REVIEW ARTICLE

Keeping Your Patient With Heart Failure Safe

A Review of Potentially Dangerous Medications

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Heart failure (HF) is a significant health problem in the United States, with a prevalence of 5 million patients and 500 000 new diagnoses each year.[1] Heart failure is also a significant health care–dollar expenditure, with 5.4% of the health care budget contributing to its treatment.[1] Furthermore, it is a disease of the elderly, affecting 6% to 10% of those older than 65 years.[2] Since the elderly with concomitant disease states are highly affected, polypharmacy may be more problematic in this subpopulation.

This review is designed to assist clinicians to provide the safest pharmacotherapy for patients with HF. The information contained will summarize data published concerning medications used to treat concomitant diseases in patients with HF. In some instances, these medications may exacerbate heart failure symptoms, may be contraindicated in HF because of heightened adverse effects, or may lead to cardiac abnormalities such as conduction problems or valvular defects. Other medications discussed may unmask previously undetected HF or cause HF in predisposed patients.

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Not all medications that are or may be harmful will be included in this article. Since a multitude of drugs at supratherapeutic levels may have cardiotoxic effects, only agents with effects at clinically used doses will be reviewed. In addition, recreational and illegal drugs that may be detrimental to the cardiovascular system will not be included. Several medications that may be harmful will not be presented because of the necessity of the agents in specific emergency situations regardless of concurrent diseases. Many drugs that have the potential to prolong the QT interval and may promote ventricular tachycardia or ventricular fibrillation, to which the patient with HF is predisposed, will also not be addressed, nor will chemotherapeutic agents despite the well-recognized cardiotoxicity of several agents. Finally, medications that are used in the acute care setting, yet have conflicting or limited data on long-term survival (eg, positive inotropes, dobutamine, and milrinone) will not be presented in this review. These agents are often used as bridge therapy in acutely decompensated patients with HF or in those awaiting heart transplant.

A MEDLINE search (1966-2002) was conducted containing the key words *heart failure* and *medications* with fields limited to human and English. A total of 24 693 citations were reviewed for relevance and the presence of adverse events. In addition, *Meyler's Side Effects of Drugs*[3] and *Davies's Textbook of Adverse Drug Reactions*[4] were assessed for entries pertaining to HF and medications. The medications or classes of medications listed in the preceding paragraph were excluded from analysis for the reasons described, and remaining agents were grouped into like categories when possible. The beginning of each section contains a brief summary including the mechanism of the adverse effect, the strength of supporting evidence (**Table 1**), time to onset of the effect, and a recommendation for use in the population with HF. Additional information is included when further clarification is necessary.

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Table 1. Relative Strength of Evidence*

Score	Description
1	Anecdotal observations or comments of investigators or patients
2	Case reports
3	Uncontrolled series of patients
4	Cases obtained from computer databases
5	Series of patients with literature controls
6	Series of patients with historical controls
7	Open-label trial
8	Randomized trial (single-blind)
9	Randomized active medicine–controlled trial (double-blind)
10	Randomized placebo-controlled trial (double-blind)
11	Randomized active medicine– and placebo-controlled trial (double-blind)
12	Confirmatory trial of a trial listed under 10 or 11

*Listed from weakest to strongest supportive evidence. Adapted with permission from Spilker.[5] Copyright 1991, Lippincott Williams & Wilkins.

ANTI-INFLAMMATORY MEDICATIONS

Corticosteroids

Major considerations for the use of corticosteroids are as follows:

- Mechanism of adverse effect: sodium and fluid retention
- Strength of evidence: 3
- Time to onset: days to weeks
- Recommendation: active monitoring for new or increased HF symptoms; conservative use with the lowest doses needed for efficacy

Corticosteroids are used for the treatment of a broad range of disease states from asthma and topical dermatitis to Addison disease and immunosuppression in transplantation. The choice of corticosteroid depends on the degree of mineralocorticoid or glucocorticoid activity necessary for treatment. Because of their wide range of uses and known adverse effects with short- and long-term administration, corticosteroid use in patients with HF has not been specifically studied.

It has been well documented that all corticosteroids cause sodium and fluid retention. Corticosteroids with substantial mineralocorticoid activity (eg, cortisone, hydrocortisone) cause more fluid retention than those with predominant glucocorticoid activity (eg, dexamethasone, triamcinolone, betamethasone). The mechanism behind corticosteroid-induced hypertension, the most common cardiovascular side effect, has not been clearly defined. Elevations in blood pressure are postulated to be due to the mineralocorticoid-associated plasma volume expansion.[6]

Inhaled corticosteroids used in the long-term management of asthma and chronic obstructive pulmonary disease have the potential to produce many of the adverse effects associated with systemic administration. The systemic effects have been associated with increased dose and frequency of administration, in addition to specific pharmacokinetic characteristics of the corticosteroid.[7-9] Increased systemic effects and absorption may be due to poor inhalation technique with deposition in the mouth and oropharynx.

Corticosteroids should be used at the lowest dose and for the shortest duration possible in any patient regardless of presence of HF. It is, however, imperative to monitor patients with HF for increased symptoms of dyspnea or weight gain with the use of corticosteroids. Loss of hypertensive control when corticosteroids are added to therapy must also be considered and closely monitored. Hence, monitoring for decompensation, minimizing dose and duration, use of agents with lower mineralocorticoid activity when possible, and periodically assessing for corticosteroid necessity are recommended in patients with HF.

Nonsteroidal Anti-inflammatory Drugs

Major considerations for the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are as follows:

- Mechanisms of adverse effect: sodium and water retention; blunted response to exogenous diuretics; increased systemic vascular resistance
- Strength of evidence: 5
- Time to onset: days up to 1 month
- Recommendations: avoid the use of nonsteroidal anti-inflammatory drugs in patients with symptomatic left ventricular (LV) dysfunction if possible; aspirin, 81-325 mg/d, should be used in patients with a history of or risk factors for atherosclerotic cardiovascular or cerebrovascular disease

Nonsteroidal anti-inflammatory drugs do not exert their detrimental effects in patients with HF through morphologic changes in heart muscle or direct myocardial damage. The therapeutic and adverse effects of NSAIDs are secondary to their inhibition of prostaglandin synthesis. This inhibition causes a decrease in renal blood flow and compensatory sodium and water retention. By expanding the intravascular volume, NSAIDs blunt the response to diuretics, an important adjunct therapy in patients with HF. Prostaglandin depletion increases systemic vascular resistance, which may also augment symptoms of HF.[10,11]

A case-control study demonstrated a significant odds ratio of developing HF equal to 26.3 in elderly patients with a history of heart disease receiving NSAIDs (ie, diclofenac, ibuprofen, ketoprofen, tiaprofenic acid, mefenamic acid, high-dose aspirin, indomethacin, sulindac, diflunisal, naproxen, piroxicam, and tenoxicam). This study also showed a significant dose response for the development of HF. Ninety-two percent of patients developing HF had New York Heart Association (NYHA) class III and IV symptoms at the time of diagnosis.[11]

In patients with known HF, there was an approximate dou bling of risk of hospitalization for worsening symptoms of HF in pa tients whose condition was stabilized with diuretics in whom a nonaspirin NSAID was initiated. There were no significant differences between the NSAIDs, and, in contrast to the previous study, no dose response was

zevident. The risk of hospitalization for HF was highest within the first few days of NSAID initiation and usually occurred within 30 days.[10] Although most of the patients studied were 65 years and older, the mechanism of NSAIDs' adverse effect in HF would apply in younger patients as well. It is recommended that nonaspirin NSAIDs be avoided in patients with HF. Appropriate monitoring for weight gain, dyspnea, edema, and other symptomatic deterioration is crucial if patients with HF must use an NSAID.

Selective cyclooxygenase 2 inhibitors were developed and marketed for their reduced adverse effect profile. Postmarketing clinical studies and reports have demonstrated that these agents have similar mechanisms in the kidney leading to sodium retention and edema. Since cyclooxygenase 2 is constitutively present in the human kidney, inhibition of its activity affects sodium and water homeostasis, producing peripheral edema. A 6-week, randomized, parallel-group, double-blind trial comparing celecoxib, 200 mg once daily, with rofecoxib, 25 mg once daily, evaluated the differences in the occurrence of edema. Significant edema was reported in 4.9% and 9.5% of patients with celecoxib and rofecoxib, respectively.[12] These results do not exclude celecoxib as a potential cause of fluid retention and HF exacerbation, but rather suggest that this side effect is more common with rofecoxib. On the basis of inconclusive and limited results, cyclooxygenase 2 selective inhibitors do not appear to offer any advantage over conventional NSAIDs with regard to edema or fluid retention.

The role of aspirin in HF has not been clearly defined. It has been postulated that, although aspirin reduces the incidence of nonfatal myocardial infarction, nonfatal stroke, and vascular death, it may interfere with efficacy of angiotensin-converting enzyme inhibitors (ACEIs) in patients with HF.[13] By inhibiting cyclooxygenase and ultimately prostaglandin synthesis, the beneficial vasodilatory effects of ACEIs are theoretically blunted with concomitant aspirin administration. Because of inadequate evidence to support a detrimental effect, the known beneficial effects of aspirin outweigh the risk of ACEI attenuation. In contrast, the benefit of aspirin in nonischemic HF in patients without other comorbid indications for aspirin (eg, diabetes) is uncertain and therefore aspirin is not recommended. Aspirin should be used in patients with HF who also have risk factors for ischemic cardiovascular events.

CARDIOVASCULAR MEDICATIONS

Antiarrhythmic Medications

Class II antiarrhythmic medications (β-blockers) (**Table 2**) will not be discussed in this section because of their known beneficial effects on morbidity and mortality in the treatment of HF. Class IV antiarrhythmic agents (calcium channel blockers [CCBs]) are evaluated under antihypertensive agents. Amiodarone, a class III agent, is also excluded because its use in HF has been well studied and it has been shown to be safe in patients with HF.[14] Amiodarone is recommended for use in patients with HF with atrial fibrillation by the American College of Cardiology–American Heart Association (ACC/AHA) guidelines.[15] Dofetilide has proven useful in the management of atrial fibrillation and, unlike other antiarrhythmics, has a neutral effect on mortality and HF.[16] Hence, it will not be discussed as a potentially dangerous medication in patients with HF.

Class I and III Antiarrhythmics. Major considerations for the use of class I and III antiarrhythmics are as follows:

- Mechanism of adverse effect: negative inotropic activity, proarrhythmic effects
- Strength of evidence: 12, ACC/AHA practice guidelines
- Time to onset: hours to months
- Recommendations: avoid the use of all class I antiarrhythmic drugs, and class III agents ibutilide and sotalol, in patients with HF; consider amiodarone or dofetilide for patients with symptomatic or non–device-managed arrhythmias

Table 2. Vaughan Williams Antiarrhythmic Drug Classification

Class	Drug
Ia	Quinidine
	Procainamide hydrochloride
	Disopyramide
Ib	Lidocaine
	Mexiletine hydrochloride
	Tocainide
Ic	Encainide hydrochloride
	Flecainide acetate
	Propafenone hydrochloride
	Moricizine
II	β-Blockers
III	Amiodarone
	Dofetilide
	Ibutilide fumarate
	Sotalol hydrochloride
IV	Verapamil
	Diltiazem

Class I Antiarrhythmics. Ventricular arrhythmias and sudden death are common among patients with HF. A meta-analysis conducted by Kjekshus[17] found that with increasing HF severity there was a parallel increase in spontaneous complex ventricular arrhythmias. However, the incidence of sudden death due to arrhythmic causes ranges from 50% to 60% in early stages of HF to 20% to 30% with advanced disease. Associated risk factors for ventricular tachyarrhythmias and sudden cardiac death in patients with HF are ventricular dilation, myocardial scar tissue, ventricular hypertrophy, hypokalemia and hypomagnesemia, inotropic support therapies, and sympathoadrenergic activation.[18] Paradoxically, class I antiarrhythmic medications produce a greater negative inotropic effect, more frequent proarrhythmic effects, and bradyarrhythmias in patients with HF compared with the normal population.[18] The Cardiac Arrhythmia Suppression Trials demonstrated a significant increase in mortality compared with placebo in patients after myocardial infarction who were receiving class Ic agents. This was due to an increase in life-threatening arrhythmias and the conversion of ischemic and HF episodes to fatal events.[19,20] A post hoc analysis of the Stroke Prevention in Atrial Fibrillation trial found that patients with HF

in the study who were receiving antiarrhythmic therapy (ie, quinidine, procainamide, disopyramide, flecainide, encainide, and amiodarone) had a greater risk of cardiac death than patients not receiving one of these agents.[21]

It is recommended that class I antiarrhythmics not be used in patients with HF if possible. First-line options to consider are β-blockers, amiodarone, dofetilide, or nonpharmacologic management (eg, implantable cardioverter-defibrillator devices). It is important to treat underlying electrolyte disturbances, transient ischemia, and neurohormonal activation to minimize the proarrhythmia potential before long-term antiarrhythmic therapy is considered.

Class III Antiarrhythmics. Sotalol is a racemic mixture of D- and L-isomers, which have differing effects on potassium channels and β-receptors. The D-isomer is a pure potassium channel blocker lacking β-adrenergic effects, while L-sotalol possesses competitive nonselective β-receptor blocking activity.[22] Sotalol has produced mixed results in clinical trials and retrospective analyses in patients with HF. Most of the studies include small numbers of patients, which makes interpretation of the outcomes difficult.

In one of the larger studies, 5.0% of patients with a history of HF experienced torsades de pointes when treated with D,L-sotalol compared with 1.7% of patients without a history of clinical HF.[23] A meta-analysis showed that proarrhythmia was most often experienced by patients taking sotalol who had a history of HF, sustained ventricular tachycardia, and myocardial infarction.[24] However, this increased incidence of torsades de pointes in patients with HF is not surprising, as they are at a higher risk of arrhythmias than the general population. The Survival With Oral D-sotalol (SWORD) trial proved that the pure class III antiarrhythmic action of D-sotalol was associated with a higher relative risk of mortality than placebo in patients with an ejection fraction (EF) of 40% or less.[25] In contrast, a small open-label trial in 38 patients demonstrated that D,L-sotalol increased EF in patients with severe LV dysfunction and that therapy up to 6 months did not result in deterioration of EF or worsening HF.[26] This suggests that the class III properties of sotalol may be responsible for the detrimental effects, while the β-blocking properties may be neutral or beneficial.

Sotalol should be used with caution in patients with LV dysfunction. Although not contraindicated, its use is not supported by the ACC/AHA HF practice guidelines, and small trials have shown conflicting results; definitive conclusions are not possible at this time. It is recommended that other first-line agents (ie, β-blockers, amiodarone, dofetilide, or implantable cardioverter-defibrillator devices) be attempted before sotalol is considered in patients with HF.

Ibutilide prolongs the refractory period by increasing the slow inward sodium current and inhibiting the outward repolarizing potassium current without slowing conduction, as with class I agents. It is administered intravenously for the restoration of normal sinus rhythm in patients with atrial fibrillation. A double-blind, randomized, placebo-controlled, dose-response trial was conducted in 197 patients to evaluate the safety of increasing doses of ibutilide. Six patients (3.6%) randomized to receive ibutilide developed polymorphic ventricular tachycardia. All 6 of these patients had a history of decreased LV function.[27] There are no studies available directly evaluating ibutilide in patients with HF. The relative scarcity of data makes complete assessment in this subset of patients difficult. However, it is recommended that ibutilide be avoided in patients with HF because of the suggestion of proarrhythmic effects.

Antihypertensive Medications

It is generally recognized that α_1-adrenergic activation is related to cardiac hypertrophy and these receptors share signaling pathways with other hypertrophic growth factors (eg, angiotensin II, endothelin).[28] The α_1-adrenergic blockers have been evaluated for use in patients with HF because of their potent venous and arteriolar vasodilating effects through selective, competitive inhibition of postsynaptic α_1-adrenergic receptors. However, the potential benefit of α_1-adrenergic blockade has not been supported in comparative trials or interim analyses of long-term, active-control trials.[28,29]

In the Vasodilator in Heart Failure Trial I conducted in the 1980s, patients were randomized to prazosin, hydralazine-isosorbide dinitrate, or placebo. After 2 years, prazosin was found to be equal to placebo, yet inferior to hydralazine-isosorbide in terms of mortality in patients with HF. Prazosin also failed to demonstrate an increase in EF, similar to the findings in patients randomized to placebo.[29] More recently, the doxazosin arm of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial was terminated early because of a significantly higher incidence of the combined cardiovascular disease end point (HF, coronary revascularization, angina, peripheral vascular disease) compared with chlorthalidone. A higher risk of the development of HF was associated with the use of doxazosin.[28]

Because previous trials have not found support of α_1-adrenergic blockers or a clear detrimental effect in the treatment of patients with HF, these agents are not specifically addressed in the ACC/AHA practice guidelines. Regardless, it is recommended that these agents not be used in the treatment of patients with HF and that treatment with other blood pressure agents be maximized before α-blockers are considered for control of hypertension. These agents are also commonly prescribed for the management of benign prostatic hypertrophy; however, there are no data to suggest that this is not appropriate therapy in patients with concomitant HF at this time.

Neither amlodipine nor felodipine increases cardiovascular morbidity or mortality in patients with HF.[30,31] However, neither have they demonstrated benefit when compared with placebo in this patient population. Studies have not clearly determined their role in HF. Hence, these 2 CCBs will not be addressed in this review, and all comments and

recommendation made concerning CCBs are in reference to verapamil, diltiazem, nifedipine, nisoldipine, and nicardipine.

Calcium Channel Blockers. Major considerations for the use of CCBs are as follows:

- Mechanisms of adverse effect: negative inotropic activity; neurohormonal activation
- Strength of evidence: 12, ACC/AHA practice guidelines
- Time to onset: average of 2 to 3 months on initiation
- Recommendation: avoid use of CCBs (verapamil, diltiazem, nifedipine, nisoldipine, nicardipine) in patients with HF

The CCBs were initially studied for use in patients with decreased LV function for several sound pathophysiologic reasons. First, it was assumed that the combination of vasodilating and antiischemic effects would benefit patients with HF in both the acute and chronic stages of treatment. Second, because coronary artery disease is the most common cause of HF, CCBs could be used to treat both angina and heart failure symptoms.[32] However, their positive effects (eg, potent arterial vasodilation, afterload reduction) have not yielded benefit with long-term administration.[33] The neurohormonal feedback response to vasodilation consists of activation of the sympathetic nervous and renin-angiotensin-aldosterone systems, and the continued activation of these systems in patients with LV dysfunction results in the progression of LV dysfunction and symptoms. Recommended heart failure therapy with an ACEI and a β-blocker provides morbidity and mortality benefit by attenuating these neurohormonal systems. In addition, negative inotropic effects of specific CCBs can acutely decrease cardiac output, potentially causing further decompensation in these patients.[32] The CCBs are a heterogeneous class with varying effects on heart muscle, sinus node function, atrioventricular conduction, coronary circulation, and peripheral blood vessels.[33] Hence, it is imperative to examine these agents on the basis of their pharmacologic actions separately.

Distinctive from the other CCBs, verapamil and diltiazem possess negative chronotropic activity. Verapamil has limited data regarding its use in patients with HF because of its known negative inotropic effects and manufacturer's warning of worsening HF.[33] An early open-label trial showed marked hemodynamic and clinical deterioration in patients with an EF of less than 35% treated with verapamil after 1 year.[34] Although diltiazem has less negative inotropy and chronotropy than verapamil, it has also been associated with HF deterioration in patients with an EF of less than 40% at baseline.[35]

Nifedipine, nisoldipine, and nicardipine (the dihydropyridine CCBs) are essentially devoid of negative chronotropic properties. Nifedipine retains significant negative inotropic effects, while nisoldipine and nicardipine have minimal to no negative inotropic effects. Their primary pharmacologic action is potent reduction of systemic vascular resistance. In early trials examining the clinical utility of these agents in HF, patients receiving one of these dihydropyridine CCBs for 2 to 4 months had marked increases in clinical deterioration and hospital admissions for HF exacerbations likely secondary to activation of detrimental neurohormonal systems.[36-38] These agents were compared with placebo, isosorbide, or standard heart failure therapy that included an ACEI.

In conclusion, CCBs have been associated with varying degrees of negative effects on clinical symptoms and hospitalization for HF. Most studies have shown an increase in the risk of detrimental effects in patients with HF who have the most severe symptoms.[39] The addition of an ACEI does not diminish the CCB's negative cardiac effects.[35,40] The CCBs are not recommended by the 2001 ACC/AHA heart failure practice guidelines. The ACC/AHA guidelines support the withdrawal of CCBs because of the potential for this class to adversely affect the clinical status of patients with HF. In addition, their use is not recommended to treat patients with HF who have comorbid disease states such as hypertension or chronic atrial fibrillation.[15] On the basis of current guidelines and previous studies, verapamil, diltiazem, nifedipine, nisoldipine, and nicardipine are not recommended for long-term treatment of patients with HF.

Minoxidil. Major considerations for the use of minoxidil are as follows:

- Mechanisms of adverse effect: fluid retention; stimulation of the renin-angiotensin-aldosterone system
- Strength of evidence: 10
- Time to onset: 2 to 4 weeks
- Recommendation: avoid use in patients with HF

Minoxidil is a potent arterial vasodilator that decreases systemic vascular resistance by direct smooth-muscle relaxation. Preliminary investigations in the 1980s, before the introduction of ACEIs, demonstrated an increase in cardiac index with short-term administration of minoxidil in patients with HF.[41] However, in another study, 6-week administration of minoxidil to patients with HF in NYHA classes III and IV produced worsening edema requiring dose escalation of furosemide from a mean baseline of 118 mg/d to 220 mg/d.[42] In these early clinical trials involving the use of minoxidil in HF, edema and fluid retention were documented as reasons for either early termination of the study or dose escalation of diuretics.[41-44] Minoxidil has not been compared with placebo as an adjunct to the standard therapy of diuretics, ACEIs, β-blockers, and spironolactone in patients with severe HF.

The postulated mechanisms for fluid retention with minoxidil use include increased circulating plasma norepinephrine enhancing sodium retention, direct vasodilating activity stimulating the renin-angiotensin system, or a combination of these mechanisms. It is recommended that minoxidil be avoided in patients with HF to prevent symptomatic worsening and because of the lack of evidence of use in combination with standard therapy. In hypertensive patients with HF, efforts should be made to maximize doses of ACEIs

and β-blockers to control blood pressure.

DIABETES MEDICATIONS

Metformin

Major considerations for the use of metformin are as follows:

- Mechanism of adverse effect: increased anaerobic glucose metabolism and subsequent elevated lactate levels
- Strength of evidence: 5
- Time to onset: anytime during therapy, partially dependent on renal function fluctuations
- Recommendations: avoid use in patients with HF with NYHA class III or IV symptoms and in those with a history of hospital admissions for HF exacerbations; use with appropriate monitoring in all other patients with HF

Metformin is a biguanide antidiabetic agent that has been proven to reduce the risk of many diabetes-related microvascular or macrovascular complications by 32% when used in overweight patients with type 2 diabetes mellitus.[45] The most serious complication associated with metformin therapy is lactic acidosis, and its occurrence is most often related to prescribing in contraindicated patient groups. The incidence of lactic acidosis is 0.03 cases per 1000 patient-years of treatment, with a mortality risk of 50%. The mechanism behind this fatal adverse event is linked to elevated concentrations of metformin in liver and intestinal tissue, which increases anaerobic glucose metabolism and raises lactate levels.[46] It may also reduce the utilization of lactate, further precipitating lactic acidosis.[47] Metformin is primarily eliminated renally; therefore, renal insufficiency and disease states that predispose patients to renal insufficiency due to decreased renal perfusion would place these patients at higher risk of lactic acidosis. Heart failure may result in decreased renal perfusion and decreased metformin elimination. In an evaluation of 47 cases of metformin-related lactic acidosis in the United States between 1995 and June 1996, 20 (43%) had a fatal outcome and 43 (91%) of these patients had one or more prior risk factors for lactic acidosis. Cardiac disease was the most common risk factor, with 18 patients (38%) having HF.[48]

Tenuous renal function and pulmonary edema–induced hypoxia are significant factors contributing to the likelihood of lactic acidosis in patients with HF. This potentially fatal adverse drug reaction can be avoided if metformin is used in the appropriate subset of this patient population. Its use should always be avoided in males with serum creatinine level of 1.5 mg/dL (133 µmol/L) or more and females with serum creatinine level of 1.4 mg/dL (124 µmol/L) or more, to minimize the accumulation of metformin due to decreased excretion. The package insert states that metformin is contraindicated in patients with HF requiring pharmacologic treatment, yet this recommendation seems overly restrictive, since diabetes is an extremely prevalent concomitant disease state, and any patient with decreased EF should receive pharmacologic treatment. Certainly patients with the more severe HF (NYHA classes III and IV) and those prone to acute pulmonary exacerbations, perhaps due to dietary or medication noncompliance, are not candidates for metformin therapy. However, patients with well-controlled or mild symptoms, without pulmonary edema and with good renal function, should not be denied the benefits of metformin therapy. Although the incidence of lactic acidosis is rare, the mortality is high, so careful patient selection is paramount.

Thiazolidinediones

Major considerations for the use of thiazolidinediones are as follows:

- Mechanism of adverse effect: fluid retention
- Strength of evidence: 7
- Time to onset: within 8 weeks of initiation
- Recommendations: actively monitor for new or increased HF symptoms; avoid use in patients with NYHA class III and IV HF

Rosiglitazone and pioglitazone are agents used as monotherapy and combination therapy for type 2 diabetes mellitus. The adverse effect profile of these antidiabetic agents includes edema, weight gain, hepatotoxicity, decreases in hemoglobin level and hematocrit, and most recently HF. An observational study showed a 4.5% risk of HF among diabetic patients receiving the thiazolidinediones vs 2.6% of those not prescribed these agents. In a controlled trial of 611 diabetic patients, rosiglitazone in combination with insulin resulted in HF in 2.5% of patients treated during a 26-week study. These patients were older, had a longer history of diabetes, and were prescribed the maximum dose of rosiglitazone (8 mg/d). In addition, rosiglitazone was associated with a 3-fold increase in the incidence of edema when used in combination with insulin compared with insulin alone. There appears to be a dose-related effect in the incidence (1% of those treated with insulin alone and 2% and 3% for those treated with insulin plus 4 mg and 8 mg of rosiglitazone, respectively).[49] Pioglitazone plus insulin was associated with a 1.1% incidence rate of HF in both the 191 patients receiving 15 mg and the 188 patients receiving 30 mg during a 16-week study.[50] It is hypothesized that the edema and documented volume expansion associated with the thiazolidinediones is responsible for the HF incidence with these agents. It has been documented that patients may gain up to 4 to 5 kg of fluid and fat accumulation when insulin therapy is combined with either rosiglitazone or pioglitazone.

The potential risk of HF has been added as a precautionary statement in the package insert of both rosiglitazone and pioglitazone. It is also recommended by the manufacturer that these agents not be used in patients with HF in NYHA class III and IV, since this population was not included in the clinical trials. Since diabetes alone carries a substantial risk of cardiac complications, the thiazolidinediones should continue to be considered as therapy for select diabetic patients with HF, especially if other agents are inadequate or unacceptable. If a thiazolidinedione is used, careful monitoring for increased symptoms of HF is required.

HEMATOLOGIC MEDICATIONS

Anagrelide

Major considerations for the use of anagrelide are as follows:

- Mechanism of adverse effect: positive inotropic activity, tachycardia
- Strength of evidence: 10
- Time to onset: not well documented, appears dose related
- Recommendation: avoid, if possible, in patients with HF

Anagrelide is a phosphodiesterase 4 inhibitor used in the treatment of proliferative hematologic disorders such as essential thrombocytosis and polycythemia vera.[51,52] Increasing cyclic adenosine monophosphate levels leads to increased calcium in the myocardium, producing positive inotropy and vasodilation. In a clinical efficacy trial in 577 patients, anagrelide induced HF in 14 patients (2.4%), with 209 patients (36.2%) experiencing cardiovascular events such as palpitations and tachycardia.[53]

The use of anagrelide has been associated with significant adverse cardiovascular events in patients with and without documented underlying cardiac disease. Anagrelide may exacerbate existing HF or potentially lead to its development. The onset of the signs and symptoms varies from days to months on initiation of therapy. Limited evidence and case reports suggest that anagrelide-induced HF may be reversible on discontinuation of therapy, although the potential for progression exists.[53]

The manufacturer recommends that baseline cardiac function tests be performed and periodic monitoring be conducted during therapy.[54] There are limited therapies for polycythemia vera and other proliferative hematologic disorders, and their associated toxicities may leave anagrelide as the only treatment option for some patients. The potential worsening of LV dysfunction and increased risk of supraventricular arrhythmias make anagrelide a dangerous choice in patients with HF. Therefore, it should be avoided if possible in these patients because of the potential for symptom exacerbations and syndrome progression.

Cilostazol

Major considerations for the use of cilostazol are as follows:

- Mechanism of adverse effect: inhibition of phosphodiesterase III, resulting in ventricular tachycardia and premature ventricular complexes
- Strength of evidence: 10
- Time to onset: unknown
- Recommendation: do not use in patients with HF

Cilostazol is a phosphodiesterase III inhibitor used in the treatment of intermittent claudication. Inhibition of phosphodiesterase 3 results in dose-proportional increases in heart rate with an average increase of 5 to 7 beats/min. Holter monitoring has demonstrated a dose-independent increased rate of premature ventricular complexes and nonsustained ventricular tachycardia in patients treated with cilostazol vs those treated with placebo.[55] Because of increased mortality in patients with HF treated long-term with previously available oral phosphodiesterase inhibitors compared with placebo, cilostazol is contraindicated by the manufacturer for use in patients with HF.[55] Alternatives to cilostazol such as antiplatelet therapy, exercise, lipid lowering, and smoking cessation should be used in patients with intermittent claudication and HF.

NEUROLOGIC AND PSYCHIATRIC MEDICATIONS

Amphetamines

Major considerations for the use of amphetamines are as follows:

- Mechanism of adverse effect: peripheral α- and β-agonist activity, tachycardia, arrhythmias
- Strength of evidence: 10
- Time to onset: unknown
- Recommendation: avoid use in patients with HF

Amphetamines (eg, racemic amphetamine, dextroamphetamine, methamphetamine) are used in narcolepsy and attention-deficit/hyperactivity disorder, and as adjunctive antidepressant therapy during initiation of antidepressants. These agents cause release of norepinephrine in the central nervous system and are agonists at peripheral α- and β-receptors, resulting in elevated systolic and diastolic blood pressures. Escalated doses promote tachycardia, while therapeutic doses may actually result in a reflexive decrease in heart rate. However, sympathetic activation is known to be detrimental in patients with HF. Patients with HF are more prone to arrhythmias, which may be exacerbated by β-adrenergic stimulation.[56]

These agents are contraindicated in patients with advanced atherosclerosis, symptomatic cardiovascular disease, and moderate to severe hypertension.[56] Since many patients with HF have one or more of these, and the pharmacologic actions mimic those known to be harmful, amphetamines should be avoided. Suspected narcolepsy should be further evaluated by ruling out sleep apnea or insomnia due to orthopnea in patients with HF. If amphetamines are considered for the short-term management of depression, the benefits when used during the initiation of antidepressant therapy to gain a more rapid onset of effect should be carefully weighed in relation to the risks in this population. For attention-deficit/hyperactivity disorder, behavioral therapy and environmental manipulations should be first-line therapy in adults with HF.

Carbamazepine

Major considerations for the use of carbamazepine are as follows:

- Mechanisms of adverse effect: negative inotropic and chronotropic effects; suppression of sinus nodal automaticity and atrioventricular conduction; anticholinergic effects accelerating the formation of reentry circuits
- Strength of evidence: 1
- Time to onset: not well documented
- Recommendations: avoid if possible in patients with HF; use

other first-line agents for seizures, depression, and affective disorders

Carbamazepine is used in the treatment of painful neuropathies, partial complex seizures, and affective disorders. Documented concentration-related cardiotoxic effects include LV dysfunction, sinus bradycardia, and varying degrees of atrioventricular block.[57] Adverse cardiovascular effects have been documented with therapeutic levels; however, most of these case reports involve elderly patients with underlying heart disease.[58,59]

Although there are no direct reports of HF exacerbations with carbamazepine at therapeutic concentrations, caution is required secondary to its intrinsic bradycardic effects in humans. Reports of tricyclic antidepressants leading to worsening of HF can be extrapolated to carbamazepine because of the similarity of their structural and adverse effect profiles. The negative chronotropic and inotropic effects of carbamazepine may induce LV failure in predisposed patients, such as the elderly or those with underlying heart disease.[60] It is recommended that carbamazepine be avoided if possible in patients with HF and that, if it is used, serum concentrations be maintained within the therapeutic range.

Clozapine

Major considerations for the use of clozapine are as follows:

- Mechanism of adverse effect: unknown
- Time to onset: weeks to years
- Strength of evidence: 4
- Recommendation: actively monitor for new or increased HF symptoms

Clozapine is an antipsychotic medication generally used in patients with schizophrenia refractory to conventional therapy or intolerant to other agents.[61] It provides benefit to approximately 30% of patients in this subpopulation. The primary drawback of clozapine therapy is a 1% incidence of agranulocytosis and the potential to lower the seizure threshold.[62] In addition, there are other well-described cardiac effects such as orthostatic hypotension and tachycardia, occurring in up to 9% and 25% of patients, respectively.[63]

There appears to be an association between clozapine therapy and the development of cardiomyopathy; however, a causal relationship cannot be established. A number of case reports describe the development of cardiomyopathy in individuals with no cardiac history.[64-66] The symptoms of HF appeared within several weeks to 3 years of clozapine initiation. The most compelling evidence for an association between clozapine and cardiomyopathy arises from an Australian clozapine registry. Investigators report the incidence of cardiomyopathy among new clozapine users to be 5 times that of the general population.[64] However, it is important to remember that patients with schizophrenia are more likely to abuse alcohol and other substances that increase the risk of cardiomyopathy.[67]

There is limited evidence to support a direct association between clozapine use and the development of cardiomyopathy. As clozapine is not first-line therapy because of its adverse effect profile, including agranulocytosis and seizures, its necessity must be established when used for the management of schizophrenia. Therefore, if a patient already has HF and clozapine therapy is required, close follow-up to assess for worsening HF symptoms and more frequent objective assessment of ventricular function may be prudent.

Ergot Alkaloids

Major considerations for the use of ergot alkaloids are as follows:

- Mechanisms of adverse effect: increased serum norepinephrine levels; excess serotonin activity resulting in cardiopulmonary fibrosis
- Strength of evidence: 2
- Time to onset: immediate (increased norepinephrine levels); years (fibrosis)
- Recommendations: avoid use if possible in patients with HF; if used, monitor regularly for new murmurs

The ergot alkaloids (eg, ergotamine, methysergide) have been used for more than 30 years for the treatment of vascular headaches. Methysergide is a competitive antagonist of serotonin peripherally and an agonist in the central nervous system. In contrast, ergotamine is a weak serotonin antagonist while it stimulates α-adrenergic receptors peripherally and inhibits the reuptake of norepinephrine.

Although methysergide and ergotamine are not directly linked to HF, these agents are associated with valvular abnormalities, which may clinically complicate the syndrome. The valve lesions described in case reports affected valves in any position and were both regurgitant and stenotic in nature.[68] The mechanism of the valvular fibrosis is thought to be related to excess serotonin activity at receptors not occupied by methysergide. The similarity in chemical structure between methysergide, ergotamine, and serotonin, in addition to the common appearance of the valvular abnormalities, suggests a causal role for ergot alkaloids in the development of fibrosis.[69] The onset of these valvular findings is typically years after long-term administration, and they do not completely resolve with drug discontinuation. Limited data suggest an incidence of 3.6% of valvular disease with methysergide, and some of these cases required valve replacements.[70] Methysergide has been associated with systolic and diastolic murmurs in young, otherwise healthy individuals.[71] Heart failure is associated with ineffective pump motion, resulting most often in mitral valve regurgitation. This predisposition would be accelerated and worsened with prolonged ergot alkaloid exposure. Primary aortic valve regurgitation caused by ergot-induced fibrosis may induce symptomatic HF.

It must also be taken into consideration that ergotamine elevates norepinephrine levels, one of the underlying neurohormonal mechanisms of cardiac remodeling in patients with HF. The impact on the symptoms or progression of HF is not known, but it is counter to the documented beneficial effects of adrenergic blockade in HF. Fibrotic heart valves, increased norepinephrine levels, and peripheral vascular constriction all have detrimental ef-

fects in patients with HF. It has been recommended that patients taking methysergide be followed up 3 to 4 times a year for the evaluation of new bruits, murmurs, or friction rubs.[72] However, it is in the best interest of patients' long-term prognosis to avoid the agents if possible.

Pergolide

Major considerations for the use of pergolide are as follows:

- Mechanism of adverse effect: excess serotonin levels resulting in valvular fibrosis similar to ergot alkaloid toxicity
- Strength of evidence: 2
- Time to onset: years
- Recommendations: avoid use if possible in patients with HF; thorough cardiovascular examination and possibly echocardiogram if new or worsening murmur develops

Pergolide is an ergot-derived dopamine receptor antagonist used in the treatment of Parkinson disease and restless leg syndrome. Pericardial, retroperitoneal, and pleural fibrosis have been documented in patients receiving pergolide therapy.[72] Recently, 3 cases of significant valvular heart disease associated with long-term pergolide administration were reported in elderly patients. These patients did not have a history of significant heart disease, and cardiac carcinoid was ruled out in each of the cases. All 3 patients received at least 4 years of pergolide therapy, which was discontinued after echocardiographic verification of severe tricuspid regurgitation. Pathological examination of the valvular tissue demonstrated a pattern indistinguishable from ergot-induced valvular fibrosis.[73]

On the basis of the similarity in serotonin axis disturbance and pathological findings in patients receiving pergolide and ergot alkaloids, it is recommended that this agent not be used in patients with HF. In patients with risk factors for developing HF in whom pergolide therapy is initiated, a complete cardiovascular examination with baseline echocardiogram would be prudent. Patients should be observed closely for new or worsening murmurs, with subsequent discontinuation of pergolide especially if patients present with HF symptoms.

Tricyclic Antidepressants

Major considerations for the use of tricyclic antidepressants are as follows:

- Mechanisms of adverse effect: negative inotropic effects; increase in automaticity; slowing of intracardiac conduction; proarrhythmic properties
- Strength of evidence: 2
- Time to onset: weeks to years
- Recommendations: avoid if possible in patients with HF; use other first-line agents for depression and neuropathy

Tricyclic antidepressants have been used for decades for the treatment of depression and insomnia. Recently, their use has expanded to the treatment of neuropathic pain, while their use in depression has fallen to second line after selective serotonin reuptake inhibitors. Tricyclic antidepressants possess class Ia antiarrhythmic activity and hence have proarrhythmic potential. The cardiotoxicity of these agents has been documented in overdoses and elevated plasma concentrations. However, therapeutic levels have also led to worsening HF and the development of HF symptoms.[74,75]

Case reports have suggested that the development of cardiomyopathy and HF may be related to the duration of therapy or the plasma concentration of parent drug and/or active metabolites.[76,77] Onset of HF and cardiomyopathy has occurred within weeks or up to several years after administration of therapeutic dosages. Resolution of HF symptoms after withdrawal and management with diuretics and digitalis in case reports ranged from 1 week up to 4 to 5 months.

The cardiotoxic potential of these agents appears to be associated with long-term use at therapeutic levels or acute toxic levels secondary to overdose. Although case reports are the evidence for the association of tricyclic antidepressants with HF, it is recommended that their use be avoided if possible. Other first-line agents should be used for depression, and very conservative use should be considered for neuropathic pain and insomnia in elderly patients with HF.

MISCELLANEOUS MEDICATIONS

β_2-Agonists

Major considerations for the use of β_2-agonists are as follows:

- Mechanism of adverse effect: direct positive chronotropic effect and hypokalemia promoting arrhythmias
- Strength of evidence: 5
- Time to onset: unknown
- Recommendations: avoid long-term systemic administration in patients with HF; use inhaled route of administration and lowest effective dose

Selective β-agonists (eg, albuterol, terbutaline) display a greater affinity for β_2- than β_1-receptors. Preferential agonist binding to β_2-receptors within the lung stimulates adenyl cyclase, causing increased formation of cyclic adenosine monophosphate from adenosine triphosphate. Increased cyclic adenosine monophosphate levels lead to accumulation of protein kinase A, which lowers intracellular calcium levels, resulting in bronchial relaxation. However, arrhythmias may occur with these selective agents when administered via the systemic and inhalation routes.[78-80] Furthermore, these agents promote hypokalemia, further increasing the potential for arrhythmias in the HF population. A cohort study of 149 patients with HF admitted to the hospital because of arrhythmias were followed up for a mean of approximately 4 years. During this period, there was an increased risk of hospitalization for arrhythmias in patients with HF taking β_2-agonists. The risk was found to be higher in those taking systemic vs inhaled β_2-agonists.[81]

Patients with HF on average are elderly and more prone to the arrhythmic potential of sympathomimetics. In addition, diuretic use in these patients has additive electrolyte disturbances when used in conjunction with selective β_2-agonists.[82] Since arrhythmias and cardiac arrest are major causes of

Table 3. Herbs Associated With Adverse Cardiac Events*

Herb	Cause of Adverse Effect
Increased Risk of Bleeding	
Dong quai	Natural coumarin
Aescin	Natural coumarin
Ginkgo	Platelet dysfunction
Garlic	Platelet dysfunction
Dan shen	Platelet dysfunction
Hypertension	
Ma huang	Sympathomimetic
Yohimbe bark	Sympathomimetic
Licorice	Aldosterone excess

*From Valli and Giardina[85] and Mashour et al.[86]

death in patients with HF, the use of sympathomimetics may carry an increased risk of adverse outcomes.[83] These agents should be avoided if possible and, if required, administered in the lowest possible dose and via the inhaled route.

Herbal Medications

It is estimated that 1 of every 5 patients taking prescription medications uses herbal remedies, suggesting that 15 million adults are at risk for adverse drug-herb or herb-disease interactions.[84] Limited clinical evidence concerning the efficacy or safety of herbal products is available despite the prevalence of use in the United States. Because of the general scarcity of published data and lack of clinical trials and/or case series with herbal therapies in patients with HF, only licorice (carbenoxolone sodium) has sufficient data to be discussed in detail. The adverse effects of some herbal products may be particularly harmful to patients with HF. **Table 3** provides a summary.

Licorice. Major considerations for the use of licorice are as follows:

- Mechanism of adverse effect: sodium retention, hypertension
- Strength of evidence: 7
- Time to onset: unknown
- Recommendation: avoid in patients with HF.

Licorice is the extract of *Glycyrrhiza glabra* roots and is used as a condiment or flavoring in candies and tobacco products. It has also been used historically for the treatment of dyspepsia and upper respiratory tract infections. The active component, glycyrrhetinic acid, has been associated with serious adverse effects such as HF, edema, hypokalemia, polyuria, polydipsia, muscle weakness, and hypertension. Carbenoxolone is a synthetic derivative that has been found to be pharmacologically similar to glycyrrhetinic acid in its activity and adverse effects.[87]

The enzymes that degrade aldosterone and glucocorticoids are inhibited by carbenoxolone and glycyrrhetinic acid. Hence, the biological half-lives and adverse effects of these steroids would be enhanced and prolonged.[88,89] This is the proposed mechanism behind the edema, sodium retention, and hypokalemia induced by licorice ingestion.

One study involving 30 healthy, normotensive volunteers found that 270 mg of glycyrrhetinic acid per day (100 g of licorice per day) during 4 weeks increased systolic blood pressure by 6.5 mm Hg.[90] The hypertensive effect of licorice would antagonize the beneficial effects of several of the therapies used to treat HF (ACEIs and β-blockers). In addition, the enhancement of aldosterone activity antagonizes the beneficial effects of ACEIs in patients with HF. Licorice should be avoided in patients with HF because of potential for harm in this population.

Itraconazole

Major considerations for the use of itraconazole are as follows:

- Mechanism of adverse effect: negative inotropic activity
- Strength of evidence: 3
- Time to onset: median, 10 days (range, 1-210 days)
- Recommendations: avoid administration for onychomycosis; use caution and increase monitoring for signs or symptoms of HF in the treatment of systemic fungal infections

Itraconazole is a triazole systemic antifungal agent used for treatment of histoplasmosis, aspergillosis, and onychomycosis. Administration of intravenous itraconazole resulted in dose-related negative inotropic effects and transient asymptomatic decreases in LV function in dogs and healthy volunteers in investigational trials. The biochemical and/or molecular mechanism of this cardiac effect is unknown.[91,92]

Between September 1992 and April 2001, 58 cases of HF associated with itraconazole were filed with the Food and Drug Administration Adverse Drug Reaction Reporting System. It appears that this is not a class-related effect because of the lack of reports with similar antifungal agents (eg, fluconazole, ketoconazole, miconazole, clotrimazole). Heart failure developed with itraconazole dosages ranging from 100 to 800 mg/d, with both oral and intravenous routes of administration, and occurred with indications for onychomycosis, systemic fungal infections, and prophylactic treatment. Signs and symptoms among these patients included pulmonary and peripheral edema, dyspnea, and significant weight gain. Documented risk factors or diseases that might have confounded the association between itraconazole and HF were present in 74% of these patients.[92]

The product labeling and package insert for itraconazole carry a black boxed warning and contraindication for its use in onychomycosis in patients with evidence of LV dysfunction. Warnings for itraconazole use include patients at risk of HF, such as those with ischemic and valvular disease, chronic obstructive pulmonary disease, renal failure, and other edematous states.[91] Other therapies for onychomycosis (eg, ciclopirox or terbinafine) should be considered first-line options in patients with existing HF. Patients with systemic fungal infections should be examined to determine whether alternative therapies might be appropriate; however, the severity of infection may outweigh the risk of HF exacerbation. If itraconazole therapy is considered essential in a patient with HF, increased monitoring and aggressive therapy for new or increased edema, weight gain, or dyspnea should be initiated immediately.

CONCLUSIONS

The information provided in this review must be used in conjunction

with clinical knowledge and patient-specific circumstances. It would be prudent to prevent morbidity and further expenditures in patients with HF resulting from hospitalizations in relation to adverse drug effects. To do so, health care providers must recognize medications that may be detrimental, assess the risk-benefit ratio in the individual patient, and monitor for adverse effects.

This review advocates patient safety and provides data to guide professional judgment to appropriately determine the medication needs of the complex patient with HF. Increased reporting of adverse drug events and the continued introduction of new agents require that the clinician remain attentive for new developments that affect the patient with HF.

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Infective Endocarditis, Cardiac Tamponade, and AIDS as Serious Complications of Acupuncture

I enjoyed reading the excellent article on adverse effects of acupuncture by Melchart et al.[1] To make their list more complete, I would like to mention 3 more serious complications of acupuncture: infective endocarditis,[2-4] cardiac tamponade,[5] and AIDS.[6] The last is of special importance. A large number of patients with AIDS have now turned to alternative therapies, including acupuncture.[6] Accordingly, this means of transmission may become increasingly important not only to thousands of patients receiving acupuncture treatments for various other ailments, but also to the acupuncturists themselves through needlestick accidents.

Acupuncture is safe but complications do occur, though rarely. According to Ernst and White,[7] hundreds of thousands of acupunturists worldwide perform millions of acupuncture procedures per year. Ernst and White[7] also stated that many cases of adverse events might not be reported, for various reasons, and those reported might not all be published. Therefore, such prospective studies as the one by Melchart et al[1] are extremely important for the sake of obtaining the true incidence of adverse events in association with such a popular therapeutic procedure as acupuncture that is used throughout the world.

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Correction

Error in Text. In the Review Article by Amabile and Spencer titled "Keeping Your Patient With Heart Failure Safe: A Review of Potentially Dangerous Medications," published in the April 12, 2004, issue of the ARCHIVES (2004;164:709-720), an error occurred in the text on page 717. On that page, in the subsection titled "Pergolide," the first sentence of the second full paragraph should have read as follows: "Pergolide is an ergot-derived dopamine receptor agonist used in the treatment of Parkinson disease and restless leg syndrome."