Chapter 6
Other Antiarrhythmic Drugs

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In previous chapters of this book several authors analyze in detail the antiarrhythmic drugs (AADs) classified in groups I-IV according to the Vaughan-Williams classification. However, some old (adenosine, digoxin) and new AADs (ivabradine, ranolazine, vernakalant) were not listed in any of the original four classes. Therefore, in this chapter, I shall review the electrophysiological effects of these drugs (Table 6.1). Their electrophysiological and pharmacokinetic properties, adverse effects, doses drug interactions, cautions, contraindications and clinical indications are summarized in Tables 6.2, 6.3, 6.4, 6.5, 6.6, and 6.7.

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Table 6.1 Other antiarrhythmic drugs

1. Adenosine
   - Adenosine A1 receptor agonists: Capadenoson (AF, angina), Selodenoson (AF, discontinued), Tecadenoson (PSVT, AF)
   - Other: Neladenoson bialanate (HF with reduced ejection fraction), Regadenoson (pharmacologic stress testing)
2. Cardiac glycosides: Digoxin, Digitoxin
3. Atrial-selective blocking drugs: Ranolazine, Vernakalant
4. Selective I_f blockers: Ivabradine
5. Other drugs:
   - GAP junction modifiers: Rotigaptide (GAP486, ZP123: discontinued), Danegaptide (GAP134, ZP1609: AF, myocardial reperfusion injury)
   - Na^+-Ca^{2+}-exchanger inhibitors: KB-R7943, SEA0400, SN-6, YM-244769

AF atrial fibrillation, *HF* heart failure, *PSVT* paroxysmal supraventricular tachycardia

Adenosine

Adenosine is a ubiquitous endogenous purine nucleoside. Activation of $G_{i/o}$ protein–bound cardiac adenosine A1 receptors present in atrial muscle, sino-atrial (SAN) and atrio-ventricular nodal (AVN) cells [1–3]: (a) activates the acetylcholine-gated inward rectifying K^+ current (I_{KACh}/I_{KAdo}) that hyperpolarizes the membrane potential, slows SAN pacemaker rate and shortens atrial action potential duration (APD) and refractoriness. (b) Inhibits the mixed Na^+-K^+ inward pacemaker current (I_f) generated via non-selective hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channels, which regulates the rate of the spontaneous depolarization of the SAN cells. (c) Reduces adenyl cyclase activity and intracellular cAMP levels, which indirectly inhibits the L-type calcium current

Table 6.2 Effect of antiarrhythmic drugs on ECG parameters and cardiac effective refractory periods

Drug	RR	PR	QRS	QTc	JT	ARP	VRP	AVNRP
Adenosine[a]	–/then +	+	0	0	0	–	0	+
Digoxin	0/+	+	0/+	0/–	0	–	0/–	+
Ivabradine	+	0	0	0	0	0	0	0
Ranolazine	0	0	0	0/+	0	+	+	0
Vernakalant[a]	0/+	0	0/+	0	0	+	0	0

RR, PR and QRS intervals of the ECG. ARP, VRP and AVNRP: atrial, ventricular and atrio-ventricular refractory periods. PRVAcc: refractory period of the accessory pathway

0: unchanged, –: decrease, +: increase

[a]Changes are transient and values return to normal within 30 s (adenosine) or 2 h (vernakalant)

Table 6.3 Pharmacokinetic properties

Drug	F (%)	T_{max} (h)	PPB (%)	Vd (L/kg)	$t_{1/2}$ (h)	Excretion H/R (%)	Dose
Adenosine (IV)	100	–	–	–	<10 s	Red blood cells	Rapid IV bolus of 6 mg (1–2 s) followed by saline flush (≤3 mg in patients taking verapamil, diltiazem, β-blockers or dipyridamole, or in the elderly). Another bolus of 12 mg after 1–2 min; this 12 mg bolus can be repeated in 1–2 min if SVT persist. Pediatric dosing: 0.1–0.3 mg/kg
Digoxin (oral/IV)	60–75	PO: 3–6 IV: 1–3	25	4	35 (30–48; up to 3–5 days in CKD)	25/75	• IV: 0.5–1 mg over 12–24 h in divided doses depending on age, lean body weight and renal function. Half of the total dose given as the first dose; further doses should be given by IV infusion over a period of 10–20 minutes at intervals of 4–8 h. Maximum loading dose: 8–12 mcg/kg given at 6–8-h intervals • Oral: (1) loading: 0.5–1 mg, with additional 0.125–0.25 mg tid for 1 day; (2) maintenance: 0.125–0.375 mg od (0.0625 mg in renal impairment)

Digitoxin (oral)	95	1	>90	0.61	6–9 days	75/25	IV bolus: 0.4–0.6 mg. Oral: 0.05–0.3 mg/day
Ivabradine[a] (oral)	40	1–1.5	70	1.3	11	95/5[b] CYP3A4	2.5–7.5 mg bid
Ranolazine (oral)	35–55	4–6	65	2.5	7	25/75 (5[b]) CYP3A4 (70–85%) CYP2D6 (10–15%)	Initial dose 375 mg bid. The dose should be titrated to a maximum dose of 750 mg bid (EMA) or 1000 mg bid (FDA)
Vernakalant – (IV)		1–5 min	45–60	2.3	3–5.5	7/93 CYP2D6	3 mg/kg IV over 10 min. Then, 2 mg/kg over 10 min after waiting for 15 min. If conversion does not occur within 15 min, a second 10-min infusion of 2 mg/kg can be administered

CKD chronic kidney disease, *F* oral bioavailability, *h* hours, *H* hepatic/biliar, *IV* intravenous, *min* minutes, *PPB* protein plasma binding, *R* renal, *s* seconds, *SVT* supraventricular tachycardia, *t1/2* drug half-life, *Tmax* time to peak plasma levels, *Vd* volume of distribution

[a]Off-label use

[b]Renal excretion without biotransformation

Table 6.4 Most common adverse effects

Adenosine	• >10%: Flushing, shortness of breath/dyspnea • 1–10%: Headache, chest pressure, light-headedness, nausea, sweating, palpitations, hypotension, bronchospasm. Seizures in susceptible patients. In patients with asthma or COPD adenosine-induced bronchospam may last more than 30 min • Sinus pauses, AV block and atrial/ventricular extrasystoles immediately after conversion that can reinitiate PSVT or degenerate to AF, sustained or non-sustained VT
Digoxin Digitoxin	• Gastrointestinal (anorexia, nausea, vomiting, abdominal pain), neurological (headache, fatigue, dizziness, drowsiness), ocular (blurred and colored vision), psychiatric (disorientation, mental confusion, depression), rash • Supraventricular or ventricular tachyarrhythmias and bradyarrhythmias (bradycardia, heart block), coronary steal • At plasma levels >2 ng/mL digoxin is toxic, produces proarrhythmia and can aggravate HF, particularly with co-existent hypokalemia. However, symptoms can appear at lower levels
Ivabradine	• Phosphenes, diplopia; bradycardia, sinus arrest and heart block, palpitations, AF; hypotension. Dizziness, fatigue
Ranolazine	• Dyspepsia, anorexia; tinnitus; bradycardia, palpitations, hypotension; hyperhydrosis. Small increases in serum creatinine without changing the glomerular filtration rate. QTc prolongation (6–15 ms) but cases of torsades de pointes are very rare
Vernakalant	• Dysgeusia, sneezing, paresthesias, nausea, cough, pruritus, hypotension, bradycardia, complete AV block, AF/AFl, PVCs, non-sustained VT

AF atrial fibrillation, *AFl* atrial flutter, *AV* atrio-ventricular, *COPD* chronic obstructive pulmonary disease, *HF* heart failure, *PSVT* paroxysmal supraventricular tachycardia, *PVCs* premature ventricular beats, *VT* ventricular tachycardia

TABLE 6.5 Drug interactions, cautions and contraindications

Drug	Drug interactions	Cautions	Contraindications
Adenosine	Digoxin, BBs, diltiazem or verapamil potentiate the bradycardiac and/or hypotensive effects. Dipyridamole inhibits the reuptake of adenosine and potentiates its effects (lower doses needed). Methylxanthines (theophylline, caffeine) antagonize its effects (higher doses needed). Higher degrees of heart block with carbamazepine. Any influence of recent intake of caffeinated beverages is disputed	It should only be used with full resuscitative equipment available. Immediate drug discontinuation in the presence of angina, severe bradycardia, hypotension, respiratory failure or cardiac arrest. Adenosine may trigger convulsions in susceptible patients. Patients who develop high-level AV block at a particular dose should not be given further dosage increments. Atrial flutter because of the risk of 1:1 conduction and serious VT	Symptomatic bradycardia, sick sinus syndrome, second- or third-degree AV block (in absence of pacemaker), known pre-excitation, long QT syndrome, severe hypotension, decompensated HF, severe bronchospasm or asthma, ACS or <2–4 days after an acute MI. Tachycardia with a wide QRS complex (unless the diagnosis of SVT with aberrancy is certain). Concomitant use of dipyridamole. Discontinue adenosine in patients who develop severe respiratory difficulties

(continued)

Table 6.5 (continued)

Drug	Drug interactions	Cautions	Contraindications
Digoxin	See Table 6.6 Monitor SDC with clarithromycin, cyclosporine, erythromycin, flecainide, itraconazole, posaconazole, propafenone, verapamil or voriconazole. Reduce the dose of digoxin when coadministered with amiodarone (30%–50%) or dronedarone (50%)	Advanced age, renal failure, hypokalemia, hypercalcemia, hypoxemia, hypothyroidism, severe myocarditis, amyloidosis and acute MI increase digitalis-related arrhythmias. Lower doses in hypothyroidism; higher doses in hyperthyroidism. Withheld digoxin for 24 h before cardioversion	Digitalis toxicity. Intermittent complete heart block or second-degree AV block, especially if there is a history of Stokes-Adams attacks, bradycardia or sick sinus syndrome (in absence of pacemaker). Hypertrophic obstructive cardiomyopathy, unless there is concomitant atrial fibrillation and HF. Supraventricular arrhythmias associated with a known or suspected accessory AV pathway (WPW); VPCs, VT and/or VT; arrhythmias caused by cardiac glycoside intoxication. Severe hypokalemia. IV digoxin in the early-phase of MI. High SDC associated with increased risk of death

Ivabradine	The risk of bradycardia increases when coadministered with amiodarone, BBs, verapamil or diltiazem. Potent CYP3A4 inhibitors and inducers markedly increased or decreased ivabradine plasma levels, respectively	Avoid use with verapamil or diltiazem. Patients with hypotension, retinitis pigmentosa and moderate hepatic or severe renal impairment. Ivabradine-induced bradycardia is a risk factor for QT prolongation. With moderate CYP3A4 inhibitors: initial dose of 2.5 mg if resting heart rate is above 70 bpm, with monitoring of heart rate.	Heart rate <60 bpm, sick sinus syndrome, sino-atrial block, third-degree AV block, AF, acute MI, unstable angina, cardiogenic shock, unstable or acute HF, severe hypotension (<90/50 mmHg), severe hepatic impairment. Avoid potent CYP3A4 inhibitors/inducers and QT prolonging drugs. Pregnancy, lactation and women of child-bearing potential not using appropriate contraceptive measures
Ranolazine	Potent CYP3A4 inhibitors/ inducers increase/decrease ranolazine exposure, respectively. Potent CYP2D6 inhibitors may increase ranolazine plasma levels.	The dose should be limited to 500 mg bid in patients treated with moderate CYP3A inhibitors. Careful dosing in patients with mild-moderate renal impairment (crCl <60 mL/min), mild hepatic impairment and HF (NYHA class III–IV).	Coadministration of potent CYP3A4 inhibitors/inducers or with class I or class III anti-arrhythmics other than amiodarone Pre-existing QT prolongation, co-administration of QT-prolonging drugs, severe renal impairment (crCL <30 mL/ min), moderate-severe hepatic impairment, treatment with QTc-prolonging drugs

(continued)

Table 6.5 (continued)

Drug	Drug interactions	Cautions	Contraindications
Vernakalant	No formal interaction studies have been conducted	Hypotension, hypertrophic obstructive, restrictive cardiomyopathies, or constrictive pericarditis, advanced hepatic impairment and HF (NYHA class I or II) due to the higher risk of hypotension and ventricular arrhythmias. Hypotension responds to drug discontinuation and intravenous fluid administration	Severe aortic stenosis, SBP <100 mmHg, NYHA class III–IV HF, recent (<30 days) ACS (including MI), basal QT >440 ms, severe bradycardia, sinus node dysfunction or second- and third-degree heart block in the absence of a pacemaker. Use of IV class I and III AADs 4 h prior/after vernakalant

AADs antiarrrhythmics, *ACS* acute coronary syndromes, *AF* atrial fibrillation, *AFl* atrial flutter, *AVN* atrio-ventricular node, *AVRT* atrioventricular reentrant tachycardia, *BB* beta-blockers, *CKD* chronic kidney disease, *COPD* chronic obstructive lung disease, *crCl* creatinine clearance, *HF* heart failure, *MI* myocardial infarction, *NYHA* New York Heart Association, *PSVT* paroxysmal supraventricular tachycardia, *SAN* sino-atrial node, *SBP* systolic blood pressure, *SDC* serum digoxin concentration, *SVT* supraventricular tachycardia, *TdP* torsades de pointes, *VPC* ventricular extrasystoles, *VT* ventricular tachycardia, *WPW* Wolf-Parkinson-White syndrome.

Potent CYP3A4 inhibitors: azole antifungals (ketoconazole, itraconazole, posaconazole, voriconazole), boceprevir, macrolide antibiotics (clarithromycin, josamycin, telithromycin), HIV protease inhibitors (indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), nefazodone, telaprevir. Mild CYP3A4 inhibitors: diltiazem, erythromycin, fluconazole, verapamil, grapefruit juice.

CYP3A4 inducers: carbamazepin, phenobarbital, phenytoin, rifampicin, St John's worth

TABLE 6.6 Effects of drugs and medical conditions on serum digoxin concentrations (SDC)

Decrease SDC (it may be necessary to increase the daily dose of digoxin)	
Decrease drug absorption	• Acarbose, adrenaline, antiacids, bupropion, cholestyramine, high-bran diet, kaolin-pectin, some bulk laxatives metoclopramide, neomycin, salbutamol, sulfasalazine, supplemental enteral nutrition • Chemotherapy drugs: cyclophosphamide, cytarabine, methotrexate, vincristine • Other drugs: phenytoin, rifampicin, St John's wort
Increase renal excretion	• Bupropion, hydralazine, nitroprusside, sympathomimetic drugs (dopamine, dobutamine)
Increase *digitalis resistance*	• Reduced oral bioavailability, inadequate intestinal absorption, increased metabolic degradation in the gut • Neonates and infants • Hyperthyroidism
Increase SDC (reduce the daily dose of digoxin)	
Increase oral absorption	• Antibiotics that inhibit intestinal microflora: macrolides (e.g. clarithromycin[a], erythromycin, telithromycin[a]), tetracyclines, gentamicin, trimethoprim • Anticholinergic drugs (propantheline, diphenoxylate), omeprazole
Decreased renal and non-renal excretion	• Alprazolam, atorvastatin, epoprostenol, lapatinib, potassium-sparing diuretics, propafenone, spironolactone • Decrease renal blood flow: β-blockers, heart failure • ARBs, ACEIs, NSAIDs, and COX-2 inhibitors may modify renal function in some patients leading to an indirect increase in SDC • Decreased glomerular filtration rate: elderly, renal impairment

(continued)

Table 6.6 (continued)

P-glycoprotein inhibitors[a]	• Amiodarone, cyclosporine, dronedarone, itraconazole, ketoconazole, lapatinib, nefazodone, quinidine, quinine, ranolazine, telmisartan, ticagrelor, verapamil • Antiretroviral HIV-1 protease inhibitors: atazanavir, darunavir, indinavir, lopinavir, nelfi-navir, ritonavir, saquinavir, telaprevir, tipranavir
Increase cardiac sensitivity to digoxin-induced proarrhythmia	• Advanced age, hypothyroidism, electrolyte disturbances (hypokalemia, hypomagnesemia, hypercalcemia), IV calcium • Sympathomimetic agents: induce cardiac arrhythmias and may also lead to hypokalaemia • Acute myocardial infarction, acute rheumatic or viral carditis, severe myocarditis, amyloidosis • Chronic kidney disease • Hypoxemia due to chronic lung disease • Drugs producing hypokalemia: thiazides and loop diuretics, amphotericin B, β-adrenergic agonists, carbenoxolone, corticosteroids, laxatives, lithium salts, NSAIDs (diclofenac, indometacin), pancuronium, suxamethonium • Amiodarone, beta-blockers, diltiazem, verapamil: increase the risk of bradycardia and AV block • Class IA and IC AADs: increase the risk of bradycardia, intracardiac conduction block and proarrhythmia

AADs antiarrhythmic drugs, *ACEIs* angiotensin converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *NSAIDs* nonsteroidal anti-inflammatory drugs

[a]P-glycoprotein inhibitors can enhance digoxin absorption and/or reduce its renal clearance

Table 6.7 Clinical recommendations of adenosine, digoxin and vernakalant in clinical guidelines

Adenosine [10, 11]	Class	Level
Adenosine is recommended for the acute treatment of narrow QRS tachycardia in the absence of an established diagnosis	I	B
Adenosine is recommended for acute treatment in patients with regular SVT, with AVNRT due to manifest or concealed accessory pathways or with orthodromic AVRT	I	B
Adenosine is recommended for acute treatment in ACHD patients and SVT	I	B
Adenosine can terminate some forms of focal AT due to a triggered mechanism in ACHD	I	B
Adenosine is recommended for acute treatment in pregnant patients with SVT	I	C
Adenosine is recommended to either restore SR or diagnose the tachycardia mechanism in patients with suspected focal AT	IIa	B
Adenosine is recommended for the acute treatment of wide QRS tachycardia if there is no pre-excitation on a resting ECG	IIa	C
Adenosine in patients with WPW syndrome who have pre-excited AF is potentially harmful because it accelerates the ventricular rate	III	B
Digoxin		
In the absence of pre-excitation, IV digoxin is recommended to acutely control heart rate in patients with HF [13, 27]	I	B
Digoxin is recommended to control heart rate in AF patients with LVEF ≥40% [13]	I	B
Digoxin is recommended to control heart rate in AF patients with LVEF <40% [13]	I	B

Table 6.7 (continued)

Digoxin is effective to control resting heart rate in patients with HFrEF, with dosage appropriate to avoid bradycardia [27]	I	C
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 heart rate in patients with AF [27]	IIa	B
Intravenous digoxin in the latest pocket Gls version should be considered for rate control of AT if beta-blockers fail [13]	IIa	C
Digoxin can be effective for ongoing management in pregnant patients with highly symptomatic SVT [11]	IIa	C
Digoxin should be considered for rate control of AT if beta-blockers fail in patients without WPW syndrome [11]	IIa	C
Oral digoxin may be reasonable for treatment of AVNRT in patients who are not candidates for, or prefer not to undergo, catheter ablation [10]	IIb	B
Digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with severe LV dysfunction and HF or hemodynamic instability [27]	IIb	C
Oral digoxin may be reasonable for ongoing management in patients with symptomatic SVT of unknown mechanism without pre-excitation who are not candidates for, or prefer not to undergo, catheter ablation [10]	IIb	C
Oral digoxin may be reasonable for ongoing management of orthodromic AVRT in patients without pre-excitation on their resting ECG who are not candidates for, or prefer not to undergo, catheter ablation [10]	IIb	C
Digoxin is potentially harmful for ongoing management in patients with AVRT or AF and pre-excitation on their resting ECG [10, 11, 13]	III	C

Table 6.7 (continued)

Ivabradine		
Ivabradine is reasonable for ongoing management in patients with symptomatic IST [10, 11]	IIa	B
The combination of beta blockers and ivabradine may be considered for ongoing management in patients with IST [10, 11]	IIb	C
Ivabradine may be considered in patients with postural orthostatic tachycardia syndrome [11]	IIb	C
Ivabradine with a beta-blocker may be considered for the chronic treatment of recurrent focal AT when other measures fail [11]	IIb	C
Ranolazine		
Ranolazine may be considered as add-on therapy to shorten the QT interval in LQTS3 patients with a QTc >500 ms [51]	IIb	C
Vernakalant		
In patients with no history of ischemic or structural heart disease, vernakalant is recommended for PCV of recent-onset AF [13]	I	A
Intravenous vernakalant is an alternative to amiodarone for PCV of AF in patients without hypotension, severe HF or severe structural heart disease (especially aortic stenosis) [13]	IIb	B
Intravenous vernakalant may be considered for cardioversion of postoperative AF in patients without severe HF, hypotension, or severe structural heart disease (especially aortic stenosis) [13]	IIb	B

ACHD adult c.ongenital heart disease, ACS acute coronary syndromes, AF atrial fibrillation, AT atrial tachycardia, AVNRT atrioventricular nodal reentrant tachycardia, AVRT atrioventricular reentrant tachycardia, GI gastrointestinal, HFrEF heart failure with reduced ejection fraction, HF heart failure, IST inappropriate sinus tachycardia, LVEF left ventricular ejection fraction, PCV pharmacological cardioversion, SR sinus rhythm, SVT supraventricular tachycardia, WPW Wolff-Parkinson-White

(I_{Ca}) during sympathetic stimulation. As a consequence, adenosine decreases SAN pacemaker activity and in the AVN slows conduction velocity and increases refractoriness. (d) Activates presynaptic purinergic receptors located on sympathetic nerve terminals decreasing the release of norepinephrine. These two later effects explain why adenosine terminates some atrial and ventricular arrhythmias and abolishes both early (EADs) and delayed (DADs) afterdepolarizations induced by catecholamines.

Activation of the Gs protein–bound A2 receptors increases adenyl cyclase activity and cAMP levels, inhibits Ca^{2+} entry and myosin light chain kinase and stimulates ATP-sensitive potassium (K_{ATP}) channels which hyperpolarizes vascular smooth muscle cells [1–3]. As a result, adenosine decreases coronary and peripheral vascular resistances, vasodilates coronary microvessels (<150 mm in diameter), adequates coronary blood flow to cardiac metabolic demands playing a key role in ischemic pre-conditioning and attenuates ischemia-reperfusion injury. Because of its coronary vasodilator properties, adenosine is indicated for stress radionuclide myocardial perfusion imaging in patients unable to undergo adequate exercise stress. Adenosine has also been used to produce controlled hypotension.

Pharmacodynamics An intravenous (IV) bolus of adenosine, preferable through a large venous or central line, rapidly (within 10–30 s) and transiently slows AV conduction velocity [due to effects on the atrial-His (AH) interval, but not on the H-V interval] and increases AV refractoriness (prolongs the PR and A-H intervals) leading to a transient AV block that is then responsible for tachycardia termination [4, 5]. Thus, adenosine the drug of choice to terminate supraventricular tachycardias (SVT) using the AVN as a portion of the reentrant circuit, such as AV nodal re-entry tachycardias (AVNRT) and AV reentrant tachycardias (AVRT). Success rates range from 78% to 96% (similar to verapamil) in acute episodes of SVT [3–11]. Adenosine also slows sinus rate, may cause sinus exit block and can terminate

SAN reentry. The effects of adenosine on the SAN and AVN are of greater and longer in patients with recent heart transplantation (<1 year). Adenosine is effective in terminating some focal atrial tachycardias (AT) due to a triggered mechanism in adult congenital heart disease patients, but does not interrupt macro-re-entrant ATs unless the reentrant circuit involves the AVN [7, 12]. Adenosine is unlikely to terminate atrial fibrillation (AF) or atrial flutter (AFl) [13], but it can produce a transient AV block, which unmask atrial activity and helps to diagnosis. Adenosine does not affect conduction velocity through the His-Purkinje or normal accessory pathways, but conduction can be blocked in accessory pathways with long conduction times or decremental conduction. Ventricular tachycardias (VT) do not respond to adenosine, but it can terminate idiopathic right outflow tract VT caused by a cAMP-mediated triggered activity caused by delayed afterdepolarizations; idiopathic left septal VT rarely responds.

Adenosine terminates AVNRT, SVT using an accessory pathway, and some forms of focal AT which account for <25% of SVT in adults with repaired congenital disease. However, evwn when it is unlikely to terminate atrial reentry tachycardia or atrial flutter, which represents >70% of SVT episodes in this population, adenosine may help to the diagnosis by producing transient AV block, which would make the atrial activity visible [1, 4, 7, 10–12].

Adenosine can help to the diagnosis of narrow-complex tachyarrhythmias [1, 4, 5, 8–12]. The appearance of transient AVN block with persistent AT can help to differentiate focal AT from AVNRT and AVRT [7]. In wide-QRS tachycardias of uncertain origin, adenosine can help to differentiate SVT (with aberrant conduction) from VT; adenosine is likely to terminate SVT with aberrancy or reveals the underlying atrial mechanism, while the VT continues. When an accessory by-pass tract is present, adenosine may increase conduction down the anomalous pathway revealing latent pre-excitation in patients with suspected Wolff-Parkinson-White (WPW) syndrome. A normal response occurs if transient high-grade AV block is observed; the presence of an

anterograde conduction accessory pathway is inferred if adenosine produces a PR shortening-QRS widening without interruption of AV conduction. Adenosine can also differentiate conduction over the AVN from that over an accessory pathway during ablative procedures of the accessory pathway, and can provide a diagnosis in VT with retrograde conduction by blocking the P wave.

Adenosine may also promote arrhythmogenesis [2, 14]. It often produces bradycardia, sinus arrest and several degrees of AVN block, and even when prolonged bradycardia is unusual, caution is recommended in patients with known sinus node disease [2, 5, 15]. The risk of bradycardia increases in recipients of denervated orthotropic heart transplants, in whom SVT is common [5, 16]. Adenosine may induce AF with fast ventricular conduction and even VT by several mechanisms as it heterogeneously shortens atrial APD and refractoriness, produces transient sympathetic stimulation (tachycardia) through baroreflex activation in response to hypotension and it can hyperpolarize dormant pulmonary vein myocytes increasing their excitability and automaticity [17, 18]; the risk of AF appears more commonly associated with AVRT than AVNRT [8]. Patients with orthodromic AVRT often present atrial or ventricular premature complexes immediately after conversion that ocassionally may induce further episodes of AVRT. In this situation, an antiarrhythmic drug may be required to prevent acute reinitiation of tachycardia [1, 9–11]. Adenosine may also occasionally cause or accelerate pre-excited atrial arrhythmias [5, 19]. Because of the risk of proarrhythmia, adenosine should be used only in-hospital and with full resuscitative equipment available.

Pharmacokinetics After IV administration adenosine is rapidly cleared from circulation via cellular uptake by erythrocytes and vascular endothelial cells, where it is metabolized by the adenosine deaminase to inosine and adenosine monophosphate which are excreted by the kidneys. Its half-life ($t_{1/2}$) is <20 s, which explains why adverse effects

even when frequent, they rapidly disappear and the repeated administration is safe within 1 min of the last dose.

The starting dose required for efficient rhythm correction is ~6 mg, given as a rapid bolus (1–2 sec) followed by a rapid saline flush. Large, centrally located (e.g. antecubital) veins are likely to deliver more effective drug concentrations to the heart than smaller distal veins [10, 11]. Another bolus of 12 mg can be administered after 1–2 min; this 12 mg bolus can be repeated in 1–2 min if SVT persist (Table 6.3).

Adverse Effects (Table 6.4) The most common include flushing, dyspnea (most likely secondary to stimulation of vagal C fibers in the lungs), chest discomfort, headache, dizziness, numbness or nausea, AV block and arrhythmias, but serious adverse adverse effects are rare because of the drug's very short half-life [2, 20]. Chest discomfort begins at approximately the same time as the delay in AV conduction and is immediately preceded by a marked increase in coronary-sinus flow, suggesting that the pain has a myocardial origin [5, 11]. Adenosine may precipitate or aggravate bronchospasm; thus, it may be reasonable to replace adenosine by verapamil in asthmatic patients.

Indications Adenosine is the drug of choice to rapidly terminate regular narrow-QRS-complex PSVT using the AVN as part of the reentry circuit when vagal manoeuvres fail, except for patients with severe asthma or angina pectoris [10, 11]. Because of its rapid onset and short duration of action, adenosine is preferable to verapamil or diltiazem, particularly in patients treated with IV β-adrenergic blockers or with history of heart failure (HF) or severe hypotension, and in neonates. Adenosine is the drug of choice for termination of SVT in pregnant patients when vagal manoeuvres fail; adverse effects to the fetus would not be expected and maternal side effects are transient given its short half-life [10, 11, 21]. Adenosine can also terminate AT, sinus node reentry and idiopathic right outflow tract VT commonly triggered by sympathetic stimulation.

Selective A1R Agonists (Table 6.1) They slow conduction velocity and prolong refractoriness in the AVN without affecting intraventricular conduction or reducing blood pressure or causing bronchospasm, two common side effects of adenosine [22]. They are effective for the conversion of PSVT to sinus rhythm (SR) and for ventricular rate control in AF without the negative inotropic and vasodilator effects of β-blockers, verapamil or diltiazem. Tecadenoson dose-dependently prolongs the AH interval (peak effect within 1 min, but returned to baseline after 10 min) without an effect on the HV interval, presents a longer $t_{1/2}$ than adenosine (20–30 min) and converts PSVT to SR in 90% of patients even after the first bolus, coincident with anterograde AV conduction block. Patients with a history of asthma or chronic obstructive pulmonary disease tolerated tecadenoson without bronchospasm. Other A1 adenosine receptor-selective full agonists and partial agonists are under development for multiple clinical indications.

Cardiac Glycosides

Cardiac glycosides (digoxin and digitoxin) increase cardiac contractility and slow AVN conduction and have been used for decades to treat patients with symptomatic heart failure (HF) or impaired left ventricular (LV) function and for ventricular rate control in patients with supraventricular arrhythmias, mainly permanent and persistent AF, respectively. However, their use have declined over the past years because of its narrow therapeutic window and multiple interactions (Table 6.7), the increasing number of evidence-based therapies for HF and the results of the DIG trial [23], where digoxin therapy was shown to reduce all-cause and HF-specific hospitalizations but had no effect on survival.

Mechanism of Action Digoxin inhibits the Na^+/K^+-ATPase (3 Na^+ out – 2 K^+ in) [24, 25]. This inhibition increases the intracellular Na^+ concentration ($[Na^+]_i$), which in turn,

activates the reverse mode of the Ca^{2+}-Na^{+} exchanger (NCX, Na^{+} efflux/Ca^{2+} influx) leading to an increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$). This increase in $[Ca^{2+}]_i$ at the level of contractile proteins might account for the positive inotropic effect and the proarrhythmic effects during digitalis intoxication. Furthermore, digitalis form calcium-conductance pathways and cation-selective Ca^{2+} channels which may play a role in Ca^{2+}-dependent cardiotoxicity [26].

At therapeutic concentrations the electrophysiologic effects of digoxin are mediated indirectly by enhancing both central and peripheral vagal and inhibiting sympathetic tone, and to a lesser extent through a direct cardiac effect [24, 25]. The increase in vagal tone: (a) inhibits I_f and accelerates the inactivation of the I_{Ca} due to the higher $[Ca^{2+}]_i$, producing a mild resting bradycardia that may increase LV performance; (b) activates the I_{KACh} leading to a nonuniform shortening of atrial APD and refractoriness; and (c) slows conduction and prolongs refractoriness in the AVN (prolongs the PR interval). This latter effect is the basis to use digoxin to control ventricular rate in patients with AF, particularly in unstabilized HF patients in whom β-blockers and calcium antagonists are contraindicated and to terminate reentrant tachyarrhythmias involving the AVN. However, digoxin exerts minimal effects on the His-Purkinje and ventricular muscle and the QRS and QT intervals are unaffected. Inhibition of Na^{+}/K^{+}-ATPase in the vagal afferent fibers restores cardiac baroreceptor sensitivity, leading to a decrease in peripheral sympathetic nerve activity; digoxin also reduces renin and angiotensin II plasma levels. This neurohumoral inactivation may play a key role at these therapeutic concentrations.

At toxic concentrations, digoxin directly causes sinus bradycardia and different degrees of AVN block, shortens atrial and ventricular APD and refractoriness, but increases $[Ca^{2+}]_i$ and sympathetic cardiac activity; these later effects increase the automaticity of cardiac pacemakers (AVN, His-Purkinje system) [24, 25]. Additionally, the inhibition of the Na^{+}/K^{+}-ATPase depolarizes the resting membrane potential, partially inactivates Na^{+} channels and decreases intra-

cardiac conduction velocity. Additionally, digoxin increases $[Ca^{2+}]_i$ and induces the spontaneous release of Ca^{2+} from the sarcoplasmic reticulum during the diastole, which, in turn, activates the forward mode of the NCX (Na^+ influx/Ca^{2+} efflux) leading to a net inward transient depolarizing current (I_{Ti}) that can generate EADs and DADs. All these effects predispose to both bradyarrhythmias and supraventricular and ventricular tachyarrhythmias that may degenerate in VT and ventricular fibrillation (VF). The increase in $[Ca^{2+}]_i$ in vascular smooth muscle cells can cause a direct vasoconstriction that may cause mesenteric artery occlusion or ischemia.

Electrophysiological Effects Digoxin effectively slows ventricular rate at rest when vagal tone predominates and in sedentary elderly patients with persistent/permanent AF [24, 25]. However, when sympathetic activity increases (i.e., during exercise, serious illness, fever, HF, hyperthyroidism, chronic lung disease, postoperative) its beneficial effects on AV conduction are reduced. Thus, digoxin is rarely used as a single agent for ventricular rate control in AF, but a satisfactory rate control can be achieved both at rest and during exercise when combined with β-blockers, verapamil or diltiazem. The ongoing RATE-AF trial is the first randomised clinical trial comparing digoxin and beta-blockers in AF.

Digoxin produces a nonuniform shortening of atrial APD and refractoriness that may explain why digoxin may increase the duration of AF, predisposes to early relapses of AF after restoration of SR and can convert the AFl to AF [24, 25]. Digoxin is no more effective than placebo to terminate AF or facilitate direct current cardioversion and may even induce episodes of AF in patients with so-called vagal AF [27]. Digoxin is contraindicated in patients with pre-excited AF because it slows AVN conduction but can accelerate anterograde conduction via the bypass tract increasing the ventricular rate during AF and the risk of provoking a life-threatening ventricular arrhythmia [13, 27–29].

In the ACC/AHA/HRS Guideline for the management of adult patients with supraventricular tachycardia oral digoxin is recommended for ongoing management in patients with symptomatic SVT without pre-excitation or with AVNRT who are not candidates for, or prefer not to undergo, catheter ablation [10]. However, digoxin should be reserved for patients who are unresponsive to, or are not candidates for β-blockers, diltiazem, or verapamil or a class IC agents (flecainide or propafenone) and it be used with caution in the presence of renal dysfunction. Interestingly, in the 2019 ESC Guidelines for the management of patients with SVT digoxin is not mentioned [11].

Because of its positive inotropic agent, digoxin is recommended for heart rate control in patients with AF and LVEF <40%, particularly in unstabilized patients in whom both β-blockers, diltiazem or verapamil are contraindicated. The combination of digoxin and carvedilol leads to better ventricular rate control than either agent, reduces symptoms, improves exercise tolerance and LV function [30]. In patients with AF (25% of the patients in NYHA class III) the IV administration of digoxin and esmolol produces a rapid rate control and conversion to SR occurs in 25% of patients [31]. In the AF-CHF trial [32], including patients with AF and LVEF ≤35%, adequate rate control was achieved in 82–88% of patients using adjusted doses of β-blockers with digoxin and in the CHF-STAT trial [33], amiodarone improved ventricular rate control when added to background therapy with digoxin in patients with AF and HF.

Several observational studies and meta-analysis associated digoxin therapy with excess mortality in patients with AF, but this finding was not confirmed in other studies [34–36]. The association is hampered by selection and prescription biases, because digoxin is commonly prescribed in sicker patients, with more comorbidities (HF, diabetes) and a higher baseline risk of mortality. A recent meta-analysis of 52 studies including over 600,000 patients with AF and concomitant HF, concluded that digoxin had a neutral effect on mortality but reduced hospital admission [36]. Thus, until

proper randomized controlled trials are available, digoxin remains a suitable treatment option for rate control in patients with AF and HF.

Digoxin Plasma Levels Digoxin presents a narrow therapeutic window. Routine monitoring of serum digoxin concentrations (SDC) is not warranted in AF patients with controlled ventricular rate and without symptoms of toxicity, but is justified in patients with suspected digoxin intoxication, impaired renal excretion, variable cardiac responses, altered volume of distribution (Vd), hyperthyroidism, or suspected drug interactions, and to monitor compliance with therapy (Table 6.7). A retrospective analysis of the DIG trial found that low SDC (0.6–0.9 ng/mL) provided hemodynamic benefit and a small decrease in all-cause mortality, while at higher SDC (≥1.2 ng/mL) digoxin increased mortality (12%) [37]. Thus, SDC should be maintained between 0.6 and 1 ng/mL.

Doses should be based on age, gender, lean body mass, serum creatinine, serum electrolytes and presence of other drugs as digoxin presents multiple pharmacodynamic/pharmacokinetic interactions (Table 6.6). In elderly patients digoxin presents a lower Vd due to a loss of lean muscle mass and decline in renal function. Renal impairment decreases digoxin clearance and prolongs its $t_{1/2}$. Thus, doses, clinical response and SDC should be carefully titrated in elderly and in patients with chronic kidney disease. No dosage adjustments are recommended for patients with hepatic impairment. Digoxin is a substrate of P-glycoprotein (P-gp) and P-gp inhibitors can enhance digoxin absorption and/or reduce its renal clearance.

Adverse Effects Digoxin presents a narrow therapeutic index and SDC should be maintained between 0.5 and 0.9 ng/mL (Table 6.7). Cardiac glycosides can produce any type of arrhythmia, including bradyarrhythmias related to an increase in vagal tone (sinus bradycardia or arrest, AV block) and supraventricular (paroxysmal AT with variable AV block,

AVN tachycardias) and ventricular tachyarrhythmias (ventricular bideminy, VT, VF), particularly when electrolyte disorders are present.

If there is suspicion of toxicity, digoxin should be discontinued and ECG and SDC monitored. Electrolyte disorders, thyroid dysfunction and drugs/factor increasing SDC should be corrected (Table 6.7). Potassium salts should be avoided in the presence of bradycardia or conduction disturbances. Bradyarrhythmias or AV block respond to atropine but a temporary cardiac pacing may be required if symptomatic; ventricular arrhythmias may respond to lidocaine. Life-threatening arrhythmias can be treated with antidigoxin Fab fragments. Direct-current cardioversion should only be used if necessary using the lowest effective energy because life-threatening VT/VF can result. For elective electrical cardioversion of AF of a patient who is taking digoxin, the drug should be withheld for 1–2 days before cardioversion is performed.

Indications Digoxin is no longer a first-line drug for acute or long-term rate control during permanent/persistent AF or AFl, but because of its low cost and accumulated knowledge in prescription during decades, digoxin would remain for rate control AF, especially for elderly-sedentary or patients with HF or LV dysfunction [13, 27].

For *acute heart rate control* in patients without evidence of reduced LVEF, digoxin can be added to β-blockers, verapamil or diltiazem where required [13, 27]. However, β-blockers and diltiazem/verapamil are preferred over digoxin because of their rapid onset of action and effectiveness at rest and/or during exercise. In patients with signs of HF or evidence of reduced LVEF, β-blockers and/or digoxin should be considered as first-line therapy to improve LV function; digoxin is indicated in unstabilized HF patients in whom β-blockers and calcium channel blockers are contraindicated. For *long-term rate control* digoxin, alone or in combination with other AV blocking drugs (beta-blockers, diltiazem, or verapamil) is recommended for long-term rate control in patients with persistent/permanent AF with

LVEF ≥40%, with dosage appropriate to avoid bradycardia, and in AF patients with LVEF <40% [13, 27]. In SVT, digoxin has been replaced by adenosine, β-blockers and verapamil, drugs with faster onset of action and better safety profile. However, in the absence of pre-excitation, digoxin may be reasonable in patients with symptomatic SVT (including pregnant patients), orthodromic AVRT who are not candidates for, or prefer not to undergo, catheter ablation, and in AVNRT in patients with SBP <110 mmHg in whom β-blockers, verapamil or diltiazem may cause symptomatic hypotension or bradycardia [10, 11]. Digoxin has no role in ventricular arrhythmias.

Atrial-Selective Sodium Channel Blockers

A new strategy for suppression of AF/AFl is the development of the so-called atrial-selective Na^+ channel blockers, drugs that predominantly depresses atrial versus ventricular Na^+ channel-dependent parameters and suppresses AF at concentrations producing little to no effect in the ventricles, thus reducing the risk of ventricular proarrhythmia. It has been hypothesized [38] that drugs like vernakalant and ranolazine that preferentially bind to the inactivated state of the Na^+ channel with fast unbinding kinetics might exhibit atrial selectivity during AF because: (a) atrial cells exhibit a more depolarized (~10 mV) resting membrane potential and a more negative half-inactivation voltage of Na^+ channels. Because reactivation depends on membrane potential, fewer Na^+ channels recover from the inactivated state during diastole in atrial as compared to ventricular cells and atrial refractoriness persist after the action potential is fully repolarized (postrepolarization refractoriness-PRR). (b) Atrial action potentials present a more gradual phase 3 which at rapid atrial rates results in a progressive disappearance of the diastolic interval in atria but not in ventricles and a less negative take-off potential further increasing the percentage of inactivated Na^+ channels. During AF, as the atria fail to fully repolarize, the

difference in resting membrane potential between the atria and ventricles increases and less atrial Na^+ channels fully recover during diastole and remain in the inactivated state leading to the accumulation of Na^+-channel block and PRR.

Vernakalant

Vernakalant is an atrial-selective multichannel blocker that inhibits the peak (I_{Na}) and late Na^+ ($I_{Na,L}$) currents, resulting in slow intra-atrial conduction and prolongation of atrial refractoriness, and several outward K^+ currents that control atrial repolarization: the ultra-rapid delayed rectifier current (I_{Kur}), the transient potassium current (I_{to}) and the inward rectifier currents I_{KAch} and I_{KATP} [39]. However, vernakalant has no effect on I_{CaL} or the rapid component of the delayed rectifier (I_{Kr}). As a consequence, vernakalant blocks I_{Na} in a rate- and voltage-dependent manner, so that Na^+ channel blockade increases at depolarized potentials and high heart rates, i.e. during AF, and selectively prolongs atrial APD and refractoriness with minimal effects on ventricular repolarization (QT interval) and refractoriness.

Pharmacodynamics The efficacy and safety of IV vernakalant for cardioversion of recent-onset AF was evaluated in six clinical trials [40, 41]. Vernakalant selectively prolongs atrial APD and refractoriness without affecting ventricular repolarization (QT interval) or refractoriness, heart rate or blood pressure. Vernakalant was significantly more effective than placebo for the conversion of AF to SR; the mean time to conversion was 8–14 min and 75–82% of patients converted after the first dose. The highest efficacy of vernakalant was observed for AF lasting for up to 72 h (51–79%), but decreased with the duration of the arrhythmia, being ineffective for the conversion of AF lasting >7 days or AFl. Interestingly, pre-treatment with vernakalant can improve the efficacy of electrical cardioversion. In the AVRO trial [42], vernakalant was more effective than IV amiodarone

but the responder rates were lower, probably because of the higher proportion of patients with HF were enrolled in this trial. The probability of conversion to SR is independent of age, sex, LVEF, left atrial size, prior use of AADs, history of coronary artery disease or renal impairment, but there was a trend towards decreased efficacy in elderly patients (aged ≥75 years), those with a history of HF and in patients receiving digoxin or class I AADs. However, vernakalant is ineffective in patients with AFl [13, 40, 41].

Drug exposure is not influenced by age, gender, race, coronary artery disease, HF, renal or hepatic impairment, CP2D6 genotype or coadministration of CYP2D6 inhibitors, AVN blockers or warfarin.

Indications Intravenous vernakalant is recommended for the rapid termination of recent-onset AF (≤7 days for non-surgery patients; ≤3 days for post-cardiac surgery patients) to SR in adults without structural heart disease or with hypertension, CAD, abnormal LV hypertrophy or moderate HF (NYHA class I–II) and for cardioversion of postoperative AF, provided they do not present severe HF, hypotension, or severe aortic stenosis [13]. Vernakalant represents a fast and effective alternative to class IC antiarrhythmics and amiodarone, presents few proarrhythmic and extracardiac effects, eliminates the need for conscious sedation or anesthesia and when pharmacological cardioversion has failed it does not modify the efficacy of subsequent electric cardioversion. However, there are no head-to-head comparison with DC cardioversion or class IC AADs.

Ranolazine

Ranolazine is approved for the treatment of chronic stable angina for patients inadequately controlled or intolerant to β-blockers and/or calcium channel blockers.

Mechanism of Action In atrial and ventricular muscle and Purkinje fibres, the rapid upstroke of the action potential is due to the activation of the I_{Na}. Most cardiac Na^+ channels open transiently (1–3 ms) during membrane depolarization, but rapidly inactivate-close and remain closed during the plateau phase of the action potential. However, some Na^+ channels do not inactivate or inactivate but reopen during the plateau generating the late Na^+ current (I_{NaL}) [43, 44]. An enhanced I_{NaL} slows the rate of repolarization, prolongs the APD (QT interval) and increases transmural dispersion of repolarization (TDR) across the ventricular wall. These effects facilitate triggered and re-entrant arrhythmias. The I_{NaL} increases under conditions associated with a high incidence of cardiac arrhythmias, including myocardial ischemia, LV hypertrophy, HF and arrhythmias associated with mutations in the cardiac Na^+ channel or their regulatory proteins (e.g. long QT and Brugada syndromes) [43, 44]. Myocardial ischemia increases the I_{NaL} and the $[Na^+]_i$ which, in turn, activates the reverse mode of the NCX, leading to a Na^+-mediated Ca^{2+} overload. This increase in Na^+ and Ca^{2+} concentrations is a major contributor to the electrical (EADs, DADs, arrhythmias), mechanical (increases diastolic wall tension and MVO_2) and metabolic disturbances (increase ATP consumption, decreases ATP formation) in the ischemic myocardium [43, 44].

Ranolazine selectively inhibits the I_{NaL}, with almost no inhibition of the peak I_{Na}. Thus, it does not widen the QRS complex or slows intracardiac conduction velocity. Ranolazine also inhibits the I_{Kr}, but the expected prolongation of the APD and QTc interval secondary to this effect is counteracted by the inhibition of I_{NaL}. Indeed, ranolazine suppresses EADs and torsades de pointes induced by selective I_{Kr}-blockers and QT-prolonging drugs. Ranolazine prolongs atrial and ventricular refractoriness, induces PRR and reduces TDR. Ranolazine, however, does not modify cardiac contractility, AVN conduction or blood pressure.

Effects on Atrial Fibrillation In experimental models, vernakalant dose-dependently prolongs atrial APD and refractoriness, slows intra-atrial conduction, induces PRR, suppresses EADs and DADs elicited in pulmonary vein sleeves and terminates and/or prevents initiation of AF [43]. The combination of ranolazine with dronedarone or amiodarone induces potent synergistic use-dependent atrial-selective depression of Na^+ channel-mediated parameters, markedly increases PRR, and prevents the induction of AF.

In small uncontrolled trials, ranolazine (500–1000 mg bid) was effective to maintain SR in patients with recurrent AF despite AF ablation and AAD therapy, facilitates electrical cardioversion in cardioversion-resistant patients, prevents post-operative AF and at high doses (2 g p.o.) produces the conversion of recent-onset AF (<48 h duration) [45, 46]. In patients with unstable angina and non-ST-segment elevation myocardial infarction, ranolazine tended to reduce the episodes of AF as compared with placebo [47].

In a meta-analysis of eight trials in patients with preserved LVEF and recent-onset AF, ranolazine significantly reduces the incidence of AF compared to the control group in various clinical settings (i.e., after cardiac surgery, acute coronary syndromes, post-electrical cardioversion of AF). In the RAFAELLO study, ranolazine (375–750 mg bid) does not prolong the time to AF recurrence as compared to placebo [48], while in the HARMONY trial the combination of ranolazine (750 mg bid) and low doses of dronedarone (225 mg bid), but not each drug in monotherapy, significantly reduces AF burden vs placebo in patients with paroxysmal AF [49].

Effects on Ventricular Arrhythmias Ranolazine suppresses experimental ventricular arrhythmias associated with reduced repolarization reserve due to an increased I_{NaL} and/or reduced I_{Kr}. In patients with unstable angina and non-ST-segment elevation myocardial infarction, ranolazine significantly reduces the incidence of non-sustained VT, SVT, bradycardias

or pauses as compared with placebo, but not sudden cardiac death [47]. In LQT3 patients with the SCN5A-ΔKPQ mutation and an increased I_{NaL}, I.V. ranolazine shortens the QTc interval without changes in PR and QRS intervals, AV conduction or blood pressure, and improves diastolic dysfunction [50]. Thus, ranolazine may be considered as add-on therapy to shorten the QT interval in LQTS3 patients with a QTc >500 ms [51].

Drug Interactions Ranolazine is a moderate/potent inhibitor of P-gp and a mild inhibitor of CYP3A4 [20]. Avoid the administration of ranolazine with strong CYP3A inhibitors/inducers; limit the dose to 500 mg bid in patients on moderate CYP3A inhibitors (Table 6.5). Dose adjustment of CYP3A4 substrates (atorvastatin, lovastatin, simvastatin; limit the dose of simvastatin to 20 mg od), particularly of drugs with a narrow therapeutic range (e.g. cyclosporin, everolimus, sirolimus, tacrolimus), may be required when coadminstred with ranolazine. Monitor the plasma levels of the immunosuppressants when coadminstred with ranolazine. Ranolazine increases the exposure to digoxin. Exposure to CYP2D6 substrates (e.g. tricyclic antidepressants, antipsychotics) may be increased by ranolazine, and lower doses of these drugs may be required. Ranolazine also increases plasma levels of digoxin and metformin (metformin dose should not exceed 1700 mg/day when ranolazine is administered at 1000 mg bid). There is a theoretical risk that concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias. There is a theoretical risk that concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias.

Clinical Indications Ranolazine is well tolerated, does not produce significant hemodynamic, organ toxicity or pro-

arrhythmic effects and its effects are more pronounced on atrial than on ventricular myocardium. Thus, it may represent a promising new AAD in patients with paroxysmal and persistent AF and structural heart diseases associated with an increase in I_{NaL}, where most AADs are contraindicated, SVT and ventricular arrhythmias. However, long-term RCTs are needed that confirm the efficacy and safety of ranolazine for the cardioversion of AF and the maintenance of SR in these patients.

Selective I_f Blockers: Ivabradine

Elevated resting heart rate is an independent risk factor of cardiovascular morbidity and mortality in the general population and in patients with cardiovascular diseases. Ivabradine is an antianginal drug that selectively inhibits the cardiac pacemaker current (I) which is responsible for normal automaticity of the sinus node and reduces heart rate in a dose-dependent manner, without influencing intracardiac conduction velocity or refractoriness, myocardial contractility and blood pressure [52].

The off-label use of ivabradine in small trials recruiting patients with inappropriate sinus tachycardia (IST) in response to exercise or orthostatic challenge reduced maximum/minimum heart rate and symptoms during exercise or daily activity and improved exercise tolerance in stress tests and quality of life with an efficacy comparable with placebo or other therapies, but is better tolerated than metoprolol [52–54]. A persistent clinical benefit was observed in some patients even after discontinuing the drug. Thus, ivabradine is recommended for symptomatic patients with IST [10, 11]. However, this is not an FDA/EMA-approved indication of ivabradine. Potential mechanisms of the antiarrhythmic effects of ivabradine includes I_f inhibition, reduction of cardiomyocyte Ca^{2+} overload and APD prolongation induced by heart rate reduction. Ivabradine may also be effective in focal AT, but there are limited data of the efficacy of ivabradine in

the treatment of postural orthostatic tachycardia syndrome, sinus tachycardia after ablation of the AVNRT and refractory junction ectopic tachycardia [10, 11, 55]. Thus, larger prospective comparative studies are needed to establish the antiarrhythmic efficacy and safety of ivabradine. However, by breaking the pressure homeostatic loop, the selective blockade of I_f is associated with a reflex increase in the activity of sympathetic efferent fibres [56]. Thus, ideally ivabradine should be preferably co-administered with a β-blocker when possible under close monitoring for the possibility of excess bradycardia; this combination may also be more beneficial than each drug alone for IST [10, 11].

Drug Interactions Ivabradine is metabolized via cytochrome CYP3A4 and it should be avoided or used with caution with potent CYP44A inhibitors/inducers (Table 6.5) [20]. Increased plasma concentrations of ivabradine may be associated with excessive bradycardia. Ranolazine is partially metabolised by CYP2D6 and potent CYP2D6 may increase its plasma concentrations. Ranolazine is also a mild inhibitor of CYP2D6 and exposure to CYP2D6 substrates (e.g. cyclophosphamide, efavirenz, flecainide, metoprolol, propafenone or tricyclic antidepressants and antipsychotics) may be increased by ivabradine, so that lower doses of these drugs may be required. Ivabradine should not be taken during pregnancy or breastfeeding [21].

Gap-Junction Coupling Enhancers

Coordinated cardiac impulse conduction is a function of membrane excitability which depends on Na^+ or Ca^{2+} channel activity, intercellular coupling of cardiomyocytes via low resistance connections (gap-junctions), and tissue architecture mainly determined by fibrosis [57]. Gap junction channels are composed of two hemichannels (connexons), formed from six connexin molecules, provided by either of the adjacent cells. The major connexins (Cx40, Cx43, and Cx45) are

expressed in a chamber-specific manner. Cx43 is found in ventricles and atria, Cx40 in the atria and specific conduction system and Cx45 in the conduction system, SAN and ANV. Cellular uncoupling due to changes in Cx expression (resulting in irregular activation patterns), location (lateralization) and function occur in many forms of heart disease (i.e., ischemia, cardiac hypertrophy, HF and AF) and contribute to cardiac arrhythmias as they slow intracardiac conduction, increase repolarization heterogeneity and modulate automaticity. Cellular uncoupling together with increased fibrosis and decreased expression of Na^+ channels, are implicated in conduction slowing during ischemia, increasing the risk of fatal ventricular arrhythmias [57, 58].

Small-molecules that enhance gap-junction conductance have been developed in an attempt to improve conduction, eliminate functional block and suppress reentry [59]. The hexapepide rotigaptide and its dipeptide analogue danegaptide, increase gap-junction conductance (electrical coupling) acting via Cx43 and Cx45 gap junctions and may represent a novel therapeutic strategy to improve conduction, eliminate functional block and abolish reentry. Both drugs improve conduction during acidosis, acute metabolic stress or myocardial ischemia without affecting sarcolemmal ion channels or cardiac contractility and suppress reentrant ventricular tachyarrhythmias during ischemia-reperfusion. However, rotigaptide partially reverses the loss of Cx43 and does not restore normal conduction or prevent arrhythmias in the healing infarct border zone, i.e. after a prolonged period of gap-junction remodeling, is ineffective against focal ventricular tachyarrhythmias and does not suppress triggered arrhythmias. Gap-junction enhancers can also reduce AF vulnerability in some models (chronic mitral regurgitation, acute ischemia, sterile pericarditis), but not in HF or atrial tachypacing models, and it is unclear whether they are equally effective in chronically remodelled atria. Therefore, gap-junction enhancers may be only effective when alterations in gap-junctions are responsible for conduction slowing, but not when conduction slowing is mainly due to decreased Na^+ channel avail-

ability or structural remodeling (fibrosis). Furthermore, their electrophysiological effects when connexins are re-distributed but their expression and function remains unaltered is uncertain and there are concerns about their safety because theoretically, pharmacological restoration of intercellular coupling may destabilize re-entry and be proarrhythmic.

Na^+/Ca^{2+} Exchanger (NCX) Inhibitors

The NCX is a bidirectional electrogenic transporter (Ca^{2+}:3Na^+) producing a net current in the direction of Na^+ transport [60]. During the upstroke of the action potential the large influx of Na^+ via the I_{Na} increases the $[Na^+]_i$ and the NCX functions in the *reverse mode* (Na^+ out/Ca^{2+} in), generating an outward repolarizing current. During the plateau and early diastole, there is a large influx of Ca^{2+} via the I_{Ca}, the $[Ca^{2+}]_i$ raises and the NCX functions in the *forward mode* (Ca^{2+} out/Na^+ in) which in conjunction with the sarcoplasmic reticulum Ca^{2+} uptake (via SERCA2a) facilitates cardiac relaxation and maintains intracellular Ca^{2+} balance.

The *reverse mode* is favoured by membrane depolarization and increased $[Na^+]_i$ (rapid pacing, sympathetic stimulation, ischemia/reperfusion, digitalis intoxication) promoting Ca^{2+} influx and cellular Ca^{2+} overload leading to contractile failure (abnormally slow relaxation) and triggered arrhythmias. NCX is overexpressed in patients with HF or cardiac hypertrophy, which enhances Ca^{2+} extrusion, compensates the reduced removal of Ca^{2+} from the cytosol due to reduced SERCA2a activity, prolongs the APD and contributes to the spontaneous release of Ca^{2+} from the sarcoplasmic reticulum and to the appearance of DADs. DADs arise from uncontrolled spontaneous Ca^{2+} release from the sarcoplasmic reticulum under conditions of abnormal Ca^{2+} overload and/or dysfunction of sarcoplasmic reticulum Ca^{2+} release (RYR2) channels (ischemia-reperfusion, HF, LV hypertrophy, catecholamine-induced polymorphic VT) [61]. The

increase of $[Ca^{2+}]_i$ activates the forward mode of the NCX and generates a transient inward depolarizing current (I_{TI}) that generates DADs and phase 3 EADs.

Inhibition of reverse NCX might be a novel antiarrhythmic strategy to reduce intracellular Ca^{2+} overload and suppress triggered activity under pathological conditions, while blockade of the forward mode at resting membrane potentials reduces Ca^{2+} extrusion and promotes intracellular Ca^{2+} overload [60, 61]. Therefore, a unique desirable property of NCX inhibitors will be the preferential inhibition of the reverse NCX based in the asymmetric nature of the cotransporter (i.e. different sensitivity for Na^+ and Ca^{2+} at the opposite sides of the membrane), but the lack of structural information about the mammalian cardiac NCX is a major drawback to achieving this goal. Currently available NCX inhibitors present limited selectivity with additional benefit arising from off-target effects as they inhibit other cardiac channels, which may explain the contradictory results in the treatment of ischemic-reperfusion injury and triggered activity. Additionally, no proof-of-concept clinical studies are not available.

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