Provider Perspective in Choosing Long-term Anticoagulation Agents

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ANCC Accredited NCPD Hours – 1 Hrs

Target Audience: RN/APRN

Need assessment

Anticoagulants are the mainstay of treatment for stroke and systemic embolism prevention in patients with atrial fibrillation or flutter. They can be used as well for prevention and treatment of venous thromboembolism and treatment of thrombus formation in other places. This class of medications must be used carefully, because using them incorrectly can lead to either ineffective prevention of clot formation or bleeding. It is vital for the clinician who uses any of these anticoagulants to have a basic understanding of their pharmacology and evidence of use.

Objectives

- Identify the different types of anticoagulants available
- Discuss the use of long term anticoagulants in atrial fibrillation
- Recognize the role of long term anticoagulants in cryptogenic stroke
- Discuss how long term anticoagulation works in Intracranial Atherosclerosis
- Describe how long term anticoagulation works in Cardiac embolism

Goals

AThe goal of this article is to discuss the provider perspective related to choosing long term anticoagulation agents with the intent of high utility and applicability for frontline providers across a multitude of care settings.

Introduction

Anticoagulants are medicines that help prevent blood clots. They are given to people at a high risk of getting clots, to reduce their chances of developing serious conditions such as strokes and heart attacks. The goal of anticoagulant therapies is to block the activity of coagulation factors. Anticoagulant agents may block specific targets in the coagulation cascade.

Anticoagulants may be used to treat blood clots or in conditions where the risk of blood clots is increased to reduce the risk. Examples of conditions where anticoagulants may be used include:

- Atrial fibrillation
- Deep vein thrombosis (DVT)
- Hip/knee replacement surgeries
- Ischemic stroke
- Myocardial infarction
- Pulmonary embolism
- Unstable angina

Anticoagulants are used in several other ***situations by practicing neurologists, including cervical artery dissection, cryptogenic stroke with or without patent foramen ovale (PFO), cerebral venous thrombosis (CVT) and fluctuating stroke.*** Anticoagulation is occasionally used in all of these cerebrovascular conditions with varying degrees of supportive evidence. Non–vitamin K antagonist oral anticoagulant (NOAC) drugs have been shown to be at least ***non-inferior to vitamin K antagonists (VKAs) in preventing ischemic stroke and systemic embolism with lower bleeding risk.*** Furthermore, one trial showed that among patients with atrial fibrillation deemed to be ineligible to receive vitamin K antagonist for various reasons, including inability to comply with monitoring regimens and high risk of hemorrhagic, apixaban reduced the risk of stroke with similar major bleeding risk compared with aspirin. Thus, one may logically consider the use of these agents in these other situations in which anticoagulation is often used or recommended. [1, Rank 4]

> **"The most commonly prescribed anticoagulant is warfarin"**

Classification of anticoagulants

There are different types of anticoagulants and they are classified on how they affect the normal coagulation pathway (as shown in figure1).

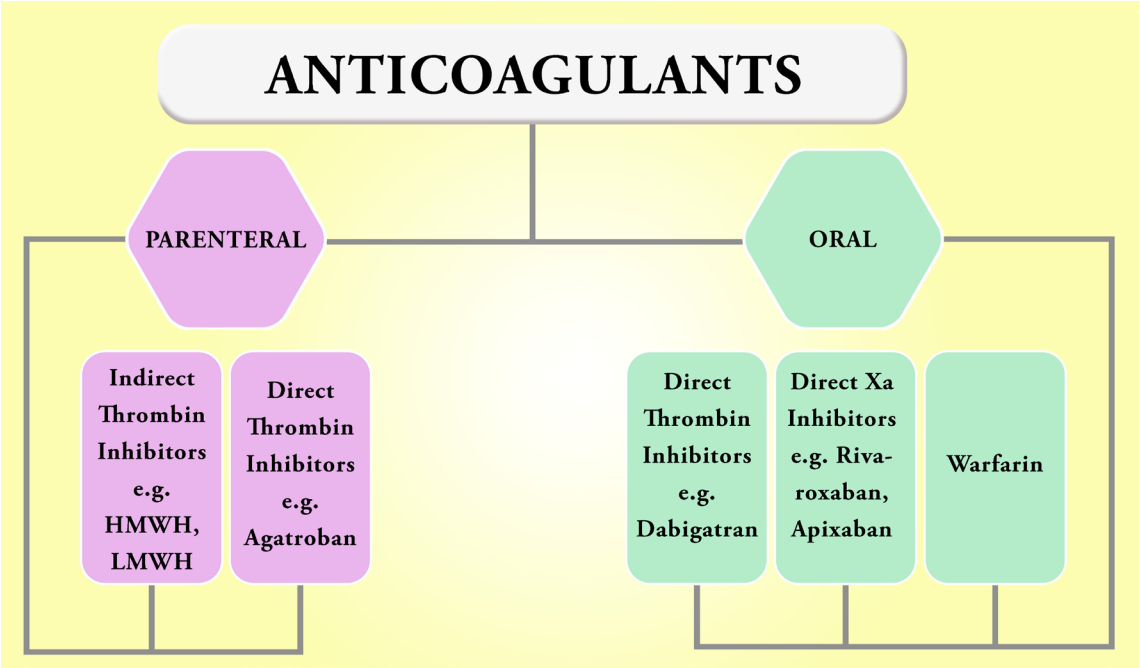

Figure 1: Classification of anticoagulants

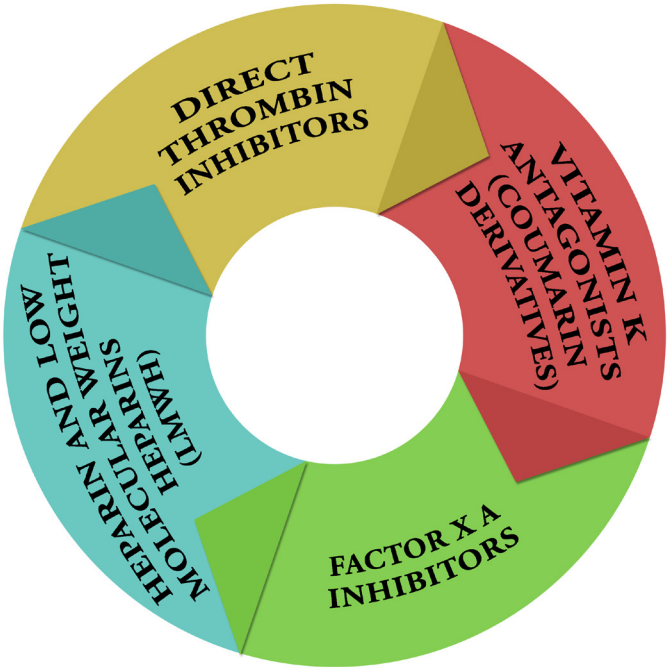

Figure 2: Main types of anticoagulants

There are three main types of anticoagulant medications: (as shown in figure 2)

- Vitamin K antagonists
- Direct oral anticoagulants (DOACs)
- Low molecular weight heparin (LMWH)

Each type works in a different way to prevent unwanted blood clots.

Vitamin K antagonists

Vitamin K helps your blood clot. Vitamin K antagonists like warfarin stop your liver from processing vitamin K into factors that normally help clot your blood. This curbs blood clotting. One of the potential advantages of this type of anticoagulant is that it's easier than others to reverse in case you have a sudden bleeding from trauma or emergency surgery.

Direct oral anticoagulants (DOACs)

Direct oral anticoagulants work more quickly than vitamin K antagonist and it can also be more predictable. These drugs tend to work for shorter periods.

- ***Direct thrombin inhibitors:*** these drugs interfere with your body's use of thrombin, a key enzyme that helps clot your blood. Though usually injected under the skin, these drugs can be taken in pill form as dabigatran (Pradaxa).
- ***Direct factor Xa inhibitors:*** this type of anticoagulant stops the Xa factor in the clotting process from working as it should. These medications include apixaben, betrixaben, edoxaban and rivaroxaban.

Low molecular weight heparin (LMWH) anticoagulants

Compared to regular unfractionated heparin (UFH), low molecular weight heparin is more predictable and long lasting e.g. dalteparin (Fragmin) or enoxaparin (Lovenox). Low molecular weight heparin is often used as a bridge to long term use of anticoagulants such as warfarin.

There are many conditions which require anticoagulant therapy. The use of anticoagulants is a decision based upon the risks and benefits of anticoagulation.

> "Low molecular weight heparin is often used as a bridge to long term use of anticoagulants"

Generally the benefit of anticoagulation is prevention or reduction of progression of a thromboembolic disease. The decision to begin therapeutic anticoagulation often involves the use of multiple bleeding risk predictable outcome tools as non –invasive pre test stratifications due to the potential for bleeds while on blood thinning agents. The risk of bleeding using risk assessment tools must be weighed against thrombotic risk in order to formally determine patients overall benefit in starting anticoagulation therapy

Anticoagulants in Atrial Fibrillation and Risk of Bleeding

Atrial fibrillation is the most common cardiac arrhythmia and is associated with heart failure, mortality and ischemic stroke. Atrial fibrillation is known to increase the risk of stroke. Among patients with atrial fibrillation, stroke and thromboembolism risk is mitigated with the addition of anticoagulants. However

> "The biggest risk of anticoagulation therapy is the increased risk of bleeding"

this is associated with increased risk of bleeding, specifically intracranial hemorrhage in the setting of warfarin. Hence the INR range in atrial fibrillation to be maintained between 2-3 (as shown in figure 3)

Figure 3: INR rang e in atrial fibrillation

Development and subsequent embolization of atrial thrombi can occur with any form of non valvular or valvular atrial fibrillation (AF). While ischemic stroke is the most frequent clinical manifestation of embolization associated with atrial fibrillation, embolization to other locations in the systemic and pulmonary circulations also occurs, but is less commonly recognized. As a result of embolic risk, chronic oral anticoagulation is recommended for all atrial fibrillation patients.

Anticoagulation is superior to antiplatelet therapy in primary and secondary stroke prevention in patients with atrial fibrillation. Recent evidence suggests that non–vitamin K antagonist oral anticoagulant is as effective as vitamin K antagonist in the prevention of recurrent ischemic stroke and systemic embolism, (as shown in figure 4) with a lower risk of intracranial haemorrhage. ***Dabigatran 150 mg twice per day compared with warfarin was associated with reduced risk of ischemic stroke, systemic embolism and intracranial hemorrhage.*** Dabigatran 110 mg twice per day was associated with reduced risk of intracranial bleeding and major bleeding but with similar risk of ischemic stroke and systemic embolism compared with warfarin. Apixaban was superior to warfarin in prevention of stroke and systemic embolism with a lower risk of intracranial hemorrhage. Rivaroxaban and edoxaban had a similar efficacy in the prevention of stroke and systemic embolism but lower risk of intracranial hemorrhage compared with warfarin.

Dabigatran is the only non–vitamin K antagonist oral anticoagulant thus far that has been associated with reduced risk of ischemic stroke as compared with warfarin, whereas ***only apixaban and edoxaban were superior to warfarin in reduced risk of major bleeding.*** In

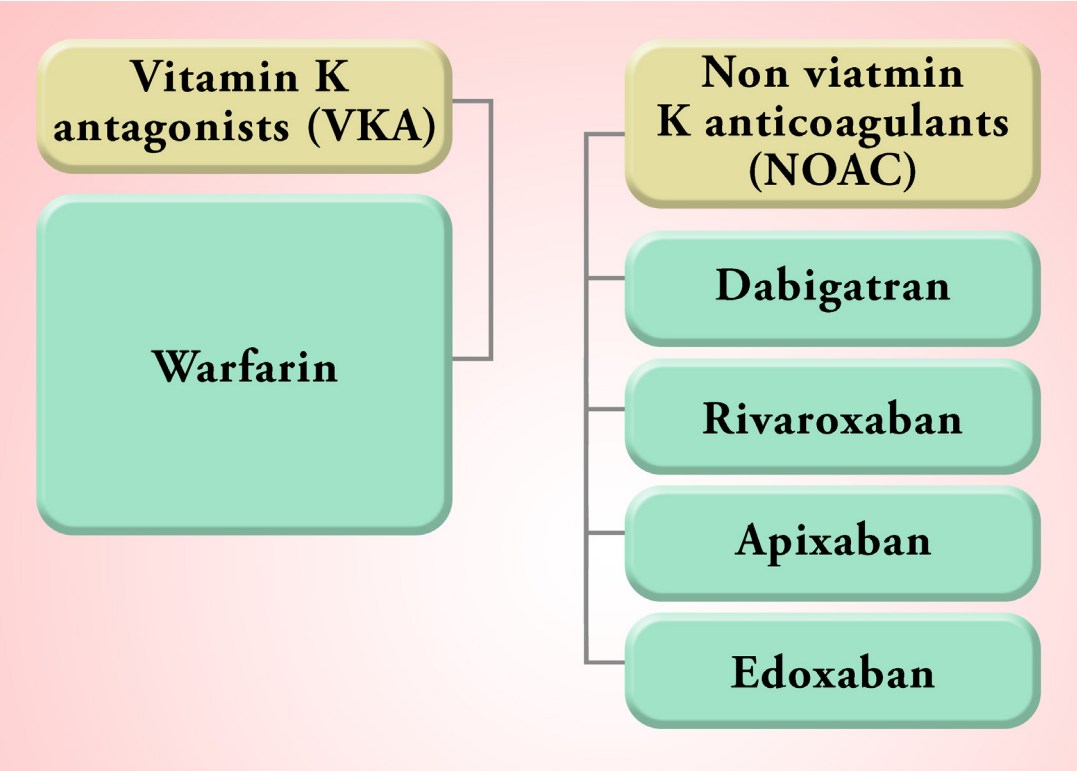

Figure 4: Oral anticoagulants used for stroke prevention in AF

addition, ***rivaroxaban and dabigatran are associated with a higher rate of major gastrointestinal bleeding when compared with warfarin.*** [2, Rank 5]

Anticoagulants in Cryptogenic Stroke

Cryptogenic stroke generally refers to a nonlacunar infarction occurring in the absence of a specific identifiable high-risk stroke mechanism, such as atrial fibrillation, valvular heart disease or large artery stenosis. In most cases, a stroke is caused by a blood clot that blocks blood flow to the brain. But in some instances, despite testing, the cause can't be determined. Strokes without a known cause are called cryptogenic.

Cryptogenic stroke accounts for 30% to 40% of ischemic strokes. The term embolic stroke of undetermined source (ESUS) has also been used recently in reference to patients with non lacunar stroke in whom there is no evidence of ipsilateral intracranial or extracranial stenosis of ≥ 50%, major risk source of cardiac embolism (such as atrial fibrillation) or other identified stroke mechanism. Use of the term ESUS implies that a thorough evaluation to exclude other causes of stroke has been performed. With the advent of mobile continuous outpatient telemetry and implantable loop recorders, ***paroxysmal atrial fibrilla-***

tion may be detected in up to one-third of patients with cryptogenic stroke, depending on the pre-test diagnostic evaluation, i.e., with a higher risk among patients with embolic-appearing infarcts or frequent atrial ectopy. In up to 65% of patients from the Stroke Databank who had infarcts of undetermined cause, the infarcts were considered to be due to less well-documented sources of embolism on further evaluation. [3, Rank 4]

Since up to 20% of patients with cryptogenic stroke are found to have paroxysmal atrial fibrillation on mobile continuous outpatient telemetry, it is reasonable to consider anticoagulation therapy in patients with ESUS pending the results of further monitoring. The major challenge in managing cryptogenic stroke is secondary stroke prevention, specifically in choosing antithrombotic therapy. The short-term use of non–vitamin K antagonist oral anticoagulant may be considered in this patient population given the higher efficacy and lower risk of bleeding as compared with warfarin in patients with paroxysmal atrial fibrillation. [4, Rank 2]

The long-term use of warfarin at an international normalized ratio (INR) of 1.4 to 2.8 was not superior to aspirin for the prevention of recurrent stroke among patients with non cardio embolic stroke in the Warfarin vs Aspirin Recurrent Stroke Study (WARSS). Among the pre specified subgroup of patients with cryptogenic stroke in WARSS, however, there was some evidence of benefit, with a reduction of 2-year stroke recurrence or death risk in patients on warfarin (hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.61–1.39). The risk of major bleeding on warfarin compared with aspirin was only marginally increased as well (2.2% on warfarin vs 1.5% on aspirin, p = 0.1). These data provide a rationale for considering oral anticoagulation for cryptogenic stroke patients and further suggest consideration of the use of anticoagulants with lower risks of bleeding than warfarin (non–vitamin K antagonist oral anticoagulant generally) or with a risk of bleeding shown to be comparable with aspirin for atrial fibrillation (apixaban) in cryptogenic stroke patients. [5, Rank 3]

Anticoagulants in Patients with Left Atrial Dysfunction

Atrial fibrillation, with its implied intracavitary stasis in the setting of irregular atrial wall contractile function, has been long considered to provide a direct mechanistic explanation for embolism. Recent evidence, however, challenges this concept of atrial fibrillation itself as the primary

> "The major challenge in managing cryptogenic stroke is secondary stroke prevention"

mechanism of stroke in patients with atrial dysfunction. ***Other biomarkers, including serum, ECG and echocardiographic markers of left atrial dysfunction, have also been associated with increased risk of stroke, even in the absence of documented atrial fibrillation. The N-terminal fragment of the pro-hormone brain natriuretic peptide (NT-proBNP), for example, is a serum biomarker of cardiac contractile dysfunction and atrial fibrillation and is associated with cardioembolism.*** Results from the left atrial appendage closure trials demonstrate that occlusion of the left atrial appendage reduces the risk of ischemic stroke to 1.7% per year, which is lower than the predicted rates based on CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/TIA) scores, suggesting that left atrial structural and functional abnormalities and not just atrial fibrillation, are the major determinants of stroke risk in this class of patients. [6, Rank 3]

Atrial arrhythmias and ECG findings have also been associated with stroke risk in the absence of atrial fibrillation. In a state-wide administrative database study, paroxysmal supraventricular tachycardia was associated with a 2-fold increase in risk of ischemic stroke even in the absence of atrial fibrillation. Furthermore, P wave terminal force in lead V1 on echocardiogram has been associated with increased risk of ischemic stroke and particularly those related to embolism (cardioembolic and cryptogenic stroke subtypes). [7, Rank 5]

Left atrial enlargement is also associated with the risk of first ischemic stroke in the absence of atrial fibrillation, subclinical cerebrovascular disease and detection of atrial fibrillation in patients with cryptogenic stroke. In population-based studies, recent evidence suggests that left atrial size is associated with increased risk of recurrent stroke related to embolism (cryptogenic or cardioembolic), an association independent of atrial fibrillation. Other left atrial findings on echocardiogram suggestive of embolism are left atrial spontaneous echocardiographic contrast or smoke. [8, Rank 3]

At present, there is no definitive evidence that anticoagulation is superior to antiplatelet therapy for patients with cryptogenic stroke and evidence of left atrial cardiopathy suggested by the presence of these atrial biomarkers. A post hoc analysis of the WARSS trial, however, which enrolled patients without known atrial

fibrillation, showed that warfarin was superior to aspirin in reducing the 2-year risk of stroke or death among the 5% of patients with the most highly elevated NT-proBNP. [9, Rank 4]

These data suggest that a biomarker of left atrial dysfunction might select a group of patients most likely to benefit from anticoagulation, even in the absence of evidence of atrial fibrillation. Given the increased efficacy and safety of non–vitamin K antagonist oral anticoagulant as compared with warfarin, stroke prevention trials comparing non–vitamin K antagonist oral anticoagulant with antiplatelet therapy among patients with atrial cardiopathies may be considered. [10, Rank 5]

Anticoagulants in Patients with Low Ejection Fraction

In patients with congestive heart failure and low ejection fraction, there is evidence from the Warfarin vs Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) study to suggest that warfarin is superior to aspirin in reducing the risk of ischemic stroke over a median of 5 years (HR 0.52, 95% CI 0.33–0.88). This benefit was offset, however, by an increased risk of major haemorrhage (HR 2.05, 95% CI 1.36–3.12), approximately 0.5% per year decreased risk of major haemorrhage as compared with warfarin, Non–vitamin K antagonist oral anticoagulant could potentially maintain the efficacy of anticoagulation in patients with stroke and low ejection fraction and attain a safety profile comparable to aspirin. This hypothesis could also be tested in randomized controlled trials; however, the relatively high mortality rate of patients with congestive heart failure poses difficulties in performing such a trial. [11, Rank 2]

Anticoagulation in Patients with Cryptogenic Stroke and Patent foramen ovale

Options for the secondary prevention of stroke in patients younger than 60 years who have had a cryptogenic ischemic stroke is thought to be secondary to patent foramen ovale (PFO) include patent foramen ovale closures (with antiplatelet therapy), antiplatelet therapy alone or anticoagulants.(Figure :5)

A patent foramen ovale is present in approximately 25% to 30% of stroke patients; with a higher prevalence in patients with cryptogenic stroke as compared with other stroke subtypes. The mechanism of stroke in patients with patent foramen ovale is unclear. ***In patients with cryptogenic stroke whose stroke is thought to be related to the patent***

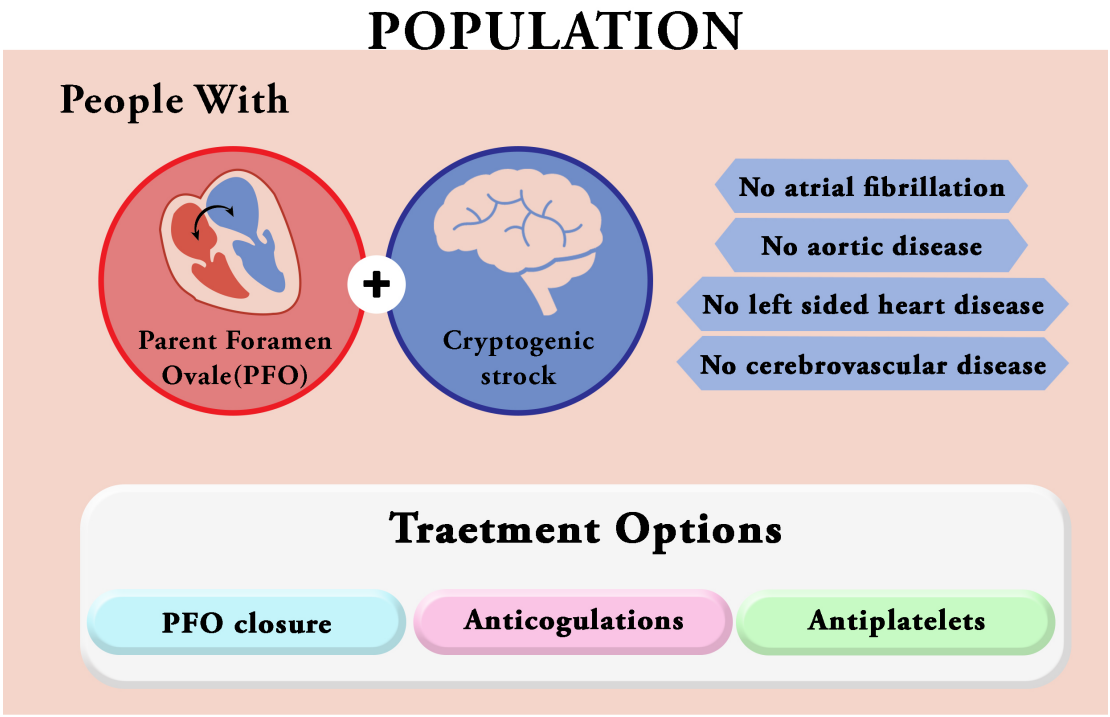

Figure 5: Treatment options in patients with cryptogenic stroke and PFO

foramen ovale, one of the major mechanisms is paradoxical embolism. This mechanism is also supported by a higher prevalence of chronic deep vein thrombosis and venous anomalies such as iliac vein compression in patients with patent foramen ovale and cryptogenic stroke as compared with other stroke subtypes. In addition, other venous anomalies have been associated with increased stroke risk, an association possibly mediated by paradoxical embolism. To date, there is no evidence to support the superiority of patent foramen ovale closure over medical therapy in patients with cryptogenic stroke, but there was a trend toward benefit in the as treated post hoc analysis of the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial. Furthermore, an ancillary study of the WARSS trial failed to provide evidence that warfarin was superior to aspirin for the prevention of recurrent stroke among patients with cryptogenic stroke and patent foramen ovale. Given the efficacy of non–vitamin K antagonist oral anticoagulant in the prevention of recurrent venous thromboembolic events, and since paradoxical embolism is the most likely mechanism of patent foramen ovale -related stroke, non–vitamin K antagonist oral anticoagulant may be considered in secondary prevention of patent foramen ovale -related stroke, although randomized trials are needed. In addition, secondary analyses of the RE-SPECT ESUS and NAVIGATE ESUS trials may provide data on the

efficacy of non–vitamin K antagonist oral anticoagulant in patients with patent foramen ovale. [12, Rank 3]

Anticoagulation in Intracranial Atherosclerosis

Patients with symptomatic intracranial atherosclerosis have high early and long-term stroke recurrence rates despite aggressive medical management, with rates of about 5% at 30 days and 20% at 2 years. The stenting and aggressive medical management for the prevention of stroke in intracranial stenosis (SAMMPRIS) study investigated the use of percutaneous angioplasty and stenting (PTAS) vs aggressive medical management and showed that aggressive medical management was superior to percutaneous angioplasty and stenting because of the relatively high stroke rate in the percutaneous angioplasty and stenting arm and the lower-than-expected stroke rate in the medical arm. Furthermore, the data from the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study comparing warfarin with aspirin in patients with symptomatic intracranial atherosclerosis showed that warfarin provided no benefit in reducing the risk of stroke as compared with aspirin but was associated with higher risk of major bleeding. However, a post hoc analysis from the WASID study showed that in patients on warfarin whose INR was maintained in the ideal therapeutic window, i.e., between 2.0 and 3.0, the risk of stroke was reduced to 5.1% per year (95% CI 2.7%–8.7%) from 24.9% per year (95% CI 15.8%–37.3%) among those whose INR was <2.0. Moreover, the risk of major haemorrhage for those whose INR was between 2.0 and 3.0 was 3.5% per year (95% CI 1.6%–6.6%) compared with 15.2% (95% CI 6.6%–30.0%) for those whose INR was 3.1 to 4.4 and even higher for those whose INR was ≥4.5. It is possible, however, that if the ideal therapeutic window had been maintained in all patients, then a benefit with warfarin would have been seen. ***NOACs could provide an opportunity to maintain a beneficial treatment effect in the narrow therapeutic window required to prevent ischemia without increasing risk of haemorrhage among patients with intracranial atherosclerosis.*** The apparent efficacy of warfarin in patients whose INR was maintained in the 2 to 3 range might also be attributable to the fact that easy-to-control patients are inherently at lower risk of stroke. Since ***anticoagulant use is theoretically geared toward preventing thrombus formation,*** the use of non–vitamin K antagonist oral anticoagulant to prevent the progression of atherosclerosis in patients with intracranial atherosclerosis is unclear and therefore

clinical trials are needed to compare non–vitamin K antagonist oral anticoagulant with antiplatelet agents to potentially improve stroke prevention strategies in such patients. [13, Rank 4]

> "For patients with symptomatic intracranial atherosclerosis, antithrombotic agents are the mainstay of therapy"

Anticoagulation in Lacunar Stroke

Lacunar stroke is a small cerebral infarct in the territory of a single perforator artery. It is a type of ischemic stroke that occurs when blood flows to one of the small arteries deep within the brain becomes blocked. ***Lipohyalinosis is thought to be the main pathomechanism in patients with lacunar stroke,*** but up 25% of patients with apparent lacunar stroke have a mechanism other than microvascular disease, including large artery atherosclerosis or embolism.

If you have a lacunar stroke, early treatment increases your chance of survival and may prevent further damages. A significant proportion of patients with lacunar strokes, moreover, have stuttering or progressive symptoms that may respond to more aggressive antithrombotic approaches. The combination of aspirin and clopidogrel in patients with mild deficits was associated with a lower risk of neurologic deterioration compared with matched matched controls (OR 17.2, p = 0.002). In those patients, patients, mechanisms such as a sub stenotic ulcerated plaque in the main vessel may be the cause. Indirect evidence for a more aggressive antithrombotic approach among patients with small vessel disease also comes from the original National Institute of Neurological Disorders and Stroke trial of IV tissue plasminogen activator in acute ischemic stroke, which demonstrated an even greater benefit for tissue plasminogen activator treatment among patients with small vessel stroke (25% absolute risk reduction of a poor outcome on the Barthel Index) than among patients with other stroke subtypes.[14, Rank 3]

Cervical Artery Dissection

The treatment of patients with cervical artery dissection is controversial. A large meta-analysis showed no difference in stroke recurrence and haemorrhage rates between patients treated with anticoagulation vs antiplatelet therapy. However, short-term anticoagulation with vitamin K antagonist is widely used. A recent single-centre retrospective study provides

> "Warfarin therapy is indicated when the risk of stroke is high, and that aspirin is preferred when the risk of stroke is low"

evidence that vascular neurologists at a major academic centre continue to use anticoagulants and have also begun to use non–vitamin K antagonist oral anticoagulant in this setting despite the absence of randomized clinical trial data to support this approach.These investigators reported that in patients with cervical artery dissection, the rate of stroke was similar in patients treated with non–vitamin K antagonist oral anticoagulant (comprising 26.2% of patients), warfarin (comprising 47%), and antiplatelet agents (comprising 26.8%). More major hemorrhagic events occurred in the warfarin group (11.4%) compared with the NOAC (0.0%) and antiplatelet (2.5%) groups (p = 0.034). These data must be interpreted with caution because there was non random allocation of treatment and the numbers are small. Nonetheless, patients with cervical artery dissection may constitute a group of patients in which non–vitamin K antagonist oral anticoagulant may prove useful. Moreover, recent evidence from the Cervical Artery Dissection in Stroke Study suggests that a randomized clinical trial of antithrombotic vs antiplatelet therapy would need to be prohibitively large and expensive, and is unlikely to be completed. Assuming an annual stroke risk of 2%, one would need 600 dissection patients in each group (total of 1,200) with average follow-up of 4 years to demonstrate a 50% relative reduction in stroke risk with non–vitamin K antagonist oral anticoagulant vs. aspirin. [15, Rank 3]

Sinus Thrombosis

CVT is an uncommon but serious condition associated with about 15% overall rate of death or functional dependence on follow-up. Despite an absence of randomized controlled trial evidence to support anticoagulation therapy in cerebro vascular thrombosis, recent American Heart Association/American Stroke Association guidelines on the diagnosis and management of cerebrovascular thrombosis state that it is reasonable to start low-molecular-weight heparin or unfractionated heparin followed by oral vitamin K antagonist even in the presence of hemorrhage. These recommendations are based on the results of small trials that in meta-analysis suggested a benefit of anticoagulation with a low rate of hemorrhage. None of the recent trials of non–vitamin K antagonist oral anticoagulant in venous

thromboembolism, however, included patients with cerebrovascular thrombosis. Therefore, extrapolating from the available evidence and current practice guidelines, one may reasonably consider non–vitamin K antagonist oral anticoagulant as alternatives to vitamin K antagonists in patients with cerebrovascular thrombosis. Performing a randomized trial comparing non–vitamin K antagonist oral anticoagulant with vitamin K antagonists may be difficult. Assuming an annual recurrence rate of 3%, one would need 1,800 patients in each group (3,600 total) with average follow-up of 4 years to demonstrate a 25% relative reduction with non–vitamin K antagonist oral anticoagulant vs warfarin for recurrent cerebrovascular thrombosis, which is very difficult to perform given the low overall prevalence of cerebrovascular thrombosis. [16, Rank 5]

Long term Anticoagulation in Cardiac Embolism

Embolism of cardiac origin accounts for about 20% of ischemic strokes. Several heart conditions enhance stroke risk. Atrial fibrillation is the most common condition of cardioembolic stroke and anticoagulation is the treatment generally indicated for secondary prevention and in some cases for primary prevention.Transesophageal-echocardiography has also provided evidence that the aortic arch is a common source of embolic material, but the risk of cerebral embolism appears to be directly related to the size of atherosclerotic plaques visualized. Most common localization for cardioembolic stroke are total or partial areas supplied by major arteries of anterior and posterior circulation, most being cortical infarcts. Emboligenous cardiopathy, as the only demonstrable etiology has been found in only 4% of lacunar infarctions, and its role as the etiology of lacunar infarction is very rare. ***Emboligenous cardiopathy especially atrial fibrillation, rheumatic valve disease, and nonbacterial thrombotic endocarditis have been reported as very infrequent causes of lacunar infarction in autopsy-based series.*** Stroke and transient ischaemic attack (TIA) in terms of primary and secondary prevention should be treated in the same way. [17, Rank 4]

Oral anticoagulation (OAC) is the treatment of choice for secondary prevention after a cardioembolic stroke. Warfarin is the commonest oral anticoagulation, non–vitamin K antagonist oral anticoagulant used worldwide, although acenocoumarol, phenprocoumon, or anisindione are frequently prescribed in many countries. The mechanisms of action of this oral anticoagulation are comparable, as they inhibit

the vitamin K-dependent post-translational carboxylation of glutamate residues on the N-terminal regions of coagulation factors II, VII, IX, and X by inhibiting the conversion of vitamin 2, 3 epoxide to reduced vitamin K. Although the benefits of oral anticoagulation are supported by a high degree of evidence for stroke prevention in cardioembolic entities, such as atrial fibrillation, they have a narrow therapeutic index, numerous drug and dietary interactions, and a significant risk of serious bleeding, including hemorrhagic stroke. Alternatives to oral anticoagulation in this setting include safer and easier to use antithrombotic drugs and definitive treatment of atrial fibrillation. [18, Rank 5]

Efficacy of Long term anticoagulation in Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, resulting in a prevalence of about 1% in the general population. Atrial fibrillation is also the most frequent cardiac condition associated to the risk of ischemic stroke, although it is only weakly associated with transient ischemic attack (TIA). Atrial fibrillation increases the risk of stroke 4- to 5-fold across all age groups, accounting for 10% to 15% of all ischemic strokes and nearly 25% of strokes in people older than 80 years. This translates to an incidence of stroke approximating 5% a year for primary events and 12% a year for recurrent events. In atrial fibrillation associated with rheumatic heart disease, stroke risk is increased even more: 17-fold compared with age-matched controls. Patients with paroxysmal and constant atrial fibrillation appear to have similar risks of stroke. [19, Rank 3]

In the late 1980s and early 1990s, 6 trials compared oral anticoagulation therapy to placebo. Meta-analysis showed that adjusted-dose oral anticoagulation [target International Normalized Ratio (INR) 2.5; range, 2.0–3.0] is highly efficacious for prevention of all strokes (both ischemic and hemorrhagic), with a risk reduction of 68% (95% CI 50%–70%) as compared to placebo. This reduction was similar for both primary and secondary prevention and for both disabling and non disabling strokes. Aspirin showed a less consistent benefit for stroke prevention than anticoagulation therapy. Aspirin compared to placebo was evaluated in 3 trials and a pooled analysis of these studies showed a mean stroke risk reduction of 21% (95% CI 0%–38%). Adjusted-dose oral anticoagulation resulted in a relative risk reduction of 52% (95% CI 37%–63%) compared to aspirin. [20, Rank 5]

In Stroke Prevention in Atrial Fibrillation Trials (SPAF I and II), which randomly assigned patients to warfarin or aspirin (325 mg per day), multivariate analysis identified 4 atrial fibrillation subgroups with a substantial stroke rate on aspirin: patients with systolic hypertension (greater than 160), patients with impaired left ventricular function, patients with a history of prior thromboembolism and women over 75 years in age. Aspirin-treated patients with 1 or more of these risk factors had a thromboembolic rate of about 6% per year where as those without these risk factors had a thromboembolic rate of about 2% per year.

A meta-analysis of randomized trials comparing oral anticoagulation with combined aspirin and anticoagulation at the same target INR showed an increased risk of bleeding in the combined therapy arm (odds ratio 1.43, 95% CI 1.00 to 2.02). The adequacy of aspirin prophylaxis was evaluated in Stroke Prevention in Atrial Fibrillation Trial III among patients without any of the 4 identified stroke risk factors. Stroke or systemic embolism occurred at a rate of 2.2% per year among patients taking aspirin. The annual rate of stroke or systemic embolism was significantly higher in patients with a history of hypertension (more than 140 mmHg but less than 160mmHg systolic) than in those without. [21, Rank 3]

The ACTIVE W trial (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events), which compared the efficacy of combined antiplatelet therapy (aspirin 75 to 100 mg and clopidogrel 75mg) versus oral anticoagulation in high-risk patients with atrial fibrillation, demonstrated clearly the superiority of oral anti-coagulation in the long-term prevention of major ischemic events and had a similar bleeding rate. In the ACTIVE A trial, 7554 patients with atrial fibrillation who were considered unsuitable to receive vitamin-K antagonist therapy were randomized to receive clopidogrel (75 mg/day) or placebo added to aspirin. The addition of clopidogrel to aspirin reduced the rate of major vascular events from 7.6% per year to 6.8%, primarily due to a reduction in the rate of stroke. However, the rate of major haemorrhage increased from 1.3% to 2.0% per year. [22, Rank 4]

Experts conclude that warfarin therapy is indicated when the risk of stroke is high, and that aspirin is preferred when the risk of stroke is low (as shown in figure 6). There are 4 most consistent independent factors for stroke: prior stroke or transient ischemic attack (relative risk 2.5, 95% CI 1.8 to 3.5), hypertension

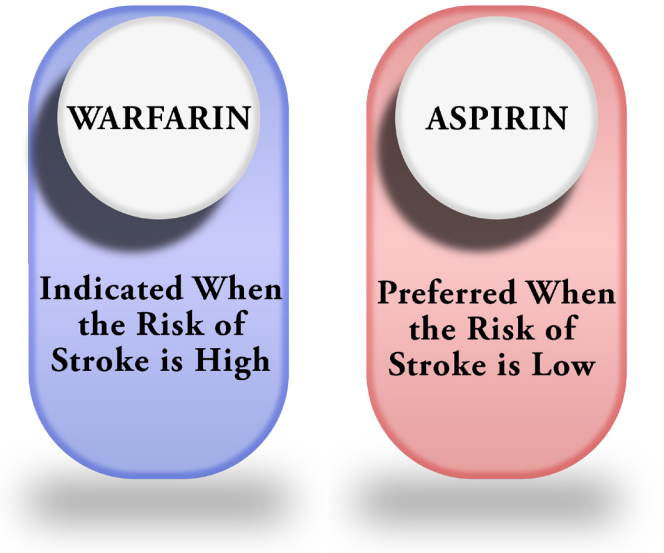

Figure 6: Oral anticoagulants based on risk

(relative risk 2.0, 95% CI 1.6 to 2.5), diabetes mellitus (relative risk 1.7, 95% CI 1.4 to 2.0), and increasing age (relative risk 1.5, 95% CI 1.3 to 1.7). The absolute rates of stroke in patients with only 1 independent risk are 6% to 9% per year for history of stroke/transient ischemic attack, 2% to 3.5% per year for diabetes mellitus, and 1.5% to 3% per year for both hypertension and age of more than 75 years. However, there is no conclusive evidence that congestive heart failure and coronary artery disease are independent risk factors for stroke. [23, Rank 5]

In primary prevention studies oral anti coagulation lowered the mortality rate by 33% (95% CI 9%–51%), and the combined outcome of stroke, systemic embolism, and death by 48% (95% CI 34%–60%). In these studies, the reported annual incidence of major bleeding and intracranial hemorrhage was 1.3% and 0.3% in anticoagulated patients, compared to 1% and 0.1% in control patients. The risk of intracranial haemorrhage is significantly increased at INR values >4.0, with increasing age and in patients with a history of stroke. From the available information it is clear that oral anticoagulation is more efficacious and more risky than aspirin to prevent first stroke in patients with atrial fibrillation. Chronic oral anticoagulation therapy is indicated in patients with atrial fibrillation and high risk of stroke unless contraindicated. The optimal intensity of anticoagulation for prevention of stroke in atrial fibrillation patients appears to be an international normalized ratio of 2.0 to 3.0, with a target of 2.5. Despite the encouraging results of oral anticoagulation in atrial fibrillation, this treatment is under utilized in clinical practice as more than one-third of eligible patients in primary care practice are not receiving it and sub therapeutic INR are encountered in 45% of patients taking OAC. [24, Rank 4]

Current Perspective

Current guidelines for antithrombotic therapy are based on the absolute risk for stroke balanced with the estimated bleeding risk.

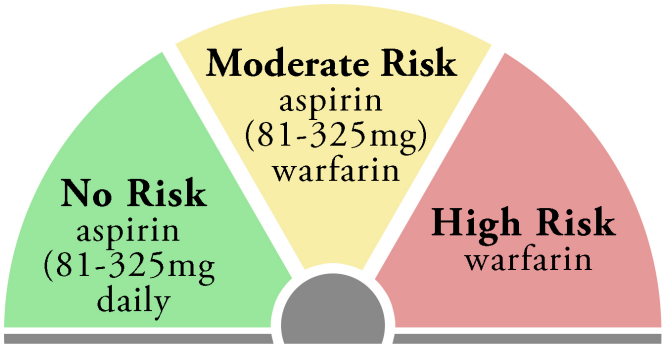

Figure 7: Antithrombotic therapy based on risk status

In brief, (as shown in figure: 7) if

- No risk factors for stroke: aspirin therapy (81 to 325 mg daily);
- 1 moderate risk factor for stroke (age over 75 years, high blood pressure, heart failure, impaired left ventricular systolic function with an ejection fraction of 35% or less, or diabetes): aspirin (81 to 325 mg) or warfarin (international normalization ratio 2.0 to 3.0, target 2.5);
- More than 1 moderate, or any high-risk factor for stroke (previous stroke, transient ischemic attack, systematic embolism, or prosthetic heart valve): warfarin (international normalization ratio 2.0 to 3.0, target 2.5; in case of a mechanical valve, target international normalization ratio is greater than 2.5) (as shown in figure: 8).

Alternative recommendations use the CHADS2 scheme for risk stratification. Stroke-prone patients are reliably identified

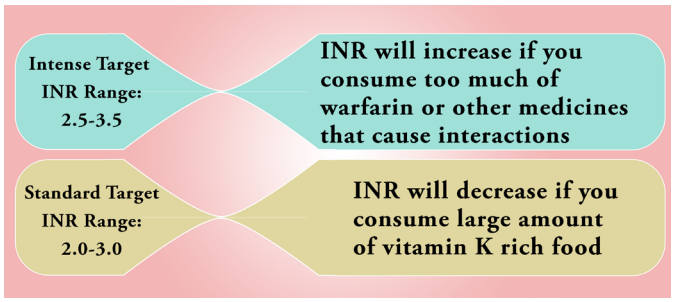

Figure 8: Target levels of INR

by a CHADS2 score >3 and they have an average risk of 5.5 strokes per 100 patient-years on aspirin. The CHADS2 scheme is comprised of 5 conditions: recent congestive heart failure, hypertension, age of 75 years or older, and diabetes (each of which accounts for 1 point) as well as prior stroke or transient ischemic attack, which accounts for 2 points in total score calculation. [25, Rank 3]

Acute Myocardial Infarction

Stroke is a rare but feared complication of acute myocardial infarction (AMI) that can complicate the course and outcome of those patients. The incidence of stroke during the acute phase following myocardial infarction varies considerably between studies. Rates are mostly in the range of 0.8% to 3.2%; approximately one-third occur within 24 hours following admission whereas about two-thirds occur in the first week after the myocardial infarction. Advanced age and atrial fibrillation are associated with higher risk of stroke. Late

stroke following myocardial infarction is rare, although patients are still at increased risk during the first 1 to 2 months. The risk for stroke remained 2- to 3-times higher than expected during the first 3 years after myocardial infarction. Most ischemic strokes after acute myocardial infarction involve the anterior circulation and are non-lacunar. Posterior circulation strokes are unusual. [28, Rank 2]

Etiology of stroke after acute myocardial infarction can be ascribed to a common pathophysiologic process: atherosclerosis; formation of mural thrombi in areas of ventricular hypokinesis after myocardial damage and atrial fibrillation and cardio version. Strokes occurring several weeks after acute myocardial infarction may be due to chronic left ventricular thrombi, an akinetic left ventricular segment or left ventricular dysfunction. Indeed, cerebral micro-embolism was detected by transcranial Doppler more often among patients with acute myocardial infarction with reduced left ventricular function, akinetic segments, or left ventricular thrombi. For every decrease of 5% in the ejection fraction, an 18% increase in the risk of long-term stroke has been found. Inflammatory changes at the endocardial surface also enhance thrombogenicity. A systemic hypercoagulable state may promote thromboembolism early after the coronary event whereas residual fresh thrombus may enhance coagulation during the first 1 to 3 months. [27, Rank 3]

Acute Cardio-embolic Stroke

Seven trials, involving 4624 patients with acute cardioembolic stroke, met the criteria for inclusion. All studies included patients with cardioembolic ischemic stroke (n = 4624) randomized within 48 hours from stroke onset. Atrial fibrillation was present in 3797 patients and other mixed cardioembolic sources in 827. Compared with other treatments, anticoagulants were associated with a non-significant reduction in recurrent ischemic stroke within 7 to 14 days (3.0% versus 4.9%, odds ratio 0.68, 95% CI: 0.44 to 1.06, P = .09, number needed to treat = 53), a significant increase in symptomatic intracranial bleeding (2.5% versus 0.7%, odds ratio 2.89; 95% CI: 1.19 to 7.01, P = .02, number needed to harm = 55), and a similar rate of death or disability at final follow-up (73.5% versus 73.8%, odds ratio 1.01; 95% CI: 0.82 to 1.24, P = .9).

In the single study in which anticoagulation was started within 3 hours from stroke onset, death or disability was reduced by anticoagulant treatment. These results should be interpreted with caution

because other trials did subgroup analyses in hyper acute patients and showed neutral results. Several studies have suggested that besides its antithrombotic effects, UFH also modulates inflammation. Thus, the positive effect of early heparin could be the result of either its antithrombotic effects and/or its modulation on the anti-inflammatory pathway that appears relevant in the first hours. Whatever the mechanism for improvement, the benefit observed in patients treated within 3 hours suggests the need for further trials on the efficacy of very early administration of anticoagulants in acute cardioembolic stroke. In selecting the study population for these trials, size of ischemia, age and blood pressure in the acute phase, all known as risk factors for hemorrhagic complications, should be considered. [30, Rank 5]

Conclusion

To date, there are no randomized trials to determine the efficacy of anticoagulation treatment for different subtypes of stroke. However, there is a recommended treatment strategy for patients with atrial fibrillation presenting with stroke or transient ischemic attack. Despite its proven efficacy in secondary prevention of stroke, anticoagulation therapy is not initiated in a major portion of especially elderly patients with atrial fibrillation, mainly because of contraindications but also because of multiple patient and physician barriers. There has been some concern about the risk/benefit of oral anticoagulation in elderly patients, because of a greater risk of hemorrhagic complications in this group of patients. However, the WASPO (Warfarin versus Aspirin for Stroke Prevention in Octogenarians) and BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) trials have shown that oral anticoagulant is safe and effective in older individuals. Therefore, there is no justification to avoid anticoagulation in very old individuals with atrial fibrillation, unless there is a clear contraindication. [26, Rank 4]

***Important information for post-test is highlighted in red letters, boxes and diagrams.**

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