REVIEW ARTICLE

Stroke Prevention in Atrial Fibrillation

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Stroke and Systolic Embolism
Primary Care Physician
Novel Oral Anticoagulants

Background: Management of anticoagulation for atrial fibrillation is often the responsibility of the primary care physician. Knowledge of current literature and recent important clinical trials is essential to choose and monitor the best anticoagulation medication for your patient.

Methods: This paper reviews mechanisms of atrial fibrillation and patient characteristics which determine stroke risk, including use of the $CHADS_2$ and $CHADS_2$-VASc scores. We discuss recent large double blinded trials of new novel oral anticoagulants, and 2014 ACC/AHA Guidelines for Atrial Fibrillation.

Conclusion: With a better understanding of stroke risk and knowledge of evidenced based trials the primary care physician can manage anticoagulation for stroke prevention.

INTRODUCTION

Stroke as a complication of atrial fibrillation (AF) has long been acknowledged. Patients with AF have 4-5 fold increase in stroke than the patient without AF.[1] It is associated with approximately 75,000 strokes per year[1] and 16% of all ischemic strokes[2]. In a large outpatient cohort, the overall risk of stroke in the AF patient without prior stroke or transient ischemic attack, not on anticoagulation was found to be 2.5%[3]. The incidence is much higher in patients with a previous stroke or risk factors for a stroke such as Diabetes Mellitus.

Consequently, stroke prevention has become the standard of care. Warfarin, a vitamin K antagonist, has been used for the prevention and treatment of thromboembolic events associated with AF for more than 60 years. Four oral anticoagulants are now available for nonvalvular AF; dabigatran, rivaroxaban, apixaban, and edoxaban. They are similar in efficacy to warfarin for stroke prevention, have a reduced incidence of intracranial hemorrhage, and do not have dietary restrictions or require serial blood testing[4]. Anticoagulation for AF is often the responsibility of the primary care physician. Stroke prevention is considered conventional therapy and can be managed with knowledge of current recommendations.

AF has been evaluated by numerous studies. A review of AF and prevention of stroke is crucial for optimal patient care and safety. Additionally, updated AF guidelines were released by the AHA/ACC in March 2014. They highlight the new agents, recommend less use of aspirin for the low risk patient, and the use of AF catheter ablation for the symptomatic AF patient[5].

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BACKGROUND

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia affecting approximately 2.2 million Americans in 2010 and may exceed 12 million by 2050 according to the American Heart Association.[5] AF prevalence is 5.5% in patients age 55 to 59, and 17.8% in patients over the age of 85.[5] More than one third of all AF patients are over the age of 80.[5] AF is more common in individuals of European descent, and less common in African Americans.[6]

Intrinsic cardiac rhythm is controlled by the SA node. In AF, electrical impulses are initiated in other zones of the atria, most notably in the area of the pulmonary vein. Rapid firing and re-entry of these impulses prevents the SA node from gaining control. This chaotic firing prevents efficient filling and contraction of the heart. Stagnant blood, particularly in the left atrial appendage (a sock-like structure attached to the left atrium) contributes to thrombus formation and emboli, creating the risk for stroke. Some cardiologists believe that AF is also an independent risk of hypercoagulopathy.[7]

The risk of stroke varies with associated morbidities. Patient risk stratification is essential to choose the best stroke prevention for each patient.[8] The $CHADS_2$ and the newer $CHADS_2$-VASc scores have been used to predict stroke risk. The $CHADS_2$, (one point each for history of CHF, hypertension, age greater than 75, or diabetes, and 2 points for a previous stroke or TIA ***(Table 1))***

Table 1: $CHADS_2$ score for risk of stroke in patients with Atrial Fibrillation.

		Score
C	History of CHF	1
H	Hypertension (Treated or untreated)	1
A	Age >75	1
D	Diabetes Mellitus (controlled or uncontrolled)	1
S2	Prior Stroke or TIA	2
		6 maximum total

Table 2: Risk of stroke using $CHADS_2$ score

$CHADS_2$ score	Number of patients N= 1733	Number of strokes N=94	NRAF Crude Stroke Rate per 100 patient years	NRAF Adjusted stroke rate (95% CI)*
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.5-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

* The Adjusted stroke rate is the expected stroke rate per 100 patient years from the exponential survival model assuming aspirin was not taken.

has traditionally been used to predict stroke. ***(Table 2)*** 2014 AHA/ACC Guidelines recommend the updated $CHADS_2$-VASc score.[6] This score uses the traditional CHADS2 score and adds one additional point each for a history of coronary or vascular disease (V), age in the range of 65-74, or two for age 75 or greater (A), and female gender (Sc). ***(Tables 3)*** The $CHADS_2$-VASC may be more reliable in predicting those who are at very low risk for stroke and do not need anticoagulation, and more

Table 3: The $CHADS_2$-VASc score for stroke risk stratification of patients with Atrial Fibrillation and stroke rate.

	Risk Factor	Score
C	CHF/ LV dysfunction	1
H	Hypertension	1
A2	Age ≥ 75	2
D	Diabetes Mellitus	1
S2	Stroke/TIA/ Thromboembolism	2
V	Vascular Disease	1
A	Age 65 to 74	1
SC	Female sex	1
Total		9

accurately defines risk for older female patients who were likely underscored with the original $CHADS_2$ tool. ***(Table 4)***[9,10,11] For a $CHADS_2$-VASc score of 2 or greater, anticoagulation with warfarin or one of the newer oral anticoagulants is indicated, with a Class I indication.[6] For a patient with a CHADS2-VASc of 1, no anticoagulation therapy, aspirin or oral anticoagulation may be considered, with a Class IIb indication. For patients with AF and a CHA2DS2-VASc of 0, it is reasonable to omit anticoagulation.[6]

Table 4: Adjusted stroke risk according to the $CHA2DS_2$-VASc score.

$CHADS_2$-VASc score	Patients (n = 7329)	Adjusted stroke rate (percent/year)
0	1	0
1	422	1.3%
2	1230	2.2 %
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Therapy can be divided into two categories: antiplatelet therapy and anticoagulation therapy.

ANTIPLATELET AGENTS

Aspirin is an antiplatelet agent which interferes with prostaglandin synthesis. Specifically, aspirin irreversibly inhibits the enzymes cyclooxygenase 1 and 2 thus preventing the production of thromboxane A_2.[12] Thromboxane A2 induces platelet aggregation and vasoconstriction. It has been used for patients with a low risk of stroke. Older studies have supported the use of aspirin in patients with AF. In 1991, the Stroke Prevention in Atrial Fibrillation (SPAF) trial found that 325mg of aspirin used in patient with AF reduced the risk of primary ischemic stroke event by 42% when compared to the control group[13]. Some benefits of aspirin therapy as an early treatment for patients with AF have been confirmed; however, concerns of bleeding remain.[14] In a 2014 study published by the American Journal of Medicine, the authors suggest that practitioners may be overprescribing aspirin for stroke prevention when alternative therapies are more efficacious with fewer side effects.[15] The 2014 AHA/ACC AF Guidelines only recommend the use of aspirin in patients with a CHADS2-VA2Sc score of 1, and with the less robust IIb indication.[6]

Clopidogrel is also an antiplatelet agent. Clopidogrel is administered as a prodrug that is metabolized by the cytochrome P450 enzyme.[16] The active metabolite irreversibly prevents adenosine 5'-diphosphate from binding to the P2Y12 platelet receptor.[16] Activation of the cytochrome P450 system may affect the metabolism or clearance of other medications. It has been shown to be beneficial in stroke prevention in patients with Arteriosclerosis.[17]

Dipyridamole inhibits platelet adhesion by causing an accumulation of adenosine, adenine nucleotides and cyclic AMP through the inhibition of adenosine deaminase and phosphodiesterase.[18] Dipyridamole has been found to be efficacious as a monotherapy and in combination with aspirin for preventing secondary stroke in select cases.[19] Nonetheless, the literature does not support use in AF.

ANTICOAGULATION AGENTS

Warfarin works by binding to vitamin K epoxide reductase to inhibit vitamin K–dependent coagulation factors II, VII, IX, and X to prevent thrombus formation in AF.[20] It has been shown to significantly reduce the risk of stroke if the INR is maintained in the range of 2.0 to 3.0.[21] In case of emergency procedures or toxicity, Vitamin K (phytonadione) may be used to reverse the effects of warfarin.

Negative aspects of this drug include lifestyle modification to include monitoring to maintain an INR in the narrow therapeutic range between 2 and 3. Patients must avoid many foods and other drugs to minimize interactions. Such foods and drugs that are contraindicated with warfarin use include: kale, collards, spinach, broccoli, and many herbs and spices.[22] To achieve the proper therapeutic range to reduce stroke risk, regular blood tests are essential, and the dose of warfarin often

needs to be adjusted. Some studies have reported that only 15% of patients on warfarin for anticoagulation were in the therapeutic range.[23] In the recent Rocket AF trial of more than 14,000 patients, time in therapeutic range was 55%.[24] In the recent ARISTOTLE trial of more than 18,000 patients, time in therapeutic range was 66%.[25]

NOVEL ORAL ANTICOAGULATION DRUGS (NOAC)

New anticoagulants were approved by the FDA and recommended for use in stroke prevention in atrial fibrillation by the 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for antithrombotic therapy and prevention of thrombosis.[26] They are now included in the ACC/AHA Guidelines for AF. Novel Oral Anticoagulants (NOAC) do not have the same dietary restrictions, drug interactions and laboratory monitoring. The NOAC are now considered first line therapy (with a level of evidence B) for AF, alongside warfarin (with a level of evidence A).[6]

The first NOAC to be released was dabigatran, which is a direct thrombin inhibitor. It inhibits thrombus formation by preventing the conversion of fibrinogen to fibrin.[27] The next two NOAC to be released were apixaban and rivaroxaban. They are factor Xa inhibitors, which inhibit the conversion of prothrombin to thrombin, thus preventing the conversion of fibrinogen to fibrin. These medications offer the advantage of fixed dosing either once or twice daily. Currently there is no reversal treatment in the event of an emergent procedure. Hemodialysis reduces the plasma concentration of dabigatran, while rivaroxaban and apixaban cannot be eliminated by dialysis.[28] Many hospitals have developed reversal guidelines for the management of bleeding, using activated prothrombin complexes and coagulation factors.

Dabigatran was the first NOAC to be approved by the FDA for stroke prevention with patients with AF. The Randomized Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY) studied patients over 65 with atrial fibrillation. Dabigatran given at a dose of 110mg twice daily was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, with lower rates of major hemorrhage.[29] Dabigatran administered at a dose of 150 mg twice daily, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. The 110mg dosing is not available in the US. There is a 75mg twice daily dose available for patients with renal impairment and a creatinine clearance of 30 mL/min. Economic analysis reveals that dabigatran is cost effective when considering the cost of INR monitoring.[30]

Rivaroxaban was the first factor Xa inhibitor on the market and has been FDA approved for stroke prevention in patients with AF. The ROCKET AF trial compared rivaroxaban (20mg/day; 15mg/day in patients with creatinine clearance 30-49ml/min) with dose-adjusted warfarin (international normalized ratio 2-3) in 14,264 patients with AF and a prior history of stroke or at least two other additional risk factors for stroke. The ROCKET AF trial demonstrated the noninferiority of rivaroxaban compared with warfarin for the prevention of stroke and systemic embolism, with a similar rate of major bleeding and a reduction in intracranial hemorrhage.[31] There is a dose adjustment for patient with renal impairment but it is not recommended in liver impairment (a Child–Pugh class of B or C). Economic analysis has stated that it is cost effective for use over warfarin.[32]

Apixaban is the second factor Xa inhibitor that has been FDA approved. The recommended dosage is 5mg twice daily. A reduced dose of 2.5mg twice daily is recommended in patients with two or more of the following: age 80 years or older, body weight 60kg or less, and a serum Cr level of 1.5mg/dL or higher.[33] In the ARISTOTLE trial, apixaban was compared to warfarin in 18,201 patients with AF and ≥ 1 additional risk factor for stroke. Apixaban reduced the risk of stroke or systemic embolism by 21% compared with warfarin (1.27% vs 1.60% per year; hazard ratio, 0.79; 95% confidence interval, 0.66-0.95). Apixaban also reduced major bleeding by 31% ($P < 0.001$) compared with warfarin. Additionally in the AVERROES trial, apixaban was more effective than aspirin for stroke prevention and had a similar rate of major bleeding.[34]

Edoxaban is the newest direct oral factor Xa inhibitor which has now been approved for stroke preventions in non-vascular AF. In the Engage AF-TIMI[48] trial Edoxaban was found to be "non-inferior" to warfarin in stroke prevention in atrial fibrillation. It was also associated with a lower risk of bleed and death from cardiovascular events.[35]

CONCLUSION

By the year 2050 5.6 million patients will have AF.[36] Many of these patients will be treated by the primary care physician. Consequently, knowledge of stroke prevention is paramount in their care. Warfarin is beneficial for stroke prevention and the NOAC should be considered first line for stroke prevention according to some authors.[37] These newer agents have a rapid onset of action, predictable pharmacokinetics, and no need for routine monitoring.[36] The NOAC have higher acquisition costs; however, the benefit of cost savings may be derived from the potential for decreasing the incidence of hemorrhagic stroke, intracranial bleeding and reducing the need for anticoagulation monitoring.[36] A recent systematic review of 27 studies demonstrated that these agents are cost effective in stroke prevention. It is difficult to recommend one NOAC over the other, as the studies were not similar in design, including patient characteristics and end points. A pubmed search revealed only studies comparing each agent to warfarin and not each other. A meta-analysis showed shows that the overall net clinical benefit of the NOA versus warfarin is favorable.[39] Additional studies with head to head comparison of NOAC, using the CHADS2-VASC score, may be helpful. Both physicians and industry look forward to a reliable antidote for the NOAV. An understanding of these agents and trials will help the primary care physician manage anticoagulation.

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REVIEW ARTICLE

Blood Component Therapy

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KEYWORDS:

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Given the frequency of inpatient transfusion and the possibility that delayed reactions may be noted during outpatient follow up, an update in blood component therapy is worthwhile. Noninfectious complications are far more frequent than infectious complications and require heightened clinician awareness to ensure recognition and provision of appropriate supportive care. Transfusion Associated Circulatory Overload, a preventable consequence of transfusion, is particularly common and may be preemptively managed in selected patients. Risks associated with transfusion therapy can be reduced through application of patient blood management strategies. In this context, a working understanding of the modern literature surrounding the primary blood components is valuable. Evidence-based transfusion guidelines for RBCs, platelets, plasma and cryoprecipitate optimize patient care and improve patient outcome. This review focuses on utilization of blood components and selected alternatives as well as pretransfusion testing.

INTRODUCTION

Transfusions are a frequent occurrence among hospitalized patients. Roubinian and colleagues, in a retrospective cohort study of hospitalized, non-obstetric adult patients, found that among 444,969 hospitalizations involving 275,874 patients, RBC transfusions occurred in 32,493 (11.8%) patients and during 61,988 (13.9%) of hospitalizations[1]. Compared to the non-transfused group, those receiving transfusions had lower admission hemoglobin values (9.9 g/dLvs 12.9 g/dL) and were more commonly admitted for gastrointestinal bleeding and orthopedic surgery.

New developments in the literature and establishment of the patient blood management movement have consistently driven transfusion thresholds for stable patients to lower and more restrictive levels. Anemic patients may benefit from perioperative anemia management to reduce the risk of intraoperative transfusion. Alternatives to transfusion, particularly as plasma alternatives, are gaining attention. Transfusion laboratory tests may be confusing to choose from, and will be addressed in this review. Complications of transfusion may be delayed and detected only during an outpatient hospital follow-up visit. This article will review recent developments in the literature, touch upon utilization of the transfusion services laboratory, and discuss utilization of blood components and selected alternatives.

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DONOR SCREENING

Transmission of blood-borne pathogens is prevented through application of a multi-layered process of donor screening. Unless labeled otherwise[2] blood components are collected from non-remunerated, volunteer donors. At the time of donation, prospective donors are asked to read an established set of donor education materials[3] that review the signs and symptoms of HIV, risk factors for acquiring blood-borne pathogens, definitions of what constitutes sexual contact, and medications and vaccines that constitute deferral criteria. This material educates donors as to risk factors they will be questioned about on the required, 48-item Donor History Questionnaire (DHQ)[4]. This questionnaire screens for high-risk behaviors and other factors that heighten risk, collects donor demographic and contact information, and provides an informed consent area that must be read and signed. Donors qualifying by DHQ, vital signs, minimal weight (50 kg) and hemoglobin (12.5 g/dL) requirements then proceed to donation.

Phlebotomists visually inspect the arms for evidence of track marks or lesions suspicious for Kaposi's Sarcoma and the skin is meticulously prepared prior to phlebotomy using either Povidone-Iodine or Chlorhexidine solutions.

Additional prevention is obtained through the use of modern collection kits incorporating a diversion pouch that prevents the first few mL of blood collected from entering the primary collection bag. This reduces the risk of bacterial contamination resulting from entrainment of residual skin bacteria. Specimens for testing are drawn from this diversion pouch and sent for routine testing ***(Table 1)***. Platelets, owing to the requirement for room-temperature storage, are additionally