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Use of New Oral Anticoagulants in Preventing Ischemic Stroke in Patients with Atrial Fibrillation

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Use of New Oral Anticoagulants in Preventing Ischemic
Stroke in Patients with Atrial Fibrillation

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A scholarly paper submitted to the faculty of
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ABSTRACT

Atrial fibrillation (AF) affects millions of Americans and puts them at increased risk for ischemic stroke. It is important for providers to recognize AF and know when it is appropriate to treat patients with anticoagulation. There are several options available for anticoagulation. Warfarin is the most widely used anticoagulant. Other alternatives to warfarin are new oral anticoagulants (NOACs) which are increasingly prescribed in recent years. It is vital providers know the differences between warfarin and NOACs, and what is the most appropriate anticoagulant to use for their patient with AF. The purpose of this paper is to review the clinical presentation of AF and compare the use of warfarin versus NOACs for the prevention of ischemic stroke.

Keywords: atrial fibrillation, new oral anticoagulants (NOACs), warfarin, anticoagulation.

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Use of New Oral Anticoagulants in Preventing Ischemic
Stroke in Patients with Atrial Fibrillation

Background

Atrial fibrillation (AF) is a common disorder many nurse practitioners will encounter in their practice. Currently, AF in the United States affects over two million people (Mahtani, Heneghan, & Tai, 2012). It is projected that more than 12 million people will be affected by AF by 2050 (Shafeeq & Tran, 2014). In fact, AF will affect one in four people at some point during their lifetime (Mahtani et al., 2012).

AF is concerning because it can lead to multiple complications. One of the most devastating complications is ischemic stroke. Ischemic stroke due to AF can occur in all populations, but it is most common in the elderly. People who are in their eighties have a 23.5% risk for an ischemic stroke compared to a 1.5% risk in those who are in their fifties (Staerk, Sherer, Ko, Benjamin, & Helm, 2017). The purpose of this paper is to review the pathophysiology, clinical presentation, diagnosis of AF, and compare and contrast the use of warfarin and the new oral anticoagulants (NOACs) for the prevention of ischemic stroke in these patients.

Pathophysiology of Atrial Fibrillation and Ischemic Stroke

AF occurs when the normal sinoatrial node in the heart's conduction is overridden by high-frequency electrical impulses outside the sinoatrial node. This alteration in conduction leads to dyssynchronous atrial contraction and an irregular ventricular conduction (Staerk et al., 2017). This ineffective atrial contraction leads to the pooling of blood within the chamber and possible formation of blood clots. When these clots are ejected, they risk being lodged within the vessels of the brain leading to ischemic stroke.

Clinical Presentation of Atrial Fibrillation

Risk Factors

Certain risk factors can make patients more prone to developing AF in their lifetime. Non-modifiable risk factors for AF include a person's age, sex, race, and genetic makeup. The modifiable risk factors for AF include decreased physical activity, smoking, obesity, diabetes, obstructive sleep apnea (OSA), and hypertension (Staerk et al., 2017).

Past Medical History

A past medical history of heart failure or myocardial infarction may put a patient at greater risk for developing AF (Staerk et al., 2017). A first-degree relative with AF puts a person at a 40% increased risk of having AF (Staerk et al., 2017).

Physical Exam Findings

When performing a physical examination, a nurse practitioner may palpate an irregular pulse or auscultate an irregular heart rate. These assessment findings may prompt the nurse practitioner to consider AF as a differential diagnosis.

Diagnosis

The diagnosis of AF is made by an electrocardiogram (ECG). The ECG will have a characteristic wavy baseline with the absence of distinct P-waves. The QRS complexes will also be irregular. The heart rate may vary, but is often greater than 100 beats per minute.

When a patient is diagnosed with AF, a complete workup should follow in an attempt to determine the underlying cause. This workup may include an evaluation of serum cardiac biomarkers and B-type natriuretic peptide (BNP) to investigate for underlying heart failure. Chest radiography, thyroid function tests, complete blood cell (CBC) count, and serum chemistries may also be helpful in determining the underlying cause (Staerk et al., 2017).

Determining Risk of Complications

Unfortunately, it is not always possible to determine the cause of AF, which will require the nurse practitioner to change the focus of care to the prevention of complications. One potentially devastating complication is an ischemic stroke. A useful tool to determine the risk of having a thromboembolic event or possible ischemic stroke is the CHADS₂ score (Table 1). The higher the score, the higher the risk for stroke.

Anticoagulation for the Prevention of Ischemic Stroke

Anticoagulation should be considered if the CHADS₂ score is greater than or equal to one (Zirlik & Bode, 2016). Up to 40% of eligible patients are not getting proper anticoagulation, which places them at considerable risk for an ischemic stroke (Zirlik & Bode, 2016).

Anticoagulation

Warfarin has been used since 1954 and has been the mainstream anticoagulant used to prevent clot formation and subsequent ischemic strokes (Bruins, Slot, & Berge, 2013). Newer anticoagulants include apixaban, dabigatran, rivaroxaban, and edoxaban and are referred to as NOACs. They have proven to lessen clot formation in the presence of AF and may be considered alternatives to warfarin (Lip et al., 2018). Patients with heart valve problems, heart valve replacement, or end-stage renal disease must be on warfarin since no other anticoagulant is currently approved for their treatment (Shafeeq & Tran, 2014).

Effects on Clotting Cascade

Each anticoagulant affects a portion of the clotting cascade (Figure 1). Warfarin acts as a vitamin K antagonist, blocking multiple areas within the clotting cascade. Dabigatran is a direct thrombin inhibitor and blocks the final step in the coagulation cascade where fibrinogen is

converted to fibrin (Salazar, del Aguila, & Cordova, 2016). Apixaban, rivaroxaban, and edoxaban are all factor Xa inhibitors (Rogers & Finks, 2018).

Monitoring

Warfarin requires continued monitoring of the International Normalized Ratio (INR) to ensure proper dosing. On the other hand, the NOACs are very predictive and constant in their effects and do not require routine laboratory monitoring. Their therapeutic window and index do not vary.

However, there may be times when laboratory monitoring of NOACs may be helpful or required. These include suspected bleeding, recent significant trauma, or upcoming surgery. When these needs occur, laboratory tests are available to check the patient's anticoagulation status (Table 3).

Diet Restrictions

It has long been known the effects of warfarin are limited by green leafy vegetables, multivitamins, some enteral feeding formulas, grapefruit juice, and alcohol (Kampouraki & Kamali, 2017). In comparison, the NOACs have no known dietary interaction (Mekaj, Mekaj, Duci, & Miftari, 2015).

Medication Interactions

Warfarin interacts with CYP1A2, CYP2A6, CYP2C8, CYP2C9, and CYP3A4 substrates (Garton, Dudzinski, & Kowey, 2014). Dabigatran, edoxaban, apixaban, and rivaroxaban are contraindicated if taking defibrotide or mifepristone. Apixaban and rivaroxaban are also contraindicated with a combined P-glycoprotein and a strong CYP3A4 inducer or inhibitor (Garton, Dudzinski, & Kowey, 2014). Examples of these medications include

antineoplastic drugs, calcium channel blockers, amiodarone, calcineurin inhibitors, digoxin, macrolide antibiotics, and protease inhibitor (Garton, Dudzinski, & Kowey, 2014).

Dabigatran has also been shown to increase the risk of severe hemorrhage when taken with ketoconazole, amiodarone, verapamil, ticagrelor, and clarithromycin (Finch & Pillans, 2014). For this reason, a careful medication history should be completed prior to beginning warfarin or a NOAC.

Reversal Agents

Reversal agents may be required when taking an anticoagulant in the cases of severe bleeding, major trauma, or in preparation for surgery. Fortunately, warfarin and most of the NOACs have reversal agents, as shown in Tables 2 and 3 (Rogers & Finks, 2018). In cases of severe bleeding, a patient would likely require blood transfusions while waiting for the reversal agent to take effect. A patient on warfarin may require the administration of vitamin K and/or fresh frozen plasma to reverse its effects (Griffiths et al., 2017).

Clinical trials are underway evaluating andexanet alfa as a reversal agent for edoxaban, but it is not currently approved (Rogers & Finks, 2018). Having a reversal agent that is quick, readily available, and reliable can be an important when considering options for anticoagulation.

Cost

The NOACs are all more expensive than warfarin when it comes to cost per pill (see Table 3). However, warfarin does require lab draws to monitor the international normalized ratio (INR) which need to be taken into consideration of overall costs. The INR test ranges from \$6 to \$145 per lab draw (Chambers, Chadda, & Plumb, 2010).

Although warfarin is the least expensive overall option, it is also the least convenient with the need for follow up labs, potential medication interactions, and dietary restrictions. The more expensive NOACs require no monitoring, so a patient is not burdened with lab draws.

Changing Anticoagulants

A patient may change from warfarin to a NOAC if there are medication interactions, barriers to obtaining lab draws, or difficulty sustaining a therapeutic INR range. Patients also may need to transition to warfarin if their kidney function worsens significantly or if they are no longer able to afford a NOAC.

Case of Poor Renal Function

The NOACs are not Food and Drug Administration (FDA) approved for use in patients currently on dialysis or in end-stage renal disease. Although not FDA approved, NOACs continue to be prescribed for patients with poor renal function. When this is the case, apixaban appears to be one of the safest options for those with chronic kidney disease. Apixaban has a lower rate of stroke, death, and major bleeding compared to warfarin in patients with a glomerular filtration rate of ≤ 50 ml/min (Shamoun, Obeid, & Ramakrishna, 2015; Siontis et al., 2018). One of the few advantages of warfarin over the NOACs is that warfarin can be used without regard to renal function and can be used in dialysis patients as shown in Table 3.

Conclusion

If anticoagulation is indicated in AF, warfarin or a NOAC should be initiated to prevent clots from forming and causing ischemic strokes. For the general population without valvular disease or significant kidney disease, NOACs offer several advantages compared to warfarin. Without routine monitoring and few interactions, NOACs simplify anticoagulation and often provide better protection from ischemic stroke and other bleeding complications. If

anticoagulation is recommended, the NOACs should be the preferred anticoagulants over warfarin (Gambino, 2018). In cases of impaired renal function, excluding hemodialysis, apixaban is the treatment of choice (Mekaj, Mekaj, Duci, & Miftari, 2015). Warfarin can be an effective anticoagulant and currently is the only approved anticoagulant for patients on dialysis, with a heart valve problem, or heart valve replacement (Mekaj, Mekaj, Duci, & Miftari, 2015).

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Table 1
CHADS2 Score

Category	Point value
C- Congestive heart failure	1
H- Hypertension	1
A- Age equal or over 75 years	1
D- Diabetes Mellitus	1
S- History of stroke or transient ischemic attack	2

Adapted from “Underuse of Anticoagulation in Older Patients with Atrial Fibrillation and CHADS2 Score ≥ 2 : Are We Doing Better Since the Marketing of Direct Oral Anticoagulants?” by S. Henrard, C. Vandenabeele, S. Marien, B. Boland, and O. Dalleur, 2017, *Drugs & Aging*, 34, p. 841-850.

Table 2
NOACs Reversal Agents

NOAC	Reversal Agent	Time Required to Reverse Medication
Apixaban	Adexanet Alpha	3 hours
Dabigatran	Idarucizumab	4 hours
Rivaroxaban	Adexanet Alpha	3 hours
Edoxaban	Adexanet Alpha (in clinical trial)	NA

(Rogers & Finks, 2018).

Table 3

Summary Table for Comparison of NOACs and Warfarin

	Apixaban (Eliquis)	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Edoxaban (Savaysa)	Warfarin (Coumadin)
Medication Class	NOAC, Factor Xa inhibitor	NOAC, direct thrombin inhibitor	NOAC, Factor Xa inhibitor	NOAC, Factor Xa inhibitor	Vitamin K Antagonist
Required Monitoring	None	None	None	None	INR
Labs Used to Monitor	Prothrombin time or chromogenic antifactory Xa assay (normal range 20-660ng/ml)	Activated partial thromboplastin time or Hemoclot assay	Prothrombin time or chromogenic antifactory Xa assay (normal range 20-660ng/ml)	Chromogenic antifactory Xa assay (normal range 20-660ng/ml)	INR
Food interaction	None	None	None	None	Foods with vitamin K, some enteral feeds, grapefruit, alcohol
Contraindicated Medication	Defibrotide and Mifepristone. Interacts with the CYP3A4 substrate.	Defibrotide and Mifepristone.	Defibrotide and Mifepristone. Interacts with the CYP3A4 substrate.	Defibrotide and Mifepristone.	Interacts with CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP3A4 substrates. Multi-vitamins containing Vitamin K
Reversal agents	Andexanet alfa	Idarucizumab	Andexanet alfa	None	Vitamin K and fresh frozen plasma,. \$4-7/30 tabs plus lab draw fees
Cost average (Good RX-as of April 2018)	\$215/30 tabs	\$194/30 tabs	\$430/30 tabs	\$350/30 tabs	
Dosing	1-2/day	2 times a day	1-2/ day	One per day	One per day
Renal function	CrCl>15 mL/min needed. No dialysis.	Dose adjustment needed with CrCl 15-30 mL/min. Not indicated CrCl < 15 mL/min. No dialysis	CrCl< 30 mL/min should avoid.	Recommended CrCl>95 mL/min. No dialysis.	Used in all kidney functions. Okay with dialysis.

(Rogers & Finks, 2018; Griffiths et al., 2017; May, 2018; Kampouraki & Kamlai, 2017; Mekaj et al., 2015; Garton, Dudzinski, & Kowey, 2014; Shamoun, Obeid, & Ramakrishna, 2015; Siontis et al., 2018; Salazar, del Aguila, & Cordova, 2016; Shafeeq & Tran, 2014; Albert, 2014)

Figure 1. Clotting Cascade

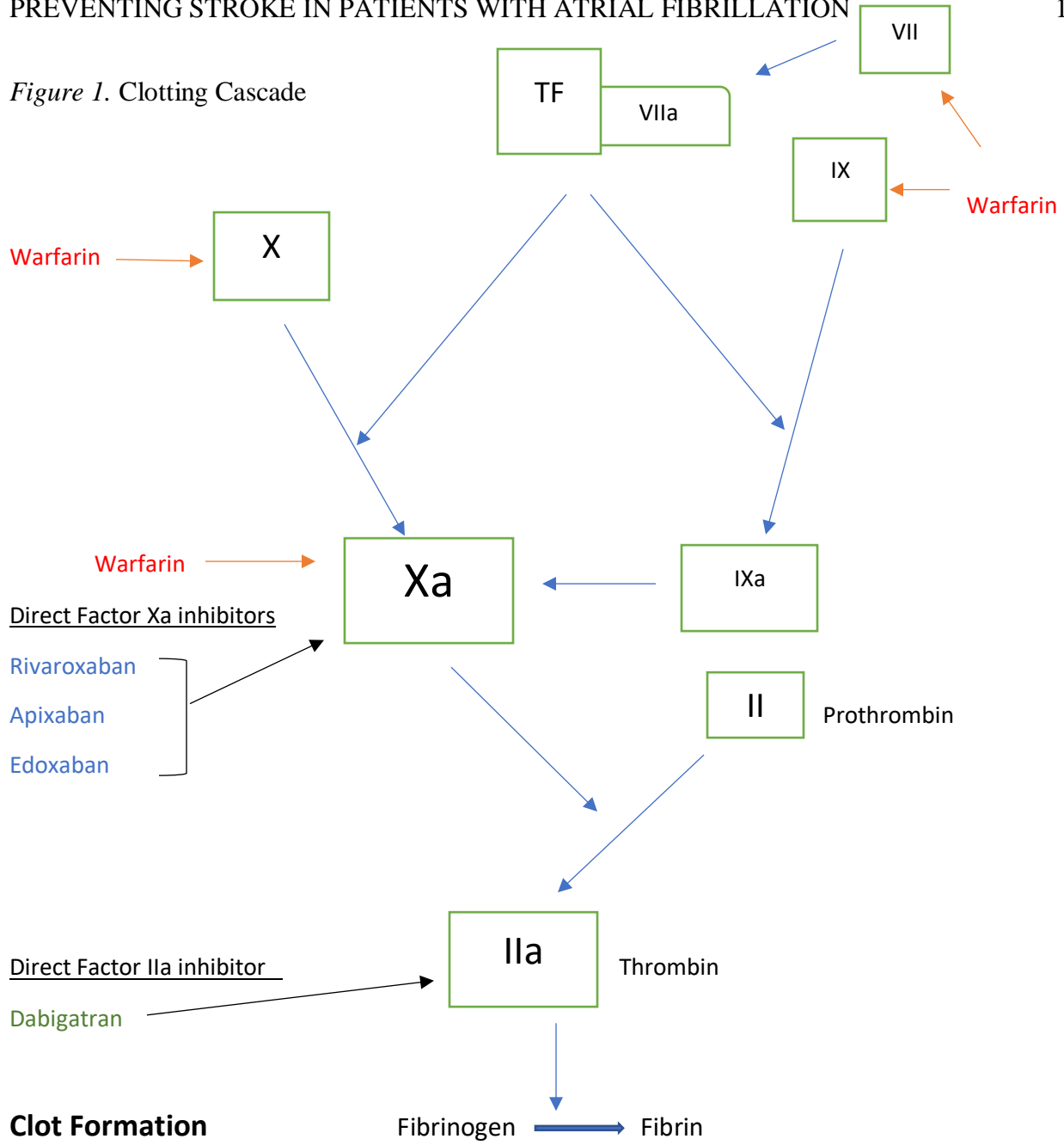


Figure 1. Where the NOACs and warfarin affect the clotting cascade. Adapted from “New Oral Anticoagulants: Their Advantages and Disadvantages Compared with Vitamin K Antagonists in the Prevention and Treatment of Patients with Thromboembolic Events,” by Y. H. Mekaj, A. Y. Mekaj, S. B. Duci, and E. I. Miftari, 2015, *Therapeutics and Clinical Risk Management*, 2015, p. 967-977.