AHA SCIENTIFIC STATEMENT

Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients With Cardiovascular Disease

A Scientific Statement From the American Heart Association

A drug-drug interaction (DDI) is a pharmacokinetic or pharmacological influence of 1 medication on another that differs from the known or anticipated effects of each agent alone.[1] A DDI may result in a change in either drug efficacy or drug toxicity for 1 or both of the interacting medications.[2] Pharmacokinetic DDIs result in altered absorption, distribution, metabolism, or excretion of a medication. A pharmacodynamic DDI occurs when 1 medication modifies the pharmacological effect of another in an additive, a synergistic, or an antagonistic fashion.

It is estimated that ≈2.8% of hospital admissions occur as a direct result of DDIs.[3] However, the actual incidence of hospitalization secondary to clinically significant DDIs is likely to be highly underestimated because medication-related issues are more commonly reported as adverse drug reactions. Complex underlying disease states also may make recognizing a DDI more challenging, further contributing to a lower reported incidence. The overall clinical impact of a DDI can range from mild to life-threatening. Therefore, not all DDIs require a modification in therapy. The variability in the clinical significance of a DDI depends on both medication-specific and patient-specific factors. Medication-specific factors include the individual pharmacokinetic characteristics of each medication implicated in the DDI (eg, binding affinity, half-life [$t_{1/2}$]), dose of the medications, serum concentrations, timing and sequence of administration, and duration of therapy. Patient-specific factors include age, sex, lifestyle, genetic polymorphisms causing differences in enzyme expression or activity, and disease impairment affecting drug metabolism (eg, hepatic or renal impairment, cardiac failure) or predisposition to differences in efficacy or safety (eg, statin intolerance in patients with a history of myopathy).

Clinically significant DDIs are usually preventable. To optimize patient safety, healthcare providers must have an understanding of the mechanisms, magnitude, and potential consequences of any given DDI. Interpreting this information will assist clinicians in the safe prescribing of medications and permits careful consideration of the benefits and risks of concomitant medications.

Statins reduce morbidity and mortality in patients with known atherosclerotic cardiovascular disease (ASCVD) and in many primary prevention patients.[4–9] Current guidelines recommend high-intensity statin therapy in all patients with ASCVD age ≤75 years and moderate- to high-intensity statin therapy in patients with ASCVD and age >75 years, diabetes mellitus, and familial hypercholesterolemia and in primary prevention patients with 10-year ASCVD risk ≥7.5%.[10] Given the important role of statins in patients with ASCVD and those at high ASCVD risk, combination therapy with statins and other cardiovascular medications is highly likely, and potentially significant DDIs must be considered in patients treated with statins.

Another important aspect of prescribing medications in combination is evaluating the risks versus benefits. Given the continuing increase in healthcare costs, trying to minimize costs to the health system through minimization of adverse effects and optimizing efficacy is of paramount importance. Prescription drug coverage and

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affordability may often dictate which medications may be prescribed. Patients who have exhausted prescription drug coverage or who are uninsured may require less-than-ideal medication combinations to provide the most cost-effective strategy possible. Therefore, a clear understanding of the magnitude and clinical significance of DDIs will enable clinicians to make well-informed decisions to provide evidence-based and cost-effective health care as safely as possible.

This document reviews the basics of DDIs, the pharmacological differences in the various statins, and the significance of statin DDIs with select medications used to treat patients with cardiovascular disease. Recommendations on the clinical management of these DDIs are provided to enable clinicians to optimize management while minimizing untoward effects. The writing committee considered data from clinical trials, case reports, prescribing information, and pharmacokinetic studies to provide guidance on how statin DDIs with select medications used in cardiovascular patients should be managed. A summary of the evidence and the specific recommendations for the clinical management of the DDIs discussed are given in Tables 1 and 2.

OVERVIEW OF DDIs, CYTOCHROME P-450 ENZYMES, AND PERMEABILITY GLYCOPROTEIN

The 2 most common pharmacokinetic DDIs involving statins are those mediated by the cytochrome P-450 (CYP450) enzyme system and permeability glycoprotein (P-gp). Pharmacodynamic DDIs with statins may also occur. All DDIs can result in altered low-density lipoprotein cholesterol reductions or an enhanced risk of muscle-related toxicity.

DDIs Involving the CYP450 Enzyme System

The CYP450 gene superfamily encodes a series of oxidative enzymes involved in the biosynthesis of several physiologically important compounds (eg, steroids and fatty acids) and the metabolism of drugs and other exogenous chemical products.[11,12] In CYP450 nomenclature, enzymes sharing ≥40% similarity are categorized into families designated by an Arabic numeral (eg, CYP2 family) and those sharing ≥55% similarity are further classified into subfamilies designated by a letter (eg, CYP2C subfamily).[11] Within each subfamily, individual enzymes responsible for a unique metabolic route are numbered (eg, CYP2C19 enzyme). For those enzymes associated with genetic polymorphisms that encode allelic variants, an asterisk followed by a number (and in some cases an additional letter) may also be used (eg, CYP2C19*2, a variant associated with diminished function compared with the wild-type allele).[12]

Most CYP450 enzymes are expressed in the liver, but some are also expressed in significant concentrations in the gastrointestinal tract, kidney, and other sites. The main role of the CYP450 enzyme system in drug metabolism is to detoxify medications and to facilitate elimination from the body, although toxic intermediates can occasionally be created during this process. Most of the CYP450-mediated reactions associated with drug metabolism occur within hepatocytes. However, enzymes present in the gastrointestinal tract can reduce oral bioavailability of some medications by degrading substrates before absorption into the bloodstream. Small subsets of enzymes are involved in the metabolic conversion of inert prodrugs to their bioactive forms. Although >50 different CYP450 enzymes have been isolated in humans, only a select few (ie, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) are responsible for metabolizing the majority of available medications.[12] Of these, CYP2C9, CYP2C19, and CYP3A4 play a substantial role in statin metabolism, and CYP2C8 plays a minor role.

DDIs involving the CYP450 enzyme system are generally classified as inhibition or induction interactions. Enzyme inhibition may occur as a result of direct competition by substrates for available binding sites, reduced enzymatic activity, or both. The onset of enzyme inhibition usually occurs rapidly after the introduction of an interacting drug. Direct competition is the most common mechanism resulting in DDIs and often occurs when 1 drug has a higher binding affinity for the enzyme or is present in significantly greater concentrations than its competing substrate. In contrast, some drugs may bind irreversibly to the enzyme and prevent its participation in subsequent metabolic reactions. Regardless of the underlying mechanism, enzyme inhibition produces increased serum concentrations of 1 or both medications. In the case of statin DDIs, the result is most often an increase in statin serum concentrations.

Enzyme induction occurs when a substrate enhances the activity of a CYP450 enzyme. The mechanism by which induction occurs is most commonly a result of increased gene expression, often via activation of transcription factors, commonly those of the nuclear receptor 1 family (eg, constitutive androstane receptor or pregnane X receptor). Other less common mechanisms include upregulation of mRNA translation and inhibition of protein degradation. Inducers frequently increase the activity of CYP450 enzymes involved in alternative metabolic pathways, although some may induce their own metabolism. Unlike enzyme inhibition, the peak effect of an induction reaction is often delayed for days to weeks as a result of the time required for alterations in gene expression to become evident. Inducers of the CYP450 enzyme system are less common. None of the medications included in this review have been associated with CYP450 enzyme induction, although clinicians should be

Table 1.   Summary of the Evidence for DDIs With Statins and Select Medications in Patients With Cardiovascular Disease

Interacting Agent	Statin	Effect	Magnitude	Recommendation
Amiodarone	Lovastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor 1.8-fold increase in AUC of lovastatin	Combination may be considered
	Simvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor 1.8-fold increase in AUC of simvastatin	Combination may be considered
Amlodipine	Lovastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor	Combination may be considered
	Simvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor 1.8-fold increase in AUC of simvastatin	Combination may be considered
Conivaptan	Lovastatin	Decreased metabolism of lovastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 3-fold increase in AUC of lovastatin	Combination is potentially harmful
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 3-fold increase in AUC of simvastatin	Combination is potentially harmful
Colchicine	Atorvastatin	Increased statin or colchicine exposure/increased risk for muscle-related toxicity	Variable	Combination may be considered
	Fluvastatin	Increased statin or colchicine exposure/increased risk for muscle-related toxicity	Variable	Combination is reasonable
	Lovastatin	Increased statin or colchicine exposure/increased risk for muscle-related toxicity	Variable	Combination is reasonable
	Pitavastatin	Increased statin or colchicine exposure/increased risk for muscle-related toxicity	Variable	Combination is reasonable
	Pravastatin	Increased statin or colchicine exposure/increased risk for muscle-related toxicity	Variable	Combination may be considered
	Rosuvastatin	Increased statin or colchicine exposure/increased risk for muscle-related toxicity	Variable	Combination is reasonable
	Simvastatin	Increased statin or colchicine exposure/increased risk for muscle-related toxicity	Variable	Combination may be considered
Cyclosporine/ tacrolimus/ everolimus/ sirolimus*	Atorvastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Severe 6- to 15-fold increase in AUC of atorvastatin	Combination may be considered
	Fluvastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Moderate 2- to 4-fold increase in AUC of fluvastatin	Combination may be considered
	Lovastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Severe 5- to 20-fold increase in AUC of lovastatin	Combination is potentially harmful
	Pitavastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Severe 5-fold increase in AUC of pitavastatin	Combination is potentially harmful
	Pravastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Severe 5- to 10-fold increase in AUC of pravastatin	Combination may be considered
	Rosuvastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Severe 7-fold increase in AUC of rosuvastatin	Combination may be considered
	Simvastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Severe 6- to 8-fold increase in AUC of simvastatin	Combination is potentially harmful

(*Continued*)

Table 1. Continued

Interacting Agent	Statin	Effect	Magnitude	Recommendation
Digoxin	Atorvastatin	Increased levels of digoxin	Minor 1.2-fold increase in AUC	Combination is reasonable
Diltiazem	Atorvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor 51% increase in AUC of atorvastatin	Combination is reasonable
	Lovastatin	Decreased metabolism of lovastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 3.6-fold increase in AUC of lovastatin	Combination may be considered
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 4.6-fold increase in AUC of simvastatin	Combination may be considered
Dronedarone	Lovastatin	Decreased metabolism of lovastatin leading to increased concentrations Increased statin exposure/increased risk for muscle-related toxicity	Unknown Expected to be similar to simvastatin 3.9-fold increase in AUC	Combination may be considered
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased statin exposure/increased risk for muscle-related toxicity	Moderate 3.9-fold increase in AUC of simvastatin	Combination may be considered
Fenofibrate/ fenofibric acid	Atorvastatin	Potential increase in muscle-related toxicity	Insignificant 1.0-fold increase in AUC of atorvastatin	Combination is reasonable
	Fluvastatin	Potential increase in muscle-related toxicity	Specific data not available but magnitude likely to be minor	Combination is reasonable
	Lovastatin	Potential increase in muscle-related toxicity	Specific data not available but magnitude likely to be minor	Combination is reasonable
	Pitavastatin	Potential increase in muscle-related toxicity	Insignificant 1.2-fold increase in AUC of pitavastatin	Combination is reasonable
	Rosuvastatin	Potential increase in muscle-related toxicity	Insignificant 1.1-fold increase in AUC of rosuvastatin	Combination is reasonable
	Simvastatin	Potential increase in muscle-related toxicity	Insignificant 1.1-fold increase in AUC of simvastatin If taken at same time, 1.05-fold increase	Combination is reasonable
Gemfibrozil	Atorvastatin†	Decreased metabolism of atorvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Minor 1.4-fold increase in AUC of atorvastatin	Combination may be considered
	Lovastatin	Decreased metabolism of lovastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 2- to 3-fold increase in AUC of lovastatin	Combination should be avoided
	Pitavastatin†	Decreased metabolism of pitavastatin leading to increased concentrations Increased risk of muscle-related toxicity	Minor 1.5-fold increase in AUC of pitavastatin	Combination may be considered
	Pravastatin	Decreased metabolism of pravastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 2.0-fold increase in AUC of pravastatin	Combination should be avoided
	Rosuvastatin†	Decreased metabolism of rosuvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Minor 1.6- to 1.9-fold increase in AUC of rosuvastatin	Combination may be considered
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 2- to 3-fold increase in AUC of simvastatin	Avoid combination

(Continued)

Table 1. Continued

Interacting Agent	Statin	Effect	Magnitude	Recommendation
Ranolazine	Lovastatin	Increased statin exposure/increased risk for muscle-related toxicity	Specific data not available but likely similar to simvastatin, which is 1.9-fold increase in AUC	Combination may be considered
	Simvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor 1.9-fold increase in AUC of simvastatin	Combination may be considered
Ticagrelor	Atorvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor 1.4-fold increase in AUC	Combination is reasonable
	Lovastatin	Decreased metabolism of lovastatin leading to increased concentrations Increased risk of muscle-related toxicity	Unknown but expected to be similar to simvastatin Moderate 2- to 3-fold increase in AUC	Combination may be considered
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 2- to 3-fold increase in AUC	Combination may be considered
Verapamil	Lovastatin	Decreased metabolism of lovastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 3.6-fold increase in AUC	Combination may be considered
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 2.5-fold increase in AUC	Combination may be considered
Warfarin	Fluvastatin	Increased INR/potential for increased bleeding	Variable	Combination therapy is useful
	Lovastatin	Increased INR/potential for increased bleeding	Variable	Combination is useful
	Rosuvastatin	Increased INR/potential for increased bleeding	Variable	Combination is useful
	Simvastatin	Increased INR/potential for increased bleeding	Up to 30% change in INR	Combination is useful

Magnitude of drug-drug interactions based on AUC increase: minor, >1.25 to <2; moderate, ≥2 to 4.9; and severe, ≥5. AUC indicates area under the curve; and INR, international normalized ratio.

*Changes in magnitude of statin AUC are reported with cyclosporine. Limited data exist with tacrolimus, everolimus, and sirolimus (see text).

†Use in combination is recommended only when other options have been exhausted.

aware because this may occur with therapies used for concomitant disease states and conditions.[13,14]

DDIs Involving P-gp

P-gp, also known as multidrug resistance-1, belongs to a superfamily of membrane-associated ATP-binding cassette transporters.[15] Like other members of this class, P-gp uses ATP to actively pump substrates across the membrane to the extracellular space, often against a concentration gradient. P-gp expression is localized primarily in the gastrointestinal tract and in hepatic, renal, and brain tissue, where it plays a critical role in drug disposition. In the gastrointestinal tract, P-gp prevents the oral absorption of medications by secreting substrates into the intestinal lumen. In renal and hepatic tissues, P-gp promotes secretion of substrates into the urine and bile, respectively. In the central nervous system, P-gp is critical to maintaining the blood-brain barrier.

As with interactions involving the CYP450 enzyme system, those involving P-gp may be broadly classified as inhibition or induction interactions. Competitive inhibition is the most common mechanism by which substrates inhibit P-gp, but mechanisms involving the regulation of ATP may also play a role. The consequence of P-gp inhibition depends largely on the location of the interaction. In the gastrointestinal tract, inhibition of P-gp results in enhanced drug bioavailability, whereas P-gp inhibition in hepatic and renal tissue results in reduced drug elimination. Enhanced central nervous system penetration results from inhibition of P-gp in the brain. Similar to CYP450 enzymes, induction most commonly involves enhanced gene expression. Many of the same transcription factors involved in the upregulation of CYP450 enzymes (eg, constitutive androstane receptor and pregnane X receptor) also enhance the expression of P-gp. Although reports vary, atorvastatin, lovastatin, pitavastatin, and simvastatin have been implicated as

Table 2. Clinical Recommendations on Management of Select DDIs With Statins*

Interacting Medication	Statin	Clinical Recommendations for Management
Amiodarone	Lovastatin	Limit dose of lovastatin to 40 mg daily
	Simvastatin	Limit dose of simvastatin to 20 mg daily
Amlodipine	Lovastatin	Limit dose of simvastatin and lovastatin to 20 mg daily
	Simvastatin	
Colchicine	Atorvastatin	Closer monitoring for muscle-related toxicity is recommended when used in combination
	Fluvastatin	
	Lovastatin	
	Pitavastatin	
	Pravastatin	
	Rosuvastatin	
	Simvastatin	
Conivaptan	Lovastatin	Avoid combination
	Simvastatin	
Cyclosporine/ tacrolimus/ everolimus/ sirolimus	Atorvastatin	Limit dose of atorvastatin to 10 mg daily
	Fluvastatin	Limit dose of fluvastatin to 40 mg daily
	Lovastatin	Avoid combination
	Pitavastatin	
	Pravastatin	Limit dose of pravastatin to 40 mg daily
	Rosuvastatin	Limit dose of rosuvastatin to 5 mg daily
	Simvastatin	Avoid combination
Diltiazem	Lovastatin	Limit dose of lovastatin to 20 mg daily
	Simvastatin	Limit dose of simvastatin to 10 mg daily
Dronedarone	Lovastatin	Limit dose of lovastatin to 10 mg daily
	Simvastatin	Limit dose of simvastatin to 10 mg daily
Gemfibrozil	Atorvastatin	Combination is acceptable to use if clinically indicated and fenofibrate (or fenofibric acid) is not an option; the Figure provides additional guidance
	Lovastatin	Avoid combination
	Pitavastatin	Combination is acceptable to use if clinically indicated and fenofibrate (or fenofibric acid) is not an option; the Figure provides additional guidance
	Pravastatin	Avoid combination
	Rosuvastatin	Combination is acceptable to use if clinically indicated and fenofibrate (or fenofibric acid) is not an option; the Figure provides additional guidance
	Simvastatin	Avoid combination

(Continued)

Table 2. Continued

Interacting Medication	Statin	Clinical Recommendations for Management
Ranolazine	Lovastatin	Combination is acceptable to use if clinically indicated and an alternative non-CYP3A4 statin cannot be used. However, doses of lovastatin or simvastatin should not exceed 20 mg daily.
	Simvastatin	
Tacrolimus	Atorvastatin	Limit dose of atorvastatin to 10 mg daily
	Fluvastatin	Limit dose of fluvastatin to 40 mg daily
	Lovastatin	Avoid combination
	Pitavastatin	
	Pravastatin	Limit dose of pravastatin to 40 mg daily
	Rosuvastatin	Limit dose of rosuvastatin to 5 mg daily
	Simvastatin	Avoid combination
Ticagrelor	Atorvastatin	Combination is acceptable without dose limitations
	Lovastatin	Limit dose of lovastatin to 40 mg daily
	Simvastatin	Limit dose of simvastatin to 40 mg daily
Verapamil	Lovastatin	Limit dose of lovastatin to 20 mg daily
	Simvastatin	Limit dose of simvastatin to 10 mg daily

Fenofibrate (or fenofibric acid) is the preferred fibrate to use in combination with statins. CYP indicates cytochrome.

*Select statin-drug interactions discussed in the article that do not appear in the table are not considered clinically significant.

both P-gp substrates and inhibitors.[15–19] Common P-gp substrates, inducers, and inhibitors that affect statin metabolism are given in Table 3.[12,16,20–22]

Other transport proteins, including organic anion-transporting polyprotein (OATP) 1B1 (OATP1B1) and efflux transporter breast cancer resistance protein, are involved in statin uptake and metabolism.[23] Similar to P-gp, breast cancer resistance protein is involved in drug efflux, whereas OATP1B1 is involved in the hepatic uptake of substrates from the portal circulation. Despite these differences in the mechanism of drug transport, the net result of inhibiting these enzymes is enhanced serum statin concentrations.

Statin Metabolism

There are a number of differences in the pharmacokinetic profiles of statin agents, including absorption, distribution, metabolism, and excretion. Clinically significant DDIs with statins often stem from a direct effect on ≥1 of these parameters. Two pharmacokinetic measures, the area under the curve (AUC) and maximum serum concentration (Cmax), can be altered in the presence of a DDI. Changes in these 2 pharmacokinetic measures are used

by the US Food and Drug Administration (FDA) to define the presence of a DDI. The AUC is specifically the calculated area under the plasma-drug concentration-time curve and reflects total body exposure to a medication after administration. The Cmax, the highest drug concentration achieved after administration of a medication, is a marker of peak drug exposure at a specific time. Table 4 compares the pharmacokinetic properties of the 7 currently available statin agents.[24–32] For the purpose of making clinical recommendations for the management of DDIs involving statins, an increase in the AUC should be used because it has been recommended in the application of the results of DDI studies. The level of increase in the AUC and the magnitude of the interaction is defined as minor (>1.25–<2.0), moderate (≥2–4.9), or severe (≥5).[33]

Absorption

Bioavailability is defined as the percentage of the statin dose that is absorbed and reaches the systemic circulation after absorption. Systemic bioavailability is generally considered low for all statins. Pitavastatin has the highest bioavailability (43%–51%); simvastatin and lovastatin have very low bioavailability (<5%). Importantly, bioavailability is relatively consistent with most statins whether administered with or without food, making differences in this pharmacokinetic parameter noncontributory. However, the overall bioavailability of lovastatin is decreased by ≈50% when given without food. The time to peak concentration after absorption is relatively short with all statins (within 4 hours) when given in their immediate-release formulations. DDIs with statins typically are not attributable to changes in absorption.

Distribution

Distribution of drug throughout the body is another important pharmacokinetic parameter. Protein binding influences drug distribution and ultimately the pharmacological effects of drugs because only the unbound or free drug is able to elicit targeted effects. Most statins except pravastatin are highly protein bound. Another aspect of drug distribution, considered a chemical property, is lipophilicity, which is measured in log P. Statins with a log P value >0 have greater drug penetration into fat than into water. All statins except pravastatin and rosuvastatin are considered lipophilic. Although adverse effects may be influenced by differences in drug distribution, DDIs with statins typically are not attributable to changes in drug distribution.

Metabolism

The most diverse pharmacokinetic parameter among statins is metabolism. In general, lipophilic statins require a greater degree of metabolism to convert the statin into hydrophilic (water soluble) salts and conjugates that

Table 3. Common P-gp Substrates, Inhibitors, and Inducers Associated With the CYP450 Enzymes Affecting Statin Metabolism[12,16,20–22]

Enzyme	Statin Substrates	Inhibitors	Inducers
CYP2C9	Fluvastatin, rosuvastatin (also CYP2C19, minor)	Amiodarone, capecitabine, etravirine, fluconazole, fluvoxamine, fluvastatin, ketoconazole, metronidazole, miconazole, oxandrolone, sulfamethoxazole/trimethoprim, voriconazole, zafirlukast	Carbamazepine, phenobarbital, phenytoin rifampin
CYP3A4	Atorvastatin, lovastatin, simvastatin	Amiodarone, amlodipine, aprepitant, atorvastatin, bicalutamide, cilostazol cimetidine, ciprofloxacin, clarithromycin, conivaptan, cyclosporine, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, imatinib, isoniazid, itraconazole, ketoconazole, mibefradil, midazolam, nefazodone, nilotinib, posaconazole, protease inhibitors, ranolazine, sertraline, tacrolimus, telithromycin, ticagrelor, tricyclic antidepressants, verapamil, voriconazole	Aprepitant, bosentan, carbamazepine, cyclophosphamide, corticosteroids, efavirenz, modafnil, nafcillin, nevirapine, phenytoin, pioglitazone, phenobarbital, rifampin, St. John's wort
P-gp	Atorvastatin, lovastatin, pitavastatin, simvastatin	Amiodarone, atorvastatin, azithromycin, captopril, carvedilol, cimetidine, clarithromycin, colchicine, conivaptan, cyclosporine, diltiazem, dipyridamole, dronedarone, erythromycin, felodipine, grapefruit juice, itraconazole, ketoconazole, lovastatin, mefloquine, nicardipine, omeprazole, protease inhibitors, quinidine, ranolazine, reserpine, sertraline, simvastatin, tacrolimus, verapamil	Carbamazepine, phenytoin rifampin, St. John's wort
OATP1B1	Atorvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin	Carbamazepine, clarithromycin, cyclosporine, erythromycin, gemfibrozil, protease inhibitors, roxithromycin, rifampin, sildenafil, sacubitril, telithromycin	Unknown
OATP1B3	Fluvastatin, pravastatin, rosuvastatin	Clarithromycin, cyclosporine, erythromycin, rifampin, roxithromycin, rifampin, sacubitril, telithromycin	Unknown

CYP indicates cytochrome P; OATP, organic anion-transporting polyprotein; and P-gp, permeability glycoprotein.

are eliminated from the body. One metabolic pathway is glucuronidation, which results in statin conversion to glucuronide conjugates. This metabolic pathway can be inhibited by certain nonstatin medications (eg, gemfibrozil) and can result in increases in systemic drug exposure with all statins to various degrees.

The primary form of drug metabolism for most statins occurs through CYP450 enzymes. The most prevalent CYP450 enzyme subcategories for statin metabolism are the 3A4 and 2C9 enzyme systems. Simvastatin and lovastatin undergo significant CYP3A4 metabolism, and atorvastatin undergoes a lesser amount as one of its minor metabolic pathways. This is in contrast to fluvastatin, pitavastatin, and rosuvastatin, which require CYP2C9. Because CYP3A4 is the most common enzyme involved in drug metabolism, simvastatin and lovastatin will have more DDIs that will likely require intervention.

Pravastatin is the only statin that does not undergo CYP450 metabolism. A number of medications coprescribed in patients with ASCVD can alter the metabolism of statins through the CYP450 metabolic pathway as inducers, inhibitors, or competitive substrates. The clinical relevance of these types of DDIs is based on the degree of inhibition or induction of CYP450 and the pharmacokinetic profile of the individual statin. The majority of DDIs with statins are typically the result of changes in drug metabolism.

Excretion

Statins undergo extensive metabolism; therefore, the amount of statin that is excreted in its unchanged form through renal elimination is small. The overall dependence of statin metabolites on renal elimination is modest, with pravastatin being the highest at 20% and atorvastatin being the lowest at <2%. Drug elimination $t_{1/2}$, the time it takes to reduce the systemic drug con-

centration by 50%, predicts the time course of overall drug elimination. Fluvastatin, lovastatin, pravastatin, and simvastatin have a relatively short $t_{1/2}$. These agents are optimally dosed in the evening or administered as an extended-release formulation (for fluvastatin or lovastatin) to maximize effect. In contrast, atorvastatin, pitavastatin, and rosuvastatin have longer half-lives and can be dosed at any time of the day. Statins are also excreted into bile and feces as a means of drug elimination. This excretion is facilitated by OATPs. Similar to CYP450, there are several subtypes of OATP that can affect the elimination of rosuvastatin and pitavastatin.[28,30] DDIs with statins may sometimes be attributable to decreased drug excretion, especially in patients with impaired glomerular filtration rate, and are related to the extent the statin is renally excreted. This potential issue is limited with atorvastatin, which has the least amount of renal excretion (<2%), but may be a consideration for other statins that have a higher degree of renal excretion (eg, pitavastatin, pravastatin, rosuvastatin, simvastatin).

DDIs WITH NONSTATIN LIPID-LOWERING AGENTS

Fibric Acid Derivatives (Fibrates)

Coadministration of a statin with a fibrate may sometimes be warranted for the treatment of complex dyslipidemias or severe hypertriglyceridemia, particularly in patients with obesity, metabolic syndrome, insulin resistance, or diabetes mellitus. In the United States, gemfibrozil, fenofibrate, and fenofibric acid are the only fibrates approved for clinical use. Both statins and fibrates have been independently associated with a risk of muscle-related toxicity as monotherapy, and statin-

Table 4. Pharmacokinetic Properties of Statins[24–32]

	Absorption			Distribution	Metabolism			Excretion	
	Bioavailability, %	T_{max}, h	Protein Binding, %	Lipophilicity, log P	Major P450 Hepatic Enzyme	Prodrug	Active Metabolites	Renal Excretion, %	$t_{1/2}$, h
Atorvastatin	14	1–2	≥98	4.1	CYP3A4	No	Yes	<2	14
Fluvastatin	24	<1	98	3.24	CYP2C9 (CYP2C8 and CYP3A4 are minor)	No	No	5	3
Lovastatin	<5	2–4	>95	4.3	CYP3A4	Yes	Yes	10	2–3
Pitavastatin	43–51	1	99	1.5	CYP2C9 (CYP2C8 is minor)	No	No	15	12
Pravastatin	17	1–1.5	50	−0.2	Non-CYP	No	No	20	1.8
Rosuvastatin	20	3–5	88	−0.3	CYP2C9	No	Minimal	10	19
Simvastatin	<5	4	95	4.7	CYP3A4	Yes	Yes	13	2

CYP indicates cytochrome P; $t_{1/2}$, drug half-life; and T_{max}, amount of time that a drug is present at the maximum concentration in serum.

fibrate combination therapy increases this risk.[34–39] Epidemiological studies have estimated that monotherapy with a fibrate is associated with a 5.5-fold increased risk of muscle-related toxicity compared with statin therapy alone.[40] Muscle-related toxicity has been reported with both available fibrates when used in combination with statins but occurs more frequently with gemfibrozil.[41,42] However, in large clinical trials with gemfibrozil monotherapy, including VA-HIT (Veterans Affairs-High-Density Lipoprotein Intervention Trial; n=2531) and HHS (Helsinki Heart Study; n=4081), there were no reported cases of rhabdomyolysis.[43,44]

The increased risk of muscle-related toxicity with statin-fibrate combination therapy was first reported with the combination of gemfibrozil and lovastatin in 1990 but has subsequently been demonstrated with other fibrates and with most statins, particularly cerivastatin, which has been removed from the market.[45,46] According to evidence from the FDA Adverse Event Reporting System database, reports of muscle symptoms were 15.7 per 1 million prescriptions for gemfibrozil compared with 8.8 per 1 million for fenofibrate (odds ratio, 1.78; $P<0.0001$), and the rate of gemfibrozil-associated rhabdomyolysis was ≈10-fold higher compared with fenofibrate.[47] This dramatic difference in reports of rhabdomyolysis between the 2 fibrates appeared to be driven largely by an increased risk in patients taking gemfibrozil with a statin. The increase in risk with coadministration of fibrates and statins is greater than the predicted sum of the monotherapy risks, suggesting both pharmacokinetic and pharmacodynamic causal mechanisms.[48]

Gemfibrozil

Gemfibrozil is rapidly absorbed after oral administration with nearly 100% bioavailability, reaching peak plasma concentrations within 1 to 2 hours. It is highly protein bound, has an elimination $t_{1/2}$ of ≈1.5 hours, and is dosed twice daily.[49] The active drug undergoes conjugation to its acyl glucuronide, gemfibrozil 1-O-β glucuronide, which is then oxidized via the CYP450 system.[50,51] The majority of the gemfibrozil dose is eliminated as the glucuronide conjugate in the urine with little excreted as unchanged gemfibrozil.

Gemfibrozil and particularly its glucuronide metabolite are potent irreversible inhibitors and inactivators of CYP2C8.[37] Both are substrates but not inhibitors of CYP3A4. Gemfibrozil 1-O-β glucuronide and, to a lesser extent, the parent compound are also potent inhibitors of OAT1B1/3-mediated hepatic uptake of statin acids, as well as OATP2B1, Na+-taurocholate cotransporting polypeptide, the renal transporter OAT3, and statin glucuronidation or lactonization.[52,53] Thus, DDIs, including hepatotoxicity and muscle-related toxicity, in patients receiving statin-gemfibrozil combination therapy may vary as a result of differences in statin susceptibility to inhibitory effects of intestinal, hepatic, and renal transporters, as well as CYP450 metabolism.

Gemfibrozil increases the AUC of active simvastatin acid and lovastatin acid by ≈2- to 3-fold.[54,55] The AUC values of atorvastatin and its active metabolites (2-hydroxyatorvastatin, 2-hydroxyatorvastatin lactone, 4-hydroxyatorvastatin lactone) are modestly (1.2- to 1.4-fold) but significantly increased when coadministered with gemfibrozil.[40,56,57] It is suggested that these interactions are likely attributable to the inhibition of OATP2-mediated hepatic uptake because these agents are metabolized by CYP3A4, which is not significantly affected by gemfibrozil.

Pravastatin is more hydrophilic than other statins and does not easily cross cell membranes, relying on transporters for absorption, tissue uptake, and elimination. The drug is minimally metabolized and is not significantly eliminated via CYP450 enzymes. Renal elimination accounts for 20% of total clearance. However, pravastatin-gemfibrozil combination therapy increases plasma pravastatin concentrations by 202% (range, 40%–412%) and significantly reduces renal clearance of the drug from 25 to 14 L/h ($P<0.0001$) in healthy volunteers.[58] These findings are consistent with the inhibition of OATP1B1-mediated uptake and inhibition of the renal transporter OAT3.

Active uptake via the OATP1B1/3, Na+-taurocholate cotransporting polypeptide, breast cancer resistance protein, and active renal tubular secretion via OAT3 are also important for the elimination of rosuvastatin. Rosuvastatin is not extensively metabolized and is primarily eliminated unchanged in urine and feces. Consistent with other statins reviewed above, gemfibrozil increased plasma concentrations of rosuvastatin by ≈1.56- to 1.88-fold.[59,60] Gemfibrozil had only a modest effect when administered with pitavastatin in 24 subjects with an increase of 45% in the AUC.[61] Metabolism is only a minor pathway for pitavastatin via CYP2C9, which is unaffected by gemfibrozil. Fluvastatin transport in hepatocytes via the OATP transporters is potently inhibited by gemfibrozil.[62] However, in at least 1 study of 17 subjects, no significant difference was observed in the AUC and Cmax in a comparison of the gemfibrozil-fluvastatin combination and gemfibrozil alone.[63]

The 2013 American College of Cardiology/American Heart Association "Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Risk in Adults" states that combination therapy with any statin and gemfibrozil should be avoided.[10] This recommendation is because of concerns for the increased risk for muscle-related toxicity.[46] However, despite these recommendations, a recent analysis of a nationwide register study found that although providers were less likely to prescribe gemfibrozil, the mean dose of statin was substantially higher in those on a statin-gemfibrozil regimen.[64] The American College of Cardiology/American Heart Association recommendation was derived

from primary and secondary prevention trials evaluating statins in which patients with serious comorbidities and those taking concomitant medications (including gemfibrozil) that may increase the risk of statin muscle-related toxicity were excluded. However, cost considerations, drug availability, and tolerability may make avoidance of this combination difficult for some patients. Pharmacokinetic evidence suggests that the magnitudes of the interactions between gemfibrozil and atorvastatin, pitavastatin, and rosuvastatin are minor and the magnitudes of the interactions between gemfibrozil and lovastatin, pravastatin, and simvastatin are moderate. Given the results of pharmacokinetic data, the combination of gemfibrozil with specific statins may be considered if clinically indicated. An algorithm is provided in the Figure for general guidance on how to optimize safety and efficacy when cost issues necessitate combination therapy.

It is important to note that observational studies clearly demonstrate that the risk of muscle-related toxicity is significantly lower with statin-fenofibrate/fenofibric acid combination therapy compared with statin-gemfibrozil combination therapy. The FDA-approved product labeling recommends that the combined use of gemfibrozil with lovastatin, fluvastatin, pravastatin, pitavastatin, atorvastatin, and rosuvastatin should be avoided.[24–28,30] However, the FDA-approved product labeling for simvastatin indicates that gemfibrozil is contraindicated with simvastatin.[29]

Fenofibrate/Fenofibric Acid

Fenofibrate is a prodrug, the ester of fenofibric acid. Ester hydrolysis converts fenofibrate to fenofibric acid, the active chemical moiety.[65,66] The drug may be administered as either a prodrug (fenofibrate) or the active metabolite (fenofibric acid). Both agents are well absorbed from the gastrointestinal tract with peak plasma concentrations within 6 to 8 hours (fenofibrate) or 4 to 5 hours (fenofibric acid). Fenofibric acid undergoes glucuronidation and is excreted in the urine primarily as the fenofibric glucuronide. Neither compound undergoes oxidative CYP450 metabolism. The elimination $t_{1/2}$ of both medications is 20 hours. Dose adjustments are recommended for patients with mild to moderate renal impairment, and the use of both drugs should be avoided in severe renal impairment because of a 2.7-fold increase in the AUC when estimated glomerular filtration is <30 mL·min^{-1}·1.73 m^{-2}.[35,67]

Fenofibric acid and fenofibrate do not inhibit CYP3A4, CYP2D6, CYP2E1, or CYP1A2; are weak inhibitors of CYP2C8, CYP2C19, and CYP2A6; and are mild to moderate inhibitors of CYP2C9. No significant effects on oxidation, glucuronidation, or plasma concentrations of statins have been identified when fenofibrate is administered in combination with statins.[68–71]

Data from the FDA Adverse Event Reporting System indicate that the number of reports of rhabdomyolysis per 1 million prescriptions was ≈15 times lower for fenofibrate than for gemfibrozil when prescribed with statins other than cerivastatin (0.58 per 1 million for fenofibrate versus 8.6 per 1 million for gemfibrozil).[42]

In the FIELD study (Fenofibrate Intervention and Event Lowering in Diabetes; n=9795), none of the ≈1000 patients on statin-fenofibrate combination therapy experienced rhabdomyolysis.[72] In the ACCORD study (Action to Control Cardiovascular Risk in Diabetes), there were no statistically significant differences in the incidence of myositis, rhabdomyolysis, or elevations of hepatic transaminases with simvastatin-fenofibrate combination therapy compared with simvastatin monotherapy in patients with type 2 diabetes mellitus.[73]

The expert panel of the 2013 American College of Cardiology/American Heart Association blood cholesterol guideline recommended that "Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are ≥500 mg/dL are judged to outweigh the potential risk for adverse effects."[10]

Summary of Evidence for Statin-Fibrate DDIs

On the basis of pharmacokinetic evidence, the combination of gemfibrozil with lovastatin, pravastatin, and simvastatin is potentially harmful and should be avoided. Although gemfibrozil interacts with atorvastatin, pitavastatin, and rosuvastatin, the result is only a minor increase in statin concentrations, and the combination may be considered if clinically indicated. Fluvastatin may be used in combination with gemfibrozil without any specific dose limitations, and this particular statin does not interact with gemfibrozil. Combination therapy with fenofibrate/fenofibric acid and any statin is reasonable when clinically indicated.

Recommendations for Statin-Fibrate DDIs

1. When statin-fibrate combination therapy is indicated, fenofibrate or fenofibric acid is preferred because of a reduced incidence of DDIs compared with statin-gemfibrozil combination therapy.

2. There are circumstances in which gemfibrozil may be the only available fibrate, cost may be a consideration, or fenofibrate may not be tolerated. Under any circumstance, the use of gemfibrozil should be avoided in combination with lovastatin, pravastatin, and simvastatin.

3. If gemfibrozil must be used in combination with atorvastatin, pitavastatin, or rosuvastatin, consideration should be given to the use of a low statin
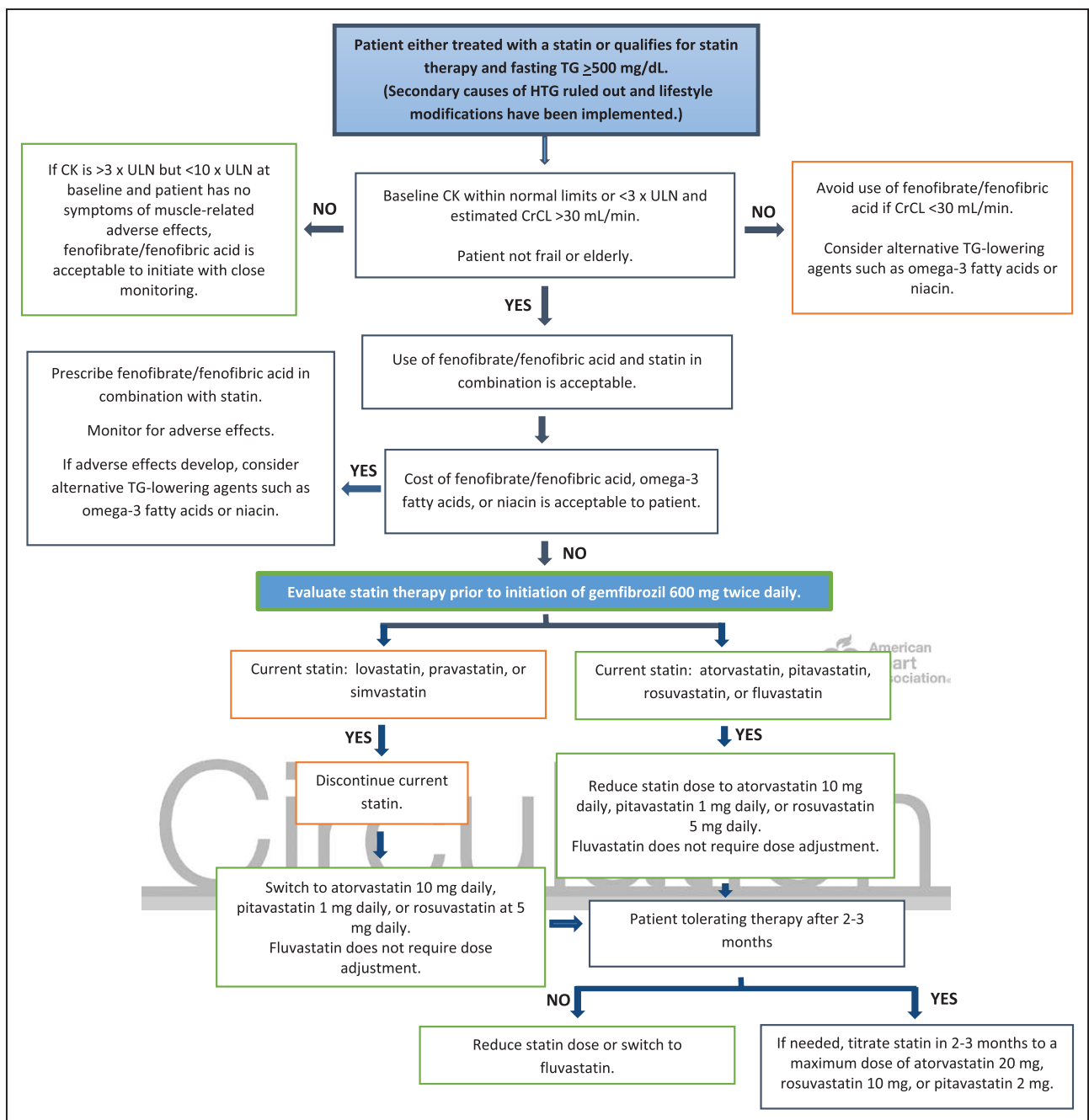
Figure. Algorithm for treating patients with statin-fibrate combination therapy.
Blue boxes indicate where it is acceptable to proceed with combination therapy. Yellow boxes indicate where caution should be used when combination therapy is considered. Red boxes indicate where combination therapy should not be used. CK indicates creatinine kinase; CrCL, creatinine clearance; HTG, hypertriglyceridemia; TG, triglyceride; and ULN, upper limit of normal.

dose to minimize risk. For example, the use of rosuvastatin in combination with gemfibrozil is included in the FDA-approved product labeling, but the labeling requires that the daily dose of rosuvastatin be limited to 10 mg daily.

4. Fluvastatin may be used in combination with gemfibrozil, fenofibrate, or fenofibric acid.

Niacin

Niacin (nicotinic acid), a naturally occurring, water-soluble vitamin of the B complex (vitamin B$_3$), has been studied extensively both as monotherapy for hypercholesterolemia and in combination with other therapies for the management of complex dyslipidemias. However, on the basis of currently available evidence of nonefficacy and

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potential harms, there are currently no clear indications for the routine use of niacin preparations in combination with statins.[74,75] Therefore, niacin is not considered in this document.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCBs) selectively inhibit voltage-gated L-type channels on cardiac myocytes, cardiac cells in the sinoatrial and atrioventricular nodes, and vascular smooth muscle cells peripherally. CCBs have a significant role in the treatment of several cardiovascular conditions such as hypertension, chronic stable angina, and supraventricular arrhythmias.[76–78] Because of clearly defined cardiovascular benefits, CCBs are often coprescribed in patients treated with statin therapy.

There are 2 recognized subclasses of CCBs based on their chemical structure, the dihydropyridines (eg, amlodipine, felodipine) and the nondihydropyridines (diltiazem and verapamil). Dihydropyridine CCBs have more specific selectivity for vascular smooth muscle cells peripherally than cardiac cells, so their primary treatment roles are in the treatment of hypertension and chronic stable angina. Nondihydropyridine CCBs have greater selectivity for myocardial cells, resulting in a decrease in sinoatrial and atrioventricular node conduction and decreased myocardial contractility. Nondihydropyridine CCBs are used primarily to treat hypertension, chronic stable angina, and supraventricular arrhythmias.

Diltiazem and Verapamil

Diltiazem and verapamil are moderate to weak inhibitors of CYP3A4, as well as substrates of CYP3A4 and P-gp. Increased exposure to simvastatin, atorvastatin, and lovastatin when coadministered with diltiazem and verapamil has been reported.[79–83] In 10 healthy volunteers, diltiazem increased the Cmax of simvastatin by 3.6-fold and simvastatin acid by 3.7-fold ($P<0.05$).[84] The AUC of simvastatin was increased by 5-fold ($P<0.05$) and the elimination $t_{1/2}$ by 2.3-fold ($P<0.05$). In a study of 10 healthy volunteers, diltiazem significantly ($P<0.05$) increased the AUC of lovastatin by 3.6-fold and Cmax from 6±2 to 26±9 ng/mL but did not change the elimination $t_{1/2}$.[85] Rhabdomyolysis has been reported in a patient on stable treatment with atorvastatin after diltiazem was added for the new diagnosis of atrial fibrillation.[86] In animal studies, simvastatin significantly enhanced the oral bioavailability of verapamil.[87]

Amlodipine

Amlodipine is a substrate of CYP3A4, and its plasma concentrations may be affected by inhibitors or inducers of this enzyme. Coadministration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared with simvastatin alone.[29] However, coadministration of amlodipine with 80 mg atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.[24] In the ALLHAT-LLT trial (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Treatment), 1122 patients (21.7%) took amlodipine in combination with pravastatin, and no incidence of muscle-related toxicity was reported.[88]

The FDA-approved product labeling for amlodipine indicates that there may be an increased risk of muscle-related toxicity when combined with simvastatin.[89] The approved labeling for diltiazem recommends the use of non–CYP3A4-metabolized statins in combination with diltiazem if possible.[90] Current labeling advises that the dose of simvastatin not exceed 10 mg daily when coprescribed with diltiazem or verapamil in adult patients and the dose of lovastatin not exceed 20 mg daily[26,29] The product labeling for atorvastatin does not include dose adjustments for combination therapy with amlodipine, diltiazem, or verapamil.[24] However, labeling for verapamil recommends that with coadministration lower doses of atorvastatin may be considered.[91]

Summary of Evidence for Statin-CCB DDIs

Pharmacokinetic data suggest a minor increase in statin exposure with coadministration of amlodipine and lovastatin or simvastatin, and combination therapy may be considered. There is no evidence of significant interaction when amlodipine is coadministered with other statins. Combination therapy with atorvastatin and diltiazem results in a minor increase in statin exposure and is reasonable in appropriate patients. Interactions between diltiazem and either lovastatin or simvastatin are associated with moderate increases in statin exposure, although combination therapy may be considered in appropriate patients. DDIs with verapamil and lovastatin or simvastatin are also of moderate intensity. Combination therapy may be considered when the potential for benefit outweighs potential risks.

Recommendations for Statin-CCB DDIs

1. Pharmacokinetic data suggest a minor increase in statin exposure with coadministration of either lovastatin or simvastatin with amlodipine, and these combination therapies may be considered.
2. There is no evidence of significant interaction when amlodipine is coadministered with atorvastatin, pitavastatin, rosuvastatin, fluvastatin, and pravastatin, and these combination therapies may be considered.

3. Combination therapy with atorvastatin and diltiazem results in a minor increase in statin exposure and this combination therapy is reasonable.

4. Diltiazem administered with either lovastatin or simvastatin is associated with moderate increases in statin exposure, although these combination therapies may be considered in appropriate patients.

5. Coadministration of verapamil with lovastatin or simvastatin results in moderate increases in statin exposure. Therefore, these combination therapies may be considered when the potential for benefit outweighs potential risks.

6. Doses of lovastatin or simvastatin >20 mg daily when coadministered with amlodipine are not recommended.

7. A non–CYP3A4-metabolized statin is preferred in combination with diltiazem or verapamil.

8. Doses of simvastatin >10 mg daily and doses of lovastatin >20 mg daily. when used with diltiazem or verapamil are not recommended. However, it should be noted that verapamil labeling recommends a higher dose limit of lovastatin of 40 mg daily when coadministered with verapamil.

9. For adult patients on stable therapy with simvastatin 80 mg daily (a dose that is no longer recommended for general use), clinicians should change to a non-CYP3A4 statin such as pravastatin, rosuvastatin, or pitavastatin if therapy with diltiazem or verapamil is initiated.

10. Caution should be exercised with statin-CCB combination therapy in patients of various ethnic backgrounds, particularly those of Asian descent.

ANTIARRHYTHMIC AGENTS

In patients with known ASCVD and multiple risk factors, antiarrhythmic agents may be prescribed for the management of supraventricular and ventricular arrhythmias, particularly atrial fibrillation and ventricular tachycardia/fibrillation. Concomitant therapy with statins and amiodarone or dronedarone is common, and DDIs are an important consideration.[92] Amiodarone and dronedarone are Vaughan-Williams class III antiarrhythmic drugs, which uniquely affect multiple ion channels and exhibit properties of class I through IV agents.[93] Both amiodarone and dronedarone prolong the duration of the action potential and the refractory period of atrial, nodal, and ventricular cardiac fibers.

Amiodarone

Amiodarone has been used for >50 years as an antiarrhythmic and antianginal medication. It is the most effective medication in maintaining normal sinus rhythm in patients with atrial fibrillation. Amiodarone is metabolized by CYP3A4 and CYP2C8 to desethylamiodarone.

Amiodarone and its metabolite are inhibitors of CYP3A4 (irreversibly and weakly for amiodarone; in a competitive manner and potently for desethylamiodarone) and P-gp (in a reversible manner), causing concern for interactions when used concomitantly with statins metabolized by this CYP450 pathway or substrates of the P-gp efflux transporter. There is also inhibition of CYP1A2, CYP2C9, and CYP2D6.[94]

There have been multiple reports of toxicity when amiodarone is prescribed in combination with statins that are CYP3A4 substrates, particularly simvastatin.[92,95–102] Pharmacokinetic data show an ≈75% increase in simvastatin and the active simvastatin acid AUC and Cmax when amiodarone and simvastatin are coadministered, but no significant pharmacokinetic interaction between amiodarone and pravastatin has been demonstrated.[103] In the SEARCH (Study Evaluating Additional Reduction in Cholesterol and Homocysteine), of 12 064 survivors of myocardial infarction, 8 cases of myopathy and 7 cases of rhabdomyolysis were identified in patients on simvastatin 80 mg in combination with amiodarone versus zero cases in patients allocated to simvastatin 20 mg (relative risk, 8.8; 95% confidence interval, 4.2–18.4).[104] As a result of an early interim review by the Data Safety Monitoring Board for SEARCH, changes to the labeling for simvastatin were approved in May 2002 recommending that the dose of simvastatin be limited to 20 mg in patients concomitantly taking amiodarone.[29]

In large clinical outcomes trials of amiodarone in patients conducted in the 1990s, concomitant therapy with statins is not mentioned, and no cases of muscle-related toxicity were reported.[105–108] In another trial in which 19% of patients were taking concomitant statin and amiodarone, again no cases of rhabdomyolysis were reported.[109] However, specific statins and doses were not reported. A review of the FDA database from 1990 through March 2002 examined cases of adverse events reported for concomitant therapy with amiodarone and simvastatin, atorvastatin, or pravastatin.[92] Muscle-related toxicity was the most commonly reported adverse event with combination therapy (77%) and tended to occur in older male patients taking multiple other medications. The percentages of simvastatin and atorvastatin adverse events reported in which amiodarone was concomitantly used were 1.0% and 0.7%, respectively (P=NS between statins). In contrast, the percentage of pravastatin adverse events in which amiodarone was used was only 0.4% (P<0.05 versus simvastatin). Patients on simvastatin-amiodarone combination therapy were more likely to be hospitalized and were on a higher statin dose compared with atorvastatin-amiodarone–treated patients.

Despite labeling changes for simvastatin that occurred in 2002 to limit doses when used in combination with amiodarone and other select medications,

coadministration continues to occur. In a retrospective analysis of a longitudinal prescription claims database of concurrent statin-amiodarone therapy dispensed during 2006, nearly half (44%) of patients on amiodarone were also prescribed a statin (atorvastatin, 23.5%; simvastatin, 13.3%).[110] A safety initiative was begun in a Veterans Affairs Medical Center in November 2008 to assess the number of patients with active prescriptions with both simvastatin at doses >20 mg daily and amiodarone.[111] Of the 17 760 patients with an active prescription for simvastatin 40 or 80 mg, 92 patients (0.52%) were also on therapy with amiodarone. The mean duration of simvastatin 40 or 80 mg daily and amiodarone was 43 months. In an observational, retrospective analysis of inpatients on a cardiology service in a teaching university hospital, potential statin-drug interactions were reviewed from July 2007 to June 2008.[112] Of the 1641 hospitalized patients, 572 were prescribed a statin, most commonly simvastatin. The exposure to potential statin-drug interactions was 26.1% at admission and 24.4% at discharge. Amiodarone was the most common CYP450 3A4 inhibitor coprescribed with statins.

The FDA-approved labeling for rosuvastatin, pravastatin, fluvastatin, and pitavastatin does not indicate that a dose adjustment in necessary when coadministered with amiodarone.[25,27,28,30] Additionally, no dose adjustments are recommended for atorvastatin because data suggest that severe interactions with amiodarone are less likely to occur than with other statins metabolized via CYP3A4 (simvastatin, lovastatin).[24,26,29] However, labeling indicates that the dose of lovastatin should not exceed 40 mg daily when prescribed in combination with amiodarone and simvastatin and should be limited to no more than 20 mg daily.

Dronedarone

Dronedarone is a class III antiarrhythmic indicated to reduce the risk of hospitalization for atrial fibrillation in patients who are currently in sinus rhythm and have a history of paroxysmal or persistent atrial fibrillation.[94,113] Dronedarone is a structurally related, non-iodinated derivative of amiodarone. Dronedarone is available only for oral administration, and the absolute bioavailability is increased 2- to 3-fold when administered with food, particularly a high-fat meal. Dronedarone is less lipophilic than amiodarone with a smaller volume of distribution.[114] Peak plasma concentrations are reached within ≈3 to 6 hours, and steady state is achieved within 4 to 8 days. The elimination $t_{1/2}$ is 13 to 19 hours.

Dronedarone is extensively metabolized by CYP3A4 to >30 metabolites, most inactive. The N-debutyl metabolite is weakly active and only 1/10th to 1/3rd as potent as dronedarone. It is excreted primarily as metabolites

in the feces (84%), with only 6% excreted in the urine. Dronedarone is a moderate inhibitor of CYP3A4 and CYP2D6 and has the potential to inhibit P-gp transport. There are no significant effects on OAT1, OAT3, OCT1, CYP1A2, CYP2C9, CYP2C19, CYP2C8, or CYP2B6. As a moderate CYP3A4 inhibitor, dronedarone significantly increases the Cmax and AUC of simvastatin and simvastatin acid.[94] However, no dose adjustments of dronedarone are necessary when given in combination with atorvastatin or simvastatin.

Concomitant statin-dronedarone therapy was reported in 22% to 39% of patients in the ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid or the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter), EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm), ADONIS (American-Australian-African Trial With Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm), and DIONYSOS (Randomized, Double-Blind Trial to Evaluate the Efficacy and Safety of Dronedarone [400 mg bid] Versus Amiodarone [600 mg qd for 28 days, Then 200 mg qd Thereafter] for at Least 6 months for the Maintenance of Sinus Rhythm in Patients With AF) trials.[114–116] Despite frequent statin-dronedarone combination therapy, none of these studies provided information on specific statins prescribed or the relationship of combination therapy and adverse events. There were no reports of muscle-related adverse effects.

The FDA-approved labeling for rosuvastatin, atorvastatin, pitavastatin, fluvastatin, and pravastatin does not recommend any contraindications or dose adjustments when coadministered with dronedarone.[24,25,27,28,30] Current FDA labeling recommends a dose limit of simvastatin 10 mg daily and lovastatin 20 mg daily when combined with dronedarone.[26,29]

Digoxin

Digoxin is used as a rate-controlling agent in patients with atrial fibrillation and as an inotrope in patients with heart failure with reduced ejection fraction. In heart failure, digoxin exerts its effect by inhibiting the sodium-potassium ATPase pump in myocardial cells. This produces a transient increase in intracellular calcium that in turn results in an influx of calcium to increase myocardial contractility. In atrial fibrillation, digoxin suppresses atrioventricular node conduction to increase the effective refractory period and to decrease conduction velocity. Digoxin has a bioavailability of ≈60% to 80%.[117] The onset of effect is observed within 1 to 3 hours after oral absorption, and digoxin has an elimination half-life of 36 to 48 hours. Approximately 50% to 70% of the drug is excreted unchanged in the urine. The metabolism of di-

goxin is not dependent on the CYP450 system because it is not known to induce or inhibit any of these enzymes. Metabolism of digoxin is primary by gut bacteria.

In a study that included 24 healthy volunteers, the addition of atorvastatin 80 mg to digoxin resulted in an average increase of 20% in the Cmax of digoxin and an average 15% increase in the AUC of digoxin.[118] However, lower doses of atorvastatin (10 mg) combined with digoxin did not alter the pharmacokinetics of digoxin.[99] Atorvastatin appears to be the only statin that is reported to have this interaction. The mechanism is not fully understood but may be mediated by an impact of atorvastatin on the intestinal secretion of digoxin medicated by the P-gp efflux transporter, resulting in increased digoxin absorption.[118]

Summary of Evidence for Statin–Antiarrhythmic Agent DDIs

On the basis of pharmacokinetic and observational data and adverse events reported in randomized, controlled trials, combination therapy with amiodarone and rosuvastatin, atorvastatin, pitavastatin, fluvastatin, or pravastatin is reasonable. Coadministration of amiodarone and dronedarone with either lovastatin or simvastatin may be considered. There are no known clinically significant interactions between dronedarone and other statins.

Digoxin coadministration with any statin is reasonable if clinically indicated.

Recommendations for Statin–Antiarrhythmic Agent DDIs

1. Combination therapy with rosuvastatin, atorvastatin, pitavastatin, fluvastatin, or pravastatin and amiodarone is reasonable.
2. When used in combination with amiodarone, the dose of lovastatin should not exceed 40 mg daily and the dose of simvastatin should not exceed 20 mg daily.
3. Digoxin coadministration with any statin is reasonable if clinically indicated.
4. Higher doses of lovastatin and simvastatin may be considered if clinically indicated with close monitoring for muscle-related toxicity.
5. In patients who are already stable on lovastatin 80 mg daily or simvastatin ≥40 mg daily in combination with amiodarone, continuation of combination therapy is reasonable without dose modifications.
6. Dronedarone significantly increases systemic exposure of both the prodrug simvastatin and the active metabolite simvastatin acid. Therefore, the dose of simvastatin should be limited to 10 mg daily when used in combination with dronedarone.
7. Although there are no specific studies evaluating lovastatin and dronedarone, it is anticipated that dronedarone may also increase the exposure of lovastatin within the same range as simvastatin.
8. There are no clinically significant interactions between dronedarone and other statins, and these combination therapies are reasonable.
9. Atorvastatin is the only statin that appears to be associated with a potential DDI when used in combination with digoxin. On the basis of the available data, patients on higher doses of atorvastatin may be at increased risk of digoxin toxicity, and closer monitoring for digoxin toxicity is recommended.

ANTIANGINAL AGENTS

Ranolazine

Ranolazine is a unique antianginal medication with a mechanism of action that remains unknown. Ranolazine is metabolized predominantly by CYP3A4 and to a lesser extent by CYP2D6, and it is also a weak inhibitor of CYP3A4.[119] As a result, some statins, particularly simvastatin, are of concern for drug interactions. Simvastatin-ranolazine combination therapy results in an ≈50% increase in AUC and doubling of Cmax of simvastatin.[120] The impact of this increased statin exposure on the risk of muscle-related toxicity in not clear. However, there have been at least 3 case reports, some of which are in elderly patients.[81,121–123] Clinically significant DDIs with ranolazine and statins other than simvastatin have not been reported.[124–127]

The FDA-approved product labeling recommends that the maximum dose of simvastatin be limited to 20 mg daily when given in combination with ranolazine. Although evidence for statin interactions with ranolazine is most abundant with simvastatin, reasonable concern could be extrapolated to other statins that are metabolized by CYP3A4. Caution is recommended when lovastatin is used in combination with ranolazine, although no specific dose limitation is recommended.[26]

Summary of Evidence for Statin-Ranolazine DDIs

Coadministration of ranolazine with rosuvastatin, atorvastatin, pitavastatin, fluvastatin, and pravastatin may be considered if clinically indicated. Combination therapy with ranolazine and simvastatin or lovastatin may be considered.

Recommendations for Statin-Ranolazine DDIs

1. Coadministration of rosuvastatin, atorvastatin, pitavastatin, fluvastatin, or pravastatin with ranolazine may be considered if clinically indicated.

2. The dose of simvastatin should be limited to 20 mg daily when coprescribed with ranolazine, and doses above this limit are not recommended.

3. Given that simvastatin and lovastatin undergo similar metabolism, it is reasonable to limit the dose of lovastatin to 20 mg daily when combined with ranolazine.

ANTICOAGULANTS

Warfarin

Warfarin is a vitamin K antagonist and the most commonly used oral anticoagulant with important roles in treating many patients with cardiovascular disease. It is also a classic example of a medication with a narrow therapeutic window and is subject to significant DDIs. Interactions between statins and warfarin are modest when viewed in the context of other potential interacting medicines; however, both classes of medications are commonly used. Potential interactions are thought to act predominantly via drug metabolism through a contribution of protein-binding effects. Warfarin is metabolized to inactive products primarily by CYP2C9, which has a minor role in the metabolism of fluvastatin and rosuvastatin.[128] The majority of reports and studies have focused on the potential for impact on the anticoagulant effects of warfarin; however, there are only rare reports of increased adverse risks of statins such as muscle-related toxicity.[129]

Several studies have demonstrated reduced warfarin dose requirements, increases in the international normalized ratio (INR), or changes in warfarin metabolite concentrations when coadministered with simvastatin.[130–133] The magnitude of effect varies, but some reports indicate up to a 30% change in INR, and 1 report showed a doubling of the number of subjects with supratherapeutic INRs. This may be specific to genetic subgroups with low functioning CYP2C9. An analysis of >1100 patients indicated that simvastatin was associated with a 29% reduced warfarin requirement in CYP2C9*3 carriers and very little change for noncarriers.[134] This may explain the varying magnitude of effect in clinical studies.[135] Case reports of INR changes after statin initiation have been published with fluvastatin,[136–138] lovastatin,[139] and rosuvastatin.[140] One study indicated that lovastatin and simvastatin affected warfarin metabolite concentrations.[131] There have been several investigations into a potential rosuvastatin-warfarin interaction. Two studies have shown a significant increase in INR, whereas 1 study did not.[141–143] The mechanism of the rosuvastatin interaction is not completely established, although CYP2C9 seems a likely contributor. Several studies have demonstrated no interaction with warfarin for pitavastatin[130,142] and atorvastatin.[144] No clinically significant drug interac-

tions have been reported or are anticipated with statins and the novel anticoagulants dabigatran, apixaban, rivaroxaban, and edoxaban.

Summary of Evidence for Statin-Warfarin DDIs

There is no clinically significant increase in statin exposure with coadministration of warfarin, and combination therapy is useful when clinically indicated.

Recommendations for Statin-Warfarin DDIs

1. Use of a statin with warfarin as combination therapy is useful when clinically indicated.

2. The INR should be monitored more closely after the initiation of a statin or a change in statin dose. The impact on the INR appears lowest for pitavastatin and atorvastatin.

ANTIPLATELET AGENTS

Ticagrelor

Ticagrelor is an oral, reversible, noncompetitive inhibitor of the platelet adenosine diphosphate receptor $P2Y_{12}$ on the surface of platelets. It is currently approved for use in patients with acute coronary syndromes to reduce the risk of thrombotic cardiovascular events.[145] Ticagrelor is rapidly absorbed and exhibits linear and predictable pharmacokinetics. The Cmax is reached in 1 to 4 hours after oral administration. The bioavailability of ticagrelor is ≈36% with an elimination $t_{1/2}$ of ≈7 hours for the parent drug and 9 hours for the active metabolite. Ticagrelor is metabolized predominantly by CYP3A4 and to a lesser extent by CYP3A5. Ticagrelor is also a P-gp substrate. In vitro metabolism studies demonstrate that ticagrelor and its active metabolite are weak inhibitors of CYP3A4 and P-gp.

Clinical trials have evaluated pharmacokinetic interactions with ticagrelor coadministered with either atorvastatin 80 mg daily or simvastatin 80 mg daily. The atorvastatin-ticagrelor combination resulted in a 23% increase in the Cmax of atorvastatin and a 36% increase in the AUC. However, these changes were not statistically significant.[146] The combination of simvastatin-ticagrelor resulted in a mean increase in Cmax of simvastatin of 81% and in the AUC of 56% (90% confidence interval, 1.30–1.87). Some subjects were observed to have greater increases in exposure to simvastatin with 2- to 3-fold increases in the Cmax and the AUC. The increases in Cmax and the AUC are likely attributable to inhibition of CYP3A4 by ticagrelor. Because of the reliance on CYP3A4 of lovastatin for metabolism that is similar to that of simvastatin, it is likely that significant increases would also be expected with lovastatin. Of note, there were no clinically significant changes in the pharmacokinetic pa-

rameters of ticagrelor when coadministered with either of these agents. Despite the use of CYP3A4-metabolized statins in 90% of participants in the PLATO trial (Platelet Inhibition and Patient Outcomes), with simvastatin being the predominantly used statin, these data cannot be used to assess clinically significant interactions between ticagrelor and CYP3A4-metabolized statins because concomitant therapy with simvastatin and lovastatin was restricted to a maximum of 40 mg daily. In addition, information on the dose of statins used in patients receiving ticagrelor was not routinely collected in the PLATO trial.[147–149] No clinically significant drug interactions have been reported with the other P2Y$_{12}$ inhibitors, prasugrel or clopidogrel, in combination with statins.

Summary of Evidence for Statin-Ticagrelor DDIs

Coadministration of ticagrelor and atorvastatin results in only a minor increase in statin systemic exposure, and the combination is reasonable for appropriate patients. Combination therapy with ticagrelor and lovastatin or simvastatin may be considered.

Recommendations for Statin-Ticagrelor DDIs

1. Coadministration of atorvastatin with ticagrelor results in only a minor increase in statin systemic exposure and is reasonable for appropriate patients.
2. When prescribed in combination with ticagrelor, the dose of simvastatin and lovastatin should not exceed 40 mg daily.
3. There are no reports of significant interactions when ticagrelor is used in combination with pravastatin, fluvastatin, pitavastatin, or rosuvastatin, and no dosing restrictions are needed.

VASOPRESSIN RECEPTOR ANTAGONISTS

Conivaptan

Conivaptan is an intravenous dual vasopressin receptor (V$_{1A}$ and V$_2$) antagonist that is currently approved to raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia.[150] Conivaptan is extensively bound to plasma proteins and has an average elimination t$_{1/2}$ of 5.3 hours. After intravenous administration, ≈83% of the dose is excreted in the feces and 12% in the urine.

Conivaptan is both a substrate and a potent inhibitor of CYP3A4. This isoenzyme has been identified as the sole cytochrome P450 isoenzyme responsible for metabolism of conivaptan. In clinical studies, conivaptan 30 mg daily resulted in a 3-fold increase in the AUC of simvastatin as a result of decreased metabolism.[150] In clinical trials with conivaptan, there have been 4 case reports of increased creatinine kinase/muscle-related toxicity and

2 cases of rhabdomyolysis in patients taking concomitant statin therapy. These cases involved simvastatin, lovastatin, and gemfibrozil/cerivastatin. No clinically significant interactions have been noted between the oral V2 receptor antagonist (tolvaptan) and lovastatin.[151]

The FDA-approved labeling states that the combination of conivaptan with lovastatin or simvastatin should be avoided. Additionally, in patients currently receiving lovastatin or simvastatin, these agents should be held if undergoing treatment with conivaptan. FDA labeling also states that lovastatin or simvastatin may be reinitiated at least 1 week after the infusion of conivaptan is completed.

Summary of Evidence for Statin-Conivaptan DDIs

The combination of conivaptan and lovastatin or simvastatin is potentially harmful and should be avoided. Atorvastatin, pravastatin, fluvastatin, rosuvastatin, or pitavastatin may be considered in combination with conivaptan when clinically indicated.

Recommendations for Statin-Vasopressin Receptor Antagonist DDIs

1. The combination of lovastatin or simvastatin with conivaptan is potentially harmful and should be avoided.
2. Atorvastatin, pravastatin, fluvastatin, rosuvastatin, or pitavastatin may be considered in combination with conivaptan when clinically indicated.
3. In the unlikely event of a need to use a statin while a patient is receiving conivaptan infusion, either atorvastatin or a statin that is not metabolized by CYP3A (pravastatin, fluvastatin, rosuvastatin, or pitavastatin) may be considered.
4. Tolvaptan may be used in combination with any statin at any approved doses.

IMMUNOSUPPRESSIVE AGENTS

In heart transplant recipients, statins are a cornerstone in immunosuppressant pharmacotherapy. The International Society of Heart and Lung Transplantation recommends the use of statins beginning 1 to 2 weeks after heart transplantation regardless of cholesterol concentrations because statins have been associated with a reduction in mortality, rejection associated with hemodynamic compromise, and frequency and severity of coronary artery vasculopathy.[152–155] Additionally, between 60% and 81% of heart transplant recipients exhibit lipid abnormalities.[156,157] Although the majority of data in this population have been with simvastatin (5–20 mg daily) and pravastatin (20–40 mg daily), considerable controversy exists on which statin and what doses to use because of potential DDIs with the

calcineurin inhibitors (eg, cyclosporine and tacrolimus) that could lead to myopathy or rhabdomyolysis.[153–156,158]

CALCINEURIN INHIBITORS

Cyclosporine and Tacrolimus

Cyclosporine and tacrolimus are extensively metabolized by hepatic and intestinal CYP3A4, act as both inhibitors and substrates of P-gp, and inhibit OATP1B1.[22,159,160] As a result of their metabolism, both calcineurin inhibitors are predisposed to potential pharmacokinetic interactions with statins because atorvastatin, simvastatin, and lovastatin are substrates of CYP3A4; atorvastatin, lovastatin, pravastatin, and simvastatin are substrates of P-gp; and all current statins on the US market are substrates for OATP1B1.[22] Simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, pitavastatin, and rosuvastatin have been associated with 6- to 8-, 5- to 20-, 6- to 15-, 5- to 10-, 2- to 4-, 5-, and 7-fold increases in the AUC, respectively, when administered with cyclosporine.[161] In addition, simvastatin, lovastatin, atorvastatin, and pravastatin have all been associated with rhabdomyolysis when used in combination with cyclosporine.[162] FDA-approved product labeling recommends avoiding atorvastatin, lovastatin, pitavastatin, and simvastatin in combination with cyclosporine.[24,26,29,30,163]

More studies have reported DDIs with cyclosporine than with tacrolimus, in large part because of its earlier availability for clinical use. Because of the metabolism of tacrolimus, the patterns of statin DDIs would be expected to be similar to those of cyclosporine.[158] Unfortunately, limited data exist on tacrolimus and statin interactions. One open-label evaluation of 13 healthy volunteers suggested that after 4 days of therapy with atorvastatin 40 mg daily, 2 doses of tacrolimus had no impact on the atorvastatin pharmacokinetics.[164]

Target of Rapamycin Inhibitors

Sirolimus and everolimus are both macrolide immunosuppressants that also have extensive hepatic and intestinal metabolism by CYP3A4 and P-gp.[158] As with tacrolimus, extremely limited data exist on the interactions between target of rapamycin inhibitors and statins. Because of their metabolism, it is feasible that interactions with statins could occur and result in tissue injury. In case reports and case series, the use of sirolimus in combination with statins has been associated with muscle-related toxicity, including rhabdomyolysis.[165–167] Only 1 randomized, open-label, 3-way crossover, single-dose study in 24 healthy volunteers has suggested that everolimus had no effect on the AUC of atorvastatin 20 mg or pravastatin 20 mg.[168] Nonetheless, until further data exist, the panel suggests that the dosing and choice of statin should follow the recommendations for the calcineurin inhibitors.

Summary of Evidence for Statin–Immunosuppressive Agent DDIs

Combination therapy of cyclosporine, tacrolimus, everolimus, or sirolimus with lovastatin, simvastatin, and pitavastatin is potentially harmful and should be avoided. The coadministration of tacrolimus and lovastatin, simvastatin, or pitavastatin is potentially harmful and should be avoided. The combination of cyclosporine, everolimus, or sirolimus with rosuvastatin, atorvastatin, fluvastatin, or pravastatin may be considered.

Recommendations for Statin–Immunosuppressive Agent DDIs

1. Combination therapy of lovastatin, simvastatin, or pitavastatin with cyclosporine, everolimus, tacrolimus, or sirolimus is potentially harmful and should be avoided.
2. The combination of rosuvastatin, atorvastatin, fluvastatin, or pravastatin with cyclosporine, tacrolimus, everolimus, or sirolimus may be considered.
3. The combination of cyclosporine, tacrolimus, everolimus, or sirolimus with daily doses of fluvastatin, pravastatin, and rosuvastatin should be limited to 40, 20, and 5 mg daily, respectively.
4. The dose of atorvastatin >10 mg daily when coadministered with cyclosporine, tacrolimus, everolimus, or sirolimus is not recommended without close monitoring of creatinine kinase and signs or symptoms of muscle-related toxicity.

MISCELLANEOUS AGENTS

Colchicine

There has been renewed interest in the anti-inflammatory properties of colchicine for the management of pericarditis and as a potential role in the prevention of cardiovascular events.[169]

Interactions between colchicine and statins that undergo several different metabolic pathways have been described in the literature, suggesting that the underlying cause is likely multifactorial. Colchicine undergoes hepatic demethylation by CYP3A4. It does not appear to impair CYP3A4 activity; thus, the DDI between colchicine and statins is likely attributable to competitive inhibition, which may result in increased concentrations of both substrates. Additionally, colchicine is a substrate for P-gp. Colchicine likely competes for P-gp–mediated efflux, resulting in accumulation of both substrates in myocytes and other target cells. Inhibition of P-gp by atorvastatin or lovastatin may further increase serum

colchicine concentrations.[15] Colchicine does not appear to interact with OATP drug transporters. A pharmacodynamic mechanism may also be partially responsible for the effects observed clinically because myopathy is a well-described adverse effect of both colchicine and statin monotherapy. Evidence suggests that coadministration of colchicine and statin therapy may produce synergistic muscle-related toxicity.

Statin-colchicine combination therapy has not been formally evaluated in clinical trials. It is unclear how specific pharmacokinetic parameters may be affected. However, clinically significant DDIs have been reported with atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin when used in combination with colchicine.[170–182] The DDI between colchicine and simvastatin is the most frequently reported in the literature, having been the subject of 6 cases. In each case, simvastatin-colchicine combination therapy resulted in myopathy, and 1 case progressed to rhabdomyolysis, multiorgan failure, and death.[180] Rosuvastatin is not subject to pathways that interact with colchicine metabolism or disposition, and only limited data support a potential P-gp–mediated interaction with pitavastatin.[19]

The reported incidence of clinically meaningful interactions between colchicine and statin therapy may be deceptively low because both drugs share muscle-related adverse effects. A lack of awareness that colchicine can independently exert myotoxic effects (or be a contributor when coadministered with a statin) may lead clinicians to attribute any muscle-related findings to statin therapy alone. Although the incidence of muscle-related adverse effects was low when colchicine was added to statin therapy for the secondary prevention of cardiovascular events, the doses of colchicine used were much lower than those documented in case reports, suggesting that the DDI may be ameliorated in part by colchicine dose adjustment.[169]

Summary of Evidence for Statin-Colchicine DDIs

Coadministration of colchicine and rosuvastatin, fluvastatin, lovastatin, pitavastatin, and pravastatin is reasonable when clinically indicated. Combination therapy with atorvastatin or simvastatin and colchicine may be considered in appropriate patients.

Recommendations for Statin-Colchicine DDIs

1. Coadministration of rosuvastatin, fluvastatin, lovastatin, pitavastatin, or pravastatin with colchicine is reasonable when clinically indicated.
2. Combination therapy with atorvastatin or simvastatin and colchicine may be considered in appropriate patients.
3. Patients receiving statin-colchicine combination therapy should be monitored closely for muscle-related signs and symptoms, given the potential for synergistic muscle-related toxicity.
4. Colchicine dose adjustments are recommended (loading doses of no more than 0.6–1.2 mg and maintenance doses of 0.3–0.6 mg daily) when used in conjunction with a CYP3A4 or P-gp inhibitor.
5. Dose reductions may be considered for atorvastatin, simvastatin, and lovastatin when coadministered with colchicine, given the potential for interactions mediated by both CYP3A4 and P-gp pathways.
6. In patients with renal impairment, reduced doses of colchicine should be considered when used in combination with a statin.

HEART FAILURE MEDICATIONS

Ivabradine

Ivabradine is a specific inhibitor of the I_f current in the sinoatrial node. Unlike β-blockers, ivabradine does not modify myocardial contractility and intracardiac conduction, even in patients with heart failure with reduced ejection fraction.[183] In 2015, ivabradine was approved in the United States to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic, chronic heart failure with reduced ejection fraction (ejection fraction ≤35%) who are in sinus rhythm with a resting heart rate ≥70 bpm and either are on maximally tolerated doses of β-blockers or have a contraindication to a β-blocker.[184] Although ivabradine is extensively metabolized in the liver and intestines by CYP3A4-mediated oxidation, specific DDI studies have shown no clinically significant effect of ivabradine on the pharmacokinetics and pharmacodynamics of simvastatin.[185] However, available pharmacokinetic and pharmacodynamic data on combination therapy with statins are limited at this time.

Sacubitril/Valsartan

Sacubitril/valsartan is a combination of a neprilysin inhibitor with the angiotensin receptor blocker valsartan. Approved in 2015 in the United States, sacubitril/valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for patients with heart failure with reduced ejection fraction (New York Heart Association class II–IV) and is typically used in combination with other heart failure therapies in place of an angiotensin receptor blocker or angiotensin-converting enzyme inhibitor.[186] Although CYP450 enzyme–mediated metabolism of sacubitril is minimal, in vitro data indicate that sacubitril inhibits OATP1B1, OATP1B3, OAT1, and OAT3 transporters. In a single phase III study, coadministration of sacubitril/valsartan with atorvastatin resulted in an increased Cmax of atorvastatin and its metabolites by up

to 2-fold and AUC by up to 1.3-fold; however, no significant adverse events related to atorvastatin were reported.[187] No dose adjustments are currently proposed for atorvastatin or other statins when coadministered with sacubitril/valsartan in US package labeling.[188] However, further pharmacokinetic studies are needed to fully address statin interactions.

Summary of Evidence for Statin–Heart Failure Medication DDIs

Current data suggest no safety concerns when ivabradine is combined with a statin. In vitro studies indicate that sacubitril/valsartan has the potential to interact with statins that are substrates of OATP1B1, OATP1B3, OAT1, and OAT3.[188] However, the clinical significance of these potential interactions is unknown.

Recommendations for Statin–Heart Failure Medication DDIs

1. Coadministration of a statin at an approved dose with ivabridine is reasonable when clinically indicated.
2. Lower doses of atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, or simvastatin may be considered when used in combination with sacubitril/valsartan.

CONCLUSIONS

Statin medications are commonly prescribed to reduce morbidity and mortality in patients with and at risk for ASCVD events. Statin DDIs in cardiovascular patients are often unavoidable and should be clinically managed. Healthcare providers should be knowledgeable about the dose limits, adverse effects, and monitoring parameters associated with these DDIs to minimize toxicity. A review of all medications that statin-treated patients are taking should be done at each clinical encounter and during transitions of care within a health system so that DDIs can be identified early, evaluated, and managed appropriately by implementing doses adjustments, changing to a safer statin medication, or discontinuing when needed. A thorough understanding of the pharmacokinetics of statins and other select medications that are often prescribed in combination is paramount in ensuring patient safety. Additional medications not reviewed here but of great

importance are the agents used to treat HIV. A review of these drug interactions is beyond the scope of this document. However, because of the extent of these interactions, particularly with statins, the reader is referred elsewhere[189] to assist with this patient population.

FOOTNOTES

Circulation is available at http://circ.ahajournals.org.

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*Modest.
†Significant.

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*Significant.

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Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients With Cardiovascular Disease: A Scientific Statement From the American Heart Association

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