Use of Antithrombotics in Non-Valvular Atrial Fibrillation – Adult – Inpatient/Ambulatory Clinical Practice Guideline

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Contact for Content:
Name: Anne Rose, PharmD; Anticoagulation Stewardship - Pharmacy
Phone Number: (608) 263-9738
Email Address: arose@uwhealth.org

Contact for Changes:
Name: Philip Trapskin, PharmD, BCPS; Drug Policy Manager - Pharmacy
Phone Number: (608) 265-0341
Email Address: ptrapskin@uwhealth.org

Guideline Author(s):
Christopher Hulstein, PharmD – Pharmacy
Anne Rose, PharmD – Pharmacy

Coordinating Team Members:
Anne O'Connor, MD – Cardiology

Review Individuals/Bodies:
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Executive Summary

Guideline Overview

This document is intended to be used by primary care providers, cardiologists, hospitalists, pharmacists, and nursing to guide the use of antithrombotics in adult patients diagnosed with non-valvular atrial fibrillation (NVAF) in the inpatient, ambulatory and emergency department settings. Guidance for transitioning between different anticoagulant agents is also included.

This guideline will review antithrombotics used in non-valvular AF and will aim to provide clinical support in selecting an anticoagulant agent that is best suited based on individual patient needs and risk factors.

Key Revisions

1. Edoxaban has been added to 2016 update as a first-line oral anticoagulant.
2. $CHADS_2$ Score has been removed from 2014 version. It is now recommended to utilize the CHA_2DS_2VASc Score to determine necessity of anticoagulation.

Key Practice Recommendations

1. Oral anticoagulation should be initiated in patients with non-valvular AF with prior stroke, transient ischemic attack (TIA), or a CHA_2DS_2-VASc score of 2 or greater.
2. Apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin are all considered first-line therapies.
3. Selection of an oral anticoagulant should be based on patient-specific factors such as renal function, age, drug-drug interactions, and cost of therapy.

Companion Documents

1. Atrial Fibrillation Management – Adult – Inpatient/Ambulatory - CPG
2. ED Atrial Fibrillation Management Algorithm
3. Ambulatory Guideline for Management of Warfarin – Adult – Ambulatory - CPG
4. Inpatient Guideline for Management of Warfarin – Adult – Inpatient - CPG
5. Procoagulant Guideline – Adult – Inpatient – CPG
6. Periprocedural Anticoagulation (Bridging) – Adult – Inpatient/Ambulatory – CPG

Scope

Disease/Condition(s):

Non-valvular atrial fibrillation (AF)

Clinical Specialty:

Primary Care, Cardiology, Pharmacy, Nursing

Intended Users:

Advanced Practice Providers, Pharmacists, Physicians, Registered Nurses

Objective(s):

To minimize stroke incidence associated with non-valvular AF and minimize bleeding rates associated with oral anticoagulation.

Target Population:
Adult patients diagnosed with non-valvular AF in the inpatient, ambulatory and emergency department settings.

Interventions and Practices Considered:
- This guideline recommends when to initiate oral anticoagulation in adult patients with non-valvular AF based on stroke and bleeding risks
- This guideline provides recommendations for appropriate oral anticoagulation selection based on patient-specific factors

Major Outcomes Considered:
- Stroke incidence in adult patients with non-valvular AF
- Incidence of major and minor bleeding events in adult patients with non-valvular AF receiving oral anticoagulation for stroke prevention

Methodology

Methods Used to Collect/Select the Evidence:
Electronic database searches (e.g., PUBMED) were conducted by the guideline author(s) and workgroup members to collect evidence for review. Expert opinion and clinical experience were also considered during discussions of the evidence.

Methods Used to Formulate the Recommendations:
The workgroup members agreed to adopt recommendations developed by external organizations and/or arrived at a consensus through discussion of the literature and expert experience. All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees (as appropriate).

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1** in Appendix A).

Rating Scheme for the Strength of the Evidence/Recommendations:
See Appendix A for the rating scheme(s) used within this document.

Cost Analysis:
Table 1 – Outpatient Cost Analysis – (AWP)

Medication	Price per day ($)
Apixaban 5 mg	**$$$**
Aspirin 81 mg	**$**
Dabigatran 150 mg	**$$$**
Edoxaban 60 mg	**$$$$**
Rivaroxaban 20 mg	**$$$$**
Warfarin 5 mg	**$**

Where $ = $0.01-$1.00, $$ = $1.01-$5.00, $$$ = 5.01-$10.00, and $$$$ = $10.01-$15.00

Recognition of Potential Health Care Disparities:
While warfarin is the least expensive medication, the cost for monitoring the INR should be considered. Additionally, the availability of INR monitoring and access, including transportation, to clinic facilities should be considered. DOACs may have medication assistance programs for patients who qualify.

Definitions

- **Creatinine Clearance**[1]
    - For patients with a BMI ≤30 kg/m^2, creatinine clearance should be calculated using the Cockcroft-Gault formula
        - Cockcroft-Gault should be calculated using adjusted body weight (ABW)
            - ABW= 0.4 (TBW – ideal body weight) + ideal body weight
    - For patients with a BMI >30 kg/m^2, creatinine clearance can be calculated using either the Salazar-Corcoran or Cockcroft-Gault formulas
        - Salazar-Corcoran should be calculated using total body weight (TBW)

- **DOAC** – Direct Oral Anticoagulant (includes apixaban, dabigatran, edoxaban, and rivaroxaban); also known as "NOAC" (Novel Oral Anticoagulant) and "TSOAC" (Target-Specific Oral Anticoagulant)

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and is responsible for one-third of hospitalizations due to arrhythmia. Currently, AF affects 2.5 million people in the United States; however, this percentage is expected to increase to an estimated 16 million people by the year 2050, due to the aging "baby-boomer" population.[2] One of the most concerning sequelae associated with AF is ischemic stroke, with an incidence of about 5% per year in the absence of appropriate prophylaxis.[3] Traditionally, dose-adjusted vitamin K antagonists, such as warfarin, have been used to prevent the occurrence of stroke in intermediate-to-high risk AF patients. However, the development of novel, more directed anticoagulants have been shown to produce more predictable anticoagulation, do not require monitoring anticoagulation status, and have demonstrated improvement in patient outcomes. This group of newer oral agents, referred to as direct oral anticoagulants (DOACs), includes apixaban, dabigatran, edoxaban, and rivaroxaban.

In 2014, the American Heart Association/American College of Cardiology/Heart Rhythm Society published the Guideline for the Management of Patients with Atrial Fibrillation.[4] This guideline recommends use of warfarin, apixaban, dabigatran, or rivaroxaban for anticoagulation in patients with non-valvular AF with prior stroke, transient ischemic attack (TIA), or a CHA_2DS_2-VASc score of 2 or greater. This recommendation did not include edoxaban as it was approved after the 2014 guideline was published. Currently there are no direct comparisons among DOACs, and the American Heart Association has not made a stance on selection of one DOAC over another. It is accepted that any of the DOACs could be considered as first line therapy.[3] Selection of oral anticoagulation, therefore, should be based on patient-specific factors such as renal function, age, drug-drug interactions, and cost of therapy.[4]

Other guidelines that provide recommendations for the management of AF have also included DOACs as considerations when oral anticoagulant therapy is indicated but have not listed them as preferred agents at this time. This was often due to agents not being FDA approved at the time of guideline update.[5,6]

Antithrombotics used in non-valvular atrial fibrillation include: (listed alphabetically)

1. **Apixaban**[7] is a direct, competitive, reversible factor Xa inhibitor. This inhibition decreases the activation of platelets and the conversion of fibrinogen to fibrin, leading to a decreased ability to form fibrin clots. It was studied versus warfarin in a randomized, double-blind trial for the prevention of ischemic or hemorrhagic stroke or systemic embolism.[8] Apixaban 5 mg BID demonstrated significantly lower rates of stroke and systemic embolism than warfarin. Additionally, apixaban showed lower rates of intracranial hemorrhage and all major bleeding as compared to warfarin. Results of the ARISTOLE trial are summarized in Table 2 and general drug information is summarized in Table 3.

Table 2 – Summarized results of apixaban versus warfarin in NVAF

Outcome (rate per year)	Apixaban 5 mg BID	Warfarin INR 2-3	P value
Stroke or embolism	1.27	1.6	0.01
Hemorrhagic stroke	0.24	0.47	<0.001
Major bleeding	4.07	6.01	<0.001
Intracranial hemorrhage	0.33	0.8	<0.001
GI bleeding	0.76	0.86	0.37
Mortality	3.5	3.9	0.047

Table 3 – Apixaban medication information

Usual Dose	5 mg BID *(for dose adjustments see Table 14)*
Onset	3-4 hours; Bioavailability is ~50%, and is not affected by food
Half Life	15 hours
Metabolism	Hepatic Predominantly via CYP3A4/5, with alternative pathways through CYP 1A2, 2C8, 2C9, 2C19, and 2J2 to inactive metabolites. Excreted through the urine (~27% as parent drug), and feces (~25% as metabolites)
Adverse Drug Reactions	Bleeding Nausea Anemia Increased transaminases
Drug Interactions	Strong CYP3A4 inhibitors (e.g. azole antifungals, nicardipine, ritonavir) may increase the serum concentrations Strong CYP3A4 inducers (e.g. carbamazepine, nafcillin, phenobarbital, phenytoin, rifampin) may decrease serum concentrations P-gp inhibitors (e.g. amiodarone, cyclosporine, ketoconazole, quinidine, verapamil) may increase the serum concentration P-gp inducers (e.g. carbamazepine, dexamethasone, phenytoin, prazosin, rifampin) may decrease the serum concentration
Black Boxed Warning	Increased risk of ischemic events when stopped without adequate anticoagulation with an alternative agent Epidural or spinal hematomas may occur in those who are receiving neuraxial anesthesia or are undergoing spinal puncture.
Contraindication	Active bleeding, Hypersensitivity to apixaban Major regional or lumbar block analgesia

2. **Aspirin** non-selectively and irreversibly inhibits cyclooxygenase, reducing prostaglandin and thromboxane A2 synthesis. This produces analgesic, anti-inflammatory, and anti-pyretic effects, and reduces platelet aggregation.
   2.1 Usual dose of aspirin is between 81 and 325 mg per day to prevent stroke in low risk patients with AF
   2.2 Time to peak serum concentration is ~1-2 hours
   2.3 Metabolism is via hydrolysis to salicylate (active form) by esterases in the GI mucosa, red blood cells, synovial fluid; metabolism occurs by hepatic conjugation
   2.4 Adverse drug reactions include dyspepsia, nausea, and bleeding events
   2.5 Contraindicated in patients with hypersensitivity to salicylates, rhinitis, nasal polyps, inherited or acquired bleeding disorders, or in patients <16 years of age for viral infections

3. **Dabigatran etexilate**[9] is an oral prodrug that is rapidly converted by serum esterases to dabigatran, direct, competitive inhibitor of both free and fibrin-bound thrombin (factor II). It was studied versus warfarin in a randomized, blinded treatment arm trial for prevention of stroke or systemic embolism in NVAF.[10] Dabigatran 150 mg BID demonstrated lower rates of stroke and embolism with a similar major bleeding rate to warfarin. Additionally, dabigatran has significantly lower rates of intracranial hemorrhage but higher rate of GI bleeding as compared to warfarin. Results of the RE-LY trial are summarized in Table 4 and general drug information is summarized in Table 5.

Table 4 – Summarized results of dabigatran versus warfarin in NVAF

Outcome (rate per year)	Dabigatran 150 mg BID	Warfarin INR 2-3	P value
Stroke or embolism	1.11	1.69	<0.001
Hemorrhagic stroke	0.10	0.38	<0.001
Major bleeding	3.11	3.36	0.31
Intracranial hemorrhage	0.3	0.7	<0.001
GI bleeding	1.51	1.02	<0.001
Mortality	3.64	4.13	0.13

Table 5 – Dabigatran medication information

Usual Dose	150 mg BID *(for dose adjustments see Table 14)*
Onset	1 hour; May be delayed 2 hours by food
Half Life	Half-life is generally 12-17 hours; increased in elderly (14-17 hours), mild-to-moderate renal impairment (15-18 hours), and severe renal impairment (28 hours).
Metabolism	Hepatic glucuronidation to active acylglucoronide isomers, and is excreted through the urine (80%)
Adverse Drug Reaction	Bleeding Dyspepsia Anemia Increased ALT
Drug Interactions	P-gp inhibitors (e.g. amiodarone, cyclosporine, ketoconazole, quinidine, verapamil) may increase serum concentrations P-gp inducers (e.g. carbamazepine, dexamethasone, phenytoin, prazosin, rifampin) may decrease the serum concentration

Black Boxed Warning	Increased risk of ischemic events when stopped without adequate anticoagulation with an alternative agent Epidural or spinal hematomas may occur in those who are receiving neuraxial anesthesia or are undergoing spinal puncture.
Contraindication	Active bleeding Hypersensitivity to dabigatran Major regional or lumbar block analgesia Mechanical prosthetic heart valves.

4. **Edoxaban**[11] is a direct, competitive, reversible factor Xa inhibitor. This inhibition decreases the activation of platelets and the conversion of fibrinogen to fibrin, leading to a decreased ability to form fibrin clots. It was studied versus warfarin in a randomized, double-blind, double-dummy trial for the prevention of stroke or systemic embolism in NVAF.[12] Edoxaban 60 mg daily was non-inferior to warfarin in regards to prevention of stroke and systemic embolism. Edoxaban showed significantly less major bleeding and intracranial hemorrhages, however, had higher incidence of GI bleeding when compared to warfarin. Results of the ENGAGE-AF trial are summarized in Table 6 and general drug information is summarized in Table 7.

Table 6 – Summarized results of edoxaban versus warfarin in NVAF

Outcome (rate per year)	Edoxaban 60 mg daily	Warfarin INR 2-3	P value
Stroke	1.49	1.69	0.11
Hemorrhagic Stroke	0.26	0.47	<0.001
Systemic Embolism	0.08	0.12	0.19
Major bleeding	2.75	3.43	<0.001
Intracranial hemorrhage	0.39	0.85	<0.001
GI bleeding	1.51	1.23	0.03

Table 7 – Edoxaban medication information

Usual Dose	60 mg daily *(for dose adjustments see Table 14)*
Onset	1 -2 hours
Half Life	10 – 14 hours
Metabolism	Approximately 50% of the drug is renally eliminated.
Adverse Drug Reaction	Bleeding events Anemia Abnormal hepatic function tests
Drug Interactions	Strong CYP3A4 inhibitors (e.g. azole antifungals, nicardipine, ritonavir) may increase serum concentrations Strong CYP3A4 inducers (e.g. carbamazepine, nafcillin, phenobarbital, phenytoin, rifampin) may decrease serum concentrations. Use of edoxaban with rifampin should be avoided P-gp inhibitors (e.g. amiodarone, cyclosporine, ketoconazole, quinidine, verapamil) may increase serum concentrations, but dose adjustment is not recommended P-gp inducers (e.g. carbamazepine, dexamethasone, phenytoin, prazosin,

	rifampin) may decrease serum concentrations. Use of edoxaban with rifampin should be avoided
Black Boxed Warning	CrCl > 95 mL/min: reduced efficacy in NVAF Increased risk of ischemic events when stopped without adequate anticoagulation with an alternative agent Epidural or spinal hematomas may occur in those who are receiving neuraxial anesthesia or are undergoing spinal puncture.
Contraindication	Active pathological bleeding

5. **Rivaroxaban**[13] is a direct, competitive, reversible Factor Xa inhibitor. This inhibition decreases the activation of platelets and the conversion of fibrinogen to fibrin, leading to a decreased ability to form fibrin clots. It was studied versus warfarin in a randomized, double blind, double dummy clinical trial for the prevention of stroke and embolism in NVAF.[14] Rivaroxaban 20 mg daily demonstrated non-inferiority to warfarin in the prevention of stroke and embolism with a similar major bleeding rate to warfarin. Additionally, rivaroxaban showed significantly lower rates of intracranial hemorrhage but higher rate of GI bleeding as compared to warfarin. Results of the ROCKET-AF trial are summarized in Table 8 and general drug information is summarized in Table 9.

Table 8 – Summarized results of rivaroxaban versus warfarin in NVAF

Outcome (rate per year)	Rivaroxaban 20 mg daily	Warfarin INR 2-3	P value
Stroke or embolism	1.7	2.2	<0.001
Hemorrhagic stroke	0.10	0.38	<0.001
Major bleeding	14.9	14.5	0.44
Intracranial hemorrhage	0.5	0.7	0.02
GI bleeding	3.2	2.2	<0.001

Table 9 – Rivaroxaban medication information

Usual Dose	20 mg daily with evening meal *(for dose adjustments see Table 14)*
Onset	2-4 hours
Half Life	5-12 hours; increased in elderly (11-19 hours)
Metabolism	Primarily hepatic, via CYP3A4/5 and CYP2J2, and is excreted through the urine (66% via tubular secretion), feces (28%)
Adverse Drug Reaction	bleeding events, peripheral edema, back pain, and rash
Drug Interactions	Strong CYP3A4 inhibitors (e.g. azole antifungals, nicardipine, ritonavir) may increase serum concentrations Strong CYP3A4 inducers (e.g. carbamazepine, nafcillin, phenobarbital, phenytoin, rifampin) may decrease serum concentrations P-gp inhibitors (e.g. amiodarone, cyclosporine, ketoconazole, quinidine, verapamil) may increase serum concentrations P-gp inducers (e.g. carbamazepine, dexamethasone, phenytoin, prazosin, rifampin) may decrease the serum concentrations

Black Boxed Warning	Increased risk of ischemic events when stopped without adequate anticoagulation with an alternative agent Epidural or spinal hematomas may occur in those who are receiving neuraxial anesthesia or are undergoing spinal puncture.
Contraindication	Active bleeding Hypersensitivity to rivaroxaban Major regional or lumbar block analgesia

6. **Warfarin** competitively inhibits vitamin K epoxide reductase complex 1, which is the enzyme responsible for reactivating vitamin K in the human body. Vitamin K is required to produce clotting factors II, VII, IX and X, which are major factors involved in clot formation. This inhibition by warfarin depletes the amount of functional vitamin K, and in turn decreases the levels of clotting factors in the body. Table 10 summarized general drug information on warfarin.

Table 10 – Warfarin medication information

Usual Dose	Dosing based on INR range (typically 2-3). Usual starting dose 5 mg May consider 2.5 mg for elderly, hepatic impairment, poor nutrition, heart failure, high bleeding risk, CYP2C9 slow metabolizers.
Onset	5-7 days of consistent dosing for full therapeutic effect.
Half Life	7 days
Metabolism	Primarily hepatic via CYP2C9, with some minor pathways through CYP 2C8, 2C18, 2C19, 1A2, and 3A4
Adverse Drug Reaction	Bleeding events Less commonly hepatitis, skin necrosis, and “purple toe” syndrome
Drug Interactions	Strong CYP3A4 inhibitors (e.g. azole antifungals, nicardipine, ritonavir) may increase serum concentrations Strong CYP3A4 inducers (e.g. carbamazepine, nafcillin, phenobarbital, phenytoin, rifampin) may decrease serum concentrations P-gp inhibitors (e.g. amiodarone, cyclosporine, ketoconazole, quinidine, verapamil) may increase serum concentrations P-gp inducers (e.g. carbamazepine, dexamethasone, phenytoin, prazosin, rifampin) may decrease the serum concentrations Increased bleed risk
Black Boxed Warning	Can cause major or fatal bleeding.
Contraindication	Pregnancy Hypersensitivity to warfarin Hemorrhagic tendencies or blood dyscrasias Recent or contemplated surgery of the CNS Traumatic surgery resulting in large open surfaces Spinal puncture or other procedures with the potential for uncontrollable bleeding Major regional or lumbar block analgesia

Recommendations

Recommendations for Determining if Anticoagulation is Necessary

1. Evaluate the patient's stroke risk using risk assessment strategy provided in Table 11 and the estimated yearly risk of stroke in Table 12 ***(AHA Class I, Level B)***[3,15]
   1.1 The CHA_2DS_2VASc Score incorporates additional risk factors for stroke. While it is not as well validated as the $CHADS_2$ Score, it has been validated in AF populations and has been shown to dependably identify low risk patients who do not need anticoagulation. The CHA_2DS_2VASc Score is the preferred risk assessment strategy.[4]

Table 11 – CHA_2DS_2VASc Score[16]

Factors	Points
Congestive Heart Failure	1
Hypertension	1
Age ≥75	2
Diabetes Mellitus	1
Stroke/TIA/Thromboembolism	2
Vascular Disease (MI, PAD, aortic plaque)	1
Age 65-74	1
Sex **C**ategory – Female	1
Score: 0 = No antithrombotic therapy preferred 1 = Oral anticoagulation may be considered* ≥ 2 = Oral anticoagulation preferred	

*if score of 1 from gender alone then no antithrombotic therapy preferred

Table 12 – Adjusted Yearly Stroke Risk for CHA_2DS_2VASc Scores

Score	CHA_2DS_2VASc (%/year)
0	0
1	1.3
2	2.2
3	3.2
4	4
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

2. Evaluate the patient's bleeding risk using the HAS-BLED risk assessment strategy outlined in Table 13. ***(AHA Class I, Level C)***[17]
   2.1 The HAS-BLED score stratifies patients as low, moderate, or high bleeding risk based on individual bleeding risk factors. It has been shown to more accurately predict the risk of major bleeding in patients receiving no antithrombotic or antiplatelet therapy than another bleeding risk score, $HEMORR_2HAGES$.
   2.2 This score should not automatically exclude patients from receiving anticoagulation if it is clinically indicated, particularly since many of the risk factors that may predispose patients to a bleeding event are also risk factors that increase their risk for stroke.
   2.3 The HAS-BLED score should be used to identify risk factors for bleeding, and attempts should be made to correct modifiable risks, such as uncontrolled hypertension.[18]

Table 13 – HAS-BLED Score[17]

Factors	Scoring
Hypertension (SBP >160 mmHg)	**Score = 0-1:** Low risk **Score = 2:** Moderate risk **Score ≥3:** High risk **High bleed risk considerations:** - Optimize blood pressure control - Check INRs frequently - Utilize anticoagulation clinic - Focus on fall prevention - Utilize DOACs
Abnormal lab values - Creatinine >2.26 mg/dL - Bilirubin >2x the upper limit of normal (ULN) *and* AST/ALT/AP >3x ULN	
Stroke history	
Bleeding history or predisposition	
Labile INRs: Time in Therapeutic Range <60%	
Elderly: >65 years	
Drugs - EtOH abuse - ASA or NSAID use	

Recommendations for Appropriate Anticoagulation Selection

Prior to initiating anticoagulation therapy the benefits and risks of anticoagulation should be discussed with the patient, being sure to incorporate their priorities in the decision making process. When anticoagulation has been identified as the therapy of choice to prevent ischemic stroke in AF, selection of the most appropriate agent should be individualized based on both clinical evidence and patient specific risk factors. ***(AHA Class I, Level C)***

3. Oral Anticoagulation
   3.1 Warfarin ***(AHA Class I, Level A)***or a DOAC ***(AHA Class I, Level B)*** may be considered. Prior to selecting an oral anticoagulant see #4 to develop an individualized patient therapy plan ***(AHA Class I, Level C)***
   3.2 Currently, there are no trials that directly compare one DOAC to another.

4. Additional considerations to evaluate:
   4.1 Prosthetic Heart Valves or Severe Valvular Disease
      4.1.1 Warfarin is recommended with mechanical heart valves. Target INR intensity should be based on the type and location of prosthesis[4] ***(AHA Class I, Level B)***

4.1.2 Dabigatran is contraindicated and should not be used in patients with AF and mechanical heart valves.[3,5,9] ***(AHA Class III: Harm, Level B)***

4.1.3 Due to the lack of data, factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) should not be used in patients with AF and mechanical heart valves. ***(AHA Class III: No Benefit, Level C)***

4.2 Renal Function ***(AHA Class I, Level B)***

4.2.1 Recommendations for dose reductions for each agent in renal insufficiency should be followed. See Table 14.

4.2.2 CrCl < 15 mL/min not on hemodialysis: warfarin is the preferred agent

4.2.3 End stage kidney disease on dialysis: warfarin is preferred, but apixaban may be considered

4.2.4 CrCl > 95 mL/min: edoxaban is not recommended

4.3 Age ***(UW GRADE moderate quality of evidence, conditional recommendation)***

4.3.1 Age > 75 years: There was a trend towards increased risk of bleeding with dabigatran when compared to warfarin.[19]

4.3.2 This trend was not observed with other DOACs[8,20,21]

4.4 History of GI disease and/or GI bleeding in the past year ***(UW GRADE moderate quality of evidence, conditional recommendation)***

4.4.1 Dabigatran, edoxaban, and rivaroxaban have been associated with an increased risk of GI bleeding events as compared to warfarin and the other DOACs[10,20,21]

4.4.2 Apixaban was shown to have a lower risk of GI bleeding compared to warfarin[8]

4.4.3 Dyspepsia is also strongly associated with dabigatran use

4.5 Combination Antiplatelet Therapy ***(UW GRADE low quality of evidence, conditional recommendation)***

4.1 The addition of an antiplatelet to anticoagulant therapy can significantly increase bleeding risk. Bleeding risk compared to stroke risk must be weighed when using concomitant therapy.

4.2 **"Triple therapy"** (Aspirin, P2Y12 agents, & anticoagulant) or higher dose aspirin (> 100 mg) and anticoagulant **should be avoided if possible** or if not possible to avoid then duration of therapy should minimized[4]

4.3 If triple therapy is warranted, it is strongly recommended to obtain a cardiology consult.

4.6 Drug Interactions ***(UW GRADE moderate quality of evidence, conditional recommendation)***

4.6.1 Warfarin has many documented drug interactions to consider. Closely following the INR can help to monitor the effects of the drug interactions.

4.6.2 There are less documented drug interactions with DOACs, however, it is not possible to monitor for increased or decreased effectiveness in the presence of an interacting agent.

4.7 Monitoring ***(UW GRADE moderate quality of evidence, conditional recommendation)***

4.7.1 DOACs do not require laboratory monitoring of anticoagulation status and may be preferred in patients who dislike frequent lab draws.

4.7.2 DOACs should have laboratory monitoring of CBC, creatinine, and liver function tests at baseline, after 3-6 months of therapy and then at least once a year.

4.7.3 Warfarin requires laboratory monitoring of the INR. The INR should be checked at least twice weekly during initiation and monthly when stable. This agent may be less preferable in patients who do not have the means

or access to commit to intensive laboratory monitoring ***(AHA Class I, Level A)***

4.8 Financial Considerations ***(UW GRADE very low quality of evidence, conditional recommendation)***

- 4.8.1 While warfarin is the least expensive medication, the cost for monitoring the INR should also be considered.
- 4.8.2 DOACs may have medication assistance programs for patients who qualify.

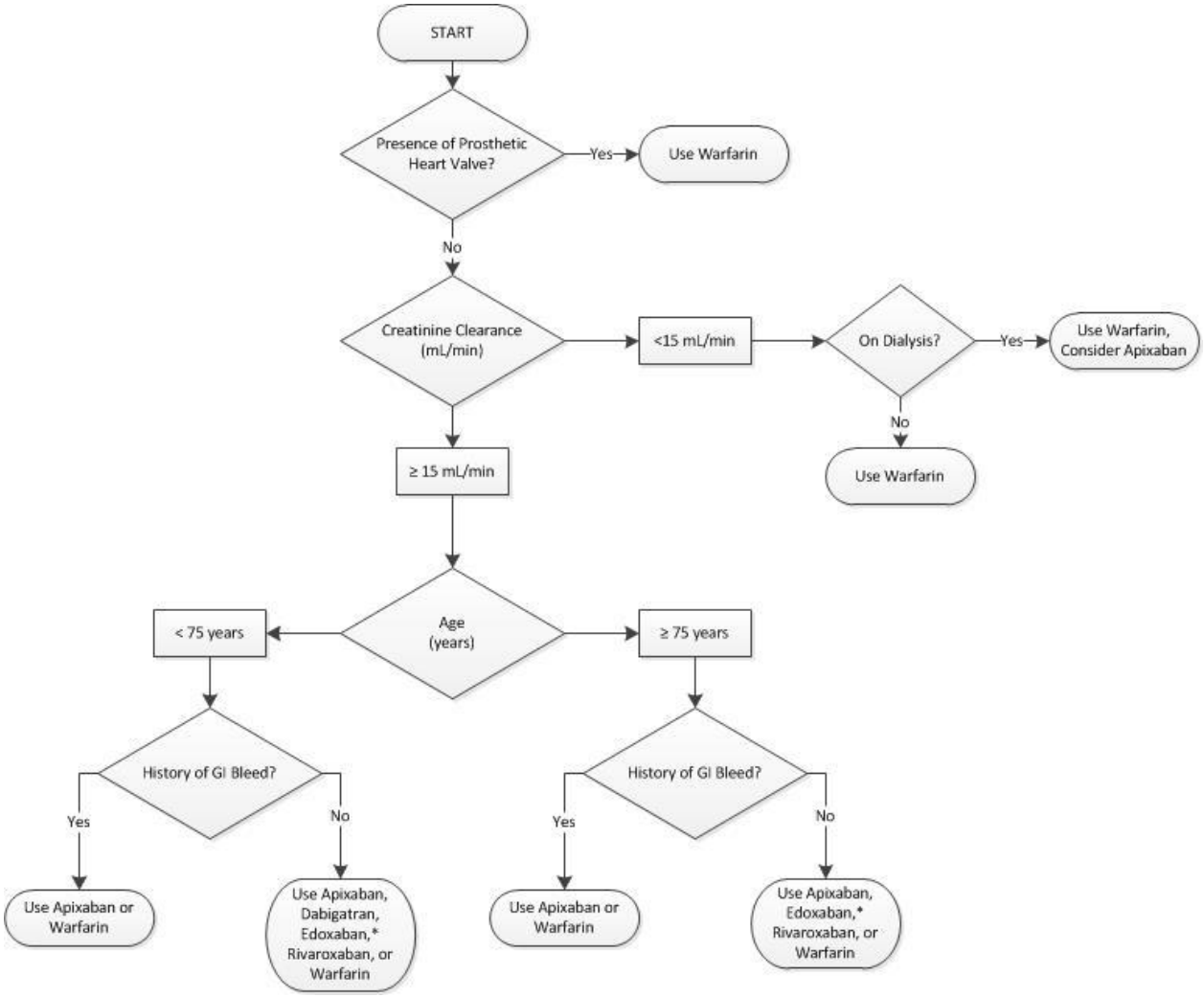
4.9 Medication Compliance ***(UW GRADE moderate quality of evidence, conditional recommendation)***

- 4.9.1 DOACs may be less preferable in patients who occasionally miss doses, as the duration of action is shorter than warfarin. One missed dose of these agents may place a patient at risk for stroke.
- 4.9.2 Warfarin may be less preferable in patients who are consistently non-compliant with doses if the target INR goal is rarely achieved. DOACs are recommended if unable to maintain a therapeutic INR on warfarin[4] ***(AHA Class I, Level C)***
- 4.9.3 If once daily regimens are preferred consider edoxaban, rivaroxaban, or warfarin.
- 4.9.4 If pill boxes or medication organizers are used to improve compliance, then dabigatran must be dispensed in sealed blister-packs. If stored in open air, it can compromise the effectiveness of the medication.

4.10 Administration ***(UW GRADE moderate quality of evidence, strong recommendation)***

- 4.10.1 Dabigatran capsules must be swallowed whole.[9]
- 4.10.2 Apixaban, rivaroxaban, and warfarin may be crushed[7,13]
  - 5.10.2.1 There is no data available on crushing edoxaban
- 4.10.3 Rivaroxaban cannot be administered via a feeding tube placed distal to the stomach[13]
- 4.10.4 Rivaroxaban should be administered with evening meal[13]
  - 5.10.4.1 Though package labeling indicates the evening meal specifically, the largest meal of the day may be considered

Algorithm to Assist in Selecting Anticoagulation



*Avoid use of edoxaban if creatinine clearance is greater than 95 mL/min

Table 14 – Anticoagulant Dosing Table[7,9,11,13]

Drug	Dosing		Monitoring	Drug Interactions
	CrCl (mL/min)	Dose		
Apixaban *Factor Xa inhibitor*	≥15	5 mg BID 2.5 mg BID with concomitant use of strong CYP3A4 and P-gp inhibitors 2.5 mg BID if 2 of the following: - age ≥80 years - body weight ≤60 kg - SCr ≥1.5 mg/dL	No routine monitoring is needed to determine anticoagulation status. Recommend baseline and annual creatinine, CBC, AST/ALT/AP	Strong CYP3A4 or P-gp inhibitors may increase serum concentrations Strong CYP3A4 or P-gp inducers may decrease serum concentrations
	<15 (on HD)	5 mg BID 2.5 mg BID if either: - age ≥80 years - body weight ≤60 kg		
	<15 (not on HD)	Avoid use		
Aspirin *COX-inhibitor*	Any	81 mg once daily	No routine monitoring is needed to determine anticoagulation status	Use in combination with other antithrombotic agents may increase the risk of bleeding
Dabigatran *Direct thrombin inhibitor*	>30	150 mg BID 75 mg BID with concomitant use of P-gp inhibitor	No routine monitoring is needed to determine anticoagulation status. Recommend baseline and periodic creatinine, CBC, AST/ALT/AP	P-gp inhibitors may increase serum concentrations P-gp inducers may decrease serum concentrations
	15-30	75 mg BID Avoid use if concomitant use of P-gp inhibitor		
	<15	Avoid use		

Table 14 – Anticoagulant Dosing Table (continued)

Edoxaban *Factor Xa inhibitor*	>95	Avoid use	No routine monitoring is needed to determine anticoagulation status Recommend baseline and annual creatinine, CBC, AST/ALT/AP	Strong CYP3A4 or P-gp inhibitors may increase serum concentrations. Strong CYP3A4 or P-gp inducers may decrease serum concentrations.
	50-95	60 mg once daily		
	15-50	30 mg once daily		
	<15	Avoid use		
Rivaroxaban *Factor Xa inhibitor*	>50	20 mg once daily	No routine monitoring is needed to determine anticoagulation status. Recommend baseline and annual creatinine, CBC, AST/ALT/AP	Strong CYP3A4 or P-gp inhibitors may increase serum concentrations Strong CYP3A4 or P-gp inducers may decrease serum concentrations
	15-50	15 mg once daily		
	<15	Avoid use		
Warfarin *Vitamin K Antagonist*	Any	Dose varies based on patient-specific factors	A baseline INR prior to initiation CBC, ALT, total bilirubin, and creatinine within the preceding 3 months, and periodically thereafter Refer to the inpatient or ambulatory warfarin guidelines for INR monitoring	Refer to Table 5 in the inpatient warfarin guideline, or Tables 10 and 11 in the ambulatory warfarin guidelines for drug interaction information

Table 15 – Anticoagulant Transitioning[7,9,11,13]

Switch	Procedure
Warfarin → Dabigatran	Stop warfarin, start dabigatran when INR <2.0
Warfarin → Rivaroxaban	Stop warfarin, start rivaroxaban when INR <3.0
Warfarin → Apixaban	Stop warfarin, start apixaban when INR <2.0
Warfarin → Edoxaban	Stop warfarin, start edoxaban when INR ≤2.5

Dabigatran → Warfarin	*Dabigatran affects the INR – measuring INRs during co-administration may not be useful for determining an appropriate dose of warfarin*
	• Start warfarin while patient is still taking dabigatran
	• Stop dabigatran 1-3 days later, depending on INR and CrCl
	  • If CrCl >50 mL/min: initiate warfarin 3 days prior to discontinuation of dabigatran
	  • If CrCl 31-50 mL/min: initiate warfarin 2 days before discontinuation of dabigatran
	  • If CrCl 15-30 mL/min: initiate warfarin 1 day before discontinuation of dabigatran

Rivaroxaban → Warfarin	*Rivaroxaban affects the INR – measuring INRs during co-administration may not be useful for determining an appropriate dose of warfarin* • Initiate warfarin and a parenteral anticoagulant 24 hours after discontinuation of rivaroxaban*
Apixaban → Warfarin	*Apixaban affects the INR – measuring INRs during co-administration may not be useful for determining an appropriate dose of warfarin* • If continuous anticoagulation is necessary, discontinue apixaban and begin both a parenteral anticoagulant with warfarin when the next dose of apixaban is due; discontinue parenteral anticoagulant when INR reaches an acceptable range*
Edoxaban → Warfarin	*Oral option:* • For patients receiving 60 mg of edoxaban, reduce dose to 30 mg and begin warfarin concomitantly. For patients receiving 30 mg of edoxaban, reduce the dose to 15 mg and begin warfarin concomitantly. • INR must be measured at least weekly and just prior to the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Once a stable INR ≥2 is achieved, edoxaban should be discontinued and the warfarin continued. *Parenteral option:* • Discontinue edoxaban and administer a parenteral anticoagulant (UFH or enoxaparin) and warfarin at the time of the next scheduled edoxaban dose. Once a stable INR ≥2 is achieved, edoxaban should be discontinued and warfarin continued.
UFH → DOAC	• Start dabigatran, rivaroxaban, or apixaban at the time of heparin discontinuation • Start edoxaban 4 hours after heparin discontinuation

Table 15 – Anticoagulant Transitioning (continued)[7,9,11,13]

DOAC → IV UFH or enoxaparin	Dabigatran: • If CrCl >30 mL/min, start UFH or enoxaparin 12 hours after the last dose of dabigatran • If CrCl <30 mL/min, consider starting UFH or enoxaparin 24 hours after the last dabigatran dose, based on the clinical interpretation of the patients bleeding and thrombosis risk Rivaroxaban: • Start UFH or enoxaparin 24 hours after the last rivaroxaban dose, based on the clinical interpretation of the patients bleeding and thrombosis risk Apixaban: • Start UFH or enoxaparin 12 hours after the last apixaban dose Edoxaban: • Start UFH or enoxaparin at the time of the next dose of edoxaban

*Overall risk stratification should focus on the patient's risk of thromboembolism since the consequences of a thromboembolic event are more likely to have serious, lasting effects compared to consequences of major bleeding. It is recommended to provide continuous therapeutic anticoagulation for patients with a recent stroke or TIA (within 3 months). Note that not all patients will require bridging with a parenteral anticoagulant.

UW Health Implementation

Potential Benefits:

- The benefit of this guideline is to identify appropriate use of DOACs and warfarin for adult patients diagnosed with non-valvular atrial fibrillation, who are at an intermediate-to-high risk of stroke.

Potential Harms:

- The risk of implementing this guideline and administering anticoagulant agents is increased bleeding and can be related to underlying conditions, age, comorbidities, and dose.

Qualifying Statements:

- The amount of data available is small and recent guidelines are based on few trials. The recommendations included in this guideline are subject to change with the publication of additional clinical trials.

Patient Resources

1. Health Facts For You #6252- Atrial Fibrillation
2. Health Facts For You #6900- Warfarin (Coumadin, Jantoven)
3. Health Facts For You #7826- Direct Oral Anticoagulants
4. Health Facts For You #6115- Stopping Anticoagulation and Antiplatelet Therapy for Patients and Providers
5. Healthwise: Atrial Fibrillation

Guideline Metrics

1. Stroke Core Measure #3: Anticoagulation therapy for atrial fibrillation/flutter
2. Incidence of stroke in adult patients with non-valvular AF
3. Incidence of major and minor bleeding events in adult patients with non-valvular AF receiving oral anticoagulation for stroke prevention

Implementation Plan/Clinical Tools.

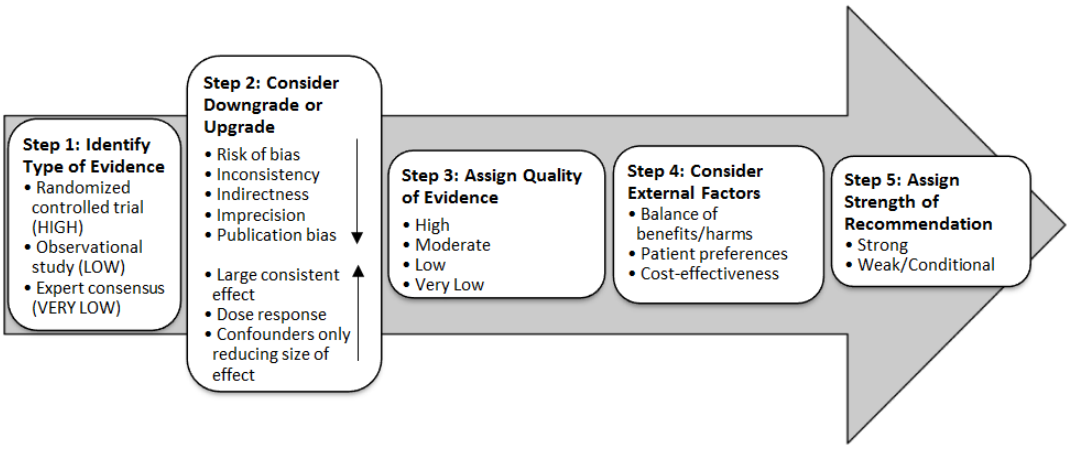
1. Guideline will be posted on uConnect in a dedicated location for Clinical Practice Guidelines.
2. Release of the guideline will be advertised in the Physician/APP Briefing newsletter.
3. Content and hyperlinks within clinical tools, documents, or Health Link related to the guideline recommendations (such as the following) will be reviewed for consistency and modified as appropriate.
4. Education on this guideline will be distributed to ambulatory care providers, nurses and pharmacists through publication of the Anticoagulation Newsletter. Recommendations will be included in the development of an atrial fibrillation order set and imbedded into an electronic clinical assessment tool for providers.

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Appendix A. Evidence Grading Scheme(s)

Figure 1. GRADE Methodology adapted by UW Health



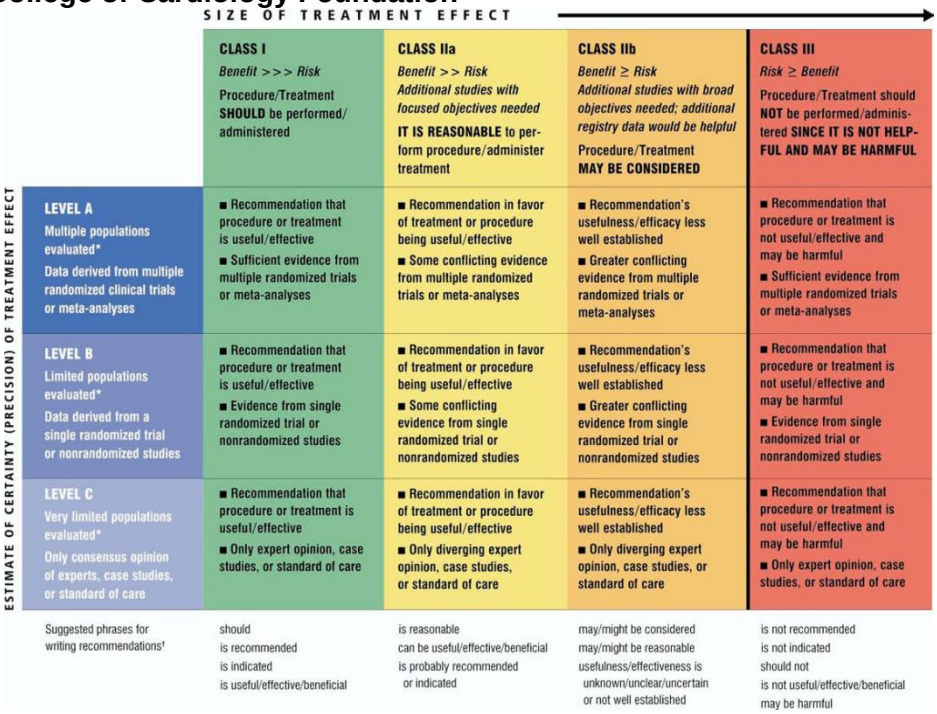
GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Weak/conditional	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

Figure 2. GRADE Methodology developed by the American Heart Association and American College of Cardiology Foundation[22]



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