RESEARCH ARTICLE

ASSESSMENT OF FREQUENCY AND OUTCOMES OF ATRIAL FIBRILLATION IN PATIENTS PRESENTING WITH ISCHEMIC STROKE

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ABSTRACT

Objective: To determine the frequency of atrial fibrillation in patients presenting with ischemic stroke and outcome in terms of death or survival at the time of discharge from the tertiary care hospital in Quetta. *Patients and methods:* This case series study was carried out in a period of one year from May 2014 to April 2015 at Neurology department, Bolan Medical Complex Hospital, Quetta, Pakistan. A sample of 136 patients of age >20 years &<60 years who were ischemic stroke diagnosed on MRI were included. Patients with the transientischemic attack, subarachnoid hemorrhage, cerebral infections Meningitis (Bacterial, tuberculous, viral) and epileptic seizures were excluded. Frequencies and percentages were expressed for categorical variables like gender, outcome variables i-e; presence or absence of AF and survival. Effect modification tested through Chi-square with P value ≤ 0.05 significant. *Results:* The mean $\pm$ SD age of patients was 49.13 $\pm$7.13 years (Range: 35-60). Mean $\pm$ SD duration of disease (presenting symptoms of stroke) was 8.62 $\pm$ 6.48 hours (Range of 1-29). Male to female ratio was 6.62:1 and male patients were 87.76% (n= 118) while only 13.24% (n= 18) were females. The frequency of AF among patients of ischemic stroke was 21.32% (n= 29) and 3.68% (n= 5) did not survive. Stratified analysis showed that the age, gender, residence and duration of disease were effect modifiers for the frequency of atrial fibrillation as well as the outcome among ischemic stroke patients. *Conclusion:* Every one out of five ischemic stroke patients may have atrial fibrillation as comorbidity or the underlying reason. Elder age, especially female after menopause, late presenters and those referred from rural areas should be screened thoroughly for atrial fibrillation as a possible underlying diagnosis.

INTRODUCTION

Stroke or cerebrovascular accident was defined as a collection of rapidly developing clinical symptoms and signs of focal/global neurological deficits and the symptom lasting >24 hours, or leading to death with no apparent cause other than that of vascular origin (WHO MONICA Project Investigators, 1988). After coronary heart disease and cancer, stroke is the third most common cause of death in most Western populations. It was a common non-communicable killer disease in low and middle-income countries as well. Stroke incidence in Asia was generally higher than in the USA. This could also be attributed to a high prevalence of risk factors such as hypertension and smoking (Dans *et al.,* 2011). According to World Health Organization estimates, 5.5million people died of a stroke in 2002, and roughly 20% of these

deaths occurred in South Asia. About a quarter of Pakistani population has suffered a cerebrovascular event (either a stroke or a Transient ischemic attack (Dans *et al.,* 2011). The estimated annual incidence of stroke in Pakistan was 250/100,000; translating to 350,000 new cases every year and these Pakistani stroke survivors have poor outcomes in the community, mostly due to complications which in fact are preventable (Dans *et al.,* 2011; Ali *et al.,* 2009). Stroke results from brain infarction (almost three-quarter of cases) or hemorrhage (Dans *et al.,* 2011). Cerebral infarction was due to ischemia which was caused by atherosclerosis of carotid and intracranial vessels or due to coexisting heart diseases, which causes emboli formation. The most common cardiac source of such emboli to the brain was atrial fibrillation (AF). AF increases the risk of stroke 5-fold and accounts for around 15-20% of all stroke cases (Dans *et al.,* 2011; Ali *et al.,* 2009). It

was estimated that without preventive treatment, approximately 1 in every 20 patients with AF will have a stroke each year (Dans *et al.,* 2011). Strokes due to AF tend to be severe, with an increased likelihood of death and disability. Previous embolic event, increasing age, hypertension, diabetes, left ventricular dysfunction, enlarged left atrium are common risk factors leading to these events in AF patients (World Health Organization, 2004). While AF can affect adults of any age, the prevalence increases with age: 3.8% among people aged >60 years rising to 9% among those age d>80 years (World Health Organization *et al.,* 2004). Paciaroni M and coworkers found that AF was present in 20.3% newly diagnosed stroke patients.4 Death occurred in 6% and other 39% cases of stroke with AF have one or other disability at the time of discharge (Kamal *et al.,* 2009). In another study, Lamassa *et al.* (2001) found that AF was diagnosed in 18% patients of stroke (World Health Organization, 2004). Further, they described that mortality at 3 months was 32.8% among AF and 19.9% among non-AF patients (p<0.001) (Khealani *et al.,* 2008). Although stroke and AF are prevalent, the frequency of AF as a determinant of stroke was very scantly investigated/ neglected in Pakistan. Upon through literature search, no study was found describing the magnitude of the burden of stroke attributed to AF, therefore currently there was need of a clinical study in this perspective. The results of this study will generate the statistics of our own context as well as it will help to renew the management strategies in order to minimize the morbidity and mortality in AF patients.

MATERIAL AND METHODS

Study design: Descriptive cross-sectional study.

Study setting: Neurology department, Bolan Medical Complex Hospital, Quetta.

Study duration: May 2014- April 2015.

Sample size: With 6% expected death rate due to AF among stroke patients, (Lamassa *et al.,* 2001) a margin of error set as 4%, and confidence level at 95%, and putting the data into least proportion formula the calculated sample size was 136.

Sampling Technique: Nonprobability consecutive sampling.

Sample Selection

Inclusion Criteria

- Patient of age between 20-60 years
- Patient of either gender
- New ischemic stroke diagnosed on MRI within the ascertainment period
- Presenting within 24 hours of the onset of stroke
- Willing to participate in the study

Exclusion Criteria

- Transient ischemic attack
- Subarachnoid hemorrhage and venous sinus thrombosis
- Transient global amnesia (TGA)
- Cerebral infections like Meningitis (Bacterial, tuberculous, viral)

- Other Cardiac conditions like Cardiac syncope, Atrial flutter alone
- Epileptic seizures with postictal symptoms
- Peripheral nerve disorders like Bell's palsy, vestibular neuritis
- intracranial masses (e.g., tumor, abscess [often differentiated by CT])
- Metabolic disorders like hyperthyroidism
- History of Cardiac pacemaker installation

Data collection procedure

The studywas started after approval from the Institutional Review Board of Bolan Medical College, Quetta. Patients presenting to the emergency department with symptoms of stroke were evaluated and those who have ischemic stroke diagnosis on history and clinical basis followed by the MRI were asked to participate in the study. Consent for the study was taken from the closest adult attendant. Only consenting cases were included in the study. Contrast MRI scan and continuous twelve-lead ECG was performed in all patients immediately in an emergency ward. Later on, the patient may be shifted to ICU or Neurological ward. The diagnosis of AF was confirmed by a cardiologist (who was blinded to the study) on the basis of 12 lead ECG. Data was gathered by a proforma that included demographic variables like name, age, gender and area of residence. Duration of symptoms was noted. Data on primary outcome variable i.e. presence or absence of atrial fibrillation was noted. After 24 hours of' death or survival of the patient was also be noted. All the patients were treated as per standard protocols of the institute. The study participants were enrolled through strictly following the selection criteria to control the confounders.

Statistical analysis: Data were entered into SPSS version 20. Continuous variables like age, duration of symptoms were analyzed as mean ± standard deviation. Frequencies and percentages were expressed for categorical variables like gender, outcome variables i-e; presence or absence of AF and death or survival. Age, gender, residence and duration of symptoms were stratified to analyze the effect of these variables on the outcome i-e; frequency of AF in stroke patients and death or survival. Chi-square was applied to test the difference taking P-value≤0.05 as significant.

RESULTS

The mean ± SD age of patients was 49.13 ± 7.13 years with a range of 35-60 years. Mean ± SD duration of disease (presenting symptoms of stroke) was 8.62 ± 6.48 hours with a range of 1-29 hours (Table 1). Male to female ratio was 6.62:1 and male patients were 87.76% (n= 118) while only 13.24% (n= 18) were females (Figure 1). Being situated in the metropolitan city, the study enrolled majority of urban patients i.e. 58.8% (n= 80) while patients brought from rural areas were 41.2% (n= 56) (Table 2). Figure 2 shows the age categories of patients, according to which majority (about 90%) was of age above 40 years. Amongst these, the patients within age 41-50 years were 47.79% (n= 65), those of age 51-60 years were 41.91% (n= 57) while the patient whose age was less than 40 years was 10.29% (n= 14). About 46% (n= 63) patients presented within initial 6 hours of developing symptoms. Those reaching hospital with 7-12 hours were 40.44% (n= 55).

Beyond that were 7.53% (n= 10) and 5.88% (n= 08) which reached within 13-24 and 25-36 hours respectively (Figure 3). This study noted that the frequency of a trial fibrillation among patients of ischemic stroke was 21.32% (n= 29) (Figure 4) and the fatal outcome among these patients was noted to be 3.68% (n= 5) (Figure 5).

Table 1. Descriptive statistics

n= 136	Mean + S.D.	Minimum	Maximum
Age (Years)	49.13 ± 7.13	35	60
Duration of disease (hours)	8.62 ± 6.48	1	29

Table 2. Residence

n= 136	Frequency	Percentage
Urban	80	58.8
Rural	56	41.2
Total	136	100

Table 3. Stratified analysis of the frequency of atrial fibrillation with age

Age in years	Atrial Fibrillation		Total	P valve
	Yes	No		
Less than 40	2 (14.3%)	12 (85.7%)	14 (100%)	
41-50	13 (20%)	52 (80%)	65 (100%)	
51-6	14 (24.6%)	43 (75.4%)	57 (100%)	0.658
Total	29 (21.3%)	107 (78.7%)	136 (100%)	

Table 4. Stratified analysis of the outcome of disease with age

Age in years	Outcome of disease		Total	P valve
	Survival	Death		
Less than 40	14 (100%)	0 (0%)	14 (100%)	
41-50	63 (96.9%)	2 (3.1%)	65 (100%)	
51-6	54 (94.7%)	3 (5.3%)	57 (100%)	0.605
Total	131 (96.3%)	5 (3.7%)	136 (100%)	

Table 5. Stratified analysis of the frequency of atrial fibrillation with gender

Gender	Atrial Fibrillation		Total	P valve
	Yes	No		
Male	25 (21.2%)	93 (78.8%)	118 (100%)	
Female	4 (22.2%)	14 (77.8%)	18 (100%)	
Total	29 (21.3%)	107 (78.7%)	136 (100%)	0.565

Table 6. Stratified analysis of the outcome of disease with gender

Gender	Outcome of disease		Total	P valve
	Survival	Death		
Male	114 (96.6%)	4 (3.4%)	118 (100%)	
Female	17 (94.4%)	1 (5.6%)	18 (100%)	
Total	131 (96.3%)	5 (3.7%)	136 (100%)	0.514

Table 7. Stratified analysis of the frequency of atrial fibrillation with the residence

Residence	Atrial Fibrillation		Total	P valve
	Yes	No		
Urban	14 (17.5%)	66 (82.5%)	80 (100%)	
Rural	15 (26.8%)	41 (73.2%)	56 (100%)	
Total	29 (21.3%)	107 (78.7%)	136 (100%)	0.138

Table 8. Stratified analysis of the outcome of disease with the residence

Residence	Outcome of disease		Total	P valve
	Survival	Death		
Urban	79 (98.8%)	1 (1.2%)	80 (100%)	
Rural	52 (92.9%)	4 (7.1%)	56 (100%)	
Total	131 (96.3%)	5 (3.7%)	136 (100%)	0.092

Stratified analysis showed that the frequency of atrial fibrillation as well as the fatal outcome was non-significantly affected by age of patients (Tables 3 and 4 with P values = 0.658 and 0.605 respectively). With increasing age, there was an increase in the rates of AF and a decrease in survival rates. Stratified analysis showed that the frequencies of atrial fibrillation as well as the fatal outcome, both were slightly higher among females than males (Tables 5 and 6 with P values = 0.565 and 0.514 respectively). Stratified analysis showed that with a difference of residence of patients there was a difference in the frequency of atrial fibrillation as well as the fatal outcome. Thus it was non-significantly; found that urban living patients havea lesser frequency of AF and lesser incubating deaths as compared to urban living patients (Tables 7 and 8 with P values = 0.138 and 0.092 respectively). Finally; it was significantly found with stratified analysis (P values = 0.024 and 0.0001 respectively) that the frequency of atrial fibrillation and the fatal outcome was affected by the duration of disease. Those patients presenting within 6 hours' development of symptoms had least frequency of AF and more favorable outcome (00% deaths) than those presenting after beyond this time such that the lately presenting (25-36 hours) patients had higher frequency of AF (62.5%) and higher death rate (75%) (Tables 9 and 10).
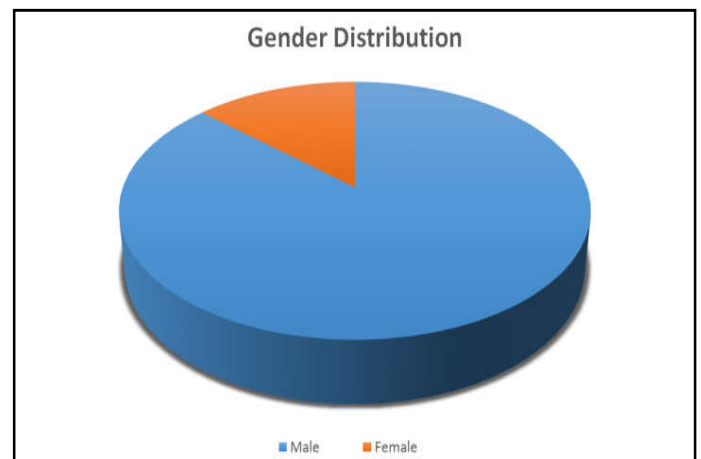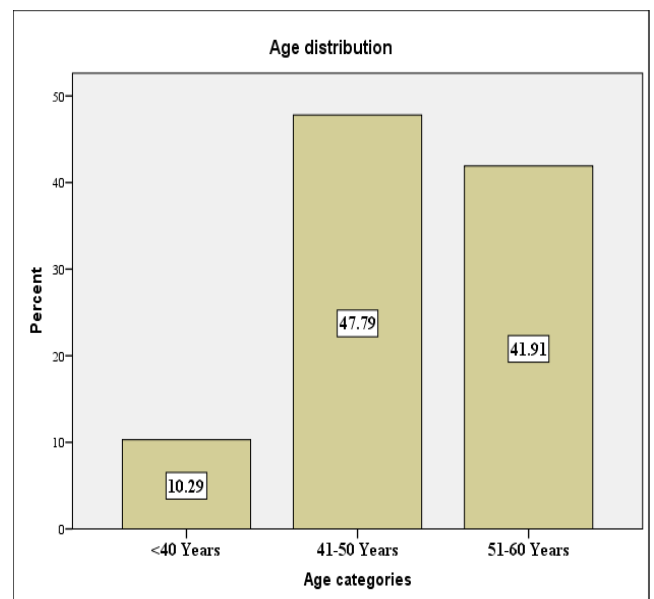

Figure 1. Gender wise distribution

Figure 2. Age distribution

Table 9. Stratified analysis of the frequency of atrial fibrillation with a duration of disease

Duration of disease (hours)	Atrial Fibrillation		Total	P valve
	Yes	No		
Up to 6 hours	11 (17.5%)	52 (82.5%)	63 (100%)	
7-12	10 (18.2%)	45 (81.8%)	55 (100%)	
13-24	3 (30%)	7 (70%)	10 (100%)	
25-36	5 (62.5%)	3 (37.5%)	8 (100%)	0.024
Total	29 (21.3%)	107 (78.7%)	136 (100%)	

Table 10. Stratified analysis of the outcome of disease with a duration of disease

Duration of disease (hours)	Outcome of disease		Total	P valve
	Survival	Death		
Up to 6 hours	63 (100%)	0 (0%)	63 (100%)	
7-12	54 (98.2%)	1 (1.8%)	55 (100%)	
13-24	8 (80%)	2 (20%)	10 (100%)	
25-36	6 (75%)	2 (25%)	8 (100%)	0.0001
Total	131 (96.3%)	5 (3.7%)	136 (100%)	

Figure 3. Duration of disease categorized

Figure 4. Frequency of Atrial fibrillation

Figure 5. Frequency of outcomes among patients

DISCUSSION

Conducting epidemiological research on the stroke incidence in different parts of the world increases our understanding of stroke etiology, risk factors, and prevention. These epidemiological studies provide the base for future advanced researches like interventional trials. The results acquired from those clinical trials and the knowledge of disease patterns and regional differences assist in targeting of programs that help to reduce risk factors (like atrial fibrillation etc.) and distribute resources for stroke management (Dans *et al.,* 2011; Kamal *et al.,* 2009; Khan *et al.,* 2012; Marini *et al.,* 2005; Lip and Halperin, 2010; Lloyd-Jones, 2004; Paciaroni *et al.,* 2005). Atrial fibrillation is known to be an important cause of death in the elderly and a powerful risk factor for stroke (Khealani *et al.,* 2008; Khan *et al.,* 2012; Alberts, 2004; Scowcroft *et al.,* 2013; Lip *et al.,* 2012; Paciaroni *et al.,* 2005). Combination of AF with stroke is lethal condition and such patients are more prone to death than non-atrial fibrillation-related strokes (Alberts, 2004; Lip and Lim, 2007; Lloyd-Jones, 2004; Paciaroni *et al.,* 2005; Lamassa *et al.,* 2001; Hart *et al.,* 2007). The current study aimed at gathering the data on the frequency of AF among patients presenting with acute stroke in the local perspective as the satisfactorily relevant data was not found. Furthermore; the study also evaluated the magnitude of the burden of deaths which occurred as a result of this association of AF and stroke. The current study found that the mean age of patients of acute ischemic stroke was 49.13 ± 7.13 years. The youngest patient was of 35 years of age while the eldest was of 60 years which was the foreset limit of the study selection criteria. The important thing was that the majority (90%) of patients belonged to 5th & 6th decades of their life. Other studies have documented that the AF patients with stroke, presented with a mean age of 71.86 ± 12.6 years (Ali *et al.,* 2009). This vast difference is due to the fact that we had very narrow age criteria on one hand while on the other hand, it is also a fact that age at birth of our population is 65 years while in western countries it is about 76 years or more. This difference was reflected truly in our study. Another explanation is that our population which is in 7th or 8th decade of life and they if, develop the ischemic stroke; does not survive long enough to reach to the hospital.

The current study noted that out of 136 ischemic stroke patients enrolled, 21.32% (n= 29) patients had atrial fibrillation diagnosed through 12 lead ECG. This rate is almost identical to that found by other international studies. To mention, a study from Italy reported that frequency of AF among ischemic stroke patients was 20.3% (Paciaroni *et al.,* 2005). One large study found that one fifth (20%) of their ischemic stroke patients had atrial fibrillation (Tsang *et al.,* 2003). Another study which also found a mimicking rate of AF among ischemic stroke patients which were 24.6% (Marini *et al.,* 2005). In Europe, slightly lower rates were documented wherein a multicenter hospital-based study found that 18% (Lamassa *et al.,* 2001) of ischemic stroke patients had atrial fibrillation. These studies did not document the mortality associated with AF in ischemic stroke patients which the current study did. It was evaluated in the current series of patients and was found that about 3.68% (n= 5) could not survive due to AF &ischemic stroke despite standard critical care provision. The current study evaluated the effect of different variables on the frequency and the outcome of AF among ischemic stroke patients. Accordingly; it was noted that higher the age of the patient, higher was the frequency of AF &
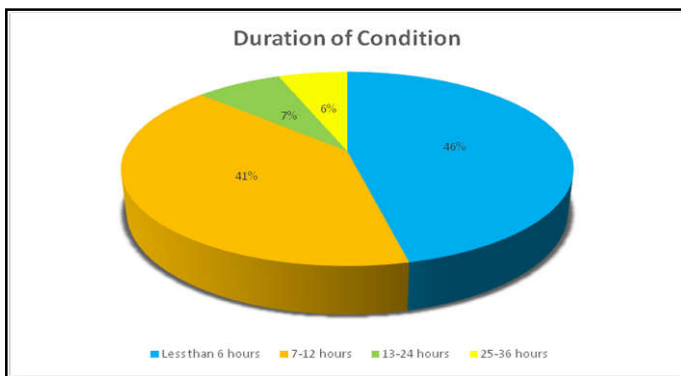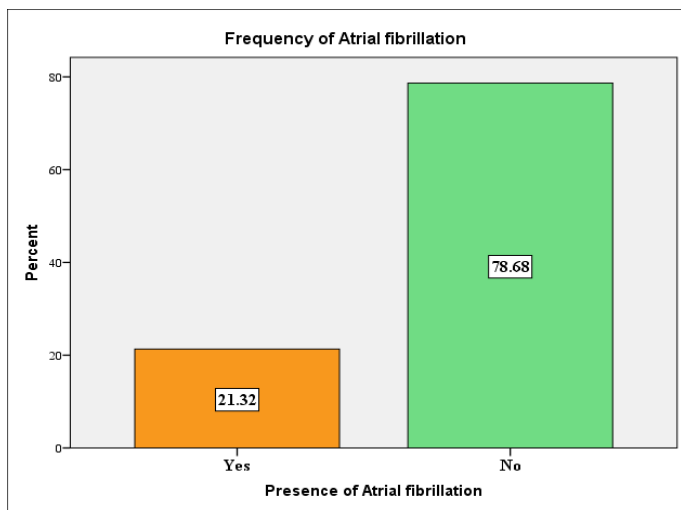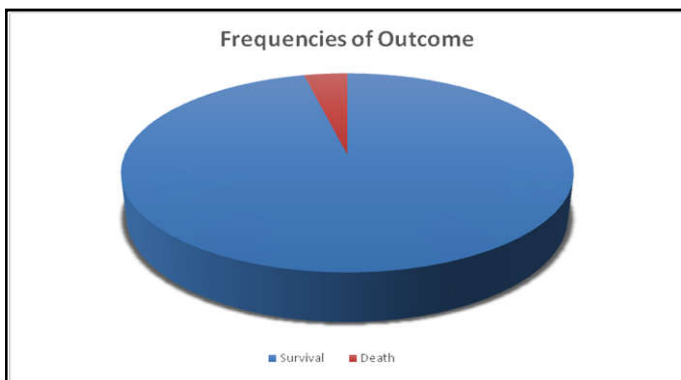
fatal outcome among these patients. Although these results were not statistically significant (P values = 0.658 and 0.605 respectively) still provide some indication regarding screenings of all ischemic stroke patients for the presence of AF. The similar trends were also explored by other studies in which one study from the USA reported that there was twice more risk of AF with every 10 years increase in age (Tsang *et al.,* 2003). The all-time famous study; the Framingham study also recommends that increasing age should be seriously considered for AF among patients who present with ischemic stroke (P value <0.001) (Kamal *et al.,* 2009). All over the world cardiovascular disease and the cerebrovascular accidents are more common in male patients and their frequency increase in women after menopause. This was found in the current study. In current study majority of patients were male which were 87.76% (n= 118) while only 13.24% (n= 18) were females but the frequency of AF and resulting in fatal outcome affected male gender more than females. (P-value = 0.476). In matching to the findings of the current study, the other studies documented that female gender has more burden of AF than males when there was ischemic stroke under consideration (Marini *et al.,* 2005; Paciaroni *et al.,* 2005; Tsang *et al.,* 2003). One study reported that nearly 2/3 of their ischemic stroke patients were females (Lamassa *et al.,* 2001). Though in the current study this difference was only slight we think that it was due to the fact the women in our sample were of 5th& 6th decade of life when the increased risk of CVDs and CVAs had started but not reached to the peak. The current study also noted that the duration of disease or presenting symptoms also had some impact on the frequency of AF and the outcome among ischemic stroke patients. It was very significantly noted that earlier the patients reached, lower were the burden of AF and further lower were the mortality (P values = 0.024 and 0.0001 respectively). This signifies the importance of early detections of signs and symptoms of stroke and reaching to the tertiary care within no time and its effect on patient outcome. The current study was a descriptive study in design, therefore, it has many limitations. The study is limited in scope because it is a hospital-based study and the results of this study cannot be inferred for the entire population. Nonetheless, the study has highlighted the importance of screening of all ischemic stroke patients for the presence of atrial fibrillation and its early and proper management. The study warrants large, prospective studies to evaluate the problem in detail.

Conclusion

The current case series study found that about every one out of five ischemic stroke patients may have atrial fibrillation as comorbidity or the underlying reason. Patients with elder age, especially female after menopause, late presenters and those brought from rural areas should be screened thoroughly for atrial fibrillation as a possible underlying diagnosis.

REFERENCES

Alberts MJ. 2004. Genetics of cerebrovascular disease. *Stroke*, 35:342-4.

Ali M, Atula S, Bath PM, Grotta J, Hacke W, Lyden P. *et al.* 2009. Stroke outcome in clinical trial patients deriving from different countries. *Stroke*, 40(1):35-40.

Dans A, Ng N, Varghese C, Tai ES, Firestone R, Bonita R. 2011. The rise of chronic-communicable diseases in southeast Asia: time for action. *Lancet*, 377(9766):680-9.

Hart RG, Pearce LA, Aguilar MI. 2007. Meta-analysis:anti-thrombotic therapy to prevent stroke in patients who have non-valvular atrial fibrillation. *Ann Intern Med.,* 146(12):857-67.

Kamal AK, Itrat A, Murtaza M, Khan M, Rasheed A, Ali A. *et al.* 2009. The burden of stroke and transient ischemic attack in Pakistan:a community-based prevalence study. *Brit Med C Neurol.,* 9:58.

Khan M, Ahmed B, Ahmed M, Najeeb M, Raza E, Khan F. *et al.* 2012. Functional, cognitive and psychological outcomes, and recurrent vascular events in Pakistani stroke survivors:across-sectional study. BMC Res Notes. 5:89.

Khealani BA, Ali S, Baig SM. 2008. Stroke in Pakistan. *J Pak Med Assoc.,* 58:365-8.

Lamassa M, Di-Carlo A, Pracucci G, Basile AM, Trefoloni G, Vanni P, *et al.* 2001. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe:data from a multicenter multinational hospital-based registry (The European Community Stroke Project). *Stroke*, 32(2):392-8.

Lip GY, Halperin JL. 2010. Improving stroke risk stratification in atrial fibrillation. *Am J Med.,* 123(6):484-8.

Lip GYH, Lim HS. 2007. AF and stroke prevention. *Lancet*, 6:981–93.

Lloyd-Jones DM. 2004. The lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation, 110:1042-6.

Marini C, Santis FD, Sacco S, Russo T, Olivieri L, Totaro R, *et al.* 2005. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke*, 36:1115-9.

Paciaroni M, Agnelli G, Caso V, Venti M, Milia P, Silvestrelli G, *et al.* 2005. Atrial fibrillation in patients with first-ever stroke:frequency, antithrombotic treatment before the event and effect on clinical outcome. *J Thromb Haemost.,* 3(6):1218-23.

Scowcroft AC, Lee S, Mant J. 2013. Thromboprophylaxis of elderly patients with AF in the UK:an analysis using the General Practice Research Database (GPRD) 2000-2009. *Heart.,* 99(2):127-32.

Tsang TS, Petty GW, Barnes ME, O'Fallon WM, Bailey KR, Wiebers DO, *et al.* 2003. The prevalence of atrial fibrillation in incident stroke cases and matched population controls in Rochester, Minnesota: changes over three decades. *J Am Coll Cardiol.,* 42(1):93-100.

WHO MONICA Project Investigators, 1988. The World Health Organization MONICA Project (Monitoring trends and determinants in cardiovascular disease). *J Clin Epidemiol.,* 41:105-14.

World Health Organization, 2004. The Atlas of Heart Disease and Stroke. *Geneva*, WHO.

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