These results were confirmed in a smaller study of Li et al., published in 2014 [23]. This is a randomized double-blind, double-dummy trial, on 332 patients comparing ivabradine 5 mg bid or 7.5 mg bid, and atenolol 12.5 or 25 mg bid for 12 weeks. Ivabradine showed to be non-inferior to Atenolol in improving exercise capacity and reducing heart rate. The rate of adverse events was slightly higher with Atenolol (66 versus 73, $p > 0.05$, respectively) [23]. Finally, Ruzyllo et al. [24] compared the effect of ivabradine 7.5 or 10 mg bid versus amlodipine 10 mg. This was a randomized, double blind, three arm parallel group trial involving 1195 patients. Also this was a well performed trial: primary and secondary endpoints as well as sample size were pre-defined (Table 2). CAD was documented by: 1) a ≥3-month history of chronic stable effort-induced angina, relieved by rest or short acting nitrates; 2) coronary artery disease (CAD) documented by occurrence of a myocardial infarction (MI) ≥3 months previously, or coronary artery bypass graft surgery (CABG) ≥3 months previously, or percutaneous coronary angioplasty (PTCA) ≥6 months previously, or by coronary angiography, stress echocardiography or scintigraphy; and 3) a positive bicycle exercise tolerance test (ETT) at selection and at inclusion (Table 2). The analyses were on an intention to treat basis, but also per-protocol population. The trial confirmed the non-inferiority of ivabradine compared to amlodipine in the improvement of total exercise duration, but also in all the secondary outcomes analyzed (time to angina onset, time to 1 mm ST segment depression, rate pressure products, short acting nitrates use and angina attack frequency). In particular, the decrease in rate pressure product was significantly greater for patients treated with ivabradine and mostly at peak exercise [24]. The most frequent adverse events were visual symptoms and sinus bradycardia with ivabradine (0.8% and 0.4% withdrawals, respectively) and peripheral oedema with amlodipine (1.5% withdrawals) [24].

4. Discussion

Our overview highlights several points that warrant special attention from the Scientific Community.

The **first** point relates to the paucity of adequate contemporary comparative data on the efficacy and tolerability of treatments with the different guideline recommended drugs for patients who have stable angina. By systematically searching Medline and Embase database and reviewing the bibliography to locate additional relevant studies published after 1999, when a meta-analysis on the comparative trials of first line antianginal drugs (beta blockers, Ca^{2+} blockers, and long-acting nitrates) was reported [11], we could identify only 11 randomized studies. It should be underlined that our requirements for inclusion were as simple as possible: a minimum of 100 patients, and at least one of the following outcomes: frequency of anginal attack, use of sublingual nitro-glycerine, or time on exercise test. Yet, in 18 years only 3925 patients have been randomized in comparative studies and out of these 3925 patients, 2130 in three trials related to ivabradine, vs atenolol, and/or amlodipine. The efficacy of another recently developed antianginal drugs, ranolazine, was compared to atenolol, in a trial randomizing 125 patients only [19]. Nicorandil, another antianginal was tested in 493 patients in three trials against isosorbide mono-nitrate (249 patients) [16], amlodipine (123 patients) [17] and diltiazem (123 patients) [18] (two of them published before 1999).

In a recent analysis of the number of subjects required to show superiority comparing two antianginals drugs in parallel groups with 90% power and exercise testing as the primary endpoint showed that approximately 350–425 subjects would be needed [23,24]. Moreover, failure to show superiority in a clinical trial does not imply equivalence unless powered accordingly [25]. On this basis, out of the eleven selected studies only the two trials involving ivabradine were adequately powered.

The **second** point underlines the even more critical lack of data available before 1999, when the only comparative meta-analysis was published [11]. Fig. 2 shows that, in 30 years, 76 studies were conducted comparing the drugs available at that time, which today are classified as first-line antianginal drugs. The 1999 meta-analysis included 69 trials plus some abstracts and studies related to outcome and/or adverse effects [11]. Interestingly, applying our criteria to these studies, only 7 out of 69 could be included in our analysis, mainly because of the relative small number of patients involved. Our initial intention was to conduct a second meta-analysis including all the new contemporary comparative studies. Once we realized the small number of reports available and of patients included along with the heterogeneity of the primary endpoints, we shifted our effort to a systematic review of the literature with the aim to alert the Scientific Community on the relative lack of evidence-based information about treatments for a pathology that affects millions of people worldwide and that is expected to further increase with the aging of the population.

The **third** point relates to the typology of the available studies which, unfortunately, does not allow a proper comparison among treatments. The comparator was often tested at different dose regimen and often under-dosed. In some studies, a background therapy, mostly with long lasting nitrates and, in some cases, even with beta blockers, was allowed, thus making difficult to test the intrinsic efficacy of the study drugs. The calculation of sample size is not always available nor the diagnostic criteria of angina. As shown in Table 1, different protocols were used for exercise testing, which also might affect the results.

The **fourth** point relates to the results of the so far available evidence which, besides all the concerns, constantly shows that the new so called "second line" drugs provide an equivalent reduction in angina severity and improvement of exercise test when compared to historical "first line beta blockers and calcium blockers. Equally resulted in similar or even reduced rate of adverse events. Earlier reviews also indicate no difference between the efficacy and occurrence of adverse events between the first and the second line drugs [4,10,11]. It should be recalled that two studies conducted with ivabradine compared to atenolol and amlodipine do not share any of the criticism of the other studies as they involved the necessary sample size calculated a priori to demonstrate non-inferiority of ivabradine in comparison with a full dose of atenolol (100 mg) and amlodipine (10 mg) [22,23]. Notably, the number of patients enrolled in these ivabradine trials (2466) is similar to the sum of all enrolled patients in all comparative trials ever conducted with all the other antianginal drugs. Furthermore, the non-inferiority of ivabradine was demonstrated for all tested doses.

The **fifth** and final point is that, surprisingly, the recent guidelines cite only 2 [18,20] of these comparative studies. Obviously, the attention has been directed more on the efficacy of any single agents. However, in

the absence of sufficient data and even considering the few available it is difficult to label some drugs as being first and other second line. This is certainly true for ivabradine.

All these points deserve some considerations. How is it possible that a disease with an annual death rate between 1.6 and 3.2% [1–3], which carries a large burden on health care has been so little investigated and, more specifically, why there are so limited comparative data? Antianginal agents are approved based on a documented improvement of total exercise duration together with a reduction in daily frequency of angina compared with placebo and/or equivalence to an active comparator. It should be said that the so-called first line choice drugs were approved many years ago, with criteria that nowadays would be insufficient. These requirements, however, are rarely fulfilled even with more recent drugs and the distinction between first line and second line antianginal drugs is clearly not supported by published trials. This attitude does not encourage innovation while angina calls for continued research and development of new pharmacological therapy in particular with regard to microvascular angina which can be treated only pharmacologically.

In **conclusion**, this systematic review of the published data including a previous meta-analysis shows a lack of comparative data between the different antianginal drugs. Medications which have different mechanisms of action and safety profiles are equally effective antianginal drugs. There is no evidence to support the use of first and second line treatments for the management of angina. Rather physicians may consider on the current review and previous publications [4,7–10] to individualize treatments for their patients with more appropriate therapy according to the pathophysiology of angina and existing comorbidities [4,10].

Acknowledgements

This review originated from a meeting at the University of Ferrara supported by a grant from Fondazione Anna Maria Sechi per il Cuore (FASC), Italy. FASC had no role in the preparation of the manuscript or the decision to publish.

Author contributions

All authors contributed to researching data, discussion of content, and reviewing and editing the manuscript before submission.

Competing interests statement

R.F. has received honoraria for steering committee membership and consulting from Novartis and Servier; and for speaking and support for travel to study meetings from Amgen, Bayer, Boehringer Ingelheim, Merck Serono, and Servier. P.G.C. is a consultant for Servier, is part of Board meetings of AstraZeneca, and has received speaking honoraria from Menarini and Servier. F.C. has received honoraria for speaking from BMS, Menarini, Novartis, Sanofi, and Servier; and received grants from Biotronik and Boeringher Ingelheim. K.F. has received personal fees, honoraria, and/or travel expenses from Armgo, AstraZeneca, Broadview Ventures, CellAegis, Servier, and TaurX; and is a director of Vesalius Trials Ltd. J.L.L.-S. has received honoraria for steering committee membership from AstraZeneca, Bayer, Boehringer-Ingelheim, GlaxoSmithKline, Menarini, Merck, Novartis, Pfizer, Sanofi, and Servier; received honoraria for speaking from Amgen and Sanofi; and received honoraria for consultancy from Boehringer Ingelheim and Menarini. The other authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.12.008.

References

[1] G. Montalescot, U. Sechtem, S. Achenbach, et al., 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology, Eur. Heart J. 34 (38) (2013) 2949–3003.
[2] 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. JACC.2012; 60:e44–e164.
[3] National Clinical Guidelines Centre. Stable Angina: Methods, Evidence & Guidance. NICE http://www.nice.org.uk/guidance/cg126/evidence/full-guideline-183176605 (2011).
[4] R. Ferrari, P.G. Camici, F. Crea, et al., Expert consensus document: A 'diamond' approach to personalized treatment of angina, Nat. Rev. Cardiol. 15 (2) (2018) 120–132.
[5] A.J. Camm, A. Manolis, G. Ambrosio, et al., Unresolved issues in the management of chronic stable angina, Int. J. Cardiol. 201 (2015) 200–207.
[6] G. Ambrosio, A. Mugelli, J. Lopez-Sendón, et al., Management of stable angina: a commentary on the European Society of Cardiology guidelines, Eur. J. Prev. Cardiol. 23 (2016) 1401–1412.
[7] A.J. Manolis, L.E. Poulimenos, G. Ambrosio, et al., Medical treatment of stable angina: a tailored therapeutic approach, Int. J. Cardiol. 220 (2016) 445–453.
[8] U. Thadani, Management of stable angina current guide lines: a critical appraisal, Cardiovasc. Drugs Ther. 30 (2016) 419–426.
[9] R. Ferrari, R. Pavasini, P.G. Camici, et al., Anti-anginal drugs-beliefs and evidence: systematic review covering 50 years of medical treatment, Eur. Heart J. 27 (2018 Aug) (Epub ahead of print).
[10] T.A. Rousan, S.T. Mathew, U. Thadani, Drug therapy for stable angina pectoris, Drugs 77 (3) (2017) 265–284.
[11] P.A. Heidenreich, K.M. McDonald, T. Hastie, et al., Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina, JAMA 281 (20) (1999) 1927–1936.
[12] J.P.T. Higgins, S. Green, Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2, The Cochrane Collaboration, (updated March 2011). Available from: http://handbook.cochrane.org/ 2009.
[13] A. Liberati, D.G. Altman, J. Tetzla, et al., The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration, BMJ 339 (2009) b2700.
[14] S.K. Pehrsson, I. Ringqvist, S. Ekdahl, B.W. Karlson, G. Ulvenstam, S. Persson, Monotherapy with amlodipine or atenolol versus their combination in stable angina pectoris, Clin. Cardiol. 23 (10) (2000) 763–770.
[15] R. Hall, C. Chong, A double-blind, parallel-group study of amlodipine versus long-acting nitrate in the management of elderly patients with stable angina, Cardiology 96 (2) (2001) 72–77.
[16] W.L. Zhu, Y.D. Shan, J.X. Guo, et al., Double-blind, multicenter, active-controlled, randomized clinical trial to assess the safety and efficacy of orally administered nicorandil in patients with stable angina pectoris in China, Circ. J. 71 (6) (2007) 826–833.
[17] T. Chatterjee, M. Fleisch, B. Meier, G. Döring, for the SWAN study group, Comparison of the antiischaemic and antianginal effects of nicorandil and amlodipine in patients with symptomatic stable angina pectoris: the SWAN study, J. Clin. Basic Cardiol. 2 (2) (1999) 213–217.
[18] J.L. Guermonprez, P. Blin, F. Peterlongo, A double-blind comparison of the long-term efficacy of a potassium channel opener and a calcium antagonist in stable angina pectoris, Eur. Heart J. 14 (Suppl B) (1993) 30–34.
[19] M. Rousseau, H. Pouleur, G. Cocco, A. Wolff, Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris, Am. J. Cardiol. 95 (2005) 311–316.
[20] J.M. Detry, P. Sellier, S. Pennaforte, D. Cokkinos, H. Dargie, P. Mathes, Trimetazidine: a new concept in the treatment of angina. Comparison with propranolol in patients with stable angina. Trimetazidine European Multicenter Study Group, Br. J. Clin. Pharmacol. 37 (3) (1994) 279–288.
[21] N. Koylan, A.K. Bilge, K. Adalet, F. Mercanoglu, K. Buyukozturk, Comparison of the effects of trimetazidine and diltiazem on exercise performance in patients with coronary heart disease. The Turkish trimetazidine study (TTS), Acta Cardiol. 59 (6) (2004) 644–650.
[22] J.C. Tardif, I. Ford, M. Tendera, M.G. Bourassa, K. Fox, INITIATIVE Investigators, Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina, Eur. Heart J. 26 (23) (2005) 2529–2536.
[23] Y. Li, L. Jing, Y. Li, et al., The efficacy and safety of ivabradine hydrochloride versus atenolol in Chinese patients with chronic stable angina pectoris, Pharmacoepidemiol. Drug Saf. 23 (11) (2014) 1183–1191.
[24] W. Ruzyllo, M. Tendera, I. Ford, K.M. Fox, Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial, Drugs 67 (3) (2007) 393–405.
[25] J.G.F. Cleland, K.V. Bunting, M.D. Flather, et al., Beta-blockers in heart failure collaborative group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials, Eur. Heart J. 39 (1) (2018) 26–35.