

Treatment of Arrhythmias

PHARMACOLOGIC THERAPY FOR CLINICAL ARRHYTHMIAS

Antiarrhythmic Agents

Adenosine

Adenosine is an intravenous (IV) purinergic blocker that inhibits sinus node and atrioventricular (AV) node automaticity and conduction, similar to high parasympathetic activity. Adenosine binds to the adenosine A1 receptor and activates a potassium current in the atrium ($I_{K_{Ado}}$) with clinical transient effects of sinus node slowing, AV node block, and atrial refractory period shortening.

INDICATIONS. Termination of AV node– and sinus node–dependent tachycardias, such as AV node reentry tachycardia (AVNRT), reentrant tachycardias using an accessory pathway and the AV node, and sinus node reentrant tachycardia. Adenosine may also terminate some atrial tachycardias (ATs) and idiopathic ventricular tachycardias (VTs), particularly those that originate from the right ventricular outflow tract.

DOSAGE. Because adenosine has a very short half-life of about 10 seconds, it should be given as a rapid 6-mg IV bolus followed by a bolus of saline. If needed, a 12- to 18-mg IV bolus can be given 1 to 2 minutes later, followed by another 12- to 18-mg IV bolus 1 to 2 minutes after the second dose. Each IV dose should be followed with a rapid saline flush (20cc).

CONTRAINDICATIONS. Avoid in drug-induced tachycardias, wide QRS tachycardias of unknown origin, heart transplant patients (it may cause prolonged asystole), patients taking dipyridamole (it may cause prolonged asystole), and in those in whom severe bronchospasm can be produced. It will be ineffective if the patient is taking theophylline and will be less effective if the patient has just consumed large amounts of caffeine-containing substances.

COMMENTS. Does not terminate AV node–independent tachycardias such as atrial fibrillation (AF), atrial flutter (AFL), and multifocal AT, although the AV block produced can allow the atrial rhythm to be more easily diagnosed. Transient side effects include flushing, chest pain, dyspnea, bronchospasm, brief asystole, bradycardia, and premature ventricular contractions (PVCs). Patients should be forewarned that such marked discomfort may occur, but reassured that the sensation should pass after a few seconds. Transient sinus bradycardia (SB) and PVCs are common after

conversion to sinus rhythm. Large doses can initiate AF. If used to diagnose the presence of AFL, the hypotension resulting from the drug can (rarely) facilitate AV conduction and produce 1:1 AV conduction.

Amiodarone

Amiodarone is a class I, II, III, and IV antiarrhythmic drug with a large volume of distribution, a long loading phase, and a long half-life. As a β -adrenergic blocker, it is noncompetitive.

INDICATIONS. Amiodarone is a complex drug with many potential arrhythmia indications. It is currently the most used antiarrhythmic drug despite the fact that it has only one U.S. Food and Drug Administration (FDA)-approved indication, which is for potentially life-threatening ventricular arrhythmias. It is the most versatile antiarrhythmic drug and can be used for virtually all ATs and VTs. Although it may be FDA approved specifically for potentially life-threatening VTs, amiodarone has not been shown to reduce the risk of death or sudden cardiac death in patients with cardiovascular disease or arrhythmias, although in patients with out-of-hospital cardiac arrest due to refractory VT/ventricular fibrillation (VF), IV amiodarone has been shown to improve survival to hospital admission. Nevertheless, the drug is excellent in reducing episodes of AF and VT. It is important to recognize that IV amiodarone has different electrophysiological effects from oral amiodarone. IV amiodarone loading does not provide the same electrophysiological benefit as oral drug therapy, and for reasons that are not entirely clear, it takes some time for IV amiodarone to be effective even if drug levels are high. IV amiodarone has a greater effect on blocking conduction through the AV node and has less effect on refractoriness. IV amiodarone can cause vasodilation and reflex sympathetic effects. The indications for IV amiodarone include cardiac arrest caused by VF or pulseless VT, VT that is hemodynamically better tolerated and has a monomorphic or polymorphic morphology with normal QT interval (and is not torsades de pointes ventricular tachycardia [TdP VT]), nonsustained VTs that are symptomatic, VTs that cause implantable cardioverter defibrillator (ICD) shocks, and atrial arrhythmias, including AT, AF, and AFL. It is useful for prevention of atrial arrhythmias after sinus rhythm has been restored and for prophylaxis of AF after open heart surgery.

DOSAGE

Intravenous Use. In the setting of a cardiac arrest, the initial IV bolus is 300 mg. Repeat 150- to 300-mg bolus doses can be given as needed up to a total maximum dose of 2.1 g in 24 hours. If there is restoration of sinus rhythm, large doses of IV amiodarone can cause hypotension and bradycardia.

For recurrent or refractory VF or VT, hemodynamically unstable VT, or stable wide QRS complex tachycardia of unknown origin, begin with IV infusion of 150 mg over no less than 10 minutes, followed by an infusion of

1 mg/minute for 6 hours, then a maintenance infusion of 0.5 mg/minute for 18 hours or until the switch to oral amiodarone is made. Additional bolus infusions of 150 mg over no less than 10 minutes can be administered for breakthrough arrhythmias.

For patients with acute-onset AF, such as in the postoperative setting, and for patients who cannot take oral drugs, IV amiodarone may be a quick way to load patients and to help control the ventricular response rate. The half-life of amiodarone given intravenously is less than it is after the patient is fully loaded and is 24 to 48 hours.

For treatment of AFL and AF, IV amiodarone can be used to rapidly obtain clinically effective levels of the drug and to help control the ventricular rate, if not restore the rhythm to normal, but it is important to recognize that IV amiodarone levels do not necessarily provide the same electrophysiological effects as does long-term use of the drug. IV amiodarone slows AV conduction, thus reducing the ventricular rate in AFL and AF. IV amiodarone is used in the setting of perioperative AFL and AF and in conditions in which paroxysmal arrhythmias have rapid rates that are hemodynamically decompensating, such as in hypertrophic cardiomyopathy.

The drug may also help block conduction through accessory pathways and the AV node. IV dosing is much the same as it is for VT, but the speed at which the infusion is given can often be reduced because the rhythm disturbance is usually better tolerated than VTs. As such, there is less risk of hypotension.

Oral Use. Oral dosing for recurrent VF or hemodynamically unstable VT and for prevention of ICD shocks: Loading dose of 800 to 1600 mg per day for 5 to 7 days (occasionally longer) until the arrhythmia is controlled or significant side effects occur. These large doses are preferably initiated in the hospital. The dose should then be reduced to 400 to 800 mg/day for 1 month, followed by the usual maintenance dose of 200 to 400 mg/day. Maintenance doses should be administered once daily (or in divided doses with meals for total daily doses that can be as low as 100 mg/day). Use lowest clinically effective doses because plasma levels do not reflect tissue levels and are therefore not useful. The half-life of oral amiodarone is approximately 40 to 45 days.

Typical oral dosing can be initiated in the hospital at up to 1200 mg/day for 3 to 5 days, with a decrease to 800 mg/day for 1 week, then 600 mg/day for 1 week, then 400 mg/day for several weeks, and finally 100 to 200 mg/day. Alternatively, the drug can be started more slowly in the outpatient setting at 600 or 400 mg/day for 3 to 4 weeks. Amiodarone is unlikely to convert AFL and AF to sinus rhythm acutely and should not be used for this purpose.

CONTRAINDICATIONS. Severe sinus node dysfunction causing marked SB, second-degree or third-degree AV block (AVB), and symptomatic

bradyarrhythmias, unless rate support is provided by a pacemaker. Although the drug is best avoided in patients with interstitial lung disease, it can be used with caution in patients with chronic obstructive pulmonary disease (COPD). Although the incidence of proarrhythmia is low using amiodarone alone, caution should be used if given with other drugs that prolong the QT interval. Avoid this in patients with hepatic dysfunction. Amiodarone is absolutely contraindicated in pregnant women because of neonatal hypothyroidism, prematurity, bradycardia, and congenital abnormalities. Statin dosing may need to be reduced.

COMMENTS. The most common serious side effects of IV amiodarone include hypotension, bradycardia, AV block, TdP VT (<2%), interstitial pulmonary fibrosis, an acute respiratory distress syndrome (ARDS)-like condition if used acutely (2%), and liver toxicity. Thyroid dysfunction and central nervous system (CNS) side effects are not rare.

Side effects of oral amiodarone include hypothyroidism, hyperthyroidism, photosensitivity, blue discoloration of the skin, corneal deposits that can cause halos around lights, liver function abnormalities, nausea, tremor, neuropathy, or difficulty with gait due to neurotoxicity, pulmonary fibrosis, and bradycardia. Although the QT interval can lengthen significantly with oral amiodarone, TdP VT is rare. Optic neuritis has been rarely reported.

When given for high-risk ventricular arrhythmias or poorly controlled atrial arrhythmias, therapy should be initiated in the hospital after withdrawal of other antiarrhythmic drugs. Liver, lung (chest x-ray at minimum and pulmonary function tests with diffusing capacity of the lung for carbon monoxide [DLCO] in selected patients), and thyroid function should be evaluated at baseline and periodically thereafter. Plasma concentrations (normal, 1 to 2.5 mcg/mL) may be helpful in evaluating nonresponsiveness or unexpected severe toxicity but do not reflect tissue levels of the drug. Patients should be monitored closely after dose adjustments because of the drug's long half-life. Amiodarone can increase serum levels of digoxin, quinidine, procainamide flecainide, cyclosporine, and warfarin (prothrombin times must be followed closely, and dosage of warfarin may need to be reduced). Because of increased risk of rhabdomyolysis, concomitant doses of simvastatin greater than 20 mg should be avoided. Phenytoin and cholestyramine can reduce amiodarone levels. Amiodarone generally does not increase myocardial stimulation threshold in patients with pacemakers but will elevate the defibrillation threshold in patients with ICDs. It may also slow VT below the programmed detection interval in patients with ICDs.

Atropine

Atropine is an IV antimuscarinic drug.

INDICATIONS AND DOSAGE. Ventricular asystole, pulseless electrical activity, bradycardia associated with hypotension: 1-mg IV push (may repeat).

Symptomatic SB or intranodal (Mobitz type I) AV block; nausea and vomiting caused by morphine: 0.5 to 1.0mg. This may be repeated up to a total dose of 3mg. Tracheal dose/route: 1 to 2.5mg in 10 to 25cc normal saline.

CONTRAINDICATIONS. Use with caution in acute coronary syndromes (increased heart rate can provoke myocardial ischemia, acute myocardial infarction [MI], and rarely VT or VF). Avoid in patients with cardiac denervation (e.g., transplant patients) and those taking dipyridamole. This can have antimuscarinic effects, including urinary retention in patients with prostate disease. Use caution if there is glaucoma. This can cause constipation and blurred vision.

COMMENTS. Atropine can worsen infranodal (Mobitz type II) second-degree AVB, due to an increase in sinus rate and enhanced AV nodal conduction, resulting in the atrial impulses encountering refractoriness in the His-fascicular system.

β -Adrenergic Blockers

This class of drugs (class II antiarrhythmics) blocks the β -sympathetic nervous system at the receptor level.

ARRHYTHMIC INDICATIONS. β -adrenergic blockers may be used acutely for patients with AFL and AF with a rapid ventricular response rate, although adequate rate control in flutter is not likely to be achieved. β -adrenergic blockers can be used chronically for rate control in AFL and AF and to prevent some recurrences of AF. β -adrenergic blockers can also be used for prevention of catecholamine-related VTs. β -adrenergic blockers reduce the risk of total mortality and sudden cardiac death in patients with underlying coronary artery disease (CAD), especially after MI. β -adrenergic blockers also reduce the risk of death in patients with cardiomyopathy and congestive heart failure (CHF) due to systolic left ventricular dysfunction.

β -adrenergic blockers may also help to prevent recurrences of ATs and other supraventricular tachycardias (SVTs) after conversion to sinus rhythm, although it is uncertain if β -adrenergic blockade alone actually helps to achieve the conversion to sinus rhythm. IV β -adrenergic blockade may also be used for VT and VF storm and for prevention of recurrent catecholaminergic-dependent VT.

The types of β -adrenergic blockers that are useful in treating arrhythmias include metoprolol, esmolol (acutely), carvedilol, and acebutolol. Metoprolol is longer acting than esmolol (half-life of approximately 9 minutes) but is more cardioselective. Propranolol and long-acting propranolol are useful because they cross the blood-brain barrier; they may have greater effects in neurocardiogenic syncope, although β -adrenergic blockade does not appear to be very effective to treat this disorder. Propranolol is no more effective than any other β -adrenergic blocker for any antiarrhythmic effects.

Atenolol is relatively short acting. It is best to use one or two β -adrenergic blockers and become familiar with them. Nadolol has been used particularly for long QT syndrome and some arrhythmias. It has a longer half-life and is a nonselective β blocker. Acebutolol and pindolol have some sympathomimetic effects. Acebutolol appears to be well tolerated in young individuals with palpitations and SVTs.

Acute Use

Indications and Dose. Start oral therapy unless there is a compelling reason to give IV (e.g., ventricular arrhythmias or significant hypertension).

Metoprolol: Begin with 12.5 or 25 mg by mouth (PO) every 12 hours \times 1, 50 mg every 12 hours \times 2, then 100 mg PO every 12 hours, as tolerated. If IV metoprolol is indicated, 2.5 to 5 mg over 1 to 2 minutes, repeated every 5 minutes to a total dose of 15 mg before transitioning to oral therapy. Initial doses can be reduced to 1 to 2 mg if a conservative regimen is desired.

Esmolol may be preferred because of its brief half-life: 0.1 mg/kg per minute (IV) infusion, titrated in increments of 0.05 mg/kg per minute every 5 to 15 minutes (as tolerated by blood pressure [BP]) until the desired therapeutic response is achieved, limiting symptoms develop, or a dose of 0.25 mg/kg per minute is reached. For more rapid onset of action, a loading dose of 0.5 mg/kg can be given IV over 2 to 5 minutes followed by the usual maintenance dose.

For patients with left ventricular ejection fraction (LVEF) less than or equal to 0.40 post-MI, carvedilol (starting dose 3.125 to 6.25 mg twice per day [BID], titrated over 4 to 6 weeks to 25 mg BID as tolerated) is reasonable. For hospitalized patients unable to tolerate β -adrenergic blockers, attempts to reinstitute therapy after 1 to 2 weeks of clinical stability are recommended.

Atenolol is not particularly good for treating arrhythmias because the half-life is relatively short. The dose starts at 25 mg twice a day and goes up to 100 mg twice a day. For atenolol to be used for arrhythmias, it should be given BID.

Contraindications (Relative). Systolic BP less than 90 mm Hg; sinus rate less than 50 bpm; initiation during severe, decompensated heart failure (although patients already receiving these drugs may be continued on them); PR interval greater than 0.24 seconds, or higher degrees of AV block or sinus node dysfunction unless rate support is provided by a permanent pacemaker; history of clinically important bronchospasm. Concurrent use with verapamil or diltiazem can result in severe hypotension, heart failure, or cardiac arrest.

Comments. Monitor heart rate, BP, echocardiogram (ECG); evaluate lungs for rales and wheezing. For mild wheezing or COPD, consider using low doses of a β_1 -selective drug (e.g., metoprolol). Patients with a contraindication to β -adrenergic blockers in the first 24 hours should be reevaluated for candidacy later in the hospital course.

Chronic Use

Indications. Long-term treatment of SVT, AFL, and AF to control the ventricular response rate, VTs to prevent recurrence, and premature ventricular beats if highly symptomatic; inappropriate sinus tachycardia and palpitations if treatment is deemed necessary. It is for any catecholamine-dependent arrhythmia.

Dose. Metoprolol 50 to 200 mg PO every 12 hours. Acebutolol 200 to 800 mg/day. Carvedilol 3.125 to 25 mg BID. Atenolol 50 to 200 mg PO every 12 hours. Propranolol short-acting 40 to 80 mg four times a day or its long-acting equivalent. Nadolol 10 to 80 mg daily (preferable β -blocker for LQTS), although higher doses to 240 to 320 mg have been used for angina or hypertension. Atenolol is generally not recommended for treatment of arrhythmias, but does have cardioselectivity. Atenolol is contraindicated in the pregnant patient. There has been no evidence of risk in humans using acebutolol and pindolol in pregnancy; the chance of fetal harm is felt to be remote with these agents. The use of other β -adrenergic blockers in pregnancy is likely safe, although risk to the fetus cannot be ruled out.

Calcium Antagonists

This class of drugs (class IV antiarrhythmics) can suppress triggered activity, slow or block AV nodal conduction, and slow sinus rates. These include diltiazem and verapamil.

INDICATIONS. Calcium antagonists are used to treat ventricular ectopy and to control rate during SVTs such as AFL, AF, and reentrant SVT (especially those that use the AV node as part of the circuit). Calcium antagonists should not be used with AF that is associated with ventricular preexcitation because AV nodal blockade can facilitate AV conduction over the accessory pathway. IV verapamil is often used in patients with AV node reentry and orthodromic AV reciprocating tachycardias if the arrhythmia recurs after adenosine or if the tachycardia is adenosine unresponsive. IV diltiazem can also be used to control the ventricular rate in AFL and AF.

DOSE. Verapamil 120 to 480 mg/day PO in single or divided doses, depending on the preparation. Diltiazem: Initial IV bolus of 0.25 mg/kg (approximately 20 mg) over 2 minutes. If response is inadequate, a second bolus of 0.35 mg/kg (approximately 25 mg) can be given 15 minutes later. For continued reduction of ventricular rate (up to 24 hours), an IV infusion of 5 to 15 mg/hour can be started immediately after the bolus and titrated to heart rate. Infusion rates of more than 15 mg/hour are not recommended. IV verapamil: Initial IV bolus of 2.5 to 5.0 mg over 1 to 2 minutes (3 minutes in older patients). The peak effect should be seen in 3 to 5 minutes. If required, a second 5- to 10-mg bolus can be given 15 to 30 minutes later; alternatively, 5-mg IV boluses can be given every 15 minutes to a cumulative dose of 30 mg.

To terminate paroxysmal SVT in patients with adequate BP and preserve left ventricle (LV) function in lieu of adenosine or if adenosine terminates SVT only temporarily: Diltiazem or verapamil IV can be given in doses as described previously.

CONTRAINDICATIONS. Diltiazem and verapamil should be used with extreme caution, if at all, with IV β -adrenergic blockers or in patients with heart failure, significant LV dysfunction, or sick sinus syndrome or greater than first-degree AVB without a functioning pacemaker. Neither drug should be used IV to slow the ventricular response to AF or AFL in Wolff-Parkinson-White (WPW) syndrome, due to an increased risk of one-to-one conduction and subsequent VF, or to treat VT (increased risk of fatal hypotension).

COMMENT. The risk to the fetus from the use of most calcium channel blocking drugs has not been excluded.

Digoxin

Digoxin enhances vagal activation of the heart to specifically slow AV nodal conduction and to have a mild effect on the sinus node function.

INDICATIONS. The main use for digoxin is to control the ventricular response rate to AF. It can also be effective in prevention of AV node-dependent SVTs. Furthermore, it can help to control the ventricular response rate to ATs and AFL.

DOSING. Digoxin is available intravenously and orally. Potassium levels should be in the therapeutic range when using digoxin. The loading dose is 1 mg over 24 hours in divided doses. It is not clear that patients need to be loaded unless they have an uncontrolled ventricular response rate to AF. The maintenance dose is usually between 0.125 and 0.25 mg. In patients with renal insufficiency and in older patients, smaller doses are recommended. For patients with renal failure, the dose may have to be much smaller and given only several times a week. Propafenone, verapamil, and amiodarone will increase digoxin levels. The Digitalis Investigation Group (DIG) trial showed that serum levels less than 0.9 ng/mL were associated with lower mortality than higher levels, and so dosing should aim at such lower levels.

COMMENTS. Used separately, in younger active individuals, digoxin is not particularly effective in controlling the ventricular response rate to AF because it is not a direct-acting AV node-blocking drug, but acts through vagal mechanisms. Its main use is in older patients and in the pediatric age range where it can have a more potent effect. The risk is that the toxic-to-therapeutic ratio is higher than for many modern drugs. Alternatively, it has important synergistic effects with β -adrenergic blockers and calcium channel antagonists. The combination of β -adrenergic blockers and digoxin

can be very effective in controlling the ventricular response rate to AF. Digoxin toxicity is often associated with evidence of high-grade AV block in the presence of triggered arrhythmias such as AT (classically with 2:1 AV conduction ratio) or frequent ventricular ectopy. It can cause VT or VF at high levels. Adverse noncardiac effects include anorexia, nausea, vomiting, and change in color perception. Treatment of digoxin toxicity or refractory proarrhythmia may include use of antidigoxin Fab antibody fragments.

Disopyramide

Disopyramide is a class IA antiarrhythmic drug that is similar to procainamide and quinidine but with greater negative inotropic and more anticholinergic effects. It should be used in individuals who are not at risk for urinary retention and should not be used in older men with known prostatic hypertrophy or patients with glaucoma.

INDICATIONS. This drug may be useful in vagally mediated AF. The main use now for disopyramide is AF with or without preexcitation. When used in patients with AF, it should be used with AV nodal blocking drugs, because it is vagolytic and can increase conduction through the AV node. Some early data suggested that it is valuable for neurocardiogenic syncope, but it now appears to be of little use. Disopyramide has been used for its negative inotropic effect in patients with hypertrophic obstructive cardiomyopathy and in neurocardiogenic syncope (with little firm evidence as to effectiveness).

DOSING. The dose is 400 to 600 mg in divided doses. With controlled-release disopyramide formulation, the dose can be given twice daily. Otherwise, it should be given three to four times daily.

COMMENTS. Disopyramide is rarely used due to its adverse effects, including TdP VT (perhaps less likely than quinidine or procainamide), negative inotropic effect, which can trigger CHF, and anticholinergic effects. It is a third-line antiarrhythmic drug but may be useful for vagally mediated AF.

Dofetilide

Dofetilide is a pure class III antiarrhythmic (I_{Kr} blocker).

INDICATIONS. It is used to treat persistent AF. It is also effective for AFL. In some instances, dofetilide will terminate persistent AF and AFL, and in other cases, it will prevent its recurrence. As with amiodarone, dofetilide is useful regardless of ventricular function and does not appear to increase the risk of death when ventricular function is poor or when there has been a recent MI. The drug is perhaps less used because of the complexity of its initiation, which requires hospitalization and a physician who is approved for its use. However, despite the 3-day observation period required to initiate the drug in the hospital, it is one of the most effective antiarrhythmic drugs for AF.

DOSE. Initiate the dose in the hospital in a monitored setting (125 to 500 mcg twice daily). The higher dose is for patients with normal renal function. The initial dose must be adjusted in patients with calculated creatinine clearance (CrCl) of less than 60 mL/minute (250 mcg twice daily if CrCl is 40 to 60 mL/minute or 125 mcg twice daily if CrCl is 20 to 40 mL/minute). Electrocardiographic monitoring must be performed for a minimum of 3 days in the hospital. ECGs must be obtained 2 to 3 hours after giving each of the first five doses of the drug. If the QTc increases more than 15% of baseline or if the QTc is more than 500 ms (550 ms in patients with abnormal ventricular conduction), the dose should be reduced. The patient must be compliant with taking the medications, because missing one or two doses means starting the dosing process over again. Medication must be given by an individual considered qualified to use the drug. The QTc interval should not exceed 500 ms.

CONTRAINDICATIONS. Patients with a long QT interval (QTc >440 ms, or if intraventricular conduction abnormality, >500 ms), severe renal dysfunction (CrCl <20 mL/minute).

COMMENTS. Dofetilide should not be used with verapamil, cimetidine, trimethoprim, and ketoconazole, because these can cause significant increases in dofetilide concentration. Other known renal cation transport system inhibitors, such as prochlorperazine and megestrol, should also not be used with dofetilide. Hydrochlorothiazide has also been shown to increase dofetilide concentrations and should not be used concurrently. Dofetilide is generally well tolerated. It has no negative inotropic effects. It does not facilitate conduction through the AV node. It must be given with adequate maintenance of potassium levels. Adherence to the hospital initiation guidelines appears to reduce the risk of TdP VT.

Dronedarone

Dronedarone is an oral antiarrhythmic drug with an uncertain mechanism of action. It has a formula similar to amiodarone except without the iodine. It appears to be less toxic than amiodarone but it is also less effective as an antiarrhythmic drug.

Dronedarone was given a class I indication to maintain sinus rhythm and to decrease cardiovascular events in patients with paroxysmal AF or after conversion of persistent atrial ablation and to control the ventricular response during AF. It was also given a class III indication; that is, there is no benefit to those patients with NYHA FC IV CHF or those patients who have had recent decompensated heart failure and for those with permanent AF, due to higher mortality with dronedarone observed in these groups in clinical trials.

INDICATIONS. For long-term use, to reduce the risk of hospitalization in patients with AFL or AF and cardiovascular risk factors (age >70 years,

hypertension, diabetes, prior stroke, left atrial diameter >50 mm, or LVEF <40%), who are in sinus rhythm or who will be cardioverted. The drug may not only reduce the incidence of AF but also slow the ventricular response rate.

DOSE. Dosage of 400 mg BID with morning and evening meals. Dronedaronone should be discontinued if the QTc interval increases to 500 ms or more.

CONTRAINDICATIONS. Dronedaronone is contraindicated in patients with New York Heart Association (NYHA) FC IV heart failure or NYHA FC II-III heart failure with recent decompensation requiring hospitalization or referral to a specialized heart failure clinic. Dronedaronone is also contraindicated in second-degree or third-degree AVB or sick sinus syndrome unless rate support is provided by a pacemaker, bradycardia less than 50 bpm, QTc greater than or equal to 500 ms, and severe hepatic dysfunction.

COMMENTS. The drug can increase serum creatinine by about 0.1 mg/dL due to an inhibition of the tubular secretion of creatinine, but with no effect on the glomerular filtration rate; it is thus not nephrotoxic and the effect on serum creatinine is reversible after drug discontinuation. The drug can be initiated in the outpatient setting. The risk of TdP VT is low. It does not have pulmonary toxicity. The most common adverse reactions ($\geq 2\%$) are diarrhea, nausea, abdominal pain, vomiting, and asthenia. Dronedaronone may increase mortality in patients with acute CHF and LVEF of less than 35%. It should not be administered together with strong cytochrome P450 3A (CYP3A) inhibitors (e.g., ketoconazole), grapefruit juice, or other QT-prolonging drugs or herbals. Simvastatin exposure is increased by dronedaronone, and adjustment of statin dose may be necessary. Discontinuation or halving of the dose of digoxin should be considered and concomitant β -adrenergic blockers and calcium channel blockers used with ECG verification of tolerability. Normal potassium and magnesium levels should be maintained. Rare, but potentially severe, liver injury has been reported. Monitoring of liver enzymes would be prudent, especially during the first 6 months of therapy. If heart failure develops or worsens, suspension or discontinuation of dronedaronone should be considered. Higher mortality was reported in one study of patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms. Dronedaronone is a teratogen and is contraindicated in pregnancy or nursing mothers. Women of childbearing potential should use appropriate contraception.

Droxidopa

Droxidopa, L-threo-dihydroxyphenylserine, is a norepinephrine precursor, that has been recently approved in the United States as an "orphan" drug for treatment of symptoms in patients who have neurogenic orthostatic hypotension; that is, symptomatic orthostatic hypotension as a result of a

neurologic deficiency as can occur in multiple-system atrophy, Parkinson disease, and pure autonomic failure. It has been used in dopamine β -hydroxylase deficiency and nondiabetic autonomic neuropathy. It can treat dizziness, lightheadedness, syncope, and falls related to changes in BP.

INDICATIONS. Droxidopa is indicated for neurogenic orthostatic hypotension. Although potentially an off-label use, some have considered using this drug in patients (younger individuals as well) with postural orthostatic tachycardia syndrome and those with a transient orthostatic drop in BP not associated with extreme elevation in heart rate but also not due to an explainable cause.

DOSE. The initial recommended dose is 100 mg PO TID with titration in increments of 100 mg TID every 24 to 48 hours, not to exceed 600 mg TID based on symptoms.

COMMENTS. Droxidopa has been used and approved for short-term use. There have been some long-term follow-up data but because it is not completely certain that the long-term efficacy is as good as the short-term efficacy, patients should be watched carefully for recurrence of symptoms. Droxidopa may cause hypertension and may exacerbate supine hypertension in patients who have severe orthostatic hypotension but have baseline supine hypertension. Droxidopa has not been tested rigorously in patients with underlying ischemic heart disease or structural heart disease with regard to safety. The drug is not been tested in patients with diabetes. For patients who have supine hypertension but have severe orthostatic hypotension, there are no specific drugs that have been used to treat both the hypertension in the supine position in combination with droxidopa, but if an antihypertensive medication is required, an angiotensin-converting enzyme inhibitor may be the best drug to consider.

Epinephrine

Epinephrine is a catecholamine that activates α - and β -receptors.

INDICATIONS. Asystole; pulseless electrical activity; VF or pulseless VT resistant to electrical defibrillation; severe hypotension; anaphylactic shock; symptomatic bradycardia after atropine.

DOSE. Cardiac arrest: 1 mg (10 cc of 1:10,000 solution) IV bolus or 2 mg (diluted in 10 cc normal saline) if given via endotracheal tube. This may be repeated every 3 to 5 minutes. Higher doses (up to 0.2 mg/kg) are not recommended. Each IV bolus should be followed by a saline flush (20 cc). Profound bradycardia or hypotension: 2 to 10 mcg/minute IV infusion.

COMMENTS. Epinephrine can precipitate myocardial ischemia even at low doses, and it may be proarrhythmic. Epinephrine may be inactivated if mixed

in the same solution as bicarbonate. If subcutaneous extravasation occurs, tissue necrosis can develop. Inadvertent overdose can be counteracted by phentolamine. Discontinue if paradoxical worsening of respiratory function occurs in sulfite-allergic patients (epinephrine contains sulfite).

Flecainide

Flecainide is a class IC antiarrhythmic drug.

INDICATION. Most commonly, flecainide is used to treat paroxysmal AF. It is highly effective at suppressing ectopy and an excellent antiarrhythmic drug to use in patients without ischemic heart disease and without structural heart disease. It also has indications for prevention of ventricular ectopy, nonsustained VT, and sustained VT, but only when there is no evidence of structural heart disease.

DOSE. It has been used as a “pill in the pocket,” given acutely to terminate AF or BID given chronically to suppress AF. The dosing is 100 to 300 for “pill in the pocket” and 50 to 200mg BID chronically. Drug levels can be measured and may be useful to determine effects.

COMMENTS. Can be started as an outpatient. Check for QRS widening of more than 20%, because this can be a toxic effect. It should be used with caution if there is evidence of His-Purkinje system disease. It can have noncardiac side effects, such as dizziness, visual disturbances, or headache, but it is generally well tolerated. It can have a negative inotropic effect. It can cause a proarrhythmic effect of sustained monomorphic VT. It can “organize” AF into a slow AFL and allow 1:1 AV conduction. It can increase pacing and defibrillation thresholds, and if initiated in these patients, thresholds should be checked. It should be avoided in patients with CAD or prior MI with LV dysfunction.

Fludrocortisone

Fludrocortisone is a mineralocorticoid that can cause sodium and thus water resorption for patients who have orthostatic hypotension, including neurogenic orthostatic hypotension. It has also been considered useful in some instances of vasovagal syncope and, perhaps, postural orthostatic tachycardia syndrome. The drug has not been rigorously tested for the latter conditions. Nevertheless, because there are few drugs that are effective for these particular conditions, fludrocortisone may be tried when other drugs have not been effective or even as an initial therapy.

INDICATIONS. Orthostatic hypotension not due to fluid depletion (e.g., neurogenic orthostatic hypotension). Fludrocortisone has also been used for postural orthostatic tachycardia syndrome and in patients with recurrent and neurocardiogenic syncope alone and in combination with other medications, such as droxidopa or midodrine.

DOSE. The dose is often initiated 0.1 mg PO per day and has been used in doses up to 0.4 mg per day. If the medication is not effective at these doses, it is not clear that a higher dose would be effective.

COMMENTS. The long-term side effects of fludrocortisone are uncertain. In diabetics, fludrocortisone may increase blood sugar levels. For the most part, the side effects are generally minor, although fluid retention and weight gain are possible. Difficulty sleeping, dizziness or lightheadedness, increased appetite, increased sweating, and nervousness may occur. Hypokalemia is a possibility. Methotrexate may increase the effectiveness of fludrocortisone, whereas phenytoin, barbiturates, estrogens, and rifampin can decrease fludrocortisone's effectiveness. Warfarin dosing may need to be adjusted. Occasionally, low blood sugar may occur.

Ibutilide

Ibutilide is an IV class III antiarrhythmic drug.

INDICATIONS. Ibutilide is used to terminate AF and AFL. It is modestly effective to terminate AF, especially if the episode of AF is relatively short lived. It is effective to treat AFL. Although there is no efficacy advantage over DC cardioversion and there is a potential risk of TdP VT that can be as high as 8% depending on the population to which it is given, ibutilide can be used in patients who require urgent cardioversion who have recently eaten, in contrast to electrical cardioversion. It is also useful in those individuals who prefer not to have an external shock. It can be used in patients with left ventricular dysfunction, although extremely low LVEF (<20%) may increase the risk of proarrhythmia.

DOSE. The dose of ibutilide is 1 mg IV given over 10 minutes. It is given in 0.1-mg aliquots or 1 cc every minute over a period of 10 minutes, observing the QT interval. If the QT interval increases to greater than 500ms, the drug needs to be stopped. When the drug is given, there should be a defibrillator at the bedside. After the drug is given over a 10-minute period, there is a 20-minute waiting period, at which time conversion of the AFL or AF is assessed. If conversion has not occurred, the drug dosing can be repeated, but no more than 2 mg total should be given. Some advocate the use of IV magnesium (1 to 3g) as a prophylaxis against TdP VT before giving ibutilide, but there is some controversy as to whether it is protective; it may also have an effect that counteracts the antiarrhythmic effect of the drug. Nevertheless, IV magnesium sulfate administration makes sense prior to initiation of ibutilide.

COMMENTS. Ibutilide needs to be used with caution in patients with acute heart failure or ongoing myocardial ischemia. It should not be used in patients with a long QT interval. After the dose, the patient needs to be observed for approximately 4 hours before discharge from the hospital

because of the risk of TdP VT, although the risk is greatest immediately after giving the drug. The drug has limited use for treatment of AFL and AF. It may have use also for early or immediate return of AF after DC cardioversion.

Ivabradine

Ivabradine blocks the hyperpolarization-activated cyclic nucleotide-gated channel current (I_f) in the sinus node, which can slow the sinus rate. It shows promise in several small studies for treatment of inappropriate sinus tachycardia (IST), although its approved indication is for heart failure.

INDICATIONS AND DOSAGE. Reduction of the risk of hospitalization for worsening heart failure in patients with stable symptomatic chronic heart failure, LVEF of 35% or less with resting heart rate of 70bpm or greater on maximally tolerated doses of β -adrenergic blockers or who have a contraindication to β -adrenergic blockers. It has been used off-label for IST. Initial dose is 2.5 to 5 mg twice daily, titrating at 2- to 4-week intervals in increments of 2.5mg for heart rate response. The maximum dose is 7.5 mg twice daily. Heart rate should be monitored, including with dose adjustments.

COMMENTS. Ivabradine can cause bradycardia, GI side effects, headache, or dizziness. It can also cause phosphenes, which are luminous visual phenomena thought to be mediated through effects on retinal photoreceptors. Ivabradine may cause bradycardia, including conduction disturbances. Contraindications include a resting heart rate less than 60bpm prior to treatment, severe hepatic impairment, sinus node dysfunction, sinoatrial block, second- or third-degree AV block unless a pacemaker is present, acute decompensated heart failure, and hypotension. CYP3A4 inhibitors increase and inducers decrease ivabradine concentrations. Concomitant use with strong CYP3A4 inhibitors (e.g., azole antifungals, macrolide antibiotics, HIV protease inhibitors, and nefazodone) are contraindicated. Concomitant use with moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, grapefruit juice) should be avoided. Females should use effective contraception due to fetal toxicity.

Lidocaine

Lidocaine is a class IB IV antiarrhythmic drug that slows phase 0 of the action potential in the ventricles but does not lengthen refractoriness. More potent effects exist in ischemic myocardium, although it has not been shown to improve mortality after MI. The drug is metabolized by the liver.

INDICATIONS AND DOSE. Used to treat and suppress VF or pulseless VT resistant to defibrillation and epinephrine, hemodynamically stable VT, and hemodynamically unstable PVCs (e.g., nonperfusing PVCs occurring frequently or in bigeminy). Normal LV function and no hepatic impairment: loading dose of 75 to 100 mg IV (1 to 1.5 mg/kg) followed by 50 mg IV

(0.5 to 0.75 mg/kg) in 5 to 10 minutes (up to a total dose of 3 mg/kg). For VF or pulseless VT (after defibrillation), may give repeat 0.5- to 0.75-mg doses every 5 to 10 minutes after the initial dose for a maximum of 3 doses. Give a maintenance infusion of 1 to 4 mg/minute. Dosage should be reduced in older patients, CHF, shock, or hepatic disease, including congestive hepatopathy. For moderate decrease in LV function, give a loading dose of 75 mg IV followed by one 50-mg IV after 5 minutes (total dose 125 mg); maintenance infusion of 1 mg/minute.

Severe decrease in LV function or significant hepatic impairment: one loading dose of 50 to 75 mg IV; maintenance infusion of 0.5 mg/minute. A single IV bolus of 1.5 mg/kg is acceptable for cardiac arrest. Tracheal administration is 2 to 4 mg/kg.

COMMENTS. Monitor for lidocaine toxicity: confusion, acute psychosis, drowsiness, respiratory depression, perioral numbness, and seizures. It may cause bradycardia due to sinus arrest or AV block. Do not give for ventricular escape beats or escape rhythms (increased risk of asystole). Use in pregnancy appears to be safe. Lidocaine levels should be monitored 4 to 6 hours after the boluses and at least daily while on the drug.

Magnesium Sulfate

Magnesium sulfate may block triggered activity that can lead to TdP VT.

INDICATIONS AND DOSE. Cardiac arrest due to TdP VT: 2 to 5 g IV push over 1 to 2 minutes in 10cc D₅W. TdP VT without cardiac arrest: 1 to 2 g in 50 to 100cc D₅W IV over 5 to 60 minutes. Consider an additional 2 g IV over the next several hours. Regimens vary.

Follow for reduction in QT interval and reduction in amplitude of the U wave as part of the therapeutic effect. It can be given without measuring magnesium levels, because they do not reflect total body magnesium stores.

COMMENTS. Magnesium is a coronary vasodilator, has antiplatelet and antiarrhythmic effects, and can prevent calcium overload of reperfused myocytes. Magnesium may be of benefit for refractory VT after lidocaine and amiodarone and for life-threatening ventricular arrhythmias caused by digitalis toxicity. It is not routinely recommended for acute MI unless magnesium deficiency is documented.

Mexiletine

Mexiletine is an oral class IB antiarrhythmic drug.

INDICATION. Mexiletine can suppress VT and ventricular ectopy. Mexiletine is indicated for symptomatic ventricular arrhythmias, although success in VT is relatively low. Generally, it is considered for use if a patient has multiple ICD shocks and appears to respond to lidocaine. It may be particularly useful in patients with LQT3 syndrome.

DOSE. 150 to 300 mg three times a day. Some side effects (e.g., gastrointestinal [GI]) may be minimized if given with meals. In the absence of an ICD, initiation in the hospital is recommended.

COMMENTS. Does not appear to increase the risk of TdP VT, but there are other potential side effects, including ataxia, dizziness, tremor, slurred speech, abdominal discomfort, anorexia, nausea, vomiting, and diarrhea. There is a risk of proarrhythmia as well as CHF, hypotension, and bradycardia. It does not cause TdP VT or affect atrial arrhythmias. Mexiletine has been used in the past in combination with quinidine, and the combination was considered relatively potent; however, there are possible proarrhythmia and side effects associated with this combination. It is now used in combination with amiodarone if amiodarone alone is ineffective in suppressing recurrent VT in patients who have ICDs. It has little effect on the sinus node, AV node, or His-Purkinje system. It does not affect atrial refractoriness. It can increase defibrillation thresholds but does not markedly slow VTs.

Midodrine

Midodrine is prodrug of desglymidodrine that is an α_1 adrenergic receptor stimulant (agonist) that has been used to treat hypotension, and in particular, orthostatic hypotension. Its effect is on venous and arteriolar vascular tone. It does not cross the blood-brain barrier well. Standing BP is elevated approximately 15 to 30 mmHg 1 hour after a 10-mg dose.

INDICATIONS. While midodrine is indicated to treat symptomatic orthostatic hypotension, the drug is also been used to treat patients who have neurocardiogenic syncope and postural orthostatic tachycardia syndrome.

DOSE. The usual dose of midodrine is 2.5 mg three times a day with increments to 10 mg PO four times per day.

COMMENTS. Midodrine can cause a sensation of “gooseflesh” and can cause hypertension. It would not make sense to use midodrine with an antihypertensive medication. The drug has a relatively short half-life of about 3 to 4 hours. Midodrine can potentially cause severe supine hypertension. It can potentially cause urinary retention by affecting the α -adrenergic receptors of the bladder neck. Midodrine should be used with caution in diabetic patients and in those people taking fludrocortisone, because it is known to increase intraocular pressure and potentially cause glaucoma. When used concomitantly with digoxin, it may precipitate bradycardia or AV block. α -Adrenergic blocking drugs, such as terazosin, can antagonize the effects of midodrine.

Procainamide

Procainamide is a class IA antiarrhythmic drug with active metabolites, including N-acetyl-procainamide, which is a class III antiarrhythmic drug.

The drug lengthens refractoriness, lengthens the QT interval, and slows atrial and ventricular conduction. The drug is metabolized in the liver and excreted by the kidneys.

INDICATIONS AND DOSE. For refractory VF or VT, especially if ischemic, 100-mg IV bolus doses repeated every 5 minutes. A loading dose of 10 to 15 mg/kg can be given up to 50 mg/minute IV with reduction of the rate of infusion if hypotension results. Procainamide may also be effective for treatment of AFL and AF acutely and chronically. For other indications (stable wide QRS complex tachycardia, reentrant SVT resistant to adenosine and vagal maneuvers, and rate control of AF in the WPW syndrome due to block in the accessory pathway), treatment of AF: 20 to 50 mg/minute IV infusion until the arrhythmia is suppressed, hypotension develops, QRS widens by 50%, or a total dose of 15 mg/kg is given, followed by an IV maintenance infusion of 1 to 4 mg/minute. Oral dosing is 500 to 1000 mg four times daily (but it is not readily available in this form anymore).

CONTRAINDICATIONS. Avoid in patients with a prolonged QT interval or TdP VT. Use with caution in conjunction with other drugs that prolong the QT interval. Do not use in patients with CrCl of less than 20 mL/minute.

COMMENTS. Can induce TdP VT, especially in patients with renal insufficiency, hypokalemia, or hypomagnesemia. For patients with heart failure or renal insufficiency, the loading dose should be reduced to 10 to 12 mg/kg, and the maintenance dose reduced to 1 to 2 mg/minute. BP and ECG should be monitored continuously during IV administration, because sharp drops in BP can occur with rapid infusion, especially in patients with LV dysfunction. Follow blood levels and renal function of procainamide and N-acetylprocainamide in renal failure and during prolonged IV use. Procainamide has been associated with a lupus-like syndrome and has several other important, although rare, side effects, including CNS effects and agranulocytosis. Procainamide can cause SB or sinus arrest in patients with sick sinus syndrome. Procainamide can cause AV block in patients with conduction system disease, including intraventricular conduction delays. Procainamide should probably not be used in pregnancy.

Its use has been superseded in most cases by IV amiodarone. The long-acting oral drug is no longer on the market.

Propafenone

Propafenone is a class IC antiarrhythmic drug that possesses some mild β -blocking properties.

INDICATION. It is mainly used to suppress or terminate paroxysmal AF. Although it may suppress ventricular ectopy, it is potentially proarrhythmic and should not be used when there is ventricular dysfunction or CAD.

It may be used to suppress some VTs, such as nonsustained idiopathic VT. It is not particularly useful for AFL, because it slows the rate of AFL and allows for 1:1 AV conduction.

DOSE. The dosage is 150 to 300 mg three times a day, although there is a long-acting form that allows twice-a-day dosing.

COMMENT. Propafenone has been used as the “pill in the pocket” technique to suppress or terminate AF after its onset. The dose is 150 to 450 mg at one time. The drug is similar to flecainide, although the metabolism is more complex. Seven percent are slow metabolizers and exhibit significant β -blocking activity. Proarrhythmia is about the same as it is for flecainide. Check for QRS widening of more than 20%, because this can be a toxic effect. The drug can be started as an outpatient. It should be used with caution if there is evidence for His-Purkinje system disease. It can have some noncardiac side effects, such as metallic taste, neutropenia, and other vague, nonspecific symptoms such as nausea, vomiting, constipation, and dizziness. It is generally well tolerated. It can have a negative inotropic effect. It can cause a proarrhythmic effect of sustained monomorphic VT as well as organization of AF to slow AFL with 1:1 AV conduction. It can increase pacing thresholds, although generally not to a clinically relevant degree.

Pyridostigmine

Pyridostigmine is an acetylcholinesterase inhibitor that can treat myasthenia gravis by increasing acetylcholine at the postsynaptic motor endplate. It can also affect ganglionic neurotransmission and enhance sympathetic activation in the standing position. It may thus improve orthostatic hypotension but not affect supine hypertension to the same extent as midodrine or droxidopa. It has been used off label for the treatment of postural orthostatic tachycardia syndrome. The drug has also been effective in combination with other therapies for the same problem.

INDICATIONS. Although pyridostigmine may be used for myasthenia gravis, it may improve orthostatic hypotension. It has been used in combination with midodrine and fludrocortisone to treat patients with orthostatic hypotension and postural orthostatic tachycardia syndrome. These indications are off label.

DOSE. For orthostatic hypotension and postural orthostatic tachycardia syndrome, low-dose therapy is generally recommended at a dose of 60 mg PO twice a day.

COMMENTS. Common side effects include GI side effects, such as diarrhea and abdominal cramping. The effects of pyridostigmine may be reduced when using quinidine.

Quinidine

Quinidine is a class IA antiarrhythmic drug with electrophysiological effects similar to procainamide. Quinidine is more vagolytic than procainamide.

INDICATIONS. Quinidine is an old, yet versatile, multipurpose antiarrhythmic drug with class IA antiarrhythmic properties. It can suppress atrial and ventricular ectopy, nonsustained AT and VT, AF and AFL, sustained VT, and accessory pathway conduction in the WPW syndrome. It is less effective than more modern antiarrhythmic drugs, and there are substantial side effects. The drug is rarely used now due to the increased risk of toxicity, GI side effects, and proarrhythmia (TdP VT); thus, it is considered a third-line antiarrhythmic drug.

Potential side effects of quinidine include thrombocytopenia, diarrhea, anticholinergic effects, and most importantly, TdP VT.

DOSE. The oral dosing of quinidine sulfate is 200 to 400 mg four times a day but it is rarely used anymore. There are long-acting (slow absorbing) preparations that can be given every 8 hours or even every 12 hours. IV quinidine can produce marked hypotension and is rarely used anymore. The dose is up to 1 g IV.

COMMENTS. Quinidine increases digoxin levels. Hypotension during IV use is due to an α -adrenergic blocking effect. Quinidine can also cause cinchonism, psychosis, depression, and agranulocytosis. Quinidine lengthens the QT interval. Prolongation of the QT interval on quinidine is associated with TdP VT. Quinidine can increase the ventricular response rate to AF. It should be started in the hospital. Because quinidine can block Ito current, it may have some use in the Brugada syndrome and in individuals with idiopathic VF.

Sotalol

Sotalol is a class III and class II antiarrhythmic drug. There are two stereoisomers to make the racemic mixture of D, L-sotalol. The L stereoisomer is a β -adrenergic blocker that is not selective and water soluble, and the D stereoisomer has class III properties.

INDICATIONS. To treat persistent and paroxysmal AF with or without the presence of structural heart disease. Sotalol is a versatile antiarrhythmic drug and can also be used to suppress nonsustained VT in patients with idiopathic VT; sustained VT in patients with structural heart disease, including arrhythmogenic right ventricular cardiomyopathy; VT; and VF in patients in whom ICDs are implanted but who have relatively intact ventricular function.

DOSE. Although the starting dose is 80 mg BID, at this low dose, the drug mainly has a β -blocking effect. The recommended starting dose is

120mg twice a day. For most, if not all, patients, in the absence of an ICD, especially for patients with structural heart disease, for older women, for patients with mild renal insufficiency, and for patients in AF, it is advisable to start sotalol in the hospital and observe until a steady state is achieved. The QTc interval should be less than 500 ms.

COMMENTS. To achieve the class III antiarrhythmic effect, the dose must be at least 120mg BID for patients with normal renal function. Caution is advised for mild renal insufficiency, and use of the drug should be avoided in patients with moderate renal insufficiency. Care must be taken for patients with poor ventricular function. As a rule, sotalol should be given to patients with an LVEF of 30% or more and/or NYHA FC I and II. Sotalol should be avoided in patients with acute hemodynamic decompensation or impaired baseline hemodynamic state. Sotalol can have a potent effect on the sinus node and can exacerbate sinus node dysfunction. It can encourage serious bradycardia in select individuals. There are no active metabolites or serious interactions with other drugs. Sotalol does not increase the pacing threshold, and it may decrease the defibrillation threshold. When using sotalol, TdP VT risk is greatest at doses of greater than 320 mg BID.

Vernakalant

Vernakalant is a novel I_{KUR} blocker.

INDICATIONS. Vernakalant is a new IV and oral antiarrhythmic drug that is an I_{KUR} blocker. It is used to terminate AF acutely and perhaps prevent its return. The advantage of this drug given intravenously is that it may have a lower risk of causing TdP VT than ibutilide or procainamide. Ultimately, after IV use of the drug to terminate AF, it may be continued orally, but the drug has not yet been approved for use.

DOSE. Oral doses tested include 150-, 300-, or 500-mg doses twice a day. The IV dose is 2 to 5 mg/kg.

CONTRAINDICATIONS. These are uncertain.

COMMENTS. Vernakalant may be more effective and safe than ibutilide to terminate AF, but this is not yet clear. It is also not yet clear that TdP VT will not occur with this drug.

Further Comments About Antiarrhythmic Drugs

The concept of proarrhythmia has developed over the years, because it has been shown that antiarrhythmic drugs can not only suppress arrhythmias, but under certain conditions, can actually increase the risk of specific arrhythmias and may even increase the risk of sudden cardiac death. There are various forms of proarrhythmic reactions, and these can include an increased number of premature atrial or ventricular depolarizations,

an increase in the ventricular response rate in AF or AFL, a slowing in tachycardia rate that can make it undetectable as an arrhythmia to be terminated by an implanted cardioverter defibrillator, an increased risk of a monomorphic VT, conversion of a nonsustained tachycardia into a sustained tachycardia, and increased risk of polymorphic VT or TdP VT. In some instances, a drug may have antiarrhythmic and proarrhythmic effects. Patients who are acutely ill, have acute exacerbations of heart failure, have recent ischemia or MI, or are older with renal and liver dysfunction are at greatest risk for developing proarrhythmic effects.

Several drugs have recently been removed from the U.S. market. These include tocainide, bretylium, some forms of long-acting procainamide, and moricizine.

ORAL ANTICOAGULANTS

For patients with AF/AFL who are at risk for thromboembolic complications, including stroke, chronic anticoagulation is often recommended (see [Chapter 5](#)).

Warfarin

Warfarin is a vitamin K antagonist and inhibits synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) and proteins C and S.

Indications

Prophylaxis and treatment of thromboembolic disorders and complications (e.g., from AF, valve replacement, LV thrombus, prolonged immobilization, low cardiac output).

Dosage

Initial dose of 2 to 10 mg PO daily for 2 to 4 days, then titrated to maintain the prothrombin time/international normalized ratio (PT/INR) target (for AF 2.0 to 3.0). Dosage should be individualized.

PRIOR TO INVASIVE OR SURGICAL PROCEDURES REQUIRING HOLDING OF ANTICOAGULANTS.

Warfarin is typically held 4 to 5 days before the procedure with need for bridging dependent upon the risk of thromboembolism versus bleeding. Warfarin can often be started 12 to 24 hours, again depending upon these risks.

Contraindications

Active bleeding; when risk of bleeding exceeds the benefit of anticoagulation; pregnancy; surgery of the CNS or eye; malignant hypertension; lack of patient cooperation. Use with caution in renal or hepatic dysfunction.

Reversal

Warfarin's anticoagulant effects can be reversed by vitamin K, fresh whole blood, fresh frozen plasma (200 to 2000 mL), or prothrombin complex concentrates (PCC).