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# Atrial Fibrillation: an Emerging Epidemic

**ATRIAL FIBRILLATION (AF)** is the most common cardiac arrhythmia in the United States (US) and is one of our most challenging health conditions. AF affects between 0.4% and 1% of the general population and prevalence increases dramatically as the population ages.[1-4] It is estimated that 1% of adults <60 years of age and up to 12% of adults between the ages of 75-84 have AF. In 2030, there will be about 72.1 million persons over the age 65, representing 19% of the US population.[5]

The American Heart Association estimated that in 2010 there were ≈2.7 million to 6.1 million cases of AF. The incidence of AF is expected to increase by between ≈5.6 and 12 million by 2050.[6]

AF is strongly associated with age, gender, race and the presence of cardiovascular disease. In the Medicare population, numerous chronic conditions are associated with the incidence of AF. These include hypertension, obesity, diabetes, chronic kidney disease, hyperlipidemia, heart failure, valvular heart disease, chronic obstructive pulmonary disease, and Type 2 Diabetes.[1,2,4]

Atrial Fibrillation carries a high economic and personal burden to individuals and to society. AF increases the risk of ischemic stroke by five-fold.[4,7] Persons with AF, especially older individuals are at higher risk for hospitalizations, thromboembolic events, heart failure, dementia and higher mortality than those in sinus rhythm.[4]

Strokes caused by AF are generally more severe, more disabling, and more-frequently fatal than strokes in persons with normal sinus rhythm.[4,8] A systematic review of the economic cost of atrial fibrillation by Wolowacz and colleagues revealed that direct cost ranged from $2,000 to $14,200 per patient year in the United States. Inpatient care was estimated at 40-50% of the annual direct cost of care with total hospitalization cost estimated at $6.65 Billion. The cost for AF is projected to rise substantially with the increasing older population.[9]

Preventing the development of atrial fibrillation is a major challenge. Although many "predisposing factors" are associated with new onset atrial fibrillation, it is estimated that between 3-11% will develop AF without identifiable predisposing factors.[10] Advancing age is the most reliable predictor for the development of AF. Research efforts focusing on preventing AF are clearly needed.

In 2004, Harwell et al. evaluated perceived risk for stroke and knowledge of stroke risk factors in adults over the age of 45 years. They found that < 40% perceived themselves to be at risk with < 50% of those with greater than 3 stroke risk factors perceiving themselves to be at risk.[11] Zerwic et al., in 2007, evaluated how individuals interpreted symptoms for stroke and how this may be related to the delay in seeking treatment. They found that only 60.5% could accurately identify at least one stroke risk factor and only 55.3 % were able to identify one stroke symptom.[12] An important lesson from their study was that inability to recognize non-motor stroke symptoms and not accessing 911 emergency care resulted in a delay to seeking treatment of > 2 hours. This delay represents a greater risk of not receiving life and brain saving therapies and interventions. Language barriers also play a role in lack of knowledge regarding stroke symptoms.[5,13]

## NURSES AND ADVANCED PRACTICE NURSES – A CALL TO ACTION

AF is a common clinical problem with significant morbidity and mortality. Health care providers are being asked to define new ways to positively impact the health outcomes from AF. Get With The Guidelines-AFIB (GWTG AFIB) is a national hospital-based AF quality improvement program. It is designed to increase adherence to evidence-based guidelines for AF and is published by the American Heart Association/American College of Cardiology. This important hospital based quality improvement program will focus on health care provider initiation of guideline recommended optimal therapies. Patient education and patient support is the foundation GWTG AFIB. Nursing will play a critical role in this important healthcare initiative.[14]

The AHA/ACC and the Heart Rhythm Society, and in collaboration with the Society of Thoracic Surgeons, jointly published the most comprehensive evidence based guideline to date on AF, superseding the 2006 document.[14] This 2014 Guideline is based on science from published studies as well as other related guidelines and statements many from national and international professional societies. The authors stated in their introduction: "Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles. In addition, patients should be informed of the risks, benefits, and alternatives to a particular treatment and should be involved in shared decision making whenever feasible."[15] This is another call to action for nursing as our roles include the initiation of recommended therapies supported by comprehensive patient centered education.

Given the enormous impact of AF on individuals and on society, the World Heart

Federation (WHF) created the Global AF Action (GAFA) campaign. This international campaign is designed improve the diagnosis and immediate care of patients with AF. This campaign includes educational materials for the public and for primary care providers and can be accessed at: http://www.world-heart-federation.org/what-we-do/awareness/atrial-fibrillation/tools-materials/toolkit-for-members.

October 29, 2013 was World Stroke Day. The "*Sign Against Stroke in Atrial Fibrillation*" supported the Global AF Action campaign. By the 29th of October, more than 500,000 individuals had signed onto the campaign calling for improved education to raise awareness of the signs of AF, earlier diagnosis of AF, and improved access to appropriate AF care. International efforts that will increase awareness of AF calls for increased efforts by nurses to initiate guideline based treatments and provide education for patients and their families regarding the prevention and management of AF. Given the identification and treatment complexities associated with AF, education is a critical component of patient care.

In support of the need for educational materials, the Preventive Cardiovascular Nurses Association developed a patient booklet for health care providers to use when counseling their patients with atrial fibrillation. This booklet is literacy appropriate and includes information about what AF is, why it is a problem, usual tests to expect with AF, types of AF, and what patients with AF can do to continue living a full life. Copies of the AF booklet, *The Beat Goes On*, are available free of charge at PCNA.net.

Hendriks and colleagues evaluated a nurse based, guideline adherent, chronic care program (ICCP). They followed 111 patients assigned to the ICCP group compared to an historical control group and concluded that "a nurse-driven, guideline based ICCP program for AF patients was feasible." Their results showed that the average number of patients who were treated based on guideline recommendations was 96% in the ICCP group compared to 70% in the control group ($p<0.001$). Hendriks and colleagues followed their initial evaluation with a larger study of 712 patients with AF who were randomly assigned to nurse-led care (ICCP) versus usual care. They found a significant reduction in hospitalizations and cardiovascular mortality in the nurse-led program versus usual care. In addition, they found that guideline adherence was also significantly better within the nurse-led ICCP program.[16,17] These results support the critical role of nursing in the management of AF. It is our job to work with our medical colleagues to incorporate guideline-based evaluation and care for all persons at risk for and with AF.

The goal of this special issue of the *Journal of Cardiovascular Nursing* is to provide you with a detailed summary of "*Evidence-Based Care for the Patient with Atrial Fibrillation: A Call to Action for Nurses and Advanced Practice Nurses.*" ■

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# Pathophysiology of Atrial Fibrillation

## PATHOGENESIS OF ATRIAL FIBRILLATION

Atrial fibrillation (AF), the most common chronic arrhythmia, affects 3-5 million Americans;[1-5] causes are unknown and there are no curative therapies. Thus the main goals of treatment are palliative to improve quality of life and relieve symptoms.[1-4] The arrhythmia is characterized by chaotic, electrical conduction in the atria. Although considerable progress in identifying underling mechanisms has occurred over the last ten years, the underlying cause of AF remains unknown. The main three hypotheses of underlying pathogenesis of AF are discussed below.

**Multiple random propagating wavelets.** The multiple wavelet theory hypothesizes that AF is caused by simultaneously occurring wavelets throughout the left and right atria which propagate randomly across both atria (also referred to as "mother waves" that spawn daughter waves).[5-7] Propagation requires a minimum number of wavelets to sustain AF which require areas of diseased atrial tissue with conduction delays and blocks including: areas of slowed conduction, shortened refractory periods, and increased atrial mass (such as large left atrial size). This hypothesis of the etiology of AF, based on Gordon Moe's early work,[8] served as the theoretical basis for development of the MAZE surgical procedure and achieved widespread acceptance up until the mid-1980s.[9] Recent findings suggest that although randomly occurring wavelets occur which help to maintain AF, there are not random areas of initiation of these wavelets.[10] There are specific areas in the atria with shorter cycle lengths (left atrium more than the right, specifically the posterior free wall of the left atrium) where the wavelets of AF are more likely to begin.[11]

**Focal electrical discharges.** The landmark breakthrough reported by Haissaguerre and colleagues[12,13] was the recognition of focal triggers at the base of the pulmonary veins, near the superior vena cava, and the posterior wall of the left atrium that could fire rapidly to initiate episodes of AF. These findings led to the theory of "focal AF" to include triggers as both a source of initiation of AF and a substrate to perpetuate the arrhythmia. Myocardial muscle tissue, a "myocardial sleeve", has been reported to extend from the left atrium into the pulmonary veins for up to 3 cm inside the veins.[6,14] These triggers, found inside and around the orifices of the pulmonary veins, are now widely accepted to be an important source of initiation of AF, and when firing rapidly, may also serve to drive or maintain the arrhythmia.[2,5,12,13] Techniques were designed in the 1990s to map and ablate specific areas of these pulmonary vein triggers to eliminate AF with mixed results.[2,5,13] These findings offer an explanation as to why AF ablation strategies currently include applying energy to multiple areas of the left atrium thereby increasing the chances of success.[5]

**Localized reentrant activity with fibrillatory conduction.** As discussed earlier, there are areas of the left atrium (especially around the pulmonary veins and posterior wall) where atrial cells have shorter cycle lengths and variable conduction between cells, which could support reentry as a way to maintain the arrhythmia once initiated.[11] Atrial remodeling, or the hypothesis of 'AF begetting AF' was first demonstrated by Allesie et al.[15] Over time with repeated episodes of AF, the atrial cells remodel electrophysiologically, meaning that cell-to-cell conduction changes in a way that actually promotes sustained AF. Remodeling also promotes the activity of triggers which further sustains the arrhythmia.[15] The presence of fibrotic changes seen with heart disease and rapid heart rates during AF over time can cause further cellular remodeling to sustain AF.[16] Although the mechanisms for why this occurs is not completely understood, these findings help explain the trajectory of AF that initially starts with short, infrequent episodes that gradually develop into permanent AF over time.

**Other causative mechanisms.** Other factors potentially involved in the initiation or maintenance of AF include inflammation, atrial ischemia, autonomic nervous system activity, atrial dilation, and structural fibrosis associated with aging.[2,3] Researchers have reported that stretch of atrial myocardial fibers from increased atrial pressure could also lead to cell to cell conduction irregularities predisposing one to rapid reentrant rhythms such as AF.[2,5,17] Increased left atrial pressure, as seen with hypertension and some valvular diseases, have been hypothesized to provide a substrate for AF, but the causal link is not clear. These findings could explain the high incidence of AF seen in hypertension, but does not make clear why all patients with hypertension do not develop AF. There are also strong associations between AF, sleep apnea, and hypertension, although the mechanisms for this currently remain unclear.[18] A specific type of AF has been reported in endurance athletes with low resting heart rates and has been hypothesized to be due to increased vagal tone, changes in electrolytes, or bradycardia; however the exact mechanism is unknown.[2,5]

Genetic forms of AF have been appreci-

ated for many years, but the incidence of this subtype of AF is rare.[2] Over the past decade, population-based studies have suggested that AF is a heritable disease.[19,20] Researchers have uncovered common genetic variants that denote increased susceptibility to the arrhythmia.[20,21] The identification of the genetic substrate underlying familial AF will hopefully lead to the development of new therapies in the future that will help diagnose and treat all types of AF.

## RISK FACTORS

**Impact of Age.** The estimated prevalence of AF in the general population is 0.1% to 1%, increasing with age.[2,22,23] By 2030, it is estimated that the number of Americans 65 years of age and older will double.[24] Because of the aging of the population and the increasing prevalence of obesity and other risk factors for AF, the upcoming decade has been described as an "epidemic of AF", emphasizing the importance of AF as a present and future healthcare burden. Miyasaka et al. estimated the number of persons with AF to increase three-fold over the next 38 years, from 5.1 million in 2000 to epidemic proportions of 15.9 million in 2050.[1] Those researchers suggest that 65% of the increase is due to the increased proportion of elderly patients as the population ages over the coming years. The reported increase in incidence with older patients was similar to that reported from the Framingham study.[1,22,23,25] Approximately 12-30% of AF has been reported to occur in athletes and younger individuals as "lone AF".[2,26] These patients typically have few comorbidities, yet are usually very symptomatic upon presentation.

There is a significantly higher prevalence of AF in men than women in all age categories (1.1% in men, 0.8% in women, $p<0.001$).[22] Researchers from the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study (N=17,974) reported that African Americans and Latinos were less likely diagnosed with AF when compared with Whites with rates of 3.6%, 2.5%, and 84.7%, respectively; however the mechanisms behind these racial differences is not known.[2,3,22-24] Others have supported the finding of a lower prevalence of AF in African Americans, Hispanics, and Asians compared to Whites.[27]

**Comorbidities.** It is well known that there are numerous risk factors that pre-dispose patients to AF, such as hypertension, increasing age, ischemic heart disease, heart failure, valvular heart disease, obesity, and diabetes.[2,3,25] Huxley et al[28] reported that modifiable cardiovascular risk factors cause more than half of AF cases, implying that not only will the incidence of AF rise with the increasing prevalence of these risk factors; but it may be an opportunity in the future to prevent AF by focusing on reduction of these modifiable risk factors. The AHA's strategic plan emphasizes a focus on "Life's Simple Seven," stressing modification of lifestyle and health risk factors, including blood pressure, weight, glucose, cholesterol, smoking, diet, and physical activity.[3,29]

## TABLE. Types of Atrial Fibrillation

| | |
|---|---|
| First diagnosed AF | The new classification developed by the ACC/AHA/ESC 2006 Guideline committee and the 2010 ESC Guidelines committee suggests that each patient who presents with AF for the first time should be labeled as "first diagnosed AF", regardless of the duration or frequency of the episodes.[2,5] |
| Paroxysmal | Atrial fibrillation that is recurrent in nature (≥ 2 episodes) and that terminates spontaneously within 7 days is defined as paroxysmal AF.[2,5] |
| Persistent | Recurrent AF that is sustained for ≥ 7 days is defined as persistent.[2,5] |
| Longstanding persistent | Continuous AF of greater than one year's duration is defined as longstanding persistent.[2,5] |
| Permanent | Continuous AF where the presence of AF is accepted by the patient and provider as permanent. This definition represents a joint decision by both patient and physician to cease attempts at restoration or maintenance of sinus rhythm. If symptoms or clinical situation changes and the patient wishes to pursue catheter or surgical ablation treatment, the definition of "permanent AF" should be changed to one of the other classifications of AF.[2,5] |
| Asymptomatic AF | Asymptomatic, or silent, AF is defined as AF without symptoms. Asymptomatic AF is typically diagnosed on routine ECG.[2,5] |

## CLASSIFICATION SCHEMES

**New definition of Types of AF.** The recently published HRS/EHRA/ECAS guideline[2,5] attempts to standardize our definitions of AF for reports on future clinical and research comparisons. The new definitions have updated the previous way of classifying AF, known as the 3 'P's of AF' as described below in the table. Patients' disease should be classified by the latest pattern of AF during a period of six months prior to presentation to their provider.[2,5] Also recommended is that providers record the patient's perspective of the average duration and frequency of the episodes, how long patients have experienced symptoms of AF, and any drugs the patient may have previously been prescribed to manage the AF.[2,5] ■

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PREVENTIVE CARDIOVASCULAR NURSES ASSOCIATION

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# Clinical Management of the Patient with Atrial Fibrillation

## ACUTE TREATMENT

The acute management of atrial fibrillation (AF) can be challenging and complex. AF is often associated with other conditions such as myocardial ischemia or pneumonia which result in more difficult rate control and concomitant hemodynamic difficulty. The patient's volume status can be difficult to assess. Patients may present with dehydration due to elevated levels of atrial natriuretic peptide or volume overload in heart failure.

Additionally, in the acute setting, AF can be very rapid and often appear regular. Careful examination of the electrocardiography (ECG) is important to differentiate AF from other supraventricular arrhythmias. The initial assessment of the patient is important in determining the course of therapy.

Identification of the possible cause/trigger of acute AF is important to the management. One of the more common clinical settings for acute onset AF is the post coronary bypass recovery period. After coronary revascularization, the incidence of AF is about 19%.[1] This risk peaks between post-operative days 2 to 5. Other acute causes of AF include the infusion of catecholamines or other stimulants such as cocaine. Excessive ethanol ingestion also can result in acute onset AF. Changes in atrial pressure can acutely induce AF. Patients with pneumonia or pulmonary embolism can present with AF. Because of the elevated sympathetic tone seen with these conditions, AF may be difficult to control. Additionally, beta blockers may be difficult to give to patients with lung disease who are actively wheezing. Chronic elevations in atrial pressure can also induce AF. Patients with obstructive sleep apnea, chronic obstructive pulmonary disease, hypertension, heart failure, acute myocardial infarction or valvular heart disease can present with AF. Patients with mitral stenosis depend on atrial systole and longer ventricular filling times to maintain stroke volume. Thus, treatment of AF in patients with mitral stenosis can be an emergency. Thyrotoxicosis can cause rapid AF that may be difficult to control. Beta blockers are the treatment of choice; digoxin may be ineffective in this situation.

When a patient presents with AF, rate control should be the first line of therapy. Controlling the rate will improve stroke volume by increasing the diastolic filling time. Additionally, rate control will aid in controlling ischemia and heart failure symptoms. The mainstays for initial heart rate control include diltiazem and beta blockers. Esmolol is a short acting beta blocker that has been used in acute AF management. The initial bolus is 0.5 mg/kg intravenously followed by 0.05 mg/kg which can be titrated up to 0.2 mg/kg with additional boluses.[2] Diltiazem has also been used for acute intravenous control of AF. The initial bolus is 0.25 mg/kg intravenously with a maintenance infusion of 5 mg/hr. which can be titrated up to 20 mg/hr.[2] The choice of the drug should be based on the concomitant clinical conditions. For example, beta blockers should be avoided in patients with acute asthma. These same drugs, however, would be appropriate in the setting of myocardial ischemia. In a study comparing diltiazem and esmolol in patients with AF after coronary artery bypass surgery, diltiazem was more effective at achieving rate control within 12 hours; conversely, esmolol was associated with successful conversion to sinus rhythm compared to dilitazem.[3] Digoxin and amiodarone can be used in patients with heart failure. In settings of high sympathetic tone, digoxin may not be very effective in controlling heart rate. It should be noted that when administered intravenously, amiodarone can result in hypotension. (*Refer to Table 1*).

In some circumstances, conversion to sinus rhythm may be the best way to achieve rate control. Patients with ischemia or significant hemodynamic consequences of AF may be candidates for cardioversion. In general, direct current cardioversion is safe in patients who have been NPO for eight hours if the duration of their AF is less than 48 hours. Beyond this, in patients with severe ischemia or hemodynamic compromise, the risks of both anesthesia and thromboembolism must be considered. Chemical cardioversion can be considered in patients where anesthesia is either unavailable or unsafe. Ibutilide, a Class III antiarrhythmic, is the most commonly used agent for pharmacological conversion of AF. Ibutilide is a potassium channel blocker, prolongs the action potential and increases atrial refractoriness resulting in restoration of sinus rhythm. Potassium channel blockers also are associated with torsades de pointes. In one study, ibutilide was significantly more effective in converting patients with AF or flutter to normal sinus rhythm when compared to procainamide.[4] The dose of ibutilide is 1 mg intravenously over ten minutes, and may be repeated. The QT interval should be monitored during and after this infusion.

In patients whose AF duration is greater than 48 hours, anticoagulation with heparin and subsequently with an oral anticoagulant should be considered, regardless of the method of conversion. The patient should receive anticoagulation for 3 consecutive weeks prior to attempted cardioversion with a target INR of 2.0-3.0 (if warfarin is used). Anticoagulation should be maintained for 4 weeks post successful cardioversion.[5]

**TABLE 1. Drug Therapy for HR Control in AF: Acute Management**

| Drug | Loading Dose | Onset | Maintenance Dose | Major Adverse Effects |
|---|---|---|---|---|
| PATIENTS WITHOUT ACCESSORY PATHWAY | | | | |
| Esmolol | 500 µg/kg IV over 1 min | 5 min | 60-200 µg/kg/min IV | ↓BP, HB, ↓HR, asthma, HF |
| Metoprolol | 2.5-5 mg IV bolus over 2 min; up to 3 doses | 5 min | NA | ↓BP, HB, ↓HR, asthma, HF |
| Diltiazem | 0.25 mg/kg IV over 2 min | 2-7 min | 5-15 mg/h IV | ↓BP, HB, HF |
| Verapamil | 0.075-0.15 mg/kg IV over 2 min | 3-5 min | NA | ↓BP, HB, HF |
| PATIENTS WITH ACCESSORY PATHWAY | | | | |
| Amiodarone | 150 mg over 10 min | Days | 0.5-1 mg/min IV | ↓BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia |
| PATIENTS WITH HEART FAILURE AND WITHOUT ACCESSORY PATHWAY | | | | |
| Digoxin | 0.25 mg IV q2 h, to 1.5 mg | ≥60 min | 0.125-0.375 mg/d IV or po | Digitalis toxicity, HB, ↓HR |
| Amiodarone | Dosing, onset, and major adverse effects as above | | | |

BP=blood pressure; HB=heart block; HR heart rate; HF=heart failure
Source: American Heart Association, Inc.

Because AF shortens the atrial refractory period, recurrence of the arrhythmia is common after conversion to sinus rhythm. Thus, treatment with antiarrhythmic drugs may be needed to maintain sinus rhythm after acute cardioversion.

## CHRONIC MANAGEMENT

### Factors involved in clinical recommendations

The basic principles of therapy for patients with AF include:

1. risk stratification and prevention of thromboembolic complications of stroke (discussed in detail in an accompanying article by Parra and Long)
2. ventricular rate control, if expedient restoration and maintenance of sinus rhythm is not contemplated
3. pharmacologic or electrical restoration and maintenance of sinus rhythm
4. choice of an appropriate long-term rhythm control strategy and identification of AF amenable to ablation
5. identification and correction of risk factors and eradication of precipitating agents
6. treatment of underlying pathology.[6]

Medical therapy remains the mainstay for treatment for the majority of patients with AF. The optimal management strategy for the individual AF patient is contingent on the underlying condition. The presence or absence of structural heart disease (SHD) will influence both the approach to patient management (rate vs. rhythm control) and the treatment options available. Rate control refers to control of the ventricular rate during AF without an attempt to restore sinus rhythm. Rhythm control refers to restoring and maintaining sinus rhythm. Upstream therapies refer to drug therapy that helps to maintain sinus rhythm but are not considered antiarrhythmic.[7]

Several basic tenets should be considered when selecting a management strategy. They include the following:[8]

- no patient wants to be in AF
- a stable rhythm is largely better than an unstable rhythm
- new onset AF is a high-risk period
- development of AF generally indicates a worse prognosis than most serious diseases
- stroke risk must be addressed
- safety should determine the initial antiarrhythmic drugs (AAD) selected for rhythm control
- therapy for underlying conditions should be optimal and guideline based.

To facilitate clinical decisions regarding management of patients with AF, the American College of Cardiology (ACC), the American Heart Association (AHA) and the European Society of Cardiology (ESC) developed joint guidelines for optimal pharmacologic and interventional approach to AF in 2006.[2] The ACC/AHA and the Heart Rhythm Society (HRS) published a 2011 focused guideline update at the end of 2010,[9] and a second update in 2014[10]. As outlined in the guidelines, the rate control strategy emphasizes the utilization of medications to control the ventricular rate with no attempt to achieve rhythm control. The rhythm control strategy focuses on restoration and maintenance of sinus rhythm through AAD therapy. These approaches are based on data from randomized clinical trials.

The major clinical trials to evaluate rate vs. rhythm control include the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)[11], the Rate Control Versus Electrical Cardioversion (RACE) Trial[12], RACE II[13], and the Atrial Fibrillation Congestive Heart Failure (AF-CHF) trials.[14] Other studies which focused on this issue include the Pharmacological Intervention in Atrial Fibrillation (PIAF)[15], Strategies of Treatment of Atrial Fibrillation (STAF)[16], and How to Treat Chronic Atrial Fibrillation (HOT CAFÉ)[17].

The AFFIRM study[11], which evaluated mortality benefit of different strategies in AF, included 4060 AF patients ≥ 65 years of age with at least one risk factor for stroke. The mean follow-up was 3.5 years, with a maximum of 6 years. There was no difference in the primary endpoint of all-cause mortality as well as quality of life and functional status between rate and rhythm control. However, this trial included an elderly population and clearly did not include young, active or

highly symptomatic patients. Interestingly, a post hoc analysis of the AFFIRM trial, after correction for any mismatch of baseline characteristics, demonstrated that being in sinus rhythm was an advantage but the use of AAD was associated with an increased risk of death.[18]

The AF-CHF trial[14] included 1376 NYHA class II –IV heart failure patients with a LVEF ≤ 35% and randomized patients to either a rate vs. rhythm-control strategy. Amiodarone was the drug of choice for AF suppression and sinus rhythm maintenance, and sotalol and dofetilide were used in selected cases. The study revealed no benefit of rhythm control in addition to optimal medical therapy with regard to the primary endpoint (cardiovascular mortality) as well as prespecified secondary endpoints, including total death, worsening heart failure, stroke, and hospitalization.

The RACE trial[12] included 522 patients with persistent AF, who had a prior cardioversion and were currently in AF. Patients were randomized to a strategy of repeat cardioversion and AAD to maintain sinus rhythm or to pharmacologic rate control. The primary end point was a composite of cardiovascular death, heart failure, thromboembolism, bleeding, pacemaker insertion, or severe side effects of antiarrhythmic drugs. The end point did not differ between the 2 groups at a mean follow-up of 2.3 years. Analysis of quality of life, a secondary end point, showed no difference between these 2 strategies. The RACE II study which included 614 patients with permanent AF, also found no significant difference in clinical outcomes including cardiovascular mortality, hospitalization for CHF, stroke, major bleeding, ventricular tachyarrhythmias, between lenient (resting heart rate < 110 beats/min) and strict (resting heart rate < 80 beats/min and heart rate during moderate exercise < 110 beats/min) rate control (12.9% vs. 14.9%). AF was treated with a variety of atrioventricular (AV) nodal blocking agents to control heart rate.[12]

The PIAF, STAF AND HOT CAFÉ studies revealed a trend for improved survival and lower cardiovascular adverse events with rate control rather than rhythm control. Overall, these studies demonstrate that choosing a rate control or rhythm control strategy for a patient should be based on symptoms and a thorough discussion of the risks and benefits of each should be undertaken.

## PHARMACOLOGIC: Maintenance of Sinus Rhythm

Rhythm control is instinctively a more attractive option because it offers physiologic rate control, normal atrial contraction and activation, the appropriate sequence of AV activation, normal hemodynamics and AV valve function and theoretically eliminates factors that encourage thrombosis within the atria and embolization of blood clots.[6] Restoration and maintenance of sinus rhythm should be strongly considered for most symptomatic patients with paroxysmal and persistent AF.[9,10] Other factors favoring rhythm control include younger patients, tachycardia induced cardiomyopathy, first episode of AF, difficulty in achieving adequate rate control, AF that was precipitated by an acute illness and patient's

**FIGURE. Strategies for rhythm control in patients with paroxysmal and persistent AF**

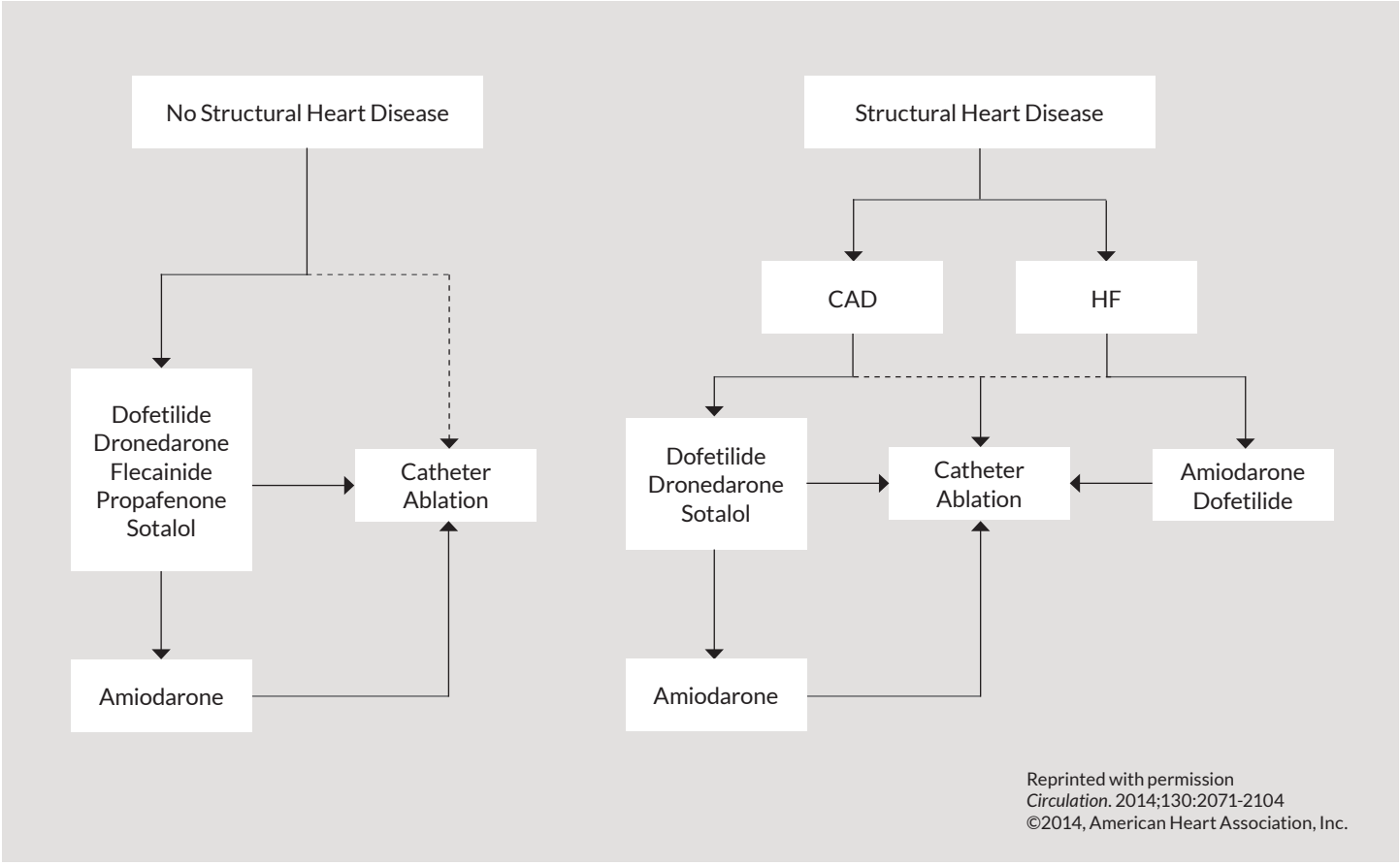


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**TABLE 2. Pharmacologic Therapy to Maintain Sinus Rhythm: Typical Dosages and Adverse Effects**

| Drug | Daily Dose | Major Adverse Effects |
|---|---|---|
| Amiodarone | 100-400 mg | Photosensitivity, pulmonary toxicity, polyneuropathy, GI upset, bradycardia, torsades de pointes (rare), hepatic toxicity, thyroid dysfunction, eye complications |
| Disopyramide | 400-700 mg | Torsades de pointes, HF, glaucoma, urinary retention, dry mouth |
| Dronedareone | 800 mg | New or worsening heart failure, QT prolongation, bradycardia |
| Dofetilide | 500-1000 µg | Torsades de pointes |
| Flecainide | 200-300 mg | VT, HF, conversion to atrial flutter with rapid conduction through the AV node |
| Propafenone | 450-900 mg | VT, HF, conversion to atrial flutter with rapid conduction through the AV node |
| Sotalol | 160-320 mg | Torsades de pointes, HF, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease |

GI=gastrointestinal; VT=ventricular tachycardia.
Source: American Heart Association, Inc.

preference.[10] Prophylactic AAD treatment is often required. The 2014 AF guidelines[10] recommend that rhythm control therapy must be individualized and that before initiating AAD therapy, treatment of precipitating or reversible causes of AF should be commenced.

However, AAD have limited efficacy and considerable unattractive adverse effects.[19] The goal of maintenance therapy is suppression of symptoms and at times, prevention of tachycardia-induced cardiomyopathy due to AF with a rapid ventricular response.[9,10] Atrial fibrillation recurrence is not equivalent to treatment failure, since most patients experience recurrence. A reduction in AF burden constitutes a partial success.[9,10] Consideration of underlying structural heart disease is essential for the selection of an AAD. *Figure 1* from the ACC/AHA/HRS 2014 updated guidelines is a summary of therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. The seriousness of heart disease progresses from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. Drugs are not in order of suggested use but are listed alphabetically.[9]

Beta blockers are usually effective in patients with exercise induced AF or lone AF. Flecainide, propafenone and sotalol are also effective in these patients without SHD. Amiodarone and dofetilide are used as alternative therapies. Patients with heart failure have fewer AAD options compared to those without SHD.

The primary pharmacologic agents for rhythm control in patients with HF are the class III AAD; however HF patients are prone to the proarrhythmic effects of AAD. Amiodarone has the greatest efficacy for maintenance of sinus rhythm but carries the potential for noncardiac toxicities. Amiodarone can prolong the QT interval and cause bradycardia, but rarely causes ventricular proarrhythmia. Dofetilide is reasonably safe and effective for HF patents.[20] Dronedarone is moderately effective in maintaining sinus rhythm and has ventricular-rate slowing properties when AF recurs, however, dronedarone is not recommended in patients with NYHA class IV HF[21] or in patients with permanent AF.[22]

In stable patients with coronary artery disease, beta blockers should be considered. Sotalol has beta blocking activity and can also be used for initial AAD therapy. Patients with LVH are at an increased risk for ventricular proarrhythmia; first line therapy should be an AAD that does not prolong the QT interval. Since the rate of torsades de pointes with class III agents is 0.9% to 3.3%[23], in hospital initiation of AAD therapy is recommended for quinidine, procainamide, sotalol, and dofetilide. Generally, AAD should be started at a lower dose with upward titration, reassessing the ECG with dose changes or if concomitant drug therapies are introduced. (*Refer to Table 2 for drug dosing and adverse effects.*)

## PHARMACOLOGIC: Rate Control

A primary strategy of rate control should be considered in the following patients[6,9,10]:

- Those with a permanent form of the arrhythmia associated with mild symptoms that can be improved by slowing heart rate
- Those patients ≥ 65 years age with recurrent AF when the AF is accepted by the patient and the provider
- Those with persistent AF with failed repeat cardioversions and serial prophylactic AAD and in whom the risk/benefit ratio from using specific antiarrhythmic agents leans toward increased risk or those who are ineligible for ablation therapy.

The ventricular rate during AF may accelerate excessively during exercise even if it is well controlled at rest. Ventricular rate reduction allows sufficient time for ventricular filling, avoids rate-related ischemia, and may improve hemodynamics. Criteria for rate control vary with patient age but usually involve achieving ventricular rates during AF between 60-80 bpm at rest and between 90-115 bpm during moderate exercise.[9,10] Generally beta blockers are the most common drugs used for rate control, followed by nondihydropyridine calcium channel blockers, digoxin and amiodarone.[10] Digoxin is effective in controlling ventricular rates at rest by prolongation of AV node conduction and refractoriness through vagal stimulation. However during exercise, most of the vagal tone is lost and the effect of digoxin is negated. Therefore, digoxin as monotherapy may be effective in elderly, sedentary patients, but a combination with beta blockers or calcium antagonists is often necessary to achieve rate control in the majority of patients. Nondihydropyridine calcium antagonists and beta blockers are also effective as primary pharmacologic therapy for rate control; however, multiple changes of drug type and dosage and/or a combination of two drugs may be needed to achieve the desired result. Amiodarone can be useful to control ventricular response but adverse effects should be considered. (*Refer to Table 3 for drug dosing and adverse effects*). Comorbidities of patients must be appreciated in order to prevent exacerbation of chronic obstructive pulmonary disease, heart failure or conduction acceleration in patients with pre-excitation.[10]

**TABLE 3. Drug Therapy for HR Control in AF: Long-Term Management**

| Drug | Loading Dose | Onset | Maintenance Dose | Major Adverse Effects |
|---|---|---|---|---|
| HEART RATE CONTROL | | | | |
| Metoprolol | Same as maintenance dose | 4-6 h | 25-100 mb bid, po | ↓BP, HB, ↓HR, asthma, HF |
| Propranolol | Same as maintenance dose | 60-90 min | 80-240 mg/d in divided doses, po | ↓BP, HB, ↓HR, asthma, HF |
| Diltiazem | Same as maintenance dose | 2-4 h | 120-360 mg/d in divided doses, po | ↓BP, HB, HF |
| Verapamil | Same as maintenance dose | 1-2 h | 120-360 mg/d in divided doses, po | ↓BP, HB, HF, digoxin interaction |
| HEART RATE CONTROL PATIENTS WITH HEART FAILURE AND WITHOUT ACCESSORY PATHWAY | | | | |
| Digoxin | 0.5 mg/d po | 2 days | 0.125 to 0.375 mg/d po | Digitalis toxicity, HB, HR, ↓BP, ↓HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia |
| Amiodarone | 800 mg/d for 1 wk, po<br>600 mg/d for 1 wk, po<br>400 mg/d for 4-6 wk, po | 1-3 wk | 200 mg/d po | |

Source: American Heart Association, Inc.

Upstream therapies refer to the use of non-antiarrhythmic medications that alter the atrial substrate or target mechanisms specific to AF to prevent recurrence. They include ACE inhibitors, angiotension receptor blockers, aldosterone antagonists, statins, and fish oil.[25] These therapies target structural changes in the atria, such as fibrosis, hypertrophy, inflammation, and oxidative stress; however, direct and indirect effects on atrial ion channels, gap junctions, and calcium handling also occur.[6]

## Ablation and Device Therapy

Since the early 1990s, it has been recognized that triggering or initiation of AF occurs predominantly from the pulmonary veins, and that the electrical isolation of those veins could prevent AF.[26] The technique involves puncturing the interatrial septum with one to two catheters and delivering radiofrequency or other energy in an encircling manner around the pulmonary veins, thereby preventing triggering beats from entering the atrium. The procedure is generally safe and is increasingly being employed in the treatment of AF. Nurses and advanced practice nurses should understand the indications for the procedure and the associated complications. While there are many theoretical benefits from treating AF with ablation, the elimination of AF symptoms is the only indication that has been proven in randomized clinical trials. Thus, the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society 2012 Consensus Statement lists "Symptomatic AF refractory to or intolerant to at least one Class I or Class III antiarrhythmic medication" as a Class I indication for ablation.[27] The success rate of this technique ranges from 66% to 89%.[27] The success rate is lower in patients with longer duration of AF, enlarged left atria and persistent versus paroxysmal AF. While this procedure is generally safe, there are several important complications to recognize. Because ablation of AF is performed in the left atrium, there is a risk of thrombus or char formation which could result in stroke or systemic embolization in 0-7% of patients.[27] After AF ablation, patients require frequent monitoring of neurological status. This risk of stroke is minimized by anticoagulation with heparin. However, because of anticoagulation, the risk of cardiac perforation and tamponade are increased (1.2% to 2.4% ).[27] While tamponade usually occurs acutely in the ablation laboratory, it must be recognized early and treated with reversal of anticoagulation therapy and percutaneous or surgical evacuation of blood from the pericardium. Complications which occur later in the post-ablation period include atrio-esophageal fistulae, which occur as a result of heating of the esophagus. This complication is associated with a high mortality if not recognized immediately. Pulmonary vein stenosis can occur as a result of ablation within or too close to the pulmonary vein ostium. Additionally, patients with AF ablation may experience rapid atrial flutter after ablation. Although ablation of AF is an effective technique for rhythm control, close monitoring of these patients in the post-operative period is required to minimize complications.

## CONCLUSION

As a collaborative team, the physician and the advanced practice nurse (APN) are committed to providing quality care for the AF patient through a comprehensive approach to patient education, problem solving, goal setting and shared decision making. (see related article by Hughes for further discussion on shared decision making).[28] In the setting of treating patients with AF, the physician and APN are most effective when they work collaboratively and interdependently.[29] Customization of treatment will be based on the patient's needs, symptoms during recurrence of AF, and the AF burden. The APN can customize treatment for the AF patient, such as medication titration, as well as manage other co-morbidities, including hypertension and heart failure. The APN can improve patient functioning and self-management, reduce complications of treatment, decrease fragmentation of care, adhere to regulatory standards, and develop patient care processes that are supported by evidence-based guidelines. ■

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PCNA
PREVENTIVE CARDIOVASCULAR NURSES ASSOCIATION

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# Reducing Cardioembolic Risk in the Patient with Atrial Fibrillation

**THE DECISION TO INITIATE** anticoagulation is shared between the patient and the provider. Once the patient's risk of stroke and bleeding is determined, and if anticoagulation is recommended, the provider and the patient should discuss the risks and benefits of currently approved anticoagulants. The choice of anticoagulant should only be partly based on the cost, type of follow up needed, and any lifestyle limitations that impact this choice.

Other factors that must be considered when selecting anticoagulation therapy include age, cognitive impairment, bleeding risk, ability to follow monitoring requirements, fall risk, co-morbid conditions, potential drug interactions, alcohol consumption, and the patient's previous history of compliance. To minimize the risk of drug interactions or adverse effects, the clinician should review all medications, including prescription and, over the counter medications, as well as herbal products.[1]

The risk of stroke is present with paroxysmal, persistent, or permanent atrial fibrillation. For patients with non-valvular atrial fibrillation, the $CHA_2DS_2$-VASc score is recommended to determine the patient's risk for stroke.[1] Anticoagulation is recommended for patients with a prior stroke, transient ischemic attack (TIA) or a $CHA_2DS_2$-VASc score of >2. For patients with mechanical heart valves warfarin is indicated with a target INR (International Normalized Ratio) between 2.0 to 3.0 or 2.5 to 3.5 depending on the location of the prosthetic valve. *Table 1* defines the scoring criteria for $CHA_2DS_2$-VASc. *Table 2* defines the oral anticoagulation criteria and level of evidence for stroke prophylaxis based on $CHA_2DS_2$-VASc.[2]

## BLEEDING RISK

In addition to assessing stroke risk, the risk of bleeding must be evaluated when considering anticoagulation. Three assessment tools are commonly used to assess the risk of bleeding for individuals: HAS-BLED, HEMORR2HAGES and ATRIA. HAS-BLED bleeding risk includes hypertension, abnormal renal or liver function, stroke, bleeding tendency or predisposition, labile INRs for patients taking warfarin, elderly considered greater than 65 years of age, and drugs including aspirin or NSAIDS or alcohol abuse. The HEMORR2HAGES bleeding risk includes liver or renal disease, alcohol abuse, malignancy, elderly, reduced platelet count or function, re-bleeding, hypertension, anemia, genetic factors, excessive fall risk, and stroke. ATRIA bleeding risk includes severe renal disease with estimated glomerular filtration rate (EGFR) <30 mL/min or dialysis, age 75 years or older, any prior hemorrhage, and the diagnosis of hypertension.

In a retrospective study, the AMADEUS trial applied the three bleeding risk models to 2293 patients who were treated with warfarin and found that HAS-BLED outperformed the other risk assessment tools although it was only modest in predicting the bleeding risk. The HAS-BLED score was better at predicting intracranial hemorrhage.[3] (*Refer to Table 3.)*

With HAS-BLED, a score of ≥3 indicates increased one year risk of bleeding with anticoagulation therapy. If the patient is found to be at high risk of bleeding and the risk and benefits have been weighed in favor of anticoagulation, regular clinical evaluation should be part of the follow up care of this patient.[4]

## WARFARIN

Warfarin is indicated for the prevention of thrombosis and thromboembolism. Warfarin is a vitamin K antagonist and inhibits the vitamin K dependent coagulation factors II, VII, IX and X as well as anticoagulant protein C and protein S. It is a racemic mixture, with equal amounts of R and S active isomers. The R and S isomers are bound to plasma proteins and accumulate in the liver. They are metabolized by

**TABLE 1. $CHA_2DS_2$-VASc Scoring System[1]**

| $CHA_2DS_2$-VASc SCORE For Patients with Non-Valvular Atrial Fibrillation | POINTS |
|---|---|
| **C**ongestive heart failure or left ventricular systolic dysfunction | 1 |
| **H**ypertension consistently >140/90 or under treatment with medication | 1 |
| **$A_2$** Age ≥75 years | 2 |
| **D**iabetes mellitus | 1 |
| **$S_2$** Prior stroke or TIA or thromboembolism | 2 |
| **V**ascular disease (peripheral arterial disease, myocardial infarction, aortic plaque) | 1 |
| **A**ge 65-74 | 1 |
| **S**ex category (female gender) | 1 |

## TABLE 2. $CHA_2DS_2$-VASc Selected Treatment Guidelines with Level of Evidence[1]

| $CHA_2DS_2$-VASc SCORE | TREATMENT | LEVEL OF EVIDENCE 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation | |
|---|---|---|---|
| 0 | Reasonable to consider no antithrombotic therapy | IIa | B |
| 1 | No antithrombotic therapy, oral anticoagulant or aspirin may be considered | IIb | C |
| Prior stroke , TIA or score ≥2 | Oral anticoagulation recommended: includes | | |
| | Warfarin INR 2-3 | I | A |
| | Dabigatran | I | B |
| | Rivaroxaban | I | B |
| | Apixaban | I | B |
| Moderate to severe CKD with score ≥2 | Treat with reduced doses of dabigatran, rivaroxaban or apixaban | IIb | C |
| End stage CKD (Crcl <15 ml/min) or on dialysis | Reasonable to treat with warfarin INR 2-3 | IIa | B |
| Following coronary revascularization (percutaneous or surgical) score ≥2 | Reasonable to use clopidogrel 75 mg QD concurrently with oral anticoagulants but without aspirin | IIb | B |

different CYP 450 pathways. The S isomer is metabolized mainly by CYP 2C9 and is 3-5 times more potent than the R isomer. It has greater clinical application when there are other medications that inhibit clearance of the S-warfarin and increase the anticoagulant effect of warfarin. Warfarin is water soluble and generally absorbed rapidly in the small bowel, but age, co-morbid disease, other medications and environmental factors can all have an effect on metabolism. The R isomer is metabolized mainly by CYP 3A4, but also by 1A1, 1A2, 2C8, 2C9, 2C18, 2C19. The effective half-life of warfarin is 20 to 60 hours.[5-7]

## DOSAGE

In 2012 the American College of Chest Physicians (ACCP) Guidelines recommended that warfarin be initiated in a healthy outpatient at 10 mg daily for two days and then adjusted based on the INR. (Grade 2C).[8] Although the 10 mg loading dose may be beneficial for younger patients, it may increase the INR too rapidly in the elderly. The 2008 ACCP Guidelines suggested initial doses of 5 mg or less in the elderly and those with co-morbid diseases.[6] Physiologic changes that occur with aging affect the pharmacokinetics of medications. Gastric acid production is decreased and gastric motility slows resulting in a decrease in the rate that the medications are absorbed. Drug distribution may change due to decreases in lean body mass, decrease in total body water and an increase in body fat. The function of the kidneys and liver also decline, all of which can affect the body's ability to clear the medication resulting in a prolonged half-life of the drug.[9] Additionally, it is important to pay attention to other medications that the patient takes that may cause drug interactions. For example, medications that inhibit CYP 2C9 inhibitors are especially important as they may increase the risk of bleeding when combined with warfarin.

## TABLE 3. HAS-BLED bleeding risk scores[4]

| LETTER | CLINICAL CHARACTERISTICS | POINTS AWARDED |
|---|---|---|
| **H** | Hypertension* | 1 |
| **A** | Abnormal renal and liver function * (1 point each) | 1 or 2 |
| **S** | Stroke* | 1 |
| **B** | Bleeding* | 1 |
| **L** | Labile INRs* | 1 |
| **E** | Elderly >65 years* | 1 |
| **D** | Drugs or alcohol *(1 point each) | 1 or 2 |

Definitions: * Hypertension SBP>160 mmHg; abnormal renal function Sr.Cr. ≥200 umol/L [2.26mg/dL], chronic dialysis or renal transplant; abnormal liver function chronic hepatic disease (eg: cirrhosis) or bilirubin ≥2 X ULN in association with aspartate aminotransferase/alanine aminotransferase/ alkaline phosphatase >3X ULN; prior stroke particularly lacunar; bleeding history or predisposition (anemia); labile INRs defined as <60% time in therapeutic range (INR 2-3); elderly >65 years; drugs (antiplatelet agents, NSAIDs), and alcohol excess described as ≥8 units per week.

## CONTRAINDICATIONS

Warfarin is contraindicated in pregnant women, patients with hemorrhagic tendencies or blood dyscrasias, recent or scheduled surgeries involving the central nervous system, eyes, traumatic surgery, ulceration and bleeding of the gastrointestinal tract, genitourinary or respiratory tracts, cerebrovascular hemorrhage, dissecting aorta or cerebral aneurysms, pericarditis and pericardial effusions, bacterial endocarditis, inadequate laboratory facilities, unsupervised patients with senility, alcoholism, psychosis or lack of patient cooperation, spinal puncture and other diagnostic or therapeutic procedures with potential uncontrollable bleeding, regional lumbar block anesthesia, malignant hypertension and known hypersensitivity to warfarin.[7]

## REVERSIBILITY

Risk of bleeding, however, should not be the sole criterion to withhold anticoagulation with a vitamin K antagonist.[7] Warfarin can be reversed with vitamin K, fresh frozen plasma, and prothrombin complex concentrate (PCC). In the event that the INR is between 4.5 and 10 and there is no evidence of bleeding, the 2012 ACCP Guideline recommend against the routine use of vitamin K, but instead the warfarin dose is held with a repeat INR in 1 to 2 days, and the dose adjusted as indicated by the INR.[8] Foods that are rich in vitamin K, such as green vegetables, also accelerate the reduction in the INR. It is important to determine the cause of the high INR by assessing: sudden dietary changes, alcohol intake, acute illness, post procedure, fever, diarrhea, vomiting, taking too much warfarin or taking a new medication that interacts with warfarin. For patients with an INR greater than 10.0 and no evidence of bleeding, the guidelines recommend oral prescription vitamin K.[8] If the INR is elevated and the patient is bleeding, he or she should be sent to the emergency room for evaluation, support and treatment.

## RECOMMENDATIONS FOR FOLLOW UP

Clinical practices must have services available for anticoagulation management. Policies that include patient education, systematic INR testing, tracking, follow up and good communication with the patient with results and dosing decision are recommended. The INR testing is generally obtained weekly until stable within the therapeutic range. The 2014 ACC/AHA Guidelines recommend that once the INR has been consistently stable, it should then be tested at least monthly as long as it remains stable. The 2012 ACCP guidelines also recommend using algorithms or computerized dosing programs. (Grade 2C).[8] However, individual judgment or institutional policy may require more frequent testing of the INR to assure a therapeutic range. The frequency of the monitoring is based on the individual's co-morbid disease factors.

## PATIENT EDUCATION

It is important to inform the patient that warfarin is a blood thinner and is for stroke prevention only. It will not control the atrial arrhythmia. Patients should be informed of the potential for drug interactions with prescription as well as over the counter and herbal products. They should be encouraged to discuss any new medication, including short term antibiotics with a healthcare professional. Any decision for dosage change is based on the patient's INR and the potential for drug interaction.

Informing the healthcare professional of any change in general health is important to minimize the risk of alteration in INR. The patient should be informed about the effect of an acute illness, such as a cold, flu, fever, vomiting, diarrhea, minor or major surgery, or procedure can have on the metabolism of warfarin. The patient should inform the healthcare professional about their health changes so that the dose may be adjusted if indicated. Over the counter pain medications such as aspirin containing products, and non-steroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen sodium and celecoxib, etc.) can increase the risk of bleeding and should be avoided unless under the careful supervision of the healthcare provider.

Patients should be informed of the interaction with warfarin and foods with vitamin K. There are numerous foods with vitamin K in varying amounts. Avoidance of vitamin K would be extremely difficult and teaching the patient to be consistent with the level of vitamin K may be most effective. The web site http://www.ptinr.com is an informative patient education site with a lengthy list of vitamin K foods divided into categories of high, moderate and low vitamin K foods. Instructing the patient to be consistent with the level of vitamin K in their daily diet will help to maintain stability of the INR.

Warfarin can only be regulated by a blood test called an INR. The goal range of the INR is between 2.0 and 3.0. The test is usually performed weekly until stable and then less frequently depending on the policy of the healthcare providers practice as well as the individual needs of the patient. Recommending that warfarin is taken around the evening dinner hour allows for results from INR testing done earlier in the day to be incorporated into any dose adjustments in a timely fashion.

## PATIENT SELF-TESTING

Point of Care (POC) INR measurements undoubtedly simplify anticoagulation treatment.[5] Patients who test their own INR have instant results and can either discuss with the healthcare provider for direction on treatment or be taught how to adjust their own warfarin dose based on the results. This is an effective method of monitoring for those patients who travel, those who want the freedom to monitor their own INRs, as well as for patients who are home bound due to illness or other reasons. A meta-analysis of 11 trials including data from 6417 people showed that self-monitoring and self-management of oral anticoagulation is safe with a reduction in thrombotic events in patients less than 55 years old and also those with mechanical heart valves. The elderly group, 85 years of age and older, showed no significant adverse effects.[10] As a result of the positive outcomes, international guidelines were published in 2005.[11] There are several companies that manufacture the monitors and the prices range from $1500 to $2000 dollars for the equipment. The equipment and testing materials (test strips and cuvettes) may be covered by Medicare and Non-Medicare insurance companies. A prescription from the healthcare provider is necessary to obtain insurance coverage.

## ADDITIONAL ORAL ANTICOAGULANTS

Although warfarin has been used for over 60 years for oral anticoagulation, the variable therapeutic blood levels, food and drug interaction and laboratory follow up have made it less than ideal as a long term treatment for many patients. In recent years, three alternative oral anticoagulants have been used successfully, including dabigatran, a direct thrombin inhibitor, and rivaroxban and apixaban, factor Xa inhibitors. The three agents offer predictable pharmacokinetics and pharmacodynamics. These medications have unique indications and contraindications.

## DABIGATRAN

Dabigatran is a concentration dependent, highly selective, and reversible direct thrombin inhibitor.[12] It competitively binds to the active site of thrombin, inhibiting the conversion of soluble fibrinogen into insoluble strands of fibrin resulting in the inhibition of clot formation. In addition, by directly inhibiting thrombin, dabigatran also reduces thrombin's ability to catalyze other coagulation reactions resulting in less amplification of the coagulation cascade.

Given the very poor bioavailability of dabigatran, it is administered as a prodrug, dabigatran etexilate, which is rapidly hydrolyzed after absorption by nonspecific esterases to active dabigatran.[12,13] Other selected pharmacokinetic and pharmacodynamics parameters for dabigatran etexilate are shown in *Table 4*.

Based on the results of the pivotal Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran was approved by the Food and Drug Administration (FDA) for use in the United States to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.[14,15] In the RE-LY trial more than 18,000 patients with atrial fibrillation and one additional risk factor (i.e. history of cerebrovascular accident (CVA) or transient ischemic attack (TIA), left ventricular ejection fraction (LVEF) < 40%, heart failure Class II or higher within the previous 6 months, age > 75 years, or age of 65-74 years with either diabetes mellitus, hypertension or coronary artery disease, were randomized to open-label therapy with warfarin to achieve an international normalized ratio (INR) of 2.0-3.0, or dabigatran etexilate at blinded doses of either 150 mg or 110 mg twice daily. Key exclusion criteria were a severe heart valve disorder, increased risk of hemorrhage, CVA within 14 days or severe CVA in the previous 6 months, active liver disease, pregnancy, indication for anticoagulation other than atrial fibrillation, or a creatinine clearance (CrCl) < 30 mL/min. Patients were, on average, 71 years of age and had an average CHADS2 score of 2.1. Those randomized to warfarin had a mean time within the therapeutic range of 64%. After a median follow-up of 2 years, dabigatran etexilate 150 mg twice daily significantly reduced the risk of the primary endpoint (stroke or systemic embolism) by 34% versus warfarin (1.11%/year versus 1.69%/year respectively) with a number need to treat (NNT) of 172 patients per year with dabigatran etexilate to prevent one stroke or systemic embolism. Dabigatran etexilate 110 mg twice daily had similar efficacy compared to warfarin. In regards to safety, major bleeding (bleeding resulting in reduction in hemoglobin of > 2 gm/dL or requiring transfusion of > 2 units, or symptomatic bleeding in a critical area or organ) was similar between warfarin and the 150 mg twice daily dose of dabigatran etexilate, but significantly lower in the 110 mg twice daily dose of dabigatran etexilate (2.71%/year versus 3.36%/year; NNT to prevent one major bleeding episode of 153 patients per year). Of particular significance was that both the 110 mg and 150 mg twice daily doses of dabigatran etexilate resulted in less intracranial hemorrhage than warfarin with a NNT of 196 and 227 patients per year, respectively, to prevent one intracranial hemorrhage. In contrast, dabigatran etexilate 150 mg twice daily (but not 110 mg twice daily) had a significantly higher risk of gastrointestinal bleeding than warfarin with a number need to harm (NNH) of 204 patients per year to result in one additional gastrointestinal hemorrhage.[15] While there was some initial concern about a slight, but statistically significant, increase in myocardial infarction with dabigatran 150 mg twice daily versus warfarin in the original trial dataset, a subsequent reanalysis with additional data determined that this difference was not statistically significant.[16] However, additional cohort studies, systemic reviews, meta-analyses and an FDA review have continued to provide conflicting results.[17-21] If there is an elevated risk it is small and probably on the order of about a 0.3% per year absolute increase in events.[19] Lastly, the benefits of dabigatran were most apparent in patients enrolled at centers with INR control below the median of 67%.[22]

Despite the noninferiority of dabigatran etexilate 110 mg twice daily when compared to warfarin in the RE-LY trial, the FDA approved only the 150 mg twice-daily regimen. This was based on an analysis by the FDA

**TABLE 4. Selected Pharmacokinetic Properties of Non-Warfarin Oral Anticoagulants[14, 34, 43, 47]**

| Parameter | Dabigatran Etexilate | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| Bioavailability | 3.7% | 80-100% (10 mg dose)*<br>6-90% (20 mg dose)* | 50% | 62% |
| Activation | Esterase-catalyzed hydrolysis | Not needed | Not needed | Not needed |
| Tmax (hours) | 1-2 | 2-4 | 3-4 | 1-2 |
| T½ (hours) | 12-17** | 5-9** | 12** | 10-14** |
| Protein binding | 35% | >90% | 87% | 55% |
| Metabolism (major) | Conjugation (no CYP450) | CYP 3A4, CYP2J2 | CYP 3A4 | Hydrolysis (<4% CYP450) |
| P-gp Substrate | Yes | Yes | Yes | Yes |
| Renal elimination of unchanged drug | 80% | 36% | 25% | 35% |
| Significant removal by dialysis | Yes (60% within 2-3 hours) | Not expected | Not expected | Not expected |
| Effect of Food | No significant effect | Doses >10 mg to be taken with dinner to enhance absorption | No significant effect | No significant effect |

Tmax = time to maximum concentration; T1/2 = half-life
* Bioavailability with 10mg is with or without food; bioavailability with 20mg dose is 66% in fasting state and 90% with food
** T1/2 displayed is for healthy individuals; half-life prolonged in patients with severe renal dysfunction

that concluded that even in patients over the age of 75 years, those with moderate renal impairment, or those with a previous hemorrhage that they were unable to establish an improved benefit-risk profile of the lower dose over the higher dose.[23] In addition, based on pharmacokinetic and pharmacodynamics modeling versus actual clinical trial efficacy and safety data, the FDA also approved a dose of 75 mg twice daily for patients with a CrCl of 15-30 mL/min.[24] There are no dosing recommendations for patients with a CrCl less than 15 mL/min or on dialysis.[14] Whether there is a potential role for the monitoring of plasma dabigatran concentrations to tailor therapy and more effectively optimize benefit and minimize risk has recently been raised. A pre-specified analysis of the RE-LY trial revealed that ischemic stroke was inversely related to trough dabigatran concentrations whereas major bleeding increased with dabigatran exposure.[25] However, the utility and practicality of tailoring dabigatran therapy based upon plasma concentrations remains unknown at this time.

Dabigatran etexilate is contraindicated in patients with active pathological bleeding, a history of a serious hypersensitivity reaction to the drug, or a mechanical prosthetic heart valve.[14] Dabigatran etexilate is generally well tolerated with the most common adverse effects consisting of gastrointestinal disturbances such as dyspepsia, nausea, or vomiting.[14,15] These occurred in about 11% of patients in the RE-LY trial randomized to dabigatran versus 6% in the warfarin group. In addition, discontinuation rates at 2 years were significantly greater with dabigatran (around 21%) versus warfarin (16.6%).[15]

Although dabigatran etexilate has much less risk for drug-drug interactions (and no significant food-drug interactions) than warfarin, it is susceptible to interactions with P-glycoprotein (P-gp) inducers and inhibitors.[26] This may be magnified in patients with moderate or severe renal impairment. While current drug-drug interactions studies have not resulted in many changes to approved dose recommendations by the FDA it should be noted that concurrent administration of dabigatran etexilate and P-gp inducers (e.g., rifampin) should be avoided. In addition, in patients with moderate renal impairment (CrCl 30-50 mL/min) consideration should be given to either reducing the dose of dabigatran etexilate to 75 mg twice daily if the patient is also receiving concomitant therapy with dronedarone or systemic ketoconazole (strong P-gp inhibitors) or avoiding it all together. Other P-gp inhibitors (verapamil, amiodarone, quinidine, and clarithromycin) in this setting do not require a dose adjustment of dabigatran etexilate. However, in patients with severe renal impairment (CrCl 15-30 mL/min) it is recommended that the concomitant use of P-gp inhibitors and dabigatran etexilate be avoided.[14] Ultimately, time and further study will further clarify the extent and significance of other potential drug-drug interactions with dabigatran, specifically strong P-gp inhibitors such as cyclosporine, itraconazole, tacrolimus and selected HIV-protease inhibitors.

Unlike warfarin, the pharmacodynamic effect of dabigatran with oral dosing is generally considered to be consistent and the routine monitoring of clotting times is not necessary.[27] In pharmacokinetic and pharmacodynamic studies, dabigatran affected the INR, activated partial thrombin test (aPTT), ecarin clotting time (ECT), and the thrombin time (TT). The INR is not a reliable indicator of dabigatran activity and may or may not be affected. The most specific measure of dabigatran activity is the ECT, but at this time the test is not readily available.[14] The aPTT provides an approximation of dabigatran's anticoagulant effect with information available from the manufacturer (package insert) depicting the average time course of dabigatran's effect on aPTT expected with various degrees of renal function and currently approved dosing regimens.[14] This information can be used to estimate the time to get to a particular aPTT, or in other words a level of recovery. However, it must be noted that there may be quantitative differences between various methods used to measure the aPTT. As a result the advantage of not needing routine laboratory monitoring to assess the degree of anticoagulation with dabigatran over warfarin is also a disadvantage in specific situations as rapid reliable measures of its anticoagulant effect are not available. In addition, a specific reversal agent for dabigatran is not currently available although a humanized antibody fragment (idarucizumab) is in development and has received the FDA's breakthrough therapy designation.[28] While dabigatran can be dialyzed with a removal of about 60% over 2-3 hours, this may not be practical in unstable patients.[29,30] The use of prothrombin complex concentrates (PCC), although suggested, has not shown an effect to date.[31] In addition, it is not known if other measures such as the use of activated prothrombin complex concentrates (aPCC) or recombinant Factor VIIa will be of clinical utility. The use of protamine sulfate and vitamin K are not expected to have any effect on dabigatran's anticoagulant activity whereas, early administration of activated charcoal after ingestion can reduce the absorption of dabigatran etexilate.[14,29] Subsequently, for a return to normal hemostasis, one must currently rely upon the body's own elimination of the drug after discontinuation. Drug levels and effects should decrease by about 50% 12-18 hours after the most recent dose, and levels reduced to 25% at 24 hours in patients with CrCl > 50 mL/min. If the patient is bleeding, along with discontinuation of the drug, early volume and red blood cell replacement, identification of the cause, and use of local measures to stop the bleeding should be implemented.[27]

When converting patients from warfarin to dabigatran etexilate, warfarin should be discontinued and dabigatran etexilate initiated when the INR is less than 2.0. When converting from dabigatran etexilate to warfarin, the starting time of warfarin is based on creatinine clearance. If the creatinine clearance is > 50 mL/min warfarin should be started 3 days before discontinuing dabigatran etexilate. If CrCl is between 30-50 mL/min warfarin should be started 2 days before discontinuing dabigatran etexilate, and if CrCl is between 15-30 mL/min, warfarin should be started 1 day before discontinuing dabigatran etexilate. The INR will reflect warfarin's activity only after dabigatran etexilate has been discontinued for at least 2 days. If converting to a parental anticoagulant from dabigatran etexilate, treatment should be initiated 12 (CrCl > 30 mL/min) or 24 hours (CrCl < 30 mL/min) after the last dose of dabigatran etexilate. If converting from a parental anticoagulant to dabigatran etexilate the first dose should be 0-2 hours before the time the next dose of the parental anticoagulant is due or if on a continuous infusion of a parental anticoagulant at the time the infusion is discontinued. The manufacturer recommends that if possible, dabigatran etexilate should be discontinued 1-2 days (CrCl > 50 mL/min) or 3-5 days (CrCl < 50 mL/min) prior to invasive or surgical procedures that require that anticoagu-

lation be discontinued. Longer times may be considered for major surgery (e.g. cardiac, abdominal, neurosurgery), spinal puncture, or placement of a spinal or epidural catheter or port.[14,32] In regards to perioperative bridging, the more predictable anticoagulant effects and shorter half-life of dabigatran should simplify management, but the best strategy at this time remains unknown. Less than 1 in 5 patients in the RE-LY trial receiving dabigatran etexilate who underwent surgery or invasive procedures received periprocedural bridging.[32] In an analysis of patients in the RE-LY trial who underwent a surgical or invasive procedure similar rates of periprocedural and thrombotic events were observed between dabigatran etexilate and warfarin with patients receiving dabigatran etexilate having a shorter period of interruption of therapy.[32] In addition, among 1270 patients in the RE-LY trial who underwent 1983 cardioversion procedures, rates of stroke and systemic embolism as well as major bleeding within 30 days post-procedure were similar between groups.[33]

Patients should be informed about the need for strict adherence with dabigatran etexilate as well as taking it with a full glass of water. In addition, it is important to stress that breaking, chewing, or emptying the capsules should not be done as this will result in an increased exposure of up to 75%.[14] If a dose is missed the patient may take the missed dose as long as it is not within 6 hours prior to the next scheduled dose. Furthermore, dabigatran etexilate must be stored in the manufacturer's original packaging to reduce the risk of exposure to moisture or humidity as this will lead to product breakdown and loss of potency. Once a bottle of dabigatran etexilate is opened it must be used within 4 months, and if dispensed in a blister package, it should be taken as soon as removed.[14] Both of these restrictions make the use of medication organizers problematic with dabigatran etexilate.

## RIVAROXABAN

Rivaroxaban is a selective, competitive, reversible, oral direct factor Xa inhibitor that reduces the rapid generation of thrombin that occurs during the propagation phase of the coagulation cascade.[27] It does not reduce the activity of thrombin that has already been generated. In contrast to dabigatran, rivaroxaban has much better bioavailability (absorption), but it is dose-dependent with doses > 10mg requiring administration with food to increase the bioavailability.[34,35] In addition, its absorption is dependent on the site of release within the gastrointestinal tract with significant reductions in absorption when released in the proximal small intestine or further downstream. As a result, it should not be administered in a manner (e.g., feeding tube) that will deposit the drug distally to the stomach (e.g. proximal small intestine).[34] Rivaroxaban is both a P-gp substrate as well as a substrate of cytochrome P450 3A4, making it more susceptible to drug interactions than dabigatran, and similar to dabigatran, it requires dose adjustments in patients with moderate renal dysfunction.[34,35] Other selected pharmacokinetic and pharmacodynamics parameters for rivaroxaban are shown in *Table 4*.

Based on the results of the Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) trial, rivaroxaban was approved by the FDA to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.[34,35] In the ROCKET AF trial, more than 14,000 patients with atrial fibrillation and a moderate-to-high risk of stroke (i.e., history of CVA, TIA, systemic embolism, or at least 2 of the following risk factors: heart failure or LVEF < 35%, hypertension, age > 75, or diabetes mellitus) were randomized in a double blind fashion to rivaroxaban 20 mg daily (15 mg daily if CrCl was 30-49 mL/min) or adjusted-dose warfarin to achieve an INR of 2.0-3.0. Key exclusion criteria were hemodynamically significant mitral valve stenosis, prosthetic heart valve, active or increased risk of hemorrhage, severe disabling CVA within the previous 3 months, TIA or other CVA within 3 or 14 days respectively, significant liver disease, pregnancy, or a CrCl <30 mL/min. The median age of patients was 73 years with an average CHADS2 score of 3.5 (much higher than the 2.1 in the RE-LY trial with dabigatran). Those randomized to warfarin had an average time within the therapeutic range of 55% (lower than the 64% in the RE-LY trial). After a median follow-up of 1.9 years the primary analysis (per-protocol) established rivaroxaban as non-inferior to warfarin in regards to the primary endpoint of stroke (ischemic or hemorrhagic) or systemic embolism (1.7%/year versus 2.2%/year). The intention-to-treat analysis also demonstrated rivaroxaban as non-inferior to warfarin in regards to the primary endpoint of stroke or systemic embolism (2.1%/year versus 2.4%/year), but not superior. In regards to safety, major (clinically overt bleeding resulting in death, reduction in hemoglobin of > 2 gm/dL or requiring transfusion of > 2 units, or involvement of a critical anatomic site or resulting in permanent disability) and non-major (overt bleeding requiring intervention via a physician visit, temporary interruption of study drug, pain, or impairment of daily activities) clinically relevant bleeding events were not significantly different between groups. However, rates of intracranial hemorrhage were significantly lower with rivaroxaban (0.5%/year) than warfarin (0.7%/year) with a number need to treat with rivaroxaban to prevent one intracranial hemorrhage of 500 patients/year. In contrast major bleeding from a gastrointestinal site occurred in 3.2% of patients assigned to rivaroxaban versus 2.2% of those assigned to warfarin; a difference which was statistically significant.[25] The non-inferiority of rivaroxaban to warfarin did not differ according to the time spent within the therapeutic range for different quartiles of treatment centers, but the study has been criticized for the overall low amount of time patients spent within the therapeutic range compared to other trials.[26,27]

The recommended dose of rivaroxaban for nonvalvular atrial fibrillation is 20 mg once daily with the evening meal in patients with a CrCl > 50 mL/min. In patients with a CrCl of 15-50 mL/min the recommended dose is 15mg once daily with the evening meal. However, it should be noted that patients with a CrCl of < 30 mL/min were excluded from the ROCKET AF trial. There are no dosing recommendations for patients with a CrCl less than 15 mL/min. In patients unable to swallow, whole tablets rivaroxaban may be crushed and mixed with applesauce immediately prior to use followed by food immediately after administration. In patients with a nasogastric tube or gastric feeding tube it can be crushed and suspended in 50 mL of water and administered. Enteral feeding should immediately follow this. The drug is stable in applesauce or water for up to 4 hours, and there is no adsorption from a water suspension to PVC or silicone nasogastric tubing.[34] Rivaroxaban is contraindicated in patients with active pathological bleeding or those with a history of a serious hypersensitivity reaction to the drug, and its use is not recommended in patients with prosthetic heart valves.[34] Rivaroxaban is

generally well tolerated without a significant difference in non-hemorrhagic adverse events than warfarin in the ROCKET AF trial.[36]

Since rivaroxaban is both a P-gp substrate as well as a substrate of cytochrome P450 3A4 it appears more susceptible to drug interactions than dabigatran, and similar to dabigatran, drug-drug interactions may be amplified in patients with renal dysfunction.[35] It is recommended to avoid concomitant administration of rivaroxaban with combined P-gp and strong CYP 3A4 inhibitors such as ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan as there are significant increases in rivaroxaban exposure. In addition, it is recommended to avoid concomitant administration of rivaroxaban with combined P-gp and strong CYP 3A4 inducers such as carbamazepine, phenytoin, rifampin, and St. John's wort. Caution is also recommended in patients with CrCl of 15-80 mL/min who are receiving combined P-gp and moderate inhibitors of CYP 3A4 such as diltiazem, verapamil, dronedarone, and erythromycin. These patients should receive therapy only if the potential benefit justifies the potential risk.[34] However, results from an analysis of the ROCKET AF trial which allowed concomitant use of combined P-gp and weak or moderate inhibitors of CYP 3A4 (e.g. amiodarone, diltiazem, verapamil, chloramphenicol, cimetidine, and erythromycin) did not show an increase risk of bleeding in patients with a CrCl of 30 to < 50 mL/min.[37] Again, it should be noted that patients with a CrCl of 15-30 mL/min were excluded from the ROCKET AF trial.[36] As with dabigatran, time and further study will further clarify the extent and significance of potential drug-drug interactions with rivaroxaban.

Similar to dabigatran the pharmacodynamic effect of rivaroxaban with oral dosing is considered consistent and the routine monitoring of clotting times is not necessary. Rivaroxaban dose dependently inhibits factor Xa activity and prolongs prothrombin time (PT), aPTT, and HepTest. There is some indication that the PT could provide a useful and timely measure of rivaroxaban exposure as it is strongly correlated with rivaroxaban concentrations with low inter-individual variability, but the clinical utility of this has not been adequately studied to provide general recommendations.[27] A specific reversal agent for rivaroxaban is not currently available although a universal factor Xa inhibitor antidote is in development and has received the FDA's breakthrough therapy designation.[38] Unlike dabigatran, there is no role for dialysis to remove rivaroxaban because of its high protein binding, but activated charcoal given early after ingestion may be useful. While the use of prothrombin complex concentrates (PCC) was shown in a small study to reverse the anticoagulant effects of rivaroxaban as assessed by both PT and the endogenous thrombin potential, it requires confirmation in larger clinical trials in which the actual physiological response is evaluated.[31] The use of protamine sulfate and vitamin K are not expected to have any effect on rivaroxaban's anticoagulant activity, and it is not known if other measures such as the use of activated prothrombin complex concentrates (aPCC) or recombinant Factor VIIa will be of clinical utility.[34] As a result, similar to dabigatran, for a return to normal hemostasis, one must currently rely upon the body's elimination of the drug after discontinuation. If the patient is bleeding, along with discontinuation of the drug, early volume and red blood cell replacement, identification of the cause, and use of local measures to stop the bleeding should be implemented.[27]

When converting patients from warfarin to rivaroxaban, warfarin should be discontinued and rivaroxaban initiated when the INR is less than 3.0 to avoid periods of inadequate anticoagulation.[34] In the ROCKET AF trial significantly more patients developed a primary event when transitioned from rivaroxaban to warfarin at the end of the trial. It was felt that this was probably related to increased difficulty transitioning from blinded therapy with rivaroxaban to warfarin.[36] Nevertheless, when converting patients from rivaroxaban to warfarin, caution must be exerted. One approach discussed in the manufacturer's package insert is to discontinue rivaroxaban and initiate therapy with both warfarin and a parenteral anticoagulant at the time the next dose of rivaroxaban is due. Since rivaroxaban affects the INR, measurements of the INR during concomitant therapy may not be useful. If converting to a non-warfarin anticoagulant with rapid onset (oral or parenteral), rivaroxaban should be discontinued and the other anticoagulant should be given at the time that the next dose of rivaroxaban would have been administered. If converting from a non-warfarin anticoagulant, rivaroxaban should be started 0 to 2 hours prior to the next scheduled evening administration of the drug (e.g., low molecular weight heparin or non-warfarin oral anticoagulant) and the other drug omitted. If the patient is receiving a continuous infusion of unfractionated heparin, the infusion should be discontinued and rivaroxaban initiated at the same time.[34] In addition, rivaroxaban should be discontinued at least 24 hours prior to invasive or surgical procedures that require anticoagulation be discontinued, and restarted as soon as adequate hemostasis has been established recognizing that the onset of its therapeutic effect is short. When spinal puncture or neuraxial anesthesia is employed patients should not have the epidural catheter removed earlier than 18 hours after the last dose of rivaroxaban, and the next dose of rivaroxaban should not be administered earlier than 6 hours after removal of the catheter (24 hours if traumatic puncture).[34] Similar to dabigatran the more predictable anticoagulant effects and shorter half-life of rivaroxaban versus warfarin should simplify periprocedural management. However, the best strategy at this time remains unknown. Although fewer patients in the ROCKET AF trial underwent cardioversion with rivaroxaban than did those with dabigatran in the RE-LY trial, similar results were observed between rivaroxaban and warfarin.[39]

Patients should be informed about the need for strict adherence with rivaroxaban as well as taking it with an evening meal. If a dose is missed the patient should take the missed dose as soon as possible on the same day and continue their usual regimen the next day.[34]

## APIXABAN

Apixaban, like rivaroxaban, is an oral direct, competitive, reversible factor Xa inhibitor.[35] Similar to the other new oral anticoagulant therapies the pharmacodynamic effect of apixaban with oral dosing is considered consistent and the routine monitoring of clotting times is not necessary. Apixaban is metabolized by the CYP 3A4 system and the potential for drug-drug interactions particularly in the setting of significant renal dysfunction exists.[29] However, since it is also metabolized by other oxidative pathways these interactions may not be as pronounced or clinically significant.[35] Other selected pharmacokinetic and pharmacodynamics parameters for apixaban are shown in *Table 4*.

Apixaban is approved by the FDA to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation based upon data from two large-scale randomized trials. In the Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial, apixaban was superior to aspirin for the prevention of stroke of systemic embolism (1.6%/year versus 3.7%/year) in 5599 patients with a NNT to prevent one stroke or systemic embolism of 45 patients per year. Rates of major bleeding, including intracranial hemorrhage were similar. When patients without a history of stroke or TIA were analyzed by CHADS2 score, apixaban was superior to aspirin in patients with a score of 2 or more, and equally safe and effective as aspirin in those with a CHADS2 of 0 or 1.[40] In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, over 18,000 patients with atrial fibrillation and at least one additional risk factor for stroke (age > 75 years, previous stroke, TIA, systemic embolism, symptomatic heart failure within the previous 3 months with a LVEF < 40%, diabetes mellitus, or hypertension requiring pharmacologic therapy) were randomized in a double blind fashion to apixaban 5 mg twice daily (2.5 mg twice daily if 2 or more of the following: age > 80 years, weight of < 60 kg, or serum creatinine (SCr) > 1.5 mg/dL) or adjusted-dose warfarin to achieve an INR of 2.0-3.0. Key exclusion criteria were moderate or severe mitral valve stenosis, prosthetic heart valve, CVA within the previous 7 days, reversible cause of atrial fibrillation, doses of aspirin > 165 mg/day, combination therapy with clopidogrel and aspirin, SCr > 2.5 mg/dL, or CrCl < 25 mL/min. The median age of patients was 70 years with an average CHADS2 score of 2.1. Those randomized to warfarin had an average time within the therapeutic range of 62%. After a median follow-up of 1.8 years the rate of the primary outcome of stroke or systemic embolism was 1.27%/year in the apixaban group versus 1.60%/year in the warfarin group establishing both noninferiority and superiority of apixaban over warfarin with a NNT of 303 patients/year to prevent one stroke or systemic embolism. In regards to safety, major bleeding (defined as clinically overt bleeding accompanied by a reduction in hemoglobin of > 2 gm/dL or requiring transfusion of > 2 units, or involvement of a critical anatomic site or resulting in death) was significantly lower with apixaban than warfarin (2.13%/year versus 3.09%/year; NNT of 104/year) as was the rate of hemorrhagic stroke (0.24%/year versus 0.47%/year; NNT of 434/year). In addition, the rate of death from any cause was also significantly lower with apixaban than warfarin (3.52% versus 3.94%).[41] However, this last finding is in contrast to the AVERROES trial where apixaban did not reduce rate of death versus aspirin, a much inferior antithrombotic in the setting of atrial fibrillation.

Apixaban is dosed as 5 mg orally twice daily unless the patient meets at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or a SCr ≥ 1.5 mg/dL, in which case the dose is 2.5 mg orally twice daily.[42] It should be emphasized that less than 1.5% of patients in the ARISTOTLE trial had an estimated glomerular filtration rate of ≤ 30 mL/min and that patients with a CrCl < 25 mL/min or SCr > 2.5 mg/dL were excluded from the trial a priori.[41] However, approved product labeling does not recommend avoiding apixaban based on renal dysfunction and even provides dosing recommendations for patients with end stage renal disease (ESRD) maintained on dialysis. This is based on pharmacokinetic and pharmacodynamic data. The recommended dose in patients receiving maintenance hemodialysis is 5 mg orally twice daily unless the patient is 80 years of age or older or weighs 60 kg or less in which case the recommended dose is 2.5 mg orally twice daily.[42] For patients unable to swallow whole tablets, apixaban tablets may be crushed and suspended in 60 mL of 5% dextrose in water and immediately administered through a nasogastric tube.[42] Patients should be informed about the need for strict adherence with apixaban. If a dose is missed the patient should take the missed dose as soon as possible on the same day (without doubling any one dose) and then continue their twice daily dosing. Apixaban is contraindicated in patients with active pathological bleeding or those with a history of a severe hypersensitivity reaction to the drugs and its use is not recommended in patients with prosthetic heart valves.[42] Apixaban is well tolerated without a significant difference in non-hemorrhagic adverse events than warfarin in the ARISTOTLE trial.[41]

Although apixaban is both a P-gp substrate as well as a substrate of cytochrome P450 3A4 its appears to be less susceptible to P-gp and P450 3A4 mediated drug interactions than rivaroxaban probably in part as it is also metabolized by other oxidative pathways as well as being less dependent on renal elimination than rivaroxaban. Nonetheless, specific drug interactions do exist and require modification of therapy. Concomitant use of apixaban with strong dual inducers of P-gp and CYP 3A4 (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) should be avoided. In patients who would generally receive 5 mg of apixaban twice daily the dose should be reduced to 2.5 mg twice daily if co-administered with strong dual inhibitors of P-gp and CYP 3A4 (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). If they would already receive 2.5 mg twice daily then concomitant use should be avoided.[42] Similar to both dabigatran and rivaroxaban further study and experience will provide additional information on these and other potential drug interactions.

The pharmacodynamic effect of apixaban with oral dosing is consistent and the routine monitoring of clotting times is not considered necessary. Apixaban, by its inhibition of factor Xa activity, prolongs the PT, INR, and aPTT. However, these changes are small and subject to a high degree of variability and therefore not useful in monitoring the anticoagulation effect of apixaban. In addition, there is no role for urgent dialysis to remove apixaban in the setting of bleeding or overdose because of its high protein binding. However, activated charcoal given at 2 and 6 hours early after ingestion may be useful. While the use of PCC, aPCC, or recombinant Factor VIIa may be considered it must be noted their efficacy and safety have not been thoroughly evaluated in clinical trials. On the other hand, the use of protamine sulfate and vitamin K are not expected to have any effect on apixaban's anticoagulant activity. As a result, similar to dabigatran and rivaroxaban, for a return to normal hemostasis, one must currently rely upon the body's elimination of the drug after discontinuation. In the case of apixaban this would be at least 24 hours. If the patient is bleeding, along with discontinuation of the drug, early volume and red blood cell replacement, identification of the cause, and use of local measures to stop the bleeding should be implemented.[27]

When converting patients from warfarin to apixaban, warfarin should be discontin-

ued and apixaban initiated when the INR is less than 2.0.[42] When converting from apixaban to warfarin, several considerations must be made. First, since apixaban affects the INR, measurements of the INR during concomitant therapy will not be very useful. Second, in the clinical trials an increased risk of stoke was observed following discontinuation of apixaban.[42] As a result, if continuous anticoagulation is required when converting from apixaban to warfarin both warfarin and a parenteral anticoagulant should be initiated at the time the next dose of apixaban would be due. If switching between apixaban and other non-warfarin anticoagulants the agent being taken should be discontinued and the other initiated at the time of the next scheduled dose. Apixaban should be discontinued at least 48 hours prior to elective invasive or surgical procedures that have a moderate or high risk of unacceptable or clinically significant bleeding, and at least 24 hours if they have a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. It should be restarted as soon as adequate hemostasis has been established recognizing that the onset of its therapeutic effect is short. When spinal puncture or neuraxial anesthesia is employed patients should not have the epidural catheter removed earlier than 24 hours after the last dose of apixaban, and the next dose of apixaban should not be administered earlier than 5 hours after removal of the catheter (48 hours if traumatic puncture).[42] Similar to dabigatran and rivaroxaban, outcomes post cardioversion were similar in regards to cardiovascular events and major bleeding for apixaban and warfarin.[43] *Table 5* lists the Level of Evidence for currently approved oral anticoagulants.

## FUTURE ORAL ANTICOAGULATION THERAPIES

Other emerging oral anticoagulants for the prevention of stroke and systemic embolism in the management of non-valvular atrial fibrillation include the direct factor Xa inhibitors edoxaban and betrixaban. Betrixaban has the advantage over other currently available agents of having both limited renal excretion, a long half-life and minimal metabolism through CYP 3A4.[44] However, it has only been evaluated in a Phase 2 trial at this time. In contrast, edoxaban has been evaluated in a large-scale Phase 3 trial and has recently been submitted to the FDA for approval. The Effective Anticoagulation with Factor

**TABLE 5. 2014 AHA/ASA Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack: Level of Evidence [1,2]**

| Guidelines | Treatment | LEVEL OF EVIDENCE | |
|---|---|---|---|
| Prevention of recurrent stroke in patients with non-valvular AF whether paroxysmal or permanent | Individualize treatment based on risk factors<br>The following are indicated:<br>VKA target INR 2.5<br>Apixaban<br>Dabigatran<br>The following is reasonable:<br>Rivaroxaban | <br><br>I<br>I<br>I<br><br>IIa | <br><br>A<br>A<br>B<br><br>B |
| | Combination of oral anticoagulation, warfarin or one of the newer agents with antiplatelet therapy is NOT recommended for all patients after ischemic stroke or TIA but is reasonable in patients with clinically apparent CAD, particularly an acute coronary syndrome or stent placement | IIb | C |
| | Patients with ischemic stroke or TIA and AF who are unable to take oral anticoagulants, aspirin alone is recommended.<br>The addition of clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable | I<br>IIb | A<br>B |
| | For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms | IIa | B |
| | In the presence of high risk for hemorrhage (ie: large infarct, hemorrhagic transformation on initial imaging uncontrolled hypertension, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days | IIa | B |
| | Patients with AF and history of stroke or TIA who require temporary interruption of oral anticoagulation, bridging therapy with low molecular weight heparin or an equivalent anticoagulant agent if intolerant to heparin, is reasonable depending on perceived risk of thromboembolism and bleeding. | IIa | C |
| For patients with clinically apparent coronary artery disease, particularly an acute coronary syndrome or stent placement | Combination of oral anticoagulation (ie, warfarin or one of newer agents ) with anti-platelet therapy is reasonable to use in this group of patients | IIb | C |
| Patients with ischemic stroke or TIA and AF unable to take oral anticoagulants | Aspirin alone is recommended<br>Addition of clopidogrel to aspirin compared with aspirin alone might be reasonable | I<br>IIb | A<br>B |
| Most patients with a stroke or TIA with AF | Reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms | IIa | B |
| In presence of high risk for hemorrhagic conversion (large cerebral infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension) | Reasonable to delay initiation of oral anticoagulation beyond 14 days | IIa | B |

Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE-AF-TIMI 48) trial evaluated two doses of edoxaban (30 mg or 60 mg once daily with dose adjustments based on renal function, weight, or concomitant medications) versus warfarin (dose adjusted to target an INR of 2.0-3.0) for stroke prevention in 21,105 patients with atrial fibrillation.[45,46] Patients 21 years of age or older with atrial fibrillation and a CHADS2 score of 2 or higher were eligible for randomization. Key exclusion criteria included atrial fibrillation due to a reversible cause, estimated CrCl < 30 mL/min, high risk of bleeding, dual antiplatelet therapy, moderate-to-severe mitral stenosis, other indications for anticoagulation therapy, acute coronary syndromes, coronary revascularization, or stroke within 30 days of randomization. Patients were randomized in a double blind fashion to edoxaban 60 mg once daily, edoxaban 30 mg once daily, or adjusted-dose warfarin to achieve an INR of 2.0-3.0. The dose of edoxaban was reduced by 50% at the time of randomization or during the study if the CrCl was 30-50 mL/min, body weight was 60 kg or less, or the patient received verapamil, quinidine, or dronedarone. The median age of patients was 72 years with an average CHADS2 score of 2.8. Those randomized to warfarin had an average time within the therapeutic range of 65%. After a median follow-up of 2.8 years the rate of the primary outcome of stroke or systemic embolism was 1.18%/year in the edoxaban 60 mg once daily group, 1.61%/year in the edoxaban 30 mg once daily group, and 1.50%/year in the warfarin group establishing noninferiority for both doses of edoxaban versus warfarin. In regards to safety, major bleeding (defined as fatal bleeding, symptomatic bleeding in a critical area or organ or clinically overt bleeding accompanied by a reduction in hemoglobin of > 2 gm/dL or requiring transfusion of > 2 units) was 3.43%/year with warfarin, 2.75%/year with edoxaban 60 mg, and 1.61%/year with edoxaban 30 mg both of which were statistically significantly lower than warfarin. The rates of life threatening bleeding, and intracranial bleeding were also significantly lower with both doses of edoxaban versus warfarin. However, the rate of major gastrointestinal bleeding was significantly higher (1.51%/year) with edoxaban 60 mg than warfarin (1.23%). Overall edoxaban, if approved, will represent yet another alternative to warfarin.[47]

While the last several years have seen the emergence of viable alternatives to warfarin therapy for the prevention of stroke in patients with atrial fibrillation, much remains to be resolved with the newer agents particularly regarding long-term efficacy and safety, reversibility, potential drug-drug interactions, head to head comparative data, adherence and persistence with therapy, as well as their management in the peri-procedural setting or concomitant use with other newer antithrombotic agents (e.g., prasugrel, ticagrelor). In addition, there remains a need to continue to improve how we manage anticoagulation with warfarin, including methods to increase the time within therapeutic range and promotion of self-management in appropriately selected patients. Ultimately, the decision regarding which agent to use will be individualized based on many of the aforementioned characteristics as well as cost and patient preference. ■

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# The Key Role of Patient as Partner

**THE IMPORTANCE** of well-informed self-care cannot be overstated for safe management of the patient with chronic atrial fibrillation, in particular for those patients who are prescribed chronic oral anticoagulation. Two strategies that contribute to safe and high quality self-care are patient education and the involvement of the patient in the shared decision-making process. Patient education is a critical underpinning of self-care and of shared decision-making.

In this era where patient-centeredness is a recurring theme, the American Medical Association framed the importance of effective patient education in the organization's 2007 monograph, *Reducing the Risk by Designing a Safer, Shame-Free Health Care Environment* reflecting that "It is neither just, nor fair, to expect a patient to make appropriate health decisions and safely manage his/her care without first understanding the information needed to do so."[1]

## PATIENT EDUCATION

A survey of hospital admissions from 2007-2009 (this predates the availability of novel anticoagulants) demonstrated that 33% of hospital admissions for adverse drug reactions were related to warfarin therapy. While even well-managed anticoagulation therapy may be associated with complications, nearly all hospitalizations involving warfarin (95.1%; 95% CI, 91.7 to 98.4 resulted from unintentional overdoses.[2]

The Joint Commission (TJC) recognized the priority of patient safety strategies around anticoagulation therapy when in 2007, the commission identified "Reduce the likelihood of patient harm associated with the use of anticoagulant therapy" as one of the TJC's national patient safety goals.[3] Further, the provision of education regarding anticoagulant therapy to prescribers, staff, patients, and families was identified as one of the strategies for safe patient care. TJC actually specifies the requisite components to be included into a comprehensive patient/family education program:

1. The importance of follow-up monitoring
2. Compliance
3. Drug-food interactions
4. The potential for adverse drug reactions and interactions

While drug/food interactions may not be relevant for patients prescribed the newer anticoagulants, no matter what therapeutic option for anticoagulation is chosen, the incorporation of a comprehensive, systematic approach to patient education is a critical safety component for this class of medications. Although the scope of the patient's understanding and participation as an active partner of his/her care is obviously greater with warfarin, patients prescribed dabigatran, rivaroxaban and apixaban also require an appreciation of the importance of long term persistence with therapy, avoidance of leisure and occupational activities that may raise bleeding risk, and the need to inform all providers (including dentists) who participate in his/her care regarding anticoagulation status. Since patients taking dabigatran, rivaroxaban and apixaban are required to interact with the healthcare system less regularly than those taking warfarin, clinicians may have fewer opportunities to educate and confirm understanding.

Although patient knowledge levels have not always correlated with improved patient adherence, several small studies had demonstrated the relationship between patient education and patient safety. Insufficient patient education was identified as the major predictor of bleeding complications in a study of over 300 (aged >80 years) patients discharged home on chronic oral anticoagulation therapy.[4] Conversely, the safety of anticoagulation therapy in well-informed older adults was shown in a study in which those who reported receiving education from either physician or nurse/pharmacist team had a 60% reduction in risk of serious bleeding events.[5]

A quasi-systematic review of articles published from 1990-2011 appears to confirm that higher levels of patient knowledge result in better anticoagulation control. This same review also highlights that a great majority (between 50% and 80%) of older patients have inadequate knowledge about fundamental aspects of their anticoagulation therapy.[6] Still other studies have revealed surprisingly low knowledge levels among patients with atrial fibrillation, from an understanding about their condition to the benefits and associated risks of their current treatment.[7]

Although anticoagulation education may be provided to most patients in some form, the quality of the information varies, as does the readability. Diamantouros et al. reported the results of a survey to assess the accuracy, comprehensiveness, and reading level of print patient education materials on anticoagulation therapy provided to patients by community pharmacies in Ontario, Canada. In addition to gaps in accuracy and comprehensiveness of content, the findings revealed that the reading level of material provided to patients was at an approximate mean of grade 11.[8] This is concerning in light of what is known about the health literacy levels of Americans. It has been shown in a study of anticoagulation therapy with

warfarin, more than half of patients were unable to comprehend clinical terms at levels beyond grade 8.[9] Studies have shown higher levels of both nonadherence (although not all research confirms this correlation) and bleeding complications in those with low literacy levels.[10]

Issues related to low health literacy and its association with suboptimal adherence and safe patient care are ubiquitous in contemporary patient education literature. The Agency for Healthcare Research and Quality (AHRQ) has defined health literacy as "…the degree to which individuals can obtain, process, and understand the basic health information and services they need to make appropriate health decisions."[11] Literacy levels are known to decline in older adults, no matter the baseline levels at age 65.[12] The National Network of Libraries of Medicine noted the following statistics associated with health literacy in older adults:

- 71% of adults older than age 60 have difficulty using print materials
- 80% have difficulty using documents such as forms or charts
- 68% have difficulty interpreting numbers and performing calculations.[13]

Given the demographic of patients with chronic atrial fibrillation, attention to providing easily understood, plain language patient education material is particularly important. Although there is of course a correlation between years of formal education and health literacy levels, it cannot be assumed that a patient with a college or even graduate level education will understand complex information or be familiar with medical terminology. Experts on effective clinician/patient communication recommend the "universal precautions" approach, that is, communicating with all patients in plain language.

AHRQ has provided a patient education booklet and video, *Blood Thinner Pills: Your Guide to Using Them Safely* (available in both English and Spanish), covering the requisite information for patients on chronic OAT. The piece has been updated to include information about other anticoagulants besides warfarin.[14] Although printed patient education pieces are an important adjunct, face-to-face communication regarding oral anticoagulation remains integral, and is one of the components of the Joint Commission's national patient safety goals. In their 2007 publication, *What Did the Doctor Say?*, the following evidence-based techniques are recommended for use in the face-to-face encounter[15]:

- Use plain language always
- Use "teach back" and "show back" techniques to assess and ensure patient understanding
- Limit information provided to two or three important points at a time (At this point, before moving on, confirm understanding with teach-back. This has been termed "chunk and check.")
- Use drawings, models or devices to demonstrate points
- Encourage patients to ask questions

It is important for the clinician to introduce the concept of teach-back as a tool with which the clinician is assessing his/her effectiveness in communicating; not a means of testing the learner (patient). An example of such an introduction might be: "I know we have gone over a lot of information this morning. I want to be sure I made clear the three major things you need to remember about this medication. Can you review with me what those are?" If the patient is unable to name the major point, the clinician would then reinforce the information, possibly stating it in a different or simpler and clearer fashion.

## SHARED DECISION MAKING

Shared Decision Making is a process by which a fully informed patient participates actively in a decision about the treatment of a "preference sensitive condition," that is, one for which there is more than one clinically appropriate treatment option for the condition, each with benefits and drawbacks. The SDM process may involve the use of decision aids, or tools that clarify the decision at hand, provide information about the options and outcomes, and help identify personal values. Interestingly, a paper in the patient education literature reviewing the perspectives of clinicians and patients on decision-making revealed discordance between the two views of the process. While clinicians perceived that patients had been involved in the decision-making process, patients reported experiencing a more paternalistic approach.[16] As the culture of our healthcare systems evolve more deliberately into a more evidence-based, patient-centered approach, it is intuitive that SDM be integrated into plans of care. SDM has been termed "the pinnacle of patient centered care."[17] There are various definitions of the concept. A definition by the Informed Medical Decisions Foundation, "… a collaborative process that allows patients and their providers to make health care decisions together, taking into account the best scientific evidence available, as well as the patient's values and preferences" is helpful in framing SDM for the patient with atrial fibrillation.[18] Descriptions of the SDM model include, at minimum, the following components[19]:

1. Both clinician and patient participate
2. Bidirectional sharing of information
3. Both clinician and patient express preferences and explore options
4. A treatment decision (options include no treatment) is reached.

The SDM process has further been conceptualized as two expert parties meeting to share their perspectives: the clinician as an expert on the disease process, various treatment options with their potential risks and benefits and the patient, as the expert on his own goals, preferences and values. There are actually two touch points in the trajectory of treatment of the patient with atrial fibrillation for which SDM is appropriate for the clinician/AF patient dyad: (1)the evaluation of the impact of AF on quality of life- which will inform treatment options for symptom control, and (2)management of thromboembolic risk.

The options for symptom (fatigue, dyspnea, palpitations) management are complex. Despite their obvious subjectivity, the impact of symptoms associated with AF is quite variable, can be significant, and may change over time. The two major categories of choices are rate control and rhythm control. The overarching category of rhythm control (achievement and maintenance of sinus rhythm), of course, contains a plethora of additional options- pharmacologic, cardioversion, and/or ablation. A SDM approach taking into account the impact of symptoms on quality of life seems particularly well-suited to the rate control/rhythm control discussion, since research to date has not demonstrated a mortality difference in the two major categories of treatment options.[19] Decision-making would of course include the consideration of thromboembolic risk reduction as part of the "mix" for those who opt for rate control. Actual standardized decision tools for rate/rhythm management choices have not been reported in the literature.

There remains a gap in the application of evidence-based guidelines for the reduction of thromboembolic risk for patients with NVAF. As reported in the American College of Cardiology's NCDR PINNACLE registry, only slightly over half of NVAF patients in the registry 2007-2009 who meet evidence-based criteria for anticoagulation were actually on (warfarin) anticoagulation, despite the clear evidence for stroke risk reduction.[20] A more recent study of the percentage of patients with AF on anticoagulation, after the availability of the first novel agent, demonstrated that the percentage of patients on warfarin decreased as the number on dabigatran increased, but the percent receiving no anticoagulation remained at 40%.[21] In December 2012, a consensus meeting was held in which leaders from academia, government, industry, and professional societies to address the barriers to optimal anticoagulation use. Among the many recommendations that rose from this meeting was enhancement of patient education efforts regarding stroke prevention as well as the incorporation of SDM into the clinical encounter.[22]

Development of a decision aid, or tool, to facilitate SDM around anticoagulation versus no anticoagulation for the patient with NVAF is based in part on a validated scoring system used for individual stroke risk estimation, such as the $CHADS_2$ or the $CHA_2DS_2$-VASc scores combined with a parallel tool to estimate bleeding risk, such as HEMORR2HAGES, HAS-BLED, and ATRIA. This is then combined with detailed information about the treatment options, and questions for the patient regarding how he feels about the options, and how he ranks the importance of the associated pros and cons. One example of an AF anticoagulation decision tool can be viewed at: http://www.nice.org.uk/guidance/cg180/resources/cg180-atrial-fibrillation-update-patient-decision-aid2.

Certain web-based tools can be accessed independently by patients outside of the space of the clinical encounter; these can be used in preparation for the clinic appointment. Other SDM tools are designed as "encounter tools"[21] and used as a tool to frame the conversation during the clinical encounter. Key to wide adoption will be the efficiency with which these tools can be integrated into the clinical flow.

With the current novel anticoagulation options in addition to warfarin, clinicians and patients can also work together to decide on the use of appropriate agent. Not all patients are candidates for all of the new agents, based on their individual clinical characteristics including stroke history and renal function. Some patients may prefer to opt against twice-daily treatment options.

In patients for whom warfarin is chosen, options for method of follow up may also be offered—traditional office based follow up with INR measurement done at an outpatient laboratory facility, point-of-care testing in a physician office setting or follow up at an anticoagulation clinic, many of which are staffed by clinical pharmacists or advanced practice nurses. Additionally, home INR monitoring is an appealing option for some patients. A meta-analysis measuring the impact of Patient Self-Testing (PST) and on Clinical Outcomes demonstrated that PST was associated with fewer deaths and thromboembolic events, without any increase in serious bleeding risk, compared to usual care.[23] In general PST compares favorably to traditional testing, but it is not suitable for all patients.

The potential for more frequent (weekly) INR measurement when testing is done at home appears to increase the time in therapeutic range (TTR). In the recently published STABLE study, of patients taking warfarin who did home self INR testing on a weekly basis, weekly testers achieving a TTR of 74% versus 68.9% for variable PST (1–4 tests per month) self-testing.[24]

## CONCLUSION

Comprehensive patient education using plain language, clear information and incorporating methods to confirm patient understanding is important to safe management of the patient with atrial fibrillation, especially those who are prescribed chronic oral anticoagulation therapy. The use of shared decision making to include the patient as a true partner in care is a growing mandate in our evidence-based patient centered culture. New options for choice of anticoagulants as well as new options for anticoagulation management processes will increase opportunities for individualized option that achieve quality outcome metrics, including the satisfaction of individual patient values, preferences, and needs. ■

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