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STATE-OF-THE-ART PAPER

The P-Glycoprotein Transport System and Cardiovascular Drugs

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Permeability glycoprotein (P-gp) mediates the export of drugs from cells located in the small intestine, blood-brain barrier, hepatocytes, and kidney proximal tubule, serving a protective function for the body against foreign substances. Intestinal absorption, biliary excretion, and urinary excretion of P-gp substrates can therefore be altered by either the inhibition or induction of P-gp. A wide spectrum of drugs, such as anticancer agents and steroids, are known P-gp substrates and/or inhibitors, and many cardiovascular drugs have recently been observed to have clinically relevant interactions as well. We review the interactions among commonly prescribed cardiovascular drugs that are P-gp substrates and observe interactions involving P-gp that may be relevant to clinical practice. Cardiovascular drugs with narrow therapeutic indexes (e.g., antiarrhythmic agents, anticoagulant agents) have demonstrated large increases in concentrations when coadministered with potent P-gp inhibitors, thus increasing the risk for drug toxicity. Therefore, dose adjustment or use of alternative agents should be considered when strong P-gp-mediated drug-drug interactions are present. Finally, interactions between novel drugs and known P-gp inhibitors are now being systematically evaluated during drug development, and recommended guidelines for the administration of P-gp substrate drugs will be expanded. (J Am Coll Cardiol 2013;61:2495–502) © 2013 by the American College of Cardiology Foundation

The availability of a drug at the site of action for pharmacological effect is characterized by the processes of absorption, distribution, metabolism, and elimination. Transporters are membrane proteins that govern the transport of drugs into and out of cells, affecting both intracellular and systemic drug concentration and reducing the cell exposure to potential toxins.

The 2 superfamilies of transporters are the adenosine triphosphate (ATP)–binding cassette and solute carrier transporters. Solute carrier transporters comprise facilitated and ion-coupled transporters, whereas ATP-binding cassette transporters rely on ATP to actively pump substrates across cell membranes. The best characterized transporter is permeability glycoprotein (P-gp; also known as ATP-binding cassette, subfamily B, member 1 or multidrug resistance-1 [MDR1]). Although many other transporters have been identified (1), P-gp appears to be the most relevant to cardiovascular medicine.

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P-gp transport system. The x-ray crystallographic structure for P-gp is depicted in Figure 1, showing ATP binding to produce conformation changes resulting in the extrusion of a substrate to the extracellular space (2). The P-gp transporter is found in the luminal membrane of the small intestine and blood-brain barrier and in the apical membranes of excretory cells such as hepatocytes and kidney proximal tubule epithelia (Fig. 2) (1). Expression on intestinal epithelial cells is responsible for efflux that limits cellular uptake and absorption into enterocytes, whereas expression on the canalicular surface of hepatocytes and renal tubular cells enhances the elimination of drugs into the bile and urine (Fig. 2) (3).

P-gp expression in the blood-brain barrier plays an important role in limiting the entry of various drugs into the central nervous system (Fig. 3) (4). Studies of wild-type and P-gp-knockout mice have demonstrated a high efflux ratio of central nervous system drug penetration due to P-gp, supporting its role in limiting the intracranial drug concentrations of its substrates (5). Inhibition of the P-gp transporter may lead to increased drug delivery to the brain (4). P-gp expression has been observed in myocardium, although generally at relatively low levels (6), and studies in knockout mice models have demonstrated no significant effect of P-gp in heart tissue (7).

Molecules that are P-gp substrates and modulators do not share any obvious structural characteristics, although many are cationic and hydrophobic (Table 1) (1,8). Drugs can act

Abbreviations and Acronyms

ATP = adenosine triphosphate
CrCl = creatinine clearance
CYP = cytochrome P450
FDA = U.S. Food and Drug Administration
MDR1 = multidrug resistance-1
P-gp = permeability glycoprotein

as inhibitors (impairing P-gp-mediated uptake or efflux), inducers (enhancing P-gp activity), or simply substrates (translocating across membranes via P-gp), but 1 drug also can have overlapping roles. The mechanism of P-gp inhibition is thought to involve modulation of the membrane transporter by 1 of 4 pathways: direct inhibition of binding sites that block the transport of substrates, ATP binding inhibition, ATP hydrolysis, or coupling of ATP hydrolysis to the translocation of the substrate. P-gp inhibition most commonly involves competition for transport with another drug with lesser P-gp affinity, and in vitro measurement of efflux ratios across cells in cell lines with high P-gp expression (e.g., Caco-2, a cell line of human epithelial colorectal adenocarcinoma cells) can be used to characterize the affinity of a molecule for P-gp and its potential for inhibition.

Although interactions of P-gp with anticancer agents have been known for decades, many drug-drug interactions involving P-gp have been recently identified (9). Because drugs metabolized by cytochrome P450 (CYP) enzymes tend to also be substrates for P-gp, it has been hypothesized that enzyme and transporter pairs act as a coordinated absorption barrier against foreign substances (1). As more drugs are systematically evaluated with in vitro systems and P-gp-knockout mice models, drug-drug interactions previously ascribed solely to CYP3A have now been identified as also involving P-gp. While substrate specificity for CYP3A and P-gp tend to overlap, some drugs are not metabolized by CYP3A, but are affected by P-gp and vice versa. The route of drug administration may also be relevant; different routes of administration (intravenous vs. oral) lead to different interactions because the amount of drug that reaches intestinal, renal, and hepatic P-gp receptors differs. Oral administration

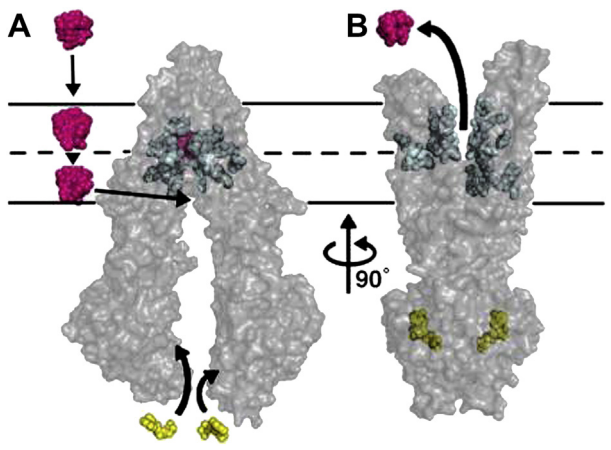

Figure 1 Structure of Permeability Glycoprotein

Model of substrate transport by permeability glycoprotein (P-gp). **(A)** Substrate (magenta) partitions into the bilayer from outside the cell to the inner leaflet and enters the internal drug-binding pocket through an open portal. The residues in the drug-binding pocket (cyan spheres) interact with inhibitors and substrates in the inward-facing conformation. **(B)** Adenosine triphosphate (ATP) (yellow) binds to the nucleotide-binding domains, causing a large conformational change presenting the substrate and drug-binding site(s) to the outer leaflet/extracellular space. Adapted, with permission, from Aller et al. (2).

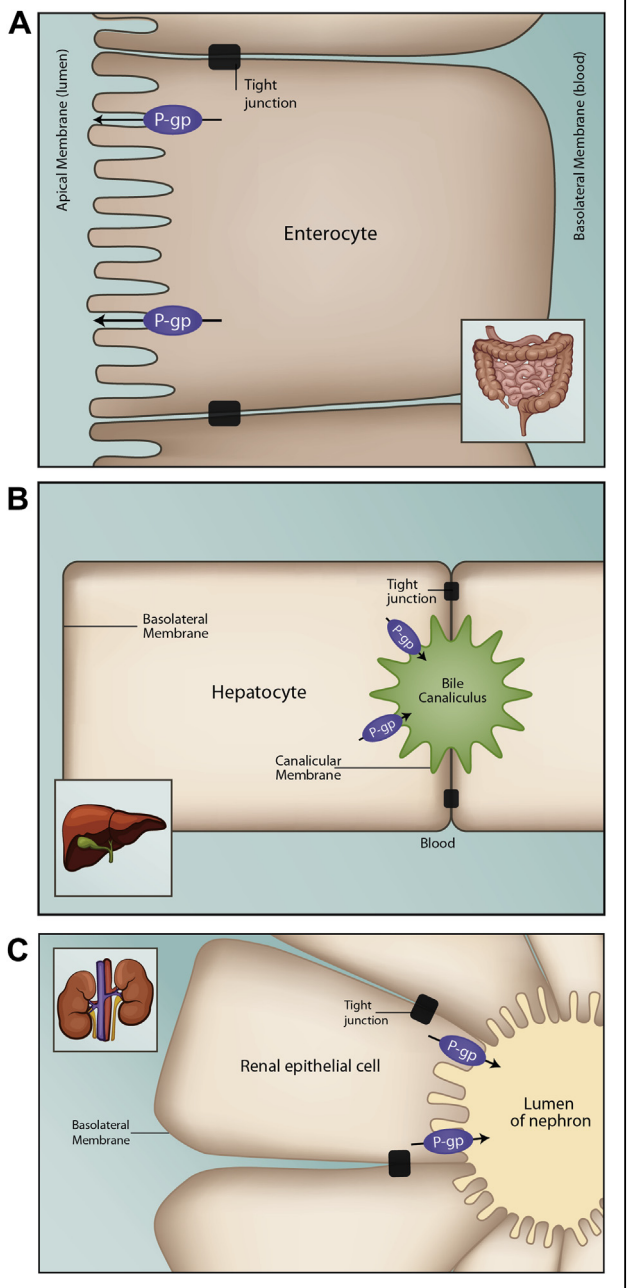

Figure 2 Mechanisms of P-gp-Directed Efflux

Permeability glycoprotein (P-gp) is found on the apical/luminal membrane of intestinal epithelial cells **(A)**, the canalicular membrane of human hepatocytes **(B)**, and the apical/luminal membrane of renal proximal tubule cells **(C)**.

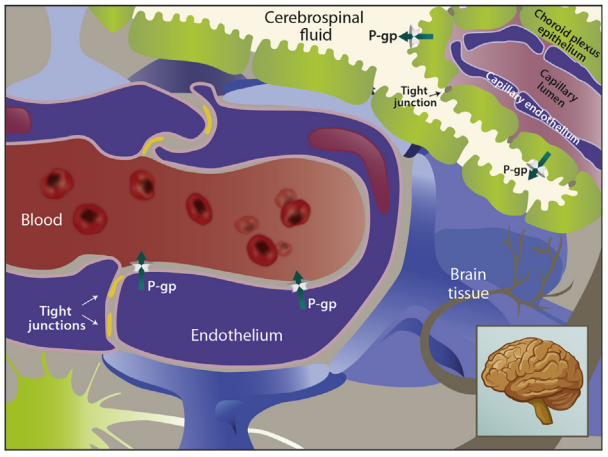

Figure 3 The Localization of P-gp at the Blood Brain Barrier

The blood-brain barrier (BBB) is formed by endothelial cells and sealed together by tight junctions; the blood–cerebrospinal fluid (CSF) barrier (BCSFB) is formed by epithelial cells of the choroid plexus. Tight junctions reduce drug transfer between blood and CSF, limiting the accessibility of the brain to polar drugs, unless they are transferred by transport systems. Permeability glycoprotein (P-gp) is an efflux transporter at the luminal membranes of the BBB and the BCSFB that removes drugs from brain interstitial fluid back to blood or into the CSF, thus preventing the drug from producing central nervous system effects. The clinical consequences of increased exposure in the brain may therefore be beneficial or harmful, depending on the drug. Adapted, with permission, from Eyal et al. (4).

generally represents the greatest potential for P-gp-mediated effects on absorption and elimination.

In addition, genetic polymorphisms of the MDR1 gene that codes for P-gp and its effects on the pharmacokinetics of various drugs have recently been elucidated. The first reported polymorphism of MDR1 influencing pharmacotherapy was the single-nucleotide polymorphism C3435T in exon 26, which affects duodenal P-gp transport of oral digoxin (10). Subsequently, at least 28 single-nucleotide polymorphisms have been identified on the MDR1 gene that affect the pharmacokinetics of a wide variety of drugs.

No recent comprehensive review of the P-gp transporter system and its substrates and inhibitors relevant to cardiovascular medicine has been published. In this report, we review the interactions among commonly prescribed cardiovascular drugs that are P-gp substrates and observe the potential drug-drug interactions involving P-gp that could be clinically relevant.

Role of Permeability Glycoprotein in Cardiovascular Therapy

The role of P-gp in cardiovascular therapy is of increasing interest because of the wide use of cardiovascular drugs that interact with the P-gp transporter combined with the narrow therapeutic indexes of many commonly prescribed antiarrhythmic and anticoagulant agents (9). Interestingly, the structure and function of P-gp resemble those of an ion channel, and many P-gp inhibitors (e.g., verapamil, quinidine) are ion channel blockers (9).

Table 1 P-gp Substrates, Inhibitors, and Inducers, Organized by Drug Class

Anticancer Agents	Cardiac Agents	Antimicrobial Agents	Rheumatologic/ Immunosuppressant Agents
Actinomycin D*	See Table 2	Azithromycin†	Cyclosporine*†‡
Colchicine*		Clarithromycin†	Dexamethasone‡
Daunorubicin*		Erythromycin*†	Everolimus*
Doxorubicin*‡		Itraconazole†	Methotrexate*
Etoposide*		Ivermectin*†	Quinine*
Imatinib*		Ketoconazole†	Tacrolimus*†
Irinotecan*		Mefloquine†	
Lapatinib*		Ofloxacin†	
Mitomycin C*		Posaconazole*	
Nilotinib*		Quinolones*	
Paclitaxel*		Rifampin*†‡	
Tariquidar†			
Taxol*			
Topotecan*			
Valspodar†			
Vinblastine*			
Vincristine*			

Gastrointestinal Agents	HIV Protease Inhibitors	Neurologic Agents	Miscellaneous
Cimetidine*†	Indinavir†	Amitriptyline†	Berberine*
Domperidone*	Lopinavir†	Carbamazepine‡	Conivaptan†
Loperamide*	Maraviroc*	Chlorpromazine†	Elacridar†
Omeprazole†	Nelfinavir†	Desipramine†	Fexofenadine*
Ondansetron*	Ritonavir†	Disulfiram†	Grapefruit juice†
	Saquinavir†	Doxepin†	Isoflavones†
	Tipranavir‡	Fluphenazine†	Orange juice†
		Haloperidol†	Progesterone†
		Imipramine†	Quercetin†
		Lidocaine*	Saxagliptin*
		Phenytoin‡	St. John's wort‡
		Sertraline†	Terfenadine*
		Varenicline†	Testosterone†
		Venlafaxine‡	Tolvaptan*
			Troglitazone†

If a drug is a substrate of P-gp and is coadministered with St. John's wort, St. John's wort will be listed in the labeling along with other known inducers as possibly decreasing plasma levels of the drug (51). *Substrate. †Inhibitor (showed >25% increases in areas under the curve for digoxin, fexofenadine, and talinolol). ‡Inducer (showed >20% decrease in area under the curve for digoxin or fexofenadine). Adapted, with permission, from Shapiro and Shear (8).

HIV = human immunodeficiency virus; P-gp = permeability glycoprotein.

Substrates, Inducers, and Inhibitors of Cardiovascular Drugs

Antiarrhythmic drugs. The interaction of digoxin, a substrate of both intestinal and renal P-gp, with drugs that inhibit P-gp can lead to toxic accumulations of this cardiac glycoside, whereas P-gp inducers lower plasma digoxin concentration (11) (Table 2). Digoxin is not metabolized by CYP3A but does have a weak affinity for P-gp, thus making it a useful "probe" substrate drug to investigate potential P-gp inhibitors (12). In the first characterized drug-drug interaction involving the P-gp transport system, induction of intestinal

P-gp by rifampin was shown to decrease the bioavailability of orally administered digoxin, thereby reducing plasma digoxin levels (13). Given the narrow therapeutic window of digoxin (i.e., a 25% increase may result in toxicity), coadministration of P-gp inhibitors is of even greater clinical concern.

The most extensively researched cardiovascular drug-drug interaction involving the P-gp system is that between digoxin and quinidine. Since the interaction was initially recognized in 1978, research 2 decades later in both mouse models and P-gp-expressing cell lines established that quinidine increased plasma digoxin concentration by reducing P-gp-mediated efflux of digoxin into the gut and kidneys, resulting in greater absorption and decreased elimination of digoxin (14).

Amiodarone, a potent inhibitor of P-gp, increased mean serum digoxin levels from 0.97 to 1.98 μg/l when administered orally at doses of 600 to 1,600 mg/day (15). Oral amiodarone inhibits intestinal P-gp membrane efflux of digoxin and its secretion from renal tubules (15). Because there is no significant change in digoxin pharmacokinetics after the administration of intravenous digoxin, the most relevant mechanism of interaction between these 2 drugs appears to be inhibition of intestinal and renal P-gp-mediated efflux of digoxin (16). Thus, when amiodarone is given to a patient taking oral digoxin, the dose of digoxin should be reduced by half and plasma levels closely monitored (17).

Dronedarone displays even greater P-gp inhibition than amiodarone, inhibiting digoxin clearance mediated by P-gp and increasing steady-state levels up to 2.5-fold (18). In the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy study, it was speculated that digoxin toxicity induced by dronedarone might have played a role in the increased cardiovascular mortality in the study group (19). Similar to amiodarone, it is important to reduce the dose of oral digoxin when dronedarone is coadministered and to measure plasma digoxin concentration (18).

Propafenone also increases steady-state serum digoxin concentrations, although the mechanism involves primarily decreasing digoxin clearance by the kidneys, rather than affecting absorption (20). Sotalol neither inhibits nor acts as a substrate of P-gp (21).

Oral anticoagulants. WARFARIN. Preliminary evidence suggests that warfarin may inhibit P-gp activity in hepatocytes, thus acting as a P-gp substrate and inhibitor in the liver (22). However, because warfarin is well absorbed from the intestine with >90% bioavailability, it is unlikely that intestinal P-gp significantly affects the absorption of warfarin (23).

DABIGATRAN. Dabigatran, an oral direct thrombin inhibitor, acts as a substrate of P-gp. The concomitant administration with strong P-gp inducers (e.g., rifampin) should be avoided because the exposure to dabigatran is reduced (maximal concentration and area under the curve reduced by 66% and 67%, respectively), thus placing patients at risk for thrombosis (24,25).

Table 2 Cardiovascular Substrates (×), Inhibitors (+), and Strong Inhibitors (++) of Permeability Glycoprotein

Drug	Substrate	Inhibitor
Antiarrhythmic agents		
Amiodarone		++
Bepridil	×	
Dronedarone		++
Digoxin	×	
Felodipine		+
Propafenone		+
Quinidine	×	++
Verapamil	×	++
Anticoagulant agents		
Apixaban	×	
Dabigatran	×	
Rivaroxaban	×	
Edoxaban	×	
Warfarin	×	+
Antihypertensive agents		
Aliskiren	×	
Captopril		+
Carvedilol		++
Celiprolol	×	
Diltiazem	×	+
Felodipine		+
Isradipine		+
Labetalol	×	
Losartan	×	+
Mibefradil		+
Nadolol	×	
Nicardipine		++
Nifedipine		+
Propranolol	×	+
Reserpine		+
Talinolol	×	+
Telmisartan		+
Timolol	×	
Antiplatelet agents		
Aspirin*		
Clopidogrel	×	
Dipyridamole		+
Prasugrel†		
Ticagrelor	×	+
Statins		
Atorvastatin	×	++
Lovastatin	×	
Other		
Avasimibe*		
Ranolazine		+
Ambrisentan	×	

Relative potency was determined from review of studies of both in vitro and clinical pharmacokinetics. *Preliminary studies suggest that aspirin and avasimibe may induce permeability glycoprotein expression, leading to reduced absorption of clopidogrel and digoxin, respectively (44,52). †No known interaction

P-gp inhibition and impaired renal function are 2 major independent factors that can increase dabigatran concentrations, with greater effects if both are present. Exposure to dabigatran increased with coadministration of the strong P-gp inhibitors ketoconazole (by up to 153%), dronedarone (by

73% to 99%), amiodarone (by 50% to 58%), quinidine (by 53% to 56%), verapamil, and clarithromycin in phase I studies (25,26). A reduced dose of dabigatran (75 mg twice daily) is recommended when combined with dronedarone or ketoconazole in patients with moderate renal impairment (estimated creatinine clearance [CrCl] 30 to 50 ml/min). Dabigatran should not be used in patients with severe renal impairment (CrCl 15 to 30 ml/min) if a P-gp inhibitor is being administered or in patients with end-stage renal failure (CrCl <15 ml/min), regardless of cotherapies (24,25). Staggering the administration of P-gp inhibitors by 2 to 4 h after the administration of dabigatran could reduce the potential effect of increased exposure.

In a case report of an elderly patient taking concomitant dabigatran (75 mg twice daily) and amiodarone (200 mg/day), a major bleeding event led to hemorrhagic shock and subsequent death. The investigators reported a very high (25-fold) blood level of dabigatran (trough plasma concentration of dabigatran 5,600 ng/ml; expected range: 31 to 225 ng/ml) that might have been due in part to the inhibition of P-gp by amiodarone, in addition to other factors such as decreased renal function (27).

In contrast, drug interaction studies with the P-gp substrates atorvastatin, digoxin, and clarithromycin did not result in any pharmacokinetic changes of either dabigatran or the coadministered drugs (24,25,28). Given the relatively narrow therapeutic index of oral anticoagulant drugs, unless dedicated pharmacokinetic studies demonstrate otherwise, dabigatran (and other novel oral anticoagulant drugs) should be used with caution in the presence of strong P-gp inhibitors and inducers (26).

RIVAROXABAN. Rivaroxaban, an oral, direct factor Xa inhibitor, acts as a substrate of P-gp. In an investigation of bidirectional efflux of the drug across Caco-2, wild-type, and P-gp-overexpressing cells, rivaroxaban was shown to be a substrate for, but not an inhibitor of, P-gp (29). These findings were confirmed using several known strong P-gp inhibitors, including ketoconazole and ritonavir, which inhibited P-gp-mediated efflux of rivaroxaban and reduced drug efflux to 45% and 76% of control values, respectively (29). As with dabigatran, the concomitant administration of rivaroxaban with strong P-gp inducers (e.g., rifampin) should be avoided because the exposure to rivaroxaban is reduced, thus placing patients at risk for thrombosis. Caution should additionally be exercised with the use of rivaroxaban in patients with renal impairment (CrCl <50 ml/min) and with drugs that are strong CYP3A4 inhibitors (30).

APIXABAN. Another oral factor Xa inhibitor, apixaban, has completed phase III studies in atrial fibrillation, venous thromboembolism, and acute coronary syndromes, and has recently been approved for use in stroke prevention in atrial fibrillation by the U.S. Food and Drug Administration (FDA) (31). Prescribing information for apixaban became available in December 2012. Apixaban is a substrate for P-gp. Concomitant administration of strong P-gp inhibitors (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) increases exposure to apixaban, thus increasing the risk for bleeding. The FDA recommends decreasing the dose of apixaban to 2.5 mg twice daily when administered with strong P-gp inhibitors and recommends avoiding coadministration of apixaban and strong P-gp inhibitors in patients already on the reduced dose of apixaban (32). Conversely, the concomitant administration of strong P-gp inducers (e.g., rifampin, St. John's wort) decreases the exposure to apixaban, thus increasing the risk for stroke. The FDA recommends avoiding the coadministration of apixaban and strong P-gp inducers (32).

EDOXABAN. Pharmacokinetic and pharmacodynamic studies were conducted with the orally administered direct factor Xa inhibitor edoxaban and several cardiovascular drugs known to be P-gp substrates and/or inhibitors (33). Edoxaban exposure, prothrombin time, and activated partial thromboplastin time were increased significantly after coadministration of quinidine, verapamil, and dronedarone (33). Atorvastatin had no effect, whereas amiodarone had an intermediate effect (33). No clinically significant pharmacokinetic or pharmacodynamic changes were observed with concomitant administration of edoxaban and digoxin (33).

In light of these data, the ENGAGE AF–TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction 48) trial mandated a dose reduction of edoxaban by 50% for patients receiving concomitant cardiovascular medications that are strong P-gp inhibitors (34). Additionally, noncardiac medications that are strong P-gp inhibitors were prohibited (34).

Atrioventricular nodal blocking agents. CALCIUM-CHANNEL BLOCKERS. In studies using Caco-2 cells, verapamil inhibited P-gp-mediated digoxin transport, contributing to increased digoxin concentration (35). The interaction is thought to occur at the apical membranes in renal tubular cells by blocking P-gp, which extrudes digoxin out of the cells; verapamil thus substantially decreases the renal clearance of digoxin (36). Clinical studies have demonstrated that verapamil administered as 240 mg/day increased digoxin concentrations by 60% to 80% (36). Verapamil and diltiazem both are substrates for P-gp (37). Because verapamil, as a P-gp inhibitor, coadministered with digoxin results in significantly increased digoxin concentrations, the prescribing information recommends reducing the dose of digoxin when starting verapamil.

In a study of the effects of several calcium-channel blockers on the transport of digoxin by P-gp, the inhibitory effects, in order, were nicardipine > verapamil > diltiazem > nifedipine (38). These data suggest that calcium-channel blockers, as a class, should be used cautiously when coadministered with P-gp substrates.

BETA-BLOCKERS. Although the interaction between P-gp and beta-blockade is limited to in vitro data, its influence on digoxin suggests that the clinical relevance may prove significant. Carvedilol inhibits P-gp activity to a similar

degree as verapamil, increasing serum digoxin levels up to 32% (39). Significant P-gp inhibition was similarly observed for bisoprolol and propranolol, whereas atenolol (39), metoprolol (21), and sotalol (21) had no effect.

STATINS. Several statins, particularly atorvastatin and lovastatin, have been shown to interact with P-gp as both substrates and inhibitors at the molecular level (40). Atorvastatin inhibits P-gp-mediated digoxin secretion by 58% (similar to the inhibition observed with verapamil); thus, the FDA recommends monitoring digoxin levels in patients taking both medications (41).

Antiplatelet agents. CLOPIDOGREL. Clopidogrel is a substrate for P-gp. Inhibition of P-gp activity by different modulators increased the absorptive clopidogrel flux by a maximum of 5- to 9-fold ($p < 0.001$) over baseline, increasing intracellular accumulation from 0.99 ± 0.11 pmol/mg protein by up to 2.5-fold ($p < 0.001$) (42). Subjects with genetic variants in ATP-binding cassette, subfamily B, member 1 (e.g., MDR1) that may lead to increased expression of P-gp have reduced absorption of clopidogrel and a corresponding decrease in exposure to active drug metabolite of clopidogrel produced by CYP2C9 and carboxyesterase (42). The relative importance of this mechanism involving MDR1 polymorphisms compared with other well-described genetic variants (e.g., CYP2C19 alleles) continues to be evaluated (43).

ASPIRIN. The role of aspirin in the P-gp–mediated transport of drugs, especially clopidogrel, remains controversial. Caco-2 cell models suggest that aspirin may reduce intestinal absorption of clopidogrel via P-gp induction (44). However, in the CURRENT–OASIS 7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes) trial comparing double-dose versus standard-dose clopidogrel and high-dose (300 to 325 mg) versus low-dose (75 to 100 mg) daily aspirin in 25,086 patients with acute coronary syndromes, there was no significant difference in the rate of cardiovascular death, reinfarction, or recurrent ischemia through 30 days with clopidogrel (at either dose) related to the aspirin dose (45). These findings from CURRENT–OASIS 7 do not preclude an important pharmacokinetic interaction, because the study duration was only 30 days (45).

DIPYRIDAMOLE. In vitro studies have shown that dipyridamole inhibits P-gp (46). Dipyridamole increased digoxin plasma concentration after a single dose of digoxin by 20% after 4 h of administration in a randomized, crossover, placebo-controlled study (47). This modest increase in digoxin level is not likely to result in a clinically significant effect in most patients.

TICLOPIDINE. Results regarding the thienopyridine antiplatelet agent ticlopidine and P-gp–mediated transport have been inconclusive. Studies suggest that ticlopidine may enhance the oral bioavailability of carvedilol, either by inhibiting CYP or P-gp-mediated efflux (48).

PRASUGREL. The third-generation thienopyridine prasugrel is not known to act as a substrate or inhibitor of P-gp, despite its structural similarity to clopidogrel (41).

TICAGRELOR. Ticagrelor, a reversible $P2Y_{12}$ inhibitor, appears to act as a substrate of P-gp and may have moderate inhibitory activity as well. Initial studies have not established whether the drug passes directly into the bile from the liver or is transported by intestinal P-gp and secreted from the systemic circulation into the intestine (49). However, ticagrelor appears to moderately inhibit P-gp-mediated digoxin transport in a dose-dependent manner (50). Thus, we believe it is prudent to monitor plasma digoxin levels when ticagrelor is coadministered.

Whether different doses of aspirin affect the P-gp transport of ticagrelor is unclear. Interestingly, in the PLATO (Platelet Inhibition and Patient Outcomes) study of 18,624 patients hospitalized with acute coronary syndromes, a statistically significant effect modification of the relative benefit of ticagrelor versus clopidogrel was observed, dependent on the dose of aspirin selected by the investigators. Because aspirin can inhibit P-gp transport and ticagrelor acts as a P-gp substrate, the findings of PLATO are intriguing. However, since higher dose aspirin was used mostly in the United States, it is also possible that the apparent interaction between aspirin dose and ticagrelor was confounded by other factors associated with care in the United States or was due to chance.

Food and Drug Administration Guidance for New Drug Development

In 2012, the FDA released guidance on drug-drug interactions to ensure that pharmaceutical companies characterize the effects of the P-gp transporter on new drugs. In this recent update, the FDA strengthened this recommendation, mandating that "all investigational drugs should be evaluated in vitro to determine whether they are a potential substrate of P-glycoprotein" (51). Using in vitro assays, decision-tree models have become the standard method to determine whether a drug is a substrate or inhibitor of P-gp and when a subsequent in vivo clinical study is needed (Fig. 4) (1).

Clinical Implications

Many cardiovascular drugs, particularly novel anticoagulant and antiplatelet therapies, act as substrates and inhibitors of P-gp, leading to clinically significant drug-drug interactions that may play a role in the increased risk for bleeding that has been reported with these agents (27). Because the use of multiple concomitant cardiovascular drugs is the rule rather than the exception, clinicians must be aware when coadministering medications with P-gp substrate or inhibitory properties. Clinicians should consider dose adjustment or alternative treatments when drugs with strong P-gp interactions and narrow therapeutic indexes are combined.

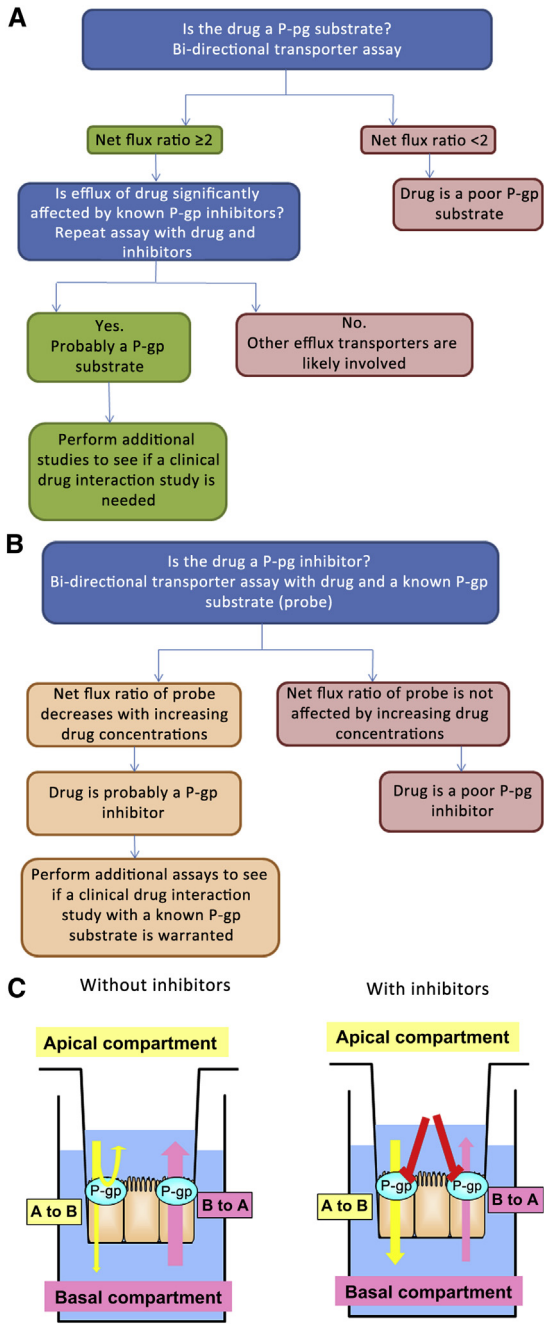

Figure 4 **Determining if a Drug Is a P-gp Substrate or Inhibitor**

A bidirectional transport assay, using a polarized epithelial monolayer that overexpresses permeability glycoprotein (P-gp), is the accepted method for identifying P-gp substrates and inhibitors (51). **(A)** In such an assay, if the ratio of measured efflux to uptake (net flux) of a drug is ≥2, it is possible that the drug is a P-gp substrate. This is confirmed with a second assay with same monolayer system and the addition of a known P-gp inhibitor, such as ketoconazole. If increasing concentrations of the P-gp inhibitor lead to decreases in the net flux of the drug, the drug is likely a P-gp substrate. **(B)** In the reverse scenario, if the net flux of a known P-gp substrate, such as digoxin, is decreased by the addition of the drug in question, the drug is likely a P-gp inhibitor. **(C)** In this bidirectional transport assay, net flux reflects the difference in movement of drug from apical (A) to basal (B) versus B to A compartments. For a P-gp substrate, net flux from B to A is ≥2. In the presence of a P-gp inhibitor, net flux is 0, reflecting equal rates of permeation from A to B and B to A.

Further research is necessary to completely characterize the extent of these interactions with the P-gp transport system in clinical pharmacokinetic studies, particularly for newer antithrombotic and antiarrhythmic agents. Additionally, the intracranial expression of P-gp has not been well studied. Whether the P-gp transport system plays an important role in the risk for intracranial hemorrhage via the modulation of cerebral concentrations of novel anticoagulant agents deserves further consideration.

Take-Home Messages

1. Important interactions between commonly used cardiovascular drugs and a wide variety of medications are mediated by the P-gp transporter.
2. Cardiovascular drugs with narrow therapeutic indexes (e.g., antiarrhythmic agents, anticoagulant agents) can have large increases in concentrations when coadministered with potent P-gp inhibitors, thus increasing the risk for drug toxicity.
3. Dose adjustment or use of alternative agents should be considered when strong P-gp-mediated drug-drug interactions are present.
4. Interactions between novel drugs and known P-gp inhibitors are now being systematically evaluated during drug development, and recommended guidelines for the administration of P-gp substrate drugs will be expanded.

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