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Incidence of Ischemic Stroke among Patients Recently Initiated on Direct Oral Anticoagulants for Atrial Fibrillation

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ABSTRACT

Background: Ischemic strokes are a leading source of disability and death globally, particularly due to atrial fibrillation (AF), which is a significant risk factor. While prescribing anticoagulation DOACs to patients with AF for cardioembolism stroke prevention, real-world scenarios show persistent stroke events, which connote suboptimal functioning of the controlled interventions. To establish the rate of ischemic stroke among patients with newly prescribed DOACs for atrial fibrillation (AF)and to evaluate the relevant demographic, clinical, and laboratory features. **Methods:** A descriptive cross-sectional study was conducted in the Emergency Department of Lady Reading Hospital, Peshawar from May 2024 to May 2025. A total of 184 patients aged 30–60 years, presenting with acute ischemic stroke and recently started on DOACs, were enrolled using consecutive non-probability sampling. Data were collected through structured clinical evaluation, ECG confirmation of AF, neuroimaging, and relevant laboratory tests. Statistical analysis was performed using SPSS version 21.0, with p-values ≤ 0.05 considered significant. **Results:** The mean age of patients was 51.3 ± 7.6 years, with females comprising 51.6% of the sample. Ischemic stroke occurred in 20.1% of patients despite recent initiation of DOACs. Atrial fibrillation was present in 60.3% of cases, but no significant association with stroke outcome was observed. In contrast, male gender showed a statistically significant link with stroke occurrence (p = 0.0191). Most patients had normal liver and renal function, though abnormalities in serum electrolytes and glucose levels were common. **Conclusion:** A notable proportion of patients developed ischemic stroke despite DOAC use, suggesting that anticoagulation alone may not be sufficient in high-risk cases. Male gender appeared to be a significant risk factor, whereas family history and documented AF were not. These findings highlight the need for comprehensive stroke prevention strategies beyond anticoagulation, including close monitoring and metabolic risk control.

INTRODUCTION

Stroke continues to be one of the most common causes of long-term disabilities and death globally. Its mortality burden remains the highest in low and middle-income countries, where over 80% of stroke-related deaths occur[1]. Although primary mortality from acute stroke has improved with advancements in acute stroke care and leads to early survivors, the majority of stroke survivors over 50 % suffer from some form of neurological disability. Almost one in five independent survivors is dependent on long-term institutional care. In addition to physical impairments, most of the patients develop secondary problems like seizures, depression, and cognitive decline, which further impact their quality of life [2, 3].

One of the most common causes of ischemic stroke is atrial fibrillation (AF), especially in older people. AF enhances the chances of developing a cardioembolic stroke because it increases the possibility of thrombus formation in the atria, which may later break off and travel to the brain[4, 5]. As a response, clinical guidelines all over the world have advised using oral anticoagulants, especially direct oral anticoagulants (DOACs), to mitigate the chances of stroke in these patients with non-valvular atrial fibrillation. Rivaroxaban, apixaban, and dabigatran, which fall under the category of DOACs, have supplanted primary traditional agents like warfarin due to their more predictable pharmacokinetics and lower risk of bleeding [6, 7].

Although DOACs have added advantages in ischemic stroke risk, they do not eliminate it. Ischemic events have been documented in fully compliant patients as well[8]. Possible explanations for inadequate responses to treatment include subtherapeutic levels, chronic undertreatment, unrecognized intermittent atrial fibrillation, or masked metabolic disorders. Reports from some bordering countries, more so from India, have

demonstrated the prevalence of atrial fibrillation in 4-10% of stroke sufferers and some continue to experience recurring events even while on anticoagulation therapy [9].

In Pakistan, data on the frequency of stroke in patients newly started on DOACs remains limited. This gap in local evidence makes it difficult to evaluate whether current treatment strategies are sufficient or require modification based on population-specific risk factors. Understanding how often ischemic strokes occur in this subgroup could inform more effective management protocols and guide physicians in early risk identification and prevention.

This study was therefore designed to determine the frequency of ischemic stroke among patients who were recently started on direct oral anticoagulants for atrial fibrillation. It also aimed to examine these patients' demographic, clinical, and laboratory characteristics, and explore possible associations with stroke occurrence.

METHODOLOGY

This descriptive cross-sectional study was conducted in the Department of Emergency Medicine at Lady Reading Hospital (MTI) in Peshawar from May 2024 to May 2025.

The study consisted of 184 patients. The sample size was calculated using the WHO sample size estimation tool, assuming an atrial fibrillation among stroke patients' prevalence of 37.5% at a 95% confidence level, and a margin of error of 7%. Ethical approval for the study was granted by the Institutional Review Board (IRB) of Lady Reading Hospital (MTI), Peshawar, under official letter number 5701/LRH/MTI, dated 25 April 2024. All participants were informed about the study objectives, and written consent was obtained before enrollment. Confidentiality and patient rights were upheld throughout the research process.

Participants were selected through consecutive non-probability sampling. All patients aged between 30 and 60 years, of either gender, who presented with acute ischemic stroke (either new or recurrent) were eligible for inclusion. Patients with transient ischemic attacks or stroke caused by hereditary, metabolic, drug-induced, or acquired coagulation disorders were excluded to avoid bias and confounding.

Once consent was obtained, a detailed history and physical examination were performed. Atrial fibrillation was diagnosed using a 12-lead electrocardiogram interpreted by the researcher and confirmed by a cardiologist. The ECG was performed using the Burdick EK10 machine, and atrial fibrillation was defined as the absence of P waves and the presence of irregularly irregular QRS complexes in lead II. To confirm the diagnosis and exclude hemorrhagic stroke, all patients underwent a non-contrast CT scan of the brain. If needed, further investigations such as MRI or CT angiography were conducted to rule out other causes like arterial dissection or intracranial lesions. Laboratory tests included liver function tests, renal profile, serum electrolytes, random blood glucose, and complete blood count. Additional evaluations, such as urine routine examination and chest X-ray, were also carried out to exclude systemic causes that could mimic stroke.

The clinical features, imaging studies, laboratory tests, demographics, and all other pertinent information were captured in a structured data collection form. The primary outcome assessed was the occurrence of ischemic stroke amongst patients who were recently commenced on DOAC therapy incorporating rivaroxaban, apixaban, or dabigatran.

Statistical analysis was performed using SPSS version 21.0. Continuous variables like age and disease duration were summarized as mean ± standard deviation, while categorical data such as gender, family history, and investigation findings were reported as frequencies and percentages. The Chi-square test was applied to assess associations between categorical variables and stroke outcome. A p-value of ≤0.05 was considered statistically significant.

RESULTS

Of the study's 184 participants, the mean age was 51.3 with a standard deviation of 7.6 years which indicates that most participants were in middle age. The sample had a near-equal gender distribution with females comprising 51.6% of the sample and males 48.4%. Many of the patients were retired (29.3%) or worked in an office (26.6%), which suggests that the stroke sufferers might commonly have a sedentary lifestyle. The most frequent presenting complaint was hemiparesis which was observed in 39.1% of patients and was followed by speech difficulties in 29.9%. Other diverse clinical presentations included vision loss (15.2%) and seizures (15.8%).

Table 1

Demographic Profile of Patients (n = 184)

Variable	Category	Frequency (%)
Age (years)	Mean ± SD	51.3 ± 7.6
Gender	Male	89 (48.4%)
	Female	95 (51.6%)
Occupation	Office Worker	49 (26.6%)
	Laborer	41 (22.3%)
	Retired	54 (29.3%)
	Unemployed	40 (21.7%)
Presenting Complaint	Hemiparesis	72 (39.1%)
	Speech Difficulty	55 (29.9%)
	Vision Loss	28 (15.2%)
	Seizure	29 (15.8%)

The average symptom duration from onset to presentation was 11.4 days, indicating that most patients presented within a clinically appropriate timeframe. Notably, a family history of stroke was diagnosed in 30.4% of the cases which denotes a possible hereditary or lifestyle factor. Atrial fibrillation present on ECG was found in 60.3% of patients, which underscores its prominence as a risk factor for this group. Remarkably, 20.1% of the study participants on DOAC therapy developed a stroke which poses serious questions about treatment efficacy or compliance with the prescribed therapy.

Table 2

Clinical Profile and Family History

Variable	Category	Frequency (%)
Duration of Disease	Mean ± SD	11.4 ± 4.9 days
Family History of Stroke	Yes	56 (30.4%)
	No	128 (69.6%)
Atrial Fibrillation (ECG)	Present	111 (60.3%)
	Absent	73 (39.7%)
Stroke after DOAC Treatment	Yes	37 (20.1%)
	No	147 (79.9%)

Laboratory evaluations showed that most patients (85.3% and 80.4%) had normal liver and renal function, respectively, which suggests a stable systemic condition at the time of presentation. Still, a quarter had abnormal serum electrolytes, and 39.7% had glucoses levels, either elevated or depressed, that may have influenced their neurological symptoms. Mild leucocytosis was noted in 13% of patients, while abnormal urine results were seen in 9.2%, suggesting the possibility of infection or some underlying systemic condition. Chest X-ray results were normal in 94% of patients; these were the only abnormal findings noted. These results in concert justify routine investigations to exclude other potential factors before accepting ischemic stroke as the definitive diagnosis.

Table 3

Laboratory and Imaging Findings

Parameter	Normal (%)	Abnormal (%)
Liver Function Tests	157 (85.3%)	27 (14.7%)
Renal Function Tests	148 (80.4%)	36 (19.6%)
Serum Electrolytes	138 (75.0%)	46 (25.0%)
Blood Glucose	111 (60.3%)	73 (39.7%)
Leucocytosis (CBC)	160 (87.0%)	24 (13.0%)
Urine Routine Exam	167 (90.8%)	17 (9.2%)
Chest X-ray	173 (94.0%)	11 (6.0%)

Radiological imaging revealed that ischemic strokes were present in 71.2% of the patients, which is in line with the inclusion criteria of the study. Minor strokes or transient ischemic attacks that resolve before imaging may explain the normal CT scans seen in 21.2% of participants. A smaller subset (7.6%) exhibited other changes which may be incidental findings of non-vascular pathology. These imaging findings corroborate the clinical impression that the majority of patients suffered an acute ischemic vascular event.

Table 4

CT Scan Findings (n = 184)

Finding	Frequency (%)
Ischemic Stroke	131 (71.2%)
Normal	39 (21.2%)
Other Abnormalities	14 (7.6%)

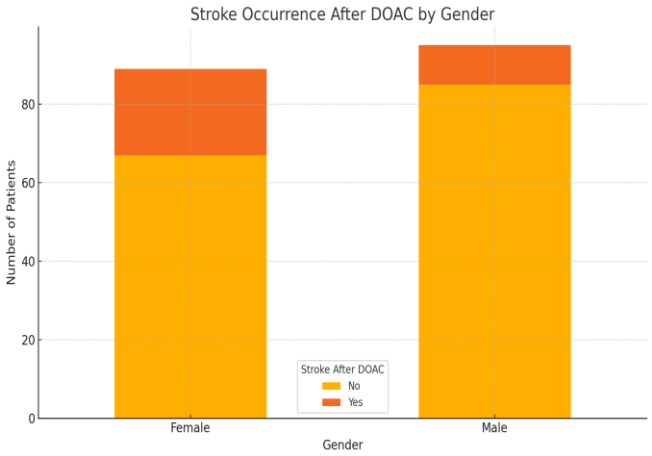
As noted previously in the results section, the chi-square test revealed a statistically significant relationship between gender and stroke occurrence after the start of DOAC therapy (p = 0.0191), indicating possible gender-related physiological differences in outcomes. For the rest of the sample, family history (p = 0.4631) and the presence of atrial fibrillation (p = 1.0000) were not significantly associated with stroke. This suggests that although atrial fibrillation is considered a major risk factor for stroke, the onset of DOAC therapy introduces other factors that may govern the patient's stroke risk.

Table 5

Association of Risk Factors with Stroke After DOAC Treatment

Comparison	p-value	Significance
Family History vs. Stroke Outcome	0.4631	Not Statistically Significant
Gender vs. Stroke Outcome	0.0191	Statistically Significant
Atrial Fibrillation vs. Stroke Outcome	1.0000	Not Statistically Significant

Figure 1



The bar graph depicts stroke events following the commencement of direct oral anticoagulants (DOACs) by gender. In comparison to females, a greater proportion of male patients sustained strokes while undergoing DOAC therapy. Although the total number of females participating in the study was slightly higher than that of males, strokes were disproportionately more common among the male subset. This particular difference observed between the two genders is in accordance with the computed gender result which showed a significant association with stroke outcome (p=0.0191). The visual trend enhances the hypothesis that male patients could be at an increased risk for experiencing ischemic events even in the setting of anticoagulation therapy, highlighting the need for greater scrutiny and possibly tailored risk evaluation.

DISCUSSION

This study explored the frequency of ischemic stroke in patients who were newly started on direct oral anticoagulants (DOACs) for atrial fibrillation, and investigated the clinical and laboratory characteristics of these patients. The findings revealed that 20.1% of the participants developed a stroke despite being on DOAC therapy, raising critical concerns about the effectiveness or timing of anticoagulation in high-risk individuals.

The mean age of participants was just above 51 years, and slightly more than half were female. Similar age and gender patterns have been reported in prior regional studies, where atrial fibrillation-related stroke was more common in older adults but did not show a consistent gender dominance. However, in this study, male gender showed a statistically significant association with stroke occurrence post-DOAC initiation. This suggests that male patients may have unique physiological or behavioral factors such as medication adherence, underlying comorbidities, or delayed presentation that could influence outcomes [10-12].

Family history of stroke, though present in about one-third of the participants, was not found to be significantly linked with stroke recurrence or treatment failure in this study. This was consistent with findings from other studies that emphasized clinical rather than genetic predispositions in recurrent stroke risk among atrial fibrillation patients [13-15].

Atrial fibrillation was detected in 60.3% of the patients,

reinforcing its role as a major underlying risk factor. Yet, surprisingly, the statistical association between atrial fibrillation and stroke recurrence was not significant in this cohort. This could be due to the inclusion of patients who were already anticoagulated, suggesting that timing, dosage, or drug metabolism variability might explain stroke events despite ongoing DOAC therapy. Literature similarly highlighted that stroke may still occur in AF patients on treatment, particularly if paroxysmal episodes go undetected or medication coverage is incomplete [16-18].

Radiologically, ischemic stroke was confirmed in over 70% of patients via CT scan, which is in line with data from Indian and Pakistani hospital-based stroke registries where ischemic forms predominate over hemorrhagic types. Laboratory findings largely showed preserved liver and kidney function, though abnormalities in serum electrolytes and glucose levels were frequent. These metabolic irregularities are known to exacerbate stroke risk and could act as additional triggers in patients already vulnerable due to AF [19, 20].

The relatively high rate of stroke occurrence after DOAC use calls for a careful reassessment of treatment protocols. Delayed diagnosis of paroxysmal AF, inadequate drug levels, and unrecognized drug interactions may all contribute. In addition, this study supports recommendations from international guidelines suggesting that stroke prevention strategies must extend beyond pharmacological treatment to include patient education, early AF detection (e.g., Holter monitoring), and aggressive risk factor control.

CONCLUSION

This study demonstrated that a notable proportion of patients initiated on DOACs for atrial fibrillation still experienced ischemic strokes. While male gender showed a significant association with stroke risk, other factors such as family history and documented AF did not show statistically meaningful relationships. These findings highlight that anticoagulation alone may not be sufficient for comprehensive stroke prevention and that gender-specific and metabolic factors must also be addressed. Routine monitoring, patient education, and broader risk factor management should be integrated into stroke prevention strategies for patients with atrial fibrillation.

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