

A Drug Review of Trimetazidine on its Role as Add-On Therapy in Stable Angina

Vikram Rajasekar^{1*} and Ravish Katira²

¹Foundation Doctor, St. Helens and Knowsley Teaching Hospitals NHS Trust, UK

²Consultant Cardiologist, St. Helens and Knowsley Teaching Hospitals NHS Trust, UK

*Corresponding Author: Vikram Rajasekar, Foundation Doctor, St. Helens and Knowsley Teaching Hospitals NHS Trust, UK.

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Abstract

Ischaemic heart disease is a very common condition affecting many. Those with stable angina are generally treated with agents such as nitrates, calcium channel and beta blockers; haemodynamic agents that affect blood pressure. This review explores the utility of trimetazidine, a non-haemodynamic agent, in patients with chronic stable angina. Out of the eight articles reviewed, evidence suggests that trimetazidine can play a role as add-on to the current class of antianginals. Trials show that using trimetazidine as an add-on therapy to beta-blockers and/or calcium channel blockers significantly reduces the frequency and severity of angina pectoris and the associated usage of short acting nitrates. The overall tolerability of the drug seems favourable for usage in those with stable angina pectoris.

Keywords: Drug; Trimetazidine; Stable Angina

Introduction

The prevalence of ischaemic heart disease is becoming ubiquitous globally. Angina pectoris is a clinical condition characterised by chest pain upon exertion that typically eases at rest or with the usage of short-acting nitrates. Fundamentally, the pain is caused by the myocardial inability to meet expected metabolic demands. Most commonly, this imbalance of oxygen supply versus demand, is a direct result of obstructed blood flow through the coronary arteries laden with atherosclerosis [1]. Heart rate, blood pressure, afterload, preload and coronary blood flow are all components that contribute to anginal symptoms and currently remain therapeutic targets.

The conventional antianginal drugs decrease cardiac work or increase the delivery of blood by altering heart rate and blood pressure. i.e. haemodynamic agents. In the 90s, a step was taken to research other methods that can be used to treat angina pectoris, mainly myocardial cytoprotection. Ranolazine and trimetazidine (TMZ) are non-haemodynamic agents. Both agents are derivatives of the substrate piperazine. Ranolazine is postulated to decrease intracellular calcium by inhibiting the sodium dependent calcium channel [4]. It affects the membrane without changing heart rate or blood pressure. The focus of this article is on TMZ. This article will discuss the use of TMZ in various studies and its appropriateness in a clinical setting.

Grade	Description
1	“Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
2	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
3	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
4	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest”

Table 1: Classifies the symptoms of angina as described by Campeau Lucien and adopted by the Canadian Cardiovascular Society (CCS) [2].

The figure below outlines the medical management of stable angina as published by NICE [3].

- NICE Guidelines for Stable Angina Therapy**
- Beta-blocker or DCCB – establish patient tolerability in either drug
 - If symptom still not controlled: Combination of beta-blocker and DCCB.
 - If both not tolerated or contraindicated, monotherapy with: Long acting nitrates/ivabradine/ranolazine
 - If one of the first line options not tolerated or contraindicated, combination with the other option plus: Long acting nitrate/ivabradine/ranolazine
 - Consider third anti-anginal when: Symptoms not controlled with two drugs AND patient awaiting revascularisation or surgery deemed inappropriate.

Figure 1

Mechanism of action

The exact mechanism of action of TMZ is yet to be discovered however it is known to achieve a metabolic shift in the membrane of cardiac myocyte. This cytoprotective drug inhibits the beta-oxidation of free fatty acids (FFA).

FFA are utilised via beta-oxidation in the body during a state of starvation however, beta- oxidation occurs in the hypoxaemic state in the heart. Beta-oxidation results in greater production of ATP at the expense of increased consumption of oxygen. Therefore, the process is one that occurs at low levels of oxygen but its sustenance relies on increased oxygen consumption. In this hypoxic state, aerobic metabolism of glucose is neglected. This disequilibrium in metabolism promotes anaerobic glycolysis and accumulation of lactate resulting in intracellular acidosis. Trimetazidine promotes the myocyte to aerobically metabolise glucose instead of beta-oxidation of FFA by inhibiting long chain 3-ketoacyl co- enzyme A thiolase (LC-3KAT). LC3-KAT is the enzyme responsible for the final step of FFA beta-oxidation. Ultimately, this results in a reduction of oxygen consumption during ATP production and accumulation of lactic acid. It is also said to decrease oxidative free radical production, accumulation of neutrophils, sodium and calcium ions in the cytoplasm promoting a stable membrane [6-11].

Method

A literature search was conducted using the terms ‘trimetazidine’ and ‘angina pectoris’ on Medline and Embase. The search was limited to English results only. The details of the search strategy are included in the appendix. Articles that pertained to trimetazidine, stable chronic angina, observational studies and randomised controlled trials were included, and conference abstracts were excluded. From 56 articles, 8 articles were used to construct this review on TMZ.

Flow chart - outlining the search strategy used

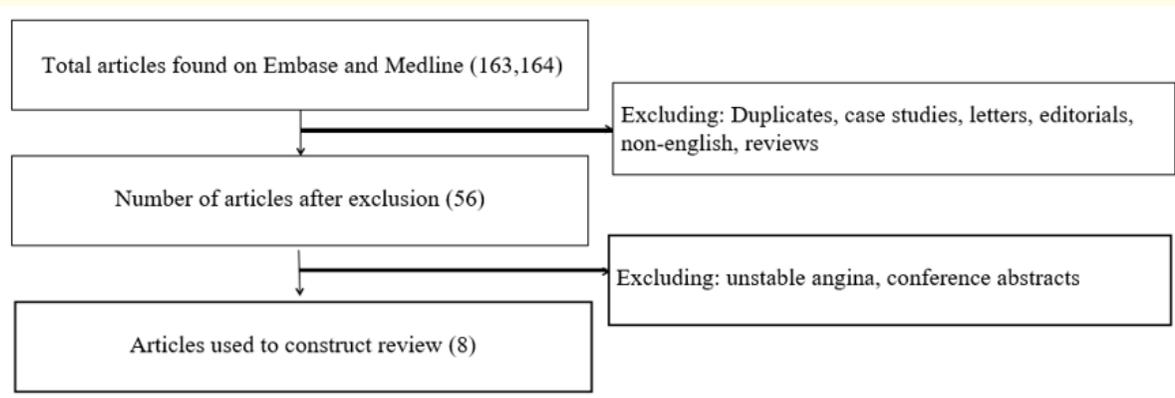


Figure 2

Article	Type	Patient Characteristics	Number of patients	Results
1. Pozdnyakov YM. Clinical acceptability of trimetazidine modified- release 90mg once daily versus trimetazidine modified-release 35 mg twice daily in stable angina pectoris [12].	RCT	Stable Angina	177	<ul style="list-style-type: none"> 80 mg OD was tolerated well and should be considered as an add-on therapy OD therapy may improve adherence
2. Glezer M. The effectiveness of Trimetazidine Treatment in Patients with Stable Angina Pectoris of Various Durations: Results from the CHOICE-2 study [13].	Observational	Stable angina	741	<ul style="list-style-type: none"> Decreased mean weekly frequency of angina, usage of short-acting nitrates and increased exercise tolerance prior to onset of pain Appropriate as add-on therapy.
3. Meiszterics Z., <i>et al.</i> Effectiveness and safety of anti-ischaemic trimetazidine in patients with stable angina pectoris and Type 2 diabetes [14].	Observational	Stable angina Type 2 Diabetes	737	<ul style="list-style-type: none"> Clinically significant decrease in HbA1C and severity and frequency of angina attacks and increased time prior to onset of exercise induced ischaemia. Particularly beneficial as add-on therapy in those with diabetes.
4. Kaur., <i>et al.</i> Role of trimetazidine, A cytoprotective agent in ischaemic heart disease [15].	RCT	Stable angina	50	<ul style="list-style-type: none"> Increased time prior to onset of exercise induced ischaemia. No reported clinical significance in symptomatic improvement
5. Peng., <i>et al.</i> The efficacy of trimetazidine on stable angina pectoris: A meta- analysis of randomized control trials [16].	RCT and meta-analysis	Stable angina	1628 (total)	<ul style="list-style-type: none"> TMZ as add-on therapy is clinically superior to haemodynamic anti-anginals as monotherapy. Clinically significant reduction in frequency of attacks, nitrate usage. Increased time prior to onset of exercise induced ischaemia.
6. Vitale., <i>et al.</i> Efficacy of trimetazidine on functional capacity in symptomatic patients with stable exertional angina – The VASCO-angina Study [17].	RCT	Stable angina	1962	<ul style="list-style-type: none"> Increased time prior to onset of exercise induced ischaemia - as add-on to atenolol. No inferiority or superiority between 70 mg vs 140 mg.

7. Danchin., <i>et al.</i> Efficacy Comparison of Trimetazidine with Therapeutic Alternatives in Stable Angina Pectoris: A network Meta- Analysis [18].	Meta-analysis	Stable angina	213 Studies	<ul style="list-style-type: none"> • Clinically significant reduction in frequency of attacks, usage of nitrates and exercised induced ischaemia when TMZ used as add-on compared to placebo. • No significance was found in the weekly frequency of anginal attacks or usage of short-acting nitrates, no clinical superiority or inferiority when used monotherapy vs other antianginals or as add-on therapy vs other antianginals that do not lower heart rate.
8. Belsey., <i>et al.</i> Relative efficacy of antianginal drugs used as add-on therapy in patients with stable angina: A systematic review and meta-analysis [19].	Systematic review and meta-analysis	Stable angina	46 studies	<ul style="list-style-type: none"> • The conventional combination of beta-blocker and DCCB remains by evidence a good therapeutic option but the addition of ranolazine or TMZ or long-acting nitrates to a beta-blocker or DCCB may also be considered. • TMZ is a viable option as add-on therapy.

Table 2: Results: Summary of articles reviewed.

Results and Discussion

Article 1

This study focused on comparing TMZ 35 mg MR BD vs TMZ 80mg OD in patients with stable angina pectoris. The primary aim of the study was to establish the tolerability of the 80mg OD dosage vs the 35 mg BD. This study was an international multicentre randomised double blinded controlled trial which was conducted for 12 weeks on 177 patients. TMZ was used as an add-on therapy to existing anti-anginal therapy. Safety and tolerability were measured based on adverse events, biological markers, vital signs, ECG and the CCS classification for symptoms of angina pectoris [2]. Indications were chronic stable angina as categorised by the CCS. Contraindications were Parkinsonism, Parkinson disease and creatine clearance (CrCl) < 60 ml/min. No clinical significance difference amongst the two groups could be found in any of the measured parameters. There were less adverse events in the TMZ 80 mg OD group. None of the adverse events were attributed to the commencement of TMZ in the study, thus there were no withdrawals or cessation of therapy.

This study depicts that TMZ 80 mg OD is as tolerable as the twice daily regime and may help adherence in chronic stable disease.

Article 2

This study was a 6-month observational study that focused on TMZ 35 mg MR BD as add-on to existing antianginal therapy. A total of 741 participants were in the study that met the inclusion criteria of confirmed diagnosis of stable angina via post stress test ECGs, prior myocardial infarctions, coronary artery bypass grafts, and stenosis of greater than 50% or commencement of anti-anginal treatment within the last 30 days. Exclusion criteria contained class 4 angina as per CCS, acute coronary syndrome admission in the last 3 months, blood pressure > 180/100 mmHg, class 3/4 heart failure as per NYHA, pregnancy or breast feeding, scheduled revascularisation within

6 months, severe chronic illness requiring ongoing therapy, renal and liver failure and contraindications to TMZ. The 741 patients were split in to four groups categorised into duration of stable angina: < 1 year, 1 - 4 years, and 4-9 years and > 9 years. The primary endpoints for the study were to measure the frequency of anginal events, the frequency of short-acting nitrate usage, time to onset of angina upon exercise and overall patient wellbeing. The study showed that the addition of TMZ showed clinically significant reduction in the weekly mean of angina pectoris event frequency in all 4 groups. All groups showed a statistically significant reduction in the usage of short acting nitrates, improved exercise tolerance before onset of angina and patient wellbeing. The non- interventional nature of the study shows that the addition of TMZ to conventional anti- anginal therapy is beneficial and applicable to a real-world scenario.

The study references other studies that show that optimisation of treatment is slow and needs improving. This study corroborates with that statement as many patients remained on monotherapy despite suffering from the condition for 9 years. As per guidelines, patients remaining symptomatic on monotherapy are recommended add-on therapy, in which TMZ can be one.

Article 3

This study was a 6-month observational, non-interventional study that studied the effectiveness and safety of TMZ in T2DM patients that had stable angina. A total of 737 participants were involved based on the inclusion criteria: >18 years, T2DM and chronic stable angina as described by the 2013 European Society of Cardiology guidelines (ESC). Patients were excluded their co-morbidities matched the TMZ product literature for contraindications, class 3/4 heart failure according the NYHA, CrCl < 30 ml/min and Parkinson disease or Parkinsonism. The measured endpoints:

1. Weekly frequency of attacks and severity (as per the CCS classification) and frequency of short-acting nitrate usage. The study showed clinically significant improvement in all three parameters.
2. Left ventricular systolic function and estimated left atrial filling pressure. Despite the addition of TMZ showing improvement in both parameters, the results were not clinically significant.
3. Exercise induced myocardial ischaemia. The time taken to onset 1mm ST depression and time to onset of angina pectoris pain both showed clinically significant improvement.
4. Change in arterial stiffness. This was measured using pulse wave velocity and augmentation index. The pulse wave velocity showed significant improvement whereas the augmentation index showed no change.
5. Change in HbA1c. The addition of TMZ shows a reduction in the HbA1c in T2DM patients that was clinically significant.
6. Clinician's global impression of change. Overall 88.6% beneficial change - 39.2% considered substantial change, 30.2% moderate change and 19.2% mild. 8.5% were considered to have no change and 2.3% were deemed to have minimal impairment.
7. Adverse effects. There were a total of eight adverse events. Five events needed hospital admission. Two of those events were ST elevation myocardial infarctions that needed primary coronary intervention, two were elective coronary intervention and one was for atrial fibrillation. Three were patients that had tremor or gait disturbances where TMZ was discontinued.

This study shows that TMZ has a clinically significant and beneficial effect as an add-on drug for stable angina in those with T2DM. In addition to its antianginal properties, it also improves the glycaemic status of the patient, something that is essential to consider in patients with diabetes.

Article 4

Kaur, *et al.* studied 50 patients diagnosed with stable chronic angina on conventional antianginal therapy. These patients were then subjected to TMZ 60 mg for 6 weeks after a baseline ECG and stress test. A repeat stress ECG was performed at the end of 6 weeks and the patients' angina symptoms were then documented. The study found clinically significant improvement for the time taken for a 1 mm ST depression to occur at 6 weeks. Furthermore, despite patients' experiencing symptomatic improvement, no statistical significance for this was stated. The study also stated favourable tolerability for TMZ as the study had no cessations in therapy, despite no statement of clinical significance.

Overall, Kaur, *et al.* recommend the use of TMZ 60 mg TDS as add-on or monotherapy in chronic stable angina, however the lack of statistical proof for certain parameters in the study need to be considered.

Article 5

Peng, *et al.* conducted a meta-analysis of RCTs. In their study, they critiqued 13 RCTs that compared the use of TMZ plus a haemodynamic agent versus a control group of just haemodynamic antianginals. Collectively, 1628 patients' data were reviewed. The meta-analysis showed that the addition of TMZ to haemodynamic antianginal therapy had clinical significance versus just haemodynamic antianginal, in reducing the number of anginal attacks and frequency of short-acting nitrate usage, prolonging the time taken for 1mm of ST depression and exercise tolerance before onset of anginal pain. They found no significant difference in treatment duration and its outcome as those treated within 8 weeks and above 12 weeks yielded similar results. Overall, this meta-analysis shows that TMZ is an efficacious treatment option for chronic stable angina versus the conventional antianginal therapy.

Article 6

This study used the data from 1962 participants that were involved in the previous VASCO study. The previous RCT studied the efficacy and safety of TMZ in doses of 70 mg/day and 140 mg/day, both moderate-releasing agents, in coronary patients who were receiving atenolol 50 mg for symptomatic or asymptomatic chronic stable angina. The VASCO-angina study went on to further evaluate the data to establish the effect of TMZ 70 mg vs 140 mg vs placebo on exercise tolerance. Their study endpoints were total exercise duration (TED) and time to 1 mm ST depression. The study proved that TMZ 70 mg and 140 mg were significantly superior to the placebo. However, no difference was established between the two TMZ groups in terms of exercise of tolerance, therefore no superiority or inferiority in dosage was elucidated.

Overall, the study showed that TMZ improves symptoms of chronic stable angina caused by stress induced ischaemia; in those already receiving atenolol and that no clinically significant difference is noted between the two doses.

Article 7

The aim of this large meta-analysis was to compare the efficacy of trimetazidine to other non- heart rate lower antianginal agents. Articles that involved negative inotropes were excluded. A total of 213 studies were critiqued. The articles were categorised into subsections:

1. TMZ + other antianginals vs. Placebo - the analysis showed that clinical significance was obtained vs placebo in prolongation of total exercise duration, time to 1mm ST depression, a decrease in mean weekly frequency of anginal episodes and weekly usage of short-acting nitrates. TMZ monotherapy analysis showed that TMZ was superior to placebo in all measured parameters.
2. TMZ vs other antianginals – no clinical or statistically significant difference was obtained between TMZ vs other agents in total exercise duration or time to 1mm ST depression. No significance was found in the weekly frequency of anginal attacks or usage of short-acting nitrates, thus showing no clinical superiority or inferiority if used as monotherapy vs other antianginals or as add-on therapy vs other antianginals that do not lower heart rate.

The study shows that TMZ is as effective as its counterparts in treating chronic stable angina and any differences found in the study are clinically insignificant. TMZ can be used as monotherapy and as part of a combination therapy.

Article 8

The aim of this meta-analysis was to “quantify the clinical benefit of beta-blockers, DCCBs, long-acting nitrates, ranolazine, trimetazidine, ivabradine or nicorandil added to first-line monotherapy” for chronic stable angina. 46 studies were critiqued that collectively studied 71 permutations of antianginal therapy. Eight studies compared the addition of TMZ to either a beta-blocker or DCCB and three studies compared the addition of ranolazine to beta-blocker or DCCB. All but one study compared the addition of beta-blocker to DCCB and vice-versa. The analysis showed that TMZ and ranolazine added to anti-anginal therapy shows statistically significant improvement in time to 1mm ST depression and time to onset of anginal symptoms. The study also showed adding ranolazine or a long-acting nitrate reduced the need for short-acting nitrates and the weekly frequency of anginal episodes. The study shows that the addition of TMZ reduced the weekly attacks of angina but showed no reduction in the usage of nitrates when TMZ is added to a beta-blocker or DCCB.

The conventional combination of beta-blocker and DCCB remains by evidence a good therapeutic option but the addition of ranolazine or TMZ or long-acting nitrates to a beta-blocker or DCCB may also be considered. Overall, this study shows that TMZ is a viable option as add-on therapy in chronic stable angina.

Summary

Upon this review, TMZ is indicated in chronic stable angina as recommended by the various articles and meta-analyses. It is strongly indicated as combination therapy in those where symptoms are uncontrolled. TMZ may have a role in chronic stable angina in those with T2DM and as monotherapy. With regards to dosage regime, there is no one universally agreed dosage. The 35 mg BD, 70 mg OD 80 mg OD, 140 mg OD and 60 mg TDS regimes all show statistically and clinically similar results. These doses show clinical efficacy and tolerability. An appropriate regime may be one that improves compliance (once daily tablet) and is cost effective. Tolerability of TMZ is widely reported as acceptable but side effects that should be noted include dyspepsia, abdominal pain, and change in appetite hypersensitivity, palpitations, sedation, headache, nausea, vomiting and extrapyramidal symptoms. Rarer reversible adverse effects reported are thrombocytopenia, agranulocytosis and liver dysfunction [20-23]. Anaphylaxis, Parkinsonism, Parkinson's disease, tremor, restless leg syndrome and problems with gait and severe renal failure are contraindications [22]. Despite evidence that systolic function is improved by TMZ, in certain studies patients with class 3 or 4 heart failure were excluded. Therefore, this should also be considered a contraindication.

The only known drug to interact with TMZ is metoclopramide. The severity of adverse effects of TMZ can be worsened in combination with metoclopramide [24].

Conclusion

In conclusion, this review shows that TMZ should be considered as a valuable alternative treatment option in tackling chronic stable angina. In the absence of any haemodynamic effect; TMZ is a viable option in patients who are bradycardic or hypotensive especially as all other antianginal drugs have haemodynamic effects. It can also be used as add on therapy for stable angina patients who are inadequately controlled or intolerant to first line antianginal therapy. It can also be a useful drug in patients with refractory angina.

Appendix

#	Database	Search term	Results
1	Medline	*TRIMETAZIDINE/	667
2	Medline	(trimetazidine).ti,ab	899
3	Medline	(1 OR 2)	934
4	Medline	"ANGINA PECTORIS"/OR"ANGINA, STABLE"/OR "ANGINA, UNSTABLE"/	40149
5	Medline	("angina pectoris").ti,ab	18571
6	Medline	(4 OR 5)	46800
7	Medline	(3 AND 6)	163
8	EMBASE	*TRIMETAZIDINE/	1191
9	EMBASE	(trimetazidine).ti,ab	1375
10	EMBASE	(8 OR 9)	1480
11	EMBASE	**"STABLE ANGINA PECTORIS"/ OR **"UNSTABLE ANGINA PECTORIS"/	7811
12	EMBASE	("angina pectoris").ti,ab	21665
13	EMBASE	(11 OR 12)	27341
14	EMBASE	(10 AND 13)	164

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