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 or for whom bleeding risk is high, consider referral for left atrial appendage closure device.[42] *Continued…*	• Decisions about antithrombotic therapy should be individualized.[2,42] Consider stroke risk, bleeding risk, and patient preference.[42] • Anticoagulation is recommended for A-fib (or A-flutter) with: ○ prior stroke or TIA.[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] ○ Elevated thromboembolic risk (e.g., ≥2% annual risk) according to a validated risk assessment tool.[42] ▪ CHA_2DS_2-VASc score[a] of ≥2 or in men or ≥3 in women (recommended).[4,42] (also see **footnote b**) ▪ CHA_2DS_2-VASc score[a] of 1 in men or 2 in women (CHEST recommends offering;[4] AHA/ACC says it is reasonable.[42]) Give consideration to other risk factors that might affect risk (e.g., smoking, kidney disease, obesity, blood pressure control).[42] (also see **footnote b**) ▪ 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] ▪ Antithrombotic therapy should **not** be offered in patients with a CHA_2DS_2-VASc score[a] of 0 in men or 1 in women.[4] ○ hypertrophic cardiomyopathy.[2,42] ○ rheumatic mitral stenosis[42] ○ mitral stenosis of at least moderate severity[42] ○ mechanical heart valve.[3] ○ need for cardioversion. ▪ Anticoagulate for at least three weeks prior to and for at least four weeks after cardioversion if: ○ AHA/ACC and CHEST: A-fib/A-flutter duration is ≥48 hrs or is unknown.[4,42] See **footnote g**. ○ 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] ▪ Start anticoagulation as soon as possible and continue for at least four weeks afterward if: ○ immediate cardioversion is needed (i.e., patient unstable).[2,4,42] ○ AHA/ACC: A-fib/A-flutter duration is ≥48 hrs and imaging excludes intracardiac thrombus.[2,4,42] See **footnote g**.

Question	Answer/Pertinent Information
Which patients with A-fib/A-flutter may need an anticoagulant, continued	○ A-fib/A-flutter duration is <48 hrs (CHEST).[4] AHA/ACC: If duration is <48 hours and CHA_2DS_2-VASc score[a] is ≥2 in men or ≥3 in women, consider imaging to exclude intracardiac thrombus.[42] See **footnote g**. ○ 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] ▪ After cardioversion, base decisions about long-term anticoagulation as for other patients.[2,4] • It may be reasonable to anticoagulate patients with a device-detected atrial high-rate episode lasting ≥24 hrs and a CHA_2DS_2-VASc score[a] ≥2 in men or ≥3 in women, or in higher risk patients with an episode lasting ≥5 min.[42]
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.[42] • 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]).[2,4,42] • For patients with **adherence issues**, warfarin may be preferred over a DOAC. ○ 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**: ○ Mechanical valve: use warfarin.[42] Don't use DOACs; dabigatran and apixaban seem to increase thrombosis risk vs warfarin, and other DOACs have insufficient data in these patients.[3,42,43] ○ Bioprosthetic valve: DOACs can be used, but some experts prefer warfarin within the first three months after surgical valve replacement because there is less evidence for DOAC efficacy during this time of relatively high risk of valve thrombosis.[3,6-8,28,42] • For patients undergoing **cardioversion**: ○ use therapeutic-dose anticoagulation with warfarin, a DOAC (may be preferred over warfarin), or parenteral agent (e.g., for patients who are hemodynamically unstable).[4,42] • For patients with a **history of a major bleed**, see our FAQ, *Managing Bleeding with Anticoagulants*.[43] • For patients with **antiphospholipid antibodies**: warfarin is preferred.[10,44]
How should anticoagulation be monitored? *Continued…*	• Periodically assess appropriateness of anticoagulation (e.g., net clinical benefit, dosing, anticoagulant choice).[2,42] • 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 monitored more frequently (e.g., have hemoglobin and hematocrit checked every three months).[4,42] • 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]

Question	**Answer/Pertinent Information**
How should anticoagulation be monitored, continued	• For warfarin patients, check INR weekly until stable, then at least every four weeks.[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, or Figure 11 in the AHA/ACC guidelines: https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000001193.[42]
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).[9,42] After a year, a DOAC alone may be enough.[2,42] • 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 in patients without a history of stent thrombosis.[2,42]

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.[2,42] • ACS.[42] • Thyrotoxicosis.[42] • Hypertrophic cardiomyopathy.[2,27] • Pre-op (A-fib prophylaxis) or post-op cardiac surgery.[42] • Pregnancy.[42] • BTK inhibitor-induced A-fib.[42]	• Hemodynamic instability.[42] • Decompensated CHF.[42] • Asthma.[42] • Pre-excitation.[42]	• If IV used, start oral agent as soon as possible for uninterrupted control.[2] • For HF*r*EF, target an evidence-based dose.[2] • Consider nonselective beta-blocker (e.g., propranolol) for thyrotoxicosis.[42] • Consider propranolol or metoprolol for pregnant patients.[42]

Continued…

Question	**Answer/Pertinent Information**			
Considerations when choosing a **rate control** agent, continued	**Drug**	**Consider for…**	**May not be appropriate for…**[f]	**Comments**
	CCB (**diltiazem** or **verapamil**)	• Thyrotoxicosis (BB alternative).[1] • Hypertrophic cardiomyopathy.[27] • Bronchospastic disease.[1] • Post-op cardiac surgery (BB alternative).[42]	• Hemodynamic instability.[1] • Decompensated CHF, or HF*r*EF with EF ≤40%.[2,42] • Pre-excitiation.[42]	• If IV used, start oral agent as soon as possible for uninterrupted control.[2] • 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).[2,42] • Pre-op cardiac surgery (A-fib prophylaxis).[42]	• Pre-excitation.[42] • Contraindications: sick sinus syndrome, cardiogenic shock, bradycardia with syncope, second- or third-degree AV block (Canada [oral]: thyroid dysfunction, interstitial lung disease, hepatitis).[13,15]	• Not a preferred first-line option.[42] • 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]
	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.[42] • Pregnancy.[42]	• Obstructive hypertrophic cardiomyopathy.[27] • Pre-excitation.[42]	• Not a preferred option.[42] • Digoxin is less effective with a slower onset than BBs or CCBs.[33] • Can combine with BB, or CCB (HF*p*EF only).[42] • 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 <100 bpm to 110 is a reasonable target, guided by patient symptoms.[42] • For patients with arrhythmia-induced cardiomyopathy or recalcitrant HF symptoms, a reasonable target is <80 bpm at rest or <110 bpm during moderate exercise .[42] • 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]			

Question	Answer/Pertinent Information
RHYTHM CONTROL	
When is rhythm control a reasonable or preferred strategy?	• Patient is hemodynamically unstable (electrical cardioversion is indicated).[42] • Patient is highly symptomatic from A-fib, or to clarify whether symptoms are due to the patient's A-fib.[42] • Patient is young, or athletic (consider catheter ablation).[42] • Patient continues to have symptoms despite rate control.[42] • Patient is newly diagnosed (<1 year duration).[2,42] ○ 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 left ventricular dysfunction or HF.[42] • Patient prefers a rhythm control strategy.[42] • Patient has a pre-excitation syndrome.[42] • Patient has a small left atrium or marked atrioventricular regurgitation.[42] • See the table below for pharmacologic options for cardioversion and maintenance of sinus rhythm.
What is the role of catheter ablation?	• Initial treatment with catheter cryoablation is associated with reduced recurrence over three years vs antiarrhythmics.[37] • Consider catheter ablation for young, healthy patients (e.g., athletes) with symptomatic paroxysmal A-fib with no or minimal structural heart disease.[42] ○ Younger patients have a long life expectancy during which to derive benefit (e.g., delayed A-fib progression).[42] • Older adults can derive CV benefit from catheter ablation due to improved rhythm control.[42] • Consider catheter ablation when antiarrhythmic drugs are not effective, can't be used, or are not preferred.[42] • Catheter ablation is recommended for patients with pre-excitation.[2,42] • Consider catheter ablation for patients with HF (especially early stage HF*r*EF with minimal structural heart disease), or A-fib-associated cardiomyopathy.[42] • Be aware that ablation does not preclude the need for anticoagulation. Catheter ablation is performed under therapeutic anticoagulation. Anticoagulation is continued for at least three months. After that, decisions about anticoagulation are made as for other A-Fib patients (e.g., using CHA_2DS_2-VASc).[42]

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.[42] • Maintenance.[42]	• CHF or EF≤40%.[2,42] • Heart disease (coronary or structural).[2,42] • Sinus or AV node dysfunction, infranodal conduction disease, or Brugada syndrome.[2] • Second-or third-degree AV block, or bi- or trifascicular block (contraindications).[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] • 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.[2,34,42] • "Pill-in-the-pocket:" at-home use for symptomatic A-fib (once shown safe in a monitored setting).[2,42] • Among the agents with the best evidence for cardioversion.[42] • Metabolized by CYP2D6.[42] • Requires initial dose reduction in kidney impairment.[23] • Check trough periodically in severe kidney or liver impairment. Trough monitoring is also 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.[42] • Maintenance.[42]	• Heart disease (coronary or structural).[42] • HF (Canada: severe or uncontrolled), cardiogenic shock, 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).[5,25]	• 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.[2,34,42] • "Pill-in-the-pocket:" at-home use for symptomatic A-fib (once shown safe in a monitored setting).[2,42] • 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]

Drug	Consider for…	May NOT be appropriate in…[f]	Comments
Propafenone, continued			• Increases digoxin level via p-glycoprotein inhibition.[17] • Inhibits warfarin metabolism via CYP2C9 inhibition. Expect a 25% increase in prothrombin time.[17]
Dofetilide (US)	• Maintenance.[42]	• QT prolongation. Contraindicated if QTc >440 ms (500 ms in patients with ventricular conduction abnormalities).[20] • Severe kidney impairment (contraindicated if CrCl<20 mL/min).[20] • Hypokalemia or hypomagnesemia.[42]	• Option for patients with HF*r*EF[42] or hypertrophic cardiomyopathy.[2] • Effective for conversion to sinus rhythm, but impractical because it takes days to work.[42] • High risk of QT prolongation (19%) and torsades (3%).[38,40] • Requires at least a three-day hospital stay for initiation and dose escalation to monitor ECG, serum potassium and magnesium, and CrCl.[42] • Monitor ECG, potassium, magnesium, and kidney function at least every three to six months.[42] • Dose based on kidney function and QTc.[20] • 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.[20]
Dronedarone *Continued…*	• Maintenance.[42]	• CHF (EF ≤40%).[2,42] Recently decompensated or Class IV CHF (Canada: any CHF) (contraindications).[21,22] Increases risk of death.[21,22] • HR <50 bpm, second- or third-degree heart block, or sick sinus syndrome (contraindications).[21,22] • Permanent A-fib. Contraindication due to increased risk of CV death, stroke, and HF hospitalization.[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.[42] • CYP3A4 substrate (metabolism inhibited by diltiazem, verapamil).[17] Contraindicated with strong CYP3A4 inhibitors.[21,22] • Moderate CYP3A4 and CYP2D6 inhibitor.[17] Inhibits p-glycoprotein.[17] Increases BB and digoxin levels.[1]

Drug	Consider for…	May NOT be appropriate in…[f]	Comments
Dronedarone, continued		• Patients with QTc ≥500 ms, or with other QT-prolonging meds or herbs (contraindications).[21,22] • Liver impairment (contraindicated in severe liver impairment).[21,22]	• May slightly increase SCr due to inhibition of tubular secretion of creatinine, without a decrease in kidney function.[17] • 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.[42]	• History of symptomatic CHF or EF ≤40%.[2,42] • QT prolongation.[2] • Suspected ACS.[2] • Patients with hypokalemia or hypomagnesemia.[2]	• High risk of QT prolongation (1.2%) and torsades (4.3%).[17,38] • ECG monitoring required for at least four hours after administration.[2] • May cause hypotension.[2] • IV magnesium, before +/- after treatment, may improve efficacy and safety.[2,42] • Faster response than amiodarone, but higher risk of QT prolongation and torsades.[42] • Improves efficacy of electrical cardioversion.[2] • Option for hemodynamically stable patients with pre-excitation, and for A-fib post-cardiac surgery.[2,42]
Procainamide	Conversion.[42]	• Complete heart block, torsades, or lupus (contraindications).[31] • EF ≤40%.[42]	• Reserve for patients in whom ibutilide or amiodarone are not appropriate.[42] • 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).[2,42] • Less effective than ibutilide.[42]
Sotalol *Continued…*	Maintenance.[42]	• Cardiogenic shock or decompensated HF (Canada: severe HF)(contraindicated).[29,30] • EF ≤40%.[2] • Bronchospastic disease (contraindicated).[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] • May cause bradycardia.[42] • Requires dose reduction in kidney impairment.[42]

Drug	Consider for…	May NOT be appropriate in…[f]	Comments
Sotalol, continued		• QT prolongation (contraindicated)[29,30] or risks for torsades.[2] • Bradycardia, second- or third-degree AV block, or sick sinus syndrome (contraindicated).[29,30] • Serum potassium <4 mEq (mmol)/L (Canada: hypokalemia)(contraindicated).[29,30]	• Do not use with a beta-blocker. Avoid in HFrEF because these patients should be taking an evidence-based BB.[42] • Inpatient initiation recommended for at least three days for initiation or reloading to monitor ECG and CrCl.[42] CSS: if started as an outpatient, check ECG at baseline and 48 to 72 hours after initiation.[2] • Monitor ECG, potassium, magnesium, and kidney function at least every three to six months.[42] • Option for mild hypertrophic cardiomyopathy.[2]

Amiodarone	• Conversion.[42]
	• Maintenance.[42]
		• Pre-excitation.[2,42]
		• Cardiogenic shock, bradycardia with syncope, second- or third-degree AV block, and sick sinus syndrome (Canada [oral]: thyroid dysfunction, interstitial lung disease, hepatitis)(contraindicated).[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**.[34,42] See **footnote c**.
			• Consider for:
			  ○ hypertrophic cardiomyopathy[2]
			  ○ CHF[42]
			• Improves efficacy of electrical cardioversion.[2]
			• Slow onset (eight to 12 hours IV).[42]
			• 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. CHA_2DS_2-VASc has the most data and was used in most clinical trials of A-fib treatment. Other validated clinical risk scores include CHA_2DS_2-VASc[2], ATRIA, and GARFIELD-AF. ATRIA and GARFIELD-AF include kidney disease and advanced age (≥85 years) as risk factors. GARFIELD also gives consideration to the impact of bleeding history, dementia, and smoking.[42]

c. **Amiodarone:**

- **Side effects:** About 50% of patients have side effects.[12] Due to amiodarone's ~60-day mean half-life, side effects may persist for several weeks to months after stopping it.[13,15] 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.[12,42] **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 by 30% to 50%; decrease IV digoxin by 15% to 30%; decrease flecainide dose by 50%; decrease warfarin by 33% 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] May require amiodarone discontinuation or thyroidectomy.[12,26] 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.
g. Imaging options include TEE or cardiac CT, preferably with delayed contrast-enhanced image acquisition protocol.[42] Imaging to exclude intracardiac thrombus and thereby shorten duration of pre-conversion anticoagulation is an option for A-fib/A-flutter duration ≥48 hrs.[2,4,42] The role of imaging and anticoagulation is unclear in patients with low thrombotic risk and A-fib/A-flutter duration <12 hrs.[42] Note that anticoagulation should be achieved before TEE.[5]

Abbreviations: 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; BTK = Bruton's tyrosine kinase; CCB = calcium channel blocker; CCS = Canadian Cardiovascular Society; CHEST = American College of Chest Physicians; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; CT = computed tomography; 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;69:548-56. https://www.aafp.org/pubs/afp/issues/2004/0201/p548.html.]

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