# Anti-anginal Drugs - Beliefs and Evidence: Systematic Review Covering 50 Years of Medical Treatment

**Manuscript Number:** EURHEARTJ-D-18-01296R1  
**Full Title:** Anti-anginal Drugs - Beliefs and Evidence: Systematic Review Covering 50 Years of Medical Treatment  
**Article Type:** Clinical review (Unsolicited)  
**Keywords:** chronic angina; anti-angina drugs; beta-blockers; calcium antagonists; channel inhibitor; ivabradine.

## Abstract
Aim: Chronic stable angina is the most prevalent symptom of ischaemic heart disease and its management is a priority. Current guidelines recommend pharmacological therapy with drugs classified as being first line (beta blockers, calcium channel blockers, short acting nitrates) or second line (long-acting nitrates, ivabradine, nicorandil, ranolazine, trimetazidine). Second line drugs are indicated for patients who have contraindications to first line agents, do not tolerate them or remain symptomatic. Evidence that one drug is superior to another has been questioned.

Methods and Results: Between January and March 2018, we performed a systematic review of articles written in English over the past 50 years English written articles in Medline and Embase following preferred reporting items and the Cochrane collaboration approach. We included double blind randomized studies comparing parallel groups on treatment of angina in patients with stable coronary artery disease, with a sample size of, at least, 100 patients (50 patients per group), with a minimum follow-up of one week and an outcome measured on exercise testing, duration of exercise being the preferred outcome. Thirteen studies fulfilled our criteria. Nine studies involved between 100 and 300 patients, (2818 in total) and a further 4 enrolled...
greater than 300 patients. Evidence of equivalence was demonstrated for the use of beta-blockers (atenolol), calcium antagonists (amlodipine, nifedipine) and channel inhibitor (ivabradine) in 3 of these studies. Taken all together, in none of the studies was there evidence that one drug was superior to another in the treatment of angina or to prolong total exercise duration. Conclusion: there is a paucity of data comparing the efficacy of antianginal agents. The little available evidence shows that no antianginal drug is superior to another and equivalence has been shown only for three classes of drugs. Guidelines draw conclusions not from evidence but from clinical beliefs.

Suggested Reviewers:

Opposed Reviewers:

Additional Information:

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<td>Please enter the names of the authors who <strong>Drafted the manuscript</strong></td>
<td>ROBERTO FERRARI; KIM FOX, RITA PAVASINI, ATHANASIOS MANOLIS, PAOLO CAMICI, FILIPPO CREA, JOSE’ LOPEZ-SENDON, MARIO MARZILLI, FAUSTO PINTO, GIUSEPPE ROSANO, NICOLAS DANCHIN</td>
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<td>ROBERTO FERRARI; KIM FOX, RITA PAVASINI, ATHANASIOS MANOLIS, PAOLO CAMICI, FILIPPO CREA, JOSE’ LOPEZ-SENDON, MARIO MARZILLI, FAUSTO PINTO, GIUSEPPE ROSANO, NICOLAS DANCHIN</td>
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<td>If asked, I will provide or fully cooperate in obtaining and providing the original data on which the manuscript is based so the editors or their designates can examine it.</td>
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<td><strong>TWITTER message</strong> (Please submit a catchy Twitter message of max. 140 characters, which we would use to promote this submission in the event of acceptance - Max 140 characters).</td>
<td>Anti-anginal Drugs - Beliefs and Evidence: Systematic Review Covering 50 Years of Medical Treatment</td>
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June, 26th 2018

Dear Tom,

Thanks for considering our paper entitled “Anti-anginal Drugs - Beliefs and Evidence: Systematic Review Covering 50 Years of Medical Treatment” for publication in the European Heart Journal.

Please find enclosed the reply to the four Reviewers. All of them liked the manuscript. We have just made the suggestions they requested.

I do believe that our paper provides an important message to the cardiological community: the incredible shortage of data for medical treatment for angina, a pathology affecting millions of patients worldwide. The message is also very timing as the ESC will shortly reconsider the guidelines for medical treatment of angina. These are the reasons why, I hope, our paper could be acceptable for publication in the European Heart Journal.

Looking forward to hear and see you soon.

Best wishes

Roberto Ferrari
Manuscript: EURHEARTJ-D-18-01296

Title: Anti-anginal Drugs - Beliefs and Evidence: Systematic Review Covering 50 Years of Medical Treatment

Corresponding Author: Roberto Ferrari, fri@unife.it

Current revision: #1
Reviewer #1

This paper is well-written and demonstrates reasonably in a simple way that no antianginal drug is superior to another and that equivalence has been shown only for three classes of drugs. I do not have any particular criticism as for the methodology and the results.

It is not clear to me the legend of Fig. 1. "....... including >300 patients". I understand that this figure illustrates 76 studies independently from the number of patients included: "(whatever the N of patients included: 76 RCTs, n=7034)"

Reply to Reviewer # 1

Thanks for the positive comments. The Reviewer is right, the legend of Figure 1 is misleading. We have modified the text.

Modified text: Page 12, Lines 3-4

Figure 1: RCT directly comparing beta-blockers, calcium antagonists, long-acting nitrates, nicorandil, trimetazidine, and ivabradine for stable angina (76 RCTs, n=7034 patients).
Reviewer #2

This is a well written review by highly reputed and well known experts in the field. The systematic analysis of the literature is thoroughly done. The major conclusion of the authors is that (contrary to statements in the current guidelines) there is no evidence for superiority of a specific class of antianginal drugs over another class of drugs used in clinical routine to treat angina. While this statement might be true for a mere view on disturbances of coronary conductance, it does not consider the major impact of „non-coronary”, cardiac and general comorbidities, that also affect the myocardium, the interstitium, and neurons. This may influence the primary choice of antianginal drugs and may be of particular interest in patients with accompanying cardiac and general comorbidities such as ischemic cardiomyopathy, accompanying mitral regurgitation, atrial fibrillation, autonomic dysfunction, diabetes, arterial hypertension, and so forth. This should be also considered in more detail by the authors. So the „genuine truth” in real world conditions may be not only reflected by the question whether or not the subclassification of antianginal drugs into first and second line type drugs rather than individualizing the antianginal therapy pending on cardiac, circulatory and general comorbidities, which in turn affect the regulation of coronary conductance and myocardial supply/demand ratio of various nutrients aside from oxygen. This aspect should be more strengthened in a revised version of the manuscript.

Reply to Reviewer #2

Thanks for the comments. Indeed we fully agree with the Reviewer and share his/her concern related to the choice of antianginal drug according to comorbidities, pathophysiology of angina (i.e. non coronary angina or angina with normal epicardial coronary arteries) and to the characteristics of the patients. Actually we have addressed this issue at length in a recent article published in Nature Review (Nat Rev Cardiol. 2018 Feb;15(2):120-132), which has originated the present systematic review. Although this was not the aim of the present systematic review, we have strengthened in the discussion the importance of considering pathogenesis of angina and patient comorbidities when choosing the optimal medical treatment.
In addition, the primary choice of antianginal drug should also take in consideration common comorbidities such as hypertension, mitral regurgitation, atrial fibrillation, autonomic dysfunction and so forth.
Reviewer #3

The aim of the manuscript is to review current treatment of chronic angina in our current Medical setting (with improved revascularisation techniques both in the acute and the chronic setting), and with new drugs that have appeared in recent years.

Criteria to include trials in the study may be arbitrary, but the weight of the evidence is weak. Another view of this serious problem would be to exclude any trial that does not fulfil all the criteria that are compulsory nowadays to include any trial in a review/meta-analysis. The problem would be that the authors would end up with very few studies to assess. For example, the studies used in drugs such as calcium antagonists used as a parameter performance in a stress test at peak plasma levels of the drug, whereas it is currently asked to show benefit with trough levels of the drugs (which has only been done with ivabradine and ranolazine). This issue has not been mentioned in the manuscript. Studies with one week follow-up would not currently be accepted either to assess chronic treatment. It is a relevant manuscript to stress that treatment of chronic angina is based upon drugs that were approved many years ago, with criteria that nowadays would not be enough.

Page 9, first paragraph. "We should try to select our first line treatment of angina according to our understanding of the predominant pathophysiological mechanisms operating in each individual patient. Similarly, add on therapy is likely to be more effective when considering the potential mechanisms of action." Although highly plausible, there is no evidence to back this sentence. It would therefore be more fair to begin the sentence with (i.e.) "It is therefore plausible to consider..."

Reply to Reviewer #3

Many thanks for the comments. Actually what discussed and suggested by the Reviewer (i.e. exclude any trial that does not fulfil criteria that are nowadays compulsory for being included in a systematic review) indeed was our first approach. However, as correctly pointed out by the
Reviewer we ended up with only few studies related to the beta-blockers, calcium channel blockers and ivabradine, we have stressed this point in the manuscript. We have modified the text on page 9 as suggested by the Reviewer.

**Modified text: Page 7, Lines 21-24**

Other issues in the earlier studies have made difficult the comparison with those conducted more recently, for example studies with calcium antagonists evaluated the effect of stress test at peak plasma levels, whereas it is currently asked to show benefit at trough level of the drugs which actually is available only for ivabradine and ranolazine.

**Modified text: Page 9, Line 21-22**

In conclusion, treatment of chronic angina with the so called first line choice is based upon drugs approved many years ago, with criteria that nowadays would be insufficient.

**Modified text: Page 9, Line 9**

*It is therefore plausible to consider* to select our first line treatment of angina according to our understanding of the predominant pathophysiological mechanisms operating in each individual patient and his or her comorbidities.
Reviewer #4

This is an interesting article confirming the paucity of data regarding the efficacy of antianginal drugs. The main statement is that the few studies available show that beta-blockers, calcium antagonists and ivabradine are similarly effective as antianginal agents. The authors argue that the recommendations of the guidelines dividing agents into first and second line drugs are not supported by evidence. Indeed, this is true and the 2013 ESC guidelines are correctly criticised for assigning an evidence level A to this recommendation. The problem with the data is also that there is little information about the efficacy of these drugs as compared to placebo. This problem should be addressed in the discussion.

Minor point: on page 9 in the first line Prinzmetal is the correct spelling.

Reply to Reviewer # 4

Thanks for the comment. We have strengthened the problem related to the paucity and quality of data through the discussion. We have corrected the spelling of Prinzmetal angina.

Modified text: Page 9 Line 5

with Prinzmetal angina

Modified text: Page 7, Lines 21-24

Other issues in the earlier studies have made difficult the comparison with the those conducted more recently, for example studies with calcium antagonists evaluated the effect of stress test at peak plasma levels, whereas it is currently asked to show benefit at trough level of the drugs which actually is available only for ivabradine and ranolazine.

Modified text: Page 9, Line 21-22

In conclusion, treatment of chronic angina with the so called first line choice is based upon drugs approved many years ago, with criteria that nowadays would be insufficient.
Anti-anginal Drugs - Beliefs and Evidence:

Systematic Review Covering 50 Years of Medical Treatment

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Abstract count: 292 words.

Keywords: chronic angina; anti-angina drugs; beta-blockers, calcium antagonists, channel inhibitor, ivabradine.
ABSTRACT

Aim: Chronic stable angina is the most prevalent symptom of ischaemic heart disease and its management is a priority. Current guidelines recommend pharmacological therapy with drugs classified as being first line (beta blockers, calcium channel blockers, short acting nitrates) or second line (long-acting nitrates, ivabradine, nicorandil, ranolazine, trimetazidine). Second line drugs are indicated for patients who have contraindications to first line agents, do not tolerate them or remain symptomatic. Evidence that one drug is superior to another has been questioned.

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Conclusion: There is a paucity of data comparing the efficacy of antianginal agents. The little available evidence shows that no antianginal drug is superior to another and equivalence has been shown only for three classes of drugs. Guidelines draw conclusions not from evidence but from clinical beliefs.
INTRODUCTION

The first effective treatment for angina, amyl nitrate, was described in 1867 (1) and subsequently in 1879 the benefits of nitroglycerine were reported (2). However it was not until 1964 that propranolol, the first clinically available beta blocker, was introduced into clinical practice for the long term oral management of chronic stable angina (3). Calcium antagonists were identified in 1964 (4) and in 1975 became available (5), licenced for the treatment of angina. Around this time, long acting nitrates in the form of isosorbide dinitrate began to be used for chronic oral therapy (6); the earlier preparations of long-acting nitrates were hampered by the development of drug tolerance (7). Subsequently, modulators of myocardial metabolism (Trimetazidine) (8), ATP-dependent potassium channel openers (Nicorandil) (9), If channel inhibitors (Ivabradine) (10) and late inward sodium channel inhibitors (Ranolazine) (11) were introduced. In the late 60s/ 70s, a better understanding of the pathophysiology of angina began to emerge and it became clear that all these various agents improved the symptoms of angina but by different mechanisms.

According to the guidelines, drugs for the symptomatic relief of angina are classified as being first line (beta blockers, calcium channel blockers with short acting nitrates on request) or second line (long-acting nitrates, Nicorandil, Ivabradine, Trimetazidine and Ranolazine) with the recommendation to reserve second line medications for patients who have contraindications to first line agents, do not tolerate them or remain symptomatic (12). However, what is the evidence that any one of these treatments is superior to another? The purpose of this systematic review is to examine the evidence accumulated over the past 50 years since the introduction of propranolol for the efficacy of one anti-anginal agent compared to another.
METHODS

We performed a systematic review of the literature following Preferred Reporting Items for systematic Reviews and Meta-analysis (PRISMA). Appropriate articles were searched in MEDLINE and in EMBASE. The search was carried out between January and March 2018 to include all papers published in English specifically for the treatment of angina in patients with a diagnosis of stable coronary artery disease and which fulfilled the following criteria: namely, double blind randomized clinical trials comparing parallel groups, two anti-anginal drugs, with a sample size of at least 100 patients (50 patients per treatment group) and a follow-up lasting at least one week. Studies of less than 100 patients (<50 patients per group) were not considered since they were under-powered to draw any meaningful conclusion. Studies comparing an anti-anginal drug versus another drug within the same class were excluded. The inclusion of the papers in the systematic review was decided after analysis of the full-text of papers selected (Figure 1s – supplemental online material).

The outcome of interest was related to the effect of the drugs on the primary outcome measured on exercise testing. Where a number of different exercise parameters were included in the primary outcome then the duration of exercise was selected as the primary outcome.

The quality of the included studies 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 (Figure 2s – supplemental online material).
RESULTS

We identified 72 controlled randomised trials comparing two anti-anginal drugs since 1964 which included 7034 patients (Figure 1). A total of 13 studies fulfilled the criteria set out (13-25), of which 9 enrolled between 100 and 300 patients with more than 50 patients per group (Figure 2). The remaining 4 enrolled more than 300 patients (>150 patients per group) (Figure 3) (17;22;23;25). Table 1 describes the 13 selected studies with the primary outcome results of beta blockers compared to other agents, calcium antagonists compared to other agents and long acting nitrates compared to other agents, respectively.

In the 9 studies enrolling between 100 and 300 patients there was a total of 1611 patients evaluated (13-16;18-21;24). There was only one study where metoprolol was found to be superior to nifedipine on the primary end point (time to 1mm ST depression); however the total exercise time was not improved (15). Thus, in none of the studies was total exercise duration prolonged by any treatment compared to another.

In the 4 studies enrolling more than 300 patients there was a total of 2818 patients evaluated. Again no evidence was found of one drug being superior to another (beta blockers, calcium antagonists and \( L \) channel inhibitors being tested) with evidence of equivalence between these agents established in three of these studies and close to identical improvement in exercise tolerance in the remaining study. (17;22;23;25).
DISCUSSION

This systematic review over the entire history of orally active treatments for the management of angina pectoris demonstrates that there is paucity of data. Guidelines draw conclusions not from what little data there is but from firmly held clinical beliefs. This is of particular concern bearing in mind that chronic stable angina is one of the most important causes of morbidity worldwide and drugs for the treatment of angina are among the most prescribed of any treatment today. On the basis of this systematic review we can conclude no one anti-anginal drug is superior to another and equivalence has only been demonstrated for the use of beta blockers (atenolol), calcium antagonists (amlodipine, nifedipine) and If channel inhibitors (ivabradine).

Although the entry criteria for our analysis was a minimum of 100 patients (at least 50 patients per group in double blind parallel group studies) we did review the literature for any crossover studies with at least 100 patients. Only one compared atenolol with ranolazine and there was no difference in the primary endpoint of time to angina onset; this was following one week of treatment without a washout phase in between the crossover (26).

The development of orally active anti-anginal agents has moved in parallel with the development of clinical trials to test these agents. Clinical trials in the early days were naive in their concept with no understanding of power calculations, hazard ratios etc. or even awareness that failure to prove superiority does not imply equivalence. Other issues in the earlier studies have made difficult the comparison with those conducted more recently, for example studies with calcium antagonists evaluated the effect of stress test at peak plasma levels, whereas it is currently asked to show benefit at trough level of the drugs which actually is available only for ivabradine and ranolazine. In an attempt to try and draw sound conclusions to confirm if any one drug is superior to another in the management of angina we have chosen to limit our analysis to those studies with at least 50 patients per treatment arm. The data presented from these early studies with different endpoints, using
different methodologies and in particular different somewhat immature methods of analysis make it impossible to perform a formal meta analysis. On the other hand, failure to show superiority in any of the selected studies with at least 100 patients would provide good evidence that no one anti-anginal therapy is superior to another. In order to say that one anti-anginal is equivalent to another we have also concentrated on those studies with more than 150 patients per treatment arm, the likely minimum number to draw this conclusion.

Several different methodologies have in the past been used to assess the success of an anti-anginal agent namely angina diaries, GTN consumption as well as different parameters of the exercise ECG. Subjective assessment of angina frequency and GTN consumption is an unreliable efficacy tool since as patients improve they may do more exercise and not necessarily reduce their angina frequency or GTN consumption; today this would be better assessed with Quality of Life questionnaires. The exercise test using exercise duration or exercise time to moderate angina is considered the gold standard to test an anti-anginal agent by the European and American Agencies (27). In the earlier studies, where a single primary endpoint was not selected we have taken exercise duration as the primary assessment criterion.

In the absence of superiority of any one anti-anginal agent over another and equivalence demonstrated between beta blockers, calcium antagonists, and I<sub>1</sub> channel inhibitors, how do we proceed to select the best anti-anginal agent for individual patients?

Studies used to test anti-anginal agents took no regard as to the underlying pathophysiology of the angina symptoms when selecting patients for investigation. It has become clear there are different mechanisms responsible for ischaemia some of which may predominate more in one patient than another. In any patient with angina, increased myocardial oxygen demand, reduction in coronary blood flow (including as a result of epicardial vasospasm or coronary microvascular dysfunction) with alterations in left ventricular filling pressure (that may affect both coronary flow and myocardial oxygen demand) may play a role to a greater or lesser extent in the pathophysiology of angina. Our
recent improved understanding of microvascular angina and the circumstances where it may occur (e.g., post angioplasty angina) has added a whole new dimension as to the appropriate treatment of angina. Various classes of drugs work in different ways, for example beta blockade effectively reduces myocardial oxygen demand but at the expense in certain instances of an increase in coronary vascular resistance; consequently, patients with Prinzmetal angina or microvascular spasm may actually deteriorate by treatment with a beta blocker but benefit from treatment with a vasodilator such as a calcium antagonist. In addition, the primary choice of antianginal drug should also take into consideration common comorbidities such as hypertension, mitral regurgitation, atrial fibrillation, autonomic dysfunction and so forth. It is therefore plausible to consider to select our first line treatment of angina according to our understanding of the predominant pathophysiological mechanisms operating in each individual patient and his or her comorbidities. Similarly, add on therapy is likely to be more effective when considering the potential mechanisms of action.

Also, co-morbidities will be important in selecting the appropriate treatment; for example, in those patients with heart failure a beta blocker and/or Ivabradine should be preferred, patients with diabetes may do better with a calcium antagonist which may also provide more effective blood pressure control. Co-morbidities that are contraindications to use a particular class of drugs will clearly define the appropriate treatments. Anti-anginal drugs without hemodynamic effects might be preferred in patients with low heart rate or low blood pressure.

In conclusion, treatment of chronic angina with the so called first line choice is based upon drugs approved many years ago, with criteria that nowadays would be insufficient. There is no evidence to support the use of first and second line treatments for the management of angina. Rather, the medical therapy of angina should be personalized and tailored towards the individual with an understanding of the likely pathophysiological mechanisms and co-morbidities.

Contributors:
RF, KF conceived and designed the study. RP selected the articles and extracted the data. All the authors analysed and interpreted the data. RF wrote the first draft of the manuscript. All authors approved the final version of the manuscript submitted.

Declaration of interest:
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. N.D. has received personal fees, honoraria, and/or travel expenses from Amgen, Astrazeneca, Bayer, BMS, Boehringer Ingelheim, MSD, Novo-Nordisk, Pfizer, Sanofi, and Servier. 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. A.P.M. has received honoraria for steering committee membership from Bayer, Cardiorentis, and Novartis; received support for travel to study meetings from the same companies; and received personal fees for speaking activities from Amgen, Lilly, Sanofi, and Servier. 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.

Acknowledgments:
This paper originated from the University of Ferrara and it was supported by an unlimited grant from Fondazione Anna Maria Sechi per il Cuore (FASC), Italy.
Table 1. Trials directly comparing beta-blockers, calcium antagonists, long-acting nitrates, nicorandil, trimetazidine, and ivabradine for stable angina.

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<td>74 (CARV)/69 (NIF)</td>
<td>25mg bid/20mg od</td>
<td>4 weeks</td>
<td>At peak (1h and 4h after last intake) PEP: TST &lt;1mm at W6: S</td>
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<td>BB vs CCB</td>
<td>138 (MET)/126 (NIF)</td>
<td>200mg od/20mg bid</td>
<td>6 weeks</td>
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<td>BB vs Trimetazidine</td>
<td>71 (TMZ)/78 (Prop)</td>
<td>20mg tid/40mg tid</td>
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<td>FOX K.M. (1996)(177)</td>
<td>BB vs CCB</td>
<td>177 (ATEN)/175 (NIF)</td>
<td>50mg bid/20mg bid</td>
<td>1 year</td>
<td>At peak (2-6h after last intake)</td>
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<td>HAUF-ZACHARIOU U. (1997)</td>
<td>BB vs Verapamil</td>
<td>126 (CARV)/122 (VER)</td>
<td>25mg bid/120mg tid</td>
<td>12 weeks</td>
<td>At peak (prior to the morning medication) PEP: TED at W12: NS</td>
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<td>PEHRSSON S.K. (2000)</td>
<td>BB vs CCB</td>
<td>116 (AML)/116 (ATEN)</td>
<td>10mg od/100 mg</td>
<td>10 weeks</td>
<td>At peak (2-3h after intake) PEP: TST &gt;1mm (NS) by Week 10: NS</td>
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<td>TARDIF J.C. (2005)</td>
<td>Ivabradine vs BB</td>
<td>632 (IVA)/307 (ATEN)</td>
<td>7.5 or 10mg bid/100 mg</td>
<td>4 months</td>
<td>At peak (12h after last intake) PEP: TED at M4 (s): NS</td>
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<td>LI Y. (2014)(22)</td>
<td>Ivabradine VS BB</td>
<td>166 (IVA)/166 (ATEN)</td>
<td>5 or 7.5mg bid/12.5 or 25mg bid</td>
<td>12 weeks</td>
<td>At trough (before morning intake) PEP: TED at W12: NS</td>
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<td><strong>Calcium Antagonist vs other</strong></td>
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<td>GUERMONPREZ J.L. (1993)(134)</td>
<td>Nicorandil vs Diltiazem</td>
<td>50 (NIC)/56 (DILT)</td>
<td>20mg bid/60mg tid</td>
<td>90 days</td>
<td>At peak (nicorandil was given at 8h and 20h, TET was done at 10h) Work to peak exercise by D90: NS 42.3 ± 19.2 ± 24.4 ± 4 kJ (NIC) From 37.3 ± 18.6 ± 10.6 ± 26 kJ (DILT), P=0.44</td>
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<td>CHATTERJEE T. (1999)(179)</td>
<td>CCB vs Nicorandil</td>
<td>57 (NIC)/64 (AML)</td>
<td>20mg bid/10mg od</td>
<td>8 weeks</td>
<td>At peak (12-24h after last intake) TET: WS (min): 6.7 ± 0.3 ± 6.0 ± 0.3 (NIC) 7.3 ± 0.4 ± 7.1 ± 0.4 (AML)</td>
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<td>KOYLAN N. (2004)(211)</td>
<td>Trimetazidine vs Diltiazem</td>
<td>58 (TMZ)/58 (DILT)</td>
<td>20mg tid/60mg tid</td>
<td>28 days</td>
<td>At peak (nicorandil was given at 8h and 20h, TET was done at 10h) Work to peak exercise by D90: NS 42.3 ± 19.2 ± 24.4 ± 4 kJ (NIC) From 37.3 ± 18.6 ± 10.6 ± 26 kJ (DILT), P=0.44</td>
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<td>RUZYLLO W. (2007)</td>
<td>Ivabradine vs CCB</td>
<td>791 (IVA)/404 (AML)</td>
<td>7.5 or 10mg bid/10mg od</td>
<td>3 months</td>
<td>At peak (12h after last intake) PEP: TED at M3 (NS) Change: 27.6 ± 91.7 (IVA) vs 31.2 ± 92.0 s (AML), p=0.011 for non-inferiority</td>
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<td>ZHU W.L. (2007)(241)</td>
<td>LAN vs Nicorandil</td>
<td>115 (NIC)/117 (ISMN)</td>
<td>5mg tid/20mg od</td>
<td>2 weeks</td>
<td>At peak (30 min and 2h after intake) PEP: TST &lt;1mm by W2: NS Change: 59.7 ± 128.6 (NIC) vs 67.7 ± 191.9, P=0.623</td>
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BB: beta blocker; CCB: dihydropyridine calcium channel blockers; LAN: long acting nitrates; TMZ: trimetazidine; IVA: ivabradine; PEP: primary endpoint; TED: total exercise duration; MET: metabolic equivalent; W: week; CARV: carvedilol; NIF: nifedipine; Prop: propranolol; NIC: nicorandil; ISMN: isosorbide mononitrites; ATEN: atenolol; DILT: diltiazem; MET: metoprolol; VER: verapamil; AML: amiodipine; NS: not specified. Studies shaded had more than 300 patients.
FIGURE LEGEND

Figure 1: RCT directly comparing beta-blockers, calcium antagonists, long-acting nitrates, nicorandil, trimetazidine, and ivabradine for stable angina (76 RCTs, n=7034 patients).

Figure 2: RCT directly comparing beta-blockers, calcium antagonists, long-acting nitrates, nicorandil, trimetazidine, and ivabradine for stable angina including 100-300 patients (9 RCTs, n=1611 patients)

Figure 3: RCT directly comparing beta-blockers, calcium antagonists, long-acting nitrates, nicorandil, trimetazidine, and ivabradine for stable angina including >300 patients (4 RCTs, n=2818 patients)
Reference List


RCTs (n=100-300)

6 RCTs\textsuperscript{13-16, 18, 19}

1200
1000
900
800
700
600
500
400
300
200
100
0

1990-1999

3 RCTs\textsuperscript{20, 21, 24}

2000-2009
Supplemental online material

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((("Angina, Stable"[Mesh] OR "Coronary Artery Disease"[Mesh]) NOT ("Angina, Unstable"[Mesh]AND "Acute Coronary Syndrome"[Mesh])))

AND


AND

("Randomized Clinical Trial" [Publication Type]) OR "Randomized Clinical Trials as Topic"[Mesh]) Sort by:
PublicationDate
Search strategy details for EMBASE
MJEMB.EXACT("stable angina pectoris") OR MJEMB.EXACT("coronary artery disease") NOT MJEMB.EXACT("unstable angina pectoris") NOT MJEMB.EXACT("acute coronary syndrome")
AND
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AND
(MJEMB.EXACT("randomized controlled trial") NOT EMB.EXACT("abstract report")) AND LA(english)
Table 1s. Trials directly comparing beta-blockers, calcium antagonists, long acting nitrates, nicorandil, trimetazidine, ranolazine and ivabradine for stable angina

Study selection:
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, use of short acting nitrates, exercise test parameters.

<table>
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<th>Medication</th>
<th>N of patients</th>
<th>Design</th>
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**BB** = Beta blockers  
**CCB** = Dihydropyridine calcium channel blockers
LAN = long acting nitrate.

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Figure 1: The flow-chart of the systematic review

- Records identified through database searches after duplicates removed (n=72)
- Records screened (n=15)
- Full text assessed for eligibility (n=14)
- Studies included in qualitative analysis (n=13)

Records excluded
(n=57):
57: study with less than 100 patients

Records excluded
(n=1):
- 1: The comparator was placebo

Records excluded
(n=1):
- 1: Cross-over design
Figure 2s: Quality assessment of studies included by Cochrane methods

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)

Legend:
- Low risk of bias
- Unclear risk of bias
- High risk of bias
PARTIAL: 2075
TOTAL: 4425
“The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.”
ABSTRACT

Aim: Chronic stable angina is the most prevalent symptom of ischaemic heart disease and its management is a priority. Current guidelines recommend pharmacological therapy with drugs classified as being first line (beta blockers, calcium channel blockers, short acting nitrates) or second line (long-acting nitrates, ivabradine, nicorandil, ranolazine, trimetazidine). Second line drugs are indicated for patients who have contraindications to first line agents, do not tolerate them or remain symptomatic. Evidence that one drug is superior to another has been questioned.

Methods and Results: Between January and March 2018, we performed a systematic review of articles written in English over the past 50 years English written articles in Medline and Embase following preferred reporting items and the Cochrane collaboration approach. We included double blind randomized studies comparing parallel groups on treatment of angina in patients with stable coronary artery disease, with a sample size of, at least, 100 patients (50 patients per group), with a minimum follow-up of one week and an outcome measured on exercise testing, duration of exercise being the preferred outcome. Thirteen studies fulfilled our criteria. Nine studies involved between 100 and 300 patients, (2818 in total) and a further 4 enrolled greater than 300 patients. Evidence of equivalence was demonstrated for the use of beta-blockers (atenolol), calcium antagonists (amlodipine, nifedipine) and channel inhibitor (ivabradine) in 3 of these studies. Taken all together, in none of the studies was there evidence that one drug was superior to another in the treatment of angina or to prolong total exercise duration.

Conclusion: there is a paucity of data comparing the efficacy of antianginal agents. The little available evidence shows that no antianginal drug is superior to another and equivalence has been shown only for three classes of drugs. Guidelines draw conclusions not from evidence but from clinical beliefs.
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