



## CHAPTER 24

# Heart Failure

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Heart failure is a major cause of morbidity and mortality in Western society.<sup>1-4</sup> It is one of the most common reasons for hospitalization, with over 5 million hospitalizations per year in the United States and 106,000 per year in Canada.<sup>4,5</sup> The duration of stay for patients hospitalized with heart failure is long, averaging about 13 days, and in-hospital mortality is high, between 3.2 and 15%.<sup>4,6</sup>

Coronary artery disease is by far the most common cause of heart failure in the United States, accounting for approximately two thirds of cases.<sup>7</sup> Other causes include hypertension, myocarditis, and cardiac toxins, including drugs, which can cause or exacerbate a stable pattern of heart failure.<sup>7,8</sup> Drug-induced heart failure in patients without pre-existing left ventricular dysfunction is quite rare, and drug-induced exacerbation of symptoms of heart failure occurs more frequently in those with established heart failure.<sup>9</sup> This chapter will focus on drug-induced heart failure, primarily heart failure with reduced ejection fraction (HFrEF), including causative agents, epidemiology, mechanism of action, and clinical presentation.

## CAUSATIVE AGENTS

Left ventricular ejection fraction (LVEF), also simply referred to as ejection fraction (EF), is used as the primary term to define heart failure.<sup>10</sup> Based on LVEF, heart failure can be divided into heart failure with reduced ejection fraction (HFrEF) if EF is <40% or heart failure with preserved ejection fraction (HFpEF) if the EF is >50%.<sup>10,11</sup>

The agents implicated in drug-induced heart failure are listed in **Table 24-1**.<sup>12-109</sup> Causality is often difficult to ascertain because of the multiplicity of factors that can exacerbate heart failure symptoms. Most calcium-channel blockers (except felodipine and amlodipine), antihyperglycemic agents (dipeptidyl peptidase 4 [DPP-4] inhibitors and thiazolidinediones [“glitazones”: rosiglitazone and pioglitazone]), antiarrhythmic agents, anthracyclines (doxorubicin), biologics (bevacizumab, infliximab, lapatinib, trastuzumab), non-steroidal anti-inflammatory agents (NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors, and adrenergic  $\beta$ -receptor antagonists ( $\beta$ -blockers) have all been implicated in drug-induced heart failure.

**Table 24-1 Agents Implicated in Drug-Induced Heart Failure**

Drug	Incidence	Level of Evidence <sup>a</sup>
$\alpha_1$ -antagonists		
Doxazosin <sup>12</sup>	RR 2.04, 95% CI 1.79–2.32	A
Amantadine <sup>13</sup>	NK	C
Aminocaproic acid <sup>14</sup>	NK	C
Amphotericin B <sup>15,16</sup>	NK	C
Anagrelide <sup>17</sup>	2.4%	B
Anthracyclines <sup>18,19</sup>		
Doxorubicin <sup>20–22,24</sup>	0–16%	A
Epirubicin <sup>24</sup>	20%	A
Digoxin immune antibody fragments <sup>25</sup>	NK	C
Antiarrhythmic agents <sup>25,26</sup>	5–10% <sup>24</sup>	A
Disopyramide <sup>29</sup>	16%	A
Dronedarone <sup>30</sup>	3.2%	A
Encainide <sup>28</sup>	2.6%	A
Flecainide <sup>27</sup>	(NYHA class III HF) 13.5%	A
Lidocaine <sup>26</sup>	9%	A
Lorcainide <sup>28</sup>	0.7%	A
Mexiletine <sup>28</sup>	0.9%	A
Morcizine <sup>28</sup>	2.4%	A
Propafenone <sup>28</sup>	4.7%	A
Tocainide <sup>28</sup>	1.6%	A
$\beta$ -blockers <sup>31</sup>	2%	B
Propranolol <sup>32</sup>	1–5.4%	B
Biologic agents		
Bevacizumab <sup>137</sup>	RR 4.74, 95% CI 1.66–11.18	A
Infliximab <sup>138</sup>	RR 2.84, 95% CI 1.01–7.97 14% vs 10% (control)	A
Trastuzumab <sup>98</sup>	Monotherapy: 3–7% <sup>99,100,102,103</sup> NYHA class III or IV: 0–3.9% <sup>101</sup> LVEF decrease >10%: 3–34% <sup>101</sup>	A
Blue cohosh <sup>33</sup>	NK	C
Bromocriptine <sup>34</sup>	NK	C
Buflomedil <sup>185</sup>	NK	C
Cabergoline <sup>35–37</sup>	NK	C
Calcium-channel blockers		
Diltiazem <sup>38</sup>	20.5%	A
Nifedipine <sup>39</sup>	24–26%	A
Verapamil <sup>40</sup>	NK	C
Carbamazepine <sup>110</sup>	NK	C
Clozapine <sup>41–44</sup>	NK	C
Corticosteroids <sup>45</sup>	Adjusted OR 2.7, 95% CI 2.5–2.9 <sup>2</sup>	B
Prednisolone <sup>46</sup>	Dose <7.5 mg/day: RR 1.5, 95% CI 1.3–1.8 Dose $\geq$ 7.5 mg/day: RR 3.7, 95% CI 2.7–5.1	B
Cyclophosphamide <sup>47,48</sup>	NK	C