An Overview of Angina Medication Treatments

Author: Patrick Huska, PharmD

Executive Summary

The pain from angina results from myocardial ischemia, which can be caused by cardiac conditions, leading to an increase in oxygen demand and/or a decrease in oxygen supply. In addition to chest pain, angina can cause pressure, tightness, or discomfort of the chest, jaw, shoulders, back, neck, upper abdomen and arms, as well as shortness of breath and fatigue. The most recent ESC guidelines and AHA scientific statement point out that none of the recommended medications have been shown to reduce the risk of death or MI in patients with just angina.

- The main goals for treatment are to improve quality of life by decreasing the severity/frequency of angina symptoms and preventing future myocardial infarction and death.
- None of the recommended medications has shown superiority in treating angina symptoms in head-to-head trials.
- The choice of specific agents is often determined by individual patient vital signs/hemodynamics (heart rate, blood pressure and left ventricular function), comorbidities, current medications, tolerance, adherence and patient preference.

Acronyms	
AF	Atrial fibrillation
AHA	American Heart Association
AV	Atrioventricular
BB	Beta blockers
CAD	Coronary artery disease
CCB	Calcium channel blocker
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
CYP3A4	Cytochrome P450 3A4 enzyme
DHP CCB	Dihydropyridine calcium channel blocker
DOAC	Direct oral anticoagulant
ESC	European Society of Cardiology
LAN	Long-acting nitrate
MI	Myocardial infarction
Non-DHP CCB	Nondihydropyridine calcium channel blocker
PRN	Prescribe as needed
SA	Sinoatrial
SBP	Systolic blood pressure

Treatment of Angina

The first goal of angina treatment is to treat angina symptoms. The second goal of angina treatment is to prevent future cardiac issues by appropriately treating patients for CAD, hyperlipidemia, hypertension and other cardiac diseases which could lead to MI or death. This article will review medications used to treat angina symptoms.

Medications to treat angina symptoms include BB, CCB, nitroglycerin (both long- and short-acting), ranolazine (Ranexa) and ivabradine (Corlanor). These agents have been shown to increase exercise tolerance and decrease angina symptoms by increasing myocardial oxygen supply (nitrates or CCB) or decreasing oxygen demand (BB, CCB, ranolazine or ivabradine). The ECS and AHA recommend BB or CCB as first-line therapy. LAN and ranolazine can be considered when BB or CCB are contraindicated, poorly tolerated or do not control symptoms effectively.

Table 1: Medications to Treat Angina Symptoms

Medication	Mechanism of Action for Treatment of Angina
Beta-Blockers	BBs lessen angina symptoms by reducing heart rate and myocardial contractility and decreasing blood pressure. This results in decreased myocardial oxygen demand.
Calcium Channel Blockers	CCBs selectively lessen angina symptoms by dilating coronary and other vascular smooth muscle, which increases coronary blood flow. DHP CCB (amlodipine, nifedipine and

	felodipine) have greater vascular selectivity. Non-DHP CCB (diltiazem and verapamil) decrease the heart rate and myocardial contractility.
Nitrates	The active component, nitric oxide, causes relief by dilation of peripheral and coronary arteries and peripheral veins which leads to decreased systemic vascular resistance, coronary blood flow redistribution and preload reduction.
Ranolazine	A selective inhibitor of the late inward sodium current, which at doses of 500 - 2000 mg daily, decreases the frequency of angina and improves exercise tolerance. This occurs without substantial changes in heart rate or blood pressure.
Ivabradine	Ivabradine is a heart rate-lowering drug that slows the firing of the SA node which reduces heart rate, thereby decreasing myocardial oxygen demand without an effect on contractility or blood pressure.

Medications

Beta-Blockers

- First-line agent. All BBs appear to be equally effective in treating stable angina symptoms.
- BBs should be used for angina in patients with other indications in which a BB would be indicated, such as myocardial infarction, heart failure, hypertension, tachyarrhythmias or left-ventricular dysfunction.
- Disease states to avoid using BBs: severe bradycardia, conduction abnormalities, vasospastic angina (symptoms may increase), asthma, COPD, severe peripheral artery disease and hypotension.

Calcium Channel Blockers

- First-line agent. CCBs significantly reduce angina episodes, increase exercise duration and decrease the frequency of nitroglycerin use.
- CCBs are first line for use in vasospastic angina, asthma and COPD.
- DHP CCBs mostly have a peripheral vasodilating action and increase heart rate.
- If combining BBs and calcium channel blockers, it is appropriate to use a DHP CCB.
- DHP CCBs should be avoided in AF, heart failure, hypotension and left-ventricular dysfunction.
- The non-DHP CCBs have a peripheral vasodilating action, cause slowing of heart rate and have myocardial depressant effects.
- A non-DHP CCB is a suitable alternative for patients with a previous myocardial infarction who do not tolerate BBs or have a contraindication to their use.
- Non-DHP CCBs should be avoided in left-ventricular dysfunction, heart failure, AV block and hypotension.

Nitrates

- Short-acting nitrates are recommended for use as needed (PRN) for immediate relief of effort angina.
- LAN are in the guidelines as second-line due to the risk of tolerance with loss of efficacy if there is no nitrate-free period of 12-14 hours per day and the risk of tachyphylaxis.
- LANs (e.g., isosorbide mononitrate or nitroglycerin patches) are a suitable choice as monotherapy for people who are intolerant of BBs or calcium channel blockers or if those medicines are contraindicated.
- LAN can be added to BB- or CCB-therapy in patients with an elevated SBP who still have angina symptoms.
- The most common side effects are hypotension, headache and flushing.

- Contraindications include hypertrophic obstructive cardiomyopathy, severe mitral/aortic stenosis, cardiac tamponade and co-administration of phosphodiesterase inhibitors (e.g., sildenafil, tadalafil, or vardenafil).

There is some evidence that the sudden withdrawal of a BB, CCB or nitrates may cause an exacerbation of angina. Therefore, a gradual reduction of the dose is preferable when either medicine needs to be stopped.

Ranolazine

- Ranolazine reduces myocardial wall rigidity and improves myocardial perfusion without changing either heart rate or blood pressure. It has a role as an add-on for patients with low blood pressure or low heart rate who still have angina symptoms.
- Side effects include dizziness, nausea and constipation. Prolongation of the QT interval may occur.
- Avoid use in severe renal impairment, moderate to severe hepatic failure, Class I or III antiarrhythmics other than amiodarone and with strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole and ritonavir).

Ivabradine

- Ivabradine lowers heart rate and inhibits the primary sinoatrial node current. Its effect is the highest in high heart rates and lowest in lower heart rates. This becomes an option as an additive or alternative to BB in patients with a heart rate over 70 bpm and a low blood pressure.
- The most common adverse effect is the induction of phosphenes, which includes an assortment of visual function changes. Excessive bradycardia has been reported.
- Avoid in bradycardia, severe hepatic impairment, sick sinus syndrome, sinoatrial block, third-degree AV block, combination with DHP CCBs, pregnancy and avoid strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole and ritonavir) or inducers (e.g., carbamazepine, phenobarbital, phenytoin, primidone and rifampin).
- Branded medication.

References

Arnold S, Bhatt D, et al. Clinical Management of Stable Coronary Artery Disease in Patients with Type 2 Diabetes Mellitus: A Scientific Statement from the American Heart Association. Originally published13 Apr 2020https://doi.org/10.1161/CIR.0000000000000766Circulation. 2020;141:e779–e806

Fox K, Garcia M, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *European Heart Journal*, Volume 27, Issue 11, June 2006, Pages 1341–1381, https://doi.org/10.1093/eurheartj/ehl001. Published: 01 June 2006.

Gayet JL, Paganell F. Update on the medical treatment of stable angina. Archives of Cardiovascular Diseases, Volume 104, Issue 10, October 2011, Pages 536-544. https://doi.org/10.1016/j.acvd.2011.08.001

Gulati M., Levy P et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Originally published28 Oct 2021https://doi.org/10.1161/CIR.0000000000001029Circulation. 2021;144:e368–e454.

Juhani Knuuti, William Wijns, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC) European Heart Journal, Volume 41, Issue 3, 14 January 2020, Pages 407–477, https://doi.org/10.1093/eurheartj/ehz425. Published: 31 August 2019.

Rousan T, Thadani U. Stable Angina Medical Therapy Management Guidelines: A Critical Review of Guidelines from the European Society of Cardiology and National Institute for Health and Care Excellence. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6523058/# Eur Cardiol. 2019 Apr; 14(1): 18–22. doi: 10.15420/ecr.2018.26.1

Tamargo J, Lopez-Sendon J. Ranolazine: a better understanding of its pathophysiology and patient profile to guide treatment of chronic stable angina. Published Online:29 Nov 2021https://doi.org/10.2217/fca-2021-0058.

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Rhythm Control in Atrial Fibrillation

Author: Rebecca Moore, PharmD

Executive Summary

AF is a common heart rhythm disorder affecting 5.2 million people in 2010 and is projected to increase to 12.1 million people in 2030. AF increases risk of stroke, heart failure, death and also impairs quality of life. Goals of care include the prevention of stroke, control of the ventricular rate and minimization of symptoms to improve quality of life.

Treatment for AF includes symptomatic improvement with rate and rhythm control and prevention of thromboembolic complications. Data has been mixed on whether rate control or rhythm control provides better clinical outcomes. This paper will discuss rhythm control, patients in which rhythm control may be preferred and medication selection.

Acronyms	
AF	Atrial fibrillation
AV	Atrioventricular
CAD	Coronary artery disease
CrCl	Creatinine clearance
DDI	Drug-drug interaction
ECG	Electrocardiogram
ER	Extended release
HF	Heart failure
IR	Immediate release

1. Situations when rhythm control may be preferred:
    a. Younger patients
    b. Patients with high cardiovascular risk
    c. Patients with HF
    d. Patients who have failed rate control therapy
2. Situations when rate control may be preferred:
    a. Patients with asymptomatic AF and rhythm control is not favored
        i. Elderly
        ii. Patients with long-standing AF
        iii. Patients with a markedly enlarged left atria

Rhythm Control: Things to Consider

1. Cardioversion restores sinus rhythm and can be repeated multiple times if first unsuccessful.
    a. Used for symptomatic patients or with newly diagnosed AF
    b. Can also be used in patients with HF
2. Antiarrhythmic drug therapy:
    a. Drugs in the chart below are listed alphabetically within each box. Individual drug selection should be based on patient preference and patient-specific risk factors for adverse effects.
    b. Dofetilide and Sotalol are started in the hospital where continuous ECG monitoring, lab monitoring and CrCl calculations can be performed as they can lead to life-threatening arrhythmias.
        i. Typically done over a course of three days, which allows for five half-lives achieving steady state concentrations
3. Always check for drug interactions with antiarrhythmic drugs, particularly dofetilide and amiodarone which have several.
4. Amiodarone and dronedarone have the least cardiotoxic adverse effects compared with other antiarrhythmic drugs. However, amiodarone has significant potential systemic effects, including liver, lung and thyroid toxicity. Dronedarone can be associated with hepatotoxicity.
    a. Dronedarone cannot be used in patients with HF due to higher mortality rate and cannot be used to treat permanent AF due to higher rates of stroke, cardiovascular death and readmission.
    b. Amiodarone, sotalol and dofetilide can be used safely in patients with structural heart disease but use caution for other antiarrhythmic drugs.
    c. Amiodarone has the greatest likelihood of maintaining sinus rhythm but also with the highest risk

of long-term complications.

i. Amiodarone is generally reserved for second and third-line treatment due to its side effect profile. See Table 2.

5. Flecainide and propafenone are generally selected first for patients **without** structural heart disease and those with hypertension who do not have left ventricular hypertrophy.
    a. Both have relatively good side effect profiles, are efficacious and fairly easy to dose.
    b. Use caution in patients over 70 years of age due to higher likelihood of underlying CAD.
6. Sotalol and dofetilide are the most recommended first-line drugs in patients **with** structural heart disease and in coronary heart disease. Dronedarone is also listed as first-line but is not used as often in practice.
7. Amiodarone and dofetilide are used in patients with AF and HF or those with a left ventricular ejection fraction less than 35%.
8. Dofetilide has minimal side effects but has increased risk of Torsades de Pointes and has multiple DDIs.
    a. Always check for DDIs when starting a new medication if the patient is on dofetilide
    b. Dose adjusted for renal function and is decreased or stopped if QTc is long
9. Catheter ablation
    b. Has best outcomes with regard to mortality and morbidity comparing catheter ablation and drug therapy (for rate control or rhythm control)
    c. Good option for patients who:
        i. Are young
        ii. Do not have left atrial dilation
        iii. Have symptomatic AF or have AF refractory to medical therapy
        iv. After shared decision making, considered for patients who have HF and for those who have no symptoms

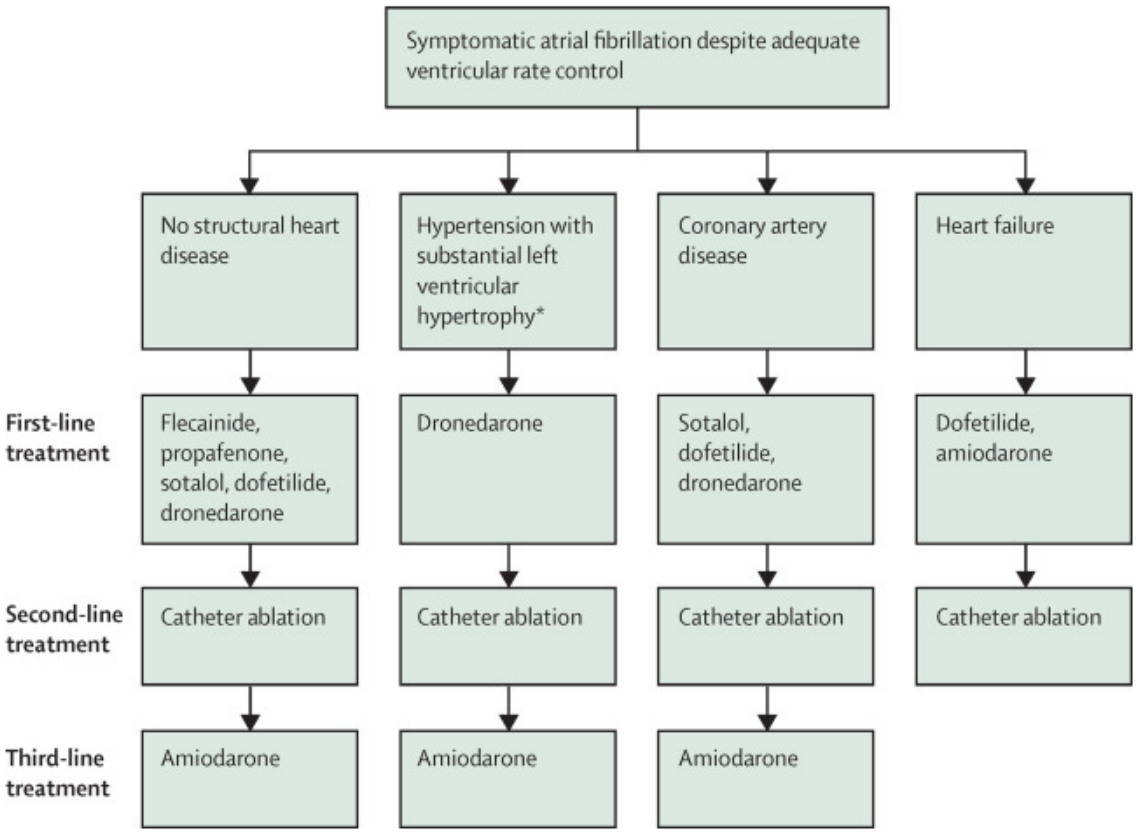

Figure 1: Symptomatic atrial fibrillation despite adequate ventricular rate control

Table 1: Antiarrhythmic Drugs Used to Maintain Sinus Rhythm in AF: Class 1C Agents

Drug	Cardioversion Dose	Maintenance Dose	Cautions or Adverse Effects	Drug Interactions
Flecainide	Oral: 200-300mg x1	50-200 q12 hr	• Sinus or AV node dysfunction • Heart failure • CAD • Atrial flutter • Brugada syndrome • Renal or liver disease	• Increases digoxin levels
Propafenone	Oral: 450-600mg x1	• IR: 150-300 mg q8 hr • ER: 225-425mg q12hr	• Sinus or AV node dysfunction Heart failure • CAD • Atrial flutter • Brugada syndrome • Liver disease • Asthma	• Increases digoxin and warfarin levels

Table 2: Antiarrhythmic Drugs Used to Maintain Sinus Rhythm in AF: Potassium Channel Blockers

Drug	Cardioversion Dose	Maintenance Dose	Cautions or Adverse effects	Drug interactions
Sotalol	40-160mg q12hr	40-160 mg q12 hr	• Prolonged QT interval • Renal disease • Hypokalemia Hypomagnesemia • Diuretic therapy • Sinus or AV nodal dysfunction • HF • Asthma	• QT prolonging drugs (Amiodarone, Azithromycin, Clozapine, Flecainide, etc.) • Antacids containing aluminum oxide and magnesium hydroxide decrease absorption (Maalox, Mylanta, Gaviscon, etc.)
Dofetilide	Oral: 125 to 500 mcg q12 hr based on renal function	125-500 mcg q12 hr Must monitor QTc interval and dose accordingly	• Prolonged QT interval • Renal disease • Hypokalemia Hypomagnesemia • Diuretic therapy	• Contraindicated with verapamil, cimetidine, trimethoprim, megestrol, prochlorperazine, hydrochlorothiazide, ketoconazole • Avoid QT-prolonging drugs (Haloperidol, Hydroxyzine, Methadone, Ondansetron, etc.)

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Amiodarone	• Oral: 600-800 mg/d divided doses, max total load of 10 g • IV: 150 mg over 10 min, then 1 mg/min for 6 hr, then 0.5 mg/hr for 18 hr	• Oral: 400-600 mg/d for 2-4 wks, then 100-200 mg/d • IV: 150 mg over 10 min, then 1 mg/min for 6 hr, then 0.5 mg/hr for 18 hr	• AV block • Bradycardia • Blue-gray skin discoloration • Corneal microdeposits Hepatotoxicity Hyperthyroidism • Hypotension (IV) Hypothyroidism • Peripheral neuropathy Photosensitivity • Pulmonary fibrosis • Phlebitis (with IV route) • Hypotension • Bradycardia • QT prolongation • GI upset • Constipation • Increased INR	• Impairs warfarin metabolism • Increases digoxin levels • Simvastatin dose not to exceed 20mg per day
Dronedarone	NA	400mg twice daily	• Prolonged QT interval • Renal disease • Hypokalemia Hypomagnesemia • Diuretic therapy	• Increase digoxin levels • Contraindicated with potent CYP3A4 inducers or inhibitors (Clarithromycin, Ketoconazole, Phenytoin, Rifampin, etc.)

References

Noel Z, Tisdale J. Arrhythmias. 2021. Cardiology Pharmacy Preparatory Review and Recertification Course - Arrhythmias, and Drug-Induced Cardiovascular Disease and Drugs to Avoid in Cardiovascular Disease - Module 3. American College of Clinical Pharmacy. https://www.accp.com

January C, Wann L, Calkins H, et al. (2019) 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. (Journal of the American College of Cardiology, Vol. 74, No. 1, 2019). The American Heart Association, Inc., The American College of Cardiology Foundation, and The Heart Rhythm Society. https://www.sciencedirect.com/science/article/pii/S0735109719302098?via%3Dihub

Van Gelder I, Rienstra M, Crijns H, Olshansky B. 2016 Atrial fibrillation 2 Rate control in atrial fibrillation. Lancet 2016; 388: 818–28. www.thelancet.com

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. J Am Coll Cardiol 2014; 64:2246–2280.

Deshpande R, Al Khadra Y, et al. 2022. Atrial fibrillation: Rate control or rhythm control? Cleveland Clinic Journal of Medicine, Vol. 89, No. 10. Downloaded from www.ccjm.org on January 26, 2023.

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Rate Control in Atrial Fibrillation

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Executive Summary

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Treatment for AF includes symptomatic improvement with rate and rhythm control and prevention of thromboembolic complications. Data has been mixed on whether rate control or rhythm control provides better clinical outcomes. This paper will discuss **rate control**, patients in which rate control may be preferred and medication selection.

1. Situations when rate control may be preferred:
    a. Patients with asymptomatic AF and rhythm control is not favored include:
        i. Elderly
        ii. Patients with long-standing AF
        iii. Patients with a markedly enlarged left atria
2. Situations when rhythm control may be preferred:
    a. Younger patients
    b. Patients with high cardiovascular risk
    c. Patients with HF
    d. Patients who have failed rate control therapy

Acronyms	
AF	Atrial fibrillation
AV	Atrioventricular
BB	Beta blockers
bpm	Beats per minute
CCB	Calcium channel blocker
DCC	Direct current cardioversion
HF	Heart failure
HR	Heart rate
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LV	Left ventricular
MI	Myocardial infarction
Non-DHP CCB	Nondihydropyridine calcium channel blocker
P-gp	P-glycoprotein
SBP	Systolic blood pressure

Rate Control: Things to Consider

1. Goal HR less than 110 bpm for long-term rate control in asymptomatic patients and those with preserved LV systolic function
2. Goal HR greater than 80 bpm for patients with AF symptoms or HFrEF
3. If a patient becomes hemodynamically unstable, immediate synchronized DCC is necessary
    a. Indicators of hemodynamic instability:
        i. SBP less than 90 mm Hg
        ii. Heart rate greater than 150 beats/minute
        iii. Ischemic chest pain
        iv. Loss of consciousness
4. Use BB or non-DHP CCB
    a. Avoid non-DHP CCBs in patients with HFrEF
    b. If rate control fails with BB or non-DHP CCB, amiodarone is a second-line option

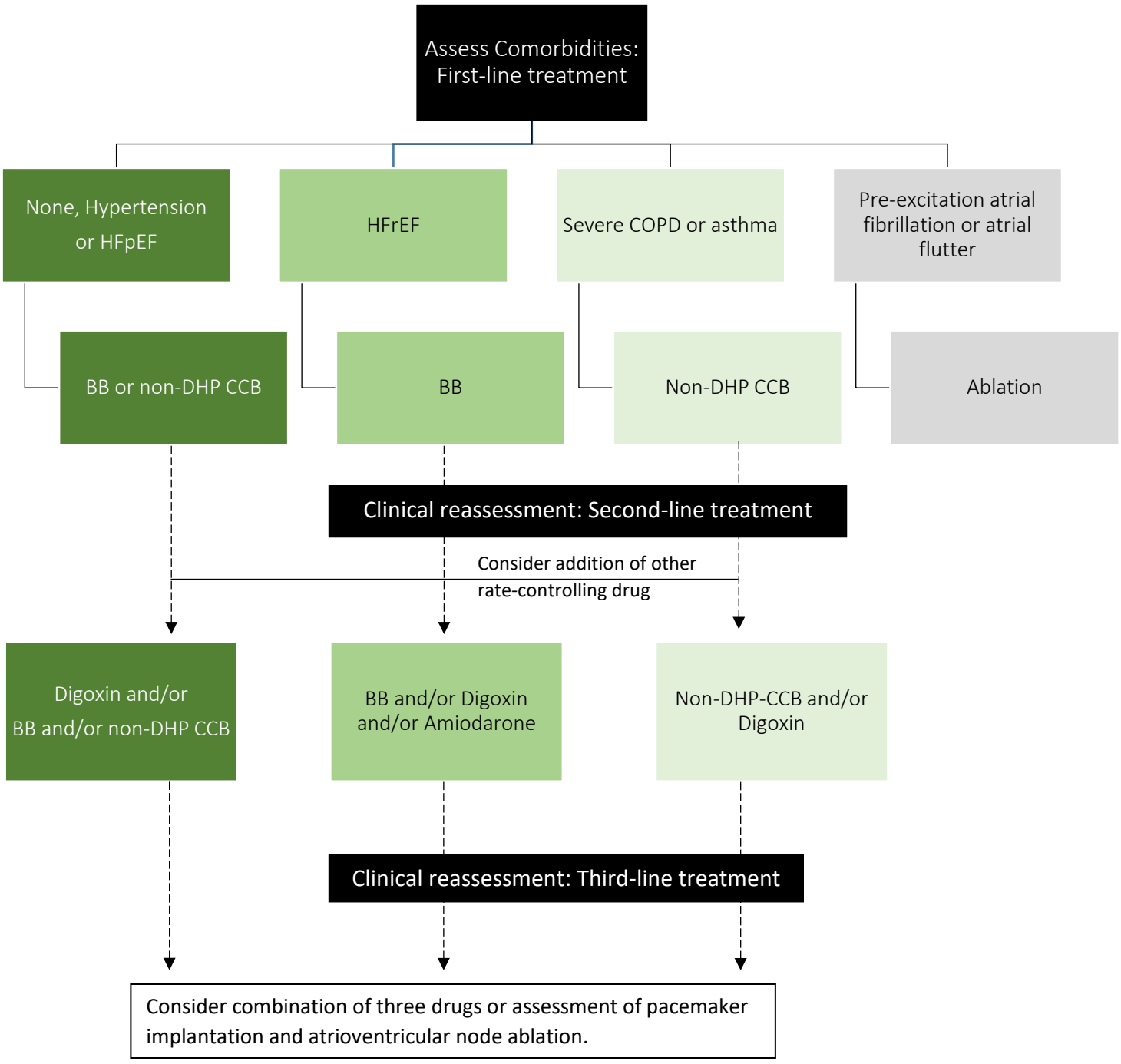

Figure 1: Choice of Drugs for Rate Control

Medications

BBs

1. BBs are preferred in the following groups:
    a. Recent MI
    b. Heart failure due to systolic dysfunction
    c. Inappropriate increase in ventricular rate during exercise
    d. Surges in sympathetic function that trigger AF (e.g., postoperative AF)
2. BBs with best rate control are listed in Table 1 below.

Non-DHP CCB (verapamil and diltiazem)

1. Preferred in patients with chronic lung disease and in patients who do not tolerate BB
    a. Verapamil has a somewhat greater blocking effect on the AV node than diltiazem
    b. Choice between these drugs is often dictated by side effects

Digoxin

1. Digoxin is most commonly used in adjunct with a BB for symptom control
    a. It has a narrow therapeutic window, requires renal adjustment and interacts with other drugs (e.g., verapamil, amiodarone and specific antibiotics)
    b. Digoxin plasma concentration assessment can help in dose adjustments

Amiodarone

1. Generally reserved for second- or third-line treatment due to its side effect profile

Table 1: Drugs for Ventricular Rate Control: Beta Blockers and Calcium Channel Blockers

Drug	Loading Dose	Maintenance Dose	Adverse Effects	Important Drug Interactions
BBs	Esmolol: 500 mcg/kg IV over 1 min	Esmolol: 50–300 mcg/kg/min continuous IV infusion (administer repeat bolus doses between each dose increase)	• AV block • Bradycardia • HF exacerbation (if dose too high or dose ↑ too aggressively) • Hypotension • Cold extremities • Bronchoconstriction • Impotence • Fatigue	• CYP2D6 inhibitors may ↑ concentrations (Bupropion, Fluoxetine, Paroxetine, Quinidine, etc.), • May ↑ lidocaine concentrations
	Propranolol: 1 mg IV over 1 min; may repeat 1 mg IV at 2-min intervals up to three doses	Propranolol (oral): 30–160 mg/day in divided doses		
	Metoprolol: 2.5–5 mg IV over 2 min; may repeat 2.5–5 mg IV every 10 min up to three doses	• Metoprolol tartrate (oral): 25–100 mg twice daily • Metoprolol succinate (oral): 50–400 mg once daily		

Diltiazem	0.25 mg/kg IV over 2 min	• IV: 5–15 mg/hr continuous infusion • Oral: 120–360 mg once daily extended release	• AV block • Bradycardia • HF exacerbation • Hypotension • Peripheral edema	• CYP3A4 inhibitors may ↑ concentrations (Itraconazole, Lopinavir, Ritonavir, Clarithromycin, etc.) • Inhibits CYP3A4: ↑ cyclosporine and statin (Atorvastatin, Lovastatin, Simvastatin) concentrations
Verapamil	0.075–0.15 mg/kg IV over at least 2 min; if necessary, an additional dose of 10 mg IV may be administered 30 min later	• IV: 0.005 mg/kg/min continuous infusion (rarely used) • Oral: 180–480 mg once daily extended release	• AV block • Bradycardia • Constipation (oral) • HF exacerbation • Hypotension • Peripheral edema	• CYP3A4 inhibitors may ↑ concentrations (Voriconazole, Saquinavir, Darunavir, Posaconazole, etc.) • Inhibits P-gp: ↑ digoxin concentrations • Inhibits CYP3A4: ↑ cyclosporine and statin (Atorvastatin, Lovastatin, Simvastatin) concentrations • ↑ dofetilide concentrations by competition for renal tubular secretion

Table 2: Drugs for Ventricular Rate Control: Digoxin and Amiodarone

Drug	Loading Dose	Maintenance Dose	Adverse Effects	Important Drug Interactions
Digoxin	0.25 mg IV every 4 hr up to a maximum, cumulative dose of 1.5 mg over 24 hr	Oral: 0.125–0.25 mg once daily	• Anorexia • Nausea • Ventricular arrhythmias • Vomiting • Bradycardia and tachycardia	• P-gp substrate: ↑ concentrations of Amiodarone, dronedarone and verapamil
Amiodarone	300 mg IV over 1 hr	• IV: 10–50 mg/hr continuous infusion over 24 hr • Oral: 100–200 mg once daily	• AV block • Bradycardia • Blue-gray skin discoloration • Corneal microdeposits • Hepatotoxicity • Hyperthyroidism • Hypotension (IV) • Hypothyroidism • Peripheral neuropathy • Photosensitivity • Pulmonary fibrosis • Phlebitis (with IV route)	• CYP3A4 inhibitors may ↑ concentrations (Ketoconazole, Clarithromycin, Lopinavir, etc.) • Inhibits CYP1A2 - ↑ concentrations (Theophylline, Tizanidine, Propranolol, Lidocaine, etc.) • Inhibits CYP2C9 - ↑ concentrations (Tolbutamide, Glimepiride, Glipizide, etc.)

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			• Hypotension • Bradycardia • QT prolongation • GI upset • Constipation • Increased INR	• Inhibits CYP2D6 - ↑ concentrations (Aripiprazole, Dextromethorphan, Desipramine, etc.) • Inhibits CYP3A4 - ↑ concentrations (Voriconazole, Lopinavir, Ritonavir, etc.) • ↑ warfarin and statin (Atorvastatin, Lovastatin, Simvastatin) concentrations • Inhibits P-gp: ↑ concentrations (Sirolimus, Doxorubicin, Topotecan, Colchicine, Vincristine, etc.) • ↑ digoxin concentrations

References

Deshpande R, Al Khadra Y, et al. 2022. Atrial fibrillation: Rate control or rhythm control? Cleveland Clinic Journal of Medicine, Vol. 89, No. 10. Downloaded from www.ccjm.org on January 26, 2023.

January C, Wann L, Calkins H, et al. (2019) 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients Withwith Atrial Fibrillation. (Journal of the American College of Cardiology, Vol. 74, No. 1, 2019). The American Heart Association, Inc., The American College of Cardiology Foundation, and The Heart Rhythm Society. https://www.sciencedirect.com/science/article/pii/S0735109719302098?via%3Dihub

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. J Am Coll Cardiol 2014; 64:2246–2280

Noel Z, Tisdale J. Arrhythmias. 2021. Cardiology Pharmacy Preparatory Review and Recertification Course - Arrhythmias, and Drug-Induced Cardiovascular Disease and Drugs to Avoid in Cardiovascular Disease - Module 3. American College of Clinical Pharmacy. https://www.accp.com

Van Gelder I, Rienstra M, Crijns H, Olshansky B. 2016 Atrial fibrillation 2 Rate control in atrial fibrillation. Lancet 2016; 388: 818–28. www.thelancet.com

When Does My Patient Qualify for a Left Atrial Appendage Occlusive Device for Atrial Fibrillation?

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Executive Summary

AF is a common heart rhythm disorder caused by degeneration of the electrical impulses in the atria resulting in a change from an organized heart rhythm to that of chaos or an irregular rhythm. Goals in the management of AF include control of ventricular rate, minimization of thromboembolism risk and restoration of sinus rhythm.

Acronyms	
AF	Atrial fibrillation
ASA	Acetylsalicylic acid (i.e., aspirin)
DAPT	Dual antiplatelet therapy
DOAC	Direct oral anticoagulant
FDA	Food and Drug Administration
INR	International normalized ratio
LAA	Left atrial appendage
LAAC	Left atrial appendage closure
LAAO	Left atrial appendage occlusive
OAC	Oral anticoagulant

AF has a formidable risk of thromboembolism and stroke. Patients with AF have five times the risk of stroke compared to their non-AF peers and the risk increases with age. The risk of stroke increases with specific risk factors.

Individual stroke risk stratification is calculated by the CHA2DS2-VASc score:

C – Congestive heart failure
H – Hypertension
A – Age, >74 years old, 2 points
D – Diabetes
S – Stroke, 2 points
V – Vascular disease
A – Age 65 to 74 years old
Sc – Sex Category, 1 point for female sex

Antithrombotic therapy with DOACs and warfarin are mainstays of therapy. These have been discussed in detail in prior articles. The LAA is the primary source for thromboembolism in AF with 90% of left atrial thrombi located in the LAA. In patients not tolerating anticoagulation, it is feasible to consider ligation, amputation or occlusion of the LAA to prevent clots.

The most used LAAO device used in the United States is the WATCHMAN™. It is a small, parachute-shaped device that is implanted in the left atrial appendage of the heart to seal it off. The LAAC procedure is designed to reduce the risk of stroke by preventing blood from pooling in the LAA and creating blood clots. The WATCHMAN device has data with efficacy and a safety profile comparable to that of warfarin.

Key Questions

Q: In what patients and when is it appropriate to consider a LAAO device for prevention of thromboembolic complications?

A: Patients with AF who have an indication for anticoagulation, who have a contraindication to long term anticoagulation.

1. Anticoagulation indication
    a. CHA2DS2-VASc score: Score of >1 in males or >2 in females, anticoagulation is indicated
2. Contraindications to long-term anticoagulation include:
    a. Thrombocytopenia or known coagulation defect associated with bleeding
    b. Recurrent bleeding, including gastrointestinal, genitourinary or respiratory sites
    c. Prior severe bleeding, including intracranial hemorrhage
    d. High risk of the patient falling, with history of falls despite safety measures

e. Poor compliance with or intolerance of anticoagulant therapy
f. Drug interactions: Comorbidities requiring treatment that interacts with oral anticoagulation

Q: Does my patient need additional anticoagulation post-LAAC procedure?

A: Patients receive the WATCHMAN device because they are not tolerating anticoagulation, however, short-term antithrombotic therapy is recommended after device placement.

Multiple anticoagulation regimens have been studied for use after the procedure.

1. Traditional strategy: an oral anticoagulant, either warfarin or a DOAC plus aspirin (81 to 325 mg daily) for 45 days, followed by once-daily clopidogrel (75 mg) plus aspirin (81 to 325 mg) for six months; then once-daily aspirin (81 to 325 mg) alone indefinitely.
    a. Warfarin target INR = 2 to 3
    b. Apixaban or rivaroxaban are the preferred DOACs for use
2. Newer strategy: DAPT (aspirin plus clopidogrel) started immediately after implant then for six months post procedure has been recently approved by the FDA for the WATCHMAN FLX™. Data shows it to be a safe alternate therapy compared to traditional regimen. With the WATCHMAN FLX after six months from implant, aspirin (81-100mg) alone is then used indefinitely.
    a. The WATCHMAN FLX is the newest WATCHMAN model on the market. The WATCHMAN and WATCHMAN FLX have the same intended use but different shaped frames.
    b. Currently WATCHMAN FLX are exclusively placed.

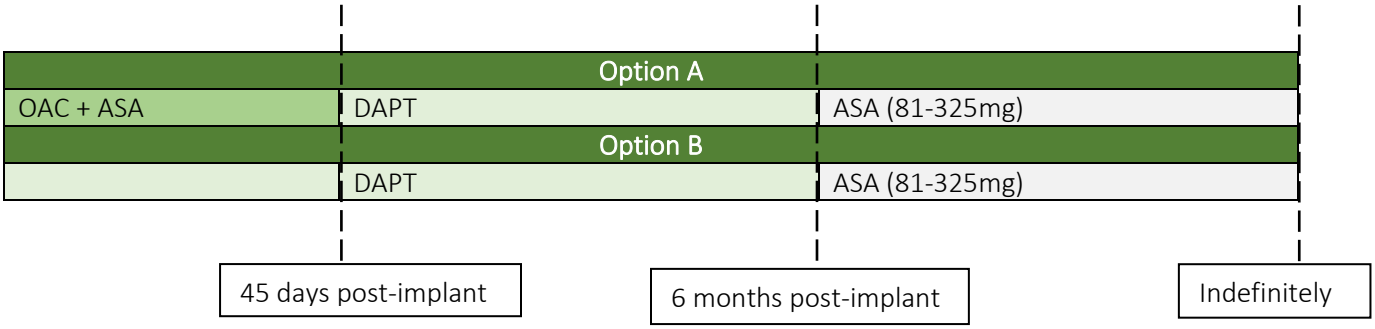

Figure 1: Drug Regimen Options

Q: Can patients have both a WATCHMAN device and long-term anticoagulation?

A: No. Efficacy and safety of a percutaneous LAAO device as an adjunct to long-term oral anticoagulation in patients with AF has not been established. There may be less risk of stroke and other systemic embolic events, but device and procedural risks may offset any benefits.

Q: What is the next step if I suspect my patient would be a good candidate for a WATCHMAN device?

A: Your patient must be referred to a medical center certified to implant LAAO devices; this would include the Avera Heart Hospital. A certified cardiologist is responsible for assessing if the patient is a good candidate for a LAAO device. Boston Scientific has resources and preliminary screening tools available here.

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References

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. J Am Coll Cardiol 2014; 64:2246–2280

Chen S, Weise FK, Chun KRJ, Schmidt B. Antithrombotic strategies after interventional left atrial appendage closure: an update. Expert Rev Cardiovasc Ther. 2018;16(9):675-678. doi:10.1080/14779072.2018.1510316

Atrial fibrillation: Left atrial appendage occlusion. UpToDate. Accessed 2/15/23.

WATCHMAN. Left atrial appendage closure device. Available at: https://www.watchman.com/en-us-hcp/home.html. (Accessed 3/23/23)