Stoke Prevention in Atrial Fibrillation

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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 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 reduced incidence of intracranial hemorrhage, and do not have dietary restrictions or require regular blood testing.4

Acitondecogulation 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 patient5.

KEYWORDS:
- Stroke and Systolic Embolism
- Primary Care Physician
- Novel Oral Anticoagulants

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.6 AF prevalence is 5.5% in patients age 55 to 59, and 17.8% in patients over the age of 85.7 More than one third of all AF patients are over the age of 80.8 AF is now common in individuals of European descent, and less common in African Americans.9

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 prevent 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.10

The risk of stroke varies with associated morbidities. Patient risk stratification is essential to choose the best stroke prevention for each patient.11 The CHADS2, and the newer CHA2DS2-VASc scores have been used to predict stroke risk. The CHADS2 (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)) score accurately defines risk for older female patients who were likely underscored with the original CHADS2 tool. (Table 4) For a CHADS2-VASc score of 2 or greater, anticoagulation with warfarin or one of the newer oral anticoagulants is indicated, with a Class I indication.12 For a patient with a CHADS2-VASc score 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.13

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 A2.14 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 group15. Some benefits of aspirin therapy as an early treatment for patients with AF have been confirmed; however, concerns of bleeding remain.16 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.17 The 2014 AHA/ACC AF Guidelines only recommend the use of aspirin in patients with a CHA2DS2-VASc score of 1, and with the less robust IIB indication.18

Clupidogrel is also an antiplatelet agent. Clogiprodogel is administered as a produg that is metabolized by the cytochrome P450 enzyme.19 The active metabolite irreversibly prevents adenosine 5'-diphosphate from binding to the P2Y12 platelet receptor. 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.20

Dipiridamole inhibits platelet adhesion by causing an accumulation of adenosine, adenine nucleotides and cyclic AMP through the inhibition of adenosine deaminase and phosphodiesterase.21 Dipiridamole has been found to be efficacious as a monotherapy and in combination with aspirin for preventing secondary stroke in select cases.22 Nonetheless, the literature does not support use in AF.

ANTICOAGULATION AGENTS

Warfarin works by binding to vitamin K epoxide reducetase to inhibit vitamin K–dependent coagulation factors II, VII, IX, and X to prevent thrombus formation in AF.23 It has been shown to significantly reduce the risk of stroke if the INR is maintained in the range of 2.0 to 3.0.24 In case of emergency procedures, 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, collard greens, broccoli, and many herbs and spices. To achieve the proper therapeutic range to reduce stroke risk, regular blood tests are essential, and the dose of warfarin often

Table 1: CHADS2 scores for risk of stroke in patients with Atrial Fibrillation.

Table 2: Risk of stroke using CHADS2 score.

Table 3: The CHADS2-VASc score for stroke risk stratification of patients with Atrial Fibrillation and stroke rate.

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New anticoagulants were approved by the FDA and recommended for use in the stroke prevention trial published by the 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for antithrombotic therapy and prevention of thrombosis. They are now included in the ACC/AHA Guidelines for 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).

The first NOAC to be released was dabigatran, which is a direct thrombin inhibitor. It inhibits thrombin formation by preventing the conversion of fibrinogen to fibrin. 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.

Many hospitals have developed reversal guidelines for the management of bleeding, using activated prothrombin complexes and coagulation factors.

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Blood Component Therapy

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\textbf{KEYWORDS:}

Red Blood Cells
Platelets
Plasma
Cryoprecipitate
Transfusion

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.

\textbf{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\textsuperscript{1}. Compared to the non-transfused group, those receiving transfusions had lower admission hemoglobin values (9.9 g/dL vs 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.

\textbf{DONOR SCREENING}

Transmission of blood-borne pathogens is prevented through application of a multi-layered process of donor screening. Unless labeled otherwise\textsuperscript{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\textsuperscript{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)\textsuperscript{2}. 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 Kapossi’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 entainment of residual skin bacteria. Specimens for testing are drawn from this diversion pouch and sent for routine testing (Table 1).

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\caption{Blood Component Therapy}
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