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CJC Online Supplement

Management of Atrial Fibrillation: Complete CCS Guidelines Listing

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** For a complete listing of the primary and secondary members of the CCS Atrial Fibrillation Guidelines Committee along with their affiliations, see the end of this document.*

This summary lists all recommendations presently in force. The recommendations indicated are the most recently established in each category, with the year in which the recommendation was established being indicated. The recommendations were developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) standards with strength of recommendations now classified as "Strong" or "Weak" (previously "Strong" or "Conditional").

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Part 1 - Initial Evaluation of Atrial Fibrillation

Recommendation 1 – Complete history and physical examination (2010)

All patients with atrial fibrillation should undergo a complete history and physical examination, electrocardiogram, echocardiogram, and basic laboratory investigations. Details are highlighted in Table S1 (Strong Recommendation; Low Quality Evidence). Other ancillary tests should be considered under specific circumstances. Details included in Table 2 (Strong Recommendation; Low Quality Evidence).

Values and preferences (2010)
This recommendation places a high value on a comprehensive evaluation of patients with AF and a lower value on initial costs to the health care system.

Recommendation 2 – Well-being, symptoms, and quality of life (2010)

We recommend that the assessment of patient well-being, symptoms, and quality of life be part of the evaluation of every patient with AF (Strong Recommendation, Low Quality Evidence).

Recommendation 3 – Quality of life – CCS-AF Scale (2010)

We suggest that the quality of life of the AF patient be assessed in routine care using the CCS SAF scale (Conditional Recommendation, Low Quality Evidence).

Values and preferences (2010)
Recommendations 2 and 3 recognize that improvement in quality of life is a high priority for therapeutic decision making.

Recommendation 4 – Identification of underlying causes or precipitating factors (2010)

Underlying causes or precipitating factors for AF including hypertension should be identified and treated. Details are highlighted in Table S3 (Strong Recommendation; High Quality of Evidence).

Recommendation 5 – Management of modifiable risk factors to reduce cardiovascular events (2018)

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

Values and preferences (2018)
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 (2018)
The detection and optimal management of risk factors and concomitant 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.

Recommendation 6 – Management of modifiable risk factors to reduce AF burden (2018)

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 (2018)
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 may result in prevention and/or progression of the substrate that causes AF as well as improving patient symptoms.

Table S1 (Updated Table 1 from 2010) Etiology and Initial Investigations: Baseline Evaluation of Atrial Fibrillation for All Patients

History
• 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 in lone AF)
• Determine thromboembolic risk
• Determine bleeding risk to guide appropriate antiplatelet or antithrombotic therapy
• Review prior pharmacologic therapy for AF, both for efficacy and adverse effects
Physical Exam
• 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
Laboratory Investigations
• Complete blood count, coagulation profile, renal function, thyroid and liver function
• Fasting lipid profile, fasting glucose
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 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

Table S2 (Table 3 from 2010) Etiology and Initial Investigations: Additional Investigations Useful in Selected Cases

Investigation	**Potential Role**
Chest radiography	Exclude concomitant lung disease, heart failure, baseline in patients receiving amiodarone
Ambulatory electrocardiography (holter monitor, event monitor, loop monitor)	Document AF, exclude alternative diagnosis (atrial tachycardia, atrial flutter. AVNRT/AVRT, ventricular tachycardia), symptom-rhythm correlation, assessment of ventricular rate control
Treadmill exercise test	Investigation of patients with symptoms of coronary artery disease, assessment of ventricular rate control
Trans-esophageal 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 defects, cor triatriatum, etc)
Electrophysiologic 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 (ambulatory 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 additional features of conduction disease, Brugada syndrome or cardiomyopathy

Table S3 (Table 4 from 2010) Etiology and Initial Investigations: Potential Causes of Atrial Fibrillation

Cardiac Causes
• Hypertension
• Coronary artery disease with prior myocardial infarction
• Heart failure*
• Left ventricular dysfunction (systolic and diastolic; Including hypertrophic, dilated and restrictive cardiomyopathies)*
• Valvular heart disease
• Congenital heart disease* (early repair of atrial septal defect)
• Pericardial disease
• Post-surgical (particularly cardiac surgery)
• Sick sinus syndrome
• Atrial fibrillation as a result of ventricular pacing*
• Supraventricular tachycardia (including Wolf-Parkinson White syndrome, atrial tachycardia, atrial flutter or other)*
• Genetic/familial
Non-Cardiac Causes
• Obstructive sleep apnea*
• Obesity*
• Excessive alcohol ingestion (acute or chronic)*
• Hyperthyrodism*
• Vagally-mediated (i.e. habitual aerobic training)*
• Pulmonary disease (pneumonia, COPD, pulmonary embolism, pulmonary hypertension)
Lone (idiopathic) Atrial Fibrillation

** Denotes cause for which treatment may prevent the development or recurrence of AF.*

Table S4 (Table 4 from 2018). Risk markers and co-morbid conditions associated with AF

<table>
<tr><th>Conventional Risk Factors</th><th>Emerging Risk Factors</th><th>Potential Risk Factors</th></tr>
<tr><td>Advancing age</td><td>Chronic obstructive pulmonary disease</td><td>Familial / Genetic factors</td></tr>
<tr><td>Male Sex</td><td>Excessive alcohol intake</td><td>Tobacco Use</td></tr>
<tr><td>Hypertension</td><td>Pre-hypertension
Increased pulse pressure</td><td rowspan="2">Echocardiographic
• Left atrial dilatation
• LV hypertrophy</td></tr>
<tr><td>HF with reduced ejection fraction</td><td>HF with preserved ejection fraction</td></tr>
<tr><td>Valvular heart disease</td><td>Congenital heart disease</td><td>Inflammation</td></tr>
<tr><td>Thyroid disease</td><td>Subclinical hyperthyroidism</td><td>Diabetes</td></tr>
<tr><td>Obstructive sleep apnea</td><td>Obesity</td><td>Pericardial fat</td></tr>
<tr><td rowspan="4"></td><td>Coronary artery disease</td><td>Subclinical atherosclerosis</td></tr>
<tr><td>Morphometric
Increased height</td><td rowspan="2">Electrocardiographic
• Atrial conduction delay
• PR interval Prolongation</td></tr>
<tr><td>Increased birth weight</td></tr>
<tr><td>Excessive endurance exercise</td><td>Chronic kidney disease</td></tr>
</table>

Part 2 – Subclinical AF / Detection of AF Patients with Stroke

Recommendation 1 – OAC therapy for highly selected patients with subclinical AF (2018, updated from 2014)

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 recent embolic stroke of unknown source) with shorter-lasting episodes might also be considered for OAC therapy (Weak Recommendation, Low-Quality Evidence).

Recommendation 2 – At least 24 hours of ECG monitoring (2014)

For patients being investigated for an acute embolic ischemic stroke or TIA, we recommend at least 24 hours of ECG monitoring to identify paroxysmal AF potential candidates for OAC therapy (Strong recommendation, Moderate Quality Evidence).

Values and preferences (2014)
This recommendation places relatively high value on the facts that brain embolism can be the first manifestation of previously undiagnosed AF and stroke/TIA patients generally do not receive OAC unless AF is detected. This recommendation places relatively less weight on the absence of clinical trials evaluating OAC therapy among patients who have only very brief subclinical AF.

Recommendation 3 – For selected older patients, additional ambulatory monitoring (2014)

For selected older patients with an acute, non-lacunar, embolic stroke of undetermined source for which AF is suspected but unproven, we suggest additional ambulatory monitoring (beyond 24 hours) for AF detection, where available, if it is likely that OAC therapy would be prescribed if prolonged* AF is detected (Conditional Recommendation, Moderate Quality Evidence)

**There are currently insufficient data to indicate what the minimum AF duration should be for OAC to be instituted, and expert opinion varies widely.*

Values and preferences (2014)
This recommendation places high value on aggressively investigating selected patients with unexplained embolic stroke. The main rationale is to improve the identification of patients who would have an evidence-based change in management aimed at preventing recurrent strokes (i.e., switching from antiplatelet therapy to OAC therapy) if a clear diagnosis of AF is found. In cases where only very brief subclinical AF is detected, the role of OAC therapy is currently uncertain and treatment decisions should be individualized.

Part 3 – Rate Management of AF

Recommendation 1 – Goals of rate control therapy (2010)

We recommend that the goals of ventricular rate control should be to improve symptoms and clinical outcomes which are attributable to excessive ventricular rates (Strong Recommendation, Low Quality Evidence).

Recommendation 2 – Ventricular rate assessment (2010)

We recommend that ventricular rate be assessed at rest in all patients with persistent and permanent AF or AFL (Strong Recommendation, Moderate Quality Evidence).

Recommendation 3 – Heart rate during exercise and exertional symptoms (2010)

We recommend that heart rate during exercise be assessed in patients with persistent or permanent AF or AFL and associated exertional symptoms (Strong Recommendation, Moderate Quality Evidence).

Recommendation 4 – Aim for a resting heart rate of <100 bpm (2010)

We recommend that treatment for rate control of persistent or permanent AF or AFL should aim for a resting heart rate of <100 bpm (Strong Recommendation, High Quality Evidence).

Values and preferences (2010)
Recommendations 3, 4, and 5 place a high value on the randomized clinical trials and other clinical studies demonstrating that ventricular rate control of AF is an effective treatment approach for many patients with AF.

Recommendation 5 – Beta-blockers or non-dihydropyridine CCBs as initial therapy (2010)

We recommend beta-blockers or non-dihydropyridine calcium channel blockers as initial therapy for rate control of AF or AFL in most patients without a past history of myocardial infarction or left ventricular dysfunction (Strong Recommendation, Moderate Quality Evidence).

Recommendation 6 – Digoxin rate control: selected sedentary and LV systolic dysfunction patients (2010)

We suggest that digoxin not be used as initial therapy for active patients and be reserved for rate control in patients who are sedentary or who have left ventricular systolic dysfunction (Conditional Recommendation, Moderate Quality Evidence).

Recommendation 7 – Digoxin added when other therapies fail (2016, updated from 2010)

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 where such rate-controlling drugs are contraindicated or not tolerated (Conditional Recommendation, Moderate Quality Evidence).

Values and preferences (2016)
Digoxin is considered as a second-line agent in that, although some published cohort, retrospective, and subgroup studies show no harm there are others that suggest possible harm.

Practical tip (2016)
When digoxin is used, dosing should be adjusted according to renal function and potential drug interactions. Given analyses suggesting higher drug concentrations are associated with adverse outcomes, maximum trough digoxin serum concentration of 1.2 ng/mL would be prudent. When digoxin is being used to treat patients with concomitant LV systolic dysfunction, its use should be dictated by the recommendations of the CCS Heart Failure Clinical Guidelines. When digoxin is being used to treat patients with concomitant LV systolic dysfunction, its use should be dictated by the recommendations of the CCS Heart Failure Clinical Guidelines.

Recommendation 8 – Amiodarone for rate control therapy in exceptional cases (2010)

We suggest that amiodarone for rate control should be reserved for exceptional cases in which other means are not feasible or are insufficient (Conditional Recommendation, Low Quality Evidence).

Values and preferences (2010)
Recommendations 6 to 9 recognize that selection of rate-control therapy needs to be individualized on the basis of the presence or absence of underlying structural heart disease, the activity level of the patient, and other individual considerations.

Recommendation 9 – Dronedarone, not for patients with permanent AF (2012)

We recommend that dronedarone not be used in patients with permanent AF nor for the sole purpose of rate control (Strong Recommendation, High Quality Evidence).

Recommendation 10 – Dronedarone, not for patients with history of HF (2012)

We recommend dronedarone not be used in patients with a history of heart failure or a left ventricular ejection fraction <0.40 (Strong Recommendation, Moderate Quality Evidence).

Recommendation 11 – Dronedarone, to be used with caution with patients taking digoxin (2012)

We suggest dronedarone be used with caution in patients taking digoxin (Conditional Recommendation, Moderate Quality Evidence).

Values and preferences (2012)
Recommendations 10-12 recognize that the mechanism(s) for the differences between the results of the ATHENA and the PALLAS trials have not yet been determined. These recommendations are based on the known differences between the 2 patient populations and are also informed by the results of the ANDROMEDA trial.

Recommendation 12 – Beta-blockers as initial therapy in patients with MI or LV systolic dysfunction (2010)

We recommend beta-blockers as initial therapy for rate control of AF or AFL in patients with myocardial infarction or left ventricular systolic dysfunction (Strong Recommendation, High Quality Evidence).

Values and preferences (2010)
This recommendation places a high value on the results of multiple randomized clinical trials reporting the benefit of beta-blockers to improve survival and decrease the risk of recurrent myocardial infarction and prevent new-onset heart failure following myocardial infarction, as well as the adverse effects of calcium channel blockers in the setting of heart failure.

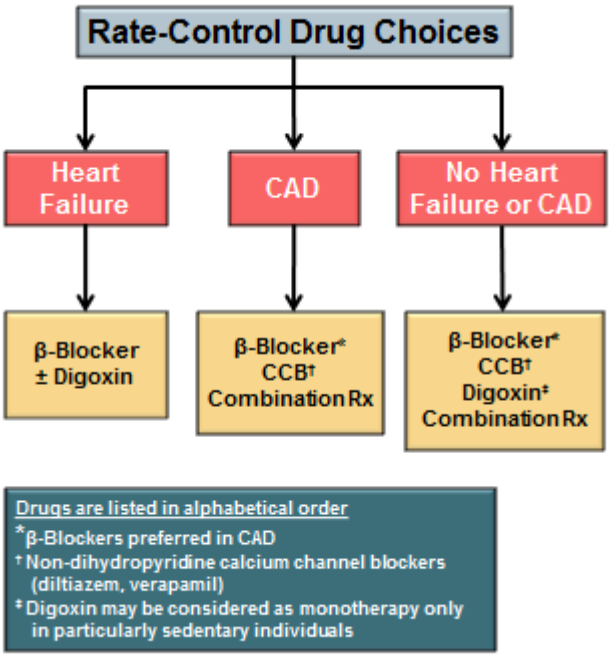
Recommendation 13 – AVN ablation/pacemaker in symptomatic drug-refractory patients (2010)

We recommend AV junction ablation and implantation of a permanent pacemaker in symptomatic patients with uncontrolled ventricular rates during AF despite maximally tolerated combination pharmacologic therapy (Strong Recommendation, Moderate Quality Evidence).

Values and preferences (2010)

This recommendation places a high value on the results of many small randomized trials and one systematic review reporting significant improvements in QOL and functional capacity as well as a decrease in hospitalizations for AF following AV junction ablation in highly symptomatic patients.

Figure S1 (Figure 3 from 2012 Update): Summary of recommendations for choice of rate-control agents for various conditions.



Part 4 – Rhythm Management of AF

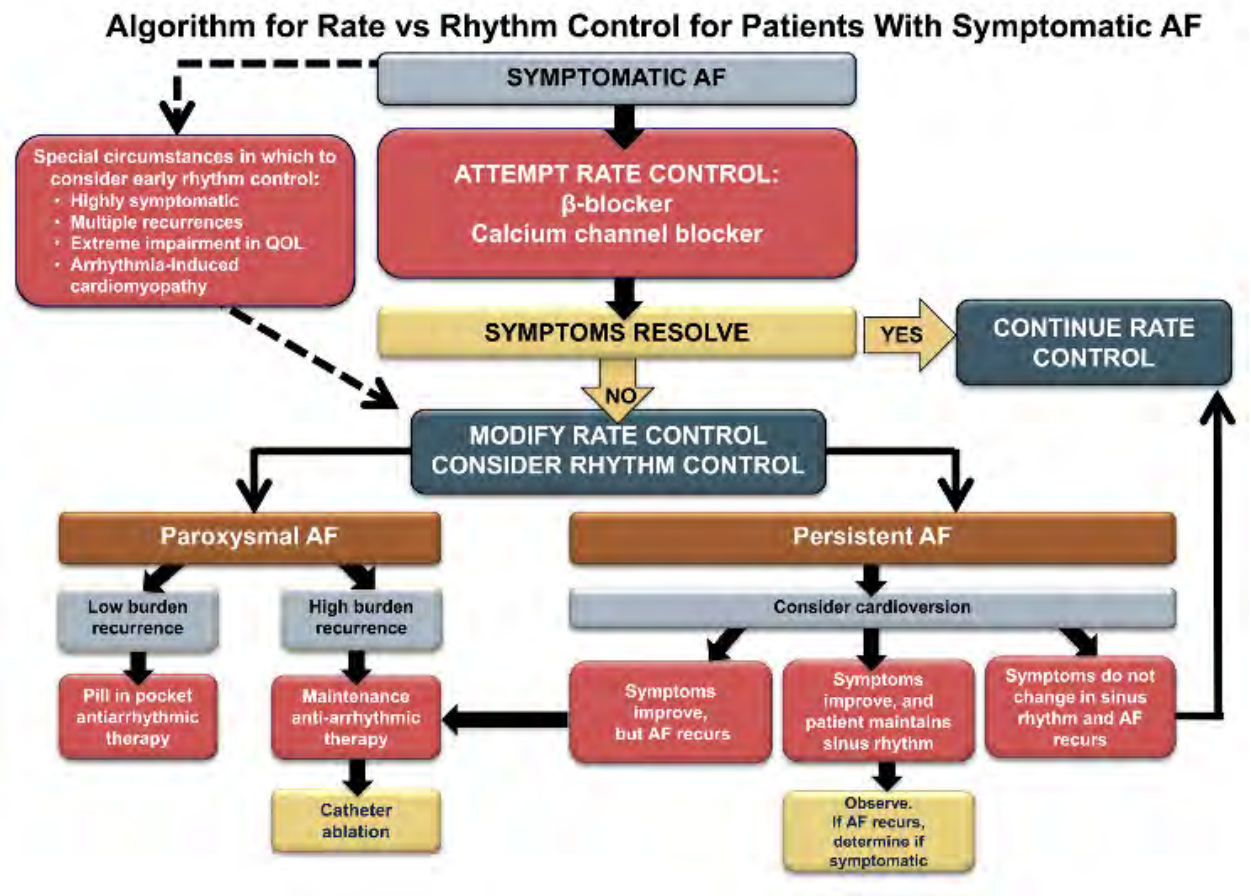
Recommendation 1 – Treatment of precipitating or reversible conditions (2010)

We recommend the optimal treatment of precipitating or reversible predisposing conditions of AF prior to attempts to restore or maintain sinus rhythm (Strong Recommendation, Low Quality Evidence).

Recommendation 2 – Rhythm control strategy for patients symptomatic on rate control therapy (2010)

We recommend a rhythm-control strategy for patients with AF or AFL who remain symptomatic with rate-control therapy or in whom rate-control therapy is unlikely to control symptoms (Strong Recommendation, Moderate Quality Evidence).

Figure S2 (Figure 3 from 2014 Update): Approach to rate and/or rhythm control of AF in patients presenting with symptomatic AF.



Recommendation 3 – Goal of rhythm control therapy (2010)

We recommend that the goal of rhythm-control therapy should be improvement in patient symptoms and clinical outcomes, and not necessarily the elimination of all AF (Strong Recommendation, Moderate Quality Evidence).

Values and preferences (2010)
Recommendations 1-3 place a high value on the decision of individual patients to balance relief of symptoms and improvement in QOL and other clinical outcomes with the potentially greater adverse effects of the addition of class I or class III antiarrhythmic drugs to rate-control therapy.

Recommendation 4 – Maintenance antiarrhythmic drugs first-line in patients with recurrent AF (2010)

We recommend use of maintenance oral antiarrhythmic therapy as first-line therapy for patients with recurrent AF in whom long-term rhythm control is desired (see Figures) (Strong Recommendation, Moderate Quality Evidence).

Figure S3 (Figure 4 from 2012 Update): Summary of recommendations for choice of rhythm-control therapy in patients with normal systolic left ventricular function and no history of congestive heart failure.

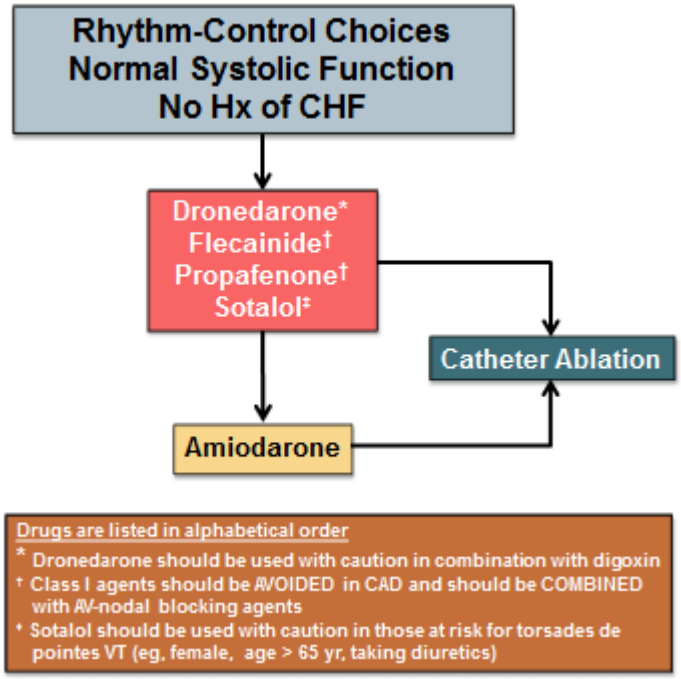
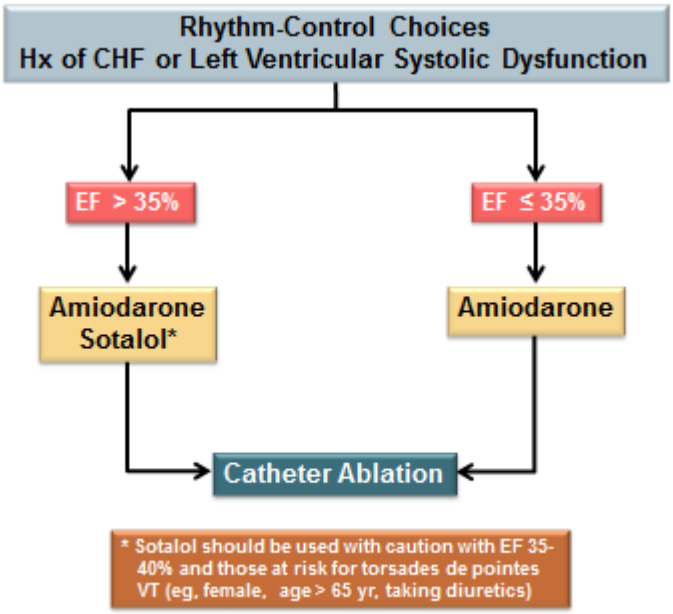


Figure S4 (Figure 5 from 2012 Update): Summary of recommendations for choice of rhythm-control therapy in patients with a history of congestive heart failure (current or remote) or left ventricular systolic dysfunction.



Recommendation 5 – Avoid antiarrhythmic in patients with advanced sinus or AV node disease (2010)

We recommend that oral antiarrhythmic drug therapy should be avoided in patients with AF or AFL and advanced sinus or AV nodal disease unless the patient has a pacemaker or implantable defibrillator (Strong Recommendation, Low Quality Evidence).

Recommendation 6 – AV blocking agent to be used along with a class I antiarrhythmic drug (2010)

We recommend that an AV blocking agent should be used in patients with AF or AFL being treated with a class I antiarrhythmic drug (eg, propafenone or flecainide) in the absence of advanced AV node disease (Strong Recommendation, Low Quality Evidence).

Values and preferences (2010)

Recommendations 4 to 6 place a high value on the decision of individual patients to balance relief of symptoms and improvement in QOL and other clinical outcomes with the potentially greater adverse effects of class I and class III antiarrhythmic drugs compared with rate-control therapy.

Recommendation 7 – 'Pill in the pocket' therapy in patients with infrequent AF (2010)

We recommend intermittent antiarrhythmic drug therapy ("pill in the pocket") in symptomatic patients with infrequent, longer-lasting episodes of AF or AFL as an alternative to daily antiarrhythmic therapy (Strong Recommendation, Moderate Quality Evidence).

Values and preferences (2010)
This recommendation places a high value on the results of clinical studies demonstrating the efficacy and safety of intermittent antiarrhythmic drug therapy in selected patients.

Table S5 (Table 1 from 2018 Update): Characteristics of antiarrhythmic medications used for acute pharmacological cardioversion

Medication	Dose	Time to Conversion	Risks
Class Ia Procainamide	15-18 mg/kg IV over 30-60 minutes	~60 minutes	Hypotension Bradycardia Ventricular proarrhythmia
Class Ic flecainide	300 mg po (> 70 kg) 200 mg po (≤ 70 kg)	2-6 hours	Hypotension Bradycardia and conversion pauses 1:1 conduction of atrial flutter*
propafenone	600 mg po (> 70 kg) 450 mg po (≤ 70 kg)	2-6 hours	
Class III ibutilide	1 mg IV over 10 min May repeat x 1	30-60 minutes	QT prolongation Torsades de pointes** Hypotension
amiodarone	150 mg IV bolus then 60 mg/h x 6 hours then 30 mg/h x 18hours	8-12 hours	Hypotension Bradycardia Atrioventricular block Torsades de pointes Phlebitis
vernakalant	3 mg/kg IV over 10 minutes, followed by 2 mg/kg IV if no conversion	12-30 minutes	Hypotension Bradycardia 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 mg of IV $MgSO_4$. 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*

Table S6 (Table 2 from 2018 Update): "Pill-In-The-Pocket" Antiarrhythmic drug therapy

Appropriate Candidates for PIP	1) symptomatic patients 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
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
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.
Instructions for subsequent use	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. Following AAD administration patients should rest in a supine or seated position for the next 4 hours, or until the episode resolves. Patients should present to the emergency department in the event that: 1) the AF episode did not terminate within 6-8 hours 2) 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) 3) more than one episode occurred in a 24-hour period (patients were advised not to take a second PIP-AAD dose within 24 hours) 4) 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.

Recommendation 8 – Electrical or pharmacological cardioversion for sinus rhythm restoration (2010)

We recommend electrical or pharmacologic cardioversion for restoration of sinus rhythm in patients with AF or AFL who are selected for rhythm-control therapy and are unlikely to convert spontaneously (Strong Recommendation, Low Quality Evidence).

Recommendation 9 – Pre-treatment with antiarrhythmic drugs before electrical cardioversion (2010)

We recommend pre-treatment with antiarrhythmic drugs prior to electrical cardioversion in patients who have had AF recurrence post cardioversion without antiarrhythmic drug pre-treatment (Strong Recommendation, Moderate Quality Evidence).

Values and preferences (2010)
Recommendations 8 and 9 place a high value on the decision of individual patients to pursue a rhythm-control strategy for improvement in QOL and functional capacity.

Recommendation 10 – For symptomatic bradycardia, dual-chamber pacing (2010)

We suggest that patients requiring pacing for the treatment of symptomatic bradycardia secondary to sinus node dysfunction, atrial or dual-chamber pacing be generally used for the prevention of AF (Conditional Recommendation, High Quality Evidence).

Recommendation 11 – Pacemaker to be programmed to minimize ventricular pacing (2010)

We suggest that, in patients with intact AV conduction, pacemakers be programmed to minimize ventricular pacing for prevention of AF (Conditional Recommendation, Moderate Quality Evidence).

Values and preferences (2010)
Recommendations 10 and 11 recognize a potential benefit of atrial or dual-chamber pacing programmed to minimize ventricular pacing to reduce the probability of AF development following pacemaker implantation.

Part 5 – Catheter Ablation of Atrial Fibrillation and Atrial Flutter

Recommendation 1 – Catheter ablation in symptomatic drug-refractory patients (2014)

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).

Values and Preferences (2014)
This recommendation recognizes that failure of multiple antiarrhythmic drugs results in few alternative strategies if maintenance of sinus rhythm is preferred based on symptom burden reduction and quality of life improvement.

Recommendation 2 – Catheter ablation as first-line therapy in highly selected patients (2014)

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).

Values and Preferences (2014)
This recommendation recognizes that individual patients may have a strong intolerance or aversion to antiarrhythmic drugs such that the risk of ablation is deemed warranted.

Table S7 (Table 2 from 2014 Update): Balance of benefit to risk for catheter ablation in patients with symptomatic atrial fibrillation

	Long-standing*	Persistent	Paroxysmal
First line	–	–	+
Failed first drug	–	+	++
Failed second drug	+	++	+++
Failed multiple drugs	++	+++	+++
+ Indicates balance of benefit to risk in favour of catheter ablation. ** Ongoing symptomatic atrial fibrillation ≥ 1 year.*			

Recommendation 3 – Catheter ablation only by operators with expertise and high volumes (2014)

We suggest that catheter ablation of AF should be performed by electrophysiologists with a high degree of expertise and high annual procedural volumes (Conditional Recommendation, Low Quality Evidence).

Values and Preferences (2014)
This recommendation recognizes that the risks of catheter ablation are directly related to operator experience and procedural volume at a given center. Although it is difficult to specify exact numerical values, the threshold seems to be 25-50 procedures/operator/year.

Recommendation 4 – Curative catheter ablation as first-line therapy for typical atrial flutter (2010)

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).

Values and preferences (2010)
This recommendation recognizes the high efficacy, low complication rate of catheter ablation and low efficacy of pharmacologic therapy, whether rate or rhythm control. 20

Recommendation 5 – Catheter ablation of accessory pathway (2010)

In patients with evidence of ventricular preexcitation during AF, we recommend catheter ablation of the accessory pathway, especially if AF is associated with rapid ventricular rates, syncope, or a pathway with a short refractory period (Strong Recommendation, Low Quality Evidence).

Values and preferences (2010)
This recommendation places a high value on the prevention of sudden cardiac death in patients at high risk and a low value on the small complication rate of catheter ablation of the accessory pathway.

Recommendation 6 – Exclude reentrant tachycardia in young patients with lone paroxysmal AF (2010)

In young patients with lone, paroxysmal AF, we suggest an electrophysiological study to exclude a reentrant tachycardia as a cause of AF; if present, we suggest curative ablation of the tachycardia (Conditional Recommendation, Very Low Quality Evidence).

Values and preferences (2010)
This recommendation recognizes that supraventricular tachycardia can initiate AF when the substrate for AF is present and can be ablated with a high success rate and minimal risk.

Recommendation 7 – Uninterrupted OAC for ablation (2018)

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).

Part 6 – Prevention of Stroke and Systemic Embolism in Atrial Fibrillation/Flutter

Recommendation 1 – Stratification of patients using a predictive index for stroke risk (2014)

We recommend that all patients with AF or AFL (paroxysmal, persistent or permanent), should be stratified using a predictive index for stroke risk (for example, the "CCS algorithm" based on the $CHADS_2$ model) (Strong Recommendation, High Quality Evidence).

Values and preferences (2014)
Use of a modified version of the $CHADS_2$ schema (the "CCS algorithm") is recommended to facilitate the choice of appropriate antithrombotic therapy by incorporating the substantial risk of stroke conferred by age 65-74 to the well validated $CHADS_2$ risk stratification scheme. However, it excludes female sex or vascular disease alone for the reasons detailed above.

Recommendation 2 – OAC therapy for patients ≥ 65 years or $CHADS_2$ ≥ 1 (2014)

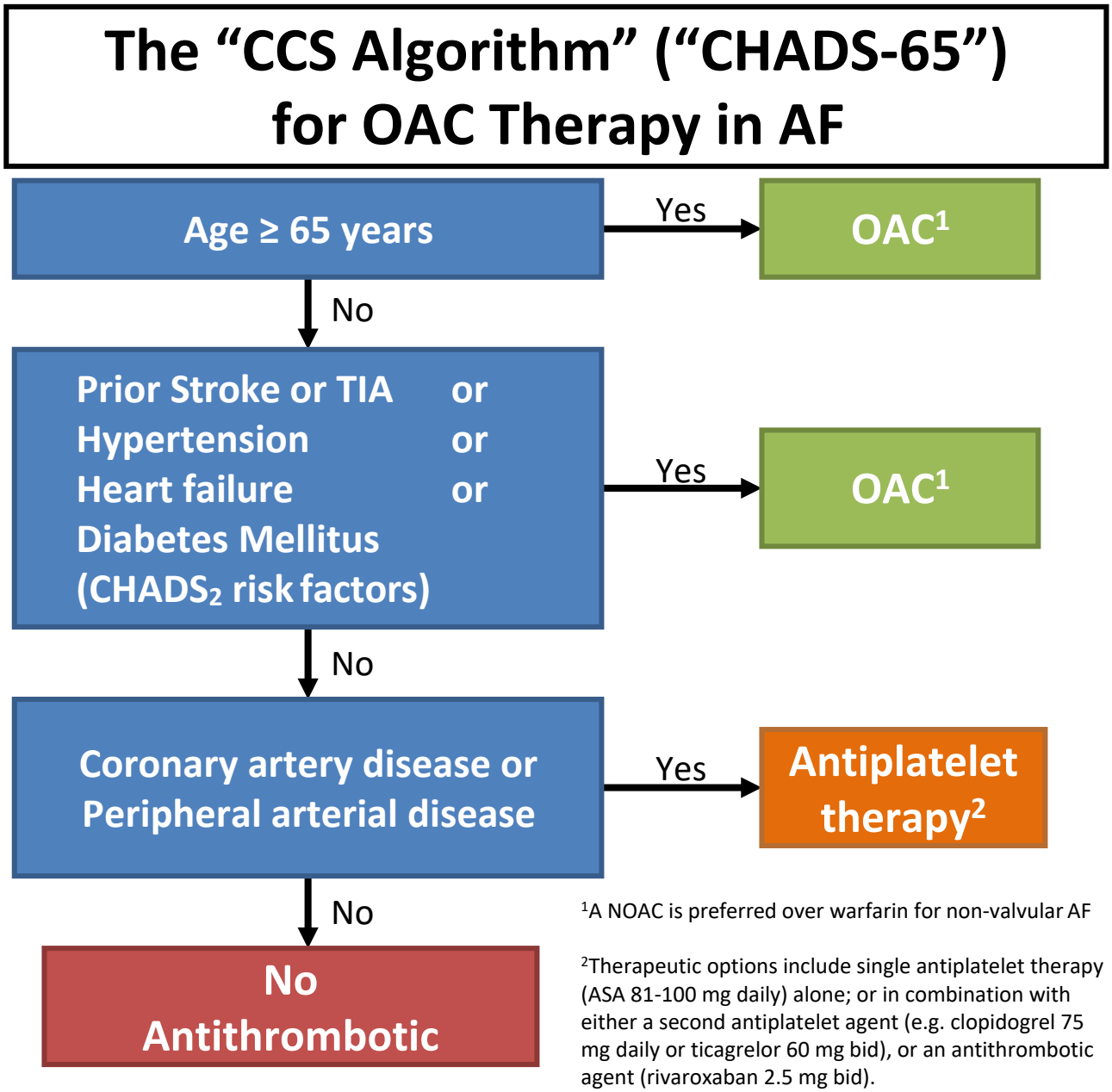
We recommend that OAC therapy be prescribed for most patients with age ≥ 65 years or $CHADS_2$ ≥ 1 (the "CCS algorithm") – see Figure S5. (Strong Recommendation, Moderate Quality Evidence) Values and preferences (2014) This recommendation places relatively greater weight on the absolute reduction of stroke risk with OACs compared to aspirin in patients aged >65 or with $CHADS_2$ ≥ 1 and less weight on the increased risk of major hemorrhage with OACs compared to aspirin.

Recommendation 3 – No OAC therapy for patients < 65 years with no CHADS2 risk factors and antiplatelet therapy for those patients with coronary or arterial vascular disease (2018)

For patients with non-valvular AF/AFL aged < 65 years with no CHADS2 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 (2018)
For patients with non-valvular AF/AFL aged < 65 years with no CHADS-65 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/arterial vascular disease (peripheral vascular disease or aortic plaque) as outlined in the 2018 CCS/CAIC Focused Update of the Guidelines for the Use of Antiplatelet Therapy. Therapeutic options include ASA 81 mg daily alone; or in combination with either clopidogrel 75 mg daily, ticagrelor 60 mg bid, or rivaroxaban 2.5 mg bid (when approved).

Figure S5 (Figure 4 from 2018 Update): The simplified "CCS Algorithm" for decisions on which patients with atrial fibrillation (AF) or atrial flutter should receive oral anticoagulation (OAC) therapy.



[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).

Table S8 (Table 1 from 2014 AF Guidelines Companion): Definitions of Stroke Risk Factors

Table 1. Definitions of stroke risk factors in the Canadian Cardiovascular Society Atrial Fibrillation Guidelines update

Factor	Definition
Congestive heart failure	Documented moderate to severe systolic dysfunction; signs and symptoms of heart failure with reduced ejection fraction; or recent decompensated heart failure that required hospitalization irrespective of ejection fraction
Hypertension	Resting blood pressure > 140 mm Hg systolic and/or > 90 mm Hg diastolic on at least 2 occasions or current antihypertensive pharmacological treatment
Age 65	Age ≥ 65 years
Diabetes mellitus	Fasting plasma glucose concentration ≥ 7.0 mmol/L (126 mg/dL) or treatment with oral hypoglycemic agents and/or insulin
Stroke/transient ischemic attack/peripheral embolism	Ischemic stroke: focal neurologic deficit of sudden onset diagnosed by a neurologist, lasting > 24 hours, and caused by ischemia; Transient ischemic attack: focal neurological deficit of sudden onset diagnosed by a neurologist, lasting < 24 hours; Peripheral embolism: thromboembolism outside the brain, heart, eyes, and lungs, or pulmonary embolism (defined by the responsible physician)
Vascular disease	Coronary artery disease, peripheral artery disease, or aortic plaque

Recommendation 4 – Most patients should receive NOAC (2014; updated 2018)

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 (2014)

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.

Recommendation 5 – Warfarin when mechanical valve, mitral stenosis or renal dysfunction (2014)

We recommend that when OAC is indicated, warfarin be used rather than one of the NOACs for those patients with a mechanical prosthetic valve, those with rheumatic mitral stenosis and those with a CrCl of 15 – 30 mL/min (Strong Recommendation, Moderate Quality Evidence).

Values and preferences (2014)

This recommendation places high value on the evidence from one RCT of the inferiority of dabigatran compared to warfarin for the prevention of thromboemboli in patients with a mechanical prosthetic valve. It places relatively high value on the long experience and clinical reports of the use of warfarin in patients with rheumatic mitral stenosis and patients with CrCl 15 – 30 mL/min and the absence of such information for NOACs.

Table S9 (Adapted from Table 5 from 2014 AF Guidelines Companion): Expert opinion regarding the clinical use of a NOAC in relation to the following commonly encountered scenarios: Would you consider NOAC use to be: (1) contraindicated or (2) not contraindicated (ie, reasonable to use) with the following valvular disorders?

NOAC use is contraindicated	NOAC use is reasonable
Mechanical heart valves (in any position) Rheumatic mitral stenosis (any degree) Non-rheumatic mitral stenosis (moderate or severe)	Bioprosthetic heart valve (in any position) Mitral annuloplasty Non-Rheumatic mitral stenosis (mild) Mitral Regurgitation Tricuspid Regurgitation Aortic Stenosis or Regurgitation

Recommendation 6 – Patients who refuse OAC should receive ASA plus clopidogrel (2014)

We recommend that patients whose risk of stroke warrants OAC therapy, but who refuse any OAC, should receive ASA 81 mg/day plus clopidogrel 75 mg/day (Strong Recommendation, High Quality Evidence).

Values and preferences (2014)
This recommendation places high value on the superiority of the combination of ASA and clopidogrel over ASA alone in the ACTIVE-A trial. However, bleeding risk of combined antiplatelet therapy may not be very different from OAC monotherapy.

Recommendation 7 – Annual renal function assessment (2012)

We recommend that patients with AF who are receiving OAC should have their renal function assessed (Strong Recommendation, Moderate Quality Evidence) and should be regularly considered for the need for alteration of OAC drug and/or dose changes based on CrCl (Strong Recommendation, Moderate Quality Evidence).

Recommendation 8 – Antithrombotic therapy should relate to CrCl (2012)

For antithrombotic therapy of CKD patients, therapy should relate to CrCl as follows:

CrCl >30 mL/min: We recommend that such patients receive antithrombotic therapy according to their risk as determined by the "CCS algorithm" as detailed in recommendations for patients for patients with normal renal function (Strong Recommendation, High Quality Evidence).

CrCl 15-30 mL/min: We suggest that such patients receive antithrombotic therapy according to their risk as determined by the "CCS algorithm" as for patients with normal renal function. The preferred agent for these patients is warfarin (Conditional Recommendation, Low Quality Evidence).

CrCl <15mL/min or on dialysis: We suggest that such patients not routinely receive either OAC (Conditional Recommendation, Low Quality Evidence) or ASA for stroke prevention in AF (Conditional Recommendation, Low Quality Evidence).

Values and preferences (2016, updated from 2012)
Recommendation 11 places a relatively higher value on prevention of ischemic stroke than on bleeding complications associated with antithrombotic therapy, as well as the limited data available for new OACs in CKD patients. They also place a relatively higher weight on observational data linking warfarin and ASA use with mortality in patients on dialysis, and relatively lower weight on the potential for these agents to prevent ischemic stroke. Patients on renal dialysis who have atrial fibrillation continue to be at high risk of both stroke and major bleeding complications. This population has been largely excluded from clinical trials evaluating stroke prevention therapies, and there have been no substantial new advances in the management of these individuals. Such studies are being planned, but until they can be completed, clinicians must continue to balance the risks of stroke against the risk of bleeding complications.

Practical tip (2012)
No antithrombotic therapy may be appropriate for some patients with CrCl 15-30 mL/min, with a stronger preference for avoiding bleeding complications than preventing ischemic stroke.

Practical tip (2016, updated from 2010)
Therapy with OACs or antiplatelet drugs may be appropriate for some patients with AF and CrCl<15 mL/min (on dialysis) in whom there is a stronger preference to avoid ischemic stroke despite uncertain benefit and likely greater bleeding risk.

Table S10 (Adapted from Table 5 from 2014 AF Guidelines Companion): Recommendations for 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.

Recommendation 9 – LAA closure devices to be used only in research and exceptional cases (2014)

We suggest these non-approved LAA closure devices not be used, except in research protocols or in systematically documented use protocols in patients who are at high risk of stroke ($CHADS_2 \geq 2$) and yet antithrombotic therapy is precluded (Conditional Recommendation, Low Quality Evidence).

Values and preferences (2014)
This recommendation places relatively great weight on the absence of RCTs showing clear benefit to risk in favor of these devices and on the need for further research and careful case series.

Recommendation 10 – Acute management of stroke in AF patients as per AHA/ASA guidelines (2010)

We recommend that patients with AF or AFL who experience a stroke be managed acutely according to the published guidelines of the American Heart and American Stroke Associations (Strong Recommendation, Moderate Quality Evidence).

Recommendation 11 – Hemorrhage on OAC to be managed per AACP guidelines (2010)

We suggest that patients with AF or AFL who experience hemorrhage while on OAC be managed according to the published practice guidelines of the American College of Chest Physicians (Conditional Recommendation, Low Quality Evidence).

Recommendation 12 – Idarucizimab for emergency reversal of dabigatran's anticoagulant effect (2018, updated from 2016)

We recommend administering idarucizimab 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 (2016)
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 RE-VERSE AD trial and on the cost of the drug.

Practical tip (2018, updated from 2016)
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.

Practical tip (2018)

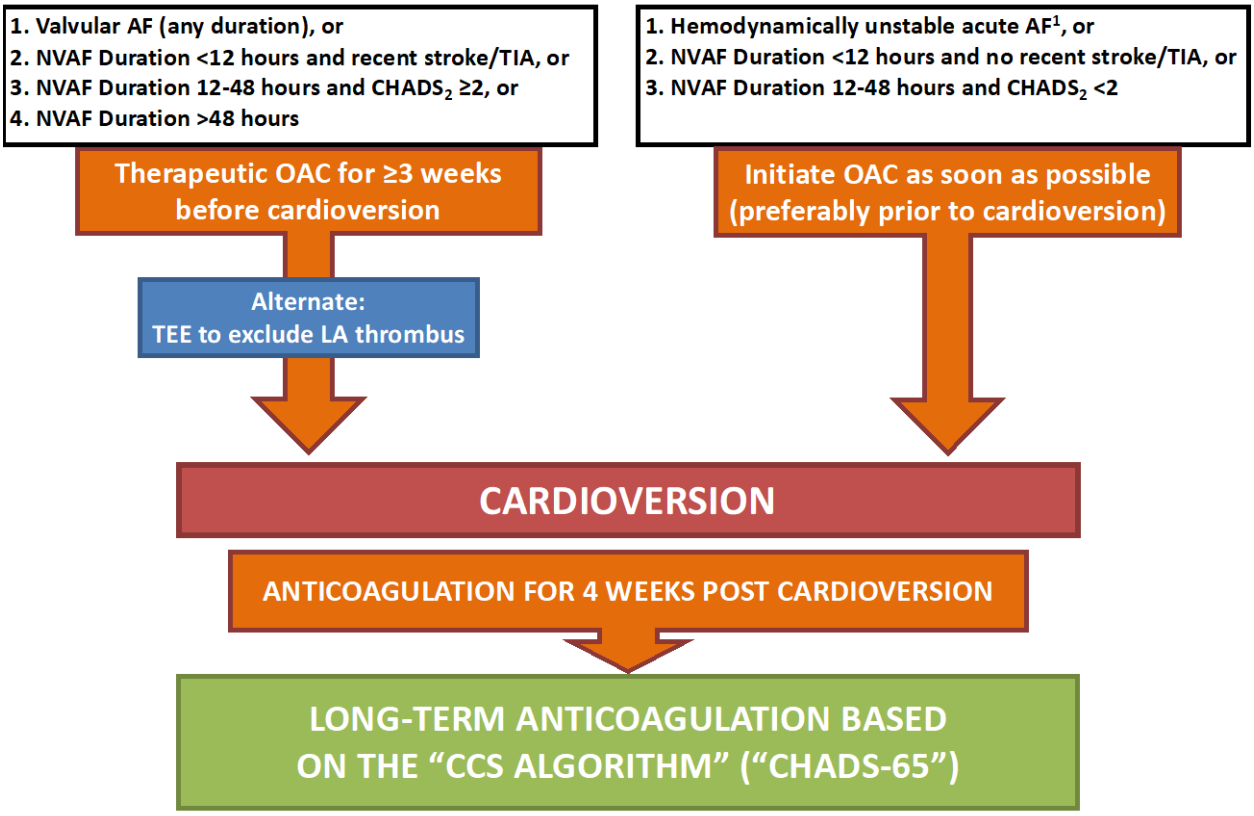
"Urgent" surgery as defined in the REVERSE-AD trial is surgery that cannot be delayed beyond 8 hours (amended from 4 hours in the initial version of the protocol). The timing of surgery should be based on the clinical indication and stability of the patient. In instances where delayed surgery is appropriate, clinicians may obtain coagulation parameters (e.g.TT or aPTT) to identify patients who would be unlikely to benefit from idarucizumab. (see Practical Tip 1 above).

Practical tip (2018)

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Oral anticoagulation should be reintroduced as soon as medically appropriate.

Part 7 – Anticoagulation in the Context of Cardioversion

Figure S6 (Figure 1 from 2018 Update): Anticoagulation in the context of cardioversion



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

Recommendation 1 – Anticoagulation for at least 3 weeks before elective cardioversion (2018, updated from 2010)

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).

Recommendation 2 – Circumstances where deferral of anticoagulation prior to cardioversion may be appropriate (2018, updated from 2010)

We suggest that pharmacological or electrical cardioversion of symptomatic AF or AFL without at least three weeks of prior therapeutic anticoagulation be reserved for patients with the following characteristics (Weak Recommendation, Low Quality Evidence):

a) patients with non-valvular AF presenting with a clear AF-onset within 12 hours in the absence of recent stroke or TIA (within 6 months)
b) patients with non-valvular AF and a CHADS2 score < 2 presenting after 12 hours but within 48 hours of AF onset

Practical tip (2018)
Non-valvular AF is defined as AF in the absence of mechanical heart valves, rheumatic mitral stenosis, or moderate to severe nonrheumatic mitral stenosis.

Recommendation 3 – The use of transesophageal echocardiography as an alternative to anticoagulation prior to cardioversion (2018, updated from 2014)

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

Recommendation 4 – Immediate electrical cardioversion for patients who are hemodynamically unstable (2018, updated from 2014)

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 (2018)
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 pre-cardioversion. Therapeutic anticoagulation therapy should be initiated as soon as possible.

Recommendation 5 – Immediate initiation of anticoagulation prior to unplanned cardioversion (2018, updated from 2010)

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).

Recommendation 6 – Anticoagulation for at least 4 weeks post cardioversion (2018, updated from 2010)

We suggest that, in the absence of a strong contraindication, all patients undergoing cardioversion of AF/AFL receive at least four 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 (2018)
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 based upon either 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 one month after cardioversion for all such patients in the absence of a strong contraindication.

Practical tip (2018)
When oral anticoagulation is to be used for only a short period (less than two months) current evidence does not substantiate either an efficacy or safety advantage for use of a NOAC over adjusted dose warfarin.

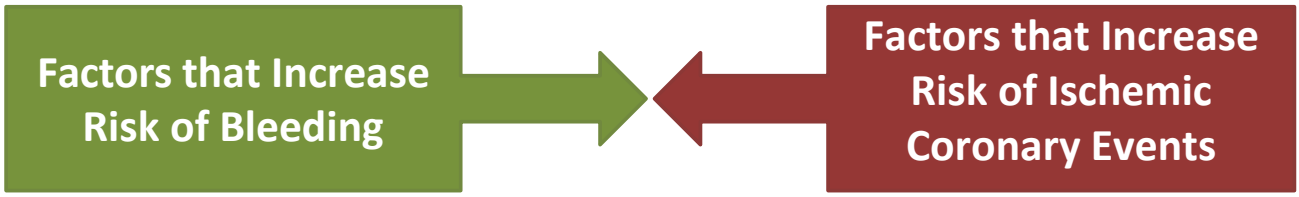
Nevertheless, the convenience of use of a NOAC over adjusted-dose warfarin in the peri-cardioversion period is substantial and the onset of therapeutic anticoagulation is nearly immediate with a NOAC while being delayed in the case of adjusted-dose warfarin. Accordingly, it is reasonable to use NOAC therapy in the peri-cardioversion period.

Part 8 – Management of Antithrombotic Therapy in patients with concomitant AF and CAD

Recommendation 1 – Antithrombotic therapy based on a balanced assessment of a patient's risk of stroke (2018, updated from 2016)

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).

Figure S7 (Figure 2 from 2018 Update): Risk factors associated with an increased risk of bleeding, and an increased risk of ischemic coronary outcomes (recurrent MI, stent thrombosis)



- **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%)

- **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

Practical tip (2018)

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 OAC; 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 S8); 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.

Recommendation 2 – Most patients with an indication for OAC in the presence of CAD should receive a NOAC (2018, updated from 2016)

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 (2018, updated from 2014, 2016)
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).

Recommendation 3 – Stable vascular disease and AF in patients at low risk of stroke/systemic thromboembolism (2018)

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 (2018)
For patients with non-valvular AF/AFL aged < 65 years with no CHADS-65 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/arterial vascular disease (peripheral vascular disease or aortic plaque) as outlined in the 2018 CCS/CAIC Focused Update of the Guidelines for the Use of Antiplatelet Therapy. Therapeutic options include ASA 81 mg daily alone; or in combination with either clopidogrel 75 mg daily, ticagrelor 60 mg bid, or rivaroxaban 2.5 mg bid (when approved).

Recommendation 4 – Stable vascular disease and AF in patients at high risk of stroke/systemic thromboembolism (2018)

For patients with AF aged ≥ 65 years or with a CHADS2 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).

Practical tip (2018)
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 alone.

Values and preferences (2018)
For patients with AF and stable coronary or arterial vascular disease, the CCS AF Guidelines committee felt that routine use of combination therapy (OAC plus single antiplatelet) was not justified owing to the increased risk of bleeding without a significant reduction in ischemic coronary and cerebrovascular thrombotic events.

Recommendation 5 – AF Patients at Higher Risk of Stroke Undergoing PCI without High-Risk Features (2018, updated from 2016)

For patients with AF aged ≥ 65 years or with a CHADS2 score ≥ 1, we suggest Dual Pathway Therapy (OAC plus clopidogrel 75 mg daily) for at least 1 month after BMS implantation and at least 3 months after DES implantation (Weak Recommendation, Moderate Quality Evidence).

Practical tip (2018, updated from 2014, 2016)
For some patients < 65 years of age with CHADS2 = 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 Dual Pathway Therapy (OAC plus clopidogrel).

Recommendation 6 – AF Patients at Higher Risk of Stroke Undergoing PCI for ACS or elective PCI with High-Risk Features (2018, adapted from 2016 and from CCS 2018 Antiplatelet Therapy Guidelines)

For patients with AF aged ≥ 65 years or with a CHADS2 score ≥ 1, we recommend an initial regimen of triple antithrobotic therapy (ASA 81 mg daily plus clopidogrel 75 mg daily plus OAC) up to 6 months following PCI (Strong Recommendation, Moderate Quality Evidence). Following ASA discontinuation, which may occur as early as the day following PCI, we suggest that Dual Pathway Therapy (OAC plus clopidogrel 75 mg daily) be continued for up to 12 months after PCI (Weak Recommendation, Moderate Quality Evidence).

Practical tip (2018)
For some patients < 65 years of age with CHADS2 = 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).

Practical tip (2018)
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])**.**

Practical tip (2018)
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 month to 3 months.

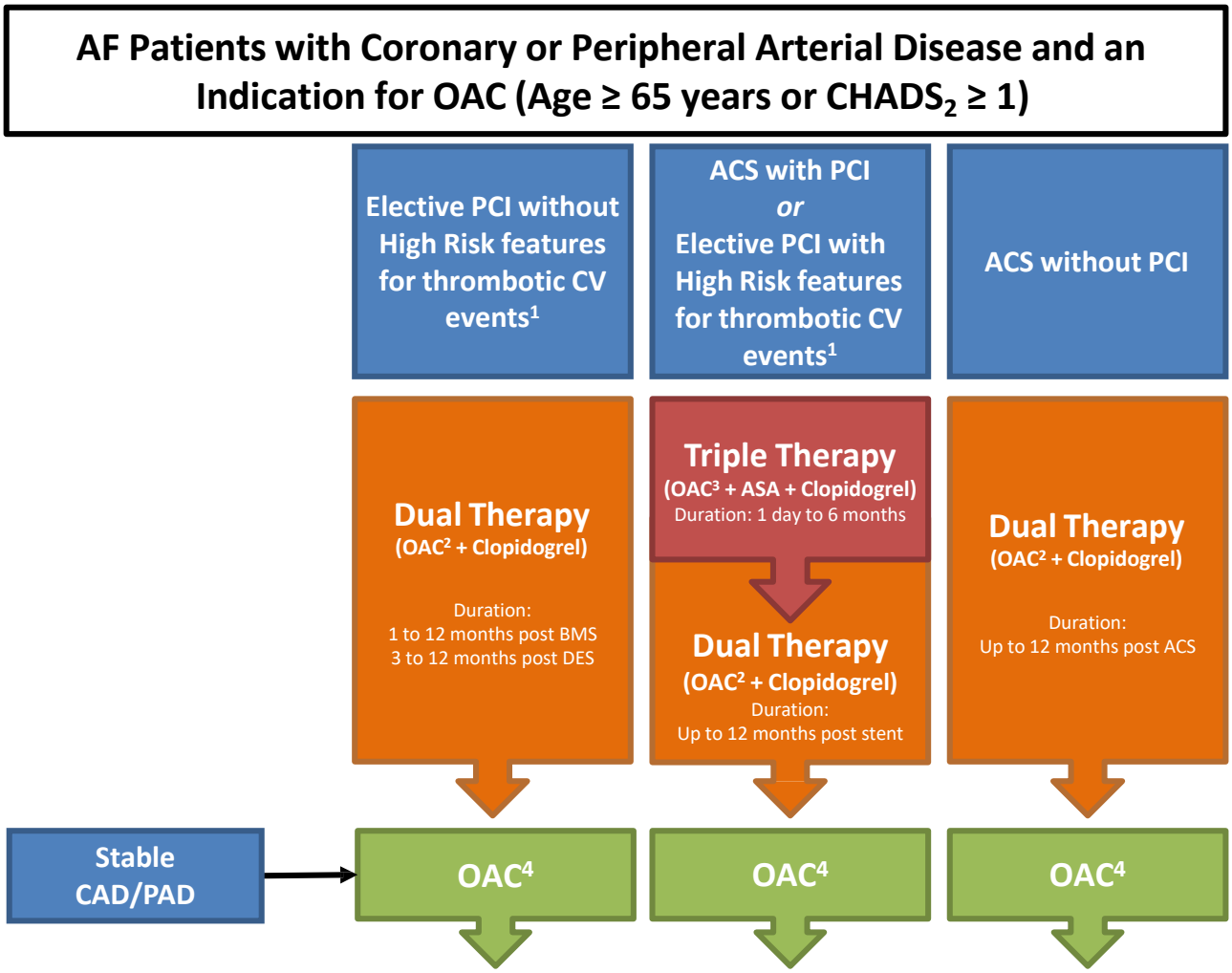
Recommendation 7 – AF Patients at Higher Risk of Stroke in association with medically managed Type I Myocardial Infarction

For patients with AF aged ≥ 65 years or with a CHADS2 score ≥ 1, we suggest that Dual Pathway Therapy (OAC plus clopidogrel 75 mg daily, rather than prasugrel or ticagrelor) be given without concomitant ASA for 12 months post ACS (Weak Recommendation, Low Quality Evidence).

Values and preferences (2018)

For patients with AF and type I MI not undergoing 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 demonstrated to be superior to ASA (0.5% absolute reduction in composite of vascular death, MI, or ischemic stroke; P = 0.043), well as the substantial efficacy and safety data for combination therapy utilizing clopidogrel and OAC (clopidogrel used in 88% of patients in RE-DUAL and 95% in PIONEER AF-PCI).

Figure S8 (Figure 3 from 2018 Update): Management of antithrombotic therapy in patients with AF and CAD or vascular disease and an indication for OAC.



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.

Part 9 – Management of Recent Onset Atrial Fibrillation and Flutter in an Acute Care setting

Recommendation 1 – Rate or rhythm control therapy for patients with recent onset AF/AFL (2010)

We recommend that in stable patients with recent-onset AF/AFL, a strategy of rate control or rhythm control could be selected (Strong Recommendation, High Quality Evidence).

Values and preferences (2010)
This recommendation places a high value on the randomized controlled trials investigating rate control as an alternative to rhythm control for AF/AFL, recognizing that these trials did not specifically address the ED environment.

Recommendation 2 – Hemodynamically stable patients with AF/AFL <48 hours (2010)

In hemodynamically stable patients with AF/AFL of known duration <48 hours in whom a strategy of rhythm control has been selected:

a) We recommend that rate-slowing agents alone are acceptable while awaiting spontaneous conversion (Strong Recommendation, Moderate Quality Evidence).

b) We recommend that synchronized electrical cardioversion or pharmacologic cardioversion may be used when a decision is made to cardiovert patients in the emergency department. See Table for drug recommendations (Strong Recommendation, Moderate Quality Evidence).

c) We suggest that antiarrhythmic drugs may be used to pre-treat patients before electrical cardioversion in ED in order to decrease early recurrence of AF and to enhance cardioversion efficacy (Conditional Recommendation, Low Quality Evidence).

Values and preferences (2010)
These recommendations place a high value on determination of the duration of AF/AFL as a determinant of stroke risk with cardioversion. Also, individual considerations of the patient and treating physician are recognized in making specific decisions about method of cardioversion.

Recommendation 3 – Electrical cardioversion with 150-200 joules biphasic waveform (2010)

We recommend that electrical cardioversion may be conducted in the ED with 150-200 joules biphasic waveform as the initial energy setting (Strong Recommendation, Low- Quality Evidence).

Values and preferences (2010)
This recommendation places a high value on the avoidance of repeated shocks and the avoidance of ventricular fibrillation that can occur with synchronized cardioversion of AF at lower energy levels. It is recognized that the induction of VF is a rare but easily avoidable event.

Recommendation 4 – WPW/rapid response, DC cardioversion for hemodynamically unstable (2010)

We recommend, in patients with rapid ventricular preexcitation during AF (Wolff-Parkinson-White syndrome):

a) Urgent electrical cardioversion if the patient is hemodynamically unstable (Strong Recommendation, Low Quality Evidence).

b) Intravenous antiarrhythmic agents (procainamide or ibutilide) in stable patients (Strong Recommendation, Low Quality Evidence).

c) AV nodal blocking agents (digoxin, calcium channel blockers, beta-blockers, adenosine) are contraindicated (Strong Recommendation, Low Quality Evidence).

Values and preferences (2010)
These recommendations place a high value on avoidance of the degeneration of preexcited AF to ventricular fibrillation. It is recognized that degeneration can occur spontaneously or it can be facilitated by the administration of specific agents that in the absence of ventricular preexcitation would be the appropriate therapy for rate control of AF.

Recommendation 5 – Hemodynamic instability: consider immediate DC cardioversion (2018, updated from 2014)

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 (2018, updated from 2014)
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 pre-cardioversion. Therapeutic anticoagulation therapy should be initiated as soon as possible.

Recommendation 6 – Lower stroke risk and AF < 48 hours, may undergo cardioversion (2018, updated from 2014)

We suggest that pharmacological or electrical cardioversion of symptomatic AF or AFL without at least three weeks of prior therapeutic anticoagulation be reserved for patients with the following characteristics (Weak Recommendation, Low Quality Evidence):

a) patients with non-valvular AF presenting with a clear AF-onset within 12 hours in the absence of recent stroke or TIA (within 6 months)

b) patients with non-valvular AF and a CHADS2 score < 2 presenting after 12 hours but within 48 hours of AF onset

Practical tip (2018)
Non-valvular AF is defined as AF in the absence of mechanical heart valves, rheumatic mitral stenosis, or moderate to severe nonrheumatic mitral stenosis.

Recommendation 7 – High stroke risk: rate control and OAC therapy 3 weeks pre-cardioversion (2014)

For patients at high risk of stroke with cardioversion (not receiving therapeutic OAC therapy for ≥3 weeks with any of the following: AF episode duration not clearly <48 hours; stroke or TIA within 6 months; rheumatic heart disease; mechanical valve), we recommend optimized rate-control and therapeutic OAC for

3 weeks before and at least 4 weeks after cardioversion. (Strong Recommendation, Moderate Quality Evidence)

Values and preferences (2014)
These recommendations place a high value on minimizing stroke risk by a strategy of rate control, appropriate anticoagulation and delayed cardioversion and a lower value on symptomatic improvement associated with immediate cardioversion.

Recommendation 8 – High stroke risk and cardioversion after TEE (2018, updated from 2014)

We suggest that, as an alternative to at least three 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 (2014)
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.

Recommendation 9 – Immediate initiation of OAC for unplanned cardioversion (2018)

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).

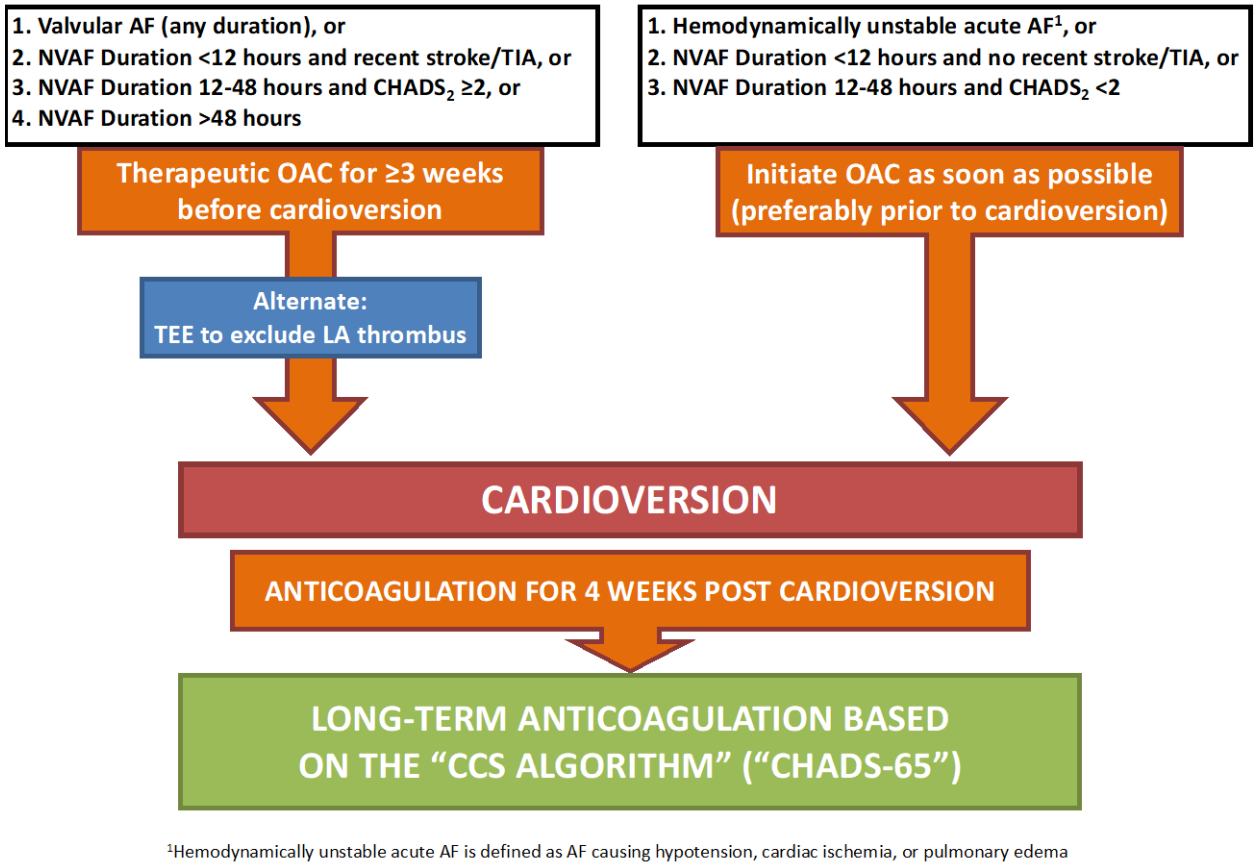
Recommendation 10 – OAC for 4 weeks post cardioversion (2018)

We suggest that, in the absence of a strong contraindication, all patients undergoing cardioversion of AF/AFL receive at least four 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 (2018)
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 based upon either 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 one month after cardioversion for all such patients in the absence of a strong contraindication.

Practical tip (2018)
When oral anticoagulation is to be used for only a short period (less than two 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 peri-cardioversion period is substantial and the onset of therapeutic anticoagulation is nearly immediate with a NOAC while being delayed in the case of adjusted-dose warfarin. Accordingly, it is reasonable to use NOAC therapy in the peri-cardioversion period.

Figure S6 (Figure 1 from 2018 Update): Anticoagulation in the context of cardioversion



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

Recommendation 11 – Hospital admission for decompensated HF or myocardial ischemia (2010)

We recommend hospital admission for highly symptomatic patients with decompensated heart failure or myocardial ischemia (Strong Recommendation, Low Quality Evidence).

Recommendation 12 – Admission for highly symptomatic patients with unachievable rate control (2010)

We suggest limiting hospital admission to highly symptomatic patients in whom adequate rate control cannot be achieved (Conditional Recommendation, Low Quality Evidence).

Values and preferences (2010)
Recommendation 9 and 10 place a high value on the need for monitoring of the response to therapy and its reassessment, as well as ancillary investigation and treatment not available in the ED in patients with complex medical conditions associated with AF/AFL. A lower value is placed on the attendant costs of admission to hospital in patients with complex medical conditions associated with AF/AFL.

Recommendation 13 – Antiarrhythmic drug therapy post-cardioversion (2010)

We suggest that after conversion to sinus rhythm has been achieved, whether antiarrhythmic drug therapy is indicated should be based on the estimated probability of recurrence and the symptoms during AF. Long-term therapy will need to be determined by an appropriate outpatient consultation (Conditional Recommendation, Low Quality Evidence).

Values and preferences (2010)

This recommendation places a high value on minimizing the risk of infrequent but serious side effects associated with long-term antiarrhythmic drugs. A high value is also placed on the appropriate use of specialty care to make patient-specific decisions to minimize these risks. A lower value is placed on the avoidance of symptoms associated with subsequent episodes of AF/AFL.

Table S11 (Table 2 from 2010): Recommended intravenous drugs for acute heart rate control

Drug	Dose	Risks
Diltiazem*	0.25 mg/kg IV bolus over 10 min; repeat at 0.35 mg/kg IV	Hypotension, bradycardia
Metoprolol	2.5-5 mg IV bolus over 2 min; up to 3 doses	Hypotension, bradycardia
Verapamil*	0.075-0.15 mg/kg over 2 min	Hypotension, bradycardia
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/ left ventricular dysfunction.*

Table S5 (Table 1 from 2018): Characteristics of antiarrhythmic medications used for acute pharmacological cardioversion

Medication	Dose	Time to Conversion	Risks
Class Ia **Procainamide**	15-18 mg/kg IV over 30-60 minutes	~60 minutes	Hypotension Bradycardia Ventricular proarrhythmia
Class Ic **flecainide**	300 mg po (> 70 kg) 200 mg po (≤ 70 kg)	2-6 hours	Hypotension Bradycardia and conversion pauses 1:1 conduction of atrial flutter*
propafenone	600 mg po (> 70 kg) 450 mg po (≤ 70 kg)	2-6 hours	
Class III **ibutilide**	1 mg IV over 10 min May repeat x 1	30-60 minutes	QT prolongation Torsades de pointes** Hypotension
amiodarone	150 mg IV bolus then 60 mg/h x 6 hours then 30 mg/h x 18hours	8-12 hours	Hypotension Bradycardia Atrioventricular block Torsades de pointes Phlebitis
vernakalant	3 mg/kg IV over 10 minutes, followed by 2 mg/kg IV if no conversion	12-30 minutes	Hypotension Bradycardia 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 mg of IV $MgSO_4$. 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

Part 10 – Surgical Therapy for Atrial Fibrillation

Recommendation 1 – Surgical AF ablation in association with cardiac surgery (2016, updated from 2010)

We suggest that a surgical AF ablation procedure should be considered in association with mitral valve, aortic valve or CABG surgery in patients with AF, when the likelihood of success is deemed to be high, the additional risk is low and sinus rhythm is expected to achieve substantial symptomatic benefit (Conditional Recommendation, Moderate Quality Evidence).

Values and preferences (2016, updated from 2010)
This recommendation recognizes that individual institutional experience and patient considerations best determine for whom the surgical procedure is performed. Importantly, the symptomatic benefit of sinus rhythm needs to be balanced with the attendant risks of ablation surgery, including the need for permanent pacing. This recommendation also recognizes that LA endocardial access is not routinely required for aortic or coronary surgery; limiting ablation to newer epicardial approaches.

Recommendation 2 – Asymptomatic lone AF, not to be considered for surgical therapy (2010)

We recommend that patients with asymptomatic lone AF, in whom AF is not expected to affect cardiac outcome, should not be considered for surgical therapy for AF (Strong Recommendation, Low Quality Evidence).

Values and preferences (2010)
This recommendation recognizes that patients with lone AF are at low risk for stroke or other adverse cardiovascular outcomes. Thus, elimination of AF in the absence of a high number of symptoms is unlikely to result in an improvement in quality of life.

Recommendation 3 – Closure of the left atrial appendage as part of surgical ablation of AF associated with cardiac surgery (2016, updated from 2010)

In patients with AF, we suggest that closure (excision or obliteration) of the LAA should be considered as part of the surgical ablation of AF associated with mitral, aortic valve or coronary artery bypass surgery if this does not increase the risk of the surgery (Conditional Recommendation, Low Quality Evidence).

Values and preferences (2016, updated from 2010)
This recommendation places a high value on the potential for stroke reduction and a lower value on loss of atrial transport-function with LAA-closure. It places less value on the need to continue OAC even after LAA surgical excision.

Recommendation 4 – Continue OAC following surgical AF ablation per risk factors (2010)

We recommend that oral anticoagulant therapy be continued following surgical AF ablation in patients with any risks identified by the new “CCS algorithm” (Strong Recommendation, Moderate Quality Evidence).

Recommendation 5 – Continue OAC following surgical AF ablation for all MVRs (2010)

We suggest that oral anticoagulant therapy be continued following surgical AF ablation in patients who have undergone mechanical or bioprosthetic mitral valve replacement (Conditional Recommendation, Low Quality Evidence).

Values and preferences (2010)
Recommendations 6 and 7 place a high value on minimizing the risk of stroke and a lower value in the utility of long-term monitoring to document the absence of AF.

Part 11 – Prevention and Treatment of Atrial Fibrillation following Cardiac Surgery

Recommendation 1 –Beta-blockers to be continued through the operative procedure (2010)

We recommend that patients who have been receiving a beta-blocker before cardiac surgery have that therapy continued through the operative procedure in the absence of the development of a new contraindication (Strong Recommendation, High Quality Evidence).

We suggest that patients who have not been receiving a beta-blocker before cardiac surgery have beta-blocker therapy initiated immediately after the operative procedure in the absence of a contraindication (Conditional Recommendation, Low Quality Evidence).

Values and preferences (2010)
These recommendations place a high value on reducing postoperative AF and a lower value on adverse hemodynamic effects of β-blockade during or after cardiac surgery. It is also noted that inherent to a strategy of prophylaxis, a number of patients will receive beta-blocker therapy without personal benefit.

Recommendation 2 – Amiodarone for patients with contraindications to beta-blockers (2010)

We recommend that patients who have a contraindication to beta-blocker therapy before or after cardiac surgery be considered for prophylactic therapy with amiodarone to prevent postoperative AF (Strong Recommendation, High Quality Evidence).

Values and preferences (2010)
This recommendation places a high value on minimizing the patient population exposed to the potential adverse effects of amiodarone and a lower value on data suggesting that amiodarone is more effective than beta-blockers for this purpose.

Recommendation 3 – Consider IV magnesium, colchicine, biatrial pacing when beta-blocker and amiodarone contraindicated (2016, updated from 2010)

We suggest that patients who have a contraindication to beta-blocker therapy and to amiodarone before or after cardiac surgery be considered for prophylactic therapy to prevent POAF with intravenous magnesium (Conditional Recommendation, Low Quality Evidence) or colchicine (Conditional Recommendation, Low Quality of Evidence) or with biatrial pacing (Conditional Recommendation, Low Quality of Evidence).

Values and preferences (2016, updated from 2010)
This recommendation places a high value on preventing POAF using novel therapies that are supported by lower-quality data; with a higher value on the lower probability of adverse effects from magnesium versus colchicine. The use of biatrial pacing needs to be individualized by patient and institution, as the potential for adverse effects may outweigh benefit based on local expertise.

Recommendation 4 – High risk and sotalol or combination prophylaxis (2010)

We suggest that patients at high risk of postoperative AF receive prophylactic therapy to prevent postoperative AF such as sotalol or combination therapy including ≥2 of a beta-blocker, amiodarone, intravenous magnesium, or biatrial pacing (Conditional Recommendation, Low- to Moderate Quality Evidence).

Values and preferences (2010)
This recommendation recognizes that data confirming the superiority of combinations of prophylactic therapies are sparse.

Recommendation 5 – Consideration of OAC for postoperative AF >72 hours (2010)

We suggest that consideration be given to anticoagulation therapy if postoperative continuous AF persists for >72 hours. This consideration will include individualized assessment of the risks of a thromboembolic event and the risk of postoperative bleeding (Conditional Recommendation, Low Quality Evidence).

Values and preferences (2010)
This recommendation places a higher value on minimizing the risk of thromboembolic events and a lower value on the potential for postoperative bleeding. Because the risk of postoperative bleeding decreases with time, the benefit-to-risk ratio favours a longer period without anticoagulation in the postoperative setting than that suggested in other settings.

Recommendation 6 – Temporary epicardial pacing electrode wires at surgery (2010)

We recommend that temporary ventricular epicardial pacing electrode wires be placed at the time of cardiac surgery to allow for backup ventricular pacing as necessary (Strong Recommendation, Low Quality Evidence).

Values and preferences (2010)
This recommendation reflects the relative ease of placement of epicardial temporary pacing wires at the time of surgery as well as the potential for significant morbidity associated with postoperative bradycardia.

Recommendation 7 – Post-op AF with rapid response: beta-blocker, CCB, or amiodarone (2010)

We recommend that postoperative AF with a rapid ventricular response be treated with a beta-blocker, a non–dihydropyridine calcium antagonist, or amiodarone to establish ventricular rate control. In the absence of a specific contraindication, the order of choice is as listed (Strong Recommendation, High Quality Evidence).

Values and preferences (2010)
This recommendation places a high value on the randomized controlled trials investigating rate control as an alternative to rhythm control for AF, recognizing that these trials did not specifically address the postoperative period.

Recommendation 8 – Rate-control or rhythm-control strategy for post-op AF (2016, updated from 2010)

We recommend that postoperative AF may be appropriately treated with either a ventricular response rate-control strategy or a rhythm-control strategy (Strong Recommendation, Moderate Quality Evidence).

Values and preferences (2016, updated from 2010)
This recommendation places a high value on the randomized controlled trials investigating rate control as an alternative to rhythm control for AF, including one trial specifically addressing the cardiac postoperative period. Choice of strategy should therefore be individualized based on the degree of symptoms experienced by the patient.

Recommendation 9 – Reconsideration of ongoing therapy 6-12 weeks post-op (2010)

We recommend that, when anticoagulation therapy, rate-control therapy, and/or rhythm control therapy has been prescribed for postoperative AF, formal reconsideration of the ongoing need for such therapy should be undertaken 6-12 weeks later (Strong Recommendation, Moderate Quality Evidence).

Values and preferences (2010)
This recommendation reflects the high probability that postoperative AF will be a self-limiting process that does not require long-term therapy.

Part 12 – Peri-procedural Anticoagulation Management

Recommendation 1 – Decision considerations (2014)

We recommend that in a patient with AF or atrial flutter, a decision to interrupt antithrombotic therapy for an invasive procedure must balance the risks of a thromboembolic event (as indicated by a higher $CHADS_2$ score, mechanical heart valve, or rheumatic heart disease) with those of a bleeding event (as indicated by a higher HASBLED score and procedures with higher bleeding risks) (Strong Recommendation, Low Quality Evidence).

Recommendation 2 – OAC interruption not necessary for most lower risk procedures (2016, updated from 2014)

We suggest that interruption of anticoagulant therapy, particularly for vitamin K antagonists, in a patient with AF/AFL is not necessary for most procedures with a low risk of bleeding, such as cardiac device implantation (pacemaker or implantable defibrillator), and most dental procedures (Table 1) (Conditional Recommendation, Moderate Quality Evidence).

Recommendation 3 – OAC interruption of anticoagulant therapy for medium to high risk procedures (2014)

We recommend that interruption of anticoagulant therapy in a patient with AF or AFL will be necessary for most procedures with an intermediate or high risk of major bleeding (see Table 1) (Strong Recommendation, Low Quality Evidence).

Values and preferences (2014)
Practitioners responsible for preventing thromboembolic events in patients with AF/AFL and practitioners responsible for preventing peri-procedural bleeding each tend to over-value their unique roles. Recommendations 1-3 are intended to promote a balanced approach to minimizing the combined outcome of peri-procedural thromboembolic events and major bleeding.

Table S12 (Updated Table 1 from 2016): Bleeding risks for various invasive/surgical procedures

High risk
• Any surgery or procedure with neuraxial (spinal or epidural) anesthesia
• Neurosurgery (intracranial or spinal)
• Cardiac surgery (e.g. CABG, heart valve replacement)
• Major intra-abdominal surgery (e.g. intestinal anastomosis surgery)
• Major vascular surgery (e.g. aortic aneurysm repair, aortofemoral bypass)
• Major orthopedic surgery (e.g. hip or knee replacement)
• Lung resection surgery
• Urological surgery (e.g. prostatectomy, bladder tumour resection)
• Extensive cancer surgery (e.g. pancreas, liver)
• Reconstructive plastic surgery
• Selected procedures (e.g. kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)
Intermediate risk
• Other intra-abdominal surgery (e.g. cholecystectomy, hernia repair, colon resection)
• Other general surgery (e.g. breast)
• Other intrathoracic surgery
• Other orthopedic surgery
• Other vascular surgery
• Non-cataract ophthalmologic surgery
• Gastroscopy or colonoscopy with biopsies
• Selected procedures (e.g. bone marrow biopsy, lymph node biopsy)
• Complex dental procedure (e.g. multiple tooth extractions)
Low risk
• Non-complex dental procedures (Dental extractions of 1 or 2 teeth, endodontic [e.g. root canal] procedure, subgingival scaling or other cleaning)
• Cataract surgery
• Dermatologic procedures (e.g. biopsy)
• Gastroscopy or colonoscopy without biopsies
• Coronary angiography
• Permanent pacemaker insertion or internal defibrillator placement (if bridging anticoagulation is not used)
• Selected procedures (e.g. thoracentesis, paracentesis, arthrocentesis)

The procedural/ surgical risk categorization list may be updated based on new information, and can be found at Thrombosis Canada (http://thrombosiscanada.ca)

Recommendation 4 – Aspirin or clopidogrel interruption 5-7 days prior to procedure (2016, updated from 2014)

When a decision to interrupt aspirin or clopidogrel (or other ADP receptor/P2Y12 inhibitors including prasugrel, ticagrelor), therapy for an invasive procedure has been made for a patient with AF/AFL, we suggest that interruption begin 5-7 days before the procedure, except for procedures with a very high risk of bleeding, in which case we suggest interruption 7-10 days before the procedure (Conditional Recommendation, Low Quality Evidence).

Recommendation 5 – Warfarin interruption 5 days prior to procedure (2014)

When a decision to interrupt warfarin therapy for an invasive procedure has been made for a patient with AF or AFL, we suggest that the interruption begin 5 days prior to the procedure and that a procedure with a low bleeding risk may proceed when the INR is <1.5 and a procedure with an intermediate or high bleeding risk may proceed when the INR is <1.2 (Conditional Recommendation, Low Quality Evidence).

Recommendation 6 – Stop apixaban or rivaroxaban 1-2 days pre-low risk; 2-3 days pre-medium or high-risk procedure (2014)*

When a decision to interrupt apixaban or rivaroxaban therapy for an invasive procedure has been made for a patient with AF or AFL, we suggest that the interruption begin 1-2 days prior to the day of a procedure with a low risk of major bleeding and 2-3 days prior to the day of a procedure with an intermediate or high risk of major bleeding (Conditional Recommendation, Low Quality Evidence).
**Note: Edoxaban was not approved at the time of the issuance of the recommendation in 2014. The information present in this recommendation also applies to Edoxaban.*

Recommendation 7 – Stop dabigatran 1-2 days prior pre-low risk; 2-3 days pre-medium or high-risk procedure, depending on renal function (2014)

When a decision to interrupt dabigatran therapy for an invasive procedure has been made for a patient with AF or AFL, we suggest that the interruption begin 1-2 days before a procedure with low risk of major bleeding and 2-3 days before a procedure with an intermediate or high risk of major bleeding for CrCl is ≥80mL/min (Conditional Recommendation, Low Quality Evidence). The upper end of these ranges should be used if CrCl is 50-80 mL/min, an additional day should be added for CrCl 30-50 mL/min, and in case CrCl is found to be <30 mL/min, yet one more day of dabigatran withdrawal should be added (Conditional Recommendation, Low Quality Evidence).

Recommendation 8 – Bridging therapy in a patient at high risk of thromboembolic events (2016, updated from 2014)

When a decision to interrupt warfarin-therapy for an invasive procedure has been made for a patient with AF/AFL, we suggest that bridging therapy with LMWH or UFH be instituted when the INR is below therapeutic level only in patients at high risk of thromboembolic events ($CHADS_2$ ≥4, mechanical heart valve, stroke/TIA within 3 months, rheumatic heart disease) (Conditional Recommendation, Low Quality Evidence).

Recommendation 9 – No bridging for patients on NOAC for procedures requiring interruption of anticoagulation (2016)

We recommend no bridging (LMWH or UFH) for NVAF patients on NOAC undergoing elective surgery or invasive procedures requiring interruption of anticoagulation (Strong recommendation, Moderate Evidence).

Practical tip (2016)
Duration of pre-procedural interruption of NOACs should be adjusted according to renal function (see supplementary appendix, part 11, recommendations 6-7). The Thrombosis Canada Perioperative Anticoagulant Management Algorithm is a helpful tool to aid decisions regarding peri-procedural anticoagulation. http://thrombosiscanada.ca/?page_id=502&calc=perioperativeAnticoagulantAlgorithm

Recommendation 10 – Heparin bridging pre-procedure (2016, updated from 2014)

We recommend that when LMWH or UFH bridging is used for an invasive procedure such therapy be started prior to the procedure when the INR is below the therapeutic level and be stopped 24 hours prior to the

procedure for LMWH and 4-6 hours prior to the procedure for UFH (Strong recommendation, Low Quality Evidence).

Recommendation 11 – Heparin bridging post-procedure (2016, updated from 2014)

When LMWH or UFH bridging is used for an invasive procedure, we suggest that such therapy be restarted after the procedure when hemostasis is established (usually 24 hours for a procedure with a low risk of bleeding and 48-72 hours for a procedure with an intermediate or high risk of bleeding) in prophylactic dosages for the first 24 to 72 hours and then increased to therapeutic dosages. Bridging is then continued until INR is in the therapeutic range (Conditional Recommendation, Low Quality Evidence).

Recommendation 12 – Warfarin, ASA, clopidogrel restarted when hemostasis is established (2014)

When warfarin, ASA, or clopidogrel therapy has been interrupted for an invasive procedure we suggest that such therapy be restarted after the procedure when hemostasis is established (usually 24-48 hours for a procedure with a low risk of bleeding and 48-72 hours for a procedure with an intermediate or high risk of bleeding) (Conditional Recommendation, Low Quality Evidence).

Recommendation 13 – NOAC restarted one day after hemostasis is established (2014)*

When apixaban, dabigatran, or rivaroxaban therapy has been withdrawn for an invasive procedure we suggest that such therapy be restarted after the procedure one day after hemostasis is established (usually 48 hours for a procedure with a low risk of bleeding and 72 hours for a procedure with an intermediate or high risk of bleeding) (Conditional Recommendation, Low Quality Evidence).
**Note: Edoxaban was not approved at the time of the issuance of the recommendation in 2014. The information present in this recommendation also applies to Edoxaban.*

Values and preferences (2016, updated from 2014)
All of these peri-procedural recommendations assume that the practitioner has weighed an individual patient's risks of thromboembolic events and of experiencing a major bleeding event in the peri-procedural period as discussed in the previous section and has elected to interrupt antithrombotic therapy. These recommendations are then intended to summarize how the goal of interrupted therapy can be achieved, with high value placed on achieving that goal just before the procedure is performed. Recommendations regarding heparin bridging place a higher value on prevention of stroke and systemic thromboembolism in patients at high risk than on the inconvenience and higher risk of major bleeding associated with heparin bridging. Recommendations regarding the timing of post-procedural re-introduction of antithrombotic therapy are intended to promote a balanced approach to minimizing the combined outcome of post-procedural thromboembolic events and major bleeding.

List of Abbreviations

AAD: Antiarrhythmic Drug

ACS: Acute Coronary Syndrome

ACTIVE-A: Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events Trial

ADP: Adenosine Diphosphate

AF: Atrial Fibrillation

AFL: Atrial Flutter

ANDROMEDA: Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease

APTT: Activated Partial Thromboplastin Time

ARISTOTLE: Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation

ASA: Acetylsalicylic Acid

ATHENA: A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with Atrial Fibrillation/Atrial Flutter

AV: Atrioventricular

AVNRT: Atrioventricular Node Re-entry Tachycardia

AVRT: Atrioventricular Re-entry Tachycardia

BMS: Bare Metal Stent

CABG: Coronary Artery Bypass Graft

CAD: Coronary Artery Disease

CAIC: Canadian Association of Interventional Cardiology

CCB: Calcium Channel Blockers

CCS: Canadian Cardiovascular Society

$CHADS_2$: The $CHADS_2$ score is a measure of the risk of stroke in patients with atrial fibrillation, with scores ranging from 0 to 6 and higher scores indicating a greater risk. Congestive heart failure, hypertension, an age of 75 years or older, and diabetes mellitus are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient.

CHF: Congestive Heart Failure

CKD: Chronic Kidney Disease`

COPD: Chronic Obstructive Pulmonary Disease

CrCl: Creatinine Clearance

CV: Cardioversion

DES: Drug-Eluting Stent

DTT: Diluted Thrombin Time

ECG: Electrocardiogram

ECT: Electroconvulsive Therapy

ED: Emergency Department

EF: Ejection Fraction

HAS-BLED: Acronym of the major factors associated with bleeding risk in patients with atrial fibrillation receiving oral anticoagulation: Hypertension [uncontrolled, >160 mmHg systolic), Abnormal renal/liver function, Stroke, Bleeding history or predisposition [anemia], Labile INR [i.e. therapeutic time in range <60%], Elderly (>65) and Drugs/alcohol concomitantly [antiplatelet agents, non-steroidal anti-inflammatory drugs]

HF: Heart Failure

Hx: History

INR: International Normalized Ratio

LA: Left Atrium

LAA: Left Atrial Appendage

LAD: Left Anterior Descending Artery

LMWH: Low Molecular Weight Heparin

LV: Left Ventricle

LVEF: Left Ventricle Ejection Fraction

MI: Myocardial Infarction

MVR: Mitral Valve Replacement

NOAC: Non-Vitamin K Antagonist Oral Anticoagulant

NSAIDS: Nonsteroidal Anti-Inflammatory Drugs

NSTEACS: Non ST-Elevation Acute Coronary Syndrome

NVAF: Non-Valvular Atrial Fibrillation. Defined as AF in the absence of mechanical heart valves, rheumatic mitral stenosis, or moderate and severe non-rheumatic mitral stenosis.

OAC: Oral Anticoagulant

P-Gp: P-Glycoprotein

PAD: Peripheral Artery Disease

PALLAS: Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy Trial

PCI: Percutaneous Coronary Intervention

PIONEER-AF PCI: A Study Exploring Two Strategies of Rivaroxaban (JNJ39039039; BAY-59-7939) and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention

PIP: "Pill-in-the-Pocket"

PIP-AAD: "Pill-in-the-Pocket" Anti-Arrhythmic Drug

POAF: Postoperative Atrial Fibrillation

QOL: Quality of Life

RCT: Randomized Controlled Trial

RE-DUAL: Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting

RE-VERSE AD: Reversal Effects of Idarucizumab on Active Dabigatran

SAF: Severity of Atrial Fibrillation
STEMI: ST-Elevation Myocardial Infarction
TEE: Trans-Esophageal Echocardiography
TIA: Transient Ischemic Attack
TT: Thrombin Time
TTR: Time in Therapeutic Range
UFH: Unfractionated Heparin
VF: Ventricular Fibrillation

CCS Atrial Fibrillation Guideline Panel

Co-Chairs:

Dr. Jason Andrade – University of BC, and Montreal Heart Institute, Université de Montréal, Montreal
Dr. Laurent Macle – Montreal Heart Institute, Université de Montréal, Montreal
Dr. Atul Verma – Southlake Regional Health Centre, Newmarket

Primary Panel:

Dr. Clare Atzema – Sunnybrook Health Sciences Centre and University of Toronto, Toronto
Dr. Alan D. Bell – University of Toronto, Toronto
Dr. John A. Cairns – University of British Columbia, Vancouver
Dr. Stuart Connolly – McMaster University and Hamilton General Hospital, Hamilton
Dr. Jafna L. Cox – QEII Health Sciences Centre, Dalhousie University, Halifax
Dr. Paul Dorian – St. Michael's Hospital, University of Toronto, Toronto
Dr. David J. Gladstone – Sunnybrook Health Sciences Centre and University of Toronto, Toronto
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Dr. Girish M. Nair – University of Ottawa Heart Institute, Ottawa
Dr. Stanley Nattel – Montreal Heart Institute, Université de Montréal, Montreal
Dr. Ratika Parkash – QEII Health Sciences Centre, Dalhousie University, Halifax
Dr. Louise Pilote – McGill University Health Centre, Montréal
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Dr. Mike Sharma – McMaster University and Hamilton General Hospital and The Canadian Stroke Network
Dr. Allan Skanes – London Heart Institute, Western University, London
Dr. Mario Talajic – Montreal Heart Institute, Université de Montréal, Montreal
Dr. Teresa S.M Tsang – University of British Columbia, Vancouver
Dr. Subodh Verma – St. Michael's Hospital, University of Toronto, Toronto
Dr. D. George Wyse – Libin Cardiovascular Institute, University of Calgary, Calgary

Secondary Panel:

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Dr. Brett Heilbron – St. Paul's Hospital, University of British Columbia, Vancouver
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Dr. Bob Kiaii – London Heart Institute, Western University, London
Dr. George J. Klein – Schulich School of Medicine & Dentistry, Western University, London
Dr. Simon Kouz – Centre Intégré de Sante et Service Sociaux de Lanaudière & Université Laval, Québec
Dr. Daniel Ngui – Vancouver, British Columbia
Dr. Pierre Pagé – Montreal Heart Institute and Hôpital Sacré-Cœur, Montreal
Dr. Calum J. Redpath – University of Ottawa Heart Institute, Ottawa
Dr. Jan Surkes – Langley Memorial Hospital, Langley
Dr. Richard P. Whitlock – McMaster University, Hamilton

Application of GRADE and Evidence Tables

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was used to assess and summarize the evidence. More information about the guideline development process can be found on the CCS website (http://ccs.ca/en/guidelines/development-process). GRADE tables for the Atrial Fibrillation guidelines, developed for each topic, are included in the following pages.

Evidence Table: Risk Factors / Integrated Management Approach (2018)

PICO Question (Population/Patients, Intervention, Comparator, Outcome)	**Literature Search Strategy** (Databases, timeframe [yrs], inclusion/exclusion terms, language restrictions, etc.).	**Study Quality Assessment Quality Assessment** *(Use separate tool -- appropriate for each study type)*							
		Reference (Author, year, journal)	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Imprecission**	**Other Considerations**	**Overall Quality** (Very Low; Low; Moderate; High)
Is an integrated management approach to AF necessary to reduce cardiovascular events related to AF, including recurrrent AF?									
1)We recommend systematic and strict guideline adherent management of traditional modifiable cardiovascular risk factors and/or conditions associated with AF, in order to reduce cardiovascular events (Strong Recommendation, High Quality Evidence).									
						none			
		Gillis, 2008, CJC	before-after	part of the study was retrospective	none		none		Low
		Carter, 2015,	before-after	part of the study was retrospective	none	none	none		Low
		Hendricks, 2012	RCT	single center	none	none	none		Moderate
2)We suggest that, in addition to appropriate rate or rhythm control, a multimodal 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).									
		pathak	cohort	single center	none	none	none	mixed rhythm control strategies	Low
		abed	rct	single center	none	none	none	surrogate endpoints	Moderate
		pathak (legacy)	cohort	single center				surrogate endpoints	Low
		pathak (cardio fit)	cohort	single center				surrogate endpoints	Low
		malmo	rct	single center, small sample size	none	none	small sample size, inconsistent treatments with anti arrhythmic drugs		Moderate
		parkash	rct	multicenter; BP control alone	negative study	none	small sample size		Moderate
		rienstra	rct	multicenter	none	none		small sample size, heart failure population only	Moderate

Evidence Table: Risk Factors / Integrated Management Approach (2018)

PICO Question (Population/Patients, Intervention, Comparator, Outcome)	**Literature Search Strategy** (Databases, timeframe [yrs], inclusion/exclusion terms, language restrictions, etc.).	**Study Quality Assessment Quality Assessment** *(Use separate tool -- appropriate for each study type)*							**Overall Quality** (Very Low; Low; Moderate; High)
		Reference (Author, year, journal)	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Imprecission**	**Other Considerations**	
Is an integrated management approach to AF necessary to reduce cardiovascular events related to AF, including recurrrent AF?									
1)We recommend systematic and strict guideline adherent management of traditional modifiable cardiovascular risk factors and/or conditions associated with AF, in order to reduce cardiovascular events (Strong Recommendation, High Quality Evidence).									
						none			
		Gillis, 2008, CJC	before-after	part of the study was retrospective	none		none		Low
		Carter, 2015,	before-after	part of the study was retrospective	none	none	none		Low
		Hendricks, 2012	RCT	single center	none	none	none		Moderate
2)We suggest that, in addition to appropriate rate or rhythm control, a multimodal 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).									
		pathak	cohort	single center	none	none	none	mixed rhythm control strategies	Low
		abed	rct	single center	none	none	none	surrogate endpoints	Moderate
		pathak (legacy)	cohort	single center				surrogate endpoints	Low
		pathak (cardio fit)	cohort	single center				surrogate endpoints	Low
		malmo	rct	single center, small sample size	none	none	small sample size, inconsistent treatments with anti arrhythmic drugs		Moderate
		parkash	rct	multicenter; BP control alone	negative study	none	small sample size		Moderate
		rienstra	rct	multicenter	none	none		small sample size, heart failure population only	Moderate

Evidence Table: Ablation (2018)								
PICO Question (Population/Patients, Intervention, Comparator, Outcome)	**Study Quality Assessment** *(Use separate tool -- appropriate for each study type)*							
	Reference (Author, year, journal)	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Imprecision**	**Other Considerations**	**Overall Quality** (Very Low; Low; Moderate; High)
Do patients with catheter ablation of atrial fibrillation benefit from uninterrupted NOAC compared to uninterrupted VKA?	Cappato R, Marchlinski FE, Hohnloser SH, et al. Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. Eur Heart J 2015;36(28):1805-11.	Randomized trial, open label, multinational.	Small sample size (exploratory study). Open label but blinded adjudication of events.	None.	None.	None. Exploratory study with small sample size.	Computer-generated randomization. 99.9% mean estimated compliance rate with rivaroxaban (pill count). No patient lost to follow-up. Interntion-to-treat and per-protocol analysis.	Moderate
	Calkins H, Willems S, Gerstenfeld EP, et al. Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation. N Engl J Med 2017;376(17):1627-36.	Randomized trial, open label, multicenter.	Trial designed by the authors in collaboration with the sponsor. Open label but adjudication by a blinded events committee.	None.	None.	None. Exploratory study.	Patients were randomly assigned in blocks. Blinded adjudication of end-point assessments. Independent data ans safety monitoring committee. Medical writer funded by the sponsor.	Moderate
	Kirchhof P, Haeusler KG, Blank B, et al. Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation. Eur Heart J 2018 Mar 20. Epub ahead of print.	Randomized trial, open label, non inferiority study.	Trial designed by the authors in collaboration with the sponsor. Open label but adjudication by a blinded events committee. Wide non-inferiority margin.	None.	None.	None.	Computer-generated randomization using permuted block. Independent data ans safety monitoring board. Modified intention-to-treat.	Moderate

Evidence Table: AF Cardioversion (2018)

PICO Question (Population/Patients, Intervention, Comparator, Outcome)	**Study Quality Assessment Quality Assessment** *(Use separate tool -- appropriate for each study type)*							
	Reference (Author, year, journal)	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Imprecision**	**Other Considerations**	**Overall Quality** (Very Low; Low; Moderate; High)
When preparing a patient for cardioverson of AF/AFL is use of a non-vitamen K antagonist at least as safe and as effective as is adjusted-dose warfarin therapy?	Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, Flaker G, Brugada J, Kamensky G, Parekh A, Reilly PA, Yusuf S, Connolly SJ. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation. 2011;123:131-136..	Post-hoc subgroup analysis of a RCT, open label, multicenter	non-randomized	none	direct	no		Moderate
	Piccini JP, Stevens SR, Lokhnygina Y, Patel MR, Halperin JL, Singer DE, Hankey GJ, Hacke W, Becker RC, Nessel CC, Mahaffey KW, Fox KAA, Califf RM, Breithardt G, ROCKET AF Steering Committee and Investigators. Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. J Am Coll Cardiol.2013;61:1998-2006.	Post-hoc subgroup analysis of a RCT, open label, multicenter	non-randomized	none	direct	no		Moderate
	Flaker G, Lopes RD, Al-Khatib SM, Hermosillo AG, Hohnloser SH, Tinga B, Zhu J, Mohan P, Garcia D, Bartunek J, Vinereanu D, Husted S, Harjola VP, Rosenqvist M, Alexander JH, Granger CB, ARISTOTLE Committees and Investigators. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). J Am Coll Cardiol 2014;63:1082-1087.	Post-hoc subgroup analysis of a RCT, open label, multicenter	non-randomized	none	direct	no		Moderate
	Plitt A, Ezekowitz MD, De Caterina R, Nordio F, Peterson N, Giugliano RP, ENGAGE AF-TIMI 48 Investigators. Cardioversion of atrial fibrillation in ENGAGE AF-TIMI 48. Clin Cardiol. 2016;39:345-346.	Post-hoc subgroup analysis of a RCT, open label, multicenter	non-randomized	none	direct	no		Moderate
	Cappato R, Ezekowitz MD, Klein AL, Camm JA, Ma C-S, Le Heuzey J-Y, Talajic M, Scanavacca M, Vardas PE, Kirchof P, Hemmrich M, Lanius V, Meng IL, Wildgoose P, van Eickels M, Hohnloser SH, X-VeRT Investigators. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. Eur Heart J. 2014;35:3346-3355.	RTC, open label, multicenter	not powered for stroke/systemic thromboembolism endpoint	none	direct	yes		Moderate
	Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, Mercuri MF, Grosso MA, Fernandez V, Al-Saady N, Pelekh N, Merkely B, Zenin S, Kushnir M, Spinar J, Batushkin V, de Groot JR, Lip GYH, ENSURE-AF Investigators. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. Lancet 2016;388:1995-2003.	RTC, open label, multicenter	not powered for stroke/systemic thromboembolism endpoint	none	direct	yes		Moderate
	Ezekowitz MD, Pollack CV Jr, Halperin JL, England RD, VanPelt Nguyen S, Spahr J, Sudworth M, Cater NB, Breazna A, Oldgren J, Kirchhof P. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. Eur Heart J 39:2959-71, 2018	RTC, open label, multicenter	not powered for stroke/systemic thromboembolism endpoint	none	direct	yes		Moderate
Under what circumstances is it appropriate to perform non-emergent cardioversion (chemical or direct current) in a patient with acute (<48 hours) AF/AFL without first being prepared for cardioversion with 3 weeks of therapeutic anticoagulation therapy or with anticoagulation therapy and transesophageal echocardiography?	Nuoto I, Hartikainen JEK, Grönberg T, Biancari F, Airaksinen KEJ. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. Letter. JAMA 312:647-9, 2014.	large, retrospective,, observational cohort study preliminary report	patients identified from registries of three hospitals in Finland, medical records of each patient retrospectively abstracted, follow-up for 30 days assumes thromboembolic event would lead to repeat hospital visit, four reports from same database	none	indirect	no	none	Low
	Airaksinen KEJ, Grönberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, Hartikainen JEK. Thromboembolic complications after cardioversion of acute atrial fibrillation. J Am Coll Cardiol 62:1187-92, 2013.	large, retrospective, observational cohort study report	patients identified from registries of three hospitals in Finland, medical records of each patient retrospectively abstracted, follow-uo for 30 days assumes thromboembolic event would lead to repeat hospital visit, four reports from same database	none	indirect	no	none	Low
	Grönberg T, Hartikainen JEK, Nuoto I, Biancari F, Ylitalo A, Airaksinen KEJ. Anticoagulation, CHA2DS2VASc score, and thromboembolic risk of cardioversion of acute atrial fibrillation (from the FinCV study). AM J Cardiol 117:1294-8, 2016.	large, retrospective, observational cohort study report	patients identified from registries of three hospitals in Finland, medical records of each patient retrospectively abstracted, follow-uo for 30 days assumes thromboembolic event would lead to repeat hospital visit, four reports from same database	none	indirect	no	none	Low
	Bah A, Nuoto I, Grönberg T, Ylitalo A, Airaksinen KEJ, Hartikainen JEK. Sex, age, and time to cardioversion. Risk factors for cardioversion if acute atrial fibrillation from the FinCV study. Ann Med 49:254-9, 2017.	large, retrospective, observational cohort study report	patients identified from registries of three hospitals in Finland, medical records of each patient retrospectively abstracted, follow-uo for 30 days assumes thromboembolic event would lead to repeat hospital visit, four reports from same database	none	indirect	no	none	Low
	Själander S, Svensson PJ, Friberg L. Atrial fibrillation patients with CHA2DS2-VASc > 1 benefit from oral anticoagulation prior to cardioversion. Int J Cardiol 215:360-3, 2016.	large, retrospective, observational cohort study report	merged Swedish National Patient Registy and Swedish Dispensed Drug Register. No direct record abstraction. Duration of AF/AFL not known - assumes that those not on anticoagulant were presenting < 48 hours.	none	indirect	no	none	Low
Should all patients undergoing cardioversion (chemical or direct current) for acute (<48 hours) AF/AFL receive at least one month or oral anticoagulation for preve tion of stroke / systemic thromboembolism?	Nuoto I, Hartikainen JEK, Grönberg T, Biancari F, Airaksinen KEJ. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. Letter. JAMA 312:647-9, 2014.	large, retrospective,, observational cohort study preliminary report	patients identified from registries of three hospitals in Finland, medical records of each patient retrospectively abstracted, follow-uo for 30 days assumes thromboembolic event would lead to repeat hospital visit, four reports from same database	none	indirect	no	none	Low
	Airaksinen KEJ, Grönberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, Hartikainen JEK. Thromboembolic complications after cardioversion of acute atrial fibrillation. J Am Coll Cardiol 62:1187-92, 2013.	large, retrospective, observational cohort study report	patients identified from registries of three hospitals in Finland, medical records of each patient retrospectively abstracted, follow-uo for 30 days assumes thromboembolic event would lead to repeat hospital visit, four reports from same database	none	indirect	no	none	Low
	Grönberg T, Hartikainen JEK, Nuoto I, Biancari F, Ylitalo A, Airaksinen KEJ. Anticoagulation, CHA2DS2VASc score, and thromboembolic risk of cardioversion of acute atrial fibrillation (from the FinCV study). AM J Cardiol 117:1294-8, 2016.	large, retrospective, observational cohort study report	patients identified from registries of three hospitals in Finland, medical records of each patient retrospectively abstracted, follow-uo for 30 days assumes thromboembolic event would lead to repeat hospital visit, four reports from same database	none	indirect	no	none	Low
	Bah A, Nuoto I, Grönberg T, Ylitalo A, Airaksinen KEJ, Hartikainen JEK. Sex, age, and time to cardioversion. Risk factors for cardioversion if acute atrial fibrillation from the FinCV study. Ann Med 49:254-9, 2017.	large, retrospective, observational cohort study report	patients identified from registries of three hospitals in Finland, medical records of each patient retrospectively abstracted, follow-uo for 30 days assumes thromboembolic event would lead to repeat hospital visit, four reports from same database	none	indirect	no	none	Low
	Själander S, Svensson PJ, Friberg L. Atrial fibrillation patients with CHA2DS2-VASc > 1 benefit from oral anticoagulation prior to cardioversion. Int J Cardiol 215:360-3, 2016.	large, retrospective, observational cohort study report	merged Swedish National Patient Registy and Swedish Dispensed Drug Register. No direct record abstraction. Duration of AF/AFL not known - assumes that those not on anticoagulant were presenting < 48 hours.	none	indirect	no	none	Low

Evidence Table: Management of antithrombotic therapy in patients with concomitant AF and CAD

PICO Question (Population/Patients, Intervention, Comparator, Outcome)	**Literature Search Strategy** (Databases, timeframe [yrs], inclusion/exclusion terms, language restrictions, etc.).	**Study Quality Assessment Quality Assessment** *(Use separate tool -- appropriate for each study type)*							
		Reference	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Imprecision**	**Other Considerations**	**Overall Quality** (Very Low; Low; Moderate; High)
PCI patients, OAC + clopidogrel vs TT; and A + C vs TT, Outcomes Major bleeding and composite of Death, MI, Stroke and stent thrombosis	Medline (OVID), accepted search strategy of D'Ascenzo et al through to June 14, 2014. The D'Ascenzo produced for A+C vs TT: **9 studies showing Major bleeds**, reduced to 3 if restricted to RCT (1 only and very small) and 2 adjusted analyses and **5 studies showing composite outcome**, reduced to none if restriucted to RCT and adjusted analyses. The D'Ascenzo produced for OAC+C vs TT: **5 studies showing major bleeds** (all were RCT (1) or adjusted analyses and **6 studies showing composite outcome**, reduced to 4 if restricted to RCT and adjusted analyses. Then ran the search again for 2013 onward and found 1 additonal Chinese meta-analysis, several additonal small studies (all retrospective) and only 2 important studies (Hess and Fiedler).	D'Ascenzo F et al. Am J Cardiol 2015;115:1185-93.	Meta-analysis	Search strategy appears appropriate and the procedures appear standard and rigorous. The presentation is suboptimal, likely because English is a second language. All trials allow assessment of major bleeding (criteria provided for each, but they vary). Many studies provide data only on bleeding, not the total outcomes.		The findings are driven primarily by non-ACS patients.	For the comparison of A+C vs TT, the Cis are relatively wide and the I^2 is 60%. When analysis confined to RCTs and adjusted analysis, Cis more narrow and I^2 =0. For C+ OAC vs TT, all trials are RCT (only 1) or adjusted analyses and I^2 =16%.	This is the most recent and best meta-analysis available.	Moderate to high
PCI patients, OAC + clopidogrel vs TT; Primary outcome TIMI bleeding, secondary and composite of Death, MI, Stroke and stent thrombosis		WOEST.DeWilde WJ et al. Lancet 2013;103:13-28.	RCT	Primary outcome was TIMI bleeding at 1 year, significantly reduced, as was BARC 3 bleeding but TIMI major bleeding not significantly reduced. Study not powered for secondary outcome of ischemic events but this was significantly reduced. Relatively small study, only 69% of subjects had AF, 75% were elective PCI, standard procedures to reduce bleeding under-utilized.		69% had AF, 75% had elective PCI.	Wide Cis for TIMI major bleed (NS), for BARC3 bleed (P=0.011) and for composite outcome (NS).		High
Patients receiving OAC + ASA who had PCI-DES. Addition of clopidogrel for 6 wk vs 6 mo. Primary outcome was composite (death, ST, stroke, TIMI major bleed) at 9 mo.		ISAR Triple. Fiedler KA. JACC 2015;65:1619-29.	RCT, open label	Primary outcome in 9.8% of 6 wk vs 8.8$ in 6 mo (p=0.63). TIMI major bleed 5.3% vs 4% (P=0.44). Relatively small ss.		The important questions are TT for how long, and the efficacy/safety of alternatives (DAPT and OAC+C). Only duration of TT assessed.	Wide CI for primary composite outcome with HR 1.14 for 6 wk vs 6 mo, also wide CI for major bleed.	All patients on TT at beginning, tests only duration of TT.	Moderate
AF patients ≥65, with AMI and stenting. TT vs DAPT. Primary effectiveness outcome 2yr MACE (death, readm for MI or stroke. Primary safety outcome readm for bleeding.		Hess CN. JACC 2015;66:616-27.	Registry-based study (ACTION Registry, US national database, 4959 patients discharged home on DAPT. Of these 27.6% on TT, 72.4% DAPT only. Unadjusted and adjusted comparisons (patient, treatment and hospital characteristics)	Registry-based, observational		These patients are all MI with PCI/stent. Limited to patients ≥ 65.	Reasonably precise for adjusted outcomes of MACE, death, MI and centered around HR of 1.0. For ischemic stroke HR 0.66 for TT, but still NS. Major bleed clearly more with TT (after adjustment HR 1.61, P<0.0001) and intracranial bleed (adj HR 2.04, P<0.01)	Large study	high (but observational)
Patients with PCI-DES (48% stable/silent angina, 45% NSTEACS, < 10% STEMI). DAPT (ASA + either clopid, prasugre or ticagrelor) for short term (<12 mo) vs 12 mo AND longer term (>12 m0) vs 12 mo. Primary outcomes: CV mortality, MI, ST, major bleed, overall mortality. Secondary repeat revsc, CVA, comb'n of cardiac and CVA.		Navarese EP. BMJ 2015;350:h1618	Meta-analysis of RCTs			This is a PCI study. No info about AF		Short term DAPT yields reduced bleeding without increasing ischemic complications. DAPT beyond 12 mo reduces isch and thrombotic events, but results in more major bleeds and all-cause deaths (not CV deaths).	High

Evidence Table: Management of antithrombotic therapy in patients with concomitant AF and CAD

PICO Question (Population/Patients, Intervention, Comparator, Outcome)	**Literature Search Strategy** (Databases, timeframe [yrs], inclusion/exclusion terms, language restrictions, etc.).	**Study Quality Assessment Quality Assessment** *(Use separate tool -- appropriate for each study type)*							
		Reference	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Imprecision**	**Other Considerations**	**Overall Quality** (Very Low; Low; Moderate; High)
Patients with PCI-DES. Most received first generation DES. DAPT (ASA + either clopid [most], prasugrel or ticagrelor) for short term vs longer term. These durations varied from trial to trial all the way from 3 mo vs 12, to 6 mo vs 12, 6 vs 24, to 12 vs 30, 12 vs 36. Primary outcome ws all-cause mortality. Secondaries included cardiac death, non-carad death, MI, stsroke, ST, major bleed, any bleed.		Palmerini T. Lancet 2015;385:2371-82.	Meta-analysis of RCTs			This is a PCI study. No info about AF		Shorter vs longer gives HR 0.82, P=0.02 for all death, 0.93, p=0.52 for card mortality and 0.67, p=0.006 for non-card mortality. Shorter had lower risk of major bleed, but higher risk of MI and ST.	high
Patients undergoing PCI (most with ACS). Cobalt chromium everolimus eluting stent vs BMS. Primary outcome cardiac mortality at longest available follow-up >1 yr. Secondary were all cause death, MI, ST, TVR, composite of card death or MI, composite of all cause death or MI.		Valmigli M. BMJ 2014;349;g6427 doi.	Individual patient meta-analysis of RCTs	Possible that everolimus had longer DAPT (no difference in <1 yr vs > 1 yr).		This is a PCI study. No info about AF		Everolimus cardiac mortality HR 0.67, P=0.01, MI 0.71, P=0.01, ST 0.48, P,0.001,, TVR 0.29, P<0.001. All cause death HR 0.83, P=0.14. No change with duration of DAPT, ACS vs stable CAD	high
Patients with AF. A NOAC vs warfarin. Outcomes storke/systemic embolus, ischemic stroke, hemorrhagic stroke, all-cause moratlity,MI, major bleed, ic hemorrhage, GI bleed.		Ruff CT. Lancet 2013	Meta-analysis of RCTs		I^2 =48% for MI. I^2 = 0% for all-cause mortality.	These were studies of AF patients, but about 11-18% had prior MI. The RRs were ischemic stroke 0.92, P=0.10, hemorrhagic stroke 0.49, P<0.0001, MI 0.97, P=0.77, all-cause mortality 0.90, P=0.0003, ic hemorrhage 0.48, P<0.0001, GI bleed 1.25, P=0,.043			high

Evidence Table: AF and CAD (2018)

Study Quality Assessment Quality Assessment *(Use separate tool -- appropriate for each study type)*							
Reference (Author, year, journal)	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Imprecision**	**Other Considerations**	**Overall Quality** (Very Low; Low; Moderate; High)
Pioneer AF-PCI[1]	RCT	Primary outcome was clinically significant bleeding (e.g. TIMI major plus minor). Not powered to detect meaningful differences in the incidence of ischaemic events such as myocardial infarction, stent thrombosis, cardiovascular death, or stroke. Standard procedures to reduce bleeding under-utilized.	Significant reduction in clinically significant bleeding but not major bleeding alone	100% AF 52% ACS Variable durations of DAPT use in the TT arms (physician judgment)	Wide CI for major bleeding alone limited statistical significance (despite clinically relevant bleeding being significantly reduced)		High
Re-DUAL PCI[2]	RCT	Primary outcome was ISTH major or clinically relevant non-major bleeding. Not powered to detect meaningful differences in the incidence of ischaemic events such as myocardial infarction, stent thrombosis, cardiovascular death, or stroke. Standard procedures to reduce bleeding under-utilized. TT arm combined DAPT with warfarin (may inflate bleeding risk vs. TT with a NOAC)		100% AF 56% ACS	Wide CI		High
Agarwal et al.[3]	Meta-analysis	Observational studies and RCT (WOEST and PIONEER)		predominant antiplatelet utilised in the dual pathway therapy group was clopidogrel (70%) with a minority receiving ASA (30%). Drug eluting stent use was variable (27-100%). Access site (femoral vs. radial), and indication for OAC was not consistently reported.	majority of the included studies were observational in nature, which are subject to selection and ascertainment biases, with likely overestimation of treatment effects		Moderate
Cavallari et al.[4]	Meta-analysis	RCTs onely (WOEST, PIONEER, RE-DUAL, and landmark analysis of ISAR-Triple)			Included the landmark analysis from ISAR-triple, meaning a period of 6 weeks of triple antithrombotic therapy was included within "dual pathway" group.	similar results were observed when the analysis was limited to the studies that provided dual pathway from the time of PCI (i.e. excluding ISAR-TRIPLE). Specifically, dual pathway therapy significantly decreased major bleeding events (2.22% vs 3.78%; OR 0.58, 95%CI 0.39-0.86, p=0.007), without an excess in the occurrence of MI (3.58% vs. 3.21%; OR 0.96, p=0.82), definite stent thrombosis (1.02% vs. 0.77%; OR 0.95, p=0.89), and stroke (1.35% vs. 1.43%; OR 0.87, p=0.69).	Moderate

1. Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med. 2016;375:2423-34.
2. Cannon CP, Bhatt DL, Oldgren J, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med. 2017;377:1513-24.
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Evidence Table: Real-life data with NOACs/ Reversal agents for NOACs

PICO Question (Population/Patients, Intervention, Comparator, Outcome)	**Literature Search Strategy** (Databases, timeframe [yrs], inclusion/exclusion terms, language restrictions, etc.).	**Study Quality Assessment Quality Assessment** *(Use separate tool -- appropriate for each study type)*							
		Reference	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Imprecision**	**Other Considerations**	**Overall Quality** (Very Low; Low; Moderate; High)
see bias and quality checklist	see bias and quality checklist	Ross B, Miller MA, Ditch K, Tran M	Case Series	Serious limitations; observational data only	N/A	Indirect	Very imprecise	retrospective; subject identification through clinician recall	Very Low
		Aronis KN, Hylek EM	Review article	Article inclusion strategy not included in paper	N/A	Indirect	N/A	narrative review; studies included healthy volunteers; ex vivo methods; animal studies	Low
		Kumar R, Smith RE, Henry BL	Retrospective Case series	Serious limitations; observational data only; small numbers	N/A	Indirect	Very imprecise	7 cases only; observational descriptive	Very Low
		Dibu JR, Weimer JM, Ahrens C, Manno E, Frontera JA	Prospective Case Series	Important limitations	N/A	Indirect	Very imprecise	Prospective data collection; standardized outcomes; standardized pre-planned follow up	Low
		Dzik WH	Review article	Important limitations	N/A	Indirect	N/A	narrative review; mix of study types and outcomes	Very Low
		Barco S, Cheung, YW, Coppens M Et al	DB, PC, crossover study in healthy volunteers	Some limitations	Inconsistencies	Indirect	Imprecise	n=6, healthy subjects, surrogate endpoints	Very low
		Grandhi R, Newman WC, Zhang X, et al	Retrospective Case Series	Important limitations	N/A	Indirect	Very imprecise	prospective database; ICH only - mix of ICH types; no established treatment paradigm; descriptive	Very Low
		Faust AC, Woodard S, Koehl JL et al	Case reports	Serious limitations	N/A	Indirect	Very imprecise	observational data only; no comparison	Very Low
		Masotti L, Lorernzini G, Servalle C et al	Consecutive case series; multicenter	Serious limitations	N/A	Indirect	Very imprecise	n=8; all spontaneous GI bleeds; 7 on dabigatran	Very Low
		Pahs L, Beavers C, Schuler P	Retrospective case review; multicenter	Serious limitations	N/A	Indirect	Very imprecise	observational and descriptive only	Very Low
		Sholzberg M, Pavenski K, Shehata N	Retrospective case review; multicenter	Serious limitations	N/A	Indirect	Very imprecise	observational and descriptive; n=26	Very Low
		Pollack CV, Reilly PA, Eikelboom J et al	Prospective Cohort Study	Important limitations	N/A	Direct	Reasonably precise	no active control (one arm cohort) with well-defined inclusion criteria and consistent; includes population of interest	Moderate

Evidence Table: Real-life data with NOACs/ Reversal agents for NOACs

PICO Question (Population/Patients, Intervention, Comparator, Outcome)	**Literature Search Strategy** (Databases, timeframe [yrs], inclusion/exclusion terms, language restrictions, etc.).	**Study Quality Assessment Quality Assessment** *(Use separate tool -- appropriate for each study type)*							
		Reference	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Imprecision**	**Other Considerations**	**Overall Quality** (Very Low; Low; Moderate; High)
		Siegal DM, Curnutte JT, Connolly SJ et al	R, DB, PC study in health older volunteers	Some limitations	N/A	Indirect	Reasonably precise	healthy volunteers;	Low

Evidence Table: Antidotes (2018)

PICO Question (Population/Patients, Intervention, Comparator, Outcome)	**Literature Search Strategy** (Databases, timeframe [yrs], inclusion/exclusion terms, language restrictions, etc.).	**Study Quality Assessment Quality Assessment** *(Use separate tool -- appropriate for each study type)*							
		Reference	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Imprecision**	**Other Considerations**	**Overall Quality** (Very Low; Low; Moderate; High)
see bias and quality checklist	see bias and quality checklist	Ross B, Miller MA, Ditch K, Tran M	Case Series	Serious limitations; observational data	N/A	Indirect	Very imprecise	retrospective; subject identification through clinician recall	Very Low
		Aronis KN, Hylek EM	Review article	article inclusion strategy not included in paper	N/A	Indirect	N/A	narrative review; studies included healthy volunteers; ex vivo methods; animal studies	Low
		Kumar R, Smith RE, Henry BL	Retrospective Case series	Serious limitations; observational data only; small	N/A	Indirect	Very imprecise	7 cases only; observational descriptive	Very Low
		Dibu JR, Weimer JM, Ahrens C, Manno E, Frontera JA	Prospective Case Series	Important limitations	N/A	Indirect	Very imprecise	Prospective data collection; standardized outcomes; standarized pre-planned follow up	Low
		Dzik WH	Review article	Important limitations	N/A	Indirect	N/A	narrative review; mix of study types and outcomes	Very Low
		Barco S, Cheung, YW, Coppens M Et al	DB, PC, crossover study in healthy volunteers	Some limitations	Inconsistencies	Indirect	Imprecise	n=6, healthy subjects, surrogate endpoints	Very low
		Grandhi R, Newman WC, Zhang X, et al	Retrospective Case Series	Important limitations	N/A	Indirect	Very imprecise	prospective database; ICH only - mix of ICH types; no established treatment paradigm; descriptive	Very Low
		Faust AC, Woodard S, Koehl JL et al	Case reports	serious limitations	N/A	Indirect	Very imprecise	observational data only; no comparison	Very Low
		Masotti L, Lorernzini G, Servalle C et al	Consecutive case series; multicenter	Serious limitations	N/A	Indirect	Very imprecise	n=8; all spontaneous GI bleeds; 7 on dabigatran	Very Low
		Pahs L, Beavers C, Schuler P	Retrospective case review; multicenter	Serious limitations	N/A	Indirect	Very imprecise	observational and descriptive only	Very Low
		Sholzberg M, Pavenski K, Shehata N	Retrospective case review; multicenter	Serious limitations	N/A	Indirect	Very imprecise	observational and descriptive; n=26	Very Low
		Pollack CV, Reilly PA, Eikelboom J et al	Prospective Cohort Study	Important limitations	N/A	Direct	Reasonably precise	no active control (one arm cohort) with well-defined inclusion criteria and consistent; includes population of interest	Moderate
		Siegal DM, Curnutte JT, Connolly SJ et al	R, DB, PC study in health older volunteers	Some limitations	N/A	Indirect	Reasonably precise	healthy volunteers;	Low
		Connolly SJ, Milling TM Jr, Eikelboom JW, et al	Prospective Cohort Study	Important limitations	N/A	Direct	Reasonably precise	no active control (one arm cohort) with well-defined inclusion criteria and consistent; includes population of interest	Moderate
		Pollack CV, Reilly PA, van Ryn J, et al	Prospective Cohort Study	Important limitations	N/A	Direct	Reasonably precise	no active control (one arm cohort) with well-defined inclusion criteria and consistent; includes population of interest	Moderate

Evidence Table: Peri-procedural anticoagulation management

PICO Question (Population/Patients, Intervention, Comparator, Outcome)	**Literature Search Strategy** (Databases, timeframe [yrs], inclusion/exclusion terms, language restrictions, etc.).	**Study Quality Assessment Quality Assessment** *(Use separate tool -- appropriate for each study type)*					
		Reference	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Overall Quality** (Very Low; Low; Moderate; High)
For AF patients on OAC undergoing elective surgical or invasive procedures, should current recommendations for OCA interruptions, with/without bridging, be revised?	PubMed/Medline: Jan 2014 - Jan 2016. Limits: Human, English. Search terms: atrial fibrillation, anticoagulation, bridging anticoagulation, perioperative bridging, peri-ablation bridging	Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015;373:823-833	RCT	No serious limitation; 89.4% of subjects underwent procedures classified as 'minor' (bleeding risk); subjects at high TE risk excluded (prior stroke, mechanical valve, etc)	No serious inconsistencies		High
	As above	Schulman S, Carrier M, Lee AYY, et al. Perioperative Management of Dabigatran: A Prospective Cohort Study. Circulation. 2015;132:167-173	Prospective multi-centre cohort study	CHADS2 score not reported	No serious inconsistencies		Moderate
	As above	Steinberg BA, Peterson ED, Kim S, et al. Use and outcomes associated with bridging during anti-coagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Circulation. 2015;131:488-494	Large, prospective, observational Registry (USA)	Sampling and reporting bias; variable protocols for bridging depending on site and investigator			Moderate
	As above	Beyer-Westendorf J, Gelbricht V, Forster K, et al. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J. 2014;35:1888-1896	Prospective observational Registry (Germany)	Sampling and reporting bias; variable protocols for bridging depending on site and investigator			Low

Evidence Table: Digoxin and mortality

PICO Question (Population/Patients, Intervention, Comparator, Outcome)	**Literature Search Strategy** (Databases, timeframe [yrs], inclusion/exclusion terms, language restrictions, etc.).	**Study Quality Assessment Quality Assessment** *(Use separate tool -- appropriate for each study type)*							
		Reference	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Imprecision**	**Other Considerations**	**Overall Quality** (Very Low; Low; Moderate; High)
Should digoxin be used for rate control in AF		Farshi et al	Clinical Trial	Open Label	No serious inconsistencies	Serious	Moderate	None	Moderate
		David et al	Nonrandomized clinical study	Small case number (28)	No serious inconsistencies	Serious	Very serious	None	Very Low
		Turakhia et al	Analysis of RCT data	Retrospective analysis complicates adjustment for potential and unseen biases	No serious inconsistencies	Moderate	Low (very large case numbers)	None	Moderate
		Vamos et al	Systemic review and meta-analysis	Only a small number of papers available for review	No serious inconsistencies	Very Low	Very Low	None	High
		Washam et al	Retrospective analysis of RCT						
		Andrade et al	Retrospective analysis of combined data from 2 RCTs						

Evidence Table: Surgical Therapy for AF

PICO Question (Population/Patients, Intervention, Comparator, Outcome)	**Literature Search Strategy** (Databases, timeframe [yrs], inclusion/exclusion terms, language restrictions, etc.).	**Study Quality Assessment Quality Assessment** *(Use separate tool -- appropriate for each study type)*							
		Reference	**Design**	**Limitations**	**Inconsistencies**	**Indirectness**	**Imprecision**	**Other Considerations**	**Overall Quality** (Very Low; Low; Moderate; High)
Does atrial pacing reduce pre-discharge POAF as compared to placebo in patients undergoing cardiac surgery	Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 8, 2011), MEDLINE (from 1946 to July 2011), EMBASE (from 1974 to July 2011) and CINAHL (from 1981 to July 2011)	Arsenault Cochrane 2013	3+	3+	2+	3+	3+	Heterogeneity in treatment specifics (all atrial pacing lumped together)	2+
Does magnesium reduce POAF (same PCO)	Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 8, 2011), MEDLINE (from 1946 to July 2011), EMBASE (from 1974 to July 2011) and CINAHL (from 1981 to July 2011)	Arsenault Cochrane 2013	3+	3+	2+	3+	2+	Dosing regimens and timing varied considerably across studies	2+
Do steroids reduce POAF(same PCO)	Embase, Medline, Cochrane, CINAHL, and OVID	Whitlock EHJ 2008	3+	3+	3+	3+	3+		3+
		Dieleman LAMA 2012	4+	4+		4+	4+	Multicenter RCT	4+
		Whitlock Lancet 2015	4+	4+		4+	4+	Multicenter RCT	4+
Do PUFA reduce POAF (same PCO)?	PUBMED, EMBASE, Cochrane Library, and Google Scholar databases	Zhang Journal of Cardiology 2013	3+	3+	2+	3+	2+	Neg analysis	2+
	PubMed, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials	Costanzo J Thorac Cardiovasc Surg 2013	3+	2+	2+	3+	3+	Positive. No funnel plot	2+
		Mozaffarian JAMA 2012	4+	4+		4+	4+	Larget RCT was negative	4+
Does Colchicine reduce POAF (same PCO)	Cochrane Collaboration Database of Randomized Trials, ClinicalTrials.gov, CINAHL, Google Scholar, PubMed, and Scopus	Imazio JAMA 2014	3+	3+	3+	3+	1+	Only 3 studies, Included PVI ablation, doses of colchicine varied, associated diarrhea (mild)	2+
	OVID versions of MEDLINE, EMBASE Classic and EMBASE (1947 through 2014 week 28), and the Cochrane Central Register of Controlled Trials	Verma et al. BMC Cardiovascular Disorders 2015	3+	3+	3+	3+	2+	4 studies, included ablation study, doses of colchicine varied	2+
Does statin therapy reduce post-operative AF (same PCO)	PubMed Cochrane since last guideines (2010), post-operative AF, statain, HMG-COA reductase inhibitor, English	Zheng, NEJM 2016	4+	4+		4+		Large very recent RCT not included in meta-Analysis by Kuhn et al.	4+
	Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 11), Ovid MEDLINE (1950 to November 2013Week 3) and Ovid EMBASE (1980 to 3 December 2013 (Week 48)	Kuhn Cochrane 2015	4+	4+	4+	3+	3+	Did not include most recent large seemingly definitive RCT by Zheng et al. (published after meta-Analysis)	3+