12-2017

Stroke Reduction in Elderly Patients With Atrial Fibrillation Through Utilization of an Anticoagulation Toolkit in the Primary Care Setting

Rachel J. Mommer

UNIVERSITY OF NORTHERN COLORADO

Greeley, Colorado

The Graduate School

STROKE REDUCTION IN ELDERLY PATIENTS WITH ATRIAL FIBRILLATION THROUGH UTILIZATION OF AN ANTICOAGULATION TOOLKIT IN THE PRIMARY CARE SETTING

A Capstone Project Submitted in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Nursing Practice

Rachel J. Mommer

College of Natural and Health Sciences
School of Nursing
Nursing Practice

December 2017

This Capstone Project by: Rachel J. Mommer

Entitled: *Stroke Reduction in Elderly Patients with Atrial Fibrillation Through Utilization of an Anticoagulation Toolkit in the Primary Care Setting*

has been approved as meeting the requirement for the Degree of Doctor of Nursing Practice in College of Natural and Health Sciences in the School of Nursing, Program of Nursing Practice.

Accepted by the Capstone Research Committee

_____

Kathleen N. Dunemn, Ph.D., APRN, CNM, Research Advisor

_____

Katrina Einhellig, Ph.D., RN, CNE, Committee Member

_____

Robert Schulz, DNP, FNP, Committee Member

Accepted by the Graduate School

_____

Linda L. Black, Ed.D.
Associate Provost and Dean
Graduate School and International Admissions

EXECUTIVE SUMMARY

Mommer, Rachel. J. *Stroke Reduction in Elderly Patients with Atrial Fibrillation Through Utilization of an Anticoagulation Toolkit in the Primary Care Setting.* Unpublished Doctor of Nursing Practice capstone project, University of Northern Colorado, 2017.

Patients, especially those older than 65-years-old, do not receive adequate assessment or management of atrial fibrillation, resulting in higher ischemic stroke rates and worse outcomes related to strokes. Oral anticoagulation is recommended indefinitely for patients with atrial fibrillation and a moderate to high risk of stroke; yet this population is not receiving oral anticoagulation consistently. Factors such as overexaggerated bleeding risk in the elderly, the lack of head-to-head studies comparing anticoagulants, cost, patient compliance, safety, lab monitoring, and reversal agents convolute the process of prescribing anticoagulation for atrial fibrillation. Variations exist with assessing bleeding risk and stroke risk for every patient through reliable tools such as HAS-BLED and CHA_2DS_2-VASc scores, respectively, and translating these scores into practice. Due to these inconsistencies and the lack of a comprehensive, universal guideline for assessment and management of atrial fibrillation, this topic was selected for a capstone project.

A retrospective chart review was completed on 100 patients to assess the current practice of diagnosing atrial fibrillation and treating with anticoagulation in the primary care setting. Through utilization of two rounds of the Delphi method, expert opinion, and

the recommendations of national and international guidelines, an evidence-based anticoagulation toolkit was created and modified to guide primary care providers on improving diagnosis of atrial fibrillation and enhanced initiation and maintenance of oral anticoagulation to reduce the incidence of stroke in elderly patients with atrial fibrillation. The Anticoagulation for Atrial Fibrillation Toolkit is a four-step, simplified guideline to guide providers on improved diagnosis and treatment of AF; it is supported by four algorithms: CHA2DS-VASc score, HAS-BLED score, comparison of anticoagulants, and patient specific factors influencing selection of anticoagulant. Additionally, this toolkit offers in one document a summary of additional information and resources for providers to improve the overall management of atrial fibrillation. The chart reviews demonstrated gaps between evidence and practice, predominantly a lack of utilization of CHA_2DS_2-VASc and HAS-BLED scores to assess for stroke and bleeding risk, respectively, in patients with atrial fibrillation, poor continued monitoring of AF in the primary care setting, a disconnect between the treatment plan and providers, and the absence of consistently diagnosing an irregular pulse as AF through an EKG.

Round 1 of the Delphi survey assessed providers' comfort level and expertise with prescribing anticoagulants and diagnosing and managing AF and Round 2 evaluated the anticoagulation toolkit and how its incorporation could influence practice. Results from Round 1 were utilized to revise the evidence-based anticoagulation toolkit; data analysis concluded 70% consensus was achieved on at least 6 of the 10 questions. Even without 70% consensus, the researcher incorporated provider expertise, suggestions, and requests into the anticoagulation toolkit. In Round 2, data analysis of greater than 70% consensus suggested the Anticoagulation for Atrial Fibrillation Toolkit was evidence-

based, user-friendly, promoted safety and efficacy of anticoagulation, and could positively impact practice; however, the toolkit was too extensive and lengthy.

A thorough evaluation concluded this capstone project successfully addressed the following problem statement: In adult patients with atrial fibrillation older than 65 years old and a moderate to high risk of stroke, how effective is an anticoagulation toolkit in guiding primary care providers on (a) diagnosing atrial fibrillation and (b) initiating and maintaining oral anticoagulation safely, to reduce the incidence of ischemic stroke? The comprehensive literature review not only provided extensive background information on atrial fibrillation and anticoagulation but also highlighted key references to first compare evidence to practice (analyze patient chart reviews) and then utilize these identified gaps to translate evidence into practice (create the anticoagulation toolkit). Furthermore, the PARIHS framework and RE-AIM model evaluated the ability to effectively facilitate the results from this research project into practice. Additionally, this capstone project met all five criteria of the EC as PIE model, concluding this was a successful Doctor of Nursing Practice capstone project. A future extension of this project suggests evaluation of patient outcomes with AF, predominantly stroke incidence, subsequent to implementation of this toolkit in the primary care setting.

ACKNOWLEDGEMENTS

I would like to thank the numerous people who provided support, knowledge, reassurance, and time to aid in the completion of this capstone project. To Dr. Kathleen Dunemn, the capstone chair, I appreciate all your guidance, attentiveness, and wisdom from the start to finish of this project, especially with the statistical analysis and keeping me aligned with stepwise progression to finalize this project. To Dr. Bob Schulz, I cannot thank you enough for your insight and compassion into the complexity of atrial fibrillation management, which greatly helped with conciseness and selecting important data to incorporate into this anticoagulation algorithm. To Dr. Katrina Einhellig, thank you for your continual inspiration and optimism, which substantially influenced the timely completion of this project. To my family, dogs, friends, and classmates, I cannot express enough my heartfelt appreciation for your loyalty, love, comfort, understanding, and encouragement, which ultimately contributed to finishing this project. For any patients and their families who have suffered the devastating impact of a stroke related to atrial fibrillation, this project is dedicated to you. My hope is the awareness and education from this Anticoagulation for Atrial Fibrillation Toolkit can be an impetus to advance primary and secondary prevention efforts to minimize complications of this poorly treated disease. This doctoral project is a summary of my commitment as a family nurse practitioner to incorporate evidence-based data into practice to improve patient outcomes--thank you all for making this dream a reality.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AF	Atrial Fibrillation
ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AHA	American Heart Association
ASA	American Stroke Association
CDC	Centers for Disease Control and Prevention
$CHADS_2$	Assesses stroke with atrial fibrillation: Congestive heart failure (1 point), Hypertension (1 point), Age ≥75 (1 point), Diabetes mellitus (1 point), Stroke (2 points)
CHA_2DS_2VASc	Assesses stroke risk with atrial fibrillation: Congestive heart failure (1 point), Hypertension (1 point), Age ≥ 75 (2 points), Diabetes mellitus (1 point), Stroke (2 points), Vascular disease (1 point), Age 65-74 (1 point), Sex (Female- 1 point)
CHEST	American College of Chest Physicians
CKD	Chronic Kidney Disease
CMS	Centers for Medicaid and Medicare Services
CrCl	Creatinine Clearance
DNP	Doctorate of Nursing Practice
DOAC	Direct Oral Anticoagulant
EC as PIE	Criteria evaluating whether the capstone project is appropriate for the doctoral practice level: Enhances, Culmination, Partnerships, Implements, Evaluation
ECG/EKG	Electrocardiogram

eGFR	estimated Glomerular Filtration Rate
EHR	Electronic Health Record
ESC	European Society of Cardiology
FDA	Food and Drug Administration
HAS-BLED	Assesses bleeding risk with anticoagulation: Hypertension (1 point), Abnormal liver/renal function (1 point each), Stroke (1 point), history of Bleeding (1 point), Labile INR (1 point), Elderly (>65 years, 1 point), Drug increasing bleeding risk/alcohol use (1 point each)
HRS	Heart Rhythm Society
INR	International Normalized Ratio
LAA	Left Atrial Appendage
LMWH	Low-Molecular Weight Heparin
LVEF	Left Ventricular Ejection Fraction
NOAC	New Oral Anticoagulant
NVAF	Non-Valvular Atrial Fibrillation
PARIHS	Promoting Action on Research Implementation in Health Services
POCT	Point-Of-Care Testing
PSM	Patient Self-Monitoring
PST	Patient Self-Testing
RE-AIM	Reach, Effectiveness/efficacy, Adoption, Implementation, Maintenance: a framework composed of five steps to enhance the translation of research
SAF	Severity of Atrial Fibrillation Scale
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack

TTR	Time in Therapeutic Range
UFH	UnFractionated Heparin
VKA	Vitamin-K Antagonist

CHAPTER I

PROBLEM STATEMENT

Background and Significance of Project

Background

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia, affecting approximately 2.7 to 6.1 million people in the United States (Centers for Disease Control and Prevention [CDC], 2015). The American Heart Association (AHA) in 2015 released the alarming estimate of the incidence of this disease increasing to 5.6 to 12 million people by the year 2050, influenced by the large aging population and its expanding cardiovascular risk factors and comorbidities (Desai, El-Chami, Leon, & Merchant, 2017). Atrial fibrillation is present in 0.5% of Americans less than 40 years old, 5% of the population older than age 65, and 10% in persons 80 years of age or older (Desai et al., 2017). Likewise, the American College of Cardiology (ACC; Doherty et al., 2017) predicted AF prevalence in 18% of the population older than 85 years old. One in four patients age 40 or older will develop atrial fibrillation with an estimated 16 million Americans diagnosed with AF by 2050 (You et al., 2012). Internationally, stroke caused by AF is most prevalent within the United States and Europe and least prevalent within Latin America, revealing a higher incidence in persons older than 75 years old and female. Globally, AF is predominantly diagnosed through a health history or captured on

an electrocardiogram with few patients receiving cardiac monitoring post stroke to assess for AF (Perera et al., 2016).

Negative Outcomes of Atrial Fibrillation

Negative outcomes with AF are related to a decrease in cardiac output, resulting in the symptoms experienced in patients as well as the formation of thrombi in the atria and atrial appendages. Thrombi substantially increase the risk of strokes and embolization in the periphery (Kumar, 2016b). Atrial fibrillation results in 750,000 hospitalizations annually and 130,000 deaths in the United States with death rates increasing exponentially for the past 20 years. In Colorado alone, as many as 77.12 per 1,000 people ages 65 and older were hospitalized from 2007 to 2012 related to AF (CDC, 2015). Overall costs for this chronic disease are greater than $6 billion annually in the United States with healthcare costs attributed solely to atrial fibrillation costing an extra $8,705 per patient annually (CDC, 2015). According to the cost of clot model (Janssen, 2014d), in a hypothetical situation of 1,000 patients with AF at a high risk of stroke, increasing prescription of anticoagulation by 10% would decrease the cost of strokes by $258,554 and increase the cost of extracranial bleeds by $1,732 and intracranial bleeds by $21,157, overall reducing healthcare costs by $235,666.

Stroke risk. The stroke rate increases four to five times with AF as well as the severity of stroke complications as AF is the predominant cause of 15-20% of ischemic strokes (CDC, 2015). Of significance, patients are unaware of the devastating effects of AF; only 50% believe they are at risk for a stroke with AF with 43% voicing concerns of developing heart disease as the predominant negative outcome of AF rather the 8% with

stroke. Approximately 86% of patients feel they can explain the definition a stroke but only 61% correctly comprehend the disease implications (AHA, n.d.).

Women diagnosed with atrial fibrillation have a two-fold increased risk of mortality compared to a 1.5-fold increased risk in men, predominantly as a cause of stroke, sudden cardiac death, or heart failure. Furthermore, left ventricular dysfunction is present in 20-30% of patients with atrial fibrillation. Atrial fibrillation is a contributing factor to 20-30% of ischemic strokes. Quality of life is diminished with AF even when cardiovascular components are removed as these patients suffer from increased depression, brain white matter lesions, cognitive decline, and vascular dementia compared to patients without AF. Resulting from the aforementioned complications with AF, 10-40% of these patients are hospitalized annually. This diagnosis is financially devastating for the economy, contributing to 1% of total healthcare costs within the United Kingdom and $6.0-26.0 billion dollars in the United States in 2008 alone (Kirchhof et al., 2016). Atrial fibrillation is correlated with a five-fold enhanced risk of ischemic stroke with a 5% risk of stroke even in patients who are properly anticoagulated (You et al, 2012).

Recommendations. To reduce unnecessary healthcare costs and hospitalizations as well as improve quality of life, atrial fibrillation treatment focuses on stroke risk minimization and symptom management. Guidelines and clinical recommendations for atrial fibrillation treatment are vast; yet the elderly population is not adequately included in research studies. The primary cause of thromboembolic stroke is atrial fibrillation, demonstrating escalating prevalence and worse outcomes in correlation with increasing age. In fact, the stroke risk with AF is heightened five-fold and is the culprit of 25% of

strokes in the older population (Desai et al., 2017). The mortality rate is doubled with the combination of ischemic strokes and atrial fibrillation and the neurological sequelae tend to be more severe. The American College of Cardiology and American Heart Associated have recommended atrial fibrillation patients with a CHA_2DS_2-VASc of 1 be treated prophylactically with anticoagulation to prevent ischemic strokes; a systematic review of evidence concluded all patients 65 years of age and older should be treated with anticoagulation to prevent strokes regardless of risk factors (Desai et al., 2017).

Patients might require hospitalization for new onset atrial fibrillation, treatment for heart failure or hypotension after rate or rhythm control, starting antiarrhythmic drugs, symptomatic atrial fibrillation, or management of concurrent medical issues resulting in arrhythmia such as infection, chronic obstructive pulmonary disease exacerbation, hypertension, thyroid storm, or pulmonary embolism (Kumar, 2016b).

Classification of Recommendations and Levels of Evidence

The American Heart Association (AHA) and American Stroke Association (ASA; 2016) evaluated the certainty of evidence-based recommendations upon the following taxonomies: Level A evidence is obtained from numerous meta-analyses and randomized clinical trials; Level B evidence is obtained from nonrandomized studies or one randomized study; and Level C evidence is based upon expert opinion, case studies, or standards of care. The treatment effect size is classified by the following: the benefits of Class I evidence greatly outweigh the risks and treatment is recommended; the benefits of Class IIa evidence outweigh the risks and with reason treatment should be implemented; the benefits of Class IIb evidence outweigh the risks and treatment may be implemented; and the harms of Class III (harm) or Class III (no benefit) evidence outweigh the benefits

and treatment is not recommended. These classifications and recommendations of evidence are illustrated in Figure 1 (January et al., 2014). These same criteria to evaluate evidence are utilized by the European Society of Cardiology (ESC; Kirchhof et al., 2016) and the Heart Rhythm Society (HRS; January et al., 2014). The American College of Chest Physicians (CHEST) evaluates the quality of evidence as follows: Grade A (strong), Grade B (moderate), and Grade C (low). The evidence quality is incorporated into the overall recommendation for the evidence: Grade 1 (strong) and Grade 2 (weak; Kearon, et al., 2016). The CHEST criteria to measure the quality of evidence is depicted in Table 1.

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated

Figure 1. Classification of recommendations and levels of evidence. Adapted from January et al. (2014, p. 2249). Copyright 2014 by the American Heart Association Inc., the American College of Cardiology Foundation, and the Heart Rhythm Society.

Table 1

American College of Chest Physicians Guideline Classifications for Evaluating the Strength and Quality of Evidence

Classification	Strength of Evidence
Grade 1	Strong
Grade 2	Weak
	Quality of Evidence
Grade A	High
Grade B	Moderate
Grade C	Low

Note. Adapted from Kearon et al. (2016). Copyright 2016 by The American College of Chest Physicians.

Epidemiology

In 2010, an estimated 20.9 million men and 12.6 million women had atrial fibrillation with higher rates evident in developed countries. Increasing incidence and prevalence of atrial fibrillation are attributed to improved diagnosis of the disease as well as rises in both the aging population and the following risk factors: heart failure, coronary artery disease, hypertension, diabetes mellitus, chronic kidney disease, obesity, and valvular heart disease. In Europe, the incidence of AF is one in four adults with an estimated 120,000-215,000 new diagnoses by the year 2030 (Kirchhof et. al., 2016).

In the Framingham Heart Study of 5,209 subjects, a 10-year follow-up demonstrated the mortality rate was higher in both men and women age 55- to 74-years-old with atrial fibrillation (Kumar, 2016b). The incidence of AF is 9% in the elderly

above 65-years-old compared to 2% in people less than 65-years-old. Atrial fibrillation is more prevalent in older women of European heritage (CDC, 2015); however, independent of age, the disease is generally more common in men (Kumar, 2016b). The risk of death from AF in women is comparable to men; yet women exhibit more risk factors to stroke than men (especially increasing age) regardless of anticoagulation status. Furthermore, women tend to be more symptomatic with AF and utilize less rhythm control treatment. Men and women both display similar bleeding risks from anticoagulation (Class IIa, Level of Evidence B*;* Kirchhof et al., 2016).

Risk Factors

Other than increasing age and sex, risk factors for AF include obesity, heart failure, diabetes, chronic kidney disease, hyperthyroidism, alcohol abuse, and left ventricular hypertrophy. Additionally, hypertension is a prevalent factor in the etiology of 14 to 22% of atrial fibrillation patients (CDC, 2015) with coronary heart disease as another predominant contributing factor to disease onset (Ganz & Spragg, 2016). The strongest predictive factor of an ischemic stroke is a prior stroke or transient ischemic attack (TIA) in addition to increasing age (65 years of age or older), diabetes mellitus, sex (women), and hypertension. One-third of patients with AF have concurrent coronary artery disease (You et al., 2012). Abnormal laboratory results increasing an AF patient's risk of stroke include labile international normalized ratio (INR) levels, low time in therapeutic range (TTR) while on warfarin, anemia, prior hemorrhage, alcoholism, chronic kidney disease, elevated N-terminal pro-B-type natriuretic peptide, and high troponin T or I (Kirchhof et al., 2016). Post coronary artery bypass graft or cardiac valve surgery also increase AF risk (Kumar, 2016b).

Clinical Manifestations

Atrial fibrillation can be asymptomatic, "silent" (Kirchhof et al., 2016), or can present with the following clinical manifestations: heart palpitations, dizziness, fatigue, shortness of breath (dyspnea), irregular heart rate, weakness, presyncope, chest pain (CDC, 2015; Kumar, 2016b), difficulty sleeping, or psychosocial distress (Kirchhof et al., 2016). Approximately 30% of AF patients present without symptoms; yet this population demonstrates a higher CHA_2DS_2-VASc score and thus a higher risk of stroke. Of significance, over 20% of people with silent AF are not diagnosed until after their first stroke (Shahid, Shantsila, & Lip, 2016).

Classifications of Atrial Fibrillation

Atrial fibrillation can be paroxysmal (terminating in less than seven days spontaneously or with electrical cardioversion or medications); persistent (episodes lasting longer than seven days including those terminated through cardioversion); or long-standing persistent (episodes lasting up to one year, often indefinitely despite rhythm control; Kirchhof et al., 2016; Olshansky & Arora, 2016; Spragg & Kumar, 2017). Non-valvular atrial fibrillation (NVAF) includes patients with moderate to severe mitral stenosis and/or a prosthetic heart valve (Guimaraes, Kaatz, & Lopes, 2015). Long-standing persistent AF is synonymous with *permanent* AF according to other sources (You et al., 2012) or can be classified as *long-standing persistent* if the arrhythmia is controlled with a rhythm control strategy (Kirchhof et al., 2016). With paroxysmal AF, the risk of stroke is smaller than with persistent or permanent AF (patients are typically younger with less risk factors); yet the risk is enhanced with the conversion of AF back to normal sinus rhythm (cardioversion; You et al., 2012).

As a result of the heightened risk of stroke regardless of the classification of atrial fibrillation, the same prevention strategies utilizing anticoagulation are recommended, especially since only 1 of 12 paroxysmal AF occurrences are symptomatic (You et al., 2012). In a patient with AF risk factors, the risk of stroke is comparable with a duration of AF greater than one year, independent of the type of AF. Other data suggest patients with permanent AF have a heightened risk of stroke and mortality (4.2%) compared to paroxysmal AF (2.1%) and persistent AF (3.0%; Shahid et al., 2016).

Severity of Atrial Fibrillation Scale

The Severity of Atrial Fibrillation scale (SAF), adopted from the Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale (CCS-SAF), accurately assesses patient symptoms, association of symptoms with atrial fibrillation, and the patient's functionality (quality of life) by assigning the patient a score of 0 (asymptomatic Afib) to 4 (severe Afib; American College of Cardiology, 2012). The CCS-SAF has proven validity in quantifying quality of life related to a diagnosis of AF (Dorian et al., 2006, 2009). The SAF can be found within the Anticoagulation for Atrial Fibrillation Toolkit in Appendix A. Approximately 25-40% of atrial fibrillation patients display mild symptoms or are asymptomatic while 15-30% display severe symptoms. The ESC also has a similar scale named Modified European Heart Rhythm Association (EHRA) symptom scale to assess for AF symptom severity (Class I, Level of Evidence C*;* Kirchhof et al., 2016).

Genetics

Background

Research has suggested early-onset AF is heritable with one-third of these patients exhibiting one or more of 14 genetic variants, better known as single nucleotide polymorphisms (SNPs), which increase the risk of disease. The most well-known genetic variant is the Pitx2 (paired-like homeodomain transcription factor 2) on chromosome 4q25, increasing the risk of AF seven-fold. Carrying these genetic variants in the genome has also been associated with an augmented risk of ischemic stroke. Theories on how these genetic variants influence the onset of AF include atrial remodeling, penetration of genetic defects, and transforming the action potential of the atrial cells (Shehab, Sperling, Kegler, & Budnitz, 2010).

Clinical Pharmacogenetics Implementation Consortium

As warfarin has a narrow therapeutic index and a vast inter-patient dosing variability to achieve a therapeutic INR, four genetic variants have been identified that contribute to 50% of the variability in warfarin dosing: CYP2C9, VKORC1, CYP4F2, and CYP2C cluster (rs12777823). In 2016 The Clinical Pharmacogenetics Implementation Consortium (CPIC), part of the National Institute of Health's Pharmacogenomics Research Network, examined peer-reviewed genetic and medication guidelines and updated the 2011 guideline on pharmacogenetics-guided warfarin dosing (Johnson et al., 2017). Literature discovered negative sequelae from incorrect warfarin dosages was one of the most common adverse drug effects reported to the Food and Drug Administration (FDA; Johnson et. al., 2017), not to mention the cause of acute hemorrhage in 2.5 per 1,000 emergency room visits (Shehab et al., 2010). Based upon

this systematic review of data, CPIC recommended pharmacogenetic warfarin dosing through an algorithm focusing on VKORC1 and CYP2C9 alleles and started loading doses of warfarin based on genetic calculations and ancestry (Johnson et al., 2017).

The mechanism of action of warfarin is inhibition of the vitamin K epoxide reductase complex; when administered, warfarin is a racemic mixture composed of S-warfarin (more potent) and R-warfarin (less potent). Gene CYP2C9 is an enzyme within the cytochrome P450 family and metabolizes S-warfarin. The normal allele, CYP2C9*1, results in normal metabolism of S-warfarin. In patients with alleles CYP2C9*2 and CYP2C9*3, the metabolism of S-warfarin is decreased; thus, these patients display an increased risk of bleeding while on warfarin and should be prescribed a lower dose. Alleles CYP2C9*5, *6, *8, and *11 are more common in African Americans and are more prominent in the general population, also influencing the dosing variability of warfarin (Johnson et al., 2017). The VKORC1 allele encodes the vitamin K epoxide reductase protein, inducing the change from vitamin-K epoxidase to vitamin K. The genetic variant VKORC1 c-1639G>A is responsible for warfarin sensitivity and suggests a lower dose of warfarin is needed compared to the variant 1639G/G. The VKORC1 genetic variant influences the dosing of warfarin amongst those of Asian, Caucasian, and African American ancestry (Johnson et al., 2017).

Benefits and Risks of Pharmacogenetic Testing for Warfarin

Benefits of pharmacogenetic warfarin testing include reaching a stable INR within a shorter time frame and more consistently, which could potentially decrease the risk of hemorrhage from inappropriate warfarin dosing and the risk of thromboembolism. Risks of this genetic testing include calculation of the wrong dose of warfarin based upon these

recommendations and calculating the incorrect genotype, which is a permanent component of the patient's medical record, especially if not following recommendations specific to ancestry. The cost-benefit ratio of warfarin genetic testing is controversial as stable international normalized ratios (INRs) can reduce costs related to INR testing itself and decrease negative sequalae of poorly managed warfarin dosing; yet the majority of insurance companies do not cover the costs of this testing. Furthermore, randomized clinical trials of CYP2C9 and VKORC1 alleles have not demonstrated reliable results and do not support the definitive benefits of genetic warfarin testing (Johnson et al., 2017).

Consensus of Major Organization

According to the CDC (2016a), routine pharmacogenomic screening of genetic variants CYP2C9 and VKORC1 to prevent myocardial infarctions, venous thrombosis, pulmonary embolism, or thromboembolic events related to AF or valve replacements is ranked a Tier 2. More specifically, to obtain a Tier 2 recommendation, an FDA label indicates genetic biomarkers. The clinical practice guideline supports the use of this genetic test but does not include a systematic review; refuting evidence is available but the use of this test is still encouraged. Conversely, only a systematic review recommends the use of this genetic test or discovers inadequate evidence but still suggests use of this test. For a Tier 2, the clinical practice guideline addresses individualized medication dosing for the patient yet does not indicate specific genetic testing (CDC, 2016b).

The Centers for Medicaid and Medicare Services (CMS; 2009) covered this test for eligible patients based upon evidence. More specifically, for CMS to cover pharmacogenetic testing for warfarin, the patient must meet the following criteria: (a) no prior genetic testing of markers CYP2C9 and VKORC1 alleles, (b) the patient has been

administered less than five days of warfarin, and (c) the patient is currently participating in a prospective, randomized, controlled clinical study for warfarin response and patient outcomes. Unless the aforementioned measures are met, CMS does not routinely recommend screening Medicare patients for pharmacogenomic testing for warfarin. In the presence of familial AF with multiple generations involved, genetic counseling and testing is an option (Class IIb, Level of Evidence C; January et al., 2014).

A systematic literature review of genetic variants for warfarin, specifically VKORC1 and CYP2C9, concluded all patients with a bleeding event while on warfarin should be tested within two weeks for VKORC1, CYP2C9*2 and CYP2C9*3 alleles including the pediatric population. Additional recommendations for pharmacogenomic testing while on warfarin include difficulties obtaining therapeutic INRs or adverse drug events while on warfarin. Evidence endorsed utilization of a specific pharmacogenetic dosing algorithm to accurately analyze the genotypes (Shaw et al., 2015). According to the ESC, genetic testing for warfarin is not recommended as evidence has failed to demonstrate an influence on time in therapeutic regimen or decreased bleeding risk (Class III, Level B; Kirchhof et al., 2016).

Pathophysiology

With AF, the two upper heart chambers called atria beat irregularly, affecting the blood flow down to the two ventricles (CDC, 2015). The rate of blood flow decreases and allows blood to pool within the atria, enhancing the risk of thrombi (blood clots) and thus stroke if a clot is expelled into the bloodstream and reaches the brain (AHA, n.d.). Regarding the mechanism, a trigger, predominantly rapid firing from the pulmonary veins, results in atrial fibrillation. Other triggers include reentry circuits, atrial stretch,

inflammation, dilatation, fibrosis, repolarization abnormalities, autonomic imbalance, and conduction disturbances. Early in the disease process, the atrium is fully functioning and can spontaneously return to sinus rhythm more easily. Persistent AF occurs from cardiac remodeling (electrical and structural) over time, inhibiting the ability of the fibrillation to resolve spontaneously. Thus, paroxysmal AF often precedes persistent atrial fibrillation (Olshansky & Arora, 2016). The complex and poorly understood mechanism of Afib is summarized in Figure 2. Predominant mechanisms for ectopy and conduction disturbances in the atria, which ultimately result in atrial fibrillation, include calcium instability, ischemia, vascular remodeling, atrial fibrosis, hypocontractility, fatty infiltration, and inflammation (Kirchhof et al., 2016).

Risk factors for AF such as hypertension and diabetes contribute to atrial remodeling in the heart, ultimately resulting in fibrosis. This fibrosis contributes to changes in atrial electrical conduction pathways to a reentry circuit, which further potentiates the risk of arrhythmias such as atrial fibrillation. Research suggested prevention of cardiac remodeling could minimize the onset of AF (Shahid et al., 2016). The increased risk of blood clot or thrombus (prothrombotic) resulted not only from the irregular rhythm associated with AF but also the remodeling in predominantly the left atrial appendage. Even brief periods of AF could contribute to stroke as this irregular rhythm harms the atrial heart muscle (myocardium), releasing inflammatory factors within the endothelium that accumulate platelets at the site of injury and increase the risk of thrombosis. Furthermore, with atrial remodeling, changes in the calcium balance within cells influences the heart rate variability (autonomic tone) and thus precipitates AF (Shahid et al., 2016).

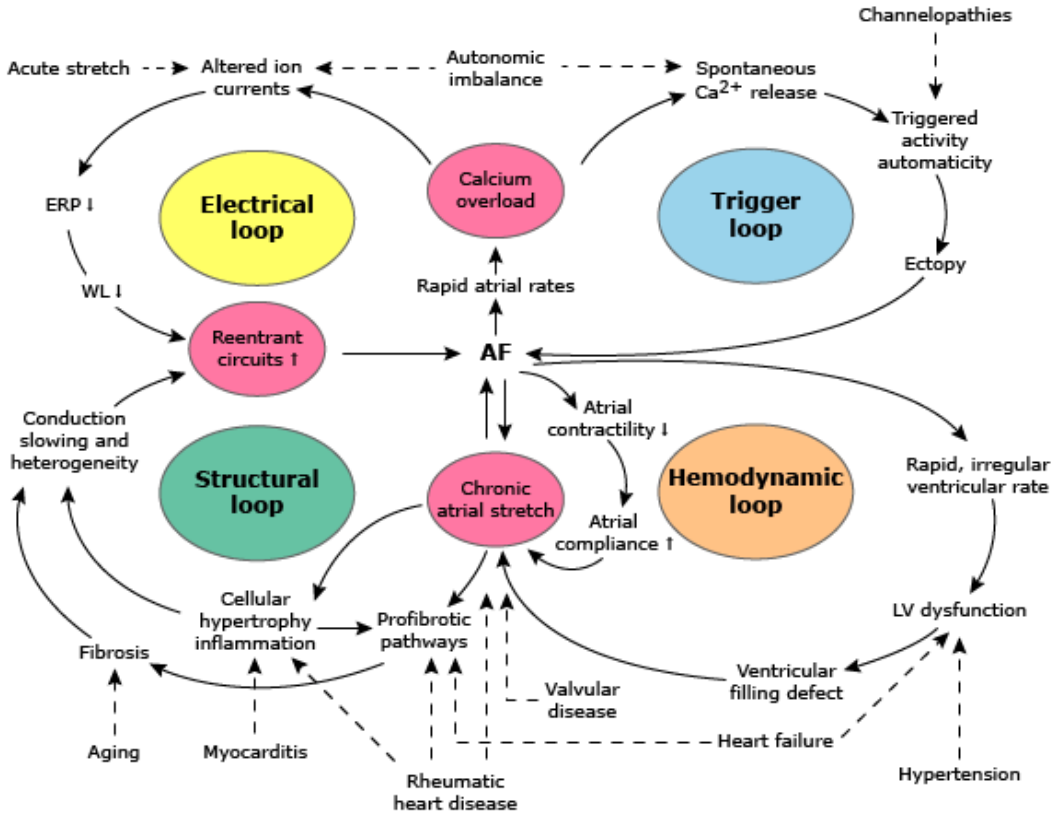


Figure 2. Mechanisms of atrial fibrillation. Adapted from Olshansky and Arora (2016).

History and Comparison of Anticoagulation

Derived in 1930, subcutaneous unfractionated heparin was the first anticoagulant (Bayer HealthCare, 2010). Other than the route of administration through injection, additional concerns with this anticoagulant included the risk of heparin-induced thrombocytopenia (HIT) and osteopenia. In the 1940s, vitamin K antagonists warfarin and acenocoumarol were released to the market (Bayer HealthCare, 2010). Prior to this time, the natural form of warfarin, dicumarol, was noted to cause hemorrhages in cattle in the 1920s and warfarin was used as rat poison in the 1950s (Williams, Riley, & Tidwell, n.d.). In the 1980s, injectable low molecular weight heparins were created; this drug does

not require the lab monitoring needed for unfractionated heparin and has a decreased risk of HIT yet should be used cautiously in patients with renal insufficiency. The first oral direct thrombin inhibitor, ximelagatran was released in Europe in the 1990s yet was removed from the market due to liver impairment. In the 2000s, the first injectable factor Xa inhibitor, fondaparinux, was released on the market. The next direct thrombin inhibitor, dabigatran, was released in Europe in 2006 (Bayer HealthCare, 2010). Rivaroxaban, the first oral direct factor Xa inhibitor, was released on the market in 2008 (Drugs.com, 2015b), followed by apixaban in 2012 (Drugs.com, 2016), and Edoxaban in 2015 (Daiichi Sankyo, 2015). A new factor Xa inhibitor, Betrixaban (Beyvxxa©), is currently under study, demonstrating a longer half-life and reduced effects on renal excretion and hepatic metabolism compared to other non-vitamin K oral anticoagulants (NOACs) on the market (Hu, Vaidya, & Asirvatham, 2016). The first reversal drug for dabigatran, idarucizumab, was released in 2015 (Boehringer Ingelheim, 2015b). Currently, no specific reversal agents for the factor Xa inhibitors have been approved for use; yet andexant alpha (a factor Xa inhibitor antidote) and ciraparantag (a universal NOAC reversal agent) are currently in the development stages. The mechanism of how the parenteral and oral anticoagulants alter the coagulation cascade is depicted in Figure 3.

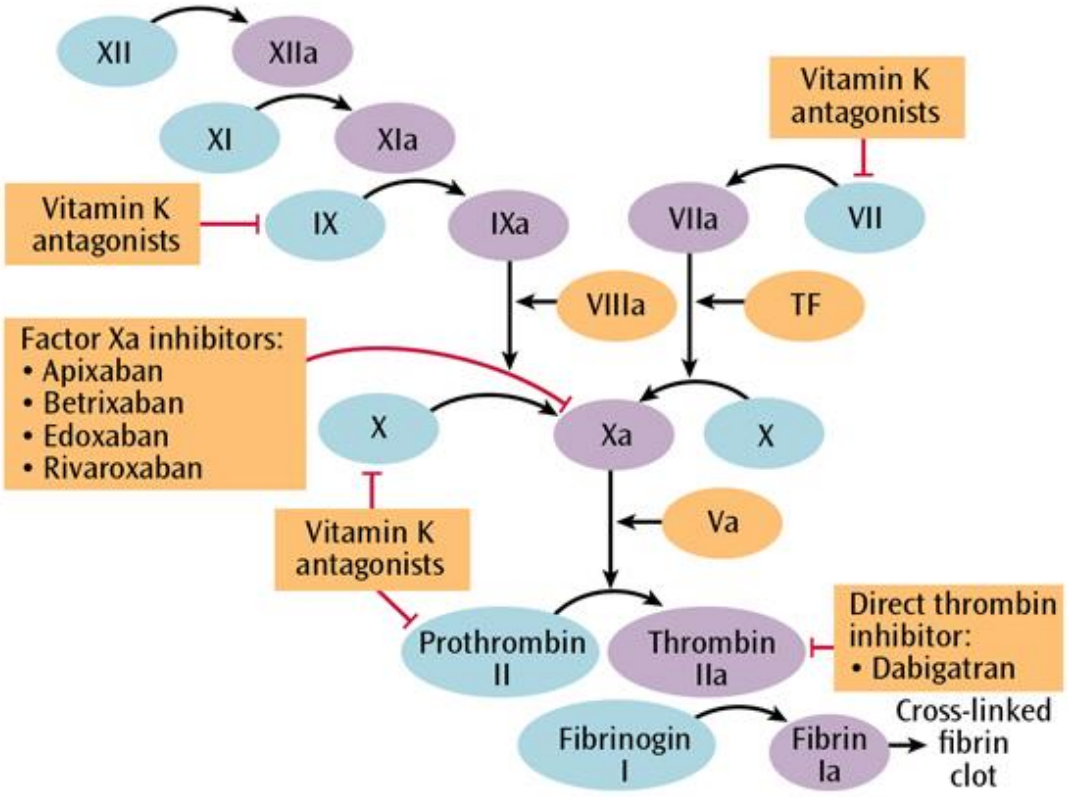


Figure 3. Coagulation cascade and the effects of oral anticoagulants.
Note. Vitamin K antagonists, such as warfarin, inhibit factors II, VII, IX, and X. Dabigatran directly inhibits factor IIa (thrombin). Apixaban, betrixaban, edoxaban, and rivaroxaban inhibit factor Xa. Abbreviation: TF, tissue factor. Adapted from Makaryus, Halperin, and Lau (2013). Copyright 2013, Macmillan Publishers Limited.

Prevention of Stroke Through Anticoagulation

The consensus of guidelines for atrial fibrillation suggests patients with risk factors for stroke should be given the opportunity to start oral anticoagulants for thromboprophylaxis unless they are low risk or have other contraindications (Shahid et al., 2016). Oral anticoagulation is recommended indefinitely to prevent thromboembolism in patients with atrial fibrillation and a moderate to high risk of stroke (Wigle, Hein, Bloomfield, Tubbe, & Doherty, 2013). Oral anticoagulation through

vitamin K antagonists (VKAs) or NOACs has demonstrated a reduction in overall mortality in patients with atrial fibrillation, predominantly strokes (Kirchhof et al., 2016). By increasing anticoagulant prophylaxis in 10% of 1,000 high-risk patients with atrial fibrillation, the stroke rate could be reduced by 8.4% as 33% of patients with low bleeding risk and high stroke risk are not treated appropriately with anticoagulation (Janssen Pharmaceuticals, 2014d). Newer studies are using the term direct oral anticoagulants (DOACs; Samuelson, Cuker, Siegal, Crowther, & Garcia, 2017); thus, DOAC and NOAC are used interchangeably in this paper.

Warfarin reduces stroke risk by two-thirds compared to aspirin or no anticoagulation. Limitations of warfarin include the narrow therapeutic index, multiple drug interactions, and frequent lab monitoring of INRs requiring dose adjustments. If warfarin requires temporary interruption, bridging with unfractionated heparin or low molecular weight heparin is initiated to decrease stroke risk in the interim (Class I, Level of Evidence C; January et al., 2014). In comparison, the effects of NOACs are predictable without necessitating lab monitoring. None of the NOACs (apixaban, edoxaban, rivaroxaban, or dabigatran) thus far have demonstrated safety for use with valvular AF (mitral stenosis) or artificial valves (Class III Harm, Level of Evidence B or C*;* Kirchhof et al., 2016).

Ischemic stroke can be the initial manifestation of atrial fibrillation in patients, occurring predominantly as an embolus from the left atrial appendage. In patients with AF, ischemic stroke severity tends to be more severe including longer durations of transient ischemic attacks (TIAs) because of larger emboli. Even with anticoagulant prophylaxis, strokes of lesser severity can still occur in patients with AF. Chronic

anticoagulation through warfarin or an NOAC (Dabigatran, Rivaroxaban, Apixaban or Edoxaban) displays the best efficacy in the long-term prevention of stroke and recurrent stroke in patients with nonvalvular atrial fibrillation (Manning, 2016). The annual risk of stroke in patients with AF is ~1.5%, with a death rate of 3% even in anticoagulated patients, attributed to either stroke, heart failure, or sudden cardiac death (Kirchhof et al., 2016). Anticoagulants have demonstrated a 70% decreased risk of systemic embolism in non-valvular AF patients; yet the risk of bleeding risk must be considered when prescribing these medications (Manning, Singer, & Lip, 2016). However, without risk factors, prophylaxis with anticoagulants or antiplatelets is contraindicated (Class III Harm, Level of Evidence B; Kirchhof et al., 2016).

Assessing Stroke and Bleeding Risk

Stroke Risk

Evaluating for stroke risk with nonvalvular (nonrheumatic) AF is evaluated through the $CHADS_2$ or CHA_2DS_2VASc scoring tools. The $CHADS_2$ tool is recommended by the chest guidelines through validation of evidence and ease of use (You et al., 2012). The CHA_2DS_2VASc tool is recommended by the ESC (Class I, Level of Evidence A*;* Kirchhof et al., 2016); AHA/ACC/HRS (Class I, Level of Evidence B; January et al., 2014); and the ASA (Meschia et al., 2014) to assess stroke risk and necessity of anticoagulation with AF. The CHA_2DS_2VASc tool is recommended over the $CHADS_2$ to assess for stroke risk as the former highlights more risk factors and demonstrates a better ability to predict patients with low, moderate, or high stroke risks. More specifically, the $CHADS_2$ does not always accurately predict if a patient is at low stroke risk, thus increasing the incidence of thromboembolism in AF patients who do not

receive anticoagulation. Risk stratifying patients with atrial fibrillation is essential as only 70% of patients necessitating oral anticoagulation receive this treatment. Furthermore, in high-risk patients with AF who suffered from a stroke, 29% were not prescribed any anticoagulation, 31% were prescribed antiplatelets, and 39% were prescribed warfarin, yet only 10% had therapeutic INR levels. Prescribing anticoagulation adequately for AF patients is a predominant means to decrease stroke risk in this population (Lane & Lip, 2012). Interpretation of $CHADS_2$ and CHA_2DS_2VASc scoring is explained within the Anticoagulation for Atrial Fibrillation Toolkit in Appendix A.

$CHADS_2$ or CHA_2DS_2VASc score of zero. Vitamin K antagonists (VKAs) have been proven to decrease all-cause mortality with atrial fibrillation diagnoses except in patients at low risk of stroke ($CHADS_2$ score of 0) attributed to the increased risk of intracranial bleeds from anticoagulation. Thus, treating patients with a $CHADS_2$ score of 0 with aspirin for one year could decrease two nonfatal strokes in a population of 1,000 people with the caveat of three extracranial bleeds. More specifically, monotherapy with aspirin could decrease the risk of stroke by 21% compared to no treatment; yet the risk of bleeding increases by 50-60%. Treatment with a VKA could decrease the risk of stroke by one-half compared to aspirin, yet increases the bleeding risk by 50% (2.5-fold increased risk; You et al., 2012). In nonvalvular AF (NVAF) and a CHA_2DS_2VASc score of 0, anticoagulation is not recommended (Class IIa, Level of Evidence C [January et al., 2014; Manning et al., 2016]; Class IIa, Level of Evidence B--Meschia et al., 2014). The American College of Chest Physicians (CHEST guidelines) made the same recommendation of no treatment with a $CHADS_2$ score of 0 (Grade 2B), proposing

aspirin (Grade 2B*)* or aspirin with clopidogrel (Grade 2B*)* if the patient requested anticoagulation for AF (You et al., 2012). In patients desiring an oral anticoagulant for a CHA_2DS_2-VASc score of 0 but with a high risk of bleeding, apixaban and dabigatran are suitable options. Consensus suggests aspirin is not recommended to prevent stroke in patients with atrial fibrillation (Lane & Lip, 2012).

$CHADS_2$ or CHA_2DS_2VASc score of one. The CHEST guidelines recommended oral anticoagulation with a $CHADS_2$ score of 1 (Grade 1B*)*, proposing the combination of aspirin and clopidogrel if the patient is unable to take oral anticoagulation (Grade 2B; You et al., 2012). Dual treatment with aspirin and clopidogrel demonstrates an increased risk of bleeding 1.5-2 times compared to warfarin (You et al., 2012). With a CHA_2DS_2-VASc score of 1, dabigatran, rivaroxaban, and apixaban have demonstrated superiority to warfarin with no increased bleeding risk (Lane & Lip, 2012). With nonvalvular AF, a low risk for bleeding, and a CHA_2DS_2VASc score of 1, multiple treatment options are appropriate depending on patient preference including no anticoagulant, aspirin, or an oral anticoagulant (Class IIb, Level of Evidence C--January et al., 2014; Class IIb, Level of Evidence C--Meschia et al., 2014). Anticoagulant therapy for a CHA_2DS_2VASc score of 1 is generally prescribed based on clinical judgment, with age 65-74 years old, hypertension, and diabetes as more significant risk factors contributing to disease onset compared to female sex and vascular disease (Manning et al., 2016).

$CHADS_2$ or CHA_2DS_2VASc score of greater than or equal to two. With a $CHA_2DS_2VAS_c$ score ≥ 2, chronic anticoagulation is suggested to decrease the risk of stroke (Grade 1a; Manning et al., 2016). Without other risk factors, sex alone is not a

strong indicator of increased stroke risk, yet age greater than 65-years-old heightens the influence of other risk factors such as sex and heart failure (You et al., 2012). With a CHA_2DS_2-VASc score ≥ 2 (regardless of bleeding risk) and with elevated bleeding and stroke risk, dabigatran, rivaroxaban, or apixaban have demonstrated superiority to warfarin (Lane & Lip, 2012).

The AHA, ACC, and HRS (2014) proposed oral anticoagulation with a $CHA_2DS_2VAS_c$ score ≥ 2, history of prior stroke, or history of TIA and recommended warfarin (Class I, Level of Evidence A), dabigatran, rivaroxaban, or apixaban as suitable anticoagulants (Class I, Level of Evidence B--January et al., 2014; Class I, Level of Evidence B--Meschia et al., 2014). Likewise, according to the CHEST guidelines (You et al., 2012), a diagnosis of valvular AF, a low risk of bleeding, and a $CHA_2DS_2VAS_c$ score ≥ 2 warrants long term anticoagulation with warfarin with a therapeutic INR of 2.0-3.0 (Class I, Level of Evidence A). With a $CHADS_2$ score of 2 or higher, the combination of aspirin and clopidogrel is proposed if the patient is unable to take oral anticoagulants (Grade 1B; You et al., 2012). Warfarin has displayed an annual reduction in stroke, myocardial infarction, and systemic embolism (3.9%) compared to dual antiplatelet therapy with aspirin and clopidogrel (5.6%). The bleeding risk increases from 1.3% to 2.0% with monotherapy aspirin compared to dual antiplatelet therapy. Based upon these findings, antiplatelet therapy is not suggested to reduce stroke risk in patients with AF (Class III Harm, Level of Evidence A; Kirchhof et al., 2016). Dabigatran 150 mg twice daily is preferred to dose-adjusted warfarin for AF, including paroxysmal, with a $CHADS_2$ score of 1 or 2 (Grade 2B*)*; however, this drug is not indicated with a creatinine clearance (CrCl) less than 30 mL/min (You et al., 2012). On

the contrary, the ESC recommends oral anticoagulation for AF patients with a $CHA_2DS_2VAS_c$ score > 2 for men (Class I, Level of Evidence A*)* and > 3 for women (Class I, Level of Evidence A) to prevent blood clots (Kirchhof et al., 2016).

Conclusions. Oral anticoagulants have proven superior in preventing stroke with AF compared to antiplatelets such as aspirin (Manning et al., 2016); due to the heightened bleeding risk, aspirin is not considered safe as monotherapy (Shahid et al., 2016). Warfarin and NOACs have demonstrated similar stroke and bleeding risks in nonvalvular AF; however, evidence suggests treatment with a NOAC (direct thrombin inhibitor or factor Xa inhibitor) is superior (Manning et al., 2016). More specifically, dabigatran, apixaban, edoxaban, and rivaroxaban have demonstrated non-inferiority to warfarin in preventing stroke with AF yet demonstrate superiority in a reduction of severe bleeding (a decrease in bleeding by 30-50%; Shahid et al., 2016). A comparison of warfarin and NOACs is summarized within the Anticoagulation for Atrial Fibrillation Toolkit in Appendix A. If a patient is unable to take an anticoagulant, dual antiplatelet therapy consisting of aspirin 75-100 mg daily in addition to clopidogrel 75 mg daily is recommended (Grade 2B; Manning et al., 2016). Due to increased bleeding risk, a combination therapy of platelet inhibitors and oral anticoagulants is contraindicated post stroke (Class III Harm, Level of Evidence B; Kirchhof et al., 2016). Based upon the above evidence-based recommendations, the stroke risk of every patient with AF should be assessed through the CHA_2DS_2-VASc score to determine if anticoagulation is the appropriate treatment regimen for each individualized patient (Kumar, 2016b).

Bleeding Risk

Overemphasizing bleeding risk is a predominant limiting factor in providers prescribing oral anticoagulation, especially to the elderly. However, despite the risk of bleeding and stroke both increasing with advanced age, aspirin becomes less effective and oral anticoagulants become more effective in preventing ischemic stroke with increasing age with a comparable bleeding profile between the two drugs (Lane & Lip, 2012). Factors increasing the risk of bleeding while on anticoagulation include alcoholism (≥ 8 drinks weekly), poorly controlled hypertension (systolic blood pressure > 160 mmHg), prior history of bleeding, labile INRs with warfarin, concurrent use of nonsteroidal anti-inflammatory drugs (NSAID)s or antiplatelet drugs, anemia, impaired renal function, impaired liver function, prior stroke, falls, dementia, age > 65 years old, genetics, malignancies, recent surgery, diabetes, recent myocardial infarction, and interruptions of anticoagulation prior to a procedure (Doherty et al., 2017, Jaffar & Bragg, 2003; Kirchhof et al., 2016). Cautious signs and symptoms suggesting bleeding while on anticoagulation include bruising, fall to the head, severe headache of a long duration, frequent nosebleeds, coughing up blood, coffee ground emesis, heavy bleeding from the gums, swelling and pain in the abdomen, severe back pain, black or bloody stools, bloody urine, heavy menstrual periods, and prolonged bleeding from lacerations (Jaffar & Bragg, 2003).

Currently, data have been inadequate to add recommendations to guidelines on assessing bleeding risk with anticoagulation through a validated tool, however, screening for bleeding risk should still be calculated through hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol

(HAS-BLED); hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, re-bleeding, hypertension, anemia, genetic factors, excessive fall risk and stroke (HEMORR$_2$HAGES), or another evidence-based tool and incorporated into the individualized treatment plan to help in the selection of anticoagulation (You et al., 2012). Data have suggested HAS-BLED more accurately predicts major bleeding risk compared to HEMORR$_2$HAGES and is declared easier to use than other scales. The AHA/ASA have endorsed the HAS-BLED score to assess for bleeding risk with anticoagulation for AF (Meschia et al., 2014). A meta-analysis and systematic review of HAS-BLED, HEMORR2HAGES and anticoagulation and risk factors in atrial fibrillation (ATRIA) concluded HAS-BLED displays a better ability to predict severe bleeding risk in patients with atrial fibrillation, has increased sensitivity, and is more user friendly (Caldeira, Costa, Fernandes, Pinto, & Ferreira, 2014).

According to the bleeding risk scores, the annual risk of bleeding while on anticoagulation increases with every positive risk factor with an overall bleeding risk of 1.5%. The scoring of these risk factors does not categorize the patient as low, intermediate, or high risk for bleeding while on anticoagulation (Hwang, 2016b). The purpose of bleeding scores is not to deter providers from prescribing anticoagulants but rather to discover and adjust modifiable risk factors to reduce bleeding risk (Lane & Lip, 2012). The ESC recommends utilization of the HAS-BLED, ORBIT, or ABC bleeding risk scale to reduce risk factors (Class IIa, Level B) yet advises against withholding oral anticoagulation merely on the high risk of bleeding, as the patient's individual bleeding risk profile and reduction of risk factors should be incorporated into the risk-benefit ratio (Kirchhof et al., 2016). If severe bleeding occurs while on anticoagulation, medications

should be stopped until the etiology of the bleeding is discovered (Class I, Level of Evidence C; Kirchhof et al., 2016). The hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol (HAS-BLED) scoring is illustrated within the Anticoagulation for Atrial Fibrillation Toolkit in Appendix A.

Summary

Research has demonstrated CHA_2DS_2-VASc and HAS-BLED scores are a simple and efficient means to assess whether anticoagulation is appropriate for a patient without warranting further testing or lab work (Shahid et al., 2016). To prevent systemic embolization and stroke, the CHA_2DS_2-VASc score is completed on patients to determine if they meet criteria for long-term anticoagulation as shown in Appendix A. If the risk of bleeding is less than the risk of stroke, all patients with AF are recommended to start antithrombotic medications (Kumar, 2016b). More specifically a CHA_2DS_2-VASc score ≥ 2 suggests chronic anticoagulation and a score of 0 implies no anticoagulant therapy. A score of 1 requires clinical judgement on whether to prescribe an anticoagulant, considering factors such as age > 75 years and sex. According to $CHADS_2$ scoring, the absolute risks of stroke annually in patients not treated with anticoagulation are 0.8% (score of 0), 2.2% (score of 1), 4.5% (score of 2), and 9.6% (score of 3-6; You et al., 2012).

Direct Oral Anticoagulants Versus Warfarin

Comparison

Oral direct thrombin inhibitors or factor Xa inhibitors are recommended over warfarin for NVAF (Grade 2B); however, research currently does not support selecting one NOAC over the other (Manning et al., 2016). The baseline risk of extracranial

bleeding per year is 0.5% in patients treated with warfarin. Randomized control trials have demonstrated vitamin K antagonists such as warfarin decrease the risk of death by one-fourth in patients with AF, in addition to the risk of nonfatal stroke by two-thirds, when compared to patients with no anticoagulation (You et al., 2012). A meta-analysis concluded morality rates decreased by 10%, stroke rates decreased by 19% (predominantly hemorrhagic), and the risk of intracranial hemorrhage was reduced by half with NOACs in comparison to warfarin, yet the rate of gastrointestinal bleeding increased (You et al., 2012). The reduced bleeding risk was more prominent in patients with labile INR values, yet the correlation of INR value and risk of intracranial hemorrhage was unable to be confirmed. In general, warfarin is suitable for patients with INRs within the therapeutic range 65% of the time who prefer lab monitoring, prefer once day dosing, cost is an issue, chronic kidney disease, prosthetic heart valves, mitral stenosis, or concurrent use of protease inhibitors or phenytoin contraindicated with DOACs (Manning et al., 2016).

Oral anticoagulants have not been tested for safety and efficacy in patients with kidney transplants. Dabigatran and rivaroxaban should be avoided with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73^2, apixaban with an eGFR < 25 mL/min/1.73^2, and edoxaban with an eGFR > 95 mL/min (Manning et al., 2016). In patients with mild or moderate chronic kidney disease (CKD), NOACs demonstrated less strokes, hemorrhages, and systemic embolisms compared to warfarin. However, only warfarin has been safely utilized in patients with moderate or moderate-severe CKD. Warfarin has displayed safety and efficacy in reducing stroke in dialysis patients (Manning et al., 2016), while the pharmacokinetics and pharmacodynamics of dabigatran

were not affected in patients with worsening renal impairment and chronic hemodialysis (Dias et al., 2016).

Recommendations

The current 2014 recommendations of the AHA/ACC/HRS do not differentiate between warfarin or DOACs for anticoagulation in AF. Since January 2016, CHEST prefers oral anticoagulants rather than warfarin to treat atrial fibrillation and thromboembolism without a cancer etiology (Samuelson et al., 2017). More specifically, with venous thromboembolism without cancer, dabigatran, rivaroxaban, apixaban, or exoxaban are recommended for long-term anticoagulation instead of warfarin (Grade 2B). In patients with venous thromboembolism and cancer, low-molecular weight heparin is preferred instead of warfarin (Grade 2B) and any of the DOACs (Grade 2C; Kearon et al., 2016). Warfarin has been used as an anticoagulant for over 60 years, yet the drug contributes to 12.5% of hospitalizations for drug-drug interactions, 43% higher costs for hemorrhages, and 33% of hospitalizations for adverse drug events in the elderly (Janssen Pharmaceuticals, 2014c).

Research Studies

Currently, no head-to-head studies have been completed comparing the DOACs (Shahid et al., 2016). Noseworthy et al. (2016) completed a retrospective analysis of adult users of dabigatran, rivaroxaban, or apixaban from 2010-2015, assessing the safety outcome of bleeding and the efficacy outcome of prevention of stroke and systemic embolism in patients with NVAF. Results demonstrated no difference in the efficacy outcome of preventing stroke or systemic embolism amongst the three drugs. Rivaroxaban demonstrated an increased risk of major and intracranial bleeding compared

to dabigatran and apixaban displayed a reduced risk of bleeding compared to both dabigatran and rivaroxaban. The study concluded the efficacy of these anticoagulants is comparable; yet the bleeding risk profiles differed with the highest risk of bleeding with rivaroxaban and the lowest risk with apixaban (Noseworthy et al., 2016). These four DOACs have demonstrated reductions in major bleeding and intracranial hemorrhage compared to warfarin; however, dabigatran, rivaroxaban, and edoxaban (excluding apixaban) demonstrated an increased risk of gastrointestinal bleeding compared to warfarin. Attributed to their significant reduction in stroke and systemic embolism reduction, the net clinical benefit of DOACs outweighed their bleeding risk. Unless the patient has a mechanical heart valve, DOACs extend anticoagulation options other than warfarin to a larger proportion of the population at risk for stroke (Shahid et al., 2016). The AHA/ASA (2016) released an analogous study comparing the safety and efficacy of apixaban, rivaroxaban, and dabigatran to warfarin with NVAF. This study concluded apixaban has decreased stroke and bleeding risks compared to warfarin, dabigatran has comparable stroke risk but lower bleeding risks compared to warfarin, and rivaroxaban has comparable stroke and bleeding risks to warfarin in patients with nonvalvular atrial fibrillation (Yao et al., 2016). The study by Noseworthy et al. appears to be a head-to-head of the three DOACs themselves; yet the study by the AHA/ASA is a comparison of the DOACs individually with warfarin. In summary, all four DOACs compared to warfarin demonstrate comparable efficacy (stable effectiveness independent of the time in therapeutic range) and improved safety (decreased intercranial hemorrhages). In fact, even with a therapeutic INR in the 2.0-3.0 range, two-thirds of intracranial bleeds still occur (Guimaraes et al., 2015). A comparison of DOACs in general and warfarin is

illustrated within the Anticoagulation for Atrial Fibrillation Toolkit located in Appendix A.

Trends

The use of warfarin and the DOACs (apixaban, rivaroxaban, and dabigatran) was reviewed in the outpatient setting from 2009 to 2014 through the IMS Health National Disease and Therapeutic Index survey (cited in Barnes, Lucas, Alexander, & Goldberger, 2015). Results demonstrated more people are receiving outpatient visits for anticoagulation, predominantly for initiation of DOACs for new onset AF (increase from 51.9% to 66.9%). Overall visits for anticoagulation increased from 2.05 quarterly to 2.83 quarterly. The use of DOACs for AF increased from 0.88 million to 1.72 million during this five-year period, yet the prescription of warfarin and DOACs for AF was equivalent. As far as individual NOACs for AF, rivaroxaban was prescribed most frequently (47.9%), followed by apixaban (26.5%), and dabigatran (25.5%). This study concluded NOACs were increasing in popularity for the AF population compared to warfarin (Barnes et al., 2015).

Research is starting to compare the safety (thromboembolism) and efficacy (bleeding) of specific dosing for DOACs versus warfarin as current dose adjustments for DOACs are based primarily on renal function, age, body weight, and drug interactions without a consensus suggesting the suitable consistent dose for patients. In a propensity weighted, nationwide cohort study of patients with NVAF, apixaban 2.5 mg twice daily demonstrated higher rates of ischemic stroke and systemic embolism compared to warfarin; conversely, rivaroxaban 15 mg once daily and dabigatran 110 mg twice daily displayed lower rates of thromboembolisms (Nielsen et al., 2017). Compared to

warfarin, bleeding rates were significantly decreased for dabigatran but not rivaroxaban and apixaban (Nielsen et al., 2017).

Cost Comparison

As atrial fibrillation is associated with more severe strokes, anticoagulation to prevent strokes is cost effective. In 2010, AF management cost $6.65 billion--44% was attributed to hospitalizations for an AF diagnosis, 29% for AF as a comorbid condition contributing to hospitalization, 23% for outpatient treatment, and 4% for medications; improving medication management would save an estimated $1.3 billion per year (Fendrick, 2010). Other costs to consider when selecting an anticoagulation include the individual agent, lab monitoring, and treatment for hemorrhages. International normalized ratio monitoring occurs every two to four weeks depending on the time in therapeutic range and cost over $600 annually in 2014 for lab monitoring. In comparison, warfarin cost $40-60 for a 30-day supply in 2014 compared to $350 each for dabigatran, rivaroxaban, and apixaban (Fendrick, 2010).

The cost to treat adverse effects must be considered with oral anticoagulation: hospitalization for a gastrointestinal bleeds costs approximately $24,000 while hospitalization for an intracranial hemorrhage costs approximately $41,000. In general, DOACs display a reduced risk of intracranial hemorrhage compared to warfarin; yet dabigatran has the highest rate of gastrointestinal bleed. Conversely, adherence to a treatment plan is important such as INR monitoring and heparin bridging with warfarin and ingesting a DOAC once or twice daily as prescribed. As DOACs have a shorter half-life, missing one dose could increase the risk of thromboembolism compared to missing four to five days of warfarin. The cost of the reversal agent should also be considered:

Vitamin K, the reversal agent for warfarin, is the cheapest treatment for overdose and bleeding compared to prothrombin complex concentrate or fresh frozen plasma (warfarin, rivaroxaban, and apixaban) with the most expensive treatment as hemodialysis for dabigatran (Crouse & Quigley, 2014).

A meta-analysis of NVAF patients concluded a risk reduction of 0.81 for stroke or systemic embolism, 0.48 for intracranial hemorrhage, and 0.90 for overall mortality for the DOACs compared to warfarin, suggesting cost savings for DOACs related to increased prevention of complications. Resulting from these benefits, DOACs are the preferred anticoagulants by the European Society of Cardiology and the Canadian Cardiovascular Society (cited in Singh & Wijeysundera, 2015). The DOACs are associated with increased costs but also higher quality adjusted life years (QALYs), demonstrating cost effectiveness compared to warfarin (specifically to the DOACs, dabigatran is most cost effective). However, warfarin is less costly when patients have increased time in the therapeutic range (Singh & Wijeysundera, 2015).

Medicare Part D covers 94-99% the cost for apixaban, rivaroxaban, and dabigatran as well as100% for warfarin but does not cover edoxaban (Medicare.gov, n.d.). When comparing the average monthly price of the anticoagulants, warfarin costs $11, rivaroxaban $371, apixaban $395, dabigatran $377, and edoxaban $326 (GoodRx.com, 2017). Manufacturers for all the DOACs offer drug savings cards and/or a free monthly trial to help reduce the higher costs for the patient (Boehringer Ingelheim, 2016; Bristol-Myers Squibb, 2016; Daiichi Sankyo, 2017; Janssen Pharmaceuticals, 2016b).

Dabigatran, rivaroxaban, and especially apixaban display higher QALYs, demonstrating cost-effectiveness compared to warfarin; yet, this is influenced by the cost of the individual anticoagulant agents (Harrington, Armstrong, Nolan, & Malone, 2014). All four DOACS (apixaban, dabigatran, edoxaban, and rivaroxaban) demonstrated decreased medical costs annually for events related to NVAF and thromboembolism compared to warfarin (-$204 for dabigatran, -$140 for rivaroxaban, -$495 for apixaban, and -$340 for edoxaban), which are estimated to continue rising within the next few years; within these drugs, apixaban is the most cost effective (Amin, Bruno, Trocio, Lin, & Lingohr-Smith, 2015). Patients with steady time in the therapeutic range display improved outcomes; thus, the quality of life for warfarin is influenced by adherence to INR monitoring and corresponding dose adjustments. Therefore, warfarin is more cost effective than DOACs in atrial fibrillation patients demonstrating quality anticoagulation (Janzic & Kos, 2013).

Screening and Diagnosis of Atrial Fibrillation

Evaluation of a patient with atrial fibrillation requires stringent monitoring and follow up to prevent complications related to the disease itself as well as adverse effects from the medications, predominantly bleeding risk. Diagnostics for this disease include an exhaustive history and physical examination, a 12-lead electrocardiogram, and a transthoracic echocardiogram. (Kumar, 2016b). Key components of the patient's medical history and examination include assessing for comorbid conditions, stroke risk, symptoms associated with AF, the pattern of AF, and risk of thromboembolism or left ventricular dysfunction (Class I, Level of Evidence C). A 12-lead EKG is necessary to diagnose AF, determine the rate of the dysrhythmia, and assess for ischemia, conduction

defects, and other signs of structural heart disease (Class I, Level of Evidence B; Kirchhof et al., 2016). Once AF is diagnosed, a transesophageal echocardiography (TEE) is recommended with all patients to drive the treatment plan and evaluate for structural valve disease, atrial size, right heart function, and left ventricular size and function (Class I, Level of Evidence C). Furthermore, a TEE is useful to assess for thrombi in the left atrial appendage, suggesting earlier cardioversion or catheter ablation. Ambulatory electrocardiogram (EKG) monitoring can be helpful to measure the effectiveness of rate control treatments, correlate symptoms with ectopy, and discover paroxysmal AF episodes (Kirchhof et al., 2016). Screening for atrial fibrillation is recommended by checking a pulse or obtaining an electrocardiogram strip annually in patients 65 years of age or older as this is the best means to detect silent atrial fibrillation in patients (Class I, Level of Evidence B--Kirchhof et al., 2016; Class IIa, Level of Evidence B--Meschia et al., 2014). In patients who have suffered from an ischemic stroke or a transient ischemic attack, a rapid EKG followed by continuous EKG monitoring for 72 hours is recommended to assess for atrial fibrillation (Class I, Level of Evidence B; Kirchhof et al., 2016). Alcohol consumption, marijuana use, and cigarette smoking all increase the risk of bleeding; thus, avoidance of these substances is urged while on any anticoagulation (Society for Vascular Medicine, 2015). In summary, primary prevention of stroke suggests screening for silent AF through a pulse check and electrocardiogram in addition to 72 hours of cardiac monitoring in patients who have developed an ischemic stroke or transient ischemic attack (Shahid et al., 2016).

Shared Decision-Making Tool

The Society of Vascular Medicine (2015) created an online shared decision-making tool for patients and providers to aid in the selection of anticoagulants. The first series of questions asked the patients to choose "yes" or "no" if any of the following conditions exist: heart failure with an ejection fraction less than 40%; age 65-74 years old; age 75 years old or greater; diabetes mellitus (treated with insulin or oral medications); hypertension; previous stroke, thromboembolism or TIA; female sex; or vascular disease (myocardial infarction, aortic plaque or peripheral vascular disease). Other questions in this set included renal dysfunction (renal transplant, dialysis, creatinine clearance greater than 2.25 mg/dL); liver dysfunction (cirrhosis or elevated liver function tests); previous hemorrhagic stroke; previous major bleeding episode; anemia; use of antiplatelets (including aspirin and nonsteroidal anti-inflammatories); mechanical value replacement; or heavy alcohol use (greater than 16 beers or 10 glasses of wine weekly). The next set of questions addressed the patient's preference for medications: choice of a medication developed in 1954 versus 2010 to prevent stroke, choice of a medication with or without frequent blood draws and follow up with healthcare providers, selection of a medication where the dose is dependent on blood draws or standardized for everyone, and availability to afford a medication co-pay costing greater than $10 per month. Based upon these results, the anticoagulant warfarin or a DOAC (direct oral anticoagulant)--apixaban, rivaroxaban, dabigatran, or edoxaban--is provided to the patient with supporting rationale (Society of Vascular Medicine, 2015).

In addition, bleeding and stroke risks while on anticoagulation are calculated for the patient and explained in depth (Society of Vascular Medicine, 2015). This tool

highlights other factors for the patient to take into consideration when selecting an anticoagulant such as interactions with foods or other medications, adverse drug effects, cost, access to labs for INR monitoring, and potential compliance issues including support systems and foreign languages. For warfarin and the DOACs, the website directs the patient to a further question and answer section, answering topics of pregnancy, food and medication interactions, consumption of alcohol and smoking, checking INRs while on vacation, steps to take when a dose of the medication is missed, physical activity while on anticoagulants, and stopping the anticoagulant prior to surgery or other invasive procedures. The algorithm does not clarify whether the patient qualifies for anticoagulation, no anticoagulation, or aspirin; the algorithm merely addresses the appropriate anticoagulation based upon individualized patient preference and medical history (Society for Vascular Medicine, 2015).

Lab Monitoring

Atrial Fibrillation

Routine monitoring of atrial fibrillation should occur annually--sooner in symptomatic patients. This monitoring includes INRs for warfarin, CrCl for antiarrhythmics and newer anticoagulants, documentation of any changes in the patient's medical history, EKG, labs assessing renal and hepatic function, and possible Holter monitoring of cardiac rhythm (Kumar, 2016b). Analysis of thyroid stimulating hormone and free T4 are also recommended for a new diagnosis in addition to a complete blood count, a serum creatinine, a urinalysis for proteinuria, tests for diabetes mellitus (Kumar, 2016b), and serum electrolytes (Kirchhof et al., 2016). Natriuretic peptide values are increased in AF; yet, evidence does not recommend these blood tests for screening

purposes. However, troponin or natriuretic peptide can further assess bleeding and stroke risk (Class IIb, Level of Evidence B). A complete blood count (CBC) should be obtained every six months with all oral anticoagulants to assess for bleeding. Renal function for all the NOACs should be obtained at least annually as well as hepatic function for rivaroxaban and apixaban annually (January et al., 2014).

Warfarin

As warfarin is contraindicated during pregnancy, a urine human chorionic gonadotropin (hCG) is recommended prior to initiating warfarin and as needed to assess for pregnancy in women of child bearing age (University of Colorado Health North, 2015). The INR was created by the World Health Organization in 1982 to standardize the prothrombin time (PT) to consistently and safely measure the effectiveness of warfarin (Jaffar & Bragg, 2003). The anticoagulant effects of warfarin occur two to seven days after starting the drug; thus, if rapid anticoagulation is needed, bridging with heparin should occur for at least four days. The initial dose of warfarin is usually 5 mg with an INR of 2 after four or five days; yet, lower doses should be used in the elderly and those with a high risk of bleeding. Heparin can be stopped after the INR is therapeutic for two days. The serum INR level should be checked daily until a therapeutic range is achieved for two days, followed by blood work two to three times weekly for one to two weeks, up to once per month with stable levels (Jaffar & Bragg, 2003; January et al., 2014; Wigle et al., 2013). More specifically, the AHA/ACA/HRS (2014) recommended a minimum of weekly INR monitoring until a therapeutic INR was achieved, then monthly lab draws (Class I, Level of Evidence A; January et al., 2014). For atrial fibrillation, the targeted INR for warfarin is 2.0-3.0 (Manning, 2016). With

dose adjustments, alcohol use, dietary or medication changes, labile INRs (January et al., 2014), when transitioning between warfarin and another anticoagulant, or during hospitalization (Hull & Garcia, 2016b), more frequent lab monitoring might be necessary. If a dose of warfarin is missed, the effect on the INR appears two to five days later. With labile INRs, factors such as patient compliance, medication changes, fluctuations in the intake of vitamin K, and acute illness (diarrhea, fever, or vomiting) should be assessed before altering the dose of warfarin (Jaffar & Bragg, 2003).

On average, it takes four months for a patient to reach a therapeutic INR with 25% failing to achieve therapeutic INRs, 30% displaying supratherapeutic or subtherapeutic INRs, and a 10-fold increase in continuing therapy once stable INRs are attained (Janssen Pharmaceuticals, 2014e). Surprisingly, only 55% of the time are AF patients within their target therapeutic range while on warfarin (Janssen Pharmaceuticals, 2014e). Poor INR control results in an increased incidence of patients discontinuing warfarin with one in four patients stopping warfarin within a year of treatment initiation. With a lower $CHADS_2$ score, patients are at a higher risk of stopping warfarin prematurely with 50% of patients failing to adhere to their warfarin regimen (Janssen Pharmaceuticals, 2014b). Furthermore, unstable INRs (< 2 or > 4) are present in 44% of patients on warfarin (Janssen Pharmaceuticals, 2014c). The risk of thromboembolism increases with an INR < 2 and the risk of bleeding increases with an INR > 4, especially > 5 (Hirsh, Fuster, Ansell, & Halperin, 2003). If a patient has labile INRs, replacement with a direct thrombin inhibitor or factor Xa inhibitor is an acceptable alternative (Class I, Level of Evidence C*;* January et al., 2014).

Direct Oral Anticoagulants

As DOACs are administered in fixed dose regimens, routine lab monitoring is not required. However, situations warranting lab monitoring include an epidural, severe bleeding, emergency surgery, or a stroke patient who may require thrombolysis. Malabsorption, obesity, malnourishment, DOAC overdose, acute kidney injury, treatment failure, or drug interactions may also necessitate lab testing for further investigation. Specifically, a dilute thrombin time (dTT), thrombin time (TT) or ecarin-based assay (also known as ecarin clotting time or ECT) are available for dabigatran anticoagulation effects and anti-Xa assays with drug-specific calibrators for rivaroxaban, edoxaban, and apixaban (Hu et al., 2016; Samuelson & Cuker, 2016; Samuelson et al., 2017). If these specialized tests are not accessible, dabigatran levels can be measured through dTT or aPTT (activated partial thromboplastin time) or INR for the factor Xa inhibitors (rivaroxaban, edoxaban, and apixaban). The level of the DOAC within plasma is influenced also by renal function, hepatic function, drug interactions, and the amount of time elapsed since the last dose was administered (Samuelson & Cuker, 2016; Samuelson et al., 2017).

Clinic Managed Versus Home Monitoring of International Normalized Ratios

Introduction

International normalized ratio monitoring is managed within an outpatient anticoagulation clinic, a provider within the community, or at home by the patient; research suggested INR levels are best managed at an anticoagulation clinic or by the patient (Hull & Garcia, 2016b). As the researcher was unable to discover a standardized warfarin dosing guideline or nomogram and anticoagulation clinics usually follow their

own protocols for dosing anticoagulation based upon the target INR, an in-depth discussion of warfarin dosing was not addressed within this paper. Of note, resources such as warfarindosing.com can help providers determine the therapeutic dose of warfarin based upon the two genes: cytochrome P450 *2C9* (CYP2C9) and vitamin K epoxide reductase (VKORC1; Washington University, 2016*).*

Clinic Managed International Normalized Ratios

An example of a guideline for registered nurses and healthcare providers who manage patients on anticoagulation includes indications and warnings for warfarin, laboratory testing (for target INRs), patient education, initiation and maintenance of warfarin therapy (including causes of abnormal INR levels), reversal agents for warfarin, perioperative management and bridging, transitioning to DOACs, quality assessment, nurse education, and how to manage non-compliant patients. In a hypothetical dosing nomogram for initiating warfarin therapy, a dosage of 5-10 mg warfarin is initiated on day one, adjusting the dose on days two to five for the target INR range of < 1.5 all the way up to > 3 depending on the patient specific indication for anticoagulation. For example, with a maintenance INR of 2.0-3.0 and if the INR is therapeutic, the serum INR would be checked within 4 to 12 weeks depending on the stability of the INR levels (University of Colorado Health North, 2015).

In the presence of subtherapeutic (low INR) and supratherapeutic INR (high INR), a search for the cause of the poorly controlled INR is sought and the weekly dosage levels of warfarin and frequency of INR monitoring are adjusted concurrently. General recommendations include checking on new warfarin patients within the first three to five days of initiating therapy and starting 5-10 mg for the first two days (3-5 mg

with impaired liver function, malnutrition, heart failure, thyroid storm, drug interactions, or elderly greater than 65 years old; University of Colorado Health North, 2015). Compared to the 10-mg loading dose of warfarin, the 5-mg loading dose exerts less anticoagulation effects and achieves a therapeutic INR quicker; it also has less risk of the hypercoagulable state that can occur during the first 36 hours of starting warfarin (Harrison et al., 1997; Wigle et al., 2013). Thus, to balance this anticoagulant and antithrombotic balance, the 5-mg loading dose is recommended (Jaffar & Bragg, 2003). Starting on day three, the maintenance dose of warfarin could be started, usually 5-mg daily (University of Colorado Health North, 2015).

This hypercoagulable state when starting warfarin is the result of the decrease of clotting factor VII and the concurrent decrease in proteins C and S, thus the importance of bridging with heparin or low molecular weight heparin until the INR is therapeutic for at least 24 hours (Jaffar & Bragg, 2003; Wigle et el., 2013). The consensus varies on the percentage to adjust warfarin doses safely per week to achieve a therapeutic INR: 5% to 20% according to research studies (Jaffar & Bragg, 2003; Wigle, et al., 2013), 15% to 20% according to an anticoagulation clinic (University of Colorado Health North, 2015), and 10% to 15% according to the RE-LY warfarin trial (Hull & Garcia, 2016b). With continued maintenance of warfarin, past and current INR trends are considered as well as adverse effects (especially bleeding) and drug interactions, targeting the warfarin therapy to the individual patient. In patients who are willing and able, home INR monitoring is preferred over monitoring within an anticoagulation clinic (University of Colorado Health North, 2015).

Home Monitoring of International Normalized Ratios

Randomized control trials have concluded in comparison to clinic-managed INR monitoring, home monitoring of INRs can decrease the risk of thromboembolic events by 42%. Patients treated with dabigatran 150 mg twice daily demonstrated a 35% decrease in strokes compared to treatment with warfarin, suggesting home-monitoring of INRs is as effective as a NOAC in patients adherent to their treatment plan with warfarin (You et al., 2012). Other benefits include reduced costs (mileage reimbursement, appointment cost, and lost wages), time savings by not requiring a clinic visit, improved convenience, and increased patient preference. In fact, 76% of patients would rather pay more money for point-of-care testing (POCT) at home than to travel to a monthly visit at an anticoagulation clinic (Meyer et al., 2013). Cons of home monitoring include increased costs of the devices and test strips needed for this monitoring (You et al., 2012). If cost is not a concern, CHEST recommends home monitoring of INRs in patients who have been thoroughly educated on how to use the devices and are willing to engage in self-monitoring of INR levels (Ansell, 2013; Barcellona, Fenu, & Marongiu, 2016; Class IIB--Pozzi, Mitchell, Henaine, Safi, & Henaine, 2016). Interestingly, 80% of patients can properly obtain a POCT INR level after education (Ansell, 2013).

Quality of Life

Quality of life assessments through the Duke Anticoagulation Satisfaction Scale (DASS; Samsa et al., 2004) suggest improved satisfaction with general treatment, self-efficacy, distress, daily hassles, and strained social network with POCT INR testing, displaying consistent results two years later (Pozzi et al., 2016). The DASS is a reliable and validated 25-question scale assessing a patient's satisfaction and dissatisfaction with

an anticoagulation routine. Negative implications of anticoagulation can result in labile INRs and reduced compliance to a treatment plan; thus, a tool such as DASS can aid in improving patient outcomes (Samsa et al., 2004). A cost-analysis of POCT and clinic managed INRs for patients with similar $CHADS_2$ scores, age, and sex demonstrated a cost of $32,484 for weekly POCT and $33,460 for the anticoagulation clinic. However, the cost per quality adjusted life gain was $5,566, suggesting cost effectiveness and patient preference for POCT (Phibbs et al., 2016).

Conclusions

Data suggest longer times in therapeutic INR range (TTR) reduce adverse patient outcomes. A study concluded physician-managed INRs achieved TTR 30-50% of the time, anticoagulation clinics achieved TTR 50-70%, and weekly POCT INRs achieved TTR 73% of the time (DeSantis et al., 2014). Patients cannot only monitor their INR levels (patient self-testing or PST) but can be trained to self-manage their warfarin dosing (patient self-management or PSM); patients with PST, with or without PSM, have demonstrated safety and efficacy in TTRs (Ansell, 2013). Weekly testing is recommended to achieve more stable TTRs and reduce critical INR values. Patient self-testing can reduce provider workload and expand access to patients requiring INR testing for warfarin (DeSantis et al., 2014). Advantages of POCT and patient self-management of INRs compared to traditional clinic monitoring include the ability to easily and quickly obtain a capillary sample of blood, increased TTR (4.86% compared to the control group), a decrease in thromboembolism in 50% of patients, and a reduction in significant bleeding by 49%. To improve the reliability of the device, as the coefficient of variation between devices can differ from 1.4-1.8%, the accuracy of the device should be checked

at the clinic at least twice annually when testing strips are changed. Inter-laboratory variability can differ from 10-30%; thus, using the same lab is recommended for accuracy of results (Pozzi et al., 2016). Point-of-care testing cannot be completed in patients with a hematocrit greater than 50% or with anti-phospholipid syndrome (Barcellona et al., 2016).

Management of Atrial Fibrillation

Treatment of atrial fibrillation includes reduction of risk factors, medications to control the rate or rhythm of the heart, anticoagulants to prevent blood clots, and thus the risk of stroke, and surgery (CDC, 2015).

Reduction of Risk Factors

Patients should be educated on reversible risk factors for AF including obesity, alcohol overuse, hypertension, coronary artery disease, diabetes, infection, and hyperthyroidism (Ganz & Spragg, 2016). Medical management of a secondary problem contributing to the atrial fibrillation should be encouraged to help determine the etiology of the disease as the inability to treat reversible comorbidities could result in recurrent AF. Risk factors could be modified through lifestyle changes including physical activity, weight loss, incorporating extra virgin olive oil and omega-3 polyunsaturated fatty acids (fish oil) into the diet, and reducing the consumption of alcohol (Kumar, 2016b). Physical activity is beneficial to the cardiovascular system; yet, it could increase the lifetime incidence of AF with > 1,500 hours of endurance activity increasing atrial hypertrophy and dilatation, further affecting volume load and autonomic tone in the heart. Therefore, moderate physical activity is recommended as well as ablation therapy to prevent AF episodes in athletes (Kirchhof et al., 2016).

Heart failure. Atrial fibrillation and heart failure display similar pathophysiology through cardiac remodeling, neurohormonal mechanisms, and impaired left ventricular functioning, resulting in worse patient outcomes with these dual diagnoses; treatment with anticoagulation could reduce the risk of strokes in this population. Research has demonstrated treatment with an angiotensin-converting-enzyme inhibitor (ACE inhibitor) or angiotensin II receptor blocker (ARB) could reduce the incidence of AF in patients with concurrent heart failure and hypertension (Kirchhof et al., 2016) and is recommended for heart failure preserved ejection fraction (HF*p*EF) patients with permanent AF (Class I, Level of Evidence B). Digoxin can control resting heart rate in AF patients with heart failure reduced ejection fraction (HF*r*EF; Class I, Level of Evidence C) or digoxin along with a beta blocker to control heart rate during exercise (Class IIa, Level of Evidence B). Intravenous amiodarone is used as the last resort in patients with AF and heart failure who are unable to achieve a normal heart rate through other pharmacological methods (Class IIa, Level of Evidence C), as well as AV node ablation or rhythm control treatments (Class IIa, Level of Evidence B/C*;* Kirchhof et al., 2016).

Other comorbid diagnoses. Echocardiograms diagnose AF with valve disease in 30% of patients. Valvular AF classifies patients with mitral stenosis or mechanical heart valves. With a diagnosis of severe mitral stenosis, referral for mitral valve surgery is recommended to decrease stroke risk. Decreasing obesity by 10-15 kg can decrease AF symptoms and recurrences. In diabetic patients, treatment with metformin can decrease the risk of AF and stroke as poorly controlled diabetes increases the risk of thromboembolism and bleeding while on NOACs. As obstructive sleep apnea

contributes to AF, screening for this disease and treatment with continuous positive airway pressure ventilation is recommended. In patients with chronic obstructive pulmonary disease, beta blockers and theophyllines used to treat bronchospasm can exacerbate AF and complicate rate control. Ventricular rate control with hyperthyroidism or chronic obstructive pulmonary disease can be managed with beta blockers or nondihydropyridine calcium channel blockers (Class I, Level of Evidence C; Kirchhof et al., 2016). After acute coronary syndrome in patients with AF, warfarin with aspirin is recommended to prevent future cardiovascular events compared to dual treatment with aspirin and clopidogrel (Grade 2C; You et al., 2012).

Approximately 15 to 20% of patients with AF have chronic kidney disease (CKD) (creatinine clearance < 60 mL/min); thus, dosages of NOACs are calculated through the Cockcroft-Gault formula to determine their utility for renal patients (Kirchhof et al., 2016). Evidence recommends all patients on oral anticoagulants have their kidney function assessed prior to initiating direct thrombin or factor Xa inhibitors and receive a minimum of annual screenings of renal function (Class I, Level of Evidence B; January et al., 2014) to assess for CKD in addition to screening of all patients with AF through serum creatinine or creatinine clearance for appropriate anticoagulation dosing (Class I, Level of Evidence A; Kirchhof et al., 2016). After acute coronary syndrome in patients with AF, warfarin with aspirin is recommended to prevent future cardiovascular events compared to dual treatment with aspirin and clopidogrel (Grade 2C; You et al., 2012).

When postoperative AF occurs, first line treatment is a beta blocker (Grade I, Level of Evidence A) with second choice of a nondihydropyridine calcium channel blocker (Grade I, Level of Evidence B). Postoperative AF can be prevented through

administration of amiodarone prior to the cardiac surgery (Class IIa, Level of Evidence A). With postoperative AF, sinus rhythm can also be achieved through antiarrhythmics, ibutilide, or direct-current cardioversion, urging the use of anticoagulants for thromboembolism prophylaxis (Class IIa, Level of Evidence B; January et al., 2014).

Treatment Options

The treatment of AF consists of stroke prevention (anticoagulation) and symptom management (rate and rhythm control; Kirchhof et al., 2016; Kumar & Manning, 2016). A summary from the AHA/ASA (2016) simplifying the atrial fibrillation treatment plan is illustrated within the Anticoagulation for Atrial Fibrillation Toolkit in Appendix A.

Anticoagulation. The selection of anticoagulant agent should be derived from shared decision-making between the patient and provider assessed through a thorough evaluation of thromboembolism, stroke risks, patient preference (Class I, Level of Evidence C), and risk of bleeding (Class I, Level of Evidence B; January et al., 2014). Atrial fibrillation management is improved when the treatment plan and patient education are individualized (Class I, Level of Evidence C; Kirchhof et al., 2016). Factors to consider when selecting an anticoagulant include risk factors, predominantly intracranial bleeding, INR lability, drug interactions, adverse effects, cost, and patient choice (Meschia et al., 2014). Furthermore, patients should be educated on the importance of adhering to the treatment plan and not missing a dose of medication; as DOACs have a shorter half-life than warfarin, missing only one dose can greatly increase the risk of stroke. Net clinical benefit suggests DOACs offer benefits of improved convenience, fewer lab monitoring and food and drug interactions, and comparable safety and efficacy

profiles in preventing stroke in AF patients; yet, the choice of anticoagulant should continue to be prescribed on a patient specific basis (Shahid et al., 2016).

The only approved anticoagulant for moderate to severe mitral valve disease (valvular AF) or mechanical heart value replacement is warfarin (Class I, Level of Evidence B--January et al., 2014; Class I, Level of Evidence B--Kirchhof et al., 2016), with a target INR of 2.0-3.0 (Grade 1B; You et al., 2012). Aspirin with clopidogrel is a suitable alternative for valve patients unable to take warfarin (Grade 1B; You et al., 2012). Due to the heightened risk of stroke, a history of mitral stenosis with either a prior embolus or a left atrial thrombus, even in the presence of sinus rhythm, warrants anticoagulation (Class I, Level of Evidence B). With a bioprosthetic aortic or mitral valve replacement, the two approaches to prevent stroke include aspirin or warfarin with a target INR of 2.0-3.0 for the first three months after the valve is replaced (Class IIa, Level of Evidence C; Meschia et al., 2014).

Rate versus rhythm control. Symptom management is dependent on patient preference and can include pharmacological treatment, cardioversion, or catheter ablation. Controlling ventricular rate is suggested initially to decrease symptoms. Subsequent rhythm versus rate control is dependent on symptoms, left ventricular systolic dysfunction, and patient preference with both methods displaying similar morbidity rates, mortality rates, and quality of life assessments. Rates of thromboembolism are comparable between rhythm and rate control therapies (You et al., 2012).

Rate control utilizes medications decreasing atrioventricular (AV) node conduction including beta-blockers, digoxin, and non-dihydropyridine calcium channel blockers (diltiazem or verapamil) or a combination of the aforementioned options

(Kirchhof et al., 2016; Kumar, 2016b). The medication combination to control heart rate is dependent on the left ventricular ejection fraction (LVEF): with an LVEF ≤40%, beta-blockers and/or digoxin is suggested while with an LVEF ≥40%, beta-blockers, digoxin, and a calcium channel blocker are recommended (Class I, Level of Evidence B). The goal of rate control therapies is a resting heart rate less than 110 beats per minute while avoiding bradycardia (Class IIa, Level of Evidence B*;* Kirchhof et al., 2016). Rate control tends to simplify the treatment regimen, costs less, and eliminates the risks associated with antiarrhythmics and catheter ablation. Thus, rate control is preferred in asymptomatic or mildly symptomatic patients 65 years of age and older (Kumar & Manning, 2016) in addition to pregnant women with AF (Class IIa, Level of Evidence C; Kirchhof et al., 2016).

Rhythm control utilizes antiarrhythmic drugs, percutaneous catheter ablation, and/or surgery (Kumar & Manning, 2016) and is recommended in patients who are unable to remain asymptomatic with rate control medications (Class I, Level of Evidence B; Kirchhof et al., 2016). Flecainide, propafenone, or beta blockers are preferred antiarrhythmics in patients without structural heart disease, bradycardia, or tachycardia; dronedarone or statolol is preferred for coronary heart disease; and the combination of amiodarone and dofetilide is preferred with heart failure (Kumar, 2016a). The European Society of Cardiology (Kirchhof et al., 2016) also recommends flecainide or propafenone for rhythm control of patients without structural heart disease (Class I, Level of Evidence A), and prescribing amiodarone to prevent recurrent AF with heart failure (Class I, Level of Evidence B) or for cardioversion with ischemic or structural heart disease (Class I, Level of Evidence A). Nondihydropyridone calcium channel blockers are

contraindicated with heart failure (Class IIb, Level of Evidence C; January et al., 2014). Rhythm control is used more frequently in younger patients (less than 65-years-old) to regain normal sinus rhythm, recurrent symptoms despite rate control, and persistent AF with irreversible remodeling of the heart (Kumar & Manning, 2016). Other options to achieve normal sinus rhythm include atrioventricular (AV) node ablation and ventricular pacing (Kumar & Manning, 2016) in AF resistant to medication management; yet, the majority of these patients eventually require pacemaker implantation to control ventricular rate (Kirchhof et al., 2016). Even if patients with AF are treated via a rhythm control method, their stroke risk and necessity for anticoagulation should be evaluated equivalently to other AF patients (Grade 2C; You et al., 2012).

Left atrial appendage closure. In patients with contraindications to long-term anticoagulation, since 2005 percutaneous left atrial appendage (LAA) procedures such as WATCHMAN© (Boston Scientific, 2016) are an alternative within the United States and Europe (Hijazi & Saw, 2016). With NVAF, greater than 90% of blood clots from the left atrium originate in the left atrial appendage; thus, implantation of the WATCHMAN device traps clots in the LAA. Under general anesthesia within the catheterization lab and with the guidance of fluoroscopy and transesophageal echocardiography (TEE) to ensure accurate LAA measurement and fit, WATCHMAN is inserted through the femoral vein, advanced transseptally into the left atrium, and finally implanted into the LAA. The WATCHMAN requires an hour to implant and approximately a one-day hospital admission. Post implant, patients are required to take aspirin and warfarin for a minimum of 45 days to ensure the LAA is encapsulated by heart tissue (confirmed by a TEE), followed by clopidogrel and a higher dose of aspirin for six months, and finally aspirin

for life. The WATCHMAN is covered by Medicare and most major insurance companies and is a permanent device only requiring a one-time insertion.

Compared to warfarin, LAA closure has demonstrated a 52% reduction in cardiovascular death, a 72% decrease in severe bleeding six months after the procedure, and a 78% decrease in hemorrhagic stroke (Boston Scientific, 2016). However, LAA has an increased risk of pericardial effusion, excessive bleeding, and procedure-related complications compared to warfarin (You et al., 2012). Evidence has demonstrated LAA closure is non-inferior to warfarin in preventing stroke in AF patients with reduced bleeding risk. The AHA/ASA (2016) endorse left atrial appendage closure with AF; patients demonstrating a high risk of stroke are poor candidates for anticoagulation if the patient can temporarily take anticoagulation 45 days after the surgery (Class IIb, Level of Evidence B; Meschia et al., 2014). The ESC (Kirchhof et al., 2016) also proposes anticoagulation after LAA to prevent strokes (Class I, Level of Evidence B). Furthermore, WATCHMAN is cost effective within seven years after implantation, costs less, is more effective than five years of treatment with DOACs, and is more effective than 10 years of treatment with warfarin (Desai et al., 2017).

Cardioversion. Patients may be candidates for cardioversion to restore sinus rhythm before initiation of antiarrhythmics (Naccarelli, Ganz, & Manning, 2016). Two forms of cardioversion are available--pharmacological and direct current (electrical); pharmacological methods can restore sinus rhythm in 50% of patients with AF without sedation or nothing by mouth while electrical methods can more successfully achieve sinus rhythm within a shorter duration of time and are recommended with hemodynamic instability. With electrical cardioversion, the patient is sedated with intravenous propofol

and/or midazolam followed by synchronized shocks delivered through a biphasic defibrillator to anterior and posterior electrodes. Risks with electrical cardioversion include bradycardia and skin burns (Kirchhof et al., 2016). Direct current cardioversion is suggested in patients with a rapid ventricular rate who are unable to be converted via pharmacological means (Class 1, Level of Evidence B). Pharmacological cardioversion can consist of the following agents: flecainide, dofetilide, propafenone, ibutilide (Class I, Level of Evidence A) or amiodarone (Class IIa, Level of Evidence A; January et al., 2014) with heart failure and ischemic heart disease. Patients with paroxysmal AF can self-cardiovert at home ("pill in the pocket") with one dose of flecainide or propafenone when symptoms arise (Kirchhof et al., 2016) concurrent with a beta blocker or nondihydropyridine calcium channel blocker (Class IIa, Level of Evidence B; January et al., 2014).

In stable patients with atrial fibrillation duration greater than 48 hours, oral anticoagulation should be started three weeks prior to cardioversion to reduce the risk of stroke (Class I, Level of Evidence B--January et al., 2014; Class I, Level of Evidence B--Kirchhof et al., 2016; Naccarelli et al., 2016) and continued four weeks after the cardioversion (Level of Evidence B--January et al., 2014; Class I, Level of Evidence B--Kirchhof et al., 2016; Class 1B--You et al., 2012; Class I). The CHEST (cited in You et al., 2012) suggests either warfarin with a target INR of 2.0-3.0, dabigatran, or low-molecular weight heparin as suitable options prior to cardioversion with AF duration longer than 48 hours (Grade 1B). An alternative to anticoagulation prior to cardioversion is a TEE to assess for the presence of cardiac thrombi; if a thrombus is not discovered in the left atrial appendage, cardioversion is completed immediately (Class I, Level of

Evidence B; Kirchhof et al., 2016). To prevent stroke, the American Academy of Chest Physicians guidelines recommend brief anticoagulation before TEE guided cardioversion (Grade 1B; You et al., 2012). The AHA/ACC/HRS (2014) recommends using warfarin as the anticoagulant for four weeks after the cardioversion (Class I, Level of Evidence B), or dabigatran, rivaroxaban, or apixaban (Class IIb, Level of Evidence C; January et al., 2014).

With AF duration less than 48 hours, anticoagulating the patient with low-molecular weight heparin or unfractionated heparin should occur prior to the cardioversion (Grade IIb, Level of Evidence C--January et al., 2014; Grade 2C; You et al., 2012); yet, starting anticoagulation should not delay an urgent cardioversion (Grade 2C; You et al., 2012). In emergent cases, heparin is utilized as the anticoagulant (Naccarelli et al., 2016). Of note, the first 72 hours and up to 10 days after cardioversion displays the highest risk of stroke and thromboembolism as it can take weeks for the atrial dysfunction to subside. Within one year after cardioversion, one-half of the patients will have a recurrence of AF (You et al., 2012). The necessity of anticoagulation after cardioversion is based upon the patient's individualized risk profile for thromboembolism (Class I, Level of Evidence C; January et al., 2014).

Ablation. Radiofrequency ablation or cryotherapy balloon catheterization of the pulmonary veins, a primary cause of paroxysmal AF, can be utilized to achieve normal sinus rhythm and symptom control in patients who have failed antiarrhythmic therapies. Anticoagulation should be prescribed eight weeks prior to the ablation to reduce the risk of stroke. Catheter ablation results in a one-year period absent of symptomatic atrial fibrillation in 80% of patients without structural heart disease; however, complications of

this procedure include cardiac tamponade, stroke, and vascular trauma. With recurrent AF after an ablation, a second ablation or antiarrhythmic medication may be warranted (Passmar, 2016). In heart failure patients with AF, catheter ablation can reduce recurrent AF and even improve LVEF (Kirchhof et al., 2016).

Cox-Maze. The Cox-Maze surgical procedure creates alternative electrical pathways from the sinoatrial node to the atrioventricular node, preventing AF conduction in patients with symptomatic persistent or long-standing persistent AF (Lee, 2017). The Cox-Maze IV is completed to improve diastolic filling and atrial synchrony plus alleviate AF. In this procedure, bipolar frequency and/or cryothermal energy are used to fabricate scar tissue on the right atrium (superior vena cava to inferior vena cava), left atrium (posterior wall), the four pulmonary veins forming a "box" attached to the mitral valve annulus, and removal of the left atrial appendage. Often, the invasive sternal approach is completed during a coronary artery bypass graft (CABG) or valve surgery or a less invasive thoracotomy approach is available. Risks include increased incidence of subsequent pacemaker implantation, pericardial tamponade, requirement of a sternotomy approach, and TIA (Kirchhof et al., 2016). Anticoagulation is recommended for three months after the Cox-Maze procedure in patients who have had the left atrial appendage ligated or removed to decrease the risk of stroke (Lee, 2017).

Atrial fibrillation management team approach. The ESC (Kirchhof et al., 2016) recommends the following approach to managing AF successfully:

1. Patient involvement (patient education, patient empowerment, reduction of risk factors, lifestyle modifications, and shared decision making)

2. Multidisciplinary team (primary care providers, cardiologists, AF specialists, surgeons, and allied health providers working together collaboratively)
3. Navigation system for providers and patients (tools and checklists to improve communication, clinical decision support, availability of information on AF, and the ability to monitor the compliance and effectiveness of the treatment plan)
4. Complex management decisions (anticoagulation, rate control, lifestyle modifications, antiarrhythmics, and catheter and surgical options).

The goals of this integrated approach to AF management include reduction of hospitalizations, enhanced patient adherence to the treatment plan by incorporating patient preference into the decision-making process, improved patient outcomes, and decreased mortality. Atrial fibrillation can be well managed within the primary care setting; however, a referral to an AF specialist is recommended in the presence of the following factors: hemodynamic instability (severe symptoms), history of TIA or stroke necessitating anticoagulation, symptomatic bradycardia, poor rate control (fast heart rate), deteriorating left ventricular function, severe angina, assessment for rhythm control, or special conditions (thyrotoxicosis, sepsis, or postoperative AF; Kirchhof et al., 2016).

Performance and quality measures. In 2016, the ACC and AHA (Heidenrich et al., 2016) released performance and quality measures related to AF management in both the inpatient and outpatient settings to improve the management, safety, and care coordination of these patients. Performance measures for the outpatient setting include documentation of a completed CHA_2DS_2-VASc score, prescribing anticoagulation when

appropriate, and completing monthly INRs for patients on warfarin. Quality measures include prescribing a beta blocker with a left ventricular ejection fraction < 40% and not prescribing a direct thrombin inhibitor or factor Xa inhibitor with mechanical heart values, end-stage kidney disease, or dialysis. Other quality measures include not prescribing oral anticoagulants and antiplatelets (unless the patient has coronary artery disease or vascular disease) to reduce bleeding risk, not prescribing a calcium channel blocker with reduced ejection failure heart failure, and the necessity of shared decision-making between the patient and provider when prescribing anticoagulation (Heidenrich et al., 2016).

Pregnancy. In pregnant women with atrial fibrillation, digoxin or beta-blockers are safe for rate control during pregnancy and breast feeding. For rhythm control, sotalol and flecainide are safe during pregnancy. Electrical cardioversion is a harmless alternative during all stages of pregnancy, especially with hemodynamic instability. Vitamin K antagonists should be avoided during the first trimester and two to four weeks prior to delivery of the fetus due to bleeding risks and teratogenic effects. A safe alternative for anticoagulation is low-molecular weight heparin as it does not cross the placenta. In pregnant women with mechanical valves who decide not to continue with warfarin, within 6 to 12 weeks of gestation, they should be transitioned to dose-adjusted, subcutaneous, low-molecular weight heparin or unfractionated heparin. During the third trimester, INRs should be checked every 10 to 14 days. Data have been inconclusive in determining whether NOACs are excreted into breastmilk (Daiichi Sankyo, Inc., 2015; Drugs.com, 2015a, 2015c, 2016). Warfarin is not present in breastmilk but should be avoided during lactation due to the increased risk of bleeding for the fetus (Drugs.com,

2015c). The pregnancy categories of NOACs are as follows: Category B--apixaban (Drugs.com, 2016); Category C--rivaroxaban (Drugs.com, 2015b), dabigatran (Drugs.com, 2015a), edoxaban (Daiichi Sankyo, 2015), and warfarin with mechanical valves (Drugs.com, 2015c); and Category X--warfarin without mechanical valves (Drugs.com, 2015c). However, due to lack of safety evidence, NOACs should be avoided during pregnancy and in women attempting to become pregnant (Class III Harm, Level C; Kirchhof et al., 2016).

Other comorbid diagnosis. With a diagnosis of hypertrophic cardiomyopathy, lifetime anticoagulation with AF is recommended to decrease the risk of stroke regardless of the CHA2DS2-VASC score (Class I, Level of Evidence B--January et al., 2014; Class I, Level of Evidence B--Kirchhof et al., 2016). In the presence of an atrial septal defect, surgical closure prior to 40-years-old or a Cox-Maze procedure are suggested to decrease the risk of atrial fibrillation or atrial flutter. Treatments for atrial flutter with anticoagulation (Class I, Level of Evidence C--January et al., 2014; Class I, Level of Evidence B--Kirchhof et al., 2016; You et al., 2012), electrical cardioversion, and antiarrhythmics are congruent with AF therapies as the stroke risk is comparable; however, rate control is often more difficult to achieve with atrial flutter (Kirchhof et al., 2016). With a CHA_2DS_2VASc score ≥ 2 in addition to hemodialysis or end-stage chronic kidney disease (creatinine clearance < 15 mL/min), warfarin is the preferred anticoagulant (Class IIa, Level of Evidence B). With the diagnosis of moderate to severe chronic kidney disease and CHA_2DS_2VASc score ≥ 2, dose adjusted direct thrombin inhibitors or factor Xa inhibitors are viable options instead of warfarin for anticoagulation (Class IIb, Level of Evidence; January et al., 2014).

With comorbid AF and acute coronary syndrome and a CHA_2DS_2VASc score ≥ 2, anticoagulation is suggested (Class I, Level of Evidence C; January et al., 2014), more specifically dose-adjusted warfarin with a target INR of 2.0-3.0 instead of warfarin combined with aspirin (Grade 2C; You et al., 2012). Furthermore, CHEST (cited in You et al., 2012) suggests triple therapy (oral anticoagulant, warfarin, and clopidogrel) for three to six months after a drug-eluting stent is placed (Grade 2C), followed by dual therapy for up to one year (Grade 2C) to prevent occlusion of the coronary artery and further ischemic events. One year after placement of the stent, the same anticoagulant recommendations for dose-adjusted warfarin in patients with stable coronary artery disease (no incidence of acute coronary syndrome within the past year) and AF apply (Grade 2C). In a patient with acute coronary syndrome and a $CHADS_2$ score of 1 or greater who does not receive a coronary stent, dose-adjusted warfarin plus aspirin of clopidogrel is recommended for one year (Grade 2C; You et al., 2012).

Reversal Agents for Anticoagulants

Introduction

If the CHA_2DS_2-VASc recommends a patient initiate or continue anticoagulation, the HAS-BLED score is useful for determining bleeding risk (Hwang, 2016b) as shown within the Anticoagulation for Atrial Fibrillation Toolkit in Appendix A. A HAS-BLED score of 1 suggests a risk of 1.13 bleeds per 100 patient-years, a score of 4 implies 8.70 bleeds, and scores > 5 display insufficient evidence to predict bleeding risk. Major bleeding may result in hospitalization, the need for blood transfusions, surgery, or the complication of intracranial hemorrhage (Manning et al., 2016). With minor bleeding such as epistaxis or ecchymosis, applying manual compression to control the source of

bleeding or stopping the anticoagulant with high bleeding risk are appropriate treatments. is an appropriate treatment. With a major bleed, cessation of the offending anticoagulant is warranted as well as administration of intravenous fluids, packed red blood cells, and platelet transfusions as needed (Hu et al., 2016). Methods to reduce bleeding risk include hypertension control using an agent other than dabigatran at patients with high risk of gastrointestinal bleeding, and reducing alcohol consumption (Kirchhof et al., 2016).

Warfarin

If the patient develops life-threatening bleeding while on warfarin, the reversal agent for warfarin is vitamin K_1 (Hull & Garcia, 2016a). According to the European Society of Cardiology, fresh frozen plasma and prothrombin complex demonstrate quicker reversal of bleeding than vitamin K_1 administration (Kirchhof et al., 2016). Managing patients with high INRs on warfarin is very specific. With a high INR, warfarin should be stopped as an INR will return to normal within four to five days. The second choice is to administer the antidote vitamin K_1 as needed. The third choice, which would most quickly return the INR to normal, is administration of fresh plasma or prothrombin concentrate. Below is a summary of the recommended reversal treatments based on INR levels:

- With an INR high but < 5, the warfarin dose can be reduced or omitted until the INR nears the normal range.
- With an INR between 5 and 9 without bleeding, the next one to two warfarin doses are held with the dose lowered when the INR approaches normal or vitamin K_1 (1.5 to 2.5 mg) can be administered orally if the risk of bleeding is high. If rapid reversal of warfarin is necessitated, such as for surgery,

vitamin K_1 (2.0 to 5.0 mg) can be given orally with a decrease in the INR within the next 24 hours. If the INR is not therapeutic within 24 hours, another dose of vitamin K_1 (1.0 or 2.0 mg) can be administered.

- With an INR >9 but without bleeding, vitamin K_1 (3.0 to 5.0 mg) can be given orally with a drop in the INR within 24 to 48 hours.
- With an INR > 20 or severe bleeding, vitamin K_1 (10 mg) should be given intravenously followed by fresh plasma or prothrombin complex concentrate; extra vitamin K_1 may be given every 12 hours as needed (Hirsh et al., 2003).

High doses of vitamin K_1 should be avoided if possible, as resistance to warfarin can occur for a duration of one week after reversal with vitamin K_1. Thus, if warfarin is administered after vitamin K_1, heparin bridging may be necessary to achieve therapeutic INRs (Hirsh et al., 2003).

Direct Oral Anticoagulants

Reversal of a DOAC can occur through drug removal, bypassing to other coagulation pathways, or sequestration using precise reversal agents. Activated charcoal (dabigatran and apixaban; Garcia & Crowther, 2017; Hull & Garcia, 2016b) and hemodialysis (dabigatran) are methods to *remove* NOACs from the body (Samuelson & Cuker, 2016), especially in the case of drug overdoses (Garcia & Crowther, 2017; Hu et al., 2016). Nonspecific prothrombin complex concentrate, activated prothrombin complex concentrate (PCC), and recombinant factor VIIa are means to *bypass* coagulation pathways. The intravenous drug-specific agents bind to the NOAC molecule to reverse the anticoagulant effects: Idarucizumab (humanized monoclonal antibody

fragment) *sequesters* dabigatran, and Andexanet alpha (factor Xa decoy) and Ciparantag (synthetic cationic molecule) are two factor Xa inhibitors currently undergoing clinical investigation. If approved by the FDA as a universal reversal agent, Ciparantag could also reverse the anticoagulant effects of dabigatran and heparin (Hu et al., 2016; Ruff, Giugliano & Antman, 2016; Samuelson & Cuker, 2016).

Until a specific factor Xa inhibitor reversal agent is developed, severe or life-threatening bleeding with these agents (edoxaban, rivaroxaban, and apixaban) can be reversed with 4-factor PCC 50 IU/kg, which contains clotting factors, heparin, and coagulation inhibitors protein C and protein S (Garcia & Crowther, 2017; Hull & Garcia, 2016a; Ruff, Giugliano, & Antman, 2016). Neither vitamin K_1 nor fresh-frozen plasma can reverse DOACs (Ruff et al., 2016). If major bleeding occurs during or post procedure, antifibrinolytics such as tranexamic and Ɛ-aminocaproic acid are cost effective and safe options (Garcia & Crowther, 2017; Hull & Garcia 2016b; Hu et al., 2016). Of significance, drug specific antidotes should only be utilized in either the presence of life threatening bleeding or for emergency surgery (Hu et al., 2016).

Switching Between Warfarin and Direct Oral Anticoagulants

Direct Oral Anticoagulants to Warfarin

Factors to consider when switching from a DOAC to warfarin and vice versa include cost, interactions, and availability. When transitioning between classes of anticoagulants (warfarin, factor Xa inhibitors, and direct thrombin inhibitors), an overlap period must occur to prevent an increased risk of stroke while new drug levels are becoming therapeutic. A minimum of a two-day overlap is recommended when

switching from a DOAC to warfarin. As a DOAC can alter the accuracy of INR levels for warfarin dosing, edoxaban and apixaban should be continued until the INR is ≥ 2.0. A recommended regimen when transitioning from any of the four approved DOACS (dabigatran, apixaban, edoxaban, and rivaroxaban) to warfarin suggests a reduced dose of the DOAC, INR testing for a goal of ≥ 2.0, and adjusted dose of warfarin for up 14 days (or until the INR is therapeutic) to decrease the risk of bleeding and stroke. Parental agents are used concurrently with the DOAC as needed to achieve a therapeutic INR quicker (Manning et al., 2016). A longer overlap is recommended between warfarin and dabigatran if the CrCl is prolonged (Drugs.com, 2015a).

Warfarin to Direct Oral Anticoagulants

When switching to apixaban (Drugs.com, 2016) or dabigatran (Drugs.com, 2015a), warfarin can be discontinued followed by initiating the DOAC once the INR is < 2.0. For rivaroxaban, warfarin can be discontinued and then followed by starting the DOAC once the INR is < 3.0 (Drugs.com, 2015b). Of note, when switching between DOACs, the current DOAC should be stopped with the new DOAC administered at the standard dose time; no period of overlap between drugs is necessary (Guimaraes et al., 2015; Manning et al., 2016). For edoxaban, warfarin can be discontinued, followed by starting the DOAC once the INR is 2.5 (Daiichi-Sankyo, 2015; Guimaraes et al., 2015).

Cessation of Anticoagulants Prior to Invasive Procedures and Surgery

Warfarin

Warfarin is usually stopped four to five days before surgery for the INR to decrease to < 1.2. With a low risk of blood clots, the warfarin dose can also be reduced

for this four to five-day period prior to surgery to achieve an INR of 1.3-1.5. For up to two to three days postoperative, the patient is at risk for a thromboembolism. As a result, prophylactic doses of heparin or low molecular weight heparin can be administered every 12 hours for four to five days until the INR becomes therapeutic again (Hirsh et al., 2003).

Direct Oral Anticoagulants

Cessation of DOACs prior to an invasive procedure to decrease bleeding risk is dependent on the anticoagulant. Recommendations for cessation of the individual DOAC agents are as follows:

- Rivaroxaban: Rivaroxaban is discontinued 24 hours pre-procedure and can be resumed 6 to 10 hours after hemostasis is achieved post-procedure (Drugs.com, 2015b).
- Dabigatran: With a CrCl >50 mL/min, dabigatran should be held one to two days prior to the procedure. With a CrCl < 50 mL/min, dabigatran should be held three to five days prior to the procedure (Drugs.com, 2015a).
- Apixaban: Apixaban should be discontinued 48 hours pre-procedure in patients with a moderate to high risk of bleeding or 24 hours pre-procedure with a low risk of bleeding. The anticoagulant should be resumed 12 to 24 hours post-procedure after hemostasis is achieved (Drugs.com, 2016).
- Edoxaban: Recommendations suggest edoxaban be discontinued 24 hours pre-procedure with a high risk of bleeding and then resumed as soon as hemostasis is achieved. Indwelling intrathecal catheters and epidural catheters should not be removed less than 12 hours after the last dose of

edoxaban to prevent bleeding; the next dose should be given two hours after the catheter is removed (Daiichi Sankyo, 2015).

In general, factor Xa inhibitors should be withheld a minimum of 24-48 hours before a procedure with an intermediate bleeding risk and 48-72 hours before a high bleeding risk procedure while direct thrombin inhibitors should be withheld a minimum of 72 hours before the procedure. With renal impairment, the DOAC should be withheld even longer. Permitting hemostasis is achieved, DOACs can be resumed within 24 hours after the procedure and up to 48 hours with a high risk of bleeding (Doherty et al., 2017; Hu et al., 2016).

Recommendations

The ACC (2012) released an expert consensus providing guidance on cessation of anticoagulants in NVAF prior to procedures (periprocedurally) as every year approximately 250,000 patients require this momentary disruption in therapy. The ACC recommends assessing for stroke risk via the CHA_2DS_2-VASc (rather than the $CHADS_2$) score and utilizing a bleeding risk score through HAS-BLED to identify risk factors for bleeding. Key components for providers to assess prior to interruption of anticoagulation therapy include the need to interrupt (low, intermediate, or high risk of bleeding periprocedure), when to interrupt, the need to bridge with a parenteral anticoagulant post-procedure, how to bridge, and when to restart oral anticoagulation. Recommendations for cessation of anticoagulants periprocedurally are as follows:

- Low bleeding risk procedures: Common procedures such as implantation of a pacemaker/defibrillator or a catheter ablation demonstrate lower rates of bleeding with uninterrupted oral anticoagulant during the procedure

compared to bridging post-procedure. Specifically, a VKA should not be interrupted prior to a procedure with a low bleeding risk and no patient specific risk factors increasing bleeding risk (Doherty et al., 2017) such as minor dental procedures, cataract surgery, and minor dermatological procedures (University of Colorado Health North, 2015).

- Intermediate and high bleeding risk procedures: A VKA should be interrupted with an intermediate bleeding risk procedure, high bleeding risk, or unknown bleeding risk. Prior to cessation of anticoagulation, an INR should be checked five to seven days before the procedure. Cessation of the INR before the procedure depends on the INR, which should be assessed 24 hours periprocedurally: the VKA should be interrupted three to four days before a procedure with an INR of 1.5-1.9, five days prior to the procedure with an INR of 2.0-3.0, and greater than five days with an INR greater than 3.0. Higher dosages of warfarin may require shorter periods of interruption (Doherty et al., 2017).

Bridging with Heparin

As warfarin takes five to seven days to regain therapeutic effects once restarted, bridging with parenteral low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is often required to prevent thromboembolism postprocedural, especially with an INR < 2.0 in NVAF. Parenteral bridging initiation is recommended within 24 hours post-procedure with an intermediate to high risk of stroke or thromboembolism in patients with NVAF and is contraindicated with high bleeding risk (delaying any anticoagulation 48-72 hours post-procedure). Bridging does not come without its own

perils such as increased cardiovascular sequalae and bleeding risk; recent evidence suggests thromboembolic events are not decreased greatly with bridging (NVAF patients have a 0.4% risk of thromboembolism regardless if they received or did not receive bridging when starting warfarin; Doherty et al., 2017).

Parenteral agents. Length of hospital stay is shortened with parenteral LMWH but UFH should be used in patients with a CrCl < 30 mL/min; both drugs demonstrate comparable bleeding and thromboembolism risks. The level of anticoagulant effect can be measured through an activated partial thromboplastin time (aPTT) for UFH and an LMWH-specific antifactory Xa assay. Post-procedure, a VKA can be restarted within 24 hours at the prior therapeutic dose if hemostasis is achieved; the parenteral drug is stopped once the INR is > 2.0. Furthermore, LMWH should be stopped 24 hours pre-procedure and UFH stopped four to six hours pre-procedure (Doherty, et al., 2017).

Direct oral anticoagulants. Despite the lack of specific reversal agents for DOACs, their short half-life requires less therapeutic interruption periprocedurally, bridging is not required, and the drug can be started as soon as hemostasis is achieved. For DOACs specifically, the bleeding risk, individual drug, and the creatinine clearance predicted through the Cockcroft-Gault equation determine when to halt and resume therapy for procedures. All the DOACs have a black box warning contraindicating the use of these medications during neuraxial analgesia to prevent the occurrence of spinal or epidural hematomas. Thus, direct thrombin inhibitors should be withheld four to five days and factor Xa inhibitors held three to five days before neuraxial analgesia; these drugs can be safely restarted 24 hours after the procedure. Current research recommends against using DOACs for anticoagulation post mechanical valve surgery but can be used

27 hours after hemostasis is obtained post coronary artery bypass grafting (Doherty et al., 2017).

Conclusions. In a patient with a low thromboembolism risk (<5% annually), a CHA_2DS_2-VASc score ≤4 with no history of a prior stroke, systemic embolism or transient ischemic attack, a VKA can be restarted post-procedure without bridging. With an intermediate risk of thromboembolism (5-10% annually) and a CHA_2DS_2 VASc score of 5-6, recommendations are based upon bleeding risk: with a higher bleeding risk, bridging is contraindicated but with a low bleeding risk, parenteral bridging is recommended only with a history of a prior stroke, systemic embolism, or TIA. With a high risk of thromboembolism (> 10% annually), a CHA_2DS_2-VASc score of 7-9, and a history of prior stroke, systemic embolism, or transient, bridging with a parenteral agent is recommended (Doherty et al., 2017).

Drug and Food Interactions with Anticoagulants

Warfarin

With warfarin, cytochrome P450 inducers and inhibitors or CYP2C9, CYP1A2, CYP2C19, and CYP3A4 isoenzymes influence the pharmacology of this medication and thus its INR values. Predominantly, drug interactions with warfarin result in severe bleeding and usually do not occur until three to five days after administration. Factors influencing the effects of warfarin include age, broad spectrum antibiotics, intake of vitamin K, sex, body surface area, substances with a high protein concentration, and genetic polymorphisms CYP2C9 and VKORC1. Foods to avoid with warfarin include grapefruit, green tea, chamomile, soybeans, mango, ginseng, St. John's wort, ginkgo biloba, cranberry, and green leafy vegetables with a high concentration of vitamin K.

Concurrent use of NSAIDs, aspirin, and clopidogrel increase the risk of bleeding while on warfarin; use of estrogen increases the risk of clotting (DiMinno et al., 2017). Specific medications which can affect the INR are illustrated within the Anticoagulation for Atrial Fibrillation Toolkit located in Appendix A.

Direct Oral Anticoagulants

Factor Xa inhibitors are influenced by administration of inducers or inhibitors of CYP3A4 and P-gp. Specific to dabigatran, P-gp inhibitors and inducers should also be avoided. Drug interactions with DOACs appear less severe than with warfarin; however, limited evidence is available on food interactions with the DOACs (DiMinno et al., 2017). Furthermore, protease inhibitors to treat human immunodeficiency infection (HIV) and enzyme-inducing antiepileptics such as phenytoin and carbamazepine are contraindicated with DOACs (Manning et al., 2016).

Anticoagulation in the Elderly Population

Research Studies

According to the AHA, "Atrial fibrillation (AF) is increasingly recognized as the single most important cause of disabling ischemic stroke in the elderly" (Perera et al., 2016, p. 2197). A survey of Medicare patients with atrial fibrillation demonstrated the average age is 80-years-old and over 55% are female; new data suggest women with AF over age 75 have a heightened risk of stroke compared to their male cohorts (Foody, 2017). When anticoagulating the elderly, a clinician should consider factors such as polypharmacy, impaired cognition, fall risk, comorbidities contributing to bleeding risk, CKD, nutritional status, and weight (Barbosa & Falcao, 2016). Other factors to investigate include compliance to the treatment plan, health literacy, ability to obtain

medications and INR monitoring, adverse drug effects, cognition, family support, and the relationship between the patient and provider. Hospitalization for AF may be related to drug-drug interactions with oral anticoagulants, contributed to the most frequent comorbidities of heart failure, renal failure, chronic obstructive pulmonary disease, and diabetes mellitus (Foody, 2017).

Advanced age ≥ 65 years old is a risk factor for thromboembolism, yet is also a risk factor for increased bleeding risk. Non-vitamin K oral anticoagulants (NOACs) selectively inhibit one coagulation pathway--either thrombin/factor IIa or factor Xa. Resulting from the mechanisms of action, the NOAC effects are more predictable, have a quicker onset of action, a reduced half-life, and a larger therapeutic window. Therefore, NOACs do not require routine lab monitoring compared to warfarin and are more highly recommended in the elderly. Non-vitamin K oral anticoagulants are not endorsed in elderly patients with chronic kidney disease (CrCl < 30 mL/min with dabigatran and CrCl < 15 mL/min with factor Xa inhibitors) nor with a body weight ≤ 60 kg (edoxaban and apixaban). Other considerations in the elderly patient on warfarin include a deficient vitamin K diet and alcohol consumption, which increase bleeding risk, as well as genetic polymorphisms affecting metabolism of this drug. The overall bleeding risk for NOACs is comparable to warfarin; however, the risk of GI bleeding is higher for NOACs. Intracranial hemorrhage is the cause of 90% of warfarin-related deaths, yet NOACs have demonstrated a reduced risk of this complication. Astonishingly, for an AF patient on long-term anticoagulation, this patient could fall 300 times annually before the risk of bleeding offsets the risk of anticoagulation use (Barbosa & Falcao, 2016). Another study

suggests patients would have to fall over 5.7 times per week before the risk-benefit ratio would favor no anticoagulation (Janssen Pharmaceuticals, 2014a).

Despite the three-fold risk of strokes in patients older than 75-years-old, only 30% to 50% of applicable patients receive anticoagulation. In studies examining stroke prevention in elderly NVAF patients, the NOACs rivaroxaban, apixaban, and dabigatran demonstrated improved efficacy and safety compared to warfarin. Additionally, these same three NOACs have been approved to decrease cardiovascular risk prior to cardioversion in NVAF. Related to safety and efficacy data, particularly the decreased risk of intracranial hemorrhage, this study concluded NOACs are superior to warfarin when anticoagulating the elderly including NVAF. In summary, despite the increased risk of stroke in this population, the elderly population is undertreated with anticoagulation (Barbosa & Falcao, 2016).

Negative Outcomes with Anticoagulation

Elderly patients demonstrate an amplified risk of hospitalization related to drug reactions convoluted by factors such as polypharmacy, comorbid diseases, fragility, and physiological changes associated with increasing age as evidenced by a seven-fold increased risk compared to a younger population. A study in the New England Journal of Medicine (Budnitz, Lovegrove, Shehab, & Richards, 2011) concluded two-thirds of hospitalizations for patients 65 years of age and older were related to accidental overdoses of four high-risk medications: warfarin (33.3%), oral antiplatelet medications (13.3%), insulins (13.9%), and oral hypoglycemic medications (10.7%). Specific to warfarin, 46.2% of emergency department visits for warfarin related adverse effects resulted in hospitalization for patients. In addition, 50% of these hospitalizations were in

patients older than 80 years of age. National hospitalization rates for adverse drug effects related to warfarin included intracranial hemorrhage (5.6%), gastrointestinal hemorrhage (40.8%), epistaxis (6.1%), hemoptysis (2.0%), genitourinary hemorrhage (4.7%), abnormal laboratory value (increased INR or drug toxicity, 23.7%), or other hemorrhage (5.3%; Budnitz et al., 2011). Furthermore, over 90% of elderly AF patients are at an increased risk of stroke and less than 50% of patients with AF in a long-term care facility receive adequate anticoagulation (Janssen Pharmaceuticals, 2014a).

Beers Criteria

The updated 2015 American Geriatrics Society (AGS) Beers Criteria, which highlights medications deemed high risk for the elderly population, emphasized specific recommendations for cautious use of aspirin, warfarin, and dabigatran in this population. Quality of evidence (high, moderate, and low) and strength of recommendations (strong, weak, and insufficient) were evaluated using the American College of Physician's guideline grading system. Aspirin to prevent cardiovascular events should be used cautiously in patients 80 years of age or older (low quality of evidence, strong strength of recommendation) due to insufficient data showing a risk-benefit ratio. Beers Criteria recommends cautious use of dabigatran in patients 75 years of age or older with a CrCl < 30 mL/min as dabigatran has demonstrated a greater risk of gastrointestinal bleeding in comparison to warfarin for anticoagulation purposes in this population (AGS, 2015). Limited evidence is available on the safety of this drug with low CrCl levels (moderate quality of evidence, strong strength of recommendation). Due the increased risk of bleeding, the combination of warfarin and amiodarone should be avoided (moderate quality of evidence, strong strength of recommendation) in addition to the combination of

warfarin and NSAIDS (high quality of evidence, strong strength of recommendation). Furthermore, to minimize the risk of bleeding, Beers Criteria lists the following recommendations: dabigatran and edoxaban should be avoided with a CrCl <25 mL/hr and <30 mL/hr, respectively; the edoxaban dose should be reduced with a CrCl of 30-50 mL/hr and avoided with a CrCl < 30 or > 95 mL/hr; and rivaroxaban dose should be reduced with a CrCl 30-50 mL/hr and avoided with a CrCl <30 mL/hr (moderate level of evidence, strong strength of recommendation; AGS, 2015).

Recommendations

Evidence has demonstrated the bleeding risk while on oral anticoagulants does not outweigh the benefits of stroke prevention including high risk populations such as the elderly, cognitive dysfunction, or patients at high risk of falls. The bleeding risk is equivalent with warfarin, NOACs, or aspirin; however, only NOACs and warfarin have demonstrated a reduction in stroke risk. Bleeding risk is the primary reason for discontinuing oral anticoagulation prematurely or failure to initially prescribe. Oral anticoagulation should only be withheld in patients with severe falls related to epilepsy or dementia where the patient is no longer able to comply with the treatment regimen (Kirchhof et al., 2016). Furthermore, elderly patients within the nursing home on anticoagulation display increased adverse outcomes: greater than 50% of patients have subtherapeutic or supratherapeutic INRs, 65% of patients stop warfarin therapy prematurely, concurrent use of warfarin with commonly used NSAIDs and antibiotics increases bleeding risk, and warfarin dosing is one of the most common medication errors within this setting (Janssen Pharmaceuticals, 2016a).

As aforementioned, the risk factor of increasing age alone augments the risk of ischemic stroke in the elderly population. As people age, bleeding risk--predominantly intracranial, traumatic from falls, and gastrointestinal--complicates the use of anticoagulation. Fear of bleeding risk in the elderly population inhibits its proper utilization as evident by a study that concluded only 64% of Medicare patients with high stroke risks were using warfarin (Desai et al., 2017). The safety of anticoagulation studies is evaluated for the risk of severe bleeding; the risk of intracranial hemorrhage is stable from age 60 to 80 years, yet rises greatly after 80 years old regardless of anticoagulation status, suggesting increasing age alone may be sufficient to intensify bleeding risk. A net clinical benefit (NCB) infers all elderly patients with AF 65 years of age or older and with at least a CHA_2DS_2-VASc score ≥ 1 would benefit from anticoagulation. Furthermore, as the CHA_2DS_2-VASc or HAS-BLED scores increase, suggesting augmented risk of stroke and bleeding, respectively, the risk of stroke still outweighs the risk of severe bleeding, thus confirming why high-risk populations require anticoagulation. Comparisons of the NOACs (apixaban, edoxaban, rivaroxaban, and dabigatran) to warfarin have demonstrated a reduced rate of intracranial hemorrhage and a decreased risk of ischemic stroke in the elderly population. However, regardless of the anticoagulant, intracranial bleeds occur in less than 1% of the population annually (Desai et al., 2017).

With increasing age, the ability to metabolize drugs slows; thus, the weekly dose of warfarin should decrease 0.4 mg/yr to prevent supratherapeutic levels and thus lower augmented bleeding risk. The cost of NOACs may be more expensive to the individual patient; yet on a system level, costs decrease significantly. Antiplatelets demonstrate

reduced efficacy in preventing strokes and should not be used in the elderly; however, left atrial appendage closure is a viable option for patients unable to take long-term oral anticoagulation. Elderly patients with AF should strive for a heart rate control less than 80 bpm, moving to a rhythm strategy (with anticoagulation) or catheter ablation with failure to control symptoms (Desai et al., 2017). A novel study examined 23,356 patients with atrial fibrillation age 80- to 100-years-old who had suffered a recent ischemic stroke from 2006 to 2013 (Appelros, Farahmand, Terént, & Asberg, 2017). Approximately 27% (6,361) patients were started on anticoagulation after the stroke, demonstrating less recurrent strokes in this population and only an increased incidence of bleeding in patients older than 90 years old. The study concluded even this increased bleeding risk in the older population did not outweigh the benefits of anticoagulation to prevent recurrent ischemic strokes (Appelros et al., 2017).

Literature Review

The literature review was exhaustive and within the past five years including systematic reviews obtained from a PubMed and an UpToDate database search. Other noteworthy data if older than five years were also included in this paper as oral anticoagulants have been utilized in practice since the 1950s. The literature review focused on a comparison between the five oral anticoagulants predominantly used to prevent thromboembolism in patients with atrial fibrillation (warfarin, apixaban, dabigatran, rivaroxaban, and edoxaban) as displayed in Appendix B. Additionally, a summary of noteworthy drug trials highlighting the safety and efficacy of oral anticoagulants, reversal agents, and other novel treatments for atrial fibrillation are displayed in Appendix C. The efficacy outcome of stroke incidence and safety outcome

of bleeding events were the primary purposes of these anticoagulant drug trials to promote their clinical relevance and utilization in practice. Finally, the most recent guidelines from the American Stroke Association, American Heart Association, American College of Chest Physicians, American College of Cardiology, and European Society of Cardiology (ESC) were the foundation and final consensus of recommendations for atrial fibrillation management addressed within this toolkit. The summaries of these guidelines are attached in the appendices as follows: (a) 2016 ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration with EACTS (see Appendix D); (b) 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: Executive Summary (see Appendix E); (c) Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis (see Appendix F); and (d) 2014 AHA/ASA Guidelines for Prevention of Primary Stroke; see Appendix G).

Problem Statement or Purpose

Integrated Summary of Literature

Research and practice have indicated patients, especially the elderly, do not receive adequate assessment or management of atrial fibrillation, resulting in higher ischemic stroke rates. A small percentage of patients with silent AF are diagnosed with arrhythmia only after suffering from a stroke; in the primary care setting, an annual pulse check with subsequent EKG for an abnormal rhythm could greatly reduce the incidence of strokes in this high-risk population. Patients at moderate to high risk for stroke are not receiving oral anticoagulants, predominantly due to the overexaggerated risk of bleeding with these medications or lack of provider knowledge on current treatment

recommendations for AF. Furthermore, inconsistencies exist with assessing bleeding risk and stroke risk for every patient through reliable tools such as HAS-BLED and CHA_2DS_2-VASc scores, respectively, as well as translating these scores into practice. Consensus is universal on initiating anticoagulation with a CHA_2DS_2-VASc score ≥ 2; yet, guidelines and organizations vary on their recommendations for anticoagulation with a CHA_2DS_2-VASc score of 1, ultimately relying on patient and provider opinions that may result in an increased frequency of stroke in patients with a higher risk profile.

Even though trends are slowly shifting, most patients are prescribed warfarin with atrial fibrillation when newer anticoagulants are available. Anticoagulation is recommended indefinitely for patients with AF and a moderate to high risk of stroke; however, prescription of these medications becomes convoluted when factors such as cost, patient compliance, adverse effects, safety, access, reversal agents, and provider preference must be involved in the decision-making process. Due to these inconsistencies and the lack of a comprehensive, universal guideline for assessment and management of atrial fibrillation, this topic was selected for a capstone project. A toolkit consisting of a guideline with algorithms and guideline was formulated to direct primary care providers on an evidence-based path to diagnose and assess for atrial fibrillation in the elderly as well as prescribe and manage anticoagulation safely and individually for the patient with the overall objective of reducing the occurrence of ischemic stroke in this high-risk population. The researcher utilized expert consensus, national and international guidelines, and current literature reviews to develop this anticoagulation toolkit in its entirety.

Question Statement

In adult patients with atrial fibrillation older than 65 and at a moderate to high risk of stroke, how effective is an anticoagulation toolkit in guiding primary care providers on (a) diagnosing atrial fibrillation and (b) initiating and maintaining oral anticoagulation safely to reduce the incidence of ischemic stroke?

Challenges

The providers themselves are a major challenge as generational gaps and individual preferences and experiences influence their decisions to prescribe anticoagulants in general--let alone a newer agent. Less safety and efficacy data are available on the DOACs compared to warfarin, further complicating the prescription of these novel drugs as providers often prescribe medications with which they are most familiar and comfortable. A recent impetus in the anticoagulation movement is to prescribe the best anticoagulant for the individual patient. By expanding the quantity of available oral anticoagulants from only one with warfarin to five with the DOACs, patients have more opportunities to find the most appropriate anticoagulant and thus reduce their risk of stroke. Additionally, providers must be consistently up to date on anticoagulant research findings and management of atrial fibrillation to utilize evidence-based practice, especially as the release of new research studies, antidotes for the new agents, and alternative treatments become available on the market. Furthermore, many providers continue to use the $CHADS_2$ scoring system to assess for stroke risk; however, this tool excludes patients with heightened risk factors that would be anticoagulated based on CHA_2DS_2-VASc criteria. The evidence-based HAS-BLED tool is rarely utilized in practice as providers deduce bleeding risk based on past history rather than

assessing for and reducing risk factors for bleeding, which is the essence of this tool. Another key problem to diagnosis and management of atrial fibrillation is the patient. With atrial fibrillation, there are varying presentations, effects on quality of life, and patient preference for anticoagulation versus WATCHMAN (Boston Scientific, 2016) or preferring no treatment at all. As far as anticoagulants themselves, cost, health literacy, lab monitoring, support systems, transportation, and resources all influence the ability of patients to take anticoagulants as prescribed. Furthermore, both patients and providers in primary care often lack knowledge on the universal impact and significance of atrial fibrillation contributing to ischemic strokes. Thus, improved education for all parties involved is essential to advance management of this chronic disease.

Problems

Multiple factors influence the decision of the type of anticoagulant prescribed by practitioners such as cost, insurance coverage, and reversal agent availability. Other factors include patient preference; patient comorbidities such as renal function, hepatic function, and artificial valves; the purpose of the anticoagulation, efficacy, and the adverse effects profile of the drugs. Patient compliance is significant as dietary changes, monitoring via lab work, access to care including lab monitoring facilities, reversal agents, and adhering to the prescription regimen as directed are all essential to the careful balance of preventing thromboembolisms while also reducing bleeding risk. Initiation of treatment is challenging to primary care providers as well as managing this chronic disease with anticoagulation. Four evidence-based guidelines exist for anticoagulation with atrial fibrillation and are considerably congruent in their recommendations. However, keeping up to date with updates is challenging for providers working in a

primary care setting who cannot focus continuing education on only one medical specialty. Providers should be familiar with multiple agents available for anticoagulation and AF including alternative treatments such as WATCHMAN (Boston Scientific, 2016). Yet, providers are often limited on their training and experience with these options and treat the patient based on what they know rather than what could be best for the patient. Providers who prescribe anticoagulation must be familiar with food and drug interactions, temporary interruption of therapy for circumstances such as surgery, how to switch between DOACs and warfarin, initiation and maintenance lab monitoring (including home versus clinic INRs), recommendations for genetic testing, and how to treat severe bleeding.

Assessing for atrial fibrillation through secondary prevention should be incorporated into the annual physical examination, especially with the elderly; yet, providers are not informed of the necessity of assessing and diagnosing an irregular rhythm to ultimately prevent strokes. Furthermore, primary prevention of disease is more significant than treating the disease after the fact; thus, providers should be aware of risk factors for AF and teach their patients how to reduce these risk factors to improve their health. Unfortunately, providers have limited time during appointments to educate patients on anticoagulation, yet alone atrial fibrillation, contributing to limited comprehension, noncompliance, and misinterpretations of the disease state or medications. Relentless advances in medicine such as genetic testing, time constraints with high patient loads, and limited or unknown resources to educate patients on anticoagulant use further complicate this decision-making process; thus, directing providers and patients to reliable resources and shared decision-making tools is essential

to improve efficiency. Atrial fibrillation can be diagnosed and managed safety within the primary care setting but providers should be trained on situations warranting a referral to a specialist.

Situations

A chart review was conducted within a private primary care clinic in northern Colorado, focusing on the diagnosis and management of patients with atrial fibrillation during 2017. Through the confidential collection and assessment of patient demographics, risk factors, patient presentation, diagnosis, treatment plan, and negative outcomes all related to AF, the researcher could compare current evidence to practice, assessing for any gaps and offering solutions.

Current evidence-based literature was utilized to formulate said toolkit with guideline and algorithms including expert opinion and national and international guidelines. Upon completion of this toolkit, it was distributed to two primary care clinics as well as two cardiology clinics within northern Colorado; the goal was to achieve 70% consensus from 13 providers (physicians, nurse practitioners, and physician assistants). Even though this toolkit was designed and intended for the primary care setting, expert opinions were obtained from specialists in cardiology when formulating and revising the guideline with algorithms. Before analyzing the toolkit in Round 1 of the Delphi method, providers within the primary care setting received via email a consent form (see Appendix H) describing the purpose and phases of the project. Consent was implied if the providers submitted the online survey through Survey Monkey within the two-week period (see Appendix I).

Opportunities

This project provided an opportunity to illustrate a comparison of the anticoagulants in a table format including pharmacology, FDA (CDC, 2016b) prescribing information, economics, and safety and efficacy of the drugs based upon clinical trials. A summary of noteworthy drug studies for the five oral anticoagulants was provided to address the safety and efficacy of these anticoagulants plus these drugs trials discussed alternative treatments for AF such as WATCHMAN (Boston Scientific, 2016) left atrial appendage implants. Additionally, providers were distributed an evidence-based toolkit comprised of a guideline and algorithms to aid in the decision-making process of the atrial fibrillation diagnosis as well as safe and effective initiation and management of the appropriate anticoagulant for the individualized patient. The purpose of this toolkit was not to persuade a provider to select one anticoagulant over another but allow an opportunity to expose and educate providers to the vast array of products available to select the best agent for each patient. This toolkit provided evidence-based practice and reliable resources within one document to improve the overall treatment for atrial fibrillation. Settings to obtain expert opinion and implement this project focused on family practice (primary care) clinics as this setting is often where AF is diagnosed and treated primarily. However, providers have limited knowledge and experience compared to cardiology and electrophysiology specialists.

Theoretical Framework

Promoting Action on Research Implementation in Health Services Framework

The Promoting Action on Research Implementation in Health Services (PARIHS) framework created in 1998 was relevant to this capstone as it integrates the three components of evidence, context, and facilitation into practice. These three elements are ranked on a scale from low to high with improved implementation of evidence into practice when all factors are ranked high. Evidence can be derived from experience (patient and clinician), research (qualitative and quantitative), and local data. The context of the practice can vary but is influenced by history, psychosocial factors, economics, and politics, especially culture, leadership, and evaluation. Facilitation improves and simplifies the process of implementing research into practice with strong facilitators encompassing the characteristics of purpose, role, skills, and attributes and strives for a holistic process (Rycroft-Malone, 2004).

The PARIHS framework has been effectively used to improve implementation of retrospective and prospective healthcare research including 40 research papers from 2011-2016 alone. For instance, PARIHS was used in a retrospective study on improving implementation of methicillin resistant staphylococcus aureus (MRSA) guidelines into the U.S. Department of Veteran's Affairs (VA), concluding high evidence, mixed content, and mixed facilitation (Rycroft-Malone, 2004). Similarly, a prospective study on the implementation of the VA's MyHealtheVet personal health record portal, which allows patients to access their medical health records, concluded low evidence, low context, and high facilitation (Hill et al., 2017). The results from these PARIHS

frameworks were used to brainstorm strategies to improve the implementation of these healthcare programs into practice. Strengths of this framework included investigating the complexity of implementing research into practice, focusing on the context of the research, ease of use, and clinical applicability (Harvey & Kitson, 2016).

A revised PARIHS framework was developed in 2008 to address limitations including a lack of prospective studies, inadequate focus on the influence of individuals and the system itself in implementation, a lack of theoretical foundations, and failure to address the intended audience and external context of the practice (Harvey & Kitson, 2016). The revised (integrated) iPARIHS framework added the element of recipient and innovation to the original triad of evidence, context, and facilitating, emphasizing facilitation as the key factor to successful research implementation. Innovation included balancing evidence, knowledge, and local practice when considering change. Recipients of the change occur at the individual, local, organizational, and system levels. Context is redefined as the inner context (local setting) and outer context (organization and system levels). The facilitator role is expanded into the interplay of novice, experienced, and expert facilitators who utilize their various skills to improve the implementation process (Harvey & Kitson, 2016).

The plan for this project was an anticoagulation toolkit guiding providers on improved diagnosis of atrial fibrillation as well as patient-centered anticoagulation initiation and maintenance. The three elements of the PARIHS framework (evidence, context, and facilitation into practice) were evaluated for this capstone project and ranked on a scale from low to high. For this project, it was necessary to review patient charts for local data, obtain a literature review on current evidence and best practice, and acquire

expert opinion (evidence). Subsequently, this evidence and experience were incorporated into an anticoagulation toolkit for managing atrial fibrillation in the primary care setting (context) by integrating the components of culture, leadership, and evaluation in this process. Applications of this project addressed the role of a facilitator in successfully implementing this written material into practice, ultimately seeking expert commentary on the efficacy and feasibility of it use (facilitation into practice). Elements of the iPARIHS model were incorporated into the evaluation of this toolkit and focused on innovation, recipients, and the influence of different context levels and experience of the facilitators.

Reach, Effectiveness/Efficacy, Adoption, Implementation, and Maintenance Model

The reach, effectiveness/efficacy, adoption, implementation, and maintenance (RE-AIM) framework is composed of five steps to "enhance the quality, speed, and public health impact of efforts to translate research into practice" (RE-AIM, 2017: Reach (target population), effectiveness/efficacy (impact of the intervention), adoption (healthcare providers and setting willing to initiate the change), implementation (reliability, costs, time constraints, transformations, and delivery to adopt the change), and maintenance (ability to continue the change over time for at least six months). The RE-AIM model has been successfully used to assess the impact of the WISEWOMAN program to improve cardiovascular disease screening and lifestyle changes in uninsured women (Farris, Will, Khavjou, & Finkelstein, 2007) and to hone strategies for chronic disease management (Glasgow, McKay, Piette, & Reynolds, 2001).

The RE-AIM model was utilized for this capstone project to assist with the effective implementation and evaluation of this anticoagulation toolkit. *Reach* addressed the target population of elderly patients with a new or chronic diagnosis of atrial fibrillation within the primary care setting. *Effectiveness* was the impact of this anticoagulation toolkit to prevent stroke in patients with atrial fibrillation. *Adoption* assessed the willingness and feasibility of primary care providers to incorporate this toolkit into practice. *Implementation* addressed the factors contributing to the successful use of this toolkit in primary care such as provider and patient preference, costs, access, time constraints, and training. *Maintenance* assesses the duration of implementing this toolkit in practice but was not feasible for this capstone project.

CHAPTER II

PROJECT DESCRIPTION

Project Description

Synthesized Summary of Project

For this quality improvement capstone project, a retrospective chart review was completed on the diagnosis and treatment of atrial fibrillation patients in the primary care setting. Through implementation of two rounds of the Delphi technique, expert opinions from providers in primary care and cardiology were utilized to create an anticoagulant toolkit emphasizing improved diagnosis of atrial fibrillation in the elderly within the primary care setting and followed by appropriate initiation and management of individualized anticoagulation to reduce the incidence of stroke. Recommendations to improve this variance between research and practice included evaluating the necessity of anticoagulation through stroke risk (CHA_2DS_2-VASc) and bleeding risk (HAS-BLED) scales, screening all elderly patients in the primary care setting for atrial fibrillation through an annual pulse check with follow-up electrocardiogram as necessary, and highlighting key resources for providers (guidelines, quality and performance measures, and a shared decision-making tool) to improve implementation of evidence-based research into practice. This toolkit also contained a tabular comparison of warfarin and direct oral anticoagulants (edoxaban, rivaroxaban, dabigatran, and apixaban), and patient-specific factors to consider when selecting an anticoagulant.

Project Objectives

The objectives of this capstone project were to (a) examine current and local diagnosis and management of atrial fibrillation within the primary care setting, (b) create a toolkit (guideline with algorithms) directing practitioners on diagnosis of atrial fibrillation as well as initiation and maintenance of oral anticoagulation, (c) promote safety and efficacy in the management of anticoagulants, (d) endorse patient-centered anticoagulation based upon current evidence-based literature and expert opinion, and (e) evaluate the effectiveness of a toolkit influencing the diagnosis of atrial fibrillation and anticoagulation management within a primary care setting.

Congruence of Organization's Strategic Plan to Project

Confidential chart reviews of atrial fibrillation patients were completed at Family Physicians of Greeley. Tentative primary care organizations in northern Colorado to implement the toolkit included Family Physicians of Greeley-Central and University of Colorado Health Family Medicine--North Loveland. Additionally, as cardiologists specialize in atrial fibrillation, their expertise and experience were incorporated into the construction and revisions of the anticoagulation algorithm and guideline. Proposed cardiology sites included the Cardiovascular Institute of Northern Colorado and the University of Colorado Health Heart Center--Fort Collins. Expert opinions from all sites were obtained from physicians, nurse practitioners, and physician assistants. To more effectively reach a diverse population with this toolkit, expert consensus was obtained from providers who delivered care to patients in both rural and urban settings and were employed at commercial and privately-owned clinics. Organizations aiding in the

execution of this capstone project display similarities in their missions, values, perspectives, and approaches to diagnosing and managing atrial fibrillation.

Project Design

Literature Review on Atrial Fibrillation and Anticoagulation

For this quality improvement project, an extensive literature review included relevant background information on AF that focused on the diagnosis and management, especially with anticoagulants. Literature was current (within the past five years) and relevant (inclusive of the key words of "atrial fibrillation"), obtained from PubMed and UpToDate databases, as well as guidelines on anticoagulation with atrial fibrillation. Additional necessary research compared oral anticoagulants (warfarin, apixaban, dabigatran, rivaroxaban, and edoxaban) for patient-specific factors as well as assessed safety and efficacy of each agent. As this project focused on a population of elderly patients with AF, noteworthy literature was analyzed to discover how best to manage this disease to reduce negative sequelae of stroke as well as its impact on patients and society in general. Ultimately, this research was the foundation for the anticoagulation toolkit designed for the primary care setting: guideline, algorithms, and provider resources to manage AF. This research was also applied to identify practice gaps, effectively translating research to practice to improve patient outcomes.

Patient Chart Reviews

A goal of 100 retrospective patient chart reviews through Next Generation was confidentially reviewed at Family Physicians of Greeley-Central. Patients were included if they had a diagnosis of atrial fibrillation and were seen in the clinic during 2017. Data collected included demographics (age, sex, race/ethnicity, insurance status, and

rural/urban residence), risk factors, patient presentation, diagnosis (focusing on pulse checks and EKG results), comorbid diagnoses, imaging/laboratory data, treatment plan (focusing on oral anticoagulants), negative outcomes, patient tolerance/quality of life, follow-up, and interdisciplinary management for patients with atrial fibrillation. Additionally, the patient charts were assessed for the use and interpretation of bleeding risk and stroke risk scores (HAS-BLED and CHA_2D_S-VASc respectively). The purpose of obtaining this data was to compare current evidence to practice.

Delphi Technique

The Delphi technique is utilized to obtain data from experts in a particular field during a short time period to establish a group consensus from a series of surveys. The Delphi technique is described as "iterative and sequential" (Hsu & Sanford, 2007, p. 5). Since the 1950s, the Delphi technique has been used as a group communication tool to obtain controlled expert consensus for "goal setting, policy investigation, or predicting the occurrence of future events" (Hsu & Sanford, 2007, p. 1). This technique can be used to offer choices, recognize assumptions, make predictions, set goals, increase knowledge, and summarize judgments within a group for the purposes of program structuring, needs evaluations, policy writing, and resource management. The researcher reviews each survey from an expert and creates a group consensus that is returned to each expert along with a summary of the expert's own viewpoint. The purpose of repetitive surveys is to obtain feedback from the experts; re-evaluations of perspectives can ultimately formulate an improved consensus and communication among the group. The Delphi technique maintains the confidentiality of subject identifiers, controls the feedback process (the summary of the prior surveys is given to experts to decrease "noise" of the individuals,

which inhibits problem solving and alters data), and multiple statistical analyses are completed, all decreasing influences of coercion and biases common in group settings. Usually a minimum of three rounds of survey distribution is sufficient for the Delphi technique but up to five can be implemented to achieve group consensus.

In Round 1, a survey with open-ended questions or derived from a literature review is given to the experts. In Round 2, a more structured survey is given to the experts that requests the subjects create a summary of the results from the first round. Also in Round 2, questions may require ranking or rationale to support their decisions. In Round 3, the experts receive a summary of the results from Round 2 and the subjects are asked to reassess their responses including rationale and to request further explanations. In Round 4, an overall summary of the prior three rounds is given to all the subjects, allowing one final chance to reassess their responses (Hsu & Sanford, 2007).

Subjects and time are essential factors to consider when determining if the Delphi technique is the appropriate tool. Choosing subjects is important for the Delphi study as it influences the quality of the data obtained. A minimum of 10-15 experts in a field is an adequate sample size with an average of 15-20 subjects per study. The Delphi technique assumes all the experts have similar experiences and knowledge of the subject matter are stakeholders who will use these results either for clinical or research purposes, and these subjects are willing to work as a team to reach a consensus. On average, 45 days are required to complete the Delphi study in its entirety with a recommended two-week period between administration and subject response for each individual survey. To decrease time constraints, the use of e-mail or teleconferencing to distribute surveys was utilized so feedback could be obtained more quickly and enhanced subject

confidentiality. Methods of data analysis included central tendency (mean, median, and mode) as well as level of dispersion (standard deviation and inter-quartile range) with median and mode preferred. Consensus was attained when "80 percent of the subjects' votes fall within two categories on a seven-point scale…at least 70 percent of Delphi subjects need to rate three or higher on a 4-point Likert-type scale and the median has to be a 3.25 or higher" (Hsu & Sanford, 2007, p. 4). Limitations of the Delphi technique included potential molding of opinions to coincide with group opinion (through persuasion of researchers or after receiving misleading feedback) and presumed all experts in the field were equal in experience and knowledge in order to develop a general rather than a topic-specific consensus. As multiple rounds are required for the Delphi technique, possible low response rates from subjects could negatively influence feedback and lengthy time commitments to collect and analyze data could limit the study's successful implementation (Hsu & Sanford, 2007).

The Delphi technique has been utilized to assess several atrial fibrillation studies such as a systematic review with a one-round Delphi technique ranking 54 outcomes and performance indicators internationally to better assess AF management (Berti, Van Vlasselaer, Moons, & Heidbuchel, 2015). The Cardiovascular Health in Ambulatory Care Research team (Tu et al., 2017) assessed performance indicators (risk factor prevalence, screening, management, intermediate outcomes, and long-term outcomes) for primary prevention of cardiovascular disease using a two round Delphi technique. This study concluded the five key risk factors for cardiovascular disease were smoking, obesity, hypertension, diabetes, dyslipidemia, and atrial fibrillation. These identified performance indicators could be measured in the outpatient setting by researchers,

stakeholders, and clinicians to prevent cardiovascular disease (Tu et al., 2017). Furthermore, the AF-SCREEN International Collaboration (Freedman et al., 2017) composed of 60 experts utilized the Delphi technique to establish a consensus on AF screening. The collaboration focused on the importance of anticoagulation to prevent stroke if AF was diagnosed via an EKG, the superiority of using handheld EKG devices for screening, increasing monitoring of patients with recent embolic stroke to better diagnose AF, and the importance of multidisciplinary management of AF regardless of the clinic or health system (Freedman et al., 2017).

For this capstone, two rounds of the Delphi technique were utilized. Round 1 focused on a qualitative, open-end survey to assess the comfort level, experience, and baseline knowledge of the expert providers diagnosing atrial fibrillation as well as prescribing and managing anticoagulation for this high-risk population within the primary care setting. Along with the first survey, the providers received a consent form highlighting the purpose and format of this project. Additionally, providers were asked to list their credentials, specialty, and years of expertise for demographic and statistical purposes. The survey for Round 1 is provided in Appendix I; the consent form to participate in the research that affirmed all identifying information would remain confidential was also sent.

In Round 2 of the Delphi method, providers received a consensus of the group from Round 1 and completed a second mixed quantitative and qualitative survey addressing ease of use, applicability, relevance, and the impact of this toolkit on practice. Providers were asked to evaluate the benefits and challenges of this toolkit and offer feedback for revisions. To clarify, providers received the first draft of the anticoagulation

toolkit composed of an algorithm and guideline during Round 2. The anticoagulation toolkit was drafted after Round 1 and then revised further after Round 2 to incorporate expert consensus into the toolkit, thus increasing relevancy and clinical applicability to the primary care setting. The survey for Round 2 is provided in Appendix J.

The goal sample size was 10 to 15 family practice and cardiology practitioners consisting of physicians, nurse practitioners, and physician assistants. Providers had two weeks to complete each survey through Survey Monkey, which was accessible through the link sent to each provider individually through e-mail. Upon completion of the two rounds of the Delphi method, data and demographics were analyzed through standard qualitative measures. Consensus was achieved if the panel agreed on the components in Round 2 at least 70% of the time. If a consensus of 70% was not accomplished after two rounds, subsequent rounds were indicated, time permitting.

Evidence-Based Projection Plan

The evidence-based projection plan consisted of the following six phases:

- Phase 1: Thorough literature review on anticoagulation and atrial fibrillation. Current literature focused on the diagnosis and management of atrial fibrillation obtained from PubMed and UpToDate databases as well as international and national guidelines. Novel drug trials and pharmacokinetics/pharmacodynamics of the five most prescribed oral anticoagulants (warfarin, dabigatran, apixaban, edoxaban, and rivaroxaban) were summarized additionally.
- Phase 2: Medical records review at Family Physicians of Greeley-Central, assessing demographics, risk factors, patient presentation, diagnosis,

comorbid diagnoses, imaging/laboratory data, treatment plan, negative outcomes, and interdisciplinary management for patients with atrial fibrillation. Records of patients on anticoagulation were reviewed for assessment of stroke risk and bleeding risk through CHA_2DS_2-VASc and HAS-BLED scores, respectively, as well as patient preference.

- Phase 3: Development of an anticoagulation toolkit guideline and algorithms based upon best evidence and expert opinion (literature review, clinical practice guidelines, review of current practice, and consensus from primary care providers and cardiologists). The design of this project was the Delphi technique with a minimum of two rounds and a goal of 70% consensus. The toolkit was devised after completion of Round 2 of the Delphi method.
- Phase 4: Distribution and revision of the anticoagulation toolkit in the primary care and cardiology settings. The goal was to reveal this toolkit to two or three different primary care clinics and one to two cardiology clinics within northern Colorado with a 100% participation rate of 10-15 providers. Providers completed the first survey during Round 1 and the second survey with toolkit evaluations during Round 2.
- Phase 5: Using qualitative statistical analysis, the data and demographics from patient charts and the Delphi surveys were evaluated to derive conclusions comparing evidence to practice.
- Phase 6: Future project involved a pilot study to assess any impact on patient outcomes related to implementation of this toolkit into the primary care setting.

Timeline of Project Phases

The researcher utilized the following timeline for the project phases:

- Phase 1 (literature review)--Completion by June 2017.
- Statement of Mutual Agreement signed—July 6, 2017 (see Appendix K)
- University of Northern Colorado (UNC) Institutional Review Board approval --Obtained August 11, 2017 (see Appendix L).
- Phase 2 (medical records review)--Completion by September 2017.
- Phase 3 (development of anticoagulation toolkit)--Completion by September 2017.
- Phase 4 (distribution and revision of toolkit)--Completion by October 2017.
- Phase 5 (data analysis)--Completion by October 2017.
- Phase 6 (pilot study)--Future research project

Subjects

Subjects for the patient chart review included any adult greater than 18 years of age who required anticoagulation for the indication of atrial fibrillation for ischemic stroke prophylaxis. Despite the focus of this project on elderly patients older than 65 years, a thorough assessment of the diagnosis of AF and anticoagulation management in all adults was essential for the data analysis portion of this project to address current practice. Subjects were obtained from the Next Generation electronic health records at Family Physicians of Greeley-Central, focusing on patients who were seen in the clinic during 2017 related to a diagnosis of atrial fibrillation. The sample size was based on availability of patients meeting inclusion criteria; yet, the researcher aspired for a goal of at least 75 patient chart reviews. The providers analyzing the toolkit were primary care

and cardiology providers within northern Colorado including either physicians, nurse practitioners, or physician assistants who prescribed anticoagulation. Specific patient characteristics such as pregnancy status, heart valve replacement, increased risk of gastrointestinal distress, decreased creatinine clearance, and poor patient compliance were addressed in the toolkit to help providers manage future anticoagulant prescriptions more safely and effectively.

Implementation Methods/Tools

An anticoagulation toolkit comprised of a guideline with algorithms was created based upon recent literature and expert opinions. Two surveys were formulated to evaluate the toolkit through the Delphi method. The first survey compared current practice to literature. The second survey focused on the safety, efficacy, comprehensiveness, and ease of administration of the toolkit. The second survey also focused on how implementation of this toolkit influenced the initiation and management of anticoagulation for AF in the primary care setting.

Resources

Personnel

Expert opinions were obtained from providers specializing in family practice and cardiology in addition to the recommendations from national and international guidelines on anticoagulation management.

Technology

Literature was acquired from the UNC library databases, PubMed, and UpToDate. Microsoft Office was utilized to generate the toolkit. Patient charts were reviewed through Next Generation. Electronic surveys were created and completed on

Survey Monkey along with the consent form, survey link, and additional relevant information delivered to providers via confidential e-mail.

Budget

At this point, no financial constraints were foreseen with planning, formulation, revision, implementation, and evaluation of this project.

Risks and Benefits

A potential risk was a provider following the toolkit but not considering the patient's comorbidities, concurrent medications, and individualized indications and contraindications, resulting in an incorrect prescription or management of anticoagulation. Other risks included the provider not following the toolkit correctly, the provider not incorporating the patient's preferences into the decision of which anticoagulation to prescribe (including self-monitoring of INRs with warfarin), or the provider not staying up to date with current evidence and best practice recommendations on anticoagulants. The primary benefit was evidence-based, patient-centered, individualized prescription and management of anticoagulants. A strength of this anticoagulation toolkit was its composition: a current and user-friendly guideline with algorithms created and revised based upon expert consensus from both cardiology and primary care experts within the field. Another benefit was a summary of the most current guidelines from the leading medical associations (American Stroke Association, American Heart Association, American College of Chest Physicians, American College of Cardiology, Heart Rhythm Society, and European Society of Cardiology) driving best practice. Additionally, key results, both positive and negative, from pharmaceutical drug trials were summarized to help guide practice as well as a conclusive summary of the five

most currently used oral anticoagulants in practice (warfarin, apixaban, edoxaban, rivaroxaban, and dabigatran). Furthermore, this toolkit did not attempt to sway practitioners toward one anticoagulant versus another but instead provided unbiased, evidence-based data to promote the best anticoagulant initiation, management, and monitoring for the individualized patient rather than provider preference.

Financial Plan

A financial plan was not applicable as no financial costs were presumed for this project other than time and labor of the researcher and subjects. No cost was incurred from the data collection and analysis completed by the researcher, and the surveys and toolkit were created and distributed electronically.

CHAPTER III

EVALUATION PLAN

The following objectives were evaluated in this capstone project:

1. Examine current and local diagnosis and management of atrial fibrillation within the primary care setting.
    - Plan: An analysis of 75 patient medical records during 2017 at a local, privately owned primary care clinic (Family Physicians of Greeley-Central) that would highlight current management and diagnosis of atrial fibrillation while also identifying gaps in practice. Patient charts were assessed for the diagnosis of atrial fibrillation, symptoms, risk factors, diagnostics, laboratory and imaging data, comorbid diagnoses, management (focusing on anticoagulation), negative outcomes, and multidisciplinary providers managing the patient. Charts were also reviewed for any assessment of stroke and bleeding risk through CHA_2DS_2-VASC and HAS-BLED tools. Patient demographics obtained included age, sex, race/ethnicity, rural or urban residence, and insurance coverage.
    - Methods of analysis: Data were analyzed statistically through measures of central tendency to determine the norms and exceptions for diagnosis and management of atrial fibrillation in a primary care

setting. These data were then compared to current evidence-based guidelines to assess for gaps in practice and offer solutions for improvement.

2. Create a toolkit (guideline with algorithms) directing practitioners on diagnosis of atrial fibrillation as well as initiation and management of oral anticoagulation.

    - Evidence-based measures/instruments: The toolkit was created based upon a literature review and expert opinions. Additionally, the most recent guidelines from the American College of Cardiology, American Stroke Association, American Heart Association, American College of Chest Physicians, Heart Rhythm Society, and European Society of Cardiology were implemented into this toolkit (see Appendices D, E, and G). Expert opinions were obtained from northern Colorado providers in primary care and cardiology. The toolkit provided a simplified, evidence-based direction in diagnosing atrial fibrillation in the primary care setting as well as prescribing and managing anticoagulation in patients with atrial fibrillation to prevent stroke.
    - Methods of analysis: The Delphi method was utilized to formulate and improve the anticoagulation toolkit through expert consensus. Two surveys consisting of 8 to 10 questions each, one from Round 1 and one from Round 2, were analyzed statistically (through measures of central tendency) to determine providers' comfort level and expertise with providing anticoagulants and diagnosing atrial fibrillation as well

as how incorporation of this toolkit could influence practice. The survey for Round 1 was administered prior to providers viewing the anticoagulation toolkit for the first time. The survey for Round 2 was administered after reviewing the toolkit and obtaining consensus from the group in Round 1 of the Delphi method. Round 1 and Round 2 Delphi survey questions can be found in Appendices I and J, respectively.

- Components of anticoagulation toolkit: Contents of this toolkit included a guideline with algorithms in addition to resources for providers on atrial fibrillation management.
    - *Guideline:* The guideline provided a step-wise recommendation to:
        1) Reduce risk factors for atrial fibrillation (AF).
        2) Diagnose AF early through an annual pulse check in all symptomatic or asymptomatic patients ≥65 years old. If an irregular pulse is detected, confirm the rhythm through an EKG.
        3) If a patient has AF, assess for bleeding and stroke risk through the HAS-BLED and CHA_2DS_2-VASc scores respectively to determine if that patient is a candidate for oral anticoagulation.
        4) Prescribe the patient specific anticoagulant with a CHA_2DS_2-VASc score ≥2 and a low risk of bleeding.

Consider anticoagulating with a CHA_2DS_2-VASc score of 1, dependent on patient preference and clinical judgment.

- Algorithms:
  1) Reduce risk factors for atrial fibrillation (AF)
  2) How to calculate and interpret the CHA2DS2VASc and HAS-BLED scores was provided for easy reference.
  3) A comparison of warfarin and direct oral anticoagulants was summarized in a table.
  4) An algorithm illustrating the indications and contraindications for specific oral anticoagulants (warfarin, dabigatran, apixaban, rivaroxaban, and edoxaban). More specifically, this algorithm addressed rationale for selecting an anticoagulant: mechanical or prosthetic valves, kidney function, liver function, pregnancy, frequency of dosing, reversal agents, lab monitoring, drug or food interactions, age, gastrointestinal distress, cost, compliance, and weight adjustments. The purpose of these algorithms was not only to encourage improved diagnosis and management of AF but to promote assessment for patient-specific factors driving prescription of a specific anticoagulant.
- Atrial Fibrillation Resources for Providers: To simplify the convoluted regimen of anticoagulation and managing AF in general, this toolkit provided resources on appropriate reversal

agents, assessment for symptom severity with AF, genetic testing, lab monitoring (including home versus clinic INRs), and discontinuation of anticoagulation prior to surgery or invasive procedures including bridging therapy with warfarin. Food and drug interactions, INR and warfarin dosing, transitioning between warfarin and DOACs safely, and when to refer to a specialist were also included. Essential anticoagulation websites for anticoagulation (genetic testing, shared decision-making tools, performance and quality measures), WATCHMAN, and national/international guidelines for anticoagulation) were briefly summarized within in the toolkit with their corresponding references. Additional resources for providers were added or eliminated based upon the results of the Delphi survey Round 1. The toolkit offered one reliable resource for providers to review when managing anticoagulants to improve safety and efficacy of these drugs as well as provided resources to better educate patients.

3. Promote safety and efficacy in the management of anticoagulants.
    - Evidence-based measures/instruments. As aforementioned in objective 2, literature review and expert opinions were the foundation of this guideline with algorithms. The purpose of this toolkit was to promote safety and efficacy when prescribing anticoagulants. Thus, available literature on all five anticoagulants (warfarin, dabigatran, apixaban,

rivaroxaban, and edoxaban) was scrutinized thoroughly and presented in a chart format. A shortened version of this chart was included in the anticoagulation toolkit with websites provided to healthcare providers on where to find more information on drug trials and individual oral anticoagulant agents.

- Methods of analysis: These data were analyzed statistically through measures of central tendency to obtain expert feedback of what factors influenced safe and efficacious prescription of anticoagulants, striving for a 70% consensus.

4. Endorse patient-centered anticoagulation based upon current evidence-based literature and expert opinion.

    - Evidence-based measures/instruments. As aforementioned in objective 2, literature review and expert opinions were the foundation of this toolkit. Summaries from key anticoagulation guidelines and landmark drug trials were also analyzed. Background information, pharmacokinetics, and pharmacodynamics on the five individualized drugs (warfarin, apixaban, rivaroxaban, edoxaban, and dabigatran) were obtained from the FDA (CDC, 2016b) prescribing information and summarized in a chart. Individual patient factors to consider when prescribing anticoagulants were compared in a chart format. A comparison of novel drug trials was included to assess the safety and efficacy of the five commonly prescribed oral anticoagulants; these

results were summarized in the capstone paper and the website link was included in the anticoagulation toolkit.

- Methods of Analysis. These data were analyzed statistically through measures of central tendency to obtain expert feedback of what factors influenced patient-centered management of anticoagulants, striving for a 70% consensus.

5. Evaluate the effectiveness of a toolkit influencing the diagnosis of atrial fibrillation and anticoagulation management within a primary care setting.
    - Plan: The effectiveness of this toolkit was evaluated through a Round 2 Delphi survey completed by two primary care clinics and two cardiology clinics within northern Colorado. Four providers examined and critiqued this guideline for its usefulness and applicability in practice. The surveys were completed through Survey Monkey with the consent forms and other corresponding communication individually delivered to providers via confidential e-mail.
    - Methods of analysis: To evaluate the effectiveness of the anticoagulation toolkit, the PARIHS and RE-AIM frameworks were utilized. Through the PARIHS framework, strategies were devised to tailor the algorithm and guideline to the target population and appropriate context while utilizing the best evidence innovatively. Furthermore, this framework aided in applying the unique skills and experience levels of the providers to improve facilitation of the intervention. The RE-AIM framework examined how to reach the

intended population, evaluate the impact of this toolkit in the primary care setting, brainstorm techniques to enhance adoption by providers, address barriers to implementation, and strengthen utilization of this toolkit over time.

CHAPTER IV

RESULTS AND OUTCOMES

Results from Literature Review

As this was a quality improvement project, the core of this capstone paper was an extensive literature review on atrial fibrillation and anticoagulation, which was successfully achieved. Through PubMed and UpToDate databases, the researcher located current research studies (including systematic reviews and nationwide cohort studies) within the past five years on atrial fibrillation diagnosis and management, displaying an impressive collection of background information on the topic. As oral anticoagulation (warfarin) has been prescribed since the 1950s, older but relevant research and evidence were included in the literature review. Approximately 145 individual references were reviewed including the most current recommendations from four international and national guidelines on anticoagulation for atrial fibrillation. Over 25 components of atrial fibrillation were researched in this literature review, e.g., novel evidence on anticoagulant reversal agents, alternative treatments for AF, epidemiology, risk factors and pathophysiology for AF, genetic testing with warfarin, lab monitoring, and the impact of AF on patient quality of life and the economics of the United States. As the focus of this project was reducing the incidence of stroke in elderly patients with AF, the researcher found numerous studies discussing how best to manage AF in this high-risk population as well as addressing the limited knowledge providers and society have on the contribution

of AF to strokes in general. The objective was to obtain literature comparing the five current oral anticoagulants (warfarin, apixaban, dabigatran, edoxaban, and rivaroxaban); this was thoroughly completed based upon FDA (CDC, 2016b) prescribing information and was ultimately summarized within a chart. This same evidence was utilized to create the algorithm comparing warfarin to DOACs as well as the algorithm highlighting patient-specific factors to consider when prescribing an oral anticoagulant. The objective to research noteworthy drug trials for the oral anticoagulants was accomplished as the researcher discovered and summarized 30 trials for these drugs including studies from 1989 to 2015 as well as discussed studies on WATCHMAN©, reversal agents, and dual antiplatelet therapy, effectively accentuating the safety and efficacy data on these drugs. The four-step guideline to diagnose and manage AF was based solely on current evidence and recommendations from guidelines including the importance of utilizing CHA_2DS_2-VASc and HAS-BLED scores to assess for stroke and bleeding risk with anticoagulants and AF. The depth of this literature review allowed the researcher to create a resource section for providers within the anticoagulation toolkit, addressed suggestions and requests to improve management of AF, enhanced shared-decision making with the patient, and promoted multidisciplinary care. Furthermore, this research was successfully utilized to compare current evidence and practice (through the patient chart reviews), identify gaps, and propose solutions through the anticoagulation toolkit. Due to the complexity of atrial fibrillation, this literature review was more timely and lengthy than originally anticipated but was highly inclusive of all necessary components to better comprehend and address this cardiac disorder.

Results from Patient Chart Reviews

Over 100 patient charts were retrospectively reviewed in the *Next Generation* electronic health records at Family Physicians of Greeley-Central. Over 396 patients who met the criteria of "atrial fibrillation" and "seen in the clinic during 2017" were identified within Next Generation. Out of this population, 100 patients were randomized alphabetically and each patient was identified with only a unique number and initials. Patient charts were evaluated to obtain the following demographics: age, sex, ethnicity, rural or urban residence, and insurance status. Other data collected included stroke or bleeding scores, patient presentation (symptomatic or asymptomatic), clinical manifestations, risk factors (AF, bleeding, and stroke), current anticoagulation agent, negative outcomes, and gaps between evidence and practice. Statistical data analysis for the patient chart reviews was calculated through measures of central tendency: mean, median, and mode.

Age

The most common ages for patients with atrial fibrillation were ages 60 to 69 years (22%), ages 70 to 79 years (33%), and ages 80-89 years (24%), coinciding with the increased incidence of patients with atrial fibrillation over 65 years of age (You et al., 2012). A summary of the age demographics of patient chart reviews is provided in Table 2 and Figure 4.

Table 2

Age Demographics of Patient Chart Reviews

Age (years)	Number of Patients
30-39	2
40-49	1
50-59	9
60-69	22
70-79	33
80-89	24
90+	9
	Total: 100

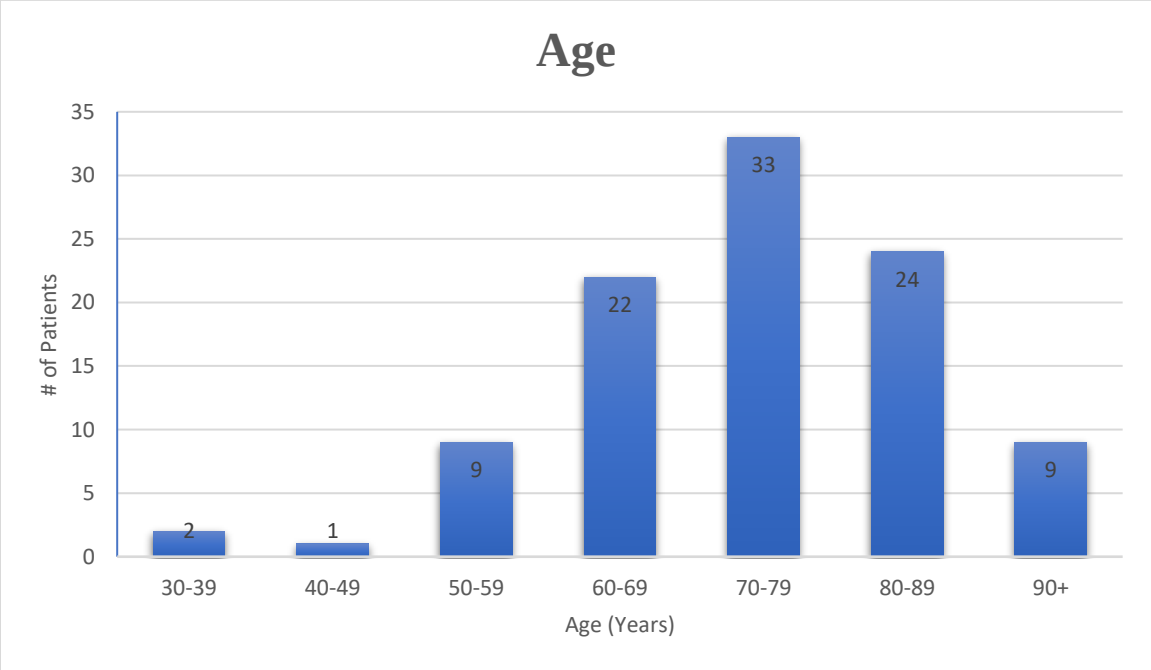


Figure 4. Age demographics of patient chart reviews.

Sex

With regard to sex, out of 100 patients, 44 were female and 56 were male, corresponding to the increased rate of AF in men compared to women (Kirchhof et al., 2016). However, with increasing age, AF is more prevalent in women (Kirchhoff et al., 2016). This statistic correlated to the chart reviews; of 33 patients older than 80 years of age, 22 were female (15 patients age 80-89 years and seven patients age 90+), and 11 were male (nine patients age 80-89 years and two patients age 90+), suggesting how with increased age comes an increased risk of disease.

Race/Ethnicity

Race/ethnicity was not mentioned in the literature as a risk factor for AF other than an increased incidence with European heritage (Centers for Disease Control and Prevention, 2015). This fact correlated with chart reviews where 94 of 100 patients were Caucasian, 49 were Hispanic, one was Asian, and one was of mixed-race.

Health Insurance

Selection of an anticoagulation is often related to health insurance coverage and the ability to pay for a prescription. Research indicated all major insurance companies and Medicare cover warfarin, rivaroxaban, dabigatran, and apixaban, yet Medicare does not cover edoxaban (GoodRx, 2017). The chart reviews displayed over 51 patients had Medicare and 20 patients had MCR Humana; only five patients had either no insurance or unknown insurance coverage. As 95% of patients had insurance coverage, the issue of cost could be reduced through copays or drugs saving cards, offering more oral anticoagulation options to fit individualized patients' preferences, medical conditions,

and budget. Insurance coverage of the patient chart reviews is provided in Table 3 and Figure 5.

Table 3

Health Insurance Coverage Reflected in Patient Chart Reviews

Health Insurance	Number of Patients
Medicare	51
Cigna	3
Anthem Blue Cross Blue Shield	8
Banner	4
Colorado Choice (Medicaid)	1
Kaiser Permanente	2
MCR Humana	20
United Healthcare	6
Unknown/None/	5
	Total: 100

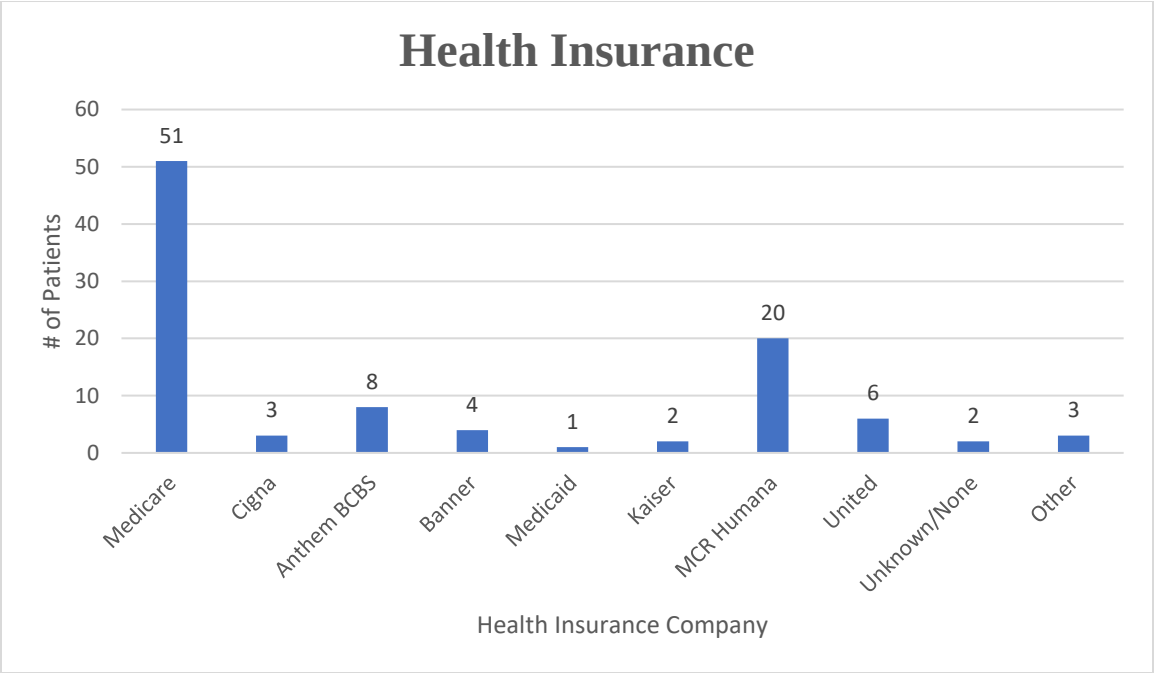


Figure 5. Health insurance coverage reflected in patient chart reviews.

Rural or Urban Residence

The researcher wanted to insure this project was inclusive of both rural and urban residences as access to care was a large issue influencing patients' ability to receive appropriate medical care. The chart review demonstrated 70 patients resided rurally while 30 patients lived in urban residences; thus, the researcher was successful in targeting a diverse population.

Stroke and Bleeding Scores

Research demonstrated CHA_2DS_2-VASc scores (stroke risk) and HAS-BLED scores (bleeding risk) are simple and efficient tools to assess whether anticoagulation is appropriate for a patient with atrial fibrillation without warranting further testing or blood work (Shahid et al., 2016). The $CHAD_2DS_2$-VASc is recommended over $CHADS_2$ to assess for stroke risk with nonvalvular AF as it highlights more risk factors and can better

classify the degree of a patient's stroke risk (Lane & Lip, 2012). Despite these recommendations, only 29 patients had a documented $CHADS_2$ score (13 patients or 9%) or CHA_2DS_2-VASc score (19 patients or 20%) mentioned in their medical charts while only 11providers utilized the more effective stroke risk tool of CHA_2DS_2-VASc. Furthermore, no patients had records of their HAS-BLED scores in their medical charts. These data greatly highlighted how providers in both primary care and cardiology were not utilizing evidence-based tools to define a patient's stroke risk and lessen their bleeding risk, which ultimately could worsen patient outcomes (increased stroke risk) by not prescribing anticoagulation appropriately. The utilization of screening tools by providers within the patient chart reviews is summarized in Table 4 and Figure 6.

Table 4

Utilization of Screening Tools by Providers Within Patient Chart Reviews

Stroke and Bleeding Scores	Number of Patients
$CHADS_2$	13 (9%)
CHA_2DS_2-VASc	19 (20%)
HAS-BLED	0 (0)%)
Unknown	68 (71%)
	Total: 100

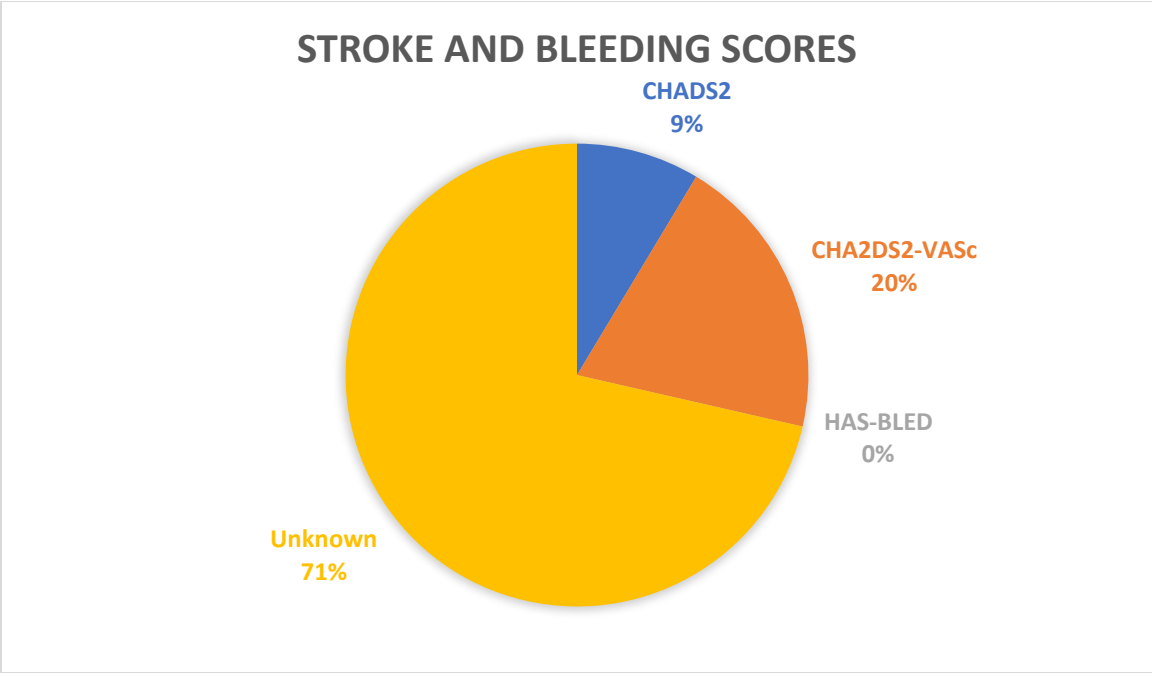


Figure 6. Screening tools utilized by providers within patient chart reviews.

Patient Presentation: Symptomatic of Asymptomatic

Approximately 30% of patients with AF present asymptomatically; yet, this population demonstrates a higher CHA_2DS_2-VASc score and increased stroke risk. Furthermore, 20% of patients are diagnosed with AF after suffering their first stroke (Shahid et al., 2016). Patient chart reviews indicated 44 patients were asymptomatic and 56 were symptomatic, which was higher than the literature suggested. However, this increase in asymptomatic patients could be related to the difficulty in determining through chart reviews whether the patient was symptomatic when diagnosed since a large percentage of patients was asymptomatic after being properly treated with rate and rhythm control strategies.

Clinical Manifestations

According to the CDC (2015), clinical manifestations of AF include heart palpitations/irregular heart rate, dizziness, fatigue, shortness of breath, presyncope, and chest pain. The researcher assessed for all the aforementioned clinical manifestations in patient chart reviews. Of 56 patients who were symptomatic with AF, the following symptoms were evident: 43 had fatigue, 21 had shortness of breath/dyspnea, 16 had chest pain, 14 had dizziness/lightheadedness, 13 had fatigue, and 7 had syncope/pre-syncope. Patients individually varied on the number of symptoms they experienced.

Risk Factors: Atrial Fibrillation, Bleeding, and Stroke

During the chart reviews, risk factors for AF, bleeding, and stroke were all evaluated. More specifically, risk factors for AF included obesity, heart failure, diabetes mellitus, chronic kidney disease, hypothyroidism, alcohol abuse, obstructive sleep apnea, and left ventricular hypertrophy (CDC, 2015; Ganz & Spragg, 2016). Risk factors for stroke risk were obtained from the CHA_2DS_2-VASc criteria and included heart failure, hypertension, age >65 years old, diabetes mellitus, prior stroke or TIA, vascular disease, and female sex (Hwang, 2016a). Risk factors for bleeding risk were gathered from the HAS-BLED criteria and included hypertension, abnormal renal disease, abnormal liver disease, history of stroke, labile INR, age greater than 65 years old, concurrent drugs increasing bleeding risk, and heavy alcohol use (Hwang, 2016b). Based upon these results, the 10 most common risk factors for these 100 patients were age greater than 65 years old (78 patients), hypertension (71 patients), obesity (72 patients), female sex (44 patients), cigarette smoker (36 patients), diabetes mellitus (33 patients), chronic kidney disease (33 patients), thromboembolism/hypercoagulable (31 patients), heart failure (29

patients) and valve disorder (29 patients). The significance of obtaining data was to assess for risk factors increasing a patient's risk for AF as treatment of these modifiable risk factors could prevent the onset or progression of disease. In a patient with AF, assessing for and reducing risk factors contributing to stroke risk and bleeding risk could improve a patient's treatment plan by ensuring the patient is receiving the correct anticoagulant while minimizing negative sequeale of bleeding. Of note, 100% of patients in these chart reviews were treated for modifiable risk factors for AF such as hypothyroidism, hypertension, diabetes, sleep apnea, chronic kidney disease, and heart failure, with appropriate lab monitoring to confirm the diseases were being controlled. Also, providers were effective in educating patients on healthy lifestyle modifications such as reducing alcohol consumption, weight loss, healthy diets, and smoking cessation, which ultimately reduce the risk of AF as well as other chronic diseases. As early AF has a genetic component (Shehab et al., 2010), patient charts were reviewed for a family history of AF; only one patient mentioned a known family history of AF.

Current Anticoagulation Agent

According to 100 charts reviewed, 43 patients were on Warfarin©, 27 were on a DOAC, 19 were on aspirin, 5 were on a combination therapy of aspirin and Plavix©, and 6 patients were on no anticoagulation to treat atrial fibrillation. The two most common DOACs prescribed were Xarelto© (11%) and Eliquis© (13%). Literature recommended aspirin for AF only with a CHA_2DS_2-VASc score of 1 (January et al., 2014; Meschia et al., 2014); yet oral anticoagulants have proven superior to aspirin (Manning et al., 2016) and due to the heightened bleeding risk, aspirin is not recommended as monotherapy (Shahid et al., 2016). Thus, in this chart review, 24 patients with AF had not been treated

according to current recommendations (monotherapty aspirin use or refusing any anticoagulant treatment) and only 27 were prescribed DOACs when research clearly demonstrated their safety and efficacy compared to warfarin. Dual antiplatelet therapy with aspirin and Plavix© is recommended only if patients are unable to take oral anticoagulants (Manning, Singer, & Lip, 2016; You, et al., 2012), thus justification can be made for the five patients on Plavix and aspirin as an alternative anticoagulant regimen. Rationales in the chart reviews for selecting an anticoagulant were limited but included stroke risk, age, bleeding risk, dosing, patient preference, provider preference, patient refusal, reversal agents, cost, food and/or drug interactions, insurance coverage, renal function, compliance, and convenience. Better comprehension and awareness of factors for prescribing a specific agent are essential to ensuring patients are receiving the best individualized anticoagulant agent. The utilization of specific oral anticoagulation agents with AF in these patient chart reviews is displayed in Table 5 and Figure 7.

Table 5

Utilization of Specific Oral Anticoagulation Agents with Atrial Fibrillation

Current Anticoagulation Agent for AF	Number of Patients
Warfarin	43
Xarelto	11
Pradaxa	3
Eliquis	13
Savaysa	0
Aspirin	19
Aspirin + Plavix	5
None	6
	Total: 100

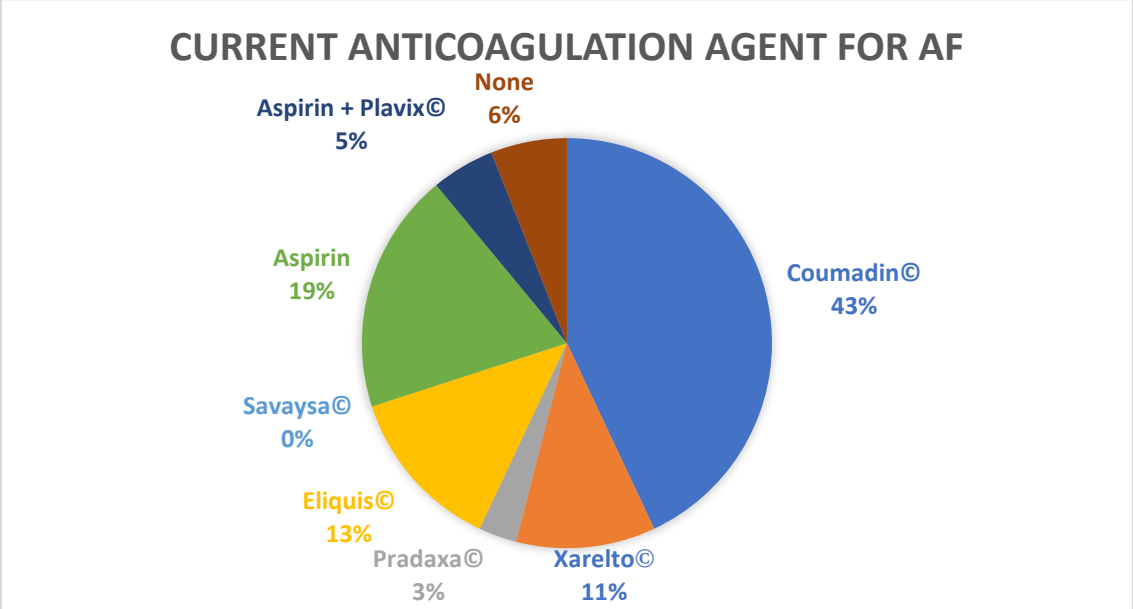


Figure 7. Specific oral anticoagulation agents utilized with atrial fibrillation.

Negative Outcomes Related to Atrial Fibrillation or Anticoagulation

The purpose of this capstone project was to decrease negative outcomes related to poorly treated AF--predominantly reducing stroke risk. Strokes or TIAs occurred in nine patients either before or after the diagnosis of AF, suggesting AF could have been a contributing cause to this medical emergency. Approximately 750,000 hospitalizations in the United States are related to AF (CDC, 2015) with 46.2% of emergency department visits related to warfarin adverse effects (Budnitz et al., 2011). The researcher wanted to evaluate how frequently patients were being hospitalized for AF (60 out of 100 patients), with some patients requiring multiple hospitalizations and others requiring none, primarily related to a new diagnosis of AF (symptomatic or atrial fibrillation rapid ventricular rate) or supratherapeutic INRs. Only 27 patients went to the emergency department related to AF, either for bleeding, supratherapeutic INRs, requiring a head contrast tomography (CT) scan after a fall to assess for an intracranial bleed while on anticoagulation or symptomatic AF.

Interesting, the annual bleeding risk while on anticoagulation is only 1.5% (Hwang, 2016b); this was relevant as 18 patients in the chart reviews had supratherapeutic (high) INRs, 13 had subtherapeutic (low) INRS, 7 suffered from epistaxis, 8 had GI bleeds, 1 had hematuria, 1 had hemoptysis, and 2 patients required reversal agents for bleeding.

The biggest concern with oral anticoagulants is intracranial hemorrhage; regardless of the anticoagulant, intracranial bleeds occur in less than 1% of the population annually (Desai et al., 2017). In these chart reviews, none of the 100 patients suffered from an intracranial hemorrhage while on oral anticoagulation, enhancing the safety

profile of these drugs to treat AF. Of note, the risk of intracranial hemorrhage was reduced by half with NOACs in comparison to warfarin, yet the rate of gastrointestinal bleeding increased, (Manning et al., 2016). This evidence corresponded to the patient chart reviews as eight patients in this population developed gastrointestinal bleeds while on anticoagulants. An assessment of HAS-BLED scores within the chart reviews would have been helpful to determine if a reduction of risk factors for bleeding could have diminished the incidence of bleeding in patients while on anticoagulation.

Approximately 17 patients displayed poor compliance to a treatment plan including taking anticoagulants as recommended or follow-up with providers and INR monitoring. Approximately 25 patients did not report any adverse outcomes related to anticoagulation for AF, inferring these drugs could be safely prescribed when taken as directed. However, these drugs do not come without risk and thus require close monitoring by providers to assess for and treat any complications that might arise. Providers must ensure they are thoroughly educating patients on the importance of taking anticoagulants as directed to reduce negative sequelae on both ends of the spectrum--bleeding and stroke. Compliance is a factor that should be considered when prescribing anticoagulation including the half-life of drugs, once or twice daily dosing, and INR monitoring to improve patient outcomes. Negative outcomes related to AF and/or anticoagulation for the patient chart reviews are summarized in Table 6.

Table 6

Negative Outcomes Related to Atrial Fibrillation and/or Anticoagulation

Negative Outcomes Related to AF and/or Anticoagulation	Number of Patients
Stroke/TIA (before or after AF diagnosis)	9
Hospitalization	60
Supratherapeutic INR	18
Subtherapeutic INR	13
Epistaxis	7
GI Bleed	8
Bleed Requiring Reversal	2
Fall	12
Emergency Department	27
Hematuria	1
Hemoptysis	1
Poor Follow-Up or Compliance	17
Intracranial Hemorrhage	0
None	25

N = 100

Gaps Between Evidence and Practice

The researcher discovered other gaps between evidence and practice for patients with AF when reviewing local patient chart reviews. No annual EKGs were obtained for patients greater than age 65 years old despite recommendations suggesting this aging

population is at the highest risk for developing AF (Kirchhof et al., 2016; Meschia et al., 2014; Shahid et al., 2016). Furthermore, providers did not consistently obtain an EKG with an irregular pulse on examination to diagnose AF (Kirchhof et al., 2016). An EKG was obtained more often in a patient who was symptomatic while in the clinic. Interestingly, five patients were diagnosed with AF pre-operation or pre-procedurally (mostly asymptomatic) and eight patients were diagnosed with AF post-operatively, which is also a risk factor for AF onset (Kumar, 2016b). Despite inconsistencies of EKG analysis, providers correctly ordered subsequent testing for AF such as thyroid stimulating hormone, echocardiography, and ambulatory EKG monitoring (Kirchhof et al., 2016). The researcher attempted to derive from chart reviews whether patients were diagnosed with paroxysmal, persistent, or permanent atrial fibrillation. However, those terms were not commonly used and were difficult to decipher within the charts as multiple terms were often used to classify the type of AF for the same patient dependent on the provider.

Commonalities between research and practice were also evident in the patient chart reviews. With atrial fibrillation, providers consistently used a goal INR of 2.0 to 3.0 for warfarin as recommended by guidelines (You, et al., 2012). For providers managing INRs within the clinic, anticoagulation tools were built into the electronic health records (EHRs) to document the history and trends of the INRs and corresponding warfarin levels as well as to determine the appropriate dose and frequency of warfarin. This tool was helpful in maintaining more therapeutic INRs. Yet, chart reviews demonstrated the INRs of 24 patients were managed by an anticoagulation clinic, INRs of 13 patients were managed by the primary care provider, and INRs of two patients were

managed at home. As noted prior, a minimum of 18 patients had documented supratherapeutic INRs and 13 had subtherapeutic INRs, suggesting the management of warfarin was less than ideal to prevent negative outcomes. The risk of thromboembolism increases with an INR < 2, and the risk of bleeding increases with an INR > 4, especially > 5 (Hirsh et al., 2003); labile INR replacement of warfarin with a DOAC is recommended (January et al., 2014). Research recommended INRs are best managed by the patient or a clinic compared to provider management (Hull & Garcia, 2016b); thus, increased utilization of anticoagulation clinics or home monitoring of INRs could reduce labile INRs and associated negative outcomes of bleeding and stroke.

Providers used multiple recommended treatment options for AF in addition to anticoagulation: rate control in 88 patients, rhythm control in 22 patients, MAZE procedure in two patients, pacemaker implantation in 16 patients, WATCHMAN insertion in three patients, ablation in 24 patients, and cardioversion in 32 patients. As aforementioned, providers were congruent with treating risk factors and chronic conditions associated with AF appropriately. However, medication reconciliation was not consistent between providers and specialists, posing a safety issue for the patients such as double dosing of anticoagulants. Also, the EHRs mislabeled patients with a thromboembolism who required chronic anticoagulation as atrial fibrillation, marking an incorrect diagnosis in patients' charts.

According to the ESC (Kirchhof et al., 2016), patient involvement, a multidisciplinary team, complex management decisions, and a navigation system are all essential for successful management of AF. Multidisciplinary care was evident in the chart reviews for patients with AF: 74 of the 100 patients were referred to cardiology, 11

patients saw electrophysiology in addition, five patients were seen at the heart failure clinic, and five patients received additional services through case management. Providers, both primary care and specialists, were excellent educators when discussing how medications such as antibiotics could affect INRs, explaining the differences between oral anticoagulants including risks and benefits, patient preference into the treatment plan, encouraging compliance to a treatment plan to reduce bleeding and stroke risk, the importance of consistent INR monitoring, and symptoms signifying AF.

Results from Delphi Surveys

Phase 1: Delphi Study Round 1
Results

The Delphi Study Round 1 Survey was created via Survey Monkey with a specific weblink e-mailed to each provider individually including the consent form as an attachment (see Appendix H). Participation was implied if the provider completed the survey via Survey Monkey. The Round 1 survey containing 10 qualitative and quantitative questions was sent to 17 providers and the researcher received responses from 13 providers. Five of these providers were forwarded the informed consent and Survey Monkey link through e-mail via another provider. The Round 1 survey took providers 2 to 20 minutes to complete with an average time of seven minutes. The researcher was notified through e-mail when new survey results were received via Survey Monkey and subsequently the data were easily accessible to statistically analyze. A statistical data analysis for the Round 1 survey was calculated through measures of central tendency: mean, median, and mode.

Regarding demographics, four providers were MDs, one was a DO, five were NPs, and three were PAs. Four of the providers specialized in family practice, five in

cardiology, two in electrophysiology, and one in cardiovascular surgery. The experience level of providers ranged from less than one year to 20 years with an average of four to seven years in practice. The comfort level of the providers in managing atrial fibrillation varied; one provider ranked the comfort level as "0"--very uncomfortable, two providers ranked the comfort level as "3," three providers ranked the comfort level with a score of "4," and seven providers ranked the comfort level as "5"--very comfortable. Therefore, the mix of survey responses was diverse and covered a wide range of specialties, didactics, training, and experience levels. Out of 10 questions, >70% consensus was achieved on the following questions:

- Palpitation (11 providers) and syncope/presyncope (8 providers) were noted as presenting symptoms of AF, warranting a further work-up.
- 100% of providers did not routinely screen for AF through a pulse check in patients >65 years old.
- An EKG was used by 12 providers to diagnose AF.
- Oral anticoagulants were prescribed by 10 providers to treat AF.
- Furthermore, the CHA_2DS_2-VASc score was a commonly used screen tool for initiating anticoagulation according to nine providers (a score of >2 warranted anticoagulation with two providers, a score of 1 warranted anticoagulation with two providers, and an unspecified score was elucidated by six providers).
- A CHA_2DS_2-VASc score was used to assess stroke risk by 11 providers, a $CHADS_2$ score was used by five providers to assess stroke risk, and the HAS-BLED score was used by 7 providers to assess bleeding risk; multiple

providers mentioned they utilized both the $CHADS_2$ and CHA_2DS_2-VASc tools.

The most common guideline utilized by providers to treat AF was the American College of Cardiology (2012), yet a 70% consensus was not reached with this question. Additionally, a 70% consensus was not achieved with questions asking what would be most helpful in a guideline, least helpful in a guideline, and improve the management of AF. Thus, the researcher attempted to include all these requests and suggestions into the revised Anticoagulation for Atrial Fibrillation Toolkit in addition to the responses achieving 70% expert consensus. The researcher originally attempted to create one algorithm for this guideline but due to the complex nature of managing AF, four algorithms were designed to simplify and clarify the treatment regimen. Providers were given a summary of the 70% consensus from Round 1 when they were given the link to take the Round 2 survey through Survey Monkey. Data analysis from Phase 1: Delphi Study Round 1 is summarized in Tables 7 through 16 including clarification of which responses obtained 70% expert consensus.

Table 7

Summary of Responses for Survey Question 1: Please Fill in the Following Demographics

Demographics	Number of Providers
Participants	
MD	4
DO	1
NP	5
PA	3
Specialty	
Family	4
Cardiology	5
Electrophysiology	2
Cardiovascular Surgery	1
Number of Years in Practice	
0-3	2
4-7	5
8-11	1
12-16	3
17-20	2

Number of Providers = 13

Table 8

Summary of Responses for Survey Question 2: What Patient Presentation (Symptoms and Risk Factors) Warrants a Work-Up for Atrial Fibrillation?

Symptom or Risk Factor	Number of Providers (13 total)
Fatigue	3
Palpitations	11 (>70% consensus)
Chest Pain	4
Syncope/Presyncope	8 (>70% consensus)
Poor Sleep	1
Weakness	1
Shortness of Breath/Dyspnea on Exertion	5
Dizziness/Lightheadedness	4
Level of Consciousness	1
EKG Results	1
Stroke/TIA	3
History of AF	1
Congestive Heart Failure	1
Coronary Artery Disease	1
Unspecified	1

Table 9

Summary of Responses for Survey Question 3: Do You Screen for Atrial Fibrillation in All Your Elderly Patients Older Than 65 Years Old?

Screening for Atrial Fibrillation	Number of Providers
Yes	0
No	13 (>70% consensus)

Table 10

Summary of Responses for Survey Question 4: Explain Your Work-Up for Diagnosing Atrial Fibrillation

Diagnostic Tool	Number of Providers
12-Lead EKG	12 (>70% consensus)
Thyroid Stimulating Hormone	3
Complete Blood Count	1
Echocardiogram	1
Event/Holter Monitor	8
Telemetry	3
Obstructive Sleep Apnea	2

Table 11

Summary of Responses for Survey Question 5: How Do You Typically Treat Patients with Atrial Fibrillation?

Treatment	Number of Providers (13 total)
Oral Anticoagulant (Warfarin or DOAC)	10 (>70% consensus)
Rate Control Medication	6
Echocardiogram	1
Treat Risk Factors	1
Cardioversion	2
Consider Rate vs. Rhythm Control	3
Rhythm Control	4
Refer to Cardiology	3
Treatment Dependent on Symptoms and Age	1
Treatment Dependent on Symptoms or Heart Failure	1

Table 12

Summary of Responses for Survey Question 6: Which Factors Influence Your Decision to Initiate Anticoagulation in a Patient With Atrial Fibrillation Including Selection of a Particular Agent?

Factors Influencing Anticoagulation	Number of Providers (13 total)
$CHA2DS_2$-VASc Score	9 (>70% consensus)
Score >1	2
Score ≥2	2
Unspecified	5
Cost of Medication/Insurance Coverage	4
Patient Compliance	1
Cognitive Ability	1
Valve Disease	2
Age	4
Patient Preference	4
Risk for Stroke	3
American College of Cardiology Guidelines	1
Bleeding Risk	2
Contraindications or Oral Anticoagulants	1
$CHADS_2$ Score	1
Provider Preference	2
AF with a Duration >5 Minutes	1
Co-morbidities	1
Ease of Use	1
Does not Manage Anticoagulants	1

Table 13

Summary of Responses for Survey Question 7: What Is Your Comfort Level with Prescribing and Managing Anticoagulation for Atrial Fibrillation?

Comfort Level Score	Number of Providers (13 total)
0	1
1	0
2	0
3	2
4	3
5	7

Note: Scale of 0 very uncomfortable to 5 very comfortable

Table 14

Summary of Responses for Survey Question 8: Do You Use Any Screening Tools to Assess for Stroke and Bleeding Risk with Anticoagulation and Atrial Fibrillation?

Screening Tool	Number of Providers (13 total)
$CHADS_2$	5
CHA_2DS_2-VASc	11 (>70% consensus)
HAS-BLED	7
None	1

Table 15

Summary of Responses for Survey Question 9: Atrial Fibrillation Guidelines and Algorithms

What guidelines, algorithms, or resources do you reference for anticoagulating and treating atrial fibrillation?	Number of Providers (13 total)
Chest Guidelines	1
AF in American Family Physician Magazine	1
UpToDate	1
American College of Cardiology (ACC)	5
CHA_2DS_2-VASc	2
American Heart Association (AHA)	1
None	2
What would you find most helpful in an AF algorithm or guideline?	Number of Providers (13 total)
Simple/Straightforward	4
Unambiguous/Easy to follow	2
Evidence-Based	2
What is Considered Valvular Disease	1
List of Medication Options (including rate and rhythm control)	2
Risk of Stroke Calculated	1
Not Applicable	2
What would you find least helpful in an AF algorithm or guideline?	Number of Providers (13 total)
Too Complex or Lengthy	2
List of Medication Options	2
Ambiguity	1
Subjectivity (ex. definitions)	1
Focusing on the Negatives of NOACs	1
No Clear Recommendations	1
Not Applicable	4

Table 16

Summary of Responses for Survey Question 10: Which of the Following Would Improve Your Management of Anticoagulation for Patients with Atrial Fibrillation: Community Resources, Specialists, Shared Decision-Making Tools, Websites, Phone Apps, More Anticoagulation Clinics, Etc.?

Tools to Improve Management of AF	Number of Providers (13 total)
Specialists	2
Phone Apps	5
More Anticoagulation Clinics	3
Simplified Algorithms	3
Patient Education Resources	2
Shared Decision-Making Tools	2
CHA_2DS_2-VASc Calculation in Algorithm	1
Know When to Refer to Specialists	1
Ease to Find Current Guidelines	1
Cost of DOACs	1

Phase 2: Delphi Study Round 2
Results

The Delphi Round 2 survey link through Survey Monkey was e-mailed to the 13 providers who completed Round 1 of the survey along with a summary of the results from Round 1, which received greater than 70% expert consensus. As the survey results were anonymous, the researcher attempted to rationalize which providers responded to the Round 1 survey based upon knowledge of the individual providers (specialty, title, or years in practice). The attrition rate for this survey was low as only four providers

completed Round 2. With no demographics listed, the researcher was unable to determine which providers responded to Round 1 and thus could not send a reminder e-mail to obtain more results nor readdress individual perspectives of the providers discovered in Round 1.

A statistical data analysis for Round 2 was calculated through measures of central tendency: mean and mode. Of these four providers, greater than 70% agreed the anticoagulation toolkit was

- Straightforward and user-friendly
- Improved safety and efficacy of anticoagulation
- Influenced future practice
- Applicable to practice
- Inclusive of evidence-based practice.

Consensus was achieved on a benefit of this toolkit as being user-friendly and straightforward; yet, this response was already analyzed and accounted for in Question 1 of the survey. Consensus otherwise was not achieved on quantitative questions addressing benefits, challenges, and other feedback for the anticoagulation toolkit. However, providers noted the toolkit was too lengthy and contained too much information, which was accounted for by the researcher and will be addressed in future revisions of this toolkit. Overall feedback from the providers implied the providers perceived this toolkit as beneficial. Table 17 provides Delphi Survey Round 2 results for qualitative questions (open-ended) where 70% consensus was not achieved.

Table 17

Delphi Survey Round 2 Results Where Consensus Was Not Achieved

Question	Open-Ended Answer	Number of Providers
6. What are the benefits of this toolkit?	Evidence-based	1
	Straightforward/Easy to Follow	3
	Compiles Many Resources into One Place	1
	Up-To-Date	1
7. What are the challenges of this toolkit?	Lengthy	1
	Too Much Information	2
	N/A	1
8. Any other feedback, questions, or concerns?		
	Thorough Toolkit	1
	Look Forward to Using It	1
	Passion for Topic	2
	Minor Changes	1

Objective One Outcomes

Objective 1 was to examine current and local diagnosis and management of atrial fibrillation within the primary care setting; this objective was fulfilled in its entirety. A total of 100 EHRs in Next Generation were confidentially reviewed retrospectively and analyzed within a privately owned primary care clinic in Greeley. Patients were included in the study if they met the criteria of a diagnosis of AF and were seen in the clinic for this diagnosis during 2017. The researcher planned to retrospectively review only 75 charts, yet exceeded this goal by obtaining data from 100 electronic patient charts. All required information was obtained from the 100 patient charts with AF including

demographics, diagnosis, management, risk factors, negative outcomes, and utilization of screening tools. Through statistical analysis of these data, the researcher was successfully able to highlight current management and diagnosis of atrial fibrillation while also identifying gaps in practice according to current evidence-based guidelines.

Objective Two Outcomes

The second objective was to create a toolkit (guideline with algorithms) directing practitioners on diagnosis of atrial fibrillation as well as initiation and management of oral anticoagulation; this objective was successfully executed. The evidence-based Anticoagulation for Atrial Fibrillation Toolkit followed its original design based upon literature review, current guidelines on anticoagulation, and expert opinion from two rounds of Delphi surveys. Round 1 assessed providers' comfort level and expertise with prescribing anticoagulants and diagnosing and managing AF while Round 2 evaluated the anticoagulation toolkit and how its incorporation could influence practice. Results from Round 1 were utilized to revise the anticoagulation toolkit the researcher had drafted based upon literature; data analysis concluded 70% consensus was achieved on at least five questions. Even without 70% consensus, the researcher incorporated provider expertise, suggestions, and requests into the anticoagulation toolkit. In Round 2, data analysis of greater than 70% consensus suggested the anticoagulation toolkit was evidence-based, safe, efficacious, user-friendly, and could positively impact practice.

The toolkit was revised after Round 1 and divided into two sections to enhance its usability and relevance to practice. The first section, composed of the guideline with algorithms, remained unchanged as these toolkit components were step-wise, straightforward, concise, and evidence-based. The guideline with algorithms achieved

the goal of not only encouraging improved diagnosis and management of AF but promoting assessment for patient specific factors driving prescription of a specific anticoagulant.

The second section of the toolkit contained multiple resources for providers and was formulated based upon requests from providers as well as evidence suggesting how best to manage atrial fibrillation. This toolkit achieved the purpose of providing one reliable resource for providers to review when managing anticoagulants as well as offering resources to better educate patients, enhance patient-provider relationships, and promote multidisciplinary care.

Objective Three Outcomes

The third objective was to promote safety and efficacy in the management of anticoagulants; this objective was completed simultaneously with the second objective as the literature review and expert opinions were the foundation for this Anticoagulation for Atrial Fibrillation Toolkit. A core element of this toolkit was promoting safety and efficacy when prescribing anticoagulants; thus, available literature on all five anticoagulants and their corresponding noteworthy drug trials, (warfarin, dabigatran, apixaban, rivaroxaban, and edoxaban) were scrutinized thoroughly and presented in a chart format in this capstone project. Two shortened versions of this chart--one comparing anticoagulants in general and one comparing individual patient factors influencing selection of a specific oral anticoagulant—as well as two algorithms were included in the anticoagulation toolkit. Providers were given multiple resources in the toolkit on where to find more reliable information on drug trials and individual oral anticoagulant agents. As calculated through statistical analysis, greater than 70%

consensus from the Delphi Round 2 survey implied providers agreed the Anticoagulation for Atrial Fibrillation Toolkit could improve safety and efficacy of anticoagulant therapy.

Objective Four Outcomes

The fourth objective was to endorse patient-centered anticoagulation based upon current evidence-based literature and expert opinion; this objective was achieved alongside the first and second objectives as the literature review and expert opinions were the foundation of this toolkit. Summaries from key anticoagulation guidelines and landmark drug trials comprised the majority of literature reviewed on this topic. As mentioned in the third objective within this capstone, background information, pharmacokinetics, and pharmacodynamics on the five individualized drugs (warfarin, apixaban, rivaroxaban, edoxaban, and dabigatran) were obtained from the FDA prescribing information (CDC, 2015) along with a comparison of novel drug trials to assess the safety and efficacy of the oral anticoagulants. The webpage link for novel drug summaries was included in the anticoagulation toolkit to provide a reliable and easy to navigate link for providers to review conclusions from drug trials on anticoagulants. Within the Anticoagulation for Atrial Fibrillation Toolkit, two algorithms focused on selecting the anticoagulant for the patient: (a) individual patient factors to consider when prescribing anticoagulants and (b) a general summary comparing warfarin to DOACs. As calculated through statistical analysis, greater than 70% consensus from the Delphi Round 2 surveys implied providers considered this toolkit as inclusive of evidence-based practice to promote individualized anticoagulation. Objectives 3 and 4 were synonymous as prescribing patient-specific anticoagulation is dependent on the safety and efficacy of the anticoagulant agent.

Objective Five Outcomes

The fifth objective was to evaluate the effectiveness of a toolkit influencing the diagnosis of atrial fibrillation and anticoagulation management within a primary care setting. This objective was effectively accomplished as the Anticoagulation for Atrial Fibrillation Toolkit was evaluated through the Round 2 Delphi survey by four providers who through greater than 70% consensus agreed this guideline was straightforward, user-friendly, influential, and applicable to practice. The Delphi surveys were 100% completed through Survey Monkey, allowing the provider to easily review the data and analyze the results. Furthermore, the PARIHS and RE-AIM frameworks were successfully utilized to evaluate the anticoagulation toolkit. In accordance with the PARIHS framework, this evidence-based and innovative toolkit was tailored to the target audience (providers treating patients with AF) and context (primary care setting). Providers who completed the Delphi surveys varied in their comfort level with AF management, experience, and specialty; thus, the results of these surveys were utilized to create a toolkit inclusive of diverse knowledge and input, which ultimately would improve its facilitation into practice. The RE-AIM framework successfully examined how this toolkit could reach its intended population (primary care providers managing AF patients), evaluate the impact of this toolkit in the primary care setting, brainstorm techniques to enhance adoption by addressing barriers to implementation, and strengthen utilization of this toolkit over time (through Delphi surveys). Implementation of this toolkit into practice and evaluating its influence on reducing stroke in AF is a future extension of this project.

Key Facilitators, Key Barriers, and Unintended Consequences to Project Objectives

Key Facilitators

This researcher was very passionate with the topic of this project, enhancing its success and contributing to its comprehensiveness and effective execution. Dedication, ambition, and curiosity fueled the extensive evidence-based literature review including a comprehensive summary of oral anticoagulants and noteworthy drug trials. For the chart reviews, the researcher was very familiar with the EHR (Next Generation) and thus could easily navigate through patient records to obtain the desired information. Also, the clinic manager selected only the patients seen in the clinic for 2017 with a diagnosis of AF, thus simplifying relevant patients to review. The researcher had a goal of 75 patient charts to review and exceeded this goal by reviewing 100 charts of diverse patients with AF. Survey Monkey streamlined the process of the Delphi surveys immensely as the researcher easily created surveys, designed a unique web-link, and e-mailed this web-link to providers individually and confidentially. The researcher was even alerted via e-mail when surveys were returned and could access and statistically analyze these results effortlessly and quickly. Measures of central tendency--mean, median, and mode--were utilized to analyze the data for the Delphi surveys and patient chart reviews. The guideline and algorithm components of this toolkit were evidence-based, user friendly, applicable and influential to practice, and could improve the safety and efficacy of anticoagulation as demonstrated by >70% consensus in Round 2 of the Delphi survey. Furthermore, the first round of the Delphi survey and consent form were forwarded and completed by five interested providers, not only increasing the number of subjects for the Delphi surveys but also expanding the specialties to include electrophysiology and

cardiovascular surgery. The researcher utilized evidence from research as well as expert requests and suggestions when modifying this Anticoagulation for Atrial Fibrillation Toolkit by adding a large section on provider resources to improve the practice of diagnosing and managing AF, especially with the targeted population of older adults. This capstone project was technologically savvy by utilizing electronic databases for literature review, EHRs to compare evidence to practice, Survey Monkey to complete surveys, e-mail communication, and Microsoft Office to formulate the capstone paper and anticoagulation toolkit.

Key Barriers

The researcher was unaware of the complexity of AF management when initiating this project as anticoagulation is only a fragment of the entire treatment plan. The researcher expanded the literature review on AF to be inclusive of all relevant avenues of risk factors, diagnosis, treatment, and negative outcomes of the disease; however, this also become problematic when trying to make the anticoagulation guideline succinct while also relevant to the desired audience. The researcher concluded EHRs are not user friendly and important data were often hidden, misconstrued, or difficult to find, especially when records from outside sources were intermingled. Consequently, the chart reviews become more complex and took longer than anticipated to obtain all the required data.

Regarding the Delphi surveys, the researcher was unable to determine which providers returned the surveys due to anonymity. A good return rate was noted for the first round of the survey (13 out of 17 providers), yet there was a poor return rate for the second round (4 of 13 providers). An original two-week return rate was proposed for the

Delphi surveys; yet due to time constraints, providers were requested to return the surveys within one week. The lack of time to complete the surveys could have contributed to the poor return rate. In Round 1, providers were reminded via e-mail to complete the survey if they did not return it within the requested time, increasing the response rate by three providers. However, time constraints and anonymity of the providers (as demographics were not collected in Round 2) limited the ability to wait for further results from the Round 2 survey. In the Round 1 survey, a limited 70% consensus was obtained so the researcher attempted to include suggestions and requests from providers to improve AF management despite this lack of consensus. In Round 2, a 70% consensus was achieved for all five of the qualitative questions; however, the poor attrition rate was attributed to the length of the toolkit and extent of content as these challenges were noted by providers in the survey. Due to the intricacy of the evidence available to diagnose and manage AF, the researcher had difficulties trying to divide the toolkit into a guideline with algorithm section followed by a provider resources section. The table of contents helped with this delineation but despite requesting providers at a minimum review the guideline and algorithms for this project, it is presumed this clarity was not apparent and providers did not choose to review a 30-page toolkit. Reformatting the toolkit to be more concise or possibly dividing it into two separate papers--one a guideline with algorithms and the other with provider resources--are plausible future expansions of this project to improve its relevancy and implementation into practice.

Unintended Consequences to Project Objectives

Unfortunately, the clinic where the chart reviews were completed displayed a poor attrition rate for the Delphi survey portion of this test. The clinic was welcoming,

helpful, and supportive of this research project but the lack of follow-up and participation with the project was discouraging. One provider wanted to know the results of the chart reviews to help utilize these conclusions to improve practice; the researcher will follow-up with the results of this entire study with any providers who voice interest in learning more about this AF toolkit, its implementation into practice, and how to improve the overall diagnosis and management of AF in the primary care setting. Even though this project was directed toward primary care providers, only four of the 13 providers who volunteered to participate in this study specialized in primary care, leaving nine providers who specialized in cardiology or some specialty. One primary care provider even noted a poor comfort level with AF, refusing to treat these patients and referring them to cardiology. Knowing one's comfort level, scope of practice, and expertise are necessary to practice medicine well; however, primary care is the first place most acute and chronic diseases are presented, diagnosed, and treated so AF cannot be the exception. These findings clearly represented how little emphasis providers, especially in the primary care realm, gave to AF despite the high risk of stroke and its effect on quality of life. The lack of response from primary care providers suggested improved education and awareness are both needed to improve the diagnosis and management of AF. The Anticoagulation for Atrial Fibrillation Toolkit is a straightforward, evidence-based, and comprehensive resource to guide providers on the recommended path to properly treat AF to reduce its negative sequelae; with implementation, it offers the possibility of improved management of AF. No issues with breeches of confidentiality with either patient- or provider-specific data occurred with this project. No harm to participants was evident and no unexpected financial costs arose.

CHAPTER V

RECOMMENDATIONS AND IMPLICATIONS FOR PRACTICE

Conclusions

The purpose of this capstone project was to address the following problem statement: In adult patients with atrial fibrillation older than 65 years old and a moderate to high risk of stroke, how effective is an anticoagulation toolkit in guiding primary care providers on (a) diagnosing atrial fibrillation and (b) initiating and maintaining oral anticoagulation safely, to reduce the incidence of ischemic stroke? An extensive and current literature review was completed on atrial fibrillation, focusing on the diagnosis and management of atrial fibrillation. As the capstone highlighted the importance of anticoagulating elderly patients with atrial fibrillation to prevent the incidence of stroke, a comprehensive comparison of warfarin and the four DOACs as well as a summary of noteworthy drug trials were included to address safety and efficacy of these drugs. The literature review not only provided extensive background information on atrial fibrillation and anticoagulation but also highlighted key references to first compare evidence to practice (analyze patient chart reviews) and then utilized these identified gaps to translate evidence into practice (create the anticoagulation toolkit).

Chart reviews were retrospectively reviewed on 100 patients in a primary care setting, assessing the diagnosis and treatment of AF. In comparing evidence to practice,

inconsistencies were evident--predominantly a lack of utilization of CHA_2DS_2-VASc and HAS-BLED scores to assess for stroke and bleeding risk, poor continued monitoring of AF in the primary care setting, a disconnect between the treatment plan and providers, and the absence of consistently diagnosing an irregular pulse as AF through an EKG.

Through utilization of two rounds of the Delphi method, expert opinions, and recommendations of national and international guidelines, an evidence-based anticoagulation toolkit was created and modified to guide primary care providers on improving diagnosis of atrial fibrillation and enhanced initiation and maintenance of oral anticoagulation to reduce the incidence of stroke in elderly patients with atrial fibrillation. This toolkit consisted of a four-step, simplified guideline supported by four algorithms: (a) CHA2DS-VASc score, (b) HAS-BLED score, (c) comparison of anticoagulants, and (d) patient-specific factors influencing selection of anticoagulant. Additionally, this toolkit offered in one document a summary of additional information and resources for providers to improve the overall management of atrial fibrillation. Round 1 of the Delphi method suggested no providers assess for AF annually through a pulse check in patients older than 65 years old despite the increased risk of AF in the elderly and the high incidence of asymptomatic patients. In Round 2 of the Delphi survey, all providers felt the AF toolkit was evidence-based, applicable, influential to practice, user-friendly, and promoted safety and efficacy; however, the toolkit was too extensive and lengthy.

In summary, this capstone project answered the problem statement. The literature review, patient chart reviews, and two rounds of the Delphi method addressed how to effectively and safely diagnose atrial fibrillation in the elderly population as well as initiate and manage anticoagulation. However, a future research project focusing on

implementation of this toolkit in practice could better evaluate the maintenance phase of anticoagulation and how this toolkit could reduce the incidence of stroke in this high-risk population.

Recommendations for Guideline Implementation Within the Framework of the Organizations' Strategic Plan

Phase 6 of this project entails a future pilot study to assess the impact on patient outcomes related to implementation of this anticoagulation toolkit into the primary care setting. Thus far, this capstone project has only completed two rounds of the Delphi method and requires further consensus on how to make the toolkit more concise and relevant to providers within the primary care setting. Obtaining input from specialists is essential to determine what resources, guidelines, and practices are utilized by experts in the field. However, the toolkit must be tailored to the audience and ultimately reflect what the primary care providers, in this instance, require and want to improve their practice while still ensuring their practice is current and based upon expert and evidence consensus. Expanding knowledge on atrial fibrillation diagnosis and management is a priority action to ensure providers are up to date and providing the best practices for their patients, thus supporting this extensive toolkit with a guideline and algorithms. Providers do not have time to seek reliable and most current resources for every diagnosis they encounter, especially in primary care; thus, by educating providers on how this toolkit summarizes multiple reliable resources in one document, the diagnosis and treatment of AF can be step-wise, simplified, and manageable to improve patient outcomes. Additionally, encouraging providers to follow this evidence-based guideline and remain up to date with guidelines is essential. For instance, the consensus from the first round of the Delphi survey suggested 100% of 13 providers did not screen annually for AF in

every elderly patient older than 65 through a pulse check, even though this is recommended by the AHA/ASA and ESC as a means of primary prevention (Kirchhof et al., 2016; Meschia et al., 2014).

Through the first round of the Delphi survey, providers were asked what resources would be beneficial to improve their management of atrial fibrillation. Although 70% consensus was not achieved for any of these requests, the researcher still incorporated all these ideas into the toolkit, especially phone apps, referrals to specialists, and shared decision-making tools. Further revisions of this toolkit through consensus of more Delphi rounds is necessary to meet the following requirements for an effective toolkit: the importance of including patients in the plan of care, making evidence easy to access and utilize, and incorporating multidisciplinary care into the treatment plan. To improve the implementation of this toolkit, organizations should provide care to a diverse population of patients with AF; display similarities in their missions, values, perspectives, and approaches to diagnosing and managing atrial fibrillation; and remain open-minded to change.

Recommendations for Evaluation of Anticoagulation Toolkit

Delphi Surveys

The Anticoagulation for Atrial Fibrillation Toolkit (guideline with algorithms) was evaluated based upon its ability to uphold the elements of the PARIHS framework and RE-AIM model. The second round of the Delphi survey evaluated the benefits and challenges of this toolkit and achieved 70% consensus for its ability to be straightforward and user-friendly, evidence-based, applicable to practice, influential to practice, and promote safety and efficacy of anticoagulation therapy. However, the responses were

limited in this second round compared to the first, contained mostly close-ended questions, and only touched the surface of how to improve this toolkit. Further rounds of the Delphi survey through Survey Monkey would be helpful to better assess and meet the requirements and requests of providers who manage AF, ensuring this toolkit is more applicable and relevant to practice. Reducing the length of this toolkit could be less intimidating to providers to review, which could reduce the low attrition rate of the surveys.

Promoting Action on Research Implementation in Health Services Framework

The three elements of the PARIHS framework (evidence, context, and facilitation into practice) were ranked on a scale from low to high (Rycroft-Malone, 2004). One-hundred patient charts in Greeley were reviewed to assess for data, a comprehensive literature review on current evidence and best practice was completed, and expert opinions from 13 providers were acquired through two rounds of the Delphi surveys (High Evidence). Evidence from the literature review and expert consensus from the Delphi surveys were incorporated into an anticoagulation toolkit for diagnosing and treating atrial fibrillation in the primary care setting (High Context). The expert consensus was diverse including primary care, cardiology, cardiothoracic surgery, and electrophysiology providers; the more experienced clinicians and those who specialized in the cardiovascular system acted as leaders when voicing their opinions on the Delphi surveys. The chart reviews were culturally diverse as well as they were composed of 100 patients in both rural and urban settings, ranging from ages 30 to 100, both male and female, and comprised of many races/ethnicities. The facilitator for this project was the

researcher who compiled a large array of research on the topic of AF into one resource (the anticoagulation toolkit) for providers to utilize to improve practice. Observations from the chart reviews were analyzed to compare evidence to practice. Utilization of the Delphi surveys was a means to seek expert comments on the efficacy and feasibility of the toolkit's use (Low Facilitation into Practice). Facilitation was ranked low as only two rounds of the Delphi surveys were completed and this toolkit has not yet reached adequate consensus to be implemented into practice. Elements of the iPARIHS model (Harvey & Kitson, 2016) were incorporated into the evaluation of this toolkit: this toolkit was comprised of a simple guideline and four complementary algorithms followed by a section summarizing additional information and resources for providers (*innovation).* Also in accordance with the iPARIHS model, the focus for this toolkit was primary care providers; the presumption was knowledge on AF was more limited for a generalist rather than a specialist (recipients, context levels, and experience of the facilitators), thus requiring a more comprehensive resource section to better manage AF.

Reach, Effectiveness/Efficacy, Adoption, Implementation, and Maintenance Model

The RE-AIM model was utilized for this capstone project to assist with the effective implementation and evaluation of this anticoagulation toolkit (RE-AIM, 2017). *Reach* addressed the target population of elderly patients with a new or chronic diagnosis of atrial fibrillation within the primary care setting including patients with diverse demographics, co-morbidities, and treatment plans. *Effectiveness* was the impact of this anticoagulation toolkit to prevent stroke in patients with atrial fibrillation. As this toolkit has not yet been implemented into practice, this element of the RE-AIM model was not

met. *Adoption* assessed the willingness and feasibility of primary care providers to incorporate this toolkit into practice. This toolkit has not been implemented into practice but in Round 2 of the Delphi Survey, greater than 70% consensus agreed this toolkit was applicable to practice and could influence future practice of AF. *Implementation* addressed the factors contributing to the successful use of this toolkit in primary care, which was evident in the algorithm comparing oral anticoagulants in general as well as the algorithm assessing patient specific factors to consider when selecting an oral anticoagulant. *Maintenance* assesses the duration of the implementation of this toolkit in practice; however, as this toolkit is only in its preliminary stages, this component of RE-AIM was not currently applicable to this capstone project.

Ongoing Activities or Evaluations Outside the Scope of the Doctor of Nursing Practice Project

This Doctor of Nursing Practice (DNP) project shed light on the limited knowledge healthcare providers and the general public have on the contribution of atrial fibrillation to strokes. For instance, the AHA/ASA (2016) created a public service poster on atrial fibrillation: even though 15% to 20% of all strokes are related to AF, only 50% of patients with AF think they are at risk for a stroke. Research and observation of practice have demonstrated healthcare providers underestimate the increased risk of stroke with AF (especially with paroxysmal AF), overestimate the bleeding risk with anticoagulants, and do not consistently utilize screening tools such as CHA_2DS_2-VASc or HAS-BLED to assess for stroke and bleeding risk with AF despite evidence-based practice suggesting otherwise.

To stay current with technological advances, medication safety, and treatment updates, subscribing to e-mail updates from reliable organizations for medication safety

(FDA MedWatch, Prescribing Letter, UpToDate) and newsletters from medical organizations (American Academy of Family Physicians, American College of Cardiology) is recommended for providers to increase evidence-based practice. To simplify the practice of medicine and have updated practice available at their fingertips, providers can access toolkits and phone apps from reliable organizations such as the American College of Cardiology, Medscape, and Epocrates. Promoting self-efficacy in patients, expanding public education efforts, and utilizing shared decision-making tools are proposals to enhance patient-provider relationships and influence patients to take control of their health to improve outcomes. Working as a multidisciplinary team, including the collaboration with case managers, specialists, and anticoagulation clinics, could ensure practice for AF is evidence-based, patient-centered, cost-effective, and incorporates all available resources. Atrial fibrillation is a complicated disease to manage, thus improving education and awareness is essential in this ever-changing and technologically advancing world of healthcare.

Personal Goals and Contributions to Advanced Practice Nursing

Nurses enter health care to help people; advanced practice nurses seek this role to make a difference not only in their patients' lives but to expand the roles, opportunities, autonomy, leadership, and abilities of their profession. Advanced practice nurses are not merely a mid-level provider but are the foundation of a unique branch of medicine, utilizing the nursing model, theoretical frameworks, and scientific advances to treat the entire patient holistically. A doctoral-prepared nurse practitioner can effectively conduct research, evaluate data impeccably, and successfully translate research into project; thus,

when passion, ambition, and fighting for a cause are intermeshed in the picture, the result is a meticulous capstone project.

The purpose of this capstone project was quality improvement. Prevention of disease is the basis for reducing health care costs, decreasing disease sequelae, and ultimately averting the onset of disease. Atrial fibrillation is a significant example of how if executed effectively, primary prevention (reduction of risk factors) and secondary prevention (screening for AF through an annual pulse check in the elderly) could minimize the incidence of stroke. Incorporating observations of practice through patient chart reviews, extensively reviewing literature, and gathering expert consensus from Delphi surveys, this Anticoagulation for Atrial Fibrillation Toolkit offers primary care providers a simple and comprehensive resource to improve the diagnosis and management of AF. Ultimately, the goal of this anticoagulation toolkit is sufficient expert consensus through Delphi surveys and enough revisions to become ready for implementation and subsequent evaluation in the primary care setting. If implementation of this toolkit in practice reduces the onset of even one stroke in a patient with atrial fibrillation, it has served its purpose to improve patient outcomes and has greatly contributed to the advanced practice of nursing.

Five Criteria for Executing a Successful Doctor of Nursing Practice Final Project

In 2004, The American Association of Colleges of Nursing (AACN; 2006) declared the Doctor of Nursing Practice (DNP) as the final degree for advanced practice nurses (nurse practitioners, nurse midwives, nurse anesthetists, and clinical nurse specialists). According to the AACN, “DNP programs’ goal are to produce nurses that are uniquely prepared to bridge the gap between the discovery of new knowledge and the

scholarship of translation, application, and integration of this new knowledge in practice (Waldrop, Caruso, Fuchs, & Hypes, 2014, p. 300). The AACN created the following eight essentials of doctoral education in advanced nursing practice:

- Scientific underpinnings in science
- Organizational and systems leadership for quality improvement and systems thinking
- Clinical scholarship and analytical methods for evidence-based practice
- Information systems/technology and patient care technology for the improvement and transformation of health care
- Health care policy for advocacy in health care
- Interprofessional collaboration for improving patient and population health outcomes
- Clinical prevention and population health for improving the nation's health
- Advanced nursing practice (p. 1).

The acronym of EC as PIE suggests five criteria that ensure DNP programs uphold these eight outcomes of the AACN: Enhances, Culmination, Partnerships, Implements, Evaluation. Upon meeting these five criteria, the project is deemed appropriate at the practice doctoral level (Waldrop et al., 2014). The EC as PIE criteria are depicted graphically in Figure 8.

Figure 8. EC as PIE: Five criteria for executing a successful Doctor of Nursing Practice final project. Adapted from Waldrop et al. (2014).

The first EC as PIE criterion for the DNP project "*enhance(s)* health outcomes, practice outcomes, or health care policy" (Waldrop et al., 2014, p. 301). This quality improvement capstone project addressed health outcomes of reduced strokes and practice outcomes of consistent, evidence-based diagnosis and management of AF. Health care policy was not addressed in this capstone but providers were encouraged to utilize national and international guidelines on anticoagulation with AF to enhance practice.

The second EC as PIE criterion reflects a "*culmination* of practice inquiry…the DNP student must identify and become an expert on a specific problem....to enact change" (Waldrop et al., 2014, p. 302). Through comprehensive literature reviews on atrial fibrillation including summarizing noteworthy drug trials and comparing oral anticoagulants, the researcher became an expert on background information, atrial

fibrillation, and anticoagulation for this capstone project. Through the step-wise guideline with corresponding algorithms, the researcher urged the change of improved diagnosis and management of atrial fibrillation in the elderly, focusing on anticoagulation to reduce the incidence of strokes.

The third EC as PIE criterion "require(s) engagement in *partnerships"* (Waldrop et al., 2014, p. 302). The patient chart reviews for this capstone project were retrospectively reviewed confidentially from the EHRs of a local and privately owned primary care clinic. Additionally, primary care and cardiology providers were invited to participate in the two Delphi surveys with the researcher collaborating to receive expert consensus for the toolkit while also building partnerships with these clinicians. Providers were encouraged to contact the researcher if they wanted additional information on the final results of this capstone project or to discuss the anticoagulation toolkit further, thereby enhancing interdisciplinary/interprofessional care.

The fourth EC as PIE criterion entails the DNP student *"implement*/apply/ translate evidence into practice" (Waldrop et al., 2014, p. 302). The researcher attained a solid comprehension of the research itself, its implications, and how best to translate this evidence into practice through an anticoagulation guideline with algorithms. This toolkit was initially derived from conclusions from the literature review and chart reviews but was modified based upon expert consensus and requests. In an extension of this project with further rounds of the Delphi method, the goal would be to implement this guideline into primary care practice. In compliance with this fourth criterion, the DNP student was able to take into account the needs of individual patients, providers, and society in general related to AF diagnosis and management.

The fifth EC as PIE criterion expects the DNP student "require *evaluation* of health care, practice or policy outcomes. The DNP may include outcome measures such as direct patient health care measures, costs, quality improvement, and accessibility of care" (Waldrop et al., 2014, p. 302). As this capstone project has not been implemented into practice, evaluation of this quality improvement *Anticoagulation for Atrial Fibrillation Toolkit for* was based upon the consensus of experts from the second round of the Delphi survey. However, greater than 70% consensus suggested this toolkit could improve the safety and efficacy of anticoagulation, influence future practice, be applicable to practice, and be inclusive of evidence-based practice. In summary, this capstone project successfully met all five EC as PIE criteria, approving it as a project at the doctoral practice level.

Summary

Atrial fibrillation is the most common cardiac arrhythmia in the United States (CDC, 2015), increasing the stroke risk by five times and contributing to 25% of strokes in the elderly population (Desai et al., 2017). Research has demonstrated the bleeding risk of oral anticoagulants does not outweigh the benefits of stroke prevention in the elderly population (Kirchhoff et al., 2016); yet only 30 to 50% of applicable elderly patients receive anticoagulation (Barbosa & Falcao, 2016) and intracranial bleeds are less than 1% of the population on anticoagulants (Desai et al., 2017). Overexaggerated bleeding risk in the elderly, the lack of head-to-head studies comparing anticoagulants, cost, patient compliance, safety, lab monitoring, and reversal agents all convolute the process of prescribing anticoagulation for atrial fibrillation, especially in a primary care setting where providers are not specialists with this disease. Furthermore, variations exist

with assessing bleeding risk and stroke risk for every patient through reliable tools such as HAS-BLED and CHA_2DS_2-VASc scores, respectively, and translating these scores into practice.

Due to inconsistencies and misconceptions observed in the diagnosis and management of atrial fibrillation, an extensive literature review, retrospective chart reviews on 100 patients, and expert consensus from two rounds of the Delphi survey method were utilized to create the Anticoagulation for Atrial Fibrillation Toolkit. A thorough review of research and statistical analysis of data clearly identified gaps between research and practice, suggesting areas to improve practice, enhanced provider education, increased multidisciplinary care and shared decision making between the patient and provider, and development of a comprehensive, all-in-one resource for providers to better diagnose and manage AF. Despite the toolkit being lengthy, expert consensus from Round 2 of the Delphi survey implied the guideline and algorithms were user friendly, evidence-based, and could safely and effectively enhance the care of patients with atrial fibrillation. This toolkit offered evidenced-based recommendations to diagnose and treat AF; in addition, it was a means to implement primary and secondary prevention efforts to reduce the incidence of stroke.

For this capstone project, the PARIHS framework and RE-AIM model were effectively utilized to assess the ability to translate this research into practice. This capstone project met all five criteria of the EC as PIE model (Waldrop et al., 2014), inferring this was a successful Doctor of Nursing Practice capstone project. A future extension of this project would evaluate patient outcomes with AF, predominantly a reduction in stroke incidence, after implementation of this toolkit in the primary care

setting. In conclusion, through improved acknowledgement of the devastating sequelae of AF in addition to consistent diagnosis and thorough treatment for all elderly patients, one of the most predominant and preventable causes of stroke could be minimized. This Anticoagulation Toolkit for Atrial Fibrillation is an innovative concept which if executed effectively could improve education and awareness of AF diagnosis and management, enhancing quality of life and ultimately saving lives.

REFERENCES

ACTIVE Investigators. (2006). Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE W): A randomised controlled trial. *Lancet, 367*(9526), 1903-1912.

ACTIVE Investigators. (2009). Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *New England Journal of Medicine, 360,* 2066-2078.

ACTIVE Investigators. (2011). Irbesartan in patients with atrial fibrillation. *New England Journal of Medicine, 364*, 925-938.

Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke prevention in atrial fibrillation III randomised clinical trial. (1996). *Lancet, 348*(9028), 633-638.

American Association of Colleges of Nursing. (2006). *The essentials of doctoral education for advanced nursing practice*. Retrieved from http://www.aacnnursing.org/DNP/DNP-Essentials

American College of Cardiology. (2012). *Severity of atrial fibrillation scale*. Retrieved from http://acc.org

American Geriatrics Society. (2015). American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *Journal of American Geriatric Society, 63,* 2227-2246. doi:10.1111/jgs.13702

American Heart Association, Inc., American College of Cardiology Foundation, and Heart Rhythm Society. (2014). 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *Journal of the American College of Cardiology, 64*(21), e1-e76.

American Heart Association and American Stroke Association. (2016). *Simplifying your atrial fibrillation treatment plan*. Retrieved from https://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable//ucm_324032.pdf.

American Heart Association. (n.d.). *Atrial fibrillation*. Retrieved from https://www.columnfivemedia.com/work-items/infographic-educating-doctors-and-patients-about-atrial-fibrillation

Amin, A., Bruno, A., Trocio, J., Lin, J., & Lingohr-Smith, M. (2015). Comparison of differences in medical costs when new oral anticoagulants are used for the treatment of patients with non-valvular atrial fibrillation and venous thromboembolism vs warfarin or placebo in the US. *Journal of Medical Economics, 18*(6), 399-409. doi:10.3111/13696998.2015.1007210

Ansell, J. (2013). Point-of-care patient self-monitoring of oral vitamin K antagonist therapy. *Journal of Thrombosis and Thrombolysis, 35*, 339-341. doi:10.1007/s11239-0878-z

Appelros, P., Farahmand, B., Terént, A., & Asberg, S. (2017, May). To treat or not to treat: Anticoagulants as secondary preventatives to the oldest old with atrial fibrillation. *Stroke,48*(6), 1617-1622. doi:10.1161/STROKEAHA.117.016902

Barbosa, M., & Falcao, L. M. (2016). Oral anticoagulation in the elderly: New oral anticoagulants--Innovative solution for an old problem? *American Journal of Therapeutics, 0,* 1-10.

Barcellona, D., Fenu, L., & Marongiu, F. (2016). Point-of-care testing INR: An overview. *Clinical Chemical Laboratory Medicine, 55*(6), 1-6. doi: 10.1515/ccim-2016-0381

Barnes, G. D., Lucas, E., Alexander, C., & Goldberger, Z. D. (2015). National trends in ambulatory oral anticoagulant use. *The American Journal of Medicine, 128,* 1300-1305.

Bayer HealthCare. (2010). *About the history of anticoagulants*. Retrieved from www.investor.bayer.com/securedl/10064

Berti, D., Van Vlasselaer, X., Moons, P., & Heidbuchel, H. (2015). Prioritized outcomes to evaluate the effectiveness of atrial fibrillation disease management: A systematic review and Delphi study. *International Journal of Cardiology, 202,* 500-503.

Boehringer Ingelheim. (2015a). Praxbind [package insert]. Retrieved from http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Praxbind/Praxbind.pdf

Boehringer Ingelheim. (2015b). *Pradaxa* [package insert]. Retrieved from http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf

Boehringer Ingelheim. (2016). *Pradaxa coverage and savings*. Retrieved from https://www.pradaxapro.com/coverage-savings

Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. (1990). The effect of low-dose warfarin on the risk of stroke in nonrheumatic atrial fibrillation. *The New England Journal of Medicine, 323,* 1505-1511.

Boston Scientific. (2016). *Think outside the pill box: WATCHMAN left atrial appendage closure device*. Retrieved from http://www.watchman.com/home.html?cid =vu157214

Bristol-Myers Squibb. (2015, October). *Coumadin* [package insert]. Retrieved from http://packageinserts.bms.com/pi/pi_coumadin.pdf

Bristol-Myers Squibb. (2016). *Eliquis coverage and reimbursement*. Retrieved from http://www.eliquis.com/eliquis/hcp/coverage-reimbursement

Budnitz, D. S., Lovegrove, M. C., Shehab, N., & Richards, C. L. (2011). Emergency hospitalizations for adverse drug events in older Americans. *New England Journal of Medicine, 365,* 2002-2012.

Caldeira, D., Costa, J., Fernandes, R.M., Pinto, F.J., & Ferreira, J. (2014). Performance of the HAS-BLED high bleeding-risk category compared to ATRIA and HEMORR2HAGES in patients with atrial fibrillation: A systematic review and meta-analysis. *Journal of Interventional Cardiology and Electrophysiology, 40*(3), 277-284. doi:10.1007/s10840-014-9930-y

Centers for Disease Control and Prevention. (2015, August 13). *Atrial fibrillation fact sheet*. Retrieved from http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_ atrial_fibrillation.htm

Centers for Disease Control and Prevention. (2016a). *Public health genomics knowledge base: Genomics general application*. Retrieved from https://phgkb.cdc.gov/GAPPKB/topicFinder.do?Mysubmit=individual &intTopicId=1012&submit.x=14&submit.y=4&submit=Home

Centers for Disease Control and Prevention. (2016b, April 26). *Public health genomics knowledge base: Tier table database*. Retrieved from https://phgkb.cdc.gov/GAPPKB/topicStartPage.do#Tier 2

Centers for Medicaid and Medicare Services. (2009, August 3). *Pharmacogenomic testing for warfarin response* (Publication No. 100-3). Retrieved from xhttps://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=333

Connolly, S. J., Wallentin, L., Ezekowitz, M., B.C., Eikelboom, J., Oldgren, J., … Yusuf, S. (2013, July 16). The long-term multicenter observational study of dabigatran treatment in patients with atrial fibrillation (RELY-ABLE) study. *Circulation, 128,* 237-243. doi:10.1161/CIRCULATIONHA.112.001139

Connolly, S. J., Eikelboom, J., Joyner, C., Diener, H.C., Hart, R., Golitsyn, S., …Yusuf, S. (2011). Apixaban in patients with atrial fibrillation. *The New England Journal of Medicine, 364*(9), 806-817. doi: 10.1056/NEJMoa1007432

Connolly, S. J., Ezekowitz, M., Salim, Y., Reily, P., & Wallentin, L. (2010, November 4). Newly identified events in the RE-LY trial. *The New England Journal of Medicine, 363*(19), 1876-1877.

Connolly, S. J., Ezekowitz, B. C., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, M. D, …Wallentin, L. (2009, September 17). Dabigatran versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine, 361*(12), 1139-1151. doi:10.1056/NEJMoa0905561

Connolly, S. J., Laupacis, A., Gent, M., Roberts, R. S., Cairns, J. A., & Joyner, C. (1991). Canadian atrial fibrillation anticoagulation (CAFA) study. *Journal of American College of Cardiology, 18*(2), 349-355.

Connolly, S. J., Wallentin, L., & Yusuf, S. (2014, October 9). Additional events in the RE-LY trial. *The New England Journal of Medicine, 371*(15), 1464-1465.

Crouse, B., & Quigley, S. (2014). *New oral anticoagulants: An economic analysis.* Retrieved from https://lecom.edu/new-oral-anticoagulants-an-economic-analysis/

Daiichi Sankyo. (2015). *Savaysa* [package insert]. Retrieved from http://dsi.com/prescribing-information portlet/getPIContent?product Name=Savaysa&inline=true

Daiichi Sankyo. (2017). *Savaysa samples and savings cards*. Retrieved from https://savaysahcp.com/registration

Desai, Y., El-Chami, M. F., Leon, A. R., & Merchant, F. M. (2017). Management of atrial fibrillation in elderly adults. *Journal of American Geriatric Society, 65,* 185-193. doi:10.1111/jgs.14483

DeSantis, G., Hogan-Schlientz, J., Liska, G., Kipp, S., Sallee, R., Wurster, M., …Ansell, J. (2014). STABLE results: Warfarin home monitoring achieves excellent INR control. *American Journal of Managed Care, 20*(3), 202-209.

Dewilde, W. J., Oirbans, T. Verheugt, F. W., Kelder, J. C., De Smet, B. J., Herman, J. P., ….WOEST study investigators. (2013). Use of clopidogrel with or without aspirin in patients taking oral anticoagulation therapy and undergoing percutaneous coronary intervention: An open-labeled, randomised, controlled trial. *Lancet, 381*(9872), 1107-1115.

Dias, C., Moore, K. T., Murphy, J., Ariyawans, J., Smith, W., Mills, R. M., & Weir, M. R. (2016). Pharmacokinetics, pharmacodynamics, and safety of single-dose rivaroxaban in chronic hemodialysis. *American Journal of Nephrology, 43,* 229-236. doi:10.1159/000445328

DiMinno, A., Frigerio, B., Spadarella, G., Ravani, A., Sansaro, D., Amato, M., …Baldassarre, D. (2017). Old and new oral anticoagulants: Food, herbal medicines and drug interactions. *Blood Reviews, 31*(4), 1-11.

Doherty, J. U., Gluckman, T. J., Hucker, W. J., Januzzi, J. L., Ortel, T. L., Saxonhouse, S. J., & Spinler, S. A. (2017, January). *2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation*. Retrieved from http://www.onlinejacc.org/content/early/2017/01/05/j.jacc.2016.11.024

Dorian, P., Cvitkovic, S. S., Kerr, C. R., Crystal, E., Gillis, A. M., Guerra, P. G., & Wyse, D. G. (2006). A novel, simple scale for assessing the symptom severity of atrial fibrillation at the bedside: The CCS-SAF scale. *Canadian Journal of Cardiology, 22*(5), 383-386.

Dorian, P., Guerra, P. G., Kerr, C. R., O'Donnel, S. S., Crystal, E., Gillis, A. M. …Wyse, G. (2009). Validation of a new simple scale to measure symptoms in atrial fibrillation- The Canadian Cardiovascular Society severity in atrial fibrillation (CCS-SAF) scale. *Circulation: Arrhythmia and Electrophysiology, 2,* 1-32.

Drugs.com (2013, December). *Vitamin K1* [package insert]. Retrieved from https://www.drugs.com/pro/vitamin-k1.html

Drugs.com (2015a, November 11). *Pradaxa* [package insert]. Retrieved from https://www.drugs.com/monograph/pradaxa.html

Drugs.com (2015b, November 12). *Xarelto* [package insert]. Retrieved from https://www.drugs.com/monograph/ xarelto.html

Drugs.com. (2015c, December). *Coumadin* [package insert]. Retrieved from https://www.drugs.com/pro/ coumadin-injection.html

Drugs.com. (2016, January 20). *Eliquis* [package insert]. Retrieved from https://www.drugs.com/monograph/eliquis.html

Eikelboom, J. W., Connolly, S., Brueckmann, M., Granger, C. B., Kappetein, A. P., Mack, M. J., …Van de Werf, F. (2013, September 26). Dabigatran versus warfarin in patients with mechanical heart valves. *The New England Journal of Medicine, 369,* 1206-1214. doi:10.1056NEJMoa1300615

European Atrial Fibrillation Trial Study Group. (1993). Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet, 342*(8882), 1255-1262.

Ezekowitz, M. D., Cappato, R., Klein, A. L., Camm, A. J., Chang-Sheng, M., Le Heuzey, J-Y, …van Eickels, M. (2014). Rationale and design of the eXplore: The efficacy and safety of once-daily oral rivaroxaban for the prevention of cardiovascular events in patients with nonvalvular aTrial fibrillation scheduled for cardioversion trial: A comparison of oral rivaroxaban once daily with dose-adjusted vitamin K antagonists in patients with nonvalvular atrial fibrillation undergoing elective cardioversion. *American Heart Journal, 167,* 646-652.

Ezekowitz, M. D., Reilly, P. A., Nehmiz, G., Simmers, T. A., Nagarakanti, R., Parcham-Azad, K., …Wallentin, L. (2007). Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO study). *American Journal of Cardiology, 100,* 1419-1426.

Farris, R. P., Will, J. C., Khavjou, O., & Finkelstein, E. A. (2007). Beyond effectiveness: Evaluating the public health impact of the WISEWOMAN program. *American Journal of Public Health, 97*(4), 641-647.

Fendrik, A. M. (2010, November). A pharmacoeconomic perspective on stroke prevention in atrial fibrillation. *American Journal of Managed Care, 16*, S284-S290.

Foody, J. M. (2017). Reducing the risk of stroke in elderly patients with non-valvular atrial fibrillation: A practical guide for clinicians. *Clinical Interventions in Aging, 12,* 175-187.

Freedman, B., Camm, J., Calkins, H., Healey, J. S., Rosenqvist, M., Wang, J., …Yan, B. P. (2017, May). Screening for atrial fibrillation: A report of the AF-SCREEN International Collaboration. *Circulation, 135*(19), 1851-1867.

Ganz, L., & Spragg, D. (2016, July 6). *Epidemiology of and risk factors for atrial fibrillation*. Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Garcia, D. A., & Crowther, M. (2017, April 10). *Management of bleeding in patients receiving direct oral anticoagulants.* Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Gibson, C. M., Mehran, R., Bode, C., Halperin, J., Verheugt, F., Wildgoose, P., …Fox, K. (2015). An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). *American Heart Journal, 169*(4), 472-485. doi: 10.1016/j.ahj.2014.12.006

Giugliano, R. P., Tuff, C. T., Braunwald, E., Murphy, S. A., Wiviott, S. D. Halperin, J. L., …Antman, E. M. (2013). Edoxaban versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine, 369,* 2093-2014. doi:10.1056/NEJMoa1310907

Glasgow, R. E., McKay, H. G., Piette, J. D., & Reynolds, K. D. (2001). The RE-AIM framework for evaluating interventions: What can it tell us about approaches to chronic illness management. *Patient Education and Counseling, 44,* 119-127.

GoodRx. (2017). *Find the lowest price.* Retrieved from www.goodrx.com

Granger, C. B., Alexander, J. H., McMurrary, J. J. V., Lopes, R. D., Hylek, E. M., Hanna, M., …Wallentin, L. (2011, September 15). Apixaban versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine, 365*(11), 981-992. doi:10.1056/NEJMoa1107039

Guimaraes, P. O., Kaatz, S., & Lopes, R. D. (2015). Practical and clinical considerations in assessing patients with atrial fibrillation for switching to non-vitamin K antagonist oral anticoagulants in primary care. *International Journal of General Medicine, 8,* 283-291.

Gullov, A. L., Koefoed, B. G., Petersen, P., Pedersen, T. S., Andersen, E. D., Godtfredsen, J., & Boysen, G. (1998). Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation. Second Copenhagen atrial fibrillation, aspirin, and anticoagulation study. *Archives of Internal Medicine, 158*(14), 1513-1521. doi:10.1001/archinte.158.14.1513

Halperin, J., Hart, R., Kronmal, R., McBride, R., Pearce, L., & Sherman, D. (1994). Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke prevention in atrial fibrillation II study. *Lancet, 343,* 687-691.

Harrington, A. R., Armstrong, E. P., Nolan, E. P., & Malone, D. C. (2014). Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. *Stroke, 44*(6), 1676-1681. doi:10.1161/STROKEAHA.111.000402

Harrison, L., Johnston, M. Massicotte, M. P., Crowther, M., Moffat, K., & Hirsh, J. (1997). Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Annuals of Internal Medicine, 126*(2), 133-136.

Harvey, G., & Kitson, A. (2016). PARIHS revisited: From heuristic to integrated framework for the successful implementation of knowledge into practice. *Implementation Science, 11*(33), 1-13.

Heidenreich, P. A., Solis, P., Estes, N. A. M., Gonarow, G. C., Jurgens, C. Y, Marine, J. E., …McNamara, R. L. (2016). 2016 ACC/AHA clinical performance and quality measures for adults with atrial fibrillation or atrial flutter. *Journal of the American College of Cardiology, 68*(5), 525-568.

Hellemons, B. S. P., Langenberg, M., Lodder, J., Vermeer, F., Shouten, H. J. A., Lemmens, T. H., …Knottnerus, J. A. (1999). Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: Randomised controlled trial comparing two intensities of coumarin with aspirin. *British Medical Journal, 319*(9), 958-964.

Hijazi, Z. M., & Saw, J. (2016, September 21). *Nonpharmacologic therapy to prevent embolization in patients with atrial fibrillation*. Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Hill, J. N., Guihan, M., Hogan, T.P., Smith, B.M., LaVela, S.L., Weaver, F. M., …Evants, C. T. (2017). Use of the PARIHS framework for retrospective and prospective implementation evaluations. *Worldviews on Evidence-Based Nursing, 14*(2), 99-107.

Hirsh, J., Fuster, V., Ansell, J., & Halperin, J. L. (2003). American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *Journal of American College of Cardiology, 41*(9), 1633-1652.

Holmes, D. R., Reddy, V. Y., Zoltan, G. T., Doshi, S. K., Sievert, H., Buchbinder, M., …Sick, P. (2009). Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: A randomised non-inferiority trial. *Lancet, 374,* 534-542.

Holmes, D. R., Saibal, K., Price, M. J., Whisenant, B., Sievert, H., Doshi, S. K., …Reddy, V.Y. (2014). Prospective randomization evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy. *Journal of the American College of Cardiology*, *64*(1), 1-12.

Hsu, C-C., & Sandford, B. A. (2007, August). The Delphi technique: Making sense of consensus. *Practical Assessment, Research and Evaluation, 12*, 1-7.

Hu, T. Y., Vaidya, V. R., & Asirvatham, S. J. (2016). Reversing anticoagulant effects of novel anticoagulants: Role of ciraparantag, andexanet alpha, and idarucizumab. *Vascular Health and Risk Management, 12,* 35-44.

Hull, R. D., & Garcia, D. A. (2016a, May 20). *Management of warfarin-associated bleeding or supratherapeutic INR*. Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Hull, R. D., & Garcia, D. A. (2016b, May 31). *Warfarin and other VKA's: Dosing and adverse effects*. Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Hwang, C. (2016a). *CHA_2DS_2-VASc score for atrial fibrillation stroke risk*. Retrieved from http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk/

Hwang, C. (2016b). *HAS-BLED score for major bleeding risk*. Retrieved from http://www.mdcalc.com/has-bled-score-for-major-bleeding-risk/

Jaffar, A., & Bragg, L. (2003, April). Practical tips for warfarin dosing and monitoring. *Cleveland Clinic Journal of Medicine, 70*(4), 361-371.

Janssen Pharmaceuticals. (2014a, January). *Challenges of anticoagulation treatment in the elderly population*. Raritan, NJ: Janssen Pharmaceuticals, Inc.

Janssen Pharmaceuticals. (2014b, August). *Patient adherence drives outcomes*. Raritan, NJ: Janssen Pharmaceuticals, Inc.

Janssen Pharmaceuticals. (2014c, December). Complexities of warfarin therapy may lead to increased resource utilization. Raritan, NJ: Janssen Pharmaceuticals, Inc.

Janssen Pharmaceuticals. (2014d, December). *Cost of stroke among high-risk AF patients*. Raritan, NJ: Janssen Pharmaceuticals, Inc.

Janssen Pharmaceuticals. (2014e, December). *Unstable INR has implications for healthcare resource use*. Raritan, NJ: Janssen Pharmaceuticals, Inc.

Janssen Pharmaceuticals. (2016a). *Challenges of warfarin management in a nursing home setting*. Raritan, NJ: Janssen Pharmaceuticals, Inc.

Janssen Pharmaceuticals. (2016b). *Xarelto formulary coverage*. Retrieved from https://www.xareltohcp.com/resources/formulary-coverage.html

January, C. T., Wann, L. S., Alpert, J. S., Calkins, H., Ciagarroa, J. E., Cleveland, J. C., …Yancy, C. W. (2014, December 2). 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive Summary. *Journal of the American College of Cardiology*, *64*(21), 2246-2280.

Janzic, A., & Kos, M. (2013, June). Cost effectiveness of novel oral anticoagulants for stroke prevention in atrial fibrillation depending on the quality of warfarin anticoagulation control. *Pharmacoeconomics*, *33*(4), 395-408. doi:10.1007/s40273-014-0246-7

Johnson, J. A., Caudle, K. E., Gong, L., Whirl-Carrillo, M., Stein, C. M., Scott, S.A. …Wadelius, M. (2017). *Clinical pharmacogenetics implementation consortium (CPIC) guideline for pharmacogenetics guided warfarin dosing: 2017 update.* Retrieved from https://www.pharmgkb.org/guideline/PA166104949

Kearon, C., Akl, E. A., Ornelas, J., Blaivas, A., Jimenez, D., Bounameaux, H., …Moores, L. (2016). Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *CHEST*, *149*(2), 315-352.

Kirchhof, P., Benussi, S., Kotecha, D., Ahlsson, A., Atar, D., Casadei, B., …Vardas, P. (2016). *2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS*. Retrieved from https://academic.oup.com/eurheartj/article/37/38/2893/2334964/2016-ESC-Guidelines-for-the-management-of-atrial

Kumar, K. (2016a, September 21). Antiarrhythmic drugs to maintain sinus rhythm in patients with atrial fibrillation. Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Kumar, K. (2016b). *Overview of atrial fibrillation*. Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Kumar, K., & Manning, W. J. (2016, October 10). *Rhythm control versus rate control in atrial fibrillation*. Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Lane, D. A., & Lip, G. Y. H. (2012). Use of the CHA2DS2-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. *Circulation, 126,* 960-865. doi:10.1161/CIRCULATIONAHA.111.060061

Lee, R. (2017, January 23). *Surgical ablation to prevent recurrent atrial fibrillation.* Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Leung, L. L. K. (2017, September 1). *Direct oral anticoagulants and parenteral direct thrombin inhibitors: Dosing and adverse effects*. Waltham, MA: WoltersKluwer Health. Available from http://www.uptodate.com

Makaryus, J. N., Halperin, J. L., & Lau, J. F. (2013). Oral anticoagulants in the management of venous thromboembolism. *Nature Reviews Cardiology, 10,* 398.

Manning, W. J. (2016, September 9). *Stroke in patients with atrial fibrillation*. Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Manning, W. J., Singer, D. E., & Lip, G. Y. H. (2016, October 31). *Atrial fibrillation: Anticoagulation therapy to prevent embolization*. Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Mant, J., Hobbs, F. D. R., Fletcher, K., Roalfe, A., Fitzmaurice, D., Lip, G. Y. H., … Midland Research Practices Network. (2007). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham atrial fibrillation treatment of the aged study, BAFTA): A randomised controlled trial. *Lancet, 370*(9586), 493-503.

Medicare.gov. (n.d.). *Costs in the coverage gap.* Retrieved from https://www.medicare.gov/part-d/costs/coverage-gap/part-d-coverage-gap.html

Meschia, J. F., Bushnelll, C., Boden-Albala, B., Braun, L. T., Bravata, D. M., Chaturvedi, S., …Wilson, J. A. (2014). Guidelines for the primary prevention of stroke. A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 45,* 3754-3832. doi:10.1161/STR.0000000000000046

Meyer, S., Frei, C. R., Daniels, K. R., Forcade, N. A., Bussey, M., Bussey-Smith, K. L., & Bussey, H. T. (2013). Impact of a new method of warfarin management on patient satisfaction, time, and cost. *Pharmacotherapy, 33*(11), 1147-1155. doi:10.1002/phar.1344

Naccarelli, G. V., Ganz, L. I., & Manning, W. J. (2016, October 10). *Atrial fibrillation: Cardioversion to sinus rhythm.* Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Nielsen, P. B., Skjoth, F., Sogaard, M., Kjaeldgaard, J. K., Lip., G. Y. H., & Larsen, T. B. (2017). Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: Propensity weighted nationwide cohort study. *British Medical Journal, 356*(j510), 1-10.

Noseworthy, P. A., Yao, X., Abraham, N. S., Sangaralingham, L. R., McBane, R. D., & Shah, N. D. (2016). Direct comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in nonvalvular atrial fibrillation. *CHEST, 150*(6), 1302-1312.

Olshansky, B., & Arora, R. (2016, November 25). *Mechanisms of atrial fibrillation*. Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Passmar, R. (2016, July 6). *Catheter ablation to prevent recurrent atrial fibrillation: Current applications*. Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Patel,. M. R., Mahaffey, K. W., Garg, J., Guohua, P., Sinder, D.E., Hacke, W., …Califf, R. M. (2011, September 8). Rivaroxaban versus Warfarin in nonvalvular atrial fibrillation. *The New England Journal of Medicine*, *365*(10), 83-891. doi:10.1056/NEJMoa1009638

Perera, K. S., Vanassche, T., Bosch, J., Swaminathan, B., Mundl, H., Giruparajah, M., …Hart, R. G. (2016, September). Global survey of the frequency of atrial fibrillation-associated stroke: Embolic stroke of undetermined source global registry. *Stroke, 47*, 2197-2202. doi:10.1161/STROKEAHA.116.013378

Petersen, P., Godtfredsen, J., Boysen, G., Andersen, E. D., & Andersen, B. (1989). Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet, 333*(8631), 175-179.

Phibbs, C. S., Love, S. R., Jacobson, A. K., Edson, R., Su, P., Uyeda, L., & Matchar, D.B. (2016). At-home versus in-clinic INR monitoring: A cost-utility analysis from the home INR study (THINRS). *Journal of General Internal Medicine, 31*(9), 1061-1067. doi:10.1007/d11606-016-3700-8

Pollack, C. V., Reilly, P. A., Eikelboo, J., Glund, S., Verhamme, P., Bernstein, R., … Weitz, J. I (2015). Idarucizumab for dabigatran reversal. *The New England Journal of Medicine, 373*(3), 511-520. doi:10.1056/NEJMoa1502000

Pozzi, M., Mitchell, J., Henaine, A.M., Safi, O., & Henaine, R. (2016). International\ normalized ratio self-testing and self-management: Improving patient outcomes. *Vascular Health and Risk Management, 12*, 387-392.

RE-AIM. (2017). *About RE-AIM*. Retrieved from http://re-aim.org

Ruff, C. T., Giugliano, R. P., & Antman, E. M. (2016). Management of bleeding with non-vitamin K antagonist oral anticoagulation in the era of specific reversal agents. *Circulation, 134*, 248-261. doi:10.1161/CIRCULATIONAHA.116.021831

Rycroft-Malone, J. (2004). The PARIHS framework- A framework for guiding the implementation of evidence-based practice. *Journal of Nursing Quality Care, 19*(4), 297-304.

Samsa, G., Matchar, D. B., Dolor, R. J., Wiklund, I., Hedner, E., Wygant, G., …Edwards, R. (2004). A new instrument for measuring anticoagulation-related quality of life: Development and preliminary validation. *Health and Quality of Life Outcomes, 2*(22), 1-11.

Samuelson, B. T., & Cuker, A. (2016). Measurement and reversal of the direct oral anticoagulants. *Blood Reviews, 31,* 77-84.

Samuelson, B. T., Cuker, A., Siegal, D. M., Crowther, M., & Garcia, D. A. (2017). Laboratory assessment of the anticoagulant activity of direct oral anticoagulants. *Chest, 151*(1), 127-138.

Shahid, F., Shantsila, E., & Lip, G. Y. H. (2016). Recent advances in the understanding and management of atrial fibrillation: A focus on stroke prevention. *F1000Research, 5,* 1-11. doi:10.12688/f1000research.10176.1

Shaw, K., Amstutz, U., Kim, R. B., Lesko, L. J., Turgeon, J., Michaud, V., …Carleton, B. C. (2015). Clinical practice recommendations on genetic testing of CYP2C9 and VKORC1 variants in warfarin testing. *Therapeutic Drug Monitoring, 37,* 428-436.

Shehab, N., Sperling, L. S., Kegler, S. R., & Budnitz, D. S. (2010). National estimates of emergency department visits for hemorrhage-related adverse events from clopidogrel plus Aspirin and from warfarin. *Archives of Internal Medicine, 170,* 1926-1933.

Siegal, D. M., Curnutte, J. T., Connolly, S. J., Genmin, L., Conley, P. B., Wiens, B. L., …Crowther, M. A. (2015). Andexanet Alfa for the reversal of factor xa inhibitor activity. *New England Journal of Medicine, 373,* 2413-2424. doi:10.1056/NEJMoa1510991

Singh, S. M., & Wijeysundera, H. C. (2015). Cost-effectiveness of novel oral anticoagulants for stroke prevention in non-valvular atrial fibrillation. *Current Cardiology Reports, 17*(61), 1-7. doi:10.1007/s11886-015-0618-4

Society of Vascular Medicine. (2015). *Atrial fibrillation (A-Fib) decision making tool*. Retrieved from http://www.mybloodclots.org/

Spragg, D., & Kumar, K. (2017, May 24). Paroxysmal atrial fibrillation. Waltham, MA: Wolters Kluwer Health. Available from http://www.uptodate.com

Stroke prevention in atrial fibrillation study: Final results. (1991). *Circulation, 84,* 527-539.

Tu, J. V., Maclagan, L. C., Ko, D. T., Atzema, C. L., Booth, G. L., Johnston, S., …Chu, A. (2017). CANHEART primary prevention indicator expert panel. *Canadian Medical Association Journal, 5*(2), E315-E321. doi:10.9778/cmajo.20160139

University of Colorado Health North. (2015, September 16). *University of Colorado Health North guideline for the management of anticoagulation care*. Retrieved from https://www.uchealth.org/

Waldrop, J., Caruso, D., Fuchs, M. A., & Hypes, K. (2014). EC as PIE: Five criteria for executing a successful DNP final project. *Journal of Professional Nursing, 30*(4), 300-306.

Wang, X., Mondal, S., Want, J., Tirucherai, G., Zhang, D., Boyd, R. A., & Frost, C. (2013). Effect of activated charcoal on apixaban pharmacokinetics in healthy subjects. *American Journal of Cardiovascular Drugs, 14,* 147-154. doi:10.1007/s40256-013-0055-y

Washington University. (2016). *Warfarin dosing.* Retrieved from http://warfarindosing.org/Source/Home.aspx

Weitz, J. I., Connolly, S. J., Patel, I., Salazar, D., Rohatagi, S., Mendell, J., …Kunitada, S. (2011). Randomised, parallel-group, multicenter, multinational, phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thrombosis and Haemostasis, 104*(3), 633-641. doi:10.1160/TH10-01-0066

Wigle, P., Hein, B., Bloomfield, H. E., Tubbe, M., & Doherty, M. (2013, April 15). Updated guidelines on outpatient anticoagulation. *American Academy of Family Physicians, 87*(8), 556-566.

Williams, D., Riley, R. S., & Tidwell, A. (n.d.). *Laboratory monitoring of warfarin therapy*. Retrieved from http://www.pathology.vcu.edu/media/pathology/clinical/coag/Warfarin.pdf

Yao, X., Abraham, N. S., Sangaranlingham, L. R., Bellolio, F., McBane, R.D., Shah, N. D., & Noseworthy, P. A. (2016). Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *Journal of the American Heart Association, 5*, e003725. doi:10.1161/JAHA.116003725

You, J. J., Singer, D. E., Howard, P. A., Lane, D. A., Eckman, M. H., Fang, M. C., …Lip, G. Y. H. (2012). Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis. *Chest, 141*(2 Suppl.), e531S-e575S. Retrieved from http://journal.publications.chestnet.org/article.aspx?articleID=1159549

APPENDIX A

ANTICOAGULATION FOR ATRIAL FIBRILLATION TOOLKIT

Anticoagulation for Atrial Fibrillation Toolkit:

Guideline with Algorithms for the Primary Care Setting

Table of Contents

Clinical Practice Guideline and Algorithms

Recommendations for Diagnosing and Anticoagulating Atrial Fibrillation in the Elderly Population to Reduce the Incidence of Stroke

1) Reduce risk factors for atrial fibrillation (AF).
2) Diagnose AF early through an annual pulse check in all symptomatic or asymptomatic patients ≥65 years old. If an irregular pulse is detected, confirm the rhythm through an EKG.
3) If a patient has AF, assess for bleeding and stroke risk through the HAS-BLED and CHA_2DS_2-VASc scores respectively to determine if that patient is a candidate for oral anticoagulation.
4) Prescribe the patient specific anticoagulation with a CHA_2DS_2-VASc score ≥2 and a low risk of bleeding. Consider anticoagulating with a CHA_2DS_2-VASc score of 1, dependent on patient preference and clinical judgment.

CHA_2DS_2-VASc Scores to Predict Risk of Stroke Within the Next Year with Atrial Fibrillation.

CHA_2DS_2-VASc Risk Factor	Score (points)
Congestive Heart Failure	1
Hypertension	1
Age ≥75 years old	2
Diabetes Mellitus	1
Prior Stroke, Transient Ischemic Attack, or Thromboembolism	2
Vascular Disease (Prior Myocardial Infarction or Peripheral Artery Disease)	1
Age 65-74 Years Old	1
Female Sex	1

Note. Less than 65 years old and male sex score 0 points. A score of 0 (low risk of stroke, 0% in 1 year) does not require anticoagulation. A score of 1 (intermediate risk of stroke, 0.6% in 1 year) suggests an antiplatelet or anticoagulant. A score of 2 of higher (moderate-high risk of stroke, 3% in 1 year) recommends anticoagulant use. Adapted from "CHA_2DS_2-VASc score for atrial fibrillation stroke risk," by C. Hwang, 2016a, http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk. Copyright 2015 by MDCalc.

HAS-BLED Score to Estimate Major Bleeding Risk While on Anticoagulation Within the Next Year.

HAS-BLED major bleeding risk factors	Score (points)
*History of **H**ypertension* (uncontrolled or systolic blood pressure >160)	1
***A**bnormal Renal Disease* (dialysis, kidney transplant, creatinine >2.26 mg/dL ***A**bnormal Liver Disease* (cirrhosis, bilirubin >2x normal, AST/ALT/AP >3x normal)	1 AND/OR 1
*History of **S**troke*	1
*History of Major **B**leeding or a Predisposition to Bleeding*	1
***L**abile INR* (unstable or high INR, INR uncontrolled <60% of the time)	1
***E**lderly: Age >65 years*	1
***D**rugs: Use of Medications Increasing Bleeding Risk* *(antiplatelets, NSAIDS)* *Alcohol Use* (≥8 drinks per week)	1 AND/OR 1
	Maximum of 9 points

Note. The annual risk of bleeding while on anticoagulation increase with every positive risk factor, with an overall bleeding risk of 1.5%. The scoring of these risk factors does not categorize the patient as low, intermediate, or high risk for bleeding while on anticoagulation. The purpose of these cumulative risk factors is to provide a risk-benefit analysis for long-term anticoagulation. Adapted from "HAS-BLED score for major bleeding risk," by C. Hwang, 2016b, http://www.mdcalc.com/has-bled-score-for-major-bleeding-risk/.

Comparison of Warfarin and Direct Oral Anticoagulants (DOACs)

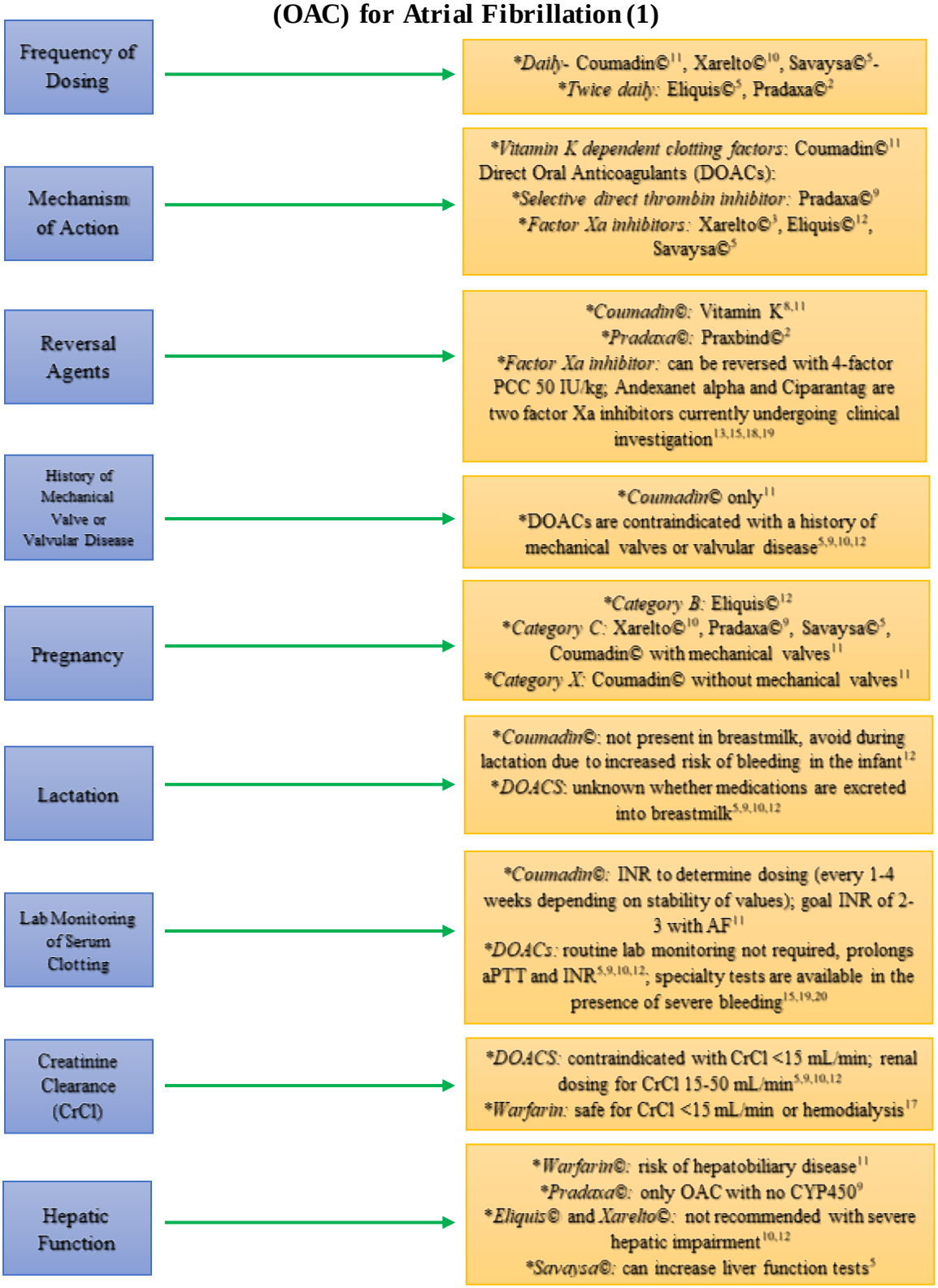
	Warfarin sodium (Coumadin®)	**DOACs** Rivaroxaban (Xarelto®) Dabigatran (Pradaxa®) Apixaban (Eliquis®) Edoxaban (Savasya®)

Pros	• Indicated for prosthetic valve[1] replacement or valvular heart disease[1]
	• Patient preference for INR monitoring[1]
	• Once daily dosing[4]
	• Suitable if INRs are therapeutic >65% of the time[1]
	• Inexpensive[1]
	• Reversal agent: Vitamin K[2]
	  ○ Others: prothrombin complex concentrate (PCC), fresh frozen plasma (FFP), and recombinant activated factor VII (rFVIIa)[4]
	• Lab monitoring for reversal: PT/INR[4]
		• Convenient (no routine lab monitoring through INR)[1]
		• Decreased risk of intracranial hemorrhage[1]
		• No dietary restrictions[1]
		  ○ Rivaroxaban should be taken with food[4]
		• Decreased drug-drug interactions[1]
		• Reversal agents:
		  ○ *Direct thrombin inhibitors*: idarucizumab, hemodialysis (severe bleeding)[3,4]
		  ○ *Factor Xa inhibitors:* no specific reversal agent but a couple are in development[3,4]
		  ○ Antifibrinolytics, prothrombin complex concentrate, and activated charcoal can be used for major bleeding[3,4]
		• Lab monitoring for reversal: thrombin time (TT) for dabigatran, anti-factor Xa for factor Xa inhibitors[4]

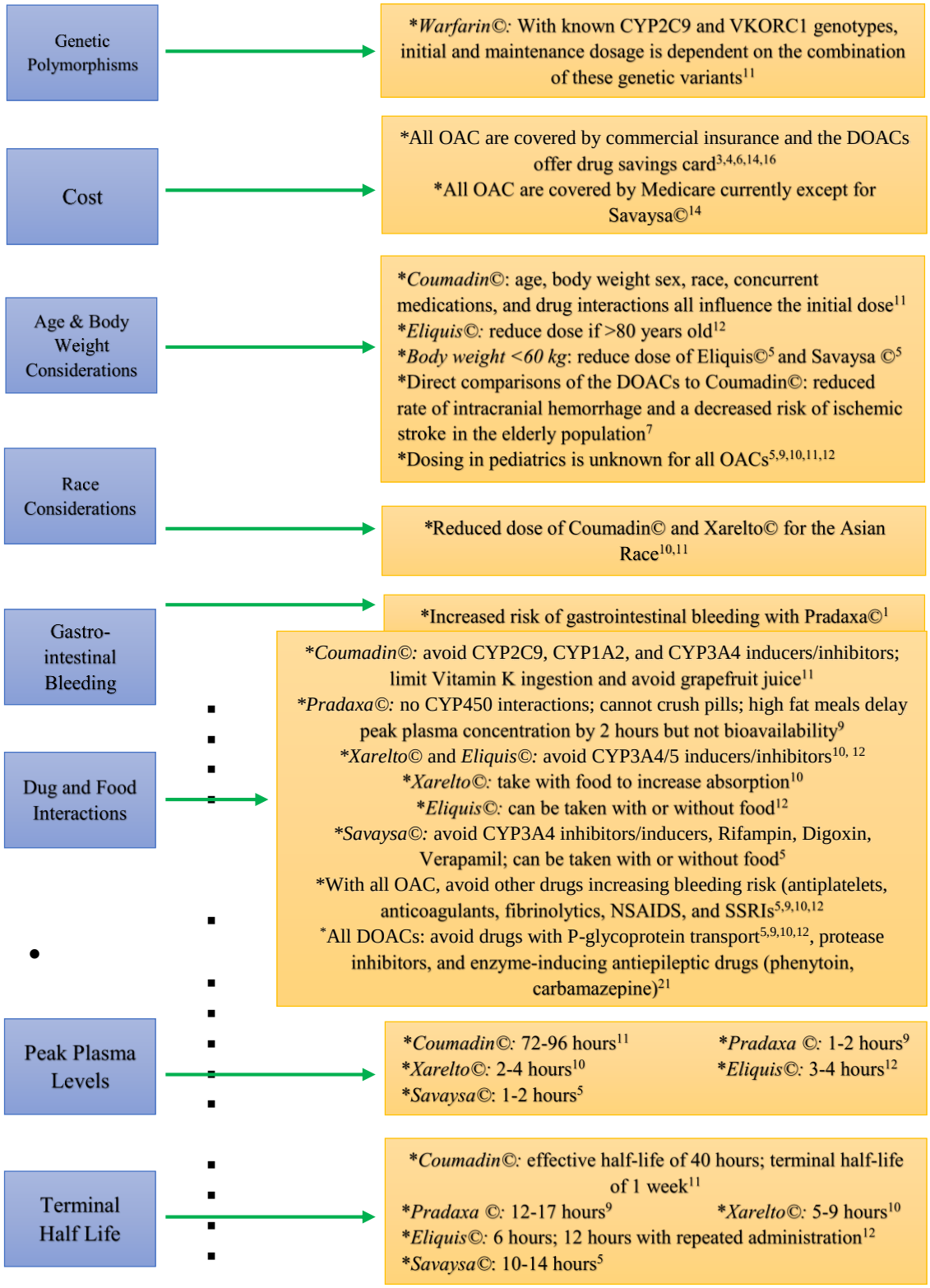
Cons	• Compliance with routine lab monitoring through INR to adjust warfarin dose[1] • Dietary restrictions of vitamin K[1] • Multiple drug-drug interactions[1] • May require a heparin bridge when initiating therapy[1]	• Require once or twice daily fixed dosing (shorter half-life)[1] • More expensive[1] • Contraindicated with concurrent protease inhibitors or phenytoin [1] • Contraindicated with chronic severe kidney disease (eGFR < 30 mL/min/1.73m^2)[1]. • Dosing unknown in patients with obesity[4]

Note: Adapted from 1) "Atrial fibrillation: Anticoagulant therapy to prevent embolization", W. Manning & D. Singer, 2016, www.uptodate.com; 2) "Management of warfarin-associated bleeding or supratherapeutic INR, R. Hull, & D. Garcia, 2016a; www.uptodate.com 3) "Management of bleeding in patients receiving direct oral anticoagulant", D. Garcia & M. Crowther, 2017, www.uptodate.com; 4) "Direct oral anticoagulants and parenteral direct thrombin inhibitors: Dosing and adverse effects", L. Leung, 2017, www.uptodate.com.

Patient Specific Factors Influencing Selection of an Oral Anticoagulant (OAC) for Atrial Fibrillation (1)



Patient Specific Factors Influencing Selection of an Oral Anticoagulant (OAC) for Atrial Fibrillation (2)



[1]American Geriatrics Society. (2015). American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *Journal of American Geriatric Society, 63,* 2227-2246. doi: 10.1111/jgs.13702
[2]Boehringer Ingelheim International. (2015). Praxbind [package insert]. Retrieved from http://docs.boehringeringelheim.com/Prescribing%20Information/PIs/Praxbind/Praxbind.pdf
[3]Boehringer Ingelheim International. (2016). Pradaxa Coverage and Savings. Retrieved from https://www.pradaxapro.com/coverage-savings
[4]Bristol-Myers Squibb. (2016). Eliquis Coverage and Reimbursement. Retrieved from http://www.eliquis.com/eliquis/hcp/coverage-reimbursement
[5]Daiichi Sankyo, Inc. (2015). Savaysa [package insert]. Retrieved from http://dsi.com/prescribing-informationportlet/getPIContent?productName=Savaysa&inline=true
[6]Daiichi Sankyo, Inc. (2017). Savaysa samples and savings cards. Retrieved from https://savaysahcp.com/registration
[7]Desai, Y., El-Chami, M.F., Leon, A.R., & Merchant, F.M. (2017). Management of atrial fibrillation in elderly adults. *Journal of American Geriatric Society, 65,* 185-193. doi:
[8]Drugs.com (2013, December). Vitamin K1 [package insert]. Retrieved from https://www.drugs.com/pro/vitamin-k1.html
[9]Drugs.com (2015a, November 11). Pradaxa [package insert]. Retrieved from https://www.drugs.com/monograph/pradaxa.html
[10]Drugs.com. (2015b, November 12). Xarelto [package insert]. Retrieved from https://www.drugs.com/monograph/ xarelto.html
[11]Drugs.com. (2015c, December). Coumadin [package insert]. Retrieved from https://www.drugs.com/pro/ coumadin-injection.html
[12]Drugs.com. (2016, January 20). Eliquis [package insert]. Retrieved from https://www.drugs.com/monograph/ eliquis.html
[13]Garcia, D.A., & Crowther, M. (2017, April 10). Management of bleeding in patients receiving direct oral anticoagulants. In. T.W. Post (Ed.), *UpToDate.* Waltham, MA: WoltersKluwer Health. Available from http://www.uptodate.com
[14]GoodRx (2017). Retrieved from www.goodrx.com
[15]Hu, T.Y., Vaidya, V.R., Asirvatham, S.J. (2016). Reversing anticoagulant effects of novel anticoagulants: Role of ciraparantag, andexanet alpha, and idarucizumab. *Vascular Health and Risk Management, 12,* pp. 35-44.
[16]Janssen Pharmaceuticals, Inc. (2016). Xarelto formulary coverage. Retrieved from https://www.xareltohcp.com/resources/formulary-coverage.html
[17]January, C.T., Wann, L.S., Alpert, J.S., Calkins, H., Ciagarroa, J.E., Cleveland, J.C., . . . Yancy, C.W. (2014, December 2). 2016 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive Summary. *Journal of the American College of Cardiology, 64*(21), pp. 2246-2280.
[18]Ruff, C.T., Giugliano, R.P., & Antman, E.M. (2016). Management of bleeding with non-vitamin K antagonist oral anticoagulation in the era of specific reversal agents. *Circulation, 134,* pp. 248-261. doi:10.1161/CIRCULATIONAHA.116.021831
[19]Samuelson, B.T., & Cuker, A. (2016). Measurement and reversal of the direct oral anticoagulants. *Blood Reviews, 31,* pp. 77-84.
[20]Samuelson, B.T., Cuker, A., Siegal, D.M., Crowther, M., & Garcia, D.A. (2017). Laboratory assessment of the anticoagulant activity of direct oral anticoagulants. *CHEST, 151*(1), pp. 127-138. doi:

- **Evidence-Based Recommendations for Diagnosing and Treating Atrial Fibrillation**

1)Reduce risk factors for atrial fibrillation (AF)

- ***PRIMARY PREVENTION***
- ***History and Physical:*** assess for comorbid conditions, stroke risk, symptoms associated with AF, the pattern of AF, and risk of thromboembolism or left ventricular dysfunction (*Class I, Level of Evidence C;* Kirchhof, et al., 2016*)*.
- ***Treat the offending disease to reduce AF onset***: obesity, heart failure, diabetes, chronic kidney disease, infection, hyperthyroidism, alcohol abuse, obstructive sleep apnea, and left ventricular hypertrophy (Centers for Disease Control and Prevention, 2015; Ganz & Spragg, 2016).
  - Hypertension is a prevalent factor in the etiology of 14 to 22% of atrial fibrillation patients (Centers for Disease Control and Prevention, 2015) and 1/3 of patients with AF have concurrent coronary artery disease (You et al., 2012).
  - Postoperative AF can be prevented through administration of amiodarone prior to the cardiac surgery (*Class IIa, Level of Evidence A;* January et al., 2014)
- The *strongest predictive factor of an ischemic stroke* is a prior stroke or transient ischemic attack (TIA), in addition to increasing age (>65 years of age), diabetes mellitus, sex (women) and hypertension (Kirchhof, et al., 2016).
- *Abnormal laboratory results* increasing an AF patient's risk of stroke include: labile INR (international normalized ratio) levels, low TTR (time in therapeutic range) while on warfarin, anemia, prior hemorrhage, elevated N-terminal pro-B-type natriuretic peptide, and high troponin T or I (Kirchhof, et al., 2016).
- *Echocardiograms* diagnose AF with valve disease in 30% of patients. *Valvular AF* classifies patients with mitral stenosis or mechanical heart valves.
  - With a diagnosis of severe mitral stenosis, referral for mitral valve surgery is recommended to decrease stroke risk (Kirchhof, et al., 2016).

2) Diagnose AF early through an annual pulse check in all symptomatic or asymptomatic patients ≥65 years old. If an irregular pulse is detected, confirm the rhythm through an EKG.

- ***Clinical manifestations of AF*** include: heart palpitations, dizziness, fatigue, shortness of breath (dyspnea), irregular heart rate, weakness, presyncope, and chest pain (Centers for Disease Control and Prevention, 2015; Kumar, 2016b).
- *Approximately 30% of AF patients present without symptoms*, yet this population demonstrates a higher CHA_2DS2-VASc score and thus a higher risk of stroke.
  - Over 20% of people with silent AF are not diagnosed until after their first stroke (Shahid, Shantsila, & Lip, 2016).
- ***SECONDARY PREVENTION:*** **Screening for atrial fibrillation is recommended by checking a pulse or obtaining an electrocardiogram strip annually in patients 65 years of age or older, as this is the best means to detect silent atrial fibrillation in patients** *(Class I, Level of Evidence B;* Kirchhof, et al., 2016; *Class IIa, Level of Evidence B;* Meschia, et al., 2014; Shahid, Shantsila, & Lip, 2016*)*.
  - A 12-lead EKG is necessary to diagnose AF, determine the rate of the dysrhythmia, and assess for ischemia, conduction defects, and other signs of structural heart disease *(Class I, Level of Evidence B;* Kirchhof, et al., 2016).
- Once AF is diagnosed, a transesophageal echocardiography (TEE) is recommended with all patients to evaluate for structural valve disease, atrial size, right heart function, and left ventricular size and function *(Class I, Level of Evidence C)*.
  - A TEE is useful to assess for thrombi in the left atrial appendage, suggesting earlier cardioversion or catheter ablation (Kirchhof, et al., 2016).
- Ambulatory EKG monitoring can be helpful to measure the effectiveness of rate control treatments, correlate symptoms with ectopy, and discover paroxysmal AF episodes (Kirchhof, et al., 2016).
- In patients who have suffered from an ischemic stroke or a transient ischemic attack, a rapid EKG followed by continuous EKG monitoring for 72 hours is recommended to assess for atrial fibrillation *(Class I, Level of Evidence B;* Kirchhof, et al., 2015; Shahid, Shantsila, & Lip, 2016*)*.
- ***Labs for a New Diagnosis of AF:*** thyroid stimulating hormone and free T4, complete blood count, serum creatinine, urinalysis for proteinuria, tests for diabetes mellitus (Kumar, 2016b), and serum electrolytes (Kirchhof, et al., 2016).

3) If a patient has AF, assess for bleeding and stroke risk through the HAS-BLED and CHA_2DS_2-VASc scores respectively to determine if the patient is a candidate for oral anticoagulation.

- ***Stroke risk:*** CHA_2DS_2VASc is recommended over $CHADS_2$ to assess for stroke risk with nonvalvular (nonrheumatic) AF as the former highlights more risk factors and demonstrates a better ability to predict patients with a low, moderate, or high stroke risk (Lane & Lip, 2012).
  - $CHADS_2$ is recommended by the Chest Guidelines through validation of evidence and ease of use (You et al., 2012).
  - CHA_2DS_2VASc is recommended by the European Society of Cardiology *(Class I, Level of Evidence A;* Kirchhof, et al., 2016), American Heart Association, American College of Cardiology, and Heart Rhythm Society *(Class I, Level of Evidence B*, January, et al., 2014),

and the American Stroke Society (Meschia, et al., 2014) to assess the stroke risk and necessity of anticoagulation with AF.
    - With a diagnosis of hypertrophic cardiomyopathy, lifetime anticoagulation with AF is recommended to decrease the risk of stroke, regardless of the CHA_2DS_2-VASC2 score (*Class I, Level of Evidence B;* January, et al., 2014; *Class I, Level of Evidence B;* Kirchhof, et al., 2016)

- ***Bleeding risk***
    - *Overemphasizing bleeding risk is a predominant limiting factor in providers prescribing oral anticoagulation, especially to the elderly* (You, et al., 2012).
    - *Currently data has been inadequate to add recommendations to guidelines on assessing bleeding risk with anticoagulation through a validated tool,* however, screening for bleeding risk should still be calculated through HAS-BLED, $HEMORR_2HAGES$, or another evidence-based tool and incorporated into the individualized treatment plan to help in the selection of anticoagulation (You et al., 2012).
        - The American Heart Association and American Stroke Association endorse the HAS-BLED score to assess for bleeding risk with anticoagulation for AF (Meschia, et al., 2014).
        - A meta-analysis and systematic review of HAS-BLED, $HEMORR_2HAGES$ and ATRIA concluded HAS-BLED displays a better ability to predict severe bleeding risk in patients with atrial fibrillation, has increased sensitivity, and is more user friendly (Caldeira, et al., 2014).
    - The purpose of bleeding scores is to not deter providers from prescribing anticoagulants but rather to *discover and adjust modifiable risk factors to reducing bleeding risk* (Kirchhof, et al., 2016; Lane & Lip, 2012).
- **Research has demonstrated CHA_2DS_2-VASc scores and HAS-BLED scores are a simple and efficient means to assess whether anticoagulation is appropriate for a patient, without warranting further testing or lab work** (Shahid, Shantsila, & Lip, 2016).

4) Prescribe the patient specific anticoagulant with a CHA_2DS_2-VASc score ≥2 and a low risk of bleeding. Consider anticoagulating with a $CHA2DS_2$-VASc score of 1, dependent on patient preference and clinical judgment.

- **CHA_2DS_2VASc score of 0**: anticoagulation is not recommended (*Class IIa, Level of Evidence C;* January, et al., 2014; Manning, Singer, & Lip, 2016; *Class IIa, Level of Evidence B;* Meschia, et al., 2014; *Grade 2B,* You et al., 2012).

- **CHA_2DS_2VASc score of 1**: Multiple treatment options are appropriate depending on patient preference, including no anticoagulant, aspirin, or an oral anticoagulant contributing (*Class IIb, Level of Evidence C*; January et al., 2014; *Class IIb, Level of Evidence C,* Meschia, et al., 2014).
    - Anticoagulant therapy for a CHA_2DS_2VASc score of 1 is prescribed based on clinical judgment, with age 65-74 years old, hypertension, and diabetes as more significant risk factors to disease onset compared to female sex and vascular disease (Manning, Singer, & Lip, 2016).

- **CHA_2DS_2VASc score of ≥2**: chronic anticoagulation is suggested to decrease the risk of stroke (*Grade 1a;* Manning, Singer, & Lip, 2016).
    - The *American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS)* propose oral anticoagulation with a $CHA_2DS_2VAS_c$

score ≥2, history of prior stroke, or history of prior transient ischemic attack, recommending warfarin *(Class I, Level of Evidence A)*, dabigatran, rivaroxaban, or apixaban as suitable anticoagulants (*Class I, Level of Evidence B;* January, et al., 2014; *Class I, Level of Evidence B;* Meschia, et al., 2014*)*.

- The only approved anticoagulant for moderate to severe mitral valve disease (valvular AF) or mechanical heart value replacement is warfarin (*Class I, Level of Evidence B,* January, et al., 2014; *Class I, Level of Evidence B;* Kirchhoff, et al., 2016;), with a target INR of 2.0-3.0 (*Grade 1B,* You, et al., 2012).
- If a patient is unable to take an oral anticoagulant, dual antiplatelet therapy with aspirin and clopidogrel is recommended (*$CHADS_2$ score >2, Grade 1B;* You, et al., 2012; Manning, Singer, & Lip, 2016).
- With a CHA_2DS_2-VASc score ≥2, regardless of bleeding risk as well as with an elevated bleeding and stroke risk, dabigatran, rivaroxaban or apixaban have demonstrated superiority to warfarin (Lane & Lip, 2016).
-

- Oral anticoagulants have proven superiority in preventing stroke with AF compared to antiplatelets such as aspirin (Manning, Singer, & Lip, 2016). Due to the heightened bleeding risk, aspirin is not considered safe as monotherapy (Shahid, Shantsila, & Lip, 2016).
- Direct oral anticoagulants (DOACS)- dabigatran, apixaban, edoxaban, and rivaroxaban- have demonstrated non-inferiority to warfarin in preventing stroke with AF (Manning, Singer, & Lip, 2016), yet demonstrate superiority in a reduction of severe bleeding (a decrease in bleeding by 30-50%; Shahid, Shantsila, & Lip, 2016).
- Due to the increased bleeding risk, combination therapy of platelet inhibitors and oral anticoagulants is contraindicated after a stroke (*Class III Harm, Level of Evidence B;* Kirchhoff, et al., 2016*)*.

- ***Most Current National and International Guidelines for Anticoagulation with Atrial Fibrillation***

  - **American Heart Association, American College of Cardiology, Heart Rhythm Society:**

  January, C.T., Wann, L.S., Alpert, J.S., Calkins, H., Ciagarroa, J.E., Cleveland, J.C., . . . Yancy, C.W. (2014, December 2). 2016 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive Summary. *Journal of the American College of Cardiology, 64*(21), pp. 2246-2280.

  - **American Heart Association and American Stroke Association:**

  Meschia, J.F., Bushnelll, C., Boden-Albala, B., Braun, L.T., Bravata, D.M., Chaturvedi, S. . . . Wilson, J.A. (2014). Guidelines for the primary prevention of stroke. A Statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 45,* pp. 3754-3832. doi: 10.1161/STR.0000000000000046

  - **CHEST Guidelines:**

  You, J. J., Singer, D. E., Howard, P. A., Lane, D. A., Eckman, M. H., Fang, M. C., … Lip, G. Y. H. (2012). Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest, 141*(2 Suppl.), e531S-e575S. Retrieved from http://journal.publications.chestnet.org/article.aspx?articleID=1159549

- **European Society of Cardiology:**

Kirchhof, P., Benussi, S., Kotecha, D., Ahlsson, A., Atar, D., Casadei, B., . . . Vardas, P. (2016). 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eurospace*. doi: 10.1093/eurospace/euw295

When to Refer Atrial Fibrillation to a Specialist

- Hemodynamic instability (severe symptoms)
- History of transient ischemic attack or stroke necessitating anticoagulation
- Symptomatic bradycardia
- Poor rate control (fast heart rate)
- Deteriorating left ventricular function
- Severe angina
- Assessment for rhythm control
- Special conditions: thyrotoxicosis, sepsis, or postoperative AF (Kirchhof, et al., 2016).

Phone Apps

- **American College of Cardiology- Guideline Clinical App**
  - This free, updated, and comprehensive phone app provides the following resources for providers managing atrial fibrillation:
    - *Executive Summary* (diagnosis, risk factors, treatments for rate control, rhythm control, and reducing thromboembolic risk)
    - *10 points* (key tips for managing non-valvular AF))
    - *Severity of AF Scale* (quality of life assessment with AF)
    - *CHA2DS2-VASc score* (calculator)
    - *HAS-BLED score* (calculator)
    - *NV-AF OAC Calculator* (calculator to select oral anticoagulation doses for patients with chronic kidney disease)
    - *Rate Control Strategy* and *Rate Control Dosing*
    - *Rhythm Control Strategy* and *Rhythm Control Dosing,*
    - *Patient Resources* – link to www.cardiosmart.org- this patient-specific website provides a question and answer section for patients, background information on atrial fibrillation, patient responsibilities to manage this disease, resources for support groups, the AF care team, and latest research.

- **American College of Cardiology Anticoag Evaluator**
  - Prescribes patient specific anticoagulation through calculation of creatinine clearance (Cockcroft-Gault equation), HAS-BLED, CHA2DS2-VASc and consideration of concomitant medications
  - Summarizes clinical drug trials and provides full prescribing information for oral anticoagulants
  - This app can also be accessed through the **American College of Cardiology-Guideline Clinical Apps**

- ***Shared Decision-Making Tool:*** **http://mybloodclots.org**
  - **The Society of Vascular Medicine** created an online shared decision-making tool for patients and providers to aid in the selection of anticoagulants.
    - The first series of questions assesses for risk factors for AF, kidney and liver function, concurrent medications, and mechanical valve surgery.
    - The next set of questions addresses the patient's preference for medications: newer versus an older agent, lab monitoring, independent versus standardized dosing, and cost. Based upon these results, the anticoagulant warfarin or a DOAC (direct oral anticoagulant) – apixaban, rivaroxaban, dabigatran, or edoxaban- is provided to the patient with supporting rationale.
    - In addition, the bleeding and stroke risks while on anticoagulation are calculated for the patient and explained in depth.
    - This tool highlights factors for the patient to take into consideration when selecting an anticoagulant, such as drug interactions, pregnancy, checking INRs while on vacation, stopping anticoagulants prior to surgery, and the consumption of alcohol and smoking while on anticoagulation.
    - The algorithm does not clarify whether the patient qualifies for anticoagulation, no anticoagulation, or aspirin; the algorithm merely addresses the appropriate anticoagulation based upon individualized patient preference and medical history (Society for Vascular Medicine, 2015).

- ***Performance and Quality Measures Related to AF Management***
  - In 2016, the American College of Cardiology and American Heart Association released performance and quality measures related to AF management in the inpatient and outpatient settings, to improve the management, safety, and care coordination of these patients.
  - Performance measures for the outpatient setting include:
    - Documentation of a completed CHA_2DS_2-VASc score
    - Prescribing anticoagulation when appropriate
    - Completing monthly INRs for patients on warfarin.
  - Quality measures include:
    - Prescribing a beta blocker with a left ventricular ejection fraction <40%
    - Not prescribing a direct thrombin inhibitor or factor Xa inhibitor with mechanical heart values, end-stage kidney disease, or dialysis.
    - Not prescribing oral anticoagulants and antiplatelets (unless the patient has coronary artery disease or vascular disease) to reduce bleeding risk
    - Not prescribing a calcium channel blocker with reduced ejection failure heart failure
    - The necessity of shared decision making between the patient and provider when prescribing anticoagulation (Heidenrich, et al., 2016).

Atrial fibrillation Management Team Approach

- The European Society of Cardiology recommends the following approach to manage AF successfully:
  1) *Patient involvement:* patient education, patient empowerment, reduction of risk factors, lifestyle modifications, and shared decision making
  2) *Multidisciplinary team:* primary care providers, cardiologists, AF specialists, surgeons, and allied health providers working together collaboratively
  3) *Navigation system for providers and* patients: tools and checklists to improve communication, clinical decision support, availability of information on AF, the ability to monitor the compliance and effectiveness of the treatment plan
  4) Complex management decisions: anticoagulation, rate control, lifestyle modifications, antiarrhythmics, and catheter and surgical options
- The goals of this integrated approach to AF management include:
  - Reduction of hospitalizations
  - Enhanced patient adherence to the treatment plan by incorporating patient preference into the decision-making process
  - Improved patient outcomes
  - Decreased mortality (Kirchhof, et al., 2016)

The Basics of Rate vs. Rhythm Control Strategies to Control Symptoms

- ***Rate control*** utilizes medications decreasing atrioventricular (AV) node conduction, including beta-blockers, digoxin, and non-dihydropyridine calcium channel blockers (diltiazem or verapamil; Kirchhof, et al., 2016; Kumar, 2016b).
  - With an LVEF ≤40%, beta-blockers and/or digoxin is suggested, while with an LVEF ≥40%, beta-blockers, digoxin, and a calcium channel blocker are recommended *(Class I, Level of Evidence B)*.
  - The goal of rate control therapies is a resting heart rate less than 110 beats per minute while avoiding bradycardia *(Class IIa, Level of Evidence B;* Kirchhof, et al., 2016).
  - Rate control tends to simplify the treatment regimen, costs less, and eliminates the risks associated with antiarrhythmics and catheter ablation (Kirchhof, et al., 2016).
  - Rate control is preferred in asymptomatic or mildly symptomatic patients 65 years of age and older (Kumar & Manning, 2016), in addition to pregnant women with AF *(Class IIa, Level of Evidence C;* Kirchhof, et al., 2016).
  - Rates of thromboembolism are comparable between rhythm and rate control therapies (You, et al., 2012).

- ***Rhythm control*** utilizes antiarrhythmic drugs, percutaneous catheter ablation, and/or surgery (Kumar & Manning, 2016) and is recommended in patients who are unable to remain asymptomatic with rate control medications *(Class I, Level of Evidence B;* Kirchhof, et al., 2016).
  - Flecainide, propafenone, or beta blockers are preferred antiarrhythmics in patients without structural heart disease, bradycardia, or tachycardia (Kumar, 2016a).
  - Dronedarone or statolol is preferred for coronary heart disease (Kumar, 2016a).
  - The combination of amiodarone and dofetilide is preferred with heart failure (Kumar, 2016a).

- Nondihydropyridone calcium channel blockers are contraindicated with heart failure (*Class IIb, Level of Evidence C;* January, et al., 2014).
- Rhythm control is used more frequently in younger patients (< 65 years old) to regain normal sinus rhythm, recurrent symptoms despite rate control, and persistent AF with irreversible remodeling of the heart (Kumar & Manning, 2016).
- Other options to achieve normal sinus rhythm include atrioventricular (AV) node ablation and ventricular pacing (Kumar and Manning, 2016) in AF resistant to medication management, yet the majority of these patients eventually require pacemaker implantation to control the ventricular rate (Kirchhof, et al., 2016).

○ *Left Atrial Appendage Closure (WATCHMAN©)*

- Percutaneous left atrial appendage (LAA) procedures such as WATCHMAN© are a surgical alternative for patients with contraindications to long-term anticoagulation within the United States and Europe (Hijazi & Saw, 2016).
- With non-valvular AF, >90% of blood clots from the left atrium originate in the left atrial appendage; implantation of WATCHMAN© traps clots in the LAA (Boston Scientific, 2016).
- Under general anesthesia within the catheterization lab and with the guidance of fluoroscopy and transesophageal echocardiography (TEE) to ensure accurate LAA measurement and fit, WATCHMAN© is inserted through the femoral vein, advanced transseptally into the left atrium, and finally implanted into the LAA (Boston Scientific, 2016).
- WATCHMAN© requires an hour to implant and approximately a one-day hospital admission. This device is permanent and requires a one-time insertion (Boston Scientific, 2016).
- Post implant, patients are required to take aspirin and warfarin for a minimum of 45 days to ensure the LAA is encapsulated by heart tissue (confirmed by a TEE), followed by clopidogrel and a higher dose of aspirin for six months, and finally aspirin for life.
- Compared to warfarin, LAA closure has demonstrated a 52% reduction in cardiovascular death, a 72% decrease in severe bleeding six months after the procedure, and a 78% decrease in hemorrhagic stroke (Boston Scientific, 2016).
- LAA has an increased risk of pericardial effusion, excessive bleeding, and procedure-related complications compared to warfarin (You, et al., 2012).
- Evidence has demonstrated LAA closure is non-inferior to warfarin in preventing stroke in AF patients, with reduced bleeding risk (Meschia, et al., 2014).
- LAA is endorsed by the American Heart Association, American Stroke Association, and European Society of Cardiology (*Class I, Level of Evidence B;* Kirchhof, et al., 2016; *Class IIb, Level of Evidence B;* Meschia, et al., 2014).

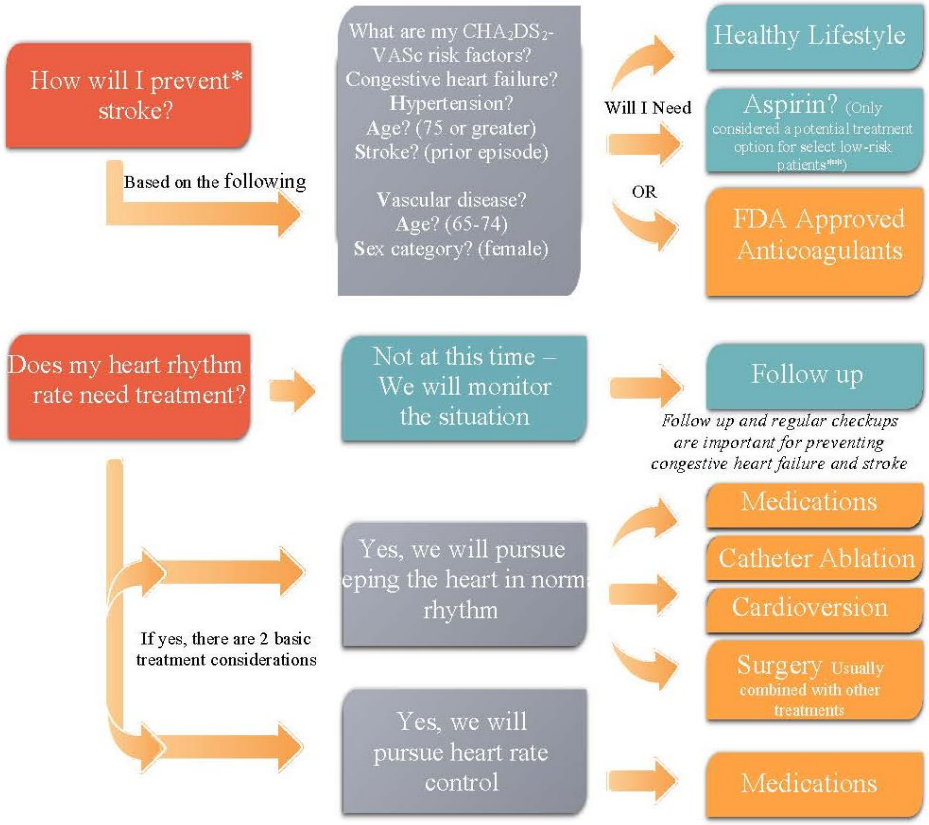
○ *Summaries of Drug Trials for Anticoagulation*

http://www.anticoagulant-trials.eu/introduction.html

SIMPLIFYING YOUR ATRIAL FIBRILLATION TREATMENT PLAN

American Heart Association | American Stroke Association

Encourage your patients to take an active role in their healthcare by using this tool to help them understand appropriate treatment options available for them.



*Afib risk factors linked to **vascular disease history** include Prior heart attack, Peripheral artery disease, aortic plaque prevention.*

It is very important to take risk reduction measures even though no method or treatment can guarantee prevention. Know the warning signs for stroke and call 9-1-1 immediately if you experience them.

**Select low-risk patients include those with non-valvular Afib and a CHA_2DS_2-VASc score of 1.*

Adapted from "Simplifying your atrial fibrillation treatment plan," American Heart Association & American Stroke Association, 2016. Retrieved from https://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable/ucm_324032.pdf. Copyright by the American Heart Association.

○ *Severity of Atrial Fibrillation (SAF) Scale*

Use this document to assess and record the symptoms and functionality of patients with atrial fibrillation.

➢ **Step 1 – Symptoms**

Identify the presence of the following symptoms (check all that apply):

- ⌋ **Palpitation**
- ⌋ **Dyspnea**
- ⌋ **Dizziness, presyncope, or syncope**
- ⌋ **Chest pain**
- ⌋ **Weakness or fatigue**
- ⌋ **Other:**

➢ **Step 2 – Association**

Is AF, when present, associated with the above-listed symptoms? For example: Ascertain if any of the above symptoms are present during AF and likely caused by AF (as opposed to some other cause).

Yes
No

➢ **Step 3 – Functionality**

Do the identified symptoms associated with AF (or the treatment of AF) affect the patient's functionality (subjective quality of life)? Refer to the table below for descriptions your patient might give.

Yes
No

Based on the responses above, assign an **SAF Class** as defined by the table below:

SAF Class	Definition
Class 0	Asymptomatic with respect to AF
Class 1	Symptoms attributable to AF have ***minimal*** effect on patient's general QOL. • minimal and/or infrequent symptoms, or • single episode of AF without syncope or heart failure
Class 2	Symptoms attributable to AF have a ***minor*** effect on patient's general QOL. • mild awareness of symptoms in patients with persistent/permanent AF, or • rare episodes (e.g. less than a few per year) in patients with paroxysmal or intermittent AF
Class 3	Symptoms attributable to AF have a ***moderate*** effect on patient's general QOL. • moderate awareness of symptoms on most days in patients with persistent/permanent AF, or • more common episodes (e.g. more than every few months) or more severe symptoms, or both, in patients with paroxysmal or intermittent AF
Class 4	Symptoms attributable to AF have a ***severe*** effect on patient's general QOL. • very unpleasant symptoms in patients with persistent/paroxysmal AF and/or • frequent and highly symptomatic episodes in patients with paroxysmal or intermittent AF and/or • syncope thought to be due to AF and/or • congestive heart failure secondary to AF

Adapted from "Severity of atrial fibrillation (SAF) scale," American College of Cardiology, 2012. Retrieved from http://acc.org.

- ***Evidence for Anticoagulating the Elderly with Atrial Fibrillation***

  - When anticoagulating the elderly, a clinician should consider factors such as polypharmacy, impaired cognition, fall risk, comorbidities contributing to bleeding risk, chronic kidney disease, nutritional status, and weight (Barbosa & Falcao, 2016). Other factors to investigate include compliance to the treatment plan, health literacy, ability to obtain medications and INR monitoring, adverse drug effects, cognition, family support, and the patient-provider relationship (Foody, 2017).
  - Advanced age ≥65 years old is a risk factor for thromboembolism, yet is also a risk factor for increased bleeding risk. For an AF patient on long-term anticoagulation, this patient could fall 300 times annually before the risk of bleeding offsets the risk of anticoagulation use (Barbosa & Falcao, 2016).
    - Another study suggests patients would have to fall over 5.7 times per week before the risk-benefit ratio would favor no anticoagulation (Janssen, 2014a).
  - Despite the three-fold risk of strokes in patients older than 75 years old, only 30% to 50% of applicable patients receive anticoagulation. In studies examining stroke prevention in elderly nonvalvular atrial fibrillation patients, the DOACs rivaroxaban, apixaban, and dabigatran have demonstrated improved efficacy and safety compared to warfarin (Barbosa & Falcao, 2016).
  - A study in the New England Journal of Medicine concluded 2/3 of hospitalizations for patients 65 years of age and older are related to accidental overdoses of four high-risk medications: warfarin (33.3%), oral antiplatelet medications (13.3%), insulins (13.9%), and oral hypoglycemic medications (10.7%; Budnitz, et.al., 2011).
  - The safety of anticoagulation studies is assessed for the risk of severe bleeding: the risk of intracranial hemorrhage is stable from age 60 to 80 years, yet rises greatly after 80 years old regardless of anticoagulation status, suggesting increasing age alone may be sufficient to increase bleeding risk (Desai, El-Chami, Leon, & Merchant, 2016).
  - A net clinical benefit (NCB) infers all elderly patients with AF 65 years of age or older and with at least a CHA_2DS_2-VASc score ≥1 would benefit from anticoagulation (Desai, El-Chami, Leon, & Merchant, 2016).
  - **Comparisons of the DOACs (apixaban, edoxaban, rivaroxaban, and dabigatran) to warfarin have demonstrated a reduced rate of intracranial hemorrhage and a decreased risk of ischemic stroke in the elderly population.**
    - Regardless of the anticoagulant, the intracranial bleeds occur in less than 1% of the population annually (Desai, El-Chami, Leon, & Merchant, 2016).
  - With increasing age, the ability to metabolize drugs slows, thus the weekly dose of warfarin should decrease 0.4 mg/year to prevent supratherapeutic levels and thus augmented bleeding risk (Desai, El-Chami, Leon, & Merchant, 2016).
  - Elderly patients with AF should strive for a heart rate control less than 80 bpm, moving to a rhythm strategy (with anticoagulation) or catheter ablation with failure to control symptoms. (Desai, El-Chami, Leon, & Merchant, 2016).
  - A novel study examined 23,356 patients with AF age 80 to 100 years old who had suffered a recent ischemic stroke from 2006 to 2013. Approximately 27% patients were started on anticoagulation after the stroke, demonstrating less recurrent strokes and only an increased incidence of bleeding in patients older than 90 years old. The study concluded even this increased bleeding risk in the older population did not outweigh the benefits of anticoagulation to prevent recurrent ischemic strokes (Appelros, Farahmand, Terént, & Asberg, 2017).

- **American Geriatric Society 2015 Beers criteria**
  - Highlights medications deemed high risk for the elderly population, emphasizes specific recommendations for cautious use of aspirin, warfarin, and dabigatran in this population.
  - *Aspirin* to prevent cardiovascular events should be used cautiously in patients 80 years of age or older (*low quality of evidence, strong strength of recommendation*), due to insufficient data showing a risk-benefit ratio.
  - *Dabigatran* should be used cautiously in patients 75 years of age or older with a CrCl <30 mL/min, as Dabigatran has demonstrated an increased risk of gastrointestinal bleeding in comparison to warfarin.
  - Due the increased risk of bleeding, the combination of *warfarin and amiodarone* should be avoided (*moderate quality of evidence, strong strength of recommendation*), in addition to the combination of *warfarin and NSAIDS* (*high quality of evidence, strong strength of recommendation*).
  - The dose of DOACs should be reduced with a CrCl <30 mL/hr (*moderate level of evidence, strong strength of recommendation*; American Geriatrics Society, 2015).

○ *Reversal Agents for Anticoagulants*

- With minor bleeding such as epistaxis or ecchymosis, applying manual compression to control the source of bleeding and stopping the anticoagulant with high bleeding risk, are appropriate treatments (Hu, Vaidya, & Asirvatham, 2016).
- With major bleeding, cessation of the offending anticoagulant is warranted, as well as administration of intravenous fluids, packed red blood cells, and platelet transfusions as needed (Hu, Vaidya, & Asirvatham, 2016).
- Methods to reduce bleeding risk include hypertension control, using an agent other than dabigatran at patients with high risk of gastrointestinal bleeding, and reducing alcohol consumption (Kirchhof, et al., 2016).

- **Warfarin**
  - If the patient develops life-threatening bleeding while on warfarin, the reversal agent for warfarin is vitamin K_1 (Hull & Garcia, 2016a).
  - With an INR <5, the warfarin dose can be reduced or omitted until the INR nears the normal range (Hirsh, Fuster, Ansell, & Haperin, 2003).
  - With an INR between 5 and 9 without bleeding, the next one to two warfarin doses are held with the dose lowered when the INR approaches normal, or vitamin K_1 (1.5 to 2.5 mg) can be administered by mouth if the risk of bleeding is high. If rapid reversal of warfarin is necessitated, vitamin K_1 (2.0 to 5.0 mg) can be given orally. If the INR is not therapeutic within 24 hours, another dose of vitamin K_1 (1.0 or 2.0 mg) can be administered (Hirsh, Fuster, Ansell, & Haperin, 2003).
  - With an INR >9 but without bleeding, vitamin K_1 (3.0 to 5.0 mg) can be given by mouth, with a drop in the INR within 24 to 48 hours (Hirsh, Fuster, Ansell, & Haperin, 2003).
  - With an INR >20 or severe bleeding, vitamin K_1 (10 mg) should be given intravenously, followed by fresh plasma or prothrombin complex concentrate; extra vitamin K_1 may be given every 12 hours as needed (Hirsh, Fuster, Ansell, & Haperin, 2003).
  - In the presence of life-threatening bleeding, prothrombin complex with 10 mg vitamin K_1 intravenously is the treatment of choice, repeated as needed.

High doses of vitamin K_1 should be avoided if possible, as resistance to warfarin can occur for a duration of one week after reversal with vitamin K_1. If warfarin is administered after vitamin K_1, heparin bridging may be necessary to achieve therapeutic INRs (Hirsh, Fuster, Ansell, & Haperin, 2003).

- **DOACs**
  - Activated charcoal (dabigatran and apixaban; Garcia & Crowther, 2017) and hemodialysis (dabigatran) are methods to *remove* NOACs from the body (Samuelson & Cuker, 2016), especially in the case of drug overdoses (Garcia & Crowther, 2017; Hu, Vaidya, & Asirvatham, 2016).
  - Nonspecific prothrombin complex concentrate, activated prothrombin complex concentrate (PCC), and recombinant factor VIIa are means to *bypass* coagulation pathways (Hu, Vaidya & Asirratham, 2016; Ruff, Giugliano & Antman, 2016; Samuelson & Cuker, 2016).
  - The intravenous drug-specific agents bind to the NOAC molecule to reverse the anticoagulant effects: Idarucizumab (humanized monoclonal antibody fragment) *sequesters* dabigatran, and Andexanet alpha (factor Xa decoy) and Ciparantag (synthetic cationic molecule) are two factor Xa inhibitors currently undergoing clinical investigation.
    - If approved by the FDA as a universal reversal agent, Ciparantag could also reverse the anticoagulant effects of dabigatran and heparin (Hu, Vaidya & Asirratham, 2016; Ruff, Giugliano & Antman, 2016; Samuelson & Cuker, 2016).
  - In the presence of life-threatening bleeding or emergency surgery, edoxaban, rivaroxaban, and apixaban can be reversed with 4-factor PCC 50 IU/kg, which contains clotting factors, heparin, and coagulation inhibitors protein C and protein S (Garcia & Crowther, 2017; Ruff, Giugliano, & Antman, 2016).
    - Neither vitamin K_1 can reverse DOACs, nor can fresh-frozen plasma (Ruff, Giugliano, & Antman, 2016).
    - If major bleeding occurs during or post procedure, antifibrinolytics such as tranexamic and Ɛ-aminocaproic acid are cost effective and safe options (Garcia & Crowther, 2017; Hu, Vaidya & Asirvatham, 2016).

Switching Between Warfarin and DOACS

- **DOAC to Warfarin**
  - Factors to consider when switching from a DOAC to warfarin and vice versa include cost, interactions, and availability (Manning, Singer, & Lip, 2016).
  - A minimum of a two-day overlap is recommended when switching from a DOAC to warfarin. A DOAC can alter the accuracy of INR levels for warfarin dosing, thus edoxaban and apixaban should be continued until the INR is ≥ 2.0 (Manning, Singer, & Lip, 2016).
  - A recommended regimen when transitioning from any of the four approved DOACS (dabigatran, apixaban, edoxaban, and rivaroxaban) to warfarin suggests a reduced dose of the DOAC, INR testing for a goal of ≥ 2.0, and adjusted dose of warfarin for up 14 days (or until the INR is therapeutic) to decrease the risk of bleeding and stroke (Manning, Singer, & Lip, 2016).
  - Parental agents are used concurrently with the DOAC as needed to achieve a therapeutic INR quicker (Manning, Singer, & Lip, 2016).

- A longer overlap is recommended between warfarin and dabigatran or if the creatinine clearance is prolonged (Drugs.com, 2015a).

- **Warfarin to DOAC**
  - When switching to apixaban (Drugs.com, 2016) or dabigatran (Drugs.com, 2015a), warfarin can be discontinued, followed by initiating the DOAC once the INR is <2.0.
  - For rivaroxaban, warfarin can be discontinued, followed by starting the DOAC once the INR is <3.0 (Drugs.com, 2015b).
  - When switching between DOAC agents, the current DOAC should be stopped when the new DOAC is administered at the standard dose time; no period of overlap between drugs is necessary (Guimaraes, Kaatz, & Lopes, 2015; Manning, Singer, & Lip, 2016).
  - For edoxaban, warfarin can be discontinued, followed by starting the DOAC once the INR is 2.5 (Daiichi-Sankyo Inc, 2015; Guimaraes, Kaatz, & Lopez, 2015).

Cessation of Anticoagulants Prior to Invasive Procedures and Surgery

- **Warfarin**
  - Warfarin is usually stopped four to five days before surgery for the INR to decrease to <1.2.
  - For up to two to three days postoperative, the patient is at risk for a thromboembolism. As a result, prophylactic doses of heparin or low molecular weight heparin can be administered every 12 hours for four to five days until the INR becomes therapeutic again (Hirsh, Fuster, Ansell, & Halperin, 2003).

- **DOACs**
  - ***Rivaroxaban:*** Rivaroxaban is discontinued 24 hours pre-procedure and can be resumed six to ten hours after hemostasis is achieved post-procedure (Drugs.com, 2015b).
  - ***Dabigatran:*** With a creatinine clearance >50 mL/min, Dabigatran should be held one to two days prior to the procedure. With a creatinine clearance <50 mL/min, Dabigatran should be held three to five days prior to the procedure (Drugs.com, 2015a).
  - ***Apixaban:*** Apixaban should be discontinued 48 hours pre-procedure in patients with a moderate to high risk of bleeding, or 24 hours pre-procedure with a low risk of bleeding. The anticoagulant should be resumed 12 to 24 hours post-procedure after hemostasis is achieved (Drugs.com, 2016).
  - ***Edoxaban:*** Recommendations suggest Edoxaban be discontinued 24-hours pre-procedure with a high risk of bleeding, then should be resumed as soon as hemostasis is achieved.
    - Indwelling intrathecal catheters and epidural catheters should not be removed less than 12 hours after the last dose of Edoxaban to prevent bleeding; the next dose should be given two hours after the catheter is removed (Daiichi, 2015).

- **American College of Cardiology 2017 expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation**
  - The ACC recommends assessing for stroke risk via the CHA_2DS_2-VASc (rather than the $CHADS_2$) score and utilizing a bleeding risk score through HAS-BLED to identify risk factors for bleeding.
  - Key components to assess prior to interruption of anticoagulation therapy include the need to interrupt (low, intermediate, or high risk of bleeding periprocedural), when to interrupt, the need to bridge with a parenteral anticoagulant post-procedure, how to bridge, and when to restart oral anticoagulants (Doherty, et al., 2017).

Lab Monitoring for Anticoagulants

- ***Maintenance of OACs:*** A complete blood count should be obtained every six months with all oral anticoagulants to assess for bleeding. Renal function for all the DOACs should be obtained at least annually, as well as hepatic function for rivaroxaban and apixaban annually (January et al, 2014).
- **Cockcroft-Gault Creatinine Clearance (CrCl) = (140 - age) x (weight in kg) x (0.85 if female) / (72 x creatinine in mg/dL)**
- ***DOACs:*** Routine lab monitoring is not required as these drugs are administered in fixed dose regimens (Hu, Vaidya, & Asirvatham, 2016; Samuelson & Cuker, 2016; Samuelson, et al., 2017).
  - Situations warranting lab monitoring include an epidural, severe bleeding, emergency surgery, or a stroke patient who may require thrombolysis.
    - A dilute thrombin time (dTT), thrombin time (TT) or ecarin clotting time (ECT) are available for dabigatran anticoagulation effects and anti-Xa assays with drug-specific calibrators for rivaroxaban, edoxaban, and apixaban (Hu, Vaidya, & Asirvatham, 2016; Samuelson & Cuker, 2016; Samuelson, et al., 2017).
    - Dabigatran levels can also be measured through dTT or aPTT (activated partial thromboplastin time) or INR for the factor Xa inhibitors (rivaroxaban, edoxaban, and apixaban; (Samuelson & Cuker, 2016; Samuelson, et al., 2017).
- ***Warfarin:*** The INR (international normalized ratio) was created by the World Health Organization in 1982 to standardize the prothrombin time (PT) to consistently and safely measure the effectiveness of warfarin (Jaffer & Bragg, 2003).

Basics of INRs and Warfarin Dosing

- **Dosing Nomogram**
  - As warfarin is contraindicated during pregnancy, a urine hCG (human chorionic gonadotropin) is recommended prior to initiating warfarin and as needed to assess for pregnancy in women of child bearing age (University of Colorado Health North, 2015).
  - The anticoagulant effects of warfarin occur two to seven days after starting the drug, thus if rapid anticoagulation is needed, bridging with heparin should occur for at least four days (University of Colorado Health North, 2015).
  - A dosage of 5-10 mg warfarin is initiated on day one, adjusting the dose on days two to five for the target INR (University of Colorado Health North, 2015).

    - Compared to the 10-mg loading dose of warfarin, the 5-mg loading dose exerts less anticoagulation effects and will achieve a therapeutic INR quicker, yet also has less risk of the hypercoagulable state which can occur during the first 36 hours of starting warfarin (Harrison et al., 1997; Wigle et al., 2013; Jaffar & Bragg, 2003).
    - The consensus varies on the percentage to adjust warfarin doses safely per week to achieve a therapeutic INR: 5-20% according to research studies (Jaffar & Bragg, 2003; Wigle, et al., 2013), 15-20% according to an anticoagulation clinic (University of Colorado Health North, 2015), and 10-15% according to the RE-LY warfarin trial (Hull & Garcia, 2016b).
    - Starting on day three, the maintenance dose can be started, usually 5-mg daily (University of Colorado Health North, 2015).
    - A lower dose of warfarin 3-5 mg should be initiated in patients with impaired liver function, malnutrition, heart failure, thyroid storm, drug interactions, or elderly >65 years old (University of Colorado Health North, 2015).
- With continued maintenance of warfarin, past and current INR trends are considered, as well as adverse effects of bleeding, drug interactions, and targeting the warfarin therapy to the individual patient (University of Colorado Health North, 2015).

- **INR Monitoring**
    - The serum INR level should be checked daily until a therapeutic range is achieved for two days, followed by blood work 2-3 times weekly for one to 1-2 weeks, up to once per month when stable (Jaffar & Bragg, 2003; January et al., 2014; Wigle, et al., 2013).
    - The AHA/ACA/HRS recommend a minimum of weekly INR monitoring until a therapeutic INR is achieved, followed by monthly lab draws (*Class I, Level of Evidence A;* January, et al., 2014).
    - For atrial fibrillation, the targeted INR for warfarin is 2.0-3.0 (Manning, 2016).
    - With dose adjustments, alcohol use, dietary or medication changes, labile INRs (January et al, 2014), transitioning between warfarin and another anticoagulant, or during hospitalization (Hull, & Garcia, 2016b), more frequent lab monitoring may be necessitated.
    - With labile INRs, factors such as patient compliance, medication changes, fluctuations in the intake of vitamin K, and acute illness (diarrhea, fever, or vomiting) should be assessed before altering the dose of warfarin (Jaffar & Bragg, 2003).
    - On average, it takes four months for a patient to reach a therapeutic INR, and only 55% of the time are AF patients within their target therapeutic range while on warfarin (Janssen, 2014c).
    - Unstable INRs (<2 or >4) are present in 44% of patients on warfarin (Janssen, 2014b). The risk of thromboembolism increases with an INR <2, and the risk of bleeding increases with an INR >4, especially >5 (Hirsh, Fuster, Ansell, & Halperin, 2003).

- ***Home monitoring of INRs***

  - INR levels are best managed at an anticoagulation clinic or by the patient rather than through provider management within the community (Hull & Garcia, 2016b).
  - Randomized control trials have concluded home monitoring of INRs can reduce the risk of thromboembolic events by 42% compared to clinic managed INRs (You et al., 2012).
  - **Benefits**: reduced costs (mileage reimbursement, appointment cost, and lost wages), time savings by not requiring a clinic visit, improved convenience, and increased patient preference (Meyer, et al., 2013).
  - **Cons**: increased costs of the devices and test strips needed (You, et al., 2012).
  - Home monitoring of INRs is encouraged in patients who have been thoroughly educated on how to use the devices and are willing to engage in self-monitoring of INR levels (Barcellona, Fenu, & Marongiu, 2016; Ansel, 2013; *Class IIB,* Pozzi, et al., 2016).

- ***Genetic Testing for Warfarin***

  - **Clinical Pharmacogenetics Implementation Consortium (CPIC)**
    - As warfarin has a narrow therapeutic index and a vast inter-patient dosing variability to achieve a therapeutic INR, four genetic variants have been identified, contributing to 50% of the variability in warfarin dosing: CYP2C9, VKORC1, CYP4F2, and CYP2C cluster (rs12777823).
    - In 2016, (CPIC), part of the National Institute of Health's Pharmacogenomics Research Network, examined peer-reviewed genetic and medication guidelines, updating the 2011 guideline on pharmacogenetics-guided warfarin dosing.
    - CPIC recommends pharmacogenetic warfarin dosing through an algorithm focusing on VKORC1 and CYP2C9 alleles, starting loading doses of warfarin based on genetic calculations and ancestry (Johnson et al., 2017).
    - https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/
  - **Benefits of pharmacogenetic warfarin testing**: reaching a stable INR within a shorter time frame and more consistently, which could decrease the risk of hemorrhage from inappropriate warfarin dosing and the risk of thromboembolism (Johnson et al., 2017).
  - **Risks of pharmacogenetic warfarin testing**: calculation of the incorrect dose of warfarin based upon these recommendations and calculating the wrong genotype which is a permanent component of the patient's medical record, especially if not following recommendations specific to ancestry (Johnson et al., 2017).
  - The cost-benefit ratio of warfarin genetic testing is controversial, as stable INRs can reduce costs related to INR testing itself and decrease negative sequalae of poorly managed warfarin dosing, yet most insurance companies will not cover the costs of this testing (Johnson et al., 2017).
  - Randomized clinical trials of CYP2C9 and VKORC1 alleles have not demonstrated reliable results, not supporting the definitive benefits of genetic warfarin testing (Johnson et al., 2017).

- ***Common Drugs and Alternative Medicines Influencing the Effects of Warfarin***

Drugs Heightening the Effects of Warfarin (Increase the INR)	Drugs Minimizing the Effects of Warfarin (Decrease the INR)
• Acetaminophen[1,2] • Alcohol[2] • Amiodarone[1,2] • Cimetidine[1,2] • Ciprofloxacin[1,2] • Clarithromycin[1,2] • Corticosteroids[2] • Diltiazem[2] • Erythromycin[1,2] • Fibric acid derivatives[1,2] • Fluvoxamine[1] • Gemfibrozil[1] • Isoniazid[2] • Levothyroxine[1,2] • Metronidazole[1,2] • NSAIDS[1] • Omeprazole[2] • Paroxetine[2] • Phenytoin (*increases initially then decreases the INR*)[1,2] • Propafenone[2] • Statins[1,2] • Tamoxifen[1] • Triazole antifungals[1,2] • Tramadol[1] • Trimethoprim-sulfamethoxazole[1,2] • Cranberry juice[2] • Fish Oil[2] • Ginkgo Biloba[2] • Red Yeast Rice[2]	• Barbituates[1,2] • Carbamazepine[1,2] • Cholesytramine[2] • Corticosteroids[2] • Dicloxacillin[1] • Griseofulvin[2] • Librium[2] • Mercaptopurine[2] • Methimazole[1] • Propylthiouracil[1] • Rifampin[1,2] • Trazadone[2] • Coenzyme Q10[2] • Ginseng[2] • St. John's Wort[2]

Note: Adapted from 1) "Practical tips for warfarin dosing and monitoring," A. Jaffar & L. Bragg, 2003, p. 366; 2) "Updated guidelines on anticoagulation management," P. Wigle, B. Hein, H. Bloomfield, M. Tubb, & M. Doherty, 2013, p. 567.

References

American College of Cardiology. (2012). Severity of Atrial Fibrillation Scale. Retrieved from h http://acc.org

American Geriatrics Society. (2015). American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *Journal of American Geriatric Society, 63,* 2227-2246. doi: 10.1111/jgs.13702

American Heart Association, American Stroke Association. (2016). Simplifying your atrial fibrillation treatment plan. Retrieved from https://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable//ucm_324032.pdf.

Ansell, J. (2013). Point-of-care patient self-monitoring of oral vitamin K antagonist therapy. *Journal of Thrombosis and Thrombolysis, 35*, pp. 339-341. doi: 10.1007/s11239-0878-z

Appelros, P., Farahmand, B., Terént, A., & Asberg, S. (2017, May). To treat or not to treat: Anticoagulants as secondary preventatives to the oldest old with atrial fibrillation. *Stroke.* doi: 10.1161/STROKEAHA.117.016902

Barboasa, M., & Falcao, L.M. (2016). Oral anticoagulation in the elderly: New oral anticoagulants- innovative solution for an old problem? *American Journal of Therapeutics, 0,* pp. 1-10.

Barcellona, D., Fenu, L., & Marongiu, F. (2016). Point-of-care testing INR: An overview. *Clinical Chemical Laboratory Medicine,* pp. 1-6. doi: 10.1515/ccim-2016-0381

Boehringer Ingelheim International. (2016). Pradaxa Coverage and Savings. Retrieved from https://www.pradaxapro.com/coverage-savings

Boehringer Ingelheim International. (2015). Praxbind [package insert]. Retrieved from http://docs.boehringeringelheim.com/Prescribing%20Information/PIs/Praxbind/Praxbind.pdf

Boston Scientific. (2016). Think outside the pill box: WATCHMAN left atrial appendage closure device.

Bristol-Myers Squibb. (2016). Eliquis Coverage and Reimbursement. Retrieved from http://www.eliquis.com/eliquis/hcp/coverage-reimbursement

Budnitz, D.S., Lovegrove, M.C., Shehab, N., & Richards, C.L. (2011). Emergency hospitalizations for adverse drug events in older Americans. *New England Journal of Medicine, 365,* pp. 2002-2012.

Caldeira, D., Costa, J., Fernandes, R.M., Pinto, F.J., & Ferreira, J. (2014). Performance of the HAS-BLED high bleeding-risk category, compared to ATRIA and HEMORR2HAGES in patients withatrial fibrillation: a systematic review and meta-analysis. *Journal of Interventional Cardiology and Electrophysiology, 40*(3), pp. 277-284. doi: 10.1007/s10840-014-9930-y

Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion, Division for Heart Disease and Stroke Prevention. (2015, August 13). Atrial fibrillation fact sheet. Retrieved from http://www.cdc.gov/dhdsp/data_ statistics/fact_sheets/fs_atrial_fibrillation.htm

Daiichi Sankyo, Inc. (2017). Savaysa samples and savings cards. Retrieved from https://savaysahcp.com/registration

Daiichi Sankyo, Inc. (2015). Savaysa [package insert]. Retrieved from http://dsi.com/prescribing -information portlet/getPIContent?productName=Savaysa&inline=true

Desai, Y., El-Chami, M.F., Leon, A.R., & Merchant, F.M. (2017). Management of atrial fibrillation in elderly adults. *Journal of American Geriatric Society, 65,* 185-193. doi: 10.1111/jgs.14483

Doherty, J.U., Gluckman, T.J., Hucker, W.J., Januzzi, J.L., Ortel, T.L., Saxonhouse, S.J., & Spinler, S.A. (2017, January). 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation. *Journal of the American College of Cardiology,* pp. 1-28. doi: 10.1016/j.jacc.2016.11.024

Drugs.com. (2016, January 20). Eliquis [package insert]. Retrieved from https://www.drugs.com /monograph/eliquis.html

Drugs.com (2015a, November 11). Pradaxa [package insert]. Retrieved from https://www.drugs.com/monograph/pradaxa.html

Drugs.com. (2015b, November 12). Xarelto [package insert]. Retrieved from https://www.drugs.com/monograph/ xarelto.html

Drugs.com. (2015c, December). Coumadin [package insert]. Retrieved from https://www.drugs.com/pro/ coumadin-injection.html

Drugs.com (2013, December). Vitamin K1 [package insert]. Retrieved from https://www.drugs.com/pro/vitamin-k1.html

Foody, J.M. (2017). Reducing the risk of stroke in elderly patients with non-valvular atrial fibrillation: A practical guide for clinicians. *Clinical Interventions in Aging, 12,* pp. 175-187.

Ganz, L., & Spragg, D. (2016, July 6). Epidemiology of and risk factors for atrial fibrillation. In. T.W. Post (Ed.), *UpToDate.* Waltham, MA: WoltersKluwer Health. Available from http://www.uptodate.com

Garcia, D.A., & Crowther, M. (2017, April 10). Management of bleeding in patients receiving direct oral anticoagulants. In. T.W. Post (Ed.), *UpToDate.* Waltham, MA: WoltersKluwer Health. Available from http://www.uptodate.com

GoodRx (2017). Retrieved from www.goodrx.com

Guimaraes, P.O., Kaatz, S., & Lopes, R.D. (2015). Practical and clinical considerations in assessing patients with atrial fibrillation for switching to non-vitamin K antagonist oral anticoagulants in primary care. *International Journal of General Medicine, 8,* pp. 283-291.

Harrison, L., Johnston, M. Massicotte, M.P., Crowther, M., Moffat, K., & Hirsh, J. (1997). Comparison of

5-mg and 10-mg loading doses in initiation of warfarin therapy. *Annuals of Internal Medicine, 126*(2), pp. 133-136.

Heidenreich, P.A., Solis, P., Estes, N.A.M., Gonarow, G.C., Jurgens, C.Y, Marine, J.E., . . . McNamara, R.L. (2016). 2016 ACC/AHA clinical performance and quality measures for adults with atrial fibrillation or atrial flutter. *Journal of the American College of Cardiology, 68*(5), pp. 525-568.

Hijazi, Z.M., & Saw, J. (2016, September 21). Nonpharmacologic therapy to prevent embolization in patients with atrial fibrillation. In. T.W. Post (Ed.), *UpToDate.* Waltham, MA: WoltersKluwer Health. Available from http://www.uptodate.com

Hirsh, J., Fuster, V., Ansell, J., & Halperrin, J.L. (2003). American Heart Association/ American College of Cardiology Foundation guide to warfarin therapy. *Journal of American College of Cardiology, 41*(9), pp. 1633-1652.

Hu, T.Y., Vaidya, V.R., Asirvatham, S.J. (2016). Reversing anticoagulant effects of novel anticoagulants: Role of ciraparantag, andexanet alpha, and idarucizumab. *Vascular Health and Risk Management, 12,* pp. 35-44.

Hull, R.D., & Garcia, D.A. (2016a, May 20). Management of warfarin-associated bleeding or supratherapeutic INR. In. T.W. Post (Ed.), *UpToDate.* Waltham, MA: WoltersKluwer Health. Available from http://www.uptodate.com

Hull, R.D., & Garcia, D.A. (2016b, May 31). Warfarin and other VKA's: Dosing and adverse effects. In. T.W. Post (Ed.), *UpToDate.* Waltham, MA: WoltersKluwer Health. Available from http://www.uptodate

Hwang, C. (2016a). CHA_2DS_2-VASc score for atrial fibrillation stroke risk. Retrieved from http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk/

Hwang, C. (2016b). HAS-BLED score for major bleeding risk. Retrieved from http://www.mdcalc.com/has-bled-score-for-major-bleeding-risk/

Jaffar, A., & Bragg, L. (2003, April). Practical tips for warfarin dosing and monitoring. *Cleveland*

Clinic Journal of Medicine, 70(4), pp. 361-371.

Janssen Pharmaceuticals, Inc. (2016). Xarelto formulary coverage. Retrieved from https://www.xareltohcp.com/resources/formulary-coverage.html

Janssen Pharmaceuticals, Inc. (2014a, January). Challenges of anticoagulation treatment in the elderly population.

Janssen Pharmaceuticals, Inc. (2014b, December). Complexities of warfarin therapy may lead to increased resource utilization.

Janssen Pharmaceuticals, Inc. (2014c, December). Unstable INR has implications for healthcare resource use.

January, C.T., Wann, L.S., Alpert, J.S., Calkins, H., Ciagarroa, J.E., Cleveland, J.C., . . . Yancy, C.W. (2014, December 2). 2016 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive Summary. *Journal of the American College of Cardiology, 64*(21), pp. 2246-2280.

Johnson, J.A., Caudle, K.E., Gong, L., Whirl-Carrillo, M., Stein, C.M., Scott, S.A. . . . Wadelius,] M. (2017). Clinical pharmacogenetics implementation consortium (CPIC) guideline for pharmacogenetics guided warfarin dosing: 2017 update. Retrieved from https://www.pharmgkb.org/guideline/PA166104949

Kirchhof, P., Benussi, S., Kotecha, D., Ahlsson, A., Atar, D., Casadei, B., . . . Vardas, P. (2016). 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eurospace.* doi: 10.1093/eurospace/euw295

Kumar, K. (2016a, September 21). Antiarrhythmic drugs to maintain sinus rhythm in patients with atrial fibrillation. In. T.W. Post (Ed.), *UpToDate.* Waltham, MA: WoltersKluwer Health. Available from http://www.uptodate.com

Kumar, K. (2016b, September 21). Overview of atrial fibrillation. In. T.W. Post (Ed.), *UpToDate.* Waltham, MA: WoltersKluwer Health. Available from http://www.uptodate.com

Kumar, K., & Manning, W.J. (2016, October 10). Rhythm control versus rate control in atrial

fibrillation. In. T.W. Post (Ed.), *UpToDate.* Waltham, MA: WoltersKluwer

Lane, D.A., & Lip, G.Y.H. (2012). Use of the CHA2DS2-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. *Circulation, 126,* pp. 960-865. doi: 10.1161/CIRCULATIONAHA.111.060061

Leung, L.L.K. (2017, September 1). Direct oral anticoagulants and parenteral direct thrombin inhibitors: Dosing and adverse effects. In T.W. Post (Ed.), *UpToDate.* Waltham, MA: WoltersKluwer Health. Available from http://www.uptodate.com

Manning, W.J., Singer, D.E., & Lip, G.Y.H. (2016, October 31). Atrial fibrillation: Anticoagulation therapy to prevent embolization. In. T.W. Post (Ed.), *UpToDate.* Waltham, MA: WoltersKluwer Health. Available from http://www.uptodate.com

Meschia, J.F., Bushnelll, C., Boden-Albala, B., Braun, L.T., Bravata, D.M., Chaturvedi, S. . . . Wilson, J.A. (2014). Guidelines for the primary prevention of stroke. A Statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 45,* pp. 3754-3832. doi: 10.1161/STR.0000000000000046

Meyer, S., Frei, C.R., Daniels, K.R., Forcade, N.A., Bussey, M., Bussey-Smith, K.L., & Bussey, H.T. (2013). Impact of a new method of warfarin management on patient satisfaction, time, and cost. *Pharmacotherapy, 33*(11), pp. 1147-1155. doi: 10.1002/phar.1344

Pozzi, M., Mitchell, J., Henaine, A.M., Safi, O., & Henaine, R. (2016). International normalized ratio self-testing and self-management: Improving patient outcomes. *Vascular Health and Risk Management, 12,* pp. 387-392.

Ruff, C.T., Giugliano, R.P., & Antman, E.M. (2016). Management of bleeding with non-vitamin K antagonist oral anticoagulation in the era of specific reversal agents. *Circulation, 134,* pp. 248-261. doi:10.1161/CIRCULATIONAHA.116.021831

Samuelson, B.T., & Cuker, A. (2016). Measurement and reversal of the direct oral anticoagulants. *Blood Reviews, 31*, pp. 77-84.

Samuelson, B.T., Cuker, A., Siegal, D.M., Crowther, M., & Garcia, D.A. (2017). Laboratory

assessment of the anticoagulant activity of direct oral anticoagulants. *CHEST, 151*(1), pp. 127-138.

Shahid, F., Shantsila, E., & Lip, G.Y.H. (2016). Recent advances in the understanding and management of atrial fibrillation: A focus on stroke prevention [version 1; referees: 3 approved]. *F1000Research, 5,* pp. 1-11. doi: 10.12688/f1000research.10176.1

Society of Vascular Medicine. (2015). Atrial fibrillation (A-Fib) decision making tool. Retrieved From http://www.mybloodclots.org/

University of Colorado Health North. (2015, September 16). University of Colorado Health North guideline for the management of anticoagulation care. Retrieved from https://www.uchealth.org/

Wigle, P., Hein, B., Bloomfield, H.E., Tubbe, M., & Doherty, M. (2013, April 15). Updated guidelines on outpatient anticoagulation. *American Academy of Family Physicians, 87*(8), pp. 556-566.

You, J. J., Singer, D. E., Howard, P. A., Lane, D. A., Eckman, M. H., Fang, M. C., … Lip, G. Y. H. (2012). Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest, 141*(2 Suppl.), e531S-e575S. Retrieved from http://journal.publications.chestnet.org/article.aspx?articleID=1159549

APPENDIX B

COMPARISON OF ANTICOAGULANTS

Name Brand (Generic)	Coumadin® (Warfarin sodium)	Xarelto® (Rivaroxaban)	Pradaxa® (Dabigatran etexilate mesylate)	Eliquis® (Apixaban)	Savaysa® (Edoxaban)
Pharma-ceutical Company (U.S. Approval Date)	Bristol-Myers Squibb Company (1954)	Janssen Pharmaceuticals (2011)	Boehringer Ingelheim Pharmaceuticals (2010)	Bristol-Myers Squibb Company (2012).	Daiichi Sankyo, Inc. (2015)
Mechanism of Action	Inhibits the production of *vitamin K-dependent coagulation factors* (Factors II, VII, IX, and X; anticoagulant proteins C and S) (Bristol-Myers Squibb, 2015; Drugs.com, 2015c).	*Selective factor Xa inhibitor* - inhibits platelet aggregation by reducing thrombin production (Drugs.com, 2015b)	*Selective, competitive, reversible direct thrombin inhibitor*- prevents conversion of fibrinogen to fibrin and inhibits thrombin-mediated platelet aggregation (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	*Reversible direct Factor Xa inhibitor*- prevents conversion of prothrombin to thrombin and thrombus production; does not require a cofactor (Drugs.com, 2016)	*Selective, factor Xa inhibitor*- prevents thrombin-induced platelet aggregation to decrease the production of thrombin (Daiichi Sankyo, 2015).
Indications	**Prophylaxis and treatment of: venous thrombosis, pulmonary embolism,* thromboembolic complications with *atrial fibrillation*, and thromboembolic complications with *cardiac valve replacements*. *Reduction in stroke, *subsequent myocardial infarction*, or death after a myocardial infarction (Bristol-Myers Squibb, 2015; Drugs.com, 2015c).	*Reduction of stroke and systemic embolism in *non-valvular atrial fibrillation (NVAF)* *Prophylaxis and treatment of deep vein thrombosis and pulmonary embolism, including knee or hip replacement surgery* *Reduction in recurrence of DVT or PE* *Nonvalvular atrial fibrillation: absence of mitral valve repair, rheumatic mitral stenosis, and a prosthetic heart valve (Drugs.com, 2015b).	*Reduction of stroke and systemic embolism in *NVAF* *Treatment and secondary prevention of DVT or PE* *Prevention of stroke and systemic embolism during *cardioversion of atrial fibrillation or atrial flutter* *Prevention of DVT and PE during total hip-replacement or total knee-replacement surgeries* *Secondary prevention of cerebral embolism in patients with TIA, ischemic stroke, or atrial fibrillation* (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	*Reduction of stroke and systemic embolism *with non-valvular atrial fibrillation* *Thromboprop hylaxis in hip or knee replacement surgery* *Treatment and secondary prevention of DVT and/or PE* (Drugs.com, 2016)	*Reduction of systemic embolism in *non- valvular atrial fibrillation* *Thromboprop hy laxis* of DVT and PE after 5-10 days of IV anticoagulation (Daiichi Sankyo, 2015).
Pharmaco-kinetics	*Peak plasma levels: 72-96 hours *Duration of 1 dose: 2-5 days *Rapid anticoagulation requires bridging with Heparin for 4- 5 days (Bristol-Myers Squibb, 2015; Drugs.com, 2015c)	Peak plasma levels following oral administration: 2-4 hours (Drugs.com, 2015b)	Peak plasma levels following oral administration: 1-2 hours (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	Peak plasma levels following oral administration: 3-4 hours (Drugs.com, 2016)	*Peak plasma levels: 1-2 hours (Daiichi Sankyo, 2015).

Name Brand (Generic)	Coumadin® (Warfarin sodium)	Xarelto® (Rivaroxaban)	Pradaxa® (Dabigatran etexilate mesylate)	Eliquis® (Apixaban)	Savaysa® (Edoxaban)
Oral Dosing	**Dose is adjusted based upon the patient's INR:** *Non-Valvular Atrial Fibrillation:* target INR 2.5 (range 2.0-3.0) *Mechanical and Bioprosthetic Heart Valves:* bileaflet mechanical aortic valve- INR 2.5 (range 2.0-3.0), bileaflet mitral valve- INR 3 (range 2.3-3.5), bioprosthetic mitral valve- INR 2.5 (range 2.0-3.0) *INR >4 increases the risk of bleeding *Initial dose:* 2-5 mg daily (dependent on age, race, body weight, sex, comorbidities, and concurrent medications) *Determination of CYP2C9 and VKORC1 genotypes influences the dosing *Maintenance dose*: 2-10 mg daily (dependent on INR) (Bristol-Myers Squibb, 2015; Drugs.com, 2015c).	**Non-valvular atrial-fibrillation:* CrCl >50 mL/min (20 mg daily with evening meal) CrCl 15-50 mL/min (15 mg daily with evening meal) CrCl <15 mL/min (not recommended) [CrCl = creatinine clearance] (Drugs.com, 2015b).	**Embolism with atrial fibrillation:* CrCl >30 mL/min (150 mg BID); CrCl 15-30 mg/Min (75 mg BID) CrCl < 15 mL/min or hemodialysis (not recommended) (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	**Embolism with atrial fibrillation:* 5 mg BID (reduce dose to 2.5 mg BID with >2 characteristics: >80 years old, body weight <60 kg, Cr >1.5 mg/dL) *Administration with inhibitors or CYP3A4 and P-glycoprotein:* reduce dose by 50% with >2.5 mg Apixaban daily (Drugs.com, 2016)	**Non-valvular atrial fibrillation:* 60 mg daily with CrCl between 50-95 mL/min 30 mg daily with CrCl 15-50 mL/min. Not indicated with a CrCl <15 or >95 mL/min. *No dosage adjustments with mild or moderate hepatic impairment *Reduce dose to 30 mg with body weight <60 kg or P-gp inhibitor use **Cockcroft-Gault CrCl =** (140-age) x (weight in kg) x (0.85 if female) / (72 x creatinine in mg/dL) (Daiichi Sankyo, 2015).
Absorption	*Bioavailability: 100% absorption orally *Tablets can be crushed *Avoid foods high in vitamin K (Bristol-Myers Squibb, 2015; Drugs.com, 2015c)	Bioavailability: *80-100% for 10 mg dose (unaffected by food) *66% for 20 mg dose without food, *76% for 20 mg dose with food *15 and 20 mg tablets should be taken with food to increase absorption. *Tablets can be crushed (Drugs.com, 2015b)	*Bioavailability: 3-7% *Tablets must be taken whole-cannot crush. *High fat meals delay peak plasma concentration by 2 hours but do not affect bioavailability (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	*Bioavailability: 50% *Tablets can be crushed *Can be taken with or without food (Drugs.com, 2016)	*Bioavailability: 62% *Unknown whether tablets can be crushed *Can be taken with or without food (Daiichi Sankyo, 2015).
Distribution	90% bound to plasma proteins (Bristol-Myers Squibb, 2015; Drugs.com, 2015c)	92-95% bound to plasma proteins (Drugs.com, 2015b)	35% bound to plasma proteins (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	87% bound to plasma proteins (Drugs.com, 2016)	55% bound to plasma proteins; steady state reached in 3 days (Daiichi Sankyo, 2015).

Name Brand (Generic)	Coumadin® (Warfarin sodium)	Xarelto® (Rivaroxaban)	Pradaxa® (Dabigatran etexilate mesylate)	Eliquis® (Apixaban)	Savaysa® (Edoxaban)
Metabolism	CYP450 enzymes, primarily CYP2C9 (Bristol-Myers Squibb, 2015; Drugs.com, 2015c)	CYP450 enzymes, primarily CYP3A4/5 (Drugs.com, 2015b)	*Not metabolized by CYP enzymes. *Dabigatran extexilate is a prodrug that is rapidly absorbed and hydrolyzed by the liver and plasma into the active form of dabigatran. (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	*CYP450 enzymes, primarily CYP3A4/5 *Substrate of P-glycoprotein but does not inhibit P-glycoprotein. (Drugs.com, 2016)	*Unchanged in plasma *Nominal metabolism through CYP3A4, hydrolysis, and conjugation *Primary metabolite is M-4 through hydrolysis (Daiichi Sankyo, 2015).
Half-Life	*Effective half-life: mean 40 hours *Terminal half-life: 1 week (Bristol-Myers Squibb, 2015; Drugs.com, 2015c)	Terminal half-life: 5-9 hours (Drugs.com, 2015b)	*Terminal half-life: 12-17 hours *Increased half-life with renal impairment (15-28 hours) (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	*Terminal half-life: 6 hours *Half-life of 12 hours with repeated administration (Drugs.com, 2016)	*Excreted as an unchanged drug *Half-life: 10-14 hours (Daiichi Sankyo, 2015).
Excretion	Inactive metabolites in urine (92%) (Bristol-Myers Squibb, 2015; Drugs.com, 2015c).	Inactive metabolites in urine (30%) and feces (21%) (Drugs.com, 2015b)	*Inactive metabolites in urine (80%), 86% of total dose is excreted into feces (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	*Inactive metabolites in urine (25%), hepatic metabolism, intestinal, and biliary excretion (Drugs.com, 2016)	*50% renal clearance, 50% intestinal and biliary clearance (Daiichi Sankyo, 2015).
Monitoring	**INR:** daily until stabilization then **every** 1-4 weeks (Bristol-Myers Squibb, 2015; Drugs.com, 2015c)	*Routine lab monitoring not required *Prolongs PT, aPTT, and Factor Xa (Drugs.com, 2015b)	*Routine lab monitoring not required *Prolongs aPTT, PT, INR, and ECT. ECT is the preferred test for Pradaxa© monitoring (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	*Routine lab monitoring not required or recommended *Inhibits Factor Xa and prolongs aPTT, PT, INR, and anti-factor Xa assays (Drugs.com, 2016)	*Routine lab monitoring not required or recommended *Prolongs aPTT, PT and INR *Does not prolong QT interval (Daiichi Sankyo, 2015).
Pregnancy Category	***Category C:** pregnant women with mechanical values ***Category X**: all other women (Warfarin embryopathy) *Crosses the placenta *Not present in breastmilk; avoid during lactation due to increased risk of bleeding in the infant (Bristol-Myers Squibb, 2015; Drugs.com, 2015c)	***Category C** ***Crosses the placenta *Unknown whether Xarelto© is excreted in breastmilk (Drugs.com, 2015b)	***Category C** *Unknown whether Pradaxa© is excreted into breastmilk (Drugs.com, 2015a; Boehringer Ingelheim, 2015b)	***Category B** *Unknown whether Eliquis© is excreted into breastmilk (Drugs.com, 2016)	***Category C** ***Discontinue prior to breastfeeding, unknown whether Savaysa® is excreted into breastmilk (Daiichi Sankyo, 2015).

Name Brand (Generic)	Coumadin® (Warfarin sodium)	Xarelto® (Rivaroxaban)	Pradaxa® (Dabigatran etexilate mesylate)	Eliquis® (Apixaban)	Savaysa® (Edoxaban)
Demographic Considerations	*Reduce dose in geriatric patients >60 years old due to increased INR *Reduce dose in **Asians** *Initial and maintenance dosing is based upon patient's: age, body weight, sex, race, concurrent medications, comorbidities, and genetic factors *Dosing in pediatrics is unknown *With known **CYP2C9 and VKORC1** genotypes, initial and maintenance dosage is dependent on the combination of these genetic variants (Bristol-Myers Squibb, 2015 Drugs.com, 2015c)	*Dosing in pediatrics is unknown *Increased risk of thrombosis and bleeding rates in the elderly - reduce dosage *Renal insufficiency: avoid use in patients with a CrCl <30 mL/min *Avoid use in patients with moderate or severe hepatic impairment (Child-Pugh B and C) *No influence of gender *Differences in effects for Asian race are reduced when corrected for body weight *No prolongment of QT/QTc interval (Drugs.com, 2015b)	*Dosing in pediatrics is unknown *No current dosage recommendations for hepatic impairment *Bleeding risk increases with age- reduce dosage *Reduce dose with renal insufficiency (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	*Dosing in pediatrics is unknown *Not recommended with severe hepatic impairment *Reduce dosage to 2.5 mg BID in patients with Cr>1.5 mg/dL if >80 years old body and weight <60 kg. *Hemodialysis: 5 mg BID. *>80 years old or body weight <60 kg: 2.5 mg BID *No adjustments based on race *Pharmacokinetics and pharmacodynamics not affected by renal impairment (Drugs.com, 2016)	*Dosing in pediatrics is unknown *Similar safety and efficacy in patients >65 years old and <65 years old *No dose adjustments based on sex or race (Asian versus Non-Asian) (Daiichi Sankyo, 2015).
Adverse Effects	***Hemorrhage/bleeding risk** *Tissue necrosis *Systemic atheroemboli or cholesterol microemboli (purple toes syndrome) *Limb ischemia, necrosis, gangrene with heparin-induced thrombocytopenia *Hypersensitivity (7.5 mg tablets containing FD&C Yellow No. 5) *Vasculitis *Hepatobiliary disorders *Nausea, vomiting, diarrhea, bloating *Rash, dermatitis, pruritus (Bristol-Myers Squibb, 2015; Drugs.com, 2015c)	***Bleeding risk** *Increased risk of stroke after discontinuation of Xarelto© in patients with non-valvular atrial fibrillation *Spinal/epidural hematoma *Abdominal pain, dyspepsia *Fatigue *Sinusitis, urinary tract infection *Back pain, osteoarthritis *Oropharyngeal pain *Pruritus *Hypersensitivity (Drugs.com, 2015b)	***Bleeding risk** ***GI:** Gastritis, GERD, GI ulcer, dyspepsia, upper abdominal pain, nausea, diarrhea, gastrointestinal hemorrhage (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	***Bleeding risk** (Drugs.com, 2016)	***Bleeding risk** **Indicated for non-valvular atrial fibrillation*: anemia, bleeding (5%) **Indicated for DVT and PE*: anemia, abnormal liver function labs, rash, bleeding (1%) *Rash *Abnormal liver function tests *Interstitial lung disease (Daiichi Sankyo, 2015).

Name Brand (Generic)	Coumadin® (Warfarin sodium)	Xarelto® (Rivaroxaban)	Pradaxa® (Dabigatran etexilate mesylate)	Eliquis® (Apixaban)	Savaysa® (Edoxaban)
Contra-indications/ Precautions	**Narrow therapeutic index* ***Contraindications:** *Pregnancy*; Blood dyscrasias; Bleeding tendencies (GI, GU, respiratory, cardiac, CNS); Threatened abortion, eclampsia, preeclampsia; Recent surgery or the CNS, eye, or large trauma; Non-compliant patients; Procedures with potential uncontrolled bleeding; Severe hypersensitivity reaction to Warfarin; Malignant hypertension; Major regional or lumbar block anesthesia ***Precautions:** Moderate to severe hepatic impairment or hypertension; Diabetes mellitus; Polycythemia Vera (Bristol-Myers Squibb, 2015; Drugs.com, 2015c)	***Contraindications:** *Active bleeding;* Severe hypersensitivity reaction to Xarelto© ***Precautions:** Increased risk of thrombotic events with premature discontinuation of anticoagulants; Risk of bleeding; Spinal/epidural anesthesia or puncture; *Renal impairment (CrCl <30 mL/min);* Moderate/severe hepatic impairment; Pregnancy-related hemorrhage; Hemodynamic instability; Prosthetic heart valves (has not been studied) (Drugs.com, 2015b)	***Contraindications:** *Active bleeding;* Severe hypersensitivity reaction to Pradaxa©; *Mechanical prosthetic heart valves* ***Precautions:** Increased risk of thrombotic events with premature discontinuation of anticoagulants; Spinal/epidural hematoma; Risk of bleeding (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	***Contraindications:** *Active bleeding;* Severe hypersensitivity reaction ***Precautions:** Increased risk of thrombotic events with premature discontinuation of anticoagulants; Spinal/epidural hematoma; Risk of bleeding; Prosthetic heart valves (Drugs.com, 2016)	***Contraindication:** active bleeding ***Precaution:** *increased risk of ischemic stroke with CrCl <95 mL/min.* *Not recommended with moderate to severe mitral stenosis or mechanical heart valves. *Increased risk of ischemic event with premature discontinuation of Savaysa® *Concurrent use of neuraxial anesthesia or spinal puncture and Savaysa® can result in spinal or epidural hematoma. (Daiichi Sankyo, 2015).
Food/Drug Interactions	*Foods high in ***vitamin K, grapefruit juice, herbal supplements*** *Drugs metabolized by ***CYP450***: *2C9, 1A2, 3A4* (inhibitors of CYP increase the INR of Warfarin; inducers of CYP decrease the INR of Warfarin) **Drugs increasing the risk of bleeding with Warfarin*: anticoagulants, antiplatelets, NSAIDS, SSRI (Bristol-Myers Squibb, 2015; Drugs.com, 2015c)	*15 and 20 mg tablets should be taken with food, 10 mg tablet can be taken with or without food *Avoid use with combined P-gp and strong *CYP3A4* inducers or inhibitors *Avoid anticoagulants, NSAIDS, Plavix©, Aspirin, and SSRI due to increased risk of bleeding (Drugs.com, 2015b)	*Avoid drugs affecting P-glycoprotein transport *Unlikely interactions with drugs metabolized by CYP isoenzymes *Avoid drugs increasing the risk of bleeding (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	*Unlikely drug interactions with P-glycoprotein or CYP3A4 *Avoid use of dual inhibitors of P-glycoprotein and CYP3A4/5 inhibitors or inducers *Avoid drugs increasing the risk of bleeding (Drugs.com, 2016)	*Avoid Rifampin (P-gp inhibitor-reduces the blood levels of edoxaban) *Avoid drugs increasing the risk of bleeding: anticoagulants, aspirin, fibrinolytics, antiplatelets, and NSAIDS *Edoxaban increases the Cmax of digoxin and decreases the Cmax of verapamil (Daiichi Sankyo, 2015).

Name Brand (Generic)	Coumadin® (Warfarin sodium)	Xarelto® (Rivaroxaban)	Pradaxa® (Dabigatran etexilate mesylate)	Eliquis® (Apixaban)	Savaysa® (Edoxaban)
Reversal Agent	Oral or parenteral **Vitamin K_1** *__Vitamin K_1__ **(Phytonadione)**- 2.5-10 mg SubQ, max of 25 mg. Can repeat dose in 6-8 hours if prothrombin time has not shortened adequately (Drugs.com, 2013).	*No specific reversal agent (Drugs.com. 2015b)	**Praxbind** (Idarucizumab) – 5 gm IV push. Limited data on a second additional dose. *Monoclonal antibody fragment *Indicated for uncontrolled or life-threatening bleeding, or for urgent/emergent surgical procedures. *Pradaxa is dialyzable- 50% can be cleared from plasma over four hours. *Approved in U.S. in 2015 (Boehringer Ingelheim, 2015a; Boehringer Ingelheim, 2015b)	*No specific reversal agent (Drugs.com, 2016)	*No specific reversal agent. *Anticoagulation effects continue 24 hours after the last dose was administered. *Hemodialysis does not improve clearance of Savaysa *Protamine sulfate, vitamin K and tranexamic acid do not reverse Savaysa's effects (Daiichi Sankyo, 2015)
Temporary Interrupt-ion of Therapy	*Obtain the INR immediately before any surgical procedures *Consider the duration of one dose lasting 2-5 days. *For minimally invasive procedures, maintain the INR at the lower end of the therapeutic range (Bristol-Myers Squibb, 2015; Drugs.com, 2015c)	*Discontinue Xarelto© 24 hours prior to the procedure to minimize bleeding risk. *Resume Xarelto© 6-10 hours after surgery once hemostasis is achieved (Drugs.com, 2015b)	*For CrCl >50 mL/min: withhold Pradaxa© 1-2 days prior to procedure. *For CrCl<50 mL/min: withhold Pradaxa© 3-5 days prior to the procedure (Drugs.com, 2015a; Boehringer Ingelheim, 2015a)	*Discontinue 48 hours prior to procedures with a moderate or high risk of bleeding. *Discontinue 24 hours prior to procedures with a low risk of bleeding. *Resume Eliquis® 12-24 hours after surgery once hemostasis is achieved (Drugs.com, 2016)	*Discontinue 24 hours prior to procedures with high bleeding risk *Resume Savaysa® as soon as hemostasis is achieved post-procedure *Do not remove indwelling intrathecal or epidural catheters < 12 hours after the last dose of Savasya®. Do not administer Savaysa® until 2 hours after the catheter is removed (Daiichi Sankyo, 2015).

Name Brand (Generic)	Coumadin® (Warfarin sodium)	Xarelto® (Rivaroxaban)	Pradaxa® (Dabigatran etexilate mesylate)	Eliquis® (Apixaban)	Savaysa® (Edoxaban)
Cost	$11 monthly (GoodRx, 2017)	$371 monthly (GoodRx, 2017) *Commercial coverage: 95% 74% of patients payed <$50 *Medicare Part D: 96% coverage, 58% paid <$50 *Medicaid: covered *Xarelto© CarePath: savings for commercial insurance: $0 copay every month for patients with commercial insurance (15 or 20 mg tablets), max of $3,400 annual benefit with no monthly cap; assistance with Medicaid, Medicare, Tricare, or commercial insurance- free 30-day trial of 15 or 20 mg tablets (Janssen Pharmaceuticals, 2016a)	$377 monthly *99% coverage in Colorado by Medicare Part D (Good Rx, 2017) *Praxbind©: available in all 50 states (Boehringer Ingelheim, 2015b) *Pradaxa© savings card: $0 monthly co-pay or a free 30-day supply (Boehringer Ingelheim, 2016).	$395 monthly (GoodRx, 2017) *Medicare D: 93% national coverage *Commercial insurance: 87% coverage with no prior authorization restriction *73% of commercially insured patients pay <$25 on a 30-day prescription *Eliquis® savings card: free 30-day trial (including Medicaid, Medicare, and cash-pay), $10 co-pay for commercial insurance for a 30-day supply, up to 24 months for a maximum annual benefit of $3,800 (Bristol-Myers Squibb, 2016)	$326 monthly (Good Rx, 2017) *Savaysa® drug savings cards: $4 for a 30-day prescription (max benefit or $12 for a 90-day prescription for 1 year (Daiichi Sankyo, 2017)

APPENDIX C

KEY DRUG TRIALS FOR ANTICOAGULANTS, REVERSAL AGENTS, AND ALTERNATIVE TREATMENTS FOR ATRIAL FIBRILLATION

Trial	Design/Method	Sample	Findings and Conclusions
APIXABAN (Eliquis®) **ARISTOTLE** (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) (Granger et al., 2011)	Randomized, double-blind, multicenter, noninferiority study comparing *apixaban to warfarin in subjects with atrial fibrillation to prevent stroke.* Apixaban was administered 5 mg BID. Warfarin was administered to reach a target INR or 2.0-3.0. These anticoagulants were administered for a median duration of 1.8 years. This study was completed from 2006-2010 at 1,034 sites in 39 countries. The efficacy outcome was ischemic stroke, hemorrhagic stroke, or systemic embolus occurrence. Safety outcomes were bleeding risk and death from any cause.	A total of 18,201 subjects with atrial fibrillation or atrial flutter and at least one other stroke risk factor were randomized to the warfarin or apixaban group. The median age of subjects was 70 years old with 35.3% women and an average $CHADS_2$ score of 2.1. *Inclusion criteria:* at least two episodes of atrial fibrillation or atrial flutter on EKG, at least 2 weeks apart within one year prior to initiation of this study. At least one risk factor for stroke: age >75 years old, prior stroke, transient ischemic attack (TIA), or systemic embolism, symptomatic heart failure within the past 3 months or a left ventricular ejection fraction (LVEF) <40%, diabetes, or hypertension. *Exclusion criteria* included moderate or severe mitral stenosis, prosthetic heart valve, atrial fibrillation due to a reversible cause, stroke within the past 7 days, the need of aspirin and Plavix© or aspirin dose >165 md daily, or severe renal insufficiency (CrCl <25 mL/Min).	The *efficacy outcome* of apixaban occurred annually in 1.27% of subjects in the apixaban group [HR (CI: 95%): 0.79 (0.66, 0.95); P<0.001 for noninferiority; P=0.01 for superiority]. Ischemic or unknown type of stroke occurred annually in 0.97% of subjects in the apixaban stroke, compared to 1.05% of subjects in the warfarin group [HR (CI: 95%): 0.92 (0.74, 1.13); P=0.42]. *Safety Outcomes:* *Major bleeding occurred annually in 2.13% of subjects in the apixaban group compared to 3.09% in the warfarin group [HR (CI: 95%): 0.69 (0.60, 0.80); P<0.001]. *Death from any cause occurred in 3.52% of subjects in the apixaban group compared to 3.94% in the warfarin group [HR (CI: 95%): 0.89 (0.80, 0.99); P=0.047]. *Hemorrhagic stroke occurred annually in 0.24% of subjects in the apixaban group compared to 0.47% of subjects in the warfarin group [HR (CI: 95%) 0.51 (0.35, 0.75); P<0.001]. *Conclusion: Apixaban was superior to warfarin in preventing systemic emboli or strokes in patients with atrial fibrillation, in addition to demonstrating decreased bleeding risk and reduced mortality.*
AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients) (Connolly et. al., 2011).	Double-blind, randomized, multicenter study investigating *subjects with atrial fibrillation, an increased risk of stroke, and an inability to take vitamin K antagonist anticoagulation. Subjects received apixaban 5 mg BID or aspirin 81- 342 mg daily, assessing for superiority.* Apixaban or aspirin were administered for a follow-up of 1.1 years. This study was completed at 522 sites within 36 countries from 2007 to 2009.	Out of 5,599 subjects, 40% used a vitamin K antagonist as a prior anticoagulant. Subjects were randomly assigned to either the apixaban or aspirin group. Approximately 37% of the subjects were from North America or Europe with a mean age of 70 years old and approximately 58- 59% men per group. The mean $CHADS_2$ score was 2.0-2.1. *Inclusion criteria:* Subjects were at least 50 years old with at least a 6-month diagnosis history of atrial fibrillation. Subjects required at least one of the following risk factors for stroke: age 74 or older, history of stroke or TIA, treated arterial	The study was terminated early due to clear superiority of apixaban to aspirin in preventing strokes. The *efficacy outcome* was evident annually in 51 (1.6%) of subjects in the apixaban group, compared to 113 (3.7%) of subject in the aspiring group [HR (CI: 95%): 0.45 (0.32, 0.62): P<0.001]. *Safety outcomes:* *Death rates occurred annually in 3.5% of subjects in the apixaban group, compared to 4.4% in the aspirin group [HR (CI: 95%): 0.79, (0.62, 1.02)]. *Major bleeding presented annually in 44 (1.4%) of subjects in the apixaban group, compared to 39 (1.2%) of

	The efficacy outcome was stroke or systemic embolus occurrence. The safety outcome was the rate of severe bleeding and death.	hypertension, treated diabetes mellitus, heart failure (New York Heart Association class 2 or higher), left ventricular ejection fraction of 35% or less, documented peripheral artery disease, or not currently on vitamin K antagonist therapy. *Exclusion criteria:* valvular heart disease requiring surgery, serious bleeding within the past 6 months or a high risk of bleeding, a condition other than atrial fibrillation necessitating anticoagulation, platelet count <100,000/mm3, hemoglobin <10 g/dL, hemorrhagic tendencies, blood dyscrasias, current alcohol or drug abuse, current psychosocial issues, life expectancy <1 year, severe renal insufficiency (CrCl <25 mL/min) liver transaminases >2x the upper limit, a bilirubin >1.5x the upper limit, or allergy to aspirin.	subjects in the warfarin group [HR (CI: 95%): 1.13 (0.74, 1.75)]. Intracranial bleeding occurred in 13 subjects in the apixaban group and 13 in the aspirin group. *Reduced risk for hospitalization annually related to a cardiovascular cause was evident in both apixaban (12%) and aspirin (15.9%); P<0.001. *Conclusion: In atrial fibrillation patients who are unable to take vitamin K antagonists as an anticoagulant to decrease the risk of stroke or systemic embolism, apixaban is a suitable alternative to aspirin without enhancing the risk of severe bleeding including intracranial hemorrhage.*
Trial	**Design/Method**	**Sample**	**Findings and Conclusions**
DABIGATRAN (Xarelto®) **PETRO** (Ezekowitz et al., 2007)	Randomized, double- blind, open-label, multicenter study comparing *dabigatran (with or without aspirin) to warfarin in preventing thromboembolism in patients with nonvalvular atrial fibrillation.* The goal of this study was to determine in patients with atrial fibrillation the safe dose of dabigatran. The study was designed for a duration of 12 weeks and was completed at 53 sites within Denmark, Netherlands, Sweden, and the United States. Labs were measured at baseline, 1, 2, 4, 8, and 12 week intervals throughout the study, evaluating dabigatran plasma concentrations, activated partial thromboplastin time, D-dimer, liver function, and urinary 11-dehydrothromboxane B_2 (DTB2). The efficacy outcome measured the incidence of stroke or	A total of 502 subjects were randomly assigned to one of four major groups 1) dabigatran 50 mg (105 subjects) 2) dabigatran 150 mg (166 patients), 3) dabigatran 300 mg (161 subjects), or 4) dose adjusted warfarin (70 subjects). Dabigatran was administered with or without aspirin. Subjects were assigned to one of a total of 10 groups. The dabigatran dose was either 50, 150 or 300 mg daily, the aspirin dose was either 81 or 325 mg daily, and the warfarin was dose adjusted to reach a therapeutic INR of 2.0-3.0; these medications were administered for 12 weeks. 411 or 81.9% of subjects were men with a mean age of 70.9 years with coronary artery disease and 68 years without coronary artery disease. *Inclusion criteria:* documented diagnosis of atrial fibrillation coronary artery disease (with the initial half of participants) with a minimum of at least one of the following high-risk factors: hypertension, diabetes, symptomatic heart failure or a left ventricular ejection fraction <40%, prior stroke or transient ischemic attack, or age >75 years old.	*Efficacy outcomes:* Thromboembolism occurred only in the 50-mg dabigatran group in 2 out of 107 subjects (2%). *Safety outcomes:* *Severe bleeding occurred only in the dabigatran 300 mg plus aspirin group in 4 out of 64 subjects. In comparison, 0 out of 105 subjects had severe bleeding the dabigatran only group (p <0.02). *Total bleeding events in the dabigatran group were as following: 300 mg (39 out of 169 subjects, 23%, p = 0.0002), 150 mg (30 out of 169 subjects, 18%; p = 0.01), and 50 mg (7 out of 107 subjects, 7%). *Labs:* *D-dimer levels were suppressed in the 300 mg and 150 mg dabigatran doses as well as warfarin. *In 0.9% of patients on dabigatran, aminotransferase levels were greater than 3 times the normal level, with 2 subjects developing gallstones (aminotransferase levels >5 times normal). *Activated partial thromboplastin times were higher than baseline in the dabigatran group (1.2 with 50 mg, 1.5 with 150 mg, and 1.8 with 300 mg). *DTB2 concentrations were higher than baseline with the dabigatran group (31% with 50 mg, 17% with 150 mg, and 23% with 300 mg). *Conclusion: Severe bleeding occurred only with the combination of*

	thromboembolism. The safety outcome measured the rate of bleeding events.	*Exclusion criteria:* mitral stenosis, prosthetic heart valves, scheduled cardioversion, myocardial infarction within the past month, recent stroke or transient ischemic attack, contraindication to anticoagulation, coronary artery stent placement within the past 6 months, major bleed within the past 6 months, glomerular filtration rate ≤30 mL/min, pregnancy, abnormal liver function, or use of any other investigational drugs within the past 30 days.	*dabigatran 300 mg with aspirin and thromboembolism only occurred with dabigatran 50 mg. Severe liver toxicity did not arise with dabigatran.*
Trial	**Design/Method**	**Sample**	**Findings and Conclusions**
RE-LY Trial (Randomized Evaluation of Long-term Anticoagulation Therapy) (Connolly et.al., 2009)	Noninferiority, randomized study comparing *dabigatran to dose-adjusted warfarin in prevention of stroke in patients with nonvalvular atrial fibrillation (NVAF).* This study was completed at 951 sites within 44 countries from 2005-2007. Median follow-up was 2 years in 99.9% of patients. The efficacy outcome measured stroke or systemic embolism occurrence. Safety outcomes measured the incidence of severe bleeding and death.	A total of 18,113 subjects with atrial fibrillation were randomly assigned to a dabigatran group (110 or 150 mg BID) or an adjusted- dose of warfarin. Subjects were from 44 countries with a mean age of 71 years, 63.6% men, mean $CHADS_2$ score of 2.1, and 50% of patients had a history of long-term term with vitamin K antagonists. *Inclusion criteria:* documented atrial fibrillation through an EKG within the past 6 months and at least one of the following characteristics: prior stroke or TIA, LVEF <40%, heart failure (New York Heart Association class II or higher) within the past 6 months, age >75 years old, or age 65-74 years old with diabetes, hypertension, or coronary artery disease. *Exclusion criteria:* severe valvular disease, stroke within 14 days before the study, severe stroke within the past 6 months, high bleeding risk, creatinine clearance <30 mL/min, liver disease, and pregnancy.	Discontinuation rates of anticoagulation: 1 year later: dabigatran 110 mg (14.4%), dabigatran 150 mg (15.5%), and warfarin (10.2%) 2 years later: dabigatran 110 mg (20.7%), dabigatran 150 mg (21.2%), and warfarin (16.6%) In the warfarin group, the INR was therapeutic 64% of the time. *Efficacy outcome*: 1.69% annually in the warfarin group compared to 1.53% annually in the 110-mg dabigatran [relative risk (CI: 95%): 0.91 (0.74, 1.11); P<0.001 for noninferiority] and 1.11% annually in the 150-mg dabigatran group [relative risk (CI: 95%): 0.66 (0.53, 0.82); P<0.001 for superiority]. *Hemorrhagic stroke occurred in 0.38% of subjects annually on warfarin, 0.12% of subjects on dabigatran 110 mg, and 0.10% of subjects on dabigatran 150 mg. *Safety outcomes:* *Major bleeding occurred annually in 3.36% of patients on warfarin, 2.71% of patients on 110 mg dabigatran, and 3.11% on 150 mg dabigatran. *Mortality rate annually was 4.13% in patients on warfarin, 375% in patients on 110 mg dabigatran, and 3.64% in patients on 150 mg dabigatran. *Conclusions:* **Dabigatran 110 mg demonstrated similar rates of stroke and embolism in patients with atrial fibrillation compared to warfarin, yet displayed less major bleeding. Dabigatran 150 mg demonstrated lower rates of toke and embolism compared to warfarin,* *but displayed more major bleeding.*

			**Increased risk of gastrointestinal bleeds and gastrointestinal effects (gastritis and dyspepsia) in patients taking 150 mg Dabigatran compared to Warfarin.* **The risk of major bleeding was similar between Dabigatran and Warfarin, except for a higher risk of bleeding evident in patients >75 years old taking Dabigatran* **The rate of all-cause mortality was lower in patients on Dabigatran than Warfarin.* *After publishing of this article, safety and efficacy outcomes were expanded to include 81 new events in 80 patients: 4 myocardial infarctions, 1 stroke, 1 systemic embolic events, 69 major hemorrhages, and 5 transient ischemic attacks. Conclusions to the original study remained the same (Connolly, et.al., 2010). *1500 cases were re-evaluated for stroke, systemic embolism, major bleeding or life-threatening bleeding as 1,387 deaths occurred during the RE-LY trial. Data was altered but even with these alterations, no changes were made to the conclusions in the original study (Connolly, et.al., 2014).
Trial	**Design/Method**	**Sample**	**Findings and Conclusions**
RELY-ABLE (Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients with Atrial Fibrillation) (Connolly et.al., 2013).	Randomized, descriptive, longitudinal cohort study evaluating the *two-year follow-up of atrial fibrillation patients taking dabigatran 110 mg or dabigatran 150 mg and their effects on the prevention of stroke or systemic embolism.* This study extended the RE-LY trial for an extra 2.25 years. The efficacy outcome measured stroke or systemic embolism occurrence. The safety outcome measured bleeding rates and death.	A total of 5,581 subjects were randomly assigned to a dabigatran group during the RE-LY trial were included in this trial if they had continued dabigatran for anticoagulation. These patients received the same dose of dabigatran (110 mg or 150 mg) they received during RE-LY for a mean follow-up of 2.25 years. Compared to RE-LY, more subjects in RELY-ABLE were male and had paroxysmal atrial fibrillation compared to permanent atrial fibrillation. Similarly, to RE-LY, patients in RELY-ABE had diabetes mellitus and coronary artery disease. *Inclusion criteria:* participants in the original RE-LY trial who were not assigned warfarin. In RELY-ABLE, subjects were 48% of the original subjects in the RE-LY trial. *Exclusion criteria* included: necessity for anticoagulation for other reasons, a gastrointestinal ulcer within the past 30 days,	*Efficacy Outcomes:* *Stroke and systemic embolism occurred in 1.46% of patients on dabigatran 150 mg BID and in 1.60% of patients on dabigatran 110 mg BID [HR (CI: 95%) 0.91 (0.69, 1.20]. *Annual hemorrhagic stroke rates were 0.13% for dabigatran 150 mg compared to 0.14% for dabigatran 100 mg. *Safety Outcomes:* *Bleeding rates were 3.74% on dabigatran 150 mg compared to 2.99% on dabigatran 110 mg [HR (CI: 95%): 1.26 (1.04-1.53)]. *Death rates were 3.02% on dabigatran 150 mg compared to 3.10% on dabigatran 110 mg [HR (CI: 95%): 0.97 (0.80, 1.19)]. *Conclusion: Longer-term use of dabigatran 150 mg BID demonstrated an increased risk or major bleeding compared to dabigatran 100 mg BID. Rates of stroke and death were similar between the two doses of dabigatran.*

		anemia (hemoglobin <100 g/L), thrombocytopenia (platelet count <100x10^{9}L), liver transaminases >2 times normal, CrCl <30 mL/min, pregnancy, high risk of bleeding, scheduled ablation for AF, and unstable cardiovascular disease.	
Trial	**Design/Method**	**Sample**	**Findings and Conclusions**
RE-ALIGN (Randomized, phase II study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran in Patients are Heart Valve Replacement) (Eikelboom et al., 2013).	Prospective, randomized, phase 2, open-label trial investigating *warfarin versus dabigatran in patients undergoing aortic or mitral valve replacement within the past 7 days or a history of a valve replacement within the past three months.* This study was completed at 39 sites within 10 countries from 2011-2012. Initial dabigatran dose was based upon kidney function, with adjustments based upon reaching a trough plasma level of 50 ng/mL. INR dose was based upon attaining an INR of 2-3 (low thromboembolic risk) or 2.5.-3.5 (immediate or high thromboembolic risk). Patients were administered the anticoagulant for 12 weeks. The efficacy outcome was the trough plasma level of dabigatran. The safety outcome measured was major bleeding.	Out of a total of 252 subjects, 168 were randomly assigned to the dabigatran group while 84 were assigned to the warfarin group in a 2:1 ratio. Approximately 64-67% of the subjects were male and the mean age was 56 years old. Approximately 79% (199) subjects were scheduled for the valve replacement, with 172 (68%) aortic, 71 (28%) mitral, and 9 (4%) both valves. Out of the subjects, 74 (24%) were low risk for thromboembolic complications after the procedure, and 178 (71%) were intermediate or high risk. *Inclusion criteria:* age 18-75 years old and either scheduled for implantation of a mechanical bileaflet valve in the aortic or mitral valve or received a mechanical bileaflet mitral valve within 3 months prior to this study. *Exclusion criteria:* prior prosthetic valve replacement, aortic surgery, endocarditis, complex congenital heart anomalies, history of hemorrhagic stroke, high bleeding risk, uncontrolled hypertension, abnormal liver functions >3 times the normal limit or active hepatitis, creatinine clearance <40mL/min, chronic anticoagulation for reasons other than AF, myocardial infarction within the past month, recent radiation treatment or cancer, pregnancy, scheduled surgery within one month, or contraindications to warfarin or dabigatran.	The trial ended prematurely after increased VTE and bleeding events presented in the dabigatran group. In 52 (32%) of the 162 dabigatran patients, dabigatran dose was adjusted or discontinued. *Efficacy outcome:* Stroke (ischemic or unspecified) manifested in 9 (5%) of dabigatran subjects compared to zero patients in the warfarin group. *Safety outcome:* Major bleeding (pericardial bleeding) presented in 7 (4%) subjects of the dabigatran group compared to 2 (2%) of the warfarin subjects. *Conclusion: Due to the increased risk of VTE and bleeding risk in patients with mechanical heart valves, dabigatran displays increased risk compared to warfarin.*
EDOXABAN (Savaysa®) **Edoxaban Study 018** (Weitz et al., 2011).	Randomized, double-blind, multicenter, multinational, parallel group, phase 2 study comparing *four doses of edoxaban to warfarin in patients with non-valvular atrial*	A total of 1,146 subjects were randomized to edoxaban (30 mg daily, 30 mg twice daily, 60 mg daily, or 60 mg twice daily) or dose-adjusted warfarin with a target INR of 2.0-3.0. The average age of subjects was 65 years old with 65.4% warfarin naïve.	*Safety outcome:* Bleeding occurred in 3.2% of subjects in the warfarin group, compared to 10.6% in the edoxaban 60 mg twice daily group (p = 0.002) and 7.8% in the edoxaban 60 mg twice daily group (p = 0.029). Bleeding occurred less in the edoxaban 60 mg daily group (3.8%)

	fibrillation to prevent stroke. Safety outcomes measures were bleeding events, elevated liver enzymes, and elevated bilirubin levels.		and edoxaban 30 mg daily group (3.0%) compared to warfarin. *Labs:* Liver enzyme levels and bilirubin levels were not significantly elevated in any of the edoxaban groups. *Conclusions: With comparable bleeding risk profiles, edoxaban 30 mg or 60 mg daily is a safe alternative to warfarin in preventing stroke in patients with atrial fibrillation. Due to the heightened bleeding risk, edoxaban 30 mg twice daily or edoxaban 60 mg twice daily are not recommended.*
Trial	**Design/Method**	**Sample**	**Findings and Conclusions**
ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation) (Giugliano et al., 2013).	Randomized, double-blind, double-dummy study *comparing edoxaban and warfarin in patients with atrial fibrillation and an intermediate to high risk of stroke or systemic embolism.* Patients received warfarin or edoxaban for a median of 2.5 years. This study was completed at 1,339 sites within 46 countries from 2008-2010. The efficacy outcome was incidence of stroke or systemic embolism. The safety outcome was major bleeding and cardiovascular deaths.	Out of 21,101 subjects with atrial fibrillation were randomly assigned to one of three groups: 1) 7,030 received edoxaban 60 mg daily, 2) 7,034 received edoxaban 30 mg daily, and 3) 7,037 received warfarin daily with a target INR of 2.0-3.0. The average age of subjects was 72 years old with 38% females per group. *Inclusion criteria:* >age 21 years old, documented AF through an EKG within the past year, and $CHADS_2$ score >2. *Exclusion criteria:* atrial fibrillation with a reversible cause, a creatinine clearance <30 mL/min, high risk of bleeding, dual antiplatelet therapy, moderate to severe mitral stenosis, chronic anticoagulation for other reasons, acute coronary syndrome, coronary revascularization, or stroke within 30 days.	*Efficacy Outcome:* stroke or thromboembolism occurred in 1.50% of subjects in the warfarin group (therapeutic INR 68.4% of the time), compared to 1.18% with edoxaban 60 mg (HR 0.78; 97. % CI 0.63-0.99; p<0.001 for noninferiority) and edoxaban 30 mg (HR 1.07; 95% CI 0.87-1.31; p = 0.005 for noninferiority). Edoxaban 60 mg was preferred to warfarin for intention-to-treat (HR 0.87; 97.5% CI 0.73-1.04; p = 0.08). Conversely, warfarin was preferred to edoxaban 30 mg in the intention-to-treat (HR 1.13; 97%F CI 0.71-0.91; p<0.0001) *Safety Outcome:* *Subjects on edoxaban 60 mg demonstrated less severe bleeding annually (3.43%) compared to warfarin (2.75%; HR 0.80; 95% CI 0.71, 0.91), p<0.001]. The same results were seen with edoxaban 30 mg, with 1.61% annual bleeding compared to warfarin (HR 0.47; 95% CI, 0.41-0.55; p<0.001). The most common site of major bleeding was in the GI tract: 205 (1.78) with edoxaban and 150 (1.27) with warfarin. *Annual cardiovascular deaths occurred in 3.17% of subjects on warfarin compared to 2.74% with edoxaban 60 mg (HR 0.86; 95% CI 0.77-0.97; p=0.01), and 2.71% with low dose edoxaban (HR 0.85; 95% CI 0.76-0.96; p=0.008). *Conclusion: In patients with atrial fibrillation, edoxaban 30 mg and 60 mg were noninferior to warfarin in preventing stroke or systemic embolism, in addition to decreased bleeding risk and cardiovascular death.*

Trial	Design/Method	Sample	Findings and Conclusions
RIVAROXABAN (Xarelto®) **ROCKET AF** (Rivaroxaban once daily, oral, direct factor Xa inhibitor Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) (Patel et al., 2011)	Multi-national double-blind, double-dummy, event driven study comparing *rivaroxaban to dose-adjusted warfarin in stroke prevention of nonvalvular atrial fibrillation* Patients were randomized to a study treatment of warfarin or rivaroxaban for a mean of 590 days. This study was complete at 1,178 sites within 45 countries from 2006-2010. Primary efficacy outcomes measured the incidence of stroke or systemic embolism. Safety outcomes measured major and non-major bleeding events.	A total of 14,264 patients were randomized to rivaroxaban (7,131 subjects) or adjusted-dose warfarin (7,133 subjects) with a target INR of 2.0-3.0. Rivaroxaban was administered 20 mg daily or 15 mg daily with a creatinine clearance of 30-49 mL/min. The mean age of subjects was 71 years, the mean $CHADS_2$ score of 3.5, 60% male, 83% Caucasian, 13% Asian, and 1.3% Black. *Inclusion criteria:* AF had to be diagnosed by EKG within 30 days. Patients were required to have the following risk factors: a prior stroke (ischemic or unknown type), transient ischemic attack, or non-CNS systemic embolism. In addition, patients were required to have 2 or more of the following risk factors: age >75 years, hypertension, heart failure or left ventricular ejection fraction <35%, or diabetes mellitus. The $CHADS_2$ score had to be >2. *Exclusion criteria:* severe mitral stenosis, prosthetic heart valve, scheduled cardioversion, AF with a reversible cause, atrial myxoma, endocarditis, active bleeding, high bleeding risk, thrombocytopenia (<90,000 μ/L), uncontrolled hypertension ≥180/100, prior stroke or TIA, chronic anticoagulation for other reasons, current use of antiplatelets, chronic NSAID use, use of cytochrome P450 3A4 inhibitors or inducers, anemia (hemoglobin <10 g/dL), pregnancy or breastfeeding, HIV positive, liver disease, or creatinine clearance <30 mL/min	*Efficacy outcomes:* *Stroke or systemic embolism occurred in 188 of the subjects in the rivaroxaban group annually (1.7%), compared to 241 in the warfarin group (2.2%; HR 0.79, 95% CI 0.66-0.96, p<0.001 for noninferiority). *In the intent-to-treat analysis, stroke or systemic embolism occurred annually in 269 subjects in the rivaroxaban group (2.1%) compared to 306 subjects in the warfarin group (2.4%; HR 0.88, 95% CI 0.74-1.03; p<0.001 for noninferiority; p=0.12 for superiority). *Safety outcomes:* *Major and non-major bleeding occurred in 1,475 patients in the rivaroxaban group annually (14.9%) and 1,449 in the warfarin group annually (14.5%). *Intracranial hemorrhage (0.5%) and fatal hemorrhage (0.2%; p=0.003) occurred less with rivaroxaban than warfarin (0.7% intracranial hemorrhage and 0.5% fatal hemorrhage, p=0.02). *Conclusions: Rivaroxaban was non-inferior to warfarin to preventing first occurrence of stroke or systemic embolism in nonvalvular atrial fibrillation* [HR (95% CI): 0.88 (0.74, 1.03)]. *Bleeding events was non-significant between groups but rivaroxaban demonstrated less fatal and intracranial bleeding compared to warfarin.*
X-VeRT (Explore the Efficacy and Safety of Once-Daily Rivaroxaban for the Prevention of Cardiovascular Events with Non-Valvular Atrial Fibrillation Scheduled for Cardioversion)	Prospective, randomized, open-label, parallel group study comparing *safety and efficacy of rivaroxaban to warfarin in patients with non- valvular atrial fibrillation scheduled for cardioversion.* This ongoing study will be completed in 17 countries.	A total of 1,500 patients will be randomized into two groups in a 2:1 ratio of rivaroxaban to warfarin. Subjects can be further randomized into two groups: 1) rivaroxaban or warfarin with heparin given 1-5 days prior to cardioversion with a transesophageal echocardiography to assess for atrial thrombi or 2) rivaroxaban or warfarin given 21-56 days before the cardioversion. Rivaroxaban or warfarin will be continued 6 weeks after the cardioversion. Rivaroxaban 20 mg	*This ongoing trial will assess the safety and efficacy of rivaroxaban versus warfarin in preventing stroke and reducing bleeding risk for non-valvular atrial fibrillation patients requiring cardioversion.*

(Ezekowitz et al., 2014)	The efficacy outcome is incidence of strokes, TIA, myocardial infarction, noncentral nervous system systemic emboli, and cardiovascular death. The safety outcome is the incidence of bleeding events.	daily will be the administered dose unless the patient has a creatinine clearance <30-40 mL/min, warranting rivaroxaban 15 mg daily. The target INR for warfarin will be 2.0-3.0. *Inclusion criteria:* adults older than 18 years old with non-valvular atrial fibrillation lasting longer than 48 hours and hemodynamic stability. These patients must be scheduled for cardioversion, either electrical or pharmacologic. *Exclusion criteria:* severe mitral stenosis, prosthetic heart valve, severe stroke within the past 3 months, left atrial thrombus, TIA, thromboembolus, or myocardial infarction within the past 2 weeks, high bleeding risk, active bleeding, chronic anticoagulation for another reason, dual antiplatelet therapy or chronic aspirin use >100 mg daily, use of CYP3A4 and P-gp inhibitors, pregnancy or breastfeeding, contraindications to rivaroxaban or warfarin, hepatic disease, or alcoholism.	
Trial	**Design/Method**	**Sample**	**Findings and Conclusions**
PIONEER AF-PCI (Gibson, et al., 2015)	Exploratory, open-label, randomized, controlled, multicenter study comparing the *safety of rivaroxaban and warfarin in patients with non-valvular atrial fibrillation who have received percutaneous coronary intervention (PCI) with stent implantation.* Safety outcomes measured the incidence of thrombolysis in myocardial infarction, major bleeding, or minor bleeding. Patients were followed-up for an average of 12 months. Dual antiplatelet therapy is considered aspirin plus clopidogrel (or an alternative P2Y12 inhibitor: prasugrel or ticagrelor). Triple therapy is considered dual therapy plus an oral anticoagulant.	A total of 2,100 subjects have been enrolled in this study and are being randomized to three groups (700 subjects per group): 1) rivaroxaban 15 mg daily with clopidogrel 75 mg daily for 12 months, 2) rivaroxaban 2.5 mg twice daily with dual antiplatelet therapy (clopidogrel 75 mg daily and aspirin 75-100 mg daily) for a predetermined duration of 1, 6, or 12 months, or 3) dose-adjusted warfarin daily (target INR 2.0-3.0) with dual antiplatelet therapy for a predetermined duration of 1, 6, or 12 months. If clopidogrel was not used, an alternative P2Y12 inhibitor could be used in its place. *Inclusion criteria:* at least 18 years old with AF diagnosed by an EKG and have completed PCI. *Exclusion criteria:* active bleeding, thrombocytopenia (platelets <90,000 µ/L), history of intracranial bleed, severe gastrointestinal bleed within the past year, history of TIA or stroke, cardiogenic shock, trauma	*This trial is currently ongoing to evaluate bleeding risks between warfarin and rivaroxaban in patients with non-valvular atrial fibrillation who have undergone PCI.*

		within 30 days, creatinine clearance <30 mL/min, anemia (hemoglobin <10 g/dL), liver disease, history of HIV, planned CABG, contraindications to aspirin, warfarin or clopidogrel.	
Trial	**Design/Method**	**Sample**	**Findings and Conclusions**
WARFARIN (Coumadin®) **AFASAK-I:** (Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation) (Petersen, Godtfredsen, Boysen, Andersen, & Andersen, 1989)	Randomized, double-blind study comparing *warfarin, aspirin, and placebo in patients with non-valvular atrial fibrillation.* This study was completed from 1985-1988 with a patient follow-up of 2 years. Primary outcomes measured included stroke, transient ischemic attack (TIA), embolic complications. Death was a secondary outcome assessed.	Subjects were randomized to a treatment group: warfarin (335), aspirin 75 mg daily (336) and placebo (336).	*Efficacy outcome:* Thromboembolic complications and mortality from a vascular etiology were decreased in the warfarin group (5 patients) compared to the placebo (20 patients) and aspirin (21 patients) groups. *Safety outcome:* Bleeding was evident in 21 subjects on warfarin, 2 on aspirin, and 0 on the placebo. *Conclusion: In patients with non-valvular atrial fibrillation, warfarin is recommended to prevent thromboembolism.*
BAATAF (Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990)	Unblended, randomized, controlled study investigating the *safety and efficacy of warfarin in preventing stroke in patients with nonvalvular atrial fibrillation.* Average follow-up time was 2.2 years. The efficacy outcome measured was incidence of ischemic stroke. The safety outcomes measured were major and minor bleeding events and death.	Patients were randomized to the warfarin group (212 subjects with a target prothrombin time ratio of 1.2-1.5) or the control group (208 subjects). The control group was given the preference of taking aspirin. The mean age of subjects was 68 years old with 72% men. *Inclusion criteria:* adults diagnosed with non-rheumatic (valvular) AF through at least two separate EKGs. With intermittent AF, an EKG must document the rhythm within 18 months of the study. Thyroid function must be normal to participate. *Exclusion criteria:* planned cardioversion, transient AF related to another diagnosis, cardiac thrombus, left ventricular aneurysm, severe heart failure, prosthetic heart valves, severe stroke within the past 6 months, TIA, intracranial hemorrhage, contraindications to anticoagulation (liver disease or peptic ulcer disease), recent thrombophlebitis, or chronic aspirin use.	Prothrombin time was therapeutic in 83% of the subjects. Approximately 10% of the subjects in the warfarin group chose to stop taking warfarin during the study. *Efficacy outcome:* The annual incidence of stroke was 2 (0.41%) in the warfarin group compared to 13 (2.98%) in the control group, suggesting warfarin decreases the risk of stroke by 86% (95% CI, 0.04-0.49; p = 0.0022). *Safety outcomes:* *A total of 37 subjects died during the study, with 2.25% annually in the warfarin group and 5.97% annually in the control group (95% CI, 0.17-0.82; p = 0.005), with one patient succumbing to a severe bleed in each group. *Bleeding requiring a transfusion or hospitalization was comparable in both groups. Minor bleeding was higher with warfarin (38 subjects) compared to the control group (21 subjects). *Warfarin at lower doses is safe and effective in preventing stroke with non- valvular atrial fibrillation.*

Trial	Design/Method	Sample	Findings and Conclusions
SPAF I: (Stroke Prevention in Atrial Fibrillation) (Stroke prevention, 1991)	Multicenter, randomized, double-blind study comparing *aspirin (325 mg daily) to warfarin group with a placebo group to prevent stroke and systemic embolization in patients with atrial fibrillation.* 1,300 patients were followed for an average of 1.3 years at 16 facilities with the United States from 1987-1992. The efficacy outcome measured incidence of stroke or systemic embolization. The safety outcome measured bleeding events.	Group 1 was composed of patients randomly assigned to the warfarin group (210 subjects), aspirin group (206 subjects), or placebo group (211 subjects). Patients unable to take anticoagulation were randomized Group 2: either the aspirin (346 subjects) or placebo group (357 subjects). Out of the 1,330 subjects, the average age of subjects was 67 years old, 71% men, 85% Caucasian, 6% Black, and 10% Asian/Hispanic/other race. *Inclusion criteria:* diagnosis through an electrocardiogram of non-valvular atrial fibrillation within the past year. *Exclusion criteria:* contraindication to aspirin or warfarin, mitral stenosis, congestive heart failure (New York Heart Association class 4), myocardial infarction within the past three months, coronary bypass surgery within the past year, unstable angina pectoris within the past year, stroke or TIA within the past two years, life expectancy less than two years, chronic renal failure, thrombocytopenia, severe alcoholism, other indications for chronic warfarin therapy, chronic NSAID use. *Exclusion criteria for anticoagulation:* age greater than 75 years old, unable to adhere to INR monitoring, history of falls, positive occult blood in stool, chronic alcoholism, uncontrolled hypertension, syncope or seizures, previous intracranial bleed, poorly controlled INR levels, or prior bleed while on anticoagulation.	*Efficacy outcomes:* *Patients assigned to the warfarin group versus placebo displayed a decrease of stroke or systemic embolism by 67% annually (2.3% with warfarin and 7.4% with placebo, p = 0.01; 95% confidence interval, 27.85%). *Patients assigned to the aspirin group versus placebo demonstrated a 42% reduction of stroke or systemic embolism annually (3.6% with aspirin and 6.3% with placebo, p = 0.02; 95% confidence interval, 9-63%). *These primary events of stroke or systemic embolism, as well as death were decreased by 58% with warfarin (p = 0.01) and 32% with aspirin (p = 0.02) with aspirin. *Safety outcome:* The annual bleeding rates 1.5% with warfarin, 1.4% with aspirin, and 1.6% with the placebo. *The risk of stroke and systemic embolism in patients with atrial fibrillation can be reduced with aspirin or warfarin, yet data is not conclusive for preferring one drug versus the other.*

Trial	Design/Method	Sample	Findings and Conclusions
CAFA: (Canadian Atrial Fibrillation Anticoagulation) (Connolly et al., 1991).	Randomized, double-blind, placebo-controlled study investigating the use of *warfarin versus a placebo in preventing stroke in patients with atrial fibrillation.* Primary efficacy outcomes measured included incidence of nonlacunar stroke and noncentral nervous system embolism. Primary safety outcomes measured included fatal bleed or intracranial bleed within 28 days of completing the study.	Patients were randomly assigned to the warfarin group with a target INR of 2.0-3.0 (187 subjects) or the placebo group (191 subjects).	This trial was stopped prematurely because of two similar studies displaying superiority in warfarin compared to a placebo in decreasing stroke risk in patients with atrial fibrillation. Over 26% of subjects stopped warfarin prematurely as well as 23% of the placebos. An average of 43.7% of the subjects maintained the therapeutic INR of 2.0-3.0 in the warfarin group. *Efficacy outcome:* A primary effect was noted in 3.5% of the warfarin subjects compared to 5.2% of the placebo patients, suggesting a 37% decrease in stroke risk with warfarin (95% CI, - 63.5%-75%%, p = 0.17). *Safety outcomes:* *Severe bleeding was present in 2.5% of the warfarin subjects compared to 0.5% in the placebo subjects. *Minor bleeding occurred in 16% of the warfarin subjects compared to 9% of the placebo subjects. *Conclusion: Warfarin is superior to a placebo in preventing stroke and non-central nervous system embolism in patients with atrial fibrillation, yet displays a high risk of minor and severe bleeding compared to a placebo.*
EAFT **(**European Atrial Fibrillation Trial Study Group, 1993)	Randomized, multicenter study assessing the *safety and efficacy of anticoagulation versus aspirin in patients with non-valvular atrial fibrillation who have suffered a minor stroke or transient ischemic attack.* This study was completed in 108 clinics in 13 countries, with an average follow-up of 2.3 years. The primary efficacy outcomes measured included the incidence of stroke, myocardial infarction, systemic embolism, or death from	In group 1, 669 patients were randomized to either open-label anticoagulation or a double-blind group receiving a placebo or 300 mg aspirin daily. In group 2, 2,338 patients were randomized to receive aspirin or placebo if they had contraindications to warfarin. The average age was 73 years old, with 55-59% men per group. *Inclusion criteria:* patients 25 years or older with non-valvular atrial fibrillation and history of a minor ischemic stroke or TIA within the past 3 months. *Exclusion criteria for the study:* secondary causes of atrial fibrillation such as hyperthyroidism, coronary surgery	*Efficacy outcomes:* *Annually, in group 1, primary events occurred in 8% of the anticoagulant group compared to 17% in the placebo group (hazard ratio [HR] 0.53; 95% confidence interval [CI] 0.36-0.79). However, the rate of strokes decreased annually in group 1 from significantly from 12% to 4% (HR 0.34; 95% CI0.20-0.57). *If the patient was on aspirin and in group 1 or group 2, primary events annually occurred in 15% of subjects compared to 19% in the placebo (HR 0.83; 95% CI 0.65-1.05). *Anticoagulation was determined to be superior to aspirin in preventing

	a vascular etiology. The primary safety outcome measured was bleeding events.	scheduled within the next 3 months *Exclusion criteria for randomization to a treatment group:* concurrent use of medications with a high bleeding risk (NSAIDS, anti-platelets, or oral anticoagulants), mechanical valves, cardiac aneurysm, atrial myxoma, myocardial infarction within the past 3 months, or coagulation disorders. The acceptable range for the INR for the anticoagulant was 2.5-4, with a goal of 3. The choice of anticoagulant was selected by the physician, predominantly coumarin. *Exclusion criteria for anticoagulation:* high bleeding risk, hypertension >180/100 mm Hg, chronic alcoholism, prior intracranial bleed, hemorrhagic retinopathy, or poor adherence to the treatment plan.	primary events (HR 0.60; 95% CI 0.41-0.87). *Safety outcome:* No intracranial bleeds were observed in patients anticoagulated, with minor bleeding present annually in only 2.8% of subjects in the warfarin group and 0.9% of the aspirin group. *Conclusion: Anticoagulation is superior to aspirin for both safety and efficacy in patients with non-valvular atrial fibrillation who have suffered from a recent TIA or stroke. If anticoagulation is contraindicated, aspirin is a safe alternative for this population to prevent stroke.*
Trial	**Design/Method**	**Sample**	**Findings and Conclusions**
SPAF-II: (Stroke Prevention in Atrial Fibrillation II) Halperin et al., 1994)	This study was a continuation of SPAF-I to better assess through two parallel randomized trials the *efficacy of warfarin compared to aspirin in reducing stroke in patients with atrial fibrillation.* The focus in this study was the incidence of thromboembolic events with warfarin compared to aspirin and to compare the effectiveness of anticoagulants based on patient age. *The goal was to determine if warfarin compared to aspirin would decrease systemic embolism or stroke in patients less than 75 years old by 2% decrease this risk by 4% in patients older than 75 years old.* The safety outcome measured was incidence of systemic embolism or stroke. This study took place from 1985-1991 at 16	The first randomized trial contained 715 subjects less than 75 years old and the second randomized trial contained 383 patients over 75 years of age. Patients randomized to the warfarin group had a goal INR of 2.0-4.5, while the aspirin group was given 325 mg daily. All 416 patients from SPAF-I were who able to take anticoagulation continued the therapy they were given during this first study. Also from SPAF-I, 265 of the patients in the placebo group were randomized to a group in SPAF-II. The other 419 patients were new patients who did not participate in SPAF-I. The same inclusion criteria as in SPAF-I were utilized. Additionally, patients were excluded from the study if they were less than 60 years old without cardiovascular disease, mitral stenosis, contraindications to warfarin or aspirin, or mechanical heart valves. Confirmation of atrial fibrillation through an electrocardiogram within the past year was necessary to participate in this study.	*Patients less than 75 years old*: *Warfarin decreased the rate or stroke or systemic embolism by 7% per year (95% CI; 0.4-1.7). In comparing warfarin to aspirin, the rate of stroke or systemic embolization was 1.3% compared to 1.9% respectively (relative risk [RR] 0.67, $p = 0.24$). *In the absence of hypertension, new onset heart failure, or a prior thromboembolism, stroke or systemic embolism occurred in 0.5% of these patients annually (95% CI; 0.1-1.9). *Patients older than 75 years old*: *Systemic embolism or stroke was reduced by 0.5% per year (95% CI, -1.7-4.1). In comparing warfarin to aspirin, the rate of stroke or systemic embolization was 3.6% compared to 4.8% respectively (relative risk [RR] 0.73, $p = 0.39$). *The overall rate of hemorrhagic or ischemic stroke with deficits was 4.3% per year in the aspirin group and 4.6% per year in the warfarin group (RR 1.1).

	sites within the United States.		*Conclusions: To prevent ischemic stroke in patients with atrial fibrillation, warfarin is superior to aspirin. In the absence of risk factors, patients less than 75 years old demonstrate a low stroke risk if treated with aspirin. In patients older than 75 years old, the hemorrhagic and ischemic stroke risk is increased, despite administration of warfarin or aspirin. Selecting the type of anticoagulation should be dependent on patient age and stroke risk with atrial fibrillation.*
Trial	**Design/Method**	**Sample**	**Findings and Conclusions**
SPAF-III: (Stroke Prevention in Atrial Fibrillation III) (Adjusted dose warfarin, 1996).	This randomized, multicenter study was a continuation of SPAF-I and SPAF-II. The goal of this study was to *compare warfarin to the combination of warfarin and aspirin to assess safety and efficacy of anticoagulation in patients with atrial fibrillation and high risk of stroke.* This study was designed to take place over 2 ½ years from 1993-1995 in 20 sites in both the United States and Canada. The primary efficacy outcomes measured were rates of ischemic stroke and systemic embolism.	Patients were randomly assigned to the adjusted-dose warfarin (INR 2.0-3.0) group (523 subjects) or to the low intensity, fixed-dose warfarin (INR 1.2-1.5) with aspirin (325 mg daily) group (521 subjects). This study was comprised of 1044 patients with atrial fibrillation and a minimum of one risk factor for stroke (female sex over 75 years old, congestive heart failure, left ventricular ejection fraction ≤25%, prior thromboembolism, or systolic blood pressure >160 mmHg). The same inclusion and exclusion criteria from SPAF-I and SPAF-II applied except: subjects who participated in the prior trials were exempt. Inclusion criteria included documented AF through an electrocardiogram within 6 months, no history of mitral stenosis, mechanical heart valves or pulmonary embolism, and no contraindications to warfarin or aspirin. Compared to prior trials, patients who suffered from an ischemic stroke or TIA within 30 days where included in SPAF-III.	*In the warfarin patients, the average INR in the aspirin with warfarin group was 1.3 compared to 2.4 for the dose adjusted warfarin. *During the mean follow-up of 1.1 years, INRs in the aspirin with warfarin group were therapeutic (1.2-1.5 range) 54% of the time and subtherapeutic (<1.2) 34% of the time. *The follow-up period was stopped prematurely, as the risk of ischemic stroke and systemic embolism was significantly higher in the aspirin with warfarin group (7.9% annually, p = 0.0001), compared to the adjusted-dose warfarin (1.9% annually, 95% CI (3.4, 8.6). *The warfarin with aspirin group displayed higher annual rates of stroke (5.6%, p = 0.0007) compared to warfarin only (1.7%), as well as higher rates of death from a vascular cause (11.8% in the combination group compared to 6.4% with warfarin, p = 0.0002). *Severe bleeding annually was similar between the combination group [2.4%, 95% CI 1.4, 4.1)] and warfarin only group [1.4%, 95% CI (1.2-3.7)]. *Conclusions: Low-intensity, fixed-dose warfarin with aspirin is not recommended to prevent stroke in patients with atrial fibrillation. Adjusted-dose warfarin with a target INR of 2.0-3.0 has demonstrated safety and efficacy in decreasing stroke in patients with atrial fibrillation.*

Trial	Design/Method	Sample	Findings and Conclusions
AFASAK-II: (Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation II) (Gullov et al., 1998)	This randomized, controlled study was a continuation of AFASAK-I to further *assess safety and efficacy of warfarin to aspirin in preventing stroke in patients with non- valvular atrial fibrillation.* Primary efficacy outcomes measures included the incidence of stroke or systemic thromboembolism. Secondary efficacy outcomes measured included death, TIA, or myocardial infraction. The safety outcome measured was bleeding events. The trial was designed to run for six years starting in 1993, was but stopped prematurely in 1996 when another study (SPAF-II) concluded low- intensity (minidose) warfarin in combination with aspirin is less effective compared to adjusted dose warfarin.	A total of 677 subjects were randomly assigned to one of four groups: 1) minidose warfarin 1.25 mg/day, 2) warfarin sodium 1.25 mg/day plus aspirin 300 mg/day, 3) aspirin 300 mg/day, and 4) adjusted dose warfarin with a target INR of 2.0-3.0. The average age of the subjects was 74 years old and 35-43% females per group. *Inclusion criteria:* documentation of atrial fibrillation through an electrocardiogram by at least one month, and age 18 or older. *Exclusion criteria:* less than age 60 with atrial fibrillation as a cause of heart disease, heart failure, hyperthyroidism, or chronic obstructive pulmonary disease; blood pressure >180/100 mmHg; history of stroke or TIA within the past 6 months; high bleeding risk; patients already on warfarin therapy; valvular atrial fibrillation; or contraindication to warfarin or aspirin.	*Efficacy outcomes:* *The incidence of stroke or thromboembolism after one year on therapy occurred in 5.8% of the minidose warfarin group, 7.2% in the combination aspirin and warfarin group, and 2.8% in the adjusted-dose warfarin group (p = .67). *No significant differences were noted when comparing treatment of one to three years. *Safety Outcomes:* *Severe bleeding was not evident in any of the groups after three years. *Minor bleeding was present in 24.7% of patients on minidose warfarin, 24.4% on combination warfarin and aspirin, group, 30.0% on aspirin, and 41.1% on adjusted dose warfarin. *With the additional factors of allergic reactions and dyspepsia, the risk of bleeding with aspirin increased to 46.2% after three years. *Conclusion: Minidose warfarin did not display statistically significance in reducing stroke in patients with atrial fibrillation, thus adjusted-dose warfarin with a target INR of 2.0-3.0 continues to be recommended.*
PATAF: Prevention of Arterial Thromboembolis m in non-valvular Atrial Fibrillation) (Hellemons et al., 1999)	Randomized control trial comparing *aspirin to warfarin preventing thromboembolism in patients with non-valvular atrial fibrillation.* The average follow-up time was 2.7 years. Efficacy outcomes measured included stroke or systemic embolism. Safety outcomes measured included vascular death or severe bleed.	729 atrial fibrillation patients in Netherland age 60 years old or older were randomly assigned to standard coumarin therapy (target INR of 2.5-3.5), low intensity coumarin therapy (target INR of 1.1-1.6) or aspirin (150 mg daily). The average age of patients was 75 years old, with 32-57% men per group. Patients unable to be take standard coumarin doses were randomized to either the aspirin or low intensity coumarin groups. *Inclusion criteria:* patients age 60 or older with atrial fibrillation diagnosed through an electrocardiogram within the past two years. *Exclusion criteria:* prior stroke, valvular atrial fibrillation,	*Efficacy outcome:* In comparing low dose anticoagulation to aspirin, the hazard ratio for stroke or thromboembolism was 0.91 (0.t1 to 1.36) and 0.78 for standard anticoagulation to aspirin (0.34 to 1.81). *Safety Outcomes:* * Out of all three groups, 108 adverse events occurred (5.5% per year), including 13 severe bleeds (0.7% annually). *Death from a non-vascular cause was lower in the anticoagulation group compared to aspirin [hazard ratio 0.41 [0.20 to 0.82]).

Trial	Design/Method	Sample	Findings and Conclusions
		myocardial infarction or cardiovascular surgery within the prior year, cardiomyopathy, heart failure, cardiac aneurysm, reversible causes of AF, pacemaker, contraindications to aspirin or coumarin, history of systemic embolism, renal infarction, prior coumarin use within 3 months, life expectancy of less than 2 years. *Exclusion criteria for standard coumarin doses:* age older than 78 years old, duodenal or gastric ulcer, retinopathy, history of a genitourinary or gastrointestinal bleed, hypertension (systolic blood pressure >185 mm Hg and/or diastolic blood pressure >105 mm Hg).	*Severe bleeding was nonsignificant when comparing the three treatment groups. *Conclusion: Coumarin therapy (both low-intensity and standard therapy) has not demonstrating superiority to aspirin in preventing thromboembolism with no reduction in bleeding risk in patients with non-valvular atrial fibrillation, thus aspirin is recommended as first line treatment in this population.*
BAFTA: Birmingham Atrial Fibrillation Treatment of the Aged Study (Mant et al., 2007)	Prospective, randomized, open-label, blind assessment of end points, controlled study investigating the *bleeding versus stroke risk in elderly patients on warfarin versus aspirin.* Subjects were gathered from 260 clinics within England and Wales from 2001-2004. Subjects were followed-up between 2-7 years. The primary efficacy and safety outcomes measures were incidence of ischemic or hemorrhagic stroke, arterial embolism, intracranial hemorrhage and extracranial hemorrhage.	A total of 937 subjects age 75 years age or older were randomly assigned to the warfarin group (target INR of 2.0-3.0) or aspirin (75 mg daily). The average age was 81.4 years old with 54-55% men per group. *Inclusion criteria:* age 75 or older with a confirmed diagnosis of atrial fibrillation by EKG within the past two years. *Exclusion criteria:* rheumatic (valvular) heart disease, intracranial hemorrhage, non-traumatic bleed within the past 5 years, esophageal varices, contraindications to warfarin or aspirin, terminal illness, surgery within the past 3 months, and blood pressure >180/110 mm Hg.	*Safety and Efficacy outcomes:* *Throughout the study there was a total of 21 strokes, 2 intracranial hemorrhages, and 1 systemic embolism in the warfarin group (annual risk 1.8%). *In comparison, the aspirin group had 44 strokes, 1 intracranial hemorrhage, and 3 systemic embolisms (annual risk of 3.5%; relative risk 0.48, 95% CI 0.28-0.80, p = 0.003: absolute yearly risk reduction 2%, 95% CI 0.7-3.2). *Regarding extracranial bleeds, 1.4% occurred yearly in the warfarin group compared to 1.6% in the aspirin group (relative risk 0.97, 0.43-1.73; absolute risk reduction 0.2%-, -0.7 to 1.2). *Conclusion: Anticoagulation with warfarin is safe and efficacious, thus it is recommended over aspirin in patients over age 75 years old with atrial fibrillation to prevent stroke.*

Trial	Design/Method	Sample	Findings and Conclusions
REVERSAL AGENTS **Activated Charcoal and Apixaban** (Wang et.al., 2013)	Open-label, randomized, three-treatment, three-period, crossover study examining a 50-gram *overdose of apixaban and the results of subsequent administration of activated charcoal*. This study was completed from May 6th-17th, 2011. Activated charcoal was ingested at 2 hours or 6 hours after the overdose of apixaban. Serum labs were obtained up to 72 hours after the administration of activated charcoal.	18 healthy subjects age 18-45 years (mean age of 31.8 years), received 50 grams of activated charcoal 2 hours OR 6 hours after administration of 20 mg apixaban PO. The average age of subjects was 31.8 years old with 10 males and 8 females, 14 Caucasians and 4 Blacks. *Inclusion criteria:* healthy males and females age 18-45 years old with a body mass index of 18-32 kg/m^2. *Exclusion criteria*: relevant acute or chronic medical diagnoses, pregnancy or breastfeeding, gastrointestinal disorders, personal history of coagulopathies, family history of first degree relatives with coagulopathies, or intracranial hemorrhage, or smoking greater than 10 cigarettes daily. Five subjected were also excluded with emesis 6 hours after administration of apixaban or 30 minutes after ingestion of activated charcoal.	*Efficacy outcomes*: *Apixaban was evident in mean plasma concentrations 72 hours after ingestion and 48 hours after activated charcoal administration, at both the 2 and 6 hour intervals post apixaban dose. *Activated charcoal decreased the apixaban exposure (AUC) by 50% when administered 2 hours after ingestion of 20 mg apixaban and 27% when administered 6 hours after the 20 mg apixaban ingestion. *The mean half-life of apixaban (13.4 hours) decreased to ~5 hours after administration of activated charcoal at 2 or 6 hours post-dose. *Safety outcomes*: *Adverse effects in patients who received activated charcoal after apixaban overdose included: diarrhea, nausea, abdominal pain, vomiting, flatulence, and abdominal distention (11%). *Adverse effects were higher in patients who received apixaban followed by activated charcoal 2 hours later (72.2%) and 6 hours later (77.8%), compared to patients who received only apixaban (16.7%). * Adverse effects were mild (38.9%) or moderate (44.4%) in patients and resolved by the end of the study. *These adverse effects are comparable to known adverse effects or activated charcoal. *Conclusion: Activated charcoal can help eliminate a 20 mg apixaban overdose up to 6 hours post-dose.*
RE-VERSE AD **Idarucizumab (Praxbind®): Reversal for Dabigatran** (Pollack et. al., 2015)	Prospective cohort study examining safety and efficacy of 5 g *idarucizumab IV to reverse the anticoagulant effects of dabigatran in the event of significant bleeding or necessity for an urgent surgery*. Idarucizumab was administered as two 50- mL boluses containing 2.5 mg of medication each. The medications were administered intravenously less than 15 minutes apart. Blood levels of idarucizumab were obtained at baseline, after the first administration of	A total of 90 subjects group A had 51 with significant bleeding; group B had 39 requiring an urgent procedure). Over 68 subjects had an elevated dilute thrombin at baseline and 81 had an elevated ecarin clotting time. The median age of the subjects was 76.5 years and 56% males, with a median creatinine clearance of 58 mL/min. Over 90% of subjects were receiving dabigatran to prevent stroke related to atrial fibrillation. In group A, the necessity for a reversal agent were as follows: 18 intracranial hemorrhages, 20 gastrointestinal bleeds, 9 trauma-related bleeding, and 11 other etiologies of bleeding.	*Efficacy outcomes*: *The median maximum percentage reversal of anticoagulant effects of dabigatran was 100% [(CI: 95%: 100 (100, 100)]. *Test results reached normal levels within minutes, in 88-98% of subjects. 24 hours later, results of unbound dabigatran were <20 ng/mL in 79% of subjects. *Hemostasis in group A was obtained at a median rate of 11.4 hours in 35 patients. *Hemostasis in group B was obtained intraoperatively in 33 patients, mildly abnormal hemostasis in 2 patients, and moderately abnormal hemostasis in 1 patient. *Thrombosis occurred 72 hours after idarucizumab in 1 patient whom anticoagulation was not re-started.

	idarucizumab, between 10 to 30 minutes, and at 1, 2, 4, 12, and 24 hours after the second administration. This study was completed at 400 sites in 38 countries from 2014-2015. Patient follow-up was for 1 month after the study. Outcomes measured included the dilute thrombin time (dTT) or ecarin clotting time (ECT)lab 4 hours after administration of idarucizumab, and hemostasis.	In Group B, the most common indications for requiring a reversal agent included bone fractures, acute cholecystitis, acute renal insufficiency with catheter placement, acute appendicitis, joint/wound infection, and acute mesenteric ischemia. *Inclusion criteria*: Group A subjects required a reversal agent for uncontrollable or serious bleeding. Group B subjects needed surgery or invasive procedures which could not be delayed for 8 hours, the normal time for hemostasis. *Exclusion criteria:* none.	*Conclusion: Idarucizumab can safely and fully reverse the anticoagulation effects of dabigatran.*
Trial	**Design/Method**	**Sample**	**Findings and Conclusions**
ANNEXA-A and ANNEXA-R: Reversal agents for Factor Xa Inhibitors (Siegal et al., 2015)	Randomized, double-blind two-part, placebo-controlled study examining *reversal of apixaban and rivaroxaban with andexanet alpha in healthy, elderly subjects.* The outcome measured was the average change in anti-factor Xa activity (inhibition), measured as a percentage. This study was completed from 2014-2015: ANNEXA-A was completed in Arizona and ANNEXA-R was completed in California. **ANNEXA-A:** Andexanet alpha antidote administered to reverse the anticoagulant effects of apixaban **ANNEXA-R:** Andexanet alpha antidote administered to reverse the anticoagulant effects of rivaroxaban Subjects were observed for 8 days after administration of the antidotes, with safety outcomes monitored for up to 43 days after administration.	A total of 101 subjects were administered apixaban 5 mg twice daily for 3.5 days (ANNEXA-A, 48 subjects) or rivaroxaban 20 mg daily for 4 days (ANNEXA-R, 53 subjects), until therapeutic drug levels were achieved. In ANNEXA-A, subjects were randomized in a 3:1 ratio of andexanet to placebo (17 subjects received placebo), while in ANNEXA-R, subjects were randomized in a 2:1 ratio of andexanet or placebo (27 subjects). Subjects also were randomized to a part 1 or part 2 portion of the study. In part 1 of the study, on day 4, andexanet was given as a 400-mg bolus in ANNEXA-A and an 800-mg bolus in ANNEXA-R. In part 2 of the study, andexanet was given as bolus with a 2-hour infusion. The mean age of the subjects was 57.9 years old with 39% women. *Inclusion criteria:* Subjects were healthy and age 50-75 years old. *Exclusion criteria:* none	*Apixaban:* *Anti-factor Xa activity of apixaban was inhibited by 94% (24 subjects) with the andexanet bolus compared to 21% (9 subjects) with the placebo (p<0.001*).* *The amount of unbound apixaban was decreased 9.3 ng/mL compared to 1.9 ng/mL with the placebo (p<0.001*).* *Thrombin was returned to normal levels within 2-5 minutes in 100% of the apixaban subjects compared to 11% of the placebo (p<0.001*).* *Rivaroxaban:* *Anti-factor Xa activity or rivaroxaban was inhibited by 92% (27 subjects) compared to 18% (14 subjects) with the placebo (p<0.001*).* *The amount of unbound rivaroxaban was decreased 23.4 ng/mL compared to 4.2 ng/mL with the placebo (p<0.001*).* *With both rivaroxaban and apixaban, the same results were evident with the 2-hour infusion with bolus compared to only the bolus. D-dimer and prothrombin increased in 1-2 subjects, yet results normalized within 1-3 days. No subjects reported any adverse events. No thrombotic events occurred. *Conclusion: andexant alpha can safely, quickly, and effectively reduce the effects of apixaban and rivaroxaban in the healthy elderly population.*

Trial	Design/Method	Sample	Findings and Conclusions
OTHER KEY TRIALS **ACTIVE W:** Atrial Fibrillation Clopidogrel (Plavix©)Trial with Irbesartan for Prevention of Vascular Events W (ACTIVE Investigators, 2006)	Randomized controlled trial comparing the *combination of clopidogrel and aspirin to anticoagulation in preventing vascular events in patients with atrial fibrillation.* Subjects were assigned to one of three ACTIVE trials based on eligibility criteria: ACTIVE W was for patients who could take oral anticoagulation, ACTIVE A was for patients unable to take oral anticoagulation, and ACTIVE I included patients from ACTIVE A or ACTIVE W who were candidates for irbesartan. Primary outcomes measured included the incidence of stroke, non-central nervous system systemic embolus, vascular death, or myocardial infarction.	Subjects were randomly assigned to either the oral anticoagulation group with a therapeutic INR of 2.0-3.0 (3,371 subjects), or the combination clopidogrel with aspirin group (3,335 subjects). The daily dose of clopidogrel was 75 mg and the daily dose of aspirin was 75-100 mg. The average age of patients was 70.2 years with 66-67% males per group. The average $CHADS_2$ score was 2.0 *Inclusion criteria:* AF confirmed by an ECG plus at least one of the following stroke risk factors: age >75 years old, hypertension, prior stroke/TIA/non-central nervous system embolism, peripheral vascular disease, left ventricular ejection fraction <45%, age 55-74 years old with either diabetes or coronary artery disease. *Exclusion criteria:* contraindications to warfarin or clopidogrel, mechanical heart valves, peptic ulcer disease within the past 6 months, prior intracerebral bleed, mitral stenosis, or severe thrombocytopenia.	*This study was terminated prematurely as oral anticoagulation displayed superiority to the clopidogrel plus aspirin treatment in decreasing vascular events (165 events or 3.93% annually with anticoagulation compared to 234 events or 5.6% annually with clopidogrel plus aspirin; relative risk 1.44 (1.17-1.76), p = 0.0003). *The risk of bleeding was reduced in patients who were taking oral anticoagulation prior to starting this study (1.30, 0.94-1.79) compared to patients newly initiating oral anticoagulation (1.27, 0.85-1.89), plus displayed a larger reduction in vascular events (relative risk 1.50, 95% CI 1.19-1.80, p = 0.03). *Conclusion: in patients with atrial fibrillation with a high risk of stroke, oral anticoagulation is superior in preventing vascular events compared to the combination of clopidogrel with aspirin.*
ACTIVE A: Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events A (ACTIVE Investigators, 2009)	Randomized, double-blind, multicenter study examining if the *combination of clopidogrel and aspirin would decrease the risk of vascular events in patients with atrial fibrillation unable to take warfarin for anticoagulation.* This study was completed at 580 sites within 33 countries. The primary outcomes measured were the incidence of myocardial infarction, non-central nervous system embolism, stroke or death from a vascular etiology.	Out of 7,554 subjects, 3,772 were randomly assigned to a clopidogrel group (75 mg) and 3,782 were randomly assigned to a placebo group. The average follow-up time was 3.6 years. Patients in both groups received daily aspirin (75-100 mg). The average age of subjects was 70.9-71.1 years old and 57-58% males per group with an average $CHADS_2$ score of 2.0. *Inclusion criteria:* the patient was currently in AF at the beginning of the trial or at least two episodes of AF within the past 6 months. At least one of the same stroke risk factors highlighted in ACTIVE W. *Exclusion criteria:* concurrent use of warfarin or clopidogrel or high bleeding risk factors (peptic ulcer disease within the last 6 months, history of an intracerebral bleed, severe thrombocytopenia, or alcoholism).	*Total vascular events arose in 832 (6.8% annually) of the clopidogrel subjects, compared to 942 placebo subjects (relative risk 0.89, 95% CI, 0.81 to 0.98, p = 0.01). *Clopidogrel was associated with a reduced risk of stroke (296 subjects, 2.4% annually) compared to the placebo (408 subjects, 3.3% annually; relative risk 0.72, 95% CI 0.62 to 0.83, p <0.001). *Myocardial infarction presented in 90 subjects (0.7% annually) of the clopidogrel patients compared to 116 placebo subjects (0.9% per year; relative risk 0.78, 95% CI 0.59 to 1.03, p = 0.08). *Severe bleeding developed in 251 clopidogrel subjects (2.0% annually) compared to 162 placebo subjects (1.3% annually; relative risk 1.57, 95% CI 1.29 to 1.92, p <0.001).

			Conclusion: clopidogrel with aspirin is a suitable alternative to decrease the risk of vascular events, especially stroke, in patients with atrial fibrillation who are unable to take warfarin, yet this combination augments major bleeding risk.
Trial	**Design/Method**	**Sample**	**Findings and Conclusions**
PROTECT-AF WATCHMAN© vs Warfarin (Holmes et al., 2009)	Multicenter, randomized, non-inferiority trial examining safety and efficacy of *WATCHMAN (percutaneous closure of the left atrial appendage) to warfarin in preventing embolic stroke in patients with non-valvular atrial fibrillation.* The study was completed at 59 sites within the United States and Europe from 2005 to 2008. The efficacy outcome measured was the incidence of death from a cardiovascular cause, stroke (ischemic or hemorrhagic), or systemic embolism. The safety outcomes measured included severe bleeding, embolization from implantation of the WATCHMAN device, and pericardial effusion.	707 subjects were randomly assigned in a 2:1 ratio of WATCHMAN (473 subjects) or dose controlled warfarin with a goal INR of 2.0-3.0 (244 subjects). Subjects were an average age of 71.7-72.7 years, 70% males, over 91% Caucasian, and with a means $CHADS_2$ score of 1-2. For 45 days after implantation of the WATCHMAN device, patients in this group received warfarin and aspirin 81 mg daily for 45 days to prevent the formation of a thrombus while the device endothelializes in the heart. Warfarin was discontinued once the transesophageal echocardiogram (completed at 45 days, 6 months, and 12 months post procedure) demonstrated complete closure (seal) of the left atrial appendage, or peri-device blood flow of <5 mm width was present in the left atrial appendage with no thrombus present on the device. After 45 days and discontinuation of warfarin, clopidogrel and aspirin were continued for 6 months post-implant, followed by aspirin administration for life. *Inclusion criteria:* adults 18 years or older with atrial fibrillation with a minimum of one of the following factors based on a $CHADS_2$ risk score of ≥1: congestive heart failure, hypertension, diabetes, ≥75 years old, or prior stroke or TIA *Exclusion criteria:* necessity of chronic warfarin use to treat a condition other than atrial fibrillation, contraindication to warfarin, thrombus in the left atrial appendage, symptomatic carotid artery disease, mobile aortic atheroma, and patent foramen ovale with atrial septal aneurysm and right-to-left shun	*Efficacy outcome:* WATCHMAN was implanted in 88% (408 out of 463) patients. At 1065 patient years of follow-up, with an average follow-up of 18 months, stroke, systemic emboli, or cardiovascular death occurred in 3 out of 100 patient years (95% credible interval [CrI] 1·9–4·5) in the WATCHMAN group and 4·9 per 100 patient-years (2·8–7·1) in the warfarin group (rate ratio [RR] 0·62, 95% CrI 0·35–1·25). Non-inferiority in the WATCHMAN group compared to warfarin was >99.9%. *Safety outcome:* Severe bleeding, embolization from implantation and pericardial effusion were more common in the WATCHMAN group compared to the warfarin group (7·4 per 100 patient years, 95% CrI 5·5–9·7, *vs* 4·4 per 100 patient-years, 95% CrI 2·5–6·7; RR 1·69, 1·01–3·19). *Conclusion:* Efficacy of WATCHMAN is non-inferior to warfarin in patients with nonvalvular atrial fibrillation to prevent stroke. Adverse safety events were more common in the WATCHMAN group; however, the events were predominantly related to the procedure itself. *The study concluded closure of left atrial appendage through WATCHMAN is an efficacious alternative to long-term anticoagulation in patients with non-valvular atrial fibrillation, as the safety concerns are related to surgery with minimal long-term negative effects identified.*

Trial	Design/Method	Sample	Findings and Conclusions
PREVAIL WATCHMAN© versus Warfarin (Holmes et al., 2014)	This randomized, double-blind study is a *continuation of PROTECT AF to further assess the safety and efficacy of WATCHAN© versus warfarin in patients with non- valvular atrial fibrillation*, as early safety concerns were discovered with WATCHMAN© in the prior study. The efficacy endpoints measured were 1) the incidence of stroke, systemic embolism and cardiovascular death and 2) stroke or systemic embolization >7 days after randomization to study group. The safety endpoint measured was ischemic stroke, systemic embolization, all-cause death, or an adverse event related to the procedure or device, requiring intervention within 7 days of the implantation of the WATCHMAN© device. Complications excluded from this safety endpoint included pericardial effusions drained through percutaneous catheter drainage, snaring of the embolized device, and treating access complications through non-surgical means.	407 patients were randomly assigned in a 2:1 ratio to either the WATCHMAN© group (269 patients) or long-term warfarin group (138 patients). The target INR for warfarin patients was 2.0-3.0. The average age of subjects was 74 years old, 67-74% males, 94% Caucasian, and 45-50% with a $CHADS_2$ score of 2. Transesophageal echocardiograms were completed at 45 days, 6 months, and 12 months, the same as in the PROTECT-AF trial. Continuing or discontinuing warfarin followed the same parameters as the PROTECT-AF trial. *Inclusion criteria:* Adult patients with nonvalvular atrial fibrillation and a $CHADS_2$ score of ≥2 (congestive heart failure, hypertension, age >75 years old, diabetes, or prior stroke/TIA) or 1 with other risk factors present. These high-risk factors include: female sex and ≥75 years old, baseline ejection fraction ≥30%, baseline ejection fraction <35% if age 65-74 years old with diabetes or coronary artery disease, or age ≥65 years old and congestive heart failure). *Exclusion criteria:* necessity of chronic warfarin use to treat a condition other than atrial fibrillation, contraindication to warfarin or aspirin, thrombus in the left atrial appendage, symptomatic carotid artery disease, prior stroke or TIA within 90 days of the study, patent foramen ovale or atrial septal defect necessitating surgery, or patients requiring clopidogrel therapy.	*Efficacy outcomes:* The incidence of stroke, systemic embolism or cardiovascular death occurred in 0.064 patients in the WATCHMAN© group compared to 0.063 patients in the warfarin group p (rate ratio 1.07 [95% credible interval (CrI): 0.57 to 1.89]; non-inferiority was not discovered for WATCHMAN© compared to warfarin (95% CrI ≥1.75). Stroke or systemic embolization greater than 7 days after randomization to a group occurred in 0.0253 of the WATCHMAN© group, compared to 0.0200 in the warfarin group [95% CrI: –0.0190 to 0.0273]), displaying noninferiority for WATCHMAN© to warfarin. *Safety outcome:* Early safety events were discovered less in in the WATCHMAN© group in PREVAIL compared to PROTECT-AF (2.2% of subjects). Compared to warfarin (8.7%), safety events were less with WATCHMAN© (4.2%, p = 0.004). Less pericardial effusions requiring surgery were noted in WATCHMAN© patients in the PREVAIL trial (0.4%) compared to the PROTECT-AF trial (1.6%, p = 0.027), as well as reduced rates of pericardiocentesis (1.5% compared to 2.9%, p = 0.36 respectively) *Conclusions: the study concluded improved procedural safety of WATCHMAN© implantation in patients with nonvalvular atrial fibrillation to prevent stroke, as long at the patient does not have a contraindication to using warfarin short-term post- procedure. WATCHMAN© is non- inferior to warfarin to prevent ischemic stroke in patients with non-valvular atrial fibrillation, as well as preventing systemic embolization greater than 7 days post-implantation.*

Trial	Design/Method	Sample	Findings and Conclusions
ACTIVE I: Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events I (ACTIVE Investigators, 2011)	Randomized, double blind study investigating whether *the addition of irbesartan to either anticoagulation or aspirin with clopidogrel would decrease the risk of cardiovascular sequelae in patients with atrial fibrillation.* Primary outcomes measures included the incidence of stroke, myocardial infarction, or death from a vascular etiology. Secondary outcomes measures included hospitalization related to heart failure. The average follow-up period was 4.1 years.	Subjects for this trial were currently partaking in either ACTIVE A or ACTIVE W, depending on their ability to take oral anticoagulation. Subjects randomly were administered irbesartan 300 mg daily (4,518 subjects) or a placebo (4,498 subjects). The average age of subjects was 69.5 years old, 60% male and with a $CHADS_2$ score of 2. *Inclusion criteria:* risk factors for stroke described in ACTIVE A and ACTIVE W plus systolic blood pressure >110 mmHg. *Exclusion criteria:* The same as ACTIVE A and ACTIVE W. Patients could not be taking any other angiotensin receptor blockers.	*Average systolic blood pressure was decreased by 2.9 mmHg more in the irbesartan group compared to the placebo, in addition to a systolic blood pressure reduction of 1.9 mmHg more. *Primary vascular events occurred in 5.4% per 100 person years in the irbesartan and placebo groups (HR 0.99, 95% CI 0.91-1.09, $p = 0.85$). *The secondary outcome of hospitalization related to heart failure occurred at 7.3% per 100 person years in the irbesartan group and 7.7% per 100 person years in the placebo group (HR 0.94%, 95% CI, 0.87-1.02, $p =$ 0.12). *Irbesartan did not prevent any hospitalizations for a diagnosis of solely atrial fibrillation. *Renal impairment (43 subjects) and hypotension (127 subjects) were more common adverse effects with irbesartan than the placebo (24 subjects and 64 subjects, respectively) *Conclusion: In patients with atrial fibrillation, irbesartan did not statistically decrease cardiovascular sequelae.*
WOEST: (What is the Optimal Antiplatelet Therapy in Patients with Oral Anticoagulation and Coronary Stenting? (Dewilde et al., 2013).	Randomized, controlled, open-label study assessing the *safety and efficacy of clopidogrel in comparison to clopidogrel with aspirin in patients who have undergone percutaneous coronary intervention (PCI) for ischemic heart disease.* Patients with mechanical valves and atrial fibrillation require chronic anticoagulation. This study was completed at 15 clinics within the Belgium and the Netherlands over a three-year period. The primary safety outcome measured bleeding within one year after the PCI.	Patients were randomly assigned to either double therapy (clopidogrel with anticoagulation, 279 subjects) or triple therapy (clopidogrel with anticoagulation and aspirin, 284 subjects). The average age of patients in the double therapy group was 70.3 years and 69.5 years in the triple therapy group. The subjects were 77-82% males with an average $CHADS_2$ score of 1-2. *Inclusion criteria:* age 18-80 years old, necessity of anticoagulation for at least one year, a minimum of 75% stenosis on angiography or a fractional flow reserve lower than 0.80 and the need for a PCI. *Exclusion criteria:* cardiogenic shock, history of intracranial hemorrhage, peptic ulcer within the past 6 months, severe thrombocytopenia (platelet count $<50x10^9$/L), severe bleeding within the past year, and pregnancy.	*Safety outcomes:* *Bleeding occurred in 54 (19.4%) of subjects in the double therapy group compared to 126 (44.4%) of subjects in the triple therapy group; HR 0.36, 95% CI, 0.26-0.60, $p <0.0001$). *Recurrent bleeding occurred more often in the triple therapy group (34 subjects or 12%) compared to the double therapy group (6 subjects or 2.2%). *Bleeding was severe enough to warrant a transfusion in 27 (9.5%) of patients in the triple therapy group, compared to 11 (3.9%) in the double therapy group (odds ratio 0.39, 95% CI 0.17-0.84, $p = 0.011$). *Conclusion: in patients post PCI who require anticoagulation, clopidogrel without aspirin is recommended due to the decrease in bleeding without a corresponding increase in thromboembolism.*

APPENDIX D

2016 EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES FOR THE MANAGEMENT OF ATRIAL FIBRILLATION DEVELOPED IN COLLABORATION WITH EUROPEAN ASSOCIATION FOR CARDIO-THORACIC SURGERY

Recommendations	Class[a]	Level[b]
Recommendations for diagnosis and screening of AF		
ECG documentation is required to establish the diagnosis of AF.	I	B
Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients >65 years of age.	I	B
In patients with TIA or ischaemic stroke, screening for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours.	I	B
It is recommended to interrogate pacemakers and ICDs on a regular basis for atrial high rate episodes (AHRE). Patients with AHRE should undergo further ECG monitoring to document AF before initiating AF therapy.	I	B
Recommendations for general management of AF		
Tailored patient education is recommended in all phases of AF management to support patients' perception of AF and to improve management.	I	C
A full cardiovascular evaluation, including an accurate history, careful clinical examination, and assessment of concomitant conditions, is recommended in all AF patients.	I	C
Use of the modified EHRA symptom scale is recommended in clinical practice and research studies to quantify AF-related symptoms.	I	C
Transthoracic echocardiography is recommended in all AF patients to guide management.	I	C
The assessment of kidney function by serum creatinine or creatinine clearance is recommended in all AF patients to detect kidney disease and to support correct dosing of AF therapy.	I	A
Recommendations for stroke prevention in AF		
The CHA2DS2-VASc score is recommended for stroke risk prediction in patients with AF.	I	A
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA2DS2-VASc score of 2 or more.	I	A
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA2DS2-VASc score of 3 or more.	I	A
When oral anticoagulation is initiated in a patient with AF who is eligible for a non vitamin-K-antagonist oral anticoagulant (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.	I	A
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to- severe mitral stenosis or mechanical heart valves.	I	B
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III (harm)	B C
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.	I	A
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.	III (harm)	B
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (harm)	B
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A
After surgical occlusion or exclusion of the left atrial appendage, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention.	I	B
Genetic testing before the initiation of vitamin K antagonist therapy is not recommended.	III (no benefit)	B

In AF patients with severe active bleeding events, it is recommended to interrupt oral anticoagulation therapy until the underlying cause is resolved.	I	C
NOACs should be avoided in pregnancy and in women planning a pregnancy.	III (harm)	C
For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF.	I	B
Management of typical atrial flutter with ablation of the cavotricuspid isthmus is recommended for patients failing antiarrhythmic drug therapy or as first-line treatment considering patient preference.	I	B
Lifelong oral anticoagulation to prevent stroke is recommended in hypertrophic cardiomyopathy patients who develop AF.	I	B
Anticoagulation with heparin or low-molecular-weight heparin immediately after ischaemic stroke is not recommended in AF patients.	III (harm)	A
Systemic thrombolysis with a recombinant tissue plasminogen activator is not recommended if the INR is above 1.7 (or, for patients on dabigatran, if activated partial thromboplastin time is outside the normal range).	III (harm)	C
After TIA or stroke, combination therapy of OAC and an antiplatelet is not recommended.	III (harm)	B

Recommendations	Class[a]	Level[b]
Recommendations for rate control of AF		
Beta-blockers, digoxin, diltiazem, or verapamil are recommended to control heart rate in AF patients with LVEF ≥40%.	I	B
Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF <40%.	I	B
In patients with permanent AF (i.e. where no attempt to restore sinus rhythm is planned), antiarrhythmic drugs should not routinely be used for rate control.	III (harm)	A
Recommendations for rhythm control of AF		
Rhythm control therapy is indicated for symptom improvement in patients with AF.	I	B
Cardioversion of AF (either electrical or pharmacological) is recommended in symptomatic patients with persistent or long-standing persistent AF as part of rhythm control therapy.	I	B
In patients with no history of ischaemic or structural heart disease, flecainide, propafenone, or vernakalant are recommended for pharmacological cardioversion of new-onset AF.	I	A
In patients with ischaemic and/or structural heart disease, amiodarone is recommended for cardioversion of AF.	I	A
For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.	I	B
Transoesophageal echocardiography (TOE) is recommended to exclude cardiac thrombus as an alternative to preprocedural anticoagulation when early cardioversion is planned.	I	B
The choice of antiarrhythmic drug needs to be carefully evaluated, taking into account the presence of comorbidities, cardiovascular risk and potential for serious proarrhythmia, extracardiac toxic effects, patient preferences, and symptom burden.	I	A
Dronedarone, flecainide, propafenone, or sotalol are recommended for prevention of recurrent symptomatic AF in patients with normal left ventricular function and without pathological left ventricular hypertrophy.	I	A
Dronedarone is recommended for prevention of recurrent symptomatic AF in patients with stable coronary artery disease, and without heart failure.	I	A
Amiodarone is recommended for prevention of recurrent symptomatic AF in patients with heart failure.	I	B
Antiarrhythmic drug therapy is not recommended in patients with prolonged QT interval (> 0.5 s) or with significant sinoatrial node disease or atrioventricular node dysfunction who do not have a functioning permanent pacemaker.	III (harm)	C
Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone, flecainide, propafenone, sotalol) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre.	I	A
ACE-Is or ARBs are not recommended for the secondary prevention of paroxysmal AF in patients with little or no underlying heart disease.	III (no benefit)	B
Moderate regular physical activity is recommended to prevent AF, while athletes should be counselled that long-lasting, more intense sports participation can promote AF.	I	A

Note: Adapted from Kirchhof et al. (2016). Copyright 2016 by the European Society of Cardiology.

APPENDIX E

AMERICAN HEART ASSOCIATION, AMERICAN COLLEGE OF CARDIOLOGY, AND HEART RHYTHM SOCIETY'S SUMMARY OF RECOMMENDATIONS FOR SPECIFIC PATIENT GROUPS AND ATRIAL FIBRILLATION

Recommendations	COR	LOE	References
Hypertrophic cardiomyopathy			
Anticoagulation is indicated in HCM with AF independent of the CHA_2DS_2-VASc score	I	B	(169,170)
Antiarrhythmic drugs can be useful to prevent recurrent AF in HCM. Amiodarone or disopyramide combined with a beta blocker or nondihydropyridine calcium channel antagonist are reasonable	IIa	C	N/A
AF catheter ablation can be beneficial for HCM to facilitate a rhythm-control strategy when antiarrhythmics fail or are not tolerated	IIa	B	(171–174)
Sotalol, dofetilide, and dronedarone may be considered for a rhythm-control strategy in HCM	IIb	C	(12)
AF complicating ACS			
Urgent cardioversion of new-onset AF in the setting of ACS is recommended for patients with hemodynamic compromise, ongoing ischemia, or inadequate rate control	I	C	N/A
IV beta blockers are recommended to slow RVR with ACS and no HF, hemodynamic instability, or bronchospasm	I	C	N/A
With ACS and AF with CHA_2DS_2-VASc score $2, anticoagulation with warfarin is recommended unless contraindicated	I	C	N/A
Amiodarone or digoxin may be considered to slow RVR with ACS and AF and severe LV dysfunction and HF or hemodynamic instability	IIb	C	N/A
Nondihydropyridine calcium antagonists might be considered to slow RVR with ACS and AF only in the absence of significant HF or hemodynamic instability	IIb	C	N/A
Hyperthyroidism			
Beta blockers are recommended to control ventricular rate with AF complicating thyrotoxicosis unless contraindicated	I	C	N/A
When beta blockers cannot be used, a nondihydropyridine calcium channel antagonist is recommended to control ventricular rate	I	C	N/A
Pulmonary diseases			
A nondihydropyridine calcium channel antagonist is recommended to control ventricular rate with AF and COPD	I	C	N/A
Cardioversion should be attempted for patients with pulmonary disease who become hemodynamically unstable with new-onset AF	I	C	N/A
WPW and pre-excitation syndromes			
Cardioversion is recommended for patients with AF, WPW syndrome, and RVR who are hemodynamically compromised	I	C	(175)
IV procainamide or ibutilide to restore sinus rhythm or slow ventricular rate is recommended for patients with pre-excited AF and RVR who are not hemodynamically compromised	I	C	(175)
Catheter ablation of the accessory pathway is recommended in symptomatic patients with pre-excited AF, especially if the accessory pathway has a short refractory period	I	C	(175)

IV amiodarone, adenosine, digoxin, or nondihydropyridine calcium channel antagonists in patients with WPW syndrome who have pre-excited AF is potentially harmful	III: Harm	B	(176–178)

Heart failure

A beta blocker or nondihydropyridine calcium channel antagonist is recommended for persistent or permanent AF in patients with HF*p*EF	I	B	(95)
In the absence of preexcitation, an IV beta blocker (or a nondihydropyridine calcium channel antagonist with HF*p*EF) is recommended to slow ventricular response to AF in the acute setting, with caution in patients with overt congestion, hypotension, or HF*r*EF	I	B	(179–182)
In the absence of pre-excitation, IV digoxin or amiodarone is recommended to control heart rate acutely	I	B	(103,180,183,184)
Assess heart rate during exercise and adjust pharmacological treatment in symptomatic patients during activity	I	C	N/A
Digoxin is effective to control resting heart rate with HF*r*EF	I	C	N/A
A combination of digoxin and beta blocker (or a nondihydropyridine calcium channel antagonist with HF*p*EF) is reasonable to control resting and exercise heart rate with AF	IIa	B	(93,180)
It is reasonable to perform AV node ablation with ventricular pacing to control heart rate when pharmacological therapy is insuf*fi*cient or not tolerated	IIa	B	(95,185,186)
IV amiodarone can be useful to control heart rate with AF when other measures are unsuccessful or contraindicated	IIa	C	N/A
With AF and RVR causing or suspected of causing tachycardia-induced cardiomyopathy, it is reasonable to achieve rate control by AV nodal blockade or a rhythm-control strategy	IIa	B	(187–189)

Recommendations	COR	LOE	References
In patients with chronic HF who remain symptomatic from AF despite a rate-control strategy, it is reasonable to use a rhythm-control strategy	IIa	C	N/A
Amiodarone may be considered when resting and exercise heart rate cannot be controlled with a beta blocker (or a nondihydropyridine calcium channel antagonist with HF*p*EF) or digoxin, alone or in combination	IIb	C	N/A
AV node ablation may be considered when rate cannot be controlled and tachycardia-mediated cardiomyopathy is suspected	IIb	C	N/A
AV node ablation should not be performed without a pharmacological trial to control ventricular rate	III: Harm	C	N/A
For rate control, IV nondihydropyridine calcium channel antagonists, IV beta blockers, and dronedarone should not be given with decompensated HF	III: Harm	C	N/A

Familial (genetic) AF

For patients with AF and multigenerational family members with AF, referral to a tertiary care center for genetic counseling and testing may be considered	IIb	C	N/A

Postoperative cardiac and thoracic surgery

A beta blocker is recommended to treat postoperative AF unless contraindicated	I	A	(190–193)

A nondihydropyridine calcium channel blocker is recommended when a beta blocker is inadequate to achieve rate control with postoperative AF	I	B	(194)
Preoperative amiodarone reduces AF with cardiac surgery and is reasonable as prophylactic therapy for patients at high risk of postoperative AF	IIa	A	(195–197)
It is reasonable to restore sinus rhythm pharmacologically with ibutilide or direct-current cardioversion with postoperative AF	IIa	B	(198)
It is reasonable to administer antiarrhythmic medications to maintain sinus rhythm with recurrent or refractory postoperative AF	IIa	B	(194)
It is reasonable to administer antithrombotic medications for postoperative AF	IIa	B	(199)
It is reasonable to manage new-onset postoperative AF with rate control and anticoagulation with cardioversion if AF does not revert spontaneously to sinus rhythm during follow-up	IIa	C	N/A
Prophylactic sotalol may be considered for patients with AF risk after cardiac surgery	IIb	B	(193,200)
Colchicine may be considered postoperatively to reduce AF after cardiac surgery	IIb	B	(201)

ACS indicates acute coronary syndromes; AF, atrial *fi*brillation; AV, atrioventricular; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age $\geq$75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category; COPD, chronic obstructive pulmonary disease; COR, Class of Recommendation; HCM, hypertrophic cardiomyopathy; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; HF*r*EF, heart failure with reduced ejection fraction; IV, intravenous; LOE, Level of Evidence; LV, left ventricular; N/A, not applicable; RVR, rapid ventricular response; and WPW, Wolff-Parkinson-White.

Note: Adapted from "2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive summary," C.T. January, L.S. Wann, J.S. Alpert, H. Calkins, J.E. Ciagarroa, J.C. Cleveland, . . . C.W. Yancy, 2014, p. 2261-2262. Copyright, 2015 by Elsevier.

APPENDIX F

ANTITHROMBOTIC THERAPY FOR ATRIAL FIBRILLATION: ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS

• Nonrheumatic atrial fibrillation (including paroxysmal) with a $CHADS_2$ score of 0 (low risk of stroke), no treatment is recommended but if a patient selects treatment, aspirin is preferred. With a $CHADS_2$ score of 1 (intermediate risk of stroke) or with a $CHADS_2$ score of ≥2 (high risk of stroke), oral anticoagulation is recommended. Assessment of stroke risk is assessed through $CHADS_2$ scoring which has been validated through research and is easy to use.
• When selecting oral anticoagulation, dabigatran 150 mg BID is preferred to warfarin (vitamin K antagonist).
• With a high risk of stroke, oral anticoagulation is the recommended treatment, yet with a low risk of stroke, managed is based on the individual patient.
• **Recommendation 2.1.8.** For patients with AF, including those with paroxysmal AF, who are at low risk of stroke (eg, $CHADS_2$ [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient attack] score = 0), we suggest no therapy rather than antithrombotic therapy (*Grade 2B*). For patients who do choose antithrombotic therapy, we suggest aspirin (75 mg to 326 mg once daily) rather than oral anticoagulation (Grade 2B) or combination therapy with aspirin and clopidogrel (*Grade 2B*; American College of Chest Physicians, 2012, p. e532S).
• **Recommendation 2.1.8.** For patients with AF, including those with paroxysmal AF, who are at low risk of stroke (eg, $CHADS_2$ [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient attack] score = 0), we suggest no therapy rather than antithrombotic therapy (*Grade 2B*). For patients who do choose antithrombotic therapy, we suggest aspirin (75 mg to 326 mg once daily) rather than oral anticoagulation (*Grade 2B*) or combination therapy with aspirin and clopidogrel (*Grade 2B*; American College of Chest Physicians, 2012, p. e532S).
• **Recommendation 2.1.9.** For patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke (eg, $CHADS_2$ score = 1), we recommend oral anticoagulation rather than no therapy (*Grade 1B*). We suggest oral anticoagulation rather than aspirin (75 mg to 325 mg once daily) (*Grade 2B*) or combination therapy with aspirin and clopidogrel (*Grade 2B*). For patients who are unsuitable for to choose not to take an oral anticoagulant (for reasons other than concerns about major), we suggest combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (*Grade 2B*; American College of Chest Physicians, 2012, p. e532S).
• **Recommendation 2.1.10.** For patients with AF, including whose with AF, including those with paroxysmal AF, who are at high risk of stroke (ex. $CHADS_2$ score = 2), we recommend oral anticoagulation rather than no therapy (*Grade 1A*), aspirin (75 mg to 325 mg once daily) (*Grade 1B*), or combination therapy with aspirin and clopidogrel (Grade 1B). For patients who are unsuitable for or chose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we recommend combination therapy with aspiring and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (*Grade 1B*; American College of Chest Physicians, 2012, pp. e532S-e533S).

• **Recommendation 2.1.11.** For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation (including 2.1.9, 2.1.10, and excluding 2.2, 3.1, 3.2, and 3.3, we suggest dabigatran 150 mg twice daily rather than adjusted-dose vitamin K antagonist (VKA) therapy (target INR range, 2.0-3.0) (*Grade 2B*; American College of Chest Physicians, 2012, p e533S).
• **Recommendation 2.2.** For patients with AF and mitral stenosis, we recommend adjusted dose VKA therapy (target INR range, 2.0-3.0) rather than no therapy, aspirin (75 mg to 325 mg once daily), or combination therapy with aspirin and clopidogrel (all *Grade 1B*). For patients with AF and mitral stenosis who are unsuitable for or choose not to take adjusted-dose VKA therapy (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily alone (*Grade 1B*; American College of Chest Physicians, 2012, p e533S).
• **Recommendation 3.1.** For patients with AF and stable coronary artery disease (eg, no acute coronary syndrome within the previous year) and who choose oral anticoagulation, we suggest adjusted-dose VKA therapy alone (target internationalized normalized ratio [INR] range, 2.0-3.0) rather than the combination of adjusted-dose VKA therapy and aspirin (*Grade 2C*; American College of Chest Physicians, 2012, p e533S).
• **Recommendation 3.2.** For patients with AF at high risk of stroke (eg, $CHADS_2$ score of 2 or greater) during the first month after placement of a bare-metal stent or the first 3 to 6 months after placement of a drug-eluting stent, we suggest triple therapy (eg, VKA therapy, aspirin, and clopidogrel) rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) (*Grade 2C*). After this initial period of triple therapy, we suggest a VKA (INR 2.0-3.0) plus a single antiplatelet drug rather than VKA alone (*Grade 2C*). At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1). For patients with AF at low to intermediate risk of stroke (eg, $CHADS_2$ score of 0 or 1 during the first 12 months after placement of an intracoronary stent (bare metal or drug eluting), we suggest dual antiplatelet therapy rather than triple therapy (*Grade 2C*). At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1; American College of Chest Physicians, 2012, p e533S).
• **Recommendation 3.3.** For patients with AF at intermediate to high risk of stroke (eg, $CHADS_2$ score of 1 or greater) who experience an acute coronary syndrome and do not undergo intracoronary stent placement, we suggest for the first 12 months, adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) or triple therapy (eg, warfarin, aspirin, and clopidogrel) (*Grade 2C*). After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1). For patients with AF at low risk of stroke (eg, CHADS2 score of 0), we suggest dual antiplatelet therapy (eg, aspirin and clopidogrel) rather than adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy or triple therapy (eg, warfarin, aspirin, and clopidogrel) (*Grade 2C*). After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1; American College of Chest Physicians, 2012, p e533S).

• **Recommendation 3.4.** For patients with AF being managed with a rhythm control strategy (pharmacologic or catheter ablation), we suggest that antithrombotic therapy decisions follow the general risk-based recommendations for patients with AF in section 2.1, regardless of the apparent persistence of normal sinus rhythm (*Grade 2C*; American College of Cardiology, 2012, p. e534S).
• **Recommendation 3.5:** For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF (American College of Chest Physicians, 2012, p. e534S).
• **Recommendation 4.1.1.** For patients with AF of greater than 48 hours or unknown duration undergoing elective electrical or pharmacologic conversion, we recommend therapeutic anticoagulation (adjusted-dose VKA therapy, target UBR range 2.0-3.0, low molecular weight heparin at full venous thromboembolism treatment doses, or dabigatran) for at least 3 weeks before cardioversion or a transesophageal echocardiography (TEE)- guided approach with abbreviated anticoagulation before cardioversion rather than no anticoagulation (*Grade 1B*). We recommend therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of the baseline risk of stroke (*Grade 1B*). Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1 (American College of Chest Physicians, 2012, p. e534S).
• **Recommendation 4.1.2.** For patients with AF of documented duration of 48 h or less undergoing elective cardioversion (electrical or pharmacologic), we suggest starting anticoagulation at presentation (low-molecular-weight heparin or unfractionated heparin at full venous thromboembolism treatment doses) and proceeding to cardioversion for 3 weeks of therapeutic anticoagulation or a TEE-guided approach (*Grade 2C*). After successful cardioversion to sinus rhythm, we recommend therapeutic anticoagulation for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk (*Grade 2C*). Decisions about long-term anticoagulation after cardioversion should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1 (American College of Chest Physicians, 2012, pp. e533S-e534S).
• **Recommendation 4.2.** For patients with AF and hemodynamic instability undergoing cardioversion (electrical or pharmacologic), we suggest that therapeutic-dose parenteral anticoagulation be started before cardioversion, if possible (*Grade 2C*), but that initiation of anticoagulation must not delay any emergency intervention (*Grade 2C*). After successful cardioversion to sinus rhythm, we suggest therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of baseline stroke risk (*Grade 2C*). Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1 (American College of Chest Physicians, 2012, p. e534S).
• **Recommendation 4.3:** "For patients with atrial flutter undergoing elective or urgent pharmacologic or electrical cardioversion, we suggest that the same approach to thromboprophylaxis be used as for patients with atrial fibrillation undergoing cardioversion (American College of Chest Physicians, 2012, p. e534S).

Note: Adapted from "Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines," J. J. You, D.E., Singer, P.A. Howard, D.A. Lane, M.H. Eckman, M. C., Fang … G.Y. H. Lip, 2012, *Chest, 368*(8), pp. e531S-e534S. Copyright 2012 by the American College of Chest Physicians.

APPENDIX G

AMERICAN HEART ASSOCIATION AND AMERICAN STROKE 2014 NEW RECOMMENDATIONS FOR PREVENTING STROKE IN PATIENTS WITH ATRIAL FIBRILLATION

• For patients with valvular atrial fibrillation at high risk for stroke, defined as a CHA_2DS_2- VASc score of ≥2, and acceptably low risk for hemorrhagic complications, chronic oral anticoagulant therapy with warfarin at a target INR of 2.0 to 3.0 is recommended (*Class I; Level of Evidence A*).
• For patients with nonvalvular atrial fibrillation, a CHA_2DS_2-VASc score of ≥2, and acceptably low risk for hemorrhagic complications, oral anticoagulants are recommended (*Class I*).
• Options include warfarin (INR, 2.0 to 3.0) (*Level of Evidence A*), dabigatran (*Level of Evidence B*), apixaban (*Level of Evidence B*), and rivaroxaban (*Level of Evidence B*). The selection of antithrombotic agent should be individualized on the basis of patient risk factors (particularly risk for intracranial hemorrhage), cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time INR is in therapeutic range for patients taking warfarin.
• For patients with nonvalvular atrial fibrillation and CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (*Class IIa; Level of Evidence B*).
• For patients with nonvalvular atrial fibrillation, a CHA_2DS_2-VASc score of 1, and acceptably low risk for hemorrhagic complication, no antithrombotic therapy, anticoagulant therapy, or aspirin therapy may be considered (*Class IIb; Level of Evidence C*). The selection of antithrombotic agent should be individualized on the basis of patient risk factors (particularly risk for intracranial hemorrhage), cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time INR is in therapeutic range for patients taking warfarin.
• Closure of the left atrial appendage may be considered for high-risk patients with atrial fibrillation who are deemed unsuitable for anticoagulation if performed at a center with low rates of periprocedural complications and the patient can tolerate the risk of at least 45 d of postprocedural anticoagulation (*Class IIb; Level of Evidence B;* Meschia et al., 2014, p. 3802).

Note: Adapted from "Guidelines for the primary prevention of stroke: A statement for healthcare professionals from the American Heart Association/American Stroke Association," J.F. Meschia, C. Bushnell, B. Boden-Albala, L.T. Braun, D.M. Bravata, M.A. Creager, . . . J.A. Wilson, 2014, p. 3802.

APPENDIX H

CONSENT FORM FOR HUMAN PARTICIPATION IN RESEARCH

CONSENT FORM FOR HUMAN PARTICIPATION IN RESEARCH
UNIVERSITY OF NORTHERN COLORADO
FAMILY PHYSICIANS OF GREELEY

INFORMED CONSENT – NO SIGNATURE DOCUMENT

Project Title: *Stroke Reduction in Elderly Patients with Atrial Fibrillation Through Utilization of an Anticoagulation Toolkit in the Primary Care Setting*
Student Researcher: Rachel J. Mommer, BSN, BS, RN-BC, DNP-S
Research Advisor: Kathleen N. Dunemn, PhD, APRN, CNM, School of Nursing

Expert Consensus: A Delphi Study

The purpose of the following Doctor of Nursing Practice Capstone Project is to develop an evidence-based anticoagulation toolkit comprised of an algorithm and guideline to assist primary care providers on improved diagnosis of atrial fibrillation and enhanced initiation and maintenance of oral anticoagulation to reduce the incidence of stroke in elderly patients with atrial fibrillation (AF). A summary of the rationale for selecting this topic and background information on AF can be forwarded by request. A chart review will be completed at Family Physicians of Greeley- Central to evaluate current practice, collecting demographics on patients with AF, in addition to diagnosis and treatment of AF in the primary care setting. All subjects' initials within the chart review will be assigned a unique numerical value to maintain confidentiality. In addition, providers within various primary care and cardiology clinics throughout Northern Colorado will be requested to participate in this research.

The evidence-based anticoagulation toolkit for this capstone project will be formulated from an extensive and current literature review, including the recommendations from national and international guidelines on anticoagulation with AF. Expert consensus will be obtained through a series of two surveys in alignment with the Delphi technique, striving for group consensus to create and evaluate the anticoagulation guideline with algorithm. Since the 1950's, the Delphi technique has been used as a group communication tool to attain controlled, expert consensus for program structuring, needs evaluations, policy writing, and resource management.

For the first round of the Delphi technique, a short survey will discuss expert experience and comfort level with diagnosing atrial fibrillation and prescribing anticoagulation for this high-risk population. For the second round of the Delphi method an anonymous summary of the 70% group consensus from the first round will be attached to a second survey assessing the benefits and challenges of this toolkit. In concordance with the Delphi technique, feedback to improve this anticoagulation toolkit is essential to improve its applicability and relevance to practice. For each round of the Delphi technique, the DNP student researcher is requesting the electronic survey be completed and returned to her private e-mail account within two weeks. Approximately 10 minutes will be required to complete the first round of the Delphi technique and 15-20 minutes for the second

round. After completion of the two rounds of the Delphi technique, the data and demographics from the surveys and chart review will be statistically analyzed to compare and identify any gaps between evidence and practice.

The purpose of this e-mail is to invite your participation in this research study. Participation is voluntary and all responses and subject identifiers will remain confidential and anonymous, including the aggregated group consensus obtained in Round 1 and summarized in Round 2. There are no foreseeable risks to the participants. All data collected from the chart reviews and Delphi surveys will be statistically analyzed and secured on a password protected zip drive, only accessible by the DNP student and her advisor. This is a quality improvement project to improve the diagnosis and management of atrial fibrillation within the primary are setting. If you have any questions, please contact one of the undersigned.

Participation is voluntary. You may decide not to participate in this study and if you begin
participation you may still decide to stop and withdraw at any time. Your decision will be respected and will not result in loss of benefits to which you are otherwise entitled. Having read
the above and having had an opportunity to ask any questions, please electronically sign below if you would like to participate in this research. A copy of this form will be given to you to retain for future reference. If you have any concerns about your selection or treatment as a research participant, please contact Sherry May, IRB Administrator, Office of Research, 25 Kepner Hall, University of Northern Colorado Greeley, CO 80639; 970-351-1910.

If you wish to participate in this study, please access and complete the attached document "Phase 1: Delphi Study Round One Survey" and return the completed survey to rachel.j.mommer@gmail.com. If you know any colleagues who would be interested in participating in this study, please forward this consent form and Delphi survey via e-mail.

Thank you for your time and consideration.

Student Researcher: Rachel J. Mommer, BSN, BA, RN-BC, DNP-S
E-mail: Rachel.j.mommer@gmail.com
Phone: (970) 481-5523

Research Advisor: Kathleen N. Dunemn, PhD, APRN, CNM
E-mail: Kathleen.Dunemn@unco.edu
Phone: (970) 351-3081/ (303) 649-5581

Participation Signature _____

APPENDIX I

ROUND 1 DELPHI SURVEY

1) Please fill in the following demographics.
Title: MD DO NP PA
Specialty: _____
Number of years in practice: _____

2) What patient presentation (symptoms and risk factors) warrants a work-up for atrial fibrillation (AF)?

3) Do you screen for atrial fibrillation in all your elderly patients older than 65 years old?
Yes
No

4) Explain your work-up for diagnosing atrial fibrillation.

5) How do you typically treat patients with atrial fibrillation?

6) Which factors influence your decision to initiate anticoagulation in a patient with atrial fibrillation, including selection of a particular agent?

7) What is your comfort level with prescribing and managing anticoagulation for atrial fibrillation (scale of *0* very uncomfortable to *5* very comfortable).

8) Do you use any screening tools to assess for stroke and bleeding risk with anticoagulation and AF (ex. $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED, etc.)?

9) This question addresses AF guidelines and algoirthms.

   a. What guidelines, algorithms, and resources do you reference for anticoagulating and treating atrial fibrillation?

   b. What would you find most helpful in an AF algorithm or guideline?

   c. What would you find least helpful in an AF algorithm or guideline?

10) What would help you improve your management of anticoagulation for patients with atrial fibrillation (ex. algorithms, community resources, specialists, shared decision-making tools, websites, phone apps, more anticoagulation clinics, etc.)?

APPENDIX J

ROUND 2 DELPHI SURVEY

1) Was the anticoagulation tool kit straightforward and user friendly?
   Yes
   No

2) Do you think this toolkit would improve safety and efficacy of anticoagulation therapy?
   Yes
   No

3) Would this toolkit influence your future practice?
   Yes
   No

4) Was this toolkit applicable to your practice and the patients you provide care for?
   Yes
   No

5) Was this toolkit inclusive of current evidence-based practice and guidelines on anticoagulation for atrial fibrillation?
   Yes
   No

6) What are the benefits of this toolkit?

7) What are the challenges of this toolkit?

8) Any other feedback, questions or concerns?

APPENDIX K

STATEMENT OF MUTUAL AGREEMENT

Statement of Mutual Agreement
University of Northern Colorado
Doctorate of Nursing Practice Capstone Project
[Rachel J. Mommer]
[July 6th, 2017]

The purpose of the "Statement of Mutual Agreement" is to describe the shared view between [**Family Physicians of Greeley**] and [**Rachel Mommer**], DNP Candidate from University of Northern Colorado, concerning his/her proposed capstone project.

Proposed Project Title: **Stroke Reduction in Elderly Patients with Atrial Fibrillation Through Utilization of an Anticoagulation Toolkit in the Primary Care Setting**

Brief Description of Proposed Project: A chart review will be completed on the diagnosis and treatment of atrial fibrillation patients in the primary care setting. Through the Delphi method, expert opinion from providers in cardiology and primary are will be utilized to create an anticoagulant toolkit emphasizing improved diagnosis of atrial fibrillation in the elderly within the primary care setting, followed by appropriate initiation and management of individualized anticoagulation to reduce the incidence of stroke. Recommendations to improve this variance between research and practice include: 1) Screening all elderly patients in the primary care setting for atrial fibrillation through an annual pulse check with follow-up electrocardiogram as necessary, 2) Evaluating the necessity of anticoagulation through stroke risk (CHA_2DS_2-VASc) and bleeding risk (HAS-BLED) scales, and 3) Highlighting key resources for providers (guidelines and a shared decision-making tool) to improve implementation of evidence-based research into practice.

Goal of Capstone Project: Through utilization of the Delphi method, expert opinion, and the recommendations of guidelines, an evidence-based anticoagulation toolkit will be created to guide primary care providers on improved diagnosis of atrial fibrillation and enhanced initiation and maintenance of oral anticoagulation to reduce the incidence of stroke in elderly patients with atrial fibrillation.

Proposed On-site Activities: An analysis of patient medical records over the past six months a will highlight current management and diagnosis of atrial fibrillation, while also identifying gaps in practice.

- Patient charts will be assessed for symptoms, risk factors, diagnostics, laboratory data, comorbid diagnoses, management (focusing on anticoagulation), negative outcomes, quality of life, multidisciplinary providers managing the patient, and assessment of stroke and bleeding risk through CHA_2DS_2-VASC and HAS-BLED tools.
- Demographics collected will include: age, sex, race/ethnicity, city of residence (rural or urban), and insurance coverage.

Confidentiality of Patient Records: No patient specific health or other identifying information will be collected from the patient chart reviews, ensuring patient confidentiality is upheld and protected through compliance with HIPPA standards. All subjects within the chart review will be assigned a unique numerical value to provide de-identification. All data collected from the chart reviews will be statistically analyzed and secured on a password protected zip drive, only accessible by the DNP student and her advisor.

The DNP Capstone project will include a final report, an abstract, potential publication or oral presentation of the report. No personal identifiers will be included and all data will be reported in aggregate form. The author welcomes any comments or suggestions from the Agency, but reserves the right to publish findings and analysis according to professional standards and principles of academic freedom. For any work of a scholarly nature, the Author agrees to follow the Agency preferences in how it is to be named (or not) in the work.

Signature of DNP Student — Date: 7/6/17

Signature of Agency Member — Date: 7/6/17

Signature of DNP Capstone Chair — Date: 7/6/17

APPENDIX L

INSTITUTIONAL REVIEW BOARD APPROVAL

UNIVERSITY OF
NORTHERN COLORADO

Institutional Review Board

DATE:	August 11, 2017
TO:	Rachel Mommer, DNP-S
FROM:	University of Northern Colorado (UNCO) IRB
PROJECT TITLE:	[1079010-2] Stroke Reduction in Elderly Patients with Atrial Fibrillation Through Utilization of an Anticoagulation Toolkit in the Primary Care Setting
SUBMISSION TYPE:	Amendment/Modification
ACTION:	APPROVAL/VERIFICATION OF EXEMPT STATUS
DECISION DATE:	August 11, 2017
EXPIRATION DATE:	August 10, 2021

Thank you for your submission of Amendment/Modification materials for this project. The University of Northern Colorado (UNCO) IRB approves this project and verifies its status as EXEMPT according to federal IRB regulations.

We will retain a copy of this correspondence within our records for a duration of 4 years.

If you have any questions, please contact Sherry May at 970-351-1910 or Sherry.May@unco.edu. Please include your project title and reference number in all correspondence with this committee.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within University of Northern Colorado (UNCO) IRB's records.