

## GUIDELINE RECOMMENDED PHARMACOLOGICAL MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION, AT A TERTIARY CARE CARDIAC CENTRE, KARACHI PAKISTAN“ARE WE PRACTICING WHAT WE TEACH”?

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Date Received: July 16,2013

Date Revised: August 02,2013

Date Accepted: August 19,2013

**Contribution**

All the authors contributed significantly to the research that resulted in the submitted manuscript.

*All authors declare no conflict of interest.*

### ABSTRACT

**Objective:** To observe the practice of guideline recommend, pharmacological management of patients with Atrial fibrillation (AF), at tertiary care cardiac center.

**Methodology:** It was a descriptive cross-sectional study of six months duration conducted in National Institute of Cardiovascular Diseases Karachi (NICVD) from April to October 2007. Two hundred indoor patients with AF were evaluated. Data was recorded and analyzed by SPSS version 16.

**Results:** Majority of the patients with AF (76%), were <65 years of age. 46.5 % of patients had valvular heart disease. Rate controlling drugs were prescribed in 180 (90%) patients. Total of 88 (44%) patients received beta blocker, 83 (41.5%) patients received digoxin. In 19% of the patients with high risk for thromboembolism, neither Aspirin nor Warfarin was prescribed. In 14 % of low risk patients, both Aspirin and Warfarin were advised.

**Conclusion:** In contrast to western studies majority of our patients with AF were younger and almost half of them had valvular heart disease. Reasonable number of our patients with AF received guideline recommended pharmacological rate controlling therapy. Preventive pharmacological strategy for thromboembolic events was highly un-acceptable.

**Key Words:** Atrial fibrillation, Valvular Heart Disease, Thromboembolism, Guidelines, Rate controlling therapy, Warfarin

## INTRODUCTION

Atrial Fibrillation (AF) is an arrhythmia that is characterized by disorganized atrial depolarization without effective atrial contraction. AF is the most common arrhythmia seen in clinical practice and its prevalence increase with age.<sup>1</sup> There are three important objectives in the management of patients with AF. They are pharmacological (ventricular) rate control, maintenance of sinus rhythm & prevention of thromboembolism. Pharmacologic therapy is the treatment used most commonly to restore and maintain sinus rhythm, to prevent recurrences, or to control ventricular rate. Pharmacological rate control may be achieved with beta-blockers, calcium-channel blockers and digoxin. International studies, such as, RACE and AFFIRM trials, evaluated strategies of rate control versus rhythm control in AF.<sup>2,3</sup> Results of these studies indicate that strategy of rate control in AF patients can be at least as effective as rhythm control. Atrial fibrillation is one of major risk factor for stroke, increasing the risk of ischemic stroke by approximately fivefold, in patients with non valvular AF and 17 folds in those with AF and underlying valvular heart disease.<sup>4-8</sup> The risk of stroke depends upon co-morbid and age.<sup>9,10</sup> Thus, depending upon the risk, use of antiplatelet and anticoagulant is essential. Risk stratification is fundamental part of the treatment for thromboembolism. Depending upon the risk, prevention of thromboembolism is achieved with either aspirin or warfarin.<sup>11-13</sup> Implementation of American College of cardiology/American Heart Association (ACC/AHA/ESC) AF guidelines can have important impact on the survival and lifestyle of patients with AF.<sup>14</sup> Are we delivering the guideline recommended treatment to patients with AF? To the best of our knowledge, there is no local literature available to address this vital question. The objective of this study was to determine the implementation of the AHA recommended guideline based strategy, in patient with AF, admitted at tertiary care public hospital.

## METHODOLOGY

It was a descriptive cross-sectional study of six months duration, conducted at National Institute of Cardiovascular Diseases Karachi from April to October 2007. Two hundred

patients were included by non-probability purposive sampling. Inclusion criteria were: Age >18 years, either sex, diagnosed cases of AF (Diagnosed on basis of ECG). Patients were excluded if they had one or more contraindications to drugs used in AF. Patients were divided into three risk categories based on the AHA/ACC guidelines i.e. High risk (Previous stroke, Transient ischemic attack(TIA) embolism, Mitral stenosis, or Prosthetic valve), moderate risk (Age greater than or equal to 75 years, Hypertension, Heart failure, LV ejection fraction 35% or less, or Diabetes mellitus) and low risk (Female gender, Age 65 to 74 years, Coronary artery disease, or Thyrotoxicosis) (the Class-I Indication for Warfarin are; 1. one or more high Risk or 2.  $\geq$  two Moderate Risks).<sup>14</sup>

Patient with AF meeting the inclusion criteria seen by the doctors of National institute of cardiovascular diseases Karachi Pakistan and admitted in ward were included in the study. Informed consent was taken regarding treatment of AF, full history, particularly regarding age, history of smoking, alcoholism, diabetes mellitus, hypertension, heart failure, stroke, valvular and prosthetic valve diseases, was documented. Information regarding rate /rhythm controlling drugs and antithrombotic was collected using a questionnaire.

On the basis of filled Performa, a data base was developed on statistical package for social sciences (SPSS )version 16 for windows. The percentage variation of recommended medication for AF with drugs prescribed on case-sheet was determined. Mean  $\pm$  SD was computed for age. Frequencies and percentages were calculated for categorical variables including gender, presenting complaint, risk factors, classification of risk factors, class-I indication for warfarin and aspirin and drugs prescribed. Chi-square test was used to compare the proportion of drug prescribed at 5% level of significance.

## RESULTS

A total of 200 patients of Atrial Fibrillation (AF) were included in this study, 106 (53%) were female. Majority of the patients, 152 (76%) had age < 65 years (and 90% <75 years). Valvular Heart Diseases was the commonest risk factor associated with AF (Table1). Regarding pharma-

**Table 1: Variables among 200 Patients with Atrial Fibrillation**

Variables	Percentages
Mean age in years $\pm$ SD	51.2 $\pm$ 17.7
% of Patients with age <65years	76 %
Gender Female	106 (53%)
Patients with underlying Rheumatic(valvular) heart disease	93(46.5%)

cology treatment out of 200 cases, 180 (90%) cases received rate controlling therapy (RCT) drugs. 95% of patients receiving RCT were on either beta blocker or Digoxin.

Many patients had multiple risk factors for thromboembolism therefore total of 366 (various) risk factors were identified in 200 subjects (Table 2).

**Table 2: Risk Factors for Thromboembolism in 200 Patients with Atrial Fibrillation**

Risk	Low risk	Moderate risk	High risk
*Number of risk factors	147	127	92

\*Some patients had multiple risk factors therefore total risk factors were >200

#ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation (AF)  
:Circulation. 2006; 114: e257-e354

136 (68%) patients had Class-I indication for warfarin. However 79 (58%) of patients were not prescribed warfarin (Figure 1). Moreover 26 of these 136 patients (19%) were neither kept on Aspirin nor warfarin. Among the group of (64) patients without indication for Warfarin, 8 patients (8/64= 12.5%) were prescribed Warfarin. 9 of these 64 patients (14%) were kept on Aspirin and warfarin both (Figure 1).

## DISCUSSION

Although the objectives of management in cardiac patients with AF are well defined, yet there is considerable diversity in the age group and underlying risk factors, among the different racial groups. Maru reported the mean age of 41 years and high (66%) prevalence of associated rheumatic heart disease in Ethiopian outpatients with AF.<sup>15</sup> In a local study by Haq et al, valvular heart disease was present in 54%.<sup>16</sup> In our study the main age was 51.2 years and 46.5% of the patients had valvular heart disease. Zarifis et al, in their series of patients with AF admitted in the British hospital, reported prevalence of underlying rheumatic heart disease <5% and mean age of 74.4years.<sup>17</sup> In Danish study of hospitalized patient with AF, main age reported was 73years with only 4.5 % having valvular heart disease.<sup>18</sup> Thus our patients with AF, unlike the west were younger (76% <65 years ) and had higher prevalence of Rheumatic (46.5 % valvular) heart disease.

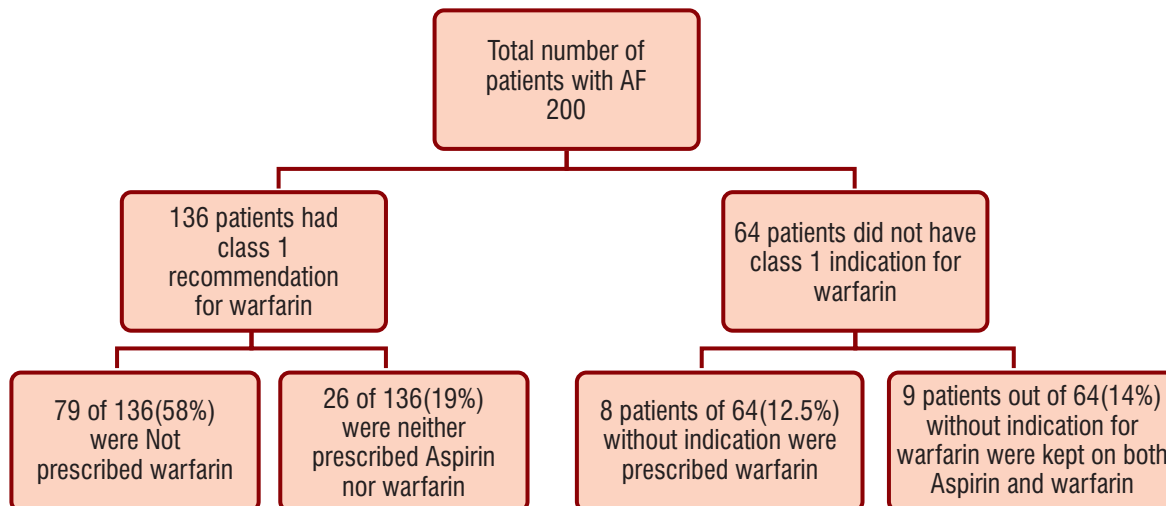
Reasonable number of our patient's ,180/200 (90%), received rate controlling drugs. More than 80% of the patients were on beta blocker or digoxin. A similar trend was reported in the series of patients, from local hospitals,

reported by Haq et al, with 80% of patients on beta blocker and digoxin.<sup>16</sup> In study of 996 patients of AF at Ben-Gurion University of the Negev, Beer Sheva, Israel (66.3%) received rate- control treatment, beta blockers (47%), digoxin (13%) and non-dihydroperidine calcium channel blockers (15.9%).<sup>19</sup> In a large Danish study, majority of patient were kept on digoxin (53 %), followed by beta blocker (23.4%) and sotalol (26%).<sup>18</sup> In a survey of 810 physicians from 11 countries treating AF patients, 61% were on rhythm control therapy, and 46% on rate control therapy.<sup>20</sup>

There are two options to address the issues of rhythm, maintenance of normal sinus rhythm (NSR) or control of the ventricular rate. The maintenance of sinus rhythm is the main therapeutic goal but due to recurrences and side effects of anti-arrhythmic drugs, the benefits of sinus rhythm are being offset. Many trials have evaluated the two treatment strategies.<sup>2,3,21</sup> Rate control was found non-inferior to the rhythm control without significant differences in quality of life and permits consideration of rate control as primary therapy. Majority of our patient with AF were young with Valvular lesion with large left atrium, not ideal for rhythm control. Thus rate control with Beta blocker calcium blocker or digoxin, was found more cost effective and safe option and was used in 90% of our patients. In practice, an attempt should be made to restore sinus rhythm, in symptomatic patients under 65 years with non valvular AF. Introduction of novel anti-arrhythmic, for maintenance of sinus rhythm in patients with AF may eventually improve patient outcomes.<sup>22</sup>

Hypertension, Diabetes mellitus, heart failure and increasing aging, are independent risk factors for developing AF, as was reported in the by Benjamin et al, in their population based Framingham heart study.<sup>23</sup> Schnabel et al, in a community-based cohort (Framingham Heart) Study of about five thousand patient with AF, developed a risk score for developing atrial fibrillation.<sup>24</sup> Interesting fact is that most of the risk factors for developing AF are also important risk factors for systemic thromboembolism in patient with AF. Gage et al, and Lip et al have developed risk scores CHADS2 and CHA2DS2-VASc respectively, for predicting stroke and thromboembolism in patient with AF.<sup>10,25</sup> Olesen et al, in their study of 73538 patients with AF, validated novel score (CHA2DS2)VASc, which was found to be better than CHADS2)score for stroke prediction.<sup>26</sup>

AF patients with Valvular heart disease, particularly mitral stenosis, even at younger age has high risk for thromboembolism due to high prevalence of left atrial thrombus.<sup>27,28</sup> Before 1990 antithrombotic therapy was mainly used in patient with valvular AF. Since then, 24 randomized trials, comparing warfarin with placebo, for prevention of embolic strokes in patient with non valvular AF, have been published. Meta-analysis by Hart et al, reported that oral anticoagulation is effective for prevention of stroke, with risk reduction of 61% versus placebo.<sup>13</sup> Aspirin offers

**Figure 1: Inappropriate Antithrombotic /Anticoagulant Therapy in Patients with AF**

only modest protection against stroke for patients with AF, a stroke reduction of 19%. Hart et al, have reported that greater the risk of disabling cardio-embolic stroke in a population of patients with AF, the less protection is afforded by Aspirin.<sup>29</sup> Combinations of oral anticoagulants plus antiplatelet agents neither reduce the risks of hemorrhage nor have higher efficacy than vitamin K antagonist (VKA). In fact dual therapy may accentuate intracranial hemorrhage.<sup>30</sup>

Based on the presence of various risk factors for thromboembolism, the AHA/ACC guideline for AF, have classified the patients into three risks categories, and have recommended the appropriate antithrombotic therapy.<sup>14</sup> Briefly Vitamin K antagonist (VKA) and Aspirin is strongly recommended for all high and low risk patient with AF respectively. Combined Aspirin and VKA is not recommended. It is the consensus of the authors of these AHA guidelines that the most important agent for the maintenance of coronary stent patency is clopidogel.<sup>14</sup> Moreover addition of aspirin in AF patient on chronic anticoagulant regimen contributes more risk than benefit.

136/200 cases with AF had class 1 indication for VKA (warfarin) in our study. However only 42% of these patient were prescribed VKA (Warfarin). More worrisome fact was that 26 patients(19%) of these 136 patients with class 1 indication for Warfarin, were neither kept on Warfarin nor Aspirin. Thus more than half of AF patient, who were at high risk for stroke, were deprived of VKA and one fifth of these patients were deprived of VKA as well as Aspirin. Showing extreme degree negligence of under treating high risk patients. As discussed above dual antithrombotic (Aspirin plus VKA) is not recommended in AF patient without other

compelling reason eg prosthetic valve. 64 of the 200 cases did not have class 1 indication for warfarin. Surprisingly 9(14%) of these 64 patients were prescribed dual antithrombotic therapy. Showing a dangerous trend of over treating low risk patients.

McBride et al, conducted a multi-centre observational study in patients with AF,(MOCA), to evaluate the current anticoagulation treatment pattern in patients with AF in Germany.<sup>31</sup> 361 patients with AF were recruited in 45 physician practices. They reported that “A gap of 40% existed between the guideline recommendations and actual practice. Younger patients (<60 years of age) with no documented risk factors for stroke were over-treated with VKAs and patients older than 75 years without contraindications for anticoagulation were under-treated.”

Po et al, in an observational study, department of Neurology, at Taiwan reported the trends of using antithrombotic treatment in AF patients prior to first ever stroke.<sup>32</sup> They concluded that “56% of patients were not on antithrombotic therapy. Only (20%) were adequately treated according to the current guidelines. At 90 days follow-up, 28% of the adequately treated patients died or were severely disabled compared with 57% of those inadequately treated.” In a Similar study at University of Perugia Italy, Paciaroni et al observed that only 10% of patients with known AF were prescribed the guideline recommended antithrombotic treatment, prior to first ever stroke.<sup>33</sup> Mashal et al, Conducted primary care study among 995 AF patients at University of the Negev, Beer Sheva, Israel.<sup>19</sup> They concluded that “Of the patients with a low CHADS2 score (< 1) 52.7% received

VKA treatment, and 39.4% with a high CHADS2 score ( $\geq 3$ ) did not receive VKA". The primary care practice studies in Far east, Mideast and Europe, mentioned above, shows considerable gap in the practical use and the guideline recommended antithrombotic in AF patient.

The status at tertiary care centre is not much different. Agarwal et al, evaluated the use of anticoagulants in 44,193 indoor, AF patients hospitalized in the American hospitals during November 2003 and 31 October 2004.<sup>34</sup> Their results showed that higher stroke risk (as indicated by CHADS2 scores) was associated with a higher likelihood of warfarin treatment. However, elderly patients aged  $\geq 75$  years were less likely to be treated with warfarin than younger patients. Hansen et al, in their study analyzed the use of oral anticoagulants (OAC) in 108504 Danish patients admitted (1995 to 2004) for AF in tertiary centre (main regional and local community hospitals).<sup>18</sup> They reported that "only 37% received OAC; ranging from 17% to 50% between the hospitals with the lowest and highest OAC use respectively". Surprisingly neither tertiary university hospitals nor high volume hospitals had higher OAC use than local community hospitals and low volume hospitals. Waldo et al, studied 945 hospitalized patients with AF, at University Hospitals of Cleveland, Ohio.<sup>35</sup> In Patients at high risk of stroke, only 55% received warfarin. Neither warfarin nor aspirin were prescribed in 21% of high-risk patients.

In unacceptable number of AF patients, our practicing pendulum, regarding antithrombotic treatment is swinging at two extremes of recommended guideline treatment "Under treating patients who need it and over treating those who do not". In some of above studies, with follow up of patients, reported significant increase in the Ischemic strokes or mortality among those with suboptimal treatment.<sup>18,32</sup> Unfortunately this global trends, has been observed in the clinical practice as well in the tertiary care centre. This is a big blow to our vision of practicing evidence based medicine.

We need to have multi dimensional interventional strategy for implementation of the guideline recommended management, for this crippling disease of our youngster. Take away message is "When you see a patient with AF, fore see Stroke". Otherwise we will continue encountering young aphasic (hemiplegic) patient, who with their staring anxious eyes, are asking us "Doc. how much is too much negligence"?

## CONCLUSION

Majority of our patients with AF were (two decade) younger and had valvular heart disease ten times more frequent, as compared to the west. Reasonable number of our patients with AF, received guideline recommended pharmacological rate controlling therapy. There was an un-acceptable trends

of over treating low risk and under treating high risk AF patients, with oral anticoagulants.

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