7 Antiarrhythmic and Anticoagulant Agents

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Anticoagulation Therapy

As outlined in the atrial fibrillation section (Chap. 9), one of the core goals in management is to prevent or reduce the risk of stroke and systemic embolism. The preferred strategy to decrease risk is systemic anticoagulation. The Atrial Arrhythmia chapter will provide the recommendations of when and to whom anticoagulation therapy should be prescribed. However, as with the antiarrhythmic agents, it is important to select the agent that optimizes efficacy and reduces risk of bleeding. Decisions should be made based on patient factors including renal function, liver function, weight, age, ability to adhere to regimen, cost, and other factors. In addition, the patient should have education provided about their anticoagulation at each encounter including benefits and risks (Tables 7.1 and 7.2).

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Table 7.1 Antiarrhythmic agents

Pharmacological targets	Electrophysiological effects	Major clinical applications	Corresponding likely therapeutic mechanisms	Example drug(s)	Pharmacokinetic parameters	Common dose(s) in adults	Cardiovascular adverse events	Non-cardiovascular events
Class 0: Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers								
HCN channel mediated pacemaker current (I_f) block	Inhibition of I_f reducing the sino-atrial node (SAN) phase 4 pacemaker depolarization rate (decreased automaticity)	Potential new off label applications for tachyarrhythmias (e.g. inappropriate sinus tachycardia; not atrial fibrillation [AF])	Reduced in SAN automaticity	*Ivabradine*	*Half-life*: Distribution 2 h; effective ~6 h *Bioavailability*: ~40% *Metabolism*: Extensively intestinal and hepatic via CYP3A4 (CYP3A4 substrate) *Excretion*: Feces and urine (~4% has unchanged drug)	*Oral*: 5 mg twice daily; maintenance: 7.5 mg twice daily	Bradycardia, hypertension, atrial fibrillation	Phosphene (transient enhanced brightness in limited area of visual field, halos, image decompositions, colored bright lights, or multiple images; occurs in first 2 months and most cases resolve with discontinuation).

Class Ia: Voltage-gated Na + channel blockers								
Nav 1.5 open state, intermediate dissociation kinetics; often concomitant K+ channel block	Reduction in peak I_{Na}, action potential (AP) generation, with increased excitation threshold	Supraventricular tachyarrhythmias, particularly recurrent AF; ventricular tachycardia, ventricular fibrillation (including short QT syndrome [SQTS] and Brugada syndrome)	Reduction in ectopic ventricular/atrial automaticity; reduction in accessory pathway conduction; increase in refractory period, decrease reentrant tendency	*Quinidine*	*Half-life*: 4–10 h *Bioavailability*: >80% *Metabolism*: Substrate: CYP2C9 (minor), CYP2E1 (minor), CYP3A4 (major), P-glycoprotein (Pgp; minor) Inhibits: CYP2D6 (strong) CYP3A4 (weak), Pgp *Excretion*: Urine		QRS prolongation with toxic doses, torsades de pointes (not dose related) *Monitoring*: ECG as needed, at least every 6 months	Thrombocytopenia, cinchonism, pruritis, rash
				Disopyramide	*Half-life*: 4–10 h *Bioavailability*: >80% *Metabolism*: Extensively intestinal and hepatic via CYP3A4 (CYP3A4 substrate) *Excretion*: Urine	*Oral*: 100–200 mg every 6 h	Heart failure exacerbations; torsades de pointes *Monitoring*: ECG as needed, at least every 6 months	Anticholinergic (contraindicated in narrow-angle glaucoma); dry mouth; urinary retention; constipation, blurry vision
				Procainamide	*Half-life*: 3–4 h *Bioavailability*: Not applicable given intravenous administration *Metabolism*: Substrate: CYP2D6 (minor) *Excretion*: Urine	*IV*: 10–17 mg/kg (ideal body weight) at a rate of 20–50 mg/min or 100 mg every 5 min; maintenance infusion: 1–6 mg/min	Hypotension, cardiac arrhythmias, heart failure exacerbation *Monitoring*: Telemetry	Limited with intravenous use

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Table 7.1 (continued)

Pharmacological targets	Electrophysiological effects	Major clinical applications	Corresponding likely therapeutic mechanisms	Example drug(s)	Pharmacokinetic parameters	Common dose(s) in adults	Cardiovascular adverse events	Non-cardiovascular events
Class Ib: Voltage-gated Na+ channel blockers								
Nav 1.5 open state; rapid dissociation; I_{Na} window current	Reduction in peak I_{Na}, AP generation with increased excitation threshold	Ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation), particular after a myocardial infarction	Reduction in ectopic ventricular automaticity; reduction in delayed afterdepolarization (DAD) induced triggered activity; reduced reentrant tendency by converting unidirectional block, particularly in ischemic, partially depolarized myocardium	*Lidocaine*	*Half-life*: 120 min *Bioavailability*: Not applicable due intravenous administration *Metabolism*: Substrate: CYP1A2 (major), CYP2A6 (minor), CYP2B6 (minor); CYP2C9 (minor), CYP3A4 (major) *Excretion*: Urine	*Intravenous (IV)*: 1–1.5 mg/kg bolus, repeat at 0.5–0.75 mg/kg every 5–10 min (up to 3 mg/kg); follow with continuous infusion at 1–4 mg/min)	Bradycardia, cardiac arrhythmia *Monitoring*: Telemetry	Dizziness, nervousness, unsteady gait, gastrointestinal distress, nausea, vomiting, tremor
				Mexiletine	*Half-life*: 9–15 h *Bioavailability*: >80% *Metabolism*: Substrate: CYP1A2 (major), CYP2D6 (major) Inhibits: CYP1A2 (moderate) *Excretion*: Urine	*Oral*: 150–200 mg every 8–12 h; adjust dose as needed in 50–100mg increments no more frequently than every 2–3 days up to 300 mg every 8–12 h	Exacerbation of cardiac arrhythmia *Monitoring*: ECG as needed, at least every 6 months	Dizziness, nervousness, unsteady gait, gastrointestinal distress, nausea, vomiting, tremor

Class 1c: Voltage-gated Na+ channel blockers								
Nav 1.5 inactivated state; slow dissociation	Reduction in peak I_{Na} AP generation and with increase excitation threshold	Supraventricular tachyarrhythmias (atrial tachycardia, atrial flutter, atrial fibrillation, and tachycardias involving accessory pathways); ventricular tachyarrhythmias resistant to other treatment in the absence of structural heart disease, premature ventricular contraction, catecholaminergic polymorphic ventricular tachycardia	Reduction in ectopic ventricular/atrial automaticity; reduction in DAD-induced triggered activity; reduced reentrant tendency by converting unidirectional block to bidirectional block; slowed conduction and reduced of excitability particularly at rapid heart rates blocking reentrant pathways showing depressed conduction	*Propafenone*	*Half-life*: 9–15 h *Bioavailability*: >80% *Metabolism*: Substrate: CYP1A2 (minor), CYP2D6 (major), CYP3A4 (major) Inhibits: CYP1A2 (weak), CYP2D6 (weak); P-gp *Excretion*: Urine	*Oral*: Immediate release: 150 mg every 8 h with increase every 3–4 days up to 300 mg every 8 h; 450 mg once for pill in pocket dosing Extended release: 225 mg every 12 h; dose may increase every 5 days up to 425 mg every 12 h	Atrial flutter with 1:1 conduction, ventricular tachycardia, may unmask Brugada-type ST elevation, contraindicated with coronary disease *Monitoring*: ECG as needed, at least every 6 months	Metallic taste, dizziness
				Flecainide	*Half-life*: 10–18 h *Bioavailability*: >80% *Metabolism*: Substrate CYP1A2 (minor) and CYP2D6 (major) *Excretion*: Urine with some fecal	*Oral*: 50–300 mg/day in divided doses 8–12 h (can go up to 400 mg for ventricular arrhythmias management)	Atrial flutter with 1:1 conduction, ventricular tachycardia, may unmask Brugada-type ST elevation, contraindicated with coronary disease *Monitoring*: ECG as needed, at least every 6 months	Dizziness, headache, visual blurring

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Table 7.1 (continued)

Pharmacological targets	Electrophysiological effects	Major clinical applications	Corresponding likely therapeutic mechanisms	Example drug(s)	Pharmacokinetic parameters	Common dose(s) in adults	Cardiovascular adverse events	Non-cardiovascular events
Class 1d: Voltage-gated Na+ channel blockers								
Nav 1.5 late current	Reduction in late Na+ current (I_{Na}) affecting AP recovery, refrac4toriness, repolarization reserve, and QT interval	Ventricular tachycardia, as a potential new class of drugs for the management of tachyarrhythmias	Decrease AP recovery time; reduction in early afterdepolarization (EAD) induced triggered activity	*Ranolazine*	*Half-life*: 7 h *Bioavailability*: >76% *Metabolism*: Substrate: CYP2D6 (minor), CYP3A4 (major), P-gp (minor) Inhibits: CYP2D6 (weak), CYP3A4 (weak), P-gp *Excretion*: Urine	*Oral*: 500 to 1000 mg twice daily, may increase to 1000 ng twice daily as needed	Bradycardia, hypotension, prolonged QT *Monitoring*: ECG as needed, at least every 6 months, renal function	Dizziness, headache, constipation

Class II: Autonomic inhibitors and activators								
Class IIa								
Non-selective β- and selective β1-adrenergic receptor inhibitors	Inhibition of adrenergically induced G_s protein-mediated effects of increased adenylyl kinase activity and cyclic AMP with effects of including slowed SAN pacemaker rate	Sinus tachycardia or other types of tachycardic, including supraventricular (atrial fibrillation, atrial flutter, atrial tachycardia), arrhythmias; rate control of atrial fibrillation and ventricular tachyarrhythmias (ventricular tachycardia, premature ventricular contraction) Note: Atenolol, propranolol, and nadolol used in long QT syndrome; nadolol used in catecholaminergic polymorphic ventricular tachycardia	Reduction in SAN automaticity; reduction in AVN automaticity; reduction in ectopic ventricular/atrial automaticity; reduction in EAD-/DAD-induced triggered activity; reduced SAN reentry; reduction in AVN conduction terminating reentry	*Non-selective β inhibitors*: Carvedilol, propranolol, nadolol. Selective *β1-adrenergic inhibitors*: Atenolol, bisoprolol, betaxolol, esmolol, metoprolol (tartrate and succinate)	*Refer to drug reference/package insert for each agent's pharmacokinetic information* *Note: atenolol is cleared renally and should be avoided in patient with renal disease*	Refer to drug reference/package insert for each agent's dosing information	Bradycardia, hypotension *Monitoring*: Blood pressure and heart rate	Dizziness, fatigue

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Table 7.1 (continued)

Pharmacological targets	Electrophysiological effects	Major clinical applications	Corresponding likely therapeutic mechanisms	Example drug(s)	Pharmacokinetic parameters	Common dose(s) in adults	Cardiovascular adverse events	Non-cardiovascular events
Class IIb								
Non-selective β-adrenergic receptor activators	Activation of adrenergically induced G_s-protein effects of increasing adenylyl kinase activity and cAMP; decrease in RR and PR intervals	Accelerating rates of ventricular escape rhythm in cases of complete atrioventricular block before definitive pacemaker implantation; acquired, often-drug related, bradycardia-dependent torsades de pointes	Increase escape ventricular automaticity; suppression of Brady-cardia dependent EAD-related triggered activity	*Isoproterenol*	*Half-life*: 2.5–5 min *Bioavailability*: Not applicable due to intravenous administration *Metabolism*: None *Excretion*: Urine	*Intravenous*: 2–10 mcg/min IV; titrate to patient response	Cardiac arrhythmias, hypertension *Monitoring*: Heart rate, blood pressure, potassium	Flushing, dizziness, headache, hypokalemia
Class IIc								
Muscarinic M_2 receptor inhibitors	Inhibition of supraventricular (SAN, atrial, AVN) muscarinic M_2 cholinergic receptors; decrease RR and PR intervals	Mild or moderate symptomatic sinus bradycardia; supra-His, AVN, conduction block, elg. In vagal syncope or acute inferior myocardial infarction	Increase in SAN automaticity; increase in AVN conduction	*Atropine*	*Half-life*: 3–4 h *Bioavailability*: Not applicable due to intravenous administration *Metabolism*: None *Excretion*: Urine	*Intravenous, intramuscular*: 0.5–1 mg every 3–5 min; 1 mg preferred for severe bradyarrhythmia; maximum total dose 3 mg	Cardiac arrhythmias *Monitoring*: Heart rate, blood pressure, electrolytes, mental status	Hyperthermia, dizziness, confusion, electrolytes abnormalities

Class IId								
Muscarinic M_2 receptor activators	Activation of supraventricular (SAN, atrial, AVN) muscarinic M_2 cholinergic receptors activates K channels, hyperpolarizing the SAN and shortening APDs in atrial and AVN tissue	Sinus tachycardia or supraventricular tachyarrhythmias	Reduction in SAN automaticity; reduced SAN reentry; reduction in AVN conduction terminating reentry	*Digoxin*	*Half-life*: 38 h *Bioavailability*: 70–85% (formulation dependent) *Metabolism*: Substrate: CYP3A4 (minor), P-gp *Excretion*: Urine	*Oral*: 0.125–0.25 mg daily *Intravenous*: 0.25–0.5 mg over several min, with a repeat dose of 0.35 mg every 6 h to a maximum dose of 1.5 mg over 24 h	Cardiac arrhythmias *Monitoring*: Heart rate, blood pressure, electrolytes, digoxin level, serum creatinine	Digoxin toxicity (nausea, vomiting, visual disturbances [yellow, blurred vision, halos], lethargy, arrhythmias, worse with hypokalemia)
Class IIe								
Adenosine A_1 receptor activators	Activation of adenosine A_1 receptors in supraventricular tissue (SAN, atrial, AVN) activates G protein-coupled inward rectifying K^+ channels and I_{KAdo} current hyperpolarizing the SAN and shortening APDs in atrial and AVN tissue	Acute termination of AVN tachycardia and cAMP mediated triggered VTs; differentiation of sinus versus atrial tachycardia	Reduction in SAN automaticity; reduction in AVN conduction, terminating reentry; reduction in EAD-/DAD-induced triggered activity	*Adenosine*	*Half-life*: <10 s *Bioavailability*: Not applicable *Metabolism*: None	*Intravenous*: Initial 6 mg IV push (rapid, with 20 mL saline flush); if not effective within 1–2 min, 12 mg maybe given; may repeat 12 mg bolus if needed. Maximum single dose 12 mg. Note: Initial dose should be reduced to 3 mg if patient is currently receiving carbamazepine or dipyridamole, has a transplanted heart or if adenosine administered via central line	Cardiac arrhythmia, chest pressure *Monitoring*: ECG, heart rate, blood pressure	Headache, dizziness, facial flushing, gastrointestinal distress, neck discomfort, dyspnea

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Table 7.1 (continued)

Pharmacological targets	Electrophysiological effects	Major clinical applications	Corresponding likely therapeutic mechanisms	Example drug(s)	Pharmacokinetic parameters	Common dose(s) in adults	Cardiovascular adverse events	Non-cardiovascular events
Class III: K^+ channel blockers and openers (note this table will focus on class IIIa; IIB or IIc not highlighted due to lack of currently approved agents at time of publication)								
Class IIIa-voltage dependent K^+ channel blockers								
Nonselective K^+ channel blockers	Block of multiple K^+ channel targets resulting in prolonged atrial, Purkinje, and/or ventricular myocyte AP recovery, increased ERP, and reduced repolarization reserve; prolonged QT intervals	Ventricular tachycardia in patients without structural heart disease or with remote myocardial infarction (*amiodarone only*) tachyarrhyhtmias with Wolff-Parkinson white syndrome; atrial fibrillation with atrioventricular conduction via accessory pathway (*amiodarone only*); ventricular fibrillation and premature ventricular contraction (*amiodarone only*); Tachyarrhyhtmias associated with supraventricular arrhythmias and atrial fibrillation	*Increase in AP recovery time; increase in refractory period with decrease reentrant tendency; note: Amiodarone also slows sinus node rate and atrioventricular conduction (has class II and IV properties)*	*Amiodarone*	*Half-life*: 40–55 days *Bioavailability*: 35–65% *Metabolism*: Substrate: CYP1A2 (minor), CYP2C19 (minor), CYP2C8 (minor), CYP2D6 (minor), CYP3A4 (major), P-gp (minor) Inhibitor: CYP2C9 (weak), CYP2D6 (weak), CYP3A4 (weak), P-gp *Excretion*: Feces	*Supraventricular arrhythmias Intravenous*: 150 mg over 10 min, then 1 mg/min for 6 h, then 0,5 mg/min for 18 h. Continue for a total load up to 10 g; may finish load with oral dosing. *Oral*: 600–800 mg daily in divided doses for a total of 10 g load then maintenance of 200–400 mg once daily *Ventricular arrhythmias*: *Intravenous*: 150 mg over 10 min, then 1 mg/min for 6 h, then 0,5 mg/min for 18 h. Continue for a total load up to 10 g; may finish load with oral dosing. *Oral*: 400 mg every 8–12 h for 1–2 weeks, followed by 200–400 mg once daily	Sinus bradycardia, QTc prolongation, cardiac arrhythmias *Monitoring*: Blood pressure, heart rate, ECG, history and physical exam every 3–6 months, pulmonary function test, chest X-ray every 3–6 months, liver function test baseline and semiannually; electrolytes, thyroid function tests before treatment and periodically thereafter (3–6 months); regular ophthalmic exams	Pulmonary (acute hypersensitivity pneumonitis, chronic interstitial infiltrates); hepatitis; thyroid (hypothyroid or hyperthyroid): Photosensitivity; blue-grey skin discoloration with chronic high doses; nausea; ataxia; tremor; alopecia

				Dronedarone	*Half-life*: 13–19 h *Bioavailability*: Without food: 4%, with high fat meal 15% *Metabolism*: Substrate: CYP3A4 (major) Inhibits: CYP2D6 (weak), CYP3A4 (moderate),P-gp *Excretion*: Feces	*Oral*: 400 mg twice daily with meals	Bradycardia, new onset or worsening heart failure (death increased in patients with symptomatic heart failure), prolonged QTc/ torsades de pointes *Monitoring*: ECG (at least every 3 months), heart rate, blood pressure, signs/ symptoms of heart failure, signs of pulmonary toxicity, liver enzymes	Anorexia, nausea, hepatotoxicity, pulmonary toxicity

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Table 7.1 (continued)

Pharmacological targets	Electrophysiological effects	Major clinical applications	Corresponding likely therapeutic mechanisms	Example drug(s)	Pharmacokinetic parameters	Common dose(s) in adults	Cardiovascular adverse events	Non-cardiovascular events
Kv11.1 (HERG) channel-mediated rapid K^+ 1current (I_K) blockers	Prolonged atrial, Purkinje and ventricular myocyte AP recovery, increase ERP, and reduced repolarization reserve; prolonged QT intervals	Ventricular tachycardia in patients without structural heart disease or with remote myocardial infarction (*sotalol only*) tachyarrhyhtmias with Wolff-Parkinson white syndrome; atrial fibrillation with atrioventricular conduction via accessory pathway (*sotalol only*); ventricular fibrillation and premature ventricular contraction (*sotalol only*); Tachyarrhyhtmias associated with supraventricular arrhythmias1 and atrial fibrillation	*Increase in AP recovery time; increase in refractory period with decrease reentrant tendency*	*Dofetilide*	*Half-life*: ~ 10 h (extended with renal impairment) *Bioavailability*: >90% *Metabolism*: Substrate: CYP3A4 (major) *Excretion*: Renal	*Oral*: Note CrCl and QTc interval must be determined prior to first dose. If QTc > 440 ms (>500 ms in patients with ventricular conduction abnormalities), doffetilide is contraindicated. Adjust dose in those with CrCL <60 mL/min. Patient requires hospitalization for 3 days when starting Initial 500mcg twice daily (reduce dose based on QTc and CrCl; refer to package insert)	Torsades de pointes *Monitoring*: ECG monitoring, baseline and regular serum creatine, electrolytes	Headache, dizziness, nausea

				Ibutilide	*Half-life*: 2–12 h *Bioavailability*: Not applicable *Metabolism*: None *Excretion*: Urine	*Intravenous*: <60 kg: 0.01 mg/kg over 10 min ≥60 kg: 1 mg over 10 min	Torsades de pointes	Nausea
				Sotalol	*Half-life*: 12 h *Bioavailability*: Well absorbed; decreased by ~20% by meals compared to fasting *Metabolism*: None *Excretion*: Renal	Note CrCl and QTc interval must be determined prior to first dose. If CrCl ≤ 60 mL/min, dose adjustment warranted. Please see package insert. *Oral*: 80 mg twice daily *Intravenous*: 75 mg infused over 5 h twice daily	Bradycadia, torsades de pointes *Monitoring*: ECG monitoring, baseline and regular serum creatine, electrolytes, heart rate	Brochospasm

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Table 7.1 (continued)

Pharmacological targets	Electrophysiological effects	Major clinical applications	Corresponding likely therapeutic mechanisms	Example drug(s)	Pharmacokinetic parameters	Common dose(s) in adults	Cardiovascular adverse events	Non-cardiovascular events
Class IV: $Ca2^{+}$ (note this table will focus on class IVa; IVb, IVc,IVd, IVe not highlighted due to lack of currently approved agents at time of publication)								
Class IVa: Surface membrane Ca^{2+} channel blockers								
L-type Ca^{2+} current blockers	Block Ca^{2+} current (I_{Ca}), resulting in inhibition of SAN pacing, inhibition of AVN conduction, prolonged ERP, increased AP recovery time	Supraventricular arrhythmias and ventricular tachycardia without structural heart disease; rate control of atrial fibrillation	Reduction in AVN conduction, terminating reentry; reduction in EAD-/DAD-induced triggered activity	*Diltiazem*	*Half-life*: 3–9 h (depending on immediate or extended release) *Bioavailability*: ~40% *Metabolism*: Substrate: CYP2C9 (minor), CYP2D6 (minor), CYP3A4 (major), P-gp (minor) Inhibits: CYP2D6 (weak), CYP3A4 (moderate) *Excretion*: Urine	*Oral*: Immediate release: 30 mg four times daily; increase as needed to achieve rate control; usual doses 120–480 mg/day in 3–4 doses Extended release: Initial 120 mg once daily or in 2 divided doses; increase as needed; usual dose 120–480 mg/day *Intravenous*: Bolus dose: 0.25 mg/kg (actual body weight) over 2 min. If rate control insufficient after 15 min a repeat bolus dose of 0.35 mg/kg can be given Continuous infusion: Initial 5–10 mg/h; infusion rate maybe increased in 5 mg/h increments every 10–15 min up to maximum of 15 mg/h	Bradycardia, hypotension, peripheral edema *Monitoring*: Blood pressure, heart rate	Headache

				Verapamil	*Half-life*: 2–12 h *Bioavailability*: 20–35% *Metabolism*: Substrate: CYP1A2 (minor), CYP2B6 (minor), CYP2C9 (minor), CYP3A4 (major), P-gp (minor) Inhibitor: CYP1A2 (weak), CYP3A4 (moderate), P-gp *Excretion: Urine*	*Oral*: Immediate release: Initial 40 mg three to four times daily; increase as needed to achieve rate control; maximum dose: 480 mg/day in 3–4 doses Extended release: 120–180 mg once daily; maximum daily dose 480 mg *Intravenous*: Bolus dose: 5–10 mg over 2 min if rate control insufficient after 15–30 min a repeat bolus dose of 0.35 mg/kg can be given Continuous infusion: Initial 5 mg/h; infusion rate maybe increased in 5 mg/h increments every 15–30 min up to maximum of 20 mg/h	Bradycardia, hypotension, peripheral edema *Monitoring*: Blood pressure, heart rate	Headache, constipation

AP-action potential; APD-action potential duration; AVN-atrioventricular node; CrCL- creatinine clearance; DAD-delayed afterdepolarization; EAD- early afterdepolarization; ERP- effective refractory period; P-gp-P-glycoprotein SAN- sino-atrial node
Adapted from the references [1–3]

Table 7.2 Oral anticoagulants used in stroke prevention for AF

Characteristic	Warfarin	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Mechanism of action	Vitamin K antagonist	Direct thrombin inhibitor	Factor Xa inhibition	Factor Xa inhibition	Factor Xa inhibition
Standard dosing	5 mg daily (avoid loading doses), adjust to achieve INR 2–3	150 mg twice daily	5 mg twice daily	60 mg daily	20 mg daily with evening meal
Renal impairment dosing	Consider starting doses of ≤2.5 mg daily if: • Age ≥65 • Weight ≤70 kg Poor nutritional status • Significant hepatic disease • Increase bleeding risk • Known warfarin sensitivity • Decompensated HF	75 mg twice daily (CrCL 15–30 mL/min)	2.5 mg twice daily If at least two of three criteria: • Age ≥80 • Weight ≤60 kg SCr ≥1.5 mg/dL	30 mg daily (CrCl 15–50 mL/min)	15 mg daily (CrCl 15–50 mL/min)
Hepatic impairment dosing	Consider starting doses of ≤ 2.5 mg daily if: • Age ≥65 • Weight ≤70 kg Poor nutritional status • Significant hepatic disease • Increase bleeding risk • Known warfarin sensitivity • Decompensated HF	No adjustment	Child-Pugh class B: Avoid or use with caution Child-Pugh class C: Avoid use	Child-Pugh class B: Avoid or use with caution Child-Pugh class C: Avoid use	Child-Pugh class B: Avoid or use with caution Child-Pugh class C: Avoid use
Time to peak	5–7 days	1–3 h	1–2 h	1–2 h	2–4 h
Half-life (h)	~40 h	8–15 h	12 h	10–14 h	7–11 h
Excretion	Hepatic, primarily through CYP2C9	80% renal	25% renal, 75% fecal	50% renal; also, bile, feces	66% renal (one-half as inactive form)
Metabolized	CYP2C9, CYP1A2, CYP3A4, CYP2C19	P-gp	P-gp and CYP3A4	P-gp	P-gp and CYP3A4
P-gp and/or strong CYP3A4 inducers	Consider higher starting dose, monitor INR closely	Avoid use	Avoid use	Avoid use	Avoid use
P-gp inhibitors	Not applicable	If CrCl <50 mL/min, avoid use or reduce dose	Not applicable	30 mg daily	Not applicable

Dual P-gp and strong CYP inhibitors	Consider lower starting dose, monitor INR closely	Not applicable	Avoid use • No dose change needed with concomitant clarithromycin	Not applicable	• Avoid use • No dose change needed with concomitant clarithromycin
Dual P-gp and moderate CYP3A4 inhibitors	Monitor INR closely	Not applicable	Use with caution	Not applicable	If CrCl <80 mL/min, avoid use unless benefit justifies potential risk
Reversal strategy	Vitamin K, prothrombin complex concentrate, or fresh frozen plasma	Idarucizumab	Andexanet alfa and prothrombin complex concentrate	Andexanet alfa and prothrombin complex concentrate	Andexanet alfa and prothrombin complex concentrate

Package inserts from https://www.nlm.nih.gov

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