PREVENTION OF CARDIOEMBOLIC STROKE IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION: BALANCING THE EVIDENCE AND PATIENT PREFERENCES

PROGRAM SYLLABUS

January 24, 2015
8:00 a.m. – 11:00 a.m.
Pointe Hilton Tapatio Cliffs Resort
Highland 1
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Prevention of Cardioembolic Stroke in Patients with Nonvalvular Atrial Fibrillation: Balancing the Evidence and Patient Preferences

Saturday, January 24, 2015
8:00 a.m. – 11:00 a.m.

CME Credits: 3

Program Director
Jose G. Merino, MD, M.Phil
Bethesda, MD

Program Schedule and Faculty
8:00 a.m. – 8:05 a.m. Introduction
Jose G. Merino, MD, M.Phil
Bethesda, MD

8:05 a.m. – 8:45 a.m. Diagnosing NVAF for Stroke Prevention
Richard A. Bernstein, MD, PhD
Chicago, IL

8:45 a.m. – 9:25 a.m. Anticoagulants in the Prevention of Stroke in Patients with NVAF
Mitchell Elkind, MD, MSc, FAAN
New York, NY

9:25 a.m. – 10:05 a.m. Using Risk Scores to Identify Patients for Treatment and Use of Anticoagulants in Special Populations
Oscar R. Benavente, MD, FRCP(C)
Vancouver, BC, Canada

10:05 a.m. – 10:30 a.m. Engaging Patients in Shared Decision Making About Stroke Prevention
Jose G. Merino, MD, M.Phil
Bethesda, MD

10:30 a.m. - 11:00 a.m. Moderated Expert Panel Questions and Answers
Faculty

Program Description:
This program will provide a review of strategies to diagnose NVAF in patients with stroke and therapeutic alternatives for stroke prevention. Emphasis will be placed on strategies to identify patients at high risk of recurrent stroke and of complications from treatment, and ways to engage patients in shared decision making. Faculty will review the evidence for long-term cardiac monitoring and the use of warfarin and new oral anticoagulants in stroke patients.

Learning Objectives:
Upon completion, participants should be able to:
1. Understand the clinical situations that warrant long-term cardiac monitoring
2. Identify the different options for long-term outpatient cardiac monitoring
3. Describe the evidence that supports the use of warfarin and other oral anticoagulants to prevent recurrent stroke
4. Use risk scores to identify patients most and least likely to benefit or be harmed from anticoagulation for stroke prevention
5. Engage patients in the decision of which prophylactic agent to use based on their preferences

Recommended Audience:
Practitioners, Academicians, Residents, and Fellows

Core Competencies:
Patient Care; Medical Knowledge; Interpersonal and Communication Skills; Practice-based Learning and Improvement; Professionalism; Systems-Based Practice

Accreditation
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AMA PRA Credit
The AAN designates these educational activities for a maximum number of hours in category 1 credit toward the AMA Physician's Recognition Award. The number of credits assigned to each individual program is outlined in the program's description. Each physician should only claim those hours of credit that he/she actually spent in the activity.

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Faculty Commercial Relationship Disclosures
- Dr. Merino has received personal compensation in an editorial capacity for BMJ.
- Dr. Bernstein has received personal compensation for activities with Boehringer Ingelheim Pharmaceuticals, Inc., and Pfizer Inc.
- Dr. Elkind has received personal compensation for activities with BMS-Pfizer Partnership, Janssen Pharmaceuticals, Daiichi-Sankyo, Boehringer-Ingelheim Biogen IDEC, Biotlemetry and Organon/Merk as a consultant. Dr. Elkind has received personal compensation in an editorial capacity for Neurology.
- Dr. Benavente has received personal compensation for Bayer Pharmaceuticals Corporation and Osaka.

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Faculty Unlabeled Use of Product Disclosures

- Dr. Merino will not include any information on unlabeled use of products or investigational uses during the presentation.
- Dr. Bernstein will not include any information on unlabeled use of products or investigational uses during the presentation.
- Dr. Elkind will discuss the use of various novel oral anticoagulants (dabigatran, rivaroxaban, apixaban, etc.) for the treatment of stroke due to atrial cardiopathy, intracranial atherosclerosis, cerebral venous thrombosis, and evolving stroke.
- Dr. Benavente will not include any information on unlabeled use of products or investigational uses during the presentation.
Atrial fibrillation and cryptogenic stroke
Richard A. Bernstein, M.D., Ph.D.
Professor of Neurology
Director, Northwestern Medicine Stroke Program
Feinberg School of Medicine of Northwestern University

Introduction:

Of the 700,000 ischemic strokes that occur in the United states every year, almost one third of are undetermined mechanism. Patients with stroke of undetermined mechanism (Cryptogenic Stroke, CS) may have stroke risk factors like hypertension, diabetes mellitus, or smoking, but have no clear mechanistic etiology for their stroke. For example, a patient may have hypertension and diabetes, but if they have an embolic appearing stroke on the cortex of the brain or with strokes in multiple territories, and have normal blood vessels, a normal heart and heart rhythm, and no hypercoagulable state, the mechanism of the stroke is unclear. Patients with stroke of unknown mechanism are normally treated with antiplatelet therapy, as up to now, no studies have shown any benefit of anticoagulation over antiplatelet therapy for patients with a clear high risk cardioembolic source.

The situation is quite different in a patient with an ischemic stroke who has atrial fibrillation (AF). Of all potential causes of stroke, AF related strokes are the easiest to prevent. Long term oral anticoagulation with Vitamin K antagonists (VKAs) reduce the risk of stroke in these patients between 65 and 80% compared to placebo; and aspirin is of dubious benefit in patients with high risk AF. The novel oral anticoagulants (NOACs) are generally more effective, dramatically safer for the brain, and much easier to take. Therefore, discovering AF in a patient with stroke is good news for the patient: the treatment is clear. Long term oral anticoagulation (OAC) is dramatically more effective in this subgroup of stroke patients than is antiplatelet therapy; but in the absence of AF (or other very high risk cardiac sources), there is no proven benefit of anticoagulation. This makes the discovery of AF in a stroke patient a major diagnostic “fork in the road”.

The dramatic response of patients with AF to oral anticoagulation also exposes both an opportunity and a problem for the medical community. Up to 25% of all AF first comes to medical attention by causing a stroke. The strokes that occur in patients with AF are the most likely to be fatal or worse compared to other stroke mechanisms. Most ischemic strokes in someone with AF could have been prevented with anticoagulation. Therefore, there it is important to maximize the chances of finding AF. This is most true in someone with a history of stroke, since such patients are at the highest risk of having another stroke, and stand to benefit the most from detection of AF and resultant anticoagulation.

That patients might have AF that eluded detection during the initial stroke evaluation (“occult AF”) gained traction when we entered the era of continuous long term monitoring for AF with either long-term external devices, or implantable monitors and pacemakers that automatically sense AF. In this lecture we will define “occult AF” as AF that was missed during stroke evaluation; an alternate definition would be AF that is only detectable with more than a few weeks of continuous monitoring. The key insight is that with prolonged electrocardiographic monitoring, we can detect AF that is brief and asymptomatic and which occurs only rarely. However, the clinical significance of this occult AF is uncertain.

First, lets discuss what the best way to find AF is. Any professor of medicine will tell you that history and exam are the bedrock of any clinical diagnosis. In the case of AF, the professor might need to go back to school. 40% of AF is asymptomatic, and 25% of AF presents with a stroke. If you perform ECG monitoring on patients and ask them to report when they have palpitations, you find no difference in reports during or not during an attack of AF. In fact, the majority of symptoms are due to arrhythmias that aren’t AF. A spot ECG is obviously sensitive to AF if the patient is having it during those 30 seconds, but is nearly useless for ruling out paroxysmal AF. Telemetry and Holter monitoring are often performed for one to 7 days to detect AF. Many stroke units use in-patient telemetry to look for AF in their patients. Unfortunately, telemetry is only as good as the people watching it. One study had patients in a stroke unit on telemetry for 3 days, during which they were on Holter simultaneously for 24 hours. The Holter found AF in 6% of patients; none of the patients had AF detected by telemetry. External patient-triggered monitors may be useful in some patients, but since we are concerned with finding AF that is asymptomatic, many episodes will be missed if the patient doesn’t trigger the loop recorder.

The landscape of AF detection changed with the advent of algorithmically driven monitors that could detect AF without any input from the patient. These include mobile cardiac telemetry devices (MCOT) which can be worn for
up to one month, and implantable devices. The latter may include pacemaker/defibrillators which are sensitive to AF and may be interrogated; or diagnostic devices that are implanted specifically to detect AF. These have become quite unobtrusive and one device on the market can be inserted in a procedure that takes 30 seconds, using an injection tool and local anesthetic.

Occult AF is a real phenomenon. One worrisome study interrogated pacemakers in 1600 patients not known to have AF. After 12 months, 30% of these patients had at least one episode of AF, right under the noses of their cardiologists. Most of the AF occurred less on less than 10% of days (half on less than 1% of days), and the majority occurred beyond the one month that a patient could conceivably wear an external monitor. This shows that longer periods of monitoring have a higher probability of finding AF.

It is not entirely clear that the brief, rare episodes of AF detected with prolonged monitoring have the same treatment implications as traditionally diagnosed AF. However, there is increasing evidence that the detection of brief occult AF is highly predictive of both going on to develop clinically manifest AF (which certainly merits anticoagulation) and stroke. It is this authors belief that the idea that there is a minimum amount of AF in a high risk patient that can be safely treated with asa instead of anticoagulation is a hypothesis. It is worthy of a clinical trial (and some are ongoing), but outside of a trial, the safest option for most patients is to treat any AF as if it were permanent AF and use OAC if the patient has other risk factors for stroke.

The ability to detect brief, asymptomatic runs of AF who are monitored for months or years raises the elegant and obvious hypothesis that some of the 30% of strokes that are of “unknown cause” may actually be due to AF. To test this hypothesis, many investigators have reported on the rate of detection of AF (variously defined) using prolonged monitoring (variously defined) in patients with cryptogenic stroke (variously defined). These preliminary studies set the stage for two landmark studies that examined this question with rigorously defined definitions for all of the above variables. These studies were both published simultaneously in the NEJM and form the pillars of evidence for guiding practice in this arena.

The utility of external monitoring was studied in patients with CS in the EMBRACE study. EMBRACE randomized 572 patients with CS in the prior 6 months to either standard monitoring or a 4 week period of continuous ECG monitoring. The endpoint was 30 seconds detected by 90 days. Importantly, only 8% of these patients underwent transesophageal echocardiography (TEE), which may detect surrogate markers for AF such as spontaneous echo contrast in the LA, LA thrombus, or mitral valve disease. The monitored group had a rate of AF at 90 days of 16.1%, vs 3.2 % in the control arm (p<0.001), suggesting that monitoring 8 patients is all that is required to find 1 additional case of AF. Interestingly, a secondary endpoint was detection of AF of duration 2.5 minutes or more; here the control group rate was 2.5% and the monitored group rate was 9.9%. (more about that later).

The second important trial in this area was the CRYSTAL AF study. CRYSTAL randomized 441 patients with CS to either standard monitoring or implantation of a AF detection device that can stay in for 3 years or more. The primary endpoint was 30 seconds of AF by 6 months, but interestingly the device is only reliably sensitive to AF episodes > 2 minutes. This biased the study AGAINST the device. The key secondary endpoint was detection of AF by 1 year. Unlike in EMBRACE, 100% of the patients in CRYSTAL had a TEE that did not reveal a high risk cardioembolic source.

The results were equally striking. By six months, AF had been found in 1.4% of control patients, vs 8.9% of monitored patients (P0.0006). By one year, only one additional case of AF was found in the control arm (2.0%) byt the rate in the device arm was 12.4%. The vast majority of patients with AF (in the device arm) had at least one day with 6 minutes or more of AF, and almost half had at least one day with 12-24 hours of AF. The earliest enrollees in this trial were monitored for up to three years. Although the numbers by 3 years are small, of those early enrolled patients, the rate of AF detection was 30% with the device, vs 3% in the control arm.

A few other observations from CRYSTAL are of interest to neurologists. First, the rate of recurrent stroke was non-significantly lower in the device arm than in the control arm. The study was not powered to show a difference in recurrent stroke, but this is encouraging. The reason for the lower rate of recurrent stroke is hard to know with certainty. Additionally, 96% of all patients who were found to haveAF were started by their neurologists on anticoagulation even though this was not specified in the protocol. Finally, to detect 4 cases of AF in the control arm over 12 months the following tests were required: 121 ECGs, 32 24 hour holter monitors, and 1 event recorder. This is compared to 29 cases of AF found with the implantable monitor in the same period.
The EMBRACE study an the CRYSTAL both showed that longer monitoring finds more AF than does shorter monitoring in patients with CS. However, it seems paradoxical that EMBRACE used an external monitor for 4 weeks and found 16% of patients had AF, whereas CRYSTAL used an implantable monitor for 1 year and found a rate of 12% AF detection. The differences probably lie in the patient populations. EMBRACE enrolled patients with a mean age of 73 vs 61 in CRYSTAL. Age is a major risk factor for AF. IN addition, only 8% of the EMBRACE patients had TEE. TEE was required in CRYSTAL. It is my hypothesis that TEE finds surrogate markers for AF such as LAA smoke or thrombus, and that many patients with "easy to find" AF were enrolled in EMBRACE and excluded due to their TEE findings from CRYSTAL. Finally, the implantable monitor is not reliably sensitive to AF episodes < 2minute. If you compare similar populations of patients with similar durations of AF to each other in EMBRACE and CRYSTAL, the rates of AF detection are similar.

In conclusion, neurologists now have several new and useful methods for detecting AF available to them for use in patients with stroke. These devices allow monitoring for months to years. They are more likely to detect AF than anything else we have been doing as routine care prior to the advent of the "era of continuous monitoring". However, the ability to detect rare, brief, asymptomatic episodes of AF raises important treatment questions and also suggests further research studies to define which patients with this difficult-to-detect AF require anticoagulation. Neurologists should look forward to an interesting few years as ongoing studies try to answer these questions.
Anticoagulants in the Prevention of Stroke in Patients with Non-Valvular Atrial Fibrillation

Mitchell S. V. Elkind, MD, MS
Columbia University
New York, NY

I. Introduction

Atrial fibrillation (AF) is a major cause of stroke. AF-associated stroke is commonly assumed to result from embolism of stasis-precipitated thrombi formed in the left atrial appendage or the left atrium itself, and the role of anticoagulants to prevent stroke in many patients with AF is well-established. Several recent scientific advances, including developments in risk assessment among patients with AF and related arrhythmias and the approval of new classes of anticoagulants, have led to a critical reappraisal of the role of AF in stroke prevention. This syllabus will review the most current approaches to estimation of risk of stroke among patients with AF, the role of antiplatelet and anticoagulant strategies to prevent stroke, and consider specific clinical scenarios that often pose challenges to treating physicians. It will touch, finally, on future directions in stroke prevention among patients with atrial fibrillation and related cardiac disorders.

An excellent and comprehensive guideline statement and review of the clinical approach to atrial fibrillation, supported by the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society, was also published in 2014, and is recommended [2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. JACC 2014;64:e71-76.]. The American Academy of Neurology has also sponsored recent guidelines reviewing approaches to the use of anticoagulants in AF.2

II. Definitions and Epidemiology of Atrial Fibrillation

Atrial fibrillation is a supraventricular tachycardia characterized by dyscoordination of atrial electrical activity and resultant ineffective atrial contraction. Electrocardiographically, it is characterized by irregularity of the R-R interval (when there is conduction from the atrium to the ventricle), absence of P waves (the electrocardiographic signature of atrial conduction), and irregular atrial activity. Non-valvular AF refers to AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

AF is strongly associated with age. Less than 2% of those under age 65 have AF, while the prevalence increases to 9% among those over age 65.3 Stroke is one of the most feared complications of AF. The risk of stroke is increased 5-fold among those with non-valvular AF, and is even more dramatically increased (as much as 20-fold) among those with valvular heart disease (primarily rheumatic mitral stenosis).4 Ischemic strokes among patients with AF are on average more severe and more often fatal than those among patients without AF. AF is also associated with an increased risk of dementia and mortality.4,5

Atrial fibrillation is often associated with other atrial arrhythmias, including atrial tachycardias, focal atrial tachycardia, multifocal atrial tachycardia, and atrial flutter. Many patients with these arrhythmias, particularly atrial flutter, also experience atrial fibrillation at other times. In fact, the vast majority (80%) of patients with atrial flutter who undergo catheter ablation for flutter develop AF within 5 years.6 For practical purposes, and particularly in considering antithrombotic preventive therapy for stroke prevention, treatment of atrial flutter remains similar to that of AF. Although evidence also exists to suggest that other supraventricular tachycardias are associated with an increased risk of stroke, optimal stroke prevention strategies in such patients have not yet been defined.7

Atrial fibrillation has been classified by its duration into paroxysmal, persistent, long-standing, and permanent types (Table 1). This classification scheme is relevant to decision-making regarding the termination of the arrhythmia, as patients with paroxysmal AF are more likely to have a successful response to cardioversion than patients with persistent AF. The classification has less relevance with regard to choice of antithrombotic agents, however, as risk prediction schemes do not include the duration of AF. The old term “lone AF,” indicative of AF in a young person without other comorbidities, is no longer used for decision-making.
Table 1. Classification of AF (Adapted from reference 1)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Duration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal</td>
<td>&lt; 7 days</td>
<td>• May terminate spontaneously or with treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May have recurrent episodes with variable frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Episodes often increase in frequency and duration over time</td>
</tr>
<tr>
<td>Persistent</td>
<td>Continuous 7 days to 12 months</td>
<td>• Both paroxysmal and persistent AF may occur in same patient</td>
</tr>
<tr>
<td>Long-standing persistent</td>
<td>&gt;12 months</td>
<td>This category implies that a decision has been made by physician and patient to forego further attempts at conversion to sinus rhythm; it thus represents a therapeutic rather than physiological category</td>
</tr>
<tr>
<td>Permanent</td>
<td>&gt;12 months</td>
<td></td>
</tr>
<tr>
<td>“Lone AF”</td>
<td>AF in younger patient in absence of echocardiographic evidence of cardiopulmonary disease, hypertension, or diabetes mellitus</td>
<td>This term is of historical interest and should no longer be used in therapeutic decision-making</td>
</tr>
</tbody>
</table>

One question which continues to be relevant, however, and has been of particular interest to neurologists caring for patients with stroke, is how long a single episode of electrocardiographic AF needs to be to permit a diagnosis of AF and justify anticoagulation. Is ten seconds enough? Thirty seconds? 5 minutes? The following scenario, for example, represents a common conundrum for clinicians caring for patients with TIA and stroke.

Case: An 87-year-old cognitively intact retired nurse with a history of hypertension, hyperlipidemia, and peripheral vascular disease was admitted with acute left hemisensory loss. Initial head CT was negative. Symptoms improved without tPA, and MRI was negative for acute infarction. Carotid ultrasound showed no significant stenosis, transcranial Dopplers were negative, and transthoracic echocardiogram was negative. On telemetry there were numerous episodes of PSVT with aberrancy. She was seen by the Cardiac Electrophysiology service and started on a low-dose beta blocker. Aspirin 81 mg daily was also prescribed. She was discharged on outpatient telemetry. Over the next 3 weeks, she had a single episode < 6 seconds of PSVT, though it was difficult to distinguish between AF and an atrial tachycardia. Aspirin 81 mg daily was continued. On subsequent further outpatient monitoring she had clear episodes of PAF of longer duration. She then began treatment with apixaban 5 mg twice daily.

As this case illustrates, there remains uncertainty about how much AF is “enough” to warrant a diagnosis and commit a patient to anticoagulation. Among patients with a history of atrial fibrillation, there is evidence to suggest that the duration and frequency of AF are associated with risk of stroke, though among patients without diagnosed or clinical AF, the minimum amount of AF needed to warrant anticoagulation therapy is unclear. The algorithms that permitted diagnosis of AF in studies that found associations of AF with risk of stroke differ among studies. In one study (ASSERT), for example, the duration of atrial arrhythmia required for a diagnosis of AF was 6 minutes or more; in that study the diagnostic algorithm also used the detection of an atrial tachyarrhythmia > 190 beats per minute as the criterion to diagnose atrial fibrillation, rather than AF per se. Another observational study (MOST) used atrial tachycardia of >220 beats per minute for at least 5 minutes, while in a trial of continuous cardiac telemetry after cryptogenic stroke, a duration of 30 seconds of AF was used as a threshold for diagnosis. In practice, it can be difficult to distinguish atrial fibrillation from flutter from atrial tachycardia, and these different entities are often grouped together as “atrial high rate events.” In the absence of a consensus, most neurologists faced with a stroke or TIA patient undergoing monitoring with AF will accept very brief runs of AF as evidence of the need for anticoagulation for AF. Further research is needed to address this question of the relevance of duration of AF to risk of stroke and response to therapy.
III. Risk of Stroke in Patients with Non-Valvular Atrial Fibrillation

The selection of the appropriate strategy to reduce risk of thromboembolism among patients with AF depends on the risk of stroke in the individual patient. Not all AF patients are at the same level of risk, as exemplified by the historical concept of “lone AF,” long considered a marker of low risk, but now quantified more specifically using risk prediction schemes. Several risk prediction schemes for patients with atrial fibrillation have become available. The most commonly used of these are the CHADS2 and CHA2DS2-VASc scores, which predict risk of thromboembolism, and the HAS-BLED score, which predicts risk of hemorrhage among patients with AF, including those on antithrombotic therapy (Tables 2 and 3).

For each point of the CHADS2 score, there is an approximately 2% increase in absolute risk of stroke or systemic thromboembolism. Limitations of the CHADS2 score are that it discriminates poorly among those at the lower end of the risk spectrum, such that even those with scores of 0 have an annual risk of approximately 2%, and those with a score of 1 are considered at intermediate risk (approximately 3% per year). It may also underestimate the risk of stroke among those with a prior history of stroke or TIA. Stroke rates are higher among patients with a prior history of stroke or TIA than in primary prevention (approximately 4% per year for patients on control therapy in primary prevention trials compared to 13% per year in secondary prevention trials).12 The CHA2DS2-VASc score incorporates additional risk factors, including levels of age, sex, and other atherosclerotic and vascular diseases that increase stroke risk. Women cannot have a score of 0 since female sex counts as at least one point. Those with CHA2DS2-VASc scores of 0-1 appear to be at very low risk of stroke. In large cohorts analyzed thus far, the CHA2DS2-VASc score demonstrated better predictive value than the CHADS2 score.13,14,15 However, the predictive value of all scores remains limited, and these scores are based on analyses of prior cohorts of patients, and current risks may be lower due to advances and increasing use of other preventive medications, such as statins and anti-hypertensives.

Table 2. Commonly used risk prediction schemes for AF

<table>
<thead>
<tr>
<th>CHADS2 items</th>
<th>Points</th>
<th>CHA2DS2-VASc items</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C=Congestive heart failure</td>
<td>1</td>
<td>C=Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H=Hypertension</td>
<td>1</td>
<td>H=Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A=Age &gt;75 years</td>
<td>1</td>
<td>A2=Age &gt;75 years (double value)</td>
<td>2</td>
</tr>
<tr>
<td>D=Diabetes mellitus</td>
<td>1</td>
<td>D=Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S2=history of stroke, TIA, or thromboembolism (double value)</td>
<td>2</td>
<td>S2=history of stroke, TIA, or thromboembolism (double value)</td>
<td>2</td>
</tr>
<tr>
<td>V=Vascular Disease (prior MI, peripheral arterial disease, aortic plaque)</td>
<td></td>
<td>V=Vascular Disease (prior MI, peripheral arterial disease, aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>A=Age 65-74 years</td>
<td>1</td>
<td>Sc=sex category (female sex)</td>
<td>1</td>
</tr>
<tr>
<td>Range</td>
<td>0-6</td>
<td>Maximum</td>
<td>9</td>
</tr>
</tbody>
</table>

Though further research is needed, current guidelines1,2 endorse the use of anti-coagulant therapy for AF patients with prior stroke or TIA or CHA2DS2-VASc scores of ≥2 (annual stroke risk of ~2%). For patients with CHA2DS2-VASc scores of 1 (annual stroke risk of ~1%), no antithrombotic, aspirin, or an anticoagulant may reasonably be used. For patients with CHA2DS2-VASc scores of 0 (~0% annual risk) it is reasonable to use no antithrombotic agent at all. Risks should be periodically updated and decision-making adjusted accordingly. Patients with atrial flutter should be treated similarly as patients with AF.
Table 3. Commonly used risk prediction schemes, annual stroke risk, and antithrombotic recommendations based on guidelines

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>Stroke risk (%/year)</th>
<th>CHA2DS2-VASc score</th>
<th>Stroke risk (%/year)</th>
<th>Recommended antithrombotic treatment based on CHA2DS2-VASc (Class of recommendation, level of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
<td>0</td>
<td>0</td>
<td>None (IIb, B)</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
<td>1</td>
<td>1.3</td>
<td>None, aspirin, or anticoagulant (IIb, C)</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>2</td>
<td>2.2</td>
<td>Anticoagulant (I, A [warfarin], B [dabigatran, rivaroxaban, apixaban])</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
<td>3</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
<td>4</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
<td>5</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
<td>6</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>6.7</td>
<td></td>
</tr>
</tbody>
</table>

The above risk stratification schemes, it should be noted, are most relevant to the setting of primary prevention, i.e., prevention of a first stroke or TIA among patients with AF. In primary prevention, patients may score a 0 or 1, levels at which risks may be deemed low enough to obviate the need for an anticoagulant. Most neurologists, however, will be evaluating patients and making recommendations after the first occurrence of a definite or possible cerebrovascular event, and therefore will be engaged in making decisions regarding secondary prevention. Because both the CHADS2 and CHA2DS2-VASc scores include 2 points for a history of stroke or TIA, and a score of 2 is considered to represent a level of risk for which anticoagulant therapy is indicated, secondary prevention for patients with AF will almost always involve the use of an anticoagulant. In the most recent guidelines, in fact, a history of stroke or TIA alone is considered an indication for an anticoagulant.1,2

Table 4. The HAS-BLED score for predicting risk of bleeding among patients with AF

<table>
<thead>
<tr>
<th>HAS-BLED items</th>
<th>Score</th>
<th>Total score</th>
<th>Bleeds per 100 patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>H=hypertension (SBP&gt;160 mm Hg)</td>
<td>1</td>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>A=abnormal liver and/or renal function (1 point for each)</td>
<td>1-2</td>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>S=stroke history</td>
<td>1</td>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>B=bleeding history or predisposition</td>
<td>1</td>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>L=labile INRs (international normalized ratios in therapeutic range&lt;60% time)</td>
<td>1</td>
<td>4</td>
<td>8.70</td>
</tr>
<tr>
<td>E=elderly (age &gt;65 years)</td>
<td>1</td>
<td>5</td>
<td>12.50</td>
</tr>
<tr>
<td>D=drugs that promote bleeding (aspirin, clopidogrel, NSAIDs) and/or excess alcohol (1 point for each)</td>
<td>1-2</td>
<td>&gt;5: Too few to assess</td>
<td>--</td>
</tr>
</tbody>
</table>

The risk of bleeding among patients with AF, meanwhile, may be estimated using the HAS-BLED score (Table 4).16,17,18 HAS-BLED has a range of 0 to 9; the risk of bleeding increases linearly. A score of 3 or higher is considered to represent a high risk of bleeding (~4% per year). The score has not been endorsed by US
IV. Choosing an Antithrombotic Agent

Choosing whether to begin an antithrombotic agent, and the choice of which agent to use, should be based upon shared decision-making between patient and physician, and involve a discussion of the benefits and risks of anticoagulation, as well as patient preferences. Different patients tolerate different levels of risk of stroke and of bleeding, and these decisions may be influenced by many factors. The medical ethical principle of patient autonomy should guide decision-making in this realm as in other realms of medicine.

Case: A 77 year old professor of orthodontics, still actively practicing and teaching, was referred for headaches and mild memory loss since heart surgery. He had a history of aortic insufficiency, congestive heart failure, syncope, and paroxysmal AF. He underwent aortic valve repair and arch repair, and again developed AF postoperatively and was treated with anticoagulation. A permanent pacemaker was placed for bradycardia. He was first seen by a neurologist 10 months later for daily headaches and memory loss since the surgery. He had had one brief episode of diplopia several months prior, which was not evaluated, and there was no history of stroke. He took ASA 81 mg daily, and did not wish to take anticoagulants. His CHA2DS2-VASc score was 4, consistent with an annual stroke risk of ~4.0%. After further discussion, he continued to decline anticoagulation, indicating that his risk of stroke might be reduced from 4% to ~1.5%, but that these changes were minor. He felt reassured by the fact that he had a >95% chance of not having a stroke.

This case illustrates that from the patient’s perspective, the changes in risk that are achieved in trials, while impressive to physicians, are not always as obvious or meaningful to patients.

Even when the choice to use an anticoagulant has been made, moreover, the choice of the specific anticoagulant will also depend on patient preferences, other risk factors, comorbidities, cost, potential drug-interactions, tolerability, time in range (for INR) and the need for monitoring.

V. Antiplatelets

The Stroke Prevention in Atrial Fibrillation (SPAF-1) trial demonstrated that aspirin 325 mg daily was more effective than placebo for prevention of stroke and systemic embolism among patients with continuous or paroxysmal AF. SPAF, a multicenter, randomized trial, followed 552 aspirin-treated patients and 568 placebo-treated patients for a mean of 1.3 years. The incidence of embolic events was reduced by 42% (95% CI 9-63%) in those assigned to aspirin (6.3% per year among those on placebo versus 3.6% per year among those on aspirin, p = 0.02). Primary events or death were reduced 32% by aspirin. The risk of significant bleeding was similar (about 1.5% per year) in patients assigned to aspirin and placebo. Aspirin was not effective among those > 75 years.

Other trials of stroke prevention using aspirin among patients with AF have not demonstrated a consistent benefit, either individually or in meta-analysis. These trials used variable doses of aspirin, however. Warfarin has also been shown to be more effective than aspirin alone in individual trials and meta-analyses (see below section on warfarin).

The combination of clopidogrel 75 mg daily and aspirin 75-100 mg daily was more effective in stroke prevention than aspirin alone in patients who were not candidates for anticoagulation in the ACTIVE-A trial (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events). Patients were included if they were ineligible for warfarin and also had at least an additional risk factor for stroke. The primary outcome was any major vascular event (stroke, systemic embolism, MI, or vascular death); stroke was a secondary outcome. Combination therapy led to an 11% risk reduction in the primary outcome (RR 0.89, 95% CI 0.81-0.98). There was a 28% risk reduction in all strokes compared to aspirin alone (RR 0.72, 95% CI 0.62 - 0.83). There was no effect on vascular or overall mortality. There was, moreover, an increase in major bleeding (RR 1.57, 95% CI 1.29 -1.92). Absolute differences between the groups were small, so that overall there was little evidence of any benefit, when accounting for both ischemic and hemorrhagic events. There was no significant difference between the rate of the combination of the primary outcome plus major hemorrhage (RR for combined therapy 0.97, 95% CI 0.89 to 1.06).

The combination of clopidogrel and aspirin was also compared with warfarin in the ACTIVE-W trial. This trial was terminated early due to the finding that warfarin (target INR 2.0-3.0) was superior to the combined antiplatelets. The recurrent stroke event rates were approximately 6% per year on antiplatelets versus 3% per year on warfarin (RR 2.13, 95% CI 1.23-3.69).
The AVERROES (Apixaban versus aspirin to reduce the risk of stroke) trial compared apixaban and aspirin in AF patients who were considered unsuitable for treatment with warfarin.\textsuperscript{22} Patients were randomized to receive either apixaban 5 mg BID or aspirin (81-325 mg daily). After an interim analysis that showed a 50% reduction in stroke and systemic embolism in patients in the apixaban treatment arm, the study was terminated before completion. Compared to aspirin, patients had better tolerance for apixaban, and there was no significant difference in hemorrhagic stroke with a rate of 0.2% per year in both treatment groups.

On the basis of these data, antiplatelet agents appear to have a limited role in the prevention of stroke among most patients with AF. Aspirin has limited efficacy compared with placebo, combined aspirin and clopidogrel have little overall benefit beyond aspirin alone and are not as effective as warfarin, and apixaban is more effective than aspirin without a significant increase in bleeding risk. Aspirin is likely to continue to have a role, however, among patients who cannot afford more expensive agents.

VI. Warfarin

Warfarin is a vitamin K antagonist that has been used for many years for stroke prevention. It works by limiting the production of the vitamin K dependent coagulation factors, factors 2, 7, 9, and 10.

The first randomized controlled trial of anticoagulant therapy in AF, published in 1989, demonstrated that warfarin markedly reduced the incidence of stroke compared to placebo.\textsuperscript{23} Meta-analyses\textsuperscript{12} have shown that adjusted-dose warfarin, with a target INR of 2.0-3.0, reduces the risk of stroke by approximately 64% (95% CI 49-74\%) compared to placebo. The effect is even greater for secondary than primary prevention, with a number needed to treat per year to prevent one stroke of 12.

Warfarin was also more effective than aspirin in meta-analyses of several trials, with significant reductions in all strokes and ischemic strokes. It was, however, associated with an almost two-fold increased risk of bleeding. In the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial, however, among 973 patients aged 75 or older with AF, warfarin was superior to aspirin (75 mg daily) in preventing stroke and systemic embolism without a significant increase in bleeding risk. The annual risk of the primary outcome was 1.8\% on warfarin compared to 3.8\% on aspirin (RR 0.48, 95\% CI 0.28-0.80) for a 2\% annual absolute risk reduction, and the risk of extracranial hemorrhage was 1.4\% on warfarin and 1.6\% on aspirin (not significantly different). These rates of bleeding were comparable to those of the SPAF-1 trial.

Warfarin and other vitamin K antagonists are effective treatments, both for primary and secondary stroke prevention, but their use is often limited due to a narrow therapeutic range, drug and food interactions, the need for consistent coagulation monitoring, and the risk of bleeding. With regard to monitoring, for example, the time in the therapeutic range, or TTR, was 55-60\% in most clinical trials. The use of warfarin, moreover, does not guarantee that embolism will not occur. The risk of stroke or systemic embolism among patients with AF on warfarin has been estimated in meta-analyses to be 1.66\% per year.

The risks of hemorrhage among patients on warfarin appear to be related to the level of elevation of the INR, with the risk increasing rapidly above INR values of 4.0.

VII. Novel Oral-Anticoagulants

The past decade has seen the development of several new alternatives to warfarin for patients with AF, most of which have similar efficacy with a lower bleeding risk. These novel oral anticoagulants (often referred to as NOACs) can be broadly divided into the direct factor Xa inhibitors, such as rivaroxaban, apixaban, and edoxaban, and the direct thrombin inhibitors, particularly dabigatran. A prior direct thrombin inhibitor, ximelagatran, was not approved for clinical use due to liver function abnormalities associated with its use.\textsuperscript{24}

The three currently FDA-approved NOACs (dabigatran, rivaroxaban, and apixaban) were compared with warfarin for stroke prevention among patients with AF in three pivotal randomized trials. All three agents represent advances over warfarin due to their more stable pharmacological profiles, obviating the need for monitoring levels, presence of fewer drug-drug interactions, absence of dietary interactions, and lower risk of bleeding, including intracranial bleeding. In a meta-analysis of 6 randomized trials using the NOACs, the risk of fatal bleeding was reduced by 40\% and the risk of major bleeding by 20\% among the NOACs compared to warfarin.\textsuperscript{25} They also have a more rapid onset and offset of action so that bridging with parenteral anticoagulants may not be needed (Table 5).

The major results of the pivotal trials of the NOACs are discussed below, and are summarized in Table 6, as well.\textsuperscript{26}
Table 5. Pharmacokinetic Properties and Dosing Considerations with the Novel Oral Anticoagulants (adapted from references 1 and 27)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mech. of action</th>
<th>Time to peak plasma concen'tn</th>
<th>Half-life</th>
<th>Standard dose schedule</th>
<th>Dose in renal impairment</th>
<th>Clinically relevant interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor</td>
<td>1.5-2 hrs</td>
<td>15-17 hrs</td>
<td>150 mg BID</td>
<td>75 mg BID for CrCl 15-30 mL/min</td>
<td>Avoid inhibitors and inducers of p-glycoprotein</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Factor Xa inhibitor</td>
<td>3-4 hrs</td>
<td>9-10 hrs</td>
<td>20 mg daily with evening meal</td>
<td>15 mg daily for CrCl 15-50 mL/min</td>
<td>Avoid inhibitors of CYP3A4 and p-glycoprotein</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Factor Xa inhibitor</td>
<td>3-4 hrs</td>
<td>8-15 hrs</td>
<td>5 mg or 2.5 BID*</td>
<td>Consider 2.5 mg BID (No definite recommendation)</td>
<td>Avoid CYP3A4 inhibitors; avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Factor Xa inhibitor</td>
<td>1-2 hrs</td>
<td>6-10 hrs</td>
<td>30-60 mg dailyǂ</td>
<td>No recommendation</td>
<td>Avoid inhibitors of p-glycoprotein</td>
</tr>
</tbody>
</table>

*Use apixaban 2.5 mg if any 2 of following patient characteristics present: Cr ≥1.5 mg/dl, ≥80 years old, weight <60 kg
ǂNot yet approved by FDA for treatment of AF

**Dabigatran:** RE-LY (Randomized Evaluation of Longterm Anticoagulant Therapy) was a randomized phase III clinical trial that compared fixed, blinded doses of dabigatran (110 mg or 150 mg twice daily) with open-label adjusted dose warfarin (INR 2.0-3.0).28 A total of 18,113 patients with non-valvular AF within the six months prior to randomization and at least one additional risk factor were randomized; 32% of the patients had a CHADS2 score of 0 or 1, 36% had a score of 2, and 33% had a score of 3-6. Stroke patients within 14 days of randomization were excluded. The study demonstrated that dabigatran at a dose of 150 mg BID was superior to warfarin treatment for the prevention of stroke and systemic embolism (primary outcome): 1.71% per year in the warfarin group, 1.54% per year in the 110 mg BID dabigatran group (p=0.34), and 1.11% of patients per year in the 150 mg BID dabigatran group (p<0.001). Results were similar for those on or off aspirin at baseline. Major bleeding occurred at a rate of 3.57% per year in warfarin-treated patients, 3.32% in patients treated with 150 mg BID dabigatran (p=0.31), and 2.87% per year in patients treated with 110 mg BID dabigatran (p=0.003). The rate of hemorrhagic stroke was reduced with both doses of dabigatran compared to warfarin treatment (0.12% per year with 110 mg and 0.10% per year with 150 mg vs. 0.38% with warfarin, p<0.001). The rate of major gastrointestinal hemorrhage was higher on dabigatran 150 mg BID, with an annual rate of 1.5% for dabigatran vs 1.0% for warfarin. This gastrointestinal selectivity for hemorrhage may reflect the fact that dabigatran is pumped back into the GI tract after absorption. There was also a reduction in overall mortality with dabigatran 150 mg BID compared to warfarin, though this did not meet statistical significance (RR 0.88, 0.77-1.00). Dabigatran was also associated with increased risk of dyspepsia.

A subgroup analysis among patients with TIA or prior stroke demonstrated that dabigatran was non-inferior to warfarin at both doses, though the number of patients was small.29 Dabigatran was approved by the FDA at a dose of 150 mg BID, and at a dose of 75 mg BID for patients with severe renal impairment (CrCl 15-30 mL/min) based on pharmacological modeling. It should not be used with CrCl< 15 mL/min. The 110 mg dose is unapproved in the US.

Table 6. Comparison of Key Studies of Novel Oral Anticoagulants in Atrial Fibrillation (adapted from reference 26)

<table>
<thead>
<tr>
<th>Drug</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>AVERROES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>dabigatran 150 mg BID</td>
<td>rivaroxaban 20 mg QD</td>
<td>apixaban 5 mg BID*</td>
<td>apixaban 5 mg BID*</td>
</tr>
<tr>
<td>Blinding</td>
<td>open-label</td>
<td>double-blind</td>
<td>double-blind</td>
<td>double-blind</td>
</tr>
<tr>
<td>Sample size</td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
<td>5599</td>
</tr>
<tr>
<td>Mean age, yrs</td>
<td>72</td>
<td>73</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Women, %</td>
<td>36</td>
<td>40</td>
<td>35</td>
<td>41</td>
</tr>
</tbody>
</table>
A pre-specified secondary analysis of the RE-LY trial found some evidence that both efficacy and risk of bleeding associated with dabigatran depended on dabigatran trough concentrations. This study has resulted in a great deal of controversy, including in the lay press, as it suggested that there could be a reason to require blood level monitoring among patients taking dabigatran, as for warfarin. These levels, however, were correlated with other patient characteristics, including age and renal function, that also predicted these outcomes. At this time, in the absence of data demonstrating the clinical utility of concentrations or how to make appropriate adjustments of dose, such monitoring is not recommended or even possible, though future studies should explore this issue further.

**Rivaroxaban**: In ROCKET-AF (Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation), patients with AF were randomized in a double-blind, double dummy manner to receive either the factor Xa inhibitor rivaroxaban 20 mg daily, or dose-adjusted warfarin (INR goal of 2.0-3.0). Inclusion criteria included two or more stroke risk factors and documented AF within six months of randomization. Most of the patients (87%) had a CHADS2 score of ≥3, so this was a higher risk population. Stroke, the primary endpoint, occurred in 2.12% among patients treated with rivaroxaban and in 2.42% of patients treated with warfarin (p=0.117). Rivaroxaban was found to be non-inferior to warfarin. The mean time in the therapeutic range for warfarin was 55%, not much different from other similar studies. Rates of major bleeding were similar in the rivaroxaban group (3.6%) as compared to those taking warfarin (3.45%) (p=0.576); fatal bleeding and intracranial hemorrhage were lower with rivaroxaban, however. The rate of intracranial hemorrhage was significantly lower with rivaroxaban (0.5% per year) compared to warfarin (0.7% per year, p=0.02). Mortality was not significantly different.

**Apixaban**: In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban was compared with adjusted-dose warfarin for the prevention of stroke or systemic embolism in patients with AF and at least one additional risk factor for stroke. The rate of the primary outcome (stroke or systemic embolism) was significantly reduced by apixaban compared with warfarin, as were the rates of major bleeding and death from any cause. The rate of hemorrhagic stroke in the apixaban group was about half the rate in the warfarin group. In a subgroup analysis of, the rate of stroke or systemic embolism in the subgroup of patients with previous stroke or TIA was 2.46 per 100 patient years of follow-up in the apixaban group and 3.24 in the warfarin group (RR 0.76, 95% CI 0.56-1.03). In patients without previous TIA or stroke, the rate of stroke or systemic embolism was 1.01 per 100 patient-years of follow-up with apixaban and 1.23 with warfarin (HR 0.82, 95% CI 0.65-1.03; p for interaction=0.71). The absolute reduction in the rate of stroke and systemic embolism with apixaban versus warfarin was 0.77 per 100 patient-years of follow-up in patients with stroke (95% CI 0.08-1.63), and 0.22 (95% CI -0.03-0.47) in those without previous stroke or TIA. The difference in major bleeding with apixaban compared with warfarin was 1.07 per 100 patient-years (95% CI 0.09-2.04) in patients with and 0.93 (95% CI 0.54-1.32) in those without previous stroke or TIA. The numbers thus indicate that the absolute benefit of apixaban may be higher, since stroke rates are higher among those with prior stroke or TIA.

**Edoxaban**: In ENGAGE AF, a double-blind trial comparing two once-daily regimens of edoxaban with warfarin in 21,105 patients with moderate-to-high-risk atrial fibrillation followed for a median of 2.8 years, both
regimens of edoxaban were non-inferior to warfarin in the prevention of stroke or systemic embolism (primary outcome) and were associated with significantly lower rates of bleeding and death from cardiovascular causes. Edoxaban is not yet approved by the FDA for atrial fibrillation.34 Other factor Xa inhibitors are under development.

The use of NOACs is a major stride towards stroke prevention in patients with AF with a prior TIA or stroke, who are at an increased risk of recurrent stroke. However, the safety and efficacy of these agents have not been determined for early strokes and TIsAs (less than 2 weeks old), as those patients were excluded from the randomized trials. Several of the trials, however, do provide evidence that the novel anticoagulants have a lower risk of intracranial bleeding compared to warfarin.

The NOACs have their own limitations, however. Compliance with these agents is essential as missing a single dose can lead to increased risk of thromboembolism. Also, there are no approved reversal agents available yet to administer to patients who experience bleeding, though research is advancing in this area. Trials also excluded patients with mechanical heart valves or hemodynamically significant mitral stenosis, so those patients should be managed with warfarin. Dabigatran was tested in patients with mechanical valves and was associated with an increased risk of stroke, systemic embolism, and bleeding, and is therefore contraindicated among patients with mechanical heart valves.35

Several of the agents, moreover, are renally excreted, necessitating dose adjustment in the setting of moderate to severe kidney disease. In endstage CKD ((CrCl < 15 mL/min), warfarin should still be used. Warfarin can be used among patients on hemodialysis, as well.36

Each of the approved NOACs, moreover, are substrates for the transporter p-glycoprotein. Thus inhibitors of p-glycoprotein may increase levels of these agents. Inhibitors include the antibiotics ketoconazole and clarithromycin, and the cardioactive medications verapamil, amiodarone, dronedarone, and quinidine. Inducers of p-glycoprotein, on the other hand, can decrease levels of the NOACs, and should be avoided; these include medications commonly prescribed by neurologists such as phenytoin and carbamazepine. Rivaroxaban and apixaban are considered contraindicated with medications that are combined P-glycoprotein and strong CYP3A4 inhibitors (ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan).

VIII. Alternatives to Anti-Coagulants

The vast majority of emboli in patients with AF appear to originate in the left atrial appendage, rather than the atrium itself. Some recent procedural alternatives to anticoagulants have recently been designed, therefore, to exclude the left atrial appendage (LAA) from the circulation, thereby obviating the need for anticoagulants. The WATCHMAN device, for example, is placed percutaneously into the LAA, effectively plugging it. Early trials provided evidence that this device was non-inferior to warfarin in preventing embolic stroke, though it was associated with a high rate (10%) of procedural complications, including pericardial injury.37 With further follow-up and improved operator experience, however, these complications have declined.38,39 The WATCHMAN device has not yet been approved, however. Another device, an epicardial snare called the LARIAT, involves cinching off the left atrial appendage using a purse string-like approach using a combined epicardial and intracardiac approach.40 While technical success has been reported in 97% of patients, the procedure can cause pericarditis and its efficacy in stroke prevention has not yet been defined. These approaches, and others under development, may offer alternatives to anticoagulation, particularly for patients who are unable to tolerate anticoagulants, including patients with amyloid angiopathy or clinical ICH.

IX. Special consideration

Concomitant antiplatelet use

Many patients with atrial fibrillation will also have coronary artery disease and atherosclerosis elsewhere, and thus may require concomitant antiplatelet therapy. The trials of NOACs included patients on antiplatelets. In each of RE-LY, ROCKET AF, and ARISTOTLE, 30-40% of patients were taking aspirin as well. Antiplatelets may generally be used along with the NOACs. There is evidence, however, that antiplatelets used together with anticoagulants increase the risk of hemorrhagic complications, particularly when more than one antiplatelet is used. In a Danish cohort study conducted using their national registry, for example, compared to warfarin alone, the combination of warfarin and clopidogrel was associated with a threefold increase in risk of hemorrhage and the combination of warfarin, clopidogrel, and aspirin was associated with nearly fourfold increase in bleeding risk (16% annually).41

The use of anticoagulants together with dual antiplatelet therapy may be required in particular after the insertion of a coronary stent, especially a drug eluting stent. A recent trial provides some evidence that clopiogrel can be used without aspirin in such patients without an increase in risk of ischemic events, but a decrease in risk
of bleeding complications. When antiplatelets are used with anticoagulants, it is reasonable to limit the number of agents, limit the duration of concomitant therapy, and to use the lowest efficacious dose, whenever possible.

Management of hemorrhagic complications in patients on anticoagulation

The management of patients who experience hemorrhagic complications while on anticoagulants will depend upon the agent being used and the location of the bleeding. For patients on warfarin, holding warfarin, using vitamin K, and the administration of factor complexes may be used. Specific therapies to counter the effects of the NOACs, however, are limited. Recombinant inactive factor Xa analogues that bind oral factor Xa inhibitors have been shown to reduce bleeding in animal models, and a monoclonal antibody against dabigatran that reduces its anticoagulant activity is under development. These antidotes are not currently available for clinical use, however. It is also notable that the mortality after major hemorrhage among patients taking warfarin was higher than among those on dabigatran in a secondary analysis of the RELY trial.

The most feared complication of anticoagulant use is intracerebral hemorrhage. Based on extrapolation from the limited data available from clinical trials of prothrombotic approaches to primary ICH, such as the factor 7a trials, it remains unclear that the use of prothrombotic agents immediately after ICH have an impact on clinical outcomes, though they may reduce rebleeding and hematoma expansion.

In the event of overdose or hemorrhage after recent ingestion of dabigatran (1-2 hrs), activated charcoal may be used to reduce absorption of dabigatran. Dabigatran may also be dialed. Activated charcoal may also be tried for rivaroxaban and apixaban. Because they are highly-protein bound, however, dialysis is not expected to be effective.

Procoagulant reversal agents such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (rFVIIa) may also be considered. Their effect may be greater for the factor Xa inhibitors than for the direct thrombin inhibitor dabigatran, however, which affects the final effector of the clotting cascade (thrombin). Further reliable data on clinical efficacy are needed.

Patients with history of ICH

The decision to anticoagulate patients with a history of intracerebral hemorrhage is difficult. Patients with lobar hemorrhages are often thought to harbor cerebral amyloid angiopathy that predispose to further life-threatening hemorrhages, particularly in the setting of use of anticoagulants. Decision analytic studies have suggested that patients with AF and a history of lobar hemorrhage in particular should not be anticoagulated. Prospective studies and randomized trials, however, have not fully resolved this issue.

Patients with microbleeds

Asymptomatic cerebral microbleeds are commonly encountered in population-based studies, particularly among the elderly, and may reflect another manifestation of cerebral amyloid angiopathy, putting patients at risk of hemorrhage. Some investigators have questioned whether the use of anticoagulants in patients with AF may provoke further microbleeds as well as clinical hemorrhages, thereby increasing the risk of dementia. Conclusive data on this point are lacking, however, and thus far it is not clear that anticoagulants should be withheld from patients with evidence of asymptomatic microbleeds.

Restarting anticoagulation after ICH

Anticoagulants may be restarted in some patients with a history of ICH. For example, anticoagulants may reasonably be restarted among patients whose ICH occurred while INR values were supratherapeutic while on warfarin, or when there is a specific precipitating cause of the hemorrhage, such as trauma or concomitant use of additional antithrombotic agents.

Bridging during interruption of therapy

Patients with AF on anticoagulation frequently require surgical or invasive procedures for one reason or another, and a common question to neurologists is whether anticoagulants should be continued or not at the time of the procedure. One approach is to recommend “bridging” therapy with a parenteral antithrombotic agent, such as unfractionated or low molecular weight heparin for several days prior to the procedure while the patient is off anticoagulants. Recent data from the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) national, community-based registry of patients with AF provide evidence that this common practice may be suboptimal. In ORBIT-AF, 30% of patients had an interruption of therapy during two years of follow up,
and of those one quarter were treated with bridging anticoagulants during this time. A prior stroke was more common in patients who underwent bridging. Of note, bleeding events were almost four times as common in patients undergoing bridging than not. While this was not surprising, perhaps, it was also found that patients undergoing bridging were twice as likely to experience a combined outcome of MI, stroke, systemic embolism, major bleeding, hospitalization, and death within 30 days (13 vs. 6%, p=0.0001). Randomized studies of whether to use bridging are ongoing.

References


