Chapter 3
Class III Antiarrhythmic Drugs

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Introduction

Class III antiarrhythmic drugs (AADs) predominantly block outward-repolarizing potassium currents and prolong cardiac action potential duration (APD) and refractoriness at concentrations at which they do not affect the sodium channels and, therefore, intracardiac conduction velocity is not significantly affected [1]. The prolongation of the APD and refractoriness, combined with the maintenance of normal conduction velocity, leads to an increase in the wavelength of the cardiac impulse, defined as the distance travelled by the depolarization wave

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during the functional refractory period, closes the excitable gap in the reentrant circuit and suppresses reentry (Fig. 3.1). Class III AADs include: amiodarone, dofetilide, dronedarone, ibutilide and sotalol.

However, class III AADs present several disadvantages. First, some of them exhibit reverse-use dependence, i.e. the prolongation of the APD increases at normal or at slower heart

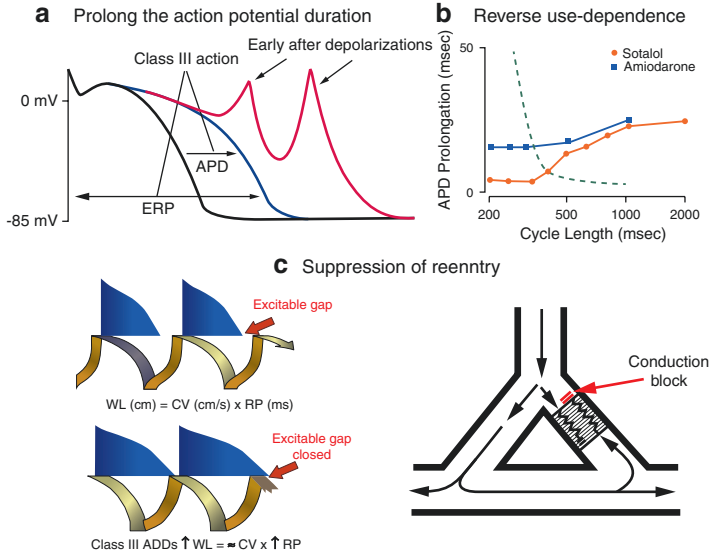

Figure 3.1 Class III antiarrhythmic drugs (AADs). (**a**) Class III AADs prolong the cardiac action potential duration (APD) and refractoriness (ERP) and under certain circumstances can induce early depolarizations that induce a polymorphic ventricular tachycardia (torsades de pointes). (**b**) Many class III AADs prolong the APD at slow but not at normal or fast heart rates, i.e., they exhibit reverse use-dependence. (**c**) Class III AADs prolong the APD/ERP, do not modify the conduction velocity (CV) and increase the wavelength of the cardiac impulse (WL), defined as the distance travelled by the depolarization wave during the functional refractory period. As a consequence, they close the excitable gap in the reentrant circuit and they can prevent or abolish reentry. Because the APD/ERP is longer than the conduction time around a reentrant circuit, class III AADs can prevent or abolish impulse reentry

rates (during bradycardia or after a long diastolic interval) but declines as heart rate is increased (i.e., during tachyarrhythmias), which limits their antiarrhythmic efficacy (Fig. 3.1). Second, they produce an excessive and sometimes inhomogeneous prolongation of the ventricular APD (QT interval), which increases the transmural dispersion of cardiac repolarization and can induce early afterdepolarizations (Fig. 3.1) that can trigger the development of polymorphic ventricular tachycardias called torsades de pointes (TdP). The risk of ventricular proarrhythmia is a serious limitation of class III AADs. Third, these drugs produce an acquired long QT syndrome and they should be avoided in combination with other QT-prolonging drugs. Table 3.1 summarizes the main QT-prolonging drugs and the risk factors that predispose to TdP.

Table 3.1 (A) Risk factors for QT prolongation, and (B) QT-prolonging drugs [11]

(A)

- Heart diseases: ischemic heart disease, heart failure, myocarditis, dilated/hypertrophic cardiomyopathy
- Age > 65 years
- Female gender
- High plasma concentrations of QT-prolonging drugs (excessive doses, decreased metabolism and/or excretion)
- Electrolyte abnormalities: hypokalemia, hypomagnesemia, hypocalcemia
- Cerebrovascular diseases: subarachnoid hemorrhage, ischemic stroke, cerebrovascular accidents
- Bradyarrhythmias: bradycardia, AV block, recent cardioversion of AF
- Premature complexes leading to short-long-short cycles
- Baseline QTc prolongation (>500 ms)
- Coadministration of drugs that prolong the QT interval
- Genetic polymorphisms (congenital long QT syndrome)

(continued)

Table 3.1 (continued)

(B)	
Antiarrhythmic drugs	Amiodarone, disopyramide, dofetilide, dronedarone, ibutilide, procainamide (n-acetylprocainamide), quinidine, sotalol
Antiemetics	Dolasetron, domperidone, ganisetron, ondansetron
Antimicrobials	Azole antifungals (fluconazole, itraconazole, ketoconazole), chloroquine, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin), macrolides (azithromycin, clarithromycin, erythromycin), pentamidine
Psychotropic drugs	Citalopram, clozapine, droperidol, escitalopram, haloperidol, phenothiazines, quetiapine, risperidone, sertindol, thioridazine, tricyclic antidepressants, venlafaxine, ziprasidone
Cancer chemotherapy drugs	Amsacrine, anthracyclines (daunorubicin, doxorubicin, epirubicin), arsenic trioxide, 5-fluorouracil, histone deacetylase inhibitors (romidepsin, panobinostat, vorinostat), mitoxantrone, paclitaxel, tamoxifen
	Tyrosine kinase inhibitors: carbozantinib, crizotinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib, vandetanib, vemurafenib
Others	Antihistamines (diphenhydramine, terfenadine, hydroxyzine), bepridil, droperidol, levomethadyl, methadone, octreotide, probucol, protease inhibitors (delavirdine, indinavir, nelfinavir, saquinavir, ritonavir), sumatriptan, thiazides, zolmitriptan

In this chapter, we review the electrophysiological and pharmacological properties, adverse effects and clinical indications of amiodarone, dofetilide, dronedarone, ibutilide and sotalol. Their pharmacokinetic properties, adverse effects, doses and clinical indications are summarized in Tables 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, and 3.8.

TABLE 3.2 Pharmacokinetic characteristics of antiarrhythmic drugs

Drugs	F (%)	T_{max} (h)	PPB (%)	Vd (L/kg)	Metabolism	$t_{½}$ (h)	Renal excretion[a] (%)
Amiodarone	35–65	3–8	99	66	CYP3A4 and 2C8	53 (20–100 days)	1
Dofetilide	95	2–3	65	3–4	CYP3A4	7–13	80
Dronedarone	5	3–6	>98	20	CYP3A4	13–19	15
Ibutilide (IV)	100	1.5	40	11	No CYP3A4/2D6	6 (2–12)	7[a]
Sotalol	90–100	2.5–4	0	1.5–2.5	Not metabolized	12 (7–18)	85

F oral bioavailability, *h* hours, *IV* intravenous, *PPB* protein plasma binding, $t_{1/2}$ drug half-life, T_{max} time to peak plasma levels, *Vd* volume of distribution

[a]Renal excretion without biotransformation

Table 3.3 Adverse effects, contraindications and cautions

Drug	Adverse effects	Contraindications and cautions
Amiodarone	1. Oral Amiodarone: • Cardiovascular: hypotension, bradycardia, AVB, QT prolongation, TdP (rare), slows VT below programmed ICD detection rate, increases defibrillation threshold • Extracardiac: gastrointestinal (nausea, emesis, constipation), ocular (corneal microdeposits, optic neuritis), thyroid abnormalities (hyper- or hypothyroidism), pulmonar (fibrosis, pneumonitis) cutaneous (photosensitivity, blue-gray skin), neurological (ataxia, dizziness, peripheral neuropathy, tremor), hepatotoxicity (increase in transaminases, hepatitis, cirrhosis). Postoperative adult respiratory distress syndrome (rare) 2. IV Amiodarone: hypotension, bradycardia, phlebitis at site of administration. QT prolongation, torsades de pointes (rare)	1. Contraindications: Sinus bradycardia, severe sinus node dysfunction, and 2nd- or 3rd-degree heart block (unless a pacemaker is present). Infranodal conduction disease, cardiogenic shock, severe lung disease, history of thyroid dysfunction or hypersensitivity to amiodarone or to iodine. Hepatic dysfunction. • Baseline QTc >470 ms, conditions and drugs that prolong the QT interval prolongation. 2. Cautions: in patients with hypokalemia and/or hypomagnesaemia, congenital or acquired LQTS, taking QT-prolonging drugs. • Delayed conversion to sinus rhythm (up to 8–12 hours) • IV amiodarone contains benzyl alcohol, which may cause fatal "gasping syndrome" in infants and children up to 3 years old

Dofetilide	• QT prolongation, VT and TdP • Headache, dizziness, nausea, chest pain, insomnia	• Contraindications: CrCl <20 mL/min, congenital or acquired long QT syndrome (baseline QTc >440 ms; >500 ms in patients with ventricular conduction problems), previous TdP or known hypersensitivity to dofetilide. Discontinue dofetilide if at any time after a second dose QTc >500 ms (550 ms with ventricular conduction abnormalities). Avoid other QT-prolonging drugs • Cautions: patients with AVB, bradycardia, hypokalemia, hypomagnesemia, diuretic therapy, moderate baseline QT interval prolongation, proarrhythmic events, liver or renal impairment. QT-prolonging drugs. • Avoid the combination with cimetidine, hydrochlorothiazide, ketoconazole, trimethoprim, prochlorperazine or megestrol.

(continued)

Table 3.3 (continued)

Drug	Adverse effects	Contraindications and cautions
Dronedarone	Diarrhea, nausea, vomiting, rash, photosensitivity. It does not affect thyroid or pulmonar functions. Increases serum creatinine levels	1. Contraindications: bradycardia (<50 bpm), 2nd- or 3rd-degree AVB, complete bundle branch block, distal block, sinus node dysfunction, atrial conduction defects, or sick sinus syndrome, unless a pacemaker is present. Patients with LV systolic dysfunction or current or previous HF, permanent AF, unstable hemodynamic conditions, baseline QTc ≥500 ms, severe hepatic or renal impairment (CrCl <30 mL/min) or liver and lung toxicity related to previous use of amiodarone. Potent CYP3A4 inhibitors and QT prolonging drugs should be avoided 2. Interactions. Dronedarone is metabolized by CYP3A: caution with inhibitors (eg., diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, verapamil, grapefruit juice) and inducers (eg., phenobarbital, phenytoin, rifampin). It inhibits CYP3A4, CYP2D6, P-glycoprotein: increases the exposure to some beta blockers, digoxin, sirolimus, statins, tacrolimus. Monitor the INR.

Ibutilide (IV)	QT prolongation, TdP (3–4% of patients). Slows ventricular rate	1. Contraindications: baseline QTc >440 ms, advanced or unstable heart disease, congenital or acquired long syndrome, uncorrected hypokalemia or hypomagnesemia, history of polymorphic VT or proarrhythmia, bradycardia or sick sinus syndrome 2. Cautions: patients with HF, liver disease or recent MI.
Sotalol	• Cardiovascular: bradycardia, AVB, hypotension, HF, syncope, QT prolongation, TdP • Others: fatigue, dizziness, weakness, lightheadedness, dyspnea, bronchitis, nausea, diarrhea, fainting, anxiety, depression	1. Contraindications: Sinus bradycardia, sick sinus syndrome, or 2nd- and 3rd-degree AVB (unless a pacemaker is present); congenital or acquired LQTS; cardiogenic shock, decompensated systolic HF, Prinzmetal's angina, Raynaud's phenomenon and severe peripheral circulatory disturbances, renal failure (CrCl <40 mL/ min), asthma or related bronchospastic conditions. Avoid other QT-prolonging drugs. 2. Cautions: patients with bradycardia, hypotension. Drugs with SA and/or AV–nodal blocking properties. Hypokalemia and diuretic therapy increase QT prolongation

AAD antiarrhythmic drugs, *AF* atrial fibrillation, *AV* atrio-ventricular, *AVB* atrio-ventricular block, *CrCl* creatinine clearance, *HF* heart failure, *ICD* implantable cardiac defibrillator, *INR* international normalized ratio, *IV* intravenous, *LQTS* long *QT* syndrome, *LV* left ventricular, *MI* myocardial infarction, *SA* sinoatrial, *TdP* torsades de pointes, *VT* ventricular tachycardia

Table 3.4 Drug interactions of amiodarone

Drug	Pharmacodynamic/pharmacokinetic	Implications
Agalsidase alfa or beta		Avoid the combination
Anesthetics, general	Increased risk of bradycardia, hypotension and decreased cardiac output	Patients should be carefully monitored for potential cardiovascular complications
Oral anticoagulants: apixaban, dabigatran, edoxaban, rivaroxaban	Amiodarone increases drug exposure and the risk of bleeding	With caution
Antihypertensives	Increase the risk of hypotension	Monitor BP when amiodarone is given IV
Antiviral drugs: daclasvir, ledipasvir/sofosbuvir, sofosbuvir	Severe bradycardia with this combination	Monitor heart rate during the first 48 h
Beta-blockers	Increase the risk of hypotension, bradycardia and AVB	Monitor BP and ECG
Bile acid sequestrants (resins)	Reduce the absorption of amiodarone	Administer amiodarone 1 h before or 4 h after the resin
Cyclosporine	Amiodarone reduces the clearance and increases the Pc of cyclosporine	Monitor cyclosporine toxicity (renal, hypertension)
Cimetidine	Inhibits the metabolism of amiodarone and increases its Pc	Decrease the dose of amiodarone

Class I and III AADs	Amiodarone increases the Pc of class I AADs. Increase the risk of proarrhythmia. Amiodarone inhibits the clearance and increases the Pc of flecainide	Avoid the combination. Monitor the ECG for excessive QT prolongation and proarrhythmia. Reduce (30–50%) the dose of flecainide
Class IV AADs: diltiazem, verapamil	Increase the risk of bradycardia, AVB, hypotension and HF. Amiodarone increases the Pc of diltiazem	Monitor the ECG and BP
Clopidogrel	Amiodarone inhibits CYP3A4 and the formation of the active metabolite of clopidogrel	Prescribe an alternative platelet $P2Y_{12}$ receptor inhibitor
Digoxin	Amiodarone inhibits P-gp, decreases the clearance and increases the Pc of digoxin and the risk of bradycardia and AVB	Monitor the digoxin plasma levels. Reduce (30–50%) the dose of digoxin and monitor the ECG
Dopamine, dobutamine	Amiodarone exhibits β-adrenergic blocking effects	Higher IV doses of dopamine and dobutamine are needed

(continued)

TABLE 3.4 (continued)

Drug	Pharmacodynamic/pharmacokinetic	Implications
Drugs that cause hypokalemia and/or hypomagnesaemia: • Amphotericin, loop and thiazide diuretics, systemic corticosteroids, tetracosactide, laxatives	Prolong the QT interval	Monitor serum potassium and magnesium levels. Monitor the ECG
Fentanyl	Increases the risk of hypotension, bradycardia, and decreases cardiac output	Monitor the hemodynamic response
Grapefruit juice	Inhibits CYP3A4 and the metabolism of amiodarone	Avoid drinking grapefruit
HIV-Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir	Inhibit CYP3A4 and increase the Pc of amiodarone	Monitor the ECG. Avoid if possible
Ivabradine	Increases the risk of bradycardia and atrial fibrillation	Monitor the ECG
Lidocaine	Increased risk of bradycardia, and seizures	Monitor the ECG. Monitor lidocaine Pc/clinical response

Lithium	Reported cases of hypothyroidism	Monitor thyroid function
Methotrexate	Amiodarone decreases the metabolism of methotrexate	Monitor for the adverse effects of methotrexate
Phenytoin	Amiodarone inhibits hepatic metabolism of phenytoin; phenytoin increases the metabolism of amiodarone reducing its antiarrhythmic efficacy	Reduce the dose of phenytoin (50%). The interaction can take several weeks to become apparent
QTc-prolonging drugs (see Table 3.1)	Increase the risk of proarrhythmia (torsades de pointes)	Avoid the combination
Rifampicin	Decreases the serum levels of amiodarone	Monitor the ECG
Sotalol	Increases the risk of hypotension, bradycardia and QT prolongation	Monitor the hemodynamic response and the ECG
Statins: atorvastatin, rosuvastatin, simvastatin	Increase the risk of myopathy	Doses of lovastatin and simvastatin should not exceed 40 mg/day and 20 mg/day, respectively

(continued)

TABLE 3.4 (continued)

Drug	Pharmacodynamic/pharmacokinetic	Implications
St. John's wort	Decreases the plasma levels of amiodarone	Avoid the combination
Theophylline	Amiodarone inhibits its metabolism	Monitor theophylline toxicity (nausea, tremor, tachycardia, nervousness)
Warfarin	Amiodarone reduces its metabolism and increases the prothrombin time and the risk of bleeding	Reduce (50%) the dose of warfarin. Monitor the INR

AADs antiarrhythmic drugs, *AV* atrio-ventricular, *AVB* atrio-ventricular block, *BP* blood pressure, *CYP* cytochrome P450 superfamily, *ECG* electrocardiogram, *HIV* human immunodeficiency virus, *HF* heart failure, *INR* international normalized ratio, *IV* intravenously, *Pc* plasma levels, *P-gp* P-glycoprotein

Table 3.5 Doses of class III antiarrhythmics

Drug	Doses
Amiodarone (oral)	• PO loading. Rapid control of an urgent arrhythmia: 800–1600 mg/day (in 2–4 divided doses) for 1–3 weeks; then 400–800 mg/day for 3–4 weeks. In less urgent settings: 600–1200 mg daily for 1–3 weeks and 400 mg/day for the next several weeks. A high-dose oral loading can suppress ventricular arrhythmias within 5 days. Maintenance dose: up to 200 mg o.d. (to minimize long-term adverse effects) • Maintenance of SR in AF. Initially 600 mg daily in divided doses for 4 weeks; 400 mg for 4 weeks; maintenance: 100–200 mg o.d. • Rate control in AF: 100–200 mg o.d • VA. Loading dose: 400 mg every 8–12 h for 1–2 weeks, then 300–400 mg daily; reduce dose to 200 mg daily if possible
Amiodarone (IV)	IV amiodarone (diluted in 5% glucose) should be initiated/maintained in hospital under specialist supervision • Loading: 150 mg over 10 min, followed by 360 mg over 6 h; then 540 mg over the remaining 24 h (total of 1050 mg over 24 h. IV maintenance: 0.5–1 mg/min • Cardioversion of AF: 5–7 mg/kg IV for 1–2 h, followed by 50 mg/h to a maximum of 1 g over 24 h • SVT: 150 mg IV over 10 min. Maintenance: 1 mg/min (360 mg) over next 6 h; then 0.5 mg/min (540 mg) over remaining 18 h. • Maintenance of SR in AF: 1 mg/min for 6 h; then 0.5 mg/min for 18 h or change to oral dosing; after 24 h, decrease the dose to 0.25 mg/min • Rate control in AF: 300 mg over 30–60 min (preferably via central venous cannula); then, 900 mg IV over 24 h diluted in 500–1000 mL. • Termination of VT: 150 mg IV over 10 minutes • Incessant VT or frequent VT episodes: 150 mg bolus over 10 min, followed by 1 mg/min over the next 6 h and 0.5 mg/min over the remaining 18 h total 1050 mg over 24 h • VF/pulseless VT arrest: 2.5–5 mg/kg bolus monitoring; another dose of 2.5 mg/kg if the VF persists after a further shock • Stable VT: 150 mg bolus. Then, 1 mg/min for 6 h, then 0.5 mg/min × 18 h

(continued)

TABLE 3.5 (continued)

Drug	Doses
Dofetilide	• PO. CrCl >60 mL/min: 500 mcg bid. CrCl 40–60 mL/min: 250 mcg bid. CrCl 20- < 40 mL/min: 125 mcg bid. CrCl <20 mL/min: Dofetilide is contraindicated • If 2–3 h after the first dose the QTc has increased >15% compared to the baseline or the QTc is >500 msec (550 msec in patients with ventricular conduction abnormalities) doses should be readjusted as follows: 500 mcg bid → 250 mscg bid; 250 mcg bid → 125 bid and 125 mcg bid → 125 mcg od. If at any time after the second dose is given the QTc is >500 msec (550 msec in patients with ventricular conduction abnormalities), dofetilide should be discontinued
Dronedarone	Rate control in AF: 400 mg bid with food
Ibutilide (IV)	0.01 mg/kg (<60 kg) or 1 mg (>60 kg) over 10 min; repeat after 10 min if the arrhythmia persists
Sotalol	1. SVT/VA. Oral: 40–80 mg bid initially. Increase the dose every 2–3 days to 120–160 mg bid. IV: 75 mg over 5 h every 12 h initially; adjusted if necessary every 3 days. Max dose: 150 mg every 12 h • Maintenance of SR in AF: 40–160 mg bid 2. Refractory life-threatening VA. Oral: 80 mg bid initially. Increase the dose as needed every 2–3 days to 160–320 mg/day divided every 8–12 h; up to 480–640 mg/day may be required if benefits outweigh the risk of adverse effects

AF atrial fibrillation, *Af* atrial flutter, *Bid* twice daily, *h* hours, *IV* intravenous, *o.d* once daily, *PO* per os (orally), *SVT* supraventricular tachycardia, *SR* sinus rhythm, *VA* ventricular arrhythmias, *VF* ventricular fibrillation, *VT* ventricular tachycardia

Table 3.6 Recommendations of class III AADs for the management of AF

I. Rate control in atrial fibrillation	*Class*	*Level*
Amiodarone is reasonable for pharmacological cardioversion of AF [24]	IIa	A
Dofetilide and IV ibutilide are useful for cardioversion of AF, provided contraindications are absent [24]	I	A
In patients with ischemic and/or structural heart disease, amiodarone is recommended for cardioversion of AF [27]	I	A
In the absence of pre-excitation, IV digoxin is recommended to control heart rate acutely in HF patients [24]	I	B
Digoxin is effective to control resting heart rate in patients with HF with reduced ejection fraction [24]	I	C
IV amiodarone can be useful for rate control in critically ill patients without pre-excitation [24]	IIa	B
A combination of digoxin and a β-blocker (or a nondihydropyridine calcium channel antagonist for patients with HFpEF) is reasonable to control resting and exercise HR in patients with AF [24]	IIa	B
In patients with hemodynamic instability or severely depressed LVEF, amiodarone may be considered for acute control of HR	IIb	B
Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated [24]	IIb	C

(continued)

Table 3.6 (continued)

In HF patients, IV amiodarone can be useful to control HR when other measures are unsuccessful or contraindicated [24]	IIa	C
Amiodarone may be considered when resting and exercise HR cannot be adequately controlled using a β-blocker (or a nondihydropyridine calcium channel antagonist in patients with HFpEF) or digoxin, alone or in combination [24]	IIb	C
Amiodarone or digoxin may be considered to slow RVR with ACS and AF and severe LV dysfunction and HF or hemodynamic instability [24]	IIb	C
In patients with pre-excitation and AF, digoxin or IV amiodarone should not be administered as they may increase the ventricular response and may result in ventricular fibrillation [24, 27]	III	B
Dronedarone should not be used to control ventricular rate with permanent AF as it increases the risk of the combined endpoint of stroke, myocardial infarction, systemic embolism, or cardiovascular death [24]	III	B
Dofetilide should not be initiated out of hospital because of the risk of excessive QT prolongation that can cause TdP [24]	III	B
Dronedarone should not be administered to patients with decompensated HF [24, 27]	III	B
2. Postoperative atrial fibrillation		
Preoperative amiodarone reduces AF with cardiac surgery and is reasonable as prophylactic therapy for patients at high risk of postoperative AF [24, 27]	IIa	A

It is reasonable to restore SR pharmacologically with ibutilide in patients with postoperative AF [24]	IIa	B
IV vernakalant may be considered for cardioversion of postoperative AF in patients without severe HF, hypotension, or severe structural heart disease (especially aortic stenosis) [27]	IIa	B
Prophylactic sotalol may be considered for patients with AF risk after cardiac surgery [24]	IIb	B
3. Pharmacological Cardioversion of atrial fibrillation		
Dofetilide and IV ibutilide are useful for cardioversion of AF, provided there are no contraindications [24]	I	A
In patients with no history of ischemic or structural heart disease, vernakalant is recommended for pharmacological cardioversion of new-onset AF [27]	I	A
In patients with ischemic and/or structural heart disease, amiodarone is recommended for cardioversion of AF [27]	I	A
Because of its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated [24]	I	C
IV ibutilide to restore SR or slow the ventricular rate is recommended for patients with pre-excited AF and rapid ventricular response who are not hemodynamically compromised [24]	I	C
Oral amiodarone is reasonable for pharmacological cardioversion of AF [24]	IIa	A
Pre-treatment with amiodarone or ibutilide should be considered to enhance success of electrical cardioversion and prevent recurrent AF [27]	IIa	B

(continued)

Table 3.6 (continued)

In patients with no history of ischemic or structural heart disease, ibutilide should be considered for pharmacological conversion of AF [27]	IIa	B
Vernakalant may be considered as an alternative to amiodarone for pharmacological conversion of AF in patients without hypotension, severe HF or severe structural heart disease (especially aortic stenosis) [27]	IIb	B
IV amiodarone can be useful to control heart rate with AF when other measures are unsuccessful or contraindicated [24]	IIb	C
Dofetilide should not be initiated out of hospital because of the risk of excessive QT prolongation that can cause TdP [24]	III	B
4. Rhythm control therapy in atrial fibrillation		
Amiodarone, dofetilide, dronedarone or sotalol are recommended in patients with AF to maintain SR, depending on underlying heart disease and comorbidities [24]	*I*	*A*
Dronedarone or sotalol are recommended for prevention of recurrent symptomatic AF in patients with normal LV function and without pathological LV hypertrophy [27]	I	A
Dronedarone is recommended for prevention of recurrent symptomatic AF in patients with stable coronary artery disease, and without HF [27]	I	A
Amiodarone is recommended for prevention of recurrent symptomatic AF in patients with HF [27]	I	B

Amiodarone is more effective in preventing AF recurrences than other AAD, but extracardiac toxic effects are common and increase with time. For this reason, other AAD should be considered first [24, 27]	I/II	C
Ibutilide should be considered for acute therapy of pre-excited AF [27]	IIa	B
Amiodarone combined with a β-blocker or nondihydropyridine calcium channel antagonists can be useful to prevent recurrent AF in patients with HCM	IIa	C
Sotalol, dofetilide, and dronedarone may be considered for a rhythm-control strategy in patients with HCM [24]	IIb	C
Dronedarone should not be used for treatment of AF in patients with NYHA class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks [24]	III	B
AADs for rhythm control should not be continued when AF becomes permanent [24, 27]	III	B
IV amiodarone is potentially harmful in patients with pre-excited AF [24, 27]	III	B
AAD therapy is not recommended in patients with prolonged QT interval (>0.5 s) or those with significant sinoatrial node disease or AV node dysfunction who do not have a functioning permanent pacemaker [27]	III	C

AAD antiarrhythmic drug, *ACS* acute coronary syndromes, *AF* atrial fibrillation, *Af* atrial flutter, *AV* atrioventricular, *HCM* hypertrophic cardiomyopathy, *HF* heart failure, *HFpEF* heart failure with preserved ejection fraction, *HR* heart rate, *IV* intravenous, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *SR* sinus rhythm, *RVR* rapid ventricular response, *TdP* torsades de pointes

Table 3.7 Recommendations of class III AADs for the management of supraventricular arrhythmias

Recommendations	Class/Level ACC/AHA/HRS [26]	Class/Level ESC [29]
1. Supraventricular tachycardia of unknown mechanism		
Ongoing Treatment		
Sotalol may be reasonable for ongoing management in patients with symptomatic SVT who are not candidates for, or prefer not to undergo, catheter ablation	IIb, B	
Dofetilide may be reasonable for ongoing management in patients with symptomatic SVT who are not candidates for, or prefer not to undergo, catheter ablation and in whom β-blockers, diltiazem, flecainide, propafenone, or verapamil are ineffective or contraindicated	IIb, B	
Oral amiodarone may be considered for ongoing management in patients with symptomatic SVT who are not candidates for, or prefer not to undergo, catheter ablation and in whom β-blockers, diltiazem, dofetilide, flecainide, propafenone, sotalol, or verapamil are ineffective or contraindicated	IIb, C	
Oral digoxin may be reasonable for ongoing management in patients with symptomatic SVT without pre-excitation who are not candidates for, or prefer not to undergo, catheter ablation	IIb, C	

2. Acute treatment of wide QRS tachycardia in the absence of an established diagnosis		
IV amiodarone may be considered if vagal manoeuvres and adenosine fail in the acute management of wide QRS tachycardia in the absence of an established diagnosis		IIb, B
3. Focal atrial tachycardia		
a) Acute Treatment		
IV amiodarone may be reasonable in the acute setting to either restore SR or slow the ventricular rate in hemodynamically stable patients with focal AT	IIb, C	IIb, C
IV ibutilide may be reasonable in the acute setting to restore SR in hemodynamically stable patients with focal AT	IIb, C	IIb, C
b) Ongoing Treatment		
Oral sotalol or amiodarone may be reasonable for ongoing management in patients with focal AT	IIb, C	
Amiodarone may be considered if other measures fail		IIb, C

(continued)

TABLE 3.7 (continued)

Recommendations	Class/Level ACC/AHA/HRS [26]	Class/Level ESC [29]
4. Atrial flutter/macro-reentrant tachycardia		
a) Acute Treatment		
Oral dofetilide or IV ibutilide, under close monitoring due to proarrhythmic risk, are useful for acute cardioversion in patients with Af	I, A	
IV ibutilide or IV or oral (in-hospital) dofetilide are recommended for conversion to in the absence of QTc interval prolongation		I, B
IV amiodarone may be tried if other measures are not available or desirable		IIb, C
IV amiodarone can be useful for acute control of the ventricular rate (in the absence of pre-excitation) in patients with Af and systolic HF when β-blockers are contraindicated or ineffective	IIa, B	
b) Ongoing Treatment		
Amiodarone, dofetilide or sotalol can be useful to maintain SR in patients with symptomatic, recurrent Af; drug choice depends on underlying heart disease and comorbidities	IIa, B	
Amiodarone may be considered to maintain SR if other measures fail		IIb, C

5. Treatment of AVNRT		
a) Acute Treatment		
IV amiodarone may be considered for acute treatment in hemodynamically stable patients with AVNRT when other therapies are ineffective or contraindicated	IIb, C	
b) Ongoing Treatment		
Oral sotalol or dofetilide may be reasonable for ongoing management in patients with AVNRT who are not candidates for, or prefer not to undergo, catheter ablation	IIb, B	
Oral digoxin or amiodarone may be reasonable for ongoing treatment of AVNRT in patients who are not candidates for, or prefer not to undergo, catheter ablation	IIb, B	
6. Therapy of AVRT due to manifest or concealed accessory pathways		
a) Acute Treatment		
IV ibutilide is beneficial for acute treatment in patients with pre-excited AF (orthodromic AVRT) who are hemodynamically stable	I, C	IIa, B

(continued)

Table 3.7 (continued)

Recommendations	Class/Level ACC/AHA/HRS [26]	Class/Level ESC [29]
b) Ongoing Treatment		
Oral amiodarone may be considered in patients with AVRT and/or pre-excited AF who are not candidates for, or prefer not to undergo, catheter ablation and in whom other AADs are ineffective or contraindicated	IIb, C	
Oral dofetilide or sotalol may be reasonable for ongoing management in patients with AVRT and/or pre-excited AF who are not candidates for, or prefer not to undergo, catheter ablation	IIb, B	
Amiodarone is not recommended and potentially harmful for acute treatment in patients with pre-excited AF	III, C	III, B
7. SVT in ACHD patients		
a) Acute Treatment		
IV ibutilide can be effective for acute treatment in ACHD patients and atrial flutter who are hemodynamically stable	IIa, B	
Oral dofetilide or sotalol may be reasonable for acute treatment in ACHD patients and AT and/or Af who are hemodynamically stable	IIb, B	

b) Ongoing Treatment		
Amiodarone may be reasonable for prevention of recurrent AT or Af in ACHD patients for whom other medications and catheter ablation are ineffective or contraindicated	IIb, B	IIb, C
Oral sotalol therapy can be useful for prevention of recurrent AT or Af in ACHD patients	IIa, B	
Oral dofetilide may be reasonable for prevention of recurrent AT or Af in ACHD patients	IIb, B	
Sotalol is not recommended as a first-line AAD as it is related to an increased risk of pro-arrhythmias and mortality		III, C
8. SVT during pregnancy		
a) Acute Treatment		
IV amiodarone may be considered for acute treatment in pregnant patients with potentially life-threatening SVT when other therapies are ineffective or contraindicated	IIb, C	
IV ibutilide may be considered for termination of atrial flutter		IIb, C

(continued)

Table 3.7 (continued)

Recommendations	Class/Level ACC/AHA/HRS [26]	Class/Level ESC [29]
b) Ongoing Treatment		
Oral amiodarone may be considered for ongoing management in pregnant patients when treatment of highly symptomatic, recurrent SVT is required and other therapies are ineffective or contraindicated	IIb, C	
Sotalol can be effective for ongoing management in pregnant patients with highly symptomatic SVT	IIa, C	
Amiodarone is not recommended in pregnant women		III, C

AADs antiarrhythmic drugs, *ACHD* adult congenital heart disease, *Af* atrial flutter, *AT* atrial tachycardia, *AVNRT* atrioventricular nodal reentrant tachycardia, *AVRT* atrioventricular reentrant tachycardia, *IV* intravenous, *SR* sinus rhythm, *SVT* supraventricular tachycardia

Table 3.8 Recommendations of class III AADs for the management of ventricular arrhythmias

Recommendations	Class	Level
Acute management of specific VA		
In patients with hemodynamically unstable VA that persist or recur after a maximal energy shock, IV amiodarone should be administered to attempt to achieve a stable rhythm after further defibrillation [28]	I	A
In patients with hemodynamically stable VT, administration of IV amiodarone or sotalol may be considered to attempt to terminate VT [28]	IIb	B
In patients with suspected acute MI, prophylactic administration of lidocaine or high-dose amiodarone for the prevention of VT is potentially harmful [28]	III	B
Management of Cardiac Arrest		
In patients with hemodynamically unstable VA that persist or recur after a maximal energy shock, IV amiodarone should be administered to attempt to achieve a stable rhythm after further defibrillation [28]	I	A
In patients with hemodynamically stable VT, administration of IV amiodarone or sotalol may be considered to attempt to terminate VT [28]	IIb	B
In patients with suspected acute MI, prophylactic administration of high-dose amiodarone for the prevention of VT is potentially harmful [28]	III	B

(continued)

Table 3.8 (continued)

Recommendations	Class	Level
Prevention and management of SCD associated with acute coronary syndromes: in-hospital phase		
IV amiodarone is recommended for the treatment of polymorphic VT [25]	I	C
Stable coronary artery disease after MI with preserved ejection fraction		
Amiodarone may be considered for relief of symptoms from VAs in survivors of a MI but it has no effect on mortality [25]	IIb	B
Treatment of PVC in patients with structural heart disease/left ventricular dysfunction		
In patients with frequent symptomatic PVC or NSVT amiodarone should be considered [25]	IIa	B
Treatment of patients with LV dysfunction and sustained recurrent monomorphic VT		
Amiodarone treatment should be considered to prevent VT in patients with or without an ICD [25]	IIa	C
Prevention of VT recurrences in patients with LV dysfunction and sustained VT		
Amiodarone is recommended in patients with recurrent ICD shocks due to sustained VT [25]	I	B
Amiodarone should be considered after a first episode of sustained VT in patients with an ICD [25]	IIa	B
Treatment and prevention of Recurrent VA in Patients With Ischemic Heart Disease		

In patients with ischemic heart disease and recurrent VA, with significant symptoms or ICD shocks despite optimal device programming and ongoing treatment with a β-blocker, amiodarone or sotalol is useful to suppress recurrent VA [28]	I	B
Secondary Prevention of SCD in Patients With NICM		
In patients with NICM who survive a cardiac arrest, have sustained VT, or have symptomatic VA who are ineligible for an ICD (due to a limited life-expectancy and/or functional status or lack of access to an ICD), amiodarone may be considered for prevention of SCD [28]	IIb	B
Treatment of Recurrent VA in Patients With NICM		
In patients with NICM and an ICD who experience spontaneous VA or recurrent appropriate shocks despite optimal device programming treatment with amiodarone or sotalol can be beneficial [28]	IIa	B
Treatment of PVC-induced cardiomyopathy		
Amiodarone is reasonable to reduce recurrent arrhythmias, and improve symptoms and LV function [28]	IIa	B
Treatment of patients with hypertrophic cardiomyopathy		
In patients with HCM and a history of sustained VT or VF, amiodarone may be considered when an ICD is not feasible or not preferred by the patient [28]	IIb	C

(continued)

Table 3.8 (continued)

Recommendations	Class	Level
Treatment of patients with dilated cardiomyopathy		
Amiodarone should be considered in patients with an ICD that experience recurrent appropriate shocks in spite of optimal device programming [25]	IIa	C
Amiodarone is not recommended for the treatment of asymptomatic NSVT in patients with DCM [25]	III	A
Arrhythmogenic right ventricular cardiomyopathy		
Amiodarone should be considered to improve symptoms in patients with frequent PVC or NSVT who are intolerant of or have contraindications to β-blockers [25]	IIa	C
Short QT Syndrome		
Sotalol may be considered in asymptomatic patients with a diagnosis of SQTS and a family history of SCD [25]	IIb	C
Management of arrhythmias during pregnancy		
Sotalol should be considered for acute conversion of hemodynamically stable monomorphic sustained VT [25]	IIa	C

IV amiodarone should be considered for acute conversion of sustained, monomorphic VT when hemodynamically unstable, refractory to electrical cardioversion or not responding to other drugs [25]	IIa	C
Adult Congenital Heart Disease		
Prophylactic treatment with anti-arrhythmic drugs (other than β-blockers) is not recommended [25]	III	B
In patients with ACHD who have asymptomatic VA, prophylactic therapy with amiodarone is potentially harmful [25, 28]	III	B
Prophylactic anti-arrhythmic therapy is not recommended for asymptomatic infrequent PVC in patients with CHD and stable ventricular function [25]	III	C

ACHD adult congenital heart disease, *CHD* coronary heart disease, *DCM* dilated cardiomyopathy, *HCM* hypertrophic cardiomyopathy, *ICD* implantable cardioverter defibrillator, *IV* intravenous, *LV* left ventricular, *MI* myocardial infarction, *NICM* non-ischemic cardiomyopathy, *NSVT* non-sustained ventricular tachycardia, *PVC* premature ventricular complexes, *SCD* sudden cardiac death, *SQTS* short QT syndrome, *VA* ventricular arrhythmia, *VT* ventricular tachycardia

Amiodarone

Amiodarone is a iodinated benzofuran derivative that exhibits a "wide-spectrum" of antiarrhythmic properties. It blocks inwardly depolarizing Na^+ (I_{Na}) and L-type Ca^{2+} (I_{CaL}) currents and several outward repolarizing K^+ currents, including the transient (I_{to}), the inward rectifier (I_{K1}), the ultrarapid (I_{Kur}), rapid (I_{Kr}), and slow (I_{Ks}) components of the delayed rectifier and the acetylcholine-activated (I_{KAch}) [2–5]. Amiodarone inhibits the I_{Na} by blocking the inactivated state of sodium channels with a fast diastolic recovery from block. This effect is accentuated in depolarized tissues (voltage-dependent block) and at fast rates (rate-dependent block), but it is almost nonexistent at slow heart rates. In fact, amiodarone reduces cardiac excitability and conduction velocity and prolongs the QRS and H-V intervals at fast rates. Additionally, amiodarone noncompetitively antagonizes α- and β-adrenoceptors (class II effect) [2–6], inhibits both the conversion of thyroxine (T4) to triiodothyronine (T3) and the entry of T3 and T4 into cells [7], and produces a vasodilator effect mediated via the blockade of I_{CaL} and β-adrenergic receptors. The blockade of I_{CaL} and β-adrenergic receptors explains why amiodarone produces bradycardia and atrio-ventricular (AV) block. Thus, amiodarone exhibits class I, III and IV antiarrhythmic actions of the Vaughan Williams classification.

Electrophysiological Actions The acute and chronic electrophysiological effects of amiodarone in humans are very different [2, 5, 6, 8, 9]. After *intravenous administration*, the main effect is the lengthening of AV nodal refractoriness and intranodal conduction (with prolongation of the PR and A-H intervals) possibly related to the blockade of I_{CaL} and the non-competitive β-adrenergic antagonism. However, the drug produces minimal effects on the APD and refractoriness of the atrial and ventricular muscle, by pass tracts, or His-Purkinje system and there is almost no effect on the QRS, H-V and QTc intervals or the monophasic action potentials [1–3, 5, 6]. Thus, the class III action of the drug is not observed.

However, *long-term treatment* with oral amiodarone prolongs the APD and refractoriness in all cardiac tissues, including bypass tracts, without affecting the resting membrane potential. Interestingly, amiodarone lengthens the APD preferentially in cardiac tissues with the shortest APD (His bundle, atrial muscle and ventricular epicardium and endocardium), with lesser effects, or even a shortening at slow rates, in Purkinje fibres and M cells [1–3, 5, 6]. Thus, in contrast to other class I and III AADs, amiodarone produces a homogeneous prolongation of the APD (QT interval) and reduces transmural dispersion of repolarization across the ventricular wall and the possible re-entry of cardiac impulses. Additionally, amiodarone prolongs the APD at all driving rates, i.e., it does not produce reverse use-dependence. Furthermore, despite amiodarone prolongs the ventricular APD, the risk of TdP is less than with other AADs, possibly because it blocks both the I_{CaL} and β-adrenoceptors, does not produce reverse use-dependence and produces a more homogenous recovery of ventricular repolarization reducing the transmural dispersion of repolarization. In chronic treatments and at fast driving rates, amiodarone blocks the I_{Na} (prolongs the QRS complex) and decreases cardiac excitability and conduction velocity and increases the VF threshold. Desethylamiodarone (DEA), the main active metabolite, has relatively greater effects on the I_{Na} and contributes to the antiarrhythmic efficacy of amiodarone [3]. On the ECG, amiodarone prolongs the RR, PR, A-H, H-V, QRS, JT and QT intervals (occasionally it can produce U waves). Oral amiodarone was more effective than IV amiodarone in lengthening the anterograde effective refractory period of the accessory AV pathway.

In the sinoatrial node and other cardiac pacemaker cells, amiodarone decreases the slope of phase 4 depolarization (pacemaker potential) and the rate of spontaneous excitation and suppresses the slow action potentials (abnormal automaticity) elicited in abnormally depolarized cardiac cells as well as the early afterdepolarizations generated in Purkinje fibres and M cells [2–5]. In the AV node, amiodarone slows intrano-

dal conduction and increases refractoriness and, therefore, reduces the ventricular rate in patients with supraventirulcar arrhythmias. In patients with AF, amiodarone prolongs the refractory periods both in the atria and in the pulmonary veins, slows AV nodal conduction and, in experimental models, it prevents atrial remodelling [10]. The effects of oral amiodarone on sinoatrial and AV nodal function are maximal within 2 weeks, whereas the effects on VT and ventricular refractoriness appear gradually, becoming maximal at ≥10 weeks.

Hemodynamic Effects Amiodarone is a peripheral and coronary vasodilator. After oral administration, amiodarone slows sinus rate (15–20%) and prolongs the PR and QT intervals but does not depress the left ventricular ejection fraction (LVEF). Indeed, the LVEF may increase slightly even in patients with reduced LVEF, possibly because its vasodilator effect reduces LV afterload. However, after IV administration amiodarone decreases heart rate, systemic vascular resistances, blood pressure and contractile force; thus, it should be given cautiously to patients with depressed LVEF because of the risk of bradycardia and hypotension [5, 6].

Pharmacokinetics (Table 3.2) After oral administration, amiodarone presents a slow, variable and incomplete absorption (bioavailability of 35–65%) and peak plasma levels are reached after 3–8 h [11]. Food increases its oral bioavailability and reduces gastrointestinal adverse effects [12]. The onset of action after oral administration occurs after 2–3 days (1–2 h after IV administration) [9]. Amiodarone is highly protein bound (99%) and extensively distributed (Vd 70 L/kg). It accumulates in the heart (cardiac levels are 10–50 times higher than in plasma), adipose tissue, liver, lungs and skin, crosses the placenta and is found in breast milk. This wide tissular distribution explains why even when the onset of drug action occurs after 2–3 days, steady-state plasma levels are reached after several months unless large loading doses are used, and why the drug effects persist for weeks or months

after drug discontinuation [9, 11]. Amiodarone is extensively metabolized in the liver by CYP450 3A4 and 2C8, leading to various active metabolites. DEA also accumulates in almost all tissues and exhibits electrophysiologic effects quite similar to those of amiodarone. Both amiodarone and DEA are excreted primarily via the hepatic-biliary route undergoing some enterohepatic recirculation, so that doses do not need to be reduced in patients with renal disease. Amiodarone is eliminated very slowly. There is an initial 50% reduction in plasma levels 3–10 days after drug discontinuation which probably represents drug elimination from well-perfused tissues, followed by a terminal elimination half-life (t) of 53 days (range 26–107 days). The therapeutic plasma levels are between 1.0 and 2.5 mg/mL [6]. Amiodarone and DEA are not dialyzable.

Adverse Effects (Table 3.3) They are reported in up to 75% of patients treated with amiodarone for more than 2 years, leading to drug discontinuation in 18–37% of patients. Some side effects may be potentially fatal [9, 13, 14]. Adverse effects are more common on chronic therapy and at high doses, but they still occur even at dosages ≤200 mg/day. Cardiac side effects include symptomatic bradycardia (especially in the elderly), AV block, conduction disturbances, worsening heart failure (HF) and QT prolongation [9, 13, 14]. However, the risk of TdP is very uncommon (<0.5%) [15], probably because of its class II and IV properties, but may occur in patients with hypokalemia or bradycardia, or those receiving QT-prolonging drugs. Phlebitis and hypotension are observed when administered IV.

Adverse extracardiac effects are gastrointestinal (nausea, vomiting, constipation, anorexia), ocular (almost all patients develop asymptomatic corneal microdeposits; rare: optic neuritis and atrophy with visual loss), neurological (proximal muscle weakness, fatigue, peripheral neuropathy, headache, ataxia, tremors, impaired memory, sleep disturbances), cutaneous (rash, photosensitivity, alopecia, blue-gray skin discoloration), hyperthyroidism or hypothyroidism and hepatotoxicity (elevated transaminase levels, hepatitis,

cirrhosis and fatal hepatic necrosis) [6, 9, 13–17]. Amiodarone can increase creatinine plasma levels due to partial inhibition of the tubular organic cationic transporter system, rather than a decline in renal function. In fact, the drug does not affect the glomerular filtration rate (GFR), renal blood flow, and Na^+ or K^+ excretion. Most of these adverse effects are reversible after dose reduction or drug discontinuation, but because of its long half-life, some of them may persist for many months (skin discoloration slowly reverses after 18 months but may not disappear). Neurological and gastrointestinal adverse effects are common during loading doses and usually improve with lower maintenance doses.

Pulmonary toxicity (interstitial pneumonitis, pulmonary fibrosis) occurs in 1–15% of patients receiving doses ≥400 mg/day. Pulmonary function tests show a restrictive pattern with reduced forced vital capacity and diffusing capacity, and chest computed tomography can reveal evidence of fibrosis and diffuse ground glass confluent opacities. Advanced age, high cumulative dose (>400 mg/day), duration of therapy (>6 months), reduced predrug diffusion capacity and preexisting pulmonary disease are risk factors for the development of pulmonary toxicity [14, 18, 19]. Pulmonary toxicity can be fatal in about 10% of patients [13]. Treatment includes drug discontinuation and administration of glucocorticoids [9].

Amiodarone inhibits the peripheral conversion of T4 to T3, producing a slight increase in T4, reverse T3 and thyroid-stimulating hormone (TSH), and a slight decrease in T3 levels. Hypothyroidism appears in 2–6% during the first year of treatment (TSH >10 mU/L) particularly in areas with high dietary iodine intake [7, 20]. Drug discontinuation and/or levothyroxine are the main treatments for amiodarone-induced hypothyroidism. Hyperthyroidism (TSH < 0.35 mU/L) appears in 0.9% of patients and predominates in areas with iodine deficiency [21]. Because it may precipitate cardiac arrhythmias, hyperthyroidism should be excluded if recurrence of arrhythmias appears during amiodarone therapy [7]. Even if amiodarone is discontinued,

thyrotoxicosis persists for up to 8 months. Type 1 amiodarone-induced thyrotoxicosis (AIT) occurs in patients with an underlying thyroid pathology and is treated with high doses of thionamides (eg, methimazole or propylthiouracil) to block thyroid hormone synthesis, adding potassium perchlorate to block iodide uptake by the thyroid and deplete intrathyroidal iodine stores. Type 2 AIT is a result of a destructive thyroiditis that results in excess release of preformed T4 and T3 into the circulation and is treated with glucocorticoids. Total thyroidectomy is the only measure that consistently allows continued use of amiodarone. Therefore, thyroid function tests should be performed every 3 months for the first year and every 6–12 months unless thyroid dysfunction appeared.

Because adverse effects are usually dose-related their incidence can be reduced by using very low doses (100–200 mg daily) [9, 14]. Additionally, it is recommended to examine before and periodically during treatment the ECG, chest x-ray, skin, peripheral nerves, thyroid, hepatic, visual and pulmonary function (including carbon monoxide diffusion capacity testing) [9].

Amiodarone and DEA cross the placenta and are detected in breast milk. Amiodarone is associated with severe adverse fetal effects (neurodevelopmental abnormalities, preterm birth, fetal growth restriction and fetal neonatal hypo-/hyperthyroidism and bradycardia) [22, 23]. Therefore, amiodarone is not recommended in women who are, or may become, pregnant (Pregnancy category X) and in nursing mothers [11]. Oral amiodarone may be considered for ongoing management in pregnant patients when treatment of highly symptomatic patients is required and other therapies are ineffective or contraindicated [24–29].

Drug Interactions Amiodarone and DEA inhibit CYP450 isoenzymes (CYP1A1/2, 3A4, 2C9 y 2D6) and some transporters [P-glycoprotein (P-gp) and organic cation transporter 2 (OCT2)]. Additionally, amiodarone is a substrate for CYP3A4 [11]. Therefore, amiodarone has the potential for

multiple interactions with other drugs that are summarized in Table 3.4.

Contraindications and Cautions See Table 3.3.

Dosage and Administration See Table 3.5.

Indications Amiodarone is indicated for a wide spectrum of supraventricular [atrial fibrillation (AF) or flutter (Af), atrial tachycardia, AV nodal reentrant tachycardia and AV reentrant tachycardia] and ventricular tachyarrhythmias [ventricular tachycardia (VT) and fibrillation (VF)] in patients with structural heart disease (coronary artery disease, LV hypertrophy, HF or LV dysfunction, hypertrophic cardiomyopathy), being the drug of choice when other AADs are ineffective, not tolerated or contraindicated [24–29]. Furthermore, because amiodarone produces less negative inotropic effects or hypotension than β-blockers, diltiazem or verapamil, it is preferred in critically ill patients or in those with hemodynamic instability. However, amiodarone presents several disadvantages, including its slow onset of action after oral administration, so that it should be administered IV or at loading doses to achieve effects rapidly, its long half-life, and its poor safety profile and multiple drug interactions. Because of long-term amiodarone therapy is associated with cardiac and extracardiac adverse effects, it remains as a second-line treatment in patients who are suitable for other AADs or in young patients [9, 24–29].

1. *Atrial fibrillation/flutter* (Table 3.6). Amiodarone is used for the maintenance of sinus rhythm (SR) conversion of AF/Af to SR and ventricular rate control. Amiodarone is the most effective drug for the maintenance of SR in patients with recurrent symptomatic AF/Af [15, 30–33]. It is superior to class I AADs and sotalol and the drug of choice in patients with structural heart disease and the

only AAD recommended in patients with congestive HF or significant aortic stenosis [24, 27, 30, 34, 35]. Amiodarone is superior to sotalol or propafenone for maintenance of SR after cardioversion [30] and in a substudy of the AFFIRM trial, amiodarone was superior to both sotalol and a mixture of class I drugs. In the SAFE-T trial, amiodarone was superior to sotalol, but both drugs had similar efficacy in the subgroup of patients with ischemic heart disease [35].

Amiodarone is also effective for the conversion of AF/Af to SR. However, most data derived from use in patients with AF, while few data are available for patients with Af [24, 27]. Although it has the disadvantage that conversion is often delayed beyond 6 h, amiodarone also slows ventricular rates and it has no risk of postconversion ventricular arrhythmias. For the acute conversion of AF, IV amiodarone is as effective as IV propafenone [36] and both amiodarone and flecainide appear more effective than sotalol in restoring SR [37–39]. Pretreatment with amiodarone can facilitate DC cardioversion and prevent AF recurrences; in relapses to AF after successful cardioversion, repeating DC cardioversion after prophylactic amiodarone can improve the efficacy of DC cardioversion to maintain the SR and prevent the recurrences [37, 40]. Furthermore, amiodarone should be considered to achieve rhythm control and maintain SR in patients with hypertrophic cardiomyopathy and recurrent symptomatic AF [24, 27, 41].

Short-term oral amiodarone treatment following ablation for paroxysmal or persistent AF did not reduce the recurrence of AF/Af at the 6-month follow-up but prolonged time to first documented recurrence and more than halved arrhythmia-related hospitalization and cardioversion rates within the blanking period [42]. Administered before cardiothoracic surgery or postoperatively, amiodarone (alone or in combination with β-blockers) decreased the incidence of post-operative AF (POAF) and hospital stay compared to β-blocker therapy [43–46] and was effective in converting POAF to SR [47, 48].

Amiodarone can be useful for rate control in patients whose heart rate cannot be controlled with combination therapy (e.g. β-blockers or verapamil/diltiazem combined with digoxin) or when these drugs are contraindicated or poorly tolerated [24, 27]. Intravenous amiodarone slows the ventricular rate (10–12 bpm after 8–12 h) [34, 49].

Amiodarone prolongs the anterograde refractory period of the accessory pathway and can be used both for rate control and to achieve conversion in patients with pre-excitation and AF, although urgent electrical cardioversion is often necessary. IV amiodarone is not recommended in these patients, because case reports of accelerated ventricular rhythms and VF [50].

2. *Supraventricular tachycardias* (SVT) (Table 3.7). Evidence for amiodarone for the ongoing management of SVT is limited [26, 29]. IV amiodarone may be considered for acute treatment in hemodynamically stable patients and for ongoing treatment, but because of its safety profile, oral amiodarone is a second-line agent recommended when catheter ablation or other AADs are ineffective or contraindicated (i.e. in patients with structural heart disease) [26, 29].
3. *Ventricular arrhythmias* (Table 3.8). Amiodarone is recommended for the treatment and prophylaxis of life-threatening recurrent ventricular arrhythmias (VT and/or VF) and life-threatening recurrent hemodynamically unstable VT not responding to other AADs, particularly in patients with structural heart disease (i.e. HF, myocardial infarction-MI, hypertension, or cardiomyopathies) or after cardiac surgery when other AADs are not tolerated or contraindicated [25, 28, 51–53]. However, there is modest evidence from randomized controlled trials supporting its use and nowadays it has been replaced by the implantable cardioverter-defibrillator (ICD) therapy. Doses of amiodarone should be as low as possible and restricted to selected patients with refractory ventricular arrhythmias and in young patients it should be reserved as a bridge to more definitive treatment options such as catheter ablation.

Amiodarone is more effective than sotalol and presents a lower risk of ventricular proarrhythmia, but chronic therapy (18–24 months) and high doses of amiodarone (>400 mg/day) increase the risk of adverse effects that require drug discontinuation [9, 51, 54]. Therefore, doses of amiodarone should be as low as possible and restricted to selected patients with refractory ventricular arrhythmias. Chronic treatment in young patients should be reserved as a bridge to more definitive treatment options such as catheter ablation [28].

Several studies compared IV amiodarone with other AADs (lidocaine, procainamide or bretylium) for the prophylaxis and treatment of VF and recurrent, hemodynamically destabilizing VT when they can no longer be controlled by successive electrical cardioversion or defibrillation [28, 55–59]. Administered during incessant VT, amiodarone produced a gradual slowing of the VT cycle length, with eventual termination of the arrhythmia [60]. However, these trials showed that IV amiodarone was moderately effective during a 24–48 h period against VT and VF and the arrhythmia frequently recurred. Furthermore, in a retrospective study, IV amiodarone produced an acute termination of sustained monomorphic VT only in 29% of patients [61]. Very recently the PROCAMIO study compared for the first time in a randomized design IV procainamide and amiodarone for the treatment of the acute episode of sustained monomorphic well-tolerated VT. Procainamide therapy was associated with less major cardiac adverse events and a higher proportion of tachycardia termination within 40 min [62].

In patients with sustained VT or VF and cardiac arrest several placebo-controlled trials and meta-analysis found that amiodarone decreased the recurrences and improved symptoms and survival, but when compared with ICD therapy there was a significant reduction (28%) in the relative risk of death with the ICD that was due almost entirely to a 50% reduction in arrhythmic death [63–66]. Therefore, in these patients amiodarone has been replaced by

ICD. However, in the ICD era amiodarone (plus β-blockade) may still be used in ICD-treated patients to decrease the frequency of shocks from VT/VF episodes or to control supraventricular tachyarrhythmias elicited by device therapy [64, 66]. When amiodarone is added to an ICD, the defibrillation threshold is usually increased and reprogramming prior to discharge from hospital may be necessary. Amiodarone is also indicated to improve symptoms in patients with DCM with an ICD who experience recurrent appropriate shocks in spite of optimal device programming and in patients with arrhythmogenic right ventricular cardiomyopathy and presenting frequent premature ventricular beats (PVBs) or non-sustained VT who are intolerant or have contraindications to β-blockers [25, 28].

The ARREST and ALIVE trials, analyzed the effects of IV amiodarone in hemodynamically destabilizing refractory VT/VF, VT when they can no longer be controlled by successive electrical cardioversion or defibrillation. In patients with out-of-hospital cardiac arrest due to refractory VT or VF after 3 direct-current shocks, those who received amiodarone were more likely than those who received placebo or lidocaine to have a return of spontaneous circulation and to survive to be admitted to the hospital [55, 57]. However, neither amiodarone nor lidocaine result in a significantly higher rate of survival to hospital discharge or favourable neurologic outcome at discharge. Thus, amiodarone may be useful for resuscitating some cardiac arrest victims.

A meta-analysis evaluated the effectiveness of amiodarone for primary or secondary prevention in sudden cardiac death (SCD) compared with placebo, no intervention or any other AAD in patients at high risk (primary prevention) or who have recovered from a cardiac arrest or a syncope due to VT and/or VF (secondary prevention) [51, 67]. There was low-to-moderate quality evidence that amiodarone reduced SCD, cardiac and all-cause mortality when compared to placebo or no intervention for primary prevention, but its effects were superior to other AADs. However, it was uncertain if amiodarone reduced or increased SCD and mortality for sec-

ondary prevention because the quality of the evidence was very low.

The CASCADE study evaluated AAD therapy in survivors of out-of-hospital VF not associated with a Q-wave MI who were at especially high-risk of recurrence of VF. All patients received an ICD in addition to randomized therapy [68]. The risk of the primary outcome, a composite of cardiac death, sustained VT/VF, or syncopal ICD shock, was significantly reduced by amiodarone. Patients on amiodarone were less likely to receive ICD shocks and syncope followed by a shock from a defibrillator was less common in patients treated with amiodarone. These results suggested a benefit of amiodarone over class I AADs. However, it is uncertain whether the observed benefit is due to the harmful effect of conventional AAD therapy and/or a beneficial effect of amiodarone, or most likely, their combination.

Intravenous amiodarone is the preferred AAD for incessant VT or frequent symptomatic VT episodes and severe LV dysfunction because in contrast to many other AADs it does not increase mortality. Two placebo-controlled studies analyzed the effects of amiodarone on the risk of resuscitated VF or arrhythmic death among survivors of MI treated with β-blockers at baseline reaching contradictory results. In the EMIAT trial, amiodarone did not modify all-cause mortality and cardiac mortality as compared with placebo [69]. Conversely, in the CAMIAT trial, amiodarone reduced the incidence of VF or arrhythmic death among survivors of acute MI with frequent or repetitive frequent or repetitive ventricular premature depolarisations. Similarly, several major trials in patients with a history of HF and LV dysfunction, arrived at conflicting results [70]. The GESICA trial suggested low-dose amiodarone improved survival, decreased hospital admissions for congestive HF, and improved functional class in patients with HF independently of the presence of complex ventricular arrhythmias [71]. However, in the STAT-CHF trial recruiting patients with HF (LVEF $\leq$40%) and $\geq$ 10 PVBs/h, amiodarone as compared to placebo was effective in suppressing ventricular arrhythmias, slowed heart

rate and increased LVEF by 42% at 2 years, but it did not reduce the incidence of SCD or prolong survival among patients with HF, except for a trend toward reduced mortality among those with nonischemic cardiomyopathy [72]. In the SCD-HeFT study, recruiting patients with New York Heart Association (NYHA) class II-III (LVEF≤35%), amiodarone had no favorable effect on survival, whereas ICD therapy reduced overall mortality by 23% [73]. In a meta-analysis of 13 trials recruiting patients with recent MI or congestive HF, prophylactic amiodarone reduced the rate of arrhythmic/sudden death (29%), but it only displayed a modest reduction (13%) on total mortality [53]. The treatment benefit was uniform across the congestive HF and post–MI trial patients and was independent of major prognostic variables, such as LV function. Furthermore, a contemporary study in patients with post-acute MI with HF and/or LV systolic dysfunction from VALIANT trial, amiodarone use was associated with an excess in early and late all-cause and cardiovascular mortality [74]. Thus, further studies are needed to define the role of amiodarone in post-MI patients with HF and/or LV systolic dysfunction.

Dofetilide

Dofetilide is a methanesulfonamide drug not available in Europe. It selectively blocks the I_{Kr} and unlike most other AADs has minimal effects on other ion channels [75]. As a consequence, dofetilide prolongs dose-dependently the APD and refractoriness of atrial and ventricular myocardium (but the effect is more prominent in the atria) and accessory pathways, without slowing intracardiac conduction. Like ibutilide and sotalol, dofetilide exhibits the phenomenon of reverse use-dependence, so that the prolongation of APD and refractoriness diminished as the heart rate increases, while at slow heart rates the prolongation of the APD and the risk of early afterdepolarizations (proarrhythmia) increases [75]. It prolongs the QT and JT intervals but has no effect on heart rate, intracardiac conduction (no changes in the PR, QRS, A-H

and H-V intervals) or significant hemodynamic effects and appears to be hemodynamically safe in patients with HF or a prior MI. Drug potency is affected by extracellular potassium concentration, and hypokalemia and hyperkalemia increases and decreases drug potency, respectively [76].

Pharmacokinetics (Table 3.2) Dofetilide is well absorbed (bioavailability 92–95%) and peak plasma levels are reached within 2–3 h. It binds to plasma proteins (60–70%) and 80% of the dose is excreted in urine (80% as unchanged dofetilide) and the remaining 20% as inactive or minimally active metabolites. Its $t_{½}$ is 7–13 hours [11, 75, 77].

Adverse Effects (Table 3.3) The most significant adverse effect of dofetilide is QT prolongation–related TdP. Rates of TdP ranged from 1% to ~3% in the DIAMOND trials [78]. The risk of TdP is highest at the time of drug initiation (80% within the first 3 days of therapy), in women, patients with severe HF, recent MI, hypokalemia, prolonged baseline QT or after conversion from AF to SR. The risk can be reduced maintaining normal serum potassium and magnesium levels, and following the manufacturer's algorithm in patients with renal disease, bradycardia, or baseline QT interval. To minimize the risk of proarrhythmia, patients initiated or re-initiated on dofetilide should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous ECG monitoring, and cardiac resuscitation. Other adverse effects include headache, chest pain, dizziness, respiratory tract infection, dyspnea, insomnia, rash, flu-like syndrome, nausea and diarrhea. There are no well-controlled studies that have been done in pregnant women (Pregnancy Category: C).

Drug Interactions Dofetilide does not inhibit or induce any CYP450 enzyme isoforms. Avoid its combinations with drugs that prolong the QT interval, other antiarrhythmic agents or potent CYP3A4 inhibitors (cimetidine, dolutegravir, grapefruit

juice, HIV protease inhibitors, macrolide antibiotics, verapamil, prochlorperazine) that increase its plasma levels [11, 77].

Contraindications and Cautions See Table 3.3.

Dosage and Administration See Table 3.5.

Dofetilide therapy should be initiated in-hospital under continuous ECG monitoring because of the risk of excessive QT prolongation, periodic calculation of creatinine clearance (CrCl) and expert personnel for the treatment of ventricular arrhythmias [24, 26, 28]. Dosage adjustments are determined by QTc changes and CrCl. Renal function and QTc should be monitored every 3 months. The drug is contraindicated if the baseline QTc >440 m or the CrCl <20 mL/min. If 2–3 h after the first dose of dofetilide the QTc increased by >15% compared with baseline or the QTc is >500 ms (550 ms in patients with ventricular conduction abnormalities), subsequent dosing should be reduced by 50%. At 2–3 h after each subsequent dose, determine QTc and if at any time after the second dose the QTc is >500 ms (550 ms in patients with ventricular conduction abnormalities), dofetilide should be discontinued [24, 26, 28].

Indications Dofetilide is indicated for the acute conversion of recent-onset AF/Af (≤7 days) and the maintenance of SR (Table 3.6) [24, 27, 79, 80]. Dofetilide can be used in patients with structural heart disease or coronary artery disease. In the SAFIRE-D study, 70% of the pharmacological conversions occurred within 24 h and 91% within 36 h [80]. Furthermore, dofetilide appears safe and effective in preventing AF in patients refractory to other AADs undergoing catheter ablation [81]. Between 40% and 60% of patients on dofetilide remained in SR at 1 year (25% on placebo). Dofetilide is not associated with an increased mortality risk in patients with AF/Af [32].

Dofetilide restores and maintains SR in patients with congestive heart failure or recent MI and left ventricular dysfunction [82–84]. In patients with AF/Af and significant LV dysfunction, the DIAMOND studies showed that dofetilide was superior to placebo for the restoration and maintenance of SR and even when it had no effect on all-cause mortality, restoration and maintenance of SR was associated with significant reduction in mortality. Additionally, dofetilide reduced the risk for either all-cause or HF rehospitalization. Thus, dofetilide is an alternative to amiodarone in patients with AF/Af and LV dysfunction. In patients with AF/Af, severe LV dysfunction and recent MI, dofetilide did not affect all-cause or cardiac mortality, or total arrhythmic deaths. Thus, unlike flecainide and propafenone, dofetilide can be used in patients with structural heart disease or coronary artery disease.

Oral dofetilide may be reasonable in: (a) patients with AVRT and/or pre-excited AF who are not candidates for, or prefer not to undergo, catheter ablation [26]. In patients with paroxysmal supraventricular tachycardia (PSVT) dofetilide and propafenone were equally effective in preventing recurrences or decreasing the frequency of PSVT compared with placebo [85]. (b) For prevention of recurrent atrial tachycardia or Af in adult congenital heart disease patients, the long-term efficacy of the drug (defined by either complete suppression or partial improvement of symptoms) ranges from 70% to 85% [86, 87].

Dofetilide decreases the VF threshold in patients undergoing defibrillation testing prior to ICD implantation, suppresses the inducibility of VT and decreases the frequency of ICD shocks. It is as effective as sotalol in preventing the induction of sustained VT, but is significantly better tolerated during the acute phase [88] and in patients with an ICD and ventricular arrhythmias, dofetilide decreases the frequency of VT/VF and ICD shocks even when other ADDs, including amiodarone, are ineffective [89].

However, dofetilide is not frequently used because therapy must be started in an inpatient setting for 3 days and the risk of proarrhythmia. Thus, it should be reserved under ECG

monitoring for highly symptomatic patients, in patients with depressed LVEF, who are not candidates for catheter ablation and/or when other AADs are ineffective or contraindicated.

Dronedarone

Dronedarone is a noniodinated benzofuran derivative with a structure similar to that of amiodarone. The lack of the iodine moiety minimizes the risk of thyroid toxicity, and the addition of a methyl-sulfonyl group decreases its lipophilicity and tissular distribution which is expected to reduce organ toxicity due to tissular accumulation and to shorten its half-life [90]. Like amiodarone, dronedarone blocks Na^+, Ca^{2+} (I_{CaL}) and several K^+ currents (I_{to}, I_{Kur}, I_{Kr}, I_{Ks}, I_{K1} and I_{KAch}) and produces a non- competitive inhibition of α- and β-adrenergic receptors and a vasodilator effect mediated via the I_{CaL} blockade and activation of the NO pathway [90–93]. Dronedarone and amiodarone exhibit similar effects on the I_{CaL}, I_{Kr} and I_{Ks}, but dronedarone is a more potent blocker of I_{Na} and I_{KAch} and exhibits more potent non-competitive antiadrenergic effects than amiodarone.

Electrophysiological Actions Dronedarone prolongs the APD and refractoriness in all cardiac tissues, an effect independent of the rate of stimulation, and reduces transmural dispersion of repolarization. It slows heart rate and AV nodal conduction and prolongs the RR, PR, QT, JT and A-H intervals on the ECG with no change in H-V and QRS intervals [91, 92]. Dronedarone decreases blood pressure, myocardial contractility and slightly increases the defibrillation threshold. Dronedarone has little effect on cardiac performance except in patients with compromised LVEF and should not be used in those with clinical signs of HF.

Pharmacokinetics (Table 3.2) Dronedarone is rapidly and well absorbed after oral administration (70–90%), but it

undergoes extensive first-pass metabolism, so that oral bioavailability is ~5% (15% when administered with a high-fat meal) [11, 90]. Dronedarone is extensively metabolized in the liver via CYP3A4 (and CYP2D6) to an active N-debutyl metabolite. Peak plasma levels of dronedarone and its metabolite are reached within 3–6 h and steady-state plasma levels within 4–8 days. Dronedarone and its active metabolite bind to plasma proteins (>98%) and are widely distributed (Vd 20 L/kg), crossing the blood–brain and placental barriers. Dronedarone presents a lower Vd (tissular accumulation) and a shorter a $t_{½}$ (13–19 h) than amiodarone and 85% of the drug being excreted in feces. Dronedarone and its metabolite are completely eliminated from the body within 2 weeks after the end of treatment. Drug pharmacokinetics is not influenced by age, gender, weight, or renal function, but dose adjustments are recommended in patients with severe hepatic dysfunction [11, 90].

Adverse Effects (Table 3.3) The most frequent are gastrointestinal (diarrhea, nausea, abdominal pain, vomiting, dyspepsia), abnormal liver function tests, asthenia, bradycardia, and QT prolongation. Uncommon adverse effects include: headache, rash and photosensitivity. Dronedarone increases serum creatinine levels due to partial inhibition of the tubular organic cationic transporter system, but the drug does not affect the GFR [94]. Sinus bradycardia is less frequent than with amiodarone and TdP have not been reported.

The ANDROMEDA trial which randomized patients with LV systolic dysfunction (LVEF 35%) and NYHA class III or IV symptoms within the prior month was prematurely discontinued because of increased mortality in the dronedarone group related to the worsening of HF [95]. In the PALLAS trial, dronedarone also increased rates of HF, stroke, and death from cardiovascular causes in patients with permanent AF who were at risk for major vascular events [96]. Thus, dronedarone should not be used in patients with recently decompensated HF or with permanent AF.

Dronedarone may cause fetal harm and it is contraindicated in women who are, or may become, pregnant (Pregnancy category X); it is not known whether dronedarone is excreted in human milk.

Drug Interactions Dronedarone is a moderate inhibitor of CYP3A4 and CYP2D6, and a potent inhibitor of P-gp and is metabolized by CYP3A4, so that it can present many drug interactions [11].

Coadministration of dronedarone with β-blockers, verapamil, or diltiazem increases their depressant effects on sinoatrial and AV nodes. Because diltiazem and verapamil are weak CYP3A4 inhibitors, in patients treated with dronedarone, diltiazem and verapamil should be initiated at low doses and dose uptitration should be done after ECG assessment. Class I or III antiarrhythmics increase the risk of proarrhythmia and should be discontinued before the administration of dronedarone. Dronedarone increases the plasma levels of digoxin (a P-gp substrate) and the risk of bradycardia and AV block. In the PALLAS trial, the use of digoxin was associated with an increased risk of arrhythmia or sudden death in dronedarone-treated patients [96]. Thus, the dose of digoxin should be halved and ECG and digoxin plasma levels carefully monitored.

Dronedarone is primarily metabolized by CYP3A4. Potent CYP3A4 inhibitors [azole antifungals (itraconazole, pozaconazole, voriconazole), cimetidine, cyclosporine, macrolides (clarithromycin, telithromycin), nefazodone, ritonavir, grapefruit juice] and inducers (carbamazepine, phenobarbital, phenytoin, rifampin, St John's Wort) significantly increase and decrease, respectively, exposure of dronedarone and should be administered with caution or avoided [90, 92]. Reduce the dose of dronedarone when coadministered with moderate CYP3A4 inhibitors (diltiazem, erythromycin, verapamil). Dronedarone can increase the exposure of statins that are substrates of CYP3A4 and/or P-gp (atorvastatin, lovastatin, simvastatin) and the risk of myopathy; thus, the dose of lovastatin and simvastatin should be limited

to 20 mg/day and 10 mg/day, respectively. Dronedarone may increase the plasma levels of immunosupressants (tacrolimus, sirolimus, everolimus, cyclosporine); monitor their plasma concentrations, and adjust doses as appropriate [11]. Unlike amiodarone, dronedarone does not modify the INR, but it increases the exposure of dabigatran and this combination should be avoided. Avoid the combination of dronedarone with QT-prolonging drugs.

Contraindications and Cautions See Table 3.3.

Dosage and Administration See Table 3.5.

Indications Dronedarone is approved for the maintenance of SR after successful cardioversion in clinically stable adult patients with paroxysmal or persistent AF [97–99], but it is less effective than amiodarone [32, 100, 101]. In patients with paroxysmal or persistent AF or Af with additional risk factors for death, the ATHENA trial showed that dronedarone significantly reduced the composite outcome of first hospitalization due to cardiovascular events or death as compared with placebo [102]. Additionally, dronedarone decreased the mean ventricular rate during the recurrence of AF [98, 99]. In a short-term study, amiodarone was significantly more effective than dronedarone at preventing recurrence of AF, but was associated with significantly more adverse thyroid, neurological, ocular, and dermatological adverse effects [103].

Ibutilide

Ibutilide is a methanesulfonamide derivative that prolongs cardiac repolarization through the inhibition of the I_{Kr} and the activation of the late inward sodium current (I_{NaL}) during the plateau phase of the cardiac action potential [104].

Electrophysiologic Actions Like other class III agents, ibutilide prolongs APD and refractoriness of the atrial and ventricular myocardium, AV node, His-Purkinje system, and accessory pathways, prolongs the QT and JT intervals and produces a mild slowing of the sinus rate, but it has no effect on the PR, A-H, QRS and H-V intervals [105–107]. The prolongation of QT interval is related to the dose, rate of infusion and heart rate. Indeed, the prolongation of APD and refractoriness becomes less pronounced at higher tachycardia rates, i.e. ibutilide exhibits reverse use dependence. Ibutilide has no significant hemodynamic effects or negative inotropic effects and can be used safely in patients with structural heart disease and prior MI. It can lower the energy threshold required for VF.

Pharmacokinetics (Table 3.2) Ibutilide is administered IV. It binds to plasma proteins (40%), presents a large Vd (11 L/kg) and is extensively metabolized in the liver; one hydroxy metabolite has weak class III effects. Ibutilide is renally excreted and its $t_{½}$ presents a marked interpatient variability (2–12 h) [107]. The pharmacokinetics of ibutilide is independent of dose, age and LV function.

Adverse Effects (Table 3.3) The most serious adverse effect is a dose-dependent QT prolongation that returns to normal values 2–4 h after stopping the IV infusion [104–106]. TdP can occur in up to 4% of patients during or shortly after the infusion period (within the first 4–6 h of dosing) and the risk increases in patients with LVEF <20% [108]. Non-sustained monomorphic VT may occur in ~5% and proarrhythmia requiring cardioversion occurred in ~2% of treated patients [109, 110]. To reduce the risk of proarrhythmia, high doses of ibutilide and rapid infusion rates should be avoided; IV pretreatment with magnesium sulfate reduces the incidence of ventricular arrhythmias, including TdP [111, 112]. Therefore, patients receiving ibutilide should undergo continuous ECG

monitoring during administration and for at least 4 hours after completion of dosing. Other noncardiac adverse effects are headache, bradycardia, hypotension, palpitations and nausea [11, 109]. The safety of ibutilide during pregnancy has not been well studied, and its use during pregnancy should be restricted to patients in whom no safer alternative exists (pregnancy category: C).

Drug Interactions (Table 3.4) Class I or class III AADs should not be given concurrently with ibutilide (or within 4 h after infusion); other antiarrhythmics should be withheld prior to conversion with ibutilide.

Contraindications and Cautions See Table 3.3.

Dosage and Administration See Table 3.5.

Because of the risk for ventricular proarrhythmia, ibutilide should be initiated in-hospital on continuous ECG monitoring by personnel trained in identification and treatment of ventricular arrhythmias during the drug administration and for 6–8 h thereafter and with resuscitation facilities available. The infusion should be stopped if the QTc is >500 ms or conversion to SR occurs. Although dose adjustment is not necessary in patients with hepatic or renal impairment, patients with liver disease may metabolize ibutilide more slowly and require longer postinfusion monitoring [107].

Indications Intravenous ibutilide is indicated for the rapid conversion of recent-onset AF/Af (≤ 7 days) to SR, but it is more effective for the conversion of Af (Table 3.6) [105–107, 110, 113–115]. In AF or Af, a single dose of ibutilide successfully converted 53% patients; an additional 22% patients is converted with the second dose, which resulted in an overall conversion rate of 75% [116]. The mean termination time was 27 min after the start of the infusion. Ibutilide was more

effective than amiodarone, procainamide or sotalol in converting recent-onset Af to SR; however, ibutilide and amiodarone are equally effective in converting recent-onset AF to SR [33,105,106,108,113,117]. In patients with persistent AF/Af the efficacy was 44% and 49%, respectively. Ibutilide is safe and effective for the rapid conversion of AF and Af after cardiac surgery (conversion rate 57% at the dose of 1 mg) [115]. Ibutilide also facilitates electrical cardioversion in patients with AF refractory to prior electrical cardioversions and prevent recurrent AF [24, 27]. All 50 patients receiving ibutilide before electrical cardioversion achieved SR while only 36 of 50 who did not receive the drug. The 14 patients who did not respond to electrical cardioversion were successfully cardioverted when a second attempt was made after ibutilide pretreatment [108]. However, because of the risk of proarrhythmia, ibutilide should not be used in patients with frequent short episodes of paroxysmal AF because even if the drug is effective to terminate the arrhythmia it is not useful for long-term prevention. The effectiveness of ibutilide for treatment of focal AT is unclear [26, 105, 106].

Furthermore, ibutilide prolongs accessory pathway refractoriness and can temporarily slow ventricular rate during pre-excited AF and may be used for the pharmacologic cardioversion of micro-reentrant AT [118] and AV reentrant tachycardia [119].

Sotalol

Sotalol is a non-selective β1-adrenoceptor blocker without intrinsic sympathomimetic activity that, in addition, inhibits the K^+ current I_{Kr}, i.e., it is a mixed class II and class III AAD [11, 120, 121].

Electrophysiological Actions Sotalol is a racemic mixture of dextro- and levo-isomers. Both isomers have comparable class III activity, but *l*-sotalol is responsible for the β-blocking activity

[121, 122]. The β-blocking effects appear at low oral doses (half-maximal at 80 mg/day), while the class III effects are observed at doses >160 mg/day. Sotalol dose-dependently prolongs atrial and ventricular APD and refractoriness, slows heart rate, decreases AV nodal conduction, increases AV nodal refractoriness and prolongs the RR, PR, A-H and QT intervals of the ECG, but does not modify the QRS and H-V intervals. It also slows conduction along any bypass tract in both directions. The prolongation of the APD is greater at slower rates (reverse use-dependence) and under these conditions, sotalol may cause early afterdepolarizations triggering TdP. Unlike amiodarone, sotalol appears to reduce the defibrillation threshold [26].

Hemodynamics. Sotalol exerts a direct negative inotropic effect through its β-blocker activity, but it may indirectly increase Ca^{2+} entry and cardiac contractility by prolonging repolarization, particularly at slow heart rates. However, in patients with reduced LVEF, sotalol can decrease the cardiac index, increase filling pressures and precipitate overt HF [120, 121]. Therefore, it must be used cautiously in patients with LV dysfunction or HF and should be avoided in patients with LVEF <20%, although is well tolerated in those with normal cardiac function. In 415 patients with AF/Af and PSVT, new or worsening HF occurred in 1.2% of patients, but in these studies patients with NYHA classes III-IV were excluded.

Pharmacokinetics (Table 3.2) Sotalol is completely absorbed (oral bioavalability 90–100%), reaching peak plasma concentrations within 2.5–4 h and steady-sate plasma levels in 2–3 days. It does not bind to plasma proteins, is not metabolized in the liver and is excreted unchanged primarily by the kidneys. Its $t_{½}$ is 7–18 h. The dose must be reduced in the elderly and in patients with renal impairment [11, 120].

Adverse Effects (Table 3.3) They are those commonly seen with other β-blockers, including bradycardia and AV block, asthenia, fatigue, hypotension, dizziness and cardiac ischemia

after abrupt discontinuation. Proarrhythmia is the most serious adverse effect. TdP appears in 0.3% of patients treated with ≤240 mg/day, in 4.4% of those treated with 480 mg/day, in ~1.3% of patients when the QTc <500 ms and in 3.4–5.6% when the QTc is between 500–550 ms. In the PAFAC trial TdP appear in 1% of patients [123]. Proarrhytmia was probably the cause of the increased mortality observed with d-sotalol in patients with LV dysfunction post-MI [32, 124]. The risk of TdP increases in females, at high doses (>320 mg/day) and in patients with bradycardia, baseline QTc intervals >450 ms, electrolyte disturbances (hypokalemia and hypomagnesaemia), severe LV failure, treated with QT-prolonging drugs or with congenital long-QT syndrome.

Sotalol crosses the placenta and is present in breast milk (Pregnancy category B). β-blockers are commonly used in pregnant women with cardiovascular conditions and are associated with intrauterine growth retardation [23].

Drug interactions (Table 3.4) Sotalol should be used with caution or avoided in patients treated with QT-prolonging drugs and additive effects are expected if co-administered with other β-blockers. Class IA, IC and III AADs are not recommended as concomitant therapy with sotalol. Coadministration with digoxin can increase the risk of bradycardia and AVB and coadministration with diltiazem or verapamil may increase the risk of hypotension, bradycardia, or AVB. In diabetic patients sotalol may mask symptoms of hypoglycemia (tachycardia, tremor) or worsen hyperglycemia; so, the doses of insulin or antidiabetic drugs may require adjustment. β2-receptor agonists should be administered at higher dosages in patients treated with sotalol. Antacids containing aluminum hydroxide and magnesium hydroxide given 2 h or less before sotalol may reduce its bioavailability.

Contraindications and Cautions See Table 3.3.

Dosage and Administration See Table 3.5.

Patients initiated or reinitiated on sotalol should be placed in a facility that can provide cardiac resuscitation and con-

tinuous electrocardiographic monitoring for a minimum of 3 days [24–28]. The starting oral dose is 80 mg bid in patients with a QT <450 ms and a CrCl >60 mL/min. Doses may be increased in increments of 80 mg/day every 2–3 days to reach steady-state levels (maximum dose of 160 mg bid) provided the QTc interval <500 ms. Higher doses (480–640 mg/day) are used in patients with refractory life-threatening ventricular arrhythmias. Because sotalol can cause TdP or severe bradycardia, it may be considered to initiate the treatment in-hospital, particularly in patients in whom sinus bradycardia may cause syncope or when the conversion of AF/Af to SR prolong the QT interval. The use of high doses of sotalol requires careful ECG monitoring, especially in patients with impaired renal function.

In patients with ventricular arrhythmias and a CrCl between 30 and 59 mL/min sotalol must be administered od; with a CrCl between 10 and 29 mL/min the dose should be administered every 36–48 h, and with a CrCl <10 mL/min the dose should be individualized.

In patients with AF/Af and renal impairment (CrCl <60 mL/min) sotalol should be administered bid; if the CrCl is between 40 and 59 mL/min sotalol should be administered od; if the CrCl <40 mL/min sotalol is contraindicated.

Indications

Sotalol is approved for the:

1. *Maintenance of SR following cardioversion of recurrent AF/Af* (Table 3.6). For the maintenance of SR sotalol is as effective as flecainide or propafenone, but it can be administered to patients with structural heart disease or coronary artery disease where class IC drugs are contraindicated and without an additional agent to slow AV-nodal conduction [26, 33]. However, sotalol is less effective than amiodarone. In patients with persistent AF amiodarone and sotalol were equally efficacious in converting AF to SR but amiodarone was superior for maintaining SR; however, both drugs had similar efficacy in patients with ischemic heart disease [125]. Furthermore, in the CTAF trial,

after a mean of 16 months of follow-up 65% of patients treated with amiodarone and 37% of patients treated with sotalol or propafanone remained free of AF recurrence [30]. Similarly, in a large meta-analysis, efficacy of sotalol is similar to that of most AADs other than amiodarone [32]. Thus, sotalol can replace amiodarone when adverse effects are expected.

Pretreatment with sotalol can facilitate DC cardioversion and prevent recurrent AF and in relapses to AF after successful cardioversion, repeating DC cardioversion after sotalol facilitates the successful cardioversion (Table 3.6). Sotalol is also effective to decrease the incidence of POAF and to control ventricular rate during AF/Af [43, 126].

2. *Supraventricular tachycardias*. Sotalol may be reasonable for ongoing management in patients with SVT who are not candidates for, or prefer not to undergo, catheter ablation (Table 3.7) [26, 127]. Additionally, sotalol slows the ventricular response to atrial tachyarrhythmias and offers an effective alternative to DC cardioversion in adults and adolescents with congenital heart disease and hemodynamically stable atrial tachyarrhythmias [128]. One study randomized patients with reentrant SVT (AVNRT or AVRT) or other atrial tachyarrhythmias (eg, AF, Af, AT) to sotalol (80–160 mg bid) or placebo and found significant reductions in recurrence risk, including for patients with reentrant SVT, with no proarrhythmic adverse effects [127]. However, because of the potential for proarrhythmia, sotalol should be reserved for patients with SVT who are not candidates for, or prefer not to undergo, catheter ablation and for whom other AADs are ineffective or cannot be prescribed.
3. *Treatment of life-threatening sustained ventricular arrhythmias and acute conversion of hemodynamically stable monomorphic sustained VT* (Table 3.8). In patients with hemodynamically stable VT, sotalol was superior to lidocaine for the acute termination of sustained VT [129]. In patients with life-threatening arrhythmias (sustained VT/VF) which were also inducible by programmed electrical

stimulation (PES), the ESVEM trial showed that sotalol was significantly more efficacious at decreasing death and ventricular arrhythmias than other six class I AADs [130]. In patients who had received an ICD for secondary prevention of serious malignant ventricular arrhythmias, the combination of amiodarone with a β-blocker prevented shocks better than the β-blocker alone, although sotalol alone tended to reduce ICD shocks [131]. However, in another placebo-controlled study in patients with ICD, sotalol reduced the risk of death from any cause or the delivery of a first shock for any reason by 48% whether or not ventricular function was depressed. Sotalol also prevented the occurrence of shocks in response to supraventricular arrhythmias [132]. Two studies that compared the efficacy of metoprolol and sotalol yielded contradictory results. In one trial, sotalol was less effective than metoprolol for reducing recurrence of ventricular arrhythmia events; however, this study did not include inappropriate shocks that were a prominent feature in the previous studies [133]. In another trial, metoprolol was as efficacious as sotalol in preventing VT/VF recurrences in patients with an ICD [134]. In patients with sustained VT/VF and a ICD, sotalol reduced the recurrences in comparison to no AAD treatment and the frequency of ICD discharges, but it did not improve survival [135].

Because of its proarrhythmic risk, the use of sotalol is not recommended in patients with less severe arrhythmias (non-sustained VT or supraventricular tachyarrhythmias), even if symptomatic. Sotalol can be used safely in patients with coronary artery disease, but it should also be avoided in patients with severe HF (NYHA functional class III or IV). Although specific studies in treating atrial arrhythmias after MI have not been conducted, the administration of sotalol started 5–15 days after the MI did not increase rate after a 12 month follow-up [136].

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