

# Triple Versus Double Antianginal Combinations in the Treatment of Patients with Stable Angina with Impaired LV Function: A Single Center Registry

Haque M<sup>1</sup>, Ahmed CM<sup>2</sup>, Khan TA<sup>3</sup>, Arzu J<sup>4</sup>

<sup>1</sup>Assistant professor, Department of Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.

<sup>2</sup>Professor, Department of Cardiology, BSMMU.

<sup>3</sup>Specialist, United Hospital, Dhaka.

<sup>4</sup>Associate Professor, Department of Cardiology, BSMMU.

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## ABSTRACT

**Background:** Aims: To compare the anti ischaemic efficiency of antianginal therapy using a combination of metoprolol, Long acting nitrate (LAN) & trimetazidine/ranolazine in patients with stable effort angina with impaired LV function. **Methods:** The study enrolled 200 patients (male & female) aged 55-70 years with stable effort induced angina (functional class II and III angina) documented coronary artery disease. When the patients taking metoprolol 50mg twice daily & LAN 2.6 mg twice daily continued to have angina, after that 120 patients received an additional 35mg of trimetazidine twice a day or ranolazine 500 mg twice daily & 80 patients had double antianginal therapy –metoprolol & LAN. Treadmill exercise test and transthoracic echocardiography were performed at weeks (WO, & W12). **Results:** After 12 weeks, treadmill exercise showed there were significantly greater improvements in the triple antianginal group (metoprolol+ LAN+ trimetazidine / ranolazine): time to 1 mm ST segment depression, maximum ST segment depression, mean weekly number of angina attacks, mean weekly nitrate consumption, & grade of angina pain and transthoracic echocardiogram showed improved left ventricular systolic and diastolic function. **Conclusion:** Triple antianginal therapy with metoprolol+ LAN+ trimetazidine/ ranolazine combinations produced significant improvement in exercise stress test & the symptoms of angina relative to double antianginal therapy (metoprolol+ LAN) as well as improved left ventricular function.

**Keywords:** Anti-anginal therapy, Metoprolol, LV function.

## INTRODUCTION

Angina is considered to be chronic & stable when symptoms are present for it least two months, without changes in severity, character or triggering circumstances.<sup>[1]</sup> Stable angina is the most common manifestation of ischemic heart disease, affecting 58% of patients with coronary artery disease (CAD).<sup>[2]</sup> Its prevalence increases with age, rising from roughly 8% in men and 3% in women aged 55-64 years, 14% in men and 8% in women aged 65-74 years, in England.<sup>[3]</sup> The annual mortality rate resulting from coronary artery disease in patients with stable angina is 0.9-1.4% per year.<sup>[4]</sup>

Betablocker are the first line therapy for angina (class I). When monotherapy with beta-blocker failed to controlled symptoms of angina, treatment of choice tends to be more empirically based. The 2011 guidelines published by UK NICE suggests

when a patient experiences residual angina symptoms on either a betablocker (BB) or calcium channel blocker (CCB) agents from both classes should be prescribed together. When this option fails to controlled symptoms then NICE recommends that one of the first-line agent should be stopped, and alternative agent be prescribed, with selection being made on an individual basis, based on consideration of co-morbidities, contraindication, patient preference and drug costs.<sup>[5]</sup>

The 2013 ESC guidelines on the management of stable coronary artery disease advocate the use of long acting nitrates (LAN) and ranolazine - class of recommendation IIa, level of evidence (LOE) B or trimetazidine (IIB, LOE B) as second line therapy according to individual patient characteristics such as heart rate, blood pressure and drug tolerance.<sup>[6]</sup>

### Effect of treatment on exercise tolerance test<sup>[7]</sup>

For total exercise time, statistically significant benefits were seen for ranolazine added to BB or LAN added to BB and trimetazidine added to BB.

For time to ST segment depression, statistically significant benefits were seen for LAN added to BB, ranolazine added to BB and trimetazidine added to BB.

### Name & Address of Corresponding Author

Dr Jahanara Arzu  
Associate Professor,  
Department of Cardiology,  
BSMMU.

For weekly angina frequency, statistically significant benefits were seen for ranolazine added to BB or trimetazidine added to BB and LAN added to BB.

For weekly nitrate consumption, statistically significant benefits were seen for ranolazine added to BB. There was no significant differences were seen with trimetazidine added to BB. There was no data for this outcome available for ivabradine.

Trimetazidine in angina combination therapy (TACT study) showed the combination of trimetazidine with BB or LAN significantly improve exercise stress test parameters and angina symptoms compared with placebo. Due to its metabolic effects, free of any hemodynamic action, trimetazidine has proven to be beneficial for combination in patients with stable angina.<sup>[8]</sup>

#### **Effects of treatment on echocardiographic parameters**

Use of trimetazidine was associated with improved LVEF, reduced NYHA functional class, decreased LVESV and LVESDV.<sup>[9]</sup> LV dimension was significantly decreased and LVEF was also significantly better with use of trimetazidine.<sup>[10]</sup>

Ranolazine preserves and improves left ventricular ejection fraction when added to guideline-directed therapy in patient with chronic heart failure.<sup>[11]</sup>

Ranolazine 500mg bid in chronic coronary patient improves parameters of left ventricular diastolic function as well as improvement in the severity of stable angina.<sup>[12]</sup> Figueredo et al showed improvement of left ventricular diastolic and systolic function following the administration of ranolazine in patients with stable angina.<sup>[13]</sup> Triple anti angina combination (bisoprolol+ivabradine +trimetazidine or ranolazine) substantially improved the results of a treadmill exercise test, improved left ventricular systolic and diastolic function and quality of life in the patients.<sup>[14]</sup>

## **MATERIALS AND METHODS**

**Study design and Location-** There was a cross sectional observational study in a single centre conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. The patient was attended at outpatient department of cardiology at BSMMU from January 2017 to July 2017.

#### **Inclusion criteria**

Male and female patient aged 55-70 years with a history of stable effort-induced angina for > 2 months and documented coronary artery disease (either >70% narrowing in at least one coronary artery on coronary angiogram, or previous myocardial infarction; and positive treadmill exercise test during first visit at start of study (W0). Study approval was obtained from local ethical committee at BSMMU and written informed consent

was obtained from each patient before participation in the study.

#### **Exclusion criteria**

myocardial infarction or unstable angina in previous 2 months, cardiac surgery, percutaneous transluminal angioplasty (PTCA), Stroke or transient ischemic attack in previous 6 months, Inadequately controlled arterial hypertension (>160/90), Moderate to severe heart failure (NYHA class III or IV), Inability to performed exercise test.

The study was divided into two phases: at the start of study (W0) each patient was on metoprolol 50 mg twice daily and long acting nitrates(LAN) 2.6 mg twice daily; and a 12 week treatment period (W0 to W12) during which patients received either trimetazidine 35 mg twice daily or ranolazine 500 mg twice daily. Throughout the study other antianginal treatments e.g. calcium channel blocker (CCB) or ivabradine or other betablockers were also not allowed. The use of short acting nitrates for relief of angina pain was permitted (patients completed a daily diary recording the number of angina attacks and nitrate consumption).

#### **Exercise testing**

Clinical examinations and maximal treadmill exercise test (according to bruce protocol) were performed at study baseline (W0), and after 12 weeks (W12). Positive exercise tests were characterized by either a horizontal or down sloping ST segment depression > 1 mm measured at 60-80 ms past the J point, during exercise or within 3 minutes of recovery in at least one lead.

In addition, following were measured: time to onset of 1 mm ST segment depression, exercise test duration, time to onset of angina and maximum ST segment depression.

#### **Echocardiography**

All patients underwent transthoracic echocardiogram at the start of study (W0) and after 12 weeks (W12) use of triple antianginal agents (BB+ LAN+ TMZ/RAN) following the guidelines of the American Society of Echocardiography, using the parasternal and the apical views to calculate dimensions and evaluate global and regional left ventricular function.

#### **Statistical analysis**

Values are given as mean±1SD. Differences in mean values between groups were assessed using the paired Student's t-test.

## **RESULTS & DISCUSSION**

Results from exercise tolerance test (mean +SD) in triple AA group (n=120) and in double AA group (n=80). Statistically significant improvement was observed in triple anti-anginal groups (P <0.0001)

Table 1:

Sl.	Variable	BB+LAN+TMZ/RAN WO W12	P-Value	BB+Lan WO W12	P-Value
1	Time to 1mm STD	389.0+ 14.8 to 478.9+16.2	<0.0001*	414.85+15.2 to 419.2+16.9	0.089
2	Exercise test duration	437.7+ 14.25 to 536.8+17.7	<0.0001*	455.3+14.8 to 459.6+18.1	0.102
3	Mean weekly number of anginal attack	5.1+0.6 to 2.1+0.5	<0.0001*	6.4+0.7 to 6.2+0.7	0.073
4	Mean weekly nitrate consumption	4.8+0.9 to 2.3+0.8	<0.0001*	5.7+0.8 to 5.5+0.9	0.139

P value reached from Paired t-test, \*significant

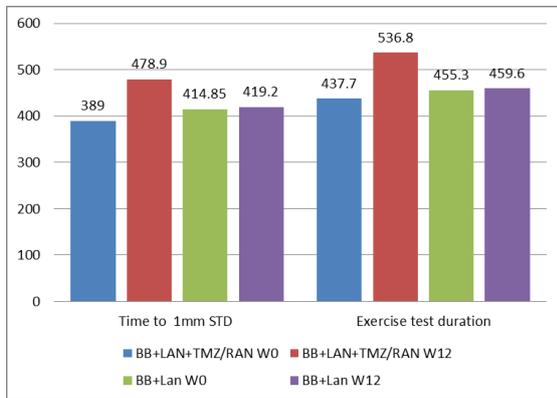


Figure 1: Time to 1 mm ST depression (STD) and exercise test duration at start (Wo) and 12 weeks (W12) between two groups.

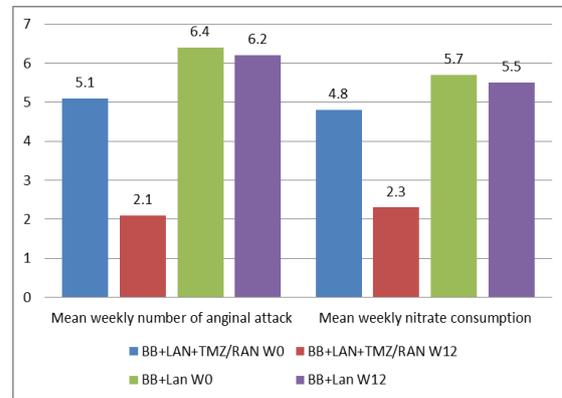


Figure 2: Mean weekly number of angina attack and mean weekly nitrate consumption at start (Wo) and 12 weeks(W12) between two groups.

Table 2: Echocardiographic parameters at start (Wo) and 12 weeks (W12) between two groups.

Variables	BB+LAN+TMZ/RAN WO W12	P-Value	BB+LAN WO W12	P-Value
1. LVIDd (mm)	58.8±1.9 to 52±1.7	<0.0001*	56.8±1.9 to 56.3±1.7	0.081
2. LVIDs (mm)	44.5±1.1 to 38.1±0.8	<0.0001*	42.4±1.8 to 41.9 ±2.1	0.108
3. LVEF (%)	47.5±3.8 to 52.6±8.3	<0.0001*	48.1±4.8 to 48.8±4.3	0.2938
4 E/A (m/s)	0.81±0.10 to 0.97±0.15	<0.0001*	0.79±0.16 to 0.78±0.17	0.6733

P value reached from Paired t-test, \*significant

Results from transthoracic echocardiogram (mean±SD) in triple anti-angina group(n=120) and double anti- angina group(n=80): Statistically significant improvement was observed in triple anti-angina group(p<0.0001). LV dimension (LVIDd-left ventricular internal dimension in diastole and LVIDs-left ventricular internal dimension in systole) was significantly decreased, Left ventricular ejection fraction(LVEF) was significantly better and for assessment of LV diastolic function LV inflow E/A ratio (peak E wave velocity and peak A wave velocity ratio) was also improved in triple anti-angina groups.

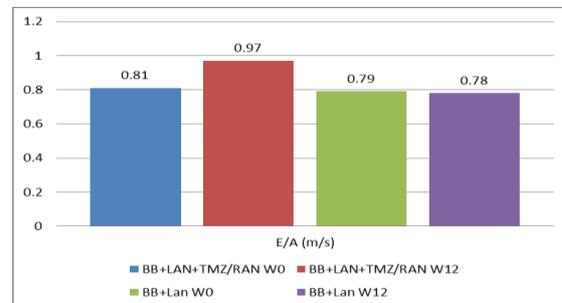


Figure 4: Left ventricular inflow (E/A ratio) for assessment of diastolic function at start (WO) and 12 weeks (W12) between two groups.

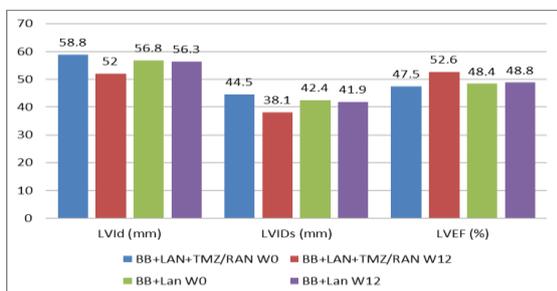


Figure 3: Left ventricular internal dimension in diastole (LVIDd), left ventricular internal dimension in systole (LVIDs) and left ventricular ejection fraction (LVEF) at strat (Wo) and 12 weeks (W12) between two groups.

### Limitations of study

We followed up the patients only for 3 months and longer-term follow-up may strengthen the results.

### CONCLUSION

The combination of trimetazidine or ranolazine with betablocker (BB) e.g metoprolol and long acting nitrate(LAN) significantly improves exercise stress test parameters of anginal symptom compare with double anti anginal (BB+LAN) therapy. These combinations also improve left ventricular diastolic and systolic function.

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