

# Drugs That May Cause or Exacerbate Heart Failure

## A Scientific Statement From the American Heart Association

**ABSTRACT:** Heart failure is a common, costly, and debilitating syndrome that is associated with a highly complex drug regimen, a large number of comorbidities, and a large and often disparate number of healthcare providers. All of these factors conspire to increase the risk of heart failure exacerbation by direct myocardial toxicity, drug-drug interactions, or both. This scientific statement is designed to serve as a comprehensive and accessible source of drugs that may cause or exacerbate heart failure to assist healthcare providers in improving the quality of care for these patients.

**H**ear failure (HF) remains the leading discharge diagnosis among patients  $\geq 65$  years of age. The estimated cost for treatment of HF in Medicare recipients is \$31 billion and is expected to increase to \$53 billion by 2030.<sup>1</sup> Hospitalization for HF is the largest segment of those costs. It is likely that the prevention of drug-drug interactions and direct myocardial toxicity would reduce hospital admissions, thus both reducing costs and improving quality of life.

Patients with HF often have a high medication burden consisting of multiple medications and complex dosing regimens. On average, HF patients take 6.8 prescription medications per day, resulting in 10.1 doses a day. This estimate does not include over-the-counter (OTC) medications or complementary and alternative medications (CAMs).<sup>2</sup> More than 15 million Americans consume vitamins or CAMs, especially those with chronic illnesses. With many prescription medications switching to OTC status, the consumption of OTC products appears to be increasing. Older adults are the largest consumers of OTC medications, taking on average 4 OTC medications per day. Unfortunately, the information on the prevalence of OTC and CAM use in patients with HF is limited. In a single-center study of 161 patients with HF, 88% reported using OTC medications, 34.8% took herbal supplements, and 65.2% took vitamins.

By definition, polypharmacy is the long-term use of  $\geq 5$  medications.<sup>3</sup> When prescription and OTC medications and CAM use are taken into account, polypharmacy may be universal in patients with HF. The reasons for polypharmacy among patients with HF can be both complex and multifactorial. Some of the reasons may be related to the increasing number of guideline-directed medications for HF and other comorbidities, as well as the increasing comorbidity burden in an aging population that may warrant an increasing number of specialist and provider visits.<sup>4,5</sup>

The HF syndrome is accompanied by a broad spectrum of both cardiovascular and noncardiovascular comorbidities. Five or more cardiovascular and noncardiovascular chronic conditions are present in 40% of Medicare patients with

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HF. This estimate is much higher compared with the general Medicare population, in which only 7.6% have  $\geq 3$  chronic conditions.<sup>6</sup> Using the National Health and Nutrition Examination Survey, Wong et al<sup>7</sup> found that the proportion of patients with  $\geq 5$  comorbidities increased from 42.1% in the period of 1988 to 1994 to 58% in the period of 2003 to 2008. From this analysis, osteoarthritis (62%), obesity (46.8%), chronic kidney disease (45.9%), and diabetes mellitus (38.3%) were the most common noncardiovascular comorbidities. In an analysis of noncardiac comorbidity in 122 630 Medicare beneficiaries, Braunstein et al<sup>8</sup> found that diabetes mellitus (31%), chronic obstructive pulmonary disease (26%), ocular disorders (24%), osteoarthritis (16%), and thyroid disorders (14%) predominated. As the burden of noncardiovascular comorbidities increases, the number of medications, medication costs, and complexity also may increase.<sup>2</sup>

In the general population, patients with  $\geq 5$  chronic conditions have an average of 14 physician visits per year compared with only 1.5 for those with no chronic conditions.<sup>8–11</sup> Medicare beneficiaries with HF see 15 to 23 different providers annually in both the inpatient and outpatient settings, which could in turn increase the number of prescription medications prescribed.<sup>6</sup> As the number of prescription medications increases, so does the potential for adverse drug events and drug-drug interactions. Goldberg et al<sup>12</sup> found that patients taking at least 2 prescription medications had a 13% risk of an adverse drug-drug interaction, which increased to 38% for 4 medications and 82% with  $\geq 7$  medications.

Drugs may cause or exacerbate HF by causing direct myocardial toxicity; by negative inotropic, lusitropic, or chronotropic effects; by exacerbating hypertension; by delivering a high sodium load; or by drug-drug interactions that limit the beneficial effects of HF medications. To avoid these negative effects, healthcare providers need a comprehensive and accessible guide of the prescription medications, OTC medications, and CAMs that could exacerbate HF.

Using case reports, case series, package inserts, meta-analyses, and prospective and observational trials, we provide a clinically relevant list of prescription medications that may cause myocardial toxicity or exacerbate underlying myocardial dysfunction, leading to the precipitation or induction of HF (Tables 1 and 2), and highlight concerns with CAM and OTC medications. Medications were selected on the basis of use in the HF population and the potential to cause an adverse drug event as defined by death; an increase in health resource use; a change in New York Heart Association (NYHA) class, cardiac function, or cardiovascular disease; and a significant or transient change in medication regimen. Table 3 defines the criteria used to evaluate the magnitude of precipitation or exacerbation of

HF, the strength of evidence for HF precipitation or exacerbation, and the onset of effect for the prescription medications discussed.

The American College of Cardiology/American Heart Association Class of Recommendation and Level of Evidence are derived independently of each other according to established criteria<sup>13</sup> (Table 4). The Class of Recommendation indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit of a clinical action in proportion to risk. The Level of Evidence rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources.

## **PRESCRIPTION MEDICATIONS**

### **Analgesics**

#### ***Nonsteroidal Anti-inflammatory Drugs***

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed in the United States, accounting for 70 million prescriptions and 30 billion OTC medications sold annually.<sup>14</sup> The majority of NSAID-related side effects can be attributed to inhibition of prostaglandin production through inhibition of cyclooxygenase (COX) isoenzymes. Traditional NSAIDs (ie, indomethacin, ketorolac, ibuprofen, and diclofenac) act by nonselectively inhibiting both the COX-1 isoenzyme (which is a constitutively expressed protein responsible for protective and regulatory functions) and COX-2 isoenzyme (which is inducible and overexpressed during inflammation). The newer coxibs (celecoxib) selectively block just the COX-2 isoenzyme. Through inhibition of COX-1, traditional NSAIDs adversely affect platelet aggregation, maintenance of the gastric mucosal barrier, and renal function. NSAIDs have the potential to trigger HF through sodium and water retention, increased systemic vascular resistance, and blunted response to diuretics.

Observational studies suggest an association between traditional NSAIDs use and HF precipitation and exacerbation.<sup>15–18</sup> In an evaluation of 7277 long-term NSAID users over 72 months, the Rotterdam study results found a trend to an increased risk for incident HF (adjusted relative risk [RR], 1.1; 95% confidence interval [CI], 0.7–1.7). Patients with prevalent HF who filled at least 1 NSAID prescription since their diagnosis of HF had a 10-fold increased risk for recurrence (adjusted RR, 9.9; 95% CI, 1.7–57.0).<sup>15</sup> Huerta et al<sup>18</sup> also found an elevated risk of a first hospital admission for HF in current users of NSAIDs (adjusted RR, 1.3; 95% CI, 1.1–1.6) that occurred independently of duration of exposure but was associated with higher-dose NSAIDs (RR, 1.44; 95% CI, 1.06–1.94).

Debate surrounds the cardiovascular safety of COX-2-selective inhibitors in patients with HF. In a large, observational cohort study of 107 092 older adults with a

**Table 1. Prescription Medications That May Cause or Exacerbate HF**

Drug or Therapeutic Class	Association With HF		Magnitude of HF Induction or Precipitation	Level of Evidence for HF Induction or Precipitation	Possible Mechanism(s)	Onset	Comments
	Causes Direct Myocardial Toxicity	Exacerbates Underlying Myocardial Dysfunction					
Analgesics							
COX, nonselective inhibitors (NSAIDs)		x	Major	B	Prostaglandin inhibition leading to sodium and water retention, increased systemic vascular resistance, and blunted response to diuretics	Immediate	
COX, selective inhibitors (COX-2 inhibitors)		x	Major	B			
Anesthesia medications							
Inhalation or volatile anesthetics							
Desflurane		x	Major	B	Myocardial depression, peripheral vasodilation, attenuated sympathetic activity	Immediate	Sole induction alone is not generally used because of hemodynamic instability and airway irritation in patients with HF
Enflurane		x	Major	B			
Halothane		x	Major	B			
Isoflurane		x	Major	B			
Sevoflurane		x	Major	B			
Intravenous anesthetics							
Dexmedetomidine		x	Moderate	B	α <sub>2</sub> -Adrenergic agonist	Immediate	
Etomidate		x	Moderate	B	Suppression of adrenal function		Not generally used for maintenance of anesthesia
Ketamine		x	Major	B	Negative inotrope		
Propofol		x	Moderate	B	Negative inotrope, vasodilation		
Diabetes mellitus medications							
Biguanide							
Metformin		x	Major	C	Increased anaerobic metabolism and elevated lactic acidosis	Immediate to delayed (depending on renal function fluctuations)	
Thiazolidinediones		x	Major	A	Possible calcium channel blockade	Intermediate	May be reversible on discontinuation; not recommended in patients with symptomatic HF
Dipeptidyl peptidase-4 inhibitors							
Saxagliptin		x	Major	B	Unknown	Intermediate to delayed	May be a class effect
Sitagliptin		x	Major	B		Intermediate to delayed	
Antiarrhythmic medications							
Class I antiarrhythmics							
Flecainide		x	Major	B	Negative inotrope, proarrhythmic effects	Immediate to intermediate	
Disopyramide		x	Major	B		Immediate to intermediate	

(Continued)

**Table 1. Continued**

Drug or Therapeutic Class	Association With HF		Magnitude of HF Induction or Precipitation	Level of Evidence for HF Induction or Precipitation	Possible Mechanism(s)	Onset	Comments
	Causes Direct Myocardial Toxicity	Exacerbates Underlying Myocardial Dysfunction					
Antiarrhythmic medications, continued							
Class III antiarrhythmics							
Sotalol		x	Major	B	Proarrhythmic properties, $\beta$ -blockade	Immediate to Intermediate	
Other antiarrhythmics							
Dronedarone		x	Major	A	Negative inotrope	Immediate to intermediate	
Antihypertensive medications							
$\alpha_1$ -Blockers							
Doxazosin		x	Moderate	B	$\beta_1$ -Receptor stimulation with increases in renin and aldosterone	Intermediate to delayed	
Calcium channel blockers							
Diltiazem		x	Major	B	Negative inotrope	Immediate to intermediate	
Verapamil		x	Major	B			
Nifedipine		x	Moderate	C			
Centrally acting $\alpha$ -adrenergic medications							
Moxonidine		x	Major	B	Possible sympathetic withdrawal	Intermediate	
Peripheral vasodilators							
Minoxidil		x	Moderate	C	Unknown	Intermediate	
Anti-infective medications							
Azole antifungal medications							
Itraconazole		x	Major	C	Negative inotrope	Immediate to intermediate	Contraindicated for treating onychomycosis; consider only in the case of life-threatening fungal infections; reversible on discontinuation
Other antifungal medications							
Amphotericin B	x		Major and moderate	C	Unknown	Intermediate	Reversible on discontinuation with some improvement in LVEF
Anticancer medications							
Anthracyclines							
Doxorubicin	x	x	Major	A	Prolonged oxidative stress caused by secondary alcohol metabolite	Immediate (rare), intermediate, and delayed	Irreversible; risk increases with increasing cumulative dose; delayed can occur >20 y after first dose
Daunorubicin	x	x		A			
Epirubicin	x	x		A			
Idarubicin	x	x		A			
Mitoxantrone	x	x		A			

(Continued)

**Table 1. Continued**

Drug or Therapeutic Class	Association With HF		Magnitude of HF Induction or Precipitation	Level of Evidence for HF Induction or Precipitation	Possible Mechanism(s)	Onset	Comments
	Causes Direct Myocardial Toxicity	Exacerbates Underlying Myocardial Dysfunction					
Anticancer medications, continued							
Alkylating agents							
Cyclophosphamide	x	x	Major and moderate	B	Oxidative stress	Immediate	Can be reversible; usually resolves within 3–4 wk
Ifosfamide	x	x		B			
Mitomycin	x	x	Moderate	C	Reduction to semiquinone radical; oxidative stress	Intermediate	Can be reversible; usually occurs after a median of 3 cycles at doses >30 mg/m <sup>2</sup>
Antimetabolites							
5-FU	x	x	Major and moderate	B	Unknown, possibly coronary vasospasm	Immediate	Can be reversible; Takotsubo cardiomyopathy presentation observed, resolves within weeks
Capecitabine	x	x		C			
Targeted therapies							
Bevacizumab	x	x	Major and moderate	A	VEGFA	Intermediate	Can be reversible; associated with significant hypertension
Imatinib	x	x	Moderate	B	Abl, PDGFR, c-kit	Intermediate	Rare; may be associated with worsening edema
Interferon	x	x	Major and moderate	C	Unknown	Immediate	Reversible on discontinuation of therapy
Interleukin-2	x		Major	C	Cytotoxic damage to the myocardium	Immediate	Rare
Lapatinib	x	x	Major and moderate	A	ErbB2	Intermediate	Can be reversible
Pertuzumab	x	x	Major and moderate	C	ErbB2, antibody-dependent cytotoxicity	Intermediate	Can be reversible
Sorafenib		x	Minor	B	VEGFR, PDGFR	Intermediate	Associated with significant hypertension
Sunitinib	x	x	Major	B	VEGFR, PDGFR, Flt-3, c-kit, AMP-kinase	Intermediate	Can be reversible; also associated with significant hypertension
Trastuzumab	x	x	Major and moderate	A	ErbB2, antibody-dependent cytotoxicity	Intermediate	Can be reversible with temporary cessation of therapy or institution of HF medications
Taxanes							
Paclitaxel	x	x	Moderate	B	Potentiation of anthracyclines	Intermediate	Can separate administration of the anthracycline from the taxane
Docetaxel	x	x		B			

(Continued)

**Table 1. Continued**

Drug or Therapeutic Class	Association With HF		Magnitude of HF Induction or Precipitation	Level of Evidence for HF Induction or Precipitation	Possible Mechanism(s)	Onset	Comments
	Causes Direct Myocardial Toxicity	Exacerbates Underlying Myocardial Dysfunction					
Anticancer medications, continued							
Other cancer medications							
Thalidomide		x	Minor	C	Unknown	Unknown	May be associated with worsening edema but also a potential HF therapy
Lenalidomide	x	x	Major	C	Hypersensitivity myocarditis	Immediate	Rare
Hematologic medications							
Anagrelide	x		Major	A	Possible inhibition of PD IV	Immediate to delayed	
Cilostazol		x	Major	A	Inhibition of PD III resulting in arrhythmias	Unknown	Contraindicated in HF patients
Neurological and psychiatric medications							
Stimulants	x		Major (with overdose) and minor	B	Peripheral $\alpha$ - and $\beta$ -agonist activity	Unknown	
Antiepileptics							
Carbamazepine		x	Major	C	Negative inotrope and chronotrope; depresses phase 2 repolarization; suppress sinus nodal automaticity and AV conduction	Immediate (with overdose) to intermediate	Reversible on discontinuation
Pregabalin		x	Moderate to minor	C	L-type calcium channel blockade	Immediate to intermediate	
Antidepressants							
Tricyclic antidepressants		x	Moderate	C	Negative inotrope, proarrhythmic properties	Intermediate to delayed	Reversible on discontinuation
Citalopram		x	Major	A	Dose-dependent QT prolongation	Intermediate	Not recommended in patients with uncompensated HF; do not exceed 40 mg/d
Antiparkinson medications							
Bromocriptine	x		Major	B	Excess serotonin activity leading to valvular damage	Intermediate to delayed	Removed from the US market but remains in Europe
Pergolide	x		Major	A			
Pramipexole	x		Major	A	Unknown		
Antipsychotics							
Clozapine	x		Major	C	IgE-mediated hypersensitivity reaction, calcium channel blockade	Intermediate to delayed	

(Continued)

**Table 1. Continued**

Drug or Therapeutic Class	Association With HF		Magnitude of HF Induction or Precipitation	Level of Evidence for HF Induction or Precipitation	Possible Mechanism(s)	Onset	Comments
	Causes Direct Myocardial Toxicity	Exacerbates Underlying Myocardial Dysfunction					
Neurological and psychiatric medications, continued							
Antimigraine medications							
Ergotamine	x		Major	C	Excess serotonin activity leading to valvular damage	Delayed	May not be reversible with drug discontinuation
Methysergide	x		Major	C			
Appetite suppressants	x		Major	A	Valvular damage	Intermediate	Fenfluramine, dexfenfluramine, and sibutramine have been removed from the US market
Bipolar medications							
Lithium	x		Major	C	Direct myofibrillar degeneration, adrenergic stimulation, calcium ion influx interference	Intermediate to delayed	Reversible on discontinuation
Ophthalmological medications							
Topical β-blockers		x	Major	C	Negative inotrope	Immediate to intermediate	Consider lowering the dose or discontinuing; reversible on discontinuation
Topical cholinergic agents		x	Minor	C	Unknown	Immediate to intermediate	
Pulmonary medications							
Albuterol	x	x	Major to moderate	B	Decreased β-receptor responsiveness with increased exposure	Intermediate to delayed	Increased risk with systemic use, dose-response risk with inhaled use
Bosentan		x	Major	A	Unknown	Delayed	
Epoprostenol		x	Major	A	Unknown	Immediate	Contraindicated in HF
Rheumatological agents							
TNF-α inhibitors	x	x	Major	A	Cytokine mediated	Intermediate	For infliximab, avoid use in patients with moderate to severe HF; do not administer doses exceeding 5 mg/kg
Antimalarials							
Chloroquine	x	x	Major	C	Intracellular inhibitor of lysosomal enzymes	Intermediate to delayed	Exhibited with long-term exposure and high doses; can be reversible; if detected, consider endomyocardial biopsy with electron microscopic examination
Hydroxychloroquine	x	x	Major	C			

(Continued)



**Table 1. Continued**

Drug or Therapeutic Class	Association With HF		Magnitude of HF Induction or Precipitation	Level of Evidence for HF Induction or Precipitation	Possible Mechanism(s)	Onset	Comments
	Causes Direct Myocardial Toxicity	Exacerbates Underlying Myocardial Dysfunction					
Urological agents							
α <sub>1</sub> -Blockers							
Doxazosin		x	Moderate	C	β <sub>1</sub> -Receptor stimulation with increases in renin and aldosterone	Delayed	
Prazosin		x	Moderate	C			
Tamsulosin		x	Moderate	C			
Terazosin		x	Moderate	C			

Abl indicates Abelson murine leukemia viral oncogene; AMP-kinase, AMP-activated protein kinase; AV, atrioventricular; c-kit, tyrosine protein kinase; COX-2, cyclooxygenase-2; Erb-B2, Erb-B2 receptor tyrosine kinase 2; 5-FU, 5-fluorouracil; Flt-3, Fms-like tyrosine kinase; HF, heart failure; IgE, immunoglobulin E; LVEF, left ventricular ejection fraction; NSAID, nonsteroidal anti-inflammatory drug; NYHA, New York Heart Association; PD, phosphodiesterase; PDGFR, platelet-derived growth factor receptor; QT, QT interval; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; VEGFA, vascular endothelial growth factor-A ligand; and VEGFR, vascular endothelial growth factor receptor.

discharge diagnosis of HF, Gislason et al<sup>19</sup> found a significant dose-related increased risk of hospitalization for HF, myocardial infarction (MI), and all-cause mortality for those taking a coxib (rofecoxib, celecoxib) or traditional NSAID (ie, ibuprofen, diclofenac, naproxen). The American College of Cardiology Foundation/American Heart Association HF guidelines recommend that this class of drugs should be avoided or withdrawn whenever possible.<sup>13</sup>

### Anesthesia Medications

With an aging population and increasing prevalence of patients with HF, a growing number of high-risk patients are undergoing surgical procedures with an increased risk of perioperative cardiac morbidity, mortality, and resource use. Hammill et al<sup>20</sup> observed a 63% increased risk of operative mortality and a 51% greater risk of 30-day all-cause readmission among patients with HF compared with patients without HF or coronary artery disease. Most anesthetics interfere with cardiovascular performance, by either direct myocardial depression (negative inotropy) or modification of cardiovascular control mechanisms (ie, heart rate, contractility, preload, afterload, and vascular resistance).

#### Inhalational or Volatile Anesthetics

The halogenated anesthetics include halothane, enflurane, isoflurane, desflurane, and sevoflurane. These inhalational or volatile anesthetics (except halothane and enflurane) are commonly used for balanced general anesthesia in all patients, including patients with cardiovascular disease and compromised ventricular function. Compared with total intravenous anesthesia with a single agent (eg, narcotic, propofol, or benzodiazepine),

supplementation of inhalational anesthetic reduces the required dose of intravenous anesthetics for minimal anesthetic concentration. General anesthetics in high doses often induce systemic hypotension attributable to myocardial depression, peripheral vasodilation, and attenuated sympathetic nervous system activity.<sup>21</sup> Inhaled anesthetic agents (eg, isoflurane, sevoflurane, and desflurane) are recommended for the maintenance of general anesthesia in patients with ventricular dysfunction because of their hemodynamic stability and ischemic preconditioning properties.<sup>22–27</sup> However, sole induction with inhalational anesthetics is generally not done because of hemodynamic instability, airway irritation, and relative slower onset compared with intravenous induction agents in patients with ventricular dysfunction.

#### Intravenous Anesthetics

Propofol is a short-acting hypnotic agent with potentiation of gamma-aminobutyric acid receptor activity.<sup>28</sup> It is the most commonly used intravenous anesthetic for the induction (2–2.5 mg/kg) and maintenance (6–12 mg·kg<sup>-1</sup>·h<sup>-1</sup>) of anesthesia and for procedural sedation. Although propofol has both negative inotropic effects and vasodilatory properties proportional to dose, the effects on myocardial contractility at clinical concentrations are minimal. Propofol protects the myocardium against ischemia/reperfusion injury because of its antioxidant and free-radical-scavenging properties, as well as the related inhibition of the mitochondrial permeability transition pore. The major hemodynamic consequences of propofol anesthesia in the setting of left ventricular (LV) dysfunction are veno-dilatation causing LV preload reduction that results in a decrease in LV diastolic pressure and a reduction in chamber dimensions.<sup>29</sup> Such changes may be beneficial, especially in the setting of elevated LV preload. Propofol may be cardioprotective and antiar-



**Table 2. Prescription Drugs Known to Cause Direct Myocardial Toxicity**

Therapeutic Class	Drug
Anthracyclines	Doxorubicin
	Daunorubicin
	Epirubicin
	Idarubicin
	Mitoxantrone
Antifungals	Amphotericin B
Antimalarials	Chloroquine
	Hydroxychloroquine
Antiparkinson agents	Bromocriptine
	Pergolide
Antipsychotics	Clozapine
Antimigraine agents	Ergotamine
	Methysergide
Antimetabolites	5-FU
	Capecitabine
Alkylating agents	Cyclophosphamide
	Ifosfamide
	Mitomycin
Biologicals	Bevacizumab
	Imatinib
	Interferon
	Interleukin-2
	Lapatinib
	Pertuzumab
	Sorafenib
	Sunitinib
	Trastuzumab
Bipolar medications	Lithium
Hematologic agents	Anagrelide
Other cancer agents	Lenalidomide
Taxanes	Docetaxel
	Paclitaxel
Stimulants	All drugs within this class (eg, racemic amphetamine, dextroamphetamine, methylphenidate, methamphetamine, and pseudoephedrine)
TNF- $\alpha$ inhibitors	All drugs within this class (eg, infliximab, etanercept, and adalimumab)

5-FU indicates 5-fluorouracil; and TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

rhythmogenic by inducing pharmacological preconditioning of the myocardium through a mechanism similar to the inhalational anesthetics.<sup>29</sup> For total intravenous anesthesia, propofol is always combined with an opioid and a

**Table 3. Definitions of Evaluation Criteria**

Magnitude of precipitation or exacerbation of HF
Major: Effects that are life-threatening or effects that lead to hospitalization or emergency room visit.
Moderate: Effects that can lead to an additional clinic visit, change in NYHA functional class, change in cardiac function, or worsening cardiovascular disease (eg, hypertension, dyslipidemia, and metabolic syndrome) or effects that lead to symptoms that warrant a permanent change in the long-term medication regimen.
Minor: Effects that lead to a transient increase in patient assessment/surveillance or effects that lead to symptoms that warrant a transient medication change.
Level of Evidence of precipitation or exacerbation of HF
Level A: Multiple populations evaluated. Data derived from multiple randomized, controlled trials or meta-analyses.
Level B: Limited populations evaluated. Data derived from a single randomized, controlled trial or nonrandomized studies.
Level C: Very limited populations evaluated. Data have been reported in case reports, case studies, expert opinion, and consensus opinion.
Onset of effect
Immediate: Effect is demonstrated within 1 wk of drug administration.
Intermediate: Effect is demonstrated within weeks to months of drug administration.
Delayed: Effect is demonstrated within $\geq 1$ y of drug administration.

HF indicates heart failure; and NYHA, New York Heart Association.

benzodiazepine, with or without a neuromuscular blockade agent.

Etomidate is a short-acting hypnotic with gamma-aminobutyric acid-like effects. It results in the least cardiovascular depression of all anesthetics, and it does not appear to elevate plasma histamine or cause histamine release when administered in recommended doses. It is commonly used to induce anesthesia (0.2–0.6 mg/kg over 30–60 seconds) in patients with cardiovascular disease; however, it is not generally used to maintain anesthesia because it suppresses adrenocortical function.<sup>29</sup>

Ketamine, a dissociative anesthetic, is a noncompetitive *N*-methyl-D-aspartate glutamate receptor antagonist with both direct negative inotropic effects and central sympathetic stimulation and inhibition of neuronal catecholamine uptake. These latter effects counteract the direct negative inotropic effects, resulting in stable hemodynamics during the induction of anesthesia. However, in patients with significant LV dysfunction, the sympathetic stimulation may not be adequate to overcome the negative inotropic effects, resulting in deterioration in cardiac performance and cardiovascular instability.<sup>29</sup>

**Table 4. Applying Classification of Recommendations and Level of Evidence**

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT					
	CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/ administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> Additional studies with focused objectives needed <b>IT IS REASONABLE</b> to per- form procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with broad objectives needed; additional registry data would be helpful Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>	Procedure/ Test	Treatment
					COR III: No benefit	No Proven Benefit
					COR III: Harm	Excess Cost w/o Benefit or Harmful
						Harmful to Patients
<b>LEVEL A</b> Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>		
<b>LEVEL B</b> Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>		
<b>LEVEL C</b> Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>		
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit	COR III: Harm	
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		is not recommended is not indicated should not be performed/ administered/ other is not useful/ beneficial/ effective	potentially harmful causes harm associated with excess morbidity/mortality should not be performed/ administered/ other	

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

Dexmedetomidine is an  $\alpha_2$ -adrenergic agonist that has been used intraoperatively as part of balanced anesthesia and postoperatively for sedation and analgesia after surgery or during mechanical ventilation. In a small, retrospective, observation study of children with HF, dexmedetomidine did not affect heart rate, mean arterial pressure, or inotrope score at the termination of infusion; however, 2 patients had a 50% decrease in mean arterial pressure and 1 patient had a 50% decrease in heart rate compared with baseline in the first 3 hours of infusion.<sup>30</sup> In neurocritical care patients, dexmedetomi-

dine exhibited similar incidences of severe hypotension (mean arterial pressure <60 mmHg) and bradycardia (heart rate <50 bpm) compared with propofol.<sup>31</sup>

## Antidiabetic Medications

### Biguanides

Metformin is a biguanide insulin sensitizer that reduces hepatic gluconeogenesis. Ninety percent of the drug is eliminated by renal excretion. Although considered a first-line agent in the management of type 2 diabetes

mellitus, metformin has a legacy of concern because of its biguanide predecessor phenformin, which demonstrated a strong causal association with lactic acidosis and was removed from clinical use in 1978. Traditionally, metformin was contraindicated primarily in conditions predisposing to lactic acidosis such as renal failure, liver disease, severe pulmonary disease, and HF. In an evaluation of 47 patients with metformin-related lactic acidosis occurring between 1995 and 1996, 43% had a fatal outcome and 91% had  $\geq 1$  risk factors for lactic acidosis, including 38% with HF.<sup>32</sup> However, in 2006, the US Food and Drug Administration (FDA) removed HF as an absolute contraindication on the basis of the findings of 2 large observational studies and clinical experience that suggested that the risk of metformin-associated lactic acidosis was minimal and similar to that of other diabetes mellitus medications in patients with HF and that metformin was associated with an overall reduction in mortality.<sup>33–35</sup> In a retrospective cohort study of 16417 Medicare beneficiaries with diabetes mellitus discharged after a HF hospitalization, Masoudi et al<sup>34</sup> demonstrated that metformin administration was linked with a reduced risk of mortality (odds ratio [OR], 0.86; 95% CI, 0.78–0.97). In a recent systematic review of trial and nontrial evidence, Eurich et al<sup>36</sup> also found metformin to be associated with a reduction in mortality (pooled adjusted risk estimate, 0.80; 95% CI, 0.74–0.87;  $P < 0.001$ ) compared with controls (mostly sulfonylurea therapy). Similar findings were reported in patients with HF and chronic kidney disease (pooled adjusted risk estimate, 0.81; 95% CI, 0.64–1.02;  $P = 0.08$ ). Of note, metformin was not associated with an increased risk for lactic acidosis in either analysis.

The 2016 American Diabetes Association standards of medical care currently recommend that metformin can be used in patients with stable HF if their renal function is normal (eg,  $>60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ) but should be avoided in unstable or hospitalized patients with HF.<sup>37</sup> However, in 2016, the FDA published a safety announcement recommending that metformin be contraindicated in patients with renal function below  $30 \text{ mL/min/1.73 m}^2$ .<sup>38</sup> Unfortunately, prospective data evaluating the safety of metformin in patients with advanced HF (stage D), in whom hepatic and renal dysfunction is often encountered, are lacking.

### Thiazolidinediones

Thiazolidinediones, rosiglitazone and pioglitazone, are proliferator-activator receptor gamma agonists that modulate the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in adipose tissue, muscle, and liver. Early postmarketing data and data from randomized, controlled trials reported increased edema and weight gain in patients receiving thiazolidinediones with preexisting cardiac disease and in those with no history of HF.<sup>39–42</sup> In the DREAM

trial (Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication), which evaluated rosiglitazone versus placebo in patients at risk for type 2 diabetes mellitus, more confirmed cases of HF were found in those patients treated with rosiglitazone ( $n=2635$ ) compared with placebo ( $n=2634$ ; hazard ratio [HR], 7.03; 95% CI, 1.60–30.9;  $P=0.01$ ).<sup>43</sup> Recent meta-analyses, which included pivotal randomized, controlled trials, and observational studies strongly suggested that thiazolidinediones exacerbate existing HF and increase the risk for new-onset HF.<sup>42,44–48</sup> In a retrospective analysis of 227571 Medicare beneficiaries treated with a thiazolidinedione, Graham et al<sup>49</sup> found that the risk of HF was greater with rosiglitazone compared with pioglitazone (HR, 1.25; 95% CI, 1.16–1.34).

Limited prospective data exist evaluating thiazolidinediones in patients with HF. Dargie et al<sup>50</sup> reported that after 52 weeks of treatment with rosiglitazone or placebo in 224 patients with diabetes mellitus and NYHA class I to II HF (LV ejection fraction [LVEF]  $\leq 45\%$ ), there was a trend for an increase in all-cause mortality (HR, 1.5; 95% CI, 0.49–4.59) and HF hospitalizations (RR, 1.30; 95% CI, 0.35–4.82) for patients receiving rosiglitazone. In a 6-month randomized, double-blind, multicenter trial of patients with type 2 diabetes mellitus and NYHA class II to III HF (LVEF  $\leq 40\%$ ), Giles et al<sup>51</sup> found that patients receiving pioglitazone ( $n=262$ ) had an earlier time to the onset of HF and a higher incidence of the composite of cardiovascular mortality and hospitalization or emergency room visits for HF compared with those receiving glyburide (13% versus 8%, respectively;  $P=0.024$ ). The 2016 American Diabetes Association standards of medical care recommend avoiding thiazolidinediones in patients with symptomatic HF.<sup>37</sup>

### Dipeptidyl Peptidase-4 Inhibitors

Sitagliptin, saxagliptin, alogliptin, and linagliptin represent a newer class of antidiabetic agents that bind reversibly to the dipeptidyl peptidase-4 enzyme, thereby preventing the degradation of endogenously released incretin hormones, glucose-dependent insulinotropic polypeptide, and glucagon-like peptide-1, which increases insulin release and decreases glucagon levels.<sup>52</sup> In the SAVOR-TIMI 53 study (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction), 16492 patients with type 2 diabetes mellitus who were high risk for cardiovascular events, of whom 12.8% had HF, were randomized to usual diabetes mellitus care with saxagliptin or usual diabetes mellitus care plus placebo. Although no difference was found in the risk of cardiovascular death, MI, or stroke after a median of 2.1 years, the investigators demonstrated an excess of HF hospitalization in patients receiving saxagliptin (HR, 1.27; 95% CI, 1.07–1.51).<sup>53</sup> In an observational US claims database analysis evaluating 7620 patients with type 2 diabetes mellitus

and incident HF treated with metformin or sulfonylurea, sitagliptin use was also associated with an increased risk of HF hospitalizations (adjusted OR, 1.84; 95% CI, 1.16–2.92).<sup>54</sup> A meta-analysis of all randomized trials of vildagliptin, sitagliptin, saxagliptin, alogliptin, linagliptin, and dutogliptin found an elevated overall risk of acute HF in those patients taking any dipeptidyl peptidase-4 inhibitor (OR, 1.19; 95% CI, 1.03–1.37), suggesting a possible class effect.<sup>55</sup> However, in the EXAMINE trial (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome), which enrolled 5380 patients with type 2 diabetes mellitus and a recent acute coronary syndrome event, the investigators found a nonsignificant trend in hospital admission rate for HF for those receiving alogliptin (3.1%) compared with placebo (2.9%) (HR, 1.07; 95% CI, 0.79–1.46).<sup>38</sup> Additionally, in the post hoc analysis, alogliptin had no effect on the composite end point of cardiovascular death and hospital admission for HF (HR, 1.00; 95% CI, 0.82–1.21).<sup>38</sup> The true mechanism of this potential increase in HF hospitalization remains unknown.

## Antiarrhythmic Medications

### Class I Antiarrhythmics

Several of the class I antiarrhythmics, which are sodium channel blockers, are known to be potentially harmful in patients with HF. Disopyramide is a negative inotrope with marked myocardial depressant effects in patients with HF.<sup>56,57</sup> Furthermore, in 100 patients treated with oral disopyramide for ventricular arrhythmias, 16 (12 with a previous history of HF) developed HF within the first 48 hours of therapy. Thus, disopyramide can both precipitate and exacerbate HF.<sup>58</sup> Flecainide may also depress LV function significantly in patients with preexisting LV dysfunction; this finding and the increased mortality associated with flecainide in CAST (Cardiac Arrhythmia Suppression Trial) suggest that it be avoided in patients with HF or structural heart disease.<sup>59–62</sup>

### Class III Antiarrhythmics

Intravenous ibutilide did not have clinically significant hemodynamic effects in patients with reduced LV function (LVEF  $\leq$  35%), but HF was an independent risk factor for ibutilide-induced torsades de pointes (TdP), presumably because of the preexisting prolongation of the QT interval in these patients.<sup>63</sup> Sotalol is a racemic mixture of d- and l-sotalol and has both Class II  $\beta$ -adrenergic blocking (mediated largely by the l-isomer) and Class III (mediated by both d- and l-isomers) antiarrhythmic properties. A study examining whether d-sotalol decreased mortality in patients surviving an MI who had reduced LV function was terminated prematurely because of increased mortality.<sup>64</sup> In contrast, racemic sotalol did not increase mortality after MI.<sup>65</sup> Sotalol can depress myocardial

contractility and exacerbate HF in some patients and should be used cautiously in patients with LV dysfunction. In premarketing studies, the incidence of new or worsened HF over 1 year was 3% in patients without previous HF and 10% in those with a history of HF.<sup>66</sup> The risk of worsening of HF increased as the severity of baseline HF increased.

### Dronedarone

Like amiodarone, dronedarone inhibits the calcium, sodium, and potassium channels and is both an  $\alpha$ - and  $\beta$ -adrenergic receptor antagonist. Dronedarone therapy reduced death and cardiovascular hospitalizations significantly in ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter).<sup>67</sup> A post hoc analysis of a subset of 209 patients (of a total of 4628) with stable HF in that study found no increase in mortality and a trend to decreased cardiovascular hospitalization with dronedarone.<sup>68</sup> However, ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease), a study that examined the effect of dronedarone on death and hospitalization for HF, was terminated prematurely for increased mortality (8.1%) in the dronedarone arm compared with placebo (3.8%). The excess mortality was caused mostly by HF.<sup>69</sup> Another study, PALLAS (Permanent Atrial Fibrillation Outcome Study), tested whether dronedarone reduced cardiovascular events in patients with permanent atrial fibrillation. PALLAS was terminated prematurely after enrolling 3236 patients because dronedarone was associated with an increase in cardiovascular death, stroke, and hospitalization for HF (HR, 1.81; 95% CI, 1.10–2.99;  $P=0.02$ ).<sup>70</sup> Thus, the prescribing information for dronedarone carries a black box warning that the drug is contraindicated in patients with symptomatic HF with recent decompensation requiring hospitalization, or NYHA class IV HF, with a doubling of the mortality in these patients.

## Antihypertensive Medications

### $\alpha_1$ -Blockers

The  $\alpha$ -blockers such as prazosin and doxazosin inhibit postsynaptic  $\alpha_1$ -adrenergic receptors and relax vascular smooth muscle resulting in vasodilation. Initially used for the management of hypertension, these agents are now used primarily for benign prostatic hypertrophy on the basis of the negative findings from ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial).<sup>71</sup> In ALLHAT, the risk of HF was doubled (RR, 2.04; 95% CI, 1.79–2.32;  $P<0.001$ ) in patients receiving doxazosin compared with chlorthalidone. The doxazosin arm of the trial was stopped prematurely. Several



reasons for the increased risk of HF in the doxazosin arm have been suggested, including misdiagnosis of vasodilator-induced edema, a smaller blood pressure reduction with doxazosin, and the unmasking of HF by the discontinuation of other antihypertensive drugs that were protective against HF.<sup>72</sup> Additionally, in VeHFT (Veterans Heart Failure Trial-1), hydralazine combined with isosorbide dinitrate decreased mortality and improved LVEF compared with placebo, whereas prazosin did not.<sup>73</sup>

### Calcium Channel Blockers

Dihydropyridine calcium channel antagonists such as nifedipine have both negative inotropic and vasodilating effects by blocking the transmembrane influx of calcium ions into cardiac and vascular smooth muscles.<sup>74</sup> In small trials assessing the potential therapeutic benefits of nifedipine in patients with HF, there was a marked worsening of HF; 5 of 21 patients treated with nifedipine required hospitalization compared with 0 of 20 who received isosorbide dinitrate.<sup>75</sup> A possible benefit of amlodipine in a subgroup of patients with non-ischemic cardiomyopathy and HF was not reproduced in a second study in which there was no evidence of a favorable or unfavorable effect of amlodipine on mortality (HR, 0.97; 95% CI, 0.83–1.13;  $P=0.66$ ).<sup>76,77</sup> Both trials, however, observed higher frequencies of peripheral edema and pulmonary edema and lower frequencies of uncontrolled hypertension and chest pain in patients treated with amlodipine. Thus, amlodipine does not improve mortality but may exacerbate HF. Diltiazem and verapamil also have negative inotropic effects and can worsen HF more than the dihydropyridine calcium channel blockers because the negative inotropic effects are not offset by vasodilation. In a study of 2466 patients with recent MI randomized to diltiazem or placebo, diltiazem increased the risk of adverse cardiac events (HR, 1.41; 95% CI, 1.01–1.96) in the subgroup of 490 patients with baseline pulmonary congestion.<sup>78</sup> The risk of adverse cardiac events in patients receiving diltiazem was directly related to the severity of baseline HF.<sup>78</sup>

### Centrally Acting $\alpha$ -Adrenergic Agonists

Sympathetic adrenergic activity is increased in HF, and the increase in activity is directly associated with higher mortality. The consistent effectiveness of  $\beta$ -adrenergic receptor antagonists in reversing myocardial remodeling and in improving mortality in patients with HF and reduced LVEF stimulated an interest in other mechanisms of decreasing sympathetic activity as a treatment for HF. Centrally acting  $\alpha_2$ -adrenergic agonists such as clonidine and moxonidine decrease sympathetic outflow and thus decrease plasma norepinephrine concentrations and blood pressure. In an animal model of HF, clonidine improved survival.<sup>79</sup> Furthermore, in small studies of patients with HF, clonidine had beneficial hemodynamic effects; for example,

clonidine 0.15 mg twice daily decreased plasma norepinephrine concentrations by >50% and decreased preload and increased stroke volume significantly.<sup>79</sup> However, both bradycardia and atrioventricular dissociation have been reported with clonidine.<sup>80,81</sup> A placebo-controlled trial of sustained-release moxonidine, an imidazoline receptor agonist, in patients with NYHA class II to IV HF was terminated prematurely after 1934 patients were enrolled. Although moxonidine significantly decreased plasma norepinephrine, there existed an increased mortality in those receiving moxonidine (54 deaths [5.5%]) compared with placebo (32 deaths [3.4%]).<sup>82,83</sup> LV reverse remodeling occurred with moxonidine. This increase in mortality could be caused by the large and rapid decrease in sympathetic outflow, leading to myocardial depression and an inability to access myocardial  $\beta$ -adrenergic support mechanisms acutely.<sup>83</sup>

### Minoxidil

Minoxidil, a vasodilator, improves hemodynamics but worsens clinical outcomes in patients with HF. In a double-blind study of minoxidil 20 mg twice daily ( $n=9$ ) versus placebo ( $n=8$ ), LVEF increased from  $29.6 \pm 17.7\%$  to  $42.7 \pm 22.3\%$  ( $P<0.05$ ) after 3 months of minoxidil and remained unchanged in the placebo group. However, there were more clinical events (eg, worsening HF, an increased need for diuretics, and death) in the minoxidil group (21 events) than the placebo group (7 events;  $P<0.01$ ).<sup>84</sup>

## Anti-Infective Medications

### Azole Antifungal Medication

Itraconazole has been associated with occasional reports of cardiotoxicity, including hypertension, premature ventricular contractions, ventricular fibrillation, and new-onset and worsening HF.<sup>85–90</sup> Using the FDA Adverse Event Reporting System from 1992 to 2001, Ahmad et al<sup>89</sup> found 58 cases of HF in patients administered itraconazole. Because of potential confounders such as hypertension, valvular heart disease, and history of HF, causality was not determined; however, of the 58 patients, there were 28 admissions to the hospital and 13 deaths. On the basis of animal and clinical pharmacology studies, itraconazole may exert negative inotropic effects; however, the mechanism is not known.<sup>89</sup> On the basis of these data, the FDA recommends avoiding itraconazole in patients with ventricular dysfunction or a history of HF for onychomycosis and only to consider itraconazole in case of life-threatening fungal infections.<sup>85–90</sup>

### Other Antifungal Medications

Several cases of new-onset dilated cardiomyopathy with subsequent HF with amphotericin B and its liposomal

formulation have been reported.<sup>91–93</sup> In each case, HF symptoms and echocardiographic findings normalized on discontinuation of therapy, which occurred within 10 days to 6 months of drug discontinuation.

## Anticancer Medications

### Anthracyclines

The anthracyclines are a highly used class of cytotoxic agents that target proliferating cells via a diverse mechanism that includes DNA intercalation, production of damaging reactive oxygen species, and inhibition of the activity of topoisomerase II. Myocytes are particularly susceptible to anthracycline-induced cellular damage because of their relative lack of reactive oxygen species–detoxifying enzymes such as catalase, resulting in cardiotoxicity. Use of these agents is often associated with a delayed cardiotoxic presentation as a result of a biochemical transformation of the parent drug into a secondary alcohol metabolite in the myocyte, which is cleared much less quickly from the cell. This produces a prolonged cellular concentration and continued damage that results in decreased contractility and subsequent cell death.<sup>94</sup> The anthracycline class of drugs includes older agents, doxorubicin and daunorubicin, and newer agents, epirubicin, idarubicin, and mitoxantrone.<sup>95</sup>

Administration of anthracyclines leads to acute, early-onset, and delayed-onset cardiotoxicity. Acute cardiotoxicity manifests within days of administration and most commonly includes rhythm abnormalities (arrhythmias) but also electrocardiographic changes, tachycardia, and pericarditis/myocarditis. Early-onset (within the first year) and delayed-onset (after the first year) cardiotoxicity from anthracyclines present as progressive and often irreversible HF. The risk of developing anthracycline-induced HF (A-HF) increases with increased cumulative dose and can occur >20 years after the completion of therapy.<sup>96</sup>

A-HF was reported beginning in the late 1960s. In response to growing case reports, a retrospective chart review of 3491 patients identified a clear cumulative increase in the risk of developing HF with increasing doses of doxorubicin, expressly at total doses >550 mg/m<sup>2</sup>, thereby suggesting the theoretical cumulative dose limit that is often used clinically today to minimize the risk of A-HF. This study showed an overall incidence of clinically recognized HF in 2.2% of all evaluated patients.<sup>97</sup> A more contemporary retrospective analysis of 630 adult patients from 3 separate clinical studies suggests an overall incidence of A-HF of 5.1% (32 of 630). This study confirmed a dose-dependent increase in the risk of HF, with an estimated cumulative percentage of patients with A-HF of 5% at 400 mg/m<sup>2</sup>, 16% at 500 mg/m<sup>2</sup>, and 26% at 550 mg/m<sup>2</sup>.<sup>98</sup>

The incidence of A-HF in pediatric populations has been reported to be 0% to 16% in available studies in

the literature.<sup>99</sup> One study evaluated a cohort of 830 pediatric cancer survivors with a mean follow-up time of 8.5 years and found a cumulative incidence of A-HF of 2.5%. On the basis of the follow-up, the authors found an estimated risk of developing A-HF after the first dose to be 2% (95% CI, 1–3) at 2 years, 2.4% (95% CI, 1.3–3.5) after 5 years, 2.6% (95% CI, 1.4–3.9) after 10 years, 3.7% (95% CI, 1.8–5.5) after 15 years, and 5.5% (95% CI, 1.5–9.5) after 20 years. Besides an increased risk with increasing time since the first dose, cumulative doses >300 mg/m<sup>2</sup> were identified as an independent risk factor for developing HF (RR=8), increasing the estimated risk of HF at 20 years after the first dose to 9.8% (95% CI, 2.2–17.4) and suggesting that pediatric populations are susceptible to cardiomyopathy at much lower cumulative doses than those first identified in adult populations.<sup>100</sup> Furthermore, a meta-analysis of 30 studies including 12 507 pediatric patients identified doses of >45 mg/m<sup>2</sup> given within 1 week as an independent predictor of developing A-HF through multivariate regression analysis. The frequency of observed A-HF in patients receiving >45 mg/m<sup>2</sup> during a 1-week period was predicted to be 5.8% higher than that for patients receiving lower weekly doses.<sup>99</sup> Despite these data, dose limits have not been lowered for pediatric patients in light of the high cure rates seen in this population. As a result, pediatric cancer survivors require lifelong cardiac monitoring because anthracycline toxicity can manifest ≥20 years after therapy.

Although many of the available studies address the incidence of clinically relevant (symptomatic) A-HF, emerging data support the presence of subclinical (lacking overt clinical symptoms but with underlying measurable cardiac dysfunction) diastolic and systolic myocardial abnormalities in a majority (up to 60%) of patients, even at low cumulative doses (100 mg/m<sup>2</sup>).<sup>94,101</sup>

The current standard for cardiac monitoring in patients receiving an anthracycline is LVEF assessment. Although useful in identifying myocardial damage, it does so only after cardiac injury has occurred. Novel approaches to identify patients with anthracycline-induced cardiotoxicity earlier in their treatment paradigm include the use of biomarkers. Elevations in cardiac troponin, a biomarker of ischemic heart disease, have been associated with the development of LV dysfunction and subclinical myocardial damage and with late cardiac abnormalities in both the adult and pediatric cancer populations.<sup>102</sup> The role of natriuretic peptides (NP) such as atrial NP, amino-terminal fragments, brain NP, and its N-terminal fragments, released from cardiomyocytes in response to increased wall stress, has also been explored. Despite data that demonstrate a correlation between increased NP and the development of subclinical cardiac injury, conflicting data that contradict this finding exist.<sup>102</sup> More recently, myeloperoxidase has been identified as another potential biomarker of chemotherapy-induced cardiac dysfunction.<sup>103</sup> Although the use of biomarkers in

this setting has exhibited potential to predict early cardiac dysfunction, standardization of routine use of these measurements in clinical practice has yet to be determined.

As stated, the major risk factor for developing A-HF is increasing cumulative dose. Other identified risk factors include female sex, black race, mediastinal radiation, young age (<4 years), old age (>66 years), pre-existing cardiovascular disorders, and shorter length of infusion.<sup>97,99,104–107</sup> Pharmacogenetic studies have demonstrated an increased risk of A-HF in patients with polymorphisms in nicotinamide adenine dinucleotide phosphate-oxidase (involved in free radical metabolism), efflux proteins, and myocardial cytosolic carbonyl reductases that are responsible for the formation of the cardiotoxic alcohol metabolites.<sup>108,109</sup> Enhanced cardiotoxicity may occur when anthracyclines are administered with taxanes, trastuzumab, cyclophosphamide, or other agents that cause further cardiac injury.<sup>95</sup>

Numerous strategies have been examined in an attempt to decrease the risk of cardiotoxicity from anthracyclines. Early studies with the chemically modified anthracyclines such as epirubicin, idrubicin, and mitoxantrone suggested a lower incidence of HF.<sup>95</sup> However, data from subsequent studies in larger populations and with increasing doses still suggest a risk at higher cumulative doses. An analysis of 469 patients treated with epirubicin for metastatic breast cancer demonstrated a cumulative risk of A-HF of 7.2%, with an estimated risk of HF of 1.9% at a cumulative dose of 800 mg/m<sup>2</sup> to 15% at 1000 mg/m<sup>2</sup>.<sup>110</sup> Dose-dependent cardiotoxicity was observed with the other anthracyclines, especially at high doses, undermining their ability to decrease cumulative HF compared with doxorubicin.<sup>111</sup>

Dexrazoxane is metabolized to an ethylenediaminetetraacetic acid-like compound in cardiomyocytes that binds iron, minimizes oxidative stress induced by anthracyclines, and has antitumor effects via inhibition of topoisomerase II. A meta-analysis of 8 studies suggested a decrease in the development of HF with the use of dexrazoxane but also showed a nonsignificant trend to a decreased response rate.<sup>112</sup> As a result of concerns for efficacy, current American Society of Clinical Oncology guidelines discourage the routine use of dexrazoxane, recommending consideration for its use primarily in adults with metastatic breast cancer once the cumulative dose of anthracyclines exceeds 300 mg/m<sup>2</sup>.<sup>113</sup>

Another approach to prevent A-HF involves modifying the pharmacokinetics of the anthracycline through the use of liposomal formulations that attain a high peak concentration and longer circulating time while minimizing free anthracycline released into the blood. The large size of the formulation minimizes its ability to penetrate the normal vasculature of the heart but allows penetration into the more porous tumor endothelium.<sup>94</sup> Although a meta-analysis using 2 randomized, controlled trials (n=520) confirmed a decrease in clinical

HF with the use of liposomal doxorubicin (RR, 0.20; 95% CI, 0.05–0.75), its use clinically is often deemed cost-prohibitive and has been hindered by supply issues.<sup>114</sup>

There are currently limited data to determine the best course of treatment for A-HF. Standard medical therapy with angiotensin-converting enzyme inhibitors (enalapril) and  $\beta$ -blockers (metoprolol, carvedilol) has been reported to result in improved symptoms and LVEF. However, long-term, prospective follow-up data are lacking.<sup>96,115</sup> Preliminary studies suggest that cardiotoxicity may be ameliorated with angiotensin-converting enzyme inhibitors or  $\beta$ -blockers. A position statement from the European Society of Cardiology recommends the use of standard, guideline-based treatment for the patient who develops chemotherapy-induced HF.<sup>116,117</sup>

### Alkylating Agents

Cyclophosphamide, a nonspecific alkylating agent that is the backbone of many “induction” bone marrow transplantation regimens, is used to treat a variety of solid and hematologic malignancies. Cyclophosphamide exerts antitumor effects by DNA cross-linking and inhibition of DNA synthesis.<sup>118</sup> Cyclophosphamide is a prodrug that requires hepatic conversion to its active phosphoramidate mustard via cytochrome P450 enzymes. In a pharmacokinetic study of 19 women with metastatic breast cancer receiving cyclophosphamide for the induction of autologous bone marrow transplantation, lower areas under the curve were observed in patients who developed HF. The authors suggest that increased metabolism of the prodrug to its active metabolite increases organ toxicity seen with the agent.<sup>119</sup> Although a precise mechanism of cardiac injury has not been elucidated, preclinical studies suggest that the active phosphoramidate mustard causes increased free radical formation in cardiac tissue, leading to cell damage.<sup>120</sup> Autopsies of patients who suffered fatal cyclophosphamide-induced HF indicate the presence of hemorrhagic myocarditis. The presence of microthrombi and proteinaceous exudates suggests significant endothelial damage with cyclophosphamide.<sup>121</sup> Acute HF has been reported in 17% to 28% of patients receiving cyclophosphamide for induction therapy (ie, at high doses used in transplantation regimens), with further evidence of subclinical decreases in LVEF in up to 50% of cases.<sup>122</sup> The onset of HF is acute, occurring within 1 to 10 days of treatment, and usually resolves over 3 to 4 weeks; however, fatalities caused by HF have been reported.<sup>123</sup> Large individual doses (>120–170 mg/kg or 1.55 mg/m<sup>2</sup> per day), old age, mediastinal radiation, and anthracycline use have been identified as risk factors for the development of HF with cyclophosphamide.<sup>118,123,124</sup>

Ifosfamide is an alkylating agent with a mechanism of action similar to that of cyclophosphamide that also requires hepatic activation to its phosphoramidate mustard. HF caused by ifosfamide occurs analogously to that seen



with cyclophosphamide as an acute (within 1–10 days) and often reversible phenomena.<sup>118</sup> In a small study of patients given ifosfamide for induction therapy, 17% (9 of 52) developed HF at doses  $>12.5$  mg/m<sup>2</sup>.<sup>125</sup>

Mitomycin C, an antibiotic isolated from *Streptomyces caespitosus*, exerts antitumor effects through alkylation and DNA cross-linking.<sup>126</sup> Mitomycin is reduced intracellularly to a semiquinone radical that, in the anaerobic environment of many tumors, is further reduced to hydroquinone, which binds DNA. However, in aerobic environments such as that seen in cardiomyocytes, the semiquinone radical is oxidized to the parent compound accompanied by free radical formation.<sup>118</sup> This increased oxidative stress is thought to be the mechanism of cardiac damage seen with mitomycin alone and may explain an increased prevalence of HF observed when mitomycin is used in combination with anthracyclines.<sup>127</sup> HF is generally observed after the administration of a median of 3 cycles and at doses  $>30$  mg/m<sup>2</sup> of mitomycin. A higher incidence of HF (15.3%) was observed when mitomycin was given after anthracycline treatment than would be expected with either agent alone.<sup>118</sup>

### Antimetabolites

Fluorouracil (5-FU) is an antimetabolite that inhibits thymidylate synthase, causing cell death. Capecitabine is an oral fluoropyrimidine that undergoes hydrolysis in the liver to form the active 5-FU metabolite.<sup>126</sup> 5-FU is well known for its cardiotoxic effects, occurring in 7.6% of patients undergoing high-dose infusions.<sup>128</sup> The most common cardiotoxicity associated with 5-FU is ischemic in nature and thought to be a result of the induction of coronary vasospasm. Overall, cardiotoxicity is more common (up to 18%) with intravenous 5-FU compared with oral capecitabine (1.9%–3.7%).<sup>129,130</sup> Although the exact incidence is unknown, a growing number of case reports recognize cardiomyopathy and acute decreases in LVEF with 5-FU treatment.<sup>131–133</sup> Apical ballooning, commonly seen in Takotsubo cardiomyopathy, has been reported on numerous occasions. Patients appear to recover normal cardiac function within weeks after discontinuing the drug.<sup>134,135</sup>

### Targeted Therapies

Trastuzumab, a humanized monoclonal antibody targeted against the extracellular domain of the human epidermal growth factor receptor 2 (ErbB2 receptor), is used widely in the treatment of ErbB2 receptor-positive breast carcinoma.<sup>136</sup> In some patients, this agent induces significant cardiac dysfunction, presumably because of the inhibition of the ErbB2 signaling pathway within cardiomyocytes.<sup>116,137</sup> Trastuzumab cardiotoxicity is also believed to be related to antibody-dependent and complement-dependent cytotoxicity.<sup>138</sup>

An independent review of 7 phase II and III clinical trials first established an increased rate of cardiac dysfunction.<sup>139</sup> Patients who received trastuzumab in addition to

anthracyclines and cyclophosphamide had a 27% incidence of cardiotoxicity compared with 8% in those who received anthracyclines and cyclophosphamide alone. The rate of NYHA class III or IV HF was 16% compared with 4%. In patients who received trastuzumab in conjunction with paclitaxel, the incidence of cardiac dysfunction was similarly increased (13% versus 1%), although patients experienced a lesser degree of functional impairment.<sup>140,141</sup> Subsequent large-scale, randomized, adjuvant clinical trials have demonstrated a significant, but predominantly reversible, cardiotoxic effect that manifests itself as an asymptomatic decline in LVEF.<sup>136</sup> In these studies, the reported incidence of severe HF and death was 3% to 4%; symptomatic HF, 2% to 5%; and asymptomatic decline in LVEF, 8% to 14%.<sup>141,142</sup> A meta-analysis of 10 281 patients from 8 randomized trials identified a combined RR of 5.11 for HF and 1.83 for LVEF decline.<sup>143</sup>

Longer-term follow-up in the Herceptin Adjuvant (HERA) study confirmed that most cardiac events occur during the first 12 months of trastuzumab exposure, while patients are undergoing active treatment.<sup>144</sup> Short-term recovery occurred in the majority (80%) of the patients after a median of 6.4 months (range, 0–33.1 months), although details on the institution of specific cardiac medications were not clear. However, among those with acute recovery, roughly 30% had at least 1 subsequent LVEF decrease to  $<50\%$ . Progressive disease and unfavorable cardiac outcomes were observed in 14 of 73 patients who had experienced a cardiac event.

Of note, patients with significant cardiovascular histories were excluded in these studies; thus, the use of these agents in patients with established HF and clinical management decisions are still anecdotal and evaluated on an individual patient basis. Moreover, in nonclinical trial populations, the incidence of cardiac dysfunction may be higher, with 1 multicenter study of 499 patients reporting an incidence of 27%.<sup>145,146</sup> Risk factors for cardiotoxicity besides prior anthracycline exposure include increased age, baseline LVEF  $\leq 50\%$ , increased body mass index, and use of antihypertensive medications.<sup>136,142</sup>

Pertuzumab is a recombinant monoclonal antibody directed against the dimerization domain of ErbB2 receptor, inhibiting ErbB2 receptor, homodimerization and heterodimerization. Like trastuzumab, pertuzumab is capable of inducing antibody-dependent cell-mediated cytotoxicity.<sup>146,147</sup> In a phase II study of pertuzumab therapy, a decline in LVEF of  $\geq 10\%$  to  $<50\%$  was observed in 8 of 78 patients, with 2 cases of symptomatic HF.<sup>148</sup> The median time to the lowest LVEF in these 8 patients was 100 days (range, 41–175 days). On repeat assessment of cardiac function after 3 weeks, there was some degree of LVEF recovery in all participants, as defined by an LVEF that was either  $>45\%$  or 40% to 45% and  $<10\%$  from baseline. A retrospective analysis of cardiac safety

data from 598 phase II study participants demonstrated that asymptomatic cardiac dysfunction occurred typically between cycles 1 and 7 in 3.4% to 6.5% of patients.<sup>147</sup> Continued experience with pertuzumab, particularly in combination with trastuzumab, will serve to further define the risks and natural history of pertuzumab-induced HF.

Lapatinib is an orally available dual tyrosine kinase inhibitor of the epidermal growth factor receptor and ErbB2.<sup>138</sup> The overall incidence of HF is low. A review of 3689 patients who received lapatinib in 44 phase I to III trials revealed a 0.2% rate of symptomatic HF and 1.4% rate of asymptomatic cardiac events.<sup>149</sup> Prior exposure to trastuzumab and anthracyclines was associated with an increased incidence of adverse cardiac events, on the order of 2.2% and 1.7%, respectively. The time to onset was 13±9 weeks, with an absolute LVEF decrease of 18.8±5.2%. Again, cardiac events were largely observed to be reversible, although 33% of the patients who experienced cardiac dysfunction did not have a follow-up evaluation.

Bevacizumab is an antivasculature endothelial growth factor monoclonal antibody that targets the vascular endothelial growth factor (VEGF)-A ligand.<sup>150</sup> In a meta-analysis including 3784 patients, the RR for HF was 4.74 compared with placebo, and the reported incidence was 1.7% to 4%.<sup>151–153</sup> These effects did not appear to be dose-dependent or clearly related to different concomitant chemotherapy regimens. Single-center reports of small numbers of patients also suggest that a decline in LVEF occurs early during therapy and is potentially reversible.<sup>154</sup>

Sunitinib is a multitargeted oral dual tyrosine kinase inhibitor used widely in the treatment of many cancers.<sup>138,155–157</sup> This small molecule inhibits many kinases, including VEGF receptor, platelet-derived growth factor, c-kit, and fms-like tyrosine kinase-3. In a pivotal phase III trial comparing sunitinib with interferon- $\alpha$  in metastatic renal cell cancer, 10% of the 375 patients in the sunitinib-treated group experienced a decline in LVEF, according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3 criteria.<sup>158</sup> A meta-analysis of phase II to III clinical trials demonstrated an increased risk for all HF of 1.81 and high-grade HF of 3.30.<sup>159</sup> Retrospective clinical reports from multiple and single centers confirm these adverse cardiac effects. In a multicenter study of 175 patients, 18.9% developed cardiac dysfunction.<sup>160</sup> Twelve of the 17 patients who developed grade 3 hypertension also developed significant cardiac dysfunction. Cardiac dysfunction occurred between 28 and 180 days after the initiation of sunitinib and most commonly after the third cycle of therapy. Additional clinical experience at single centers corroborate these findings, with a 15% incidence of National Cancer Institute Common Terminology Criteria for Adverse Events grade 3 (LVEF between 20% and 39%) or grade 4 (LVEF<20%) cardiac dysfunction within the first 3

months of treatment initiation.<sup>161</sup> In the imatinib-resistant gastrointestinal stromal tumor population, sunitinib was associated with an 8% incidence of HF.<sup>156</sup> In 36 patients who received the full dose of sunitinib, 10 had an LVEF decline of at least 10%, and 7 had LVEF reductions of  $\geq 15\%$ . Independent predictors of HF were hypertension and coronary disease, with the effects of dose, duration, or biological predictors of toxicity remaining poorly defined. Again, use in patients with preexistent HF has been limited and purely anecdotal.

The biological mechanisms of cardiotoxicity are under active investigation. The VEGF receptors are clearly important in mediating the ventricular remodeling response to increased afterload, as indicated by basic science studies.<sup>162</sup> Additional studies suggest that inhibition of AMP-kinase activity and the inositol-requiring enzyme stress response by sunitinib may play a critical role in mediating cardiac dysfunction.<sup>157,163</sup> Sunitinib is believed to compete with adenosine triphosphate for binding to AMP-kinase, thereby preventing its activity and exacerbating energy depletion under states of increased cardiomyocytes stress. However, there are no human-level data yet to support these hypotheses.<sup>156,163</sup>

Sorafenib is a small-molecule multiple tyrosine kinase inhibitor that inhibits cell surface kinases, including VEGF receptor-2, VEGF receptor-3, and platelet-derived growth factor- $\beta$ , and intracellular kinases such as BRAF and CRAF. HF is less common with sorafenib compared with sunitinib, and sorafenib has been used safely in patients with recovered sunitinib-induced cardiac dysfunction.<sup>164</sup> However, this agent is associated with significant hypertension in 3% to 17% of treated individuals. The National Cancer Institute has offered a collection of principles to aid in the approach to treating these dual tyrosine kinase inhibitor-induced toxic side effects.<sup>165</sup> Imatinib is a kinase inhibitor that targets Bcr-Abl, with effects on platelet-derived growth factor- $\alpha$  and - $\beta$ .<sup>138</sup> Known side effects are peripheral edema, shortness of breath, and fatigue. Severe HF is uncommon, occurring in <1% of treated patients, and hypothesized to be related to mitochondrial abnormalities and activation of the endoplasmic reticulum stress response system.<sup>166,167</sup> Erlotinib is an epidermal growth factor receptor inhibitor that to date has been shown not to be associated with significant cardiovascular toxicity.<sup>116,138,168</sup> Many second-generation tyrosine kinase inhibitors, such as pazopanib, have emerged, and additional studies are necessary to understand their cardiac safety profile and use in HF.

### Taxanes

The taxanes paclitaxel and docetaxel act by binding and disrupting microtubule function, which are highly regulated and integral components of the cellular cytoskeleton. The most frequent cardiac side effects of these agents are arrhythmias, although paclitaxel also has been associated with an increased incidence of cardiac dysfunction.

tion, most notably when administered in conjunction with anthracyclines.<sup>127,169</sup> This effect may be related to a pharmacokinetic interaction between the 2 agents whereby doxorubicin levels are significantly increased when administered with paclitaxel.<sup>170</sup> Similarly, docetaxel when used in combination with doxorubicin and cyclophosphamide is associated with a nonsignificant increase in HF incidence compared with nondocetaxel regimens (1.6% versus 0.9%;  $P=0.10$ ).<sup>171</sup> In another study comparing docetaxel and trastuzumab in metastatic breast cancer, 8% of the patients treated with docetaxel alone had a decline in LVEF  $\geq 15\%$ . More than half of these patients were previously exposed to anthracyclines.<sup>172</sup>

### Other Anticancer Medications

Thalidomide and lenalidomide are structurally similar immunomodulatory agents used in the treatment of multiple myeloma. Thalidomide has been associated with edema, sinus bradycardia, and venous thromboembolism.<sup>173</sup> Secondary to its anti-inflammatory and immunomodulating effects, thalidomide has been studied as a potential HF therapeutic agent with beneficial effects on LVEF and matrix metalloproteinase production.<sup>174</sup> Lenalidomide has been associated with hypersensitivity myocarditis in case reports.<sup>175</sup>

Similarly, high-dose interleukin-2 has been associated with fulminant myocarditis, which is poorly understood but may be related to the capillary leak syndrome and cytotoxic damage from migration of lymphocytes and inflammatory cells to the interstitium.<sup>176</sup> High-dose interferon inhibits cell growth and upregulates immunological cancer defenses. Studies in animal models suggest a dose-dependent negative inotropic effect of interferon- $\alpha$  that may be mediated in part by nitric oxide.<sup>177</sup> Numerous cardiotoxicities, including arrhythmias, ischemia, infarction, and cardiomyopathy, occur during and immediately after infusion.<sup>126</sup> Cardiomyopathy is reversible after discontinuation of the infusion.<sup>178,179</sup> Cardiomyopathy and HF are rare, occurring in  $<1\%$  of patients.<sup>180</sup>

### Hematologic Medications

#### Anagrelide

Anagrelide is indicated to decrease the platelet count and the risk of thrombosis associated with myeloproliferative disorders such as essential thrombocythemia, polycythemia vera, and chronic myelogenous leukemia.<sup>181</sup> In addition to its pharmacological effects that decrease megakaryocyte hypermaturation, anagrelide inhibits phosphodiesterase type 4, similar to milrinone and other positive inotropic agents. Via this pharmacological effect, anagrelide induces high-output HF.<sup>182</sup> The effect appears to be dose related and may occur days to years after the drug is initiated, although a temporal association with a dose increase is often reported. Case reports suggest

that anagrelide-induced HF may be reversible on discontinuation of therapy.<sup>182,183</sup>

An early study with anagrelide reported common cardiovascular effects of palpitations, tachycardia, and edema, which may have actually been symptoms of high-output HF.<sup>184</sup> A later study quantified the incidence of anagrelide-induced HF as 2.4% ( $n=14$ ), and 2 of these patients experienced sudden death.<sup>183</sup>

#### Cilostazol

Cilostazol is an antiplatelet and vasodilatory agent used primarily in patients with intermittent claudication to increase walking distance.<sup>185</sup> A selective inhibitor of phosphodiesterase type 3, it is believed to heighten the risk of fatal arrhythmias in patients with HF. It has never been directly studied in patients with HF; however, the increased risk is presumed to occur within 1 month of initiation because of the nature of the observed electrophysiological effects and extrapolation from the effects of oral milrinone, a pharmacologically similar medication.<sup>186</sup>

It is known that cilostazol produces a dose-related increase in heart rate of 5 to 7 bpm and a higher rate of ventricular premature beats and nonsustained ventricular tachycardia, regardless of dose received. Cilostazol is contraindicated in patients with HF of any severity.<sup>185</sup>

### Neurological and Psychiatric Medications

#### Stimulants

Sympathomimetic stimulants (racemic amphetamine, dextroamphetamine, methylphenidate, and methamphetamine) have similar mechanisms of action and are likely to have similar cardiac effects. The stimulant sympathomimetics can increase blood pressure by a few millimeters of mercury, but more concerning are reports of sudden death, acute coronary syndrome, MI, stroke, and cardiomyopathy associated with their use.<sup>187–196</sup> Despite these case reports and small series documenting cardiac toxicity associated with stimulants, large epidemiological studies performed in children and adults treated with stimulants found no increase in the risk of serious cardiovascular events (stroke, MI, and sudden death).<sup>197,198</sup> Considering the case reports and well-recognized risk of sympathetic stimulation in patients with serious cardiac disease, sympathomimetic stimulants are not generally used in patients with HF.

#### Antiepileptic Medications

Carbamazepine is a first-generation antiepileptic that is structurally similar to the tricyclic antidepressants (TCAs) that is also used as a mood stabilizer and for neuropathic pain. Carbamazepine is believed to stabilize hyperexcited nerve membranes, to inhibit repetitive neuronal discharges, and to reduce synaptic propagation of excitatory impulses, possibly through voltage-dependent blockage of sodium channels. The



medication has been associated with hypotension, bradycardia, and atrioventricular block, as well as signs and symptoms of HF in patients without cardiovascular disease.<sup>199,200</sup> Severe LV dysfunction with a reduction in LVEF <35% has only been documented in cases of overdose.<sup>201,202</sup>

Pregabalin is an analogue of the neurotransmitter  $\gamma$ -aminobutyric acid that exhibits analgesic, anticonvulsant, and anxiolytic properties. In controlled clinical trials, the incidence of peripheral edema was 6% in patients taking pregabalin compared with 2% in the placebo group. The possible mechanism may be antagonism of the L-type calcium channels, which are also blocked by the thiazolidinediones and dihydropyridines. Although data in patients with HF are limited to case reports, the FDA suggests caution be taken when using pregabalin in patients with NYHA class III to IV HF, especially in combination with thiazolidinediones, due to possible development of peripheral edema and HF exacerbation.<sup>203</sup>

### Antipsychotic Medications

Several of the antipsychotic medications, both typical and atypical, have been associated with numerous cardiovascular side effects consisting of significant dose-related sudden cardiac death, cardiac arrhythmias, in particular TdP secondary to the corrected QT interval (QTc) prolongation, tachycardia, and orthostatic hypotension.<sup>204–207</sup> Myocarditis and cardiomyopathy are rare but potentially fatal complications of antipsychotic therapy. Both disorders have been demonstrated with clozapine. In an analysis of reports to the Australian Adverse Drug Reaction Unit, the incidence rates of clozapine-induced myocarditis were estimated to be between 0.7% and 1.2% over 10 years for all patients treated with clozapine. This type of myocarditis occurred within the first 2 months of beginning therapy and did not appear to be dose related. Of this cohort, 52% of patients recovered and 10% died.<sup>208</sup>

In a study of 8000 patients started on clozapine between 1993 and 1999, Kilian et al<sup>209</sup> identified 8 cases of cardiomyopathy with 1 death and 15 cases of myocarditis. The onset of cardiomyopathy occurred on average at 6 to 9 months of treatment. In 1 patient, clozapine discontinuation led to improvement in cardiomyopathy. Using data reported to the FDA, La Grenade et al<sup>210</sup> found that of 190 000 patients taking clozapine between 1989 and 1999, 28 cases of myocarditis with 18 deaths and 41 cases of cardiomyopathy with 10 deaths were reported. Although the mechanism is not fully elucidated, clozapine-induced cardiotoxicity may be a result of an IgE-mediated hypersensitivity reaction.<sup>211</sup> Other potential mechanisms include elevations in catecholamine levels, blockade of calcium-dependent ion channels, and increased production of inflammatory mediators. Numer-

ous other atypical antipsychotics without these effects are available.

In a case series, 3 of 5 patients with clozapine-induced myocarditis demonstrated elevated brain NP levels, which decreased after discontinuation of clozapine, in concert with alleviation of the patients' symptoms.<sup>212</sup> Measuring brain NP levels may therefore offer a means of monitoring patients taking clozapine to detect early, asymptomatic myocarditis, reducing the need for regular echocardiograms.

### Antidepressants

TCAs have numerous documented cardiovascular side effects, including sinus tachycardia and postural hypotension attributed to its Class Ia antiarrhythmic activity, peripheral antiadrenergic action, and negative inotropic and  $\alpha$ -adrenergic blocking effects.<sup>213</sup> TCAs also affect atrioventricular conduction by prolonging conduction time in the His bundle and bundle branches, thus prolonging the duration of the QRS interval and QTc interval.<sup>213</sup> Additionally, second- and third-degree heart block can develop because of the anticholinergic and quinidine-like properties of the TCAs, interference with reuptake of adrenergic amines, and direct myocardial depression.<sup>213</sup> Case reports have suggested that TCA use can be associated with the development of cardiomyopathy within weeks to years of initiation.<sup>214,215</sup> In several small studies in patients with decreased LVEF, TCAs had no significant effects on LVEF; however, long-term information on the effect on ventricular performance and development of new-onset HF is limited.<sup>216–219</sup>

Selective serotonin reuptake inhibitors have a very low rate of adverse cardiovascular effects. In prospective studies of patients with HF, post-MI, or unstable angina, fluoxetine, sertraline, paroxetine, and fluvoxamine had minimal to no effect on electrocardiographic and echocardiographic indexes of cardiac function.<sup>220–223</sup> However, like the TCAs, some selective serotonin reuptake inhibitors may prolong the QTc. In 2011, the FDA issued a safety announcement that citalopram should not exceed 40 mg/d because of the risk of dose-dependent QTc prolongation, which could lead to TdP in which HF was listed as a risk factor.<sup>224</sup> Additionally, the FDA recommended avoiding use in patients with decompensated HF.

### Antiparkinson Medications

Pergolide is an ergot-derived dopamine receptor agonist with potent agonism of the 5-hydroxytryptamine 2B receptor. After the publication of several case reports, comparative studies reported heart valve disease associated with pergolide.<sup>225–231</sup> In a large case-control study of 155 patients with Parkinson disease, Zanettini et al<sup>228</sup> found that patients receiving either pergolide or cabergoline had a significantly greater frequency of moderate to severe grade 3 to 4 regurgitation in any valve compared with those not receiving a dopamine

receptor agonist (23.4% versus 28.6% versus 0%, respectively). The RR for moderate or severe valve regurgitation in the pergolide group was 6.3 for mitral regurgitation ( $P=0.008$ ), 4.2 for aortic regurgitation ( $P=0.001$ ), and 5.6 for tricuspid regurgitation ( $P=0.16$ ) compared with other groups. Corvol et al<sup>232</sup> also demonstrated similar findings in a meta-analysis of 7 trials (394 patients treated with pergolide and 280 control subjects). Overall, the odds of developing moderate to severe regurgitation were 3-fold higher in those receiving pergolide compared with those in the control group (OR, 3.1; 95% CI, 1.7–5.6;  $P<0.001$ ). In both studies, higher risk for valvular disease correlated with a higher mean cumulative pergolide dose. In 2007, pergolide was removed from the US market, but it remains available in Europe.

Bromocriptine is also an ergot-derived dopamine agonist but has only partial agonist activity at the 5-hydroxytryptamine 2B receptor. Although exposure has been associated with valvular heart disease, the data are limited to case reports and a few prospective studies.<sup>233–235</sup> In a case-control study of 140 patients with Parkinson disease receiving either bromocriptine ( $n=71$ ) or pergolide ( $n=21$ ), Tan et al<sup>235</sup> found the risk for any abnormal valvular regurgitation to be 3.2-fold higher for those receiving bromocriptine (OR, 3.32; 95% CI, 1.11–9.92;  $P=0.03$ ) and 3.7-fold higher for those receiving pergolide (OR, 3.66; 95% CI, 1.22–10.97;  $P=0.02$ ) compared with age-matched controls ( $n=47$ ). The postulated mechanism has been stimulation of the 5-hydroxytryptamine 2B receptor expressed on the heart valve, which may induce fibrotic changes, leading to valve thickening and stiffening.<sup>235</sup>

Recently, 2 large, population-based, epidemiological studies did not find a significant increase in new-onset HF with either pergolide or bromocriptine but did with the non-ergot-derived dopamine agonist pramipexole, especially within the first 3 months of therapy and in patients  $\geq 80$  years of age.<sup>236,237</sup> Additionally, in a pooled analysis of randomized, placebo-controlled, parallel phase II and III clinical trials, the FDA calculated the incidence of newly diagnosed HF to be more frequent, although not significant, in patients taking pramipexole ( $n=12$  of 4157) compared with those taking placebo ( $n=4$  of 2820).<sup>238</sup> On the basis of these data, the FDA issued a Drug Safety Communication to providers on this association.

### Antimigraine Medications

Methysergide and ergotamine are both ergot derivatives used in the treatment of migraines. Ergotamine is an  $\alpha$ -adrenergic blocking agent with direct stimulating effects on the smooth muscle of the peripheral and cranial blood vessels and serotonin antagonistic properties. Methysergide is a potent peripheral inhibitor of 5-hydroxytryptamine, demonstrating a competitive

blockade of vascular 5-hydroxytryptamine receptors, but is a central 5-hydroxytryptamine agonist, primarily at therapeutic nuclei. Several case reports have found both drugs to be associated with mitral, aortic, and tricuspid valve lesions that in some cases led to right-sided HF.<sup>239–242</sup> The onset of these findings occurred typically after years of long-term administration, and the valve abnormalities did not completely resolve on drug discontinuation.<sup>243</sup> The mechanism of the valve fibrosis is thought to be related to excess serotonin activity because both methysergide and ergotamine are partial serotonin agonists.<sup>242</sup> With the advent of newer agents to acutely treat migraines (eg, triptans), both methysergide and ergotamine should be avoided. According to the Triptan Cardiovascular Safety Expert Panel, the safety profile of triptans is well defined and appears to reflect a very low risk of serious cardiovascular adverse events in patients without known or suspected coronary artery disease.<sup>244</sup>

### Appetite Suppressants

Fenfluramine and its d-isomer, dexfenfluramine, when used alone or in combination with another appetite suppressant, phentermine, can cause pulmonary hypertension and cardiac valve abnormalities.<sup>245–247</sup> These agents appear to promote the rapid release of serotonin and to inhibit its reuptake, but they also exert serotonin receptor agonist activity. Valvular regurgitation occurred in 12% of patients treated for  $>90$  days compared with 5.9% of unexposed patients (OR, 2.2; 95% CI, 1.7–2.7). Fenfluramine and dexfenfluramine have been withdrawn from the market. Rare cases of valvulopathy and pulmonary hypertension have been submitted to the FDA in patients who reportedly took phentermine alone.<sup>248</sup> Another appetite suppressant, sibutramine, was withdrawn from the market for increased risk of nonfatal MI and stroke.<sup>249</sup>

### Bipolar Medications

Lithium is a mood stabilizer that alters sodium transport in nerve and muscle cells, resulting in intraneuronal metabolism of catecholamines. In single case reports and case series, lithium salts have been associated with severe cardiac side effects, including bradyarrhythmias caused by sinus node dysfunction, premature ventricular beats, atrioventricular block, T-wave depression, interstitial myocarditis, and cardiomyopathy.<sup>250–257</sup> Stancner and Kivi<sup>258</sup> reported 5 patients with edema during lithium carbonate use; 2 of these patients developed new-onset HF. In the majority of these cases, lithium was within its therapeutic serum concentration range (0.6–1.2 mEq/L), and the cardiotoxicity resolved on lithium discontinuation. Although still unclear, the potential mechanisms of these cardiotoxicities consist of myofibrillar degeneration with myocardial lymphocyte cell infiltration, adrenergic stimulation, and interference with calcium ion influx in pacing cells.<sup>255,257</sup> Alternative

agents for the treatment of bipolar disease such as valproic acid or lamotrigine are available.

## Ophthalmological Agents

### $\beta$ -Blockers

Topical  $\beta$ -blockers are the best studied with regard to hemodynamic effects. Small case series evaluating topical timolol usually involving young healthy volunteers have variably demonstrated changes in blood pressure and heart rate, which have been considered clinically insignificant.<sup>259–261</sup> However, several case series and case reports with topical  $\beta$ -blockers, primarily timolol, have demonstrated clinically significant issues in patients with HF, including arrhythmias such as bradycardia, myocardial ischemia, hypotension, and pulmonary edema.<sup>262,263</sup> In 2 HF patients, topical timolol administration led to an exacerbation of symptoms of HF.<sup>263</sup> Discontinuation or dose reduction of the ophthalmic  $\beta$ -blocker led to rapid resolution of cardiac side effects.<sup>263</sup>

### Cholinergic Agonists

Cholinergic agonists, including cholinesterase inhibitors, have been associated with changes in heart rate, including atrioventricular block, but this effect appears uncommon with the caveat that this class appears to be the least studied.<sup>262,264</sup>

## Pulmonary Agents

### $\beta_2$ -Agonists

Several small studies have suggested an association with  $\beta_2$ -agonist use and cardiotoxicity. In a retrospective case-control study, Coughlin et al<sup>265</sup> demonstrated a 3-fold increase in the risk of cardiomyopathy with the use of systemic or inhaled  $\beta_2$ -agonist. Although other studies have not confirmed this association, Au et al<sup>266</sup> identified a dose-related increase in risk for hospital admission with deteriorating HF in patients with HF with reduced EF using inhaled  $\beta_2$ -agonists (1–2 canisters per month: adjusted OR, 1.8; 95% CI, 1.1–3.0;  $\geq 3$  canisters per month: adjusted OR, 2.1; 95% CI, 1.2–3.8). Bouvy et al<sup>267</sup> also found an increased risk of hospitalization for ventricular arrhythmia (OR, 4.0; 95% CI, 1.0–15.1) in patients receiving  $\beta_2$ -agonists, an effect that was higher in patients receiving systemic compared with inhaled formulations. Although  $\beta_2$ -agonists are known to exert small positive inotropic and chronotropic effects on the heart, the proposed mechanism of this association has been that regular exposure to  $\beta_2$ -agonists could lead to decreased receptor responsiveness, which could theoretically lead to HF deterioration.<sup>268</sup>

### Bosentan and Epoprostenol

Both epoprostenol, an intravenous prostaglandin, and bosentan, an oral endothelin-1 antagonist, are used in the

management of patients with pulmonary hypertension. In FIRST (Randomized Controlled Trial of Epoprostenol Therapy for Severe Congestive Heart Failure: The Flolan International Randomized Survival Trial), epoprostenol was associated with an increased risk of death in patients with NYHA class IIIB/IV HF and therefore is contraindicated for long-term use in patients with HF with reduced EF.<sup>269</sup> In pooled, placebo-controlled studies lasting between 4 weeks and 6 months, leg edema was reported in 5% of patients receiving between 100 and 2000 mg daily of bosentan (n=677) compared with 1% of patients receiving placebo (n=288).<sup>270</sup> During the first 4 to 8 weeks, patients with severe HF were at increased risk of hospitalization because of weight gain and increased leg edema. Long-term studies in patients with symptomatic HF have been conducted: REACH (Research on Endothelin Antagonism in Chronic Heart Failure) and ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) trials. The REACH trial was stopped prematurely because of elevations in hepatic transaminases. It demonstrated an increased risk of death or worsening HF in the bosentan group within the first month of therapy but not at months 4 to 6.<sup>271,272</sup> The ENABLE trial found similar findings in which bosentan appeared to confer an early risk of worsening HF that warranted hospitalization related to fluid retention.<sup>273</sup>

## Rheumatological Medications

### Tumor Necrosis Factor- $\alpha$ Inhibitors

The tumor necrosis factor- $\alpha$  inhibitors infliximab, etanercept, and adalimumab play a major role in the management of patients with rheumatoid arthritis and Crohn disease; however, postmarketing data have suggested that these medications can be associated with new-onset or worsening HF. In the RENAISSANCE (Randomized Etanercept North American Strategy to Study Antagonism of Cytokines) and RECOVER (Research into Etanercept Cytokine Antagonism in Ventricular Dysfunction) trials, etanercept had no impact on the clinical status in patients with NYHA class II, III, or IV HF compared with control subjects.<sup>274</sup> In the ATTACH trial (Anti-TNF Alpha Therapy Against CHF), higher rates of HF-related hospitalization or death were noted in the patients with NYHA class III or IV HF receiving infliximab 10 mg/kg compared with the 5-mg/kg dose (HR, 2.84; 95% CI, 1.01–7.97).<sup>275</sup> However, a recent systematic review in patients with rheumatoid arthritis and HF that included observational studies and a meta-analysis found no increase in the risk of incident or worsening HF in patients treated with tumor necrosis factor- $\alpha$  inhibitors (infliximab, etanercept, and adalimumab) except for patients  $\geq 65$  years of age, who had a higher risk of HF hospitalization (HR, 1.7; 95% CI, 1.07–2.69) and death (HR, 4.19; 95% CI, 1.48–11.89).<sup>276</sup> The 2015 American College of Rheumatology treatment guidelines for rheumatoid arthritis recom-



mend that a tumor necrosis factor- $\alpha$  inhibitor should only be considered in patients with HF if there are no other reasonable treatment options, and then consider only in patients with compensated HF.<sup>277</sup>

### Antimalarial Agents

Hydroxychloroquine is an antimalarial that has become a mainstay in the management of systemic lupus erythematosus and rheumatoid arthritis. Similar to chloroquine in structure, hydroxychloroquine is used more frequently because it has less toxicity. More than 70 cases of cardiotoxicity have been reported with these agents in which chloroquine has primarily been implicated.<sup>278</sup> Cardiotoxicity manifests as restrictive or dilated cardiomyopathy or with conduction system abnormalities such as atrioventricular and bundle-branch block.<sup>279,280</sup> Because both chloroquine and hydroxychloroquine are cationic amphiphilic drugs, they are hypothesized to bind to phospholipids within the myocyte, accumulating in the lysosomes and inhibiting lysosomal enzymes. This impairs intracellular degradation and leads to accumulation of pathological metabolic products such as phospholipid and glycogen.<sup>279,280</sup> On histology, these appear as granulovacuolar cell mutations and ultrastructurally as lamellar membranous inclusion bodies and curvilinear bodies in the cytoplasm. Prognosis can vary from death to cardiac transplantation to partial or complete improvement within 1 month to 1 year on medication discontinuation. Risk factors consist of older age, female sex, longer duration of therapy (3 months–27 years; mean >10 years), elevated milligram per kilogram daily dose, preexisting cardiac disease, and renal insufficiency.<sup>279,280</sup>

### Urological Medications

#### $\alpha_1$ -Blockers

Limited data exist on the specific use of the uroselective (eg, tamsulosin) and nonuroselective (eg, prazosin, terazosin, doxazosin)  $\alpha_1$ -blockers in the management of benign prostatic hypertrophy for patients with HF. In the case of the nonuroselective agents, which have greater systemic  $\alpha$ -blockade effects, much of the evidence has been extrapolated from the results of ALLHAT and VeHFT-1.<sup>71,73</sup> In a retrospective analysis of 388 patients with HF and benign prostatic hypertrophy receiving prazosin, terazosin, doxazosin, or tamsulosin, Dhaliwal et al<sup>281</sup> found no significant increase in all-cause mortality and HF rehospitalization in those receiving  $\beta$ -blockers. However, in those not receiving  $\beta$ -blockade,  $\alpha$ -blockade exposure was associated with an increase in HF hospitalization (HR, 1.94; 95% CI, 1.14–3.32). Of note, the majority of patients were receiving tamsulosin (58%). It has been hypothesized that unopposed  $\alpha_1$  blockade could lead to  $\beta_1$ -receptor stimulation with increases in renin and aldosterone, leading to edema and weight

gain.<sup>281</sup> Chronic  $\alpha_1$  antagonism may lead to tachyphylaxis with a loss of hemodynamic benefits and gradual increases in norepinephrine. In VeHFT-1, reported in 1986 before the use of  $\beta$ -blockers for HF, prazosin did not affect overall mortality compared with placebo, but no data on HF hospitalizations were reported.<sup>73</sup> Despite uncertainty about the mechanism, the balance of data suggest that  $\alpha_1$ -blockers may exacerbate HF in those with established disease, perhaps even with uroselective agents.

### Erectile Dysfunction Medications

On the basis of findings from a single HF center, at least 75% of men with HF admitted to experiencing erectile dysfunction, regardless of the cause of their HF.<sup>282</sup> Sildenafil, vardenafil, and tadalafil are all selective inhibitors of cGMP-specific phosphodiesterase type 5, which increases the amount of cGMP that relaxes the smooth muscle of the corpus cavernosum. However, these agents may increase the hypotensive effects of nitrates and are contraindicated with concomitant nitrates.<sup>282</sup> Additionally, this effect would be expected to be seen if these agents are combined with other phosphodiesterase inhibitors such as milrinone.

## MISCELLANEOUS PRESCRIPTION MEDICATIONS

### QT-Prolonging Medications

Drug-induced prolongation of the QT interval is a significant and potentially dangerous drug toxicity that can lead to the polymorphic ventricular tachycardia TdP. Numerous drugs from various therapeutic classes have been implicated in prolonging the QT interval, including antibiotics, antidepressants, antipsychotics, and antiemetics, all of which are commonly used by patients with HF.<sup>283,284</sup> Numerous risk factors exist for drug-induced QT interval prolongation that potentially leads to TdP such as hypokalemia, hypomagnesemia, bradycardia, genetic predisposition, female sex, and use of drugs that either prolong the QT interval or disrupt the metabolism or distribution of QT-prolonging drugs. HF is a risk factor for TdP because of frequent prolongation of the QT interval and diuretic-induced hypokalemia and hypomagnesemia. CredibleMeds, a program of the Arizona Center for Education and Research on Therapeutics, maintains an evidence-based list of potential QT-prolonging medications stratified by their risk of TdP (risk, possible, conditional, and avoided). Table 5 summarizes these medications and their effects.<sup>285</sup>

### Sodium-Containing Medications

Sodium restriction is often recommended for patients with HF. Consideration is often given to dietary sodium restriction; however, evaluation of nondietary sources



may not be considered. Not only is sodium chloride often a common vehicle for administration of intravenous medications, but many medications administered in the inpatient setting may also be high in sodium. In a retrospective, single-center analysis of 82 patients admitted to the cardiac intensive care unit for acute HF exacerbation, the mean nondietary sodium load was  $4.0 \pm 5.0$  g/d, which was correlated with an increase in hospital stay.<sup>286</sup> An average of 1.2 g of daily nondietary sodium correlated with hospital stays of up to 5 days, whereas an average of 2.6 g/d led to stays of up to 10 days.<sup>286</sup> Table 6 summarizes the sodium content for both intravenous and oral prescription medications that could be used in the inpatient or outpatient setting.<sup>287–301</sup>

## OTC MEDICATIONS

Currently, 35% of adult Americans use an OTC medication on a regular basis. In a 2011 survey ( $n=1880$ ), the most common choice of products for ailments such as headache, heartburn, allergies, and cough/cold was OTC medications. Unfortunately, one third of Americans admit that they have taken more than the recommended dose of an OTC product, and only half report reviewing the package labeling before using an OTC product for the first time.<sup>302</sup> OTC NSAIDs, like their prescription counterparts, can exacerbate HF and increase the risk for HF hospitalization particularly when taken at higher doses.<sup>18</sup> Many OTC medications have high sodium content or have actions that could exacerbate HF or common comorbid conditions. For example, many cough, cold, and allergy and sinus preparations may have NSAIDs such as ibuprofen or vasoconstrictors such as phenylephrine or pseudoephedrine. Because both phenylephrine and pseudoephedrine exert their effects on adrenergic receptors, cardiotoxicity such as myocardial ischemia, MI, stroke, and arrhythmias can be seen with high dose and prolonged, excessive use.<sup>303,304</sup> Pepto-Bismol contains 261 mg/30 mL and 99 mg per tablet of salicylate.<sup>305</sup> Nasal decongestants typically contain oxymetazoline, phenylephrine, and the ocular decongestant naphazoline, all of which are vasoconstrictors. When these agents are topically applied, case reports have suggested that excessive use or prolonged exposure beyond package labeling can lead to systemic exposure resulting in stroke, hypertension, and bradycardia.<sup>306–309</sup> Inhaled and oral OTC asthma products may contain potent nonselective sympathomimetic amines such as racemic epinephrine and ephedrine, and they have been associated with chest pain, hypertension, tachycardia, and hemoptysis.<sup>310–313</sup>

Many of the newer aluminum- and magnesium-containing antacids have minimal to no sodium; however, other

products for cough/cold and gastrointestinal ailments may contain sodium. Nyquil and Dayquil contain 37 and 15 mg/30 mL, respectively, of sodium.<sup>314,315</sup> Gaviscon has 52 mg of sodium per 15 mL, which, if the recommended 30-mL dose is taken 4 times daily, equates to  $>400$  mg of sodium per day.<sup>316</sup>

Because OTC product formulation can rapidly change from year to year, it is valuable for patients to be taught to read and evaluate OTC labels. Unfortunately, many inactive ingredients such as sodium and sodium bicarbonate may be difficult to find in the package labeling.

## COMPLEMENTARY/ALTERNATIVE MEDICATIONS

The incorporation of naturoceutical products into standard medical practice is handicapped by a dearth of quality efficacy and safety data. In addition, there is no rigorous oversight for their manufacture, and adulterated products abound. However, these shortcomings do not inhibit the availability of these products for retail and Internet sale, and most individuals believe that the US government regulates these products.<sup>317</sup>

In a 2007 national survey, it was observed that 38% of adults in the United States use CAMs. This phenomenon is not isolated to the young or middle-aged; 1 in 4 individuals  $>85$  years of age reported the use of at least 1 CAM therapy.<sup>318</sup> This underscores the importance of the 2010 HF practice guidelines, which state “documentation of the type and dose of naturoceutical products used by patients with HF is recommended” to facilitate an individualized assessment of risk to benefit.<sup>319</sup> These guidelines further recommend 3 specific measures concerning these products in patients with HF:

1. No naturoceutical should be used for the management of HF symptoms or the secondary prevention of cardiovascular events.
2. Ephedra-like products (ma-huang) should be avoided because of their stimulant effects on blood pressure and heart rate and their increased risk of mortality and morbidity.
3. Products with significant interactions with digoxin, vasodilators,  $\beta$ -blockers, antiarrhythmic agents, and anticoagulants should be avoided (Tables 7 and 8<sup>320</sup>).

The American College of Cardiology Foundation/American Heart Association HF guidelines recommend that nutritional supplements not be used for the treatment of HF.<sup>13</sup>

There is evidence that supplementation with vitamin E  $\geq 400$  IU/d may increase the risk of developing new-onset HF; it seems prudent to avoid it in individuals with established HF. Post hoc analyses of large, long-term,

**Table 5. Medications That Could Prolong the QT Interval and Induce TdP Based on Risk Category<sup>285\*</sup>**

Risk Category	Medications
Known risk of TdP	Amiodarone, anegrelide, arsenic trioxide, azithromycin, bepridil,† chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride,† citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin,† grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levomethadyl,† mesoridazine,† methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine, pentamidine, pimozone, probucol,† procainamide, propofol, quinidine, sevoflurane, sotalol, sparfloxacin,† sulpiride, terfenadine,† thioridazine, vandetanib
Possible risk of TdP	Alfuzosin, apomorphine, aripiprazole, arteminol+piperaquine, asenapine, atazanavir, atomoxetine, bedaquiline, bortezomib, bosutinib, ceritinib, clomipramine, clozapine, crizotinib, cyamemazine, dabrafenib, dasatinib, degarelix, delamanid, desipramine, dexmedetomidine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, gemifloxacin, granisetron, hydrocodone extended release, iloperidone, imipramine, isradipine, lapatinib, lenvatinib, leuprolide, lithium, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, nifedipine, nilotinib, norfloxacin, nortriptyline, ofloxacin, osimertinib, olanzapine, oxytocin, paliperidone, panobinostat, pasireotide, pazopanib, perflutren lipid microspheres, pipamperone, promethazine, ranolazine, rilpivirine, risperidone, roxithromycin, saquinavir, sertindole, sorafenib, sunitinib, tacrolimus, tamoxifen, telavancin, telithromycin, tizanidine, tetrabenazine, tizanidine, tolterodine, toremifene, trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine
Conditional risk of TdP	Amantadine, amisulpride, amitriptyline, chloral hydrate, diphenhydramine, doxepin, fluoxetine, furosemide, galantamine, hydrochlorothiazide, hydroxychloroquine, hydroxyzine, indapamide, itraconazole, ivabradine, ketoconazole, metoclopramide, metronidazole, nelfinavir, pantoprazole, paroxetine, posaconazole, quetiapine, quinine sulfate, ritonavir, sertraline, solifenacin, telaprevir, torsemide, trazodone, voriconazole, ziprasidone
Drugs to avoid in congenital long QT	Albuterol, alfuzosin, amantadine, amiodarone, amisulpride, amitriptyline, amphetamine, anagrelide, apomorphine, arformoterol, aripiprazole, arsenic trioxide, arteminol+piperaquine, asenapine, astemizole,† atazanavir, atomoxetine, azithromycin, bedaquiline, bepridil,† bortezomib, bosutinib, ceritinib, chloral hydrate, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride,† citalopram, clarithromycin, clomipramine, clozapine, cocaine, crizotinib, cyamemazine, dabrafenib, dasatinib, degarelix, delamanid, desipramine, dexmedetomidine, dextroamphetamine, diphenhydramine, disopyramide, dobutamine, dofetilide, dolasetron, domperidone, donepezil, dopamine, doxepin, dronedarone, droperidol, ephedrine, epinephrine, eribulin, erythromycin, escitalopram, famotidine, felbamate, fenfluramine,† fingolimod, flecainide, fluconazole, fluoxetine, formoterol, foscarnet, furosemide, galantamine, gatifloxacin,† gemifloxacin, granisetron, grepafloxacin, halofantrine, haloperidol, hydrochlorothiazide, hydrocodone extended release, hydroxychloroquine, hydroxyzine, ibutilide, iloperidone, imipramine, indapamide, isoproterenol, isradipine, itraconazole, ivabradine, ketoconazole, lapatinib, lenvatinib, leuprolide, levalbuterol, levofloxacin, levomepromazine, lisexamfetamine, lithium, mesoridazine,† metaproterenol, methadone, methamphetamine, methylphenidate, metoclopramide, metronidazole, midodrine, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, moxifloxacin, nelfinavir, nifedipine, nilotinib, norepinephrine, norfloxacin, nortriptyline, ofloxacin, olanzapine, ondansetron, osimertinib, oxaliplatin, oxytocin, paliperidone, panobinostat, pantoprazole, papaverine, paroxetine, pasireotide, pazopanib, pentamidine, perflutren lipid microspheres, phentermine, phenylephrine, phenylpropanolamine, pimozone, pipamperone, posaconazole, probucol,† procainamide, promethazine, propofol, pseudoephedrine, quetiapine, quinidine, quinine sulfate, ranolazine, rilpivirine, risperidone, ritodrine,† ritonavir, roxithromycin, salmeterol, saquinavir, sertindole, sertraline, sevoflurane, sibutramine,† solifenacin, sorafenib, sotalol, sparfloxacin,† sulpiride, sunitinib, tacrolimus, tamoxifen, telaprevir, telavancin, telithromycin, terbutaline, terfenadine,† tetrabenazine, thioridazine, tizanidine, tolterodine, toremifene, trazodone, trimethoprim/sulfamethoxazole, trimipramine, tropisetron, vandetanib, vardenafil, vemurafenib, venlafaxine, voriconazole, vorinostat, ziprasidone

Known risk of TdP: These drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended. Possible risk of TdP: These drugs can cause QT prolongation but currently lack evidence for a risk of TdP when taken as recommended. Conditional risk of TdP: These drugs are associated with TdP but only under certain circumstances of their use (eg, excessive dose, in patients such as those with hypokalemia, or when taken with interacting drugs) or by creating conditions that facilitate or induce TdP (eg, by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP). Drugs to avoid in congenital long QT: These drugs pose a special risk of TdP for patients with congenital long-QT syndrome and include those in the above 3 categories plus additional drugs that do not prolong the QT interval per se but have a special risk because of their adrenaline-like actions. HCTZ indicates hydrochlorothiazide; QT, QT interval; and TdP, torsades de pointes.

\*The CredibleMeds online lists are revised regularly and should be consulted before clinical decisions are made on the safe use of any of these medicines.

†Removed from the market.

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randomized trials involving vitamin E suggest that cardiovascular harm may be present. In patients without HF, 1 study reported a 21% increased risk for hospitalization for HF compared with placebo, and a second

study reported up to a 50% increased risk for developing clinically overt HF compared with placebo.<sup>321,322</sup>

Because of the lack of rigorous study, few declarative statements can be made about the safe use of

**Table 6. Selected Intravenous and Oral Prescription Medications High in Sodium**

Medication	Sodium Content Per Unit
Alendronate effervescent tablet <sup>287</sup>	650 mg sodium/tablet
Ampicillin/sulbactam, injection <sup>288</sup>	115 mg sodium/1.5 g vial
Azithromycin, injection <sup>289</sup>	114 mg/500 mg vial
Erythromycin ethylsuccinate <sup>290,291</sup>	47 mg/tablet 23.7 mg/mL
Metronidazole, injection <sup>292</sup>	790 mg/500 mg vial
Nafcillin, injection <sup>293</sup>	132 mg/2 g vial
Omeprazole/sodium bicarbonate <sup>294</sup>	304 mg/capsule 406 mg/packet
Oxacillin, injection <sup>295</sup>	128 mg/2g vial
Piperacillin/tazobactam, injection <sup>296</sup>	128 mg/2.25 g vial 192 mg/3.375 g vial 256 mg/4.5 g vial
Polyethylene glycol powder for solution (Colyte, Golytely) <sup>297</sup>	1.46 g/1 L
Ranitidine, pre-mixed bag <sup>298</sup>	225 mg/50 mg vial
Sodium phosphates solution (Fleet Enema) <sup>299</sup>	4.4 g/118 mL
Sodium polystyrene sulfonate suspension <sup>300</sup>	1500 mg/60 mL
Ticarcillin/clavulanate potassium, injection <sup>301</sup>	429 mg/3.1 g vial

most CAM products in patients with HF. Even for the products with mostly modest benefit for a noncardiac condition, the possibility of off-target effects harmful to patients with HF exists. On the basis of what is known about their side effects in healthy people and the mechanism of action, many of these therapies have plausible risks if used in patients with HF (Table 9).<sup>320</sup>

**Table 7. CAMs With Significant Interactions With Cardiovascular Medications Used in Patients With HF<sup>320</sup>**

CAM Product	Digoxin	ACE-I/ARBs	$\beta$ -Blockers	CCB	Amiodarone	Warfarin
St. John's wort	x	x	x	x	x	x
Grapefruit juice		x	x	x	x	x
Ginseng						x
Hawthorn	x					
Danshen						x
Black cohosh		x	x		x	
Green tea						x

ACE-I, indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CAM, complementary and alternative medicine; CCB, calcium channel blockers; and HF, heart failure.

**Table 8. CAMs That Increase Bleeding Risk With Anticoagulants via Platelet and/or Clotting Factor Effects<sup>320</sup>**

Antiplatelet Effects	Anticoagulant Effects
Danshen	Dong quai
Garlic	Motherwort
Ginkgo	Liquorice
Motherwort	
Saw palmetto	
Hawthorn	
Liquorice	

CAM indicates complementary and alternative medicine.

## SUMMARY AND RECOMMENDATIONS

Polypharmacy is a significant concern in patients with HF because of the burden of both cardiovascular and noncardiovascular conditions. It is not unusual to have medications ordered and adjusted by different clinicians, many times with minimal consideration for drug-drug or drug-condition interactions, or to have prescriptions filled at different pharmacies. The following strategies may be helpful in detecting inappropriate and potentially hazardous medications that could exacerbate HF.

## Considerations for Minimizing Polypharmacy and Improving Drug Safety

1. Healthcare providers should conduct comprehensive medication reconciliation at each clinical visit and with each admission. Patients should be specifically asked about drug, dose, and frequency of all their medications, including OTC medications and CAMs. If possible, these should be verified with the pharmacy or prescriber<sup>323</sup> (Class I; Level of Evidence B).

**Table 9. CAMs That May Be Mechanistically Harmful in Patients With Heart Failure<sup>320</sup>**

CAM Product	Possibly Harmful Cardiovascular Effects
Aconite	Decreased heart rate (central brainstem effect) Ventricular tachycardia (direct myocardium effect)
Ginseng	Hypotension (increased nitric oxide synthesis) Hypertension (chronic use) Decreased diuretic responsiveness (damaged loop of Henle)
Gossypol	Increased effects of diuretics
Gynura	Hypotension (inhibits ACE)
Licorice	Hypertension, fluid retention (pseudohyperaldosteronism)
Lily of the valley	Bradycardia (digitalis glycoside)
Tetrandrine	Hypotension (inhibits L-type calcium channels)
Yohimbine	Hypertension (increased norepinephrine via $\alpha_2$ -adrenergic receptor antagonism)

ACE indicates angiotensin-converting enzyme; and CAM, complementary and alternative medicine.

2. Although not associated with improved outcome, the use of complexity tools may be considered to identify issues within a medication regimen<sup>324,325</sup> (**Class IIb; Level of Evidence C**).
3. It can be beneficial to implement a medication flow sheet and to update it at each visit. This flow sheet may include any laboratory tests needed for specific medications such as warfarin or amiodarone. It can be useful to provide patients with a copy of this final list and to encourage them to carry it with them at all times<sup>326</sup> (**Class IIa; Level of Evidence C**).
4. Evaluating the potential risks and benefits of each medication should be considered before initiation. Medications should be categorized as either essential to desired outcomes or optional, with an attempt made to reduce or eliminate optional medications<sup>327,328</sup> (**Class I; Level of Evidence C**).
5. It is reasonable to discontinue medications that do not have an indication or are contraindicated<sup>327–329</sup> (**Class IIa; Level of Evidence C**).
6. When possible and affordable, it is reasonable to consider combination medications to reduce the number of medications taken daily or medications that can be used to treat >1 condition<sup>327</sup> (**Class IIa; Level of Evidence C**).
7. It is reasonable to consider avoiding prescribing new medications to treat side effects

of other medications. The use of as-needed medications should be limited to only those that are absolutely necessary<sup>327–329</sup> (**Class IIa; Level of Evidence C**).

8. It can be beneficial to educate patients on the following aspects of OTC medications and CAMs: Communicate with their healthcare provider first before taking any OTC medications and CAMs; avoid the use of OTC medications and CAMs with uncertain efficacy and safety; and evaluate all labels of OTC medications and CAMs for sodium content<sup>327,330</sup> (**Class IIa; Level of Evidence C**).
9. It is reasonable to establish a team management approach in which a healthcare provider acts as “captain” of the medications and instructs patients to notify this individual whenever a medication is changed or added to the medication list. Ideally, this call should be made before the product is purchased or the prescription is filled<sup>330</sup> (**Class IIa, Level of Evidence C**).

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## FOOTNOTES

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be “significant” if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

\*Dr Lindenfeld is now at Vanderbilt University, School of Medicine.

†Modest.

‡Significant.

§Dr Trupp is now at Roche Diagnostics Corporation.



## Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Biykem Bozkurt	Baylor College of Medicine and MEDVAMC	None	None	None	None	None	None	None
Eldrin Lewis	Brigham & Women's Hospital	Sanofi*; Novartis*; Amgen*	None	None	None	None	None	None
Kinya Otsu	King's College London (UK)	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Significant.

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