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An Overview of Antithrombotics in Ischemic Stroke

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An overview of antithrom in ischemic stroke

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Abstract: The use of antithrombotic medications is an important component of ischemic stroke treatment and prevention. This article reviews the evidence for best practices for antithrombotic use in stroke with focused discussion on the specific agents used to treat and prevent stroke.

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botics

Ischemic stroke is caused by an obstruction of cerebral blood flow, often due to a blood clot or severe atherosclerotic plaque with ulceration or plaque rupture. An important part of treatment and prevention of ischemic stroke is the use of antithrombotic agents. Patient medical history, health status, etiology of stroke, vascular imaging appearance, and stroke burden determine which antithrombotic therapies are used. After an initial stroke, preventing a second stroke is the main focus. In many cases, the risk of recurrent stroke can be reduced through lifestyle modifications and medications.

Antithrombotic medications, such as aspirin, clopidogrel, and warfarin, are important strategies in stroke prevention, and adherence to antithrombotics reduces the risk of recurrent stroke.[1] New target-specific antithrombotics add complexity to the armamentarium of antithrombotic therapy in stroke. This article provides an overview of antithrombotics in ischemic stroke for the primary care nurse practitioner (PCNP). The evidence for best practices for antithrombotic use in stroke is reviewed, along with a discussion of the specific agents and their use in managing and preventing ischemic stroke.

Background

Throughout the 14th to 19th centuries, apoplexy was described as the sudden loss of consciousness followed by sudden death (what is now referred to as stroke).[2] Today, ischemic stroke is defined as pathologic, imaging, or clinical evidence of cerebral, spinal, or retinal focal ischemic injury in a defined vascular distribution.[3] The term *stroke illness* was first used in 1962 by the Chest and Heart Association, and the term *stroke* continues to be used today to describe this serious global disease that affects 15 million individuals worldwide and 6.6 million individuals throughout the United States.[4]

Someone has a stroke every 40 seconds in the United States, making it a leading cause of death.[4] There are 6.4 million stroke survivors in the United States, and stroke is the leading cause of long-term disability. Stroke has a 2.6% nationwide prevalence and a projected 20.5% increased

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prevalence, equaling a 3.12% national increase by 2030.[4] Stroke disproportionately affects vulnerable, ethnic, and underserved populations due to the high prevalence of vascular risk factors, which lead to higher stroke risk.

Strokes are classified as ischemic or hemorrhagic and may occur in the arterial or venous system. Arterial ischemic strokes occur mainly in the setting of thrombus formation, emboli, or critical stenosis, causing an occlusion or hemodynamically significant obstruction of blood flow to the brain.[5] Dramatic improvement in understanding stroke has been gained from advanced central nervous system medical imaging and researching the nature of ischemia and cerebral infarction.

Stroke systems of care utilize an organized team approach to decrease hospital stay and mortality for acute stroke patients admitted to a dedicated stroke unit. This has led to advanced treatments for stroke and the development of team-based care for delivery and management.[6]

As stroke patients transition across the healthcare continuum, many return home. Most stroke patients will need antithrombotics continued after discharge, and often, this responsibility is returned to the primary care provider. Prescribed medication nonadherence is considered a universal cardiovascular risk factor.[7] Nonadherence to antithrombotic secondary prevention strategies in ischemic stroke results from a variety of factors, including adverse reactions, cost, inability to travel to their provider or local pharmacy, or discontinuation by the patient or primary care provider.

Stroke systems of care utilize an organized team approach to decrease hospital stay and mortality for acute stroke patients.

Nonadherence disrupts the effectiveness of therapy and directly increases risk of subsequent stroke.[1] Improved communication and collaboration are necessary to enhance stroke patient transitions.[6] Stroke team specialists should communicate directly with the PCNP related to continuing antithrombotic therapies. Best-practice evidence related to adherence to antithrombotics and the relationship to decreasing stroke or recurrent stroke risk should be shared with the PCNP.

Additionally, the stroke team should openly communicate with PCNPs and ensure antithrombotic treatments begun in the hospital are continued. PCNPs can participate by contacting stroke team specialists to determine which antithrombotic medications were prescribed should there be a communication delay from the stroke team specialist to the PCNP.

Initial stroke treatment with fibrinolytics

Since 1995, tissue plasminogen activator (tPA), which is produced by recombinant DNA technology, has been central to treating acute ischemic stroke, and it remains the only FDA-approved drug treatment for acute ischemic stroke. Initial clinical trials demonstrated benefits of I.V. fibrinolysis in patients with acute ischemic stroke treated within 3 hours of symptom onset, and subsequent studies have extended that time window to 4.5 hours in selected patients (although use of tPA beyond 3 hours from stroke onset remains off-label use).[8,9] Intra-arterial fibrinolysis and mechanical thrombectomy are also treatment options for acute ischemic stroke.

The tPA alteplase is the only FDA-approved fibrinolytic agent used in acute ischemic stroke. It is a natural enzyme that initiates local fibrinolysis by binding to fibrin within a clot while also directly activating plasminogen to promote further fibrinolysis. It can be administered I.V. or intra-arterially. Alteplase is the drug of choice for reperfusion in acute ischemic stroke and improves stroke outcomes by 30%. I.V. doses are based upon weight up to a maximum total of 90 mg. Intracranial hemorrhage must be excluded prior to administration. Other exclusion criteria include, but are not limited to: BP greater than 185/110; international normalized ratio (INR) greater than 1.7; prothrombin time (PT) greater than 15 seconds; and platelets less than 100,000/mm^3.[8,9]

Evaluation of the data from five stent retriever stroke trials (MR CLEAN, ESCAPE, SWIFT-PRIME, EXTEND-IA and REVASCAT) resulted in new recommendations in the 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment. Class IA evidence changes include treating patients who meet appropriate criteria with stent retrievers; performing non-invasive vascular imaging as part of the initial imaging assessment of stroke as long as it does not delay delivery of I.V. tPA. The updated guidelines are available at http://stroke.ahajournals.org/content/early/2015/06/26/R.0000000000000074.

Antithrombotics in stroke

Antithrombotic agents (medications that inhibit platelet function or affect the coagulation pathway to inhibit thrombus propagation or activate thrombolysis) represent an integral component of ischemic stroke management and prevention. Acute ischemic stroke treatment has been revolutionized by two major therapeutic advancements in the

last 20 years: thrombolytic therapy and mechanical thrombectomy.

Antiplatelet agents provide benefits in acute ischemic stroke treatment. Randomized control trials have demonstrated that early administration of aspirin (160 mg or 325 mg) results in a mild reduction in mortality and improvement in functional outcome when administered within 24 to 48 hours of symptom onset.[10] Earlier administration of aspirin carries a small risk of hemorrhage. Early general administration of anticoagulants for arterial ischemic stroke has also been evaluated, demonstrating an increase in mortality and unfavorable clinical outcomes compared with placebo or aspirin.[11] As a complication of stroke, deep venous thromboembolic disease remains an important consideration in patients immobilized with acute ischemic stroke. These patients benefit from subcutaneous heparin or low-molecular-weight heparin prophylactic dose anticoagulation and/or mechanical thromboprophylaxis.

Early administration of aspirin results in a mild reduction in mortality when given within 24 to 48 hours of symptom onset.

Antiplatelets and anticoagulants are important in both primary and secondary stroke prevention. In patients with noncardioembolic ischemic stroke, antiplatelet agents play a secondary and somewhat debatable role in primary stroke prevention, behind modifiable risk factors, including appropriate diet; adequate exercise; and BP, glycemic, and cholesterol management. An individualized approach is advocated for antiplatelet agents for primary stroke prevention, and aspirin is often recommended in patients with clinical atherosclerotic disease, elevated cholesterol, obesity, and lifestyle risk factors that increase stroke risk.[12]

In secondary prevention of noncardioembolic ischemic stroke, the data are clear that antiplatelet agents demonstrate decreased mortality, a reduction in recurrent strokes, and reduction in myocardial infarction (with a slight increase in major extracranial hemorrhage). The majority of clinical evidence comes from evaluating adult-dose aspirin (325 mg), although newer antiplatelet agents have also been evaluated.

The choice of antiplatelet agent remains somewhat controversial, with studies suggesting slightly improved patient outcomes with clopidogrel or aspirin/extended-release dipyridamole over aspirin alone. The use of a dual antiplatelet regimen appears to produce no significant clinical benefit over monotherapy, at the cost of an increased risk of symptomatic hemorrhage.[13] The use of oral anticoagulation also appears to produce no significant clinical benefit over antiplatelet treatment and noncardioembolic stroke, with an increased risk of symptomatic hemorrhage.[13]

The majority of cardioembolic ischemic strokes arise from cardiac dysrhythmias (most commonly atrial fibrillation [AF]). AF is known to increase the risk of ischemic stroke as much as fivefold; primary stroke prevention in this population involves oral anticoagulation.[14] A number of newer anticoagulants now complement warfarin, and treatment regimens can be tailored to account for variability in the risk-benefit ratio for individual patients. Scoring systems such as the $CHA2DS2\text{-}VAS_C$ allow for individual risk stratification.[15]

Secondary stroke prevention may involve anticoagulant or antiplatelet therapy. As with primary prevention, formulating an appropriate management plan in this patient population is complex, with multiple variables to consider, including:

- patient preference
- risk of complications or other drug interactions
- age
- comorbidities (such as kidney dysfunction)
- ability to afford medication
- ability to maintain therapeutic INR range.

Oral anticoagulation is the treatment of choice for secondary stroke prevention in the setting of AF in patients with no major contraindication to anticoagulation therapy.

Ideally, anticoagulation should begin within 2 weeks of stroke onset, although the risk of hemorrhage related to early anticoagulation in patients with large strokes is higher, often times necessitating delayed initiation. Antiplatelet agents have demonstrated reduction of recurrent strokes in patients with AF who have a contraindication for oral anticoagulation as secondary stroke prevention. Dual antiplatelet therapies appear to be more effective than monotherapy in this patient population.[13]

Heparin

Unfractionated heparin (heparin). Heparin is used in acute stroke during mechanical thrombectomy, when administering intrarterial alteplase, and in presence of a large, intraluminal thrombotic or embolic filling defect of the major cerebral arteries.[16] Heparin inhibits clot formation by binding to antithrombin III, converting it from a slow inhibitor to a very rapid inhibitor. This interaction leads to overall inhibition of procoagulant activity by inactivating thrombin as well as activated factors IX, X, XI, XII, and plasmin; therefore, it inhibits further growth and propagation of a thrombus.

Heparin can be administered I.V. or subcutaneously. I.V. infusion is the recommended route of administration

due to consistent outcomes. Subcutaneous dosing needs to be higher due to decreased bioavailability, and dosing is based on weight. Heparin can be reversed with protamine. Bleeding complications appear to be dose dependent. Achieving therapeutic activated partial thromboplastin time (APTT) values is the treatment goal by tailoring a dose to each individual. A number of weight-based and dose titration nomograms are available as guidelines. The relative short half-life (0.4 to 2.5 hours) of heparin enables achievement of therapeutic values quickly while also providing the flexibility to withhold anticoagulation as necessary (preprocedural).[16,17]

Low-molecular-weight heparin (LMWH). LMWHs potentiate antithrombin III activity to inhibit thrombus formation and are used as a bridge when converting to or from oral anticoagulants, although equivalent anticoagulant agents can be used if the patient is intolerant to heparin. Due to their smaller size, LMWHs promote specific factor Xa inactivation and just a small amount of thrombin inactivation when compared with heparin. Each LMWH is derived slightly differently from one another, giving each medication a unique pharmacokinetic profile and dosing regimen.

LMWHs are most commonly given subcutaneously but can also be administered I.V. They are an excellent choice for outpatient use and when a bridging anticoagulant is necessary (for example, while initiating warfarin therapy). Therapeutic levels can be reached relatively easily and reliably due to excellent bioavailability and little interpatient variability. Dose adjustments might be necessary in patients with decreased kidney function and for those who are morbidly obese.

The most common vitamin K antagonist, warfarin is used to prevent stroke in AF and other cardioembolic conditions.

Although routine monitoring is not considered necessary, antifactor Xa levels can be useful to confirm therapeutic levels, although it does not help in determining the reversal's effect. There is currently no documented reversal for LMWH. Protamine can be used to reverse bleeding in some patients using LMWH, but it only partially affects anti-Xa levels. Cross-reactivity with LMWH is possible in a patient with previously documented heparin-induced thrombocytopenia.[16]

Oral anticoagulants

Warfarin. The most common vitamin K antagonist, warfarin is used to prevent stroke in AF and other cardioembolic conditions; it imparts a 70% relative risk reduction. The antithrombotic effect of warfarin is attributed to its anticoagulant effect and interferes with the hepatic synthesis of the vitamin K-dependent coagulation factors II (prothrombin), VII, IX, and X, and proteins C and S. It takes approximately 5 to 6 days for full antithrombotic effect to take place. This is due to the relatively long half-life (60 to 72 hours) of factor II compared with the other vitamin K-dependent coagulation factors (6 to 24 hours).

The time it takes to lower factor II levels is the basis for overlapping a parenteral anticoagulant with warfarin for approximately 5 days. Known genetic polymorphisms, drug-drug interactions, nutritional supplements, and herbal products can affect therapeutic outcomes. Additionally, a narrow therapeutic index combined with interpatient variability can make determining an appropriate dose for each patient challenging. PT/INR values are commonly used to monitor therapy. Withholding doses, administration of phytonadione, and administration of blood derivatives such as fresh frozen plasma are all strategies for reversal. The reversal choice depends upon how urgently the patient needs reversal.[18-20]

Dabigatran. This direct oral anticoagulant is an alternative to the common disadvantages of warfarin. It is FDA approved for stroke prevention in nonvalvular AF. Dabigatran is a direct thrombin inhibitor, which is currently available in an oral formulation and does not require a cofactor to inhibit thrombin. Unlike warfarin, doses are fixed and based on kidney function. Dose adjustments are recommended based on kidney function, and dabigatran should be avoided in severe kidney failure. Both PT and APTT are unchanged with treatment. Proton pump inhibitors often used for gastroesophageal reflux disease or gastrointestinal acid reflux may decrease its absorption, and coadministration should be avoided.

Coadministration with strong P-glycoprotein inhibitors (ketoconazole, amiodarone) or inducers (rifampicin) may significantly increase or decrease dabigatran levels, respectively, and should be avoided. Depending upon kidney function, doses need to be held anywhere from 1 to 4 days prior to any invasive procedure. The monoclonal antibody fragment idarucizumab is a recently FDA approved (October 2015) antidote that firmly binds to dabigatran reversing the anticoagulant effects. Discontinuing dabigatran followed by volume and red blood cell replacement (or hemodialysis) is also recommended for clinical management of any major bleeding.[18,21]

Rivaroxaban. This direct oral anticoagulant is a direct factor Xa inhibitor. It is available in an oral formulation dosed once daily for all indications. Specific doses depend upon kidney function and indication. Avoid use in severe kidney impairment. Just as with dabigatran, coadministration with strong P-glycoprotein inhibitors or inducers should be avoided. Additionally, concomitant use of strong inhibitors of both CYP3A4 and P-glycoprotein (ketoconazole, HIV protease inhibitors) is contraindicated due to increased levels of rivaroxaban. PT and APTT should not be used to monitor therapy. There is no reversal agent available at this time although reversal agents for rivaroxaban and apixaban are in clinical trials. There is risk of thromboembolic events due to a hypercoagulable state with premature discontinuation.[18,21,22]

Apixaban. This factor Xa inhibitor is more effective than warfarin in prevention of strokes in nonvalvular AF.[23] The reduction of intracranial hemorrhage risk and overall mortality is an advantage of apixaban over warfarin, although there is no significant risk reduction of cerebral embolism. Apixaban is dosed twice daily and dosing is adjusted in patients over age 80, weighing less than 60 kg, or having a creatinine level 1.5 mg/dL or greater; or when coadministered with drugs that are strong inhibitors of CYP3A and P-glycoprotein. Apixaban has a Black Box Warning regarding premature discontinuation that increases the risk of thromboembolic events without a replacement anticoagulant. No reversal agent is currently approved for apixaban, and routine blood monitoring is not required.[23]

Edoxaban. This once-daily direct factor Xa inhibitor was approved for prevention of stroke in January 2015 in patients with stroke due to nonvalvular AF. It is contraindicated in patients with a creatinine clearance greater than 95 mL/minute, as this was shown to increase the risk of ischemic stroke when compared with warfarin. Edoxaban is given as a once-daily dose based on the creatinine clearance level. It should not be used with creatinine clearance above 95 or below 14 mL/min.[24]

Kidney function should be monitored when using edoxaban. Like other direct factor Xa inhibitors, bleeding is the most common adverse reaction, and infusion of blood coagulation factors are used as reversal agents as there is no specific reversal agent for edoxaban. Edoxaban requires a 50% dose reduction in patients under 60 kg, or in patients who use the P-glycoprotein inducer rifampin or P-glycoprotein inhibitors. Serial coagulation monitoring is not indicated, but PT and aPTT may be altered.

Antiplatelets

Aspirin. Antiplatelets are used in stroke to decrease stroke risk and recurrence. Aspirin blocks prostaglandin synthesis, which prevents formation of the platelet-aggregating substance thromboxane A_2. Antiplatelet effects can be attained at low doses due to their selective inhibition of COX-1. Aspirin is absorbed rapidly from the stomach and small intestine.

Enteric-coated or sustained-release formulations should be used cautiously due to lower bioavailability. Aspirin has been widely studied in both preventive and treatment settings. Aspirin 160 mg to 325 mg daily should be initiated within 48 hours of onset of acute ischemic stroke in all patients after considering any possible contraindications. Continue treatment for approximately 1 to 2 weeks before initiating a long-term antiplatelet regimen.[19,25,26]

Apixaban, a factor Xa inhibitor, is more effective than warfarin in prevention of strokes in nonvalvular AF.

Dipyridamole. This oral pyridopyrimidine derivative has antiplatelet and vasodilatory properties. Extended-release dipyridamole is available as a combination product with aspirin and may be useful in secondary prevention in patients with a history of transient ischemic attack (TIA) or stroke.[13] Although the mechanism of dipyridamole as an antiplatelet is controversial, increases in plasma adenosine and inhibition of cyclic nucleotide phosphodiesterase have been suggested. It should not be given to those with severe kidney or hepatic impairment or those with a known allergy to nonsteroidal anti-inflammatory drugs.[26]

Thienopyridines

Ticlopidine, clopidogrel, and prasugrel attain their antiplatelet effects by irreversibly inhibiting adenosine diphosphate to bind to the $P2Y_{12}$ receptor on platelets. All are prodrugs that must be activated via the hepatic CYP450 system.[19,26]

Ticlopidine. The current therapeutic role for ticlopidine is currently uncertain due to its association with hypercholesterolemia, neutropenia, thrombocytopenia, aplastic anemia, and thrombotic thrombocytopenic purpura.[19,26]

Clopidogrel. An oral $P2Y_{12}$-receptor antagonist, clopidogrel binds irreversibly to the $P2Y_{12}$ site for the life of the platelet, inhibiting adenosine diphosphate-induced platelet aggregation. The degree of inhibition can vary between patients, causing an increase in thrombotic events in patients with clopidogrel resistance. Smoking can cause active

metabolite levels to vary. Medications that induce or inhibit CYP450 isoenzymes involved in converting clopidogrel to its active form, as well as genetic polymorphisms of CYP450, can cause variable active metabolite generation.

Of note, omeprazole and esomeprazole, both of which are substrates and inhibitors of CYP2C19, are associated with a decrease in effectiveness of clopidogrel. Pantoprazole offers an option with a lesser degree of interaction. Loading doses of clopidogrel provide more rapid platelet inhibition; onset of action is approximately 2 to 4 hours. Platelet function returns to normal 7 to 10 days after discontinuation.[19,26]

Prasugrel. This oral $P2Y_{12}$-receptor inhibitor is rapidly absorbed, reaching peak concentrations within 30 minutes. Absorption is unaffected by food. Currently, no evidence is available to show that genetic polymorphisms or use of proton pump inhibitors interfere with metabolism. Platelet function returns to normal 7 to 10 days after discontinuation. Prasugrel carries an FDA Black Box Warning for significant or sometimes fatal bleeding. Its use is contraindicated in patients with active pathologic bleeding, TIA, or history of stroke.[19,26]

Cyclopentyl-triazolo-pyrimidines

Ticagrelor. This rapidly absorbed oral direct-acting P2Y12-receptor antagonist binds reversibly and noncompetitively to the $P2Y_{12}$ site. Unlike the thienopyridines, it is not a prodrug, so is not dependent on metabolism for activation. It provides low interindividual variability, and onset is about 30 minutes. No dose adjustment in kidney impairment or mild hepatic impairment is considered necessary; however, avoid use in patients with moderate-to-severe hepatic impairment. Coadministration with CYP3A4 inhibitors and inducers (simvastatin) as well as P-glycoprotein substrates (digoxin) should be used with caution.

Ticagrelor carries an FDA Black Box Warning stating that maintenance of daily doses of aspirin greater than 100 mg should be avoided due to decreased effectiveness of ticagrelor. There is no statistically significant risk of bleeding with ticagrelor when compared with clopidogrel. Ticagrelor has been associated with dyspnea and an increase in ventricular pauses (longer than 2.5 seconds, possibly due to its ability to delay adenosine metabolism).[19,26,27]

Moving forward

Antithrombotics are an integral part of ischemic stroke treatment, management, and prevention. Continuing antithrombotics after discharge is an important strategy to decrease recurrent stroke risk. There is a complex algorithm of radiographic and clinical assessments involved in the clinical decision-making that determines which antithrombotic therapy is recommended to the patient by the stroke team. Each anticoagulant and antiplatelet has advantages and disadvantages that may affect patient adherence.

Recommendations should be communicated clearly to the patient by the stroke team and the PCNP for improved patient adherence. Additionally, the PCNP should be included in the community of stroke team providers as they assist the patient in managing stroke risk factors after discharge and can help the patient understand the importance of continuing their antithrombotics as part of a stroke risk reduction program. Improved communication between the stroke team and the PCNP can also lead to identifying methods and models of improved communication and collaboration in stroke care. NP

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