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Society Guidelines

# The 2012 Canadian Cardiovascular Society Heart Failure Management Guidelines Update: Focus on Acute and Chronic Heart Failure

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The disclosure information of the authors and reviewers is available from the CCS on the following websites: www.ccs.ca and/or www.ccsguidelineprograms.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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**ABSTRACT**

**The 2012 Canadian Cardiovascular Society Heart Failure (HF) Guidelines Update provides management recommendations for acute and chronic HF. In 2006, the Canadian Cardiovascular Society HF Guidelines committee first published an overview of HF management. Since then, significant additions to and changes in many of these recommendations have become apparent. With this in mind and in response to stakeholder feedback, the Guidelines Committee in 2012 has updated the overview of both acute and chronic heart failure diagnosis and management. The 2012 Update also includes recommendations, values and preferences, and practical tips to assist the medical practitioner manage their patients with HF.**

**RÉSUMÉ**

**La mise à jour 2012 des Linges directrices sur l'insuffisance cardiaque (IC) de la Société canadienne de cardiologie fournit des recommandations sur la prise en charge de l'IC aiguë et de l'IC chronique. En 2006, le comité des lignes directrices sur l'IC de la Société canadienne de cardiologie a publié pour la première fois un aperçu de la prise en charge de l'IC. Depuis lors, des ajouts et des changements importants à plusieurs de ces recommandations sont devenus nécessaires. À cet égard et en réponse aux commentaires des parties prenantes, le comité des lignes directrices a mis à jour en 2012 l'aperçu du diagnostic et de la prise en charge de l'IC aiguë et l'IC chronique. La mise à jour 2012 inclut également des recommandations, des valeurs et des préférences, ainsi que des conseils pratiques pour aider le praticien à prendre en charge ses patients ayant une IC.**

The Canadian Cardiovascular Society (CCS) has published heart failure (HF) guidelines since 2006 and implemented the National HF Workshop Initiative; a series of workshops initiated to discuss Guideline implementation and identify challenges facing health care providers in HF management. The annual updates have produced a series of evidence-based reports with recommendations and practical tips outlining HF management.

The constitution and roles of the primary and secondary panels, systematic review strategy, and methods for formulating the recommendations are described in detail on the CCS HF Consensus Web site (www.ccsguidelineprograms.ca).

The 2012 CCS HF Consensus Update objectives are to provide an overall review of HF management and recommendations. The Guidelines deal with the areas of (1) acute HF (AHF) and (2) chronic stable HF.

The recommendations follow the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[1] The GRADE system classifies the quality of evidence as High (further research very unlikely to change confidence in the estimate of effect), Moderate (further research likely to have an important impact on confidence in the estimate of effect and may change the estimate), Low (further research very likely to have an important impact on confidence in the estimate of effect and likely to change the estimate), and Very Low (estimate of the effect very uncertain). The GRADE system offers 2 grades of recommendations: "Strong" (desirable effects clearly outweigh undesirable effects or clearly do not) and "Weak." When trade-offs are less certain, either because of low-quality evidence or because evidence suggests desirable and undesirable effects are closely balanced, weak recommendations become mandatory. Also new this year is the inclusion of values and preferences[2] that complement the GRADE system of recommendations.

## Acute Heart Failure

### Diagnosis, evaluations, and investigation

The diagnosis of AHF is based on a constellation of symptoms (eg, orthopnea and shortness of breath on exertion) and signs (eg, edema and respiratory crackles).[2,3] Physical examination evaluates systemic perfusion and presence of congestion (cold or warm, wet or dry; Supplemental Figure S1).[3-6] Laboratory testing, electrocardiogram (ECG), chest x-ray, and echocardiogram are all important to obtain.[5] A slight mild elevation of cardiac troponin is not infrequently observed in acute decompensation and not necessarily indicative of myocardial infarction (MI).[7] The utility of natriuretic peptide (NP) to exclude ("rule out") or confirm ("rule in") the diagnosis in the appropriate clinical scenario is well established.[5,8-10] NPs are best used when the diagnosis is uncertain; their clinical utility and relevant cut points have been well established.[5] Several clinical scoring systems have been derived and validated and combine commonly used clinical features with NP values to improve diagnosis and decision-making.[11,12] The most commonly used clinical scoring system (Table 1) was developed by Baggish et al. (Supplemental Table S1).[11] Prospective trials are under way, testing variations of these systems.

**RECOMMENDATION**

1. We recommend a thorough clinical evaluation of the patient to assess their clinical hemodynamic profile (Strong Recommendation, Low-Quality Evidence).
2. We recommend the use of a validated diagnostic scoring system for patients in whom the diagnosis of AHF is being considered (Strong Recommendation, Moderate-Quality Evidence).
3. We recommend that in the clinical scenario when the clinical diagnosis of AHF is of intermediate pretest probability, NP level be obtained to rule out (brain NP [BNP] $<$ 100 pg/mL; N-terminal [NT]-proBNP $<$ 300 pg/mL) or rule in (BNP $>$ 500 pg/mL; NT-proBNP $>$ 900 pg/mL if age 50-75 years, NT-proBNP $>$ 1800 if age $>$ 75 years) AHF as the cause for the presenting symptoms suspicious of AHF (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** This recommendation places a relatively high value on evaluating the constellation of clinical findings in a patient with suspected AHF and less value on an individual physical examination finding, presenting symptom, or investigation.

**Practical tip.** A precipitating cause for AHF should be sought.

**Table 1.** A clinical scoring system for diagnosis of AHF

| Predictor | | Possible score | Your patient's score |
|---|---|---|---|
| Age > 75 y | | 1 | |
| Orthopnea present | | 2 | |
| Lack of cough | | 1 | |
| Current loop diuretic use (before presentation) | | 1 | |
| Rales on lung exam | | 1 | |
| Lack of fever | | 2 | |
| Elevated NT-proBNP* | | 4 | |
| Interstitial edema on chest x-ray | | 2 | |
| | | 14 | Total = |
| Likelihood of heart failure | Low | | 0-5 |
| | Intermediate | | 6-8 |
| | High | | 9-14 |

AHF, acute heart failure; NT-proBNP, N-terminal pro brain natriuretic peptide.

*Elevated NT-proBNP was defined as > 450 pg/mL if age < 50 years and > 900 pg/mL if age > 50 years.[11]

An ECG and a chest x-ray should be performed within 2 hours of initial presentation.

Initial blood tests should include: complete blood count, creatinine, blood urea nitrogen, glucose, sodium, potassium, and troponin.

A transthoracic echocardiogram should be performed within 72 hours of presentation. For patients with a previous echocardiogram, another is not required unless there has been a significant change in clinical status requiring investigation, a lack of clinical response to appropriate therapy, and/or it is greater than 12 months since the previous echocardiogram.

Measurement of BNP or NT-proBNP measurements might be considered even with an already established diagnosis of HF in order to obtain prognostic information.

## Treatment, monitoring, and disposition

Oxygen should be used cautiously in normoxic patients because of concerns of increasing systemic vascular resistance and reducing cardiac output.[13] Bilevel positive airway pressure (BIPAP) or continuous positive airway pressure (CPAP) should be considered for patients with a high respiratory rate (eg, > 25 breaths per minute) and persistent systemic arterial hypoxemia despite high flow oxygen administration.[14] However, routine use of noninvasive ventilation (NIV) is not advisable. In the **Three** Interventions in **C**ardiogenic **P**ulmonary **O**edema (3CPO) trial,[15] patients with acute pulmonary edema were randomized to standard oxygen therapy, CPAP, or NIV, and followed to the primary end point of 7-day mortality. There was no difference between the 3 arms on 7-day mortality rate and 30-day mortality rates, intubation rates, or admission to an intensive care unit. Therefore NIV should be used only in patients with acute respiratory distress unresponsive to medical therapy. NIV caries the risk of worsening right HF, hypercapnia, aspiration, and pneumothorax. Endotracheal intubation may be used if less invasive modes of oxygen delivery fail or if the patient is in cardiogenic shock. There is a paucity of evidence to support the use of intravenous morphine to treat dyspnea, however some data suggest there might be adverse effects.[15,16]

Oral and intravenous diuretics remain the mainstay of early therapy directed toward AHF (Supplemental Table S2).[17] Intravenous diuretics increase urine output by excretion of sodium and water, leading to a decrease in extracellular fluid volume, total body water, and sodium. Reduction in cardiac filling pressures, peripheral congestion, and pulmonary edema usually follow.[18] Intravenous loop diuretics also cause an early decrease in right atrial and pulmonary capillary wedge pressure through a vasodilatory effect.[19] When using high intravenous doses reflex vasoconstriction might occur. In AHF, by normalizing loading conditions, these high doses might reduce neurohormonal activation in the short-term.[19] Patients presenting with AHF and congestion should receive intravenous loop diuretics. Therapy may be initiated in the ambulance,[20] HF clinic,[21] or in-hospital. Combining loop diuretics with thiazides[21,22] or spironolactone[23] has been proposed and seems to be effective, with fewer side effects than a higher dose of a loop diuretic. In patients with severe edema, oral loop diuretics might not be adequately absorbed and might be of little use.[5] The **D**iuretic **O**ptimization **S**trategies **E**valuation (DOSE) trial enrolled 308 patients with AHF and tested 2 intravenous strategies (high vs low dose furosemide; continuous infusion vs bolus intermittent dose) for the primary end point of global symptom assessment and creatinine at 72 hours.[17] There was no significant difference between the continuous infusion and bolus dosing in either symptoms or renal function. There was greater early symptom improvement with high compared with low dose diuretics without a significant difference in renal function. A number of secondary end points favoured high dose: a greater diuresis, more weight loss, and lower NT-proBNP level. Thus, there is no advantage in the routine use of continuous diuretic infusions and a higher dose of diuretics could be considered for many patients, with careful observation of renal function and electrolytes.

Vasodilators have not been shown to reduce mortality. Intravenous isosorbide dinitrate (in conjunction with low dose furosemide) was tested against low dose nitrates with high dose diuretics.[24] This prehospital trial of 110 patients showed that the strategy of early and high dose nitroglycerin (compared with high dose intravenous diuretics) reduced mechanical ventilation rates, and improved oxygen saturation. Another trial compared nesiritide, nitroglycerin, or placebo added to standard therapy for 3 hours, followed by nesiritide or nitroglycerin added to standard treatment for 24 hours in AHF.[25] The primary end points of changes in pulmonary capillary wedge pressure and patient self-evaluation of dyspnea at 3 hours were improved with nesiritide vs placebo. However, nitroglycerin improved early, short-term dyspnea assessment compared with placebo. The **A**cute **S**tudy of **C**linical **E**ffectiveness of **N**esiritide in **D**ecompensated **H**eart **F**ailure (ASCEND-HF) trial tested nesiritide vs placebo in 7007 patients with AHF enrolled within 24 hours of first intravenous medication.[26] Nesiritide did not reduce mortality, rehospitalization, or the composite of these end points at 30 days. The use of nitroprusside in AHF has not been supported by any randomized controlled trial (RCT). However, observational studies support its use in advanced HF by clinicians with experience and expertise in managing low-output acute or sub-acute HF.[27]

Inotropic agents have not been shown to improve patient outcomes.[5,28-30] The **O**utcomes of a **P**rospective **T**rial of **I**ntravenous **M**ilrinone for **E**xacerbations of **C**hronic **H**eart **F**ail-

ure (OPTIME-CHF) trial randomized 951 patients admitted for exacerbation of HF to a 48-hour infusion of milrinone or placebo.[29] New-onset atrial arrhythmias, worsening HF, and symptomatic hypotension requiring intervention occurred more frequently in the milrinone group. A nonsignificant increase in the number of deaths in-hospital and after 60 days was seen in the milrinone group. A post hoc analysis demonstrated a higher incidence of death or rehospitalization in patients with underlying ischemic HF aetiology.[30]

Angiotensin-converting enzyme (ACE) inhibitors should not be used early in the management of AHF. Though calcium channel blockers (CCBs) are also not advised,[5] in patients with HF with preserved ejection fraction (HF-PEF) and atrial fibrillation, a rate-limiting CCB may be used to control rapid ventricular rate.[5] Continuation of $\beta$-blocker upon admission for AHF is safe.[31,32] In an RCT of 169 patients with AHF, patients either discontinued $\beta$-blockade for 3 days or continued the medication unchanged. The trial showed that continuing the $\beta$-blocker was noninferior for the primary end point of dyspnea and well-being and was associated with a higher rate of $\beta$-blocker prescription at 3 months.[32]

Venovenous ultrafiltration may be of benefit in relieving congestion particularly in diuretic-resistant patients.[33] However, a recent study suggests this technology may be no more effective than pharmacologic therapy in most patients.[34] Vasopressin receptor antagonists (eg, tolvaptan) can rapidly and effectively reduce body weight and restore serum sodium in hyponatremic patients with circulatory congestion,[35,36] and can be used for this purpose but their use has not yet been associated with mortality benefits.[37]

The extent of monitoring will depend on the disease severity and the response to therapy.[5] Vital signs should be measured on a regular basis until stabilization. Laboratory tests have to be repeated regularly (eg, daily in the first 2-3 days): electrolytes, creatinine, and complete blood count, if abnormal.[5] Electrolyte abnormalities should be prevented or corrected promptly. Significant renal impairment might require more frequent laboratory testing. Clinical deterioration despite initial therapy requires closer supervision, such as transfer to an intensive care unit. Patients in cardiogenic shock or those who have difficulty voiding should have a urinary catheter to monitor urinary output.[5] The decision to insert an arterial line depends on the need for either continuous analysis of blood pressure (BP) because of hemodynamic instability or the requirement for repeated arterial blood gas analyses.[5] The use of a central intravenous line depends on the need for delivery of fluids and drugs or for monitoring central venous pressure and oxygen saturation. However, in the critically ill, right atrial pressure does not correlate well with left-sided filling pressures.[38] The insertion of a pulmonary artery catheter is not usually necessary for making a diagnosis of AHF.[5] It might, however, be useful to distinguish between cardiogenic and noncardiogenic shock, to guide therapy in the presence of severe diffuse pulmonary disease, or in hemodynamically unstable patients who do not respond in a predictable fashion to therapy.[39] Certain clinical features (eg, multiple previous admissions and respiratory disease) are associated with increased short-term mortality.[31,40]

**RECOMMENDATION**

1. We recommend supplemental oxygen be considered for patients who are hypoxemic; titrated to an oxygen saturation $>$ 90% (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** This recommendation places relatively higher value on the physiologic studies demonstrating potential harm with the use of excess oxygen in normoxic patients and less value on long-term clinical usage of supplemental oxygen without supportive data.

2. We recommend CPAP or BIPAP not be used routinely (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** This recommendation places high weight on RCT data with a demonstrated lack of efficacy and with safety concerns in routine use. Treatment with BIPAP/CPAP might be appropriate for patients with persistent hypoxia and pulmonary edema.

3. We recommend intravenous diuretics be given as first-line therapy for patients with congestion (Strong Recommendation, Moderate-Quality Evidence).
4. We recommend for patients requiring intravenous diuretic therapy, furosemide may be dosed intermittently (eg, twice daily) or as a continuous infusion (Strong Recommendation, Moderate-Quality Evidence).
5. We recommend the following intravenous vasodilators, titrated to systolic BP (SBP) $>$ 100 mm Hg, for relief of dyspnea in hemodynamically stable patients (SBP $>$ 100 mm Hg):
   i. Nitroglycerin (Strong Recommendation, Moderate-Quality Evidence);
   ii. Nesiritide (Weak Recommendation, High-Quality Evidence);
   iii. Nitroprusside (Weak Recommendation, Low-Quality Evidence).

**Values and preferences.** This recommendation places a high value on the relief of the symptom of dyspnea and less value on the lack of efficacy of vasodilators or diuretics to reduce hospitalization or mortality.

6. We recommend hemodynamically stable patients do not routinely receive inotropes like dobutamine, dopamine, or milrinone (Strong Recommendation, High-Quality Evidence).

**Values and preferences.** This recommendation for inotropes place high value on the potential harm demonstrated when systematically studied in clinical trials and less value on potential short term hemodynamic effects of inotropes.

7. We recommend continuation of chronic $\beta$-blocker therapy with AHF, unless the patient is symptomatic from hypotension or bradycardia (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** This recommendation places higher value on the RCT evidence of efficacy and safety to continue β-blockers, the ability of clinicians to use clinical judgement and lesser value on observational evidence for patients with AHF.

8. We recommend tolvaptan be considered for patients with symptomatic or severe hyponatremia (< 130 mmol/L) and persistent congestion despite standard therapy, to correct hyponatremia and the related symptoms (Weak Recommendation, Moderate-Quality Evidence).

**Values and preferences.** This recommendation places higher value on the correction of symptoms and complications related to hyponatremia and lesser value on the lack of efficacy of vasopressin antagonists to reduce HF-related hospitalizations or mortality.

**Practical tip.** In patients at risk or with a previous history of $CO_2$ retention (eg, chronic obstructive lung disease) permissive hypoxemia might be necessary and can be evaluated with arterial blood gas measurement.

In situations in which intravenous nitroglycerin is not appropriate or available, repeated sublingual nitroglycerin, a nitroglycerin patch, or oral isosorbide dinitrate might be useful for dyspnea relief in patients with a SBP > 100 mm Hg.

Intravenous vasoconstrictor agents (eg, phenylephrine, norepinephrine) should generally be avoided for AHF management except for patients hypotensive with SBP < 90 mm Hg, associated signs or symptoms, and significant change from baseline.

In patients with low SBP (< 90 mm Hg), low cardiac output and either euvolemia or hypervolemia, inotropes may be used for stabilization.

Patients with persistent congestion despite diuretic therapy, with or without impaired renal function, may, under experienced supervision, receive continuous venovenous ultrafiltration.

An ACE inhibitor should not be started in the acute setting (eg, the first 8-12 hours) unless elevated BP is present, and should be initiated after the acute event (eg, > 24 hours), and be continued particularly if the patient is already being treated with chronic ACE inhibitor therapy.

CCBs should be avoided as treatment in the setting of reduced ejection fraction (REF) < 40%.

## Chronic Heart Failure

### Diagnosis, evaluation, and investigation

The diagnosis of HF is made when symptoms and physical signs of congestion and reduced tissue perfusion are documented in the setting of abnormal systolic and/or diastolic cardiac function.[41-43] Making a diagnosis of HF can be difficult because the cardinal triad of edema, fatigue, and dyspnea are neither sensitive nor specific manifestations and atypical presentations should be recognized particularly when evaluating women, obese patients, and the elderly.[41-43] A history and physical examination should be performed in all patients; initial investigations should confirm or exclude HF and identify systemic disorders (eg, thyroid dysfunction) that can be etiologic or potentially affect disease progression. Measurements of NPs are useful when the initial diagnosis or diagnosis of decompensation is uncertain.[8,9,44] Echocardiography is useful to assess systolic and diastolic function, cardiac anatomy (eg, volume, geometry, and left ventricular mass), and pericardial disease.[41,45,46] Radionuclide angiography is useful to assess cardiac function and volumes where echocardiographic images are suboptimal (eg, obese patients, patients with emphysema).[45] Coronary angiography should also be considered in patients who have angina or positive noninvasive tests and might be potential candidates for revascularization.[47] Cardiac magnetic resonance might be useful in identifying inflammatory and infiltrative disorders and provide prognostic information.[48] Functional capacity should be assessed and the New York Heart Association (NYHA) functional classification is a simple, validated measure of HF clinical severity (Fig. 1).[49]

**RECOMMENDATION**

1. We recommend conducting a thorough medical history and physical examination when making a diagnosis of HF. Diseases that can cause HF or contribute to its progression should be screened. These include: family history of cardiomyopathy or sudden death, alcohol abuse, hemochromatosis, sarcoidosis, amyloidosis, HIV infection, neuroendocrinopathies (eg, pheochromocytoma, hypothyroidism), rheumatologic diseases (eg, collagen vascular diseases), nutritional deficiencies (eg, thiamine), and sleep apnea (Strong Recommendation, Low-Quality Evidence).
2. We recommend that a 12-lead ECG be performed to determine heart rhythm, heart rate, QRS duration, and morphology, and to detect possible aetiologies (Strong Recommendation, Low-Quality Evidence).
3. We recommend, if available, the measurement of NP (BNP and NT-proBNP) to rule in or rule out a diagnosis of HF and to obtain prognostic information (Strong Recommendation, High-Quality Evidence).
4. We recommend that echocardiography be performed in all patients with suspected HF to assess cardiac structure and function, to quantify systolic function for planning and monitoring of treatment, and for prognostic stratification (Strong Recommendation, Moderate-Quality of Evidence).
5. We recommend coronary angiography be performed in patients with angina pectoris who are deemed suitable candidates for coronary revascularization to document coronary anatomy (Strong Recommendation, Low-Quality of Evidence).
6. We recommend a validated measure of severity of symptoms and physical activity, such as the NYHA classification to document functional capacity (Strong Recommendation, High-Quality Evidence).

**Values and preferences.** These recommendations place greater value on basic evaluations that are widely available and less value on more advanced tests (eg, cardiac magnetic resonance) that should be reserved for selected patients.

### Heart failure with preserved ejection fraction

Approximately 50% of HF patients seen in clinics have HF-PEF.[43,50] HF-PEF is more prevalent in the elderly,

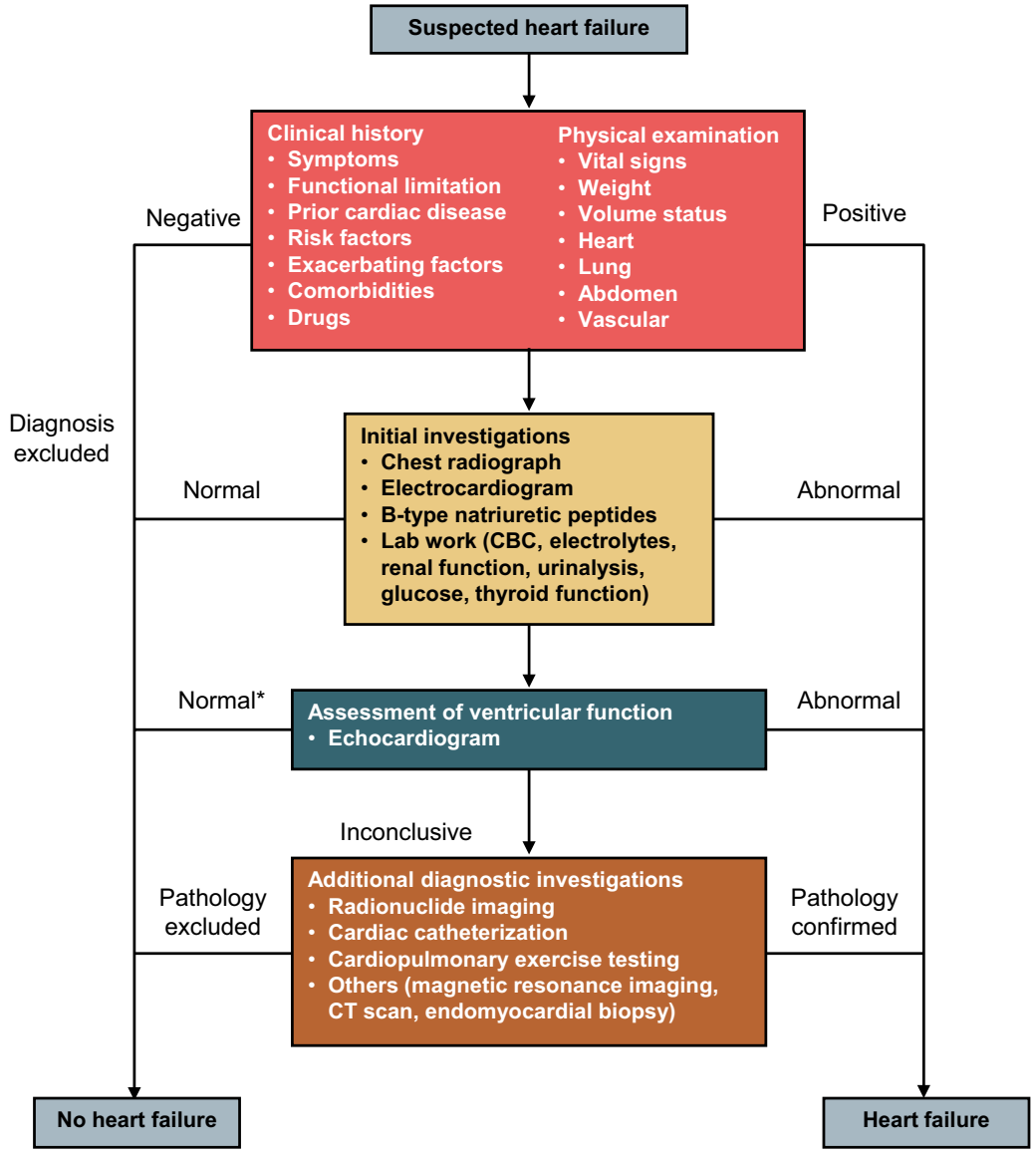


**Figure 1.** Algorithm for diagnosis of heart failure. CBC, complete blood count; CT, computed tomography. *Normal ejection fraction does not rule out heart failure with preserved ejection fraction. Adapted with permission from Arnold et al.[4]

women, and in patients with a history of hypertension.[50] In practice, HF-PEF is diagnosed when typical clinical HF findings are accompanied by PEF and the absence of significant valvular abnormalities.[51] The reported mortality rate for HF-PEF is less than found for HF with REF (HF-REF), although it is unacceptably high;[50,52] however, the studies have generally shown that morbidity, especially in HF hospitalizations, is similar to HF-REF.[50] There are still very limited evidence-based outcome-modifying therapies for HF-PEF, with most RCTs evaluating ACE inhibitors and angiotensin receptor blockers (ARBs) showing neutral or marginal benefits.[53-55] The main approach therefore is to control the risk factors potentially etiologic for the syndrome such as hypertension and myocardial ischemia.[56] Diuretics are typically used to control symptoms of congestion, and $\beta$-blockers and rate-lowering CCBs to control heart rate, if required.[57] ACE inhibitors and ARBs may be used if there are other non-HF indications for their use.[56]

**RECOMMENDATION**

1. We recommend systolic/diastolic hypertension be controlled according to the hypertension guidelines to prevent and treat HF-PEF (Strong Recommendation, High-Quality Evidence).
2. We recommend diuretics be used to control symptoms from pulmonary congestion and peripheral edema (Strong Recommendation, High-Quality Evidence).

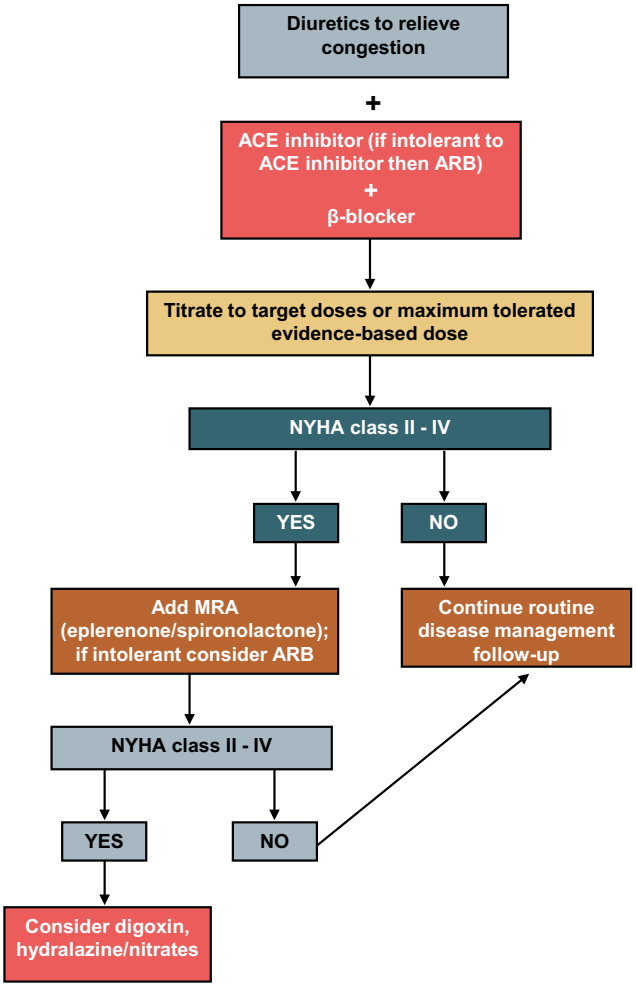


**Figure 2.** Pharmacologic management options for symptomatic heart failure with reduced ejection fraction (≤ 40%). ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

**Values and preferences.** These recommendations place a high value on the known aetiologic factors for HF-PEF and less on known outcome-modifying treatments which, unlike in HF-REF, are still quite limited.

## Pharmacological management of heart failure with reduced ejection fraction

Pharmacological therapy represents the most important component of the management of patients with HF-REF (Fig. 2). Several landmark RCTs have demonstrated that an ACE inhibitor improves survival in patients with HF-REF[58,59] and in patients with MI complicated by REF[60,61] and/or HF.[62] ARBs are noninferior to ACE inhibitors in patients with MI complicated by REF and/or HF,[63] modestly improves clinical outcome in HF-REF patients intolerant to ACE inhibitors,[64] or not taking a β-blocker.[65] Addition of an ARB to ACE inhibitor and β-blockade therapy modestly improves clinical outcome predominantly by reducing HF hospitalizations. Mineralocorticoid receptor antagonists (MRAs) greatly improve mortality/morbidity in patients with MI complicated by left ventricular dysfunction and HF,[66] patients with HF-REF with mild to moderate symptoms accompanied by high risk features,[67] and patients with advanced HF.[68] There is, however, limited trial experience with the combined use of ACE inhibitors, ARBs, and MRAs.[69]

β-Blockers such as bisoprolol, metoprolol CR/XL, and carvedilol reduce mortality in patients with HF-REF on ACE inhibitors.[70-73] However, bucindolol did not reduce mortality.[74] β-Blocker should be initiated in stable patients although it can also be initiated with caution in patients with recent decompensation.[75]

Diuretics relieve dyspnea and edema effectively. Although there are no large trials of diuretic therapy, a meta-analysis suggests they reduce the risk of worsening HF, death, and improve exercise capacity.[76]

Digoxin reduced HF hospitalization in patients with REF in sinus rhythm in 1 RCT[77] and systematic review of small trials suggested some benefits in symptoms and worsening HF.[78] These trials were performed before the widespread use of β-blockers.

An early RCT performed before the recognition of the benefits of ACE inhibitors and β-blockers demonstrated marginal mortality and symptom benefit from a combination of hydralazine and isosorbide dinitrate.[79] The **A**frican-American **He**art **F**ailure **T**rial (A-HeFT) showed that adding a fixed-dose combination of isosorbide dinitrate plus hydralazine to a contemporary standard therapy reduced mortality, first hospitalization for HF, and improved quality of life among African-American patients with HF-REF.[80]

A recent study in patients with NYHA class II-IV symptoms and ejection fraction (EF) ≤ 40% has demonstrated that the use of omega-3 polyunsaturated fatty acids (1 g daily) results in a modest reduction in cardiovascular (CV) mortality and hospitalization.[81]

Resting heart rate independently predicts CV events, including HF hospitalization.[82] Ivabradine, a drug that inhibits the $I_f$ channel, when approved might be considered in patients who remain symptomatic with a heart rate > 70 beats per minute despite optimal medical therapy including β-blockers, to reduce hospitalizations and deaths because of HF.[83]

An RCT in patients with HF-REF has demonstrated that patients randomized to receive aspirin 300 mg daily have increased risk of HF hospitalization.[84] Antiplatelet agents such as aspirin should therefore be administered only to patients with HF who have a documented history of coronary artery disease and stroke or who are deemed high risk for CV events. A recent RCT has demonstrated that in patients with REF who are in sinus rhythm, there is no significant difference between treatment with warfarin and aspirin in the risk of stroke.[85]

Commonly used medications such as the thiazodinineediones, nonsteroidal anti-inflammatory agents and cyclooxygenase-2 inhibitors have been implicated in the exacerbation of HF and should be avoided if possible.[86-88]

A list of evidence-based HF pharmacologic agents and the doses in the management of HF-REF is shown in Supplemental Table S3.

**RECOMMENDATION**

**ACE inhibitor**

1. We recommend an ACE inhibitor be used in all patients as soon as safely possible after a MI and be continued indefinitely if EF $<$ 40% or if HF complicates a MI (Strong Recommendation, High-Quality Evidence).
2. We recommend ACE inhibitors be used in all asymptomatic patients with an EF $<$ 35% (Strong Recommendation, Moderate-Quality Evidence).
3. We recommend ACE inhibitors be used in all symptomatic HF patients and EF $<$ 40%. (Strong Recommendation, High-Quality Evidence).

**ARB**

4. We recommend an ARB be used in patients who cannot tolerate an ACE inhibitor (Strong Recommendation, High-Quality Evidence).
5. We recommend an ARB be added to an ACE inhibitor for patients with NYHA class II-IV HF and EF $\leq$ 40% deemed at increased risk of HF events despite optimal treatment with an ACE inhibitor and $\beta$-blocker as tolerated (Strong Recommendation, Moderate-Quality Evidence).
6. We recommend an ARB be considered instead of an ACE inhibitor for patients with acute MI with HF or an EF $<$ 40% who cannot tolerate an ACE inhibitor (Strong Recommendation, Moderate-Quality Evidence).
7. We recommend ARBs be considered as adjunctive therapy to ACE inhibitors when $\beta$-blockers are either contraindicated or not tolerated after careful attempts at initiation (Weak Recommendation, Low-Quality Evidence).
8. We recommend routine combination of an ACE inhibitor, ARB, and MRA not be used for patients with current or previous symptoms of HF and REF (Strong Recommendation, Low-Quality Evidence).

**MRA**

9. We recommend an MRA such as eplerenone be considered for patients $>$ 55 years with mild to moderate HF during standard HF treatments with EF $\leq$ 30% (or $\leq$ 35% if QRS duration $>$ 130 ms) and recent (6 months) hospitalization for CV disease or with elevated BNP or NT-proBNP levels (Strong Recommendation, High-Quality Evidence).
10. We recommend an MRA such as eplerenone be considered in patients after an MI with EF $\leq$ 30% and HF or EF $\leq$ 30% alone in the presence of diabetes (Strong Recommendation, High-Quality Evidence).
11. We recommend an MRA such as spironolactone be considered for patients with an EF $<$ 30% and severe chronic HF (NYHA IIIB-IV) despite optimization of other recommended treatments (Strong Recommendation, High-Quality Evidence).

**Values and preferences.** The above recommendations place a high value on an understanding that among a given drug class, only drugs proven to be beneficial in large trials can be used because their effective target doses capable of modifying clinical outcome are known, and less value on individual response. If a drug with proven mortality or morbidity benefits is not tolerated by the patient, other concomitant drugs with less proven benefit can be carefully re-evaluated to determine whether their dose can be reduced or the drug discontinued to allow for better tolerance of the drug with proven benefit. These values and preferences also apply to the recommendations of other classes of drugs discussed below. Furthermore, because there are still no data on outcome-modifying pharmacologic treatment in HF-PEF, the above recommendations apply predominantly to patients with HF-REF.

**Practical tip.** Consider reducing the dose of diuretic if the patient is otherwise stable, and reassess the need and the dose of other vasodilators, such as long-acting nitrate, if no longer clinically needed.

An increase in serum creatinine of up to 30% is not unexpected in many HF patients when an ACE inhibitor or ARB is introduced; if the increase stabilizes at 30% or less, there is no immediate need to decrease the drug dose but closer long-term monitoring might be required.

MRAs can increase serum potassium, especially during an acute dehydrating illness in which renal dysfunction can worsen, and close monitoring of serum creatinine and potassium is required.

Combining an ARB with an ACE inhibitor increases the risk of hypotension, hyperkalemia, and renal dysfunction, and it should be used with caution.

**RECOMMENDATION**

***β*-Blocker**

1. We recommend all HF patients with an EF $\leq$ 40% receive a $\beta$-blocker proven to be beneficial in clinical trials (Strong Recommendation, High-Quality Evidence).
2. We recommend NYHA class IV patients be stabilized before initiation of a $\beta$-blocker (Strong Recommendation, High-Quality Evidence).
3. We recommend therapy be initiated at a low dose and titrated to the target dose used in large trials or the maximum tolerated dose if less than the target dose (Strong Recommendation, Moderate-Quality Evidence).
4. We recommend a $\beta$-blocker not be generally introduced to patients with symptomatic hypotension despite adjustment of other therapies, patients with severe reactive airways disease, symptomatic bradycardia, or with significant atrioventricular block without a permanent pacemaker; stable chronic obstructive pulmonary disease is not a contraindication for use of $\beta$ blockade (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** These recommendations place a very high value on the understanding that only $\beta$-blockers that have been shown to improve clinical outcomes should be used.

**Practical tip.** Objective improvement in cardiac function might not be apparent for 6-12 months after initiation.

Major reduction in dose or abrupt withdrawal should be avoided in the case of worsening HF. If the patient is hypotensive, consider reducing the dose of other medications before reducing the β-blocker dosage. Temporary discontinuation might occasionally be necessary in patients with shock. Whenever possible, reinstitution of treatment should be attempted before hospital discharge.

**RECOMMENDATION**

**Diuretics**

1. We recommend a loop diuretic, such as furosemide, for most patients with HF and congestive symptoms. When acute congestion is cleared, the lowest dose should be used that is compatible with stable signs and symptoms (Strong Recommendation, Low-Quality Evidence).
2. We recommend that for patients with persistent volume overload despite optimal medical therapy and increases in loop diuretics, cautious addition of a second diuretic (a thiazide or low dose metolazone) may be considered as long as it is possible to closely monitor morning weight, renal function, and serum potassium (Weak Recommendation, Moderate-Quality Evidence).

**Values and preferences.** These recommendations place a high value on the understanding that diuretics have not been shown to improve survival like the ACE inhibitors and β-blockers but are frequently required to relieve congestion.

**Digoxin**

3. We recommend digoxin in patients in sinus rhythm who continue to have moderate to severe symptoms, despite optimized HF therapy to relieve symptoms and reduce hospitalizations (Strong Recommendation, Moderate-Quality Evidence).
4. We recommend digoxin in patients with chronic atrial fibrillation (AF) and poor control of ventricular rate despite optimal β-blocker therapy, or when β-blockers cannot be used (Strong Recommendation, Low-Quality Evidence).

**Values and preferences.** These recommendations place a high value on the understanding that the use of cardiac glycosides in chronic HF remains controversial. Digoxin can cause atrial and ventricular arrhythmias particularly in the presence of hypokalemia. Not all glycosides and not all preparations have been studied in terms of efficacy and safety.

**Isosorbide dinitrate and hydralazine**

5. We recommend the combination of isosorbide dinitrate and hydralazine be considered in addition to standard therapy for black Canadians with HF-REF (Strong Recommendation, Moderate-Quality Evidence) and may be considered for others including non-black HF patients unable to tolerate an ACE inhbitor or ARB because of intolerance, hyperkalemia, or renal dysfunction (Strong Recommendation, Low-Quality Evidence).

**Values and preferences.** Adverse effects such as headache, nausea, dizziness, and hypotension are common and frequently require a reduction in dose or discontinuation.

**Omega-3 polyunsaturated fatty acids**

6. We recommend omega-3 polyunsaturated fatty acid therapy at a dose of 1 g daily be considered for reduction in morbidity and CV mortality in patients with mild to severe HF and reduced EF (Strong Recommendation, Moderate-Quality Evidence).

**Practical tip.** In presence of significant renal dysfunction, higher doses or combination diuretic agents might be needed; blood work needs to be closely followed.

Patients with recurrent fluid retention who are able to follow instructions can be taught to adjust their diuretic dose based on symptoms and changes in daily body weight.

In patients receiving digoxin, serum potassium and creatinine should be measured with increases in digoxin or diuretic dose, addition or discontinuation of an interacting drug, or during a dehydrating illness, to reduce the risk of digoxin toxicity. Patients with reduced or fluctuating renal function, the elderly, those with low body weight, and women are at increased risk of digoxin toxicity and might require more frequent monitoring including digoxin levels.

Nitrates alone can be useful to relieve dyspnea or angina but continuous use should generally be avoided because of the risk of development of tolerance.

**RECOMMENDATION**

**Platelet inhibition and anticoagulation**

1. We recommend aspirin at a dose of between 81 and 325 mg be considered only in HF patients with clear indications for secondary prevention of CV events (Strong Recommendation, High-Quality Evidence).
2. We recommend anticoagulation not be used routinely for HF patients who are in sinus rhythm (Strong Recommendation, High-Quality Evidence).
3. We recommend anticoagulation be considered for patients with demonstrated intracardiac thrombus, previous systemic embolism, or after a large anterior MI (Weak Recommendation, Low-Quality Evidence).

## Implantable cardioverter-defibrillator

The evidence for the recommendations for implantable cardioverter-defibrillator (ICD) therapy in HF management has been discussed extensively in the 2009 CCS HF Guidelines.[89] In brief, primary ICD therapy improves survival in patients with NYHA II-III ischemic and nonischemic HF with EF $\leq$ 35%[90] and in patients with a previous MI with EF $\leq$ 30%.[91] In contrast, ICD therapy does not provide any survival benefit early after an MI.[92,93]

**RECOMMENDATION**

1. We recommend an ICD be implanted in patients with HF-REF with a history of hemodynamically significant or sustained ventricular arrhythmia (secondary prevention) (Strong Recommendation, High-Quality Evidence).
2. We recommend consideration of primary ICD therapy in patients with:
   i. Ischemic cardiomyopathy, NYHA class II-III, EF ≤ 35%, measured at least 1 month post MI, and at least 3 months post coronary revascularization procedure (Strong Recommendation, High-Quality Evidence);
   ii. Ischemic cardiomyopathy, NYHA class I, and an EF ≤ 30% at least 1 month post MI, and at least 3 months post coronary revascularization procedure (Strong Recommendation, High-Quality Evidence);
   iii. Nonischemic cardiomyopathy, NYHA class II-III, EF ≤ 35%, measured at least 9 months after optimal medical therapy (Strong Recommendation, High-Quality Evidence).
3. We recommend an ICD not be implanted in NYHA class IV HF patients who are not expected to improve with any further therapy and who are not candidates for cardiac transplant or mechanical circulatory support (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** These recommendations place a very high value on the recognition that patients and family members should be carefully counselled as to the purpose of an ICD and the associated complications. If HF progresses to terminal stage, deactivation of the ICD can be considered after careful discussion.

## Cardiac resynchronization therapy

Since the previously published CCS HF guideline recommendations on cardiac resynchronization therapy (CRT)[4,89] which were based on earlier landmark RCTs conducted in patients with more severe symptoms,[94,95] additional trials and analyses have been published mandating the revision of the previous recommendations to include patients with mild HF symptoms and to place more emphasis on QRS morphology and duration, and the importance of sinus rhythm in the selection of patients.[96-102] These broad recommendations are in principal in general agreement with the more comprehensive recommendations discussed in the CCS CRT guidelines.

**RECOMMENDATION**

1. We recommend CRT in patients with NYHA III and ambulatory NYHA IV HF despite optimal medical therapy, in sinus rhythm with QRS duration ≥ 130 ms and left bundle branch block (LBBB) QRS morphology and EF ≤ 35% (Strong Recommendation, High-Quality Evidence).
2. We recommend CRT with an ICD in NYHA II HF patients despite optimal medical therapy, in sinus rhythm with a QRS duration ≥ 130 ms with LBBB QRS morphology and EF ≤ 30% (Strong Recommendation, High-Quality Evidence).
3. We recommend that CRT be considered in NYHA class II, NYHA class III, and ambulatory NYHA class IV HF patients, in sinus rhythm, EF ≤ 35%, and QRS duration ≥ 150 ms with non-LBBB QRS morphology (Weak Recommendation, Low-Quality Evidence).
4. We recommend the addition of ICD therapy be considered for patients referred for CRT who meet primary ICD requirements (Strong Recommendation, High-Quality Evidence).

**Values and preferences.** These recommendations place a significant value on the derived benefit of CRT in patient groups specifically included in the landmark RCTs, and less value on post hoc subgroup analyses and systematic analyses. Based on these trials, there is insufficient evidence to recommend CRT in patients with NYHA class I status or in hospitalized NYHA class IV patients, or those in AF. Patients with a QRS duration ≥ 150 ms are universally more likely to benefit from CRT than patients with less prolongation. CRT pacemaker therapy should also be considered in patients who are not candidates for ICD therapy such as those with a limited life expectancy because of significant comorbidities, and in patients who decline to receive an ICD.

## Atrial fibrillation

AF is a common arrhythmia in HF, and is associated with higher rates of adverse clinical events[103] and increased risk of thromboembolism including stroke.[104] AF should be managed and classified according to current AF guidelines.[105] The general approach is to control rate.[106] There are limited data to support a specific upper heart rate target; however, the current CCS AF guidelines recommend the target rate be < 100 beats per minute.[105] β-Blockers are preferred over digoxin for rate control.[107] Rate-lowering CCBs are acceptable alternatives in patients with HF-PEF.[108] The combination of β-blocker and digoxin is more effective than β-blocker alone in controlling ventricular response.[109] A rhythm control strategy has not been demonstrated to be superior to a rate-control strategy in reducing mortality or morbidity in patients with HF.[110] When rhythm control is required because of symptoms, amiodarone is preferred over class I agents and dronedarone.[111,112] Unless contraindicated, oral anticoagulants should be initiated in patients deemed high risk for stroke as per current AF guidelines.[105]

**RECOMMENDATION**

1. We recommend in patients with HF and AF that the ventricular rate be controlled at rest and during exercise (Strong Recommendation, Moderate-Quality Evidence).

2. We recommend that restoration and maintenance of sinus rhythm not be performed routinely (Strong Recommendation, High-Quality Evidence).
3. We recommend β-blockers for rate control particularly in those with HF-REF (Strong Recommendation, Moderate-Quality Evidence).
4. We recommend β-blockers combined with digoxin for uncontrolled ventricular rates on β-blocker therapy at optimal dose alone (Strong Recommendation, Moderate-Quality Evidence).
5. We recommend rate-limiting CCBs be considered for rate control in HF-PEF (Weak Recommendation, Low-Quality Evidence).
6. We recommend the use of antiarrhythmic therapy to achieve and maintain sinus rhythm, if rhythm control is indicated, be restricted to amiodarone (Strong Recommendation, Moderate-Quality Evidence).
7. We recommend oral anticoagulation for AF in HF patients deemed high risk for stroke unless contraindicated as per current AF guidelines, and not to coadminister with antiplatelet agents unless the latter are needed for other indications (Strong Recommendation, High-Quality Evidence).

**Values and preferences.** These recommendations are based on an understanding that the management of HF patients with AF should be individualized with respect to the need to identify precipitating factors, to assess the risk of therapy such as the development of bradycardia and proarrhythmia with antiarrhythmic agents, and the bleeding risk of systemic anticoagulation.

**Practical tip.** Nondihydropyridine CCBs should not be used to control heart rate in patients with HF-REF because they can depress cardiac function and worsen HF.

Dronedarone should not be used in patients with an EF $<$ 35% and/or with recent decompensated HF because of increased risk of mortality. Agents such as sotalol, flecainide, and propafenone should also be avoided.

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## References

1. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
2. McCormack JP, Loewen P. Adding "value" to clinical practice guidelines. Can Fam Physician 2007;53:1326-7.
3. Adams KF Jr, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005;149:209-16.
4. Arnold JM, Liu P, Demers C, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management. Can J Cardiol 2006;22:23-45.
5. Arnold JM, Howlett JG, Dorian P, et al. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure update 2007: prevention, management during intercurrent illness or acute decompensation, and use of biomarkers. Can J Cardiol 2007; 23:21-45.
6. Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol 2003;41:1797-804.
7. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. J Am Coll Cardiol 2010;56:1071-8.
8. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161-7.
9. Moe GW. BNP in the diagnosis and risk stratification of heart failure. Heart Fail Monit 2005;4:116-22.
10. Moe GW, Howlett J, Januzzi JL, Zowall H. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation 2007;115: 3103-10.
11. Baggish AL, Siebert U, Lainchbury JG, et al. A validated clinical and biochemical score for the diagnosis of acute heart failure: the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Acute Heart Failure Score. Am Heart J 2006;151:48-54.
12. Steinhart B, Thorpe KE, Bayoumi AM, Moe G, Januzzi JL Jr, Mazer CD. Improving the diagnosis of acute heart failure using a validated prediction model. J Am Coll Cardiol 2009;54:1515-21.
13. Park JH, Balmain S, Berry C, Morton JJ, McMurray JJ. Potentially detrimental cardiovascular effects of oxygen in patients with chronic left ventricular systolic dysfunction. Heart 2010;96:533-8.
14. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med 2008;359:142-51.
15. Gray A, Goodacre S, Seah M, Tilley S. Diuretic, opiate and nitrate use in severe acidotic acute cardiogenic pulmonary oedema: analysis from the 3CPO trial. QJM 2010;103:573-81.
16. Peacock WF, Hollander JE, Diercks DB, Lopatin M, Fonarow G, Emerman CL. Morphine and outcomes in acute decompensated heart failure: an ADHERE analysis. Emerg Med J 2008;25:205-9.
17. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797-805.
18. Brater DC. Diuretic therapy. N Engl J Med 1998;339:387-95.
19. Wilson JR, Reichek N, Dunkman WB, Goldberg S. Effect of diuresis on the performance of the failing left ventricle in man. Am J Med 1981;70: 234-9.
20. Gardtman M, Waagstein L, Karlsson T, Herlitz J. Has an intensified treatment in the ambulance of patients with acute severe left heart failure improved the outcome? Eur J Emerg Med 2000;7:15-24.
21. Ducharme A, Doyon O, White M, Rouleau JL, Brophy JM. Impact of care at a multidisciplinary congestive heart failure clinic: a randomized trial. CMAJ 2005;173:40-5.

22. Kiyingi A, Field MJ, Pawsey CC, Yiannikas J, Lawrence JR, Arter WJ. Metolazone in treatment of severe refractory congestive cardiac failure. Lancet 1990;335:29-31.

23. van Vliet AA, Donker AJ, Nauta JJ, Verheugt FW. Spironolactone in congestive heart failure refractory to high-dose loop diuretic and low-dose angiotensin-converting enzyme inhibitor. Am J Cardiol 1993;71: 21A-8A.

24. Cotter G, Metzkor E, Kaluski E, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet 1998;351:389-93.

25. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial [erratum in 2002;288:577]. JAMA 2002;287:1531-40.

26. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011; 365:32-43.

27. Mullens W, Abrahams Z, Francis GS, et al. Sodium nitroprusside for advanced low-output heart failure. J Am Coll Cardiol 2008;52:200-7.

28. Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. Eur J Heart Fail 2006;8:105-10.

29. Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002;287:1541-7.

30. Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. J Am Coll Cardiol 2003;41:997-1003.

31. Ezekowitz JA, Bakal JA, Kaul P, Westerhout CM, Armstrong PW. Acute heart failure in the emergency department: short and long-term outcomes of elderly patients with heart failure. Eur J Heart Fail 2008;10: 308-14.

32. Jondeau G, Neuder Y, Eicher JC, et al. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. Eur Heart J 2009;30: 2186-92.

33. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2007;49:675-83.

34. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367:2296-304.

35. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA 2004;291:1963-71.

36. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099-112.

37. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 2007;297:1319-31.

38. Cecconi M, Reynolds TE, Al-Subaie N, Rhodes A. Haemodynamic monitoring in acute heart failure. Heart Fail Rev 2007;12:105-11.

39. Marik PE. Pulmonary artery catheterization and esophageal doppler monitoring in the ICU. Chest 1999;116:1085-91.

40. Lee DS, Schull MJ, Alter DA, et al. Early deaths in patients with heart failure discharged from the emergency department: a population-based analysis. Circ Heart Fail 2010;3:228-35.

41. Kelder JC, Cramer MJ, van WJ, et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. Circulation 2011;124:2865-73.

42. Mant J, Doust J, Roalfe A, et al. Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care. Health Technol Assess 2009;13:1-207, iii.

43. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. Prog Cardiovasc Dis 2005;47:320-32.

44. Hildebrandt P, Collinson PO, Doughty RN, et al. Age-dependent values of N-terminal pro-B-type natriuretic peptide are superior to a single cut-point for ruling out suspected systolic dysfunction in primary care. Eur Heart J 2010;31:1881-9.

45. Kirkpatrick JN, Vannan MA, Narula J, Lang RM. Echocardiography in heart failure: applications, utility, and new horizons. J Am Coll Cardiol 2007;50:381-96.

46. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713.

47. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501-55.

48. Schwitter J, Arai AE. Assessment of cardiac ischaemia and viability: role of cardiovascular magnetic resonance. Eur Heart J 2011;32:799-809.

49. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th Ed. Boston: Little, Brown, 1994.

50. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 2004;43:317-27.

51. Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure. Arch Intern Med 1996;156:146-57.

52. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2011;33:1750-7.

53. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.

54. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338-45.

55. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359: 2456-67.

56. Hogg K, McMurray J. The treatment of heart failure with preserved ejection fraction ("diastolic heart failure"). Heart Fail Rev 2006;11: 141-6.

57. Hung MJ, Cherng WJ, Kuo LT, Wang CH. Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure. Int J Clin Pract 2002;56:57-62.

58. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 1987; 316:1429-35.

59. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 1991;325:293-302.

60. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333: 1670-6.

61. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327: 669-77.

62. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet 1993;342: 821-8.

63. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893-906.

64. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772-6.

65. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345: 1667-75.

66. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309-21.

67. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364: 11-21.

68. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341: 709-17.

69. McMurray J, Cohen-Solal A, Dietz R, et al. Practical recommendations for the use of ACE inhibitors, beta-blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. Eur J Heart Fail 2005;7:710-21.

70. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9-13.

71. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-7.

72. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996;334:1349-55.

73. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651-8.

74. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001;344:1659-67.

75. Krum H, Roecker EB, Mohacsi P, et al. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. JAMA 2003;289:712-8.

76. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. Int J Cardiol 2002;82:149-58.

77. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. N Engl J Med 1997; 336:525-33.

78. Hood WB Jr, Dans AL, Guyatt GH, Jaeschke R, McMurray JJ. Digitalis for treatment of congestive heart failure in patients in sinus rhythm: a systematic review and meta-analysis. J Card Fail 2004;10:155-64.

79. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303-10.

80. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004; 351:2049-57.

81. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1223-30.

82. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet 2008;372:817-21.

83. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875-85.

84. Cleland JG, Findlay I, Jafri S, et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. Am Heart J 2004;148:157-64.

85. Homma S, Thompson JL, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med 2012;366: 1859-69.

86. Amabile CM, Spencer AP. Keeping your patient with heart failure safe: a review of potentially dangerous medications. Arch Intern Med 2004; 164:709-20.

87. Feenstra J, Grobbee DE, Remme WJ, Stricker BH. Drug-induced heart failure. J Am Coll Cardiol 1999;33:1152-62.

88. Mamdani M, Juurlink DN, Lee DS, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. Lancet 2004;363:1751-6.

89. Howlett JG, McKelvie RS, Arnold JM, et al. Canadian Cardiovascular Society Consensus Conference guidelines on heart failure, update 2009: diagnosis and management of right-sided heart failure, myocarditis, device therapy and recent important clinical trials. Can J Cardiol 2009;25: 85-105.

90. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37.

91. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for

ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-40.

92. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004;351:2481-8.

93. Steinbeck G, Andresen D, Seidl K, et al. Defibrillator implantation early after myocardial infarction. N Engl J Med 2009;361:1427-36.

94. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.

95. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.

96. Dupont M, Rickard J, Baranowski B, et al. Differential echocardiographic response to cardiac resynchronization therapy and clinical outcomes according to QRS morphology and QRS duration. J Am Coll Cardiol 2012;60:592-8.

97. Hsu JC, Solomon SD, Bourgoun M, et al. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) study. J Am Coll Cardiol 2012;59:2366-73.

98. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-38.

99. Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Arch Intern Med 2011;171:1454-62.

100. Sipahi I, Chou JC, Hyden M, Rowland DY, Simon DI, Fang JC. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Am Heart J 2012;163:260-7.

101. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385-95.

102. Healey JS, Hohnloser SH, Derek V, et al. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the resynchronization for ambulatory heart failure trial (RAFT). Circ Heart Fail 2012;5:566-70.

103. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. Eur J Heart Fail 2009;11:676-83.

104. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-8.

105. Skanes AC, Healey JS, Cairns JA, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. Can J Cardiol 2012;28:125-36.

106. Gillis AM, Verma A, Talajic M, Nattel S, Dorian P. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: rate and rhythm management. Can J Cardiol 2011;27:47-59.

107. Fauchier L, Grimard C, Pierre B, et al. Comparison of beta blocker and digoxin alone and in combination for management of patients with atrial fibrillation and heart failure. Am J Cardiol 2009;103:248-54.

108. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369-429.

109. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? J Am Coll Cardiol 2003;42:1944-51.

110. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667-77.

111. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. Circulation 1998;98:2574-9.

112. Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358:2678-87.

## Supplementary Material

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