Untreated atrial fibrillation in the United States of America: Understanding the barriers and treatment options

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Atrial fibrillation is the most commonly treated arrhythmia in the United States of America. Stroke is the most devastating consequence of atrial fibrillation. For decades, warfarin has been the most recommended treatment for patients with atrial fibrillation at risk for stroke and systemic emboli. However, many patients at risk are not treated with anticoagulants. Several reasons exist, including physician underestimation of patient stroke risk, physician overestimation of bleeding risk, and patients' reluctance to take chronic warfarin due to the difficulties of this medication in relation to its pharmacokinetics and interactions with food and other medications. Risk scores have helped to better define patient risks and benefits from chronic anticoagulation. Novel anticoagulants (NOACs) have improved the ability for patients to be compliant with anticoagulation.

Keywords: Atrial fibrillation, Anticoagulation

Contents

Atrial fibrillation is the most commonly treated arrhythmia in the United States of America. Since atrial fibrillation occurs most often in older individuals, and since the average age of the population is increasing, the incidence and prevalence of atrial fibrillation continue to grow at an alarming pace. Atrial fibrillation has many hemodynamic consequences caused by the loss of the atrial contribution to cardiac output as well as the rapid ventricular rates that occur in patients

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with normal AV node function. Structural changes which occur in the fibrillating atria, such as enlargement of the chamber and fibrosis of the atrial tissue, are well described. Some patients with atrial fibrillation present without any symptoms whatsoever, but others complain of palpitations, breathlessness, fatigue, and decreased exercise tolerance. Some patients remain asymptomatic until rapid rates lead to a cardiomyopathy, and symptomatic pulmonary edema may be the first manifestation of atrial fibrillation. Treatment for symptomatic patients with atrial fibrillation includes AV nodal blockers to control rate and sodium and potassium channel blocking agents such as Class I and Class III antiarrhythmic drugs to attempt to maintain sinus rhythm. Catheter ablation to isolate the pulmonary veins from the body of the left atrium has been shown to be an effective strategy in patients with paroxysmal atrial fibrillation refractory to antiarrhythmic drugs. Other strategies often include ablation of other foci along with pulmonary vein isolation and are employed in patients with persistent atrial fibrillation, usually with less success.

Abbreviations

ACC	American College of Cardiology
AFASAK	Atrial Fibrillation, Aspirin, and Anticoagulation
AHA	American Heart Association
ARISTOTLE	Apixaban for Reduction In Stroke and Other ThromboembolLic Events in Atrial Fibrillation
AV	atrioventricular
BAATAF	Boston Area Anticoagulation Trial for Atrial Fibrillation
CAFA	Canadian Atrial Fibrillation Anticoagulation
EAFT	European Atrial Fibrillation Trial
HRS	Heart Rhythm Society
INR	International Normalized Ratio
NOACs	novel anticoagulants
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
ROCKET-AF	Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared to vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation
SPAF	Stroke Prevention in Atrial Fibrillation
SPINAF	Stroke Prevention in Nonrheumatic Atrial Fibrillation

Although atrial fibrillation can have many consequences for individuals, the most devastating consequence of atrial fibrillation is stroke. Having atrial fibrillation increases the incidence of stroke by several-fold [1]. The left atrial appendage appears to be the most common place in the left atrium for thrombus to form due to stasis of blood as a consequence of poor atrial contraction in the fibrillating atrium, but thrombus can form in any portion of the atria.

Unlike the antiarrhythmic agents that attempt to maintain sinus rhythm with mediocre success, anticoagulant agents have been shown to be very effective in preventing thromboembolic complications of atrial fibrillation. For several decades, warfarin has been the standard treatment in preventing thromboembolism in patients with atrial fibrillation. Multiple studies published in the 1980s have shown both morbidity and mortality benefits in patients treated with warfarin with a target International Normalized Ratio (INR) of 2–3 as compared to those treated with placebo. In fact, when examining the results of the six major studies which addressed this issue – Atrial Fibrillation, Aspirin, and Anticoagulation (AFASAK), Stroke Prevention in Atrial Fibrillation (SPAF), Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF), Canadian Atrial Fibrillation Anticoagulation (CAFA), European Atrial Fibrillation Trial (EAFT) – only one crosses the line of identity. This occurred because the study was terminated prematurely after the review board felt it unethical to continue the study when the results of similar trials were so impressive with warfarin being convincingly superior to placebo in stroke prevention. A meta-analysis of the data has demonstrated a statistically significant 62% relative risk reduction for stroke and a 26% relative risk reduction in all cause mortality in patients with atrial fibrillation treated with warfarin as compared to placebo [1]. Aspirin has also been used for stroke prevention in patients with atrial fibrillation, but the results are far inferior when compared to warfarin [2].

However, unlike the use of aspirin for patients with coronary artery disease, the use of warfarin in patients with atrial fibrillation remains unacceptably low. An analysis of the PINNACLE database (a volunteer registry of outpatient cardiology practices) demonstrated that only 55.1% of patients deemed eligible for warfarin without contraindications were treated with this agent [3]. Of the almost 45% of patients not on warfarin, slightly over half were treated with only an aspirin, about 5% were treated with a thienopyridine alone, and about 10% were treated with both an aspirin and a thienopyridine. Almost 35% of those not treated with warfarin were taking no antithrombotic or antiplatelet agent at all. Furthermore, there were wide ranges of compliance with

the guidelines across practices with some achieving 80% compliance with the use of warfarin in appropriate patients and others less than 30%.

Why is treatment with anticoagulants so difficult in patients with atrial fibrillation at high risk of stroke? I believe three main reasons exist.

(1) First, it is possible that some practitioners have difficulty identifying the appropriate patient for anticoagulation partly because they may be unaware of the conditions that place a patient at higher risk of stroke. However, identifying patients with atrial fibrillation at high risk of stroke is actually quite easy. Studies have shown that the total amount of time spent in atrial fibrillation does not correlate linearly to the risk of atrial fibrillation. Therefore, patients with paroxysmal or self-limiting atrial fibrillation are at equally high risk as those in persistent or permanent atrial fibrillation. In patients with non-valvular atrial fibrillation, anticoagulation with warfarin with a target INR of 2.0–3.0 has been recommended for many years. INR targets are often higher in patients with mechanical heart valves or those who experience thromboembolic complications despite INR levels in the recommended target range. For most other patients with atrial fibrillation, the $CHADS_2$ score has been useful. The score works by giving one point for each of the following conditions: congestive heart failure (C), hypertension (H), age >75 (A), and diabetes mellitus (D) in patients with atrial fibrillation. Two points are given if the patient suffered a stroke or other thromboembolic complication (S2) in the past [4]. According to the ACC/AHA/HRS guidelines last published in 2011, patients with a score of 0 can be treated with aspirin. For those with a score of 2 or greater, warfarin is recommended, and those with a score of 1 can be treated with either aspirin or warfarin [5].
Although easy to remember, the $CHADS_2$ score has some limitations. It does not include patients with hyperthyroidism who should be treated with warfarin due to their high risk of thromboembolism. Women, patients with vascular disease, and older patients who are not quite 75 years old also have higher incidences of stroke when they experience atrial fibrillation. The CHA_2DS_2-VASc score was developed in order to better define the stroke risk in patients with relatively low $CHADS_2$ scores [6]. The same 1 point is given for patients with heart failure, hypertension and diabetes, and 2 points are still given to those who experience a stroke or systemic embolization. However, if a patient is over age 75, 2 points are given. One point is now given for patients between 65 and 75 years, women, and patients with a history of vascular disease, including myocardial infarction, peripheral vascular disease and even asymptomatic atherosclerosis in the arterial system. The European Heart Association recommends systemic anticoagulation with warfarin or other novel antithrombotic agents for patients with CHA_2DS_2-VASc scores of 1 or greater and no therapy for those patients with CHA_2DS_2-VASc scores of 0. Aspirin is no longer recommended [7].

(2) The second reason for the low use of anticoagulation among patients with atrial fibrillation at risk of stroke is practitioners' overestimation of the bleeding risk of anticoagulants, especially in elderly patients. Certainly, the incidence of gastrointestinal bleeding is higher in patients treated with anticoagulation than those who are not. A fall in a patient treated with anticoagulation is more likely to cause traumatic bleeding. And, in patients with poorly controlled hypertension or those with supra-therapeutic levels of anticoagulation, intracranial hemorrhage may be more likely to occur and more difficult to treat as compared to patients not treated with anticoagulation. However, bleeding risk can be calculated by several scoring systems. The HAS-BLED scoring system assigns a point for each of the following conditions: Hypertension, Abnormal liver or renal function, Stroke history, Bleeding predisposition, Labile INRs, Elderly (age >65 years) and Drug or alcohol use [8]. Adding up the score can help predict the risk of major bleeding. A score of 3 or more predicts a high risk of bleeding, but does not necessarily suggest that anticoagulation is contraindicated. The practitioner can determine risk of stroke from the CHA_2DS_2-VASc score and the risk of major bleeding from the HAS-BLED score to better understand the risk–benefit ratio. It is important to remember that many patients would accept a much higher risk of major bleeding as compared to a moderate risk of stroke. Strokes are devastating to most patients

and families, and most bleeding events, although stressful at the time of bleeding for the patient and family, do not lead to long term health impairment and do not affect patient quality of life in the long term.

(3) The third major obstacle in the use of anticoagulants is patients' reluctance to take these medications. Until only a few years ago, warfarin was the only oral agent approved to prevent thromboembolism in patients with atrial fibrillation, and this agent is quite difficult for patients to use. The dosage for patients is not standardized to patient age, weight, or renal function, so most dosing is empiric, with refinement of dosage taking place over several weeks, based on INR blood testing. This requires the patient to undergo once or twice weekly phlebotomy with frequent drug dosing adjustments. Even after a dosage is determined, it continues to be a moving target, and dosage adjustments are often a constant occurrence for patients taking warfarin. Interactions with other pharmacologic agents are numerous – too numerous for most physicians to remember. I still look up online drug interactions with warfarin whenever prescribing new drugs to my patients taking warfarin. But it is not so much the interactions with drugs that make the use of warfarin difficult. It is the fact that so many foods affect Vitamin K homeostasis, that even minor changes in a patient's diet can have profound effects on INR levels. Patients' diets tend to vary by season of the year, as do personal food preferences. Asking patients to eat a similar diet of green leafy vegetables and other high fiber and vitamin K rich foods is easy to do, but often not feasible or desired by patients. Another factor making warfarin difficult is the constant change of dosage, especially in elderly patients who already use polypharmacy. It is not uncommon to have a patient taking 5 mg of warfarin alternating with 2.5 mg for one week, but then change to 5 mg, 5 mg, 2.5 mg in daily sequence. It can be difficult for patients to remember their current dose.

Another problem with warfarin is its relatively long half-life which makes it difficult to start and stop the medication for invasive procedures. In some high risk patients, this might require in-hospital continuous administration of intravenous heparin until the INR reaches a therapeutic level, prolonging patient hospital stay. An inpatient stay may not be required for subcutaneous administration of enoxaparin, but patients and family members may be reluctant to administer injections if they are unfamiliar with this practice. Lastly, the fact that warfarin was developed as a poison for rodents is largely known by the general population, and causes reluctance to its use by many patients who may be unfamiliar with the benefits of this medication in lessening the devastating consequences of stroke and systemic emboli in patients with atrial fibrillation.

So, how can these three issues be addressed in order to increase the usage of anticoagulant agents in patients with atrial fibrillation at high risk for stroke? Certainly, physician education is a good place to begin. The use of the $CHADS_2$ and CHA_2DS_2-VASc scores is a frequent topic for discussion at national and local conferences. Committees of experts from national and international organizations have reviewed the entirety of published data on this subject and compiled guidelines that make it easier for practitioners to use anticoagulation appropriately. With the use of the PINNACLE initiative, the American College of Cardiology has helped practices to review their compliance with the guidelines for the use of antithrombotic drugs in patients with atrial fibrillation. A random sample of patient charts are reviewed in order to determine if a $CHADS_2$ or CHA_2DS_2-VASc score has been calculated, and if the patient is being appropriately treated according to guidelines. If contraindications to anticoagulation are noted in the chart, they are taken into account as well. When the results from individual practitioners and the group as a whole are compiled, a meeting is arranged. If results are below national norms and do not conform to those recommended by national and international guidelines, the College brings in national experts to the practice in order to educate the practitioners. After several months, the College works with the practice to re-audit patient charts, specifically looking for improvements in patient care in the use of antithrombotic agents.

Patient education is also very important in treating patients with antithrombotic agents. Unfortunately, until recently, direct education to patients has been a very difficult issue, as it is time consuming for practitioners to individually educate patients, while resources from industry, government and national organizations have been scant. As warfarin has been a generic and inexpensive medication for many years, there is little incentive

from the pharmaceutical industry to promote the use of the drug alongside patient education touting its benefits.

The release of the novel oral anticoagulants (NOACs) in the United States over the past several years has helped overcome many of the challenges of treating patients with atrial fibrillation with oral anticoagulants. In October 2010, dabigatran was the first oral anticoagulant approved for the prevention of stroke in patients with non-valvular atrial fibrillation. Approval for rivaroxaban and apixaban soon followed. Landmark studies, including Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) [9], Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared to vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) [10], and Apixaban for Reduction In Stroke and Other ThromboembolLic Events in Atrial Fibrillation (ARISTOTLE) [11], have helped raise awareness of new ways to prevent stroke. Several different advertisements now appear in the latest issues of most journals further reminding physicians of the benefits of anticoagulants. One of the most beneficial effects of all three NOACs is their low incidence of intracranial hemorrhage as compared to warfarin. This particularly combats physician reluctance to use an antithrombotic agent. Although minor bleeding may occur more frequently with the three agents, major bleeding, the main concern of the prescriber of these medications, is actually lower in patients treated with NOACs compared to those treated with warfarin.

Probably the greatest advantage of the NOACs is increased patient compliance. There are no dietary restrictions for patients taking NOACs, a big difference when compared to warfarin. Dosing the NOACs is much easier as modifications are only advised based on renal clearance. In fact, the NOACs are only available in a couple of different dosages. One potential disadvantage is that dabigatran and apixaban are administered as a twice daily regimen whereas warfarin is once daily. However, since many patients with atrial fibrillation take medications on a twice daily regimen, this is rarely a problem. For patients who take medications once daily, rivaroxaban is a good option, as it is a once daily medication. Weekly or monthly blood testing is not required for dosing or toxicities for the NOACs, again a substantial benefit when compared to warfarin. Drug interactions with the NOACs do exist, but are far less common when compared to warfarin. Due to the relative rapid onset of action, NOACs do not require heparin or enoxaparin bridging for patients, often shortening in-patient hospital stays.

Because the NOACs are all currently under patent by the pharmaceutical industry, cost remains high. This is likely the greatest disadvantage of these drugs when compared to warfarin, which is available generically and very inexpensive. Cost can be especially problematic if the patient does not have a prescription plan or has to pay a substantial co-pay fee. However, since these agents do not require blood testing, many insurers cover the NOACs with only a small additional fee. The high cost of the medication has created competition between the manufacturers and led to greater advertising in newspapers, magazines, and on television. This has likely permitted the consumer to obtain a greater awareness of the risk of stroke in patients with atrial fibrillation, a significant benefit for patients affected by these conditions.

In conclusion, as the population ages in the United States of America, the incidence and prevalence of atrial fibrillation are increasing. The barriers to treating patients with anticoagulants are most commonly related to physician underestimation of the risk of stroke and overestimation of the risks of bleeding, and to patients' reluctance to take warfarin, a difficult medication due to its interactions with food and other drugs and its requirement for frequent blood testing and dosage adjustments. Scoring systems such as the $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores have allowed practitioners to easily calculate risk and benefits for individual patients. National and international guidelines are very clear in their recommendations. The advent of NOACs has decreased bleeding risks in patients compared to warfarin and has simplified the use of anticoagulation for many patients with atrial fibrillation.

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