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Review Article

Anticoagulant in Acute Ischemic Stroke with Atrial Fibrillation: A Narrative Review

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Abstract

Embolic stroke due to atrial fibrillation is often underdiagnosed and has high morbidity and mortality among ischemic stroke. So it is of paramount importance to start anticoagulants as early as possible to prevent further ischemic stroke. However, early initiation of anticoagulants has created much debate, major & minor bleeding related to it are a major concern, and resumption of anticoagulants after intracranial hemorrhage is still a gray zone. Here, we described a narrative review to shed some light on the major concerns such as the optimal time to start an anticoagulant, the best agent to administer, the resumption of anticoagulant after a hemorrhagic stroke, and anticoagulant therapy in chronic rheumatic heart disease (CRHD) based on the recently published article.

Keywords: *Anticoagulant, Atrial fibrillation, Ischemic stroke.*

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Introduction

Stroke is the leading global burden today, being the second most common cause of mortality worldwide and the third most common cause of disability. According to the American Stroke Association, 1 in 4 stroke survivors will have another stroke[1]. In Bangladesh, the prevalence of stroke is 1.34%, among those 85% are ischemic stroke[2]. Among ischemic stroke, the hospital prevalence of cardio-embolic stroke is 22.64%[3], although the worldwide prevalence is approximately 15-30%[1]. Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and its prevalence increases with age, predisposing elderly patients to an increased risk of embolic stroke[4]. Patients with AF have a 4- to 5-fold increased risk of developing a stroke. While the attributable risk for stroke associated with AF is 1.5% at age 50-59 years, this steeply increases to 23.5% by the age of 80-89 years[5]. Nowadays anticoagulation therapy in acute ischemic stroke due to atrial fibrillation is well established. Anticoagulants are often prescribed to patients with recent strokes to prevent early recurrent strokes and improve neurological outcomes. The Cerebral Embolism Study Group estimated that the risk of early recurrent embolism was 12% among untreated patients with embolic stroke[6]. However, the usefulness of emergency anticoagulation is a subject of debate. The major concern is now when to start anticoagulation for long-term secondary stroke prevention, especially in patients with atrial fibrillation. Another feared complication of anticoagulants is intracranial hemorrhage. The short review highlights the major concerns such as the optimal time to start an anticoagulant, the best agent to administer, the resumption of anticoagulant after a hemorrhagic stroke, and anticoagulant therapy in chronic rheumatic heart disease (CRHD) based on the recently published article.

Methods

This is a narrative review examining the evidence of the preferable time to start anticoagulants, the best agents to administer, the resumption of anticoagulants after a hemorrhagic stroke, and indications in chronic rheumatic heart disease. Here, we searched recently published articles

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related to acute ischemic stroke due to atrial fibrillation receiving anticoagulants till 2023 in Pubmed and Google Scholar.

Assessment of Patients Requiring Anticoagulation

Before anticoagulation assessment of patients is of paramount importance. CHA2DVAS2 score is the cornerstone for non-valvular atrial fibrillation patients needing anticoagulants. Simultaneously, it is a time-demanding approach to assess bleeding scores with the HASBLED scoring system. Moreover, the severity of a stroke should be measured by the National Institute of Health Stroke Scale (clinically) and radiologically by The Alberta Stroke Program Early CT score (ASPECT)[1]. A comprehensive decision, based on these scoring systems usually rational, and beneficial to prevent not only further stroke but also anticoagulant-induced bleeding.

NOAC Paradigm in the Management of Atrial Fibrillation in Ischemic Stroke

In the past decade, observational studies of direct oral anticoagulants (DOACs) for persons with nonvalvular atrial fibrillation who have had an acute ischemic stroke started to explore the use of brain imaging and stroke severity to guide the decision regarding when to initiate treatment. The non-vitamin K antagonist oral anticoagulants (NOACs)—including the direct thrombin inhibitor dabigatran and factor Xa inhibitors rivaroxaban, apixaban, and edoxaban—have revolutionized the management of atrial fibrillation (AF) since their approval in the 2010s. Landmark clinical trials demonstrated that each NOAC was non-inferior to vitamin K antagonists (VKAs) for the prevention of stroke and systemic embolism, and caused fewer episodes of major bleeding [6]. However, the concern is now on the initiation of DOAC, early or delayed. Current clinical practice is to delay the initiation of anticoagulation after ischemic stroke, recommended by several guidelines that are based on expert consensus. European guidelines suggest delay of anticoagulation for 3 days after minor stroke, 6 days after moderate stroke, and 12 days after severe stroke based on this score. For, a high risk of hemorrhagic transformation of an ischemic brain infarct, American Stroke Association guidelines recommend delaying anticoagulation beyond 14 days. However, anticoagulation can be started between day 2 and day 14 if the risk of this complication is low[7].

The Early versus Late Initiation of Direct Oral Anticoagulants in Post-ischemic Stroke Patients with Atrial Fibrillation (ELAN) trial which has been recently published sheds some light on the optimal duration of initiation and bleeding risk. This trial compares the Early Treatment Group means (1, 2, 3, and 4) with the Late Treatment Group means (1,3,6, and 12 days) after a transient ischemic attack (TIA) or after a minor, moderate, or severe stroke, respectively. The results of the ELAN trial showed no major differences between the early-treatment group and the later-treatment group concerning the primary outcome (recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days of enrollment). The results in the article are expressed as the potential for a 2.8-percentage-point advantage and a 0.5-percentage-point disadvantage of early initiation concerning the composite primary outcome. 2.8 % reduction or advantage over the late initiation group regarding recurrent ischemic stroke and systemic embolism. However, a 0.5 % increase in the rate of both intracranial, and extracranial hemorrhage, and overall vascular death in the early Initiation group[7]. We can say from these results that there is a high probability that early direct-acting oral anticoagulant (DOAC) treatment does not cause harm and further a reasonable probability that it reduces the risks of a recurrent ischemic stroke.

Safety of NOAC Regarding Bleeding

Rates of both ICH and hemorrhagic stroke are lower with dabigatran, edoxaban, apixaban, and rivaroxaban, and compared with warfarin[8-11]. In the RE-LY study, the rates of major bleeding were 3.36%, 2.71% (P= .003) and 3.11% (P= .31) per year, and that of hemorrhagic stroke were .38%, .12% (P< .001), and .10% (P< .001), in the warfarin, dabigatran 110 and 150 mg groups, respectively[8]. The ENGAGE AF-TIMI study demonstrated that edoxaban reduced cardiovascular mortality and the incidence of major bleeding including intracerebral hemorrhage (ICH) compared with warfarin [9]. In the ARISTOTLE study, the rate of major bleeding with apixaban was 2.13% per year versus 3.09% per year with warfarin (P< .001) [10]. The risk of intracerebral hemorrhage was significantly lower in patients with AF and heart failure who received rivaroxaban instead of warfarin (HR: .60; [95% CI: .44, .82])[11].

DOAC in Chronic Rheumatic Heart Disease (CRHD) with Atrial Fibrillation

Before the era of NOAC, Vitamine K antagonist oral anticoagulant (warfarin) was the standard of care for both valvular and nonvalvular AF with rheumatic heart diseases. After NOAC paradigm shifts (ROCKET-AF, ARISTOTOLE, ENGAGE –AF, RE-LY) from 2010, it is clear that NOAC is superior to VKA anticoagulant in nonvalvular AF. However, a debate is still going on about the efficacy and safety of NOAC over VKA anticoagulants in CRHD patients. Patients with AF and aortic stenosis, aortic regurgitation, mitral

regurgitation, and mild mitral stenosis were included in the multiple pivotal trials (RIVER, ATLANTIS, RE-ALIGN) comparing NOACs vs. VKAs, and documented NOACs should be used in preference to VKAs in these patients[6]. Nevertheless, for moderate to severe mitral stenosis or mechanical valve replacement, it is quite evident that VKA anticoagulants are superior to DOAC. However, for bio-prosthetic valves in the aortic or mitral position, DOAC is safe, and as effective as VKA anticoagulant.

Low Molecular Weight Heparin or Unfractionated Heparin

Subcutaneous low-molecular-weight heparin (LMWH), subcutaneous unfractionated heparin (UFH), and intravenous heparinoids early after ischemic stroke failed to show a significant treatment benefit over controls. Among those TOAST, FRISS-Triss trials were landmark trials and demonstrated no treatment effect in achieving either a favorable or very favorable outcome at 3 months after stroke. Interestingly, post hoc analysis, showed a significant benefit of LMWH was found in patients with symptomatic posterior circulation stenosis, which suggests that LMWH may be efficacious in patients with posterior circulation disease[12]].

Restarting Anticoagulant Therapy Following Intracranial Hemorrhage

Resuming oral anticoagulant (OAC) after intracerebral hemorrhage (ICH) is a matter of concern among clinicians. Interestingly such patients have been excluded from randomized clinical trials. Initiation of OAC does not increase the risk of recurrent ICH and can also reduce the risk of all-cause mortality. Cessation of oral anticoagulant exposes patients to a significantly higher risk of thromboembolism. The optimal timing of anticoagulation resumption after intracerebral hemorrhage is still a gray zone. The use of NOACs following a cardio-embolic stroke has been assessed in several observational studies. The SAMURAI-NVAF study demonstrated that resumption of a novel oral anticoagulant (NOAC) within 4 days of stroke, did not cause intracerebral hemorrhage[13]. Furthermore, in another observational study, no significant difference in recurrent ischemic events was observed with post-stroke NOAC initiation either less than or equal to 7 days or greater than 7 days following the initial event (P= .53)[14].

Nevertheless, both early (< 2 weeks) and late (>4 weeks) resumption should be reached only after a meticulous assessment of risks for intracerebral hemorrhage recurrence and thromboembolism. It is worthwhile to mention that, In elderly persons (>55 years), lobar hemorrhage, sulcal hemorrhage, cortical micro bleed, and deep bleeding are important factors for delaying anticoagulant therapy at least 4 weeks apart[15].

Limitations:

This is a nonsystematic review, meta-analysis was not done, and observation was described only qualitatively.

Conclusion

Taken as a whole, there is a low likelihood that early anticoagulation, causes harm in terms of excess risk of hemorrhage, rather it prevents further stroke in atrial fibrillation. DOACs are preferably safe and as effective as VKA anticoagulants except in moderate to severe mitral stenosis and mechanical valve replacement. Resumption of anticoagulant after intracerebral hemorrhage is still a gray zone, it should be individualized based on comorbidities, the severity of the stroke, site, and volume of hematoma.

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