Problems and Pitfalls in Cardiac Drug Therapy

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Medical errors in the care of patients may account for 44,000 to 98,000 deaths per year, and 7,000 deaths per year are attributed to medication errors alone. Increasing awareness among health care providers of potential errors is a critical step toward improving the safety of medical care. Because today's medications are increasingly complex, approved at an accelerated rate, and often have a narrow therapeutic window with only a small margin of safety, patient and provider education is critical in assuring optimal therapeutic outcomes. Providers can use electronic resources such as Web sites to keep informed on drug–drug, drug–food, and drug–nutritional supplements interactions.

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An Institute of Medicine report released in late 1999 brought to the forefront the issue of errors in the care of patients. The report's estimate of deaths ranging from 44,000 to 98,000 per year due to medical errors was a sobering statistic that has fueled the fire of research evaluating potentially safer health care delivery systems.[1] Medication errors alone, in either the inpatient or outpatient setting, account for 7,000 deaths per year. Medication mix-ups and harmful drug interactions are the most common fears cited by patients in a study by the American Society for Health-System Pharmacists.[2]

Table 1
Medications Designated as "High Alert" by JCAHO[5]

Insulin
Opiates/narcotics
Injectable potassium (chloride and phosphate)
Heparin
Concentrated sodium chloride (> 0.9%)

Increasing the awareness of potential errors among health care providers, including physicians, pharmacists, and nurses, is a critical step toward improving the safety of medical care. Today, medications are increasingly complex, approved at an accelerated rate, and often have a narrow therapeutic window, leaving only a small margin of safety. For this reason, patient and provider education is critical in assuring optimal therapeutic outcomes.

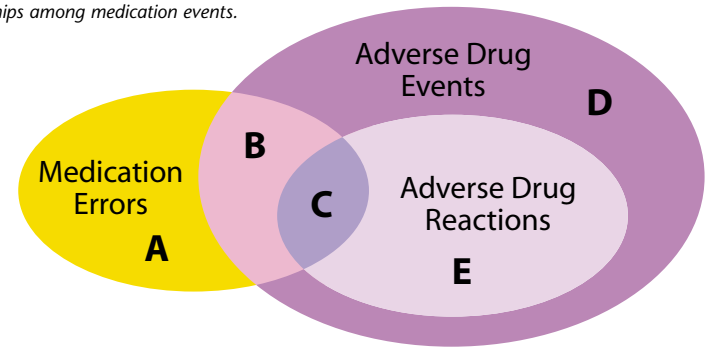
This article will review potential adverse drug events, including interactions, dosing errors, and name confusion for selected medications commonly used in cardiology. Additionally, the patient's role in assuring safe use of medications is discussed, as well as some electronic resources for the practitioner.

Adverse Events

Several terms have been developed to describe unintended medication events. Figure 1 describes the relationship of these terms.[3]

A *medication error* is defined as any error in the process of prescribing, dispensing, or administering a drug, whether or not consequences result (Area A in Figure 1). An *adverse drug event* (ADE) is defined as an injury from a medicine (or lack of an intended medicine), whereas an *adverse drug reaction* (ADR) is any unexpected, unintended, undesired, or excessive response to a medicine when used in the usual manner and dosage (Areas D and E, respectively).[4] Some medication errors, however, do lead to injuries; therefore they are both medication errors and adverse drug events (Area B). Some adverse drug reactions are caused by medication errors (Area C), whereas other adverse drug reactions occur without an actual mistake (Area E).

Figure 1. *Relationships among medication events.*



The Joint Commission on Accreditation of Health Care Organizations (JCAHO) has identified several specific medications as "high alert," meaning they carry a high risk of causing injury when misused (Table 1).[5] Additionally, the 10 most common lethal medication errors in patients (Table 2)[6] have been identified and involve many of the agents listed in Table 1.

Several recommendations have been made specifically for prescribers to reduce the risk of an error occurring (Table 3).[7] Among these recommendations are using legible handwriting in the absence of a physician order entry (POE) system, and avoiding abbreviations. Table 4 lists the top five dangerous abbreviations and their potential misinterpretations.[8]

In addition to medical abbrevia-

Table 2
Ten Most Common Lethal Medication Errors in Hospitalized Patients[6]

Administration of concentrated potassium chloride
Errors in insulin dosing
Administration of IV calcium or magnesium
Inadvertent administration of 50% dextrose
Medication administration despite documented allergy
Miscalculated digoxin dosing in pediatrics
Confusion between vincristine and vinblastine
Administration of concentrated sodium chloride
Administration of IV narcotics
Errors in aminophylline dosing

Table 3
Recommendations for Prescribers[7]

Obtain updated patient-specific information (weight, age, allergies, etc).
Use both generic and brand names when ordering medications.
Avoid abbreviations when ordering medications.
Provide complete and clear directions for patient use.
Include indication with order.

tions often leading to medical errors, look-alike and sound-alike medication names are equally problematic, especially when combined with nonstandard abbreviations. Table 5 describes some potential pitfalls.[7]

Due to their narrow therapeutic window and other characteristics (name, route, or dose) the medications addressed in Table 6 are prone to be involved in errors. These agents were chosen based on their prevalence in the outpatient and inpatient settings as well as from feedback from a practicing cardiologist.[9–13]

Noteworthy Drug Interactions in Cardiology

A recent consumer research survey of 1,000 Americans revealed that 51% of adults take two or more medications (including prescription, nonprescription, and/or herbal supplements and vitamins) each day.[14] In addition, 46% of the respondents took at least one prescription medication per day, and more than 25% took multiple prescription medications.

Because many patients are taking multiple medications, and the number of new medications approved by the U.S. Food and Drug Administration (FDA) increases every year, drug interactions represent a difficult dilemma for health care providers. A *drug interaction* occurs when two or more drugs are taken concurrently and an effect is observed that is different from the anticipated or known effects of either agent given alone. This interaction may result in an increase or decrease in the therapeutic effect of one of the drugs involved. For the most part, drug interactions are of greatest concern following the addition, discontinuation, or change in the dose of an interacting drug. Drug interactions can be further categorized based on their action: drug–drug, drug–food, and drug–herbal supplement/vitamin interactions.

Since 1997, an unprecedented number of prescription drugs have been withdrawn from the market for safety reasons discovered through postmarketing surveillance. Serious drug interactions were involved in the withdrawal of mibefradil (Posicor®), terfenadine (Seldane®), astemizole (Hismanal®) and cisapride (Propulsid®).

The classification of drug interactions is based on their involvement with the pharmacokinetic or pharmacodynamic properties of a drug.[15] Pharmacokinetic interactions involve alterations in the absorption, distri-

Table 4
Top Five Types of Toxic Abbreviations and Potential Misinterpretations[8]

Abbreviation	Errors
U = units	Mistaken as a "zero" or a number 4, resulting in overdoses of insulin and heparin, for example.
IU = international units	Mistaken as "IV" (intravenous).
SC or SQ = subcutaneous	Mistaken as "SL" (sublingual).
& = and	Mistaken for a number, especially when written close to a number.
/ = slash mark	Mistaken for a "1."
μg = micrograms	Mistaken for mg (milligrams).
Q.D. = every day	The period after the Q has been misinterpreted as an "I," resulting in QID dosing.
QOD = every other day	Misinterpreted as daily or QID if the O is unclear.
AU, AS, AD = both ears, left ear, right ear	Misinterpreted as "OU," "OS," or "OD" for both eyes, left eye, right eye.
D/C = discharge or discontinue	Premature discontinuation of a medication when patient discharge was intended.
HS = half strength	Misinterpreted as "hs," hour of sleep.

Table 5
Look-Alike/Sound-Alike Medications[7]

Atrovent® Inhaler (ipratropium HCl)	Alupent® Inhaler (metaproterenol sulfate)
Dicloxacillin 100 mg	Doxycycline 100 mg
Xanax®	Zantac®
Cefuroxime	Cefotaxime
Zostrix® (capsaicin)	Zovirax® (acyclovir)
Lantus® (new long-acting insulin)	Lente Insulin
Atgam (antithymocyte globulin equine)	Thymoglobulin (antithymocyte globulin rabbit)
Folinic acid (leucovorin)	Folic acid
Diamox® (acetazolamide)	Diabinese® (chlorpropamide)
Quinine 200 mg PO	Quinidine 200 mg PO
Lamotrigine 150 mg PO	Lamivudine 150 mg PO
Vinblastine	Vincristine
Sulfasalazine 500 mg QID	Sulfadiazine 500 mg QID
Indapamide 2.5 mg PO	Isradipine 2.5 mg PO
Norvasc® (amlodipine) 10 mg PO	Navane® (thiothixene) 10 mg PO
Hydroxyzine 25 mg PO	Hydralazine 25 mg PO
Lasix (furosemide) 20 mg PO QD	Prilosec (omeprazole) 20 mg PO QD
Klonopin (clonazepam) 0.5 mg	Clonidine 0.5 mg PO
Coumadin (warfarin)	Kemadrin (procyclidine)
Cardene (nicardipine)	Codeine
Norflox (norfloxacin)	Norflex® (orphenadrine)
AZT	Zidovudine, azathioprine, or aztreonam
5-FU vs. 5-FC	Fluorouracil vs. flucytosine
HCT	Hematocrit or hydrochlorothiazide

bution, metabolism, or elimination of drugs, resulting in a change in plasma/tissue drug concentration, onset of action, or half-life. Like all other types of drug interactions, pharmacokinetic interactions between drugs may or may not result in altered pharmacologic response or therapeutic effect.

Drug absorption may be affected by a number of factors, including the following[16,17]:

- binding in the GI tract;
- alterations in GI motility;
- alterations in GI pH;
- alterations in intestinal flora;
- alterations in drug metabolism within the intestinal wall;
- alterations in GI blood flow.

Most clinically important interactions involving absorption result from the binding of drugs in the GI tract, or the formation of a nonabsorbable complex by chelation or ion exchange.[16] Some agents with a large surface area can adsorb or bind other drugs on their surface, thus preventing passage of the drug across the wall of the intestine. Examples of such agents include activated charcoal, kaolin-pectin, and antacids. The interaction between certain quinolone antibiotics (eg, ciprofloxacin) and antacids or dairy products containing di- and trivalent cations is an example of chelation. Ion exchange resins, such as cholestyramine and colestipol, not only bind bile salts in the intestine but can inhibit the absorption of many drugs, including warfarin, digoxin, and thyroid replacement. These types of interactions can be avoided by separating drug administration times between the interacting drugs.

Drug distribution throughout the body is affected primarily by lipid solubility and protein binding. When two or more highly protein-bound drugs are administered concurrently, competitive binding for the same site may result in displacement of one of the drugs from protein binding, increasing the amount of "active" drug in the blood. This type of interaction is usually short-lived, because increasing the concentration of free drug increases the amount available for metabolism and excretion. Some drug interactions result from drug

Table 6
Common Cardiac Medications and Potential Pitfalls[11,12]

Medication	Potential Pitfalls
Abciximab (and other GPIIb/IIIa inhibitors–eg, eptifibatide, tirofiban)	Potential for dosing/administration errors, especially in places where all agents are available simultaneously.
Amiodarone	Confusion between amrinone (Inocor®), an inotrope, and amiodarone (Cordarone®), an antiarrhythmic with negative chronotropic effects that have caused deaths of some patients. Amrinone recently renamed "inamrinone" to decrease potential for error.
Atorvastatin (and other HMG-CoA reductase inhibitors–simvastatin, lovastatin, fluvastatin, etc)	Potential for rhabdomyolysis when used in combination with a number of medications, including protease inhibitors.
Clonidine	Potential for dosing errors when not written clearly (eg, 3 mg vs 0.3 mg).
Digoxin	Potential for dosing errors when not written clearly.
Heparin	Potential for dosing errors when "units" is abbreviated as "u" and is misinterpreted as a zero.
Isosorbide dinitrate	Potential confusion between Plendil® (felodipine) and Isordil® (isosorbide dinitrate) when poorly written.
Nifedipine	Potential for acute myocardial infarction or cerebrovascular ischemia secondary to administration of SL nifedipine.[13]
Potassium chloride	Potential for lethal arrhythmias due to excessive rate of administration (eg, IVP concentrated KCl).
Quinidine	Potential confusion with quinine when not clearly written.
Warfarin	Potential for anaphylaxis due to administration of phytonadione IV.

displacement from its receptor site by another drug. For instance, quinidine can displace digoxin from binding sites in the skeletal muscle, increasing the serum concentration of digoxin. Displacement reactions bear clinical significance only if the displaced drug is normally highly protein-bound (eg, warfarin, phenytoin), has a small volume of distribution, or has a narrow therapeutic index (eg, digoxin).[17]

Drug metabolism occurs primarily via the enzyme system known as the cytochrome P-450 (CYP-450) system. The CYP-450 enzymes are further subdivided based on the similarity of the amino acid sequences of the encoded P-450 isoenzyme protein.[18] Although the highest levels of CYP-450 activity are found in the liver, they are present in most tissues, including the small intestine, kidneys, lungs, skin, and brain. These enzymes are responsible for phase I metabolism (eg, oxidation, reduction, and hydrolysis) of drugs. Oxidative metabolism increases the hydrophilicity of these compounds, known as substrates, by forming water-soluble metabolites that can be efficiently excreted from the body. The agents may then undergo phase II metabolism (conjugation and glucuronidation), which does not require CYP-450 biotransformation.[19] Although more than 30 human CYP-450 isoenzymes have been identified, the major ones responsible for drug metabolism are CYP-3A4, CYP-2D6, CYP-1A2, and the CYP-2C subfamily. CYP-3A4, which accounts for almost 60% of the total CYP-450 in the liver and approximately 70% of that in the intestine, metabolizes the greatest number of drugs.[20] Many substrates, inhibitors, and inducers of the CYP-3A4 have been identified. A CYP-450 inhibitor is any drug that inhibits the metabolism of a P-450

substrate (a drug that is metabolized by one or more P-450 isoforms) and may lead to an increase in the serum concentration of the substrate.[21] Like most enzymatic inhibition, this process is almost always competitive and reversible. Propafenone, which inhibits CYP-2D6, has been shown to decrease the metabolism of metoprolol, which is metabolized by the same isoenzyme. Other common enzyme inhibitors include cimetidine, macrolide antibiotics, azole antifungals, protease inhibitors, and calcium channel blockers.[22]

Generally, with enzyme inhibition, the interaction occurs within 24 hours and also diminishes rapidly when the precipitating agent is discontinued. A drug that induces a CYP isoenzyme may increase the metabolism and possibly decrease the effects of drugs that are substrates for that isoenzyme. Unlike enzyme inhibition, enzyme induction interactions may not be apparent for up to a week or more, because new enzymes need to be synthesized. Once the inducing agent is removed, the interaction may similarly take weeks to resolve. Rifampin, phenobarbital, phenytoin, and carbamazepine are common enzyme inducers.[23]

Drugs are primarily removed from the body by two mechanisms: biliary tract excretion and renal elimination. Renal elimination may be affected by concurrently administered medications, resulting in clinically relevant changes. Interactions with renal elimination may involve changing the glomerular filtration rate, extent of active tubular secretion, or changes in urinary pH, which can affect the passive transport of weak acids and bases.[16]

Pharmacodynamic interactions occur when the pharmacologic response of one drug is modified by another drug without a change in drug concentration or other pharmacokinetic properties. Interactions involving additive effects or antagonism of pharmacologic response are characterized as pharmacodynamic interactions. For example, loop and thiazide diuretics can potentiate the arrythmogenic effects of digoxin by decreasing serum potassium levels. In general, pharmacodynamic interactions have been less studied than pharmacokinetic interactions and are more difficult to predict and prevent.

When evaluating a drug interaction between two or more agents, the drug with the altered effect is referred to as the *object drug*. The *precipitant drug* is the drug causing the change. With most pharmacologic interactions there may be no object or precipitant drug, because there are additive or antagonistic effects. The focus of this article is on drug interactions that are of major clinical significance involving commonly prescribed medications in cardiac patients. These interactions are well documented and have the potential for serious adverse outcome. Serious drug interactions are frequently avoidable simply by switching one drug in the combination with an alternative noninteracting agent, by dosage adjustment, or by careful patient monitoring. An awareness of significant drug interactions can minimize the risks and maximize the benefits of drug therapy. Tables 7 to 12 provide a summary of selected drug interactions involving commonly prescribed medications in cardiology patients.[24–31]

Food–Drug Interactions

Grapefruit juice. Perhaps some of the more intriguing interactions are those seen with grapefruit juice. A variety of studies have been done evaluating the clinical effect of average grapefruit juice consumption on medication kinetics. Bioflavonoids present in grapefruit juice act as inhibitors and/or inactivators of various CYP-450 isoenzymes, specifically, CYP-1A2, CYP-3A3, and CYP-3A4, which are present in the liver and gut wall. The result is a downregulation of first-pass metabolism.[32] It was initially believed that naringin, metabolized by gut-wall bacteria to narigenin was primarily responsible for this interaction. However, recent data has suggested that naringin is responsible for only 10% of the enzyme inhibition seen with grapefruit juice.[33] Newly identified compounds known as furanocoumarins are potent CYP-3A4 inhibitors and are believed to be at least partly responsible for the inhibition seen with grapefruit juice. Further studies are needed to elucidate the specific compounds.[34]

Because it has been demonstrated that separating the ingestion of grapefruit juice and the interacting medication is insufficient in preventing the interaction, it is recommended that grapefruit juice be avoided when taking medications. This also suggests that the responsible inhibitory compound demonstrates a long half-life, making it capable of affecting enzyme function long after ingestion.

The first medications suspected of interacting with grapefruit juice were the dihydropyridine calcium channel blockers, felodipine and nifedipine.[35] Hypertensive patients given double-strength grapefruit juice with felodipine experienced dramatic (184%) increases in area under the curve (AUC) concentrations as well as increases in side effects such as tachycardia and dizziness. The proposed mechanism was enzyme inhibition leading to higher serum levels of these agents and subsequent clinical manifestations, such as hypotension, headache, and tachycardia. The effect was clearly unique to grapefruit juice, as it did not occur in the presence of orange

Table 7
Select Drug Interactions with Warfarin (Coumadin®) Leading to Enhanced Warfarin Effect[16,24–31]

Frequent monitoring of prothrombin time recommended with initiation, discontinuation, or change in dosage of interacting agents

Precipitant	Mechanism of Interaction	Recommendations
Amiodarone (Cordarone®)	Increased anticoagulant effect due to inhibition of warfarin metabolism	Monitor prothrombin time; a 30% to 50% reduction in warfarin dose may be required; effect on prothrombin time may be delayed, necessitating close monitoring for 2 to 4 weeks; effect may also persist for months after amiodarone is discontinued
Aspirin	Increased risk of bleeding due to platelet inhibition and risk of gastric erosions; at high doses > 3 g aspirin per day, anticoagulant activity may be enhanced	Monitor patient for signs and symptoms of bleeding; consider acetaminophen as an alternative analgesic
Azole antifungals fluconazole (Diflucan®) itraconazole (Sporanox®) ketoconazole (Nizoral®)	Increased anticoagulant effect due to inhibition of warfarin metabolism	Monitor prothrombin time
Cimetidine (Tagamet®)	Increased anticoagulant effect due to inhibition of warfarin metabolism	Avoid combination; famotidine (Pepcid®) and nizatidine (Axid®) do not interact with warfarin; based on current data, unlikely that there is an interaction between ranitidine (Zantac®) and warfarin
Cotrimoxazole (Bactrim®, Septra®)	Increased anticoagulant effect; mechanism not established	Monitor prothrombin time
Fibric acid derivatives clofibrate (Atromid-S®) gemfibrozil (Lopid®) fenofibrate (Tricor®)	Increased anticoagulant effect; mechanism not established	Monitor prothrombin time
HMG CoA reductase inhibitors fluvastatin (Lescol®) lovastatin (Mevacor®) simvastatin (Zocor®)	Increased anticoagulant effect due to inhibition of warfarin metabolism	Atorvastatin (Lipitor®), cerivastatin (Baycol®), and pravastatin (Pravachol®) do not appear to interact with warfarin
Macrolide antibiotics erythromycin (E-mycin®) clarithromycin (Biaxin®)	Increased anticoagulant effect due to reduction in clearance of warfarin	Monitor prothrombin time; azithromycin (Zithromax®) less likely to interact
Metronidazole (Flagyl®)	Increased anticoagulant effect due to inhibition of warfarin metabolism	Monitor prothrombin time
NSAIDs (eg, ibuprofen, indomethacin, ketoprofen, naproxen)	Increased risk of bleeding due to platelet inhibition and risk of gastric erosions	Monitor patient for signs and symptoms of bleeding; consider acetaminophen as an analgesic alternative
Quinidine (Quinidex®, Quinaglute®)	Increased anticoagulant effect; quinine derivatives may inhibit synthesis of clotting factors	Monitor prothrombin time
Thyroid hormones levothyroxine (Synthroid®) liothyronine (Cytomel®) thyroid (Armour Thyroid®)	Increase in turnover of vitamin K-dependent clotting factors with initiation of thyroid replacement leading to increased anticoagulant effect	Monitor prothrombin time

Table 8
Select Drug Interactions with Warfarin (Coumadin®) Leading to Diminished Warfarin Effect[16,24–31]

Frequent monitoring of prothrombin time recommended with initiation, discontinuation, or change in dosage of interacting agents

Precipitant	Mechanism of Interaction	Recommendations
Bile acid sequestrants cholestyramine (Questran®) colestipol (Colestid®)	Decreased anticoagulant effect due to binding in the GI tract and decreased warfarin absorption	Warfarin should be administered 1 hour prior to or 4 to 6 hours after bile acid sequestrants

Table 9
Select Drug Interactions with Digoxin (Lanoxin®) Leading to Enhanced Digoxin Effect[16,24–31]

Interactions may lead to increased digoxin serum levels and/or digoxin toxicity. Frequent monitoring of digoxin serum levels is recommended with initiation, discontinuation, or change in dosage of interacting agents.

Precipitant	Mechanism of Interaction	Recommendations
Amiodarone (Cordarone®)	Increase in digoxin serum levels; mechanism not established; multiple mechanisms probably involved	Monitor digoxin levels
Azole antifungals itraconazole (Sporanox®)	Increased serum digoxin levels; mechanism unknown but may involve increased absorption and reduced renal elimination	Monitor digoxin levels; conflicting data regarding interaction with digoxin and other azole antifungals
Cyclosporine (Neoral®)	Pharmacologic effects of digoxin may be increased; digoxin levels may increase; mechanism unknown	Monitor digoxin levels
Diuretics, potassium depleting Loop diuretics (eg, furosemide, torsemide) thiazide diuretics (eg, hydrochlorothiazide, metolazone)	Increased risk of digoxin toxicity resulting from hypokalemia and/or hypomagnesemia	Monitor electrolytes and supplement as necessary
Macrolide antibiotics erythromycin (E-mycin®) clarithromycin (Biaxin®)	Increased serum digoxin levels due to alteration in GI flora leading to increased absorption of digoxin	Monitor digoxin levels
Propafenone (Rythmol®)	Increased serum digoxin levels; mechanism unknown but may involve decreased digoxin volume of distribution and decreased elimination	Monitor digoxin levels
Quinidine (Quinidex®, Quinaglute®)	Increased serum digoxin levels due to decreased volume of distribution and decreased elimination	Monitor digoxin levels; it may be necessary to reduce the digoxin dose by up to 50% when initiating quinidine therapy
Verapamil (Calan®, Isoptin®)	Increased serum digoxin levels due to reduced digoxin clearance	Monitor digoxin levels

Table 10
Select Drug Interactions with Digoxin (Lanoxin®) Leading to Diminished Digoxin Effect[16,24–31]

Frequent monitoring of digoxin serum levels is recommended with initiation, discontinuation, or change in dosage of interacting agents

Precipitant	Mechanism of Interaction	Recommendations
Bile acid sequestrants cholestyramine (Questran®) colestipol (Colestid®)	Decreased serum digoxin levels due to binding and inhibition of absorption; may also interfere with enterohepatic recycling of digoxin	Monitor digoxin levels; digoxin should be administered 1 hour prior to or 4 to 6 hours after bile acid sequestrants
Thyroid hormones levothyroxine (Synthroid®) liothyronine (Cytomel®) thyroid (Armour Thyroid®ä)	Serum levels of digoxin are decreased when hypothyroid patients receive thyroid hormone and become euthyroid; mechanism unknown	Monitor digoxin levels

juice. Interestingly, an increase in AUC has also been demonstrated when verapamil, a non-dihydropyridine calcium channel blocker, was administered with grapefruit juice, but the clinical effects were not as prominent as those seen with felodipine and nifedipine.[36] Diltiazem was not shown to interact with grapefruit juice.[37] It is important to remember that the studies evaluating these interactions were done in healthy patients. Patients with comorbid cardiovascular disease or other conditions may experience more dramatic interactions. Advising patients to avoid grapefruit juice when initiating antihypertensive therapy is best. However, in patients already routinely consuming grapefruit juice with their antihypertensives, it is best to advise them to continue and not stop, because they have been stabilized on that regimen and are more prone to adverse effects by abruptly discontinuing grapefruit juice.[38]

Cyclosporine has poor and variable absorption under even ideal circumstances. Because of the narrow therapeutic window of this agent, it is critical that patients understand the important role that food plays in cyclosporine absorption, in order to avoid the renal insufficiency and hypertension seen with toxicity. In one study evaluating the effect of 8 ounces of grapefruit juice on trough cyclosporine levels among kidney transplant patients, it was found that trough levels increased an average of 32% in 8 of 11 patients when the drug was administered with grapefruit juice.[39] This and other studies demonstrating similar results were done with the Sandimmune® formulation of cyclosporine. It is unclear if this effect is seen with the currently marketed Neoral® formulation. A prudent recommendation is that patients be counseled to avoid grapefruit juice while taking any formulation of cyclosporine and that this interaction be considered in cases of supratherapeutic trough levels.

The effect of grapefruit juice on HMG-CoA reductase inhibitors was studied among healthy patients con-

Table 11
Select Drug Interactions with Digoxin (Lanoxin®) Leading to Enhanced or Diminished Digoxin Effect[16,24–31]

Interactions may lead to increased or decreased digoxin serum levels. Frequent monitoring of digoxin serum levels is recommended with initiation, discontinuation, or change in dosage of interacting agents.

Precipitant	Mechanism of Interaction	Recommendations
Spironolactone (Aldactone®)	Spironolactone may inhibit positive inotropic effect of digoxin and may also inhibit renal clearance, resulting in increased digoxin level	Monitor digoxin levels; spironolactone can interfere with some digoxin assays, leading to falsely elevated serum levels

Table 12
Select Drug Interactions with Common Cardiac Medications[16,24–31]

Management of drug interaction usually involves avoiding combination if possible. If agents are used concurrently, careful monitoring and adjustment of medication doses may be necessary.

Precipitant Drug	Object Drug	Mechanism	Recommendations
ACE inhibitors	Lithium (Eskalith®)	Elevated lithium serum levels; mechanism unknown	Monitor lithium serum levels; observe the patient for signs of lithium toxicity
Amiloride (Midamor®)	Quinidine (Quinidex®, Quinaglute®)	Possible synergistic increase in mycoardial sodium blockade may contribute to proarrhythmia	Avoid this combination
Amiodarone (Cordarone®)	Cyclosporine (Neoral®)	Amiodarone may increase cyclosporine serum levels, possibly by inhibiting metabolism	Monitor cyclosporine serum levels and adjust dose as necessary
Amiodarone (Cordarone®)	Procainamide (Pronestyl®)	Increased procainamide levels; mechanism unknown	Monitor procainamide and NAPA levels
Amiodarone (Cordarone®)	Quinidine (Quinidex®, Quinaglute®)	Increased quinidine levels; mechanism unknown	Monitor quinidine levels
Antacids	Quinidine (Quinidex®, Quinaglute®)	Increase in quinidine serum levels, possibly due to decreased renal elimination	Avoid combination
Azole antifungals itraconazole (Sporanox®)	Quinidine (Quinidex®, Quinaglute®)	Increase in quinidine serum levels due to inhibition of metabolism	Monitor quinidine levels; not known if interaction occurs with other azole antifungals
Azole antifungals itraconazole (Sporanox®)	HMG CoA reductase inhibitors atorvastatin (Lipitor®) cerivastatin (Baycol®) lovastatin (Mevacor®) simvastatin (Zocor®)	Inhibition of HMG CoA reductase inhibitor metabolism increasing the risk of toxicity (eg, rhabdomyolysis)	Pravastatin (Pravachol®) and fluvastatin (Lescol®) less likely to interact
Beta blockers	Alpha blockers doxazosin (Cardura®) prazosin (Minipress®) terazosin (Hytrin®)	Increase risk of acute postural hypotensive reaction	Initiate alpha blockers at low doses and monitor blood pressure
Beta blockers	Clonidine (Catapres®)	When clonidine is discontinued there is an increase in sympathetic activity, leading to hypertension	Closely monitor blood pressure if agents are given concurrently; beta blockers should be discontinued gradually prior to clonidine withdrawal; cardioselective beta blockers (ie, atenolol, metoprolol) are less likely to cause rebound hypertension
Cimetidine (Tagamet®)	Beta blockers	Inhibition of metoprolol, labetalol, and propranolol metabolism has been documented; increased risk of hypotension	Avoid combination; interaction has not been reported with the use of ranitidine (Zantac®)
Cimetidine (Tagamet®)	Nifedipine (Procardia®, Adalat®)	Effects of nifedipine may be increased; mechanism unknown but may be due to inhibition of metabolism	Avoid combination; interaction has not been reported with the use of ranitidine (Zantac®)
Cimetidine (Tagamet®)	Quinidine (Quinidex®, Quinaglute®)	Increase in serum quinidine level due to decreased metabolism and possibly increased absorption	Avoid combination; interaction has not been reported with the use of ranitidine (Zantac®)
Cimetidine (Tagamet®)	Procainamide (Pronestyl®)	Increase in serum procainamide level due to reduced renal clearance	Avoid combination; interaction has not been reported with the use of ranitidine (Zantac®)

Table 12 *continued*

Precipitant Drug	Object Drug	Mechanism	Recommendations
Cyclosporine (Neoral®)	Lovastatin (Mevacor®)	Severe myopathy or rhabdomyolysis may occur; mechanism unknown	Avoid combination; no interaction with other HMG-CoA reductase inhibitors
Diltiazem (Cardizem®)	Cyclosporine (Neoral®)	Increase in cyclosporine levels due to inhibition of metabolism	Monitor cyclosporine levels and adjust dose as necessary
Diltiazem (Cardizem®)	HMG CoA reductase inhibitors atorvastatin (Lipitor®) cerivastatin (Baycol®) lovastatin (Mevacor®) simvastatin (Zocor®)	Diltiazem may inhibit the metabolism of HMG CoA reductase inhibitors increasing the risk of toxicity (eg, rhabdomyolysis)	Pravastatin (Pravachol®) and fluvastatin (Lescol®) less likely to interact
Diltiazem (Cardizem®)	Quinidine (Quinidex®, Quinaglute®)	Increased serum quinidine levels due to inhibition of metabolism	Monitor quinidine levels
Gemfibrozil (Lopid®)	HMG CoA reductase inhibitors atorvastatin (Lipitor®) cerivastatin (Baycol®) fluvastatin (Lescol®) lovastatin (Mevacor®) pravastatin (Pravachol®) simvastatin (Zocor®)	Increased additive risk of myopathy and rhabdomyolysis	Avoid combination
Macrolide antibiotics: clarithromycin (Biaxin®) erythromycin (E-mycin®)	HMG CoA reductase inhibitors atorvastatin (Lipitor®) cerivastatin (Baycol®) lovastatin (Mevacor®) simvastatin (Zocor®)	Inhibition of HMG CoA reductase inhibitor metabolism increasing the risk of toxicity (eg, rhabdomyolysis)	Avoid combination
NSAIDs	ACE inhibitors (eg, enalapril, captopril)	NSAIDs which occasionally may reduce hypotensive effect	If used in combination monitor blood pressure
Potassium-sparing diuretics: amiloride (Midamor®) spironolactone (Aldactone®) triamterene (Dyrenium®)	ACE inhibitors (eg, enalapril, captopril)	Combination may result in elevated serum potassium levels, especially in renally impaired patients	Monitor serum potassium levels and renal function; ensure adequate salt intake
Propafenone (Rythmol®)	Beta blockers	Increased beta blocker effect; propafenone inhibits the metabolism of metoprolol and propranolol	Monitor cardiac function; decrease doses as needed
Quinidine (Quinidex®, Quinaglute®)	Propafenone (Rythmol®)	Increased propafenone levels due to inhibition of metabolism	Monitor cardiac function; decrease doses as needed
Quinidine (Quinidex®, Quinaglute®)	Beta blockers	Increased beta blocker effect; quinidine inhibits the metabolism of atenolol, metoprolol, propranolol, and timolol	Monitor cardiac function; decrease doses as needed
Sildenafil (Viagra®)	Nitrates isosorbide dinitrate/mononitrate (Isordil®, ISMO®) nitroglycerin (Nitro-Bid®)	Sildenafil potentiates the hypotensive effects of nitrates	Concomitant use is contraindicated
Thiazide diuretics (eg, hydrochlorothiazide, metolazone)	Lithium (Eskalith®)	Elevated lithium serum levels due to decreased renal clearance	Monitor lithium serum levels; observe the patient for signs of lithium toxicity
Verapamil (Calan®, Isoptin®)	Beta blockers	Additive hypotensive effect; in addition verapamil may inhibit metabolism of beta blockers	Monitor cardiac function; decrease doses as needed

Table 12 *continued*

Precipitant Drug	Object Drug	Mechanism	Recommendations
Verapamil (Calan®, Isoptin®)	HMG CoA reductase inhibitors atorvastatin (Lipitor®) cerivastatin (Baycol®) lovastatin (Mevacor®) simvastatin (Zocor®)	Verapamil may inhibit the metabolism of HMG CoA reductase inhibitors, increasing the risk of toxicity (eg, rhabdomyolysis)	Pravastatin (Pravachol®) and fluvastatin (Lescol®) less likely to interact
Verapamil (Calan®, Isoptin®)	Cyclosporine (Neoral®)	Increased cyclosporine levels due to inhibition of metabolism	Monitor cyclosporine levels and adjust dose as necessary
Verapamil (Calan®, Isoptin®)	Prazosin (Minipress®)	Increase risk of acute postural hypotensive reaction	Initiate prazosin at low doses and monitor blood pressure
Verapamil (Calan®, Isoptin®)	Quinidine (Quinidex®, Quinaglute®)	Increased quinidine levels due to inhibition of clearance	Avoid this combination

suming double-strength juice and higher-than-usual doses of medication. Patients taking 80 mg of lovastatin (Mevacor®) with 200 mL of double-strength juice experienced a 15-fold increase in the AUC of lovastatin.[40] Similar results were seen with simvastatin (Zocor®) and atorvastatin (Lipitor®).[41,42] This is potentially concerning in light of the fact that rhabdomyolysis is associated with increased plasma levels of HMG-CoA reductase inhibitors. Merck, the manufacturer of lovastatin, evaluated 8 ounces of regular-strength juice in conjunction with 40 mg of lovastatin and found a doubling of the AUC of lovastatin.[43] It appears that large amounts of grapefruit juice are required to impact plasma levels significantly, but more studies are needed. In the meantime, a safe recommendation for patients is to avoid grapefruit juice while taking these medications. Another option for patients unwilling or unable to avoid grapefruit juice is to prescribe pravastatin (Pravachol®). Because this agent is not dependent on CYP-3A4 for its metabolism, grapefruit juice has no effect on plasma levels.

The following medications have not demonstrated significant interactions when administered with grapefruit juice: quinine, warfarin, theophylline, and clarithromycin.

Oral anticoagulants. Perhaps the best known food–drug interactions involve those seen between warfarin and vitamin K–containing foods. Warfarin's mechanism of action antagonizes the production of vitamin K–dependent clotting factors (II, VII, IX, and X). Consequently, fluctuations in vitamin K can result in either an increased bleeding risk or subtherapeutic anticoagulation. The threshold for dose adjustment is 250 μg of vitamin K; to avoid fluctuations, daily variations should not exceed 250 to 500 μg.[44] When considering sources of vitamin K, such as leafy green vegetables and liver, it is also important to consider over-the-counter (OTC) nutritional supplements and enteral feedings, which are often overlooked but are significant sources of vitamin K. Products considered high in vitamin K include: Sustacal®, Isocal®, and

Table 13
Vitamin K Content of Nutritional Supplements[45]

OTC Nutritional Supplement	μg Vitamin K per 1000 kcal
Sustacal®	230
Isocal®	125
Travasorb®	75
Ensure HN®	52
Ensure Plus®	37
Osmolite®	36
* Vivonex®	22
* Meritene®	Trace
* Citrotein®	0

*Lowest vitamin K content.

Table 14
Vitamin K Content of Foods[46,47]

Product	μg Vitamin K per 100 g*
Kale	750
Parsley	700
Soybean oil/olive oil	200–400
Spinach	350
Turnip greens	300
Brussels sprouts	220
Broccoli and watercress	200
Chinese cabbage	175
Liver	20–100

*100 grams = 1 cup raw or 1/2 cup cooked.

Travasorb®. Several published case reports describe the disruption of anticoagulation regimens by as little as 1 to 2 cans of supplement per day.

Patients should not be counseled to avoid leafy green vegetables; rather they should be reminded to consume a consistent amount of these items and to inform their health care provider if the amount changes. Table 13 lists nutritional supplements containing vitamin K[45]; Table 14 lists vegetables containing vitamin K.[46,47]

Antihypertensives. *ACE-inhibitors and angiotension II receptor antagonists*. Patients who are stabilized on ACE-inhibitor (ACE-I) therapy (ie, enalapril, captopril) can take these agents either with or without food, but should do so consistently in order to minimize blood pressure fluctuations. Often, salt-sensitive hypertensive patients are advised to use salt substitutes. This advice should usually be avoided in patients on ACE-I therapy, because many salt substitutes contain potassium, which could lead to hyperkalemia. Angiotensin II receptor antagonists (ie, valsartan, irbesartan, losartan) may be taken with or without food, depending on patient preference and tolerance.[48]

Beta blockers. Although studies have shown altered bioavailability when metoprolol, propranolol, labetalol, sotalol, or atenolol were given with food, it is not likely that this has a detrimental effect on blood pressure control over the course of chronic therapy. As with ACE-I therapy, patients should be advised to take beta blockers consistently with respect to meals in order to minimize fluctuations.

Calcium channel blockers. Nifedipine (Adalat®, Procardia®) is associated with unpleasant side effects, such as tachycardia, flushing, and headache. Because fed patients exhibit lower peak concentrations without changes in overall blood pressure control when compared to fasted patients, it is recommended that nifedipine be given with food to minimize the side effects often seen with initial peak plasma concentrations. Patients on sustained-release nifedipine who have not yet achieved target blood pressure ranges may benefit from taking the medication on an empty stomach. A study evaluating blood pressure reduction following administration of sustained-release nifedipine in the fasted and fed state found a significant difference in diastolic blood pressure reduction in fasted subjects. This may be useful in patients not receiving the maximum benefit from sustained-release nifedipine therapy.[49] Extended-release diltiazem capsules or tablets (Cardizem®, Cardizem CD®, Dilacor®, Tiazac®) are most effective when administered on an empty stomach, whereas verapamil (Calan®, Calan SR®, Isoptin®), regardless of formulation, should be given with food or milk.

Diuretics. The diuretic effect of furosemide (Lasix®) is decreased when administered after a meal. For patients able to tolerate furosemide on an empty stomach, optimal responses occur when the drug is administered either 1 hour before or 2 hours after a meal. If the GI side effects contribute to noncompliance, it is best for the medication to be taken consistently with respect to meals. Spironolactone (Aldactone®) is maximally absorbed postprandially, and patients should be counseled accordingly. Hydrochlorothiazide is not significantly affected by the presence of food.

Medications are more efficiently absorbed in a dilute solution. For optimal therapy, patients should be counseled to take medications with plenty of plain water, avoiding mineral water, fruit juices, and carbonated and caffeine-containing beverages. The elderly should be specifically counseled regarding adequate fluid intake, because dehydration is a common problem in this population.

Alternative Therapy/Herbal Supplements

It has been estimated that more

Table 15
Recommended Web Sites

Web Address	Types of Information Available on Web Site
www.heartinfo.org	Helix Web site with comprehensive cardiology information database. Site is updated daily and offers free subscriptions to weekly email newsletters. Not all drugs are listed, but each medication is linked to its related clinical trials and studies. Site also provides the latest news on drug approval status and experimental drugs.
www.medscape.com	Covers a range of various subjects and specialties, including highlights of the latest meetings and conferences. Medical news is updated on a daily basis. An efficient search engine on drug information displays results obtained from both the Internet and Medline. Also links references to other articles and abstracts.
www.druginfonet.com	Easily navigable, one-step link to other health care organizations, pharmaceutical company Web sites and government Web sites (eg, CDC, NIH, USFDA, etc). One of the few sites that provides product prescribing literature (ie, package insert).
www.healthinfo.com	Useful search capability regarding drug information; includes information that appears on Yahoo Headline News/Public Radio/*New York Times*. Excellent site for patient education material. General medical library contains all Web site links to major medical associations, government sites, most medical specialties/societies, and sites with information on drugs and alternative medicines.
www.emedicine.com	Textbook format of reliable medical information developed by groups of physicians. Topics are categorized by disease state and include information on current drug treatment.
www.docguide.com	One of the fastest online resources for the latest drug information. Offers free weekly email subscription for latest medical news, medical-related Web searches, Medline, and conferences/meetings. One-step link to major medical journals.
www.drugchecker.drkoop.com	Quick and simple way to look for drug-drug and drug-herb interactions. Designed mainly for the consumer, but has great summaries on drug interactions with research data and references provided.

than one third of Americans use alternative medication therapies, including herbal products. With the popularity of herbal medication use, there is an increasing risk of herbal–drug interactions. Until recently, there was a limited amount of information published about herbal–drug interactions, making it difficult for clinicians to advise patients appropriately about safe concomitant use of alternative therapies and prescription medications. New information regarding the therapeutic efficacy, adverse effects, and potential drug interactions is now frequently reported in the literature.

Resources for the Practitioner

Recently, the Internet has become one of the fastest ways to search for drug information.[50] The World Wide Web has provided not only a comprehensive health care portal but also an extremely effective way to communicate and distribute information on up-to-date medical resources. Many professionals spend more time "surfing the Web" than reading textbooks and journals to retrieve drug information. Drug information centers are utilizing the Internet to search for everything from the latest clinical trials to obscure herbal supplements.[51–53] Through various Web sites, links, and search engines, physicians receive real-time medical news and information of interest as well as information on the status of clinical studies around the world.[54] Many editors are physician associates who have an interest in Web site publication. Some of these Web sites are even especially designed for their own specialties.

Unfortunately, despite the plethora of drug information for both health care professionals and consumers, many Web sites are designed principally for product purchasing and advertising and may not provide

Table 16
Recommended Government Web Sites

Web Address	Types of Information Available on Web Site
www.fdcreports.com	Access to a variety of different FDA reports (ie, Pink Sheets, Green Sheets, etc).
www.guideline.gov (National Guideline Clearinghouse)	Resource on evidence-based clinical practice guidelines. Provides links to some summaries and full-text reports for evidence and technology assessments.
www.nih.gov (National Institutes of Health)	Contains information regarding the latest clinical trials and research studies. Links to many other health-related centers.
www.fda.gov	Provides access to Medwatch error/adverse reaction reporting program, drug news (latest approvals as well as withdrawals from the market), drug shortages, book of therapeutic equivalence, and consumer information.

accurate, comprehensive information. Information regarding the authors and their credentials must be evaluated when determining the credibility of information on any Web site. All published information should be attributed and referenced. The ownership, sponsorship, editorial policy, advertising, and support should also be accessible in evaluating the quality of a Web site.[37,55]

A useful Web site for the health care professional should be designed such that the presentation and graphics are simple, quick to load, and easy to navigate. Topics should include drug information, review articles, case reports, editorials, lectures, book reviews, and one-click linkage to related Web sites. Frequently ask questions (FAQs) and answers and on-line video images and procedures would be valuable. For providers interested in obtaining drug information via the Web, Table 15 has a summary of some recommended sites.

Most drug information, including drug–drug interaction, drug–food interaction, and drug–herb interaction, can be found easily through the Web sites mentioned above. Web sites such as www.medscape.com and www.docguide.com provide powerful search engines that can extract information relevant to your request from Web sites, journal articles, multimedia, news, and Medline. Others, such as www.heart-info.mediconsult.com, have narrower searches. Some sites such as www.medmatrix.org offer links to other quality Web sites, such as www.drugfacts.com and www.rxcentric.com/search/advsearch for further resources. For patient education material on common drug–drug and drug–food interaction, the www.rxlist.com and www.drugchecker.drkoop.com sites have proven beneficial.

Sites developed by the government usually provide the public with the most reliable and current information about clinical trials under way and the latest drug approval status (Table 16). Although the level of detail on these sites may be slightly overwhelming for the general public, the presentation is generally simple and easy to navigate. They are valuable resources for both health care consumers and professionals.

Patient Role in Optimizing Drug Therapy

As patients become more involved in and educated about their health care, their ability to take active roles in assuring safe and effective medication use increases. Patients who are involved and aware of the care they receive are more likely to do what needs to be done to optimize the benefits of therapy. The Agency for Healthcare Research and Quality (AHRQ) has compiled a patient fact sheet of 20 tips to help prevent medical errors in the outpatient, inpatient, and surgical setting.[56] Table 17 lists tips for patients to help them get involved in their care as inpatients and outpatients.

An abstract published in the *Annals of Emergency Medicine* highlighted the degree of misunderstanding exhibited by patients regarding dosing instructions.[57] Misunderstandings occurred in 77% of prescriptions specifying an hourly interval (eg, every 6 hours). This highlights the importance of communication and education between caregivers and patients.

Conclusion

Despite increasingly complicated therapies, many resources are available for both consumers and practitioners to maximize the benefit and minimize the associated risk. Keeping abreast is facilitated by electronic access to a wide variety of

Table 17
How Patients Can Get Involved in Their Care*

Outpatient

1. Be an active member of your health care team.
2. Notify each of your physicians about all the medications you are taking, including over-the-counter medications, vitamins, and herbal supplements.
3. Make your doctor aware of any allergies and/or adverse reactions to medications which you have experienced.
4. Make sure you can read the prescription that the doctor writes for you.
5. Ask for information regarding all of your medications in terms you can understand. Both your doctor and pharmacist should provide this information.
6. Ask your pharmacist "Is this the medication my doctor prescribed?" when picking up your prescriptions.
7. Question the directions on your medication labels if they are unclear or inconsistent.
8. Ask your pharmacist for the best device to measure liquid medications.
9. Ask for written information about the side effects your medicine could cause.

Inpatient

10. If you have a choice, choose a hospital at which many patients have the procedure or surgery you require.
11. When in a hospital, ask all health care workers who come in contact with you whether they have washed their hands.
12. When you are discharged from the hospital, ask the doctor to explain the treatment plan you should use at home.

Additional Steps

13. If you are having surgery, make sure that you, your doctor, and your surgeon all agree on exactly what will be done.
14. Speak up if you have questions or concerns.
15. Make sure that someone, such as your personal doctor, is in charge of your care.
16. Make sure that all health professionals involved in your care know the important health information about you (ie, allergies, etc).
17. Ask a family member or friend to act as your advocate.
18. Understand that "more" (ie, treatments, tests, etc) is not always better.
19. If you have a test, do not assume that no news is good news. Call your doctor for the results.
20. Learn as much as you can about your condition and treatment from your health care providers.

*From the Agency for Healthcare Research and Quality (AHRQ) fact sheet. Available at http://www.ahrq.gov/consumer/20tips.htm

resources. Additionally, advances in the safe administration of medications (eg, physician order entry, computerized safety programs) can optimize therapy. ■

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Main Points

- Medical errors in the care of patients may account for 44,000 to 98,000 deaths per year, and 7,000 deaths per year are attributed to medication errors alone.
- A *medication error* is any error in the process of prescribing, dispensing, or administering a drug, whether or not consequences result.
- An *adverse drug event* is as an injury from a medicine (or lack of an intended medicine).
- An *adverse drug reaction* is any unexpected, unintended, undesired, or excessive response to a medicine when used in the usual manner and dosage.
- A *drug interaction* occurs when two or more drugs are taken concurrently and an effect is observed that is different from the anticipated or known effects of either agent given alone.
- Some medication errors do lead to injuries and therefore are both medication errors and adverse drug events.
- Some adverse drug reactions are caused by medication errors, whereas other adverse drug reactions occur without an actual mistake.
- Prescribers are recommended to use legible handwriting, in the absence of a physician order entry (POE) system, and to avoid abbreviations.
- Information on drug–drug interaction, drug–food interaction, and drug–herb interaction, can be found through authoritative Web sites.