8 – Antiarrhythmic drugs and strategies

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> *"Devices and radiofrequency ablation have revolutionized the therapy of life-threatening and highly symptomatic arrhythmias."*
>
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Overview of new developments

There have been several major trends since the last edition of this book: (1) The persistent imperfections of current antiarrhythmic drugs and rapidly expanding technologies have led to a continued explosion in the use of devices and ablative techniques for both supraventricular and ventricular arrhythmias. (2) Atrial fibrillation (AF) has become a very active focus of research, with the recognition that with our aging population it is now a major health hazard, yet with persisting problems in management such as the continuing controversy regarding rate versus rhythm control with an ever increasing trend toward intervention by ablation. (3) There has been increasing interest in the use of so-called upstream therapy in arrhythmia management, particularly AF. Upstream therapy involves the targeting of processes leading to the development of the arrhythmia substrate, with the hope of preventing initial arrhythmia occurrence (primary prevention) or reducing the likelihood of arrhythmia recurrence after initial presentation (secondary prevention). (4) Stroke is recognized as the principal clinically significant complication of AF and the introduction of new antithrombotic agents, so that stroke prevention has become one of the primary considerations in the science of AF management. (5) Important gender differences in cardiac electrophysiology exist. Compared with men, women have higher resting heart rates and longer QT intervals with greater risk of drug-induced torsades de pointes. Women with AF are at a higher risk of stroke, and they are less likely to receive anticoagulation and ablation procedures. Women have a better response to cardiac resynchronization therapy (CRT) in terms of reduced numbers of hospitalizations and more robust reverse ventricular remodeling. Further studies are required to elucidate the underlying pathophysiologic characteristics of these sex differences in cardiac arrhythmias.[1]

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Antiarrhythmic drugs

Antiarrhythmic drugs are used either to alleviate significant symptoms or to prolong survival. The wisdom of treating arrhythmias “prophylactically” has been severely questioned by a large trial (Cardiac Arrhythmia Suppression Trial)[2] and by a metaanalysis of nearly 100,000 patients with acute myocardial infarction (AMI) treated with antiarrhythmic drugs.[3] These studies stress that arrhythmias should be treated with antiarrhythmic drugs only when their power to prevent hard negative outcomes outweighs the adverse effect potential, which appears to be the case for only a few drugs and indications such as β-blockers following myocardial infarction (MI).[4] Interestingly, evidence for sudden-death prevention in ischemic heart disease and heart failure has been obtained for drugs like aldosterone antagonists, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, statins, and omega-3 fatty acids,[4] whereas most antiarrhythmic agents have not demonstrated such properties. These observations reinforce the notion that lethal arrhythmias are not simply an “electrical accident” and that effective therapy must target upstream causes.[5] The only antiarrhythmic agent that does appear to prevent sudden cardiac death (SCD) is amiodarone,[6] a drug acting on multiple ionic channels, which is effective against a wide spectrum of arrhythmias. However, even amiodarone is inferior to implantable cardioverter defibrillators (ICDs) for sudden-death prevention in the patients at highest risk.[7]

Classification.

There are four established classes of antiarrhythmic action (Table 8-1). The original Vaughan Williams classification with four classes now incorporates ionic mechanisms and receptors as the basis of the more complex Sicilian Gambit system for antiarrhythmic drug classification (Fig. 8-1).[8] Another descriptive division is into those drugs used only in the therapy of supraventricular tachycardias (VTs; Table 8-2) and those used chiefly against VTs (Table 8-3).

Table 8-1 -- Antiarrhythmic Drug Classes

Class	Channel Effects	Repolarization Time	Drug Examples
1A	Sodium blockEffect + +	Prolongs	QuinidineDisopyramide Procainamide
1B	Sodium blockEffect +	Shortens	LidocainePhenytoin Mexiletine Tocainide
1C	Sodium blockEffect + + +	Unchanged	FlecainidePropafenone
II	I_f, a pacemaker and depolarizing current; indirect Ca^{2+} channel block	Unchanged	β-blockers (excluding sotalol that also has class III effects)
III	Repolarizing K^+ currents	Markedly prolongs	AmiodaroneSotalol Ibutilide Dofetilide
IV	AV nodal Ca^{2+} block	Unchanged	VerapamilDiltiazem
IV-like	K^+ channel opener (hyperpolarization)	Unchanged	Adenosine

AV, Atrioventricular.

+ = inhibitory effect; + + = markedly inhibitory effect; + + + = major inhibitory effect.

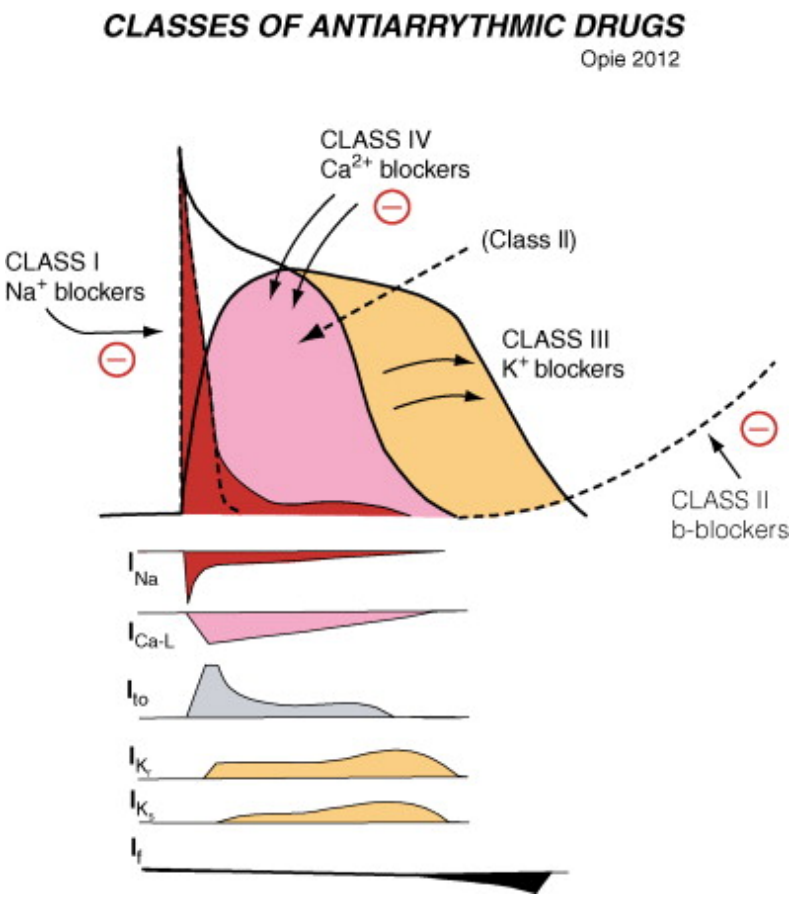

Figure 8-1 The classical four types of antiarrhythmic agents. Class I agents decrease phase zero of the rapid depolarization of the action potential (rapid sodium channel). Class II agents, β-blocking drugs, have complex actions including inhibition of spontaneous depolarization (phase 4) and indirect closure of calcium channels, which are less likely to be in the "open" state when not phosphorylated by cyclic adenosine monophosphate. Class III agents block the outward potassium channels to prolong the action potential duration and hence refractoriness. Class IV agents, verapamil and diltiazem, and the indirect calcium antagonist, adenosine, all inhibit the inward calcium channel, which is most prominent in nodal tissue, particularly the atrioventricular node. Most antiarrhythmic drugs have more than one action. In the *lower panel* are shown the major currents on which antiarrhythmics act, according to the Sicilian gambit. *Ca-L,* long-lasting calcium; *I,* current; If, inward funny current; *Kr*, rapid component of repolarizing potassium current; *Ks*, slow component; *Na,* sodium; *to*, transient outward.
(Figure © L.H. Opie, 2012.)

Table 8-2 -- Antiarrhythmic Drugs Used Only in Therapy of Supraventricular Arrhythmias

Agent	Dose	Pharmacokinetics and Metabolism	Side Effects and Contraindications	Interactions and Precautions
Adenosine (class IV-like)	For paroxysmal SVT, initial dose 6 mg by rapid IV. If the dose is ineffective within 1 to 2 minutes, 12 mg may be given and if necessary, 12 mg after a further 1 to 2 minutes. A dose of 0.0375 to 0.25 mg/kg body weight is reported to be effective in children.	T½ = 10-30 seconds. Rapidly taken by active transport system into erythrocytes and vascular endothelial cells (major route of elimination) where it is metabolized to inosine and adenosine monophosphate.	Usually transient and include nausea, light-headedness, headache, flushing, provocation of chest pain, sinus or AV nodal inhibition, bradycardia, and with large dose infusion rare side effects hypotension, tachycardia, bronchospasm.Contraindication in asthmatic, second- or third-degree AV block, sick sinus syndrome.	Caution: In atrial flutter, adenosine may precipitate 1:1 conduction. Dipyridamole inhibits the breakdown of adenosine; therefore dose of adenosine should be reduced.Methylxanthines (caffeine, theophylline) antagonize the interaction of adenosine with its receptors.

Esmolol (class II)	IV 500 mcg/min loading dose over 1 minute before each titration/maintenance step. Use steps of 50, 100, 150, and 200 mcg/min over 4 minutes each, stopping at the desired therapeutic effect.	T½ = 9 minutes. Following an initial bolus and infusion, onset of action occurs within 2 minutes and a 90% steady-state level is reached within 5 minutes. Following discontinuation full recovery from β-blockade properties occur at 18-30 minutes. Esmolol metabolized in red blood cells without renal or hepatic metabolism.	Hypotension, peripheral ischemia, confusion, thrombophlebitis and skin necrosis from extravasation, bradycardia, bronchospasm.Contraindicated in severe bradycardia heart block (>1 degree), cardiogenic shock, and overt heart failure.	Interactions with warfarin and catecholamine-depleting drugs. Can increase digoxin blood levels and prolong the action of succinylcholine.
Verapamil (class IV)	5-10 mg by slow IV push (over 2-3 minutes), which can be repeated with 10 mg in 10-15 minutes if tolerated. In US a second dose of 10 mg given after 10 minutes if required.Oral dose: 120-480 mg daily in three to four divided doses.	T½ 2-8 hours after an oral dose or after IV administration. After repeated oral doses this increases to 4.5-12 hours. Verapamil acts within 5 minutes of IV administration and 1-2 hours after oral administration with a peak plasma level after 1-2 hours. Approximately 90% absorbed from the GI tract with intersubject variation and considerable first-pass metabolism in the liver. The bioavailability is only approximately 20%.	Contraindicated in hypotension, cardiogenic shock, marked bradycardia, second or third degree block, WPW syndrome, wide-complex tachycardia, VT and uncompensated heart failure. Also in sick sinus syndrome without a pacemaker.	Decreased serum concentrations of phenobarbital, phenytoin, sulfinpyrazone, and rifampin. Increased serum concentrations of digoxin, quinidine, carbamazepine, and cyclosporin. Increased toxicity with rifampin and cimetidine.Dose reduced if liver function is impaired.
Diltiazem (class IV)	Initial dose 0.25 mg/kg over 2 min, ECG, BP monitoring. Further dose of 0.35 mg/kg after 15 min if required.For AF or flutter, initial infusion of 5-10 mg/h, may increase by 5 mg/h	T½ = 3-5 hours (longer in older adults). After absorption diltiazem extensively metabolized by cytochrome P450 with bioavailability	AV block, bradycardia, and rarely asystole or sinus arrest.C/I in sick sinus syndrome, preexisting second or third degree heart block, wide QRS tachycardia, marked bradycardia, or LV failure.	Risk of bradycardia, AV block with amiodarone, β-blockers, digoxin and mefloquine.Blood diltiazem may ↑ with cimetidine and ↓ with inducers: barbiturates, phenytoin, and rifampin. Reduce doses of

	up to 15 mg/h, up to 24 h.	of approximately 40% with considerable interindividual variation. 80% bound to plasma protein. No effect of renal or hepatic dysfunction on plasma concentration of diltiazem.		carbamazepine, cyclosporine. Digoxin level variable, may ↑, watch AV node.
Ibutilide (class III)	IV infusion: 1 mg over 10 min, (under 60 kg: 0.1 mg/kg).If needed, repeat after 10 min.	Initial distribution T½ is 1.5 minutes. Elimination T½ averages 6 h (range 2-12 h).Efficacy is usually within 40 min.	Nausea, headache, hypotension, bundle branch block, AV nodal block, bradycardia, torsades de pointes, sustained monomorphic VT, tachycardia, ventricular extrasystoles.Avoid concurrent therapy with class I or III agents. Care with amiodarone or sotalol. C/I: previous torsades de pointes, decompensated heart failure.	Interactions with Class IA and other Class III antiarrhythmic drugs that prolong the QT interval (e.g., antipsychotics, antidepressants, macrolide antibiotics, and some antihistamines). Check QT (see Fig. 8-4).Correct hypokalemia and hypomagnesemia.
Dofetilide (class III)	Dose 250 mcg twice daily, maximum 500 mcg twice daily if normal renal and cardiac function. If LV dysfunction, 250 mcg twice daily. Check QT 2-3 h after dose, if QTc is >15% or >500 msec, reduce dose. If QTc >500 msec, stop.	Oral peak plasma concentration in 2.5 hours and a steady state within 48 h. 50% excreted by kidneys unchanged.	Torsades de pointes in 3% of patients which can be reduced by ensuring normal serum K, avoiding dofetilide or reducing the dose if abnormal renal function, bradycardia, or base-line QT↑. Avoid with other drugs increasing QT. C/I: previous torsades, creatinine clearance <20 mL/min.	Increased blood levels with ketoconazole, verapamil, cimetidine, or inhibitors of cytochrome CYP3 A4, including macrolide antibiotics, protease inhibitors such as ritonavir. Other precautions as previously.

AF, Atrial fibrillation; *AV,* atrioventricular; *BP,* blood pressure; *C/I,* contraindication; *ECG,* electrocardiogram; *GI,* gastrointestinal; *IV,* intravenous; *LV,* left ventricular; *SVT,* supraventricular tachycardia; *T½,* plasma half-life; *VT,* ventricular tachycardia; *WPW,* Wolff-Parkinson-White.

Table 8-3 -- Antiarrhythmic Drugs Used in Therapy of Ventricular Arrhythmias

Agent	Dose	Pharmacokinetics and Metabolism	Side Effects and Contraindications	Interactions and Precautions
Lidocaine (class 1B)	IV 75-200 mg; then 2-4 mg/min for 24-30 h. (No oral use)	Effect of single bolus lasts only few min, then T½ approximately 2 h. Rapid hepatic metabolism. Level 1.4-5 mcg/mL; toxic > 9 mcg/mL.	Reduce dose by half if liver blood flow low (shock, β-blockade, cirrhosis, cimetidine, severe heart failure). High-dose CNS effects.	β-blockers decrease hepatic blood flow and increase blood levels.Cimetidine (decreased hepatic metabolism of lidocaine).

Mexiletine (class IB)	*IV 100-250 mg at 12.5 mg/min, then 2 mg/kg/h for 3.5 h, then 0.5 mg/kg/h.Oral 100-400 mg 8-hourly; loading dose 400 mg.	T½ 10-17 h. Level 1-2 mcg/mL.Hepatic metabolism, inactive metabolites.	CNS, GI side effects. Bradycardia, hypotension especially during co-therapy.	Enzyme inducers; disopyramide and β-blockade; increases the theophylline levels.
Phenytoin (class IB)	IV 10-15 mg/kg over 1 h.Oral 1 g; 500 mg for 2 days; then 400-600 mg daily.	T½ 24 h. Level 10-18 mcg/mL.Hepatic metabolism. Hepatic or renal disease requires reduced doses.	Hypotension, vertigo, dysarthria, lethargy, gingivitis, macrocytic anemia, lupus, pulmonary infiltrates.	Hepatic enzyme inducers.
Flecainide (class IC)	*IV 1-2 mg/kg over 10 min, then 0.15-0.25 mg/kg/h.Oral 100-400 mg 2 times daily. Hospitalize.	T½ 13-19 h. Hepatic ⅔; ⅓ renal excretion unchanged. Keep trough level below 1 mcg/mL.	QRS prolongation. Proarrhythmia.Depressed LV function. CNS side effects. Increased incidence of death postinfarct.	Many, especially added inhibition of conduction and nodal tissue.
Propafenone (class IC)	*IV 2 mg/kg then 2 mg/min.Oral 150-300 mg 3 times daily.	T½ variable 2-10 h, up to 32 h in nonmetabolizers. Level 0.2-3 mcg/mL.Variable hepatic metabolism (P-450 deficiency slows).	QRS prolongation. Modest negative inotropic effect. GI side effects.Proarrhythmia.	Digoxin level increased.Hepatic inducers.
Sotalol (class III)	160-640 mg daily, occasionally higher in two divided doses.	T½ 12 h.Not metabolized. Hydrophilic. Renal loss.	Myocardial depression, sinus bradycardia, AV block. Torsades if hypokalemic.	Added risk of torsades with IA agents or diuretics. Decrease dose in renal failure.
Amiodarone (class III)	Oral loading dose 1200-1600 mg daily; maintenance 200-400 mg daily, sometimes less. IV 150 mg over 10 min, then 360 mg over 6 h, then 540 mg over remaining 24 h, then 0.5 mg/min.	T½ 25-110 days.Level 1-2.5 mcg/mL. Hepatic metabolism. Lipid soluble with extensive distribution in body. Excretion by skin, biliary tract, lachrymal glands.	Complex dose-dependent side effects including pulmonary fibrosis. QT prolongation. Torsades uncommon.	Class IA agents predispose to torsades.β-blockers predispose to nodal depression, yet give better therapeutic effects.

AV, Atrioventricular; *CNS,* central nervous system; *GI,* gastrointestinal; *IV,* intravenous; *LV,* left ventricular; *T½,* plasma half-life.

Class IA agents (Table 8-1) are no longer recommended, and tocainide, mexiletine, and bretylium are rarely used. These agents were considered in the previous editions of this book.

Enzyme hepatic inducers are barbiturates, phenytoin, and rifampin, which induce hepatic enzymes, thereby decreasing blood levels of the drug.

* Not licensed for intravenous use in the United States.

Class IA: Quinidine and similar compounds

Historically, quinidine was the first antiarrhythmic drug used, and its classification as a class IA agent (the others being disopyramide and procainamide) might suggest excellent effects with superiority to other agents. That is not so, and now that the defects and dangers of quinidine are better understood, it is used less and less. Class IA agents are those that act chiefly by inhibiting the fast sodium channel with depression of phase 0 of the action potential. In addition, they prolong the action potential duration (APD) and thereby have a mild class III action (see Fig. 8-1). Such compounds can cause proarrhythmic complications by prolonging the QT interval in certain genetically predisposed individuals or by depressing conduction and promoting reentry. There are no large-scale outcome trials to suggest that quinidine or other class I agents decrease mortality; rather there is indirect evidence that suggests increased or at best neutral, mortality. For quinidine and procainamide, see Table 8-3.

Class IB: Lidocaine

As a group, class IB agents inhibit the fast sodium current (typical class I effect; see Fig. 8-1) while shortening the APD in nondiseased tissue. The former has the more powerful effect, whereas the latter might actually predispose to arrhythmias, but ensures that QT prolongation does not occur. Class IB agents act selectively on diseased or ischemic tissue, where they are thought to promote conduction block, thereby interrupting reentry circuits. They have a particular affinity for binding with inactivated sodium channels with rapid onset-offset kinetics, which may be why such drugs are ineffective in atrial arrhythmias, because the APD is so short. For mexiletene, see Table 8-3.

Lidocaine

Lidocaine (Xylocaine, Xylocard) has become a standard intravenous agent for suppression of serious ventricular arrhythmias associated with AMI and with cardiac surgery. The concept of prophylactic lidocaine to prevent VT and ventricular fibrillation (VF) in AMI is now outmoded.[9],[10] This intravenous drug has no role in the control of chronic recurrent ventricular arrhythmias. Lidocaine acts preferentially on the ischemic myocardium and is more effective in the presence of a high external potassium concentration. Therefore hypokalemia must be corrected for maximum efficacy (also for other class I agents). Lidocaine has no value in treating supraventricular tachyarrhythmias.

Pharmacokinetics.

The bulk of an intravenous dose of lidocaine is rapidly deethylated by liver microsomes (see Table 8-3). The two critical factors governing lidocaine metabolism and hence its efficacy are liver blood flow (decreased in old age and by heart failure, β-blockade, and cimetidine) and liver microsomal activity (enzyme inducers). Because lidocaine is so rapidly distributed within minutes after an initial intravenous loading dose, there must be a subsequent infusion or repetitive doses to maintain therapeutic blood levels (Fig. 8-2). Lidocaine metabolites circulate in high concentrations and may contribute to toxic and therapeutic actions. After prolonged infusions, the half-life may be longer (up to 24 hours) because of redistribution from poorly perfused tissues.

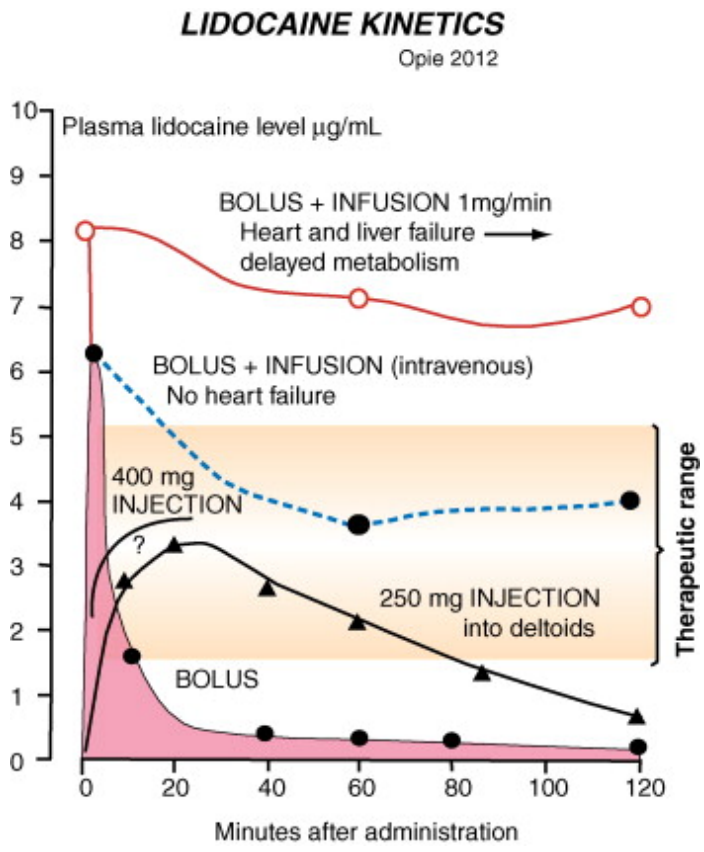

Figure 8-2 Lidocaine kinetics. To achieve and to maintain an adequate blood level of lidocaine requires an initial bolus followed by an infusion. For an intramuscular injection to give sustained high blood levels may require a dose of 400 mg. Note that in the presence of cardiac or liver failure, delayed metabolism increases the blood level with danger of toxic effects.
(Figure © L.H. Opie, 2012.)

Dose.

A constant infusion would take 5 to 9 hours to achieve therapeutic levels (1.4 to 5 mcg/mL), so standard therapy includes a loading dose of 75 to 100 mg intravenously, followed after 30 minutes by a second loading dose, or 400 mg intramuscularly. Thereafter lidocaine is infused at 2 to 4 mg/minute for 24 to 30 hours, aiming at 3 mg/minute, which prevents VF but may cause serious side effects in approximately 15% of patients, in half of whom the lidocaine dose may have to be reduced. Poor liver blood flow (low cardiac output or β-blockade), liver disease, or cimetidine or halothane therapy calls for halved dosage. The dose should also be decreased for older adult patients in whom toxicity develops more frequently and after 12 to 24 hours of infusion.

Clinical use.

Should lidocaine be administered routinely to all patients with AMI? The question has been asked for at least 25 years. Today the answer is no. Evidence from more than 20 randomized trials and 4 metaanalyses have shown that lidocaine reduces VF but adversely affects mortality rates, presumably because of bradyarrhythmias and asystole.[10],[11] *When can it be used?* Lidocaine can be used when tachyarrhythmias or very frequent premature ventricular contractions seriously interfere with hemodynamic status in patients with AMI (especially when already β-blocked) and during cardiac surgery or general anesthesia. *When should lidocaine not be used?* Lidocaine should not be used prophylactically or when there is bradycardia or bradycardia plus ventricular tachyarrhythmias, when atropine (or pacing) and not lidocaine is required.

Side effects.

Lidocaine is generally free of hemodynamic side effects, even in patients with congestive heart failure (CHF), and it seldom impairs nodal function or conduction (Table 8-4). The higher infusion rate of 3 to 4 mg/minute

may result in drowsiness, numbness, speech disturbances, and dizziness, especially in patients older than 60 years of age. Minor adverse neural reactions can occur in approximately half the patients, even with 2 to 3 mg/minute of lidocaine. Occasionally there is sinoatrial (SA) arrest, especially during co-administration of other drugs that potentially depress nodal function.

Table 8-4 -- Effects and Side Effects of Some Ventricular Antiarrhythmic Agents on Electrophysiology and Hemodynamics

Agent	Sinus Node	Sinus Rate	A-His	PR	AV Block	H-P	WPW	QRS	QT	Serious Hemodynamic Effects	Risk of Torsades	Risk of Monomorphic VT
Lidocaine	0	0	0/↓	0	0	0	↓ /0	0	0	Toxic doses	0	0
Phenytoin	0	0	↑/0	0	Lessens	0	↓ /0	0	←	IV hypotension	0, +	0, +
Flecainide	0/↓	0	↓↓↓	→	Avoid	↓↓	↓ A/R	→	→ (via QRS)	LV ↓↓	0	+++
Propafenone	0/↓	0	↓↓	→	Avoid	↓↓	↓ A/R	→	0	LV ↓	0	+++
Sotalol	↓↓	↓↓	↓	→	Avoid	0	A/R	0	→→	IV use	+ +	0, +
Amiodarone	↓	↓	↓	0/→	Avoid	0/↓	A/R	0	→→ →	IV use	++/-	0, +

A, antegrade; *A-His,* Atria-His conduction; *AV,* atrioventricular; *H-P,* His-Purkinje conduction; *IV,* intravenous; *LV,* left ventricular; *PR,* PR interval; R, retrograde; *VT,* ventricular tachycardia; *WPW,* Wolff-Parkinson-White syndrome accessory pathways.

Drug interactions and combination.

In patients receiving cimetidine, propranolol, or halothane, the hepatic clearance of lidocaine is reduced and toxicity may occur more readily, so that the dose should be reduced. With hepatic enzyme inducers (barbiturates, phenytoin, and rifampin) the dose needs to be increased. Combination of lidocaine with early β-blockade is not a contraindication, although there is no reported experience. The obvious precaution is that bradyarrhythmias may become more common because β-blockade reduces liver blood flow. Hence a standard dose of lidocaine would have potentially more side effects, including sinus node inhibition.

Lidocaine failure in ami-related VT and VF.

If lidocaine apparently fails, is there hypokalemia, severe ongoing ischemia, or other reversible underlying factor? Are there technical errors in drug administration? Is the drug really called for or should another class of agent (e.g., β-blockade, class III agent like intravenous amiodarone) be used? In a retrospective analysis of AMI patients, 6% developed sustained VT and VF, and of those who survived 3 hours, amiodarone, but not lidocaine, was associated with an increased risk of death.[12] However, it remains unclear whether the worse outcome of amiodarone-treated patients was due to an effect of the drug or to selection of sicker patients to receive amiodarone, reinforcing the need for randomized trials in this population.

Conclusions.

Lidocaine remains a reasonable initial therapy for treatment of sustained VT, predominantly because of ease of use and a low incidence of hemodynamic side effects and drug interactions. However, the efficacy of lidocaine is relatively low (15% to 20%) compared with other class I antiarrhythmic drugs (procainamide —approximately 80%). Thus the use of lidocaine allows about one fifth of monomorphic VTs to be terminated and suppressed with virtually no risk of side effects.

Phenytoin (diphenylhydantoin)

Phenytoin (Dilantin, Epanutin) is now much less used. It may be effective against the ventricular arrhythmias occurring after congenital heart surgery. Occasionally in patients with epilepsy and arrhythmias a dual

antiarrhythmic and antiepileptic action comes to the fore.

Class IC agents

Class IC agents have acquired a particularly bad reputation as a result of the proarrhythmic effects seen in the Cardiac Arrhythmia Suppression Trial (CAST)[2] (flecainide) and the Cardiac Arrest Study Hamburg (CASH) study[13] (propafenone). Nonetheless, when carefully chosen they fulfill a niche not provided by other drugs. As a group they have three major electrophysiologic (EP) effects. First, they are powerful inhibitors of the fast sodium channel, causing a marked depression of the upstroke of the cardiac action potential, which may explain their marked inhibitory effect on His-Purkinje conduction with QRS widening. In addition they may variably prolong the APD by delaying inactivation of the slow sodium channel[14] and inhibition of the rapid repolarizing current (I_{Kr}).[15] Class IC agents are all potent antiarrhythmics used largely in the control of paroxysmal supraventricular tachyarrhythmias, especially AF and VAs resistant to other drugs. They are effective in the unusual condition of catecholaminergic polymorphic VT.[16] Their markedly depressant effect on conduction, together with prolongation of the APD, may explain the development of electrical heterogeneity and proarrhythmias. In addition, faster heart rates, increased sympathetic activity, and diseased or ischemic myocardium all contribute to the proarrhythmic effects.[17] These drugs must therefore be avoided in patients with structural heart disease (Fig. 8-3). In others, they are widely used to prevent recurrences of AF. Here the evidence is strong for propafenone and moderate for flecainide.[18]

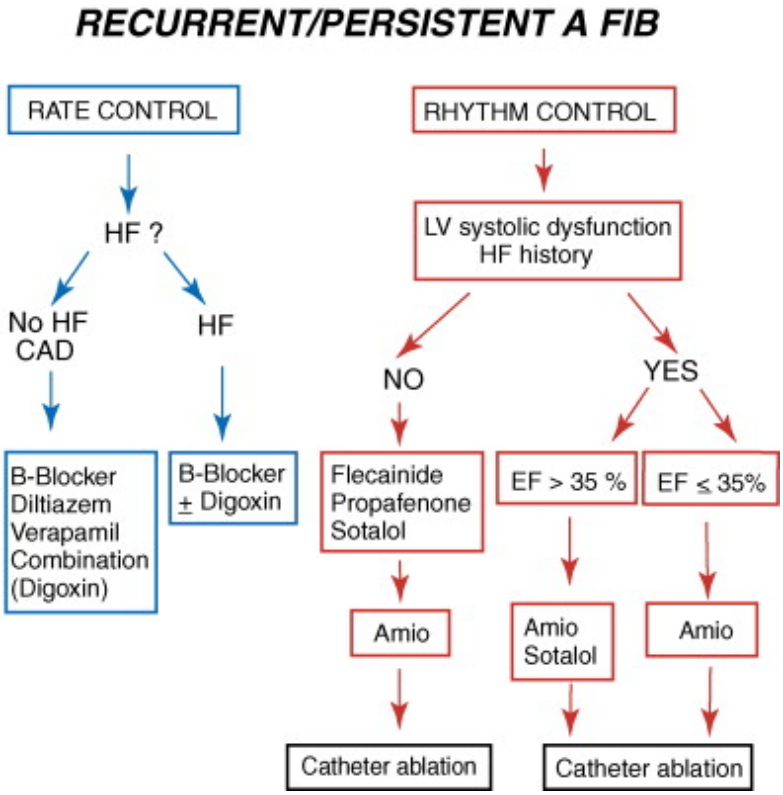

Figure 8-3 Algorithm for drug therapy for rate control or rhythm control. Modified from recommendations of Canadian Cardiovascular Society, with dronaderone removed in view of recent European Medicines Agency warnings about the safety of this drug and their recommendation to use it only to maintain sinus rhythm in selected patients with persistent or paroxysmal atrial fibrillation after successful restoration of sinus rhythm. *A fib,* Atrial fibrillation; Amio, amiodarone; *CAD,* coronary artery disease; *EF,* ejection fraction; *HF,* heart failure; *LV,* left ventricular.
(Modified from Skanes AC, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. Can J Cardiol 2012;28:125–136.)

Flecainide

Flecainide (Tambocor) is effective for the treatment of both supraventricular and ventricular arrhythmias. Its

associated proarrhythmic potential limits its use, especially in the presence of structural heart disease. The drug should be started under careful observation, using a gradually increasing low oral dose with regular electrocardiograms (ECGs) to assess QRS complex duration and occasionally serum levels. Once steady-state treatment has been reached (usually five times the half-life of the drug), it is advisable to perform a 24-hour Holter analysis or a symptom-limited exercise stress test to detect potential arrhythmias.[19] For pharmacokinetics, side effects, and drug interactions see Tables 8-3 to 8-5.

Table 8-5 -- Interactions (Kinetic and Dynamic) of Antiarrhythmic Drugs

Drug	Interaction With	Result
Lidocaine	β-blockers, cimetidine, halothane, enzyme inducers	Reduced liver blood flow (increased blood levels) Decreased blood levels
Flecainide	Major kinetic interaction with amiodarone Added negative inotropic effects (β-blockers, quinidine, disopyramide) Added AV conduction depression (quinidine, procainamide)	Increase of blood F levels; half-dose As previously Conduction block
Propafenone	As for flecainide (but amiodarone interaction not reported); digoxin; warfarin	Enhanced SA, AV, and myocardial depression; digoxin level increased; anticoagulant effect enhanced
Sotalol	Diuretics, Class IA agents, amiodarone, tricyclics, phenothiazines (see Fig. 8-4)	Risk of torsades; avoid hypokalemia
Amiodarone	As for sotalol digoxin phenytoin flecainide warfarin	Risk of torsades Increased digoxin levels Double interaction, see text Increased flecainide levels Increased warfarin effect
Ibutilide	All agents increasing QT	Risk of torsades
Dofetilide	All agents increasing QT Liver interactions with verapamil, cimetidine, ketoconazole, trimethoprim	Risk of torsades Increased dofetilide blood level, more risk of torsades
VerapamilDiltiazem	β-blockers, excess digoxin, myocardial depressants, quinidine	Increased myocardial or nodal depression
Adenosine	Dipyridamole Methylxanthines (caffeine, theophylline)	Adenosine catabolism inhibited; much increased half-life; reduce A dose Inhibit receptor; decreased drug effects

For references, see Table 8-4 in 5th edition.

AV, Atrioventricular; *IV,* intravenous; *SA,* sinoatrial.

Enzyme inducers = hepatic enzyme inducers (i.e. barbiturates, phenytoin, rifampin).

Indications.

Indications are (1) paroxysmal supraventricular tachycardia (PSVT) including paroxysmal atrial flutter or fibrillation and Wolff-Parkinson-White (WPW) arrhythmias, and always only in patients without structural heart disease; (2) life-threatening sustained VT in which benefit outweighs proarrhythmic risks; and (3) catecholaminergic polymorphic VT, by blocking open RyR2 channels.[16] For maintenance of sinus rhythm after cardioversion of AF, it is moderately successful.[18] Flecainide is *contraindicated* in patients with structural heart disease and in patients with right bundle branch block and left anterior hemiblock unless a pacemaker is implanted (package insert). It is also contraindicated in the sick sinus syndrome, when the left ventricle is depressed, and in the postinfarct state. There is a boxed warning in the package insert against use in chronic sustained AF.

Cardiac proarrhythmic effects.

The cardiac proarrhythmic effects of flecainide include aggravation of ventricular arrhythmias and threat of sudden death as in the CAST study.[2] The proarrhythmic effect is related to nonuniform slowing of conduction and the risk is greatest in patients with prior MI, especially those with significant ventricular ectopy. Patients at risk of AMI are probably also at increased risk. Monitoring the QRS interval is logical but “safe limits” are not established. Furthermore, as shown in the CAST study,[2] late proarrhythmic effects can occur. In patients with preexisting sinus node or atrioventricular (AV) conduction problems, there may be worsening of arrhythmia. Flecainide increases the endocardial pacing threshold. Atrial proarrhythmic effects are of two varieties. As the atrial rate falls the ventricular rate might rise. Second, VAs may be precipitated.

Propafenone

Propafenone (Rythmol in the United States, Arythmol in the United Kingdom, Rytmonorm in the rest of Europe) has a spectrum of activity and some side effects that resemble those of other class IC agents, including the proarrhythmic effect. In the CASH study, propafenone was withdrawn from one arm because of increased total mortality and cardiac arrest recurrence.[13] Propafenone is regarded as relatively safe in suppressing supraventricular arrhythmias including those of the WPW syndrome and recurrent AF,[20] always bearing in mind the need to first eliminate structural heart disease.

Pharmacologic characteristics.

In keeping with its class IC effects, propafenone blocks the fast inward sodium channel, has a potent membrane stabilizing activity, and increases PR and QRS intervals without effect on the QT interval. It also has mild β-blocking and calcium (L-type channel) antagonist properties. For pharmacokinetics, side effects, drug interactions, and combinations, see Tables 8-3 to 8-5. Note that in 7% of white patients, the hepatic cytochrome isoenzyme, P-450 2D6, is genetically absent, so that propafenone breakdown is much slower.

Dose.

Dose is 150 to 300 mg three times daily, up to a total of 1200 mg daily, with some patients needing four daily doses and some only two. The UK trial[20] compared 300 mg twice with three times daily; the latter was both more effective and gave more adverse effects. Marked interindividual variations in its metabolism mean that the dose must be individualized.

Indications for propafenone.

In the United States (only oral form), indications are (1) life-threatening ventricular arrhythmias, and (2) suppression of supraventricular arrhythmias, including those of WPW syndrome and recurrent atrial flutter or fibrillation.[9],[10] These must be in the absence of structural heart disease (risk of proarrhythymia). There is strong evidence in favor of propafenone in acute conversion of AF and for maintenance of sinus rhythm.[18] *Intravenous propafenone* (not licensed in the United Kingdom or the United States) followed by oral propafenone, is as effective as amiodarone in the conversion of chronic AF.[21] Intravenous propafenone is also effective in catecholaminergic polymorphic VT.[16] *Propafenone “on-demand,”* also called the “pill in the pocket,” may be tried for paroxysmal AF although it is not licensed for this purpose, after a trial under strict observation. Oral propafenone, 500 mg, for recent-onset AF was more effective than placebo for conversion to sinus rhythm within 8 hours and had a favorable safety profile. The rate of spontaneous conversion to sinus rhythm was higher in patients without structural heart disease.[22] *Relative contraindications* include preexisting sinus, AV or bundle branch abnormalities, or depressed left ventricular (LV) function. Patients with asthma and bronchospastic disease including chronic bronchitis should not, in general, be given propafenone (package insert). Propafenone has mild β-blocking properties, especially when the dose exceeds 450 mg daily. It is estimated that the β-blockade effect is approximately ¼0 that of propranolol.[23]

Class II agents: β-adrenoceptor antagonists

Whereas class I agents are increasingly suspect from the long-term point of view, β-blockers have an excellent record in reducing post-MI mortality.[3],[24] These agents act on (1) the current I_f, now recognized as an important pacemaker current (Fig. 8-4) that also promotes proarrhythmic depolarization in damaged heart tissue; and (2) the inward calcium current, $I_{Ca\text{-}L}$, which is indirectly inhibited as the level of tissue cyclic adenosine monophosphate (cAMP) falls. The general arguments for β-blockade include (1) the role of tachycardia in precipitating some arrhythmias, especially those based on triggered activity; (2) the increased

sympathetic activity in patients with sustained VT and in patients with AMI; (3) the fundamental role of the second messenger of β-adrenergic activity, cyclic AMP, in the causation of ischemia-related VF; and (4) the associated antihypertensive and antiischemic effects of these drugs. The mechanism of benefit of β-blockade in postinfarct patients is uncertain, but is likely to be multifactorial and probably antiarrhythmic in part.[24]

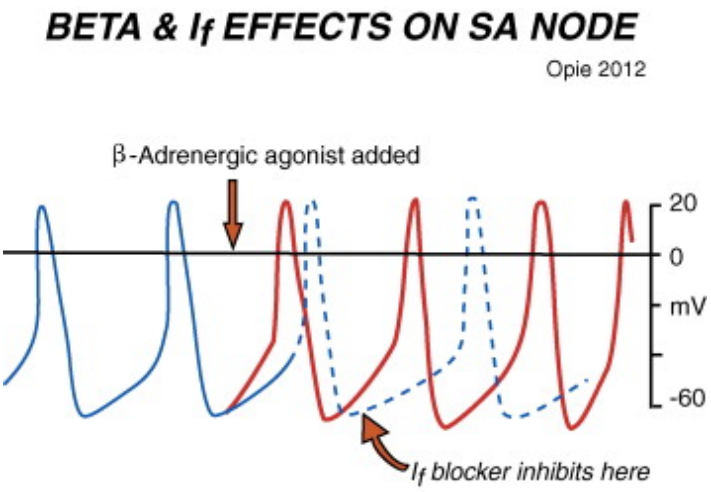

Figure 8-4 Action potential of sinoatrial (SA) node, with effect of β-adrenergic stimulation and of inhibition of current If, relevant to recent development of a specific If blocker.
(Figure © L.H. Opie, 2012.)

Indications.

Antiarrhythmic therapy by β-blockade is indicated for the following: It is used especially for inappropriate or unwanted sinus tachycardia, for paroxysmal atrial tachycardia provoked by emotion or exercise, for exercise-induced ventricular arrhythmias, in the arrhythmias of pheochromocytoma (combined with α-blockade to avoid hypertensive crises), in the hereditary prolonged QT syndrome, in heart failure,[25] and sometimes in the arrhythmias of mitral valve prolapse. A common denominator to most of these indications is increased sympathetic β-adrenergic activity. In patients with stable controlled heart failure, β-blockers reduce all-cause, cardiovascular, and sudden death mortality rates.[25-27] β-blockers are also effective as monotherapy in severe recurrent VT not obviously ischemic in origin, and empirical β-blocker therapy seems as good as EP guided therapy with class I or class III agents. β-blocker therapy improved survival in patients with VF or symptomatic VT not treated by specific antiarrhythmics in the AVID trial.[28] β-blockers in combination with amiodarone have a synergistic effect to significantly reduce cardiac mortality.[29] β-blockers with amiodarone may be effective in treating episodes of “electrical storm.”[30]

Which β-blocker for arrhythmias?

The antiarrhythmic activity of the various β-blockers is reasonably uniform, the critical property being that of β_1-adrenergic blockade,[25] without any major role for associated properties such as membrane depression (local anesthetic action), cardioselectivity, and intrinsic sympathomimetic activity (see Figs. 1-9 and 1-10). These additional properties have no major influence on the antiarrhythmic potency. *Esmolol,* a selective β_1 antagonist, has a half-life of 9 minutes with full recovery from its β-blockade properties at 18 to 30 minutes.[31] Esmolol is quickly metabolized in red blood cells, independently of renal and hepatic function. Because of its short half-life, esmolol can be useful in situations in which there are relative contraindications or concerns about the use of a β-blocker. For instance, in a patient with a supraventricular tachycardia, fast AF, or atrial flutter and associated chronic obstructive airway disease or moderate LV dysfunction, esmolol would be advantageous as a therapeutic intervention.

In the United States, the β-blockers licensed for antiarrhythmic activity include propranolol, sotalol, and acebutolol. The latter is attractive because of its cardioselectivity, its favorable or neutral effect on the blood lipid profile (see Table 10-5), and its specific benefit in one large postinfarct survival trial. However, the potential capacity of acebutolol to suppress serious VAs has never been shown in a large trial. Metoprolol 25 to 100 mg twice daily, not licensed for this purpose in the United States, was the agent chosen when

empirical β-blockade was compared with EP guided antiarrhythmic therapy for the treatment of ventricular tachyarrhythmias. Both sotalol (class II and III activities) and metoprolol (class II) reduce the recurrence of ventricular tachyarrhythmias and inappropriate discharges following ICD implantation.[32],[33] In the CASH study, amiodarone was compared with metoprolol, propafenone, and ICDs.[13] ICDs were best. The propafenone arm was stopped prematurely because of excess mortality compared with other therapies, whereas patients on metoprolol had a survival equivalent to that of those treated with amiodarone.

Drawbacks to β-blockade antiarrhythmic therapy.

There continue to be many patients with absolute or relative contraindications including pulmonary problems, conduction defects, or overt untreated severe heart failure. A large metaanalysis[34] showed that a mortality reduction of up to 40% could still be achieved despite such relative contraindications. It is important to recognize that mild to moderate LV dysfunction, already treated by ACE inhibitors and diuretics, is no longer an absolute contraindication, but rather a strong indication for β-blockers, especially if there is symptomatic heart failure (class II and III). Another drawback is that the efficacy of β-blockers against symptomatic ventricular arrhythmias is less certain. *At present, β-blockers are the closest to an ideal class of antiarrhythmic agents for general use because of their broad spectrum of activity and established safety record.* Furthermore, the use of β-blockers in combination with other antiarrhythmic agents may have a synergistic role and can reduce the proarrhythmic effects seen with some of these agents. On the other hand, β-blockers are relatively ineffective for such indications as preventing AF recurrence, promoting sinus-rhythm maintenance in AF patients, and acute termination of most sustained tachyarrhythmias.

Mixed class III agents: Amiodarone and sotalol

As the evidence for increased mortality in several patient groups with class I agents mounted, attention shifted to class III agents. Two widely used agents with important class III properties, as well as actions of other drug classes, are amiodarone and sotalol. In the ESVEM trial[35] sotalol was better than six class I antiarrhythmic agents (Table 8-6).[36-43] Amiodarone, in contrast to class I agents, exerts a favorable effect on a variety of serious arrhythmias.[44] Both amiodarone and sotalol are mixed, not pure, class III agents, a quality that may be of crucial importance.

Table 8-6 -- Key Trials with Antiarrythmics or Devices for Ventricular Arrhythmias

Drug Class or Device	Acronym	Hypothesis	Key Results
Class IC	CAST—Cardiac Arrhythmia Suppression Trial[2]	PVC suppression gives benefit.	Mortality doubled in treatment group.
Class II	Steinbeck[36]	EPS guided versus empiric β-blockade with metoprolol.	Equal benefits; EPS not needed.
Class II, III (Sotalol)	ESVEM—Electrophysiological Study Versus ECG Monitoring, 1993[37]	Which drug class is better? Which selection method is better?	Sotalol better than 6 Class I agents; Holter = EPS.
Class III	EMIAT—European Myocardial Infarct Amiodarone Trial, 1997[38]	Amiodarone can reduce sudden death in post-MI with low ejection fraction.	Arrhythmia deaths decreased, total deaths unchanged.
Class III	CAMIAT—Canadian Acute Myocardial Infarction Amiodarone Trial[39]	Post-AMI with frequent VPS or nonsustained VT—? Reduced mortality.	Sudden death and mortality reduced.
ICD	MADIT—Multicenter Automatic Defibrillator Implantation Trial[40]	ICD in high-risk patients (coronary artery disease + NSVT on EPS) would improve beyond drugs.	Mortality reduced by half, trial stopped.
ICD	AVID—Antiarrhythmic Versus Implantable Defibrillators[41]	Resuscitated VF or VT (with low ejection fraction) better on ICD	26%-31% mortality reduction with ICD; trial terminated.
ICD	MUSTT—Multicenter Unsustained Tachycardia Trial[42]	EPS-guided therapy can reduce death in survivors of AMI.	Cardiac arrest or death from arrhythmia reduced by 27% in ICD group.

Drug Class or Device	Acronym	Hypothesis	Key Results
ICD	CIDS—Canadian Implantable Defibrillator Study[7]	VF, cardiac arrest, or sustained VT; all-cause deaths, ICD vs. amiodarone.	ICD better than amiodarone only in highest-risk patients; 50% less risk with ICD.
ICD	MADIT-2[43]	Post-MI, LV ejection fraction ≤30%.	All-cause mortality reduced by 31% by ICD.
ICD	SCD-HeFT—Sudden Cardiac Death—Heart Failure	Dilated cardiomyopathy, Class II or III symptoms ejection fraction ≤35%.	All-cause mortality reduced 23% by ICD; amiodarone no benefit.

AMI, Acute myocardial infarction; *ECG,* electrocardiogram; *EPS,* electrophysiologic stimulation; *ICD,* implanted cardioverter defibrillator; *LV,* left ventricular; *MI,* myocardial infarction; *NSVT,* nonsustained ventricular tachycardia; *PVC,* premature ventricular complex; *VF,* ventricular fibrillation; *VPS,* ventricular premature systoles; *VT,* ventricular tachycardia.

The *intrinsic problem* with class III agents is that these compounds act by lengthening the APD and hence the effective refractory period, and must inevitably prolong the QT interval to be effective. In the presence of hypokalemia, hypomagnesemia, bradycardia, or genetic predisposition, QT prolongation may predispose to torsades de pointes. This may especially occur with agents such as sotalol that simultaneously cause bradycardia and prolong the APD. By acting only on the repolarization phase of the action potential, class III agents should leave conduction unchanged. However, amiodarone and sotalol have additional properties that modify conduction—amiodarone being a significant sodium and calcium channel inhibitor and sotalol a β-blocker. Amiodarone makes the action potential pattern more uniform throughout the myocardium, thereby opposing EP heterogeneity that underlies some serious ventricular arrhythmias. The efficacy of amiodarone exceeds that of other antiarrhythmic compounds including sotalol. Furthermore, the incidence of torsades with amiodarone is much lower than expected from its class III effects. Yet amiodarone has a host of potentially serious extracardiac side effects that sotalol does not.

Amiodarone

Amiodarone (Cordarone) is a unique “wide-spectrum” antiarrhythmic agent, chiefly class III but also with powerful class I activity and ancillary class II and class IV activity. Thus it blocks sodium, calcium, and repolarizing potassium channels. In general, the status of this drug has changed from that of a “last-ditch” agent to one that is increasingly used (1) when life-threatening arrhythmias are being treated, and (2) in low doses for AF (Fig. 8-5). Its established antiarrhythmic benefits and potential for *mortality reduction*[45] need to be balanced against several considerations: First, the slow onset of action of oral therapy may require large intravenous or oral loading doses to achieve effects rapidly. Second, the many serious side effects, especially pulmonary infiltrates and thyroid problems (Fig. 8-5), dictate that there must be a fine balance between the maximum antiarrhythmic effect of the drug and the potential for side effects. Third, the half-life is extremely long. Fourth, there are a large number of potentially serious drug interactions, some of which predispose to torsades de pointes, which is nonetheless rare when amiodarone is used as a single agent. For recurrent AF, amiodarone may be strikingly effective with little risk of side effects.[46],[47] Otherwise the use of amiodarone in as low a dose as possible should be restricted to selected patients with refractory ventricular arrhythmias in which an ICD is not appropriate (see later, section on ICDs, page 320, section on Secondary Prevention).

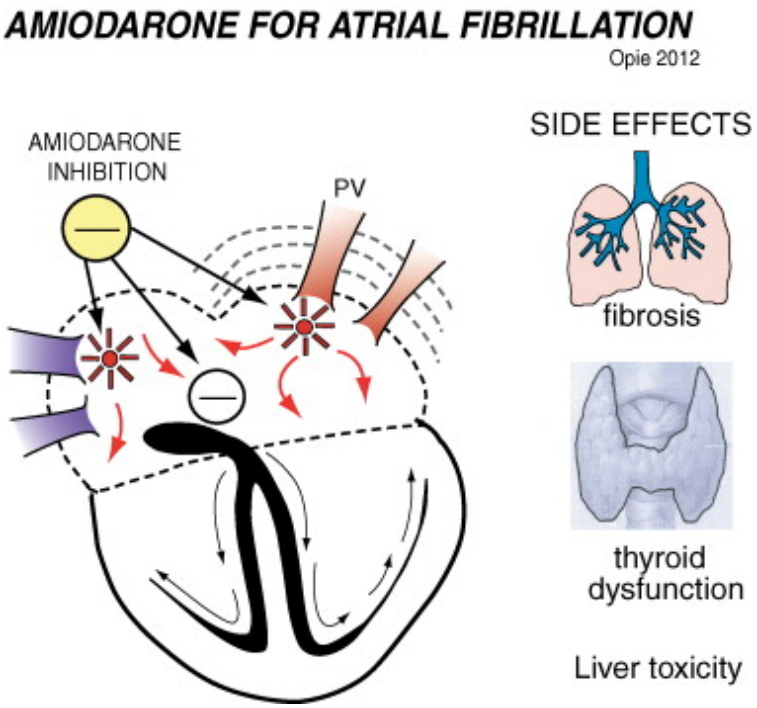

Figure 8-5 Amiodarone inhibition of atrial fibrillation. Benefits must be balanced against risks of pulmonary fibrosis, thyroid dysfunction, and other side effects. *PV,* pulmonary vein.
(Figure © L.H. Opie, 2012.)

Electrophysiologic characteristics.

Amiodarone is a complex antiarrhythmic agent, predominantly class III, that shares at least some of the properties of each of the other three EP classes of antiarrhythmics. The class III activity means that amiodarone lengthens the effective refractory period by prolonging the APD in all cardiac tissues, including bypass tracts. It also has a powerful class I antiarrhythmic effect inhibiting inactivated sodium channels at high stimulation frequencies. Its benefits in AF may be explained at least in part by prolongation of the refractory periods of both the left and right superior pulmonary veins,[48] and inhibition of the AV node (see Fig. 8-5). Furthermore, it is “uniquely effective” against AF in experimental atrial remodeling.[49] Amiodarone noncompetitively blocks α- and β-adrenergic receptors (class II effect), and this effect is additive to competitive receptor inhibition by β-blockers.[45] The weak calcium antagonist (class IV) effect might explain bradycardia and AV nodal inhibition and the relatively low incidence of torsades de pointes. Furthermore, there are relatively weak coronary and peripheral vasodilator actions.

Pharmacokinetics.

The pharmacokinetics of this highly lipid soluble drug differ markedly from other cardiovascular agents.[45] After variable (30% to 50%) and slow gastrointestinal (GI) absorption, amiodarone distributes slowly but very extensive into adipose tissues.[50] Because of this, amiodarone must fill an enormous peripheral-tissue depot to achieve adequate blood and cardiac concentrations, accounting for its slow onset of action. In addition, when oral administration is stopped, most of the drug is in peripheral stores unavailable to elimination systems, causing very slow elimination with a very long half-life, up to 6 months.[51] The onset of action after oral administration is delayed and a steady-state drug effect (*amiodaronization*) may not be established for several months unless large loading doses are used. Even when given intravenously, its full EP effect is delayed,[52] although major benefit can be achieved within minutes as shown by its effect on shock-resistant VF.[53] Amiodarone is lipid soluble, extensively distributed in the body and highly concentrated in many tissues, especially in the liver and lungs. It undergoes extensive hepatic metabolism to the pharmacologically active metabolite, desethylamiodarone. A correlation between the clinical effects and serum concentrations of the drug or its metabolite has not been clearly shown, although there is a direct relation between the oral dose and the plasma concentration, and between metabolite concentration and some late effects, such as that on the ventricular functional refractory period. The therapeutic range is not well defined, but may be

between 1 and 2.5 mg/mL, almost all of which (95%) is protein bound. Higher levels are associated with increased toxicity.[45] Amiodarone is not excreted by the kidneys, but rather by the lachrymal glands, the skin, and the biliary tract.

Dose.

When reasonably rapid control of an urgent arrhythmia is needed, the initial loading regimen is up to 1600 mg daily in two to four divided doses usually given for 7 to 14 days, which is then reduced to 400 to 800 mg/day for a further 1 to 3 weeks. By using a loading dose, sustained VT can be controlled after a mean interval of 5 days. Practice varies widely however, with loading doses of as low as 600 mg daily being used in less urgent settings. Maintenance doses vary. For high-dose therapy, 400 mg daily or occasionally more is employed, but the risk of side effects is substantial over time. For prevention of recurrent AF, one loading regimen used was 800 mg daily for 14 days, 600 mg daily for the next 14 days, 300 mg daily for the first year and 200 mg thereafter.[54] Downward dose adjustment may be required during prolonged therapy to avoid development of side effects while maintaining optimal antiarrhythmic effect. Maintenance doses for atrial flutter or fibrillation are generally lower (200 mg daily or even 100 mg[55]) than those needed for serious ventricular arrhythmias. *Intravenous amiodarone* (approved in the United States) may be used for intractable arrhythmias. The aim is an infusion over 24 hours. Start with 150 mg/10 minutes, then 360 mg over the 6 next hours, then 540 mg over the remaining time up to a total of 24 hours, to give a total of 1050 mg over 24 hours, or for AF in AMI or after cardiac surgery (see next section), 5 mg/kg over 20 minutes, 500 to 1000 mg over 24 hours, then orally, and then 0.5 mg/minute. Deliver by volumetric infusion pump. Higher intravenous loading doses are more likely to give hypotension. For shock-resistant cardiac arrest, the intravenous dose is 5 mg/kg of estimated body weight, with a further dose of 2.5 mg/kg if the VF persists after a further shock.[53]

Indications.

In the United States, the license is only for recurrent VF or hemodynamically unstable VT after adequate doses of other ventricular antiarrhythmics have been tested or are not tolerated, because its use is accompanied by substantial toxicity. Amiodarone is not uncommonly used for AF, especially in lower, relatively nontoxic doses and in older patents at lower risk of long-term toxicity. With the increasing use of ablation therapy for AF, amiodarone use has lately decreased considerably. In the prophylactic control of *life-threatening ventricular tachyarrhythmias* (especially post-MI and in association with congestive cardiac failure), or after cardiac surgery,[56] amiodarone has been regarded as one of the most effective agents available,[57] yet is now being replaced by ICDs. To reduce mortality in chronic LV failure, amiodarone was no better than placebo whereas an ICD was much better, reducing mortality by 23%.[58] However, in the ICD era, there is a new role for amiodarone (plus β-blockade) to inhibit repetitive, unpleasant ICD shocks.[59]

Intravenous amiodarone.

Intravenous amiodarone is indicated for the initiation of treatment and prophylaxis of frequently recurring VF or destabilizing VT and those refractory to other therapies. When oral amiodarone cannot be used, then the intravenous form is also indicated. *Caution*: Be aware of the risk of hypotension with intravenous amiodarone. Generally, intravenous amiodarone is used for 48 to 96 hours while oral amiodarone is instituted. In the ARREST study amiodarone was better than placebo (44% versus 34%, $P = 0.03$) in reducing immediate mortality.[60] Similar data were obtained when amiodarone was compared with lidocaine for shock-resistant VF.[53] For the acute conversion of chronic AF, intravenous amiodarone is as effective as intravenous propafenone,[21] both having strong evidence in their favor.[18] However, amiodarone-induced conversion is often delayed beyond 6 hours, thereby limiting its usefulness.

Preventing recurrences of paroxysmal atrial fibrillation or flutter.

Amiodarone is probably the most effective of the available drugs to prevent recurrences of paroxysmal AF or flutter,[18],[46],[47],[54] and is an entirely reasonable choice for patients with structural cardiac disease or CHF.[51] Sinus rhythm is maintained much more successfully with low-dose 200 mg/day amiodarone than with either sotalol or class I agents, and in the virtual absence of torsades as found with the other agents (except for propafenone).[61] This benefit must be balanced against the cost of side effects (see following sections on side effects), which may be reduced by very low doses (100 mg daily).[55] Amiodarone is not licensed in the United States for supraventricular arrhythmias despite its very frequent use in AF, a common disease. *Contraindications* to amiodarone are severe sinus node dysfunction with marked sinus bradycardia or syncope, second- or third-degree heart block, known hypersensitivity, cardiogenic shock, and probably severe chronic lung disease.

Side effects.

The most common side effects are sinus bradycardia, especially in older adults, and QT prolongation with, however, a very low incidence of torsades (<0.5%).[51] Serious adverse effects, listed in a thorough review of 92 studies, include optic neuropathy/neuritis (≤1%-2%), blue-gray skin discoloration (4%-9%), photosensitivity (25%-75%), hypothyroidism (6%), hyperthyroidism (0.9%-2%), pulmonary toxicity (1%-17%), peripheral neuropathy (0.3% annually), and hepatotoxicity (elevated enzyme levels, 15%-30%; hepatitis and cirrhosis, <3%, 0.6% annually).[62] Recommended preventative actions are baseline and 6-monthly thyroid function tests and liver enzymes and baseline and yearly ECG and chest radiograph with physical examination of skin, eyes, and peripheral nerves if symptoms develop. Corneal microdeposits (>90%) are usually asymptomatic.

Thyroid side effects.

Amiodarone has a complex effect on the metabolism of thyroid hormones (it contains iodine and shares a structural similarity to thyroxin), the main action being to inhibit the peripheral conversion of T4 to T3 with a rise in the serum level of T4 and a small fall in the level of T3. In most patients, thyroid function is not altered by amiodarone. In approximately 6% hypothyroidism may develop during the first year of treatment, but hyperthyroidism only in 0.9%[45]; the exact incidence varies geographically. Hyperthyroidism may precipitate arrhythmia breakthrough and should be excluded if new arrhythmias appear during amiodarone therapy. Once established, the prognosis of amiodarone-induced thyrotoxicosis is poor so that early vigilance is appropriate.[63] In older men (mean age 67 years), subclinical hypothyroidism (thyroid-stimulating hormone 4.5-10 mU/L) can be common, up to 20% more than in controls, suggesting extra alertness (thyroid tests at 3 months) and treatment by levothyroxine.[64] Thyrotoxicosis may be much more common in iodine-deficient areas (20% versus 3% in normal iodine areas).[51]

Cardiac side effects and torsades de pointes.

Amiodarone may inhibit the SA or AV node (approximately 2% to 5%), which can be serious in those with prior sinus node dysfunction or heart block. It is probably a safe drug from the hemodynamic point of view. Only 1.6% required discontinuation of amiodarone because of bradycardia in a metaanalysis.[45]

Pulmonary side effects.

In higher doses, there is an unusual spectrum of toxicity, the most serious being pneumonitis, potentially leading to pulmonary fibrosis and occurring in 10% to 17% at doses of approximately 400 mg/day, which may be fatal in 10% of those affected (package insert). Metaanalysis of double-blind amiodarone trials suggests that there is an absolute risk of 1% of pulmonary toxicity per year, with some fatal cases. Of note, pulmonary toxicity may be dose-related, and very rarely occurs with the low doses of about 200 mg daily, used for prevention of recurrent AF.[47],[65] Pulmonary complications usually regress if recognized early and if amiodarone is discontinued. Symptomatic therapy may include steroids.

Other extracardiac side effects.

Central nervous system side effects like proximal muscle weakness, peripheral neuropathy, and other neural symptoms (headache, ataxia, tremors, impaired memory, dyssomnia, bad dreams) occur with variable incidence. *GI side effects* were uncommon in the GESICA study.[66] Yet nausea can occur in 25% of patients with CHF, even at a dose of only 200 mg daily; exclude increased plasma levels of liver function enzymes. These effects usually resolve with dose reduction. *Testicular dysfunction* may be a side effect, detected by increased gonadotropin levels in patients on long-term amiodarone. *Less serious side effects* are as follows: Corneal microdeposits develop in nearly all adult patients given prolonged amiodarone. Symptoms and impairment of visual acuity are rare and respond to reduced dosage. Macular degeneration rarely occurs during therapy, without proof of a causal relationship. A photosensitive slate-gray or bluish skin discoloration may develop after prolonged therapy, usually exceeding 18 months. Avoid exposure to sun and use a sunscreen ointment with ultraviolet A (UVA) and UVB protection. The pigmentation regresses slowly on drug withdrawal.

Drug withdrawal for side effects.

When amiodarone must be withdrawn, as for pulmonary toxicity, the plasma concentration falls by 50% within 3 to 10 days, then as tissue stores deplete slowly (very long half-life).

Dose-dependency of side effects.

A full and comprehensive metaanalysis of the side effects of amiodarone showed that even low doses may not be free of adverse effects.[65] At a mean dose of 152 to 330 mg/day, drug withdrawal because of side effects was 1.5 times more common than with placebo.[65] Specifically, however, low-dose amiodarone was not associated with torsades.

Drug interactions.

The most serious interaction is an additive proarrhythmic effect with other drugs prolonging the QT interval, such as class IA antiarrhythmic agents, phenothiazines, tricyclic antidepressants, thiazide diuretics, and sotalol. Amiodarone may increase quinidine and procainamide levels (these combinations are not advised). With phenytoin, there is a double drug interaction. Amiodarone increases phenytoin levels while at the same time phenytoin enhances the conversion of amiodarone to desethylamiodarone. *A serious and common interaction is with warfarin.* Amiodarone prolongs the prothrombin time and may cause bleeding in patients on warfarin, perhaps by a hepatic interaction; decrease warfarin by about one-third and retest the international normalized ratio (INR). Amiodarone increases the plasma digoxin concentration, predisposing to digitalis toxic effects (not arrhythmias because amiodarone protects); decrease digoxin by approximately half and remeasure digoxin levels. Amiodarone, by virtue of its weak β-blocking and calcium antagonist effect, tends to inhibit nodal activity and may therefore interact adversely with β-blocking agents and calcium antagonists. However, the antiarrhythmic efficacy of amiodarone is generally increased by co-prescription with β-blocking drugs.[29]

Hospitalization.

To initiate therapy, there is some controversy about the need for hospitalization, which is required for life-threatening VT and VF. For recurrences of AF (not licensed in the United States), low-dose therapy can be initiated on an outpatient basis. If amiodarone is added to an ICD, the defibrillation threshold is usually increased and must be rechecked prior to discharge from hospital.

Sotalol

Sotalol (Betapace in the United States, Sotacor in Europe) was first licensed in the United States for control of severe ventricular arrhythmias. It is now licensed as Betapace AF for maintenance of sinus rhythm in patients with recurrent symptomatic AF or atrial flutter. Although less effective than amiodarone,[44],[46],[47] sotalol is chosen, particularly when amiodarone toxicity is feared. As a mixed class II and class III agent, it also has all the beneficial actions of the β-blocker. Inevitably, it is also susceptible to the “Achilles’s heel” of all class III agents, namely torsades de pointes.

Electrophysiology.

Sotalol is a racemic mixture of dextro and levo isomers, and these differ in their EP effects. Although these agents have comparable class III activity, the class II activity arises from l-sotalol.[67] The pure class III investigational agent d-sotalol increased mortality in postinfarct patients with a low ejection fraction (EF) in the SWORD study.[68] This result suggests that the class III activity, perhaps acting through torsades, can detract from the positive β-blocking qualities of the standard dl-sotalol. In practice, class III activity is not evident at low doses (<160 mg/day) of the racemic drug. In humans, class II effects are sinus and AV node depression. Class III effects are prolongation of the action potential in atrial and ventricular tissue and prolonged atrial and ventricular refractory periods, as well as inhibition of conduction along any bypass tract in both directions. APD prolongation with, possibly, enhanced calcium entry may explain why it causes proarrhythmic after-depolarizations and why the negative inotropic effect is less than expected. It is a noncardioselective, water-soluble (hydrophilic), non–protein-bound agent, excreted solely by the kidneys, with a plasma half-life of 12 hours (US package insert). Dosing every 12 hours gives trough concentrations half of the peak values.

Indications.

Because of its combined class II and class III properties, sotalol is active against a wide variety of arrhythmias, including sinus tachycardia, PSVT, WPW arrhythmias with either antegrade or retrograde conduction, recurrence of AF,[18] ischemic ventricular arrhythmias, and recurrent sustained VT or fibrillation. In ventricular arrhythmias, the major outcome study with sotalol was the ESVEM trial[37] in which this drug in

a mean dose of approximately 400 mg daily was better at decreasing death and ventricular arrhythmias than any of six class I agents. The major indication was sustained monomorphic VT (or VF) induced in an EP study. Of the wide indications, the major current use is in maintenance of sinus rhythm after cardioversion for AF,[18] for which sotalol is about as effective as flecainide or propafenone, with the advantages that it can be given to patients with structural heart disease and can be given without an additional agent to slow AV-nodal conduction. However, the efficacy of all three is outclassed by amiodarone.[46],[47]

Dose.

For patients with a history of AF or atrial flutter, and currently in sinus rhythm, the detailed package insert indicates that 320 mg/day (two doses) may give the ideal ratio between therapeutic actions and side effects (especially torsades). The latter risk is 0.3% at 320 mg/day, but goes up to 3.2% at higher doses when used for AF or flutter (US package insert). For ventricular arrhythmias, the dose range is 160 to 640 mg/day given in two divided doses. Keeping the daily dose at 320 mg or lower (as recommended for AF recurrences) lessens side effects, including torsades de pointes. Yet doses of 320 to 480 mg may be needed to prevent recurrent VT or VF. When given in two divided doses, steady-state plasma concentrations are reached in 2 to 3 days. In patients with renal impairment or in older adults, or when there are risk factors for proarrhythmia, the dose should be reduced and the dosing interval increased.

Side effects.

Side effects are those of β-blockade, including fatigue (20%) (which appears to be more of a problem in younger patients) and bradycardia (13%), to which is added the risk of torsades de pointes. Being a nonselective β-blocker, bronchospasm may be precipitated. For drug interactions see Tables 8-3 and 8-5.

Precautions and contraindications.

For the initial treatment in patients with recurrent AF or flutter, the patient should be hospitalized and monitored for 3 days while the dose is increased (package insert). The drug should be avoided in patients with serious conduction defects, including sick sinus syndrome, second- or third-degree AV block (unless there is a pacemaker), in bronchospastic disease, and when there are evident risks of proarrhythmia. Asthma is a contraindication and bronchospastic disease a strong caution (sotalol is a nonselective β-blocker). The drug is contraindicated in patients with reduced creatinine clearance, below 40 mL/minute (renal excretion). *Torsades de pointes* is more likely when the sotalol dose is high, exceeding 320 mg/day, or when there is bradycardia, when the baseline QT exceeds 450 milliseconds (package insert), in severe LV failure, in women, in patients for whom there are other factors increasing risk (diuretic therapy, other QT-prolonging drugs), or in the congenital long-QT syndrome (LQTS). Co-therapy with class IA drugs, amiodarone, or other drugs prolonging the QT interval should be avoided (Fig. 8-6). In pregnancy, the drug is category B. It is not teratogenic, but does cross the placenta and may depress fetal vital functions. Sotalol is also excreted in mother's milk.

VF.[53] For the acute conversion of chronic AF, intravenous amiodarone is as effective as intravenous propafenone,[21] both having strong evidence in their favor.[18] However, amiodarone-induced conversion is often delayed beyond 6 hours, thereby limiting its usefulness.

Preventing recurrences of paroxysmal atrial fibrillation or flutter.

Amiodarone is probably the most effective of the available drugs to prevent recurrences of paroxysmal AF or flutter,[18],[46],[47],[54] and is an entirely reasonable choice for patients with structural cardiac disease or CHF.[51] Sinus rhythm is maintained much more successfully with low-dose 200 mg/day amiodarone than with either sotalol or class I agents, and in the virtual absence of torsades as found with the other agents (except for propafenone).[61] This benefit must be balanced against the cost of side effects (see following sections on side effects), which may be reduced by very low doses (100 mg daily).[55] Amiodarone is not licensed in the United States for supraventricular arrhythmias despite its very frequent use in AF, a common disease. *Contraindications* to amiodarone are severe sinus node dysfunction with marked sinus bradycardia or syncope, second- or third-degree heart block, known hypersensitivity, cardiogenic shock, and probably severe chronic lung disease.

Side effects.

The most common side effects are sinus bradycardia, especially in older adults, and QT prolongation with, however, a very low incidence of torsades (<0.5%).[51] Serious adverse effects, listed in a thorough review of 92 studies, include optic neuropathy/neuritis (≤1%-2%), blue-gray skin discoloration (4%-9%), photosensitivity (25%-75%), hypothyroidism (6%), hyperthyroidism (0.9%-2%), pulmonary toxicity (1%-17%), peripheral neuropathy (0.3% annually), and hepatotoxicity (elevated enzyme levels, 15%-30%; hepatitis and cirrhosis, <3%, 0.6% annually).[62] Recommended preventative actions are baseline and 6-monthly thyroid function tests and liver enzymes and baseline and yearly ECG and chest radiograph with physical examination of skin, eyes, and peripheral nerves if symptoms develop. Corneal microdeposits (>90%) are usually asymptomatic.

Update: New Content Added *Date Added: 18 July 2013*

Amiodarone and Pulmonary toxicity with dose-effect table.

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Summary

Background: Amiodarone is a widely used and very potent antiarrhythmic substance. Among its adverse effects, pulmonary toxicity is the most dangerous without any direct treatment option. Due to a very long half-life, accumulation can only be prevented by strict adherence to certain dosage patterns. In this review, we outline different safe and proven dosing schemes of amiodarone and compare the incidence and description of pulmonary toxicity. In the case report, an accidental overdose led to fatality from respiratory failure due to bilateral pneumonitis.

Causes of pulmonary toxicity. Of the adverse side-effects, especially potentially fatal and non-reversible acute and chronic pulmonary toxicity.is associated with older age, longer duration of treatment and higher cumulative dosage, high levels of its desethyl metabolite, history of cardiothoracic surgery and/or use of high oxygen mixtures, use of iodinated contrast media, as well as co-existing respiratory infections. Amiodarone-related adverse pulmonary effects may develop as early as from the first few days of treatment to several years later. The onset of pulmonary toxicity may be either insidious or rapidly progressive.

Clinical features of toxicity: Cough, new chest infiltrates and reduced lung diffusing capacity are the cardinal for diagnosis.

Pulmonary involvement includes; : (i) the ubiquitous ‘lipoid pneumonia’, also called ‘amiodarone effect’, which is usually asymptomatic; and (ii) true ‘amiodarone toxicity’, which includes several distinct clinical entities such as eosinophilic pneumonia, chronic organizing pneumonia, acute fibrinous organizing pneumonia, nodules or mass-like lesions, nonspecific interstitial pneumonia-like and idiopathic pulmonary

fibrosis-like interstitial pneumonia, desquamative interstitial pneumonia, acute lung injury/acute respiratory distress syndrome (ARDS) and diffuse alveolar hemorrhage.

Mortality ranges from 9% for those who develop chronic pneumonia to 50% for those who develop ARDS. Discontinuation of the drug, control of risk factors and, in the more severe cases, corticosteroids may be of therapeutic value. Supportive measures for supervening ARDS in the intensive care setting may become necessary

Dose-effect table, Modified from Range FT et al, 2013 (reference 1)

Daily dose	Comment	When used	How given	Duration
1.8 g/day	No longer used, high incidence of lung toxicity	Now never	Not applicable	Not applicable
1.0-1.2 g/day	Common loading dose over 5-15 days	Initial saturation phase	Orally; i.v. if life-threatening arrhythmias or malabsorption	5-15 days
800 mg/d	Reduced loading dose in elderly or reduced organ function	Initial saturation phase for selected patients	As above	As above
600 mg/day	Usual maximum daily dose. Limited to 4-8 weeks	After loading phase; or for re-saturation	Orally; i.v. if malabsorption	4-8 weeks
400 mg/day	Down from higher dose; 4-8 weeks	Follows above phase	Orally; i.v. if malabsorption	4 weeks
200 mg/day *	Normal maintenance	Maintenance	Orally	Maintenance
100 mg/day	Maintenance in the elderly with reduced organ function	Elderly maintenance. Also if 200 mg daily is toxic	Orally	Maintenance

Table 1 Pulmonary toxicity rare with 200 mg/day; pulmonary complications usually regress if amiodarone is discontinued. Unusually steroids are needed.

References

1. Range FT, Hilker E, Breithardt G, et al: Amiodarone-induced pulmonary toxicity-a fatal case report and literature review. *Cardiovasc Drugs Ther* 2013; 27:247-254.

Thyroid side effects.

Amiodarone has a complex effect on the metabolism of thyroid hormones (it contains iodine and shares a structural similarity to thyroxin), the main action being to inhibit the peripheral conversion of T4 to T3 with a rise in the serum level of T4 and a small fall in the level of T3. In most patients, thyroid function is not altered by amiodarone. In approximately 6% hypothyroidism may develop during the first year of treatment, but hyperthyroidism only in 0.9%[45]; the exact incidence varies geographically. Hyperthyroidism may precipitate arrhythmia breakthrough and should be excluded if new arrhythmias appear during amiodarone therapy. Once established, the prognosis of amiodarone-induced thyrotoxicosis is poor so that early vigilance is appropriate.[63] In older men (mean age 67 years), subclinical hypothyroidism (thyroid-stimulating hormone 4.5-10 mU/L) can be common, up to 20% more than in controls, suggesting extra alertness (thyroid tests at 3 months) and treatment by levothyroxine.[64] Thyrotoxicosis may be much more common in iodine-deficient

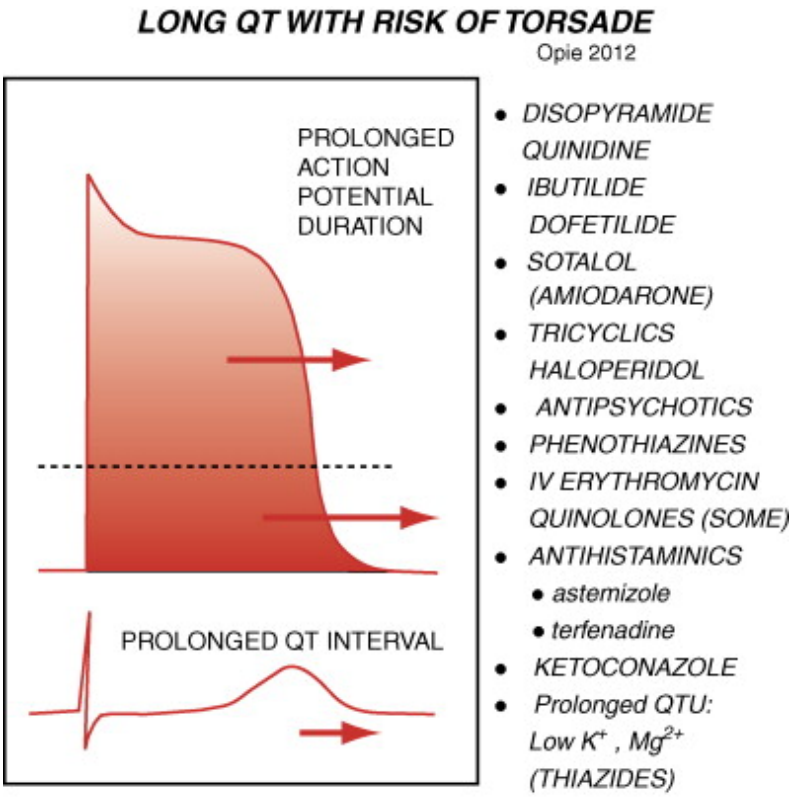

Figure 8-6 Therapeutic agents, including antiarrhythmics that may cause QT prolongation. Hypokalemia causes QTU, not QT, prolongation. Some antiarrhythmic agents act at least in part chiefly by prolonging the action potential duration, such as amiodarone and sotalol. QT prolongation is therefore an integral part of their therapeutic benefit. On the other hand, QT or QTU prolongation, especially in the presence of hypokalemia or hypomagnesemia or when there is co-therapy with one of the other agents prolonging the QT interval, may precipitate torsades de pointes. *IV,* Intravenous.
(Figure © L.H. Opie, 2012.)

Dronedarone

Dronedarone increases serum digoxin concentrations, and should be used very cautiously in patients taking digitalis.[69],[70] Unlike amiodarone, thyroid adverse effects are not an appreciable risk. The European Medicines Agency's Committee has recommended[71] new restrictions (http://www.ema.europa.eu/ema/index.jsp?curl5pages/medicines/human/public_health_alerts/2011/09/human_pha_detail_000038.jsp&murl 5menus/medicines/medicines.jsp&mid5WC0b01ac058001d126) on the use of dronedarone that are consistent with the consensus recommendations of the Canadian Cardiovascular Society.[72] This antiarrhythmic medicine should only be prescribed for maintaining sinus rhythm in patients with paroxysmal AF or persistent AF after successful cardioversion. Because of an increased risk of cardiovascular and possibly liver adverse events, dronedarone should only be prescribed to patients without a history of heart failure and with good ventricular function, after alternative treatment options have been considered. Torsades de pointes has not been reported with any frequency.

Pure class III agents: Ibutilide, dofetilide, and azimilide

The effectiveness of class III antiarrhythmic drugs such as amiodarone and sotalol has prompted the development of purer class III agents. Two such drugs, ibutilide and dofetilide, are presently in clinical practice. The efficacy of ibutilide and dofetilide in the conversion of atrial flutter is noteworthy because, prior to their introduction, drugs have not been found to be efficacious in the cardioversion of atrial flutter.

Ibutilide

Ibutilide (Corvert) is a methanesulfonamide derivative, which prolongs repolarization primarily by inhibition of

the delayed rectifier potassium current (I_{Kr}). Ibutilide has no known negative inotropic effects.

Pharmacokinetics.

Ibutilide is available only as an intravenous preparation because it undergoes extensive first-pass metabolism when administered orally. The pharmacokinetics of ibutilide are linear and are independent of dose, age, sex, and LV function. Its extracellular distribution is extensive, and its systemic clearance is high. The elimination half-life is variable, 2 to 12 hours (mean of 6), reflecting considerable individual variation.[73]

Efficacy of ibutilide.

This drug is efficacious in the termination of atrial flutter and, to a lesser extent, AF.[73] It is as effective as amiodarone in cardioversion of AF.[18],[74] In patients who had persistent AF or atrial flutter, ibutilide had a conversion efficacy of 44% for a single dose and 49% for a second dose.[75] The mean termination time was 27 minutes after the start of the infusion. The efficacy of ibutilide in the cardioversion of atrial flutter is related to an effect on the variability of the cycle length of the tachycardia.[76] Like sotalol, ibutilide exhibits the phenomenon of reverse use dependence in that prolongation of refractoriness becomes less pronounced at higher tachycardia rates. *After cardiac surgery* ibutilide has a dose-dependent effect in conversion of atrial arrhythmias with 57% conversion at a dose of 10 mg.[77] Ibutilide pretreatment facilitates direct-current (DC) cardioversion of AF, but must be followed with 3 to 4 hours of ECG monitoring to exclude torsades.[78]

Adverse effects.

QT- and QT_c-interval prolongation is a consistent feature in patients treated with ibutilide. QT prolongation is dose-dependent, maximal at the end of the infusion, and returns to baseline within 2 to 4 hours following infusion.[73] *Torsades de pointes* (polymorphic VT with QT prolongation) occurs in approximately 4.3%,[79] and may require cardioversion (in almost 2% of patients).[79] Torsades tends to occur during or shortly after the infusion period (within 1 hour).[79] Patients should be continuously monitored for at least 4 hours after the start of the ibutilide infusion. To avoid proarrhythmia, higher doses of ibutilide and rapid infusion are avoided, the drug is not given to those with preexisting QT prolongation or advanced or unstable heart disease, and the serum K must be greater than 4 mmol/L. Theoretically, other cardiac and noncardiac drugs, which prolong the QT interval, may increase the likelihood of torsades. However, in one study, prior therapy with sotalol or amiodarone did not appear to provoke torsades.[78]

Dose.

The recommended dose is 1 mg by intravenous infusion over 10 minutes. If the arrhythmia is not terminated within 10 minutes, the dose may be repeated. For patients who weigh less than 60 kg, the dose should be 0.01 mg/kg.

Drug interactions.

Apart from the proposed interaction with sotalol, amiodarone, and other drugs prolonging the QT interval, there are no known drug interactions.

Dofetilide

Like ibutilide, dofetilide (Tikosyn) is a methanesulfonamide drug. Dofetilide prolongs the APD and QT_c in a concentration-related manner. Dofetilide exerts its effect solely by inhibition of the rapid component of the delayed rectifier potassium current I_{Kr}. Like ibutilide and sotalol, dofetilide exhibits the phenomenon of reverse use dependence. Dofetilide has mild negative chronotropic effects, is devoid of negative inotropic activity, and may be mildly positively inotropic. Whereas ibutilide is given only intravenously, dofetilide is given only orally.

Pharmacokinetics.

After oral administration, dofetilide is almost completely (92% to 96%) absorbed, and mean maximal plasma concentrations are achieved roughly 2.5 hours after administration. Twice-daily administration of oral dofetilide results in steady state within 48 hours. Fifty percent of the drug is excreted through the kidneys unchanged and there are no active metabolites.

Efficacy.

Dofetilide has good efficacy in the cardioversion of AF[18] and is even more effective in the cardioversion of atrial flutter. In addition, dofetilide may also be active against ventricular arrhythmias (not licensed). Dofetilide decreases the VF threshold in patients undergoing defibrillation testing prior to ICD implantation, and suppresses the inducibility of VT. Dofetilide is as effective as sotalol against inducible VT, with fewer side effects.[80] In patients with depressed LV function both with and without a history of MI,[81] dofetilide has a neutral effect on mortality. However, dofetilide reduced the development of new AF, increased the conversion of preexisting AF to sinus rhythm, and improved the maintenance of sinus rhythm in these patients with significant structural heart disease. In this study dofetilide also reduced hospitalization.

Indications.

Indications include (1) cardioversion of persistent AF or atrial flutter to normal sinus rhythm in patients in whom cardioversion by electrical means is not appropriate and in whom the duration of the arrhythmic episode is less than 6 months, and (2) maintenance of sinus rhythm (after conversion) in patients with persistent AF or atrial flutter. Because dofetilide can cause ventricular arrhythmias, it should be reserved for patients in whom AF and atrial flutter is highly symptomatic and in whom other antiarrhythmic therapy is not appropriate. Dofetilide has stronger evidence in its favor for acute cardioversion of AF than for maintenance thereafter, according to a metaanalysis.[18] An important point in its favor is that it can be given to those with a depressed EF.

Dose of dofetilide.

The package insert *warns in bold* that the dose must be individualized by the calculated creatinine clearance and the QT_c. There must be continuous ECG monitoring to detect and manage any serious ventricular arrhythmias. For the complex six-step dosing instructions, see the package insert. The calculated dose could be 125-500 mcg twice daily. Those with a creatinine clearance of less than 20 mL/minute should not be given dofetilide. If the increase in the QT_c is more than 15%, or if the QT_c is more than 500 milliseconds, the dose of dofetilide should be reduced. If at any time after the second dose the QT_c is greater than 500 milliseconds, dofetilide should be discontinued.

Adverse effects.

The major significant adverse effect is torsades de pointes in 3% of patients.[81] The risk of torsades de pointes (80% of events within the first 3 days of therapy) can be reduced by normal serum potassium and magnesium levels, and by avoiding the drug (or reducing its dosage according to the manufacturer's algorithm) in patients with abnormal renal function, or with bradycardia, or with baseline QT prolongation (QT_c should be less than 429 milliseconds).[82] To detect early torsades, patients need continuous ECG monitoring in hospital for the first 3 days of dofetilide therapy.

Drug interactions.

Drugs that increase levels of dofetilide should not be co-administered. These include ketoconazole and other inhibitors of cytochrome CYP 3A4, including macrolide antibiotics and protease inhibitors such as the antiviral agent ritonavir, verapamil, and cimetidine. Check for QT_c prolongation (hypokalemia), especially with diuretics or chronic diarrhea and the co-administration of drugs that increase the QT_c (see Fig. 8-6).

Class IV and class IV-like agents

Verapamil and diltiazem.

Calcium channel blockade slows conduction through the AV node, and increases the refractory period of AV nodal tissue. Because of vascular selectivity, *dihydropyridine* compounds do not have significant EP effects (see Table 3-3). The nondihydropyridine agents *verapamil* and *diltiazem* are similar in their EP properties. They slow the ventricular response rate in atrial arrhythmias, particularly AF. They can also terminate or prevent reentrant arrhythmias in which the circuit involves the AV node. For the termination of AV nodal dependent supraventricular tachycardias, verapamil and diltiazem are alternatives to adenosine.

Rare use in ventricular tachycardia.

A few unusual forms of VT respond to verapamil or diltiazem. In idiopathic right ventricular outflow tract (RVOT) tachycardia, verapamil is chosen after β-blockade. Fascicular tachycardias often respond to verapamil and torsades de pointes may terminate following verapamil. In all other ventricular arrhythmias, *these agents are contraindicated* because of their hemodynamic effects and inefficacy. Verapamil must be administered cautiously in patients who have received either oral or recent intravenous β-blockade. Severe and irreversible electromechanical dissociation may occur.

Intravenous magnesium.

Intravenous magnesium weakly blocks the calcium channel, as well as inhibiting sodium and potassium channels. The relative importance of these mechanisms is unknown. It can be used to slow the ventricular rate in AF but is poor at terminating PSVTs. It may be the agent of choice in torsades de pointes.[83] It has an additional use in refractory VF.

Adenosine

Adenosine (Adenocard) has multiple cellular effects mediated by opening of the adenosine-sensitive inward rectifier potassium channel, with inhibition of the sinus and especially the AV node (Fig. 8-7). It is a first-line agent for terminating narrow complex PSVTs.[84] It is also used in the diagnosis of wide-complex tachycardia of uncertain origin.

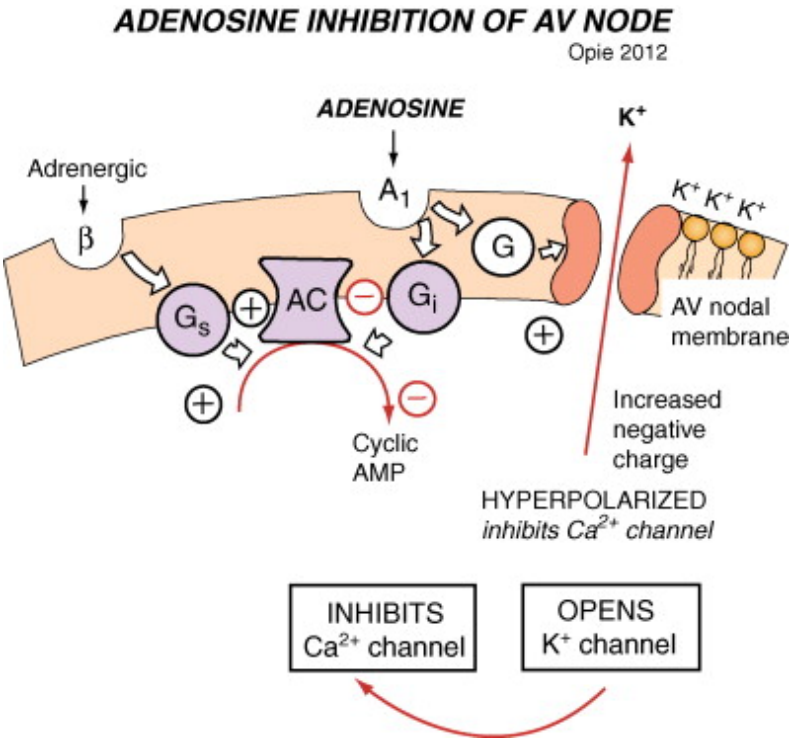

Figure 8-7 Adenosine inhibits the atrioventricular (AV) node by effects on ion channels. Adenosine acting on the adenosine 1 (A1) surface receptor opens the adenosine-sensitive potassium channel to hyperpolarize and inhibit the AV node and also indirectly to inhibit calcium channel opening. *AC,* Adenylate cyclase; *AMP,* adenosine monophosphate; *β,* β-adrenoreceptor; *G,* G protein, nonspecific; *Gi*, inhibitory G protein; *Gs*, stimulatory G protein.
(Figure © L.H. Opie, 2012.)

Dose.

Adenosine is given as an initial rapid intravenous bolus of 6 mg followed by a saline flush to obtain high concentrations in the heart.[84] If it does not work within 1 to 2 minutes, a 12-mg bolus is given that may be repeated once. At the appropriate dose, the antiarrhythmic effect occurs as soon as the drug reaches the AV node, usually within 15 to 30 seconds. The initial dose needs to be reduced to 3 mg or less in patients taking verapamil, diltiazem, or β-blockers or dipyridamole (see drug interactions in “Side Effects and

Contraindications" later in this section), or in older adults at risk of sick sinus syndrome. Note the extremely short half-life of less than 10 seconds.

Indications.

The chief indication is for *paroxysmal narrow complex SVT* (usually AV nodal reentry or AV reentry such as in the WPW syndrome or in patients with a concealed accessory pathway). In *wide-complex tachycardia* of uncertain origin, adenosine can help the management by differentiating between VT or SVT (with aberrant conduction). In the latter case, adenosine is likely to stop the tachycardia, whereas in the case of VT there is unlikely to be any major adverse hemodynamic effect and the tachycardia continues. It may be particularly helpful in VT with retrograde conduction to block the P wave and to show the diagnosis. Finally, intravenous adenosine may be used to reveal *latent preexcitation* in patients suspected of having the WPW syndrome.[85] When used for this indication adenosine is administered during sinus rhythm while a multichannel ECG rhythm strip is recorded (ideally all 12 leads) and a normal response occurs if transient high-grade AV block is observed. On the other hand, following adenosine the presence of an anterograde conduction accessory pathway is inferred if there is PR interval shortening–QRS widening without interruption in AV conduction.

Side effects and contraindications.

Side effects ascribed to the effect of adenosine on the potassium channel are short lived, such as headache (via vasodilation), chest discomfort, flushing, nausea, and excess sinus or AV nodal inhibition. The precipitation of bronchoconstriction in asthmatic patients is of unknown mechanism and can last for 30 minutes. *Transient new arrhythmias* can occur at the time of chemical cardioversion. Because of abbreviating effects on atrial and ventricular refractoriness, adenosine may cause a range of *proarrhythmic consequences,* including atrial and ventricular ectopy, and degeneration of atrial flutter or PSVT into AF.[86] Contraindications are as follows: asthma or history of asthma, second- or third-degree AV block, sick sinus syndrome. Atrial flutter is a relative contraindication, because of the risk of 1:1 conduction and serious tachycardia. *Drug interactions* are as follows: Dipyridamole inhibits the breakdown of adenosine and therefore the dose of adenosine must be markedly reduced in patients receiving dipyridamole. Methylxanthines (caffeine, theophylline) competitively antagonize the interaction of adenosine with its receptors, so that it becomes less effective.

Adenosine versus verapamil or diltiazem.

Adenosine is as effective as intravenous verapamil or diltiazem for the rapid termination of narrow QRS complex SVT. It needs to be reemphasized that verapamil or diltiazem, by myocardial depression and peripheral vasodilation, can be fatal when given to patients with VT, whereas adenosine with its very transient effects leaves true VT virtually unchanged. The transience of adenosine's effects is an advantage; on the other hand, adenosine very commonly produces brief but severe systemic discomfort that does not occur with verapamil or diltiazem.

Proarrhythmia, QT prolongation, and torsades de pointes

Proarrhythmic effects of antiarrhythmics

Proarrhythmia can offset the potential benefits of an antiarrhythmic agent.[2] There are two basic mechanisms for proarrhythmia: first, prolongation of the APD and QT interval (see Fig. 8-6), and, second, incessant wide-complex tachycardia often terminating in VF (Fig. 8-8). The former typically occurs with class IA and class III agents, the latter with class IC agents. In addition, incessant VT can complicate therapy with any class I agent when conduction is sufficiently severely depressed. A third type of proarrhythmia is when the patient's own tachycardia, previously paroxysmal, becomes incessant—the result of either class IA or IC agents. Not only is early vigilance required with the institution of therapy with antiarrhythmics of the class IA, IC, and III types, but continuous vigilance is required throughout therapy. Furthermore, the CAST study shows that proarrhythmic sudden death can occur even when ventricular premature complexes are apparently eliminated. Solutions to this problem include (1) avoiding the use of class I, and especially class IC agents, in patients with structural heart disease; (2) not treating unless the overall effect will clearly be beneficial; and (3) ultimately defining better those subjects at high risk for proarrhythmia and arrhythmic death. The latter would now often be treated by an ICD.

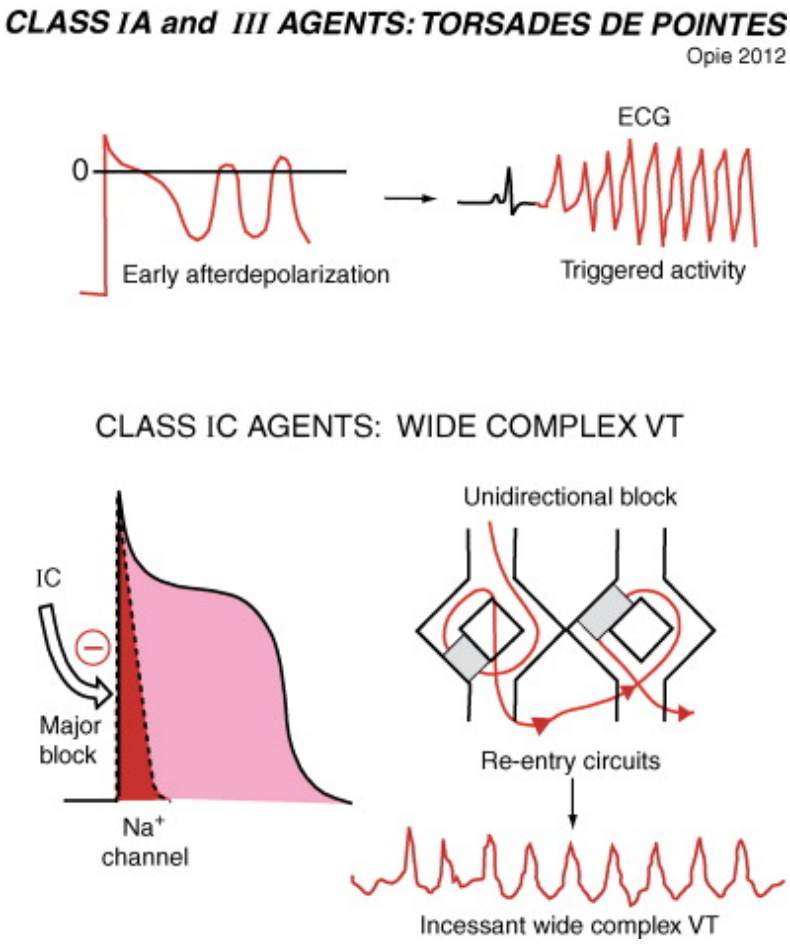

Figure 8-8 Major proarrhythmic mechanisms. *Top:* Class IA and class III agents widen the action potential duration and in the presence of an early after-depolarization can give rise to triggered activity known as *torsades de pointes.* Note major role of QT prolongation (see Fig. 8-6). *Bottom:* Class IC agents have as their major proarrhythmic mechanism a powerful inhibition of the sodium channel, particularly in conduction tissue. Increasing heterogeneity together with unidirectional block sets the stage for reentry circuits and monomorphic wide-complex ventricular tachycardia (VT). *ECG,* Electrocardiogram.
(Figure © L.H. Opie, 2012.)

Long-QT syndrome and torsades de pointes

The LQTS with delayed repolarization is clinically recognized by a prolonged QT or QT_c (corrected for heart rate exceeding 440 milliseconds) or QTU interval. LQTS may be either an acquired or a congenital abnormality. The realization that quinidine, disopyramide, procainamide, and related class IA agents, class III agents, and others (see Fig. 8-6) can all prolong the QT interval has led to a reassessment of the mode of use of such agents in antiarrhythmic therapy. The concept of “repolarisation reserve” is an important idea in the understanding of the risk of long-QT arrhythmias.[87] Cardiac cells have several repolarizing currents, so that if one is blocked, the others increase to compensate (Fig. 8-9). Consequently, in a person with normal repolarisation reserve, drug-induced reduction in potassium current will produce little or no effect on the QT interval or APD (Fig. 8-9, *dashed blue line*). However, when repolarization reserve is already reduced, the same drug will produce marked QT/APD prolongation in the presence of reduced repolarisation reserve (Fig. 8-9, *dashed red line*). Repolarisation reserve is decreased by genetic abnormalities in ion channel subunits, by electrolyte disturbances (e.g., hypokalemia, hypocalcemia, hypomagnesemia), by drugs that block potassium channels, and even as a function of gender in normal women.[87]

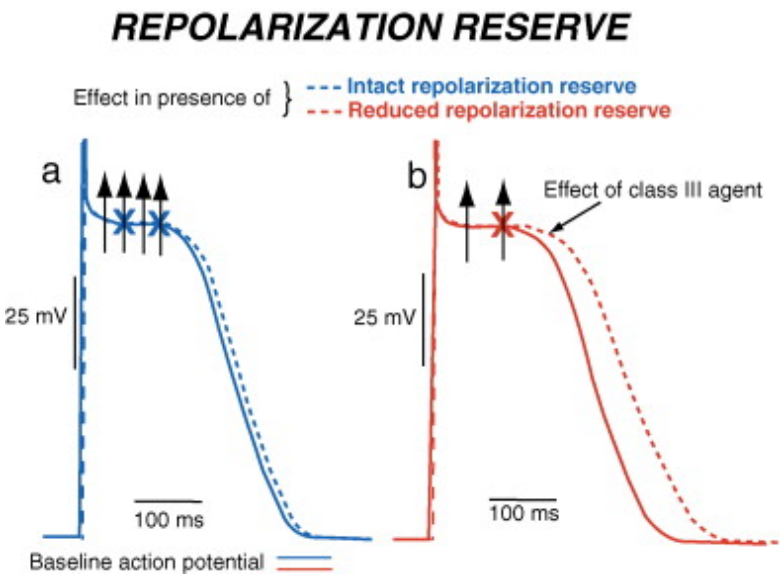

Figure 8-9 Repolarization reserve as a determinant of action potential and QT prolongation. The idea of "repolarization reserve," as illustrated in this schematic, has emerged as an important notion in understanding the risk of arrhythmias associated with delayed repolarization. In the normal heart (*Panel a*), there are substantial repolarizing currents (*black arrows*) flowing during the action potential plateau. When one outward current is reduced (e.g., by a class III antiarrhythmic drug), the others increase, so that action potential prolongation (*dashed lines*) is minimized. However, when baseline currents are reduced (e.g., by a congenital gene variant decreasing a potassium current, by hypokalemia, etc.), as in *Panel b,* the reserve currents are reduced and the same class III drug will produce substantial prolongation of the action potential (and QT interval), with an increased risk of proarrhythmia.
(Figure © S. Nattel, 2012.)

The risk of torsades de pointes is determined not only by the QT interval, but also by other channels that are involved in generating the arrhythmia, such as inward sodium and calcium channels.[87] For example, amiodarone is relatively safe for a given degree of QT prolongation, because of concomitant effects on sodium and calcium channels that limit the risk of torsades. Serious problems may arise when QT prolongation by sotalol or class 1A drugs or even amiodarone is combined with any other factor increasing the QT interval or QTU, such as bradycardia, hypokalemia, hypomagnesemia, hypocalcemia, intense or prolonged use of potassium-wasting diuretic therapy, or combined class IA and class III therapy. A number of noncardiac drugs prolong the QT interval by blocking I_{Kr} potassium channels (see Fig. 8-6), including tricyclic antidepressants, phenothiazines, erythromycin, and some antihistamines, such as terfenadine and astemizole. Note that a drug concentration that might slightly prolong the action potential plateau in some patients might in others produce excessive prolongation because of differences in repolarisation reserve and drug pharmacokinetics.

Treatment.

The management of patients with drug-induced torsades includes identifying and withdrawing the offending drugs, replenishing the potassium level to 4.5 to 5 mmol/L, and infusing intravenous magnesium (1 to 2 g). An interesting preventative approach is by chronic therapy with the potassium-retaining aldosterone blocker, spironolactone.[88] In resistant cases, isoproterenol or temporary cardiac pacing may be needed to increase the heart rate and shorten the QT interval. Isoproterenol is contraindicated in ischemic heart disease and the congenital LQTS.

Congenital long-QT syndrome.

The congenital LQTS is typically caused by genetically based "channelopathies," which are congenital disorders of the cardiac ion channels predisposing to lethal cardiac arrhythmias. The three most common involve loss-of-function mutations in the genes encoding proteins responsible for the slow (LQT1) and rapid (LQT2) components of the repolarising potassium current, and mutations impairing inactivation of the inward sodium current, producing an increased "late" component that retards repolarisation (LQT3). LQT3 is logically treated by sodium channel inhibitors (class I drugs), of which mexiletine and flecainide have been documented to be effective.[89],[90] In patients with LQT1, the defect is in the slow delayed-rectifier potassium

channel I_{Ks}, which is adrenergic-dependent. I_{Ks} enhancement normally offsets the calcium-current increase caused by adrenergic activation, thus preventing excess APD prolongation in response to adrenergic drive. LQT1 patients have a defective I_{Ks} response that allows unopposed calcium current enhancement to induce excess QT prolongation and torsades de pointes: appropriate treatment is therefore to block β-adrenergic effects with a β-adrenoceptor antagonist.

Which β-blocker? For all forms of symptomatic LQTS patients, β-blockers are the agents of choice. The risk of recurrences is markedly higher with metoprolol than with either propranolol or nadolol.[90A] The underlying reason might be, in part, on the differential effect on the sodium current (peak and delayed) of propranolol, nadolol, and metoprolol (in descending order).[90B] Other drugs that should not be used are flecainide and mexilitine.[90C]

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Expert CONSULT

Which antiarrhythmic drug or device?

Paroxysmal supraventricular tachycardia

Acute therapy.

Understanding the mechanism responsible for this arrhythmia (see Fig. 8-9) is the key to appropriate therapy for PSVT.[91],[92] Atrioventricular nodal reentrant tachycardia (AVNRT) and atrioventricular reentrant tachycardia (AVRT) are the forms most frequently seen in patients without structural heart disease (see Fig. 8-14) and maintenance of both arrhythmias depends on intact 1:1 AV nodal conduction. Many patients learn on their own to abort episodes soon after initiation with vagal maneuvers such as gagging, Valsalva, or carotid massage. In infants, facial immersion is effective. If the arrhythmia persists, sympathetic tone increases and these maneuvers then become less effective.

Parenteral therapy.

During PSVT, bioavailability of orally administered drugs is delayed, so parenteral drug administration is usually required.[93] One report described oral self-administration of crushed diltiazem and propranolol, but this is not frequently recommended.[94] Adenosine and a nondihydropyridine calcium channel blocker (CCB; verapamil or diltiazem) are the intravenous drugs of choice.[91],[92]

Adenosine.

After intravenous administration, adenosine is cleared from the circulation within seconds by cellular uptake and metabolism.[84] Administration of an intravenous bolus results in transient AV nodal block when the bolus reaches the heart, usually within 15 to 30 seconds. Central administration results in a more rapid onset of effect, and dosage reduction is required. The recommended adult dosage for peripheral intravenous infusion is 6 mg followed by a second dose of 12 mg if necessary. Higher doses may be required in selected patients. Because adenosine is cleared so rapidly, sequential doses do not result in a cumulative effect. Most patients report transient dyspnea or chest pain after receiving a bolus of adenosine. Sinus bradycardia with or without accompanying AV block is also common after PSVT termination. However, the bradycardia typically resolves within seconds and is replaced with a mild sinus tachycardia. Atrial and ventricular premature beats may occur and can reinitiate PSVT or AF. (For further details and drug interactions of adenosine, see this chapter, p. 299).

Verapamil and diltiazem.

Verapamil and diltiazem administered intravenously are alternates to adenosine.[84],[91] Both of these drugs affect the calcium-dependent AV nodal action potential and can produce transient AV nodal block, which terminates the intranodal reentry and stops the tachycardia. The recommended initial dose of verapamil is 5 mg intravenously infused over 2 minutes. A second dose of 5 to 7.5 mg may be given 5 to 10 minutes later, if necessary. Diltiazem, 20 mg initially, followed by a second dose of 25 to 35 mg, is equally effective.[95] PSVT termination within 5 minutes of the end of the first or second infusion is expected in more than 90% of patients with AV nodal reentrant tachycardia or AV reentrant tachycardia. Verapamil and diltiazem are vasodilators and may produce hypotension if the PSVT does not terminate. Atrial arrhythmias and bradycardia may also be seen. CCBs should not be used to treat preexcitation arrhythmias (WPW syndrome) or wide-complex tachycardias unless the mechanism of the arrhythmia is known to be AV nodal dependent. Drug-induced hypotension with persistent arrhythmia may lead to cardiovascular collapse and VF in these settings, as in neonates.[96]

Adenosine versus CCBs.

In most patients with PSVT caused by an AV node–dependent mechanism, either adenosine or a CCB can

be selected.[91],[97] Adenosine is preferred in infants and neonates, patients with severe hypotension, if intravenous β-blockers have been recently administered, and in those with a history of heart failure and poor LV function. CCBs are preferred in patients with venous access unsuitable for delivering a rapid bolus infusion, in patients with acute bronchospasm, and in the presence of agents that interfere with adenosine's actions or its metabolism.[92]

Atrial tachycardias.

Atrial tachycardias may be due to a number of possible mechanisms, and few data about acute pharmacologic termination of atrial tachycardias are available.[91],[94] CCBs or β-blockers may be effective when there is sinus node reentry or in some automatic atrial tachycardias. Atrial tachycardias related to reentry around atriotomy scars are often drug resistant, and their management should resemble that of atrial flutter (see earlier in this chapter, p. 300).

Chronic therapy of PSVT.

Many patients with recurrent PSVT do not require chronic therapy. If episodes produce only minor symptoms and can be broken easily by the patient, chronic drug therapy may be avoided. In cases in which recurrent episodes produce significant symptoms or require outside intervention for termination, either pharmacologic therapy or catheter ablation is appropriate. In AV node–dependent PSVT, CCBs and β-blockers are the first-line choices if chronic drug therapy is necessary. Flecainide and propafenone also are effective and are frequently used in combination with a β-adrenergic blocker.[20],[98],[99] Sotalol, dofetilide, azimilide, and amiodarone may be effective but are second- or third-line agents. Because of very high efficacy and acceptable safety, ablation procedures directed to a portion of the reentry circuit (either one of two AV-nodal pathways in AVNRT and or the accessory pathway in AVRT) are often the treatment of choice for recurrent PSVTs. Chronic drug therapy of atrial tachycardias (as opposed to AV nodal–dependent tachycardias) has not been extensively studied in clinical trials. Empiric testing of β-blockers, CCBs, and either class I or class III antiarrhythmics may be appropriate.[91],[92] Ablation is also often successfully used for atrial tachycardias.

Radiofrequency catheter ablation.

Although antiarrhythmic drug therapy is usually efficacious in 70% to 90% of PSVT patients, up to half of these patients will have unwanted side effects and daily therapy is often undesirable. Catheter ablation is an attractive alternative for AV nodal reentrant tachycardias and AV reentrant tachycardias with or without manifest preexcitation that is highly effective, produces a life-long "cure," and in experienced centers, is a low-risk procedure.[91],[100] In AV nodal reentry, the slow AV nodal pathway is the usual target. For AV reentry, the accessory pathway is mapped and ablated. Radiofrequency energy is the most frequent ablation technique but cryoablation may be useful, particularly if the ablation target is close to the normal AV conduction system. Most atrial tachycardias can also be approached with catheter ablation but more complex three-dimensional mapping procedures may be required and the success rate is lower than observed with AV nodal or AV reentry. Patients with extensive atrial scarring, especially those with postoperative congenital heart disease, may have multiple atrial arrhythmias and total elimination of tachycardia in such patients remains challenging. Given the excellent results of catheter ablation in most patients with PSVT, current guidelines allow catheter ablation to be offered to patients as either a first option before any chronic drug trials or if drug treatment has been unsuccessful (Fig. 8-10).[91],[92],[94]

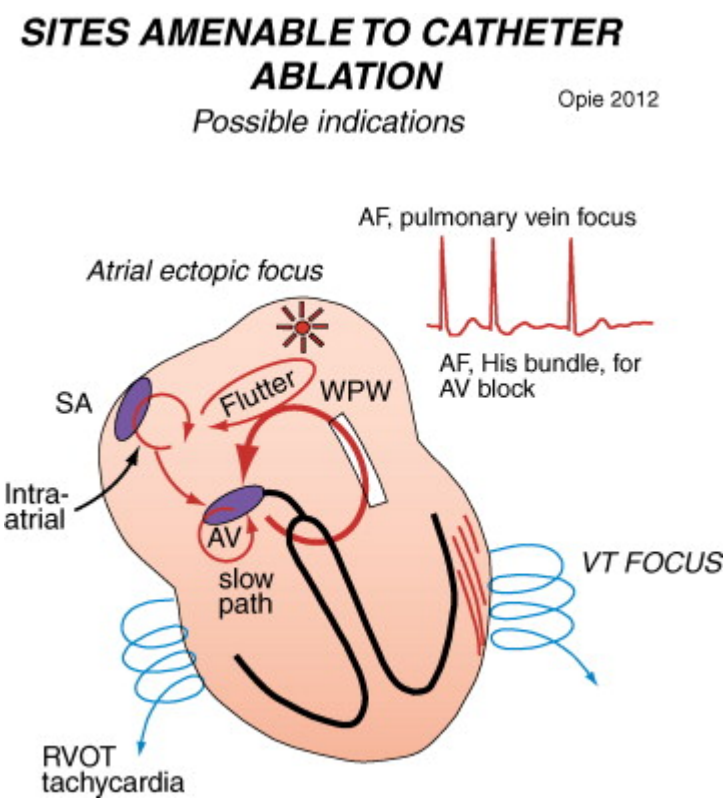

Figure 8-10 Possible sites for intervention by catheter ablation techniques. *AF,* Atrial fibrillation; *AV,* atrioventricular node; *flutter,* atrial flutter; *RVOT,* right ventricular outflow tract; *SA,* sinoatrial node; *VT,* ventricular tachycardia; *WPW,* Wolff-Parkinson-White preexcitation syndrome.
(Figure © L.H. Opie, 2012.)

Atrial fibrillation

AF is an old disease, first described in 1903, with a “new look” given by the significance of the adverse predisposing factors of left atrial structural and ionic remodeling (Fig. 8-11),[101-103] which have led to the current interest in the initiation and perpetuation of this very common arrhythmia.[104],[105] In the United States, approximately 20% of all hospital admissions have AF as either a primary or secondary diagnosis.[106] The ECG in AF is characterized by an undulating baseline without discrete atrial activity, which often has its origin in the pulmonary veins as they enter the atria, to provide sites for therapeutic ablation (Fig. 8-12). The rapid and mostly disorganized atrial rates averaging more than 350 per minute bombard the AV node during all phases of its refractory period. Some impulses that do not conduct to the ventricle will reset the refractory period of the AV node and thereby delay or prevent conduction of subsequent impulses, a phenomenon called *concealed conduction.*

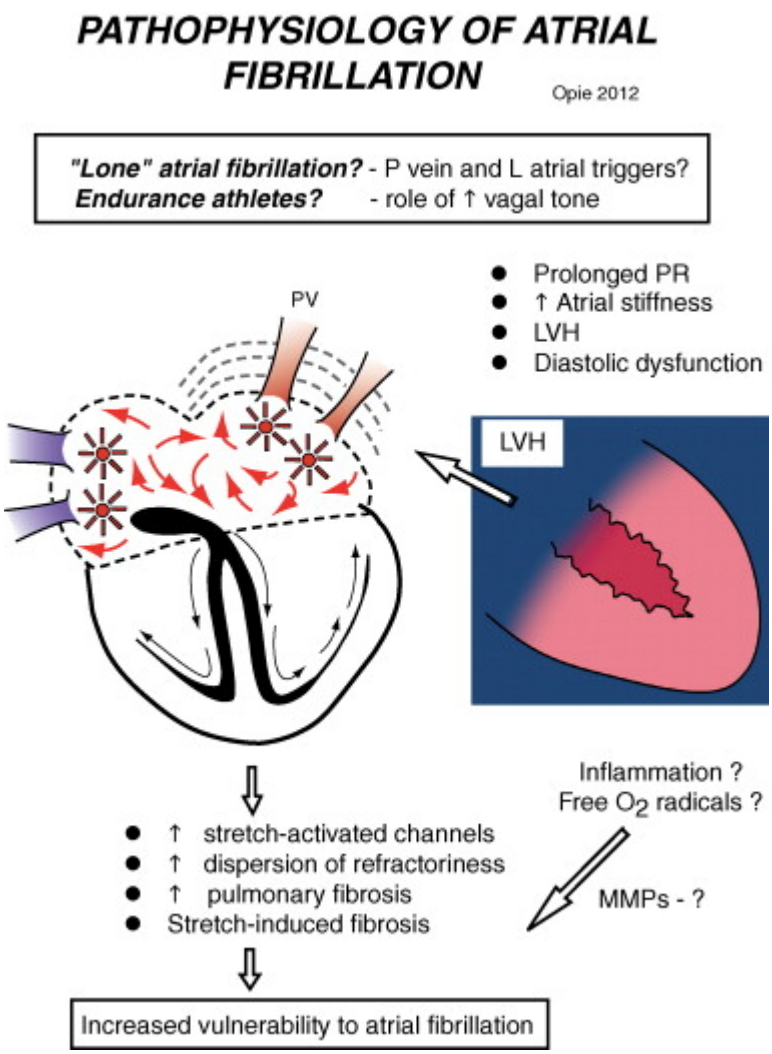

Figure 8-11 Pathophysiologic characteristics of atrial fibrillation, with emphasis on multiple contributory or perpetuating factors. Note role of atrial triggers, increased vagal tone, left ventricular hypertrophy (LVH), atrial stretch, and fibrosis. Inflammatory mediators may also play a role. *L,* left; *MMP,* Metalloproteinases; *P,* pulmonary; PR, as measured by the electrocardiogram. *(Figure © B.J. Gersh, 2012.)*

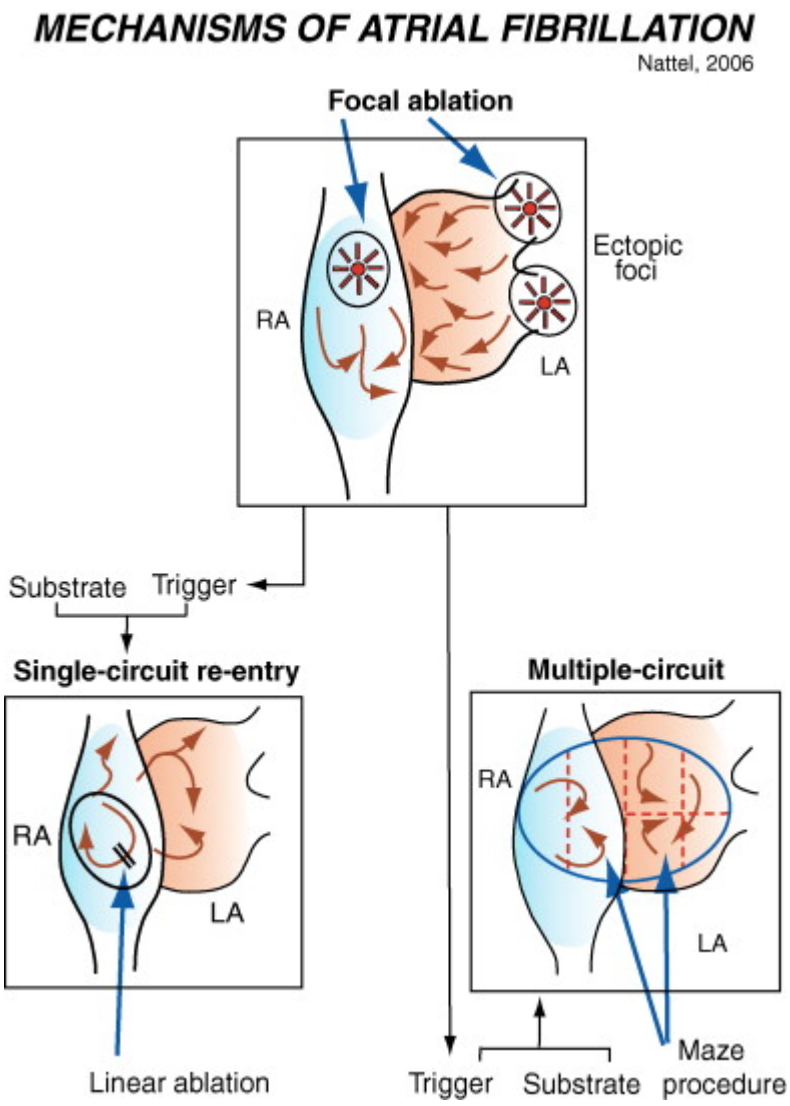

Figure 8-12 Mechanisms of atrial fibrillation, with sites of possible intervention by ablation. Maze procedure (*bottom right panel*) involves multiple incisions of which only two are shown. *LA,* Left atrium; *RA,* right atrium.
(Modified from Nattel S, et al., Lancet 2006;367:262.)

Symptoms of atrial fibrillation.

Patients with AF may present with a variety of symptoms, including palpitations, exercise intolerance, dyspnea, heart failure, chest pain, syncope, dizziness, and stroke. Some patients, however, are asymptomatic during some, or even all, episodes. AF is also frequently associated with sinus node dysfunction or AV conduction disease, and patients may experience severe symptoms as a result of bradycardia. Loss of atrial contraction, disturbed atrial endothelial function, and activation of coagulation factor all predispose toward clot formation in the atria.[105] Therapy of AF, therefore, may involve measures to control ventricular rates, to restore and maintain sinus rhythm, and to prevent thromboembolic complications (Fig. 8-13)

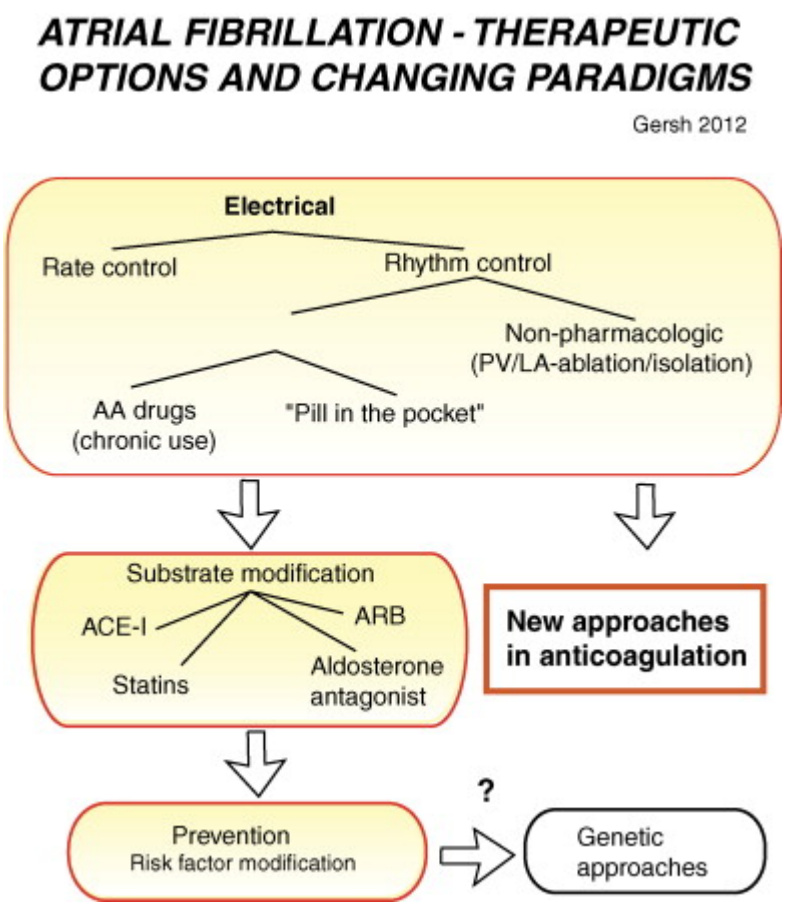

Figure 8-13 Current therapeutic options for atrial fibrillation. *AA,* antiarrhythmic; *ACE-I,* angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *LA,* left atrium; *PV,* pulmonary vein.
(Figure © B.J. Gersh, 2012.)

Presentation of atrial fibrillation.

AF may present in a number of ways, and a classification based on its temporal pattern is often used.[107],[108] At the time of first presentation of an acute episode of AF, the future temporal pattern may be difficult to predict so first episodes are often classified separately. If episodes are self-terminating within less than 7 days (usually less than 1 day), they are classified as *paroxysmal.* When episodes require drug or electrical therapy for termination, they are classified as *persistent.* Persistent AF that is resistant to cardioversion or in which cardioversion is not attempted is classified as *permanent.* Unfortunately, individual patients may experience both paroxysmal and persistent episodes in an unpredictable pattern; yet the terms are helpful in analyzing trials dealing with drug therapy for AF.

Rate versus rhythm control in atrial fibrillation

Is it better to control rate or rhythm in AF? In five randomized trials on chronic AF, there were no differences between these strategies.[102],[107] The major risk remains that of thromboembolic stroke, often requiring chronic anticoagulation. Nonetheless, controlling abnormal ventricular rates mostly improves symptoms and exercise capacity. *How strict should rate control be?* Optimal criteria for rate control are presently unknown. Excess bradycardia may lead to syncope or fatigue, whereas consistently faster rates may result in a tachycardia-induced cardiomyopathy. Strict rate control is a resting heart rate less than 80 beats per minute (bpm) and less than 110 bpm with minor exercise.[109],[110] The Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE 2) trial[109],[110] showed that strict rate control is not essential, and that in selected patients a target heart rate of less than 100 bpm may suffice.[111]

Although some guidelines[112] recommend that rate control and anticoagulation be the preferred strategy in

patients with AF, this may not always be appropriate. The patients who were enrolled in the rate-control versus rhythm-control strategy trials cited previously were considered candidates for either strategy. Patients who were highly symptomatic despite good rate control and those who had failed numerous drug trials to maintain sinus rhythm could not be randomized. Physicians managing patients with AF must base individual therapy on the patient's symptoms, quality of life, and tolerance for procedures. Importantly, it has not been demonstrated that even an apparently successful rhythm control strategy eliminates a need for anticoagulation in patients with risk factors for stroke because there are still frequent episodes of subjectively undetected episodes of AF.[113]

Rate control in heart failure.

In those with CHF, rate control is simpler with less cardioversion and fewer hospitalizations. The large, randomized AF-CHF trial showed no advantage to a rhythm control strategy in terms of LV function, exercise tolerance, or mortality.[114] At present, the only indications for trying to maintain sinus rhythm in patients with CHF are persistent symptoms, a clear correlation between the development of AF, and deterioration in CHF status or failure to achieve rate control.[115] The combination of digoxin with carvedilol is logical and effective in reducing the ventricular rate and increasing the EF.[116] It has been suggested that ablation therapy for sinus-rhythm maintenance may improve the cardiac function and prognosis in CHF patients.[117] A small randomized study that was underpowered showed no improvement with an AF-ablation approach.[118] Larger studies are ongoing.

Combinations of two av-nodal blocking agents.

Combinations of two AV-nodal blocking agents may be more effective than higher-dose therapy with a single drug and are required for optimal rate control in many patients, always excluding those with accessory paths (WPW). CCBs should be avoided in patients with CHF resulting from systolic dysfunction, but may add benefit in patients with hypertension and good systolic function. Adding digoxin may also allow lower doses of other AV nodal inhibitors.

Pacemakers.

In some patients, it is not possible to achieve effective rate control during AF. Excess bradycardia or prolonged pauses causing syncope may prevent administration of therapy that would be effective for preventing or controlling rates during AF. Bradycardia during sleep or rest may limit control of rates during exercise or stress. Implantation of a permanent pacemaker may be required in such patients. Ablation of AV conduction and insertion of an adaptive rate pacemaker constitutes an effective strategy in patients in whom control of inappropriately rapid rates cannot be achieved with pharmacologic therapy alone. A dual-chamber pacemaker with mode switching during periods of AF may be used in patients with paroxysmal AF. A single-chamber pacemaker is used in patients with permanent AF. Thus *ablate and pace* is a useful alternative for rate control. In patients with baseline LV dysfunction that is not solely due to inadequate rate control, use of a resynchronization device can minimize the deleterious effects of right ventricular apical pacing.[119]

Ventricular preexcitation with atrial fibrillation.

The combination of ventricular preexcitation with AF presents a unique problem (see *WPW,* Fig. 8-14). Agents acting primarily on the AV node may paradoxically increase ventricular rates either by shortening the effective refractory period of the accessory pathway or by eliminating concealed conduction into the accessory pathway. Agents that prolong the anterograde refractory period of the accessory pathway (e.g., procainamide, flecainide, and amiodarone) should be used both for rate control and to achieve conversion, but urgent electrical cardioversion is often necessary.

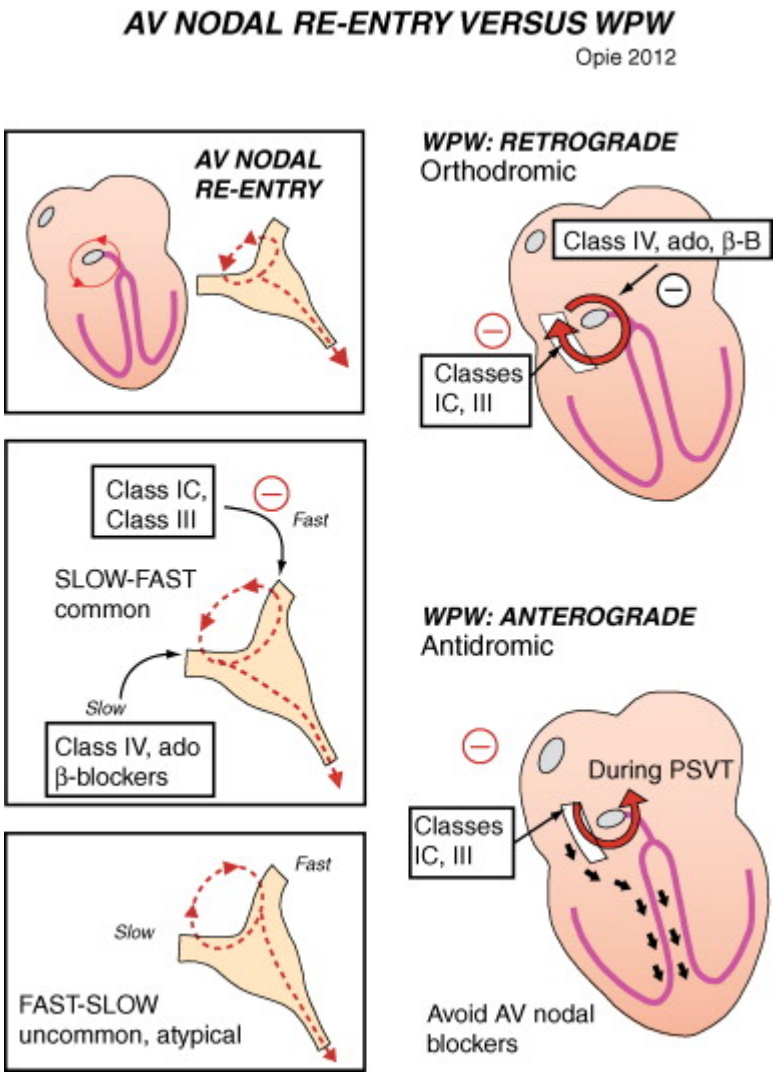

Figure 8-14 Atrioventricular (AV) nodal reentry and Wolff-Parkinson-White (WPW) or preexcitation syndrome. The *top left panel* shows AV nodal reentry without WPW. The common pattern is slow-fast (*middle panel*), whereas fast-slow conduction (*bottom left panel*) is uncommon. The slow and fast fibers of the AV node are artificially separated for diagrammatic purposes. The right panel shows WPW with the bypass tract as a white band. During paroxysmal supraventricular tachycardia (PSVT), when anterograde conduction occurs over the AV node and retrograde conduction most commonly through the accessory pathway, the QRS pattern should be normal (orthodromic supraventricular tachycardia [SVT], *top right panel*). Less commonly, the accessory pathway is used as the anterograde limb and the AV node (or a second accessory pathway) is the retrograde limb (antidromic SVT, *bottom right panel*). The QRS pattern shows the pattern of full preexcitation. In such preexcited atrial tachycardias, agents that block the AV node may enhance conduction over the accessory pathway to the ventricles (*red downward arrows*), leading to rapid ventricular rates that predispose to ventricular fibrillation. Sites of action of various classes of antiarrhythmics are indicated. *Ado,* Adenosine; *β-B*, β-blocker.
(Figure © L.H. Opie, 2012.)

Therapy for acute rate control.

Intravenous therapy is usually employed in patients who present acutely with severe symptoms. In this situation, rapid relief of these symptoms is important. Except in patients with preexcitation WPW, rate control is usually achieved with drugs that act primarily on the AV node (Table 8-7). *Digoxin* has historically been the drug of choice for rate control in AF, but its onset of rate-slowing action is delayed and it is ineffective for pharmacologic cardioversion.[107],[120],[121] *β-blockers* will all slow ventricular rates in AF, and many are available as intravenous, oral short-acting, or oral long-acting preparations (see Table 1-3). Sotalol, a β-blocker with a class III activity, should not be given acutely because of risk of torsades. The *nondihydropyridine CCBs,* verapamil and diltiazem, reduce heart rates in AF during both rest and exercise. For patients with severe heart failure or marked hemodynamic instability, electrical cardioversion may be

required. Intravenous amiodarone is also a pharmacologic option for rate control,[122] with the added advantage that it may facilitate rhythm reversion.

Table 8-7 -- Drug Loading and Maintenance Regimens for Control of Ventricular Rate in Atrial Fibrillation

		Acute Intravenous Therapy	Chronic Oral Therapy
β-blockers	Metoprolol	2.5-5 mg every 5 min up to 15 mg	50-200 mg/day
	Propranolol	0.15 mg/kg (1 mg every 2 min)	40-240 mg/day
	Esmolol	0.5 mg bolus, then 0.05-0.2 mg/kg per min	NA
	Pindolol	NA	7.5-30 mg/day
	Atenolol	5 mg over 5 min, repeat in 10 min	25-100 mg/day
	Nadolol	NA	20-80 mg/day
Calcium-channel blockers	Verapamil	0.075-0.15 mg/kg over 2 min; 0.005 mg/kg per min	120-360 mg/day
	Diltiazem	0.25-0.35 mg/kg followed by 5-15 mg/hour	120-360 mg/day

NA, Not available.

Other β-blockers in addition to those listed may also be useful.

Restoration and maintenance of sinus rhythm.

Restoration and maintenance of sinus rhythm is the alternate management strategy in patients with AF. Intuitively, patients feel better when in sinus rhythm, as found in a nonrandomized observational study.[123] The agents used for conversion of acute episodes and for long-term prevention of recurrence of AF are listed in Table 8-8. Although early cardioversion can experimentally prevent tachycardia-driven atrial remodeling, such remodeling is only one component of the pathophysiologic characteristics of AF and *should not be an important consideration in decisions regarding the timing of cardioversion.*[102]

Table 8-8 -- Recommended Antiarrhythmic Drug Doses for Pharmacologic Cardioversion and Prevention of Recurrences of Atrial Fibrillation

		IV or Oral Therapy for Rapid Conversion	Chronic Oral Drug Therapy to Prevent Recurrence*
Class IA	Procainamide	500-1200 mg IV over 30-60 min	2000-4000 mg/day
Class IC	Flecainide	1.5-3.0 mg/kg IV over 10 min[†];	
		200-400 mg orally	150-300 mg/day
	Propafenone	1.5-2 mg/kg IV over 10-20 min[†]	400-600 mg/day
Class III	Ibutilide	1 mg IV over 10 min, repeat once	Not available
	Sotalol	Not recommended	160-320 mg/day
	Amiodarone	5-7 mg/kg IV over 30 min, then 1.2-1.8 g/day	400-1200 mg/day for 7 days, then taper to 100-300 mg/day
	Dofetilide	Insufficient data	125-500 mcg every 12 hours

IV, Intravenous.

* Initiation of oral therapy without loading may also result in conversion.

† Not available in North America.

DC conversion for distressing acute-onset atrial fibrillation.

DC electrical cardioversion is generally the procedure of choice for distressing acute-onset AF. Pharmacologic conversion is useful when DC cardioversion is not possible or has to be delayed. DC cardioversion stops AF in more than 90% of cases.[102] Potential complications include burns, iatrogenic VF (if shocks are not QRS synchronized), and the need for general anesthesia (in North America, or in some other countries if the patient is neuroleptic). Current guidelines give a class I recommendation for DC cardioversion for (1) a rapid ventricular response and ongoing myocardial ischemia, symptomatic hypotension, angina, or heart failure and no prompt response to pharmacologic agents (level of evidence: C); (2) AF involving preexcitation (WPW) with very rapid tachycardia or hemodynamic instability (level of evidence: B); and (3) symptoms unacceptable to the patient.[107]

Pharmacologic facilitation of DC cardioversion.

Guidelines also suggest that pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol can facilitate DC cardioversion and prevent recurrent AF (evidence: class IIA, benefit is much decreased risk). In relapses to AF after successful cardioversion, repeating DC cardioversion after prophylactic drugs may be more successful (level of evidence: C).[107]

Pharmacologic conversion of AF.

The drugs under consideration are summarized in Table 8-8. They may be used alone or with DC shocks to restore sinus rhythm. Drug therapy is superior to placebo in patients with AF of recent onset, but many episodes will terminate spontaneously without specific therapy within the initial 24 to 48 hours. Most studies suggest higher pharmacologic conversion rates in atrial flutter than in AF. The combined American and European guidelines (see their Table 13[107]) recommend four drugs: dofetilide, flecainide, ibutilide, and propafenone with a class IA recommendation for conversion of AF with a duration of 7 days or less.[107] Of these, dofetilide is only given orally and ibutilide only intravenously. Amiodarone was given a class IIA recommendation because of its delayed onset of action, but amiodarone may be useful in many patients because it also slows ventricular rates and, unlike the others, has no risk of postconversion ventricular arrhythmias. Quinidine was considered effective, but received a lower rating because of potential toxicity. All drugs are less effective in AF of more than 7 days in duration when oral dofetilide, requiring hospitalization, was the only agent given a class I recommendation. Vernakalant (see later) is a mixed channel blocker that has been developed for intravenous AF cardioversion.[124] It is highly effective, generally well tolerated, and available in more than 30 countries (many in Europe), but not yet in the United States.[125]

"Pill-in-the-pocket."

Intermittent oral administration of single doses of flecainide (200 to 300 mg) or propafenone (450 to 600 mg) when an episode begins—the "pill-in-the-pocket technique"—may be effective in selected patients with AF and no structural heart disease.[22],[126] The major potential complication of this approach is the possibility for organization and slowing of the arrhythmia to atrial flutter, which may then conduct with a 1:1 AV ratio at a very high ventricular rate. Intermittent drug self-administration should be used cautiously and only in patients likely to tolerate this potential proarrhythmic effect. The efficacy of this approach is often tested in a monitored setting before being used on an outpatient basis.

Maintenance of sinus rhythm after cardioversion.

In most patients, AF proves to be a recurrent disorder. Unfortunately, the effectiveness of available antiarrhythmic agents is quite limited.[18],[61],[107] In patients with paroxysmal AF, reduction in the frequency and severity of episodes is the usual goal of therapy. In patients with persistent AF, prolongation of the interval between cardioversions is a reasonable target. Drugs from classes IA, IC, and III are more effective than placebo for maintaining sinus rhythm in patients with AF.[18],[107] Only limited data are available comparing two or more agents in similar populations. In the Canadian Trial of Atrial Fibrillation (CTAF),[47] amiodarone was superior to sotalol or propafenone. In a substudy of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, amiodarone was superior to both sotalol and a mixture of class I drugs.[46] In the Sotalol-Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), amiodarone was

superior to sotalol in the entire group, but the drugs had similar efficacy in the subgroup of patients with ischemic heart disease.[54]

Algorithm for drug choice for repeat or persistent atrial fibrillation.

In patients with no or minimal structural heart disease, the first-line agents are flecainide, propafenone, or sotalol (see Fig. 8-14). Amiodarone or dofetilide are secondary options. In patients with CHF, only amiodarone and dofetilide are thought to be safe and effective. In patients with coronary artery disease, class IC agents are associated with increased mortality, so dofetilide or sotalol followed by amiodarone should be selected. In hypertensive patients without significant LV hypertrophy, flecainide, propafenone, or sotalol may be safely used as first-line agents followed by sotalol or dofetilide. In patients with significant LV hypertrophy, only amiodarone is recommended. By employing several drugs in sequence along with selective use of electrical cardioversion, 75% to 80% of patients with recent AF can maintain sinus rhythm for up to one year.[46]

Newer antiarrhythmic drugs for atrial fibrillation.

Vernakalant (Kynapid, injectable) is a mixed potassium and sodium ion channel blocker now approved in Europe for acute conversion of AF to sinus rhythm. Contraindications are recent MI, advanced CHF, and obstructive heart disease. Hypotension is another risk. In a phase 3 trial, 336 patients with AF were given an infusion of vernakalant (3 mg/kg over 10 min, followed by a second infusion 15 min later if the arrhythmia had not terminated) resulting in a 52% conversion rate, versus 4% with placebo, in those with short duration of AF (3 hours to 7 days).[114] In patients with longer arrhythmia duration (8 to 45 days), vernakalant was much less successful (8% converted versus zero in the placebo group). A rare possible side effect was transient hypotension. There is no head-to-head comparison with DC cardioversion, which is now standard practice for acute onset AF, with some risks and discomforts, nor with dofetilide and ibutilide, which are the only other currently used drugs with Food and Drug Administration (FDA) approval for the conversion of AF, yet with risk of ventricular arrhythmias.

Dronedarone.

Dronedarone (see previous) has structural similarities to amiodarone and a similar antiarrhythmic profile. Without containing iodine and with reduced lipophilicity, dronedarone has fewer adverse effects than amiodarone but is less effective for rhythm control in AF patients.[127] Dronedarone is widely available and is a useful addition to the clinical armamentarium for AF therapy, specifically after conversion to sinus rhythm, but major caution is required because of adverse effects in patients with heart failure and in those with permanent AF,[72] and because of toxic side effects.[71]

Proarrhythmia risk.

This drug selection algorithm is heavily influenced by the potential for each drug to cause proarrhythmia in susceptible individuals. All agents, with the possible exception of dofetilide, may cause sinus node dysfunction or AV block. Atrial flutter with 1:1 conduction is a risk with flecainide, propafenone, and quinidine unless other agents are also used to block AV nodal conduction. Flecainide increased mortality in patients with ischemic heart disease and propafenone probably has a similar effect. Agents in classes IA and III prolong the QT interval and may result in polymorphic VT. Patients with LV hypertrophy and CHF are particularly susceptible to proarrhythmia during attempts at therapy for AF.

Postoperative atrial fibrillation.

AF in the early postoperative period after cardiac surgery is often self-limited and may not require long-term therapy.[128] In untreated patients, the incidence may be 30% to 40% after coronary revascularization and is even higher in patients undergoing valve surgery. Based on data from randomized trials, short-term therapy with β-blockers and amiodarone, amiodarone alone, or CCBs decreases the incidence of AF.[56],[128-130]

Invasive approaches to the maintenance of sinus rhythm.

Given the disappointing results of pharmacologic therapy in the maintenance of sinus rhythm after cardioversion, there is growing interest in nonpharmacologic approaches. The initial surgical experience with the “corridor” and “maze” procedures[131] plus the observation that ectopic beats originating from a muscular sleeve surrounding the pulmonary vein orifices can initiate AF, paved the way for radiofrequency

catheter-based ablation of AF.[132-136] Focal pulmonary vein stenosis was initially a major complication when lesions were placed within the veins themselves but newer techniques in which the pulmonary veins are circumferentially isolated, in conjunction with the placement of additional left atrial ablation lines, have resulted in a major improvement both in terms of procedural success and complication rates. The ideal candidates are younger patients with paroxysmal AF and without structural heart disease. However, with increased experience, radiofrequency ablation for AF may now be considered in older patients and in those with underlying structural heart disease.[132] There are now detailed recommendations for AF ablation therapy.[137] *Radiofrequency ablation* and antiarrhythmic drug therapy as first-line treatment for patients with paroxysmal atrial fibrillation were compared in a 2-year study. The two modalities were equally effective.[137A]

Predisposing causes.

Left atrial size increases with LV hypertrophy and diastolic dysfunction, thereby predisposing to AF (see Fig. 8-11). Thus hypertension is an indirect but common predisposing cause of AF. These conditions should be sought and treated.

Renin-angiotensin inhibition.

There is a lower prevalence of AF among patients treated with ACE inhibitors or angiotensin receptor blockers,[138] the proposed mechanisms being reversal of left atrial remodeling,[101] reduced atrial stretch, and lessened atrial fibrosis. To translate this into clinical practice requires results of prospective double-blind trials, one of which is testing the effects of telmisartan. Studies are also underway to determine if antiinflammatory agents will decrease the incidence or prevalence of AF.

Anticoagulation for atrial fibrillation.

Nonvalvular AF is associated with an increased risk for stroke. Loss of atrial systolic function results in sluggish blood flow in the atrium. Atrial distention disturbs the atrial endothelium and activates hemostatic factors leading to a hypercoagulable state.[18],[107],[139] Several factors increase the risk for stroke in patients with AF. The primary risk factors are increased age, history of stroke or transient ischemic attack, hypertension, left atrial enlargement, diabetes, and CHF. The $CHADS_2$ scoring system[140] is now widely used and forms the basis for current guidelines.[107] In $CHADS_2$, one point is given for the following risk factors: recent CHF, hypertension, age older than 75, and diabetes; two points are given for a prior stroke. Patients with a $CHADS_2$ score of 0 should not require antithrombotic therapy. Considering conventional treatment by warfarin, patients with a score of 1 may be treated with either aspirin or warfarin. Patients with a $CHADS_2$ score of 2 or more should be treated with warfarin with a target INR of 2-3. Regarding patients more than 75 years old, the Birmingham Atrial Fibrillation Treatment of the Aged Study supported the use of warfarin, unless there are contraindications or the patient decides that the benefits are not worth the inconvenience.[141]

New antithrombotics.

In general, antithrombotics (see Fig. 9-10) have either been approved or are likely to be approved by the FDA and European authorities for stroke prevention in nonvalvular AF. The Canadian Cardiovascular Society Recommendations are that when oral anticoagulant therapy is indicated, the new anticoagulants are preferable to warfarin for most patients.[72] Three agents are listed alphabetically. The major problem with all three drugs is the risk of rare but potentially fatal uncontrollable bleeding. No studies in patients have yet assessed the ability of prohemostatic drugs to antagonize excess anticoagulant effects. Regardless of the relatively short half-life of these agents, immediate reversal of the anticoagulant effect may be needed in case of major bleeding or emergency surgery. The major positive aspects of these agents include the following: (1) no need for monitoring of INR, as required for warfarin; (2) reduced risk of adverse interactions following a change in diet or concomitant drugs; and (3) an enhanced ability to prevent strokes (Fig. 8-15).

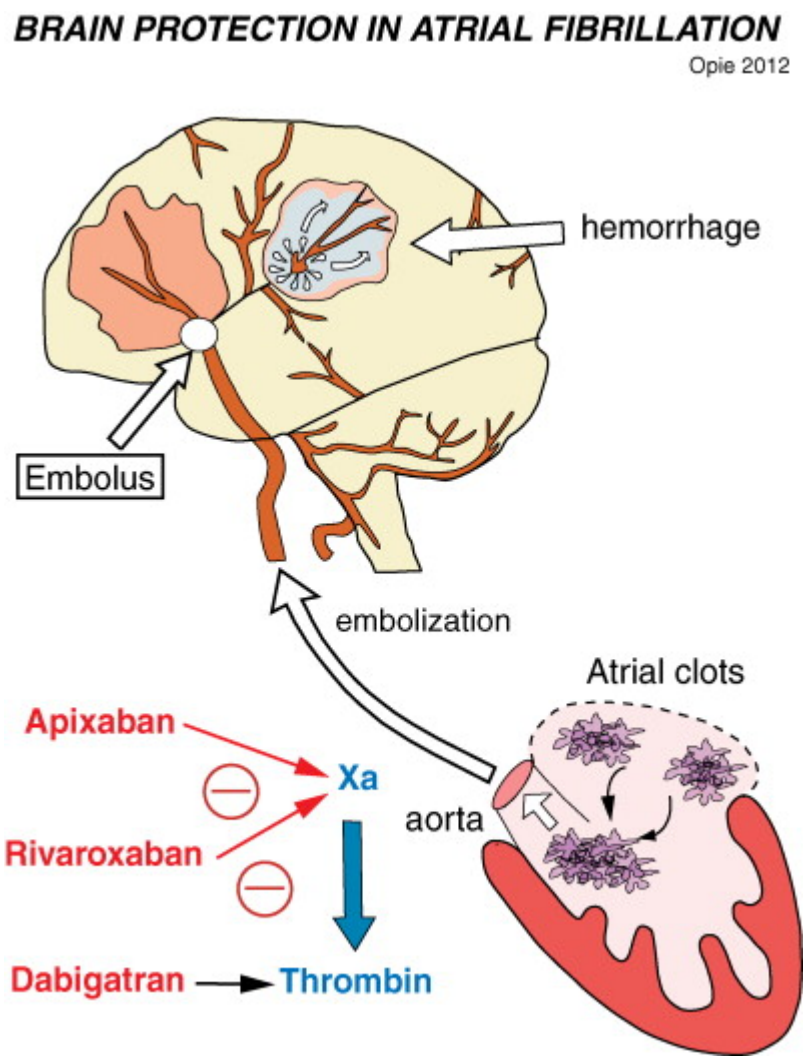

Figure 8-15 Brain protection in atrial fibrillation. Protection of the brain has become the focus of better control of embolization by the newer antithrombin and anti-Xa agents.
(Figure © L.H. Opie 2012.)

Using early outcome data with the new agents, and drawing on data with nonvalvular AF from the Danish National Patient Registry, the *net clinical benefit* estimates the benefit of reducing ischemic stroke versus the risk of intracranial hemorrhage.[142] For patients at high risk as assessed by a modified $CHADS_2$ score, all three novel agents can be expected to provide at least as much benefit as warfarin in terms of stroke prevention and have less risk of intracranial hemorrhage by this model. In those at intermediate risk, the net clinical benefit is particularly favorable with apixaban and both doses of dabigatran (110 mg and 150 mg twice daily). For those at low risk, apixaban and dabigatran 110 mg twice daily had a positive net clinical benefit. As comparative trials between these three agents will probably never be done, this provisional modeling approach provides extrapolations of clinical interest.

Apixaban.

Apixaban, a factor Xa inhibitor (see Fig. 9-10) was superior to aspirin in patients with AF.[143] The AVERROES trial study, which compared apixaban with aspirin, was terminated early because of a clear difference in favor of apixaban. Primary outcome events (stroke) were reduced (stroke) without any increase in major bleeding (hazard ratio [HR] 0.45; $P < 0.001$). The decisive ARISTOTLE trial evaluated apixaban against warfarin in more than 18,000 patients with AF.[144] Apixaban was clearly superior to warfarin in preventing stroke or systemic embolism (HR, 0.79; $P = 0.01$ for superiority), caused less bleeding, and resulted in lower mortality ($P = 0.047$).

Dabigatran.

Dabigatran (as dabigatran-etexilate, Pradax, FDA- and European Union [EU]-approved for prevention of stroke in AF) is a direct thrombin inhibitor approved in 2010 for preventing stroke in AF and has the potential to become a long-term preventive medication for millions of patients with AF worldwide. Despite the greater efficacy of dabigatran versus warfarin in preventing thromboembolism, increasing $CHADS_2$ scores were associated with increased risks for stroke or systemic embolism, major and intracranial bleeding, and death in patients with AF treated with either agent.[145] Rates of stroke or systemic embolism were lower with dabigatran, 150 mg twice daily, and rates of intracranial bleeding were lower with both dabigatran doses (110 or 150 mg).

However, despite its lower risk of hemorrhagic complications compared with warfarin, lack of an antidote or an effective antagonist remains a major concern in the event of severe bleeding, including intracerebral hemorrhage (ICH). The latter, although very unusual, is the most serious and lethal complication of long-term use of oral anticoagulation (OAC). A major goal of ICH management is to prevent secondary hematoma growth because hematoma size substantially affects outcome after ICH. In a murine model of OAC-ICH, hematoma expansion was limited by prothrombin complex concentrate (PCC).[146] The efficacy and safety of this strategy must be further evaluated in appropriate clinical studies.

Rivaroxaban.

Rivaroxaban (FDA- and EU-approved for prevention of stroke in AF), an inhibitor of activated Xa (see Fig. 9-10), was an effective anticoagulant in 14,264 patients with nonvalvular AF, adjudged to be at increased risk of stroke in the ROCKET AF trial.[147] Rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. The rivaroxaban group showed no difference from warfarin-treated patients in the risk of major bleeding, but intracranial hemorrhage (0.5% versus 0.7%, P = 0.02) and fatal bleeding (0.2% verus 0.5%, P = 0.003) were reduced.

Regarding the risk of unexpected bleeding, PCC could overcome the anticoagulant effect induced by thrombin and factor Xa inhibitors because PCC-4 contains the coagulation factors II, VII, IX, and X in a high concentration and in general enhances thrombin generation. In a randomized, double-blind, placebo-controlled study, 12 healthy male volunteers received rivaroxaban 20 mg twice daily (n = 6) or dabigatran 150 mg twice daily (n = 6) for 2½ days, followed by either a single bolus of 50 IU/kg PCC (Cofact) or a similar volume of saline. PCC immediately and completely reversed the anticoagulant effect of rivaroxaban in healthy subjects,[148] but had no influence on the anticoagulant action of dabigatran at the PCC dose used in this human study. However, there are no formal trials on patients with excess bleeding.

Practical considerations with warfarin.

Separate guidelines for warfarin anticoagulation around the time of cardioversion have been published.[107],[149] For cardioversion of acute episodes of less than 48 hours duration, warfarin anticoagulation is not required. For episodes of greater than 48 hours duration or when the duration is uncertain, 3 to 4 weeks of anticoagulation with warfarin (INR between 2 and 3) before cardioversion is recommended. Alternatively, a transesophageal ECG during anticoagulation can be used to exclude the presence of a left atrial thrombus. If none is found, cardioversion may be performed while anticoagulation is continued. Even in patients without risk factors for stroke, anticoagulation is maintained for at least 4 weeks after conversion. In the AFFIRM trial, the majority of strokes occurred in patients with either subtherapeutic INRs or those who were not on warfarin.[150] Furthermore, many brief recurrences of AF may be asymptomatic. Hence the current trend is for lifelong anticoagulation unless there is unequivocal proof that recurrences are not occurring. Randomized trials show the benefit of anticoagulation with warfarin in patients with nonvalvular AF; yet because warfarin therapy is fraught with potential complications, it is often difficult to judge when a patient's risk for stroke is high enough to warrant long-term warfarin therapy.[107],[149],[151] The availability of the new anticoagulants may alter risk/benefit ratios for anticoagulation and modify the indications compared with those established with warfarin; however, much more work needs to be done before this issue can be clarified.

Atrial flutter

Traditionally, atrial flutter has been defined as a regular atrial rhythm with a rate between 250 and 350 bpm in the absence of antiarrhythmic drugs. Several EP mechanisms are responsible. The most common form,

typical or classical atrial flutter, involves a macroreentrant circuit with a counterclockwise rotation in the right atrium.[152] This circuit passes through the isthmus between the inferior vena cava and the tricuspid valve. Atrial activity is seen on the ECG as negative flutter waves in the inferior leads II, III, and aVF. Less commonly, a reverse circuit involving a clockwise rotation occurs. These two forms are also called *isthmus-dependent flutters.* Other atrial rhythms at similar rates that do not require conduction through the isthmus are referred to as *atypical flutters.* Most clinical reports on the acute management of atrial flutter have included all types of flutter. Atrial flutter is also commonly associated with AF. There is an extensive literature concerning ablation therapy of atrial flutter and some studies on acute conversion rates, but most studies of long-term pharmacologic therapy have combined atrial flutter patients with those with AF.

Acute therapy.

Patients with new-onset atrial flutter commonly are usually highly symptomatic. In the absence of antiarrhythmic drug therapy or disease in the AV conduction system, there is typically 2:1 AV conduction, because alternating atrial impulses either conduct normally or encounter the absolute refractory period of the AV node. There is therefore little concealed conduction in the AV node, and it is difficult to achieve stable control of ventricular rates by the modest increases in AV nodal refractory periods produced with AV nodal blocking agents. AV nodal blocking agents are, however, important adjuncts to protect against 1:1 AV conduction should drug therapy slow the atrial rate.[152]

Acute cardioversion.

As with all reentrant arrhythmias, patients with severe symptoms or hemodynamic collapse during atrial flutter should be electrically cardioverted as soon as possible. Atrial flutter is associated with a significant thromboembolic risk, so the same concerns for precardioversion anticoagulation or the exclusion of atrial thrombus with transesophageal echocardiography applies as for AF in the absence of urgent hemodynamic indications.[153] Most patients can tolerate rates of 150 bpm or less during 2:1 or higher AV block. In such patients, either electrical or pharmacologic conversion may be chosen. Both synchronized DC shocks and overdrive atrial pacing are effective techniques for electrical conversion. Intravenous *ibutilide* (1 to 2 mg IV) is reported to correct 38% to 78% of episodes of atrial flutter.[75],[78],[107] Ibutilide should not be administered to patients with long QT interval or with significant hypokalemia or hypomagnesemia. The major complication of intravenous ibutilide is polymorphic VT with a long QT interval, in approximately 2% of individual trials. Patients with severe LV dysfunction (EF less than 0.21), LV hypertrophy, bradycardia, electrolyte imbalance, and prolonged QT intervals at baseline are at increased risk for developing polymorphic VT. Women are more susceptible than men.

Drug choice.

Randomized, double-blind studies show that intravenous ibutilide is more effective than intravenous procainamide or sotalol.[18],[75],[78] Conversion to sinus rhythm, when it occurs, is seen within 60 minutes, and most commonly within 30 minutes, of the end of the infusion. Polymorphic VT also is seen principally during this interval; therefore monitoring for at least 4 hours is recommended. Class IC drugs and amiodarone, either intravenously or orally, are less effective than ibutilide. Dofetilide is also effective for converting atrial flutter, but an intravenous preparation is not currently available for clinical use.[154] If long-term antiarrhythmic therapy is not planned and there are no contraindications, intravenous ibutilide and electrical therapy are appropriate first-line choices. If long-term antiarrhythmic therapy is planned, it may be preferable to begin therapy with amiodarone, sotalol, dofetilide, or a class IC agent, often with an AV nodal blocking agent, with electrical cardioversion after 24 to 48 hours of therapy if a pharmacologic conversion does not occur.

Chronic therapy.

There are insufficient data on chronic drug therapy of atrial flutter on which to base firm clinical recommendations. For patients with normal atrial anatomy and no history of AF, ablation to produce conduction block in the cavotricuspid isthmus is often preferable to drug therapy. In patients with a history of AF, flutter ablation may eliminate the flutter, but AF is likely to recur in the future.[155] Some patients who present with AF and then develop atrial flutter while on an antiarrhythmic drug will do well on drug therapy after flutter ablation. In patients with concomitant AF or abnormal atrial anatomy, chronic drug therapy as discussed previously, either alone or in combination with ablation therapy, is the best approach.

Anticoagulation for atrial flutter.

Patients with atrial flutter are at risk for cardioembolic stroke and systemic embolism. Guidelines for anticoagulation during acute and chronic management are the same as those for patients with AF.[107],[149]

Ventricular arrhythmias

Acute management.

VT with a stable uniform QRS morphologic structure is often referred to as *monomorphic VT.* Monomorphic VT can present in a variety of cardiac conditions and may be caused by several distinct EP mechanisms. Reentry related to scars (MI, surgical incisions, and fibrosis) is the most common mechanism seen clinically. Guidelines for pharmacologic management of sustained monomorphic VT are based almost exclusively on experience treating scar- or fibrosis-related arrhythmias.[156],[157] Unless there is specific clinical information available to suggest another mechanism, therapy for patients with sustained monomorphic VT should be based on a presumed reentrant mechanism.

Hemodynamic status.

The patient's hemodynamic status should determine the initial therapy used to terminate an episode of sustained monomorphic VT.[156] Patients who are unconscious, severely hypotensive, or highly symptomatic should be treated with synchronized DC shocks. Preadministration of an intravenous anesthetic agent or sedative should be used, if possible. Antiarrhythmic drug therapy, if used at all, in this situation is used to prevent recurrences. In patients with stable hemodynamics during sustained VT, pharmacologic termination may be considered. There are only a few randomized trials published dealing with VT termination. Griffith and colleagues[158] evaluated intravenous lidocaine (1.5 mg/kg), disopyramide (2 mg/kg, ≤ 150 mg), flecainide (2 mg/kg), and sotalol (1 mg/kg) in patients with sustained VT induced during EP studies. Of the 24 patients in the trial, 20 had coronary artery disease with a history of MI. Flecainide and disopyramide were the most effective agents for terminating VT, but especially flecainide was associated with significant side effects and neither would be appropriate chronic therapy in a patient with VT after MI. All drugs worked best in patients without prior infarctions. They recommended lidocaine as a first-line and disopyramide as a second-line drug.

Procainamide (see table 8-3).

Even though procainamide may be useful for terminating an acute episode of sustained VT, it is now almost never used as a single agent for chronic therapy.

Intravenous amiodarone.

Intravenous amiodarone has been recommended for patients who present with sustained monomorphic VT.[156],[157] Current guidelines suggest it should be preferred over procainamide in patients with severe LV dysfunction,[158] but published data concerning the efficacy of amiodarone for quickly terminating an episode of VT are limited. In one recent survey of the use of intravenous amiodarone in sustained monomorphic VT,[159] termination was seen in only 8 of 28 (29%) patients. The most common use of intravenous amiodarone is in patients with either incessant VT or frequent VT episodes.[160-162] In these patients, an initial intravenous bolus of 150 mg over 10 minutes is followed by an infusion of 360 mg (1 mg/minute) over the next 6 hours and 540 mg (0.5 mg/minute) over the remaining 18 hours. If given during incessant VT, the expected response will be gradual slowing of the VT cycle length with eventual termination. Transition to oral therapy can be made at any time.

Cardiac arrest and amiodarone.

In patients with cardiac arrest caused by VF, amiodarone can be an *adjunct to defibrillation.* Two randomized controlled trials have addressed this issue. In the ARREST study,[60] intravenous amiodarone (300 mg) was given to patients not resuscitated after three or more precordial shocks, rather late in the resuscitation attempts (mean time, over 40min). Patients who received amiodarone were more likely to survive to hospital admission (44% versus 34% with placebo, $P = 0.03$), but survival to hospital discharge was not significantly improved (13.4% versus 13.2%). The ALIVE study compared amiodarone (5 mg/kg estimated body weight) and lidocaine (1.5 mg/ kg) in patients with out-of-hospital VF.[52] The mean interval

from paramedic dispatch to drug administration was 25 ± 8 minutes. Amiodarone gave better survival to hospital admission (22.8% amiodarone versus 12% lidocaine). Survival to hospital discharge (5% amiodarone, 3% lidocaine) was not significantly improved. These two studies indicate that amiodarone may be useful for resuscitating some cardiac arrest victims. Antiarrhythmic therapy in this setting is an adjunct to defibrillation. Prevention of recurrent episodes of VT or VF after electrical termination is the primary reason for drug administration during resuscitation.

Chronic therapy of VT.

Antiarrhythmic drugs can be used in patients with a history of sustained VT and cardiac arrest to decrease the probability of recurrence or to improve symptoms during a recurrence. However, in randomized trials, antiarrhythmic drug therapy has consistently proven inferior to ICDs as initial therapy.[41],[163-166] In patients with life-threatening arrhythmias, antiarrhythmic drugs (particularly amiodarone) are often used in conjunction with ICDs to reduce the risk of ICD shocks (see section on ICDs, below).

Ventricular tachycardia in the absence of structural heart disease.

In patients without structural heart disease, treatment of VT requires a different approach. The two most common types of monomorphic sustained VT in patients without structural heart disease arise in the RVOT or in the inferior LV septum and have characteristic ECG patterns and mechanisms.[167] When VT starts in the RVOT, the ECG will show a predominant left bundle block pattern with an inferior axis. This arrhythmia presents with both nonsustained bursts and, less commonly, sustained episodes that are often provoked by stress or exercise. The postulated mechanism is cAMP-mediated activity. Acutely, this arrhythmia responds to *intravenous β-blockers or verapamil.* Chronic oral therapy with agents like verapamil, β-blockers, flecainide, or propafenone can be effective, although ablation of the arrhythmogenic region is often preferred. In idiopathic left VT, calcium channel–dependent reentry occurs in or near the left posterior fascicle. The ECG shows a left-axis deviation and a right bundle branch block pattern. This arrhythmia terminates with verapamil administration, and *verapamil* is also the preferred choice for chronic therapy. Both these forms of VT are susceptible to catheter ablation (see Fig. 8-10) and many individuals prefer to undergo ablation as opposed to lifelong drug therapy, particularly because many of these patients are young.

Inherited long-QT syndrome and other channelopathies.

There is a rapidly expanding fount of knowledge about arrhythmias caused by genetic mutations in ion channels.[168] For patients with an inherited LQTS, long-acting β-blockers (e.g., nadolol) are often effective, particularly in type 1 and also to some extent in type 2 LQTS.[169] Genotyping of individual patients is still not commonly available, but mutation-specific therapy for patients with LQTS and other genetically determined arrhythmias may be possible in the future.

ICDs for prevention of sudden cardiac death

Secondary prevention

In patients with serious symptomatic postinfarct ventricular arrhythmias, trial data conclusively demonstrated the superiority of the ICD over drugs, primarily amiodarone.[170] However, ICD shocks are painful and best avoided. Hence antiarrhythmic drugs (particularly amiodarone) are often used in conjunction with an ICD in many patients, to decrease the need for shocks or to allow termination by antitachycardia pacing.[33] In the OPTIC Trial, amiodarone plus a β-blocker was better than a β-blocker or sotalol alone without major adverse effects on defibrillation threshold.[59],[171] In practice β-blockade plus amiodarone is standard therapy for recurrent VT in ICD patients. Catheter ablation of the arrhythmogenic substrate is an effective approach[172] that is being increasingly applied.

Primary prevention: Post–myocardial infarction

In the *primary* prevention of SCD in patients without symptomatic arrhythmias, five trials of patients with underlying coronary artery disease, almost all including patients with a prior history of MI (months to years previously) and low EFs, have provided guidelines. These are MADIT I,[173],[174] MUSTT,[42] MADIT II,[175] SCD-HeFT[58] and DINAMIT.[176] What has been problematic and has led to a degree of inconsistency between guidelines has been the relatively wide range of EFs chosen for enrollment into different trials.

Nonetheless, a consensus has emerged as reflected in current ICD guidelines.[177]

1. In patients with coronary artery disease and a documented prior MI (>40 days), New York Heart Association (NYHA) Class 2-3 CHF, ICD implantation is indicated in patients with an EF of 35% or less, irrespective of QRS width. This also applies to patients with inducible sustained arrhythmias on EP testing, approximately 4 weeks or more following MI. In patients with NYHA Class 1 symptoms, the evidence is less conclusive and a more stringent EF cut-off of 30% or less is recommended. In patients with an EF of 35% to 40%, invasive EP testing to assess inducibility remains an option although the use of the EP study is declining.
2. In patients with an EF of more than 40%, there is no need for further arrhythmia evaluation unless the patient is experiencing symptomatic palpitations, near syncope, or syncope. The problem arises in the extrapolation of these trials to predischarge survivors of an AMI, because the DINAMIT trial of patients 8-40 days post-MI was neutral.[176] The decision is further complicated by changes in the EF during the first 4 weeks after infarction, especially in patients receiving reperfusion therapy. This underlies current recommendations to wait at least 40 days before deciding whether to implant an ICD for primary prevention of SCD post-MI. The role of the ambulatory external defibrillator during the “waiting period” is currently the subject of an ongoing trial.

ICDs in dilated cardiomyopathy

The majority of prior trials were confined to patients with ischemic cardiomyopathy, but recent trials demonstrate that the results appear to apply equally to patients with nonischemic dilated cardiomyopathy although the results of the initial smaller trials were inconclusive.[44],[178]

In the DEFINITE multicenter study on 458 patients with a mean EF of 21% and almost all on modern medical therapy including β-blockers and ACE inhibitors, the ICD substantially reduced arrhythmic but not all-cause mortality.[179] A large multicenter trial on approximately 2500 patients with heart failure, the Sudden Cardiac Death-Heart Failure Trial (SCD-HEFT), showed a 23% fall in mortality compared with placebo with ICD therapy but no difference with amiodarone treatment.[58] Results were equally impressive whether or not the origin of the heart failure was ischemic or nonischemic, which is the first time this has been shown. The consensus is that recommendations should be the same for patients with ischemic or nonischemic cardiomyopathy. Thus patients with NYHA Class 2-3 CHF, EFs lower than 35%, and nonischemic dilated cardiomyopathy are candidates for ICD implantation. In patients with Class 1 symptoms this remains a zone of some uncertainty because of a lack of data, and the EF cut-off is 30% or less. Class 4 CHF is a contraindication to ICD use unless the patient has met the requirements for CRT therapy.

In the future, more exact risk stratification will probably help guide the decision of whether to use an ICD. In the meantime, a practical point also discerned in SCD-HEFT[58] is that lack of β-blocker use is an important risk predictor of arrhythmia.[180] Of note, in those with severe LV dysfunction (mean EF only 21%) plus an arrhythmia marker, optimal medical therapy including β-blockade and ACE inhibition reduced the annual mortality to only 6% to 7%, and standard heart failure medications[179],[180] are an essential adjunct to ICD implantation. In addition, in two post-MI trials in which there was no ICD aldosterone blockade reduced SCD (EPHESUS and RALES). Co-morbidities play an important role in deciding whether an ICD will improve survival.[181]

ICD plus cardiac resynchronization therapy

The previous arguments for ICD placement in selected patients with severe heart failure lead to a further question: Can added CRT by biventricular pacing do even better? This issue arises especially in those with a prolonged QRS interval, who in their own right are candidates for resynchronization. In the large COMPANION study this combination of devices reduced all-cause mortality in those with class III or IV chronic heart failure (QRS interval ≥120 milliseconds) by 36% (Fig. 8-16).[182] Unfortunately, the effect of an ICD alone was not assessed, so that this combined approach is not yet firmly established. CRT acts in complex ways to achieve some remodeling of the failing left ventricle, which in itself may reduce the incidence of SCD.[183] Although CRT gave benefit in some studies even with a “narrow” QRS, a wide QRS means a greater likelihood of mechanical delay and thus a greater potential for success.[184],[185]

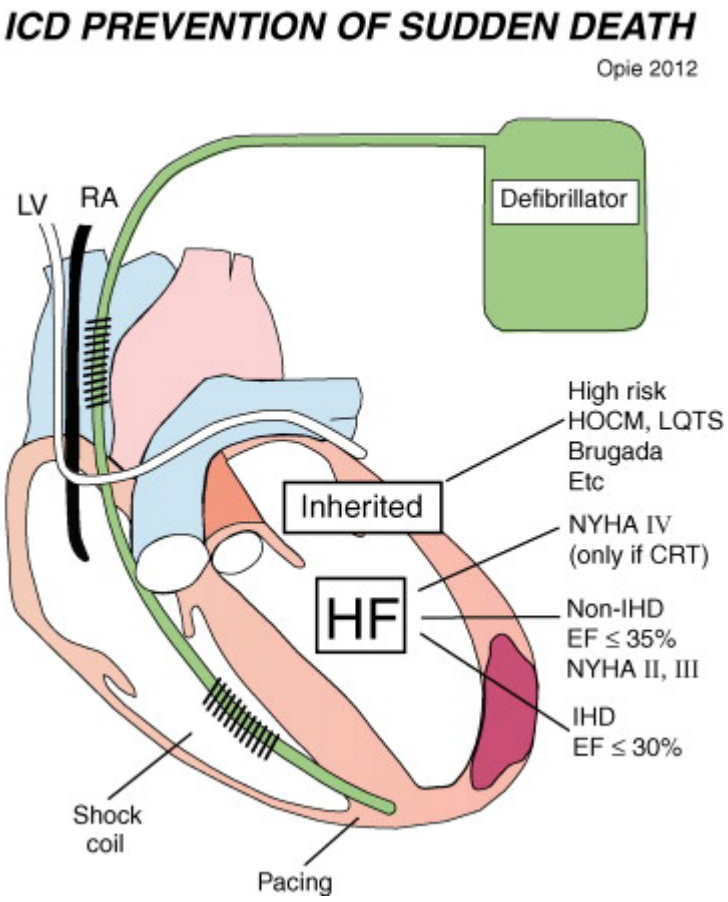

Figure 8-16 Suggested policy for use of implantable cardioverter defibrillator to prevent sudden cardiac death, including patients with ischemic heart disease (IHD) and heart failure (HF). The implantable automatic defibrillator is an electronic device designed to detect and treat life-threatening tachyarrhythmias. The device consists of a pulse generator and electrodes for sensing and defibrillating. *CRT,* cardiac resynchronization therapy; *EF,* ejection fraction; *HOCM,* hypertrophic obstructive cardiomyopathy; *LQTS,* long-QT syndrome; *LV,* left ventricular; *NYHA,* New York Heart Association; *R,* Right atrial. For further details see Epstein A et al., 2008.
(Figure © L.H. Opie, 2012.)

ICD shocks: Antiarrhythmic drug prophylaxis

ICDs deliver high-voltage shocks to terminate potentially fatal ventricular arrhythmias. Shocks may also be caused by atrial arrhythmias. Modern dual-chamber ICDs are able to terminate some ventricular arrhythmias, thereby reducing but not eliminating shocks, which still occur especially in the first year after ICDS implant.[59] Although β-blockade is standard therapy, the combination with amiodarone is much better.[59]

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Summary

1. ***Antiarrhythmic drug classification.*** These are grouped into four classes: class I, sodium channel blockers; class II, β-adrenergic blockers; class III, repolarization blockers; and class IV, those agents that block the calcium current in the AV node, such as some CCBs (verapamil and diltiazem) and adenosine. Class I agents are used less and less because of adverse long-term effects, except for the acute use of intravenous lidocaine or procainamide, and agents that are safe only in the absence of structural heart disease (flecainide and propafenone). Class II, the β-blockers, are especially effective in hyperadrenergic states such as chronic heart failure, some repetitive tachycardias, and ischemic arrhythmias. Among class III agents, amiodarone is a powerful antiarrhythmic agent, acting on both supraventricular and ventricular arrhythmias, but potentially toxic, sometimes even when used in a very low dose, and therefore often not regarded as a first-line agent except when intravenously given as in cardiac arrest. Class IV agents are excellent in arresting acute supraventricular tachycardias (adenosine is preferred), and also reduce ventricular rates in chronic AF (verapamil and diltiazem).
2. ***Current trends in arrhythmia therapy.*** The complexity of the numerous agents available and the ever-increasing problems with side effects and proarrhythmic events have promoted a strong trend toward intervention by ablation or devices. For example, an ICD is now increasingly used in the presence of severe heart failure.
3. ***Supraventricular arrhythmias.*** In terms of drug effects, the acute therapy of supraventricular arrhythmias is assuming an increasingly rational basis with a prominent role for adenosine, verapamil, or diltiazem in inhibition of supraventricular tachycardias involving conduction through the AV node. Sodium blockers can inhibit the bypass tract or retrograde fast AV nodal conduction, as can class III agents, such as sotalol or amiodarone. Ablation is increasingly used for long-term management of most symptomatic cases of SVT.
4. ***Atrial flutter.*** Ibutilide, given intravenously, or dofetilide, given orally, are effective for drug-induced reversion of atrial flutter. These should not be given to patients at risk of torsades de pointes (check QT interval, electrolyte status, and other drugs taken). Cardioversion is often the treatment of choice. Ibutilide sensitizes the flutter to the effects of cardioversion. Ablation is often chosen for chronic therapy.
5. ***Acute-onset AF.*** For acute-onset AF, control of the ventricular rate can be achieved by AV nodal inhibitors, such as verapamil or diltiazem, or intravenous β-blockade by esmolol, metoprolol, or propranolol, or by combinations. Pharmacologic conversion can usually be achieved by intravenous ibutilide or, if there is no structural heart disease, flecainide or propafenone. Note the risk of postconversion ventricular arrhythmias. Amiodarone has a slower onset of action, but also slows the heart rate and has no postconversion ventricular arrhythmias. If drugs fail to restore sinus rhythm, DC defibrillation given externally or (even better) transvenously has a very high success rate.
6. ***Recurrent AF: rate control.*** For patients with recurrent forms of AF, the choice between rate and rhythm control is never easy. With either policy, optimal anticoagulation should be continued indefinitely because many episodes of AF are asymptomatic and unsuspected. The AFFIRM and smaller European trials have, however, changed practice by showing that rate control has similar outcomes to rhythm control. *One practical policy* is to attempt cardioversion for the first episode of AF. Then if this arrhythmia returns and is asymptomatic, rate control is in order. In the absence of heart failure, the drugs of choice are β-blockers, rate-lowering CCBs (verapamil and diltiazem), or combination therapy, with digoxin for selected patients. In those with heart failure, the rate-lowering CCBs are omitted, leaving β-blockers with or without digoxin. In those with coronary artery disease, β-blockers and rate-lowering CCBs are preferred because of their concomitant antianginal actions. Radiofrequency ablation of the AV node (followed by pacing) is increasingly selected for patients who find drugs difficult or who are refractory to their effects.

7. ***Algorithm for rhythm control for recurrent or persistent AF.*** In patients with normal systolic function and no history of heart failure, the first-line agents are flecainide, propafenone, or sotalol. Thereafter, amiodarone becomes a secondary option, in view of its potentially serious side effects. Use of dronedarone is now more limited because of recent warnings about the risk of serious organ side effects, although it can nevertheless be quite useful in selected patients.
8. ***Rhythm control for patients with a history of heart failure or with LV systolic dysfunction.*** If the EF is more than 35%, then amiodarone or sotalol are the choices. If the EF is 35% or less, amiodarone is chosen. Repeated cardioversion may also be required. There may be a rapidly firing pulmonary vein focus that responds to ablation.
9. ***Chronic AF.*** Here again the choice is between rate and rhythm control with careful anticoagulation. However, defibrillation is less likely when AF is more than 7 days in duration when dofetilide is chosen.
10. ***New anticoagulant agents for chronic AF.*** The major recent advance has been the introduction of the new specific anticoagulants, dabigatran as an antithrombin agent and the antifactor Xa agents apixaban and rivaroxaban. These drugs have simple fixed doses that do not require monitoring. They reduce the risk of intracranial strokes or bleeding when compared with warfarin. Rarely, they may give rise to excess bleeding for which there is no clinically established therapeutic antidote. PCC may be tried without, however, any solid positive clinical evidence as yet.
11. ***Ventricular arrhythmias.*** Ventricular arrhythmias and their therapy remain controversial and constantly evolving. Antiarrhythmic drug therapy is only one avenue of overall management, as ICDs are increasingly used in severe ventricular arrhythmias, especially when the EF is low. Moreover, antiarrhythmic drugs have been disappointing in preventing SCD, other than β-blockers and other antifailure drugs. A distinction must be made between suppression of premature ventricular complexes, which is useless (unless causing persistent symptoms) and the control of VT and VF, which can prolong life. In acute AMI, lidocaine is no longer given prophylactically. In postinfarct patients, β-blockers remain the drugs of choice, although amiodarone has good evidence in its favor. ICDs are now the standard of choice in selected patients.
12. ***ICDs.*** In CHF, optimal management of the hemodynamic and neurohumoral status, including the use of ACE inhibitors and β-blockade, must be instituted before the prophylactic use of antiarrhythmic drugs or an ICD. In severe heart failure, ICD therapy is probably the single most important aspect of antiarrhythmic therapy. The combination of ICD and cardiac resynchronization by biventricular pacing is increasingly considered, especially when there is QRS prolongation.
13. ***Hybrid pharmacologic drugs and device or ablation therapy.*** Hybrid pharmacologic drugs and device or ablation therapy are options increasingly used for disabling AF or for severe and serious ventricular arrhythmias. Thus β-blockade and amiodarone may be combined with ICDs to give optimal results.
14. ***New antiarrhythmic agents.*** New agents have been investigated in recent years. Most have been variations of the class IC or class III drugs that are already available. In many instances the assessment of these drugs has revealed a negative benefit-risk ratio. Only ibutilide and dofetilide have so far been approved for clinical use. Ibutilide is given intravenously and dofetilide orally. Both benefit atrial tachyarrhythmias, yet both have prominent warnings regarding torsades. Dronedarone has proven value in preventing hospitalizations and reducing cardiovascular death rates in patients with paroxysmal and persistent cardioverted AF, but concerns have been raised by risk profiles in permanent-AF patients and those with a history of heart failure.

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