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Efficacy of Trimetazidine 80mg in Treatment of Stable Angina: A Systematic Analysis

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ABSTRACT

Background: Stable angina is a prevalent form of ischemic heart disease characterized by recurrent, predictable chest pain or discomfort associated with physical or emotional stress. Trimetazidine, an anti-ischemic agent, has shown promise in alleviating angina symptoms. This systematic analysis aims to evaluate the efficacy of Trimetazidine 80mg in the treatment of stable angina. Literature research on studies published between 2015 and 2022 was performed on a computerized database through PubMed, Google Scholar, Scopus, and Web of Science. **Methods:** In this meta-analysis, only the randomized control trial studies published between 2015 and 2022 were selected for quantitative analysis. Four parameters, i.e., mean arterial pressure, number of stable angina attacks per week, nitrate consumption, exercise tolerance test, and Canadian Cardiovascular Society classification of stable angina, were selected for evaluation. A specific criterion was used to assess the quality of trails. The standard statistical methods, pooled odds ratio, 95% confidence interval, and pooled z and p values were applied in the analysis. **Results:** This systematic analysis included six randomized clinical trial studies clinically examining a total of 10238 patients of stable angina for the efficacy of Trimetazidine 80 mg single dose per day. The data was analyzed through RevMen software 5.4. The outcomes state that the lower number of per week angina attacks, nitrate consumption, and reduction in mean arterial pressure are associated with Trimetazidine 80 mg. However, Trimetazidine 80 mg improves response to exercise tolerance test and Canadian Cardiovascular Society classification. **Conclusion:** It is concluded through this systematic review that Trimetazidine 80 mg, a single dose per day, is more effective in improving cardiovascular health in comparison to conventional anti-angina therapies and placebo drugs. Patients with stable angina suffer from a limited number of angina attacks by using a single dose of Trimetazidine 80 mg. Therefore, Trimetazidine is the choice of drug against stable angina pectoris.

Keywords: Trimetazidine, Stable Angina, Ischemic Heart Disease, Anti-ischemic Agent, Nitrate Consumption, Mean Arterial Pressure

INTRODUCTION

The field of medicine has been divided into numerous fields depending upon their core fields of specialization. Cardiology uses Trimetazidine to treat ischemic heart issues. Trimetazidine is frequently available in all signatory states of the United Nations [1]. It is a commonly available metabolic drug used as an anti-ischemic drug. It can be administered both in combination and with single agents for treatment [2]. Chest pain is the most prominent sign of angina. It is a characteristic representation of oxygen supply and demand mismatch. The treatment goal of angina pectoris or stable angina is to correct the ratio of oxygen supply and demand [3]. The treatment aims to improve prognosis and reduce the chances of mortality. The frequent treatment strategies include non-pharmacological treatment such as control and reversible risk factors such as smoking, weight, and sedentary lifestyle through exercise and behavioural modification [4]. The non-pharmacological treatment extended to control high blood pressure and comorbid diseases such as diabetes and anaemia [5]. Similarly, pharmacological treatment includes pharmaceutical products such as drugs that reduce the lipid concentration in blood, as well as symptomatic drugs and anti-anginal agents [6]. It also includes primary prevention drugs such as aspirin. The other widely acceptable drugs include Beta blockers, calcium channel blockers, and nitrates (both short-acting and long-acting) [7]. All these drugs are relatively effective in reducing the angina attack by correcting the oxygen supply demand and supply mismatch. However, the mechanism of action of Trimetazidine (TMZ), a metabolic drug, is different from other routine drugs to treat angina and myocardial infarction. It applies a new approach to treating angina attacks. It belongs to a well-known class of drug 3-ketoacyl 1-COA thiolate (KAT) inhibitor [8].

Similarly, it is routinely applicable in the guidelines of American and European physicians [9]. The TMZ shifts the metabolic pathway of the body to a cyclic process in which a limited supply of oxygen is required to produce ATPs from the metabolism of glucose [9]. The limited use of oxygen decreases the body's consumption of oxygen and promotes the relationship between oxygen supply and the demand of the body. In individuals with newly diagnosed conditions or cardiac patients who were resistant to hemodynamic medications, TMZ was demonstrated to offer symptom alleviation and functional improvement. Its metabolic mechanism of action can, in fact, be advantageous when used in conjunction with hemodynamic agents, providing full additional efficacy while maintaining tolerability [9].

In contrast, there is little evidence of hemodynamic combination treatment whether there is an advantage over immunotherapy [10]. The systematic analysis of the randomized control trial to assess the efficacy of Trimetazidine is available in the literature [10-12]. These systematic analyses involve a significant number of multicentre international studies to provide effective outcomes related to the efficacy and safety measures of Trimetazidine in comparison to other conventional therapies. However, in recent times, the Trimetazidine 80 mg, one dose per day treatment regime, has become commonly adopted for the treatment of stable angina [13, 14]. The previous systematic analysis provides inconclusive and heterogenetic information with limited consideration to the efficacy of Trimetazidine 80 mg single dose per day treatment regime. The current systematic analysis systematically evaluates the efficacy of Trimetazidine 80 mg in treating stable angina by including publications from the post-2015 period. The main objective of this research study is to systematically analyse the efficacy of Trimetazidine 80 mg in the treatment of stable angina by the pre-existing scientific literature.

MATERIAL AND METHODS

The scientific protocol involved in conducting this systematic analysis is summarized as follows.

PROTOCOL AND REGISTRATION

This systematic analysis is conducted in accordance with the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines 2020 [15]. The systematical quantitative data was analyzed through Review Manager (RevMen 5.4) to answer the question of the efficacy of Trimetazidine 80mg for the treatment of stable angina in comparison to various placebo groups and treatment regimes.

ELIGIBILITY CRITERIA

The published scientific literature was included in this systematic analysis through the PICOS principle [16]. The PICOS principle evaluates research studies on the base of participants, applied intervention, comparison, primary or secondary outcomes, and scientific study design. The research articles have (Participants of all age groups and genders, cardiovascular patients having

coronary artery diseases with acute or prolonged stable angina pectoris, Intervention: Trimetazidine 80 mg, comparison with different treatment regimens and placebo groups, Outcomes in terms of Hypertension control, frequency of episode of stable angina, reduction in the use of Nitrates, improvement in Canadian Cardiovascular Society classification, physical exercise tolerance, Study Design: randomized control trial, parallel arm, double-blind placebo) were included in this systematic analysis. The non-randomized control trial research studies with participants having comorbid diseases of renal failure or other systematic complications were excluded from this systematic analysis—the included studies are freely available in PDF form in the English language. The systematic review included the research studies published after 2015 because of evidence from previously published meta-analyses on this topic in 2014 [17].

INFORMATION SOURCES, SEARCH STRATEGY AND SELECTION PROCESS

The electronic database was created by searching research articles with specific MeSH terms (medical subject headings) from major database sources, i.e., PubMed, Scopus, Web of Knowledge, and Google Scholar. The used MeSH terms include Trimetazidine (MeSH Unique ID: D014292, Trimetazidine Dihydrochloride), Stable Angina (Angina Pectoris, MeSH Unique ID: D060050), and coronary artery diseases. The electronic database was prepared in five days, from January 1 to 5, 2023. The author selected the studies by evaluating them research studies through research titles, abstracts, and full-text studies. The data from the selected studies was extracted in terms of study design, country, participants' age and gender, dose of interventional drug, comparison, observational period, and outcomes.

DATA COLLECTION PROCESS AND DATA ITEMS

The included research studies were first evaluated based on the title and abstracted—the in-depth reading of the full-text articles done to collect the data. The single author independently studied and extracted the data from selected studies in five days from January 6 to January 10, 2023. The extracted data was in terms of frequencies, percentages, and descriptive statistics, i.e., mean and standard deviations. The data of demographic characteristics such as age, gender, body mass index, BMI, and core variables, i.e., blood pressure, heart rate, episodes of stable angina, use of nitrate, and changes in the class of CCS classification, were extracted in frequency distribution and descriptive statistics. The data was collected in a Microsoft Excel Sheet and transported to RevMen version 5.4 for further analysis.

RISK OF BIAS ASSESSMENT AMONG STUDIES

The risk of bias in the individual studies was assessed indecently by following the instructions and guidelines provided by the Cochrane Collaboration ROB-2 [18]. The author indecently evaluated the studies for different biases, i.e., random sequence generation bias, blinding of personnel and participants, blinding of outcome assessment, incomplete outcome data, and selective reporting.

DATA SYNTHESIS AND SUMMARY MEASUREMENT

The data pool was synthesized by collecting the mean and standard deviation values of selected parameters (per week stable angina attack, nitrate consumption, mean atrial pressure, and exercise tolerance test) for six selected research studies [13, 19-23]. The frequency and percentage values were taken for the Canadian Cardiovascular Society classification of stable angina patients. The data pool was synthesized separately for each study in a Microsoft Excel sheet and transported to RevMen 5.4. The analysis was performed in terms of weight mean difference WMD, 95% confidence interval. The significance level of weight difference was measured through the Z value and P value.

ADDITIONAL ANALYSIS AND THE RISK OF BIAS ACROSS STUDIES

An additional analysis sheet of characteristics was prepared to assess the research design, study setting, given intervention, population, and outcomes of individual studies. The risk of bias ROB-2 was calculated and presented through graphs. The risk of bias was categorized into low, unclear, and high levels.

RESULTS

STUDY SELECTION

The total number of identified research studies using specific keywords such as Trimetazidine, stable angina, and coronary artery diseases was 125. At initial identification based on title review, 30 studies were removed because of duplication, and 10 were removed based on ineligibility and other reasons. Eighty-five studies were evaluated for abstract, methodology, and conclusion. In this analysis, 35 studies were removed through automation and 25 manually, respectively. The remaining 20 studies were subject to full-text review, among which 15 were found ineligible because they were not randomized n=6, published before n=3, not available in PDF n=3, and studies other than in English language n=2. Therefore, 6 studies were involved in the quantitative analysis [13, 19-23].

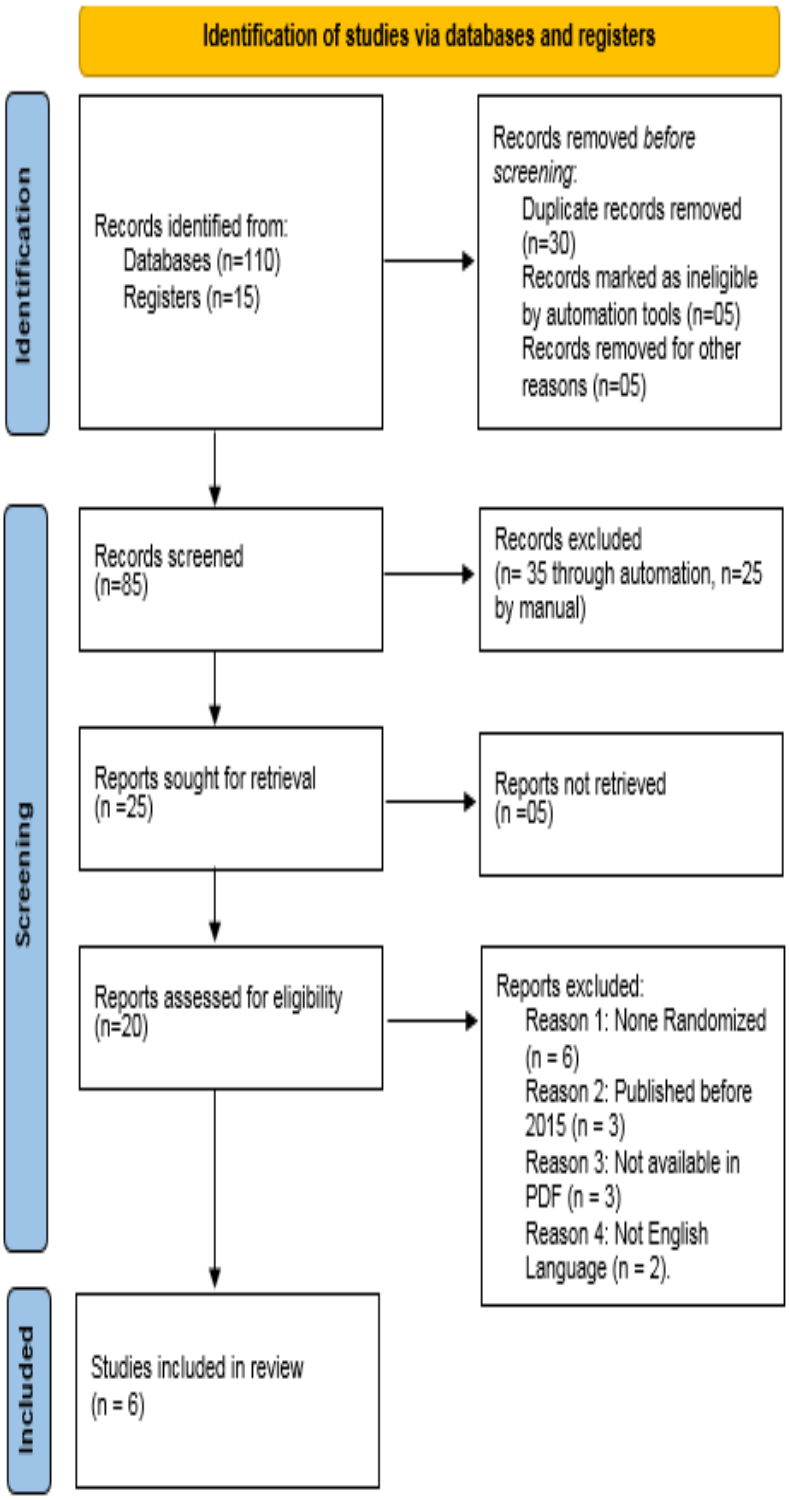

Figure 1:PRISMA Flowchart Diagram of Selected Studies

STUDY CHARACTERISTICS

Table 1 explains the characteristics of 6 included research studies [13, 19-23]. Out of these included studies, (1/6: 16.6%) was randomized, placebo control, multi-centered study, and (16.6%) randomized control, double-blind, parallel-group multi-centered International study, respectively. Whereas (4/6: 66.67%) were randomized control, observational multicenter studies. Most studies (3/6: 50%) were conducted in the Russian Federation, and the remaining were conducted in three countries, i.e., the USA, the United Kingdom, and China, one from each, respectively. These studies evaluated the efficacy of Trimetazidine 80 mg in ŋ=10238 patients. The major proportion of studies measured the efficacy of the drug in terms of reduction in the frequency of stable angina episodes, reduction in consumption of nitrate, improvement in Canadian Cardiovascular Society, and improvement in exercise tolerance.

Table 1: Characteristics of Included Studies

Study	Research Design	Setting	Populatoin (Age+M/F)	Intervention	Data Collection Tool	Study Duration	Outcomes
(Chazov et al., 2015)	Randomized, Placebo-Controlled, Multicenter Study	China	165 diagnosed stable angina patients, mean age 55.8± 0.8 years, M/F	Trimetazidine 80 mg OD intervention group, and Placebo in control group	Clinical Obervagtion, Monitoring and Examination	12 Weeks Study	Trimetazidine alone & in combination significantly reduced nitrated consompiton, aningn attacts & improved exerices tollerance, CCS society
(Glezer & Vygodin, 2018)	Randomized Control, Observational, Multicenter Study	Russia	3066 (M/F, age 18 to 75 years, diagnosed stable angina patients), 350 Physicians	Trimetazidine 80 mg, Single dose per day	Questionnaire for patietnts satisfaction and adherance to therapy, clinical observation for effect	3 month Study (March to June 2017)	The use of single dose 80 mg Trimetazidine significantly reduced the episode of stable angina and use of Nitrate consumption. It improved the adherence to therapy and patients satisfaction.
(Pozdnyakov & therapy, 2018)	Randomized Control, Double Blind, Parallel Group Multi Centered International Study	Russia & Serbia	165 Stable Angina Patients, both Male and Female, Above 25 Yeaqr, 35 Serbian, 130 Russian	Intervention Group=Trimetazidine 80 mg, Single dose/day control Group= Trimetazidine 30mg/two dose per day	Prsopective Clinical Observation in real time setting	12 Weeks Study	The Trimetazidine 80 mg/single dose per day has the similar effects in term of safety and efficacy as compare to the Trimetazidine 35 mg two dose per day. The safety was measured in term of adverse effects.
(Glezer, 2018)	Randamized Control, Multicenter, Open-Label, Prospective Observational Study	The USA, Californi a	741 CAD, Stable Angina Patiens with Known duration of disease, both M/F, Mean age 66.78± 9.7 Years	Intervention Group=Trimetazidine 80 mg, Single dose/day control Group= Trimetazidine 30mg/two dose per day	Clinical Examination and History	6 Months Duration	The Trimetazidine 80 mg reduced the stable angina attacks, consumption of sort acting Nitrates and improved walking distance, CCS classification of Patients
(Glezer, Vygodin, & therapy, 2019)	Randamized control, Observational, Multicenter, Prospective Study	Russia	3066, Diagnosed Stable Angina Patients, both M/F, Age between 18 to 75 Years	Intervention Group=Trimetazidine 80 mg, Single dose/day control Group= Trimetazidine 30mg/two dose per day	Questionnaire for patietnts satisfaction and adherance to therapy, clinical observation for effect	3 month Study, data collected at three stages	Reduced frequecy of angina attack, Nitrate consumption and improved the physical activity
(Glezer, Vygodin, Cardiology, & therapy, 2020)	Randomized Control, Observational, Multicenter study	United Kingdom	3032 Stable Angina Patients, Both M/F, Age 18 to 75 Years	Trimetazidine 80 mg, OD, and Placebo	Questionnaire for patietnts satisfaction and adherance to therapy, clinical observation for effect	3 months study	Reduced frequecy of angina attack, Nitrate consumption and improved the physical activity

RISK OF BIAS ASSESSMENT

Figure 2&3 explains the risk of bias in studies. It is indicated in the figures that a higher proportion of research studies have a risk of bias in the form of randomized sequence generation, allocation concealment, blinding of participants, and personal and incomplete outcomes. In the figure, it is indicated that 66.67% of research studies had a 75% higher risk of bias.

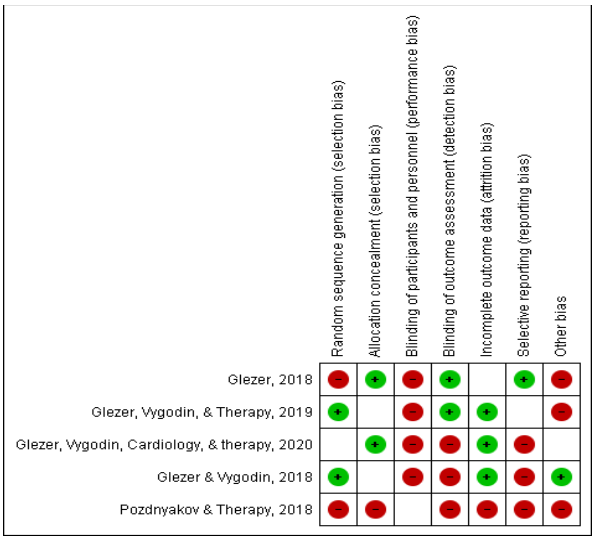

Figure 2: Summary of Risk of Bias

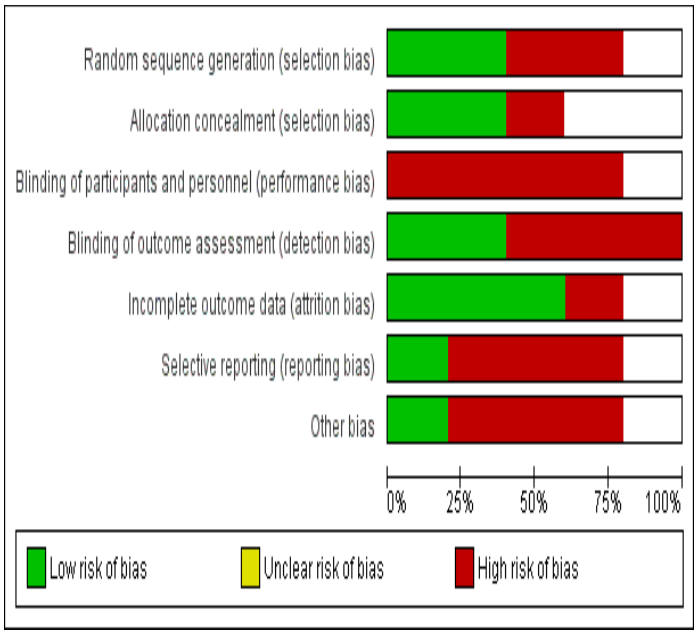

Figure 3: Risk of Bias Graph

RESULT OF INDIVIDUAL STUDIES AND DATA SYNTHESIS

The meta-analysis of the specified variables such as blood pressure, number of stable angina attacks per week, mean weekly consumption of the short-acting and long-acting nitrate, exercise tolerance (seconds), and Canadian cardiovascular classification was performed on the data extracted from six included studies. The total number of patients evaluated in these six studies was 10,238. The patients in the intervention group were treated with Trimetazidine 80 milligrams. In contrast, the control group was treated with placebo drugs, Trimetazidine 35 milligrams, or the conventional therapies differently in different research studies. The meta-analysis was performed using the outcomes visible in Figures 4-8.

In Figure 4, the foster plot for the mean arterial pressure shows the comparison of treatment effects with the Trimetazidine 80 milligram and the control group treated with a placebo drug, conventional therapy, and Trimetazidine 35 milligram in different studies. It indicates that the Trimetazidine 80 milligram is associated with a smaller mean arterial blood pressure with (WMD= -5.50, 95% Confidence Interval, lower limit - 7.11, and upper limit - 3.89, Z-value= 6.15 and P value less than 0.001). It indicates that there is a higher level of mean arterial pressure in patients in the control group. Furthermore, it is evident from the forest plot that Trimetazidine 80mg is effective in controlling mean arterial pressure as compared to the control group.

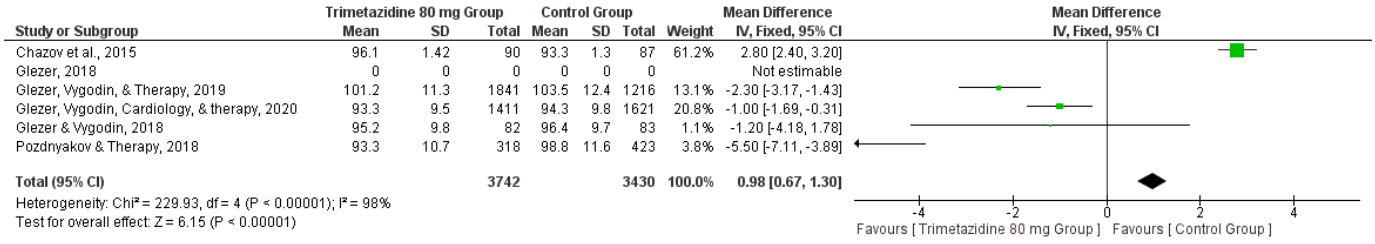

Figure 4: Forest Plot for the Mean Arterial Pressure Treated with Trimetazidine 80 mg in Comparison of Control Group

Figure 5 indicates the mean number of stable angina attacks among 10,238 patients evaluated in six included studies being treated with Trimetazidine 80 milligrams and a control group treated with a placebo drug, conventional therapies, and Trimetazidine 35 milligrams in different studies. The forest plot indicates that several of the mean stable angina attacks are associated with Trimetazidine 80 milligram (WMB=0.10, 95% CI= - 0.04- 0.25, test for the overall effect by Z= 39.49 and P value less than 0.001. It means that out of 10238 patients, 5275 were treated with Trimetazidine 80 milligrams, and 4963 were treated

in the control group with placebo and other conventional therapies; the mean number of stable angina patient attacks was less in patients treated with Trimetazidine 80 milligram as compared to the control group. It indicates that the Trimetazidine 80 milligram single dose per day is effective in controlling the weekly mean number of stable angina attacks in patients.

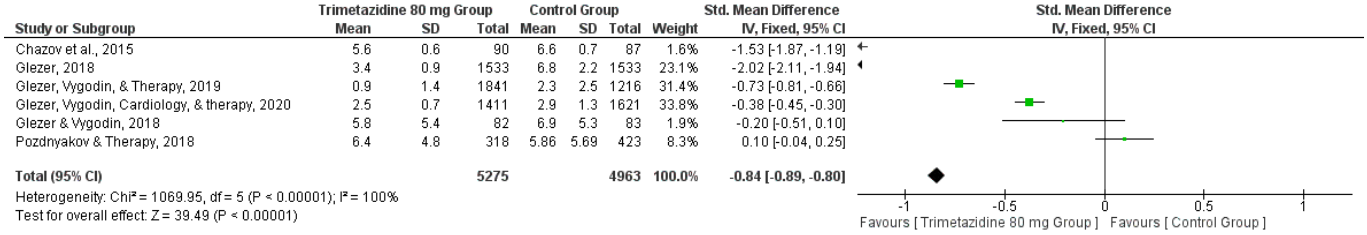

Figure 5: Forest Plot for the Weekly Mean Number of Stable Angina Attacks Treated with Trimetazidine 80 mg in Comparison of Control Group

The forest plot in Figure 6 indicates the mean weekly consumption of short and long-acting nitrates. The low degree of average weekly nitrate consumption is associated with the treatment of Trimetazidine 80 mg with WMD= -0.10, 95%CI [-1.11, -0.99], Z= 36.49, and p-value = 0.0001. This indicates that the average weekly consumption of nitrate in the Trimetazidine 80 mg group is low compared to that of the control group. It further proved the efficacy of Trimetazidine 80 mg in a single dose per day to treat stable angina.

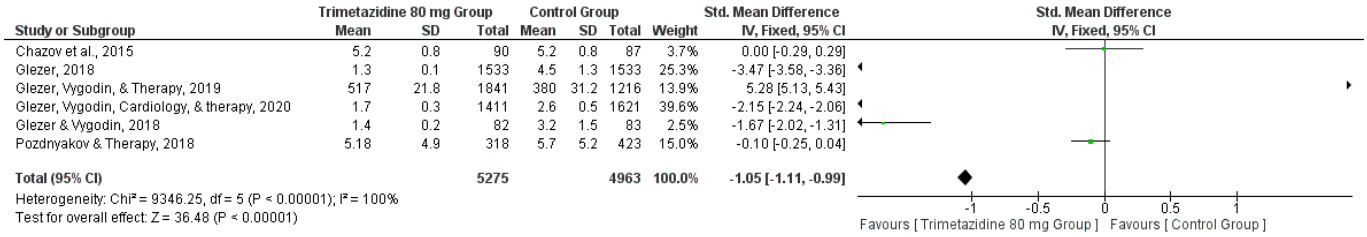

Figure 6: Forest Plot for the Weekly Mean Consumption of Nitrate after being Treated with Trimetazidine 80 mg in Comparison of Control Group

Figure 7 shows the exercise tolerance of stable angina patients treated with Trimetazidine 80 mg in comparison to the control group. The higher degree of improvement in (seconds of exercise tolerance test) was associated with Trimetazidine 80 mg treatment WMD =87.01, 95%CI [86.39, 87.63], Z= 275.26, p≤ 0.0001. There was little improvement in the exercise tolerance test of a control group of patients.

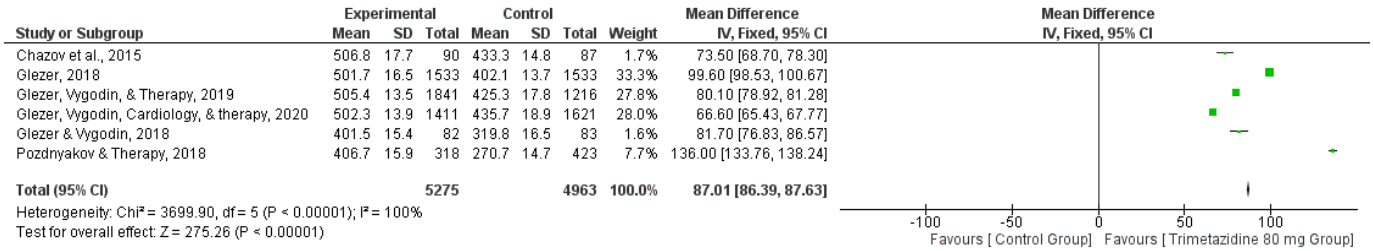

Figure 7: Forest Plot for Mean Exercise Tolerance (in Seconds) after Treated with Trimetazidine 80 mg in Comparison of Control Group

It is indicated in the figure that the higher degree of improvement in the Canadian Cardiovascular Society Classification of stable angina patients was associated with Trimetazidine 80 mg treatment with WMD = 1.26, 95%CI 1.13, 140, Z = 4.09 and P ≤ 0.0001. There was less significant improvement in the CCS classification of stable angina patients in the control group.

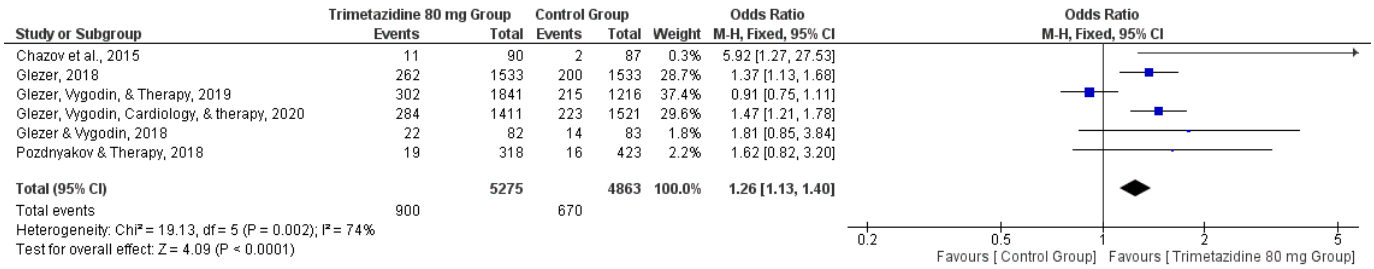

Figure 8: Forest Plot for Canadian Cardiovascular Classification of Patients after Treated with Trimetazidine 80 mg in Comparison of Control Group

The principle of the randomized model effect was performed to analyze the outcomes of variables of interest. The heterogeneity measures for the weekly mean number of stable angina attacks were Chi^2= 1069.95, df = 5, p≤0.001, and I^2=100%. Similarly, for nitrate consumption, Chi^2= 9346.25, df = 5, P≤0.0001, and I^2=100%.

DISCUSSION

The current systematic meta-analysis was performed to analyse the efficacy of Trimetazidine 80 milligrams single dose per day in comparison to the other conventional anti-angina therapies, and out of initially identified 125 research studies, six research studies were selected for the quantitative analysis according to the defined criteria. The research studies involved randomized trials, placebo control, and parallel-arm research. The total number of patients evaluated through these research studies was 10,238. In a randomized, placebo-controlled multicentre study, Trimetazidine 80 milligrams, one dose per day, was compared with the placebo control group. Similarly, in another double-blind, parallel arm, multi-cantered international study, 165 stable angina patients were physically examined to analyse the efficacy of Trimetazidine 80 milligrams in comparison to Trimetazidine 35 milligrams two doses per day. Similarly, all included research studies assessed the efficacy of Trimetazidine in terms of control on the number of angina attacks per week, a reduction in nitrate consumption, improvement in Canadian Cardiovascular Society classification, and improvement in exercise tolerance test. The meta-analysis has revealed that Trimetazidine, 80 milligrams of a single dose per day, is significantly associated with a lower number of weekly angina attacks and a reduction in nitrate consumption and blood pressure as compared to the other conventional anti-angina therapies. Trimetazidine 80 milligrams is significantly associated with a higher degree of improvement in the exercise tolerance test and Canadian Cardiovascular Society classification of stable angina, which indicates an improvement in the general and cardiovascular health of the patient.

The previous meta-analysis published in the International Journal of Cardiology in October 2014 involved 13 studies to assess the efficacy of Trimetazidine 80 mg in comparison to the other conventional therapies and placebo drugs [10]. The outcome of that meta-analysis is closer to the recent outcomes. It was concluded in that meta-analysis that in 1628 patients, a small number of angina attacks are significantly associated with the treatment of Trimetazidine 80 milligrams. Similarly, trimetazidine has been shown to reduce the weekly consumption of Nitro-glycerine and improve exercise tolerance tests and the CCS classification [10]. Similarly, another meta-analysis reviewing the efficacy of anti-angina drugs compared 71 therapies by analysing 46 qualifying research studies according to defied inclusion criteria [17]. The meta-analysis indicated a better outcome for Trimetazidine in combination with beta-blockers and calcium channel blockers in unstable angina patients. The recent outcomes of the systematic meta-analysis are further enhancing the credibility of previous literature on the efficacy of Trimetazidine 80 milligrams for the treatment of angina pectoris [17]. A single dose of 80 mg of Trimetazidine reduces patient dissatisfaction and improves adherence to the therapy, which improves the outcome. Single therapy is more convenient for the patient than multiple doses per day. Likewise, a meta-analysis of randomized double-anonymized controlled trials to analyse the efficacy and tolerability of Trimetazidine was performed on the research publications between 1985 and 2001 [11]. There were 12 clinical studies meeting the criteria of that analysis. The outcome of that analysis also indicated that Trimetazidine is significantly effective to reduce the number of weekly angina attacks in coronary artery disease patient.

LIMITATIONS AND RECOMMENDATIONS

The current systematic analysis was performed on a recently published randomized control trial international study. The statistical meta-analysis was performed through RevMen version 5.4. The outcomes are generalizable and widely acceptable to accept the efficacy of Trimetazidine in comparison to conventional anti-angina agents. However, the meta-analysis was limited to a small number of research studies from a contracted period.

CONCLUSION

The meta-analysis concluded that the Trimetazidine 80 milligram is more effective than the conventional anti-angina treatment. Trimetazidine 80 milligrams, a single dose per day, is significantly effective in reducing the number of stable angina attacks per week. It also reduces the nitrate consumption. The patients taking a single dose of Trimetazidine 80 milligrams per day show significant improvement in their exercise tolerance test, and the Canadian Cardiovascular Society classification shows an overall improvement in general and cardiovascular health. A single dose of 80 milligrams improves adherence to the therapy and patient satisfaction with the treatment. The overall safety factors are comparably equal in Trimetazidine 35 milligrams two dose/day and 80 milligrams single dose. However, the Trimetazidine 80 milligram single dose per day is the best choice in comparison to the other conventional treatment regime.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTION

All authors equally contributed to this study.

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REFERENCES

1. Wouters, O.J., P.G. Kanavos, and M.J.T.M.Q. McKee, *Comparing generic drug markets in Europe and the United States: prices, volumes, and spending.* 2017. **95**(3): p. 554-601.
2. Engin, S., et al., *Trimetazidine attenuates cyclophosphamide-induced cystitis by inhibiting TLR4-mediated NFκB signaling in mice.* 2022. **301**: p. 120590.
3. Alisherovna, K.M., T.D. Rustamovich, and U.J.J.C.J.o.M.I. Baxtiyorovich, *The Use of Trimetazidine in Patients with Type 2 Diabetes Mellitus Who Have Suffered a Myocardial Infarction.* 2022. **10**: p. 35-41.
4. Engin, S., et al., *The inhibitory effect of trimetazidine on detrusor contractility–a potential repositioning of trimetazidine for the treatment of overactive bladder.* 2022. **74**(1): p. 94-102.
5. Naito, R. and K.J.I.h.j. Miyauchi, *Coronary artery disease and type 2 diabetes mellitus current treatment strategies and future perspective.* 2017: p. 17-191.
6. Tarkin, J.M. and J.C.J.C.m. Kaski, *Pharmacological treatment of chronic stable angina pectoris.* 2013. **13**(1): p. 63.
7. Liu, Y., et al., *Acupuncture therapy for the treatment of stable angina pectoris: an updated meta-analysis of randomized controlled trials.* 2019. **34**: p. 247-253.
8. Ussher, J.R., et al., *Treatment with the 3-ketoacyl-CoA thiolase inhibitor trimetazidine does not exacerbate whole-body insulin resistance in obese mice.* 2014. **349**(3): p. 487-496.

9. Pelliccia, A., D.P. Zipes, and B.J.J.J.o.t.A.C.o.C. Maron, *Bethesda Conference# 36 and the European Society of Cardiology Consensus Recommendations revisited: a comparison of US and European criteria for eligibility and disqualification of competitive athletes with cardiovascular abnormalities.* 2008. **52**(24): p. 1990-1996.
10. Peng, S., et al., *The efficacy of trimetazidine on stable angina pectoris: a meta-analysis of randomized clinical trials.* 2014. **177**(3): p. 780-785.
11. Marzilli, M. and W.W.J.C.a.d. Klein, *Efficacy and tolerability of trimetazidine in stable angina: a meta-analysis of randomized, double-blind, controlled trials.* 2003. **14**(2): p. 171-179.
12. Marzilli, M.J.C.M.r. and opinion, *Cardioprotective effects of trimetazidine: a review.* 2003. **19**(7): p. 661-672.
13. Pozdnyakov, Y.M.J.C. and therapy, *Clinical acceptability of trimetazidine modified-release 80 mg once daily versus trimetazidine modified-release 35 mg twice daily in stable angina pectoris.* 2018. **7**: p. 61-70.
14. Lopatin, Y., P.J.C. Petrova, and Therapy, *Effectiveness and Tolerability of Trimetazidine 80 Mg Once Daily in Patients with Stable Angina Uncontrolled with Bisoprolol-Based Therapy: The Modus Vivendi Observational Study.* 2022. **11**(1): p. 93-111.
15. Zhang, X., et al., *PRISMA (preferred reporting items for systematic reviews and meta-analyses) extension for Chinese herbal medicines 2020 (PRISMA-CHM 2020).* 2020. **48**(06): p. 1279-1313.
16. Amir-Behghadami, M. and A.J.E.M.J. Janati, *Population, Intervention, Comparison, Outcomes and Study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews.* 2020.
17. Belsey, J., et al., *Relative efficacy of anti-anginal drugs used as add-on therapy in patients with stable angina: a systematic review and meta-analysis.* 2015. **22**(7): p. 837-848.
18. Higgins, J.P., et al., *Assessing risk of bias in a randomized trial.* 2019: p. 205-228.
19. Chazov, E., et al., *Trimetazidine in Angina Combination Therapy-the TACT study: trimetazidine versus conventional treatment in patients with stable angina pectoris in a randomized, placebo-controlled, multicenter study.* 2015. **12**(1): p. 35-42.
20. Glezer, M.G. and V.A.J.A.i.T. Vygodin, *Anti-anginal effectiveness and tolerability of trimetazidine modified release 80 mg once daily in stable angina patients in real-world practice.* 2018. **35**: p. 1368-1377.
21. Glezer, M.J.A.i.T., *The Effectiveness of trimetazidine treatment in patients with stable angina pectoris of various durations: results from the CHOICE-2 study.* 2018. **35**: p. 1103-1113.
22. Glezer, M.G., V.A.J.C. Vygodin, and therapy, *Effectiveness of long-acting trimetazidine in different clinical situations in patients with stable angina pectoris: findings from ODA trial.* 2019. **8**: p. 69-78.
23. Glezer, M.G., et al., *Effectiveness of trimetazidine in patients with stable angina pectoris of various durations: results from ODA.* 2020. **9**: p. 395-408.

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