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Review Article

Anticoagulant initiation after cardioembolic stroke: practical timing and options

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ABSTRACT

Cardioembolic stroke (CES) is a leading cause of acute ischemic stroke (AIS) and is linked to worse outcomes. There is a notably increased risk of "hemorrhagic transformation" (HT) in CES cases, where anticoagulant therapy is essential for patients with atrial fibrillation (AF) to prevent future strokes. Additionally, larger infarcts are associated with a higher risk of HT, effectively doubling the mortality risk. Currently, there are no clear guidelines connecting infarct size to "anticoagulation" decisions or management of HT cases. This review specifically focuses on the timing of "anticoagulation" initiation in patients with AF. Out of 380 articles evaluated, 50 relevant studies were included in this review. Generally, existing guidelines recommend starting "anticoagulation" between 4 to 14 days after anAIS. The review seeks to summarize current research on early versus late "anticoagulation" initiation in AF patients who experience AIS, providing clinicians with practical insights on optimal timing and the selection of effective and safe anticoagulants.

Keywords: Anticoagulation, Timing, Atrial fibrillation, Stroke

INTRODUCTION

Cardioembolic stroke (CES) constitutes about 20% of AIS cases and tends to result in poorer outcomes compared to other ischemic stroke types.[1] This is largely due to the increased risk of HT that can occur when the blood-brain barrier is disrupted in AIS patients. AF stands out as the most significant risk factor for CES.[2]

Administering anticoagulant therapy is crucial to mitigate the risk of future strokes. It is essential to weigh the likelihood of recurrence against the risk of HT following an AIS or transient ischemic attack (TIA) in AF patients.[3] The 2019 guidelines set forth by the "American Heart Association" (AHA) and the "American Stroke Association" (ASA) are comprehensive, recommending "anticoagulation" initiation within 4 to 14 days after an AIS.[4] This recommendation also applies to patients with HT, necessitating a thorough evaluation of risks and benefits, with consideration for temporary antiplatelet therapy until "anticoagulation" is initiated. Currently, clinicians navigate the decision-making process to determine the best timing for "anticoagulation" initiation, focusing on minimizing the risks of HT and recurrent ischemic events in CES patients. This narrative review aims to evaluate recent observational and randomized controlled trial (RCT) findings regarding the timing of "anticoagulation" initiation across various CES subtypes.

Additionally, it will offer guidance on the optimal timing for starting oral anticoagulant therapy, taking into account the extent of HT and the severity of the stroke. A thorough search of the PubMed and Scopus databases identified appropriate literature using keywords such as "Cardioembolic stroke," "Anticoagulant initiation," "Timing of "anticoagulation"," "Warfarin," "Vitamin K antagonists (VKA)," "non-vitamin K antagonist oral anticoagulants (NOACs)," and "Direct oral anticoagulants (DOACs)." A total of 380 articles were initially reviewed, which was narrowed down to 71 relevant articles on "anticoagulation" timing, ultimately selecting 50 for this narrative review.

DEFINITIONS

Severity of stroke

AIS can be classified into mild, moderate, and severe categories based on the National Institute of Health Stroke Scale ("NIHSS"). A score of 1 to 7 indicates mild AIS, while moderate AIS is defined by a score of 8 to 15. Severe strokes are represented by an "NIHSS" score of 16 or higher.[5]

Hemorrhagic transformation

The European cooperative acute stroke study (ECASS) II provides radiological criteria for categorizing HT.[6] This includes hemorrhagic infarction (HI) 1, characterized by small petechiae without a space-occupying effect, and HI-2, which presents as confluent petechiae without a space-occupying effect.

Parenchymal hematoma (PH) 1 is defined as hemorrhage impacting less than 30% of the infarcted area with minimal mass effect. Whereas PH-2 denotes hemorrhage that involves more than 30% of the infarcted area with a significant space-occupying effect.

Symptomatic intracranial hemorrhage

Both ECASS II and ECASS III characterized "sICH" as any intracranial hemorrhage (ICH) detected on follow-up imaging that results in an increase of at least 4 points on the "NIHSS" from the initial evaluation, or that correlates with mortality; ECASS III particularly highlighted the necessity of establishing a causal link between ICH occurring within the first 7 days post-treatment and clinical worsening.[7]

WHEN TO SUSPECT A "CARDIOEMBOLIC STROKE"

Clinical signs for CES, include the sudden onset of neurological deficits that attain their peak within 5 minutes, the absence of a stepwise increase, a striking phenomenon of rapidly regressing deficits (spectacular shrinking deficit syndrome), disturbances in consciousness, the presence of cortical symptoms (such as aphasia or hemispatial neglect), a high "NIHSS" score, seizures at onset, a history of TIA, and the emergence of symptoms following actions that trigger the Valsalva manoeuvre (like coughing or bending over).[8-10]

Radiological signs consist of involvement of cortical areas, multiple territory involvement, hemorrhagic infarcts, significant infarction, a sudden interruption of blood flow in the middle cerebral artery, or a normal angiogram, large artery occlusion, and the absence of significant atherosclerotic stenosis in the proximal neck vessels (Figure 1).[11]

SHOULD "ANTICOAGULATION" BE INITIATED FOR ALL CASES OF CES

The 2021 AHA/ASA guidelines for the prevention of secondary strokes and TIAs endorse the use of anticoagulants (Class 1) for patients with "AF" (both valvular and non-valvular), atrial flutter, sinus rhythm in conjunction with a mechanical heart valve, left ventricle (LV) thrombus, left atrium (LA) thrombus, cardiomyopathy associated with LV dysfunction along with LA and left atrial appendage (LAA) thrombus, or congenital heart disease that has undergone Fontan palliation.[4]

"AF" is the most common arrhythmia among adults and can be categorized based on the duration a patient experiences "AF" into paroxysmal, persistent, or permanent forms. Even brief, unidentified episodes of AF pose a heightened risk of stroke. Paroxysmal "AF" lasts less than 7 days, persistent exceeds 7 days and does not self-terminate, and permanent lasts more than 1 year. "Anticoagulation" therapy is recommended for individuals with a prior history of stroke or TIA, regardless of the duration for which they have been in AF.[12]

Unlike "AF", atrial flutter is a more organized macro-re-entrant arrhythmia that usually affects the tricuspid isthmus. Although less common than "AF", individuals with atrial flutter are more likely to develop "AF", and the stroke risk associated with atrial flutter is comparable to that of "AF".[13]

INDICATIONS FOR NON-CARDIOEMBOLIC "ANTICOAGULATION" FOLLOWING A STROKE

In patients with AIS, intraluminal thrombus is seen in 1.6% to 3.2% of cases identified through computed tomography angiography, primarily related to large artery atherosclerotic disease (82%), but may also arise from dissection, hypercoagulability, or cardioembolism.[14] Due to the presumed high risk of recurrent stroke, either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) at therapeutic doses, with or without aspirin are recommended.[15] Deep vein thrombosis, pulmonary embolism and pre-existing malignancies are other indication of anticoagulation.

RISK OF RECURRENCE AND HT AFTER STROKE/TIA IN THE SETTING OF AF

The chance of early recurrence of AIS related to "AF" may range from 4% to 8% in the first 14 days post-symptom onset without "anticoagulation".[16] The risk of HT, occur in 1% to 5% of cases during the initial 14 days, and is associated with a 2- to 3-fold increase in both mortality and morbidity (Figure 2).[17,18] sICHs mainly occur within hours after EVT and are rare after 24 hours.[19]

FACTORS THAT INFLUENCE THE DECISION TO COMMENCE ANTICOAGULANT THERAPY

Before starting "anticoagulation", healthcare providers should assess for any risk of stroke recurrence (RIS) in AF using the ALESSA score and CHA2DS2-VASc score.[20-22] The HAS-BLED score to evaluate the bleeding risk and the size of the infarct should be determined, as a larger infarct size is linked to a higher probability of HT (Figure 3).[23]

ALESSA score

First described by Paciaroni et al include patient's age, lesion size, and the existence of significant atrial enlargement on a transthoracic echocardiogram; higher scores signify an increased risk of embolic events, which necessitates earlier initiation of anticoagulant therapy.[20] Patients aged 80 years or older receive 2 points, whereas those aged between 70 and 79 receive 1 point; having an infarct size greater than 1.5 cm adds an additional point, and severe atrial enlargement (determined by left atrial diameter or volume) contributes one more point.

A score between 0 and 2 reflects a low risk for ischemic recurrence and bleeding, while scores of 3 or 4 indicate a higher likelihood of recurrent events, although not associated with severe bleeding. Patients scoring 3 or 4 on the ALESSA scale should receive timely "anticoagulation" treatment and are likely to benefit significantly from early initiation of this therapy.

CHA2DS2-VASc score

The CHA2DS2-VASc score, which takes into account factors such as congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke, vascular disease, age 65–74 years, and sex, serves as a clinical instrument for assessing risk, primarily to evaluate stroke risk in patients with non-valvular AF.[21] A score of ≥2 is recognized as indicating high risk.

According to CHA2DS2-VASc scoring, 43.8% classified as low to intermediate risk and 56.2% categorized as high risk.[24] For male patients, a score of 0 indicates low risk, a score of 1 signifies intermediate risk, and a score of 2 or higher is viewed as high risk. Those identified as high risk necessitate the initiation of oral "anticoagulation" treatment.

HAS-BLED score

The HAS-BLED score, which represents Hypertension, Abnormal renal/liver function, Stroke, History of bleeding, Labile INR, Age over 65, and Drug/alcohol use, is a tool used to assess the likelihood of bleeding in patients with AF.[22]

A score of 0 reflects a low annual risk of major bleeding (2%), while scores of 1-2 indicate moderate risk (2-4% annually), and scores of 3 or more signify a high risk (exceeding 4% per year).

Infarct size

The 2016 ESO (European Stroke Organisation) Karolinska Stroke Update emphasized the significance of infarct size and presented the "4-7-14" day guideline: 4 days after a mild AIS with a small lesion (≤1.5 cm), 7 days post moderate stroke, and 14 days after a severe AIS presenting with a large lesion.[25] The severity of the infarct is categorized based on its effect on superficial or deep branches, according to Paciaroni et al.[26]

A small infarct is defined as an ischemic lesion measuring ≤1.5 cm; a medium infarct, classified by "NIHSS" <8, impacts specific branches of the middle (MCA), posterior (PCA), or anterior cerebral artery (ACA). A large infarct in the anterior circulation involves the total area of the MCA, PCA, or ACA, or affects multiple branches, whereas in the posterior circulation, a large infarct is characterized by a lesion in the brain stem or cerebellum measuring more than 1.5 cm (Figure 4).[27]

Concomitant stroke mechanism

The IAC (Initiation of anticoagulant after cardioembolic stroke) study regarding the introduction of "anticoagulation" following CES indicated that the recurrence of strokes is linked to factors such as hypercoagulability due to cancer, small vessel disease, and atherosclerosis of large arteries.

Therefore, in patients with AF, efficient secondary prevention of AIS may require strategies beyond just "anticoagulation", especially for those already receiving "anticoagulation".[28]

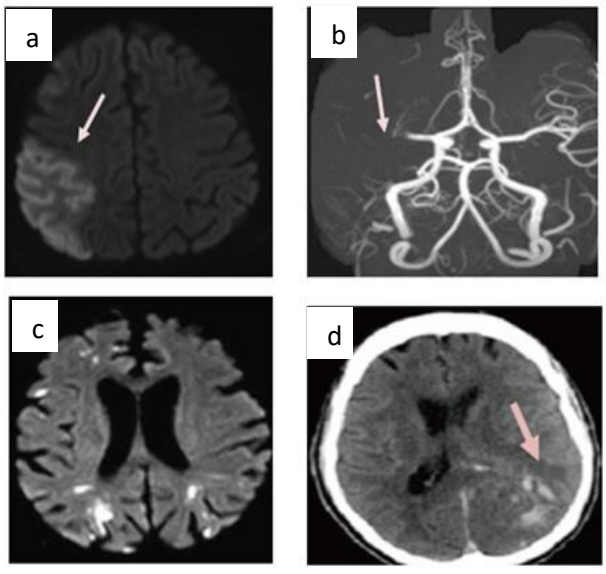

Figure 1 (a-d): Radiological clue for cardioembolic stroke.

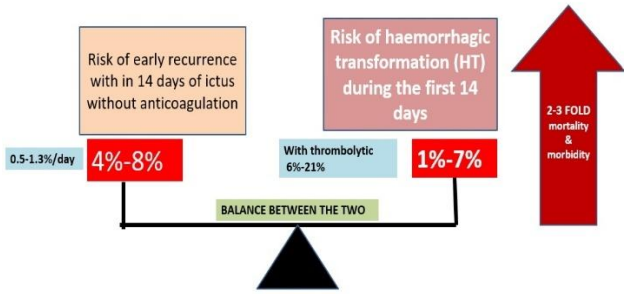

Figure 2: The pictorial representation of risk of recurrence and hemorrhagic transformation after acute ischemic stroke in the setting of atrial fibrillation.

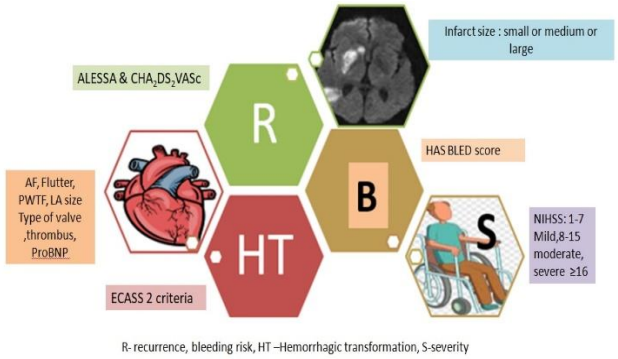

Figure 3: Factors to be considered before initiating "anticoagulation".

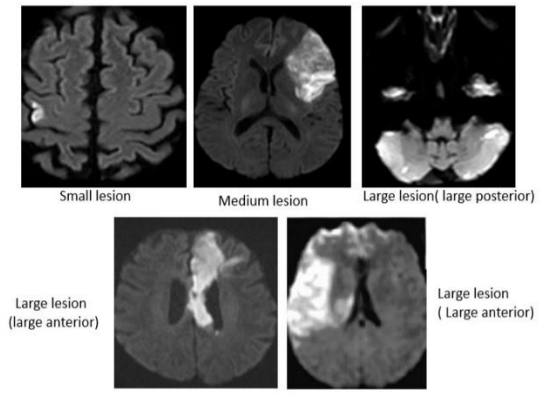

Figure 4: Severity of stroke based on infarct size.

WHICH ANTICOAGULANTS SHOULD BE SELECTED

Available anticoagulants include injectable forms like LMWH and UFH. Oral anticoagulants comprise "VKAs" and NOACs, such as dabigatran, edoxaban, apixaban, and rivaroxaban. These medications predominantly inhibit factor IIa (thrombin) and factor Xa within the coagulation cascade. Factor XI inhibitors, such as asundexian and milvexian, signify a potential new generation of anticoagulants. The OCEANIC-AF trial indicated that Asundexian (50 mg twice daily) resulted in fewer major bleeding incidents but a greater stroke risk compared to Apixaban, resulting in the study's early cessation due to reduced efficacy.[29]

Milvexian is currently under investigation for its potential in preventing secondary ischemic strokes in patients who have experienced acute non-cardioembolic ischemic strokes.[30] Injectable are advised for intraluminal thrombus due to risks of recurrence, while oral anticoagulants are recommended for "Cardioembolic Stroke"based on specific cardiac conditions. Recommended dosing for NOACs can be found in the 2021 guidelines issued by the European heart rhythm association (Table 1).[31]

PREFERRED ANTICOAGULANTS FOR VARIOUS CARDIAC CONDITIONS

Anticoagulants are advised for patients with either valvular or non-valvular heart diseases who suffer from AF or atrial flutter, particularly in cases of AIS or TIA. Certain conditions for their use are detailed in Table 2, including uncommon instances such as left ventricular (LV) non-compaction and Fontan palliation in congenital heart disease.[32] LV non-compaction is an uncommon cardiomyopathy caused by developmental irregularities that lead to prominent trabeculations in the LV wall, typically affecting the inferior and lateral walls and is associated with a risk of cerebral embolism of up to 24% during follow-up.[33]

"ANTICOAGULATION" IN CES WITH UNDERLYING RENAL DISEASE

Patients undergoing dialysis due to renal failure are at an increased risk of both bleeding and thrombotic events. All NOACs are cleared through the kidneys, which heightens the chances of drug accumulation and bleeding issues in those with renal impairment. Although comprehensive data is limited, a retrospective study involving 2,351 patients with AF on dialysis who were given apixaban demonstrated a 28% lower incidence of bleeding events compared to individuals receiving warfarin.[34] This finding supports the use of apixaban as an alternative anticoagulant for patients with AF on dialysis.

CHANGES IN GUIDELINES REGARDING THE START DATE FOR "ANTICOAGULATION"

The recommendations for starting "anticoagulation" have evolved from 2016 to 2019 (Table 3).[4,5,25,32,35] As of 2024, the 2019 ASA guidelines remain applicable, suggesting "anticoagulation" should begin between 4 to 14 days following a CES. This presents challenges for healthcare providers regarding the timing of "anticoagulation" after an AIS or TIA in patients with AF. Should treatment commence immediately, risking HT, or should the focus be on preventing stroke recurrence. Recent research has investigated the timing of early versus delayed "anticoagulation", HT-related "anticoagulation", and initiation following CES.

Table 1: NOACs dosage and recommendations.

NOACs	Standard dose	Dose reduction
Dabigatran	150 mg BID or 110 mg BID	No pre-specified dose-reduction
Edoxaban	60 mg QD (Once daily)	30 mg QD if: weight ≤60 kg or CrCl 15–49 ml/min or concomitant therapy with strong, P-Gp inhibitor
Apixaban	5 mg BID	2.5 mg BID if two out of three fulfilled: weight ≤60 kg, age ≥80 years, serum creatinine ≥133 mmol/l (1.5 mg/dl), (or single criterion: if CrCl 15–29 ml/min)
Rivaroxaban	20 mg QD	15 mg QD if CrCl ≤15–49 ml/min

Table 2: Anticoagulant of choice in various cardiac conditions associated with ischemic stroke or transient ischemic attack.

S. no	Cardiac condition	Anticoagulant of choice	Class of recommendation[32]
I	Valvular heart disease with AF		
	Moderate or severe MS With AF	Warfarin (VKA)	Class 1
	Mechanical valve with AF	Warfarin (VKA)	Class 1
	All other valvular heart disease with AF	DOACs (NOACs)	Class 1
II	Valvular heart disease with sinus rhythm		
	Mechanical MV or AV	Warfarin	Class 1
	Bioprostheis MV or AV	Antiplatelets, DOACs or warfarin (anticoagulants if develop stroke while on antiplatelets)	Class 1, Warrants further investigation
III	Cardiomyopathy in sinus rhythm		
	With LV thrombus	Warfarin	Class 1
	With LA thrombus	Warfarin	Class 1
	With LVAD	Warfarin and aspirin	Class 2 a
	With LV non- compaction	Warfarin	Class 2 a
	With reduced ejection fraction only	"anticoagulation"	Class 2b
IV	Cardiomyopathy with AF	DOACs	Class 1
V	Congenital heart disease		
	Congenital heart disease with fontanpaliation	Warfarin	Class 1
	Cyanotic congenital heart disease	Warfarin	Class 2a
VI	Atrial flutter		
	Valvular heart disease (moderate or severe MS and mechanical valve)	Warfarin	Class 1
	Other valvular heart disease	DOACs/NOACs	Class 1

Table 3: Evolution of guidelines/ rules for initiation "anticoagulation" in cardioembolic stroke.

Guidelines and year	ESC guidelines 2016, Kirchhof et al[5]	ESO-Karolinska Stroke Update 2016 Ahmed et al[25,] Same ESO 2019 guidelines[35]	AHA /ASA guidelines 2019 Powers et al[4] Same followed AHA/ASA 2021 guidelines Kleindorfer et al[32]	ESO 2023 guidelines Based on Elan et al[42]
Rules	1-3-6-12 rule after exclusion of ICH on imaging based on NIHSS (Dieners rule)	4-7-14" day rule based on infarct size and NIHSS	Broad and suggest initiation of AC between 4-14 days	Early anticoagulation Early anticoagulation is safe and effective, challenging older "1-3-6-12 day" rules.

Continued.

Guidelines and year	ESC guidelines 2016, Kirchhof et al[5]	ESO-Karolinska Stroke Update 2016 Ahmed et al[25,] Same ESO 2019 guidelines[35]	AHA /ASA guidelines 2019 Powers et al[4] Same followed AHA/ASA 2021 guidelines Kleindorfer et al[32]	ESO 2023 guidelines Based on Elan et al[42]
Day of initiation of "anticoagulation"	1 day after transient ischemic attack (TIA) 3 days after mild AIS (NIHSS score <8 points), 6 days after moderate AIS (NIHSS score: 8–15 points), 12 days after severe stroke (NIHSS score >15 points)	4 days after mild AIS and small infarct size (lesion ≤1.5 cm), 7 days after moderate stroke and medium infarct size, 14 days after severe AIS and large infarct size in NVAF. First 48 hours antiplatelet.	Even in the context of HT after individual assessment of risks and benefits, considering antiplatelet therapy until AC initiation	Early anticoagulation (within 0–3 days for minor stroke, 4–7 days for moderate, 7–14 for major stroke)

Table 4: Summary of data.

	Day of "Anticoagulation" initiation				
	Drug of choice Rule	**TIA**	**Mild stroke**	**Moderate stroke**	**Severe stroke**
Valvular AF (Moderate MS severe MS, mechanical prosthetic valve) LA thrombus, LV thrombus	VKA (warfarin) 1.3.6.12 days rule (Diener rule)[5]	After a day	After 3 days NIHSS 1-7	After 6 days NIHSS 8-15	After 12 days NIHSS ≥16
Non valvular AF (MildMS/MR, moderate – severe AS/AR, mitral valve prolapses, mitral annulus calcification.)	NOACs, Kimura et al[40] 1,2,3,4, days rule	After 1 day	After 2 days NIHSS 1-7	After 3 days NIHSS 8-15	After 4 days NISHSS 8-15
	NOACs timing[41]		Early initiation within 4 days all AIS		
	NOACs ELAN based on infarct size[42]		Within 48 hours	Within 48 hours	6 -7 days
	NOACs OPTIMAS based on NIHSS[43]		Early initiation within 4 days all AIS		
Non valvular AF With HT	NOACs ELAN HT[44] Severity of stroke based on infarct size		HI 1 and 2 within 48 hours PH-after 12 days	HI 1 and 2 within 48 hours PH-after 12 days	HI 1 and 2 6 -7 days PH-after 12 days
ICH and mechanical heart valves	VKA (warfarin) Sakusic et al[45]		Late initiation after 7 days		
After EVT (non valvular disease)	NOACs, Ma et al[49]		late initiation 5-14 days		
After EVT with HT (non valvular disease)	NOACs, Nishimoto et al[50]		HI2 -6 days PH after 7 days		

ANTIPLATELETS VERSUS VKA / NOACS IN CES

The stroke prevention in atrial fibrillation study evaluated the effectiveness of 325 mg of aspirin daily and warfarin against a placebo for preventing ischemic strokes and systemic embolism with AF without rheumatic valve disease.[36] The findings showed that warfarin lowered the risk of stroke by 67%, while aspirin was effective in 42% of cases. The IAC study suggested that NOACs are more effective than "VKAs" in preventing early recurrence.[37]

Initiating VKA therapy early could lead to a higher risk of fatal intracerebral hemorrhage (ICH) in the first month. Various observational studies and meta-analyses indicate that NOACs generally outperform "VKAs" in reducing ischemic strokes during the early stages of treatment.[38]

EARLY "ANTICOAGULATION" IN INDIVIDUALS AT ELEVATED RISK OF RECURRENT EMBOLISM

An analysis of the RAF-NOACs (Early recurrence and major bleeding in patients with AIS and atrial fibrillation treated with non-vitamin-K oral anticoagulants) study highlighted that 5% of patients who were started NOACs within 24–48 hours after an AIS experienced HT, suggesting that early "anticoagulation" might not be advisable. The study revealed no significant rise in recurrent ischemic strokes when comparing the initiation of "anticoagulation" after a 12-day delay in patients with HT to those without HT.[39] The two Japanese registries, SAMURAI-NVAF (stroke acute management with urgent risk-factor assessment and improvement-non-valvular AF) and RELAXED (Recurrent embolism lessened by rivaroxaban, an anti-xa agent, of early dosing), explored the safety and effectiveness of early initiation of NOACs based on the severity of stroke. Beginning NOACs after one day post-TIA, two days post-mild stroke ("NIHSS": 1-7), three days post-moderate stroke ("NIHSS": 8-15), and four days post-severe stroke ("NIHSS" ≥16) correlated with improved efficacy and comparable safety compared to delayed initiation.[40]

The TIMING study, which focused on the timing of oral anticoagulant treatment in AIS with AF, found that commencing NOACs within four days post-stroke was non-inferior to treatment between five to ten days, with no reported cases of symptomatic ICH among AIS patients. The rates of RIS and mortality were numerically lower in the treatment group that started earlier.[41] The ELAN (early versus late initiation of DOACs in post-ischemic stroke patients with AF) trial included patients with various stroke severities. Participants received either early "anticoagulation" (within 48 hours of a minor or moderate stroke, or on day's 6-7 post-major stroke) or delayed "anticoagulation". The study concluded that the occurrence of adverse outcomes at 30 days with early use of DOACs was estimated to range from 2.8 percentage points lower and 0.5 percentage points higher in comparison to later use.[42] The optimal timing of "anticoagulation" following AIS with AF (OPTIMAS) study was a multicentre, open-label RCT. Participants received early "anticoagulation" (within 4 days of stroke symptoms) or delayed "anticoagulation" (between 7 to 14 days) with any NOACs. The primary outcome evaluated was a composite measure of RIS, "sICH", unclassified stroke, and systemic embolism occurring within 90 days. The results indicated that the early initiation of NOACs was not inferior to the delayed initiation.[43]

INITIATING NOACS AFTER HT

The ELAN subgroup analysis reviewed the initiation of anticoagulants in individuals with HT. HT group were further subdivided, into HI or PH identified through imaging conducted prior to randomization. The rates of "sICH" were comparable between the groups; however, early treatment was linked to an 11.5% risk difference for unfavourable functional outcomes (modified Rankin Scale scores of 3-6) in HT patients (7.4% for HI and 25.1% for PH), while it was -2.6% for those not experiencing HT. The analysis showed no significant differences in treatment effects or safety concerns between early and late initiation of direct oral anticoagulants, but early initiation could adversely impact functional outcomes for patients with PH.[44]

INITIATING "VKAS" AFTER HT

A study conducted by Sakusi et al examined the timing and risks of resuming "anticoagulation" in patients with mechanical heart valves who experienced ICH.[45] The focus was on thromboembolic events occurring while "anticoagulation" was temporarily halted and the potential for ICH expansion following the restart of treatment. Their findings suggested that postponing "anticoagulation" for at least 7 days after ICH may be safe, while using heparin bridging could increase the risk of bleeding. The prospective record of the use of dabigatran in patients with acute stroke or transient ischemic attack (PRODAST) study evaluated the timing of Dabigatran in comparison to "VKAs" in patients with AIS or TIA.[46] The study investigated the incidence of significant hemorrhagic events within three months based on the timing of treatment initiation, categorized as early (≤ 7 days) or late (> 7 days). The research concluded that both early and late initiation of dabigatran presented a lower risk for major haemorrhages, particularly ICH, compared to "VKAs". Dabigatran may serve as an alternative for patients on warfarin who are at heightened risk for bleeding.

WHEN IS IT APPROPRIATE TO START "ANTICOAGULATION" AFTER "EVT"

The timing of "EVT" can influence the risk of "sICH", with later treatment windows and posterior circulation strokes associated with a greater risk of "sICH". According to the HERMES (highly effective reperfusion evaluated in multiple endovascular stroke). Trials meta-analysis of RCTs focusing on anterior circulation strokes, no increase in "sICH" risk was observed; however, the MR CLEAN (Multicenter Randomized Clinical trial of Endovascular Treatment for AIS in the Netherlands) late trial showed an elevated risk of "sICH".[47,48] A prospective study from China suggests that initiating "anticoagulation" too soon could be harmful. This study included patients who received "anticoagulation" within five days after "EVT", between five and fourteen days,

and after fifteen days from the event. Significant "sICH" cases were recorded only in the early initiation group.[49]

There is limited evidence concerning the start of "anticoagulation" in patients who experience early HT after "EVT". A recent retrospective study from Japan.[50] investigated patients treated with "EVT" for AIS in the anterior circulation. In this study, NOACs were initiated after a median of 1 day for the group without HT, at 3 days for those with HI, and at 7 days for the group with PH. The study showed that the likelihood of developing late HT while on NOACs is low. Overall, the evidence points to the safety of postponing "anticoagulation" initiation after "EVT". Further research is required on the timing of "anticoagulation" after "EVT" in cases of early HT.

IS BRIDGING "ANTICOAGULATION" THERAPY DURING AIS BENEFICIAL OR HARMFUL

Bridging therapy consists of starting a full dose of LMWH either prior to or simultaneously with "VKAs" until the international normalized ratio (INR) reaches the therapeutic range, or administering a full dose of LMWH before beginning NOACs. Findings from the IAC and RAF-NOACs studies indicate that this type of bridging therapy significantly doubles the risk of both ischemic and hemorrhagic events.[37,39] The shortcomings of our review include the possibility of bias, and the absence of quantitative analysis. A summary of the current data related to starting "anticoagulation" therapy is presented in Table 4.

CONCLUSION

The timing of "anticoagulation" therapy initiation should be tailored to each individual, weighing their bleeding risk against the potential for embolism recurrence. It's crucial to perform repeat imaging prior to starting "anticoagulation". According to the current guidelines (AHA/ASA 2021), "anticoagulation" should be initiated between 4 to 14 days after AIS, even in cases of "hemorrhagic transformation", following a careful assessment of risks and benefits. Antiplatelet therapy should be an option until "anticoagulation" is initiated.

The prompt use of NOACs has been proven to be both effective and safe in cases of CES without HT and with HI. When CES occurs alongside PH, the delayed start of NOACs and "VKAs" is clearly safe. It is vital to postpone "anticoagulation" after "EVT" to enhance patient outcomes. There is an urgent necessity for more RCTs to thoroughly explore the initiation of "VKAs" based on infarct size, where "VKAs" are favoured, and to identify the best timing for resuming "anticoagulation" in relation to "EVT", particularly with early HT. Additionally, the guidelines for starting "anticoagulation" in cases of CES need to be revised to incorporate findings from recent RCTs. Moreover, future studies should aim for uniformity in the methodologies concerning the initiation of anticoagulants, both early and delayed.

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