DOI: 10.7860/JCDR/2015/10594.5448

Original Article

Internal Medicine Section

Comparison of Ranolazine and Trimetazidine on Glycemic Status in Diabetic Patients with Coronary Artery Disease – A Randomized Controlled Trial

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ABSTRACT

Introduction: Cardiovascular diseases have become the leading cause of death around the globe and diabetes mellitus (DM) is considered to be a coronary artery disease (CAD) risk equivalent. Ranolazine, an anti anginal drug has been found to reduce Glycated haemoglobin (HbA_{1c}) in diabetes patients with chronic angina. However the effect of another antianginal drug trimetazidine, on glycemic status is not clear.

Aim: To compare the effect of ranolazine and trimetazidine on glycemic status in diabetic patients with CAD.

Settings and Design: Patients diagnosed with CAD and diabetes mellitus attending Cardiology Out Patient Department (OPD), Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Puducherry, India were recruited for this randomized open label parallel arm trial.

Materials and Methods: The study conducted from January-2012 to April-2013 had 47 eligible patients diagnosed with CAD and diabetes mellitus. They were randomized to receive either ranolazine 500 mg BD or trimetazidine 35 mg BD for 12 weeks. HbA_{1c} levels, fasting blood glucose (FBG), lipid profile, QT and QTc intervals were measured at baseline and after 12 weeks.

Statistical Analysis: Unpaired t-test was used to compare the baseline characteristics of between the groups while comparison within the groups were done using Paired t-test. Wilcoxon and Mann Whitney U-tests were used for non parametric data. Graph pad instat version-3 was used for statistical analysis. Values were expressed as mean ± SD. A $p < 0.05$ was considered statistically significant.

Results: The study could not find any change in HbA_{1c} levels in both ranolazine and trimetazidine groups. The adverse effects reported from patients on ranolazine include angina, constipation, postural hypotension, headache, dizziness, nausea and weakness while patients on trimetazidine complained of constipation, weakness, palpitations, angina, dizziness, nausea, dyspepsia, headache, gastric discomfort, joint pain, etc.

Conclusion: In patients with chronic angina and diabetes mellitus Ranolazine 500mg BD and Trimetazidine 35mg BD did not show any effect on HbA_{1c} and fasting blood glucose lebel.

Keywords: Glycemic status, HbA_{1c}, QTc, Ranolazine, Trimetazidine

INTRODUCTION

Cardiovascular disease has become the leading cause of death around the globe owing to the changing pattern of life style habits and sedentary life style. Diabetes mellitus, the fifth leading cause of death worldwide is one of the common co-morbid conditions associated with CAD and is considered as a CAD risk equivalent [1,2]. Besides hyperglycemia has been found to be an independent risk factor for the occurrence of cardiovascular diseases [3]. Moreover the coexisting diseases with diabetes mellitus namely dyslipidemia and hypertension, further enhance the risk for cardiovascular complications [4]. It is estimated that 85% of the global cardiovascular diseases will be occurring in the developing nations by 2020 [5]. An estimated 2.6 million deaths are expected to occur among Indians due to CAD [6]. In Indians, the risk of CAD has been reported to occur one to two decades earlier than the Western population with additional burden of CAD occurring two to three decades prior in diabetic patients compared to non diabetic population [7-8]. In this scenario, discovery of drugs with potential role in both CAD and diabetes mellitus could be an advantage to the healthcare society.

Ranolazine, a selective inhibitor of late sodium channels (I_{Na}) in the myocardium is an anti anginal drug effective in both combination and monotherapy among patients not responding to conventional anti anginal therapy [9-10]. Post-hoc subgroup analysis of MERLIN TIMI-36 study with ranolazine in patients with concurrent chronic angina and diabetes mellitus had found reduction in HbA_{1c} by 1.2% [11]. Though, the exact mechanism of glycemic control with ranolazine is unknown, this knowledge may pave way for adjusting the dose of anti-diabetic drugs in diabetic patients receiving ranolazine for chronic angina. Trimetazidine, a metabolic modulator approved as both combination and monotherapy prior to ranolazine for chronic angina is a partial inhibitor of long-chain 3-ketoacyl thiolase (3-KAT) resulting in shifting of myocardial metabolism towards less oxygen consuming glucose oxidation [12]. Akin to ranolazine, trimetazidine is cardio protective, improves exercise tolerance and is free of hemodynamic changes [13]. In a preliminary study done in Sprague Dawley rats with fasting hyperglycemia, trimetazidine was found to reduce FBG levels [14]. However, in a randomized cross over trial conducted in diabetic patients with angina, trimetazidine did not show any change in glycemic status [15].

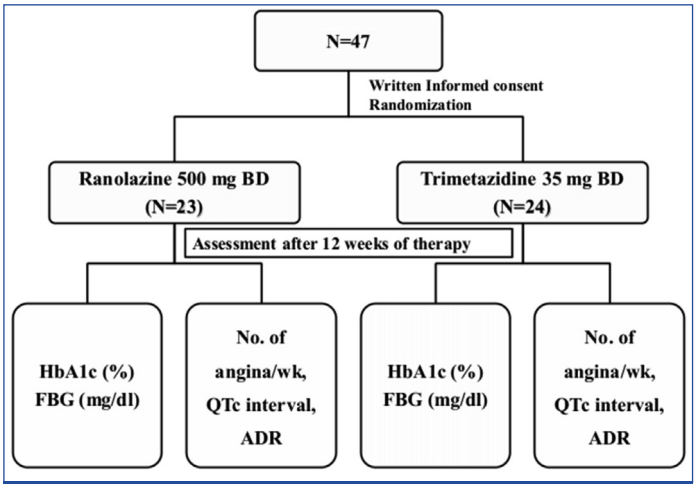
Though ranolazine is claimed to reduce HbA_{1c} in patients with CAD and diabetes mellitus, trimetazidine's effect on glycemic status in patients with CAD and diabetes mellitus needs to be explored [16,17]. Hence, the present study, aims to find out the role of ranolazine and trimetazidine on HbA_{1c} (%) and FBG (mg/dl) levels in patients with CAD and diabetes mellitus. To the best of our knowledge, this is the first study to compare the effect of ranolazine and trimetazidine on glycemic status in diabetic patients apart from being the first to compare the adverse effect profiles of ranolazine and trimetazidine in patients with CAD.

MATERIALS AND METHODS

The study was a randomized controlled trial and included all eligible patients attending Cardiology OPD, JIPMER, Puducherry , India

from January 1st 2012 to April 11th 2013. Since this was a student project of one year duration, all the patients with coronary artery disease and diabetes mellitus fulfilling the eligibility criteria were included in the study with a convenience sampling of 25 in each group. Patients of either gender, aged ≥18 y, diagnosed with CAD (documented by coronary angiography/ minimum three months history of exertional angina) and diabetes mellitus with HbA_{1c} > 7% were included for the study. Patients with history of myocardial infarction (MI) in the previous three months, heart failure, valvular heart diseases, alcoholic cardiomyopathy, renal failure, chronic lung disease, hepatic failure, baseline electrocardiography (ECG) abnormalities, hyperthyroidism, secondary causes of angina, pregnancy/absence of contraceptive use in women of child-bearing age/lactating mothers, patients on P-glycoprotein inhibitors, drugs known to prolong QT interval, CYP3A4 inhibitors, CYP3A4 inducers, pacemaker, patients participating in other clinical trials and those participated in any clinical trial within last three months were excluded.

Eligible patients were randomly assigned in a 1:1 ratio to receive either ranolazine 500 mg twice daily or trimetazidine 35 mg twice daily for three months. Sequentially numbered opaque sealed envelopes were used to maintain allocation concealment. Participants were followed up every fourth week for twelve weeks and during follow up visits, vitals were examined. The patients were questioned regarding adherence, frequency of angina attacks and adverse effects during each follow up visit [Table/Fig-1].



[Table/Fig-1]: Flow chart showing the study design

Blood samples were collected before and after 12 wk to measure HbA_{1c} (%), (FBG, mg/dl) and postprandial blood glucose (PBG), (mg/dl) levels. Ion exchange chromatography was used for estimation of HbA_{1c} and glucose oxidase (GOD) method was used for estimation of FBG and PBG. ECG recordings were taken at baseline, every 4th week and after 12 weeks of therapy. QTc interval was calculated using Bazett's formula based on QT interval measured from each participant's ECG taken at a speed 50 mm/s and 20 mv. The background medications received by the patients remained unaltered while changes made in the dose of anti-diabetic drugs as well as addition of new anti-diabetic drug throughout the study period was recorded during follow up visits. Institute Ethics Committee, JIPMER prior to starting the study. Written informed consent was obtained from all the participating patients before screening them for the study. The study was registered in clinical trials registry of India (CTRI/2012/02/002418).

STATISTICAL ANALYSIS

Unpaired t-test was used between ranolazine and trimetazidine groups to compare the baseline characteristics of HbA_{1c}, FBG, QT, QTc intervals, lipid profile, hemodynamic parameters and renal function. Paired t-test was used to compare HbA_{1c}, FBG, QT, QTc intervals, lipid profile, hemodynamic parameters and renal function before and 12 wk after treatment with either ranolazine 500 mg BD or trimetazidine 35 mg BD. Wilcoxon signed rank and Mann Whitney U-tests were used for parameters that failed to pass normality test. Graph pad Instat version 3 was used for statistical analysis of the data. Values were expressed as mean ± SD. A $p < 0.05$ was considered statistically significant.

RESULTS

A total of 47 patients, including 39 males and 8 females had completed the study by April 11, 2013. The participants in both ranolazine and trimetazidine groups had similar baseline characteristics with respect to age, body mass index, duration of disease, HbA_{1c}, FBG, QT, QTc intervals, heart rate, blood pressure, lipid profile, blood urea and serum creatinine as shown in [Table/Fig-2]. Similarly the background medication of the patients as shown in [Table/Fig-3] was not different between the two groups.

After 12 wk of treatment, there was no difference in the glycemic status of the patients in both ranolazine 500 mg BD and trimetazidine 35 mg BD groups [Table/Fig-4]. Similarly both ranolazine and trimetazidine groups did not show significant difference in QT, QTc intervals and hemodynamic parameters after the study period of 12 wk [Table/Fig-4].

In ranolazine group, the frequency of angina attacks per week changed from 1.7 ± 6.1 to 1.2 ± 1.7 (p=0.5). Similarly in trimetazidine group, the frequency of angina attacks per week changed from 2 ± 4.7 to 1.4 ± 2.2 (p=0.9) as shown in [Table/Fig-4].

The adverse effects reported among the patients on ranolazine include angina, constipation, postural hypotension, headache, dizziness, nausea and weakness. The adverse drug reactions seen in trimetazidine group were constipation, weakness, palpitations,

S. No.	Baseline characteristics	Ranolazine 500 mg BD (N=23)	Trimetazidine 35 mg BD (N=24)
1	Age (yrs)	58 ± 8.1	57.4 ± 9.1
2	Male (%): Female (%)	18 (78.3): 5 (21.7)	21 (87.5): 3 (12.5)
3	BMI (Kg/m^2)	24.9 ± 3.1	26.2 ± 3.1
4	†Duration of CAD (months)	28.1 ± 29	42 ± 41.1
5	†Duration of DM (months)	91.2 ± 80.1	66.2 ± 56.9
6	$HbA1_c$ (%)	9.2 ± 1.7	8.5±1.4
7	†Fasting blood glucose (mg/dl)	168.5 ± 49.3	148.2 ± 59
8	Post prandial blood glucose (mg/dl)	284.5 ± 85.8	239.9 ± 77.1
9	QT (ms)	359.8 ± 28.8	356.3 ± 32.7
10	QTc (ms)	401.1 ± 42.2	396.3 ± 38.2
11	HR (bpm)	76.5 ± 15.8	74.8 ± 14.6
12	†SBP (mmHg)	128.6 ± 19.5	130.5 ± 21.9
13	†DBP (mmHg)	80.1 ± 14	82 ± 11.6
14	Urea (mg/dl)	25.2 ± 8.3	27.3 ± 9.6
15	†Creatinine (mg/dl)	0.9 ± 0.3	1.1 ± 0.4
16	†Frequency of angina / wk	1.6 ± 5.8	1.8 ± 4.5
17	† Isosorbide dinitrate consumption / wk	1.7 ± 3.1	2.5 ± 7.7
18	Total cholesterol (mg/dl)	158.9 ± 33.5	149.1 ± 37
19	†Triglycerides (mg/dl)	167.7 ± 128	142.5 ± 60.4
20	†High density lipoprotein (mg/dl)	37.4 ± 18.1	34 ± 9.4
21	Low density lipoprotein (mg/dl)	93.4 ± 20.3	92.6 ± 33.2
22	†Very low density lipoprotein (mg/dl)	31.1 ± 20.8	28.2 ± 12

[Table/Fig-2]: Baseline characteristics of study subjects
Values are expressed as mean ± SD (Standard deviation)
† Mann Whitney U test (Non parametric test used as Kolmogorov and Smirnov normality was not passed)

S. No	Background therapy	Ranolazine N = 23 (%)	Trimetazidine N = 24 (%)
1	Aspirin (150 mg) + Clopidogrel (75 mg)/day	5 (22.7)	8 (33.3)
2	Aspirin (150) mg/day	18 (78.3)	14 (58.3)
3	Clopidogrel (75/150) mg/day	13 (56.5)	13 (54.2)
4	Statins (Atorvastatin 10/20/40 mg hs; Rosuvastatin 10/20 mg hs)	23 (100.0)	24 (100)
5	ACE inhibitors (2.5/5/7.5/10/20) mg/day	18 (78.3)	15 (62.5)
6	Angiotensin Receptor Blocker (Losartan 25 mg/50 mg /day; Telmisartan 20 mg/day)	2 (8.7)	2 (8.3)
7	β blocker (Atenolol 25/50/100 mg OD, Metoprolol 12.5/25/50/100/150 mg OD)	19 (82.6)	20 (83.3)
8	Hydrochlorothiazide (12.5/25) mg/day	2 (8.7)	2 (8.3)
9	Furosemide (20/40) mg/day	5 (21.7)	5 (20.8)
10	Spironolactone (25/50) mg/day	4 (17.4)	5 (20.8)
11	Amlodipine (2.5/5/20) mg/day	4 (17.4)	6 (25)
12	Metformin (250/500/750/1000/2000) mg/day	18 (78.3)	16 (66.7)
13	Sulfonylureas (Glibenclamide 2.5 mg OD/ 5 mg OD / 7.5 mg OD/ 10 mg OD/ 10 mg BD, Glimepiride 1 mg OD)	15 (65.2)	10 (41.7)
14	Insulin (H. Mixtard; H. Insulatard; H. Monotard)	4 (17.4)	4 (16.7)
15	Famotidine 20 mg BD	5 (21.7)	7 (29.2)
16	Omeprazole 20 mg BD	2 (8.7)	3 (12.5)
17	Pantoprazole 40 mg OD	1 (4.3)	0 (0)
18	Isosorbide Mononitrate (10/20/30/40/60/80) mg/day	11 (47.8)	10 (41.7)
19	Isosorbide dinitrate (5/10/30) mg SL SOS	16 (69.6)	9 (37.5)
20	Nicorandil 10 mg/day	0 (0)	3 (12.5)
21	Diazepam 5 mg hs	1(4.3)	0 (0)
22	Gabapentin 300 mg TDS	1(4.3)	0 (0)
23	Pregabalin 75 mg/day	0 (0)	1 (4.2)
24	B Complex Tablets BD	0 (0)	2 (8.3)
25	Cilostazole 100 mg OD	0 (0)	1 (4.2)
26	Acarbose 25 mg OD	1 (4.3)	0 (0)
27	Pioglitazone 15 mg OD	1 (4.3)	0 (0)

[Table/Fig-3]: Baseline drug therapy of study subjects

angina, dizziness, nausea, dyspepsia, headache, gastric discomfort and joint pain.

DISCUSSION

The present study conducted in patients with chronic stable angina and diabetes mellitus did not show reduction in HbA_{1c} or FBG levels with either ranolazine or trimetazidine. This result was in conflict to the CARISA study that showed an absolute reduction of 0.5 ± 0.1% as well as 0.7 ± 0.2% in HbA_{1c} levels with ranolazine 750 mg BD and 1000 mg BD respectively compared to placebo group after 12 wk of treatment in 189 diabetic patients [9]. Another study conducted among 4918 patients with concomitant acute coronary syndrome and diabetes mellitus found a decline in mean HbA_{1c} levels from 7.5 to 6.9% with a reduction of 0.64% after 16 wk of treatment with ranolazine 1000 mg twice daily [16]. A preclinical study with ranolazine at a dose of 20 mg/kg was found to produce significant improvement in glycemic control in streptozotocin - induced diabetes mice following 6 wks of treatment with HbA_{1c} levels showing significant reduction at the end of 8 wk [18]. This study found an increase in the number of insulin positive β cells in islets which was similar to the effect of sitagliptin on STZ - induced diabetic mice [18,19].

S. No	Parameters studied	Ranolazine 500 mg BD (N=23)		Trimetazidine 35 mg BD (N=24)	
		Before Mean ± SD	After 12 wks Mean ± SD	Before Mean ± SD	After 12 wks Mean ± SD
1	HbA_{1c} (%)	9.0 ± 1.6	8.7 ± 1.5	8.6 ± 1.5	8.6 ± 2.4
2	FBG (mg/dl)	163.9 ± 45.2	158.2 ± 41.6	153.6 ± 60.8	168.1 ± 68.1
3	PBG (mg/dl)	271.1 ± 78.4	295.3 ± 91.6	248.3 ± 78.7	259.7 ± 75.5
4	†Angina attacks / wk	1.7 ± 6.1	1.2 ± 1.7	2.0 ± 4.7	1.4 ± 2.2
5	† Sublingual nitrate consumption / wk	1.7 ± 3.1	2 ± 4.7	2.7 ± 8.1	1.4 ± 2.6
6	†QT interval (ms)	360.1 ± 29.5	367.1 ± 35.5	354.8 ± 29.4	362.6 ± 37.4
7	QTc interval (ms)	401.1 ± 43.2	408.2 ± 33.2	395 ± 40.3	399.4 ± 24.8
8	Heart rate (bpm)	76.5 ± 16.2	76.4 ± 16.7	75.5 ± 14.5	76.9 ± 11.9
9	Systolic blood pressure (mmHg)	128.5 ± 19.9	126.4 ± 19.7	131.7 ± 22.8	126.3± 20.9
10	†Diastolic blood pressure (mmHg)	80.5 ± 14.2	81.4 ± 9.9	81.3 ± 12.1	79.4 ± 13.4

[Table/Fig-4]: Effect of ranolazine and trimetazidine on glycemic, hemodynamic parameters and QTc interval
HbA1c- glycated haemoglobin, FBG – fasting blood glucose, PBG – post prandial blood glucose, Values are expressed as mean±SD (Standard deviation); † Wilcoxon matched-pairs signed-ranks test (Non parametric test used as Kolmogorov and Smirnov normality was not passed)

The reason that our study could not find a significant reduction in HbA_{1c} could be attributed to the use of ranolazine at a dose of 500 mg BD as opposed to the previous studies that have used a higher dose of 750 mg and 1000 mg BD. Moreover, in one of the previous studies, ranolazine was administered for a period of 16 wk as opposed to 12 wk in the present study [20]. These findings suggest that there is a possibility of improved glycemic control with higher doses of ranolazine given for a longer duration. However, the reason for using a dose of 500 mg BD in the present study was to ensure patient safety with regards to QTc interval as it is seen at doses above 1000 mg BD. Moreover 500 mg BD is the standard dose prescribed in our setting and we wanted to find out if any change in glycemic status occurs at this dose. Correspondingly trimetazidine group also did not show any reduction in HbA_{1c} and FBG levels after 12 wk of treatment. This finding was similar to an earlier randomized trial done in diabetic patients with angina (N=10), in which trimetazidine did not show any change in glycemic status at a dose of 20 mg/day TDS given for six weeks [15].

In the present study, ranolazine showed mean increase in QTc interval by 7.6 ms which was not significant both statistically and clinically. This was similar to average increase in the QTc interval of <10 ms by ranolazine at a dose of 1000 mg twice daily in an earlier study [16,21]. Similarly trimetazidine group had mean increase in QTc interval by 4.4 ms which was insignificant. This was different from a previous study with trimetazidine (35 mg BD) in which statistically significant shortening of QTc interval by >20 ms was observed in 64% (14 of 22) of patients with heart failure [22]. Similarly another study done in 30 patients with chronic heart failure showed significant reduction in QTc interval after 6 months of treatment with trimetazidine [23]. However, the mechanism of QTc shortening with trimetazidine is not clear and this has been observed only in patients with heart failure.

The hemodynamic parameters did not differ significantly in both ranolazine and trimetazidine groups after 12 wk of treatment, which was in consonance with earlier studies [10,24,25]. In ranolazine group, the frequency of angina per week changed from 1.7 ± 6.1 to 1.2 ± 1.7 with mean reduction of 0.5 per week after 12 wk.

However, the ERICA trial, conducted in 565 patients with chronic angina, showed significant reduction in the frequency of angina by 2.88 ± 0.19 in 281 patients randomized to ranolazine 1000 mg BD for 6 wk compared to 3.31 ± 0.22 in the placebo group. This study also claims that better antianginal effects were observed with ranolazine in patients with increased frequency of angina episodes [26]. Similarly the TERISA trial showed significant reduction in angina frequency from 6.6 to 3.8 per wk after 8 wk of treatment with ranolazine 1000 mg BD compared to placebo group [27]. Since the frequency of angina episodes at baseline were less in our patients, ranolazine could not show statistical significance in reduction of angina episodes per week.

In trimetazidine group, the frequency of angina per week reduced from 2.1 ± 4.8 to 1.5 ± 2.2 with a mean reduction of 0.6 attacks per week which was of statistical insignificance. In a previous study done in 50 diabetic patients with stable angina for a minimum of three months, trimetazidine showed a significant reduction in the mean frequency of angina attacks by 3.1 per week compared to 4.8 per week in the placebo group [28]. At the end of 12 wk of study duration, both ranolazine and trimetazidine arms did not show any significant change in the lipid profile and renal function. This was similar to the results of a study done with ranolazine in patients with chronic angina and diabetes mellitus which was not associated with significant change in lipid profile [16]. The present study assessed the patient's adherence to drug therapy at the end of 4 wk, 8 wk and 12 wk by counting the number of unused tablets as well by checking the adherence form given to the patients during each follow up visits. All the subjects who completed the study were found to be compliant throughout the study period.

The adverse effects reported among the patients on ranolazine include angina, constipation, postural hypotension, dizziness, headache, nausea and weakness. These reactions were similar to the adverse effects reported in other studies with ranolazine [10,29]. In MERLIN–TIMI 36 trial, the most common adverse reactions seen with ranolazine (500 mg BD/750 mg BD/1000 mg BD) were dizziness, nausea, constipation and syncope. However, in the present study, syncope was not reported in the ranolazine group. This could be attributed to the dose of 500 mg BD used in our study compared to 500 / 750 / 1000 mg BD used in the MERLIN–TIMI 36 trial [30]. Syncope and postural hypotension have been found to occur with ranolazine probably due to it's α blockade action at a higher dose of 2000 mg [9]. The adverse drug reactions seen in trimetazidine group were weakness, constipation, nausea, palpitations, dizziness, dyspepsia, gastric discomfort, headache, joint pain, angina etc. This was similar to the adverse effect profiles reported in the previous study with trimetazidine [31].

Strengths of the present study are inclusion of homogenous group of patients with CAD and diabetes mellitus without any other co-morbid illness except for hypertension. Our study was carried out for 12 wk to evaluate the effect of ranolazine and trimetazidine on HbA_{1c} levels, an indicator of glycemic status. Adherence was ensured during the follow up visits by checking the blister packs of the tablets given as well as by checking the adherence sheet. Randomization and allocation concealment were done to reduce bias.

Limitations of the study include the diverse nature of background antidiabetic medications. In addition due to small sample we were unable to analyze the individual influence of antidiabetic drugs on HbA_{1c} level. Moreover as the study was to be completed in one year duration, patient recruitment was stopped at the end of nine months so as to complete the study at the end of one year.

CONCLUSION

The present study reveals that ranolazine and trimetazidine do not improve the glycemic status of type 2 diabetic patients with CAD when administered at a dose of 500 mg BD and 35 mg BD respectively. However, the results regarding the glycemic status of ranolazine in diabetic patients need to be confirmed with a higher dose in a larger population for a longer duration of more than 12 wk.

TRIAL REGISTRATION

The study was registered in clinical trials registry of India (CTRI) (CTRI/2012/02/002418).

ACKNOWLEDGEMENT

I acknowledge all faculty, Senior Residents, ECG technicians and supporting staff of Cardiology Department, JIPMER for extending their support to complete the project. I would like to thank the technicians of Central Lab and Medicine Side Lab, JIPMER for their co-operation in performing routine biochemistry as well as HbA1c investigations. My sincere thanks to Dr. B. Karthikeyan, Assistant Professor, Department of Cardiology, SRM Medical College Hospital & Research Centre, Kattankulathur, Chennai for providing useful suggestions from inception to completion of the study.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jul 16, 2014**
Date of Peer Review: **Oct 21, 2014**
Date of Acceptance: **Oct 31, 2014**
Date of Publishing: **Jan 01, 2015**