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Comparative Effectiveness and Safety of Non-Vitamin K Antagonists Oral Anticoagulants and  
Warfarin in Elderly Patients with Non-Valvular Atrial Fibrillation and Diabetes

A Thesis presented in partial fulfillment of requirements

for the

Master of Science of Pharmaceutical Sciences

in the Department of Pharmacy Administration

The University of Mississippi

By

Siddhi Korgaonkar

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## ABSTRACT

This study compared the relative effectiveness and safety of non-vitamin K antagonists oral anticoagulants (NOACs) versus warfarin in elderly Medicare beneficiaries with NVAF and diabetes mellitus (DM).

A retrospective cohort study using 2014 - 2016 5% national Medicare data was undertaken. NVAF patients with DM aged  $\geq 65$  years having at least one prescription for NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) or warfarin between July, 2014 and December, 2015 were selected from the database. Date of first NOAC or warfarin prescription was defined as the index date. Patients initiating NOACs were 1:1 matched to warfarin patients on propensity score and index date. Stratified Cox proportional hazards models were used to estimate the clinical outcomes among patients initiating NOAC therapy versus warfarin therapy in the matched cohort.

The matched sample consisted of 4578 patients (2291 in each group). NOACs were found to significantly reduce the risk of stroke/SE compared to warfarin (Hazard Ratio (HR): 0.373, 95% confidence interval (CI): 0.247 - 0.564,  $p < 0.001$ ); but, no significant difference was seen between NOACs and warfarin in terms of reducing the risk of MI (HR: 0.864, CI: 0.594 – 1.257,  $p = 0.446$ ). NOACs were found to significantly reduce the risk of ICH (HR: 0.500, CI: 0.300 – 0.834,  $p = 0.008$ ) and OB (HR: 0.608, CI: 0.424 – 0.870,  $p = 0.007$ ); but no difference was seen in the risk of MGB (HR: 0.862, CI: 0.640 – 1.160,  $p = 0.326$ ) between NOACs and warfarin. NOACs were also found to reduce the risk of all-cause mortality (HR: 0.783, CI: 0.656 – 0.873,  $p = 0.007$ ). The composite of effectiveness and safety outcomes, and all-cause mortality was statistically significant proving

superior overall effectiveness and safety of NOAC therapy to warfarin therapy in terms of risk reduction (HR:0.685, CI:0.587 – 0.801,  $p < 0.001$ ).

Oral anticoagulation therapy with NOACs was found to be more effective than warfarin therapy. Results of this study may assist in clinical decision-making about anticoagulation therapies used in elderly NVAF patients with DM.

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## CHAPTER I: BACKGROUND

### INTRODUCTION

Atrial fibrillation (AF) is the most common heart rhythm disorder in the United States <sup>1</sup>. The annual prevalence of AF in the US population was estimated at 5.2 million in 2010 and projected to increase to 12.1 million by 2030, corresponding to an annual growth rate of 4.3 percent <sup>2</sup>. Advancing age is the most prominent risk factor for AF with a 1-in-4 lifetime risk after age 40 years <sup>3,4</sup>. The Framingham study reported a five-fold increase in the risk of stroke with advancing age in AF patients <sup>5</sup>, while the Scottish Renfrew/Paisley study with a 20-year follow-up found a three-fold increase in the risk of stroke among AF patients <sup>6</sup>. Diabetes is another independent risk factor of AF with a prevalence of ranging from 24 – 30 percent among AF patients <sup>7,8</sup>. The relationship between diabetes mellitus and AF is mutual and reciprocal. Incidence of AF in patients with diabetes has been reported around 14.9% <sup>9</sup>. An observational study assessing the impact of diabetes mellitus (DM) on AF reported that over a mean follow-up of  $7.2 \pm 2.8$  years, diabetic patients without AF at baseline had an age- and sex-adjusted incidence rate of AF 9.1 per 1,000 person-years (95% CI: 8.6–9.7) compared with a rate of 6.6 (95% CI: 6.2–7.1) among nondiabetic patients <sup>10</sup>. Among diabetes patients, AF was independently associated with a 61 percent greater risk for vascular death and all-cause mortality and higher risks for cardiovascular death and heart failure when compared with patients without AF <sup>11</sup>.

Since 1950s, vitamin K antagonists (VKA) such as warfarin and low molecular weight heparins (LMWH) were used for anticoagulation treatment in AF patients. A meta-analysis of



thromboembolic and bleeding outcomes by Hart et al. comparing warfarin to antiplatelet drugs in AF patients found warfarin to reduce the risk of stroke by 60 percent <sup>12</sup>. Bleeding is the most common side effect of warfarin and occurs in up to 41 percent of patients treated with warfarin. Additionally, its use can be cumbersome because of its food and drug interactions, dose adjustment, and need for constant monitoring through laboratory testing <sup>12,13</sup>. Literature reports VKA therapy discontinuation rates of nearly 30-60 percent among patients with AF, and patients who discontinued therapy had significantly poor anticoagulation control in terms of poor International Normalized Ratio (INR), lesser Time in Therapeutic Range (TTR), and resultant underanticoagulation <sup>14-16</sup>. Beginning 2010, a new class of oral anticoagulants, non-vitamin K antagonists oral anticoagulants (NOACs) were introduced in the US market. Between 2010 and 2015, the US Food and Drug Administration (FDA) approved four NOACs – dabigatran, apixaban, rivaroxaban and edoxaban – indicated for thromboprophylaxis in patients with non-valvular AF (NVAf). Of these, dabigatran is a direct thrombin inhibitor while others are factor Xa inhibitors. Direct targeting of factor Xa and thrombin provides a faster onset of action compared to warfarin, predictable pharmacokinetics and pharmacodynamics with a lesser potential for food and drug interactions allows for better fixed dosing schedules without dietary restrictions or routine coagulation monitoring <sup>13</sup>.

Several randomized clinical trials (RCTs) have demonstrated that NOACs have at least equivalent efficacy and safety as compared to warfarin in terms of stroke/systemic embolism (SE) reduction and major hemorrhage rates, in patients with NVAf <sup>17-20</sup>. Results of phase III RCTs conducted in a sub-group of NVAf patients with diabetes report that NOACs have superior efficacy compared to warfarin. However, the safety profile of NOACs present a complex scenario. Bleeding events of NOACs were found to vary by a specific NOAC and dosage. While high dose

edoxaban (60 mg)<sup>20</sup>, as compared to low dose edoxaban (30 mg) and warfarin, reduced major bleeding in both NVAf patients with and without diabetes, apixaban<sup>21</sup> reduced major bleeding only among nondiabetic patients with NVAf, with no significant interaction by diabetes status. Interestingly, in patients with diabetes and NVAf, dabigatran and rivaroxaban were not significantly different from warfarin in reducing the risk of major bleeding, and there was no significant interaction by diabetes status<sup>22,23</sup>.

Proven efficacy and safety in RCTs, and the pharmacological characteristics of NOACs contribute to their practical advantages over traditional VKA therapy in reducing thromboembolic risk<sup>13</sup>. With widespread adoption of NOACs in the routine practice, several observational studies have been conducted to assess real world effectiveness and safety of these drugs<sup>24-31</sup>. These studies report a comparable or superior performance of NOACs to warfarin in stroke/SE reduction in patients with AF, but a variation in bleeding outcomes. Apixaban was found to have the lowest bleeding risk as compared to warfarin followed by dabigatran and rivaroxaban. Rivaroxaban was associated with higher bleeding risk as compared to warfarin, especially in elderly population<sup>32-34</sup>.

While research has been conducted in the geriatric population with AF and diabetic patients with NVAf, no real world evidence is available in comparing the effectiveness and safety of NOAC therapy with warfarin in elderly NVAf patients with comorbid diabetes<sup>35</sup>. NVAf patients with DM are at an increased risk of thromboembolic and bleeding events due to the synergistic effect of DM and aging. Given the complex clinical interactions between AF and diabetes, care for elderly NVAf patients with DM can be complicated. Evidence obtained through this observational study may assist in clinical decision-making pertaining to the choice of oral anticoagulation therapy in patients with simultaneous presence of both AF and DM<sup>35,36</sup>. This study

assessed the comparative effectiveness and safety of NOAC therapy versus traditional warfarin therapy in elderly NVAF patients with concomitant diabetes mellitus using 5% national Medicare data.

## LITERATURE REVIEW

### Atrial Fibrillation – Pathophysiology and Etiology

According to the American Heart Association, atrial fibrillation (AF) is defined as “*a quivering or irregular heartbeat (arrhythmia) that can lead to blood clots, stroke, heart failure and other heart-related complications.*”<sup>1</sup> It is a type of supraventricular tachycardia which starts as brief periods of abnormal beating which become longer and possibly constant over time. The arrhythmia is characterized by chaotic, electrical conduction in the atria. In AF, the cardiac neuronal signals begin in another part of atria or near the pulmonary veins instead of sinoatrial (SA) node. Spreading of faulty neuronal signals in a rapid, disorganized way can cause the atria to fibrillate. These signals then flood the atrioventricular (AV) node causing the ventricles to beat faster.

AF may be classified based on etiology, depending on whether it occurs without identifiable etiology in patients with a structurally normal heart (lone AF), or whether it complicates hypertensive, valvar, ischemic or other structural heart disease. Lone AF accounts for about 15% of the total AF cases.<sup>37</sup> AF maybe termed as non-valvular AF (NVAF) in absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair. If AF occurs in the setting of a primary condition that maybe the cause of the AF such as acute myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute pulmonary disease, it may be classified as secondary AF.<sup>37</sup>

Based on the temporal pattern of the arrhythmia, a system of clinical classification has been recommended. The American College of Cardiology (ACC), American Heart Association (AHA), and the European Society of Cardiology (ESC) recommend in their guidelines the following classification system based on simplicity and clinical relevance.<sup>38</sup> Patients presenting to medical attention may have a *first detected episode* of AF or, if previous episodes have been documented,

*recurrent arrhythmia*. Episodes themselves may be *paroxysmal*, if they terminate spontaneously, usually within seven days, or *persistent* if the arrhythmia continues requiring electrical or pharmacological cardioversion for termination. AF that cannot be successfully terminated by cardioversion, and longstanding (>1 year) AF, where cardioversion is not indicated or has not been attempted, is termed *permanent*.

### **Epidemiology of AF**

AF is the most common clinically significant cardiac arrhythmia in the US.<sup>5</sup> Global prevalence of AF in 2010 was estimated to be around 33.5 million (20.9 million males and 12.6 million females). AF was found to be more prevalent among men than women. Between 1990-2010, the global incidence rate increased from 60.7 per 1000 person-years in males to 77.5 per 1000 person-years, and from 43.8 to 59.5 per 1000 person-years in females.<sup>39</sup> The annual prevalence of AF in the US population was estimated at 5.2 million in 2010 and projected to increase to 12.1 million by 2030, corresponding to a growth rate of 4.3%.<sup>2</sup> The prevalence of AF was found to increase with age, and it is estimated that over 80% of US adults with AF are 65 years or older and approximately 37% are 80 years or older.<sup>40</sup> Aging is associated with regional conduction slowing, anatomically determined conduction delay at the crista, and structural changes that include areas of low voltage in cardiac musculature. In addition, impairment of sinus node function and an increase in atrial refractoriness occurs with aging. This electrical and structural remodeling may explain the increased propensity to AF with aging.<sup>41</sup>

Apart from the elderly population, approximately 12-30% of AF has been reported to occur in athletes and younger individuals as “lone AF” (AF with no underlying heart disease).<sup>40</sup> These patients typically have few comorbidities, yet are usually very symptomatic upon presentation. Researchers from the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study

(N=17,974) reported that African Americans and Latinos were less likely diagnosed with AF when compared with Whites with rates of 3.6%, 2.5%, and 84.7%, respectively. Others have supported the finding of a lower prevalence of AF in African Americans, Hispanics, and Asians compared to Whites.<sup>40,42-44</sup>

### **Economic and Disability Burden Of AF**

High mortality and morbidity associated with AF imposes a significant financial burden. However, coexistent cardiovascular and non-cardiovascular comorbidities make estimation of direct healthcare costs attributable to AF difficult. The total costs of AF were estimated to be around 6.65 billion USD (2005 dollars). Nearly 75% of the costs of AF represent the direct and indirect costs associated with hospitalization. Hospital costs are higher among AF patients not only because of the initial stay but also because of the frequent need for readmission.<sup>45</sup> One study reported that medical costs for people with AF were \$8,705 higher than people without AF.<sup>46</sup> Stroke and hemorrhage associated with non-valvular atrial fibrillation (NVAf) represent a substantial fraction of the economic burden. A retrospective analysis of Medicare beneficiaries found that the hemorrhage and stroke-related cost per NVAf patient was \$64,956 and \$63,781 USD respectively as compared to \$35,474 per NVAf patient without stroke or hemorrhage.<sup>47</sup>

The pathophysiology of AF predisposes patients with AF at a greater thromboembolic risk. It is associated with a 3- to 5- fold increase in risk of stroke and causes 15%–20% of ischemic strokes, which occur when blood flow to the brain is blocked by a clot or by fatty deposits called plaque in the blood vessel lining.<sup>42,6</sup> Strokes caused by complications from AF tend to be more severe than strokes with other underlying causes.<sup>42</sup> AF is a chronic, debilitating disorder which has a progressive negative impact on patients' quality of life. Burden associated with AF, measured as disability adjusted life-years (DALYs), increased by 18.8% in males and 18.9% in females, from

1990 to 2010. Mortality associated with AF was greater among women, and increased 2-fold and 1.9-fold in males and females respectively from 1990-2010.<sup>39</sup> The growing epidemic of AF is responsible for about 750,000 hospitalizations annually and contributes to an estimated 130,000 deaths each year.<sup>48</sup>

### **Risk Factors Of AF**

Other than structural heart diseases, other factors involved in initiation or maintenance of AF may include inflammation, atrial ischemia, autonomic nervous system activity, atrial dilation, and structural fibrosis associated with aging. Familial AF is well described, although at present this subtype of AF is rare.<sup>43</sup> Over the past decade, population-based studies have suggested that AF is a heritable disease.<sup>49,50</sup>

While age and genetics are non-modifiable risk factors for AF, several modifiable risk factors for AF have been identified in the literature. Many modifiable risk factors associated with atherosclerotic vascular disease have also been associated with development of AF.<sup>51</sup> Increased left atrial pressure, as seen with hypertension and some valvular diseases, have been hypothesized to provide a substrate for AF, but the causal link remains unclear. This might explain higher incidence of AF seen among hypertensive patients.<sup>52</sup> Obesity has been found to be associated with increase pericardial fat volume and increased epicardial fat thickness, which may lead to altered atrial electrophysiology and sympathovagal imbalance of the atria.<sup>53,54</sup> Clinically, epicardial fat has been associated with AF.<sup>55</sup> Obstructive sleep apnea is highly prevalent among AF patients. In a prospective analysis, approximately 50% of AF patients had OSA, as compared with 32% of controls.<sup>56</sup> Mechanisms by which OSA contributes to AF risk include intermittent nocturnal hypoxemia/ hypercapnia, surges in sympathetic tone and blood pressure during apneic episodes,

and increased inflammation. These factors may contribute to left atrial remodeling and chamber dilation, contributing to development of AF.<sup>57,58</sup>

Diabetes is an independent risk factor for AF.<sup>59,60</sup> Both AF and type 2 diabetes are chronic diseases that increase in prevalence and severity with age and are each independently associated with an increased risk for stroke, heart failure, and death. In 2015, 30.3 million Americans, or 9.4% of the population, had diabetes. Among older Americans aged 65 years and older, nearly 25.2% or 12.0 million had diabetes.<sup>61</sup> The annual prevalence of AF in the US population was estimated at 5.2 million in 2010 and projected to increase to 12.1 million by 2030, corresponding to a growth rate of 4.3%.<sup>2</sup> Significant research has been conducted to understand the pathophysiological association between diabetes and AF. Diabetes is associated with numerous metabolic defects including insulin resistance, impaired glucose tolerance, proinflammatory mediators, abnormalities of hemostasis, fibrinolysis, angiogenesis and extracellular matrix turnover.<sup>62-64</sup> All of these metabolic changes lead to endothelial dysfunction, abnormal activation of the renin-angiotensin-aldosterone system (RAAS) and acceleration of atherogenesis, which could be responsible for AF occurrence. Diabetes could also cause structural, electrical, electromechanical and autonomic remodeling.<sup>65</sup>

Literature reports that diabetes is associated with a 35% to 60% relative increase in the risk for developing AF after adjustment for confounders.<sup>66-68</sup> Also, AF patients with diabetes were found to have higher mortality and higher rates of myocardial infarction as compared to those with diabetes mellitus alone.<sup>69</sup> The Action in Diabetes and Vascular Disease: preterAx and diamicroN-MR Controlled Evaluation Trial found that in patients with type 2 diabetes, after adjusting for confounders, AF was independently associated with a 61% greater risk for death and all-cause



mortality and higher risks for cardiovascular death and heart failure when compared with patients without AF.<sup>11</sup>

### **Thromboembolic Risk Estimation In AF**

Given the diversity of risk factors involved in development or exacerbation of AF and thromboembolism, several risk scoring systems have been developed to calculate and stratify the risk of stroke. The risk of stroke is estimated using the CHADS<sub>2</sub> score or the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. These scores calculate the risk of stroke by assigning specific weights to major risk factors of AF which can cause stroke. The 2014 American Heart Association (AHA) /American College of Cardiology (ACC) /Heart Rhythm Society (HRS) guidelines and the 2016 European Society of Cardiology (ESC) guidelines on AF recommend using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score for thromboembolic risk estimation.<sup>43,70</sup> However, the major clinical trials of non-vitamin K antagonists oral anticoagulants (NOACs) – the RE-LY trial (dabigatran versus warfarin), the ARISTOTLE trial (apixaban versus warfarin), the ROCKET-AF trial (rivaroxaban versus warfarin) and the edoxaban versus warfarin trial – have used CHADS<sub>2</sub> score for estimating the thromboembolic risk.<sup>17-20</sup>

The CHADS<sub>2</sub> score system is based upon a cumulative scoring system focusing on five major risk factors: congestive heart failure, hypertension, age  $\geq 75$  years, diabetes, and history of stroke or transient ischemic attack.<sup>71</sup> Each factor is scored 1, except the cerebral events scored 2 points, reflecting their increased weight. The original validation of the score classified CHADS<sub>2</sub> score of 1-2 as moderate, and CHADS<sub>2</sub>  $> 2$  as high risk.<sup>71</sup> The CHA<sub>2</sub>DS<sub>2</sub>-VASc score is also based upon a cumulative scoring system focusing on congestive heart failure, hypertension, age  $>75$  years [doubled], diabetes, stroke [doubled], vascular disease, age 65-74 years, sex category [female] to estimate the risk for stroke in patients with AF.<sup>72,73</sup> Both, the 2014 AHA/ACC/HRS

guidelines and the 2016 ESC guidelines on AF recommend using CHA<sub>2</sub>DS<sub>2</sub>-VASc score for calculation of thromboembolic risk since it is more comprehensive and considers more risk factors in predicting the risk of stroke.<sup>43,70,74</sup>

### **Anticoagulation in AF**

Since 1950s, warfarin, a vitamin K antagonist (VKA), has been the mainstay treatment thromboprophylaxis in NVAF (NVAF) patients.<sup>43</sup> It is an oral medication to be administered once daily. Treatment is monitored using prothrombin time (PT) or international normalized ratio (INR) to calculate the time for blood clotting. Bleeding is the most common side effect of warfarin and occurs in up to 41% of patients treated with warfarin, with rates of major bleeding in practice of about 7 – 8% per year.<sup>75,76</sup> An observational study reported that warfarin-related hemorrhage rates were 11.8% among older adults and were highest during first 30 days of warfarin therapy.<sup>14</sup> Other rare yet severe adverse effects include tissue necrosis, calciphylaxis, and systemic atheroemboli and cholesterol microemboli.<sup>77</sup> Thus, although the treatment with warfarin can reduce the risk of stroke by 60% to 70%, its use can be cumbersome because of its food and drug interactions, hemorrhage, dose adjustment and need for constant monitoring through laboratory testing.<sup>43,77</sup>

Recently, the US Food and Drug Administration approved a new class of non-vitamin K antagonist oral anticoagulants (NOACs). NOACs are direct thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban) inhibitors indicated for oral anticoagulation among NVAF patients. Currently, four NOACs are available in the market – dabigatran, apixaban, rivaroxaban and edoxaban.

Phase III clinical trials of these NOACs have demonstrated at least equivalent efficacy and safety as compared to warfarin in terms of stroke/systemic embolism (SE) reduction and major hemorrhage rates, respectively in patients with NVAF.<sup>17–20</sup> For example, in the ARISTOTLE trial

comparing apixaban to warfarin, apixaban at a dose of 5 mg twice daily was found superior to warfarin in preventing stroke/SE (1.27% per year vs 1.60% in warfarin group, hazard ratio with apixaban- 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P = 0.01 for superiority), caused less bleeding (2.13% per year vs 3.09% per year in the warfarin group, hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001) and had lower mortality rates (3.52% vs 3.94%, (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P = 0.047).<sup>17</sup>

### *Comparison of NOACs and VKAs*

The pharmacological characteristics of NOACs contribute to their practical advantages over VKA therapy in reducing thromboembolic risk.<sup>13</sup> Direct targeting of factor Xa and thrombin provides a faster onset of action, predictable pharmacokinetics and pharmacodynamics with a lesser potential for food and drug interactions allows for better fixed dosing schedules without dietary restrictions or routine coagulation monitoring. However, there are disadvantages to NOAC therapy as well. Unlike VKAs, NOACs are eliminated renally; renal impairment affects the efficacy of NOACs and increases the associated risk of bleeding.<sup>14,75,76</sup> Hence, NOACs are not indicated in patients with creatinine clearance (CrCl) < 15 mL/min (apixaban, edoxaban and rivaroxaban) and < 30 mL/min (dabigatran).<sup>78-81</sup> NOACs have a faster onset of action with a short elimination half-life. Hemostasis is restored approximately 12–24 h after cessation of NOACs, assuming normal renal function. If a patient is experiencing non-life-threatening bleeding, discontinuation of the NOACs and supportive management should suffice. However, in case of life-threatening bleeding, in addition to discontinuation of the NOAC, administration of a reversal agent should be considered.<sup>82</sup> Currently, only one reversal agent, idarucizumab is available in the market for reversal of dabigatran-induced anticoagulation.<sup>83</sup> Another factor Xa inhibitor reversal agent-andexanet alfa has demonstrated efficacy in preclinical studies. Similarly, a synthetic small

molecule antidote ciraparantag has shown efficacy in reversal of anticoagulation of all NOACs in rat models.<sup>84</sup> Till these specific reversal agents become available, life-threatening bleeding with NOACs can be a potential deterrent of use.

Indirect mechanism of action of VKAs which results in slower onset and offset of anticoagulation effect, inherent prothrombotic effect of VKAs which increases the risk of stroke in the first 30 days on therapy initiation, narrow therapeutic range necessitating constant monitoring of international normalized ratio (INR) and food and drug interactions with VKA therapy are contributing to their under-prescription in patients with high risk of stroke and systemic embolism.<sup>13</sup> In the GARFIELD-AF registry, 38.0% of patients with a CHADS<sub>2</sub> score  $\geq 2$  did not receive anticoagulant therapy; 7.2% of patients with AF and CHADS<sub>2</sub>  $\geq 2$  had refused treatment for various reasons, including inconvenience of regular blood tests, dietary restrictions, bleeding risk and an under-appreciation or lack of knowledge regarding the risk of stroke.<sup>85</sup> As well as being unwilling to start VKA therapy, many patients with AF who initiated VKA therapy discontinue or are non-adherent. For example, of 125,195 patients newly diagnosed with AF in Canada from 1997 to 2008, 9% did not collect their second prescription of warfarin within the first half year and 32% discontinued therapy within 1 year, rising to 43% at 2 years and 61% at 5 years.<sup>14</sup> Similarly, in a US study, more than one in four new warfarin starters discontinued therapy within a year.<sup>15</sup> In another study, 40% of patients were non-adherent to VKA therapy (>20% of days with missed doses or >10% of days where extra doses were taken in addition to the prescribed dose), and this percentage was significantly associated with poor anticoagulation control.<sup>16</sup> These limitations and inconvenience with VKA therapy and the equivalent efficacy of NOACs, faster onset of action, lack of food and drug interactions, convenient and hassle-free monitoring of

therapy has made NOACs the first choice of treatment for thromboprophylaxis in patients with NVAF.<sup>43,70</sup>

### *Effectiveness of NOACs in-the-real-world studies*

The safety and efficacy of NOACs seen in the randomized clinical trials may not always reflect in real world practice because of the differences in the patient populations, the intensity of follow-up, and the variations in care received by the patients. Several systematic reviews and meta analyses of randomized clinical trials and observational studies have been conducted to compare the efficacy and safety of NOACs versus VKAs in patients with AF.<sup>86-90</sup>

Lin et al. found NOACs to be associated with lower risk systemic stroke/embolism and intracranial bleeding as compared to warfarin. Dabigatran 150 mg and rivaroxaban were associated with greater risk of major bleeding in the elderly population.<sup>86</sup> In a systematic review and meta analyses of 13 RCTs and 27 observational studies (32 for AF), Almutairi et al. found dabigatran and VKAs were comparable for stroke/SE risk in 1 RCT (HR, 0.77 [95% CI, 0.57–1.03]) and 6 observational studies (HR, 1.03 [95% CI, 0.83–1.27]). Rivaroxaban had a 20% decreased risk of stroke/SE in 3 RCTs (HR, 0.80 [95% CI, 0.67–0.95]) compared with VKA, but the effect was nonsignificant in 3 observational studies (HR, 0.78 [95% CI, 0.59–1.04]). Apixaban decreased stroke/SE risk (HR, 0.79 [95% CI, 0.66–0.95]) compared with VKA in 1 RCT, but edoxaban was comparable to VKA (HR, 0.99 [95% CI, 0.77–1.28]) in 1 RCT (no observational studies available for apixaban/edoxaban). Dabigatran, apixaban, and edoxaban decreased the risk of hemorrhagic stroke, mortality, major bleeding, and ICH by 10% to 71% compared with VKAs but not rivaroxaban.<sup>87</sup> Apart from rivaroxaban, all NOACs had a decreased risk of major bleeding. An exhaustive review by Raschi et al. found NOACs to be comparable to VKAs in terms of safety,

efficacy and effectiveness, and indicated a consistent and clinically relevant reduced risk (more than 50%) of intracranial bleeding.<sup>88</sup>

With widespread adoption of NOACs in the routine practice, several observational studies have been conducted worldwide to assess real world safety and effectiveness of these drugs.<sup>24-31</sup> Since edoxaban was approved in early 2015, these studies have compared only 3 NOACs - apixaban, dabigatran and rivaroxaban to warfarin in assessing the effectiveness and safety in AF patients.

Many of these real-world observational studies have been conducted using Danish patient registries. All Danish studies found NOACs to be of comparable effectiveness in reducing stroke/SE as compared to warfarin. However, the bleeding rates differed between individual NOAC.<sup>24-27,91</sup> The advantages with NOAC treatment were most pronounced with standard dose in patients below 80 years, and with dose reduction in patients aged 80 and above.<sup>26</sup>

In the US, real world observational studies to assess effectiveness and safety of NOACs as compared to warfarin have been conducted using administrative claims data.<sup>28-31</sup> In the observational study of elderly NVAf patients using Medicare data, Amin et al. found apixaban (HR, 0.40; 95% CI, 0.31-0.53) and rivaroxaban (HR, 0.72; 95% CI, 0.63-0.83) were significantly associated with lower risk of stroke/SE compared to warfarin. Apixaban (HR, 0.51; 95% CI, 0.44-0.58) and dabigatran (HR,0.79; 95% CI 0.69-0.91) were significantly associated with lower risk of major bleeding; rivaroxaban (HR, 1.17; 95% CI 1.10-1.26) was significantly associated with higher risk of major bleeding compared to warfarin.<sup>31</sup> Yao et al. found that for stroke or systemic embolism, apixaban was associated with lower risk (hazard ratio [HR] 0.67, 95% CI 0.46–0.98, P=0.04), but dabigatran and rivaroxaban were associated with a similar risk (dabigatran: HR 0.98, 95% CI 0.76–1.26, P=0.98; rivaroxaban: HR 0.93, 95% CI 0.72–1.19, P=0.56). For major

bleeding, apixaban and dabigatran were associated with lower risk (apixaban: HR, 0.45, 95% CI 0.34–0.59, P<0.001; dabigatran: HR 0.79, 95% CI 0.67–0.94, P<0.01), and rivaroxaban was associated with a similar risk (HR 1.04, 95% CI 0.90–1.20], P=0.60). All NOACs were associated with a lower risk of ICH.<sup>30</sup> Thus, there were minor consistencies reported in the differential bleeding rates of NOACs amongst themselves and as compared to warfarin.

#### *Comparison of bleeding rates between NOACs and warfarin*

To facilitate a better understanding of NOAC therapy safety, significant amount of research has been conducted to evaluate major bleedings (gastrointestinal, intracranial and other sites) rates associated with NOAC therapy.<sup>32,33,91–97</sup> Some studies have focused on a specific bleeding rates such as gastrointestinal bleeding,<sup>94,95,98</sup> while other have looked into major bleeding rates as a whole.<sup>32,33,91,96,97,99,100</sup> In a systematic review and meta analyses of 16 RCTs and 31 observational studies, Roskell et al. reported that the overall median incidence of major bleeding was 2.1 per 100 patient-years (range, 0.9– 3.4 per 100 patient-years) for RCTs and 2.0 per 100 patient-years (range, 0.2 –7.6 per 100 patient-years) for observational studies.<sup>93</sup> The risk of bleeding increased with age and NOAC-related bleeding risk was higher in patients 65 years of age and older.<sup>32,95</sup> In almost all studies, apixaban was found to have the lowest bleeding risk as compared to warfarin followed by dabigatran and rivaroxaban. Rivaroxaban was associated with higher bleeding risk as compared to warfarin, especially in elderly population. Adeboyeje et al. found that relative to warfarin, dabigatran and apixaban were associated with a 33% lower major bleeding risk, while dabigatran and apixaban were associated with a 48% lower risk of major bleeding compared with rivaroxaban.<sup>100</sup> Xu et al. have ranked NOACs in terms of their gastrointestinal and intracranial bleeding risk. Apixaban 5 mg had the lowest gastrointestinal bleeding risk, while apixaban 5 mg, dabigatran 110 mg, and edoxaban 30 mg had lowest risk of intracranial bleeding.<sup>34</sup>

### *Comparison of NOACs versus warfarin in the elderly population*

Elderly NVAF patients are likely to be more severe and have more comorbidities than their younger counterparts.<sup>40</sup> An aging heart is characterized by several anatomical changes such as regional conduction slowing, atrial remodeling, and structural changes that include areas of low voltage in cardiac musculature. In addition, impairment of sinus node function and an increase in atrial refractoriness occurs with aging.<sup>41</sup> Advancing age is associated with multiple changes in the pharmacokinetics of drugs and volume of distribution, albumin concentrations, impaired renal function, and gastric acid secretion. Of note, advancing age may result in declining renal function and diminished clearance of medications. These patients are also at an increased risk of bleeding from anticoagulants.<sup>101</sup> Patients aged 65 years and older are predisposed to a greater risk of thromboembolic and bleeding events because of their age and require special considerations while initiating anticoagulation therapy.

In separate meta-analyses of NOAC therapy in patients aged 75 years and older, researchers found a similar or superior efficacy of NOACs compared to warfarin in patients with AF.<sup>102,103</sup> A lack of statistical interaction with age in this analysis indicated that the conclusions to be drawn from the benefits of NOACs are similar for elderly patients. In a separate study, Sharma et al reported a similar or superior efficacy of NOACs as compared to VKA in stroke/SE reduction in the elderly. A non-significantly, higher risk of major bleeding than VKA was observed with dabigatran 150mg (OR, 1.18, 95% CI, 0.97-1.44) but not with the 110mg dose. Significantly higher gastrointestinal bleeding risks with dabigatran 150mg (1.78, 1.35-2.35) and 110mg (1.40, 1.04-1.90) and lower intracranial bleeding risks than VKA for dabigatran 150mg (0.43, 0.26-0.72) and dabigatran 110mg (0.36, 0.22-0.61) were also observed. A significantly lower major bleeding risk



compared to VKA was observed for apixaban (0.63, 0.51-0.77), edoxaban 60mg (0.81, 0.67-0.98) and 30mg (0.46, 0.38-0.57) while rivaroxaban showed similar risk.<sup>89</sup>

Observational studies have been conducted to explore the NOAC therapy outcomes in elderly population.<sup>31,104–106</sup> Most of these studies found NOACs to be comparable or superior to warfarin in reduction of stroke/systemic embolism rates in elderly NVAF patients. However, the bleeding rates were different within the NOACs – apixaban had the lowest major bleeding rate followed by low-dose dabigatran 110 mg and edoxaban 30 mg and 60 mg. Higher bleeding risk was associated with rivaroxaban and high-dose dabigatran 150 mg.

#### *Comparison of NOACs versus warfarin in the Diabetes sub-group of AF patients*

While NOACs are indicated for thromboprophylaxis in patients with NVAF, their efficacy and safety has been tested in different sub-groups of NVAF patients such as diabetes, hypertension and chronic kidney disease during the phase III clinical trials.<sup>21–23,107–111</sup>

In a meta-analysis of 7 prospective cohort studies and 4 case-control studies, Huxley et al. found that DM increased the risk of AF by 40% compared to normal patients.<sup>60</sup> In an observational study of the HMO diabetes registry, diabetes was found to be an independent risk factor (26% elevated risk) for AF among women (HR, 1.26 95% CI, 1.08 –1.46), but diabetes was not a statistically significant factor among men (1.09, 0.96 –1.24).<sup>10</sup> In two observational studies, Huang et al. and Peacock et al. found DM coexisting with NVAF to be associated with an increased risk of 1-year all-cause mortality, cardiovascular mortality and a greater incidence of major bleeding.<sup>112,113</sup>

Among different patient subgroups, studies have been conducted to evaluate efficacy and safety of NOACs in AF patients with coexistent diabetes. A meta-analysis by Ruff et al. of the four available NOACs showed no significant association between diabetes and the benefit–risk ratio of NOACs in patients with AF.<sup>102</sup> However, contradictory results related to hemorrhagic risk

have been reported in clinical trials of AF patients with diabetes receiving NOAC therapy. In the ARISTOTLE study comparing apixaban to warfarin, apixaban was associated with significantly lower hemorrhagic risk as compared to warfarin.<sup>21</sup> The RE-LY study comparing dabigatran to warfarin showed comparable bleeding risk but a greater risk reduction of thromboembolic events.<sup>23</sup> A significantly reduced rate of intracranial hemorrhage was reported in diabetic patients receiving dabigatran 110 mg twice daily compared to warfarin, but a non-significant reduction in diabetic patients receiving dabigatran 150 mg twice daily. In the ROCKET-AF study comparing rivaroxaban and warfarin, there was no significant association between diabetes and the risk of hemorrhagic complications.<sup>22</sup>

In another meta-analysis of phase III randomized trials of NOACs versus warfarin in diabetic NVAf patients, Patti et al. did not find any interaction between diabetic status and the benefits of NOACs was found for the occurrence of ischemic stroke, major bleeding, or intracranial bleeding. However, a significant decrease in vascular deaths (1.02% vs. 0.27%) in diabetic NVAf patients as compared to non-diabetics (4.97% vs. 5.99% with warfarin) was reported.<sup>114</sup>

### **Significance of The Study**

AF and diabetes, especially type 2 diabetes, have emerged as global epidemics with significant effects on morbidity and mortality. The prevalence and incidence of AF increases with age.<sup>8</sup> Approximately 5% of the population over the age of 65 years and 10% over the age of 79 years are affected by AF.<sup>115</sup> Nearly 24% of the total population with AF has comorbid diabetes.<sup>116</sup> Based on the meta-analysis of 11 observational studies of 1.6 million patients, diabetes was associated with a 40% increased risk for AF.<sup>42</sup> Given the complex clinical interactions between AF and type 2 diabetes and their associated comorbidities, care for these patients can be complicated, and

whether the simultaneous presence of both AF and type 2 diabetes deserves special consideration with regard to clinical decision making remains unclear.<sup>35</sup>

Randomized clinical trials of NOACs have evaluated the efficacy and safety in different subgroups of patients such as hypertension, diabetes, heart failure and chronic kidney disease, but the idealized conditions of the clinical trials are not always replicated in real-world.<sup>98-105</sup> Several observational studies have explored the safety and effectiveness of NOACs in the general patient population with AF; however, there is a paucity of real-world studies exploring the comparative safety and effectiveness of NOACs versus warfarin in different subgroups of NVAF patients. No observational study has been conducted to evaluate the safety and efficacy of NOAC therapy in elderly NVAF patients with coexistent diabetes. Diabetes and AF are both chronic, severe and infrequently reversible diseases with significant economic and disability burden. With NOACs becoming the first line of anticoagulation therapy for stroke prevention, it is important and necessary to evaluate NOAC therapy outcomes as compared to the traditional warfarin therapy in elderly NVAF patients with diabetes. This study seeks to provide information to assist in clinical decision-making about the comparative effectiveness and safety of NOAC therapy versus warfarin in elderly NVAF patients with coexistent diabetes.

## **RESEARCH OBJECTIVE**

To compare the effectiveness and safety of non-vitamin K antagonists oral anticoagulants (NOACs) (dabigatran, rivaroxaban, apixaban, and edoxaban) versus warfarin in elderly Medicare beneficiaries with non-valvular atrial fibrillation (NVAf) and diabetes mellitus (DM).

## CHAPTER II: METHODOLOGY

### DATA SOURCE

A retrospective cohort study was conducted using the 2014-2016 5% national Medicare administrative claims data from the Centers of Medicare and Medicaid Services (CMS). Medicare is the federal health insurance program for those aged  $\geq 65$  years, people with disabilities, and people with end-stage renal disease in the United States, with an estimated 38 million fee-for-service beneficiaries<sup>117</sup>. Medicare administrative claims include information on hospital inpatient, outpatient, Medicare carrier, Part D, skilled nursing facility, home health agency, and durable medical equipment claims. The medical claims are coded using International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) and 10th Revision (ICD-10-CM), Current Procedural Terminology, or Healthcare Common Procedure Coding System codes. Pharmacy claims include information on drugs dispensed using the National Drug Code coding system.

#### *Study Population*

Elderly patients aged  $\geq 65$  years with NVAF and diabetes mellitus having at least one pharmacy claim for a NOAC (dabigatran, rivaroxaban, apixaban or edoxaban) or warfarin between July 1, 2014 to December 31, 2015 were selected. Index date was defined as the date of first new prescription claim for a NOAC or warfarin between July 1, 2014 to December 31, 2015. To ensure the inclusion of only treatment-naïve NOAC and warfarin users, a rolling pre-index

period of six months was used to confirm that the patients did not have a prior exposure to NOACs or warfarin. The time period from index date to December 31, 2016 was used for identification of outcomes; thus, ensuring that each patient had at least 12 months of follow-up period.

Patients were required to have continuous medical (Part A and Part B) and pharmacy (Part D) enrolment for six months prior to the index date. In Medicare data, beneficiary Part A and Part B enrollment information is available as single variables showing number of months a beneficiary was enrolled in Medicare Part A and Part B in a given calendar year. Since, a rolling pre-index period was used, patients having pre-index period spread across 2014 and 2015 were required to have at least three months of Part A and Part B continuous enrollment in each calendar year. Patients were required to have one or more inpatient or outpatient claims carrying a diagnosis code for NVAf (ICD-9-CM code 427.31 and ICD-10-CM code I48.0, I48.1, I48.2, I48.91)<sup>118</sup> and have at least two outpatient claims or at least one inpatient claim for diabetes (ICD-9-CM code 250.\* and ICD-10-CM code E11.\*) within the six-month pre-index period.<sup>119</sup>

Patients with evidence of valvular heart disease, heart valve replacement or surgery, venous thromboembolism (VTE), pulmonary embolism, transient AF (pericarditis, hyperthyroidism, thyrotoxicity), and end-stage renal disease in the pre-index period were excluded from the study. Patients who underwent hip or knee replacement surgery within six weeks prior to the index date were excluded. This study also excluded beneficiaries with dual eligibility for Medicare and Medicaid, and those enrolled in health maintenance organizations (HMOs) during the study period.

Patients were followed from the index date till the oral anticoagulant (OAC) prescription discontinuation date, switch to another class of OAC drug other than the index drug class, death, loss of continuous enrollment or end of the study period (December 31, 2016), whichever occurred first. Fill dates and days supplied per prescription were used to determine patients' treatment episodes, defined as the period from the first fill date to the date when there were no residual days of supply. Patients were considered as continuing on the treatment as long as they had another medication fill of the same drug class within 45 days of the end of the last treatment episode.<sup>100,104,120,121</sup>

## **OUTCOME MEASURES**

Clinical outcomes associated with NOAC or warfarin therapy were measured from the index date of NOAC or warfarin therapy till the oral anticoagulant (OAC) prescription discontinuation date, switch to another class of OAC drug other than the index drug class, death, loss of continuous enrollment or end of the study period (December 31, 2016), whichever occurred first. Primary outcomes were classified as effectiveness and safety outcomes. Effectiveness outcomes included thromboembolic episodes – stroke or systemic embolism (SE), and myocardial infarction (MI). Safety outcomes included major bleeding episodes - gastrointestinal bleeding (MGB), intracranial bleeding (ICH), and major bleeding from other sites (OB). Composite effectiveness and composite safety outcomes comprising of occurrence of any of the effectiveness or safety outcomes, respectively, were also evaluated. Secondary outcome was a composite of stroke or systemic embolism (SE), myocardial infarction (MI), gastrointestinal bleeding, intracranial bleeding, bleeding from other sites, and all-cause mortality. In case a patient encountered multiple clinical outcomes, the occurrence of the first event was considered for the composite outcome measure. Outcomes were identified using the Medpar, Outpatient, and Carrier files in the Medicare data.

All-cause mortality (i.e. patients who died regardless of the reason for death) was identified based on the date of death information from the Medicare beneficiary summary file.

## COVARIATES`

Pre-index period was used for assessment of patient demographics and clinical characteristics (clinical risk scores, comorbidities, and concomitant medication use). Comorbidities were evaluated using Charlson comorbidity index and chronic disease count. Chronic disease count was a simple total of all chronic conditions ever documented for a patient before the index date. This information was obtained using the Medicare Beneficiary Summary File – Chronic Condition Summary File. Baseline risk of stroke and major bleeding was assessed using the CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc, and HAS-BLED scores. CHA<sub>2</sub>DS<sub>2</sub>-VASc stroke risk score was based on CHADS<sub>2</sub> and calculated as the summed total of the points determined for each diagnosis (congestive heart failure, hypertension, age>75 years, diabetes, and prior stroke or transient ischemic attack, or thromboembolism, vascular disease, aged 65-74 years, and sex). Modified HAS-BLED bleeding risk score was calculated based on evidence of hypertension, abnormal kidney or liver function, stroke, bleeding, age>65 years, and drugs/alcohol abuse or dependence. Labile International Normalized Ratio (INR) is a component of HAS-BLED score. However, since this information is not available in Medicare administrative claims data, modified HAS-BLED score with range 0 to 8 was calculated.<sup>31</sup> Concurrent medication use was assessed based on paper by Kocis et al. which describes the extent to which patients with NVAF take chronic medications, other than anticoagulants, more frequently than once daily.<sup>122</sup>



## STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the baseline characteristics of the study cohort. Frequencies and proportions were reported for categorical variables and means with standard deviations (SD) were reported for continuous variables.

Patients initiating NOAC or warfarin therapy were expected to differ on baseline demographic and clinical characteristics and comorbidities. Since the treatment was main variable of interest, propensity score matching was used to create the final analysis cohort. Propensity scores were calculated for each patient using multivariable logistic regression. Each patient who initiated NOAC therapy was matched with a patient who initiated warfarin therapy using a greedy matching algorithm (i.e. the Mayo gmatch macro)<sup>123</sup> based on the calculated propensity scores and the index date of the therapy. Patients were matched on a 1:1 basis using a caliper width of 0.05 for the propensity score and time period of  $\pm 15$  days for the index date. Standardized mean differences were used to assess the balance of the measured covariates and a difference of less than 10% was used to indicate clinically irrelevant difference in the measured variables between the matched groups.<sup>124,125</sup> Since the propensity score matching algorithm picks out the nearest available match based on the caliper width, patients who initiated NOAC therapy could still differ on baseline characteristics from patients who initiated warfarin therapy. These group differences were calculated using standardized differences in the total and the matched sample (Table 1).

The time to each outcome of interest for the propensity-score-matched NOAC and warfarin treatment cohort was compared using Kaplan–Meier survival curves and tested for differences using log-rank tests. Incidence rates of stroke or SE, MI, and major bleeding episodes in the propensity score-matched cohort were calculated as the number of stroke/SE, MI, and major bleeding events per 100-person years. Stratified Cox proportional hazards regression were used to

compare outcomes in the propensity score-matched cohort, with STRATA statement in PROC PHREG procedure to account for the clustering within matched groups. Proportional hazards assumption was tested and found valid for all outcomes.<sup>126</sup> All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

CHAPTER III:  
COMPARATIVE EFFECTIVENESS AND SAFETY OF NON-VITAMIN K ANTAGONISTS  
ORAL ANTICOAGULANTS AND WARFARIN IN ELDERLY PATIENTS WITH NON-  
VALVULAR ATRIAL FIBRILLATION AND DIABETES

*Formatted as per the requirements of Current Medical Research and Opinion*

# **Comparative Effectiveness and Safety of Non-Vitamin K Antagonists Oral Anticoagulants and Warfarin in Elderly Patients with Non-Valvular Atrial Fibrillation and Diabetes**

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## **Abstract:**

**Objective:** To compare the relative effectiveness and safety of non-vitamin K antagonists oral anticoagulants (NOACs) versus warfarin in elderly Medicare beneficiaries with NVAF and diabetes mellitus (DM).

**Methods:** A retrospective cohort study using 2014 - 2016 5% national Medicare data was undertaken. NVAF patients with DM aged  $\geq 65$  years having at least one prescription for NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) or warfarin between July, 2014 and December, 2015 were selected from the database. Date of first NOAC or warfarin prescription was defined as the index date. Patients initiating NOACs were 1:1 matched to warfarin patients on propensity score and index date. Stratified Cox proportional hazards models were used to estimate the clinical outcomes among patients initiating NOAC therapy versus warfarin therapy in the matched cohort.

**Results:** The matched sample consisted of 4578 patients (2291 in each group). NOACs were found to significantly reduce the risk of stroke/SE compared to warfarin (Hazard Ratio (HR): 0.373, 95% confidence interval (CI): 0.247 - 0.564,  $p < 0.001$ ); but, no significant difference was seen between NOACs and warfarin in terms of reducing the risk of MI (HR: 0.864, CI: 0.594 – 1.257,  $p = 0.446$ ). NOACs were found to significantly reduce the risk of ICH (HR: 0.500, CI: 0.300 – 0.834,  $p = 0.008$ ) and OB (HR: 0.608, CI: 0.424 – 0.870,  $p = 0.007$ ); but no difference was seen in the risk of MGB (HR: 0.862, CI: 0.640 – 1.160,  $p = 0.326$ ) between NOACs and warfarin. NOACs were also found to reduce the risk of all-cause mortality (HR: 0.783, CI: 0.656 – 0.873,  $p = 0.007$ ). The composite of effectiveness and safety outcomes, and all-cause mortality was statistically significant proving superior overall effectiveness and safety of NOAC therapy to warfarin therapy in terms of risk reduction (HR: 0.685, CI: 0.587 – 0.801,  $p < 0.001$ ).

**Conclusion:** Oral anticoagulation therapy with NOACs was found to be more effective than warfarin therapy. Results of this study may assist in clinical decision-making about anticoagulation therapies used in elderly NVAf patients with DM.

**Keywords:** warfarin, stroke, novel oral anticoagulants, atrial fibrillation, diabetes

## INTRODUCTION

Atrial fibrillation (AF) is the most common heart rhythm disorder in the United States [1]. The annual prevalence of AF in the US population was estimated at 5.2 million in 2010 and projected to increase to 12.1 million by 2030, corresponding to an annual growth rate of 4.3 percent [2]. Advancing age is the most prominent risk factor for AF with a 1-in-4 lifetime risk after age 40 years [3,4]. The Framingham study reported a five-fold increase in the risk of stroke with advancing age in AF patients [5], while the Scottish Renfrew/Paisley study with a 20-year follow-up found a three-fold increase in the risk of stroke among AF patients [6]. Diabetes is another independent risk factor of AF with a prevalence of ranging from 24 – 30 percent among AF patients [7,8]. The relationship between diabetes mellitus and AF is mutual and reciprocal. Incidence of AF in patients with diabetes has been reported around 14.9% [9]. An observational study assessing the impact of diabetes mellitus (DM) on AF reported that over a mean follow-up of  $7.2 \pm 2.8$  years, diabetic patients without AF at baseline had an age- and sex-adjusted incidence rate of AF 9.1 per 1,000 person-years (95% CI: 8.6–9.7) compared with a rate of 6.6 (95% CI: 6.2–7.1) among nondiabetic patients [10]. Among diabetes patients, AF was independently associated with a 61 percent greater risk for vascular death and all-cause mortality and higher risks for cardiovascular death and heart failure when compared with patients without AF [11].

Since 1950s, vitamin K antagonists (VKA) such as warfarin and low molecular weight heparins (LMWH) were used for anticoagulation treatment in AF patients. A meta-analysis of thromboembolic and bleeding outcomes by Hart et al. comparing warfarin to antiplatelet drugs in AF patients found warfarin to reduce the risk of stroke by 60 percent [12]. Bleeding is the most common side effect of warfarin and occurs in up to 41 percent of patients treated with warfarin. Additionally, its use can be cumbersome because of its food and drug interactions, dose

adjustment, and need for constant monitoring through laboratory testing [12,13]. Literature reports VKA therapy discontinuation rates of nearly 30-60 percent among patients with AF, and patients who discontinued therapy had significantly poor anticoagulation control in terms of poor International Normalized Ratio (INR), lesser Time in Therapeutic Range (TTR), and resultant underanticoagulation [14–16]. Beginning 2010, a new class of oral anticoagulants, non-vitamin K antagonists oral anticoagulants (NOACs) were introduced in the US market. Between 2010 and 2015, the US Food and Drug Administration (FDA) approved four NOACs – dabigatran, apixaban, rivaroxaban and edoxaban – indicated for thromboprophylaxis in patients with non-valvular AF (NVAf). Of these, dabigatran is a direct thrombin inhibitor while others are factor Xa inhibitors. Direct targeting of factor Xa and thrombin provides a faster onset of action compared to warfarin, predictable pharmacokinetics and pharmacodynamics with a lesser potential for food and drug interactions allows for better fixed dosing schedules without dietary restrictions or routine coagulation monitoring [13].

Several randomized clinical trials (RCTs) have demonstrated that NOACs have at least equivalent efficacy and safety as compared to warfarin in terms of stroke/systemic embolism (SE) reduction and major hemorrhage rates, in patients with NVAf [17–20]. Results of phase III RCTs conducted in a sub-group of NVAf patients with diabetes report that NOACs have superior efficacy compared to warfarin. However, the safety profile of NOACs present a complex scenario. Bleeding events of NOACs were found to vary by a specific NOAC and dosage. While high dose edoxaban (60 mg) [20], as compared to low dose edoxaban (30 mg) and warfarin, reduced major bleeding in both NVAf patients with and without diabetes, apixaban [21] reduced major bleeding only among nondiabetic patients with NVAf, with no significant interaction by diabetes status. Interestingly, in patients with diabetes and NVAf, dabigatran and rivaroxaban were not



significantly different from warfarin in reducing the risk of major bleeding, and there was no significant interaction by diabetes status [22,23].

Proven efficacy and safety in RCTs, and the pharmacological characteristics of NOACs contribute to their practical advantages over traditional VKA therapy in reducing thromboembolic risk [13]. With widespread adoption of NOACs in the routine practice, several observational studies have been conducted to assess real world effectiveness and safety of these drugs [24–31]. These studies report a comparable or superior performance of NOACs to warfarin in stroke/SE reduction in patients with AF, but a variation in bleeding outcomes. Apixaban was found to have the lowest bleeding risk as compared to warfarin followed by dabigatran and rivaroxaban. Rivaroxaban was associated with higher bleeding risk as compared to warfarin, especially in elderly population [32–34].

While research has been conducted in the geriatric population with AF and diabetic patients with NVAf, no real world evidence is available in comparing the effectiveness and safety of NOAC therapy with warfarin in elderly NVAf patients with comorbid diabetes [35]. NVAf patients with DM are at an increased risk of thromboembolic and bleeding events due to the synergistic effect of DM and aging. Given the complex clinical interactions between AF and diabetes, care for elderly NVAf patients with DM can be complicated. Evidence obtained through this observational study may assist in clinical decision-making pertaining to the choice of oral anticoagulation therapy in patients with simultaneous presence of both AF and DM [35,36]. This study seeks to assess the comparative effectiveness and safety of NOAC therapy versus traditional warfarin therapy in elderly NVAf patients with concomitant diabetes mellitus using 5% national Medicare data.

## METHODS

### **Data Source**

A retrospective cohort study was conducted using the 2014-2016 5% national Medicare administrative claims data from the Centers of Medicare and Medicaid Services (CMS). Medicare is the federal health insurance program for those aged  $\geq 65$  years, people with disabilities, and people with end-stage renal disease in the United States, with an estimated 38 million fee-for-service beneficiaries [37]. Medicare administrative claims include information on hospital inpatient, outpatient, Medicare carrier, Part D, skilled nursing facility, home health agency, and durable medical equipment claims. The medical claims are coded using International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) and 10th Revision (ICD-10-CM), Current Procedural Terminology, or Healthcare Common Procedure Coding System codes. Pharmacy claims include information on drugs dispensed using the National Drug Code coding system.

### ***Study Population***

Elderly patients aged  $\geq 65$  years with NVAF and diabetes mellitus having at least one pharmacy claim for a NOAC (dabigatran, rivaroxaban, apixaban or edoxaban) or warfarin between July 1, 2014 to December 31, 2015 were selected. Index date was defined as the date of first new prescription claim for a NOAC or warfarin between July 1, 2014 to December 31, 2015. To ensure the inclusion of only treatment-naïve NOAC and warfarin users, a rolling pre-index period of six months was used to confirm that the patients did not have a prior exposure to NOACs or warfarin. The time period from index date to December 31, 2016 was used for identification of outcomes; thus, ensuring that each patient had at least 12 months of follow-up period.

Patients were required to have continuous medical (Part A and Part B) and pharmacy (Part D) enrolment for six months prior to the index date. In Medicare data, beneficiary Part A and Part B enrollment information is available as single variables showing number of months a beneficiary was enrolled in Medicare Part A and Part B in a given calendar year. Since, a rolling pre-index period was used, patients having pre-index period spread across 2014 and 2015 were required to have at least three months of Part A and Part B continuous enrollment in each calendar year. Patients were required to have one or more inpatient or outpatient claims carrying a diagnosis code for NVAf (ICD-9-CM code 427.31 and ICD-10-CM code I48.0, I48.1, I48.2, I48.91) [38] and have at least two outpatient claims or at least one inpatient claim for diabetes (ICD-9-CM code 250.\* and ICD-10-CM code E11.\*) within the six-month pre-index period [39].

Patients with evidence of valvular heart disease, heart valve replacement or surgery, venous thromboembolism (VTE), pulmonary embolism, transient AF (pericarditis, hyperthyroidism, thyrotoxicity), and end-stage renal disease in the pre-index period were excluded from the study.[30,31] Patients who underwent hip or knee replacement surgery within six weeks prior to the index date were excluded. This study also excluded beneficiaries with dual eligibility for Medicare and Medicaid, and those enrolled in health maintenance organizations (HMOs) during the study period.

Patients were followed from the index date till the oral anticoagulant (OAC) prescription discontinuation date, switch to another class of OAC drug other than the index drug class, death, loss of continuous enrollment or end of the study period (December 31, 2016), whichever occurred first. Fill dates and days supplied per prescription were used to determine patients' treatment episodes, defined as the period from the first fill date to the date when there were no residual days of supply. Patients were considered as continuing on the treatment as long as they had another

medication fill of the same drug class within 45 days of the end of the last treatment episode [40–43].

### **Outcome Measures**

Clinical outcomes associated with NOAC or warfarin therapy were measured from the index date of NOAC or warfarin therapy till the oral anticoagulant (OAC) prescription discontinuation date, switch to another class of OAC drug other than the index drug class, death, loss of continuous enrollment or end of the study period (December 31, 2016), whichever occurred first. Primary outcomes were classified as effectiveness and safety outcomes. Effectiveness outcomes included thromboembolic episodes – stroke or systemic embolism (SE), and myocardial infarction (MI). Safety outcomes included major bleeding episodes - gastrointestinal bleeding (MGB), intracranial bleeding (ICH), and major bleeding from other sites (OB). Composite effectiveness and composite safety outcomes comprising of occurrence of any of the effectiveness or safety outcomes, respectively, were also evaluated. Secondary outcome was a composite of stroke or systemic embolism (SE), myocardial infarction (MI), gastrointestinal bleeding, intracranial bleeding, bleeding from other sites, and all-cause mortality. In case a patient encountered multiple clinical outcomes, the occurrence of the first event was considered for the composite outcome measure. Outcomes were identified using the Medpar, Outpatient, and Carrier files in the Medicare data. All-cause mortality (i.e. patients who died regardless of the reason for death) was identified based on the date of death information from the Medicare beneficiary summary file.

## **Covariates**

Pre-index period was used for assessment of patient demographics and clinical characteristics (clinical risk scores, comorbidities, and concomitant medication use). Comorbidities were evaluated using Charlson comorbidity index and chronic disease count. Chronic disease count was a simple total of all chronic conditions ever documented for a patient before the index date. This information was obtained using the Medicare Beneficiary Summary File – Chronic Condition Summary File. Baseline risk of stroke and major bleeding was assessed using the modified CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc, and HAS-BLED scores. Since the study population consists of NVAF patients with diabetes, diabetes was excluded as a risk factor in calculating CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc risk scores. CHA<sub>2</sub>DS<sub>2</sub>-VASc stroke risk score was based on CHADS<sub>2</sub> and calculated as the summed total of the points determined for each diagnosis (congestive heart failure, hypertension, aged >75 years, prior stroke or transient ischemic attack, or thromboembolism, vascular disease, aged 65-74 years, and sex). Modified HAS-BLED bleeding risk score was calculated based on evidence of hypertension, abnormal kidney or liver function, stroke, bleeding, age >65 years, and drugs/alcohol abuse or dependence. Labile International Normalized Ratio (INR) is a component of HAS-BLED score. However, since this information is not available in Medicare administrative claims data, modified HAS-BLED score with range 0 to 8 was calculated [31]. Concurrent medication use was assessed based on paper by Kocis et al. which describes the extent to which patients with NVAF take chronic medications, other than anticoagulants, more frequently than once daily [44].

## **Statistical Analysis**

Descriptive statistics were used to summarize the baseline characteristics of the study cohort. Frequencies and proportions were reported for categorical variables and means with standard deviations (SD) were reported for continuous variables.

Patients initiating NOAC or warfarin therapy were expected to differ on baseline demographic and clinical characteristics and comorbidities. Since the treatment was main variable of interest, propensity score matching was used to create the final analysis cohort. Propensity scores were calculated for each patient using multivariable logistic regression. Each patient who initiated NOAC therapy was matched with a patient who initiated warfarin therapy using a greedy matching algorithm (i.e. the Mayo gmatch macro) [45] based on the calculated propensity scores and the index date of the therapy. Patients were matched on a 1:1 basis using a caliper width of 0.05 for the propensity score and time period of  $\pm 15$  days for the index date. Standardized mean differences were used to assess the balance of the measured covariates and a difference of less than 10% was used to indicate clinically irrelevant difference in the measured variables between the matched groups [46,47]. Since the propensity score matching algorithm picks out the nearest available match based on the caliper width, patients who initiated NOAC therapy could still differ on baseline characteristics from patients who initiated warfarin therapy. These group differences were calculated using standardized differences in the total and the matched sample (Table 1).

The time to each outcome of interest for the propensity-score-matched NOAC and warfarin treatment cohort was compared using Kaplan–Meier survival curves and tested for differences using log-rank tests. Incidence rates of stroke or SE, MI, and major bleeding episodes in the propensity score-matched cohort were calculated as the number of stroke/SE, MI, and major bleeding events per 100-person years. Stratified Cox proportional hazards regression were used to compare outcomes in the propensity score-matched cohort, with STRATA statement in PROC

PHREG procedure to account for the clustering within matched groups. Proportional hazards assumption was tested and found valid for all outcomes [48]. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

Of 5,833 eligible patients with NVAF and diabetes before propensity score matching, 2,509 patients (43.01%) were initiated on warfarin therapy and 3,324 patients (56.99%) initiated on NOAC therapy between July 1, 2014 and December 31, 2015. Demographic and clinical characteristics of treatment groups before matching are outlined in Table 1a. Patients initiating warfarin therapy were more likely to have history of prior bleeding (21.96% vs. 16.94%,  $p<0.001$ ), congestive heart failure (65.80% vs. 57.19%,  $p<0.001$ ), myocardial infarction (10.20% vs. 7.49%,  $p<0.001$ ), coronary artery disease (46.99% vs. 43.74%,  $p=0.014$ ), and renal disease (60.46% vs. 50.06%,  $p<0.001$ ). However, no significant difference was seen between two treatment groups in the history of stroke (15.46% vs. 14.89%,  $p=0.546$ ). Mean follow-up time for patients initiating NOAC and warfarin therapy was  $12.07\pm 8.23$  months and  $10.11\pm 7.74$  months respectively.

After 1:1 propensity score matching, 2291 warfarin-NOAC matched pairs were obtained. Demographic and clinical characteristics of the matched treatment groups are outlined in Table 1b. Comparison of treatment groups after propensity score matching on baseline demographic and clinical characteristics did not show significant differences (standardized difference  $>10\%$ ). Figure 1 depicts the distribution of the propensity scores before and after matching. Before matching, the distribution of the propensity scores was different between the NOAC and warfarin treatment groups, which indicates that the groups differed significantly in baseline demographics and comorbidities. The graphs overlap almost perfectly in the matched sample indicating that the two groups have a similar distribution of propensity scores. All further analyses were carried out on the propensity-score matched sample.

An evaluation of long-term effectiveness and safety outcomes revealed that a significantly higher proportion of patients initiating warfarin therapy experienced stroke/SE (4.23% vs. 2.44%,



p<0.001) and composite outcome (23.13% vs. 20.12%, p=0.013) as compared to patients who initiated NOAC therapy. Although a greater proportion of patients who initiated warfarin therapy experienced ICH (2.62% vs. 1.79%, p=0.056), OB (4.41% vs. 3.32%, p=0.055), and death (11.17% vs. 10.08%, p=0.231), these differences were not statistically significant. No differences were seen in the proportion of patients experiencing MI (3.58% vs. 3.36%, p=0.686) and MGB (5.33% vs. 5.63%, p=0.649).

**Table 1a. Baseline demographic and clinical characteristics of the study before propensity score matching**

Variable	Warfarin users (N= 2509)		NOAC users (N= 3324)		Absolute Standardized difference
	N /Mean	% / SD	N /Mean	% / SD	
<b>Age, years</b>	77.15	7.22	77	7.29	0.196
<b>Age, years</b>					
<b>65 - 74</b>	990	39.46	1382	41.58	0.050
<b>75 - 84</b>	1072	42.73	1342	40.37	
<b>85 and above</b>	447	17.82	600	18.05	
<b>Gender</b>					0.045
<b>Female</b>	1131	45.08	1526	45.91	
<b>Male</b>	1378	54.92	1798	54.09	
<b>Race</b>					0.043
<b>White</b>	2326	92.71	3086	92.84	
<b>Non-white</b>	183	7.29	238	7.16	
<b>US geographic region</b>					0.186
<b>Northeast</b>	620	24.71	720	21.66	
<b>North Central</b>	682	27.18	733	22.05	
<b>West</b>	350	13.95	449	13.51	
<b>South</b>	857	34.16	1422	42.78	
<b>Baseline clinical characteristics</b>					
<b>Charlson Comorbidity Index score</b>	3.07	2.95	2.54	2.79	0.184
<b>Chronic Disease Count Score</b>	9.00	2.91	8.56	2.98	0.149

<b>Modified CHA<sub>2</sub>DS<sub>2</sub>-VASc score</b>	5.23	1.34	5.10	1.37	0.108
<b>CHADS<sub>2</sub> score</b>	3.57	1.07	3.45	1.10	0.111
<b>Modified HAS-BLED score</b>	3.30	1.01	3.14	0.99	0.157
<b>Medical history</b>					
<b>Prior bleeding</b>	551	21.96	563	16.94	0.127
<b>Prior stroke</b>	388	15.46	495	14.89	0.016
<b>Prior systemic embolism</b>	55	2.19	32	0.96	0.099
<b>Congestive heart failure</b>	1651	65.80	1901	57.19	0.178
<b>Hypertension</b>	2481	98.88	3266	98.26	0.053
<b>Renal disease</b>	1517	60.46	1664	50.06	0.210
<b>Myocardial infarction</b>	256	10.20	249	7.49	0.096
<b>Coronary artery disease</b>	1179	46.99	1454	43.74	0.065
<b>Transient ischemic attack</b>	184	7.33	269	8.09	0.028
<b>Peripheral vascular disease</b>	503	20.05	597	17.96	0.053
<b>Abnormal liver function</b>	178	7.09	187	5.63	0.060
<b>Baseline medication use</b>					
<b>Angiotensin converting enzyme (ACE) inhibitors</b>	903	35.99	1212	36.46	0.010
<b>Diuretics</b>	1318	52.53	1630	49.04	0.070
<b>Statins</b>	1676	66.80	2209	66.46	0.007
<b>Beta blockers</b>	1830	72.94	2454	73.83	0.020
<b>Calcium channel blockers</b>	893	35.59	1185	35.65	0.001
<b>H<sub>2</sub> receptor antagonists</b>	177	7.05	204	6.14	0.037
<b>Proton pump inhibitors</b>	833	33.20	1059	31.86	0.029
<b>Anti-platelet agents</b>	438	17.46	602	18.11	0.017
<b>NSAIDs</b>	206	8.21	347	10.44	0.077
<b>Anti-arrhythmic agents</b>	908	36.19	1239	37.27	0.023
<b>Anti-anginal agents</b>	445	17.74	425	12.79	0.134
<b>Antidiabetic agents</b>	1444	57.55	1896	57.04	0.010
<b>Opioids</b>	901	35.91	1143	34.39	0.032
<b>Antidepressants</b>	630	25.11	834	25.09	0.004
<b>Benzodiazepines</b>	235	9.37	312	9.39	0.006
<b>Potassium supplements</b>	582	23.20	690	20.76	0.060
<b>Thyroid hormonal drugs</b>	543	21.64	789	23.74	0.050
<b>Anti-gout drugs</b>	218	8.69	218	6.56	0.080
<b>Anti-adrenal agents</b>	461	18.37	591	17.78	0.015

NOACs, Non-vitamin K antagonists oral anticoagulants; SD, Standard Deviation

**Table 1b. Baseline demographic and clinical characteristics of the study after propensity score matching**

Variable	Warfarin users (N= 2291)		NOAC users (N= 2291)		Absolute Standardized difference
	N /Mean	% / SD	N /Mean	% / SD	
Age, years	77.15	7.22	77.20	7.25	0.008
Age, years					0.016
65 - 74	909	39.68	926	40.42	
75 - 84	974	42.51	941	41.07	
85 and above	408	17.81	424	18.51	
Gender					0.015
Female	1051	45.88	1036	45.22	
Male	1240	54.12	1255	54.78	
Race					0.015
White	2131	93.02	2130	92.97	
Non-white	160	6.98	161	7.03	
US geographic region					0.034
Northeast	554	24.18	559	24.40	
North Central	601	26.23	568	24.79	
West	313	13.66	317	13.84	
South	823	35.92	847	36.97	
Baseline clinical characteristics					
Charlson Comorbidity Index score	2.98	2.91	2.74	2.86	0.045
Chronic Disease Count Score	8.91	2.93	8.86	2.93	0.016
Modified CHA <sub>2</sub> DS <sub>2</sub> -VASc score	5.23	1.34	5.18	1.37	0.025
CHADS <sub>2</sub> score	3.55	1.08	3.53	1.09	0.017
Modified HAS-BLED score	3.26	1.01	3.23	0.98	0.035
Medical history					
Prior bleeding	474	20.69	447	19.51	0.029
Prior stroke	348	15.19	343	14.97	0.006
Prior systemic embolism	36	1.57	26	1.13	0.038
Congestive heart failure	1456	63.55	1450	63.29	0.005
Hypertension	2263	98.78	2262	98.73	0.004
Renal disease	1331	58.10	1302	56.83	0.025

<b>Myocardial infarction</b>	221	9.65	197	8.60	0.036
<b>Coronary artery disease</b>	1066	46.53	1050	45.83	0.014
<b>Transient ischemic attack</b>	174	7.59	163	7.11	0.018
<b>Peripheral vascular disease</b>	450	19.64	444	19.38	0.007
<b>Abnormal liver function</b>	155	6.77	146	6.37	0.016
<b>Baseline medication use</b>					
<b>Angiotensin converting enzyme (ACE) inhibitors</b>	841	36.71	827	36.10	0.013
<b>Diuretics</b>	1170	51.07	1182	51.59	0.010
<b>Statins</b>	1531	66.83	1540	67.22	0.008
<b>Beta blockers</b>	1680	73.33	1673	73.02	0.007
<b>Calcium channel blockers</b>	825	36.01	824	35.97	0.001
<b>H<sub>2</sub> receptor antagonists</b>	157	6.85	159	6.94	0.003
<b>Proton pump inhibitors</b>	752	32.82	769	33.57	0.016
<b>Anti-platelet agents</b>	413	18.03	396	17.29	0.019
<b>NSAIDs</b>	199	8.69	208	9.08	0.014
<b>Anti-arrhythmic agents</b>	824	35.97	862	37.63	0.034
<b>Anti-anginal agents</b>	375	16.37	343	14.97	0.038
<b>Antidiabetic agents</b>	1310	57.18	1306	57.01	0.003
<b>Opioids</b>	815	35.57	796	34.74	0.017
<b>Antidepressants</b>	562	24.53	599	26.15	0.037
<b>Benzodiazepines</b>	219	9.56	224	9.78	0.007
<b>Potassium supplements</b>	509	22.22	494	21.56	0.016
<b>Thyroid hormonal drugs</b>	495	21.61	550	24.01	0.057
<b>Anti-gout drugs</b>	194	8.47	149	6.50	0.005
<b>Anti-adrenal agents</b>	414	18.07	413	18.03	0.001

NOACs, Non-vitamin K antagonists oral anticoagulants; SD, Standard Deviation

Incidence rates of clinical outcomes are presented in Table 2 and Table 3. As compared to patients initiating warfarin therapy, patients initiating NOAC therapy were found to have significantly lower incidence of stroke/SE as compared to warfarin (2.322 per 100 person-years vs. 4.776 per 100 person-years,  $p < 0.001$ ), ICH (2.909 vs. 1.685,  $p = 0.008$ ), OB (4.966 vs. 3.162,  $p = 0.003$ ), and all-cause mortality (12.330 vs. 9.451,  $p = 0.004$ ). No significant differences were observed in the incidence rates of MI (4.003 vs. 3.186,  $p = 0.383$ ) and MGB (5.991 vs. 5.385,  $p = 0.916$ ) between patients initiating NOACs versus patients initiating warfarin.

**Table 2. Hazard ratio of effectiveness outcomes in propensity-score matched cohort**

Outcome	Incidence rate per 100 person-years		Hazard ratio (95% confidence intervals)	p value
	<i>Warfarin</i>	<i>NOACs</i>		
<b>Stroke/SE</b>	4.776	2.322	0.373 (0.247 - 0.564)	<0.001
<b>Myocardial infarction</b>	4.003	3.186	0.864 (0.594 - 1.257)	0.446
<b>Composite effectiveness outcome<sup>a</sup></b>	8.481	5.279	0.567 (0.428 - 0.757)	<0.001

<sup>a</sup> A composite of stroke, systemic embolism (SE), and myocardial infarction (MI)

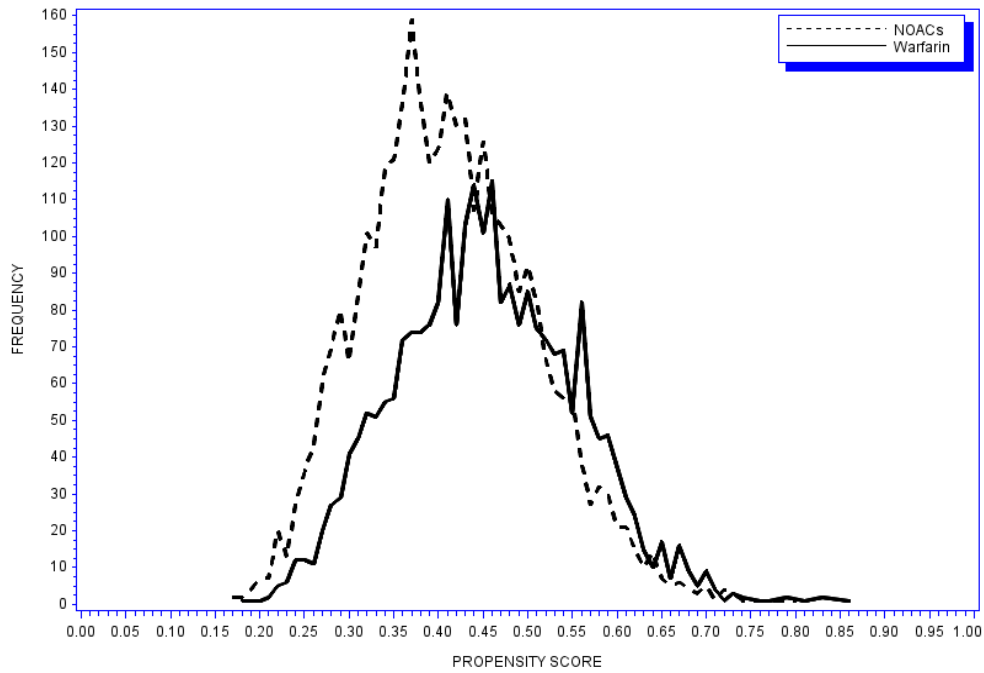
**Table 3. Hazard ratio of safety outcomes in propensity-score matched cohort**

Outcome	Incidence rate per 100 person-years		Hazard ratio (95% confidence intervals)	p value
	<i>Warfarin</i>	<i>NOACs</i>		
<b>Major Bleeding</b>				
<b>Intracranial</b>	2.909	1.685	0.500 (0.300 – 0.834)	0.008
<b>Gastrointestinal</b>	5.991	5.385	0.862 (0.640 – 1.160)	0.326
<b>Other</b>	4.966	3.162	0.608 (0.424 – 0.870)	0.007
<b>Composite safety outcome<sup>a</sup></b>	12.786	9.669	0.701 (0.563 - 0.873)	0.002
<b>All-cause mortality</b>	12.330	9.451	0.783 (0.656 – 0.935)	0.007
<b>Composite outcome<sup>b</sup></b>	27.444	19.999	0.685 (0.587 - 0.801)	<0.001

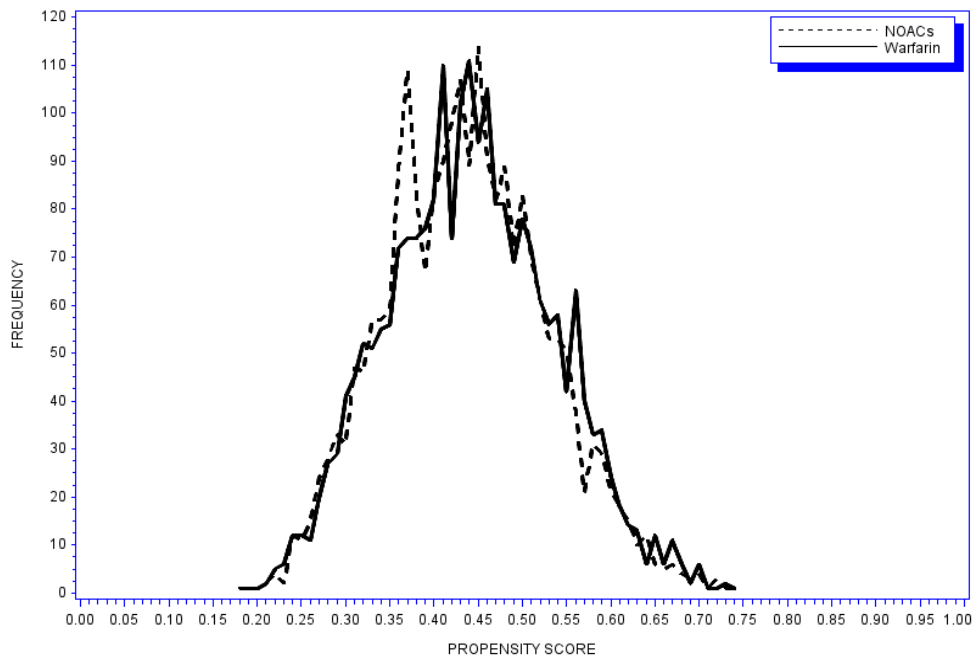
<sup>a</sup> A composite of ICH, MGB, and OB

<sup>b</sup> A composite of stroke, systemic embolism (SE), myocardial infarction (MI), gastrointestinal bleeding (MGB), intracranial bleeding (ICH), bleeding from other sites (OB), and all-cause mortality

**Distribution of Propensity Scores of the Sample before Matching**

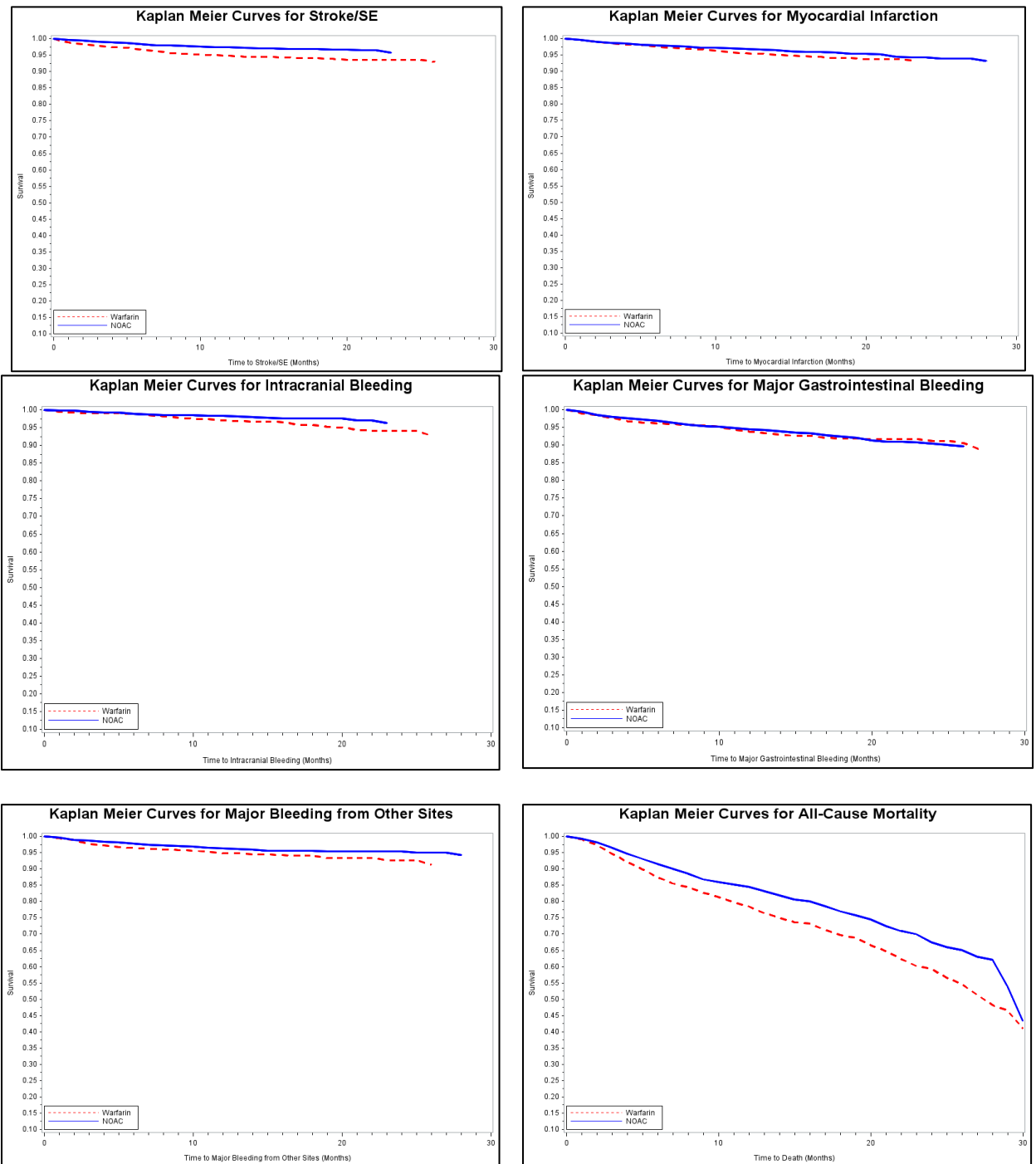


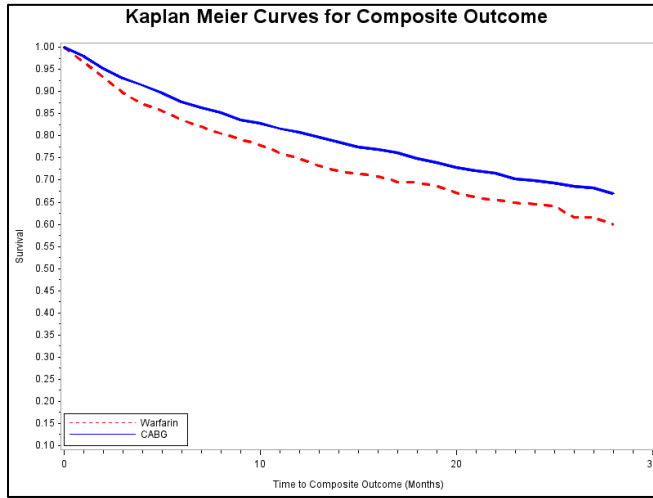
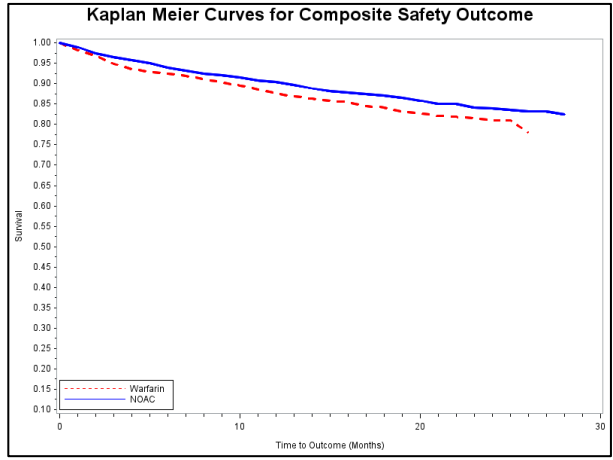
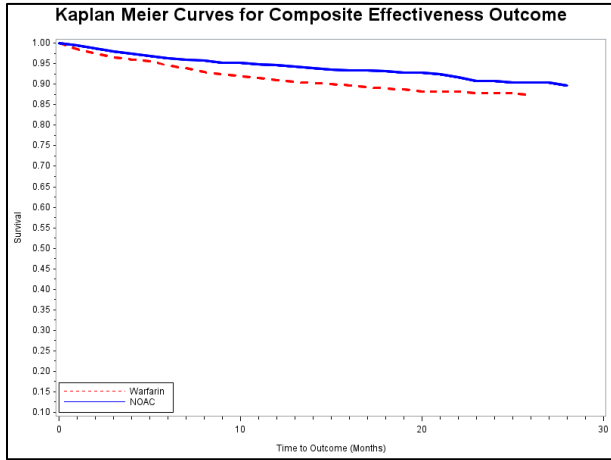
**Distribution of Propensity Scores of the Sample after Matching**



**Figure 1. Distribution of propensity scores before and after matching for NOAC and warfarin therapy among Medicare beneficiaries matched on propensity score and date of surgery**

**Figure 2. Kaplan-Meier survival curves for NOAC and warfarin therapy among Medicare beneficiaries with NVAF and DM**







Hazard ratios for effectiveness outcomes are presented in Table 2. Refer Figure 2 for Kaplan Meier (KM) plots of effectiveness and safety outcomes. Survival curves for occurrence of stroke/SE were significantly different for NOAC patients and warfarin patients as evident from significant log-rank test ( $p < 0.001$ ); however, the survival curves for MI with two therapies seemed to overlap ( $p = 0.215$ ). NOACs were found to significantly reduce the risk of stroke/SE compared to warfarin (Hazard Ratio (HR): 0.373, 95% confidence interval (CI): 0.247 - 0.564,  $p < 0.001$ ); but, no significant difference was seen between NOACs and warfarin in terms of reducing the risk of myocardial infarction (HR: 0.864, CI: 0.594 – 1.257,  $p = 0.446$ ). Overall, effectiveness of NOACs was found to be superior compared to warfarin as measured using the composite effectiveness outcome comprising of occurrence of either stroke/SE or MI. Superiority was seen in both – risk reduction of stroke/SE or MI (HR: 0.629, CI: 0.457 – 0.866) and longer survival time for these outcomes ( $p < 0.001$ ).

Hazard ratios for safety outcomes are presented in Table 3. NOACs were found to significantly reduce the risk of ICH (HR: 0.500, CI: 0.300 – 0.834,  $p = 0.008$ ) and bleeding from other sites (HR: 0.608, CI: 0.424 – 0.870,  $p = 0.007$ ) and prolong the occurrence as seen from significantly different survival curves for ICH ( $p = 0.006$ ) and OB ( $p = 0.008$ ). However, the survival curves for MGB almost overlapped ( $p = 0.562$ ) and no difference was seen in the risk of MGB (HR: 0.862, CI: 0.640 – 1.160,  $p = 0.326$ ) between NOACs and warfarin. The composite safety outcome of major bleeding events (occurrence of any of the three safety outcomes) was significant (HR: 0.701, CI: 0.563 – 0.935,  $p = 0.002$ ). NOACs were also found to reduce the risk of all-cause mortality (HR: 0.783, CI: 0.656 – 0.873,  $p = 0.007$ ) and increase overall survival ( $p < 0.001$ ). The composite of effectiveness and safety outcomes, and all-cause mortality was statistically significant proving superior overall effectiveness and safety of NOAC therapy to warfarin therapy

in terms of risk reduction (HR:0.685, CI:0.587 – 0.801,  $p<0.001$ ) and prolongation of survival ( $p<0.001$ ).

## **DISCUSSION**

Given their practical advantages over traditional warfarin therapy, NOACs have become first choice of oral anticoagulation therapy in patients with NVAF. However, patients with DM constitute a unique subgroup among NVAF patients, having a significantly higher risk of both thromboembolic episodes and hemorrhagic events. Given the diabetes-related propensity for both thromboembolic and hemorrhagic events, the issue of whether NOACs maintain their better efficacy and safety profile as compared to warfarin in the high-risk setting of diabetic patients is clinically relevant. Further, care of elderly NVAF patients with concomitant diabetes presents a highly vulnerable segment of population which demands special consideration with respect to oral anticoagulation therapy. While several observational studies have been conducted to assess comparative effectiveness and safety of NOACs versus warfarin in elderly NVAF population, ours is the first study to evaluate the effectiveness and safety of NOACs compared to warfarin in elderly NVAF population with DM. In this study, we compared the risk of thromboembolic episodes and hemorrhagic events in elderly NVAF patients with concomitant DM using the 5% national Medicare sample from 2014-2016. Propensity score matching was used to control for baseline patient demographic and clinical characteristics.

Our study found a greater incidence rate of stroke/SE, ICH, OB, and all-cause mortality among patients on warfarin therapy compared to patients using NOACs. We believe a greater incidence of clinical outcomes was observed given the baseline demographic composition and clinical characteristics of our study population which represents a high-risk and vulnerable group of patients with AF. High risk of stroke in our study population is evident through higher

CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (mean modified CHA<sub>2</sub>DS<sub>2</sub>-VASc~5) after adjusting for diabetes status in both treatment groups. A significant proportion of study population had a history of prior stroke and prior bleeding. Prior stroke has been known to increase the risk of recurrent ischemic attack and major hemorrhage which might explain higher incidence of stroke/SE and bleeding events in our study [49,50]. Additionally, a substantial portion of patients in our study were on several concomitant medication which might increase the risk of hemorrhage [51]. NVAF patients in our study had a substantial comorbidity burden as evident from the baseline clinical characteristics. Overall higher incidence of clinical outcomes and all-cause mortality may also be associated to general presence multiple comorbidities along with NVAF and diabetes in this population.

Using Cox proportional hazards models, the results of the current study showed that compared to warfarin, NOACs were found to significantly lower the risk of stroke/SE, intracranial bleeding, bleeding from other sites, and all-cause mortality in elderly patients with NVAF and DM treated in routine clinical practice. Differences in the risk reduction associated with NOAC and warfarin therapies may be influenced by differences in pathophysiology of NVAF and DM and pharmacological action of two drug classes. Pathophysiology of NVAF with concomitant DM is different from NVAF alone due to complex interaction in molecular mechanisms between NVAF and DM [36]. Variability of glycemic control in diabetic patients may affect the pharmacokinetics and anticoagulant activity of warfarin [52]. Additionally, the anticoagulant activity of warfarin is expressed through non-specific mechanism of action which affects several proteins outside the coagulation system, in turn, increasing the risk of cardiovascular and hemorrhagic events [53]. These factors may explain increased risk of hemorrhagic events associated with warfarin in comparison to NOACs.

Findings of this study are in agreement with the results of 4 large phase III clinical trials of NOACs - (apixaban in ARISTOTLE [17], dabigatran in RE-LY[18], rivaroxaban in ROCKET AF [19], and edoxaban in ENGAGE AF-TIMI 8 [54]) in which 23 - 40 percent of NVAF patients had diabetes at the baseline. In two meta-analyses of these four clinical trials, NOACs, compared with warfarin, were found to reduce the rate of stroke/SE, ICH, and death. This effect was similar among AF patients with and without diabetes. Similarly, no difference was seen among NVAF patients with and without diabetes with respect to bleeding events, although the relative safety of NOACs was apparent more among patients without diabetes [55,56]. Similar pattern of results was observed in the meta-analysis by Patti et al. [57] which focused specifically on NVAF patients with concomitant diabetes from the above mentioned 4 phase III clinical trials. Patti et al. reported that despite patients with diabetes having higher rates of thromboembolic episodes and mortality and compared to patients without diabetes, similar efficacy of NOACs was observed in both patients with or without diabetes. The safety of NOACs however, presented a more complex scenario where rate of hemorrhagic events was found to depend on specific NOAC and its dose leading to conclusion that risk reduction in hemorrhagic events was higher in AF patients without diabetes as compared to AF patients with diabetes. Our study found NOACs to significantly reduce the risk of ICH and bleeding from other sites in elderly NVAF patients with diabetes. However, no differences were seen in rates of gastrointestinal bleeding between NOACs and warfarin. Comparability to results found by Patti et al. may be limited since we did not evaluate drug- or dose-specific effects of NOACs compared to warfarin. Additionally, our study focused only on NVAF patients with diabetes and hence, assessing comparative effectiveness and safety of NOACs over warfarin in patients without diabetes was not undertaken.

Since findings obtained in clinical trials may not always replicate in routine clinical practice, understanding real-world effectiveness and safety of NOACs versus warfarin in elderly NVAF population with diabetes is necessary. We found two observational studies evaluating effectiveness and safety of these drugs. The ARISTOPHANES Diabetes Subgroup Analysis study[58] used CMS Medicare data and data from four US commercial databases to evaluate relative effectiveness and safety of NOACs versus warfarin in NVAF patients with diabetes. The study reported apixaban and rivaroxaban to be associated with lower rates of stroke/SE, while apixaban and dabigatran had lower rates of MGB compared to warfarin demonstrating overall superiority of NOACs over warfarin. Coleman et al. assessed effectiveness and safety of rivaroxaban compared to warfarin in NVAF patients with diabetes using administrative claims data and found nonsignificant risk reductions in stroke/SE and major bleeding; thus, providing evidence of rivaroxaban's non-inferior effectiveness and safety profile in this population [59]. Results of our study agree with the findings of these studies. Comparison of NOACs, as a drug class, to warfarin in this study provides evidence of better overall effectiveness and safety on NOACs compared to warfarin.

The synergistic effect of aging and diabetes predisposes patients with NVAF to thromboembolic and hemorrhagic episodes. Diabetes is associated with numerous metabolic defects including insulin resistance, impaired glucose tolerance, proinflammatory mediators, abnormalities of hemostasis, fibrinolysis, and angiogenesis which could lead to precipitation of adverse cardiovascular events [60,61]. With the advent of NOACs with better pharmacological profile, warfarin is losing its status as the preferred therapy for thromboprophylaxis, especially in NVAF patients with DM [52,53]. As NOACs become a preferred therapy for oral thromboprophylaxis in NVAF patients [62], there is a need for more real-world evidence

supporting the effectiveness and safety profile of NOACs compared to warfarin in the high-risk group of elderly AF patients with concomitant diabetes.

The current study has several strengths. First, this study used real world data on patients receiving care in actual clinical practice. The study results are therefore more generalizable compared to results of previous randomized clinical trials. Second, patients initiating NOAC or warfarin therapy were matched on baseline demographics and comorbidities using propensity scores. In addition, patients were also matched on the index date of the NOAC and warfarin prescription. The matching process reduces the likelihood of selection bias in observational studies ensuring that all baseline characteristics are balanced equally across treatment groups. Thirdly, effectiveness and safety of NOACs versus warfarin was assessed in a high-risk group of elderly patients over a broad set of clinical outcomes which better characterized the superiority of NOACs, as a drug class, over warfarin.

Results of this study should be interpreted in the light of some limitations. Owing to sample size limitations, we evaluated effectiveness and safety of NOACs as a drug class instead of comparing individual NOAC to warfarin. It is possible that effectiveness or safety outcomes of individual NOACs may not exhibit similar results. Although, the treatment groups were matched using propensity scores, potential residual confounders still exist; e.g. over-the counter aspirin use and warfarin dose adjustment, which are not available in the dataset. Claims data lack laboratory data and accuracy in coding diagnoses. AF and DM were identified using ICD-9-CM and ICD-10-CM codes, which is different from clinical trials. Additionally, the presence of a claim for a filled prescription does not indicate whether the medication was consumed or taken as prescribed. Compared with clinical trials, the follow-up period for the cohort in this study was also shorter, which may impact our results. Finally, although understanding the US Medicare population is

important in managing NVAF, findings from this elderly population may not be generalized to other populations.

## CHAPTER IV

### CONCLUSION

NOACs and warfarin are common drugs of choice for thromboprophylaxis in patients with AF. The current study compared relative effectiveness and safety of NOACs versus warfarin in a broad set of clinical outcomes in real world patients after accounting for baseline differences between the two patient groups. Our study found that NOACs, as a class, reduced the risk of stroke/SE, intracranial bleeding, bleeding from other sites, and all-cause mortality in elderly NVAF patients with diabetes. No significant differences were seen in the risk of myocardial infarction and major gastrointestinal bleeding. Overall, NOACs appeared to be the superior oral anticoagulation strategy for elderly NVAF patients with diabetes. Evidence from this study can assist clinical decision-making about choice of thromboprophylaxis therapy in elderly NVAF patients with diabetes. However, individual patient factors should be taken into consideration in addition to clinical evidence while making clinical decisions about anticoagulation therapy.



## **LIST OF APPENDICES**

**APPENDIX A: SUPPLEMENTAL TABLES**

**Supplemental table 1. ICD-9-CM and ICD-10-CM codes for exclusion criteria**

<b>Diagnosis</b>	<b>ICD-9-CM Diagnosis or Procedural Codes</b>	<b>ICD-10-CM Diagnosis or Procedural Codes</b>
Rheumatic mitral valvular heart disease, mitral valve stenosis	394.0, 394.1, 394.2, 394.9, 396.0, 396.1, 396.8, 396.9, 424.0, 745.xx	I05.0-I05.9, I06.0-I06.9, I34.0-I34.9, I35.0-I35.9
Heart valve replacement or surgery	V422, V433, 35.05-35.09, 35.20-35.28, 35.97	Z95.2, Z95.3, Z95.4
Venous thromboembolism	451-453, 671.3, 671.4, 671.9, 415.1, 673.2, 673.8	I80.0-I80.3, I80.8, I80.9, I82.0-I82.9, I82.A, I82.B, I82.C
Transient AF (Heart valve replacement / transplant, pericarditis, thyrotoxicity)	Pericarditis: 006.8, 017.9, 036.41, 074.21, 093.81, 098.83, 115.93, 390, 391, 392.0, 393, 411.0, 420.90, 420.91, 420.99, 423.0, 423.1, 423.2, 423.8, 423.9 Thyrotoxicity: 242.0, 242.1, 242.2, 242.3, 242.4, 242.8, 242.9	I30.0, I30.1, I30.8, I30.9, I31.0, I31.1, I31.2, I31.3, I31.4, I31.8, I31.9, I32 Thyrotoxicity: E05.0-E05.9
Knee replacement surgery	V43.65 CPT codes: 27445, 27446, 27447, 27486, 27487	Z96.65 CPT codes: 27445, 27446, 27447, 27486, 27487
Hip replacement surgery	V43.64 CPT codes: 27120, 27122, 27125, 27130, 27132, 27134, 27137, 27138	Z96.64 CPT codes: 27120, 27122, 27125, 27130, 27132, 27134, 27137, 27138

**Supplemental Table 2. ICD-9-CM and ICD-10-CM diagnosis codeads for clinical outcomes**

<b>Diagnosis</b>	<b>ICD-9-CM codes</b>	<b>ICD-10-CM codes</b>
<b>Stroke or Systemic Embolism</b>		
Stroke	430.xx - 432.xx, 433.x1, 434.x1, 436	I60.0-I60.9, I61.0-I61.9, I62.0-I62.9, I63.0-I63.9, I64.9

Systemic embolism	444.x, 445.x	I74.0-I74.9
Transient ischemic attack	435.x	G45.0-G45.9*
<b>Major Bleeding</b>		
Major intracranial hemorrhage (ICH)	430, 431, 432.x, 852.x, 853.x	I60, I61, I62.0, I62.1, I62.9
Major gastrointestinal bleeding (MGB)	456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x Procedure code: 44.43	K92.0, K92.1, I85.0, I98.20, I98.3, K22.10, K22.12, K22.14, K22.16, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K63.80, K31.80, K55.20, K62.5, K92.2
Major bleeding from other sites (OB)	285.1, 360.43, 362.43, 362.81, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 423.0x, 596.7x, 599.7x, 602.1x, 620.1, 621.4, 626.2, 626.5, 626.7, 626.8, 626.9, 719.1x, 782.7, 784.7, 784.8, 786.3x, 958.2, 997.02, 998.11 Procedure code: 99.04	N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, K66.1, N93.8, N93.9, N95.0, R04.1, R04.2, R04.8, R04.9, R31.0, R31.1, R31.8, R58, D68.3, H35.6, H43.1, H45.0, M25.0

**Supplemental Table 3. ICD-9-CM and ICD-10-CM codes for comorbidities**

<b>Disorder/Disease</b>	<b>ICD-9-CM codes</b>	<b>ICD-10 codes</b>
Congenital heart disease	746.9	Q20-Q28
Congestive heart failure	428.0	I50.0-I50.9, I11.0, I13.0, I13.2
Hypertension	401.9	I10.0-I10.9, I11.0-I11.9, I12.0-I12.9, I13.0-I13.9, I15.0-I15.9
Peripheral vascular disease	443.9	I21.0-I21.9, I23.0-I23.9, I70.0, I70.2-I70.9, I71.0-I71.9, I73.9
Hemiplegia	342.0	G81
Dementia	294.20	G31.0
Leukemia	208.0	C91-C96
Lymphoma	202.8*	C81-C88
Alcohol use	303.9*	F10.1, F10.2, F10.9
Tobacco use	305.1	F17.2

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## CURRICULUM VITAE

### **Siddhi Korgaonkar**

#### **EDUCATION**

- **The University of Mississippi** (August 2016 – May 2019)  
**Masters Student, Department of Pharmacy Administration (Track: Health Economics and Outcomes Research)**

**Doctoral Student, Department of Pharmacy Administration (Track: Health Economics and Outcomes Research)** (May 2019 – May 2021 (Expected))

**CGPA: 3.98**

**Relevant coursework:** Pharmacoepidemiology, Pharmacoeconomics, Patient-reported Outcomes, Quantitative Methods in Psychology I & II, Mediation and Moderation, General Linear Models, Applied Multivariate Analysis, Primary Data Techniques, Secondary Data Techniques, Applied Political Research, Advanced Marketing and Patient Behavior, Drug Development and Marketing, Health Economics, Pharmaceutical and Healthcare Policy

- **University of Mumbai, India** (August 2010 – May 2014)  
**Bachelor of Pharmacy (B. Pharm)**

#### **KEY SKILLS**

- Proficient in retrospective database analyses of survey databases and administrative claims data
- Possess a working knowledge of statistical software packages like SPSS, SAS, STATA, Instant Health Data (IHD) platform
- Well versed in conceptualizing study designs and using advanced statistical techniques such as propensity score matching and survival analysis
- Experience in economic modeling using TreeAge Pro
- Experience in primary data techniques such as designing surveys using Qualtrics, conducting qualitative interviews, focus groups and content analyses

## Databases

- **Claims databases:** 5% national Medicare sample, Mississippi Medicaid, Optum Humedica, Truven Health MarketScan
- **Public databases:** National Health Interview Survey (NHIS), National Survey on Drug Use and Health (NSDUH)

## WORK EXPERIENCE

- **Research Assistant, Mississippi Medicaid Drug Utilization Review** (June 2017 – present)
  - Responsibilities include undertaking ad-hoc MS Medicaid Drug Utilization Review projects that investigate patient profiling, treatment patterns, resource utilization, adherence and quality measures using MS Medicaid data
  - SAS programming is used for data management and analyses
- **HEOR Intern, Alkermes Inc., MA** (June 2018 – August 2018)
  - Evidence synthesis to support the clinical and safety value of a pipeline molecule in Major Depressive Disorder (MDD)
  - Targeted literature review to quantify the risk of tardive dyskinesia and akathisia in MDD patients treated with antipsychotics
  - Multiple feasibility assessments with Truven commercial database and Optum Humedica database on Instant Health Data (IHD) platform to estimate the patient counts and characteristics of patients with MDD and schizophrenia
- **Clinical Pharmacist, Tata Memorial Hospital, India** (August 2014 – July 2015)
  - Preparation and monitoring of chemotherapy and supportive therapy to pediatric patients
  - Counseling the caregivers regarding the chemotherapy and supportive therapy

## RESEARCH EXPERIENCE

### Master's Thesis

- **‘Comparative Effectiveness and Safety of Non-Vitamin K Antagonists Oral Anticoagulants (NOACs) Versus Warfarin in Elderly Patients with Non-Valvular Atrial Fibrillation and Diabetes’** (*Abstract submitted for ISPOR 2019, New Orleans, LA*)
  - Patients initiating NOACs were matched 1:1 to warfarin patients on propensity score to balance demographic and clinical characteristics.
  - Primary effectiveness was measured as the risk of stroke/systemic embolism (SE) or myocardial infarction (MI). Primary safety measures included major bleeding -

intracranial hemorrhage (ICH), gastrointestinal bleeding (MGB), and bleeding from other sites (OB).

- Cox proportional hazards models were used to estimate the effectiveness and safety outcomes of NOACs vs warfarin in the matched cohort.

### **Posters**

- **Korgaonkar S**, Banahan B, Pittman E, Noble S. Effect of Depression on Medication Adherence to Asthma Controller Medications and Healthcare Resource Utilization in Severe Asthma Patients. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 23<sup>rd</sup> Annual International Meeting. Baltimore, Maryland. May 19-23, 2018.
- **Korgaonkar S**, Inguva S, Yang Y. Cost-Effectiveness of Mepolizumab Versus Omalizumab As an Adjunct Therapy in Patients with Uncontrolled Allergic Asthma. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 23<sup>rd</sup> Annual International Meeting. Baltimore, Maryland. May 19-23, 2018.
- Dunn T, **Korgaonkar S**, Ramachandran S. Association Between Stimulant Use and Misuse of Other Prescription Medications. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 23<sup>rd</sup> Annual International Meeting. Baltimore, Maryland. May 19-23, 2018.
- **Korgaonkar S**, Ward L, Pohl L, Nicks A. Exploring First Year Professional Pharmacy Students' Perceptions and Knowledge of Older Adults. American Association of Colleges of Pharmacy Annual Meeting, Boston, MA. July 21–25, 2018.

### **Projects**

- **Impact of Diverse Inclusion Criteria on Assessment of HEDIS Asthma Medication Ratio (AMR) Quality Measure in Mississippi Medicaid** (*Abstract submitted for ISPOR 2019, New Orleans, LA*)
  - Sensitivity analyses using varied inclusion criteria was conducted to explore differential effect on AMR
  - Potential misclassification of acute asthma cases as persistent asthma cases was identified
- **Impact of Occupational Psychosocial Risk Factors on Frequent, Severe Low Back Pain in the US Working Population** (*Abstract submitted for ISPOR 2019, New Orleans, LA*)
  - Multivariable logistic regression was used to measure the association between diverse work-related psychosocial risk factors and frequent, severe low back pain using 2015 NHIS database
- **Assessment first year professional pharmacy students' perceptions of older adults**
  - Designed a questionnaire based on Geriatric Attitudes Scale and Facts on Aging Quiz using Qualtrics platform to assess students' perceptions pre- and post-interview with an older adult
  - Assessed the change in students' perceptions pre- and post-interview with an older adult

- **Long-acting reversible contraceptives (LARCs) and Depo-Provera utilization in Mississippi Medicaid population**
  - Profiling of Mississippi Medicaid beneficiaries based on LARC and Depo-Provera utilization according to Code of Eligibility type
- **Pediatric use of multiple antipsychotics in Mississippi Medicaid population**
  - Measured monthly use of multiple antipsychotics among children in Mississippi Medicaid population

#### **PROFESSIONAL AFFILIATIONS AND RESPONSIBILITIES**

- Secretary, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) - University of Mississippi student chapter (2017-2018)
- Secretary, Rho Chi Honor Society- University of Mississippi Chapter, (2018-present)
- Initiated into Phi Kappa Phi (2018)

#### **AWARDS**

- William E. Farlow Fellowship 2018-2019, Department of Pharmacy Administration, University of Mississippi, August 2018.
- Member of runner-up team, Pharmacy Quality Alliance (PQA) - Healthcare Quality Innovation Challenge, Baltimore, Maryland. May 2018.