



TO DETERMINE THE ROLE OF RANOLAZINE FOR RHYTHM CONTROL STRATEGY IN PATIENTS WITH NON- VALVULAR ATRIAL FIBRILLATION- AN OBSERVATIONAL STUDY FROM A TERTIARY CARE CENTER. (RANOVA STUDY)

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ABSTRACT

Objectives – Non- valvular atrial fibrillation (NVAF) is the most commonly occurring arrhythmia worldwide. Ranolazine is an emerging drug with a ray of hope in the management of NVAF. This is the first large observational study with longer follow up of one year.

Methods - It is a hospital based observational prospective study. A total of 100 patients was recruited for the study. The primary objective was to determine the efficacy of ranolazine in converting NVAF to sinus rhythm & the secondary objective was to study epidemiological aspects of NVAF.

Results –After 1 month of follow up conversion to normal sinus rhythm was 12% in group A & 6% in group B (6%), it was not significant statistically ($Z=1.48p=0.13$). After 6 months, conversion to normal sinus rhythm was increased from 12% to 18% in group A which was preserved at 12 months of follow up and statistically significant and higher than that of group B (6.0%) ($Z=2.61p=0.009$). In predisposing risk factors & other co-morbidities HTN was present in 61%, obesity together with overweight in 37%, smoking in 44%, history of moderate amount of alcohol intake in 35%, history of CVA/TIA in 13%, DM in 11%, CKD in 4%, CAD in 30%, COPD in 20% and congestive heart failure in 15% of the patients.

Conclusion- Ranolazine is an effective option when used for rhythm control strategy in NVAF. HTN is the predominant predisposing risk factor.

KEYWORDS : Atrial fibrillation; Ranolazine; Cardio version; Rhythm control; Anti-arrhythmic drug

INTRODUCTION

Non-valvular Atrial fibrillation (NVAF) is the most commonly occurring rhythm abnormality across the globe, and a major public health problem.^{1,3} Most patients with NVAF have hypertension, ischemic heart disease, cardiomyopathy, constrictive pericarditis, cardiac tumours, chronic obstructive lung disease (COPD) and obesity. The estimated global prevalence estimated to be 0.47%, with significant regional variation. With the advancing age prevalence of AF increases, reaching a rate as high as 10% in octogenarians.^{4,5} AF that terminates spontaneously or with treatment within 7 days termed paroxysmal and that persist continuously for more than 7 days called persistent. AF which is persisting for longer than 1 year and refractory to cardio version is termed as permanent AF. However, "permanent AF" is not necessarily permanent nowadays because it may be eliminated successfully by surgical or catheter ablation. Lone AF is another type of AF that occurs in patients younger than 60 years of age in the absence of structural heart disease. This designation is very relevant because patients with lone AF are at lower risk of thromboembolic complications, thus eliminating the necessity for anticoagulation with warfarin or NOAC (novel oral anticoagulants). There are two electrophysiological mechanisms of AF: one or more automatic, triggered, or microreentrant foci, so-called drivers, which fire at rapid rates and cause fibrillation-like activity, and the second is multiple re-entrant circuits in the atria that, annihilate and reform wavelets, thereby perpetuating the fibrillation. Sometime both mechanisms may be present simultaneously. Several randomized controlled studies have

compared a rate-control strategy with a rhythm-control strategy in patients with AF. The largest study by far was the AFFIRM study, which convincingly demonstrated that a rate-control strategy is better than rhythm-control strategy in asymptomatic or minimally symptomatic patients 65 years or older. While rhythm control strategy should be preferred in those having active life style, symptomatic AF and age less than 65 years. But there are limited available option of anti-arrhythmic drugs for rhythm control strategy in view of serious side effects and sub-optimal efficacy. The first-line agents commonly used for rate control are beta-blockers and the calcium channel antagonists. For pharmacological cardio version and maintaining sinus rhythm amiodarone is the most used with a success rate of approximately 50%. Recently, it has been found that ranolazine, a drug, which has been approved initially as an anti-angina drug has been shown to have anti-arrhythmic properties both in experimental and clinical studies.^{6,7} Several case studies from western literature have shown the use of ranolazine in the treatment of atrial fibrillation, some even as a 'pill in the pocket' approach.^{8,9} The most important anti-arrhythmic mechanism of ranolazine is thought to be mediated by inhibiting IKr, early INa+, and late INa+ currents in a selective, use-dependent way in atrial myocytes.^{10,11} The recent reclassification of anti-arrhythmic agents has designated drugs with this action in Class Id.

There are several large number of randomized controlled trials and meta-analysis of these trials shows that ranolazine effectively suppress the atrial fibrillation in patients with coronary artery disease, heart failure and post electrical

cardioversion.¹²⁻¹⁴ All these studies are in favour of the role of ranolazine in suppression and cardioversion of atrial fibrillation. Though there are evidences from western literature favouring its use as a rhythm controlling agent in AF. But there is a scarcity of data from third world countries. This is the first large observational study over a broad spectrum of patient comorbidities and with longer follows up from this part of the globe investigating the role of ranolazine as a rhythm controlling agent and different epidemiological aspects in patients with non-valvular AF.

MATERIALS AND METHODS

It is a hospital based observational prospective study done at a tertiary cardiac care centre for 1 year. A total of 100 patients were recruited for the study from both outdoor and indoor patient clinics. Determination of sample size was done using the formula, $n = z^2pq/e^2$, here n = sample size, $z = 1.96$ at 95% confidence level, p = prevalence of atrial fibrillation i.e. 1-4% and taken maximum as 4%. $q = (1-p)$, and e = Absolute precision / margin of error (5%). On using the formula and above values, calculated sample size was 60. For the ease of calculations, a total sample size of 100 was taken. Each of them selected, by consecutive sampling technique.¹⁵ Patients were equally distributed into two groups without any bias for age & sex. Thus, the patients in the two groups were in the ratio 1:1. In group A, patients, were treated both Ranolazine and Rate Controlling Drugs while in group B only rate controlling drugs were used. Ranolazine used in a dose of 500 mg twice daily in all patients. Rate controlling drugs used mainly were beta blocker i.e. metoprolol succinate in starting doses of 12.5mg and gradual escalation of the dose up to a maximum tolerated dose, i.e. 200 mg per day as per rate control response of patients. Patients in whom, metoprolol were not tolerated or contraindicated, were treated with calcium channel blockers i.e. verapamil and diltiazem, mean doses used were 80mg and 120 mg per day respectively. The doses of both drugs were same in two groups.

Aims And Objectives Of The Study-

The primary objective of the study was to determine the role of ranolazine for rhythm control strategy in patients with NVAF. The secondary objective was to study epidemiological aspects of AF in the studied population.

Eligibility Criteria

Inclusion Criteria

1. Male or non-pregnant female > 18 years of age with non valvular AF.
2. Ability and willingness to participate based on information given to patient and to a health facility.

Exclusion Criteria

1. Patients with valvular AF.
2. Concomitant digoxin, antiarrhythmic drug (AAD) use
3. Use of potent CYP3A4 inhibitors or inducers
4. Long QT syndrome or QTc interval \geq 500ms
5. ESRD requiring haemodialysis
6. Hepatic dysfunction
7. Patients those were intolerant to the drug or any adverse drug reaction.

The study was begun after due clearance from ethical committee. Patients attending Cardiology OPD and indoor satisfying the inclusion and exclusion criteria were enrolled. Detailed clinical history was taken from either patient, or attendants (in case if the patient was not able to communicate properly). Full clinical examination of patients done and recorded in predesigned schedule. Reports of blood parameter collected and reviewed. Echocardiography (2D, M-mode and Doppler) performed and results documented. Patients were put on a study directed medical therapy and followed up at 1, 6 and 12 months.

Statistical Analysis:

Statistical analysis performed with the help of Epi Info (TM). EPI INFO is a trademark of the Centres for Disease Control and Prevention (CDC). Descriptive statistical analyses performed to calculate the means with corresponding standard deviations (SD). Test of proportion used to find the Standard Normal Deviate (Z) to compare the difference proportions and Chi-square test was performed to find the associations. In the cases, where one of the cell frequencies was less than five corrected Chi-square (χ^2) was used to find the association between variables. Also One Way Analysis of variance (ANOVA) followed by post hoc Tukey's Test was performed with the help of Critical Difference (CD) at 5% and 1% level of significance to compare the mean values. $p < 0.05$ was taken to be statistically significant.

RESULT

There was no significant difference in age and gender between Group A and Group B. The mean age of the study population in Group A and Group B was 63.98 ± 8.61 years and 64.06 ± 8.25 years respectively (p -value 0.83). A total number of male subjects in both the groups were 23 (50%) (p -value of 0.99) while the number of female subjects in both the groups was 27 (p -value of 0.99). There was no significant association between socio-economic status ($p = 0.99$) and symptomatic presentation of the patients of the two groups ($p > 0.05$). [Table1].

Table1- Distribution Of Symptomatic Presentation Of The Patients. Ns-non-significant

Symptoms	Group-A		Group-B		Z-Values	p-values
	Number	%	Number	%		
Chest pain	22	44.0%	21	42.0%	0.28	0.77 NS
Palpitation	45	90.0%	47	94.0%	1.04	0.29 NS
Fatigue	39	78.0%	44	88.0%	1.88	0.06 NS
Dyspnea	22	44.0%	24	48.0%	0.56	0.57 NS

There were no significant differences in co-morbidities and personal habits of the patients of the two groups. Thus, the patients of the two groups were well matched for their co-morbidities and personal habits. [Table2].

Table 2- Distribution Of Co-morbidities & Personal Habits Of The Patients. Ns-non-significant

Co-morbidities	Group-A		Group-B		p-values
	Number	%	Number	%	
DM	5	10.0%	6	12.0%	0.65 NS
HTN	30	60.0%	31	62.0%	0.77 NS
CVA/TIA	6	12.0%	7	14.0%	0.67 NS
CAD	15	30.0%	15	30.0%	0.99 NS
CKD	1	2.0%	3	6.0%	0.14 NS
COPD	9	18.0%	11	22.0%	0.47 NS
CHF	8	16.0%	7	14.0%	0.68 NS
Smoking	20	40.0%	24	48.0%	>0.05 NS
Alcohol intake	15	30.0%	20	40.0%	>0.05 NS

There was no significant difference in mean of all the investigational parameters of the patients of the two groups. [Table3].

Table-3: Comparison Of Different Investigational Parameters Of The Patients Of The Two Groups. Ns-non-significant

Parameters	Group	Mean	SD	t98	p-value
SBP (mmHg)	A	134.96	14.194	0.573	0.568 NS
	B	133.54	10.276		
Hb%	A	11.902	1.1291	0.947	0.346 NS
	B	11.610	1.8650		
Blood Urea (mg/dl)	A	27.09	6.596	0.177	0.860 NS
	B	26.82	8.342		

S. Creatinine (mg/dl)	A	1.3726	0.33979	1.55	0.124 NS
	B	1.2532	0.42526		
S. Na+ (m mole/L)	A	137.70	3.471	0.919	0.360 NS
	B	138.38	3.912		
S.K+ (mmol/l)	A	4.384	0.4405	0.647	0.519 NS
	B	4.442	0.4558		
TSH (μIU/mL)	A	3.304	0.8471	1.93	0.056 NS
	B	3.698	1.1611		

Mean BMI in group A was 22.53±3.14 and in group B was 22.11±3.11 (Z=0.40, p=0.81 NS). Thus, the patients of the two groups more or less equally distributed over BMI. The patients of the two groups were matched for their pulse rate (PR) at baseline. There was no significant difference in mean baseline pulse rate (PR) among the patients of the two groups (t98=1.42; p=0.16). On comparing the pulse rate of the patients of both groups at different time intervals on subsequent follow up, it was observed that in both groups mean pulse rate decreased significantly towards its normal range at different time interval compared to baseline. [Group-A one way ANOVA F3,196 = 20.18; p<0.0001 & Group -B one way ANOVA F3,196 = 5.66;p<0.0001]. [Table 4&5].

Table 4- Comparison Of Pulse Rate Of The Patients Of Group-a At Different Time Intervals

Pulse rate (PR)	At baseline		After 1 Month		After 6 month		After 12 month	
	Numb er	%	Numbe r	%	Number	%	Num ber	%
Normal	7	14.0	19	38.0	32	64.0	39	68.0
High	43	86.0	31	62.0	18	36.0	11	22.0
Mean± SD	81.28±8.43		76.94±6.86		73.78±6.25		71.04±5.88	

Table 5- Comparison Of Pulse Rate Of The Patients Of Group-b At Different Time Intervals

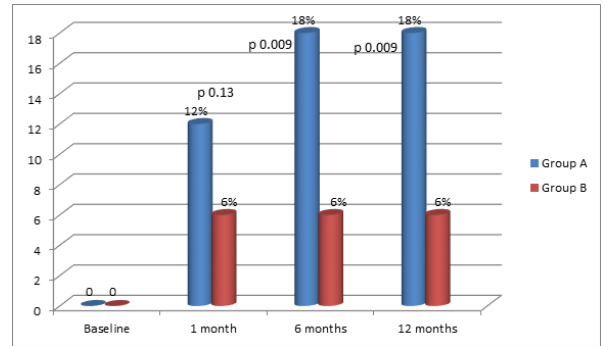
Pulse rate (PR)	At baseline		After 1 Month		After 6 month		After 12 month	
	Numb er	%	Numbe r	%	Number	%	Num ber	%
Normal	9	18.0	9	18.0	29	58.0	39	68.0
High	41	82.0	41	82.0	21	42.0	11	22.0
Mean± SD	79.06±6.82		74.66±6.68		74.26±6.11		71.14±4.85	

At baseline in both the groups all the patients had atrial fibrillation (Z=0.01;p=0.99). After 1 month of follow up conversion to normal sinus rhythm was observed in 12% of the patients in group A which was higher than that of group B (6%) but it was not significant (Z=1.48p=0.13).After 6 months, conversion to normal sinus rhythm was increased from 12% to 18% in Group-A which was significantly higher than that of Group-B (6.0%) (Z=2.61p=0.009). (Z=2.61p=0.009). After 12 months of follow up, there was no new case of conversion to sinus rhythm in both the groups with preserved sinus rhythm in Group-A (18%) which was significantly higher than that of Group-B (6.0%) (Z=2.61p=0.009). [Table 6, Figure 1].

Table 6- Comparison Of Pulse Rhythm Of The Patients After 1 Month. Nsr -normal Sinus Rhythm. Af- Atrial Fibrillation, Ns- Non Significant, S- Significant

Follow up	Rhythm	Group-A		Group-B		P value
		Number	%	Number	%	
1 month	NSR	6	12.0%	3	6.0%	0.13 NS
	AF	44	88.0%	47	94.0%	
6 month	NSR	9	18.0%	3	6.0%	0.009 S
	AF	41	82.0%	47	94.0%	
12 month	NSR	9	18.0%	3	6.0%	0.009 S
	AF	41	82.0%	47	94.0%	

Figure 1- Percentage Of Patients Converted To Sinus Rhythm In Both Groups At Different Time Intervals.



When we analyse different risk factors & co-morbidities associated with NVAF in this part of globe, we observed that HTN was present in 61%, obesity together with overweight in 37%, smoking in 44%, history of moderate amount of alcohol intake (two drinks a day for men, or one drink a day for women) in 35%, history of CVA/TIA in 13%, DM in 11%, CKD in 4%, CAD in 30%, COPD in 20% and congestive heart failure in 15% of the patients.

DISCUSSION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and its prevalence rises with increasing age. The strategy of rhythm control is a mainstay of AF treatment based on available evidences but it cannot be effectively achieved without the risk of side effects such as pro arrhythmia, hypotension, or organ toxicity with current drugs. So there is an unmet need to discover a new drug based on the pathophysiology of AF. There are reports and studies from western part of globe regarding the anti-angina late sodium current inhibitor, ranolazine, and its beneficial effects against AF. But unfortunately there is a significant lack of information regarding this from the developing nations or third world countries. There is no long-term observational study with ranolazine, which is in support of effective cardio version and persistent of sinus rhythm during follow-up in those having NVAF. This is the first observational study done in any developing country in an effort to recognize different risk factors responsible for NVAF and to see effective conversion and persistent of sinus rhythm in NVAF with ranolazine. In this study it was reported that during 12 months of treatment with ranolazine conversion to normal sinus rhythm was observed in 18.0% of the patients of Group A which was significantly higher than that of Group B (6.0%) (Z=2.61p=0.009). So in this study patients who are taking both rate controlling drugs and ranolazine having a higher conversion rate towards sinus rhythm as compared to patients only taking rate controlling drugs over a period of one year. (Z=2.61p=0.009). There was also a significant decline in mean pulse rate significantly towards its normal range at different time interval compared to baseline supporting the rate controlling effect of ranolazine also. Previous studies on this subject were done either on post ACS patients or post-operative patients with similar results supporting the role of ranolazine as a rhythm controlling drug. The first non-randomized retrospective cohort study, which was done by Miles et al. (2011)¹⁶, in this he gave ranolazine to 182 and amiodarone to 211 post CABG patients. Patients who were on ranolazine had significantly fewer occurrences of post CABG AF. Tagarakis et al. (2013)¹⁷ in a single centre randomized trial on 34 post CABG patients also had similar findings with significantly fewer occurrences of postoperative AF with ranolazine. Simopoulos et al. (2014)¹⁸ in a single centre randomized trial on 21 post CABG AF patients concluded that combined use of ranolazine & IV amiodarone is associated with a significantly shorter time to conversion rate in the combo group as compared to IV amiodarone alone. Similar to this Koskinas, et al. (2014)⁹ concluded that in 60 patients of symptomatic patients following STEMI

combination of ranolazine (1500mg) and amiodarone is associated with a significantly higher conversion rate and shorter conversion times. All these studies undoubtedly support the findings of the present study and provide a strong platform for the use of ranolazine against NVAF in third world population also. These findings are further supported by one of the earlier reports by Murdock et al.¹⁹ regarding the role of ranolazine in atrial fibrillation (AF). He reported a case series which was published in 2008 that include seven patients who developed AF within hours to days of ablation and / or failure of other anti-arrhythmic agents. Four of them had no recurrence of AF while on ranolazine, two did not respond and one had a delayed recurrence. Inspired by his findings the same author proposed "Pill in the pocket" approach to AF using ranolazine the next year. 13 of their 18 patients converted to sinus rhythm without any proarrhythmic effects following a single dose of 2000 mg of ranolazine. The 72% conversion rate was comparable to other reported protocols for "pill in the pocket" approach.²⁰ The findings in our study were also on similar trends though we didn't study it for "Pill in the pocket" approach at such a higher dose. The rate of cardioversion in our study was 12% at one month, 18% at six months with no new conversion but persistence of sinus rhythm at 12 months. Though our rate of cardioversion was less as compared to case series by Murdock et al. There was an additive effect of ranolazine with amiodarone in the above studies. In our study though we didn't focus on this concept and excluded the patients on amiodarone.³ But our findings seem to be more realistic in view of large sample size as compared to previous studies. As per review of literature, ranolazine induced inhibition of peak INa in the atria, reduces atrial excitability and effective refractory period. This prevents rapid activation of the atria in AF. The blockade of IKr by ranolazine delays atrial repolarization thus abbreviating the diastolic interval. It is during the diastolic interval that much of the recovery of the sodium channel from drug block occurs. As a result recovery of the sodium channel from ranolazine block is impaired, resulting in a greater accumulation of the block and reduction of INa. The maintenance of a diastolic interval in the ventricle, even at rapid rates of activation, accounts for the lesser effect of ranolazine in the ventricles when compared with the atria. Block of both peak and late sodium current by ranolazine in the atria reduces intracellular calcium activity which in turn suppresses after depolarization-mediated triggers of AF.¹¹ In the HARMONY trial²¹ which was a randomized, placebo-controlled; parallel-arm study that evaluated combination of ranolazine 750 mg twice daily and low doses of dronedarone (225 mg twice daily or 150 mg twice daily) to 131 patients with paroxysmal AF and it was reported that 12 week of treatment period with the combination therapy was superior to either drug alone in reducing the burden of atrial fibrillation (AF). This trial further emphasized the role of ranolazine in cardioversion of AF similar to our findings in third world population. Further supporting studies in the form of randomized MERLIN-TIMI 36 Trial²² in which the effect of ranolazine on the incidence of atrial fibrillation in patients with acute coronary syndrome was studied. New-onset atrial fibrillation was observed in lesser patients in the ranolazine group [55 (1.7%) vs. 75 (2.4%) in the placebo group; p = 0.08]. There was no pro-arrhythmia with ranolazine therapy and there were few patients with episodes of ventricular tachycardia lasting greater than eight beats in the ranolazine group. In the present study, we observed the findings for the rate of cardioversion between two groups in which one receiving ranolazine (1000mg) plus rate controlling agents and other only rate controlling agents. Both the groups were observed for 1 year with follow up at 1, 6 and 12 months. At one month of follow up 12% of the patients converted to sinus rhythm in combination therapy which was clinically not significant as compared to other group receiving rate controlling drugs alone. At 6 months of follow up there was significant conversion to sinus rhythm (18%) with combination therapy while at 12 months there was no new conversion but

persistence of sinus rhythm with combination therapy. These findings were suggested that the likelihood of cardioversion is maximum up to 6 months with the perseverance of rhythm thereafter. The rate of cardioversion in other group receiving rate controlling agents was only 3% at one month of follow up with no new conversion at 6 & 12 months. The initial conversion to sinus rhythm in these patients was likely to be due to spontaneous cardioversion. As per literature patients with atrial fibrillation (AF) of less than 48 hours duration have a very high rate of spontaneous conversion (SC) to sinus rhythm (SR). Spontaneous conversion to sinus rhythm occurs in almost 70% of patients presenting with atrial fibrillation of <72-h duration. While patients with AF of >48 hour duration (range, 2 to 453 days) who were not receiving antiarrhythmic drug 16% experienced spontaneous conversion to sinus rhythm.^{23,24} In our study no major adverse effect of ranolazine was seen during the entire follow up period. As per different study adverse effect of ranolazine is very minimal only 4% as compared to placebo. Main adverse effects of drug are dizziness, constipation, headache and nausea. These symptoms, especially asked in follow-up visit. No patient excluded from the study, just because of the adverse effect. All patients tolerated minor adverse effects of the drug. When we review the literature from third world countries regarding epidemiological aspects of NVAF then as per different studies it was found that in India, mean age at diagnosis of NVAF is 65.8 years, and 26.3% of the patients were older than 75 years. In our study, mean age of diagnosis of non-valvular atrial fibrillation is too 64.00 ± 8.66 yrs. Most of the patients were with age > 55 years. Thus, based on these it can be concluded that non-valvular atrial fibrillation was most prevalent among the patients with age > 55 years. Few studies from India have shown that the mean age of patients with AF is nearly a decade younger than western cohort. In a similar study hospital data records of patients with chronic AF from Andhra Pradesh, revealed a mean age of 45.4 years, with most (51%) aged < 50 years and only 16.3% older than 60 years. In an observational hospital based study carried amongst indoor patients of AF by Vidya et al. reported that the mean age of the patients was 47 years and the majority of patients were aged between 51-60 years (48%).^{25,26} There is now greater recognition that the epidemiology of AF differs between men and women. The age-adjusted incidence of AF is higher in men compared to women in North American and European populations. In study by KO, d et al.²⁷ the incidence of AF was higher among men than women. Similar to western literature in Asian populations also a higher incidence of AF in observed in men; although less data are available. A study by Chugh et al.³ found higher incidence of AF among men. In GARFIELD-AF data by Jitendra PS. Sawhney et al who found that atrial fibrillation among the 40.1% in Indian women as compared to 44.2% in all other countries. (p value = 0.002).²⁸ Contrary to this in our study, the incidence of non-valvular atrial fibrillation is higher among female (54%) than male (46 %) and the prevalence was more than reported previously. This seems to be due to low threshold for a symptomatic presentation like palpitation in this part of globe as compared to the male counterpart. When we analyse different risk factors and comorbidities among NVAF in this part of globe, we observed that HTN was present in 61%, obesity together with overweight in 37%, smoking was present in 44%, history of moderate amount of alcohol intake (two drinks a day for men, or one drink a day for women) in 35%, history of CVA/TIA in 13%, DM in 11%, CKD in 4%, CAD in 30%, COPD in 20% and congestive heart failure in 15% of the patients. Hypertension was present in 61% of the patient in our study. Epidemiologic studies have shown that HTN is associated with a 1.8-fold increased risk of developing new-onset AF and a 1.5-fold increased risk of progression to permanent AF. In some studies, up to 90% of AF patients are observed to be hypertensive.²⁹ In the present study habit of smoking is present in 44.0%. The prevalence of smoking habit is almost similar to other previous studies. In few prior studies, it was reported that smoking is associated

with new onset AF. The FHS showed that within the last 50 years, the frequency of smoking with new-onset AF has decreased.³⁰ In GARFIELD-AF²⁸, data by Jitendra PS. Sawhney smoking current /ex-smoker found among 16% of patients in India a multicentre study conducted in different cities of India. Among all other countries data smoking habit was significantly lower among Indian patients ,smoking habits were as high as 34.6 % as compared to India where smoking habits current/ ex-smoker was 16%.(p-value less than 0.0001).In our study, a higher incidence of smoking is due to different smoking habits in rural and urban population and regional variation of smoking habits. Numerous studies have shown an association between elevated BMI and increased risk of AF.^{31,32} A meta-analyses of five studies found that obesity had a 49% increased risk of developing AFA dose-response relationship was observed with each 1 unit increase in BMI associated with a 3%–4.7% increase in AF risk.^{33,34} Moreover, obesity is now the second biggest attributable risk factor for AF after hypertension. Together with overweight, it accounted for 17.9% of all AF cases in the Atherosclerosis Risk in Communities (ARIC) study.³⁵ In our study prevalence of obesity together with overweight is somewhat higher i.e. 37% in comparison to western counterpart, the reason behind the increased prevalence seem to genetic predisposition and unhealthy diet more so in this part of the globe. Moderate alcohol consumption was reported in 35% of the patients in our study. As per data from Norwegian HUNT (Nord-Trøndelag Health) Study among 47002 participants, although alcohol consumption was associated with an increasing risk of AF in general, the attributable risk of alcohol consumption within recommended limits among participants without binge or problem drinking was negligible.³⁶ As per data from our study CVA/TIA present in 13% studied population. As per literature patients with non-valvular AF has a 5-fold excess risk of stroke. Weather stroke is due to AF or stroke predisposes AF incidence is still a matter of debate.³⁷ CAD and CHF were reported as an important risk factor for AF in our study. CAD was reported in 30%, while CHF was in 15% of the study population. In few studies the incidence of coronary artery disease (CAD) in patients with atrial fibrillation (AF) ranged between 24 and 46.5% which was in line with our study. The majority of the prior studies of the use of ranolazine as a cardioversion drug in AF were done on CAD patients.³⁸ On the other hand, in an analysis of the Framingham Heart Study, atrial fibrillation (AF) and congestive heart failure (CHF) have been found to be associated with each other, and the presence of either one increases the risk of developing the other and also increases the mortality risk associated with the other. In FHS analysis, patients who had CHF, 24% had a prior or concurrent diagnosis of AF, and 17% developed AF during the follow up period of 4.2 years.³⁹ So both CHF and AF are interrelated to each other. DM is one of the most common concomitant diseases in patients with AF. It was present in 11% of patients in our study. The multivariate analysis showed that DM is independently associated with AF (OR, 1.46).⁴⁰ COPD and CKD are an important predisposing risk factor for NVAf. The atrial fibrillation rhythm was 1.5-2 times more frequent in COPD patients in comparison to those without COPD. In our study COPD was reported in 20% of patients.⁴¹ Similarly AF frequently complicates chronic kidney disease (CKD) which was present in 4% of the patients in present study population. CKD and AF share risk factors and putative mechanisms, suggesting that common pathophysiologic processes may drive both pathologies. One possible common link between AF and CKD is activation of the renin-angio tensin-aldosterone system (RAAS).⁴²

Study Limitations

This study has a few limitations. The important ones which deserve mention are outlined. First, it is a single centre study and may not be representative of the population at large. Second is that event loop recording was not done in those patients who were converted into sinus rhythm, to rule out the

remote possibility of paroxysmal atrial fibrillation. And the last one is lack of blinded controls.

CONCLUSION

Ranolazine is an effective option to be used for rhythm control in NVAf in third world population also. As per study outcome predominant risk factors for non-valvular AF and associated co-morbidities in this part of the globe are hypertension, diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular accidents, chronic kidney disease, smoking and alcohol use. The findings in favour of ranolazine as an effective antiarrhythmic drug warrant future studies in the form of blind randomized controlled trials involving a large population across the globe with inclusion of event loop recording for rhythm monitoring.

ABBREVIATION- NVAf (Non Valvular Atrial Fibrillation), NOAC (novel oral anticoagulant), BMI (Body Mass Index), DM(Diabetes mellitus), CKD(Chronic Kidney Disease), CVA(Cerebro Vascular Accident), TIA(Transient Ischemic Attack), COPD(Chronic Obstructive Pulmonary Disease), CHF(Congestive Heart Failure), HTN(Hypertension).

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