Atrial Fibrillation

A Clinical Review and Comparison of Warfarin versus Dabigatran for Anticoagulation Therapy.

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Introduction:

Atrial fibrillation (AF), or AFib, is the most commonly occurring type of cardiac arrhythmia [1]. AF is commonly referred to as an "irregularly irregular" rhythm and is defined as a supraventricular tachyarrhythmia in which an irregular electrical impulse in the upper chambers (atria) of the heart produces an uncoordinated depolarization and thus an inefficient contraction of the atria. As a result, there is a reduction in cardiac output and potential for pooling of blood in the atria which increases the risk of clot formation and mortality from a cerebrovascular accident or pulmonary embolism. AFib is a public health concern that affects up to 6 million people in the United States and is associated with more than 130,000 deaths per year. It also costs the U.S. healthcare system nearly $6 billion per year [2]. AF becomes more prevalent with age, and with the steadily increasing elderly population worldwide, prevention and treatment of this condition becomes more important clinically and economically. Due to the immense burden on the healthcare system, there have been many advances in surgical and pharmacological modalities for treatment AF, however long-term anticoagulation therapy for prevention of thromboembolism has remained a guideline recommended treatment for AF. The goal of this article is to review the clinical aspects of atrial fibrillation including prevalence, pathophysiology, diagnosis, and treatment, with a focus on comparing traditional anticoagulation therapy of Warfarin with the newer non-Vitamin K anti-coagulant Dabigatran (Pradaxa). This article will also serve to review recently collected data from the VA Medical Center in regard to implementation of anticoagulation guidelines in the management of non-valvular AFib.

Epidemiology:

Heart disease and stroke statistics collected by the American Heart Association have shown that the prevalence and incidence of AF has been steadily increasing, and this trend is expected to continue. As of 2010 approximately 2.6 to 6.1 million people in the United States have a diagnosis of AF, with that number estimated to reach as high as 12 million by 2050 [3]. Age, gender, race, lifestyle, and comorbid conditions all play a significant role in the lifetime prevalence of AF. Studies have shown that the prevalence of AF increases as much as two-fold in men and women with each decade of life [4]. The mean age at onset is 66.8 for men and 74.6 for women, with the point prevalence of AF increasing to more than 10% in the population over 80 years old [1,3]. Men have consistently higher rates of AF compared to women throughout a majority of studies putting men at 1.5 times greater risk of AF [3,4]. Multiples studies have also found that white people have significantly higher rate of AF when compared to blacks and other races, with white people accounting for more than 70% of AF related hospital admissions. Interestingly, the non-white races had higher rates of overall risk factors for developing AF [3,4]. Data has consistently shown that the incidence of newly diagnosed AF has also followed the same trend and has been highest among older white males, with the rates growing exponentially after 70 years of age across all genders and races [4]. Many of these statistics are presumed to be underestimated due to undiagnosed cases of AF and patients who are asymptomatic or have only paroxysmal AF. Many of the current studies are also done with predominantly white populations [5].

Additional factors outside of age, gender, and race that increase the lifetime risk of AF include lifestyle and comorbid conditions. Modifiable lifestyle factors that increase the risk of AF include smoking, alcohol, and obesity. Smoking is a known risk factor for increasing the

likelihood of cardiovascular disease which increases the lifetime risk of developing AF. Multiple studies have shown that mild alcohol consumption does not significantly increase the likelihood of developing AF, however binge drinking and heavy alcohol consumption have been shown to be a risk factor. Cardiac arrhythmias, most commonly AF, associated with short periods of binge drinking is a phenomenon known as "holiday heart syndrome" and may be indicative of future cardiomyopathy [6]. Multiple studies have shown that as many as 3 drinks per day, and heavy long-term alcohol consumption significantly increases the relative risk of AF [3,7]. Although the exact pathophysiology is not known, obesity is considered a major risk factor for the development of AF, with a linear relationship existing in which there is a 4.7% increase in risk with each kilogram per square meter above average BMI [8]. Hypertension and coronary artery disease (CAD) are the most common chronic conditions associated with an increased risk of AF. Hypertension has been shown to increase the risk of AF 70% in women and 80% in men, even when the condition is properly treated [3]. While CAD itself does not cause AF, an increased risk of developing AF is generally association with CAD with prior myocardial infarction (MI). This is thought to be caused by ischemia and structural damage to the heart in the setting of MI [9]. Diabetes, chronic kidney disease, obstructive sleep apnea and hyperthyroidism have also been associated with increased incidence and prevalence of AF. There are multiple risk prediction models and online calculators, such as those found on the Framingham Heart Study website, that can be used by clinicians to help identify and reduce lifetime risk and mortality due to atrial fibrillation.

Pathophysiology:

AF is a cardiac arrhythmia in which there is an uncoordinated electrical impulse generated in the upper chambers of the heart that causes an incomplete or inefficient contraction of the atria. The electrocardiogram (ECG) of AF is characterized by irregular R-R intervals, the absence of distinct P waves, and irregular atrial activity (Fig 1). Clinically, the ECG rhythm of AFib is referred to as irregularly irregular [2]. Due to the lack of sufficient impulse and contraction in the atria, AF can cause hemodynamic instability from decreased cardiac output, as well as thrombotic events from stasis of blood in the atria.

AFib occurs when the combination of structural and electrophysiological abnormalities alters the normal functioning of the atrial heart tissue preventing a consistent electrical impulse (Fig 2). The exact mechanism that leads to AF is not well understood, however AF is thought to be the physical manifestation of multiple disease pathways that change the structure and function of the heart. Structural abnormalities that contribute to AF include fibrosis, dilation, ischemia, and hypertrophy, all of which are physical signs of damage caused by heart disease and various other health conditions. These disease processes produce structural remodeling, most significantly fibrosis, that decreases the heart tissue's ability to generate and propagate an electrical impulse. The exact mechanism by which electrical impulses in the atria are altered is not well understood. Some research suggests that a potential trigger for AF may arise from rapidly firing foci that originate in the left atrium and into the pulmonary artery. Unique anatomy of the myocardial fibers within the veins may lead to a reentry impulse that triggers AF. This area is also the target of some surgical treatments for AF [10].

There are multiple types of AF which are classified by the duration of symptoms. The shortest and most benign type is paroxysmal AF, which involves intermittent episodes that generally resolve with or without treatment within 7 days of onset. Persistent AF is a sustained

irregular rhythm that last greater than 7 days, although it may resolve later. Long-standing persistent AF lasts greater than 12 months and is refractory to treatment. Permanent AF is a subcategory of long-standing AF in which the patient and provider have tried all means of treatment and mutually decide to no longer attempt to restore a normal sinus rhythm [2]. AF can also be classified is valvular or non-valvular, which is important when determining the proper type of anticoagulation therapy. The exact definition of valvular versus non-valvular AFib remains unclear, although it is important when considering anticoagulation therapy. Currently, valvular AF is associated with mitral stenosis, mechanical heart valves, and any valve repair, with non-valvular AFib including any valvular disease that does not limit the rate of blood flow to the left atrium such as mitral regurgitation or aortic stenosis, and AFib without valvular disease. [11]. The distinction between valvular non-valvular is important because the guidelines recommend treatment of valvular AFib with vitamin K antagonists, whereas non-valvular can be treated with direct thrombin inhibitors as well [2].

Presentation & Diagnosis:

The evaluation of a patient with suspected AF should include a thorough history to elicit the length and characteristics of symptoms to determine the classification of AF, and a complete physical examination to rule out other possible comorbidities and assess the need for emergent management. The history should cover the events preceding the onset of symptoms such as exercise, stress, or alcohol consumption in order to identify possible triggers or alternative causes of onset. Past medical history, symptoms, prior episodes with treatments, and family history should be reviewed to assess for associated cardiac and non-cardiac disease processes that may

be contributing. A thorough history will help determine future prognosis, risk of thrombotic event, and treatment options. [12].

Patients with AF can have a wide spectrum of presentation from severe to completely asymptomatic, and is an incidental finding in 25-30% of cases [12]. Patients with recurrent or paroxysmal types of AF are more likely to be symptomatic, although the described symptoms and physical exam findings can vary from patient to patient. In contrast, patients with permanent AF, particularly the elderly, often present with very few or no symptoms at all. The most common associated symptoms include palpitations, dyspnea, lightheadedness or dizziness, syncope, and chest pain/angina. Dyspnea is the most common symptom in chronic forms of AF (46.8%), and palpitations the most common with paroxysmal types of AF (79.0%) [12].

The presence of tachycardia, irregular pulses, variations in the intensity of S1 heart sounds, or absence of a previously heard 4th heart sound may be suggestive of a patient with AF. Many patients with AF may be presenting for the first time during an embolic event or heart failure, therefore the physical exam should include inspection for signs of neurovascular compromise or pulmonary and peripheral edema[2].

The diagnosis of AF requires documentation of the arrhythmia with an electrocardiogram (ECG) (Fig. 1). The recording can be done by a single-lead rhythm strip, 12-lead ECG, or ambulatory telemetry devices such as a Holter monitor. All patients with suspected AF should have a chest x-ray to evaluate for possible pulmonary pathology or cardiac enlargement. When AF is confirmed by ECG, patients should also receive a transesophageal echocardiograph (TEE) to identify cardiac abnormalities such as atrial or ventricular enlargement, pericardial disease, and to assess cardiac function. [12]. TEE can also be useful in assessing for the presence of left atrial thrombus which would be a potential source of future emboli, and help guide the timing of

cardioversion and catheter ablation. Prior to cardioversion, 5% - 15% of patients with AF have revealed a LA thrombus with TEE [2].

Additional laboratory testing that should be performed on patients with known or suspected AF include a complete blood count, serum electrolytes, liver and renal function, as well as thyroid function to rule out hyperthyroidism as a potential cause of arrhythmia. If more acute cardiac pathologies are suspected such as heart failure or infarction, the appropriate studies should also be ordered.

Treatment:

Once a full evaluation, including a thorough history, physical exam, and diagnostic workup has been completed to and determine the type of AF and rule out potential underlying causes or risk factors, management options for AF should be considered. Management of AF includes modalities directly targeting the arrhythmia through rate and rhythm control, as well as anticoagulation therapy which mitigate the risk of a major thromboembolic event [13]. The management of AF with therapy directed towards correcting the arrhythmia will be covered briefly here, though the focus of this article is anticoagulation therapy.

Strategies for managing AF focused on correction of the arrhythmia can be divided into rate control and rhythm control. Rate control consists of chronotropic drugs or electrophysiological ablation to reduce the ventricular rate of the heart. The guideline recommended heart rate (HR) goal is a resting HR less than 80 beats per minute (bpm), and less than 115 bpm during mild to moderate physical activity [2]. Medications recommended in the use of rate control include beta blockers, calcium channel blockers, digoxin, and amiodarone. Beta blockers and calcium channel blockers are used for patient without heart failure, whereas digoxin

and amiodarone are recommended for those patients with AF and heart failure [2]. Atrioventricular nodal ablation with a pacemaker implantation is a surgical procedure directed at rate control. While this option eliminates the need for rate control medications, it does require the permanent use of an implanted pacemaker as well as anticoagulation therapy.

The second approach in the management of AF arrhythmia is rhythm control. Rhythm control is accomplished through electrical cardioversion and pharmacological management. Rhythm control with AF is the preferred method of treatment because studies have shown that successful sinus rhythm maintenance is associated with improvements in symptoms and quality of life for most patients. It is the preferred treatment for younger patients, initial episodes of AF, or AF caused by comorbid illness. Direct current cardioversion is the most effective rhythm control method that consists of delivering an electrical shock synchronized to the QRS complex with the goal of restoring a normal sinus rhythm. Pharmacological cardioversion is more effective when given within 7 days after onset. Intravenous administration of Ibutilide has been shown to restore sinus rhythm in up to 50% of patients within 30 minutes, however QT prolongation and torsades de pointes is associated with the use of these medications and can be potentially fatal [2].

Anticoagulation Therapy:

The current guidelines by the American Heart Association, American College of Cardiology, and the Heart Rhythm Society (AHA/ACC/HRS) recommend that all patients with new onset AF undergo a risk stratification assessment and consideration for an oral antithrombotic medication regimen. The presence of AF can increase the risk of thromboembolic event such as stroke or myocardial infarction by up to 20 times compared to those with normal

rhythms, and result in more severe disability and higher rates of mortality [14]. Not every patient with AF will require anticoagulation therapy, and there is no single recommendation that is common to all patients. The decision to begin anticoagulation therapy should be a joint decision between the patient and provider that takes into consideration risk factors, lifestyle, medication type, cost, and side effects. The CHA_2DS_2-VASc score is the recommended tool for calculating risk of stroke and need for anticoagulation therapy [2,15].

The CHA_2DS_2-VASc risk stratification tool (Chart 2), or calculator, is used to determine the risk of stroke or thrombotic event in patients with AF and determine the need for anticoagulation therapy. The tool works by assigning a number value to known risk factors for stroke, including congestive heart failure, hypertension, age >75 years, diabetes, previous stroke, vascular disease, age 65-75 years, and female gender. Each factor is assigned a value of 1 point, while age >75 and previous stroke accounts for 2 points each. The total scores are then used to determine the overall risk and make recommendations for treatment based on the current recommended guidelines. The most recent AHA/ACC/HRS guidelines for the treatment of non-valvular AF recommend anticoagulation therapy, with Warfarin or Dabigatran, for all patients with prior stroke or CHA_2DS_2-VASc score >2. Patients with non-valvular AF and a CHA_2DS_2-VASc score of 1 should be considered for anticoagulation therapy, and those with a score of 0, no anticoagulation therapy is needed [2]. Once the risk of future thrombotic events and need for anticoagulation therapy has been determined, the patient and provider can consider the best medication to use for that individual. Antithrombotic medications reduce the risk of future stroke and emboli by preventing the formation of clots that may form in the atria due to the arrhythmia. One meta-analysis showed an average rate of stroke of just 4.1% per year for patients without previous stroke and 13% for patient with prior stroke, among patients treated with

anticoagulation therapy [2,16]. Common agents used for the prevention of thromboembolism include anticoagulants such as Heparin, Warfarin, and direct thrombin inhibitors, as well as antiplatelet drugs including Aspirin and Clopidogrel. This article will focus on Warfarin and the direct thrombin inhibitor Dabigatran.

Warfarin:

Warfarin has been used to prevent stroke in patients with AF since the 1950's. Warfarin, or Coumadin, is a vitamin K antagonist which works by preventing the synthesis of the vitamin K dependent clotting factors II, VII, IX, X, as well as protein C & S. During the synthesis of these clotting factors the enzyme vitamin K epoxide reductase complex 1 (VKORC1) reactivates vitamin K from an inactive form which is then used as a cofactor in the production of the clotting factors. Warfarin binds to the C1 subunit of the VKORC1 enzyme complex and prevents the reactivation of vitamin K, thus reducing the available vitamin K and synthesis of clotting factors. By reducing the amount of available clotting factors, there is a reduction in the ability to form a clot, thus decreasing the risk of thrombotic event and stroke [17–19].

The dosing of Warfarin should be individualized for each patient and take into consideration comorbid conditions and current state of the patient. While there are no current dosage adjustment recommendations for comorbid conditions, geriatric patients, those with renal, hepatic, or cardiac dysfunction, or those who are at increased risk of bleeding should be closely monitored. Warfarin has a very narrow therapeutic range and therefore requires strict adherence, regular monitoring, dosage adjustments, and dietary restrictions in order to remain safe and effective. The anticoagulation effect of Warfarin is monitored using a blood test that measures the prothrombin time and international normalized ratio referred to as the PT/INR. The

target INR for AFib treated with Warfarin is 2.5 with a range of 2-3 [2]. When a patient's INR is above this recommended range, they are at increased risk of major bleeding, and if it is below the recommended range they are at risk of a thromboembolic event, such as stroke, which the medication is indicated to prevent. In order to maintain within the therapeutic range it is recommended that patients have their INR checked two to three times per week upon starting the medication until they reach a therapeutic level, then every 1-4 weeks thereafter, dependent on their ability to maintain with the range [18,20]. The determination of frequency of monitoring should take into consideration the patient's preference, access, medication adherence, and past success maintaining within the therapeutic range. Initial dosing of Warfarin is 2 to 5 mg once daily, or 10 mg once daily for healthy patients with daily INR monitoring until the recommended target INR is achieved. The onset of action of Warfarin is 24 to 72 hours and the peak effect taking 5 to 7 days, therefore patients with an acute thromboembolism should be started on more rapidly acting Heparin with Warfarin started on the first or second day of treatment. Once a patient has reached the target INR they should be placed on maintenance therapy between 2 to 10 mg per day in order to maintain within the range. It is also recommended that the medication be taken at a regular time each day without interruption. Inconsistency with medication adherence can cause large variations in INR and put the patient at risk of stroke or hemorrhage [17].

Due to Warfarin's effect of preventing the formation of clots by lowering the amount of available clotting factors, there is inherently an increased risk of bleeding associated with its use. In fact, the increased risk of major bleeding defined as that which requires hospitalization, surgery, transfusion, or bleeding that occurs in the head, is the number one risk factor associated with the use of Warfarin as long-term anticoagulation therapy for AFib. The FDA has issued a Boxed Warning recognizing the increased risk of bleeding and recommending interventions to

reduce the risk, including regular INR monitoring and immediately reporting any signs or symptoms of irregular bleeding [21]. Multiple clinical trials and observational studies have shown that the overall risk of major bleeding associated with the use of Warfarin ranges between 1 to 3 percent per person per year [13]. Of the most concern, due to its high rates of mortality and potential for long-term neurological disability, is intracranial hemorrhage (ICH), which accounts for up to 90% of deaths and permanent disability related to Warfarin-associated bleeding. The reported risk of ICH attributed to Warfarin therapy for AFib ranges between 0.2 to 0.4 percent per year, however this number may be higher dependent on additional patient risk factors. While the risk of major bleeding is increased, the overall risk of stroke while on adjusted-dose Warfarin therapy for AFib is reduced by two-thirds when compared to placebo or no therapy [22]. The provider and patient must determine if the benefit offsets the potential risk with the anticoagulation therapy. They must also be counseled on the importance of regular dosing, monitoring, and reporting of anything that increases the risk of bleeding including accidents, falls, surgeries, changes to other medications, or eating habits.

In the event that a patient presents with a supratherapeutic INR(>4) without bleeding, the American College of Chest Physician Guidelines recommends lowering or withholding the dose until INR returns to normal and administration of oral vitamin K1 depending on the level of INR. If a patient experiences a major bleeding event the guidelines recommend discontinuation of the medication, administration of intravenous vitamin K1, and possible supplementation with four-factor prothrombin complex concentrate (PCC). Other possible treatments include fresh frozen plasma and activated factor VII in urgent cases. [18,23].

Other considerations that should be taken into account when a patient is treated with Warfarin for AFib include dietary restrictions, alcohol consumption, and sports participation.

The effectiveness of Warfarin and the ability to stay within the therapeutic INR range is greatly affected by dietary intake of vitamin K. While it is not recommended that patients refrain entirely from all foods rich in vitamin K, they should be educated on the vitamin K content of food and encouraged to maintain a consistent intake of vitamin K through their diet to maximize the therapeutic effect of the medication [17]. The mechanism by which alcohol disrupts the effect of Warfarin is not completely understood, though studies have shown that the risk of major bleeding increases with moderate to severe alcohol consumption. As with dietary intake of vitamin K, patients should be encouraged to limit alcohol consumption and binge drinking while taking Warfarin [24]. There are currently no recommendations or guidelines addressing activity level or participation in sports while on Warfarin, however the increased risk of severe bleeding is greater than that of the general population and the patient should be informed that a potential injury may be complicated by the increased risk of bleeding [17].

Dabigatran:

For patients with non-valvular atrial fibrillation who require anticoagulation therapy and are unable to or elect not to take Warfarin, an alternative option is to choose from a class of anticoagulation medications referred to as newer, novel, or direct oral anticoagulants (NOAC/DOAC). These anticoagulation medications work on different sections of the clotting cascade than Warfarin while providing the same, if not better, therapeutic effect with less laboratory monitoring, and in some cases less risk of bleeding. Of these newer medications, Dabigatran was the first to be approved by the FDA in 2010 for the prevention of embolic stroke in patients with non-valvular AFib after the RE-LY study showed it to be non-inferior to Warfarin. Dabigatran is a competitive direct thrombin inhibiting prodrug that binds to thrombin

(Factor IIa) and prevents the conversion of fibrinogen to fibrin and activation of platelet receptors and platelet aggregation. Once dabigatran is activated in vivo it binds to the active site of free, fibrin-bound, and clot-bound thrombin receptor sites preventing further activation of the clotting cycle and inducing its anticoagulation effects [25].

The current recommended dose of Dabigatran for prevention of embolic stroke in patients with AFib is 150 mg twice daily, however the 2014 AHA/ACC/HRS guidelines recommend adjusted dosing for patients with chronic and end stage kidney disease. Patients with a creatinine clearance (CrCl) between 30-50 ml/min require no dosage adjustment unless concurrently prescribed Dronedarone or oral Ketoconazole, and those with CrCl of 15-30 ml/min should be adjusted to 75 mg twice daily. The AHA guidelines and the American College of Chest Physicians both recommend against the usage of Dabigatran in patients with severe renal dysfunction whose CrCl is less than 15 ml/min due to lack of evidence from clinical trials [2,26]. Unlike Warfarin, Dabigatran produces consistent and linear dose-dependent anticoagulation properties that are not affected by the patient's diet or activity, and therefore does not require regular laboratory monitoring or frequent dosage changes based on INR values[25,26].

Dabigatran has absolute contraindications for patients with a hypersensitivity to the drug or its components and those with pathological active bleeding. The 2014 AHA guidelines for management of patients with atrial fibrillation also has a class III for harm recommendation against the use of dabigatran for patients with a mechanical prosthetic heart valve [2,26]. As with Warfarin, and all other anticoagulant medications, Dabigatran increases the risk of bleeding, although data from the RE-LY study and multiple meta analyses have shown that the risk of major bleeding including intracranial hemorrhage are less with Dabigatran when compared to Warfarin [27,28]. The product labeling for Dabigatran does include a Boxed Warning concerning

the increased risk of epidural and/or spinal hematomas which may occur in patients who undergo neuraxial anesthesia or spinal puncture procedures, and may result in long-term or permanent paralysis. It is recommended that these patients receive frequent monitoring of neurological symptoms in this setting [26,29]. The most common side effect associated with the use of Dabigatran are gastrointestinal symptoms which can occur in 25-40% of patients [26].

In 2015 the FDA approved the drug Idarucizumab (Praxbind) as a reversal agent for Dabigatran based on a preliminary report from the ongoing RE-VERSE AD study. Prior to the approval of Idarucizumab, many patients and providers were hesitant to choose Dabigatran over Warfarin for anticoagulation therapy because dabigatran does not respond to vitamin K and there was no reversal agent in the event of major hemorrhage due to accidental overdose or bleeding due to trauma. In August 2017 the final report from the RE-VERSE AD study based on 503 patients treated with Idarucizumab to reverse the effects of dabigatran prior to a surgical procedure or in the event of major bleeding showed that a single 5 gram dose of the medication completely reversed the anticoagulation effect in 98% of patients for at least 24 hours [30].

Warfarin vs. Dabigatran:

The risk of stroke is increased up to 5 times in patients with non valvular atrial fibrillation, and is attributed to higher rates of recurrent stroke and mortality, as well as more severe disability following a thrombotic event when compared to those with a normal sinus rhythm [2]. Since the 1950's, Warfarin has been the oral anticoagulation medication of choice until the FDA approval of Dabigatran in 2010. Multiple studies have shown that oral anticoagulation therapy is superior in the prevention of stroke as a primary outcome for patients with non valvular AFib, when compared to antiplatelet or no therapy at all [31]. A 2007 meta-analysis that

reviewed 29 randomized controlled trials comparing adjusted dose Warfarin to placebo and antiplatelet therapy showed that Warfarin was nearly 40% more effective in preventing stroke than antiplatelet therapy alone. Warfarin reduced the risk of stroke by 64% (95% CI: 49% to 74%) with an absolute risk reduction of 2.7% per year with the number needed to treat to prevent 1 stroke in one year of 37 [16]. These results have been consistent across multiple trials and reviews.

The efficacy and safety of Dabigatran for use in patients with AFib on long term anticoagulation therapy was compared to Warfarin in the RE-LY (Randomized Evaluation of Long Term Anticoagulation Therapy) trial in 2009 [2]. The RE-LY trial included 18,113 patients with AFib and an increased risk of stroke who were randomly assigned Dabigatran at 110mg and 150mg doses or adjusted dose Warfarin, and had a primary outcome of stroke or systemic embolism. All patients were randomly assigned a treatment group with each dose of Dabigatran (110mg/150mg) double blinded and Warfarin being open label and unblinded. The mean age of the participants was 71 years, with 63.6% male, and the mean $CHADS_2$ score being 2.1. The mean follow-up period was 2.0 years with a 99.9% follow up rate and only 20 patients lost to follow up [32].

The results of the RE-LY trial showed that Dabigatran dosed at 110mg was non-inferior to Warfarin in prevention of stroke and systemic embolism, and showed lower rates of life threatening hemorrhage. Dabigatran dosed at 150mg showed significantly lower rates of stroke and embolism with similar rates of bleeding when compared to Warfarin. In the primary outcome of stroke, Warfarin had a rate of 1.69% per year compared to 1.53% for the 110mg Dabigatran group (RR 0.91; 95% CI 0.74 to 1.11; $P<0.001$ for non-inferiority) and 1.11% for the 150mg group (RR 0.66; 95% CI, 0.53 to 0.82; $P<0.001$ for superiority) [32]. Both doses of

Dabigatran were found to be non-inferior to Warfarin however the 150mg dose was superior to dose adjusted Warfarin. The primary safety outcome studied was major bleeding defined as a reduction in hemoglobin level of at least 20g/L, transfusion of at least 2 units of blood, or symptomatic bleeding in a major organ or critical region. Warfarin had a major bleeding rate of 3.36% per year, and both the 110mg and 150mg doses of Dabigatran showed lower rates of 2.71% and 3.11% respectively [32]. The secondary outcomes included both hemorrhagic stroke and mortality with both doses of Dabigatran having significantly lower rates when compared to Warfarin. The rate of hemorrhagic stroke in patients on each dose of Dabigatran was nearly 75% less than that of Warfarin, with the 150mg dose of Dabigatran having lower rates than the 110mg dose [2]. The rates of mortality for Warfarin, 110mg and 150 mg Dabigatran were 4.13%, 3.75%, and 3.64% respectively [32]. The study also showed that Warfarin had higher rates of life threatening bleeding, intracranial bleeding, and minor bleeding when compared to each dose of Dabigatran, however there was a significantly higher rate of gastrointestinal bleeding with the 150mg dose of Dabigatran. Also, each dose of Dabigatran had higher rates of myocardial infarction compared to Warfarin (150mg – 0.75%, 110mg – 0.72%, Warfarin – 0.53%) [32].

Discussion:

The results of the RE-LY trial revealed that Dabigatran dosed at 150mg twice per day was superior to Warfarin in stroke prevention without an increase in major bleeding or intracranial hemorrhage in patients with non-valvular AFib. These finding have been reproduced in multiple studies across multiple age groups with all variations of AFib. The 2014 American Heart Association guidelines for the management of non-valvular atrial fibrillation recommends the use of both dose adjusted Warfarin and 150mg dose Dabigatran for anticoagulation therapy.

Both are Class A recommendations however Warfarin is a level A and Dabigatran is a level B due to much more available research on Warfarin [2]. The 2012 American College of Chest Physicians guidelines for antithrombotic therapy for atrial fibrillation recommends Dabigatran 150mg twice daily in favor of dose adjusted Warfarin for stroke prevention with AFib [33].

Both Warfarin and Dabigatran are acceptable and guideline recommended options for anticoagulation therapy and stroke prevention with AFib. The decision on which medication to choose should be a joint decision-making process between the patient and provider that takes into consideration multiple factors including potential risk of major or life-threatening bleeding, potential side effects, patient lifestyle and adherence ability, and cost as well as the providers experience using one medication over another. Dabigatran is more regularly dosed and does not require frequent blood monitoring or dosage adjustments, which may lead to better medication adherence when compared to Warfarin. It also has no dietary restrictions, less drug interactions, and poses less risk of major bleeding. Dabigatran also has more gastrointestinal side effects, and until recently, a major concern for some patients has been the lack of reversal agent for Dabigatran in case of bleeding emergency. While Warfarin has a higher risk of major bleeding compared to Dabigatran, it has been a reliable and effective medication for many years and is a medication that both patients and providers are familiar with and comfortable using. Warfarin also has lower rates of non-bleeding side effects and a lower risk of myocardial infarction compared to Dabigatran. In many cases the most influential factor in choosing an anticoagulation medication is cost. Currently the cost of Dabigatran is much higher than Warfarin with 150mg Dabigatran $7.42 per dose and Warfarin $3.71 per 10mg dose [20,26]. These costs are strictly the per dosage cost for each medication and do not take into account the overall cost including office visits, laboratory testing, and hospital visits. A study from the Journal of Medical Economics in

2015 presented that the overall medical cost of those on Dabigatran was $204 less per year than those on Warfarin for anticoagulation therapy and they predict the medical cost difference to increase by 2018 [34]. Once it is determined that a patient meets criteria for anticoagulation therapy based on their risk stratification, careful consideration should be given to all of these factors, and the patient should be provided all of the benefit-to-risk information so that they may make an informed logical decision.

Anticoagulation Therapy at the VA:

Treating patients at a VA medical center is a unique clinical experience with a challenging patient population that can alter the medical decision-making process and ultimately change the way a provider implements guideline recommended therapy. This is especially true when considering anticoagulation therapy for veterans with non-valvular atrial fibrillation. VA statistics show that the median age of the veteran patient population is higher than that of the non-veteran population (64 years to 44 years respectively), and the number of significant comorbid medical conditions, including mental health, is higher among the veteran population compared to non-veterans [35,36]. Many of these veterans may also have a physical disability that limits their mobility or ability to drive and leave their homes. Because veterans can only receive care at VA facilities, some patients who do not live near a VA medical center may need to travel long distances for regular care, and thus might only seek care in an emergency. All of these factors can increase the risk of a veteran patient acquiring atrial fibrillation or having potentially serious or life-threatening complications, making the anticoagulation treatment decision more complex. Another important factor is cost. Veterans receive care at the VA free of cost, or at a highly discounted rate, which can change the anticoagulation therapy decision. As was discussed

earlier, the cost of Dabigatran is much greater than that of Warfarin, therefore a patient who prefers to be on the latter may decide to receive his care from the VA in order to get the medication free of cost.

Recently, the Home Based Primary Care (HBPC) team at the Durham VA medical center conducted a quality control study to look at the implementation of guideline recommended anticoagulation therapy for veteran patients with non-valvular atrial fibrillation. Their main objective was to determine if the Veteran patients with AFib receiving home based primary care are on guideline appropriate antithrombotic therapy (either Warfarin or novel anticoagulant; not aspirin alone). The HBPC team also wanted to examine why a veteran was, or was not, adherent to guidelines, why they were on a particular medication over another, and how they could improve compliance to the guidelines. The team used the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation as their recommendations for therapy. The study included 190 of the home based primary care patients who receive all of their non-emergent medical care by a team of providers that come to their home at least once per month. Each patient's CHA_2DS_2VASc score was calculated and a chart review was conducted to determine current anticoagulation therapy, reason for currently recommended therapy, and comorbid conditions [37].

The results of the study showed that 20% (39/190) of the HBPC patients had a diagnosis of AFib. The average age was 81 years with a range of 64-94 years, and a CHA_2DS_2VASc score of 5 being the most common. The increased age and high CHA_2DS_2VASc score put these patients at very high risk of a thromboembolic event and anticoagulation therapy was indicated. Of the 39 patients being treated for AFib, 82% were prescribed Warfarin or a direct thrombin/factor Xa inhibitor such as Dabigatran, and were considered adherent to antithrombotic

guidelines (Fig 3). Of the remaining 7 patients who were not being treated with adequate anticoagulation therapy and considered non-adherent to guideline recommendations, 4 had history of recurrent or life-threatening bleeds, 2 were medication refusal by patients or family, and one had history of medication non-adherence due severe dementia [37].

While the sample population in this study was small, it indicated that the overall compliance of the HBPC team to antithrombotic guidelines was good, and the reasons for non-adherence were clinically acceptable. It also showed that the decision to treat a patient with anticoagulation therapy and what medication to use can become very complex when taking into account advancing age, comorbid conditions, and mental status. The HBPC program poses a unique set of complications when deciding between Warfarin or Dabigatran for anticoagulation therapy. These patients are severely ill or disabled and are only seen by healthcare providers once a month. With these patients, it is hard to frequently monitor INR values in order to maintain within the therapeutic INR window, and there is also a question of the accuracy of the handheld point of care testing machines. On the other hand, a patient who might be at higher risk of medication non-adherence who is already on Warfarin, switching to a NOAC provides no way to monitor the anticoagulation effects, which may make them a poor candidate for Dabigatran despite easier dosing. The HBPC team's study suggests that guideline adherence for anticoagulation therapy at the VA medical center is a complex issue that warrants further examination for the health and safety of veteran population [37].

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Appendix

Chart 1. Clinical Comparison of Warfarin and Dabigatran

Clinical Consideration	Warfarin	Dabigatran
Valvular or Non-Valvular	Valvular & Non-Valvular	Non-Valvular
Cost	$3.71 / 10mg	$7.41 / 150mg
Side Effects	Few	Gastrointestinal
Dosing	2-10mg Adjusted to INR	150mg Twice per day
Monitoring	Every 1-4 weeks	None Recommended
Dietary Restrictions	Stable Vitamin K_1 Intake	None Recommended
Bleeding Risk (RE-LY)	3.36% / year	3.11% / year
Rate of Stroke / yr. (RE-LY)	1.69% / year	1.11% / year
Reversal Agent	Vitamin K	Idarucizumab
Drug/Drug Interactions	850 (213 major)	390 (118 major)
Precautions (Dosage Adjustments)	INR Dependent	CrCl <30 mL/min – 75mg twice per day
Mechanism of Action	Vitamin K antagonist	Direct Thrombin Inhibitor

Chart 2. CHA_2DS_2-VASc Calculation

Category	Score
Congestive Heart Failure	1
Hypertension	1
Age >75	2
Diabetes Mellitus	1
Stroke/TIA	2
Vascular Disease (Prior MI, PAD, aortic plaque)	1
Age 65-74 years	1
Female Gender	1

Fig. 1. Atrial Fibrillation ECG Rhythm Strip.

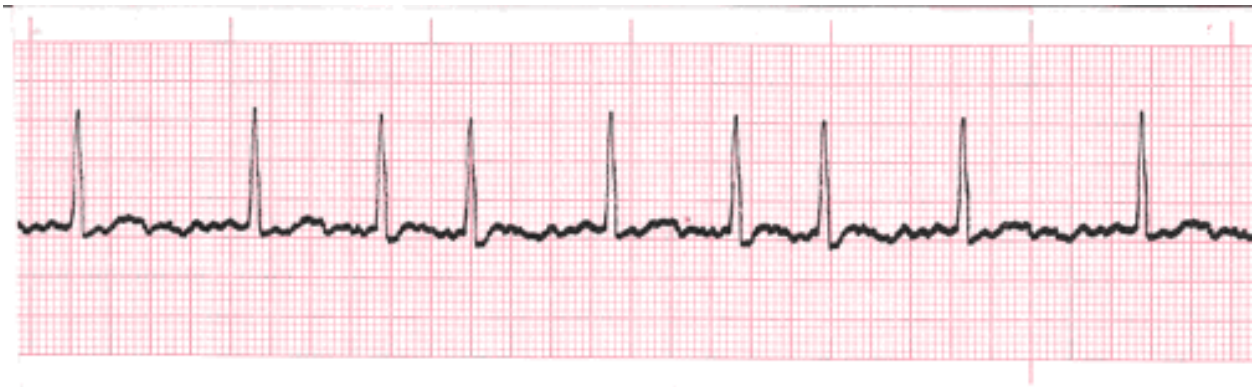

Fig 2.

Mechanisms of AF. AF indicates atrial fibrillation; Ca++, ionized calcium; and RAAS, renin-angiotensin-aldosterone system.

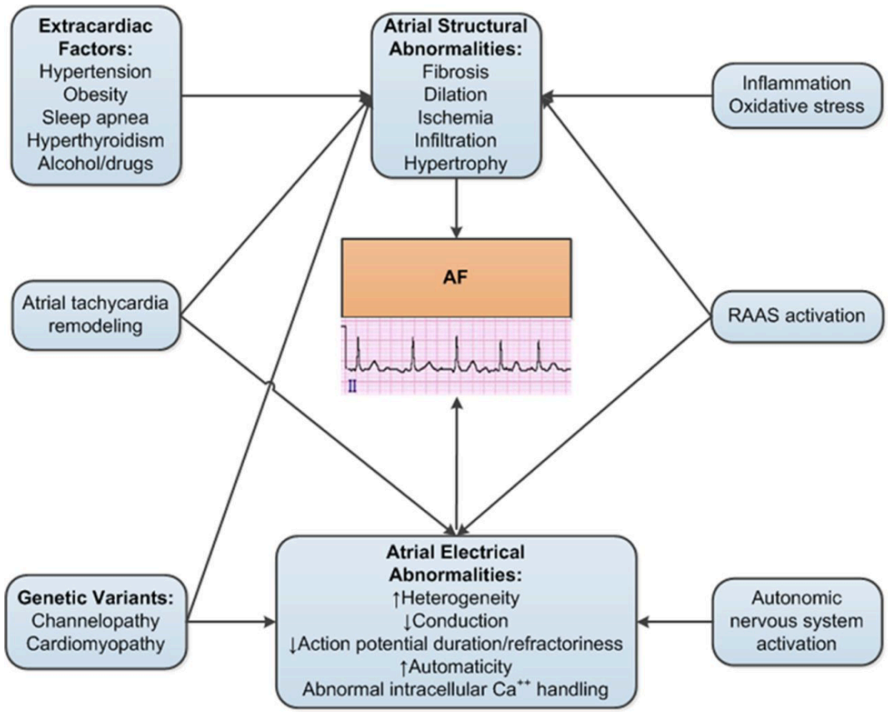

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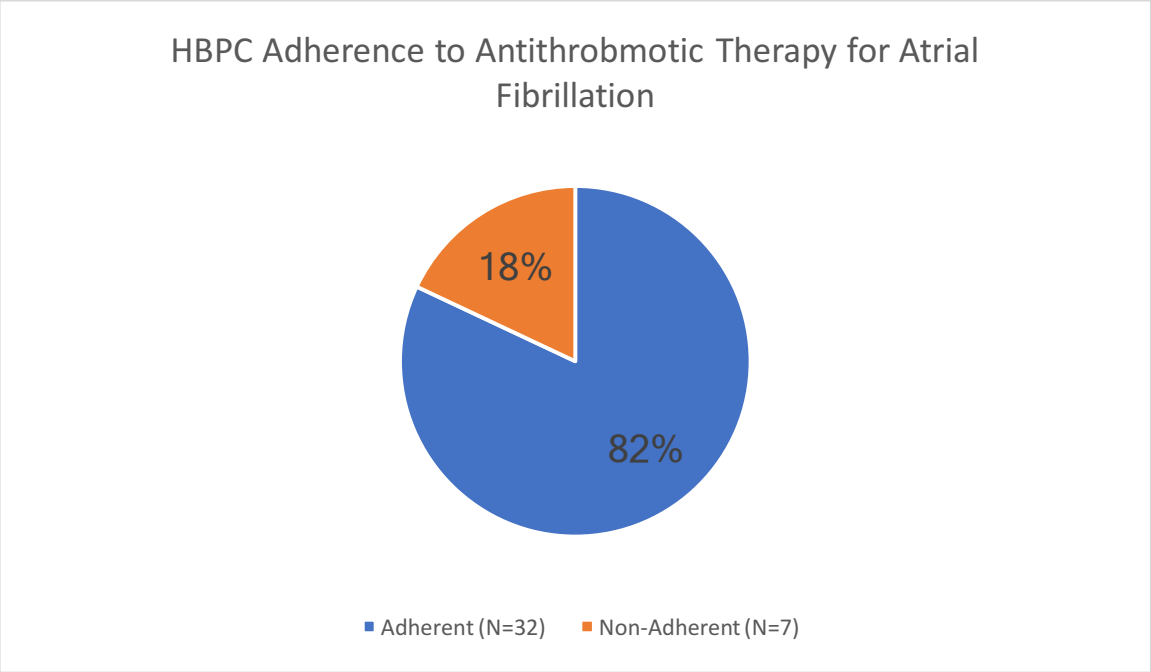
Fig 3.



Search Methods:

A PubMed search was completed using the key words atrial fibrillation, Warfarin, Dabigatran, and anticoagulation therapy. Additional search terms included Warfarin versus Dabigatran, reversal agent for warfarin and dabigatran, and treatment guidelines for atrial fibrillation. An UpToDate search was also completed using the key words atrial fibrillation, Warfarin, and Dabigatran. In order to obtain additional articles for this clinical review a reference search of the systematic reviews and treatment guidelines identified during the primary PubMed and UpToDate searches was used to identify additional pertinent articles.

Cochrane Tool for Risk of Bias:

Risk of bias in the included studies with respect to sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting was assessed using the Cochrane Collaboration's risk-of-bias assessment tool

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of outcome assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Hylek 2014	Unclear	Unclear	Low	Low	Low	Low	Low
Connolly 2009	Low	Low	High	Low	Unclear	Low	Low