HEALTH OUTCOMES OF ADULTS WITH ATRIAL FIBRILLATION AND FALLS, FRAILTY, AND/OR DEMENTIA TREATED FOR THE PREVENTION OF THROMBOEMBOLISM

by

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ABSTRACT

Atrial fibrillation (AF) is the most common clinical arrhythmia, posing a major risk for occurrence of ischemic stroke. Oral anticoagulation and antiplatelet agents are used to prevent stroke. One major complication related to these therapies is the development of a hemorrhage. Providers are faced with treating older adults with AF who have concomitant geriatric syndromes that potentially alter treatment outcomes. This study involved examining records of subjects age ≥ 65 diagnosed with AF and concomitant geriatric syndromes (dementia, frailty, and/or falls) to describe differences in incidence of strokes and hemorrhages, depending upon the type of prevention therapy, and differences in incidences of stroke in patients with and without geriatric syndromes.

Older adult patients with geriatric syndromes were divided into three groups based on the type of antithrombotic therapy prescribed at diagnosis of AF: oral anticoagulation, antiplatelet agents, or no oral anticoagulants or antiplatelet agents, with primary outcomes of a stroke or hemorrhage. In a separate analysis, older adults with and without geriatric syndromes across the three therapy groups were compared with primary outcome for stroke. Multivariable Cox hazard, logistic regression, and Kaplan Meier survival curves were utilized to determine association of treatment with risk-adjusted stroke and hemorrhage incidence.

Compared to patients prescribed no antithrombotic therapy, the reduced stroke occurrence was 75% to 82% oral anticoagulants and 70% to 74% in those prescribed

antiplatelet agents (both $p < .001$), after controlling for risk. Patients prescribed antiplatelet agents and oral anticoagulants were 3.28 and 3.19 times more likely, respectively, than patients not prescribed antithrombotics to develop noncranial hemorrhage ($p < .05$). Patients with geriatric syndromes experienced higher incidence of stroke when prescribed oral anticoagulants ($p = 0.00$) and antiplatelet agents ($p < 0.001$), compared to patients without geriatric syndromes.

Subjects with geriatric syndromes had benefit and risk profiles when prescribed oral anticoagulant and antiplatelet therapies to prevent thromboembolism similar to other populations recorded, although overall stroke incidence was greater. This suggests that populations with geriatric syndromes should be specifically incorporated into the guidelines clinicians use to tailor antithrombotic therapies to individual patient risk.

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CHAPTER 1

INTRODUCTION

Statement of the Problem

Atrial fibrillation (AF), the most common form of irregular heart rhythm, has increased prevalence in older adults (Olesen, Lip, & Lane, 2011). Baseline frequency in patients age 65 and older has been estimated at 7.2% (Lip, Tse, & Lane, 2012). This arrhythmia is projected to affect 15.9 million older adults in the United States by the year 2050 (Lip et al., 2012). According to the National Institutes of Health (2010), it has been estimated that the cost of this disease is $6.4 billion annually in the United States alone.

AF is associated with 15% to 25% of ischemic strokes (Hendriks, de Wit, Vrijhoef, Tieleman, & Crijns, 2010). Treatment with oral anticoagulants (OAC) to prevent the formation of blood clots due to blood stasis in a fibrillating atria decreases the risk of stroke by 68% (Jacobs, Billett, Freeman, Dinglas, & Jumaquio, 2009). Treatment of this same condition with antiplatelet therapy decreases the risk of stroke by 40% (Hart, Pearce, & Aguilar, 2007).

Studies show that OAC causes an increase in the likelihood of intracranial and other types of hemorrhages, as well as death in older populations (Pieracci, Eachempati, Shou, Hydo, & Barie, 2007). Despite the fact that research shows that using OAC in

older adults is beneficial, providers are often reluctant to prescribe this therapy for patients with geriatric syndromes such as falls and/or dementia and/or frailty (Morley, 2008). The use of OAC also correlates with the highest number of preventable hospitalizations of older adults, with warfarin contributing to 33.3% of these adverse drug events (Budnitz, Lovegrove, Shehab, & Richards, 2011).

The older patient with AF exists on a continuum of risks. At one extreme is a stroke risk if inadequately treated, and at the other is a bleeding risk. Somewhere in the middle is the optimal balance, but the dilemma is that the optimal point differs based on individual patient characteristics; this is why it is necessary to examine other aspects of thromboembolism-prevention therapy. Simply applying existing methods and recommendations has proven to lead only to more debate on the subject, both nationally and internationally, resulting in more questions as opposed to more answers (Gladstone et al., 2011). Providers are expected to follow guidelines for prevention of a stroke, but following the guidelines puts patients at risk for a life-threatening bleed, which prevents many providers from prescribing oral anticoagulants (Garwood & Corbett, 2008).

Personalized medicine, the concept of providing medical care based on phenotype and patient preferences, is the future of healthcare (Kravitz, 2014). For example, patients may decide to forgo OAC therapy after having examined their risk factors and life quality issues with their provider. Clinicians practicing personalized medicine are poised to participate in balancing both extremes of the spectrum of therapy with OAC.

Within the clinical arena the two most widely used predictive schemas to determine the appropriate therapy for prevention of cerebrovascular accident (CVA) in those with AF are CHA_2DS_2-VASc (congestive heart failure, hypertension, diabetes

mellitus, vascular disease (coronary artery disease, peripheral artery disease or aortic plaque), age 65 to 74 years old, and sex (female gender). This schema includes risk factors for the initiation of OAC in clinical settings for the prevention of a stroke. In this schema, the risk of a stroke is calculated as a percentage-per-year value. Guidelines for stroke-prevention therapy include consideration of scores of these schemas. This schema does not include consideration of falls, dementia, and frailty, but providers do consider these factors when assessing for the initiation of OAC therapy. According to guidelines, these conditions do not contraindicate the use of OAC therapy; however, in practice, many providers are reluctant to initiate this therapy in patients with falls, dementia, and frailty, contributing to the underutilization of OAC in older adults (Garwood & Corbett, 2008; Tulner et al., 2010). A patient with dementia who is administering his or her own medications may mix up their OACs and take too much or not enough, which may lead to a stroke or a bleed. Fall-prone patients on OACs may sustain trauma with resultant bleed that can be life threatening. Frail patients are not only prone to falls, but may also have impaired organ function, increasing the risk of medication toxicity.

Significance of the Problem

Within the overall population, the number of people age 65 and older will increase from 40.4 million in 2010 to 55 million in 2020 (U.S. Department of Health and Human Services, 2011). The prevalence of AF increases with age, from 5% in individuals over age 65 to 10% in people age 80 and older (Marinigh, Lip, Fiotti, Giansante, & Lane, 2010). AF also has a high mortality rate: up to 15% within the first 30 days of diagnosis (Benjamin et al., 1998); yet older patients are at greater risk of adverse effects of OAC

(Bajorek, Krass, Ogle, Duguid, & Shenfield, 2005). The need for development and testing of a risk stratification tool for AF and its thromboembolic complications was specifically identified in a recent National Institutes of Health (NIH) report (NIH, 2010).

The Patient-Centered Outcomes Research Institute (PCORI) is committed to providing beneficial research outcomes to patients and providers (Wallis, 2014). In the spirit of PCORI, this proposed study contributes to an understanding of antithrombotic therapy as a basis for future intervention protocols that may lead to patient-centered outcomes for older adults on OACs.

This study will begin the research trajectory toward that end, and provides information about achieving more effective OAC management in older adults. This retrospective descriptive study was designed to inform clinicians and patients with AF about the outcomes of suboptimal preventive therapy, including stroke and hemorrhage in older adults with AF, by assessing the association of these outcomes with OAC use, and to examine the implications of the falls, dementia, and frailty on this therapy.

Innovation

The disciplines of cardiology and internal medicine provide a body of research concerning OAC in stroke prevention, while pharmacology and geriatrics provide cautious information concerning adverse drug effects and poor outcomes of OAC therapy associated with aging. Geriatric providers are concerned with quality-of-life issues of older individuals, tailoring therapy to the needs of each patient across multiple chronic conditions; however, these patients most likely are treated by several providers, which places them in the position of receiving inputs from various providers with regard to the

use of OACs. There is no consensus among providers or among disciplines when it comes to the use of OACs. This transdisciplinary study brought together the disciplines of nursing, cardiology, internal medicine, and pharmacology to determine the risk-versus-benefit ratio of using OACs. The study provides answers to clinicians and patients to aid in decisions regarding the use of OACs.

There is a vital need to re-evaluate this complex issue from the standpoint of patient-centered outcomes. Examining this problem by exploring patient comorbidity outcomes will provide additional considerations that are missing from the use of this therapy. This study will better equip providers and patients for future decisions they will make in prescribing OACs in older adults with AF. The study will also lead to future studies seeking interventions that deliver maximum benefit to older patients with AF. Such studies may ultimately lead to the reexamination of existing guidelines and the incorporation of additional risk considerations, allowing individual patients a more suitably tailored therapy.

Purpose of the Study

Complications resulting from AF increase both the burden of healthcare cost and what is ultimately the most feared outcome, the potential for stroke. Current research confirms that the optimal use of OACs in this population would reduce thromboembolic events, in turn decreasing debility, hospitalization, and healthcare expenditures without incurring debility, hospitalizations, and undue burden resulting from treatment (Gorin et al., 2011). Fewer than 50% of high-stroke-risk patients are treated with anticoagulants, confirming this real and persistent problem (Ogilvie, Newton, Welner, Cowell, & Lip,

2010).

The potential for misuse of OACs demands answers regarding their optimal use. Recorded within the literature is the fact that the presence of one or more specific geriatric syndromes (falls, dementia, frailty) directly influences decision making on the part of providers. Although these factors have been mentioned in the literature individually, they have not been studied in combination with one another, nor have they been explored thoroughly enough to explain the issues related to their occurrence as it pertains to the opposing ends of the continuum for prescribing antithrombotic therapy.

Specific Aims

The following were the specific aims of the study: Among older adults with atrial fibrillation,

1. Identify differences in risk-adjusted stroke rates depending on CHA_2DS_2-VASc among older adults with a geriatric syndrome (falls, dementia, and/or frailty) prescribed an OAC, antiplatelet agents, or no antithrombotic therapy. Hypothesis: Contingent on CHA_2DS_2-VASc scores, patients with a geriatric syndrome who are prescribed an OAC or antiplatelet agent will have a higher rate of strokes and TIAs than patients who are prescribed an OAC or antiplatelet agent.
2. Describe the difference in risk-adjusted hemorrhage rates contingent on HAS-BLED scores in older adults with a geriatric syndrome (falls, dementia, and/or frailty) prescribed an OAC, an antiplatelet agent, and no OAC or antiplatelet agent.

Hypothesis: Contingent on HAS-BLED scores, patients with a geriatric syndrome who are not prescribed an OAC or antiplatelet agent will report a lower rate of hemorrhages than patients who are prescribed an OAC or antiplatelet agent.

3. Using a factorial design, determine the main and interaction effects of thromboembolic therapy for older adults with chronic atrial fibrillation and the presence of a geriatric syndrome (falls, dementia, and/or frailty), contingent on CHA_2DS_2-VASc scores.

   Hypothesis 3A: Contingent on CHA_2DS_2-VASc scores, there is a main effect of thromboembolism prevention therapy for older adult patients with AF on incidence of stroke and TIA, with the order from lowest to highest being OACs, antiplatelet agents, and no antithrombotic therapy groups.

   Hypothesis 3B: Contingent on CHA_2DS_2-VASc scores, there is a main effect of geriatric syndromes (falls, dementia, and/or frailty) on incidences of strokes and TIAs in older adults having atrial fibrillation diagnosis, with those without a geriatric syndrome having a lower incidence.

   Hypothesis 3C: Contingent on the CHA_2DS_2-VASc score is an interaction of thromboembolism prevention therapy and the presence of a geriatric syndrome (falls, dementia, and/r frailty) on incidences of strokes and TIAs in older adults.

Organization of the Dissertation

This dissertation is organized into seven chapters. Chapter 2 is a review of the literature on cerebrovascular accident (CVA)/transient ischemic attack (TIA), atrial fibrillation, therapy, management of heart rhythm, thromboembolism, stroke prevention, risk stratification schema for the assessment of stroke risk, adverse effects: hemorrhages, risk stratification schema for the assessment of a bleeding risk, existing guidelines, falls, dementia, and frailty. The methods used in the entire study compose Chapter 3. Chapter 4 describes differences in incidence of stroke in AF patients with geriatric syndromes over 3-year follow up depending on the type of stroke-prevention therapy: oral anticoagulants (OAC), antiplatelet agents (ATPL), or none of these (No OAC/ATPL). Chapter 5 discusses the surveying of medical records of AF patients age 65 years and older also diagnosed with geriatric syndromes to contrast hemorrhage incidence differences during the 3-year follow up, while considering the following stroke prevention therapies: OAC, ATPLs, or no OAC/ATPL. Chapter 6 contains a discussion of observed electronic medical records of participants age 65 years and over with AF and geriatric syndromes and another group with AF and no geriatric syndromes, to ascertain variations in stroke occurrence over a 3-year follow up, while considering the type of stroke-prevention therapy used (OAC), ATPL, or no OAC/ATPL). Discussion and the conclusions of the study are presented in Chapter 7.

References

Bajorek, B. V., Krass, I., Ogle, S. J., Duguid, M. J., & Shenfield, G. M. (2005). Optimizing the use of antithrombotic therapy for atrial fibrillation in older people: A pharmacist-led multidisciplinary intervention. *Journal of the American Geriatrics Society, 53*(11), 1912–1920.

Benjamin, E. J., Wolf, P. A., D'Agostino, R. B., Silbershatz, H., Kannel, W. B., & Levy, D. (1998). Impact of atrial fibrillation on the risk of death. *Circulation, 98*(10), 946–952. doi:10.1161/01.cir.98.10.946

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*(21), 2002–2012. doi:10.1056/NEJMsa1103053

Garwood, C. L., & Corbett, T. L. (2008). Use of anticoagulation in elderly patients with atrial fibrillation who are at risk for falls. *Annals of Pharmacotherapy, 42*(4), 523–532. doi:10.1345/aph.1K498

Gladstone, D. J., Earl, K. M., Bungard, T. J., Cox, J. L., Bell, A., Dorian, P., . . . Shuaib, A. (2011). New anticoagulants for atrial fibrillation: The beginning of a new era in stroke prevention. *Canadian Journal of Neurological Sciences, 38*(5), 777–782.

Gorin, L., Fauchier, L., Nonin, E., Charbonnier, B., Babuty, D., & Lip, G. Y. H. (2011). Prognosis and guideline-adherent antithrombotic treatment in patients with atrial fibrillation and atrial flutter. *CHEST, 140*(4), 911–917. doi:10.1378/chest.10-2436

Hart, R. G., Pearce, L. A., & Aguilar, M. I. (2007). Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of Internal Medicine, 146*(12), 857-867.

Hendriks, J. M., de Wit, R., Vrijhoef, H. J., Tieleman, R. G., & Crijns, H. J. (2010). An integrated chronic care program for patients with atrial fibrillation: Study protocol and methodology for an ongoing prospective randomised controlled trial. *International Journal of Nursing Studies, 47*(10), 1310–1316. doi:10.1016/j.ijnurstu.2009.12.017

Jacobs, L. G., Billett, H. H., Freeman, K., Dinglas, C., & Jumaquio, L. (2009). Anticoagulation for stroke prevention in elderly patients with atrial fibrillation, including those with falls and/or early-stage dementia: A single-center, retrospective, observational study. *American Journal of Geriatric Pharmacotherapy, 7*(3), 159–166. doi:10.1016/j.amjopharm.2009.06.002

Kravitz, R. L. (2014). Personalized medicine without the "omics." *Journal of General Internal Medicine, 29*(4), 551. doi:10.1007/s11606-014-2789-x

Lip, G. Y. H., Tse, H. F., & Lane, D. A. (2012). Atrial fibrillation. *Lancet, 379*(9816), 648–661. doi:10.1016/s0140-6736(11)61514-6

Marinigh, R., Lip, G. Y. H., Fiotti, N., Giansante, C., & Lane, D. A. (2010). Age as a risk factor for stroke in atrial fibrillation patients: Implications for thromboprophylaxis. *Journal of the American College of Cardiology, 56*(11), 827–837. doi:10.1016/j.jacc.2010.05.028

Morley, J. E. (2008). Hot topics in geriatrics. *Journal of the American Medical Directors Association, 9*(9), 613–616. doi:10.1016/j.jamda.2008.09.002

National Institutes of Health. (2010). *ARRA investments in atrial fibrillation*. Retrieved from http://report.nih.gov/recovery/investmentreports/ViewARRAInvRpt.aspx?csid=158

Ogilvie, I. M., Newton, N., Welner, S. A., Cowell, W., & Lip, G. Y. H. (2010). Underuse of oral anticoagulants in atrial fibrillation: A systematic review. *American Journal of Medicine, 123*(7), 638–645. doi:10.1016/j.amjmed.2009.11.025

Olesen, J. B., Lip, G. Y. H., & Lane, D. A. (2011). An epidemic of atrial fibrillation? *Europace, 13*(8), 1059–1060. doi:10.1093/europace/eur141

Pieracci, F. M., Eachempati, S. R., Shou, J., Hydo, L. J., & Barie, P. S. (2007). Use of long-term anticoagulation is associated with traumatic intracranial hemorrhage and subsequent mortality in elderly patients hospitalized after falls: Analysis of the New York State Administrative Database. *Journal of Trauma, 63*(3), 519–524. doi:10.1097/TA.0b013e31812e519b

Tulner, L. R., Van Campen, J. P., Kuper, I. M. J., Gijsen, G. J. P., Koks, C. H. W., MacGillavry, M. R., . . . Brandjes, D. P. M. (2010). Reasons for undertreatment with oral anticoagulants in frail geriatric outpatients with atrial fibrillation: A prospective, descriptive study. *Drugs & Aging, 27*(1), 39–50. doi:10.2165/11319540-000000000-00000

U.S. Department of Health and Human Services, Administration for Community Living. (2015). A profile of older Americans: 2015. Retrieved from www.aoa.acl.gov/Aging_Statistics/Profile/2015/4.aspx

Wallis, L. (2014). Report outlines best practices in patient-centered outcomes research. *American Journal of Nursing, 114*(2), 16. doi:10.1097/01.NAJ.0000443760.99818.a0

CHAPTER 2

REVIEW OF THE LITERATURE

Cerebrovascular Accident and Transient Ischemic Attack

Definition

It is estimated that in the United States there are 795,000 strokes, or cerebrovascular accidents, every year, with 137, 000 of those resulting in death (Fonarow et al., 2010). Age is the most important risk factor for all strokes, including ischemic stroke, related to atrial fibrillation (AF), with a doubling of the risk for a stroke for every 10 years, starting at the age of 55 years (Fonarow et al., 2010). In the 34 years of follow-ups in the Framingham Study, records show that among people ages 50 to 89 there were 572 strokes (122 ischemic CVAs, 256 thrombotic brain infarcts, 114 embolisms, 27 intracerebral hemorrhages, 39 subarachnoid hemorrhages, 14 miscellaneous causes), with AF diagnosed in 311 of these subjects (Wolf, Abbott, & Kannel, 1991). The researchers concluded that warfarin, a drug used for oral anticoagulation, prevents up to 80% of strokes that are caused by AF (Wolf et al., 1991).

Incidence

In a study of age-related difference among patients who experienced a stroke, older patients had more comorbid conditions, were more likely to be female, and were less likely to receive oral anticoagulants indicated to prevent stroke (Saposnik et al., 2009). The researchers found that morbidity at 7 days, 30 days, and 1 year were the highest among patients 80 years and older. Providers are faced with complex issues related to the care of older patients and are expected to make the "right" treatment decisions, which may be substantially complicated due to the variety of contributing factors. Under certain conditions, patients experiencing a stroke and treated in a hospital within a critical window of time can be given tissue plasminogen activator (tPA), which is used to dissolve blood clots; however, older patients are less likely to receive this therapy, primarily due to the concern about a subsequent hemorrhage (Fonarow et al., 2010).

Types and Contributing Factors

A transient ischemic attack (TIA) is a brief interruption of blood flow to the brain that generally results in no sequela, or very minor symptomology, compared to a stroke. Acute ischemic stroke is an interruption of blood flow to the brain that results in cellular death and permanent damage. Aggressive rehabilitation after a stroke may result in better outcomes for patients; however, older patients may not completely recover. Acute ischemic stroke results in death one third of the time, and physicians must decide what kind of poststroke care should be developed for surviving patients (O'Donnell et al., 2012). Of the patients who survive a stroke, 30% are permanently disabled and 20%

require institutional care for 3 months or longer (Holloway et al., 2010). Each year in the United Sates between 1999 and 2009, 795,000 people experienced a stroke (ischemic or hemorrhagic); this represents 6.8 million stroke victims in the United States during this period. AF increases ischemic stroke risk 5-fold in individuals of all ages (Go et al., 2013). Ischemic strokes are estimated to comprise 87% of all strokes occurring in the United States. Of post-ischemic-stroke patient discharges, only 45% returned directly to their home, while 24% were admitted to inpatient rehabilitation facilities and the remaining 31% were admitted to skilled nursing facilities. People age 85 years and older comprise 17% of all strokes. In 2009 the estimated healthcare cost of all strokes in the United States was $22.8 billion (Go et al., 2013).

In summary, older patients with AF are more likely to have a stroke, and these same patients are less likely to be treated with OAC therapy, as recommended in the guidelines. Older patients are more likely to have comorbid conditions, complicating their course of therapy following a stroke, and many may require institutionalization following an ischemic stroke. When institutionalized following a stroke, many older patients are completely reliant on their caregivers.

Atrial Fibrillation

Definition

In a normally functioning heart, electrical impulses are generated in the sinoatrial node, which is located at the top of the right atria and acts as the natural pacemaker of the heart. The electrical signal generated spreads first through the right atria and then through the left atria, and is what causes them both to contract (Waktare, 2002). Following

contraction of the atria, blood is pushed into the ventricles, which are the main pumping chambers of the heart. The electrical impulse then travels to the atrioventricular node and then down both ventricles, causing them to contract as well (Waktare, 2002). The term *normal sinus rhythm* is used to describe a normal heart rhythm, which is between 60 and 100 beats per minute (BPM).

AF is an irregular heart rhythm that occurs with the abnormal introduction of disorganized electrical impulses generated in various foci within the atria. These are most commonly found around pulmonary veins, and cause the atria to experience a rate of 300 to 600 BPM; however, during AF the atrioventricular node does not allow all of the 300 to 600 impulses to be conducted from the atria to the ventricles. It acts something like a toll gate in that it typically allows conduction of only between 110 and 180 BPM, which is the common range associated with the presence of AF (Waktare, 2002). During AF there is stagnation of the blood in the atria, which is what contributes to the formation of a blood clot, or thromboembolism. These blood clots, or thrombi, may travel to the brain, causing a stroke or cerebrovascular accident by occluding the blood vessel and causing severe restriction of blood flow; thus the name ischemic stroke (Padanilam & Prystowsky, 2009). AF is the most commonly encountered tachyarrhythmia, which in itself is not causative of death; however, complications of this tachyarrhythmia may lead to a stroke, congestive heart failure, and/or death. AF is prevalent in older adults, with an incidence of 6% in those 65 to 74 years of age, 12% in those 75 to 84 years, and 16% in adults age 85 years and older (Hobbs et al., 2011).

Incidence and Risk Factors

One effect of the Baby Boom generation is a dramatic increase in the number of older adults in the United States. Between 2004 and 2014 the U.S. population ≥ age 65 experienced a 28% increase, growing from 36.2 to 46.2 million, and it is expected to reach 98 million by 2060. Older adults in the United Sates represent the largest segment of the population and account for 36% of healthcare expenditures and 42% of prescription drug costs (Herrera et al., 2010).

Currently, AF affects 2.3 million people in the United States and 6 million people in Europe (Chinitz, Castellano, Kovacic, & Fuster, 2012). The incidence of AF is known to increase with age and is conservatively projected to double, at the very least, within the next 50 years (Chinitz et al., 2012). Age increases the potential for stroke by as much as 3 to 5 times (Benjamin et al., 1998; Tsang et al., 2003), and although women in the United States typically live longer than men, advanced age predicts greater prevalence of AF regardless of gender. In 2010 in the United States, women outnumbered men, representing 57% of the population age 65 and older and 67% of the population age 85 and older. These statistics clearly demonstrate that in the near future clinicians will be treating many more patients with AF, and will encounter more comorbidity issues associated with AF than they do currently. This dilemma is faced not only by the United Sates but most European countries as well, and is contributing directly to the ongoing research efforts on this subject that are taking place in Europe, Canada, and elsewhere.

AF is strongly associated with significant comorbidities that are common in older adults, such as congestive heart failure, coronary artery disease, hypertension, and diabetes mellitus. The presence of longstanding hypertension predisposes the left

ventricle to enlarge over time, causing stretching of the tissue and making it more irritable around pulmonary veins, thereby causing AF (Padanilam & Prystowsky, 2009).

Sequelae

Studies have shown that AF is responsible for 36% of the ischemic strokes occurring in adults age 80 and older (Padanilam & Prystowsky, 2009). In the Framingham Study, AF was associated with increased mortality in adults of 65 years and older. Mortality was high within 30 days of the diagnosis of AF, at 15%. After the 30-day period, AF was associated with a doubling of the mortality rate (Benjamin et al., 1998). Something else being studied is the comorbid conditions contributing to or associated with AF and their impact on the associated increase in mortality. The research surrounding this question so far has determined that AF independently adds a risk of stroke, myocardial infarction (MI), and death in addition to the other risk factors (Crandall et al., 2009). Despite the fact that scientists and clinicians are utilizing clinical trials to discover new management strategies for AF, mortality remains high. The Institute of Medicine declared that AF treatment strategies are a national priority for comparative effectiveness research (Piccini et al., 2012)

Therapy

Treatment of AF is complex because it involves both prevention of thromboembolism and management of the heart rhythm. Oral anticoagulants are used for the prevention of thromboembolism, and have a demonstrated 64% overall reduction in stroke and 26% reduction in mortality in older adults (Lip, Tse, & Lane, 2012).

Management of Heart Rhythm

In a clinical setting, some patients are left in persistent atrial fibrillation, with heart-rate control accomplished through the use of beta blockers or calcium channel blockers. Rate control may also be enhanced by the addition of digoxin; however, this medication has been associated with an increase in all-cause mortality (Whitbeck et al., 2012). Most frequently, patients having persistent AF are older and are not symptomatic with AF. If rate control becomes a problem, these patients may undergo atrioventricular node ablation with permanent pacemaker implantation. This allows the patient to continue having AF in the atria while the pacemaker controls the heart rate in the ventricles, decreasing symptoms of palpitation and preventing ventricles from beating fast when AF beats are conducted rapidly to the ventricles. Rhythm control may be achieved through the administration of antiarrhythmic drugs; direct current cardioversion, which involves shocking the patient to convert to normal sinus rhythm; and radiofrequency catheter ablation.

In the Pharmacological Intervention in Atrial Fibrillation (PIAF) trial of rate versus rhythm control in symptomatic patients, it was shown that there was no superiority of one or the other strategy in improvement of the AF symptoms (Hohnloser, Kuck, & Lilienthal, 2000). The Strategies of Treatment of Atrial Fibrillation (STAF) study compared rhythm versus rate control in a randomized controlled trial, with the final result showing no superiority of rate versus rhythm-control treatment strategy (Carlsson et al., 2003). In the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study, rhythm and rate control were compared and neither one showed superiority over the other (Corley et al., 2004). The Danish Investigations of Arrhythmia

and Mortality on Dofetilide (DIAMOND) study showed that patients who had normal sinus rhythm with or without antiarrhythmic medications had a better prognosis than patients in AF (Corley et al., 2004).

The AFFIRM investigators followed with an assessment of the survival rate of their subjects; that analysis showed that the presence of a normal sinus rhythm was associated with a significant reduction in the risk of mortality, displaying consistency with the DIAMOND study (Corley et al., 2004). In a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400mg twice a day for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter (ATHENA) trial, it was shown that patients who took dronedarone, an antiarrhythmic medication, had a lower risk of stroke (Connolly, Crijns, et al., 2009). These studies aided us in the development of our understanding that patients on antiarrhythmic medications who maintain a normal sinus rhythm have a lower risk of stroke. In a recent study from Intermountain Medical Center in Salt Lake City, Utah, it was shown that patients who undergo radiofrequency catheter ablation (RFCA) exhibit lower rates of death, stroke, and dementia when compared to their counterparts who did not undergo RFCA (Bunch et al., 2013). These results are encouraging and reinforce the assertion that management of rhythm is superior to other therapies. Furthermore, patients who undergo an AF radiofrequency catheter ablation and maintain a normal sinus rhythm are likely to have the same mortality outcomes as patients who never experience AF (Bunch et al., 2013). The Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial is presently ongoing and will answer questions regarding the efficacy of radiofrequency catheter ablation compared to that of

antiarrhythmic medications in maintaining a normal sinus rhythm (Bunch et al., 2013); the researchers are also examining mortality rates associated with AF.

Thromboembolism and Stroke Prevention

Rates of thromboembolism vary depending on coexisting conditions that patients may have. In this section the criteria used to assess the risks of stroke and need for preventative treatment, as well as adverse effects of treatment with anticoagulants, are discussed, followed by a presentation of oral anticoagulants used to prevent stroke.

Risk Stratification Schemas for the Assessment of Stroke Risk

$CHADS_2$ is a scoring system used for assessment of the risk factors for stroke in patients with AF. $CHADS_2$ assigns one point for each of the following: congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus; additionally, it assigns 2 points for each previous stroke or TIA.

Subsequent to the development and use of the $CHADS_2$ schema was the development and implementation of another stroke risk assessment tool, the CHA_2DS_2-VAS_c schema, which was used in this study. The CHA_2DS_2-VAS_c schema assigns one point for each of the following: congestive heart failure, hypertension, diabetes mellitus, vascular disease (coronary artery disease, peripheral artery disease, or aortic plaque), age 65 to 74 years, and sex (female gender); in addition, 2 points are assigned for previous stroke or TIA and age ≥ 75 years.

An aggregate score of 0 to 9 is derived and used to predict annual stroke risk, from 0.2% for a CHA_2DS_2-VAS_c score of 0, up to 15.2% for a CHA_2DS_2-VAS_c score of

9. When utilizing this scoring system, patients are divided into the following categories: (a) low risk, which is associated with a CHA_2DS_2-VAS_c score of 0, which may or may not require aspirin; (b) intermediate risk, which is associated with a CHA_2DS_2-VAS_c score of 1, which indicates antiplatelet (aspirin or aspirin and clopidogrel) or OAC; and (c) high risk, which is associated with a CHA_2DS_2-VAS_c score of 2 or higher, which recommends OAC (Pamukcu, Lip, & Lane, 2010).

CHA_2DS_2-VASc was compared to the $CHADS_2$ schema in 2009. In a cohort of 1,084 patients diagnosed with AF it was found to be as predictive as the $CHADS_2$ schema. The average age of patients included in the analyses was 66 years; 40.8% of them were women. Hypertension was the most prevalent stroke risk in this sample. This schema validation demonstrated a C-statistic value of 0.66, and possessed a superior predictive ability compared to that of other schemas (Gage et al., 2001). C-statistics (c stands for concordance) is an accepted method used to assess predictive and observed outcomes (Harrell, Lee, & Mark, 1996). C-statistic 0.5 indicates no predictive ability and 1.00 indicates perfect predictive ability. Validity of an instrument is determined by assessing the correlation between variables and predictive abilities of the instrument (DeVellis, 2011).

The CHA_2DS_2-VASc schema was incorporated into the European Society of Cardiology guidelines in 2010. It was proposed as an alternative to $CHADS_2$ and was found to be more specific in predicting stroke risk in low-risk-group patients (Piccini & Singer, 2012). Sandhu, Bakal, Ezekowitz, and McAlister (2011) demonstrated that the CHA_2DS_2-VASc schema predicted the risk of thromboembolism better than did the $CHADS_2$ in hospitalized patients.

Adverse Effects: Hemorrhages

The major adverse event associated with OACs is hemorrhage. Ogilvie, Welner, Cowell, and Lip (2011), in a meta-analysis, reported that patients treated with OACs did have higher rates of hemorrhages when compared to patients treated with antiplatelet therapy. They also found that patients who began taking OACs were more likely to develop a major bleed during the first 90 days of the OAC therapy, especially if they were age 80 or older. The risk of hemorrhage is highest during the first 30 days of OAC therapy, with resulting hemorrhages at 1% and an increased risk of bleeding in patients with a $CHADS_2$ score of 4 or higher. Additionally, clinical trials have revealed lower rates of hemorrhages resulting from careful selection of subjects, strict adherence to the protocol, and aggressive patient monitoring—circumstances that are not always present in real-life settings. Consequently, hemorrhage rates are higher in clinical settings outside of clinical trials (Gomes et al., 2013).

In a prospective study of 783 older AF patients age 80 and older who were using warfarin, the rate of a major bleeding was low, at 2.5/100 patient years (Poli et al., 2009). Participants were followed closely throughout the study, and any bleeding event that occurred was immediately treated aggressively. This type of close scrutiny during a study better positions the study population for early detection of any bleeding events. Another advantage among this population was that they had few comorbidities that predisposed them to increased risk of a major bleed (Poli et al., 2009). The cohort also lacked frail patients who were less likely to be referred to an outpatient service (Poli et al., 2009).

It has been shown previously that patients age 65 years and older are predisposed to a higher risk of bleeding. Antiplatelet therapy administered concomitantly with

warfarin increases the risk of major bleeding 2.3 to 2.5 times (Lane, Kamphuisen, Minini, Büller, & Lip, 2011). It is also noted in the literature that the definition of major bleeding has not been consistent among various trials, which makes it tremendously difficult to compare bleeding risk based on these trials (Lane et al., 2011). The association of increased bleeding risk with concomitant OAC and antiplatelet therapy is related to the treatment of older patients with more comorbid conditions, such as coronary artery disease, diabetes mellitus, or previous stroke; they therefore require the addition of antiplatelet therapy, such as aspirin, which predisposes to a higher risk of bleeding.

Another Canadian study of 266,460 patients age 66 years and older explored the rate of hemorrhages associated with OAC therapy and found the rates of bleeding at 3.8% per person year, compared to the 6.8% to 7.2% per person year reported in the literature (Gomes et al., 2012). Healthcare costs are increased for patients who are hospitalized for a major bleed. For example, in their study, Ghate, Biskupiak, Ye, Kwong, and Brixner (2011) found that the cost for patients with a minor gastrointestinal (GI) bleed was $22,507, for patients with an intracranial bleed was $42, 574, and for patients with a major GI bleed was $36,571.

Providers are less likely to prescribe OACs to patients age 80 years and older due to the increased fear of bleeding. Moreover, physicians are more likely to stop OAC therapy and prescribe antiplatelet therapy for older patients, although it is less efficacious (Riva, Smith, & Lane, 2011). In particular, this situation occurs when older adults are suffering from frailty, falls, or dementia. These cognitive and physical declines predispose older patients to complications due to comorbid conditions coupled with OAC therapy, which may lead to a bleed. There are endless scenarios that may lead to an

increase in bleeding risk in older individuals with the above-mentioned conditions.

Risk Stratification Schema for the Assessment of a Bleeding Risk

The development of the HAS-BLED schema arose from the database of the SPORTIF trial, in which the sample consisted of 5,272 patients age 18 years and older (mean age = 79.3 years; Hankey et al., 2012). The acronym HAS-BLED represents the risk factors of hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly (age 65 and older), drug or alcohol use. The researchers in the SPORTIF trial (Hankey et al., 2012) used univariate analysis for the potential risk factors for a bleed ($p < 0.01$); these factors were subsequently included in the multivariate logistic regression in addition to the clinically known risk factors. In the final model, variables with a p value of <0.05 were considered to be significant. The resulting model was the basis for the HAS-BLED schema, which is the most commonly used clinical bleeding risk schema. The presence of any of the risk factors contained in the schema indicates an increased risk for the development of a bleed.

Each HAS-BLED risk factor is assigned a 1-point value, for a maximum of 9 points. The annual bleeding risk varies from 1.13% for a HAS-BLED score of 0, up to 19.6% for a HAS-BLED score of 9. When interpreting these results for a bleed risk, 0 and 1 are low risk, 2 is moderate risk, and scores of 3 and above are high risk. The HAS-BLED schema validation demonstrated a C-statistic value of 0.72 and possessed a superior predictive ability compared to that of other schemas (Pisters et al., 2010).

The particular type of bleed makes a significant difference in the clinical course

that must be followed. When contemplating the use of an OAC, clinicians use the HAS-BLED schema to assist them in determining whether or not to withhold OACs (Piccini & Singer, 2012).

Warfarin

Pharmacology

Warfarin is a vitamin K antagonist that has been known to be an effective anticoagulant for about 60 years. It reduces the synthesis of vitamin K and in turn prevents the formation of coagulation factors II, VII, IX, and X (Davie, 1995; Nutescu, Shapiro, Ibrahim, & West, 2006). Metabolism and plasma concentrations of warfarin are affected by liver function, genetics, alcohol, and food consumption. Warfarin therapy has a very narrow therapeutic range, and is measured by the international normalized ratio (INR), with 2.5 (range 2.0 to 3.0) being the usual therapeutic target for the INR during warfarin therapy for AF (Davie, 1995; Ghate, Biskupiak, Ye, Hagan, et al., 2011). The antidote for warfarin is vitamin K, which may be administered through intravenous or oral routes.

Warfarin dosing requires close monitoring due to multiple patient variables that may affect drug-level fluctuations, such as food, medication, and alcohol intake. Because many of the foods that patients normally consume contain vitamin K, diet significantly affects coagulant properties, as well as the target levels of warfarin within the blood (Custodio das Dores et al., 2007). Moderation in the consumption of green leafy vegetables and vegetable oils, which affect vitamin K levels the most, may be required when using warfarin (Custodio das Dores et al., 2007).

Efficacy

In 1991, the Canadian Atrial Fibrillation Anticoagulation (CAFA) study (Connolly et al., 1991) randomized patients into two groups: one was receiving warfarin with therapeutic INR between 2 and 3,and another group was receiving a placebo. This study was discontinued prematurely when the ethics oversight committee determined that the warfarin group was receiving stroke-prevention benefits, whereas the control group was not; it was deemed unethical to withhold warfarin from the control group (Connolly et al., 1991). A similar study conducted in the United Sates, the Stroke Prevention in Atrial Fibrillation (SPAF) study, and the Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation (AFASAK) study, found similar results of thromboembolism prevention with the use of warfarin (Connolly et al., 1991; Mant et al., 2007; Petersen, Boysen, Godtfredsen, Andersen, & Andersen, 1989; Stroke Prevention in Atrial Fibrillation Investigators, 1991). The Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) study also showed high efficacy of warfarin in preventing strokes, but was terminated early by the ethics committee for the same reason as the CAFA study (Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990). These studies helped providers recognize that therapeutic levels of warfarin are highly effective in the prevention of strokes.

Additionally, it was demonstrated that warfarin at lower therapeutic levels of INR—between 1.3 and 1.6—is still protective against strokes (Kistler et al., 1993). The AFFIRM trail showed not only that warfarin reduced strokes, but that it also reduced the risk of death (Corley et al., 2004). Patients who are on warfarin therapy and have already experienced a stroke or a TIA are at increased risk for another event (2.87%) versus

patients without previous events (1.66%; Hankey et al., 2012). Another consideration of warfarin therapy is suboptimal therapeutic INR range in high-risk patients, indicating deficiencies of care and the need for improvement (Hankey et al., 2012). Although it has been shown in numerous studies that warfarin is superior to aspirin in the prevention of strokes, providers are still reluctant to prescribe OACs to older adults. As the $CHADS_2$ scores increase, warfarin prescriptions decrease, when in fact warfarin prescriptions should be increasing with rising $CHADS_2$ scores (Kalus, 2010).

Safety

Warfarin is broken down by the cytochrome P450 (CYP) in the liver. The variability in age, weight, albumin levels, and other medications correlates with changes in the warfarin dose to achieve effective anticoagulation (Nutescu et al., 2006). Warfarin metabolism is decreased by medications that inhibit cytochrome P450 enzymes, resulting in increased warfarin concentrations and effects. As older adults age, the composition of their body changes, requiring continual adjustment to their individual warfarin dose. This is an ongoing trial-and-error process of adjusting the dose until the therapeutic range is reached. Additionally, changes in other medications, chronic diseases, and changes in body weight will contribute to changes in warfarin dosing (Singla & Morrill, 2005). As the geriatric population ages and their body mass index decreases, the warfarin dose required to reach a therapeutic level also decreases (Singla & Morrill, 2005). Despite the fact that some models were published to predict warfarin maintenance dosing, octogenarians were not adequately represented, and therefore we still do not have a good guide on warfarin maintenance dosing in these older patients (Garcia, Regan, Crowther,

Hughes, & Hylek, 2005).

The most common food sources of vitamin K are dark green vegetables and oils (Nutescu et al., 2006). The challenges of maintaining warfarin levels within the therapeutic range in older individuals are associated with their diet, other medications, comorbid conditions, and the problem of transportation to and from clinics for necessary and sometimes frequent INR checks. This may contribute to missed appointments and has the potential to lead to a spontaneous hemorrhage or stroke due to the lack of a properly adjusted therapeutic dose. This particular dilemma encountered by providers contributes to underutilization of warfarin due to a fear of noncompliance with follow-up and maintenance doses (Garcia et al., 2005).

Individual responses to warfarin therapy depend on the genetic composition of the vitamin K receptors and warfarin metabolism. Determination of genetic coding for the CYP2C9 (metabolizing enzyme) and VKORC1 (receptor) enzymes has proven clinically useful in managing warfarin therapy (Custodio das Dores et al., 2007). The CYP2C9 and VKORC1 genotypic variants have been examined and do influence warfarin dosing; however, it has been shown that outcomes of pharmacogenomics-guided dosing and regular warfarin INR-tested dosing are similar (Hynicka, Cahoon, & Bukaveckas, 2008). Presently, health insurance companies do not cover any warfarin-related genetic testing, as it has not been shown to be beneficial in maintaining warfarin therapy (Gandara & Wells, 2010). Age bias is also an issue; often, a patient's age rather than the patient's well-being is what affects decision making on the part of providers when assessing for the use of OACs (Herrera et al., 2010).

A potential help for patients is to obtain a home monitor and be able to call INR

results in to the office. This would allow for dose adjustments to be made via telephone for virtually all patients. Unfortunately, home monitors for INRs maybe cost-prohibitive for some older adults.

Of the 99,628 general emergency hospitalizations in the United States from 2007 to 2009, a full one third were attributed to the implications of warfarin therapy, and the majority of this one third were due to unintentional overdoses causing bleeding (Budnitz, Lovegrove, Shehab, & Richards, 2011). Therefore, the capacity to take the drug may influence the decision to prescribe warfarin. If a particular patient has a major bleed, he or she is not likely to be prescribed warfarin again, and as an alternative, aspirin or aspirin plus clopidogrel would be considered for the prevention of thromboembolism. Patients' preferences should also be taken into consideration.

We do not have a wealth of information concerning the degree to which patients actually understand the broader picture regarding warfarin therapy. In a study that surveyed patients prescribed warfarin, it was discovered that patients with the highest $CHADS_2$ score and subsequently the highest risk of thromboembolism demonstrated average and below-average knowledge of OAC drugs (Smith et al., 2010). These patients were not aware of the vitamin K content in various foods, and 68% of them were unaware of the fact that their food choices were directly related to their warfarin therapy, or that various drugs and herbal products can also affect warfarin levels (Smith et al., 2010). This study illuminates various aspects of the lack of education, ineffective education, and/or reinforcement of education, in patients on warfarin therapy.

European studies have demonstrated that older adults are less aggressively rehabilitated after a stroke and less aggressively treated with OACs as they continue to

age (Fonarow et al., 2010). The reasons for less evidence-based adherence on the part of providers may be related to various factors, such as underrepresentation of older individuals in the studies, comorbid conditions, polypharmacy, lack of an available caregiver, and end-of-life issues (Fonarow et al., 2010). Rates of thromboembolism vary, depending on coexisting conditions that patients may have. OACs are used for the prevention of thromboembolism, and have provided a demonstrated 64% reduction in stroke and 26% reduction in overall mortality in older adults (Lip et al., 2012).

Aspirin and Aspirin Plus Clopidogrel

Pharmacology

Aspirin, or acetylsalicylic acid, inhibits cyclooxygenase 1 and 2, resulting in the inhibition of prostaglandins and thromboxane A2 and subsequently inhibiting platelet aggregation. It has anti-inflammatory, antipyretic, and analgesic properties (Roth & Majerus, 1975). This drug has been in use since the 1950s in the United States. In the 1970s, the first trials showed that aspirin was effective in preventing the frequency of strokes and TIAs (Caplan, 2006).

Efficacy and Safety

Aspirin has been compared to warfarin or placebo in randomized controlled trial and has been found to be less effective than warfarin in the prevention of thromboembolic events (Healey et al., 2008). The therapeutic dose of aspirin is still controversial. In the ACTIVE W trial, which included 6,706 patients who were randomly assigned to either a combined therapy of aspirin (75mg to 100mg) and clopidogrel

(75mg) or to warfarin (INR 2 to 3), warfarin was shown to be superior to the combination of clopidogrel and aspirin (3.9% versus 5.6%), relative risk 0.69 (confidence interval [CI] 0.57 to 0.85), in the prevention of strokes (Healey et al., 2008). Another discovery of the BAATAF study (Kistler et al., 1993) was that aspirin was also effective in preventing strokes, but the SPAF (Stroke Prevention in Atrial Fibrillation Study Investigators, 1991) and AFASAK (Petersen, Boysen, Godtfredsen, Andersen, & Andersen, 1989) studies were inconsistent with aspirin doses, as SPAF used aspirin 325mg/day and AFASAK recommended 75mg/day.

Clopidogrel

Pharmacology

Clopidogrel works by blocking the P2Y12 component of the adenosine 5'-diphosphate pathway on the platelet surface, which blocks activation of GPIIb/IIIa receptors, subsequently decreasing platelet aggregation for the duration of their lifespan of 7 to 10 days (Caplan, 2006).

Efficacy and Safety

In a study of clopidogrel (75mg) versus aspirin (325mg) in patients at risk of ischemic events, a randomized double-blind trial of 19,185 patients, clopidogrel demonstrated an 8.7% decrease of relative risk when compared to aspirin (Caplan, 2006). The resultant stroke rate for the clopidogrel group was 405/17,636, or 2.3%, compared to the resultant stroke rate for the aspirin group, which was 430/17, 519, or 2.5%. In a recent meta-analysis of the efficacy of clopidogrel in people with acute ischemic stroke, it was

concluded that there is not enough evidence to support this use (Ciccone, Motto, Abraha, Cozzolino, & Santilli, 2014).

Combined Aspirin and Clopidogrel Therapy

The ACTIVE W trial (Healey et al., 2008) demonstrated that patients with a $CHADS_2$ score of 1 treated with clopidogrel plus aspirin had a very low stroke rate of 1.2% per year, patients with a $CHADS_2$ score of 2 had a stroke rate at 1.9% per year, and those with a $CHADS_2$ score of 3 had a stroke rate of 2.8% per year, all of which were lower compared to patients treated with aspirin alone. Treatment with warfarin reduces the risk of stroke by 64%, whereas aspirin plus clopidogrel is associated with a smaller stroke risk of 22% (Duke Clinical Research Institute, 2010). In a meta-analysis of antiplatelet therapy with a placebo, or no treatment, it was shown that aspirin was associated with a 19% reduction of strokes, with absolute stroke risk reduction of 0.8% per year (Hart, Pearce, & Aguilar, 2007). In the ACTIVE W trial, OAC was superior in the prevention of strokes compared to aspirin plus clopidogrel (Healey et al., 2007). Aspirin reduces the risk of stroke by 36%, regardless of the aspirin dose; aspirin plus clopidogrel reduces it by 40% (Hart et al., 2007).

Direct Oral Anticoagulants

Direct oral anticoagulants (DOACs), which began with the release of Pradaxa, became available in 2010. They do not require laboratory monitoring of blood level concentrations or any other tests. It is notable that there is no antidote for any of the DOAC medications.

Dabigatran

Dabigatran is a direct thrombin inhibitor with a half-life of 12 to 17 hours. The U.S. Food and Drug Administration (FDA) approved dabigatran for the prevention of thromboembolism related to nonvalvular AF in 2010 (Sanford & Plosker, 2008). The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial (Eikelboom et al., 2011) included 18,113 patients who were randomly assigned to taking dabigatran at either 110mg twice a day or 150mg twice a day, with patients on warfarin at proper INR levels. The investigators concluded that dabigatran at 110mg twice a day was similar to warfarin in preventing stroke, but did exhibit a lower risk of bleeding than warfarin (relative risk 0.90, 95% CI 0.74 to 1.10). Dabigatran at 150mg twice a day was superior to warfarin in preventing stroke, but exhibited a risk of bleeding that is similar to that of warfarin (relative risk 0.65, 95% CI 0.52 to 0.81). Dabigatran was approved at doses of 110mg twice a day and 150mg twice a day. Both doses were associated with lower risks of intracranial bleeding; however, higher doses of dabigatran correlated with higher incidences of gastrointestinal bleeding compared to that of warfarin (5.10% versus 4.37% per year; $p = 0.07$). There was significant correlation between patient age and the number of major bleeding events. Patients younger than age 75 had a lower risk of bleeding when

compared to their counterparts who were age 75 and older. Patients exhibiting a creatinine clearance of less than 50 mL/min, when compared to patients at 80 mL/min or higher, experienced a 2-fold increase in risk of bleeding. This is because dabigatran is 80% renally excreted, whereas warfarin is not renally excreted, and the fact that older patients suffer from deteriorated renal function explains the higher concentrations of the drug in the blood, which causes the increased risk of bleeding (Eikelboom et al., 2011).

Comparing death rates in the RE-LY trial, warfarin deaths were at 4.13% per year, dabigatran 110mg twice a day at 3.75% per year, and dabigatran 150mg twice a day at 3.64% per year. The risk of myocardial infarction was 0.53% with warfarin, 0.72% with dabigatran at 110mg twice a day, and 0.74% with dabigatran 150mg twice a day. Major bleeding events with warfarin were at 3.36%, compared to 2.71% with dabigatran 110mg twice a day, and 3.11% with dabigatran 150mg twice a day (Connolly, Ezekowitz, et al., 2009). An analysis of a subgroup of patients in the RE-LY trial who had previously suffered one or more strokes also revealed that dabigatran (150mg twice a day) was superior to warfarin in preventing further strokes (Diener et al., 2010). In the RE-LY trial (Eikelboom et al., 2011), 40% of the patients were taking aspirin in addition to dabigatran or warfarin, and adjuvant treatment with aspirin did not predispose either group to an increase in major bleeding events (Alberts, Bernstein, Naccarelli, & Garcia, 2012).

There is no antidote for dabigatran, which presents a challenge for providers in the case of a major bleed. Although hemodialysis may be useful, it takes hours to accomplish. Activated prothrombin complex concentrate preparations may be effective; however, the dose for humans is unknown. Preclinical data show that the recombinant factor VIIa may reverse the effects of dabigatran (Alberts et al., 2012).

A May 2012 case report from the Neurosurgery Department of the University of Utah Hospital described the case of an 83-year-old male who was brought to the hospital after a fall and was diagnosed with an intracranial hemorrhage. He was taking dabigatran 150mg twice a day for AF, and died several hours after his presentation, despite the efforts of the neurosurgery team to reverse the dabigatran effects (Garber, Sivakumar, & Schmidt, 2012).

Rivaroxaban

Rivaroxaban was approved by the FDA in 2011 for the prevention of thromboembolism in patients with nonvalvular AF; it is a direct factor Xa inhibitor. A full one third of each rivaroxaban dose is eliminated unchanged through the kidneys, while the remaining two thirds are metabolized by the liver (Duke Clinical Research Institute, 2010). In the ROCKET AF trial (Patel et al., 2011), it was found that rivaroxaban was not inferior to warfarin, with no significant differences in rates of major bleedings, and that fatal bleedings occurred less frequently in the rivaroxaban group. The researchers concluded that a stroke or systemic embolism occurred at the rate of 1.7% in the rivaroxaban group and 2.2% in the warfarin group. In the same trial, major bleeding outcomes in the rivaroxaban group were at 3.6% and 3.4% in the warfarin group, with fewer fatal bleeds in the rivaroxaban group. In the rivaroxaban group, death occurred at 1.9%, while in the warfarin group these occurrences were at 2.2% (Patel et al., 2011). The ROCKET AF trail also showed that patients treated with rivaroxaban who underwent rivaroxaban drug discontinuation had higher rates of stroke and systemic embolism within 30 days after stopping the therapy. This suggests that providers need to ensure that

overlapping treatment occurs with another OAC or aspirin when stopping this therapy (Patel et al., 2013). There is currently no reversal agent for rivaroxaban, although the search for a reversal agent continues.

Apixaban

Apixaban is a direct factor Xa inhibitor that was approved in the United States in 2012 for thromboembolism prevention in nonvalvular AF; it is renally excreted at a rate of 25% of the dose. Granger et al. (2011), in their study, compared apixaban with warfarin, finding an event rate per year for strokes in the apixaban group at 1.19% and the warfarin group at 1.51%; the event rate per year for major bleeding was 2.13% in the apixaban group and 3.09% in the warfarin group. Death outcome event rates per year were 3.52% for the apixaban group and 3.94% for the warfarin group (Granger et al., 2011).

Granger et al. (2011) had similar findings regarding the reduced rate for stroke with apixaban compared to aspirin, without finding any difference in the rates of major bleeds. Lower rates of MI were also demonstrated in the apixaban group versus both the warfarin and aspirin groups. In the AVERROS trial, apixaban evidenced stroke rates of 1.6% per year, while aspirin and clopidogrel produced stoke rates of 3.7% per year, leading to the early discontinuation of the trial due to the superiority of apixaban (Skanes et al., 2012).

In the subgroup of the ARISTOTLE trial (Easton et al., 2010), the researchers found a 2-3 times higher risk of stroke or systemic embolism among patients with a previous stroke or TIA than among patients without prior events. Patients with AF who

experienced a previous stroke or TIA comprised 15% to 25% of the treated AF population, who were at high risk of subsequent thromboembolic events as well as increased risk of bleeding (Easton et al., 2012). Additionally, previous stroke was associated with an increased risk of death, which is consistent with previous studies. In patients with ischemic stroke, prescribing an OAC is a controversial issue. In the ARISTOTLE trial (Easton et al., 2010), patients who experienced a stroke or TIA within the previous 7 days were excluded; however, 234 patients who experienced a stroke or TIA within the previous 8 to 30 days were included. In the RE-LY trial (Connolly et al., 2009), patients who experienced a stroke or TIA within the previous 14 days, and patients with severe stroke within the previous 6 months, were excluded. In the ROCKET AF trial (Patel et al., 2011), patients who experienced a severe stroke within the previous 3 months or any stroke within 14 days were excluded. As a result of these variances, we have no confirmed answer as to whether it is safe to restart an OAC with novel agents after a stroke or a TIA (Easton et al., 2012).

Antidote

Scientists continue to search for a means to reverse the effects of DOACs, as well as for ways to develop blood-concentration tests for novel OACs. These strategies are of paramount importance in addressing the needs of patients who may suffer a major bleed, urgent surgery, or trauma.

Costs

The overall cost burden of AF on the U.S. healthcare system is $26 billion annually, with hospitalizations generating 52% of these costs and medications generating 23% of them (Limone, Baker, Kluger, & Coleman, 2013). The debate about the high cost of novel OACs continues, and one point made by the industry is that novel OACs do not require INR checks and therefore do not cost as much as is perceived by the public. When calculating related healthcare costs, dabigatran dosed at 150mg twice a day and at 110mg twice a day was shown to be more cost effective compared to the cost of warfarin combined with the costs of the requisite INR check visits (Limone et al., 2013). It is presently quite difficult to assess the cost effectiveness of novel OACs, first because they have not been available for a sufficient length of time to allow for that assessment, and second because we are on the brink of discovering new agents, and reversal agents, making these new or potential novel OACs impossible to include in the overall assessment.

Existing Guidelines

Clinicians rely heavily on guidelines for the prevention of thromboembolism in patients with AF.

Guidelines for the Management of Atrial Fibrillation: The Task Force for Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

According to the 2010 ESC guidelines for the management of AF, the focus is on prevention of thromboembolism, as well as elimination of symptoms and complications of AF. Patients who are diagnosed with paroxysmal AF should be treated similarly to patients with persistent AF with regard to their stroke risk (Camm et al., 2010). The $CHADS_2$ schema should be used initially as a rapid screen for assessing stroke risk, and if it produces a score of 2 or higher, then warfarin should be recommended (INR 2–3). INR is an internationally established biologic test for the effects of warfarin on clotting activity. In these guidelines, the emphasis on the prevention of strokes was evident by the addition of the CHA_2DS_2-VASc schema to capture a wider number of patients who will benefit from an oral OAC (Camm et al., 2010). Researchers reported that annual stroke risk was decreased by 67% when using warfarin according to the guidelines for primary and secondary prevention; there was also a 26% reduction of all-cause mortality (Camm et al., 2010). The final consensus was to recommend warfarin treatment for patients with one or more risk factors.

Aspirin was also discussed in light of stroke prevention, reporting that aspirin alone reduces stroke by 22% (Camm et al., 2010). The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study (Mant et al., 2007) showed that warfarin therapy, with target INR between 2 and 3, was superior to aspirin therapy by 52%, and revealed no difference in the occurrence of major hemorrhages between aspirin and warfarin groups. The ACTIVE W study (Healey et al., 2008) showed that OAC was superior to

both the combination of clopidogrel with aspirin and aspirin alone. The ACTIVE A study (Camm et al., 2010) demonstrated that the use of aspirin alone is inferior to that of aspirin plus clopidogrel therapy.

The ESC guidelines currently rely on the $CHADS_2$ schema for stroke prevention, with a score of 2 or more requiring chronic OAC with warfarin, with target INR between 2 and 3. It is recommended that patients with a $CHADS_2$ score of 0 to 1 use CHA_2DS_2-VASc schema scores, as well as weighing the additional risk factors for bleeding (Camm et al., 2010).

American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) Task Force on Practice Guidelines With "Focused Update" in 2011

The ACCF/AHA/HRS 2006 guidelines (Fuster et al., 2006) do not include recommendations based on the $CHADS_2$ schema, although it is mentioned in the text of the guidelines. According to the guidelines, patients with no risk factors should be on aspirin 81mg to 325mg. Patients with one moderate risk factor should be on aspirin 81mg to 325mg, or warfarin with an INR between 2 and 3. Moderate risk factors include age 75 years and older, hypertension, heart failure, impaired left ventricular systolic function with ejection fraction of 35% or less, and diabetes mellitus (Fuster et al., 2006). Patients with more than one moderate risk should also be anticoagulated with warfarin with INR between 2 and 3 (Fuster et al., 2006). The recommendations for warfarin are in place for patients at high risk, such as those with previous stroke, TIA, or systemic embolism.

These guidelines emphasize the existing controversy surrounding the treatment of patients with an intermediate stroke risk (3% to 5% per year), accentuating bleeding risks and patient preference (Fuster et al., 2006).

The ACC/AHA/HRS 2006 guidelines were updated in 2011 due to the emergence of new evidence discovered in the RE-LY trial (Connolly et al., 2009), a significant trial that changed the practice of providers. It focused on dabigatran etexilate and its use for AF (Wann et al., 2011). Results of the study were published in 2009, showing the noninferiority of dabigatran when compared with warfarin in the prevention of strokes. In fact, 150mg of dabigatran twice a day showed superiority in the reduction of annual stroke risk at 1.11%, when compared to warfarin, demonstrating a reduction of stroke risk annually to only 1.71%, (Wann et al., 2011). A dabigatran dose of 110mg twice a day was noninferior to warfarin, with dabigatran causing bleeds at the rate of 2.87% compared to warfarin at 3.57%, with INRs in the target range of 64.4% (Wann et al., 2011). Dabigatran 150mg twice a day was approved and recommended in the United States for patients with creatinine clearance of 30 or higher (Wann et al., 2011).

Canadian Cardiovascular Society (CCS) 2012

The CCS guidelines recommend using $CHADS_2$ for stroke risk and HAS-BLED for bleeding risk. They also recommend the use of dabigatran, rivaroxaban, or apixaban in preference to warfarin (Skanes et al., 2012). In further discussion of novel OACs compared to warfarin, the researchers observed that dabigatran and apixaban have greater efficacy than warfarin, and that rivaroxaban exhibits the same efficacy as warfarin in preventing strokes (Skanes et al., 2012). Patients with a $CHADS_2$ score equal to or

greater than 2 should be started on an OAC; intermediate-risk patients with a $CHADS_2$ score equal to 1 should receive an OAC, with aspirin being considered for some patients based on individual risk factors; and low-risk patients with a $CHADS_2$ score of 0 should be evaluated for additional risk factors, such as age 64 to 74 years, female gender, and vascular disease. Within this category, an OAC is recommended for patients with high risks, such as age greater than 65 years or the combination of female gender and vascular disease. Aspirin 75mg to 325mg is recommended for patients with lower risks, such as female gender or vascular disease, and antithrombotic therapy is recommended for patients with the lowest risk (Skanes et al., 2012).

National Institute of Health and Care Excellence (NICE) 2012 Update

The 2012 update of the NICE guidelines occurred after the approval of dabigatran twice-per-day dosing at both 150mg and 110mg. The U.S. FDA did not approve dabigatran 110mg twice a day, instead approving 75mg twice a day for patients with renal insufficiency; however, this dose is not included in the NICE guidelines, as it has not yet been studied in randomized clinical trials (Ahmad & Lip, 2012). In the United Kingdom and European countries, dabigatran 110mg twice a day was approved and is presently in use. The NICE guidelines indicate that dabigatran should not be used in people in the following categories: patients with severe renal impairment, as this drug is renally excreted; patients with acute bleeding or who are at risk for bleeding; patients with impaired hemostasis; patients with liver impairment; and patients using certain drugs, such as systemic ketoconazole, cyclosporine, itraconazole, and tacrolimus (Ahmad

& Lip, 2012). Another point made by these guidelines is that the $CHADS_2$ schema is not very sensitive to patients with a score of 0, and that the CHA_2DS_2-VASc schema should be used for these patients (Ahmad & Lip, 2012). The use of the HAS-BLED schema is emphasized and recommended. It is also noted that patients with a high HAS-BLED score experience a greater clinical benefit from an OAC, as their risk of stroke is higher than their bleeding risk (Ahmad & Lip, 2012). These guidelines do not address the management of major bleeding situations on dabigatran, the replacement of dabigatran with other OAC, or perioperative situations.

Antithrombotic Therapy and Prevention of Thrombosis, Ninth Edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

These guidelines recommend no therapy for patients with a $CHADS_2$ score of 0, or aspirin 75mg to 325mg a day, or a combination of aspirin and clopidogrel. For these patients it is recommended that other risk factors be assessed, such as bleeding risk, age 65 to 74 years, and female gender, which would impact the decision regarding the use of an OAC. For patients with a $CHADS_2$ score of 1, OAC is recommended, or an aspirin and clopidogrel combination for patients who choose not to take an OAC (Guyatt et al., 2012). For patients with a $CHADS_2$ score of 2, an OAC is recommended, or aspirin (75mg to 325mg/day), or a combination therapy of aspirin and clopidogrel. Dabigatran 150mg twice a day instead of warfarin is also recommended for patients who are in need of an OAC (Guyatt et al., 2012).

Summary

Clinicians in the United States rely on the various guidelines discussed above, and this presents a challenge, as there are differences among them. European and Canadian guidelines include CHA_2DS_2-VASc scores for further determination of a stroke risk. The U.S. guidelines do not use CHA_2DS_2-VASc scores and this is less advantageous for patients, as the CHA_2DS_2-VASc assesses more risk factors than $CHADS_2$ does. For example, a 70-year-old female patient with AF who has a stroke risk of 0 according to the $CHADS_2$ schema will have a stroke risk of 2 according to assessment by the CHA_2DS_2-VASc schema (which scores for age and female gender), placing her in the category of a 2.2% stroke risk per year and calling for the initiation of at least aspirin (Lip, Nieuwlaat, Pisters, Lane, & Crijns, 2010).

As the guidelines evolve, the CHA_2DS_2-VASc schema scoring system will be implemented for use in the United States as it has been in Europe and Canada since 2011–2012. Our understanding of this disease process affords us the insight to treat AF more aggressively to prevent devastating strokes. The controversy among clinicians with regard to treatment with an OAC is ongoing, because there is no present consensus among the guidelines or among clinicians.

Frailty

Frailty has been defined as the loss of reserves, to include physical, cognitive, and energetic. Another definition is the presence of three or more of the following symptoms: unintentional weight loss, feeling exhausted, weak grip strength, slow walking speed, and low physical activity (Rockwood et al., 2005). As people age, they experience age-related

changes in pharmacokinetics, such as drug absorption; slowing of liver metabolism; and reduction in creatinine clearance; and these may be amplified in frailty. Morley et al. (2013) described frailty as physical and psychological declines, which are parts of the "medical syndrome." There is currently no consensus regarding the definition of frailty within the medical community, which has led to various attempts to define this phenomenon; however, it is known that numerous body systems are involved in the condition. Frailty predicts disability, as well as both physical and cognitive declines (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004).

Frailty is a biologic syndrome characterized by the inability to withstand stressors; it also increases patient vulnerability to adverse outcomes. These characteristics arise from the aggregate deterioration of various biological systems of the patient. The declines manifest as decreases in strength, mobility, balance, body mass, and overall activity levels. The result is a disturbance of homeostasis, which renders affected individuals unable to react appropriately to stressors. In the presence of an OAC, these individuals are also more likely to develop hemorrhage that will typically be accompanied by further complications (Fried et al., 2001). The ICD-9 codes (International Classification of Diseases, 9th edition; Buck, 2012) used within this study include a variety of conditions related to these aging declines, and the presence of at least one of these declines is considered as the presence of frailty.

Providers are faced with treating older frail patients—already at risk due to the decline in their health—with an OAC for AF. In a study of 228 adults age 76 years and older (mean age = 81 years) with AF and frailty, 30% of the participants died during the study period (Johnson, Lim, & Workman, 2005). In the same study, only 26% of the

participants were treated with warfarin for AF, and they exhibited a 10% annual rate of major hemorrhage. In a study by Shivkumar, Jafri, and Gheorghiade (1996), a separate analysis of participants 75 years and older showed a hemorrhage rate of 4.2%. Another study with participants age 75 years and older discovered that hemorrhage rates were 9.8% with therapeutic INR (Johnson et al., 2005). These facts illustrate that older people, who are more likely to be frail, are at higher risk for hemorrhage from using OACs. GI bleeds occur in patients age 75 years and older at the rate of 30.2%; the stroke risk for those same patients is 8%. The hemorrhage risk is greater than 3.9% in frail individuals (Johnson et al., 2005).

Our society views aging somewhat negatively, inspiring older individuals to strive to remain healthy, and age stigma may actually contribute to a more "fit" older population. These older adults are able to participate in clinical trials and take regular medications. Conversely, frail older adults are less likely to participate in clinical trials or take various medications and treatments (Herrera et al., 2010). Providers are faced with making decisions about recommending OACs to adults age 75 years and older. While this population is underrepresented in clinical trials, they must still be treated with OACs according to the guidelines; however, they are at risk for a hemorrhage as a result of increased frailty. Although the literature recommends treatment of adults age 75 years and older with an OAC because they are at the higher risk for stroke, in practice, OACs are underutilized. It has been clearly demonstrated that this causes embolic strokes, and in frail individuals this risk is up to 12.3% without an OAC (Tay, Lane, & Lip, 2009).

Clinicians are aware that frailty is a state of vulnerability which in and of itself contributes to poor outcomes in older adults, regardless of comorbid conditions.

Moreover, frailty is the strongest predictor of underutilization of OAC or antithrombotic medications prescribed to older patients with AF upon discharge from the hospital. This was discerned from a prospective study of 220 patients admitted to an inpatient unit in one of the teaching hospitals in Australia (Perera, Bajorek, Matthews, & Hilmer, 2009). All of the patients were age 70 years or older and they were followed up for 6 months after their discharge. The resultant underutilization of warfarin was associated with a high risk of falls, history of bleeding, and impaired cognition. The picture of frail individuals is complex, and it is further compounded by increased mortality, functional limitations, and cognitive declines that may lead to the loss of personal autonomy and eventual institutionalization (Fumagalli et al., 2010).

Falls

Falls are common among older adults, with an incidence of 33% in those age 65 years and older and 50% in those age 80 years and older, causing most of the common injuries among older trauma patients and a mortality rate of 6% (Pieracci, Eachempati, Shou, Hydo, & Barie, 2007). In a retrospective study of 47,717 patients age 65 years and older who were hospitalized as a result of a fall that produced traumatic injury, intracranial hemorrhages were linked with falls in 2,517 patients (5.1%); the mortality rate from these fall-related hemorrhages was 15.5% (n = 394; Pieracci et al., 2007).

This problem is multifactorial and requires a systematic approach by providers. Falls may be triggered by drug interactions, anemia, and dehydration. Physical therapy consisting of strength and balance exercises will help in the prevention of falls (Morley, 2008). Depression is another reason for weight loss, frailty and, subsequently, falls. For

older patients taking warfarin who experience falls, usually 1 in 10 of those falls will cause a major injury, such as a fracture, and those patients are more likely to develop an intracranial hemorrhage (Tay et al., 2009).

The subject of polypharmacy, or patients taking five or more prescriptions simultaneously, occurs in 20% to 40% of older people. This can predispose patients to a myriad of side effects that may in turn result in falls. If taking six or more medications simultaneously, 81% of patients experience falls (Le Couteur, Hilmer, Glasgow, Naganathan, & Cumming, 2004). The risk of falling increases by 71% when older adults take psychotropic medications. Benzodiazepines cause an increase in falls at a rate of 50% to 110%, frequently causing confusion in 11% to 30% of patients and delirium in 2% to 12% (Le Couteur et al., 2004). These falls are preventable; in fact, the withdrawal of psychotropic and other medications reduces falls. As older individuals age, they are less likely to be prescribed an OAC due to their age, increased risk of falls, and other comorbidities (Riva et al., 2011).

Older people on a long-term OAC, hospitalized after a fall, are at 50% increased risk of intracranial hemorrhage and 57% risk of mortality (Pieracci et al., 2007). These numbers are due to the fact that patients on a long-term OAC are older and have more comorbidity. Because elderly subjects have been excluded from clinical trials, we do not have sufficient information about fall-related injuries while patients are taking an OAC. Falls, and injuries resulting from falls, are not included in the guidelines, but in real practice falls play a very important role in making a decision about the initiation of OACs in older adults with AF. Indeed, current guidelines take age into consideration, but not falls, frailty, and dementia; consequently, the guidelines do not accurately reflect real-life

situations in which providers use common risk schemas in addition to considering falls, frailty, and dementia (Poli et al., 2011).

Patients age 85 and older are at greater risk of bleeding due to malignancies, renal failure, history of previous bleeding, and falling, which increase bleeding risk fivefold (Poli et al., 2011). AF itself maybe a source of falls and syncope due to associated bradyarrhythmias, which typically require the use of a pacemaker (Maurer & Bloomfield, 2002).

Jacobs, Billett, Freeman, Dinglas, and Jumaquio (2009) found that falls are prevalent in older adults, at a rate of 21% compared to the 32% that is reported in the literature, and that falls are the most frequently cited reason by providers for nonprescription of an OAC. The same study revealed that intracranial hemorrhage risk is smaller than ischemic stroke risk, at 2.8% and 13.7%, respectively, suggesting that these patients would benefit from the use of an OAC. Patients on an OAC who suffer from falls exhibit an overall mortality rate of 45%; it is unclear if this is attributable to the risk factors for falls, AF, or warfarin use, or a combination of these factors (Jacobs et al., 2009). Although warfarin use is clearly beneficial for those at risk for stroke, it remains unclear exactly who should be prescribed an OACs in light of the fact that the benefits of OACs outweigh the risks of falls (Garwood & Corbett, 2008).

Dementia

The health problem known as dementia is described as the impairment of memory combined with at least one or more cognitive declines (Bunch et al., 2010). Dementia primarily affects the aged population. Between 60% and 80% of patients suffering from

dementia are afflicted with Alzheimer's disease, the most common form of dementia, and another 10% to 20% of the dementia population is afflicted by vascular dementia (Bunch et al., 2010). AF has been associated with all forms of dementia, increasing mortality rates for these individuals as they age (Bunch et al., 2010). Older women make up the largest of the groups with cognitive impairment and AF, which is associated with dementia (Ott et al., 1997). Because age is the greatest risk factor for Alzheimer's disease as well as AF, the presence of both conditions is not surprising (Moschetti, Cummings, Sorvillo, & Kuo, 2012). The idea has been proposed that patients with AF are more likely to develop silent cerebral infarctions, causing the development of dementia (Kilander et al., 1998; Marengoni, Qiu, Winblad, & Fratiglioni, 2011). Another mechanism that may cause an increased prevalence of dementia in AF patients is cardiac output fluctuations, contributing to hypoperfusion of the brain (Forti et al., 2007). AF is associated with a 40% to 50% higher risk of dementia, independent of stroke (Dublin et al., 2011).

In addition to age, the underutilization of OACs may contribute to dementia, with AF possibly contributing to cognitive decline due to a previous cerebrovascular accident (CVA) or TIA (Jacobs et al., 2009). Older patients with a stroke are more likely to be female and have comorbid conditions and dementia (Dharmarajan, Varma, Akkaladevi, Lebelt, & Norkus, 2006; Saposnik et al., 2009). As reported in the ACTIVE W trial (Healey et al., 2008), patients treated with warfarin remained within the INR therapeutic level less than 65% of the time, which could predispose to microemboli that might manifest as cognitive impairment (Flaker et al., 2010). Also discussed was the fact that patients with subtherapeutic INR levels of warfarin are more likely to develop dementia, and these same patients are also more likely to develop vascular complications and

bleeding (Flaker et al., 2010).

Another form of dementia is post-CVA dementia. The presence of AF is driving patient risk for dementia to increase, as well as increasing the incidence of post-CVA dementia. Given the fact that providers are more likely not to prescribe OACs to older adults with dementia, those patients end up with an even higher risk for the occurrence of poststroke dementia (Kwok, Loke, Hale, Potter, & Myint, 2011). The role that OACs play in patients with dementia is unclear, as it has not been studied, and as a result it is difficult to discern which of these maladies occurs first, AF or dementia (Kwok et al., 2011). Because CVA affects cognition, and the symptoms of this type of injury may also be attributed to cognitive weakness associated with age, clinicians may find it difficult to distinguish between these two causative factors (DeCarli, 2013). Older patients with cognitive impairment were followed for a 10-year period; notably, 40% of them did develop dementia (Cacciatore et al., 2012).

In older populations, falls, frailty, and dementia are significant contributors to decision making with regard to OACs for patients with AF. These three conditions are among the most common geriatric syndromes. These are usually described as conditions that lack clear definition, presenting a constellation of symptoms rather than a single disease process (Inouye, Studenski, Tinetti, & Kuchel, 2007). These problems are more likely to affect older patients with more severe comorbid conditions, and this presents a significant dilemma for clinicians. Although the combination of these factors will contribute to the initiation of OACs, falls, frailty, and dementia are not mentioned in the guidelines. As the population in the United States ages and clinicians encounter these questions more often, we must look for more specific answers related to administering

OACs, and the related morbidity and mortality. If our understanding of these problems improves sufficiently, we will be better equipped to answer questions that are related to the initiation of OACs in patients experiencing falls, frailty, and/or dementia.

References

Ahmad, Y., & Lip, G. Y. (2012). Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: NICE guidance. *Heart, 98*(19), 1404–1406. doi:10.1136/heartjnl-2012-302101

Alberts, M. J., Bernstein, R. A., Naccarelli, G. V., & Garcia, D. A. (2012). Using dabigatran in patients with stroke: A practical guide for clinicians. *Stroke, 43*(1), 271–279. doi:10.1161/strokeaha.111.622498

Benjamin, E. J., Wolf, P. A., D'Agostino, R. B., Silbershatz, H., Kannel, W. B., & Levy, D. (1998). Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. *Circulation, 98*(10), 946–952.

Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. (1990). The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *New England Journal of Medicine, 323*(22), 1505–1511. doi:10.1056/nejm199011293232201

Buck, C. (2012). *ICD-9-CM for Hospitals, Volumes 1, 2 and 3 professional edition.* Chicago: American Medical Association Press.

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*(21), 2002–2012. doi:10.1056/NEJMsa1103053

Bunch, T. J., May, H. T., Bair, T. L., Weiss, J. P., Crandall, B. G., Osborn, J. S., . . . Day, J. D. (2013). Atrial fibrillation ablation patients have long-term stroke rates similar to patients without atrial fibrillation regardless of CHADS2 score. *Heart Rhythm, 10*(9), 1272–1277. doi:10.1016/j.hrthm.2013.07.002

Bunch, T. J., Weiss, J. P., Crandall, B. G., May, H. T., Bair, T. L., Osborn, J. S., . . . Day, J. D. (2010). Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm, 7*(4), 433–437. doi:10.1016/j.hrthm.2009.12.004

Cacciatore, F., Testa, G., Langellotto, A., Galizia, G., Della-Morte, D., Gargiulo, G., . . . Abete, P. (2012). Role of ventricular rate response on dementia in cognitively impaired elderly subjects with atrial fibrillation: A 10-year study. *Dementia and Geriatric Cognitive Disorders, 34*(3–4), 143–148.

Camm, A. J., Kirchhof, P., Lip, G. Y., Schotten, U., Savelieva, I., Ernst, S., . . . Zupan, I. (2010). Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace, 12*(10), 1360–1420. doi:10.1093/europace/euq350

Caplan, L. R. (2006). Antiplatelet therapy in stroke prevention: Present and future. *Cerebrovascular Disease Journal, 21*(Suppl. 1), 1–6. doi:10.1159/000090356

Carlsson, J., Miketic, S., Windeler, J., Cuneo, A., Haun, S., Micus, S., . . . Tebbe, U. (2003). Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: The Strategies of Treatment of Atrial Fibrillation (STAF) study. *Journal of the American College of Cardiology, 41*(10), 1690–1696.

Chinitz, J. S., Castellano, J. M., Kovacic, J. C., & Fuster, V. (2012). Atrial fibrillation, stroke, and quality of life. *Annals of the New York Academy of Sciences, 1254*, 140–150. doi:10.1111/j.1749-6632.2012.06494.x

Ciccone, A., Motto, C., Abraha, I., Cozzolino, F., & Santilli, I. (2014). Glycoprotein IIb-IIIa inhibitors for acute ischaemic stroke. *Cochrane Database Syst Rev, 3*, Cd005208. doi:10.1002/14651858.CD005208.pub3

Connolly, S. J., Crijns, H. J., Torp-Pedersen, C., van Eickels, M., Gaudin, C., Page, R. L., & Hohnloser, S. H. (2009). Analysis of stroke in ATHENA: A placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. *Circulation, 120*(13), 1174–1180. doi:10.1161/circulationaha.109.875252

Connolly, S. J., Ezekowitz, M. D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., . . . Wallentin, L. (2009). Dabigatran versus warfarin in patients with atrial fibrillation. *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 the American College of Cardiology, 18*(2), 349–355.

Corley, S. D., Epstein, A. E., DiMarco, J. P., Domanski, M. J., Geller, N., Greene, H. L., . . . Wyse, D. G. (2004). Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation, 109*(12), 1509–1513. doi:10.1161/01.cir.0000121736.16643.11

Crandall, M. A., Horne, B. D., Day, J. D., Anderson, J. L., Muhlestein, J. B., Crandall, B. G., . . . Bunch, T. J. (2009). Atrial fibrillation significantly increases total mortality and stroke risk beyond that conveyed by the CHADS2 risk factors. *Pacing and Clinical Electrophysiology, 32*(8), 981–986. doi:10.1111/j.1540-8159.2009.02427.x

Custodio das Dores, S. M., Booth, S. L., Martini, L. A., de Carvalho Gouvea, V. H., Padovani, C. R., de Abreu Maffei, F. H., . . . Rupp de Paiva, S. A. (2007). Relationship between diet and anticoagulant response to warfarin: A factor analysis. *European Journal of Nutrition, 46*(3), 147–154. doi:10.1007/s00394-007-0645-z

Davie, E. W. (1995). Biochemical and molecular aspects of the coagulation cascade.

Thrombosis and Haemostasis, 74(1), 1–6.

DeCarli, C. (2013). Clinically asymptomatic vascular brain injury: A potent cause of cognitive impairment among older individuals. *Journal of Alzheimers Disease, 33*(Suppl. 1), S417–S426. doi:10.3233/jad-2012-129004

DeVellis, R. F. (2011). *Scale development: Theory and applications*. Thousand Oaks, CA: Sage.

Dharmarajan, T. S., Varma, S., Akkaladevi, S., Lebelt, A. S., & Norkus, E. P. (2006). To anticoagulate or not to anticoagulate? A common dilemma for the provider: Physicians' opinion poll based on a case study of an older long-term care facility resident with dementia and atrial fibrillation. *Journal of the American Medical Directors Association, 7*(1), 23–28.

Diener, H. C., Connolly, S. J., Ezekowitz, M. D., Wallentin, L., Reilly, P. A., Yang, S., . . . Yusuf, S. (2010). Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: A subgroup analysis of the RE-LY trial. *Lancet Neurology, 9*(12), 1157–1163. doi:10.1016/s1474-4422(10)70274-x

Dublin, S., Anderson, M. L., Haneuse, S. J., Heckbert, S. R., Crane, P. K., Breitner, J. C., . . . Larson, E. B. (2011). Atrial fibrillation and risk of dementia: A prospective cohort study. *Journal of American Geriatrics Society, 59*(8), 1369–1375. doi:10.1111/j.1532-5415.2011.03508.x

Duke Clinical Research Institute. (2010). Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: Rationale and design of the ROCKET AF study. (2010). *American Heart Journal, 159*(3), 340–347. doi:10.1016/j.ahj.2009.11.025

Easton, J. D., Lopes, R. D., Bahit, M. C., Wojdyla, D. M., Granger, C. B., Wallentin, L., . . . Diener, H. C. (2012). Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: A subgroup analysis of the ARISTOTLE trial. *Lancet Neurology, 11*(6), 503–511. doi:10.1016/s1474-4422(12)70092-3

Eikelboom, J. W., Wallentin, L., Connolly, S. J., Ezekowitz, M., Healey, J. S., Oldgren, J., . . . Yusuf, S. (2011). Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation/clinical perspective. *Circulation, 123*(21), 2363–2372. doi:10.1161/circulationaha.110.004747

Flaker, G. C., Pogue, J., Yusuf, S., Pfeffer, M. A., Goldhaber, S. Z., Granger, C. B., . . . Connolly, S. J. (2010). Cognitive function and anticoagulation control in patients with atrial fibrillation. *Circulation: Cardiovascular Quality and Outcomes, 3*(3), 277–283. doi:10.1161/circoutcomes.109.884171

Fonarow, G. C., Reeves, M. J., Zhao, X., Olson, D. M., Smith, E. E., Saver, J. L., & Schwamm, L. H. (2010). Age-related differences in characteristics, performance measures, treatment trends, and outcomes in patients with ischemic stroke. *Circulation, 121*(7), 879–891. doi:10.1161/circulationaha.109.892497

Forti, P., Maioli, F., Pisacane, N., Rietti, E., Montesi, F., & Ravaglia, G. (2007). Atrial fibrillation and risk of dementia in non-demented elderly subjects with and without mild cognitive impairment (MCI). *Archives of Gerontology and Geriatrics, 44*(Suppl. 0), 155–165. doi:10.1016/j.archger.2007.01.023

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 59*(3), 255–263.

Fumagalli, S., Tarantini, F., Guarducci, L., Pozzi, C., Pepe, G., Boncinelli, L., . . . Marchionni, N. (2010). Atrial fibrillation is a possible marker of frailty in hospitalized patients: Results of the GIFA Study. *Aging Clinical & Experimental Research, 22*(2), 129–133. doi:10.3275/6592

Fuster, V., Rydén, L. E., Cannom, D. S., Crijns, H. J., Curtis, A. B., Ellenbogen, K. A., . . . Zamorano, J. L. (2006). ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation, 114*(7), e257–354.

Gage, B. F., Waterman, A. D., Shannon, W., Boechler, M., Rich, M. W., & Radford, M. J. (2001). Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation. *JAMA, 285*(22), 2864–2870.

Gandara, E., & Wells, P. S. (2010). Will there be a role for genotyping in warfarin therapy? *Current Opinion in Hematology, 17*(5), 439–443. doi:10.1097/MOH.0b013e32833c06b3

Garber, S. T., Sivakumar, W., & Schmidt, R. H. (2012). Neurosurgical complications of direct thrombin inhibitors—Catastrophic hemorrhage after mild traumatic brain injury in a patient receiving dabigatran. *Journal of Neurosurgery, 116*(5), 1093–1096. doi:10.3171/2012.2.JNS112132

Garcia, D., Regan, S., Crowther, M., Hughes, R. A., & Hylek, E. M. (2005). Warfarin maintenance dosing patterns in clinical practice: Implications for safer anticoagulation in the elderly population. *Chest, 127*(6), 2049–2056.

Garwood, C. L., & Corbett, T. L. (2008). Use of anticoagulation in elderly patients with

atrial fibrillation who are at risk for falls. *Annals of Pharmacotherapy*, *42*(4), 523–532. doi:10.1345/aph.1K498

Ghate, S. R., Biskupiak, J., Ye, X., Kwong, W. J., & Brixner, D. I. (2011). All-cause and bleeding-related health care costs in warfarin-treated patients with atrial fibrillation. *Journal of Managed Care Pharmacy*, *17*(9), 672–684.

Ghate, S. R., Biskupiak, J. E., Ye, X., Hagan, M., Kwong, W. J., Fox, E. S., & Brixner, D. I. (2011). Hemorrhagic and thrombotic events associated with generic substitution of warfarin in patients with atrial fibrillation: A retrospective analysis. *Annals of Pharmacotherapy, 45*(6), 701–712. doi:10.1345/aph.1P593

Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Borden, W. B., . . . Turner, M. B. (2013). Heart disease and stroke statistics—2013 update: A report from the American Heart Association. *Circulation, 127*(1), e6–e245. doi:10.1161/CIR.0b013e31828124ad

Gomes, T., Mamdani, M. M., Holbrook, A. M., Paterson, J. M., Hellings, C., & Juurlink, D. N. (2013). Rates of hemorrhage during warfarin therapy for atrial fibrillation. *Canadian Medical Association Journal, 185*(2), E121–E127. doi:10.1503/cmaj.121218

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

Guyatt, G. H., Akl, E. A., Crowther, M., Gutterman, D. D., Schuünemann, H. J., & the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. (2012). Executive summary. *Chest, 141*(2 Suppl.), 7S–47S. doi:10.1378/chest.1412S3

Hankey, G. J., Patel, M. R., Stevens, S. R., Becker, R. C., Breithardt, G., Carolei, A., . . . Hacke, W. (2012). Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: A subgroup analysis of ROCKET AF. *Lancet Neurology, 11*(4), 315–322. doi:10.1016/s1474-4422(12)70042-x

Harrell, F. E., Lee, K. L., & Mark, D. B. (1996). Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Statistics in Medicine, 15*(4), 361–387. doi:10.1002/(sici)1097-0258(19960229)15:4<361::aid-sim168>3.0.co;2-4

Hart, R. G., Pearce, L. A., & Aguilar, M. I. (2007). Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of Internal Medicine, 146*(12), 857–867.

Healey, J. S., Hart, R. G., Pogue, J., Pfeffer, M. A., Hohnloser, S. H., De Caterina, R., . . .

Connolly, S. J. (2008). Risks and benefits of oral anticoagulation compared with clopidogrel plus aspirin in patients with atrial fibrillation according to stroke risk: The atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE-W). *Stroke, 39*(5), 1482–1486. doi:10.1161/strokeaha.107.500199

Herrera, A. P., Snipes, S. A., King, D. W., Torres-Vigil, I., Goldberg, D. S., & Weinberg, A. D. (2010). Disparate inclusion of older adults in clinical trials: Priorities and opportunities for policy and practice change. *American Journal of Public Health, 100*(S1), S105–S112. doi:10.2105/ajph.2009.162982

Hobbs, F. D., Roalfe, A. K., Lip, G. Y., Fletcher, K., Fitzmaurice, D. A., & Mant, J. (2011). Performance of stroke risk scores in older people with atrial fibrillation not taking warfarin: Comparative cohort study from BAFTA trial. *BMJ, 342*, d3653. doi:10.1136/bmj.d3653

Hohnloser, S. H., Kuck, K. H., & Lilienthal, J. (2000). Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): A randomised trial. *Lancet, 356*(9244), 1789–1794.

Holloway, R. G., Ladwig, S., Robb, J., Kelly, A., Nielsen, E., & Quill, T. E. (2010). Palliative care consultations in hospitalized stroke patients. *Journal of Palliative Medicine, 13*(4), 407–412. doi:10.1089/jpm.2009.0278

Hynicka, L. M., Cahoon, W. D., Jr., & Bukaveckas, B. L. (2008). Genetic testing for warfarin therapy initiation. *Annals of Pharmacotherapy, 42*(9), 1298–1303.

Inouye, S. K., Studenski, S., Tinetti, M. E., & Kuchel, G. A. (2007). Geriatric syndromes: Clinical, research, and policy implications of a core geriatric concept. *Journal of the American Geriatrics Society, 55*(5), 780–791. doi:10.1111/j.1532-5415.2007.01156.x

Jacobs, L. G., Billett, H. H., Freeman, K., Dinglas, C., & Jumaquio, L. (2009). Anticoagulation for stroke prevention in elderly patients with atrial fibrillation, including those with falls and/or early-stage dementia: A single-center, retrospective, observational study. *American Journal of Geriatric Pharmacotherapy, 7*(3), 159–166. doi:10.1016/j.amjopharm.2009.06.002

Johnson, C. E., Lim, W. K., & Workman, B. S. (2005). People aged over 75 in atrial fibrillation on warfarin: The rate of major hemorrhage and stroke in more than 500 patient-years of follow-up. *Journal of the American Geriatrics Society, 53*(4), 655–659.

Kalus, J. S. (2010). Pharmacotherapeutic decision-making for patients with atrial fibrillation. *American Journal of Health-System Pharmacy, 67*(9), S17–S25. doi:10.2146/ajhp100149

Kilander, L., Andren, B., Nyman, H., Lind, L., Boberg, M., & Lithell, H. (1998). Atrial

fibrillation is an independent determinant of low cognitive function: a cross-sectional study in elderly men. *Stroke*, 29(9), 1816-1820.

Kistler, J. P., Singer, D. E., Millenson, M. M., Bauer, K. A., Gress, D. R., Barzegar, S., . . . Oertel, L. B. (1993). Effect of low-intensity warfarin anticoagulation on level of activity of the hemostatic system in patients with atrial fibrillation. BAATAF Investigators. *Stroke*, 24(9), 1360-1365. doi:10.1161/01.str.24.9.1360

Kwok, C. S., Loke, Y. K., Hale, R., Potter, J. F., & Myint, P. K. (2011). Atrial fibrillation and incidence of dementia: A systematic review and meta-analysis. *Neurology, 76*(10), 914–922. doi:10.1212/WNL.0b013e31820f2e38

Lane, D. A., Kamphuisen, P. W., Minini, P., Büller, H. R., & Lip, G. Y. (2011). Bleeding risk in patients with atrial fibrillation: The AMADEUS Study. *Chest, 140*(1), 146–155. doi:10.1378/chest.10-3270

Le Couteur, D. G., Hilmer, S. N., Glasgow, N., Naganathan, V., & Cumming, R. G. (2004). Prescribing in older people. *Australian Family Physician, 33*(10), 777.

Limone, B. L., Baker, W. L., Kluger, J., & Coleman, C. I. (2013). Novel anticoagulants for stroke prevention in atrial fibrillation: A systematic review of cost-effectiveness models. *PLoS One, 8*(4), e62183. doi:10.1371/journal.pone.0062183

Lip, G. Y. H., Nieuwlaat, R., Pisters, R., Lane, D. A., & Crijns, H. J. G. M. (2010). Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro heart survey on atrial fibrillation. *Chest, 137*(2), 263–272. doi:10.1378/chest.09-1584

Lip, G. Y. H., Tse, H. F., & Lane, D. A. (2012). Atrial fibrillation. *Lancet, 379*(9816), 648–661. doi:10.1016/s0140-6736(11)61514-6

Mant, J., Hobbs, F. D., Fletcher, K., Roalfe, A., Fitzmaurice, D., Lip, G. Y., & Murray, E. (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.

Marengoni, A., Qiu, C., Winblad, B., & Fratiglioni, L. (2011). Atrial fibrillation, stroke and dementia in the very old: A population-based study. *Neurobiology of Aging, 32*(7), 1336–1337. doi:10.1016/j.neurobiolaging.2009.08.002

Maurer, M. S., & Bloomfield, D. M. (2002). Atrial fibrillation and falls in the elderly. *Clinics in Geriatric Medicine, 18*(2), 323–337.

Morley, J. E. (2008). Hot topics in geriatrics. *Journal of the American Medical Directors Association, 9*(9), 613–616. doi:10.1016/j.jamda.2008.09.002

Morley, J. E., Vellas, B., van Kan, G. A., Anker, S. D., Bauer, J. M., Bernabei, R., . . .

Walston, J. (2013). Frailty consensus: A call to action. *Journal of the American Medical Directors Association, 14*(6), 392–397. doi:10.1016/j.jamda.2013.03.022

Moschetti, K., Cummings, P. L., Sorvillo, F., & Kuo, T. (2012). Burden of Alzheimer's disease–Related mortality in the United States, 1999–2008. *Journal of the American Geriatrics Society, 60*(8), 1509–1514. doi:10.1111/j.1532-5415.2012.04056.x

Naccarelli, G. V., Varker, H., Lin, J., & Schulman, K. L. (2009). Increasing prevalence of atrial fibrillation and flutter in the United States. *American Journal of Cardiology, 104*(11), 1534–1539. doi:10.1016/j.amjcard.2009.07.022

Nutescu, E. A., Shapiro, N. L., Ibrahim, S., & West, P. (2006). Warfarin and its interactions with foods, herbs and other dietary supplements. *Expert Opinion on Drug Safety, 5*(3), 433–451. doi:10.1517/14740338.5.3.433

O'Donnell, M. J., Fang, J., D'Uva, C., Saposnik, G., Gould, L., McGrath, E., & Kapral, M. K. (2012). The PLAN score: A bedside prediction rule for death and severe disability following acute ischemic stroke. *Archives of Internal Medicine, 172*(20),1548–1556. doi:10.1001/archinternmed.2013.30

Ogilvie, I. M., Welner, S. A., Cowell, W., & Lip, G. Y. (2011). Ischaemic stroke and bleeding rates in 'real-world' atrial fibrillation patients. *Thrombosis and Haemostasis, 106*(1), 34–44. doi:10.1160/th10-10-0674

Ott, A., Breteler, M. M. B., de Bruyne, M. C., van Harskamp, F., Grobbee, D. E., & Hofman, A. (1997). Atrial fibrillation and dementia in a population-based study. *Stroke, 28*(2), 316–321. doi:10.1161/01.str.28.2.316

Padanilam, B. J., & Prystowsky, E. N. (2009). Atrial fibrillation: Goals of therapy and management strategies to achieve the goals. *Cardiology Clinics, 27*(1), 189–200. doi:10.1016/j.ccl.2008.09.006

Pamukcu, B., Lip, G. Y., & Lane, D. A. (2010). Simplifying stroke risk stratification in atrial fibrillation patients: Implications of the CHA2DS2-VASc risk stratification scores. *Age & Ageing, 39*(5), 533–535. doi:10.1093/ageing/afq059

Patel, M. R., Hellkamp, A. S., Lokhnygina, Y., Piccini, J. P., Zhang, Z., Mohanty, S., . . . Mahaffey, K. W. (2013). Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: Analysis from the ROCKET AF trial (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). *Journal of the American College of Cardiology, 61*(6), 651–658. doi:10.1016/j.jacc.2012.09.057

Perera, V., Bajorek, B. V., Matthews, S., & Hilmer, S. N. (2009). The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation. *Age & Ageing, 38*(2), 156–162.

Petersen, P., Boysen, G., Godtfredsen, J., 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, 1*(8631), 175–179.

Piccini, J. P., Hammill, B. G., Sinner, M. F., Jensen, P. N., Hernandez, A. F., Heckbert, S. R., . . . Curtis, L. H. (2012). Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993–2007. *Circulation: Cardiovascular Quality and Outcomes, 5*(1), 85–93. doi:10.1161/circoutcomes.111.962688

Piccini, J. P., & Singer, D. E. (2012). Putting risk prediction in atrial fibrillation into perspective. *European Heart Journal, 33*(12):1431–1433. doi.10.1093/eurheartj/ehs031

Pieracci, F. M., Eachempati, S. R., Shou, J., Hydo, L. J., & Barie, P. S. (2007). Use of long-term anticoagulation is associated with traumatic intracranial hemorrhage and subsequent mortality in elderly patients hospitalized after falls: Analysis of the New York State Administrative Database. *Journal of Trauma and Acute Care Surgery, 63*(3), 519–524. doi:10.1097/TA.0b013e31812e519b

Pisters, R., Lane, D. A., Nieuwlaat, R., de Vos, C. B., Crijns, H. J., & Lip, G. Y. (2010). A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. *Chest, 138*(5), 1093–1100. doi:10.1378/chest.10-0134

Poli, D., Antonucci, E., Grifoni, E., Abbate, R., Gensini, G. F., & Prisco, D. (2009). Bleeding risk during oral anticoagulation in atrial fibrillation patients older than 80 years. *Journal of the American College of Cardiology, 54*(11), 999–1002. doi:10.1016/j.jacc.2009.05.046

Poli, D., Antonucci, E., Testa, S., Tosetto, A., Ageno, W., & Palareti, G. (2011). Bleeding risk in very old patients on vitamin K antagonist treatment: Results of a prospective collaborative study on elderly patients followed by Italian Centres for Anticoagulation. *Circulation, 124*(7), 824–829. doi:10.1161/circulationaha.110.007864

Riva, N., Smith, D. E. H., & Lane, D. A. (2011). Advancing age and bleeding risk are the strongest barriers to anticoagulant prescription in atrial fibrillation. *Age & Ageing, 40*(6), 653–655. doi:10.1093/ageing/afr128

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *Canadian Medical Association Journal, 173*(5), 489–495. doi:10.1503/cmaj.050051

Roth, G. J., & Majerus, P. W. (1975). The mechanism of the effect of aspirin on human platelets. I. Acetylation of a particulate fraction protein. *Journal of Clinical*

Investigation, *56*(3), 624–632. doi:10.1172/jci108132

Sanford, M., & Plosker, G. L. (2008). Dabigatran etexilate. *Drugs, 68*(12), 1699–1709.

Saposnik, G., Black, S. E., Hakim, A., Fang, J., Tu, J. V., & Kapral, M. K. (2009). Age disparities in stroke quality of care and delivery of health services. *Stroke, 40*(10), 3328–3335. doi:10.1161/strokeaha.109.558759

Shivkumar, K., Jafri, S. M., & Gheorghiade, M. (1996). Antithrombotic therapy in atrial fibrillation: A review of randomized trials with special reference to the Stroke Prevention in Atrial Fibrillation II (SPAF II) Trial. *Programs for Cardiovascular Disease*, *38*(4), 337–342.

Singla, D. L., & Morrill, G. B. (2005). Warfarin maintenance dosages in the very elderly. *American Journal of Health-System Pharmacy*, *62*(10), 1062–1066.

Skanes, A. C., Healey, J. S., Cairns, J. A., Dorian, P., Gillis, A. M., McMurtry, M. S., . . . Nattel, S. (2012). Focused 2012 update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for stroke prevention and rate/rhythm control. *Canadian Journal of Cardiology*, *28*(2), 125–136. doi:10.1016/j.cjca.2012.01.021

Smith, M. B., Christensen, N., Wang, S., Strohecker, J., Day, J. D., Weiss, J. P., . . . Bunch, T. J. (2010). Warfarin knowledge in patients with atrial fibrillation: Implications for safety, efficacy, and education strategies. *Cardiology*, *116*(1), 61–69. doi:10.1159/000314936

Stroke Prevention in Atrial Fibrillation Investigators. (1991). Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation, 84*(2), 527–539.

Tay, K. H., Lane, D. A., & Lip, G. Y. H. (2009). Challenges facing anticoagulation among the elderly and frail. *Age and Ageing, 38*(2), 140–142. doi:10.1093/ageing/afn295

Tsang, T. S., Petty, G. W., Barnes, M. E., O'Fallon, W. M., Bailey, K. R., Wiebers, D. O., . . . Gersh, B. J. (2003). The prevalence of atrial fibrillation in incident stroke cases and matched population controls in Rochester, Minnesota: Changes over three decades. *Journal of the American College of Cardiology*, *42*(1), 93–100.

Waktare, J. E. P. (2002). Atrial fibrillation. *Circulation*, *106*(1), 14–16. doi:10.1161/01.cir.0000022730.66617.d9

Whitbeck, M. G., Charnigo, R. J., Khairy, P., Ziada, K., Bailey, A. L., Zegarra, M. M., . . . Elayi, C. S. (2012). Increased mortality among patients taking digoxin-analysis from the AFFIRM study. *European Heart Journal, 34*(20), 1481–1488. doi.10.1093/eurheartj/ehs348

Wolf, P. A., Abbott, R. D., & Kannel, W. B. (1991). Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*, 22(8), 983-988.

CHAPTER 3

METHODS

Research Design

Using a retrospective, descriptive, longitudinal design, we investigated the difference in outcomes among patients using oral anticoagulants (OACs), antiplatelet agents (ATPLs), and patients who do not take oral anticoagulation or antiplatelet agents (No OAC/ATPL) for the prevention of thromboembolism due to atrial fibrillation (AF), exploring stroke and hemorrhage outcomes in patients with concomitant geriatric syndromes (falls, dementia, frailty). AF is a disorganized rhythm of the atria causing the creation of emboli.

The goal was to determine what impact previously diagnosed falls and/or frailty and/or dementia would have in patients who are prescribed oral anticoagulants versus antiplatelet agents versus those who are not prescribed either oral anticoagulants or antiplatelet agents. Given the recommendations in current guidelines, a randomized controlled trial was not feasible for this type of study for ethical reasons, so we chose a naturalistic observational approach. This retrospective study utilized baseline characteristics and risk factors using multivariate regression modeling while taking into consideration the confounding variables. Standardized methods of information collection

were used. The use of a survival analysis assisted in predicting overall hazards of the groups. The methods model described below was developed to guide the statistical analysis and hypothesized relationships among variables, as well as identification of the variables included in the analysis.

Methods Model

The model was tested sequentially, adding relevant factors at each step. The first step was to address the main question: What would happen if patients with AF and geriatric syndromes who are older than 65 years of age were to take oral antithrombotic therapy (see Figure 3.1)?

When assessing the relationship between treatment and oral anticoagulants or antiplatelet agents for AF, the main events or outcomes to consider are a stroke or a hemorrhage. Comprehensive assessments of outcomes allowed for accounting of all variables contributing to all-cause mortality rates in these patients.

The model was tested using data from electronic records, which were stored in an enterprise data warehouse (EDW) containing electronic information. Documentation of these outcomes and the use of OAC medications compiled for the period of January 1, 2010 to December 31, 2014, was used. All outcomes were binary, but some were right-censored. The use of survival analysis, or time-to event analysis, as well as logistic regression, helped to examine these data. At the time of each stroke or hemorrhage event, a definite result was recorded, but most patients did not experience the event and the data became censored at the time of last observation. The Kaplan-Meier method of estimating continuous-time survival function incorporates censoring to provide a valid statistical

analysis (Figure 3.1), treated as a simple predictive relationship. In the Kaplan-Meier approach, each event is represented by an interval which is one observed event time, and each interval ends before the beginning of the next, with separate cumulative probabilities by OAC or antiplatelet treatments (Singer & Willett, 2003). When examining this simple relationship, the main question was answered based on the occurrence or nonoccurrence of an event.

In reality, this relationship is more complex than is expressed in Figure 3.1 because of the presence of important covariates that also affect the outcomes (see Figure 3.2).

The question of what would happen if a patient were to take OACs can be answered more accurately by conditioning on these covariates (examining the OAC difference within levels of the covariates). Kaplan-Meier analysis can adjust properly for categorical covariates, but proper adjustment for continuous covariates requires a Cox regression analysis.

When assessing stroke outcomes, the first relationship requiring assessment is the association of the CHA_2DS_2-VASc risk schema with the stroke. The CHA_2DS_2-VASc was developed to evaluate the risk of a stroke in patients with AF. When assessing hemorrhage outcomes, the first relationship requiring assessment is the association of the HAS-BLED schema with hemorrhage. HAS-BLED is a tool developed to evaluate the risk of bleeding when treated with OAC therapy. Although it is possible to treat these covariates as categorical, the more general approach requires the flexibility of Cox regression.

Providers who follow guidelines and calculate both schemas should see a

reduction in the instance of cerebrovascular accident (stroke or TIA) and hemorrhage outcomes. In practice, however, the importance of both schemas, HAS-BLED and CHA_2DS_2-VASc, is well known and is routinely used prognostically to help determine whether to place patients on oral anticoagulants. This makes the relationship considerably complex, as shown in Figure 3.3.

When assessing geriatric syndromes (falls, dementia, and/or frailty), it is evident in both the literature and clinical practice that because they are considered when assessing the risk factors for determining the initiation of OAC, they do in fact act as predictors of this therapy, while they are not included in any stroke- or bleed-related schemas. Answering the main question demands taking all variables into consideration, as illustrated in the full model represented by the detailed schematic in Figure 3.4. This model also represents comparison of two groups of patients with and without the geriatric syndromes of dementia, and/or falls and/or frailty.

Setting

This study was conducted using records generated at the University of Utah Hospitals and Clinics, located in Salt Lake City. Specific hospital locations include Clinical Neurosciences Center, Health and Wellness Center, Huntsman Cancer Institute, John A. Moran Eye Center, the Pain Management Center, Riverton Hospital, Surgical Specialty Center, University Neuropsychiatric Institute, and University Orthopedic Center. Specific satellite locations include Centerville Health Center, Davis Vision Center, Greenwood Health Center, Madsen Health Center, Murray Dermatology Clinics, Park City Mountain Resort Urgent Care Ski Clinic, Parkway Health Center, Redstone

Health Center, Redwood Health Center, South Jordan Health Center, Stansbury Health Center, Sugar House Health Center, and Westridge Health Center.

Sample

Participants were chosen based on the following criteria: patients diagnosed with AF at age 65 or older. Participants with incomplete datasets were excluded, as were those with a history of stroke or a hemorrhage prior to time zero.

Variables

Inclusion Criteria Variables

All variables listed below were requested from the EDW if the dates of the diagnosis of atrial fibrillation were made between January 1, 2010 and December 31, 2014. Consistent with procedures developed by previous investigators to validate the target diagnosis, subjects were included in the sample only if they had two or more visits related to the AF diagnosis, assuring that they were treated on a long-term basis for this disease (Piccini et al., 2012).

Only patients with atrial fibrillation (ICD-9 code 427.31) were included in this sample. All patients in the sample were age 65 years and older. To determine the accuracy of the AF diagnosis in the final pool of subjects, 532 individual chart reviews were performed. This process was facilitated by using the WartHog program at the EDW. This program allows researchers to instantly locate specific phrases in the medical records, such as *atrial fibrillation*, eliminating records unrelated to the term searched and highlighting only the search terms used. Not only does WartHog allow for rapid

searching, it is also extremely accurate. Of a subsample of 532 charts retrieved based on the ICD-9 code, we were able to document the diagnosis of AF in all but 11. This represents 98% accuracy in locating AF diagnoses, which is higher than the average of 82.2% found in the literature for accuracy of ICD-9 diagnoses of AF (Thigpen et al., 2015).

Exclusion Criteria Variables

Only patients with nonvalvular AF were included in this study; consequently, patients with diagnoses of any prior valvular problems were excluded. The purpose for this decision was to capture oral anticoagulant use only for AF. Patients with a diagnosis of mural thrombus, pulmonary embolism, or deep vein thrombosis were excluded to ensure that the warfarin use was directly attributable to patients taking it for AF, and not for other problems (see Table 3.1).

Therapy Group Variables

Medications initiated following the identification of a diagnosis of AF were extracted to detect use of anticoagulant or antiplatelet agents commonly used to prevent thrombotic complications. Subjects were divided into one of three therapy groups: oral anticoagulation (warfarin, apixaban, rivaroxaban, dabigatran); antiplatelet agents (aspirin, clopidogrel, prasugrel, ticagrelor); and no oral anticoagulation or antiplatelet agents. If subjects had a record of both antiplatelet and oral anticoagulant therapy, they were assigned to the oral anticoagulant group. It is difficult to separate these therapies because of comorbidities in these older individuals, particularly coronary artery disease, for which

many patients take aspirin.

Geriatric Syndromes

Causal relationship chains may be explained by using confounding variables to help to elucidate certain conditions that produce certain explanations of descriptive causal effects (Shadish, 2002). The following geriatric syndromes were included in the study: falls, and/or dementia, and/or frailty (see Table 3.2).

Outcome Variables

CVA/TIA and hemorrhages were the two outcomes captured in this study, as shown in Table 3.3. Although TIA does not cause permanent brain damage, it is one of the comorbidities measured by the CHA_2DS_2-VAS_c scoring system, as it is typically considered to be a warning for stroke. It evaluates as an equivalent of a stroke, so both stroke and TIA were included as positive indicators of a cerebrovascular event, the outcome in this study (Lip, Tse, & Lane, 2012).

In this study, patients were followed from the start of their medication until they either dropped from observation or experienced an event. These types of data are right-censored (Singer & Willett, 2003).

CHA_2DS_2-VASc Covariate Variables

Covariates are variables that we control for in a study to eliminate the effects of one variable on another (Trochim, 1999). This study used a calculated CHA_2DS_2-VASc risk score as a covariate for the cerebrovascular accident (CVA) outcomes to minimize

other risk factors for a CVA and maximize the predictive ability of the confounding covariates (see Table 3.4).

HAS-BLED Covariate Variables

Covariates for hemorrhage outcomes are derived from the HAS-BLED schema, which includes the most common risk factors for hemorrhages. All diagnoses derived from this schema were coded with the appropriate ICD-9 code and verified utilizing previously published literature (Casciano, Dotiwala, Martin, & Kwong, 2013; see Table 3.5).

Procedures

The electronic EDW at the University of Utah was utilized to create a dataset for use in this study. After institutional review board approval, the electronic records of eligible patients were used to create the dataset, beginning with January 1, 2010 and continuing through December 31, 2014.

All patients included in the dataset had a diagnosis of AF in their inpatient or outpatient records. Falls were included if a patient experienced one or more falls. Frailty was included if any of the diagnoses used to describe frailty were present. Dementia diagnosis was included if any diagnoses related to dementia were present.

Dataset Groundworks

The EDW was queried to retrieve records of patients with AF from 2010 to 2014 (N = 4,293). Medication histories for those patients were obtained from the EDW over the same period.

After the AF diagnosis, AF medication was classified as oral anticoagulation agent, antiplatelet agent, or no oral anticoagulation or antiplatelet agent. Numeric values of "2" for oral anticoagulants, "1" for antiplatelet agents, and "0" for no oral anticoagulation or antiplatelet agents were used in the data. Oral anticoagulants were present if the patient had any medication record of warfarin, rivaroxaban, apixaban, or dabigatran. Antiplatelet agents were present if patients had any medication record of aspirin, clopidogrel, prasugrel, or ticagrelor. It is possible that an individual was prescribed OAC and antiplatelet therapy concomitantly.

According to the CHA_2DS_2-VAS_c schema, diseases included were stroke, hypertension (HTN), aortic plaque (Aorticp), congestive heart failure (CHF), coronary artery disease (CAD), diabetes mellitus (DM), and peripheral vascular disease (PVD). Scores were computed using the CHA_2DS_2-VAS_c scoring system and ICD-9 codes. Each of these diseases, and each patient time to disease, was measured as the number of days from the date of diagnosis of AF to the first incidence of the disease.

According to the HAS-BLED schema, diseases included were hypertension (HTN), abnormal renal function, abnormal liver function, stroke, bleeding predisposition, labile INR, elderly (age 65 and older), and drug or alcohol use. Scores were computed using the HAS-BLED scoring system and ICD-9 codes. Each of these diseases, and each patient time to disease, was measured as the number of days from the date of diagnosis of

AF to the first incidence of the disease. Due to the lack of labile INR information in the dataset, we anticipated that value to be 0 for all patients, as described in the literature (Pisters et al., 2010).

A geriatric syndrome variable for the presence of dementia and/or falls and/or frailty was also created from this information. Disease incidence and time to disease allowed estimation of the effect of medication therapy on those who suffered from dementia and/or falls and/or frailty, using the statistical survival methods (Singer & Willett, 2003).

Data Analysis

When the dataset was received, exploratory data analyses were performed to determine distributions in age, gender, different medications, comorbidities, falls, dementia, frailty, strokes, and hemorrhages. Another exploratory procedure determined how many people had changes in medications and how long the follow up was available in the dataset. These procedures defined the study's sample.

Standard statistical techniques were used to find differences among groups in the demographic data (Singer & Willett, 2003). The focus of these analyses was on the magnitude of the coefficients and determining how great the differences or correlations were in pragmatic terms.

Data for this study involved following patients over time. Over this time interval, patients experienced death or an event of interest at a certain time. Patients were followed from the start of their medication until they died, dropped from observation, or experienced an event. These types of data are right-censored (Singer & Willett, 2003). A

Cox-proportional hazard regression model was used to estimate the risk-outcomes of different variables in a right-censored setting (Singer & Willett, 2003). This statistical model gave the advantage (nonparametric) of comparisons of risk between groups of interest, without having to specify the baseline risk of each group. Hazard ratios from this model were produced to estimate risks for variables such as CVAs and hemorrhages. The Kaplan-Meier method was used to estimate the discrete time of survival function (Singer & Willett, 2003). The Kaplan-Meier curves represented grouping of the variables of OAC group, antiplatelet agents group, and non-OAC group.

The following are examples of the application of a Cox regression equation used to establish the basic relationships in the model and covariates represented in Figures 3.1 and 3.2 (throughout, all explanatory covariates are binary 0/1 with *OAC* symbolizing whether OACs were taken or not; *f* (demographics) indicates standard regression control for categorical and continuous demographic and medical predictors):

- Y = f (demographics) + OAC
- Y = f (demographics) + OAC + HAS-BLED + CHA_2DS_2-VASc
- Y = f (demographics) + OAC * HAS-BLED

Two-way ANOVA was performed for AIM 3, with post hoc testing when the omnibus *F* was significant. An alpha level of .05 was set a priori for all analyses.

Protection of Human Subjects

This was an exempt study that used deidentified patient information. According to the University of Utah Institutional Review Board:

> Exempt studies are minimal risk and fit within a set of established exemption categories. Studies that qualify for exemption are only required to adhere to

certain federal regulations and must also follow state laws and University policies applicable to research. Studies that qualify for exemption must adhere to principles of sound research design and ethics. Participant rights and welfare must also be protected in a manner appropriate for research that poses minimal risk. Exemption determinations are made by the IRB and may not be made by the individual investigator. IRB review of exempt studies ensures that these standards and requirements are met prior to initiation of the research.

Table 3.1

Exclusion Variables

Variable	ICD-9 Codes
Closed heart valvotomy, unspecified valve	35
Closed heart valvotomy, aortic valve	35.01
Closed heart valvotomy, mitral valve	35.02
Closed heart valvotomy, pulmonary valve	35.03
Closed heart valvotomy, tricuspid valve	35.04
Open heart valvuloplasty of unspecified valve, without replacement	35.1
Open heart valvuloplasty of aortic valve, without replacement	35.11
Open heart valvuloplasty of mitral valve, without replacement	35.12
Open heart valvuloplasty of pulmonary valve, without replacement	35.13
Open heart valvuloplasty of tricuspid valve, without replacement	35.14
Replacement of unspecified heart valve	35.2
Replacement of aortic valve with tissue graft	35.21
Other replacement of aortic valve	35.22
Replacement of mitral valve with tissue graft	35.23
Other replacement of mitral valve	35.24
Replacement of pulmonary valve with tissue graft	35.25
Other replacement of pulmonary valve	35.26
Replacement of tricuspid valve with tissue graft	35.27
Other replacement of tricuspid valve	35.28
Mitral stenosis	394
Mitral stenosis with insufficiency	394.2
Mitral valve stenosis and aortic valve stenosis	396
Mitral valve stenosis and aortic valve insufficiency	396.1
Multiple involvement of mitral and aortic valves	396.8
Organ or tissue replaced by transplant	V42
Heart valve	V42.2
Organ or tissue replaced by other means	V43
Heart valve	V43.3
Operations of structures adjacent to heart valves	35.3
Operations on papillary muscle	35.31
Operations on chordae tendinaea	35.32
Annuloplasty	35.33
Infundibulectomy	35.34
Operations on trabeculae cordis	35.35
Operations on other structures adjacent to valves of heart	35.39
Pulmonary embolism	415.12, 449, 513.0, 415.12-septic, 415.11-iatrogenic, 673.80, 673.82, 673.84-obstetrical, V12.55-healed/old, 415.19-other or not elsewhere classified, 416.2-chronic
Deep venous thrombosis	453.40-acute, 671.5, 453.41-acute, 453.42-acute, 453.50-chronic, 453.51-chronic, 453.52-chronic, V12.51-history of
Mural thrombus	429.79

Table 3.2

Geriatric Syndromes

Variable	ICD-9 Codes
Dementia	Dementia in other conditions (Alzheimer's, Lewy bodies, Parkinsonism, epilepsy, frontal, multiple sclerosis, and so forth) 294.10–294.20, 293
	Uncomplicated, 294.8
	Use the following underlying conditions followed by one of the dementia codes listed above:
	Alzheimer's 331.0
	Senile degeneration of brain 331.2
	Dementia with Lewy bodies/Parkinsonism 331.82
	Dementia unspecified 294.10-294.21
	Presenile 290.10–290.13, 290.39
	Senile uncomplicated 290.0
	Senile dementia w/Delusional features 290.20
	Senile dementia w/Depressive features 290.21
	Senile dementia w/Delirium or confusion 290.3
Falls	Fall on or from sidewalk curb E880.1
	Fall on or from stairs or steps E880.9
	Fall from wheelchair E884.3
	Fall from bed E884.4
	Fall on the same level from slipping, tripping, or stumbling E885.9
	Other and unspecified fall E888.0-E888.9
	History of falling V15.88
Frailty	Senility without mention of psychosis (frailty) 797
	Cachexia 799.4

Table 3.3

Outcomes Variables

Variable	ICD-9 Codes
Cerebrovascular Accident/Transient Ischemic Attack	Ischemic, stroke 434.91
	Embolic, stroke 434.11
	Thrombotic, stroke 434.01
	Impending 435.9
	Postoperative 997.02
	Personal history without deficits V12.54
	Late effects 438.0–438.9
	Personal history of TIA V12.54
	Unspecified transient cerebral ischemia 435.9
	Hemorrhage not otherwise specified 459.0
Hemorrhage	Postoperative 998.11
	Brain hemorrhage iatrogenic/postoperative 997.02
	Subarachnoid hemorrhage 430
	Intracerebral hemorrhage 431
	Nontraumatic extradural hemorrhage 432.0
	Subdural hemorrhage 432.1
	Unspecified Intracranial hemorrhage 432.9
	Esophageal hemorrhage 530.82
	Gastric ulcer with hemorrhage 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61
	Duodenal ulcer with hemorrhage 532.00, 532.01, 532.20, 532.21, 532.40, 532.41, 532.60, 532.61
	Peptic ulcer with hemorrhage 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.60, 533.61
	Gastrojejunal ulcer with hemorrhage 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.60, 534.61
	Gastritis and duodenitis with hemorrhage 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71
	Diverticulosis small intestine with hemorrhage 562.02
	Diverticulitis small intestine with hemorrhage 562.03
	Diverticulosis colon with hemorrhage 562.12
	Diverticulitis colon with hemorrhage 562.13
	Hemorrhage of rectum and anus 569.3
	Hematemesis 578.0
	Melena/blood in stool 578.1
	Hemorrhage of gastrointestinal tract unspecified 578.9
	Hemoptysis unspecified 786.30
	Cough with hemorrhage 786.39
	Traumatic brain hemorrhage 852.00-853.19
	Traumatic hemothorax 860.2-860.5

Table 3.4

Covariate Variables, CHA_2DS_2-VASc

Variable	ICD-9 Codes
Cerebrovascular Accident/Transient Ischemic Attack	Ischemic, stroke 434.91
	Embolic, stroke 434.11
	Thrombotic, stroke 434.01
	Impending 435.9
	Postoperative 997.02
	Personal history without deficits V12.54
	Late effects 438.0 – 438.9
	Personal history of transient ischemic attack V12.54
	Unspecified transient cerebral ischemia 435.9
Diabetes Mellitus (DM)	DM without mention of complication 250.00-250.03
	DM with renal manifestations 250.40-250.43
	DM with ophthalmic manifestations 250.50-250.53
	DM with neurological manifestations 250.60-250.63
	DM with peripheral circulatory disorders 250.70-250.73
	DM with other specified manifestations 250.80-250.83
	DM with unspecified complication 250.90-250.93
	Secondary DM without mention of complication 249.00-249.01
	Secondary DM with renal manifestations 249.40-249.41
	Secondary DM with ophthalmic manifestations 249.50-249.51
	Secondary DM with neurological manifestations 249.60-249.61
	Secondary DM with peripheral circulatory disorders 249.70-249.71
	Secondary DM with other specified manifestations 249.80-249.81
	Secondary DM with unspecified complication 249.90-249.91
Congestive Heart Failure	Congestive heart failure, unspecified 428.0
	Systolic heart failure 428.20-428.23
	Diastolic heart failure 428.30-428.33
	Combined systolic and diastolic heart failure 428.40-428.43
	Rheumatic heart failure (congestive) 398.91
Coronary Artery Disease	Coronary atherosclerosis 414.00-414.07
	Chronic total occlusion of coronary artery 414.2
	Coronary atherosclerosis due to lipid-rich plaque 414.3
	Coronary atherosclerosis due to calcified coronary lesion 414.4
Peripheral Vascular Disease (PVD)	Peripheral vascular disease unspecified 443.9
	PVD in other disease (DM) 443.81
	Atherosclerosis of extremities 440.20-440.4
	Atherosclerosis of other specified arteries 440.8
	Generalized & unspecified atherosclerosis 440.9
	Raynaud's syndrome 443.0
	Occlusion/stenosis precerebral arteries 433.00-433.91
	Atherosclerosis of renal artery 440.1
	Aneurysm–peripheral arteries 442.0-442.9
	Dissection–peripheral arteries 443.21-443.29
Aortic Plaque	Atherosclerosis of aorta 440.0

Table 3.5

Covariate Variables, HAS-BLED

Variable	ICD-9 Codes
Cerebrovascular Accident/Transient Ischemic Attack (TIA)	Ischemic, stroke 434.91 Embolic, stroke 434.11 Thrombotic, stroke 434.01 Impending 435.9 Postoperative 997.02 Personal history without deficits V12.54 Late effects 438.0–438.9 Personal history of TIA V12.54 Unspecified transient cerebral ischemia 435.9
Hypertension	Essential hypertension 401.0–401.9 Hypertensive heart disease 402.00–402.91 Hypertensive chronic kidney disease 403.00–403.91 Hypertensive heart and chronic kidney disease 404.00–404.93 Secondary hypertension 405.01–405.99 Hypertensive cerebrovascular disease 437.2 Intracranial hypertension benign 348.2 Postoperative Hypertension 997.91
Alcohol Use	Alcohol dependence 303.90, 303,91, 303.92, 303.93 Alcohol abuse 291.0-291.5, 291.8, 291.81, 291.82, 291.89, 291.9, 303.00–303.03, 305.00, 305.01, 305.02, 305.03, 760.71, 980.0
Abnormal Renal Function	794.4, acute renal failure 584.5–584.9, unspecified renal failure 586, chronic renal failure 585, 585.3–585.6, 585.9, 792.5, V42.0, V45.1, V45.11, V45.12, V56.0, V56.1, V56.2, V56.31, V56.32, V56.8
Abnormal Liver Function	794.8, cirrhosis of the liver without mention of alcohol 571.5, liver abscess and sequela of chronic liver disease 572.0-572.4, 572.8, ascites 789.5, 789.59, other and unspecified liver disorders 570, 571.6, 571.8, 579.9, 573.0, 573.4, 573.8, 573.9, 782.4, 789.1, 790.4, 790.5, 794.8, V42.7
Prior Bleed	Hemorrhage not otherwise specified 459.0 Postoperative 998.11 Brain hemorrhage iatrogenic/postoperative 997.02 Subarachnoid hemorrhage 430 Intracerebral hemorrhage 431 Nontraumatic extradural hemorrhage 432.0 Subdural hemorrhage 432.1 Unspecified Intracranial hemorrhage 432.9 Esophageal hemorrhage 530.82 Gastric ulcer with hemorrhage 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61 Duodenal ulcer with hemorrhage 532.00, 532.01, 532.20, 532.21, 532.40, 532.41, 532.60, 532.61 Peptic ulcer with hemorrhage 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.60, 533.61 Gastrojejunal ulcer with hemorrhage 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.60, 534.61 Gastritis and duodenitis with hemorrhage 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71

Table 3.5, Continued

Variable	ICD-9 Codes
Prior Bleed (Continued)	Diverticulosis small intestine with hemorrhage 562.02
	Diverticulitis small intestine with hemorrhage 562.03
	Diverticulosis colon with hemorrhage 562.12
	Diverticulitis colon with hemorrhage 562.13
	Hemorrhage of rectum and anus 569.3
	Hematemesis 578.0
	Melena/blood in stool 578.1
	Hemorrhage of gastrointestinal tract unspecified 578.9
	Hemoptysis unspecified 786.30
	Cough with hemorrhage 786.39
	Traumatic brain hemorrhage 852.00-853.19
	Traumatic hemothorax 860.2-860.5
Labile International Normalized Ratios	Not available in the data; anticipated to be 0 for all patients

Figure 3.1 Basic relationship represented in the model.
Note. AF = atrial fibrillation; OAC = oral anticoagulant; ATPL = antiplatelet.

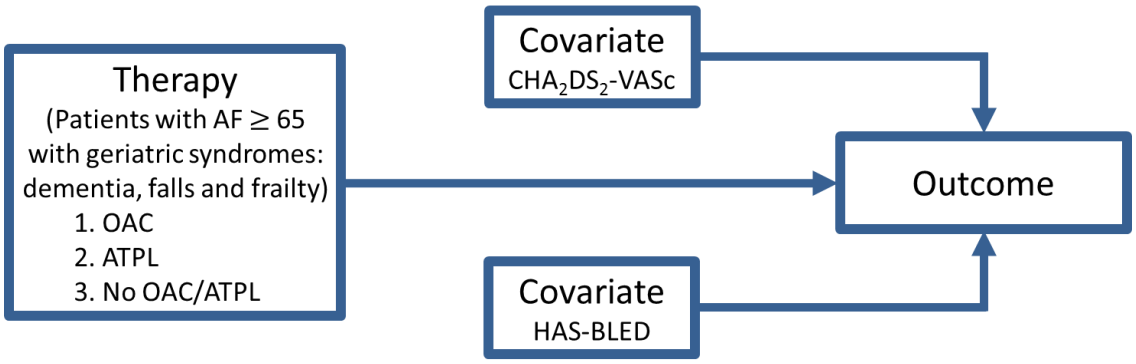

Figure 3.2 Covariates represented in the model.
Note. AF = atrial fibrillation; OAC = oral anticoagulant; ATPL = antiplatelet agent.

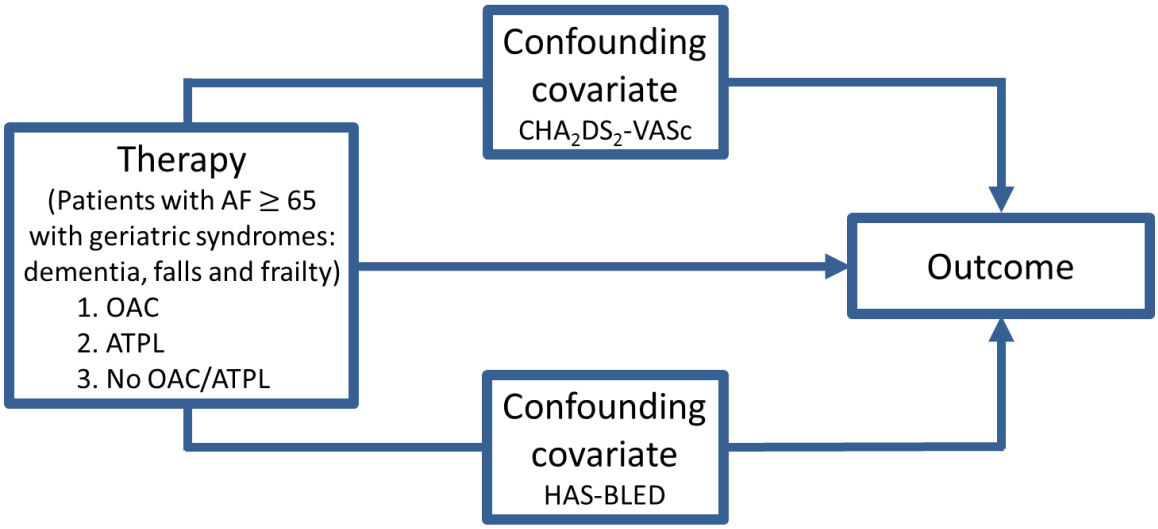

Figure 3.3 Confounding covariates.
Note. AF = atrial fibrillation; OAC = oral anticoagulant; ATPL = antiplatelet agent.

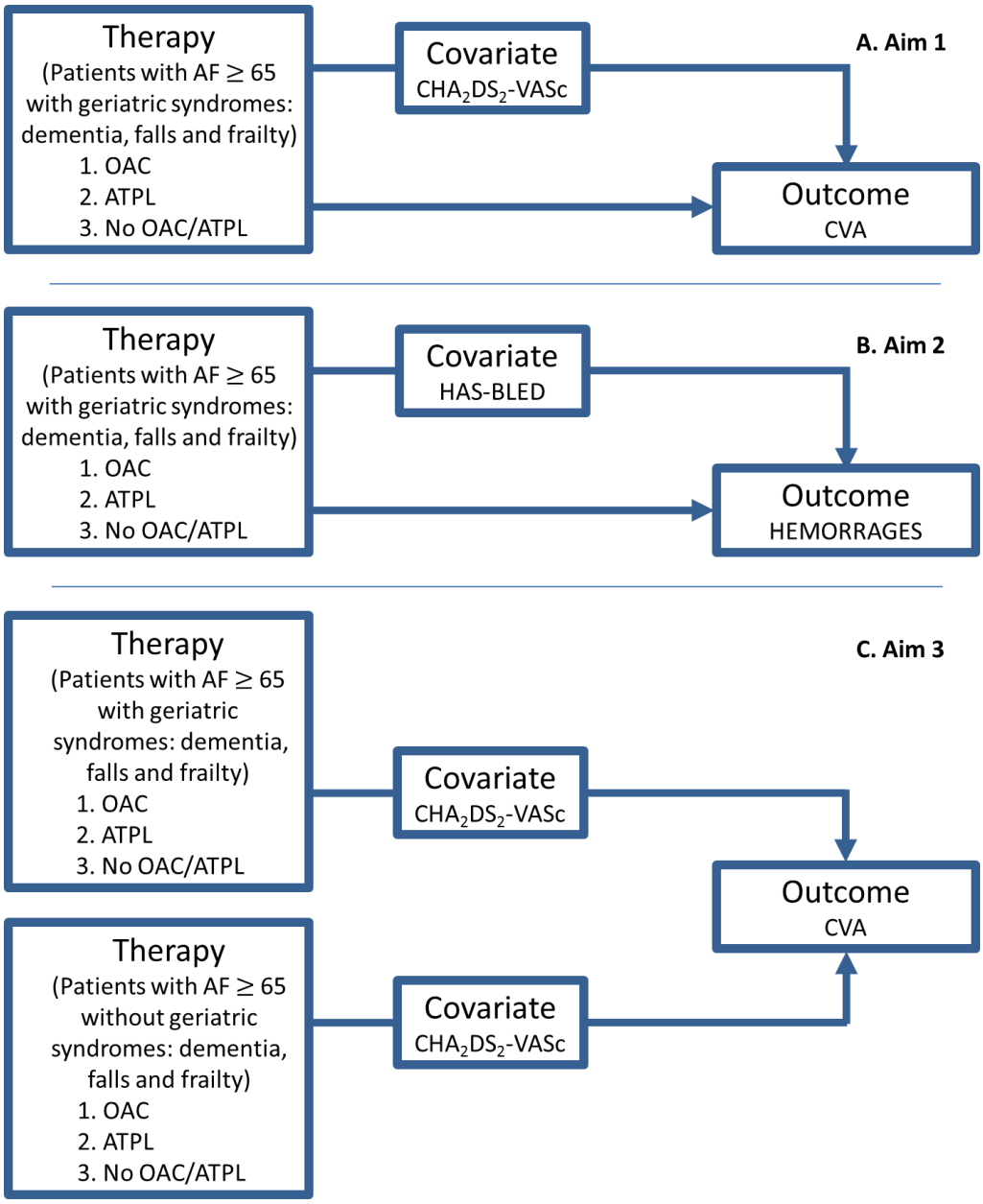

Figure 3.4 Methods model A, B, C. Key:
A. Aim 1: Difference in risk-adjusted stroke rates contingent on CHA_2DS_2-VASc in patients with geriatric syndromes (falls, dementia, and/or frailty) prescribed OACs, antiplatelet agents, and no antithrombotic therapy.
B. Aim 2: Difference in adjusted hemorrhage rates contingent on HAS-BLED scores in patients with geriatric syndromes (falls, dementia, and/or frailty) prescribed OACs, antiplatelet agents, and no OAC/antiplatelet agents.
C. Aim 3: Determine the main and interaction effects of type of thromboembolic therapy for older adults with chronic atrial fibrillation and presence of geriatric syndromes (falls, dementia, and/or frailty) contingent on CHA2DS2-VASc scores.
Note. AF = atrial fibrillation; OAC = oral anticoagulant; ATPL = antiplatelet agent; CVA = cerebrovascular accident.

References

Casciano, J. P., Dotiwala, Z. J., Martin, B. C., & Kwong, W. J. (2013). The costs of warfarin underuse and nonadherence in patients with atrial fibrillation: A commercial insurer perspective. *Journal of Managed Care Pharmacy, 19*(4), 302–316.

Lip, G. Y. H., Tse, H. F., & Lane, D. A. (2012). Atrial fibrillation. *Lancet, 379*(9816), 648–661. doi:10.1016/s0140-6736(11)61514-6

Piccini, J. P., Hammill, B. G., Sinner, M. F., Jensen, P. N., Hernandez, A. F., Heckbert, S. R., . . . Curtis, L. H. (2012). Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993–2007. *Circulation: Cardiovascular Quality and Outcomes, 5*(1), 85–93. doi:10.1161/circoutcomes.111.962688

Pisters, R., Lane, D. A., Nieuwlaat, R., de Vos, C. B., Crijns, H. J., & Lip, G. Y. (2010). A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. *Chest, 138*(5), 1093–1100. doi:10.1378/chest.10-0134

Shadish, W. R. (2002). *Experimental and quasi-experimental designs for generalized causal inference*. Boston: Houghton Mifflin.

Singer, J. D., & Willett, J. B. (2003). *Applied longitudinal data analysis: Modeling change and event occurrence*. Oxford: Oxford University Press.

Thigpen, J. L., Dillon, C., Forster, K. B., Henault, L., Quinn, E. K., Tripodis, Y., . . . Limdi, N. A. (2015). Validity of international classification of disease codes to identify ischemic stroke and intracranial hemorrhage among individuals with associated diagnosis of atrial fibrillation. *Circulation Cardiovascular Quality and Outcomes, 8*(1), 8-14. doi:10.1161/circoutcomes.113.000371

Trochim, W. M. K. (1999). *The research methods knowledge base: William M.K. Trochim*. Ithaca, NY: Cornell University.

CHAPTER 4

STROKE OUTCOMES IN ATRIAL FIBRILLATION PATIENTS WITH GERIATRIC SYNDROMES TREATED FOR THE PREVENTION OF THROMBOEMBOLISM

Abstract

Atrial fibrillation (AF) is the most commonly encountered arrhythmia, which presents a major risk for an ischemic stroke and transient ischemic attack (TIA). Oral anticoagulation and antiplatelet agents are used to prevent stroke by emboli generated in AF. Providers are faced with treating AF in older adults with geriatric syndromes, such as dementia, frailty, or falls, that may complicate therapy with anticoagulation drugs used to prevent emboli. The goal of this study was to describe differences in incidence of stroke over 1- to 3-year follow up depending upon the type of stroke prevention therapy: oral anticoagulants (OAC), antiplatelet agents (ATPL), or none of these (No OAC/ATPL). Patients age 65 years and older with a diagnosis of AF with concomitant geriatric syndromes (dementia, falls, and frailty) were included in this study, using retrospective data from an electronic medical record. The primary outcome was the presence of a stroke or TIA. Multivariable Cox hazard regression was utilized to determine the association between treatment with risk-adjusted stroke incidence; Kaplan-Meier survival

curves were used for survival analysis. The 758 older adults in the sample who had AF and one or more geriatric syndromes in the sample had an average age of 79.2 ± 7.3, and 357 (47.1%) were males. Even after stroke risk was controlled, patients prescribed oral anticoagulants were 75% to 82% less likely to develop stroke than patients on no oral anticoagulation/antiplatelet therapy ($p < .001$) in all 3 years of follow up. Patients prescribed antiplatelet agents were 70% to 74% less likely to develop a stroke or TIA when compared to patients on no oral anticoagulation/antiplatelet therapy ($p < .001$). In this study, we found that patients age 65 years and older and diagnosed with AF as well as geriatric syndromes (dementia and/or falls and/or frailty) benefit from oral anticoagulation and antiplatelet therapies in the first, second, and third years of therapy. Such therapies are crucial for these patients in preventing strokes.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting 2.3 million individuals in the United States (Olesen, Fauchier, Lane, Taillandier, & Lip, 2012). AF causes loss of well-organized atrial contracture, resulting in stagnation of the blood and thrombus formation (Padanilam & Prystowsky, 2009). AF is a major risk for a stroke (cerebrovascular accident [CVA] or transient ischemic attack [TIA]), accounting for 15% to 25% of all ischemic stroke. The majority of patients experiencing strokes related to AF are age 65 years and older (Fang et al., 2010; Hart, Pearce, & Aguilar, 2007). One meta-analysis of adjusted-dose warfarin studies indicated stroke reduction at 64% with this therapy (95% CI, 49% to 74%) in patients of an average age of 71 years (Hart et al., 2007).

Depending on individual preferences, comorbidities, and bleeding history, these patients may be prescribed antiplatelet therapy consisting of only aspirin or a combination of aspirin and clopidogrel. Hart et al. (2007) found that with aspirin and clopidogrel, the risk for a stroke is reduced by 40% (95% CI, 18% to 56%).

Providers rely on numerous guidelines developed in the United States and Europe when initiating oral anticoagulation or antiplatelet therapy for the prevention of thromboembolism in patients with AF (Ahmad & Lip, 2012; Camm et al., 2010; Fuster et al., 2006; Guyatt et al., 2012; Skanes et al., 2012; Wann et al., 2011).

Geriatric syndromes such as dementia, falls, and frailty represent multifactorial problems of overall health decline and are associated with poor outcomes in older individuals (Inouye, Studenski, Tinetti, & Kuchel, 2007). These problems are more likely to affect older patients with more severe comorbid conditions, and this presents a significant dilemma for clinicians when choosing thromboembolic prevention therapy, due to concerns about efficacy and safety issues. One reason for differences in the stroke prevention regimen followed by older adults is the presence of geriatric syndromes, which are highlighted by distinctive features commonly shared only by older adults. Although the combination of these factors will contribute to the decision to initiate oral anticoagulation, dementia, falls, and frailty are not mentioned within the guidelines. As older individuals are more likely to suffer any or all of these problems, providers are less likely to treat them with oral anticoagulation (Johnson, Lim, & Workman, 2005; Morley, 2008).

When initiating thromboembolic prevention therapy, clinicians use the CHA_2DS_2-VAS_c scoring system, which was developed to assess risk factors for a stroke. The

CHA_2DS_2-VAS_c schema assigns one point for each of the following: congestive heart failure, hypertension, diabetes mellitus, vascular disease (coronary artery disease, peripheral artery disease, or aortic plaque), age 65 to 74 years, and sex (female gender). The CHA_2DS_2-VAS_c, schema additionally assigns two points each for previous stroke/TIA and age $\geq$ 75 years. An aggregate score from 0 to 9 is derived and is used to predict annual stroke and TIA risk values, from 0.2% for a CHA_2DS_2-VAS_c score of 0, up to 15.2% for a CHA_2DS_2-VAS_c score of 9 (Lip, Frison, Halperin, & Lane, 2011). When this scoring system is utilized, patients are divided into the following categories: (a) low risk, which is associated with a CHA_2DS_2-VAS_c score of 0, which may or may not require aspirin; (b) intermediate risk, which is associated with a CHA_2DS_2-VAS_c score of 1, which recommends an antiplatelet agent or oral anticoagulant; or (c) high risk, which is associated with a CHA_2DS_2-VAS_c score of 2 or higher, which recommends an oral anticoagulant (Pamukcu, Lip, & Lane, 2010).

Dementia manifests as memory problems combined with decline in one or more cognitive functions, which may complicate implementation of oral anticoagulation. The most common form of dementia is Alzheimer's dementia, affecting between 60% and 80% of all individuals diagnosed with dementia, followed by vascular dementia, which affects 10% to 20% of older individuals (Bunch et al., 2010). Age is the greatest risk factor for both Alzheimer's disease and AF, so the coexistence of both conditions is not surprising (Moschetti, Cummings, Sorvillo, & Kuo, 2012). In addition to age, AF contributes to cognitive decline due to the presence of cerebrovascular accidents (CVAs), and may affect the ability of a patient to manage anticoagulation therapy (Jacobs, Billett, Freeman, Dinglas, & Jumaquio, 2009).

Frailty is a state of increased vulnerability and decline in abilities to react to stressors, with multiple systems weakening. These declines manifest as decreases in strength; mobility; balance; body mass; overall activity levels; increased risk of falls; and changes in serum protein concentrations, which may alter the pharmacokinetics of oral anticoagulation or antiplatelet therapy (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004; McIsaac, Bryson, & van Walraven, 2016). Frail patients are more likely to develop complications related to oral anticoagulation therapy. The stroke risk in frail patients age 75 years and older is 8% (Johnson et al., 2005).

Falls are more common among older individuals than their younger counterparts, with an incidence of 33% annually in people ages 65 to 80, increasing to 50% in people 80 and older. Falls are the most common cause of injuries among older trauma patients, resulting in a mortality rate of 6% (Pieracci, Eachempati, Shou, Hydo, & Barie, 2007). This problem is multifactorial and requires a systematic approach by providers. Falls may be triggered by drug interactions, frailty, dementia, and dehydration. Typically, 10% of older patients taking warfarin who fall will experience a major injury, such as a fracture (Tay, Lane, & Lip, 2009). The overall mortality rate for patients on oral anticoagulants who fall is 45%.

In this study we examined the records of subjects age 65 and over with a diagnosis of AF who had an indication of geriatric syndromes (dementia and/or frailty and/or falls). The goal of this study was to describe differences in incidence of stroke over 1- to 3-year follow up, depending on the type of stroke prevention therapy (oral anticoagulants [OAC], antiplatelet agents [ATPL], or none of these [No OAC/ATPL]).

Methods

Sampling and Setting

This was a database study of electronic medical records, which were obtained from the EDW at the University of Utah. This was a retrospective, descriptive, longitudinal study in which each patient was determined to have the diagnosis of AF using ICD-9 code 427.31, recorded by the healthcare providers in the patient's visit notes, electrocardiogram, or both during the period from January 1, 2010 to December 31, 2014. Subjects included in the study had the diagnosis of AF for varying periods of time. According to the literature and the advice of a professional coder, ICD-9 code 427.31 is generally used to capture patients with the diagnosis of AF (Piccini et al., 2012).

The dataset included outpatient and inpatient records. Consistent with procedures developed by previous investigators to validate the target diagnosis, subjects were included in the sample only if they had two or more visits related to the AF diagnosis, assuring that they were treated on a long-term basis for this disease (Piccini et al., 2012). Patients with a confirmed diagnosis of AF who were over age 65 were selected in the first tier of sampling (see Figure 4.1).

Exclusion Criteria

In an attempt to ensure that subjects with AF were not taking anticoagulant therapy for an indication other than stroke prevention, patients with diagnoses of mural thrombus, deep vein thrombosis, pulmonary embolism, and any mechanical heart valves were excluded from analysis. After the exclusion criteria were applied, 1,398 of the original 4,293 individuals with confirmed AF and minimum age of 65 years remained in

the sampling frame.

Sample Verification

To determine the accuracy of AF diagnosis in the final pool of subjects, 532 individual chart reviews were performed. This process was facilitated by using the WartHog program at the EDW at the University of Utah. This program allows researchers to instantly locate specific phrases in the medical records, such as *atrial fibrillation*, eliminating records unrelated to the term searched and highlighting only the search terms used. Not only does WartHog allow for rapid searching, it is also extremely accurate. Of a subsample of 532 charts retrieved based on ICD-9 codes, we were able to document the diagnosis of AF in all but 11. This represents 98% accuracy in locating AF diagnoses, which is higher than the average of 82.2% found in the literature for accuracy of ICD-9 diagnoses of AF (Thigpen et al., 2015).

Additional Inclusion Criteria

Additional inclusion criteria were applied to ensure that all patients in the sample had one of, or any combination of, the following geriatric syndromes: dementia, fall(s), and frailty. All such diagnoses occurred prior to the first event of a stroke or last observation. All codes for diagnoses were derived from the literature and personal communication with a professional coder and local and internationally recognized researchers in frailty (Garwood & Corbett, 2008; Hubbard et al., 2015; Jacobs et al., 2009; Jacobs et al., 2014; Morley et al., 2013; Piccini et al., 2012; Rockwood et al., 2005; Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). ICD-9 codes used to define

geriatric syndromes and experts consulted are identified in Table 4.1. Subjects were included only if one or more geriatric syndromes were identified between the date of study entry and the occurrence of a stroke, to ensure that the syndrome was a pre-existing condition relative to a stroke.

Procedures

Medication and disease files were summarized by patient identification number using aggregate/structure query language (SQL) commands in SPSS (Green & Salkind, 2010) and R (version 3.2.0; Team, 2013). The ICD-9 diagnoses were determined for all covariate variables included in the CHA_2DS_2-VAS_c schema (see Table 4.1).

Therapy Groups

Data on medications initiated following the diagnosis of AF were extracted to detect the use of anticoagulant or antiplatelet agents commonly used to prevent thrombotic complications. Subjects were divided into one of three therapy groups: oral anticoagulation group (warfarin, apixaban, rivaroxaban, dabigatran); antiplatelet agents group (aspirin, clopidogrel, prasugrel, ticagrelor); and no oral anticoagulation or antiplatelet agents. If subjects had a record of both antiplatelet and oral anticoagulant therapy, they were assigned to the oral anticoagulant group. Of the 758 subjects, 168 (22.2%) were prescribed both therapies concomitantly. It is difficult to separate these therapies because of comorbidities in these older individuals, particularly coronary artery disease, for which many patients take aspirin.

Outcome Variables

The outcome variables for stroke were derived from the dataset using ICD-9 codes (see Table 4.1). Although TIA does not cause permanent brain damage, it is one of the comorbidities measured by the CHA_2DS_2-VAS_c scoring system, as it is typically considered to be a warning for stroke,. TIA evaluates as an equivalent of a stroke, so both stroke and TIA were included as positive indicators of a cerebrovascular event, the outcome in this study (Lip, Tse, & Lane, 2012).

In this study patients were followed from the start of their medication until they dropped from observation or experienced an event. This type of data is right-censored (Singer & Willett, 2003).

Statistical Analysis

Omnibus tests were performed to detect general differences among means and proportions using ANOVA and chi-square tests (Kutner, Nachtsheim, Neter, & Li, 2005). Post hoc pairwise comparisons among categorical and continuous variables were made using proportion and Tukey tests. *P* values for the post hoc comparisons were adjusted using Bonferroni method, declaring significance at $\alpha = .05/3$. *P* values for the post hoc comparisons involving continuous variables were adjusted using Tukey method, with significance at $\alpha = .05$ (Kutner et al., 2005). Adjustments to post hoc *p* values were made in order to control the probability of encountering one or more Type-I error rates (Kutner et al., 2005). All other statistical tests and estimates were carried out at a significance level of $\alpha = .05$.

Multivariable Cox hazard regression was utilized to determine stroke outcomes by

medication groups. Three models were utilized to determine if significant differences existed in stroke outcomes by medication group. The first Cox model, 1-year follow up, observed individuals only over a 1-year period. If an individual's observation time was more than one period, then that person was considered as being observed for 1 full year, and as having no stroke event. Similar constructions were done for the 2-year and 3-year follow-up models.

In each Cox model, the censoring variable was 0 if a stroke did not occur within the observation period and 1 if it did. Individuals in the Cox models were censored for either of two circumstances: a subject's last event was not a stroke (another type of medical event, moved away, or died—lost to follow-up), or a subject reached the end of the observation period alive, not having experienced a stroke. A single covariate was used for the Cox model, a summed version of the CHA_2DS_2-VAS_c schema, which comprises the baseline risk factors for stroke. An overall hazard ratio is estimated from a dataset in which patients are censored only when they are lost to follow up. 1-, 2-, and 3-year hazard ratios are estimated from datasets in which patients can be censored if they reach 1, 2, or 3 years without experiencing any event, or are lost to follow up before those respective times.

Kaplan-Meier curves were used to help compare risk differences in medication groups visually, according to stroke outcomes. A Kaplan-Meier curve is a nonparametric estimate of a survival curve. The formula used to construct the curve does not include an adjustment for risk factors; to compare survival curves controlling for risks, a Cox model was used instead (Singer & Willett, 2003). Visual separation of curves between drug groups may imply that one drug group has a lower survival rate than another.

Results

Description of Groups

Overall, the average patient age was 79.2 years ±7.3, and 357 (47.1%) were males. The distribution of patients within each medication category was as follows: oral anticoagulation, *n* = 379 (50.0%); ATPL, *n* = 137 (18.1%); no OAC/ATPL, *n* = 242 (31.9%). In Table 4.2, we compare these three treatment groups on demographic and treatment variables. The three groups did not differ by age, but there were differences in the prevalence of geriatric syndromes between groups.

The OAC group had the highest prevalence of diagnosed falls, at 72%, with a statistically significant difference from the group receiving no antithrombotic prophylaxis. The rate of dementia diagnosis differed between the antiplatelet group (55.5%) and the oral anticoagulant group (41.7%), but neither differed from the group receiving no antithrombotic prophylaxis drugs. The rate of frailty diagnosis (13.2%) in the group receiving no antithrombotic drugs was more than twice that in any other group (13.2%). The proportion of females differed between two groups ($p < .001$), with the OAC group having the highest number of females (57/3%; Table 4.3). Although the mean CHA_2DS_2-VAS_c scores indicated high average risk in all groups, scores were lower in the no-drug group compared to the two groups receiving antithrombotic agents. The higher CHA_2DS_2-VAS_c scores of the ATPL and OAC groups represented more comorbidities and demographic characteristics that increase stroke risk (Table 4.3).

Group Differences on Outcomes

The mean time to stroke was less for the no-drug group than for either of the therapy groups (see Table 4.4). Time used was measured in days, using time to event. Two groups differed on cumulative incidence of stroke/TIA at 1, 2, and 3 years, with the rank order from highest to lowest rate of strokes being no antithrombotic drugs, antiplatelet, and oral anticoagulants ($p < .001$); however, these findings are not controlled for risk. The mean time until censored for these subjects was 855.03 ± 611.36 days. Kaplan-Meier survival estimates are presented in Figures 4.2 and 4.3, showing the survival curves for the time to stroke of the three treatment groups. Initially, during the first year (Figure 4.2), when risk of stroke was controlled with CHA_2DS_2-VAS_c score, the oral anticoagulation and antiplatelet agent groups were similar, with a possible slight advantage for antiplatelet agents, but at 6 months oral anticoagulation and antiplatelet therapy begin to diverge in favor of oral anticoagulants, a trend which continued through Year 3, but it is not certain that the differences were significant. However, the no-oral-anticoagulation/antiplatelet group had notably lower survival throughout the first year. The 3-year outcome demonstrated by Kaplan-Meier curves (Figure 4.3) presented possibly greater survival rates (no stroke) for patients prescribed oral anticoagulation than for patients prescribed antiplatelet agents, and reduced survival across the 3 years for patients who took no anticoagulants/antiplatelet agents.

Risk-Adjusted Hazard Ratios

Patients prescribed OACs were 82% less likely to develop stroke than patients on no OAC/ATPL therapy in the first year of therapy (HR 0.18 [0.10, 0.31]; $p < .001$).

Patients prescribed antiplatelet agents were 74% less likely to develop stroke when compared to patients on no OAC/ATPL therapy in the first year therapy (HR 0.26 [0.13, 0.51]; $p < .001$; see Table 4.5).

Patients prescribed OACs were 79% less likely to develop stroke than patients on no OAC/ATPL therapy in the second year of therapy (HR 0.21 [0.13, 0.34]; $p < 001$). Patients prescribed ATPLs were 70% less likely to develop stroke when compared to patients on no OAC/ATPL therapy in the second year of therapy (HR 0.30 [0.16, 0.54]; $p < .001$; Table 4.5).

Patients prescribed OACs were 75% less likely to develop stroke than patients on no OAC/ATPL therapy in the third year of therapy (HR 0.25 [0.16, 0.39]; $p < .001$). Patients prescribed ATPL agents were 71% less likely to develop stroke compared to patients on no OAC/ATPL therapy in the third year of therapy (HR 0.29 [0.16, 0.52]; $p < .001$).

Discussion

In this study, we found that patients with AF and geriatric syndromes (dementia and/or falls and/or frailty) who take oral anticoagulation and antiplatelet agents have lower risk-adjusted rates of stoke/TIA in the first, second, and third years of both therapies when compared to patients not prescribed oral anticoagulation or antiplatelet therapies, a finding that persists when results are controlled for stroke risk. The study included a sample of very old individuals with multiple comorbidities. It allowed surveillance of the interplay of risk, treatment, and outcomes of this older group in real life. The CHA_2DS_2-VAS_c scoring of this group was quite high, at an average of 4, which

coincides with multiple risk factors for a stroke in these patients and indicates that according to treatment guidelines, the majority of the patients were candidates for OAC therapy.

Our findings of OACs lowering the risk of stroke in the first, second, and third years of observation are similar to the findings of studies reported in the literature (Baker, Cios, Sander, & Coleman, 2009; Casciano, Dotiwala, Martin, & Kwong, 2013; Fang et al., 2010; Gumbinger et al., 2015; Piccini et al., 2012). It is thought provoking that both OAC and ATPL agents were similarly preventive of stroke, when prior studies indicated that OACs were more effective than ATPL agents (Lip et al., 2012). This might be explained by the fact that TIA was included with stroke as a positive cerebrovascular event. Interestingly, in spite of the considerable geriatric syndrome burden of the subjects in the current study, the results for OACs are the same as in studies conducted with younger populations having substantially fewer syndrome burdens (Lip, Nieuwlaat, Pisters, Lane, & Crijns, 2010; Lip et al., 2012; Mant et al., 2007). It has been recognized that OACs prevent strokes; however, it is challenging to keep these patients on OACs due to the increased burden of geriatric syndromes.

The no-OAC/ATPL therapy group was represented by 242 (31.9%) of the 758 patients examined in this study. Of the three groups, this group had the lowest CHA_2DS_2-VAS_c scores; however, those scores still indicated for the use of oral anticoagulation. This leaves the question of why these subjects were not on oral anticoagulation or antiplatelet therapy. Possibly they were taking OACs in the past but stopped before study entry, or were never started on this therapy due to dementia, falls, or frailty. This group did have the highest rate of frailty (13.2%) and a substantially higher rate of dementia

than the OAC group (51.2% vs 41.7%), but had the lowest rate of falls. In the clinical setting, it is not uncommon for patients to take oral anticoagulation at first and then switch to antiplatelet agents, or to have no antithrombotic therapy due to increased severity of dementia, falls, or other adverse events.

The majority of the OAC group (335, 88.4%) was prescribed warfarin. Warfarin presents limitations in use related to narrow therapeutic index, requirement for frequent international normalized ratio (INR) monitoring appointments, dietary changes, and dosing changes. All of these factors contribute to the challenges associated with the use of warfarin for the prevention of thromboembolism among aging populations (Ruff et al., 2014).

In the first 15 months of observation during one observational study of 1,049 older patients, the patients were adherent to taking oral anticoagulants, which is associated with lowering the risk of stroke or TIA; however, after 15 months the rate of nonadherence to oral anticoagulation therapy was high. Two thirds of patients were not taking oral anticoagulation at follow up (Gumbinger et al., 2015). In another observational study of 13,289 patients it was found that only 40% of patients who were prescribed oral anticoagulation were adherent to this therapy in the 3 years of observation (Casciano et al., 2013). Fang et al. (2010), in a different longitudinal study of 4,188 patients, found that more than one in four patients who were started on warfarin discontinued this therapy within the first year. Despite the fact that there is no reason to believe this population of older adults with geriatric syndromes has better adherence to warfarin therapy than reported in previous studies, the effectiveness of OAC therapy for prevention of stroke and TIA was clear in the current study.

In fact, patients with geriatric syndromes (dementia, falls, frailty) are more likely to discontinue oral anticoagulation therapy (Gumbinger et al., 2015). Moreover, patients with a diagnosis of dementia and residing in a nursing home are less likely to take prescribed OAC therapy. Fear of complications from bleeding, challenges in getting to the clinic for warfarin monitoring, and physicians stopping this therapy in patients who developed falls are common reasons for stopping this therapy (Gumbinger et al., 2015). In the current study, both therapies—oral anticoagulation and antiplatelet agents—were effective in prevention of stroke.

It was reported previously in a meta-analysis of quality of warfarin control that patients with AF prescribed warfarin spent less than the recommended time in the INR therapeutic range (55%, 95% CI 51%, 58%; Baker et al., 2009). When patients are out of therapeutic range, they are more likely to develop bleeding complications and thromboembolic complications, leading to discontinuation of the therapy (Baker et al., 2009; Costa, Ferreira, Valacio, & Vieira Moreira Mda, 2011; Costa, Lamego, Colosimo, Valacio, & Moreira Mda, 2012). Another longitudinal study showed that patients who spent less than the recommended time in the therapeutic range were more likely to stop warfarin therapy (Fang et al., 2010).

In the ACTIVE W trial (Connolly et al., 2006), it was determined that patients taking warfarin spent only 65% of the recommended time in the therapeutic range. Taking this one step further was an observational study showing that subtherapeutic INR levels contribute to more likely development of microemboli, while supratherapeutic INR levels lead to the development of microbleeds (Charidimou et al., 2015; Jacobs et al., 2014). Consequently, patients prescribed warfarin on a long-term basis are more likely to

be diagnosed with dementia, which is most likely to deteriorate if these patients are spending less time in the therapeutic range. As individuals 65 and older age, they become more prone to hemorrhages and strokes. Moreover, being out of therapeutic range may cause the development or progression of dementia in some of these individuals over time. In our sample, subjects in the oral anticoagulation group had the highest rate of dementia, at 44.7% of all dementia occurrences in the study.

Limitations

An observational, retrospective, longitudinal study of patients with AF can be used only to identify associations, and is unable to establish causality or to determine mechanisms. The study relied on medical record information and, as such, the ability of providers to make and document the disease states and outcomes. This was an observational study, and although baseline characteristics and one multifactorial risk indicator were utilized in the multivariable modeling, residual confounding may still be present.

While the academic health system had an integrated EMR for inpatient and outpatient services, we acknowledge that we were unable to detect events and diagnoses that occurred outside this healthcare system. We also acknowledge that cases of falls and frailty were generally underreported, which contributed to the reduced number of subjects with these conditions being included in the study. We used diagnosis codes from the literature and personal communications to define frailty, and some of these codes may have resulted in false positives. While we could confirm that a drug was ordered, there was no way to determine whether patients adhered to the medications.

Some patients in the study were lost to follow up; no further medical record documentation was available, although the subjects may still have been alive and treated elsewhere. These patients could potentially have contributed more stroke events had they remained in the study, which may have provided more statistical power in comparisons among the treatment groups.

Conclusions

In this study, oral anticoagulation and antiplatelet agents lowered the risk-adjusted incidence of stroke in patients with common geriatric syndromes during the first, second, and third years of observation. In real-world practice, some patients in this population are not prescribed oral anticoagulants due to comorbidities. These individuals may benefit from antiplatelet therapy, which is a potential alternative to oral anticoagulation therapy.

Presently, available guidelines do not reflect such intricate situations as treatment of patients with dementia and/or falls and/or frailty; this is something that needs to be addressed for both clinicians and patients. Also, no consensus currently exists in relation to the treatment of these populations. Further studies should address these issues in order to find solutions for the treatment of these complex patients.

Table 4.1

ICD-9 Codes Used to Define Stroke Outcomes Variables

Disease	ICD-9 Codes
Dementia	Dementia in other conditions (Alzheimer's, Lewy bodies, Parkinsonism, epilepsy, frontal, multiple sclerosis, and so forth) 294.10–294.20, 293
	Uncomplicated, 294.8
	Use the following underlying conditions followed by one of the dementia codes listed above:
	Alzheimer's 331.0
	Senile degeneration of brain 331.2
	Dementia with Lewy bodies/Parkinsonism 331.82
	Dementia unspecified 294.10–294.21
	Presenile 290.10–290.13, 290.39
	Senile uncomplicated 290.0
	Senile dementia with delusional features 290.20
	Senile dementia with depressive features 290.21
	Senile dementia with delirium or confusion 290.3
Falls	Fall on or from sidewalk curb E880.1
	Fall on or from stairs or steps E880.9
	Fall from wheelchair E884.3
	Fall from bed E884.4
	Fall on the same level from slipping, tripping, or stumbling E885.9
	Other and unspecified fall E888.0-E888.9
	History of falling-V15.88
Frailty	Senility without mention of psychosis (frailty) 797
	Cachexia 799.4 (personal communication, Kenneth Rockwood)
Cerebrovascular Accident/Transient Ischemic Attack (CVA/TIA)	Ischemic, stroke and TIA 434.91
	Embolic, stroke and TIA 434.11
	Thrombotic, stroke and TIA 434.01
	Impending 435.9
	Postoperative 997.02
	Personal history without deficits V12.54
	Late effects 438.0–438.9
	Personal history of TIA V12.54
	Unspecified transient cerebral ischemia 435.9
Hypertension (HTN)	Essential hypertension 401.0–401.9
	Hypertensive heart disease 402.00–402.91
	Hypertensive chronic kidney disease 403.00–403.91
	Hypertensive heart and chronic kidney disease 404.00–404.93
	Secondary hypertension 405.01–405.99
	Hypertensive cerebrovascular disease 437.2
	Intracranial hypertension benign 348.2
	Postoperative hypertension 997.91
Diabetes Mellitus (DM)	DM without mention of complication 250.00–250.03
	DM with renal manifestations 250.40–250.43
	DM with ophthalmic manifestations 250.50-250.53
	DM with neurological manifestations 250.60–250.63
	DM with peripheral circulatory disorders 250.70–250.73
	DM with other specified manifestations 250.80–250.83

Table 4.1, Continued

Disease	ICD-9 Codes
Diabetes Mellitus (DM), Continued	DM with unspecified complication 250.90–-250.93
	Secondary DM without mention of complication 249.00–249.01
	Secondary DM with renal manifestations 249.40–249.41
	Secondary DM with ophthalmic manifestations 249.50–249.51
	Secondary DM with neurological manifestations 249.60–249.61
	Secondary DM with peripheral circulatory disorders 249.70–249.71
	Secondary DM with other specified manifestations 249.80–249.81
	Secondary DM with unspecified complication 249.90–249.91
Congestive Heart Failure	Congestive heart failure, unspecified 428.0
	Systolic heart failure 428.20–428.23
	Diastolic heart failure 428.30–428.33
	Combined systolic and diastolic heart failure 428.40–428.43
	Rheumatic heart failure (congestive) 398.91
Coronary Artery Disease	Coronary atherosclerosis 414.00–414.07
	Chronic total occlusion of coronary artery 414.2
	Coronary atherosclerosis due to lipid-rich plaque 414.3
	Coronary atherosclerosis due to calcified coronary lesion 414.4
Peripheral Vascular Disease (PVD)	Peripheral vascular disease unspecified 443.9
	PVD in other disease (DM) 443.81
	Atherosclerosis of extremities 440.20–440.4
	Atherosclerosis of other specified arteries 440.8
	Generalized and unspecified atherosclerosis 440.9
	Raynaud's syndrome 443.0
	Occlusion/stenosis precerebral arteries 433.00–433.91
	Atherosclerosis of renal artery 440.1
	Aneurysm–peripheral arteries 442.0–442.9
	Dissection–peripheral arteries 443.21–443.29
Aortic Plaque	Atherosclerosis of aorta 440.0

Table 4.2

Sample Characteristics at Study Entry

Variable	Type of Antithrombotic Therapy			*p* Value*
	No Drug	Antiplatelet	Oral Anticoagulant	
Total number of subjects	242 (31.9%)	137 (18.1%)	379 (50%)	
Age-years (mean ± *SD*)	79.3 ± 7.9	78.9 ± 8	79.2 ± 6.8	0.9
Fall (% Yes)	138 (57%)	92 (67.2%)	273 (72%)	< .0001[a]
Dementia (% Yes)	124 (51.2%)	76 (55.5%)	158 (41.7%)	< .0001[c]
Frailty (% Yes)	32 (13.2%)	7 (5.1%)	24 (6.3%)	< .001[a,b]
CHA2DS2-VASC score (mean/± *SD*)	3.4 ± 1.3	4 ± 1.4	4.1 ± 1.3	< .0001[a,b]
Medications				
Warfarin (% Yes)	0 (0%)	0 (0%)	335 (88.4%)	
Apixaban (% Yes)	0 (0%)	0 (0%)	28 (7.4%)	
Rivaroxaban (% Yes)	0 (0%)	0 (0%)	20 (5.3%)	
Dabigatran (% Yes)	0 (0%)	0 (0%)	24 (6.3%)	
Aspirin (% Yes)	0 (0%)	123 (89.8%)	144 (38%)	
Clopidogrel (% Yes)	0 (0%)	40 (29.2%)	23 (6.1%)	
Ticagrelor (% Yes)	0 (0%)	1 (0.7%)	0 (0%)	
Prasugrel (% Yes)	0 (0%)	0 (0%)	1 (0.3%)	

Note. $p < .05$. Omnibus F test (continuous variables) or chi-square (categorical variables). [a] No drug versus oral anticoagulant. [b] No drug versus antiplatelet. [c] Oral anticoagulant versus antiplatelet.

Table 4.3

CHA_2DS_2-VASC Score Composition

Variable	Type of Antithrombotic Therapy			*p* Value*
	No Drug	Antiplatelet	Oral Anticoagulant	
Hypertension (% Yes)	85 (35.1%)	75 (54.7%)	242 (63.9%)	< .0001[a,b]
Age 75+ (% Yes)	167 (69%)	92 (67.2%)	280 (73.9%)	0.2
Age 65-74 (% Yes)	75 (31%)	45 (32.8%)	99 (26.1%)	0.2
Diabetes Mellitus (% Yes)	77 (31.8%)	42 (30.7%)	125 (33%)	0.9
Coronary Artery Disease (% Yes)	92 (38%)	80 (58.4%)	175 (46.2%)	< .0001[b,c]
Peripheral Vascular Disease (% Yes)	31 (12.8%)	31 (22.6%)	87 (23%)	< .0001[a,b]
Aortic Plaque (% Yes)	25 (10.3%)	25 (18.2%)	61 (16.1%)	0.05
Female (% Yes)	114 (47.1%)	70 (51.1%)	217 (57.3%)	< .0001[a]

Note. $p < .05$. Omnibus F test (continuous variables) or chi-square (categorical variables). [a] No drug versus oral anticoagulant. [b] No drug versus antiplatelet. [c] Oral anticoagulant versus antiplatelet.

Table 4.4

Outcomes of Stroke

Variable	Type of Antithrombotic Therapy			*p* Value*
	No Drug	Antiplatelet	Oral Anticoagulant	
Mean time to stroke and TIA	407.1+/-478.2	875.3+/-567.7	1001+/-602.8	< .0001[a,b]
1-Year stroke and TIA (% Yes)	48 (19.8%)	11 (8%)	22 (5.8%)	< .0001[a,b]
2-Year cumulative stroke and TIA (% Yes)	52 (21.5%)	14 (10.2%)	29 (7.7%)	< .0001[a,b]
3-Year cumulative stroke and TIA (% Yes)	54 (22.3%)	16 (11.7%)	41 (10.8%)	< .0001[a,b]

Note. $p < .05$. Omnibus F test. [a]No drug versus oral anticoagulant. [b]No drug versus antiplatelet. [c]Oral anticoagulant versus antiplatelet.

Table 4.5

Risk of Stroke With Oral Anticoagulants and Antiplatelet Agents Versus No Oral Anticoagulation/Antiplatelet Agents

Hazard Ratios	1-Year	2-Year	3-Year
Estimate (95% CI)			
Antiplatelet agents	0.26 (0.13,0.51)	0.30 (0.16,0.54)	0.29 (0.16,0.52)
Oral anticoagulants	0.18 (0.10,0.31)	0.21 (0.13,0.34)	0.25 (0.16,0.39)
p values			
Antiplatelet agents	< .001	< .001	< .001
Oral anticoagulants	< .001	< .001	< .001

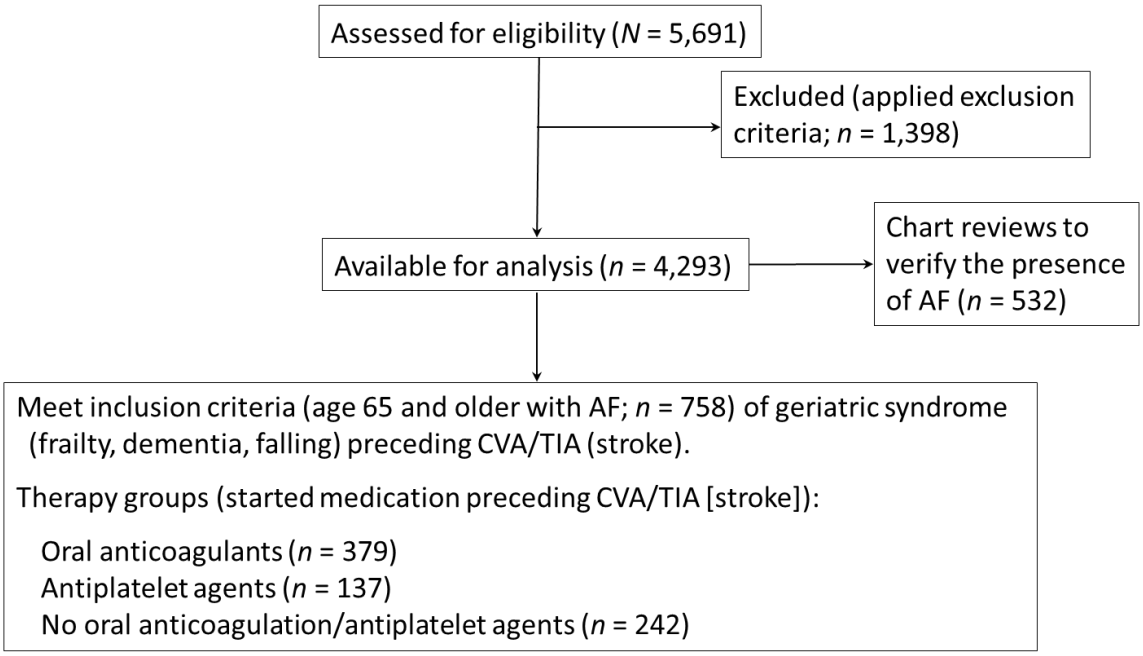

Figure 4.1 Sample selection for the outcome of stroke.
Note. AF = atrial fibrillation; CVA/TIA = cerebrovascular accident/transient ischemic attack.

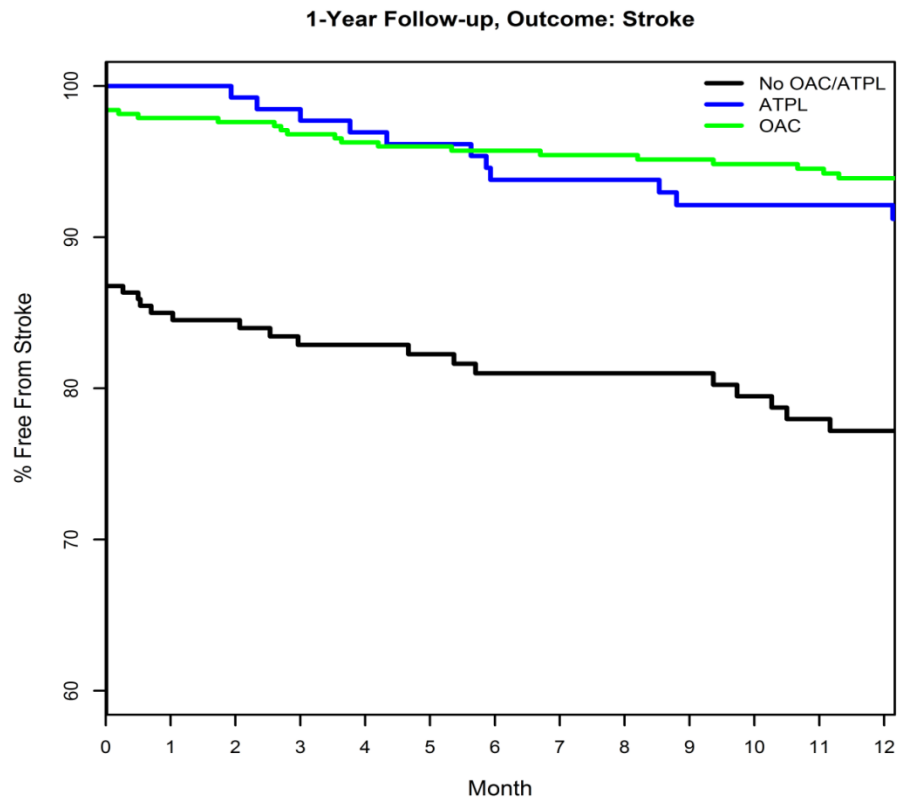

Figure 4.2 Unadjusted Kaplan-Meier results for Year 1.
Note. OAC = oral anticoagulant; ATPL = antiplatelet agent.

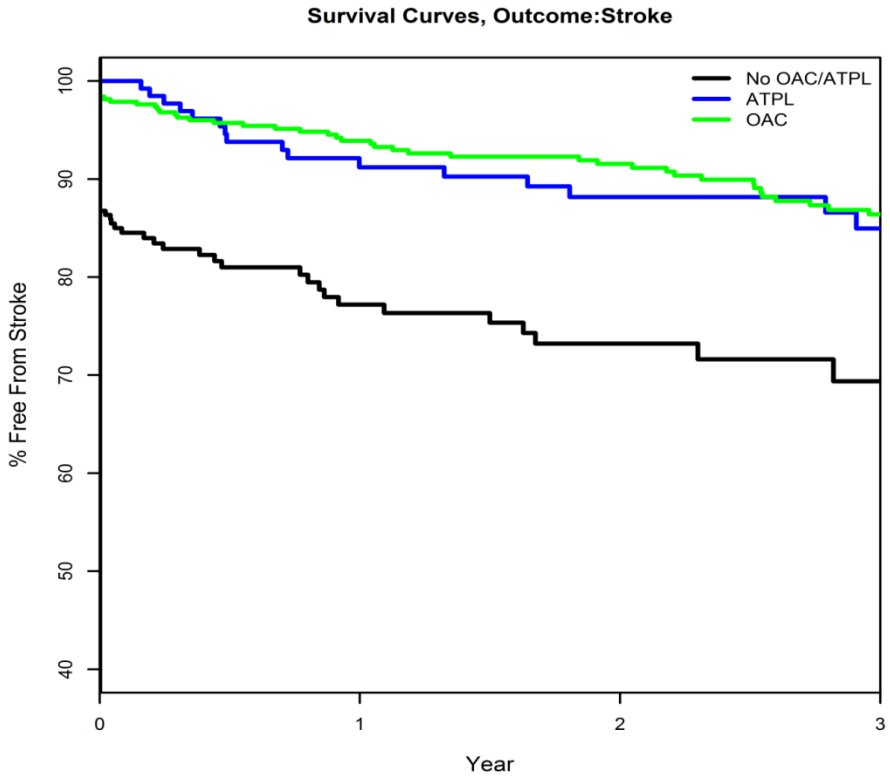

Figure 4.3 Unadjusted overall (3-year) Kaplan-Meier results.
Note. OAC = oral anticoagulant; ATPL = antiplatelet agent.

References

Ahmad, Y., & Lip, G. Y. (2012). Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: NICE guidance. *Heart, 98*(19), 1404–1406. doi:10.1136/heartjnl-2012-302101

Baker, W. L., Cios, D. A., Sander, S. D., & Coleman, C. I. (2009). Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *Journal of Managed Care Pharmacy*, *15*(3), 244–252.

Bunch, T. J., Weiss, J. P., Crandall, B. G., May, H. T., Bair, T. L., Osborn, J. S., . . . Day, J. D. (2010). Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm, 7*(4), 433–437. doi:10.1016/j.hrthm.2009.12.004

Camm, A. J., Kirchhof, P., Lip, G. Y., Schotten, U., Savelieva, I., Ernst, S., . . . Zupan, I. (2010). Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace, 12*(10), 1360–1420. doi:10.1093/europace/euq350

Casciano, J. P., Dotiwala, Z. J., Martin, B. C., & Kwong, W. J. (2013). The costs of warfarin underuse and nonadherence in patients with atrial fibrillation: A commercial insurer perspective. *Journal of Managed Care Pharmacy*, *19*(4), 302–316.

Charidimou, A., Wilson, D., Shakeshaft, C., Ambler, G., White, M., Cohen, H., . . . Werring, D. J. (2015). The Clinical Relevance of Microbleeds in Stroke study (CROMIS-2): Rationale, design, and methods. *International Journal of Stroke*. doi:10.1111/ijs.12569

Connolly, S., Yusuf, S., Budaj, A., Camm, J., Chrolavicius, S., Commerford, P. J., . . . Varigos, J. (2006). Rationale and design of ACTIVE: The atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. *American Heart Journal*, *151*(6), 1187–1193. doi:10.1016/j.ahj.2005.06.026

Costa, G. L., Ferreira, D. C., Valacio, R. A., & Vieira Moreira Mda, C. (2011). Quality of management of oral anticoagulation as assessed by time in therapeutic INR range in elderly and younger patients with low mean years of formal education: A prospective cohort study. *Age & Ageing, 40*(3), 375–381. doi:10.1093/ageing/afr020

Costa, G. L., Lamego, R. M., Colosimo, E. A., Valacio, R. A., & Moreira Mda, C. (2012). Identifying potential predictors of high-quality oral anticoagulation assessed by time in therapeutic international normalized ratio range: A prospective, long-term, single-center, observational study. *Clinical Therapeutics, 34*(7), 1511–1520. doi:10.1016/j.clinthera.2012.06.002

Fang, M. C., Go, A. S., Chang, Y., Borowsky, L. H., Pomernacki, N. K., Udaltsova, N.,

& Singer, D. E. (2010). Warfarin discontinuation after starting warfarin for atrial fibrillation. *Circulation: Cardiovascular Quality and Outcomes*, *3*(6), 624–631. doi:10.1161/circoutcomes.110.937680

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, *59*(3), 255–263.

Fuster, V., Rydén, L. E., Cannom, D. S., Crijns, H. J., Curtis, A. B., Ellenbogen, K. A., . . . Zamorano, J. L. (2006). ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*, *114*(7), e257–e354. doi: 10.1093/europace/eul097

Garwood, C. L., & Corbett, T. L. (2008). Use of anticoagulation in elderly patients with atrial fibrillation who are at risk for falls. *Annals of Pharmacotherapy*, *42*(4), 523–532. doi:10.1345/aph.1K498

Green, S. B., & Salkind, N. J. (2010). *Using SPSS for Windows and Macintosh: Analyzing and understanding data*. Upper Saddle River, NJ: Prentice Hall Press.

Gumbinger, C., Holstein, T., Stock, C., Rizos, T., Horstmann, S., & Veltkamp, R. (2015). Reasons underlying non-adherence to and discontinuation of anticoagulation in secondary stroke prevention among patients with atrial fibrillation. *European Journal of Neurology*, *73*(3–4), 184–191. doi:10.1159/000371574

Guyatt, G. H., Akl, E. A., Crowther, M., Gutterman, D. D., Schuünemann, H. J., & the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. (2012). Executive summary. *Chest*, *141*(Suppl. 2), 7S-47S. doi:10.1378/chest.1412S3

Hart, R. G., Pearce, L. A., & Aguilar, M. I. (2007). Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of Internal Medicine*, *146*(12), 857–867.

Hubbard, R. E., Peel, N. M., Samanta, M., Gray, L. C., Fries, B. E., Mitnitski, A., & Rockwood, K. (2015). Derivation of a frailty index from the interRAI acute care instrument. *BioMed Central Geriatrics*, *15*, 27. doi:10.1186/s12877-015-0026-z

Inouye, S. K., Studenski, S., Tinetti, M. E., & Kuchel, G. A. (2007). Geriatric syndromes: Clinical, research, and policy implications of a core geriatric concept. *Journal of the American Geriatrics Society*, *55*(5), 780–791. doi:10.1111/j.1532-5415.2007.01156.x

Jacobs, L. G., Billett, H. H., Freeman, K., Dinglas, C., & Jumaquio, L. (2009). Anticoagulation for stroke prevention in elderly patients with atrial fibrillation, including those with falls and/or early-stage dementia: A single-center, retrospective, observational study. *American Journal of Geriatric Pharmacotherapy, 7*(3), 159–166. doi:10.1016/j.amjopharm.2009.06.002

Jacobs, V., Woller, S. C., Stevens, S., May, H. T., Bair, T. L., Anderson, J. L., . . . Bunch, T. J. (2014). Time outside of therapeutic range in atrial fibrillation patients is associated with long-term risk of dementia. *Heart Rhythm*. doi:10.1016/j.hrthm.2014.08.013

Johnson, C. E., Lim, W. K., & Workman, B. S. (2005). People aged over 75 in atrial fibrillation on warfarin: The rate of major hemorrhage and stroke in more than 500 patient-years of follow-up. *Journal of the American Geriatrics Society, 53*(4), 655–659. doi: 10.1111/j.1532-5415.2005.53215.x

Kutner, M. H., Nachtsheim, C. J., Neter, J., & Li, W. (2005). *Applied linear statistical models.* New York, NY: McGraw-Hill.

Lip, G. Y., Frison, L., Halperin, J. L., & Lane, D. A. (2011). Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) Score. *Journal of the American College of Cardiology (JACC), 57*(2), 173–180. doi: 10.1016/j.jacc.2010.09.024

Lip, G. Y., Nieuwlaat, R., Pisters, R., Lane, D. A., & Crijns, H. J. (2010). Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro heart survey on atrial fibrillation. *Chest, 137*(2), 263–272. doi:10.1378/chest.09-1584

Lip, G. Y. H., Tse, H. F., & Lane, D. A. (2012). Atrial fibrillation. *Lancet, 379*(9816), 648–661. doi:10.1016/s0140-6736(11)61514-6

Mant, J., Hobbs, F. D., Fletcher, K., Roalfe, A., Fitzmaurice, D., Lip, G. Y., & Murray, E. (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. doi: 10.1016/s0140-6736(07)61233-1

McIsaac, D. I., Bryson, G. L., & van Walraven, C. (2016). Association of frailty and 1-year postoperative mortality following major elective noncardiac surgery: A population-based cohort study. *JAMA Surgery*. doi:10.1001/jamasurg.2015.5085

Morley, J. E. (2008). Hot topics in geriatrics. *Journal of the American Medical Directors Association, 9*(9), 613–616. doi:10.1016/j.jamda.2008.09.002

Morley, J. E., Vellas, B., van Kan, G. A., Anker, S. D., Bauer, J. M., Bernabei, R., . . .

Walston, J. (2013). Frailty consensus: A call to action. *Journal of the American Medical Directors Association, 14*(6), 392–397. doi:10.1016/j.jamda.2013.03.022

Moschetti, K., Cummings, P. L., Sorvillo, F., & Kuo, T. (2012). Burden of Alzheimer's disease–Related mortality in the United States, 1999–2008. *Journal of the American Geriatrics Society, 60*(8), 1509–1514. doi:10.1111/j.1532-5415.2012.04056.x

Olesen, J. B., Fauchier, L., Lane, D. A., Taillandier, S., & Lip, G. Y. H. (2012). Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation. *Chest, 141*(1), 147–153. doi:10.1378/chest.11-0862

Padanilam, B. J., & Prystowsky, E. N. (2009). Atrial fibrillation: Goals of therapy and management strategies to achieve the goals. *Cardiology Clinics, 27*(1), 189–200. doi:10.1016/j.ccl.2008.09.006

Pamukcu, B., Lip, G. Y., & Lane, D. A. (2010). Simplifying stroke risk stratification in atrial fibrillation patients: Implications of the CHA2DS2-VASc risk stratification scores. *Age & Ageing*, *39*(5), 533–535. doi:10.1093/ageing/afq059

Piccini, J. P., Hammill, B. G., Sinner, M. F., Jensen, P. N., Hernandez, A. F., Heckbert, S. R., . . . Curtis, L. H. (2012). Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993–2007. *Circulation: Cardiovascular Quality and Outcomes*, *5*(1), 85–93. doi:10.1161/circoutcomes.111.962688

Pieracci, F. M., Eachempati, S. R., Shou, J., Hydo, L. J., & Barie, P. S. (2007). Use of long-term anticoagulation is associated with traumatic intracranial hemorrhage and subsequent mortality in elderly patients hospitalized after falls: Analysis of the New York State Administrative Database. *Journal of Trauma and Acute Care Surgery*, *63*(3), 519–524. doi:10.1097/TA.0b013e31812e519b

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *Canadian Medical Association Journal*, *173*(5), 489–495. doi:10.1503/cmaj.050051

Ruff, C. T., Giugliano, R. P., Braunwald, E., Hoffman, E. B., Deenadayalu, N., Ezekowitz, M. D., . . . Antman, E. M. (2014). Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *Lancet, 383*(9921), 955–962. doi:10.1016/s0140-6736(13)62343-0

Searle, S. D., Mitnitski, A., Gahbauer, E. A., Gill, T. M., & Rockwood, K. (2008). A standard procedure for creating a frailty index. *BioMed Central Geriatrics*, *8*, 24. doi:10.1186/1471-2318-8-24

Singer, J. D., & Willett, J. B. (2003). *Applied longitudinal data analysis: Modeling*

change and event occurrence. Oxford: Oxford University Press.

Skanes, A. C., Healey, J. S., Cairns, J. A., Dorian, P., Gillis, A. M., McMurtry, M. S., . . . Nattel, S. (2012). Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: Recommendations for stroke prevention and rate/rhythm control. *Canadian Journal of Cardiology*, *28*(2), 125–136. doi:10.1016/j.cjca.2012.01.021

Tay, K. H., Lane, D. A., & Lip, G. Y. H. (2009). Challenges facing anticoagulation among the elderly and frail. *Age & Ageing*, *38*(2), 140–142. doi:10.1093/ageing/afn295

Team, R. C. (2013). *A language and environment for statistical computing.* Vienna, Austria: R Foundation for Statistical Computing.

Thigpen, J. L., Dillon, C., Forster, K. B., Henault, L., Quinn, E. K., Tripodis, Y., . . . Limdi, N. A. (2015). Validity of international classification of disease codes to identify ischemic stroke and intracranial hemorrhage among individuals with associated diagnosis of atrial fibrillation. *Circulation: Cardiovascular Quality and Outcomes*, *8*(1), 8–14. doi:10.1161/circoutcomes.113.000371

Wann, L. S., Curtis, A. B., Ellenbogen, K. A., Estes, N. A., 3rd, Ezekowitz, M. D., Jackman, W. M., . . . Tracy, C. M. (2011). 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Journal of the American College of Cardiology*, *57*(11), 1330–1337. doi:10.1016/j.jacc.2011.01.010

CHAPTER 5

HEMORRHAGE OUTCOMES IN ATRIAL FIBRILLATION PATIENTS WITH GERIATRIC SYNDROMES TREATED FOR THE PREVENTION OF THROMBOEMBOLISM

Abstract

Although the benefits of oral anticoagulants in the prevention of thromboembolism in patients with atrial fibrillation are well established, these agents are underutilized in the older adult population, in part due to the prevalence of geriatric syndromes that potentially increase risks of adverse events, particularly bleeding. This study surveyed medical records of AF patients age 65 years and older who were also diagnosed with geriatric syndromes (dementia and/or frailty and/or falls), to contrast hemorrhage incidence differences during the 3-year follow up while considering the following stroke-prevention therapies: oral anticoagulants (OACs), antiplatelet agents (ATPLs), or none of these (No OAC/ATPL). Using electronic medical records in a retrospective longitudinal design, we identified and included patients age 65 years and older with a diagnosis of AF and concomitant geriatric syndromes. Logistic regression and Kaplan-Meier survival analysis were utilized to determine differences in the incidence of hemorrhages. The hemorrhage outcome was separated into cranial and other

hemorrhages. The 617 older AF patients in the sample averaged 79.2 ± 7.1 years, of which 259 (42.0%) were males. When compared to subjects not prescribed antithrombotic agents over the period of 3 years, both those prescribed antiplatelet drugs (OR 3.28, $p = 0.04$) and those prescribed anticoagulants (OR 3.19; $p = 0.03$) were more likely to develop noncranial bleeding when adjusted for bleeding risk. Older AF patients age 65 years and older with concomitant geriatric syndromes who are prescribed antiplatelet agents and oral anticoagulation therapy should be monitored closely for risk of bleeding.

Introduction

Currently in the United States, atrial fibrillation (AF) affects 2.3 million older individuals; as our population ages, the incidence of AF will also increase (Benjamin et al., 1998, Waktare, 2002)**.** AF causes blood stasis due to erratic atrial contractions, which contributes to thrombus formation. This presents a risk factor for stroke that can be reduced by the use of oral OAC or ATPL agents. The use of OACs reduces the possibility of stroke by 68% (Jacobs, Billett, Freeman, Dinglas, & Jumaquio, 2009). The use of ATPL agents is correlated with a stroke risk reduction of 40% (Hart, Pearce, & Aguilar, 2007). An adverse event commonly associated with OAC and ATPL therapies is a hemorrhage. A meta-analysis of major hemorrhages in patients with AF reported that patients treated with oral anticoagulation exhibited higher rates of hemorrhages when compared to patients treated with antiplatelet therapy (Ogilvie, Welner, Cowell, & Lip, 2011). Although warfarin trials report major bleeding rates of 1% to 3% per person-year, observational studies report higher rates of major bleeds, at 7% per person-year (Gomes

et al., 2013). Also noted in recent literature is that the definition of a major hemorrhage has not been consistent among various trials, making it tremendously difficult to compare bleeding risks based on these trials (Lane, Kamphuisen, Minini, Büller, & Lip, 2011).

Clinicians rely on various guidelines established in the United States and Europe to determine appropriate therapy when initiating oral anticoagulation or antiplatelet therapy for the prevention of stroke in patients with AF (Ahmad & Lip, 2012; Camm et al., 2010; Fuster et al., 2006; Guyatt et al., 2012; Skanes et al., 2012; Wann et al., 2011).

Contingent on the personal inclinations of prescriber and patient, comorbidities, and bleeding histories of individual patients, patients with AF may be prescribed antiplatelet agents—aspirin only, or a combination of aspirin and clopidogrel—for the prevention of stroke.

Guidelines recommend the use of the HAS-BLED scoring system for predicting bleeding risk in patients who require antithrombotic therapy (Lip, Frison, Halperin, & Lane, 2011; Lip, Tse, & Lane, 2012). The acronym HAS-BLED represents the risk factors of hypertension, abnormal renal or liver function, stroke, bleeding predisposition, labile INR, elderly (age 65 and older), and drug or alcohol use. Each HAS-BLED risk factor is assigned a 1-point value, for a maximum of 9 points. The annual bleeding risk varies from 1.13% for a HAS-BLED score of 0, up to 19.6% for a HAS-BLED score of 9. When interpreting these results for a bleed risk, 0 and 1 are low risk, 2 is moderate risk, and scores of 3 and above are high risk (Lip et al., 2011).

Geriatric syndromes are defined as a clinical disorder in older individuals that is not described by the distinct disease processes (Inouye, Studenski, Tinetti, & Kuchel, 2007). Three common geriatric syndromes that have implications for anticoagulation are

dementia, falls, and frailty. These geriatric syndromes are significant contributors to decision making with respect to the use of oral anticoagulants, which is a substantial stumbling block for clinicians faced with this type of scenario. Although the combination of the presence of dementia and/or frailty and/or falls can affect the initiation of OACs, these conditions are not considered within the guidelines. Because older individuals are more likely to be diagnosed with geriatric syndromes, clinicians are less likely to treat them with OACs due to the potential for hemorrhage.

Any medication regimen is more challenging to implement and maintain in patients with dementia, which impairs memory. Studies show that 60% to 80% of individuals with dementia are afflicted with its most common form— Alzheimer's— while vascular dementia accounts for 10% to 20% of dementia diagnoses (Bunch et al., 2010). Patients with dementia are at greater risk of medication error when using drug therapies with narrow therapeutic margins, such as warfarin. In addition, individuals with dementia usually require caregiver support to access laboratory monitoring. Early signs of bleeding might not be evident to or reported by these patients, leading to additional complications related to hemorrhage outcomes (Morley, 2008).

Frail individuals are biologically unable to withstand stressors, whether physical or psychological (Fried et al., 2001). Frailty includes unintentional weight loss, feelings of exhaustion, weak grip strength, slow walking speed, and low physical activity (Rockwood et al., 2005). This "medical syndrome" leads to multiple system failures and increases mortality (Morley et al., 2013). The presence of oral anticoagulation in these individuals renders them more likely to develop a bleed (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004).

Falls may be a part of the process of frailty, or they may exist independently in older individuals (Pieracci, Eachempati, Shou, Hydo, & Barie, 2007). Fall prevalence in older individuals is 33% for those age 65 to 80 years and 50% for those age 80 years or older (Pieracci et al., 2007). Falls are related to various problems such as frailty and dementia and may cause head trauma, resulting in intracranial hemorrhage or subdural hematoma (Man-Son-Hing, Nichol, Lau, & Laupacis, 1999).

In the literature, investigators make an unambiguous distinction between intracranial hemorrhages and other types of hemorrhages encountered in patients using antithrombotic therapies. This distinction is due to the fact that intracranial hemorrhages are most likely to be fatal, infrequent, and require thorough examination (Gage et al., 2005), whereas other types of hemorrhages must also be understood, but are less likely to be fatal. Moreover, to obtain valuable information on various types of hemorrhages, investigators must create categories for improved interpretation. Intracranial hemorrhages are 7 to 10 times more likely to occur in patients prescribed antithrombotic therapy (Veltkamp, Rizos, & Horstmann, 2013). The mortality rate of 52% to 67% in patients with an intracranial hemorrhage surpasses patients who are not taking any antithrombotic therapy (Veltkamp et al., 2013). Older patients who are prone to falls and take oral anticoagulation are more likely to develop traumatic intracranial hemorrhages (Dodson et al., 2016).

The current study surveyed medical records of AF patients age 65 years and older who were also diagnosed with geriatric syndromes to contrast hemorrhage incidence differences during the 3-year follow up, while considering the following stroke prevention therapies: oral anticoagulants (OACs), antiplatelet agents (ATPLs), or none of

these (No OAC/ATPL).

Methods

Sampling and Setting

This was a database study of electronic medical records which were received from the enterprise data warehouse (EDW) at the University of Utah. This was a retrospective, descriptive, longitudinal study in which each patient was determined to have the diagnosis of AF using ICD-9 code 427.31 recorded by the healthcare providers in the patient's visit notes, electrocardiogram, or both. According to the literature and a professional coder who was consulted, this ICD-9 code is generally used to capture patients with the diagnosis of AF (Piccini et al., 2012). The dataset included outpatient and inpatient records. Consistent with previous investigations, patients who were included in the sample had two or more visits related to the AF diagnosis, which ensured that they were treated on a long-term basis for this disease (Piccini et al., 2012). Patients with a confirmed diagnosis of AF who were age 65 years or older were selected in the first tier of sampling (see Figure 5.1).

Exclusion Criteria

In an attempt to ensure that subjects with AF were not prescribed anticoagulant therapy for an indication other than stroke prevention, patients with diagnoses of mural thrombus, deep vein thrombosis, pulmonary embolism, and any mechanical heart valves were excluded from analysis. After the exclusion criteria were applied, 1,398 of the original 4,293 individuals with confirmed AF and minimum age of 65 years remained in

the sampling frame.

Sample Verification

To determine the accuracy of an AF diagnosis in the final pool of subjects, 532 individual chart reviews were performed. This process was facilitated by using the WartHog program at the EDW at the University. This program allows researchers to instantly locate specific phrases in the medical records, such as *atrial fibrillation*, eliminating records unrelated to the term searched and highlighting only the search terms used. Not only does WartHog allow for rapid searching, it is also extremely accurate.

Of a subsample of 532 charts retrieved based on the ICD-9 code, we were able to document the diagnosis of AF in all but 11. This represents 98% accuracy in locating AF diagnoses, which is higher than the average of 82.2% found in the literature for accuracy of ICD-9 diagnoses of AF (Thigpen et al., 2015).

Additional Inclusion Criteria

Additional inclusion criteria were then applied to ensure that all patients in this sample had one of, or any combination of, the following geriatric syndromes: dementia, fall(s), or frailty. All geriatric syndrome diagnoses occurred prior to the first event of a hemorrhage or the last observation. All codes for diagnoses were derived from the literature, personal communications with a professional coder, and local and national researchers on the topic of frailty (Garwood & Corbett, 2008; Hubbard et al., 2015; Jacobs et al., 2009; Jacobs et al., 2014; Morley et al., 2013; Piccini et al., 2012; Rockwood et al., 2005; Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). ICD-9

codes used to define geriatric syndromes and experts consulted are identified in Table 5.1. Subjects were included only if one or more geriatric syndromes were identified between the date of study entry and the occurrence of a hemorrhage, to ensure that the syndrome was a preexisting condition relative to a hemorrhage.

Procedures

Medication and disease files were summarized by patient identification number using aggregate/structure query language (SQL) commands in SPSS (version 23.0) (Green & Salkind, 2010) and R (version 3.2.0; Team, 2013). The ICD-9 diagnoses were also determined for all covariate variables included in the HAS-BLED schema (see Table 5.1). Owing to the lack of labile INR information in the dataset, we anticipated that value to be 0 for all patients, as described in the literature (Pisters et al., 2010).

Therapy Groups

Medication orders following a diagnosis of AF were extracted to identify the use of anticoagulant or antiplatelet agents commonly used to prevent thrombotic complications. Subjects were divided into one of three therapy groups: oral anticoagulants (OACs; warfarin, apixaban, rivaxaban, dabigatran); antiplatelet agents (ATPLs; aspirin, clopidogrel, prasugrel, ticagrelor), or no oral anticoagulation or antiplatelet agents (no OAC/ATPL). Of the 617 subjects, 182 (29.5%) were taking both antiplatelet and oral anticoagulant therapies concomitantly. It is difficult to separate therapies in these older individuals due to the presence of comorbidities, particularly coronary artery disease, for which many of these patients take low-dose aspirin; all of

these subjects were assigned to the oral anticoagulant group.

Outcome Variables

The outcome variables of cranial and noncranial hemorrhages were derived from the dataset using ICD-9 codes. Cranial hemorrhages included any head-related hemorrhages (intracranial hemorrhages, subarachnoid hemorrhages); noncranial hemorrhages included any gastrointestinal and other type of hemorrhages (see Table 5.1). In this study, patients were followed from the start of their medication until they dropped from observation or experienced an event. These types of data are right-censored (Singer & Willett, 2003).

Statistical Analysis

Following omnibus tests of ANOVA for continuous variables and chi-square for categorical variables, post hoc pairwise comparisons among categorical and continuous variables for significant omnibus tests were conducted using proportion and Tukey tests. *P* values for the post hoc comparisons were adjusted using the Bonferroni method, declaring significance at $\alpha = .05/3$. *P* values for the post hoc comparisons involving continuous variables were adjusted using the Tukey method, with significance at $\alpha = .05$ (Kutner, Nachtsheim, Neter, & Li, 2005). Adjustments to post hoc *p* values were made in order to control the probability of encountering one or more Type-I error rates (Kutner et al., 2005). All other statistical tests and estimates were carried out at a significance level of $\alpha = .05$.

Logistic regression was utilized for this set of patients because it was a better

fitting model for this dataset. Logistic models were verified in a simple manner using the Hosmer-Lemeshow test (Agresti & Kateri, 2011). This helped to check if the predicted hemorrhage counts from the models were statistically different from the bleeding counts within the data. The application of the Hosmer-Lemeshow test was unable to find evidence of predicted counts of hemorrhage differing from the observed counts ($p > 0.05$). The HAS-BLED score was used as a covariate in the logistic model to account for differences in characteristics among the treatment groups.

Kaplan-Meier curves were also used to help compare risk differences in medication groups visually according to hemorrhages. A Kaplan-Meier curve is a nonparametric estimate of a survival curve. The formula used to construct the curve does not include an adjustment for risk factors. To compare survival curves controlling for risks, a Cox model was used instead (Singer & Willett, 2003). Visual separation of curves between drug groups may imply that one drug group had lower survival rates (hemorrhage-free time) than another.

Results

Description of Groups

Overall, the average patient age was 79.2 ± 7.1 years, and 259 (42.0%) were males (see Table 5.2). The distribution of patients within each medication category was OACs 65.3% (n = 403), APTL agents 19.8% (n = 122), and no OAC/ATPL 14.9% (n = 92).

In Table 5.2, we compare these three treatment groups on demographic and treatment variables. The three groups did not differ by age, and there were no significant

differences in the prevalence of geriatric syndromes by group.

The mean HAS-BLED scores indicated high risk for a hemorrhage in all groups. The antiplatelet group represented the highest HAS-BLED scores, demonstrating the most risk-related comorbidities (see Table 5.3).

Group Differences on Outcomes

All hemorrhage outcomes are presented in Table 5.4. The group prescribed no antithrombotic therapy had the highest rate of cranial hemorrhages at 1 year (10.9%); there were four cases of cranial hemorrhage in this group during the first year and none in subsequent years. Both groups receiving antithrombotic therapy had a higher prevalence of diagnosed noncranial hemorrhages (13.9%), greater than the no-drug group (4.3%). Like the cranial hemorrhages, all of the noncranial hemorrhages in the no-drug group were diagnosed in the first year. Nevertheless, the highest rate of cranial and noncranial hemorrhages overall was detected in the no-drug group (15.2%), even though these findings are not controlled for risk. The number of subjects lost to follow up and presumed to have experienced no hemorrhages during the 3 years was 540 (87.5%).

Kaplan Meier survival estimates for the first year (Figure 5.2) and over all 3 years (Figure 5.3) are shown for the three antithrombotic treatment groups of oral anticoagulation, antiplatelet therapy, and no oral anticoagulation or antiplatelet therapies, controlled for bleeding risk using HAS-BLED scores. These graphs demonstrate a crossing of the Kaplan Meyer curves, which may happen when there is the presence of confounding variables, due to data collection and recording, or a small number of events or lack of power (Mok et al., 2009; Singer & Willett, 2003). The 3-year outcome showed

by Kaplan-Meyer curves (Figure 5.3) represent possibly greater survival rates (avoidance of noncranial hemorrhages) among patients prescribed no OAC/ATPL agents than patients prescribed OACs.

Logistic Regression Results

We present logistic regression results for all hemorrhages and noncranial hemorrhages, but not for cranial hemorrhages because of the small sample size. For all hemorrhages (combined cranial and noncranial), the results were counterintuitive, similar to the nonadjusted findings, with those prescribed ATPLs and OACs having a 16% to 70% less risk of bleeding than those prescribed no antithrombotic therapy (see Table 5.5).

Subjects who were prescribed antiplatelet agents were 3.28 times more likely to develop noncranial hemorrhages when compared to subjects not prescribed OAC/ATPL agents over the period of 3 years (OR 3.28 [1.14, 11.8], $p = 0.04$) when bleeding risk was controlled. Subjects who were prescribed oral anticoagulation were 3.19 times more likely to develop noncranial hemorrhages when compared to subjects not prescribed OAC or ATPL agents over the period of 3 years (OR 3.19 [1.25, 10.7], $p = 0.03$) when bleeding risk was controlled (Table 5.6).

Discussion

The three treatment groups were similar on age and prevalence of geriatric syndromes. However, while all groups were considered high risk for bleeding based on the HAS-BLED score, it is notable that the lowest HAS-BLED scores were in the group of patients who were prescribed neither OACs nor ATPLs, indicating that the reason

these patients were not on anticoagulants was probably not related to established risk factors or the three specific geriatric syndromes (falls, dementia, and frailty).

The results of this study demonstrate that patients diagnosed with AF and geriatric syndromes that use oral anticoagulant and/or antiplatelet therapies are more likely to develop noncranial hemorrhages, to include gastrointestinal bleeding. This is consistent with analogous findings in the literature. The most common type of bleeding in patients taking oral anticoagulation is gastrointestinal, which most commonly affects the upper gastrointestinal tract (Hylek et al., 2014). Similarly, hospital admissions of patients taking OACs most frequently involves gastrointestinal hemorrhages (Gomes et al., 2012). It is also a common finding that patients who develop bleeding events are older, with a higher number of comorbidities in addition to AF (Ghate, Biskupiak, Ye, Kwong, & Brixner, 2011). The rates of gastrointestinal hemorrhage found in various studies may differ due to variations in the definition of the gastrointestinal bleeding events. In this study we combined gastrointestinal bleeding events with all other noncranial bleeding events.

In numerous studies gastrointestinal hemorrhages have been defined differently due to the specifics of the gastrointestinal bleeding event. For example, studies that examined only gastrointestinal bleeds associated with oral anticoagulation have typically classified major events as hospitalizations due to the gastrointestinal bleed (Ghate et al., 2011). In this study we included all inpatient and outpatient gastrointestinal bleeding events in the noncranial hemorrhages category.

As this group ages and experiences more incidences of falls, antithrombotic therapy may potentially cause noncranial hemorrhages. A meta-analysis of the presence of hemorrhages in patients with AF treated with oral anticoagulation showed that those

patients have higher rates of hemorrhages when compared to patients treated with antiplatelet therapy (Ogilvie et al., 2011). In the current study the risk of noncranial hemorrhages was similar among oral anticoagulation and antiplatelet groups. This finding could be related to the various comorbidities of this group, and specifically geriatric syndromes. As patients with geriatric syndromes age they are more likely to experience a progression of their declining health. This in turn may lead to increased sensitivity not only to oral anticoagulants but also to antiplatelet agents.

Intracranial hemorrhage most commonly results in mortality outcomes of 67% in patients taking oral anticoagulation (Steiner, Rosand, & Diringer, 2006). In the current study, cranial bleeding was represented by such a small number of events that the sample size was insufficient for assessment of this outcome. It is possible that all of the hemorrhage events in the no-antithrombotic therapy group were accounted for in the first year. Perhaps these subjects had been on anticoagulants, possibly in another system, and were erroneously assigned to this group, or stopped their oral anticoagulation therapy for other reasons.

In this study, when bleeding risk was not controlled in nonadjusted analyses, the group receiving no antithrombotic therapy had more instances of both cranial and noncranial bleeding events. This could be related to the fact that the majority of these events happened in the first year of observation. For the following two years of observation, the recording of data was either lacking or was very infrequent, which may be related to the recording practices of the providers, the possibility of events occurring outside the study-site system, or lack of patient follow up. These patients could have been declining or perhaps relocated from their home to other facilities, precluding our ability

to perform sufficient follow up. In a recent analysis, researchers discovered that the presence of dementia doubled the risk for a traumatic intracranial hemorrhage due to falls (Dodson et al., 2016). In our study, almost half of the subjects had a diagnosis of dementia, leading to the progression of overall declines in these patients. However, we did not have enough cranial hemorrhage events to draw conclusions for this patient group.

Antiplatelet therapy administered concomitantly with warfarin increases the risk of major bleeding by 2.3 to 2.5 times (Lane et al., 2011). The post hoc analysis of the AMADEUS trial (Lane et al., 2011) showed that age and use of concomitant antiplatelet therapy with oral anticoagulation increased bleeding risk among AF patients. The use of antiplatelet therapy in addition to oral anticoagulation increases the risk of a major bleed by a factor of two. In the current study, 182 subjects out of 403 had been prescribed oral anticoagulation and antiplatelet agents concomitantly; however, their risk of noncranial hemorrhage was similar to patients who were prescribed antiplatelet therapy alone. This could relate to the comorbidities of this group, recording of follow ups, or recording of the hemorrhage events in this group.

Our understanding of the development of dementia in patients with AF has been evolving. As these patients develop dementia, they are more likely to develop frailty and falls, which leads to increased risk of bleeding.

In this study of older patients with AF and geriatric syndromes, we confirmed that if risk of hemorrhage is controlled using a common risk scale, those prescribed oral anticoagulation and antiplatelet therapy are more likely to develop gastrointestinal and other noncranial hemorrhages than those prescribed no antithrombotic therapy. As such,

these therapies may be unsafe for older patients, especially in the presence of falls and/or dementia and/or frailty. Providers must reassess these therapies in light of individualized benefit–harm ratios and ensure that patients and caregivers receive appropriate education for minimization of hemorrhage and early detection of any bleeding.

Limitations

Because this was a longitudinal, observational, retrospective study of AF patients, we were limited to ascertaining associations and were not able to determine causality mechanisms. The medical records reviewed in the study reflect the accuracy and comprehensiveness of the providers who recorded the disease states and outcomes. Residual confounding may exist in this observational study, despite the fact that the multivariable modeling included several risk factors and baseline characteristics.

We acknowledge including only fall and frailty events that were reported, knowing that the incidence of falls and frailty are traditionally underreported, contributing to the smaller number of subjects in these groups. No consensus currently exists for the definition of frailty or definitive ICD-9 codes for it, necessitating the use of diagnosis codes extracted from the literature as well as personal communications with experts specializing in frailty to acquire a definition.

There was a potential for loss to follow up of some group participants from death or other events unrelated to the study topic. Loss to follow up may underrepresent numbers of hemorrhages. The duration of presence of disease varied in length within the studied group of older individuals.

We were unable to elicit information about cranial hemorrhages because of

counterintuitive erroneous results of logistic regression, due to various factors, such as the small number of cranial hemorrhages, small sample size, dataset collection practices, the recording of ICD-9 codes by the providers, and the presence of covariation. This limitation must be addressed in future studies, to secure further knowledge about the impact of cranial hemorrhages in the geriatric-syndrome population. This can potentially be achieved through the use of prospective observational studies, which may be designed to acquire the necessary information to overcome these stated limitations.

Table 5.1

ICD-9 Codes Used to Define Hemorrhage Outcomes Variables.

Disease	CD-9 Codes
Dementia	Dementia in other conditions (Alzheimer's, Lewy bodies, Parkinsonism, epilepsy, frontal, multiple sclerosis, and so forth) 294.10–294.20, 293
	Uncomplicated, 294.8
	Use the following underlying conditions followed by one of the dementia codes listed above:
	Alzheimer's 331.0
	Senile degeneration of brain 331.2
	Dementia with Lewy bodies/Parkinsonism 331.82
	Dementia unspecified 294.10-294.21
	Presenile 290.10–290.13, 290.39
	Senile uncomplicated 290.0
	Senile dementia with delusional features 290.20
	Senile dementia with depressive features 290.21
	Senile dementia with delirium or confusion 290.3
Fall(s)	Fall on or from sidewalk curb E880.1
	Fall on or from stairs or steps E880.9
	Fall from wheelchair E884.3
	Fall from bed E884.4
	Fall on the same level from slipping, tripping, or stumbling E885.9
	Other and unspecified fall E888.0-E888.9
	History of falling V15.88
Frailty	Senility without mention of psychosis (frailty) 797
	Cachexia 799.4 (personal communication with Kenneth Rockwood, January 23, 2016)
Cerebrovascular Accident/Transient Ischemic Attack (CVA/TIA)	Ischemic, stroke 434.91
	Embolic, stroke 434.11
	Thrombotic, stroke 434.01
	Impending 435.9
	Postoperative 997.02
	Personal history without deficits V12.54
	Late effects 438.0–438.9
	Personal history of TIA V12.54
	Unspecified transient cerebral ischemia 435.9
Hypertension	Essential hypertension 401.0–401.9
	Hypertensive heart disease 402.00–402.91
	Hypertensive chronic kidney disease 403.00–403.91
	Hypertensive heart & chronic kidney disease 404.00–404.93
	Secondary hypertension 405.01–405.99
	Hypertensive cerebrovascular disease 437.2
	Intracranial hypertension benign 348.2
	Postoperative hypertension 997.91
Alcohol Use	Alcohol dependence 303.90, 303,91, 303.92, 303.93
	Alcohol abuse 291.0–291.5, 291.8, 291.81, 291.82, 291.89, 291.9, 303.00–303.03, 305.00, 305.01, 305.02, 305.03, 760.71, 980.0
Abnormal Renal Function	794.4, acute renal failure 584.5–584.9, unspecified renal failure 586, chronic renal failure 585, 585.3–585.6, 585.9, 792.5, V42.0, V45.1, V45.11, V45.12,

Table 5.1, Continued

Disease	ICD-9 Codes
Abnormal Renal Function, Continued	V56.0, V56.1, V56.2, V56.31, V56.32, V56.8
Abnormal Liver Function	794.8, cirrhosis of the liver without mention of alcohol 571.5, liver abscess and sequela of chronic liver disease 572.0–572.4, 572.8, ascites 789.5, 789.59, other and unspecified liver disorders 570, 571.6, 571.8, 579.9, 573.0, 573.4, 573.8, 573.9, 782.4, 789.1, 790.4, 790.5, 794.8, V42.7
Prior Bleed	Hemorrhage not otherwise specified 459.0 Postoperative 998.11 Brain hemorrhage iatrogenic/postoperative 997.02 Subarachnoid hemorrhage 430 Intracerebral hemorrhage 431 Nontraumatic extradural hemorrhage 432.0 Subdural hemorrhage 432.1 Unspecified Intracranial hemorrhage 432.9 Esophageal hemorrhage 530.82 Gastric ulcer with hemorrhage 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61 Duodenal ulcer with hemorrhage 532.00, 532.01, 532.20, 532.21, 532.40, 532.41, 532.60, 532.61 Peptic ulcer with hemorrhage 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.60, 533.61 Gastrojejunal ulcer with hemorrhage 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.60, 534.61 Gastritis and duodenitis with hemorrhage 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71 Diverticulosis small intestine with hemorrhage 562.02 Diverticulitis small intestine with hemorrhage 562.03 Diverticulosis colon with hemorrhage 562.12 Diverticulitis colon with hemorrhage 562.13 Hemorrhage of rectum and anus 569.3 Hematemesis 578.0 Melena/blood in stool 578.1 Hemorrhage of gastrointestinal tract unspecified 578.9 Hemoptysis unspecified 786.30 Cough with hemorrhage 786.39 Traumatic brain hemorrhage 852.00–853.19 Traumatic hemothorax 860.2–860.5

Table 5.2

Sample Characteristics at Study Entry

Variable	Type of Antithrombotic Therapy			*p* Value*
	No Drug	Antiplatelet	Oral Anticoagulant	
Subject Count	92 (14.9%)	122 (19.8%)	403 (65.3%)	
Age in years (mean ± *SD*)	79.2 ± 7.9	79 ± 8	79.3 ± 6.7	0.9
Fall (% Yes)	62 (67.4%)	88 (72.1%)	286 (71%)	0.7
Dementia (% Yes)	42 (45.7%)	65 (53.3%)	186 (46.2%)	0.08
Frailty (% Yes)	8 (8.7%)	10 (8.2%)	17 (4.2%)	0.2
HAS-BLED (mean ± *SD*)	2.3 ± 1	2.5 ± (1)	2.5 ± (0.9)	< .05[a]
Medications				
Warfarin (% Yes)	0 (0%)	0 (0%)	363 (90.1%)	
Apixaban (% Yes)	0 (0%)	0 (0%)	31 (7.7%)	
Rivaroxaban (% Yes)	0 (0%)	0 (0%)	26 (6.5%)	
Dabigatran (% Yes)	0 (0%)	0 (0%)	22 (5.5%)	
Aspirin (% Yes)	0 (0%)	113 (92.6%)	156 (38.7%)	
Clopidogrel (% Yes)	0 (0%)	32 (26.2%)	26 (6.5%)	
Ticagrelor (% Yes)	0 (0%)	2 (1.6%)	0 (0%)	
Prasugrel (% Yes)	0 (0%)	0 (0%)	0 (0%)	

Note. $p < .05$; *SD* = standard deviation.

Omnibus F test (continuous variables) or chi-square (categorical variables).

[a] No drug versus oral anticoagulant.

[b] No drug versus antiplatelet.

[c] Oral anticoagulant versus antiplatelet.

Table 5.3

HAS-BLED Score Composition

Variable	Type of Antithrombotic Therapy			*p* Value*
	No Drug	Antiplatelet	Oral Anticoagulant	
Age 65+ (% Yes)	92 (100%)	122 (100%)	403 (100%)	1.0
Hypertension (% Yes)	45 (48.9%)	66 (54.1%)	259 (64.3%)	<.0001[a]
Renal disease (% Yes)	32 (34.8%)	39 (32%)	139 (34.5%)	0.9
Liver disease (% Yes)	5 (5.4%)	8 (6.6%)	20 (5%)	0.7
Stroke history (% Yes)	24 (26.1%)	46 (37.7%)	164 (40.7%)	<.0001[a]
Antiplatelet use (% Yes)	0 (0%)	122 (100%)	0 (0%)	
NSAIDS use (% Yes)	3 (3.3%)	9 (7.4%)	19 (4.7%)	0.4
Alcohol use (% Yes)	7 (7.6%)	9 (7.4%)	19 (4.7%)	0.3

Note. $p < .05$.

Omnibus F test (continuous variables) or chi-square (categorical variables).

[a] No drug versus oral anticoagulant.

[b] No drug versus antiplatelet.

[c] Oral anticoagulant versus antiplatelet.

Table 5.4

Cranial and Noncranial Hemorrhage Outcomes

Hemorrhages Outcomes	Type of Antithrombotic Therapy			*p* Value
	No Drug	Antiplatelet	Oral Anticoagulant	
Cranial Hemorrhages Overall (% Yes)	10 (10.9%)	7 (5.7%)	32 (7.9%)	0.4
Cranial Hemorrhage 1 year (% Yes)	10 (10.9%)	4 (3.3%)	16 (4%)	< .05[a]
Cranial Hemorrhage 3 year (% Yes)	10 (10.9%)	5 (4.1%)	25 (6.2%)	0.1
Noncranial Hemorrhage Overall (% Yes)	4 (4.3%)	17 (13.9%)	56 (13.9%)	< .0001[a]
Noncranial Hemorrhage 1 year (% Yes)	4 (4.3%)	7 (5.7%)	14 (3.5%)	0.5
Noncranial Hemorrhage 3 year (% Yes)	4 (4.3%)	9 (7.4%)	32 (7.9%)	0.6
Total Hemorrhage Overall (Cranial and Noncranial) (% Yes)	14 (15.2%)	14 (11.5%)	56 (13.9%)	0.7
Total Hemorrhage (Cranial and Noncranial) 1 year (% Yes)	14 (15.2%)	7 (5.7%)	22 (5.5%)	< .05[a]
Total Hemorrhage (Cranial and Noncranial) 3 year (% Yes)	14 (15.2%)	8 (6.6%)	45 (11.2%)	0.1

Note. $p < .05$.

Chi-square

[a] No drug versus oral anticoagulant

[b] No drug versus antiplatelet.

[c] Oral anticoagulant versus antiplatelet.

Table 5.5

Logistic Model Results for All Hemorrhages (Cranial and Noncranial)

Odds Ratio	Overall	1-Year	2-Year	3-Year
Estimate (95% CI)				
ATPL	0.68 (0.30,1.53)	0.32 (0.11,0.82)	0.32 (0.11,0.83)	0.37 (0.14,0.92)
OAC	0.84 (0.45,1.65)	0.30 (0.15,0.64)	0.46 (0.23,0.93)	0.66 (0.35,1.31)
p values				
ATPL	0.35	0.02	0.02	0.03
OAC	0.6	0.001	0.02	0.21

Note. Reference group = no antithrombotic drug; covariate: HAS-BLED score; ATPL= antiplatelet drugs; OAC = oral anticoagulant drugs.

Table 5.6

Logistic Model Results for Noncranial Hemorrhages

Odds Ratio	Overall	1-Year	2-Year	3-Year
Estimate (95% CI)				
ATPL	3.28 (1.14,11.8)	1.29 (0.37,5.06)	1.49 (0.45,5.75)	1.63 (0.5,6.21)
OAC	3.19 (1.25,10.78)	0.75 (0.26,2.71)	1.15 (0.42,4.04)	1.73 (0.66,5.96)
p values				
ATPL	0.04	0.69	0.52	0.42
OAC	0.03	0.62	0.79	0.31

Note. Reference group = no antithrombotic drug; covariate = HAS-BLED score; ATPL = antiplatelet drugs; OAC = oral anticoagulant drugs.

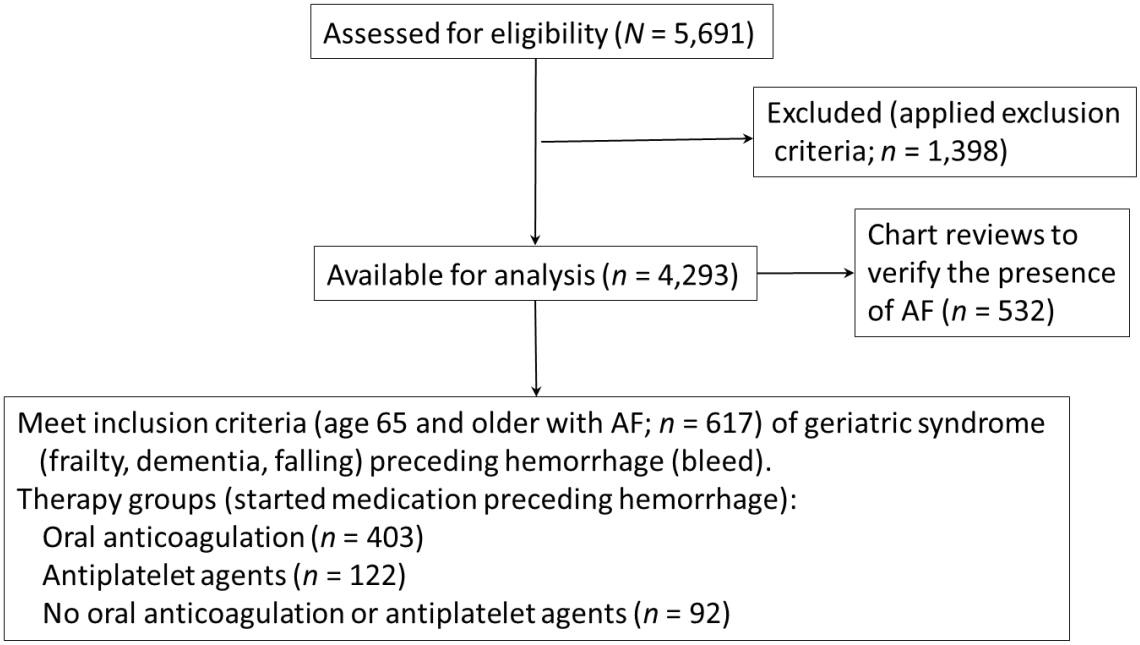

Figure 5.1 Sample selection for the outcome of hemorrhage.

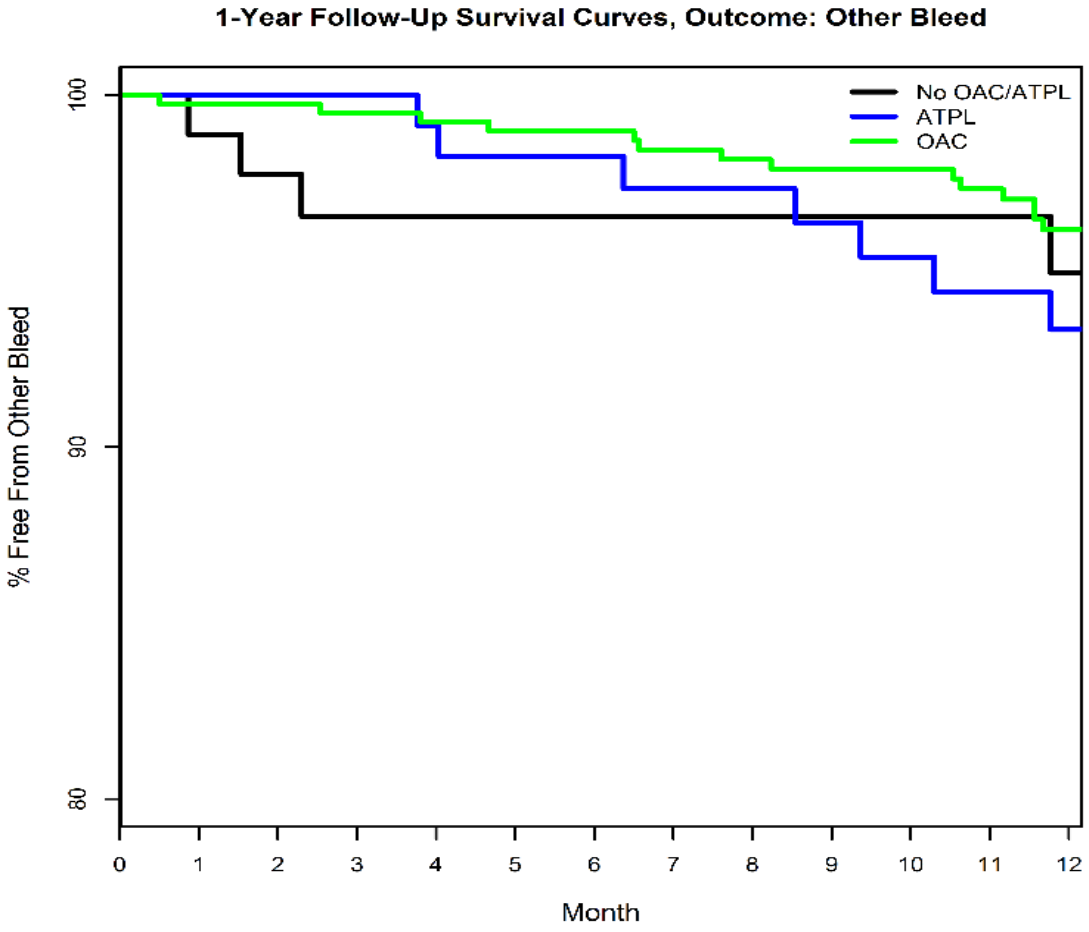

Figure 5.2 Unadjusted Kaplan-Meier noncranial hemorrhages.
Note. OAC = Oral anticoagulant; ATPL = antiplatelet agent.

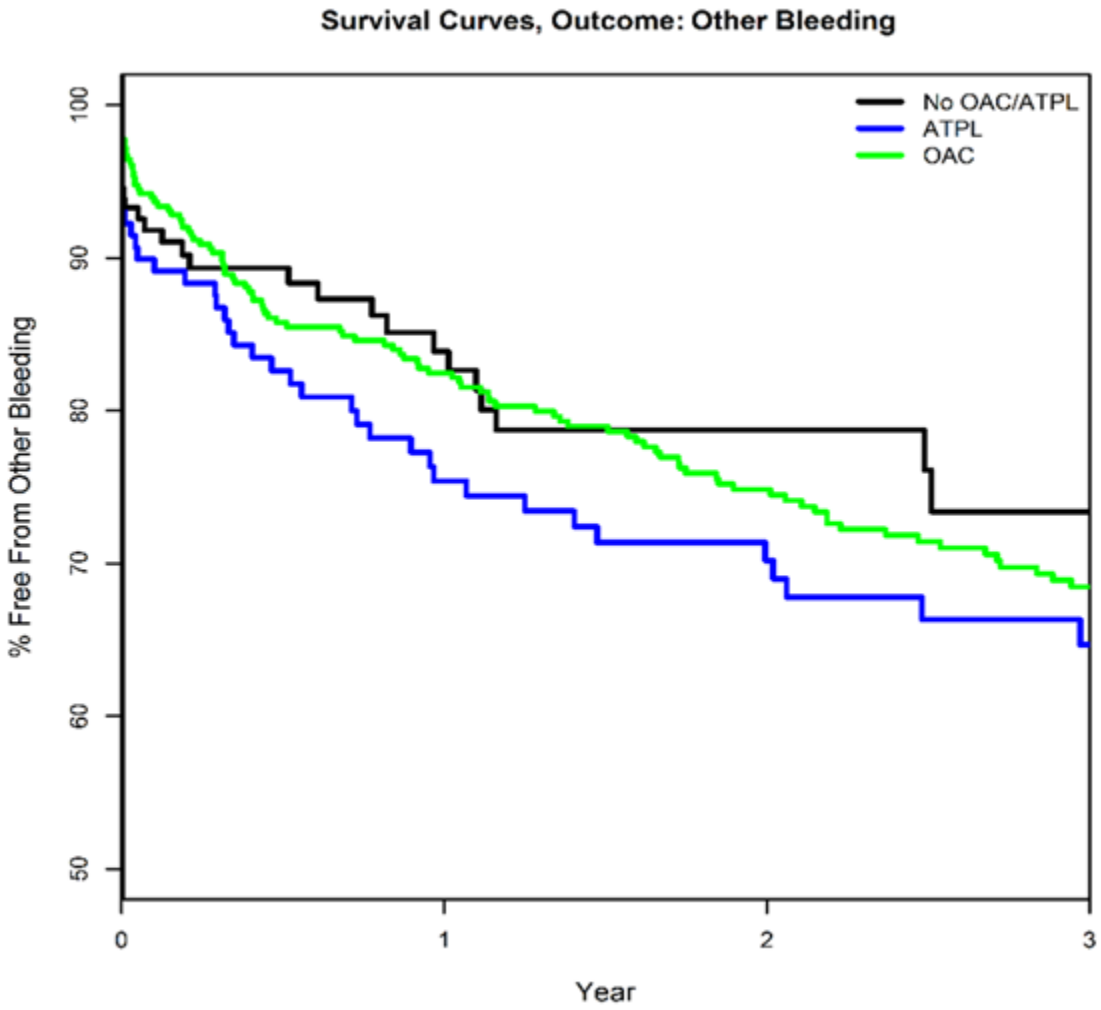

Figure 5.3 Unadjusted overall (3-year) Kaplan-Meier results (noncranial hemorrhages).
Note. OAC = oral anticoagulant; ATPL = antiplatelet agent.

References

Agresti, A., & Kateri, M. (2011). *Categorical data analysis*. Hoboken, NJ: Springer.

Ahmad, Y., & Lip, G. Y. (2012). Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: NICE guidance. *Heart, 98*(19), 1404–1406. doi:10.1136/heartjnl-2012-302101

Benjamin, E. J., Wolf, P. A., D'Agostino, R. B., Silbershatz, H., Kannel, W. B., & Levy, D. (1998). Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation, 98*(10), 946–952.

Bunch, T. J., Weiss, J. P., Crandall, B. G., May, H. T., Bair, T. L., Osborn, J. S., . . . Day, J. D. (2010). Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm, 7*(4), 433–437. doi:10.1016/j.hrthm.2009.12.004

Camm, A. J., Kirchhof, P., Lip, G. Y., Schotten, U., Savelieva, I., Ernst, S., . . . Zupan, I. (2010). Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace, 12*(10), 1360–1420. doi:10.1093/europace/euq350

Dodson, J. A., Petrone, A., Gagnon, D. R., Tinetti, M. E., Krumholz, H. M., & Gaziano, J. (2016). Incidence and determinants of traumatic intracranial bleeding among older veterans receiving warfarin for atrial fibrillation. *JAMA Cardiology*. doi:10.1001/jamacardio.2015.0345

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 59*(3), 255–263.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., . . . McBurnie, M. A. (2001). Frailty in older adults: evidence for a phenotype. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 56*(3), M146–M156.

Fuster, V., Rydén, L. E., Cannom, D. S., Crijns, H. J., Curtis, A. B., Ellenbogen, K. A., . . . Zamorano, J. L. (2006). ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation, 114*(7), e257–e354.

Gage, B. F., Birman-Deych, E., Kerzner, R., Radford, M. J., Nilasena, D. S., & Rich, M. W. (2005). Incidence of intracranial hemorrhage in patients with atrial fibrillation

who are prone to fall. *American Journal of Medicine, 118*(6), 612–617. doi:10.1016/j.amjmed.2005.02.022

Garwood, C. L., & Corbett, T. L. (2008). Use of anticoagulation in elderly patients with atrial fibrillation who are at risk for falls. *Annals of Pharmacotherapy, 42*(4), 523–532. doi:10.1345/aph.1K498

Ghate, S. R., Biskupiak, J., Ye, X., Kwong, W. J., & Brixner, D. I. (2011). All-cause and bleeding-related health care costs in warfarin-treated patients with atrial fibrillation. *Journal of Managed Care Pharmacy, 17*(9), 672–684.

Gomes, T., Mamdani, M. M., Holbrook, A. M., Paterson, J. M., Hellings, C., & Juurlink, D. N. (2012). Rates of hemorrhage during warfarin therapy for atrial fibrillation. *Canadian Medical Association Journal*. doi:10.1503/cmaj.121218

Gomes, T., Mamdani, M. M., Holbrook, A. M., Paterson, J. M., Hellings, C., & Juurlink, D. N. (2013). Rates of hemorrhage during warfarin therapy for atrial fibrillation. *Canadian Medical Association Journal, 185*(2), E121–E127. doi:10.1503/cmaj.121218

Green, S. B., & Salkind, N. J. (2010). *Using SPSS for Windows and Macintosh: Analyzing and understanding data*. Upper Saddle River, NJ: Prentice Hall Press.

Guyatt, G. H., Akl, E. A., Crowther, M., Gutterman, D. D., Schuünemann, H. J., & the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. (2012). Executive summary. *Chest, 141*(Suppl. 2), 7S–47S. doi:10.1378/chest.1412S3

Hart, R. G., Pearce, L. A., & Aguilar, M. I. (2007). Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of Internal Medicine, 146*(12), 857–867.

Hubbard, R. E., Peel, N. M., Samanta, M., Gray, L. C., Fries, B. E., Mitnitski, A., & Rockwood, K. (2015). Derivation of a frailty index from the interRAI acute care instrument. *BioMed Central Geriatrics, 15*, 27. doi:10.1186/s12877-015-0026-z

Hylek, E. M., Held, C., Alexander, J. H., Lopes, R. D., De Caterina, R., Wojdyla, D. M., . . . Granger, C. B. (2014). Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation): Predictors, characteristics, and clinical outcomes. *Journal of the American College of Cardiology, 63*(20), 2141–2147. doi:10.1016/j.jacc.2014.02.549

Inouye, S. K., Studenski, S., Tinetti, M. E., & Kuchel, G. A. (2007). Geriatric syndromes: Clinical, research, and policy implications of a core geriatric concept. *Journal of the American Geriatrics Society, 55*(5), 780–791. doi:10.1111/j.1532-5415.2007.01156.x

Jacobs, L. G., Billett, H. H., Freeman, K., Dinglas, C., & Jumaquio, L. (2009). Anticoagulation for stroke prevention in elderly patients with atrial fibrillation, including those with falls and/or early-stage dementia: A single-center, retrospective, observational study. *American Journal of Geriatric Pharmacotherapy, 7*(3), 159–166. doi:10.1016/j.amjopharm.2009.06.002

Jacobs, V., Woller, S. C., Stevens, S., May, H. T., Bair, T. L., Anderson, J. L., . . . Bunch, T. J. (2014). Time outside of therapeutic range in atrial fibrillation patients is associated with long-term risk of dementia. *Heart Rhythm*. doi:10.1016/j.hrthm.2014.08.013

Kutner, M. H., Nachtsheim, C. J., Neter, J., & Li, W. (2005). *Applied linear statistical models.* New York, NY: McGraw-Hill.

Lane, D. A., Kamphuisen, P. W., Minini, P., Büller, H. R., & Lip, G. Y. (2011). Bleeding risk in patients with atrial fibrillation: The AMADEUS Study. *Chest, 140*(1), 146–155. doi:10.1378/chest.10-3270

Lip, G. Y., Frison, L., Halperin, J. L., & Lane, D. A. (2011). Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: The HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) Score. *Journal of the American College of Cardiology (JACC), 57*(2), 173–180.

Lip, G. Y. H., Tse, H. F., & Lane, D. A. (2012). Atrial fibrillation. *Lancet, 379*(9816), 648–661. doi:10.1016/s0140-6736(11)61514-6

Man-Son-Hing, M., Nichol, G., Lau, A., & Laupacis, A. (1999). Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Archives of Internal Medicine, 159*(7), 677–685. doi:10.1001/archinte.159.7.677

Mok, T. S., Wu, Y.-L., Thongprasert, S., Yang, C.-H., Chu, D.-T., Saijo, N., . . . Fukuoka, M. (2009). Gefitinib or carboplatin–Paclitaxel in pulmonary adenocarcinoma. *New England Journal of Medicine, 361*(10), 947–957. doi:doi:10.1056/NEJMoa0810699

Morley, J. E. (2008). Hot topics in geriatrics. *Journal of the American Medical Directors Association, 9*(9), 613–616. doi:10.1016/j.jamda.2008.09.002

Morley, J. E., Vellas, B., van Kan, G. A., Anker, S. D., Bauer, J. M., Bernabei, R., . . . Walston, J. (2013). Frailty consensus: A call to action. *Journal of the American Medical Directors Association, 14*(6), 392–397. doi:10.1016/j.jamda.2013.03.022

Ogilvie, I. M., Welner, S. A., Cowell, W., & Lip, G. Y. (2011). Ischaemic stroke and bleeding rates in 'real-world' atrial fibrillation patients. *Thrombosis and Haemostasis, 106*(1), 34–44. doi:10.1160/th10-10-0674

Piccini, J. P., Hammill, B. G., Sinner, M. F., Jensen, P. N., Hernandez, A. F., Heckbert, S. R., . . . Curtis, L. H. (2012). Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993–2007. *Circulation: Cardiovascular Quality and Outcomes, 5*(1), 85–93. doi:10.1161/circoutcomes.111.962688

Pieracci, F. M., Eachempati, S. R., Shou, J., Hydo, L. J., & Barie, P. S. (2007). Use of long-term anticoagulation is associated with traumatic intracranial hemorrhage and subsequent mortality in elderly patients hospitalized after falls: Analysis of the New York State Administrative Database. *Journal of Trauma and Acute Care Surgery, 63*(3), 519–524. doi:10.1097/TA.0b013e31812e519b

Pisters, R., Lane, D. A., Nieuwlaat, R., de Vos, C. B., Crijns, H. J., & Lip, G. Y. (2010). A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. *Chest, 138*(5), 1093–1100. doi:10.1378/chest.10-0134

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *Canadian Medical Association Journal, 173*(5), 489–495. doi:10.1503/cmaj.050051

Searle, S. D., Mitnitski, A., Gahbauer, E. A., Gill, T. M., & Rockwood, K. (2008). A standard procedure for creating a frailty index. *BioMed Central Geriatrics, 8*, 24. doi:10.1186/1471-2318-8-24

Singer, J. D., & Willett, J. B. (2003). *Applied longitudinal data analysis: Modeling change and event occurrence*. Oxford: Oxford University Press.

Skanes, A. C., Healey, J. S., Cairns, J. A., Dorian, P., Gillis, A. M., McMurtry, M. S., . . . Nattel, S. (2012). Focused 2012 update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for stroke prevention and rate/rhythm control. *Canadian Journal of Cardiology, 28*(2), 125–136. doi:10.1016/j.cjca.2012.01.021

Steiner, T., Rosand, J., & Diringer, M. (2006). Intracerebral hemorrhage associated with oral anticoagulant therapy: Current practices and unresolved questions. *Stroke, 37*(1), 256–262. doi:10.1161/01.STR.0000196989.09900.f8

Team, R. C. (2013). *A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.

Thigpen, J. L., Dillon, C., Forster, K. B., Henault, L., Quinn, E. K., Tripodis, Y., . . . Limdi, N. A. (2015). Validity of international classification of disease codes to identify ischemic stroke and intracranial hemorrhage among individuals with associated diagnosis of atrial fibrillation. *Circulation: Cardiovascular Quality and Outcomes, 8*(1), 8–14. doi:10.1161/circoutcomes.113.000371

Veltkamp, R., Rizos, T., & Horstmann, S. (2013). Intracerebral bleeding in patients on antithrombotic agents. *Seminars in Thrombosis and Hemostasis, 39*(8), 963–971. doi:10.1055/s-0033-1357506

Waktare, J. E. P. (2002). Atrial fibrillation. *Circulation, 106*(1), 14–16. doi:10.1161/01.cir.0000022730.66617.d9

Wann, L. S., Curtis, A. B., Ellenbogen, K. A., Estes, N. A., 3rd, Ezekowitz, M. D., Jackman, W. M., . . . Tracy, C. M. (2011). 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Journal of the American College of Cardiology*, *57*(11), 1330–1337. doi:10.1016/j.jacc.2011.01.010

CHAPTER 6

STROKE OUTCOMES IN ATRIAL FIBRILLATION PATIENTS RELATED TO GERIATRIC SYNDROMES AND ORAL ANTITHROMBOTIC THERAPIES FOR THE PREVENTION OF THROMBOEMBOLISM

Abstract

In patients having both AF and geriatric syndromes (dementia, frailty, and falls), the use of antithrombotic therapy may produce complications. This study observed electronic medical records of participants age 65 years and older with AF and geriatric syndromes, and another group with AF and no geriatric syndromes, to ascertain variations in stroke occurrence over a 3-year follow up, while considering the type of stroke prevention therapy used: oral anticoagulants (OACs), antiplatelet agents (ATPLs), or none of these (No OAC/ATPL). The primary outcome was the presence of a stroke. Multivariable Cox hazard regression determined the treatment correlation with risk-adjusted stroke incidence. Kaplan-Meier survival curves were used for survival analysis. The 1,580 older adults with AF in the sample had an average age of 75.8 ± 7.6 years, and of those, 822 (52.1%) were males. After adjustment for risk, older adults with atrial fibrillation and geriatric syndrome(s) prescribed antiplatelet drugs were 9.1 times more

likely to have a stroke or TIA than those without geriatric syndrome(s) (HR = 9.11; CI 2.52, 32.97; $p < .0001$). For those prescribed oral anticoagulants, the risk of stroke was increased by 89% in the presence of geriatric syndromes (HR = 3.4; CI 1.25, 2.87; $p = .003$), while the increased risk for those on no antithrombotic therapy was more than 3-fold, although differences were not significant (HR = 3.4; CI 0.5, 21.77; $p = .196$). Older AF patients with geriatric syndromes are at higher risk of developing strokes than older AF patients without dementia and/or frailty and /or falls, regardless of whether they are prescribed oral anticoagulant drugs, antiplatelet drugs, or no drugs for thromboembolism prophylaxis.

Introduction

As the Baby Boom generation ages, the number of older people in the United States is increasing, and the cardiac arrhythmia known as atrial fibrillation (AF) is projected to increase from the currently affected 2.3 million people to 5.6 million people by 2050 (Tsang et al., 2003). AF represents the most significant stroke (cerebrovascular accident [CVA] or transient ischemic attack [TIA]) risk factor due to the formation of a thrombus resulting from blood immobility in the atria. In clinical practice, oral anticoagulation therapy diminishes stroke burden by 64% (Hart, Pearce, & Aguilar, 2007). Some patients are not able to take oral anticoagulants due to previous bleeding, a history of falls, or personal preference; in this case, ATPLs such as aspirin and/or clopidogrel may be prescribed instead, reducing the stroke risk as much as 40% (Hart et al., 2007).

Common geriatric syndromes with high relevance to therapy for the prevention of

thromboembolism in AF are dementia, frailty, and falls. As patients age, these conditions typically increase in prevalence, presenting clinicians with questions relating to their treatment. These patients present a challenge due to higher incidences of comorbidities (Morley, 2008; Morley et al., 2013).

Caregivers utilize guidelines from Europe and the United States to implement the correct thromboembolism-prevention treatment. Providers generally use the CHA_2DS_2-VAS_c scoring system to predict individual stroke risk (Lip, Frison, Halperin, & Lane, 2011; Lip, Tse, & Lane, 2012). This schema assists providers in reaching conclusions about recommending oral anticoagulation to older individuals. The CHA_2DS_2-VAS_c schema assigns one point for each of the following: congestive heart failure, hypertension, diabetes mellitus, vascular disease (coronary artery disease, peripheral artery disease, or aortic plaque), age 65 to 74 years, and sex (female gender). The schema additionally assigns 2 points each for previous **s**troke/TIA or age $\geq$ 75 years. A combined score of 0 to 9 results from using this schema, and is used to calculate annual stroke risk values from 0.2% for a CHA_2DS_2-VAS_c score of 0, up to 15.2% for a CHA_2DS_2-VAS_c score of 9 (Pamukcu, Lip, & Lane, 2010).

Dementia affects predominantly older individuals, who are difficult to treat due to impaired memory, and its most pervasive form is Alzheimer's dementia, constituting 60% to 80% of all dementias; vascular dementia comprises 20% of all dementias (Bunch et al., 2010). Patients diagnosed with AF and taking oral anticoagulation are at increased risk for the development of dementia (Kwok, Loke, Hale, Potter, & Myint, 2011).

Frailty expresses as decreases in strength, mobility, balance, body mass, overall activity levels, and capacity to endure physical or psychological stress. Frailty also

contributes to serum protein concentration changes, potentially modifying the pharmacokinetics of oral anticoagulation or antiplatelet therapy (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004; McIsaac, Bryson, & van Walraven, 2016). Frail older individuals are very vulnerable, and are at higher risk for stroke from AF than their nonfrail counterparts.

The occurrence of falls is also a problem related to aging, and may also result from diseases, medications, or a combination of these factors. Falls are also associated with the development of frailty and dementia. They specifically present a problem in individuals taking oral anticoagulation because of the potential to develop a hemorrhage. In older individuals who experience falls, 1 in 10 will sustain a major injury (Tay, Lane, & Lip, 2009). A mortality rate of 45% is attributed to patients on oral anticoagulation who suffer from falls (Jacobs, Billett, Freeman, Dinglas, & Jumaquio, 2009).

This study observed electronic medical records of participants age 65 years and older with both AF and geriatric syndromes (dementia, frailty, and falls), and another group with AF and no geriatric syndromes, to ascertain variations in stroke occurrence over a 3-year follow up, while considering the type of stroke prevention therapy used (OACs, ATPLs, or no OAC/ATPL).

Methods

Sampling and Setting

This was a database study of electronic medical records, which were obtained from the enterprise data warehouse (EDW) at the University of Utah. This was a retrospective, descriptive, longitudinal study in which each patient was determined to

have a diagnosis of AF using ICD-9 code 427.31 recorded by the healthcare providers in the patient's visit notes, electrocardiogram, or both during the period January 1, 2010 to December 31, 2014. Subjects included in the study had the diagnosis of AF for varying periods of time. According to the literature and the advice of a professional coder, ICD-9 code 427.31 is generally used to capture patients with the diagnosis of AF (Piccini et al., 2012). The dataset included outpatient and inpatient records. Consistent with procedures developed by previous investigators to validate the target diagnosis, subjects were included in the sample only if they had two or more visits related to the AF diagnosis, ensuring that they were treated on a long-term basis for this disease (Piccini et al., 2012). Patients with a confirmed diagnosis of AF who were older than 65 years were selected in the first tier of sampling (see Figure 6.1).

Exclusion Criteria

In an attempt to ensure that subjects with AF were not taking anticoagulant therapy for an indication other than stroke prevention, patients with diagnoses of mural thrombus, deep vein thrombosis, pulmonary embolism, and any mechanical heart valves were excluded from analysis. The final sample size was 1,580 patients.

Sample Verification

To determine the accuracy of AF diagnosis in the final pool of subjects, 532 individual chart reviews were performed. This process was facilitated by using the WartHog program at the EDW at the University of Utah. This program allows researchers to instantly locate specific phrases in the medical records, such as *atrial*

fibrillation, eliminating records unrelated to the term searched and highlighting only the search terms used. Not only does WartHog allow for rapid searching, it is also extremely accurate. Of the 532 charts retrieved based on the ICD-9 code applied, we were able to document the diagnosis of AF in all but 11. This represents 98% accuracy in locating AF diagnoses, which is higher than the average of 82.2% that is found in the literature when assessing accuracy of ICD-9 diagnoses of AF (Thigpen et al., 2015).

Procedures

Medication and disease files were summarized by patient identification number, using aggregate/structure query language (SQL) commands in SPSS (version 23.0; Green & Salkind, 2010) and R (version 3.2; Team, 2013). The ICD-9 diagnoses were also determined for all covariate variables included in the CHA_2DS_2-VAS_c schema. Those variables are listed in Table 6.1.

Geriatric-Syndrome Groups

The 1,580 subjects were divided into those who did and did not have diagnoses indicative of one of three geriatric syndromes: falls, dementia, or frailty. All geriatric syndrome diagnoses occurred prior to the first event of a stroke or last observation. All codes for diagnoses were derived from the literature and personal communications with a professional coder and local and internationally recognized researchers on the topic of frailty (Garwood & Corbett, 2008; Hubbard et al., 2015; Jacobs et al., 2009; Jacobs et al., 2014; Morley et al., 2013; Piccini et al., 2012; Rockwood et al., 2005; Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). The ICD-9 codes used to define geriatric

syndromes and experts who were consulted are identified in Table 6.1. Subjects without indication of these ICD-9 codes prior to a stroke or TIA event constituted the no-geriatric-syndrome group.

Therapy Groups

Medication orders following the diagnosis of AF were extracted to identify the use of anticoagulant or antiplatelet agents commonly used to prevent thrombotic complications. All subjects were divided into 1 of 3 therapy groups: oral anticoagulation group (OAC; warfarin, apixaban, rivaroxaban, dabigatran), antiplatelet agents group (ATPL; aspirin, clopidogrel, prasugrel, ticagrelor), and no-oral anticoagulation/antiplatelet agents (no OAC/ATPL). If subjects had a record of both antiplatelet and oral anticoagulant therapy, they were assigned to the oral anticoagulant group. Of the 1,580 subjects, 440 (27.8%) were prescribed both therapies concomitantly. It is difficult to separate these therapies because of comorbidities in older individuals, particularly coronary artery disease, for which many patients take aspirin.

Outcome Variables

The outcomes variables for stroke were derived from the dataset using the ICD-9 codes listed in Table 6.1. In this study patients were followed from the beginning of their medication therapy until they dropped from observation or experienced an event. These types of data are right-censored (Singer & Willett, 2003).

Statistical Analysis

Omnibus tests were performed in order to detect general differences among means, and proportions using ANOVA and chi-square tests on demographic variables, components of the covariate, and outcomes by therapy group and presence of geriatric syndromes (Kutner, Nachtsheim, Neter, & Li, 2005). Post hoc pairwise comparisons among categorical and continuous variables were completed using proportion and Tukey tests. *P* values for the post hoc comparisons were adjusted using the Bonferroni method, declaring significance at $\alpha = .05/3$. *P* values for the post hoc comparisons involving continuous variables were adjusted using the Tukey method, with significance at $\alpha = .05$ (Kutner et al., 2005). Adjustments to post hoc *p* values were made in order to control the probability of encountering one or more Type-I error rates (Kutner et al., 2005). All other statistical tests and estimates were carried out at a significance level of $\alpha = .05$.

Multivariable Cox hazard regression was utilized to determine stroke outcomes by medication groups. Six multivariable Cox hazard regression models were utilized to determine if significant differences existed in stroke outcomes by medication group in the groups with and without geriatric syndromes. The first Cox model, 1-year follow up, observed individuals only over a 1-year period. If an individual's observation time was more than one period, then that person was considered as being observed for 1 full year, and having no stroke event. Similar constructions were done for the 2-year and 3-year follow-up models. In each Cox model, the censoring variable was 0 if the stroke did not occur within the observation period, and 1 if it did. Individuals in the Cox models were censored for either of two circumstances: a subject's last event was not a stroke (another type of medical event, moved away, or died—lost to follow-up), or a subject reached the

end of the observation period alive, not having experienced a stroke. A single covariate was used for the Cox model, a summed version of the CHA_2DS_2-VAS_c schema, which comprises the baseline risk factors for stroke. An overall hazard ratio was estimated from a dataset in which patients were censored only when they were lost to follow-up. One-, two-, and three-year hazard ratios are estimated from datasets in which patients can be censored if they reach one, two, or three years without experiencing any event, or are lost to follow up before those respective times.

Kaplan-Meier curves were also used to help compare differences in survival according to stroke outcomes of those with and without geriatric syndromes. A Kaplan-Meier curve is a nonparametric estimate of a survival curve. The formula used to construct the curve does not include an adjustment for risk factors. To compare survival curves controlling for risks, a Cox model was used instead (Singer & Willett, 2003). Visual separation of the curves between drug groups may imply that one drug group has lower survival than another.

Results

Description of Groups

Among the 1,580 subjects in this study, the average patient age was 75.7 ± 7.6 years; 822 (52.1%) were male; 542 had geriatric syndromes; 364 (63.8%) were prescribed an OAC; 115 (21.2%) were prescribed ATPL therapy; 81 (14.9%) were not prescribed either OAC or ATPL therapy; and 1,038 had no geriatric syndrome.

In Table 6.2, we compare groups with and without geriatric syndromes and groups prescribed three types of thromboembolic prophylaxis treatment; those with

geriatric syndromes were older. Within the group without geriatric syndromes, those prescribed anticoagulants were older than those prescribed antiplatelet drugs. Higher average CHA_2DS_2-VAS_c risk scores were found in the group with geriatric syndromes. Those who did not have geriatric syndromes were more likely to be prescribed an OAC, both warfarin and the direct anticoagulant drugs, while those with geriatric syndromes were more likely to be prescribed clopidogrel. Approximately 44% of both groups were prescribed aspirin. On the components of the CHA2DS2-VAS_c scores, those with geriatric syndromes were more likely to be female, to have hypertension, and to have peripheral vascular disease. Aortic plaque, diabetes, and coronary artery disease had similar prevalence regardless of the presence of geriatric syndromes (see Table 6.3). Mean time until censored for subjects with geriatric syndromes was 1003.21 ± 588.84 days. Mean time until censored for subjects without geriatric syndromes was 1074.03 ± 551.01 days.

Differences on Outcomes

The mean time to stroke or TIA was shorter for those with geriatric syndromes. Regardless of the presence of geriatric syndromes, the mean time to stroke was the shortest, measured in days, for those not prescribed antithrombotic therapy (see Table 6.4). Those with geriatric syndromes had a higher stroke incidence at all time points; however, all strokes/TIAs in those not prescribed antithrombotic therapy occurred in the first year, and the cumulative incidence over 3 years was lower in those not prescribed antithrombotic therapy, whether or not they had geriatric syndromes. However, these findings are not controlled for risk.

Kaplan-Meier survival estimates controlled for risk are shown comparing subjects with and without ATPL drugs according to the antithrombotic therapy group: those prescribed oral OACs (Figure 6.2), those prescribed ATPLs (Figure 6.3), and those prescribed no OAC/ATPL (Figure 6.4). Overall, when risk of stroke was controlled based on the application of CHA_2DS_2-VAS_c scoring, the two curves diverge, indicating that subjects without geriatric syndromes were less likely to develop a stroke when prescribed either OAC, ATPL, or no OAC/ATPL.

Risk-Adjusted Hazard Ratios

When risk was controlled, patients with geriatric syndromes were more likely to have a stroke or TIA than those without geriatric syndromes at every time point (Table 6.5). Overall, the increased risk ranged from 89% for those prescribed oral anticoagulants to over 9-fold for those prescribed antiplatelet agents. Older adults with geriatric syndromes who were prescribed no antithrombotic therapy had 3.5 times the risk of stroke or TIA than those without diagnosed geriatric syndromes.

Discussion

In this study we compared older adults with atrial fibrillation who had geriatric syndromes to those without geriatric syndromes to examine the outcomes of stroke and TIA in patients prescribed oral anticoagulants, antiplatelet drugs, and no oral anticoagulation or antiplatelet therapies. The results of the study confirm that patients with AF and geriatric syndromes are more likely to develop strokes when compared to their counterparts without geriatric syndromes.

CHA_2DS_2-VAS_c scores were higher in those with geriatric syndromes. This

observation was anticipated because patients with geriatric syndromes have increased numbers of comorbidities, such as cardiovascular disease and diabetes, as well as other risk factors for the development of thromboembolism. In clinical practice, these patients are the most difficult to treat. Not only do they typically have numerous comorbidities, but they may also experience falls. Subsequent to the development of falls, clinicians are reluctant to continue oral anticoagulation and will most commonly stop this therapy (Zimetbaum et al., 2010). In some instances these patients will be switched to antiplatelet therapy, which may also cause bleeding events (Cairns et al., 2008). Although debated in the literature, no consensus currently exists regarding the use of antiplatelet therapy, such as whether patients should be on aspirin only, the appropriate dosing of aspirin, and whether clopidogrel needs to be used in addition to aspirin. Antiplatelet therapy typically reduces stroke risk by 40%, whereas warfarin reduces stroke risk by 68% (Hart et al., 2007). In the ACTIVE-W trial (Hart et al., 2007), oral anticoagulation was superior to the combination of aspirin and clopidogrel. Despite the fact that current national and international guidelines recommend oral anticoagulation therapy for aging individuals, in real practice, patients with geriatric syndromes will be offered this therapy 51% of the time (Bo et al., 2016); thus, only half of these patients will have the opportunity to discuss this therapy with their family and clinicians.

Our understandings of the processes related to the development of dementia are still emerging. It has been noted previously that patients with AF are at increased risk for the development of dementia when compared to patients without AF (Bunch et al., 2010; Charidimou et al., 2015). The process of the progression of dementia is multifactorial and complex, but as this process initiates, these older individuals are more likely to begin

displaying physical and cognitive deficits, typically leading to prescription noncompliance, which will in turn lead to the inability to follow up and check INR levels as recommended. AF patients taking warfarin for thromboembolism prevention who do not spend the requisite time within the therapeutic range (INR 2–3) are more likely to develop dementia. If these patients' INR levels are subtherapeutic, they are more likely to develop microemboli; if INR levels are supratherapeutic, they are more likely to develop microbleeds (Bunch et al., 2010, Jacobs et al., 2014). These micro rather than macro insults to the brain lead to the development or more rapid progression of dementia. The decline of these patients, both cognitively and physically, leads to frailty and falls. Providers are faced with these common scenarios in geriatric settings. Direct OACs (apixaban, rivaroxaban, and dabigatran) are new on the market and present an attractive alternative to warfarin in that they do not require blood-level monitoring or dietary adjustments, pose fewer side effects, and cause fewer drug interactions. Perhaps these medications will offer a better option for oral anticoagulation therapy, when compared to warfarin, as use outcomes of these drugs are evaluated over time.

The major challenge in managing these frail patients is that we do not have a standard definition of frailty, which contributes to the potential for patients to not receive appropriate diagnoses and/or therapy. Moreover, these patients may reside in the community as opposed to being institutionalized or hospitalized (Fried et al., 2001).

Most often, geriatric syndromes are interrelated and will evolve simultaneously. For example, an older individual with developing dementia will most likely suffer from falls due to balance problems, and over time will become frail due to decreased appetite, increased struggles with mobility, weakening of the muscles, and inability to withstand

stress. If this type of individual resides at home, family assistance will become absolutely necessary; the other alternative would be placement in an assisted care facility.

Many older individuals are quite resistant to relocation from their cherished home, but most often they will not be able to function at full capacity, performing the necessary daily tasks of cleaning, cooking, buying groceries, and so forth. These concerns can be doubly impactful if an older husband and wife reside in the same home, with both of them requiring outside assistance. This is a scenario frequently encountered by healthcare providers, and because the potential for a fall in this type of situation is quite high, providers are somewhat reluctant to prescribe oral anticoagulation due to the potential for a fall and a resultant bleed (Pugh, Pugh, & Mead, 2011).

In this study we determined that patients with geriatric syndromes were more likely to develop stroke/TIA than patients with no geriatric syndromes. These same patients with geriatric syndromes also had greater numbers of comorbidities and were older when compared to those with no geriatric syndromes. These findings are consistent within the literature and suggest that the potential reasons for the underutilization of oral anticoagulation are at least partially due to the greater number of comorbidities and older age of these patients (Jacobs, Cutler, Day, & Bunch, 2014). Patients without geriatric syndromes have fewer comorbidities and are more likely to be anticoagulated; however, in this study we had patients without geriatric syndromes not being anticoagulated and not taking antithrombotic therapy or antiplatelet agents. This leads to the possible conclusion that patients both with and without geriatric syndromes have some similar disease processes such as diabetes, coronary artery disease, or peripheral vascular disease, contributing to no use of oral anticoagulation therapy. For example, patients with

coronary artery and peripheral vascular diseases are typically prescribed aspirin and clopidogrel for these conditions. Frequently, patients do not wish to add a third antithrombotic agent in the form of an oral anticoagulant due to the fear of bleeding.

Future research should examine this complex problem of oral antithrombotic use in patients with dementia and/or frailty and /or falls. Early identification of these conditions may help to determine further treatment strategies. Looking at various times when oral anticoagulation could be unsafe would allow for the development of improved therapies. Examining frailty and whether to offer palliative versus active treatments is extremely important. Another significant question is when to switch from oral anticoagulation to antiplatelet therapy, if appropriate, and what type of antiplatelet therapy to employ—aspirin only or aspirin plus clopidogrel. This study indicated that the greatest increase in incidence of stroke and TIA among older adults with geriatric syndromes was in the group prescribed antiplatelet therapy, so extreme caution may be warranted. Direct oral anticoagulants present a newer and potentially safer treatment modality to that of warfarin. Because these agents are relatively new, their efficacy and safety in geriatric patients need to be established through future studies.

Limitations

This observational study included baseline characteristics and used one multifactorial risk indicator in the multivariable modeling, but may still contain residual confounding. Observational, retrospective, and longitudinal in design, the study cannot define causality but can recognize associations. The accuracy and comprehensiveness of the study is directly related to the charting done in patient records by their providers. The

integrated EMR did not allow us to include diagnoses, drugs prescribed, or events that took place external to the academic healthcare system at which the study was conducted. While falls and frailty are known to be underreported as a general rule, we included only falls and frailty cases recorded in patient charts. This fact contributed to the lesser number of subjects in the groups with these diagnoses. As no consensus exists on the description of frailty, experts in that field were consulted; in addition, we extracted diagnosis codes from within the literature to secure a usable definition of frailty for this study. Some patients in the study were lost to follow up (no further EMR documentation was available, although the subject may still have been alive and treated elsewhere). These patients could potentially have contributed more stroke events had they remained in the study, which may have provided more statistical power in comparisons among the treatment groups. The duration of AF varied within this group. While we could confirm a drug was ordered, there was no way to determine whether patients adhered to the medication.

Although data in this study included more than 1,500 patient records, the incidence of stroke events in some of the antithrombotic therapy subgroups was still small, and this may have affected the power of the analysis.

Table 6.1

ICD-9 Codes Used to Define Stroke Outcomes Variables

Disease	ICD-9 Codes
Dementia	Dementia in other conditions (Alzheimer's, Lewy bodies, Parkinsonism, epilepsy, frontal, multiple sclerosis, and so forth) 294.10–294.20, 293
	Uncomplicated, 294.8
	Use the following underlying conditions followed by one of the dementia codes listed above:
	Alzheimer's 331.0
	Senile degeneration of brain 331.2
	Dementia with Lewy bodies/Parkinsonism 331.82
	Dementia unspecified 294.10–294.21
	Presenile 290.10–290.13, 290.39
	Senile uncomplicated 290.0
	Senile dementia with delusional features 290.20
	Senile dementia with depressive features 290.21
	Senile dementia with delirium or confusion 290.3
Falls	Fall on or from sidewalk curb E880.1
	Fall on or from stairs or steps E880.9
	Fall from wheelchair E884.3
	Fall from bed E884.4
	Fall on the same level from slipping, tripping, or stumbling E885.9
	Other and unspecified fall E888.0-E888.9
	History of falling V15.88
Frailty	Senility without mention of psychosis (frailty) 797
	Cachexia 799.4 (personal communication with Kenneth Rockwood, January 23, 2016)
Cerebrovascular Accident/Transient Ischemic Attack (CVA/TIA)	Ischemic, stroke 434.91
	Embolic, stroke 434.11
	Thrombotic, stroke 434.01
	Impending 435.9
	Postoperative 997.02
	Personal history without deficits V12.54
	Late effects 438.0–438.9
	Personal history of TIA V12.54
	Unspecified transient cerebral ischemia 435.9
Hypertension	Essential hypertension 401.0–401.9
	Hypertensive heart disease 402.00–402.91
	Hypertensive chronic kidney disease 403.00–403.91
	Hypertensive heart and chronic kidney disease 404.00–404.93
	Secondary hypertension 405.01–405.99
	Hypertensive cerebrovascular disease 437.2
	Intracranial hypertension benign 348.2
	Postoperative hypertension 997.91
Diabetes Mellitus	DM with other specified manifestations 250.80–-250.83
	DM with unspecified complication 250.90–250.93
	Secondary DM without mention of complication 249.00–249.01
	Secondary DM with renal manifestations 249.40–249.41
	Secondary DM with ophthalmic manifestations 249.50–249.51

Table 6.1, Continued

Disease	ICD-9 Codes
Diabetes Mellitus, Continued	Secondary DM with neurological manifestations 249.60–249.61
	Secondary DM with peripheral circulatory disorders 249.70–249.71
	Secondary DM with other specified manifestations 249.80–249.81
	Secondary DM with unspecified complication 249.90–249.91
Congestive Heart Failure (CHF)	Congestive heart failure, unspecified 428.0
	Systolic heart failure 428.20–428.23
	Diastolic heart failure 428.30–428.33
	Combined systolic and diastolic heart failure 428.40–428.43
	Rheumatic heart failure (congestive) 398.91
Coronary Artery Disease (CAD)	Coronary atherosclerosis 414.00–414.07
	Chronic total occlusion of coronary artery 414.2
	Coronary atherosclerosis due to lipid-rich plaque 414.3
	Coronary atherosclerosis due to calcified coronary lesion 414.4
Peripheral Vascular Disease (PVD)	Peripheral vascular disease unspecified 443.9
	PVD in other disease (DM) 443.81
	Atherosclerosis of extremities 440.20-440.4
	Atherosclerosis of other specified arteries 440.8
	Generalized and unspecified atherosclerosis 440.9
	Raynaud's syndrome 443.0
	Occlusion/stenosis precerebral arteries 433.00–433.91
	Atherosclerosis of renal artery 440.1
	Aneurysm–peripheral arteries 442.0–442.9
	Dissection–peripheral arteries 443.21–443.29
Aortic Plaque	Atherosclerosis of aorta 440.0

Table 6.2

Sample Characteristics at Study Entry for Patients With and Without Geriatric Syndromes by Type of Antithrombotic Therapy

Variable	Geriatric-Syndrome Group					No Geriatric Syndrome Group					*p* Value Syndrome Group
	No Drug	Antiplatelet	Oral Anticoagulant	Total	*p* Value Therapy	No Drug	Antiplatelet	Oral Anticoagulant	Total	*p* Value Therapy	
Subject Count (%)	81 (14.9%)	115 (21.2%)	346 (63.8%)	542 (100%)		166 (16%)	224 (21.6%)	648 (62.4%)	1038 (100%)		
Age-Years, Mean (*SD*)	78.8 ± (7.9)	78.9 ± (8.0)	79.2 ± (6.8)	79.1 ± (7.3)	0.9	74.1 ± (7.1)	72.8 ± (6.8)	74.5 ± (7.3)	74.1 ± (7.2)	< .01[c]	< .0001
Fall (% Yes)	53 (65.4%)	85 (73.9%)	259 (74.9%)	397 (73.3%)	0.2						
Dementia (% Yes)	34 (42.0%)	60 (52.2%)	135 (39.0%)	229 (42.3%)	< .0001[c]						
Frailty (% Yes)	11 (13.6%)	5 (4.3%)	22 (6.4%)	38 (7.0%)	0.05						
CHADS-VASC, Mean + (*SD*)	3.5 ± (1.2)	4.1± (1.3)	4.2 ± (1.3)	4.1 ± (1.3)	< .001[a,b]	3 ± (1.1)	3.2 ± (1.3)	3.4 ± (1.3)	3.3 ± (1.3)	< .0001[a,c]	< .0001
Medications											
Warfarin (% Yes)	0 (0%)	0 (0%)	309 (89.3%)	309 (57.0%)		0 (0%)	0 (0%)	517 (79.8%)	517 (49.8%)		< .01
Direct Oral Anticoagulants* (Yes %)	0 (0%)	0 (0%)	60 (17.3%)	60 (11.1%)		0 (0%)	0 (0%)	203 (31.3%)	203 (19.6%)		< .0001
Aspirin (% Yes)	0 (0%)	105 (91.3%)	133 (38.4%)	238 (43.9%)		0 (0%)	209 (93.3%)	247 (38.1%)	456 (43.9%)		1
Clopidogrel (% Yes)	0 (0%)	35 (30.4%)	23 (6.6%)	58 (10.7%)		0 (0%)	52 (23.2%)	37 (5.7%)	89 (8.57%)		0.2
Ticagrelor (% Yes)	0 (0%)	0 (0%)	0 (0%)	1 (0.18%)		0 (0%)	2 (0.9%)	0 (0%)	2 (0.2%)		1

Note. $p < .05$. *Direct oral anticoagulants (apixaban, rivaroxaban, dabigatran). Omnibus F test (continuous variables) or chi-square (categorical variables). [a]No drug versus oral anticoagulant. [b] No drug versus antiplatelet. [c]Oral anticoagulant versus antiplatelet.

Table 6.3

CHA_2DS_2-VASC Score Composition for Patients With and Without Geriatric Syndromes by Type of Antithrombotic Therapy

Variable	Geriatric Syndrome					No Geriatric Syndrome					
	No Drug	Antiplatelet	Oral Anticoagulant	Total	*p* Value[a] Therapy	No Drug	Antiplatelet	Oral Anticoagulant	Total	*p* Value* Therapy	*p* Value Syndrome
Hypertension (% Yes)	39 (48.1%)	69 (60.0%)	231 (66.8%)	339 (62.6%)	< .0001[a]	63 (38.0%)	105 (46.9%)	331 (51.1%)	499 (48.1%)	< .0001[a]	< .0001
Age 75+ (% Yes)	56 (69.1%)	77 (67.0%)	256 (74.0%)	389 (71.8%)	0.3	73 (44.0%)	66 (29.5%)	304 (46.9%)	443 (42.7%)	< .0001[b,c]	< .0001
Age 65–74 (% Yes)	25 (30.9%)	38 (33.0%)	90 (26.0%)	153 (28.2%)	0.3	93 (56.0%)	158 (70.5%)	344 (53.1%)	595 (57.3%)	< .0001[b,c]	< .0001
Diabetes Mellitus (% Yes)	24 (29.6%)	33 (28.7%)	115 (33.2%)	172 (31.7%)	0.6	38 (22.9%)	60 (26.8%)	225 (34.7%)	323 (31.1%)	< .0001[a]	0.9
Coronary Artery Disease (% Yes)	26 (32.1%)	68 (59.1%)	159 (46.0%)	253 (46.7%)	< .0001[b,c]	51 (30.7%)	100 (44.6%)	292 (45.1%)	443 (42.7%)	< .0001[a,b]	0.2
Peripheral Vascular Disease (% Yes)	8 (9.9%)	30 (26.1%)	82 (23.7%)	120 (22.1%)	< .0001[a,b]	15 (9.0%)	28 (12.5%)	76 (11.7%)	119 (11.5%)	0.6	< .0001
Aortic Plaque (% Yes)	7 (8.6%)	22 (19.1%)	58 (16.8%)	87 (16.1%)	0.1	9 (5.4%)	27 (12.1%)	71 (11%)	107 (10.3%)	0.05	< .01
Female Gender (% Yes)	46 (56.8%)	57 (49.6%)	201 (58.1%)	304 (56.1%)	0.3	81 (48.8%)	96 (42.9%)	277 (42.7%)	454 (43.7%)	0.3	< .0001

Note. $p < .05$. Omnibus F test (continuous variables) or chi-square (categorical variables). [a]No drug versus oral anticoagulant. [b]No drug versus antiplatelet. [c]Oral anticoagulant versus antiplatelet.

Table 6.4

Outcomes of Stroke Patients With and Without Geriatric Syndromes On Antithrombotic Therapies and No Antithrombotic Therapies

Variable	Geriatric Syndrome					No Geriatric Syndrome					
	No Drug	Antiplatelet	Oral Anti-coagulant	Total	*p* Value* Therapy	No Drug	Antiplatelet	Oral Anti-coagulant	Total	*p* Value*	*p* Value Syndrome
Mean days to stroke or TIA (mean ± *SD*)	719.4 ± (550.1)	917.1 ± (577.2)	1054.7 ± (584.4)	975.4 ± (589.3)	< .0001[a,b]	930.1 ± (558)	1107.1 ± (529.6)	1067.9 ± (559.3)	1054.3 ± (555.2)	< .01[a,b]	< .01
Overall stroke or TIA (% Yes)	3 (3.7%)	16 (13.9%)	54 (15.6%)	73 (13.5%)	< .0001[a]	2 (1.2%)	3 (1.3%)	43 (6.6%)	48 (4.6%)	< .0001[a,c]	< .0001
1-Year stroke/TIA (% Yes)	3 (3.7%)	8 (7.0%)	14 (4.0%)	25 (4.6%)	0.4	1 (0.6%)	1 (0.4%)	13 (2.0%)	15 (1.5%)	0.2	< .001
2-Year stroke/TIA (% Yes)	3 (3.7%)	10 (8.7%)	21 (6.1%)	34 (6.3%)	0.4	2 (1.2%)	3 (1.3%)	26 (4.0%)	31 (3.0%)	0.05	< .01
3-Year stroke/TIA (% Yes)	3 (3.7%)	12 (10.4%)	32 (9.2%)	47 (8.7%)	0.2	2 (1.2%)	3 (1.3%)	32 (4.9%)	37 (3.6%)	0.08	< .0001

Note. $p < .05$. Omnibus F test (continuous variables) or chi-square (categorical variables). [a]No drug versus oral anticoagulant. [b]No drug versus antiplatelet. [c]Oral anticoagulant versus antiplatelet.

Table 6.5

Risk of Stroke Among Older Adults With Geriatric Syndromes
by Type of Antithrombotic Therapy

Stroke prevention therapies	Hazard Ratio	Standard Error	*p* Value
Oral anticoagulants			
Overall	1.89	0.21	0.0028, CI (1.25, 2.87)
1 Year	1.59	0.4	0.2448, CI (0.73, 3.5)
3 Year	1.57	0.26	0.0823, CI (0.94, 2.62)
Antiplatelet therapy			
Overall	9.11	0.66	8.00E-04, CI (2.52, 32.97)
1 Year	15.07	1.09	0.0128, CI (1.78, 127.6)
3 Year	7.54	0.68	0.0029, CI (1.99, 28.49)
No oral anticoagulant/antiplatelet therapy			
Overall	3.4	0.95	0.1959, CI (0.53, 21.77)
1 Year	6.59	1.19	0.1115, CI (0.65, 67.28)
3 Year	3.4	0.95	0.1959, CI (0.53, 21.77)

Note. Referent = older adults without geriatric syndromes.

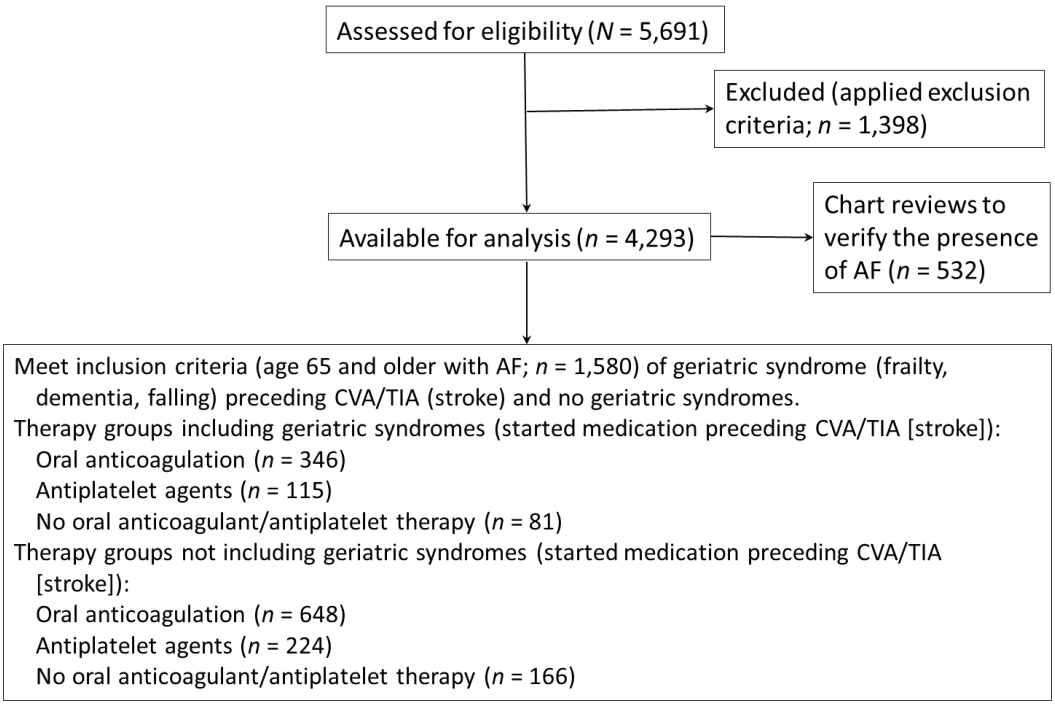

Figure 6.1 Sample selection for the outcome of stroke.

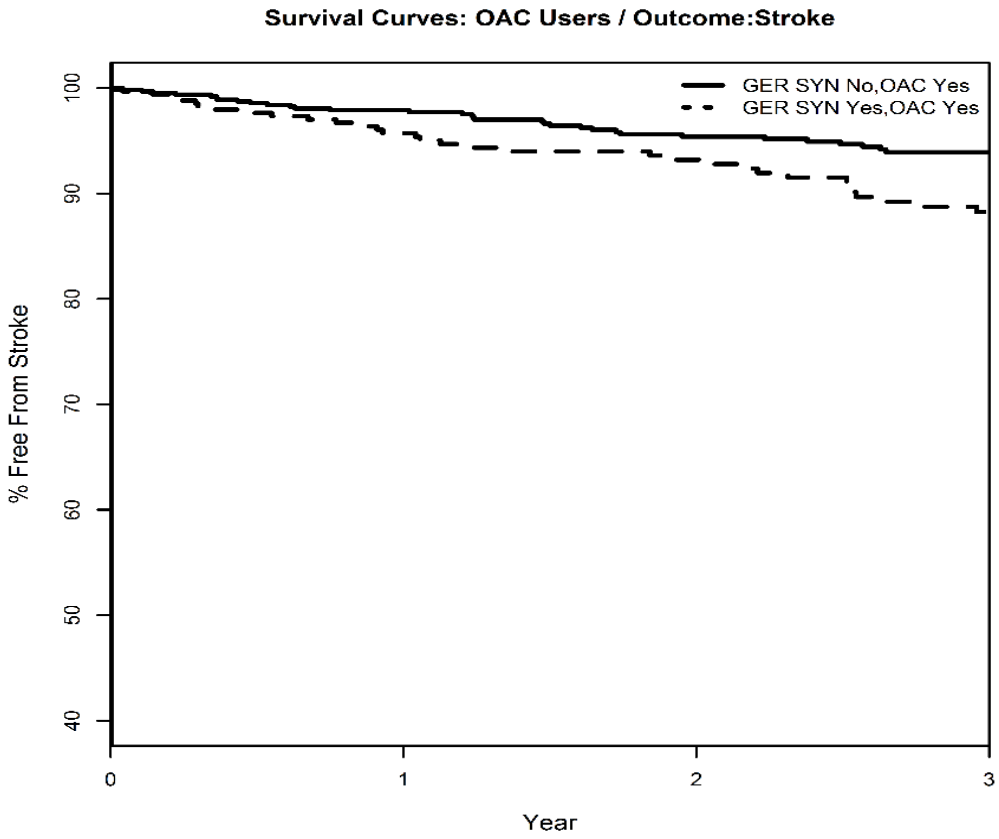

Figure 6.2 Unadjusted overall (3-year) Kaplan-Meier of oral anticoagulant (OAC) with and without geriatric syndromes (GER SYN).

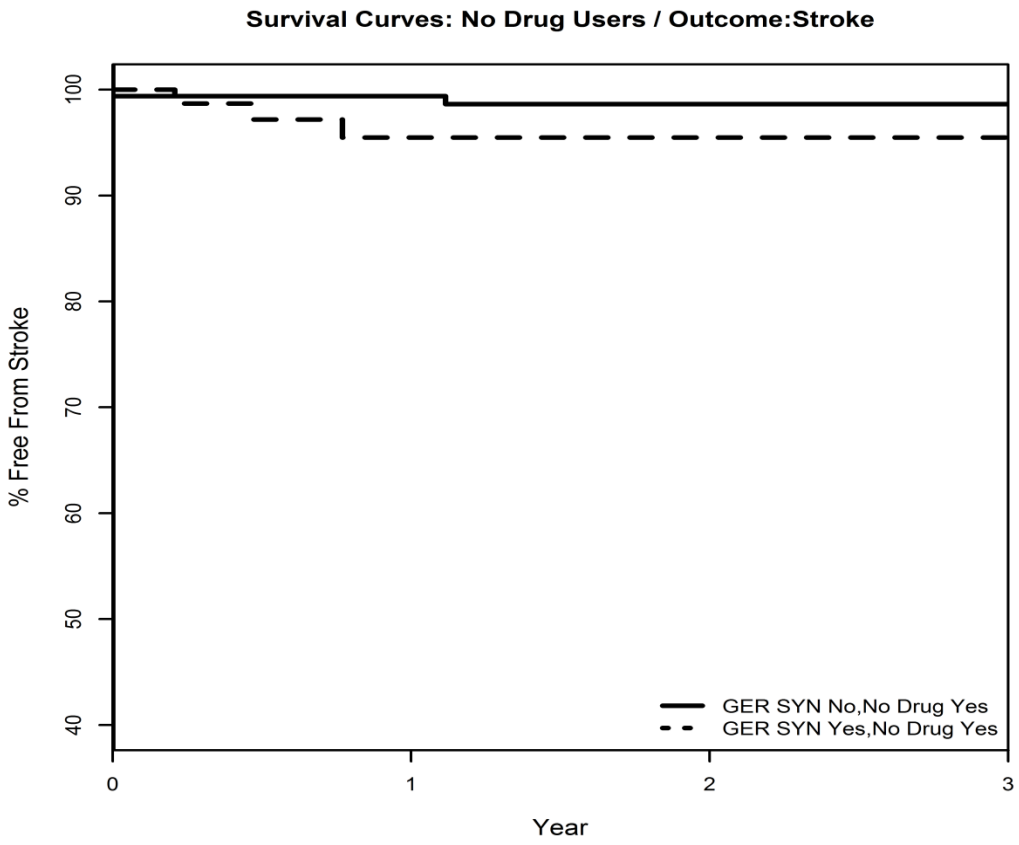

Figure 6.3 Unadjusted overall (3-year) Kaplan-Meier of no oral anticoagulant (OAC) or antiplatelet agents with and without geriatric syndromes (GER SYN).

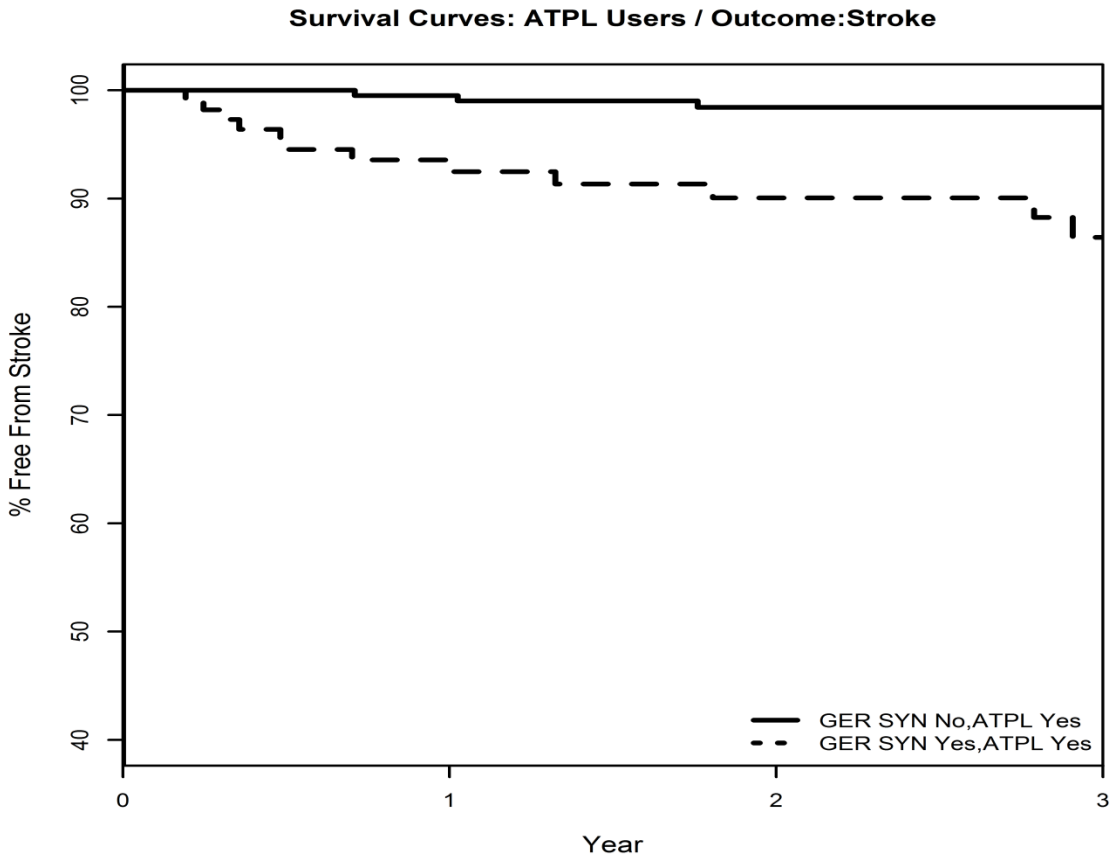

Figure 6.4 Unadjusted overall (3-year) Kaplan-Meier of antiplatelet agents (ATPL) with and without geriatric syndromes (GER SYN).

References

Ahmad, Y., & Lip, G. Y. (2012). Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: NICE guidance. *Heart, 98*(19), 1404–1406. doi:10.1136/heartjnl-2012-302101

Bo, M., Sciarrillo, I., Maggiani, G., Falcone, Y., Iacovino, M., Grisoglio, E., . . . Gaita, F. (2016). Health status, geriatric syndromes and prescription of oral anticoagulant therapy in elderly medical inpatients with atrial fibrillation. *Geriatrics & Gerontology International*. doi:10.1111/ggi.12730

Bunch, T. J., Weiss, J. P., Crandall, B. G., May, H. T., Bair, T. L., Osborn, J. S., . . . Day, J. D. (2010). Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm, 7*(4), 433–437. doi:10.1016/j.hrthm.2009.12.004

Cairns, J. A., Wittes, J., Wyse, D. G., Pogue, J., Gent, M., Hirsh, J., . . . Pritchett, E. L. (2008). Monitoring the ACTIVE-W trial: Some issues in monitoring a noninferiority trial. *American Heart Journal, 155*(1), 33–41. doi:10.1016/j.ahj.2007.09.011

Camm, A. J., Kirchhof, P., Lip, G. Y., Schotten, U., Savelieva, I., Ernst, S., . . . Zupan, I. (2010). Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace, 12*(10), 1360–1420. doi:10.1093/europace/euq350

Charidimou, A., Shoamanesh, A., Wilson, D., Gang, Q., Fox, Z., Jager, H. R., . . . Werring, D. J. (2015). Cerebral microbleeds and postthrombolysis intracerebral hemorrhage risk: Updated meta-analysis. *Neurology*. doi:10.1212/wnl.0000000000001923

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 59*(3), 255–263.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., . . . McBurnie, M. A. (2001). Frailty in older adults: Evidence for a phenotype. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 56*(3), M146–M156.

Fuster, V., Rydén, L. E., Cannom, D. S., Crijns, H. J., Curtis, A. B., Ellenbogen, K. A., . . . Zamorano, J. L. (2006). ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): Developed in collaboration with the European Heart Rhythm

Association and the Heart Rhythm Society. *Circulation, 114*(7), e257–e354.doi: 10.1093/europace/eul097

Garwood, C. L., & Corbett, T. L. (2008). Use of anticoagulation in elderly patients with atrial fibrillation who are at risk for falls. *Annals of Pharmacotherapy, 42*(4), 523–532. doi:10.1345/aph.1K498

Green, S. B., & Salkind, N. J. (2010). *Using SPSS for Windows and Macintosh: Analyzing and understanding data*. Upper Saddle River, NJ: Prentice Hall Press.

Guyatt, G. H., Akl, E. A., Crowther, M., Gutterman, D. D., Schuünemann, H. J., & the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. (2012). Executive summary. *Chest, 141*(Suppl. 2), 7S–47S. doi:10.1378/chest.1412S3

Hart, R. G., Pearce, L. A., & Aguilar, M. I. (2007). Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of Internal Medicine, 146*(12), 857–867.

Hubbard, R. E., Peel, N. M., Samanta, M., Gray, L. C., Fries, B. E., Mitnitski, A., & Rockwood, K. (2015). Derivation of a frailty index from the interRAI acute care instrument. *BioMed Central Geriatrics, 15*, 27. doi:10.1186/s12877-015-0026-z

Jacobs, L. G., Billett, H. H., Freeman, K., Dinglas, C., & Jumaquio, L. (2009). Anticoagulation for stroke prevention in elderly patients with atrial fibrillation, including those with falls and/or early-stage dementia: A single-center, retrospective, observational study. *American Journal of Geriatric Pharmacotherapy, 7*(3), 159–166. doi:10.1016/j.amjopharm.2009.06.002

Jacobs, V., Cutler, M. J., Day, J. D., & Bunch, T. J. (2014). Atrial fibrillation and dementia. *Trends in Cardiovascular Medicine*. doi:10.1016/j.tcm.2014.09.002

Jacobs, V., Woller, S. C., Stevens, S., May, H. T., Bair, T. L., Anderson, J. L., . . . Bunch, T. J. (2014). Time outside of therapeutic range in atrial fibrillation patients is associated with long-term risk of dementia. *Heart Rhythm*. doi:10.1016/j.hrthm.2014.08.013

Kutner, M. H., Nachtsheim, C. J., Neter, J., & Li, W. (2005). *Applied linear statistical models.* New York, NY: McGraw-Hill.

Kwok, C. S., Loke, Y. K., Hale, R., Potter, J. F., & Myint, P. K. (2011). Atrial fibrillation and incidence of dementia: A systematic review and meta-analysis. *Neurology, 76*(10), 914–922. doi:10.1212/WNL.0b013e31820f2e38

Lip, G. Y., Frison, L., Halperin, J. L., & Lane, D. A. (2011). Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: The HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol

Concomitantly) Score. *Journal of the American College of Cardiology (JACC), 57*(2), 173–180. doi: 10.1016/j.jacc.2010.09.024

Lip, G. Y. H., Tse, H. F., & Lane, D. A. (2012). Atrial fibrillation. *Lancet, 379*(9816), 648–661. doi:10.1016/s0140-6736(11)61514-6

McIsaac, D. I., Bryson, G. L., & van Walraven, C. (2016). Association of frailty and 1-year postoperative mortality following major elective noncardiac surgery: A population-based cohort study. *JAMA Surgery*. doi:10.1001/jamasurg.2015.5085

Morley, J. E. (2008). Hot topics in geriatrics. *Journal of the American Medical Directors Association, 9*(9), 613–616. doi:10.1016/j.jamda.2008.09.002

Morley, J. E., Vellas, B., van Kan, G. A., Anker, S. D., Bauer, J. M., Bernabei, R., . . . Walston, J. (2013). Frailty consensus: A call to action. *Journal of the American Medical Directors Association, 14*(6), 392–397. doi:10.1016/j.jamda.2013.03.022

Pamukcu, B., Lip, G. Y., & Lane, D. A. (2010). Simplifying stroke risk stratification in atrial fibrillation patients: Implications of the CHA2DS2-VASc risk stratification scores. *Age & Ageing, 39*(5), 533–535. doi:10.1093/ageing/afq059

Piccini, J. P., Hammill, B. G., Sinner, M. F., Jensen, P. N., Hernandez, A. F., Heckbert, S. R., . . . Curtis, L. H. (2012). Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993–2007. *Circulation: Cardiovascular Quality and Outcomes, 5*(1), 85–93. doi:10.1161/circoutcomes.111.962688

Pugh, D., Pugh, J., & Mead, G. E. (2011). Attitudes of physicians regarding anticoagulation for atrial fibrillation: A systematic review. *Age & Ageing, 40*(6), 675–683. doi:10.1093/ageing/afr097

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *Canadian Medical Association Journal, 173*(5), 489–495. doi:10.1503/cmaj.050051

Searle, S. D., Mitnitski, A., Gahbauer, E. A., Gill, T. M., & Rockwood, K. (2008). A standard procedure for creating a frailty index. *BioMed Central Geriatrics, 8*, 24. doi:10.1186/1471-2318-8-24

Singer, J. D., & Willett, J. B. (2003). *Applied longitudinal data analysis: Modeling change and event occurrence*. Oxford: Oxford University Press.

Skanes, A. C., Healey, J. S., Cairns, J. A., Dorian, P., Gillis, A. M., McMurtry, M. S., . . . Nattel, S. (2012). Focused 2012 update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for stroke prevention and rate/rhythm control. *Canadian Journal of Cardiology, 28*(2), 125–136. doi:10.1016/j.cjca.2012.01.021

Tay, K. H., Lane, D. A., & Lip, G. Y. H. (2009). Challenges facing anticoagulation among the elderly and frail. *Age & Ageing*, *38*(2), 140–142. doi:10.1093/ageing/afn295

Team, R. C. (2013). *A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.

Thigpen, J. L., Dillon, C., Forster, K. B., Henault, L., Quinn, E. K., Tripodis, Y., . . . Limdi, N. A. (2015). Validity of international classification of disease codes to identify ischemic stroke and intracranial hemorrhage among individuals with associated diagnosis of atrial fibrillation. *Circulation: Cardiovascular Quality and Outcomes, 8*(1), 8–14. doi:10.1161/circoutcomes.113.000371

Tsang, T. S., Petty, G. W., Barnes, M. E., O'Fallon, W. M., Bailey, K. R., Wiebers, D. O., . . . Gersh, B. J. (2003). The prevalence of atrial fibrillation in incident stroke cases and matched population controls in Rochester, Minnesota: Changes over three decades. *Journal of the American College of Cardiology*, *42*(1), 93–100.

Wann, L. S., Curtis, A. B., Ellenbogen, K. A., Estes, N. A., 3rd, Ezekowitz, M. D., Jackman, W. M., . . . Tracy, C. M. (2011). 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Journal of the American College of Cardiology*, *57*(11), 1330–1337. doi:10.1016/j.jacc.2011.01.010

Zimetbaum, P. J., Thosani, A., Yu, H. T., Xiong, Y., Lin, J., Kothawala, P., & Emons, M. (2010). Are atrial fibrillation patients receiving warfarin in accordance with stroke risk? *American Journal of Medicine, 123*(5), 446–453. doi:10.1016/j.amjmed.2009.11.015

CHAPTER 7

CONCLUSIONS, FUTURE NURSING RESEARCH, AND IMPLICATIONS FOR NURSING SCIENCE

The number of older people in the United States increases as the Baby Boom generation ages. America's population distribution is changing due to the 10,000 Baby Boomers turning 65 each day during the next decade (Cohn & Taylor, 2010; Harden & Watman, 2015). Our healthcare system is evolving as older people live longer with numerous comorbidities, providing healthcare that is becoming more individualized and personalized. These factors require more resources and that more research be dedicated to finding more efficient ways of delivering care to older individuals. It is evident that improvement of our healthcare system is essential.

The nursing profession is at the forefront of increasing knowledge about personalized care. Nursing professionals are faced with challenges linked to providing care to the aging population. Preparation for this care is vital due to the increased demand for gerontological nurses. The National Hartford Center of Gerontological Nursing Excellence exists to prepare more and better educated nursing professionals in gerontological nursing (Harden & Watman, 2015). This initiative started in 2000 and continues its efforts to educate nurses nationally and internationally. The current shortage

of gerontological nurses requires that more nursing professionals be trained. Future nurses must be proficient in gerontological topics, research, collaboration, and overall public health (Sheetz, 2012).

One of the initiatives of the National Institute of Nursing Research (NINR) was to develop innovative questions that will lead the way to an innovative future in nursing research (Grady, 2015). One of the NINR's innovative question topics is related to the integration of new technologies to provide physiological feedback, such as detection of AF, and how it can be integrated to provide better healthcare outcomes (Grady, 2015). The presence of new technologies and innovative ways of managing patients with home monitoring, personal emails, innumerable smart devices, and frequent nursing interventions will direct our healthcare system in the future. Nursing science is also undergoing scientific advances related to patient care. Nurses provide care based on previous research that allows them to incorporate this knowledge into practice. Nurses provide care to older individuals at every level of nursing practice, whether in a doctor's office, hospital, home care, or hospice, advanced practice nurses provide care to older individuals in an even wider variety of settings.

Many older individuals who require care will have AF, which brings along with it another potential comorbidity in the form of increased stroke risk, making OACs central to the care of those patients. Nursing research informs nurses as providers of care with regard to AF.

Our understanding of complex conditions such as frailty and dementia is evolving, and currently nurses provide care to an increased number of older individuals with these conditions (Morley, 2008; Rockwood et al., 2005). It is absolutely necessary to

focus on these conditions when educating gerontological nurses. Gerontological research frequently focuses on these difficult and multifaceted conditions because it is encountered more frequently as nurses provide care to older individuals. The definition of frailty is still debated, but it is agreed that this multipart condition encompasses psychological and physiological components that are not completely understood (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004; Fried et al., 2001).

Geriatric syndromes are conditions that share similarities but are not accepted as diagnostic criteria for a particular disease process, as they are typically not well defined (Inouye, Studenski, Tinetti, & Kuchel, 2007). Healthcare providers encounter geriatric syndromes in various settings when working with older individuals. Most frequently, medical professionals focus on the main complaint and how to treat that. The nursing profession is the link that brings together various disciplines for assessing and treating these geriatric syndromes. The nursing profession focuses on the individual as a whole and assesses all facets of the patient's life. The most important task of the nursing professional in this setting is to determine how best to assist these older individuals in each particular situation.

Declines associated with dementia are gradual, slowly progressing into cognitive and physical deficits. The physical deficits will ultimately result in frailty and falls, whereas the cognitive deficits will result in the inability to withstand psychological stress. Nursing professionals must consider each patient's social and economic situation in order to determine their comprehensive care requirements. Another vital help that nursing professionals provide these patients is bringing patient and family together to discuss the patient's situation and concerns, while educating them all on the most important points of

the patient's circumstance. Patient education is extremely important in all areas, particularly when it comes to oral anticoagulation for thromboembolism prevention in the older frail individual.

The presence of geriatric syndromes in these individuals presents additional aspects of care which need to be considered and discussed with family and other providers. Issues related to oral anticoagulation, stroke risk in AF patients, and hemorrhage risk should be discussed with the patient and family, especially if a patient is presenting with dementia after a fall. Normally, family members will rely on providers, but these decisions are extremely important and must be made by informed family members and healthcare providers. Geriatric syndromes affect families of older individuals in many ways; for example, change of residence, placement in a nursing care facility, caregiver assistance, which medication will be continued, and how to get to scheduled appointments. As nursing professionals assist in a multidisciplinary approach to these and other problems, patients and their families will enjoy a better chance of making informed decisions about their healthcare.

This retrospective observational study addressed the incidences of strokes and hemorrhages in AF patients age 65 and older who had been diagnosed with dementia, frailty, and/or falls. Focusing on three therapeutic approaches to thromboembolism prevention, the study revealed that patients who are prescribed OAC and antiplatelet therapy benefit from these therapies. This potentially happens because the subgroup population is older, with increased comorbidities and high mortality rates. Additionally, these patients are more likely to develop complications from prescribed OACs and need to be switched to antiplatelet therapy. The role of the nursing provider is to anticipate

these complications to allow for changes in patient treatment plans and to be vigilant about possible complications of these therapies. Whether nursing professionals are working in the clinic or hospital environment, they will encounter older patients prescribed OACs. It is common knowledge among nurses that those patients prescribed OACs are at increased risk of bleeding. Moreover, patients who are prone to falls and have been diagnosed with dementia and/or frailty are more likely to develop hemorrhages and potential complications due to the number of existing comorbidities.

Through this study, we have shown that not only are patients with the above diagnoses prone to the development of bleeds when prescribed OACs, but also when prescribed antiplatelet therapy. In fact, antiplatelet therapy in this subgroup of patients may be as harmful in terms of bleeds as OACs. This is an interesting finding, demanding that caregivers of these patients ensure that appropriate monitoring is ongoing. The presumption that antiplatelet therapy is less harmful than OACs was not confirmed in this study, which warns providers to be extremely careful working with this patient subgroup.

In the comparison of the incidence of strokes in the subgroup of AF patients with dementia, falls, and frailty to AF patients without dementia, falls, and frailty, we found that strokes are more frequent among patients with these three geriatric syndromes. This allows caregivers to be more alert to any stroke symptoms in this subgroup. Antiplatelet therapy is also used in this population, which had similar patterns as those taking OACs.

Distributions of CHA_2DS_2-VAS_c/HAS-BLED Scores by Group

In Chapter 4 we examined the incidence of strokes in AF patients with geriatric syndromes according to the type of stroke-prevention therapy: OAC, ATPL, and no

OAC/ATPL. CHA2DS2-VASc scores in the oral anticoagulation group were represented by a nice bell-shaped distribution, with the highest number of subjects having a score of 4. This group represents high stroke risk and was appropriately anticoagulated. CHA2DS2-VASc scores in the antiplatelet agents group were also represented by a bell-shaped distribution, with the highest number of subjects having a score of 4. This group represents high stroke risk, which according to guidelines should be anticoagulated. CHA2DS2-VASc scores in the no-antithrombotic group were represented by a bell-shaped distribution as well, with the highest number of subjects having a score of 3. This group represents high stroke risk, which according to guidelines also needs to be anticoagulated. It is thought-provoking that all of the subjects in this study were at high risk for a stroke; however, not all of them were anticoagulated. On the other hand, the presence of geriatric syndromes causes providers and patients either to stop completely, or not even begin oral anticoagulation therapy due to the perceived risks associated with geriatric syndromes (Hylek et al., 2006).

In Chapter 5 we observed occurrences of hemorrhages in AF patients with geriatric syndromes, contingent on the type of stroke-prevention therapy. HAS-BLED scores in the oral anticoagulation group were represented by a bell-shaped distribution, with the highest number of subjects having a score of 3, which represents the highest bleeding risk. HAS-BLED scores in the antiplatelet agent group indicated the highest number of subjects having a score of 2. HAS-BLED scores in the no-antithrombotic therapy group indicated the highest number of subjects also having a score of 2. Interestingly, the OAC group had the highest HAS-BLED score: 3. Typically patients with high CHA2DS2-VASc scores will have high HAS-BLED scores; however,

guidelines recommend that these patients be anticoagulated to prevent a stroke/TIA (Camm et al., 2010).

In Chapter 6 we compared two groups of patients with and without geriatric syndromes while taking into consideration three types of stroke-prevention therapy: OAC, ATPL, and no OAC/ATPL. For the geriatric syndromes groups, CHA2DS2-VASc scores in the OAC group were represented by a bell-shaped distribution, with the highest number of subjects having a score of 4; the CHA2DS2-VASc scores in the ATPL therapy group were represented by a bell-shaped distribution, with the highest number of subjects having a score of 4; the CHA2DS2-VASc scores in the no-OAC/ATPL group were represented by a bell-shaped distribution, with the highest number of subjects having a score of 4. For the no-geriatric-syndrome groups, the CHA2DS2-VASc scores in the OAC group were represented by a bell-shaped distribution, with the highest number of subjects having a score of 4; the CHA2DS2-VASc scores in the ATPL therapy group were represented by a bell-shaped distribution, with the highest number of subjects having a score of 3; the CHA2DS2-VASc scores in the no-OAC/ATPL group were represented by a bell-shaped distribution, with the highest number of subjects having a score of 3.

If we compare the geriatric-syndromes group to the no-geriatric-syndromes groups, we can conclude that patients in the geriatric syndromes groups were represented by the higher numbers of comorbidities, with higher CHA2DS2-VASc scores. Oral anticoagulation groups in geriatric-syndromes and no-geriatric-syndromes groups had the highest CHA2DS2-VASc scores and were appropriately anticoagulated. Antiplatelet agent groups were also represented by high CHA2DS2-VASc scores, with the no-

geriatric-syndromes group having the lowest CHA2DS2-VASc scores; however, according to guidelines, these subjects should be anticoagulated. The no antithrombotic therapies groups with geriatric syndromes had higher CHA2DS2-VASc scores when compared to no geriatric syndromes. Nevertheless, both groups should have been anticoagulated according to guidelines.

This study revealed that patients with geriatric syndromes exhibit higher CHA2DS2-VASc scores when compared to those with no geriatric syndromes, and that they exhibit higher HAS-BLED scores in the OAC group. Yet, not all of these patients in the study were anticoagulated, even when indicated according to guidelines. Subjects who were taking antiplatelet therapy and were also indicated for anticoagulant therapy according to guidelines may have declined the addition of oral anticoagulant therapy due to the fear of bleeding complications, or may possibly have experienced bleeding complications in the past. Subjects not taking any antithrombotic therapy, but according to guidelines were indicated as candidates for anticoagulant therapy, may have declined these therapies due to experiencing previous falls and hemorrhages.

Future Research

Presently, existing guidelines do not include recommendations that would include older individuals with dementia, frailty, and falls. This is something that needs to be considered, especially in the future, when our healthcare system will need to accommodate larger numbers of older individuals with these conditions. This study lays the groundwork for future research that will provide information that should be included in the guidelines, and inform providers and patients about treatments and outcomes of AF

patients with these conditions.

Future research is required to address numerous questions related to this issue; the inclusion of randomized controlled trials or pragmatic clinical trials that address and correct one glaring inadequacy of this type of trial, which does not typically include the very old individuals with multiple comorbidities and multiple medications; and prospective and retrospective studies to examine the following questions:

- Should we consider both age and comorbidities in deciding on the treatment for AF in older patients with dementia, falls, and frailty?
- What is the optimal OAC treatment for this subgroup—warfarin, or the newer direct oral anticoagulants (DOACs)?
- What is the dose of DOACs?
- What are the outcomes of strokes/TIAs, hemorrhages, and mortality for these older individuals on these therapies?
- What is the optimal antiplatelet therapy for this subgroup of older individuals—aspirin, and which dose, aspirin and clopidogrel, and which dose?
- What are the preferences of patients and caregivers in relation to these therapies, and how can they obtain help from clinicians?

These and other questions, if answered, will paint a picture of optimal treatment for older individuals with these conditions. Nursing science strives to optimize patient care and treatment of older individuals with AF and dementia, frailty, and falls; it is one of many challenging areas of research and nursing practice.

References

Camm, A. J., Kirchhof, P., Lip, G. Y., Schotten, U., Savelieva, I., Ernst, S., . . . Zupan, I. (2010). Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace, 12*(10), 1360–1420. doi:10.1093/europace/euq350

Cohn, D., & Taylor, P. (2010). Baby boomers approach 65—Glumly. *Pew Research Social & Demographic Trends*. Retrieved from http://www.pewsocialtrends.org/2010/12/20/baby-boomers-approach-65-glumly/

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 59*(3), 255–263.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., . . . McBurnie, M. A. (2001). Frailty in older adults: Evidence for a phenotype. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 56*(3), M146–M156.

Grady, P. A. (2015). A pathway for the future: An update on NINR's innovative questions initiative. *Journal of Nursing Scholarship, 47*(2), 105. doi:10.1111/jnu.12124

Harden, J. T., & Watman, R. A. (2015). The National Hartford Center of Gerontological Nursing Excellence: An evolution of a nursing initiative to improve care of older adults. *Gerontologist, 55*(Supp. 1), S1–S12. doi:10.1093/geront/gnv056

Hylek, E. M., D'Antonio, J., Evans-Molina, C., Shea, C., Henault, L. E., & Regan, S. (2006). Translating the results of randomized trials into clinical practice: The challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. *Stroke, 37*(4), 1075–1080. doi:10.1161/01.STR.0000209239.71702.ce

Inouye, S. K., Studenski, S., Tinetti, M. E., & Kuchel, G. A. (2007). Geriatric syndromes: Clinical, research, and policy implications of a core geriatric concept. *Journal of the American Geriatrics Society*, 55(5), 780–791. doi:10.1111/j.1532-5415.2007.01156.x

Morley, J. E. (2008). Hot topics in geriatrics. *Journal of the American Medical Directors Association, 9*(9), 613–616. doi:10.1016/j.jamda.2008.09.002

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *Canadian Medical Association Journal, 173*(5), 489–495. doi:10.1503/cmaj.050051

Sheetz, A. H. (2012). What are the implications of the Institute of Medicine report “The

future of nursing: Leading change, advancing health" for school nursing practice? *NASN School Nurse, 27*(6), 293–295. doi:10.1177/1942602x12458326