PROPHYLACTIC ANTITHROMBOTICS IN ATRIAL FIBRILLATION;HOW OPTIMAL IS THE USE ?

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ABSTRACT

Aims & objectives; To determine the frequency of use of prophylactic antithrombotics in patients with atrial fibrillation presenting as stroke

Exclusion criteria; All those patients having intracranial tumor, myeloproliferative disorders, aplastic anemia, acute leukemia, bleeding/coagulation disorders not due to antiplatelets /anticoagulants use, stroke not related to atrial fibrillation or its treatment, cases with AF and stroke but not fulfilling the criteria for indications of prophylactic antithrombotics and all cases with rheumatic valvular disease were excluded from the study.

Inclusion criteria; All cases with stroke and AF of age 18 years or more and not having the above mentioned exclusion criteria

Material & Methods; Patients presenting with features of stroke were thoroughly examined after obtaining a detailed history of their current and previous cardiac/noncardiac illnesses and previous or current use of antithrombotics. A predesigned proforma was filled from each patient and subsequently the data was processed through SPSS.

Conclusion; Majority(64.1 %) of patients with AF and stroke were not on antithrombotics. Among those on antithrombotics (35.9 %), Aspirin was the most commonly prescribed agent. Use of prophylactic antithrombotic agents in our set up is still not upto the mark. Adhernce to Criterias meant for estimating the risks of thrombosis and bleed may help in recommending antithrombotic agents in atrial fibrillation .

Study setting; Hayat Abad Medical Complex Medical A unit

Duration of study; one year (Feb 2011 to 2012)

Keywords; Antithrombotic Agents (ATA), Atrial Fibrillation(AF), Stroke

INTRODUCTION

Anticoagulants(AC) are not only used for prevention and treatment of venous thromboembolism but are also given to reduce the risk of ischaemic stroke[1] especially among patients with atrial fibrillation(AF). The use of AC is likely to increase in future, especially since guidelines from the UK National Institute for Health and Care Excellence (NICE) encourage more systematic identification of patients at high risk of venous thromboembolism or stroke who might benefit from anticoagulation. For example, in 2010 NICE issued new guidance to improve the prevention of venous thromboembolism for patients, using cost effective interventions[2] . In January 2014 NICE issued draft guidance on the management of atrial fibrillation, which included assessment of the risks of stroke as well as the risks and benefits associated with anticoagulation.[3]

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AF is a major preventable cause of stroke[4] . Despite the fact that anticoagulation is very effective in preventing strokes due to AF[1] there is extensive evidence that AC remain underused[5,6]. This underuse of AC is reflected in the low utilisation among patients with known AF presenting with stroke[7]. Appropriate AC is particularly important among the elderly, as this group is at greatest risk of strokes attributable to AF[8].

Though antithrombotic agents have a key role in minimizing thromboembolic risks however they also have a potential to cause hemorrhagic strokes and bleed elsewhere. Careful monitoring of such patients is therefore mandatory. Labaoratory facilities for monitoring are available in main cities of Khyber pukhtoonkhwa(KPK) but not in remote areas.Unmonitored use of AC causes fear among physicians especially those practicing in remote areas of KPK province.

Should Prophylactic anticoagulants be advised to all pts with AF? Are all pts with AF equally at risk of ischaemic stroke? The CHADS2 score is a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation (AF). It is used to determine whether or not treatment is required with anticoagulation therapy or antiplatelet therapy [9]. A high CHADS2 score corresponds to a greater risk of stroke, while a low CHADS2 score corresponds to a lower risk

of stroke. The **$CHADS_2$** score is simple and has been validated by many studies[10].

The **$CHADS_2$** scoring scheme [11] is adding together the points (given below against each condition) that correspond to the conditions that are present, which is used to estimate stroke risk consist of;

C Congestive heart failure (1), H Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) (1) A Age ≥75 years (1) D; Diabetes mellitus (1) S2; Prior Stroke or TIA or Thromboembolism (2) The annual stroke risk associated with different CHADS2 scores and the treatment stratigies recommended are given in table 1 and 2 respectively[10].

In clinical use, the CHADS2 score has been superseded by the CHA2DS2-VASc score that gives a better stratification of low-risk patients. CHA2DS2-VASc[12] score is a refinement of CHADS2[13] score and extends the latter by including additional common stroke risk factors, as discussed below.

The maximum CHADS2 score is 6, whilst the maximum CHA2DS2-VASc score is 9 (for age, either the patient is ≥75 years and gets two points, is between 65-74 and gets one point, or is under 65 and does not get points). Female gender only scores one point if the patient has at least one other risk factor, and does not score any points in isolation

CHA2DS2-VASc Condition Points are

C Congestive heart failure (or Left ventricular systolic dysfunction) (1) H Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) (1) A2 Age ≥75 years (2) D Diabetes Mellitus (1) S2 Prior Stroke or TIA or thromboembolism (2) V Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque) (1) A Age 65–74 years (1) Sc Sex category (i.e female sex) 1 While offering prophylactic antithrombotics in AF, not only thromboembolic phenomena and its risk calculation through CHADS2 or CHADS2-VASc score needs to be considered but equally important are bleeding risks associated with such type of treatment.

Several clinical risk prediction rules have been developed to assess the risk of bleed. Among the first were the HEMORRHAGES,[14]ATRIA scores,[15] and RIETE and OBRI scores.[16] More recently the HAS-BLED score[17] has been developed and is recommended in the European Society of Cardiology guidelines.[18] HAS-BLED has several advantages compared with previous scores as it does not require information unlikely to be available in clinical practice, such as genetic information. It has also has out-performed previous scores in identifying clinically relevant bleeding.[19] HAS-BLED score is a therapeutic bleeding risk stratification score for those on oral anticoagulants in AF[17]. It is matched to the CHA2DS2-VASc score used for stroke risk stratification but has not as of 2010 been externally validated.

HAS-BLED score for bleeding risk on oral anticoagulation in atrial fibrillation takes into account Feature like, Hypertension (Systolic ≥ 160mmHg) ,Abnormal renal function ,Abnormal liver function ,Age ≥ 65 years ,Stroke in past ,Bleeding ,Labile INRs ,Taking other drugs as well ,Alcohol intake at same time. Presence of each feature is scored one ,thus maximum score is nine.

A score of 3 or more indicates increased one year bleed risk on anticoagulation sufficient to justify caution or more regular review. The risk is for intracranial bleed, bleed requiring hospitalization or a haemoglobin drop > 2g/L or that needs transfusion.

Finaly our work will help to resolve the issues regarding underuse or otherwise of antithrombotic agents in AF which may direct physicians regarding incorporation of recent criterias in their practices.

RESULTS

A total of 78 pts were studied. Of them 41 were females and 37 were males. 67 were of age 40 years or above while 11 were below age 40. Table 3 shows antithrombotic agents and the type of findings on CT brain in each case. Table 4 shows the overall % ages of pts on or off antithrombotics Table 5 shows pts on antithrombotics and the type of stroke with which they presented Table 6 shows the % age of pts who were not on antithrombotic agents but presented with

Table-1; Annual stroke risk

CHADS2 Score	Stroke risk %	95% CI
0	1.9	1.2-3.0
1	2.8	2.0-3.8
2	4.0	3.1-5.1
3	5.9	4.6-7.3
4	8.5	6.3-11.1
5	12.5	8.2-17.5
6	18.2	10.5-27.4

Table-2; Treatment strategies recommended based on the CHADS2 score

Score	Risk	Anticoagulation Therapy	Considerations
0	Low	None or Aspirin	Aspirin daily
1	Moderate	Aspirin, Warfarin, or other oral anti-coagulant	Aspirin daily or raise INR to 2.0-3.0, depending on patient preference
2 or greater	Moderate or high	Warfarin or other oral anti-coagulant	Raise INR to 2.0-3.0, unless contraindicated

Table-3; Type of Antithrombotic agent and CT scan brain findings in patients with AF

Antithrombotic Agent/s	CT Scan findings			
	infarct	hemorrhage	Cerebral atrophy	normal
Warfarin	03	04	00	00
Heparin	00	00	00	00
Aspirin	09	03	00	00
Clopidogrel	03	00	00	00
Aspirin plus clopidogrel	00	00	00	00
Anticoagulants plus antiplatelets	03	00	03	00
None	22	07	09	12
Total	40	14	12	12

Table-4; Profile of pts with AF & Stroke on/off antithrombotic agents

Status	No of pts	%age
On antithrombotics	28	35.9
Not on antithrombotics	50	64.1

Table 5-; Type of stroke in pts with AF on antithrombotics

No of pts on ATA	Type of Stroke	%age
7	hemorrhagic	25
21	Non hemorrhagic	75

Table -6; Type of stroke in pts with AF not on antithrombotics

No of pts not on ATA	Type of stroke	%age
7	hemorrhagic	14
43	Non hemorrhagic	86

Table -7; Type of stroke and Antithrombotic agents in pts with AF & STROKE

CT findings	warfarin	Heparin	aspirin	Clopidogrel	Asp+-clopid	Anticoag-+antiplat	none	Total
Hemorrhagic stroke	4	00	3	00	00	00	7	14
Non hemorrhagic stroke	3	00	9	3	00	6	43	64
Total	7	00	12	3	00	6	50	78

Table-8 Frequency of antithrombotics

N	Valid		78	
	Missing		0	
Antithrombotic Agents				
Valid Aspirin	12	15.4	15.4	15.4
Warfarin	7	9.0	9.0	24.4
Clopidogrel	3	3.8	3.8	28.2
Aspirin+warfarin	6	7.7	7.7	35.9
None	50	64.1	64.1	100
total	78	100.0	100.0	

stroke(hemorrhagic in 14 % and nonhemorrhagic in 86%).

Out of 7 pts on warfarin 4 had hemorrhagic stroke while 3 had nonhemorrhagic stroke. Similarly Out of 12 pts on Aspirin 3 had hemorrhagic strokes and 9 had non hemorrhagic strokes,Table -7.

The frequency of antithrombotic agents is shown in table 8. Out of total 78 pts 50(64.1%) were not on antithrombotics. Aspirin was taken by 12 pt(15.4%) and warfarin by 7 (9%).

DISCUSSION

Atrial fibrillation is a potent risk factor for ischemic stroke. The incidence of stroke associated with AF is 3 to 5 percent per year in the absence of anticoagulation which is significantly higher compared to the general population without AF(relative risk 2.4 in men and 3.0 in women)[20]. Oral anticoagulants such as warfarin can largely reverse this stroke risk[21]. However, warfarin therapy can lead to significant bleeding complications, the most important type of which is intracranial hemorrhage[21].

Out of our 78 patients with AF and Stroke only 28 were on antithrombotic agents while 50 were not on such agents despite having indications. Thus findings of our study correlates with that of Campbell Cowan et al [22] who concluded that Over one-third of patients with AF and known risk factors who are eligible for anticoagulants(AC) do not receive them.Others have also shown in their studies that Despite the fact that anticoagulation is very effective in preventing strokes due to AF[1], there is extensive evidence that AC remain underused[5,6]. This underuse of AC is reflected in the low utilisation among patients with known AF presenting with stroke[7] . Contrary to others Bradley BC et al examined the rate of AC in 998 pts with AF who attended a veterans affairs medical center over a two year period. Warfarin was prescribed for 504(51%) pts and not prescribed for 494 (49%)pts. They concluded that the use of warfarin for AF in this setting is higher than previously reported and approaching ideal levels[23].

Shane B et al has also shown that the use of anticoagulation for AF has slowly increased in the last dacade.Though this increased use is encouraging there are two important caveats. First many pts are still not receiving anticoagulation.Patients receiving therapy meant to maintain sinus rhythm might be at a higher risk for underuse of anticoagulation than those taking rate control therapy. Second the increase in use of anticoagulation seems to have been particularly notable among pts who might not benefit from this therapy[24].

Although our study was not designed to determine the factors responsible for underuse or otherwise of antithrombotic agents we found that underprescription and poor compliance were the two important factors .In our study Fifty pts with AF and non hemorrhagic stroke (NHS) on presentation were not on ATAs. Among them 17 pts were noncompliant, while 33 pts were not advised such treatment.

Out of 28 pts on ATA 7(25%) had hemorrhagic stroke (HS) while 21(75%)had NHS.Why despite anticoagulation more pts had nonhemorhagic stroke and whether ischaemic stroke in a pt on antithrombotics is due to insufficient doses of ATA or has some other reason, further studies can resolve the issues.

The anticoagulation decision in a patient with atrial fibrillation depends in large part on the expected reduction in ischemic stroke risk due to warfarin versus its expected increase in risk of intracranial hemorrhage[25]. However, the anticoagulation decision should also depend on the impact of anticoagulant therapy on the severity of incident ischemic and hemorrhagic events[26]. Based on the findings that anticoagulants even if failed to control the ischaemic stroke may reduce the severity of such strokes further studies can be conducted to clarify the issues.

Out of the total 78 pts 50 were not on ATA. Out of those 50 not on ATA 43 had NHS highlighting the fact that these strokes could have been prevented or atleast their severity reduced and course modified if antithrombotic agents were prescribed.

Another important observation was finding hemorrhagic strokes in 7 pts who were not on ATA and non hemorrhagic strokes in 21 pts who were on ATA.

This finding points to the more complex mechanisms that possibly are involved in causation of both types of strokes not just the over or underuse of ATA.

Overall in our study pts not on ATA dominated over those who were on ATA in both types of stroke. Occurrence of hemorrhagic stroke in pts not on ATA indirectly unmask the fact that hemorrhagic stroke in pts with AF on ATA may not always be due to over anticoagulation. In simple words other factors responsible for bleed in straight forward cases (not on AC) of hemorrhagic stroke may also be the cause of HS in pts on AC.

Finally we conclude that majority(64.1 %) of our patients with AF and stroke were not on antithrombotics. Among those on antithrombotics (35.9 %) , Aspirin was the most commonly prescribed agent. It is clear from our study that the use of prophylactic antithrombotic agents in our set up is still not upto the mark. This can be improved by adhernce to Criterias meant for estimating risks of thrombosis due to AF and bleed due to antithrombotic agents. Such strategies will help physicians in decisions regarding treatment of pts with AF. Considering newer criterias for indications of ATA in pts with AF and calculating bleeding risks associated with them further studies can be conducted.

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