REVIEW
Oral Anticoagulation in Patients with Acute Stroke and Atrial Fibrillation

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Abstract. Introduction. *Patients who have experienced acute ischemic stroke (AIS) and have atrial fibrillation (AF) are often prescribed oral anticoagulants (OACs) to lower their risk of recurrent stroke or vascular embolism. This therapy is rarely advised as a preventive measure for reducing the risk of recurrent ischemic stroke associated with non-valvular atrial AF. The ideal timing for initiating oral anticoagulation in these patients remains uncertain.* ***Methods.*** *Research was conducted in the major medical databases containing articles. The following terms were used: atrial fibrillation, acute ischemic stroke, oral anticoagulants, stroke recurrence, and prevention. We excluded studies performed earlier than 10 years since the medical information was no longer valid in practice. Results. Information gathered from observational studies and control groups in randomized trials indicates that the early recurrence rate following an atrial fibrillation-related ischemic stroke falls within the range of approximately 0.5% to 1.3% per day during the initial two weeks. The research targeted adults (aged ≥18 years) with AF and a recent ischemic stroke (IS) (occurring within 72 hours of symptom onset) who satisfied the criteria for and were amenable to starting treatment with NOACs. Atrial fibrillation encompassed paroxysmal, persistent, and permanent forms, whether they were pre-existing conditions or diagnosed during the initial hospitalization. Observational studies indicate that the risk of recurrent stroke is seven times higher than the risk of hemorrhagic transformation during the early phase after a recent stroke.* ***Conclusions.*** *Early prevention treatments are critical because the acute phase after an ischemic stroke increases the risk of stroke recurrence. It is critical to balance the possible benefits of early oral anticoagulation against the dangers of developing intracerebral hemorrhage or hemorrhagic transformation of the ischemic injury at this critical time.*

Keywords*: atrial fibrillation, acute ischemic stroke, oral anticoagulants, strokerecurrence, prevention.*

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Abbreviations
AIS, acute ischemic stroke
AF, atrial fibrillation
OAC, oral anticoagulation
TIA, transient ischemic attack
IS, ischemic stroke
DOACs, direct oral anticoagulants
VKASs, vitamin K antagonists
DOAC, direct oral anticoagulant

INTRODUCTION

Patients with acute ischemic stroke (IS) and atrial fibrillation (AF) are prevented from having a stroke again and from having a vascular embolism by oral anticoagulants. Oral anticoagulant (OAC) therapy is advised as a preventive measure for reducing the risk of recurrent ischemic stroke associated with non-valvular atrial AF [1]. Patients who receive OAC in accordance with recommended guidelines have a better prognosis than those whose therapy deviates from suggested guidelines [2]. However, the ideal timing for initiating OAC after an acute ischemic stroke (AIS) or transient ischemic attack (TIA) remains uncertain. For the AIS related to AF, the likelihood of experiencing an early recurrence (within 7–14 days) ranges from 0.4% to 1.3% daily.

Ischemic strokes associated with atrial fibrillation tend to result in more frequent disabilities or fatalities compared to other types of strokes. They lead to extended hospitalizations and increased medical expenses, making the prevention of early recurrence a critical clinical concern [3,4]. While oral anticoagulation is remarkably efficient for preventing long-term strokes in AF, its safety and overall benefit in the context of acute AF-related strokes have not yet been firmly established. Additionally, a lower use of oral anticoagulation was found to be associated with an increased risk of ischemic strokes and death overall. The percentage of patients not receiving oral anticoagulant treatment varies globally, ranging from roughly 20% to 60%, according to several studies looking into the underuse of anticoagulation therapy for atrial fibrillation in stroke patients [5,6]. This presents an opportunity to enhance AF management and draws attention to a notable difference in care.

Despite the lack of comprehensive data on the undertreatment of anticoagulant therapy in hospitalized patients with AIS and AF, the Asian region is recognized for its higher risk of inadequate treatment. Moreover, the variables impacting a person's likelihood of receiving suboptimal therapy are still unknown. The European Heart Rhythm Association and the European Society of Cardiology recommend starting anticoagulation after an AF-related TIA or mild, moderate, or severe AIS according to the "1-3–6–12 day rule" if randomized trial data are not available [7].

METHODS

A comprehensive literature review was systematically conducted to identify suitable studies that reported on patients who had experienced AF-related AIS or TIA and were given anticoagulant therapy with either direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs) within the early post-stroke period.

We conducted searches on PubMed, Medscape, and UpToDate using specific search terms such as "stroke," "atrial fibrillation," "direct oral anticoagulants," "initiation," and "recurrent stroke." No language or other limitations were imposed. Moreover, we conducted a manual review of the reference lists of published articles to guarantee the comprehensiveness of the bibliography. Some studies were excluded because they were very old, and the medical information was no longer current.

Eligible studies were required to evaluate safety and effectiveness outcomes in patients prescribed DOACs versus VKAs. Safety outcomes included major bleeding, intracerebral hemorrhage, and all-cause mortality. There were excluded the case reports, commentary, editorials, narrative reviews, and case series. When data from several studies overlapped, the study with the biggest dataset was chosen for inclusion first. Most patients were monitored for 90 days.

Patients

The study focused on adults (aged ≥18 years) with AF and a recent ischemic stroke who met the criteria for and were willing to begin treatment with DOACs. AF encompassed paroxysmal, persistent, and permanent forms, whether they were pre-existing conditions or diagnosed during the initial hospitalization.

Patients who had contraindications to DOAC therapy, such as ongoing bleeding or

mechanical heart valve prostheses, were excluded from the study.

We also included a trial that compared the safety and efficacy of VKA and DOACs and was conducted on geriatric patients aged over 85 with AF who had experienced a recent stroke.

Stroke classification

Stroke is a leading cause of mortality and disability, with the costs of post-stroke treatment being substantial. Compared to other non-atrial fibrillation-related strokes, cardioembolic strokes, which are most caused by AF, are known to have poorer outcomes.

Participants were categorized as having a minor, moderate, or major ischemic stroke, based on the size of the infarct observed on CT and/or MRI scans conducted before randomization. The NIHSS scale was also used for classifying the severity of the stroke.

RESULTS

Data from observational studies and control groups in randomized trials suggest that the early recurrence rate after an atrial fibrillation-related ischemic stroke ranges from approximately 0.5% to 1.3% per day during the first two weeks [8].

Age, the existence of a significant ischemic lesion, and atrial enlargement have all been found to be risk factors in observational studies for recurrent ischemic strokes associated with AF [9]. Even though atrial thrombus is rare, the chance of recurrence increases dramatically when one is discovered. Furthermore, the development of hemorrhagic transformation is thought to be at risk in the presence of a massive infarction [10].

Clinical scoring methods, such as CHA_2DS_2-VASc (risk of ischemic events) and HAS-BLED (risk of hemorrhagic events), are frequently used in AF patients receiving oral anticoagulant therapy to evaluate the risk of ischemic or hemorrhagic episodes.

Nevertheless, these scoring systems are not specifically tailored for application in the acute stroke scenario, possess a limited predictive capacity, and overlap with several constituent risk factors (such as hypertension, age or prior ischemic stroke) that are commonly found in individuals with ischemic strokes [11].

Oral anticoagulation therapy is essential for AF patients to prevent ischemic strokes, both first and recurrent. Non-vitamin K antagonists, or DOACs, have supplanted warfarin as the recommended treatment in this situation in recent years. Four significant randomized controlled trials support this view,

showing that DOACs have a major bleeding event risk that is either equivalent to or lower than warfarin while being at least as effective in preventing strokes. Notably, DOACs are associated with a markedly lower risk of cerebral hemorrhages.

In a randomized trial with 195 participants from Korea, there was no statistically significant difference in the primary outcome of new ischemic or hemorrhagic lesions found on brain imaging after one month. The trial assessed whether patients with AF should begin treatment with rivaroxaban or warfarin within 5 days after suffering a mild stroke [8].

It was reported in a 2022 study with 888 patients that, for the course of the 90-day study period, none of the subjects had a symptomatic intracerebral hemorrhage. Furthermore, within the first four weeks, there was a very low overall rate of significant bleeding, including cerebral hemorrhages. The average time to start DOAC in the randomized group was 66.8 hours, which is equivalent to day 3 following the start of the stroke in the early initiation group. On the other hand, DOAC was started after an average of 116.8 hours, or day 5 following the beginning of the stroke, in the delayed initiation group. Numerous observational studies that were either released simultaneously with this trial or after it was finished demonstrated markedly lower rates of symptomatic cerebral hemorrhages in patients who received early DOAC treatment following a stroke in the context of AF [11].

Based on the severity of neurological symptoms, a Japanese study that used data from two Japanese registries found the best

time to start direct DOACs after an ischemic stroke or transient ischemic attack associated with non-valvular atrial fibrillation. The study found that a graded delay in anticoagulation initiation, ranging from 1 to 4 days after the index IS/TIA based on neurological severity (within 1 day after TIA, 2 days after mild IS, 3 days after moderate IS, and 4 days after severe IS - known as the "1-2-3-4-day rule"), was linked to improved effectiveness and a comparable level of safety compared to later initiation of DOACs in the Japanese population [7]. The investigation attested to this principle's similar safety and effectiveness. Due primarily to the prevention of recurrent thromboembolism in the early days of the research, the chances of stroke/systemic embolism, and ischemic stroke were both reduced in the early group compared to the late group. Furthermore, despite comparable CHADS2-VASc and HAS-BLED scores between the groups, there were more high-risk patients in the late group, which at first prompted worries about early anticoagulation. The investigation revealed that the mortality rates of the two groups were comparable.

In a study conducted in 2021 involving 2,321 patients, the findings suggested that initiating anticoagulation earlier after an acute ischemic stroke may lead to a reduction in ischemic events but could also potentially increase the risk of hemorrhage [12].

There have also been other recent studies in 2022 with a similar design, namely reviews and meta-analyses, that have investigated similar aspects. They included 5616 patients with AIS and AF, and we found that the risk of recurrent ischemic stroke was comparable when oral anticoagulants were initiated within the first week, in contrast to initiating them after two weeks from the onset of AIS. Commencing anticoagulation therapy during the first week following AIS did not result in a greater risk of symptomatic intracerebral hemorrhage or all-cause mortality. However, patients treated within one week of AIS had a slightly elevated risk of experiencing any form of intracranial hemorrhage (whether symptomatic or asymptomatic) compared to the patients treated within 14 days after AIS [13].

It is noteworthy that individuals with similar cardiovascular risk factors and bleeding risk profiles were those who began anticoagulant therapy one or two weeks after AIS. Furthermore, the pooled analysis of patient characteristics revealed that most trials comprised patients with modest infarct volumes and moderate stroke severity, with a mean NIHSS score of five points and an infarct volume of five milliliters, respectively. In relation to the relative effectiveness of oral anticoagulants, they found that patients treated with DOACs had a lower risk of ischemic stroke recurrence than patients treated with VKAs, independent of when treatment was started (i.e., in both time frames).

According to Elan research (2022), observational studies suggest that in the early post-stroke phase, the risk of hemorrhagic transformation is seven times lower than the risk of recurrent stroke. However, numerous physicians are reluctant to start anticoagulation too soon, considering the concern that it might harm the patient. The '1-3-6-12 day guideline' has been widely embraced by doctors across the globe in the absence of hard data. An expert opinion statement from the European Stroke Organization supports this treatment. On the other hand, there might be benefits to beginning DOAC therapy sooner [5].

Furthermore, a study conducted in China in 2022 revealed that less than 50% of patients with AIS and concomitant AF were prescribed anticoagulation therapy following the guidelines at the time of discharge. This discrepancy underscores a significant disparity between recommended guidelines and real-world practice [7].

Individuals who had previously suffered from hemorrhagic diseases and those who contracted pneumonia while staying in the hospital were less likely to be prescribed anticoagulant medication. Furthermore, only 20% of patients with a history of AF and a high risk of stroke received anticoagulant medication in accordance with the

recommended criteria. This emphasizes how crucial the management of AF is [14].

Increasing patient and healthcare professional education is necessary to improve AF management. The goal of these initiatives should be to improve anticoagulant strategies and increase the rate at which anticoagulation is used. This includes strengthening patient health education, raising the standard of thorough acute stroke care, and giving physicians better anticoagulant treatment experiences [15,16].

Additionally, a trial with geriatric patients (age > 85) was carried out in 2021. Compared to younger patients, they had higher NIHSS scores, lower eGFR, a greater frequency of hypertension, a history of ischemic stroke or transient ischemic attack, and higher CHA_2DS_2-VASc scores. Younger patients had higher rates of dyslipidemia, diabetes mellitus, and current smoking. The eldest had a shorter period after the index incident before starting oral anticoagulants [17].

Whether people are 85 years of age or older, the benefits of DOACs were still evident in this sample. This observation is highly relevant to clinical practice since it refutes the beliefs of numerous healthcare practitioners who are reluctant to prescribe DOACs to this age group, particularly those who have several comorbidities. The fact that the benefits of DOACs over VKA continued to hold true even after taking the elderly population's higher risk profile into account has therapeutic implications.

Early anticoagulation after a stroke has long been a contentious topic that requires careful consideration of the advantages and disadvantages of avoiding early recurrent thrombosis and intracranial hemorrhage. It is counterintuitive rise in the risk of the IS during the first seven days. This is most likely because warfarin temporarily deactivates proteins C and S, which causes a hypercoagulable condition [18]. Considering that they lower the risk of cerebral hemorrhage, DOACs are very beneficial. With careful consideration given to avoiding patients with variables favoring delayed commencement of anticoagulation, such as large infarcts, hemorrhagic transformation of infarcts, and hypertension, the "1-2-3-4-day rule" looks to be practicable in real-world clinical settings. Nonetheless, it's critical to recognize that observational studies conducted in hospitals may be biased or contaminated. Thus, information from continuing randomized trials will be essential in determining future modifications to treatment protocols or clinical practices.

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CONCLUSIONS

The higher risk of stroke recurrence in the early stages after an ischemic stroke justifies very early stroke preventive therapy. There is a risk of hemorrhagic change of the ischemic lesion or intracerebral hemorrhage at this critical time, so it is important to carefully consider the possible benefit of early oral anticoagulation.

It was determined that early anticoagulation reduced the risk of recurrent ischemic strokes; however, this advantage was offset by a corresponding rise in intracranial hemorrhages. In patients with atrial fibrillation, several observational studies point to a possible therapeutic benefit of starting NOACs early in the acute period after an ischemic stroke. Nevertheless, there is a considerable data deficiency in randomized research in this area.

In individuals with AF, initiating DOAC treatment as soon as possible after an AIS proved to be equally effective as delaying it. Early DOAC commencement is a safe strategy, as evidenced by the decreased rates of ischemic stroke and death, the lack of symptomatic intracerebral hemorrhages, and the generally low incidence of significant bleeding episodes. Acute secondary stroke prevention should be taken into consideration for patients who suffer from AIS and AF. More research is still needed to determine whether early initiation is preferable to delayed initiation

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I.M.A and L.C.I conceived the original draft preparation. A.M. was responsible for the data acquisition**,** collection and assembly of the articles, M.M.L was responsible for the conception and design. F.M. was responsible with the supervision of the manuscript.

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