

APPENDIX 3

Clinically Significant Antiarrhythmic Drug Interactions

Class IV	Dofetilide	Dofetilide	Hydrochlorothiazide	Inhibition of renal cationic transport, decreasing dofetilide clearance, and significantly increasing risk of TdP ²	These drugs are contraindicated in patients taking dofetilide; substitute with alternatives
			Trimethoprim		
			Ketoconazole		
			Verapamil		
			Cimetidine		
	Amiodarone	Some statins (lovastatin, simvastatin)	Amiodarone	Inhibits CYP3A4 ⁵⁴	Simvastatin dose should not exceed 20 mg/d; Lovastatin dose should not exceed 40 mg/d. Consider reducing other doses of statins that are substrates for CYP 3A4
			Cyclosporine	Increases blood concentrations of cyclosporine by inhibiting CYP3A4 ^{55, 56}	Decrease dose of cyclosporine by 50% or monitor blood cyclosporine concentrations closely
		Warfarin	Amiodarone	Increases plasma warfarin concentrations by inhibition of CYP2C9 ⁵⁷	Reduce dose of warfarin by amount of amiodarone initiated ⁵⁸ ; 40% if 400 mg/d; 35% if 300 mg/d; 30% if 200 mg/d; 25% if 100 mg/d and monitor INR closely
		Digoxin	Amiodarone	Inhibition of P-gp may double serum digoxin concentrations ⁵⁹	Reduce dose of digoxin by 50% ⁶⁰
		Amiodarone	Grapefruit juice	Inhibition of CYP3A4 may increase plasma amiodarone concentrations by 84% ⁶¹	Avoid grapefruit juice
		Amiodarone	Sofosbuvir	Severe bradycardia; etiology is unknown ¹²	Avoid amiodarone in patients taking sofosbuvir-based treatments ¹²
	Dronedarone	Simvastatin	Dronedarone	Inhibition of CYP3A4 increases plasma concentrations of simvastatin ⁶⁴	Limit simvastatin dose to no more than 10 mg/d
		Digoxin	Dronedarone	Inhibition of P-gp leading to increased serum digoxin concentrations ⁶²	Decrease dose of digoxin and monitor serum concentrations closely after initiation of dronedarone ⁶³
		Dabigatran	Dronedarone	Inhibition of P-gp may increase plasma dabigatran concentrations ⁶⁴	Administer dronedarone 2 h after dabigatran or consider alternative
		Dronedarone	St. John's Wort	Induces CYP 3A4, reducing plasma dronedarone concentrations ⁶³	Avoid St. John's Wort
		Dronedarone	Grapefruit juice	Inhibits CYP3A4 and may triple plasma dronedarone concentrations ⁶³	Avoid grapefruit juice
	Verapamil	Verapamil	Rifampin	Induces CYP3A4, decreasing plasma verapamil concentrations ^{65, 66}	Adjust dose of verapamil clinically while on CYP3A4 inducers
			Carbamazepine		
			Phenobarbital		
		Verapamil	St. John's Wort	Induces CYP3A4, decreasing plasma verapamil concentrations ⁶⁷	Avoid St. John's Wort
	Diltiazem	Simvastatin	Diltiazem	Inhibition of CYP3A4 ⁶⁴	Limit dose of simvastatin to no more than 10 mg daily and dose of lovastatin to no more than 20 mg daily ⁶⁴
	Verapamil	Lovastatin	Verapamil		
	Diltiazem	Cyclosporine	Diltiazem	Inhibition of CYP3A4 ⁶⁸	Consider cyclosporine dose reduction and closely monitor blood cyclosporine concentrations after diltiazem initiation
Misc.	Digoxin	Digoxin	Antacids	Decrease absorption of digoxin ⁷²	Digoxin should be given 1 h before or 2 h after these medications.
			Kaolin-pectin		
			Bile acid sequestrants		
			Aluminum and magnesium hydroxide		
		Digoxin	Sulfur compounds	Reduce absorption by disruption of gut wall function ⁶⁹	Closely follow serum digoxin concentrations after initiating these agents
			Neomycin		
		Digoxin	Macrolide antibiotics	Increase oral absorption by alteration of gastrointestinal flora ⁷⁰	Closely follow serum digoxin concentrations after initiating these agents
		Digoxin	Atorvastatin	Inhibition of digoxin secretion from intestinal wall may increase serum digoxin concentrations by 15-20% ⁷¹	Decrease dose of digoxin and closely follow serum digoxin concentrations after initiation of atorvastatin

	Digoxin	Verapamil	Inhibition of P-gp can increase plasma digoxin concentration by 90% ⁷²	Use another agent or monitor digoxin levels closely
Ibutilide	Ibutilide	Class IA antiarrhythmic agents	Additive QT prolongation may precipitate ventricular arrhythmias ¹	These agents should not be given concomitantly or within 4 h of ibutilide administration ¹
		Class III antiarrhythmic agents		
Ranolazine	Ranolazine	Strong CYP3A4 inhibitors	Potent CYP3A4 inhibition may lead to accumulation of ranolazine	Contraindicated ⁷³
		Ketoconazole		
		Itraconazole		
		Clarithromycin		
		Nelfinavir		
	Ranolazine	Other CYP3A4 inhibitors	CYP3A4 inhibition may lead to accumulation of ranolazine ⁷⁴	Ranolazine dose should not exceed 500 mg twice daily ⁷³
		Amiodarone		
		Dronedarone		
		Diltiazem		
		Verapamil		
	Digoxin	Ranolazine	Ranolazine may increase serum digoxin concentrations through P-gp inhibition	Closely monitor serum digoxin concentrations when ranolazine is initiated ⁷⁴
Ivabradine	Ivabradine	Ketoconazole	Potent CYP3A4 inhibition may lead to accumulation of ivabradine	Contraindicated ⁷⁵
	Ivabradine	Other CYP3A4 inhibitors	CYP3A4 inhibition may lead to accumulation of ivabradine	Concomitant use is not recommended ⁷
		Amiodarone		
		Diltiazem		
		Verapamil		
		Grapefruit juice		
		Macrolide antibiotics		
		Azole antifungals		
	Ivabradine	CYP3A4 enzyme inducers	Inducers of CYP3A4 may decrease plasma ivabradine concentrations	Concomitant use is not recommended ⁷
		Rifampin		
		St. John's Wort		

AUC indicates area under the curve; CYP, cytochrome P450; INR, international normalized ratio; P-gp, p-glycoprotein; SSRI, selective serotonin reuptake inhibitors; and TdP, torsade de pointes.

*Any medication that prolongs the QT interval will interact with class III antiarrhythmic drugs.

Mar PL, et al; from the American Heart Association Electrocardiography and Arrhythmias Committee of the Council of Clinical Cardiology. Drug Interactions Affecting Antiarrhythmic Drug Use. Circ Arrhythm Electrophysiol. 2022 May;15(5):e007955.