Atrial Fibrillation: Focus on Pharmacotherapy

The FAQ below addresses common clinical questions about the pharmacotherapy of atrial fibrillation, with a focus on drugs for anticoagulation, rate control, and rhythm control.

Question	Answer/Pertinent Information
ANTICOAGULATION	
For which patients with A-fib/A-flutter should an antithrombotic be considered? **Note**: for patients who qualify for long-term anticoagulation but for whom it is contraindicated, consider referral for left atrial appendage closure device.[5]	• Decisions about antithrombotic therapy should be individualized.[1,2] Consider stroke risk, bleeding risk, and patient preference.[1] • Anticoagulation is recommended for A-fib (or A-flutter) with: ○ prior stroke or TIA.[1,2,4] An anticoagulant should generally be prescribed within two weeks, but the best timing is unclear.[4] CCS: consider initiation within 24 hours of TIA onset. Post-stroke, timing depends on NIHSS score. Also take into account risk factors for thrombosis or bleeding (See Figure 15 in CCS guideline: https://www.onlinecjc.ca/action/showPdf?pii=S0828-282X%2820%2930991-0).[2] ○ nonvalvular (see footnote b) A-fib/A-flutter:[2,4,5] ▪ CHA_2DS_2-VASc score[a] of ≥1 in men or ≥2 in women[5] (ACCP **recommends** offering;[4] AHA/ACC says it can be **considered**.[5]) ▪ CHA_2DS_2-VASc score[a] of ≥2 or in men or ≥3 in women (**recommended**), or ≥2 with ACS (AHA/ACC).[5] ▪ Canadian guidelines recommend using the CHAD-65 (CCS Algorithm) to guide decisions (Figure 8 in CCS guideline: https://www.onlinecjc.ca/action/showPdf?pii=S0828-282X%2820%2930991-0).[2] ○ hypertrophic cardiomyopathy.[1,2] ○ mechanical heart valve.[1] ○ need for cardioversion.[2,5] ▪ Start anticoagulation as soon as possible and continue for at least four weeks afterward if: ○ immediate cardioversion is needed (i.e., patient unstable).[2,4,5] ○ AHA/ACCP: A-fib/A-flutter duration is <48 hrs and CHA_2DS_2-VASc score ≥2 in men or ≥3 in women (pre-cardioversion anticoagulation could also be considered for lower-risk patients, without post-conversion oral anticoagulant).[5] ○ CCS: A-fib/A-flutter duration is <12 hrs without recent stroke/TIA, or A-fib/A-flutter duration is 12 to 48 hours and $CHADS_2$ is 0 to 1.[2] ▪ Anticoagulate for at least three weeks prior to and at least four weeks after cardioversion if: ○ AHA/ACCP: A-fib/A-flutter duration is ≥48 hrs or is unknown.[4,5] ○ CCS: A-fib/A-flutter duration is >48 hrs, patient has valvular A-fib/A-flutter; A-fib/A-flutter duration <12 hrs and recent stroke/TIA; A-fib/A-flutter duration 12 to 48 hours and $CHADS_2$ ≥2.[2]

Continued…

Question	Answer/Pertinent Information
Which patients with A-fib/A-flutter may need an anticoagulant, continued	▪ Alternatively, check a TEE before cardioversion and forgo three-weeks' anticoagulation before cardioversion if no left atrial thrombus is seen.[2,4,5] However, anticoagulation should be achieved before TEE[5] and continued for at least four weeks post-cardioversion.[2,4,5] ▪ Base decisions about long-term anticoagulation on CHA_2DS_2-VASc score or CHAD-65 (CCS).[2,4,5] • It is reasonable to forgo antithrombotic therapy in patients with a CHA_2DS_2-VASc score[a] of 0 in men or 1 in women.[5] (ACCP: should not be offered.[4])
What are some considerations when choosing an antithrombotic for a patient with A-fib?	• **Individualize** based on bleeding risk, cost, adherence, interactions, comorbidities, and patient preferences.[1] • Our toolbox, *Appropriate Use of Oral Anticoagulants*, provides information to help you choose an anticoagulant based on efficacy, comorbidities (e.g., **kidney** or **liver** impairment), other patient characteristics (e.g., body weight, age), and concomitant medications. • DOACs (apixaban, dabigatran, edoxaban, or rivaroxaban) are **usually** preferred over warfarin, especially in patients who cannot maintain a therapeutic INR (e.g., time in therapeutic range <65%[4]).[2,4,5] • For patients with **adherence issues**, warfarin may be preferred over a DOAC. o Patients with SAMe-TT2R2 score 0 to 2 are likely to achieve a good INR control (see footnote d). But if DOAC adherence may be an issue, warfarin may be the better option due to longer persistence of effect.[4] • For patients with **prosthetic heart valves**: o Mechanical aortic or mitral valve: use warfarin. Don't use DOACs; dabigatran is linked to increased bleeding and clotting, and other DOACs have insufficient data.[3] o Bioprosthetic aortic or mitral valve (surgical): For A-fib within the first three months, warfarin is preferred.[3] (Data is conflicting regarding DOAC efficacy early post-procedure for prevention of bioprosthetic valve thrombosis.[3] An open-label study, suggests that rivaroxaban is noninferior to warfarin for A-fib-related thrombosis early post-procedure.[6]) For A-fib >3 months post-procedure, a DOAC or warfarin could be used.[3,7,8] • For patients undergoing **cardioversion**: o use therapeutic-dose anticoagulation with a DOAC or parenteral agent (e.g., for hemodynamic instability).[4,5] • For patients with a **history of a major bleed**, see our FAQ, *Managing Bleeding with Anticoagulants*.
How should anticoagulation be monitored?	• Periodically assess appropriateness of anticoagulation.[1,2] • Assess bleeding risk at every patient contact using the HAS-BLED score (see footnote e).[4] Patients with a HAS-BLED score ≥3 should be assessed frequently.[4] • Address potentially modifiable risk factors such as poorly controlled INR or blood pressure, alcohol use, aspirin or NSAID use, GI ulcer. In kidney or liver impairment, ensure appropriate anticoagulant choice and dose.[4] • For warfarin patients, check INR weekly until stable, then at least monthly.[1] Goal is to keep INR in therapeutic range (2 to 3) at least 70% of time.[4] • DOACs may require baseline and periodic monitoring or dose adjustment for kidney or liver function. See our chart, *Comparison of Oral Anticoagulants*, for specific guidance.

Question	**Answer/Pertinent Information**			
What if anticoagulation requires interruption?	• See our FAQ, *Managing Bleeding with Anticoagulants*, and our chart, *Perioperative Management of Chronic Medications in Noncardiac Surgery*.			
What if an anticoagulated patient requires an antiplatelet agent?	• Control modifiable bleeding risk factors.[2] • Consider PPI use.[2] • Consider clopidogrel over prasugrel or ticagrelor if a P2Y12 inhibitor is indicated.[2] • In warfarin patients, target the lower end of the therapeutic INR range (2 to 2.5).[2] • In patients receiving DAPT post-PCI, stop aspirin after one to four weeks and maintain the P2Y12 inhibitor (clopidogrel) plus oral anticoagulant (DOAC preferred; most evidence with apixaban).[9] After a year, a DOAC alone may be enough.[2] • In patients post-ACS without PCI, continue the oral anticoagulant plus clopidogrel for one to 12 months. After a year, an oral anticoagulant alone may be enough.[2]			
RATE CONTROL				
What are some considerations when choosing a **rate control** agent?	**Drug**	**Consider for…**	**May not be appropriate in…[f]**	**Comments**
	Beta-blocker	• HF*r*EF.[2] • ACS.[1] • Thyrotoxicosis.[1] • Acute illness.[1] • Hypertrophic cardiomyopathy.[2]	• Hemodynamic instability.[1] • Decompensated CHF.[1] • Bronchospasm.[1] • Pre-excitation (see comments).[1]	• Pre-excitation: avoid IV BB. Consult electrophysiologist about oral BB.[1] • If IV used, start oral agent as soon as possible for uninterrupted control.[2] • For HF*r*EF, target an evidence-based dose.[2]
	CCB (**diltiazem** or **verapamil**)	• Thyrotoxicosis (BB alternative).[1] • COPD or bronchospasm.[1]	• Hemodynamic instability.[1] • Decompensated CHF, or HF*r*EF with EF ≤40%.[1,2] • Pre-excitiation.[1]	• If IV used, start oral agent as soon as possible for uninterrupted control.[1] • IV diltiazem seems to work faster than IV metoprolol, but they are similarly effective at getting to goal HR within two hours.[32]
	Amiodarone	• Acute rate control in decompensated HF, mild hypotension, or EF ≤40% (IV).[2,5]	• Pre-excitation.[1] • Contraindications: cardiogenic shock, bradycardia with syncope, second- or third-degree AV block, sick sinus syndrome (Canada [oral]: thyroid dysfunction, interstitial lung disease, hepatitis).[13,15]	• Not a preferred first-line option.[1] • Rhythm control agent; risk of stroke with if non-anticoagulated patient converts.[2] • Drug interactions and adverse effects limit usefulness. See **footnote c**. • If IV used, start oral agent as soon as possible for uninterrupted control.[2]

Question	**Answer/Pertinent Information**			
Continued… Considerations when choosing a **rate control** agent, continued	**Drug**	**Consider for…**	**May not be appropriate in…**[f]	**Comments**
	Digoxin	• Acute rate control in acute CHF, EF ≤40%, or mild hypotension (IV).[2] • Permanent A-fib in elderly or sedentery.[2] • Add or alternative to first-line agents.[2]	• Hypertrophic cardiomyopathy.[1,2] • Pre-excitation.[1]	• Not a preferred option.[1] • Digoxin is less effective with a slower onset than BBs or CCBs.[33] • Can combine with BB, or CCB (HF*p*EF only).[1] • If IV used, start oral agent as soon as possible for uninterrupted control.[2]
What is the target heart rate for patients with A-fib?	• Resting HR <80 bpm is a reasonable target.[1] • Resting HR <110 bpm is reasonable if tolerated and left ventricular systolic function is preserved.[1] • CCS: Resting HR ≤100 bpm is the recommended long-term target and when titrating rate-controlling agents in patients who present to the acute care setting with a primary diagnosis of A-fib.[2] • For patients with A-fib symptoms during exertion, keep the ventricular rate within the physiological range during activity.[1]			
RHYTHM CONTROL				
When is rhythm control a reasonable or preferred strategy?	• Patient is hemodynamically unstable (electrical cardioversion is indicated).[1] • New onset A-fib in patient with ACS with hemodynamic instability, ischemia, or poor rate control (electrical cardioversion indicated).[1] • Rapid ventricular response does not resolve quickly with pharmacological treatment, exacerbating cardiac ischemia, hypotension, or CHF (electrical cardioversion recommended).[1] • Patient is symptomatic from A-fib despite attempt at rate control.[1,2] • Patient is young, or athletic (consider "pill-in-pocket").[1] • Patient is newly diagnosed (<1 year duration).[2] ○ For patients with high CV risk (>75 years of age, prior TIA or stroke, or two of the following: age >65 years, female, CHF, diabetes, hypertension, severe coronary artery disease, chronic kidney disease, left ventricular hypertrophy [diastolic septal wall width >15 mm]), rhythm control plus usual care (rate control and anticoagulation) was more effective than usual care (NNT = 91 for five years to prevent one death, stroke, or hospitalization) [Evidence level B-1]. Antiarrhythmic side effects occurred in 2% of the rhythm control patients.[35] • Patient has cardiomyopathy due to tachycardia.[1] • Patient prefers a rhythm control strategy.[1] • Patient is symptomatic and has pre-excitation, especially if the accessory pathway has a short refractory period allowing for fast antegrade conduction (catheter ablation recommended).[1]			

Question	Answer/Pertinent Information
RHYTHM CONTROL	
What are some general considerations for rhythm control?	• For patients with pre-excitation, consult electrophysiologist.[1] • It is reasonable to continue antiarrhythmics despite infrequent, tolerable recurrences after initial control.[1] • Antiarrhythmic agents should be stopped once A-fib becomes permanent.[1] • See the table below for pharmacologic options for cardioversion and maintenance of sinus rhythm.
What is the role of catheter ablation?	• Consider ablation for patients who choose a rhythm control (either as an initial strategy, or when an antiarrhythmic doesn't work or is not tolerated), to control symptoms.[1] o Initial treatment with catheter cryoablation is associated with reduced recurrence over three years vs antiarrhythmics.[37] • Evidence of benefit is greatest for younger patients with paroxysmal A-fib with no or minimal structural heart disease.[1] • Be aware that ablation does not preclude the need for anticoagulation.[1]

Continue to the next page for a Comparison of Antiarrhythmics for Atrial Fibrillation

Antiarrhythmics for Atrial Fibrillation

--Information in chart may differ from product labeling and is not comprehensive.—

Drug	Consider for…	May NOT be appropriate in…[f]	Comments
Flecainide	• Conversion.[1] • Maintenance.[1]	• CHF or EF≤40%.[1,2] • Heart disease (coronary or structural).[1] • Sinus or AV node dysfunction, infranodal conduction disease, or Brugada syndrome.[1] Contraindicated in second-degree or bifascicular block or higher.[23,24]	• Low risk of QT prolongation and torsades (<1%).[17,38,39] • Increased mortality risk in patients with history of MI.[2] • Mild to moderate negative inotrope.[17] • May cause hypotension.[1] • Visual impairment common.[17] • Must use with a BB, diltiazem or verapamil to prevent ventricular arrhythmias. For cardioversion or "pill-in-pocket" (see below), start ≥30 min prior to flecainide use to prevent ventricular arrhythmias.[1,2,34] • Among the agents with the best evidence for cardioversion.[1] • "Pill-in-the-pocket:" at-home use for symptomatic A-fib (once shown safe in a monitored setting).[1,2] • Metabolized by CYP2D6.[1] • Requires initial dose reduction in kidney impairment.[23] • Check trough periodically in severe kidney or liver impairment. Trough monitoring is also strongly recommended with amiodarone, CHF, moderate kidney impairment, or elderly (Canada).[23,24] Therapeutic range may be 0.2 to 1 mcg/mL.[23,24]
Propafenone *Continued…*	• Conversion.[1] • Maintenance.[1]	• Heart disease (coronary or structural).[1] • CHF (Canada: severe or uncontrolled), cardiac impulse generation or conduction disorders, bradycardia, Brugada syndrome, bronchospasm, severe COPD, marked hypotension or electrolyte imbalance (Canada: myocardial infarction in the past three months, myasthenia gravis, or severe liver impairment) (contraindications).[25,26]	• Low risk of QT prolongation and torsades.[38] • Dysgeusia common.[17] • Must use with a BB, diltiazem or verapamil to prevent ventricular arrhythmias. For cardioversion or "pill-in-pocket" (see below), start ≥30 min prior propafenone use to prevent ventricular arrhythmias.[1,2,34] • "Pill-in-the-pocket:" at-home use for symptomatic A-fib (once shown safe in a monitored setting).[1,2]

Drug	Consider for…	May NOT be appropriate in…[f]	Comments
Propafenone, continued			• Metabolized primarily by CYPD6, and to a lesser extent by CYP3A4 and CYP1A2.[17] Avoid use with drugs that are both a CYP2D6 and CYP3A4 inhibitor.[25] • Increases digoxin level via p-glycoprotein inhibition.[1] • Inhibits warfarin metabolism via CYP2C9 inhibition. Expect a 25% increase in INR.[1]
Disopyramide	• Maintenance.[1]	• CHF.[1] • QT prolongation (contraindicated).[27,28] • Second- or third-degree AV block (contraindicated).[27,28] • Intraventricular conduction defects (Canada: contraindicated).[28] • Enlarged prostate (Canada: contraindicated with urinary retention).[1,28] • Glaucoma (contraindicated).[27,28] • Kidney impairment (Canada: contraindicated).[28]	• Significant QT prolongation but risk of torsades may be low.[10] Some experts recommend inpatient initiation, especially in high-risk patients.[10] • CYP3A4 substrate (metabolism inhibited by diltiazem, verapamil). • Option for hypertrophic cardiomyopathy, with a BB, diltiazem, or verapamil.[1]
Dofetilide (US)	• Conversion.[1] • Maintenance.[1]	• QT prolongation. Contraindicated if QTc >440 ms (500 ms in patients with ventricular conduction abnormalities).[20] • Left ventricular wall thickness >1.5 cm.[1] • Severe kidney impairment (contraindicated if CrCl<20 mL/min).[20]	• High risk of QT prolongation (19%) and torsades (3%).[38,40] Reserve for patients at low risk of QT prolongation/torsades.[1] • Inpatient initiation and dose escalation required for ECG monitoring.[1] • Among the agents with the best evidence for cardioversion.[1] • Dose based on kidney function and QTc.[1] • Option for hypertrophic cardiomyopathy (CSS: a preferred option).[1] • Contraindicated with drugs that impair its kidney elimination (e.g., verapamil, cimetidine, trimethoprim, prochlorperazine, dolutegravir, megestrol, hydrochlorothiazide, ketoconazole).[20] • Stop amiodarone at least three months prior to initiation.[1]

Drug	Consider for…	May NOT be appropriate in…[f]	Comments
Dronedarone	Maintenance.[1]	• CHF (EF ≤40%).[1,2] Contraindicated in recently decompensated or Class IV CHF; Canada: any CHF.[21,22] Increases combined end point of stroke, MI, systemic embolism, CV death.[1] • Bradycardia.[1] Contraindicated with HR <50 bpm, second- or third-degree heart block, or sick sinus syndrome.[21,22] • Permanent A-fib. Contraindication due to association with CV events.[21,22] • QT prolongation.[1] Contraindicated if QTc ≥500 ms, or with other QT-prolonging meds or herbs.[21,22] • Liver impairment (contraindicated in severe liver impairment).[21,22]	• QT prolongation common (28%).[17] Low risk of torsades.[38] • Similar to amiodarone, but without iodine and with a shorter half-life (~24 hrs).[2] Contraindicated in patients with a history of amiodarone-induced lung or liver toxicity.[21,22] • Can cause bradycardia.[1] • CYP3A4 substrate (metabolism inhibited by diltiazem, verapamil).[1] Contraindicated with strong CYP3A4 inhibitors.[21,22] • Moderate CYP3A4 and CYP2D6 inhibitor.[17] Inhibits p-glycoprotein.[17] Increases BB and digoxin levels.[1] • May slightly increase SCr due to inhibition of tubular secretion of creatinine, without a decrease in kidney function.[17] • Option for hypertrophic cardiomyopathy.[1] • Check liver function tests periodically, especially during the first six months (CCS: every three months for the first year, then every six months).[2,21,22]
Ibutilide	Conversion.[1]	• History of symptomatic CHF.[2] • EF <30%.[1] • QT prolongation.[2] • Suspected ACS.[2]	• High risk of QT prolongation (1.2%) and torsades (4.3%).[17,38] • ECG monitoring required for at least four hours after administration.[1] • May cause hypotension.[1] • IV magnesium, before and after treatment, improves efficacy and safety.[1,2] • Improves efficacy of electrical cardioversion.[1] • Option for hemodynamically stable patients with pre-excitation, or post-op A-fib.[1,2]

Drug	Consider for…	May NOT be appropriate in…[f]	Comments
Procainamide	Conversion.[1]	• Complete heart block, torsades, or lupus (contraindicated).[31]	• Risk of QT prolongation and torsades appear low.[11,41] • Hypotension may limit its use.[41] • Appropriate for hemodynamically stable patients with pre-excitation (IV).[1,2]
Sotalol	Maintenance.[1]	• CHF (contraindicated in cardiogenic shock or decompensated HF).[1,29] • EF ≤40%.[2] • Left ventricular wall thickness >1.5 cm.[1] • Bronchospastic disease (contraindicated).[29,30] • QT prolongation (contraindicated)[29,30] or risks for torsades.[2] • Bradycardia, second- or third-degree heart block, or sick sinus syndrome (contraindicated).[29,30] • Serum potassium <4 mEq (mmol)/L (Canada: hypokalemia).[29,30]	• High risk of QT prolongation (4% to 12%) and torsades (0.6% to 4%).[17] Moderately lower risk of torsades than ibutilide.[38] • Consider inpatient initiation.[1] If started as an outpatient, check ECG at baseline and 48 to 72 hours after initiation.[2] • Requires dose reduction in kidney impairment.[29,30] • Option for hypertrophic cardiomyopathy (CSS: reserve for mild hypertrophy).[1,2]

Amiodarone	• Conversion.[1]
	• Maintenance.[1]
		• Pre-excitation.[1]
		• Contraindicated in cardiogenic shock, bradycardia with syncope, second- or third-degree AV block, and sick sinus syndrome (Canada [oral]: thyroid dysfunction, interstitial lung disease, hepatitis).[13,15]
			• QT prolongation common, but rarely associated with torsades (≤0.5%).[34]
			• High efficacy, but usually a last-line option; **drug interactions and adverse effects limit usefulness**.[1,34] See **footnote c**.
			• Consider for:
			  ○ hypertrophic cardiomyopathy (CSS: a preferred option).[1,2]
			  ○ CHF.[1]
			• Slow onset (eight hours IV, several weeks oral).[1,2]
			• Comparable hospitalization and mortality rates to rate control.[14]

a. **CHA_2DS_2-VASc score**: **C**HF = 1 point; **H**ypertension = 1 point; **A**ge 75 or older = 2 points; **D**iabetes = 1 point; prior **S**troke, TIA, or thromboembolism = 2 points; **V**ascular disease (aortic plaque, peripheral artery disease, or history of MI) = 1 point; **A**ge 65 to 74 years = 1

point; **S**ex **c**ategory female = 1 point. Scores correlate with approximate annual stroke risk (based on a 2001 hospitalized cohort) of 0% for score of 0, 1.3% for score of 1, 2.2% for score of 2, 3.2% for score of 3, 4% for score of 4, 6.7% for score of 5, 9.8% for score of 6, 9.6% for score of 7, 6.7% for score of 8, and 15.2% for score of 9. An online calculator is available at http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk/. The CHA_2DS_2-VASc score is **not** for use in patients with mechanical heart valve or moderate to severe mitral stenosis.[5] These patients were excluded from DOAC clinical trials.[4]

b. **Nonvalvular A-fib** means A-fib in the absence of moderate-to-severe mitral stenosis or a mechanical heart valve.[2,5]

c. **Amiodarone:**

- **Side effects:** About 50% of patients have side effects.[12] Due to amiodarone's almost 60-day mean half-life, side effects and drug interactions persist after stopping it.[13] With IV administration, the most common adverse effects are hypotension, bradycardia, and phlebitis.[2] Causes bradycardia in 5%, and ventricular arrhythmias (e.g., torsades de pointes) in <1% of patients.[1,12] **Pulmonary toxicity** occurs in up to 2% of patients, and may occur as early as two weeks into treatment.[16,18] Potentially fatal.[12] Dose-dependent blue **skin discoloration** in <10% of patients; slow reversal (over years) with discontinuation.[12,15] Advise sunscreen use or sun avoidance due to **photosensitivity**.[12] Incidence of **hyperthyroidism** may be as high as 12%.[12] Incidence of **hypothyroidism** may be as high as 22%.[12] Hypothyroidism is more common, but hyperthyroidism is more dangerous.[12]
- **Drug interactions:**
  - Amiodarone inhibits multiple enzymes (e.g., CYP3A, CYP2C9, CYP2D6), and transporters (e.g., p-glycoprotein). Substrate of CYP2C8 and CYP3A4.[17]
  - Among DOACs, apixaban appears to be the least likely to interact.[36] Kidney function affects the significance of the interaction with other DOACs.[36] Avoid rivaroxaban with amiodarone if CrCl is <80 mL/min.[36] Avoid dabigatran for A-fib if CrCl <30 mL/min.[36]
  - When starting amiodarone, doses of other drugs may need to be decreased (e.g., decrease oral digoxin or flecainide dose by 50%; decrease IV digoxin by 15% to 30%; decrease warfarin by 20% to 50%).[17]
  - Once amiodarone is initiated, expect to make INR-guided warfarin dose reductions weekly for the next six to eight weeks.[19] Thereafter, the warfarin dose will need to be increased gradually, per INR measurements, as the amiodarone dose is adjusted downward.[19] Expect dose reductions (relative to baseline) of 25%, 30%, 35%, or 40% for patients taking amiodarone 100 mg, 200 mg, 300 mg, or 400 mg daily, respectively.[19]
  - Limit the dose of simvastatin to 20 mg daily, and lovastatin to 40 mg daily.[17]
  - Advise patients to avoid grapefruit juice.[17]
  - Must be avoided with many hepatitis C drugs due to risk of dangerous bradycardia.
- **Monitoring**:
  - **Liver function** tests: baseline and every six months.[12] Transaminase elevation >2 times normal occurs in 15% to 30% of patients, but hepatitis/cirrhosis occurs <3% of patients.[12] If hepatotoxicity is suspected (e.g., clinical signs and symptoms or hepatitis), consider discontinuation and/or investigation for cirrhosis.[12] Also consider discontinuation or dose reduction if levels are significantly (>3 times normal, or twice normal in patient with baseline elevation) or persistently elevated.[13,15]
  - **Pulmonary function**: chest x-ray at baseline and yearly.[12] Baseline pulmonary function tests, including DLCO.[12] Repeat if pulmonary toxicity suspected (e.g., unexplained cough or dyspnea; abnormal x-ray).[12] In the event of toxicity, discontinue amiodarone and consider prednisone 40 to 60 mg daily for four to eight weeks, followed by a taper.[12]

- **Electrocardiogram**: baseline, after starting, yearly, and when clinically indicated.[12,18]
- **Thyroid function**: baseline TSH, free T4, and total or free T3, and then TSH every six months.[12] Discontinue and consult endocrinologist if hyperthyroidism suspected.[1,12] Management options for hypothyroidism include discontinuation or levothyroxine.[12]
- **Eye exam**: baseline, yearly, and in the event of visual changes.[12,18] Optic neuropathy requires discontinuation.[12]

d. **SAMe-TT_2R_2 score**: female = 1 point; age <60 years = 1 point; ≥3 comorbidities (hypertension, diabetes, coronary heart disease/myocardial infarction, peripheral artery disease, HF, prior stroke, lung disease, liver or kidney failure) = 1 point; interacting drug (e.g., amiodarone) = 1 point; tobacco use within 2 years = 2 points; non-Caucasian = 2 points.
e. HAS-BLED score: elevated systolic blood pressure = 1 point; severe kidney/liver disease = 1 point each; stroke = 1 point; bleeding = 1 point; labile INR = 1 point; age > 65 years = 1 point; antiplatelet or NSAID = 1 point; alcohol excess = 1 point.[4]
f. Consult labeling for a complete list of contraindications.

Abbreviations: ACCP = American College of Chest Physicians; ACS = acute coronary syndrome; A-fib = atrial fibrillation; A-flutter = atrial flutter; AHA/ACC = American Heart Association/American College of Cardiology; BB = beta-blocker; bpm = beats per minute; CCB = calcium channel blocker; CCS = Canadian Cardiovascular Society; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; CV = cardiovascular; DOAC = direct-acting oral anticoagulant; ECG = electrocardiogram; EF = ejection fraction; GI = gastrointestinal; HF = heart failure; HF*p*EF = heart failure with preserved ejection fraction; HF*r*EF = heart failure with reduced ejection fraction; HR = heart rate; INR = international normalized ratio; IV = intravenous; SCr = serum creatinine; TEE = transesophageal echocardiogram; TIA = transient ischemic attack

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician. 2004 Feb 1;69(3):548-56.
https://www.aafp.org/pubs/afp/issues/2004/0201/p548.html.]

References

1. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014 Dec 2;130(23):e199-267. Erratum in: Circulation. 2014 Dec 2;130(23):e272-4.
2. Andrade JG, Aguilar M, Atzema C, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2020 Dec;36(12):1847-1948.
3. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021 Feb 2;143(5):e72-e227. Erratum in: Circulation. 2021 Feb 2;143(5):e229.
4. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest. 2018 Nov;154(5):1121-1201.
5. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019 Jul 9;140(2):e125-e151. Erratum in: Circulation. 2019 Aug 6;140(6):e285.
6. Guimarães HP, Lopes RD, de Barros E, et al. Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve. N Engl J Med. 2020 Nov 26;383(22):2117-2126.
7. Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in Comparison With Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: Findings From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Circulation. 2015 Aug 25;132(8):624-32.
8. Carnicelli AP, De Caterina R, Halperin JL, et al. Edoxaban for the Prevention of Thromboembolism in Patients With Atrial Fibrillation and Bioprosthetic Valves. Circulation. 2017 Mar 28;135(13):1273-1275.
9. Writing Committee Members, Lawton JS, Tamis-Holland JE, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022 Jan 18;79(2):e21-e129. Erratum in: J Am Coll Cardiol. 2022 Apr 19;79(15):1547.
10. Adler A, Fourey D, Weissler-Snir A, et al. Safety of Outpatient Initiation of Disopyramide for Obstructive Hypertrophic Cardiomyopathy Patients. J Am Heart Assoc. 2017 May 26;6(6):e005152.
11. Stiell IG, Sivilotti MLA, Taljaard M, et al. Electrical versus pharmacological cardioversion for emergency department patients with acute atrial fibrillation (RAFF2): a partial factorial randomised trial. Lancet. 2020 Feb 1;395(10221):339-349.
12. Epstein AE, Olshansky B, Naccarelli GV, et al. Practical Management Guide for Clinicians Who Treat Patients with Amiodarone. Am J Med. 2016 May;129(5):468-75.
13. Product information for *Pacerone*. Upsher-Smith Laboratories. Maple Grove, MN 55369. November 2018.
14. Cadrin-Tourigny J, Wyse DG, Roy D, et al. Efficacy of amiodarone in patients with atrial fibrillation with and without left ventricular dysfunction: a pooled analysis of AFFIRM and AF-CHF trials. J Cardiovasc Electrophysiol. 2014 Dec;25(12):1306-13.
15. Product monograph for amiodarone. Sanis Health. Brampton, ON L6Y 5S5. April 2022.
16. Kharabsheh S, Abendroth CS, Kozak M. Fatal pulmonary toxicity occurring within two weeks of initiation of amiodarone. Am J Cardiol. 2002 Apr 1;89(7):896-8.

17. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. 2022.http://www.clinicalkey.com. (Accessed December 5, 2022).
18. Hamilton D Sr, Nandkeolyar S, Lan H, et al. Amiodarone: A Comprehensive Guide for Clinicians. Am J Cardiovasc Drugs. 2020 Dec;20(6):549-558.
19. Sanoski CA, Bauman JL. Clinical observations with the amiodarone/warfarin interaction: dosing relationships with long-term therapy. Chest. 2002 Jan;121(1):19-23.
20. Product information for Tikosyn. Pfizer. New York, NY 10017. August 2019.
21. Product information for Multaq. Sanofi-Aventis US. Bridgewater, NJ 08807. November 2020.
22. Product monograph for Multaq. Sanofi-Aventis Canada. Laval, QC H7V 0A3. June 2020.
23. Product information for flecainide. Epic Pharma. Laurelton, NY 11413. August 2022.
24. Product monograph for JAMP flecainide. JAMP Pharma. Boucherville, QC J4B 5H34. November 2019.
25. Product information for propafenone. Aurobindo Pharma. East Windsor, NJ 08520. December 2021.
26. Product monograph for Rythmol. BGP Pharma. Etobicoke, ON M8Z 2S6. August 2021.
27. Prescribing information for Norpace/Norpace CR. Pfizer. New York, NY 10017. December 2020.
28. Product monograph for Rythmodan. Xediton Pharmaceuticals. Mississauga, ON L5N 1W1. December 2020.
29. Product information for Betapace/Betapace AF. Covis Pharma. Zug, Switzerland 6300. June 2021.
30. Product monograph for Apo-sotalol. Apotex. Weston, ON M9L 1T9. July 2022.
31. Product information for procainamide. Nexus Pharmaceuticals. Lincolnshire, IL 60069. September 2021.
32. Lan Q, Wu F, Han B, et al. Intravenous diltiazem versus metoprolol for atrial fibrillation with rapid ventricular rate: A meta-analysis. Am J Emerg Med. 2022 Jan;51:248-256.
33. Alsagaff MY, Susilo H, Pramudia C, et al. Rapid Atrial Fibrillation in the Emergency Department. Heart Int. 2022 Jun 30;16(1):12-19.
34. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021 Feb 1;42(5):373-498. Erratum in: Eur Heart J. 2021 Feb 1;42(5):507. Erratum in: Eur Heart J. 2021 Feb 1;42(5):546-547. Erratum in: Eur Heart J. 2021 Oct 21;42(40):4194.
35. Kirchhof P, Camm AJ, Goette A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. N Engl J Med. 2020 Oct 1;383(14):1305-1316.
36. Wiggins BS, Dixon DL, Neyens RR, et al. Select Drug-Drug Interactions With Direct Oral Anticoagulants: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Mar 24;75(11):1341-1350.
37. Andrade JG, Deyell MW, Macle L, et al. Progression of Atrial Fibrillation after Cryoablation or Drug Therapy. N Engl J Med. 2023 Jan 12;388(2):105-116.
38. Verma A. Antiarrhythmic drugs. In: Bhatt DL. Opie's Cardiovascular Drugs: A Companion to Braunwald's Heart Disease. 9th ed. Elsevier, 2021:533-592.
39. Nasser M, Idris S, Marinelli K, Machado C. Flecainide-induced Torsades de Pointes: Case Report and Review of Literature. Rev Cardiovasc Med. 2015;16(3):214-20 [abstract].
40. Anand V, Vakil K, Tholakanahalli V, et al. Discontinuation of Dofetilide From QT Prolongation and Ventricular Tachycardia in the Real World. JACC Clin Electrophysiol. 2016 Dec;2(7):777-781.
41. Volgman AS, Carberry PA, Stambler B, et al. Conversion efficacy and safety of intravenous ibutilide compared with intravenous procainamide in patients with atrial flutter or fibrillation. J Am Coll Cardiol. 1998 May;31(6):1414-9.

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