Clinical Practice Guideline for Anticoagulation Management of Atrial Fibrillation

This guideline is to inform practitioners of the Standard of Care for evaluation & treatment of patients with atrial fibrillation (AF), & is not intended to replace a practitioner’s judgment.

AF is the most common form of arrhythmia & one of the most detrimental complications is ischemic stroke. The rate of ischemic stroke averages 5% a year. While the prevalence of Stroke is low, <0.5% in patients younger than 60, the prevalence doubles with each decade in patients older than 70. Risk varies depending upon the patient’s CHA2DS2-VASc score. Treatment of AF with anticoagulant therapy is known to reduce the incidence of CVA.

The Benefits of Anticoagulant Therapy:

- Reduces the risk of ischemic stroke by about 2/3, irrespective of baseline risk.
- **Non-Vitamin K Antagonist Oral Anticoagulants (NOACs), also referred to as Direct Oral Anticoagulants (DOACs)** are chosen over warfarin for non-valvular AF. They include:
  - **Factor Xa Inhibitors** (blocks the action of a certain natural substance that helps blood clots to form):
    - apixaban (Eliquis)
    - edoxaban (Lixiana)
    - rivaroxaban (Xarelto)
    - betrixaban (Bevyxxa)
    - edoxaban (Savaysa)
  - **Direct Thrombin Inhibitor** (prevents blood clots from forming in the body):
    - dabigatran (Pradaxa)
  - **Advantages:**
    - Convenience (no requirement for routine PT/INR testing).
    - High relative but small absolute reduction in the risk of ICH.
    - Lack of susceptibility to dietary interactions.
    - Markedly reduced susceptibility to drug interactions.
  - **Disadvantages:**
    - Lack of efficacy & safety data in patients with severe CKD.
    - Lack of easily available monitoring of blood levels & compliance.
    - Higher cost
    - Potential that unanticipated side effects will subsequently become evident.

- *NOACs/DOACs information including drug interactions ([table 5A-C](#)).
- **Vitamin K Antagonists** (inhibits the synthesis of Vitamin K dependent clotting factors):
  - **warfarin (Coumadin):**
    - There is evidence that warfarin compared with no anticoagulant therapy leads to less severe stroke episodes & a lower 30-day stroke mortality.
• In general, the non-vitamin K antagonist oral anticoagulants, such as apixiban and rivaroxaban for example (NOACs), are chosen over warfarin when anticoagulation is needed for non-valvular AF.
• There are several settings in which warfarin may be preferable to one of the DOACs, or in which a DOAC is contraindicated (eg, mechanical prosthetic heart valve, pregnancy). In addition, patients who are receiving warfarin with excellent stable INR control and minimal bleeding side effects may have little to gain by switching to a different agent.

*Trials of Warfarin vs. Newer Anticoagulants in patients with nonvalvular AF (table 6).

• **Anti-platelets** (prevents blood cells from clumping together to form a clot):
  - **Aspirin (ASA):**
    - Is better than placebo & should be used in patients with no risk factors or those who refuse to take warfarin.
    - ASA is NOT recommended as therapy for preventing thromboembolic events in very low-risk patients with non-valvular AF.
    - Has not been well addressed as the individual trials enrolled very few patients.
  - **ASA plus Clopidigrel (Plavix):**
    - Both dual antiplatelet therapy & oral anticoagulation have similar bleeding risks.
  - **ASA (300-325mg/day) plus Low-Dose Warfarin (1.25mg/day or target INR between 1.2 and 1.5):**
    - Should NOT be used to reduce stroke risk in patients with non-valvular AF.
    - Has a higher rate of morbidity & mortality than full dose warfarin.
  - **ASA plus Full-Dose Warfarin:**
    - The combination of ASA plus full dose warfarin vs. warfarin alone has not been well studied for greater efficacy.

*Low-dose warfarin plus ASA not optimal in high risk AF (figure 3A-B).
*Trials of warfarin & ASA for primary prevention of stroke in AF (table 2).

The major safety concern with the use of all antithrombotic agents is the increased risk of bleeding which includes events that require hospitalization, transfusion, surgery, or involves particularly sensitive anatomic locations. This may include:
• Intracranial hemorrhage (ICH) which is the most serious bleeding complication.

*Index for predicting risk of bleeding with warfarin (table 10).

**Contraindications with Prescribing Anticoagulation may include:**

• **Uncorrected Major Bleeding Disorders such as:**
  - Thrombocytopenia
  - Hemophilias
  - Liver Failure
  - Renal Failure

• **Uncontrolled Severe Hypertension such as:**
  - Systolic > 200mmHg *or*
  - Diastolic > 120 mmHg
• Potential Bleeding Lesions such as:
  o Active Peptic Ulcer
  o Esophageal Varices
  o Aneurysm
  o Proliferative Retinopathy
  o Recent Organ Biopsy
  o Recent Trauma or Surgery to the Head, Orbit or Spine
  o Recent Stroke
  o Confirmed Intracranial or Intraspinal Bleed
• Uncooperative/unreliable patient
• Repeated falls or unstable gait
• Concomitant use of NSAIDS that may result in:
  o Increased risk of GI bleed
• Protein C Deficiency puts a patient at risk for:
  o Skin necrosis on initiation of treatment, so caution needed
• Combined use of anticoagulant and antiplatelet agents.

*Possible contraindications to anticoagulation are presented in a table (table 4).
*Contraindications to anticoagulants should be documented & readily visible in the patient’s medical record.

**CHA$_2$DS$_2$-VASc Risk Model is the Preferred Tool for Estimating Embolic Risk:**
• The patient will have a score of 0, 1, or $\geq$2 which represents a range of risk, with a mean rate of stroke of 0.2%, 0.6%, and 2.2% per year, respectively.
  CKD is a strong risk factor for embolization and is not listed in the CHA$_2$DS$_2$-VASc risk model due to few patients with severe CKD were enrolled in the derivation studies that led to the model.
• CHA$_2$DS$_2$-VASc score $\geq$2 in men and $\geq$3 in women:
  o Oral anticoagulation is strongly recommended.
• CHA$_2$DS$_2$-VASc score of 1:
  o Different providers recommend no antithrombotic therapy, some recommend oral anticoagulant therapy, & some recommend therapy for selected patients.
  Uncertainty is related to:
  ▪ Few patients have been enrolled in clinical trials.
  ▪ The risk of embolization attributable to the individual risk factors is not equal including:
    • Female sex and vascular disease carry a lower risk than diabetes, HTN, or age 65-74 years.
    • Many experts don’t anti-coagulate women with no other risk factors.
    • The issue of whether vascular disease is an independent predictor of embolic risk is debated.
  o The particular risk factor present may influence decision making.
Older age is the most significant risk factor in these considerations. Gender alone may be the least significant. Clinical judgement plays an important role in helping patients choose between anticoagulation or no anticoagulation.

- **CHA\(_2\)DS\(_2\)-VASc score of 0:**
  - No oral anticoagulation is suggested; however, use of ASA 81-325 mg daily is reasonable in these patients.
  - Clinical judgement plays an important role in decision making.

*More detailed information, including the CHA\(_2\)DS\(_2\)-VASc risk scoring system, can be found in the Clinical Practice Guideline #10 – Anticoagulation Management.*

*Comparison of the CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASc risk stratification scores for patients with nonvalvular AF (table 1).*

*CHADS\(_2\) Score, Thromboembolic risk, & Effect of warfarin Anticoagulation (table 7).*

**HAS-BLED Bleeding Risk Score is a Tool to Assess Bleeding Risk in Patients Taking Oral Anticoagulants:**
- Has imprecise estimates in the individual patient.
- Bleeding risk scores were developed from studies that included bleeds of differing severity.

* HAS-BLED bleeding risk score (table 3).

**Patients who have the following should be anticoagulated for 3 weeks on DOACs or therapeutic on warfarin for 3 consecutive weeks & re-evaluated by their provider:**
- Paroxysmal Atrial Fib (PAF)
- Reoccurrences of AF
- Been in AF longer than 48 hours prior to conversion to a sinus rhythm.

*Strong consideration should be given to prescribing indefinite anticoagulation particularly in high risk patients.*

**Clinical Use of Anticoagulants:**
- **Initiation of Therapy:**
  - For most patients in whom therapy will be started, bridging with IV heparin is NOT recommended, particularly if a NOAC/DOAC is used, as the time to full anticoagulation is relatively short.
  - The only exception would be a patient who presents with AF in the setting of a new small stroke or TIA.
  - The choice of whether to start oral anticoagulant alone or in combination with unfractionated heparin or low-molecular-weight heparin (bridging) is based on a comparison of the risk of a thrombus developing within the next several days compared with the risk of bleeding complications.
- **In patients with AF without a prior history of thromboembolism:**
The risk of a thromboembolic event during the several days typically required to achieve therapeutic anticoagulation with warfarin is very low. 

Reasonable for outpatients to initiate warfarin without bridging.

- **Patients deemed to be at high risk for thromboembolism & low risk of ICH may include:**
  - Prior CVA, TIA, or Intracardiac Thrombus
  - Moderate/Severe Mitral Stenosis
  - Initiation of warfarin with heparin bridging regimen is reasonable

- **Patients with non-valvular AF who present with acute stroke have a relatively high risk of recurrent embolism and/or progressive ischemia (approximately 5% during the first 2 weeks):**
  - Use of Heparin reduces the rate of recurrent embolism &/or progressive ischemia.
  - This is balanced by an increased incidence of transformation to hemorrhagic stroke, especially in patients with large strokes.
  - There is no overall benefit to early heparin therapy & it is NOT recommended for heparin bridging in patients with acute stroke.

**Reasons to Switch Oral Anticoagulants:**
- Development of renal insufficiency
- Burdens of lab testing for warfarin, poor compliance or difficulty with INR testing
- Cost
- Need for repeated invasive procedures
- Recurrence despite therapeutic anticoagulation
- Development of a thrombus or neurologic event while on NOAC.

* Switching between oral Anticoagulants ([table 8](#)).

**Specific Patient Groups:**
- **Elderly:**
  - Increased risk of ICH with mechanical falls.
  - Leads to reduced use of oral anticoagulants.
  - Benefits vs risks are carefully assessed.
  - In patients with documented frequent falls, oral anticoagulation is NOT recommended.
  - For most older patients including those over age 75:
    - NOACs are preferred to warfarin.

- **Obese patients:**
  - Data are limited on the efficacy and toxicity of direct factor Xa inhibitors and direct thrombin inhibitors in obese individuals.
  - Based on a 2016 review of available literature, the International Society of Hemostasis and Thrombosis (ISTH) recommends *avoidance* of these agents in individuals with a **body mass index (BMI) >40 kg/m2, or weight ≥120 kg**.
  - Standard dose can be used for patients with a BMI ≤40 kg/m2
  - A 2017 review specific to rivaroxaban (Xarelto) concluded that it could be administered to individuals with a BMI >40 kg/m2 (or weight >120 kg) without dose adjustment, although data were limited.
• **Short duration Atrial Fibrillation:**
  - Some patients with PAF have episodes lasting as short as 30 seconds that may be clinically significant or silent.
  - Unknown whether these patients are at the same level of risk as those with longer or more frequent episodes at the same CHA2DS2-VASc risk score.
  - Some experts recommend a single threshold as short as 30 seconds & others use a threshold as long as 6 hours which may influence their recommendations.
  - For patients with episodes of short duration PAF, the decision to anticoagulate may be influenced by a patient’s CHA2DS2-VASc risk score, similar to the broad population of patients with non-valvular AF.

• **CKD:**
  - AF is **significantly higher** in patients with CKD than the general population.
  - Most providers choose a NOAC or DOAC rather than warfarin.
  - The reduction in thromboembolic risk with anticoagulation outweighs the bleeding risk in most cases.

  - **The following is the approach to deciding whether to anticoagulate based on CKD stage:**
    - **Stage 3 CKD:**
      - Anticoagulation in patients is similar to the broad population of patients with AF.
    - **Stage 4 CKD:**
      - Patients are anticoagulated who are felt to be at an acceptable bleeding risk.
    - **Stage 5 CKD (not on dialysis):**
      - There is minimal data to make informed decisions regarding anticoagulation among patients with end-stage renal disease (ESRD).
      - It is suggested that such patients be treated the same as patients who have CKD stage 4.
      - The decision to treat is based on an individual assessment of estimated risks & benefits.
    - **Dialysis patients:**
      - Patients are anticoagulated based on the CHA2DS2-VASc score after shared decision-making and discussion of risks & benefits between the clinician & the patient.

  - **NOAC Preferred:**
    - **apixaban (Eliquis)** for Stage 4 or 5 CKD or Dialysis Patients
      - Less dependent on kidney function for clearance than others.

  - **NOAC Avoided:**
    - **dabigatran (Pradaxa)** due to its high % of clearance by the kidney.

  - **Warfarin may be Preferred:**
    - In patients with Stage 4 or 5 CKD due to them having a higher risk of unpredictable sudden deterioration in renal function, which could suddenly result in less clearance of a NOAC that depends on renal metabolism.
It is reasonable to NOT anti-coagulate the following patients with Stage 4 or 5 CKD given the uncertainty of the benefit-to-risk ratio:

- Patients at high frailty
- Patients with prior life-threatening bleeding or recurrent bleeding
- Patients with poorly controlled hypertension

**Acute Stroke:**
- AF patients for whom anticoagulant therapy is being considered & who have had an ischemic stroke within 30 days should be referred to a Neurologist or other practitioner who is experienced in managing antithrombotic care.

**Rhythm Control:**
- Anticoagulant therapy is used similarly to the broad population of patients with AF.

**Hyperthyroidism:**
- For patients with AF attributable to hyperthyroidism, it is recommend starting antithrombotic therapy similar to the broad population.
- After successful treatment & after documentation that AF has NOT been present for at least 3 months, some providers suggest:
  - To discontinue treatment with periodic reassessment for recurrence of AF OR
  - Make a decision about continuing anticoagulant therapy based on the CHA2DS2-VASc score independent of rhythm.
- The absence of s/s of AF & a 24-hour continuous monitoring showing no AF is adequate documentation, however some providers prefer more documentation.

**Recommended Treatment Plan for Patients Age 65 or Older or Under 65 with Structural Heart Disease**

- Appropriate use of warfarin in patients with AF who do not have contraindications:
  - INR level should be 2-3.
  - Patients with INR levels outside 2-3, should have dosage adjustments.
  - If the practitioner does not adjust dosages when the INR is not within the recommended range, there should be documentation in the patient’s medical record regarding the reason adjustment was not performed.
- Increase education for patients regarding warfarin therapy.
- Increase appropriate monitoring for patients.
- Encourage the use of diagnostic tests with Echo/TEE in patients with new onset AF.
- Encourage the use of thyroid studies and consider secondary causes (ie caffeine, alcohol etc.) in patients with new-onset AF.

**References**


UpToDate “Atrial Fibrillation: Anticoagulant Therapy to Prevent Thromboembolism”; Authors: Dr. Warren J Manning, Dr. Daniel E Singer, Dr. Gregory YH Lip; Apr 2021; https://www.uptodate.com/contents/atrial-fibrillation-anticoagulant-therapy-to-prevent-thromboembolism