Anti-anginal Drugs - Beliefs and Evidence:

Systematic Review Covering 50 Years of Medical Treatment

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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.

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), I_f 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 I_f 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 I_f 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 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. 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_f 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 in 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.

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Table 1. Trials directly comparing beta-blockers, calcium antagonists, long-acting nitrates, nicorandil, trimetazidine, and ivabradine for stable angina.

Author	Medication	N of patients per arm	Dosage	FU	At trough or peak activity Results for PEP
Beta-Blockers vs other					
VAN DER DOES R. (1992)[13]	BB vs CCB	74 (CARV)/ 69 (NIF)	25mg bid/ 20mg od	4 weeks	At trough (12 h after last intake) TED at W4 (W x min): NS 350 ± 195 to 471 ± 226 (CARV) 387 ± 286 to 471 ± 261 (NIF)
ARDISSINO D. (1995) [15]	BB vs CCB	138 (MET)/ 126 (NIF)	200mg od/ 20mg bid	6 weeks	At peak (1h and 4h after last intake) PEP: TST <1mm at W6: S TST: 68 s (MET) vs 42 s (NIF), p<0.05 in favour of MET TED: 44 s(MET) vs 33 s (NIF), NS
DETRY J.M.R. (1995) [16]	BB vs Trimetazidine	71 (TMZ)/ 78 (Prop)	20mg tid/ 40mg tid	3 months	At peak (3-4h after last intake) PEP: number of AA, TED, TST >1mm at D90: NS AA: -3.5 (TMZ) vs -5.5 (Prop), P =0.117 TED (s): 33 (TMZ) vs 33 (Prop), p=0.982, TST (s): 50 (TMZ) vs 64 (Prop), p=0.481
FOX K.M. (1996) [17]	BB vs CCB	177 (ATEN)/ 175 (NIF)	50mg bid/ SR 20mg bid	1 year	At peak (2-6h after last intake) TED at W6: NS 91.4 (10) s (ATEN) vs 90.5 (11.1) (NIF) (treadmill) 63.2 (11) (ATEN) vs 63.6 (13.3) (NIF) (bicycle)
HAUF-ZACHARIOU U. (1997) [18]	BB vs Verapamil	126 (CARV)/ 122 (VER)	25mg bid/ 120mg tid	12 weeks	At trough (prior to the morning medication) PEP: TED at W12: NS 380 (9) to 436 (11) (Carved) vs 386 (9) to 438 (11) (VER), P=0.6841
PEHRSSON S.K. (2000) [20]	BB vs CCB	116 (AML)/ 116 (ATEN)	10mg od/ 100 mg	10 weeks	At peak (2-3h after intake) PEP: TST >1mm (NS) by Week 10: NS 1 min (AML) vs 0.8 (ATEN)
TARDIF J.C. (2005) [22]	Ivabradine vs BB	632 (IVA)/ 307 (ATEN)	7.5 or 10mg bid/ 100 mg	4 months	At trough (12h after last intake) PEP: TED at M4 (s): NS Change: +86.8±129.0 (IVA) vs. +78.8±133.4 s (ATEN). P< 0.001 for non-inferiority
LI Y. (2014) [25]	Ivabradine VS BB	166 (IVA)/ 166 (ATEN)	5 or 7.5mg bid/ 12.5 or 25mg bid	12 weeks	At trough (before morning intake) PEP: TED at W12: NS Change: +84.1 ± 130.5 s (IVA) vs 77.8 ± 126.6 s (ATEN), p = 0.0011 for noninferiority
Calcium Antagonist vs other					
GUERMONPREZ J.L. (1993) [14]	Nicorandil vs Diltiazem	50 (NIC)/ 56 (DILT)	20mg bid/ 60mg tid	90 days	At peak (nicorandil was given at 8h and 20h, TET was done at 10h) Work to peak exercise by D90: NS 42.3 ± 19 to 49.2 ±24.4 kJ (NIC) From 37.3 ± 18.6 to 46.8 ± 20.6 kJ (DILT), P=0.44
CHATTERJEE T. (1999) [19]	CCB vs Nicorandil	57 (NIC)/ 64 (AML)	20mg bid/ 10mg od	8 weeks	At trough (12-24 h after last intake) TED , W8 (min): NS 6.7 ± 0.3 to 7.2 ± 0.3 (NIC) 7.3 ± 0.4 to 7.9 ± 0.4 (AML)
KOYLAN N. (2004)[21]	Trimetazidine vs Diltiazem	58 (TMZ)/ 58 (DILT)	20mg tid/ 60mg tid	28 days	No information if it was at peak or at trough PEP: TED at D28 (NS) 443.8 ± 117.1 to 477.5 ± 196.7 sec (TMZ) 476.1 ± 187.5 to 493.5 ± 189.3 sec (DILT)
RUZYLLO W. (2007) [23]	Ivabradine vs CCB	791 (IVA)/ 404 (AML)	7.5 or 10mg bid/ 10mg od	3 months	At trough (12 h after last intake) PEP: TED at M3 (NS) Change: 27.6 ±91.7 (IVA) vs 31.2± 92.0 s (AML), p-value for non-inferiority < 0.001
Long Acting Nitrates vs other					
ZHU W.L. (2007) [24]	LAN vs Nicorandil	115 (NIC)/ 117 (ISMN)	5mg tid/ 20mg bid	2 weeks	At peak (30 min and 2h after intake) PEP: TST <1mm by W2: NS Change: 59.7 ± 128.6 (NIC) vs 67.7 ±119.1, P=0.623

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 mononitrates; ATEN: atenolol; DILT:diltiazem; MET: metoprolol; VER:verapamil; AML: amlodipine; 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)

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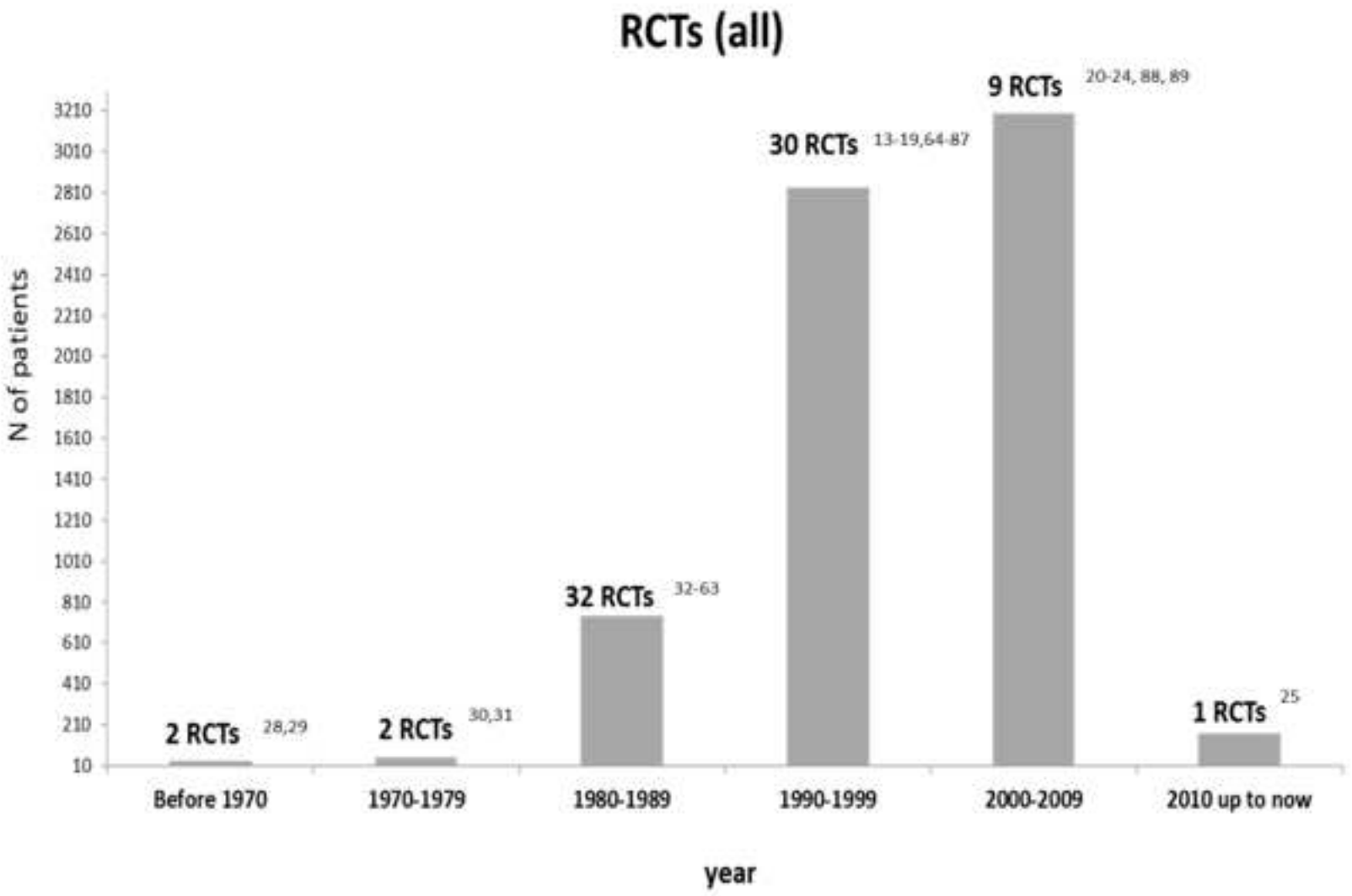
figure 1



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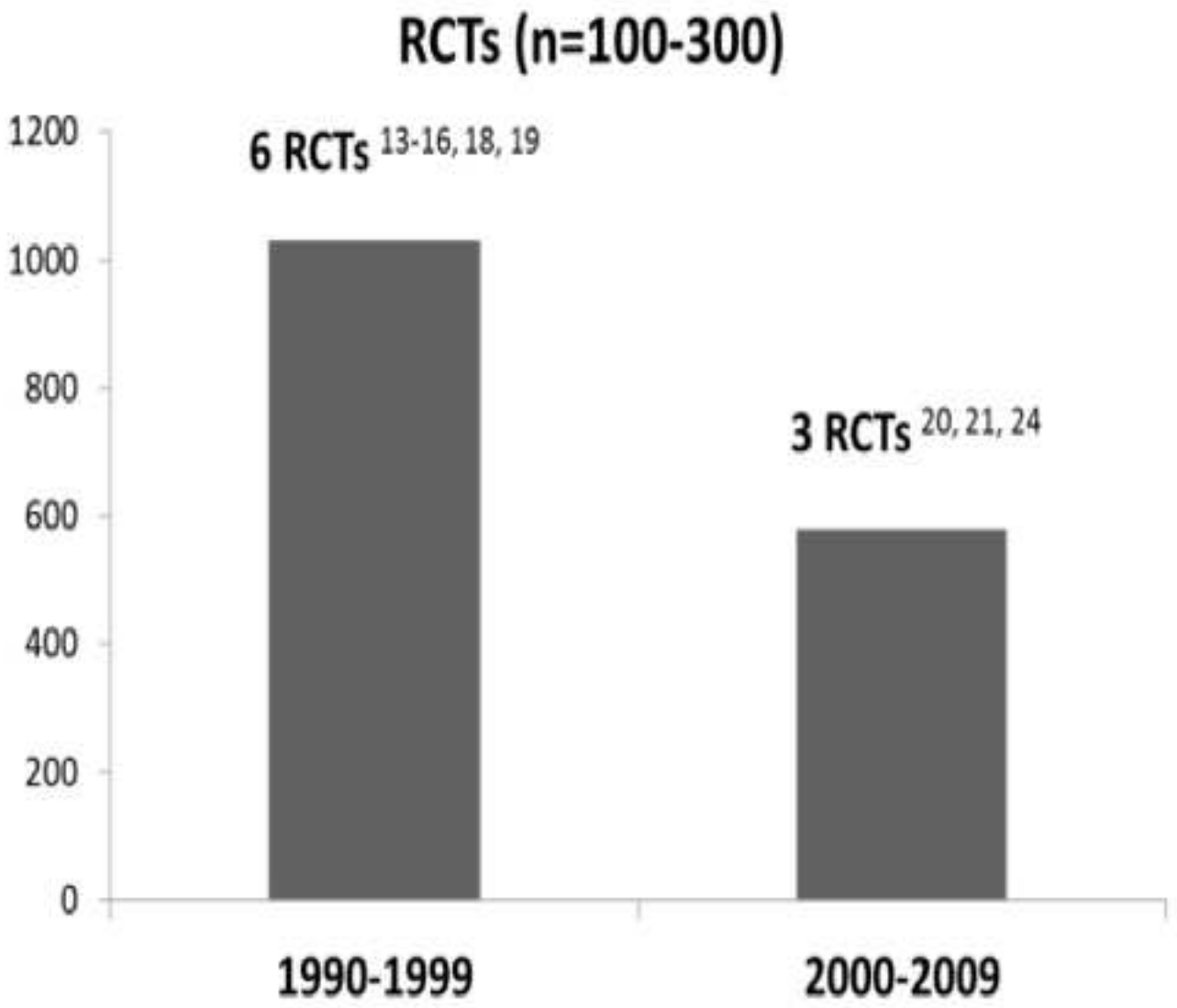
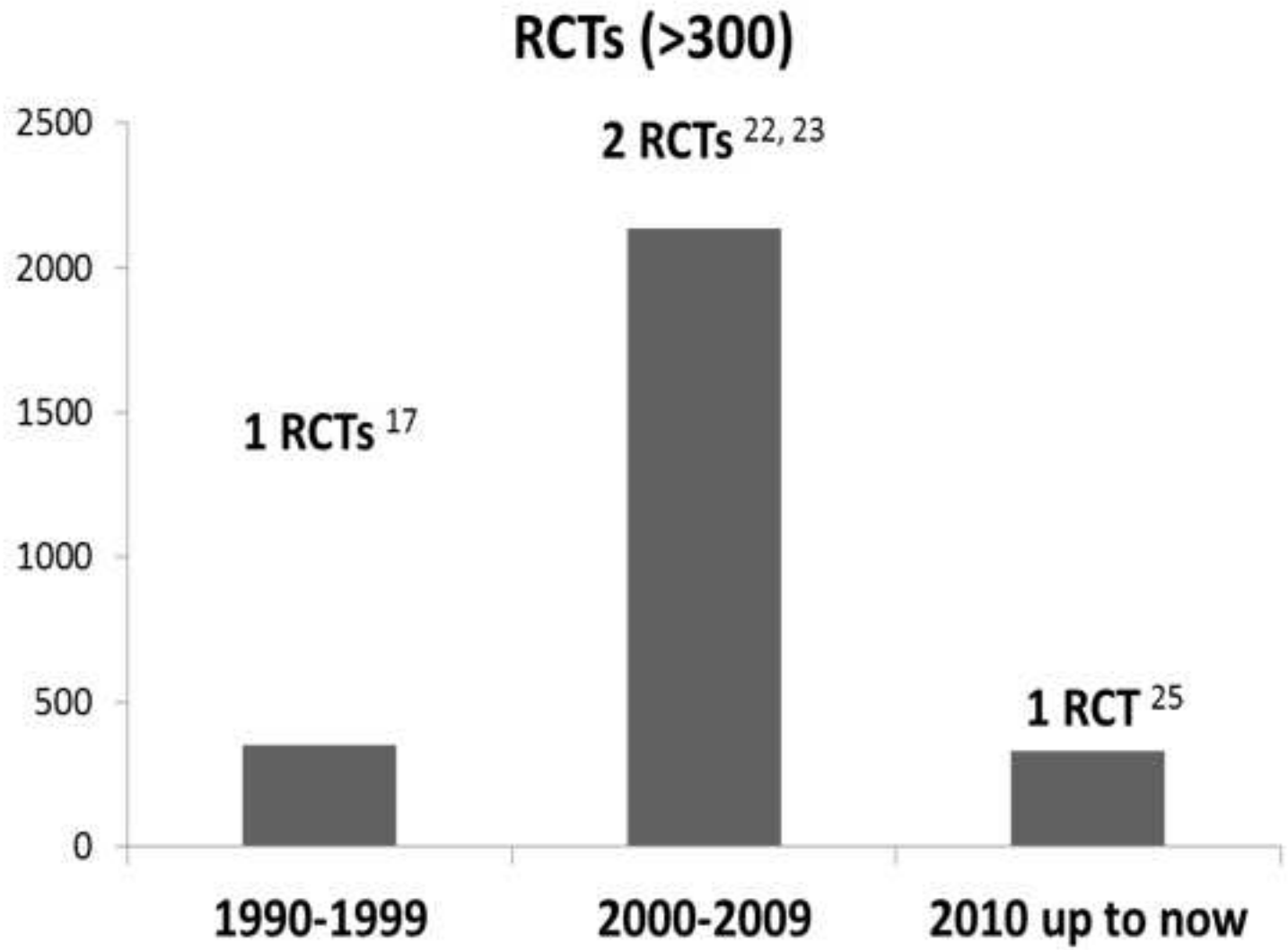


figure 3



Supplemental online material

Index

Search strategy details for Pubmed

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

AND

("Diltiazem"[Mesh] OR "Verapamil"[Mesh] OR "Bepridil"[Mesh] OR "Nifedipine"[Mesh] OR "Amlodipine"[Mesh] OR "Felodipine"[Mesh] OR "Isradipine"[Mesh] OR "lacidipine" [Supplementary concept]"Nicardipine"[Mesh] OR "Nitrendipine"[Mesh] OR "Nimodipine"[Mesh] OR "lacidipine" [Supplementary Concept] OR "Isosorbide Dinitrate"[Mesh] OR "isosorbide-5-mononitrate" [Supplementary Concept] OR "Molsidomine"[Mesh] OR "Nicorandil"[Mesh] OR "Ranolazine"[Mesh] OR "fasudil" [Supplementary Concept] OR "Gallopamil"[Mesh] OR "Trapidil"[Mesh] OR "Trimetazidine"[Mesh] OR "Acebutolol"[Mesh] OR "Atenolol"[Mesh] OR "Betaxolol"[Mesh] OR "Bisoprolol"[Mesh] OR "Celiprolol"[Mesh] OR "Metoprolol"[Mesh] OR "Nadolol"[Mesh] OR "Oxprenolol"[Mesh] OR "Pindolol"[Mesh] OR "Propranolol"[Mesh] OR "Timolol"[Mesh] OR "bopindolol" [Supplementary Concept] OR "Carteolol"[Mesh] OR "carvedilol" [Supplementary Concept] OR "Penbutolol"[Mesh] OR "Nebivolol"[Mesh] OR "Labetalol"[Mesh] OR "Sotalol"[Mesh] OR "ivabradine" [Supplementary Concept]))

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

EMB.EXACT("nifedipine") OR EMB.EXACT("verapamil") OR EMB.EXACT("nicardipine") OR EMB.EXACT("bepridil") OR EMB.EXACT("lacidipine") OR EMB.EXACT("felodipine") OR EMB.EXACT("diltiazem") OR EMB.EXACT("amlodipine") OR EMB.EXACT("isradipine") OR EMB.EXACT("nitrendipine") OR EMB.EXACT("lacidipine") OR EMB.EXACT("isosorbide mononitrate") OR EMB.EXACT("nimodipine") OR EMB.EXACT("isosorbide dinitrate") OR EMB.EXACT("ranolazine") OR EMB.EXACT("molsidomine") OR EMB.EXACT("trapidil") OR EMB.EXACT("nicorandil") OR EMB.EXACT("fasudil") OR EMB.EXACT("betaxolol") OR EMB.EXACT("acebutolol") OR EMB.EXACT("gallopamil") OR EMB.EXACT("atenolol") OR EMB.EXACT("trimetazidine") OR EMB.EXACT("nebivolol") OR EMB.EXACT("celiprolol") OR EMB.EXACT("penbutolol") OR EMB.EXACT("propranolol derivative") OR EMB.EXACT("labetalol") OR EMB.EXACT("sotalol") OR EMB.EXACT("timolol") OR EMB.EXACT("bopindolol") OR EMB.EXACT("metoprolol") OR EMB.EXACT("pindolol") OR EMB.EXACT("ivabradine") OR EMB.EXACT("carteolol") OR EMB.EXACT("bisoprolol") OR EMB.EXACT("nadolol") OR EMB.EXACT("oxprenolol") OR EMB.EXACT("carvedilol")

AND

(MJEMB.EXACT("randomized controlled trial") NOT EMB.EXACT("abstract report")) AND LA(english)

Field Code Changed

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.

Year	Author	Medication	N of patients	Design
1969	BATTOCK D.J.[1]	BB vs LAN	12	Cross-over
1969	GOLDBARG A.N. [2]	BB vs LAN	21	Cross-over
1970	AUBERT A. [3]	BB vs LAN	21	Cross-over
1973	LIVESLEY B. [4]	BB vs Verapamil vs LAN	32	Parallel
1980	LYNCH P. [5]	BB vs CCB	16	Parallel
1981	BOWLES M.J. [6]	BB vs Verapamil	21	Cross-over
1981	JOHNSON S.M.[7]	BB vs Verapamil	18	Parallel
1982	ARNMAN K. [8]	BB vs Verapamil	20	Cross-over
1982	FRISHMAN W.H. [9]	BB vs Verapamil	12	Cross-over
1982	SADICK N.N. [10]	BB vs Verapamil	18	Latin square
1982	SOUTHALL E. [11]	BB vs Verapamil	19	Cross-over
1982	SUBRAMANIAN V.B. [12]	BB vs Verapamil	22	Cross-over
1983	BOWLES M.J. [13]	BB vs Verapamil	21	Cross-over
1983	FINDLAY I.N. [14]	BB vs CCB	14	Latin square
1983	HUNG J. [15]	BB vs Diltiazem	12	Parallel
1985	KENNY J. [16]	BB vs Diltiazem	15	Cross-over
1985	LIANG C.S. [17]	CCB vs LAN	34	Parallel
1985	RAE A.P. [18]	BB vs CCB	35	Parallel
1985	WHEATLEY D. [19]	BB vs Diltiazem	78	Parallel
1986	BJERLE P. [20]	BB vs CCB	18	Cross-over
1986	FINDLAY I.N. [21]	BB vs CCB	16	Latin square
1986	LOGAN R.L. [22]	BB vs CCB	50	Cross-over
1986	McGILL D. [23]	BB vs CCB	25	Cross-over
1986	PARKER J.O. [24]	BB vs CCB	18	Cross-over
1986	ROMANO M. [25]	BB vs Diltiazem	13	Cross-over
1987	DE DIVITIIS O. [26]	BB vs Verapamil	26	Parallel
1987	FINDLAY I.N. [27]	BB vs Verapamil	15	Parallel
1987	PFLUGFELDER P.W. [28]	BB vs CCB	24	Cross-over
1988	CRAKE T. [29]	BB vs CCB	11	Cross-over
1988	FRISHMAN W. [30]	CCB vs Diltiazem	20	Cross-over
1988	KLINKE W.P. [31]	CCB vs Diltiazem	21	Cross-over
1988	SCHNEIDER W. [32]	LAN vs Verapamil	14	Cross-over
1988	VAN DIJK R.B. [33]	BB vs Diltiazem	33	Cross-over

1988	EMANUELSSON H. [34]	LAN vs Diltiazem	25	Parallel
1989	HIGGINBOTHAM M.B. [35]	BB vs CCB	21	Cross-over
1989	SHAPIRO W. [36]	BB vs CCB	39	Parallel
1990	DALLA-VOLTA S. [37]	CCB vs Trimetazidine	39	Cross-over
1990	HUGHES L.O. [38]	BB vs Nicorandil	37	Parallel
1990	STONE P.H. [39]	BB vs Diltiazem vs CCB	63	Cross-over
1991	BERNINK P.J.L.M. [40]	CCB vs Diltiazem	39	Parallel
1991	KREPP H.P. [42]	BB vs LAN	30	Parallel
1991	WAYSBORT J. [43]	BB vs LAN	20	Parallel
1992	FRISHMAN W.H. [44]	BB vs CCB	75	Parallel
1992	KAWANISHI D.T. [45]	BB vs CCB	74	Parallel
1992	LAI C. [46]	BB vs CCB	16	Cross-over
1992	MEETER K. [47]	BB vs Nicorandil	71	Parallel
1992	ULVENSTAM G. [48]	CCB vs Nicorandil	58	Parallel
1992	VAN DER DOES R. [49]	BB vs CCB	166	Parallel
1993	EGSTRUP K. [50]	BB vs CCB	41	Parallel
1993	GUERMONPREZ J.L. [51]	Nicorandil vs Diltiazem	123	Parallel
1993	PARAMESHWAR J. [52]	BB vs CCB	30	Cross-over
1993	RAFTERY E.B. [53]	BB vs Nicorandil	31	Parallel
1993	SINGH S. [54]	BB vs CCB	80	Parallel
1994	NADAZDIN A. [55]	BB vs Diltiazem	15	Cross-over
1994	WALLACE W.A. [56]	BB vs CCB	17	Cross-over
1995	ARDISSINO D. [57]	BB vs CCB	280	Parallel
1995	DETRY J.M.R. [58]	BB vs Trimetazidine	149	Parallel
1995	VAN DE VEN L.L.M. [59]	BB vs LAN	22	Cross-over
1996	DI SOMMA S. [60]	BB vs CCB	20	Latin square
1996	FOX K.M. [61]	BB vs CCB	608	Parallel
1996	HEUBLEIN B. [62]	CCB vs LAN	91	Parallel
1996	SAVONITTO S. [63]	BB vs CCB	200	Parallel
1997	HAUF-ZACHARIOU U. [64]	BB vs Verapamil	313	Parallel
1997	KLEIN G. [65]	BB vs CCB	52	Cross-over
1997	STEFFENSEN R. [66]	CCB vs LAN	59	Cross-over
1998	*KNIGHT C.J.* [67]	*CCB vs Diltiazem*	*97*	*Parallel*
1999	CHATTERJEE T. [68]	CCB vs Nicorandil	121	Parallel
2000	BASU S.K. [69]	CCB vs Diltiazem	20	Cross-over
2000	*PEHRSSON S.K.* [70]	*BB vs CCB*	*442*	*Parallel*
2001	HALL R. [71]	CCB vs LAN	97	Parallel
2004	KOYLAN N. [72]	Trimetazidine vs Diltiazem	116	Parallel
2005	ROUSSEAU M.F. [73]	BB vs Ranolazine	158	Cross-over
2005	TARDIF J.C. [74]	Ivabradine vs BB	939	Parallel
2007	RUZYLLO W. [75]	Ivabradine vs CCB	1195	Parallel
2007	ZHU W.L. [76]	LAN vs Nicorandil	232	Parallel
2014	LI Y. [77]	Ivabradine VS BB	168	Parallel

BB = Beta blockers
CC~~B~~H = dihydropyridine calcium channel blockers

LAN = long acting nitrate.

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Figure 1s: The flow-chart of the systematic review

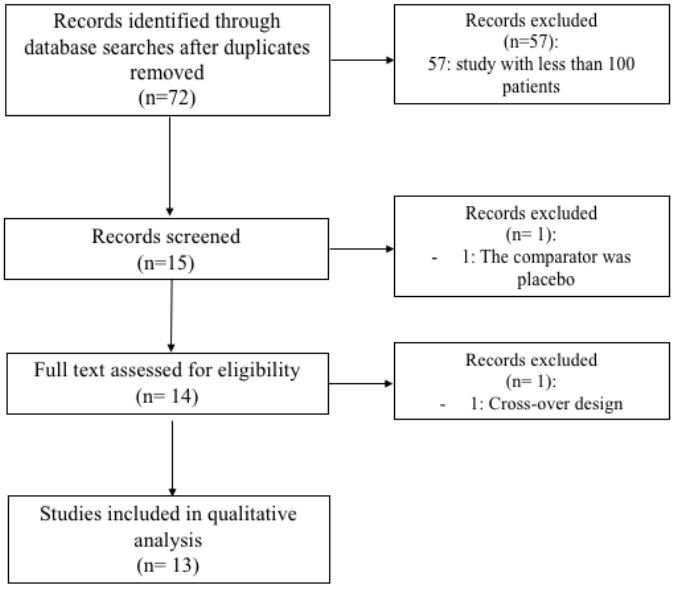
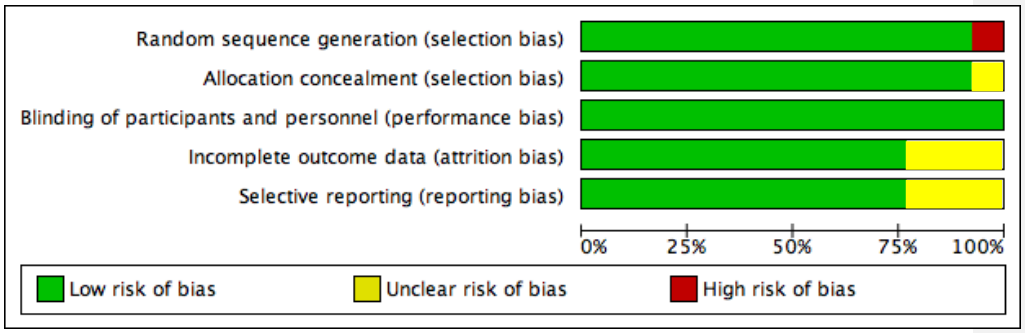


Figure 2s: Quality assessment of studies included by Cochrane methods



WORD COUNT

PARTIAL: 2075

TOTAL: 4425

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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.