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Review Article

To Evaluate the 'Real World' Clinical Performance of Bisoprolol in Post-Myocardial Infarction with Left-Ventricular Dysfunction: TENACITY Study

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Abstract

Objective: To Study the impact of Bisoprolol on Heart Rate (HR) and Left Ventricular Ejection Fraction (LVEF) along with metabolic indicators of HbA1C and lipid profile in post-ACS Asians patients at 1 year. **Methods:** Retrospective data of 400 patients was collected and assessed for the effectiveness of oral Bisoprolol (1.25, 2.5, 5 and 10 mg) over a 1-year, in post-ACS patients with LVSD. Change in LVEF and HR as primary endpoints, and change in Lipid profile, HbA1C and ST segment deviation of J point as secondary endpoints were evaluated. **Results:** Patients having mean age of 55.28±7.9 years (29.75% female), showed significant improvement in LVEF (41.45±5.1% vs 48.73±5.5%) with a reduction in HR (85.06±5.64 vs 76.73±4.6 bpm) at the end of 1-year treatment (p=0.0001) with Bisoprolol (mean 4.15+1.4 mg). NYHA class improved from mean 1.6+0.5 to 1.11+0.31. Bisoprolol along with GDMT was neutral for HbA1C (6.2±0.6 % vs 6.1±0.7%; p=0.64), while serum lipids (Total Cholesterol: 199.7+7.6 vs 127.6+4.85 mg, p=0.001; TG: 196.2 +12.1 vs 111.7+6.88 mg%, p=0.001; LDL: 126.9+9.1 vs 62.4+5.51 p=0.001; HDL: 33.7+3 vs 42.8+1.9 p=0.001) improved due to statins started at baseline. Maximum ST deviation at J point in resting ECG was also lesser at 1 year as compared to baseline (0.29+1.5 mm vs 0.05+0.22 mm; p=0.0001). **Conclusion:** Bisoprolol started along with GDMT to patients in acute phase of post-ACS with LVSD significantly improved LVEF, with significant reduction in HR and ST segment deviation at J point, without adverse effect on lipid and HbA1C.

Keywords: Acute Coronary Syndrome; Bisoprolol; Heart Failure; Hfmref; Hfref

Introduction

Oral beta (β)-blockers have been an important part of primary pharmacotherapy and secondary prevention following acute myocardial infarction (AMI) irrespective of its severity, since almost 40 years. [1-3] Major guidelines recommend β-blocker therapy early after AMI in the absence of contraindications such as acute heart failure or risk of cardiogenic shock [4]. Early beta blockade (within 24 h of presentation) in AMI has been shown to improve patient outcomes [5].

According to the 2017 ESC Guidelines for the management of AMI, in patients presenting with ST-segment elevation, routine administration of β-blockers should be considered. β-blockers are recommended in patients with reduced left ventricular ejection fraction (LVEF). In hemodynamically stable patients, oral β-blocker initiation should be considered within the first 24 h [6]. The AHA/ACC guidelines for the management of patients with ST-elevation myocardial infarction (STEMI) recommended that oral β-blockers should be initiated in the first 24 hours in patients with no contraindications for the use of oral β-blockers (Level of Evidence: B) [1]. For patients with non-ST-elevation myocardial infarction (NSTEMI), the recommendation by the 2014 AHA/ACC guidelines is initiation of oral β-blockers within the first 24 h in the absence of heart failure (HF), low-output state, risk for cardiogenic shock, or other contraindications for β-blocker therapy (Level of Evidence: A) [2]. β-blockers reduce the heart rate (HR) and blood pressure thereby reducing the myocardial workload, and thus, oxygen demand [6- 7].

Cardiovascular disease (CVD) is often also associated with comorbidities such as diabetes mellitus (DM) and obesity; such patients are at an increased risk of developing major CV events. Moreover, metabolic syndrome and DM are associated with high adrenergic activity and cardiac output, further leading to myocardial and vascular damage [8]. Although β-blockers reduce the myocardial workload, they might also lead to elevation of blood sugar and glycated hemoglobin (HbA1c), worsening of insulin sensitivity, and changes in triglyceride and lipoprotein levels. These changes are mainly associated with β2 and β3 receptor blockade [9]. However, these effects are much lower with β1-selective agents. Further, it might be advisable to use β-blockers without intrinsic sympathomimetic activity (ISA) in patients with CVD. This is because β-blockers with ISA produce partial sympathetic activity while inhibiting the normal and activated sympathetic activity [10]. Chronic activation of the sympathetic nervous system increases myocardial oxygen demand, ischemia, and oxidative stress; moreover, high catecholamine levels induce peripheral vasoconstriction and increase both cardiac pre- and after-load, thus causing additional stress to the cardiac muscle [11]. The next generation β-blockers without ISA indicated for heart failure, include carvedilol, a non-selective β-blocker and Bisoprolol and metoprolol succinate, both of which are highly selective β-1 adrenergic receptor (cardio selective) blockers. These next generation β-blockers also improve insulin-sensitivity [12]. Bisoprolol and metoprolol succinate are generally administered once-daily while carvedilol is used twice-daily. This might also ensure better compliance to therapy [13].

Despite the recommendation for use of β-blockers following AMI, there is limited evidence about their benefit in patients with HFmEF (LVEF 40-50%) and their use in these patients is less documented. There are further concerns about the use of β-blockers in patients of HF with associated comorbidities, due to a potential negative effect of these drugs on symptoms, quality of life, and progression of the co-morbid condition. Thus, optimized pharmacological treatment for HF in these patients is critical [14] and hence each molecule from the class needs to be evaluated for its own efficacy and safety. There is paucity of data esp. for Bisoprolol in AMI especially in Asian Indians.

This study aimed to assess the effect of oral Bisoprolol treatment on HR after 1 year of treatment in patients with ACS with left ventricular dysfunction (LVD) with HFmHF and HFrEF (LVEF<50%). The patients were initiated on Bisoprolol during hospitalization for MI or at discharge. Additionally, the study aimed to assess the effect of Bisoprolol on LVEF as seen on echocardiography and ST segment changes on electrocardiogram (ECG). The real-world cohort included patients with comorbidities like diabetes, hypertension, and dyslipidemia. To evaluate the lipid and glycemic neutrality of oral Bisoprolol, blood glucose, HbA1c, and serum lipid levels were also measured.

Methods

This was a retrospective, observational, single-center study among consecutive adult patients who presented with ACS and having left ventricular dysfunction (LVD) with HFmHF or HFrEF (LVEF <50%). The study was conducted at a Tertiary care multispecialty Hospital in Western India. The primary objective was to assess the impact of oral Bisoprolol treatment on heart rate (HR) after 1 year of treatment. The secondary objectives were to assess the effect of Bisoprolol on LVEF as seen on echocardiography and ST segment changes on ECG. The secondary outcomes also analyzed the lipid and glycemic neutrality of oral Bisoprolol by measuring the blood glucose, HbA1c, and serum lipid levels. The data was obtained from indoor/outpatient case papers, ECG, echocardiography reports, and lab reports. The study was conducted according to the Good Clinical Practices (GCP) consensus and the Indian guidelines.

Patients admitted for AMI with LVD between 1st August 2016 to 30th June 2019 and initiated on oral Bisoprolol for the first time at the time of index hospitalization or at the time of discharge were included. The dose of Bisoprolol prescribed was 1.25 mg, 2.5 mg, 5 mg, or 10 mg at the discretion of the treating physician. Patients who had comorbidities like hypertension, dyslipidemia, or diabetes were treated with other concomitant medications as warranted, and per current practice guidelines at the discretion of the treating physician/cardiologist along with the dose adjustments for the concomitant medications. The patients' data was captured every 6 months for at least 1 year after discharge. The parameters evaluated were HR, BP, ST segment on EKG, LVEF on echocardiography, HbA1c, lipid profile, blood glucose levels, and New York Heart Association (NYHA) class.

Inclusion Criteria:

- AMI (NSTEMI and STEMI) with systolic LVD i.e., HFmEF or HFrEF (LVEF < 50%).
- Prescribed oral Bisoprolol (Concor) during hospitalization or at discharge after index hospitalization between 1st August 2016 to 30th June 2019.
- Availability of follow-up data for up to 1 year from the date of discharge and initiation of treatment.

Exclusion Criteria:

- Age <18 years at hospitalization.
- Patients prescribed β-blocker other than Bisoprolol on the index date.
- Patients who sought discharge against medical advice during hospitalization for AMI with incomplete revascularization.
- Patients who died during hospitalization for AMI.
- Patients presenting with high grade (II degree and III degree) AV block at the index date (contra-indication for β-blocker therapy)

Primary Outcome

- Mean change in HR from baseline to 1-year follow-up
- Mean change in LVEF at 6 months and at 1 year after initiation of Bisoprolol.

Secondary Outcomes

- Change in blood glucose levels (fasting and post prandial) and HbA1c at 6 months and at 1 year after initiation of Bisoprolol.
- Change in serum lipids levels at 6 months and at 1 year after initiation of Bisoprolol.
- ST segment changes on ECG from J point at 6 months and at 1 year after initiation of Bisoprolol.

Sample Size

The sample size was calculated as 385 and was rounded off to 400, based on the number of eligible patients treated with Bisoprolol at the site. The statistical considerations for calculating the sample size were as below:

- A difference of approximately 5% at 95% confidence interval in the primary endpoint from baseline to the end of the study.
- Precision = 5%
- Prevalence = 50%
- Population size = infinite
- 95% Confidence Interval specified limits [45% - 55%]

Statistical Analysis

Demographic and baseline characteristics are presented as descriptive statistics; categorical variables are presented as frequency and percentage. Continuous variables are presented as count, mean, standard deviation, median, minimum, and maximum. The statistical analysis was performed using SPSS v.22.

Results

The mean age of 400 patients was 55.28±7.9 years, and 29.75% were female. Significant improvement in LVEF (41.45±5.1% vs. 48.73±5.5%) see in (Figure 1) and significant reduction in HR (85.06±5.64 bpm vs. 76.73±4.6 bpm) compared to baseline was observed at the end of 1 year of treatment (p=0.0001 and p=0.0001 respectively) see in (Figure 2) with Bisoprolol (mean 4.15 + 1.4 mg). NYHA class improved from 1.6 + 0.5 to 1.11 + 0.31 at the end of 1 year.

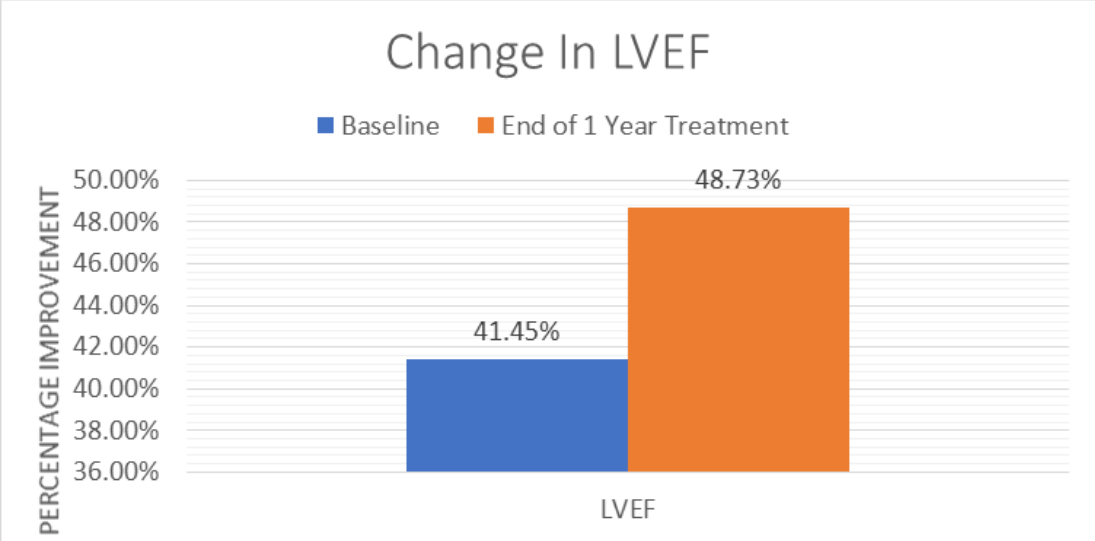

Figure:1 Change in LVEF

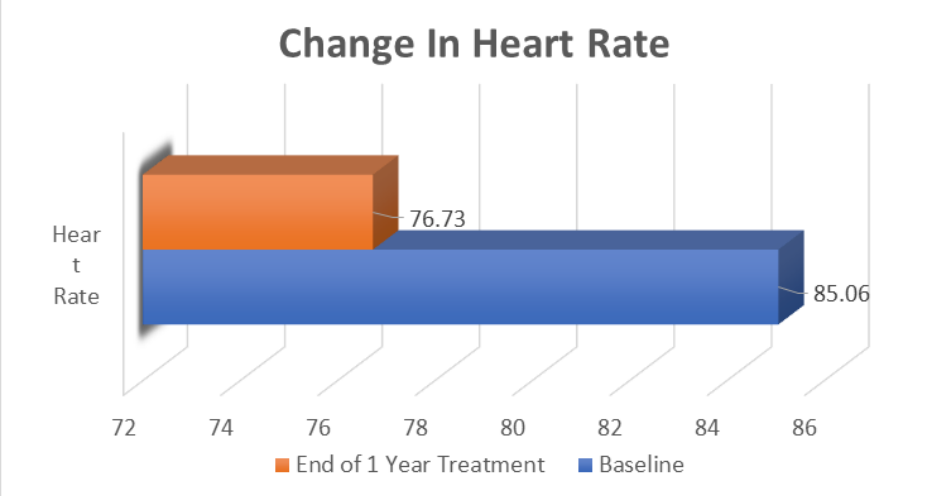

Figure:2 Change in Heart Rate

Bisoprolol therapy along with Guideline directed medical treatment (GDMT) showed no significant change in HbA1c (6.2±0.6 % vs. 6.1±0.7%; p=0.64) see in (Figure 3) Serum lipids (total cholesterol: 199.7 + 7.6 vs. 127.6 + 4.85 mg/dL, p=0.001; TG: 196.2 +12.1 vs. 111.7 + 6.88 mg/dL, p=0.001; LDL: 126.9 + 9.1 vs. 62.4 + 5.51 mg/dL, p=0.001; HDL: 33.7 + 3 vs. 42.8 +1.9 mg/dL, p=0.001) improved at 1 year due to statins see in (Figure 4) Maximum ST deviation at J point in resting ECG was also lesser at 1 year compared to baseline (0.29 + 1.5 mm vs. 0.05 + 0.22 mm; p=0.0001).

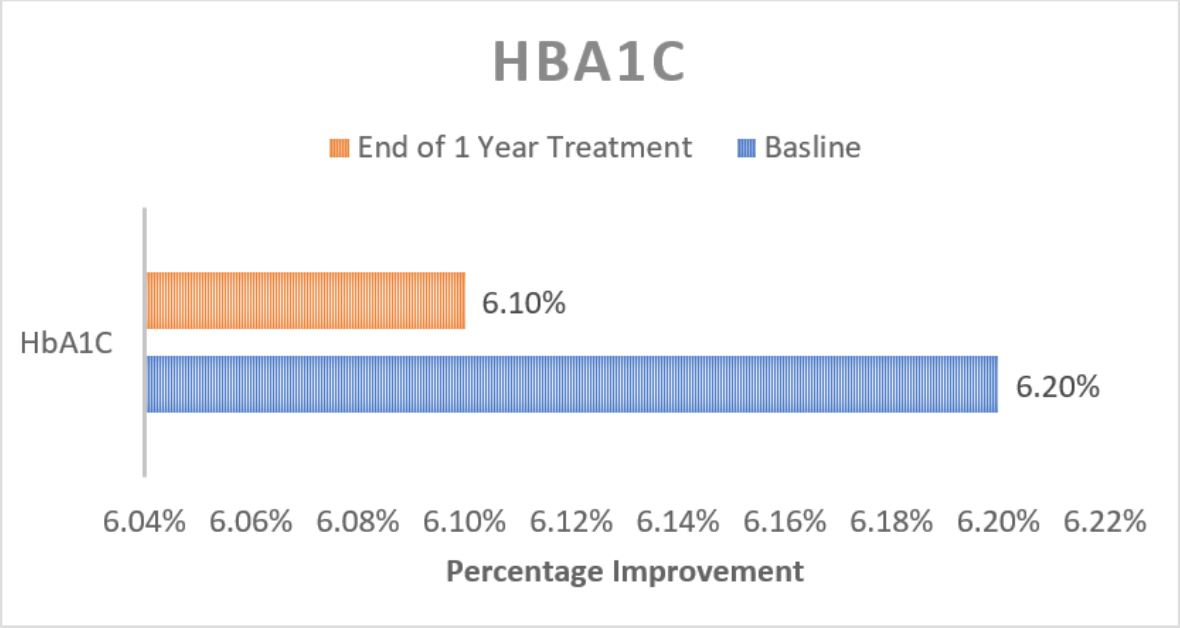

Figure 3: Change in HbA1c.

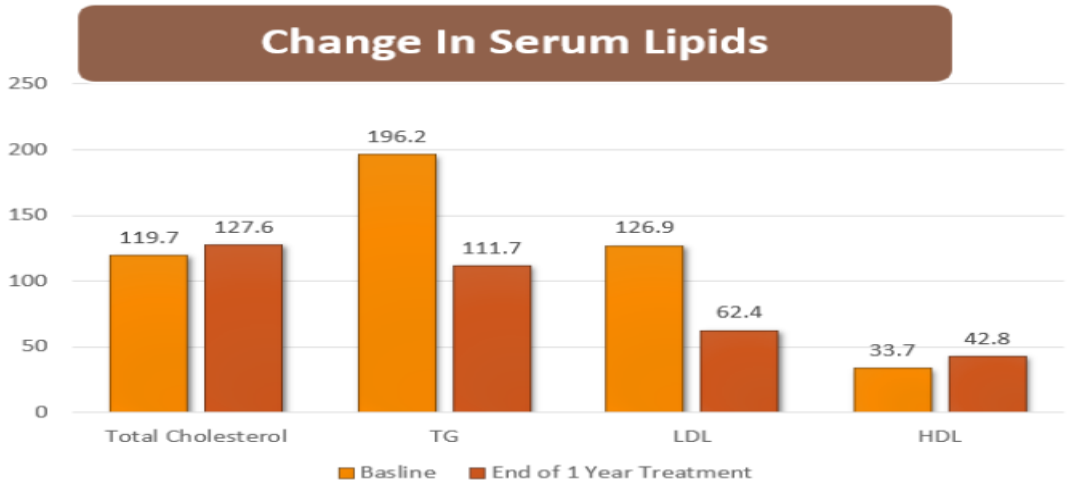

Figure 4: Change in Serum Lipids.

Discussion

The main findings of the study were an improvement in LVEF and decrease in HR after 1 year of treatment with Bisoprolol in patients with AMI, who were initiated on the drug during hospitalization for MI or at discharge. Maximum ST deviation at J point in resting ECG was also lesser at 1 year than at baseline. Reduced HR is associated with improved prognosis in patients with HF. ESC guidelines for the management of chronic IHD include a target for resting HR of 55–60 bpm, and US guidelines have recommended a target for HR of 50–60 bpm in these patients [4]. However, there is no clear consensus regarding the appropriate time to initiate treatment with β-blockers in patients with acute coronary syndrome (ACS). Clinical trials and meta-analyses have demonstrated the benefit of starting β-blocker therapy early after AMI. Nicolau et al. retrospectively analyzed the short-term in-hospital mortality and the long-term outcome in patients receiving oral β-blockers within the initial 24 h of hospitalization vs. those who did not receive β-blocker therapy. Those receiving β-blocker therapy showed a lower rate of in-hospital mortality and a greater long-term mean survival time (11.9 years vs. 9.9 years, $p<0.001$). Further, it was seen that there was no significant benefit in terms of lower in-hospital mortality in patients with LVEF> 55% [15]. Bu Giardini et al. also compared the outcomes of early (<24 hrs after hospital admission) vs. later (>24 hours) administration of β-blockers in patients with ACS. They found that early β-blocker therapy was significantly associated with reduced in-hospital mortality and reduced incidence of severe LVD [16]. A large meta-analysis of observational studies (26 trials, N=863,335) conducted in 2014 in patients with IHD who also underwent percutaneous revascularization found a reduction in the risk of mortality among patients taking vs. those not taking β-blocker therapy. This beneficial effect was seen irrespective of the nature of the IHD (ACS or chronic stable angina), or LVEF [17]. Fernando et al. reported that in patients with post-ACS having mid-range ejection fraction, β-blocker administration was associated with in-hospital survival benefit [18]. Another study among 2028 patients with LVEF>40 after AMI reported that prior β-blocker use or its administration within 24 hours decreased in-hospital mortality. Further, initiation of β-blocker on discharge decreased 1-month mortality; however, there was a neutral effect on mortality, reinfarction, and stroke at 6 and 12 months [19]. Most studies about the effect of Bisoprolol in patients post MI were performed in the pre-revascularization era. Among recent studies, a study involving 399 patients with NSTEMI administered low-dose oral Bisoprolol (1.25–2.5 mg) within 24 hrs of admission showed reduced incidence of major adverse cardiovascular events (MACE—defined as ventricular arrhythmia, cardiac death or repeat infarction). The outcomes were better in those who received early Bisoprolol therapy (≤4 h), than in those who were initiated on Bisoprolol later (5–24 h). For each hour that Bisoprolol administration was delayed, the risk of subsequent inpatient MACE increased by 8% [20]. Another study among 1806 patients treated with Bisoprolol at the time of discharge post-MI demonstrated the benefit of Bisoprolol in the secondary prevention of AMI regardless of the presence of heart failure [21]. A cohort study of patients with STEMI by Hirschl et al found that administering 2.5 mg of oral Bisoprolol within 30 min of presentation reduced all-cause and cardiovascular mortality compared with conventional Bisoprolol therapy given at 24 h [22]. Lin et al investigated the long-term outcomes of patients with STEMI treated with different β-blockers (carvedilol, Bisoprolol and propranolol) and found that the use of Bisoprolol or propranolol is associated with a reduction in all-cause death and cardiovascular death compared with use of carvedilol. Nevertheless, after adjusting for baseline characteristics, no significant differences were observed between the three β-blockers in terms of decrease in mortality [23]. However, unlike our study, the previous studies did not investigate the effect of early β-blocker therapy in improving the HR, LVEF, and ST deviation at 1 year post MI. Most studies focused on mortality and MACE outcomes. Thus, our findings make a significant contribution to the existing evidence.

Our study also showed that in patients with diabetes, treatment with Bisoprolol did not affect the HbA1c at the end of 1 year. Another important finding was a significant improvement in lipid levels due to concomitant administration of statins in drug naïve patients. Many reports have described a worsening of glycemic control during treatment with a β-blocker and use of a cardio-selective agent helps to minimize these effects. It has been reported that Bisoprolol has not been associated with worsening of glycemia [24]. Previous evidence indicates that use of Bisoprolol for patients with HFrEF having DM

substantially reduces morbidity and mortality [25]. A study evaluated the impact of β-blockers over 6 months on insulin resistance and lipid metabolism. It found that Bisoprolol significantly decreased homeostasis model assessment-estimated insulin resistance (HOMA-IR) index by 17.4% ($p < 0.05$), and fasting glucose by 10% ($p<0.05$). It was also seen that the TG decreased from 1.67 ± 0.13 mmol/l to 1.58 ± 0.15 mmol/l, ($p>0.05$) and total cholesterol decreased from 6.35 ± 0.19 mmol/l to 5.78 ± 0.18 mmol/l ($p=0.02$) in patients taking Bisoprolol [26]. A recent meta-analysis found that HDL cholesterol levels increased significantly in essential HT patients treated with Bisoprolol at 26 weeks, 78 weeks, and 104 weeks [27]. However, no previous studies have investigated the metabolic neutrality of Bisoprolol in post-ACS patients with HFmEF or HFrEF. Moreover, most studies were conducted in the pre-vascularization era when the management of patients during and post MI was different than that followed in current times. Thus, our findings make an important contribution to the literature about the metabolic neutrality of selective β1-blocker Bisoprolol in the contemporary management of patients post MI.

Limitations

The first limitation of the study is that Bisoprolol dose titration was left to the discretion of the treating consultant leading to heterogeneity of the sample. Second, the dose of antidiabetic, anti-dyslipidemia, and antihypertensive medications were adjusted as necessary. Hence, it is difficult to conclusively confirm the metabolic neutrality of Bisoprolol. Being a single center, retrospective study, the results need to be evaluated further in prospective, randomized multi-centric study.

Conclusion

Bisoprolol started along with GDMT to patients in acute phase of post-ACS with LVSD significantly improved LVEF with significant reduction in heart rate and ST segment deviation at J point at 1 year without adverse effect on lipid and HbA1C.

Ethics Approval and Informed Consent

This study was approved by the Sanjivani Super Specialty Hospital Pvt. Ltd Ethics Committee. Informed consent was obtained from all individual participants included in the study.

Data Transparency

All data and materials as well as software application or custom code used in the current study support the data presented and claims made in the current study and comply with the field standards of scientific writing, credibility, authenticity and personal honesty.

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Authors Contributions

Kamal Sharma was the Principal Investigator and proposer for Investigator initiated study. All authors contributed equally towards the manuscript.

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published. The authors thank Dr. Punit Srivastava Mediception Science Pvt. Ltd (www.mediception.com) for providing medical writing support as and when required in the preparation of this manuscript.

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