ORIGINAL RESEARCH

Comparative efficacy and impact on quality of life with add-on therapy of emerging newer anti anginal drugs in Stable angina - A meta-analysis

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Received: 18 April, 2023 Accepted: 21 May, 2023

ABSTRACT

Introduction: Myocardial ischemia, brought on by a discrepancy between myocardial perfusion and oxygen demand, is the usual culprit in cases of angina pectoris. Beta-blockers (BBs) and calcium channel blockers (CCBs) are the drugs of choice for initial treatment of stable angina, with other classes of drugs used in case the first two are insufficient. The development of methods to enhance care for patients with chronic stable angina is ongoing. It was anticipated that this systematic review will help quantify the therapeutic benefit of using Ivabradine, Ranolazine, Trimetazidine, and Nicorandil in addition to first-line monotherapy for stable coronary artery disease. **Materials and Methods:** The PICOS framework, a standardised worldwide method for defining inclusion and exclusion criteria, was used, as indicated by the PRISMA guidelines. Individuals that were a part of the research population. **Results:** After an initial literature search, 36 out of 45 studies that could be fully analysed were deemed ineligible for further consideration because either they did not provide any results or their entire texts were unavailable. Each of the prescription medications for adjunctive treatment proved to be efficient, risk-free, and well-tolerated. The frequency of angina events decreased, and so did the need for nitrates, suggesting that angina pectoris symptoms had improved. Add-on Trimetazidine is a fast-acting, low-risk method of lowering both angina episodes and nitrate use in the real-world clinical environment. Moreover, it improves physical fitness and overall health. When combined to regular antianginal medication, nicorandil significantly reduced the frequency of ischemia episodes in coronary heart disease (CHD)patients with stable angina. It has a favourable safety profile, with no unexpected adverse effects found. Quality of life(QoL) was shown to improve in individuals with stable angina and coronary artery disease (CAD) when Ivabradine was coupled with metoprolol. The positive effects seen with this combination are likely the cause of its high rate of adherence. **Conclusion:** The results of the current research indicate that adjunctive therapy is an effective and safe method of lowering the frequency of angina episodes and the need for nitrates. In addition, evidence suggests that therapy for angina should be tailored to each individual patient, their comorbidities, and the underlying cause of their condition.

Keywords: Ivabradine, Ranolazine, Trimetazidine, Nicorandil

INTRODUCTION

Myocardial ischemia, brought on by a discrepancy between myocardial perfusion and oxygen demand, is the usual culprit in cases of angina pectoris. An increased heart rate increases the oxygen demand of the heart and decreases tissue perfusion by shortening diastole, when the majority of myocardial perfusion occurs. [1] William Heberden first provided a formal definition for it in 1768. He said it felt like something was pressing down on his chest and could spread to his left arm or both arms, as well as his jaw and back. Having a heavy meal shortly after exercising or experiencing emotional stress can make the condition worse. Stopping the exercise or taking some sublingual nitroglycerin typically alleviates the pain. When an individual has no change in the frequency or severity of their angina attacks over a period of three to six months, they are said to have stable angina. [2] Several medical diseases are negatively impacted by elevated HR. Heart failure that persists, or chronic

heart failure (CHF), is a leading cause of hospitalisation and a significant continuous cost to the healthcare system. The issue of managing CHF has persisted despite medical progress. Beta-blockers (BB) and calcium channel blockers (CCB) are often used for the initial treatment of stable angina, with other classes of medicine added if necessary. There is presently insufficient evidence to recommend a specific second-line agent. [4] Efforts to enhance care for patients with chronic stable angina continue to be a focus of attention. Almost a third of patients get subpar care, with many missing out on life-changing recommendations, antianginal medication optimization, and/or percutaneous and/or surgical cardiac revascularization. [5] It was anticipated that this systematic review will help quantify the therapeutic benefit of using Ivabradine, Ranolazine, Trimetazidine, and Nicorandil in addition to first-line monotherapy for stable coronary artery disease.

MATERIALS AND METHODS

The inclusion criteria were framed as per internationally standardized PICOS framework, as recommended by PRISMA guidelines:

Participants/Population: Baseline antianginal treatments (beta-blockers, calcium-channel blockers, short-acting nitrates) were given to all of the participants in the study, and those whose angina pectoris symptoms persisted were prescribed second-line medicationsIvabradine, Ranolazine, Trimetazidine, and Nicorandil as add-on therapy.

Intervention: We considered studies that looked at the effects of supplemental therapies for managing angina pectoris, such as the use of second-line medicines, on vital signs including heart rate and ECG parameters, the frequency of angina episodes, and the need for nitroglycerin.

Comparator(s)/Control: Included were studies of any of the aforementioned therapies, with or without a control group.

Outcome: the key outcomes consider were

Primary efficacy objectives were changes from baseline in heart rate or echocardiographic parameters, number of weekly angina episodes, and number of weekly short-acting nitrate doses in patients who did not respond to first treatment with add on therapy viz.Ivabradine, Ranolazine, Trimetazidine, or Nicorandil. The quality of life was measured by a visual analogue scale (VAS) [ref…]and/or the EuroQol-5D (EQ-5D) questionnaire[ref…..].

STUDY DESIGN

All papers, both experimental and observational, as well as case series, reporting the results of the aforementioned treatment modality were included in the meta-analysis.

INCLUSION CRITERIA

The research included studies from all across the globe as well as publications published after 2012 and up to June 2022. The search focused only on articles published in academic peer-reviewed publications written in English.

EXCLUSION CRITERIA

The research did not include case studies.

The researchers did not include data from any experiments performed on animals.

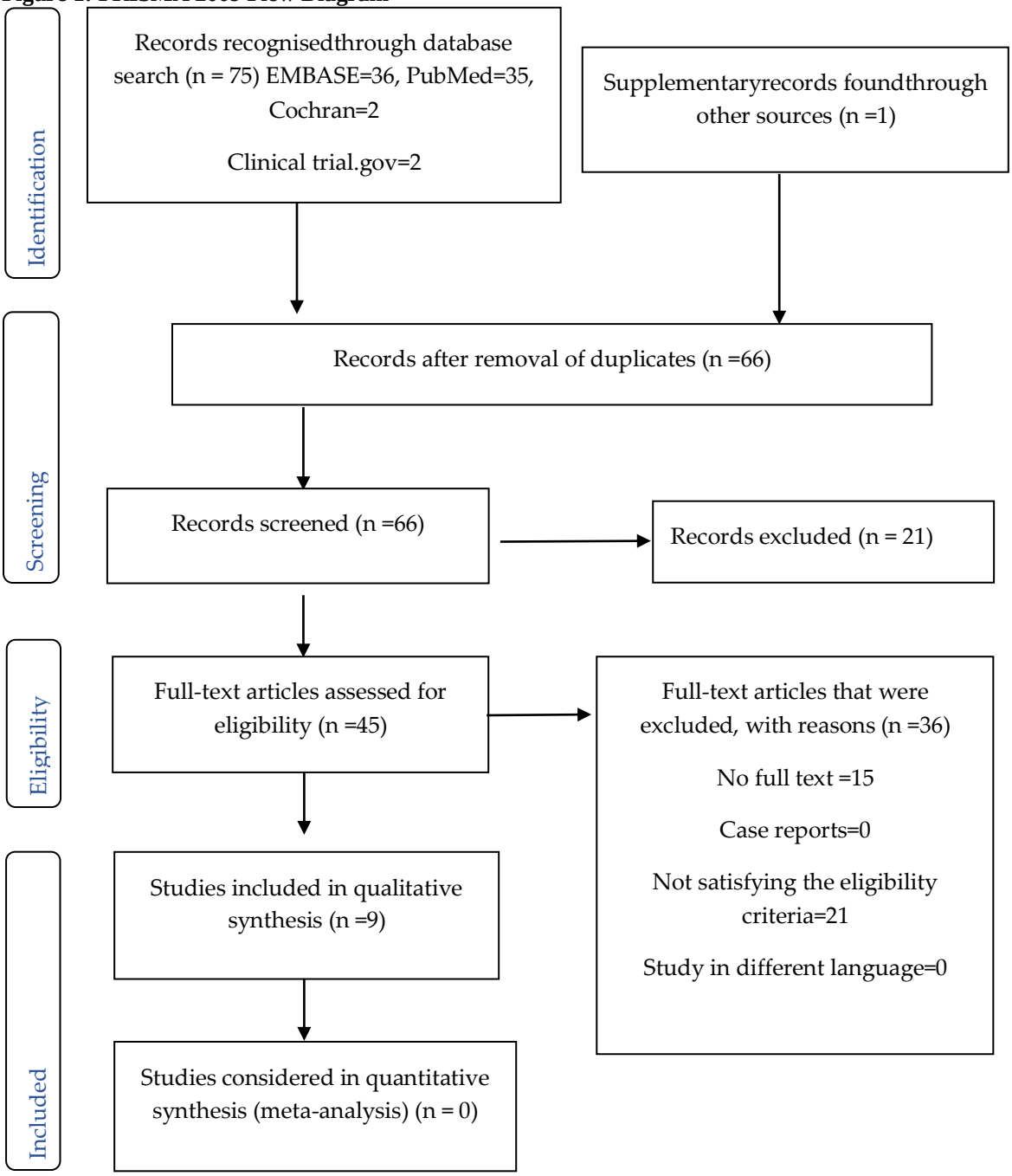
LITERATURE SEARCH

PubMed, Embase, clinicaltrials.gov, and the Cochrane Library, all in the English language, were searched systematically by three writers using a predetermined search strategy up to June 2022. References from chosen publications were used to narrow the searches down to those that would not have been found in the databases alone. Due to the sheer volume of available research, further citations could not be found by a simple Google search. Table 1 provides the specifics of the search methodology.

PROCESS OF SCREENING AND SELECTION OF ARTICLES:

After adding each reference to an endnote library and deleting any duplicates, a final list of papers was compiled for inclusion in the research. Three researchers performed a meticulous title and abstract screening to identify papers that would most likely meet the review's inclusion criteria. All of the studies on the final list were looked at in detail to see whether they met the inclusion and exclusion criteria, and their full-text papers were sought for where possible. Research that didn't meet the inclusion criteria was also disregarded. The "characteristics of omitted studies" table detailed the studies that were not included and the reasons for their absence. The screening and selection procedure was shown using a "PRISMA flow chart" for simplicity(Figure 1).

Figure 1: PRISMA 2009 Flow Diagram



DATA EXTRACTION

Manual data extraction was performed by reading each included study carefully and recording relevant information on a predesigned form. Qualityoflife (QoL) related outcomes were evaluated by measuring changes from baseline to follow-up in terms of heart rate or echocardiographic parameters, frequency of angina events, and frequency of short-acting nitrate usage.

RISK OF BIAS IN INDIVIDUAL STUDIES

Fowkes and Fulton quality evaluation was used to evaluate the study designs of the included papers in the systematic review. [6]

STUDY OUTCOMES

Table 1: Evaluation of studies reporting baseline parameters, improvement of heart rate or echocardiographic parameters, weekly angina attacks and weekly use of short-acting nitrates with add-on therapy of emerging newer anti anginal drugs

Author (year)	Number of patients	add-on therapy of emerging newer anti anginal drugs	Time duration	Heart rate/ ECG parameters	Mean number of angina attacks	nitroglycerin consumption
Lopatin Y et al (2022)[7]	1939 patients	Trimetazidine 80 mg added to patients with maximum dose of Bisoprolol	3 months	resting HR was 75.1 ± 9.5 bpm.	At V1, the mean number of angina attacks per week was 6.2 ± 6.5 baselineand following the addition of Trimetazidine 80 OD, this decreased to 3.4 ± 4.2 attacks per week after 1 month, and 1.6 ± 2.6 at 3-month ($P < 0.05$)	The mean consumption of short-acting nitrates per week decreased from 4.9 ± 5.9 at baseline to 2.6 ± 3.8 at 1 month and 1.1 ± 2.2 at 3 months
Sowjanya K et al (2020)[8]	100 patients	Trimetazidine 35 mgper oral twice daily	6-month prospective observational comparative study	significant improvement in left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular end-diastolic volume, left ventricular end-systolic volume, ($p<0.05$); wall motion index score, E/A ratio, (p-value < 0.05)	-	-
Zweiker R et al (2019)[9]	292 patients	Ranolazine on top of beta blockers or calcium channel blockers after failure of first-line therapy	at intervals of 12 weeks	-	reduce angina pectoris (77.1%).	nitrate use reduced from 3.4 ± 4.1 to 0.4 ± 0.9 applications per week
Glezer M et al (2017)[10]	896 patients	Trimetazidine 35 mg Add-on Therapy (Baseline antianginal treatments comprised beta-	6 months	heart rate was 65.8 ± 6.1 bpm	Angina frequency fell significantly (p < 0.0001) from 5.36 ± 5.38 to 1.12 ± 1.7	Short-acting nitrate use fell significantly (p < 0.0001) from 5.12 ± 5.23 to 0.87 ± 1.43

		blocker monotherapy (45%) and two-drug combination therapy (41%); overall, 93% of patients were taking a beta-blocker alone or in combination)			attacks/week	intakes/week
Jiang J et al (2016)[11]	202 patients	Patients in the nicorandil group received an additional 12-week treatment of nicorandil (5 mg thrice daily).	Anti-anginal treatment and patients received an additional treatment of nicorandil (5 mg thrice daily)	No significant differences in heart rate variability	myocardial ischemia attacks after treatment were significantly lower in the nicorandil group (LSMEANS 0.896) than the control group (LSMEANS 1.782), with an adjusted ratio of 0.503 (95% CI: 0.301, 0.840; $P = 0.0086$).	-
Zarifis J et al (2015)[12]	636 patients	Ivabradine combined with metoprolol	4 months	from 80.8 ± 9.6 to 64.2 ± 6.2 bpm (P < 0.001).	decreased from 2.0 ± 2.0/wk to 0.2 ± 0.6/wk (P < 0.001),	decreased from 1.4 ± 1.9 times/wk to 0.1 ± 0.4 times/wk (P < 0.001).
Werdan K et al (2015)[13]	2,319 patients	Ivabradine in combination with beta-blocker in patients with angina who have had a percutaneous coronary intervention (PCI).	4 months	no difference in the effect of Ivabradine on mean heart rate between patients with a previous PCI [64.4 ± 7.6 beats per minute (bpm)] than those without (66.8 ± 8.5 bpm) at 4 months (both $P < 0.0001$).	the number of angina attacks decreased from 1.9 ± 2.4 to 0.5 ± 1.5 per week in patients with a previous PCI and 1.5 ± 2.0 to 0.3 ± 1.0 per week in patients without a previous PCI (both $P < 0.0001$)	nitrate consumption fell from 2.7 ± 3.7 to 1.0 ± 1.9 per week and 1.8 ± 2.8 to 0.6 ± 1.5 per week (both $P < 0.0001$) in patients with and without a previous PCI, respectively.
Zaky H et al (2013)[14]	20 patients	All patients in whom Ivabradine were added were on aspirin, statin, and β-blocker, and the majority were on clopidogrel and an angiotensin-converting enzyme inhibitor/angioten	4 months	Reduced from an average of 82 ± 8 to 68 ± 6 bpm ($P < 0.001$).	Canadian Cardiac Society (CCS) class of chest pain improved in 16/20 patients by one or two classes	-

		sin receptor blocker.				
Werdan K et al (2012)[15]	2,330 patients	Ivabradine added to beta-blocker	4 months	reduced heart rate by 19.4 ± 11.4 to 65.6 ± 8.2 bpm (p < 0.0001)	angina attacks reduced by 1.4 ± 1.9 per week (p < 0.0001)	nitrate consumption by 1.9 ± 2.9 U per week (p < 0.0001).

Table 2: Assessment of quality of life after add on therapy

Author (year)	Type of study	Quality of life after add on therapy
Lopatin Y et al (2022)[7]	Multicenter, prospective, observational, open-label, uncontrolled study	The improvement in all five dimensions of the EQ-5D-3L was statistically significant between V1 and V3 ($P < 0.05$). When analyzed with the VAS, mean QoL scores were 48.5 at V1, 61.7 at V2, and 75.7 at V3.
Sowjanya K et al (2020)[8]	prospective observational comparative study	analyzed using SF-36 questionnaire, All eight domains of quality of life were significantly improved in group B with *P*-value < 0.05,
Zweiker R et al (2019)[9]	Multicenter, prospective, uncontrolled, non-interventional study	QoL) scale: At visit 1, the average assessment was 5.7 ± 1.8 by physicians and 6.1 ± 2.0 by patients. At visit 2, this rating had improved to 3.0 ± 1.7, as equally assessed by physicians and patients. (p< 0.001 for both physicians and patients).
Glezer M et al (2017)[10]	Large-scale, multicentre, 6-month, open-label, prospective observational study	Increases exercise capacity and well-being.
	Prospective, Non-interventional, Observational Study	Improvement of symptoms and angina class led to a significant 14.7-point increase in EQ-5D questionnaire score (P < 0.001).
Werdan K et al (2015)[11]	Non-interventional, multicenter prospective study	After 4 months, the EQ-5D score indicated that patient QoL had improved in both subgroups increasing from 0.65 ± 0.28 to 0.83 ± 0.20 in patients with a previous PCI and 0.68 ± 0.26 to 0.82 ± 0.20 for patients without ($P < 0.0001$
Zaky et al (2013)[12]	Observational, prospective study	The quality of life score improved significantly from 3.46 ± 0.87 at the first visit to 4.67 ± 0.71 at 4 months visit, $P < 0.0001$.
Werdan K et al (2012)[13]	non-interventional, multicenter, prospective study	The EQ-5D index improved by 0.17 ± 0.23 (p < 0.0001).

Initial literature search yielded 45 studies, but full texts were unavailable for 15 of them, and among the remaining 21, some were describing pharmacotherapy of drugs, and others failed to report outcomes.As an adjunctive treatment, Trimetazidine was used in 3 studies, Ivabradine in 4, Ranolazine in 1, and Nicorandil in 1.

All the prescribed medications for adjunctive therapy proved to be efficient, risk-free, and well-tolerated. Reducing the frequency of angina attacks and taking fewer nitrates both indicate that AP symptoms have been alleviated (table1). Supplemental Trimetazidine reduced angina frequency and short-acting nitrate use within 2 weeks (both p 0.0001) and maintained this effect over 6 months regardless of background therapy. The number of patients with class I angina increased by six times, while the number with class 3 angina decreased by nearly four times. Six months later, both walking distance and overall happiness had increased significantly (p 0.0001). Add-on Trimetazidine is a safe and rapidly effective treatment for reducing angina attacks and nitrate use in the real-world clinical setting, and it was well tolerated by patients during treatment. Both the ability to exercise and general happiness are boosted.

As an adjunct to standard antianginal treatment, nicorandil significantly reduced the number of ischemic attacks in CHD patients with stable angina. There was no unexpected safety signal and it was well tolerated.

Patients with stable angina and CAD who took Ivabradine in combination with metoprolol had a marked improvement in quality of life. The positive effects seen with this combination can be credited for the high rate of adherence. The evaluation of quality of life after augmentation therapy is shown in Table 2.

DISCUSSION

Changes in lifestyle, reduction of coronary artery disease risk factors, and both invasive and

noninvasive treatment options are all part of the management of chronic stable angina. The primary objective of pharmacological treatment is symptom relief, which includes extending the amount of time patients can walk without experiencing chest pain (known as "angina-free walking time") and enhancing their quality of life. [16] Clinical guidelines recommend using beta-blockers, calcium-channel blockers, and short-acting nitrates first in patients with symptomatic angina, while saving second-choice medications (Ivabradine, nicorandil, ranolazine, and Trimetazidine) for those who cannot take or do not respond to beta-blockers, calcium-channel blockers, or short-acting nitrates. The superiority of either the first- or second-choice treatments has not been established through head-to-head comparisons. The effectiveness of antianginal drugs in relieving symptoms is comparable, but there is no evidence that they improve survival, according to meta-analyses. Evidence-based clinical data for the newer, second-choice drugs are more up-to-date than that for the conventional, first-choice drugs. Therefore, it is challenging to consider some drugs as first choice while not considering others. In addition, it is not uncommon for angina to require dual or even triple treatment. Multiple co-morbidities and multiple aetiologies for the patient's symptoms of angina are not uncommon. [5]

Ivabradine works by blocking the ionic current I(f) in the heart's pacemaker, slowing the heart's natural rhythm. Ivabradine treatment results primarily in a marked reduction of HR. It has zero effect on electrical activity within the heart, cardiac contraction, or ventricular repolarization. [3] Zarifis J et al.[12] found that when Ivabradine was added to metoprolol, the HR reduction was much more pronounced. Patients with stable angina must have their heart rates lowered since a higher HR is linked to higher myocardial oxygen demand and ischemia. Although metoprolol was used, the average heart rate (HR) was still only around 81 bpm at baseline. In addition to lowering the risk of mortality due to heart failure (HF) or other cardiovascular reasons, Ivabradine has been shown to enhance clinical outcomes and quality of life in multiple clinical investigations. Ivabradine's effectiveness in treating ischemic heart disease, septic shock, and multiple organ dysfunction syndrome has been investigated on the basis of the advantages of lowering HR. As an added bonus, it may be an effective drug for HR lowering in individuals who either cannot take beta-blockers or whose usage would be contraindicated. [3] Nicorandil is a well-rounded vasodilator since it acts as both a nitric oxide (NO) donor and a K+ATP channel agonist. N-[2-(Nitro-oxy) ethyl]-3-pyridine carboxamide is a nicotinamide derivative that also contains a nitrate moiety. [17] The antianginal effects of nicorandil are achieved by its ability to increase coronary blood flow, inhibit coronary artery spasms, and cause arterial vasodilatation. Therefore, nicorandil enhances the equilibrium between oxygen demand and supply, much like nitrates and dihydropyridine calcium-channel blockers. Additionally, nicorandil's ability to activate ATP-sensitive potassium channels causes it to have both metabolic effects and a sort of preconditioning on the myocardium. [16,18] Patients with stable angina due to coronary heart disease (CHD) were tested for the effectiveness and safety of oral nicorandil in a research by Jiang et al.[11]. Patients who met the inclusion criteria were assigned at random to either the nicorandil or placebo group. Both groups kept their regular antianginal medications, but the nicorandil group also got an extra 12 weeks of the drug (5mg thrice daily). Patients were divided into two groups: 200 who received normal treatment plus nicorandil, and 202 who received no treatment. Both groups had similar qualities to start with. With an adjusted ratio of 0.503 (95% CI: 0.301, 0.840; P=0.0086), the nicorandil group had substantially fewer episodes of myocardial ischemia following therapy than the control group.

Long-term therapy of stable angina requires Trimetazidine because of its cytoprotective effects during ischaemia. It has complementary effects to agents with hemodynamic activity. Exercise performance is enhanced and the frequency of anginal episodes is decreased without any change in haemodynamic parameters. Animal studies and human patients with coronary artery disease or heart failure have shown that certain compounds have cardioprotective effects. Trimetazidine counteracts the effects of ischaemia by increasing the efficiency with which ATP is produced inside heart cells. [10] Urinary excretion of Trimetazidine is the major route of elimination. For a single dosage, the elimination half-life is 6.5 hours, and there is no accumulation. Patients of any age or renal function status should take the whole recommended dosage. Trimetazidine may accumulate in people with impaired renal clearance, thus they should be treated with care. Trimetazidine's clinical benefits may not become apparent until 2–6 weeks following therapy initiation. [19] Clinical symptoms, cardiac function, and left ventricular remodelling in patients with chronic heart failure were all improved by Trimetazidine, according to a review study conducted by Lu Y et al.[20]. In another systematic study, 884 individuals with CHF were included (Zhang L et al., [21]). Trimetazidine medication was associated with a lower risk of cardiac-related hospitalizations (RR: 0.43, $p = 0.03$) but not overall mortality (RR: 0.47, $p = 0.27$). In addition to an improved left ventricular ejection fraction (WMD: 6.46%, $p< 0.0001$) and total exercise time (WMD: 63.75 seconds, p 0.0001), Trimetazidine therapy was also linked to a lower New York Heart Association functional class (WMD: 0.57, $p = 0.0003$), smaller left ventricular end-systolic diameter (WMD: 6.67 mm, $p< 0.0001$) and Adding Trimetazidine 80 OD to other antianginal therapies, such as maximally tolerated bisoprolol, was

associated with significant reductions in mean weekly angina attacks and consumption of short-acting nitrates, as well as improvements in quality of life, regardless of background therapy, as reported in a study by Lopintin Y et al.[7]. Patients with chronic angina may safely use Trimetazidine 80 OD in addition to other first-line antianginal treatments.

Quality of life was evaluated using a 10-point scale in a research conducted by Zweiker R et al.[9] following patients using Ranolazine for increased exercise tolerance, less symptoms, and less AP. QoL improved from visit 1 to visit 2 across the board, as measured by both doctors and patients on a scale from 10 (very bad QoL) to 1 (very high QoL). The average physician evaluation at the first visit was 5.7 1.8, whereas the average patient assessment was 6.1± 2.0. At the second appointment, both doctors and patients gave this metric a more positive evaluation: 3.0± 1.7. (both doctors and patients had a $p< 0.001$).

Recent evidence suggests that heart rate plays a crucial role in the development of ischemia and angina. An increase in heart rate raises oxygen demand in the heart, shortening diastole and increasing the risk of ischemia and the associated symptoms of angina. An increased risk of cardiovascular events is related with a greater mean heart rate in people with stable coronary artery disease. For this reason, medicinal interventions that efficiently lower heart rate need considerable attention, but are presently under-prescribed in the treatment of CAD and stable angina. [13] Double or even triple treatment is frequently necessary to manage angina, as acknowledged by the authors of a recent review article by Ferrari R et al. Many co-morbidities and multiple aetiologies for the patient's symptoms of angina are not uncommon. Guidelines do not give recommendations on the ideal combinations of medicines, even if certain agents have features that might be advantageous depending on comorbidities present and the causes of angina in addition to having antianginal effects. As this research shows, however, combining second-line anti-angina medications with first-line treatment not only decreases heart rate, frequency of angina episodes, and nitrate use, but also improves quality of life in patients with stable angina pectoris.

Only a small number of trials conducted in the recent past were available for analysis, preventing a more robust assessment of the results of comparisons between different add on second line medications

CONCLUSION

The results of the current research indicate that adjunctive therapy is an effective and safe method of lowering the frequency of angina episodes and the need for nitrates. In addition, evidence suggests that therapy for angina should be tailored to each individual patient, their comorbidities, and the underlying cause of their condition.

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