

An Observational Study to Compare the Anti Anginal Efficacy of Ranolazine versus Nicorandil in Ischemic Heart Disease Patients Attending a Tertiary care Hospital in Kolkata India

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Abstract

Ischemic Heart disease (IHD) occurs due to an imbalance between myocardial oxygen supply and demand. In stable IHD, second-line anti-anginal drugs like Ranolazine and Nicorandil are used as add-on therapy with first-line agents like Nitrates and beta-blockers. Our study compared the efficacy of Ranolazine versus Nicorandil utilizing the patient's responses to Short Seattle Angina Questionnaire (SAQ7) score. A prospective observational study on stable IHD patients attending the cardiology Outpatient Department (OPD) of IPGME&R and SSKM Hospital, Kolkata, with either Ranolazine or Nicorandil as add-on therapy (50 patients in each group). SAQ7 score was recorded at baseline and three follow-up visits (1.5, 3, and 6 months). Adverse effects and the changes in HbA1C levels in diabetic patients among these patients were also compared. There was a significant increase in SAQ7 score in Ranolazine [median (IQR) - 26.50 (25.00 - 29.25) to 32.00 (30.75 - 34.00), $p < 0.0001$] and also in Nicorandil [median (IQR) - 27.00 (24.00 - 30.00) to 32.50 (31.00 - 34.00), $p < 0.0001$] group in third follow up visits from baseline. The comparison between the groups didn't show any significant changes. There were no significant changes in HbA1C levels between the pre and post-treatment period. Adverse effects were more in the Nicorandil group. Both drugs significantly improved IHD patients' symptom control and were well tolerated. There were no significant differences in the change of HbA1C level in Diabetic patients. However, a larger study is required to decide whether these drugs can be used as a single agent alone.

Keywords: Ischemic Heart disease, Ranolazine, Nicorandil, Short Seattle Angina Questionnaire (SAQ7) score

Introduction

Ischemic Heart disease (IHD) is a condition characterized by an inadequate supply of blood and oxygen to a portion of the myocardium due to an imbalance between myocardial oxygen supply and demand. The patients typically complain of episodes of chest discomfort, heaviness, or squeezing sensation, and rarely frank pain. Upon clinical suspicion of angina, the patient undergoes several biochemical tests and imaging, i.e., blood tests for lipid profile (total cholesterol, LDL, HDL, and triglycerides), glucose including HbA1C, creatinine, ECG, and Echocardiogram to assess the systolic and diastolic function of heart and cardiovascular system.¹

The anti-anginal agent Ranolazine exerts its effects without affecting the heart rate, arterial blood flow, or coronary blood flow. Ranolazine inhibits late Na⁺ current, which may contribute to arrhythmias in IHD patients. Inhibition of this current decreases Na⁺-dependent Ca²⁺ overload and its detrimental effects on myocardial ATP hydrolysis and cardiac function.² Few studies revealed that Ranolazine has additional HbA1C lowering effects, which provides additional benefits in Type 2 Diabetes Mellitus patients without any accompanying hypoglycemia.

Nicorandil has nitrate-like (cGMP-dependent) properties and has agonistic action at ATP-sensitive potassium (K_{ATP}) channels. It dilates both arterial and venous vascular beds, thereby reducing afterload and preload of the heart. Experimental and clinical studies suggested a cardioprotective effect of Nicorandil mimicking that of ischemic preconditioning. It is a phenomenon in which short periods of ischemia preceding prolonged stopping of perfusion (as in MI) reduce myocardial injury.¹ Trimetazidine, another anti-anginal drug, is a metabolic modulator also known as a partial Fatty Acid Oxidation (pFOX) inhibitor

that partially inhibits the fatty acid oxidation pathway in myocardium.² Ivabradine is a newer anti-anginal drug causing bradycardia by inhibiting hyperpolarization-activated sodium channels in the sinoatrial node.³

Seattle Angina Questionnaire (SAQ) is a validated disease-specific health status instrument for coronary artery disease (CAD) with high test-retest reliability, predictive power, and responsiveness.⁴ A shortened version of this instrument, SAQ-7, has also been validated and can be used to evaluate patients with stable CAD.⁴ The European Society of Cardiology (ESC) guidelines⁵ and National Institute for Health and Care Excellence, UK (NICE) guidelines⁶ recommend the use of a second-line anti-anginal drug like Ranolazine, Nicorandil, Trimetazidine or Ivabradine as an add-on therapy in patients inadequately responding or poorly tolerating the first line anti-anginal drugs. While some studies and meta-analyses were conducted with anti-anginal first-line medicines as well as a few second-line drugs, studies comparing the efficacy of Ranolazine versus Nicorandil as an add-on therapy are lacking, especially in India. The present study, therefore, was planned to address this issue involving these two commonly used drugs.

Methods

A prospective observational study with longitudinal follow-up was undertaken with patients attending the cardiology OPD of IPGME&R and SSKM Hospital, Kolkata, India. Patients were recruited according to the inclusion and exclusion criteria stated below. The study period was 18 months from commencement. Fifty patients having stable IHD who received Tab Ranolazine 500 mg twice daily and 50 others who received Tab Nicorandil 5 mg twice daily as add-on therapy were followed up for 6 months with 2 interim follow-up visits at 1.5 months and 3 months.

Inclusion criteria were stable IHD patients of either gender between ages 20-65 years and poorly controlled on any of the first-line anti-anginal agents like nitrates, beta-blockers, or calcium channel blockers.

Exclusion criteria were any life-threatening comorbidity, anemia or critical conditions like acute coronary syndrome or acute heart failure. Baseline demographic and clinical variables were noted. SAQ 7 score was used as an outcome parameter and was recorded at the beginning of the study and each follow-up visit.⁶ Primary objective was to assess the anti-anginal efficacy of Ranolazine versus Nicorandil as add-on therapy with first-line anti-anginal-agents in known IHD patients. The secondary objective was to assess changes in HbA1C level caused by both the drugs, if any, and to assess the adverse effects caused by them.

The study commenced after ethical approval from the Institutional Ethics Committee at IPGME&R, Kolkata - India. Written informed consent was taken from all patients and with all respect for their privacy and confidentiality. The study was registered with Clinical Trials Registry-India (CTRI) with reg no. CTRI/2020/10/028644.

Data was analyzed by routine descriptive statistics, namely mean and standard deviation for numerical variables and counts and percentages for categorical variables. Intragroup comparisons were done using a paired T-test for parametric data and a Wilcoxon matched-pairs signed-ranks test for nonparametric data, as applicable. The chi-square test was employed for the intergroup comparison of categorical variables. Analyses were two-tailed, and the level of statistical significance was set at $p < 0.05$ for all comparisons. (Software used: IBM SPSS statistics version 20).

Results and Discussion

Results

Table 1. Baseline age (mean + SD) in Ranolazine group was (53.30 +7.675) years and baseline age in Nicorandil group was (53.20 +6.899) years; $p = 0.9455$.

Table 2. At baseline in Ranolazine group, FBS (mean + SD) was 106.74 + 17.72 where as in Nicorandil group it was 104.64 + 16.86; $p = 0.2435$.

Table 7. Changes in FBS in Ranolazine after 6 months: At baseline in Ranolazine group, the mean + SD of FBS was 106.74 +17.72 and after 6 months of treatment became 106.12 +32.73, $p = 0.0019$.

Table 8. Changes in FBS in Nicorandil after 6 months: At baseline in Nicorandil group, mean + SD of FBS was 104.6 +16.86 and after 6 months of treatment became 104.0 +25.38, $p = 0.0053$

Figure 1. In Ranolazine group 35 were male, 15 female and in Nicorandil group 36 were male and 14 were female; $p > 0.05$.

Figure 2. In Ranolazine group, 20 participants were businessmen, 4 farmers, 7 housewives, 11 retired, 7 service-men, 1 painter. In Nicorandil group, 18 participants were businessmen, 4 farmers, 8 housewives, 9 retired, 10 service-men, 1 painter; $p > 0.05$.

Figure 3. About 15 people in the Ranolazine group were diabetics where, whereas 13 people in the Nicorandil group were diabetics. In the Ranolazine group, 20 people had hypertension whereas in the Nicorandil group, 17 patients had hypertension. About 12 people in the Ranolazine group had dyslipidemia where, whereas 9 people in the Nicorandil group had dyslipidemia. In the Ranolazine group, 17 patients had family

H/O IHD, whereas in the Nicorandil group, 19 people had family H/O IHD.

Figure 4. At baseline in Ranolazine group, PPBS (mean + SD) was $135.0 + 55.34$. In Nicorandil group it was $(123.1 + 32.55)$; $p = 0.4715$

Figure 5. At baseline in the Ranolazine group, total Cholesterol (mean + SD) was $161.7 + 41.73$. In Nicorandil group it was $151.7 + 40.30$; $p = 0.2227$.

Figure 6. At baseline in Ranolazine group, the mean + SD of LDL was $51.18 + 14.82$. In Nicorandil group it was $50.26 + 13.01$; $p = 0.9521$.

Figure 7. Data analysis was done with patients who completed 6 months of treatments and attended at-least 2 follow-up visits. The baseline age (mean + SD) in the Ranolazine add-on group was $53.30 + 7.675$ years, and in the Nicorandil add-on group was $53.20 + 6.899$ years, and there was no significant difference between the two groups ($p = 0.9455$). In the Ranolazine group, 35 were male, 15 were female, 36 were male and 14 were female in the Nicorandil group. There were no significant differences in gender and occupation between the groups ($p > 0.05$).

In the Ranolazine group, 17 people had a family history of IHD; in Nicorandil, group 19 had a family history of IHD with no significant difference between groups ($p > 0.05$). Regarding comorbidities among subjects, in the Ranolazine group, 20 had Hypertension, 15 had Diabetes Mellitus, and 12 had Dyslipidemia, and in the Nicorandil group, 17 had hypertension, 13 had Diabetes Mellitus, and 9 had Dyslipidemia. There was no significant difference between groups ($p = 0.1991$).

Regarding other laboratory parameters, i.e., Fasting and post-prandial blood sugar (FBS, PPBS), Total Cholesterol, and LDL, there were no significant differences between the groups ($p > 0.05$). But after 6 months of treatment, in the case of Ranolazine and Nicorandil, there were changes in (mean + SD) FBS, $p = 0.0019$ and $p = 0.0053$, respectively, from the baseline. This may not be a reflection of potential anti-diabetic activity as the SD was relatively wide (Fig. 16, Fig. 18). In case of baseline SBP and DBP, there were no significant differences between two groups.

Figure 8. Regarding Seattle Angina Questionnaire 7 score or Short SAQ7 score baseline values were comparable between the study groups.. There were significant differences in SAQ7 score from baseline in both groups separately at 3 and 6 months both ($p < 0.0001$) but a comparison of changes in SAQ7 score after 3 and 6 months in between the group found no significant difference ($p = 0.6257$ and $p = 0.5301$ respectively).

Figure 12. HbA1C: In Ranolazine group among 15 diabetics patients, the mean+ SD of HbA1C was $7.260 + 1.137$ and after 6 months of treatment the mean+ SD of HbA1C became $7.093 + 0.8319$, $p = 0.7971$. In Nicorandil group among 13 diabetics patients, the mean+ SD of HbA1C was $7.054 + 0.7264$ and after 6 months of treatment became $6.923 + 0.5434$, $p = 0.8491$.

Figure 14. Several adverse effects were observed in both groups which were self limiting in nature and didn't require treatment discontinuation. However the number of adverse effects was greater in Nicorandil group with no significant difference between groups regarding any adverse effect.

Figure 16. Changes in SBP in Ranolazine after 6 months: At baseline in Ranolazine group,

the (mean + SD SBP was 129.8 +15.71 and after 6 months of treatment became 123.4 +9.817, $p = 0.0216$. Such significant lowering of SBP was not observed in Nicorandil group

Figure 18. The baseline SAQ7 score [median (IQR)] in Ranolazine group was 26.50 (25.00-29.25) which significantly increased to 31.00 (29.00-33.00) and 32.00 (30.75-34.00) after 3 and 6 months of follow-up respectively ($p < 0.0001$ in both the scenario). In case of Nicorandil, the baseline SAQ7 score [median (IQR)] was 27.00 (24.00-30.00) which significantly increased to 31.00 (29.00-33.00) and 32.50 (31.00-34.00) after 3 and 6 months of follow-up respectively ($p < 0.0001$).

In both groups there were few adverse effects, mostly self-limiting and with no significant intergroup difference for any of them. No adverse effect required treatment discontinuation. In Ranolazine group there were altogether 16 adverse effects, most common being dizziness, 8 in number followed by Headache (6) and Palpitations (2). In Nicorandil group also Dizziness was the leading adverse effect, 10 in number followed by Flushing (7) and Palpitations (4). There were altogether 21 adverse effects in Nicorandil group.

Discussion

Ischemic Heart disease (IHD) causes considerable morbidity and mortality across the world and warrants lifestyle modification along with pharmacotherapy with first line anti anginal drugs like nitrates and beta blockers for satisfactory management. Existing guidelines also recommend the use of second line drugs like Ranolazine, Nicorandil, Trimetazidine or Ivabradine as add on therapy in patients inadequately responding or poorly tolerating the first line drugs. While some researches were conducted on these drugs, no study in South East Asia till date has compared these

two commonly used drugs Ranolazine and Nicorandil for their efficacy and tolerability. Our study attempted to address this issue using SAQ⁷ score for improvement in stable IHD patients. The ARETHA AT observational study⁷ (Austria) found a significant reduction in angina frequency and Nitroglycerin consumptions when Ranolazine was used as add on therapy with Calcium channel blockers (CCB) or Beta blockers.

The TERISA trial⁸ found that weekly angina frequency was significantly lower with Ranolazine versus placebo. A meta-analysis of randomized controlled trials of Ranolazine, Nicorandil and Ivabradine was conducted where the secondary outcome was the Seattle Angina Questionnaire (SAQ) scores showed Ranolazine and Ivabradine improved 3 of the 5 SAQ scores. Our study also found significant improvement in SAQ score with Ranolazine after 3 months of use but not at 1.5 months. It also recorded a significant reduction of systolic blood pressure upon 6 months of use. Kobara et al⁹ had shown that Nicorandil suppresses ischemia-induced norepinephrine release and ventricular arrhythmias in hypertrophic hearts.

In an animal model of myocardial infarction with rats Chen et al¹⁰ found that Nicorandil inhibits TLR4/ MyD88/NF- κ B/NLRP3 signaling pathway to reduce pyroptosis. The CHANGE Trial¹¹ documented that administration of nicorandil before primary percutaneous coronary intervention led to improved myocardial perfusion grade and reduced infarct size in patients with ST segment-elevation myocardial infarction. Tarkin et al¹² found that nicorandil is comparably effective for angina prophylaxis to long-acting nitrates and other conventional anti-anginal drugs. Ito et al¹³ showed a beneficial effect of intracoronary nicorandil on microvascular dysfunction after primary percutaneous coronary intervention:

demonstrated its superiority to nitroglycerin in a cross-over study. Our study has found a significant improvement in stable IHD patients on Nicorandil as add on therapy after 3 months and 6 months of use but not after 1.5 months.

Another meta-analysis involving the effects of Ranolazine on HbA1C in diabetic patients had shown that Ranolazine improves HbA1c without increasing the risk of hypoglycaemia.¹⁴. However, in our study, among 15 diabetic patients in Ranolazine group and 13 in Nicorandil group no significant change of FBS, PPBS or HBA1C upon 6 months of use was found. Both drugs were well tolerated and no significant difference was found between them in terms of efficacy and tolerability. Moreover, the significant SBP reduction with Ranolazine found in our study was not reported in earlier research conducted and may warrant another study in future regarding the same.

Conclusion

This study shows significant improvements in patients after adding the second line agents for both the drugs with comparable efficacy. No significant changes in HbA1C level between pre and post treatment period in any group was found, though a larger sample size is required to comment on this. The incidences of adverse effects were more in Nicorandil group though none of them was serious enough to warrant treatment discontinuation and both of the drugs seem suitable as second line antianginal agents.

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Conflict of Interest

None declared.

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Table 1. Baseline Characteristics

Characteristics	Number (n)	Number (%)
Sex		
Male	71	71
Female	29	29
Marital Status		
Single	2	2
Married	82	82
Widow	16	16
Age (Years)		
20-35	2	2
36-50	30	30
51-65	68	68
Comorbidities		
Diabetes	28	28
Hypertension	37	37
Dyslipidemia	21	21

Table 2. Baseline Laboratory and Clinical Parameter

Variabel	Ranolazine Add-on Group (n=50)	Nicorandil Add-on Group (n=50)	P-value
FBS (mg/dL) (mean $\pm$ SD)	106.74 $\pm$ 17.72	104.64 $\pm$ 16.86	0.2435
PPBS (mg/dL) (mean $\pm$ SD)	135.0 $\pm$ 55.34	123.1 $\pm$ 32.55	0.4715
Total Cholesterol (mg/dL) (mean $\pm$ SD)	161.7 $\pm$ 41.73	151.7 $\pm$ 40.30	0.2227
LDL (mg/dL) (mean $\pm$ SD)	51.18 $\pm$ 14.82	50.26 $\pm$ 13.01	0.9521
SBP (mmHg) (mean $\pm$ SD)	129.8 $\pm$ 15.71	128.8 $\pm$ 16.24	0.6461
DBP (mmHg) (mean $\pm$ SD)	71.80 $\pm$ 8.734	74.60 $\pm$ 7.879	0.0770

**Table 3. SAQ7 Score [median (IQR)] at Different Time-points
of the Study in Both the Group**

Groups		SAQ 7 score [median (IQR)]			
Timeline	Baseline	1.5 months	3 months	6 months	
Ranolazine	26.50 (25.00-29.25)	29.00 (27.25- 32.00)	31.00 (29.00-33.00)	32.00 (30.75-34.00)	
Nicorandil	27.00 (24.00-30.00)	29.00 (27.00-31.00)	31.00 (29.00-33.00)	32.50 (31.00-34.00)	

**Table 4. Changes in SAQ7 Scores Over Time from Baseline
Between Ranolazine and Nicorandil [median (IQR)]**

Timeline	Ranolazine	Nicorandil	P value
3 months	3.500 (2.000-5.000)	4.000 (3.000-5.250)	0.6257
6 months	5.000 (3.000-7.000)	5.000 (4.000-7.000)	0.5301

Table 5. Changes in HbA1C level (mean + SD) among Diabetic Patients after 6 months

Groups	Baseline	6 months	P value
Ranolazine (n=15)	7.260 ± 1.137	7.093 ± 0.8319	0.7971
Nicorandil (n=13)	7.054 ± 0.7264	6.923 ± 0.5434	0.8491

Table 6. Adverse Effects

Adverse effects	Ranolazine	Nicorandil
Dizziness	8	10
Headache	6	0
Flushing	0	7
Palpitation	2	4
Total	16	21

Table 7. Changes in Laboratory and Clinical Parameters in Ranolazine group

Variables	Baseline	6 months	P value
FBS (mg/dl) (mean ± SD)	106.7 ± 17.72	106.12 ± 32.73	0.0019*
PPBS (mg/dl) (mean ± SD)	132.8 ± 35.76	135.0 ± 55.34	0.1273
Total Cholesterol (mg/dl) (mean ± SD)	161.7 ± 41.73	160.8 ± 36.74	0.9003
LDL (mg/dl) (mean ± SD)	51.18 ± 14.82	51.10 ± 11.88	0.5907
SBP (mmHg) (mean ± SD)	129.8 ± 15.71	123.4 ± 9.817	0.0216**
DBP (mmHg) (mean ± SD)	71.80 ± 8.734	73.60 ± 7.762	0.2052

* Significant changes observed in FBS after 6 months of treatment (p= 0.0019)

**Significant changes observed in SBP after 6 months of treatment (p= 0.0216)

Table 8. Changes in Laboratory and Clinical Parameters in Nicorandil group

Variables	Baseline	6 months	P value
FBS (mg/dl) (mean ± SD)	104.6 ± 16.86	104.0 ± 25.38	0.0053*
PPBS (mg/dl) (mean ± SD)	121.8 ± 24.43	123.1 ± 32.55	0.6002
Total Cholesterol (mg/dl) (mean ± SD)	151.7 ± 40.30	149.9 ± 34.60	0.9877
LDL (mg/dl) (mean ± SD)	50.26 ± 13.01	49.94 ± 9.305	0.3681
SBP (mmHg) (mean ± SD)	128.8 ± 16.24	123.0 ± 10.15	0.0768
DBP (mmHg) (mean ± SD)	74.60 ± 7.879	71.40 ± 7.287	0.0561

* Significant changes observed in FBS after 6 months of treatment (p= 0.0053)

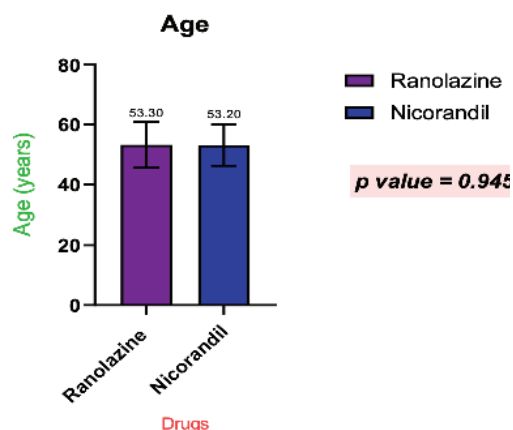


Figure 1. Baseline age (mean + SD) (N=100)

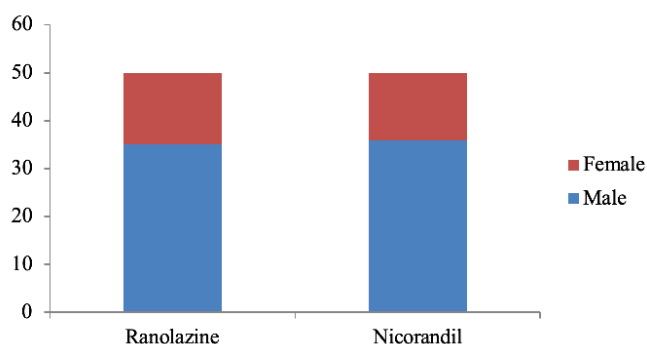


Figure 2. Gender of the Subjects of Both the Group

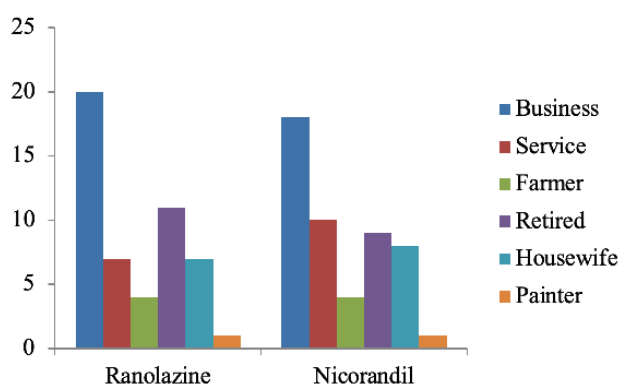


Figure 3. Occupations of the Subjects of both the Group

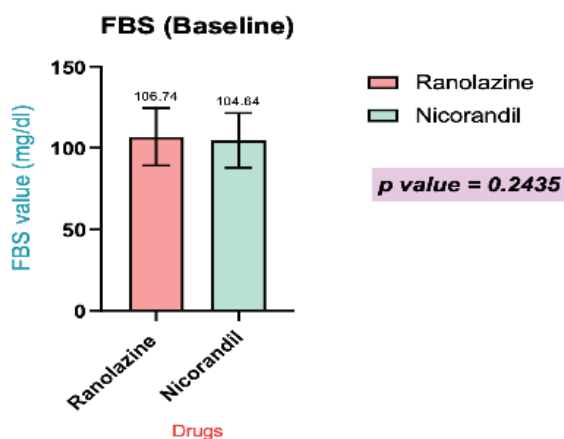


Figure 4. Baseline FBS (mean + SD) (N=100)

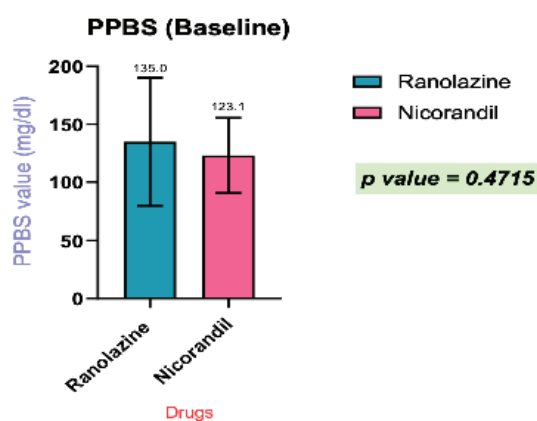


Figure 5. Baseline PPBS (mean + SD) (N=100)

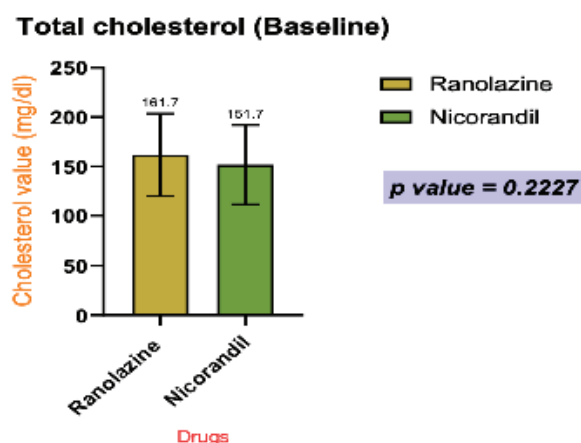


Figure 6. Baseline Total Cholesterol (mean + SD)(N=100)

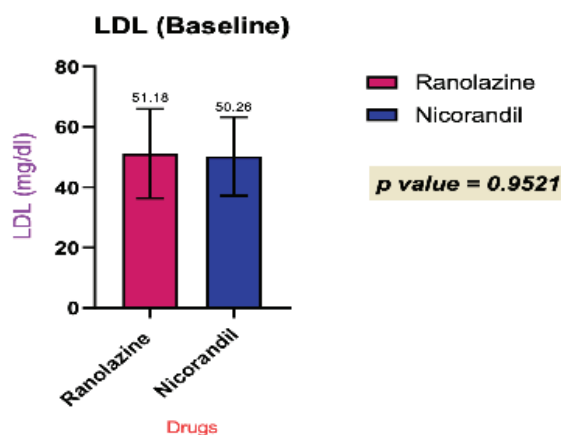


Figure 7. Baseline LDL (mean + SD) (N=100)

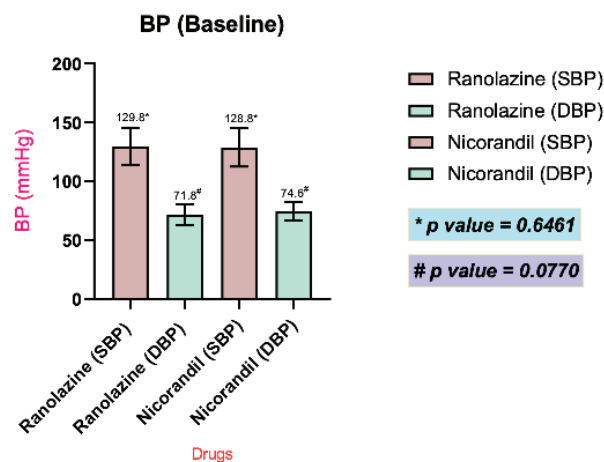


Figure 8. Baseline BP (SBP and DBP) (mean + SD) (N=100)

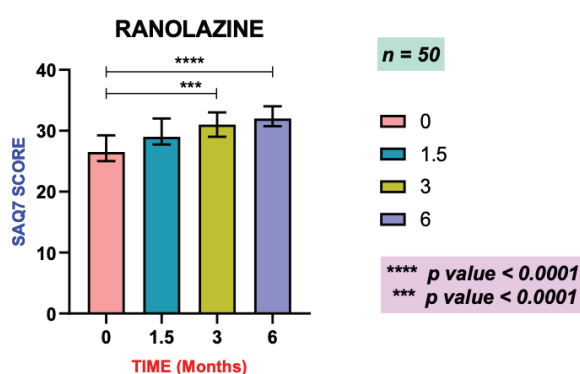


Figure 9. Change of SAQ7 score [median (IQR)] over time with Ranolazine

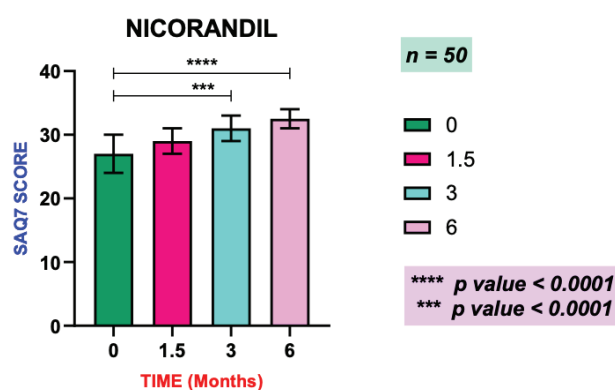


Figure 10. Change of SAQ7 score [median (IQR)] over time with Nicorandil

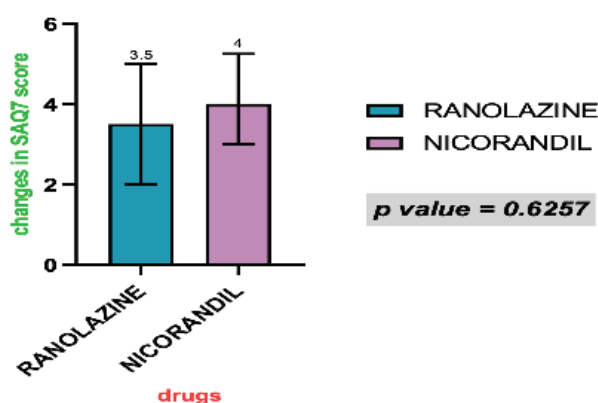


Figure 11. Changes in SAQ7 scores after 3 months between Ranolazine and Nicorandil [median (IQR)]

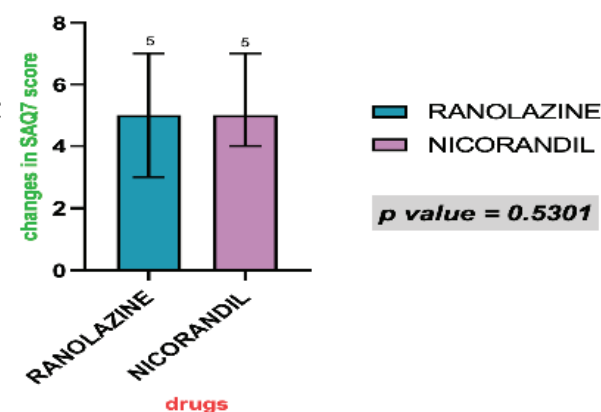


Figure 12. Changes in SAQ7 scores after 6 months between Ranolazine and Nicorandil [median (IQR)]

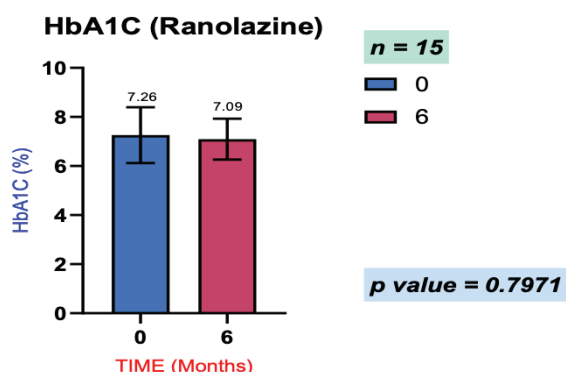


Figure 13. Changes in HbA1C level (mean + SD) among diabetic patients in Ranolazine group after 6 months

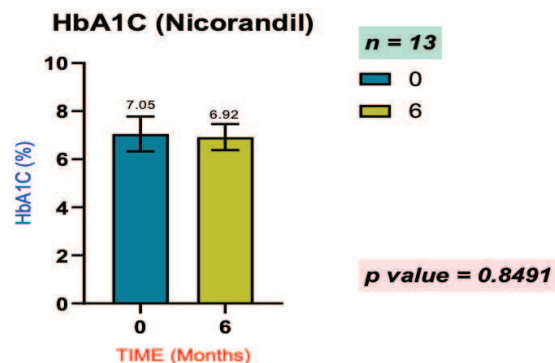


Figure 14. Changes in HbA1C level (mean + SD) among diabetic patients in Nicorandil group after 6 months

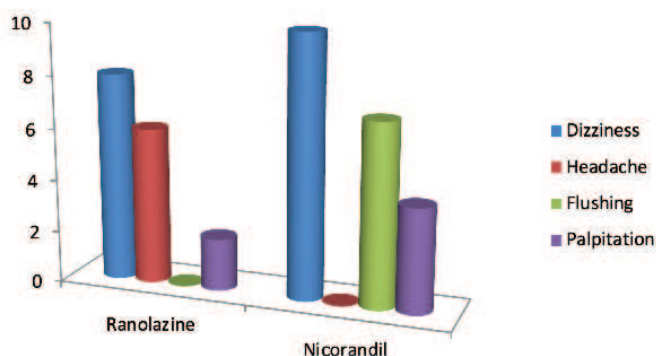


Figure 15. Adverse Effects in both Groups

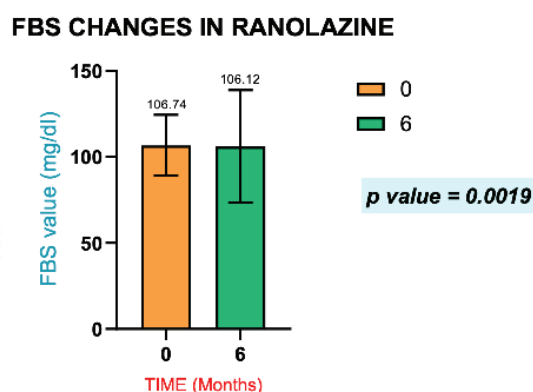


Figure 16. Changes in FBS (mean + SD) in Ranolazine after 6 months

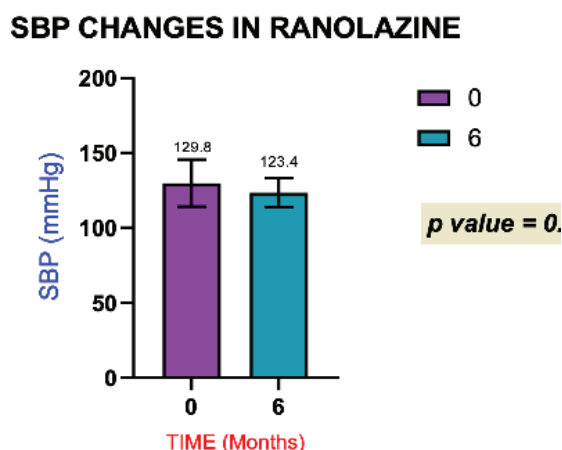


Figure 17. Changes in SBP (mean + SD) in Ranolazine after 6 months.

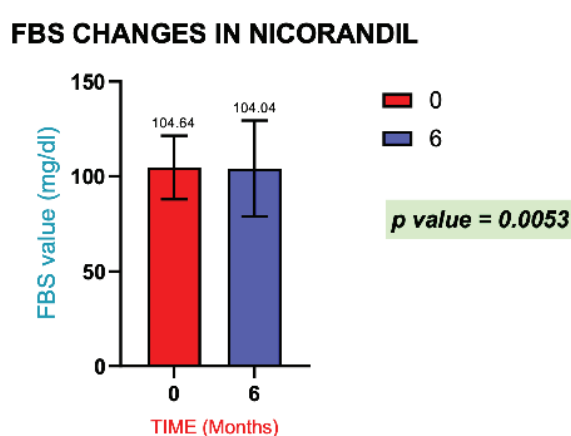


Figure 18. Changes in FBS (mean + SD) in Nicorandil after 6 months