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REVIEW ARTICLE

THE ANTICOAGULATION STRATEGIES FOR MANAGEMENT AND PREVENTION OF STROKE IN NEUROLOGICAL PRACTICE

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Abstract

Strokes are categorized as either ischemic or hemorrhagic and the specific interventions will be based on the type of stroke. About 13% of stroke is hemorrhagic and 87% is ischemic. Transient Ischemic Attacks require emergency intervention to decrease the threat of stroke, which is thought to be maximum within the first few days after TIA. Anticoagulants play a major role in the primary and secondary prevention of ischemic strokes.
The optimal timing of anticoagulants initiation or resumption inpreventing and managing ischemic strokes is very important. This article will explore certain controversies surrounding this issue, while also highlighting the benefits of antithrombotic therapy used in prevention of ischemic strokes in antiphospholipid antibody syndrome (APS), atrial fibrillation, prosthetic heart valve, cancer, and vascular disorders. Aggressive local and regional efforts to organize stroke care and greater use of evidence-based recommendations may help improve outcomes.
Keywords: Anticoagulants, atrial fibrillation, cerebral hemorrhage, ischemic stroke.

INTRODUCTION

Stroke is a leading cause of death and long-term disability worldwide. With advances in medical management, the incidence and mortality of stroke have decreased, with most strokes occurring as ischemic strokes rather than hemorrhagic strokes. One of the most important steps is determining the time of onset of ischemic stroke symptoms, as this will help determine the need for medical treatment or endovascular intervention. The physical examination goals are to determine stroke location, distinguish stroke mimics, complete neurological deficit assessment, and identify comorbidities and conditions that can affect treatment[1].
The following baseline tests should be performed in all patients: blood cell count and platelet count, blood electrolytes, cardiac examination, kidney function, the partial thromboplastin time (PTT), prothrombin time, standardized prothrombin time (INR), and electrocardiogram (ECG). If the results of previous tests are desired, treatment should not be delayed while awaiting the results unless thrombocytopenia or abnormal bleeding is suspected with the use of heparin, warfarin, or other Anticoagulants[2-5]

Anticoagulation is indicated in neurology practice for primary and recurrent stroke prevention in atrial fibrillation (AF), prosthetic mechanical valve; dilated cardiomyopathy (DCMP) and cerebral venous sinus thrombosis (CVST).Oral anticoagulants (OACs) are used lifelong in most of these conditions[6].
Oral anticoagulants have a narrow therapeutic range and increase the risk of bleeding. They have been shown to predispose patients to thromboembolism. The effectiveness of OAC therapy is monitored by measuring the prothrombin time expressed as the international normalized ratio (INR). Monitoring timeframe depends on the stability of the INR and can range from daily to three months[7].
CHADS2 and CHA2DS2-VASc scales help professionals to understand risk factors for cardioembolic stroke due to atrial fibrillation and identify bleeding complications.CHA2DS2VASc Score consists from eight items[8] (Table 1). This score varies from 1 to 9. The annual risk of stroke was 15.2% in patients with a CHA2DS2-VASc score of 9. The European Society of Cardiology atrial fibrillation guidelines recommend dividing AF patients into three groups according to CHA2DS2-VASc score: low risk-score 0, medium risk- score 1, high risk -score ≥2 of a stroke risk[9].

Table 1: CHA2DS2VASc score.

Condition	Points
Congestive heart failure	1
Hypertension	1
Age ≥ 75	2
Diabetic Mellitus	1
TIA or Prior Stroke	2
Vascular disease	1
Age between 65-75	1
Gender: Female	1
Maximum Sore	9

There are important updates in the literature regarding the effective and appropriate management of patients with ischemic stroke. AHA/ASA has released guidelines, most updating in 2018, stating the best treatment options for early treatment of patients with ischemic stroke. Anticoagulants used in ischemic stroke include thrombolytic agents, anticoagulants, and antiplatelet agents. Previously, anticoagulants played a significant role in the acute treatment of ischemic stroke. Recently, anticoagulants play a major role in the primary and secondary prevention of ischemic strokes[10]. This article will discuss some of the controversies surrounding this issue, while also highlighting the benefits of anticoagulation therapy in the secondary prevention of cardioembolic stroke and other conditions.

The indications for anticoagulation in stroke prophylaxis and recurrent.

1. Atrial Fibrillation

Atrial fibrillation (AF) increases the risk of stroke fivefold and is the leading cause of cardiogenic stroke, accounting for approximately 20% of ischemic strokes. Left atrial appendage (LAA) thrombosis secondary to atrial arrhythmia hemostasis is a common explanation for stroke in patients with AF. Anticoagulation with vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) reduces the risk of stroke in patients with AF. Therefore, anticoagulation is considered the first-line therapy for thromboembolism prevention in people with AF based on their CHA2DS2-VASc score, and people who have a history of stroke or transient ischemic attack (TIA) automatically meet the indication[9].

AHA guidelines suggested DOAC therapy for nonvalvular AF without mechanical heart valve after acute ischemic stroke (AIS) or TIA to decrease the risk of recurrence stroke[11].

VKAs are the preferred anticoagulant for patients with valvular atrial fibrillation or mechanical heart valves. Among DOACs, apixaban appears to have a lower risk of bleeding compared with rivaroxaban. It should be considered as a viable alternative in patients with hypertension and a risk of stroke.LAA closure has been shown to be effective and safe in reducing the risk of stroke in patients with AF and high bleeding risk and should be considered a valid alternative[12].

2. Cardiac Thrombus

Left ventricular (LV) thrombus is a significant complication following myocardial infarction and heart failure with low ejection fraction. Previous investigations have shown that the risk of embolism or stroke or increased when there is a left-sided artery. Oral anticoagulants, particularly VKAs, may decrease the risk of embolism[13].

Although DOACs have been shown to be as effective as VKAs in preventing embolic complications of AF and venous thromboembolism (VTE) and have lower and milder bleeding complications, data regarding their use in LV thrombosis are conflicting. The most recent AHA/American Stroke Association (ASA) guidelines (as of 2021) recommend anticoagulation with VKA therapy for at least 3 months in patients with stroke or TIA and LV thrombus[14].

3. Mechanical Heart Valve

Vitamin K Antagonist (VKA) with INR range between 2.5 to 3.5 is shown to reduce the risk of stroke in patients with a mechanical heart valve. Mitral valve replacement has a higher risk than aortic valve replacement. Aspirin is recommended to be added to VKA for high-risk individuals with a previous stroke or TIA and for valve replacement in some clinical situations[15]. Regarding DOAC use, dabigatran has a higher risk of thromboembolic and bleeding conditions than VKA in patients with a mechanical heart valve. The DOACs have not been reported for this indication and are not indicated[16].

4. Venous Thromboembolism (VTE)

VTE is an under diagnosed and inadequately treated condition in primary care stroke patients. The deep vein thrombosis (DVT) has an incidence about 50% within 2 weeks in hemiplegic stroke patients not receiving chemoprophylaxis. This risk persists in the post-stroke phase, where the risk of DVT persists for up to 9 weeks after stroke[17]. DOACs is considered the first line treatment of VTE. The ACCP 2016 Guidelines and the ESC 2017 Guidelines recommending their use. According to previous reports, DOACs are ineffective for secondary VTE prevention and may be related to increase the risk of major bleeding such as systemic bleeding, in contrasting to LMWH associated with VKA in subsequent therapy[18].

5. Antiphospholipid Syndrome

Antiphospholipid syndrome (APS), also known as Hughes syndrome, is a disease of the immune system that causes an increased risk of blood clots such as deep vein thrombosis and stroke. APS strokes account for 20% of stroke cases in people under the age of 45. The risk of recurrent thromboembolic events in APS patients after 6 years of follow-up is as high as 69%[19]. There was no evidence of a higher risk of VTE in APS patients receiving DOACs compared with patients receiving VKAs, but the risk of venous return was elevated. Anticoagulant therapy is required with VKAs with range of INR 2 to 3[20].

6. Cancer-Related Stroke

The active cancer increases the risk of ischemic stroke. Cancer-related hypercoagulability can cause embolic stroke of unknown origin (ESUS) from thrombosis in the cerebral vasculature. Another process associated with cancer-related hypercoagulability in ESUS that can lead to stroke is paradoxical embolism. About 20% of patients with cancer will develop venous thromboembolism during their lifetime[21].

Hypercoagulable states are associated with decrease survival rate after stroke in cancer patients. OASIS-CANCER (Optimal Anticoagulation Strategies in Cancer-Related Stroke) shows that anticoagulant therapy corrects hypercoagulable states and improves survival by 1-year in cancer patients[22]. The Canadian Stroke Best Practice Guidelines recommend that cancer patients who have a stroke or TIA secondary to suspicion of a cancer-related hypercoagulation, anticoagulant therapy should be considered instead of antiplatelet therapy[23].

7. Vascular Disorders:

Carotid artery dissection is a mostrisk of stroke in young adults. American heart association guidelines recommend that antithrombotic medications be indicated for at least 3 months to prevent events of TIA and stroke. VKAs have traditionally been used to treat carotid artery disease, but DOACs are also used because they are convenient and safe[24].

The incidence of intraluminal thrombosis in patients with AIS ranges from 1.6% to 3.2%. Intraluminal thrombosis occurs in the setting of atherosclerotic disease of the large arteries and in conditions complicated by local hemostasis and inflammation, embolism, or hypercoagulable states. The most commonly used treatment strategy is intravenous unfractionated heparin as alone or in combination with a single antiplatelet such as aspirin. In this situation, a dual antiplatelet strategy may be an appropriate treatment, especially since most intraluminal thrombi occur in areas of atherosclerosis[25].

Drugs-Induced Ischemic Stroke

Erythropoietin and ESAs are indicated to elevate hemoglobin levels in anemic patients. FDA and EMA documentation confirms that erythropoietin and erythropoiesis-stimulating agents with hemoglobin levels greater than 11 or 12 g/dL may increase the stroke risk[26]. Estrogen therapy combines hormone replacement therapy and anti-inflammatory drugs in postmenopausal women. Oral estrogen replacement (in combination with progestins or as alone) is related to increase the risk of ischemic stroke. Protease inhibitors such as darunavir, and atazanavir and reverse transcriptase inhibitors such as abacavir are drugs indicated to manage and prevent HIV infection. In a big data analysis, darunavir was associated with an increased risk of stroke, in contrast to atazanavir. Bevacizumab inhibits angiogenesis by inhibiting vascular endothelial growth factor. It is recommended to treat a variety of cancers, including breast cancer and others. Patients treated with bevacizumab, especially those receiving high doses, are at risk for ischemic stroke (IS). TKIs such as nilotinib, ponatinib, and dasatinib have approval for the treatment of acute lymphoblastic leukemia and acute myeloid leukemia. The arterial thromboembolic event (ATE) warning for ponatinib and nilotinib are included in the EMA and FDA labels. TKIs such as sunitinib and sorafenib are approved for the treatment of renal cell carcinoma, hepatocellular carcinoma, and gastrointestinal stromal tumors. FDA and EMA warning about ATE. GnRH agonists such as goserelin and leuprolide are frequently recommended for treatment of patients with prostate cancer as hormone therapy. The FDA label has a black box warning about vascular events such as stroke. Tamoxifen is with both agonist and antagonist effects, based on the individual's target organism. It is recommended for in situ treatment of breast cancer with estrogen receptor-positive and ductal carcinoma and for decreasing the incidence of breast cancer in women with high-risk. The FDA releases a black box warning regarding the risk of stroke. Aromatase inhibitors (AIs) such asanastrozole, letrozole, and exemestane may treat breast cancer by decreasing the level of estrogen and theses drugs are indicated for the treatment of patients with breast cancer. Most literature investigations comparing A is, known to increase the ischemic stroke risk, to tamoxifen show no difference or reduction in the risk of cardiovascular events (CVE). The FDA notice warns that use of anastrozole in women with ischemic heart disease may increase the risk of ischemic CVE. There are no specific issues for other aromatase inhibitors. Lenalidomide and thalidomide are indicated for the management of multiple myeloma. Thalidomide is prescribed as a sedative and sleep-inducing drug which cause severe pain. These two drugs increase the risk of venous thromboembolic events, so the anticoagulants are recommended. Despite the high-level evidence for lenalidomide, EMA and FDA have released warnings about ATE, such as stroke. Alemtuzumab is indicated for the treatment of acute lymphocytic leukemia and relapsing-remitting multiple sclerosis. Ischemic stroke events with alemtuzumab are typically demonstrated in the post-marketing setting within three days of use. So, stroke is a boxed warning in the FDA label. FDA and EMA labels for various NSAIDs and highly selective coxibs also shown to increase the stroke risk. The risks associated with this medication depend on the dose and course duration. Antipsychotics such as haloperidol, risperidone and quetiapineare a broad class of medications used to treat psychosis in schizophrenia, bipolar disorder, depression, and to control behavior in dementia. There is evidence that medication use is a risk factor for stroke. FDA and EMA reports include warnings about CVEs in adults with associated dementia. Benzodiazepines are GABA agonists with effects such as sedative, anxiolytic, hypnotic, antispasmodic, and muscle relaxant. The association of stroke risk with benzodiazepines use has been reported to vary with annual dose, ranging from protection at lower doses (<1 g per year) to greater risk (≤4 g per year). Ergotamine derivatives are the first available migraine treatments. Ergotamine has broad receptor agonist properties (serotonin, dopamine, and alpha-adrenergic receptors) and promotes vasoconstriction. The FDA label has a black box warning for life-threatening ischemia when used with strong cytochrome 3A4 inhibitors. Over-the-counter nasal phenylpropanolamine has been withdrawn from the market due to the risk of hemorrhagic stroke. Idarucizumab reverses the anticoagulant effects of dabigatran. It is recommended for use in patients treated with dabigatran who require urgent surgery interventions or uncontrolled/severe bleeding. Idarucizumab does not exhibit prothrombotic effects

compared with other agents prescribed to reverse acquired coagulation deficiencies. EMA and FDA documents have warnings about the risk of thromboembolism because discontinuation of dabigatran treatment puts patients at risk of thrombosis in their underlying systems.

Management of Ischemic Stroke

Acute Treatment:

The ASA Stroke Committee develops and publishes guidelines for the treatment of ischemic stroke. There are only two types of drugs that recommend for acute treatment: alteplase (start within 4.5 hours of stroke) and aspirin (start within 24 to 48 hours of stroke). Early treatment with intravenous alteplase (started within 4.5 hours of symptom onset) has become an important part of intensive therapy to improve functional capacity after ischemic stroke without interruption[27]. Tissue plasminogen activator (rt-PA) is a fibrinolytic agent that has an affinity for fibrin and promotes the conversion of plasminogen to plasmin, causing fibrin clots to disintegrate. Alteplase has a short half-life (approximately 4 minutes). The total dose for ischemic stroke is 0.9 mg/kg (maximum 90 mg), 10% as a bolus injection over 1 minute, and the remaining 90% as an intravenous injection over 60 minutes. Intervention due to increased risk of bleeding, including cerebral hemorrhage. Therefore, it is important to follow the recommended guidelines to achieve good outcomes and minimize risks. These procedures can be evaluated as (a) stroke team, (b) brain investigation (such as CT scan), (c) early treatment within 4.5 hours of test results, (d) including and excluding, (e) ati Total dose alteplase 0.9 mg/kg (maximum dose 90 mg), 10% as a bolus injection over 1 minute, 90% remaining after intravenous injection over 1 hour, (f) Do not use antithrombotic drugs (anticoagulants or antiplatelets) for 24 hours after alteplase, and (g) carefully monitor the patient's blood pressure, nervous system status, and bleeding. Endovascular interventional treatment is not a contraindication to alteplase, and patients who are suitable for alteplase should receive additional treatment with any thrombectomy.

Tenecteplase

Unlike alteplase, tenecteplase can be administered as a rapid injection. Although tenecteplase is FDA-approved for the treatment of patients with ST-segment elevation myocardial infarction, it is not yet registered for use in ischemic stroke. Tenecteplase has been studied in a variety of stroke patients and is specifically mentioned in the 2019 updated AHA/ASA guidelines, which state that tenecteplase at 0.25 mg/kg (maximum 25 mg) would be considered an alternative to alteplase for patients who are also eligible to undergo mechanical thrombectomy[11].

The 2019 AHA/ASA guideline update also recommends considering tenecteplase at 0.4 mg/kg (maximum 40 mg) as an alternative to alteplase in patients with an NIHSS score of 7 or less who are receiving thrombolytic therapy. Recently, a study investigating the 0.4 mg/kg dose of tenecteplase was stopped early due to safety concerns[28].

More comments on the specific dosage of tenecteplase and its place in therapy compared to alteplase are expected to change in the next AHA/ASA guidelines based on this information. Based on this new data, the European Stroke Group published new guidelines for the use of tenecteplase in 2023, stating that tenecteplase 0.25 mg/kg (more than 25 mg) is as safe as alteplase 0.9 mg/kg. It is recommended that tenecteplase not be used at a dose of 0.4 mg/kg[29].

Aspirin

In the absence of aspirin allergy or other allergic reactions, patients with ischemic stroke should receive aspirin therapy within 24 to 48 hours of symptom onset. In patients receiving alteplase, aspirin and other anti-inflammatory drugs are generally withheld for 24 hours after alteplase administration to reduce the risk of bleeding. AHA/ASA guidelines recommend early use of aspirin to reduce the risk of death and long-term disability in patients with ischemic stroke. There is some information regarding the use of non-aspirin antiplatelet agents in combination during acute stroke. However, ischemic stroke patients with severe allergy or contraindications to aspirin may require the use of other anticoagulants[11]. Studies indicate that the lowest effective dose may be in the range of 75 mg/day[30].

Upper gastrointestinal (GI) discomfort and bleeding are the most common side effects of aspirin and have been shown to be dose-related. Patients taking aspirin had a 43% higher risk of major bleeding compared to patients not taking aspirin. The risk of bleeding is dose-related and increases with age; therefore, the upper limit for aspirin is 300 mg to 325 mg[11].

Several factors contribute to aspirin resistance including aging, diabetes, hyperlipidemia, smoking, chronic kidney disease, and drug-drug interactions (eg, nonsteroidal anti-inflammatory drugs)[31].

Genetic polymorphisms, including those affecting the activity of COX-1, COX-2, glycoprotein IIb/IIIa receptors, and adenosine diphosphate (ADP) receptors, may cause aspirin resistance. Despite increasing evidence of low aspirin responsiveness is related with suboptimal goals in stroke patients, routine assessing for low responsiveness of aspirin is not recommended[32].

Therapeutic Anticoagulation

The use of anticoagulants (e.g. unfractionated heparin or low molecular weight heparin) is not recommended in the early stages of ischemic stroke treatment. The medical benefits of anticoagulant therapy in the setting of stroke with non-occlusive intraluminal thrombus are limited. Anticoagulant therapy for non-stroke indications (e.g. prevention or treatment of venous thromboembolism) should be weighed against the risk of hemorrhagic changes in patients with ischemic stroke. Medical or pharmacological venous thromboembolism prophylaxis should be administered to immobile patients after stroke. The choice of drug, dosage, and duration of pharmacologic VTE prophylaxis will depend on the patient's condition and medical history, including stroke[11].

Antiplatelet Agents

Antiplatelet therapy is the mainstay of antithrombotic therapy for secondary prevention of ischemic stroke and should be used in non-cardioembolic stroke. Aspirin, extended-release dipyridamole plus aspirin,

clopidogrel, and ticagrelor are all recommended for secondary stroke prevention. Oral anticoagulants such as apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin are recommended for prevention of second stroke in patients with atrial fibrillation[33]. Although aspirin is an antiplatelet drug and most data support its use, there is also evidence to support the use of the combination of clopidogrel and extended-release dipyridamole in addition to aspirin as an alternative approach for secondary stroke prevention. For patients already taking aspirin at the time of a non-cardioembolic stroke or TIA, there is no evidence that increasing the aspirin dose is better for preventing another stroke[14].

Clopidogrel

Clopidogrel is a drug that must be activated by the cytochrome P450 isoenzyme 2C19 (CYP2C19) to achieve its antiplatelet effects. Polymorphisms exist in several alleles encoding this enzyme, including *1 being the wild type, *17 leading to increased metabolism, and *2 and *3 leading to decreased metabolism. Therefore, individuals with one copy of *2 or *3 are classified as intermediate metabolizers, while individuals with two copies of *2 or *3, or one copy each (*2/*3), are known as poor metabolizers. Poor metabolizers are found in about 2% of Caucasians, 4% of African Americans, and 14% of Chinese[34].

Drugs that inhibit CYP2C19 may also reduce the antiplatelet activity of clopidogrel. Omeprazole and lansoprazole both inhibit CYP2C19 and should not be used in patients taking clopidogrel. Opioids slow digestion, slow absorption, and reduce antiplatelet activity, potentially leading to decreased activity[35,36].

Extended-Release Dipyridamole Plus Aspirin

Early studies of the role of dipyridamole in stroke prevention failed to show a benefit over aspirin alone. However, 25% of the patients who received a combination of dipyridamole and aspirin discontinued the therapy early, many due to adverse drug reactions. The discontinuation due to headache was more than threefold higher (10%) than the aspirin-alone group (3%)[37].

Another study showed that the combination of extended-release dipyridamole and aspirin and clopidogrel was equally effective in preventing stroke. However, clopidogrel was more effective, with less bleeding and headache. Despite careful patient education and instructions on headache management, discontinuation of treatment due to headache was six times more common in the extended-release dipyridamole than in the clopidogrel group (5.9% vs. 0.9%). The use of immediate-release dipyridamole in combination with regular aspirin to reduce costs is unproven and should be encouraged[38].

Ticagrelor

Ticagrelor (loading dose of 180 mg then 90 mg twice daily for 90 days) was compared to aspirin (300 mg loading dose then 100 mg daily 90 days) in a large clinical trial of patients with non-cardioembolic stroke not treated with alteplase. Ticagrelor did not demonstrate superiority to aspirin in this trial[39].

However, in a subgroup analysis of patients with atherosclerotic stroke, ticagrelor-treated patients had a 32% reduction in the risk of a secondary stroke within 90 days. Despite this subgroup analysis, ticagrelor is not FDA-approved for the prevention of secondary stroke[40].

Dual Antiplatelet Therapy

The combination of clopidogrel and aspirin is the best studied of the two antiplatelet strategies. A systematic review concluded that short-term (≤90 days) use of dual antiplatelet therapy reduces the risk of stroke and is not associated with a major increase in the risk of bleeding[41]. In long-term studies (>90 days), dual therapy was not associated with a reduction in blood pressure but was associated with an increased risk of major bleeding. Therefore, the combined antiplatelet therapy of clopidogrel and aspirin for more than 90 days is not considered[14]. Ticagrelor (180 mg loading dose followed by 90 mg twice daily for 30 days) plus aspirin (300-325 mg loading dose followed by 75-100 mg daily) compared with aspirin alone in patients with mild to moderate noncardioembolic stroke[42].

The combination of ticagrelor and aspirin for secondary stroke prevention is recommended only in patients with minor stroke or TIA with ipsilateral intracranial artery stenosis greater than 30%. The duration of combination should be limited to 30 days. Therefore, triple antiplatelet therapy is not recommended[14]. Oral anticoagulants are the preferred therapy for primary stroke prevention in individuals with atrial fibrillation and atrial flutter[33,44]. Patients with atrial fibrillation and a recent history of stroke or TIA are at greatest risk for stroke. However, anticoagulant therapy carries a risk of bleeding. Therefore, a stroke risk stratification tool called CHA2DS2-VASc was developed to determine a patient's risk of stroke. CHA2DS2-VASc score greater than zero in men and greater than 1 in women should receive oral anticoagulation therapy[33].Various risk stratification methods have been developed to assess and identify bleeding risk. HAS-BLED is a widely used simple tool. A HAS-BLED score >2 indicates a higher risk of bleeding and requires further follow-up[44]. With warfarin, an international ratio (INR) of 2 to 3 prevents stroke with the least possible bleeding. Warfarin should be used in cases of atrial fibrillation or moderate to severe mitral stenosis with a mechanical heart valve[14]. Direct-acting oral anticoagulants (DOACs), including direct thrombin inhibitors (dabigatran) and direct Xa inhibitors (rivaroxaban, edoxaban, and apixaban), are easily administered via intercourse and have lower drug-food interactions. It is better for patients with creatinine clearance below 15 mL/minute (0.25 mL/s) or those requiring hemodialysis (warfarin or apixaban). Additionally, patients with creatinine clearance above 95 mL/minute should not receive edoxaban because of the increased risk of stroke compared to warfarin[43]. There is limited information on the use of these agents in patients with a body mass index over 40 kg/m^2[45].

Guidelines recommend initiating anticoagulant therapy 2 to 14 days after stroke in patients at low risk of hemorrhagic transition, but waiting at least 14 days is recommended in patients at high risk of hemorrhagic transformation[14].

Management of Hemorrhagic Stroke

Although the role of pharmacological interventions in this type of stroke is limited, reversal of coagulopathy should be considered in intracerebral hemorrhages due to anticoagulants[46].

Anticoagulation Reversal

When intracerebral hemorrhage occurs in a patient receiving anticoagulants, the use of reversal agents to correct the medication-induced coagulopathy should be considered. In patients receiving warfarin with an elevated INR, reversal with four-factor prothrombin complex concentrate and vitamin K (usually intravenously) is recommended. Fresh frozen blood may be used in place of prothrombin complex concentrate, if necessary, but this is not preferred[46]. Idarucizumab may be considered for reversing the effect of dabigatran specifically[47]. Factor Xa inhibitors, such as rivaroxaban and apixaban, may be reversed with andexan[48].

CONCLUSIONS AND RECOMMENDATIONS

Early pharmacologic reperfusion (initiated within 4.5 hours of symptom onset) with intravenous alteplase or tenecteplase has been shown to improve functional capacity after ischemic stroke. Antiplatelet therapy is the mainstay of antithrombotic therapy for secondary prevention of noncardioembolic ischemic stroke. Oral anticoagulants are recommended for secondary prevention of cardioembolic stroke in patients with moderate to high risk. It is important to select the right patient for anticoagulation therapy. The stroke care according to evidence-based and national guideline-based recommendations can improve the outcomes.

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AUTHOR'S CONTRIBUTIONS

Measar M: conceived the idea, manuscript writing. **Alyahawi A:** manuscript writing, literature survey, critical review. All authors reviewed the article and approved the final version.

DATA AVAILABILITY

The data will be available to anyone upon request from the corresponding author.

CONFLICT OF INTEREST

None to declare.

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