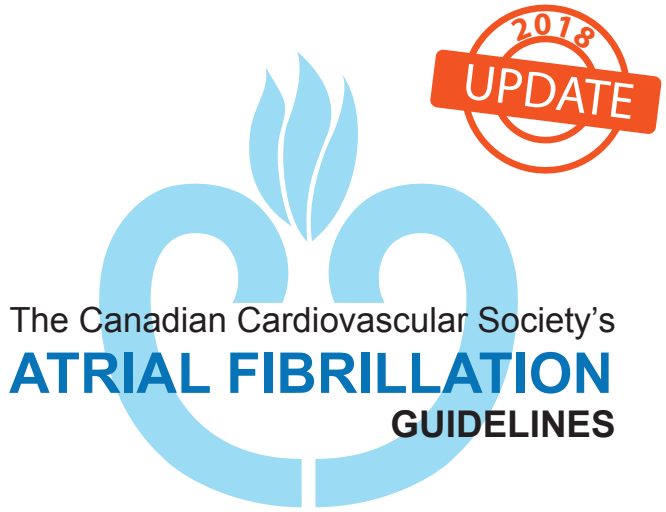
ATRIAL FIBRILLATION




The Canadian Cardiovascular Society's

# ATRIAL FIBRILLATION GUIDELINES

Canadian Cardiovascular Society
*Leadership. Knowledge. Community.*

ATRIAL FIBRILLATION

## Table of Contents



## Baseline Evaluation for All Patients



### HISTORY AND PHYSICAL EXAM

- Establish pattern (new onset, paroxysmal, persistent or permanent)
- Establish severity (including impact on quality of life)
- Identify etiology
- Identify reversible causes (hyperthyroidism, ventricular pacing, supraventricular tachycardia, exercise, etc)
- Identify risk factors whose treatment could reduce recurrent AF or improve overall prognosis (i.e. hypertension, sleep apnea, left ventricular dysfunction, etc)
- Take social history to identify potential triggers (i.e. alcohol, intensive aerobic training, etc)
- Elicit family history to identify potentially heritable causes of AF (particularly lone AF)
- Determine thromboembolic risk
- Determine bleeding risk to guide appropriate antiplatelet or antithrombotic therapy
- Review prior pharmacological therapy for AF, both for efficacy and adverse effects
- Measure blood pressure and heart rate
- Determine patient height and weight
- Comprehensive precordial cardiac examination and assessment of jugular venous pressure, carotid and peripheral pulses to detect evidence of structural heart disease

### 12-LEAD ELECTROCARDIOGRAM

- Document presence of AF
- Assess for structural heart disease (myocardial infarction, ventricular hypertrophy atrial enlargement, congenital heart disease) or electrical heart disease (ventricular pre-excitation, Brugada syndrome)
- Identify risk factors for complications of therapy for AF (conduction disturbance, sinus node dysfunction or abnormal repolarization)
- Document baseline PR, QT or QRS intervals

### ECHOCARDIOGRAM

- Document ventricular size, wall thickness and function
- Evaluate left atrial size (if possible, left atrial volume)
- Exclude significant valvular or congenital heart disease (particularly atrial septal defects)
- Estimate ventricular filling pressures and pulmonary arterial pressure

### LABORATORY INVESTIGATIONS

- Complete blood count
- Coagulation profile
- Renal function
- Thyroid and liver function
- Fasting lipid profile
- Fasting glucose



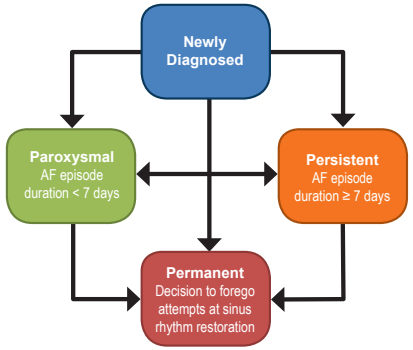
## Additional Investigations for Selected Patients

| Investigation | Potential Role |
|---|---|
| Chest radiography | Exclude concomitant lung disease, heart failure<br>Baseline in patients receiving amiodarone |
| Ambulatory electrocardiography (Holter, event, or loop monitor) | Document AF, exclude alternative diagnosis (atrial tachycardia, atrial flutter, AVNRT/AVRT, venticular tachycardia), establish symptom-rhythm correlation, assess venticular rate control |
| Treadmill exercise test | Investigation of patients with symptoms of coronary artery disease, assessment of ventricular rate control |
| Transesophageal echocardiography | Rule out left atrial appendage thrombus, facilitate cardioversion in patients not receiving oral anticoagulation, more precise characterization of structural heart disease (mitral valve disease, atrial septal defect, cor triatriatum, etc.) |
| Electrophysiology study | Patients with documented regular supraventricular tachycardia (i.e. atrial tachycardia, AVNRT/AVRT, atrial flutter) that is amenable to catheter ablation |
| Serum calcium and magnesium | In cases of suspected deficiency (i.e. diuretic use, gastrointestinal losses) which could influence therapy (i.e. sotalol) |
| Sleep study (overnight oximetry or polysomnography) | In patients with symptoms of obstructive sleep apnea or in select patients with advanced symptomatic heart failure |
| Ambulatory blood pressure monitoring | In cases of borderline hypertension |
| Genetic testing | In rare cases of apparent familial AF (particularly with onset at a young age) with additionnal features of conduction disease, Brugada syndrome or cardiomyopathy |

## Established Patterns and Severity of Atrial Fibrillation



### Patterns of Atrial Fibrillation




### SAF Score*

| SAF Score | Impact on QOL** |
|---|---|
| Class 0 | Asymptomatic |
| 1 | Minimal effect on QOL |
| 2 | Minor effect on QOL |
| 3 | Moderate effect on QOL |
| 4 | Severe effect on QOL |

** Dorian P, Cvitkovic SS, Kerr CR; et al. Can J Cardiol. 2006; 22(5):383-386*

*** QOL = Quality of life*



## Risk Markers and Co-morbid Conditions Associated with AF

| Conventional Risk Factors | Emerging Risk Factors | Potential Risk Factors |
|---|---|---|
| • Advancing age | • Chronic obstructive pulmonary disease | • Familial / Genetic factors |
| • Male Sex | • Excessive alcohol intake | • Tobacco Use |
| • Hypertension | • Pre-hypertension | • Echocardiographic (left atrial dilation, LV hypertrophy) |
| • HF with reduced ejection fraction | • Increased pulse pressure | • Inflammation |
| • Valvular heart disease | • HF with preserved ejection fraction | • Diabetes |
| • Thyroid disease | • Congenital heart disease | • Pericardial fat |
| • Obstructive sleep apnea | • Subclinical hyperthyroidism | • Subclinical atherosclerosis |
| | • Obesity | • Electrocardiographic (atrial conduction delay, PR interval prolongation) |
| | • Coronary artery disease | • Chronic kidney disease |
| | • Morphometric (increased height, increased birth weight) | |
| | • Excessive endurance exercise | |



## Modifiable Cardiovascular Risk Factors



**Management of modifiable risk factors to reduce cardiovascular events**

- We recommend systematic and strict guideline-adherent management of traditional modifiable cardiovascular risk factors and/or conditions associated with AF, to reduce cardiovascular events (e.g. stroke, MI, etc.) *(Strong Recommendation, High-Quality Evidence)*.

**Values and preferences:** This recommendation places a high value on a systematic approach to providing guideline-directed therapy for any cardiovascular risk factors and/or conditions associated with AF.

**Practical tip:** The detection and optimal management of risk factors and concomitant disorders together with appropriate rate/rhythm control and stroke prevention may contribute to a reduction in cardiovascular-related emergency department visits and hospitalizations. Addressing such risk factors might be most comprehensively and efficiently accomplished through a specialized clinic or other multidisciplinary management approach, and through a standardized, systematic protocol-based approach.

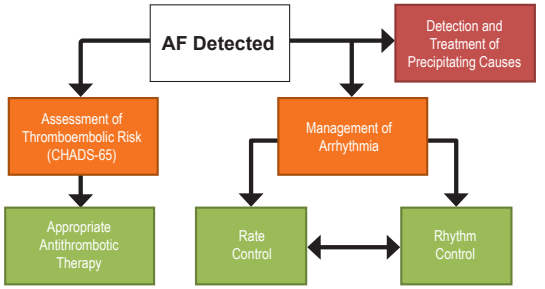
**Management of modifiable risk factors to reduce AF burden**

- We suggest that, in addition to implementing appropriate rate or rhythm control measures, an approach targeting modifiable risk markers and conditions associated with AF should be applied to prevent recurrence of the arrhythmia and/or decrease its symptom burden *(Weak Recommendation, Low-Quality Evidence)*.

**Values and preferences:** The aggressive treatment of obesity and cardiometabolic risk markers/conditions (including hypertension, heart failure, diabetes, sleep apnea) has been shown to reduce AF burden and improve quality of life. This recommendation places a high value on the recognized association between these potential risk markers and conditions that are known to aggravate AF, and the possibility that treatment of these conditions might result in improvement of patient symptoms through reduction of AF burden and/or regression of the substrate that causes AF.



## Overview of AF Management

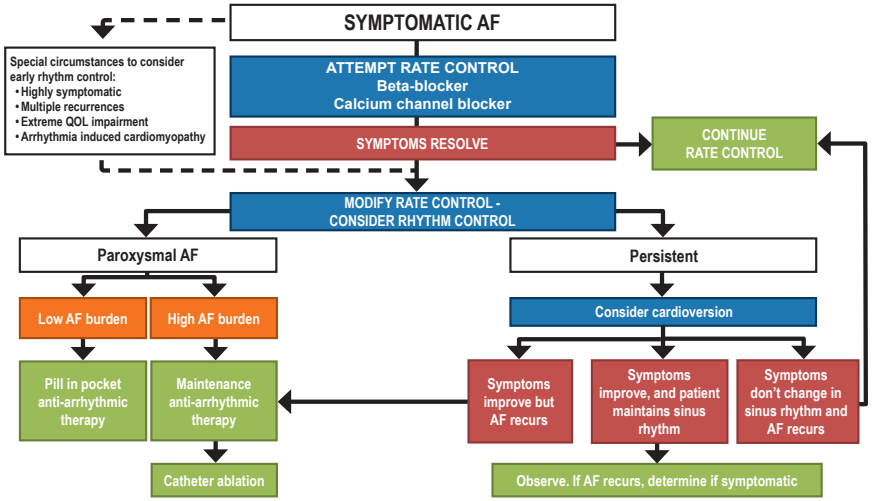



**Major Goals of AF/AFL Arrhythmia Management**

- Identify and treat underlying structural heart disease and other predisposing conditions
- Relieve symptoms
- Improve functional capacity/quality of life
- Reduce morbidity/mortality associated with AF/AFL
  - ✓ Prevent tachycardia-induced cardiomyopathy
  - ✓ Reduce/prevent emergency room visits or hospitalizations secondary to AF/AFL
- Prevent stroke or systemic thromboembolism

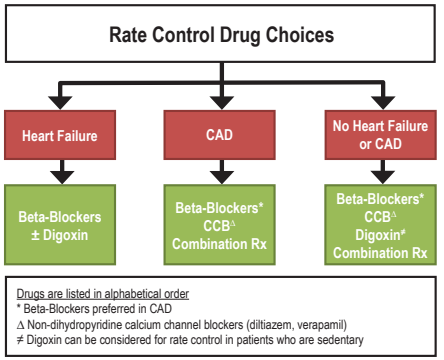
## Algorithm for Rate vs Rhythm Control for Patients with Symptomatic AF








## Overview of Rate Management




- We suggest that digoxin can be considered as a therapeutic option to achieve rate-control in patients with AF and symptoms caused by rapid ventricular rates whose response to beta-blockers and/or calcium channel blockers is inadequate, or in whom such rate-controlling drugs are contraindicated or not tolerated *(Conditional Recommendation, Moderate-Quality Evidence)*.



## Managing Rate Control – Recommended Drugs



### ß-Blockers

| Drug | Dose | Potential side-effects |
|---|---|---|
| Atenolol | 50 – 150 mg p.o. daily | Bradycardia, hypotension, fatigue, depression, bronchospasm |
| Bisoprolol | 2.5 – 10 mg p.o. daily | As per atenolol |
| Metoprolol | 25 – 200 mg p.o. bid | As per atenolol |
| Nadolol | 20 – 160 mg p.o. daily - bid | As per atenolol |
| Propranolol | 80 – 240 mg p.o. bid - tid | As per atenolol |

### Calcium Channel Blockers

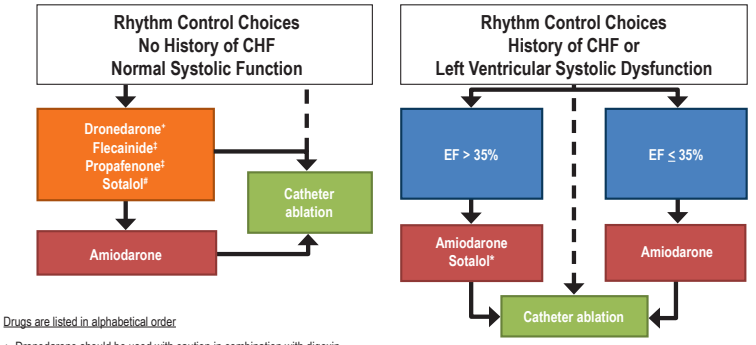
| Drug | Dose | Potential side-effects |
|---|---|---|
| Verapamil | 240 – 480 mg/day p.o. divided tid - qid (short acting)<br>120 – 320 mg p.o. daily (long acting) | Bradycardia, hypotension, constipation |
| Diltiazem | 180 – 360 mg/day p.o. divided tid - qid (short acting)<br>120 – 320 mg p.o. daily (long acting) | Bradycardia, hypotension, ankle swelling |

### Digoxin

| Drug | Dose | Potential side-effects |
|---|---|---|
| Digoxin | 0.0625 mg – 0.25 mg p.o. daily | Bradycardia, nausea, vomiting, visual disturbance |



## Overview of Rhythm Management




Drugs are listed in alphabetical order

\+ Dronedarone should be used with caution in combination with digoxin

‡ Class I agents should be AVOIDED in CAD and should be COMBINED with AV-nodal blocking agents

\# Sotalol should be used with caution in those at risk for torsades de pointes VT (e.g. female sex, age < 65 yr, taking diuretics)

* Sotalol should be used with caution with EF 35-40% and those at risk for torsades de pointes VT (e.g. female sex, age < 65 yr, taking diuretics)

## Managing Rhythm Control – Recommended Drugs



| Drug/Dose | Efficacy | Toxicity | Comments |
|---|---|---|---|
| Flecainide<br>50 – 150 mg<br>BID | 30 – 50% | Ventricular tachycardia<br>Bradycardia<br>Rapid ventricular response to AF or atrial flutter (1:1 conduction) | Contraindicated in patients with CAD or LV dysfunction<br>Should be combined with an AV nodal blocking agent |
| Propafenone<br>150 – 300 mg<br>TID | 30 – 50% | Ventricular tachycardia<br>Bradycardia<br>Rapid ventricular response to AF or atrial flutter (1:1 conduction)<br>Abnormal taste | Contraindicated in patients with CAD or LV dysfunction<br>Should be combined with an AV nodal blocking agent |
| Amiodarone<br>100 – 200 mg<br>OD (after 10g loading) | 60 – 70% | Photosensitivity, Bradycardia,<br>GI upset, Thyroid dysfunction,<br>Hepatic toxicity, Neuropathy,<br>Tremor, Pulmonary toxicity,<br>Torsades de pointes (rare) | Low risk of proarrhythmia<br>Limited by systemic side effets<br>Most side effects are dose & duration related |
| Dronedarone<br>400 mg BID | 40% | GI upset<br>Bradycardia,<br>Hepatic toxicity | Should not be used for rate control or for rhythm control in patients with a history of CHF or LVEF < 40%<br>Should be used with caution when added to digoxin<br>Liver enzyme monitoring required<br>Limited experience outside clinical trials |
| Sotalol<br>80 – 160 mg BID | 30 – 50% | Torsades de pointes<br>Bradycardia<br>Beta-Blocker side effects | Should be avoided in patients at high risk of torsades de pointes VT – especially women > 65 years taking diuretics or those with renal insufficiency<br>QT interval should be monitored 1 week after starting<br>Use cautionly when LVEF < 40% |



## Rate and Rhythm Management of AF in the Acute Care Setting

### Recommended IV Drugs for Rate Control

| Drug | Dose | Risks |
|---|---|---|
| Metoprolol | 2.5-5 mg IV bolus over 2 min; up to 3 doses | Hypotension, bradycardia |
| Diltiazem* | 0.25 mg/kg IV over 2 min; repeat at 0.35 mg/kg IV after 15 min. | Hypotension, bradycardia |
| Verapamil* | 0.075-0.15 mg/kg over 2 min. | Hypotension, bradycardia, bronchospasm |
| Digoxin | 0.25 mg IV each 2 h; up to 1.5 mg | Bradycardia, Digitalis toxicity |

* Calcium-channel blockers should not be used in patients with heart failure or left ventricular dysfunction

### Recommended Drugs for Cardioversion

| Medication | Dose | Time to Conversion | Risks |
|---|---|---|---|
| Class Ia<br>Procainamide | 15-18 mg/kg IV over<br>30-60 minutes | ~60 minutes | Hypotension, Bradycardia<br>Ventricular proarrhythmia |
| Class Ic<br>Flecainide | 300 mg po (> 70 kg)<br>200 mg po (≤ 70 kg) | 2-6 hours | Hypotension<br>Bradycardia and conversion pauses<br>1:1 conduction of atrial flutter* |
| Propafenone | 600 mg po (> 70 kg)<br>450 mg po (≤ 70 kg) | | |
| Class III | | | |
| Ibutilide | 1 mg IV over 10 min<br>May repeat x 1 | 30-60 minutes | QT prolongation, Torsades de pointes**<br>Hypotension |
| Amiodarone | 150 mg IV bolus then<br>60 mg/h x 6 hours then<br>30 mg/h x 18 hours | 8-12 hours | Hypotension<br>Bradycardia, Atrioventricular block<br>Torsades de pointes<br>Phlebitis |
| Vernakalant | 3 mg/kg IV over 10 minutes, followed by<br>2 mg/kg IV if no conversion | 12-30 minutes | Hypotension, Bradycardia<br>Non-sustained ventricular tachycardia*** |

*Class Ic drugs (flecainide and propafenone) should be used in combination with AV nodal blocking agents (beta-blockers or calcium channel inhibitors). Class IC agents should be avoided in patients with ischemic heart disease or significant structural heart disease
**Consider pre-treating with 1-4 g of IV MgSO4. Ibutilide should be avoided in patients with hypokalemia, baseline QT prolongation, or significant structural heart disease
***Vernakalant should be avoided in patients with hypotension, recent ACS, or significant structural heart disease





## "Pill-In-The-Pocket" Antiarrhythmic Drug Therapy



**Appropriate candidates for PIP**
1) patients with symptomatic AF
2) sustained AF episodes (e.g. ≥ 2 hours)
3) AF episodes that occur less frequently than monthly
4) absence of severe or disabling symptoms during an AF episode (e.g. fainting, severe chest pain, or breathlessness)
5) ability to comply with instructions, and proper medication use

**PIP administration**
Immediate release oral AV nodal blocker (one of diltiazem 60 mg, verapamil 80 mg, or metoprolol tartrate 25 mg) 30 minutes prior to the administration of a class Ic AAD (300 mg of flecainide or 600 mg of propafenone if ≥ 70 kg; 200 mg of flecainide or 450 mg of propafenone if < 70 kg)

**Initial ED monitoring**
Telemetry for at least 6 hours
Blood pressure monitoring every 30 minutes
12-lead ECG monitoring every 2 hours

**Determinants of initial treatment failure**
1) AF persistence > 6 hours after PIP-AAD administration or electrical cardioversion required for termination
2) Adverse events including symptomatic hypotension (systolic BP ≤ 90 mmHg), symptomatic conversion pauses (> 5 seconds), symptomatic bradycardia after sinus rhythm restoration, pro-arrhythmia (conversion to atrial flutter/tachycardia, or episodes of ventricular tachycardia), severe symptoms (dyspnea, presyncope, syncope), or a > 50% increase in QRS interval duration from baseline.

**Contraindication to PIP**
1) significant structural heart disease (e.g. left ventricular systolic dysfunction [LVEF < 50%], active ischemic heart disease, severe left ventricular hypertrophy)
2) abnormal conduction parameters at baseline (e.g. QRS duration > 120 msec, PR interval > 200 msec; or evidence of pre-excitation)
3) clinical or electrocardiographic evidence of sinus node dysfunction/bradycardia or advanced AV block
4) hypotension (systolic BP < 100mmHg)
5) prior intolerance to any of the PIP-AAD medications

**Instructions for subsequent out-of-hospital use**
1) Patients should take the AV nodal agent 30 minutes after the perceived arrhythmia onset, followed by the Class Ic AAD 30 minutes following the AV nodal agent.
2) Following AAD administration patients should rest in a supine or seated position for the next 4 hours, or until the episode resolves.
3) Patients should present to the emergency department in the event that:
   a) the AF episode did not terminate within 6-8 hours
   b) they felt unwell after taking the medication at home (e.g. a subjective worsening of the arrhythmia following AAD ingestion, or if they developed new or severe symptoms such as dyspnea, presyncope, or syncope)
   c) more than one episode occurred in a 24-hour period (patients should not take a second PIP-AAD dose within 24 hours)
   d) if the AF episode was associated with severe symptoms at baseline (e.g. significant dyspnea, chest pain, pre-syncope, or symptoms of stroke), even in the absence of PIP-AAD use.

*AAD, antiarrhythmic drug; AF, atrial fibrillation; AV, atrioventricular; BP, blood pressure; ECG, electrocardiogram; ED, emergency department; PIP, "pill-in-the-pocket".*



## Catheter Ablation

- We recommend catheter ablation of AF in patients who remain symptomatic following an adequate trial of antiarrhythmic drug therapy and in whom a rhythm control strategy remains desired *(Strong Recommendation, Moderate-Quality Evidence)*.
- We suggest catheter ablation to maintain sinus rhythm as first-line therapy for relief of symptoms in highly selected patients with symptomatic, paroxysmal atrial fibrillation *(Conditional Recommendation, Moderate-Quality Evidence)*.
- We recommend curative catheter ablation for symptomatic patients with typical atrial flutter as first line therapy or as a reasonable alternative to pharmacologic rhythm or rate control therapy *(Strong Recommendation, Moderate-Quality Evidence)*.
- We suggest that catheter ablation may be performed using uninterrupted therapeutic oral anticoagulation with either a NOAC or adjusted-dose warfarin *(Weak Recommendation, Moderate-Quality Evidence)*.

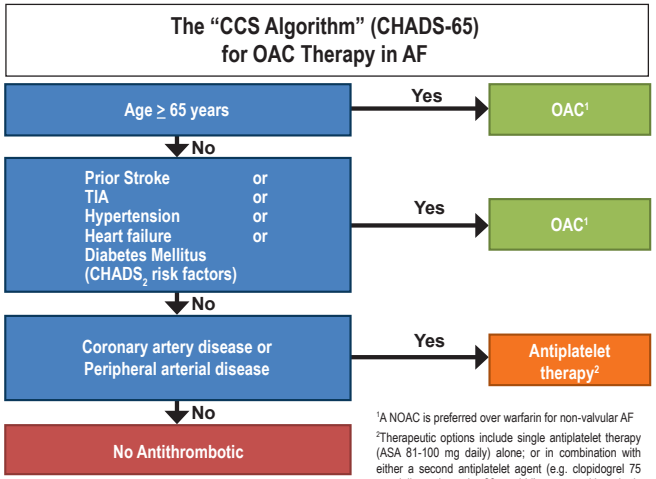
### Risk/Benefit Ratio* for Ablation in Patients with Symptomatic AF

| | Longstanding¶ | Persistent | Paroxysmal |
|---|---|---|---|
| 1st line | -- | -- | + |
| Failed 1st drug | -- | + | + + |
| Failed 2nd drug | + | + + | + + + |
| Failed multiple drugs | + + | + + + | + + + |

** irrespective of the presence or absence of HF or ventricular dysfunction*
*+ indicates balance of benefit to risk in favour of catheter ablation*
*¶ ongoing symptomatic AF ≥ 1 year*

## Prevention of Stroke in AF and Atrial Flutter






[1]A NOAC is preferred over warfarin for non-valvular AF

[2]Therapeutic options include single antiplatelet therapy (ASA 81-100 mg daily) alone; or in combination with either a second antiplatelet agent (e.g. clopidogrel 75 mg daily or ticagrelor 60 mg bid), or an antithrombotic agent (rivaroxaban 2.5 mg bid).



## Prevention of Stroke in AF and Atrial Flutter

**No OAC therapy for patients < 65 years with no $CHADS_2$ risk factors and antiplatelet therapy for those patients with coronary or arterial vascular disease**

- For patients with non-valvular AF/AFL aged < 65 years with no $CHADS_2$ risk factors, we suggest no antithrombotic therapy for stroke prevention *(Weak Recommendation, Moderate-Quality Evidence)*, with management of their coronary or arterial vascular disease as directed by the 2018 CCS/CAIC Focused Update of the Guidelines for the Use of Antiplatelet Therapy.

**Practical tip:** For patients with non-valvular AF/AFL aged < 65 years with no $CHADS_2$ risk factors, the risk of stroke associated with AF is not sufficiently elevated to justify OAC therapy. For this group treatment should be directed at the underlying coronary/peripheral arterial disease as outlined in the 2018 CCS/CAIC Focused Update of the Guidelines for the Use of Antiplatelet Therapy. Therapeutic options include ASA 81-100 mg daily alone; or ASA in combination with either clopidogrel 75 mg daily, ticagrelor 60 mg BID, or rivaroxaban 2.5 mg BID.

**Most patients should receive NOAC**

- We recommend that when OAC-therapy is indicated for patients with non-valvular AF, most patients should receive dabigatran, rivaroxaban, apixaban or edoxaban in preference to warfarin *(Strong Recommendation, High-Quality Evidence)*.

**Values and preferences:** This recommendation places a relatively high value on the greater ease of use of the NOACs in comparison to warfarin, and the results of large RCTs showing that the NOACs are either non-inferior or superior to warfarin in stroke prevention; the drugs have no more major bleeding or less bleeding vs warfarin and especially less intracranial hemorrhage. The recommendation places less value on the shorter clinical experience, lack of a specific antidote, and lack of a simple test for intensity of anticoagulant effect with the NOACs. The preference for one of the NOACs over warfarin is less marked among patients already receiving warfarin with stable therapeutic INRs, no bleeding complications, and who are not requesting a change in OAC therapy.



## Dosage of Oral Anticoagulants Based on Renal Function



| CrCl | Warfarin | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|---|
| CrCl >50 mL/min | Dose adjusted for INR 2.0-3.0 | 150 mg bid* | 20 mg daily | 5 mg bid | 60 mg daily∞ |
| CrCl 30-49 mL/min | Dose adjusted for INR 2.0-3.0 | Consider 110 mg bid in preference to 150 bid | 15 mg daily | 5 mg bid (Consider 2.5 mg bid)† | 30 mg daily |
| CrCl 15-29 mL/min | No RCT Data ** | No RCT Data¶ | No RCT Data | Very limited RCT Data§ | No RCT Data¶ |
| CrCl < 15 mL/min (or on dialysis) | No RCT Data‡ | No RCT Data¶ | No RCT Data¶ | No RCT Data¶ | No RCT Data¶ |

bid, twice daily; INR, international normalized ratio; RCT, randomized clinical trial.

* Consider Dabigatran 110 mg po bid if age >75 years
† Consider Apixaban 2.5 mg po bid if 2 of the 3 following criteria are present: 1) age >80 years, 2) body weight <60 kg, or 3) serum creatinine >133 µmol/L
∞ Consider Edoxaban 30mg daily if weight ≤60 kg or concomitant potent P-Gp inhibitor therapy
** Dose adjusted warfarin has been used, but data regarding safety and efficacy is conflicting
‡ Dose adjusted warfarin has been used, but data regarding safety and efficacy is conflicting and may lean towards causing harm.
§ The ARISTOTLE trial did include patients with a CrCl as low as 25 mL/min, but this was a very small number of patients (1.5% of patients in the trial).
¶ No published randomised studies support a dose for this level of renal function; product monographs suggest the drug is contraindicated for this level of renal function.



## Reversal Agents for NOACs - Recommendation

**Idarucizimab for emergency reversal of dabigatran's anticoagulant effect**

- We recommend administering idarucizumab for emergency reversal of dabigatran's anticoagulant effect in patients with uncontrollable or potentially life-threatening bleeding and/or in patients who require urgent surgery for which normal hemostasis is necessary *(Strong Recommendation, Moderate-Quality Evidence)*.

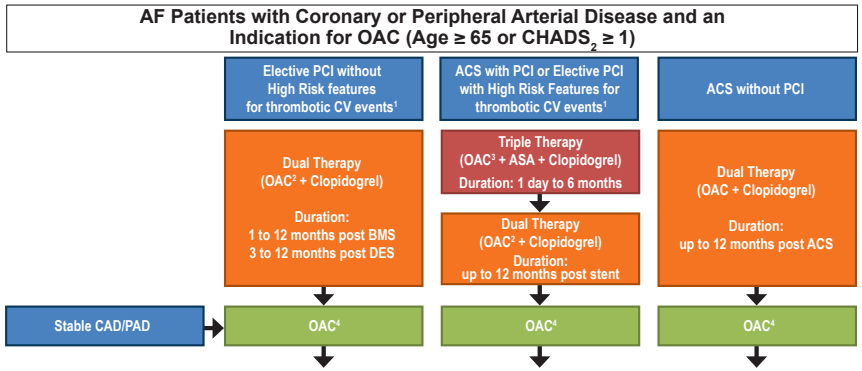
**Values and preferences:** This recommendation places relatively greater value on the ability of idarucizimab to reverse coagulation parameters indicative of dabigatran's effect, its potential to decrease bleeding-related outcomes and risks of urgent surgery, and its safety and tolerability profile, and less value on the absence of a control group in the REVERSE-AD trial and on the cost of the drug.

**Practical tips:**

- In acute, life-threatening bleeding situations in which standard resuscitation (such as local measures, transfusion, etc) is anticipated to be insufficient (eg, intracranial hemorrhage), or in situations in which standard resuscitation has not stabilized the patient, idarucizumab 5g IV should be administered as soon as possible. Activated partial thromboplastin time (aPTT) and thrombin time (TT) may be used to qualitatively identify the presence of active dabigatran at baseline in a patient, although they are less sensitive than dilute thrombin time (DTT) and ecarin clotting time (ECT; 92% of patients in the REVERSE-AD trial had an elevated DTT or ECT,whereas only 74% had an elevated aPTT). However, obtaining these measures should not delay the administration of idarucizumab. In many instances of life-threatening bleeding, clinicians have to make a treatment decision on the basis of a history of dabigatran use rather than laboratory evidence. Renal function and timing of the last dose of dabigatran provide key information regarding the likely extent of remaining dabigatran effect.
- "Urgent" surgery as defined in the REVERSE-AD trial is surgery that cannot be delayed beyond 8 hours (amended from 4 hours in the initial version of the protocol). The timing of surgery should be based on the clinical indication and stability of the patient. In instances where delayed surgery is appropriate, clinicians may obtain coagulation parameters (e.g.TT or aPTT) to identify patients who would be unlikely to benefit from idarucizumab.
- Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Oral anticoagulation should be reintroduced as soon as medically appropriate.

## Antithrombotic Therapy in Patients with AF and CAD or Vascular Disease






1. A PCI is considered high-risk based on clinical and angiographic features such as: diabetes mellitus, current smoker, chronic renal dysfunction (eGFR < 60 mL/min), prior ACS, prior stent thrombosis, multi-vessel disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, chronic total occlusion intervention, or bioabsorbable vascular scaffold (BVS) implantation.
2. Regimens evaluated in this context include: warfarin daily, rivaroxaban 15 mg PO daily (10 mg in patients with CrCl 30-50 mL/min), dabigatran 110 mg or 150 mg PO BID. A NOAC is preferred over warfarin, however if warfarin is to be used the lower end of the recommended INR target range is preferred. All patients should receive a loading dose of ASA 160 mg at the time of PCI (if previously ASA naïve).
3. Regimens evaluated in this context include: warfarin daily, or rivaroxaban 2.5 mg PO BID. A NOAC is preferred over warfarin, however if warfarin is to be used the recommended INR target is 2.0-2.5. All patients should receive a loading dose of ASA 160 mg at the time of PCI (if previously ASA naïve). Thereafter, ASA may be discontinued as early as the day following PCI or it can be continued longer term (e.g. 1 to 6 months after PCI). The timing of when to discontinue ASA will depend on the individual patient's ischemic and bleeding risk.
4. The dose of OAC beyond year after PCI should be the standard stroke prevention dose. Single antiplatelet therapy with ASA or clopidogrel may be added to OAC if high-risk clinical or angiographic features of ischemic events and low risk of bleeding.



## Anticoagulation in the Context of AF and CAD

**Antithrombotic therapy based on a balanced assessment of a patient's risk of stroke**

- We recommend that patients who have concomitant AF and coronary/arterial vascular disease (peripheral vascular disease or aortic plaque), receive an antithrombotic therapy regimen that is based on a balanced assessment of their risk of AF-related stroke, ischemic coronary event, and clinically relevant bleeding associated with the use of antithrombotic agents *(Strong Recommendation, High-Quality Evidence)*.

**Practical tip:** For patients requiring combinations of antiplatelet and OAC agents for concomitant AF and coronary/arterial vascular disease, we suggest that measures be employed to reduce the risk of bleeding, including: careful consideration of modifiable bleeding risk factors with vigorous efforts to mitigate them; consideration of proton pump inhibitor use; avoidance of prasugrel and ticagrelor in conjunction with OACs; the use of warfarin in the lower target INR (e.g. 2.0-2.5); consideration of the lower effective doses of NOACs in selected patients (See Figure on page 19); specific measures during coronary invasive procedures (radial access, small-diameter sheaths, early sheath removal from femoral site, and minimized use of acute procedural anti-thrombotic therapies); delaying non-urgent procedures until dual pathway therapy is no longer required; use of walking aids for those with gait or balance disorders; avoidance of NSAIDs or other drugs that may increase bleeding risk; and, strict blood pressure control.

**Most patients with an indication for OAC in the presence of CAD should receive a NOAC**

- When OAC is indicated in the presence of coronary or arterial vascular disease, we suggest a NOAC in preference to warfarin *(Weak Recommendation, Moderate-Quality Evidence)*.

**Values and preferences:** The suggestion for use of a NOAC rather than warfarin places relatively greater weight on the ease of use of NOACs versus warfarin, as well as the data from RCTs of NOACs versus warfarin for NVAF (e.g. equal or greater reduction of stroke, equal or greater reduction in all-cause mortality, equal or less major bleeding, less intracranial bleeding and no net increase in CAD outcomes).



## Risk Factors Associated with an Increased Risk of Bleeding and Ischemic Coronary Outcomes



**Factors that Increase Risk of Bleeding**

- **Patient Factors**
  - Age (> 65 years)
  - Low body weight (< 60 kg)
  - Hypertension
  - History of bleeding (esp. within 1y)
  - Prior stroke or intracranial bleed
  - Combined OAC and antiplatelet use
  - Concomitant NSAID or prednisone use
  - Excess alcohol consumption
  - Abnormal liver function
  - CKD (eGFR < 60 mL/min)
  - Anemia (hemoglobin <110 g/L)
  - Labile INR (TTR <60%)

**Factors that Increase Risk of Ischemic Coronary Events**

- **Patient Factors**
  - Diabetes mellitus treated with OHG or insulin
  - Current smoker
  - CKD (eGFR < 60 mL/min)
  - Prior ACS
  - Prior stent thrombosis
- **Clinical Presentation**
  - ACS (STEMI, NSTEMI, UA)
- **Angiographic factors**
  - Multi-vessel disease
  - Multiple (≥ 3) stents implanted
  - Stenting of a bifurcation lesion
  - Total stent length > 60 mm
  - Left main or proximal LAD stenting
  - Chronic occlusion intervention
  - Bioabsorbable vascular scaffold

ACS, acute coronary syndrome; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; LAD, left anterior descending artery; NSAID, nonsteroidal anti-inflammatory drug; NSTEMI, noneST-elevation myocardial infarction; OHG, oral hypoglycemic agents; STEMI, ST-elevation myocardial infarction; TTR, Time in Therapeutic Range; UA, unstable angina.



## AF Patients with Stable Coronary Artery Disease or Vascular Disease

**Stable vascular disease and AF in patients at high risk of stroke/systemic thromboembolism**

- For patients with AF aged ≥ 65 years or with a $CHADS_2$ score ≥ 1 and coronary or arterial vascular disease (peripheral vascular disease or aortic plaque), we recommend long-term therapy with OAC alone *(Strong Recommendation, High-Quality Evidence)*.

**Values and preferences:** For patients with AF and stable coronary or arterial vascular disease, the CCS AF Guidelines Committee believe that routine use of combination therapy (an OAC with a single antiplatelet agent) was not justified because of the increased risk of bleeding without a significant reduction in ischemic coronary and cerebrovascular thrombotic events.

**Practical tips:**

- For patients with high-risk clinical or angiographic features for ischemic coronary outcomes who are at low risk of bleeding, some clinicians prefer a combination of an OAC and single antiplatelet therapy (either aspirin or clopidogrel) in preference to OAC therapy alone.
- Stable coronary artery disease is defined by the absence of acute coronary syndrome for the preceding 12 months.

## AF Patients Undergoing PCI



**AF patients at higher risk of stroke undergoing PCI without high-risk features**

- For patients with AF aged ≥ 65 years or with a $CHADS_2$ score ≥ 1, we suggest dual pathway therapy (OAC plus clopidogrel 75 mg/d) for at least 1 month after BMS implantation and at least 3 months after DES implantation *(Weak Recommendation, Moderate-Quality Evidence)*.

**AF patients at higher risk of stroke undergoing PCI for ACS or elective PCI with high-risk features**

- For patients with AF aged ≥ 65 years or with a $CHADS_2$ score ≥ 1, we recommend an initial regimen of triple antithrombotic therapy (ASA 81 mg daily plus clopidogrel 75 mg/d plus OAC) up to 6 months following PCI *(Strong Recommendation, Moderate-Quality Evidence)*. After ASA discontinuation, which may occur as early as the day after PCI, we suggest that dual pathway therapy (OAC plus clopidogrel 75 mg/d) be continued for up to 12 months after PCI *(Weak Recommendation, Moderate-Quality Evidence)*.

**Practical tips:**

- For some patients < 65 years of age with $CHADS_2$ = 1 at the lower end of the stroke risk spectrum (e.g. isolated hypertension), some clinicians prefer dual antiplatelet therapy (e.g. aspirin and ticagrelor or prasugrel) in preference to triple therapy (OAC plus dual antiplatelet).
- A PCI is considered high-risk for ischemic coronary outcomes based on the clinical presentation (e.g. ACS), patient characteristics (co-morbid diabetes mellitus treated with oral hypoglycemics or insulin, chronic kidney disease [eGFR < 60 mL/min], current tobacco use, prior ACS, or prior stent thrombosis), as well as PCI-related factors (multivessel PCI, multiple [≥ 3] stents implanted, total stent length > 60 mm, complex bifurcation lesion, chronic total occlusion intervention, and stent type [e.g. bioabsorbable vascular scaffold]).
- All patients should receive ASA 81 mg (or a minimum of 160 mg if ASA-naïve) on the day of the PCI procedure. ASA may be continued as part of triple antithrombotic therapy for up to 6 months for patients with a high risk of thrombotic coronary events and low risk of bleeding. ASA can be discontinued as early as the day after PCI for patients with a low risk of thrombotic coronary events and a high risk of bleeding. For patients at intermediate risk of thrombotic coronary events and intermediate risk of bleeding, ASA can be continued as part of triple antithrombotic therapy for 1-3 months.



## AF Patients with Medically Managed Type I Myocardial Infarction

**AF patients at higher risk of stroke in association with medically managed type I myocardial infarction**

- For patients with AF aged ≥ 65 years or with a $CHADS_2$ score ≥ 1, we suggest that dual pathway therapy (OAC plus clopidogrel 75 mg/d, rather than prasugrel or ticagrelor) be given without concomitant ASA for 12 months after ACS *(Weak Recommendation, Low-Quality Evidence)*.

**Values and preferences:** For patients with AF and type I MI who do not undergo revascularisation, the CCS AF Guidelines Committee places relatively greater emphasis on the reduction in ischemic coronary and cerebrovascular thrombotic events, rather than the increase in bleeding observed with combination therapy. When combination therapy is used the preference for clopidogrel rather than ASA is based on the findings from the CAPRIE study, where clopidogrel was shown to be superior to ASA (0.5% absolute reduction in composite of vascular death, MI, or ischemic stroke; P = 0.043), as well as the substantial efficacy and safety data for combination therapy utilizing clopidogrel and OAC (clopidogrel used in 88% of patients in RE-DUAL PCI and 95% in PIONEER AF-PCI).



## Anticoagulation in the Context of Cardioversion



**1. Valvular AF (any duration), or**
**2. NVAF Duration <12 hours and recent stroke/TIA, or**
**3. NVAF Duration 12-48 hours and $CHADS_2$≥2, or**
**4. NVAF Duration >48 hours**

Therapeutic OAC for ≥3 weeks before cardioversion

Alternate: TEE to exclude LA thrombus

**1. Hemodynamically unstable acute AF[1], or**
**2. NVAF Duration <12 hours and no recent stroke/TIA, or**
**3. NVAF Duration 12-48 hours and $CHADS_2$<2**

Initiate OAC as soon as possible (preferably prior to cardioversion)

**CARDIOVERSION**

**ANTICOAGULATION FOR 4 WEEKS POST CARDIOVERSION**

**LONG-TERM ANTICOAGULATION BASED ON THE "CCS ALGORITHM" (CHADS-65)**

[1] Hemodynamically unstable acute AF is defined as AF causing hypotension, cardiac ischemia, or pulmonary edema



## Anticoagulation in the Context of Cardioversion

**Anticoagulation for at least 3 weeks before elective cardioversion**

- We recommend that in addition to appropriate rate-control, most hemodynamically stable patients with AF or AFL for whom elective electrical or pharmacological cardioversion is planned should receive therapeutic anticoagulation for 3 weeks before cardioversion *(Strong Recommendation, Moderate-Quality Evidence)*.

**Circumstances where cardioversion may be performed without a preceding period of anticoagulation**

- We suggest that pharmacological or electrical cardioversion of symptomatic AF or AFL without at least 3 weeks of prior therapeutic anticoagulation be reserved for patients with the following characteristics *(Weak Recommendation, Low-Quality Evidence)*:
  i) patients with non-valvular AF who present with a clear AF onset within 12 hours in the absence of recent stroke or TIA (within 6 months);
  ii) patients with non-valvular AF and a $CHADS_2$ score < 2 who present after 12 hours but within 48 hours of AF onset.

**Practical tip:** Non-valvular AF is defined as AF in the absence of mechanical heart valves, rheumatic mitral stenosis, or moderate to severe nonrheumatic mitral stenosis.

**The use of transesophageal echocardiography as an alternative to anticoagulation prior to cardioversion**

- We suggest that, as an alternative to at least 3 weeks of therapeutic anticoagulation prior to cardioversion, transesophageal echocardiography (TEE) may be employed to exclude cardiac thrombus *(Weak Recommendation, Moderate-Quality Evidence)*.

**Values and preferences:** This recommendation places a high value on the symptomatic improvement with immediate cardioversion as well as the reduced risk of peri-cardioversion stroke conferred by a transesophageal echocardiogram demonstrating an absence of intracardiac thrombus. Lower value is placed on the small risks associated with the TEE.

## Anticoagulation in the Context of Cardioversion



**Immediate electrical cardioversion for patients who are hemodynamically unstable**

- We recommend that immediate electrical cardioversion be considered for patients whose recent-onset AF/AFL is the direct cause of instability with hypotension, acute coronary syndrome, or pulmonary edema *(Strong Recommendation, Low-Quality Evidence)*.

**Values and preferences:** This recommendation places a high value on immediately addressing instability by attempting cardioversion, and a lower value on reducing the risk of cardioversion-associated stroke with a period of anticoagulation before cardioversion. Therapeutic anticoagulation therapy should be initiated as soon as possible.

**Immediate initiation of anticoagulation prior to unplanned cardioversion**

- When a decision has been reached that a patient will be undergoing unplanned cardioversion of AF/AFL, we suggest that therapeutic anticoagulation therapy be initiated immediately (preferably before cardioversion) with either a NOAC, or with heparin followed by adjusted-dose warfarin *(Weak recommendation, Low-Quality Evidence)*.

*Cardioversion*

## Anticoagulation in the Context of Cardioversion

**Anticoagulation for at least 4 weeks post cardioversion**

- We suggest that, in the absence of a strong contraindication, all patients undergoing cardioversion of AF/AFL receive at least 4 weeks of therapeutic anticoagulation (adjusted-dose warfarin or a NOAC) after cardioversion *(Weak Recommendation, Low-Quality Evidence)*. Thereafter, we recommend that the need for ongoing antithrombotic therapy should be based upon the risk of stroke as determined by the CCS Algorithm (CHADS-65) (*Strong Recommendation, Moderate-Quality Evidence)*.

**Values and preferences:** This approach places relatively greater emphasis on the benefits of stroke prevention in comparison to the risks of bleeding with a short course of anticoagulation therapy. Although it may be possible to parse these risks either on the basis of patient characteristics or the duration of acute AF/AFL, the CCS AF Guidelines Committee at this point has chosen to simplify by recommending anticoagulation for 1 month after cardioversion for all such patients in the absence of a strong contraindication.

**Practical tip:** When oral anticoagulation is to be used for only a short period (< 2 months) current evidence does not substantiate either an efficacy or safety advantage for use of a NOAC over adjusted-dose warfarin. Nevertheless, the convenience of use of a NOAC over adjusted-dose warfarin in the pericardioversion period is substantial and the onset of therapeutic anticoagulation is nearly immediate with a NOAC whereas it is delayed in the case of adjusted-dose warfarin. Accordingly, it is reasonable to use NOAC therapy in the pericardioversion period.



*Cardioversion*

## Investigation and Management of Subclinical AF



**OAC therapy for highly selected patients with subclinical AF**

- We suggest that it is reasonable to prescribe OAC therapy for patients who are aged 65 or older, or with a $CHADS_2$ score of ≥ 1 (CHADS-65) who have episodes of subclinical AF lasting > 24 continuous hours in duration. Additionally, high-risk patients (such as those with a recent embolic stroke of unknown source) with shorter-lasting episodes might also be considered for OAC therapy *(Weak Recommendation, Low-Quality Evidence)*.

*Subclinical AF*