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Oral anticoagulation in patients with non-valvular atrial fibrillation: Stroke prevention
and bleeding risks with a focus on warfarin and novel oral anticoagulants

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Capstone Literature Review

A Paper Presented to Meet Partial Requirements

For NRSG- 594

MSN Capstone

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Chapter 1

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice. Approximately four percent of individuals' older than 60 years of age, and eight percent of persons older than 80 years of age, are affected by AF (Rosenthal, et al., 2014). AF is defined by type: paroxysmal AF (heart returns to normal rhythm on its own and can occur daily or a few times a year), persistent AF (heart does not return to normal rhythm within 48 hours, needs treatment to convert rhythm back to normal), and permanent or chronic AF (last indefinitely, rhythm cannot be controlled with medication) (www.heart.org). AF is associated with a number of risk factors to include familial AF, endocrine disorders, alcohol and drug use, inflammation, atrial ischemia, and advancing age, and places the patient at increased risk for stroke (Crijns, et al., 2010). Stroke in the presence of AF is caused by a thromboembolic event that occurs with blood stasis in the heart that can lead to a thrombus being formed in the left atrial appendage. The thrombus being dislodged into the circulation can lead to an embolic event that may cause an embolic stroke. AF accounts for 15% of strokes in all age groups and 30% of strokes for patients' 80-years-old and above (Patel, et al., 2011).

Assessing a patient's risk for stroke with atrial fibrillation can be challenging for providers. The CHADS₂ scoring schema measures the stroke risk factors for patients in AF by assigning one or two points for each risk factor with a maximum score of six. Patients with a CHADS₂ score of zero require no antithrombotic treatment, CHADS₂ score of one may benefit from oral anticoagulation (OAC) treatment of aspirin or antiplatelet drug, and CHADS₂ score of two to six require treatment with OAC (Aguilar,

Kuo and Freeman, 2013). The CHA₂DS₂-VASc score, an improved version of the CHADS₂, is now being used to predict stroke risk for patients with a CHADS₂ score of one due to uncertainty about need for oral anticoagulation treatment (Coppens, M., 2013).

Table 1

CHADS ₂ Score	Stroke risk %	95% CI
0	1.9	1.2–3.0
1	2.8	2.0–3.8
2	4.0	3.1–5.1
3	5.9	4.6–7.3
4	8.5	6.3–11.1
5	12.5	8.2–17.5
6	18.2	10.5–27.4

Nottingham, F. (2010). Diagnosis and treatment of atrial fibrillation in the acute care setting. *Journal of the American Association of Nurse Practitioners*, 22, 280-287.

Table 2

CHA ₂ DS ₂ VASc SCORE	ADJUSTED STROKE RATE (% year)
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

Lip et al., 2010 found at <http://stroke.ahajournals.org/content/41/12/2731.full.pdf>

Anticoagulation is one of the most important treatments for acute atrial fibrillation in an effort to prevent thromboembolic events. The bleeding risks associated with oral anticoagulants have been well documented. Warfarin and aspirin have been the most commonly used drugs up until a few a years ago. The first-line treatment for stroke prevention has been warfarin, a vitamin K antagonist (VKA), for over 70 years. The problems associated with warfarin therapy are the dietary restrictions placed on patients, multiple drug interactions, the cost and time associated with frequent monitoring of

patient's prothrombin time (PT) and international normalized ratio (INR), and frequent changes in dosage (Patel et al., 2011). Anticoagulation with warfarin reduces the risk for stroke by two thirds (Granger et al., 2011), but has an increased risk for hemorrhage. VKAs have a narrow therapeutic window, require regular laboratory monitoring, have multiple interactions with other drugs and foods and have a delayed onset of action. Three novel oral anticoagulants (NOACs) have received United States Food and Drug Administration (FDA) approval in the past five years for stroke prevention in AF. These drugs, dabigatran, a direct thrombin inhibitor; rivaroxaban, and apixaban, factor Xa inhibitors are supposed to have fewer bleeding risks, be equal or superior to warfarin in thrombus prevention, without the additional time and cost of regular laboratory testing. The American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) guidelines for AF list warfarin as a class I recommendation and dabigatran as a class Ib recommendation (Wann et al., 2011)

Definition of terms

Atrial fibrillation (AF) is used throughout the paper to describe a common cardiac arrhythmia. Novel oral anticoagulants (NOAC), vitamin K antagonist (VKA) and warfarin are used throughout to describe oral anticoagulation drugs currently used for stroke prevention in patients with AF.

The CHADS₂ score is used to assess the risk for thromboembolism in patient's with atrial fibrillation by assigning one point for each: a patient's history of Congestive heart failure, **H**ypertension (controlled or uncontrolled), **A**ge ≥ 75 years, **D**iabetes mellitus (type one or two, controlled or uncontrolled), and two points for previous **S**troke or transient ischemic attack (Davis, 2013). The CHA₂DS₂-VASc score uses the same

measurements as the CHADS₂ score, but also assigns one point to additional risk factors: female Sex, Age 65-75, and Vascular disease (Lopes et al., 2012).

The HAS-BLED score estimates the risk for major bleeding in patients with atrial fibrillation. HAS-BLED assigns one point for each: **H**ypertension history (systolic > 160), **A**bnormal renal function and liver function (Cr > 2.6 mg/dl, dialysis, transplant; cirrhosis, bilirubin > 2x normal, AST/ALT/AP > 3x normal), **S**troke history, **B**leeding history or predisposition for bleeding, **L**abile international normalized ratio (time in therapeutic range (TTR) < 60%), **E**lderly (> 65 years), and **D**rugs/alcohol usage predisposing to bleeding (antiplatelet agents, NSAIDS; > 8 drinks/week) (Pisters et al., 2010).

The International Society on Thrombosis and Haemostasis' (ISTH) definition of major bleeding. Major bleeding is defined according to the ISTH recommendations:

- fatal bleeding or
- reduction in haemoglobin level of at least 20 g per litre or
- transfusion of at least two units of blood or
- symptomatic bleeding in a critical area or organ (Miesbach, W. and Seifried, E., 2012).

Theoretical framework

Betty Neuman's Systems Theory is used for the framework because it combines the idea of environment to include internal, external and created environments. The thought process is that the patient and nurse practitioner interact synergistically within all three environments, helping the patient to achieve the greatest level of anticoagulation with the least complications.

The left atrium is the usual focus of atrial fibrillation and this is where the left atrial appendage (LAA) lies. The stasis of blood caused by the decreased contractility of the left atrium increases the likelihood of a thrombus being formed in the LAA. For this reason anticoagulation is generally required to prevent thrombus formation. The use of oral anticoagulants will increase a patient's risk for bleeding, which decreases their lines of resistance.

A patient's first line of defense in regards to atrial fibrillation is to decrease the initiating risk factors. When this line of defense is broken then a second line of defense is to treat the symptoms with medication. For the purpose of this paper the medications in question are oral anticoagulants, specifically warfarin and the NOACs. Anticoagulants are used in atrial fibrillation for the prevention of stroke and systemic embolism. This line of defense, however, can be broken when a patient experiences bleeding due to over-anticoagulation. The nurse practitioner can help the patient to maintain a level of internal defense by closely monitoring the patient's compliance with anticoagulation therapy and also monitoring their blood levels (particularly INR & PTT).

Purpose statement

The purpose of this literature review is to provide the most up to date information to nurse practitioners about oral anticoagulation for patients with atrial fibrillation. The main focus is to increase the level of knowledge of stroke prevention and bleeding risks associated with warfarin and the novel oral anticoagulants and determining the best medication for the patient.

Chapter 2

Methods and Results

Search strategy

A review of the literature regarding bleeding complications with warfarin, a VKA, and the NOACs was performed on MEDLINE and ScienceDirect. The search on MEDLINE and Science Direct used search terms oral anticoagulation, novel oral anticoagulant, bleeding complications, warfarin, rivaroxaban, dabigatran, apixaban, atrial fibrillation, CHADS₂, CHA₂DS₂-VASc, HAS-BLED. The search was limited to human subjects between the years 2009 to 2014. The articles that list these particular topics in the title were reviewed, and articles were chosen that listed bleeding complications within the title or abstract.

Search results

A total of 104 reports were identified from MEDLINE. The search was narrowed to include articles with human subjects, atrial fibrillation and major bleeding, which resulted in 68 reports from MEDLINE. ScienceDirect was used to locate full-text articles that were not retrievable on MEDLINE. The titles and abstracts of all results were screened to extract 28 reports to read fully, and included 22 of these in the review. The 22 studies retrieved include: eight randomized controlled trials (RCT), four prospective observational studies, three meta-analyses of RCTs, four post-hoc analysis of RCTs, two observational retrospective studies, and one case-control analysis.

Chapter 3

Discussion

Clotting cascade and the mode of action of anticoagulants

The clotting cascade is made up of intrinsic and extrinsic pathways, which join together to form the common pathway. The intrinsic, or partial thromboplastin time (PTT), pathway begins with blood being exposed to collagen and activation of Factor XII. The cascade then flows down through Factors XI, IX, VIII to activate Factor X. The extrinsic, or prothrombin time (PT) pathway is the quicker pathway to clot formation. Damage to the endothelial cells of a blood vessel release tissue factor (TF), or Factor III. Factor III combines with calcium activates Factor VII, which activates Factor X. The common pathway begins at Factor X. Factor Xa and Factor Va convert prothrombin into thrombin (Factor IIa). Thrombin converts fibrinogen to fibrin, which stabilizes a clot (Porth, 2011)

Warfarin inhibits vitamin K which is essential for formation of clotting factors II, VII, IX, X, and Protein C and S. The anticoagulation effect is influenced by the half-life of warfarin's R- and S- isomers (45 hours and 29 hours, respectively) and the four vitamin K-dependent factors: II (42-72 hours), VII (four to six hours), IX (21-30 hours), X (27-48 hours). The lag time associated with warfarin's initiation, dosage change, discontinuation, and a clinical effect are due to the long half-life of Factor II. Warfarin can take up to 120 hours to reach steady-state concentration, and up to five days after being discontinued before it is completely eliminated (Nutescu, 2013). The benefits of warfarin are as follows: 1) the ability to monitor drug levels with the PT/INR, 2) the ability to titrate the medication to a desired level of anticoagulation (INR 2.0 to 3.0 for

stroke prophylaxis) based on extensive data, and 3) numerous reversal agents to include Vitamin K (reversal in 12 to 24 hours), fresh frozen plasma (short term reversal of < 12 hours), and 3- or 4-factor prothrombin complex concentrates (vitamin K–dependent factors) that are effective in minutes (Ansell, 2012).

Dabigatran, direct thrombin inhibitor, binds to thrombin and blocks the conversion of fibrinogen to fibrin, which prevents thrombin-induced activation of platelets and other coagulation factors. The onset of action is one-half to four hours, a half-life of 12 to 17 hours for CrCl >80 mL/min, 14 to 17 hours for CrCl 30-80 mL/min, and 28 hours for CrCl < 30 mL/min. There is no routine monitoring of coagulation effect due to the predictability of the pharmacological effect. There is no reversal agent at this time, but the drug can be removed by hemodialysis (Grove, Husted, & Poulsen, 2012).

Rivaroxaban and apixaban, direct Factor Xa inhibitors, selectively block the active site of Factor Xa, and inhibit platelet activation. Peak plasma time of rivaroxaban is two to four hours, and elimination half-life of five to nine hours in young healthy adults and 11 to 13 hours for elderly. Apixaban's onset of action is three to four hours with a mean half-life of eight to 15 hours. Routine monitoring is not necessary for either drug due to their predictable pharmacological effect, and there is no reversal agent currently available. Neither drug can be removed with hemodialysis (Grove, Husted, & Poulsen, 2012).

Comparison of VKAs with NOACs

Randomized control trials The RE-LY (Randomized Evaluation of Long-term anticoagulation therapy) trial was done to compare the use of an adjusted-dose of warfarin with dabigatran in the treatment of atrial fibrillation. The patients had to have a

diagnosis of atrial fibrillation that was documented on electrocardiogram (EKG) within the previous six months. They also had to have one other condition: previous stroke or transient ischemic attack (TIA), left ventricular ejection fraction (LVEF) of less than 40%, New York Heart Association (NYHA) class II or higher heart-failure symptoms and an age of at least 75, or 65 to 74 years plus diabetes, hypertension, or coronary artery disease.

The participants were randomly assigned to receive dabigatran 110-mg, dabigatran 150-mg, or warfarin. The dabigatran was administered in unlabeled capsules, either having 110-mg or 150-mg of the drug. Warfarin was administered, un-blinded, in 1-, 3-, or 5-mg tablets and was adjusted to maintain an INR between 2.0 and 3.0, that was measured at least monthly. The participants were seen at follow-up visits at 14 days, one month, three months, and then every three months in the first year. The second year follow-ups were every four months.

The primary outcome was either systemic embolism or stroke, with occurrences being 1.69% per year of warfarin group versus 1.53% per year of 110 mg dabigatran group (RR 0.91, 95% CI (0.74–1.11), $p = 0.34$) and 1.11% per year of 150 mg dabigatran group (RR 0.66, 95% CI [0.53–0.82], $p < 0.001$). Dabigatran 150-mg was found to be superior to warfarin. Major bleeding rates for the warfarin group were 3.36% per year versus 2.71% of 110 mg dabigatran group (RR with dabigatran, 0.80; 95% CI, [0.69 to 0.93]; $p = 0.003$), and 3.11% of 150 mg dabigatran group (RR 0.93; 95% CI, [0.81 to 1.07]; $P = 0.31$). Dabigatran 150-mg had a higher incidence of gastrointestinal bleeding compared with warfarin (1.51% vs. 1.02%, RR 1.50; 95% CI [1.19–1.89], $p < 0.001$), while warfarin had a higher risk for intracranial hemorrhage compared with both doses of

dabigatran (0.74% vs. 0.23% [110-mg] & 0.30% [150-mg], RR 0.31; 95% CI [0.20–0.47], $p < 0.001$; and RR 0.40; 95% CI [0.27–0.60], $p < 0.001$). Overall, dabigatran 110-mg was similar to warfarin in its rates of stroke and systemic embolism, and had lower rates of major hemorrhage. Compared to warfarin, dabigatran 150 mg was found to have lower rates of stroke and systemic embolism with a similar rate of major bleeding (Connolly et al., 2009).

The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study (Patel et al., 2011), was a comparison of rivaroxaban with warfarin. The 14,264 participants chosen, based on EKG-documented nonvalvular atrial fibrillation that were at moderate-to-high risk for stroke, were randomly selected to receive either rivaroxaban 20 mg or dose-adjusted warfarin once a day.

In the rivaroxaban group, the patients were given either 20 mg daily or 15 mg (if creatinine clearance [CrCl] was 30 to 49 ml/min) or adjusted-dose warfarin, to maintain INR of 2.0 to 3.0, along with a placebo tablet to maintain blinding. The significant findings are as follows: in primary analysis, 188 (1.7%) participants from the rivaroxaban group and 241 (2.2%) of the warfarin group had primary end point (stroke/systemic embolism) occurrences (HR, 0.79; [0.66–0.96], $p < 0.001$ for non-inferiority). Major bleeding occurrences (as defined by ISTH) were similar in both groups with 395 (5.6%) events in the rivaroxaban group and 386 (5.4%) events in the warfarin group (HR 1.04; 95% CI [0.90–1.20], $p = 0.58$). There were fewer intracranial hemorrhages in the rivaroxaban group versus warfarin group (0.8% vs. 1.2%; HR 0.67; 95% CI [0.47–0.93], $p = 0.02$). The limitations that were observed were the amount of time the intensity of

anticoagulation in the warfarin group was therapeutic [mean, 55%] (Patel et al., 2011).

The ARISTOTLE trial was a comparison of apixaban with warfarin in patients with AF. The trial enrolled 18,201 patients with atrial fibrillation and at least one other risk factor for stroke. It was a double-blind, double-dummy study with patients randomly assigned to either dose-adjusted warfarin or apixaban. Apixaban was given as either 5-mg dose or 2.5-mg dose for patients had two or more criteria: age \geq 80 years, body weight \leq 60 kg, or a creatinine level \geq 1.5 mg/dl. Warfarin dose was started at 2-mg and titrated to a target INR of 2.0 to 3.0. The primary efficacy outcome was stroke or systemic embolism, and the primary safety outcome was major bleeding as defined by ISTH (Granger et al., 2011).

Apixaban, when compared with warfarin, decreased the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death by 11%. The significant findings for apixaban versus warfarin are as follows: primary end-point of stroke or systemic embolism found that apixaban has a lower incidence with 1.27% of patients with events versus warfarin's 1.60% of patients with events (HR, 0.79; 95% CI [0.66–0.95], $p = 0.01$). Major bleeding occurred in 4.07% of apixaban patients versus 6.01% of warfarin patients (HR, 0.68; 95% CI [0.61-0.75], $p < 0.001$), with the rate of any bleeding in the warfarin group was 25.8% per year compared with 18.1% per year of the apixaban group. The rate of intracranial bleeding in the apixaban group was 0.33% compared with 0.80% of the warfarin group (HR, 0.42; 95% CI [0.30-0.58], $p < 0.001$). Overall, apixaban was found to be superior to warfarin for the prevention of stroke or systemic embolism, and had a lower incidence of bleeding (Granger et al., 2011)

Calvi, Capodanno, Capranzano, Giacchi, & Tamburino (2012) performed a meta-

analysis of 50,578 patients from three randomized control trials (RCT) comparing warfarin to the NOACs found that NOACs decrease the incidence of stroke and systemic embolism (2.8% vs. 3.5%; OR 0.82, 95% CI [0.74–0.91], $p < 0.001$), a slight decrease of major bleeding (5.6% vs. 5.0%; OR 0.85, 95% CI [0.69–1.05], $p = 0.14$), a decrease of intracranial hemorrhage (0.6% vs. 1.3%; OR 0.46, 95% CI [0.38–0.55], $p < 0.001$), and an increase of gastrointestinal bleeding (2.3% vs. 1.3%; OR 1.68, 95% CI [1.03–2.72], $p = 0.036$). The NOACs have shown a more predictable pharmacokinetics, with less drug interactions and shorter half-lives.

Eisenberg, Filion, Grandi, Miller, & Shimony (2012) performed a meta-analysis of 44, 563 patients was done of three studies to measure the efficacy and safety of NOACs versus warfarin. A decreased risk for all-cause stroke and systemic embolism (RR 0.78, 95% CI, 0.67 to 0.92) for patients in the NOAC group was found, with dabigatran and apixaban showing superiority over warfarin for this outcome respectively (RR 0.66, 95% CI, 0.53 to 0.82 and RR 0.80, 95% CI, 0.67 to 0.95). They found a comparable risk for major bleeding between dabigatran (RR 0.94, 95% CI, 0.82 to 1.07) and rivaroxaban (RR 1.03, 95% CI, 0.89 to 1.18) compared to warfarin, while apixaban showed a decreased risk for major bleeding (RR 0.70, 95% CI, 0.61 to 0.81).

Lopes et al., (2012), calculated HAS-BLED, CHADS₂ and CHA₂DS₂-VASc scores for every patient to compare the safety and efficacy of apixaban versus warfarin. Apixaban significantly reduced stroke or systemic embolism with no evidence of a differential effect by risk of stroke (CHADS₂ 1, 2, or ≥ 3 , p for interaction=0.4457; or CHA₂DS₂VASc 1, 2, or ≥ 3 , p for interaction=0.1210) or bleeding (HAS-BLED 0–1, 2, or ≥ 3 , p for interaction=0.9422). The patients that received apixaban had lower rates of

major bleeding compared to the warfarin group with no difference seen in all scoring categories between apixaban and warfarin groups (CHADS₂, p for interaction = 0.0418, CHA₂DS₂-VASc, p for interaction=0.2059; and HAS-BLED, p for interaction = 0.07127).

Berger, Salhanick, Chase, & Ganetsky (2013), assessed the course of bleeding complications for emergency department patients while on either warfarin or dabigatran. The study was a prospective cohort chart review of adult patients that listed either warfarin or dabigatran on their medication list upon admission. The sample size was 15 patients admitted with bleeding from dabigatran and 25 patients with bleeding from warfarin. The study was performed at an urban academic tertiary care hospital emergency department (ED).

A computer-generated list of patients, that were either on dabigatran or warfarin, seen between June and December 2011 was created. The records of patients that listed “hemorrhage” or “bleed” diagnoses were then used for the study. The data collection tool was used to collect patient demographics, bleeding diagnosis, interventions, laboratory values, and outcomes. The tool, a standardized data abstraction form, was designed by two of the researchers. The definitions of bleeding episodes was based on the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, and the Acute Kidney Injury Network diagnostic criteria was used to described acute kidney injury (Berger et al, 2013).

Patients on dabigatran had a shorter hospital stay (3.5 vs. 6.0 days) compared to the patients on warfarin. The most common site of bleeding was gastrointestinal with the dabigatran group having eight events (67%, 95% CI [35 to 98]) and the warfarin group

with nine events (75%, 95% CI [46 to 104]). Intracranial hemorrhage occurred in eight warfarin cases, with five of the eight occurring from trauma. There were none in the dabigatran cases (32% versus 0%). Researchers were unable to say which agent was more likely to cause bleeding, and the results found were similar to those of the RE-LY trial (Berger et al., 2013).

Chapter 4

Conclusion

Atrial fibrillation, the most common cardiac arrhythmia, has numerous causes. The greatest risk with AF is stroke or systemic embolism, and the greatest risk with oral anticoagulation is bleeding. The three risk assessment scores, CHADS₂, CHA₂DS₂-VASc, and HAS-BLED, are useful for determining which patients are at greatest risk for stroke and bleeding. The best oral anticoagulant is one that has a quick onset of action with a low probability of complications and a way to reverse the effects (Shaafiq, H. and Tran, T., 2013). Although warfarin can reduce the likelihood of stroke by 64% in patients with atrial fibrillation, and is considered a class I recommendation for treatment, it has been underutilized by providers due to its numerous limitations (Al-Kahtib, Ansell, Lopes, Wallentin, & Yang, 2012). Randomized control trials have been done to compare the three NOACs with warfarin, along with meta-analyses of the three trials. Overall, NOACs and warfarin are similar in comparison for stroke/systemic embolism prevention, with dabigatran and apixaban showing superiority for prevention of strokes over warfarin. NOACs are comparable to warfarin for bleeding complications, with warfarin having higher incidence of intracranial bleeding and NOACs having a higher incidence of gastrointestinal bleeding. Warfarin has the benefit of reversal agents and a consistent

form of monitoring, while NOACs have neither a reversal agent nor a consistent way to monitor coagulation effect. Research is continuing for newer oral anticoagulants with greater safety and efficacy over warfarin, as well as research for reversal agents for the NOACs.

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