Cardiovascular Effects of Noncardiovascular Drugs

Satish R. Raj, MD, MSCI; C. Michael Stein, MB, ChB; Pablo J. Saavedra, MD; Dan M. Roden, MD

Most drugs are not used to treat heart disease. However, such “noncardiovascular” medications can often have cardiovascular effects. In this review, we discuss some cardiovascular manifestations of drugs used for noncardiovascular indications. We discuss these in the text according to the manifestations with which patients present; selected drugs are listed in Table 1 by their indication/drug class. The same medication may appear in different sections, reflecting the varied cardiovascular consequences of a particular drug. We also discuss cardiovascular effects of noncardiovascular drugs that arise indirectly from drug interactions that cause an increase or decrease in the concentration of a cardiovascular drug.

Arrhythmias

Atrial Fibrillation
Most reports of atrial fibrillation (AF) induced by noncardiovascular drugs are case reports, and because AF is so common, it is difficult to determine whether the association is causal or incidental. The ability to reproduce AF with drug rechallenges supports causality, as does a mechanistic rationale. Table 1 lists drugs with a well-established association with AF.

After numerous case reports of the onset of AF after pulse methylprednisolone, van der Hooft et al.1 conducted a nested case-control study in the Rotterdam study that comprised almost 8000 adults. They found that high-dose corticosteroid use (≥7.5 mg prednisone equivalents) was associated with a significantly increased risk of new-onset AF (odds ratio [OR]=6.1; 95% confidence interval [CI], 3.9 to 9.4) but that low-dose corticosteroid use was not associated with AF (OR=1.4; 95% CI, 0.7 to 2.8). This increase in AF risk was seen with all indications for high-dose corticosteroids. It has been postulated that high-dose corticosteroids might mediate cellular potassium efflux and that this may in turn predispose to arrhythmia.2

There is concern that bisphosphonates may increase the risk of serious AF (AF resulting in hospitalization or disability or deemed to be life threatening). The HORIZON Pivotal Fracture Trial randomized >7000 patients to annual zoledronic acid infusions or placebo over a 3-year period.3 The study showed a significant decrease in vertebral fractures (the primary end point) but also a significant increase in serious AF with zoledronic acid (50 patients [1.3%]) compared with placebo (20 patients [0.5%]; P<0.001). Similarly, in the Fracture Intervention Trial study,4 a 6459-patient randomized placebo-controlled trial of alendronate versus placebo, AF was detected in 47 patients (1.5%) receiving alendronate compared with 31 patients (1.0%) receiving placebo (hazard ratio=1.5; 95% CI, 0.97 to 2.4; P=0.07). However, the more recent HORIZON Recurrent Fracture Trial5 (n=2000) found no difference in the incidence of serious AF. Thus, the preponderance of evidence suggests a small increased risk of serious AF from bisphosphonate therapy. Possible mechanisms for bisphosphonate-induced AF include an increase in inflammatory cytokines or alterations in calcium handling.6

Most other reports of drug-induced AF are sporadic cases. Donepezil, an acetylcholinesterase inhibitor used for dementia, has been found to be associated with AF.6 This association might be due to alterations in sympathovagal balance. Intravenous aminophylline was associated with AF in a handful of case reports, including one in which rechallenge with the drug again resulted in AF. There have been several case reports of AF with the antimigraine agent sumatriptan, including reinduction of AF with drug rechallenge.7 An association also has been reported between sildenafil and AF, including a positive drug rechallenge test in 1 case.8 There are several case reports, including some with drug rechallenge, of chemotherapeutic agents (cisplatin9 and gemcitabine10) associated with AF. There are many possible mechanisms, including direct myocardial toxicity affecting the atrium, AF resulting from ventricular cardiomyopathy, and cytokine release.11

QT Prolongation, Torsades de Pointes Ventricular Tachycardia, and Sudden Cardiac Death
Drug therapy is the most common cause of the acquired long-QT syndrome. Excessive prolongation of cardiac repolarization reflected in the QT interval (a surface manifestation of cardiac action potential duration) can lead to the development of early afterdepolarizations that can then trigger the initiation of torsades de pointes ventricular tachycardia.12 Virtually all drugs that cause acquired long-QT syndrome reduce the delayed rectifier potassium current (I_K) and prolong the cardiac action potential13; case series support the idea that genetic variants in ion channels can increase the risk. Although the most common class of drugs implicated in acquired long-QT syndrome is QT-prolonging antiarrhythmic

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drugs, particularly \( \text{IKr} \) blockers such as sotalol, dofetilide, quinidine, and ibutilide,\(^{12} \) this form of proarrhythmia can also occur with noncardiovascular drugs.\(^{14} \) In fact, QT interval prolongation has been a leading cause of medication withdrawal from the US market over the last 15 years, prompting pharmaceutical companies to routinely screen for drug-induced QT prolongation during drug development. Table 2 lists commonly used medications known to be associated with torsades de pointes ventricular tachycardia.\(^{15} \) An up-to-date comprehensive listing is maintained at www.qtdrugs.org.

Using a large insurance database, Ray et al\(^{16} \) assessed the risk of sudden cardiac death (SCD) associated with antidepressants. They found a dose-dependent increase in the risk of SCD with tricyclic antidepressants. The risk ratio for SCD for doses of \( \frac{\text{Amitriptyline}}{300} \) mg (or equivalent) was 2.53 (95% CI, 1.04 to 6.12), whereas there was no increased risk at doses of amitriptyline (or equivalent) \( \frac{100}{100} \) mg. This study design does not define the mechanisms underlying the SCD, but tricyclic antidepressants have ion channel–blocking properties and block the norepinephrine clearance transporter, resulting in heightened cardiac sympathetic tone.\(^{17} \) In the same study, selective serotonin reuptake inhibitors did not increase the risk of SCD.\(^{16} \)

The same group assessed the risk of SCD with commonly used antibiotics.\(^{18} \) Using the Tennessee Medicaid insurance database, they found that the adjusted rate of SCD among patients currently using erythromycin was twice as high (incidence rate ratio=2.01; 95% CI, 1.04 to 6.12), whereas there was no increased risk at doses of amitriptyline (or equivalent) <100 mg. This study design does not define the mechanisms underlying the SCD, but tricyclic antidepressants have ion channel–blocking properties and block the norepinephrine clearance transporter, resulting in heightened cardiac sympathetic tone.\(^{17} \) In the same study, selective serotonin reuptake inhibitors did not increase the risk of SCD.\(^{16} \)

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Table 1. Selected Noncardiovascular Drugs With Cardiovascular Effects by Indication/Drug Class

<table>
<thead>
<tr>
<th>Drug Indication</th>
<th>Cardiovascular Effect</th>
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<tbody>
<tr>
<td>Antibiotic</td>
<td></td>
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<tr>
<td>Erythromycin</td>
<td>SCD</td>
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<tr>
<td>Antihypertensive drugs</td>
<td>Bradycardia</td>
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<tr>
<td>Clonidine</td>
<td>Pulmonary hypertension, valvular heart disease</td>
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<tr>
<td>Appetite suppression</td>
<td>Pulmonary hypertension, valvular heart disease</td>
</tr>
<tr>
<td>Dextrofetilide</td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>Valvular heart disease</td>
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<tr>
<td>Phenetermine</td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Cancer drugs</td>
<td></td>
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<tr>
<td>Anthracyline</td>
<td>Cardiomyopathy and heart failure</td>
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<tr>
<td>Cliplatin</td>
<td>Atrial fibrillation</td>
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<tr>
<td>Cyclophosphamide</td>
<td>Cardiomyopathy and heart failure</td>
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<tr>
<td>5-Fluouracil</td>
<td>Atrial fibrillation</td>
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<tr>
<td>Gemcitabine</td>
<td>Atrial fibrillation</td>
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<tr>
<td>HIV medications</td>
<td></td>
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<tr>
<td>Protease inhibitors</td>
<td>Metabolic syndrome</td>
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<tr>
<td>Neurological Drugs</td>
<td></td>
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<tr>
<td>Cabergoline</td>
<td>Valvular heart disease</td>
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<tr>
<td>Donepezil</td>
<td>Atrial fibrillation</td>
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<tr>
<td>Pergolide</td>
<td>Valvular heart disease</td>
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<tr>
<td>Sumatriptan</td>
<td>Atrial fibrillation</td>
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<tr>
<td>Psychiatric drugs</td>
<td></td>
</tr>
<tr>
<td>Antipsychotic drugs</td>
<td>SCD</td>
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<tr>
<td>Chlorpromazine</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Dextrofetilide</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Tachycardia, hypertension</td>
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<tr>
<td>Venlafaxine</td>
<td>Tachycardia, hypertension</td>
</tr>
<tr>
<td>Rheumatological drugs</td>
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<tr>
<td>Bisphosphonates</td>
<td>Atrial fibrillation</td>
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<tr>
<td>Corticosteroids</td>
<td>Atrial fibrillation</td>
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<tr>
<td>Tumor necrosis factor antagonists</td>
<td>Heart failure</td>
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<tr>
<td>NSAIDs</td>
<td>Hyper tension</td>
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<tr>
<td>Rofecoxib</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Urological and erectile dysfunction</td>
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<tr>
<td>( a_1 )-Adrenergic receptor antagonists</td>
<td>Hypertension</td>
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<tr>
<td>Phosphodiesterase type 5 inhibitors</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>Hypertension</td>
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<tr>
<td>Miscellaneous drugs</td>
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<tr>
<td>Neostigmine</td>
<td>Bradycardia</td>
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<tr>
<td>Pseudoephedrine</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Heart failure, myocardial infarction</td>
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</table>

Table 2. Selected Common Noncardiovascular Drugs Implicated in Torsades de Pointes Ventricular Tachycardia

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Drug</th>
</tr>
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<tbody>
<tr>
<td>Antimicrobial medications</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Clarithromycin</td>
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</tr>
<tr>
<td>Pentamidine</td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td></td>
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<tr>
<td>Antipsychotic medications</td>
<td>Thioridazine</td>
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<tr>
<td>Chlorpromazine</td>
<td></td>
</tr>
<tr>
<td>Droperidol</td>
<td></td>
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<tr>
<td>Haloperidol</td>
<td></td>
</tr>
<tr>
<td>Pimozide</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Methadone</td>
</tr>
<tr>
<td>Supplements and herbal medications</td>
<td>Licorice, Cesium</td>
</tr>
</tbody>
</table>

List adapted from Gupta et al,\(^{15} \) copyright © 2007, with permission from Elsevier.
de pointes ventricular tachycardia. Thioridazine, a typical antipsychotic drug, has a Food and Drug Administration (FDA) “black-box warning” because of an increased risk of SCD.24 Ray et al25 found that use of newer (“atypical”) antipsychotic drugs is associated with a greater-than-double risk of SCD compared with nonusers (incidence rate ratio, 2.26; 95% CI, 1.88 to 2.72), a risk similar to that of the older typical antipsychotics. This risk increased with increasing drug dose of clozapine, olanzapine, quetiapine, and risperidone (low-dose incidence rate ratio = 1.59; high-dose incidence rate ratio = 2.46; \( P=0.01 \)).

Stratton et al30 published a case series of 18 patients who suffered SCD during restraint for excited delirium and compared their characteristics with those of 196 surviving patients with excited delirium. Stimulant drugs (such as cocaine and amphetamine) were identified in 78% of the patients who died compared with only 22% of the surviving patients. More recently, the US FDA recommended a black-box warning because of reports of cardiovascular events and SCD associated with the use of stimulant drugs27 such as amphetamines.

**Bradycardia and Tachycardia**

It is rare for a noncardiovascular drug to cause clinically important bradycardia at usual doses. The peripherally acting acetylcholinesterase inhibitor neostigmine can increase sympathetic acetylcholine availability, and the resultant increase in vagal tone can cause bradyarrhythmia.28,29

The antihypertensive drug clonidine can produce striking bradycardia. For example, Nieminen et al30 reported that the incidence of bradyarrhythmia was 20% in those receiving intraarticular clonidine, reinforcing the concept that cardiovascular drugs administered by nonconventional routes (such as intraarticular clonidine or ophthalmic \( \beta \)-blockers) can have cardiovascular manifestations.

Tachycardia can result from a wide range of drugs that are adrenergic agonists (eg, \( \beta \)-adrenergic receptor agonists) but also can occur with other drugs. Duloxetine, an antidepressant also used for neuropathic pain and urinary incontinence, inhibits both serotonin reuptake and the presynaptic norepinephrine transporter. High doses of duloxetine can cause significant sinus tachycardia,31 even in subjects without cardiovascular disease. Venlafaxine, another antidepressant with similar pharmacological properties, can increase heart rate.32

**Hypotension**

Medications for erectile dysfunction can have notable systemic hemodynamic effects. The phosphodiesterase type 5 inhibitors (including sildenafil, tadalafil, and vardenafil) are the most widely prescribed drugs for erectile dysfunction, with the most data available for sildenafil. The expert consensus statements indicate that sildenafil can cause a transient modest reduction in systolic and diastolic blood pressures without a significant effect on heart rate.33 More recently, Arruda-Olson et al34 found that sildenafil decreased systolic blood pressure an average of 7 mm Hg among men with known or suspected coronary artery disease. The decrease in blood pressure can be especially dramatic when sildenafil is used in patients taking nitrates,33 a combination that is contraindicated.

The use of \( \alpha \)-adrenergic receptor antagonists to treat hypertension has decreased. However, this class of agent is still commonly used to treat benign prostatic hypertrophy. \( \alpha \)-Adrenergic receptor antagonists can cause or worsen orthostatic hypotension and syncope, particularly in the elderly.35–37 especially when used with a phosphodiesterase type 5 inhibitor.38

**Hypertension**

Venlafaxine can increase not only heart rate but also blood pressure. In a recent study of major depression, newly diagnosed hypertension was attributed to high-dose venlafaxine in 12.5% of patients.32 The \( \alpha \)-adrenergic receptor antagonist yohimbine increases sympathetic neuronal activity (through a decrease in the negative feedback on norepinephrine release) and consequently leads to an increase in blood pressure.39

There is concern that ephedra alkaloids (common in cold remedies and appetite suppressants) can raise blood pressure as a result of their sympathomimetic effects. Phenylpropanolamine was associated with an increased risk of hemorrhagic stroke in women taking it as an appetite suppressant (adjusted OR = 16.5; \( P=0.02 \)),40 which led to its removal from the US drug market.41

Nonsteroidal antiinflammatory drugs (NSAIDs) can precipitate new hypertension or exacerbate existing disease. NSAIDs inhibit renal prostaglandins, which mediate increased renal perfusion,42 thus causing sodium retention, edema, and hypertension. NSAID use is associated with hypertension in the elderly (OR = 1.4; 95% CI, 1.1 to 1.7),43 and NSAID users are more likely to be on antihypertensive therapy (OR = 1.66; 95% CI, 1.54 to 1.80).44

Some forms of licorice contain glycyrrhizin. This inhibitor of 11\( \beta \)-hydroxy-steroid dehydrogenase can cause excessive levels of cortisol, with subsequent stimulation of the mineralocorticoid receptor and hypertension.45

**Valvular Heart Disease**

In 1997, Connolly et al46 described 24 women with cardiac valvular regurgitation who had been taking combination fenfluramine and phentermine appetite suppressants. Initial estimates reported the prevalence of valvular disease with these drugs as 23%,47 and fenfluramine was withdrawn from the market. A recent meta-analysis suggests that the prevalence of valvular regurgitation with long-term combination use (>90 days) was 12.0% versus 5.9% for nonusers.48 The number of prescriptions for the combination of fenfluramine and phentermine is estimated to be >18 million,49 and >30 000 cases of valvular disease have been attributed to this combination.48

This drug-induced valvular disease had a characteristic pattern of thickened, glistening, white valves reminiscent of the valvular heart disease seen in carcinoid heart disease.50 In carcinoid syndrome, tumors of midgut origin release vasoactive substances, including serotonin; long-term serotonin administration in animal models can induce morphological and echocardiographic changes similar to those seen in carcinoid heart disease. Both phentermine and fenfluramine can increase the circulating levels of serotonin.51
Recently, there have been case reports of a similar valvular disease with the use of the ergot-derived dopamine agonists pergolide\(^6^2\) and cabergoline, used to treat Parkinson disease. In a nested case-control pharmacoepidemiological study\(^5^3\) there was an increased risk of valvular disease with the use of pergolide (risk ratio=7.1; 95% CI, 2.3 to 22.3) and cabergoline (risk ratio=4.9; 95% CI, 1.5 to 15.6) but not with other dopamine agonists. These effects were dose and duration dependent. In addition to their effects on dopamine receptors, both pergolide and cabergoline are potent agonists of the serotonin 2B receptor.\(^5^4\) The cardiac valvular damage associated with dopamine agonists and appetite suppressants may have similar mechanisms.

**Pulmonary Hypertension**

Appetite suppressants (mainly fenfluramine and dexfenfluramine) also are associated with an increased risk of pulmonary hypertension. In 1 European case-control study, the use of either drug was associated with a 6.3-fold increased risk of pulmonary hypertension (95% CI, 3.0 to 13.2), and if a patient was exposed for >3 months, the risk was 23.1-fold higher (95% CI, 6.9 to 77.7) than in the nonexposed group.\(^5^5\) These findings were confirmed in a North American prospective surveillance study in which fenfluramine was associated with a 7.5-fold increased risk (95% CI, 1.7 to 32.4) for the development of pulmonary hypertension.\(^5^6\) It is possible that the underlying mechanism relates to excess serotonin, as outlined above. In contrast to fenfluramine, phentermine, and dexfenfluramine, the newer anorexigenes such as sibutramine have not been found to be associated with either valvular disease or pulmonary hypertension.\(^5^7,5^8\)

**Cardiomyopathy and Heart Failure**

Cardiotoxicity from anthracyclines can limit the use of these highly effective chemotherapeutic agents. Chronic anthracycline cardiotoxicity is dependent on the cumulative dose of drug, with rates of <0.2% with doxorubicin doses <400 mg/m\(^2\) but 18% with doses >700 mg/m\(^2\).\(^5^9\) Risk factors for cardiotoxicity include combination chemotherapy and a young age at the time of exposure.\(^4^2\) Children may develop cardiotoxicity at lower cumulative doses of anthracycline than adults.\(^6^0\) The mechanisms underlying the cardiac injury are not fully known, but free-radical generation and lipid peroxidation are thought to be important.\(^6^1\) Dextrazoxane, a free-radical scavenger, can reduce anthracycline-induced cardiotoxicity, and its use has been recommended when the risk of cardiotoxicity is high.\(^6^2\)

Cyclophosphamide, an alkylating agent used in many bone marrow transplantation regimens, can also cause dose-dependent cardiotoxicity. This can be fatal in up to 11% of cases.\(^6^3\) Fluorouracil, a pyrimidine derivative, can cause acute cardiotoxicity in 1% to 18% of patients.\(^6^4\) Manifestations include angina pectoris, myocardial infarction, hypotension, and atrial or ventricular arrhythmia.\(^6^5\)

Trastuzumab is a monoclonal antibody against the human epidermal growth factor receptor (HER-2) and a mainstay of therapy for breast cancers overexpressing HER-2.\(^4^2\) Trastuzumab is associated with an incidence of heart failure ranging from 2.6% as a first-line agent to 8.5% when used after other chemotherapeutic agents, including anthracycline derivatives.\(^6^4\) The vast majority of patients with symptomatic heart failure following trastuzumab administration improved after discontinuation of the drug.

Sunitinib, a tyrosine kinase inhibitor, extends survival of patients with metastatic renal cell carcinoma and certain gastrointestinal tumors. Multiple reports\(^5^5–^6^7\) document symptomatic left ventricular dysfunction and congestive heart failure in 10% to 15% of patients treated with sunitinib. Mitochondrial injury and cardiomyocyte apoptosis have been found in treated mice.\(^6^6\)

Imatinib, a monoclonal antibody that inhibits proliferation of hematopoietic cells expressing BCR-ABL, has revolutionized the treatment of chronic myeloid leukemia. Atallah et al\(^6^8\) recently reported symptoms caused by systolic heart failure in 22 of 1276 patients (1.7%), mainly the elderly and patients with prior cardiac disease.

Tumor necrosis factor antagonists are commonly used to treat disorders such as rheumatoid arthritis. Initially, the hope that infliximab, a tumor necrosis factor antagonist, would improve the course of heart failure led to randomized studies in patients with New York Heart Association class III or IV heart failure.\(^6^9\) These trials showed a dose-dependent increase in mortality or heart failure hospitalizations, with a significant 2.8-fold increase in risk in the group that received the highest dose of infliximab (10 mg/kg). This drug and other tumor necrosis factor antagonists are now contraindicated in patients with severe heart failure and should be used with caution in patients with even mild heart failure. There are also case reports of myocarditis and dilated cardiomyopathy after treatment with interferon-α,\(^7^0\) chloroquine,\(^7^1\) or interleukin-2.\(^7^2\)

Other agents can precipitate heart failure resulting from effects on volume expansion or sodium retention. In addition to promoting hypertension, NSAID-induced renal sodium retention and total body water expansion can precipitate heart failure. Glucocorticoids can also worsen heart failure through stimulation of mineralocorticoid receptors. Epidemiological studies have found that use of a glucocorticoid was associated with an increased risk of heart failure ranging from 1.5-fold to 3.7-fold\(^7^3,7^4\) and that the relationship was dose dependent.\(^7^4\) Similarly, licorice\(^4^5\) can promote fluid overload and precipitate heart failure, in addition to increasing blood pressure.

Thiazolidinediones, used to treat type 2 diabetes mellitus, lead to fluid retention\(^7^5\) and an increased risk of hospital admission for heart failure.\(^7^6\) This is likely due to peroxisome proliferator–activated receptor–γ-induced stimulation of epithelial sodium channels promoting salt absorption\(^7^7\) with a resultant increase in total body water.

**Metabolic Syndrome and Accelerated Atherosclerosis**

**Antipsychotic Agents**

Some traditional antipsychotic medications (eg, chlorpromazine) and some newer “atypical” antipsychotics promote weight gain and the metabolic syndrome. Schizophrenic patients are more obese than persons without schizophrenia,\(^7^8\) and it has been postulated that this was due, at least in part, to the antipsychotic agents. In the Clinical Antipsychotic
Trials of Intervention Effectiveness (CATIE) schizophrenia trial, olanzapine was associated with a mean increase in weight of 9.4 lb, with 30% of patients reporting a weight gain >7 lbs. Quetiapine was associated with a mean weight increase of only 1.1 lb, but 16% of patients still reported a weight gain >7 lb. Of concern is that this weight gain has been associated with insulin resistance, higher blood glucose levels, and type II diabetes mellitus. There was a higher rate of metabolic syndrome in the CATIE study compared with the National Health and Nutrition Examination Survey (NHANES) III of the general population in both men (36.0% versus 19.7%; P<0.0001) and women (51.6% versus 25.1%; P<0.0001). The rate of metabolic syndrome is even higher for clozapine, another atypical antipsychotic drug.81

Atypical antipsychotic drugs may also lead to altered glucose regulation independently of weight gain. One study matched patients for age and adiposity, treated the patients with various antipsychotic drugs (or no treatment), and then performed a homeostasis model assessment from an oral glucose tolerance test. Patients taking olanzapine and clozapine had greater insulin resistance compared with patients taking typical antipsychotic drugs or no treatment. Another study supported these findings and found that olanzapine and clozapine were also associated with significant weight gain but are reported to have a lower risk of metabolic dysregulation.85

**HIV and Accelerated Atherosclerosis**

There has been a decrease in HIV-related cardiomyopathy and pericarditis with contemporary highly active antiretroviral therapy, but premature coronary atherosclerosis related to antiretroviral drugs remains a problem.86 Some nucleoside reverse transcriptase inhibitors are associated with an increased risk of myocardial infarction. Excess myocardial infarction has been seen with didanosine (adjusted relative risk [RR] = 1.49; 95% CI, 1.14 to 1.95) and abacavir (adjusted RR = 1.89; 95% CI, 1.47 to 2.45) but not with zidovudine, stavudine, or lamivudine.87 The use of combination antiretroviral therapy (including a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor) has been associated with an increased risk of myocardial infarction (adjusted RR = 1.26; 95% CI, 1.12 to 1.41). Further analysis found that the risk of myocardial infarction was increased with protease inhibitors (adjusted RR = 1.10; 95% CI, 1.04 to 1.18) but not with nonnucleoside reverse transcriptase inhibitor (adjusted RR = 1.00; 95% CI, 0.93 to 1.09). One prospective study found the annual incidence of myocardial infarction to be higher in HIV-positive patients treated with a protease inhibitor (5.1 per 1000 patient-years) compared with a nonnucleoside reverse transcriptase inhibitor (0.4 per 1000 patients-years; P<0.001). Diverse mechanisms may contribute to these findings. More than 50% of patients receiving protease inhibitor develop lipodystrophy, with fat wasting of the extremities, buttocks, and face, along with central fat accumulation.86 Several protease inhibitors (including ritonavir, indinavir, and amprenavir) have been found to upregulate CD36, a receptor mediating cholesterol uptake in macrophages, providing a direct mechanism for the promotion of atherosclerosis. Protease inhibitors also impair endothelium-dependent vasodilation and increase carotid intima-media thickness.84

There is also the potential for drug interactions with lipid-lowering drugs. Many statins (eg, simvastatin, atorvastatin, and lovastatin) are metabolized by CYP3A4, which is inhibited by several protease inhibitors (eg, delavirdine, indinavir, nelfinavir, and ritonavir). When given with the combination of ritonavir and saquinavir, area-under-the-curve concentrations of simvastatin increased >3000%, atorvastatin increased 79%, and pravastatin decreased 50%.88 Statin-related rhabdomyolysis has been reported, which likely resulted from elevated statin levels.89

**Myocardial Infarction**

**Cyclooxygenase-2 Inhibitors**

The Vioxx GI Outcomes Research (VIGOR) study found that the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib decreased gastrointestinal complications by 60% compared with naproxen but was associated with a 5-fold higher incidence of myocardial infarction. Ray et al98 found that users of high-dose rofecoxib (greater than the recommended maximum long-term dose of 25 mg) were 1.7-fold more likely than nonusers to have serious coronary artery disease events, whereas this risk was not seen at lower doses of rofecoxib or other NSAIDs. Patients often use higher doses than recommended for longer than the 2-week maximum duration approved by the FDA. A similar increase in coronary artery disease events was not reported in the Celecoxib Long-Term Arthritis Safety Study (CLASS) of celecoxib, another selective COX-2 inhibitor.99 Graham et al100 found that rofecoxib was associated with a higher risk of acute myocardial infarction or SCD compared with celecoxib (OR = 1.59; 95% CI, 1.10 to 2.32) and that the risk was even higher for rofecoxib doses of >25 mg/d (OR = 3.58; 95% CI, 1.27 to 10.11). It is not clear to what extent these findings represent a “class effect” of COX-2 inhibitors because increased risks also have been reported with many nonselective NSAIDs. There are significant differences in the relative selectivity of the COX-2 inhibitors,101 which may explain the observed differences in risk between rofecoxib and celecoxib and the differences among NSAIDs.

**Rosiglitazone**

A meta-analysis of trials of the thiazolidinedione rosiglitazone found an increased risk of myocardial infarction (OR = 1.43; 95% CI, 1.03 to 1.98) with a nonsignificant trend toward an increase in cardiovascular death (OR = 1.64; 95% CI, 0.98 to 2.74).102 These findings were supported by a nested case-control study using a Canadian healthcare database. Lipscombe et al103 found that thiazolidinedione use...
(primarily with rosiglitazone) was associated with an increased risk of congestive heart failure, acute myocardial infarction, and mortality compared with other oral hypoglycemic medications. In July 2007, a joint US FDA Advisory Committee concluded that the use of rosiglitazone was associated with a greater risk for myocardial ischemic events than placebo, metformin, or sulfonylureas.\textsuperscript{104}

Hormone Replacement Therapy

Many observational studies suggested that hormone replacement therapy decreased cardiovascular risk, but these data may have been biased by the preferential use of hormone replacement therapy by otherwise healthier women.\textsuperscript{105} To overcome this bias, the Women’s Health Initiative randomized 16 608 postmenopausal women to receive conjugated equine estrogen plus medroxyprogesterone acetate or placebo.\textsuperscript{106} The trial was terminated early because there was an excess risk of nonfatal myocardial infarction or death resulting from coronary heart disease events in the hormone replacement therapy group (OR = 1.24; 95% CI, 1.00 to 1.54). A separate cohort of 10 739 postmenopausal women were randomized to conjugated equine estrogen alone versus placebo.\textsuperscript{107} Estrogen replacement did not significantly lower the risk of coronary heart disease events (OR = 0.91; 95% CI, 0.75 to 1.12), but coronary heart disease risk was not increased, unlike when estrogen was combined with progesterone.

Congenital Heart Disease

Kallen and Otterblad\textsuperscript{108} performed a case-control study in Sweden that included >5000 cases of cardiovascular defects in the absence of known chromosomal abnormalities. There were >500 000 births in Sweden during the 6.5-year period of case accrual. Drugs associated with a significantly increased risk for infant cardiovascular defects, including insulin (OR = 3.69; 95% CI, 2.85 to 4.78), fertility drugs (OR = 1.81; 95% CI, 1.22 to 2.70), anticonvulsants (OR = 1.60; 95% CI, 1.02 to 2.52), tricyclic antidepressants (OR = 1.77; 95% CI, 1.07 to 2.91), clomipramine (OR = 2.03; 95% CI, 1.22 to 3.40), and naproxen (OR = 1.70; 95% CI, 1.14 to 2.54). Using a Canadian provincial registry, Ofoti et al\textsuperscript{109} identified a risk from the maternal use of NSAIDs, with an adjusted OR of 2.21 for any congenital abnormality and 3.34 for cardiac septal defects.

Kallen and Otterblad\textsuperscript{108} also reported a significantly increased risk of any congenital malformation (OR = 1.24) after erythromycin but an even higher risk of a cardiovascular malformation (OR = 1.92).\textsuperscript{110} No increased risk was noted with the use of penicillin V. An intriguing drug effect was that of antihistamines, which were found to have a protective effect on infant cardiovascular defects (OR = 0.76).\textsuperscript{108} Although some of the drug associations likely represent markers of underlying medical risks (such as the use of insulin and diabetes), the data suggest possible teratogenic risks even with commonly used medications.

Angiotensin-converting enzyme inhibitors are contraindicated during the second and third trimesters of pregnancy because of fetal malformation and death, but they had traditionally been thought to be safe in the first trimester. However, Cooper et al\textsuperscript{111} found that isolated first-trimester use of angiotensin-converting enzyme inhibitors increased the risk of major congenital malformation (RR = 2.71) and cardiovascular malformations (RR = 3.72). First-trimester use of other antihypertensive (excluding angiotensin receptor blockers, which might have an effect similar to angiotensin-converting enzyme inhibitors) medications did not confer an increased risk (RR = 0.66).

Drug Interactions: Noncardiovascular Drugs Can Affect Cardiovascular Drugs

Aspirin and Ibuprofen

Catella-Lawson et al\textsuperscript{112} studied the effects of aspirin alone and in combination with rofecoxib, acetylsalicylic acid, diclofenac, or ibuprofen on thromboxane formation and platelet aggregation. Aspirin alone or aspirin before any of the other drugs inhibited thromboxane formation and platelet aggregation. However, this inhibition was attenuated when ibuprofen was administered before aspirin. Ibuprofen is thought to reversibly block the acetylation site in the COX-1 enzyme and thus prevent the aspirin-mediated irreversible inhibition of thromboxane synthesis. This effect was not seen with rofecoxib, acetylsalicylic acid, or diclofenac.

CYP3A4 and CYP3A5

Drugs and grapefruit juice inhibit CYP3A4 and 3A5 and can cause clinically significant drug interactions. Grapefruit juice preferentially inhibits intestinal CYP3A (as opposed to hepatic CYP3A), leading to decreased intestinal drug metabolism and thus greater systemic availability of multiple CYP3A substrates, including amiodipine, felodipine, diltiazem, verapamil, and simvastatin.\textsuperscript{80} Because the magnitude of this response is unpredictable, large doses of grapefruit juice are contraindicated in patients receiving drugs that undergo extensive CYP3A metabolism. Concentrations of the CYP3A substrates terfenadine, cisapride, or erythromycin and their QT-prolonging effects are exaggerated when drugs that inhibit CYP3A (including cardiovascular drugs like verapamil or diltiazem and noncardiovascular agents like ketoconazole) are coadministered.\textsuperscript{18,113,114}

CYP2D6

Some selective serotonin reuptake inhibitors (paroxetine and fluoxetine) are potent inhibitors of CYP2D6. Such drugs can convert an extensive metabolizer (90% to 95% of the population) to a poor metabolizer and, if coadministered with CYP2D6 substrate drugs such as metoprolol, increase concentrations. This can result in loss of metoprolol cardioselectivity.

CYP2C9

This enzyme is responsible for the metabolism of warfarin and the bioactivation of certain angiotensin receptor blockers (eg, losartan). CYP2C9 inhibitors include phenytoin, sertraline, and fluconazole; coadministration of these drugs can lead to warfarin overanticoagulation or loss of antihypertensive effect of substrate angiotensin receptor blockers.

CYP2C19

This enzyme is responsible for the bioactivation of clopidogrel. Data from large clinical trials and drug use databases indicate a higher incidence of serious cardiovascular events
during clopidogrel therapy not only in subjects with loss of function alleles but also in those exposed to CYP2C19 inhibitors. Proton pump inhibitors have been implicated as “class” CYP2C19 inhibitors, but the effect varies across individual drugs, with potent in vitro inhibition by lansoprazole and omeprazole, less inhibition by rabeprazole, and much less inhibition by pantoprazole. Using the Ontario Public Drug Program database, Juurlink et al reported that among patients receiving clopidogrel after a myocardial infarction, concomitant use of omeprazole, lansoprazole, or rabeprazole (but not pantoprazole) was associated with an increased risk of recurrent myocardial infarction. Ho et al reported that the combined use of clopidogrel and a proton pump inhibitor after acute coronary syndrome was associated with a greater risk of death and rehospitalization for acute coronary syndrome than clopidogrel alone. A list of CYP enzymes, enzyme substrates, enzyme inhibitors, and enzyme inducers is maintained at http://medicine.iupui.edu/flockhart.

P-Glycoprotein
P-glycoprotein (P-gp) is the membrane efflux transporter responsible for digoxin elimination. “Noncardiovascular” P-glycoprotein inhibitors such as erythromycin, ketoconazole, and clarithromycin can lead to digoxin toxicity. The same effect is seen with several cardiovascular drugs (eg, amiodarone, verapamil, and quinidine) that inhibit P-glycoprotein.

Cholestyramine
Cholestyramine is an exchange resin that is used primarily to bind bile acids, which can then lower low-density lipoprotein cholesterol. Because of the physical interaction between the drug and the resin, cholestyramine can decrease the absorption of digoxin by 30% to 40%.

Herbal Medicines
A large number of patients consume herbal medicines in addition to prescription medicines. The US National Center for Complementary and Alternative Medicines estimated that >60 million Americans used a nonvitamin, nonmineral natural products in 2007. Many of these herbal medicines can interact with cardiovascular drugs. The most common interactions occur with warfarin and digoxin but can also include increased bleeding when aspirin is used in conjunction with herbs containing salicylates such as gingko.

Conclusions
Drugs that are not used primarily to treat cardiovascular disease commonly have cardiovascular effects. Some effects are common and their mechanisms are understood; others are rare, unproven, or not well understood. In addition, drug interactions between cardiovascular and noncardiovascular drugs can affect cardiovascular responses. Therefore, the cardiologist’s therapeutic consciousness needs to encompass a range of drugs not usually considered to be of cardiovascular consequence.

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Disclosures
Dr Raj has consulted for attorneys about the effects of yohimbine on blood pressure. Dr Stein has consulted for attorneys regarding antipsychotic drugs. The other authors report no conflicts.

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