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CLINICAL REVIEW
Controversies in cardiovascular medicine

Anti-anginal drugs–beliefs and evidence: systematic review covering 50 years of medical treatment

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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, and 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. 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 1 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 four 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 three 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. There is a paucity of data comparing the efficacy of anti-anginal agents. The little available evidence shows that no anti-anginal 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.

Keywords Chronic angina • Anti-angina drugs • Beta-blockers • Calcium antagonists • Channel inhibitor • Ivabradine

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

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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 with 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 vs. 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 (Supplementary material online, *Figure S1*).

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 (Supplementary material online, *Figure S2*).

Results

We identified 72 controlled randomized 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 nine enrolled between 100 and 300 patients with more than 50 patients per group (*Figure 2*). The remaining four 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 with other agents, calcium antagonists compared with other agents, and long acting nitrates compared with other agents, respectively.

In the nine 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 endpoint (time to 1 mm 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 with another.

In the four 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

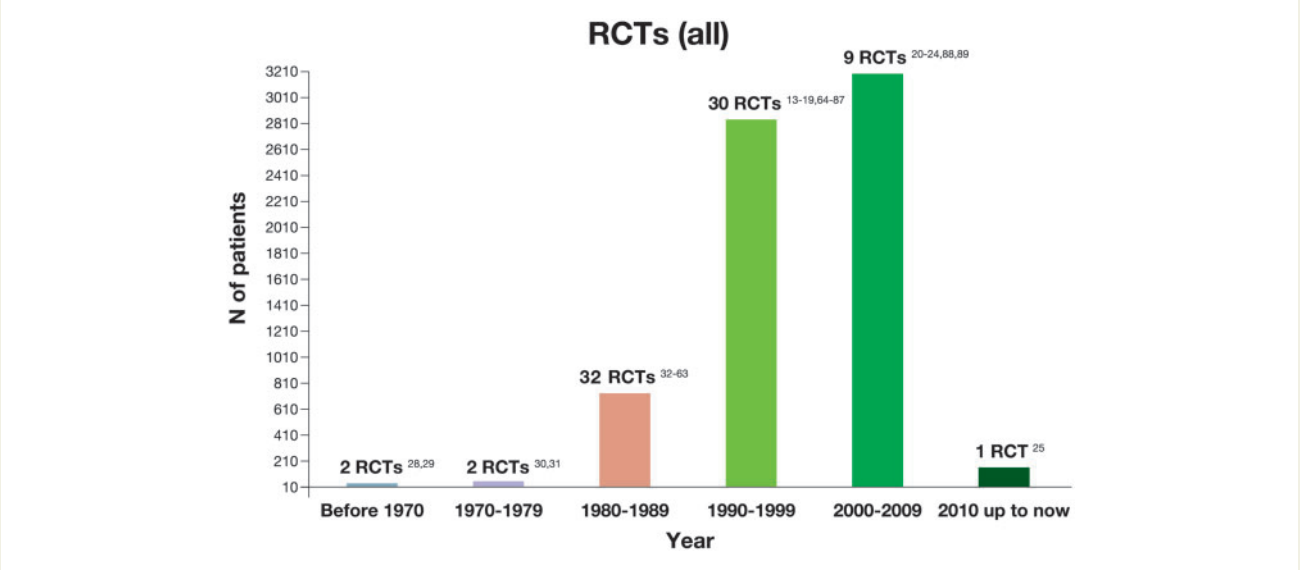

Figure 1 Randomized clinical trials directly comparing beta-blockers, calcium antagonists, long-acting nitrates, nicorandil, trimetazidine, and ivabradine for stable angina (76 randomized clinical trials, $n = 7034$ patients).

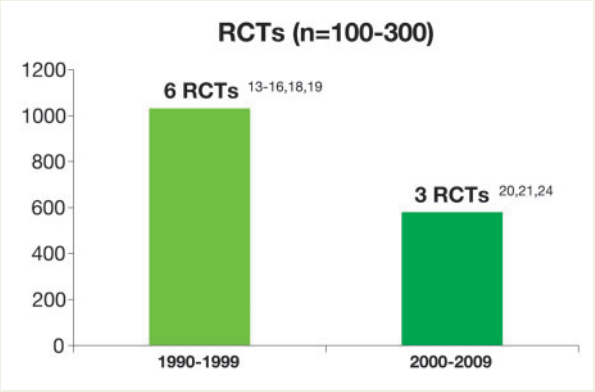

Figure 2 Randomized clinical trials directly comparing beta-blockers, calcium antagonists, long-acting nitrates, nicorandil, trimetazidine, and ivabradine for stable angina including 100–300 patients (9 randomized clinical trials, $n = 1611$ patients).

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 electrocardiogram. 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 anti-anginal 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

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

Authors	Medication	*N* of patients per arm	Dosage	FU	At trough or peak activity Results for PEP
Beta-blockers vs. other					
van der Does *et al.*[13]	BB vs. CCB	74 (CARV)/69 (NIF)	25 mg bid/20 mg od	4 weeks	At trough (12 h after last intake) TED at W4 (W × min): NS 350 ± 195 to 471 ± 226 (CARV) 387 ± 286 to 471 ± 261 (NIF)
Ardissino *et al.*[15]	BB vs. CCB	138 (MET)/126 (NIF)	200 mg od/20 mg bid	6 weeks	At peak (1 h and 4 h after last intake) PEP: TST <1 mm 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 *et al.*[16]	BB vs. Trimetazidine	71 (TMZ)/78 (Prop)	20 mg tid/40 mg tid	3 months	At peak (3–4 h after last intake) PEP: number of AA, TED, TST >1 mm 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 *et al.*[17]	BB vs. CCB	177 (ATEN)/175 (NIF)	50 mg bid/SR 20 mg 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 *et al.*[18]	BB vs. Verapamil	126 (CARV)/122 (VER)	25 mg bid/120 mg 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 *et al.*[20]	BB vs. CCB	116 (AML)/116 (ATEN)	10 mg od/100 mg	10 weeks	At peak (2–3 h after intake) PEP: TST >1 mm (NS) by Week 10: NS 1 min (AML) vs. 0.8 (ATEN)
Tardif *et al.*[22]	Ivabradine vs. BB	632 (IVA)/ 307 (ATEN)	7.5 or 10 mg bid/100 mg	4 months	At trough (12 h 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 *et al.*[25]	Ivabradine vs. BB	166 (IVA)/166 (ATEN)	5 or 7.5 mg bid/12.5 or 25 mg 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 non-inferiority
Calcium antagonist vs. other					
Guermonprez *et al.*[14]	Nicorandil vs. Diltiazem	50 (NIC)/56 (DILT)	20 mg bid/60 mg tid	90 days	At peak (nicorandil was given at 8 h and 20 h, TET was done at 10 h) 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[19]	CCB vs. Nicorandil	57 (NIC)/64 (AML)	20 mg bid/10 mg 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 *et al.*[21]	Trimetazidine vs. Diltiazem	58 (TMZ)/58 (DILT)	20 mg tid/60 mg 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 s (TMZ) 476.1 ± 187.5 to 493.5 ± 189.3 s (DILT)

Continued

Table I *Continued*

Authors	Medication	N of patients per arm	Dosage	FU	At trough or peak activity Results for PEP
Ruzyllo *et al.*[23]	Ivabradine vs. CCB	791 (IVA)/404 (AML)	7.5 or 10 mg bid/10 mg 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 *et al.*[24]	LAN vs. Nicorandil	115 (NIC)/117 (ISMN)	5 mg tid/20 mg bid	2 weeks	At peak (30 min and 2 h after intake) PEP: TST <1 mm by W2: NS Change: 59.7 ± 128.6 (NIC) vs 67.7 ± 119.1, *P* = 0.623

AML, amlodipine; ATEN, atenolol; BB, beta blocker; CCB, dihydropyridine calcium channel blockers; CARV, carvedilol; DILT, diltiazem; ISMN, isosorbide mononitrates; IVA, ivabradine; LAN, long acting nitrates; MET, metabolic equivalent; MET, metoprolol; NIC, nicorandil; NIF, nifedipine; NS, not specified; PEP, primary endpoint; Prop, propranolol; TED, total exercise duration;TMZ, trimetazidine; VER, verapamil; W, week.
Studies shaded had more than 300 patients.

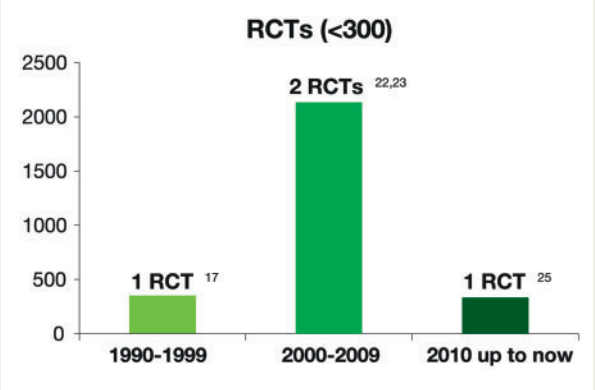

Figure 3 Randomized clinical trials directly comparing beta-blockers, calcium antagonists, long-acting nitrates, nicorandil, trimetazidine, and ivabradine for stable angina including >300 patients (4 randomized clinical trials, *n* = 2818 patients).

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.

Conclusion

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.

Supplementary material

Supplementary material online is available at *European Heart Journal* online.

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