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Clinical meta-analysis of Trimetazidine with Ranolazine in angina pectoris

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Abstract

Angina pectoris is a significant cause of ischemic heart disease and a cause of high morbidity and mortality in cardiovascular diseases worldwide. Trimetazidine and ranolazine are metabolite antianginal agents employed as an adjunct treatment in those with chronic stable angina. But there is no consistent evidence on their clinical effectiveness and safety as compared to other evidence. To compare and contrast the effectiveness and safety of trimetazidine and ranolazine with placebo in the management of angina pectoris in patients. It is a systematic review and a meta-analysis of randomized controlled trials by the PRISMA guidelines, published between 2000 and 2022. Search was done on databases such as PubMed, MEDLINE, Cochrane Library, Elsevier and ScienceDirect. Patients with angina pectoris or ischemic heart disease treated with either trimetazidine or ranolazine and reporting exercise-based and clinical outcomes were included in the trials. The main outcomes comprised the heart rate during peak exercise, duration of exercise test, the time to onset of angina, the number of attacks with angina per week, ST-segment depression 1-mm, and adverse drug reactions. Statistical tools were used to conduct statistical analysis using SPSS version 26. It consisted of 18 randomized trials, including 7,505 patients who were treated with trimetazidine and 6,823 who were treated with ranolazine. Both drugs resulted in no clinically significant difference between the heart rate at peak exercise and placebo. Ranolazine showed statistically significant and consistent increase in the exercise test duration, time to angina onset, st-segment depression and anginal frequency, though the heterogeneity between studies was minimal. Trimetazidine resulted in large depression of 1-mm ST-segments and angina attacks weekly, and lower heart rates during exercise albeit with a high degree of heterogeneity. There was no significant difference between the adverse drug reactions of the two agents and placebo, and the trimetazidine has a relatively good safety profile. Both ranolazine and trimetazidine are effective and are normally safe in the treatment of chronic stable angina pectoris. Ranolazine was more consistent and statistically stronger between exercises and ischemic, whereas trimetazidine was more effective in the reduction of ST-segment depression, lowering exercise heart rates, increasing exercise durations, and decreasing the frequency of angina weekly. On the whole, the overall meta-analysis results prove that trimetazidine is a more effective agent regarding the criteria measured, but more high-quality head-to-head trials are justified to define their clinical roles in comparison with each other.

Keywords: Angina pectoris, ischemic heart disease, Trimetazidine, Ranolazine, antianginal agents, systematic review, meta-analysis, randomized controlled trials

Introduction

Angina pectoris is an epitome of a cardiac disorder, which is typically serious. It refers to a form of substernal chest pain, strain, or irritation which is heightened by exercise, fear, or any other physical or mental strain, and which lasts over 30 or 60 seconds and is relieved by rest or nitroglycerin [1]. The World Health Organization (WHO) emphasized cardiovascular diseases (CVDs) as the main cause of death in the world, which claims 19.8 million lives in 2022, with angina pectoris being the main symptom of the disease. More than three-quarters of these deaths are in low- and middle-income countries. Angina pectoris is a disease afflicting over 100 million people in the world. The prevalence is high among both men and women with age. In the western world, the prevalence rate among individuals aged between 45-64 years is estimated to be between 4-7, and 10-15 among individuals 65-84 year [2, 3]. Angina pectoris is an epidemiology that is dependent on various factors such as age, gender, diet, physical inactivity, etc. and other illnesses such as hypertension, high cholesterol, diabetes and obesity is likewise a contributing factor to the risk [4].

Ranolazine is a new drug which has been discovered to treat angina. It is an anti-anginal agent that is used in the treatment of the symptoms of chronic stable angina pectoris such as chest pains that are as a result of reduced blood flow to the heart [5, 6]. It is generally used as an adjunct treatment to patients whose symptoms could not be sufficiently treated with first-line drugs such as beta-blockers or calcium channel blockers and to patients who could not tolerate these other medications because of side effects such as low blood pressure or heart rate [7]. The main action of Ranolazine in angina is also associated with the selective inhibition of the late sodium current (INaL) of heart muscle cells. This inhibition aids in avoiding overload of sodium and, consequently, calcium in the cells which happens during ischemia (lack of oxygen). This mechanism enhances relaxation of the heart muscle (diastolic functioning) and decreases the tension of the left ventricular wall and this in effect enhances blood flow in the heart muscle and minimizes oxygen demand hence alleviates symptoms of angina [8, 9]. Ranolazine lowers the rate of angina attacks, lowers the necessity of nitroglycerine and lengthens the exercise duration and tolerance [6].

Trimetazidine is a cytoprotective anti-ischemic agent, an add-on therapy applicable to symptomatic management of chronic stable angina pectoris [10]. Trimetazidine, unlike the traditional anti-anginal drugs, does not work at a hemodynamic level (heart rate, blood pressure, blood vessel dilation) but instead at a cellular level to optimize the energy production by the heart muscle at times of low oxygen (ischemia) [11]. The main way of action of trimetazidine is where the heart normally obtains the majority of its energy through oxidation of fatty acids, which is an oxygen-demanding process. This process becomes ineffective during an angina attack, when the supply of oxygen is limited. The Trimetazidine blocks a certain enzyme (mitochondrial long-chain 3-ketoacyl CoA thiolase) and causes the heart muscle to increase metabolism to the more oxygen-efficient glucose oxidation. Such a change consumes less oxygen to generate an equivalent quantity of Adenosine Triphosphate (ATP), the primary energy source of the heart. It assists in the maintenance of intracellular ATP and cellular homeostasis and eliminates the accumulation of toxic by-products such as excess sodium, calcium and free radicals in heart cells thereby spared of damage [12, 13, 14]. Trimetazidine is able to decrease the intensity and frequency of angina attacks, cut down on short-acting rescue nitrates, enhance tolerance and duration to exercise, and has its effects without producing any substantial changes in heart rate or blood pressure and therefore is a useful option in patients with low blood pressure or slow heart rates [15, 16].

The aim of the meta-analysis and systematic review is to identify the effectiveness of Ranolazine versus the Trimetazidine in the prevention of angina pectoris.

Method

This meta-analysis and systematic review were done to compare the effects of trimetazidine and ranolazine to placebo on the main clinical outcomes, such as the heart rate at peak exercise, ST-segment depression 1mm, angina attack in a week, angina onset and the total adverse drug reactions. They included randomised controlled trials published in the period between 2000 and 2022, which had patients with angina caused by coronary artery disease or ischemic heart disease receiving either ranolazine or trimetazidine and exercise-based measurements were done. The studies that did not qualify as the inclusion criteria, those that did not represent randomised controlled designs, and those that involved patients with inappropriate clinical condition were excluded. The databases (Elsevier, PubMed, MEDLINE, Cochrane Library and ScienceDirect) were accessed to carry out literature searches using such keywords as Ranolazine, Trimetazidine, Angina pectoris, Ranolazine randomized control trials, and Trimetazidine randomized control trials. The PRISMA guidelines were used in the review process as indicated in Figure 1 [17]. All of the study details were captured in an electronic format through the use of Excel, and SPSS version 26. The assessment and collection of data were carried out during a six-month period of observation and only publications that included all the criteria described were recruited.

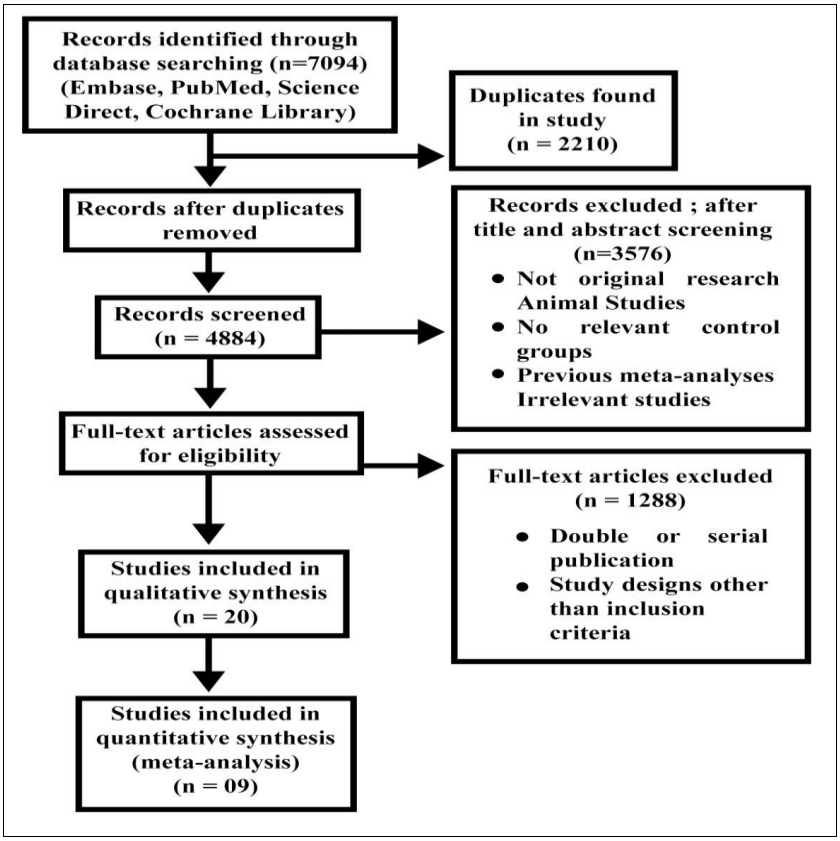

Fig 1: The review process in method followed by PRISMA guidelines

Results

A total of 18 trials were studied including eight trials in Trimetazidine, and six trials in Ranolazine versus placebo groups were enrolled, and additional data for different doses of these two drugs were found 1 in Trimetazidine and 3 in the Ranolazine group. The Trimetazidine group had 7505

members, while the Ranolazine group had 6823. For the heart rate contrast at the peak of exercise, the mean difference in heart rate at maximal exercise for Trimetazidine vs placebo was 0.24 [-1.24, 1.72], and for Ranolazine vs placebo, it was 2.00 [1.77, 2.23] as shown in table 1. Trimetazidine I^2 89% with $\chi 2$ was 64.38 with the degree off reedom 7 (P<0.00001) at the 95% confidence interval overall effect was found the Z=0.32 (p=0.75) and Ranolazine $\chi 2$ was0.44 with the degree of freedom 2 (P=0.80) in the test with overall effect Z=16.84 (p<0.00001) as shown in Figure 2a and 2b. For exercise, the test duration timing, the mean difference between overall workout the test time in seconds was observed to be 1.33[10.81, 13.47] for Trimetazidine vs placebo and 35.98 [35.58, 36.39] for Ranolazine vs placebo as shown in Table 1. Trimetazidine $\chi 2$ was observed to be 52.82with the degree of freedom 5 (P = 0.00001) at the 95% confidence interval the overall impact was found to be Z=0.21 (p=0.83) and Ranolazine $\chi 2$ was observed to be 1329.51 with the degree of freedom 7 (P0.00001) at 95percent confidence interval and the test for overall effect Z=173.80(p<0.00001) as shown in Figure 2c and 2d.

Trimetazidine vs placebo for time of onset on angina, the mean difference was -14.41[-27.56,-1.26] seconds, and for Ranolazine vs placebo, it was 31.53[31.11, 31.95] seconds as shown in Table 1. At the 95% confidence interval, TrimetazidineX2 was found to be 35.58 with the degree off reedom 6(P<0.00001). The Overall impact was Z=0.21(p=0.83) and Ranolazine $\chi 2$ was 52.70 with the degree of freedom 4 (P<0.00001) at 95% confidence interval and the test for overall effect Z=146.60 (p<0.00001) as shown in Figure 2e and 2f. The weekly number of anginal attacks was compared. The mean gap in the overall weekly amount of Anginal attacks for Trimetazidine vs placebo was - 0.67 [-1.37,-0.03] and 0.40 [0.24, 0.56] for Ranolazine vs placebo as shown in Table 1. Trimetazidine X2 was 4.22 with the degree of freedom 2 (P=0.12) at the 95% confidence interval. Ranolazine $\chi 2$ was 2.81 with the degreeof freedom 4 (P=0.59) at 95% confidence interval and the test for overall effect Z=4.95 (Fig.5.8). Overall impact Z=1.87 (p=0.06), and Ranolazine $\chi 2$ was 2.81 with the degreeof freedom 4 (P=0.59). (p<0.00001) as shown in Figure 2g and 2h.

The mean difference in net adverse drug reaction between Trimetazidine versus placebo was 0.97 [0.88, 1.07], and between Ranolazine versus placebo was 1.75 [0.90, 3.39] as shown in Table 1. Trimetazidine $\chi 2$ was observed to be 1.25 with the degree of freedom 2 (P=0.54) at the 95 percent confidence interval. The overall effect was Z=0.62 (p=0.52) and Ranolazine $\chi 2$ was 37.67 with the degree of freedom 3 (P<0.00001) at 95 percent confidence interval, and the test for overall effect Z=1.65 (p=0.10) as shown in Figure 2i and Figure 2j. For Trimetazidine vs placebo, the mean difference in overall 1 mm ST-segment depression was -62.62 [-75.98, -55.26], and for Ranolazine vs placebo, it was 30.0 [29.54, 30.46] as shown in Table 1. At the 95% confidence interval, I^2 was 92% which means it has substantial. The Trimetazidine $\chi 2$ was found to be 74.96 with the degree of freedom 5 (P<0.00001). The Overall impact was Z=12.41(p=0.83), and Ranolazine $\chi 2$ was0.85 with the degree of freedom 2 (P=65) at 95% confidence interval and the test for overall effect was Z=127.95 (p<0.00001) as shown in Figure 2k and Figure 2l.

Table 1: Effect of Ranolazine and Trimetazidine vs Placebo on various variables

Variable	Drug vs Placebo	Studies	Participants	Statistical Method	Effect Estimate
Heart Rate	Trimetazidine	9	7505	Mean Difference (IV, Fixed, 95%CI)	0.24 [-1.24, 1.72]
	Ranolazine	9	6823	Mean Difference (IV, Fixed, 95%CI)	2.00 [1.77, 2.23]
Exercise Duration	Trimetazidine	9	7750	Mean Difference (IV, Fixed, 95%CI)	1.33 [-10.81, 13.47]
	Ranolazine	9	6823	Mean Difference (IV, Fixed, 95% CI)	35.98 [35.58, 36.39]
Time of Onset of Angina	Trimetazidine	9	7505	Mean Difference (IV, Fixed, 95% CI)	-14.41 [-27.56, -1.26]
	Ranolazine	9	6823	Mean Difference (IV, Fixed, 95% CI)	31.53 [31.11, 31.95]
Weekly Anginal Attacks	Trimetazidine	9	7505	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-1.37, 0.03]
	Ranolazine	9	6823	Mean Difference (IV, Fixed, 95% CI)	0.40 [0.24, 0.56]
Adverse Drug Events	Trimetazidine	9	7505	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.07]
	Ranolazine	9	6823	Odds Ratio (M-H, Random, 95% CI)	1.75 [0.90, 3.39]
Time to 1mm ST segment depression	Trimetazidine	9	7505	Mean Difference (IV, Fixed, 95% CI)	-65.62 [-75.98, -55.26]
	Ranolazine	9	6823	Mean Difference (IV, Fixed, 95% CI)	30.00 [29.54, 30.46]

Discussion and Conclusion

In this meta-analysis, the authors compared the clinical effectiveness and safety between trimetazidine and ranolazine in patients with angina pectoris with the parameters related to exercise, anginal symptoms, electrocardiographic alterations, and adverse drug events. There were 18 randomized trials, which had a large pooled population and that provided a solid opportunity in comparing these two metabolic antianginal agents with placebo. Both drugs did not show a clinical significant decrease in heart rate during peak exercise. There was no significant difference between Trimetazidine and placebo with a high heterogeneity (I 2 = 89%), indicating that trials differed, and/or trials may have varied study designs, patient characteristics, or dosage. Being statistically significant, Ranolazine showed a very small degree of heterogeneity, which suggested that the results were uniform across the trials. These findings go in accordance with the previously established mechanisms of both medications, which mostly influence the metabolism of the heart and not the heart rate or the hemodynamics.

The effect of Ranolazine on exercise test time was both significant and greatly improved over placebo and the results were very consistent across studies. This result confirms its proven capability in the enhancement of exercise tolerance in chronic stable angina. Conversely, trimetazidine did not exhibit a statistically significant difference on the duration of the exercise even though there was an encouraging numerical pattern. So a considerable heterogeneity in trimetazidine trials is to be expected, which implies that the effect of trimetazidine on exercise capacity is possibly related to the selection of the patients, historical therapy or methodology. The two drugs showed enhancement in the results with regard to angina, although

the extent was different and the response varied. Ranolazine had a strong statistically significant increase in the duration of angina onset during exercise testing, which had moderately stable outcomes. Trimetazidine had a slight lowering effect on time to angina onset than placebo, however the effect was not statistically significant and had a great deal of heterogeneity. The results of this study are indicative of the idea that ranolazine can provide more reliable improvements in postponing ischemic symptoms on an exercise.

The Trimetazidine was accompanied by a small yet statistically significant decrease in the number of anginal attacks per week in comparison with placebo, whereas the ranolazine presented a statistically significant effect with more consistency among trials. Despite the low level of heterogeneity with either drug, the overall effect of trimetazidine was significant, but not always and statistically significant. This is an indication that, whereas the trimetazidine can decrease the angina frequency in certain patients, ranolazine can be observed to be more consistent in decreasing the burden of symptoms. The two agents showed a positive response on ischemic parameters. The effect of Trimetazidine on the ST-segment depression was considerably small, which is an indication that myocardial ischemia is reduced, but with a high degree of heterogeneity, which restricted the confidence of the pooled estimate. Ranolazine was also found to significantly and reproducibly increase ST-segment parameters with little heterogeneity supporting its anti-ischemic effect during exercise testing.

The adverse drug reaction analysis showed that neither drug showed a statistically significant number of overall adverse events in comparison to placebo. Trimetazidine had a better safety profile and heterogeneity was minimal whereas ranolazine had higher heterogeneity across studies. Notably, no major safety issues were noted in either of the agents and this contributes to their overall tolerability in angina pectoris patients. All in all, the results indicate that ranolazine has greater consistency and statistical strength in the changes of exercise tolerance, time to angina onset, and depression of ST-segment and anginal frequency than placebo. Although Trimetazidine, in contrast to digoxin, exhibits some promising results regarding the decrease in anginal attacks and ischemic burden, it is a heterogenous and less statistically significant impact of the results. Such differences might be differences in the quality of trials, dosage approaches, and patient groups, and also they may be differences in pharmacologic actions.

In this paper, I have concluded that both trimetazidine and ranolazine are useful and relatively safe antianginal drugs in patients with angina pectoris. Nonetheless, ranolazine shows consistent and clinically significant changes in major exercise and ischemic outcomes. Trimetazidine can be useful in the selected cases especially when patients are intolerant to the hemodynamically active agents, although additional high-quality and head-to-head trials are necessary to clarify their relative position in the management of angina.

It was found that Trimetazidine has more side effects but is superior when compared to the criteria that are being used in the study, that Trimetazidine is more successful in the treatment of 1mm ST-segment depression, and that Trimetazidine was more successful in maintaining the heartrate at the bare minimum during exercise testing, that patients can perform the exercise longer once Trimetazidine is taken, and that the frequency of angina attacks per week was lower in Trimetazidine when compared to Ranolazine. Consequently, the aggregate Meta-analysis outcome supported Trimetazidine to be a more efficient medication compared to Ranolazine.

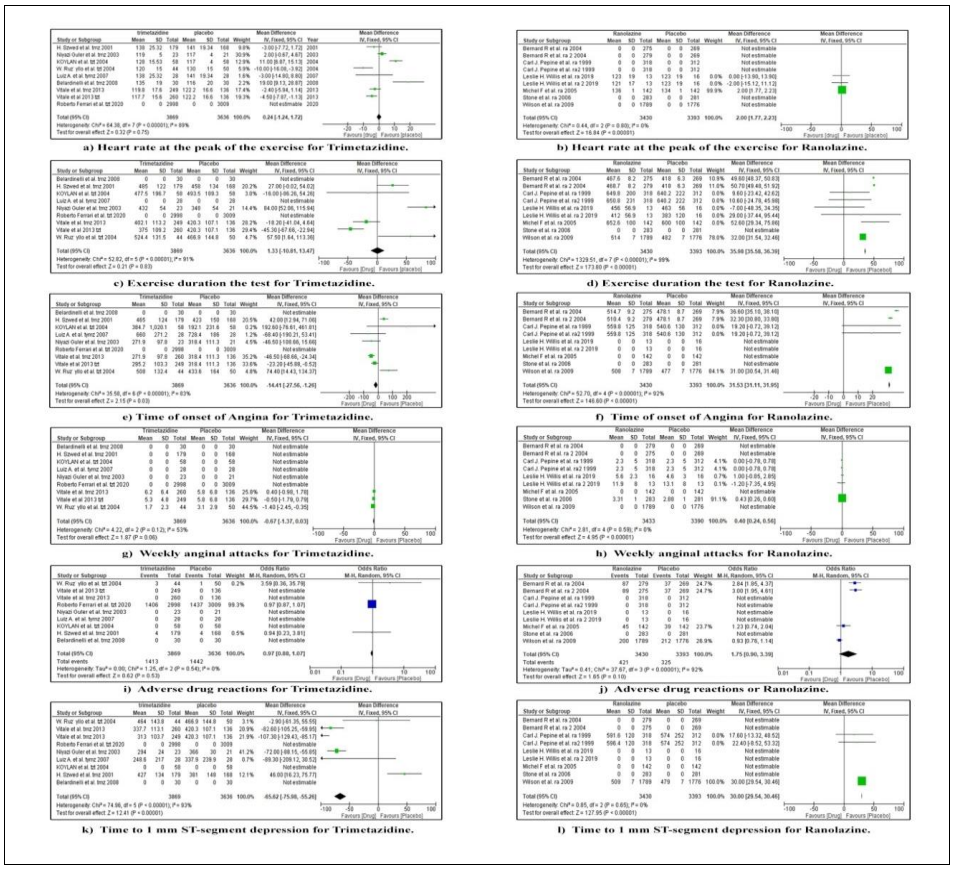

Fig 2: Forest plot of Trimetazidine and Ranolazine vs placebo groups in relation to various variables

References

1. Kaski JC. Essentials in stable angina pectoris. Springer, 2016.
2. World Health Organization. Cardiovascular diseases (CVDs) Key facts [Internet], 2025. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
3. Agho AV, Disu F, Figueroa AS, Wiredu B, Okorigba EM, Olanite M, *et al*. Prevalence of Angina Pectoris : An Analysis of the National Health Interview Survey (NHIS) Database Data source and study design, 2025, 17(4).
4. Khasanjanova FO, Tashkenbaeva EN, Muinova KK, Samadova NA. Traditional risk factors associated with the development of unstable angina pectoris in young adults. In: Colloquium-journal. Голопристанський міськрайонний центр зайнятості, 2020, 11–6.
5. Stanley WC. Ranolazine: new approach for the treatment of stable angina pectoris. Expert Rev Cardiovasc Ther,2005:3(5):821–9.
6. Tamargo J, Lopez-Sendon J. Ranolazine: a better understanding of its pathophysiology and patient profile to guide treatment of chronic stable angina. Future Cardiol,2022:18(3):235–51.
7. Tentolouris KN, Anastasiou IA, Mourouzis I, Pantos C, Tentolouris N. Ranolazine: An Established Anti-Anginal Drug with Emerging Antidiabetic Potential Supported by Preclinical and Clinical Evidence. Cardiovasc Hematol Disord Targets, 2025.
8. Patra S, Gupta P, Kumari R, Jana S, Haldar PK, Bhowmik R, *et al*. Insights into the mode of action of antianginal and vasodilating agents. In: How synthetic drugs work. Elsevier, 2023, 329–48.
9. Belardinelli L, Shryock JC, Fraser H. Inhibition of the late sodium current as a potential cardioprotective principle: effects of the late sodium current inhibitor ranolazine. Heart,2006:92(4):6–14.
10. Kallistratos MS, Poulimenos LE, Giannitsi S, Tsinivizov P, Manolis AJ. Trimetazidine in the prevention of tissue ischemic conditions. Angiology,2019:70(4):291–8.
11. Goel H, Roma N, Morgan M, Arora R, Sreejith N, Goyal D, *et al*. Trimetazidine in Cardiovascular Disease and Beyond: A Comprehensive Review. Am J Cardiovasc Drugs, 2025, 1–18.
12. Baroch M, Dejmkova H, Matysik FM. Determination of trimetazidine in urine by capillary electrophoresis with amperometric detection. Monatshefte für Chemie-Chemical Mon,2023:154(9):1013–8.
13. Zhuravleva MV, Granovskaya MV, Zaslavskaya KY, Kazaishvili YG, Scherbakova VS, Andreev-Andrievskiy AA, *et al*. Synergic effect of preparation with coordination complex “trimethydrazinium propionate+ ethymth methylhydroxypiridine succinate” on energy metabolism and cell respiration. Pharm Pharmacol,2022:10(4):387–99.
14. Yu F, McLean B, Badiwala M, Billia F. Heart failure and drug therapies: a metabolic review. Int J Mol Sci,2022:23(6):2960.
15. Ciapponi A, Pizarro R, Harrison J. Trimetazidine for stable angina. Cochrane Database Syst Rev, 2005, (4).
16. Dézsi CA. Trimetazidine in practice: review of the clinical and experimental evidence. Am J Ther,2016:23(3):871–9.
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj, 2021, 372.