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A PROSPECTIVE STUDY ON EFFICACY OF TRIMETAZIDINE AND ISOSORBIDE DINITRATE IN CORONARY ARTERY DISEASE

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Keywords:

Coronary artery disease, Observational group, Conventional therapy, Trimetazidine, Isosorbide dinitrate, C-reactive protein, Left Ventricular Ejection Fraction

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ABSTRACT: Background: The aim of this prospective study was to observe the efficacy of Trimetazidine (TMZ) and Isosorbide dinitrate (ISDN) in Coronary Artery Disease (CAD). Through inhibition of cardiac fatty acid oxidation, trimetazidine strengthens the treatment of CAD, by relieving aggravation; enhancing heart function, essential to prevent heart failure and other serious complications. **Methods:** 120 patients with CAD were selected as research subjects and randomly divided into two groups as observational (Group O) and control (Group C), with 60 patients in each group. The control group was on the conventional treatment of CAD whereas the observational group was using TMZ and ISDN along with the conventional treatment. The blood pressure, C-reactive protein (CRP), left ventricular ejection fraction (LVEF), troponin T and ST-segment levels of two groups were measured and compared at the baseline and after 2nd & 4th month respectively. **Results:** This study analyzed, compared to the baseline ($P>0.05$) the BP, CRP, troponin T and ST-segment levels after 2nd and 4th month were significantly decreased while LVEF increased significantly in between the observational and control groups, showing significant differences ($P<0.05$) using one-way ANOVA. Similarly, significant improvement among each group was statistically interpreted by an independent t-test. **Conclusions:** The addition of trimetazidine and isosorbide dinitrate along with a conventional regimen of CAD was probed to have an important association with LVEF and inflammatory mediators, which can significantly improve cardiac functions, and also prevent other cardiovascular complications in patients with coronary artery disease.

INTRODUCTION: Coronary artery disease (CAD) is one of the important causes of cardiovascular morbidity and mortality globally, giving rise to more than 7 million deaths annually. An increasing burden of CAD in India is a major cause of concern with angina being the leading manifestation.

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Angina is also associated with an increased risk of major adverse cardiovascular event (MACE) outcomes (cardiovascular mortality, hospitalization for myocardial infarction, heart failure or stroke) [1].

Coronary heart disease on a longer course can induce a variety of complications, especially in advanced heart failure dangerous condition, may lead to death [2]. Therefore, strengthening the treatment of coronary heart disease, to relieve disease progression and improve heart function is essential to prevent heart failure and other serious complications [3]. Conventional anti-anginal therapy improves myocardial ischemia through hemodynamic mechanisms and although haemo-

dynamic drugs are often used in combination, it is associated with a higher risk of drug-interaction and adverse effects. The guidelines recommend a beta-blocker or calcium channel blocker as the first-line medication for angina, supplemented by other agents for additional symptoms. One such agent is trimetazidine (TMZ), which has been shown to reduce the frequency of anginal episodes and improve exercise performance without affecting hemodynamic parameters [4, 16]. TMZ improves angina and myocardial ischemia either in monotherapy or in association with hemodynamic agents through inhibition of cardiac fatty acid oxidation.

This study was designed to observe the effect of Trimetazidine and Isosorbide dinitrate in coronary artery disease by evaluating cardiac functions and to prevent other cardiovascular complications.

METHODOLOGY:

Study Population: The study population included 120 patients of men and women with coronary artery disease with or without complaints of either stable angina or chronic stable angina, post-acute myocardial infarction, hypertension, hyperlipidemia, systolic heart failure and type 2 diabetes mellitus from both inpatients and outpatients. All the patients fulfilled the diagnostic criteria for coronary artery disease as defined according to the American College of Cardiology (ACC) guidelines.

Patients with clinical findings such as existing hepatic dysfunction (impaired first-pass metabolism) and renal dysfunction (GFR <30ml/min), parkinsonism and restless leg syndrome (contraindicated), malignant tumors (chemotherapy-induced cardiac events), psychiatric disorders (individual may not adhere to the treatment) were excluded from the study.

At inclusion, eligible patients were informed about the study, and written consent was obtained from them. During the study period, patients therapies routinely used for the treatment of coronary artery disease (*e.g.* anti-platelet agents, hypolipidaemic agents, anti-anginal therapy) were continued.

Study Design: The study design was a prospective cohort that included two groups: Observational group (Group O) and Control group (Group C). Each group possessed 60 patients. Both the groups received conventional drug therapy, but Group O was additionally treated with Trimetazidine (35 mg SR BD) and Isosorbide dinitrate (5 mg BD) orally. The two groups showed no significant differences in sex ratio, age and disease distribution (P>0.05), indicating that the two groups were comparable as in **Table 1** and **Table 2.**

TABLE 1: DEMOGRAPHICS AND CO-MORBID CHARACTERISTICS OF THE STUDY POPULATION

Characteristics	Group O (n = 60)	Group C (n= 60)
Age	63 (52%)[1]	61 (48%)[1]
Male	37 (61.7%)[1]	32 (53.3%)[1]
Female	23 (38.3%)[1]	28(46.7%)[1]
Hypertension	30 (50%)[1]	24 (40%)[1]
Heart failure	6 (10%)[1]	5 (8.3%)[1]
Post MI	2 (3.3%)[1]	4 (6.7%)[1]
Type 2 DM	22 (36.72)[1]	27 (45%)[1]

[1]Data were shown as number (%) appropriate to show age, gender, and co-morbidities distribution.

TABLE 2: BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Characteristics	Group O (n = 60)	Group C (n= 60)	P value
Age	65.9 ± 6.4[2]	65.3 ± 7.1[2]	0.6208
Systolic BP	140.1 ± 4.01[2]	142.1 ± 19.5[2]	0.5219
Diastolic BP	89.1 ± 4.8[2]	90.1 ± 8.7[2]	0.4423
CRP	2.11 ± 0.4[2]	2.51 ± 0.2[2]	< 0.0001
LVEF	57.4 ± 4.4[2]	56.2 ± 3.7[2]	0.0003
Troponin T	0.012 ± 0.004[2]	0.014 ± 0.003[2]	0.1154
ST segment	99.4 ± 7.6[2]	101.08 ± 6.8[2]	0.2109

[2]Data were shown as mean ± SD and independent t-test were used to determine significance (p>0.05).

This study was approved by the Institutional Ethics Committee of VISTAS (Approval no.: VISTAS-SPS/IEC/VI/2018/09) before commencement and it was conducted in the Employee State Insurance (ESI) hospital for a period of 7 months (November 2018 – May 2019). All the procedures used in the study complied with the ethical standards of ICH GCP.

Observation Indexes: After a baseline evaluation of all study parameters, each group was followed up once every 2 months and the changes in the parameters such as blood pressure, inflammatory mediators, ECG parameters, heart function were assessed. Each patient performed the echocardiography, electrocardiography, laboratory test, and ELISA (enzyme-linked immune sorbent assay) kit to measure study parameters such as systolic & diastolic Blood Pressure, C-reactive

Protein (CRP), Left ventricular ejection fraction (LVEF), Troponin T and ST-segment at the end of 2nd and 4th month, to evaluate the effect of the treatment provided.

Statistical Analysis: Data collected were analyzed using the SPSS 21.0.0 version and Graphpad Prism with 95% confidence interval. The statistical differences between and within the groups were determined using independent t-test and one way ANOVA (analysis of variance) since data collected are parametric. The measurement data were expressed as mean ± SD. Both intergroup and within-group comparison with P values <0.05 considered to indicate statistically significant differences.

RESULTS: A total of 120 patients with coronary artery disease met the inclusion criteria entered the study. Demographic and baseline clinical characterristics in **Table 1** and **2** showed an age of above 60 years approximately, male individuals with co-morbidity of type 2 DM are more predominantly affected with CAD are taken into account for this study.

Effect of Trimetazidine and Isosorbide Dinitrate: After two months, compared to patients treated with conventional therapy, coronary artery disease patients treated with trimetazidine showed a significant difference in study parameters, while poor significant changes compared to baseline values were detected in control (Group C) group. Similar significant differences were observed in the study parameters after four months as shown in **Table 3**. A significant difference in systolic and diastolic blood pressure, C-reactive protein, Troponin T, ST-segment was noted **Fig. 1, 2, 3, 4, 5** in patients treated with trimetazidine and isosorbide dinitrate with p<0.05 compared to conventional therapy from 2nd month to 4th month while a significant increase in left ventricular ejection fraction (from 61.3 ± 3.1 to 66.4 ± 2.3) was found in the observational group when compared to the control group **Fig. 6**. Only a marginal difference in blood pressure was observed between both the groups and a more significant difference was seen between the two groups with P<0.05. There was only a marginal difference in study parameters of control group.

TABLE 3: COMPARISON OF STUDY PARAMETERS WITHIN AND BETWEEN THE TWO GROUPS AT THE 2nd MONTH AND 4th MONTH

Characteristics	Group O (n = 60)	Group C (n= 60)	P-value
Systolic BP (mmHg)			
2nd month	132.16 ± 15.08[3]	135.33 ± 13.20[3]	0.2236
4th month	120.16 ± 7.70[3]	126.33 ± 11.92[3]	<0.0010
P	<0.0001	<0.0001	
Diastolic BP (mmHg)			
2nd month	86.1 ± 6.9[3]	88.3 ± 5.8[3]	0.0667
4th month	80.1 ± 7.4[3]	8.3 ± 5.0[3]	<0.0001
P value	<0.0001	0.0568	
C - reactive protein (mg/L)			
2nd month	1.69 ± 0.3[3]	2.08 ± 0.3[3]	<0.0001
4th month	1.24 ± 0.4[3]	1.81 ± 0.3[3]	<0.0001
P	<0.0001	<0.0001	
LVEF (%)			
2nd month	61.3 ± 3.1[3]	58.4 ± 2.5[3]	<0.0001
4th month	66.4 ± 2.3[3]	61.0 ± 3.5[3]	<0.0001
P	<0.0001	<0.0001	
Troponin T (ng/ml)			
2nd month	0.009 ± 0.003[3]	0.012 ± 0.003[3]	<0.0001
4th month	0.003 ± 0.001[3]	0.008 ± 0.003[3]	<0.0001
P value	<0.0001	<0.0001	
ST segment (ms)			
2nd month	94.2 ± 5.0[3]	98.1 ± 6.8[3]	<0.0006
4th month	87.1 ± 2.7[3]	93.0 ± 5.2[3]	<0.0001
P	<0.0001	<0.0001	

[3]Data were shown as mean ± SD and independent t-test & analysis of variance were used to determine significance (p<0.05).

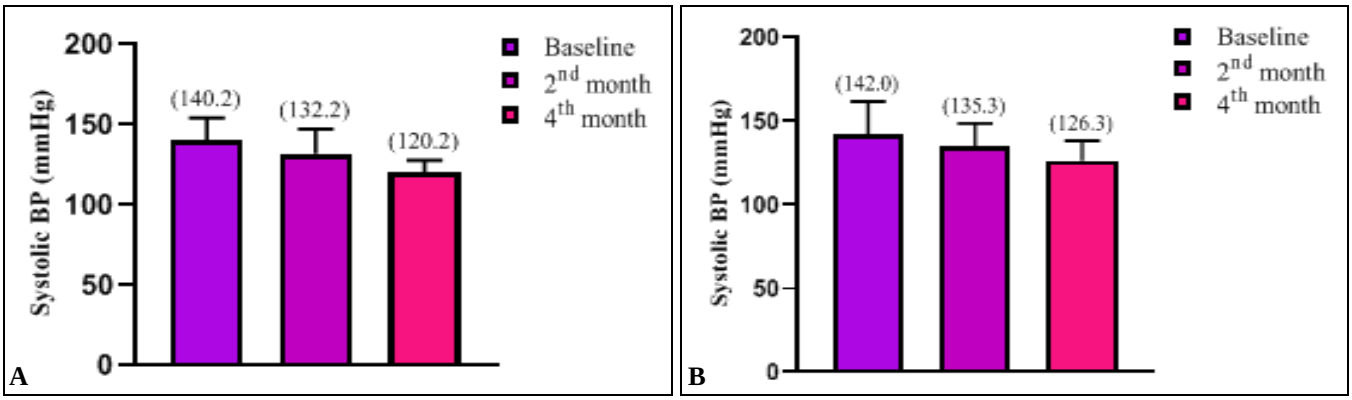

FIG. 1: COMPARATIVE DECLINE OF SYSTOLIC BLOOD PRESSURE ASSOCIATED WITH A - OBSERVATIONAL GROUP AND B - CONTROL GROUP IN CORONARY ARTERY DISEASE

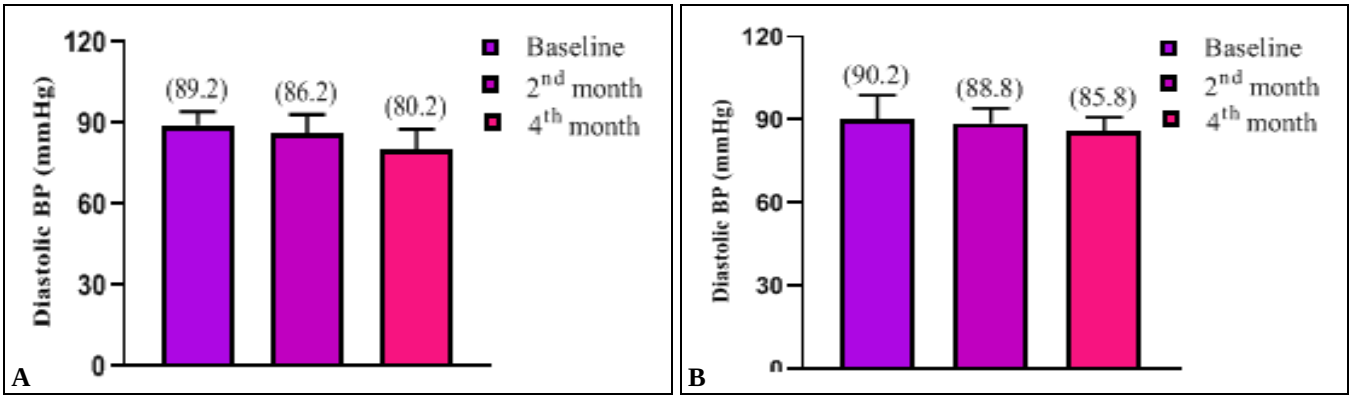

FIG. 2: COMPARATIVE DECLINE OF DIASTOLIC BLOOD PRESSURE ASSOCIATED WITH A - OBSERVATIONAL GROUP AND B - CONTROL GROUP IN CORONARY ARTERY DISEASE

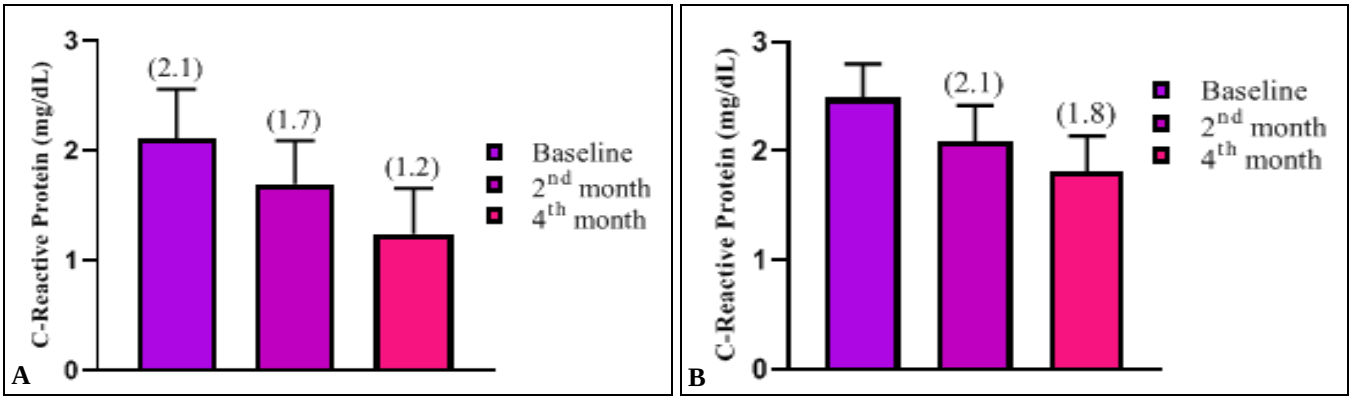

FIG. 3: COMPARATIVE DECLINE OF C-REACTIVE PROTEIN ASSOCIATED WITH A - OBSERVATIONAL GROUP AND B - CONTROL GROUP IN CORONARY ARTERY DISEASE

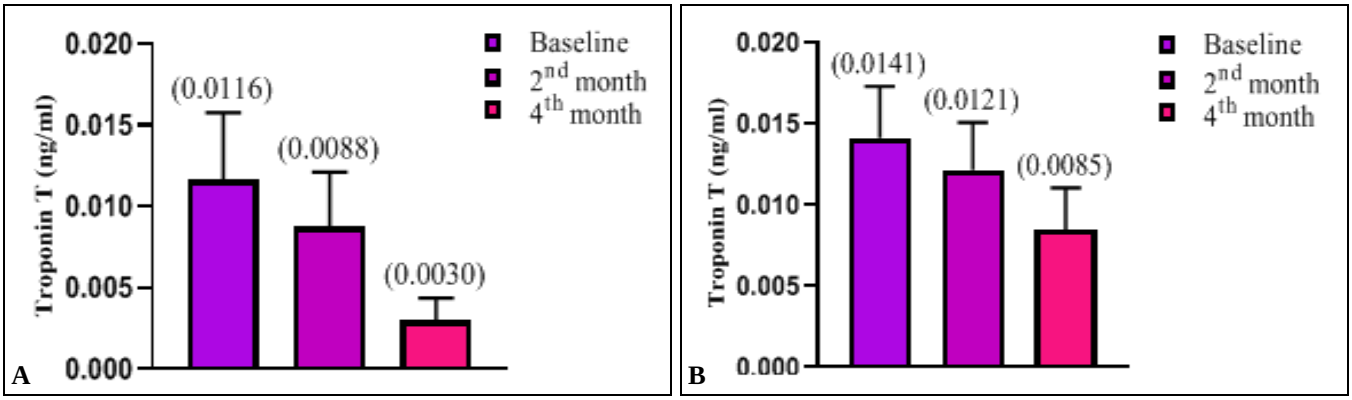

FIG. 4: COMPARATIVE DECLINE OF TROPONIN T ASSOCIATED WITH A - OBSERVATIONAL GROUP AND B - CONTROL GROUP IN CORONARY ARTERY DISEASE

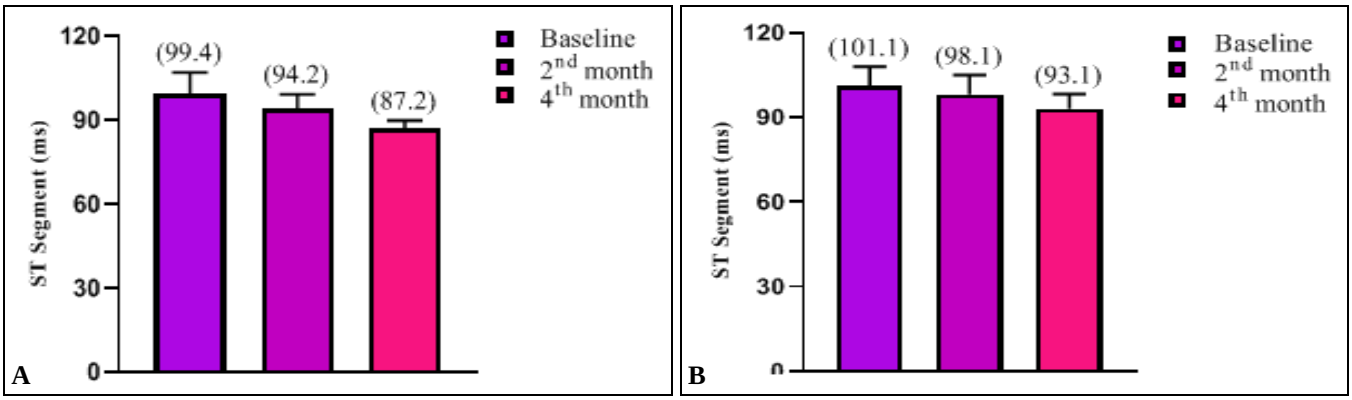

FIG. 5: COMPARATIVE DECLINE OF ST SEGMENT ASSOCIATED WITH A - OBSERVATIONAL GROUP AND B - CONTROL GROUP IN CORONARY ARTERY DISEASE

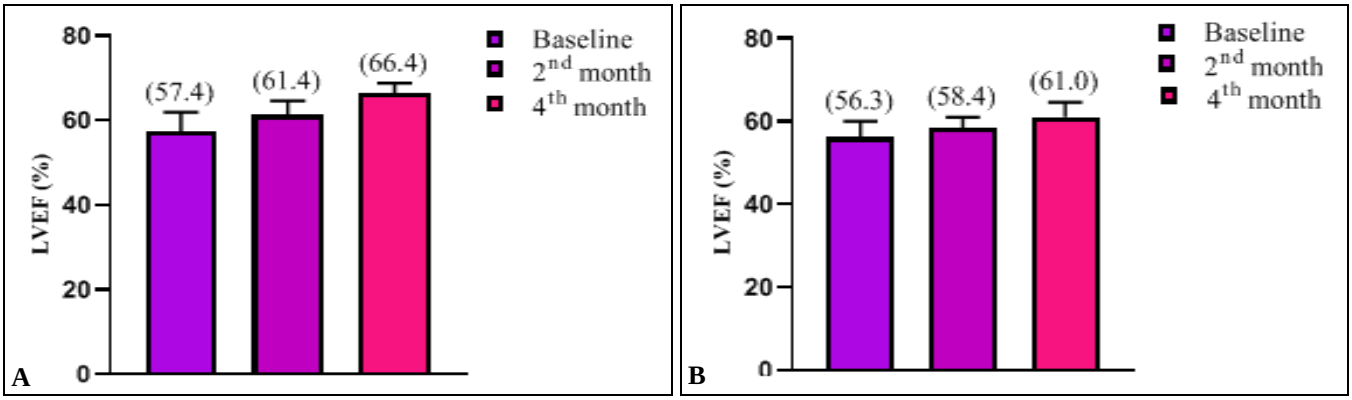

FIG. 6: COMPARATIVE ELEVATION OF LEFT VENTRICULAR EJECTION FRACTION (LVEF) ASSOCIATED WITH A - OBSERVATIONAL GROUP AND B - CONTROL GROUP IN CORONARY ARTERY DISEASE

Adverse Reactions: All the patients completed the clinical study. The routine urinalysis revealed no obvious abnormalities in liver and kidney functions and blood lipid and glucose levels in the two groups during the treatment period. There were two patients of muscle cramp and mild headache in the observation group and one patient of abdominal discomfort in the control group, no serious complications occurred in both the groups.

DISCUSSION: Coronary artery disease (CAD), involves the reduction of blood flow to the heart muscle due to buildup of plaque in the arteries of the heart. And is caused by an imbalance between myocardial blood supply and oxygen demand (ischemia or hypoxia). The symptoms (absent at rest) are usually brought on by exertion, emotional stress, exercise, cold or heavy meal manifestation such as substernal discomfort, heaviness or a pressure-like feeling, which may radiate to the jaw, shoulder back or arm. Electrocardiographic evidence of ST-T changes at rest or after exercise or conduction disturbances can be present as a consequence of CAD [5, 6]. Specifically, it suggests that a heart attack is more likely to happen in the future. Coronary angiography the reference-investigation for the diagnosis of conventional medical treatment for CAD is classified as antianginal or vascular protective drugs.

Antianginal compounds improve exercise duration until the onset of angina and reduce myocardial ischemia by decreasing the main determinants like severity and frequency of anginal episodes and time to onset of exercise inducing S-T depression of myocardial work. On the contrary, vascular protective agents may reduce the progression of atherosclerosis and of intracoronary thrombi growth/rupture and stabilize coronary plaques, consequently reducing the number of future cardiovascular events [4, 7].

Sometimes, conventional anti-ischemic drugs can be insufficient to improve the symptoms in the presence of CAD. But, their association with agents having different mechanisms from traditional anti-ischemic compounds, such as Trimetazidine (second line of treatment) may be effective when conventional drugs alone were ineffective.

Isosorbide dinitrate when administered orally was rapidly absorbed from the gastrointestinal tract and exert sustained hemodynamic (vasodilatation causing a reduction in preload) and antianginal (relaxation of vascular smooth muscles) effects [9, 10]. The anti-ischemic effect of trimetazidine is obtained at a cellular level by shifting the energy substrate preference from fatty acid oxidation to glucose oxidation, secondary to selective inhibition of 3-ketoacylCoA thiolase (3-KAT) [3, 8, 21] which inhibit the formation of oxygen free radicals in cardiomyocytes, reduce the damage of inflammatory factors on myocardial cells, but also enhance cardiac systolic and diastolic function, improve coronary blood circulation, maintaining normal myocardial function [12, 14, 15, 16].

Since, more ATP is produced per oxygen consumed when glycogen is a substrate, compared with fatty acids, less oxygen is required for a given amount of work [11, 18]. In experimental in vitro studies, trimetazidine has been shown to have a cardioprotective effect during myocardial ischemia because of a more rapid restoration of phosphorylation processes, protection of cardiac cells against the accumulation of hydrogen ions,

and prevention of the intracellular accumulation of sodium and calcium ions [18, 19]. Because of the preferential promotion of glucose and pyruvate oxidation, trimetazidine improves the activity of the sodium-potassium ATPase and the calcium uptake pump of the sarcoplasmic reticulum, that are respectively responsible for left ventricular systolic depolarization and diastolic relaxation. Hence Trimetazidine (especially when given in association with nitrates) obtained significant results in CAD.

The anti-ischemic effect of trimetazidine has been proven by the TRIMPOL-1 study group in diabetic patients receiving background anti-ischemic treatment [21, 22]. In the TRIMPOL-1 study, it has been shown that trimetazidine exerts its anti-ischemic effect without influencing either blood pressure or heart rate. The double-blind TRIMPOL-II (TRIMetazidine in POLand-II) study randomized 426 angina patients with documented CAD to TMZ 60 mg daily or placebo in addition to first-line metoprolol 100 mg daily [20, 22]. Exercise testing, and angina frequency & intensity all showed significant improvement at 3 months versus baseline in the TMZ group compared to placebo [23, 24]. A recent Ukrainian study added TMZ MR 35 mg bid to the regimen of 1213 outpatients with angina inadequately controlled by standard beta-blocker therapy alone or combined with calcium channel blocker [10, 25]. At 2 months TMZ significantly reduced weekly angina attacks from 6.4 ± 0.1 to 1.9 ± 0.1 ($p<0.001$). Not only was a significant reduction in attack frequency seen in patients with more severe angina (>7 angina attacks per week) regardless of first-line therapy, but maximal antianginal efficacy was achieved only with the dual combination of beta-blocker + TMZ [1].

This study observed and compared efficacy and improvement of cardiac function between two groups to analyze the clinical effect of trimetazidine and isosorbide dinitrate. The present study shows that the efficacy of trimetazidine and isosorbide dinitrate in Group O was significantly higher than in Group C, indicating that its efficacy in the treatment of CAD is significantly better than those of the other conventional therapies, which primarily increase myocardial oxygen supply capacity.

This study also observed the cardiac functions in the Group O, being improved by decreasing cardiac function indexes such as C-reactive protein (CRP) an important inflammatory factor affecting the development of coronary artery disease, which can promote the formation of foam cells and then release the formation of lipid plaques, activate the atherosclerotic plaque intima complement, damage the function of vascular endothelial cells [1], Troponin T a vital biomarker to determine acute MI and ST-segment and increasing Left ventricular ejection fraction (LVEF), thus improving myocardial ischemia, metabolism and reducing cardiac load compared to the Group C.

The limitations of the study included burden to patients by adding up drugs (multiple drug therapy) and increasing treatment cost owing to the wide variety of the drugs required and also limited follow uptime.

CONCLUSION: The results of this study demonstrate that Trimetazidine (TMZ) and Isosorbide dinitrate (ISDN) can be effective along with the conventional therapy given alone in patients with Coronary artery disease by enhancing cardiac functions, decreasing inflammatory mediator which promote progression of CAD and reduce the future cardiovascular complications.

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